Statistical Analysis Plan

CTI Biopharma Corp.
PRE-VENT Phase 3

A Phase 3 Randomized, Double-blind, Placebo-controlled, Multicenter Study of Pacritinib Plus Standard of Care Versus Placebo and Standard of Care in Hospitalized Patients With Severe COVID-19 With or Without Cancer

Protocol Amendment 4

Sponsor:
CTI Biopharma Corp.
3101 Western Avenue, Suite 800
Seattle, WA 98121

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This Statistical Analysis Plan has been reviewed and approved by:

Jirui Wang

Electronically signed by: Jirui Wang Reason: Approved Date: Sep 13, 2021 17:32 EDT

Jirui Wang, PhD
Biostatistician
Medpace, Inc.

Date

Electronically signed by: Lyon Gleich Reason: Approved Date: Sep 13, 2021 18:20 EDT

Lyon Gleich, MD
Vice President, Medical Department
Medpace Inc.

Date

Electronically signed by: Brian Murphy Reason: Reviewed Date: Sep 14, 2021 13:36 EDT

Herve Mommeja-Marin, MD
Vice President, Medical Department
Medpace Inc.

Date

DocuSigned by:
Jennifer Smith
Signer Name: Jennifer Smith
Signing Reason: I approve this document
Signing Time: 14-Sep-2021 | 11:17:19 AM PDT
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Jennifer Smith, PhD
Sr. VP, Biometrics
CTI Biopharma Corp.

Date

DocuSigned by:
Karisse Roman-Torres
Signer Name: Karisse Roman-Torres
Signing Reason: I approve this document
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Karisse Roman-Torres, MSPH
Lead Statistician
CTI Biopharma Corp.

Date

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Version History

Version and Date	Description
Version 1.0, 13 September 2021	Initial version

Table 1: List of Abbreviations and Definitions of Terms

ABBREVIATION	DEFINITION
AE	Adverse Event
ADI	Actual Dose Intensity
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
CI	Confidence interval
CK	Creatine kinase
CMH	Cochran-Mantel-Haenszel
COVID-19	Coronavirus disease 2019
CTCAE	Common Terminology Criteria for Adverse Events
ECG	Electrocardiogram
ECMO	Extracorporeal Membrane Oxygenation
eCRF	Electronic Case Report Form
EOT	End of Treatment
FiO2	Fraction of inspired oxygen
IDMC	Independent Data Monitoring Committee
IMV	Invasive Mechanical Ventilation
MedDRA	Medical Dictionary for Regulatory Activities
PaO2	Arterial oxygen partial pressure
PT	Preferred Term
RDI	Relative Dose Intensity
SAE	Serious adverse advent
SAP	Statistical Analysis Plan
SoA	Schedule of Assessments
SMQ	Standardised MedDRA Query
SOC	Standard of care
SpO2	Blood oxygen saturation
TEAE	Treatment-emergent adverse event
TESAE	Serious treatment-emergent adverse event
TFLs	Tables, Figures, and Listings
WHO	World Health Organization
WHODD	World Health Organization Drug Dictionary
WHO-DDE	World Health Organization Drug Dictionary Enhanced

1 INTRODUCTION

This Statistical Analysis Plan (SAP) describes the statistical analyses and data presentations to be performed for protocol PAC319, "A Phase 2 Randomized, Double-blind, Placebo-controlled, Multicenter Study of Pacritinib Plus Standard of Care Versus Placebo and Standard of Care in Hospitalized Patients With Severe COVID-19 With or Without Cancer" (Amendment 4).

This document provides additional details concerning the statistical analyses that were mentioned in the protocol. If additional analyses are required to supplement the planned analyses described in this SAP, they will be identified as post hoc in the clinical study report.

2 STUDY OBJECTIVES

2.1 Primary Objective

To compare the efficacy of pacritinib + standard of care (SOC) versus placebo + SOC in hospitalized patients with severe COVID-19 with or without cancer, as the proportion of patients who require invasive mechanical ventilation (IMV) and/or extracorporeal membrane oxygenation (ECMO) or die by Day 28. Severe COVID-19 is defined as confirmed disease in patients who are hospitalized with hypoxia (SpO2 ≤93% on room air at sea level), respiratory rate >30, PaO2/FiO2 <300 but do not require IMV.

2.2 Secondary Objectives

1. To compare the number of ventilator-free days, defined as the number of days that patients are alive and not intubated, from randomization to Day 28 between pacritinib + SOC versus placebo + SOC

2. To compare the mortality rate between pacritinib + SOC versus placebo + SOC at Day 28

3. To compare the mortality rate between pacritinib + SOC versus placebo + SOC at Day 15

4. To compare the time to improvement by at least 2 points relative to Baseline on the 7-point ordinal scale of clinical status between pacritinib + SOC versus placebo + SOC

5. To compare the clinical status assessed by the 7-point ordinal scale of clinical status at Days 8, 15, 22, and 28 between pacritinib + SOC versus placebo + SOC

6. To compare the rate of use of immunomodulatory agents as treatment for COVID-19 during the 28 days following randomization between pacritinib + SOC versus placebo + SOC

7. To evaluate the toxicity profile of pacritinib therapy in hospitalized patients with severe COVID-19 with or without cancer

2.3 Tertiary Objectives

To evaluate the treatment effects of pacritinib + SOC vs. placebo + SOC on the following markers of disease severity:

- Serum concentrations of C-reactive protein (CRP)
- Serum concentrations of ferritin
- Serum concentrations of D-dimer
- Serum concentrations of Interleukin 6 (IL-6)
- Serum troponin-I
- Serum lactate dehydrogenase (LDH)
- Serum brain natriuretic peptide (BNP)
- Procalcitonin
- Triglycerides
- Creatine kinase (CK)

3 STUDY OVERVIEW

3.1 Study Design

This is a Phase 2 randomized, double-blind, placebo-controlled, multicenter study to evaluate the efficacy and safety of pacritinib in hospitalized patients with severe COVID-19 with or without cancer. Severe COVID-19 is defined as confirmed disease in patients who are hospitalized with hypoxia (SpO2 ≤93% on room air), respiratory rate >30, PaO2/FiO2 <300, or lung infiltrates >50% but do not require IMV.

Patients will be randomized 1:1 to receive pacritinib (400 mg QD on Day 1, then 200 mg BID from Day 2 to Day 14) + SOC or placebo + SOC stratified by age (< 60 years versus ≥ 60 years) and the 7-point ordinal scale of clinical status scale (baseline 3 or 4 versus 5). The study duration will be 8 weeks.

Assigned treatment will continue for up to Day 14 or until the patient experiences intolerable adverse events (AEs), withdraws consent, or initiates another investigational therapy, or until the study is terminated. Assigned therapy may be given for an additional 7 days (for a total of 21 days) with the approval of the Medical Monitor if, in the opinion of the investigator, the patient's clinical signs and symptoms are improving and the potential benefit outweighs the potential risk. In the event of hospital discharge, patients will complete treatment with the assigned therapy as an outpatient.

The primary endpoint is the effect of treatment on the proportion of patients who require IMV and/or ECMO or die by Day 28.

Ongoing safety monitoring will be conducted by an independent data monitoring committee (IDMC). The IDMC will comprise a multidisciplinary group of at least three voting members in the fields of hematology, infectious disease, and biostatistics. Additional personnel may be

added to the IDMC at the request of the IDMC membership. The membership, roles, and responsibilities of the IDMC will be fully defined by an IDMC charter.

Safety will be monitored with physical examinations, clinical laboratory assessments, and electrocardiogram (ECG) monitoring for inpatients. Patients who are discharged from the hospital while still on study will be monitored weekly. Outpatient monitoring will include telephone contact and may also include review of the patient's electronic medical record. Laboratory and ECG assessments will not be required for monitoring outpatients, including those completing their course of study drug. Specified pacritinib/placebo dosage modifications will be followed to address identified abnormalities. AE data will be collected from the time of randomization through 30 days following the last dose of pacritinib/placebo. Serious adverse events (SAEs) assessed as related (i.e., possibly related per protocol) to pacritinib/placebo or study procedure by the investigator or Sponsor shall be followed until the event resolves, stabilizes or the patient is lost to follow-up. SAEs assessed as unrelated to pacritinib/placebo or study procedures shall be followed for 30 days after the last dose of pacritinib/placebo, or until the event resolves, returns to baseline, stabilizes, or the patient is lost to follow-up, whichever comes first.

3.2 Study Centers

The study will take place at approximately 21 centers in the United States (number of centers and countries may be reassessed as patient enrollment increases).

3.3 Randomization and Blinding

Eligible patients will be centrally randomized in a 1:1 allocation ratio to receive pacritinib (400 mg QD on Day 1, then 200 mg BID from Day 2 to Day 14) + SOC or placebo + SOC according to a stratified permuted block design stratified by age (< 60 years versus ≥ 60 years) and the 7-point clinical status scale (baseline 3 or 4 versus 5).

This study is double-blind; the Sponsor, study patients, and Investigators will be blinded to treatment assignments. The IDMC will have access to unblinded data. Individual patient unblinding may occur at the request of the Investigators if necessary for medical reasons and to assess suspected unexpected serious adverse reactions.

3.4 Sample Size Determination

The study sample size will be approximately 200 patients (randomized in a 1:1 ratio). This provides 80% power to detect at least 13% treatment difference in the proportion of patients who progress to IMV and/or ECMO or die by Day 28, assuming that the response rate is 13.5% in the pacritinib + SOC arm and 26.5% in the placebo+SOC arm, with a one-sided Type I error rate of 0.10.

3.5 Duration of Study

The approximate study duration for each patient will be 8 weeks. The estimated duration of the entire study is approximately 1 year if the maximum number of patients are enrolled.

3.6 Schedule of Assessments (SoA)

The Schedule of Assessments is presented in Protocol Table 1.

4 ANALYSIS POPULATIONS

The study analysis populations and planned analysis for each population are as follows.

Table 2 Analysis Populations

Population Name	Planned Analyses	Definition
Intent-to-Treat (ITT) Population	Patient disposition, demographics, clinical baseline characteristics, and efficacy	The Intent-to-treat (ITT) population is defined as all patients randomized. Note: Patients in this population will be analyzed according to the treatment arm to which they were assigned at randomization. This population will be used for efficacy analyses.
Safety Population	Safety	The Safety population is defined as all randomized patients who received at least one dose of study treatment. Note: Patients in this population will be analyzed according to the treatment actually received. This population will be used for the analysis of safety endpoints.

5 STUDY ASSESSMENTS

5.1 Efficacy Assessments

This section describes the assessments that will be performed to evaluate the efficacy endpoints.

5.1.1 Ordinal Scale of Clinical Status

The following scale adapted from Cao et al. will be used in order to assess the clinical status for the derivation of primary and secondary endpoints.

Table 3 Ordinal Scale of Clinical Status (adapted from Cao et al.)

Ordinal Value and Description
1. Not hospitalized with resumption of normal activities
2. Not hospitalized but unable to resume normal activities
3. Hospitalization, not requiring supplemental oxygen
4. Hospitalization, requiring supplemental oxygen not meeting criteria for categories 5 or 6
5. Hospitalization, on non-invasive positive pressure ventilation or high-flow nasal cannula
6. Hospitalization, requiring IMV and/or ECMO
7. Death

5.1.2 Marker of Disease Severity Assessments

The following markers of disease severity will be assessed:

• Creatinine Kinase,

• Serum concentrations of C-reactive protein (CRP),

• Serum concentrations of ferritin,

• Serum concentrations of D-dimer,

• Serum concentrations of IL-6,

• Serum troponin-I,

• Serum lactate dehydrogenase (LDH),

• Serum brain natriuretic peptide (BNP),

• Procalcitonin,

• Triglycerides.

5.1.3 Lung Function Assessment

Lung function will be assessed by SpO2 in ambient air (if possible), SpO2 with oxygen supplementation (if applicable), documentation of oxygen delivery method, highest oxygen delivery flow rate (if receiving noninvasive oxygen), highest fraction of inspired oxygen (%FiO2) (if on continuous positive airway pressure ventilation [CPAP], bilevel positive air pressure (BiPAP), or invasive mechanical ventilation [IMV]), highest positive end-expiratory pressure (PEEP; if on positive pressure ventilation), and lowest PaO2:FiO2 ratio (if arterial blood gas [ABG] is obtained and the patient is on positive pressure ventilation).

5.1.4 Immunomodulatory Agents

The use of immunomodulatory agents as treatment for COVID-19 such as corticosteroids, tocilizumab, anakinra, or eculizamab, will be assessed.

5.2 Safety Assessments

This section describes the assessments that will be performed to evaluate safety.

Safety assessments include adverse event reporting, laboratory assessments, vital signs, ECG assessments, and physical examinations.

5.2.1 Adverse Events

An AE is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment.

AEs will be collected during the clinical study from the time of randomization through 30 days following the last dose of pacritinib/placebo. AEs that occur after the 30-Day Post EOT Visit that are considered possibly related to pacritinib/placebo or procedure should also be recorded. For screened patients who are not randomized, only SAEs occurring between the time of informed consent and determination of screen failure are reported.

The following information should be captured for all AEs: date of onset and resolution, severity per Common Terminology Criteria for Adverse Events (CTCAE), seriousness, the investigator's assessment of relationship to pacritinib/placebo, event outcome, and action taken with study medication due to the reported event. If concomitant treatment is given for the AE, this information should be captured on the appropriate electronic case report form (eCRF). If an AE results in early termination of the patient's pacritinib/placebo treatment period, "AE" should be selected as the reason for discontinuation on the eCRF.

The CTCAE version 4.03 will be used for the grading of adverse events.

Table 4 Adverse Event Relationship to Pacritinib/Placebo

Relationship Category	Description
Possible	There is a reasonable causal relationship between the event and pacritinib/placebo, the event occurred within a plausible time relationship to pacritinib/placebo administration, but the event could also possibly be explained by the condition under study, concurrent disease, other drugs or

Relationship Category	Description
	chemicals, or other circumstances. Dechallenge information is lacking or unclear.
Unlikely	There is a temporal relationship of the event to pacritinib/placebo but not a reasonable causal relationship; there is no temporal relationship to pacritinib/placebo administration or the condition under study, concurrent disease, and other drugs or chemicals; or other circumstances provide a plausible explanation for the event.

5.2.2 Laboratory Assessments

Clinical laboratory assessments will be performed at the times specified in protocol Table 1.

The following clinical laboratory parameters will be evaluated during the study.

Table 5 Laboratory Assessments and Parameters

Laboratory Test	**Parameters**
Serum chemistry	Sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, and magnesium
Liver Panel	AST, ALT, alkaline phosphatase, total bilirubin, and albumin.
Hematology	WBC count, hemoglobin, hematocrit, and platelet count Note: WBC subsets may be reported as either differential or absolute counts on the eCRF. Additional white cell counts (e.g. bands) may also be reported if available.
Coagulation	INR, PTT, and fibrinogen
Other	Ferritin, LDH, CRP, IL-6, Troponin-I, LDH, BNP, procalcitonin, triglycerides, and CK Serum pregnancy test for women of childbearing potential

5.2.3 Vital Signs

Vital signs will be assessed at the times specified in protocol Table 1. The vital signs assessment will include recording of the systolic blood pressure (mmHg), diastolic blood pressure (mmHg), respiratory rate (breaths/minute), maximum temperature, maximum heart rate, SpO2, and body weight.

5.2.4 Electrocardiograms (ECGs)

The ECG assessment will be performed at the times specified in protocol Table 1.

The Fridericia-Corrected QT interval (QTcF) and overall interpretation will be recorded.

5.2.5 Physical Examinations

The Physical Examination assessment will be performed at the times specified in protocol Table 1.

6 CLINICAL OUTCOME VARIABLES

This section describes the clinical outcomes and derivation of variables considered for this study.

6.1 Primary Efficacy Endpoint

The primary endpoint is the proportion of patients with progression to IMV and/or ECMO or death by Day 28 (+/- 2 days) for the Intent-to-Treat (ITT) Population. Patients will be considered to have progression to IMV and/or ECMO or death based on the Cao et al. (Table 3) clinical status assessment of 6 or 7. Specifically, the proportion of patients with progression to IMV and/or ECMO or death by Day 28 (+/- 2 days) will be calculated in each treatment arm as:

- (Number of patients with clinical status of 6 or 7 at any time on or before Day 28 (+/- 2 days)) / (Number of patients in the ITT population)

Patients who discontinued early and did not progress to IMV and/or ECMO or death (a clinical status of 6 or 7) will be considered as having progression unless they were discharged from the clinical facility (discharge date is not missing), in which case they will be considered non-progression.

Patients will be summarized based on the randomized (planned) treatment arm. Patients can meet this endpoint in two ways by progressing to IMV and/or ECMO or dying.

6.2 Secondary Efficacy Endpoints

6.2.1 Number of Ventilator-Free Days

The number of total ventilator-free days is defined as the number of total days that patients are alive and not intubated, from Day 1 to Day 28. The number of total ventilator-free days will be calculated as:

- Number of ventilator free days = Number of total days with clinical status assessment of 5 or less from Day 1 until Day 28

Ventilator-free days includes all episodes a patient is not on IMV and/or ECMO and report a clinical status form of 5 or less from Day 1 to Day 28.

Patients who discontinued early will be considered as being ventilator-free up to Day 28 if they were discharged from the clinical facility (discharge date is not missing), in which case they will be considered as not having an event of IMV and/or ECMO up to Day 28. Patients who discontinued early and were not discharged from the clinical facility will be considered as being ventilator-free up to the time of study discontinuation.

6.2.2 Mortality Rate at Days 15 and 28

The 15-day mortality rate is defined as the proportion of patients with outcome of death during the 15 days following randomization. The Day 15 mortality rate is calculated as:

- (Number of patients that die by Day 15) / (Number of patients in the ITT population)

The 28-day mortality rate is defined as the proportion of patients with outcome of death during the 28 days following randomization. The Day 28 mortality rate is calculated as:

- (Number of patients that die by Day 28) / (Number of patients in the ITT population)

6.2.3 Time to Improvement in Clinical Status

The time to improvement in clinical status from baseline will be calculated as:

- Time to Improvement in Clinical Status (days) = Date of improvement in clinical status – date of randomization + 1

The date of improvement in clinical status is defined as the first ordinal scale assessment with a decrease of 2 or more points from the baseline clinical status assessment. For example, for a patient that has a baseline clinical status of 4, the date of improvement would be the first post-baseline clinical status assessment of 2 or 1.

6.2.4 Ordinal Scale of Clinical Status

The clinical status adapted from Cao et al. (as described in Table 3), will be a secondary efficacy outcome variable. The 7-point clinical status score at Day 8, 15, 22 and 28 will be presented by treatment arm using the ITT population.

6.2.5 Rate of Use of Immunomodulatory Agents

The use of other immunomodulatory agents as treatment for COVID-19, such as corticosteroids, tocilizumab, anakinra, or eculizumab, will be assessed as a secondary endpoint. These medications will be identified on the CRF as concomitant medications and defined by groups of certain WHODD preferred names. The list of WHODD terms is provided in Appendix 1.

A patient will be considered to have used an immunomodulatory agent if any medication used by the patient between Day 1 and Day 28 is coded to the list of preferred names in Appendix 1.

The rate of use of immunomodulatory agents will be calculated as:

- (Number of patients using an immunomodulatory agent between Day 1 and Day 28) / (Number of patients in the ITT population)

6.3 Secondary Endpoints – Safety

A secondary endpoint is to evaluate the toxicity profile of pacritinib therapy in hospitalized patients with severe COVID-19 with or without cancer. In general, this will be assessed through the analysis of treatment-emergent adverse events including incidence, seriousness, relatedness to pacritinib, and severity.

6.3.1 Adverse Events

Adverse Events (AEs) will be coded using the Medical Dictionary for Regulatory Activities MedDRA v23.1. The severity of all adverse events will be graded according to NCI CTCAE version 4.03.

A treatment-emergent adverse event (TEAE) is defined as an adverse event occurring on or after the first dose of study treatment and within 30 days after the last study treatment date.

TEAEs will be summarized by presenting, for each treatment arm, the count and percentage of patients having any TEAE, having a TEAE in each system organ class, and having an individual event according to version 23.1 of the MedDRA dictionary (or later as specified in the Data Management Plan). The version of MedDRA used for the purpose of coding events in the clinical database will be static for the duration of the study. CTCAE (version 4.03) grades and relationship to study drug will be summarized as appropriate. For summaries by CTCAE grade or relatedness, only the highest CTCAE grade or degree of relatedness of each

System Organ Class and/or preferred term (PT) will be summarized. A patient having the same event more than once will be counted only once and by greatest severity or closest relationship.

Cardiac TEAEs are all the PTs in the Standardised MedDRA Queries (SMQs) of Cardiac Arrhythmias, Cardiac Failure, Ischaemic Heart Disease, and Embolic and Thrombotic Events.

Haemorrhage TEAEs are all PTs in the SMQ of Haemorrhages.

7 STATISTICAL ANALYSES

This section describes the statistical analyses to be conducted in relation to the primary, secondary, and exploratory objectives of the study.

7.1 General Statistical Considerations

Unless specified otherwise, the analyses of data collected will be descriptive and summaries will be presented separately for each treatment arm and in total for the specified analysis population. Statistical analyses will be descriptive and no formal hypothesis testing or comparative analyses between treatment arms will be performed unless stated. Confidence intervals (CIs) will be constructed at the 95% confidence level where appropriate. For categorical variables, confidence intervals will be calculated using the Clopper-Pearson method where appropriate.

For continuous variables, the number of observations (n), mean, standard deviation, median, q1, q3, minimum, and maximum will be provided as summary statistics. For categorical variables, the frequency and percentage in each category will be displayed.

Sumary tables will in general display 2 treatment arms:

- Pacritinib 400 mg
- Placebo

A total column will be added for table summaries if appropriate.

Efficacy analyses will in general be based on the ITT Population according to the randomized (planned) treatment arm.

Safety analyses will in general be performed using the Safety Population according to the treatment actually received.

Subject disposition, demographics, and clinical baseline characteristics data will be summarized for the ITT Population. If the ITT Population differs from other defined analysis populations, additional patient characteristic summaries may be generated using other analysis populations.

7.1.1 Baseline Definition

The baseline value for analyses will be defined as the last assessment prior to the start of treatment, unless otherwise specified.

Study Day 1 will be considered as the first dose of treatment. Note that randomization may occur before study Day 1.

7.1.2 Covariate Adjustment

No adjustment for other covariates is planned.

7.1.3 Multicenter Studies

The center effect will not be considered for this study.

7.1.4 Handling of Dropouts or Missing Data

Unrecorded data values will be recorded as missing. Only recorded (i.e. complete) data values will be used for statistical analyses. In general, invalid or missing values will not be imputed in the data unless stated otherwise.

In addition, analysis methods for handling dropouts are specified under the endpoint definition.

7.1.4.1 Partial or Missing AE Onset and Resolution Dates

For AE summaries, the missing day of onset of an adverse event will conservatively be set to:

- First day of the month that the AE occurred if this is after the date of the start of first treatment.
- One day after the first treatment if this is the same month that the AE occurred.
- The 15th of the month and year if the AE month and year are before the month and year of the first treatment.

If the onset date of an adverse event is missing both day and month, it will be set to:

- January 1 of the year of onset, as long as this is after the first study treatment.
- One day after the first study treatment if this is the same year that the AE occurred.
- July 1st of the year if the AE year is before the year of the first study treatment.

If the day of resolution of an adverse event is missing, it will conservatively be set to the last day of the month or 30 days after the last dose of study treatment if this day is in the same month and year, whichever is earlier. If the day of resolution of an adverse event is missing both day and month, it will conservatively be set to the last day of the year or 30 days after the last dose of study treatment if this day is in the same year, whichever is earlier.

All missing and partial dates will be presented “as is” in listings.

7.1.5 Subgroup Analyses

The following subgroup analyses of the primary endpoint may be performed:

• Age (< 60 years, ⩾ 60 years)

• Sex (male versus female)

• Race (Caucasian versus all other races)

• Baseline 7-point ordinal scale of clinical status scale (baseline 3 or 4 versus 5)

• Baseline IL-6 (normal versus elevated)

• Procalcitonin (normal or indeterminate versus elevated)

• Ferritin (< 500 ug/L versus ⩾ 500 ug/L)

• Other markers of disease severity (D-dimer, CRP, Troponin-I, triglycerides)

Additional subgroups may be identified on the basis of other factors including, but not limited to, use of certain medications (e.g. immunomodulatory agents) or medical history.

7.2 Study Population Data

7.2.1 Patient Disposition

Patient disposition will be summarized using counts and percentages for the ITT Population.

The following patient disposition categories will be summarized:

- Patients screened;
- Patients randomized;
- Patients who received study treatment;
- Patients that completed planned study treatment;
- Patients discontinued from study treatment;
- Patients that completed the study;
- Patients who discontinued the study.

For patients who discontinued study treatment and patients who discontinued the study, reason for discontinuation will be provided.

The total number of patients in each defined analysis population will be tabulated.

7.2.2 Demographics and COVID-19 Baseline Characteristics

Descriptive summaries of demographic and COVID-19 disease criteria will be presented separately for the ITT Population. If other analysis populations differ form the ITT population then additional table summaries based on these populations may be presented.

Demographic characteristics may include, but are not limited to: age, sex, race, and ethnicity.

COVID-19 baseline disease characteristics may include the following: percent of patients with hypoxemia (SpO_2 ≤93% on room air), SpO_2 for both on room air and on supplemental oxygen, type of oxygen delivery devices used (percent of patients using each device type), percent of patients with tachypnea (RR>20 breaths/min), percent of patients with RR>30 breaths/min, percent of patients with P:F <300 (among patients in whom P:F ratio was calculable), percent of patients with fever (temperature >100.4F), percent of patients with tachycardia (HR>100 beats/min), and baseline clinical status.

Additional summaries of disease markers of severity at baseline (normal vs above upper limit of normal) may be presented.

Demographics and COVID-19 disease criteria will be listed.

7.2.3 Medical History and Comorbidities

Medical history items will be coded using MedDRA v23.1 (or later as specified in the Data Management Plan). Recorded medical history items will be summarized by System Organ Class and PT. A patient will be counted only once within each System Organ Class and PT but may contribute to more than one PT within a System Organ Class.

The number of patients with pre-defined comorbidities (e.g. diabetes mellitus) will be summarized.

Medical history and comorbidities will be listed.

7.2.4 Prior and Concomitant Medications

Concomitant medications will be collected from the time of consent through 30 days following the last dose of pacritinib/placebo.

Prior medications are medications that were started and stopped prior to the first dose of study drug. Concomitant medications are medications that were taken on or after the first dose of study drug. Recorded prior and concomitant medications will be coded using the WHO Drug Dictionary (version March 2020 or later as specified in the Data Management Plan).

Recorded concomitant medications will be summarized by Anatomical Therapeutic Chemical (ATC) levels and PT. Concomitant medications of special interest (e.g. immunomodulary agents/antiviral) will be summarized separately. A patient will be counted only once within each ATC level and PT but may contribute to more than one PT within an ATC.

Prior and concomitant medications as well as concomitant medications of special interest (immunomodulary agents/ antiviral) will be listed.

7.2.5 Lung Function Assessment

Descriptive statistics will be provided by timepoint for SpO2 in ambient air (if applicable), SpO2 with oxygen supplementation (if applicable), and oxygen delivery method.

Lung function assessments will be listed by patient.

7.3 Exposure to Pacritinib/Placebo

Exposure to study treatment will be evaluated by the duration of treatment, cumulative dose, actual dose intensity, and relative dose intensity in the Safety Population.

Duration of treatment (days) is defined as the duration from first day of study treatment to the last day of study treatment, i.e.,

- Duration of treatment (days) =

  Date of last dose of study treatment – date of first dose of study treatment + 1

Descriptive statistics will be provided for duration of treatment by treatment arm.

Cumulative dose (mg) is defined as the sum of all pacritinib doses of study treatment taken. Descriptive statistics will be provided for the cumulative dose. The counts and percentages of patients with any dose modifications will be provided by treatment arm. Reasons for dose modifications will also be summarized. In addition, the actual dose intensity (ADI) and relative dose intensity (RDI) will be defined as follows:

- ADI (mg/day) = (total dose taken in mg) ÷ (duration of treatment in days).
- RDI (%) = (ADI) ÷ (planned daily dose) × 100.

The planned pacritinib dose is 400 mg/day. Descriptive statistics will be provided for both ADI and RDI.

Exposure data will be listed.

7.4 Efficacy Analyses

Efficacy analyses described in this section will performed using the ITT Population according to the randomized treatment arm.

7.4.1 Primary Efficacy Analysis

The primary efficacy analysis is the proportion of patients with progression to IMV and/or ECMO or death by Day 28 in the Intent-to-Treat Population.

The primary efficacy endpoint of proportion of patients with progression to IMV and/or ECMO or death will be compared between treatment arms using the Cochran-Mantel-Haenszel (CMH) test stratified by randomization stratification factors age (< 60 years versus ≥ 60 years) and 7-point clinical status scale (baseline 3 or 4 versus 5) as entered in the IXRS. The point estimates and 95% confidence intervals of the proportion of patients who progress to IMV and/or ECMO or death will be presented by treatment arm. The CMH odds ratio, difference in progressionrates, and associated 95% confidence intervals will be presented.

Patients who discontinued early and did not progress to IMV and/or ECMO or death (a clinical status of 6 or 7) will be considered as having progression unless they were discharged from the clinical facility (discharge date is not missing), in which case they will be considered non-progression.

To evaluate the impact of missing data on the primary analysis, two sensitivity analyses will be performed:

1. A conservative analysis in the ITT population that considers all patients who discontinued early and did not progress to IMV and/or ECMO or death (a clinical status of 6 or 7) as having progression regardless of hospital discharge status.
2. An analysis in the ITT population that considers patients who discontinue early and did not progress to IMV and/or ECMO or death (a clinical status of 6 or 7) as having non-progression.

An additional analysis of the time to event (IMV/ECMO or Death) will be performed.

The time to IMV/ECMO or Death will be calculated as the earliest date of a clinical status assessment of 6 or 7– date of randomization + 1. Table 6 provides the rules for IMV/ECMO or death events and censoring for the time to event analysis. .

Table 6 Event and Censoring Rules for IMV/ECMO

	Situation	**Date of Event or Censoring**
IMV/ECMO or Death Event	IMV/ECMO documented in the clinical status form (6)	Earliest date when IMV/ECMO is observed
	Death	Date of death if no IMV/ECMO was observed
Censor	No post-baseline clinical status assessments	Randomization date
	No IMV/ECMO or death by Day 28	Date of last clinical status assessment
	Lost to follow-up	Date of last clinical status assessment
The rules apply to dates up to study Day 28 +2 day window (Day 30).		

Kaplan-Meier methods will be used to estimate the time to IMV/ECMO or death by treatment arm. Summary statistics, including median time to IMV/ECMO or death and corresponding

95% confidence intervals, will be presented by treatment arm. The time to IMV/ECMO or death will be analyzed using the log-rank test stratified by age (< 60 years versus ≥ 60 years) and baseline 7-point clinical status scale (baseline 3 or 4 versus 5).

The hazard ratio (HR) of the time to IMV/ECMO or death by treatment arm will be estimated using a stratified Cox proportional hazards model stratified by age (< 60 years versus ≥ 60 years) and baseline 7-point clinical status scale (baseline 3 or 4 versus 5).

Kaplan-Meier plots of the time to improvement in clinical status will be generated by treatment arm.

The clinical status assessments will be listed.

7.4.2 Secondary Efficacy Analysis

7.4.2.1 Number of Ventilator-Free Days

The number of ventilator-free days will be presented by treatment arm using descriptive statistics. The 95% confidence intervals will be provided. The treatment arm comparison will be performed using the Wilcoxon rank sum test.

In addition, the number of patients that remain ventilator-free for certain clinically significant thresholds (e.g. 21 days) may be summarized.

7.4.2.2 Mortality Rate at Day 15 and 28

The Day 15 and Day 28 mortality rates and associated 95% confidence interval will be summarized by treatment arm.

The mortality rate at Day 15 and Day 28 will be compared between treatment arms using the CMH test stratified by age (< 60 years versus ⩾ 60 years) and baseline 7-point clinical status scale (baseline3 or 4 versus 5). The point estimates and 95% confidence intervals of the mortality rates at Day 15 and Day 28 will be presented by treatment arm. The CMH odds ratio, difference in mortality rates at Day 15 and Day 28, and associated 95% confidence intervals will be presented.

7.4.2.3 Clinical Status

The clinical status at Day 8 (+/- 1 day), Day 15 (+/- 1 day), Day 22 (+/- 1 day), and Day 28 (+/- 2 day) will be summarized by treatment arm using counts and percentages.

Clinical status assessments will be listed by patient.

7.4.2.4 Time to Improvement in Clinical Status

Time to improvement in clinical status is defined as the first ordinal scale assessment with 2 points reduction from the baseline clinical status assessment. Patients not known to have improved by Day 28 will be censored at the date of their last clinical status assessment. Patients who have died will be censored at Day 28. Table 7 provides the rules for improvement in clinical status and censoring for the time to event analysis

Table 7 Event and Censoring Rules for Improvement in Clinical Status

	Situation	Date of Event or Censoring
2-point reduction from baseline in the clinical status form (event)	2-point reduction from baseline documented in the clinical status form	Earliest date when a 2-point reduction from baseline in the clinical status form is observed
Censor	Death	Day 28
	No post-baseline clinical status assessments	Randomization Date
	No 2-point reduction from baseline	Date of last clinical status assessment
	Lost to follow-up	Date of last clinical status assessment
The rules apply to dates up to study Day 28 +2 day window (Day 30).		

Kaplan-Meier methods will be used to estimate time to improvement by treatment arm. Summary statistics, including median time to improvement and corresponding 95% confidence intervals, will be presented by treatment arm. The time to improvement will be analyzed using the log-rank test stratified by age (< 60 years versus ≥ 60 years) and baseline 7-point clinical status scale (baseline 3 or 4 versus 5).

The hazard ratio (HR) for time to improvement by treatment arm will be estimated using a stratified Cox proportional hazards model stratified by age (< 60 years versus ≥ 60 years) and baseline 7-point clinical status scale (baseline 3 or 4 versus 5).

Kaplan-Meier plots of the time to improvement in clinical status will be generated by treatment arm.

7.4.2.5 Use of Immunomodulatory Agents

The rate of use of immunomodulatory agents as treatment for COVID-19 will be compared between treatment arms using the CMH test stratified by age (< 60 years versus ⩾ 60 years) and baseline 7-point clinical status scale (baseline 3 or 4 versus 5). The point estimates and 95% confidence intervals of the rates of immunomodulatory agents use will be presented by treatment arm. The CMH odds ratio, difference in rates of immunomodulatory agent use, and associated 95% confidence intervals will be presented.

In addition, the number of immunomodulatory agents will be summarized using descriptive statistics (e.g. number of immunomodulatory agents used per patient). Additional summaries presenting the percentage of patients using immunomodulatory agents in each defined category in Appendix 1 and the immunomodulatory agents summarized by preferred term may be generated.

Immunomodulatory agents used will be listed by patient.

7.4.3 Tertiary Analyses

7.4.3.1 Markers of Disease Severity

Markers of disease severity will be summarized with descriptive statistics. The summary will include both recorded values and change from baseline for each scheduled assessment and maximum and minimum post-baseline assessment. Both scheduled and unscheduled visits will be considered in derivations of the maximum and minimum post-baseline assessments.

Markers of disease severity data will be listed by patient.

7.5 Safety Analyses

Safety will be assessed through 30 days of follow-up after the last dose of study treatment andassessed by the cumulative incidence, severity and seriousness of TEAEs, drug discontinuations, laboratory values, and clinical assessments.

Summaries will be tabulated by treatment arm and in total for the Safety Population.

7.5.1 Adverse Events

Summaries of adverse events will be presented by treatment arm and in total for the Safety Population.

An overview of treatment-emergent adverse events will be provided which summarizes the patient incidence of the following for the Safety Population. This overview will include the number and percentage of patients with:

- Any TEAEs,
- TEAEs related to study treatment,
- Serious TEAEs (TESAEs),
- CTCAE Grade 3+ TEAEs,
- TEAEs with outcome of death,
- TEAEs leading to study drug discontinuation, interruption, or dose reduction,
- Cardiac TEAEs (defined by MedDRA SMQ List),

- Haemorrhage TEAEs (defined by MedDRA SMQ List),

The number and percentage of patients with TEAEs will be tabulated by the highest CTCAE Grade, System Organ Class, and Preferred Term (PT).

In addition, serious TEAEs (TESAEs), CTCAE grade 3 or more TEAEs, TEAEs leading to study drug discontinuation, interruption, or dose reduction, TEAEs with an outcome of death, and related TEAEs will be summarized by System Organ Class and PT.

The PT of TEAEs of all grades and grade 3 or more TEAEs will also be presented for each treatment arm in order of decreasing frequency.

Cardiac and haemorrhage TEAEs will also be summarized by System Organ Class and PT.

For all above summaries, patients with multiple adverse events will be counted only once per System Organ Class and PT.

Listings of all AEs (i.e. including those that are not treatment-emergent), SAEs, AEs leading to treatment discontinuation, AEs leading to treatment interruption or dose reduction, AEs with outcome of death, Cardiac TEAEs, and Haemorrhage TEAEs will be provided.

7.5.2 Laboratory Assessments

Clinical laboratory evaluations will be summarized using descriptive statistics for all laboratory parameters including absolute measurements and changes from baseline by scheduled time of evaluation. Changes from baseline by scheduled time of evaluation will include last visit on-study, maximum post-treatment value, and minimum post-treatment value. Both scheduled and unscheduled post-treatment visits will be considered for the summaries of the maximum and minimum post-treatment values. Results will be presented in SI units.

Laboratory results will be graded according to NCI-CTCAE version 4.03 as applicable. A shift table, presenting the frequency tabulation for baseline to each timepoint and the worst post-treatment value according to the NCI-CTCAE grade, will be provided for selected clinical laboratory tests. For select parameters (e.g. glucose), separate shift tables indicating hyper– and hypo-directionality of change may be produced. Both scheduled and unscheduled post-treatment visits will be considered in tabulation of the worst post-treatment value.

Clinical laboratory evaluations in SI units will be listed, including high and low flags, CTCAE grades where applicable, and the corresponding normal range.

7.5.3 Vital Signs

A table summarizing clinically notable blood pressure and weight measurements which are aligned with CTCAE cut-offs, where available, will be displayed. The proportion of subjects whose worst observed values while on study (on or after the first day of treatment) meet the following clinically notable criteria will be tabulated by treatment arm:

- Systolic Blood Pressure
  - < 85 mm Hg
  - ⩾ 140 - < 160 mm Hg
  - ⩾ 160 mm Hg
- Diastolic Blood Pressure
  - < 50 mm Hg
  - ⩾ 90 - < 100 mm Hg
  - ⩾ 100 mm Hg
- Weight gain from baseline
  - ⩾ 5% - < 10% increase
  - ⩾ 10% - < 20% increase
  - ⩾ 20% increase
- Weight loss from baseline
  - ⩾ 5% - < 10% decrease
  - ⩾ 10% - < 20% decrease
  - ⩾ 20% decrease

Vital signs will be listed by patient.

7.5.4 Electrocardiograms

The frequency distribution of abnormal mean QTcF interval measurements on study (after the first study drug treatment through the last dose of study drug) will be summarized. That is, the proportion of subjects with the worst mean QTcF interval on study will be reported, and the following QTcF intervals will be tabulated by treatment arm:

- A measured value
  - > 450 ms
  - > 480 ms
  - > 500 ms
- Change
  - > 0 and ≤ 10 ms above baseline
  - > 10 and < 20 ms above baseline
  - ≥ 20 ms above baseline

- > 30 ms above baseline
- > 60 ms above baseline

Plots of the QTcF across study day (Day8, Day 15, Day 22 and Day28)will also be presented for each treatment arm.

ECG assessments including clinical significance will be listed by patient.

7.5.5 Other Safety Assessments

If applicable, other safety assessments will be listed by patient.

8 GENERAL INFORMATION

8.1 Statistical Software

The generation of analysis datasets and analysis tables, figures, and listings (TFLs) will be done using SAS® version 9.4 or higher. The Medpace standard operating procedures (Medpace Standard Operating Procedures GL-DS-02-S4 and GL-DS-03-S3) will be followed for the validation of all SAS programs and outputs.

8.2 Format of Tables, Listings, and Figures

The format of tables, listings, and figures will be described in a stand-alone programming specifications document that will be prepared before database lock.

9 CHANGES FROM PROTOCOL-SPECIFIED ANALYSIS

No changes from the protocol-specified analysis are planned.

10 REFERENCES

Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., ... & Li, X. (2020). A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *New England Journal of Medicine*.

Goyal, P., Choi, J. J., Pinheiro, L. C., Schenck, E. J., Chen, R., Jabri, A., ... & Hoffman, K. L. (2020). Clinical Characteristics of Covid-19 in New York City. *New England Journal of Medicine*.

11 APPENDIX 1: IMMUNOMODULATORY AGENTS

Immunomdulatory agent usage will be identified based on concomitant medications that are classified according to the following WHODD preferred names.

Table 8 MedDRA Preferred Term List for Immunomodulatory Agents

Immunomodulatory Agent Category	Preferred Names(s)*
Corticosteroids	Decadron, Dexamethason, Hydrocortisone, Metholprednisiolne, Prednisone, Solumedrol
IL-6 inhibitors	Tocilizumab
IL-1 inhibitors	Anakinra
Antiretrovirals	Remdesivir

*WHO-DDE B3, March, 2020.