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Phase 3 randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy and safety of ruxolitinib in patients with COVID-19 associated cytokine storm (RUXCOVID)

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List of abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
ANCOVA	Analysis of covariance
ARDS	Acute respiratory distress syndrome
AST	Aspartate Aminotransferase
b.i.d.	bis in die/twice a day
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CART	Chimeric antigen receptor T cells
CK	Creatine Kinase
CMO&PS	Chief Medical Office and Patient Safety
CoV	Corona virus
COVID-19	Coronavirus disease 2019
CPAP	Continuous Positive Airway Pressure
CrCl	Creatinine clearance
[redacted]	[redacted]
CRS	Cytokine Release Syndrome
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CXRAY	Chest X-Ray
CYP3A4	cytochrome P450 3A4
dL	deciliter
DMC	Data Monitoring Committee
[redacted]	[redacted]
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic Case Report/Record Form
EDC	Electronic Data Capture
eSource	Electronic Source
FDA	Food and Drug Administration
FiO_2	Fraction of inspired oxygen
GCP	Good Clinical Practice
GCS	Global Clinical Supply
GGT	Gamma-glutamyl transferase
GLDH	Glutamate dehydrogenase
GvHD	Graft versus host disease
HBsAg	Hepatitis B surface antigen
hCG	Human Chorionic Gonadotrophin
HECTD2	HECT Domain E3 Ubiquitin Protein Ligase 2
HHS	Health and Human Services

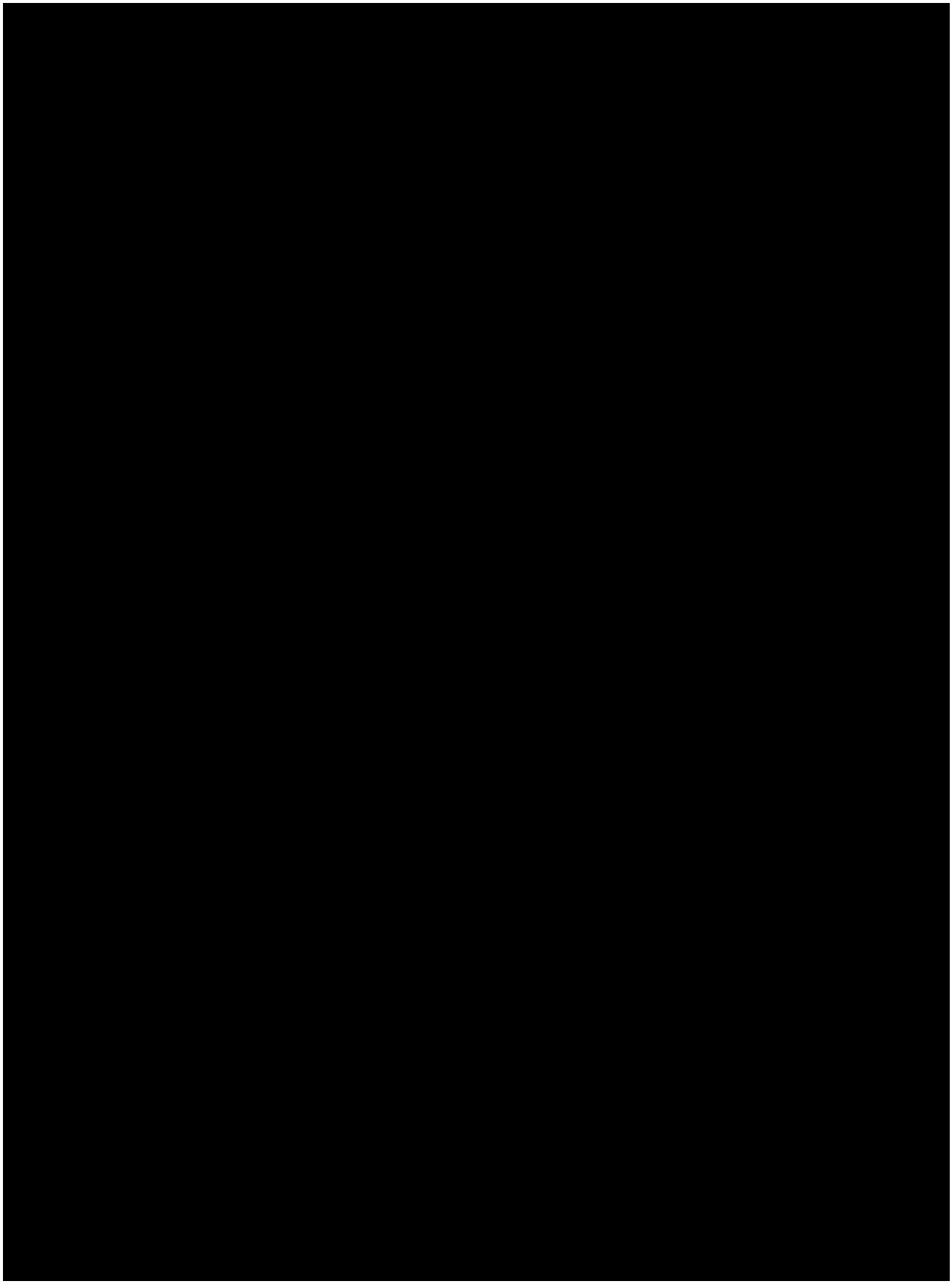
HLH	haemophagocytic lymphohistiocytosis
HU	hydroxyurea
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
IN	Investigator Notification
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
JAK	Janus kinase
LPS	Lipopolysaccharides
MedDRA	Medical dictionary for regulatory activities
MF	Myelofibrosis
mg	milligram(s)
mL	milliliter(s)
MOF	Multi organ failure
NEWS2	National Early Warning Score 2
PaO_2	Partial pressure of arterial oxygen
PCR	Polymerase chain reaction
PD	Pharmacodynamic(s)
PET-MF	post-essential thrombocythemia myelofibrosis
PIAS	Protein Inhibitor of Activated STAT
PK	Pharmacokinetic(s)
PMF	Primary myelofibrosis
PML	Progressive multifocal leuko-encephalopathy
POM	Proportional odds model
PPV-MF	post-polycythemia vera myelofibrosis
PREP Act	Public Readiness and Emergency Preparedness Act
PT	prothrombin time
QMS	Quality Management System
RBC	red blood cell(s)
RDO	Retrieved Drop Out
RNA	Ribonucleic acid
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV	severe acute respiratory syndrome-corona virus
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase

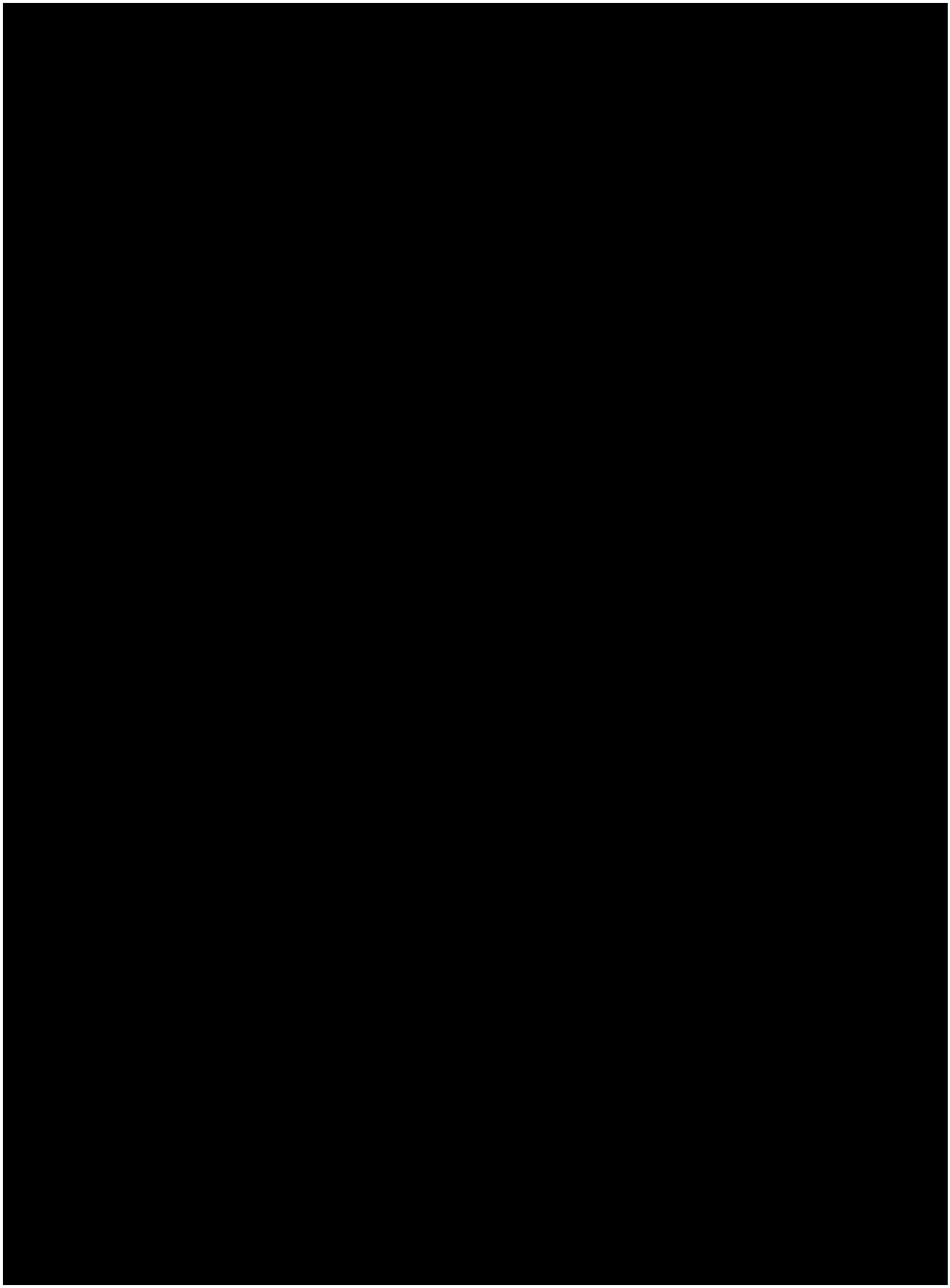
SoC	Standard-of-Care
STAT	signal transducers and activators of transcription
TD	Study Treatment Discontinuation
ULN	upper limit of normal
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

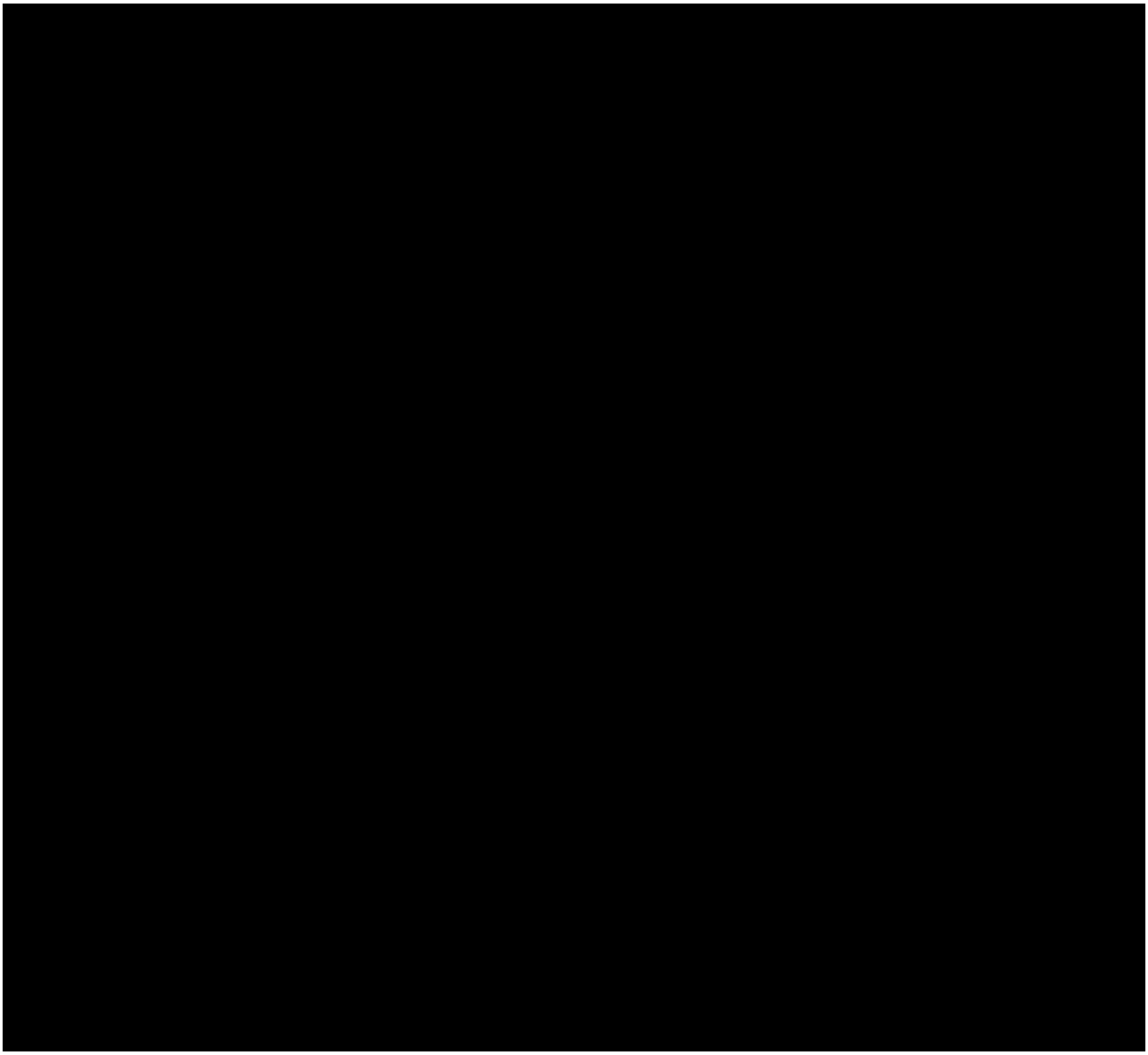
Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Cohort	A specific group of participants fulfilling certain criteria and generally treated at the same time
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intensive care unit (ICU)	An Intensive Care Unit is defined as any setting in which patients are receiving therapy typically associated with critical illness (e.g., vasopressors, mechanical ventilation, etc.) or monitoring that is typically associated with such care (e.g.,invasive arterial or central venous monitoring).
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient)

Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis
Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized participant
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data







Protocol summary

Protocol number	CINC424J12301
Full Title	Phase 3 randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy and safety of ruxolitinib in patients with COVID-19 associated cytokine storm
Brief title	RUXCOVID
Sponsor and Clinical Phase	Novartis III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	There are no approved treatments for COVID-19 pneumonia. The purpose of this study is to evaluate the efficacy and safety of ruxolitinib in the treatment of patients with COVID-19 pneumonia.
Primary Objective(s)	To evaluate the efficacy (as measured by a composite endpoint of proportion of patients who die, develop respiratory failure [require mechanical ventilation], or require intensive care unit [ICU] care) of ruxolitinib + standard-of-care (SoC) therapy compared with placebo + SoC therapy, for the treatment of COVID-19 by Day 29.
Secondary Objectives	To evaluate the efficacy (as measured by clinical status using a 9-point ordinal scale) of ruxolitinib + SoC therapy compared with placebo + SoC therapy, for the treatment of COVID-19. To evaluate the efficacy of ruxolitinib + standard-of-care (SoC) therapy compared with placebo + SoC therapy, on in-hospital outcomes in patients with COVID-19. To evaluate the efficacy of ruxolitinib + SoC therapy, compared with placebo + SoC therapy, in change in the National Early Warning Score (NEWS2) score in patients with COVID-19. To evaluate the efficacy of ruxolitinib + SoC therapy, compared with placebo + SoC therapy, in change in SpO_2/FiO_2 ratio in patients with COVID-19. To evaluate the efficacy of ruxolitinib + SoC therapy, compared with placebo + SoC therapy, in proportion of patients with no oxygen therapy (defined as oxygen saturation ≥ 94% on room air) in patients with COVID-19. To evaluate the safety of ruxolitinib + standard-of-care (SoC) therapy compared with placebo + SoC therapy, in the treatment of patients with COVID-19.
Study design	This is a randomized, double-blind, placebo-controlled, 29-day, multi-center study to assess the efficacy and safety of ruxolitinib + SoC therapy, compared with placebo + SoC therapy, in patients aged ≥12 years with COVID-19 pneumonia.
Study population	Approximately 402 males and females ages 12 and older with COVID-19 pneumonia.

Key Inclusion criteria	• Patient or guardian/health proxy must provide informed consent (and assent if applicable) before any study assessment is performed.
	• Male and female patients aged ≥ 12 years (or ≥ the lower age limit allowed by Health Authority and/or Ethics Committee/Institutional Review Board approvals).
	• Patients with coronavirus (SARS-CoV-2) infection confirmed by polymerase chain reaction (PCR) test or another rapid test from the respiratory tract prior to randomization.
	• Patients currently hospitalized or will be hospitalized prior to randomization.
	• Patients, who meet **at least one** of the below criteria:
	  • Pulmonary infiltrates (chest X ray or chest CT scan);
	  • Respiratory frequency ≥ 30/min;
	  • Requiring supplemental oxygen;
	  • Oxygen saturation ≤ 94% on room air;
	  • Arterial oxygen partial pressure (PaO2)/ fraction of inspired oxygen (FiO_2) < 300mmHg (1mmHg=0.133kPa) (corrective formulation should be used for higher altitude regions (over 1000m).

Key Exclusion criteria	• History of hypersensitivity to any drugs or metabolites of similar chemical classes as ruxolitinib. • Presence of severely impaired renal function defined by serum creatinine > 2 mg/dL (>176.8 µmol/L), or have estimated creatinine clearance < 30 ml/min measured or calculated by Cockroft Gault equation or calculated by the updated bedside Schwartz equation. • Suspected uncontrolled bacterial, fungal, viral, or other infection (besides COVID-19). • Currently intubated or intubated between screening and randomization. • In intensive care unit (ICU) at time of randomization. • Intubated or in ICU for COVID-19 disease prior to screening. • Patients who are on anti-rejection, immunosuppressant or immunomodulatory drugs (i.e. tocilizumab, ruxolitinib, canakinumab, sarilumab, anakinra). • Unable to ingest tablets at randomization. • Pregnant or nursing (lactating) women.
Study treatment	Ruxolitinib 5 mg tablets b.i.d. or matching-image placebo for 14 days with possible extension of treatment to 28 days
Treatment of interest	Ruxolitinib 5 mg tablets

Efficacy assessments	Clinical status using a 9-category ordinal scale Vital signs and oxygen saturation National Early Warning Score (NEWS2) In-hospital outcomes Ventilatory status
Key safety assessments	Adverse event monitoring, physical examinations, monitoring of laboratory markers in blood, ECGs.
[redacted]	[redacted]
Data analysis	The primary endpoint will be analyzed using the randomized set. The odds of clinical failure will be analyzed by a logistic regression model with treatment group, country, age, and gender as covariates. The estimated odds ratio, p-values, and 95% confidence intervals will be presented.
Key words	COVID-19 pneumonia, SARS-COV-2, ruxolitinib

1 Introduction

1.1 Background

In December 2019, the Wuhan Municipal Health Committee identified an outbreak of viral pneumonia cases of unknown cause. This outbreak of viral pneumonia was reported to the World Health Organization (WHO) Country Office in China on December 31, 2019. Subsequently, Coronavirus (CoV) RNA was identified in some of 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 (MERS-CoV) and severe acute respiratory syndrome (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, an acronym for "coronavirus disease 2019". This new coronavirus strain was not previously identified in humans and was newly named on 11 February 2020 by the WHO. Genetic sequencing of the virus suggests that SARS-CoV-2 is a beta-coronavirus closely linked to the SARS virus.

On 11 March 2020, the WHO declared a pandemic for COVID-19. According to the WHO, as of 24 March 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 intensive care unit (China CDC Weekly 2020). In severe cases, COVID-19 can be complicated by acute respiratory distress syndrome (ARDS), sepsis and septic shock, and/or multiorgan failure (MOF), including acute kidney injury and cardiac injury (Yang et al 2020). Of note, many patients with severe respiratory disease due to COVID-19 have features consistent with the cytokine release syndrome (CRS), also referred to as cytokine storm, and increased activation of the JAK/STAT pathway (Wang et al 2020; Hermans et al 2020).

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

There is sparse data on 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 co-infection has been

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

1.1.1 Ruxolitinib

Ruxolitinib (INCB018424 phosphate, INC424, ruxolitinib phosphate) is a well-established, potent and selective inhibitor of Janus kinase (JAK)1 and JAK2, with modest to marked selectivity against tyrosine kinase (TYK)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 Investigator Brochure.

JAK signaling involves recruitment of signal transducers and activators of transcription (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 majority of patients with Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs), including myelofibrosis (MF) and polycythemia vera (PV), demonstrating that JAK inhibition is efficacious in these diseases.

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

In the United States (US), ruxolitinib (JAKAFI®) is approved for the treatment of intermediate or high-risk MF, including PMF, PPV-MF and PET-MF in adults and for 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 acute graft versus host disease (GvHD).

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

1.1.2 Additional evidence for CRS and JAK/STAT activation in severe respiratory disease

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

1.1.2.1 Laboratory evidence

Hermans et al (2020) 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 an interesting target for therapy to release symptom burden in mastocytosis and many other mast cell mediator related diseases such as the CRS.

Hoffman et al (2016) demonstrated that viral and bacterial co-infection 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.

1.1.2.2 Animal models

Zhao et al (2016) looked at LPS-induced lung injury in mice, which models some of the ARDS (e.g. cytokine increases and cell influx) manifestations, 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 (e.g. dexamethasone) is absent from the in vivo studies. Using conditional knockouts of SOCS3 (an antinflammatory protein which negatively regulates JAK activity) they provide further evidence that the effects are STAT3 pathway dependent. They also show increased STAT3 expression in PBMC 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 which 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. HECTD2 inhibitor reduces lung inflammation in the same model (no positive control). They also identify a polymorphism (loss of function) in the HECTD2 gene which 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 CART 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 CART 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.

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

1.1.2.3 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 need for more toxic therapies. (Ahmed 2019; Goldsmith 2019).

1.1.3 Background summary

It is reasonable to consider the use of ruxolitinib in the treatment of COVID-19 patients with severe respiratory disease because these patients have clinical features consistent with CRS and increased activation of the JAK/STAT pathway (Wang et al 2020; Hermans et al 2020). Moreover, recent literature specifically suggests consideration of molecules for treatment of

COVID-19 that block inflammatory pathways, including inhibition of the JAK/STAT pathway where a number of cytokines converge (Zumla et al 2020, Mehta 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 trial setting.

1.2 Purpose

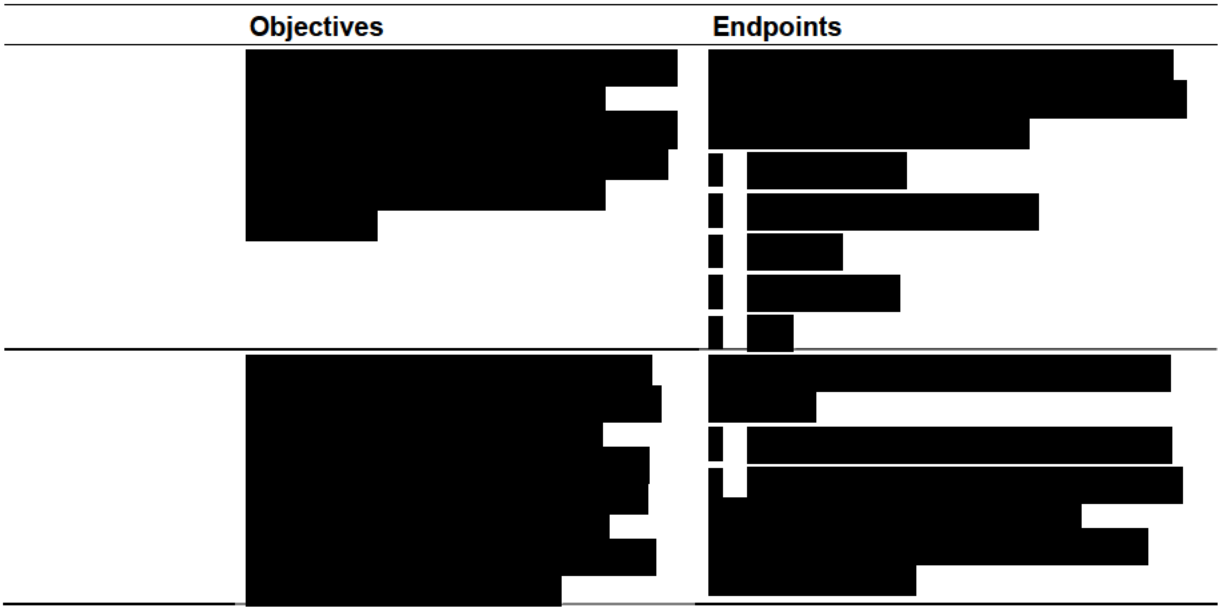
There are no approved treatments for COVID-19 pneumonia. The purpose of this study is to evaluate the efficacy and safety of ruxolitinib in the treatment of patients with COVID-19 pneumonia.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

	Objectives	Endpoints
Primary Objective	To evaluate the efficacy (as measured by a composite endpoint of proportion of patients who die, develop respiratory failure [require mechanical ventilation], or require intensive care unit [ICU] care) of ruxolitinib + standard-of-care (SoC) therapy compared with placebo + SoC therapy, for the treatment of COVID-19 by Day 29.	Composite endpoint defined as: • Death **OR** • Respiratory failure (require mechanical ventilation) **OR** • Intensive care unit (ICU) care by Day 29.
Secondary Objectives	To evaluate the efficacy (as measured by clinical status using a 9-point ordinal scale) of ruxolitinib + SoC therapy compared with placebo + SoC therapy, for the treatment of COVID-19 (WHO 18-Feb-2020).	Clinical status assessed using a 9-point ordinal scale (Appendix 2) at Day 15 and Day 29. • Percentage of patients with a better category (lower number) in clinical status at Day 15 and at Day 29. • Percentage of patients with at least two-point improvement in clinical status at Day 15 and at Day 29. • Percentage of patients with at least one-point improvement in clinical status at Day 15 and at Day 29. • Percentage of patients with at least one-point deterioration in clinical status at Day 15 and at Day 29. • Time to improvement from baseline category to one less severe category of the ordinal scale. • Mean change in the 9-point ordinal scale from baseline to Days 15 and 29.

	Objectives	**Endpoints**
	To evaluate the efficacy of ruxolitinib + SoC therapy, compared with placebo + SoC therapy, on in-hospital outcomes in patients with COVID-19.	Mortality rate at Day 15 and at Day 29; Proportion of patients requiring mechanical ventilation by Day 29; Duration of hospitalization.
	To evaluate the efficacy of ruxolitinib + SoC therapy, compared with placebo + SoC therapy, in change in the National Early Warning Score (NEWS2) score in patients with COVID-19.	The time to discharge or to a NEWS2 (Appendix 3) score of ≤2 and maintained for 24 hours whichever comes first. Change from baseline to Days 3, 5, 8, 11, 15, and 29 in NEWS2 score.
	To evaluate the efficacy of ruxolitinib + SoC therapy, compared with placebo + SoC therapy, in change in SpO_2/FiO_2 ratio in patients with COVID-19.	Change from baseline to Days 15 and 29 in SpO_2/FiO_2 ratio.
	To evaluate the efficacy of ruxolitinib + SoC therapy, compared with placebo + SoC therapy, in proportion of patients with no oxygen therapy (defined as oxygen saturation ≥ 94% on room air) in patients with COVID-19.	Proportion of patients with no oxygen therapy (defined as oxygen saturation ≥ 94% on room air) at Days 15 and 29.
	To evaluate the safety of ruxolitinib + SoC therapy, compared with placebo + SoC therapy, in the treatment of patients with COVID-19.	Number of participants with treatment-related adverse events (as assessed by Common Terminology Criteria for Adverse Event version 5.0), serious adverse events, clinically significant changes in laboratory measures and vital signs during the 29-day Study Period.
[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]



2.1 Primary estimands

- Treatment - ruxolitinib added to SoC therapy.
- Population – Hospitalized patients with coronavirus (SARS-CoV-2) infection confirmed by polymerase chain reaction (PCR) test or another rapid test from the respiratory tract prior to randomization as described in Section 5.1.
- Endpoint - Primary efficacy endpoint is clinical failure, defined as the occurrence of death, respiratory failure (require mechanical ventilation), or ICU care by Day 29.
- Population-level summary - Odds-ratio comparing ruxolitinib added to SoC therapy to placebo added to SoC therapy.
- Intercurrent event(s) - Discontinuation of study treatment.

3 Study design

This is a randomized, double-blind, placebo-controlled, 29-day, multicenter study to assess the efficacy and safety of ruxolitinib + SoC therapy, compared with placebo + SoC therapy, in patients aged ≥12 years with COVID-19 pneumonia (Figure 3-1).

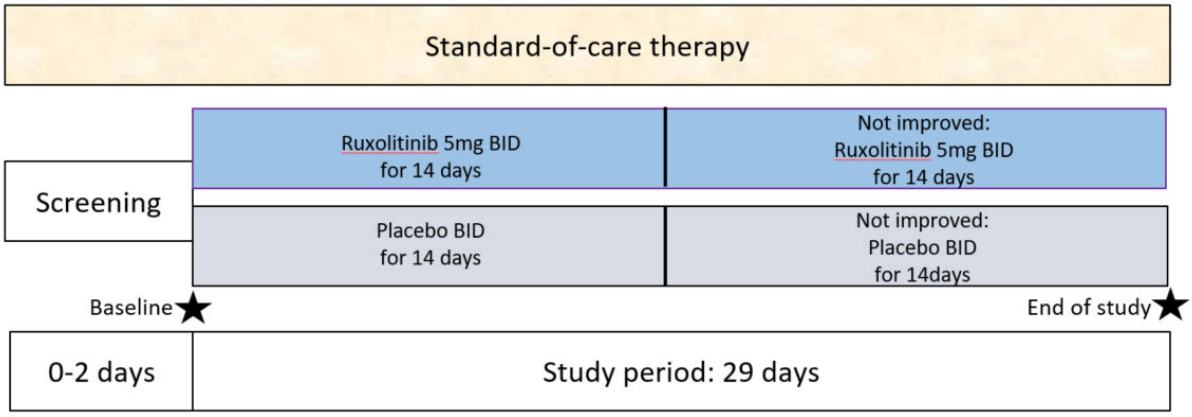
Approximately 402 patients aged ≥12 years with confirmed SARS-CoV-2 virus infection and hospitalized or will be hospitalized with COVID-19 pneumonia (demonstrated by CXRAY or chest CT) (supportive therapy, anti-viral treatment) are eligible. Patients with active tuberculosis or suspected uncontrolled bacterial, fungal, viral, or other infection (besides SARS-CoV-2 virus) will be excluded from the study.

An informed consent (and assent, if applicable) will be obtained from patients before any study related assessments or procedures are performed. Thereafter, medications and eligibility criteria will be reviewed by study personnel. All patients signing informed consent must be registered by study staff in the Interactive Response Technology (IRT).

The study will include:

- **Screening period** of 0-2 days
- **Study period** of 29 days (treatment of 14 days; an additional 14 days of study drug may be given, if in the opinion of the investigator, the patient's clinical signs and symptoms are not improved or worsen and the potential benefit outweighs the potential risk) – see below.

Figure 3-1 Study design



Note: Should a patient become intubated during the Study Period, study medication may be given via a nasogastric tube (see Section 6.1.1 for directions).

Eligible patients will be randomized on the same day as screening or up to two days after completing the screening procedures. At Day 1 (randomization visit), patients will be assigned in a 2:1 ratio to receive oral ruxolitinib 5 mg twice daily or oral matching-image placebo for a total of 14 days (Section 6.1). An additional 14 days of study drug may be given, if in the opinion of the investigator, the patient's clinical signs and symptoms are not improved or worsen and the potential benefit outweighs the potential risk.

Study treatment will be given in combination with SoC therapy according to the investigator's clinical judgement. Should a patient become intubated during the Study Period, study medication may be given via a nasogastric tube (see Section 6.1.1 for directions). Randomization will be stratified by region (North America, Europe).

Patients who do not meet the criteria for participation in this study (screen failures) may not be re-screened.

Assessments during the Study Period will occur per the schedule of study assessments (See Section 8) for specific assessments and timing for these assessments). The primary endpoint for the study will be the proportion of patients who die, develop respiratory failure (require mechanical ventilation), or require ICU care by Day 29. Should a patient be discharged from the hospital during the 29-day study period, daily assessment of clinical status will be made via a telephone call to the patient each day (between 7 AM and 12 PM), with the exception of Day 15 and Day 29, during which discharged patients will return for an in-clinic visit. For Day 15 and Day 29, if an in-clinic visit is not possible, the visit may be performed in an appropriate setting, including at home, with appropriate study personnel.

This study will include an internal data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study.

4 Rationale

4.1 Rationale for study design

This randomized, double-blind, parallel-group, placebo-controlled, design supports the rigorous assessment of efficacy as well as safety of ruxolitinib as add-on to SoC therapy for patients with COVID-19 pneumonia.

Screening Period

The screening period allows for assessment of patient entry criteria to ensure suitable patients are entered into the study. Screening and randomization may occur on the same day.

Study Period

During this period, oral ruxolitinib 5 mg twice daily or oral matching-image placebo twice daily (randomized 2:1) will be administered 14 days. An additional 14 days of study drug may be given, if in the opinion of the investigator, the patient's clinical signs and symptoms are not improved or worsen and the potential benefit outweighs the potential risk. The endpoints included in this study measure clinical status, clinical and in-hospital outcomes, and laboratory values during the 29-day Study Period. These measurements are consistent with endpoints and measurement times for other studies of therapies in the treatment of COVID-19 (WHO 18-Feb-2020; Cao et al 2020).

4.2 Rationale for choice of background therapy

Although there are no approved treatments for COVID-19, SoC therapy for patients with COVID-19 pneumonia generally includes supportive care and anti-viral treatments. Thus, placebo + SoC therapy is appropriate as a control in this study.

4.3 Rationale for dose/regimen and duration of treatment

The ruxolitinib dose regimen chosen in this study is the lowest efficacious dose based on pharmacokinetic data. Ruxolitinib 5 mg twice daily is the approved starting dose for treatment of steroid-refractory acute graft versus host disease in the US with demonstrated anti-inflammatory effect (Jagasia et al 2020). Ruxolitinib 5 mg twice daily is also the starting dose recommended for patients with myleofibrosis when platelets are 50 x 10^9/ L – <100 x 10^9/L.

Cao et al (2020) reported the median hospital stay for COVID-19 was 12 days with an interquartile range of 1 to 14 days. Therefore, a duration of treatment for 14 days seems reasonable and has been selected for this study. An additional 14 days of study drug may be given, if in the opinion of the investigator, the patient's clinical signs and symptoms are not improved or worsen and the potential benefit outweighs the potential risk.

4.4 Rationale for choice of control drugs (comparator/placebo) or combination drugs

The study will evaluate the efficacy and safety of oral ruxolitinib + SoC therapy, compared with matching-image placebo + SoC therapy. Despite the lack of targeted treatments for COVID-19, SoC for patients with severe COVID-19 respiratory disease generally includes supportive care and may include available anti-viral agents. Therefore, SoC + placebo treatment is appropriate as a control in this study.

4.5 Purpose and timing of interim analyses/design adaptations

No interim analysis is planned. An internal Data Monitoring Committee at Novartis will be established to conduct periodic unblinded safety reviews.

4.6 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 the CRS and the course of severe respiratory disease/ARDS in patients with COVID-19. Additionally, there is some clinical evidence of efficacy with ruxolitinib in pilot studies in another recognized disease with CRS: secondary HLH (See Section 1.1.1). However, ruxolitinib has not previously been studied in patients with COVID-19 pneumonia. 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 patients with myelofibrosis, which involved longer-term dosing and, in general, higher doses than that proposed in this protocol, the most frequent treatment-emergent adverse events (AEs) were dose-dependent, reversible thrombocytopenia, anemia, and neutropenia. The above events could increase the risk of infection, including pneumonia and bronchitis, 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 non-hematologic AEs were mild, reversible increases in alanine aminotransferase (ALT) and aspartate aminotransferase (AST); bruising; hypercholesterolemia; dizziness; headache; and urinary tract infections. Tuberculosis has been infrequently reported in patients receiving ruxolitinib to treat myelofibrosis (<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 myelofibrosis, particularly those who have stopped taking ruxolitinib suddenly, have reported return of MF symptoms such as fatigue, bone pain, fever, pruritus, night sweats, symptomatic splenomegaly and weight loss. In very few patients, respiratory distress, disseminated intravascular coagulation (DIC), 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 progressive multifocal leuko-encephalopathy (PML), has been reported with ruxolitinib. It is important to note that PML and infections are complications associated with MF that has been previously described in the absence of ruxolitinib. Additionally, non-melanoma skin cancers (NMSCs), including basal cell, squamous cell, and a rare and aggressive type of skin cancer called merkel cell carcinoma has been reported in patients who took ruxolitinib, it is unknown whether this was due to ruxolitinib treatment.

In the presence of potent CYP3A4 inhibitors, there is the possibility of increased exposure to ruxolitinib and more frequent monitoring of hematology parameters is recommended, although no automatic dose adjustment of ruxolitinib is required. See Appendix 4 for a list of cytochrome P450 3A4 (CYP3A4) inhibitors and inducers.

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

5 Study Population

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria:

1. Patient or guardian/health proxy must provide informed consent (and assent if applicable) before any study assessment is performed.
2. Male and female patients aged ≥ 12 years (or ≥ the lower age limit allowed by Health Authority and/or Ethics Committee/Institutional Review Board approvals).
3. Patients with coronavirus (SARS-CoV-2) infection confirmed by polymerase chain reaction (PCR) test or another rapid test from the respiratory tract prior to randomization.
4. Patient is currently hospitalized or will be hospitalized prior to randomization.
5. Patients, who meet **at least one** of the below criteria:
   - Pulmonary infiltrates (chest X ray or chest CT scan);
   - Respiratory frequency ≥ 30/min;
   - Requiring supplemental oxygen;
   - Oxygen saturation ≤ 94% on room air;
   - Arterial oxygen partial pressure (PaO_2)/ fraction of inspired oxygen (FiO_2) < 300mmHg (1mmHg=0.133kPa) (corrective formulation should be used for higher altitude regions (over 1000m).

5.2 Exclusion criteria

Participants meeting **any** of the following criteria are **not** eligible for inclusion in this study.

1. History of hypersensitivity to any drugs or metabolites of similar chemical classes as ruxolitinib.
2. Presence of severely impaired renal function defined by serum creatinine > 2 mg/dL (>176.8 μmol/L), or have estimated creatinine clearance < 30 ml/min measured or calculated by Cockroft Gault equation or calculated by the updated bedside Schwartz equation.
3. Suspected uncontrolled, active bacterial, fungal, viral, or other infection (besides COVID-19).
4. Current or history of active TB infection.
5. History of progressive multifocal leukoencephalopathy (PML).
6. Currently intubated or intubated between screening and randomization.
7. In intensive care unit (ICU) at time of randomization.
8. Patients who are on anti-rejection, immunosuppressant or immunomodulatory drugs (i.e. tocilizumab, ruxolitinib, canakinumab, sarilumab, anakinra).
9. Intubated or in ICU for COVID-19 disease prior to screening.
10. Participating in any other investigational or interventional trials.
11. Unable to ingest tablets at randomization.
12. ALT ≥ 5 x ULN detected at screening (according to local laboratory reference ranges).
13. Patients who have evidence of liver cirrhosis (Child A to C).
14. ANC < 1000/μL at screening.
15. Platelet count < 50,000/μL at screening.
16. Pregnant or nursing (lactating) women.
17. Females ≥ 12 and < 18 years of age and of childbearing potential (e.g. are menstruating) who do not agree to abstinence or, if sexually active, do not agree to the use of highly effective contraception as defined below, throughout the study and for up to 30 days after stopping treatment,

    OR

    Females ≥ 18 years of age and of child-bearing 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 include:

    - Total abstinence (when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy or tubal ligation at least six 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.

- Male sterilization (at least 6 months prior to screening). The vasectomized male partner should be the sole partner for that patient.
- Use of oral, injected or implanted hormonal methods of contraception. Placement of an intrauterine device (IUD) or intrauterine system (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, patients should have been using the same pill on a stable dose for a minimum of 3 months before Screening).

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or tubal ligation at least six weeks ago. 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 child bearing potential.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

Ruxolitinib 5 mg tablets or matching placebo will be administered orally twice per day approximately 12 hours apart (morning and night) without regards to food.

Dose reductions or interruptions for any toxicity attributed to study drug are permitted in order to allow the patient to continue on the study treatment. See Section 6.6.2.

If a patient becomes intubated during the course of the study, study drug can be administered as follows (Jakafi 2011):

- For patients unable to ingest tablets, study drug can be administered through a nasogastric tube (8 French or greater) as follows:
  - Suspend one tablet in approximately 40 mL of water with stirring for approximately 10 minutes.
  - Within 6 hours after the tablet has dispersed, the suspension can be administered through a nasogastric tube using an appropriate syringe.
- The tube should be rinsed with approximately 75 mL of water

Table 6-1 Investigational and control drug

Investigational/ Control Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type
INC424 5mg	Tablet	Oral use	Double-blind supply; bottles
INC424 Placebo to 5mg	Tablet	Oral use	Double-blind supply; bottles

6.1.2 Supply of study treatment

No additional treatment beyond ruxolitinib 5 mg or matching image placebo will be provided.

6.1.3 Treatment arms/group

Participants will be assigned at randomization to one of the following treatment arms/groups in a ratio of 2:1:

- ruxolitinib 5 mg tablets twice daily; or
- matching image placebo tablets twice daily.

6.1.4 Treatment duration

The planned duration of treatment is 14 days. An additional 14 days of study drug may be given, if in the opinion of the investigator, the patient's clinical signs and symptoms are not improved or worsen and the potential benefit outweighs the potential risk. Participants may be discontinued from treatment earlier due to unacceptable toxicity, disease progression and/or treatment is discontinued at the discretion of the investigator or the participant. Treatment will not be provided upon completion of the study.

6.2 Other treatments

6.2.1 Concomitant therapy

All medications, procedures, and significant non-drug therapies (including physical therapy and blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate electronic Case Report Forms (eCRFs).

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

The patient must be told to notify the Treating Physician about any new medications he/she takes after the start of study drug.

6.2.1.1 Permitted concomitant therapy requiring caution and/or action

Patients may receive: anti-virals, inhaled or systemic corticosteroids, heparin, low molecular weight heparin (LMWH), direct oral anticoagulants, anti-emetics, calcineurin inhibitors, azole fungal prophylaxis, broad spectrum antibiotics (either semi-synthetic penicillin or third generation cephalosporin with vancomycin, gentamycin or equivalent), acyclovir prophylaxis, G-CSF, steroid pre-meds prior to RBC/platelet transfusions, narcotics, and sedatives warrant close monitoring of potential drug-drug interaction effects of these concurrent drugs.

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

In patients taking warfarin, heparin, LMWH, or direct oral anticoagulants, the degree of thrombocytopenia should be considered, platelet counts and coagulation parameters monitored, and the dose of anti-coagulant or non-steroidal anti-inflammatory drug adjusted accordingly.

In patients taking drugs that affect platelet function/count, the degree of thrombocytopenia should be considered, platelet counts and coagulation parameters monitored, and the dose of drug adjusted accordingly.

In the presence of potent CYP3A4 inhibitors, there is the possibility of increased exposure to ruxolitinib and more frequent monitoring of hematology parameters is recommended, although no automatic dose adjustment is required. See Appendix 4 for a list of cytochrome P450 3A4 (CYP3A4) inhibitors and inducers.

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

For additional information, please refer to the Investigator Brochure.

6.2.2 Prohibited medication

The following medications are prohibited until treatment discontinuation:

- Concomitant use of another JAK inhibitor
- Aspirin in doses >150 mg/day
- Fluconazole > 200 mg daily

For additional information, please refer to the Investigator Brochure.

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis 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 completion of informed consent, the participant is assigned to the next sequential Participant No. available.

Screen failures cannot be rescreened. Screen failures should be called into IRT.

6.3.2 Treatment assignment, randomization

At the randomization visit, all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The investigator or his/her delegate will contact the IRT after confirming that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and will specify a unique medication number for the first package of study treatment to be dispensed to the participant.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms, which in turn are linked to medication numbers. A separate medication list will be produced by or under the responsibility of Novartis Global Clinical Supply (GCS) using a validated system that automates the random assignment of medication numbers to packs containing the study treatment.

Randomization will be stratified by regions. Stratification ensures a balanced allocation of subjects to treatment groups within the strata.

The randomization scheme for subjects will be reviewed and approved by a member of the Randomization Office.

6.4 Treatment blinding

Participants, investigator staff, persons performing the assessments, and CTT will remain blind to the identity of the treatment from the time of randomization until database lock, using the following methods: (1) Randomization data are kept strictly confidential until the time of unblinding and will not be accessible by anyone else involved in the study, (2) the identity of the treatments will be concealed by the use of study treatment 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.

6.5 Dose escalation and dose modification

Study drug dose adjustments and/or interruptions are described in Section 6.6.2.

6.5.1 Dose modifications

Dose reductions or interruptions for patients that do not tolerate the dosing schedule and are attributed to study drug are permitted in order to allow the patient to continue on the study treatment (see Section 6.6.2 for more guidance).

Dose modifications must be reported in the appropriate eCRFs.

For subjects with moderate renal impairment (creatinine clearance (CrCl) 30–59 mL/min) or any level of hepatic impairment, i.e. Mild, Moderate, or Severe (Child-Pugh categories A, B, C), AND platelet counts between 50 – 100 X 10^9 /L, the dose should be reduced to one tablet per day.

If renal/hepatic impairment AND platelet count improves > 100x 10^9/L, dosing may be resumed at one tablet twice per day.

6.5.1.1 Follow up on potential drug-induced liver injury (DILI) cases

Participants with transaminase increase combined with total bilirubin increase may be indicative of potentially severe DILI, and should be considered as clinically important events and assessed appropriately to establish the diagnosis. The required clinical information, as detailed below, 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 value; participants meeting any of the following criteria will require further follow-up as outlined below:

- For participants with normal ALT and AST and total bilirubin value at baseline: AST or ALT > 3.0 x ULN combined with total bilirubin > 2.0 x ULN
- For participants with elevated AST or ALT or total bilirubin value at baseline: [AST or ALT > 2 x baseline]OR [AST or ALT >300 U/L]whichever occurs first combined with [total bilirubin > 2 x baseline AND > 2.0 x ULN]

As 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, 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, GGT, GLDH (if available at local laboratory), prothrombin time (PT)/INR, alkaline phosphatase, albumin, and creatine kinase.

6.6 Additional treatment guidance

6.6.1 Treatment compliance

Treatment will be recorded on the appropriate eCRF.

6.6.2 Recommended treatment of adverse events

Dose reductions or interruptions for patients that do not tolerate the dosing schedule and are attributed to study drug are permitted in order to allow the patient to continue on the study treatment. Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 as described in Section 10.1.1.

Neutropenia (Growth factor supplementation and transfusion should be provided as clinically indicated.)

Grade 3 (ANC < 750 - 500/mm3): Reduce dose to one tablet per day, monitor ANC daily until resolved to ≤Grade 2, then resume initial dose level.

Grade 4 (ANC < 500/mm3): Hold dose, monitor ANC daily until resolved to ≤ Grade 3, then resume with reduced dose of one tablet per day. If resolves to ≤ Grade 2, can resume initial dose level.

Thrombocytopenia (transfusion support should be provided as clinically indicated)

For platelet counts < 20,000/mm3: Hold dose until resolved to > 35,000/mm3, then resume at a reduced dose level of one tablet per day. If counts are stable, dose may be cautiously re-escalated.

Dose reductions or interruptions for non-hematologic toxicity are permitted in order to allow the patient to continue on the study treatment. Dose adjustments for different ranges of non-hematologic toxicity are described below. The objective of the dose adjustment rules is to optimize treatment response for each individual patient while avoiding significant non-hematologic toxicities.

AST/ALT elevation

See Appendix 1 for stopping or interrupting study drug for elevated ALT/AST.

Other adverse events (non-hematological) attributed to study drug

Recommendation for Grade 1 or 2: Maintain dose level.

Grade 3: Hold dose until resolved to baseline or Grade 1.

Grade 4: Discontinue from study treatment.

Medication used to treat adverse events (AEs) must be recorded on the appropriate eCRF.

6.6.3 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely. Blinding codes may also be broken after a participant discontinues treatment due to disease progression if deemed essential to allow the investigator to select the participant's next treatment regimen, and after discussion and agreement with the Novartis. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- participant number

In addition, oral and written information to the participant must be provided on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

6.7 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

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

6.7.1 Handling of study treatment and additional treatment

6.7.1.1 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 Investigator's Brochure.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis CO Quality Assurance.

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 site visits or remotely and at the completion of the trial. 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.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site or destroyed as per local regulation.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

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 informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

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

Information about common side effects already known about the investigational drug can be found in the Investigator's Brochure (IB). This information will be included in the participant informed consent 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 and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent (or, as applicable, parental consent and adolescent assent)
- As applicable, Pregnancy Outcomes Reporting Consent for female subjects

[redacted]

Women of child bearing 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:

[redacted]

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation. Participants who prematurely discontinue the **study** (see Section 9.1.1) for any reason should be scheduled for a visit 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 adverse event and concomitant medications recorded on the eCRF.

When possible, the sequence of assessments at each visit should be as follows (at visits required in the schedule of assessments).

- Efficacy assessments: clinical status, clinical signs and symptoms, oxygen saturation, consciousness, ventilatory status;
- Safety assessments: vital signs, review of adverse events, concomitant medications;

Laboratory samples: on days indicated in schedule of assessments.

Results from tests or examinations done as part of routine care prior to the screening visit may be used for the study as indicated in Table 8-1 (Assessment Schedule). **However, the above-mentioned efficacy assessments (clinical status, clinical signs and symptoms, oxygen saturation, consciousness, ventilatory status) must be done in the morning of randomization between 7 AM and 12 PM, prior to administering study drug.**

If a patient is discharged from the hospital during the study period, the Clinical Status Evaluation with 9-point ordinal scale will be performed via telephone call (between 7 AM and 12 PM local time) daily except for Day 15 and Day 29 when it will be performed in clinic. For Day 15 and Day 29, if an in-clinic visit is not possible, the visit may be performed in an appropriate setting, including at home, with appropriate study personnel.

Table 8-1 Assessment Schedule

All assessments will be obtained while patient is in hospital. Once patient is discharged, assessments will be done via the telephone as indicated in the table below with the exception of Day 15 and Day 29 which require in-clinic assessments. For Day 15 and Day 29, if an in-clinic visit is not possible, the visit may be performed in an appropriate setting, including at home, with appropriate study personnel.

	Screening	**Study Period**				
Study Day	**Screening**	**Day 1 (Randomization)**	**Day 2-14 (every day unless otherwise specified below)**	**Day 15**	**Day 16-28 (every day unless otherwise specified below)**	**Day 29 (End of study)**
Informed consent (and assent if applicable)[1]	x					
Inclusion / Exclusion criteria	x	x				
Demographics / medical history (including co-morbidities checklist)	x					
SARS-CoV-2 virus confirmation[2]	s					
Vital signs[3] (between 7 AM and 12 PM local time)	x[4]	x	x (while in hospital)	x	x (while in hospital)	x
SpO_2 assessment (between 7 AM and 12 PM local time – done at same time as vital signs)	x[4]	x	x (while in hospital)	x	x (while in hospital)	x
SpO_2 assessment on room air (for patients on oxygen by nasal cannula (≤ 2L/min) (based on investigator medical judgement) (between 7 AM and 12 PM local time – done at same time as vital signs)			(only on day of discharge)	x	(only on day of discharge)	x
FiO_2 assessment (between 7 AM and 12 PM local time – done at same time as vital signs)	x[4]	x	x (while in hospital)	x	x (while in hospital)	x

	Screening	Study Period				
Study Day	**Screening**	**Day 1 (Randomization)**	**Day 2-14 (every day unless otherwise specified below)**	**Day 15**	**Day 16-28 (every day unless otherwise specified below)**	**Day 29 (End of study)**
Consciousness assessment (between 7 AM and 12 PM local time – done at same time as vital signs)		x	x (while in hospital)	x	x (while in hospital)	x
Clinical Status Evaluation with 9-point ordinal scale (if patient is discharged to home, telephone call daily except for Day 15 and Day 29 when in clinic) (between 7 AM and 12 PM local time)		x	x (via telephone if not in hospital)	x	x (via telephone if not in hospital)	x
Height (measured or patient or guardian/health proxy reported), weight, BMI	x[4]					x
Physical exam	s[4]					
Ventilatory status (e.g. mechanical ventilation, supplemental oxygen, intubation and non-invasive ventilation [e.g. CPAP, BIPAP, etc.])	x[4]	x	x (via telephone if not in hospital)	x	x (via telephone if not in hospital)	x
Drug dispensation and administration		x	Days 2-14	x (if applicable)	Days 16-28 (if applicable)	x (if applicable)
Assessment of re-treatment (if second course of 14 day treatment is needed)				s		
Reconcile study medication				s		s
Collect unused study medication				s		s
Hematology[5] (local labs)	x[6]	x[7]	Days 3, 5, 7, 9, 11, 13 (while in hospital)	x	Days 17, 19, 21, 23, 25, 27 (while in hospital)	x
Clinical chemistry, [redacted][5]	x[6]	x[7]	Days 3, 5, 7, 9, 11, 13 (while in hospital)	x	Days 17, 19, 21, 23, 25, 27 (while in hospital)	x

	Screening	**Study Period**				
Study Day	**Screening**	**Day 1 (Randomization)**	**Day 2-14 (every day unless otherwise specified below)**	**Day 15**	**Day 16-28 (every day unless otherwise specified below)**	**Day 29 (End of study)**
Serum pregnancy test (local labs); results must be reviewed prior to randomization	x[8]					x
Chest x-ray (CXR) or chest CT scan[9]	x					
ECG (local)[4]	s					
Adverse events	x	x	x (via telephone if not in hospital)	x	x (via telephone if not in hospital)	x
Prior and concomitant non-drug therapies (including surgeries and procedures)	x	x	x (via telephone if not in hospital)	x	x (via telephone if not in hospital)	x
Prior/concomitant medications	x	x	x (via telephone if not in hospital)	x	x (via telephone if not in hospital)	x
In-hospital outcomes[10]	x	x	x (while in hospital)	x	x (while in hospital)	x
[redacted]						
[redacted]						
Contact IRT[11]	x	x				

	Screening	**Study Period**				
Study Day	**Screening**	**Day 1 (Randomization)**	**Day 2-14 (every day unless otherwise specified below)**	**Day 15**	**Day 16-28 (every day unless otherwise specified below)**	**Day 29 (End of study)**
1. Informed consent must be obtained prior to any study-related procedure. 2. SARS-CoV-2 virus to be measured by polymerase chain reaction (PCR) test or another rapid test from the respiratory tract prior to randomization (may use test done as part of routine care prior to screening). If no SARS-CoV-2 virus test available from routine care, test should be obtained at screening. 3. Vital signs include pulse rate, respiratory rate (if not on mechanical ventilation), systolic and diastolic blood pressure and body temperature. 4. Results from tests or examinations done as part of routine care and performed up to 24 hours prior to the screening visit may be used for the screening visit values. 5. Hematology, clinical chemistry [redacted] should be measured by the local laboratory. Hematology, clinical chemistry, [redacted] obtained as part of routine care may be used. 6. Hematology, clinical chemistry, [redacted] done as part of routine care and performed up to 48 hours prior to the screening visit may be used for the screening visit values. Also, blood drawn and banked up to 48 hours prior to the screening visit may be used to obtain the screening visit laboratory values. 7. If the randomization visit occurs on the same day as the screening visit, the screening hematology, clinical chemistry, [redacted] values can serve as the randomization laboratory values. If the randomization visit occurs on a day different from the screening visit, hematology, clinical chemistry, [redacted] are to be obtained on that day prior to randomization. 8. Pregnancy test: Only for females of childbearing potential, serum pregnancy test (serum hCG). Pregnancy tests done as part of routine care up to 24 hours prior to the screening visit may be used. Also, blood drawn and banked up to 24 hours prior to the screening visit may be used to obtain the required pregnancy test. 9. Chest X-ray or chest CT scan prior to randomization (may use chest X-ray or chest CT done as part of routine care prior to screening). If no chest X-ray or chest CT scan available from routine care, chest X-ray or chest CT scan should be obtained at screening. 10. In-hospital outcomes to be reported as described on eCRFs. 11. Screen failures must be called into IRT. (s) = assessment to be recorded in source documents only; assessment will not be entered into the eCRFs; (x) = assessment to be recorded in source documents and entered into the eCRF						

8.1 Screening

No rescreening will be allowed.

8.1.1 Information to be collected on screening failures

Participants who sign an informed consent form and 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 Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see Section 10.1.3 for reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Participant demographics/other baseline characteristics

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.

8.3 Efficacy

8.3.1 Clinical status (9-point ordinal scale)

Assessment of clinical status using a 9-category ordinal scale (WHO 18-Feb-2020) will be recorded at baseline on Day 1 and then again once daily every morning (between 7AM and 12PM) through Day 29 of the Study Period. If a patient is discharged from the hospital, the assessment will be made by phone (between 7AM and 12PM). Each day, the worse score for the previous day will be recorded, i.e. on Day 3, Day 2 score is obtained and recorded as Day 2. The scale is as follows:

Table 8-2 Clinical status 9-category ordinal scale

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory (defined as not in hospital or in hospital and ready for discharge)	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

Patient State	Descriptor	Score
Hospitalized Severe Disease	Non-invasive ventilation or high-flow oxygen	5
	Intubation and mechanical ventilation	6
	Ventilation + additional organ support – pressors, RRT (renal replacement therapy), ECMO (extracorporeal membrane oxygenation)	7
Dead	Death	8

8.3.2 Vital signs and oxygen saturation

Results from tests or examinations done as part of routine care may be used as specified in the table of assessments (See Table 8-1).

Vital sign measurement include respiratory rate, pulse rate, systolic and diastolic blood pressure, and body temperature. Peripheral oxygen saturation (SpO_2) should also be measured at the same time as the vitals. For patients on oxygen by nasal cannula (≤ 2L/min), SpO_2 assessment on room air (based on investigator medical judgement) will also be performed at the same time as the vitals on Days 15, 29 and at discharge. For patients requiring supplemental oxygen, the oxygen flow rate (L/min) and/or fraction of inspired oxygen (FiO_2) should be recorded at the same time as the vitals.

In order to allow assessment of the NEWS2 score (Appendix 3), the vital sign parameters and oxygen saturation should be recorded together once per day (between 7AM and 12PM), for the duration of the hospitalization during the study. Following hospital discharge these parameters should be recorded once on Days 15 and 29.

8.3.3 National Early Warning Score 2 (NEWS2)

In addition to the vital signs, the patient's level of consciousness and the presence/absence of respiratory support must be recorded. The NEWS2 parameter for respiratory support is the selection of either air or "oxygen" can include other forms of ventilation to maintain oxygen saturation (see Appendix 3).

These should be recorded at the same time points as the vital sign measurements (between 7AM and 12 PM) (see Section 8.3.2).

NEWS2 values will be calculated electronically by Novartis based on vital sign parameters and NEWS2 related assessments recorded by the investigator in the appropriate eCRFs.

8.3.4 In-hospital outcomes

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

- Start and end date of mechanical ventilation
- Start and end date of hospital stay

8.3.5 Ventilatory status

Ventilatory status (mechanical ventilation, supplemental oxygen, intubation and non-invasive ventilation [e.g. CPAP, BIPAP, etc.]) will be collected at timepoints designated in Table 8-1 and recorded by the investigator in the appropriate eCRFs.

8.3.6 Appropriateness of efficacy assessments

Efficacy endpoints are those employed in other studies of patients with COVID-19 pneumonia (WHO 2020; Cao et al 2020).

8.4 Safety

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

For details on AE collection and reporting, refer to Section 10.1.1.

8.4.1 Laboratory evaluations

Laboratory evaluations will be performed by a local laboratory. Results from tests or examinations done as part of routine care may be used as specified in the table of assessments (See Table 8-1).

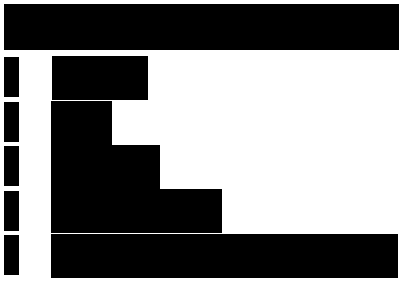
Hematology

Hemoglobin, hematocrit, red blood cell count, white blood cell count with differential, and platelet count will be measured according to the assessment schedule in Table 8-1.

Chemistry

BUN/urea, creatinine, creatine kinase, total bilirubin, AST, ALT, alkaline phosphatase, sodium, potassium, chloride, calcium, bicarbonate, total protein, albumin, and glucose will be measured according to the assessment schedule in Table 8-1. 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 times the upper limit of normal range, the total bilirubin will differentiated into the direct and indirect reacting bilirubin.



Sample(s) will be collected at the time point(s) defined in the Assessment Schedule (Table 8-1). If a given test is not available locally, this should be documented on the eCRF.

Drug-induced liver injury monitoring

For patients with elevated liver tests, additional laboratory tests as denoted in Appendix 1 (Table 16-1, Table 16-2 and Table 16-3) should be obtained as specified.

8.4.2 Physical Exam

A physical examination will be performed at Screening and any abnormalities will be recorded in source documents. Results from tests or examinations done as part of routine care may be used as per Table 8-1.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to informed consent being granted must be included in the Relevant Medical History/Current Medical Conditions screen on the patient's eCRF. Significant findings made after informed consent is given which meet the definition of an Adverse Event must be recorded on the Adverse Event screen of the patient's eCRF.

8.4.3 Height, weight, BMI

Results from tests or examinations done as part of routine care may be used as specified in the table of assessments (See Table 8-1).

If possible, height will be measured at the Screening visit as specified in the table of assessments (See Table 8-1). Otherwise, patient or guardian/health proxy reported height will be obtained.

Body weight will be measured at the Screening visit as specified in the table of assessments (See Table 8-1).

Body Mass Index (BMI) will be calculated as the weight in kg divided by the height in meters squared.

8.4.4 Electrocardiogram (ECG)

Results from tests or examinations done as part of routine care may be used as specified in the table of assessments (See Table 8-1).

An ECG will be taken at Screening and recorded in source documents.

The ECG should be recorded after 10 minutes of rest in the supine position to ensure a stable baseline.

Clinically significant abnormalities should be recorded on the relevant section of the medical history/Current medical conditions/AE eCRF page as appropriate.

If necessary, a cardiologist may be consulted.

8.4.5 Pregnancy and assessments of fertility

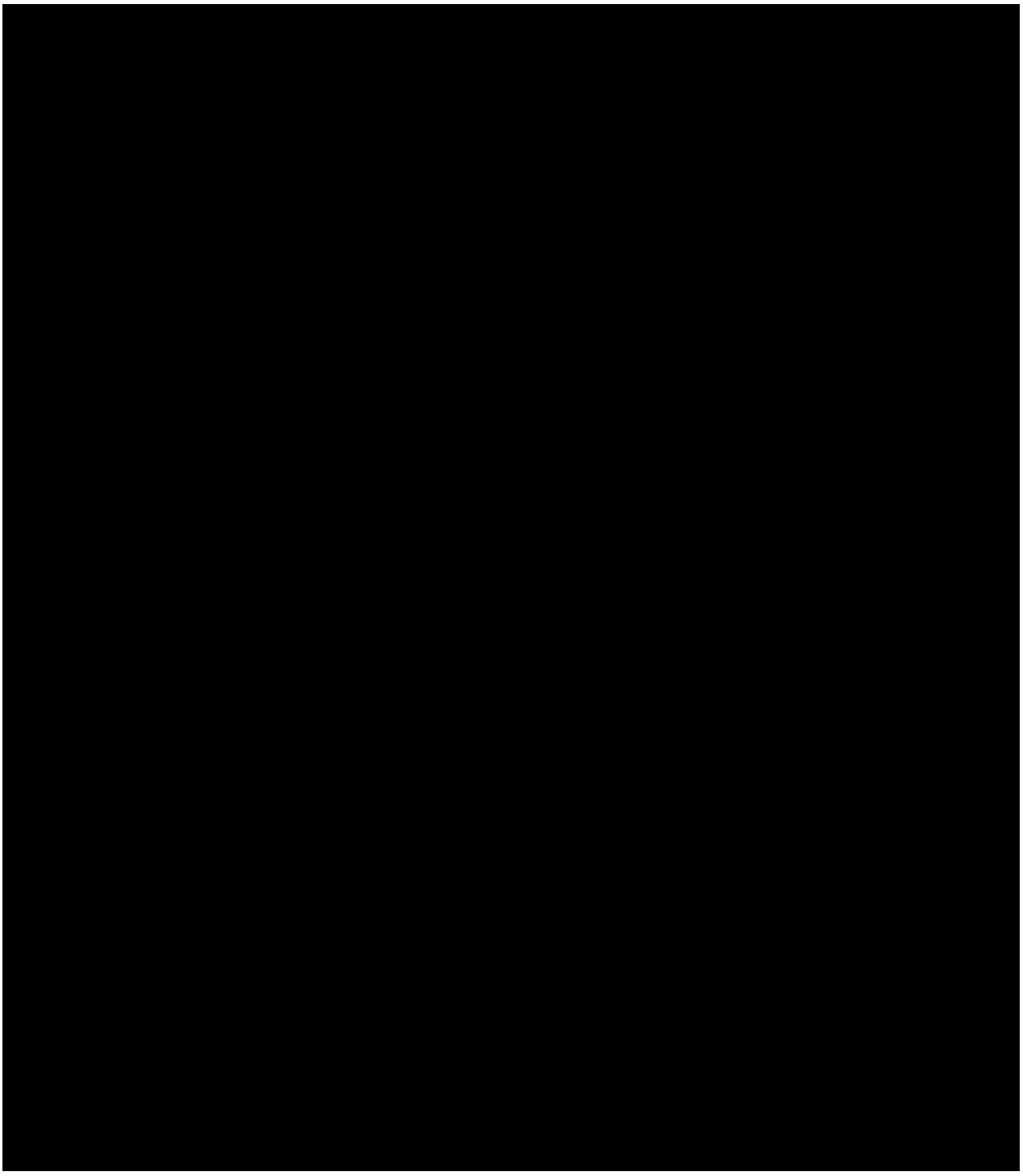
Results from tests or examinations done as part of routine care may be used as specified in the table of assessments (See Table 8-1).

All women of child bearing potential will have a serum pregnancy test at Screening and at designated visits (Table 8-1).

A positive pregnancy test at any time will result in study discontinuation.

8.4.6 Appropriateness of safety measurements

The safety assessments selected are appropriate for this protocol which utilizes a marketed compound where the safety profile has been established. The assessments are relevant to the critical care setting and will enable determination of therapeutic response in this setting.



9 Study discontinuation and treatment

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

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 impact the participant's well-being.

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Abnormal liver laboratory results as specified in Appendix 1
- Grade 4 non-hematologic adverse events attributed to study drug
- 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, prevents 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 'Withdrawal of Informed Consent' section). **Where possible, they should return for the assessments indicated** in the Assessment Schedule. If they fail to return for these assessments for unknown reasons, every effort (e.g. telephone, e-mail, letter) should be made to contact the participant/pre-designated contact as specified in the lost to follow-up section. 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 pre-designated 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/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

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, please refer to Emergency breaking of treatment code section.

9.1.2 Replacement policy

Patients discontinuing the study will not be replaced.

9.1.3 Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant:

- Does not want to participate in the study anymore,
  and
- Does not want any further visits or assessments
  and
- Does not want any further study related contacts

In this situation, the investigator should make a reasonable effort to understand the primary reason for the participant's decision to withdraw his/her consent and record this information.

Where consent to the use of personal and coded data is not required, participant therefore 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 communicating 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.

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

9.1.4 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.5 Early study termination by the sponsor

The study can be terminated by Novartis at any time.

Reasons for early termination:

- 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 taking the decision to terminate, Novartis will always consider participant welfare and safety. Should early termination be necessary, participants must be seen as soon as possible and treated as a prematurely withdrawn participant. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator or sponsor depending on local regulation will be responsible for informing IRBs/IECs of the early termination of the trial.

9.2 Study completion

Study completion is defined as when the last participant finishes their Study Completion visit and any repeat 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 (e.g. Each participant will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them).

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.3):

1. Adverse events will be assessed and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. Whether it constitutes a SAE (see Section 10.1.3 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding with study treatment.

All adverse events must be treated appropriately. Treatment may include one or more of the following:

- Dose not changed
- Dose Reduced/increased
- Drug interrupted/withdrawn

6. Its outcome (i.e. recovery status or whether it was fatal)

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drug can be found in the Investigator's Brochure (IB).

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the participant's general condition
    - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until the last study visit must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

Screen Failures (e.g. a participant who is screened but is not treated or randomized): SAEs occurring after the participant has provided informed consent until the time the participant is deemed a Screen Failure must be reported to Novartis.

If the SAE is not previously documented in the Investigator's Brochure or Package Insert (new occurrence) and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the after the last study visit should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up 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.

Pregnancy should be recorded and reported by the investigator to the Novartis Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the *study treatment* any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate eCRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing eCRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective Sections.

10.2 Additional Safety Monitoring

Not applicable.

10.2.1 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Appendix 1 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2 and Table 16-3. Repeat liver chemistry tests (i.e. ALT, AST, TBL, PT/INR, ALP and G-GT) to confirm elevation.

These liver chemistry repeats should be performed using the local laboratory used by the site. Repeated laboratory test results must be reported as appropriate.

- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment Section 9.1), if appropriate
- Hospitalization of the participant if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include

- These investigations can include based on investigator's discretion: serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the eCRF.

10.2.2 Data Monitoring Committee

This study will include an internal data monitoring committee (DMC) which will function independently of all other individuals associated with the conduct of this clinical trial, including the site investigators participating in the study.

Specific details regarding composition, responsibilities, data monitoring, and meeting frequency, and documentation of DMC reports, minutes, and recommendations will be described in a separate charter.

11 Data Collection and Database management

11.1 Data collection

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Designated investigator staff will enter the data required by the protocol and defined in the Assessment Schedule (Table 8-1) into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on eCRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

This study may also incorporate electronic technology (eSource DDE) to capture source documents and source data electronically, consistent with final (CDER 2013) FDA guidance regarding electronic source and regulations related to the maintenance of adequate participant case histories (21 CFR 312.62 [b]).

A Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE and/or eCRFs) with the investigators and their staff.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

11.2 Database management and quality control

Novartis personnel (or designated CRO) will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures and study completion, as well as randomization codes and data about all study treatment (s) dispensed to the participant and all dosage changes will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis.

Once all the necessary actions have been completed and the database has been declared to be complete and accurate, it will be locked **and the treatment codes will be unblinded** and made available for data analysis/moved to restricted area to be accessed by independent programmer and statistician. Any changes to the database after that time can only be made after written agreement by Novartis development management.

11.3 Site monitoring

Before study initiation, at an initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE and/or eCRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor in conducting these activities. Continuous monitoring of each site's data will be performed throughout the conduct of the study. Additionally, a central analytics organization may analyze data & identify risks & trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight.

The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on eCRFs must be traceable to the respective source documents.

The investigator must also keep the original informed consent form signed by the participant and/or legal representative (a signed copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Source data verification may be done on-site, if possible, or remotely, if the field monitor does not have access or have limited access to the site due to the current COVID-19 pandemic. Different approaches can be used depending on site medical records, and some of them could include sharing the information through electronic systems or platforms provided by a third party. In all cases investigator and sponsor must adhere to the recommendations established by the applicable Health Authorities. Novartis monitoring standards require verification for the presence of all informed consents, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Randomized Analysis Set (RAS) consists of all randomized participants.

According to the intent to treat principle, participants will be analyzed according to the treatment they have been assigned to during the randomization procedure.

The Safety Set includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

The analysis of the primary objective and all other efficacy variables will be performed on the RAS. The Safety Set will be used in the analysis of all safety variables.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for the RAS.

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Relevant medical histories and current medical conditions at baseline will be summarized by system organ class and preferred term, by treatment group.

12.3 Treatments

The duration of exposure in days to ruxolitinib and standard of care therapies will be summarized by means of descriptive statistics using the Safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system, by treatment group.

12.4 Analysis of the primary endpoint(s)/estimand(s)

The primary analysis for this study will be conducted on the RAS according the intention to treat principle.

12.4.1 Definition of primary endpoint(s)/estimand(s)

The estimand framework for the primary objective is as follows:

- Treatment - ruxolitinib added to SoC therapy
- Population – Hospitalized patients with coronavirus (SARS-CoV-2) infection confirmed by polymerase chain reaction (PCR) test or another rapid test from the respiratory tract prior to randomization as described in Section 5.1.
- Endpoint - Primary efficacy endpoint is clinical failure, defined as the occurrence of death, respiratory failure (require mechanical ventilation), or ICU care by Day 29.
- Population-level summary - Odds-ratio comparing ruxolitinib added to SoC therapy to placebo added to SoC therapy.
- Intercurrent event(s) - Discontinuation of study treatment

12.4.2 Statistical model, hypothesis, and method of analysis

The statistical hypothesis tested for clinical failure is that there is no difference in the proportion of subjects developing clinical failure by Day 29 with ruxolitinib + SoC versus placebo + SoC therapy.

Let p_i denote the proportion of clinical failures by Day 29 for treatment groups j, j = 0, 1 where

- 0 corresponds to placebo + SoC
- 1 corresponds to ruxolitinib + SoC

The following statistical hypothesis will be tested to address the primary objective:

H_0: $p_0 = p_1$, H_1: $p_0 \neq p_1$.

The odds of clinical failure will be analyzed by a logistic regression model with treatment group, region (North America, Europe), baseline clinical status based on the 9-point ordinal scale (≤4, ≥5), age, and gender as covariates. The estimated odds ratio, p-values, and 95% confidence intervals will be presented.

The study will be considered positive, if ruxolitinib demonstrates a statistically significant greater reduction in clinical failure. This implies observing an odds ratio of < 1.

12.4.3 Handling of remaining intercurrent events of primary estimand

Discontinuation of study treatment for any reason: Retrieved drop out (RDO) data after study treatment discontinuation will be collected. If RDO data is available up to Day 29 this will be used for analysis. If no RDO data was collected after study treatment discontinuation or the RDO data is not complete to Day 29 then the patient will be considered as a clinical failure, unless they are in one of the scenarios below:

- There was no occurrence of death, mechanical ventilation, nor ICU care in all the available data and patients were discharged from the hospital
- The last available data (either on-treatment or off-treatment) is from Day 15 or later, and there was no occurrence of death, mechanical ventilation, nor ICU care in all the available data

12.4.4 Handling of missing values not related to intercurrent event

For patients who withdraw from the study, their clinical failure status will be handled similarly as in Section 12.4.3. Other missing data handling rules will be specified in the SAP.

12.4.5 Sensitivity analyses for primary endpoint/estimand

In order to determine the robustness of the logistic regression model used for the primary analysis of clinical failure by Day 29, a non-parametric regression model (Koch et al 1998) will also be evaluated using the same explanatory variables as the logistic regression model.

12.4.6 Supplementary analysis

To assess the effect of classifying patients' clinical failure status with missing data, a multiple imputation based analysis will be conducted. More details of this approach will be included in the study analysis plan. Other imputation approaches, for example, a worst case analysis, will be considered and may be included in the study analysis plan.

12.4.7 Supportive analyses

The primary analysis of the clinical failure will be repeated for each of the events in the composite endpoint: occurrence of death, mechanical ventilation, and ICU care. Separate logistic regression models will be fitted to compare the odds between treatment groups for each of the endpoints. The analysis will be performed for both Days 15 and 29.

As there is uncertainty around the covariates to be included in the primary analysis model for the clinical failure by Day 29, analyses will be performed considering additional covariates, for example, co-morbidities. These analyses will be defined further in the study analysis plan.

12.5 Analysis of secondary endpoints/estimands

12.5.1 Efficacy and/or Pharmacodynamic endpoint(s)

Full details of all planned analyses will be included in the study analysis plan. However, a brief description of the approaches used for each endpoint are given below.

12.5.1.1 9-category ordinal scale

The odds of observing a better category (lower number) of clinical status (9-category ordinal scale, WHO 18-Feb-2020) at Day 15 will be analyzed with a proportional odds model (POM). The odds ratio for treatment group (ruxolitinib + SoC therapy vs. placebo + SoC therapy) 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 (e.g. the cutoff of level 5 'Non-invasive ventilation or high-flow oxygen' 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 proportional odds assumption will be checked by a score test. The model will include treatment group, country, age, gender, and baseline clinical status as covariates. The estimated odds ratios, p-values and 95% confidence intervals will be presented. The analysis will be repeated for the data at Day 29.

The treatment groups will also be compared in terms of at least a one-point improvement, at least a two-point improvement, and at least a one-point deterioration in clinical status at Days 15 and 29 using respective logistic regression models with the same covariates as for the POM.

Time to improvement from baseline category to one less severe category of the ordinal scale will be analyzed using a competing risk analysis framework (death will be treated as a competing risk). Baseline clinical status will also be included in the model.

Mean change from baseline in the clinical status on the 9-point ordinal scale to Days 15 and 29 will be summarized by treatment arm. This endpoint will also be analyzed using an analysis of covariance (ANCOVA) model with factors for treatment group and country, as well as the baseline clinical status as a continuous linear covariate.

12.5.1.2 Oxygen saturation

The proportion of patients with no oxygen therapy (defined as oxygen saturation ≥ 94% on room air) at Days 15 and 29 will be analyzed separately using a logistic regression model with the same covariates as for the primary analyses, with baseline oxygen therapy status included.

12.5.1.3 In-hospital outcomes

Duration of hospitalization will be analyzed using a competing risk analysis framework (death will be treated as a competing risk). More details will be provided in the statistical analysis plan. The analyses of mortality rates at Day 15 and at Day 29, and proportion of patients requiring mechanical ventilation by Day 29 are described in Section 12.4.7.

12.5.1.4 National Early Warning Score (NEWS2)

Time to discharge or to a National Early Warning Score (NEWS2) of ≤2 and maintained for 24 hours (whichever comes first) will be analyzed using a competing risk analysis framework (death will be a competing risk) (Royal College of Physicians 2017). The model will also include treatment group, age, and gender (in the case of the analysis of NEWS2, the baseline NEWS2 score will also be included).

Change from baseline to Days 3, 5, 8, 11, 15, and 29 in the National Early Warning Score (NEWS2) and change from baseline to Days 15 and 29 in SpO_2/FiO_2 ratio will be summarized by treatment arm.

12.5.2 Safety endpoints

Full details of all planned analyses will be included in the study analysis plan. However, a brief description of the approaches used are given below.

12.5.2.1 Adverse events

All information obtained on adverse events will be displayed by treatment group and participant.

The number (and percentage) of participants with treatment emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term and up to last study visit will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity (based on CTCAE Version 5.0 grades).

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

The number (and proportion) of participants with adverse events of special interest (AESI) such as worsening cytopenias, infections, etc. will be summarized by treatment.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

12.5.2.2 Vital signs

All vital signs data will be listed by treatment group, participant, and visit/time and if ranges are available, abnormalities (and relevant orthostatic changes) will be flagged. Summary statistics will be provided by treatment and visit/time.

12.5.2.3 Clinical laboratory evaluations

All laboratory data will be listed by treatment group, participant, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time.

[redacted]

12.7 Interim analyses

No interim analysis is planned. An internal Data Monitoring Committee at Novartis will be established to conduct periodic unblinded safety reviews.

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Assuming a true treatment difference in clinical failure rate of 15% for ruxolitinib added to SoC therapy compared to placebo added to SoC therapy, a sample size of approximately 402 participants provides at least 80% power that the primary analysis will be statistically significant at the two-sided 5% significance level. This holds for a variety of different assumptions with respect to clinical failure rates (Table 12-1).

These sample size assumptions were evaluated in East Version 6.4.

Table 12-1 Sensitivity of sample size assumptions to different failure rates for level of significance alpha = 0.05

Standard of care failure rate (%)	Ruxolitinib failure rate (%)	Power (%)
80	65	91
70	55	85
60	45	82
50	35	82
40	25	85
30	15	91

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

(Applicable to US only) This study is being conducted to determine whether ruxolitinib can safely and effectively be used to mitigate, treat, or cure COVID-19 or limit the harm of the COVID-19 pandemic in accordance with the Secretary of the Department of Health and Human Services' (HHS's) Declaration under the Public Readiness and Emergency Preparedness Act for medical countermeasures against COVID-19 (COVID-19 Declaration) effective February 4, 2020. The purpose of this study is to test the efficacy and safety of ruxolitinib in patients with COVID-19 associated cytokine storm. This study is authorized to proceed under an approved investigational new drug application (IND) in accordance with the public health and medical response of FDA, an Authority Having Jurisdiction as described under the PREP Act, to prescribe, administer, deliver, distribute or dispense this Covered Countermeasure as defined by and following the HHS's COVID-19 Declaration.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, written informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last patient last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials that were provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

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16 Appendices

16.1 Appendix 1: Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*
If ALT or AST abnormal at baseline:	• ALT or AST > 2x baseline or > 300 U/L (whichever occurs first)

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms ULN: upper limit of normal

Table 16-2 Follow up requirements for liver laboratory triggers with liver symptoms

	ALT	TBL	Liver Symptoms	Action
ALT increase without bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	• **No change to study treatment** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH (if available at local laboratory) in 48-72 hours. • Follow-up for symptoms.
	If normal at baseline: ALT > 5 x ULN for more than two weeks **If elevated at baseline:** ALT > 3 x baseline and > 10x ULN	Normal For patients with Gilbert's syndrome: No change in baseline TBL	None	• **Interrupt study drug** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH (if available at local laboratory) in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
	If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline	TBL > 2 x ULN For patients with Gilbert's syndrome: Doubling of direct bilirubin	None	
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	

Table 16-3 Follow up requirements for liver laboratory triggers

Criteria **Total Bilirubin (isolated)**	Actions required	Follow-up monitoring
>1.5 – 3.0 ULN	• Maintain treatment • Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	• Interrupt treatment • Repeat LFT within 48-72 hours • Hospitalize if clinically appropriate • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate eCRF	Monitor LFTs weekly until resolution to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	• Discontinue the study treatment immediately • Hospitalize the participant • Establish causality • Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate eCRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution[a] (frequency at investigator discretion)
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Hospitalization if clinically appropriate • Establish causality • Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate eCRF	Investigator discretion

*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms ULN: upper limit of normal

[a] Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death.

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.2 Appendix 2: Clinical status 9-point scale

Clinical status (9-point ordinal scale):

Patient State	Descriptor	Score
Uninfected	No clinical or virological evidence of infection	0
Ambulatory (defined as not in hospital or in hospital and ready for discharge)	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 – pressors, RRT (renal replacement therapy), ECMO (extracorporeal membrane oxygenation)	7
Dead	Death	8

Reference: WHO (18-Feb-2020). WHO R&D Blueprint. Novel coronavirus. COVID-19 Therapeutic Trial Synopsis (Dated 18-Feb-2020).

16.3 Appendix 3: National Early Warning Score 2 (NEWS2)

Physiological parameter	Score 3	2	1	0	1	2	3
Respiration rate (per minute)	≤8		9–11	12–20		21–24	≥25
SpO_2 Scale 1 (%)	≤91	92–93	94–95	≥96			
SpO_2 Scale 2 (%)	≤83	84–85	86–87	88–92 ≥93 on air	93–94 on oxygen	95–96 on oxygen	≥97 on oxygen
Air or oxygen?		Oxygen		Air			
Systolic blood pressure (mmHg)	≤90	91–100	101–110	111–219			≥220
Pulse (per minute)	≤40		41–50	51–90	91–110	111–130	≥131
Consciousness				Alert			CVPU
Temperature (°C)	≤35.0		35.1–36.0	36.1–38.0	38.1–39.0	≥39.1	

SpO_2 = oxygen saturation.

The oxygen saturation should be scored according to either the SpO_2 Scale 1 or 2 presented in the table above. The SpO_2 Scale 2 is for patients with a target oxygen saturation requirement of 88%-92% (e.g., in patients with hypercapnic respiratory failure related to advanced lung diseases, such as chronic obstructive pulmonary disease [COPD]). This should only be used in patients confirmed to have hypercapnic respiratory failure by blood gas analysis on either a prior or their current hospital admission.

The decision to use the SpO_2 Scale 2 should be made by the treating physician and should be recorded in the eCRF. In all other circumstances, the SpO_2 Scale 1 should be used.

For physiological parameter "Air or Oxygen?": Any patients requiring the use of oxygen or other forms of ventilation to maintain oxygen saturations and support respiration should be assigned a score of 2.

The consciousness level should be recorded according to the best clinical condition of the patient during the assessment. Patients who are assessed as "Alert" (A) should be assigned a score of 0. Patients assessed as "New Confusion" (C), "Responsive to Voice" (V), "Responsive to Pain" (P), or "Unconscious" should be assigned a score of 3.

Scores should be assigned for respiratory rate, systolic blood pressure, pulse, and temperature according to the table above.

NEWS2 values will be calculated electronically throughout the study by the Sponsor based upon entry of vital sign parameters by the investigator in the appropriate eCRF.

Example Case Calculation:

An 82-year-old lady was admitted, tested positive to COVID-19 and admitted to high dependency unit for non-invasive ventilation. Her taken observations and corresponding NEWS2 score are as follows:

Physiological Parameter	Observation	Component Score
Respiratory rate (per min)	26	3
Oxygen saturation (SpO_2 %)	95%	1
Supplemental Oxygen	Yes	2
Systolic blood pressure (mmHg)	95	2
Pulse Rate (bpm)	109	1
Conscious level	New confusion	3
Temperature (^oC)	39	1
	Total NEWS2 Score	**13**

Reference:

Royal College of Physicians. National Early Warning Score (NEWS) 2: Standardising the assessment of acute-illness severity in the NHS. Updated report of a working party. London: RCP, 2017.

16.4 Appendix 4: List of CYP3A4 inhibitors and inducers

Table 16-4 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. Please refer to Section 6.2.

Category	Drug Names
Strong inhibitors[a] of CYP3A	boceprevir, clarithromycin, cobicistat, conivaptan, danoprevir/ritonavir, eltegravir/ritonavir, grapefruit juice[1], 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[b] of CYP3A	amprenavir, aprepitant, atazanavir, atazanavir/ritonavir,, casopitant, cimetidine, ciprofloxacin, crizotinib, cyclosporin, duranavir, darunavir/ritonavir, diltiazem, dronedarone, erythromycin, faldaprevilr, fluconazole[2], fosamprenavir, grapefruit juice[1], imatinib, lomitapide, netupitant,nilotinib, schisandra sphenanthera[3], tofisopam, verapamil
Strong inducers[c] of CYP3A	avasimibe, carbamazepine, enzalutamide, mitotane,phenytoin, rifampin, St. John's wort[3], rifabutin, phenobarbital,
Moderate inducers[d] of CYP3A	bosentan, efavirenz, etravirine, genistein[3], lersivirine, lopinavir, modafinil, nafcillin, ritonavir, semagacestat[4], talviraline[4], thioridazine, tipranavir,

The list of CYP inhibitors and inducers was compiled from the FDA's "Guidance for Industry, Drug Interaction Studies;" from the Indiana University School of Medicine's "Clinically Relevant" Table and from the University of Washington's Drug Interaction Database. Note that this may not be an exhaustive list. For a complete and most updated drug list, please check the website https://.crediblemeds.org/healthcareproviders/drug-list.

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

[2] 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.

[3] Herbal product.

[4] Drugs not available in the US Market.

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. 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

[c] 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%.

[d.] 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%.