CTI BioPharma Corp.

PRE-VENT Phase 2

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

PAC319

IND # 149,611

Amendment 4

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Abbreviations

Abbreviation	Full Term
AE	adverse event
ABG	arterial blood gas
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
BAT	best available therapy
BID	twice daily
BiPAP	bilevel positive airway pressure
BNP	brain natriuretic peptide
CBC	complete blood count
CD4	cluster of differentiation 4
CK	creatine kinase
CMH	Cochran-Mantel-Haenszel
COVID-19	coronavirus disease 2019
CRF	case report form
CPAP	continuous positive airway pressure
CRP	C-reactive protein
CSF-1R	colony-stimulating factor 1 receptor
CTCAE	Common Terminology Criteria for Adverse Events
CYP3A4	cytochrome P450 3A4
CYP450	cytochrome P450
DC	dendritic cell
EC	Ethics Committee
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDC	electronic data capture
EOT	End of Treatment
ER	emergency room
FiO2	fraction of inspired oxygen
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HR	hazard ratio

Abbreviation	Full Term
HR_{max}	maximum documented heart rate during calendar day
IC_{50}	half maximum inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IDMC	Independent Data Monitoring Committee
IEC	Independent Ethics Committee
IL	interleukin
IMV	invasive mechanical ventilation
IND	Investigational New Drug
INR	international normalized ratio
IRAK1	interleukin-1 receptor-associated kinase-1
IRB	Institutional Review Board
ITT	Intent-to-treat
JAK	Janus kinase
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
PaO_2	arterial oxygen partial pressure
PD	pharmacodynamic(s)
PEEP	positive end-expiratory pressure
PK	pharmacokinetic(s)
PT	preferred term
PTT	partial thromboplastin time
QD	once daily
QTc	corrected QT interval
QTcF	QT corrected by the Fridericia method
RBC	red blood cell
REB	Research Ethics Board
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SOC	standard of care
SpO_2	blood oxygen saturation
STAT	signal transducer and activator of transcription

Abbreviation	Full Term
TEAE	treatment-emergent adverse event
Th17	T helper 17
T_{max}	maximum documented temperature during calendar day
TSS	total symptom score
TYK	cytoplasmic tyrosine kinase
US	United States
WOCBP	Woman of child-bearing potential
WBC	white blood cell

Protocol Synopsis

Name of Investigational Drug	Pacritinib
Protocol ID	PRE-VENT Phase 2 Study PAC319, IND # 149,611
Protocol Title	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
Version	Amendment 4

Primary Objective

To compare the efficacy of pacritinib + standard of care (SOC) versus placebo + SOC in hospitalized patients who have 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.

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

Tertiary Objectives

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

- C-reactive protein (CRP)
- Ferritin
- D-dimer
- Interleukin-6 (IL-6)
- Troponin-I
- Lactate dehydrogenase (LDH)
- Brain natriuretic peptide (BNP)
- Procalcitonin
- Triglycerides
- Creatine kinase (CK)

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 (blood oxygen saturation [SpO2] ≤93% on room air at sea level), respiratory rate >30, arterial oxygen partial pressure [PaO2]/fraction of inspired oxygen [FiO2] <300, but do not require IMV.

Patients will be randomized 1:1 to receive pacritinib (400 mg once daily [QD] on Day 1, then 200 mg twice daily [BID] from Day 2 to Day 14) + SOC or placebo + SOC.

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.

Data analyses will be conducted during the study by an Independent Data Monitoring Committee (IDMC). 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. 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 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.

At the request of an investigator, and with agreement of the Chief Medical Officer at CTI, the assigned treatment for an individual patient may be unblinded for the purposes of discussing the ongoing care of that patient.

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.

The schedule of study assessments for all patients is provided in Table 1.

Number of Centers	Approximately 21 centers in the United States (number of centers and countries may be reassessed as patient enrollment increases)
Number of Patients	Approximately 200 patients
Randomization	1:1 to either pacritinib + SOC or placebo + SOC
Stratification	Age (< 60 years, ≥ 60 years) 7-point ordinal scale of clinical status scale (baseline 3 or 4 versus 5)

Inclusion/ Exclusion Criteria	Inclusion Criteria 1. Hospitalized or will be hospitalized prior to randomization for the treatment of severe COVID-19 with SARS-CoV-2 infection confirmed by either a) a positive reverse transcriptase polymerase chain reaction (RT-PCR) or b) an antigen-based test from any respiratory, nasopharyngeal, saliva, blood, or stool specimen at Screening or documented within 1 week prior to the start of Screening (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, but do not require IMV). 2. Age ≥ 18 years 3. Platelet count ≥ 50,000/µL 4. If fertile, willing to use effective birth control methods during the study 5. Provision of informed consent within 96 hours after hospitalization Exclusion Criteria 1. In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments 2. Currently intubated or intubated between screening and randomization 3. Suspected active uncontrolled bacterial, fungal, viral, or other infection (besides COVID-19) 4. Prior allogenic hematopoietic stem cell transplantation 5. Active lung cancer or history of lung cancer within the past 12 months 6. Any active grade 2 or higher hemorrhage 7. Any active gastrointestinal or metabolic condition that could interfere with absorption of oral medication 8. Uncontrolled intercurrent illness that, in the judgment of the treating physician, would limit compliance with study requirements 9. Known seropositivity for human immunodeficiency virus with cluster of differentiation 4 (CD4) count < 200/mm^3 within 3 months prior to randomization 10. Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination 11. Concurrent enrollment in another interventional trial (investigational COVID-19 antiviral studies are permitted) 12. Serum creatinine > 2.5 mg/dL 13. Total bilirubin > 4× the upper limit of normal 14. QT corrected by the Fridericia method (QTcF) prolongation > 480 msec 15. Known history of New York Heart Association Class II, III, or IV congestive heart failure prior to hospital admission 16. Known allergic reaction to any Janus kinase 2 (JAK2) inhibitor 17. Exposure to any JAK2 inhibitor within 28 days 18. Currently receiving a strong CYP3A4 inhibitor or strong P450 inducer (Appendix 1 and Appendix 2, respectively) and unable to stop the medication

	prior to the first dose of study drug and throughout the duration of study drug administration 19. Treatment with cytoreductive chemotherapy administered within 14 days prior to randomization 20. Administration of an IL-1 or IL-6 blocking immunomodulatory agent (such as tocilizumab, canakinumab, sarilumab, anakinra) within 48 hours prior to randomization 21. Currently receiving therapeutic anticoagulation or anti-platelet medication and unable to stop the medication prior to randomization. Prophylactic anticoagulation therapy or aspirin (≤ 100mg) are permitted. 22. Unable to ingest capsules or tablets at randomization
Study Treatments	Pacritinib: Dosage Form: 100 mg capsules Dose Regimen: 4 capsules QD on Day 1 followed by 2 capsules BID. Administered orally or via oro/nasogastric tube. Placebo: Dosage Form: Placebo capsules matching pacritinib 100 mg capsule Dose Regimen: 4 capsules QD on Day 1 followed by 2 capsules BID. Administered orally or via oro/nasogastric tube.
Concomitant and Excluded Therapies, Including Procedures	Treatment with cytoreductive therapy is not permitted during the assigned treatment period. Pacritinib is metabolized by the P450 system, including cytochrome P450 3A4 (CYP3A4). Use of strong CYP3A4 inhibitors is not permitted as these can lead to significantly increased concentrations of pacritinib. Use of strong cytochrome P450 (CYP450) inducers is not permitted as these can lead to significantly reduced concentrations of pacritinib. Lists of selected strong CYP3A4 inhibitors and P450 inducers are found in Appendix 1 and Appendix 2, respectively. Concomitant use of investigational agents (those administered as part of a clinical trial) for the treatment of COVID-19 is prohibited with the exception of antiviral agents. The use of IL-1 or IL-6 blocking immunomodulatory agents (such as tocilizumab, canakinumab, sarilumab, anakinra) is allowed if, in the opinion of the investigator, a patient is clinically deteriorating. However, patients who require IL-1 or IL-6 blocking agents must be discontinued from study drug. Hydroxychloroquine, chloroquine, azithromycin, corticosteroids, and antiviral agents are permitted concomitant medications. Treatment-dose anticoagulation and anti-platelet therapy may be administered after randomization, if required; patients do not need to discontinue pacritinib/placebo if one of these medications is initiated. However, patients should not receive such agents concomitant with study drug administration if their platelet counts drop to < 50,000/µL. Cytotoxic chemotherapy or cancer-directed immunotherapy is prohibited during the pacritinib/placebo treatment period (14 or 21 days).
Efficacy Assessments	7-point ordinal scale of clinical status (adapted from Cao et al 2020) The following 7-point ordinal scale of clinical status will be used to assess the ordinal scale secondary endpoints. The ordinal scale score is to be documented daily on study through Day 28 for all patients, including those who have been discharged from the hospital: 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 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.
Safety Assessments	Adverse Events AEs will be collected during the clinical study from the time the patient is randomized through 30 days following the last dose of pacritinib/placebo. AEs will be identified and reported to the Sponsor, in addition to any clinically indicated diagnostic, monitoring, treatment, and follow-up measures used to manage the reported AE. Pregnancy alone will not be considered as an AE. Pregnancy will be reported on a Pregnancy Reporting Form (Section 8.1.4.4). Abnormal pregnancy outcomes and/or any AE for the child or fetus (including miscarriage) will be reported as SAEs. Occurrences of overdose will be reported as SAEs. Hematology Hematology parameters, (complete blood count [CBC], white blood cell count [WBC], hemoglobin, hematocrit, and platelet count), will be evaluated at Screening (may be performed within 24 hours prior to the start of Screening) and daily from Days 2 through 28 or EOT, and on the day of hospital discharge. WBC differential will be evaluated at Screening (may be performed within 24 hours prior to the start of Screening), Day 8, Day 15 or EOT, Day 22, Day 28, and on the day of hospital discharge. Hematology tests are not required after hospital discharge. Results from unscheduled hematology tests should be entered into the electronic database using an Unscheduled Hematology case report form (CRF). Analysis of CBC results will be performed at local laboratories. Pacritinib/placebo dosage modifications will be implemented for clinically significant AEs identified with this testing per the guidelines for "Treatment-Related Thrombocytopenia and Bleeding" (Section 6.5.3). Coagulation Assessments Coagulation testing will include international normalized ratio, partial thromboplastin time, and fibrinogen at Screening (may be performed within 24 hours prior to the start of Screening), Day 8, Day 15 or EOT, Day 22, Day 28, and on the day of hospital discharge. Coagulation tests are not required after hospital discharge. Results from unscheduled coagulation tests should be entered into the electronic database using an Unscheduled Coagulation Test CRF. Analysis of serum chemistry results will be performed at local laboratories. Serum Chemistry Serum chemistry parameters (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, and magnesium) will be evaluated at Screening (may be performed within 24 hours prior to the start of Screening) and daily from Days 2 through 28 or EOT and on the day of hospital discharge. Serum chemistry tests are not required after hospital discharge. Results from unscheduled serum chemistry tests should be entered into the electronic database using an Unscheduled Serum Chemistry CRF. Analysis of serum chemistry results will be performed at local laboratories.

	Pacritinib/placebo dosage modifications will be implemented for clinically significant AEs identified with serum chemistry testing per the guidelines for "Treatment-Related Toxicities Other than QTcF Prolongation, Diarrhea, Bleeding, or Thrombocytopenia" (Section 6.5.6). Liver Function Panel Liver function parameters (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, and albumin) will be evaluated at Screening (may be performed within 24 hours prior to the start of Screening) and Day 8, Day 15 or EOT, Day 22, Day 28 and on the day of hospital discharge. Liver function panel tests are not required after hospital discharge. Results from unscheduled liver function panel tests should be entered into the electronic database using an Unscheduled Liver Function Panel CRF. Analysis of serum chemistry results will be performed at local laboratories. Pacritinib/placebo dosage modifications will be implemented for clinically significant AEs identified with serum chemistry testing per the guidelines for "Treatment-Related Toxicities Other than QTcF Prolongation, Diarrhea, Bleeding, or Thrombocytopenia" (Section 6.5.6). ECG An ECG will be performed at Screening (may be performed within 48 hours prior to the start of Screening), Day 3, Day 8, Day 15 or EOT, Day 22, and Day 28, and on the day of hospital discharge if before EOT. Eligibility is to be based on mean QTcF of ≤ 480 msec. An ECG will also be performed on the day of hospital discharge if the patient will be continuing pacritinib/placebo as an outpatient; however, ECGs do not need to be assessed after hospital discharge. Results from unscheduled ECG assessments should be entered into the electronic database using an Unscheduled ECG CRF. ECGs should be assessed using at least 3 leads; rhythm strips from telemetry monitoring are acceptable. Pacritinib/placebo modifications and follow-up monitoring for clinically significant ECG changes will be implemented as per the guidelines for "Dosage Management Guidelines for QTcF Interval Prolongation" (Section 6.5.4). Additional ECG testing shall be done as clinically indicated.
Markers of disease severity	Blood samples for analysis of markers of disease severity (CRP, ferritin, D-dimer, IL-6, troponin-I, LDH, BNP, procalcitonin, CK, and triglycerides) will be collected at Screening (may be performed within 24 hours prior to the start of Screening), before the morning dose Day 3, Day 8, Day 15 or EOT, Day 22, Day 28 and on the day of hospital discharge. These markers do not need to be assessed after hospital discharge. The assessments for markers of disease severity are required if they can be performed at a local laboratory or if the study center has access to an external laboratory where the samples can be sent for analysis. If a study center does not have access to a local or external laboratory that can perform these assessments, the Investigator must provide written confirmation of the inability to perform the assessment(s), and approval from the CTI Medical Monitor is required to omit the assessment(s). Results from unscheduled tests for markers of disease severity should be entered into the electronic database using an Unscheduled Markers of Disease Severity CRF.
Pacritinib Dosage Modifications	Pacritinib/placebo may be interrupted or the dosage may be modified for treatment-related hematologic toxicities, bleeding, severe infections, cardiac toxicities (including QTcF interval prolongation), diarrhea, and other treatment-related non-hematologic toxicities. Pacritinib/placebo may also be held for invasive procedures or at the discretion of the investigator. Refer to Section 6.5 for treatment dosage management guidelines.

STATISTICAL METHODS

Sample Size

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 and SOC arm and 26.5% in the placebo and SOC arm, with a one-sided Type I error rate of 0.10.

Analysis Populations

The Intent-to-treat population is defined as all patients randomized. 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.

The Safety population is defined as all randomized patients who received at least one dose of study treatment. Patients in this population will be analyzed according to the treatment actually received. This population will be used for the analysis of safety endpoints.

Efficacy

Primary Endpoint

The primary efficacy endpoint is the proportion of patients who progress to IMV and/or ECMO or death during the 28 days following randomization.

Secondary Efficacy Endpoints

1. The number of ventilator-free days, defined as the number of days that patients are alive and not intubated, from randomization to Day 28
2. The 28-day mortality rate, defined as the proportion of patients with outcome of death during the 28 days following randomization
3. The 15-day mortality rate, defined as the proportion of patients with outcome of death during the 15 days following randomization
4. The time to improvement by at least 2 points relative to Baseline on the 7-point ordinal scale of clinical status
5. The clinical status as assessed by the 7-point ordinal scale of clinical status at Days 8, 15, 22, and 28
6. The rate of use of immunomodulatory agents as treatment for COVID-19 is defined as the proportion of patients reporting use of medications such as corticosteroids, tocilizumab, anakinra, or eculizumab as treatment for COVID-19, during 28 days following randomization.

Tertiary Endpoints

- CRP
- Ferritin
- D-dimer
- IL-6
- Troponin-I
- LDH
- BNP
- Procalcitonin
- Triglycerides
- CK

Safety Endpoints

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

References

Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19 [published online ahead of print, 2020 Mar 18]. N Engl J Med. 2020;NEJMoa2001282. doi:10.1056/NEJMoa2001282

Table 1 PRE-VENT Phase 2 (PAC319) Schedule of Assessments

Study Day	**Screening Window[1]**	**Pre-Dose (Day 1)**	**Inpatient Assessment**	**EOT (For Inpatients Only)**	**Day of Hospital Discharge[2]**	**Outpatient[3] Assessment**	**30-day Post-EOT Follow-up**
Window		**± 0 days**					**± 3 days**
Informed consent[1]	x						
Demographics (age, sex, race, and ethnicity)	x						
Medical history	x						
Vital signs[4]	x						
Clinical status assessment (7-point ordinal scale)[3,5]	x	x (Unless the same time point as Screening)	Daily (Days 2 through 28)	x	x	x	
Physical examination		X[6]	Days 8, 15, 22, and 28	x	x		
T_{max}		x	Daily (Days 2 through 28)	x	x		
HR_{max}		x	Daily (Days 2 through 14)	x	x		
SpO_2 in ambient air (if possible)	x		Daily (Days 2 through 28)	x	x		
SpO_2 with oxygen supplementation (if applicable)	x		Daily (Days 2 through 28)	x	x		

Table 1 PRE-VENT Phase 2 (PAC319) Schedule of Assessments

Study Day	**Screening Window[1]**	**Pre-Dose (Day 1)**	**Inpatient Assessment**	**EOT (For Inpatients Only)**	**Day of Hospital Discharge[2]**	**Outpatient[3] Assessment**	**30-day Post-EOT Follow-up**
Window		**± 0 days**					**± 3 days**
ECG[7]	x		Days 3, 8, 15, 22, and 28	x	x (only if continuing pacritinib/ placebo as an outpatient)		
Serum chemistry[8]	x		Daily (Days 2 through 28)	x	x		
Liver function panel[9]	x		Days 8, 15, 22, and 28;	x	x		
CBC[10]	x		Daily (Days 2 through 28)	x	x		
WBC differential[11]	x		Days 8, 15, 22, and 28	x	x		
RT-PCR test or antigen-based test for SARS-CoV-2[12]	x						
Coagulation tests[13]	x		Days 8, 15, 22, and 28	x	x		
Markers of disease severity[14]	x		Days 3, 8, 15, 22, and 28	x	x		
Serum pregnancy test[15]	x						
Chest imaging[16]	x						

Table 1 PRE-VENT Phase 2 (PAC319) Schedule of Assessments

Study Day	Screening Window[1]	Pre-Dose (Day 1)	Inpatient Assessment	EOT (For Inpatients Only)	Day of Hospital Discharge[2]	Outpatient[3] Assessment	30-day Post-EOT Follow-up
Window		**± 0 days**					**± 3 days**
Documentation of oxygen delivery method[17]	x	x (Unless the same time point as Screening)	Daily (Days 2 to 28)	x	x		
Highest oxygen delivery flow rate (if on non-invasive oxygen)		x	Daily (Days 2 to 28)	x	x		
Highest %FiO2 (if on CPAP, BiPAP, or IMV)	x	x	Daily (Days 2 to 28)	x			
Highest PEEP (if on positive pressure ventilation)	x	x	Daily (Days 2 to 28)	x			
Lowest PaO_2:FiO_2 ratio (if applicable)			Daily (Days 2 to 28)	x	x		
Randomization		x					
Administer pacritinib/placebo[3, 18]		x	Daily (Days 2 through 14)[18]	x	x (If on Days 2 to 14)[18]		
Documentation of pacritinib/placebo dosing[18]		x	Daily (Days 2 through 14)	x	x[18]	x	
Adverse events[3,19]		x	Daily (Days 2 through 28)	x	x	x	x

Table 1 PRE-VENT Phase 2 (PAC319) Schedule of Assessments

Study Day	Screening Window[1]	Pre-Dose (Day 1)	Inpatient Assessment	EOT (For Inpatients Only)	Day of Hospital Discharge[2]	Outpatient[3] Assessment	30-day Post-EOT Follow-up
Window		**± 0 days**					**± 3 days**
Concomitant medications[3,20]	x	x	Daily (Days 2 through 28)	x	x	x	x

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BiPAP = bilevel positive airway pressure; CBC = complete blood count; CK = creatine kinase; CPAP = continuous positive airway pressure; CRF = case report form; CRP=C-reactive protein; ECG = electrocardiogram; ECMO = extracorporeal membrane oxygenation; EOT = End of Treatment; FiO_2 = fraction of inspired oxygen; HR_{max} = maximum documented heart rate during calendar day; IMV = invasive mechanical ventilation; ICF = informed consent form; INR = international normalized ratio; PaO_2 = partial pressure of oxygen; PEEP = positive end-expiratory pressure; PTT = partial thromboplastin time; RT-PCR = reverse transcriptase polymerase chain reaction; SARS-CoV-2 = severe acute respiratory distress syndrome coronavirus 2; SpO_2 = blood oxygen saturation; T_{max} = maximum documented temperature during calendar day; WBC = white blood cell WOCBP = women of child-bearing potential.

1 Note: Screening and randomization may occur on either Day -1 or Day 1. Patients may be screened, randomized, and start treatment on the same day (Day 1). Patients must provide informed consent within 96 hours after hospital admission.
- Clinical laboratory assessments (serum chemistry, liver function panel tests, CBC with differential, and coagulation tests) obtained within 24 hours prior to the start of Screening may be used in determination of eligibility and do not need to be repeated.
- ECG assessments performed within 48 hours prior to the start of Screening may be used in determination of eligibility and do not need to be repeated.
- Chest imaging (performed in the ER or upon hospital admission) may be used for documentation and does not need to be repeated.

2 Assessments required on the day of hospital discharge do not need to be repeated if they are already performed that day as part of the protocol-defined inpatient assessments for that study day.

3 Outpatient assessments should be based on weekly telephone/videoconference communication with the patient to document an evaluation of the **daily** 7-point ordinal scale score for the days between contacts confirmation of pacritinib/ placebo dosing if continuing on treatment as an outpatient, AEs, and the use of concomitant medications. More frequent telephone/videoconference contact may occur as needed to supplement the above assessments. Review of medical records may also be performed as needed to supplement these assessments; medical records should be reviewed for patients who cannot be reached by telephone/videoconference.

4 Vital signs include blood pressure, pulse, respiratory rate, temperature, SpO2, and body weight.

5 The 7-point ordinal scale of clinical status is as follows: category 7 = death; 6 = hospitalization, requiring IMV and/or ECMO; 5 = hospitalization, on non-invasive positive pressure ventilation or high-flow nasal cannula; 4 = hospitalization, requiring supplemental oxygen not meeting the criteria for categories 5 or 6; 3 = hospitalization, not requiring supplemental oxygen; 2 = not hospitalized but unable to resume normal activities; 1 = not hospitalized with resumption of normal activities.

6 Any physical examination performed as part of routine care on Day 1 prior to signing of informed consent may be used for documentation

7 ECG will be performed at Screening (may be performed within 48 hours prior to the start of Screening), Day 3, Day 8, Day 15 or EOT, Day 22, Day 28, and on the day of hospital discharge if before EOT. ECGs are not required after hospital discharge but must be performed on the day of discharge if the patient will be continuing pacritinib/placebo as an outpatient. Results from unscheduled ECG assessments should be entered into the electronic database using an Unscheduled ECG CRF. ECGs should be assessed using at least 3 leads; rhythm strips from telemetry monitoring are acceptable.

8 Serum chemistry, which includes sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, and magnesium, will be evaluated at Screening (the results of laboratory assessments performed in the ER or upon hospital admission that are relevant for the determination of eligibility may be used to confirm eligibility provided that they have been performed within 24 hours prior to the start of Screening) and daily from Days 2 to 28 or EOT, and on the day of hospital discharge. Serum chemistry tests are not required after hospital discharge. Results from unscheduled serum chemistry tests should be entered into the electronic database using an Unscheduled Serum Chemistry CRF.

9 Liver function panel, which includes AST, ALT, alkaline phosphatase, total bilirubin, and albumin will be evaluated at Screening (the results of laboratory assessments performed in the ER or upon hospital admission that are relevant for the determination of eligibility may be used to confirm eligibility provided that they have been performed within 24 hours prior to the start of Screening), Day 8, Day 15 or EOT, Day 22, Day 28, and on the day of hospital discharge. Liver function panel tests are not required after hospital discharge. Results from unscheduled liver function panel tests should be entered into the electronic database using an Unscheduled Liver Function Panel CRF.

10 CBC, which includes WBC count, hemoglobin, hematocrit, and platelet count, will be evaluated at Screening (the results of laboratory assessments performed in the ER or upon hospital admission that are relevant for the determination of eligibility may be used to confirm eligibility provided that they have been performed within 24 hours prior to the start of Screening) and daily from Days 2 to 28 or EOT, and on the day of hospital discharge. Hematology tests are not required after hospital discharge. Results from unscheduled hematology tests should be entered into the electronic database using an Unscheduled Hematology CRF.

11 WBC differential will be evaluated at Screening (the results of laboratory assessments performed in the ER or upon hospital admission that are relevant for the determination of eligibility may be used to confirm eligibility provided that they have been performed within 24 hours prior to the start of Screening), Day 8, Day 15 or EOT, Day 22, Day 28, and on the day of hospital discharge.

12 SARS-CoV-2 RT-PCR test or an antigen-based test from a respiratory, nasopharyngeal, saliva, blood, or stool specimen at Screening or documented within 1 week prior to the start of Screening.

13 Coagulation tests (INR, PTT, and fibrinogen) will be performed at Screening (the results of laboratory assessments performed in the ER or upon hospital admission that are relevant for the determination of eligibility may be used to confirm eligibility provided that they have been performed within 24 hours prior to the start of Screening), Day 8, Day 15 or EOT, Day 22, Day 28, and the day of hospital discharge. Coagulation testing does not need to be performed after hospital discharge. Results from unscheduled coagulation tests should be entered into the electronic database using an Unscheduled Coagulation CRF.

14 Blood samples for markers of disease severity (CRP, ferritin, D-dimer, IL-6, troponin I, LDH, BNP, procalcitonin, CK, and triglycerides) will be collected at Screening (may be performed within 24 hours prior to the start of Screening), before the morning dose on Day 3, Day 8, Day 15 or EOT, Day 22, Day 28, and the day of hospital discharge. These markers do not need to be assessed after hospital discharge. The assessments for markers of disease severity are required if they can be performed at a local laboratory or if the study center has access to an external laboratory where the samples can be sent for analysis. If a study center does not have access to a local or external laboratory that can perform these assessments, the investigator must provide written confirmation of the inability to perform the assessment(s), and approval from the CTI Medical Monitor is required to omit the assessment(s). Results from unscheduled tests for markers of disease severity should be entered into the electronic database using an Unscheduled Markers of Disease Severity CRF.

15 WOCBP must have a serum pregnancy test prior to randomization, which may be performed at any time after arrival to the emergency room or hospital admission.

16 Chest imaging assessments performed in the ER or upon hospital admission may be used for screening documentation.

17 Oxygen delivery method may include nasal cannula, non-rebreather, non-invasive positive-pressure ventilation (eg, CPAP or BiPAP), or IMV. If multiple delivery methods were used, the method that provides the highest concentration of oxygen will be documented.
18 Patients will receive pacritinib/placebo from Day 1 through Day 14. 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 and documentation of dosing is to recorded during outpatient assessment via telephone/videoconference.
19 AEs will be documented during the clinical study from the time the patient is randomized through 30 days following the last dose of pacritinib/placebo.
20 Concomitant medications will be documented from the time of consent through 30 days following the last dose of pacritinib/placebo.

1 BACKGROUND INFORMATION

1.1 COVID-19

1.1.1 Clinical Presentation and Disease-Related Symptoms

Coronavirus disease 2019 (COVID-19) is a viral infection due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a positive-sense, single-stranded, enveloped RNA virus that can cause life-threatening infection, and has recently become a global pandemic. Overall mortality rate from COVID-19 is approximately 3% but reaches approximately 25% in patients who require hospitalization (Zhou et al 2020). Mortality from COVID-19 is largely due to the development of two sequelae: acute respiratory distress syndrome (ARDS), a syndrome of widespread pulmonary inflammation leading to severe hypoxemia, and cytokine storm, an exaggerated systemic inflammatory response that can lead to shock and multiorgan failure. To date, no therapy has proven effective for treating or preventing these complications of COVID-19 beyond supportive care. Thus, there is an urgent unmet need for novel therapies to treat or prevent the inflammatory sequelae of COVID-19.

ARDS is mediated by cellular infiltration and inflammation of the lung, causing hypoxemic respiratory failure (Zhou et al 2020). The interleukin (IL)-6 is an important inflammatory mediator that has been linked to the pathogenesis of both ARDS and cytokine storm (Meduri et al 1995). Patients with COVID-19 have markedly increased plasma levels of IL-6. Based on the published experience of cases from Wuhan, China, elevated levels of ferritin, a blood protein containing iron, and IL-6 were both associated with mortality, suggesting that death may be driven by a hyperinflammatory response to the virus.

IL-6 induces differentiation of T helper 17 (Th17) cells. Th17 cells are critical players in cellular host defense against extracellular pathogens such as viruses, as they mediate the recruitment of neutrophils and macrophages to infected tissues. Emerging evidence implicates Th17 cells in the pathogenesis of ARDS (Yu et al 2015; Mikacenic et al 2016; Li et al 2015). Supporting evidence includes an autopsy study of victims of COVID-19 that showed classic histological findings of ARDS and markedly increased concentrations of Th17 cells (Xu et al 2020). Th17 activation may potentiate the cytokine storm and macrophage activation phenotypes seen in patients with COVID-19 who have elevated levels of ferritin, IL-2, IL-6, IL-7, IL-10, granulocyte-macrophage colony-stimulating factor, interferon-gamma inducible protein 10, macrophage inflammatory protein 1 alpha, and tumor necrosis factor alpha (Ruan et al 2020; Huang et al 2020).

These novel findings suggest that blocking IL-6 signaling and attenuating Th17 cell differentiation could prevent or mitigate ARDS and cytokine storm due to COVID-19. Thus, a targeted immunomodulatory strategy is necessary.

1.1.2 Current Strategies for Prevention and Treatment of COVID-19

There is currently no vaccine available to protect from SARS-CoV-2 infections and no approved treatments of COVID-19 (Zhou et al 2020). Rigorous self-isolation and preventative lockdown measures have been put in place to mitigate the rate of SARS-CoV-2 infections, and patients with COVID-19 are mainly administered supportive care. Therapeutic interventions are usually used only in symptomatic patients with COVID-19, since asymptomatic patients demonstrate

better survival and are asked to self-isolate. Current therapeutic approaches are aimed at mitigating specific COVID-19 symptoms, such as ARDS by placing patients on mechanical ventilatory support, and at evaluating novel antivirals to treat the cytokine storm.

1.1.3 Pacritinib as a Therapeutic Strategy for COVID-19-Related ARDS and Cytokine Storm

The Janus kinases (JAKs) are a family of cytoplasmic tyrosine kinases (TYKs) consisting of JAK1, JAK2, JAK3, and TYK2. They play a pivotal role in the signaling pathways of numerous cytokines, hormones, and growth factors. Their intracellular substrates include the signal transducer and activator of transcription (STAT) family of proteins. The JAK/STAT pathways, through the proper actions of the ligands, regulate important physiological processes, such as the immune response to viruses, hematopoiesis, among others.

Pacritinib is a highly selective inhibitor of JAK2, with no off-target effects on JAK1 (Singer et al 2016). The major advantage of pacritinib for the treatment of patients with COVID-19 is its ability to block IL-6 downstream signaling and prevent induction of Th17 cells, thereby potentially preventing the pathogenesis of both ARDS and cytokine storm while preserving antiviral immunity.

The JAK2/STAT3 signaling pathway is necessary for the differentiation and function of Th17 cells. Selective JAK2 inhibition decreases IL-17 production by dendritic cell (DC)-allostimulated cluster of differentiation 4 (CD4+) T cells and suppresses expression of the retinoic acid receptor-related orphan receptor gamma t, a key Th17 cell differentiation factor (Betts et al 2011). A recent study demonstrated that JAK2 inhibition can selectively inhibit the Th17 cell response in COVID-19 (Wu et al 2020). Furthermore, JAK2/STAT3 is required for IL-6 signaling (Johnson et al 2018), which stimulates Th17 cell response and which has been implicated in the pathogenesis of COVID-19 (Gong et al 2020). IL-6 blockade via JAK2 inhibition may have several salubrious effects in patients with COVID-19. JAK2 inhibitors have been used to abrogate the Th17 cell pathway in the setting of acute graft-versus-host disease (GVHD), which is characterized by elevated levels of Th17 cells in affected organs. Ruxolitinib, a JAK2 inhibitor, has been successful in treating steroid-refractory acute GVHD (Meduri et al 1995) and has been proposed as a novel treatment for COVID-19. Similarly, pacritinib has shown potential efficacy in reducing GVHD in early phase studies, with reduction in Th17 cell cytokines (Betts et al 2011).

As a non-selective JAK1 and JAK2 inhibitor, ruxolitinib may be associated with reduced antiviral response and viral clearance (Heine et al 2013a; Heine et al 2013b). In contrast to JAK2/STAT3 signaling, JAK1/STAT1 is necessary for interferon-γ production, which is important in containing infections. Inhibitors of JAK1 therefore may increase the risk of infection. Multiple studies have demonstrated increased risk of fungal, bacterial, and viral infections in the setting of JAK1 inhibitors, including tofacitinib (which has a black box warning for increased risk of infection) and ruxolitinib (Sant'Antonio et al 2019). Pacritinib, as a selective JAK2 inhibitor without effects on JAK1, was not associated with an excess in infections compared to best available therapy (BAT) in two large Phase 3 myelofibrosis trials, nor was it associated with opportunistic infections (Mascarenhas et al 2018; Mesa et al 2017). In addition, stimulation of DCs with influenza virus peptide in the presence of selective JAK2 inhibition elicited an intact cytotoxic T cell response, leading to the conclusion that, in contrast

to nonselective JAK inhibitors, JAK2 selective inhibitors did not increase the risk of viral infection (Betts et al 2011).

In addition to its desirable selective kinase inhibition profile on the JAKs, pacritinib also inhibits interleukin-1 receptor-associated kinase-1 (IRAK1) and colony-stimulating factor 1 receptor (CSF1R), both of which may be targets of interest in COVID-19 (Singer et al 2016; Singer et al 2018). IRAK1 is a key component of the inflammatory cascade that acts downstream of IL-1 and toll-like receptor (TLR) and potentiates IL-6. IRAK1 is an emerging target for inflammatory and malignant diseases, including sepsis. In fact, among patients with sepsis, those with a variant haplotype of IRAK1 leading to elevated levels of the nuclear factor kappa-light chain-enhancer of activated B cells transcription factor were more likely to develop shock, prolonged respiratory failure, and death (Arcaroli et al 2006). CSF-1R is a cell surface receptor for the colony-stimulating factor 1, a cytokine that controls production, function, and differentiation of macrophages, and therefore a potential target in the setting of viral-induced macrophage activation, which is thought to occur in COVID-19 (Mehta et al 2020).

Pacritinib represents a potential treatment for the pathologic inflammation associated with COVID-19 leading to ARDS. As a selective JAK2 inhibitor, pacritinib may ameliorate the effects of cytokine storm via inhibition of Th17 cell differentiation and IL-6 blockade while permitting antiviral response via JAK1. Additional potential therapeutic pathways exist via inhibition of IRAK1 and CSF-1R. We proposed a randomized placebo-controlled study of standard-of-care with or without pacritinib to treat and prevent worsening of COVID-19 in hospitalized patients with severe disease with or without cancer.

1.2 Pacritinib

Pacritinib is a novel JAK2/IRAK1/CSF-1R inhibitor that is being developed as a treatment for advanced myelofibrosis. It has been studied in one Phase 2 dose-ranging study (PAC203) and two large randomized Phase 3 studies (PERSIST-1 and PERSIST-2). In all studies, pacritinib has demonstrated clinical efficacy based on spleen volume response and a reduction in total symptom scores (TSS). A randomized Phase 3 trial of pacritinib for the treatment of myelofibrosis and severe thrombocytopenia (PACIFICA) is currently enrolling. In the Phase 2 PAC203 study, the most common nonhematologic adverse events (AEs) were gastrointestinal, including diarrhea (30%), and nausea (28%); these were largely low grade and manageable with standard antidiarrheal medications. The most common hematologic event reported was thrombocytopenia (35%), which was manageable with dose modifications and which was not associated with serious bleeding events (Gerds et al 2019).

1.2.1 Pharmacology

Pooled Pharmacokinetic/Pharmacodynamic Modeling

Population pharmacokinetics (PK) for pacritinib was established based on pooled data from 16 studies including 630 patients who received pacritinib at total daily doses ranging from 100 to 600 mg. Pacritinib population PK was characterized by a two-compartment disposition model with first-order absorption and elimination. Systemic exposure (area under the concentration-time curve, maximum concentration, and minimum concentration) for the 100 mg once daily (QD) and 100 mg twice daily (BID) regimens was generally lower than that achieved with higher doses (200 mg BID and 400 mg QD), although there was an overlap. Population PK/pharmacodynamics (PD) modeling and exposure-response analysis confirmed that higher

pacritinib doses and exposures were associated with greater reductions in both spleen volume and TSS.

The half maximum inhibitory concentration (IC_{50}) of pacritinib against the key kinases it inhibits is as follows: JAK2 (6 nM), IRAK1 (13.6 nM), and CSF-1R (39.5 nM). Pacritinib does not inhibit JAK1 at physiologic doses. Oral dosing of 200 mg BID of pacritinib provides more than 200 nM free drug concentration, which is many fold higher than the IC_{50}.

As some patients with COVID-19 may be unable to swallow or intubated, pacritinib/placebo may require administration via an oro- or nasogastric tube. Currently, there are no data available regarding administration of pacritinib as a suspension via enteral tube. However, currently available PK data and physicochemical properties do not suggest any untoward effects with enteral administration of pacritinib in suspension. Pacritinib is a conventional immediate-release, non-granulated powder mixed with excipients in a capsule dosage form; hence it is suitable for opening the capsule and flushing down enteral tubes after mixing with water or commonly used liquids without substantially impacting safety and efficacy. Pacritinib is poorly soluble in water in the pH range of 3.0-9.0; thus, suspension of the capsule contents in liquid before dosing is expected to have a minimal effect on the rate and extent of drug absorption.

1.2.2 Preclinical Toxicology

The adverse effects of pacritinib were evaluated in 30-day repeated oral dose toxicity studies, with 14-day recovery in both mice and dogs, and in 26- and 39-week chronic toxicity studies in mice and dogs, respectively. Key findings included dose-dependent leukopenia accompanied by neutropenia (dog) and neutrophilia (mice) that partially reversed during recovery. Mice also showed dose-dependent but reversible thrombocytosis and anemia. In the chronic toxicity studies, low-magnitude decreases in neutrophils and red blood cell (RBC) parameters were observed. No treatment-related hepatic changes were observed, with the exception of increased aspartate transaminase (to +109%, male dogs) and increased triglycerides (to +57%, male and female dogs).

In the 30-day study in dogs, animals receiving mid and high dosages of pacritinib experienced vomiting and diarrhea that increased in severity despite treatment with antiemetic and antidiarrheal medication. Similarly, in the 39-week study in dogs, an increased incidence of nausea and vomiting was observed at dosages of 20 mg/kg/day and higher. Periods of low food consumption in individual animals receiving 40 and 50 mg/kg/day were accompanied by rapid weight loss, which was controlled and reversed with subcutaneous fluid and supplemental food, and were considered treatment related and adverse.

Based on these studies, the no observed adverse effect level was determined to be 100 mg/kg BID in mice and 10 mg/kg BID in dogs.

Please refer to the IB for available information concerning the nonclinical safety of pacritinib.

1.2.3 Summary of Clinical Pharmacology and Early Phase Studies With Healthy Subjects of Pacritinib

Two PK studies for pacritinib have been completed in healthy subjects, including a food effect study (SB1518-2010-006) characterizing the effects of a high-calorie, high-fat meal on the bioavailability and PK of pacritinib and a study assessing inter- and intra-individual variability of

oral pacritinib in healthy subjects under fasted conditions at 100, 200, and 400 mg doses (SB15182010-004). In addition, the single- and multiple-dose population PK of pacritinib has been characterized following multiple-dose administration of pacritinib in two studies (SB1518-2007-001 and SB1518-2008-003) in patients with advanced myeloid malignancies. After administration of single doses of pacritinib in a randomized, three-treatment, three-period crossover study (SB1518-2010-004) in healthy subjects under fasted conditions, peak plasma concentrations were reached at a median time of maximum concentration (T_{max}) ranging from 4.5 to 5.5 hours across the 100 to 400 mg dose range. While between-patient variability was relatively high (28% to 45%), the within-patient variability was low (13% to 15%), highlighting the consistent systemic exposure for pacritinib in individual patients. The mean elimination half-life was approximately 34 hours and was not dependent on dose. After oral administration of single 200 mg doses of pacritinib under fed and fasted conditions, no effect of food on absorption of pacritinib was observed. Given these data, pacritinib can be orally administered without regard to timing of meals.

Pooled analyses of PK assessments from the two clinical studies in patients at pacritinib dosages up to 600 mg QD showed slow absorption (T_{max} 4 to 6 hours) and dose-related increases in systemic exposure up to 400 mg QD. The rate of absorption was linear at doses up to 300 mg and thereafter appeared to be rate limited. Therefore, modeling suggested that, at doses of over 200 mg per day, divided doses would yield increased steady study blood levels. Beyond the 400 mg QD dosage, there was a minimal increase in exposure with doses up to 600 mg QD, suggesting the involvement of a saturable process in oral absorption of pacritinib.

On the basis of these studies, a total daily dose of 400 mg was selected for future study. Subsequent Phase 3 studies, described in Section 1.2.4, used 400 mg QD and 200 mg BID dosing.

1.2.4 Overview of Clinical Safety of Pacritinib

Approximately 1128 patients have received pacritinib in 16 completed studies, including 713 patients with myelofibrosis who were assigned to a pacritinib arm. Completed studies include two controlled studies in myelofibrosis (PERSIST-1 and PERSIST-2), five uncontrolled clinical studies in patients with cancer (including the PAC203 Phase 2 dose finding study in patients with myelofibrosis), and nine clinical pharmacology/PK studies.

Among the patients with myelofibrosis treated with pacritinib in the completed controlled and uncontrolled studies, the most commonly (> 10% of all patients) reported treatment-emergent adverse events (TEAEs) related to study drug, by preferred term (PT), were in the system organ class of gastrointestinal (GI) disorders, including diarrhea (56%), nausea (34%), and vomiting (20%), and the System Organ Class of blood and lymphatic system disorders, including thrombocytopenia (25%) and anemia (25%). Although GI-related events were common, they were generally reversible, were of low grade, and rarely led to treatment discontinuation.

Overview of the PAC203 Phase 2 Dose-Finding Study in Patients with Myelofibrosis

PAC203 was a dose-finding study in patients with advanced myelofibrosis who experienced intolerance or treatment failure with ruxolitinib. Compared to the PERSIST studies, PAC203 included additional eligibility and monitoring guidelines to mitigate the risk of cardiac and bleeding events. Enrollment was not restricted based on platelet count. The primary objective of the study was to determine the optimal dosage of pacritinib, spanning the dose-response curve

for safety and efficacy established in previous phase 1/2 clinical studies and the phase 3 PERSIST-1 and PERSIST-2 studies. Patients were randomized 1:1:1 to pacritinib 200 mg BID, pacritinib 100 mg BID, or pacritinib 100 mg QD. Of the 161 patients who were randomized and who received treatment, median platelet count was 55,000/μL, and hemoglobin was < 10 g/dL in 70.8% of patients (n = 114). Median duration of treatment was 23 weeks (100 mg QD), 20 weeks (100 mg BID), and 21 weeks (200 mg BID).

At Week 24, the spleen volume reduction response rate (≥35% reduction) was highest in the 200 mg BID arm (9.3%) compared to lower dose arms (100 mg QD: 0% and 100 mg BID: 1.8%). The TSS response rate (≥50% reduction) was similar across all arms (100 mg QD: 7.7%, 100 mg BID: 7.3%, and 200 mg BID: 7.4%), with deepest responses in questions relating to spleen symptoms (satiety, abdominal discomfort, and left rib pain) and cytokine-related symptoms (night sweats, itching, and bone pain), particularly at 200 mg BID. The percentage of patients describing at least minimal improvement of their symptoms based on the Patient Global Impression Assessment (PGIA) at Week 24 was greatest in the 200 mg BID arm (33.3%, n = 18/54) compared with 100 mg BID (23.6%, n = 13/55) or 100 mg QD (19.2%, n = 10/52).

The majority of non-hematologic AEs was mild or moderate in severity, and rates were generally similar across dosing arms with the exception of gastrointestinal events, which occurred more commonly in patients treated at 200 mg BID (39/54, 72.2%) than in patients treated at lower doses (100 mg QD: 26/52, 50.0%; 100 mg BID: 30/55, 54.5%). These events were largely grade 1 or 2 and usually occurred within the first 8 weeks on treatment. Diarrhea was common but generally manageable with standard antidiarrheal agents and tended to be short-lived: the median duration of pacritinib-related diarrhea was 2 weeks. The most common hematologic AEs were thrombocytopenia and anemia, both of which occurred more frequently in patients treated at 200 mg BID (40.7% and 24.1% respectively). Cardiac events were more common in patients treated at 200 mg BID (40.7%, n = 22) than in patients treated at lower doses (100 mg QD: 21.2%, n = 11; 100 mg BID: 21.8%, n = 12) but were largely grade 1 or 2 in severity, with the most common being peripheral edema (200 mg BID: 16.7%) and QT prolongation (200 mg BID: 7.4%). There was no excess in grade 3 or 4 cardiac events in patients treated at the highest dose (100 mg QD: 5.8%, n = 3; 100 mg BID: 5.5%, n = 3; and 200 mg BID: 3.7%, n = 2; no grade 4 events). The mean change in corrected QT interval (QTc) between Baseline and Week 24 was roughly +10 msec on all arms; no patient had a QTc > 500 msec. Bleeding events were more common in patients treated at 200 mg BID (42.6%, n = 23) than in patients treated at lower doses (100 mg QD: 36.5%, n = 19; 100 mg BID: 25.5%, n = 14) but were largely grade 1 or 2 in severity, with the most common being epistaxis (200 mg BID: 14.8%) and bruising (200 mg BID: 9.3%). There was no excess in grade 3 or 4 bleeding events in patients treated at the highest dose (100 mg QD: 7.7%, n = 4; 100 mg BID: 3.6%, n = 2; and 200 mg BID: 5.6%, n = 3; no grade 4 events). The rate of fatal events was similar across all arms: 100 mg QD: 7.7%, n = 4 (sepsis, disease progression, tuberculosis, and general state deterioration); 100 mg BID: 5.5%, n = 3 (myelofibrosis, subdural hemorrhage, and heart failure); and 200 mg BID: 5.6%, n = 3 (sepsis, respiratory failure, and subdural hematoma).

2 STUDY RATIONALE AND OBJECTIVES

This study is being conducted to establish the safety and efficacy of pacritinib + standard of care (SOC) compared to placebo + SOC in hospitalized patients with severe COVID-19 with or without cancer as the proportion of patients who progress to IMV and/or ECMO or die by

Day 28. This study will additionally confirm the safety and efficacy of pacritinib administered at 400 mg QD on Day 1 followed by 200 mg BID for up to 14 days, with the option of extending 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. Determination of the selected dose is detailed in Section 3.1.

2.1 Justification of Included Patient Population

The study population will consist of hospitalized adult 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, but do not require IMV (NIH COVID-19 Treatment Guidelines 2020). Patients with moderate COVID-19 are not eligible for the study because it is likely that they will not be receiving supplemental oxygen and will not be hospitalized. Patients with critical COVID-19 are not included because the goal of pacritinib therapy is to prevent patients from progressing to the acute respiratory distress syndrome associated with COVID-19.

2.2 Independent Data Monitoring Committee

This study will be monitored 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 the IDMC charter.

The IDMC will make independent recommendations to the Sponsor on study continuation (continue without modification, continue with modification, or terminate) and on patient enrollment (hold or stop enrollment or enroll additional patients).

The IDMC charter will be written in collaboration between the Sponsor and members of the IDMC. In keeping with the terms of the charter, each IDMC meeting will have an open and closed session.

The IDMC will convene for a formal safety review after the first 40 patients (approximately 20 patients per arm) have completed treatment and then quarterly thereafter. Subsequent meetings will be triggered at the interim analysis. Ad hoc meetings can be called at any time by either the IDMC or by CTI.

Meeting minutes will be generated from each IDMC meeting and provided to the Food and Drug Administration (FDA) within 10 business days of the meeting conclusion.

2.3 Study Objectives

2.3.1 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.

2.3.2 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

2.3.3 Tertiary Objectives

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

- C-reactive protein (CRP)
- Ferritin
- D-dimer
- IL-6
- Troponin-I
- Lactate dehydrogenase (LDH)
- Brain natriuretic peptide (BNP)

- Procalcitonin
- Triglycerides
- Creatine kinase (CK)

3 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, 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.

The study will be monitored by an IDMC comprising 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/videoconference 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 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.

At the request of an investigator, and with agreement of the Chief Medical Officer at CTI, the assigned treatment for an individual patient may be unblinded for the purposes of discussing the ongoing care of that patient.

The approximate study duration for each patient will be 8 weeks. The estimated duration of the entire study is approximately 1 year and is subject to increase as patient enrollment increases.

The schedules of study assessments for all patients are provided in Table 1.

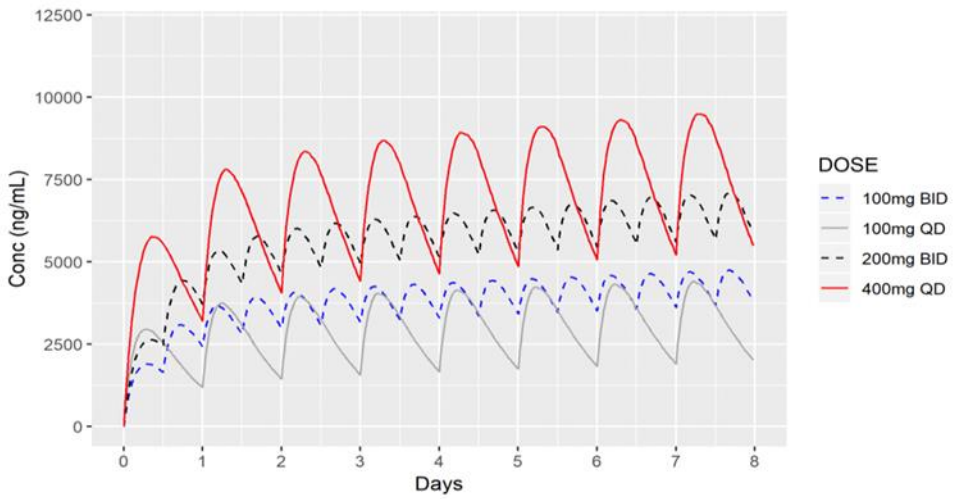
3.1 Rationale for Dosage Selection

The pacritinib IC_{50} for the therapeutic targets is as follows:

- JAK2: 6 nM
- IRAK-1: 13.6 nM
- CSF-1R: 39.5 nM

Inhibition of these targets is thought to mediate the cytokine storm and development of acute respiratory distress syndrome seen in patients with COVID-19. The goal of dose selection in this study is to rapidly achieve many-fold higher free pacritinib plasma concentrations than the IC_{50}. Following oral administration of 200 mg BID and 400 mg QD, free plasma drug concentration observed is about 200 nM and 250 nM, respectively. As COVID-19 is a rapidly progressing disease with significant cytokine storm, the treatment goal should be rapid control of cytokine storm; hence, the dosage regimen that provides rapid plasma concentration many folds higher than IC_{50} is desired. Therefore, dosing 400 mg QD on Day 1 followed by 200 mg BID provides steady-state equivalent plasma concentration on Day 1, which is similar to the steady-state concentration seen with 200 mg BID (Figure 1).

Figure 1 Simulated Median Concentration-Time Course in Myelofibrosis Patients (Day 1 to Day 8)



Abbreviations: BID = twice daily; QD = once daily.

Based on all available data from pre-clinical studies to clinical data in both healthy subjects and patients with hematologic malignancies including myelofibrosis, pacritinib 400 mg QD on Day 1 followed by 200 mg BID dosing starting on Day 2 has been selected as the dosing for the PRE-VENT study.

4 PATIENT SELECTION AND WITHDRAWAL

4.1 Target Population

4.1.1 Inclusion Criteria

1. Hospitalized or will be hospitalized prior to randomization for the treatment of severe COVID-19 with SARS-CoV-2 infection confirmed by either a) a positive reverse transcriptase polymerase chain reaction (RT-PCR) or b) an antigen-based test from any respiratory, nasopharyngeal, saliva, blood, or stool specimen at Screening or documented within 1 week prior to the start of Screening (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, but do not require IMV).

2. Age ≥ 18 years

3. Platelet count ≥ 50,000/μL

4. If fertile, willing to use effective birth control methods during the study

5. Provision of informed consent within 96 hours after hospitalization

4.1.2 Exclusion Criteria

1. In the opinion of the investigator, progression to death is imminent and inevitable within the next 24 hours, irrespective of the provision of treatments
2. Currently intubated or intubated between screening and randomization
3. Suspected active uncontrolled bacterial, fungal, viral, or other infection (besides COVID-19)
4. Prior allogenic hematopoietic stem cell transplantation
5. Active lung cancer or history of lung cancer within the past 12 months
6. Any active grade 2 or higher hemorrhage
7. Any active gastrointestinal or metabolic condition that could interfere with absorption of oral medication
8. Uncontrolled intercurrent illness that, in the judgment of the treating physician, would limit compliance with study requirements
9. Known seropositivity for human immunodeficiency virus with CD4 count < 200/mm^3 within 3 months prior to randomization
10. Pregnant or breastfeeding, or positive pregnancy test in a pre-dose examination
11. Concurrent enrollment in another interventional trial (investigational COVID-19 antiviral studies are permitted)
12. Serum creatinine > 2.5 mg/dL
13. Total bilirubin > 4× the upper limit of normal
14. QT corrected by the Fridericia method (QTcF) prolongation > 480 msec
15. Known history of New York Heart Association Class II, III, or IV congestive heart failure prior to hospital admission
16. Known allergic reaction to any JAK2 inhibitor
17. Exposure to any JAK2 inhibitor within 28 days
18. Currently receiving a strong CYP3A4 inhibitor or strong P450 inducer (Appendix 1 and Appendix 2, respectively) and unable to stop the medication prior to the first dose of study drug and throughout the duration of study drug administration
19. Treatment with cytoreductive chemotherapy administered within 14 days prior to randomization

20. Administration of an IL-1 or IL-6 blocking immunomodulatory agent (such as tocilizumab, canakinumab, sarilumab, anakinra) within 48 hours prior to randomization

21. Currently receiving therapeutic anticoagulation or anti-platelet medication and unable to stop the medication prior to randomization. Prophylactic anticoagulation therapy or aspirin (≤ 100mg) are permitted.

22. Unable to ingest capsules or tablets at randomization

4.2 Withdrawal of Patients from Study

Patients have the right to stop study participation at any time and for any reason without prejudice to his or her future medical care. Patients (or a legally acceptable representative) may decline to continue receiving pacritinib/placebo and/or other protocol-required therapies or procedures at any time during the study. Patients will be encouraged to allow continued follow-up for study procedures and safety monitoring; however, patients may withdraw consent for all study procedures or for specific study procedures. Data collected up to the date of withdrawal of consent will be included in the analysis of the study. The Investigator is to discuss with the patient the appropriate procedures for withdrawal from the study. The Investigator or Sponsor has the right to discontinue any patient from study participation.

Reasons for patient discontinuation may include, but are not limited to, the following:

- Patient's request, with or without a stated reason
- Noncompliance
- Physician's decision
- Sponsor's discretion
- Lost to follow-up

5 METHOD OF TREATMENT ASSIGNMENT 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). 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.

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.

6 STUDY TREATMENT

6.1 Study Treatment Administration

Patients will be supplied with blinded pacritinib 100 mg capsules or matching placebo.

Table 2. Study Treatments

Treatment	Dosage/Regimen
Pacritinib + SOC	400 mg (4 capsules) QD on Day 1, then 200 mg (2 capsules) BID from Day 2 to Day 14 + SOC. Pacritinib/placebo is administered orally or via oro/nasogastric tube. 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.
Placebo + SOC	4 capsules QD on Day 1, then 2 capsules BID from Day 2 to Day 14 + SOC. Pacritinib/placebo is administered orally or via oro/nasogastric tube. 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.

Abbreviations: BID = twice daily; QD = once daily; SOC = standard of care.

6.2 Study Treatment Description and Storage

6.2.1 Pacritinib

Pacritinib for oral or oro/nasogastric tube administration is supplied in capsules containing 100 mg (as the free base) in body size 0, red cap/gray opaque hard gelatin capsules. The inactive ingredients are microcrystalline cellulose, magnesium stearate, and polyethylene glycol 8000.

Each capsule contains 146 mg of pacritinib citrate, which is equivalent to 100 mg pacritinib free base.

Direct contact of the powder in pacritinib capsules with the skin or mucous membranes should be avoided. If such contact occurs, affected areas should be washed thoroughly with water.

Pacritinib capsules should be stored at controlled room temperature 20°C to 25°C or 68°F to 77°F, with excursions allowed from 15°C to 30°C or 59°F to 86°F. All pacritinib supplies must be kept in a restricted access area.

6.2.2 Placebo

Placebo for oral or oro/nasogastric tube administration will be supplied as capsules that match the pacritinib 100 mg capsules in appearance.

The excipients, container, handling instructions, and storage conditions are the same as those described for the pacritinib capsules (Section 6.2.1).

6.3 Dosage, Route, and Mode of Administration

Patients will take 4 capsules of pacritinib/placebo at one time on Day 1 and two capsules BID from Day 2 to Day 14. 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. Pacritinib/placebo will be taken orally or via oro/nasogastric tube at the same time of day, with or without food.

Any missed or vomited doses should not be retaken or replaced.

6.4 Drug Accountability

At the Day 15 or EOT assessment, any unused pacritinib/placebo capsules will be returned to the pharmacy. Compliance with pacritinib/placebo will be reported by the site as the number of missed doses.

6.5 Pacritinib Treatment Adjustments for Adverse Events

6.5.1 Treatment Interruption and Discontinuation

Safety parameters including AEs, complete blood count (CBC) with differential, serum chemistry, and ECGs will be assessed according to protocol.

Pacritinib/placebo should be interrupted in the setting of certain AEs described below. Where possible, pacritinib/placebo should be held if an invasive procedure, including central venous catheter insertion, is performed; drug should be restarted after 24 hours without signs or symptoms of active bleeding. Pacritinib/placebo may also be held at the discretion of the investigator. The Medical Monitor should be notified of all such drug holds.

Pacritinib/placebo should be discontinued in the setting of intolerable AEs described below, or if the patient withdraws consent to continue pacritinib/placebo. Pacritinib/placebo may also be discontinued at the discretion of the investigator; the Medical Monitor should be notified of all such drug discontinuations.

6.5.2 Dosage Management Guidelines for Adverse Events

In prior studies, pacritinib has been associated with diarrhea, nausea, anemia, thrombocytopenia, QTc prolongation (generally mild), and risk of bleeding. Safety assessments will include hematologic parameters (CBC with differential), assessment of organ function (serum chemistry), monitoring for QTc prolongation, and general AE monitoring.

Patients who develop worsening gastrointestinal symptoms with the initiation of pacritinib/placebo treatment may be treated with standard antidiarrheal and/or anti-emetic medications.

Patients receiving study drug may also receive treatment-dose anticoagulants or anti-platelet agents, if required; patients do not need to discontinue study drug if one of these medications is

initiated. However, patients should not receive such agents concomitant with study drug administration if their platelet counts drop to < 50,000/μL; prophylaxis-dose anticoagulants are permitted for all patients on study. Treatment-dose anticoagulants and anti-platelet agents may be administered at any dose after the study drug treatment period has ended.

Additional dose modifications for treatment-related AEs are described in this section. Dose modifications for any instance of QTcF prolongation (irrespective of relationship to study drug) are also described in this section. AEs are deemed treatment-related if they are considered possibly related to pacritinib/placebo; AEs that are considered unlikely related to pacritinib/placebo do not require dose modification. Dose levels referenced in the following tables refer to the following available doses: 200 mg BID, 100 mg BID, and 100 mg QD.

Patients who require dose reduction may not subsequently re-escalate the dose.

6.5.3 Dosage Management Guidelines for Bleeding and Thrombocytopenia

Hematology parameters, including CBC (which includes white blood cell [WBC] count, differential, hemoglobin count, hematocrit, and platelet count), will be evaluated for inpatients during the study. These parameters should be monitored more frequently if clinically required.

Table 3 indicates the required dose interruptions and modifications for treatment-related bleeding and thrombocytopenia. Of note, if more than one toxicity is experienced simultaneously, the higher-grade toxicity should determine the dose interruption/modification.

Table 3. Treatment-Related Thrombocytopenia and Bleeding

Event	CTCAE (v4.03) Grade	Management/Action
Thrombocytopenia	**2** (Management required only for patients starting with normal platelet counts; patients starting with grade 1 or 2 thrombocytopenia at Baseline do not require dose adjustments)	• Reduce to 50% of the prior dose
	3 (Management required only for patients starting with normal platelet count or grade 1 thrombocytopenia; patients starting with grade 2 or 3 thrombocytopenia at Baseline do not require dose adjustments)	• Hold pacritinib/placebo. If the toxicity resolves to Baseline grade within 7 days, treatment may be resumed at the same level or at 50% of the dose. If the toxicity does not resolve or if it occurs at the lowest dose level, pacritinib/placebo must be discontinued. • If criterion is met on the day of hospital discharge, pacritinib/placebo should not be administered as an outpatient.
	4 (Management required only for patients starting with normal platelet count or grade	• Hold pacritinib/placebo. If the toxicity resolves to Baseline grade within 7 days, treatment may be resumed at the same level or at 50% of the dose. If the toxicity does not resolve

Table 3. Treatment-Related Thrombocytopenia and Bleeding

Event	CTCAE (v4.03) Grade	Management/Action
	1 or 2 thrombocytopenia; patients starting with grade 3 or 4 thrombocytopenia at Baseline do not require dose adjustments)	or if it occurs at the lowest dose level, pacritinib/placebo must be discontinued. • If criterion is met on the day of hospital discharge, pacritinib/placebo should not be administered as an outpatient.
Bleeding	**1**	• No change
	2	• Hold pacritinib/placebo until bleeding resolves for up to 2 days. Restart pacritinib/placebo at the same dose. If bleeding recurs, hold again for up to 2 days and restart at 50% of the prior dose. • If bleeding is ongoing after 2 days, discontinue pacritinib/placebo. • If treatment-related bleeding grade 2 or higher occurred on study, pacritinib/placebo should not be administered as an outpatient.
	3	• Hold pacritinib/placebo until bleeding resolves for up to 2 days. Restart pacritinib/placebo at 50% of the prior dose. If bleeding recurs, hold again for up to 2 days and restart at 50% of the prior dose. • If bleeding is ongoing after 2 days, discontinue pacritinib/placebo. • If treatment-related bleeding grade 2 or higher occurred on study, pacritinib/placebo should not be administered as an outpatient.
	4	• Discontinue pacritinib/placebo.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

Dose interruptions and modifications for SOC agents will be based on the prescribing information described in the most current versions of the agents' approved labeling.

6.5.4 Dosage Management Guidelines for QTcF Interval Prolongation

An ECG will be performed at Screening (Baseline), Days 3, 8, 15 (or End of Treatment [EOT]), 22, 28, and on the day of hospital discharge (for patients who will be continuing pacritinib/placebo as outpatient), and as clinically indicated.

Treatment should be modified as shown in Table 4, as recommended by FDA in case of QTcF interval prolongation. Dose modifications for any instance of QTcF prolongation (irrespective of relationship to study drug) are also described in this section. Dose levels referenced in the

following tables refer to the following available doses: 200 mg BID, 100 mg BID, and 100 mg QD.

Table 4. QTcF Prolongation

CTCAE (v4.03) Toxicity Grade	Management/Action
1	• No change
2	• No change
3 (including QTcF ≥ 501 on any occasion)	• For QTcF ≥ 501 msec on any assessment, hold pacritinib/placebo and assess daily ECGs while inpatient until toxicity resolves to grade ≤ 2 (QTc ≤ 500 msec). If toxicity resolves to grade ≤ 2, treatment may be resumed. If this is the second occurrence, the dose must be reduced by 50%. If already at the 100 mg QD dose, discontinue pacritinib/placebo. • If the QTcF on the date of discharge is >500 msec, pacritinib/placebo cannot be administered in an outpatient setting.
4	• Discontinue pacritinib/placebo

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; QD = once daily; QTcF = QT corrected by the Fridericia method.

Electrolyte repletion should be considered for patients who have electrolyte levels below the lower limit of normal upon entry into the study or while receiving pactritinib/placebo.

6.5.5 Dosage Management Guidelines for Diarrhea

Treatment with antidiarrheals such as loperamide (Imodium®) is advised for all patients who experience new onset diarrhea (Table 5). Dose levels referenced in the tables refer to the following available doses: 200 mg BID, 100 mg BID, and 100 mg QD.

Table 5. Dosage Management for Treatment-Related Diarrhea

CTCAE (v4.03) Toxicity Grade	Management/Action
1 or 2	• No change
3	• Hold pacritinib/placebo. If the toxicity resolves to grade ≤ 1 or to the Baseline grade within 7 days, treatment may be resumed at the same level or at 50% of the dose. Concomitant antidiarrheal treatment is required for patients restarting pacritinib/placebo. If the toxicity does not resolve or if it occurs at the lowest dose level, pacritinib/placebo must be discontinued.
4	• Hold pacritinib/placebo. If the toxicity resolves to grade ≤ 1 or to the Baseline grade within 7 days, treatment may be resumed at 50% of the dose. Concomitant antidiarrheal treatment is required for patients restarting pacritinib/placebo. If the toxicity does not resolve or if it occurs at the lowest dose level, pacritinib/placebo must be discontinued.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events.

6.5.6 Dosage Management Guidelines for Treatment-Related Toxicities Other than QTcF Prolongation, Diarrhea, Bleeding, or Thrombocytopenia

Treatment should be modified as shown in Table 6 in the event of related nonhematologic toxicities other than QTcF prolongation or diarrhea. Dose levels referenced in the following tables refer to the following available doses: 200 mg BID, 100 mg BID, and 100 mg QD.

Table 6. Treatment Toxicity and Dosage Management: Treatment-Related Toxicities Other than QTcF Prolongation, Diarrhea, or Thrombocytopenia

CTCAE (v4.03) Toxicity Grade	Management/Action
1 or 2	• No change
3	• Hold treatment • If the toxicity resolves to grade ≤ 1 or to the Baseline grade within 7 days, treatment may be resumed at the same level or at the 50% dose level, at the discretion of the investigator. Otherwise, treatment should be discontinued.
4	• Hold treatment • If the toxicity resolves to grade < 1 or to the Baseline grade within 7 days, treatment may be resumed, but dosage will be reduced to 50% from the level at which the toxicity was observed. If grade 4 toxicity occurs at the lowest dosage of 100 mg QD or if there is no resolution within 7 days, the patient should be discontinued from pacritinib/placebo.

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; QD = once daily; QTcF = QT corrected by the Fridericia method.

6.6 Concomitant and Excluded Therapies

Treatment with cytoreductive therapy is not permitted during the assigned treatment period. Pacritinib is metabolized by the P450 system, including cytochrome P450 3A4 (CYP3A4). Use of strong CYP3A4 inhibitors is not permitted as these can lead to significantly increased concentrations of pacritinib. Use of strong cytochrome P450 (CYP450) inducers is not permitted as these can lead to significantly reduced concentrations of pacritinib. Lists of selected strong CYP3A4 inhibitors and P450 inducers are found in Appendix 1 and Appendix 2, respectively.

Concomitant use of investigational agents (those administered as part of a clinical trial) for the treatment of COVID-19 is prohibited with the exception of antiviral agents. The use of IL-1 or IL-6 blocking immunomodulatory agents (such as tocilizumab, canakinumab, sarilumab, anakinra) is allowed if, in the opinion of the investigator, a patient is clinically deteriorating. However, patients who require IL-1 or IL-6 blocking agents must be discontinued from study drug. Hydroxychloroquine, chloroquine, azithromycin, corticosteroids, and antiviral agents are permitted concomitant medications.

Electrolyte repletion should be considered for patients who have electrolyte levels below the lower limit of normal upon entry into the study or while receiving pac~~t~~ritinib/placebo.

Patients who develop worsening gastrointestinal symptoms with the initiation of pacritinib/placebo treatment may be treated with standard antidiarrheal and/or anti-emetic medications (Section 6.6.1).

Treatment-dose anticoagulation and anti-platelet therapy may be administered after randomization, if required; patients do not need to discontinue pacritinib/placebo if one of these medications is initiated. However, patients should not receive such agents concomitant with study drug administration if their platelet counts drop to < 50,000/μL; prophylaxis-dose anticoagulants are permitted for all patients on study. Treatment-dose anticoagulants and anti-platelet agents may be administered at any dose after the study drug treatment period has ended.

Cytotoxic chemotherapy or cancer-directed immunotherapy is prohibited during the pacritinib/placebo treatment period (14 or 21 days). Cancer-directed immunotherapy includes immune checkpoint inhibitors, antibody-based cancer therapy, and cell-based cancer therapy.

6.6.1 Management of Gastrointestinal Toxicity

The need for managing gastrointestinal effects of pacritinib, particularly diarrhea, should be anticipated. A careful Baseline evaluation of bowel habits (frequency and consistency of bowel movements) should be obtained prior to the first dose.

Loperamide (Imodium®) or a similarly effective antidiarrheal drug may be administered at the Investigator's discretion if changes in frequency or consistency of bowel movements occur after starting pacritinib/placebo.

Early intervention for diarrhea should be initiated for patients with increases of one grade or more in diarrhea (Appendix 3). Standard supportive care measures to control symptoms of gastrointestinal toxicity such as diarrhea, constipation, and nausea should be provided.

7 STUDY ASSESSMENTS

7.1 Criteria for Evaluation

7.1.1 Efficacy

7.1.1.1 7-Point Ordinal Scale of Clinical Status

The following 7-point ordinal scale of clinical status (Cao et al 2020) will be used to assess the ordinal scale secondary endpoints. The ordinal scale score is to be documented daily on study through Day 28 for all patients, including those who have been discharged from the hospital.

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

7.1.1.2 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.

7.1.1.3 Lung Function Assessments

Lung function will be assessed by SpO_2 in ambient air (if possible), SpO_2 with oxygen supplementation (if applicable), documentation of oxygen delivery method, highest oxygen delivery flow rate (if receiving non-invasive oxygen), highest fraction of inspired oxygen (%FiO_2) (if on continuous positive airway pressure [CPAP], bilevel positive air pressure [BiPAP], or invasive mechanical ventilation [IMV]), highest positive end-expiratory pressure (PEEP; if on positive pressure ventilation), and lowest PaO_2:FiO_2 ratio (if arterial blood gas [ABG] is obtained and the patient is on positive pressure ventilation).

7.1.2 Safety

7.1.2.1 Adverse Events

AEs will be collected during the clinical study from the time the patient is randomized through 30 days following the last dose of pacritinib/placebo. AEs will be identified and reported to the Sponsor, in addition to any clinically indicated diagnostic, monitoring, treatment, and follow-up measures used to manage the reported AE. Pregnancy alone will not be considered as an AE. Pregnancy will be reported on a Pregnancy Reporting Form (Section 8.1.4.4). Abnormal pregnancy outcomes and/or any AE for the child or fetus (including miscarriage) will be reported as SAEs. Occurrences of overdose will be reported as SAEs.

7.1.2.2 Hematology

Hematology parameters, (CBC, WBC, hemoglobin, hematocrit, and platelet count), will be evaluated at Screening (may be performed within 24 hours prior to the start of Screening) and daily from Days 2 through 28 or EOT, and on the day of hospital discharge. WBC differential will be evaluated at Screening (may be performed within 24 hours prior to the start of Screening), Day 8, Day 15 or EOT, Day 22, Day 28, and on the day of hospital discharge. Hematology tests are not required after hospital discharge. Analysis of CBC results will be performed at local laboratories. Results from unscheduled hematology tests should be entered into the electronic database using an Unscheduled Hematology case report form (CRF). Pacritinib/placebo dosage modifications will be implemented for clinically significant AEs identified with this testing per the guidelines for “Treatment-Related Thrombocytopenia and Bleeding” (Section 6.5.3).

7.1.2.3 Coagulation Testing

Coagulation testing will include international normalized ratio (INR), partial thromboplastin time (PTT), and fibrinogen at Screening (may be performed within 24 hours prior to the start of Screening), Day 8, Day 15 or EOT, Day 22, Day 28, and on the day of hospital discharge. Coagulation tests are not required after hospital discharge. Results from unscheduled coagulation tests should be entered into the electronic database using an Unscheduled Coagulation CRF. Analysis of coagulation results will be performed at local laboratories.

7.1.2.4 Serum Chemistry

Serum chemistry parameters (sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, and magnesium) will be evaluated at Screening (may be performed within 24 hours prior to the start of Screening) and Day 2 through Day 28 or EOT, and on the day of hospital discharge. Serum chemistry tests are not required after hospital discharge. Results from unscheduled serum chemistry tests should be entered into the electronic database using an Unscheduled Serum Chemistry CRF. Analysis of serum chemistry results will be performed at local laboratories. Pacritinib/placebo dosage modifications will be implemented for clinically significant AEs identified with serum chemistry testing per the guidelines for "Treatment-Related Toxicities Other than QTcF Prolongation, Diarrhea, Bleeding, or Thrombocytopenia" (Section 6.5.6).

7.1.2.5 Liver Function Panel

Liver function parameters (aspartate aminotransferase [AST], alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, and albumin) will be evaluated at Screening (may be performed within 24 hours prior to the start of Screening), Day 8, Day 15 or EOT, Day 22, Day 28, and on the day of hospital discharge. Liver function panel tests are not required after hospital discharge. Results from unscheduled liver function panel tests should be entered into the electronic database using an Unscheduled Liver Function Panel CRF. Analysis of serum chemistry results will be performed at local laboratories. Pacritinib/placebo dosage modifications will be implemented for clinically significant AEs identified with serum chemistry testing per the guidelines for "Treatment-Related Toxicities Other than QTcF Prolongation, Diarrhea, Bleeding, or Thrombocytopenia" (Section 6.5.6).

7.1.2.6 ECG Assessment

An ECG will be performed at Screening (may be performed within 48 hours prior to the start of Screening), Day 3, Day 8, Day 15 or EOT, Day 22, Day 28, and on the day of hospital discharge if before EOT. Eligibility is to be based on QTcF of $\leq$ 480 msec. An ECG will also be performed on the day of hospital discharge if the patient will be continuing pacritinib/placebo as an outpatient; however, ECGs are not required after hospital discharge. Results from unscheduled ECG assessments should be entered into the electronic database using an Unscheduled ECG CRF. ECGs should be assessed using at least 3 leads; rhythm strips from telemetry monitoring are acceptable. Pacritinib/placebo modifications and follow-up monitoring for clinically significant ECG changes will be implemented as per the guidelines for "Dosage

Management Guidelines for QTcF Interval Prolongation" (Section 6.5.4). Additional ECG testing shall be done as clinically indicated.

7.1.2.7 Markers of Disease Severity

Blood samples for analysis of markers of disease severity (CRP, ferritin, D-dimer, IL-6, troponin-I, LDH, BNP, procalcitonin, , triglycerides, and CK) will be collected from all patients at Screening (may be performed within 24 hours prior to the start of Screening), before the morning dose on Day 3, Day 8, Day 15 or EOT, Day 22, Day 28, and on the day of hospital discharge. These markers do not need to be assessed after hospital discharge. The assessments for markers of disease severity are required if they can be performed at a local laboratory or if the study center has access to an external laboratory where the samples can be sent for analysis. If a study center does not have access to a local or external laboratory that can perform these assessments, the Investigator must provide written confirmation of the inability to perform the assessment(s), and approval from the CTI Medical Monitor is required to omit the assessment(s). Results from unscheduled tests for markers of disease severity should be entered into the electronic database using an Unscheduled Markers of Disease Severity CRF.

7.1.3 Informed Consent, Screening, and Washout of Prohibited Concomitant Medications Before Beginning Pacritinib/placebo

Informed consent must be obtained before any study procedures and Screening evaluations are performed, unless those evaluations are performed as part of SOC. Patients must provide informed consent within 96 hours after hospital admission. Patients who do not meet eligibility criteria at Screening may be rescreened at a later date.

The informed consent process should be documented in the patient's medical chart.

7.1.4 Summary of Study Assessments and Events by Day

7.1.4.1 Screening (Study Day -1 or 1)

The Screening evaluations listed below are to be carried out between Day -1 and Day 1 (prior to the start of treatment). Screening and randomization may occur on either Day -1 or Day 1. Patients may be screened, randomized, and started treatment on the same day (Day 1).

- Signing of ICF within 96 hours after hospital admission
- Demographics (age, sex, race, and ethnicity)
- Medical history
- Vital signs (blood pressure, pulse, respiratory rate, temperature, SpO2, and body weight)
- 7-point ordinal scale of clinical status
- SpO_2 in ambient air (if possible)

- SpO_2 with oxygen supplementation (if applicable)
- Highest %FiO2 (if on CPAP, BiPAP, or IMV)
- Highest PEEP)(if on positive pressure ventilation)
- ECG (at least 3 leads; may be performed within 48 hours prior to the start of Screening)
- Serum chemistry, including sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, and magnesium (The results of laboratory assessments performed in the emergency room [ER] or upon hospital admission that are relevant for the determination of eligibility may be used to confirm eligibility provided that they have been performed within 24 hours prior to the start of Screening.)
- Liver function panel, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin, and albumin (The results of laboratory assessments performed in the ER or upon hospital admission that are relevant for the determination of eligibility may be used to confirm eligibility provided that they have been performed within 24 hours prior to the start of Screening.)
- CBC, including WBC count, hemoglobin, hematocrit, and platelet count (The results of laboratory assessments performed in the ER or upon hospital admission that are relevant for the determination of eligibility may be used to confirm eligibility provided that they have been performed within 24 hours prior to the start of Screening.)
- WBC differential (The results of laboratory assessments performed in the ER or upon hospital admission that are relevant for the determination of eligibility may be used to confirm eligibility provided that they have been performed within 24 hours prior to the start of Screening.)
- SARS-CoV-2 RT-PCR test or an antigen-based test from any respiratory, nasopharyngeal, saliva, blood, or stool specimen at Screening or documented within 1 week prior to the start of Screening
- Coagulation tests, including INR, PTT, and fibrinogen
- CRP
- Ferritin
- D-dimer
- IL-6
- Troponin-I
- LDH

- BNP
- Procalcitonin
- Triglycerides
- CK
- Serum pregnancy test for women of childbearing potential prior to randomization, which may be performed at any time after arrival to the emergency room or hospital admission
- Chest imaging assessments performed in the ER or upon hospital admission may be used for screening documentation.
- Documentation of oxygen delivery method, which may include nasal cannula, non-rebreather, non-invasive positive pressure ventilation (eg, CPAP or BiPAP), or IMV
- Concomitant medications

7.1.4.2 Randomization (Study Day -1 or 1)

Patients must have provided informed consent, then completed all Screening procedures, and met all eligibility criteria.

Note: Screening and randomization may occur on either Day -1 or Day 1. Patients may be screened, randomized, and start treatment on the same day (Day 1).

- AE reporting will begin at the time of randomization

7.1.4.3 Study Day 1 (Pre-dose)

Note: Patients may be screened, randomized and start treatment on the same day.

- Randomization
- 7-point ordinal scale of clinical status (unless the same time point as Screening)
- Physical examination (any physical examination performed as part of routine care on Day 1 prior to signing of informed consent may be used for documentation)
- Maximum documented temperature in the 24 hours prior to dose of pacritinib/placebo (T_{max})
- Maximum documented heart rate in the 24 hours prior to dose of pacritinib/placebo (HR_{max})

- Documentation of oxygen delivery method (unless the same time point as Screening). If multiple delivery methods were used, the method that provides the highest concentration of oxygen will be documented.
- Highest oxygen delivery flow rate (if on non-invasive oxygen)
- Highest %FiO2 (if on CPAP, BiPAP, or IMV)
- Highest PEEP (if on positive pressure ventilation)
- Begin pacritinib/placebo dosing
- Document pacritinib/placebo dosing
- AEs
- Concomitant medications

7.1.4.4 Daily Assessment (Day 2 to Day 28)

Daily assessment evaluations listed below are to be carried out from Day 2 to Day 28 unless otherwise noted. If patient is discharged, refer to Section 7.1.4.8 for outpatient assessments.

- 7-point ordinal scale of clinical status
- Physical examination (Day 8 [or on the day of hospital discharge if before EOT], Day 15 or EOT, Day 22, and Day 28)
- Maximum temperature documented during the calendar day (T_{max})
- Maximum heart rate documented during the calendar day (HR_{max}) (Days 2 through 14)
- SpO_2 in ambient air (if possible) (lowest value documented during the calendar day)
- SpO_2 with oxygen supplementation (if applicable) (lowest value documented during the calendar day)
- ECG (Day 3, Day 8, Day 15, Day 22, Day 28, and on the day of hospital discharge if before EOT; not required after hospital discharge but must be performed on the day of discharge if the patient will be continuing pacritinib/placebo as an outpatient)
- Serum chemistry, including sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, and magnesium
- Liver function panel, including AST, ALT, alkaline phosphatase, total bilirubin, and albumin (Day 8, Day 15, Day 22, Day 28)
- CBC, including WBC count, hemoglobin, hematocrit, and platelet count

- WBC differential (Day 8, Day 15, Day 22, and Day 28)
- Coagulation tests, including INR, PTT, and fibrinogen (Day 8, Day 15, Day 22, and Day 28; samples can be collected on other days as clinically indicated)
- CRP (before the morning dose on Day 3, Day 8, Day 15 or EOT, Day 22, and Day 28; samples can be collected on other days as clinically indicated)
- Ferritin (before the morning dose on Day 3, Day 8, Day 15, Day 22, and Day 28; samples can be collected on other days as clinically indicated)
- D-dimer (before the morning dose on Day 3, Day 8, Day 15, Day 22, and Day 28; samples can be collected on other days as clinically indicated)
- IL-6 (before the morning dose on Day 3, Day 8, Day 15 or EOT, Day 22, and Day 28; samples can be collected on other days as clinically indicated)
- Troponin-I (before the morning dose on Day 3, Day 8, Day 15 or EOT, Day 22, and Day 28; samples can be collected on other days as clinically indicated)
- LDH (before the morning dose on Day 3, Day 8, Day 15, Day 22, and Day 28; samples can be collected on other days as clinically indicated)
- BNP (before the morning dose on Day 3, Day 8, Day 15 or EOT, Day 22, and Day 28; samples can be collected on other days as clinically indicated)
- Procalcitonin (before the morning dose on Day 3, Day 8, Day 15 or EOT, Day 22, and Day 28; samples can be collected on other days as clinically indicated)
- Triglycerides (before the morning dose on Day 3, Day 8, Day 15, Day 22, and Day 28)
- CK (before the morning dose on Day 3, Day 8, Day 15, Day 22, and Day 28; samples can be collected on other days as clinically indicated)
- Documentation of oxygen delivery method, which may include nasal cannula, non-rebreather, non-invasive positive-pressure ventilation (eg, CPAP or BiPAP), or IMV. If multiple delivery methods were used, the method that provides the highest concentration of oxygen will be documented.
- Highest oxygen delivery flow rate (if on non-invasive oxygen)
- Highest %FiO2 (if on CPAP, BiPAP, or IMV)
- Highest PEEP (if on positive pressure ventilation)

- Lowest partial pressure of oxygen (PaO2):FiO2 ratio (if applicable); if ABG has been assessed while the patient is on IMV, then the PaO2 should be documented along with the FiO2 set on the ventilator at the time of the ABG assessment

- Administer pacritinib/placebo (Days 2 through 14; Pacritinib/placebo may be given for an additional 7 days [through Day 21] 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.)

- Documentation of pacritinib/placebo dosing (Days 2 through 14; Pacritinib/placebo may be given for an additional 7 days [through Day 21] 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.)

- AEs

- Concomitant medications

7.1.4.5 End of Treatment

- 7-point ordinal scale of clinical status

- Physical examination

- T_{max}

- HR_{max}

- SpO_2 in ambient air (if possible) (lowest value documented during the calendar day)

- SpO_2 with oxygen supplementation (if applicable) (lowest value documented during the calendar day)

- ECG

- Serum chemistry, including sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, and magnesium

- Liver function panel, including AST, ALT, alkaline phosphatase, total bilirubin, and albumin

- CBC, including WBC count, hemoglobin, hematocrit, and platelet count

- WBC differential

- Coagulation tests, including INR, PTT, and fibrinogen

- CRP

- Ferritin
- D-dimer
- IL-6
- Troponin-I
- LDH
- BNP
- Procalcitonin
- Triglycerides
- CK
- Documentation of oxygen delivery method, which may include nasal cannula, non-rebreather, non-invasive positive pressure ventilation (eg, CPAP or BiPAP), or IMV. If multiple delivery methods were used, the method that provides the highest concentration of oxygen will be documented.
- Highest oxygen delivery flow rate (if on non-invasive oxygen)
- Highest $\%FiO_2$ (if on CPAP, BiPAP, or IMV)
- Highest positive end-expiratory pressure (PEEP; if on positive pressure ventilation)
- Lowest partial pressure of oxygen (PaO_2):FiO_2 ratio (if applicable); if arterial blood gas (ABG) has been assessed while the patient was on IMV, then the PaO_2 should be documented along with the FiO_2 set on the ventilator at the time of the ABG assessment
- Administer pacritinib/placebo (Days 2 through 14; Pacritinib/placebo may be given for an additional 7 days [through Day 21] 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.)
- Documentation of pacritinib/placebo dosing (Days 2 through 14; Pacritinib/placebo may be given for an additional 7 days [through Day 21] 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.)
- AEs
- Concomitant medications

7.1.4.6 30-day Post-EOT Follow-up (± 3 days)

AEs and concomitant medications are to be documented through 30 days after the last dose of pacritinib/placebo.

- AEs
- Concomitant medications

7.1.4.7 Day of Hospital Discharge

- 7-point ordinal scale of clinical status
- Physical examination
- Maximum temperature documented during the calendar day (T_{max})
- Maximum heart rate documented during the calendar day (HR_{max})
- SpO_2 in ambient air (if possible) (lowest value documented during the calendar day)
- SpO_2 with oxygen supplementation (if applicable) (lowest value documented during the calendar day)
- ECG (only if the patient will be continuing pacritinib/placebo as an outpatient)
- Serum chemistry, including sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, glucose, calcium, and magnesium
- Liver function panel, including AST, ALT, ALP, total bilirubin, and albumin
- CBC, including WBC count, hemoglobin, hematocrit, and platelet count
- WBC differential
- Coagulation tests, including INR, PTT, and fibrinogen
- CRP
- Ferritin
- D-dimer
- IL-6
- Troponin-I
- LDH

- BNP
- Procalcitonin
- Triglycerides
- CK
- Documentation of oxygen delivery method, which may include nasal cannula, non-rebreather, non-invasive positive pressure ventilation (eg, CPAP or BiPAP), or IMV. If multiple delivery methods were used, the method that provides the highest concentration of oxygen will be documented.
- Highest oxygen delivery flow rate (if on non-invasive oxygen)
- Lowest partial pressure of oxygen (PaO_2):FiO_2 ratio (if applicable); if ABG has been assessed while the patient was on IMV, then the PaO2 should be documented along with the FiO_2 set on the ventilator at the time of the ABG assessment
- Administer pacritinib/placebo (Days 2 through 14; pacritinib/placebo may be given for an additional 7 days [through Day 21] 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.)
- Documentation of pacritinib/placebo dosing (Days 2 through 14; pacritinib/placebo may be given for an additional 7 days [through Day 21] 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.)
- AEs
- Concomitant medications

7.1.4.8 Outpatient Assessments

- 7-point ordinal scale of clinical status (Daily scores through Day 28 will be evaluated and will be based on weekly assessments performed on Day 8, Day15, Day 22, and Day 28 [±2 days].)
- Documentation of pacritinib/placebo dosing for patients who continue treatment after discharge from the hospital
- AEs (will be documented through 30 days after the last dose of pacritinib/placebo and will be based on weekly assessments [±2 days] through 30 days after last dose)

- Concomitant medications (will be documented through 30 days after the last dose of pacritinib/placebo and will be based on weekly assessments [±2 days] through 30 days after last dose)

Note: Outpatient assessments should be based on weekly telephone/videoconference communication with the patient and include an evaluation of the **daily** 7-point ordinal scale score for the days between contacts and daily pacritinib/placebo dosing as outlined in Table 1. More frequent telephone/videoconference contact may occur as needed to supplement the above assessments. Review of medical records may also be performed as needed to supplement these assessments; medical records should be reviewed for patients who cannot be reached by telephone/videoconference.

8 ASSESSMENT OF SAFETY

8.1 Adverse Events

8.1.1 Definition of an Adverse Event

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

Examples of AEs are as follows:

- Any unfavorable and unintended sign, including an abnormal laboratory finding, symptom, medical diagnosis, or concomitant disease temporally associated with the use of pacritinib/placebo, whether considered related to pacritinib/placebo or not

- Abnormalities observed during the study that meet any of the criteria below:

  – A laboratory or other test result that is clinically significant or requires active intervention, retesting, or ongoing medical monitoring

  – Requires discontinuation, dosage reduction, or delay of pacritinib/placebo

  – Requires that the patient receive specific corrective or supportive therapy

  – Clinically significant changes noted during physical examinations, cardiac monitoring, imaging studies, biopsies, and other safety assessments, whether or not these procedures were required by the protocol

Progressive disease and signs and symptoms of progressive disease should not be reported as AEs.

8.1.2 Reporting Adverse Events

Baseline conditions and medical history will be collected at the time of informed consent. 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.

AEs can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of the patient or may be detected through a clinically meaningful procedure. To prevent bias, patients should not be questioned regarding the specific occurrence of one or more AEs.

The following information should be captured for all AEs: date of onset and resolution, severity per Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, 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).

When recording AEs, the diagnosis of the underlying illness or disorder should be used as the event term or description on the eCRF and symptoms of the illness or disorder should not be reported as separate AEs. It is expected that whenever possible the clinical term, rather than the laboratory term, for the AE will be used by the reporting investigator (e.g., "anemia" versus "low hemoglobin value").

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.

Special Considerations

- Elective procedures or routinely scheduled treatments are not AEs. However, any untoward medical event occurring during a prescheduled elective procedure or routinely scheduled treatment should be documented as an AE.

- Baseline conditions are not AEs; however, worsening of a Baseline condition following pacritinib/placebo administration is an AE.

- Death alone is not considered an AE; it can be an outcome of an AE. Reports of death should be accompanied by the corresponding AE term for the event that led to the outcome of death. However, sudden death or death due to unexplainable cause(s) should be reported as an SAE, while follow-up is pursued to determine the cause.

8.1.3 Criteria for Assessing Adverse Events

8.1.3.1 Severity

The term "severe" is a measure of intensity; a severe event is not necessarily serious.

The National Cancer Institute CTCAE version 4.03 should be used to assess and grade AE severity, including laboratory abnormalities identified as AEs. A copy of these criteria is

provided in the study manual; however, minor version updates (i.e., 4.01, 4.02, and above) may be used at the discretion of the Sponsor.

8.1.3.2 Relationship

The relationship of an AE to pacritinib/placebo will be assessed using the guidelines described below. Any AE for which there is no assessed causal relationship shall be assessed by the Sponsor as related and will require immediate follow-up with the site to determine the investigator's assessment.

Possibly

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 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.

8.1.3.3 Outcome

AEs will be characterized according to the outcomes described in Table 7.

Table 7. Outcomes of Adverse Events

Outcome	Description
Recovered/Resolved	One of the possible results of an adverse event outcome that indicates that the event has improved or recuperated
Recovered/Resolved with Sequelae	One of the possible results of an adverse event outcome where the patient recuperated but retained pathological conditions resulting from the prior disease or injury
Recovering/Resolving	One of the possible results of an adverse event outcome that indicates that the event is improving
Not Recovered/Not Resolved	One of the possible results of an adverse event outcome that indicates that the event has not improved or recuperated
Fatal	The termination of life as a result of an adverse event
Unknown	Not known, not observed, not recorded, or refused

8.1.3.4 Action Taken With Pacritinib/placebo

Action taken with pacritinib/placebo in relation to the AE will be characterized as follows:

- Dosage not changed
- Dosage reduced (includes dose holds followed by dose reduction)
- Drug interrupted (and resumed at the same dose)
- Drug withdrawn
- Not applicable (patients who did not receive a dose of pacritinib/placebo)
- Unknown

8.1.4 Serious Adverse Events

8.1.4.1 Definition of a Serious Adverse Event

An SAE is an AE that, at any dosage, suggests a significant hazard or side effect, regardless of its relationship to pacritinib/placebo. An AE is serious if it meets any of the criteria below:

1. Results in death
2. Is life-threatening: in the view of the investigator, the event placed the patient at immediate risk of death. This does not include an AE that, had it occurred in a more severe form, might have caused death.
3. Requires rehospitalization after discharge from the hospital or prolongation of an existing hospitalization (see Section 8.1.4.2)
4. Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions
5. Is a congenital anomaly/birth defect
6. Is an important medical event that is not fatal, life threatening, or requiring hospitalization but may be considered serious if, based on appropriate medical judgment, the event jeopardized the patient and required medical or surgical intervention to prevent one of the outcomes listed above (Items 1 to 5)
7. Cancer/overdose: All cases of new cancers and drug overdose (defined as accidental or intentional ingestion of any dosage of a product that is considered both excessive and medically important) must be reported immediately using the SAE form. All cases of drug overdose, irrespective of seriousness or association with AE(s), must be reported to the Sponsor within 24 hours. Determination of seriousness will be reached in consultation with the Safety Physician, CTI BioPharma Corp. Pharmacovigilance United

States (US) Headquarters or designee. Additional instructions for reporting cancer/overdose information will be provided by the Sponsor in the study binder.

8.1.4.2 Exceptions

Re-hospitalizations not reported as SAEs include admissions for the following:

1. Planned, non-life-threatening medical/surgical procedures (e.g., admission for transfusion as required per local medical practice)

2. Routine health assessments requiring admission for health status documentation (e.g., routine gastroscopy, and colonoscopy)

3. Other life circumstances that have no bearing on health status and require no medical/surgical intervention (e.g., lack of housing and family circumstances)

4. Administration of study medication

8.1.4.3 Reporting Serious Adverse Events to the Sponsor

SAEs, irrespective of causal relationship, will be collected during the clinical study from the time the patient provides informed consent through 30 days following the last dose of pacritinib/placebo. The site must send the paper SAE form via email (SAE@CTIbiopharma.com) within 24 hours of the site's first awareness of an SAE.

Special Considerations:

- SAEs considered to be possibly related 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 unlikely related 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.

- For screened patients who are not randomized, only SAEs occurring between the time of informed consent and determination of screen failure are reported.

- All SAEs for randomized patients must have a corresponding AE recorded on the eCRF with an exact match to the event term or description.

- An SAE form should be completed for any event for which doubt exists regarding its seriousness.

- If an ongoing SAE changes in intensity, relationship to pacritinib/placebo, or as new information becomes available and/or known for the event, a follow-up SAE report

should be completed and sent to the Sponsor within 24 hours of the change in SAE assessment.

- Any SAE that occurs after treatment completion and is considered by the investigator to be related to pacritinib should be reported to the Sponsor.

A brief narrative outlining the details of the SAE and treatment and outcome is to be included on the SAE form. Follow-up information, such as laboratory reports, discharge summaries, autopsy reports, and information concerning outcome of the event, should be provided, as soon as the information becomes available and provided to CTI Pharmacovigilance via email at SAE@CTIbiopharma.com or fax (1-866-660-8967).

Source documents should be submitted in English. If source documents are not in English, the investigator must summarize the source documents and provide a complete English narrative that includes a description of the event as it evolved, the results of all diagnostic procedures performed and treatments administered, and the outcome of the event.

8.1.4.4 Reporting Serious Adverse Events to the Regulatory Agencies, Institutional Review Boards, and/or Ethics Committees

The Sponsor will assess SAEs for expedited reporting against the most current approved version of the Investigator Brochure. Until an AE is identified in the Reference Safety Information of the Investigator's Brochure or Summary of Product Characteristics, it is considered unexpected, regardless of whether the AE has been submitted previously as an expedited report.

Expedited reporting will be performed by the Sponsor in accordance with regulatory requirement.

Upon receiving an expedited report, the investigator must review and retain the notice with the Investigator Brochure and shall be responsible for submitting expedited reports to their Institutional Review Board (IRB)/Ethics Committee (EC) in accordance with institutional guidelines. Regardless of institutional guidelines, investigators shall submit expedited reports to their IRB/EC in the event that the Sponsor identifies an expedited report to represent a new and/or unforeseen risk.

In support of required progress reports, the Sponsor will provide the investigator and/or EC with a summary of all SAEs reported for the study at predefined intervals (e.g., quarterly) and/or upon request.

Pregnancy

Pregnancy alone is not considered as an AE. However, if a patient becomes pregnant or causes a pregnancy during treatment and/or within 3 months of ending treatment even if the patient is withdrawn from study, this must be reported to the Sponsor immediately on the Pregnancy Reporting Form. The investigator must obtain written authorization (medical records release) from a female partner of a male patient prior to obtaining follow-up.

The investigator must follow the pregnancy either to term or termination and will collect data on both maternal and fetal outcome. All pregnancy outcomes will be recorded on the Pregnancy Reporting Form. Additional instructions for reporting pregnancy information will be provided by the Sponsor in the study binder.

Normal outcomes will be communicated to the Sponsor within 30 calendar days of birth/delivery. Abnormal pregnancy outcomes and/or any AE for the child or fetus (including miscarriage) will also be recorded in the AE eCRF and on the SAE form. The associated SAE Report Form should be sent to the Sponsor per the procedure and timelines described within Section 8.1.4.3.

Overdose

Overdose is defined as any deviation from the defined or prescribed use of pacritinib/placebo as applicable for the drug and study design. Occurrences of overdose should be reported to the Sponsor on an SAE Report Form. Reports of overdose will be evaluated on a case by case basis. Additional instructions for reporting overdose information will be provided by the Sponsor in the study binder.

Deaths

All deaths that occur during the study must be recorded on the appropriate eCRF. As described in Sections 8.1.2 and 8.1.3.1, death alone is not considered as an AE; it is an outcome of an AE. Reports of death should be accompanied by the corresponding AE term for the event that led to the outcome of death.

Sudden death or death due to unexplainable cause(s) should be reported as an SAE, while follow-up is pursued to determine the cause.

8.2 Laboratory Evaluation

All clinical laboratory test values collected during the study will be evaluated by local laboratories and entered into the electronic data capture (EDC). In addition, any unscheduled laboratory test results must be entered into the EDC using an Unscheduled Local Laboratory CRF.

8.3 Vital Signs and Physical Examination

Vital signs (blood pressure, pulse, respiratory rate, temperature, SpO2, and body weight) and physical examinations will be obtained at Screening.

8.4 Safety Surveillance

8.4.1 Routine Pharmacovigilance Monitoring

The Sponsor will monitor safety data during the clinical study by examining the incidence and severity of AEs and changes in laboratory results. Clinically important increases in the rate of serious adverse reactions will be communicated to the IDMC (see Section 2.2), investigators, and

regulatory agencies, as appropriate. A clinically important increase will be considered an increase in frequency and/or severity in an event that leads to a serious outcome and exceeds the rate(s) of the reported event listed in the Investigator Brochure reference safety information. In addition, if the sponsor observes a difference of > 6% in the frequency (and a difference of ≥ 2 patients between the 2 arms) of grade 4 or 5 treatment-related AEs in the pacritinib arm compared to the placebo + SOC arm, the IDMC will be convened to review the risk profile and render a recommendation regarding study continuation. The FDA and other Competent Authorities will be notified of any IDMC meeting that is convened under these circumstances, and the resultant decision will be reported to the FDA within 2 business days.

Single events assessed as serious, unexpected, and related will continue to be reported on an expedited basis per regulatory requirement.

9 MARKERS OF DISEASE SEVERITY

9.1 Blood Sample Collection, Handling, and Shipping

Blood samples for analysis of markers of disease severity should be collected in appropriate blood collection tubes as defined in the study manuals. Analyses will be performed in local or external laboratories. The time/date when the prior dose was administered must be recorded in the source documents and on the appropriate CRF page.

9.2 Disease Severity Assessments

Blood samples for analysis of markers of disease severity will be collected from all patients at Screening (may be performed within 24 hours prior to the start of Screening), before the morning dose on Day 3, Day 8, Day 15 or EOT, Day 22, Day 28, and on the day of hospital discharge. Samples may be collected on other days as clinically indicated. These markers do not need to be assessed after hospital discharge. The assessments for markers of disease severity are required if they can be performed at a local laboratory or if the study center has access to an external laboratory where the samples can be sent for analysis. If a study center does not have access to a local or external laboratory that can perform these assessments, the Investigator must provide written confirmation of the inability to perform the assessment(s), and approval from the CTI Medical Monitor is required to omit the assessment(s). Results from unscheduled tests for markers of disease severity should be entered into the electronic database using an Unscheduled Markers of Disease Severity CRF.

Markers of disease severity will be analyzed for Baseline characteristics and changes over time.

10 DATA MANAGEMENT

The CTI BioPharma Corp. Clinical Data Management Department or its designee will prepare guidelines for data entry and data handling, which will include procedures for data verification and electronic edit checks. The complete data management process will be described in the Data Management Plan.

10.1 Data Collection

An EDC system will be used for this study. Designated site personnel will enter patient data required by the protocol into eCRFs based on source documents. Personnel will not receive access to the EDC system until they have completed all training requirements. The EDC system will provide an automatic audit trail of all changes made to the clinical database.

10.2 Data Entry and Quality Control

Data items will be entered directly from source documents by designated site personnel using single data entry. Concomitant medications entered into the database will be encoded using the World Health Organization Drug Reference Dictionary. AEs, coexisting disease, and other data items will be encoded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

CTI BioPharma Corp. staff or designees will review the data on a periodic basis to ensure validity, accuracy, and completeness. Data suspected to be discrepant or incomplete will be questioned using data queries. Data queries resulting from these reviews will be sent to the study sites via the EDC system. The staff at the study sites will respond to the queries in the EDC system, and these responses will be reviewed by CTI BioPharma Corp. staff or designee.

11 STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

Statistical analysis of the study data will be the responsibility of CTI BioPharma Corp. Biostatistics Department or its designee. This section describes the statistical methodology used in the analysis of the primary and secondary safety and efficacy endpoints. Details of the analyses will be specified in a separate statistical analysis plan (SAP).

Categorical and nominal variables will be summarized by frequency and percentage. Continuous variables will be summarized by descriptive statistics such as n, mean, median, standard deviation, minimum, and maximum. Ordinal variables will be summarized by frequency distribution of scores and by summary statistics on the scores or shift tables, as appropriate. Where appropriate, 95% confidence intervals around point estimates will be presented.

11.1 Endpoints for the Analysis

11.1.1 Efficacy

Primary Endpoint

The primary efficacy endpoint is the proportion of patients who progress to IMV and/or ECMO or death during the 28 days following randomization. The proportion is calculated as the number of patients who progress divided by the total number of patients in the ITT population.

Secondary Endpoints

1. The number of ventilator-free days, defined as the number of days that patients are alive and not intubated, from randomization to Day 28

2. The mortality rate at Day 28 is defined as the number of patients with outcome of death during the 28 days following randomization divided by the total number of patients in the ITT population

3. The mortality rate at Day 15 is defined as the number of patients with outcome of death in the 15 days following randomization divided by the total number of patients in the ITT population.

4. The time to improvement by at least 2 points relative to Baseline on the 7-point ordinal scale of clinical status. All enrolled patients will have a score between 3 and 5 by virtue of being hospitalized and non-intubated; therefore, patients who progress from 3 to 1, from 4 to 2, or from 5 to 3 will have met the definition of improvement.

5. The clinical status as assessed by the 7-point ordinal scale of clinical status at Days 8, 15, 22, and 28.

6. The rate of use of immunomodulatory agents as treatment for COVID-19 is defined as the proportion of patients reporting use of medications such as corticosteroids, tocilizumab, anakinra, or eculizumab as treatment for COVID-19, during 28 days following randomization divided by the patients in the ITT population.

Tertiary Endpoints

- CRP
- Ferritin
- D-dimer
- IL-6
- Troponin-I
- LDH
- BNP
- Procalcitonin
- Triglycerides

- CK
- Triglycerides

11.1.2 Safety Endpoints

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

11.2 Analysis Populations

11.2.1 Primary Analysis Intent-to-Treat Population

The Intent-to-treat (ITT) population is defined as all patients randomized. 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.

11.2.2 Safety Population

The Safety population is defined as all randomized patients who received at least one dose of study treatment. Patients in this population will be analyzed according to the treatment actually received. This population will be used for the analysis of safety endpoints.

11.3 Efficacy Analysis

All efficacy analyses will be performed using the ITT population.

Primary Endpoint

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 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 proportion of patients who progress to IMV and/or ECMO or death will be presented by treatment arm. The CMH odds ratio, difference in progression rates, and associated 95% confidence intervals will be presented.

Secondary Endpoints

The number of ventilator-free days will be presented by treatment arm using descriptive statistics including mean, median, standard deviation, interquartile range, and may include frequency distributions.

The mortality rate at 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 (baseline 3 or 4 versus 5). The point estimates and 95% confidence intervals of the mortality rates at

Day 28 will be presented by treatment arm. The CMH odds ratio, difference in mortality rates at Day 28, and associated 95% confidence intervals will be presented.

The mortality rate at Day 15 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 mortality rates at Day 15 will be presented by treatment arm. The CMH odds ratio, difference in mortality rates at Day 15, and associated 95% confidence intervals will be presented.

The time from randomization to improvement by at least 2 points relative to Baseline on the 7-point clinical status will be compared between treatment arms using a stratified log-rank test stratified by age (< 60 years versus ≥ 60 years) and baseline 7-point clinical status scale (baseline 3 or 4 versus 5). All enrolled patients will have a score between 3 and 5 by virtue of being hospitalized and non-intubated; therefore, patients who progress from 3 to 1, from 4 to 2, or from 5 to 3 will have met the definition of improvement. 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 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).

The clinical status assessed by the 7-point ordinal scale of clinical status at Days 8, 15, 22, and 28 will be presented by treatment arm using counts and percent of patients at each level of the 7-point scale score.

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.

Details of the analysis of tertiary endpoints will be specified in the SAP.

11.4 Safety Analysis

All safety analyses will be performed on the Safety population.

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

TEAEs will be coded using MedDRA and summarized by SOC, PT, and treatment arm as the number and percentage of patients with an event. The following subsets of TEAEs will also be summarized by treatment arm: AEs related to study treatment, AEs by CTCAE v4.03 grade, AEs leading to treatment discontinuation, and SAEs.

Clinical laboratory data will be assigned a CTCAE v4.03 grade and summarized with descriptive statistics and, where possible, in shift tables comparing the worst post-baseline shift relative to baseline.

11.5 Subgroup Analysis

The following subgroup analyses may be performed:

- Age (< 60 years, ≥ 60 years)
- Sex (male versus female)
- Race (Caucasian versus all others)
- 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)
- History of invasive cancer (yes/no)

11.6 Determination of Sample Size

Our hypothesis is that pacritinib would reduce the risk of these events to 13.5% by Day 28. 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 death by Day 28, assuming that the response rate is 13.5% in the pacritinib and SOC arm and 26.5% in the placebo and SOC arm, with a one-sided Type I error rate of 0.10.

11.7 Analysis of Markers of Disease Severity

Markers of disease severity data will be summarized using descriptive statistics.

12 INDEPENDENT DATA MONITORING COMMITTEE

See Section 2.2 for a description of the composition and responsibilities of the IDMC.

13 STUDY ADMINISTRATION AND INVESTIGATOR OBLIGATIONS

For studies conducted outside the US under a US Investigational New Drug (IND), the principal investigator must comply with US FDA IND regulations and with those of relevant national and local health authorities.

13.1 Pacritinib Accountability

CTI BioPharma Corp. will provide pacritinib and matching placebo. The recipient will acknowledge receipt of the drug by returning the appropriate shipping receipt form according to the study-specific pharmacy manual. Damaged supplies will be replaced.

Accurate records of all pacritinib/placebo dispensed from and returned to the study site should be recorded by using the Drug Inventory Log (refer to study-specific pharmacy manual).

Pacritinib/placebo will be disposed of at the study site according to institutional standard operating procedures after study monitors have completed the drug inventory reconciliation. If a site cannot or prefers not to dispose the clinical material locally, the pacritinib/placebo must be returned by the site to the clinical supplier, Almac. The method of destruction must be documented. A copy of the destruction certification along with the inventory of destroyed clinical material will be provided to CTI BioPharma Corp.

13.2 Informed Consent

CTI BioPharma Corp. will provide a sample ICF to each site for submission and approval by site's IRB, Research Ethics Board (REB), or Independent Ethics Committee (IEC). CTI BioPharma Corp. or its designee must review and approve any proposed deviations from the sample ICF. Patients must be re-consented to the most current IRB/REB/IEC approved version of the ICF during their participation in the study. The investigator must provide the final IRB/REC/IEC approved ICF to CTI BioPharma Corp. for regulatory purposes.

The patient or the patient's legally authorized representative must sign the ICF before his or her participation in the study. The source record for each patient shall document that informed consent was obtained prior to participation in the study. A copy of each signed ICF or Addendum to an existing ICF must be provided to the patient or the patient's legally authorized representative. If applicable, it will be provided in a certified translation of the local language.

All signed consent forms must remain in each patient's study file and must be available for verification by the study monitor, Sponsor representative, or regulatory agency at any time.

13.3 Disclosure of Data

Patient medical information obtained by this study is confidential, and disclosure to third parties other than those noted below is prohibited.

Upon the patient's permission, medical information may be given to his or her personal physician or other appropriate medical personnel responsible for his or her welfare.

Data generated by this study must be available for inspection upon request by representatives of the US FDA, national and local health authorities, CTI BioPharma Corp., its designees and the IRB/REB/IEC for each study site, if appropriate.

13.4 Case Report Forms

CTI BioPharma Corp. will provide eCRFs, which should be completed in accordance with instructions from CTI BioPharma Corp.

13.5 Study Monitoring

Representatives of CTI BioPharma Corp. or their designee must be allowed to monitor all study site locations at appropriate intervals to assure compliance with Good Clinical Practice (GCP), satisfactory enrollment rate, data recording, and protocol adherence. The frequency of monitoring may vary depending on enrollment rate and the quality of data collected. The investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. The investigator agrees to cooperate with the monitor to ensure any problems detected in the course of these monitoring visits are resolved. In addition to these visits, CTI BioPharma Corp. or designee may monitor each site by phone to keep abreast of patient status and to answer questions.

In order for the investigator to participate in this study, the study monitor must be able to perform source data for verification remotely (ie, without having to physically visit the site). This will be done by comparing data from the eCRFs with data from the patient's clinic or hospital records (permission will be sought from the patient as part of the consent process).

In addition, CTI BioPharma Corp. internal auditors and government inspectors may evaluate the study. They must be allowed access to eCRFs, source documents, and other study files. CTI BioPharma Corp. audit reports will be kept confidential.

The investigator should promptly notify CTI BioPharma Corp. of an audit scheduled by any regulatory authority, and immediately forward copies of audit reports.

13.6 Record Retention

US FDA regulations (21CFR§312.62[c]) and the International Council for Harmonisation (ICH) Guideline for GCP (see Section 4.9 of the guideline) require that the principal investigator retain records and documents pertaining to the conduct of the study and distribution of investigational drug, including eCRFs, consent forms, laboratory test results, radiographic assessments, and medication inventory records for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply. CTI BioPharma Corp. will notify the principal investigator of these events.

No records should be disposed of without the written approval of CTI BioPharma Corp.

14 ETHICS

14.1 Good Clinical Practice

The investigator and Sponsor will ensure that this study is conducted in full compliance with Declaration of Helsinki, ICH guidelines, US FDA regulations 21 CFR Parts 50, 56, and 312, and

with the laws and regulations of the country in which the research is conducted, whichever affords the greatest protection to the study patient.

14.2 Institutional Review Board/Research Ethics Board/Independent Ethics Committee

The appropriate IRB, REB, or IEC must approve in writing the protocol and ICF for this study in accordance with the laws and regulation of the country in which the research is conducted prior to any patient being registered in this study.

Before the investigational drug will be shipped to the investigator, the investigator must provide CTI BioPharma Corp. with a copy of the IRB/REB/IEC approval letter stating that the study protocol and ICF have been reviewed and approved. Original US FDA Form 1572 (for all studies conducted under US IND regulations) signed by the principal investigator, and a copy of the curriculum vitae for the principal investigator, and a copy of an IRB/REB/IEC approved ICF are also required.

The investigator must also report all serious and medically significant AEs to the IRB/REB/IEC according to the local regulation. Appendix 4 lists the responsibilities of the investigator.

15 TERMINATION OF STUDY

CTI BioPharma Corp. will retain the right to terminate the study and remove all the study materials from the study site at any time. Specific instances that may precipitate such termination are as follows:

- Unsatisfactory enrollment with regard to quality or quantity
- Deviations from GCP
- Deviation from protocol requirements, without prior approval from CTI BioPharma Corp.
- Inaccurate and/or incomplete data recording on a recurrent basis
- The incidence and/or severity of adverse drug events in this or other studies indicating a potential health hazard caused by the treatment

In addition, if the sponsor observes a difference of > 6% in the frequency (and a difference of ≥ 2 patients between the 2 arms) of grade 4 or 5 treatment-related AEs in the pacritinib arm compared to the placebo + SOC arm, the IDMC will be convened to review the risk profile and render a recommendation regarding study continuation. The FDA and other Competent

Authorities will be notified of any IDMC meeting that is convened under these circumstances, and the resultant decision will be reported to the FDA within 2 business days.

In terminating the study, CTI BioPharma Corp. and the investigator will assure adequate consideration to the protection of the patients' interest.

16 STUDY AMENDMENTS

Changes in any portion of this protocol must be documented in the form of an amendment from CTI BioPharma Corp. and must be approved by the site's IRB/REB/IEC before the amendment can be implemented at the site. The IRB/REB/IEC chairperson may approve minor changes, or may designate one or more regulatory members to approve revisions. In addition, substantial amendments made to this protocol will require approval by the appropriate regulatory authority prior to implementation.

17 USE OF INFORMATION AND PUBLICATION

CTI BioPharma Corp. recognizes the importance of communicating medical study data and therefore encourages their publication in reputable scientific journals and at seminars or conferences. The Clinical Study Agreement will describe the details of the processes of producing and reviewing reports, manuscripts, and presentations based on the data from this study.

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19 APPENDICES

Appendix 1 - Selected Strong Inhibitors of CYP3A4

boceprevir	nefazodone
ciprofloxacin	nelfinavir
clarithromycin	norfloxacin
conivaptan	posaconazole
erythromycin	quinidine
fluconazole	ritonavir
grapefruit	saquinavir
grapefruit juice	Seville oranges
indinavir	star fruit
itraconazole	telaprevir
ketoconazole	telithromycin
lopinavir	troleandomycin
mibefradil	voriconazole

This list is not comprehensive. When considering using an agent that could be a potential CYP3A4 inhibitor, please discuss this with the medical monitor.
Source: http://medicine.iupui.edu/clinpharm/ddis/table.asp and http://www.pharmacytimescom/issue/pharmacy/2008/2008-09/2008-09-8687.

Appendix 2 – Selected Strong Inducers of CYP450

carbamazepine
efavirenz
nevirapine
phenobarbital
phenytoin
pioglitazone
rifabutin
rifampin
St. John's Wort
troglitazone

This list is not comprehensive. When considering using an agent that could be a potential CYP450 inducer, please discuss this with the medical monitor.
Source: http://medicine.iupui.edu/clinpharm/ddis/table.asp and http://www.pharmacytimescom/issue/pharmacy/2008/2008-09/2008-09-8687.

Appendix 3 - Common Terminology Criteria for Adverse Events: Diarrhea (Version 4.03)

Definition: A Disorder Characterized by Frequent and Watery Bowel Movements.	
1	Increase of < 4 stools per day over Baseline; mild increase in ostomy output compared to Baseline
2	Increase of 4 – 6 stools per day over Baseline; moderate increase in ostomy output compared to Baseline
3	Increase of ≥ 7 stools per day over Baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to Baseline; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated
5	Death

Appendix 4 - Investigator Responsibilities, Required Documentation, and Signature

CTI BioPharma Corp. will select the investigator(s) on the basis of their expertise in the field of clinical studies in hematologic oncology and in the care and treatment of patients with chronic myeloproliferative diseases. Investigators will also be selected on the appropriateness of their facility to conduct a research study of this nature, and the characteristics of the patient population treated at the institution. The investigator will:

- Obtain Institutional Review Board (IRB), Research Ethics Board (REB), or Independent Ethics Committee (IEC) approval of the protocol and amendments to the protocol and Informed Consent Form before initiation of the protocol or any amendments for the study, and obtain annual IRB or IEC renewal, as required.

- Ensure that current FDA and/or ICH-E6 regulations are followed.

- Select all patients in accordance with the selection criteria outlined in the study protocol.

- Treat and follow patients as described in this research protocol. Complete all electronic case report forms (eCRFs) in a timely manner and review eCRFs for accuracy and completeness. Provide the original clinical source documents to verify all data entered on eCRFs or SAE reports and all data that document the course of the patient throughout their participation on the study. Provide a clinical summary to the Sponsor's clinical research monitor.

- Report all adverse events to CTI BioPharma Corp. or designee, as required by the protocol.

- Ensure that the investigational drug is kept in a secured, limited access area and stored under proper conditions. Ensure that all investigational drug receipt and dispensing information is recorded and all drug can be accounted for at all times.

- Before initiation of the study, each participating investigator will submit to CTI:

    - FDA Form 1572 and, if applicable, other ministry of health required forms

    - Copies of the medical licenses of principal investigators and subinvestigators

    - Addresses and descriptions of all clinical laboratory facilities to be used

    - Laboratory certification and expiration dates

    - Normal ranges and effective dates for all required laboratory tests

    - IRB/REB/IEC approval letter referencing the protocol (and amendments, if applicable)

    - IRB/REB/IEC Membership List: A list of the IRB/REB/EC members, their respective titles or occupations, and their institutional affiliations

- A sample copy of the IRB/REB/IEC-approved Informed Consent Form
- Curricula vitae: Curricula vitae for the principal investigator and all subinvestigators
- Financial disclosure for the principal investigator and all subinvestigators
- Protocol signature page, signed by the principal investigator

Investigator Statement and Signature:

I attest that I have read this protocol, understand and agree to the provisions of the protocol, and accept the responsibilities listed above in my role as principal investigator for the study.

Principal Investigator Signature Date

Principal Investigator Name, Printed