TITLE PAGE

Protocol

A Double-blind, Placebo-controlled, Phase 2a Proof-of-concept Trial of Dalcetrapib in Patients with Confirmed Mild to Moderate COVID-19

Protocol Status: Final
Protocol Date: 14 December 2020
Protocol Version: 1.1

Investigational Product: Dalcetrapib

Protocol Reference Number: DAL-401
IND Number: 152693

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SYNOPSIS

Title of study:

A Double-blind, Placebo-controlled, Phase 2a Proof-of-concept Trial of Dalcetrapib in Patients with Confirmed Mild to Moderate COVID-19

Indication: Coronavirus disease of 2019 (COVID-19)

Number of Investigators and study centers:

Up to 60 sites in the United States and Canada, site distribution will depend on the pandemic status.

Development Phase: 2a

Objectives:

The primary efficacy objective of the study is:

- To evaluate the time to sustained clinical resolution of symptoms in patients with confirmed, mild to moderate, symptomatic COVID-19 treated with dalcetrapib.

  Sustained clinical resolution is defined as occurring when no key COVID-19 related symptom has a score higher than 1 over a 72-hour period (as documented using an electronic patient-reported outcome [ePRO] instrument), except for sense of smell and taste (items 13 and 14) where the score should be 0 over a 72-hour period. The time to resolution will be taken as the time from randomization until the first day of the last 72-hour period where the patient meets the definition of resolution within 28 days. Patients who do not meet the definition of resolution 28 days after randomization will be considered not resolved.

The secondary efficacy objectives of the study are:

- To evaluate the change from baseline in COVID-19 symptom severity score at all collected time points
- To evaluate time to complete clinical resolution, defined in the same way as the primary endpoint, but considering that all symptoms must resolve to a score of 0 for 72 hours
- To evaluate the time to viral clearance using SARS-CoV-2 polymerase chain reaction (PCR)
- To evaluate change from baseline in log10 viral load
- To evaluate the World Health Organization (WHO) clinical outcome scale (9-point scale) at Day 3, Day 5, Day 10, and Day 28
- Rate of hospitalization through Day 28
- To evaluate the rate of progression to oxygen therapy through Day 28
- To evaluate the duration of hospitalization
- To evaluate the mortality rate by Day 28

The safety objective of the study is:

- To assess the safety and tolerability of dalcetrapib active doses compared to placebo in patients with COVID-19

The pharmacokinetics (PK) objective of the study is:

- To evaluate the PK of dalcetrapib in patients with COVID-19

Methodology/study design:

This is a randomized, double-blind, multicenter Phase 2a proof-of-concept study in outpatients with confirmed, mild to moderate, symptomatic COVID-19. Electronic informed consent must be obtained from all patients or their legally authorized representative during screening before any study-related procedures are performed. The Screening/Baseline assessments may be performed at the study site or as a home visit.

A total of 208 patients will be randomized to receive 900, 1800, or 3600 mg of dalcetrapib or placebo once daily (52 patients to each of 900 mg, 1800 mg, 3600 mg and placebo) for 10 days. Patients will be randomized and receive first dose of study drug within 72 hours of receiving a positive PCR or Point-of-care test for SARS-CoV-2. Patients need to have at least two of the 14 common COVID-19-related symptoms described in the inclusion criteria rated as mild or moderate, as evaluated by ePRO assessment. Symptoms will be assessed at each study visit daily for the first 10 days, then at Day 14 and Day 28, and as clinically indicated. Symptoms will be evaluated as absent, mild, moderate, or severe depending on their impact on activities of daily living. SARS-CoV-2 viral loads will be obtained by both saliva (Oragene) collection and mid-turbinate nasal swab self-collection under supervision of a healthcare professional (virtual or home visit) at Screening/Baseline, Day 1, Day 3, Day 5, Day 7, Day 10, and Day 28. Patients who require hospitalization after initiation of study treatment will be followed for safety assessment through Day 28.

The study will be overseen by an independent Data Monitoring Committee (DMC). The DMC will review the safety data throughout the study. The DMC and Sponsor will review efficacy data at the interim analysis and at the end of the study. A DMC Charter, which includes detailed processes, will be prepared. One interim analysis will be conducted once 97 resolution events have been observed.

All patients will be closely monitored for adverse events (AEs) from informed consent for at least 18 days after the final dose of study treatment (until Day 28±2). Patients who withdraw early from the study will have follow-up phone calls to collect safety data until End of Study on Day 28±2. On days of laboratory assessments and PK sample collection, outpatient subjects may have a home visit.

Study Visit Procedures

Study visits (virtual, study site or home visits by a healthcare professional) will take place on Days 1, 3, 5, 7, 10, 14, and 28. Screening/Baseline assessments may all be performed on the same calendar day and may be performed at the study site or as a home visit. For visits which include bloodwork, sample collection may be done by a visiting healthcare professional or at the study site (as long as the patient has no worsening of respiratory symptoms or no fever within 24 hours). Other visits may be conducted remotely using telemedicine.
The samples for viral load testing will be both saliva (Oragene) collection and mid-turbinate nasal swab self-collected under supervision of a healthcare professional. Telemedicine visits such as phone calls or other digital media are to be utilized as much as possible.

Number of patients:

It is anticipated that 208 patients will be randomized into the study in a 1:1:1:1 ratio to 900, 1800, or 3600 mg dalcetrapib or placebo.

Determination of Sample Size:

The purpose of the proof-of-concept study is to identify whether there is sufficient promise of efficacy to justify conducting a Phase 3 study in a larger sample size and to determine efficacious dose to be used in Phase 3. While the entirety of data will be considered at the end of study, the sample size has been chosen to ensure that a positive trend will be present with alpha of 0.2 when considering the two highest doses combined compared to placebo. One-hundred twenty-seven (127) resolution events provides 80% power to demonstrate a positive trend if the average hazard ratio (HR) of the two dalcetrapib groups is 1.4 relative to placebo. Allowing for 20% of patients not resolving, 156 patients (52 per treatment arm) will be enrolled across the two highest dose levels and placebo arms, and an additional 52 will be randomized to 900 mg for a total sample size of 208 patients. One interim analysis will be conducted once 97 resolution events have occurred to allow 73 resolution events to have occurred in the two highest dose levels and placebo arm. At the interim analysis, if the average HR of the two highest dose levels relative to placebo is greater than 1.45, the study will stop due to efficacy and the program will be able to proceed directly to Phase 3. At the interim analysis, if the average HR of the two highest dose levels relative to placebo is between 1.0 and 1.45, the study will continue enrollment until 169 resolution events have occurred. At the interim analysis, if the average HR of the two highest dose levels is less than 1.0, the study will be stopped for lack of efficacy. The final analysis will be performed at an alpha of 0.186. These boundaries were determined by setting the efficacy boundary to follow the power family boundary with $\rho=2$ and the futility boundary is manually set to HR=1.

Diagnosis and criteria for inclusion and exclusion:

The following are the inclusion criteria:

1. Willing and able to provide informed consent
2. Male or female patients > 18 years of age on the day of informed consent
3. Have received a confirmed diagnosis of COVID-19 (positive for SARS-CoV-2), as assessed by PCR or point-of-care within 72 hours of first dose on Day 1
4. Have mild to moderate signs or symptoms of COVID-19 with onset within 5 days of first dose on Day 1, at least two of the following symptoms:
    - stuffy or runny nose
    - sore throat
    - shortness of breath
    - cough
    - fatigue
    - myalgia
    - headache
    - chills or shivering
    - feeling hot or feverish
    - nausea
    - vomiting
    - diarrhea
    - anosmia
    - ageusia

5. Outpatient with COVID-19 disease (not requiring oxygen therapy [WHO COVID-19 Clinical Improvement Ordinal Scale, score of 3])
6. Patient is aware of the investigational nature of this study and willing to comply with protocol treatments, blood tests, and other evaluations listed in the ICF.

The following are the exclusion criteria:

1. Females who are pregnant (negative pregnancy test required for all women of child-bearing potential at Screening) or breast-feeding
2. Male patients and women of childbearing potential (women who are not surgically sterile or postmenopausal defined as amenorrhea for >12 months) who are not using at least one protocol-specified method of contraception
3. Severe COVID-19 disease as defined by the WHO COVID-19 Clinical Improvement Ordinal Scale, scores of 5 (non-invasive ventilation or high-flow oxygen), 6 (intubation and mechanical ventilation), or 7 (ventilation + additional organ support pressors, renal replacement therapy [RRT], extracorporeal membrane oxygenation [ECMO])
4. Expected survival less than 72 hours
5. Peripheral capillary oxygen saturation (SpO2) <90% while breathing room air
6. Treatment with other drugs thought to possibly have activity against SARS-CoV-2 infection like remdesivir, favipiravir, within 7 days prior to enrollment or concurrently
7. History of abuse of drugs or alcohol that could interfere with adherence to study requirements as judged by the Investigator
8. Use of any other concurrent investigational drugs while participating in the present study
9. Patient requires frequent or prolonged use of systemic corticosteroids (≥20 mg of prednisone/day or equivalent for >4 weeks) or other immunosuppressive drugs (e.g., for organ transplantation or autoimmune conditions)
10. Known renal disease with an estimated glomerular filtration rate (eGFR) <50 mL/min based on local laboratory results
11. Patients with clinically apparent liver disease, e.g., jaundice, cholestasis, hepatic synthetic impairment, or active hepatitis
12. Alanine transaminase (ALT) or aspartate transaminase (AST) >3 × upper limit of normal (ULN) or alkaline phosphatase or bilirubin levels > 2 × ULN based on local laboratory results
13. Co-administration of clinical doses of orlistat with dalcetrapib
14. Inability to swallow oral medications or a gastrointestinal disorder with diarrhea (e.g., Crohn's disease) or malabsorption at Screening
15. Any other clinically significant medical condition or laboratory abnormality that, in the opinion of the Investigator, would jeopardize the safety of the patient or potentially impact patient compliance or the safety/efficacy observations in the study
16. History of an allergic reaction or hypersensitivity to the study drug or any component of the study drug formulation.

Test products, dose, and mode of administration:

Dalcetrapib in a dose of 900, 1800, or 3600 mg (300 mg tablets) administered once daily, orally, for 10 days

Reference therapy, dose, dose form, and mode of administration:

Matching placebo tablets administered once daily, orally, for 10 days

Duration of patient participation in study:

Planned screening duration: 1 to 2 days
Planned treatment duration: 10 days
Planned follow-up duration: 18 days
Total duration of study participation: up to 30 to 32 days

Study populations:

Intention-to-treat (ITT) Population: The Intent to Treat Population will include all participants who received at least 1 dose of study drug. Participant data will be summarized by treatment assigned.

Per Protocol (PP) population: All participants from the ITT population who have no important study protocol deviations during the study and who received at least 1 dose of study drug. Patients with any important protocol deviations shall be excluded from the PP population prior to database lock.

Safety Population: The Safety Population will include all participants who received at least 1 dose of study drug. Participant data will be summarized by actual treatment received.

Pharmacokinetic Population: The PK Population will include all participants who received at least 1 dose of study drug, had at least one measurable plasma concentrations, and had no protocol deviations thought to impact the PK of study drug.

Evaluation: Efficacy

Primary Endpoint:

- Time to sustained clinical resolution.
  Sustained clinical resolution is defined as occurring when no key COVID-19 related symptom has a score higher than 1 over a 72-hour period (as documented using an electronic patient-reported outcome [ePRO] instrument), except for sense of smell and taste (items 13 and 14) where the score should be 0 over a 72-hour period. The time to resolution will be taken as the time from randomization until the first day of the last 72-hour period where the patient meets the definition of resolution within 28 days. Patients who do not meet the definition of resolution 28 days after randomization will be considered not resolved.

Secondary endpoints:

- Time to complete clinical resolution
- Change from baseline in COVID-19 total symptom score
- Scoring of WHO Clinical Outcome Scale (9-point scale)
- Rate of hospitalization
- Rate of progression to oxygen therapy
- Duration of hospitalization
- Time to viral clearance based on PCR test for SARS-CoV-2
- Change from baseline in log10 viral load
- Mortality rate

Evaluation: Safety

The number and percentage of patients with treatment-emergent AEs (TEAEs), serious AEs (SAEs), TEAEs related to study treatment, SAEs related to study treatment, TEAEs leading to treatment discontinuation, and TEAEs leading to death will be summarized by system organ class (SOC), preferred term (PT), and treatment group. In addition, the severity of TEAEs and relationship to study treatment will be summarized by SOC, PT, and treatment group.

Test values and change from baseline will be summarized descriptively by treatment group for specific laboratory test results and vital signs. Where applicable, shift tabulations by treatment group will be presented.

Evaluation: Pharmacokinetics

Dalcetrapib concentrations will be determined in the PK samples collected according to the Schedule of Assessments.

Statistical methods:

Continuous variables will be summarized by the standard descriptive statistics: number of patients (n), mean, standard deviation, median, minimum, and maximum for baseline variables, and n, mean, standard error, and confidence interval (CI) for outcome measures. Frequency of patient or events and percentages will be summarized for categorical variables. Time to event variables will be summarized using Kaplan-Meier methods.

Unless otherwise specified, all regression models will be stratified by maximum symptom severity at baseline (presence vs absence of moderate or severe symptoms) and by age (≤65 years vs >65 years), and Wald p-values will be considered primary.

Efficacy Analysis

The analysis of treatment efficacy will be based on the Intent-to-Treat Population. The PP population will be used for secondary analysis. This section is a summary of the planned efficacy analyses of the most important efficacy endpoints including primary and key secondary efficacy endpoints.

Analysis of Primary Endpoints

Time to Sustained Clinical Resolution

The primary endpoint is time to sustained clinical resolution as determined by symptom score. The primary analysis of this endpoint will be performed on the ITT population. Time to sustained clinical resolution will be summarized by treatment group using Kaplan-Meier methods. Median and associated 95% CI, 25-75 percentiles, and minimum and maximum values will be presented. The number and percentage of patients whose symptoms resolved, and patients censored will be presented.

The differences in time to sustained clinical resolution between the treatment groups will be evaluated using a 2-sided log-rank test, stratified for baseline symptom severity (presence vs absence of moderate or severe symptoms) and by age (≤65 years vs >65 years). The combined two highest treatment groups will be compared to placebo in addition to the comparison of individual doses.

Analysis of Secondary Efficacy Endpoints

Time to Complete Clinical Resolution

Time to complete clinical resolution will be analyzed using the same model as time to sustained clinical resolution, but with all symptoms required to have resolved to a score of 0 rather than 1.

Change from Baseline in COVID-19 Total Symptom Severity Score

COVID-19 total symptom severity score will be summarized by treatment group using descriptive statistics (N, mean, median, standard deviation, minimum, and maximum) for each visit as well as for changes from baseline (N, mean, standard error, CI). A Mixed-Effect Model Repeated Measure (MMRM) will be performed to analyze the average difference between treatment groups over 28 days and at the designated assessment days.

Scoring of WHO Clinical Outcome Scale (9-point scale)

The number and percentage of patients for each WHO clinical outcome score will be summarized. An ordinal logistic regression analysis for the specified time points will be presented as odds ratio, with associated 95% CI and p-value.

Rate of Hospitalization through Day 28

The analysis of this endpoint will be performed on the ITT population. The number and percentage of patients who were hospitalized and reason for hospitalized will be presented. The percentage of patients who were hospitalized will be compared using a logistic regression analysis for specified time points. The results will be presented as odds ratios, with associated 95% CIs and p-value.

Rate of Progression to Oxygen Therapy through Day 28

The analysis of this endpoint will be performed on the ITT population. The number and percentage of patients who progress to oxygen therapy and type of oxygen therapy will be presented. The percentage of patients who had progressed to oxygen therapy will be compared using a logistic regression analysis for specified time points. The results will be presented as odds ratios, with associated 95% CIs and p-value.

Duration of Hospitalization

The duration of hospitalization will be performed on the ITT population. Duration of hospitalization will be summarized by treatment group using descriptive statistics (N, mean, median, standard deviation, standard error, CI, minimum, and maximum). Linear regression will be performed to analyze the difference between treatment groups. The results will be presented as mean treatment difference with associated 95% CI and p-value.

Mortality Rate

The analysis of this endpoint will be performed on the ITT population. The number and percentage of patients who died and reason for death will be presented. The percentage of patients who died will be compared using a logistic regression analysis for specified time points. The results will be presented as odds ratios, with associated 95% CIs and p-values.

Time to Viral Clearance based on PCR Test for SARS-CoV-2

The time to viral clearance based on PCR test for SARS-CoV-2 will be performed on the ITT population. Time to viral clearance will be summarized by treatment group using Kaplan-Meier methods. Median and associated 95% CI, 25-75 percentiles, and minimum and

maximum values will be presented. The number and percentage of patients who do not show virus, show virus, and patients censored will be presented.

Change from Baseline in log10 Viral Load

The change from baseline in log10 viral load will be assessed at specified time points by a MMRM. Patients who have achieved a level below the limit of detection will be included in the analysis at half the lower limit of detection. For this endpoint, Last Observation Carried Forward (LOCF) will be used to impute values for all patients. The treatment effect for the difference at each time point, and the average slope up to each time point for each treatment group will be presented along with a 95% CI.

Safety Analysis

Safety variables include incidence of AEs (or TEAEs), laboratory test results, and vital signs. All safety analyses will be based on the Safety Population. No formal statistical analysis of the safety data will be performed.

Adverse events will be coded according to MedDRA, version 23.0 dated 19 Apr 2020 (exclusively meant for COVID-19) or later.

The number and percentage of patients with TEAEs, SAEs, TEAEs related to study treatment, SAEs related to study treatment, TEAEs leading to treatment discontinuation, TEAEs leading to study discontinuation, and TEAEs leading to death will be summarized by SOC, PT, and treatment group. In addition, the severity of TEAEs and relationship to study treatment will be summarized by SOC, PT, and treatment group.

Test values and change from baseline will be summarized descriptively by treatment group for specific laboratory test results and vital signs. Where applicable, shift tabulations will be presented for specific laboratory test results by treatment group. Where applicable, number and frequency of clinically significant abnormal values for specific laboratory test results will be presented.

Pharmacokinetic Analysis

Pharmacokinetic parameters will be determined using population PK modeling approach. The sparse PK samples will be pooled with PK data from other clinical studies for population PK analysis. PK profiles will be predicted and subsequently PK parameters will be estimated. Correlations between PK and pharmacodynamic (efficacy or safety) may be explored, including the relationship between drug exposure and viral elimination dynamics, if data permit. The methodology for PK analysis will be documented in a PK Analysis and Reporting Plan outside of this protocol.

Interim Analysis

A single interim analysis will be conducted after 97 resolution events have occurred.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANOVA	analysis of variance
AST	aspartate aminotransferase
AUC_{0-24}	area under the concentration-time curve during 24 hours
CETP	Cholesteryl Ester transfer protein
CFR	Code of Federal Regulations
CHD	coronary heart disease
CI	confidence interval
C_{max}	maximum concentration
COVID-19	Coronavirus Disease of 2019
CRO	Contract Research Organization
CT	computerized tomography
DMC	Data Monitoring Committee
EC	Ethics Committee
ECMO	extracorporeal membrane oxygenation
eCRF	electronic Case Report Form
EOT	End of treatment
ePRO	electronic patient-reported outcome
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDL-C	high-density lipoprotein cholesterol
HR	hazard ratio
IC_{50}	half maximal inhibitory concentration
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IRB	Institutional Review Board
ITT	Intention-to-treat
IVRS/IWRS	Interactive Voice/Web Response System
LOCF	Last Observation Carried Forward
MDRD	Modification of Diet in Renal Disease
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-Effect Model Repeated Measure
PCR	polymerase chain reaction
PK	pharmacokinetic
PP	Per Protocol
PT	preferred term
QTc	corrected QT
SAE	serious adverse event
SARS-CoV-2	Severe Acute Respiratory Syndrome CoronaVirus 2
SOC	system organ class (MedDRA classification)
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

In 2019, an outbreak of respiratory disease caused by a novel coronavirus was first detected in Wuhan City, Hubei Province, China.[1] The virus has been named Severe Acute Respiratory Syndrome COronaVirus 2 (SARS-CoV-2), and the disease it causes has been named Coronavirus Disease of 2019 (COVID-19). This virus has now been detected in many locations internationally, and COVID-19 was characterized as a pandemic by the World Health Organization (WHO) on 11 March 2020.[2] As of 22 October 2020, WHO reported approximately 41 million COVID-19 positive cases and included approximately 1,128,000 deaths.[3]

SARS-CoV-2 can cause a potentially fatal disease. COVID-19 can range from mild to severe disease, the latter including pneumonia, severe acute respiratory syndrome, multi-organ failure, and death. FDA provided emergency use authorization to remdesivir for the treatment of hospitalized COVID-19 patients.[4] However, there is a need for treatment, as well as to have a clinically effective antiviral drug for the prevention of COVID-19. Clinical management includes symptomatic and supportive care, such as supplemental oxygen, mechanical ventilation, and extracorporeal membrane oxygenation (ECMO) when indicated. There is an urgent need for safe and effective anti-SARS-CoV-2 drugs.[1]

The main protease (Mpro) of SARS-CoV-2 is a key enzyme that plays a pivotal role in mediating viral replication and transcription. Dalcetrapib and its metabolite dalcetrapib-thiol is known to covalently bind to Cysteine13 of the Cholesteryl Ester transfer protein (CETP). It is speculated that it may form a disulfide bond with Cysteine145 of Main Protease (3CLMpro) of SARS-CoV-2 and inactivate the enzyme therefore stopping the viral replication and transcription in cells. In vitro results are provided in Section 1.2.

1.1. Study Rationale

This placebo-controlled, Phase 2a proof-of-concept clinical study will evaluate efficacy and safety of dalcetrapib in outpatients patients with mild to moderate, symptomatic, confirmed COVID-19.

Selection of doses in the study is discussed in Section 3.4.

1.2. Background

Dalcetrapib is being investigated for coronary heart disease (CHD) (NCT00658515) in CHD patients. Dalcetrapib is a compound selected for its capacity to modulate plasma CETP activity and increase high-density lipoprotein cholesterol (HDL-C) levels. Dalcetrapib has been evaluated in several large clinical trials, most notably dal-OUTCOMES, a 15,871 patient trial designed to evaluate its effect in patients with recent acute coronary syndrome. As compared with placebo, dalcetrapib did not alter the risk of cardiovascular morbidity and mortality or total mortality despite an effect on HDL-C levels (30% increase). However, the trial demonstrated the safety and tolerability of dalcetrapib in this population.[5]

Molecular docking investigations suggested that dalcetrapib-thiol binds to the active site of the SARS-CoV-2 main 3CL protease with a delta G value of -8.5 kcal/mol (Table 1).

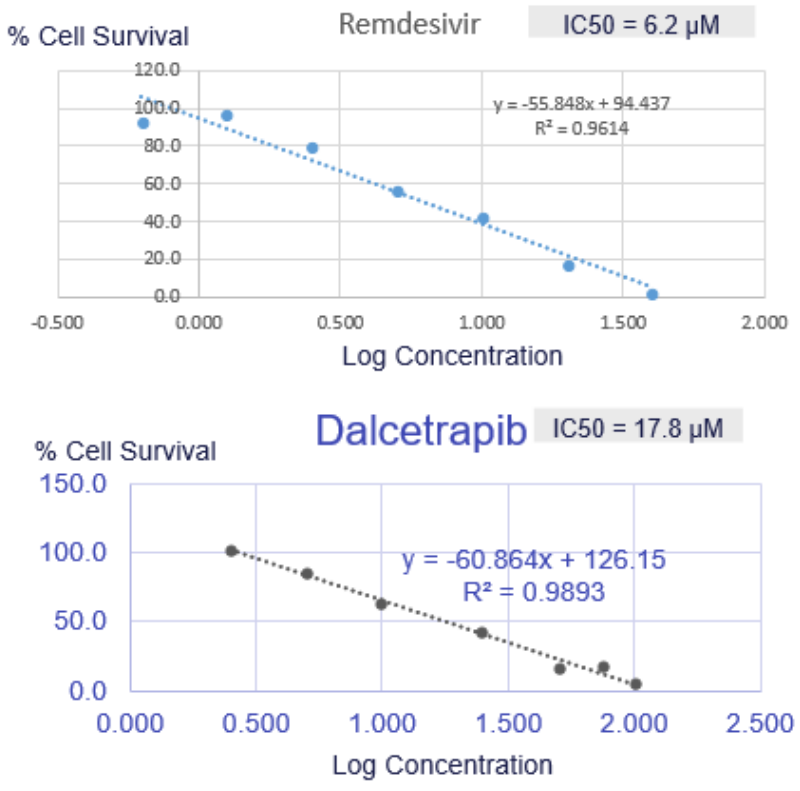
Table 1: Molecular Docking Data of Dal-thiol and Dal-dimer

	MPro ΔG Kcal/mol	CETP ΔG Kcal/mol
Dal-ester	-8.62	-8.90
Dal-Thiol	-8.72	-8.07
Dal-DIMER	-10.14	-10.66
Natural substrate of Main Protease	-10.99	-

In vitro data from SARS-CoV-2 infected cultured cell line confirmed antiviral activity and no obvious toxicity was observed in the in vivo toxicity study.[6]

Remdesivir, an injectable intravenous treatment for severe forms of COVID-19, is currently the only treatment approved by the FDA. In vitro data for remdesivir and dalcetrapib confirm the inhibition of viral replication in renal monkey cells with pre-incubation to achieve lower half maximal inhibitory concentration (IC_{50}). Dalcetrapib inhibited main 3CL protease activity both in vitro and viral replication in cells with IC_{50} values of 14.4±3.3 µM and 17.5±3.5 µM. Near-complete inhibition of protease activity persisted despite elution of dalcetrapib approximately 100 times below its IC_{50}, suggesting stable protease-drug interaction.

Figure 1: Inhibition of Viral Replication in Renal Human Cell



IC50 = half maximal inhibitory concentration

1.3. Risk-benefit Assessment

Dalcetrapib is an oral, safe and generally well-tolerated drug which could target mild, moderate, and severe forms of the COVID-19, and possibly prevent COVID-19 in high-risk or exposed patients.[7]

No obvious toxicity was observed in the in-vivo toxicity studies. The major dose-limiting finding associated with dalcetrapib in monkeys was gastrointestinal toxicity (diarrhea and loose stools). In general, dalcetrapib has been well-tolerated in patients with CHD. In the short-term (<12 weeks) Phase 1 and 2 studies, the incidence of adverse events (AEs) leading to discontinuation of dalcetrapib (300, 600, and 900 mg) was low across the Phase1 healthy volunteer and Phase 2 patient studies. The majority of the AEs were of mild or moderate intensity. The most frequently reported AEs were those from body system organ classes of gastrointestinal system and nervous system, and included diarrhea, stool abnormalities, and headache.

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of dalcetrapib may be found in the Investigator's Brochure.

As the study subjects targeted are patients with limited treatment options, the study supports further investigation of dalcetrapib in patients with mild to moderate symptoms due to COVID-19 in a Phase 2a setting.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary efficacy objective of the study is:

- To evaluate the time to sustained clinical resolution of symptoms in patients with confirmed, mild to moderate, symptomatic COVID-19 treated with dalcetrapib.

  Sustained clinical resolution is defined as occurring when no key COVID-19 related symptom has a score higher than 1 over a 72-hour period (as documented using an electronic patient-reported outcome [ePRO] instrument), except for sense of smell and taste (items 13 and 14) where the score should be 0 over a 72-hour period. The time to resolution will be taken as the time from randomization until the first day of the last 72-hour period where the patient meets the definition of resolution within 28 days. Patients who do not meet the definition of resolution 28 days after randomization will be considered not resolved.

The secondary efficacy objectives of the study are:

- To evaluate the change from baseline in COVID-19 symptom severity score at all collected time points
- To evaluate time to complete clinical resolution, defined in the same way as the primary endpoint, but considering that all symptoms must resolve to a score of 0 for 72 hours
- To evaluate the time to viral clearance using SARS-CoV-2 polymerase chain reaction (PCR)
- To evaluate change from baseline in log10 viral load
- To evaluate the WHO Clinical Outcome Scale (9-point scale) at Day 3, Day 5, Day 10, and Day 28
- Rate of hospitalization through Day 28
- To evaluate the rate of progression to oxygen therapy through Day 28
- To evaluate the duration of hospitalization
- To evaluate the mortality rate by Day 28

The safety objective of the study is:

- To assess the safety and tolerability of dalcetrapib active doses compared to placebo in patients with COVID-19

The pharmacokinetics (PK) objective of the study is:

- To evaluate the PK of dalcetrapib in patients with COVID-19

2.2. Endpoints

The primary efficacy endpoint is:

- Time to sustained clinical resolution.

  Sustained clinical resolution is defined as occurring when no key COVID-19 related symptom has a score higher than 1 over a 72-hour period (as documented using an electronic patient-reported outcome [ePRO] instrument), except for sense of smell and taste (items 13 and 14) where the score should be 0 over a 72-hour period. The time to resolution will be taken as the time from randomization until the first day of the last 72-hour period where the patient meets the definition of resolution within 28 days. Patients who do not meet the definition of resolution 28 days after randomization will be considered not resolved.

The secondary efficacy endpoints are:

- Time to complete clinical resolution
- Change from baseline in COVID-19 total symptom score
- Score on the WHO Clinical Outcome Scale (9-point scale)
- Rate of hospitalization
- Rate of progression to oxygen therapy
- Duration of hospitalization
- Time to viral clearance based on PCR test for SARS-CoV-2
- Change from baseline in log10 viral load
- Mortality rate

3. INVESTIGATION PLAN

3.1. Overall Study Design and Plan Description

This is a randomized, double-blind, multicenter, Phase 2a proof-of-concept study in outpatients with confirmed, mild to moderate, symptomatic COVID-19. Dalcetrapib inactivates the 3CLMpro enzyme of Corona virus and therefore stops the viral replication and transcription in cells. It is being planned to use for treatment in patients with COVID-19.

Up to 60 sites in the United States and Canada, and other countries as appropriate based on the pandemic situation, are planned to enroll patients.

Total duration of study participation is up to 32 days. The screening period is planned to occur between 48 to 24 hours prior to dosing. Randomization will occur during the Screening/Baseline visit in order for treatment to be dispensed in time for start of first dose on Day 1. Patients will either receive dalcetrapib 900, 1800, or 3600 mg or placebo for 10 days and be followed for 18 days of follow-up. The study design is summarized in Figure 2.

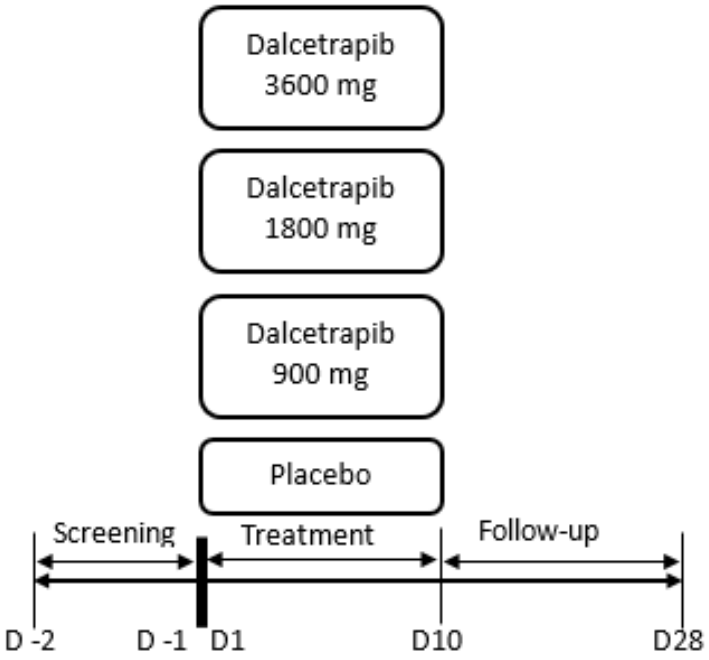
It is anticipated that 208 patients will be randomized in one of the dalcetrapib treatment arms or placebo (52 patients to each of 900 mg, 1800 mg, 3600 mg and placebo) for 10 days. Patients will be randomized and receive first dose of study drug within 72 hours of receiving a positive PCR or Point-of-care test for SARS-CoV-2. Patients need to have at least two of the 14 common COVID-19-related symptoms described in the inclusion criteria rated as mild or moderate, as evaluated by ePRO assessment. Symptoms will be assessed at each study visit daily for the first 10 days, then at Day 14 and Day 28, and as clinically indicated. Symptoms will be evaluated as absent, mild, moderate, or severe depending on their impact on activity of daily living. SARS-CoV-2 viral loads will be obtained by both saliva (Oragene) collection and mid-turbinate nasal swab self-collected under supervision of healthcare professional (virtual or home visit) at Screening/Baseline, Day 1, Day 3, Day 5, Day 7, Day 10, and Day 28. Patients who require hospitalization after initiation of study treatment will be followed for vital status through Day 28.

Study Visit Procedures

Study visits (virtual, study site or home visits by a healthcare professional) will take place on Days 1, 3, 5, 7, 10, 14, and 28. Screening/Baseline assessments may all be performed on the same calendar day and may be performed at the study site or as a home visit. For visits which include bloodwork, sample collection may be done by a visiting healthcare professional or at the study site (as long as the patient has no worsening of respiratory symptoms or no fever within 24 hours). Other visits may be conducted remotely using telemedicine.

The samples for viral load testing will be both saliva (Oragene) collection and mid-turbinate nasal swab self-collected under supervision of a healthcare professional. Telemedicine visits such as phone calls or other digital media are to be utilized as much as possible. Study procedures are presented in detail in Section 7.

Figure 2: Study Design



D=Day.

3.1.1. Data Monitoring Committee

The study will be overseen by an independent Data Monitoring Committee (DMC). The DMC will review safety data throughout the study. The DMC and Sponsor will review efficacy data at the interim analysis and at the end of the study. A DMC Charter, which includes detailed processes, will be prepared.

One interim analysis will be conducted for efficacy once 97 resolution events have occurred to allow 73 resolution events to have occurred in the two highest dose levels and placebo arm. At the interim analysis, if the average hazard ratio (HR) of the two highest dose levels relative to placebo is greater than 1.45, the study will stop due to efficacy and the program will be able to proceed directly to Phase 3. At the interim analysis, if the HR of the two highest dose levels relative to placebo is between 1.0 and 1.45, the study will continue enrollment until 169 resolution events have occurred. At the interim analysis, if the HR of the two highest dose levels is less than 1.0, the study will be stopped for lack of efficacy.

The members of the committee will include appropriately qualified medical personnel, and other members, as required. Detailed responsibilities of the DMC will be provided in the DMC Charter.

3.2. Discussion of Study Design, Including the Choice of Control Groups

This study will be double-blind and placebo-controlled to avoid bias in the collection and evaluation of data during its conduct. The Sponsor will remain blinded to the treatment

randomization code until after the database has locked. The Sponsor will perform ongoing review of blinded data. The placebo has been chosen as the control treatment to assess whether any observed effects are treatment-related or simply reflect the study conditions.

3.3. End of Study Definition

The end of the study is defined as the date of the last visit of the last patient in the study.

3.4. Selection of Doses in the Study

Dalcetrapib is already in clinical development (NCT02525939), and of 11,799 subjects that have been dosed to date, a total of 546 subjects have received single oral doses of between 100 and 4500 mg and 467 subjects have received consecutive doses between 300 and 3900 mg. Available information at higher doses showed systemic exposure of 1.73-2.68, 4.30, 3.78, 3.26, 5.63, and 7.11 µg/mL (maximum concentration [C_{max}]) and 18.2-19.1, 31.3, 30.4, 25.3, 42.3, and 51.1 µg.h/mL (area under the concentration-time curve during 24 hours [AUC_{0-24}]) at 900, 1200, 1800, 2100, 3000, and 3900 mg, respectively. In vitro testing showed a protease inhibition IC_{50} value of 14.4 µM and inhibition of replication IC_{50} value of 17.8 µM. Proposed oral dose levels of dalcetrapib at 900, 1800, or 3600 mg for 10 days is centered on the following:

- 900 mg: based on actual C_{max} values of 1.73-2.68 µg/mL = 5.4-8.37 µM which are 2.7-1.7- and 3.3-2.1-fold lower than protease inhibition and inhibition of replication IC_{50} values, respectively to establish whether that this is not an efficacious dose.

- 1800 mg: based on actual C_{max} value of 3.78 µg/mL = 11.8 µM which is approximately 0.8-fold and 0.65-fold the values for protease inhibition and inhibition of replication IC_{50} values, respectively, to establish whether this is an efficacious dose.

- 3600 mg: based on actual C_{max} values for the 3000 and 3900 mg doses of 5.63 and 7.10 µg/mL = 17.6 and 22.2 µM which are at or higher the values for protease inhibition and inhibition of replication IC_{50} values, respectively, to establish whether this is an efficacious dose.

4. SELECTION OF STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

4.1. Inclusion Criteria

Patients must satisfy all of the following criteria unless otherwise stated:

1. Willing and able to provide informed consent
2. Male or female patients > 18 years of age on the day of informed consent
3. Have received a confirmed diagnosis of COVID-19 (positive for SARS-CoV-2), as assessed by PCR or point-of-care within 72 hours of first dose on Day 1
4. Have mild to moderate signs or symptoms of COVID-19 with onset within 5 days of first dose on Day 1, at least two of the following symptoms:
    - stuffy or runny nose
    - sore throat
    - shortness of breath
    - cough
    - fatigue
    - myalgia
    - headache
    - chills or shivering
    - feeling hot or feverish
    - nausea
    - vomiting
    - diarrhea
    - anosmia
    - ageusia
5. Outpatient with COVID-19 disease (not requiring oxygen therapy [WHO COVID-19 Clinical Improvement Ordinal Scale, score of 3])
6. Patient is aware of the investigational nature of this study and willing to comply with protocol treatments, blood tests, and other evaluations listed in the ICF.

4.2. Exclusion Criteria

Patients will be excluded from the study if they satisfy any of the following criteria unless otherwise stated:

1. Females who are pregnant (negative pregnancy test required for all women of child-bearing potential at Screening) or breast-feeding
2. Male patients and women of childbearing potential (women who are not surgically sterile or postmenopausal defined as amenorrhea for >12 months) who are not using at least one protocol-specified method of contraception

3. Severe COVID-19 disease as defined by the WHO COVID-19 Clinical Improvement Ordinal Scale, scores of 5 (non-invasive ventilation or high-flow oxygen), 6 (intubation and mechanical ventilation), or 7 (ventilation + additional organ support pressors, renal replacement therapy [RRT], extracorporeal membrane oxygenation [ECMO])
4. Expected survival less than 72 hours
5. Peripheral capillary oxygen saturation (SpO2) <90% while breathing room air
6. Treatment with other drugs thought to possibly have activity against SARS-CoV-2 infection like remdesivir, favipiravir, within 7 days prior to enrollment or concurrently
7. History of abuse of drugs or alcohol that could interfere with adherence to study requirements as judged by the Investigator
8. Use of any other concurrent investigational drugs while participating in the present study
9. Patient requires frequent or prolonged use of systemic corticosteroids (≥20 mg of prednisone/day or equivalent for >4 weeks) or other immunosuppressive drugs (e.g., for organ transplantation or autoimmune conditions)
10. Known renal disease with an estimated glomerular filtration rate (eGFR) <50 mL/min based on local laboratory results
11. Patients with clinically apparent liver disease, e.g., jaundice, cholestasis, hepatic synthetic impairment, or active hepatitis
12. Alanine transaminase (ALT) or aspartate transaminase (AST) >3 × upper limit of normal (ULN) or alkaline phosphatase or bilirubin levels > 2 × ULN based on local laboratory results
13. Co-administration of clinical doses of orlistat with dalcetrapib
14. Inability to swallow oral medications or a gastrointestinal disorder with diarrhea (e.g., Crohn's disease) or malabsorption at Screening
15. Any other clinically significant medical condition or laboratory abnormality that, in the opinion of the Investigator, would jeopardize the safety of the patient or potentially impact patient compliance or the safety/efficacy observations in the study
16. History of an allergic reaction or hypersensitivity to the study drug or any component of the study drug formulation.

4.3. Disease Diagnostic Criteria

Patients with SARS-CoV-2 infection confirmed (nasal, nasopharyngeal, oropharyngeal, or respiratory samples, not serology testing, or patients with pre-study confirmed PCR test) and mild to moderate symptoms related to COVID-19 disease are required for enrollment.

The entry testing is performed locally based on testing methods available at the site, such as PCR or rapid antigen test, to confirm the presence of SARS-CoV-2 in a person with symptoms compatible with COVID-19. Both saliva (Oragene) collection and self-collection of mid-turbinate nasal swab under supervision of a healthcare professional (virtual or home visit) will also occur at Screening/Baseline, Day 1, Day 3, Day 5, Day 7, Day 10, and Day 28.

4.4. Discontinuation Criteria

4.4.1. Screen Failures

Screen failures are defined as patients who have provided informed consent to participate in the clinical study but are not subsequently enrolled in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure patients to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any serious adverse events (SAEs).

Re-screening will be allowed in a screen failed patient if there is a change in the situation of the patient which allows him/her to fulfill inclusion/exclusion criteria with the permission from the Medical Monitor.

4.4.2. Discontinuation of Study Treatment

Study medication will be discontinued for the following reasons:

- Patients whose screening labs indicate an eGFR <50mL/min using CKD-EPI will discontinue study medication and be followed for safety
- Withdrawal by patient (patient is free to discontinue at any point of time; specify reason of discontinuation in the eCRF)
- At the discretion of the Investigator for safety, behavioral, or administrative reasons
- Lack of efficacy (e.g., patients who require nonstudy antiviral or anticytokine therapy due to progression of COVID-19). Note: Study medication would be discontinued upon worsening of symptoms requiring hospitalization, in such cases patients could receive remdesivir
- Adverse event

Study will be discontinued for the following reasons:

- Withdrawal of consent (patient is free to discontinue at any point of time; specify reason of discontinuation in the eCRF)
- Sponsor determination
- Unexpected safety concerns
- Medical or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of patients

4.4.2.1. Liver Injury

Discontinuation of study treatment for abnormal liver tests should be considered by the Investigator when a patient meets one of the conditions mentioned below or if the Investigator believes that it is in the best interest of the patient.

- Discontinue the study treatment if AST/ALT >8 × ULN
- Discontinue the study treatment if AST/ALT >3 × ULN and serum total bilirubin levels >2 × ULN (Hy's law)
- Discontinue the study treatment if repeat AST/ALT >5 × ULN

4.4.2.2. Pregnancy

Female patients who are pregnant or are breastfeeding or who do not agree to use a reliable method of birth control during the study will be permanently discontinued from study drug.

4.4.3. Lost to Follow-up

A patient will be considered lost to follow-up if he/she repeatedly is unable to be contacted.

The following actions must be taken if a patient repeatedly is unable to be contacted.

- The site must attempt to contact the patient and reschedule the missed visit as soon as possible, counsel the patient on the importance of maintaining the assigned visit schedule, and ascertain whether or not the patient wishes to and/or should continue in the study.

- In cases in which the patient is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the patient (where possible, 3 telephone calls and, if necessary, a certified letter to the patient's last known mailing address or local equivalent methods). These contact attempts should be documented in the patient's medical record.

- Should the patient continue to be unreachable, he/she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

4.4.4. Replacement Procedures

Patients who discontinue from the study will not be replaced.

4.4.5. Follow-up of Patients Prematurely Discontinued from the Study Treatment Regimen or Withdrawn from Study

Due to continued scientific importance of patient data even if study treatment is discontinued early, patients who withdraw from the study will be asked to complete all subsequent study procedures (Follow-up/EOS), as described in the Schedule of Assessments (Appendix 4). Patients who are no longer hospitalized may complete their assessments by telephone or via telemedicine or other means of remote communication.

All SAEs that are ongoing at the time of discontinuation, or that develop prior to the final Follow-up/EOS, will be followed until resolution or stabilization, or up to 28 days (±2 days) following the last dose of study treatment, by Covance Patient Safety Services group.

Steps will be taken by the sites to ascertain vital status in all randomized patients (e.g., with a vital records search) up to Day 28±2.

4.5. Stopping Rules

The study will enroll 208 patients (52 patients to each of 900 mg, 1800 mg, 3600 mg and placebo). One interim analysis will be conducted for efficacy once 97 resolution events have occurred to allow 73 resolution events to have occurred in the two highest dose levels and placebo arm. At the interim analysis, if the average HR of the two highest dose levels relative to placebo is greater than 1.45, the study will stop due to efficacy and the program will be able to proceed directly to Phase 3. At the interim analysis, if the HR of the two highest dose levels relative to placebo is between 1.0 and 1.45, the study will continue enrollment until 169 resolution events have occurred. At the interim analysis, if the HR of the two highest dose levels is less than 1.0, the study will be stopped for lack of efficacy. The DMC will issue a recommendation to enroll patients, or to stop the study depending on interim analysis assessment. The DMC may recommend dropping one or more treatment arms. The DMC will continue to review safety and assess the risk/benefit profile on an ongoing basis.

A DMC Charter, which includes detailed processes, will be prepared.

4.6. Study Termination

The study will finish when all patients have completed all study visits.

The Sponsor reserves the right to close a study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study site closure visit has been performed. Reasons for study termination may include, but are not limited to:

- Adverse events unknown to date (i.e., not previously reported in any similar investigational study drug trial with respect to their nature, severity, and/or duration)
- Increased frequency and/or severity and/or duration of known, anticipated, or previously reported AEs (this may also apply to AEs defined as baseline signs and symptoms)
- Medical or ethical reasons affecting the continued performance of the study

- Difficulties in the recruitment of patients
- Cancellation of drug development
- At the recommendation of the DMC

The Investigator may initiate study site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination. Reasons for the early closure of a study site by the Sponsor or Investigator may include, but are not limited to:

- Failure of the Investigator to comply with the protocol, the requirements of the Institutional Review Board (IRB)/Ethics Committee (EC) or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of participants by the Investigator

5. STUDY TREATMENTS

5.1. Treatments Administered

Details on the active treatment and placebo provided to patients are summarized in Table 2.

Table 2: Treatment Details

Study Treatment Name:	Dalcetrapib (or matching placebo tablets)
Dosage Formulation:	Film-coated white to off-white tablets
Unit Dose Strength(s)	300 mg per tablet
Route of Administration:	Oral (recommended to be taken with the largest meal of the day)
Dosing Instructions:	• For 900 mg dose: 3 active tablets and 9 placebo tablets • For 1800 mg dose: 6 active tablets and 6 placebo tablets • For 3600 mg dose: 12 active tablets • Placebo dose: 12 placebo tablets
Packaging and Labeling:	The tablets can be stored in glass and plastic bottles or aluminum blisters. The recommended storage conditions are on the packaging and should be followed. For batch specific details and information on shelf-life, see the packaging.
Manufacturer:	Dalcetrapib tablets: Recipharm, Leganés, Spain Placebo tablets: Catalent, Kansas City, MO, United States

The physicochemical properties and the pharmaceutical specifications of dalcetrapib are provided in the Investigator's Brochure.[6]

5.2. Preparation, Storage, Handling, and Accountability

The study drug will be supplied by the Sponsor (or designee), along with the batch/lot numbers and Certificates of Analysis. A Certificate of Release authorized by a Qualified Person in the European Union will also be issued for the investigational medicinal product. The study treatment will be provided in bottles, 10 bottles with 12 tablets per bottle, with 1 bottle to be taken per day.

The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study treatment received and any discrepancies are reported and resolved before use of the study treatment.

All study treatments must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.

Only patients enrolled in the study may receive study treatment and only authorized site staff may supply study treatment. The Investigator, institution, or the head of the medical institution

(where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

Further guidance and information for the final disposition of unused study treatment are provided in a separate document.

5.3. Method of Treatment Assignment

All patients will be centrally randomized using an Interactive Voice/Web Response System (IVRS/IWRS). Before the study is initiated, the telephone number and call-in directions for the IVRS and/or the log-in information and directions for the IWRS will be provided to each site.

The study will be stratified by presence or absence of moderate or severe symptoms and by age (≤65 years vs >65 years).

Patients who confirmed eligible at the screening will be assigned a patient identifier before having study treatment dispensed. The patient identifier will consist of the country number, site number, and patient number. The country number will comprise the first 2 digits, the site number will comprise the next 3 digits, and the patient number will comprise the final 3 digits, e.g., 01002003 is Country 1, Site 2, Patient 3.

Study treatment will be dispensed to patients at the Screening/Baseline visit (see Schedule of Assessments, Appendix 4).

5.3.1. Dose Modification

Dose modification will not be allowed. If a dose modification is needed, the patient should be discontinued from treatment and all end of treatment (EOT) assessments completed.

5.4. Blinding

This is a double-blind study.

The Sponsor and the Contract Research Organization (CRO) must be notified as soon as possible (e.g., within 24 hours) when the blind is broken, in the case identification of the study treatment is required for a medical emergency and knowledge of the specific blinded study treatment will affect the immediate management of the patient's condition. The date and reason that the blind was broken must be recorded in the source documentation and eCRF, as applicable.

5.5. Treatment Compliance

Records shall be maintained of the delivery of study treatment to the study sites, the inventory at the study sites, the use for each patient, and the return to the Sponsor.

These records shall include dates, quantities, batch/lot information, expiry dates, and the unique code numbers assigned to the study treatment and study patients.

The Investigator shall be responsible for ensuring that the records adequately document that the patients were provided the doses specified in the protocol and that all study treatment received from the Sponsor is reconciled.

Site staff will monitor compliance of patients with their assigned randomized treatment (dalcetrapib 900, 1800, or 3600 mg or placebo) by recording the number of tablets actually used.

For patients who are hospitalized, patients will be administered treatment by the site staff during hospitalization. On discharge, all patients are to be reminded of the importance of compliance with the treatment with an emphasis on taking their study treatment on schedule and contacting the study site for an appointment as soon as possible if they think they are experiencing worsening of condition.

Compliance information will be captured via eSource (if a patient version is used) or telemedicine. Patient will return unused supply at the EOT visit.

6. CONCOMITANT THERAPIES AND OTHER RESTRICTIONS

6.1. Concomitant Therapy

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

- reason for use
- dates of administration including start and end dates
- dosage information including dose and frequency

Patients must be instructed not to take any medications, including over-the-counter products, without first consulting with the Investigator. The Medical Monitor should be contacted if there are any questions regarding concomitant or prior therapy.

Medications, other than that those listed as prohibited medications and other restrictions, which are considered necessary for the patient's safety and well-being, may be given at the discretion of the Investigator and must be recorded in the appropriate sections of the eCRF.

6.2. Prohibited Medications

Simultaneous participation in other clinical treatment study protocols is not allowed.

Treatment with any antiviral drugs expected to have activity against SARS-CoV-2 are not allowed during therapy with study treatment but may be used as rescue medications. Orlistat results in lowered serum levels of dalcetrapib and is not allowed as this may result in decreased efficacy.

Patients who begin to receive nonstudy rescue antiviral medication for COVID-19 after the start of study treatment will be discontinued from study treatment, they will remain in the study and complete all follow-up assessments.

7. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Assessments (Appendix 4). As protocol waivers or exemptions are not allowed, with the exception of immediate safety concerns, these should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the patient should continue or discontinue the study drug. Adherence to the study design requirements, including those specified in the Schedule of Assessments, is essential and required for study conduct.

All screening evaluations must be completed and reviewed to confirm that potential patients meet all eligibility criteria. The Investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure (Section 4.4.1), as applicable. Procedures conducted as part of the patient's routine clinical management (e.g., blood count) and obtained before informed consent may be utilized for screening or baseline purposes provided the procedure met the protocol-specified criteria and was performed within the timeframe defined in the Schedule of Assessments.

7.1. Efficacy Assessments

7.1.1. COVID-19 Symptom Severity

COVID-19 symptoms will be evaluated by ePRO assessment on the specified days at approximately the same time. Symptoms are described in Table 3.

Table 3: Assessment of 14 Common COVID-19-Related Symptoms: Items and Response

Symptom	Response and scoring
1. Stuffy or runny nose	None = 0 Mild = 1 Moderate = 2 Severe = 3
2. Sore throat	
3. Shortness of breath (difficulty breathing)	
4. Cough	
5. Low energy or tiredness	
6. Muscle or body aches	
7. Headache	
8. Chills or shivering	
9. Feeling hot or feverish	
10. Nausea (feeling like you wanted to throw up)	
11. How many times did you have vomiting in the last 24 hours?	I did not vomit at all = 0 1–2 times = 1 3–4 times = 2 5 or more times = 3

Symptom	Response and scoring
12. How many times did you have diarrhea (loose or watery stools) in the last 24 hours?	I did not have diarrhea at all = 0 1–2 times = 1 3–4 times = 2 5 or more times = 3
13. Rate your sense of smell in the last 24 hours	My sense of smell is THE SAME AS usual = 0 My sense of smell is LESS THAN usual = 1 I have NO sense of smell = 2
14. Rate your sense of taste in the last 24 hours	My sense of taste is THE SAME AS usual = 0 My sense of taste is LESS THAN usual = 1 I have NO sense of taste = 2

Sustained clinical resolution is defined as occurring when no key COVID-19 related symptom has a score higher than 1 over a 72-hour period (as documented using an ePRO instrument), except for sense of smell and taste (items 13 and 14) where the score should be 0 over a 72-hour period. The time to resolution will be taken as the time from randomization until the first day of the last 72-hour period where the patient meets the definition of resolution within 28 days. Patients who do not meet the definition of resolution 28 days after randomization will be considered not resolved.

7.1.2. COVID-19 Clinical Outcome Scale

COVID-19 clinical outcome scale will be evaluated by a healthcare professional.

The WHO Clinical Outcome Scale (ordinal) is a 9-point scale (Table 4).

Table 4: WHO Clinical Outcome Scale

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory	No Limitation of Activities	1
	Limitation of Activities	2
Hospitalized, Mild Disease	Hospitalized no oxygen therapy	3
	Oxygen by mask or nasal prongs	4
Hospitalized, Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support -pressors, RRT, ECMO	7
Death	Death	8

ECMO = extracorporeal membrane oxygenation; RRT = renal replacement therapy; WHO = World Health Organization

7.1.3. Hospitalization

The duration of hospitalization will be from the date of first hospitalization until date of discharge. The duration of hospitalization will be the total number of days hospitalized.

7.1.4. Viral Clearance as Measured Based on PCR Test for SARS-CoV-2

Each patient will be tested to determine if the patient has COVID-19 by obtaining a PCR or rapid antigen test as long as it confirms the presence of SARS-CoV-2 per Schedule of Assessments (Appendix 4). Saliva and nasal secretions will be collected as noted in the schedule of assessments and assessed centrally by PCR for the presence or absence of SARS-CoV-2.
A patient will be considered to no longer have COVID-19 if two consecutive PCRs do not detect SARS-CoV-2. Time to viral clearance using PCR test for SARS-CoV-2 will be the period between randomization and the date of the first negative PCR test for SARS-CoV-2.

7.1.5. Viral Load for SARS-CoV-2

SARS-CoV-2 presence or absence will be determined by PCR from both mid-turbinate nasal swabs and saliva. Positive results will have a quantitative viral load determined at the central laboratory.

7.2. Safety and Tolerability Assessments

7.2.1. Adverse Events

Adverse event definitions, assignment of severity and causality, and procedures for reporting SAEs are detailed in Appendix 1.

The condition of each patient will be monitored from the time of providing informed consent to completion of study participation. Patients will be observed for any signs or symptoms and asked about their condition by open questioning, such as “How have you been feeling since you were last asked?” at each patient contact. Patients will also be encouraged to spontaneously report AEs occurring at any other time during the study.

Any AEs and remedial action required will be recorded in the patient’s source data. The nature, time of onset, duration, and severity will be documented, together with an Investigator’s (or designee’s) opinion of the relationship to study drug.

AEs recorded during the course of the study will be followed up, where possible, until resolution or until the unresolved AEs are judged by the Investigator (or designee) to have stabilized. This will be completed at the Investigator’s (or designee’s) discretion.

For any participants who require hospitalization, if possible, study drug should be continued and an effort made to collect study-related data and conduct End of Study procedures. Every attempt should be made for a visit to be scheduled after discharge from the hospital, providing that the visit is within 28 days of initiation of dosing, or to visit the patient in the hospital, where permitted. In lieu of a study visit, study site staff should obtain equivalent data from hospital records. Pertinent information from hospitalization will be collected, including need for

supplemental oxygenation, mechanical ventilation, days of hospitalization and ventilation, and death.

Serious AEs of worsening COVID-19, with the exception of death, will be considered disease progression and will not be collected for the safety database.

7.2.2. Pregnancy

Female patients of childbearing potential will have a pregnancy test during Screening/Baseline and at the Day 28 Follow-up/EOS.

Urine pregnancy test must be performed but may be confirmed with a serum pregnancy test (screening only). The Follow-up/EOS test will be a urine pregnancy test only (pregnancy test kit will be provided to the patient).

Following administration of study treatment, any pregnancy in a patient who is a female of childbearing potential or female partner of a male patient will be reported if known until the completion of pregnancy provided that the patient agrees and all the outcome are assessed. The pregnancy will be reported immediately by telephone and by faxing a completed pregnancy report to the Sponsor (or designee) within 24 hours of knowledge of the event. The pregnancy will not be processed as an SAE; however, the Investigator will follow the patient until completion of the pregnancy and must assess the outcome in the shortest possible time. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date.

The Investigator should notify the Sponsor (or designee) of the pregnancy outcome by submitting a follow-up pregnancy report. If the outcome of the pregnancy meets the criteria for immediate classification of an SAE (e.g., 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 telephone and by faxing a completed SAE form to the Sponsor (or designee) within 24 hours of knowledge of the event.

7.3. Clinical Laboratory Evaluations

Blood and urine samples will be collected for clinical laboratory evaluations at the times indicated in the Schedule of Assessments in Appendix 4. Clinical laboratory evaluations are as listed in Appendix 2. Additional clinical laboratory evaluations will be performed at other times if judged to be clinically appropriate or if the ongoing review of the data suggests a more detailed assessment of clinical laboratory safety evaluations is required.

Screening/Baseline laboratory tests will be assessed by a local laboratory for eligibility criteria and a central laboratory. An Investigator (or designee) will perform a clinical assessment of all reported clinical laboratory data.

7.4. Vital Signs, Physical Examination, and Other Safety Evaluations

7.4.1. Vital Signs

Pulse oximetry will be measured as a safety assessment, with saturation <90% triggering a telemedicine assessment.

7.4.2. Physical Examination

Not applicable.

7.5. Pharmacokinetic Assessments

Dalcetrapib concentrations will be determined in the PK samples collected according to the Schedule of Assessments (Appendix 4).

Samples will be collected, labelled, stored, and shipped as detailed in the Laboratory Manual. Full details of the analytical method used will be described in a separate Bioanalytical Validation Report.

8. SAMPLE SIZE AND DATA ANALYSES

8.1. Determination of Sample Size

The purpose of the proof-of-concept study is to identify whether there is sufficient promise of efficacy to justify conducting a Phase 3 study in a larger sample size and to determine efficacious dose to be used in Phase 3. While the entirety of data will be considered at the end of study, the sample size has been chosen to ensure that a positive trend will be present with alpha of 0.2 when considering the two highest doses combined compared to placebo. One-hundred twenty-seven (127) resolution events provides 80% power to demonstrate a positive trend if the average HR of the two dalcetrapib groups is 1.4 relative to placebo. Allowing for 20% of patients not resolving, 208 patients (52 per treatment arm) will be enrolled. One interim analysis will be conducted once 97 resolution events have occurred to allow 73 resolution events to have occurred in the two highest dose levels and placebo arm. At the interim analysis, if the average HR of the two highest dose levels relative to placebo is greater than 1.45, the study will stop due to efficacy and the program will be able to proceed directly to Phase 3. At the interim analysis, if the average HR of the two highest dose levels relative to placebo is between 1.0 and 1.45, the study will continue enrollment until 169 resolution events have occurred. At the interim analysis, if the average HR of the two highest dose levels is less than 1.0, the study will be stopped for lack of efficacy. The final analysis will be performed at an alpha of 0.186. These boundaries were determined by setting the efficacy boundary to follow the power family boundary with $\rho=2$ and the futility boundary is manually set to HR=1.

8.2. Analysis Populations

8.2.1. Intent-to-Treat Population

The Intent-To-Treat Population will include all participants who received at least 1 dose of study drug. Participant data will be summarized by treatment assigned.

8.2.2. Per Protocol Population

The Per Protocol (PP) Population will include all participants from the ITT population who have no important study protocol deviations during the study and who received at least 1 dose of study drug. Patients with any important protocol deviations shall be excluded from the PP population prior to database lock.

8.2.3. Safety Population

The Safety Population will include all participants who received at least 1 dose of study drug. Participant data will be summarized by actual treatment received.

8.2.4. Pharmacokinetic Population

The PK Population will include all participants who received at least 1 dose of study drug, had at least one measurable plasma concentrations, and had no protocol deviations thought to impact the PK of study drug.

8.3. General Considerations

Continuous variables will be summarized by the standard descriptive statistics: number of patients (n), mean, standard deviation, median, minimum, and maximum for baseline variables, and n, mean, standard error, and confidence interval (CI) for outcome measures. Frequency of patient or events and percentages will be summarized for categorical variables. Time to event variables will be summarized using Kaplan-Meier methods.

Unless otherwise specified, all regression models will be stratified by maximum symptom severity at baseline (presence vs absence of moderate or severe symptoms) and by age (≤65 years vs >65 years), and Wald p-values will be considered primary.

The statistical analysis plan will be finalized prior to unblinding and it will include a more technical and detailed description of the statistical analyses.

8.4. Efficacy Analysis

The analysis of treatment efficacy will be based on the Intent-to-Treat Population. The PP population will be used for secondary analysis. This section is a summary of the planned efficacy analyses of the most important efficacy endpoints including primary and key secondary efficacy endpoints.

8.4.1. Analysis of Primary Endpoints

The primary analysis will be conducted when all patients have either withdrawn from the study, died, or been followed for at least 28 days (±2 days) since first dose on Day 1.

8.4.1.1. Time to Sustained Clinical Resolution

The primary endpoint is time to sustained clinical resolution as determined by symptom score. Sustained clinical resolution is defined in Section 7.1.1. The primary analysis of this endpoint will be performed on the ITT population. Time to sustained clinical resolution will be summarized by treatment group using Kaplan-Meier methods. Median and associated 95% CI, 25-75 percentiles, and minimum and maximum values will be presented. The number and percentage of patients whose symptoms resolved, and patients censored will be presented.

The differences in time to sustained clinical resolution between the treatment groups will be evaluated using a 2-sided log-rank test, stratified for baseline symptom severity (presence vs absence of moderate or severe symptoms) and by age (≤65 years vs >65 years). The combined two highest treatment groups will be compared to placebo in addition to the comparison of individual doses.

8.4.2. Analysis of Secondary Efficacy Endpoints

8.4.2.1. Time to Complete Clinical Resolution

Time to complete clinical resolution will be analyzed using the same model as time to sustained clinical resolution, but with all symptoms required to have resolved to a score of 0 rather than 1.

8.4.2.2. Change from Baseline in COVID-19 Symptom Severity Score

COVID-19 total symptom severity score will be summarized by treatment group using descriptive statistics (N, mean, median, standard deviation, minimum, and maximum) for each visit as well as for changes from baseline (N, mean, standard error, CI). A Mixed-Effect Model Repeated Measure (MMRM) will be performed to analyze the average difference between treatment groups over 28 days and at the designated assessment days.

8.4.2.3. Scoring of WHO Clinical Outcome Scale (9-point Scale)

The number and percentage of patients for each WHO clinical outcome score will be summarized. An ordinal logistic regression analysis for the specified time points will be presented as odds ratio, with associated 95% CI and p-value.

8.4.2.4. Rate of Hospitalization Through Day 28

The analysis of this endpoint will be performed on the ITT population. The number and percentage of patients who were hospitalized and reason for hospitalized will be presented. The percentage of patients who were hospitalized will be compared using a logistic regression analysis for specified time points. The results will be presented as odds ratios, with associated 95% CIs and p-value.

8.4.2.5. Rate of Progression to Oxygen Therapy Through Day 28

The analysis of this endpoint will be performed on the ITT population. The number and percentage of patients who progress to oxygen therapy and type of oxygen therapy will be presented. The percentage of patients who had progressed to oxygen therapy will be compared using a logistic regression analysis for specified time points. The results will be presented as odds ratios, with associated 95% CIs and p-value.

8.4.2.6. Duration of Hospitalization

The duration of hospitalization will be performed on the ITT population. Duration of hospitalization will be summarized by treatment group using descriptive statistics (N, mean, median, standard deviation, standard error, CI, minimum, and maximum). Linear regression will be performed to analyze the difference between treatment groups. The results will be presented as mean treatment difference with associated 95% CI and p-value.

8.4.2.7. Mortality Rate

The analysis of this endpoint will be performed on the ITT population. The number and percentage of patients who died and reason for death will be presented. The percentage of patients who died will be compared using a logistic regression analysis for specified time points. The results will be presented as odds ratios, with associated 95% CIs and p-values.

8.4.2.8. Time to Viral Clearance Based on PCR Test for SARS-CoV-2

The time to viral clearance based on PCR test for SARS-CoV-2 will be performed on the ITT population. Time to viral clearance will be summarized by treatment group using Kaplan-Meier methods. Median and associated 95% CI, 25-75 percentiles, and minimum and maximum values will be presented. The number and percentage of patients who do not show virus, show virus, and patients censored will be presented.

8.4.2.9. Change from Baseline in log10 Viral Load

The change from baseline in log10 viral load will be assessed at specified time points by a MMRM. Patients who have achieved a level below the limit of detection will be included in the analysis at half the lower limit of detection. For this endpoint, Last Observation Carried Forward (LOCF) will be used to impute values for all patients. The treatment effect for the difference at each time point, and the average slope up to each time point for each treatment group will be presented along with a 95% CI.

8.5. Safety Analysis

Safety variables include incidence of AEs (or TEAEs), laboratory test results, and vital signs. All safety analyses will be based on the Safety Population. No formal statistical analysis of the safety data will be performed.

Adverse events will be coded according to MedDRA, version 23.0 released 19 Apr 2020 (exclusively meant for COVID-19) or later.

The number and percentage of patients with TEAEs, SAEs, TEAEs related to study treatment, SAEs related to study treatment, TEAEs leading to treatment discontinuation, TEAEs leading to study discontinuation, and TEAEs leading to death will be summarized by SOC, preferred term (PT), and treatment group. In addition, the severity of TEAEs and relationship to study treatment will be summarized by SOC, PT, and treatment group.

The AE summary tables will include counts of patients. Therefore, if a patient experiences more than 1 episode of a particular AE, the patient will be counted only once for that event. If a patient has more than one AE that is coded to the same PT, the patient will be counted only once for that PT. Similarly, if a patient has more than 1 AE within a SOC, the patient will be counted only once in that SOC.

Test values and change from baseline will be summarized descriptively by treatment group for specific laboratory test results and vital signs. Where applicable, shift tabulations will be presented for specific laboratory test results by treatment group. Where applicable, number and frequency of clinically significant abnormal values for specific laboratory test results will be presented.

Pregnancy test results and patients with confirmed positive pregnancy test result will be listed.

8.6. Pharmacokinetic Analysis

Pharmacokinetic parameters will be determined using population PK modeling approach. The sparse PK samples will be pooled with PK data from other clinical studies for population PK analysis. PK profiles will be predicted and subsequently PK parameters will be estimated. Correlations between PK and pharmacodynamic (efficacy or safety) may be explored, including the relationship between drug exposure and viral elimination dynamics, if data permit. The methodology for PK analysis will be documented in a PK Analysis and Reporting Plan outside of this protocol.

8.7. Interim Analysis

One interim analyses will be conducted when 97 resolution events have occurred.

8.8. Handling of Missing Data

8.8.1. Imputation

Severity Symptom Score: Missing values on severity symptom score will not be imputed. Where a patient has died, their status will not be considered missing, but will be imputed with maximum severity score at each timepoint.

Clinical Outcome Scale: Missing values on clinical outcome scale will not be imputed. Where a patient has died, their status will not be considered missing, but will be imputed with maximum clinical outcome scale at each timepoint.

8.8.2. Censoring

Severity Symptom Score: For time to resolution, a patient will be censored if the patient has not had the required timepoint assessment if not due to death. If patient has died or received another antiviral therapy prior to the assessment endpoint, then the patient will be considered as having a moderate or severe COVID-19 symptom for all COVID-19 symptoms and imputed to maximum severity score at the assessment day.

Viral Clearance: For time to viral clearance, a patient will be censored if the patient has not had the required timepoint assessment.

8.9. Multiplicity/Multiple Testing

The primary analysis compares the combined two highest dalcetrapib dose groups against placebo as well as each treatment group individually. For the purposes of inference, if the test of the combined two highest dose groups against placebo is significant at two-sided alpha of 0.05, then the individual doses will be compared against placebo following the Hochberg step-up procedure at two-sided alpha of 0.05.

9. REFERENCES

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10. APPENDICES

Appendix 1 – Adverse Event Definitions

Definitions

An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. This includes the following:

- Any clinically significant worsening of a pre-existing condition.
- Note: Emergence of a new pathogen associated with a clinical event during therapy at a site other than the initial site of infection will be considered to be an AE.
- Any recurrence of a pre-existing condition.
- An AE occurring from overdose of a Sponsor study drug whether accidental or intentional (i.e., a dose higher than that prescribed by a health care professional for clinical reasons).
- An AE occurring from abuse of a Sponsor study drug (i.e., use for nonclinical reasons).
- An AE that has been associated with the discontinuation of the use of a Sponsor study drug.

Note: A procedure is not an AE, but the reason for a procedure may be an AE.

A pre-existing condition is a clinical condition (including a condition being treated) that is diagnosed before the patient signs the ICF and that is documented as part of the patient's medical history.

The questions concerning whether the condition existed before the start of the active phase of the study and whether it has increased in severity and/or frequency will be used to determine whether an event is a treatment-emergent AE. An AE is considered to be treatment-emergent if (1) it is not present when the active phase of the study begins and is not a chronic condition that is part of the patient's medical history, or (2) it is present at the start of the active phase of the study or as part of the patient's medical history, but the severity or frequency increases during the active phase. The active phase of the study begins at the time of the first dose of the study drug. The active phase of the study ends at the Follow-up/EOS.

Reporting of Adverse Events

At each visit the Investigator, or delegate, will determine whether or not any AEs have occurred. Non-leading questions such as "How are you feeling today?" or "Have you had any health concerns since your last visit?" should be used to elicit the patient to report any possible AEs. If any AEs have occurred, they will be recorded in the AE section of the electronic Case Report Form (eCRF) and in the patient's source documents. If known, the diagnosis should be recorded, in preference to listing the individual signs and symptoms.

Adverse event reporting begins from the time of informed consent and ends 30 days after the last dose of study drug.

Assessment of Severity

The Investigator will be asked to provide an assessment of the severity of the AE using the following categories:

- **Mild**: Usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
- **Moderate**: Usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the patient.
- **Severe**: Interrupts usual activities of daily living, significantly affects clinical status, or may require intensive therapeutic intervention.

Relationship to Study Treatment

The Investigator will make a determination of the relationship of the AE to the study drug using a four-category system according to the following guidelines:

- **Not related**: when the AE is definitely caused by the patient's clinical state, or the study procedure/conditions.
- **Unlikely Related**: when the temporal association between the AE and the drug is such that the drug is not likely to have any reasonable association with the AE.
- **Possibly Related**: when the AE follows a reasonable temporal sequence from the time of drug administration but could have been produced by the patient's clinical state or the study procedures/conditions.
- **Related**: when the AE follows a reasonable temporal sequence from administration of the drug, abates upon discontinuation of the drug, follows a known or hypothesized cause-effect relationship, and (if appropriate) reappears when the drug is reintroduced.

Action Taken for Adverse Events

The Investigator or designee will record the action taken for the AE in the eCRF. Actions taken will include:

- **Dose increased**: The medication schedule was modified by addition, either by changing the frequency, strength, or amount.
- **Dose not changed**: The medication schedule was not changed.

- **Dose reduced**: The medication schedule was modified by subtraction, either by changing the frequency, strength, or amount.
- **Drug interrupted**: The medication schedule was modified by temporarily terminating the prescribed regimen of medication.
- **Drug withdrawn**: The medication schedule was modified through termination of the prescribed regimen of medication.
- **Not applicable**
- **Unknown**

Follow-up of Adverse Events

All (S)AEs that are ongoing at the time of discontinuation, or that develop prior to the final follow-up telephone call, will be followed for 28 days, or until resolution or stabilization.

Adverse Drug Reactions

All noxious and unintended responses to an investigational medicinal product (i.e., where a causal relationship between an investigational medicinal product and an AE is at least a reasonable possibility) related to any dose should be considered adverse drug reactions.

For marketed medicinal products, a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of diseases or for modification of physiological function, is to be considered an adverse drug reaction.

An unexpected adverse drug reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g., Investigator's Brochure for an unapproved IMP).

Serious Adverse Events

An SAE is any AE occurring at any dose that meets 1 or more of the following criteria:

- Results in death
- Is life-threatening (see below)
- Requires patient hospitalization or prolongation of an existing hospitalization (see below)
- Results in a persistent or significant disability or incapacity (see below)
- Results in a congenital anomaly or birth defect
- Results in an important medical event (see below)

Additionally, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered SAEs when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not require hospitalization, or development of drug dependency or drug abuse.

A ***life-threatening adverse event*** is any AE that places the patient at immediate risk of death from the event as it occurred. A life-threatening event does not include an event that might have caused death had it occurred in a more severe form but that did not create an immediate risk of death as it actually occurred. For example, drug-induced hepatitis that resolved without evidence of hepatic failure would not be considered life-threatening, even though drug-induced hepatitis of a more severe nature can be fatal. Hospitalization is to be considered only as an overnight admission.

Hospitalization or prolongation of a hospitalization is a criterion for considering an AE to be serious. In the absence of an AE, the participating Investigator should not report hospitalization or prolongation of hospitalization. This is the case in the following situations:

- Hospitalization or prolongation of hospitalization is needed for a procedure required by the protocol. Day or night survey visits for biopsy or surgery required by the protocol are not considered serious.

- Hospitalization or prolongation of hospitalization is part of a routine procedure followed by the study center (e.g., stent removal after surgery). This should be recorded in the study file.

- Hospitalization for survey visits or annual physicals fall in the same category.

In addition, a hospitalization planned before the start of the study for a pre-existing condition that has not worsened does not constitute an SAE (e.g., elective hospitalization for a total knee replacement due to a pre-existing condition of osteoarthritis of the knee that has not worsened during the study).

Disability is defined as a substantial disruption in a person's ability to conduct normal life functions (i.e., the AE resulted in a significant, persistent, or permanent change, impairment, damage, or disruption in the patient's bodily function/structure, physical activities, or quality of life).

Medical and scientific judgment should be exercised in deciding whether a case is serious in those situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability, or incapacity. These include events that may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. Such events should usually be considered as serious.

Appendix 2 – Clinical Laboratory Evaluations

The following clinical laboratory analytes will be assessed:

Chemistry(Chem-20):	Hematology (CBC):
Albumin	Hematocrit
Alkaline phosphatase	Hemoglobin
ALT	MCH
AST	MCHC
Blood urea nitrogen	MCV
Calcium	Platelet count
Chloride	Red blood cell (RBC) count
Cholesterol	White blood cell (WBC) count
Creatinine	WBC differential
Gamma glutamyl transferas	(Percent and Absolute):
Glucose	Basophils
Lactate dehydrogenase	Eosinophils
Phosphorus	Lymphocytes
Potassium	Monocytes
Sodium	Neutrophils
Total Bilirubin	
Total CO_2 (measured as bicarbonate)	For women of childbearing potential only:
Total Protein	Urine Pregnancy Test
Triglycerides	
Uric acid	

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; CBC = complete blood count; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume

Appendix 3 – Regulatory, Ethical, and Study Oversight Considerations

Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences International Ethical Guidelines
- Applicable International Council for Harmonisation (ICH) Good Clinical Practice (GCP) Guidelines
- Applicable laws and regulations

The protocol, protocol amendments, Informed Consent Form (ICF), Investigator's Brochure, and other relevant documents (e.g., advertisements) must be submitted to an Institutional Review Board (IRB)/EC by the Investigator and reviewed and approved by the IRB/EC before the study is initiated.

- Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The Investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulations (CFR), ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

Finances and Insurance

Financing and insurance will be addressed in a separate agreement.

Informed Consent

Prior to starting participation in the study, each patient will be provided with a study-specific ICF giving details of the study drugs, procedures, and potential risks of the study. Patients will be instructed that they are free to obtain further information from the Investigator (or designee) and that their participation is voluntary and they are free to withdraw from the study at any time.

Patients will be given an opportunity to ask questions about the study prior to providing consent for participation.

Electronic informed consent will be obtained from the patients or their legally authorized representative that meets the requirements of local regulations, ICH guidelines, and the IRB/EC or study center, where applicable. The patient will be given a copy of the electronic informed consent, and the original will be maintained with the patient's records.

Patients must be re-consented to the most current version of the ICF(s) during their participation in the study.

Patient Data Protection

Patients will be assigned a unique identifier and will not be identified by name in electronic Case Report Forms (eCRFs), study-related forms, study reports, or any related publications. Patient and Investigator personal data will be treated in compliance with all applicable laws and regulations. In the event the study protocol, study report, or study data are included in a public registry, all identifiable information from individual patients or Investigators will be redacted according to applicable laws and regulations.

The patient must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the patient. The patient must also be informed that his/her medical records may be examined by Sponsor or CRO auditors or other authorized personnel appointed by the **S**ponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

Committees Structure

A DMC will review safety data throughout the study. The DMC will review efficacy data as detailed in the protocol and DMC Charter.

Disclosure

All information provided regarding the study, as well as all information collected and/or documented during the course of the study, will be regarded as confidential. The Investigator (or designee) agrees not to disclose such information in any way without prior written permission from the Sponsor.

Data Quality Assurance

The following data quality steps will be implemented:

- All patient data relating to the study will be recorded on eCRFs unless directly transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by electronically signing the eCRF.

- The Investigator must maintain accurate documentation (source data) that supports the information entered in the eCRF.

- The Investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents.

- The Sponsor or designee is responsible for the data management of this study including quality checking of the data. Pre-defined, agreed risks, monitoring thresholds, quality tolerance thresholds, controls, and mitigation plans will be documented in a risk management register. Additional details of quality checking to be performed on the data may be included in a Data Management Plan.

- Study monitors will perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of patients are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

- Records and documents, including electronic informed consent, pertaining to the conduct of this study must be retained by the Investigator in accordance with 21 CFR 312.62(c) (US site) or in the study site archive for at least 5 years after the end of the study (UK site) unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

Investigator Documentation Responsibilities

All individual, patient-specific study data will be entered into a 21 CFR Part 11-compliant electronic data capture system on an eCRF in a timely fashion. All data generated from external sources (e.g., central laboratory, pharmacokinetics, pharmacodynamics, electrocardiogram central readers) and transmitted to the Sponsor or designee electronically will be integrated with the patient's eCRF data in accordance with the Data Management Plan.

An eCRF must be completed for each patient who signs an ICF and undergoes any pre-screening or screening procedures, according to the eCRF completion instructions. The Sponsor, or CRO, will review the supporting source documentation against the data entered into the eCRFs to verify the accuracy of the electronic data. The Investigator will ensure that corrections are made to the eCRFs and that data queries are resolved in a timely fashion by the study staff.

The Investigator will sign and date the eCRF via the electronic data capture system's electronic signature procedure. These signatures will indicate that the Investigator reviewed and approved the data on the eCRF, the data queries, and the site notifications.

Publications

If on completion of the study the data warrant publication, the Investigator may publish the results in recognized (refereed) scientific journals subject to the provisions of the clinical study agreement. Unless otherwise specified in the clinical study agreement, the following process shall occur:

The institution and Investigator shall not publish or present data from an individual study center until the complete multicenter study has been presented in full or for 2 years after the termination of the multicenter study, whichever occurs first. Subsequent publications must refer to the multicenter findings. Thereafter, if the Investigator expects to participate in the publication of data generated from this site, the institution and Investigator shall submit reports, abstracts, manuscripts, and/or other presentation materials to the Sponsor for review before submission for publication or presentation. The Sponsor shall have 60 days to respond with any requested revisions, including (without limitation) the deletion of confidential information. The Investigator shall act in good faith upon requested revisions, except the Investigator shall delete any confidential information from such proposed publications. The Investigator shall delay submission of such publication or presentation materials for up to an additional 90 days in order to have a patent application(s) filed.

Appendix 4 – Schedule of Assessments

Table 5: Schedule of Assessments

Study Period	Screening/ Baseline	Treatment Period					Follow-up Visit 1	Follow-up/EOS Visit 2
Study Day	**-2 to -1[a]**	**1**	**3**	**5**	**7**	**EOT 10**	**14 ± 2 days**	**28 ± 2 days**
Informed consent	X							
Randomization[b]	X							
Inclusion/exclusion criteria	X	X						
SARS-CoV-2 test[c]	X							
Demographics	X							
Medical history	X							
Pregnancy test (urine)	X							X
COVID-19 symptoms ePRO assessment[d]	X	X	X	X	X	X	X	X
Efficacy								
Clinical improvement score (WHO COVID-19 Clinical Improvement Ordinal Scale)[e]	X	X	X	X		X		X
Confirm setting (outpatient, in hospital)	X		X		X		X	X
Saliva (Oragene)[f]	X	X	X	X	X	X		X
Mid-turbinate nasal swab[f]	X	X	X	X	X	X		X
Safety								
Adverse events	X	X	X	X	X	X	X	X
Blood sampling for laboratory assessments	X					X		X
Pulse oximetry	X	X	X	X	X	X	X	X
Prior and concomitant medications	X	X	X	X	X	X	X	X
Pharmacokinetics								
PK sampling[g]						X		
Other								
Patient training on use of ePRO and pulse oximeter and swab self-collection	X							
Dispense study drug	X							
Study drug administration[h]		X	X	X	X	X		
Return unused treatment		X[i]				X		

COVID-19 = Coronavirus disease of 2019; EOS = end of study; EOT = end of treatment; PCR = polymerase chain reaction; PK=pharmacokinetic; ePRO = electronic patient-reported outcome; SARS-CoV-2= Severe Acute Respiratory Syndrome CoronaVirus 2; WHO = World Health Organization

Note that any visits other than Screening/Baseline may be conducted via telephone or digital media. Missed samples/assessments when phone visits occur will not be counted as protocol deviations. Safety laboratory samples for hematology and chemistry, and study drug accountability, are obtained via a site visit or home visit by a healthcare professional.

a. Screening/Baseline assessments may all be performed on the same calendar day and should be performed at the study site or as a home visit within 72 hours of first dose. Baseline assessments that are also performed at Screening do not need to be repeated if on the same calendar day. Study drug should be dispensed at the Screening/Baseline visit and only taken after the Day 1 virtual visit confirming the positive COVID-19 test has occurred. If the PCR test is negative or laboratory results exclude the patient, they will not to take the first dose of study drug and be withdrawn from the study.
b. Patients will be randomized to receive either 900, 1800, or 3600 mg of dalcetrapib treatment or placebo.
c. The entry testing is performed locally based on testing methods available at the site, such as PCR or rapid antigen test.
d. Patients must have at least two mild to moderate signs or symptoms of COVID-19, as described in the inclusion criteria, with onset within 5 days of first dose on Day 1. Symptoms will be assessed daily for the first 10 days, then at Day 14 and Day 28 and as clinically indicated.
e. Dates of change in WHO scale status between visits will be recorded over the course of the 28-day study period.
f. SARS-CoV-2 viral loads will be obtained by both saliva (Oragene) and mid-turbinate nasal swab self-collected under supervision of a healthcare professional at Screening/Baseline, Day 1, Day 3, Day 5, Day 7, Day 10, and Day 28.
g. Two PK samples will be collected on Day 10, one at predose and one at postdose in a sampling window of 0-2, 2-4, 4-6, 6-10, or 10-24 hours postdose. Patients will be evenly randomized to one of the sampling windows on Day 10.
h. Study drug is self-administered as once daily oral tablets on Days 1 to 10.
i. In case of screen failure only.

Appendix 5 – Contraceptive Guidance

Definitions

Female Patients of Childbearing Potential: Premenopausal female study patients who are anatomically and physiologically capable of becoming pregnant following menarche.

Female Patients of Nonchildbearing Potential:

1. **Surgically sterile:** Female study patients who are permanently sterile via hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy by reported medical history and/or medical records. Surgical sterilization to have occurred a minimum of 6 weeks, or at the Investigator's discretion, prior to screening.
2. **Postmenopausal:** Female study patients who are at least 1 year postmenopausal.

Fertile male: A male that is considered fertile after puberty.

Infertile male: Permanently sterile male via bilateral orchiectomy.

Contraception Guidance

Female Patients

Female patients who are of nonchildbearing potential will not be required to use contraception. Female patients of childbearing potential must be confirmed as not being pregnant at Screening/Baseline and be willing to use an acceptable highly-effective method of birth control from the time of informed consent until 90 days after the last dose of study treatment. Acceptable methods of contraception include:

- Hormonal injection (as prescribed)
- Combined oral contraceptive pill or progestin/progestogen-only pill (as prescribed)
- Combined hormonal patch (as prescribed)
- Combined hormonal vaginal ring (as prescribed)
- Surgical method performed at least 90 days prior to the screening visit:
    - Bilateral tubal ligation
    - Essure (hysteroscopic bilateral tubal occlusion) with confirmation of occlusion of the fallopian tubes
- Hormonal implant
- Hormonal or nonhormonal intrauterine device
- Vasectomized male partner (sterilization performed at least 90 days prior to the screening visit) with verbal confirmation of surgical success, and the sole partner for the female patient.

Female patients of childbearing potential should refrain from donation of ova from the first dose through 90 days after the last dose of study treatment.

Male Patients

Male patients (even with a history of vasectomy) with partners of childbearing potential must use a male barrier method of contraception (i.e., male condom with spermicide) in addition to a second highly effective method of acceptable contraception from the first dose through 90 days after the last dose of study treatment. Acceptable methods of contraception for female partners include:

- Hormonal injection
- Combined oral contraceptive pill or progestin/progestogen-only pill
- Combined hormonal patch
- Combined hormonal vaginal ring
- Surgical method (bilateral tubal ligation or Essure [hysteroscopic bilateral tubal occlusion])
- Hormonal implant
- Hormonal or nonhormonal intrauterine device.

An acceptable second method of contraception for male patients is vasectomy that has been performed at least 90 days prior to the screening visit, with verbal confirmation of surgical success.

For male patients (even with a history of vasectomy), sexual intercourse with female partners who are pregnant or breastfeeding should be avoided unless condoms are used from the first dose until 90 days after the last dose of study treatment. Male patients are required to refrain from donation of sperm from the first dose through 90 days after the last dose of study treatment.

Sexual Abstinence and Same-sex Relationships

Patients who practice true abstinence, because of the patient's lifestyle choice (i.e., the patient should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception. If a patient who is abstinent at the time of informed consent becomes sexually active, he or she must agree to use contraception as described previously.

For patients who are exclusively in same-sex relationships, contraceptive requirements do not apply. If a patient who is in a same-sex relationship at the time of informed consent becomes engaged in a heterosexual relationship, he or she must agree to use contraception as described previously.