NCT #: NCT04439071

CLINICAL PROTOCOL

EVALUATION OF THE EFFICACY AND SAFETY OF PTC299 IN HOSPITALIZED SUBJECTS WITH COVID-19 (FITE19)

PTC299-VIR-015-COV19

02 JUNE 2021

VERSION 7.0

PTC THERAPEUTICS, INC.
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PROTOCOL IDENTIFIERS AND STUDY PERSONNEL

Project Code	PTC299
Therapeutic Area	Virology
PTC Therapeutics Substance Identifier	PTC299
Nonproprietary Name	Emvododstat
IND Number	IND 149385
EudraCT Number	2020-001872-13
Protocol Number	PTC299-VIR-015-COV19
Protocol Version	7.0
Protocol Version Date	02 June 2021
Protocol Phase	Phase 2/3
Protocol Title	Evaluation of the efficacy and safety of PTC299 in hospitalized subjects with COVID-19 (FITE19)
PTC Clinical Lead	[redacted]
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The eSignature page is located on the last page.

PRINCIPAL INVESTIGATOR AGREEMENT AND SIGNATURE

I have read the protocol document and, on behalf of my institution, agree to comply with the protocol and all applicable regulations.

Principal Investigator	**Date**

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SYNOPSIS

Study Number	PTC299-VIR-015-COV19
Name of Investigational Product	Emvododstat (PTC299)
Study Title	Evaluation of the efficacy and safety of PTC299 in hospitalized subjects with COVID-19 (FITE19)
Proposed Indication	Treatment of COVID-19
Number of Study Sites	Approximately 50
Phase of Trial	Phase 2/3
Study Objectives	***Primary Study Objective*** To evaluate the clinical efficacy of PTC299 compared with placebo assessed by time to respiratory improvement in adult subjects hospitalized with COVID-19.
	Secondary Study Objectives • To evaluate the clinical efficacy of PTC299 compared with placebo, as assessed by respiratory function, immune response, length of hospitalization, and mortality. • To evaluate the safety of PTC299 as assessed by drug-related adverse events.
Study Endpoints	***Primary Endpoint*** • Time from randomization to respiratory improvement, defined as peripheral oxygen saturation (SpO_2) ≥94% on room air, sustained until discharge from the hospital or the end of the study (Day 28).
	Secondary Endpoints • The proportion of subjects requiring invasive ventilation at any point during the study • The proportion of subjects requiring supplemental oxygen or non-invasive ventilation at any point during the study in subjects who did not require supplemental oxygen at baseline • Time from randomization to defervescence in subjects presenting with fever at enrollment (temperature of ≥37.6°C axilla, ≥38.0°C oral, or ≥38.6°C tympanic or rectal) • Time from randomization to respiratory rate ≤24 breaths/minute on room air • Time from randomization to cough reported as mild or absent (on a scale of severe, moderate, mild, absent, in those with cough at enrollment rated severe or moderate)

	• Time from randomization to dyspnea reported as mild or absent (on a scale of severe, moderate, mild, absent, in those with dyspnea at enrollment rated as severe or moderate) • Attenuation of immune responses as indicated by: – reduction in cytokine levels, potentially including interleukin (IL)-2, IL-6, IL-7, IL-17, granulocyte-colony stimulating factor, interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α – reduction in levels of acute phase proteins, potentially including ferritin, C-reactive protein, D-dimer, and cardiac troponin – normalization in the complete blood count – changes in other laboratory parameters potentially including decreases in lactate dehydrogenase, prothrombin time, and albumin • Reduction in viral load • Duration of hospitalization measured in days • Mortality at Day 28 • Overall safety profile characterized by type, frequency, severity, timing, and relationship to study treatment of any adverse events (AEs) or laboratory abnormalities.
Study Population	Hospitalized adult subjects with confirmed pneumonia, diagnosed with COVID-19, and not requiring mechanical ventilation. For the purposes of enrollment of subjects into the study, "hospitalized patients" will include any COVID-19 patient either admitted or under observation in the hospital for a continuous period of 24 hours or more who otherwise fulfills the eligibility criteria.
Sample Size	A total of 326 events in the study will provide more than 80% of power to detect a hazard ratio of 1.38 at two-sided type I error of 0.05. Approximately 380 subjects, in total, will be needed. 190 randomized to PTC299 and 190 randomized to placebo. Enrollment will be halted when approximately 40 subjects (20 in each arm) have been enrolled and an interim analysis of safety data will be conducted when those 40 subjects have received 14 days of treatment and 14 days of follow-up. Enrollment will continue if there are no safety concerns.
Methodology/Study Design	This is a randomized, double-blind, placebo-controlled, multicenter 28 -day study with safety follow-up by telephone call at Day 60.

	Subjects will be randomized 1:1 to PTC299 treatment or placebo, with approximately 190 subjects in each cohort. The randomization will be stratified by age (≤62 vs >62), remdesivir use (yes vs no), and dexamethasone use (yes vs no). All subjects will also receive standard of care (SOC) defined per local written policies or guidelines. The use of steroids (except dexamethasone), sensitive CYP2D6 substrates, CYP2C inducers, IL-6 neutralizing antibodies, IL-6 receptor inhibitors, and any investigational therapy are prohibited. Following eligibility screening and enrollment, subjects will receive oral tablets containing PTC299 or matching placebo 200 mg twice daily (morning and evening) on Days 1 to 7 and 50 mg once daily (morning) on Days 8 to 14. Approximately 40 subjects (20 in each arm) will be enrolled initially, enrollment will then halt, and an interim analysis will be performed to assess safety. No formal statistical testing will be performed at the first interim analysis. An independent data and safety monitoring board (DSMB) will review available data for the 40 subjects. Enrollment will continue if there are no safety concerns. In addition to the DSMB, an independent Hepatic Advisory Safety Committee (HAC) will also review data related to liver events. A second interim analysis is planned to assess futility. It will be performed when 50% of respiratory improvement events have been reached, ie, 163 events have been observed (approximately 190 subjects). The unblinded interim analyses will be conducted by an independent statistician and the results will be only shared with the closed session of the DSMB. DSMB will make the go- or no-go recommendations and the recommendations will be communicated with the study team. The study team will be kept blinded for results related to the interim analyses. Subjects will be assessed daily while hospitalized. All subjects will undergo efficacy, safety, and laboratory assessments as summarized in Table 3. There will be a follow-up telephone call at Day 60 to assess AEs, serious AEs, and deaths. For subjects who are discharged from the hospital prior to Day 28: • If SpO_2 is <94%, SpO_2 measurements will be taken daily until Day 28 • Subject-reported assessments for cough and dyspnea will continue to Day 28 • No other assessments will take place except for those specified at Day 14, 28 and Day 60 in the protocol. All subjects will undergo the assessments specified for Day 14 and Day 28, and participate in the Day 60 telephone call, even if they are discharged from the hospital prior to Day 28.

Main Inclusion Criteria	1. Subject (or legally authorized representative) is willing and able to provide informed consent and comply with all protocol requirements. 2. Agrees to the collection of nasopharyngeal swabs and venous blood and all other protocol-specified procedures. 3. Male or non-pregnant female adult ≥18 years of age at time of enrollment. 4. Hospitalized and has laboratory-confirmed infection with SARS-CoV-2. 5. Symptom onset was ≤14 days prior to Screening. 6. Has SpO_2 <94% on room air 7. Has at least one of respiratory rate >24 breaths/minute or cough 8. Lung involvement as confirmed by radiographic infiltrates observed on imaging (chest X-ray, CT scan, or an equivalent test) 9. Women of childbearing potential (as defined in (CTFG 2014)) must have a negative pregnancy test at screening and agree to abstinence or the use at least one of the following highly effective forms of contraception (with a failure rate of <1% per year when used consistently and correctly). Contraception or abstinence must be continued for the duration of the study following discharge from the hospital, and for up to 50 days after the last dose of study drug: • combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation: – oral – intravaginal – transdermal • progestogen-only hormonal contraception associated with inhibition of ovulation: – oral – injectable – implantable • intrauterine device • intrauterine hormone-releasing system • vasectomized partner with confirmed azoospermia All females will be considered of childbearing potential unless they are postmenopausal (at least 12 months consecutive amenorrhea in the appropriate age group without other known or suspected cause) or have been sterilized surgically (eg, bilateral tubal ligation, hysterectomy, bilateral oophorectomy). 10. Men sexually active with women of childbearing potential who have not had a vasectomy must agree to use a barrier method of birth control during the study following discharge from the hospital and for up to 50 days after the last dose of study drug.

Main Exclusion Criteria	1. Requires mechanical ventilation 2. Current participation in any other interventional study 3. Alanine transaminase/aspartate transaminase levels ≥3times the upper limit of normal(×ULN) or total bilirubin (Tbili) ≥2×ULN 4. Lymphocyte count <500 lymphocytes/μL or hemoglobin <11.0 g/dL 5. Stage 4 severe chronic kidney disease or requiring dialysis (ie, estimated glomerular filtration rate <30) 6. Any other condition, that in the opinion of the investigator, may be cause to exclude the subject from the study. 7. Use of steroids (except dexamethasone), sensitive CYP2D6 substrates, CYP2C inducers, IL-6 neutralizing antibodies, IL-6 receptor inhibitors, or any investigational therapy. 8. Pregnancy or breast feeding. 9. Anticipated transfer to another hospital which is not a study site within 72 hours. 10. Known allergy to PTC299 or excipients
Pharmacokinetics	At select sites, pharmacokinetics (PK) will be assessed after the single dose (Day 1) and repeated dosing Day 7 and 14. Blood samples will be collected on Days 1 and 7 at pre-dose (0), and 6 hours post-dose and on Day 14 at pre-dose (0) and 4 hours post-dose (morning dose only).
Study Treatment	PTC299 or matching placebo orally administered tablets at a dose of 200 mg twice per day for Days 1 to 7 followed 50 mg orally administered once daily on Days 8 to 14.
Duration of Treatment	Subjects will receive treatment for 14 days then follow-up for 14 days to give a total study duration of 28 days, with a safety follow-up telephone call at Day 60.
Safety Monitoring	Subjects will be monitored closely for AEs and laboratory abnormalities during the study. An independent DSMB will monitor ongoing results to ensure subject well-being and safety as well as study integrity. The DSMB will make recommendations about early study closure or changes to study arms. Additionally, an independent HAC will oversee the hepatic safety of subjects in the study.
Statistical Methods	The primary endpoint is time from randomization to respiratory improvement, defined as SpO_2 ≥94% on room air sustained until discharge from the hospital or the end of the study (Day 28). Kaplan-Meier plots of time to respiratory improvement will be presented. Median time to respiratory improvement will be estimated via the Kaplan-Meier product limit method. A two-sided 95% confidence interval (CI) for the median time to respiratory improvement will be computed for PTC299 and placebo cohorts based on a log-log transformed CI for the survivor function S(t). Time to respiratory improvement will be compared between treatment groups using stratified log-rank test.

	Hazard ratio and corresponding two-sided 95% CIs will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the stratification factors. Respiratory improvement rates at Days 7, 14, and 28 will also be estimated using Kaplan-Meier estimates on the time to respiratory improvement curve. Associated two-sided 95% CIs for each treatment group and the difference between the 2 treatment groups will be calculated using Greenwood's formula for variance derivation. Subjects will be randomized 1:1 to PTC299 or placebo (approximately 190 subjects in each cohort). The randomization will be stratified by age (≤62 vs >62), remdesivir use (yes vs no), and dexamethasone use (yes vs no). This is a group sequential design with 2 interim analyses planned. The first interim analysis will only assess the safety and the trial will not be stopped for futility or superiority of efficacy. It will be performed after the first 40 randomized subjects have completed Day 28 or discontinued due to death, withdrew consent, or were lost-to-follow-up. The second interim analysis is to assess futility and will be performed when 50% of respiratory improvement events have been reached, ie, 163 events have been observed (approximately 190 subjects). All subjects who have completed through Day 28, were discharged with SpO_2 ≥94% on room air, withdrew consent, died, were lost to follow-up, or took any COVID-19 rescue therapy during the study will be included in the interim analysis. Subjects whose primary event cannot be determined at the interim cut, ie, ongoing subjects, will not be included in the interim efficacy analysis. Subjects who died, withdrew consent, were lost to follow-up, or took any COVID-19 rescue therapy will be censored at Day 28. A stratified log-rank test will be performed and the hazard ratio (treatment vs placebo) will be compared with the futility boundary. The trial may be stopped for futility if the hazard ratio is less than 1.091. The futility boundary is based on Lan-DeMets beta spending function (non-binding option) with overall beta of 80%. The sample size was calculated based on the primary endpoint of time to respiratory improvement. It is anticipated that the median time to respiratory improvement for the placebo group is 11 days and PTC299 treatment will decrease it to 8 days, an improvement of 3-days. Subjects will be followed for the fixed amount of time of 28 days from randomization (corresponding to the anticipated improvement rates of 0.829 and 0.912 at Day 28 for placebo and PTC299, respectively). A total of 326 events will provide more than 80% of power to detect a hazard ratio of 1.38 at two-sided type I error of 0.05. Approximately 380 subjects, in total, will be needed. Demographic and baseline characteristics, disposition, and safety will be summarized descriptively by treatment group.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialized Term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AML	Acute myeloid leukemia
aPTT	Activated partial thromboplastin time
ARDS	Acute respiratory distress syndrome
AST	Aspartate transaminase
AUC	Area under the curve
$AUC_{0\text{-last}}$	Area under the curve from time 0 to last measurement
BCRP	Breast cancer resistance protein
BID	Three times per day
βHCG	beta human chorionic gonadotropin
CBC	Complete blood count
CI	Confidence interval
C_{max}	maximum observed concentration
COVID-19	Coronavirus disease 2019
CPK	Creatine phosphokinase
CRF	Case report form
CRO	Contract Research Organization
CRP	C-reactive protein
DHO	Dihydroorotate
DHODH	Dihydroorotate dehydrogenase
DILI	Drug-induced liver injury
DSMB	Data and safety monitoring board
EC	Ethics committee
eCRF	Electronic case report form
GCP	Good Laboratory Practice
G-CSF	Granulocyte-colony stimulating factor
GGT	Gamma-glutamyl transpeptidase
EDC	Electronic data capture system
HAC	Hepatic advisory safety committee
HV	Healthy volunteer
ICF	Informed consent form
ICH	International Council for Harmonisation
ICU	Intensive care unit
IL	Interleukin
INR	International normalized ratio
IP-10	Interferon gamma-induced protein 10
IRB	Institutional Review Board
ITT	Intent-to-treat
LFTs	Liver function tests
LDH	Lactate dehydrogenase
MCP	Monocyte chemoattractant protein
MedDRA	Medical Dictionary for Regulatory Activities
MIP	Macrophage inflammatory protein
PD	Pharmacodynamics
PK	Pharmacokinetic
PTC	PTC Therapeutics
QD	Once daily

Abbreviation or Specialized Term	Explanation
RSI	Reference Safety Information
RNA	Ribonucleic acid
SAE	Severe adverse event
SAP	Statistical analysis plan
SOC	Standard of care
SOP	Standard Operating Procedure
SpO_2	Peripheral oxygen saturation
$t_{1/2}$	Half-life
Tbili	Total bilirubin
TEAEs	Treatment-emergent adverse events
TID	Three times per day
T_{max}	Time to C_{max}
TNF-α	Tumor necrosis factor-alpha
ULN	Upper limits of normal
VEGF	Vascular endothelial growth factor
WBC	White blood cell
WOCBP	Women of childbearing potential

1. INTRODUCTION

Since the first patient with a pneumonia of unknown origin in late December 2019 in Wuhan City, China, a new coronavirus, designated SARS-CoV-2, has resulted in a rapidly spreading world-wide pandemic of respiratory illness termed coronavirus disease 2019 (COVID-19). SARS-CoV-2 is a positive sense, ribonucleic acid (RNA) virus of zoonotic origin and is a member of the coronavirus family. Due to its novelty and the apparent lack of population or group immunity, COVID-19 has been spreading rapidly in many countries across the globe causing great harm to human health, economic activity, and disrupting the social fabric on many levels (Wang 2020a). Since it was first described in November 2019, COVID-19 has rapidly spread across the globe and millions of people have become infected.

All ages are susceptible to infection with SARS-CoV-2 (Cheng 2020, Li 2020). The clinical features of COVID-19 are varied, ranging from an asymptomatic state to acute respiratory distress syndrome (ARDS), multi-organ dysfunction, and death (Chen 2020a, Huang 2020, Liu 2020a, Wang 2020b). According to current analyses, about 80% of the cases resolve with at home care and supporting therapy and 20% require hospitalization of which 25% to 30% develop severe respiratory complications. The overall fatality from COVID-19 is estimated to range from 1% to 5% with a higher risk of death in the elderly and persons with underlying comorbidities (50% to 70% of fatal cases) (CEBM 2020, Coronavirus Outbreak 2020).

COVID-19 can be broadly divided into 3 stages (Shi 2020, Siddiqi 2020):

- An asymptomatic incubation period;
- Non-severe period of early stage typified by rapid viral proliferation;
- Severe respiratory symptomatic stage of the disease typified by a rise in inflammatory cytokines and the influence of comorbidities on disease progression and prognosis.

The common clinical features of COVID-19 include fever, cough, sore throat, headache, fatigue, myalgia, and shortness of breath. In a subset of patients, by the end of the first week, the disease can progress to pneumonia, respiratory failure, organ failure, and death. SARSCoV-2 targets ciliated cells that are subsequently shed. The disease progression is also associated with extreme rise in inflammatory cytokines including interleukin (IL)-2, IL-7, IL-10, granulocyte-colony stimulating factor (G-CSF), interferon gamma-induced protein 10 (IP-10), monocyte chemoattractant protein (MCP)1, macrophage inflammatory protein (MIP)1A, tumor necrosis factor alpha (TNF-α), and vascular endothelial growth factor (VEGF) (Chen 2020a, Huang 2020). Both IL-6 and IL-17 have been implicated in ARDS (Wang 2020b, Xu 2020). Levels of IL-6 appear to play an important role in COVID-19 disease severity as there is strong evidence that IL-6 peak levels are associated with severity of pulmonary complications (Russell 2020).

The hyper-induction of pro-inflammatory cytokines - also referred to as a “cytokine storm” or cytokine release syndrome - is common in acute viral infections and can lead to tissue damage and pulmonary pathology (Liu 2020b). VEGF, which plays a role in the pathogenesis of ARDs, has also been found to be increased in patients with COVID-19 (Liu 2020b) The viral load of SARS-CoV-2 detected in the patient’s respiratory tract is positively linked to lung disease severity (Liu 2020b).

PTC299 (emvododstat) is an orally available inhibitor of dihydroorotate dehydrogenase (DHODH), a key enzyme in de novo pyrimidine nucleotide synthesis. Inhibition of DHODH results in the depletion of pyrimidine nucleotides in rapidly dividing cells, leading to a G1/S phase cell cycle arrest and subsequent differentiation or cell death. Therefore, by limiting host pyrimidine nucleotide levels, PTC299 can arrest viral RNA replication, reduce viral load, and reduce cytokine release.

Compounds that inhibit DHODH enzyme activity have been shown to have broad-spectrum antiviral activity (Lucas-Hourani 2015, Munier-Lehmann 2015, Lewis 2016, Diedrichs-Mohring 2018, Lolli 2018, Sykes 2018, Chen 2019, Mei-jiao 2019, Xiong 2020). This is due to the central role of DHODH in pyrimidine nucleotide synthesis and the high need for new pyrimidine nucleotide synthesis in viral RNA replication. The DHODH inhibitors are particularly active against RNA viruses of both positive and negative strand genome polarity and have shown efficacy against coronaviruses and a number of other respiratory RNA viruses (Hoffmann 2011, Wang 2011, Lucas-Hourani 2013, Ortiz-Riano 2014, Cheung 2017, Lucas-Hourani 2017, Luthra 2018, Yang 2018, Chen 2019, Xiong 2020). As DHODH inhibitors target a host protein, they are expected to retain antiviral activity against all strains of SARS-CoV-2 and minimize the emergence of viral resistance.

In addition to their potential antiviral effects, DHODH inhibitors also suppress the excessive immune response common to viral infections which results from increased cytokine expression (cytokine storm) (Xiong 2020). This hyperactive immune response results in an extreme inflammatory response, resulting in pulmonary and multi-organ dysfunction and damage, ultimately leading to multiple organ failure. In the lung, the inflammatory response can lead to fatal pneumonia, pulmonary infiltration and down-stream fibrosis that can result in the need for ventilatory support. Lung inflammation is the leading cause of mortality in SARS-CoV-2 infection. Therefore, PTC299 may not only affect viral replication, but can provide protection against the hyperinflammatory process that underpins virus-related mortality.

Pre-clinical data indicate PTC299 inhibits a range of RNA viruses and suppresses hyper cytokine expression. PTC299 has been extensively evaluated in 9 completed clinical studies; 5 were in oncology (n=134) and 4 were in healthy volunteers (n=169). A further study in oncology patients is ongoing. Across these studies, PTC299 was generally well-tolerated over a range of dosing regimens.

1.1. Study Rationale

The rationale to assess PTC299 for the treatment of COVID-19 is based on experimentally validated evidence of PTC299's ability to target two key aspects of COVID-19 pathogenesis: 1) inhibition of DHODH reduces SARS-CoV-2 replication (Xiong 2020) and 2) PTC299 inhibits excessive cytokine production associated with viral infections (Xiong 2020).

PTC299, similar to other DHODH inhibitors, demonstrates broad-spectrum antiviral activity in vitro inhibiting both positive- and negative-sense RNA viruses (PTC299-2020-007, PTC299-2020-009, and PTC299-2020-011). Importantly, PTC299 inhibits SARS-CoV-2 in cell culture models (data on file).

DHODH inhibitors also attenuate cytokine storms that can significantly contribute to pulmonary pathology, organ failure, and death in viral infections, specifically with SARS-CoV-2 (Yoshikawa 2009, Xiong 2020). Levels of IL-2, IL-7, IL-10, G-CSF, IP-10, MCP-1, MIP-1A, and TNF were found to be higher in COVID-19 patients in the intensive care unit (ICU) than in those patients not in the ICU, indicating that these cytokines may be specific markers of severe disease (Huang 2020). The effect of PTC299 on cytokine production was assessed using BioMAP profiling (BioSeek, now part of Eurofins). PTC299 was found to be a potent inhibitor of immunomodulatory and inflammation-related processes. Compared with vehicle control, PTC299 resulted in:

- Decreases in immunomodulatory-associated proteins: CD40, soluble (s)IgG, sIL-17A, sIL-17F, sIL-6, sIL-2, sIL-10
- Decreases in inflammation-related proteins: MCP-1, IL-8, and sTNF-α
- Decreases in tissue remodeling proteins: MMP-1 and sVEGF

The strong rationale supporting the development of PTC299 for the treatment of COVID-19 is based on the following reasons:

- PTC299 is an inhibitor of cellular DHODH enzyme activity.
  - DHODH inhibitors have been shown to inhibit SARS-CoV-2 replication (Xiong 2020).
- PTC299 has demonstrated inhibition of SARS-CoV-2 replication in vitro
- PTC299 inhibits a host cell-protein, and similar to other host-targeting antivirals, has broad antiviral activity.
  - Host-targeting antivirals have advantages over direct virus-acting antivirals as they are not virus-specific – hence they can remain effective even if the virus mutates, thus minimizing the emergence of viral resistance.
- PTC299 inhibits cytokine storms due to viral infection that can cause tissue damage, pneumonia, and organ failure.
  - PTC299 reduces levels of IL-6 along with other cytokines; elevated levels of IL-6 are positively associated with severity of pulmonary complications

To date, there are no specific therapeutic agents for COVID-19 and currently treatment is supportive and based on symptomatology (Chen 2020b, Jin 2020). A therapeutic agent that targets both viral replication and the hyper-reactive immune response would offer a highly desirable treatment for COVID-19 management.

1.2. Risk/Benefit Assessment

Extensive clinical knowledge exists for PTC299 as it has been evaluated in >300 subjects in 9 completed clinical studies. In general, throughout this prior clinical experience, PTC299 was well-tolerated with minimal and manageable side-effects. Study PTC299-VIR-015-COV19 will have a data and safety monitoring board (DSMB) that will closely monitor the safety of patients. In addition, an independent Hepatic Advisory Safety Committee (HAC) will review all markers of possible liver toxicity.

The COVID-19 pandemic is a large, acute unmet medical need. The mechanism of action of PTC299 and the findings that it: a) has broad-spectrum antiviral activity and inhibits SARS-CoV-2 replication; b) reduces cytokine storms; and c) is well-tolerated indicate there is a positive benefit/risk profile for evaluating the drug in patients with COVID-19.

2. STUDY OBJECTIVE AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

The primary objective of the study is to evaluate the clinical efficacy of PTC299 compared with placebo assessed by time to respiratory improvement in adult subjects hospitalized with COVID-19.

2.1.2. Secondary Objectives

Secondary objectives of the study are as follows:

- To evaluate the clinical efficacy of PTC299 compared with placebo, as assessed by respiratory function, immune response, length of hospitalization, and mortality.
- To evaluate the safety of PTC299 as assessed by drug related adverse events.

2.1.3. Exploratory Objectives

There are no exploratory objectives in this study.

2.2. Endpoints

2.2.1. Primary Endpoint

The primary endpoint is the time from randomization to respiratory improvement, defined as peripheral oxygen saturation (SpO_2) ≥94% on room air sustained until discharge from the hospital or the end of the study (Day 28).

2.2.2. Secondary Endpoints

Secondary endpoints of the study are as follows:

- The proportion of subjects requiring invasive ventilation at any point during the study
- The proportion of subjects requiring supplemental oxygen or non-invasive ventilation at any point during the study in subjects who did not require supplemental oxygen at baseline
- Time from randomization to defervescence in subjects presenting with fever at enrollment (temperature of ≥37.6°C axilla, ≥38.0°C oral, or ≥38.6°C tympanic or rectal)
- Time from randomization to respiratory rate ≤24 breaths/minute on room air
- Time from randomization to cough reported as mild or absent (on a scale of severe, moderate, mild, absent, in those with cough at enrollment rated severe or moderate)

- Time from randomization to dyspnea reported as mild or absent (on a scale of severe, moderate, mild, absent, in those with dyspnea at enrollment rated as severe or moderate)
- Attenuation of immune responses as indicated by:
  - reduction in cytokine levels, potentially including interleukin (IL)-2, IL-6, IL-7, IL-17, G-CSF, IP-10, MCP-1, MIP1-α, and TNF-α
  - reduction in levels of acute phase proteins, potentially including ferritin, C-reactive protein, D-dimer, and cardiac troponin
  - normalization in the complete blood count
  - changes in other laboratory parameters potentially including decreases in lactate dehydrogenase, prothrombin time, albumin
- Reduction in viral load
- Duration of hospitalization measured in days
- Mortality at Day 28
- Overall safety profile characterized by type, frequency, severity, timing, and relationship to study treatment of any adverse events (AEs) or laboratory abnormalities.

2.2.3. Exploratory Endpoints

There are no exploratory endpoints in this study.

3. STUDY DESIGN

3.1. Overall Design

This is a randomized, double-blind, placebo-controlled, multicenter 28-day study, with a safety follow-up telephone call at Day 60.

The study population is hospitalized adult subjects with confirmed pneumonia, diagnosed with COVID-19, and not requiring mechanical ventilation. For the purposes of enrollment of subjects into the study, "hospitalized patients" will include any COVID-19 patient either admitted or under observation in the hospital for a continuous period of 24 hours or more who otherwise fulfills the eligibility criteria.

Subjects will be randomized 1:1 to PTC299 treatment or placebo using a central randomization process, with approximately 190 subjects in each cohort. The randomization will be stratified by age (≤62 vs >62), remdesivir use (yes vs no), and dexamethasone use (yes vs no). All subjects will also receive standard of care (SOC), defined as the SOC per local written policies or guidelines. The use of steroids (except dexamethasone), sensitive CYP2D6 substrates, CYP2C inducers, IL-6 neutralizing antibodies, IL-6 receptor inhibitors, and any investigational therapies are prohibited.

Following eligibility screening and enrollment, subjects will receive oral tablets containing PTC299 or matching placebo 200 mg twice daily (BID) (morning and evening) on Days 1 to 7 and 50 mg once daily (QD) in the morning on Days 8 to 14.

Approximately 40 subjects (20 in each arm) will be enrolled initially, enrollment will then halt, and an interim analysis will be performed to assess safety. No formal statistical testing will be performed at the interim analysis. An independent data safety monitoring board (DSMB) and an independent HAC will review available data for the 40 subjects. Enrollment will continue if there are no safety concerns.

A second interim analysis is planned to assess futility. It will be performed when 50% of respiratory improvement events have been reached, ie, 163 events have been observed (approximately 190 subjects).

Subjects will be assessed daily while hospitalized. All subjects will undergo efficacy, safety, and laboratory assessments as summarized in Table 3. There will be a follow-up telephone call at Day 60 to assess AEs, SAEs, and deaths.

For subjects who are discharged from the hospital prior to Day 28:

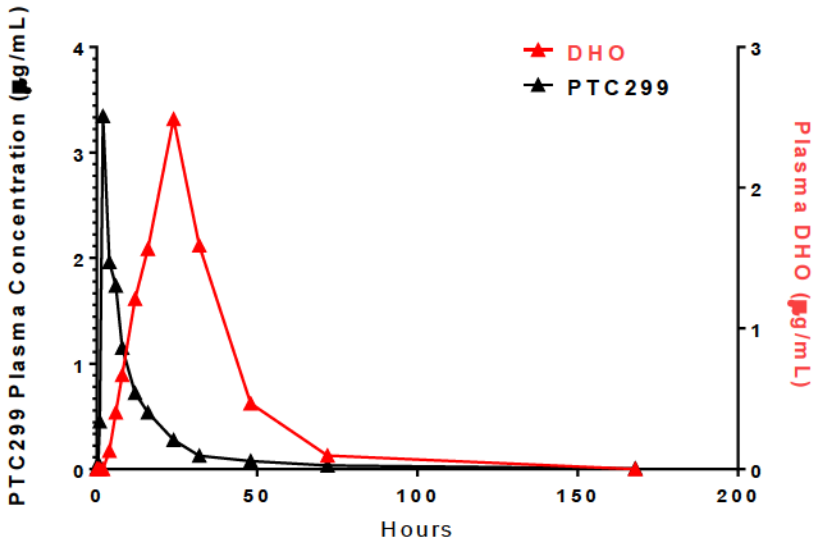
- If SpO_2 is <94%, SpO_2 measurements will be taken daily until Day 28
- Subject-reported assessments for cough and dyspnea will continue to Day 28
- No other assessments will take place except for those specified at Day 14, 28 and Day 60 in the protocol.

All subjects will undergo the assessments specified for Day 14 (End of Treatment) and Day 28 (End of Study), and participate in the Day 60 telephone call, even if they are discharged from the hospital prior to Day 28.

3.2. Justification of Dose

In a preclinical study, monkeys were given a single oral 10 mg/kg capsule dose of PTC299. Plasma levels of DHO, the substrate for DHODH, increased after dosing, peaked at 24 hours and then decreased (Figure 1). The exposure for PTC299 was 22.5 µg*hr/mL. The attainment of the peak DHO concentration was delayed relative to the peak concentration of PTC299 (24 hours vs. 2 hours) (Table 1). These data suggest that an exposure of approximately 22.5 µg*hr/mL will result in significant DHODH inhibition.

Figure 1: Plasma DHO and PTC299 Concentrations after a Single Oral Dose of PTC299



Abbreviations: DHO, dihydroorotate

Table 1: Summary of PK and PD Parameters

	PTC299	DHO
$AUC_{0\text{-last}}$ (µg·hr/mL)	22.5	71.4
C_{max} (µg/mL)	2.51	2.48
T_{max} (hr post-dose)	2	24
Half-life (hr)	33	10

Abbreviations: AUC, area under the curve: DHO, dihydroorotate

Clinical Data

The ability of PTC299 to inhibit DHODH in humans was examined in the Phase 2 clinical study PTC299-ONC-007-NF2 (Study 007). Study 007 evaluated PTC299 monotherapy in adult patients with neurofibromatosis type 2 (NF2). PTC299 was administered at a dose of 100 mg capsule BID (corresponding to 250 mg BID of the tablet formulation).

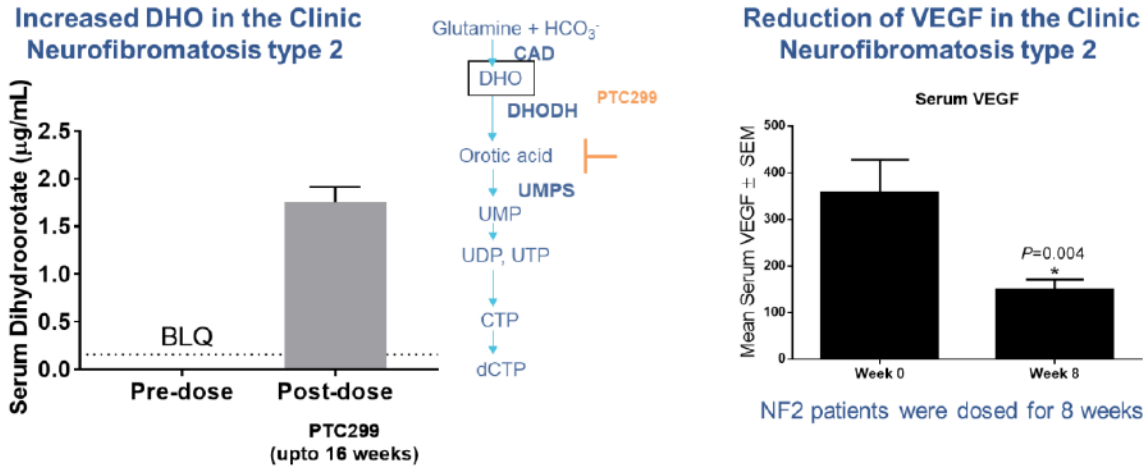
The serum levels of DHO were below the lower limit of quantification prior to dosing and were significantly elevated at either 8 or 16 weeks (Figure 2A), consistent with inhibition of DHODH by PTC299. The elevation of DHO levels (about 1.7 µg/mL) after PTC299 therapy is similar if not greater to that observed in a patient with Miller syndrome (0.537 µg/mL) (Duley 2016). Miller syndrome is caused by a mutation in the *DHODH* gene resulting in a deficiency in DHODH enzyme activity, which leads to elevated serum DHO levels (Duley 2016).

The activity of PTC299 as a DHODH inhibitor was also tested by assessing the effect on the production of the cytokine vascular endothelial growth factor (VEGF). VEGF levels are known to be abnormally elevated in NF2 patients (Plotkin 2009). DHODH inhibitors have been shown to suppress VEGF expression (Diedrichs-Mohring 2018). As shown in Figure 2B, serum VEGF levels were elevated prior to dosing but were normalized after 8 weeks of treatment to levels similar to those reported for healthy subjects (Raimondo 2001, Kut 2007), a statistically significant reduction.

The PTC299-dependent changes in DHO and VEGF levels strongly indicate the drug directly inhibits DHODH in these patients and elicits appropriate pharmacodynamic changes.

The reduction of VEGF levels was associated with a plasma concentration of PTC299 4 -hours post dose of 1.9 µg/mL, which is known to be close to C_{max}.

Figure 2: PTC299 Inhibits DHODH in Patients with Neurofibromatosis Type 2 Tumors



Legend: (A) DHO samples from a total of 4 patients pre- and post-dosing with PTC299 dosing. (B) VEGF plasma levels for 11 patients pre- and post-PTC299 dosing.
Source: Panel A (DH): PTC299-17030

Prediction based on in vitro SARS-CoV-2 data

A concentration of 250 nM PTC299 (117 ng/mL) reduced SARS-CoV-2 viral titer by 3-logs in media with 5% serum (PTC299-20-012). To maintain levels 10-fold above this concentration, or 1170 ng/mL, for 24 hours would result in an $AUC_{0\text{-}24h}$ of 28.1 µg*hr/mL. This is above the target level required for DHODH inhibition of 22.5 µg*hr/mL.

Dose Regimen Required to Reach AUC Shown to Inhibit DHODH

Clinical Study PTC299-ONC-002-HV evaluated the PK and safety of increasing doses of the capsule formulation of PTC299 in healthy volunteers (N=32; n=24 received PTC299 and n=8 received placebo).

Study 002 had 2 stages; in Stage 1, doses ranged from 0.3 to 1.2 mg/kg BID, and in Stage 2, a 1.6 mg/kg dose was administered TID (Table 2). Patients received the capsule formulation of PTC299 for 7 days in both stages. The 1.2 mg/kg capsule formulation should have similar exposure to the about 200 mg of the tablet formulation based on relative bioavailability; the tablet formulation has approximately 40% relative bioavailability compared with the capsule. For reference, Table 2 presents the approximate dose of the tablet formulation, which will be used in PTC299-VIR-015-COV19, for each dose of the capsule formulation administered in Study 002.

The exposure observed following the 1.2 mg/kg BID dose at Day 1 was 18 µg*hr/mL and at Day 7 was 32.9 µg*hr/mL (Table 2). The Day 1 exposure is similar to the exposure of 22.5 µg*hr/mL observed after about 24 hours in the rhesus monkey experiment that demonstrated DHODH inhibition. The C_{max} of PTC299 was 2.11 µg/mL, which is similar to that associated with DHODH inhibition (ie, 1.9 µg/mL) seen in patients in Study 007.

Based on the biological data outlined above, the PTC299 exposure after dosing at 1.2 mg/kg BID would result in significant reduction of DHODH enzyme activity in the clinic.

No serious adverse events were reported in Study 002.

Table 2: Summary of PTC299 Pharmacokinetics in Healthy Volunteers when Administered with the Capsule Formulation (~2.5x of the Bioavailability of the Tablet Formulation) (Study PTC299-ONC-002-HV)

Approximate Corresponding Dose[a]		Dose Frequency	Day	PTC299			
Tablet (mg)	Capsule (mg/kg)			T_{max} (h)	$T_{1/2}$ (h)	C_{max} (µg/mL)	AUC_{0-4} (µg·hr/mL)
50	0.3	BID	1	4.0	NA	0.28	4.31
125	0.6			3.0		0.71	10.1
200	**1.2**			**3.5**		**1.14**	**18.0**
280	1.6	TID		3.0		1.67	37.1
50	0.3	BID	7	3.5	164	0.51	8.44
125	0.6			4.0	210	1.11	18.6
200	**1.2**			**4.0**	**228**	**2.11**	**32.9**
280	1.6	TID		3.0	225	3.53	78.6

Abbreviations: AUC_{0-4}, area under the concentration curve from hour 0 to 4; C_{max}, maximal concentration; $T_{1/2}$, half-life; T_{max}, time to maximal concentration

[a] Study 002 only administered the capsule formulation of PTC299. The values for the tablet represent the approximate dose of the tablet formulation for reference. The dose calculations assume about a 70 kg body weight.
Note: The values in bold show the dose that results in exposures that are similar to those measured in Study PTC299-ONC-007-NF2.

Proposed dosing regimen

Subjects will be dosed for a total of 14 days and followed for an additional 14 days without dosing. Subjects will receive oral tablets containing PTC299 or matched placebo 200 mg BID (morning and evening) on Days 1 to 7 and 50 mg QD on Days 8 to 14. Subjects will subsequently be followed from Day 15 to 28, and there will be a telephone call at Day 60 to assess AEs, SAEs, and deaths.

The dosing regimen takes into consideration the typical progression of the disease including the disease characteristics in patients who are hospitalized with COVID-19. The dosing of 200 mg BID for the first 7 days will raise the exposure of the drug quickly to accommodate the need for rapid onset of PTC299 activity. The dosing of 50 mg QD for the second 7 days will prevent the exposure from substantially decreasing. Importantly, clinical evidence indicates that this dosing regimen should be well tolerated.

The dosing regimen is based on extensive clinical, safety, and clinical pharmacology experience with the capsule formulation of PTC299, which was used in the prior solid tumor clinical studies. The results from clinical study PTC299-ONC-002-HV (Study 002) indicate that 200 mg BID dosing would raise the exposure of PTC299 within 7 days to the anticipated therapeutic range (23 to 33 µg*hr/mL).

PTC299 200 mg tablet BID for 7 days is expected to be tolerated in patients.

The expected exposure from the proposed dosing regimen is expected to be well-tolerated, as the comparable exposure in Study 002 did not cause SAEs. The C_{max} after giving the 200 mg tablet BID for 7 days is anticipated to be about 2.11 µg/mL and is not expected to cause any safety concern, as similar plasma concentrations were observed in the patients who were treated with PTC299 capsule for >40 days.

Safety events with regard to increases in PTC299 levels due to saturation of elimination are unlikely as elimination of the drug will not be saturated with 7 days of 200 mg tablet BID dosing followed by 7 days of 50 mg tablet QD dosing. This is supported by results from Study 002 in which relative dose linearity was observed from 0.3 mg/kg to 1.2 mg/kg BID doses of PTC299 capsules (equivalent to 200 mg BID tablets). It is also supported by the ongoing AML open-label, non-randomized, phase 1b study, PTC299-HEM-001-LEU in which the steady state was reached at approximately Day 15 after administration of an 80 mg QD loading dose of the tablet formulation of PTC299 for 7 days followed by a 40 mg QD maintenance dose.

3.3. End of Study Definition

The study will end when the last subject has completed the final assessment.

4. STUDY POPULATION

4.1. Overview

The study population is hospitalized adult subjects with confirmed pneumonia, diagnosed with COVID-19, and not requiring mechanical ventilation. Approximately 380 subjects will be randomized: 190 subjects to placebo and 190 subjects to PTC299.

4.2. Inclusion Criteria

Before enrollment in the study, subjects must fulfil all of the following criteria:

1. Subject (or legally authorized representative) is willing and able to provide informed consent and comply with all protocol requirements.
2. Agrees to the collection of nasopharyngeal swabs and venous blood and all other protocol-specified procedures.
3. Male or non-pregnant female adult ≥18 years of age at time of enrollment.
4. Hospitalized and has laboratory-confirmed infection with SARS-CoV-2.
5. Symptom onset was ≤14 days prior to Screening
6. Has SpO_2 <94% on room air
7. Has at least one of respiratory rate >24 breaths/minute or cough
8. Lung involvement as confirmed by radiographic infiltrates observed on imaging (chest X-ray, CT scan, or an equivalent test)

9. Women of childbearing potential (as defined in (CTFG 2014)) must have a negative pregnancy test at screening and agree to abstinence or the use at least one of the following highly effective forms of contraception (with a failure rate of <1% per year when used consistently and correctly). Contraception or abstinence must be continued for the duration of the study following discharge from the hospital, and for up to 50 days after the last dose of study drug:
    - combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
        - oral
        - intravaginal
        - transdermal
    - progestogen-only hormonal contraception associated with inhibition of ovulation:
        - oral
        - injectable
        - implantable
    - intrauterine device
    - intrauterine hormone-releasing system
    - vasectomized partner with confirmed azoospermia

    All females will be considered of childbearing potential unless they are postmenopausal (at least 12 months consecutive amenorrhea in the appropriate age group without other known or suspected cause) or have been sterilized surgically (eg, bilateral tubal ligation, hysterectomy, bilateral oophorectomy).
10. Men sexually active with women of childbearing potential who have not had a vasectomy must agree to use a barrier method of birth control during the study following discharge from the hospital and for up to 50 days after the last dose of study drug.

4.3. Exclusion Criteria

Subjects will not be permitted to enroll in the study if any of the following criteria apply:

1. Requires mechanical ventilation
2. Current participation in any other interventional study.
3. Alanine transaminase/aspartate transaminase levels (ALT/AST) ≥3times the upper limit of normal (×ULN) or total bilirubin (Tbili) ≥2×ULN.
4. Lymphocyte count <500 lymphocytes/µL or hemoglobin <11.0 g/dL
5. Stage 4 severe chronic kidney disease or requiring dialysis (ie, estimated glomerular filtration rate <30)
6. Any other condition, that in the opinion of the investigator, may be cause to exclude the subject from the study.

7. Use of steroids (except dexamethasone), sensitive CYP2D6 substrates, CYP2C inducers, IL-6 neutralizing antibodies, IL-6 receptor inhibitors, or any investigational therapy.
8. Pregnancy or breast feeding.
9. Anticipated transfer to another hospital which is not a study site within 72 hours.
10. Known allergy to PTC299 or excipients.

4.4. Screen Failures

Any subject that does not meet inclusion or exclusion criteria within the defined screening window prior to randomization, will be considered a screen failure. Screening and randomization should occur within a 1-day period. Screen failures will be captured in the electronic data capture system (EDC). Screen failures can be rescreened after consultation with the Medical Monitor.

4.5. Strategies for Recruitment and Retention

Subjects will be recruited via existing populations with COVID-19 at identified investigational sites.

5. STUDY INTERVENTION

5.1. Study Intervention(s) Administration

5.1.1. Study Intervention Description

PTC299 or matching placebo tablets for oral administration will be provided in the 50 mg dosage strength.

5.1.2. Dosing and Administration

PTC299 or matching placebo oral tablets will be administered at a dose of 200 mg BID (morning and evening at approximately 12-hour intervals) on Days 1 to 7 followed by 50 mg QD (in the morning) on Days 8 to 14. It is recommended that PTC299 be administered with food.

Tablets will be administered in the hospital; should a subject be discharged prior to Day 14, tablets will be dispensed to take at home.

5.2. Preparation/Handling/Storage/Accountability

5.2.1. Accountability

Study personnel must ensure that all study drug supplies are kept in a secure locked area with access limited to authorized personnel. Study drug must not be used outside the context of this protocol. Under no circumstances should the investigator or site personnel supply study drug to other investigators or clinics or allow study drug to be used other than as directed by this protocol.

The investigator is responsible for keeping accurate records of the clinical supplies received from PTC or designee, the amount dispensed to and returned by the subjects, and the amount remaining at the conclusion of the trial.

Used and unused clinical supplies must be returned to PTC Therapeutics (PTC) or its designee after the study is completed. If the Standard Operating Procedure (SOP) at any site states that the drug cannot be returned and must be disposed of onsite, PTC must review the SOP of that site prior to any final disposition done by site. Records documenting the date of study medication destruction or shipping, and amount destroyed or shipped should be kept.

5.2.2. Formulation, Appearance, Packaging, and Labeling

PTC299 and matching placebo tablets for oral administration will be provided in 50 mg dosage strength.

Tablets will be packaged in bottles for distribution to investigational sites.

PTC299 and matching placebo tablets must be stored per the labeled storage conditions.

5.3. Measures to Minimize Bias: Randomization and Blinding

The study is performed in a double-blind fashion. The Investigator and study staff (including processing lab personnel), the subjects, and the sponsor's staff will remain blinded to the treatment until study closure. The investigational drug and its matching placebo are indistinguishable and will be packaged in the same way.

The randomization code will be kept strictly confidential. Further details are provided in the Pharmacy Manual.

Subjects will be randomized 1:1 to either PTC299 or placebo using a central randomization process. The randomization will be stratified by age (≤62 vs >62), remdesivir use (yes vs no), and dexamethasone use (yes vs no).

5.3.1. Emergency Procedure for Unblinding

The Investigator and the study staff must remain blinded to the subject's treatment assignment, even if the subject refuses to participate in any study procedures or experiences an AE. The identity of the study drug may be revealed only if the subject experiences a medical emergency whose management would be improved by the knowledge of the blinded treatment assignment.

The occurrence of any code break during the study must be clearly justified and explained by the Investigator. Before unblinding, every attempt must be made by the Investigator to discuss the intended code break with PTC. In all cases, the sponsor must be informed as soon as possible before or after the code break.

Any code break must be documented in a detailed report with the date and time of the code break and signed by the Investigator. This report is to be attached to the source documents and the date and time of code break will be documented in the eCRF.

5.4. Study Intervention and Compliance

Compliance will be calculated as described in Section 8.4.4.3.

5.5. Concomitant Therapy

All subjects in both cohorts will receive SOC, according to written local guidelines and practices.

Concomitant use of steroids (except dexamethasone), sensitive CYP2D6 substrates, CYP2C inducers, IL-6 neutralizing antibodies, IL-6 receptor inhibitors, or any investigational therapy will not be permitted.

Caution should be used in the concomitant administration of breast cancer resistance protein (BCRP) substrate drugs as intestinal BCRP inhibition by PTC299 following a 200 mg BID dose of PTC299 cannot be excluded; guidance should be sought from the study Medical Monitor in each case.

An attempt will be made to record all medications taken by subjects 30 days prior to the first dose of study drug and through Day 28.

All concomitant medications (prescription and over the counter), vitamin and mineral supplements, and herbs taken during the study will be documented on the concomitant medication electronic case report form (eCRF). Information recorded will include start and stop dates, dose and route of administration, and indication.

6. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

6.1. Discontinuation of Study Intervention

Subjects will receive study treatment until treatment discontinuation for one of the reasons listed below. However, subjects may discontinue study treatment or withdraw their consent to participate in the study at any time without prejudice.

The following conditions require subject discontinuation from all study treatment:

1. At their own request or at the request of their legally authorized representative
2. If a subject experiences an AE that is deemed related to treatment with PTC299 and in the Investigator's or the Sponsor's medical judgment continuation of treatment would be detrimental to the subject
3. At the specific request of a regulatory agency for termination of treatment of an individual subject or all subjects under the protocol
4. Subject participation in another clinical study using an investigational agent or investigational medical device
5. Refusal of sexually active fertile subjects (excluding subjects who have been sterilized) to use medically accepted methods of contraception
6. If a subject becomes pregnant
7. Significant noncompliance with the protocol in the opinion of the investigator or the sponsor
8. Disease progression necessitating (in the opinion of the investigator) discontinuation of study treatment

Subjects who discontinue study treatment will be treated at the discretion of the investigator, including, as appropriate, any medications.

6.1.1. Discontinuation due to Abnormal Liver Function

Several specific measures will be undertaken to identify the risk of hepatotoxicity in subjects and manage high drug exposure. To avoid hepatotoxicity, PTC has implemented a comprehensive monitoring of liver function tests (LFTs), including ALT, AST, total bilirubin (Tbili), and alkaline phosphatase (ALP). During hospitalization, the LFTs will be monitored daily during treatment and at Day 28. An HAC will comprehensively monitor all hepatic abnormalities and continually evaluate hepatic safety during the study.

Consistent with the Food and Drug Administration Drug Induced Liver Injury (DILI) guidance (FDA 2009), subjects will be closely monitored for any of the following:

- Any serum ALT or AST Grade ≥3 (>5×ULN), regardless of baseline
- Tbili (>2×ULN), whether or not serum ALT or AST values are elevated; if such an elevation occurs, direct bilirubin will be measured

If any of the above conditions are met, the following steps will be taken:

- Temporarily stop dosing study drug and retest ALT, AST, and Tbili within 72 hours to confirm changes. Subjects with Grade 3 liver function abnormalities will be monitored until these values return to the baseline.
- Notify the sponsor and medical monitor (see also Section 7.5.3 and Section 7.5.10)
- Resume dosing with study drug if the retesting does not confirm the magnitude of the abnormality(ies), after discussion with the medical monitor.
- Evaluate ALT, AST, Tbili, and ALP daily, until stable or resolved.
- Consider further work-up in consultation with the medical monitor.

Permanent discontinuation of study drug for abnormal liver function should be considered by the investigator when a subject meets one of the conditions outlined above or if the investigator believes that it is in best interest of the subject. After each abnormal liver function event that meets the criteria for discontinuation, the HAC will meet to assess the severity and causality of the event and generate a case report.

6.1.2. Discontinuation due to Abnormal Blood Test Results

Subjects will be monitored for anemia and low lymphocyte count. If either of the following occurs:

- Lymphocyte count <500 lymphocytes/µL
- Hemoglobin <11.0 g/dL (110 g/L)

Then the following steps will be taken:

- Temporarily stop dosing study drug and retest lymphocyte count and hemoglobin within 72 hours to confirm changes.
- Resume dosing with study drug if the retesting does not confirm the magnitude of the abnormality(ies).
- Notify the medical monitor if the retesting confirms abnormalities.

Permanent discontinuation of study drug for abnormal blood test results should be considered by the investigator when a subject meets one of the conditions outlined above or if the investigator believes that it is in best interest of the subject.

6.2. Participant Discontinuation/Withdrawal from the Study

In all cases of subject withdrawal or discontinuation, the reason for withdrawal must be recorded in the eCRF and in the subject's medical records. If the reason is not known, the subject must be followed to establish whether the reason was due to an AE, and, if so, this must be reported in accordance with the procedures in Section 7.5.9.

All subjects will undergo assessments until Day 28 unless they die, are lost to follow-up or withdraw consent. For subjects who are discharged from the hospital prior to Day 28:

- If SpO_2 is <94%, SpO_2 measurements will be taken daily until Day 28
- Subject-reported assessments for cough and dyspnea will continue to Day 28
- No other assessments will take place except for those specified at Day 14, 28 and Day 60 in the protocol.

The investigator will make every effort to contact subjects lost to follow-up. Subjects who have an ongoing AE at the time of study completion will be followed until the event resolves, or until the Sponsor and the Investigator agree that further follow-up is not medically necessary.

6.3. Lost to Follow-up

A subject is considered lost to follow-up if the he or she leaves the hospital and does not complete the study and attempts to contact the subject are unsuccessful. Efforts must be made on the part of the site to avoid any subject being lost to follow-up during the study. Before any subject is considered lost to follow-up, a minimum of 2 documented telephone contact attempts and 1 certified letter within a week of the most recent planned study assessment must be sent in efforts to contact the subject. After being considered lost to follow-up, a subject's status may be changed if the subject makes contact at a later time provided the trial is ongoing.

7. STUDY ASSESSMENT AND PROCEDURES

7.1. Schedule of Events and Study Parameters

Table 3: Schedule of Events

Assessment/Activity	Screening	Day 1	Treatment Period				Follow-up			Notes
			Days 2-6	Day 7	Days 8-13	Day 14/ EOT	Days 15-27	Day 28/ EOS	Day 60 ±3	**Screening and Day 1 should occur within a 1-day period; where they occur on the same day, assessments need not be repeated. Subjects remaining in hospital will undergo the assessments specified. All subjects will undergo the assessments specified for Day 14, Day 28, and Day 60 even if they are discharged from the hospital prior to Day 28.**
Informed consent	X									
Medical history	X									
WHO ordinal scale assessment	X									(WHO 2020)
Pregnancy test	X							X	X	WOCBP only. Pregnancy test can be serum βHCG or urine. The Day 60 test should be taken at home and self-reported during telephone contact.
Vital signs	X	X	X	X	X	X	X	X		Vital signs will include oxygen saturation daily for primary endpoint assessment in addition, temperature, respiratory rate, and blood pressure will also be assessed.
Cough and dyspnea assessments	X	X	X	X	X	X	X	X		Cough and dyspnea are assessed daily on a patient reported scale of severe, moderate, mild, or absent.
Body weight and height	X									
Physical examination	X	X	X	X	X	X		X		Full physical examination (including a minimum of general appearance, head, eyes, ears, nose, mouth, throat, heart, thyroid, chest and lungs, abdomen, extremities, neuromuscular system, skin, and lymph nodes) will be completed during screening; at all other timepoints the examination will be targeted.

Assessment/Activity	Screening	Day 1	Treatment Period				Follow-up			Notes
			Days 2-6	Day 7	Days 8-13	Day 14/ EOT	Days 15-27	Day 28/ EOS	Day 60 ±3	**Screening and Day 1 should occur within a 1-day period; where they occur on the same day, assessments need not be repeated. Subjects remaining in hospital will undergo the assessments specified. All subjects will undergo the assessments specified for Day 14, Day 28, and Day 60 even if they are discharged from the hospital prior to Day 28.**
Chest X-ray	X					X				X-ray taken within 24 hours prior to Screening will be accepted. CT scan will be accepted in place of the X-ray if taken with 48 hours prior to Screening.
Nasopharyngeal swab		X	X	X		X		X		Nasopharyngeal swab will be taken on Days 1, 2, 4, 7, 14, and 28.
Hematology, coagulation, and clinical chemistry assessment	X	X	X	X	X	X		X		Assessments taken within 24 hours prior to Screening will be accepted.
Urinalysis	X	X	X	X	X	X				
Concomitant medications	X	X	X	X	X	X	X	X		
Study drug administration		X	X	X	X	X				Study drug will be administered orally at 200 mg BID on Days 1 to 7 followed by 50 mg QD on Days 8 to 14. Should a subject be discharged prior to Day 14, tablets will be dispensed to take at home and compliance will be recorded at Day 14.
Blood draw for PK		X		X		X				On Days 1 and 7, blood samples for PK assessment will be collected pre-dose (0) and at 6 hours post-dose and on Day 14 at pre-dose (0) and 4 hours post-dose (morning dose only). An ad hoc PK assessment will be performed in the case of hepatotoxicity (see also Section 7.3).
Blood draw for cytokine assessment		X	X	X		X		X		
Blood draw for acute phase protein assessment		X	X	X		X		X		
Antibody titer assessment		X						X		

Assessment/Activity	Screening	Day 1	Treatment Period				Follow-up			Notes
			Days 2-6	Day 7	Days 8-13	Day 14/ EOT	Days 15-27	Day 28/ EOS	Day 60 ±3	**Screening and Day 1 should occur within a 1-day period; where they occur on the same day, assessments need not be repeated. Subjects remaining in hospital will undergo the assessments specified. All subjects will undergo the assessments specified for Day 14, Day 28, and Day 60 even if they are discharged from the hospital prior to Day 28.**
Adverse events	X	X	X	X	X	X	X	X	X	At Day 60, the visit will be a telephone call to record AEs, SAEs, and deaths for all subjects except those who die or are lost to follow-up or withdraw consent.

Abbreviations: βHCG, beta human chorionic gonadotropin; BID, twice daily; EOS, end of study; EOT, end of treatment; PK, pharmacokinetic; QD, once daily, WHO, World Health Organization; WOCBP, women of childbearing potential.

7.2. Efficacy Assessments

All assessments will be in line with the site's COVID-19 assessment guidelines.

Fever (body temperature), respiratory rate, and SpO_2 will be monitored regularly throughout each day during hospitalization. If a subject has received an antipyretic, assessment of fever should occur ≥4 hours after administration of the antipyretic.

Cough severity and dyspnea will be assessed daily via subject-reported scales as severe, moderate, mild, or absent.

For subjects who are discharged from the hospital prior to Day 28:

- If SpO_2 is <94%, SpO_2 measurements will be taken daily until Day 28
- Patient-reported assessments for cough and dyspnea will continue to Day 28
- No other assessments will take place except for those specified at Day 14, 28 and Day 60 in the protocol.

For any subjects who are transferred to the Intensive Care Unit during the study, assessments per protocol should be performed wherever reasonably practicable.

Collection of blood, serum and nasopharyngeal swabs for assessment of cytokine levels, acute phase proteins, complete blood count, other laboratory parameters, and viral load will be performed by qualified and trained personnel during hospitalization, or after discharge at a medical facility as agreed by the medical monitor. Laboratory parameters assessed will include, but not be limited to, those in Table 4.

Table 4: Laboratory Parameters to be Assessed

Laboratory Assessments	Parameters
Nasopharyngeal swab	RPP[a]
Hematology	CBC count with WBC differential
Clinical Chemistry	Comprehensive metabolic panel to include: • AST • ALT • GGT • LDH • ALP • Tbili (direct and indirect bilirubin, if appropriate[b]) • CPK • Total protein • Albumin
Coagulation	aPTT PT/INR
Urinalysis	Blood Bilirubin Glucose Ketones pH Protein
Pregnancy (WOCBP only)	Urine or Serum βHCG [Reflective from Chemistry Sample]

Laboratory Assessments	Parameters
Others	Cytokines[a] Antibody titers[a] Acute phase proteins • Ferritin • CRP • D-dimer Cardiac troponin

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; βHCG, beta human chorionic gonadotropin; CBC, complete blood count; CRP, C-reactive protein; CPK, creatinine phosphokinase; GGT, gamma-glutamyl transpeptidase; INR, international normalized ratio; LDH, lactate dehydrogenase; PT, prothrombin time; RPP, respiratory pathogen panel; Tbili, total bilirubin; WBC, white blood cell; WOCBP, women of childbearing potential.
[a] To be analyzed at a central laboratory.
[b] Direct and indirect bilirubin will be measured if part of the local laboratory usual assessment panel. In the case of Tbili >2xULN direct bilirubin must be assessed (Section 6.1.1).

All laboratory parameters should be assessed prior to dosing on Day 1.

7.3. PK and/or Other Assessments

At select sites, PK will be assessed after the single dose (Day 1) and repeated dosing Day 7 and 14. Blood samples will be collected on Days 1 and 7 at pre-dose (0), and 6 hours post-dose and on Day 14 at pre-dose (0) and 4 hours post-dose (morning dose only). Plasma concentrations of PTC299 and *O*-desmethyl PTC299 will be evaluated for at least 12 evaluable patients who receive PTC299. Analyses will take place at a central laboratory.

For those subjects discharged from the hospital prior to Day 7, PK sampling should be obtained on the last day of hospitalization, if possible. For subjects discharged prior to Day 14, PK samples on Day 14 should be collected pre-dose and at 4 hours post-dose.

An ad hoc PK assessment will also be performed in the case of hepatotoxicity, regardless of whether the subject has undergone other PK assessments.

7.4. Safety Assessments

Subjects will be monitored closely for AEs and laboratory abnormalities, including assessment of vital signs, during the study.

For AEs and laboratory abnormalities, the investigator should use his/her judgment in determining whether the event or abnormality is clinically significant, whether diagnostic evaluation is warranted, and whether potential interruption of study drug therapy is appropriate. In general, life-threatening (Grade 4) or severe (Grade 3) AE or laboratory abnormalities should be considered clinically significant, although recurrent or persistent moderate events (Grade 2) may also be considered clinically significant in certain circumstances. Reference should be made to the CTCAE Version 5.0 for grading the severity of AEs and laboratory abnormalities.

7.5. Adverse Events and Serious Adverse Events

7.5.1. Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence associated with the use of a drug in humans, whether or not it is considered related to the drug. An AE can therefore be any

unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease in a study subject who is administered study drug in this study.

For this protocol, untoward medical occurrences that should be reported as AEs include the following:

- All AEs during the course of treatment with study drug administration
- All AEs resulting from medication misuse, abuse, withdrawal, or overdose, of study drug
- All AEs resulting from medication errors such as dispensing or administration error outside of what is described in the protocol
- Apparently unrelated illnesses, including worsening of a preexisting illness
- Worsening of symptoms related to COVID-19
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate AEs. The outcome of the accident (hip fracture secondary to the fall) should be recorded in source documents.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test)
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event should be captured in the source documents. Laboratory abnormalities not requiring clinical intervention or further investigation will be captured as part of overall laboratory monitoring and should not be reported as AEs.
- A preexisting condition (eg, allergic rhinitis) must be noted on the appropriate CRF for screening but should not be reported as an AE unless the condition worsens, or episodes increase in frequency during the AE reporting period. Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that occurs during the treatment with study drug should be reported as the AE and the resulting appendectomy should be recorded in the source documents and eCRF. If a surgical procedure was planned prior to entry into the study, and the surgery is not performed because of a worsening of a baseline condition, this should not be reported as an AE. Note that, as described in Section 7.5.2 any hospitalization occurring as the consequence of an AE during the study period should be reported as an SAE.

Each AE is to be classified as serious or non-serious by the investigator using medical and scientific judgment.

7.5.2. Definition of Serious Adverse Events

An SAE is an untoward medical occurrence or effect associated with the use of a study drug at any dose, regardless of whether it is considered to be related to the study drug, which results in one of the following:

- Death. This includes all deaths on treatment or within 30 days after last study drug administration, including deaths due to disease progression. Any death occurring later than 30 days following the last dose need not be reported as an SAE unless it is a result of an event that started within the period covered by the on-study definition. The reported AE should be the event that caused the death. In addition, any AE resulting in death that occurs subsequently to the AE reporting period and that the investigator assesses as possibly related to the study drug should also be reported as serious.
- A life-threatening condition. This refers to an event in which the subject was at risk of death at the time of the event. It does not include an event that, had it occurred in a more severe form, hypothetically might have caused death.
- Hospitalization or prolongation of existing hospitalization (excluding hospitalizations for administration of the study drug, procedures required by the study protocol, or treatment-related diagnostic procedures; other planned hospitalizations; or hospitalizations related only to progression of disease). Progression of disease resulting in transfer to ICU, mechanical ventilation, or other medically important event (at the discretion of the investigator) would be considered SAEs. Treatments in the emergency room for procedures such as hydration that do not require admitting the subject to the hospital and observational durations in the emergency room for less than 24 hours do not fall into this category.
- Persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions.
- Any other medically important event that the investigator or the sponsor judges to be serious or which is defined as serious by the regulatory agency in the local country. These are AEs that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject or might require intervention to prevent one of the other outcomes listed above. Medical judgment should be exercised in deciding whether an AE is serious based on above definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- A pregnancy resulting in spontaneous abortion, stillbirth, neonatal death, or congenital anomaly (including that in an aborted fetus).

Note that any SAEs occurring at any time up to Day 60 should be reported to the sponsor if the investigator becomes aware of them.

7.5.3. Adverse Events of Special Interest

Events that may be indicative of hepatotoxicity (including the lower level MedDRA term of hepatotoxicity or drug-induced hepatotoxicity) are considered adverse events of special interest (AESIs) and will be reported on an expedited basis. These include:

- ALT increase Grade ≥3 (>5×ULN)
- AST increase Grade ≥3 (>5×ULN)
- Tbili increase >2×ULN
- ALP ≥ 2×ULN

All instances meeting the above criteria should be reported within 24 hours to the PTC Therapeutics Pharmacovigilance Department on the SAE form. If the event is considered non-serious by the investigator then the SAE form and AE CRF page should be marked as non-serious. Medically significant liver events that are considered SAEs and consist of marked elevations of LFTs and / or pre-specified AEs may also be included in expedited reporting.

7.5.4. Unexpected Adverse Events

The Investigator's Brochure contains the Reference Safety Information (RSI) which will be used for assessing expectedness. If an event is not listed in the RSI, it should be considered unexpected or if the AE occurs at a greater severity, specificity or frequency, it should be considered unexpected.

Any hepatic abnormalities/ hepatotoxicity (hyperbilirubinemia, aspartate aminotransferase increase, alanine aminotransferase increase) of Grade ≥4 will be considered unexpected.

7.5.5. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject/parent(s)/legal guardian/legally acceptable representative. In addition, each study subject/parent(s)/legal guardian/legally acceptable representative will be questioned about AEs at each scheduled clinic visit after study drug administration or during any telephone contact with the subject/parent(s)/legal guardian/legally acceptable representative. The type of question asked should be open-ended, for example, "*How have you been feeling*?" or a similar type of query.

7.5.6. Recording Non-serious AEs and SAEs

All AEs (both serious and non-serious) that occur in subjects during the AE reporting period must be recorded, whether or not the event is considered drug related. In addition, any known untoward event that occurs subsequently to the AE reporting period that the investigator assesses as possibly related to the investigational drug/product should also be recorded as an AE.

All AEs are to be recorded in the source documents and on the eCRF using concise medical terminology; whenever possible, terms contained in the Medical Dictionary for Regulatory Activities (MedDRA) should be employed. In addition, the following information should be recorded:

- Indication of whether the event is serious or non-serious (see Section 7.5.2)
- Relationship to study drug (see Section 7.5.7)

- Severity of the event (see Section 7.5.8)
- Onset date
- Resolution date, or date of death
- Action taken
- Outcome of the event

Classification of the event as serious or non-serious determines the reporting procedures to be followed.

7.5.7. Describing Adverse Event Relationship to Study Drug

The investigator should provide an assessment of the relationship of the AE to the study drug, ie, whether there is a reasonable possibility that the study drug caused the AE, using the considerations outlined in Table 5.

Table 5: Relationship of Study Drug to Adverse Event Relationship

	Description
Probable	A clinical event in which a relationship to the study drug seems probable because of such factors as consistency with known effects of the drug; a clear temporal association with the use of the drug; improvement upon withdrawal of the drug; recurrence upon re-challenge with the drug; lack of alternative explanations for the event.
Possible	A clinical event occurring coincident with administration of the study drug and which may or may not be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal or re-challenge may be lacking.
Unlikely	A clinical event with a temporal relationship to the study drug exposure that does not preclude causality but for which there is a clear alternate cause that is more likely to have caused the adverse event than study drug. Such alternatives include a concomitantly administered drug, the subject's disease state, other medical conditions, or environmental factors.
Unrelated	A clinical event, for which a relationship to the study drug seems improbable because of factors such as inconsistency with known effects of the study drug, lack of a temporal association with study drug administration, lack of association of the event with study drug withdrawal or re-challenge, and/or presence of alternative explanations for the event. Alternative explanations might include a known relationship of the adverse event to a concomitant drug, medical history of a similar event, the subject's disease state, other medical conditions, or environmental factors.

7.5.8. Grading of Severity of Adverse Event

The severity of AE will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (refer to the study manual). For each episode, the highest severity grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 6.

Table 6: Grading of Adverse Event Severity Grade

	Adjective	Description
Grade 1	Mild	Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the subject's overall health and well-being, does not interfere with the subject's usual function, and is not likely to require medical attention
Grade 2	Moderate	Sign or symptom causes interference with usual activity or affects clinical status, and may require medical intervention
Grade 3	Severe	Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up
Grade 4	Life-threatening	Sign or symptom results in a potential threat to life
Grade 5	Fatal	Sign or symptom results in death

7.5.9. Adverse Event Reporting

Investigator site reporting requirements for AEs are summarized in Table 7.

Table 7: Investigator Site Requirements for Reporting Adverse Events

Event	Recorded on the eCRF	Reported on the SAE Report Form to PTC Pharmacovigilance Within 24 Hours of Awareness
Serious AE	All	All
Non-Serious AE	All	None
Exposure to the study drug during pregnancy or breastfeeding, and occupational exposure	All (regardless of whether associated with an AE), except occupational exposure	Exposure during pregnancy, exposure via breastfeeding, occupational exposure (regardless of whether associated with an AE)

Abbreviations: AE, adverse event; eCRF, electronic case report form; SAE, serious adverse event

All AEs should be followed up by the investigator until they are resolved, or the investigator assesses them as chronic or stable. The investigator should consider protocol guidelines and use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events. In the event of additional investigations, the PTC Therapeutics Pharmacovigilance Department or designee should be informed via e-mail or fax. A subject withdrawn from the study because of an AE must be followed by the investigator until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. Follow-up may need to continue after the subject has discontinued from the study, and additional investigations may be requested by the medical monitoring team.

The first day of AE reporting will coincide with the date of signing of Informed Consent.

7.5.10. Serious Adverse Event Reporting

All SAEs should be reported via the "SAE Report Form" to PTC Therapeutics within 24 hours of becoming aware of the event(s). In addition, the AE portion of the eCRF must also be completed in EDC.

The SAE report form should be signed by the investigator; however, if the investigator is unable to sign at the time of the event or within 24 hours, the form should be signed by the clinical staff member reporting the SAE (eg, the study coordinator). The SAE report form must be faxed or e-mailed to the PTC Therapeutics Pharmacovigilance Department or designee and to the site Institutional Review Board/Ethics Committee IRB/EC (if required by local regulations) within 24 hours.

Follow-up information to the SAE should be clearly documented with "Follow-up" box checked and the follow-up number in the SAE Report Form completed and faxed or e-mailed to the same party. All follow-up SAE report forms for the event must be signed by the investigator. Any source documents (eg, progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries) provided to the sponsor should be redacted so that the subject's name, address, and other personal identity information are obscured. Only the subject's study number and initials are to be provided (in regions where the provision of such information is permitted). The information in the AE portion of the eCRF and the SAE report form(s) must match or be reconciled. Where the same data are collected, the information on the SAE Report Form must be completed in a consistent manner.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (for example, if a subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and to document his/her first awareness of the AE.

The PTC Therapeutics Pharmacovigilance Department contact information for reporting SAEs is provided below. This information is also provided in the Study Manual and in the SAE report form.

PTC Therapeutics Safety Department
Attention: Pharmacovigilance
E-mail: [redacted]
Facsimile: [redacted]

7.5.11. Reporting Pregnancy

PTC Therapeutics should be notified in the event that a female subject in the study, or a female partner of a male subject in the study, becomes pregnant on-study or within 50 days of the last administration of study drug must be reported on an electronic form "Investigational and Marketed Products Pregnancy Report Form" (see study manual for details).

This must be done whether or not an AE has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of birth or pregnancy termination.

Written consent is required prior to collecting and reporting any information on a female partner of a male subject in the study.

If possible, the investigator should follow the subject, or the pregnant female partner of a male subject, until completion of the pregnancy and notify the medical monitor of the outcome within 5 days or as specified below. The investigator will provide this information with 'Follow-up" box checked and the follow-up number completed on the Pregnancy Report Form (see the study manual for details).

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (ie, preterm termination, elective abortion, intrauterine death, or other), the investigator should follow the procedures for reporting SAEs, ie, report the event to the PTC Therapeutics Safety Department or designee and follow-up by submission of appropriate AE eCRFs (see Section 7.5.10).

7.5.12. PTC Therapeutics Adverse Event Reporting Requirement

As the sponsor of the study, PTC Therapeutics is responsible for reporting certain safety information, particularly AESIs, SAEs and subject deaths related to participation in the study, to each investigator in an expedited manner. If notification of an AE requiring expedited reporting to investigators is received, PTC Therapeutics or its designated representative will contact each investigational site participating in this study by e-mail, fax, and/or overnight mail such that the investigator can promptly notify the site IRB/EC per their local requirements. The initial expedited safety report will be provided as required according to local regulations (eg, within 15 days) after the earliest date PTC Therapeutics or an agent of PTC Therapeutics (eg, a site monitor) becomes aware of an AE. This awareness date is the date the regulatory reporting clock begins, and the date is considered Day 0.

8. STATISTICAL CONSIDERATIONS

A statistical analysis plan (SAP) will be prepared and approved prior to the first unblinded interim analysis to provide a more detailed description of the nature of the analyses and the manner in which results will be compiled. The SAP will include details of the statistical models to be used and the test statistics to be employed.

8.1. Statistical Hypotheses

The null hypothesis for the primary efficacy comparison is that the distribution of time to respiratory improvement in hospitalized subjects with COVID-19 is the same between the 2 groups of PTC299 and placebo. The alternative hypothesis is that the distribution of time to respiratory improvement between the 2 treatment groups is not the same. Rejecting the null hypothesis with shortened time to respiratory improvement in the PTC299, for the intent-to-treat (ITT) population, will be considered a successful demonstration of efficacy.

8.2. Sample Size Determination

This is a group sequential design with 2 interim analyses planned. The first interim analysis will only assess the safety and the trial will not be stopped for futility or superiority of efficacy. It will be performed after the first 40 randomized subjects have completed Day 28 or discontinued due to death, withdrew consent, or were lost-to-follow-up.

The second interim analysis is to assess futility and will be performed when 50% of respiratory improvement events have been reached, ie, 163 events have been observed (approximately 190 subjects). Lan-DeMets beta spending function (non-binding option) is used to define the boundary for the 2nd interim futility analysis and the final analysis to ensure the overall beta of 80%. The sample size was calculated to reflect the primary endpoint of time from randomization to respiratory improvement, which is defined as the time from randomization to respiratory improvement ($SpO_2 \geq 94\%$ in room air), sustained until discharge from the hospital or the end of the study (Day 28). Median time to respiratory improvement was not readily available from the literature. Based on very limited data, it is anticipated that the median time to respiratory improvement for the placebo group is 11 days and PTC299 treatment will decrease it to 8 days, an improvement of 3-days. Subjects will be followed for the fixed amount of time of 28 days from randomization (corresponding to the anticipated improvement rates of 0.829 and 0.912 at Day 28 for placebo and PTC299, respectively). A total of 326 events will provide more than 80%

of power to detect a hazard ratio of 1.38 at two-sided type I error of 0.05. Approximately 380 subjects, in total, will be needed.

8.3. Population for Analyses

Intent-to-treat (ITT) population: will include all randomized subjects. The ITT population will be used in all efficacy analysis and subjects will be grouped based on the arm they are randomized to. In the event that a subject received treatment in the arm different from the one to which he/she was randomized, the subject's efficacy data will be analyzed "as randomized."

Safety population: will include all randomized subjects who received at least one dose of study drug. In the event that a subject received treatment in the arm different from the one to which he/she was randomized, the subject's safety data will be analyzed "as treated." The Safety Analysis population will be used in the statistical analyses for safety.

PK population: will include safety population subjects who had at least one PK profile assessment.

8.4. Statistical Analyses

8.4.1. General Approach

For continuous variables, median, mean, standard deviation, minimum, maximum, and the number of subjects with non-missing data will be provided for each treatment group. For categorical variables, the number (percent) of subjects in each category will be provided.

8.4.2. Analysis of Primary Efficacy Endpoints

The primary endpoint is time from randomization to respiratory improvement, defined as SpO_2 ≥94% on room air sustained until discharge from the hospital or the end of the study (Day 28).

All hospitalized subjects will be followed fully to Day 28 with efficacy measurements taken daily unless they die, are lost to follow-up, or withdraw consent. For subjects who are discharged from the hospital prior to Day 28 without achieving respiratory improvement, SpO_2 measurements will be taken daily until Day 28. All measurements recorded will be used for efficacy analysis.

Subjects who achieved SpO_2 ≥94% on room air and sustained this to Day 28 or discharge without taking any COVID-19 rescue therapy during the study will be considered as achieving the respiratory improvement event and the event date will be the first date of achieving SpO_2 ≥94%. Subjects will be censored at Day 28 if any of the following apply:

- randomized but had no follow-up
- took any COVID-19 rescue therapy during the study
- lost to follow-up prior to Day 28
- died prior to Day 28
- withdrew consent prior to Day 28
- had full follow-up without achieving sustained SpO_2 ≥94%.

Rescue therapy is defined as any additional medication, exclusive of SOC, used to treat a worsening of COVID-19 symptoms and recorded as rescue therapy on the eCRF.

Kaplan-Meier plots of time to respiratory improvement will be presented. Median time to respiratory improvement will be estimated via the Kaplan-Meier product limit method. A two-sided 95% confidence interval (CI) for the median time to respiratory improvement will be computed for PTC299 and placebo cohorts based on a log-log transformed CI for the survivor function S(t). Time to respiratory improvement will be compared between treatment groups using stratified log-rank test.

Hazard ratio and corresponding two-sided 95% CIs will be estimated using a Cox proportional hazards model, with treatment arm as a single covariate, stratified by the stratification factors.

Respiratory improvement rates at Days 7, 14, and 28 will also be estimated using Kaplan-Meier estimates on the time to respiratory improvement curve. Associated two-sided 95% CIs for each treatment group and the difference between the 2 treatment groups will be calculated using Greenwood's formula for variance derivation.

8.4.3. Analysis of Secondary Efficacy Endpoints

Similar to the primary endpoint, Kaplan-Meier estimate, median and rate at Days 7, 14, and 28 will be presented for time from randomization to defervescence (in subjects presenting with fever at enrollment), time from randomization to respiratory rate ≤24 breaths/minute on room air, time from randomization to cough reported as mild or absent (in those with cough at enrollment rated severe or moderate), and time from randomization to dyspnea reported as mild or absent (on a scale of severe, moderate, mild, absent, in those with dyspnea at enrollment rated as severe or moderate).

The proportion of subjects requiring invasive ventilation at any point during the study, subjects requiring supplemental oxygen or non-invasive ventilation at any point in the study in subjects without supplemental oxygen or non-invasive ventilation at baseline, subjects with normalization of the complete blood count, and the number of subjects who died at the end of the study will be summarized by frequency and percent.

The following secondary endpoints will be summarized descriptively

- Reduction in cytokine levels, potentially including IL-2, IL-6, IL-7, IL-17, G-CSF, IP-10, MCP1, MIP1-α, and TNF-α,
- Reduction in levels of acute phase proteins, potentially including ferritin and C-reactive protein, D-dimer, and cardiac troponin,
- Changes in other laboratory parameters including lactate dehydrogenase, prothrombin time, albumin,
- Reduction in viral load, and
- Duration of hospitalization measured in days

8.4.4. Safety Analyses

8.4.4.1. Subject Disposition

The disposition of subjects, including the number of subjects screened, the number of randomized subjects, the number of randomized subjects who received at least 1 dose of study drug, and the number of subjects who prematurely discontinue study drug, as well as the reason for the premature termination, will be tabulated.

8.4.4.2. Medical History and Prior Medication

Medical history and prior medication information will be summarized.

8.4.4.3. Extent of Exposure and Treatment Compliance

The extent of exposure to study medication is defined as the last dose date minus the first dose date + 1 day. Compliance will be assessed in terms of the percentage of drug actually taken relative to the amount that should have been taken during the study. Exposure and compliance will be summarized descriptively.

8.4.4.4. Adverse Events

Summary information (the number and percent of subjects by treatment) will be tabulated for:

- Treatment-emergent adverse events (TEAEs)
- Treatment-related AEs
- TEAEs by severity
- SAEs
- AEs leading to discontinuation
- AESIs

Summaries will be presented by treatment group and categorized by MedDRA System Organ Class and Preferred Term. The frequencies of AEs displayed will be the crude rates that represent the number of subjects experiencing AEs divided by the total number of subjects.

8.4.4.5. Laboratory Parameters

Changes in clinical laboratory tests from baseline (last measurement prior to first dose) and laboratory marked abnormalities using pre-defined abnormality criteria will be descriptively summarized.

8.4.5. Baseline Descriptive Statistics

Demographic and baseline characteristics of subjects (including ordinal scale score (WHO 2020) will be summarized descriptively by means and standard deviations for continuous variables, and frequency distribution for categorical variables. Summaries will be performed based on all randomized subjects.

8.4.6. Planned Interim Analyses

Two interim analyses are planned. The first interim analysis will be conducted when approximately 40 randomized subjects (20 in each arm) have received 14 days of treatment and completed 14 days of follow-up or discontinued due to death, withdrew consent, or were lost-to-follow-up. No formal statistical testing will be performed at the first interim analysis. An independent data safety monitoring board will review the safety data. Enrollment will continue if there are no safety concerns. A second interim analysis will be conducted for futility. It will be performed when 50% of respiratory improvement events have been reached, ie, 163 events have been observed (approximately 190 subjects). Respiratory improvement is defined as $SpO_2 \geq 94\%$ in room air until discharge from the hospital or the end of study (Day28). All subjects who have completed through Day 28, were discharged with $SpO_2 \geq 94\%$ on room air, withdrew consent, died, were lost to follow-up, or took any COVID-19 rescue therapy during the study will be included in the interim analysis. Subjects whose primary event cannot be determined at the interim cut, ie, ongoing subjects, will not be included in the interim efficacy analysis. Subjects who died, withdrew consent, were lost to follow-up, or took any COVID-19 rescue therapy will be censored at Day 28. A stratified log-rank test will be performed and the hazard ratio (treatment vs placebo) will be compared with the futility boundary. The trial may be stopped for futility if the hazard ratio is less than 1.091. The futility boundary is based on Lan-DeMets beta spending function (non-binding option) with overall beta of 80%.

The unblinded interim analyses will be conducted by an independent statistician and the results will be only shared with the closed session of the DSMB. DSMB will make the go- or no-go recommendations and only the recommendations will be communicated with the study team. The study team will be kept blinded for results related to the interim analyses.

8.4.7. Subgroup Analyses

Subgroup analyses of the primary endpoint by baseline disease risk factors will be explored as deemed appropriate. In such analyses, an un-stratified log-rank test and the hazard ratio will be estimated using the unstratified Cox proportional hazards model.

8.4.8. Exploratory Analyses

Not applicable.

9. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1. Regulatory, Ethical, and Study Oversight Considerations

9.1.1. Informed Consent Process

By signing the protocol, the investigator assures that informed consent will be obtained from each subject or legally authorized representative prior to study entry and that the informed consent will be obtained in accordance with current regulations.

The investigator or qualified representative will give each subject or legally authorized representative full and adequate verbal and written information regarding the objectives and procedures of the study and the possible risks involved. An informed consent document will be provided to each subject or legally authorized representative in a language in which the subject is fluent, or translated, according to local regulations. This information must be provided to the subject or legally authorized representative prior to undertaking any study related procedure. Adequate time should be provided for the subject or legally authorized representative to read the informed consent, to understand the risks and benefits of participating in the study, and to ask any questions that the subject may have about the study. The subject or legally authorized representative should be able to ask additional questions as and when needed during the conduct of the study. The subject or legally authorized representative's signature on the informed consent form should be obtained at the investigator site in the presence of the investigator or a qualified representative (eg, sub investigator).

Each subject will be given a copy of the signed consent/assent form. The original signed informed consent forms will be retained by the investigator with the study records.

9.1.2. Study Discontinuation and Closure

PTC Therapeutics reserves the right to discontinue the study prior to inclusion of the intended number of subjects. The investigator, after consultation with the medical monitor, reserves the right to discontinue the study at the investigator site for safety reasons at any time.

After a decision to terminate the study, investigators must contact all subjects who are continuing their participation in the study and must do so within a time period set by PTC Therapeutics. As directed by PTC Therapeutics, all study materials must be collected, and all electronic data entry forms completed to the greatest extent possible.

9.1.3. Confidentiality and Privacy

Research records will be collected and stored in a manner that protects the confidentiality of subject information. The names and identities of all research subjects will be kept in strict confidence and will not appear on eCRFs, paper CRFs, or other records provided to or retained by PTC Therapeutics (or its authorized designee). The names and identities of the subjects need not be divulged; however, the records must nevertheless be inspected. This will be accomplished by blanking out the subject's name and replacing the name with the subject's study identification number on any record provided to or retained by PTC Therapeutics. The informed consent form must include appropriate statements explaining these requirements.

By signing this protocol, the investigator affirms to PTC Therapeutics that the investigator will maintain, in confidence, information furnished by PTC Therapeutics and will divulge such information to the IRB/IEC under an appropriate understanding of confidentiality with such board.

9.1.4. Future use of Stored Specimens and Data

As part of the current study blood, serum, urine, and nasopharyngeal swabs will be collected.

Sample processing will be performed by a laboratory under the direction of the sponsor. Processing, analysis, and storage will be performed at a secure laboratory facility to protect the validity of the data and maintain subject privacy.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis on behalf of the sponsor will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples. The sponsor will not sell the samples to a third party.

Samples will be stored until the completion of the study (defined as submission of the clinical study report to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a health authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with any of the biologic samples. All samples will be single coded. The sponsor will take steps to ensure that data are protected accordingly, and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed world-wide, regardless of location of collection.

The sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- Contract Research Organizations (CROs) retained by the sponsor
- IECs or IRBs that have responsibility for this research study
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the laboratory analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the patients or their physicians.

9.1.5. Safety Oversight

9.1.5.1. Data and Safety Monitoring Board

External oversight for this trial will be provided by a DSMB. The primary responsibility of the DSMB is to protect the safety and welfare of subjects participating in this clinical trial and to ensure the integrity of the clinical trial. To maintain the blinding and integrity of the study, procedures will be implemented to ensure the DSMB and independent statistician have sole access to unblinded safety data.

Specifically, for this study, the DSMB will be responsible for:

- Examining accumulated safety data, PK, and compliance data in order to make recommendations concerning continuation, termination, or modification of the trial based on the safety of the interventions under study

- Reviewing major study design modifications proposed by PTC Therapeutics or the investigators prior to implementation of those modifications
- Reviewing the general progress of the study as regards accrual, protocol violations, and study conduct

The DSMB will review the interim PK (Day 1 and 7) and safety data when approximately 40 subjects have received 14 days of study treatment. The DSMB may review the safety data at other times as warranted by emerging results. Based on review of the safety data, the DSMB can recommend continuation of the study unchanged, study interruption, study termination, modification of the trial, or alteration. Full details of the DSMB procedures, including primary responsibilities, will be documented in a DSMB Charter.

9.1.5.2. Hepatic Advisory Safety Committee

A HAC comprised of hepatologists experienced in the monitoring and identification of DILI will oversee the hepatic safety of subjects enrolled in the study. The HAC will meet regularly to assess the severity and causality of all hepatotoxicity events. Full details of the HAC procedures will be documented in the HAC Charter.

9.1.6. Clinical Monitoring

In accordance with 21 Code of Federal Regulations Part 312.56 and/or relevant International Council for Harmonisation (ICH) guidelines, PTC Therapeutics or a designee will periodically inspect all eCRFs, study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times, before, during, and after completion of the study. As required by applicable regulations (Responsibilities of Sponsors and Investigators), the monitoring visits provide PTC Therapeutics with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of data in the eCRFs; ensure that all protocol requirements, relevant regulations, and investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records required to be maintained by the investigator, including but not limited to medical records (office, clinic, or hospital) for the subjects in this study. The names and identities of all research subjects will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by PTC Therapeutics. The investigator/institution guarantees direct access to source documents by PTC Therapeutics and appropriate regulatory authorities.

It is important that the investigator and relevant institutional personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

9.1.7. Quality Assurance and Quality Control

To ensure compliance with Good Clinical Practice (GCP) and all applicable regulatory requirements, PTC, PTC's representatives, a regulatory authority or and Institutional Review board may conduct a quality assurance audit. Reasons for quality assurance audit may include but are not limited to random selection, geographic proximity, suspected GCP violation, high enrolling site, and recurring protocol deviations. The purpose of a Sponsor audit or inspection is to systematically and independently examine all study related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, Good Clinical Practice guidelines of the ICH, and any applicable regulatory requirements. The investigator should contact the Sponsor immediately if contacted by a regulatory agency about an inspection.

9.1.8. Data Handling and Record Keeping

To enable evaluations and/or audits from regulatory authorities or PTC Therapeutics, the investigator agrees to keep accurate and complete records, including the identity of all participating subjects (sufficient information to link eCRFs and clinic records/source documents), all original signed informed consent forms, electronic copies (ie, CD-ROM, USB, etc.) or paper copies of the data that have been captured in the EDC for each subject (eCRFs), and detailed records of study drug disposition. All records and documents pertaining to the study will be maintained by the investigator until notification is received from PTC Therapeutics that the records no longer need to be retained.

The investigator must obtain written permission from PTC Therapeutics before disposing of any records. The investigator will promptly notify PTC Therapeutics in the event of accidental loss or destruction of any study records. If the investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator, another institution, or to PTC Therapeutics as applicable.

9.1.9. Protocol Deviations

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements. Deviations may result from the action or inaction of the subject, investigator, or site staff. Examples of deviations include, but are not limited to:

- Failure to adhere to study exclusion and inclusion criteria
- Failure to comply with dispensing or dosing requirements
- Use of medications that are specifically prohibited in the protocol
- Missed or out-of-window visits
- Drug dosing not administered within the time frame specified in the protocol
- Failure to adhere to test requirements, including vital signs, laboratory tests, physical examinations, PK blood draws, medical history, etc. - either tests not done, incorrect tests done, or not done within the time frame specified in the protocol

- Procedural deviations such as incorrect storage of study drug, failure to update the informed consent form (ICF) when new risks become known, or failure to obtain IRB/IEC approvals for the protocol and ICF revisions

Major deviations are any deviations that impact subject eligibility (ie, protocol inclusion/exclusion violations), subject safety or a subject's ability to continue in the clinical trial.

At the outset of the study, a process for defining and handling protocol deviations will be established with the CRO. This will include determining which deviations will be designated major; thus, requiring immediate notification to the medical monitor and the sponsor.

Prospective deviations (eg, protocol waivers) are prohibited per PTC policy.

The investigator is responsible for seeing that any known protocol deviations are recorded as agreed.

9.1.10. Publication and Data Sharing Policy

The information developed during the conduct of this clinical study is considered confidential by PTC Therapeutics. This information may be disclosed as deemed necessary by PTC Therapeutics.

PTC Therapeutics intends that the data from this study will be presented and published. The PTC Therapeutics staff under the direction of the PTC Therapeutics Chief Medical Officer or designee in collaboration with the investigator will be responsible for writing presentations and manuscripts for publication. Investigators will not be allowed to publish or present the data from this study without prior agreement with PTC Therapeutics.

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During the study, only the sponsor may make study information available to other study Investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the Clinical Study Site Agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the Investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

Data from all sites participating in the study will be pooled and analyzed by the sponsor or the sponsor's designee. The first publication of the study results shall be made in conjunction with the results from other study sites as a multicenter publication. If a multicenter publication is not forthcoming within 24 months of completion of the study at all sites, the Investigator may publish or present the results generated at his or her site.

The investigator will provide the sponsor with a copy of any proposed publication or presentation for review and comment at least 60 days prior to such presentation or submission for publication. The sponsor shall inform the investigator in writing of any changes or deletions in such presentation or publication required to protect the sponsor's confidential and proprietary technical information and to address inaccurate data or inappropriate interpretations in the context of any pooled multicenter results. At the expiration of such 60-day period, the investigator may proceed with the presentation or submission for publication unless the sponsor has notified the institution or the investigator in writing that such proposed publication or presentation discloses the sponsor's confidential and proprietary technical information. Further, upon the request of the sponsor, the investigator will delay the publication or presentation for an additional 90 days to permit the sponsor to take necessary actions to protect its intellectual property interests.

9.2. Protocol Amendment History

Version 1.0: 17 April 2020

9.2.1. Version 2.0: 08 May 2020

Overall reason for Version 2.0: The overall reason for Version 2.0 of the protocol was to incorporate Health Authority feedback.

Item No.	Protocol Section	Version 2/Update	Reason/Rationale
1	Protocol	The protocol was updated throughout to replace the SOC comparison arm with placebo control. The version number and date were updated throughout. Editorial and administrative revisions (eg, typographical error, punctuation, tenses, abbreviations) were incorporated to provide clarity. The synopsis and schedule of events were updated to be consistent with changes in the protocol.	Update
2	Section 1	Updated with latest spread of disease.	Update
3	Section 1.1	New nonclinical data were added	Update
4	Section 2.1.1	The primary objective was updated to be the time to respiratory improvement.	Update
5	Section 2.2.1	The primary endpoint was updated, consistent with the new primary objective.	Update
6	Section 2.2.2	For those secondary endpoints recording time to improvement, it was clarified that the time starts at randomization. Clarification was added on the cough severity scale. D-dimer and cardiac troponin were specified in the list of potential acute phase proteins to be assessed.	Clarification
7	Section 3.1	The study design was updated to reflect the change to a placebo-controlled, double blind study and to include stratification by remdesivir, prohibition of sensitive CYP2D6 substrates and investigational therapies, an increased sample size, and the addition of the Day 60 safety telephone call.	Update
8	Section 3.2	Additional clinical experience was added to the dose justification.	Update
9	Section 4.1	The study population size was increased.	Update

Item No.	Protocol Section	Version 2/Update	Reason/Rationale
10	Section 4.2	Inclusion criterion #1 was amended to Subject (or legally authorized representative) is willing and able to provide informed consent and comply with all protocol requirements "Or equivalent test" was added to chest X-ray or CT scan in Inclusion criterion #9. Up to 50 days after last dose was added to Inclusion criterion #10	Clarification
11	Section 4.3	Exclusion criterion #3 was changed to exclude subjects with ≥3 × ULN ALT or AST or ≥2 × ULN Tbili. Exclusion criterion #4 was added to exclude subjects with low lymphocyte count or hemoglobin levels. Sensitive CYP2D6 substrates and any investigational therapy were added to prohibited medicines in Exclusion criterion #7. Excipients were included in Exclusion criterion #10.	Update
12	Section 5.1.2	A recommendation to take PTC299 with food was added.	Update
13	Section 5.3	The section was updated to reflect the change in study design from open-label to double blind and to include the emergency unblinding procedure.	Update
14	Section 5.5	Sensitive CYP2D6 substrates and investigational therapies were added to the prohibited concomitant medication.	Update
15	Section 6.1	Clarification was added around treatment of subjects after discontinuation.	Clarification
16	Section 6.1.2	Stopping rules were added for low lymphocyte counts and low hemoglobin levels.	Update
17	Section 7.1	A safety telephone call at Day 60 was added and clarification was added around Screening and Day 1 occurring on the same day or 1 day apart.	Update and clarification
18	Section 7.2	D-dimer and cardiac troponin were specified in the list of potential laboratory parameters to be assessed	Clarification
19	Section 7.3	The section was updated to specify that PK assessments will be at select sites. Clarification around PK assessments following discharge from the hospital was added.	Update
20	Section 7.4	Clarification was added that vital signs are part of safety assessments.	Clarification
21	Section 7.5.1	ECGs were removed	Update
22	Section 7.5.2	Updated to align with the new Day 60 safety telephone call.	Update
23	Section 7.5.10	Text concerning the SAE form was updated.	Update
24	Section 7.5.11	Text concerning the pregnancy form was updated.	Update
25	Section 8	Updates were made throughout consistent with the updated endpoints and addition of placebo, including an increased sample size.	Update
26	Section 9.1.5	Further details of the DSMB were added.	Clarification

9.2.2. Version 3.0: 05 June 2020

Overall reason for Version 3.0: The overall reason for Version 3.0 of the protocol was to incorporate feedback from the FDA.

Item No.	Protocol Section	Version 3/Update	Reason/Rationale
1	Protocol	The version number and date were updated throughout. Editorial and administrative revisions (eg, typographical error, punctuation, tenses, abbreviations) were incorporated to provide clarity. The synopsis and schedule of events were updated to be consistent with changes in the protocol.	Update
2	Sections 1.2 and 6.1.1	An independent Hepatic Advisory Safety Committee will monitor hepatic safety throughout the study and the protocol was amended accordingly.	Update
3	Sections 2.2.1, 8.2, and 8.4.2	The primary endpoint was amended to the time from randomization to respiratory improvement, defined as peripheral oxygen saturation (SpO_2) ≥94% on room air sustained until discharge from the hospital or the end of the study (Day 28)	Update
4	Section 3.1	The study design was amended to reflect changes made elsewhere, namely exclusion of CYP2C inducers, inclusion of the HAC, and addition of the interim analysis for futility.	Update
5	Sections 4.3 and 5.5	CYP2C inducers were added to the excluded therapies in exclusion criterion #7.	Update
6	Section 7.1	The schedule of events was updated to include WHO ordinal scale assessment at baseline, drug compliance check on Day 14, additional PK assessment on Day 28 and in the case of hepatotoxicity, and to clarify which subjects must attend the Day 60 telephone call.	Update and clarification
7	Section 7.2	Antibody titers were added to the list of laboratory parameters	Clarification
8	Section 7.3	Additional PK assessments on Day 28 and in the case of hepatotoxicity were added.	Update
9	Section 7.5.3	A section was added to define adverse events of special interest (AESIs).	Update
10	Section 7.5.12	AESIs were added to the events to be reported in an expedited manner.	Update
11	Section 8	The statistical considerations sections were updated to include the updated primary endpoint, details of the second interim analysis for futility, the resulting sample size changes, and to include AESIs.	Update
12	Section 8.4.5	Baseline classification on the WHO ordinal scale was specified	Update
13	Section 9.1.5.2	Section added to describe the HAC	Update

9.2.3. Version 4.0: 23 July 2020

Overall reason for Version 4.0: The overall reason for Version 4.0 of the protocol was to incorporate feedback from Health Authorities.

Item No.	Protocol Section	Version 4/Update	Reason/Rationale
1	Protocol	The version number and date were updated throughout. Editorial and administrative revisions (eg, typographical error, punctuation, tenses, abbreviations) were incorporated to provide clarity. The synopsis and schedule of events were updated to be consistent with changes in the protocol.	Update
2	Synopsis	The number of sites was increased to approximately 40	Update
3	Section 3.1	A definition of hospitalization was added.	Clarification
4	Section 3.1 and 4.1	An error in the number of study subjects was corrected	Clarification
5	Sections3.1, 5.3, and 8.4.7	Stratification factors were amended to remove hydroxychloroquine and add dexamethasone.	Update
6	Sections3.1, 6.2, and 7.2	Clarification was added regarding ongoing assessment of subjects discharged from the hospital before Day 28.	Clarification
7	Sections 4.2 and 7.2	Inclusion Criterion #5 was modified to specify Screening not enrollment and Inclusion Criterion #7 was modified for use of antipyretics.	Clarification
8	Section 4.3	Exclusion Criterion #2 was amended to clarify that participation in interventional studies is not permitted and Exclusion Criterion #7 was amended to permit use of dexamethasone	Clarification and update
9	Section 5.3	Text regarding the randomization code was removed and reference was made to the Pharmacy Manual.	Clarification
10	Section 5.5	Concomitant dexamethasone use was permitted and a cautionary note was added regarding BCRP substrates.	Update
11	Section 6.2	Erroneous text regarding replacement of dropouts was removed.	Clarification
12	Section 7.1	A pregnancy test was added at Day 60 and the nasopharyngeal swab at Screening was removed. Clarification was added that CT scans would be acceptable in the place of X-rays if taken within 48 hours before Screening and that laboratory assessments taken up to 24 hours before Screening are acceptable.	Update and clarification
13	Section 8.4	Statistical methods were updated to reflect changes elsewhere in the protocol and for clarity.	Update
14	Section 8.4.6	Text regarding recommendations from the DSMB was clarified.	Clarification

9.2.4. Version 5.0: 08 October 2020

Overall reason for Version 5.0: The overall reason for Version 5.0 of the protocol was to incorporate feedback from study sites.

Item No.	Protocol Section	Version 5/Update	Reason/Rationale
1	Protocol	The version number and date were updated throughout. Editorial and administrative revisions (eg, typographical error, punctuation, tenses, abbreviations) were incorporated to provide clarity. The synopsis was updated to be consistent with changes in the protocol.	Update
2	Section 2.2.2 and 8.4.3	Clarification was added that the secondary endpoint of time from randomization to defervescence applies only to subjects with fever at enrollment.	Clarification
3	Section 4.2	Inclusion Criterion #7, requiring subjects to present with fever, was removed.	Update
4	Section 4.3	Exclusion Criterion #4 was modified to exclude subjects with lymphocyte count <500 lymphocytes/μL and any subject with hemoglobin <11.0 g/dL	Update
5	Section 6.1	The text was updated to clarify that subjects would be discontinued from study treatment, not the study, in case of disease progression.	Clarification
6	Section 6.1.2	Levels of lymphocytes and hemoglobin indicating anemia or low lymphocyte count were reduced to <500 lymphocytes/μL and 11 g/dL, respectively.	Update

9.2.5. Version 6.0: 18 December 2020

Overall reason for Version 6.0: The overall reason for Version 6.0 of the protocol was to incorporate feedback from study sites and Health Authorities.

Item No.	Protocol Section	Version 6/Update	Reason/Rationale
1	Protocol	The version number and date were updated throughout. Editorial and administrative revisions (eg, typographical error, punctuation, tenses, abbreviations) were incorporated to provide clarity. The synopsis was updated to be consistent with changes in the protocol.	Update
2	Section 4.2	In Inclusion Criterion #5, the window for symptom onset prior to Screening was changed from 7 to 10 days. In Inclusion Criterion #9 the contraception requirements and definition of WOCBP were updated in line with the CITG guidelines.	Update
3	Section 6.1.1 and Section 6.1.2	Text was amended to clarify the distinction between temporarily stopping study drug and permanent discontinuation, and to ensure notification of the medical monitor in case of abnormal LFTs.	Clarification
4	Section 7.1	A window of ±3 days was added to the Day 60 telephone call. A pregnancy test was added at Day 28. Cytokine and acute phase protein blood draws were separated onto 2 different rows for clarity. Further definition of the physical examination was added.	Update

Item No.	Protocol Section	Version 6/Update	Reason/Rationale
5	Section 7.2	Text was amended to clarify that the laboratory assessments should include all parameters, which analyses occur at a central laboratory, to clarify assessment of direct and indirect bilirubin, and that all laboratory parameters should be assessed at baseline.	Clarification
6	Section 7.3	Text was added to confirm that analyses will be at central laboratory.	Clarification
7	Section 7.5.2	Clarification was added that transfer to ICU, mechanical ventilation, or another medically important event (at the discretion of the investigator) as a result of disease progression would be classified as an SAE.	Update
8	Section 8.2 and Section 8.4.6	Text was amended to clarify that the first interim analysis would be after the first 40 subjects reached Day 28 or died, withdrew consent, or were lost to follow-up and to clarify those subjects who would be censored.	Clarification
9	Section 8.4.2	Text was amended to clarify that subjects would be followed unless they or died, withdrew consent, or were lost to follow-up; to clarify achievement of the primary endpoint; and to clarify those subjects who would be censored.	Clarification
10	Section 8.4.3	Assessment of overall survival had been erroneously included and was removed.	Update
11	Section 8.4.4.5	The baseline laboratory assessment was clarified as being prior to first dose.	Clarification

9.2.6. Version 7.0: 02 June 2021

Overall reason for Version 7.0: The overall reason for Version 7.0 of the protocol was to incorporate feedback from study sites and Health Authorities.

Protocol Section	Version 7/Update	Reason/Rationale
Protocol	The new nonproprietary name was added. The version number and date were updated throughout. Editorial and administrative revisions (eg, typographical error, punctuation, tenses, abbreviations) were incorporated to provide clarity. The synopsis and Schedule of Events were updated to be consistent with changes in the protocol.	Update
Synopsis	The number of sites was increased to approximately 50.	Update
Section 4.2	Inclusion criterion #5 was changed to allow symptom onset ≤14 days.	Update
Section 6.1.1	The text was amended to clarify that LFT monitoring is daily during hospitalization.	Clarification
Section 7.2	Details of what assessments take place should a subject be transferred to the ICU were clarified.	Clarification
Section 7.3	The PK assessments were reduced to give sparce PK sampling.	Update
Section 7.5.4	Hepatic abnormalities of Grade ≥4 will be considered unexpected adverse events.	Update
Section 8.4.2	Rescue therapy was defined.	Update

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