Clinical Study Protocol

INCB 18424-369/NCT04377620

A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Efficacy and Safety of Ruxolitinib in Participants With COVID-19–Associated ARDS Who Require Mechanical Ventilation (RUXCOVID-DEVENT)

Product:	**Ruxolitinib (INCB018424)**
IND Number:	**149,270**
Phase of Study:	**3**
Sponsor:	**Incyte Corporation** **1801 Augustine Cut-Off** **Wilmington, DE 19803**
Original Protocol:	**21 APR 2020**
Protocol Amendment 1:	**02 JUN 2020**

This study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and conducted in adherence to the study Protocol, applicable Good Clinical Practices, and applicable laws and country-specific regulations in which the study is being conducted.

INVESTIGATOR'S AGREEMENT

I have read the INCB 18424-369 Protocol Amendment 1 (dated 02 JUN 2020) and agree to conduct the study as outlined. I agree to maintain the confidentiality of all information received or developed in connection with this Protocol.

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(Printed Name of Investigator)

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(Signature of Investigator) (Date)

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviations and Special Terms	Definition
AE	adverse event
aGVHD	acute graft versus host disease
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
BAL	bronchoalveolar lavage
BID	bis in die/twice a day
BMI	body mass index
CAR	chimeric antigen receptor
CK	creatine kinase
CK-MB	creatine kinase myocardial band
CoV	coronavirus
COVID-19	coronavirus disease 2019
CRP	C-reactive protein
CRRT	continuous renal replacement therapy
CRS	cytokine release syndrome
CT	computerized tomography
CYP	cytochrome P450
DILI	drug-induced liver injury
DMC	data monitoring committee
ECG	electrocardiogram
ECMO	extracorporeal membrane oxygenation
eCRF	electronic case report form
EDC	electronic data capture
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GM-CSF	granulocyte macrophage colony-stimulating factor
HLH	hemophagocytic lymphohistiocytosis
HSD	Hwang-Shih-DeCani
HU	hydroxyurea

Abbreviations and Special Terms	Definition
ICU	intensive care unit
IB	Investigator's Brochure
ICF	informed consent form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IL	interleukin
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
JAK	Janus kinase
LPS	lipopolysaccharide
MedDRA	Medical Dictionary for Regulatory Activities
MF	myelofibrosis
PD	pharmacodynamic(s)
PET-MF	post–essential thrombocythemia myelofibrosis
PMF	primary myelofibrosis
PML	progressive multifocal leukoencephalopathy
POM	proportional odds model
PP	per protocol
PPV-MF	post–polycythemia vera myelofibrosis
PV	polycythemia vera
QD	once a day
RBC	red blood cell
RNA	ribonucleic acid
RRT	renal replacement therapy
SAE	serious adverse event
SARS-CoV	severe acute respiratory syndrome coronavirus
sHLH	secondary hemophagocytic lymphohistiocytosis
SoC	standard-of-care
SOFA	sequential organ failure assessment
STAT	signal transducer and activator of transcription
TEAE	treatment-emergent adverse event
ULN	upper limit of normal
US	United States
WHO	World Health Organization

1. PROTOCOL SUMMARY

Protocol Title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Assess the Efficacy and Safety of Ruxolitinib in Participants With COVID-19–Associated ARDS Who Require Mechanical Ventilation (RUXCOVID-DEVENT)

Protocol Number: INCB 18424-369

Objectives and Endpoints:

Table 1 presents the primary and major/key secondary objectives and endpoints.

Table 1: Primary and Secondary Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the 28-day mortality rate of ruxolitinib 5 mg BID + SoC therapy and ruxolitinib 15 mg BID + SoC compared with placebo + SoC therapy, in participants with COVID-19–associated ARDS who require mechanical ventilation.	Proportion of participants who have died due to any cause through Study Day 29.
Secondary	
To evaluate the efficacy of ruxolitinib 5 mg BID + SoC therapy and ruxolitinib 15 mg BID + SoC therapy compared with placebo + SoC therapy on in-hospital outcomes, in participants with COVID-19–associated ARDS who require mechanical ventilation.	At Day 29, the number of ventilator-free days, ICU-free days, oxygen-free days, vasopressor-free days, and hospital-free days will be summarized by treatment group.
To evaluate the efficacy of ruxolitinib 5 mg BID + SoC therapy and ruxolitinib 15 mg BID + SoC therapy compared with placebo + SoC therapy using a 9-point ordinal scale at Study Days 15 and 29, in participants with COVID-19–associated ARDS who require mechanical ventilation.	Ordinal scale: • Percentage of participants with at least 2-point improvement in clinical status at Day 15 and at Day 29. • Percentage of participants with at least 1-point improvement in clinical status at Day 15 and at Day 29. • Time to improvement from baseline category to earliest 1-point improvement in the ordinal scale. • Percentage of participants in each 9-point ordinal scale category Day 29. • Mean change in the 9-point ordinal scale from baseline to Days 15 and 29.
To evaluate the efficacy of ruxolitinib 5 mg BID + SoC therapy and ruxolitinib 15 mg BID + SoC therapy compared with placebo + SoC therapy on change from baseline SOFA score, in participants with COVID-19–associated ARDS who require mechanical ventilation.	Change from baseline to Days 3, 5, 8, 11, 15, and 29 in SOFA score.
To evaluate the safety of ruxolitinib 5 mg BID + SoC therapy and ruxolitinib 15 mg BID + SoC therapy compared with placebo + SoC therapy, in the treatment of participants with COVID-19–associated ARDS who require mechanical ventilation.	Number and proportion of participants with treatment-related side effects (as assessed by CTCAE v5.0) and SAEs; includes clinically significant changes in laboratory measures and vital signs.

Overall Design:

Table 2 presents the key study design elements. Further study details are presented after the table.

Table 2: Key Study Design Elements

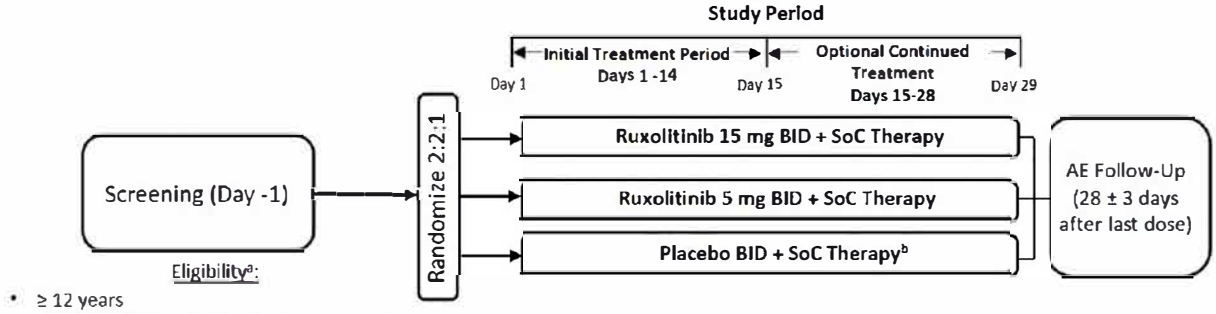
Sponsor and clinical phase	Incyte/Phase 3
Investigation type	Drug (ruxolitinib/INCB018424)
Study type	Interventional
Purpose and rationale	There are no approved treatments for COVID-19–associated ARDS. The purpose of this study is to evaluate the efficacy and safety of ruxolitinib in the treatment of participants with COVID-19–associated ARDS who require mechanical ventilation.
Study design	This is a randomized (2:2:1, ruxolitinib 5 mg BID to ruxolitinib 15 mg BID to placebo [placebo randomized 1:1 to 5 mg or 15 mg]), double-blind, placebo-controlled, 29-day, multicenter study to assess the efficacy and safety of 2 doses of ruxolitinib (5 mg and 15 mg BID) + SoC therapy, compared with placebo + SoC therapy, in participants aged ≥ 12 years with COVID-19–associated ARDS who require mechanical ventilation.
Study population	Approximately 500 participants ages 12 and older with COVID-19–associated ARDS who require mechanical ventilation at study enrollment.
Key inclusion criteria	• Participant or guardian/health proxy must provide informed consent (and assent, if applicable) before any study assessment is performed. • Male or female participants aged ≥ 12 years. • Participants with coronavirus (SARS-CoV-2) infection confirmed ≤ 3 weeks prior to randomization by any test with local regulatory approval. • Participants who are intubated and receiving mechanical ventilation due to COVID-19–associated ARDS and have a PaO_2/FiO_2 of ≤ 300 mmHg within 6 hours of randomization. • Participants with lung imaging showing bilateral or diffuse pulmonary infiltrates on chest x-ray or CT scan.

Key exclusion criteria	• Known history of hypersensitivity to any drugs or metabolites of similar chemical classes as ruxolitinib. • Presence of severely impaired renal function defined by estimated creatinine clearance < 15 mL/min measured or calculated by Cockcroft-Gault equation or calculated by the updated bedside Schwartz equation. Participants must not be receiving CRRT or intermittent hemodialysis at screening. • In the opinion of the investigator, unlikely to survive for > 24 hours from randomization. • Suspected active uncontrolled bacterial, fungal, viral, or other infection (besides COVID-19). • Currently receiving ECMO. • Participant may not be sharing a ventilator, or co-ventilating, with any other patient. • Treatment with anti–IL-6, IL-6R, IL-1RA, IL-1β, or GM-CSF antagonists, or a BTK inhibitor, within 7 days of randomization. • Treatment with a JAK inhibitor within 30 days of randomization. • Participants who are on long-term use of antirejection or immunomodulatory drugs. • Pregnant or nursing (lactating) women.
Study treatment	Ruxolitinib 5 mg BID, ruxolitinib 15 mg BID, or matching-image placebo (placebo randomized 1:1 to match ruxolitinib 5 mg or 15 mg) for 14 days with possible extension of treatment to 28 days
Treatment of interest	Ruxolitinib 5 mg tablets
Principal coordinating investigator	[redacted]
Efficacy assessments	• Overall survival through Study Day 29 • In-hospital outcomes • Clinical status using a 9-point ordinal scale • Vital signs, oxygenation and ventilator parameters • SOFA score
Key safety assessments	• Adverse event monitoring through safety follow-up period • Laboratory markers • SARS-CoV-2 viral load
Other assessments	Inflammatory markers including ferritin, CRP, D-dimer, procalcitonin, IL-6 at sites where feasible

Data analysis	Individual comparisons between placebo and ruxolitinib treatment groups will be performed in a pairwise fashion (placebo vs 5 mg BID and placebo vs 15 mg BID). The primary endpoint of the Day 28 mortality rate will be analyzed using the ITT population using a logistic regression model including treatment group, ARDS severity mild/moderate ($PaO_2/FiO_2 > 100$ to ≤ 300 mmHg) vs severe ($PaO_2/FiO_2 \leq 100$ mmHg), and gender as fixed effects and investigational site as a random effect. The statistical test will test the null hypothesis that the odds-ratio between ruxolitinib and placebo treatment is 1 with a 1-sided test. Overall familywise Type I error control of 2.5% (1-sided) will be accomplished using a Dunnett's procedure, where the nominal alpha level for the individual comparisons will be adjusted to 0.01436968. An interim analysis for efficacy is intended when the first 40% of the planned randomized participants have died or have reached their Day 29 assessment, and additional futility analyses for the primary endpoint based on a Cox regression model are planned weekly for the study. If both ruxolitinib groups are found to be superior to placebo, then a statistical comparison will be performed between the 2 ruxolitinib groups in an alpha-controlled fashion. The approach will account for Type I error expended at the interim analysis. The distribution of 9-point ordinal scale will be summarized by treatment arm as percentages. The odds of observing a better category on the ordinal scale (lower number) will be analyzed with a POM separately at Days 15 and 29. Each model will include treatment group, ARDS severity category (mild or moderate vs severe), and gender as fixed covariates and investigational site as a random effect. The estimated odds ratios, p-values, and 95% confidence intervals will be presented. The study will be considered positive if ruxolitinib demonstrates a statistically significant greater reduction Day 28 mortality rate.
DMC	An DMC will be formed. The DMC will consist of qualified individuals who are not involved with the conduct of the study. The establishment, composition, roles, duties, and responsibilities of the DMC are addressed in the approved DMC charter.
Key words	Cytokine storm, COVID-19, ARDS, SARS-CoV-2, ruxolitinib

The study design is presented in Figure 1. Adherence to the study design requirements, including those specified in the SoA (see Table 3), is essential and required for study conduct.

Figure 1: Study Design Schema



Eligibility[a]:

- ≥ 12 years
- Confirmed SARS-CoV-2 infection confirmed ≤ 3 weeks prior to randomization
- Patients with COVID-19–associated ARDS who require mechanical ventilation
- Lung imaging demonstrating bilateral or diffuse pulmonary infiltrates

[a] Not inclusive; see Section 6 for complete eligibility criteria.
[b] Placebo arm will be randomized between a 5 mg BID (1 tablet/dose) and 15 mg BID (3 tablets/dose).

Table 3: Schedule of Activities

	Screening	Study Period					AE Follow-Up
Study Day	**Day −1 (Screening)**	**Day 1[a]**	**Day 2-14 (every day unless otherwise specified below)**	**Day 15[b,c]**	**Day 16-28 (every day unless otherwise specified below)**	**Day 29[c]**	**28 ± 3 days after last dose[d]**
Informed consent (assent, if applicable)[e]	X						
Inclusion/exclusion criteria	X	X					
Contact IRT	X	X		X		X	X
Demographics/medical history	X						
SARS-CoV-2 virus/viral load/antibody testing[f]	X			X		X	
Vital signs[g]	X	X	X	X	X	X	
Height (if feasible) and weight	X						
ABGs, PaO_2/FiO_2, and pulse oximetry[h]	X	X	X	X	X	X	
Ventilator/oxygen support[i]	X	X	X	X	X	X	
Clinical status evaluation with 9-point ordinal scale[j]	X	X	X	X	X	X	
Drug dispensation and administration[k]		X	Days 2 through14	Days 15 through 28 **(if applicable)**			
Hematology (local laboratory assessments)[l]	X	X	Days 3, 5, 7, 9, 11, 13 (while in hospital)	X	Days 17, 19, 21, 23, 25, 27 (while in hospital)	X	
Clinical chemistry (local laboratory assessments)[l]	X	X	Days 3, 5, 7, 9, 11, 13 (while in hospital)	X	Days 17, 19, 21, 23, 25, 27 (while in hospital)	X	
Inflammatory markers (ferritin, CRP, D-dimer, procalcitonin, IL-6 [if feasible]; local laboratory assessments)[l]	X	X	Days 3, 5, 7, 9, 11, 13 (while in hospital)	X	Days 17, 19, 21, 23, 25, 27 (while in hospital)	X	
Correlative serum collection (**optional**)[m]		X	Day 7 only	X			
Pregnancy test (local laboratory assessments)[n]	X					X	
Lung imaging (chest x-ray or CT scan)[o]	X						
Adverse events	X	X	X	X	X	X	X
Prior/concomitant medications[p]	X	X	X	X	X	X	
Surgeries and procedures[p]	X	X	X	X	X	X	
SOFA score[q]	X	X	X	X	X	X	
In-hospital outcomes[r]	X	X	X	X	X	X	X

[a] The Day 1 visit may occur on the same day as the screening visit. If this occurs, non-laboratory assessments that occur at both visits do not have to be repeated.
[b] If treatment is approved to continue beyond the initial 14-day period (ie, Day 15 through 28), if needed, contact IRT to dispense additional study drug.
[c] If participant is discharged from the hospital, the scheduled assessments may be performed remotely, via telephone.

[d] A follow-up assessment for patient-reported AEs and in-hospital outcomes (if applicable) will be conducted 28 ± 3 days after the last dose of study treatment. If participant has been discharged, the assessment may be performed remotely, via telephone.
[e] Participant must provide informed consent (and assent, if applicable) before any study assessment is performed; informed consent may be obtained from a health care proxy where appropriate.
[f] Confirmation of SARS-CoV-2 infection ≤ 3 weeks prior to randomization by any test with local regulatory approval. Confirmation prior to informed consent (and assent, if applicable) is acceptable. Viral load and antibody testing may be performed by any approved method and is only required if local capabilities allow; a consistent method and specimen source should be used at all timepoints.
[g] Vital signs will be collected once daily while hospitalized between 7:00 AM and 12:00 PM local time and include heart rate, respiratory rate, systolic and diastolic blood pressure, and body temperature. Not required after discharge.
[h] Arterial blood gases will be collected during screening, within 6 hours of planned randomization, to assess PaO_2/FiO_2. Thereafter, ABGs will be performed daily while 1) the participant is receiving mechanical ventilation, OR 2) the participant has an arterial line. Parameters including pH, PaO_2, $PaCO_2$, and SaO_2 will be collected for each ABG. SpO_2 (pulse oximetry) will be recorded in the eCRF once daily while hospitalized. ABGs and SpO_2 not required after discharge.
[i] Ventilator settings (as applicable) will be collected once daily between 7:00 AM and 12:00 PM local time. Settings to be collected include mode, FiO_2, PEEP, VT, and respiratory rate. Dates of intubation and extubation (if applicable) will be recorded. Supplemental oxygen support post-extubation will be collected daily through Day 29, until hospital discharge.
[j] If participant is discharged, a telephone call may be used to perform assessment. See Appendix B for scale.
[k] Beginning at Day 15, the participant may continue treatment up to Day 28 at the discretion of the investigator and after approval by the sponsor medical monitor.
[l] Hematology, clinical chemistry, and markers of inflammation should be measured by the local laboratory. See Section 9.4.3 for required analytes. If participant is discharged, local laboratory assessments may be performed on Day 15 and/or Day 29 if feasible.
[m] An optional serum sample will be collected at Day 1 (predose) and Day 7 and 15 for cytokine analysis. See Section 9.5.1 for collection, processing, storage and shipment instructions.
[n] Pregnancy test: only for females of childbearing potential, serum pregnancy test (serum hCG) will be performed at screening assessment. Serum or urine test is acceptable at subsequent assessment(s).
[o] Screening chest imaging may be ≤ 2 days prior to Day 1.
[p] All medications, procedures, and significant non-drug therapies administered from randomization through Day 29 must be recorded on the appropriate eCRF. Additionally, antivirals and therapeutic agents administered for SaRS-CoV-2 infection/COVID-19 infection and treatments for COVID-19 pneumonia/ARDS administered within 14 days of randomization must also be recorded. If participant is discharged from the hospital, the scheduled assessments may be performed via telephone.
[q] The SOFA score is to be determined per Appendix C. Not required after discharge from the ICU. SpO_2 method for calculating respiratory score may be used if arterial blood gases were not performed on corresponding assessment day.
[r] In-hospital outcomes will be collected on eCRFs as outlined in Section 9.3.5.

2. INTRODUCTION

2.1. Background

In DEC 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of an unknown cause. This outbreak of viral pneumonia was reported to the WHO Country Office in China on 31 DEC 2019. Subsequently, CoV RNA was identified in some of the patients with viral pneumonia.

Coronaviruses are positive-stranded RNA viruses with a crown-like appearance under an electron microscope due to the presence of spike glycoproteins on the envelope. They are a large family of viruses that cause illness ranging from the common cold to more severe diseases such as Middle East respiratory syndrome and SARS-CoV.

The novel coronavirus detected in late 2019 has been designated SARS-CoV-2, and the disease caused by this virus has been designated COVID-19. This new coronavirus strain was not previously identified in humans and was newly named on 11 FEB 2020 by the WHO. Genetic sequencing of the virus suggests that SARS-CoV-2 is a beta-coronavirus closely linked to SARS-CoV.

On 11 MAR 2020, the WHO declared a pandemic for COVID-19. According to the WHO, as of 24 MAR 2020 over 409,000 cases of COVID-19 were reported in over 100 countries worldwide, with over 18,000 deaths. To date, there is no vaccine and no specific antiviral medicine shown to be effective in preventing or treating COVID-19.

While most people with COVID-19 develop mild or uncomplicated illness, approximately 14% develop severe disease requiring hospitalization and oxygen support, and 5% require admission to an ICU (China CDC Weekly 2020). In severe cases, COVID-19 can be complicated by ARDS, sepsis and septic shock, and/or multiorgan failure, including acute kidney injury and cardiac injury (Yang et al 2020). Of those cases that develop ARDS, there is an approximate 50% to 80% mortality rate (Grasselli et al 2020, Zhou et al 2020). Additionally, many patients with severe respiratory disease due to COVID-19 have features consistent with CRS, also referred to as cytokine storm, and increased activation of the JAK-STAT pathway (Hermans et al 2018, Wang et al 2020).

According to the WHO interim guidance of 13 MAR 2020 on the clinical management of severe acute respiratory infection when COVID-19 is suspected, "older age and comorbid disease have been reported as risk factors for death, and recent multivariable analysis confirmed older age, higher SOFA score and d-dimer > 1 µg/L on admission were associated with higher mortality" (WHO 2020b). The same study quoted by the WHO also noted that the median duration of viral RNA detection was 20.0 days (interquartile range 17.0–24.0) in survivors, but SARS-CoV-2 was detectable until death in nonsurvivors. The longest observed duration of viral shedding in survivors was 37 days (Huang et al 2020, Zhou et al 2020).

There are sparse data on the clinical presentation of COVID-19 in specific populations, such as children and pregnant women. In children with COVID-19, the symptoms are usually less severe than in adults and present mainly with cough and fever, and coinfection has been

observed (Cai et al 2020, Xia et al 2020). Relatively few cases have been reported of infants with confirmed COVID-19, and they experienced mild illness (Wei et al 2020).

2.1.1. Ruxolitinib

Ruxolitinib (INCB018424 phosphate, INC424, ruxolitinib phosphate) is a well-established, potent and selective inhibitor of JAK1 and JAK2, with modest to marked selectivity against tyrosine kinase 2 and JAK3, respectively. Ruxolitinib interferes with the signaling of a number of cytokines and growth factors that are important for hematopoiesis and immune function as noted in the ruxolitinib IB.

Janus kinase signaling involves recruitment of STATs to cytokine receptors, activation, and subsequent localization of STATs to the nucleus leading to modulation of gene expression. Dysregulation of the JAK-STAT pathway has been associated with several types of cancers and increased proliferation as well as survival of malignant cells. In particular, this pathway may be dysregulated in the majority of patients with Philadelphia chromosome-negative myeloproliferative neoplasms, including MF and PV, demonstrating that JAK inhibition may be efficacious in these diseases.

Ruxolitinib (JAKAVI®) is currently approved in the EU for the treatment of disease-related splenomegaly or symptoms in adult patients with PMF (also known as chronic idiopathic MF), PPV-MF, or PET-MF and for the treatment of adult patients with PV who are resistant to or intolerant of HU.

In the US, ruxolitinib (JAKAFI®) is approved for the treatment of intermediate or high-risk MF, including PMF, PPV-MF, and PET-MF in adults; for the treatment of adult patients with PV who have had an inadequate response to or are intolerant of HU; and for patients 12 years and older with steroid refractory aGVHD.

Ruxolitinib is currently under further development for the treatment of MF, PV, essential thrombocytopenia, and other hematologic malignancies.

2.1.2. Additional Evidence for Cytokine Release Syndrome and JAK-STAT Activation in COVID-19–Associated Acute Respiratory Distress Syndrome

There is preclinical evidence from both laboratory and animal models that blockade/inhibition of the JAK-STAT pathway could have a beneficial effect of the cytokine driven ARDS in patients with COVID-19.

2.1.2.1. Laboratory Evidence

Hermans et al (2018) studied human mast cell lines and demonstrated that ruxolitinib can inhibit mast cell activity, possibly through prevention of STAT5 activation. They postulated that the JAK-STAT pathway is a potential target for therapy to release symptom burden in mastocytosis and many other mast cell mediator-related diseases such as CRS.

Hoffmann et al (2016) demonstrated that viral and bacterial coinfection in a macrophage model modulates the JAK-STAT signaling pathway and leads to exacerbated IP-10 expression, which could play a major role in the pathogenesis of pneumonia, suggesting that targeting this pathway could have a beneficial effect.

2.1.2.2. Animal Models

Zhao et al (2016) looked at LPS-induced lung injury in mice, which models some of the ARDS manifestations (eg, cytokine increases and cell influx) as well as an increase in STAT3 expression. STAT3 is downstream of JAK and the authors show that STAT3 inhibition with a tool compound partly inhibits cytokine and cell increases after LPS challenge. A caveat is that a positive control (eg, dexamethasone) is absent from the in vivo studies. Using conditional knockouts of SOCS3 (an antinflammatory protein that negatively regulates JAK activity), they provide further evidence that the effects are STAT3 pathway–dependent. They also show increased STAT3 expression in peripheral blood mononuclear cells from ARDS patients could be blocked with the same tool compound.

Coon et al (2015) identified a new ubiquitinylating ligase, HECTD2, which degrades PIAS-1, an antinflammatory protein that negatively regulates the JAK-STAT pathway. They show degradation of PIAS by HECTD2 induces lung inflammation (cytokine increases and cell counts) in a mouse pneumonia challenge model. An HECTD2 inhibitor reduces lung inflammation in the same model (no positive control). They also identify a polymorphism (loss of function) in the HECTD2 gene that appears to be protective against ARDS.

Kenderian et al (2017) described for the first time a clinically relevant animal model of human CRS and demonstrated that the JAK-STAT inhibitor ruxolitinib can prevent the development of severe CRS without impairing the anti-tumor effect of CAR-T cells. These findings provide a useful platform for the future study of CRS prevention and treatment modalities. These experiments indicate that ruxolitinib could also be combined with CAR–T-cell therapy for the prevention of CRS in patients identified to be at high risk for the development of CRS.

Calbet et al (2019) studied a novel pan-JAK inhibitor and showed that it reduced allergen-induced airway inflammation, late asthmatic response, and pSTAT activation in rats.

In a mouse model of HLH (model of CRS), Maschalidi et al (2016) found that administration of ruxolitinib suppressed the harmful consequences of macrophage activation with improvement in vital signs and hematologic parameters.

2.1.2.3. Clinical Evidence

There is clinical evidence of efficacy with ruxolitinib in another recognized disease with CRS, secondary HLH. Two pilot studies of ruxolitinib led to resolution of symptoms and associated laboratory abnormalities in the patients studied, alleviating the need for more toxic therapies (Ahmed et al 2019, Goldsmith et al 2019).

2.1.3. Background Summary

It is reasonable to consider the use of ruxolitinib in the treatment of COVID-19 patients with severe respiratory disease/ARDS because these patients have clinical features consistent with CRS/cytokine storm and increased activation of the JAK-STAT pathway (Hermans et al 2018, Wang et al 2020). Moreover, recent literature specifically suggests consideration of molecules that block inflammatory pathways, including inhibition of the JAK-STAT pathway, where a number of cytokines converge, for the treatment of COVID-19 (Mehta et al 2020, Zumla et al 2020).

In summary, the above-mentioned data provide scientific justification for the study of a JAK-STAT inhibitor, such as ruxolitinib, in a controlled clinical study setting.

2.2. Purpose

There are no approved treatments for COVID-19–associated ARDS. The purpose of this study is to evaluate the efficacy and safety of ruxolitinib in the treatment of participants with COVID-19–associated ARDS who require mechanical ventilation.

3. OBJECTIVES AND ENDPOINTS

Table 4 presents the objectives and endpoints.

Table 4: Objectives and Endpoints

Objectives	Endpoints
Primary	
To evaluate the 28-day mortality rate of ruxolitinib 5 mg BID + SoC therapy and ruxolitinib 15 mg BID + SoC therapy compared with placebo + SoC therapy, in participants with COVID-19–associated ARDS who require mechanical ventilation.	Proportion of participants who have died due to any cause through Study Day 29.
Secondary	
To evaluate the efficacy of ruxolitinib 5 mg BID + SoC therapy and ruxolitinib 15 mg BID + SoC therapy compared with placebo + SoC therapy on in-hospital outcomes, in participants with COVID-19–associated ARDS who require mechanical ventilation.	At Day 29, the number of ventilator-free days, ICU-free days, oxygen-free days, vasopressor-free days, and hospital-free days will be summarized by treatment group.
To evaluate the efficacy of ruxolitinib 5 mg BID + SoC therapy and ruxolitinib 15 mg BID + SoC therapy compared with placebo + SoC therapy using a 9-point ordinal scale at Study Days 15 and 29, in participants with COVID-19–associated ARDS who require mechanical ventilation.	Ordinal scale: • Percentage of participants with at least 2-point improvement in clinical status at Day 15 and at Day 29. • Percentage of participants with at least 1-point improvement in clinical status at Day 15 and at Day 29. • Time to improvement from baseline category to earliest 1-point improvement in the ordinal scale. • Percentage of participants in each 9-point ordinal scale category Day 29. • Mean change in the 9-point ordinal scale from baseline to Days 15 and 29.

Table 4: Objectives and Endpoints (Continued)

Objectives	Endpoints
Secondary (continued)	
To evaluate the efficacy of ruxolitinib 5 mg BID + SoC therapy and ruxolitinib 15 mg BID + SoC therapy compared with placebo + SoC therapy on change from baseline SOFA score, in participants with COVID-19–associated ARDS who require mechanical ventilation.	Change from baseline to Days 3, 5, 8, 11, 15, and 29 in SOFA score.
To evaluate the safety of ruxolitinib 5 mg BID + SoC therapy and ruxolitinib 15 mg BID + SoC therapy compared with placebo + SoC therapy, in the treatment of participants with COVID-19–associated ARDS who require mechanical ventilation.	Number and proportion of participants with treatment-related side effects (as assessed by CTCAE v5.0) and SAEs; includes clinically significant changes in laboratory measures and vital signs.
Exploratory	
To evaluate the efficacy of ruxolitinib + SoC therapy compared with placebo + SoC therapy in proportion of participants requiring IL-6, IL-1, GM-CSF, or JAK-directed therapies.	Proportion of participants requiring treatments with IL-6, IL-6R, IL-1RA, IL-1β, GM-CSF, BTK, or JAK-directed therapies by Day 15 and by Day 29
To evaluate ruxolitinib + SoC therapy compared with placebo + SoC therapy on change in inflammatory markers (when available).	Change from baseline to Day 15 and to Day 29 in the following clinical chemistry measurements: • Serum ferritin • CRP • D-dimer • Procalcitonin • IL-6
To evaluate ruxolitinib + SoC therapy compared with placebo + SoC therapy on change in COVID-19 virologic and serologic parameters.	Change from baseline to Day 15 and to Day 29 in viral load and anti-SARS-CoV2-antibody titer.

3.1. Primary Estimates

- Treatment – ruxolitinib added to SoC therapy.
- Population – Participants with SARS-CoV-2 infection confirmed ≤ 3 weeks before randomization and with COVID-19–associated ARDS requiring mechanical ventilation.
- Endpoint – Primary efficacy endpoint is the proportion of participants who have died due to any cause through Study Day 29.

- Population-level summary – Odds-ratio comparing each of 2 doses of ruxolitinib (5 mg BID and 15 mg BID) + SoC therapy with SoC therapy alone. Odds-ratio comparing 5 mg BID ruxolitinib + SoC therapy with 15 mg BID ruxolitinib + SoC therapy, tested only if both odds-ratios for pairwise comparisons are statistically significant.
- Intercurrent event(s) – Discontinuation from study for reasons other than death.

4. STUDY DESIGN

4.1. Overall Design

This is a randomized, double-blind, placebo-controlled, 29-day, multicenter study to assess the efficacy and safety of ruxolitinib 5 mg BID + SoC therapy and 15 mg BID + SoC therapy compared with placebo + SoC therapy, in participants aged ≥ 12 years with COVID-19–associated ARDS who require mechanical ventilation (see Figure 1).

Participants aged ≥ 12 years with SARS-CoV-2 virus infection confirmed ≤ 3 weeks before randomization by any test with local regulatory approval, hospitalized with COVID-19–associated ARDS (demonstrated by chest x-ray or chest CT and $PaO_2/FiO_2 \leq 300$ mmHg) who have been intubated and are receiving mechanical ventilation. Participants who are unlikely to survive for > 24 hours after randomization (in the opinion of the treating investigator); who have active tuberculosis or active and uncontrolled bacterial, fungal, viral, or other infection (besides SARS-CoV-2 virus); or who are currently receiving ECMO support will be excluded from the study.

Informed consent (written or verbal) and assent (if applicable) will be obtained from the participant or health care proxy before any study-related assessments or procedures are performed. Thereafter, medications and eligibility criteria will be reviewed by study personnel. All participants signing informed consent (or by health care proxy) and assent (if applicable) must be registered in the IRT.

The study will include the following:

- Screening period of 1 day.
- Study period of 29 days. Treatment with ruxolitinib 5 mg BID/placebo or ruxolitinib 15 mg BID/placebo will initially be administered for 14 days. If in the opinion of the treating investigator the benefit/risk is appropriate for the participant, then continued treatment up to 28 days is permitted with approval from the sponsor medical monitor. Approval must be requested ≥ 24 hours before initiation of dosing on Day 15.
- AE follow-up assessment 28 (± 3) days following the last dose of study treatment.

Eligible participants will be randomized after completing the screening period (Day −1) and having been confirmed eligible. Screening and randomization may occur on the same day. Participants will be assigned in a 2:2:1 ratio to receive ruxolitinib 5 mg BID, 15 mg BID, or matching-image placebo for an initial period of 14 days (see Section 7.1); participants randomized to placebo will be randomized 1:1 to either receive matching placebo for 5 mg BID (1 tablet BID) or matching placebo for 15 mg BID (3 tablets BID). On Day 15, if in the opinion

of the investigator the benefit/risk is appropriate, then continued treatment up to 28 days is permitted with medical monitor approval. There is no crossover between treatment groups. Study treatment will be given in combination with SoC therapy according to the investigator's clinical judgment. Study treatment will be administered via an enteric feeding tube (see Section 7.1 for directions) while the participant is intubated. Randomization will be stratified by ARDS severity (mild/moderate [PaO_2/FiO_2 > 100 and ≤ 300 mmHg] vs severe [PaO_2/FiO_2 ≤ 100 mmHg]; ARDS Definition Task Force et al 2012) and investigative site.

Participants who do not meet the criteria for participation in this study (screen failures) may not be rescreened.

Assessments during the 29-day study period will occur per the SoA. See Section 9 and Table 3 for specific assessments and timing for these assessments. The primary endpoint of the study is the 28-day mortality rate. Should a participant be discharged from the hospital during the 29-day study period, assessments will be performed remotely (eg, telephone call, video call) as per Table 3.

A follow-up assessment (in person or remote telephone contact) for AE and clinical status will occur approximately 28 (± 3) days following the last dose of study treatment to complete safety assessments.

This study will include a DMC, which will function independently of all other individuals associated with the conduct of this clinical study, including the site investigators participating in the study.

5. RATIONALE

5.1. Rationale for Study Design

This randomized, double-blind, parallel-group, placebo-controlled design supports the rigorous assessment of efficacy as well as safety of 2 doses of ruxolitinib (5 mg BID and 15 mg BID) as an add-on to SoC therapy for participants with COVID-19–associated ARDS requiring mechanical ventilation.

5.1.1. Screening Period

The screening period allows for the assessment of participant entry criteria to ensure suitable participants are entered into the study.

5.1.2. Study/Treatment Period

During the treatment period, ruxolitinib 5 mg BID, 15 mg BID, or matching-image placebo BID (treatment arms will be randomized 2:2:1; participants randomized to placebo will be randomized 1:1 to either receive matching placebo for 5 mg BID [1 tablet BID] or matching placebo for 15 mg BID [3 tablets BID]). Study treatment will initially be administered for 14 days; if on Day 15, the benefit/risk is appropriate in the opinion of the investigator, continued treatment up to 28 days is permitted with approval from the sponsor's medical monitor. The endpoints included in this study measure overall mortality, clinical, laboratory, and virologic status, and in-hospital outcomes during the 29-day study period. These measurements are

consistent with endpoints and measurement times of the WHO COVID-19 adaptive design protocol (WHO 2020a, Cao et al 2020).

The safety follow-up 28 days after last dose of study treatment will assess the long-term safety and tolerability profile after completion of ruxolitinib/placebo dosing.

5.2. Rationale for Choice of Background Therapy

Although there are no approved treatments for COVID-19, SoC therapy for participants with COVID-19 pneumonia generally includes supportive care, antiviral treatments, and when required, mechanical ventilation. Thus, placebo + SoC therapy is appropriate as a control in this study.

5.3. Rationale for Dose/Regimen and Duration of Treatment

Ruxolitinib is currently approved in the US at doses up to 25 mg BID for the following indications (Jakafi 2019):

- Intermediate or high-risk MF, including primary MF, PV-MF and PET-MF (approved 2011; starting dose of 5, 15, or 20 mg BID)
- Patients with PV who have had an inadequate response to or are intolerant of HU (approved 2014; starting dose of 10 mg BID)
- Steroid-refractory aGVHD in adult and pediatric patients 12 years and older (approved 2019; starting dose of 5 mg BID)

In addition to the FDA-approved indications above, sHLH shares many of the same characteristics of COVID-19–associated cytokine storm, including being commonly virally induced; patients have persistent fevers, cytopenias, and hyperferritinemia and frequently progress to pneumonitis/ARDS. In addition, the cytokine profile seen in COVID-19–associated cytokine storm demonstrates elevation in many of the same cytokines associated with sHLH, including IL-2, IL-7, G-CSF, IP-10, MIP-1a, MCP1, and TNF-alpha (Mehta et al 2020). Further, there is evidence of macrophage activation in the BAL of patients with COVID-19. The BAL from patients with severe disease shows that immunosuppressive alveolar macrophages are replaced with activated and highly cytokine/chemokine secretory FCN1+ macrophages (Liao et al 2020). Such activated macrophages are hallmarks of the sHLH syndrome. Ruxolitinib has demonstrated efficacy in the treatment of patients with sHLH (Ahmed et al 2019, Goldsmith et al 2019, Wang et al 2019). In these studies, participants received ruxolitinib doses between 5 and 20 mg BID with improvement in symptoms and inflammatory markers. Thirty-four participants treated in the Wang study were treated at 0.3 mg/kg, which corresponds to a dose of approximately 10 mg BID. The overall response rate was 73.5% with a complete response rate of 14.7%. Seven participants in the Ahmed study were treated at 15 mg BID. The overall response rate was 100% with a complete response rate of 42.8%. In addition to clinical responses, hematologic parameters including platelet, RBC, and neutrophil counts improved while on ruxolitinib, likely as a result of decreased inflammation from treatment of the underlying sHLH. At 15 mg BID, ruxolitinib was well-tolerated in this population with 1 participant coming off study for pain in extremity. All others remained on therapy at the time of publication.

This study will evaluate both a 5 mg BID dose of ruxolitinib, based on the approved and lowest effective dose for aGVHD, and a 15 mg BID dose of ruxolitinib, which demonstrated preliminary efficacy and a tolerable safety profile in the sHLH study (Ahmed et al 2019). The initial 14-day duration of treatment should further reduce the risk of significant side effects in this setting. Deaths and SAEs will be monitored in real time with routine pharmacovigilance and a DMC in order to detect any unexpected safety signal. The DMC will function independently of all other individuals associated with the conduct of this clinical study.

5.4. Rationale for Choice of Control Drugs (Comparator/Placebo) or Combination Drugs

This study will compare the efficacy and safety of 2 doses (5 mg BID and 15 mg BID) of ruxolitinib + SoC therapy compared with matching-image placebo + SoC therapy. Despite the lack of targeted treatments for COVID-19, SoC for participants with severe COVID-19 respiratory disease generally includes supportive care and may include available antiviral agents and corticosteroids. Therefore, SoC plus placebo treatment is appropriate as a control in this study.

5.5. Purpose and Timing of Interim Analyses/Design Adaptations

A DMC will be formed. The DMC will consist of qualified individuals who are not involved with the conduct of the study. The establishment, composition, roles, duties, and responsibilities of the DMC are addressed in the approved DMC charter. Additional details regarding interim analyses may be found in Section 12.5.

There will be 1 planned interim analysis conducted for efficacy based on the first 40% of participants enrolled in the study. The efficacy interim analysis will be conducted when the first 40% of the planned randomized participants (approximately 200 randomized participants) have died or have reached their Day 29 assessment. Based on the results of this interim analysis, the DMC may choose to terminate the study for positive efficacy or continue the study with no changes to enrollment.

5.6. Risks and Benefits

There is preclinical evidence from both laboratory and animal models that blockade/inhibition of the JAK-STAT pathway could have a beneficial effect on cytokine storm and the course of ARDS in patients with COVID-19. Additionally, there is clinical evidence of efficacy with ruxolitinib in pilot studies in another recognized disease associated with CRS/cytokine storm: sHLH (see Section 5.3). However, ruxolitinib has not previously been studied in patients with COVID-19–associated ARDS. Therefore, it is unknown as to whether there will be a benefit for patients being treated with ruxolitinib in this disease.

The primary clinical risks with ruxolitinib treatment are the potential sequelae of decreased hematopoietic proliferation attributable to the inhibition of growth factor pathways associated with JAK inhibition. In the Phase 3 clinical studies of ruxolitinib in participants with MF, which involved longer-term dosing and, in general, higher doses than those proposed in this Protocol, the most frequent TEAEs were dose-dependent, reversible thrombocytopenia, anemia, and neutropenia. These events could increase the risk of infection, including pneumonia and

bronchitis, and the possibility of developing anemia, bleeding, fatigue, and/or shortness of breath. In healthy volunteers, rheumatoid arthritis patients, and patients with pancreatic cancer or hormone-refractory prostate cancer, the effects on hematopoietic proliferation are less pronounced, presumably because of greater bone marrow reserve. The most frequent nonhematologic AEs were mild, reversible increases in ALT and AST; bruising; hypercholesterolemia; dizziness; headache; and urinary tract infections. Tuberculosis has been infrequently reported in patients receiving ruxolitinib to treat MF (< 1/100 patients). The symptoms of tuberculosis include chronic cough with blood-tinged sputum, fever, night sweats, and weight loss. There may be risks associated with rapid discontinuation of ruxolitinib.

Patients with MF, particularly those who have stopped taking ruxolitinib suddenly after long-term administration, have reported return of MF symptoms such as fatigue, bone pain, fever, pruritus, night sweats, symptomatic splenomegaly, and weight loss. In very few MF patients, respiratory distress, disseminated intravascular coagulation, and multiorgan failure have been reported.

Hepatitis B viral load increases, with and without associated elevations in ALT and AST, have been reported in patients with chronic hepatitis B infections taking ruxolitinib. The effect of ruxolitinib on viral replication in patients with chronic hepatitis B virus is unknown. A rare disease called PML has been reported during treatment with ruxolitinib. It is important to note that PML and infections are complications associated with MF that have been previously described in the absence of ruxolitinib. Additionally, non–melanoma skin cancers, including basal cell, squamous cell, and a rare and aggressive type of skin cancer called Merkel cell carcinoma have been reported in patients who took ruxolitinib; it is unknown whether this was due to ruxolitinib treatment.

In the presence of potent CYP3A4 inhibitors (see Appendix D), there is the possibility of increased exposure to ruxolitinib. A dose adjustment for the 15 mg BID ruxolitinib/placebo group is required when coadministered with potent CYP3A4 inhibitors (see Section 7.2.1.2). No dose adjustment of ruxolitinib is required for participants assigned to 5 mg BID ruxolitinib/placebo.

To date, there have been multiple reports of increased thromboembolic events in COVID-19 patients. In addition, high prevalence of lupus anticoagulant has been noted in severe cases of COVID-19, which predisposes patients to thromboembolic sequelae. Participants should be monitored as per SoC for elevated D-dimer, aPTT, and fibrinogen, as these may be associated with an increased risk of thromboembolic disease. In addition, participants deemed at high risk for thromboembolic sequelae and eligible for prophylactic or therapeutic intervention per local evaluation should be considered for appropriate anticoagulation. Anticoagulation with either prophylactic or therapeutic doses of warfarin, heparin, low-molecular-weight heparin, or anti-Factor Xa therapies are allowed per protocol.

For a comprehensive assessment of the risks of ruxolitinib, refer to the IB.

6. STUDY POPULATION

Deviations from eligibility criteria are not allowed because they can potentially jeopardize the scientific integrity of the study, regulatory acceptability, and/or participant safety. Therefore, adherence to the criteria as specified in the Protocol is essential. Prospective approval of Protocol deviations to recruitment and enrollment criteria, also known as Protocol waivers or exemptions, are not permitted.

6.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

1. Participant must provide informed consent (participant should provide assent if 12-17 years of age, if possible) before any study specific assessment is performed; informed consent may be obtained from a health care proxy where appropriate and/or institutionally approved method of consenting when applicable (verbal consent) as defined in their local consent form.
2. Male or female participants aged ≥ 12 years.
3. Participants with coronavirus (SARS-CoV-2) infection confirmed ≤ 3 weeks prior to randomization by any test with local regulatory approval.
4. Participants who are currently hospitalized, intubated (orotracheal or nasotracheal), and receiving invasive mechanical ventilation due to COVID-19–associated ARDS. Participants must have confirmed PaO_2/FiO_2 of ≤ 300 mmHg within 6 hours of randomization.
5. Participants with lung imaging showing bilateral or diffuse pulmonary infiltrates on chest x-ray or CT scan.

6.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

1. Known history of hypersensitivity to any drugs or metabolites of similar chemical classes as ruxolitinib.
2. Presence of severely impaired renal function defined by estimated creatinine clearance < 15 mL/min measured or calculated by Cockroft-Gault equation or calculated by the updated bedside Schwartz equation. Participants must not be receiving CRRT or intermittent hemodialysis at screening.
3. Suspected active uncontrolled bacterial, fungal, viral, or other infection (besides COVID-19).
4. Known active TB infection.
5. In the opinion of the investigator, unlikely to survive for > 24 hours from randomization.
6. Currently receiving ECMO.
7. Participant may not be sharing a ventilator, or coventilating, with any other patient.

8. Participants who are on long-term use of antirejection or immunomodulatory drugs (eg, JAK inhibitors, IL-6/IL-6R/IL-1RA or IL-1β inhibitors).

   Note: Participants who are taking tacrolimus, cyclosporine, and mycophenolate mofetil are eligible for study.

9. Treatment with anti–IL-6, IL-6R, IL-1RA, IL-1β, or GM-CSF antagonists, or a BTK inhibitor, within 7 days of randomization.
10. Treatment with a JAK inhibitor within 30 days of randomization.
11. Concurrent participation in any other interventional clinical study or experimental treatment for COVID-19 or ARDS.

    Note: Participants on clinical studies evaluating investigational antivirals are allowed.

12. ALT or AST > 5 × ULN detected within 24 hours at screening (according to local laboratory reference ranges).
13. Participants who have known evidence of liver cirrhosis (Child-Pugh A to C).
14. Active metastatic malignancy within 1 year of screening, unless with medical monitor approval.
15. ANC < 1.0×10^9/L at screening (according to local laboratory).
16. Platelet count < 50×10^9/L at screening (according to local laboratory).
17. Pregnant or nursing (lactating) women.
18. Females of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using highly effective methods of contraception as defined below, throughout the study and for up to 30 days after stopping treatment.

    Highly effective contraception methods (Appendix A) include the following:

    a. Total abstinence (when this is in line with the preferred and usual lifestyle of the participant). Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not acceptable methods of contraception.
    b. Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least 6 weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment.
    c. Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that participant.
    d. Use of oral, injected, or implanted hormonal methods of contraception. Placement of an IUD or IUS or other forms of hormonal contraception that have comparable efficacy (failure rate < 1%), for example hormone vaginal ring or transdermal hormone contraception (in case of oral contraception, participants should have been using the same pill on a stable dose for a minimum of 3 months before screening).

    Women are considered postmenopausal and not of childbearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (eg, age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy, or tubal ligation at

least 6 weeks before screening. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow-up hormone level assessment is she considered not of childbearing potential.

7. STUDY TREATMENT

7.1. Study Treatment Administered

Ruxolitinib 5 mg tablets or matching placebo will be administered BID approximately 12 hours apart (morning and night) without regard to food/feeding. One or 3 tablets will be administered per dose, depending on the assigned treatment arm (ie, 1 tablet per dose for 5 mg ruxolitinib/placebo and 3 tablets per dose for 15 mg ruxolitinib/placebo).

Initially, ruxolitinib will be administered through an enteric feeding tube as follows:

- Suspend tablet(s) in approximately 40 mL of water with stirring for approximately 10 minutes.
  - For 5mg BID ruxolitinib/placebo treatment assignment: one 5 mg tablet in 40 mL water
  - For 15 mg BID ruxolitinib/placebo treatment assignment: three 5 mg tablets in 40 mL water

  Within 6 hours after the tablet has dispersed, the suspension can be administered through the enteric feeding tube using an appropriate syringe.
- The tube should be rinsed with approximately 75 mL of water.

Dosing of ruxolitinib during prone positioning is permitted if consistent with institutional policy. If enteric medication administration is not possible during prone positioning, administration of ruxolitinib should occur before or after proning sessions, adhering as closely to the BID dosing schedule as possible.

If a participant is extubated during the study and is able to take oral medication, study drug may be administered orally with water, without regard to food.

The recommended duration of treatment is up to 14 days. Beginning on Day 15, treatment may be extended another 14 days (through Day 28) at the discretion of the investigator, if the benefits of treatment outweigh the risks, and with approval from the sponsor medical monitor.

Dose reductions or interruptions for any toxicity attributed to ruxolitinib are permitted to allow the participant to continue on study treatment (see Section 7.6.2).

Table 5 presents the study treatment information.

Table 5: Study Treatment Information

Investigational/Control Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type
Ruxolitinib 5 mg	Tablet	Enteric feeding tube or oral	Double-blind supply; bottles
Placebo for 5 mg ruxolitinib	Tablet	Enteric feeding tube or oral	Double-blind supply; bottles

7.1.1. Supply of Study Treatment

No additional treatment beyond ruxolitinib 5 mg tablets or matching image placebo tablets will be provided. Ruxolitinib will packaged in 60-count high-density polyethylene bottles. All tablet excipients comply with the requirements of the applicable compendial monographs.

If the participant continues treatment beyond the initial 14-day treatment period, if needed, the IRT should be contacted to dispense additional study drug.

7.1.2. Treatment Duration

The planned initial duration of treatment is 14 days. Treatment may be extended to an additional 14 days (ie, Days 15-28) at the discretion of the investigator, if the benefits of treatment outweigh the risks, and with approval from the sponsor medical monitor. Approval must be requested ≥ 24 hours before initiation of dosing on Day 15. Participants may be discontinued from treatment earlier due to unacceptable toxicity, progression/worsening of COVID-19 ARDS, or resolution/improvement of COVID-19 symptoms and/or at the discretion of the investigator or the participant. Treatment will not be provided upon completion of the study.

7.2. Other Treatments

7.2.1. Concomitant Therapy

All medications, procedures, and significant nondrug therapies administered from randomization through Day 29 must be recorded on the appropriate eCRFs. Additionally, antivirals and therapeutic agents administered for SaRS-CoV-2 infection/COVID-19 infection and treatments for COVID-19–associated ARDS administered within 14 days of randomization must also be recorded.

Each concomitant drug must be individually assessed against all exclusion criteria/prohibited medication. If in doubt, the investigator should contact the Incyte medical monitor before randomizing a participant or allowing a new medication to be started. If the participant is already enrolled, contact Incyte to determine if the participant should continue participation in the study.

7.2.1.1. Permitted Concomitant Therapy Requiring Caution and/or Action

Participants may receive the following (not inclusive): antiemetics, calcineurin inhibitors, azole fungal prophylaxis, antibiotics, acyclovir prophylaxis, granulocyte-colony stimulating factor, corticosteroid premedications prior to RBC/platelet transfusions, narcotics, and sedatives; however, close monitoring of potential drug-drug interaction effects of these concurrent drugs is warranted.

Use of oral, injected, or implanted hormonal methods of contraception are allowed while on ruxolitinib.

In the presence of potent CYP3A4 inhibitors, there is the possibility of increased exposure to ruxolitinib. Dose adjustment when coadministering ruxolitinib and a potent CYP3A4 inhibitor is only required for participants assigned to the 15 mg BID ruxolitinib/placebo arm; see Section 7.2.1.2 for additional details. No dose adjustment is required for participants

randomized to the 5 mg BID ruxolitinib/placebo arm. See Appendix D for a list of CYP3A4 inhibitors and inducers.

The participant and the treating investigator should be aware of potential signs of overdose of the concomitant medications; in the event of suspected study drug–related toxicity, administration of ruxolitinib should be dose reduced or held according to the treating investigator's judgement.

For additional information, please refer to the IB.

7.2.1.2. Coadministration With Potent CYP3A4 Inhibitors

Coadministration of ruxolitinib and potent CYP3A4 inhibitors may result in increased ruxolitinib exposure; in the setting of potent CYP3A4 inhibitors (see Appendix D for a list), participants assigned **to the 15 mg BID ruxolitinib/placebo arm only** should be reduced 1 dose level (see Table 6) with daily complete blood cell count monitoring during the period of coadministration.

7.2.1.3. CRRT and Intermittent Hemodialysis

If a participant requires CRRT during the study treatment period, the ruxolitinib/placebo dose frequency should be reduced from BID to QD. If a participant requires intermittent hemodialysis during the study treatment period, the assigned ruxolitinib/placebo dose should only be given on hemodialysis days and following each hemodialysis session.

7.2.2. Prohibited Medication

The following medications are prohibited until treatment discontinuation:

- Concomitant use of another JAK inhibitor or IL-6/IL-6R, IL-1RA, IL-1β, or GM-CSF antibodies.
- Any investigational medication except antivirals being used to treat SARS-CoV-2 infection or ARDS.
- Aspirin in doses exceeding 150 mg/day.

For additional information, refer to the IB.

7.3. Participant Numbering, Treatment Assignment, and Randomization

7.3.1. Participant Numbering

Each participant is identified in the study by a participant number that is assigned by the IRT when the participant is enrolled for screening and is retained for the participant throughout participation in the study. A new participant number will be assigned at every subsequent enrollment if the participant is rescreened. The participant number consists of the center number (as assigned by Incyte to the investigative site) with a sequential participant number suffixed to it so that each participant's participation is numbered uniquely across the entire database. Upon signing the ICF (or having the consent signed on their behalf by their legal guardian/health care proxy) and assent (if applicable), participants are assigned to the next sequential participant number available.

7.3.2. Treatment Assignment, and Randomization

Block randomization with stratification for severity of ARDS (mild/moderate [$PaO_2/FiO_2 > 100$ to ≤ 300 mmHg] vs severe [$PaO_2/FiO_2 \leq 100$ mmHg]) and investigational site will be used. Participants will be randomly assigned to either ruxolitinib 5 mg BID, ruxolitinib 15 mg BID, or placebo. All participants will be centrally assigned to study treatment using an IRT system. The randomization schedule will be generated by a sponsor-independent statistician and sent directly to the IRT vendor without being provided to the Sponsor. Before the study is initiated, the URL and contact information (if applicable) for the IRT and/or the log-in information and directions for the IRT will be provided to each site. Full details will be provided in the IRT manual.

7.4. Treatment Blinding

Participants, investigator staff, persons performing the assessments, and the Incyte study team will remain blind to the identity of the treatment from the time of randomization until database lock using the following methods: (a) randomization data will be kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study, and (b) the identity of the treatments will be concealed by the use of study treatments that are all identical in packaging, schedule of administration, appearance, taste, and odor.

Unblinding will occur in the case of participant emergencies and at the conclusion of the study. If the investigator feels that unblinding prior to completion of the treatment period is clinically indicated, consult the Medical Monitor.

7.5. Dose Modification

7.5.1. Dose Modifications

Dose reductions or interruptions for worsening cytopenias or nonhematologic toxicity attributed to ruxolitinib are permitted to allow the participant to continue on study treatment (see Section 7.6.2 for additional guidance). For the purpose of dose modifications, Table 6 will be used to guide dose reductions based on treatment arm assignment.

Table 6: Ruxolitinib Dose Levels

Treatment Arm	Dose Level 1 (Initial Dose)	Dose Level −1
Ruxolitinib/placebo: 5 mg BID	5 mg BID	5 mg QD
Ruxolitinib/placebo: 15 mg BID	15 mg BID	5 mg BID

Dose modifications must be reported in the appropriate eCRFs.

7.5.1.1. Follow-Up on Potential Drug-Induced Liver Injury Cases

Transaminase increase combined with total bilirubin increase may be indicative of potentially severe DILI, which should be considered a clinically important event and assessed appropriately to establish the diagnosis. The required clinical information, as detailed in the following text, should be sought to obtain the medical diagnosis of the most likely cause of the observed laboratory abnormalities.

The threshold for potential DILI may depend on the participant's baseline AST/ALT and total bilirubin; participants meeting any of the following criteria will require further follow-up as outlined as follows:

- For participants with normal ALT and AST and total bilirubin at baseline: AST or ALT > 3.0 × ULN combined with total bilirubin > 2.0 × ULN.
- For participants with elevated AST or ALT or total bilirubin value at baseline: (AST or ALT > 2 × baseline) OR (AST or ALT > 300 U/L), whichever occurs first, combined with (total bilirubin > 2 × baseline AND > 2.0 × ULN).

Because DILI is essentially a diagnosis of exclusion, other causes of abnormal liver tests should be considered and their role clarified before DILI is assumed as the cause of liver injury.

A detailed history, including relevant information such as review of ethanol consumption, concomitant medications, herbal remedies, supplement consumption, and history of any pre-existing liver conditions or risk factors, should be collected.

Laboratory tests should include ALT, AST, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, glutamate dehydrogenase, prothrombin time/international normalized ratio, ALP, albumin, and CK.

7.6. Additional Treatment Guidance

7.6.1. Treatment Compliance

Treatment will be recorded on the appropriate eCRF.

7.6.2. Recommended Treatment of Adverse Events

Dose reductions or interruptions for worsening cytopenias attributed to ruxolitinib/placebo are permitted to allow the participant to continue on study treatment. Table 6 describes dose levels of ruxolitinib by treatment arm. Dose adjustments for different ranges of cytopenias are described in the following text. Use of transfusion support is allowed during the study.

7.6.2.1. Neutropenia

Grade 3 (ANC < 1.0 to 0.5×10^9/L): Reduce by 1 dose level, monitor ANC daily until resolved to ≤ Grade 2, and then resume initial dose level.

Grade 4 (ANC < 0.5×10^9/L): Hold dose, monitor ANC daily until resolved to ≤ Grade 3, and then resume at 1 dose level lower. If resolves to ≤ Grade 2, can resume at initial dose level.

7.6.2.2. Thrombocytopenia

Transfusion support should be provided as clinically indicated.

For platelet counts < 20×10^9/L: hold dose until resolved to ≥ 20×10^9/L and then resume at 1 dose level lower. If counts are stable, dose may be cautiously re-escalated to initial dose level.

Dose reductions or interruptions for nonhematologic toxicity are permitted to allow the participant to continue on study treatment. Dose adjustments for different ranges of nonhematologic toxicity are described in the following text. The objective of the dose

adjustment rules is to optimize treatment response for each individual participant while avoiding significant nonhematologic toxicities.

7.6.2.3. Other Adverse Events (Nonhematologic) Attributed to Ruxolitinib/Placebo

Recommendation for Grade 1 or 2: maintain dose level.

Recommendation for Grade 3: reduce by 1 dose level until resolved to ≤ Grade 2.

Recommendation for Grade 4: discontinue from study treatment.

Medication used to treat AEs must be recorded on the appropriate eCRF.

7.7. Preparation and Dispensation

Each study site will be supplied with study drug in packaging as described in Section 7.4.

A unique medication number is printed on the study medication label.

7.7.1. Handling of Study Treatment

Study treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designated site personnel have access. Upon receipt, all study treatment must be stored according to the instructions specified in the IB (or Pharmacy Manual). Bottles of ruxolitinib tablets should be stored at room temperature (15°C-30°C [59°F-86°F]).

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

The investigator must maintain an accurate record of the shipment and dispensing of study treatment in a drug accountability log. Monitoring of drug accountability will be performed by monitors during on-site visits or remotely and at the completion of the study (on-site or remotely). Participants will be asked to return all unused study treatment and packaging at the end of the study or at the time of discontinuation of study treatment.

The study site may destroy all unused study treatment, packaging, and drug labels locally per site policies and procedures, which are subject to review and prior approval by Incyte. If local destruction or procedure is not available, the site may return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the address indicated in the Pharmacy Manual.

8. INFORMED CONSENT PROCEDURES

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB-approved informed consent (and assent, as applicable); informed consent may be obtained from a health care proxy where appropriate and/or institutionally approved method of consenting when applicable (verbal consent) as defined in their local consent form.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent (and assent, as applicable) must be obtained before conducting any study-specific procedures (eg, all of the procedures described in the Protocol). The process of obtaining informed consent (and assent, as applicable) must be documented in the participant source documents. The date when a participant's informed consent was actually obtained will be captured in their eCRFs.

Incyte will provide to investigators in a separate document a proposed ICF that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent/assent form suggested by the investigator must be agreed upon by Incyte before submission to the IRB.

Information about common side effects already known about the investigational drug can be found in the IB. This information will be included in the participant informed consent/assent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drug that is identified between IB updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent/assent and then must be discussed with the participant.

Women of childbearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study, they must adhere to the contraception requirements during treatment and after discharge from hospital.

Male participants must be informed that if a female partner becomes pregnant during treatment or after discharge from the hospital and within 30 days of the last dose of study medication, contact with the female partner will be attempted to request her consent/assent to collect pregnancy outcome information.

A copy of the approved version of all consent and assent forms must be provided to Incyte after IRB approval.

9. VISIT SCHEDULE AND ASSESSMENTS

The SoA (see Table 3) lists all of the assessments and when they are performed. All data obtained from these assessments must be supported in the participant's source documentation. Any assessments outlined in Table 3 otherwise performed per standard of care may be used to satisfy study requirements.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (see Table 3) or as close to the designated day/time as possible. Missed or omitted visits or assessments should not lead to automatic discontinuation. Participants who prematurely discontinue the study (see Section 10.1.1) for any reason should be scheduled for a visit (in person or remote) as soon as possible, at which time all of the assessments listed for the final visit will be performed. At this final visit, all dispensed investigational product should be reconciled, and the AE and concomitant medications should be recorded on the eCRF.

If a participant is discharged from the hospital during the study period, the clinical status evaluation with 9-point ordinal scale will be performed via telephone call (7:00 AM-12:00 PM local time) daily, except for Day 15 and Day 29 when it will be performed in clinic, when possible (telephone contact is an acceptable alternative for clinic visits). If the participant is unable to return to the clinic on Day 15 and Day 29, all scheduled assessments may be performed by telephone; local laboratory assessments may be performed on Day 15 and/or Day 29 if feasible.

9.1. Screening

The screening assessments should be performed within 1 day (defined as a 24-hour period, independent of calendar days) prior to randomization and Day 1 assessments. If the screening and Day 1 visits are conducted on the same day, overlapping assessments do not need to be repeated. Screening laboratory assessments may be repeated if considered spurious or invalid. No rescreening will be allowed.

9.1.1. Information to Be Collected on Screening Failures

Participants who give informed consent (directly or via legal guardian/health care proxy; with assent as applicable) and are subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate eCRF. The demographic information, informed consent/assent (as applicable), and eligibility forms must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures. If the participant fails to be randomized, the IRT must be notified within 1 day of the screen failure that the participant was not randomized.

Participants who are randomized and fail to start treatment (eg, participants randomized in error) will be considered an early terminator. The reason for early termination should be recorded on the appropriate eCRF.

9.2. Participant Demographics/General Medical History

Country-specific regulations should be considered for the collection of demographic and baseline characteristics in alignment with eCRF.

Participant race and ethnicity are collected and analyzed to identify variations in safety or efficacy due to these factors as well as to assess the diversity of the study population as required by Health Authorities.

Medical history will include relevant medical or surgical treatment unrelated to SARS-CoV-2 infection or COVID-19 within the past 6 months that are considered to be clinically significant by the investigator.

9.3. Efficacy

9.3.1. Clinical Status (9-Point Scale)

Assessment of clinical status using a 9-point ordinal scale (WHO 2020b) will be recorded at baseline on Day 1 and then again once daily every morning (between 7:00 AM and 12:00 PM local time) through Day 29 of the study period. If a participant is discharged from the hospital, the assessment will be made by phone (between 7:00 AM and 12:00 PM local time). Each day, the worst score for the previous day will be recorded (ie, on Day 3, Day 2 score is obtained and recorded as Day 2). The scale is shown in Table 7.

Table 7: COVID-19 9-Point Ordinal Clinical Status

Participant State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory[a]	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild Disease	Hospitalized, no oxygen therapy (defined as $SpO_2 \geq 94\%$ on room air)	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – vasopressors, RRT, ECMO	7
Dead	Death	8

[a] Defined as not in hospital or in hospital and ready for discharge.

If the participant dies, the date of death will be collected in the eCRF.

9.3.2. Vital Signs

Vital sign measurement include respiratory rate, heart rate, systolic and diastolic blood pressure, and body temperature; one set of vital signs will be collected daily while hospitalized. While the participant is in the ICU, the daily vital sign collection should be the same as that used for the cardiovascular component (mean arterial pressure) of the of the SOFA score.

9.3.3. Arterial Blood Gases, PaO_2/FiO_2, and Pulse Oximetry

Arterial blood gases will be collected during screening, within 6 hours of planned randomization, to assess PaO_2/FiO_2 for eligibility, and daily thereafter while on a ventilator or if an arterial line is present. The FiO_2 being administered at the time of ABG collection should be recorded. The following parameters will be collected for each ABG: pH, PaO_2, $PaCO_2$, and SaO_2. Oxygen saturation (SpO_2 via pulse oximetry) will be recorded once daily while hospitalized; SpO_2 is not required after hospital discharge.

9.3.4. Sequential Organ Failure Assessment Score

The SOFA score (Appendix C) is a scoring system to determine the extent of a person's organ function or rate of failure. The score is based on 6 different scores, 1 each for the respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems. The screening/Day 1 assessment should be based on data collected closest to (but also prior to) randomization. Each subsequent day should use the worst value for each parameter in the preceding 24-hour period.

At each required timepoint, the SOFA score will be calculated by the investigative site and recorded in the appropriate eCRF. The SOFA score assessments are no longer required after discharge from the ICU.

9.3.5. In-Hospital Outcomes

In addition to endpoints mentioned above, the following in-hospital outcomes will be captured on eCRFs:

- Ventilator-free days
- ICU-free days
- Vasopressor-free days
- Hospital-free days
- Oxygen-free days

9.3.6. Lung Imaging

A chest x-ray or chest CT scan is required at the screening assessment. If a chest x-ray or chest CT has been performed per standard of care within the 2 days prior to the screening visit, no additional chest imaging needs to be performed. Chest x-ray/CT findings performed as standard of care during the study should be recorded on the appropriate eCRF.

9.4. Safety

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

9.4.1. Adverse Events

Adverse events will be monitored from the time the participant signs the ICF until the 28-day post-treatment AE assessment (28 ± 3 days after last dose of study treatment). Adverse events that begin or worsen after informed consent should be recorded on the Adverse Events Form in

the eCRF regardless of the assumption of a causal relationship with ruxolitinib/placebo. Conditions that were already present at the time of informed consent should be recorded on the Medical History Form in the eCRF. Adverse events (including laboratory abnormalities that constitute AEs) should be described using a diagnosis whenever possible rather than by individual underlying signs and symptoms.

All SAEs will be recorded and reported to the sponsor or designee within 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 10.1.4).

9.4.2. Presence SARS-CoV-2 Virus/Viral Load/Antibody Testing

For the screening inclusion criterion, SARS-CoV-2 virus is to be measured by PCR or by other locally approved diagnostic methodology ≤ 3 weeks of randomization. Documentation of the method used should be available in the source notes. Viral load and antibody testing may be performed by any approved method and is only required if local capabilities allow; a consistent method and specimen source should be used at all timepoints.

9.4.3. Laboratory Evaluations

Laboratory evaluations will be performed by a local laboratory.

9.4.3.1. Hematology

Hemoglobin, hematocrit, RBC count, white blood cell count with differential, and platelet count will be measured according to the assessment schedule in Table 3.

9.4.3.2. Chemistry

Blood urea nitrogen/urea, creatinine, CK (total), CK-MB, total bilirubin, AST, ALT, ALP, sodium, potassium, chloride, calcium, bicarbonate, total protein, albumin, and glucose will be measured according to the assessment schedule in Table 3. If a given test is not available locally, this should be documented on the eCRF.

If the total bilirubin concentration is increased above 1.5 × ULN, the total bilirubin will differentiated into the direct and indirect reacting bilirubin.

9.4.3.3. Inflammatory Markers

- Ferritin
- CRP
- D-dimer
- Procalcitonin
- IL-6 at sites where feasible

Samples will be collected at the timepoints defined in Table 3. If a given test is not available locally, this should be documented on the eCRF.

9.4.3.4. Monitoring of Thromboembolic Risk

Laboratory parameters to assess thromboembolic risk, including D-dimer, aPTT, and fibrinogen, should be monitored per SoC.

Participants deemed at high risk for thromboembolic sequelae and eligible for prophylactic or therapeutic intervention per local evaluation should be considered for appropriate anticoagulation.

9.4.4. Height and Weight

If possible, height in centimeters will be measured at screening as specified in the SoA (see Table 3). Otherwise, participant- or legal guardian/health proxy-reported height will be obtained.

Body weight will be measured at the screening visit as specified in Table 3.

9.4.5. Pregnancy and Assessments of Fertility

A serum pregnancy test (serum hCG) will be performed at screening assessment in women of childbearing potential. Serum or urine pregnancy testing is acceptable at subsequent assessment(s) (see Table 3).

9.5. Correlative Studies

9.5.1. Sample Collection, Processing, and Shipment

An optional serum sample will be collected at Day 1 (predose) and Day 7 and 15 for cytokine analysis. See Appendix E for instructions on sample collection, processing, storage and shipment.

9.5.2. Biomarker Analysis

Proteomic analysis will be conducted on serum samples to evaluate the levels of circulating inflammatory mediators including, but not limited to, GM-CSFα, TNF-α, IFN-γ, and IL-1a at Day 1 (predose) and on Days 7 and 15. These assessments will improve our understanding of the role of JAK inhibition in resolving the cytokine storm associated with COVID-19–associated ARDS participants.

10. TREATMENT DISCONTINUATION AND STUDY WITHDRAWAL

10.1. Discontinuation and Completion

10.1.1. Study Treatment Discontinuation and Study Withdrawal

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the participant or the investigator.

The investigator must discontinue study treatment for a given participant if he/she believes that continuation would negatively affect the participant's well-being.

Study treatment must be discontinued under the following circumstances:

- Participant/health care proxy decision.
- Pregnancy.
- Use of prohibited treatment as per recommendations in the prohibited treatment section (see Section 7.2.2).
- Any situation in which study participation might result in a safety risk to the participant.
- Following emergency unblinding.
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant's overall status, prevent the participant from continuing participation in the study.

If discontinuation of study treatment occurs, the investigator should make a reasonable effort to understand the primary reason for the participant's premature discontinuation of study treatment and record this information.

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see Section 10.1.3). If they fail to return (either in person or remotely) for these assessments for unknown reasons, every effort (eg, telephone, e-mail, letter) should be made to contact the participant/predesignated contact as specified in Section 10.1.4. This contact should preferably be done according to the study visit schedule.

If the participant cannot or is unwilling to attend any visit(s), the site staff should maintain regular telephone contact with the participant or with a person predesignated by the participant. This telephone contact should preferably be done according to the study visit schedule.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/e-mail contact:

- New/concomitant treatments.
- AEs/SAEs.

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, see Section 11.5.

10.1.2. Replacement Policy

Participants discontinuing the study will not be replaced.

10.1.3. Withdrawal of Informed Consent

Participants (or health care proxy who provided consent on behalf of the participant) may voluntarily withdraw consent (or assent) to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant does not want the following:

- To participate in the study anymore.
- Any further visits or assessments.
- Any further study-related contacts.

In this situation, the investigator should make a reasonable effort (eg, telephone, e-mail, letter) to understand the primary reason for the participant's decision to withdraw consent and record this information.

Where consent to the use of personal and coded data is not required, participants cannot withdraw consent. They still retain the right to object to the further use of personal data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communication or follow-up.

All efforts should be made to complete the assessments prior to study discontinuation. A final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table.

Incyte will continue to retain and use all research results (data) that have already been collected for the study evaluation.

10.1.4. Lost to Follow-Up

A participant will be considered lost to follow-up if he/she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

10.1.5. Early Study Termination by the Sponsor

The study can be terminated by Incyte at any time.

Reasons for early termination include the following:

- Individual treatment arms or the entire study may be stopped based on review and recommendation from the DMC, including futility as defined in Section 12.5.2.
- Unexpected, significant, or unacceptable safety risk to participants enrolled in the study.
- Decision based on recommendations from applicable board(s) after review of safety and efficacy data.
- Discontinuation of study drug development.

In making the decision to terminate, Incyte will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as prematurely withdrawn participants. The investigator may be informed of additional procedures to be followed to ensure that adequate consideration is given to the protection of the participants' interests. The investigator or sponsor, depending on local regulation, will be responsible for informing IRBs of the early termination of the study.

10.2. Study Completion and Post–Study Treatment

Study completion is defined as when the last participant finishes the final assessment and any procedures or assessments associated with this visit have been documented and followed up appropriately by the investigator or, in the event of an early study termination decision, the date of that decision (eg, each participant will be required to complete the study in its entirety and thereafter no further study treatment will be made available to that participant).

All randomized and/or treated participants should have a safety follow-up assessment conducted by telephone or video call 28 days (± 3 days) for AE review after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 11.4. Documentation of attempts to contact the participant should be recorded in the source documentation.

11. ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

11.1. Definition of Adverse Event

Adverse Event Definition
• An AE is any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug-related. • An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study treatment.
Additional Guidance for Events Meeting the Adverse Event Definition
• Any safety assessments (eg, ECG, vital signs measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator (ie, not related to worsening of underlying disease), should be reported as an AE. • Abnormal laboratory test results constitute an AE if they are considered clinically meaningful, induce clinical signs or symptoms, require concomitant therapy, or require changes in study drug. Whenever possible, a diagnosis (eg, anemia, thrombocytopenia) should be recorded in the eCRF rather than the abnormal laboratory test result (eg, low hemoglobin, platelet count decreased). • Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition constitute an AE. • New conditions detected or diagnosed after study treatment administration even though they may have been present before the start of the study, should be reported as an AE. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction constitute an AE. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study treatment or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae. • "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE (including disease progression). Such instances will be captured in the efficacy assessments. • A condition that leads to a medical or surgical procedure (eg, endoscopy, appendectomy) is an AE if it occurred after signing informed consent. If present before entering the study, the condition should be captured as medical history. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital) need not be considered AEs. • Anticipated day-to-day fluctuations of pre-existing disease(s), or condition(s) present, or detected at the start of the study judged by the investigator to have worsened more than expected for the participant's condition since study participation should be reported as an AE.

11.2. Definition of Serious Adverse Event

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A Serious Adverse Event is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an adverse drug experience that places the participant, in the opinion of the initial reporter, at immediate risk of death from the adverse experience as it occurred. This does not include an adverse drug experience that, had it occurred in a more severe form, might have caused death.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether hospitalization occurred or was necessary, the AE should be considered serious. Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
d. Results in persistent or significant disability/incapacity • The term "disability" means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), that may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
e. Is a congenital anomaly/birth defect
f. Other situations (Important Medical Event) An event that may not result in death, be immediately life-threatening, or require hospitalization but may be considered serious when, based on appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent 1 of the outcomes listed in the above definition. Examples of such events include new invasive or malignant cancers, intensive treatment in an emergency department or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

11.3. Recording and Follow-Up of Adverse Events and/or Serious Adverse Events

Adverse Event and Serious Adverse Event Recording

- An AE/SAE that begins or worsens after informed consent is signed through safety follow-up should be recorded on the Adverse Event Form in the eCRF. Conditions that were present at the time informed consent was given should be recorded on the Medical History Form in the eCRF.
- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The investigator (or delegate) will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records in lieu of completing the AE eCRF page.
- There may be instances when copies of medical records for certain cases are requested. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission.
- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE. When a clear diagnosis cannot be identified, each sign or symptom should be reported as a separate AE/SAE.

To the extent possible, each AE/SAE should be evaluated to determine:

- The severity grade (CTCAE v5.0 Grade 1 to 5). See below for further instructions on the assessment of intensity.
- Whether there is at least a reasonable possibility that the AE is related to the study treatment (including study drug): suspected (yes) or not suspected (no). See below for further instructions on the assessment of causality.
- The start and end dates, unless unresolved at final follow-up.
- The action taken with regard to study drug as a result of the AE/SAE(s).
- The event outcome (eg, not recovered/not resolved, recovered/resolved, recovering/resolving, recovered/resolved with sequelae, fatal, unknown).
- The seriousness, as per the SAE definition provided in Section 11.2.
- The action taken with regard to the event. Note: If an AE is treated with a concomitant medication or nondrug therapy, this action should be recorded on Adverse Event Form and the treatment should be specified on the appropriate eCRF (eg, Prior/Concomitant Medications, Procedures and Non-Drug Therapy).

Assessment of Intensity

The severity of AEs will be assessed using CTCAE v5.0 Grades 1 through 5. If an event is not classified by CTCAE, the severity of the AE will be graded according to the scale below to estimate the grade of severity.

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- **Grade 1:** Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; treatment not indicated.
- **Grade 2:** Moderate; minimal, local, or noninvasive treatment indicated; limiting age appropriate activities of daily living.

- **Grade 3:** Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
- **Grade 4:** Life-threatening consequences; urgent treatment indicated.
- **Grade 5:** Fatal.

Assessment of Causality

- The investigator is obligated to assess the relationship between study treatment and each occurrence of each AE/SAE. If reference therapy is used in combination with an Incyte study drug or multiple Incyte study drugs are used, the relationship to each study drug must be assessed (ie, for the Incyte product(s) and for the other product(s) that is used in combination with the Incyte product). If appropriate, the relationship to the combination may be assessed as well.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than that a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- The investigator will also consult the Reference Safety Information in the IB and/or Product Information, for marketed products, in his/her assessment.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study treatment administration, will be considered and investigated.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- With regard to assessing causality of SAEs:
  - There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report. However, the causality assessment is one of the criteria used when determining regulatory reporting requirements. **Therefore, it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE.**
  - The investigator may change his/her opinion of causality in light of follow-up information and send a follow-up SAE report with the updated causality assessment.

Follow-Up of Adverse Events and Serious Adverse Events

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- New or updated information will be recorded in the eCRF.
- Any updated SAE data will be submitted to the sponsor (or designee) within 24 hours of receipt of the information.
- Once an AE is detected, it should be followed until it has resolved or until it is judged to be permanent; assessment should be made at each visit (or more frequently if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat the event, and the outcome.
- When the severity of an AE changes over time for a reporting period (eg, between visits), each change in severity will be reported as a separate AE until the event resolves.

11.4. Reporting of Serious Adverse Events

Regardless of suspected causality (eg, relationship to study drug or study procedures), all SAEs occurring after the participant has signed the ICF through AE/safety follow-up (28 ± 3 days after last dose of study treatment) must be reported to the sponsor (or designee) within **24 hours** of learning of its occurrence, unless otherwise specified by the Protocol. The investigator will submit any updated SAE data to the sponsor (or designee) within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE information after conclusion of study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study treatment or study participation, the investigator must notify the sponsor (or designee) within 24 hours of becoming aware of the event.

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 10.1.4).

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study treatment under clinical investigation are met.

If the SAE is not documented in the IB for the study drug (new occurrence) and is thought to be related to the sponsor's study drug, the sponsor or its designee may urgently require further information from the investigator for reporting to health authorities. The sponsor or its designee may need to issue an Investigator Notification to inform all investigators involved in any study with the same drug that this SAE has been reported. Suspected unexpected serious adverse reactions will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC, or as per national regulatory requirements in participating countries.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study treatment under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRB, and investigators.

Investigator safety reports must be prepared for suspected unexpected serious adverse reactions according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives an investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the IB and will notify the IRB, if appropriate according to local requirements.

Serious Adverse Event Reporting
• Information about all SAEs is collected and recorded on the Adverse Event Form in the eCRF. • The investigator must report within 24 hours of learning of its occurrence any SAEs via the EDC system (primary method) or by completing the Incyte Serious Adverse Event Report Form, in English (only if EDC system is not available). • Follow-up information is also recorded in the eCRF and transmitted to Incyte PhV via the EDC system. The follow-up report should include information that was not provided previously, such as the outcome of the event (eg, resolved or ongoing), treatment provided, action taken with study drug because of the SAE (eg, dose reduced, interrupted, or discontinued), or participant disposition (eg, continued or withdrew from study participation). Each recurrence, complication, or progression of the original event should be reported as follow-up to that event, regardless of when it occurs. • In circumstances where the EDC system would not work properly, initial and/or follow-up SAE information shall be documented on new or amended Serious Adverse Event Report Form. Refer to the Incyte Reference Guide for Completing the Serious Adverse Event Report Form. • Email transmission (or facsimile) of the Serious Adverse Event Report Form is the preferred method to transmit this information to the PhV/designee. The contact information of the sponsor's study-specific representatives is listed in the Study Reference Manual provided to each site. The original copy of the Serious Adverse Event Report Form and the confirmation sheet must be kept at the study site. • Contacts for SAE reporting can be found in the Study Procedures Manual.

11.5. Emergency Unblinding of Treatment Assignment

In a medical emergency, if knowledge of the treatment assignment is necessary to determine optimal medical management of the participant, the procedure for emergency unblinding is provided in the IRT Manual. This option may be used only if the participant's well-being requires the investigator to be aware of the participant's treatment assignment. If a participant's treatment assignment is unblinded, the sponsor or its designee must be notified immediately by telephone.

If an investigator, site personnel performing assessments, or participant is unblinded, the participant must be withdrawn from the study treatment, unless there are ethical reasons to have the participant remain on the study treatment. In these cases, the investigator must obtain specific approval from the sponsor's (or its designee's) medical monitor for the participant to continue in the study.

11.6. Pregnancy

Pregnancy, in and of itself, is not regarded as an AE unless there is suspicion that study drug may have interfered with the effectiveness of a contraceptive medication or method. When a pregnancy has been confirmed in a participant during maternal or paternal exposure to study drug, the following procedures should be followed in order to ensure safety:

- The study drug must be discontinued immediately unless the investigator, with approval from the medical monitor, agrees that the risks of continued treatment do not outweigh the potential benefits of continuing, given the life-threatening nature of COVID-19–associated ARDS (female participants only).

- The investigator must complete and submit the Incyte Clinical Trial Pregnancy Form to the sponsor or its designee within **24 hours** of learning of the pregnancy.

Data on fetal outcome are collected for regulatory reporting and drug safety evaluation. Follow-up should be conducted for each pregnancy to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, by following until the first well-baby visit. Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the sponsor or its designee. Pregnancy follow-up information should be recorded on the same form and should include an assessment of the possible causal relationship to the sponsor's study drug to any pregnancy outcome, as well as follow-up to the first well-baby visit or the duration specified in local regulations, whichever is later. Refer to the Incyte Reference Guide for Completing the Clinical Trial Pregnancy Form.

Any SAE occurring during pregnancy of a study participant must be recorded on the Serious Adverse Event Report Form and submitted to the sponsor or designee.

Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, or ectopic pregnancy) are considered SAEs (if occurring in the study participant) and must be reported as described in Section 11.4. If an abnormal pregnancy outcome is reported in a study participant's partner, the event should be reported to the sponsor on the Clinical Trial Pregnancy Form.

11.7. Warnings and Precautions

Special warnings or precautions for the study drug, derived from safety information collected by the sponsor or its designee, are presented in the IB. Additional safety information collected between IB updates will be communicated in the form of Investigator Notifications. Any important new safety information should be discussed with the participant during the study, as necessary. If new significant risks are identified, they will be added to the ICF.

11.8. Product Complaints

The sponsor collects product complaints on study drugs and drug delivery systems used in clinical studies in order to ensure the safety of study participants, monitor quality, and facilitate process and product improvements.

All product complaints associated with material packaged, labeled, and released by the sponsor or its designee will be reported to the sponsor.

The investigator or his/her designee is responsible for reporting a complete description of the product complaint via email or other written communication to the sponsor contact or respective manufacturer as noted in the packaging information. Any AE associated with a product complaint should be recorded as described in Section 11.3.

If the investigator is asked to return the product for investigation, he/she will return a copy of the product complaint communication with the product.

11.9. Treatment of Overdose

For this study, any dose of study treatment greater than 30 mg ruxolitinib/placebo within a 24-hour time period will be considered an overdose.

Incyte does not recommend specific treatment for an overdose.

In the event of an overdose, the investigator should:

- Contact the medical monitor immediately.
- Closely monitor the participant for any AE/SAE and laboratory abnormalities.
- Document the quantity of the excess dose as well as the duration of the overdose in the eCRF.

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

12. STATISTICS

12.1. Sample Size Determination

The primary endpoint of this study is the proportion of participants who die on or prior to Day 29. Participants will be randomized at a 2:2:1 (5 mg BID ruxolitinib:15 mg BID ruxolitinib:placebo) ratio. The primary endpoint will be tested using a logistic regression mixed model including treatment group, ARDS severity (mild/moderate [$PaO_2/FiO_2 > 100$ to ≤ 300] vs severe [$PaO_2/FiO_2 \leq 100$]), and gender as covariates and investigational site as a random (intercept) effect. The Wald test for the treatment regression coefficient will test the primary endpoint. Individual comparisons between placebo and ruxolitinib treatment arms will be performed in a pairwise fashion (placebo vs 5 mg BID and placebo vs 15 mg BID), with alpha-control accomplished using a Dunnett's procedure. Based on the expected correlation between the 2 statistical tests of 2/3, the adjusted nominal p-values for each treatment group is approximately 0.01436968.

Assuming a 40% mortality rate for ruxolitinib vs 60%, a sample size for a pairwise comparison of 100 placebo and 200 ruxolitinib participants (with 500 participants total) will achieve approximately 83% power to detect a statistically significant difference with a nominal 1-sided Type I error of 1.436968%. Estimated power for various scenarios, based on a simulation study of 1000 study replications, are provided in Table 8.

Table 8: Simulation Estimates for Power and Type 1 Error for Various Mortality Rates

Mortality Rates			Probability to Reject H_0 for		
PLB	**5 mg BID**	**15 mg BID**	**5 mg BID**	**15 mg BID**	**Either RUX**
60%	60%	60%	0.015	0.016	0.027
60%	60%	40%	0.012	0.873	0.873
60%	50%	40%	0.268	0.865	0.866
60%	40%	40%	0.868	0.872	0.940
60%	40%	30%	0.861	0.998	0.998

Note: For the simulation, investigational site was drawn from a integer uniform distribution (1, 2, …, 10) and probability (ARDS severe) = 0.5, fitting a mixed logistic regression model with no direct effects for the ARDS severity or site.

12.2. Populations for Analysis

The populations for analysis are provided in Table 9.

Table 9: Populations for Analysis

Population	Description
ITT	All randomized participants. The ITT population will be used for the summary of demographics, baseline characteristics, participant disposition, and analyses of all efficacy data. Participants will be analyzed according to the treatment group to which they were randomized regardless of the treatment received during the study.
PP population	Participants in the ITT population who are considered to be sufficiently compliant with the Protocol compose the PP population. Review of individual randomized participants will take place in a blinded fashion, and a list of excluded participants will be prepared and signed before unblinding and database freeze. Data review for identification of excluded participants will include clinical review of major Protocol deviations, clinical review of concomitant medications, and clinical review of the dose administration and drug accountability listings.
Safety	The safety population includes all randomized participants who received at least 1 dose of study drug. Treatment groups for this population will be determined according to the actual treatment the participant received regardless of assigned study drug treatment. All safety analyses will be conducted using the safety population.
PD evaluable	The PD evaluable population will include all participants who received at least 1 dose of study drug and provided at least 1 post-treatment PD measurement.

12.3. Level of Significance

The overall familywise error level for the primary endpoint is 1-sided 2.5%. Familywise error control for the primary endpoint, comparing each ruxolitinib treatment group individually against placebo, will be accomplished using Dunnett's procedure by using a nominal significance level of 0.01436968 to control the overall 1-sided Type I error at 2.5%.

One interim analysis for efficacy is planned for the study, which will use an alpha-spending function and is planned when the first 40% of participants have died or have reached their planned Day 29 visit. The nominal overall significance level of 0.01436968 will be used for each alpha-spending function. Details of the interim analysis plan are provided in Section 12.5.

12.4. Statistical Analyses

12.4.1. Primary and Secondary Analysis

Unless otherwise noted, all statistical comparisons of each ruxolitinib treatment groups will be performed as pairwise comparisons against placebo. See Table 10 for analyses of primary and secondary endpoints.

Table 10: Analyses of Primary and Secondary Endpoints

Endpoint	Statistical Method	Analysis Population	Primary (P) or Supportive (S)
Primary Endpoint			
Proportion of participants who have died due to any cause through Study Day 29.	Logistic regression with treatment group, ARDS severity (mild/moderate vs severe), gender (male or female) as fixed covariates, and investigational site as a random effect. Wald test for treatment group regression coefficient = 0. Estimation: Odds-ratio for treatment effect and associated 95% CI.	ITT	P
		PP	S
Overall survival up to Day 29 determined from the date of randomization until death due to any cause	Inference: Cox proportional hazards model including treatment group, ARDS severity (mild/moderate vs severe), and gender (male or female) as fixed covariates, and investigational site as a random effect. Estimation: Kaplan-Meier.	ITT	S

Table 10: Analyses of Primary and Secondary Endpoints (Continued)

Endpoint	Statistical Method	Analysis Population	Primary (P) or Supportive (S)
Secondary Endpoint			
Improvement in the COVID-19 ordinal scale at Day 15 and 29	Proportional odds model including treatment group, ARDS severity (mild/moderate vs severe), and gender (male or female) as fixed covariates, and investigational site as a random effect.	ITT	P
		PP	S

All other secondary endpoints will be tabulated by summary statistics.

The primary endpoint will also be compared between the treatment groups within each of the following subgroups. In the event that any subgroup category has fewer than 10 participants, the subgroup in question may be excluded.

- ARDS severity: mild/moderate versus severe
- Gender: male or female
- Age group: < 18 years, 18-64 years, or ≥ 65 years
- Baseline CRP: ≤ 100 mg/L or > 100 mg/L
- D-dimer at baseline: ≤ 1000 ng/mL or > 1000 ng/mL
- Ferritin at baseline: ≤ 300 ng/mL or > 300 ng/mL
- Race: White/Caucasian, Black/African-American, Asian, American-Indian/Alaska Native, Native Hawaiian/Pacific Islander, or Other
- Ethnicity: Hispanic/Latino, Not Hispanic/Latino, or Other
- Hours of mechanical ventilation at baseline: ≤ 48 hours or > 48 hours
- BMI at baseline: ≥ 30 or < 30

In addition, the 28-day mortality rates and participants lost to follow-up in the placebo group will be compared by the placebo image assigned (5 mg BID and 15 mg BID) to determine if the rate is consistent across the 2 treatment images. Additional endpoints may also be compared within placebo-assigned participants by treatment image.

The 9-point ordinal scale will be tabulated by visit. The odds of observing an improvement in the 9-point ordinal scale on Days 15 and 29 will be analyzed using a POM, which will include treatment group, ARDS severity (mild/moderate vs severe), and gender (male or female) as fixed covariates and investigational site as a random effect. The odds ratio for treatment group (ruxolitinib vs placebo) estimated from the POM can be interpreted as a summary of the odds ratios obtained from separate binary logistic regressions using all possible cutoff points of the ordinal outcome (eg, the cutoff of level 5, "Hospitalized, on non-invasive ventilation or high flow oxygen device" will combine levels 0, 1, 2, 3, and 4 versus combined levels 5, 6, 7, and 8).

The assumption of POM is that the effect of treatment is identical across all possible cutoff points of the ordinal outcome.

The number and percentage of participants with a 1-point improvement at Days 15 and 29 will be tabulated and summarized by treatment group. A logistic regression model will be used to model the probability of such an improvement that includes treatment group, ARDS severity (mild/moderate vs severe), and gender (male or female) as fixed covariates and investigational site as a random effect. A similar summary will be used for two-point improvements at Days 15 and 29.

The time from randomization to first improvement in the COVID-19 9-point ordinal scale will be derived. Participants who never improve on-study will be censored at their last assessment or Study Day 29, whichever is earlier. A Kaplan-Meier analysis will be used to describe the time to first improvement.

Endpoints related to clinical outcomes are defined in Table 11. Outcome-free days between Days 2 and 29 will be summarized descriptively (mean, mean, standard deviation) with treatment-group statistical comparisons using a Kruskal-Wallis test.

Table 11: In-Hospital Outcome Event-Free Days Variable Definition

Endpoint	The Number of Study Days That a Participant Was Alive and…
Ventilator-free days	did not require mechanical ventilation.[a]
ICU-free days	is out of the ICU.[a]
Vasopressor-free days	without use of vasopressor therapy.[a]
Hospital-free days	is out of the hospital.[a]
Oxygen-free days	did not receive supplemental oxygen.[a]

[a] Participants who do not survive through Day 29 will have 0 assigned days.

12.4.2. Safety Analyses

Safety analyses will be conducted for the safety population. Adverse events will be coded by the MedDRA dictionary, and TEAEs (ie, AEs reported for the first time or worsening of a pre-existing event after first dose of study drug/treatment) will be tabulated by preferred term and system organ class for all events, related events, SAEs, and events of Grade 3 or higher. Quantitative safety variables and their changes from baseline (eg, laboratory, vital signs) will be summarized with descriptive statistics.

The clinical laboratory data will be analyzed using summary statistics; no formal treatment group comparisons are planned. In addition, distributions of key laboratory parameters (eg, IL-6, ferritin, platelets) may be plotted over time; these values will also be classified into CTCAE toxicity grades, and tabulated. Descriptive statistics and mean change from baseline will be determined for vital signs at each assessment time.

Measures of exposure (eg, days of exposure, duration of treatment, and average daily dose) of study drug and/or reference therapy will be summarized by means of summary statistics.

12.4.3. Exploratory Efficacy Analyses

Change from baseline to Day 15 and Day 29 in serum ferritin, C-reactive protein (CRP), D-dimer, IL-6, and viral load will be summarized by treatment arm. Additional details will be provided in the Statistical Analysis Plan.

Exploratory endpoints will be summarized descriptively using ITT population.

12.5. Interim Analysis

12.5.1. Efficacy Analysis

There will be 1 planned interim analyses conducted for efficacy for this study, based on the first 40% of participants enrolled in the study. The efficacy interim analysis will be conducted when the first 40% of the planned randomized participants (approximately 200 randomized participants) have died or have reached their Day 29 assessment. Based on the results of this interim analysis, the DMC may choose to terminate the study for positive efficacy or continue the study with no changes to enrollment.

At the efficacy interim analysis, Day 28 mortality will be tested using an overall nominal Type I error of 0.01436968 within each ruxolitinib treatment arm in comparison versus placebo. An HSD (Hwang et al 1990) alpha-spending function with $\gamma = -4$ will be used to determine the efficacy boundary for the primary endpoint. The study will reject the null hypothesis for a given ruxolitinib treatment group if the Day 29 mortality endpoint crosses the efficacy boundary. Table 12 provides the projected stopping rules if the interim analysis is conducted at the projected number of participants.

Table 12: Interim Analysis for Day 29 Mortality With HSD(–4)

	Interim Analysis		Final Analysis	
Number of Participants	**200**		**500**	
Decision Outcome	**Continue**	**Stop for Early Efficacy**	**Do Not Reject Null Hypothesis**	**Reject Null Hypothesis**
Z-statistic	≤ 3.07	> 3.07	≤ 2.20	> 2.20
One-sided p-value	≥ 0.001	< 0.001	≥ 0.013	< 0.013
Ruxolitinib mortality at Day 29[a]	≥ 30.0%	< 30.0%	≥ 46.0%	< 46.0%

[a] Assumes overall mortality rate at Day 29 is 60% for placebo.

In the event that the null hypothesis regarding 28-day mortality is rejected for a given ruxolitinib treatment group when compared with placebo at the interim analysis, but not the other ruxolitinib treatment group, the DMC may provide guidance to the sponsor to terminate the study or allow the study to continue in order to better characterize the treatment effects within the other ruxolitinib treatment group. For treatment groups continued beyond rejection of their specific null hypothesis, final reported p-values will be based on the highest level of significance achieved, either at the interim or final analysis.

If the null hypotheses are rejected for both ruxolitinib treatment groups when compared with placebo for the primary endpoint, then a statistical comparison will be performed between the 2 ruxolitinib groups in an alpha-controlled fashion. The 1-sided for the comparison will be based on the timing of the rejection (interim or final analysis) for the individual ruxolitinib comparisons versus placebo, while accounting for the Type I error expended at the interim analysis as appropriate (Table 13).

Table 13: Type 1 Error Allocated to 5 mg BID to 15 mg BID Comparison Based on Timing for Rejection of Each Null Hypothesis

Timing of Rejection of Null Hypothesis	Alpha Expended	2-Sided Alpha for Comparison if IA Occurs at 40% of Data
Both at interim analysis	0	5.00%
One at interim analysis, one at final analysis	Alpha spent for single comparison at IA: HSD(–4) × 0.01436968	4.79%
Both at final analysis	Alpha spent in both comparisons at IA: ~HSD(–4) × 0.025	4.63%

12.5.2. Futility Analysis for Overall Survival

A weekly futility analysis, starting 14 days after first randomized participant, is planned for this study. The futility analyses, upon agreement of the DMC, may not be performed if rapid study enrollment does not permit operationalizing the analysis.

The analysis will use a Cox regression model, for each ruxolitinib treatment arm individually when compared with placebo, including treatment, ARDS severity, and gender as fixed covariates and investigational site as a random effect. The planned nonbinding futility rule for the analysis will use a beta-spending approach with an HSD(–1) spending function assuming an overall power of 94.5% to detect a hazard ratio of 0.55. As the exact number of events for the final analysis is unknown, the interim analysis will be a function of the number of participant days after randomization (up to and including Day 28) for randomized participants. Assuming enrollment day for participant i follows the function

$$f(i) = 28 \bullet (i / n)^{0.7},$$

the resulting spending function will have the boundaries for futility shown in Table 14.

Table 14: Projected Futility Analysis Rules for Example Enrollment Profile

Interim Analysis No	Proportion of Monitoring Days	Number of Participants Enrolled in Placebo & Ruxolitinib Comparison	Number of Participants Completed Day 28	Stop for Futility if Z <
1	0.058	111	0	–1.98
2	0.151	198	0	–1.21
3	0.300	300	0	–0.37
4	0.475	300	41	0.35
5	0.650	300	111	0.94
6	0.825	300	198	1.47

13. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

13.1. Investigator Responsibilities

- The Protocol, Protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB by the investigator and reviewed and approved by the IRB before the study is initiated.
- The investigator is responsible for ensuring that the safety reports provided by the sponsor are reviewed and processed in accordance with regulatory requirements, the policies and procedures established by the IRB, and institutional requirements.
- Any amendments to the Protocol will require approval from both Health Authorities and IRB before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB.
  - Notifying the IRB of SAEs or other significant safety findings as required by IRB procedures.
  - Providing oversight of the conduct of the study at the site and adherence to GCP, IRB requirements, institutional requirements, and applicable laws and country-specific regulations.
- Adhering to the Protocol as described in this document and agreeing that changes to the Protocol procedures, with the exception of medical emergencies, must be discussed and approved, first, by the sponsor or its designee and, second, by the IRB. Each investigator is responsible for enrolling participants who have met the specified eligibility criteria.
- Decentralized assessments, which are study assessments performed at a facility other than the primary site, are acceptable as indicated in the SoA. The investigator is responsible to provide oversight of all study assessments.
- Retaining records in accordance with all local, national, and regulatory laws but for a minimum period of at least 2 years after the last marketing application approval in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or if not approved, 2 years after the termination of the test article for investigation to ensure the availability of study documentation should it become necessary for the sponsor or a regulatory authority to review.

- The investigator must not destroy any records associated with the study without receiving approval from the sponsor. The investigator must notify the sponsor or its designee in the event of accidental loss or destruction of any study records. If the investigator leaves the institution where the study was conducted, the sponsor or its designee must be contacted to arrange alternative record storage options.
- All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The sponsor will retain the original eCRF data and audit trail.

13.2. Data Management

Data management will be performed in a validated EDC system. The investigator will be provided with access to an EDC system so that an eCRF can be completed for each participant.

The site will be provided with eCRF completion guidelines for instructions on data entry in the eCRF. The study monitor will reference the Monitoring Plan in order to ensure that each issue identified is appropriately documented, reported, and resolved in a timely manner in accordance with the plan's requirements. Other data outside the EDC system required in the study conduct of the Protocol such as documents or results transmitted to the sponsor via a central laboratory or specialized technical vendors and, as designated by the sponsor, will have their own data flow management plans, study charters, or biomarker plans, as applicable.

The sponsor (or designee) will be responsible for:

- Managing the integrity of the data and the quality of the conduct of the study, such as ensuring that study monitors perform ongoing source data verification to confirm that data entered into the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved Protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements. Remote monitoring and remote source data review will be performed as defined in the monitoring plan.
- Managing and reconciling the data generated, and/or collected including documents and results such as laboratory or imaging data analyzed centrally by a designated vendor of the sponsor.

The investigator will be responsible for:

- Recording, or ensuring the recording of, all relevant data relating to the study in the eCRF.
- Delivering, or ensuring the delivery of, all other results, documents, data, know-how, or formulas relating to the study to the sponsor or designee electronically or as otherwise specified in the Protocol.
- Verifying that data entries are accurate and correct by physically or electronically signing the eCRF.

- Maintaining accurate documentation (source data) that supports the information entered in the eCRF, or sent to a central vendor designated by the sponsor, or as described in other study and data flow manuals.
  - Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.
  - Data entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study. Current applicable medical records must be available.
- May have responsibility for sending participants' data, either as unique samples, or copies, or photographs, to be evaluated centrally or analyzed centrally, or both, by a qualified vendor designated by the sponsor.
- Permitting study-related monitoring, sponsor audits, IRB review, and regulatory inspections by providing direct access to source data and other relevant clinical study documents.
  - Monitoring: Qualified representatives of the sponsor or its designee, study monitors, will monitor the study according to a predetermined plan. The investigator must allow the study monitors to review any study materials and participant records at each monitoring visit.
  - Auditing: Qualified representatives of the sponsor or its designee may audit the clinical study site and study data to evaluate compliance with the Protocol, applicable local clinical study regulations, and overall study conduct. The investigator must allow the auditors to review original source records and study documentation for all participants.
  - Regulatory inspection: Regulatory authorities may conduct an inspection of the study and the site at any time during the development of an investigational product. The investigator and staff are expected to cooperate with the inspectors and allow access to all source documents supporting the eCRFs and other study-related documents. The investigator must immediately notify the sponsor when contacted by any regulatory authority for the purposes of conducting an inspection.

13.3. Data Privacy and Confidentiality of Study Records

The investigator and the sponsor or its designee must adhere to applicable data protection laws and regulations. The investigator and the sponsor or its designee are responsible for ensuring that sensitive personal information is handled in accordance with local requirements (eg, HIPAA). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of personal information must be obtained.

Participant names will not be supplied to the sponsor or its designee. Only the participant number will be recorded in the eCRF, where permitted; if the participant's name appears on any other document (eg, laboratory report), it must be obliterated on the copy of the document to be

supplied to the sponsor or its designee. Study findings stored on a computer will be stored in accordance with appropriate technical and organizational measures as required by local data protection laws.

Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the investigator for 2 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor.

13.4. Financial Disclosure

Before study initiation, all clinical investigators participating in clinical studies subject to FDA Regulation Title 21 CFR Part 54 – Financial Disclosure by Clinical Investigators (ie, "covered studies") are required to submit a completed Clinical Investigator Financial Disclosure form that sufficiently details any financial interests and arrangements that apply. For the purpose of this regulation, "clinical investigator" is defined as any investigator or subinvestigator who is directly involved in the treatment or evaluation of research participants, including the spouse and each dependent child of the clinical investigator or subinvestigator. These requirements apply to both US and foreign clinical investigators conducting covered clinical studies.

Any new clinical investigators added to the covered clinical study during its conduct must also submit a completed Investigator Financial Disclosure Form. During a covered clinical study, any changes to the financial information previously reported by a clinical investigator must be reported to the sponsor or its designee. At the conclusion of the covered clinical study, the clinical investigators will be reminded of their obligations. In the event that the clinical investigator is not reminded, they nevertheless will remain obligated to report to the sponsor or its designee any changes to the financial information previously reported, as well as any changes in their financial information for a period of 1 year after completion of the covered clinical study.

13.5. Publication Policy

By signing the study Protocol, the investigator and his/her institution agree that the results of the study may be used by the sponsor, Incyte Corporation, for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals. Study results will be published in accordance with applicable local and national regulations. If necessary, the authorities will be notified of the investigator's name, address, qualifications, and extent of involvement. The terms regarding the publication of study results are contained in the agreement signed with the sponsor or its designee. A signed agreement will be retained by the sponsor or its designee.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

Authorship will be determined in line with International Committee of Medical Journal Editors authorship requirements.

13.6. Study and Site Closure

The sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the sponsor or investigator may include but are not limited to:

- Failure of the investigator to comply with the Protocol, the requirements of the IRB or local health authorities, the sponsor's procedures, or GCP guidelines.
- Inadequate recruitment of participants by the investigator.
- Discontinuation of further study treatment development.

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APPENDIX A. INFORMATION REGARDING EFFECTIVENESS OF CONTRACEPTIVE METHODS

For female participants in the study:

The following methods that can achieve a failure rate of less than 1% per year when used consistently and correctly are considered as highly effective birth control methods:

- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[a]
  - oral
  - intravaginal
  - transdermal
- Progestogen-only hormonal contraception associated with inhibition of ovulation[a]
  - oral
  - injectable
  - implantable[b]
- Intrauterine device[b]
- Intrauterine hormone-releasing system[b]
- Bilateral tubal occlusion[b]
- Vasectomized partner[bc]
- Sexual abstinence[d]

Acceptable birth control methods that result in a failure rate of more than 1% per year include:

- Progestogen-only oral hormonal contraception, where inhibition of ovulation is not the primary mode of action
- Male or female condom with or without spermicide[e]
- Cap, diaphragm, or sponge with spermicide[e]
- Tubal ligation

[a] Hormonal contraception may be susceptible to interaction with the investigational medicinal product, which may reduce the efficacy of the contraception method.

[b] Contraception methods that in the context of this guidance are considered to have low user dependency.

[c] Vasectomized partner is a highly effective method of avoiding pregnancy provided that partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of the surgical success.

[d] In the context of this guidance, sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the participant.

[e] A combination of male condom with either cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods.

Source: Clinical Trials Facilitation and Coordination Group 2014.

APPENDIX B. 9-POINT ORDINAL SCALE (SECONDARY ENDPOINT)

Clinical status of participant at Day 15 and 29 (9-point ordinal scale):

Participant State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory[a]	No limitation of activities	1
	Limitation of activities	2
Hospitalized Mild Disease	Hospitalized, no oxygen therapy (defined as $SpO_2 \geq 94\%$ on room air)	3
	Oxygen by mask or nasal prongs	4
Hospitalized Severe Disease	Noninvasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – vasopressors, RRT, ECMO	7
Dead	Death	8

[a] Defined as not in hospital or in hospital and ready for discharge.
Source: WHO 2020a.

APPENDIX C. SEQUENTIAL ORGAN FAILURE ASSESSMENT SCORE

The SOFA score is a scoring system to determine the extent of a person's organ function or rate of failure (Vincent et al 1996, Vincent et al 1998). The score is based on six different scores, one each for the respiratory, cardiovascular, hepatic, coagulation, renal, and neurological systems. Baseline assessment should be based on data collected closest to (but also prior to) randomization. Each subsequent day should use the worst value for each parameter in the preceding 24-hour period.

Respiratory System

When using PaO_2:

PaO_2/FiO_2 (mmHg)
- 0 = $PaO_2/FiO_2 \geq 400$
- 1 = $PaO_2/FiO_2 < 400$
- 2 = $PaO_2/FiO_2 < 300$
- 3 = $PaO_2/FiO_2 < 200$ and mechanically ventilated
- 4 = $PaO_2/FiO_2 < 100$ and mechanically ventilated

PaO_2 should be used if available. However, if PaO_2 is not available, the following table can be used to generate the SOFA score with SpO_2 (Pandharipande et al 2009):

Use of SpO_2/FiO_2 in SOFA Score

SOFA Respiratory System Points (Using SpO_2)	SpO_2/FiO_2 Ratio		
	PEEP < 8 or Not Intubated	PEEP 8-12	PEEP > 12
0	≥ 457	≥ 515	≥ 425
1	< 457	< 515	< 425
2	< 370	< 387	< 332
3	< 240	< 259	< 234
4	< 115	< 130	< 129

Note: The original SpO_2/FiO_2 Ratio as published would require a $SpO_2 > 110\%$ to achieve a SOFA score of 0. Therefore, this score has been modified to accept a SpO_2 of 96% or greater on room air as normal (ie, an SpO_2/FiO_2 ratio of ≥ 457 would be a SOFA score = 0).

Nervous System

Glasgow coma score
- 0 = GCS score of 15
- 1 = GCS score of 13-14
- 2 = GCS score of 10-12
- 3 = GCS score of 6-9
- 4 = GCS score of < 6

Cardiovascular System

Mean arterial pressure (MAP) OR administration of vasopressors required (vasopressor drug doses are in mcg/kg/min)

0 = No hypotension
1 = MAP < 70 mmHg
2 = dopamine ≤ 5 or dobutamine (any dose)
3 = dopamine > 5 OR epinephrine ≤ 0.1 OR norepinephrine ≤ 0.1
4 = dopamine > 15 OR epinephrine > 0.1 OR norepinephrine > 0.1

Liver

Total bilirubin (mg/dL)

0 = Total Bilirubin < 1.2
1 = Total Bilirubin 1.2 - 1.9
2 = Total Bilirubin 2.0 - 5.9
3 = Total Bilirubin 6.0 - 11.9
4 = Total Bilirubin ≥ 12.0

Coagulation

Platelets×103/µL

0 = Platelets ≥ 150 ×103/µL
1 = Platelets < 150 ×103/µL
2 = Platelets < 100 ×103/µL
3 = Platelets < 50 ×103/µL
4 = Platelets < 20 ×103/µL

Renal System

Creatinine (mg/dL) (or urine output)

0 = Creatinine < 1.2 mg/dL
1 = Creatinine 1.2 - 1.9 mg/dL
2 = Creatinine 2.0 - 3.4 mg/dL
3 = Creatinine 3.5 - 4.9 mg/dL, or urine output < 500 mL/d
4 = Creatinine ≥ 5.0 mg/dL, or urine output < 200 mL/d, or dialysis requirement

Source: Pandharipande et al 2009, Vincent et al 1996, Vincent et al 1998.

APPENDIX D. LIST OF CYP3A4 INHIBITORS AND INDUCERS

Dual CYP2C9/CYP3A4 inhibitor:

Fluconazole: Avoid the concomitant use of ruxolitinib with fluconazole doses ≥ 200 mg daily; if clinically necessary to use doses ≥ 200 mg daily consultation with sponsor is required (see Section 7.2).

Table D1: CYP3A4 Inhibitors and Inducers

Category	Drug Names
Strong inhibitors[a] of CYP3A	boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, eltegravir/ritonavir, grapefruit juice[b], idelalisib, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, LCL161, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, sequinavir/ritonavir, telaprevir, telithromycin, voriconazole, indinavir/ritonavir, tipranoavir/ritonavir, troleandomycin
Moderate inhibitors[c] of CYP3A	amprenavir, aprepitant, atazanavir, atazanavir/ritonavir, casopitant, cimetidine, ciprofloxacin, crizotinib, cyclosporin, duranavir, darunavir/ritonavir, diltiazem, dronedarone, erythromycin, faldaprevir, fluconazole[d], fosamprenavir, grapefruit juice[b], imatinib, lomitapide, netupitant, nilotinib, schisandra, sphenanthera[e], tofisopam, verapamil
Strong inducers[f] of CYP3A	avasimibe, carbamazepine, enzalutamide, mitotane,phenytoin, rifampin, St John's wort[e], rifabutin, phenobarbital
Moderate inducers[g] of CYP3A	bosentan, efavirenz, etravirine, genistein[e], lersivirine, lopinavir, modafinil, nafcillin, ritonavir, semagacestat[h], talviraline[h], thioridazine, tipranavir

Note: This may not be an exhaustive list. For a complete and most updated drug list, check the website https://www.crediblemeds.org/healthcareproviders/drug-list.

[a] A strong inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by equal or more than 5-fold.

[b] Effect seems to be due to CYP2C19 inhibition by ethinyl estradiol.

[c] A moderate inhibitor for a specific CYP is defined as an inhibitor that increases the AUC of a sensitive substrate for that CYP by less than 5-fold but equal to or more than 2-fold

[d] Fluconazole is a dual CYP3A4 and CYP2C9 inhibitor. Fluconazole is a strong CYP2C9 inhibitor based on the AUC ratio of omeprazole, which is also metabolized by CYP3A; fluconazole is a moderate CYP3A inhibitor.

[e] Herbal product.

[f] A strong inducer for a specific CYP is defined as an inducer that decreases the AUC of a sensitive substrate for that CYP by equal or more than 80%.

[g] A moderate inducer for a specific CYP is defined as an inducer that decreases the AUC of a substrate for that CYP by 50-80%.

[h] Drugs not available in the US market.

Source: FDA 2012, Indiana University School of Medicine 2007, University of Washington School of Pharmacy 2002.

APPENDIX E. CORRELATIVE SERUM COLLECTION, PROCESSING, AND SHIPPING INFORMATION

Day 1, Day 7, and Day 15 Serum Collection

1. Collect blood sample in 4 to 6 mL SST collection tube.
2. After obtaining sample, immediately invert collection tube 5 times gently to mix clot activator with blood.
3. Allow blood to clot for 30 minutes in a vertical position.
4. Process the collection tubes by centrifugation between 1100 and 1300 × g for 10 minutes for swing-head units or 15 minutes for fixed angle units. Barrier will form, separating serum specimen from clot.
5. Transfer serum into labeled tube/cryovial with the Incyte study INCB 18424-369, participant ID, and date/time of collection.
6. Freeze and store aliquots immediately in a freezer set to maintain a temperature of –70°C or colder until ready for shipment. Samples must be maintained in the frozen state until assayed. Short-term storage (< 7 days) at –20°C is acceptable when –70°C freezer is not available.
7. Ship samples weekly to Incyte with a 2-day supply of dry ice following instruction below.
8. When sending the sample shipment, if possible, please send an electronic sample listing in Microsoft Excel format and sample shipment tracking information before sending to [redacted].
9. The shipping address is as follows:

   Incyte Research Institute
   [redacted]
   1801 Augustine Cut-Off
   Wilmington, DE 19803

   Email: [redacted]

   Lab Phone Number: [redacted]

APPENDIX F. PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document	Date
Amendment 1:	02 JUN 2020

Amendment 1 (02 JUN 2020)

Overall Rationale for the Amendment:

The primary purpose of this amendment is to incorporate Health Authority comments.

1. **Section 1, Protocol Summary (Figure 1: Study Design Schema; Table 2: Key Study Design Elements; Table 3: Schedule of Activities); Section 3.1, Primary Estimates; Section 4.1, Overall Design; Section 6.1, Inclusion Criteria; Section 9.4.2, Presence SARS-CoV-2 Virus/Viral Load/Antibody Testing**

   Description of change: The requirement for confirmation of SARS-CoV-2 infection prior to randomization was changed from 2 weeks to 3 weeks.

   Rationale for the change: To include participants who may have had initial SARS-CoV-2 diagnosis within 3 weeks and who have not had repeat testing.

2. **Section 1, Protocol Summary (Figure 1: Study Design Schema; Table 2: Key Study Design Elements; Table 3: Schedule of Activities); Section 4.1, Overall Design; Section 6.1, Inclusion Criteria; Section 7.3.1, Participant Numbering; Section 8, Informed Consent Procedures; Section 9.1.1, Information to Be Collected on Screening Failures; Section 10.1.3, Withdrawal of Informed Consent; Section 12.4.1, Primary and Secondary Analysis**

   Description of change: The eligibility criteria were updated to allow participants who are ≥ 12 years of age to enroll, requirements to obtain assent when applicable were added, and subgroup analysis for age was updated accordingly.

   Rationale for the change: To incorporate Health Authority comments.

3. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 4.1, Overall Design; Section 6.2, Exclusion Criteria**

   Description of change: Exclusion criterion 6 was updated to allow participants who are receiving nitric oxide and/or high frequency oscillatory ventilation.

   Rationale for the change: Nitric oxide and high frequency oscillatory ventilation are treatment modalities that are occasionally used as standard therapy in the study population.

4. **Section 1, Protocol Summary (Table 3: Schedule of Activities); Section 9.1, Screening**

   Description of change: The requirement that laboratory assessments performed for screening be repeated if not done within 6 hours of randomization was deleted.

   Rationale for the change: As all screening assessments are performed within 24 hours of randomization, the initial screening laboratory assessments are sufficient for study baseline.

5. **Section 5.6, Risks and Benefits; Section 9.4.3.4, Monitoring of Thromboembolic Risk**

   Description of change: Guidance for monitoring and prophylaxis of thrombosis was added.

   Rationale for the change: To incorporate Health Authority comments.

6. **Section 7.1, Study Treatment Administered**

   Description of change: Guidance for dosing during prone positioning was added.

   Rationale for the change: Given the frequent use of prone positioning in the study population, it is appropriate to provide dosing guidance in this scenario.

7. **Section 10.1.5, Early Study Termination by the Sponsor**

   Description of change: The study stopping criteria were clarified to indicate that individual treatment arms or the entire study may stop upon recommendation of the DMC.

   Rationale for the change: To incorporate Health Authority comments.

8. **Section 12.4.1, Primary and Secondary Analysis**

   Description of change: Added analyses comparing participants by assigned placebo image to determine if the rate is consistent across the 2 treatment images.

   Rationale for the change: To incorporate Health Authority comments.

9. **Incorporation of administrative changes.** Other minor, administrative changes have been incorporated throughout the Protocol and are noted in the redline version of the amendment.

Signature Manifest

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