NCT #: NCT04439071

STATISTICAL ANALYSIS PLAN

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

PTC299-VIR-015-COV19

19AUG2022

VERSION 3.0

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APPROVAL SIGNATURE PAGE

Protocol Title:	EVALUATION OF THE EFFICACY AND SAFETY OF PTC299 IN HOSPITALIZED SUBJECTS WITH COVID-19 (FITE19)
SAP Version and Date	Final version 3.0, 19 August 2022
Protocol Number:	PTC299-VIR-015-COV19
Phase:	2/3

SAP Author

[redacted]
PTC Therapeutics, Inc.

Date

Signature Statement

By signing this document, I acknowledge that I have read the document and approve of the planned statistical analyses described herein. I agree that the planned statistical analyses are appropriate for this study, are in accordance with the study objectives, and are consistent with the statistical methodology described in the protocol, clinical development plan, and all applicable regulatory guidance and guidelines.

[redacted]
PTC Therapeutics, Inc.

Date

[redacted]
PTC Therapeutics, Inc.

Date

[redacted]
PTC Therapeutics, Inc.

Date

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REVISION HISTORY

Date	Version	Description	Author
22FEB2021	1.0	Initial version	[redacted]
21JUL2021	2.0	Revised per protocol version 7.0 - Section 3.2: study population was changed to subjects with symptom onset ≤14 days - Section 4.9.1: Added definition of rescue therapies - Section 4.9.1.1: Added two additional sensitivity analyses - Section 4.9.2.2: Added handling of transformation of viral load/cytokine/protein data. - Appendix 6.3: Added the details of handling of laboratory/viral load/cytokine/protein data	[redacted]
19AUG2022	3.0	Added subgroup analysis in section 4.11 - Days from symptom to randomization less than or equal to 5 days (yes vs no)	[redacted]

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialist Term	Explanation
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AST	Aspartate transaminase
BID	Twice a day
BLQ	Below the limit of quantitation
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CRO	Contract Research Organization
CTCAE	Common terminology criteria for adverse event
DSMB	Data and safety monitoring board
G-CSF	Granulocyte-colony stimulating factor
eCRF	Electronic case report form
HAC	Hepatic advisory safety committee
IL	Interleukin
IP-10	Interferon gamma-induced protein 10
ITT	Intent-to-treat
KM	Kaplan-Meier
LLOQ	Lower limit of quantitation
MCP	Monocyte chemoattractant protein
MedDRA	Medical Dictionary for Regulatory Activities
NCI	National Cancer Institute
PK	Pharmacokinetic
PTC	PTC Therapeutics
QD	Once daily
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical analysis system
SOC	Standard of care
SpO_2	Peripheral oxygen saturation
Tbili	Total bilirubin
T2RI	Time to respiratory improvement
TEAE	Treatment-emergent adverse event
TNF-α	Tumor necrosis factor-alpha
ULN	Upper limit of normal
ULOQ	Upper limit of quantitation
VEGF	Vascular endothelial growth factor
WBC	White blood cell
WHODD	World Health Organization Drug Dictionary
WOCBP	Women of childbearing potential

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1. INTRODUCTION

This statistical analysis plan (SAP) describes the analysis method for PTC's protocol "Evaluation of the efficacy and safety of PTC299 in hospitalized subjects with COVID-19 (FITE19)"; Protocol Version 7.0 was issued on 02 June 2021. It contains definitions of analysis populations, derived variables, data handling rules, format of data presentation and statistical methods for the analysis of efficacy and safety.

This SAP provides a comprehensive and detailed description of the strategy, rationale, and statistical techniques to evaluate the necessary efficacy and safety endpoints. The purpose of this SAP is to ensure the credibility of the study findings by pre-specified statistical approaches to the study data prior to the database lock. The PK analyses will be addressed separately and not included in this SAP

The SAP will be finalized and approved prior to the data base lock.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study 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

- 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. Study Endpoints

2.2.1. Primary Endpoints

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

- 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, Phase 2/3, 28-day study with safety follow-up by telephone call at Day 60. The study is designed to evaluate the efficacy and safety of PTC299 as compared with placebo in hospitalized adult subjects with confirmed pneumonia, diagnosed with COVID-19, and not requiring mechanical ventilation. All subjects regardless of receiving PTC299 or placebo, will also receive standard of care as defined per local written policies or guidelines. Eligible subjects will be equally (1:1) randomized to one of the two following treatment arms:

Arm A - Subjects in arm A will receive PTC299 200mg twice a day (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. Subjects will be followed up to Day 28 with a safety follow-up phone call at Day 60.

Arm B - Subjects in arm B will receive the matching placebo BID (morning and evening at approximately 12-hour intervals) on Days 1 to 7 followed by the matching placebo QD (in the morning) on Days 8 to 14. Subjects will be followed up to Day 28 with a safety follow-up phone call at Day 60.

Randomization will be stratified by the following three stratification factors:

- Age (≤62 vs >62)
- Remdesivir use (yes vs no)
- Dexamethasone use (yes vs no)

The study is expected to enroll approximately 380 subjects with two planned interim analyses. The first interim analysis is planned when approximately 40 randomized subjects (20 in each arm) have been enrolled and followed to Day 28 or discontinued due to death, or withdrawal consent, or lost-to-follow-up to assess the safety of the study drug. The 2nd interim analysis is planned when approximately 163 events have been observed (approximately 190 subjects have been followed up to 28 days) to assess the futility of the study.

An independent data and safety monitoring board (DSMB) will review available interim analyses data. After the first 40 subjects (20 in each arm) are enrolled, enrollment will then be temporarily halted, and an interim analysis will be performed to assess safety. The enrollment will continue if there are no safety concerns. During the 2nd interim analysis, the DSMB will make go- or no-go recommendation based on the futility and the recommendation will be communicated to the study team. In addition to the scheduled data review meetings for the 1st and 2nd interim analyses, the DSMB may request ad hoc reports and/or meetings.

In addition to the DSMB, an independent Hepatic Advisory Safety Committee (HAC) will also review each case related to liver toxicity in an ongoing basis.

3.2. Study Population

The study will enroll male and female subjects aged ≥18 years, who are hospitalized and infected with a new coronavirus, SARS-Co-V-2, resulting in coronavirus disease 2019 (COVID 2019). Subjects are required to have had symptom onset ≤14 days prior to enrollment; had SpO_2 <94% on room air; had at least one of respiratory rate >24 breaths/minute or cough; and had confirmed lung involvement by radiographic imaging. Women of childbearing potential (WOCBP) or men who are sexually active with WOCBP must be willing to use birth control methods as detailed in the protocol for up to 50 days after the last dose of study drug, and all subjects have to understand and be willing to sign a written informed consent and agree to adhere to the study visit schedule and other protocol procedures. The inclusion and exclusion criteria are detailed in protocol Section 4.

3.3. Study Treatment

PTC299 tablets with dosage strengths of 50 mg and matching placebo will be provided. Eligible subjects will receive PTC299 200 mg (or matching placebo) orally BID (morning and evening at approximately 12-hour intervals) on Days 1 to 7 followed by PTC299 50 mg (or matching placebo) QD (in the morning) on Days 8 to 14. Subjects will be followed up to Day 28 with a safety follow-up phone call at Day 60.

3.4. Study Assessments and Procedures

Subjects will be assessed daily while hospitalized. All subjects will undergo efficacy, safety, and laboratory assessments as summarized in Table 2. 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, Day 28 and Day 60 in the protocol

A follow-up telephone call at Day 60 will be performed to assess AEs, serious AEs, and deaths. The Day 60 pregnancy test will be taken at home and self-reported during the telephone contact. All subjects will undergo the assessments specified for Day 14 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.

3.5. Stratification, Randomization, and Blinding

Randomization will occur at each subject's baseline (screening) visit using an Interactive Response Technology (IRT) system. Assignment to treatment groups is determined by a computer-generated random sequence. Randomization will be stratified by the following three stratification factors:

- Age (≤62 vs >62)
- Remdesivir use (yes vs no)
- Dexamethasone use (yes vs no)

This is a double-blind study. PTC personnel who are directly involved in the conduct of the study will remain blinded until the final database lock. Dummy treatment codes will be used for programming and review before final database lock.

The unblinded interim analyses will be conducted by an independent statistician and the results will be only shared in the closed session of the DSMB. The study team will be kept blinded for results related to the interim analyses.

3.6. 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, or withdrawal consent, or 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 ≥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.

3.7. Interim Analyses

Two interim analyses are planned. The first interim analysis will be conducted when 40 randomized subjects (approximately 20 in treatment arm and 20 in placebo 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.

The 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 (Day 28). 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, i.e., 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. The detailed censoring rules for the primary endpoint are described in Section 4.9.1.

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 recommendation and only the recommendation will be communicated to the study team. The study team will be kept blinded for results related to the interim analyses.

For the first and second interim analyses, all safety analyses will be based on safety population and all efficacy analyses will be based on ITT population.

3.8. Data and Safety Monitoring Board (DSMB) and Hepatic Advisory Safety Committee (HAC)

An external DSMB is established in this study. The DSMB will review the interim analyses data and results and make the go- or no-go recommendation. The recommendation will be communicated to the study team. The composition and responsibilities of DSMB are detailed in the DSMB Charter.

A HAC is also established in the trial. The HAC will review safety data with respect to the liver related toxicities on an ongoing case by case basis. HAC will also provide recommendations to the DSMB. Additional information can be obtained in the HAC charter.

4. STATISTICAL CONSIDERATIONS

4.1. General Methods and Reporting Conventions

Data will be summarized by treatment groups. Categorical variables will be summarized by frequency distributions (number and percentage of subjects). A missing category will be created for subjects with missing information. If no subjects in a category for a categorical variable, the category will be presented with zero count. Continuous variables will be summarized by descriptive statistics (such as number of subjects, mean, standard deviations, median, minimum, maximum, and number of missing if any). All tests of hypotheses will be considered nominally statistically significant if the 2-sided p-value is less than 0.05 or a pre-specified significance level.

Statistical analyses will be performed using the Statistical Analysis System (SAS) version 9.4 or higher.

4.2. Analysis Populations

4.2.1. Intent-to-Treat (ITT) Population

ITT population will include all randomized subjects. The ITT population will be used in all efficacy analyses and subjects will be grouped based on the arm they are randomized to. If a subject receives treatment different from the one to which he/she was randomized, the subject's efficacy data will be analyzed "as randomized."

4.2.2. Safety Population

Safety population will include all randomized subjects who received at least one dose of study drug. If a subject receives treatment 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.

4.2.3. Pharmacokinetic (PK) Population

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

4.3. Subject Disposition

A summary of subject disposition (analysis population allocation, treated, early treatment discontinued, the primary reason for treatment discontinuation, completed the study, discontinued the study, and the reason for study discontinuation) will be presented by treatment groups and overall using frequency and percentage.

The reasons for treatment discontinuations will be summarized based on the following categories:

- Withdrew Consent
- Disease Progression
- Adverse Event
- Protocol Deviation
- Investigator/Sponsor Decision
- Lost to Follow up
- Death
- Other

The reasons of study discontinuations will be summarized based on the following categories:

- Study Completed
- Adverse Event
- Lost to Follow up
- Investigator/Sponsor Decision
- Withdrawal of Consent
- Death
- Other

A separate summary of the number of subjects screened screen failure and reasons for screen failure will be provided as well.

A by-subject data listing of treatment/study completion information including the reason for study withdrawal, if applicable, as well as a by-subject data listing for subjects with reasons for screening failure will be presented.

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

Protocol deviations will be defined and handled by CRO and reviewed by PTC. Protocol deviations will be finalized and documented prior to the database lock.

All protocol deviations will be presented in a data listing.

4.5. Demographic and Baseline Characteristics

The demographics and baseline characteristics will be summarized in the ITT population.

4.5.1. Demographics

The following demographics will be summarized by treatment arms and overall

- Age (years): as reported in the screen visit
- Gender
- Race
- Ethnicity
- Height (cm)
- Weight(kg)
- Body Mass Index (BMI) (kg/m^2): weight (kg)/(height in m)^2
- BMI categories (underweight (<18.5), normal (18.5 - 24.9), overweight (25.0 - 29.9), obesity (≥30)
- Smoking history (smoker, non-smoker, former smoker)
- Years of smoking (years)
- Average packs smoked per week

4.5.2. Baseline Characteristics

The following baseline characteristics will be summarized by treatment arms and overall.

Stratification factors:

- Age (≤62 vs >62)
- Dexamethasone use (yes vs no)
- Remdesivir use (yes vs no)

Baseline disease risk factors:

- Chronic kidney disease (yes vs no)
- COPD/asthma (yes vs no)
- Immunocompromised (yes vs no)
- Type 2 diabetes (yes vs no)
- Heart disease (yes vs no)
- Sickle cell disease (yes vs no)
- Obesity (yes vs no)
- Hypertension (yes vs no)

Baseline disease characteristics:

- WHO ordinal scale for clinical improvement
- Received any of COVID-19 treatment as SOC (yes vs no)
- Time from symptom onset to randomization
- Time from COVID-19 diagnosis to randomization
- COVID-19 initial symptoms

4.6. Medical History

All medical history will be coded using Medical Dictionary for Regulatory Activities (MedDRA). The MedDRA version will be indicated in the footnote of the relevant tables and listings based on the version used in the clinical data. A summary of medical and surgical history will be presented by MedDRA system and organ class and preferred term (PT).

Medical history will be presented in by-subject listings as well.

4.7. Prior/Concomitant/Post Medications/Procedures

Prior medications/procedures are defined as non-study medications/procedures that were initiated prior to the start of study treatment. Concomitant medications/procedures are defined as non-study medications/procedures that were initiated before the first dose of study drug and continued during the study treatment or initiated on/after the first dose date but before the end of study treatment. Post medication/procedures are defined as non-study medications/procedures that were initiated after the last dose of study treatment up to Day 28 or medications/procedures initiated prior to the last study treatment and continued after the last dose. It is possible that some medications/procedures can be counted in more than 1 category. A medication/procedure flag will be created for each medication/procedure to indicate the type of the medication/procedure (ie, prior or concomitant or post). Medications with missing start or end dates will be categorized as either prior or concomitant or post or all unless there is evidence contradictory. For example, if the start date of a medication/procedure is missing and the end date is prior to the first study treatment date, the medication/procedure will be considered as prior. If the end date is after the first study treatment date or is missing or the medication/procedure is ongoing, the medication/procedure will be considered concomitant or post.

All non-study drugs and therapies will be coded by Anatomical Therapeutic Chemical (ATC) code and PT using the World Health Organization Drug Dictionary (WHODD). All procedures will be coded by the MedDRA. The WHODD and MedDRA versions will be indicated in the footnote of the relevant tables and listings based on the versions used in the clinical data.

4.7.1. COVID-19 Standard of Care Medications

All prior/concomitant COVID-19 standard of care medications will be categorized as:

- COVID-19 medications initiated and ended prior to the first study treatment
- COVID-19 medications initiated prior to the first study treatment and continued during the study
- COVID-19 medications initiated after the first study treatment as part of SOC but not as rescue medications
- COVID-19 medications initiated after the first study treatment as rescue medications

COVID-19 standard of care medications will be summarized with subject counts and percentages by the above medication categories, WHO ATC level 3, and PT and by treatment groups.

4.7.2. COVID-19 Procedures

Number and percent of the subjects who undergo COVID-19 procedures (i.e., CT scan, x-ray, and other) as well as the results (normal and abnormal) will be summarized by study visit, and treatment groups. Subjects requires mechanical ventilation during the study will be summarized by treatment groups.

4.7.3. Other Prior/Concomitant/Post Medications

Prior medications other than medications used for COVID-19 will be summarized with subject counts and percentages by WHO ATC level 3 and PT and by treatment groups and overall.

Concomitant medications other than medications used for COVID-19 will be summarized with subject counts and percentages by WHO ATC level 3 and PT and by treatment groups and overall.

Post medications other than medications used for COVID-19 will be summarized with subject counts and percentages by WHO ATC level 3 and PT and by treatment groups and overall.

All prior concomitant and post medications/procedures including medications/procedures used for COVID-19 will be listed.

4.8. Study Drug Exposure

Treatment duration, and treatment compliance will be summarized by treatment groups and overall.

4.8.1. Treatment Duration

Treatment duration (days) is defined as the date of last study dose - the date of first study dose +1. For subjects who are still on treatment at a data cut-off (extraction) date, the last dose date is the last dosing date on or prior to the data cut-off date.

4.8.2. Treatment Compliance

Treatment compliance is defined as [total cumulative dose received/total cumulative dose prescribed]x100%, where the total cumulative dose received is defined as the sum of all doses taken in mg during the treatment period and the total cumulative dose prescribed is defined as the sum of all doses prescribed. For example, if a subject completed 14 days of treatment, the total cumulative dose prescribed is calculated as 200 (mg) x 2 (BID) x first 7 (days) +50 (mg) x 1(QD) x second 7 (days)=3150 (mg)

Study drug exposure will also be presented in by-subject listings.

4.9. Efficacy Analysis

Efficacy analyses will be based on the ITT population. The null hypothesis for primary efficacy comparison is that the distribution of time to respiratory improvement (T2RI) between the two treatment groups is the same. The alternative hypothesis is that the distribution of T2RI between the two treatment groups is not the same. Rejecting the null hypothesis with shortened T2RI in PTC299 as compared with the placebo arm in the ITT population will be considered a successful demonstration of efficacy.

All statistical tests will be 2-sided at the significance level of 0.05. The corresponding p-values and 2-sided 95% CIs for intended point estimates will be reported.

4.9.1. Primary Efficacy Analysis

The primary endpoint is the time from randomization to respiratory improvement (T2RI), 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 SpO2 ≥94% and sustained to Day 28 or discharge without taking any COVID-19 rescue therapy during the study will be considered as achieving respiratory improvement event and the event date will be the first date of achieving SpO2 ≥94%. For all other subjects i.e., a). randomized but had no follow-up; b). initiated any COVID-19 rescue therapy during the study, where a rescue therapy is defined as any additional medication, exclusive of SOC, used to treat worsening of COVID-19 symptoms and recorded as rescue therapy on the eCRF; c). lost follow-up prior to Day 28 d). died prior to Day 28; e). withdrawn consent prior to Day 28; f). had full follow-up without achieving sustained SpO2 ≥94%, will be censored at Day 28.

Kaplan-Meier (KM) 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 by randomization strata.

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 KM 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.

4.9.1.1. Sensitivity Analysis for Primary Endpoint

Three sensitivity analyses will be performed for the primary endpoint as follows:

- Randomized subjects without any follow-up will be censored at the randomization date.
- Subjects will not be censored by rescue therapy in the primary analysis.
- An additional variable of time from symptom onset to randomization (≤7 days versus >7 days) will be added in the primary analysis model.

4.9.2. Secondary Efficacy Analyses

4.9.2.1. Respiratory Functions

The proportion of subjects requiring invasive ventilation at any point during the study

Number and the percentage of subjects requiring invasive ventilation during the study will be summarized by treatment groups. Cochran Mantel-Haenszel test will be used to compare the treatment difference.

A by-subject listing will also be provided for subjects requiring invasive ventilation.

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

Number and the percentage of subjects requiring supplemental oxygen or noninvasive ventilation during the study in subjects who did not require supplemental oxygen at baseline will be summarized by treatment groups. Cochran Mantel-Haenszel test will be used to compare the treatment difference.

A by-subject listing will also be provided for subjects requiring supplemental oxygen or non-invasive ventilation.

Time from randomization to defervescence

Time from randomization to defervescence will be analyzed in subjects who had fever (body temperature of ≥37.6°C axilla, ≥38.0°C oral, or ≥38.6°C tympanic or rectal) at baseline. Defervescence is defined as body temperature of <37.6°C axilla, <38.0°C oral, or <38.6°C tympanic or rectal without taking any antipyretic treatment and sustained until discharge or Day 28. Time from randomization to the first defervescence event will be analyzed using KM method by treatment groups in subjects who had fever at baseline. A summary table of the number of events, the number of censors, and KM estimates (25th, 50th, 75th percentile of time to defervescence along with the 95% CI), and the defervescence rate at Day 7, Day 14, and Day 28 will be provided.

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.

A KM plot by treatment groups will be provided for time from randomization to defervescence and a by-subject listing will also be provided.

Time from randomization to respiratory rate ≤24 breaths/minute on room air

Respiratory rate ≤24 breaths/minute on room air and sustained until discharge or Day 28 will be considered as achieving the respiratory rate normalization event. Time from randomization to the first date of achieving normalization of respiratory rate will be analyzed using KM method by treatment groups. A summary table of the number of events, the number of censors, and KM estimates (25th, 50th, 75th percentile of time to normalization of respiratory rate along with the 95% CI), and the rate of normalization of respiratory rate at Day 7, Day 14, and Day 28 will be provided.

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.

A KM plot by treatment groups will be provided for time from randomization to respiratory rate normalization and a by-subject listing will also be provided.

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 as severe or moderate)

Time from randomization to cough relief will only be analyzed in subjects with cough self-reported as severe or moderate at baseline on a scale of severe, moderate, mild, or absent. Cough relief event is defined as subjects with cough self-reported as severe or moderate at baseline and reported as mild or absent during the study and sustained until discharge or Day 28. Time from randomization to the first date of achieving cough relief event will be analyzed using KM method by treatment groups. A summary table of the number of events, the number of censors, and KM estimates (25th, 50th, 75th percentile of time to cough relief along with the 95% CI), and the cough relief rate at Day 7, Day 14, and Day 28 will be provided.

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.

A KM plot by treatment groups will be provided for time from randomization to cough relief and a by-subject listing will also be provided.

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)

Time from randomization to dyspnea relief will only be analyzed in subjects with dyspnea self-reported as severe or moderate at baseline on a scale of severe, moderate, mild, or absent. Dyspnea relief event is defined as subjects with dyspnea self-reported as severe or moderate at baseline and reported as mild or absent during the study and sustained until discharge or Day 28. Time from randomization to the first date of achieving dyspnea relief event will be analyzed using KM method by treatment groups. A summary table of the number of events, the number of censors, and KM estimates (25th, 50th, 75th percentile of time to dyspnea relief along with the 95% CI), and the dyspnea relief rate at Day 7, Day 14, and Day 28 will be provided.

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.

A KM plot by treatment groups will be provided for time from randomization to dyspnea relief and a by-subject listing will also be provided.

4.9.2.2. Immune Response

For viral load, cytokine, and protein data, descriptive summaries and analyses will be performed on logarithm base 10 transformed data and a value of 1 will be added to the original value before the transformation. Plasma concentration values that are below the limit of quantitation (BLQ) will be presented as "BLQ" in the concentration data listing. Values that are BLQ will be treated one-half the value of the lower limit of quantitation (LLOQ). The conventions are detailed in Section 6.3 .

Reduction in cytokine levels, potentially including interleukin (IL)-2, IL-6, IL-7, IL-17, granulocyte-colony stimulating factor (GSF), interferon-γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1-α, and tumor necrosis factor-α

Descriptive statistics will be provided for each inflammatory cytokine such as IL-2, IL-6, IL-7, IL-17, GSF etc.at baseline, at each study visit post baseline for actual values and changes from baseline by treatment groups. Unless otherwise specified, only scheduled visits will be included in the summary tables. In the event of repeated values for a test at a visit, the last non-missing value at that visit will be used.

A by-subject listing will also be provided for cytokine data.

Reduction in levels of acute phase proteins, potentially including ferritin, C-reactive protein, D-dimer, and cardiac troponin

Descriptive statistics will be provided for each acute phase protein at baseline, at each study visit post baseline for actual values and changes from baseline by treatment groups. Unless otherwise specified, only scheduled visits will be included in the summary tables. In the event of repeated values for a test at a visit, the last non-missing value at that visit will be used.

A by-subject listing will also be provided for acute phase protein data.

Normalization in the complete blood count

Normalization of complete blood count is defined as all blood components such as WBC, RBC, HGB, HT, HCV, HCH, HCHC, and platelets return to the lab normal range post baseline during the study for subjects who had out of the normal range value of any of the blood component at baseline.

Number and percentage of subject achieving normalization of complete blood count in subjects with abnormal complete blood count at baseline will be summarized by treatment groups.

Changes in other laboratory parameters potentially including decreases in lactate dehydrogenase, prothrombin time, and albumin

Descriptive statistics will be provided for each laboratory parameter at baseline, at each study visit post baseline for actual values and changes from baseline by treatment groups. Unless otherwise specified, only scheduled visits will be included in the summary tables. In the event of repeated values for a test at a visit, the last non-missing value at that visit will be used.

A by-subject listing will also be provided for laboratory data.

4.9.2.3. Reduction in Viral Load

Descriptive statistics will be provided for subjects' viral load at baseline, at each study visit post baseline for actual values and changes from baseline by treatment groups. Unless otherwise specified, only scheduled visits will be included in the summary tables. In the event of repeated values for a test at a visit, the last non-missing value at that visit will be used.

A by-subject listing will also be provided for the viral load data.

4.9.2.4. Duration of Hospitalization

Duration of hospitalization is defined as the sum of the days stayed in hospital. Descriptive statistics (such as mean, standard deviation, median, minimum, and maximum) of duration of hospitalization will be provided by treatment groups.

A by-subject listing will also be provided.

4.10. Safety Analysis

All safety analyses will be performed on the safety population. Summary tables will be provided by treatment groups.

4.10.1. Adverse Events

All adverse events (AEs) will be coded using the MedDRA. The MedDRA version will be indicated in the footnote of relevant AE tables based on the current version used in the clinical data.

AEs will be analyzed in terms of treatment-emergent adverse events (TEAEs), which are defined as any AEs that occurring on or after the first study treatment through 30 days after the last dose, or any AEs occurring before the first study treatment but worsening during the treatment through 30 days after the last dose.

A treatment related TEAE is defined as TEAE that is suspected (possibly or probably related) by the investigator to be related to the study treatment. The severity/intensity of AEs will be graded 1 to 5 according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. For AEs not described in CTCAE criteria, the intensity will be assessed by the investigator as mild (Grade 1), moderate (Grade 2), severe (Grade 3), life threatening (Grade 4), and fatal (Grade 5).

An overview of TEAE summary by treatment groups table will be provided with following information:

- The number of subjects with at least one TEAE
- The number of subjects with at least one treatment related TEAE
- The number of subjects with at least one Grade 3 or Grade 4 TEAE
- The number of subjects with a Grade 5 TEAE (Fatal)
- The number of subjects with at least one SAE

The number of subjects with at least one TEAE leading to treatment discontinuation.

All TEAEs will be summarized by MedDRA system organ class (SOC), and PT. If a subject experiences multiple AEs under the same SOC, the subject will be only counted once for the SOC with the greatest severity. Similarly, if a subject experiences multiple AEs under the same PT and SOC, the subject will be counted only once for the PT with the greatest severity.
The table will be sorted by the descending order of the frequency of SOC then by the descending order of the frequency of PT under SOC based on the PTC299 column.

In addition, the following summary tables will be provided:

- All TEAE by descending frequency of PT
- All TEAE by maximum severity under each SOC and PT
- SAE by SOC and PT
- Treatment related TEAE by SOC and PT
- TEAE leading to treatment discontinuation by SOC and PT

All TEAEs will be presented in a by-subject listing. Listings for non-treatment-emergent AEs, DLTs, SAEs, TEAEs leading to treatment discontinuation, TEAEs leading to dose reduction/interruption, and TEAEs leading to death will also be provided.

4.10.2. Death

The number and the percentage of deaths at Day 28 and Day 60, respectively, will be summarized by treatment groups.

All deaths will be presented in a by-subject listing.

4.10.3. Adverse Events of Special Interest (AESI)

Adverse 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). These include:

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

The number and the percentage of subjects experiencing AESIs will be summarized by each criterion and overall, and by treatment groups.

4.10.4. Clinical Laboratory Evaluations

Laboratory values will be presented in standard units. If any assessment is performed at both local and central laboratories, the value from central laboratory will be used in the analysis. In the event of repeated values for a test at a visit from same laboratory, the last non-missing value at that visit will be used

Descriptive statistics will be provided for each clinical laboratory parameter at baseline, at each study visit post baseline for actual values and changes from baseline by treatment groups. Unless otherwise specified, only scheduled visits will be included in the summary tables.

Clinical laboratory values will be graded according to NCI CTCAE version 5.0 for applicable tests. A summary table of the worst CTC grade post baseline during the treatment period of laboratory data will be provided by treatment groups. For the worst CTC grade tables, unscheduled laboratory values will be considered as well.

A by-subject listing will also be provided for laboratory data. Laboratory values that are outside the normal range will also be flagged in the data listings. Any out-of-range values that are identified by the investigator as being clinically significant will also be shown in a listing.

4.10.4.1. Liver Related Laboratory Parameters

The liver function related parameters will be assessed and summarized. The potential Hy's law cases (as serum ALT or AST >3xULN and total bilirubin >2xULN) will be evaluated and summarized based on the criteria listed in Table 1:

Table 1: Liver Function Test Result Categories

Parameter	Criteria
ALT	>3ULN and <=5ULN >5ULN and <=8ULN >8ULN
AST	>3ULN and <=5ULN >5ULN and <=8ULN >8ULN
Total Bilirubin	>2ULN >3ULN
Total Bilirubin>2ULN and ALT	>3ULN and <=5ULN >5ULN and <=8ULN >8ULN
Total Bilirubin>2ULN and AST	>3ULN and <=5ULN >5ULN and <=8ULN >8ULN

4.10.5. Vital Signs

Vital sign parameters will be summarized for both actual and change from baseline values by study visit, by treatment groups.

Vital signs will also be listed.

4.10.6. Physical Examination

Physical examination results will be presented in a by-subject listing.

4.11. Subgroup Analysis

To evaluate treatment effect in a more homogeneous population, the primary endpoint will be explored within the following subgroups as deemed appropriate:

- Age (≤62 vs >62)
- Remdesivir use (yes vs no)
- Dexamethasone use (yes vs no)
- Chronic kidney disease (yes vs no)
- COPD/asthma (yes vs no)
- Immunocompromised (yes vs no)
- Type 2 diabetes (yes vs no)
- Heart disease (yes vs no)
- Sickle cell disease (yes vs no)
- Obesity (yes vs no)
- Hypertension (yes vs no)
- Days from symptom to randomization less than or equal to 5 days (yes vs no)

If any of the subgroup levels has less than 10% of subjects the subgroup analysis will not be performed.

The treatment effect in the subgroup analysis will be evaluated by an un-stratified log-rank test and the hazard ratio will be estimated using the unstratified Cox proportional hazards model.

The subgroup analysis will be performed in ITT population in each subgroup.

4.12. Pharmacokinetic Analysis

PK analyses will be discussed in a separate SAP.

5. CHANGES TO THE PLANNED STATISTICAL ANALYSIS IN THE PROTOCOL

There is no change relative to the planned statistical analyses in the protocol amendment.

6. APPENDICES

6.1. General Data Presentation

Common data presentation conventions to be used in this study are as following:

- Data from all study centers will be combined for analysis.
- All mean and median values will be formatted to one more decimal place than the measured value. Standard deviation values will be formatted to two more decimal places than the measured value.
- All percentages will be rounded to one decimal place. The number and percentage of values will be presented in the form XX (XX.X%), where the percentage is in the parentheses.
- Confidence intervals (CIs) will be presented as 2-sided 95% CIs unless specified.
- The day of the first dose of study drug will be defined as Day 1.
- In general, unless otherwise specified, baseline value will be defined as the last non-missing value before the first dose of study drug is administrated for safety parameters. (The date of baseline assessment can be on or before the date of first dose of study drug). For randomized subjects who did not receive any of the study drug, the baseline is defined as the last non-missing value before or on the date of randomization.
- To summarize efficacy/safety data by visit, the post-baseline results will be summarized by the scheduled visit as appropriate
- All analysis and summary tables will have the analysis population sample size for each cohort in the column heading (i.e., number of subjects).
- All listings will be sorted in order of treatment group, study center, subject, and date of procedure or event.

6.2. Handling of Dates

Dates will be stored as numeric variables in the SAS analysis files and reported in DDMMMYYYY format (i.e., the Date9. datetime format in SAS). Dates in the clinical database are classified into the categories of procedure dates, log dates, milestone dates, outcome dates, and special dates.

- Procedure Dates are the dates on which given protocol-specified procedures are performed. They include the dates of laboratory testing, physical examinations, imaging (chest X-ray, CT scan, or an equivalent test), etc. They should be present whenever data for a protocol-specified procedure is present and should only be missing when a procedure is not done in the database. Procedure dates will not be imputed.

- Log Dates are dates recorded in the case report form (eCRF) data logs. Specifically, they are the start and end dates for AEs and concomitant medications/procedures. They should not be missing unless an event or medication is marked as ongoing in the database. Otherwise, incomplete log dates will be imputed according to the rules in Section 6.2.2.2 of this SAP. However, in listings, log dates will be shown as recorded without imputation.
- Milestone Dates are dates of protocol milestones such as enrollment date, study drug start date, study termination, etc. They should not be missing if the milestone occurs for a subject. They will not be imputed.
- Outcome Dates are dates corresponding to study endpoints such as the first date of achieving the primary or secondary endpoints, disease progression, etc. They may be subject to endpoint-specific censoring rules if the outcome event, for instance, did not occur; otherwise, they are not subject to imputation.
- Special Dates cannot be classified in any of the above categories and they include, for example, the date of birth. They may be subject to variable-specific censoring and imputation rules.

6.2.1. Calculation Using Dates

Calculations using dates will adhere to the following conventions:

- Relative study day is calculated as:
  - Assessment Date - First Dose Date +1, if the assessment date is done on or after the first dose date
  - Assessment Date - First Dose Date, if the assessment date is done prior to the first dose date.
  - Date of first dose is defined as Study Day 1.
- Intervals that are presented in weeks will be transformed from days (as calculated above) to weeks by using (without truncation) the following conversion formula:
- WEEKS=DAYS/7
- Intervals that are presented in months will be transformed from days (as calculated above) to months by using (without truncation) the following conversion formula:
- MONTHS=DAYS/30.4167
- Intervals that are presented in years will be transformed from days (as calculated above) to years by using (without truncation) the following conversion formula:
  - YEARS=DAYS/365.25

6.2.2. Missing Date Imputation

6.2.2.1. Imputation of Adverse Events/Medication Start Dates

- Missing day only
  - If the month and year are the same as the year and month of the first study treatment date, then the first dosing date will be assigned to the missing field.
  - If the partial date (year and month) is prior to the first study treatment date (year and month), then the last day of the month will be assigned to the missing field.
  - If the partial date (year and months) is after the first study treatment date (year and month), then the first day of the month will be assigned to the missing field.
- Missing month only
  - The day will be treated as missing and both month and day will be imputed according to the imputation's rules for missing day and month.
- Missing day and month
  - If the year is the same as the year of the first dosing date, then the first dosing date will be assigned to the missing field.
  - If the year is prior to the year of the first dosing date, then December 31 will be assigned to the missing field.
  - If the year is after the year of the first dosing date, then January 1st will be assigned to the missing field.
- Missing year
  - No Imputation will be done.
  - The AE will be considered as TEAE if the end date is missing or after the first dosing date.
  - The medication will be considered as both prior and concomitant if the end date is missing or after the first dosing date.

If the stop date is non-missing and the imputed start date is after the stop date, the start date will be imputed by stop date.

6.2.2.2. Imputation of Adverse Events/Medication Stop Dates

- Missing day only
  - If the month and year are the same as the year and month of the last study treatment date, then the last dosing date will be assigned to the missing field.
  - If the partial date (year and month) is prior to the last study treatment date (year and month), then the last day of the month will be assigned to the missing field.

  - If the partial date (year and months) is after the last study treatment date (year and month), then the first day of the month will be assigned to the missing field.

- Missing month only
  - The day will be treated as missing and both month and day will be imputed according to the imputations rules for missing day and month.
- Missing day and month
  - If the year is the same as the year of the last dosing date, then the last dosing date will be assigned to the missing field.
  - If the year is prior to the year of the last dosing date, then December 31 will be assigned to the missing field.
  - If the year is after the year of the last dosing date, then January 1st will be assigned to the missing field.
- Missing year
  - No Imputation will be done.
  - If both start and stop date of an AE are missing, the AE will be considered as TEAE
  - If both start and stop date of a medication are missing, the medication will be considered as both prior and concomitant medication.

If the start date is non-missing and the imputed stop date is before the start date, the stop date will be imputed by start date.

6.3. Handling of Laboratory/Viral Load/Cytokine/Protein Data

In the continuous laboratory, viral load, cytokine, and acute phase protein data, if the value is less than the LLOQ or above the upper limit of quantitation (ULOQ), it will be imputed as following:

- A ½ value of the LLOQ will be used for calculation of descriptive statistics if the data is reported in the form of "<x". For example, if the value is reported as <3, the value will be reported as 1.5.
- A 2 times ULOQ value will be used for calculation of descriptive statistics if the data is reported in the form of ">x". For example, if the value is reported as >3, the value will be reported as 6.
- The limit of quantitation will be used for calculation of descriptive statistics if the data is reported in the form of "≥x" or "≤x", where x is considered as the limit of quantitation.

Table 2: Schedule of Events and Study Parameters

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.
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.

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.**
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 predose (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 protocol 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		
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. REFERENCES

WHO. WHO R&D Blueprint novel Coronavirus: COVID-19 Therapeutic Trial Synopsis. 2020.