1 CLINICAL STUDY PROTOCOL

SAGENT®

Sagent Pharmaceuticals, Inc.

Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy of Camostat Mesilate for the Treatment of Confirmed COVID-19 in Outpatients

(**CAM**ostat **E**fficacy vs. p**L**acebo for **O**utpatient **T**reatment of COVID-19 [CAMELOT])

Protocol Number: NI03-CV19-001

IND Number:	149504
Name of Investigational Product:	Camostat mesilate
Phase of Development:	2
Indication:	COVID-19
Sponsor:	Sagent Pharmaceuticals 1901 N. Roselle Road, Suite 450 Schaumburg, IL 60195
Protocol Version:	4.0
Protocol Date:	07-October-2020

PROTOCOL APPROVAL SIGNATURES

Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy of Camostat Mesilate for the Treatment of Confirmed COVID-19 in Outpatients

Protocol Number: NI03-CV19-001

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP), and applicable regulatory requirements.

Sponsor Signatory

Bob Szurgot
VP Specialty Pharmaceuticals
Sagent Pharmaceuticals

Signature

07-10-2020
Date (DD-MM-YYYY)

Atasi Jana, MD
Manager Medical Affairs
Sagent Pharmaceuticals

Signature

07/10/2020
Date (DD-MM-YYYY)

INVESTIGATOR SIGNATURE PAGE

Protocol Title: A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy of Camostat Mesilate for the Treatment of Confirmed COVID-19 in Outpatients

Protocol Number: NI03-CV19-001

Confidentiality and Current Good Clinical Practice (GCP)/E6(R2)/Compliance Statement

- I, the undersigned, have reviewed this protocol, including appendices, and I will conduct the study as described in compliance with this protocol (and any amendments), GCP, and relevant International Council for Harmonisation (ICH) guidelines.
- I am thoroughly familiar with the appropriate use of the study drug, as described in this protocol and any other information provided by Sagent Pharmaceuticals including, but not limited to, the current investigator's brochure.
- Once the protocol has been approved by the institutional review board (IRB), I will not modify this protocol without obtaining prior approval of Sagent Pharmaceuticals and of the IRB. I will submit the protocol amendments and/or any informed consent form modifications to Sagent Pharmaceuticals and the IRB, and approval will be obtained before any amendments are implemented.
- I ensure that all persons or party assisting me with the study are adequately qualified and informed about the Sagent Pharmaceuticals study drug and of their delegated study-related duties and functions as described in the protocol.
- I ensure that source documents and trial records that include all pertinent observations on each of the site's trial subjects will be attributable, legible, contemporaneous, original, accurate, and complete.
- I understand that all information obtained during the conduct of the study with regard to the subjects' state of health will be regarded as confidential. No subjects' names will be disclosed. All subjects will be identified by assigned numbers on all case report forms, laboratory samples, or source documents forwarded to the Sponsor. Clinical information may be reviewed by the Sponsor or its agents or regulatory agencies. Agreement must be obtained from the subject before disclosure of subject information to a third party.
- Information developed in this clinical study may be disclosed by Sagent Pharmaceuticals to other clinical investigators, regulatory agencies, or other health authority or government agencies as required.

<Name>

<Title>

_____
Investigator Signature

_____
Date (DD-MM-YYYY)

_____
Institution

2 SYNOPSIS

Title of Study:	**CAM**ostat **E**fficacy vs. p**L**acebo for **O**utpatient **T**reatment of COVID-19 (CAMELOT Trial) A Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial of the Efficacy of Camostat Mesilate for Treatment of COVID-19 in Outpatients
Protocol Number:	NI03-CV19-001
Investigators/Study Sites:	Up to ~25 sites planned in United States
Subjects	Approximately 300 outpatients (200 in the camostat mesilate group and 100 in the placebo group)
Indication	Treatment of non-hospitalized adult subjects diagnosed with coronavirus disease 2019 (COVID-19) infection
Phase of Development:	Phase 2
Objectives:	The primary objective of this study is: • To evaluate the clinical efficacy of camostat mesilate in ambulatory subjects with confirmed COVID-19 The secondary objective of this study is: • Evaluate the safety profile of camostat mesilate in ambulatory subjects with confirmed COVID-19
Study Endpoints:	**Primary endpoint:** • Proportion of subjects requiring COVID-19 related hospitalization (including emergency room visit) or who die due to any cause within 28 days of randomization **Secondary Endpoints:** *Survival/Mortality* • The overall survival rate (the proportion of randomized subjects who survive up to Day 15 and Day 28) *Clinical Improvement* • Time to resolution of fever from randomization up to Day 28 • Time to hospitalization or death following randomization up to Day 28 • Proportion of subjects with no viral shedding (yes/no) using reverse transcriptase-polymerase chain reaction (RT-PCR) at Day 7, Day 15, and at Early Termination. *Safety/Tolerability* • Incidence of adverse events (AEs) and serious adverse events (SAEs) of any grade from randomization up to Day 28 • Cumulative incidence of grade 3 and 4 AEs from randomization up to Day 28 • Incidence of discontinuation from study due to an AE/SAE (discontinued subjects will be followed up to Day 28)

	• Change from baseline in clinical laboratory parameters • Change from baseline in vital signs (heart rate, blood pressure, peripheral capillary oxygen saturation [SpO2])
Study Design:	This is a randomized, double-blind, placebo-controlled study of camostat mesilate in ambulatory outpatients with confirmed COVID-19 with at least one risk factor for severe illness. Subjects will be randomized in a 2:1 ratio of camostat mesilate:placebo. Approximately 300 subjects are planned to be enrolled (200 subjects to camostat mesilate and 100 subjects to placebo). Subjects will be treated with camostat mesilate 200 mg orally 4 times a day for 14 days, and receive local standard of care (SOC) in addition to study drug. Subjects in the control arm will receive 2 placebo tablets 4 times a day for 14 days, as well as local SOC. Subjects will be followed until Day 28. Subjects will complete a symptom eDiary daily from Day 1 (first dose of study drug) through Day 15. Subjects will be seen in the clinic for assessments on Day 1, Day 7 and Day 15. Mid-turbinate nasal samples will be obtained at Screening, Day 7 and Day 15. Instructions for obtaining proper nasal samples will be provided. Subjects who withdraw from the study prior to completion of the 14-day treatment period will be asked to return for an Early Termination visit for blood draws and a mid-turbinate swab collection.
Selection of Subjects:	Inclusion Criteria: 1. Adults willing and able to provide informed consent before performing study procedures 2. Adults aged ≥ 18 years at time of informed consent 3. Subjects must have written notification of laboratory confirmed COVID-19 infection performed prior to screening, at a local laboratory by RT-PCR or other commercial or public health assay in any specimen. Subjects should be randomized within 72 hours of receiving this notification (note that all subjects will also undergo RT-PCR testing of mid-turbinate samples at a central laboratory on a specimen collected during the baseline visit (Day 1), but entry to the study is based on previously completed local testing for clinical purposes). 4. Have a mild or moderate form of COVID-19 defined as a SpO2 > 94% at screening 5. Subjects must have at least 1 of the following risk factors for severe illness: a. Aged 65 years or older b. Hypertension c. Diabetes mellitus d. Chronic lung disease including asthma, chronic obstructive pulmonary disease (COPD), and interstitial lung disease (e.g., idiopathic pulmonary fibrosis) e. Chronic cardiac conditions, including coronary artery disease (CAD), heart failure, congenital heart disease, cardiomyopathy f. Severe obesity (body mass index [BMI] ≥ 40 kg/m^2)

	g. Chronic liver disease, including cirrhosis 6. Must agree not to enroll in another study of an investigational agent or take any other drug that has been granted Emergency Use Authorization prior to completion of Day 28 7. If women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP, must be able and willing to use at least 1 highly effective method of contraception during the study and for 90 days after receiving the last dose of study drug. A female subject is considered to be a WOCBP following menarche and until she is in a postmenopausal state for 12 months or otherwise permanently sterile (for which acceptable methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). Contraceptive use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. Exclusion Criteria: 1. Physician makes a decision that trial involvement is not in subjects' best interest, or any condition that does not allow the protocol to be followed safely 2. Known severe liver disease (e.g., Child Pugh score > 12, AST > 5 times upper limit) 3. $SaO_2/SpO_2 \leq 94\%$ in room air condition, or the arterial oxygen partial pressure (PaO_2)/fractional inspired oxygen (FiO_2) ratio < 300 mmHg 4. Known allergic reaction to camostat mesilate or one of its excipients 5. Known severe renal impairment or receiving dialysis 6. Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination 7. Receipt of any experimental treatment for COVID-19, including agents with actual or possible direct acting antiviral activity, including, but not limited to, hydroxychloroquine, lopinavir/ritonavir, tocilizumab, ivermectin, or remdesivir within the 30 days prior to the time of the screening evaluation. No off-label use of a drug for COVID-19 is allowed. 8. History of human immunodeficiency virus infection on highly active antiretroviral therapy (HAART)
Planned Sample Size:	Assuming that the proportions of outpatients who are hospitalized for COVID-19 related disease or die due to any reason within 28 days of randomization are 30% and 15% for placebo and camostat mesilate groups, respectively, based on the two-sided Fisher's Exact Test, at the target significance level of 5%, 275 outpatients (183 in camostat mesilate group and 92 in placebo group) are needed to achieve 80% power. Thus, approximately 300 outpatients (200 in the camostat mesilate group and 100 in the placebo group) will be randomized to account for subject drop-out.
Investigational Therapy:	Camostat mesilate as 100 mg tablets, taken orally. Study dose: two 100 mg tablets (200 mg total) taken 4 times a day for 14 days.

Reference Therapy:	Placebo tablet identical in appearance to camostat mesilate. Study dose: two placebo tablets taken 4 times a day for 14 days.
Treatment Duration:	Subjects will be treated for 14 days and followed until Day 28
Efficacy Assessments:	Hospitalization (Primary Efficacy Endpoint) is defined as status changing from ambulatory care to COVID-19 related hospitalization or death due to any cause on or prior to Day 28. Presenting to the emergency room is considered hospitalization. Resolution of fever is defined as the time (in hours) from initiation of study treatment (active or placebo) until normalization of fever (≤ 37.2 °C oral) and sustained for at least 72 hours; this will only be assessed in subjects who experienced a fever within 24 hours of enrollment. Overall survival rate defined as the proportion of randomized subjects who survive up to Day 15 and Day 28. Proportion of subjects with no viral shedding (yes/no) using RT-PCR at Day 7 and Day 15.
Safety Assessments:	• Incidence of AEs: overall, treatment-related, grade 3 or higher in severity, serious, fatal, and those resulting in treatment discontinuation • Changes from baseline in clinical laboratory values judged as clinically significant will be listed as AEs. Laboratory values of interest will be monitored, including platelet counts, liver function tests (aspartate aminotransferase [AST], alanine aminotransferase [ALT], alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT]), and potassium levels. • Changes from baseline of vital signs (i.e., blood pressure, SpO2, and heart rate)
Statistical Methods and Planned Analyses:	The detailed methodology for summary and statistical analysis of the data collected in this trial will be documented in a Statistical Analysis Plan (SAP). In general, all efficacy endpoints and major safety endpoints will be summarized using descriptive statistics (e.g., proportions for categorical data, means and standard deviations for continuous data, median for time-to-event data). The primary and key secondary efficacy endpoints will be analyzed using appropriate statistical models. Analysis Populations: The Intent-to-Treat (ITT) population will include all subjects who are randomized. Subjects will be analyzed according to their study treatment assignment, not according to the treatment actually received. The ITT population will be used for evaluating primary and secondary efficacy endpoints and subject characteristics. The Per-Protocol (PP) population will include all subjects in the ITT population who complete the 28-day study and have no major protocol deviations. The PP population will be used for primary and secondary efficacy endpoints.

	The Safety population will consist of subjects who receive at least 1 dose of study medication (camostat mesilate or placebo). The Safety population will be used for all summaries of safety and tolerability data. Efficacy Analyses The primary endpoint (the proportion of subjects requiring COVID-19 related hospitalization or who died due to any cause within 28 days of randomization) will be analyzed using the Fisher exact test in ITT and PP populations. The primary endpoint will also be analyzed using the Mantel-Haenszel (MH) test, and the 95% Clopper-Pearson confidence interval (CI) will be reported. In addition, the continuity-corrected Newcombe CI for the proportional difference between treatment groups will be reported. The logistic regression model with treatment group, sex, race, duration of symptoms prior to enrollment, age groups (<65 versus ≥ 65 years) and other risk factors as covariates may be used to investigate the potential influences of demographic and baseline characteristics. The odds ratios and their 95% CIs will be estimated. The overall survival rate up to Day 28 will be analyzed in ITT and PP populations similar to the primary analysis. Similar methods, as per the primary endpoint, will be used to analyze the proportion of subjects with no viral shedding at Day 7 and Day 15. Time to resolution of fever from randomization up to Day 28 and time to hospitalization or death following randomization up to Day 28 will be summarized with Kaplan-Meier curves. A log-rank test will be used to analyze these time-to-event endpoints. The median event time and their corresponding 2-sided 95% CIs will be provided for each treatment arm. The Cox proportional hazard model with treatment group, sex, race, duration of symptoms, age groups (< 65 versus ≥ 65 years) and other risk factors as covariates may be used to investigate the potential influences of demographic and baseline characteristics. The hazard ratios and their 95% CIs will be estimated. Additionally, the change from baseline in clinical symptoms and viral shedding will be summarized using shift tables. A sensitivity analysis for efficacy endpoints will be performed for central laboratory confirmed COVID-19 subjects in the ITT population. Safety Analyses All AEs will be coded using the current MedDRA dictionary. Treatment-emergent AEs (TEAEs), SAEs, grade 3 or 4 TEAEs, and TEAEs leading to study discontinuations will be summarized using discrete summaries by system organ class and preferred term for each treatment group. TEAEs will be summarized by severity and relationship separately. Laboratory data and vital signs will be summarized descriptively. Missing Data Handling Missing data handling methods will be described in the SAP.

3 TABLE OF CONTENTS

3.1 List of In-text Tables

3.2 List of In-text Figures

4 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE2	angiotensin converting enzyme II
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area under the curve
BMI	body mass index
BUN	blood urea nitrogen
CAD	coronary artery disease
CBC	complete blood count
CDC	Centers for Disease Control
CFR	Code of Federal Regulations
CI	confidence interval
Cmax	maximum serum concentration
COPD	chronic obstructive pulmonary disease
COVID-19	coronavirus disease 2019
eCRF	electronic case report form
EDC	electronic data capture
FiO2	fractional inspired oxygen
FSH	follicle stimulating hormone
GCP	good clinical practice
GGT	gamma-glutamyl transferase
HAART	highly active antiretroviral therapy
HIPAA	Health Insurance Portability Accountability Act
IB	investigator's brochure
ICF	informed consent form
ICH	International Council for Harmonisation
IRB	institutional review board
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
MOA	mechanism of action
NSAID	nonsteroidal anti-inflammatory drug
PaO2	arterial oxygen partial pressure
PCR	polymerase chain reaction
PI	principal investigator
PK	pharmacokinetic
PP	per protocol
QID	4 times daily

Abbreviation	Definition
RT-PCR	reverse transcriptase-polymerase chain reaction
SAE	serious adverse event
SaO2	oxygen saturation
SAP	statistical analysis plan
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SpO2	peripheral capillary oxygen saturation
SOC	standard of care
SUSAR	Suspected unexpected serious adverse reaction
TEAE	treatment-emergent adverse event
TID	3 times daily
WHO	World Health Organization
WOCBP	women of childbearing potential
US	United States

5 INTRODUCTION

On 31 December 2019, the World Health Organization (WHO) was informed of a cluster of cases of pneumonia of unknown cause detected in Wuhan City, Hubei Province of China. The severe acute respiratory syndrome – coronavirus-2 (SARS-CoV-2) was identified as the causative virus of the disease currently referred to as coronavirus disease 2019 (COVID-19) by Chinese authorities on 07 January 2020 (WHO, 2020).

The rapid spread of COVID-19 presents an increasing threat to human health globally. The virus has subsequently spread throughout the world and was declared a pandemic by the WHO on 11 March 2020. Among patients infected with SARS CoV-2 are cases progressing to severe disease symptoms including acute respiratory distress syndrome (ARDS), pneumonia, pulmonary edema, and organ failure. These pathologies are driven by local and systemic inflammatory events (Cascella et al, 2020). As of the writing of this protocol, the number of cases of COVID-19 exceeds 7 million and the resulting number of deaths worldwide continue to climb.

5.1 Background on COVID-19

5.1.1 Overview of COVID-19 Disease

Gandhi et al, 2020 discusses the presentation, management, prevention, and control of patients with mild or moderate COVID-19. SARS-CoV-2 is a novel betacoronavirus related to bat coronaviruses that was thought to originate from a seafood market in Wuhan, China, where live animals were sold. There is much still unknown about COVID-19, but data from China indicated that 81% of people who become infected have a mild or moderate form of the disease (with no or mild pneumonia), 14% have a severe disease, and 5% have a critical form of the disease.

COVID-19 is spread from person to person through an infected person's respiratory droplets from coughs, sneezes, or even just speaking. It may also be contracted from a contaminated surface when a person touches the surface and then touches their face, transferring the virus to a mucosal membrane. Droplets are able to travel for approximately 2 meters from the infected person and then fall. Standing at least 1.8 meters (6 feet) apart from others will reduce the likelihood of transmission. The virus may live on certain surfaces (cardboard, plastic, and stainless steel) for days; therefore, sterilizing surfaces with antibacterial cleaners will also reduce transmission. Personal protective equipment for health care workers is essential to prevent the spread of COVID-19. Testing and diagnosis of patients is important so that those who are infected can self-isolate to prevent the spread to others (Gandhi et al, 2020).

An infected person may or may not display symptoms. Presymptomatic people may infect others for 1 to 3 days before displaying symptoms, and the virus is detectable during this time. The time from exposure to the time of displaying symptoms can be from 2 to 14 days, with 97.5% of people displaying symptoms within 11.5 days after infection. Patients usually have high viral levels in nasopharyngeal samples just before or soon after symptoms start. Viral levels will

continue to be detectable but will fall over the next week. Patients with severe COVID-19 illness may continue viral shedding longer, but how long viral shedding continues is not known at this time (Gandhi et al, 2020).

COVID-19 is diagnosed by using reverse transcriptase-polymerase chain reaction (RT-PCR) from a nasopharyngeal swab sample. The sensitivity of this assay is high but not 100%; therefore repeat testing is important if the person continues to exhibit symptoms, has knowingly been exposed, or lives in an area where there are a high number of COVID-19 cases (Gandhi et al, 2020).

The most common symptoms of a mild to moderate COVID-19 infection are fever, cough, sore throat, malaise, and myalgia. Anorexia, nausea, diarrhea, anosmia, and ageusia are often reported. Dyspnea may occur (usually 5 to 8 days after symptom onset) and is suggestive of more severe disease, often a precursor to hospitalization. Dyspnea can occur in patients with moderate disease but the oxygen saturation is usually at least 94% on room air (Gandhi et al, 2020). Importantly, clinical deterioration typically does not occur until more than 5 to 7 days following symptom onset, suggesting there is a window of opportunity for antiviral therapy early in the infection prior to the subsequent onset of severe systemic inflammation.

Certain comorbid conditions render a person more susceptible to contracting COVID-19 and contribute to worsening of the disease to a more severe version. These conditions include: age ≥ 65 years, cardiovascular disease, chronic lung disease, hypertension, diabetes, obesity, and diseases that weaken the immune system (Gandhi et al, 2020).

Patients with mild or moderate COVID-19 are usually instructed to recover at home, where they can be isolated, observed, monitored, and receive supportive care. However, some patient's conditions may deteriorate, especially those with comorbid conditions, which most often happens a week after onset of symptoms. These patients should be monitored closely. Patients with mild to moderate disease are able to monitor their own oxygen saturation levels if they are given a pulse oximeter (Gandhi et al, 2020).

Other than supportive care, remdesivir is the only treatment at this time that has proven efficacy from a Phase 3 randomized, placebo-controlled clinical trial, but, importantly, this was only administered to hospitalized patients with severe COVID-19. A preliminary report of early unblinding of the results showed a statistically significant, shortened time to recovery in the group that received remdesivir (11 days) compared with those who received placebo (15 days). Kaplan-Meier estimates of mortality by 14 days were 7.1% for remdesivir and 11.9% for placebo, which was not a statistically significant difference (Beigel JH et al, 2020). There currently is no vaccine that provides immunity against COVID-19.

5.2 Background on Camostat Mesilate

Camostat mesilate was approved for human use in Japan with the indication of "remission of acute symptoms of chronic pancreatitis" on 31 January 1985. Subsequent post-marketing surveillance revealed no significant problems with the efficacy or safety.

A paper by Hoffman et al published 16 April 2020 provided key insights into the first step of SARS-CoV-2 infection; namely, how the virus is able to get into human cells. Scientists found that the cellular protein protease TMPRSS2 is necessary for SARS-CoV-2 to enter lung cells, which is similar to SARS-CoV-1 (Hoffmann et al, 2020). Entry of SARS-CoV-2 into the cell depends on the cell entry receptor protein angiotensin converting enzyme II (ACE2) and the serine protease TMPRSS2. A protein on the viral surface called a spike attaches to the ACE2 receptor on the human cell and then TMPRSS2 cleaves the spike protein, allowing the virus to enter the cell and replicate inside of it. In this study, viral entry was inhibited by camostat mesilate, which is a known TMPRSS2 inhibitor. Therefore, camostat mesilate is a biologically plausible candidate to prevent the infection of SARS-CoV-2 or stop the progression of COVID-19 once a person is infected.

Camostat mesilate is already licensed in Japan and South Korea to treat chronic pancreatitis and reflux esophagitis. A clinical trial using camostat mesilate for chronic pancreatitis is currently ongoing in the United States (US) and is sponsored by Nichi-Iko Pharmaceutical Co., Ltd, Sagent's parent company. Because camostat mesilate is a known inhibitor of TMPRSS2 and has already been approved in Japan and South Korea and is currently under study for approval to treat pancreatitis in the United States, it is a potential candidate for the treatment of COVID-19, one that could be available much sooner than a drug that would still have to go through all development phases.

A Danish clinical trial using camostat mesilate is currently ongoing in subjects diagnosed with COVID-19. Subjects in this trial will receive two 100 mg pills of camostat mesilate or placebo 3 times daily (TID) for 5 days; however, justification for this dosing is not publicly available.

This study is designed to treat subjects in the United States with mild to moderate confirmed COVID-19 with a dosing regimen of 200 mg 4 times daily (QID) for 14 days. Dosing is based on the antiviral indication, as well as current data related to pharmacokinetics (PK) and safety.

5.2.1 Nonclinical Studies

Because camostat mesilate has been approved since 1985 in Japan, numerous nonclinical studies have been performed to evaluate its safety. Camostat mesilate has been studied in rats, mice, dogs, rabbits, hamster cells (hERG gene), various bacteria (Ames mutation test), and healthy humans. Nonclinical studies, including in-vitro and in-vivo pharmacology; PK including administration, distribution, metabolism, and excretion; safety pharmacology; toxicology and toxicokinetic evaluations; genotoxicity; tolerance studies; and reproduction and development studies have all been completed. Camostat mesilate's effect on general symptoms, central nervous system, autonomic nervous system, cardiorespiratory system, reproduction, and urinary system as well as local irritation and antigenicity have all been evaluated. The test methods and results of these studies can be found in the current version of the Investigator's Brochure (Sagent Pharmaceuticals, 2020).

5.2.2 Clinical Studies

Camostat mesilate or Foipan®, has been approved in Japan since 1985 for the remission of acute symptoms of chronic pancreatitis and postoperative reflux esophagitis. Much of the results and data in this section are from clinical studies presented as part of the Japanese drug approval process.

FOY-251 and GBA were found to be the primary metabolites of camostat mesilate when administered to normal, healthy subjects. FOY-251, the active metabolite, has a half-life in blood of approximately 75 minutes. Plasma kallikrein was suppressed for 2 to 4 hours following administration of camostat mesilate.

Nine studies using camostat mesilate enrolling a total population of 216 subjects with acute, chronic, or postoperative pancreatitis were conducted, with the majority of subjects dosed at 200 mg TID. The duration of dosing ranged from 2 weeks to more than 13 weeks. Few adverse events (AEs) were reported and no serious adverse events (SAEs) were documented from these studies. These studies did not have formal statistical tests, but did show a decrease in serum and urinary amylase levels throughout the treatment period (Kinami et al, 1980; Hirayama et al, 1980a; Abe et al, 1980; Fujiwara et al, 1980; Hayawaka et al, 1980; Hirono, 1980; Horiguchi et al, 1980; Kubota and Meada, 1980; Tanaka and Tsuchiya, 1980).

Two studies by Hirayama et al were conducted on subjects with pancreatitis (Hirayama et al, 1980a, Hirayama et al, 1980b). In both of these studies, camostat mesilate was dosed at 200 mg TID. Both studies showed that camostat mesilate significantly reduced serum and urine amylase levels. Only 1 AE was reported in the camostat mesilate group compared with none in the placebo group.

A PK and safety Phase 1/2 study (NI03-001) is currently being conducted in the United States with 2 phases (Ramsey et al, 2019). In the first phase, a single-dose of camostat mesilate at doses of 100 mg, 200 mg, and 300 mg were administered to 18 subjects with chronic pancreatitis. At all doses, camostat mesilate displayed markedly lower exposure (maximum serum concentration [Cmax] and area under the curve [AUC]) than the 2 metabolites. 4-GBA exposure appeared to be 2 to 3 times higher than that of FOY-251. Camostat mesilate exposure did not increase as the doses of camostat mesilate increased, which may be explained by the markedly low exposure of camostat mesilate at all doses. FOY-251 exposure increased as the doses of camostat mesilate increased from 100 mg to the 200 mg, but not from the 200 mg to the 300 mg. 4-GBA exposure (both Cmax and AUC) increased as the doses of camostat mesilate increased from 100 mg to the 200 mg, but only the AUC slightly increased from the 200 mg to the 300 mg. There were no deaths or SAEs, and 3 out of 18 subjects reported 4 treatment-emergent adverse events (TEAEs). Two TEAEs were mild and 2 were moderate in severity, with both of the mild TEAEs considered by the investigator to be possibly related to camostat mesilate. They occurred in the same subject and were an episode of dizziness and one episode of hot flashes after a single dose of 100 mg dose. Three of the TEAEs were reported following a dose of 100 mg camostat mesilate and the fourth TEAE was reported following a dose of 300 mg camostat mesilate. Laboratory hematology and clinical chemistry data showed no trends

following camostat mesilate administration and there were no individual clinically significant abnormalities. Camostat mesilate had no significant effect on heart rate or blood pressure at any dose tested. The data from the first phase of this study suggested that the camostat mesilate is safe to administer to subjects with chronic pancreatitis as a single dose up to and including 300 mg.

The second phase of Study NI03-001 is a randomized, double-blind, placebo-controlled study of 3 doses of camostat mesilate (100 mg, 200 mg, and 300 mg) administered TID for 28 days for the treatment of chronic pancreatitis associated pain. This study is still ongoing and data remain blinded. Six SAEs (nephrolithiasis, diabetic ketoacidosis, abdominal pain [2 events], pancreatitis, pancreatitis acute) have been reported from 3 subjects. All events required hospitalization and each event resolved. All events were considered by the investigator as not related to study drug. All but 1 event occurred in the 28-day follow-up period after the last treatment.

There are no expected concerns of safety for camostat mesilate. The safety profile of this class of drugs is favorable. Two studies done as far back as 1980 in subjects with pancreatitis reported that adverse effects were rare (< 3%), mostly mild, such as pruritus, increased thirst and appetite, and lightheadedness (Abe et al, 1980; Ishii et al, 1980).

5.3 Clinical Risks/Benefits of Camostat Mesilate

Camostat mesilate has been available in Japan for 30 years where it is used for the treatment for relief of the acute symptoms of chronic pancreatitis and postoperative reflux esophagitis. The following is taken directly from the package insert for Foipan® (camostat mesilate) and is considered an important precaution:

> Foipan Tablet® 100 mg should not be administered to patients with severe chronic pancreatitis requiring dietary restrictions such as gastric aspiration, or abstaining from food or drink.
>
> In terms of the AEs seen in humans with chronic pancreatitis, in 3806 subjects subject to reporting of adverse reactions in the clinical trial at the approval stage and in the post-marketing surveillance study, 83 adverse reactions (including abnormal clinical laboratory test values) were observed in 69 of 3806 subjects (1.8%). The main adverse reactions were 15 cases of rash (0.4%), 9 cases of itching (pruritus; 0.2%), 10 cases of nausea (0.3%), 7 cases of abdominal discomfort (0.2%), and 6 cases of abdominal bloating (0.2%).
>
> From a postoperative reflux esophagitis investigation for FOIPAN performed up to the time of approval and in the Drug Use Investigation, 75 AEs were reported in 57 (1.3%) out of 4224 subjects. The major AEs were 12 (0.3%) cases of hepatic function abnormalities such as increased AST and ALT, 8 (0.2%) cases of diarrhea, and 5 (0.1%) cases of nausea.

The Foipan® package insert also details the following significant adverse reactions:

> Symptoms of Shock and Anaphylaxis

Shock or anaphylactoid symptoms were reported from post-marketing surveillance. No specific antibody production has been reported with the drug in antigenicity studies in animals. However, in view of time course of symptom development (symptoms developed within 30 minutes after dosing in most cases), initial symptoms (dermatitis such as welts, itching sensation, and erythema, vertigo, feeling poorly, dull headache, sweaty, cold sweat, edema/swelling, dyspnea, and decrease in blood pressure), and subjects who had a past history of administration of this drug had experienced symptoms of hypersensitivity (e.g., urticaria, itching sensation and edema), these may have occurred due to anaphylactic reactions.

Thrombocytopenia

Serious decreased platelets have been reported from post-marketing surveillance. Symptoms included subcutaneous hemorrhage, oral hemorrhage, and epistaxis. The number of days until the onset was within 1 month after administration in most cases. Possible idiopathic thrombocytopenic purpura was suspected in some reported cases. In subacute and chronic toxicity studies of the drug, the decrease in platelets was not observed, and the mechanism of pathogenesis remains unknown.

Hepatic Function Disorder, Jaundice

Hepatic function disorder and jaundice (both with unknown frequency), accompanied by extreme elevation of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and gamma-glutamyl transferase (GGT), and alkaline phosphatase (ALP) have been reported from post-marketing surveillance. Initial symptoms included general fatigue, nausea and vomiting, and jaundice. Most of disorders occurred without subjective symptoms and identified by medical examinations. The duration from the beginning of dosage to onset was 12 months in many cases. Some disorders occurred (identified) after the end of administration of the drug. In subacute and chronic toxicity studies of the drug, hepatic function abnormal was not observed, and the mechanism of pathogenesis remains unknown.

Hyperkalemia

Serious hyperkalemia has been reported from post-marketing surveillance, although the frequency is unknown due to spontaneous reporting. Most of the disorders occurred without subjective symptoms and were identified by medical examinations. Abnormal electrocardiograms or electrocardiogram abnormalities with clinical symptoms (general fatigue and sensation of heaviness in chest) were observed in some cases. The duration from the beginning of dosage to the onset was within 2 months in most cases. In subacute and chronic toxicity studies of the drug, abnormal changes in potassium levels were not observed, and the mechanism of pathogenesis remains unknown.

Overall, the evidence of clinical activity and the AE profile observed support a positive benefit-to-risk ratio for subjects with COVID-19 who are treated with camostat mesilate.

Details regarding known or anticipated benefits and risks, as well as reasonably anticipated AEs for camostat mesilate may be found in the IB (Sagent Pharmaceuticals, 2020).

5.4 Study Rationale

The primary objective is to evaluate the efficacy of camostat mesilate in ambulatory subjects with confirmed COVID-19 infection. Based on the mechanism of action (MOA) of camostat in vitro to inhibit viral entry, subjects with nonsevere disease will be enrolled. Secondary objectives and endpoints include an assessment of efficacy of camostat mesilate evaluating the proportion of subjects requiring COVID-19 related hospitalization or death due to any cause, the overall survival rate, time to hospitalization, resolution of fever, and viral shedding. Safety objectives include assessments of AEs, vital signs, and laboratory parameters.

This study will be executed during a worldwide outbreak of COVID-19, resulting in capacity issues at many medical facilities and concerns about the safety of healthcare providers caring for these sick patients. Consequently, this study is designed to minimize the burden on clinical sites, including minimizing the number of required assessments and interventions, while protecting the safety of participants and retaining scientific rigor.

The investigational product and reference product (placebo) will be identical and indistinguishable to masked study personnel to limit bias in study assessments. Most interventions and assessments may be accomplished in conjunction with the schedule dictated by standard of care (SOC).

6 STUDY OBJECTIVES AND ENDPOINTS

6.1 Study Objectives

6.1.1 Primary Objective

The primary objective of this study is:

- To evaluate the clinical efficacy of camostat mesilate in ambulatory subjects with confirmed COVID-19

6.1.2 Secondary Objectives

The secondary objective of this study is:

- Evaluate the safety profile of camostat mesilate in ambulatory subjects with confirmed COVID-19

6.2 Study Endpoints

6.2.1 Primary Endpoint

- Proportion of subjects requiring COVID-19 related hospitalization (including emergency room visit) or who die due to any cause within 28 days of randomization

6.2.2 Secondary Endpoints

Survival/Mortality

- The overall survival rate (the proportion of randomized subjects who survive up to Day 15 and Day 28)

Clinical Improvement

- Time to resolution of fever from randomization up to Day 28
- Time to hospitalization or death following randomization up to Day 28
- Proportion of subjects with no viral shedding (yes/no) using RT-PCR at Day 7, Day 15, and at Early Termination (for subjects withdrawn prior to completing the 14-day treatment period)

Safety/Tolerability

- Incidence of AEs and SAEs of any grade from randomization up to Day 28
- Cumulative incidence of grade 3 and 4 AEs from randomization up to Day 28
- Incidence of discontinuation from study due to an AE/SAE (discontinued subjects will be followed up until Day 28)
- Change from baseline in clinical laboratory parameters
- Change from baseline in vital signs (heart rate, blood pressure, peripheral capillary oxygen saturation [SpO2])

7 INVESTIGATIONAL PLAN

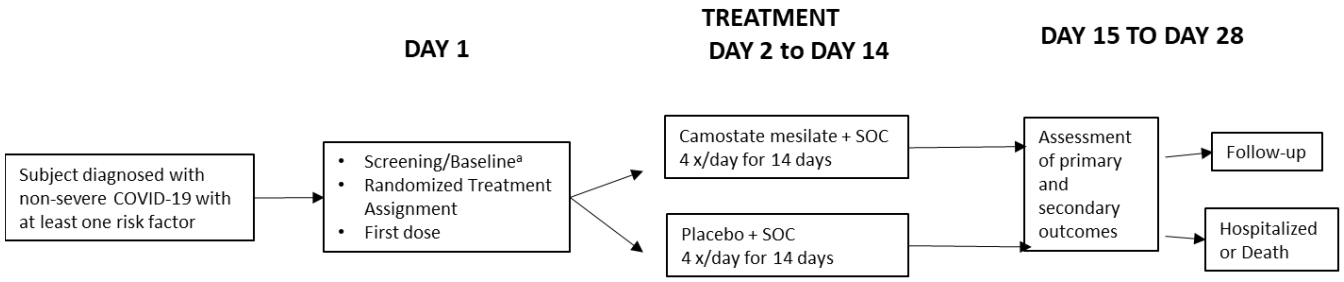
7.1 Description of Overall Study Design and Plan

This is a randomized, double-blind, placebo-controlled study of camostat mesilate in ambulatory outpatients with confirmed COVID-19 with at least one risk factor for severe illness. Subjects will be randomized in a 2:1 ratio of camostat mesilate:placebo. Approximately 300 subjects are planned to be enrolled (200 subjects to camostat mesilate and 100 subjects to placebo). Subjects will be treated with camostat mesilate 200 mg orally QID for 14 days and receive local SOC in addition to study drug. Subjects in the control arm will receive 2 placebo tablets orally QID for 14 days, as well as local SOC. All subjects will be followed until Day 28. Subjects will complete a symptom eDiary daily from Day 1 (first dose of study drug) through Day 15. Subjects will be coming into the clinic for assessments on Day 1, Day 7 and Day 15. Mid-turbinate nasal samples will be obtained at Screening, Day 7 and Day 15. Instructions for obtaining proper nasal samples will be provided. Subjects who withdraw from the study prior to completion of the 14-day

treatment period will be asked to return for an Early Termination visit for blood draws and a mid-turbinate swab collection. On Day 28 (end of study), a study team member will record subject disposition.

Figure 1 presents the study design.

Figure 1. Study Schematic



Abbreviations: COVID-19 = coronavirus disease 2019; SOC=standard of care.

[a] The Screening/Baseline and Day 1 visit assessments can be done on the same day.

7.2 Discussion of Study Design and Dosing

Camostat mesilate will be dosed at 200 mg (two 100 mg tablets) taken orally QID (800 mg/day total) for 14 days. This dosing was selected based on the requirement to have a constant presence of camostat mesilate in the circulation. It is well accepted that after 5 half-lives there is no, or negligible amounts, of drug left in the blood stream. The measurable half-life of camostat is in the region of 75 minutes and therefore 5 half-lives would be 6.25 hours. The approved dose of camostat in Japan is 200 mg TID but taking that dose in the treatment of COVID-19 would only provide coverage for approximately 18 to 19 hours and not the 24 hours coverage that is required. Therefore, a dose of 200 mg QID would theoretically offer 24 hours coverage at some level. In order to have 24 hours coverage of serine protease inhibition, a dose of 200 mg QID is appropriate and would not be expected to cause SAEs, especially if given for a limited period of 14 days. More detailed information can be found in the camostat mesilate IB.

The target population in this study is ambulatory subjects who have confirmed, mild to moderate COVID-19 who have at least 1 risk factor to develop complications. Subjects with mild to moderate disease were chosen because of the known method of action of camostat mesilate to block entry of the SARS-CoV-2 virus into the human cell. Camostat mesilate blocks TMPRSS2, a cellular protein protease that is necessary for SARS-CoV-2 to enter lung cells. It is hypothesized that a drug with this MOA will prevent the worsening and progression of COVID-19 and prevent hospitalization.

7.3 End of Study

A subject will have fulfilled the requirements for study completion if/when the subject has completed all study periods, including the end of study visit on Day 28, which is the last

scheduled visit as indicated in the Schedule of Assessments (Table 1). Subjects who terminate prior to completing the 14-day treatment period are asked to complete the Early Termination visit.

8 SELECTION OF STUDY POPULATION

Section 7.1 provides information regarding number of subjects planned to be enrolled.

8.1 Inclusion Criteria

Individuals must meet all of the following criteria to be included in the study:

1. Adults willing and able to provide informed consent before performing study procedures
2. Adults aged ≥ 18 years at time of informed consent
3. Subjects must have written notification of laboratory confirmed COVID-19 infection performed prior to screening, at a local laboratory by RT-PCR or other commercial or public health assay in any specimen. Subjects should be randomized within 72 hours of receiving this notification.
   (NOTE: all subjects will also undergo RT-PCR testing of mid-turbinate samples at a central laboratory on a specimen collected during the Screening/Baseline and Day 1 visit, but entry to the study is based on previously completed local testing for clinical purposes).
4. Have a mild or moderate form of COVID-19 defined as a SpO2 > 94% at screening
5. Subjects must have at least 1 of the following risk factors for severe illness:
   a. Aged 65 years or older
   b. Hypertension
   c. Diabetes mellitus
   d. Chronic lung disease including asthma, chronic obstructive pulmonary disease (COPD), and interstitial lung disease (e.g., idiopathic pulmonary fibrosis)
   e. Chronic cardiac conditions, including coronary artery disease (CAD), heart failure, congenital heart disease, cardiomyopathy
   f. Severe obesity (body mass index [BMI] ≥ 40 kg/m^2)
   g. Chronic liver disease, including cirrhosis
6. Must agree not to enroll in another study of an investigational agent or take any other drug that has been granted Emergency Use Authorization prior to completion of Day 28
7. If women of childbearing potential (WOCBP) or men whose sexual partners are WOCBP, must be able and willing to use at least 1 highly effective method of contraception during the study and for 90 days after receiving the last dose of study drug. A female subject is considered to be a WOCBP following menarche and until she is in a postmenopausal state for 12 months or otherwise permanently sterile (for which acceptable methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy). Contraceptive use by men or women should be consistent with local regulations regarding the methods of

contraception for those participating in clinical studies. Information on contraceptive use during the study is presented in Appendix 1.

8.2 Exclusion Criteria

Individuals meeting any of the following criteria at screening or baseline are ineligible to participate in this study:

1. Physician makes a decision that trial involvement is not in subjects' best interest, or any condition that does not allow the protocol to be followed safely
2. Known severe liver disease (e.g., Child Pugh score > 12, AST > 5 times upper limit)
3. Oxygen saturation (SaO2)/SpO2 ≤ 94% in room air condition, or the arterial oxygen partial pressure (PaO2)/fractional inspired oxygen (FiO2) ratio < 300 mmHg
4. Known allergic reaction to camostat mesilate or one of its excipients
5. Known severe renal impairment or receiving dialysis
6. Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination
7. Receipt of any experimental treatment for COVID-19, including agents with actual or possible direct acting antiviral activity, including, but not limited to, hydroxychloroquine, lopinavir/ritonavir, tocilizumab, ivermectin, or remdesivir within the 30 days prior to the time of the screening evaluation. No off-label use of a drug for COVID-19 is allowed.
8. History of human immunodeficiency virus infection on highly active antiretroviral therapy (HAART).

8.3 COVID-19 RT-PCR Test at Central Laboratory

Subjects who test positive for COVID-19 at the local laboratory will be enrolled if the subject meets all other entry criteria requirements. Nasal mid-turbinate swab samples are also to be obtained at the Screening/Baseline and Day 1 visit for central laboratory viral testing for COVID-19 as a baseline assessment and to test for viral shedding. If a subjects' test performed at the local laboratory is positive for COVID-19 but the test performed at the central laboratory is negative, the subject will stay in the study and complete all study visits. The reason for this is that RT-PCR testing is not sensitive enough to be accurate 100% of the time. These subjects will provide safety data for camostat mesilate. Statistical analysis for efficacy endpoints may be adjusted for subjects who fall into this category.

8.4 Rescreening

Individuals who sign the informed consent form (ICF) to participate in the study but who do not subsequently meet all the requirements as outlined in the inclusion and exclusion criteria and therefore do not enroll (screen failures) may not be rescreened.

8.5 Study Withdrawal, Removal, and Discontinuation of Subjects

Subjects who discontinue study treatment or who are withdrawn from the study for any reason must have the date and the reason for study discontinuation recorded on the electronic case

report form (eCRF). Subjects who discontinue early from the study will be asked to return to the study site within 3 to 7 days of the last administration of study drug to complete assessments as indicated in the Schedule of Assessments (Table 1) (Early Termination Visit).

In the event that a subject discontinues prematurely from the study because of a TEAE or SAE, the TEAE or SAE will be followed up until it resolves (returns to normal or baseline values) or stabilizes, or until it is judged by the investigator to no longer be clinically significant and thereafter until Day 28.

Upon discontinuation every effort will be made to follow the subjects until Day 28 for all study outcomes unless there is death of the subject, hospitalization, withdrawal of consent by the subject or the subject is lost to follow up.

Once a subject is withdrawn from the study, the subject may not reenter the study.

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- AE and/or SAE
- subject withdrawal of consent: at any time, a subject's participation in the study may be terminated at his/her request or on the basis of the investigator’s clinical judgment. The reason for subject withdrawal will be noted on the eCRF.
- intercurrent illness: a condition, injury, or disease unrelated to the primary diagnosis that became apparent during treatment and necessitated the subject’s termination from the study
- general or specific changes in the subject's condition that renders him/her ineligible for further treatment according to the inclusion/exclusion criteria
- subject fails to adhere to the protocol requirements (e.g., drug noncompliance, failure to return for defined number of visits)
- lost to follow-up: the subject stopped coming for visits, and study personnel were unable to contact the subject
- pregnancy, as indicated in Section 12.4.5.

Additionally, the Sponsor may stop the study at any time for safety, regulatory, legal, or other reasons aligned with good clinical practice (GCP). This study may be terminated at the discretion of the Sponsor or any regulatory agency. An investigator may elect to discontinue or stop the study at his or her study site for any reason, including safety or low enrollment.

9 TREATMENTS

9.1 Details of Study Treatments

Camostat mesilate, N, N-dimethylcarbamoylmethyl 4-(4-guanidinobenzoyloxy)-phenylacetate methanesulfonate, a guanidinobenzoic acid derivative is an orally active protease inhibitor with potent inhibitory effects on trypsin, plasma kallikrein, plasmin, thrombin, C_1r and C_1 esterase but does not attenuate α-chymotrypsin, pepsin, or pancreatin. Camostat mesilate is presented as a film-coated tablet that is white to yellowish white in appearance. Each tablet contains 100 mg camostat mesilate.

All drug supplies will be provided by the Sponsor. Camostat mesilate will be manufactured in tablet form by Nichi-Iko Pharmaceutical Co., Ltd. (Japan). Placebo tablets will be manufactured by Stason Pharmaceuticals, Inc. (Irvine CA).

Active Treatment Arm: two 100 mg tablets of camostat mesilate taken orally QID (total daily dose of 800 mg)

Placebo Arm: 2 matching placebo tablets taken orally QID

Study drug will be supplied in high density polyethylene (HDPE) bottles, each bottle containing 112 tablets of active drug or matching placebo. Each bottle will be labeled with a randomized bottle number, the name and address of the Sponsor, expiration date, and other information required by the US Food and Drug Administration (FDA) regulations.

Study drug must be stored at controlled room temperature (15°C to 30°C; 59°F to 86°F) in a limited access, secured storage area until dispensed. The storage conditions should be monitored daily.

9.2 Dosage Schedule

Study drug is administered as 2 tablets taken orally QID for 14 days. Study drug should ideally be taken with a meal or snack (breakfast, lunch, dinner), but it is not required. Tablets should be taken 3 times during the day and the fourth dose should be taken in the late evening (bedtime), with the dosing spaced approximately 5 hours apart. If a subject misses a dose, there should be no less than 2 hours between doses.

9.3 Measures to Minimize Bias: Study Treatment Assignment and Blinding

9.3.1 Method of Study Treatment Assignment

Subjects will be screened and enrolled in the order they present to the study centers and will be assigned the next available sequential subject number.

According to the randomization schedule as indicated in the Schedule of Assessments (Table 1), the investigator or designee will obtain the randomization number from the IWRS software. The IWRS software will use the blinded study arm linked to the randomization number to select a bottle number containing the correct study product (active or placebo) which is known to the IWRS to be in the possession of the site. The pharmacist or designee will provide the assigned bottle to the subject. No

study site personnel, subjects, Sponsor personnel, or Sponsor designees will be unblinded to treatment assignment throughout the duration of the study unless unblinding is required. If an investigator becomes unblinded to a given subject's study treatment, that subject will be discontinued from the study unless there are ethical reasons for that subject not to be discontinued; approval from the Sponsor's Medical Monitor must be obtained in such instances.

In the event that emergency unblinding is required for a given subject because of AEs or concerns for the subject's safety or wellbeing, the IWRS software will perform the unblinding. The IWRS software limits access to the emergency unblinding function to designated personnel and records the date, time, and person performing the unblinding. The unblinding and its cause will also be documented on the eCRF via automated entry by the IWRS.

9.3.2 Blinding

This is randomized, double-blind, placebo-controlled study. Subjects will be randomized in a 2:1 ratio to camostat mesilate:placebo. None of the investigators, study site personnel, Sponsor, or subjects will know to which treatment the subjects were randomized. To maintain the blind, camostat mesilate and placebo tablets will be indistinguishable from one another and are identified in distribution to study sites and dispensing to study subjects by a randomized number assigned to each bottle known only to the packager (Stason) and the IWRS.

The labeling, shipment, and receipt of the bottles at the study sites are all recorded in the IWRS software, contributing to the blinding of the assigned product after study randomization by preventing site personnel from knowing the exact contents of bottles assigned to study subjects. The assignment of the blinded randomization number to a subject and selection of a bottle number for the corresponding blind-labeled product bottle are controlled by the IWRS with no visibility of underlying study arm or product assignment to any party.

9.4 Dosage Modification

No dose modifications will be allowed.

9.5 Treatment Accountability and Compliance

The pharmacist or other designated individual will maintain electronic records of study drug delivered to the study site, the inventory at the study site, the distribution to and use by each subject, and the return of materials to the Sponsor for storage or disposal. These records should include dates, quantities, batch/serial numbers, expiration dates, in-clinic temperature logs, and unique code numbers assigned to the product and study subjects.

At each visit after initiation of treatment, study site personnel will record compliance. Subjects will be instructed to bring their unused/partially used bottles back for inspection at each study visit. Subjects are to be reminded of the importance of compliance with an emphasis on taking their study drug on schedule and maintaining the prescribed interval between doses.

Investigators will maintain records that adequately document that the subjects were provided with the correct study treatment allocation and reconcile the products received from the drug

dispensing center. Used or unused Investigational product will be returned to Stason Pharmaceuticals, Inc. (drug packager) if not destroyed at the clinical site.

Medication containers must be returned at the end of treatment visit, as compliance will be assessed by tablet counts. Noncompliance is defined as taking less than 80% of study drug. Discontinuation for noncompliance is at the investigator's discretion and is to be noted on the eCRF.

9.6 Prior and Concomitant Therapies/Interventions

9.6.1 Prior and Concomitant Medications

Restricted prior therapies are provided in Section 8.2 and are prohibited within 30 days before the time of screening. All medications taken by or administered to the subject within 30 days of screening will be recorded on the eCRF.

After the baseline visit, medication to treat minor treatment-emergent illness is generally permitted; however, the following therapies are expressly prohibited throughout the study:

- Any antiviral medications, including but not limited to, hydroxychloroquine, lopinavir/ritonavir, tocilizumab, ivermectin, or remdesivir
- Experimental drug or off-label use of any drug.
- Antipyretics are not allowed with the exception of acetaminophen.

Any medication or therapy that is taken by or administered to the subject during the course of the study must be recorded on the eCRF. The entry must include the dose, regimen, route, indication, and dates of use.

Cough expectorants (e.g., guaifenesin) and cough suppressants (e.g., dextromethorphan) are allowed during the study.

Acetaminophen for fever is allowed

Antihistamines are allowed for congestion

10 STUDY PROCEDURES

Table 1 outlines the timing of procedures and assessments to be performed throughout the study. Section 12.3 specifies laboratory assessment samples to be obtained. See Section 11 and Section 12 for additional details regarding efficacy assessments and safety assessments, respectively.

Table 1. Schedule of Assessments

Study Day: **Assessment / Procedure**	**Screening/Baseline & D1[a,b]**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D 10**	**D 11**	**D 12**	**D 13**	**D 14**	**D 15**	**D 21**	**Unscheduled Visit[i]**	**End of Study D 28**	**Early Termination**
Informed consent[a]	X																		
Verify notification of local COVID-19 positive test result occurred within 72 hours of screening[a]	X																		
Eligibility criteria[a]	X																		
Demographics[a]	X																		
Medical history[a]	X																		
Concomitant medications[a,]	X						X								X	X	X		
Urine pregnancy test (as applicable)[a]	X																		
Clinic visit[d]	X						X ± 1 day								X ± 1 day	☎ ± 1 day	X	☎ ± 1 day	X ± 1 day
Height / Weight[a]	X																		
Randomization, assign subject ID, dispense study drug[b]	X																		
Complete eDiary[c,e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
Vital signs (heart rate, blood pressure, SpO2)[a]	X						X								X		X		X
Adverse events[a,g],	X						X								X	X	X		X
Laboratory assessments[a,g]	X														X		X		X

Study Day: **Assessment / Procedure**	**Screening/Baseline & D1[a,b]**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D 10**	**D 11**	**D 12**	**D 13**	**D 14**	**D 15**	**D 21**	**Unscheduled Visit[i]**	**End of Study D 28**	**Early Termination**
Sample for viral shedding by RT-PCR (mid-turbinate swab) [a]	X						X								X				X
Body temperature assessment[a,c,h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Study drug administration	X	X	X	X	X	X	X	X	X	X	X	X	X	X					

Abbreviations: AE = adverse event; ALT = alanine transaminase; ALP = alkaline phosphatase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CBC = complete blood count; COVID-19 = coronavirus disease 2019; CRP = C-reactive protein; D = day; GGT = gamma-glutamyl transferase; ID = identification; LDH = lactate dehydrogenase; MCV = mean corpuscular volume; RBC = red blood cell; RT-PCR = reverse transcriptase – polymerase chain reaction; SAE = serious adverse event; SpO2 = peripheral capillary oxygen saturation; WBC = white blood cell.

[a] Denotes a baseline assessment. Baseline is defined as before the first dose of study drug. Baseline assessments should be performed before administration of study drug. Subjects are enrolled following completion of eligibility requirements and who are randomized in the IWR. Subjects who are screened to determine eligibility, but do not undergo any baseline assessments are not considered enrolled. All eligible subjects must have documented COVID-19 infection diagnosed at the local level.

[b] Study Day 1= first dose of study drug.

[c] Assessments to be done daily.

[d] X = clinic visit, ☎ = telephone visit. All post-baseline visits are ± 1 day in the event a visit occurs on a weekend.

[e] Subjects will be given access and instructions to complete their eDiary on Day 1 using the web portal. Subjects will complete their eDiary daily from Day 1 through Day 15, Data to be collected in the eDiary daily will include 1) the number of study medication doses taken/missed and 2) the highest temperature recorded over the past 24 hour period.

[f] All AEs must be recorded from the time of administration of the first dose of study drug until the subject has completed the end of study or early withdrawal. Any study procedure-related SAE that occurs after the study participant has signed the informed consent form and prior to administration of the first dose of study drug will be considered as Medical History. The study will collect only Treatment Emergent Adverse Events (TEAE).

[g] Laboratory assessments including hematology (CBC including hemoglobin, hematocrit, WBC with differential, RBC, MCV, and platelet count) and clinical chemistry (albumin, ALT, ALP, AST, BUN, GGT, creatinine, electrolytes [sodium, potassium, carbon dioxide, chloride], glucose, total bilirubin, direct bilirubin, LDH, CRP) will be collected. Laboratory tests will be performed at the central laboratory.

[h] Absence of fever is defined as ≤ 37.2°C oral.

[i] The indicated assessments may be done at the investigators discretion but are not required.

10.1 Study Visits

10.1.1 Screening/Baseline and Day 1 Visit

The following procedures and assessments will be done at the onsite Screening/Baseline and Day 1 visit:

- Verify subject has written notification from a local laboratory confirming COVID-19 infection within 72 hours of randomization (i.e., Day 1). In most instances, the Screening/Baseline visit will occur on the same date as Day 1. If needed, the Screening/Baseline may occur before Day 1 as long as randomization can be completed within the 72-hour window.
- Obtain informed consent
- Review of inclusion/exclusion criteria, including urine pregnancy test, if applicable
- Assign a subject ID number (ID number = XXX site number followed by 001, 002, 003 subject number)
- Obtain mid-turbinate nasal swab sample to be sent to the central laboratory to test for a baseline assessment and to test for viral shedding of COVID-19 by RT-PCR
- Draw blood for central laboratory testing
- Record demographics, medical history (including current COVID-19 symptoms), and concomitant medications
- Obtain vital signs (height, weight, heart rate, blood pressure, SpO2)
- Measure oral body temperature
- Perform randomization and dispensing of study drug
- Provide subject with instructions for accessing eDiary portal for collection of daily information
- Administer first dose of study drug after all assessments are completed
- Record of any TEAEs

10.1.2 Onsite Visits on Day 7, Day 15, Unscheduled Visit, Early Termination Visits / Telephone Visits on Day 21, Day 28

The following procedures and assessments will be done on Day 7, Day 15, Day 21, Day 28, and early termination by telephone or at onsite visits:

- Verify subject compliance for completing daily eDiary entrees by accessing the web portal for the subject's eDiary
- Review concomitant medications and record any TEAEs
- Assess vital signs (heart rate, blood pressure, SpO2) during on-site visits only
- Measure oral body temperature
- Draw blood for central laboratory testing (Day 15, Unscheduled Visit and Early Termination) during on-site visits only

- Obtain mid-turbinate nasal swab sample for viral shedding test (Day 7, Day 15, and Early Termination Visits) for central laboratory during on-site visits only

10.1.3 Daily Assessments and Procedures by Subject

The following procedures and assessments will be done daily by the subjects themselves:

- Complete the daily eDiary entries using the web portal
- Measure oral body temperature
- Administer study drug QID

10.2 Informed Consent

Before performing any study-related procedures, the investigator (or designee) will obtain informed consent from the subject.

10.3 Study Procedures

Assessments and their timing are to be performed as outlined in the Schedule of Assessments (Table 1). Section 12.3 specifies laboratory assessment samples to be obtained.

Assessments and procedures scheduled at a visit where study drug is administered should be performed before administration of study drug unless otherwise indicated in the Schedule of Assessments (Table 1).

Efficacy assessments are described in Section 11 and include recording of hospitalization or death for any cause (if not hospitalized), resolution of fever, overall survival rate, and viral shedding.

Safety assessments are described in Section 12 and include concomitant medications, vital signs, laboratory assessments, pregnancy test, and AEs.

The investigator may, at his/her discretion, arrange for a subject to have an unscheduled assessment, especially in the case of AEs that require follow-up or are considered by the investigator to be possibly related to the use of study drug. The unscheduled visit page on the eCRF must be completed.

Study discontinuation procedures are described in Section 8.5.

Follow-up of AEs and SAEs leading to study discontinuation is discussed in Section 8.5.

11 EFFICACY ASSESSMENTS

The Schedule of Assessments (Table 1) outlines the efficacy assessments to be performed throughout the study and their timing.

11.1 Subject eDiary

- Subjects will be provided access to an eDiary and completion instructions at the baseline visit (Day 1). Adequate time should be allocated on Day 1 to ensure that the subject understands how to access the eDiary portal to complete the daily eDiary and is willing and able to do so every day throughout the study. **NOTE**: The objectives and endpoints for this study relies on subject reported data collected via the eDiary. It is critical that the Investigator and subject understand that accurate, complete, and contemporaneous eDiary data is required to meet the study primary objective. It is particularly important to ensure that each subject completes the eDiary every day. The eDiary will have reminders for subjects to take the study drug and to complete the eDiary daily. The site will check the portal to be sure the subject is completing the eDiary daily. It is suggested that the sites should call the subject on Day 2 about eDiary completion if it is felt the subject will not remember.

Subjects will be asked to record the following details in their eDiary:

- Number of doses taken in the previous 24 hours
- Oral body temperature at the time of diary completion
- Highest oral temperature obtained in the last 24 hours (if additional temperatures were obtained the previous day that were not recorded in the diary the day before)

Information from the eDiary will be used directly for analysis of the secondary endpoints. The Investigator or designee will be required to monitor the subject's eDiary entries and contact the subject to discuss any omissions or inaccurate entries.

11.2 Hospitalization (Primary Efficacy Endpoint)

Hospitalization is defined as the subject's status changing from ambulatory care to COVID-19 related hospitalization or death due to any cause before Day 28. Presenting to the emergency room is considered hospitalization.

11.3 Resolution of Fever (Secondary Efficacy Endpoint)

Body temperature will be measured orally and recorded daily. Oral temperature will also be collected by study staff at an onsite study visit. Subjects will be given an oral temperature device and instructed in the proper use of the device at the Day 1 visit. Temperatures are to be recorded in the eDiary every day from Day 1 through Day 15.

11.4 Viral Shedding

Subjects will have mid-turbinate nasal samples taken using flocked swabs at onsite study visits according to Table 1. Investigators and study site staff will be trained on proper mid-turbinate nasal sample collection and handling of the swab after the sample has been collected. The proper handling of the swab after the nasal sample has been collected are described in the laboratory manual. The procedure for collecting mid-turbinate swabs is also located in Appendix 2. The same nostril should be used for sampling each time it is done, and the nostril (right or left)

should be recorded on the eCRF. Processing samples should be performed according to the central lab manual instructions.

Swab samples will be tested for COVID-19 virus using RT-PCR. Results will be reported as either yes or no for shedding the virus.

12 SAFETY ASSESSMENTS

Safety assessments (vital signs, AEs, SAEs, clinical laboratory results [routine hematology and biochemistry] are to be performed at protocol-specified visits, as specified in the Schedule of Assessments (Table 1).

12.1 Medical History

Medical history will be recorded at screening. Investigators should document the occurrence, signs, and symptoms of the subject's preexisting and currently ongoing conditions, including comorbid conditions, present at the time when informed consent is given and up to the time of first dosing (Day 1). Medical history will include alcohol consumption and smoking history, if applicable.

Illnesses first occurring or detected during the study and/or worsening of a concomitant illness during the study are to be documented as AEs on the eCRF in accordance with Section 12.4. All changes not present at baseline or described in the past medical history and identified as clinically noteworthy must be recorded as AEs.

Additionally, demographic data will be collected for all subjects and include age, sex, race, and ethnicity.

Prior and concomitant medications are to be recorded on the eCRF. Refer to Section 9.6.1 for details.

12.2 Vital Signs and Body Temperature – On-Site Visits

Vital signs (heart rate, systolic and diastolic blood pressure measurements, and SpO2) and body temperature will be evaluated at the visits indicated in the Schedule of Assessments (Table 1). All vital signs will be measured after the subject has been resting in a sitting position for at least 5 minutes. Blood pressure measurements are to be taken in the same arm for the duration of the study. Body weight (without shoes) and height (without shoes) will be recorded at screening only.

Vital sign measurements will be repeated if clinically significant or machine/equipment errors occur. Out-of-range blood pressure or heart rate measurements will be repeated at the investigator's discretion.

12.3 Laboratory Assessments

Laboratory assessment samples (Table 2) to be obtained at designated visits as detailed in the Schedule of Assessments (Table 1).

Table 2. Laboratory Assessments

Hematology	Serum Chemistry	Pregnancy Test
Complete blood count: Hct Hb MCV Platelet count RBC count WBC count with differential	Albumin ALT ALP AST GGT BUN Sodium Potassium Chloride Carbon dioxide Creatinine Glucose Total bilirubin Direct bilirubin LDH CRP	A urine HCG pregnancy test will be performed on all women of childbearing potential at screening

Abbreviations: ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CRP = C-reactive protein; GGT = gamma-glutamyl transferase; HCG = human chorionic gonadotropin; Hb = hemoglobin; Hct = hematocrit; LDH = lactate dehydrogenase; MCV = mean corpuscular volume; RBC = red blood cell; WBC = white blood cell.

Blood will be analyzed at a central laboratory. A urine sample for pregnancy testing should be obtained for testing at the site using the provided test kits. All laboratory reports must be reviewed, signed, and dated by the investigator. A legible copy of all reports must be filed with the subject's electronic source documents for that visit. Clinically significant abnormal values occurring during the study will be followed up until repeat test results return to normal, stabilize, or are no longer clinically significant.

12.4 Adverse Events

12.4.1 Adverse Events

An AE is any symptom, physical sign, syndrome, or disease that either emerges during the study or, if present at screening, worsens during the study, regardless of the suspected cause of the event. All medical and psychiatric conditions (except those related to the indication under study) present at screening will be documented in the medical history eCRF. Changes in these conditions and new symptoms, physical signs, syndromes, or diseases should be noted on the AE eCRF during the rest of the study.

Subjects will be instructed to report AEs at each study visit. All AEs are to be followed up until resolution or a stable clinical endpoint is reached.

Each AE is to be documented on the eCRF with reference to date of onset, duration, frequency, severity, relationship to study drug, action taken with study drug, treatment of event, and outcome. Furthermore, each AE is to be classified as being serious or nonserious. Changes in AEs and resolution dates are to be documented on the eCRF.

For the purposes of this study, the period of observation for collection of AEs extends from the time the subject is administered study medication (Day 1) until Day 28 or early termination. Subjects with early termination will be followed up until Day 28. Follow-up of the AE, even after the date of therapy discontinuation, is required if the AE persists until the event resolves or stabilizes at a level acceptable to the investigator.

When changes in the intensity of an AE occur more frequently than once a day, the maximum intensity for the event should be noted. If the intensity category changes over a number of days, then those changes should be recorded separately (with distinct onset dates).

Specific guidelines for classifying AEs by intensity and relationship to study drug are given in Table 3 and Table 4.

Table 3. Classification of Adverse Events by Intensity

MILD: An event that is easily tolerated by the subject, causing minimal discomfort and not interfering with everyday activities.
MODERATE: An event that is sufficiently discomforting to interfere with normal everyday activities.
SEVERE: An event that prevents normal everyday activities.

Table 4. Classification of Adverse Events by Relationship to Study Drug

UNRELATED: This category applies to those AEs that are clearly and incontrovertibly due to extraneous causes (disease, environment, etc.).
UNLIKELY: This category applies to those AEs that are judged to be unrelated to the study drug but for which no extraneous cause may be found. An AE may be considered unlikely to be related to study drug if or when it meets 2 of the following criteria: (1) it does not follow a reasonable temporal sequence from administration of the study drug; (2) it could readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it does not follow a known pattern of response to the study drug; or (4) it does not reappear or worsen when the drug is readministered.
POSSIBLY: This category applies to those AEs for which a connection with the study drug administration appears unlikely but cannot be ruled out with certainty. An AE may be considered possibly related if or when it meets 2 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not readily have been produced by the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; or (3) it follows a known pattern of response to the study drug.
PROBABLY: This category applies to those AEs that the investigator feels with a high degree of certainty are related to the study drug. An AE may be considered probably related if or when it meets 3 of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose (note that there are exceptions when an AE does not disappear upon discontinuation of the drug, yet drug-relatedness clearly exists; for example, as in bone marrow depression, fixed drug eruptions, or tardive dyskinesia); or (4) it follows a known pattern of response to the study drug.
DEFINITELY: This category applies to those AEs that the investigator feels are incontrovertibly related to study drug. An AE may be assigned an attribution of definitely related if or when it meets all of the following criteria: (1) it follows a reasonable temporal sequence from administration of the drug; (2) it could not be reasonably explained by the known characteristics of the subject's clinical state, environmental or toxic factors, or other modes of therapy administered to the subject; (3) it disappears or decreases on cessation or reduction in dose and recurs with reexposure to drug (if rechallenge occurs); and (4) it follows a known pattern of response to the study drug.

Abbreviation: AE = adverse event.

12.4.2 **Serious Adverse Events**

In general for any clinical trial an SAE is any untoward medical occurrence, in the view of either the investigator or Sponsor, that:

- results in death,
- is life-threatening,
- results in inpatient hospitalization or prolongation of existing hospitalization,
- results in persistent or significant disability/incapacity, and/or
- is a congenital anomaly/birth defect

For the purposes of this study, death and inpatient hospitalization will not be considered as an SAE, as the primary end point of this study is the proportion of subjects requiring COVID-19 related hospitalization (including emergency room visit) or who die due to any cause within 28 days of randomization

Other important non-COVID-19 medical events that may not be immediately life-threatening or result in death or hospitalization, based upon appropriate medical judgment, are considered SAEs if they are thought to jeopardize the subject and/or require medical or surgical intervention to prevent one of the outcomes defining an SAE. SAEs are critically important for the identification of significant safety problems; therefore, it is important to take into account both the investigator's and the Sponsor's assessment. If either the Sponsor or the investigator believes that an event is serious, the event must be considered serious and evaluated by the Sponsor for expedited reporting.

12.4.3 **Serious Adverse Event Reporting**

An SAE occurring from the first dose administered until Day 28 must be reported to EVERSANA Pharmacovigilance and will be communicated to the Sponsor. Any such SAE due to any cause, whether or not related to the study drug, must be reported within 24 hours of occurrence or when the investigator becomes aware of the event. Notification can be made using the dedicated fax line or email for the EVERSANA Pharmacovigilance group:

EVERSANA Pharmacovigilance fax number: 1-510-295-6449

EVERSANA Pharmacovigilance email address: sagentPV@eversana.com

If the investigator contacts the EVERSANA Pharmacovigilance group by telephone, then a written report must follow within 24 hours and is to include a full description of the event and sequelae in the format detailed in the SAE reporting form.

EVERSANA Pharmacovigilance telephone number: 1-510-595-8289

The event must also be recorded on the standard AE eCRF. Preliminary reports of SAEs must be followed up by detailed descriptions later on, including clear and anonymized photocopies of hospital case reports, consultant reports, autopsy reports, and other documents when requested and applicable. SAE reports must be made whether or not the investigator considers the event to be related to the investigational drug.

Appropriate remedial measures should be taken to treat the SAE, and the response should be recorded. Clinical, laboratory, and diagnostic measures should be employed as needed in order to determine the etiology of the problem. The investigator must report all additional follow-up evaluations to the EVERSANA Pharmacovigilance group within 24 hours of becoming aware of the additional information or as soon as is practicable. All SAEs will be followed up until the investigator and Sponsor agree the event is satisfactorily resolved.

Any SAE that is not resolved by the end of the study or upon discontinuation of the subject's participation in the study is to be followed up until it either resolves, stabilizes, returns to baseline values (if a baseline value is available), or is shown to not be attributable to the study drug or procedures.

12.4.4 **Suspected Unexpected Serious Adverse Reactions**

Adverse events that meet all of the following criteria will be classified as suspected unexpected serious adverse reactions (SUSARs) and reported to the appropriate regulatory authorities in accordance with applicable regulatory requirements for expedited reporting:

- serious
- unexpected (i.e., the event is not consistent with the safety information in the IB)
- there is at least a reasonable possibility that there is a causal relationship between the event and the study treatment

The investigator will assess whether an event is causally related to study treatment. The Sponsor (or EVERSANA) will consider the investigator's assessment and determine whether the event meets the criteria for being reportable as a 7-day or 15-day safety report. SUSARs that are life-threatening must be reported to the regulatory authorities and the institutional review board (IRBs; where required) within 7 days after the Sponsor (or EVERSANA) has first knowledge of them, with a follow-up report submitted within a further 8 calendar days. Other SUSARs must be reported to the relevant regulatory authorities and the IRBs within 15 calendar days after the Sponsor (or EVERSANA) first has knowledge of them.

The Sponsor (or EVERSANA) is responsible for reporting SUSARs and any other events required to be reported in an expedited manner to the regulatory authorities and for informing investigators of reportable events, in compliance with applicable regulatory requirements within specific timeframes. Investigators will notify the relevant IRBs of reportable events within the applicable timeframes.

12.4.5 **Pregnancy**

WOCBP must have a negative urine pregnancy test at screening. Following administration of study drug, any known cases of pregnancy in female subjects will be reported until the subject completes or withdraws from the study. The pregnancy will be reported immediately by faxing/emailing a completed pregnancy report to the Sponsor (or EVERSANA) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the investigator will follow up with the subject until completion of the pregnancy and must assess the outcome in the shortest possible time but not more than 30 days after completion of the pregnancy. The investigator should notify the Sponsor (or EVERSANA) of the pregnancy outcome by submitting a follow-up pregnancy report. If the outcome of the pregnancy involved spontaneous or therapeutic abortion (any congenital anomaly detected in an aborted fetus is to be documented), stillbirth, neonatal death, or congenital anomaly, the investigator will report the event by faxing/emailing a completed pregnancy report form to the Sponsor (or EVERSANA) within 24 hours of knowledge of the event.

If the investigator becomes aware of a pregnancy occurring in the partner of a subject participating in the study, the pregnancy should be reported to the Sponsor (or EVERSANA)

within 24 hours of knowledge of the event. Information regarding the pregnancy must only be submitted after obtaining written consent from the pregnant partner. The investigator will arrange counseling for the pregnant partner by a specialist to discuss the risks of continuing with the pregnancy and the possible effects on the fetus.

Upon discontinuation from the study, only those procedures that would not expose the subject to undue risk will be performed. The investigator should also be notified of pregnancy occurring during the study but confirmed after completion of the study. In the event that a subject is subsequently found to be pregnant after inclusion in the study, any pregnancy will be followed to term, and the status of mother and child will be reported to the Sponsor after delivery.

13 STATISTICAL ANALYSIS

A statistical analysis plan (SAP) will be prepared after the protocol is approved and subsequently submitted to the Investigational New Drug application before completion of the study. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. The SAP will serve as a companion document to the protocol and supersedes it in case of differences.

The statistical evaluation will be performed using SAS® software version 9.4 or higher (SAS Institute, Cary, NC). All data will be listed, and summary tables will be provided. Summary statistics will be presented by treatment group. For continuous variables, data will be summarized with the number of subjects (N), mean, standard deviation, median, minimum, and maximum by treatment group. For categorical variables, data will be tabulated with the number and proportion of subjects for each category by treatment group.

In general, all efficacy endpoints and major safety endpoints will be summarized using descriptive statistics (e.g., proportions for categorical data, means and standard deviations for continuous data, median for time-to-event data). The primary and key secondary efficacy endpoints will be analyzed using appropriate statistical models.

A statistical analysis plan (SAP) will further describe the statistical analyses prior to unblinding of study and database lock. Missing data procedures will be described in the SAP.

13.1 Determination of Sample Size

Assuming that the proportions of outpatients who are hospitalized for COVID-19 related disease or die due to any reason within 28 days of randomization are 30% and 15% for placebo and camostat mesilate groups, respectively, based on the two-sided Fisher's Exact Test, at the target significance level of 5%, 275 outpatients (183 in camostat mesilate group and 92 in placebo group) are needed to achieve 80% power. Thus, approximately 300 outpatients (200 in the camostat mesilate group and 100 in the placebo group) will be randomized to account for subject drop-out.

13.2 Analysis Populations

Intent-to-Treat Population (ITT)

The Intent-to-Treat (ITT) population will include all subjects who are randomized. Subjects will be analyzed according to their study treatment assignment, not according to the treatment actually received. The ITT population will be used for evaluating primary and secondary efficacy endpoints and subject characteristics.

Per-Protocol Population (PP)

The Per-Protocol (PP) population will include all subjects in the ITT population who complete the 28-day study and have no major protocol deviations. The PP population will be used for primary and secondary efficacy endpoints.

Safety Population

The Safety population will consist of subjects who receive at least 1 dose of study medication (camostat mesilate or placebo). The Safety population will be used for all summaries of safety and tolerability data.

13.3 Efficacy Analysis

13.3.1 Analysis of Primary Efficacy Endpoint

The primary endpoint (the proportion of subjects requiring COVID-19 related hospitalization or who died due to any cause within 28 days of randomization) will be analyzed using the Fisher exact test in ITT and PP populations. The primary endpoint will also be analyzed using the Mantel-Haenszel (MH) test, and the 95% Clopper-Pearson confidence interval (CI) will be reported. In addition, the continuity-corrected Newcombe CI for the proportional difference between treatment groups will be reported. The logistic regression model with treatment group, sex, race, duration of symptoms prior to enrollment, age groups (< 65 versus ≥ 65 years) and other risk factors as covariates may be used to investigate the potential influences of demographic and baseline characteristics. The odds ratios and their 95% CIs will be estimated.

A sensitivity analysis for the primary efficacy endpoint will be performed for central laboratory confirmed COVID-19 subjects in the ITT population.

13.3.2 Analysis of Secondary Efficacy Endpoints

Secondary analysis include:

- The overall survival rate (the proportion of randomized subjects who survive up to Day 15 and Day 28)
- Time to resolution of fever from randomization up to Day 28
- Time to hospitalization or death following randomization up to Day 28

- Proportion of subjects with no viral shedding (yes/no) using RT-PCR at Day 7 and Day 15

The overall survival rate up to Day 15 and Day 28 will be analyzed in ITT and PP populations similar to the primary analysis.

Similar methods, as per the primary endpoint, will be used to analyze the proportion of subjects with no viral shedding at Day 7 and Day 15. Time to resolution of fever from randomization up to Day 28 and time to hospitalization or death will be summarized with Kaplan-Meier curves. A log-rank test will be used to analyze those time-to-event endpoints. The median event time and their corresponding 2-sided 95% CIs will be provided for each treatment arm. The Cox proportional hazard model with treatment group, sex, race, duration of symptoms prior to enrollment, age groups (< 65 versus ≥ 65 years) and other risk factors as covariates may be used to investigate the potential influences of demographic and baseline characteristics. The hazard ratios and their 95% CIs will be estimated. Additionally, the change from baseline in clinical symptoms and viral shedding will be summarized using shift tables.

A sensitivity analysis for the secondary efficacy endpoints will also be performed for central laboratory confirmed COVID-19 subjects in the ITT population.

13.4 Safety Analysis

All reported AEs will be coded using the latest version of the Medical Dictionary for Regulatory Activities (MedDRA). The incidence of TEAEs will be included in incidence tables. Events with missing onset dates will be included as treatment-emergent. If a subject experiences more than 1 occurrence of the same AE, the occurrence with the greatest severity and the closest association with the study drug will be used in the summary tables. SAEs, grade 3 or 4 TEAEs, and TEAEs causing discontinuation will be summarized using discrete summaries by system organ class and preferred term for each treatment group. All AEs will be listed by subject, along with information regarding onset, duration, relationship and severity to study drug, action taken with study drug, treatment of event, and outcome. TEAEs will be summarized by severity and relationship separately.

Clinical laboratory data and vital signs will be summarized using descriptive statistics, including mean values and mean change from baseline values, as well as numbers of subjects with values outside limits of the normal range at each time point.

Summary tables will be provided for concomitant medications initiated during the study period.

13.5 Interim Analysis

No interim analysis is planned.

14 STUDY MANAGEMENT

14.1 Approval and Consent

14.1.1 Regulatory Guidelines

This study will be conducted in accordance with the accepted version of the Declaration of Helsinki and all relevant regulations as set forth in Parts 50, 56, 312, Subpart D, of Title 21 of the United States Code of Federal Regulations (CFR), in compliance with International Council for Harmonisation (ICH) and GCP guidelines and according to the appropriate regulatory requirements in the countries where the study was conducted.

14.1.2 Institutional Review Board

Conduct of the study must be approved by an appropriately constituted IRB. Approval is required for the study protocol, protocol amendments (if applicable), IB, ICFs, recruitment material and subject information sheets, and other subject-facing material.

14.1.3 Informed Consent

For each study subject, electronic informed consent will be obtained before any protocol-related activities. As part of this procedure, the principal investigator (PI) or designee must explain orally the nature of the study, its purpose, procedures, expected duration, alternative therapy available, and the benefits and risks involved in study participation and this should be documented in the medical record. The subject should be informed that he/she may withdraw from the study at any time, and the subject will receive all information that is required by local regulations and guidelines for ICH. The PI will provide the subject with a copy of the fully executed ICF. The investigator will provide the Sponsor or its representative with a copy of the IRB-approved ICF before the start of the study.

14.2 Data Handling

Any data to be recorded directly on the eCRFs (to be considered as source data) will be identified at the start of the study. Data reported on the eCRF that are derived from source documents should be consistent with the source documents, or the discrepancies must be explained (See also Section 14.3).

Clinical data will be entered by site personnel on eCRFs for transmission to the Sponsor. Data on eCRFs transmitted via the web-based data system must correspond to and be supported by source documentation maintained at the study site, unless the study site makes direct data entry to the databases for which no other original or source documentation is maintained. In such cases, the study site should document which eCRFs are subject to direct data entry and should have in place procedures to obtain and retain copies of the information submitted by direct data entry. All study forms and records transmitted to the Sponsor must only include coded identifiers such that directly identifying personal information is not transmitted. The primary method of data

transmittal is via the secure, internet-based EDC. Access to the EDC system is available to only authorized users via the study's internet website, where a user unique assigned username and password are required for access.

Any changes made to data after collection will be made through the use of data clarification forms or the EDC system. Electronic CRFs will be considered complete when all missing and/or incorrect data have been resolved.

14.3 Source Documents

Source documents are considered to be all information in electronic copies of records of clinical findings, observations, data, or other activities in a clinical study necessary for the reconstruction and evaluation of the study. The investigator will provide direct access to electronic data in the facilitation of trial-related monitoring, audits, review by IRBs, and regulatory inspections.

The investigator/institution should maintain adequate and accurate electronic source documents and trial records that include all pertinent observations on each of the site's trial subjects. Electronic source data should be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data should be traceable, not obscure the original entry, and be explained if necessary.

14.4 Record Retention

Electronic study records and source documents must be preserved for at least 15 years after the completion or discontinuation of/withdrawal from the study, at least 2 years after the drug being studied has received its last approval for sale, or at least 2 years after the drug development has stopped, and in accordance with the applicable local privacy laws, whichever is the longer time period.

The investigator agrees to comply with all applicable federal, state, and local laws and regulations relating to the privacy of subject health information, including, but not limited to, the Standards for Individually Identifiable Health Information, 45 CFR, Parts 160 and 164 (the Health Insurance Portability Accountability Act of 1996 [HIPAA] Privacy Regulation). The investigator shall ensure that study subjects authorize the use and disclosure of protected health information in accordance with HIPAA Privacy Regulation and in a form satisfactory to the Sponsor.

14.5 Monitoring

The study will be monitored according to the clinical monitoring plan to ensure that it is conducted and documented properly according to the protocol, GCP, and all applicable regulatory requirements.

Remote Monitoring visits and telephone contacts will be made at appropriate times during the study. The PI will assure he/she and adequate site personnel are available throughout the study to collaborate with clinical monitors. Clinical monitors must have direct access to electronic source

documentation in order to check the completeness, clarity, and consistency of the data recorded on the eCRFs for each subject.

The investigator will make available to the clinical monitor all electronic source documents and medical records necessary to review protocol adherence and eCRFs. In addition, the investigator will work closely with the clinical monitor and, as needed, provide them appropriate evidence that the study is being conducted in accordance with the protocol, applicable regulations, and GCP guidelines.

14.6 Quality Control and Quality Assurance

The Sponsor or its designee will perform the quality assurance and quality control activities of this study; however, responsibility for the accuracy, completeness, security, and reliability of the study data presented to the Sponsor lies with the investigator generating the data.

The Sponsor may arrange audits as part of the implementation of quality assurance to ensure that the study is being conducted in compliance with the protocol, standard operating procedures, GCP, and all applicable regulatory requirements. Audits will be independent of and separate from the routine monitoring and quality control functions. Quality assurance procedures will be performed remotely and during data management to assure that safety and efficacy data are adequate and well documented.

14.7 Protocol Amendment and Protocol Deviation

14.7.1 Protocol Amendment

Amendments to the protocol that entail corrections of typographical errors, clarifications of confusing wording, changes in study personnel, and minor modifications that have no effect on the safety of subjects or the conduct of the study will be classed as administrative amendments and will be submitted to the IRB for information only. The Sponsor will ensure that acknowledgement is received and filed electronically. Amendments that are classed as substantial amendments must be submitted to the appropriate regulatory authorities and the IRBs for approval and will not be implemented at sites until such approvals are received other than in the case of an urgent safety measure.

14.7.2 Protocol Deviations

Should a protocol deviation occur, the Sponsor must be informed as soon as possible. Protocol deviations and/or violations and the reasons they occurred will be included in the clinical study report. Reporting of protocol deviations to the IRB and in accordance with applicable regulatory authority mandates is an investigator responsibility.

14.8 Ethical Considerations

This study will be conducted in accordance with this protocol, the accepted version of the Declaration of Helsinki and/or all relevant federal regulations, as set forth in Parts 50, 56, 312,

Subpart D, of Title 21 of the CFR; EU 536/2014, Annex 1, D, 17 (a); and in compliance with GCP guidelines.

IRBs will review and approve this protocol and the ICF. All subjects are required to give electronic informed consent before participation in the study.

14.9 Financing and Insurance

Before the study commences, the Sponsor (or its designee) and the investigator (or the institution, as applicable) will agree on costs necessary to perform the study. This agreement will be documented in a financial agreement that will be signed by the investigator (or the institution signatory) and the Sponsor (or its designee).

The investigator is required to have adequate current insurance to cover claims for negligence and/or malpractice. The Sponsor will provide no-exclusion insurance coverage for the clinical study as required by national regulations.

14.10 Publication Policy/Disclosure of Data

Both the use of data and the publication policy are detailed within the clinical study agreement. Intellectual property rights (and related matters) generated by the investigator and others performing the clinical study will be subject to the terms of a clinical study agreement that will be agreed between the institution and the Sponsor or their designee. With respect to such rights, the Sponsor or its designee will solely own all rights and interests in any materials, data, and intellectual property rights developed by investigators and others performing the clinical study described in this protocol, subject to the terms of any such agreement. In order to facilitate such ownership, investigators will be required to assign all such inventions either to their institution or directly to the Sponsor or its designee, as will be set forth in the clinical study agreement.

15 REFERENCES

Abe M, Hara Y, Kuwano K et al. Use of FOY-305 for the treatment of pain attacks associated with chronic pancreatitis. New Horizons for Medicine (1980); 12 (Extra Edition) 233.

Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19-preliminary report. N Engl J Med. May 22, 2020. Online ahead of print. https://pubmed.ncbi.nlm.nih.gov/32445440/. Assessed 15 June 2020.

Cascella M, Rajnik M, Cuomo A, Dulebohn SC, Di Napoli R. Features, Evaluation and Treatment Coronavirus (COVID-19). https[KC1]://www.ncbi.nlm.nih.gov/books/NBK554776. Accessed 13April 2020.

Centers for Disease Control and Prevention (CDC). Interim guidelines for collecting, handling, and testing clinical specimens for COVID-19. 22 May 2020. https://www.cdc.gov/coronavirus/2019-ncov/lab/guidelines-clinical-specimens.html. Assessed 04 June 2020.

Foipan® package insert. Oral protease inhibitor FOIPAN Tablets 100 mg <Camostat mesilate tables>. Revised August 2009. http://www.shijiebiaopin.net/upload/product/201272318373223.PDF. Accessed 28 April 2020.

Fujiwara 5, Iwamoto K, Miyazaki A. Clinical experience with oral FOY-305 for pancreatitis. New Horizons for Medicine (1980); 12 (Extra Edition) 104.

Gandhi RT, Lynch JB, del Rio C. Mild or moderate Covid-19. New England Journal of Medicine. April 2020. https://www.nejm.org/doi/pdf/10.1056/NEJMcp2009249. Accessed 12 June 2020.

Hayawaka T, Noda T, Kondo T et al. Effect of oral administration of FOY-305 on pancreatitis. New Horizons for Medicine (1980); 12 (Extra Edition) 236.

[HMA] Heads of Medicines Agencies. Clinical Trial Facilitation Group page. Recommendations related to contraception and pregnancy testing in clinical trials. http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2014_09_HMA_CTFG_Contraception.pdf. September 15, 2014. Accessed 27 May 2020.

Hirayama A, Izumiyama S, Itagaki Y et al. Clinical investigation of FOY-305 against pancreatitis. New Horizons for Medicine (1980a); 12 (Extra Edition) 245.

Hirayama A, Izumiyama S, Itagaki Y et al. Clinical analysis of FOY-305 for pancreatitis - A Small Double-blind Clinical Trial. New Horizons for Medicine (1980b); 12 (Extra Edition) 253.

Hirono T. Clinical Experience with oral anti-enzyme agent FOY-305 for pancreatitis. New Horizons for Medicine (1980); 12 (Extra Edition) 215.

Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell. 2020;181:1-10.

Horiguchi Y, Nakajima S, Ito M. Clinical experience with FOY-305 for pancreatitis. New Horizons for Medicine (1980); 12 (Extra Edition) 227.

Ishii K, et al. Evaluation of the efficacy of FOY-305 in pancreatitis: multicenter, double-blind study. New Horiz Med. 1980;12:261.

Kinami Y, Takita Y, Shinmura K et al. Clinical effect of FOY-305 on pancreatitis. New Horizons for Medicine (1980); 12 (Extra Edition) 108.

Kubota Y, Meada S. Experience with FOY-305 in patients with pancreatitis. New Horizons for Medicine (1980); 12 (Extra Edition) 211.

Ramsey ML, Nuttall J, Hart PA, TACTIC Investigative Team. A phase 1/2 trial to evaluate the pharmacokinetics, safety, and efficacy of NI-03 in patients with chronic pancreatitis: study protocol for a randomized controlled trial on the assessment of camostat treatment in chronic pancreatitis (TACTIC). Trials. 2019;20(1):501.

Sagent Pharmaceuticals, Inc. Investigator Brochure Camostat mesilate Edition 1. Schaumburg, IL. 11 June 2020.

Tanaka N, Tsuchiya R. Clinical efficacy of FOY-305 in pancreatitis. New Horizons for Medicine (1980); 12 (Extra Edition) 223.

World Health Organization. https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus/en/Accessed 13-APR-2020.

Wu C, Chen X, Cai, Y. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020; Published online March 13, 2020. doi:10.1001/jamainternmed.2020.0994.

16 APPENDICES

APPENDIX 1 describes the contraception guidelines applicable for this study.

APPENDIX 2 describes the proper collection method for mid-turbinate swab samples.

16.1 APPENDIX 1 - CONTRACEPTION GUIDELINES

Women of childbearing potential (WOCBP) and men whose sexual partners are WOCBP must use at least 1 highly effective method of contraception during the study and for 90 days after the last dose of study treatment.

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

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

Highly effective methods of contraception are those which have a failure rate of <1% (when implemented consistently and correctly) and include:

- combined (containing estrogen and progestogen) hormonal contraception associated with inhibition of ovulation (administration may be oral, intravaginal, or transdermal)
- progestogen-only hormonal contraception associated with inhibition of ovulation (administration may be oral, injectable, or implantable)
- intrauterine device
- intrauterine hormone-releasing system
- bilateral tubal ligation or occlusion
- vasectomy (provided that the male has a medical assessment of surgical success)
- sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk in relation to the duration of the clinical trial, in line with the preferred and usual lifestyle of the subject)

All subjects will be strongly advised that they (or the female partners of male subjects) should not become pregnant while on study treatment or for the above-specified period after the last dose. A female subject will be advised that she must report immediately to the study site for pregnancy testing and appropriate management in the event that she may be pregnant.

(HMA, 2014)

16.2 APPENDIX 2 – GUIDELINES FOR NASAL TURBINATE SWAB COLLECTION PROCEDURE

General Guidelines

Proper collection of specimens is the most important step in the laboratory diagnosis of infectious diseases. A specimen that is not collected correctly may lead to false negative test results. The following specimen collection guidelines follow standard recommended procedures. These instructions are provided by the Centers for Disease Control and Prevention (CDC, 2020**)**

A nasal mid-turbinate swab is to be collected by a healthcare provider using a flocked tapered swab. Use only synthetic fiber swabs with plastic or wire shafts. Do not use calcium alginate swabs or swabs with wooden shafts, as they may contain substances that inactivate some viruses and inhibit PCR testing.

Collecting and Handling Specimens Safely

For providers collecting specimens or within 6 feet of subjects suspected or known to be infected with SARS-CoV-2, maintain proper infection control and use recommended personal protective equipment (PPE), which includes an N95 or higher-level respirator (or facemask if a respirator is not available), eye protection, gloves, and a gown, when collecting specimens.

For providers who are handling specimens, but are not directly involved in collection (e.g., self-collection) and not working within 6 feet of the subject, follow standard precautions; gloves are recommended. Healthcare personnel are recommended to wear a form of source control (facemask or cloth face covering) at all times while in the healthcare facility.

Collecting Mid-turbinate Swab Specimens

Use a flocked tapered swab, and grasp only the distal end of the swab handle using gloved hands. Tilt subject's head back 70 degrees. While gently rotating the swab, insert swab less than one inch (about 2 cm) into nostril until resistance is met at turbinates. Rotate the swab several times against nasal wall. In the subject eCRF, record the subject's nostril used for sampling. Use the same nostril throughout the study each time a swab specimen is collected.

Storage

Swabs should be placed immediately into a sterile transport tube containing 2 to 3 mL of either viral transport medium (VTM), Amies transport medium, or sterile saline, unless using a test designed to analyze a specimen directly, (i.e., without placement in VTM), such as some point-of-care tests.

Label the specimen appropriately, including the subject ID, study number, specimen type (nasal mid-turbinate swab sample), and date and time of collection.

Refer to the central laboratory manual for further processing of swab samples.