Protocol

A Phase 2, Double-blind, Placebo-controlled, Efficacy, and Safety Study of APX-115 in Hospitalized Patients with Confirmed Mild to Moderate COVID-19

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Sponsor Reference: A01-115-03 [redacted]

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SPONSOR APPROVAL

I have read the following and approve it:

[redacted]

INVESTIGATOR AGREEMENT

I have read the following protocol and agree to conduct the study as described herein.

Signature	Date
Name, Qualifications	Position in Organization
Institution	

SYNOPSIS

Title of study:

A Phase 2, Double-blind, Placebo-controlled, Efficacy, and Safety Study of APX-115 in Hospitalized Patients with Confirmed Mild to Moderate COVID-19

Indication: Coronavirus disease of 2019 (COVID-19)

Number of investigators and study centers:

Approximately 12 sites in the United States; other countries based on the pandemic situation.

Development Phase: 2

Objectives:

The primary objective of the study is:

- to assess the safety and tolerability of APX-115 active doses compared to placebo following multiple oral dosing in hospitalized patients with confirmed, mild to moderate, symptomatic COVID-19.

The secondary objectives of the study are:

- to evaluate the efficacy of APX-115 active doses compared to placebo following multiple oral dosing in hospitalized patients with confirmed, mild to moderate, symptomatic COVID-19
- to assess the pharmacokinetics (PK) of APX-115 in a subset of 20 patients.

The exploratory objective of the study is:

- to evaluate the response of biomarkers to APX-115 active doses compared to placebo following multiple oral dosing in hospitalized patients with confirmed, mild to moderate, symptomatic COVID-19
- to evaluate change from baseline in viral load and rate of switch to other treatments

Methodology/study design:

This will be a Phase 2, randomized, double-blind, placebo-controlled, multicenter, efficacy, and safety study in hospitalized patients with confirmed, mild to moderate, symptomatic COVID-19. Pharmacokinetic assessment will be performed in a subset of 20 patients.

The study will consist of a sentinel cohort of 30 patients (15 patients on active drug and 15 patients on placebo) and an expansion cohort of approximately 50 patients (in a 1:1 ratio of APX-115 or placebo). Enrollment will pause after the 30th patient in the sentinel cohort has been enrolled and started treatment, until the results of the interim analysis are known. Once either 25 patients have recovered, or the 30th patient in the sentinel cohort has completed 14 days of treatment, an unblinded Data Monitoring Committee (DMC) will assess the safety, tolerability, efficacy, and PK [redacted] once daily (QD) APX-115 in COVID-19 patients in the sentinel cohort. The DMC will issue a recommendation to enroll patients for the expansion cohort, or to stop the study depending on the safety and futility assessment. 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 prior to start of patient enrollment.

Informed consent must be obtained from all patients or their legally authorized representative during screening (up to 4 days, maximum, before dosing) and before any study-related procedures are performed.

Patients will be randomized within 14 days after a laboratory-confirmed Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection as determined by real time

reverse transcription (RT)-polymerase chain reaction (PCR) or other commercial or public health assay authorized by Food and Drug Administration (FDA) or other applicable health authority. Patients need to have at least one symptom of COVID-19 (fever, cough, shortness of breath, myalgia [muscle or body aches], ageusia [loss of taste], anosmia [loss of smell], fatigue, or weakness) at screening.

Patients will receive an oral dose [redacted] APX-115 or placebo capsules QD for 14 consecutive days. Patients will undergo assessments during hospitalization or could be discharged after the start of study treatment as early as Day 2 if judged to be ready for discharge. Eligible patients must be in hospital for at least 24 hours after start of study treatment. If discharged, patients will then be requested to take study treatment at home (as prescribed) up to and including Day 14. Study drug will be administered in a fasted state at approximately the same time in the morning, at least 2 hours after a morning meal if a morning meal is consumed, on Days 1 to 14.

If the patient has already been discharged, a telephone or digital media visit will be conducted on days for which no laboratory assessments are required (Days 3, 10, 22, 29, and 60) and an at-home or an on-site visit will be required on days requiring laboratory assessments (Days 5 and 14).

Allowable windows for scheduling of study visits are -1 day for Day 3, ±1 day for Day 5, and ±2 days for Days 10, 22, 29, and 60. The Day 14 visit may be scheduled up to 2 days past the actual Day 14 date; however, dose administration will end at Day 14.

Symptoms will be documented daily through Day 60 using an electronic patient-reported outcome (ePRO) instrument based on the September 2020 FDA guidance for assessing COVID-19-related symptoms. All patients will be closely monitored for adverse events (AEs) from informed consent through Day 60, and followed for safety assessments through Day 60. SARS-CoV-2 viral loads will be obtained by [redacted]) self-collection at baseline (Day 1) and Days 5 and 14. Any new infections that occur in the study, regardless of organism (ie, viral or non-viral), will be captured. Additionally, the site of infection and source of culture (bronchoalveolar lavage, tracheal aspirate, sputum, blood, urine, etc.) will also be recorded.

Oxygen saturation (SpO2) will be collected daily in the hospital or self-collected daily upon discharge until end of study using ePRO. Clinical improvement based on the World Health Organization (WHO) Clinical Improvement Ordinal Scale (9-point scale) will be documented based on scores obtained daily while hospitalized, the day after hospital discharge via telephone contact with the patient, at the scheduled visit(s) after hospital discharge, and if the patient is readmitted to the hospital or dies.

Blood samples for analysis of APX-115 in plasma will be collected from 20 patients at prespecified timepoints in hospitalized patients only.

Number of patients:

It is anticipated that approximately 80 patients will be randomized into the study in a 1:1 ratio to [redacted] APX-115 or placebo:

- 30 patients in the sentinel cohort (15 patients on active drug and 15 patients on placebo)
- Approximately 50 patients in the expansion cohort (1:1 ratio [redacted] APX-115 or placebo)

Determination of sample size:

The study does not test a formal hypothesis and instead uses descriptive statistics to summarize the data. Therefore, the sample size was not determined based on formal statistical power

calculations but using clinical considerations to provide a reasonable clinical database to assess safety and efficacy in COVID-19 patients. However, the ability of the study to identify a potentially promising treatment was assessed by considering that further study would likely be dependent on observing at least a numeric trend towards benefit of the treatment. On the key secondary endpoint of time to clinical recovery, a sample size of 80 patients provides 91% power to ensure that the outcome is numerically in favor of treatment if the true treatment effect is a hazard ratio of 1.4. This calculation assumes one interim analysis at [redacted] information, a median time to recovery of 14 days in the control arm, and a follow-up time for each patient capped at 28 days. For the purposes of estimating power, it is assumed that the DMC would be unlikely to recommend stopping the study for efficacy unless there was a significant detrimental effect of treatment, simulated by the O'Brien-Fleming rule for futility.

Diagnosis and criteria for inclusion and exclusion:

Patients must satisfy all of the following criteria:

1. Willing and able to provide informed consent themselves or through their legally authorized representative.
2. Male or female patients, of any race or ethnicity, 18 to 80 years of age, inclusive, on the day of informed consent. Racial and ethnic minorities should be included in the study population to the greatest extent possible.
3. Laboratory-confirmed SARS-CoV-2 infection as determined within 14 days of randomization by real time RT-PCR or other commercial or public health assay authorized by FDA or other applicable health authority .
4. Onset of COVID-19 symptoms within 14 days prior to randomization.
5. Have at least one of the following symptoms at screening: fever, cough, shortness of breath, myalgia, ageusia, anosmia, fatigue, or weakness.
6. Hospitalized with COVID-19 disease (WHO COVID-19 Clinical Improvement Ordinal Scale score of 3 [hospitalized, no oxygen therapy], 4 [hospitalized, oxygen by mask or nasal prongs], or 5 [high-flow oxygen or non-invasive mechanical ventilation])

   Note: Hospitalized patients can also include patients admitted to centers conditioned as hospitals to treat COVID-19 patients.
7. 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 informed consent form.

Patients will be excluded from the study if any of the following criteria are applicable:

1. Females who are pregnant (negative pregnancy test required for all women of childbearing potential at screening) or breastfeeding.
2. Male patients and women of childbearing potential (women who are not surgically sterile or postmenopausal defined as postmenopausal for >12 months) who are not using at least one protocol-specified method of contraception.
3. COVID-19 disease as defined by the WHO COVID-19 Clinical Improvement Ordinal Scale, scores of 6 (intubation and mechanical ventilation) or 7 (ventilation + additional organ support - pressors, renal replacement therapy, extracorporeal membrane oxygenation).
4. Expected survival less than 72 hours.
5. Treatment with other drugs thought to possibly have activity against SARS-CoV-2 infection within 7 days or within 5 half-lives, whichever is longer, prior to enrollment

or concurrently. Drugs that have received FDA emergency use authorization or COVID-19 approval are allowed.

6. Treatment with immunosuppressants, combination of 2 or [redacted]
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 (eg, for organ transplantation or autoimmune conditions).
10. Known renal disease [redacted]
11. Patients with clinically apparent liver disease (eg, jaundice, cholestasis, hepatic synthetic impairment, or active hepatitis) or moderate or severe hepatic impairment as determined by Child-Pugh score Class B or C.
12. Alanine aminotransaminase (ALT) or aspartate aminotransaminase (AST) >3 × upper limit of normal (ULN) AND total bilirubin levels >2 × ULN OR ALT or AST >5 × ULN.
13. Total bilirubin >1.5 × ULN, unless the patient has known Gilbert's syndrome.
14. Hemoglobin <9 g/dL for females or <11 g/dL for males.
15. Absolute neutrophil count <1500/mm^3.
16. Thrombocytopenia (platelets count <100 × 10^9/L).
17. Inability to swallow oral medications or a gastrointestinal disorder with diarrhea (eg, Crohn's disease) or malabsorption at screening.
18. 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.
19. History of an allergic reaction or hypersensitivity to the study drug or any component of the study drug formulation.

Investigational product, dose, and mode of administration:

APX-115 hydrochloride [redacted] administered QD, orally, for 14 consecutive days

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

Matching placebo capsules administered QD, orally, for 14 consecutive days

Duration of patient participation in study:

Planned screening duration: up to 4 days

Planned treatment duration: 14 days

Planned follow-up duration: 46 days

Total duration of study participation: approximately 64 days

Endpoints

Primary endpoints:

- safety and tolerability evaluations including clinical laboratory evaluations, vital signs, electrocardiogram (ECG), and AE reporting over the 60-day period.

Secondary endpoints:

- time to clinical recovery monitored over 28 days. Clinical recovery is defined as occurring when the WHO Clinical Improvement Ordinal Scale is no higher than 3 for baseline WHO scale greater than 3 or no greater than 2 for baseline scale of 3. The time to recovery will be taken as the time from randomization until the first day that the patient meets the definition of recovery. Patients who die or do not meet the definition of recovery 28 days after randomization will be considered not recovered
    - patients who relapse will be included in the analysis as the first day of the last period in which they score no higher than 3, and sustain that status until the end of the 28 days
    - the justification for using data up to 28 days is that although the WHO Clinical Improvement Scale will be collected up to Day 60, it is anticipated that recoveries past Day 29 (ie, more than 14 days after the end of treatment) are unlikely to be caused by study treatment. Therefore, key analyses will consider only time up to Day 29, and analysis of later recoveries may be investigated and described in the statistical analysis plan.
    - patients who score 3 or lower at the start of the study will be included in the analysis, and if they never require oxygen, will be considered to have never required oxygen therapy altogether and will therefore have met the endpoint on Day 1. Other analyses will address alternative definitions of recovery, including time to discharge.
- time to discharge, defined in the same way as clinical recovery, but occurring when the WHO Clinical Improvement Ordinal Scale is no higher than 2
- time to symptomatic recovery, defined in the same way as clinical recovery, but occurring when none of the COVID-19 Symptom Assessment scores are higher than 1
- time to complete symptomatic recovery, defined in the same way as clinical recovery, but occurring when none of the COVID-19 Symptom Assessment scores are higher than 0
- proportion of patients in clinical recovery on key analysis days. Patients who die will be considered as not being in clinical recovery.
- scoring of WHO Clinical Improvement Ordinal Scale (9-point scale) on key analysis days for levels ≥3. Patients who die will be included in the analysis.
- number of days at or above each level of the WHO Clinical Improvement Ordinal Scale (9-point scale) on key analysis days for levels ≥3. Patients who die will be included in the analysis as scoring the maximum score on every day after death until Day 29.
- proportion of patients whose maximum score is at or above each level of the WHO Clinical Improvement Ordinal Scale on key analysis days, for levels ≥3
- mortality by each of the key analysis days
- change in SpO2
- PK parameters to be assessed from plasma samples (subset of patients only), including, but not limited to:
    - trough (predose) plasma concentration (C_{trough})
    - maximum observed plasma concentration (C_{max})
    - time to C_{max} (T_{max})

- area under the plasma concentration versus time curve (AUC) from time zero to the time of last quantifiable concentration ($AUC_{0\text{-last}}$)
- AUC within a dosing interval (AUC_{tau}, where tau = 12 hours).

Exploratory endpoints:

- anti-inflammatory: C-reactive protein, [redacted]
- [redacted]
- [redacted]
- change from baseline in log10 SARS-CoV-2 viral load as measured by RT-PCR by Days 5 and 14. Patients who die will be included in the analysis as having the worst viral load score of any patient included in the analysis.
- rate of switch to other COVID-19-specific treatment by Day60. Treatments for patients who die will be included up to the date of death.

Statistical methods:

Continuous variables will be compared between treatment groups using normal regression, and the mean, standard error, 95% confidence interval (CI), and p-value will be presented. They 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 CI for outcome measures.

Key analysis days will be Days 3, 5, 10, 14, 29 and 60.

Binary (yes/no) variables will be compared between treatment groups using logistic regression. The odds ratio, p-value, and 95% CI will be presented and summarized for categorical variables. Differences in probabilities and associated 95% confidence interval, calculated from the odds ratio, will be presented for the reference probabilities on the control arm. The justification for using the logistic regression model is that the odds ratio for the treatment effect is anticipated to be more robust to differences in reference probabilities than directly modelling the probability difference. Therefore, the odds ratio estimand is more likely to be applicable to the populations involved in further study in the rapidly evolving pandemic. Nevertheless, to assist in interpretation, the equivalent probability difference within the enrolled population will also be presented.

Time-to-event variables will be compared between treatment groups using proportional hazards modeling. The hazard ratio, p-value, and associated 95% CI will be presented. Proportions at each timepoint will be summarized using Kaplan-Meier methods. The estimand of the hazard ratio has been chosen because it is robust to variations in reference hazard rates. For intercurrent events other than death, the treatment policy strategy will be adopted (ie, patients will be followed for the event regardless of whether they receive alternative therapies, have protocol violations, of discontinue the investigative product).

Unless otherwise specified, all regression models will be stratified by age (≤65 years versus >65 years). Wald p-values will be considered primary.

Analysis of Primary Endpoints

Safety and tolerability

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 clinical laboratory evaluations, ECGs, and vital signs. Where applicable, shift tabulations by treatment group will be presented.

Analysis of Secondary Endpoints

Time to clinical recovery

Time to clinical recovery will be analyzed as a time-to-event variable.

Time to discharge

Time to discharge will be analyzed as a time-to-event variable.

Time to symptomatic recovery

Time to symptomatic recovery will be analyzed as a time-to-event variable.

Time to complete symptomatic recovery

Time to complete symptomatic recovery will be analyzed as a time-to-event variable.

Proportion of patients in clinical recovery

The proportion of patients in clinical recovery will be analyzed as a binary variable on key analysis days. Patients who die will be considered as not being in clinical recovery.

Scoring of WHO Clinical Improvement Ordinal Scale (9-point scale)

The score on the WHO Clinical Improvement Ordinal Scale will be analyzed on the key analysis days. A separate analysis will be conducted for each level from 3 to 9, in which each patient will be scored as being above or below each level, and analyzed as a binary variable, with an additional covariate to the default in the model of baseline score. Patients who die will be included in the analysis.

Number of days at or above each level of the WHO Clinical Improvement Ordinal Scale (9-point scale)

The number of days at or above each level of the WHO Clinical Improvement Ordinal Scale on key analysis days for levels ≥3 will be analyzed as a continuous variable. Patients who die will be included in the analysis as scoring the maximum score on every day after death until Day 29.

Maximum score of the WHO Clinical Improvement Ordinal Scale (9-point scale)

The proportion of patients whose maximum score is at or above each level of the WHO scale on key analysis days for levels ≥3 will be analyzed as a binary variable.

Mortality

Mortality will be analyzed as a binary variable on each key analysis day.

Change from Baseline in Oxygen Saturation

Change in SpO2 from baseline will be analyzed using a mixed model with repeated measures, including baseline SpO2 as an additional baseline covariate. The treatment effect on each key analysis day and the average treatment effect will be presented along with the 95% CI and p-value.

Pharmacokinetic Analysis

Descriptive statistics will be provided for APX-115 plasma concentrations at pre-specified timepoints and derived PK parameters.

Interim Analysis

A single interim analysis will be conducted after enrollment and the start of treatment of 30 patients. The interim analysis will be reviewed by the unblinded DMC. The DMC may recommend additional interim analyses, and will consider the entirety of the safety data for any recommendation. The operation of the DMC will be covered by a DMC Charter. A separate unblinded statistical analysis group (USAG) from the main study team will prepare the unblinded reports for the DMC, and only the USAG and DMC will have access to unblinded data.

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Abbreviation	Definition
ADR	adverse drug reaction
AE	adverse event
ALT	alanine aminotransaminase
AST	aspartate aminotransaminase
AUC	area under the plasma concentration versus time curve
$AUC_{0\text{-last}}$	area under the plasma concentration versus time curve from time zero to the time of last quantifiable concentration
AUC_{tau}	area under the plasma concentration versus time curve within a dosing interval
CC_{50}	50% cytotoxic concentration
CFR	Code of Federal Regulations
CI	confidence interval
C_{max}	maximum observed plasma concentration
COVID-19	coronavirus 2019
CRO	contract research organization
C_{trough}	trough (predose) plasma concentration
CYP	cytochrome P450
DMC	Data Monitoring Committee
ECG	electrocardiogram
eCRF	electronic case report form
eGFR	estimated glomerular filtration rate
EOS	end of study
EOT	end of treatment
ePRO	electronic patient-reported outcome
EW	early withdrawal
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IB	Investigator's Brochure
IC_{50}	half maximal inhibitory concentration
ICF	informed consent form
ICH	International Council for/Conference on Harmonisation
[redacted]	[redacted]
IMP	investigational medicinal product

IRB	Institutional Review Board
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
n	number of patients
Nox	NADPH-oxidase
PCR	polymerase chain reaction
PK	pharmacokinetic(s)
PT	preferred term
QD	once daily
ROS	reactive oxygen species
RT	reverse transcription
SAE	serious adverse event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
sNox2-dp	soluble Nox2-derived peptide
SoC	standard of care
SOC	system organ class
SpO2	oxygen saturation
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
T_{max}	time to maximum observed plasma concentration
TRAF6	tumor necrosis factor receptor-associated factor 6
UGT	UDP-glucuronosyltransferase
ULN	upper limit of normal
USAG	unblinded statistical analysis group
WHO	World Health Organization

1. INTRODUCTION

APX-115 is a potent small molecule inhibitor of NADPH-oxidase (Nox) isozymes being developed by Aptabio Therapeutics Inc. for the treatment of diabetic kidney disease.

The Nox enzymes represent a family of 7 membrane enzymes (Nox1, Nox2, Nox3, Nox4, Nox5, Duox1, and Duox2) which catalyze NADPH-dependent generation of superoxide and secondary reactive oxygen species (ROS).[1]

Reactive oxygen species are involved not only in cellular damage and killing of pathogens, but also in a large number of reversible regulatory processes in virtually all cells and tissues. However, despite the importance of ROS in the regulation of fundamental physiological processes, ROS production can also irreversibly destroy or alter the function of the target molecule. Consequently, ROS have been increasingly identified as major contributors to damage in biological organisms, so-called "oxidative stress."

During inflammation, Nox is one of the most important sources of ROS production in vascular cells under inflammatory conditions.[2]

In general, ROS are processes that protect plants, fungi, and animals from invading pathogens, including bacteria. However, the production of ROS in mammals, paradoxically, promotes viral pathogenicity by a mechanism not yet defined. Produced for antibacterial purposes, ROS plays a mandatory role in mitochondria, which serve as a central hub that promotes innate immune signaling. In contrast, the sRNA virus does not use this antibacterial ROS production pathway.[3,4,5,6]

ROS are often generated during virus infection, thus promoting apoptosis, lung injury, and inflammation/allergy.[7,8] Inhibitors of Nox2, an enzyme that is responsible for ROS production, are useful to protect mammals against severe virus infection. These studies[7,8] indicate the crucial roles of ROS in virus infection, which may have implications for therapy.

[redacted]

[redacted]

Indeed, in the absence of Nox2, influenza A virus causes substantially less lung damage and dysfunction, suggesting that by lowering the viral burden, Nox2-induced ROS promotes rather than suppresses viral infection.

Nox2 is expressed and activated in endosomes by viral infection in mouse and human cells (eg, a) single-stranded RNA virus; influenza A viruses, respiratory syncytial virus, rhinovirus, Dengue virus, and human immunodeficiency virus or b) DNA virus: vaccinia virus and herpes simplex virus).[7,8]

These studies support the notion that low levels of ROS maintain an enhanced immune response.

[redacted]

[redacted]

Nox2 is responsible for artery dysfunction via production of ROS. RNA viruses may activate Nox2, but it is unknown if this occurs in coronavirus 2019 (COVID-19). Nox2 activation by soluble Nox2-derived peptide (sNox2-dp) was measured in patients hospitalized for COVID-19 (n=182) and controls (n=91).[10] The sNox2-dp values were higher in COVID-19 patients versus controls and in severe versus non-severe COVID-19.[10] COVID-19 is associated with Nox2-derived oxidative stress, which indicates a possible therapeutic approach to fight Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[10]

[redacted]

[redacted]

Nox4 is selectively up-regulated in the lungs of patients with idiopathic pulmonary fibrosis, with expression in myofibroblasts within fibrotic foci, vascular smooth muscle cells surrounding remodeled pulmonary arteries, and hyperplastic alveolar epithelial cells, as well as in a rodent model of bleomycin induced pulmonary fibrosis. Mice deficient in Nox4 were found to be protected from bleomycin induced acute lung injury and alveolar epithelial cell apoptosis that proceeds onset of fibrosis.[11,12,13]

[redacted]

Therapeutic treatment with a small molecule Nox inhibitor markedly attenuates an established fibrotic response in the bleomycin model of pulmonary fibrosis, with a reduction in the extent of alveolar injury, collagen fiber deposition, and remodeling of pulmonary arteries within localized areas of alveolar injury and fibrosis along with a reduction in the extent of neovascularization. APX-115 may become a new therapeutic strategy and is being studied against COVID-19 infected by SARS-CoV-2 virus due to its antiviral, anti-inflammatory, and anti-fibrotic activity.

1.1. Summary of Clinical Studies

1.1.1. Completed Phase 1 Clinical Study

1.1.1.1. Safety

One Phase 1 clinical study (Study OP101817.APT) has been performed with APX-115. This study was a double-blind, randomized study assessing the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of single ascending doses or multiple ascending doses of APX-115 carried out on healthy male volunteers.

All the TEAEs were of mild to moderate intensity and resolved before the end of the study. No SAEs were reported during this study. In addition, no clinically relevant findings were observed in the clinical examinations, biological, vital signs, or electrocardiogram (ECG) parameters.

1.1.1.2. Pharmacokinetics

[redacted]

1.1.1.3. Food Effect

[redacted]

1.1.1.4. Drug-Drug Interaction

[redacted]

1.1.2. Ongoing Phase 2 Clinical Study

A randomized, placebo-controlled, double-blinded, multicenter, Phase 2 study (Study A01-115-02-EU / EudraCT 2019-004155-37/ NCT04534439) is being conducted in 4 countries of Europe to evaluate safety, tolerability, and renal effects of APX-115 in 140 patients with type 2 diabetes and nephropathy. [redacted]

1.2. Study Rationale

This is a Phase 2 clinical trial to evaluate the safety and efficacy of APX-115 in patients hospitalized with mild to moderate COVID-19.

Currently, there is one Food and Drug Administration (FDA)-approved treatment for COVID-19. Additional effective therapeutic agents are urgently needed.

COVID-19 infection is characterized by the presence of systemic symptoms followed by a cytokine storm with elevated IL-6 leading to lung injury and requirement of mechanic ventilation, multi organ failure, and death.[14]

Considering the antiviral, anti-inflammatory, and anti-fibrotic activity of APX-115 and known safety profile to date, this study will assess the safety and efficacy of APX-115 for the treatment of hospitalized patients with mild to moderate COVID-19, with the goal to assess suppression of the virus, improvement of symptoms, and prevention of disease progression.

[redacted]

1.3. Risk-benefit Assessment

More detailed information about the known and expected benefits and risks and reasonably expected AEs of APX-115 may be found in the Investigator's Brochure (IB).[15]

[redacted]

[redacted]

As the study subjects targeted are patients with limited treatment options, the study supports further investigation of APX-115 in hospitalized patients with mild to moderate symptoms due to COVID-19 in a Phase 2 setting.

2. OBJECTIVES AND ENDPOINTS

2.1. Objectives

The primary objective of the study is:

- to assess the safety and tolerability of APX-115 active doses compared to placebo following multiple oral dosing in hospitalized patients with confirmed, mild to moderate, symptomatic COVID-19.

The secondary objectives of the study are:

- to evaluate the efficacy of APX-115 active doses compared to placebo following multiple oral dosing in hospitalized patients with confirmed, mild to moderate, symptomatic COVID-19
- to assess the PK of APX-115 in a subset of 20 patients.

The exploratory objective of the study is:

- to evaluate the response of biomarkers to APX-115 active doses compared to placebo following multiple oral dosing in hospitalized patients with confirmed, mild to moderate, symptomatic COVID-19
- to evaluate change from baseline in viral load and rate of switch to other treatments.

2.2. Endpoints

The primary endpoints are safety and tolerability endpoints including clinical laboratory evaluations, vital signs, ECG, and AE reporting over the 60-day period.

The secondary endpoints are:

- time to clinical recovery monitored over 28 days. Clinical recovery is defined as occurring when the World Health Organization (WHO) Clinical Improvement Ordinal Scale is no higher than 3 for baseline WHO scale greater than 3 or no greater than 2 for baseline scale of 3. The time to recovery will be taken as the time from randomization until the first day that the patient meets the definition of recovery. Patients who die or do not meet the definition of recovery 28 days after randomization will be considered not recovered.

  - patients who relapse will be included in the analysis as the first day of the last period in which they score no higher than 3, and sustain that status until the end of the 28 days
  - the justification for using data up to 28 days is that although the WHO Clinical Improvement Scale will be collected up to Day 60, it is anticipated that recoveries past Day 29 (ie, more than 14 days after the end of treatment) are unlikely to be caused by study treatment. Therefore, key analyses will consider only time up to Day 29, and analysis of later recoveries may be investigated and described in the statistical analysis plan.
  - patients who score 3 or lower at the start of the study will be included in the analysis, and if they never require oxygen, will be considered to have never required oxygen therapy altogether and will therefore have met the endpoint on Day 1. Other analyses will address alternative definitions of recovery, including time to discharge.

- time to discharge, defined in the same way as clinical recovery, but occurring when the WHO Clinical Improvement Ordinal Scale is no higher than 2
- time to symptomatic recovery, defined in the same way as clinical recovery, but occurring when none of the COVID-19 Symptom Assessment scores are higher than 1
- time to complete symptomatic recovery, defined in the same way as clinical recovery, but occurring when none of the COVID-19 Symptom Assessment scores are higher than 0
- proportion of patients in clinical recovery on key analysis days. Patients who die will be considered as not being in clinical recovery.
- scoring of WHO Clinical Improvement Ordinal Scale (9-point scale) on key analysis days for levels ≥3. Patients who die will be included in the analysis.
- number of days at or above each level of the WHO Clinical Improvement Ordinal Scale (9-point scale) on key analysis days for levels ≥3. Patients who die will be included in the analysis as scoring the maximum score on every day after death until Day 29.
- proportion of patients whose maximum score is at or above each level of the WHO Clinical Improvement Ordinal Scale on key analysis days, for levels ≥3.
- mortality by each of the key analysis days
- change from baseline in oxygen saturation (SpO2)
- PK parameters to be assessed from plasma samples (subset of patients only), including, but not limited to:
  - Trough (predose) plasma concentration (C_{trough})
  - C_{max}
  - T_{max}
  - AUC from time zero to the time of last quantifiable concentration ($AUC_{0\text{-}last}$)
  - AUC within a dosing interval (AUC_{tau}, where tau = 12 hours).

The exploratory endpoints are:

- [redacted]
- [redacted]
- [redacted]
- [redacted]
- [redacted]

3. INVESTIGATION PLAN

3.1. Overall Study Design and Plan Description

This will be a Phase 2, randomized, double-blind, placebo-controlled, multicenter, efficacy, and safety study in hospitalized patients with confirmed, mild to moderate, symptomatic COVID-19. Pharmacokinetic assessment will be performed in a subset of 20 patients.

The study will consist of a sentinel cohort of 30 patients (15 patients on active drug and 15 patients on placebo) and an expansion cohort of approximately 50 patients (in a 1:1 ratio of APX-115 or placebo). Enrollment will pause after the 30th patient in the sentinel cohort has been enrolled and started treatment, until the results of the interim analysis are known. Once either 25 patients have recovered, or the 30th patient in the sentinel cohort has completed 14 days of treatment, an unblinded Data Monitoring Committee (DMC) will assess the safety, tolerability, efficacy, and PK [redacted] QD APX-115 in COVID-19 patients in the sentinel cohort. The DMC will issue a recommendation to enroll patients for the expansion cohort, or to stop the study depending on the safety and futility assessment. 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 prior to start of patient enrollment.

Informed consent must be obtained from all patients or their legally authorized representative during screening (up to 4 days, maximum, before dosing) and before any study-related procedures are performed.

Approximately 12 sites in the United States, and other countries based on the pandemic situation, are planned to enroll patients.

Patients will be randomized within 14 days after a laboratory-confirmed SARS-CoV-2 infection as determined by real time RT-PCR or other commercial or public health assay authorized by FDA or other applicable health authority. Patients need to have at least one symptom of COVID-19 (fever, cough, shortness of breath, myalgia [muscle or body aches], ageusia [loss of taste], anosmia [loss of smell], fatigue, or weakness) at screening.

Patients will receive an oral dose [redacted] of APX-115 or placebo capsules QD for 14 consecutive days. Patients will undergo assessments during hospitalization or could be discharged after the start of study treatment as early as Day 2 if judged to be ready for discharge. Eligible patients must be in hospital for at least 24 hours after start of study treatment. If discharged, patients will then be requested to take study treatment at home (as prescribed) up to and including Day 14. Study drug will be administered in a fasted state at approximately the same time in the morning, at least 2 hours after a morning meal if a morning meal is consumed on Days 1 to 14.

If the patient has already been discharged, a telephone or digital media visit will be conducted on days for which no laboratory assessments are required (Days 3, 10, 22, 29, and 60) and an at-home or an on-site visit will be required on days requiring laboratory assessments (Days 5 and 14). The study design is illustrated in Figure 3.

Allowable windows for scheduling of study visits are -1 day for Day 3, ±1 day for Day 5, and ±2 days for Days 10, 22, 29, and 60. The Day 14 visit may be scheduled up to 2 days past the actual Day 14 date; however, dose administration will end at Day 14.

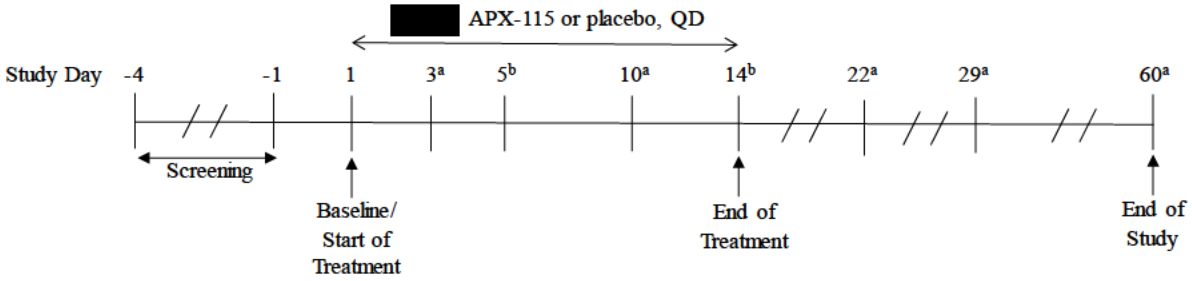
Symptoms will be documented daily through Day 60 using an electronic patient-reported outcome (ePRO) instrument based on the September 2020 FDA guidance for assessing COVID-19-related symptoms. All patients will be closely monitored for AEs from informed consent through Day 60, and followed for safety assessments through Day 60. SARS-CoV-2 viral loads will be obtained by [redacted] self-collection at baseline (Day 1) and Days 5 and 14. Any new infections that occur in the study, regardless of organism (ie, viral or non-viral), will be captured. Additionally, the site of infection and source of culture (bronchoalveolar lavage, tracheal aspirate, sputum, blood, urine, etc.) will also be recorded.

Oxygen saturation will be collected daily in the hospital or self-collected daily upon discharge until end of study (EOS) using ePRO. Clinical improvement based on the WHO Clinical Improvement Ordinal Scale (9-point scale; Appendix 6) will be documented based on scores obtained daily while hospitalized, the day after hospital discharge via telephone contact with the patient, at the scheduled visit(s) after hospital discharge, and if the patient is readmitted to the hospital or dies.

Blood samples for analysis of APX-115 in plasma will be collected from 20 patients at prespecified timepoints (see Section 7.3) in hospitalized patients only.

Study procedures are detailed in the Schedule of Assessments (Appendix 5).

Figure 3: Study Design



Abbreviation: QD = once daily.
Note: Allowable windows for scheduling of study visits are -1 day for Day 3, ±1 day for Day 5, and ±2 days for Days 10, 22, 29, and 60. The Day 14 visit may be scheduled up to 2 days past the actual Day 14 date; however, dose administration will end at Day 14.
[a] If the patient has already been discharged from hospital, a telephone or digital media visit will be conducted on days for which no laboratory assessments are required (Days 3, 10, 22, 29, and 60).
[b] If the patient has already been discharged from hospital, an at-home or an on-site visit will be required on days requiring laboratory assessments (Days 5 and 14).

The total duration of study participation for each patient (from screening through EOS/early withdrawal [EW] visit) is anticipated to be approximately 64 days.

The start of the study is defined as the date the first patient (or their legally authorized representative) signs an informed consent form (ICF). The point of enrollment occurs at the time of patient number allocation. The end of the study is defined as the date of the last visit of the last patient in the study.

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

This is a randomized, double-blind, placebo-controlled, Phase 2, safety and efficacy study in hospitalized patients with mild to moderate COVID-19. The rationale for this study is outlined in Section 1.2 and described in detail below.

APX-115 exerted anti-inflammatory effects in mice through the inhibition of macrophage infiltration and by the regulation of inflammation-related signals.[9] COVID-19 is associated with Nox2-derived oxidative stress, which indicates a possible therapeutic approach to fight SARS-CoV-2.[10]

In vitro, the SARS-CoV-2 virus assay was performed on the Calu-3 cell, and APX-115 showed a very favorable antiviral activity on about 1.6 µM concentration. Based on this, the IC_{50} of APX-115 is applied to 1.6 µM. The CC_{50} is 164.5 µM; thus the selectivity index is 98.5, which is considered as a very safe compound.

[redacted]

Hence, the sponsor has planned to assess the safety and efficacy of APX-115 in the COVID-19 patient population.

The variability of individual clinical courses in COVID-19 and the incomplete understanding of this newly recognized disease can seriously affect the reliability of any conclusions based on uncontrolled data. Therefore, per the FDA's recommendation, this is a randomized, placebo-controlled study.

There are safety concerns in this patient population, both because of risks associated with the disease and because of the potential for AEs from the treatment. For example, development of acute kidney injury has been reported as a possible complication during the disease progression of COVID-19. Patients developing renal impairment [redacted] during conduct of the study will be closely monitored, and, at the discretion of the medical monitor, the patient may be withdrawn from the study if associated AEs become intolerable.

In addition, altering the immune response during an acute infection could theoretically have either beneficial or harmful consequences that cannot be precisely predicted. For this reason, only hospitalized patients with mild or moderate COVID-19 will be enrolled, and the DMC will continuously monitor for safety until completion.

The safety endpoints in this study are standard. Assessment of AEs, vital signs, 12-lead ECGs, and safety laboratory tests are planned to be conducted and provide a robust approach to assess the safety of this patient population.

Efficacy endpoints have been chosen to assess virological and clinical parameters to evaluate clinical improvement including measures that maximize objectivity, such as duration of hospitalization and vital status, and also include the WHO COVID-19 Clinical Improvement Ordinal Scale.

The PK of APX-115 will be assessed from serial blood sample collections taken on Day 1, with trough collections scheduled on Day 5 and serial blood sample collections taken on Day 14 (if patients are still hospitalized). Every effort will be made to have PK samples taken as close as possible to the times of blood sampling for clinical laboratory evaluations to reduce the number of contacts between hospital staff and the patient.

3.3. Selection of Dose in the Study

[redacted]

The proposed APX-115 dose reflects appropriate plasma exposure level and safety margins. The ideal amount for more effective inhibition of oxidase stress in patients with COVID-19 Nox inhibitor is not known because APX-115 is the first compound of this class. [redacted]

[redacted]

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:

1. Willing and able to provide informed consent themselves or through their legally authorized representative.
2. Male or female patients, of any race or ethnicity, 18 to 80 years of age, inclusive, on the day of informed consent. Racial and ethnic minorities should be included in the study population to the greatest extent possible.
3. Laboratory-confirmed SARS-CoV-2 infection as determined within 14 days of randomization by real time RT-PCR or other commercial or public health assay authorized by FDA or other applicable health authority.
4. Onset of COVID-19 symptoms within 14 days prior to randomization.
5. Have at least one of the following symptoms at screening: fever, cough, shortness of breath, myalgia, ageusia, anosmia, fatigue, or weakness.
6. Hospitalized with COVID-19 disease (WHO COVID-19 Clinical Improvement Ordinal Scale score [Appendix 6] of 3 [hospitalized, no oxygen therapy], 4 [hospitalized, oxygen by mask or nasal prongs], or 5 [non-invasive ventilation or high-flow oxygen]).

   Note: Hospitalized patients can also include patients admitted to centers conditioned as hospitals to treat COVID-19 patients.
7. 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 any of the following criteria are applicable:

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

3. COVID-19 disease as defined by the WHO COVID-19 Clinical Improvement Ordinal Scale (Appendix 6), scores of 6 (intubation and mechanical ventilation) or 7 (ventilation + additional organ support - pressors, renal replacement therapy, extracorporeal membrane oxygenation).
4. Expected survival less than 72 hours.
5. Treatment with other drugs thought to possibly have activity against SARS-CoV-2 infection within 7 days or within 5 half-lives, whichever is longer, prior to enrollment or concurrently. Drugs that have received FDA emergency use authorization or COVID-19 approval are allowed.
6. Treatment with immunosuppressants, combination of [redacted]
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 (eg, for organ transplantation or autoimmune conditions).
10. [redacted]
11. Patients with clinically apparent liver disease (eg, jaundice, cholestasis, hepatic synthetic impairment, or active hepatitis) or moderate or severe hepatic impairment as determined by Child-Pugh score (Class B or C).
12. Alanine aminotransaminase (ALT) or aspartate aminotransaminase (AST) >3 × upper limit of normal (ULN) AND total bilirubin levels >2 × ULN OR ALT or AST >5 × ULN.
13. Total bilirubin >1.5 × ULN, unless the patient has known Gilbert's syndrome.
14. Hemoglobin <9 g/dL for females or <11 g/dL for males.
15. Absolute neutrophil count <1500/mm^3.
16. Thrombocytopenia (platelets count <100 × 10^9/L).
17. Inability to swallow oral medications or a gastrointestinal disorder with diarrhea (eg, Crohn's disease) or malabsorption at screening.
18. 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.
19. History of an allergic reaction or hypersensitivity to the study drug or any component of the study drug formulation.

4.3. Discontinuation Criteria

4.3.1. 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 SAEs.

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

4.3.2. Hepatic Injury

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

- AST or ALT >8 × ULN
- AST or ALT >3 × ULN AND total bilirubin >2 × ULN (Hy's law)
- repeat AST or ALT >5 × ULN.

4.3.3. Discontinuation of Study Treatment

Upon discontinuation of study treatment, receipt of alternate therapies, or record of protocol violations, investigators will continue to follow protocol-driven procedures, where possible, to monitor the patient up to 60 days after randomization. Study drug administration will be discontinued for the following reasons:

- withdrawal by patient (patient is free to discontinue at any point of time; reason of discontinuation will be specified in the electronic case report form [eCRF])
- change in compliance with any inclusion/exclusion criterion that is clinically relevant and affects patient safety as determined by the investigator
- noncompliance with the study restrictions that might affect patient safety or study assessments/objectives, as considered applicable by the investigator
- lack of efficacy (eg, patients who require nonstudy antiviral or anticytokine therapy due to progression of COVID-19 as judged by the investigator)
- any clinically relevant sign or symptom that, in the opinion of the investigator (or designee), warrants patient withdrawal
- any severe AE possibly related to study drug or any SAE possibly related to the study drug.

4.3.4. Study Withdrawal

A patient may be discontinued early from the study for the following reasons:

- withdrawal by patient (reason will be specified in the eCRF)
- lost to follow-up
- death
- physician decision (ie, investigator decision based on protocol deviation, assessment that it is not in the patient's best interest to continue, or other reason [reason will be specified in the eCRF])
- sponsor decision (reason will be specified in the eCRF).

If the patient withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent. Additionally, patients may request destruction of any samples taken and not tested, and the investigator must document this in the site study records. Refer to the Schedule of Assessments (Appendix 5) for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. Patients will be asked to complete EOS/EW evaluations.

4.3.5. 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.

4.3.6. Replacement Procedures

Patients who discontinue from the study will not be replaced.

4.3.7. 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 will be asked to complete all subsequent study procedures (EOS/EW visit), as described in the Schedule of Assessments (Appendix 5).

All SAEs that are ongoing at the time of discontinuation, or that develop prior to the final EOS/EW visit, will be followed until resolution or stabilization, or up to 60 days following randomization, by the Covance Patient Safety Services group.

Steps will be taken by the sites to ascertain vital status in all randomized patients (eg, with a vital records search) up to Day 60.

4.4. Stopping Rules

Enrollment will pause after the 30th patient in the sentinel cohort has been enrolled and started treatment, until the results of the interim analysis are known. Once either 25 patients have recovered, or the 30th patient in the sentinel cohort has completed 14 days of treatment, an unblinded DMC will assess the safety, tolerability, efficacy, and PK [redacted] QD APX-115 in COVID-19 patients in the sentinel cohort. The DMC will issue a recommendation to enroll patients for the expansion cohort, or to stop the study depending on the safety and futility assessment. The DMC will continue to review safety and assess the risk/benefit profile on an ongoing basis.

Enrollment will pause pending unscheduled DMC review of safety data when any of the following criteria is met:

- ≥2 patients experience SAE possibly related to study drug, or
- ≥2 patients experience a severe AE possibly related to study drug that are of a similar nature.

Enrollment and dosing may restart following review of relevant safety data by the DMC.

A DMC Charter, which includes detailed processes, will be prepared prior to start of patient enrollment.

4.5. Study Termination

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:

- AEs unknown to date (ie, 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
- 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 or local health authorities, the sponsor's procedures, or Good Clinical Practice guidelines
- Inadequate recruitment of participants by the investigator.

5. STUDY TREATMENTS

5.1. Description, Storage, Packaging, and Labeling

[redacted]

Investigational medicinal product (IMP) and placebo will be stored according to the instructions on the label at the study site in a location that is locked with restricted access.

The bulk drug container and unit dose containers will be labeled in accordance with national laws and regulations. The IMP and placebo will be transferred from bulk supplies into the patient's dose container by qualified clinical staff.

5.2. Study Treatment Administration

Study drug [redacted] or 1 placebo capsule (as per randomization; see Section 5.3) will be administered QD for 14 consecutive days in a fasted state at approximately the same time in the morning, at least 2 hours after a morning meal if a morning meal is consumed.

If a patient is discharged during the study treatment period, a quantity of APX-115 or placebo sufficient for QD dosing through Day 14 will be dispensed at the time of patient discharge from the hospital.

Only patients enrolled in the study may receive study treatment and only authorized site staff may dispense study treatment. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study treatment accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

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

5.3. Method of Treatment Assignment

A total of approximately 80 patients will be randomized in a 1:1 ratio to receive [redacted] APX 115 or placebo. 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 age (≤65 years versus >65 years).

Patients confirmed as eligible at screening will be assigned a patient identifier before having study treatment dispensed. The patient identifier will consist of the site number and patient number. The site number will comprise 3 digits, and the patient number will comprise the final 3 digits (eg, 002003 is Site 2, Patient 3).

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 must be notified as soon as possible (eg, within 24 hours) when the blind is broken, which may occur when 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 (APX-115 [redacted] or placebo) by recording the number of capsules actually used. A patient diary

will be provided to the patient at the time of discharge from the hospital (if discharge occurs before EOS), which will be used to record the date and time of dose administration and confirmation that the dose was taken in a fasted state at approximately the same time in the morning, at least 2 hours after a morning meal if a morning meal is consumed. The patient diary will be reviewed at each scheduled visit post-hospital discharge.

Compliance information will be captured via eSource (if a patient version is used) or telemedicine. The patient will return unused supply at the EOT visit if discharged prior to the EOS treatment period.

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.

Background standard of care (SoC) will be maintained in both treatment arms. Acceptable SoC-specific treatment for COVID-19 include those authorized by the FDA and other regulatory agencies or recommended by regulatory authorities, including therapeutic interventions studied under randomized controlled clinical trials. Data on background therapy for COVID-19 will be collected. Prior and concomitant medications given as SoC for COVID-19 will be captured in the eCRFs throughout the study, including whether the medication is given as anti-viral treatment, anti-inflammatory, or other specified therapeutic intervention (eg, oxygenation treatment).

If SoC therapies are not able to be delivered due to resource limitations or if care decisions are made based on resource limitations, this will be recorded in the eCRFs. Reasons for any withdrawal of care will be recorded in the eCRFs.

[redacted]

[redacted]

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. Drugs that have received FDA emergency use authorization or COVID-19 approval are allowed.

Patients who begin to receive nonstudy rescue antiviral medication for COVID-19 after the start of study treatment will be discontinued from study treatment if due to disease progression as judged by the investigator; however, the patient will remain in the study and complete all follow-up assessments.

Patients receiving any drugs that fall within the following categories will be excluded from the study:

- Immunosuppressants, eg, steroids, cyclosporine, or tacrolimus, or other immunosuppressant drugs
- [redacted]

7. STUDY ASSESSMENTS AND PROCEDURES

Study procedures and their timing are summarized in the Schedule of Assessments (Appendix 5). 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 4.3.1), as applicable. Procedures conducted as part of the patient's routine clinical management (eg, 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 (Appendix 5).

7.1. Safety and Tolerability Assessments

7.1.1. Adverse Events

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

Adverse events will be elicited from the patient (or, when appropriate, from a caregiver, surrogate, or the patient's legally authorized representative) by the study site staff using a nonleading question such as "How are you feeling today?" or "Have you had any health concerns since your last visit?"

The investigator and any designees are responsible for detecting, documenting, and reporting events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study treatment or the study, or that caused the patient to discontinue the study treatment.

Adverse events will be assessed from signing the ICF until 60 days after randomization (Day 60) as noted in the Schedule of Assessments (Appendix 5). Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 dated 19 April 2020 (exclusively meant for COVID-19) or later.

Events due to disease progression (eg, new or worsening COVID-19 symptoms) will not be reported as AEs. 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.

7.1.2. Pregnancy

Female patients of childbearing potential will have a pregnancy test during screening and at the Day 60 EOS/EW visit.

A urine pregnancy test must be performed but may be confirmed with a serum pregnancy test (screening only). The Day 60 EOS/EW visit 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 outcomes 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 (eg, 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.

7.1.3. 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 5. 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.

The screening laboratory test will be assessed by a local laboratory. Clinical laboratory tests done as per SoC do not need to be repeated if done within 24 to 48 hours of screening and the patient is stable. Baseline and post-baseline laboratory tests will be assessed by the central laboratory. An investigator (or qualified designee) will perform a clinical assessment of all reported clinical laboratory data.

7.1.4. Vital Signs

Blood pressure, pulse rate, respiratory rate, and body temperature will be measured as safety assessments at the times indicated in the Schedule of Assessments in Appendix 5. Vital signs may also 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 vital signs is required.

Oxygen saturation will be collected daily in the hospital or, if the patient is discharged from the hospital prior to EOS, pulse oximetry devices will be provided to the patient for daily self-collection and reporting using ePRO.

7.1.5. Twelve-lead Safety Electrocardiogram

Resting 12-lead ECGs will be recorded after the patient has been supine and at rest for at least 5 minutes at the times indicated in the Schedule of Assessments in Appendix 5.

Additional 12-lead ECGs may 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 ECGs is required. The investigator (or designee) will perform a clinical assessment of each 12-lead ECG.

7.1.6. Chest Imaging

A chest x-ray or computed tomography scan will be performed at the times indicated in the Schedule of Assessments in Appendix 5.

7.2. Efficacy Assessments

7.2.1. COVID-19 Symptom Assessment

If the patient is discharged from the hospital prior to EOS, COVID-19 symptoms (Appendix 7) will be self-evaluated at approximately the same time each day for each previous 24-hour period using an ePRO instrument through Day 60. COVID-19-related symptoms based on FDA guidance[16] (rhinitis [stuffy or runny nose], sore throat, shortness of breath, cough, fatigue [low energy or tiredness], weakness, muscle or body aches, headache, chills or shivering, feeling hot or feverish, and nausea) will be scored. Each individual symptom, as well as severity of symptoms overall, will be rated on a 4-point scale ranging from 0 to 3 using ePRO as follows:

0 = None
1 = Mild
2 = Moderate
3 = Severe

The number of instances of vomiting or diarrhea in the previous 24-hour period using ePRO will be recorded and rated on a 4-point scale ranging from 0 to 3 as follows:

0 = Not at all
1 = 1 or 2 times
2 = 3 or 4 times
3 = 5 or more times

Senses of smell and taste will be evaluated for the previous 24-hour period using ePRO and rated on a 3-point scale ranging from 0 to 2 as follows:

0 = the same as usual
1 = less than usual
2 = no sense of taste or smell

Lastly, the patient will indicate (via yes or no) using ePRO whether in the previous 24-hour period he/she has returned to normal health and usual activities as before the COVID-19 illness.

7.2.2. COVID-19 Clinical Improvement Ordinal Scale

The COVID-19 clinical outcome will be evaluated for the 24 hours leading up to the assessment daily while hospitalized, the day after hospital discharge via telephone contact with the patient, at the scheduled visit(s) after hospital discharge, and if the patient is readmitted to the hospital or dies using the WHO 9-point Clinical Improvement Ordinal Scale (Appendix 6). Only the highest score in the 24 hours leading up to each assessment will be recorded.

Requirements for hospitalization and oxygen therapy and instances of mortality will be obtained through this evaluation.

7.2.3. Virological Clearance

Laboratory-confirmed SARS-CoV-2 infection using real time RT-PCR testing or other commercial or public health assay authorized by FDA or other applicable health authority for SARS-CoV-2 will be obtained within 14 days of randomization. All subsequent SARS-CoV-2 viral loads will be obtained by [redacted] self-collection at the timepoints detailed in the Schedule of Assessments (Appendix 5).

Virological clearance will be measured by:

- Rate of change in viral load: if quantitative PCR results are performed, the level of virus will be measured over time (days).

7.3. Pharmacokinetic Assessments

The PK evaluation of APX-115 in a subset of 20 patients includes C_{trough}, C_{max}, T_{max}, $AUC_{0\text{-}1ast}$, and AUC_{tau}.

Blood samples for PK evaluations will be collected on Day 1 at predose and 1, 2, 8, and 12 hours postdose. On Day 5, if patient is still hospitalized, a predose sample will be collected. On Day 14, if patient is still hospitalized, blood samples will be collected at predose and 1, 2, 8, and 12 hours postdose.

For patients discharged from the hospital prior to Day 5 or Day 14, the blood sample collections on Day 5 and/or Day 14 can be omitted.

7.4. Exploratory Assessments

7.4.1. Biomarker Evaluations

Blood samples will be collected for assessment of relevant biomarkers, including [redacted] Appendix 2) at the times indicated in the Schedule of Assessments in Appendix 5.

8. SAMPLE SIZE AND DATA ANALYSES

8.1. Determination of Sample Size

The study does not test a formal hypothesis and instead uses descriptive statistics to summarize the data. Therefore, the sample size was not determined based on formal statistical power calculations but using clinical considerations to provide a reasonable clinical database to assess safety and efficacy in COVID-19 patients. However, the ability of the study to identify a potentially promising treatment was assessed by considering that further study would likely be dependent on observing at least a numeric trend towards benefit of the treatment. On the key secondary endpoint of time to clinical recovery, a sample size of 80 patients provides 91% power to ensure that the outcome is numerically in favor of treatment if the true treatment effect is a hazard ratio of 1.4. This calculation assumes one interim analysis at 39.7% information, a median time to recovery of 14 days in the control arm, and a follow-up time for each patient capped at 28 days. For the purposes of estimating power, it was assumed that the DMC would be

unlikely to recommend stopping the study for efficacy unless there was a significant detrimental effect of treatment, simulated by the O'Brien-Fleming rule for futility.

8.2. Analysis Populations

8.2.1. Intent-to-Treat Population

The Intent-to-Treat Population will include all randomized patients. Participant data will be summarized by treatment assigned.

8.2.2. Safety Population

The Safety Population will include all participants who received at least 1 dose of APX-115 or placebo. Participant data will be summarized by actual treatment received.

8.2.3. Pharmacokinetic Population

The subset of patients who receive at least 1 dose of APX-115 and have at least 1 evaluable plasma concentration without important protocol deviations or events thought to significantly affect the PK will be included in the PK Population.

8.3. General Considerations

Continuous variables will be compared between treatment groups using normal regression, and the mean, standard error, 95% confidence interval (CI), and p-value will be presented. They 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 CI for outcome measures.

Key analysis days will be Days 3, 5, 10, 14, 29, and 60.

Binary (yes/no) variables will be compared between treatment groups using logistic regression. The odds ratio, p-value, and 95% CI will be presented and summarized for categorical variables. Differences in probabilities and associated 95% confidence interval, calculated from the odds ratio, will be presented for the reference probabilities on the control arm. The justification for using the logistic regression model is that the odds ratio for the treatment effect is anticipated to be more robust to differences in reference probabilities than directly modelling the probability difference. Therefore, the odds ratio estimand is more likely to be applicable to the populations involved in further study in the rapidly evolving pandemic. Nevertheless, to assist in interpretation, the equivalent probability difference within the enrolled population will also be presented.

Time-to-event variables will be compared between treatment groups using proportional hazards modeling. The hazard ratio, p-value, and associated 95% CI will be presented. Proportions at each timepoint will be summarized using Kaplan-Meier methods. The estimand of the hazard ratio has been chosen because it is robust to variations in reference hazard rates. For intercurrent events other than death, the treatment policy strategy will be adopted (ie, patients will be

followed for the event regardless of whether they receive alternative therapies, have protocol violations, of discontinue the investigative product).

Unless otherwise specified, all regression models will be stratified by age (≤65 years versus >65 years). 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. Safety Analysis

8.4.1. Analysis of Primary Endpoints

Safety variables include incidence of AEs (or TEAEs), clinical laboratory evaluations, ECGs, 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 April 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, and TEAEs leading to death will be summarized by system organ class (SOC), preferred term (PT), and treatment group. In the event of death, whether the death occurred after withdrawal of care and, if so, the reason for withdrawal of care will be documented. 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 clinical laboratory evaluations, ECGs, and vital signs. Where applicable, shift tabulations by treatment group will be presented.

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

8.5. Efficacy Analysis

The analysis of treatment efficacy will be based on the Intent-to-Treat Population. This section is a summary of the planned efficacy analyses of the most important efficacy endpoints.

8.5.1. Analysis of Secondary Endpoints

8.5.1.1. Time to Clinical Recovery

Time to clinical recovery (see Section 2.2) will be analyzed as a time-to-event variable.

8.5.1.2. Time to Discharge

Time to discharge will be analyzed as a time-to-event variable.

8.5.1.3. Time to Symptomatic Recovery

Time to symptomatic recovery will be analyzed as a time-to-event variable.

8.5.1.4. Time to Complete Symptomatic Recovery

Time to complete symptomatic recovery will be analyzed as a time-to-event variable.

8.5.1.5. Proportion of Patients in Clinical Recovery

The proportion of patients in clinical recovery will be analyzed as a binary variable on key analysis days. Patients who die will be considered as not being in clinical recovery.

8.5.1.6. Scoring of WHO Clinical Improvement Ordinal Scale (9-point scale)

The score on the WHO Clinical Improvement Ordinal Scale will be analyzed on the key analysis days. A separate analysis will be conducted for each level from 3 to 9, in which each patient will be scored as being above or below each level, and analyzed as a binary variable, with an additional covariate to the default in the model of baseline score. Patients who die will be included in the analysis.

8.5.1.7. Number of Days At or Above Each Level of the WHO Clinical Improvement Ordinal Scale (9-point scale)

The number of days at or above each level of the WHO Clinical Improvement Ordinal Scale on key analysis days for levels ≥3 will be analyzed as a continuous variable. Patients who die will be included in the analysis as scoring the maximum score on every day after death until Day 29.

8.5.1.8. Maximum Score of the WHO Clinical Improvement Ordinal Scale (9-point scale)

The proportion of patients whose maximum score is at or above each level of the WHO scale on key analysis days for levels ≥3 will be analyzed as a binary variable.

8.5.1.9. Mortality

Mortality will be analyzed as a binary variable on each key analysis day.

8.5.1.10. Change from Baseline in Oxygen Saturation

Change in SpO2 from baseline will be analyzed using a mixed model with repeated measures, including baseline SpO2 as an additional baseline covariate. The treatment effect on each key analysis day and the average treatment effect will be presented along with the 95% CI and p-value.

8.5.1.11. Pharmacokinetic Analysis

Descriptive statistics will be provided for APX-115 plasma concentrations at pre-specified timepoints and derived PK parameters (listed in Section 7.3).

8.6. Interim Analysis

A single interim analysis will be conducted after enrollment and the start of treatment of 30 patients. The interim analysis will be reviewed by the unblinded DMC. The DMC may recommend additional interim analyses, and will consider the entirety of the safety data for any recommendation. The operation of the DMC will be covered by a DMC Charter. A separate unblinded statistical analysis group (USAG) from the main study team will prepare the unblinded reports for the DMC, and only the USAG and DMC will have access to unblinded data.

8.7. Handling of Missing Data

8.7.1. 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.

8.7.2. Censoring

Severity Symptom Score: For time to no, moderate, or severe COVID-19 symptoms, a patient will be censored if the patient has not had the required timepoint assessment if not due to death. If the 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 total severity score at the assessment day.

8.8. Multiplicity/Multiple Testing

Not applicable.

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10. APPENDICES

Appendix 1: Adverse Event Reporting

Definitions

An adverse event (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 (ie, a dose higher than that prescribed by a health care professional for clinical reasons).
- An AE occurring from abuse of a sponsor study drug (ie, use for nonclinical reasons).
- An AE that has been associated with the discontinuation of the use of a sponsor study drug.
- Clinically significant laboratory abnormalities (ie, the laboratory abnormality is associated with symptoms, requires medical intervention, or requires changes to study drug treatment).

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 or their legally authorized representative signs the informed consent form 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/end of study visit.

Reporting of Adverse Events

At each visit the investigator, or delegate, will determine whether or not any AEs have occurred. Nonleading 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 60 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 4-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:

- **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 AEs or serious adverse events (SAEs) that are ongoing at the time of discontinuation, or that develop prior to the EOS/EW visit, will be followed for up to 60 days following the last dose of study treatment, or until resolution or stabilization.

Adverse Drug Reactions

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

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 ADR.

An unexpected ADR is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information (eg, 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 AE*** 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 (eg, 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 (eg, 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 (ie, 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 and Biomarker Evaluations

Clinical Chemistry:	Hematology:	Urinalysis:
Alanine aminotransferase Albumin Alkaline phosphatase Aspartate aminotransferase Blood urea nitrogen Calcium Chloride Cholesterol Creatinine Gamma-glutamyl transferase Glucose Lactate dehydrogenase Phosphorus Potassium Sodium Total bilirubin Total CO_2 (measured as bicarbonate) Total protein Triglycerides Uric acid	Hematocrit Hemoglobin Mean cell hemoglobin Mean cell hemoglobin concentration Mean cell volume Platelet count Red blood cell (RBC) count RBC distribution width US White blood cell (WBC) count WBC differential (percent and absolute): Basophils Eosinophils Lymphocytes Monocytes Neutrophils	Bilirubin Blood Glucose Ketones Leukocyte esterase Nitrite pH Protein Specific gravity Urobilinogen Microscopic examination (if protein, leukocyte esterase, nitrite, or blood is positive) **Other Tests** Pregnancy test (serum and urine)[a]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Abbreviations: [redacted]

[a] For female patients of child bearing potential, serum pregnancy at screening and urine pregnancy at end-of-study. The site will provide the urine pregnancy kit to the patient at the previous visit or at hospital discharge.

Appendix 3: Contraception 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 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 (ie, 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 (ie, the patient should not become abstinent just for the purpose of study participation), are exempt from contraceptive requirements. Periodic abstinence (eg, 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.

Appendix 4: 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 (eg, advertisements) must be submitted to an Institutional Review Board (IRB) by the investigator and reviewed and approved by the IRB before the study is initiated.

Any amendments to the protocol will require IRB 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 annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB
- Notifying the IRB of serious adverse events or other significant safety findings as required by IRB 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, 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 or their legally authorized representative 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.

Paper or electronic informed consent will be obtained from the patient or their legally authorized representative that meets the requirements of local regulations, ICH guidelines, and the IRB or

study center, where applicable. The patient will be given a copy of the paper or 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 contract research organization (CRO) auditors or other authorized personnel appointed by the **s**ponsor, by appropriate IRB members, and by inspectors from regulatory authorities.

Committees Structure

A Data Monitoring Committee (DMC) will review safety data throughout the study. The DMC will review efficacy data as detailed in the protocol.

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 (eg, 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 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 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) 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 (eg, 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 5: Schedule of Assessments

		Treatment Period						Follow-up visits		
Study Day	**Screening -4 to -1[a]**	**Baseline Day 1**	**[Day after Hospital Discharge[q]]**	**Day 3 (-1 day)**	**Day 5 (±1 day)**	**Day 10 (±2 days)**	**EOT (ET) Visit Day 14 (+2 days)**	**Day 22 (±2 days)**	**Day 29 (±2 days)**	**EOS (EW) Visit Day 60 (±2 days)**
Informed consent	X									
Inclusion/exclusion criteria	X	X								
SARS-CoV-2 test[a]	X									
Demographics	X									
Medical history	X									
Pregnancy test[p]	X									X
Estimated glomerular filtration rate	X									
Randomization[b]		X								
Efficacy										
Clinical improvement score (WHO COVID-19 Clinical Improvement Ordinal Scale)[c]	X	X								
[redacted]		X		X	X	X	X			
Patient diary[e]		Post-hospital discharge - ongoing until EOT visit								
Patient-reported assessment of signs and symptoms of COVID-19[f]		Post-hospital discharge - ongoing until EOS								
Safety										
Adverse events/serious adverse events	X	Ongoing								
Prior and concomitant medications	X	Ongoing								
Clinical laboratory assessments[g]	X	X			X		X			
Blood sampling for biomarkers[h]		X					X			
Oxygen saturation[i]		Once daily - ongoing until EOS								
Vital signs[j]	X	X		X	X	X	X	X		
12-lead ECG[k]	X	X					X			
Chest x-ray or CT scan[l]	X						X			
Pharmacokinetics										
Blood sampling for PK[m]		X			X		X			
Other										
Study drug administration[n]		Once daily, Day 1 through Day 14, inclusive								
Dispense study drug[o]		X								
Return unused study drug[o]							X			

Abbreviations: COVID-19 = Coronavirus 2019; CT = computed tomography; ECG = electrocardiogram; EOS = end of study; EOT = end of treatment; ePRO = electronic patient-reported outcome; ET= early termination (from treatment); EW = early withdrawal (from study); FDA = Food and Drug Administration; PCR = polymerase chain reaction; PK=pharmacokinetic; QD = once daily; RT = reverse transcription; SARS-CoV-2= Severe Acute Respiratory Syndrome Coronavirus 2; SoC = standard of care; WHO = World Health Organization.

Note that patients will undergo assessments during hospitalization or could be discharged after the start of study treatment as early as Day 2 if judged to be ready for discharge. Eligible patients must be in hospital for at least 24 hours after start of study treatment. If discharged, patients will then be requested to take study treatment at home (as prescribed) up to and including Day 14. If the patient has already been discharged, a telephone or digital media visit will be conducted on days for which no laboratory assessments are required (Days 3, 10, 22, 29, and 60) and an at-home or an on-site visit will be required on days requiring laboratory assessments (Days 5 and 14). Allowable windows for scheduling of study visits are -1 day for Day 3, ±1 day for Day 5, and ±2 days for Days 10, 22, 29, and 60. The Day 14 visit may be scheduled up to 2 days past the actual Day 14 date; however, dose administration will end at Day 14. Missed samples/assessments when phone visits occur will not be counted as protocol deviations.

a. Patients will be randomized after a laboratory-confirmed SARS-CoV-2 infection within 14 days of randomization as determined by real time RT-PCR or other commercial or public health assay authorized by FDA or other applicable health authority.
b. Patients will be randomized to receive either [redacted] of APX-115 treatment or placebo.
c. The COVID-19 clinical outcome will be evaluated for the 24 hours leading up to the assessment daily while hospitalized, the day after hospital discharge via telephone contact with the patient, at the scheduled visit(s) after hospital discharge, and if the patient is readmitted to the hospital or dies. Only the highest WHO scale score in the 24 hours leading up to each assessment will be recorded.
d. SARS-CoV-2 viral loads will be obtained by [redacted] self-collection at baseline (Day 1) and on Days 3, 5, 10, and 14 while hospitalized or on Days 5 and 14 if patient is discharged from hospital prior to Day 3.
e. A patient diary will be provided to the patient at the time of discharge from the hospital (if discharge occurs before EOT), which will be used to record date and time of dose administration and confirmation that dose was taken in a fasted state at approximately the same time in the morning, at least 2 hours after a morning meal if a morning meal is consumed. The patient diary will be reviewed at each scheduled visit post-hospital discharge.
f. If the patient is discharged from the hospital prior to EOS, patient-reported assessment of signs and symptoms of COVID-19 (see Appendix 7) will be self-evaluated at approximately the same time each day for each previous 24-hour period using an ePRO instrument through Day 60.
g. Screening laboratory tests will be assessed by a local laboratory. The clinical laboratory assessments do not need to be repeated if already done as SoC (eg, performed within 24 to 48 hours of screening or visit day and patient is clinically stable). Baseline and post-baseline laboratory tests will be assessed by the central laboratory. Post-baseline clinical laboratory assessment blood samples do not need to be taken predose. See Appendix 2 for a list of clinical chemistry, hematology, and urinalysis tests required.
h. Blood sampling for assessment of relevant biomarkers, [redacted] (Appendix 2), will occur predose on Day 1 and on Day 14.
i. Oxygen saturation will be collected daily in the hospital or, if the patient is discharged from the hospital prior to EOS, pulse oximetry devices will be provided to the patient for daily self-collection and reporting using ePRO.
j. Vital signs including blood pressure, pulse rate, respiratory rate, and body temperature will be obtained at screening and on Days 1, 3, 5, 10, 14, and 22 while hospitalized or on Days 5 and 14 if patient is discharged from hospital prior to Day 3.
k. A 12-lead ECG will be scheduled prior to first study drug administration either at screening or Day 1 predose and on Day 14. If the patient is discharged from hospital before Day 14, an ECG will be performed on the day of hospital discharge instead of on Day 14. The 12-lead ECG does not need to be repeated if already done as SoC (eg, performed within 24 to 48 hours of screening or visit day and patient is clinically stable).
l. Chest x-ray or CT scan will be performed at screening and either at hospital discharge, at ET, or at EW, whichever comes first. (Note: only 1 scan must be done for hospital discharge, ET, or EW). Chest x-ray or CT scan does not need to be repeated at screening if performed as SoC and done within 48 hours of screening. Chest x-ray or CT scan is not required post-hospital discharge.
m. Blood samples will be collected for 20 hospitalized patients on Day 1 at predose and 1, 2, 8, and 12 hours postdose. On Day 5, if patient is still hospitalized, a predose sample will be collected. On Day 14, if patient is still hospitalized, blood samples will be collected at predose and 1, 2, 8, and 12 hours postdose. For patients discharged from hospital prior to Day 5 or Day 14, the blood sample collections on Day 5 and/or Day 14 can be omitted.
n. Study drug (either [redacted] of APX-115 or placebo as per randomization) will be administered QD for 14 consecutive days in a fasted state at approximately the same time in the morning, at least 2 hours after a morning meal if a morning meal is consumed on Days 1 to 14, inclusive. If patient is discharged during the study treatment period, a quantity of APX-115 or placebo sufficient for QD dosing through Day 14 will be dispensed at the time of patient discharge from the hospital.

o. If patient is discharged during the study treatment period, a quantity of APX-115 or placebo sufficient for QD dosing through Day 14 will be dispensed at the time of patient discharge from the hospital. The patient will return any unused study drug after final dose administration on Day 14.
p. For female patients of child bearing potential, serum pregnancy at screening and urine pregnancy at end-of-study. The site will provide the urine pregnancy kit to the patient at the previous visit or at hospital discharge.
q. On the day after hospital discharge, a telephone call will be made to the patient to obtain a clinical improvement score (WHO COVID-19 Clinical Improvement Ordinal Scale) assessment covering the 24-hour period after hospital discharge. Only the highest WHO scale score in the 24 hours leading up to the assessment will be recorded.

Appendix 6: World Health Organization COVID-19 Clinical Improvement Ordinal 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
Dead	Death	8

Abbreviations: ECMO = extracorporeal membrane oxygenation; RRT = renal replacement therapy.

Source: World Health Organization. WHO R&D Blueprint. Novel Coronavirus COVID-19 Therapeutic Trial Synopsis. Draft 18 February 2020. Available at: https://www.who.int/publications/i/item/covid-19-therapeutic-trial-synopsis

Appendix 7: Patient-Reported Assessment of COVID-19-Related Symptoms

What was the **severity of each of the following symptoms** over the **last 24 hours?** (Select the severity you experienced for each of the symptoms)				
Stuffy or runny nose	None	Mild	Moderate	Severe
Sore throat	None	Mild	Moderate	Severe
Shortness of breath (difficulty breathing)	None	Mild	Moderate	Severe
Cough	None	Mild	Moderate	Severe
Fatigue (low energy or tiredness)	None	Mild	Moderate	Severe
Weakness	None	Mild	Moderate	Severe
Muscle or body aches	None	Mild	Moderate	Severe
Headache	None	Mild	Moderate	Severe
Chills or shivering	None	Mild	Moderate	Severe
Feeling hot or feverish	None	Mild	Moderate	Severe
Nausea (feeling like you wanted to throw up)	None	Mild	Moderate	Severe
How many times did you **vomit (throw up)** in the **last 24 hours**? (Select the number of times)	Not at all	1 or 2 times	3 or 4 times	5 or more times
How many times did you have **diarrhea (loose or watery stools)** in the **last 24 hours**? (Select the number of times)	Not at all	1 or 2 times	3 or 4 times	5 or more times
Rate your sense of **smell** in the **last 24 hours** (Select the appropriate description)	THE SAME AS usual	LESS THAN usual	NO sense of smell	
Rate your sense of **taste** in the **last 24 hours** (Select the appropriate description)	THE SAME AS usual	LESS THAN usual	NO sense of taste	
In the **last 24 hours**, have you **returned to your usual health** (before your COVID-19 illness)? (Select "Yes" or "No".)	Yes	No		
In the **last 24 hours**, have you **returned to your usual activities** (before your COVID-19 illness)? (Select "Yes" or "No".)	Yes	No		
In the past **24 hours**, what was the **severity** of your **overall** COVID-19-related symptoms at their worst? (Select the severity you experienced overall)	None	Mild	Moderate	Severe