NCT04382586

CLINICAL RESEARCH PROTOCOL

Protocol Title:	A Phase 2, Randomized, Double Blind, Placebo-Controlled Study of Zanubrutinib Treatment in Patients Hospitalized for COVID-19 Infection and Pulmonary Distress
Protocol Identifier:	BGB-3111-219
Phase:	2
Investigational Product:	Zanubrutinib (BGB-3111)
Indication:	COVID-19 Pulmonary Complications
Sponsor:	BeiGene, Ltd. c/o BeiGene USA, Inc. 2955 Campus Drive, Suite 200 San Mateo, CA 94403 USA
Sponsor Medical Monitor	[redacted] Telephone: [redacted] Email: [redacted]
Original Protocol (Version 0.0):	13 April 2020
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Amendment 2.0:	22 July 2020
Amendment 3.0:	16 October 2020
Amendment 4.0:	08 January 2021

FI NAL PROTOCOL APPROVAL SHEET

A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of Zanubrutinib Treatment in Patients Hospitalized for COVID-19 Infection and Pulmonary Distress

BeiGene, Ltd. Approval:

1/8/2021
Date

SYNOPSIS

Name of Sponsor/Company: BeiGene, Ltd.

Investigational Product: Zanubrutinib (BGB-3111)

Title of Study: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of Zanubrutinib Treatment in Patients Hospitalized for COVID-19 Infection and Pulmonary Distress

Protocol Identifier: BGB-3111-219

Phase of Development: 2

Number of Patients: Approximately 73

Study Centers: Multicenter

Study Objectives:

Primary Objectives (Cohort 1)

- To evaluate if the addition of zanubrutinib to supportive care increases the respiratory failure-free survival rate at Day 28
- To evaluate if the addition of zanubrutinib to supportive care reduces the time to breathing room air

Secondary Objectives (Cohort 1)

- To compare the efficacy of zanubrutinib plus supportive care versus best supportive care as measured by secondary endpoints
- To compare the safety of zanubrutinib plus supportive care versus best supportive care

Exploratory

- [redacted]
- [redacted]
- [redacted]

Study Design:

This is a Phase 2, randomized, double-blind, placebo-controlled, multicenter study of zanubrutinib plus supportive care versus placebo plus supportive care in approximately 63 patients (Cohort 1) with confirmed COVID-19 by reverse transcription polymerase chain reaction (RT-PCR) from swabs, who require hospitalization and have been on supplemental oxygen for a duration of ≤ 96 hours for pulmonary distress related to COVID-19. Randomization will be stratified by age (< 65 years or ≥ 65 years) and use of antiviral therapy (yes or no). The first dose of study drug should be given ≤ 12 hours after randomization. Study drug (zanubrutinib 320 mg once daily or placebo 4 capsules once daily) will be administered for up to 28 days. Approximately 63 patients will be enrolled in Cohort 1.

[redacted]

[redacted]

The primary endpoints for this study are the respiratory failure-free survival rate at Day 28 and the time to breathing room air, both in the randomized cohort. Secondary endpoints include:

- Proportion of patients experiencing respiratory failure or death
- All-cause mortality
- Proportion of patients discharged alive
- Proportion of patients discharged from the ICU alive
- Median reduction in days spent on supplemental oxygen
- Mechanical ventilation-free survival
- Days on mechanical ventilation
- Duration of hospitalization
- Time to discharge
- Change in WHO 8-point scale from baseline
- P_{AO_2}:F_{IO_2} and/or oxygenation index, for patients on mechanical ventilation
- Safety and tolerability of zanubrutinib as an adjuvant therapy to standard of care as assessed by treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), related adverse events (AEs), TEAEs by grade, and abnormal laboratory findings
- Clinical status assessed using an ordinal scale at a pre-specified timepoint
- Time to objective measure of recovery

Study Assessments:

Efficacy will be assessed by the number of patients who are respiratory failure free at Day 28 and the time to breathing room air. The assessments will include level of oxygenation, amount of supplemental O_2, functional status, and mechanical ventilation status.

Secondary efficacy assessments will explore days on mechanical ventilation if required and the number of days of oxygen, all-cause mortality, duration of hospitalization, and change in WHO 8-point scale from baseline.

Assessments of safety will include TEAEs, SAEs, and changes from baseline in selected laboratory analytes, physical findings, electrocardiograms, and vital signs.

[redacted]

Efficacy will be assessed through 28 days after first dose of study drug. Safety will be followed through 56 days after last dose of study drug.

Main Eligibility Criteria:

To participate in this study, patients must be ≥ 18 years of age, have a confirmed diagnosis of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, and have been on supplemental O_2 for ≤ 96 hours. A smaller cohort of patients requiring mechanical ventilation at study entry will be accrued.

Test Product, Dose, and Mode of Administration:

Cohort 1: Zanubrutinib (320 mg once daily) or placebo administered orally for 28 days.

[redacted]

Statistical Methods:

Analysis Sets:

The Safety Analysis Set includes all patients who received any dose of study drug. The Safety Analysis Set will be the primary analysis set for all safety analyses. The intent-to-treat analysis (ITT) set will be the primary analysis set for all efficacy analyses. The Safety Analysis Set will also be used for selected efficacy analyses.

Analysis of Primary Endpoints:

The coprimary endpoints for this study are the respiratory failure-free survival rate at Day 28 and the time to breathing room air, both in Cohort 1. The respiratory failure-free survival rate will be compared between the two treatment arms by Fisher's exact test. The time to breathing room air will be compared between the two arms using a Cox model with the stratification factors in the randomization and the WHO 8-point scale at baseline as covariates. Two analyses (interim and final) will be performed for the coprimary endpoints in Cohort 1, with the interim analysis performed when the first 42 patients complete 28 days of treatment. The type 1 error increase owing to these the interim and final analyses will be controlled by the O'Brien Fleming alpha spending function for each test. The boundary for efficacy stop will be based on the p-value controlled from the Fisher's exact test for respiratory failure-free survival at Day 28 and the p-value from the Cox model for time to breathing room air.

Analysis of Secondary Endpoints:

The secondary endpoints include

Efficacy:

- Median reduction in days spent on supplemental oxygen, with time on supplemental oxygen imputed to the maximum number of days on supplemental oxygen observed in the study + 1 for all points following the death of a patient
- All-cause mortality at Study Days 7, 14, 21, and 28
- Proportion of patients discharged alive at Days 7, 14, 21, and 28
- Proportion of patients discharged from the ICU alive at Days 7, 14, 21 and 28
- Change from baseline in the WHO 8-point ordinal scale
- Proportion of patients experiencing respiratory failure or death on Study Days 7, 14, 21, and 28
- Mechanical ventilation-free survival
- Days on mechanical ventilation

- Duration of hospitalization
- Time to discharge
- PaO2:FiO2 and/or oxygenation index
- Clinical status assessed using an ordinal scale at a pre-specified timepoint
- Time to objective measure of recovery (eg, return to baseline oxygen requirement, as appropriate
- Proportion of patients discharged alive [redacted].

Safety and Tolerability:

- TEAEs and SAEs, frequency, seriousness and relatedness of TEAEs will be analyzed according to the Medical Dictionary for Regulatory Activities (MedDRA). Laboratory abnormalities will be analyzed according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) v5.0.

Safety Analysis:

Adverse event verbatim descriptions (as recorded by the investigator) will be coded to standardized medical terminology using MedDRA and graded according to the NCI-CTCAE v5.0. All TEAEs will be summarized. SAEs, deaths, TEAEs ≥ Grade 3, and TEAEs that led to treatment discontinuation, dose reduction, or treatment interruption, will be summarized.

Clinical laboratory data with values outside of the normal range will be identified. Select laboratory data will be summarized by visit and grade.

Exploratory Pharmacokinetic Analysis*:*

- [redacted]

Sample Size:

The study will enroll approximately 67 to 73 patients with 63 patients in Cohort 1 randomized to either zanubrutinib and supportive care (Arm A) or placebo plus supportive care (Arm B). Assuming 10% dropout, unrelated to efficacy, 42 patients total in Cohort 1 will provide approximately 81% of power to detect the increase in the respiratory failure-free rate of 25% (70% vs 95%) under a z-test at 1-sided level of 0.1. Sixty-three patients will provide 81% power to detect and increase in the respiratory failure-free survival rate from 70% to 91%. Fifty-nine of 63 patients breathing room air will provide 80% power to detect a hazard ratio of 0.57 (an event is breathing room air). [redacted]

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
ACE2	angiotensin-converting enzyme 2
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATII	alveolar type II
BTK	Bruton tyrosine kinase
C_{max}	maximum concentration
COVID-19	coronavirus disease 2019
CRF	case report form
CYP	cytochrome P450
ECG	electrocardiogram
eCRF	electronic case report form
GCP	Good Clinical Practice
HBcAb	hepatitis B core antibody
HBsAb	hepatitis B surface antibody
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCK	hematopoietic cell kinase
HCV	hepatitis C virus
IC_{50}	50% maximum inhibitory concentration
ICF	informed consent form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MedDRA	Medical Dictionary for Regulatory Activities
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
PCR	polymerase chain reaction
[redacted]	[redacted]
SAE	serious adverse event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMC	Safety Monitoring Committee
TEAE	treatment-emergent adverse event
TLR	Toll-like receptors
ULN	upper limit of normal
WHO	World Health Organization

1. INTRODUCTION

1.1. Study Disease(s)

Patients with confirmed coronavirus disease 2019 (COVID-19) by reverse transcription polymerase chain reaction (RT-PCR) from swabs, and who require hospitalization, have been on supplemental oxygen for a duration of ≤ 96 hours, and have pulmonary distress related to COVID-19, are eligible for this study. An additional pilot cohort of 4 to 10 patients, who have been on mechanical ventilation for ≤ 24 hours, will be treated on the protocol.

1.2. Investigational New Drug

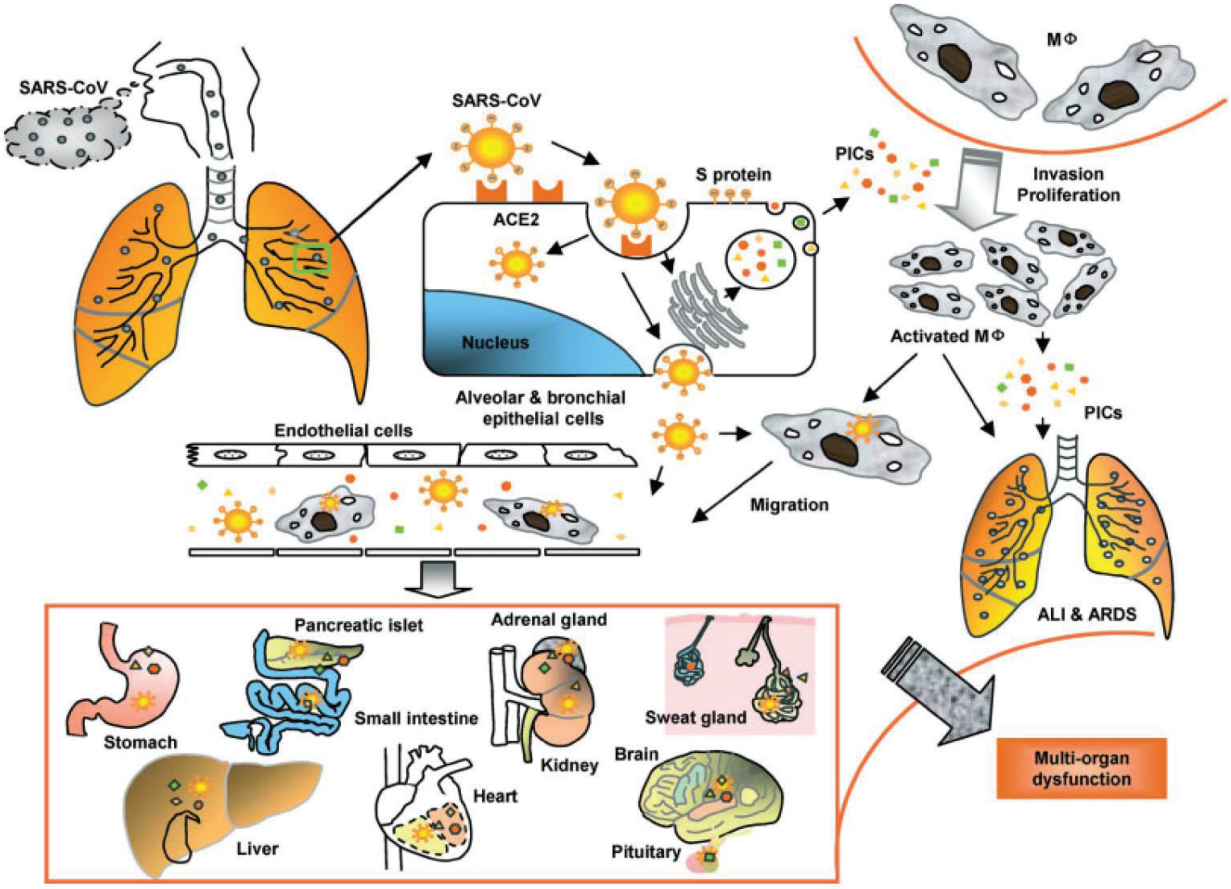
Zanubrutinib (also known as BGB-3111) is an irreversible inhibitor of Bruton tyrosine kinase (BTK) that is approved by the United States Food and Drug Administration (FDA) for the treatment of adult patients with mantle cell lymphoma (MCL) who have received at least one prior therapy. Accelerated approval was granted for this indication based on overall response rate. Continued approval for this indication may be contingent upon verification and description of clinical benefit in a confirmatory trial.

1.3. Rationale

COVID-19 is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Guan et al 2020). Pulmonary failure is the main cause of mortality related to COVID-19 (Bhatraju et al 2020; Wang et al 2020). Up to 80% of patients who require hospitalization for COVID-19 require supplemental oxygenation for an average of 13 days (Cao et al 2020). Furthermore 30% to 40% of those hospitalized for pulmonary distress may require mechanical ventilation (Wang et al 2020; Wu et al 2020). Therapies that block COVID-19-related lung injury and improve pulmonary function are, therefore, urgently needed.

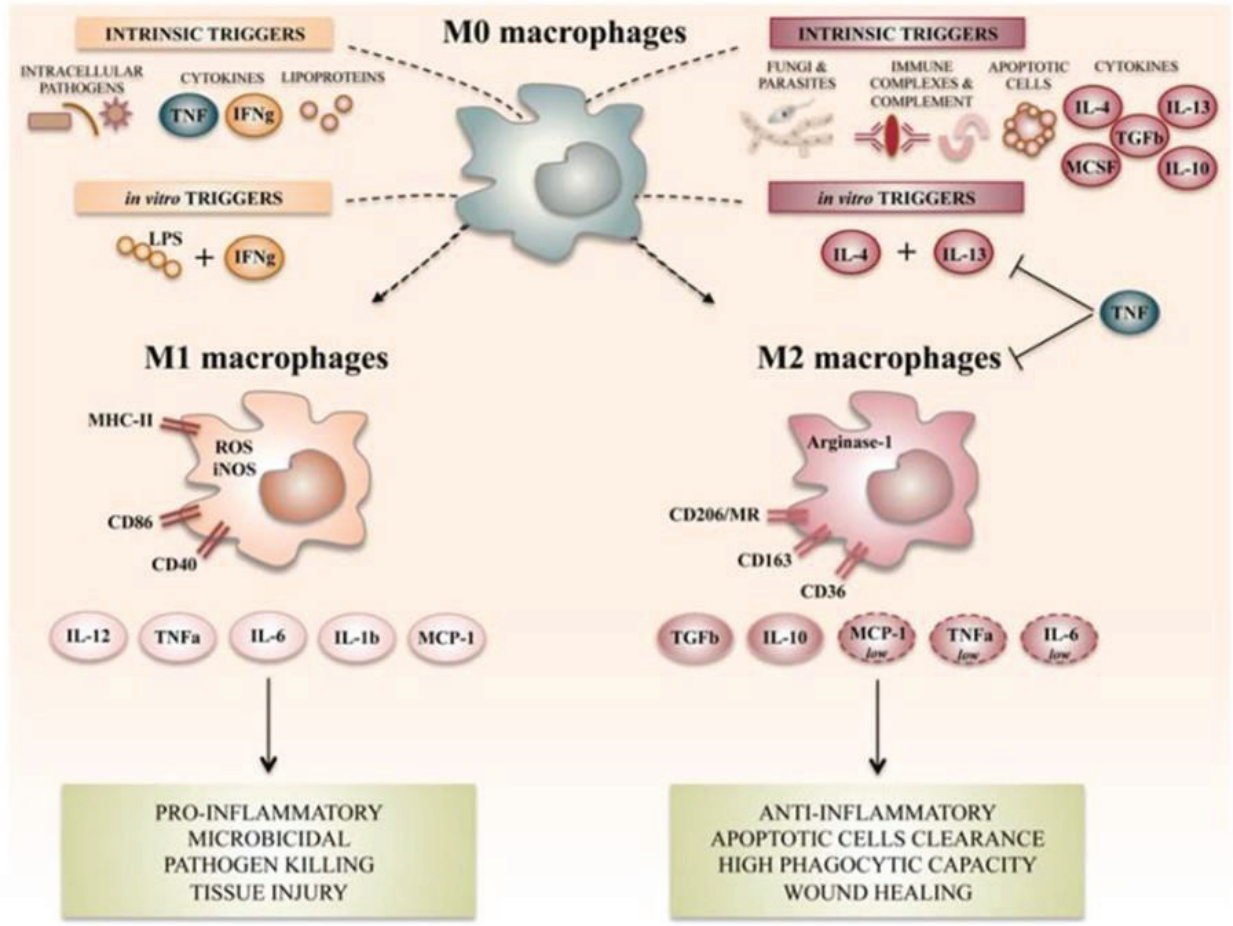
SARS-CoV-2 binds via the angiotensin-converting enzyme 2 (ACE2) receptor that is highly expressed on alveolar type II (ATII) cells in the lung (Du et al 2009; Hoffman et al 2020). ATII cells constitute 5% to 15% of the lung epithelium. While alveolar type I cells are highly adapted for gas exchange, ATII cells have a specialized role in innate immune response (Fujino et al 2011). ATII cells express Toll-like receptors (TLRs) and can trigger inflammatory cytokines and chemoattractants in response to viral and bacterial pathogens that recruit and activate other immune cells, including macrophages and neutrophils (Pechkovsky et al 2005; Wang et al 2009; Thorley et al 2010; Chuquimia et al 2013; Werner and Steele 2014). Highly relevant to coronavirus infection, expression of pro-inflammatory and chemoattractant cytokines IL1-B, IL-6, IP-10/CXCL-10, MCP-1, and TNF-α were identified in the ACE2-positive cells from autopsy tissue of SARS-CoV-1 infected patients, that appeared causally related to the acute lung injury and pathogenesis observed with SARS-CoV-1 (Figure 1, He et al 2006). A similar profile of elevated cytokine levels of IL-6, IL-8, IP-10/CXCL-10 and MCP-1 was also reported in the plasma of SARS-CoV-1 patients during the progressive and end stage of infection (Jiang et al 2005), a profile more consistent with M1-polarized macrophage response (Figure 2, Ley 2017; Atri et al 2018).

Figure 1: A Model for the Immunopathogenesis of SARS Based on SARS-CoV-1 Model



Source: Figure and notes taken from He et al 2006.
Abbreviations: ACE2, angiotensin-converting enzyme 2; ALI, acute lung injury; ARDS, acute respiratory distress syndrome; MΦ, macrophages; PICs, pro-inflammatory cytokines; SARS-CoV, severe acute respiratory syndrome coronavirus.
Notes: SARS-CoV in droplets enters into the lung, where the virus binds via its S protein to ACE2 on the alveolar or bronchial epithelial cells. The virus replicates in these cells, from which new virions are released into the blood. The infected cells under the stimulation of SARS-CoV and some uninfected cells induced by viral antigens or PIC-regulatory factors produce high levels of PICs to mediate inflammatory responses for combating the virus. However, these PICs also damage the host cells. Some of the PICs, eg monocyte chemoattractant protein-1 (MCP-1), attract monocytes in blood to migrate to the alveolar cavities, where the monocytes are stimulated by other PICs to become proliferative and/or activated macrophages (MΦ). The activated macrophages can produce more PICs and may transmit SARS-CoV to other sites. Some of the PICs, including TGF-β1 and TNF-α, may induce apoptotic death of the epithelial cells, pneumocytes, and lymphocytes, or mediate pulmonary fibronosis, resulting in ALI and ARDS. The cell-free and MΦ-associated SARS-CoV in the blood can be transmitted from the lung to other organs to infect the ACE2-expressing cells in the local sites. More PICs are produced and the level of PICs in the blood is rapidly elevated, leading to multi-organ dysfunction.

Figure 2: Summary of the Main Macrophage Polarization States of Activated Macrophages



Source: Figure and notes taken from Atri et al 2018.
Abbreviations: IFNγ, interferon gamma; iNOS, inducible nitric oxide synthase; IL, interleukin; LPS, lipopolysaccharide; MCP, monocyte chemoattractant protein; MCSF, macrophage colony stimulating-factor; MHC, major histocompatibility complex; MR, mannose receptor; ROS, reactive oxygen species; TGF, transforming growth factor; TNF, tumor necrosis factor.
Notes: Summary of the main macrophage polarization states of activated macrophages. Different stimuli and signaling pathways have been described as inducers of M1-like or M2-like activation states, of which the most widely referenced ones are summarized here. M1-like or M2-like polarization has been reported in humans as being related to distinct defensive or healing schemas. Many roles have been ascribed to the polarization status, of which pro- and anti-inflammatory macrophage potentiation has for a long time been classically associated to the M1-like/M2-like-like dichotomy.

SARS-CoV-1 shares 86% homology and has a similar pathogenetic mechanism to SARS-CoV-2 (Chan et al 2020; Heurich et al 2014). Similar to SARS-CoV-1 patients, SARS-CoV-2 patients that required intensive care showed elevated plasma levels of inflammatory cytokines and chemoattractants such as IL-2, IL-6, IL-7, IL-10, G-CSF, IP-10/CXCL-10, MCP-1/CCL2, MIP-1a/CCL3, and TNF-α (Huang et al 2020). The importance of inflammatory cytokines to lung injury in SARS-CoV-2 infected patients has been suggested by reports of benefit with IL-6 and IL-6-receptor-blocking antibodies, and clinical trials to examine their use have been initiated (ClinicalTrials.gov IDs: NCT04317092, NCT04306705, NCT04315298).

Studies have shown an important role for the TEC family member BTK, and its upstream activator, hematopoietic cell kinase (HCK), an SRC family member that triggers TLR-mediated signaling (Jeffries et al 2003; Yang et al 2013; Yang et al 2016). Both BTK and HCK can be triggered by MYD88, a TLR-adaptor protein that signals for all TLRs except TLR3 in response to viral and bacterial pathogens, including coronaviruses (Wang and Liu 2016). ATII cells express TLRs, as do alveolar macrophages that coordinate inflammatory responses with ATII cells (Pechkovsky et al 2005; Wang et al 2009; Thorley et al 2010; Chuquimia et al 2013; Werner and Steele 2014). As components of TLR/MYD88 signaling, BTK and HCK can drive inflammatory cytokine production through ERK1/2 (Chen et al 2018).

In a transgenic mouse model, overexpression of activated HCK promoted extensive pulmonary inflammation and enhanced innate immune response characterized by extensive eosinophilic and mononuclear cell infiltration within the lung parenchyma, alveolar air spaces, and around blood vessels, as well as marked epithelial mucus metaplasia in conducting airways (Ernst et al 2002). Lungs from these mice show areas of emphysema and pulmonary fibrosis, which together with inflammation resulted in altered lung function and respiratory distress, particularly in aging mice (Ernst et al 2002). Elevated levels of TNF-α were also identified in the bronchoalveolar lavage fluids of these mice following LPS challenge. The pulmonary pathology findings from these mice show great overlap with those described in the lungs of patients with COVID-19 infection which showed serous and fibrin exudation with alveolar infiltration consisting majorly of macrophages and monocytes. The blood vessels of alveolar septum were also congested, edematous and widened, with modest infiltration of monocytes and lymphocytes (Tian et al 2020; Yao et al 2020).

Ibrutinib is a highly potent, covalent inhibitor of BTK (biochemical 50% maximum inhibitory concentration [IC_{50}] 0.5 nM). Ibrutinib is also a potent reversible inhibitor of HCK (IC_{50} 49 nM) (Yang et al 2016, Harvard Medical School LINCS Project 2020). The IC_{50} levels for BTK and HCK are well within the pharmacologically attainable dosimetry of orally administered ibrutinib, although HCK inhibition has not yet been demonstrated in patients under ibrutinib therapy, possibly due to the rapid clearance (Byrd et al 2013). Serially collected blood samples from patients with chronic lymphocytic leukemia, Waldenström macroglobulinemia, and chronic graft versus host disease on ibrutinib monotherapy showed marked reductions in proinflammatory and chemoattractant cytokines that greatly overlapped with those reported elevated in the plasma of SARS-CoV-1 and SARS-CoV-2 patients, and in ACE2-positive cells from lung tissue of SARS-CoV-1 patients (Table 1, He et al 2006; Jiang et al 2005; Huang et al 2020; Niemann et al 2016; Vos et al 2017; Miklos et al 2017). In the iLLUMINATE randomized study, chronic lymphocytic leukemia patients treated with ibrutinib immediately prior to infusion with obinutuzumab also showed significantly decreased levels of inflammatory cytokines associated with infusion-related reactions (a cytokine release syndrome) (Greil et al 2019).

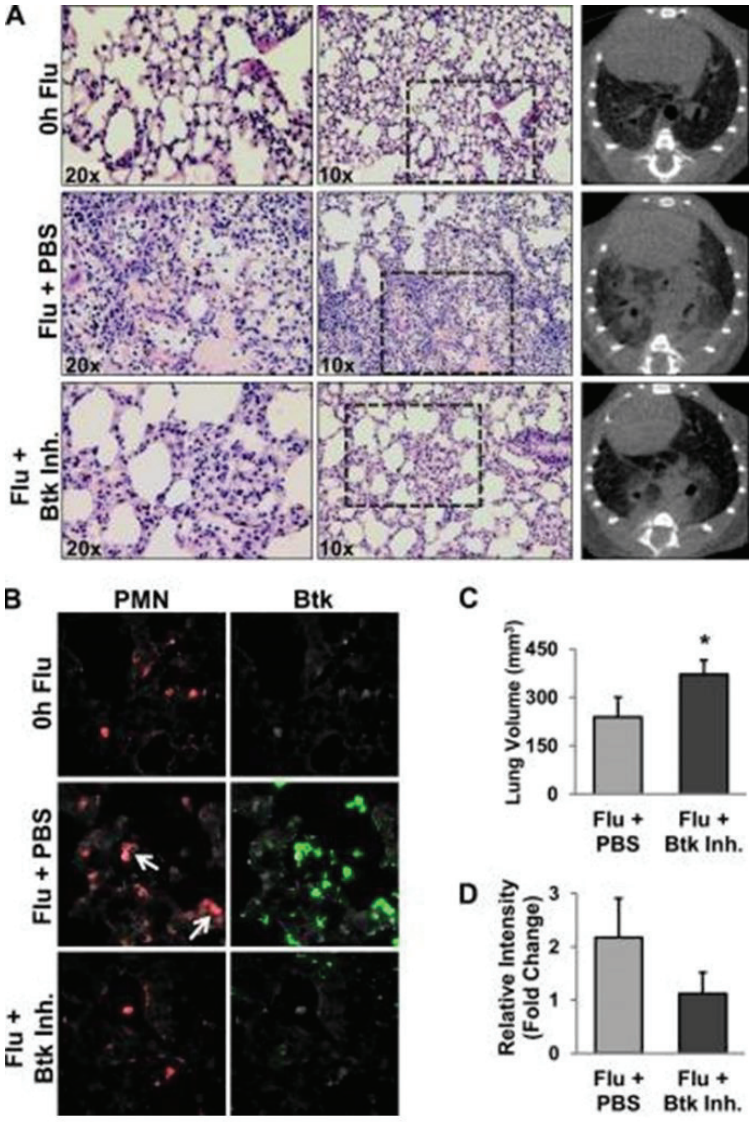
Table 1: Summary of Pro-Inflammatory and Chemoattractant Cytokine Patterns in Patients Infected With SARS-CoV-1 and SARS-CoV-2 (*highlighted in red*), and Following Ibrutinib Treatment in Patients With CLL, WM, and cGVHD (*highlighted in green*)

	He et al 2006	Jiang et al 2005	Huang et al 2020	Niemann et al 2016	Greil et al 2019	Vos et al 2017	Miklos et al 2017
Patients	CoV-1	CoV-1	CoV-2	CLL on ibrutinib	CLL on ibrutinib	WM on ibrutinib	cGVHD on ibrutinib
Tissue	ACE2+ cells	Plasma	Plasma	Plasma	Plasma	Plasma	Plasma
GMCSF			↑				↓
IL1B	↑						
IL2			↑				↓ (IL2RA)
IL6	↑	↑		↓	↓	↓	
IL7			↑				
IL8		↑		↓	↓	↓	↓
IL10			↑	↓	↓	Variable	
IP10/CXCL10		↑	↑	↓		↓	↓
MCP-1/CCL2	↑	↑	↑	↓	↓		↓
MIP-1A/CCL3			↑	↓			↓
MIP1B/CCL4			↑	↓		↓	↓
TNFA	↑			↓	↓	↓	↓

Abbreviations: ACE2, angiotensin-converting enzyme 2; CCL, C-C motif chemokine ligand; cGVHD, chronic graft versus host disease; CLL, chronic lymphocytic leukemia; CXCL10, C-X-C motif chemokine 10; GMCSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; IP-10, interferon gamma-induced protein 10; MCP-1, monocyte chemoattractant protein-1; MIP, macrophage inflammatory protein; TNFA, tumor necrosis factor alpha; WM, Waldenström macroglobulinemia.

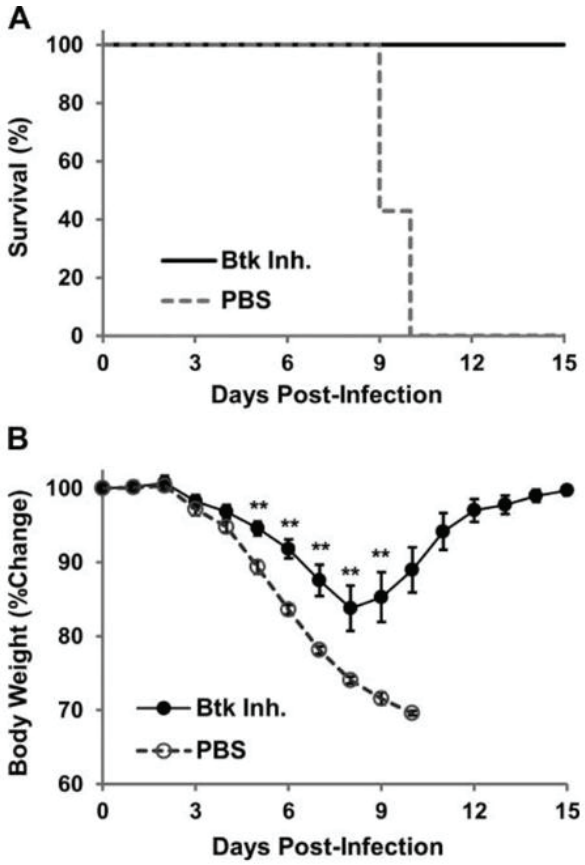
The potential for ibrutinib to abrogate lung injury and death was demonstrated in an experimental model wherein mice challenged with a lethal intranasal inoculum of a mouse adapted strain of H1N1 influenza virus were protected against lung injury. Control mice that received phosphate buffered saline (PBS) developed respiratory failure, along with histological and CT findings consistent with lung injury in sharp contrast to the mice that received ibrutinib (Figure 3, Florence et al 2018). Mice treated with PBS also lost weight and died, whereas those treated with ibrutinib recovered their weight after a brief loss and all survived (Figure 4, Florence et al 2018). Notably, mice treated with ibrutinib also showed decreased inflammatory cell infiltration as well as proinflammatory cytokines in lung tissues that included pro-inflammatory and chemoattractant cytokines such as IL-1β, IL-6, KC/CXCL1, TNFα, and MCP-1 observed in SARS-CoV-1 and SARS-CoV-2 patients (Figure 5, Florence et al 2018).

Figure 3: Pulmonary Findings for Mice Treated With PBS or Ibrutinib Following Lethal Intranasal Challenge With Mouse Adapted H1N1 Influenza



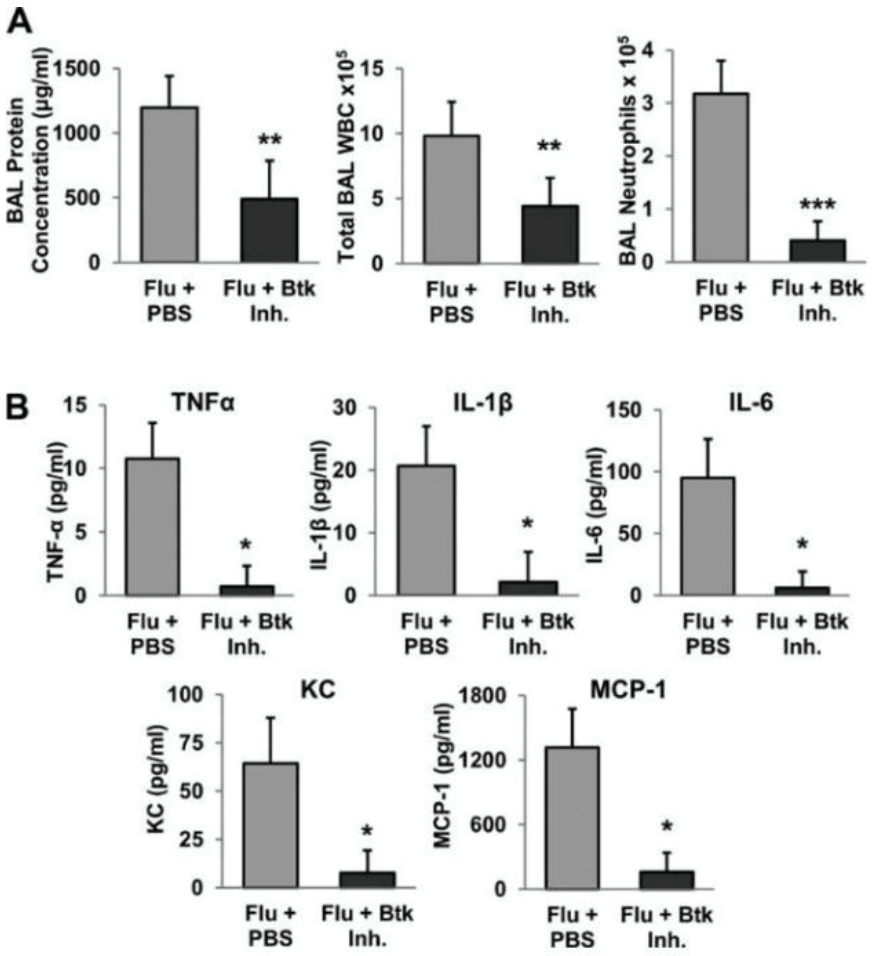
Source: Figures and notes taken from Florence et al 2018.
Abbreviations: Btk Inh, Bruton tyrosine kinase inhibitor; Flu, influenza A virus; PBS, phosphate buffered saline; PMN, polymorphonuclear leukocyte.
A: representative hematoxylin-eosin-stained lung sections (left and middle) and CT images (right) from mice 7 days after influenza A virus (Flu) infection [*n* = 10 and 5 mice for PBS- and Btk inhibitor (Inh)-treated groups, respectively].
B: representative images of Bruton tyrosine kinase (Btk) in lungs of influenza A virus-infected mice. Tissue sections were analyzed by immunofluorescent staining for Btk and a PMN marker (Ly6G 1A8). White arrows indicate Ly6G/Btk double-positive cells; note differences in Btk staining between PBS- and Btk inhibitor-treated groups.
Figure
C: lung volume derived from CT data (*n* = 10 and 5 mice for PBS- and Btk inhibitor-treated groups, respectively). Values are means ± SD; n = 3 mice in each group. **P* < 0.05 (by Mann-Whitney rank sum test).
D: average intensity of Btk staining expressed as fold change over control. Values are means ± SD; n = 3 mice in each group.

Figure 4: Survival and Body Weight Loss for Mice Treated With PBS or Ibrutinib Following Lethal Intranasal Challenge With Mouse Adapted H1N1 Influenza



Source; Figures and legend taken from Florence et al 2018.
Abbreviations: Btk Inh, Bruton tyrosine kinase inhibitor; PBS, phosphate buffered saline.
Notes: Survival (A) and weight loss (B) of C57BL/6 mice infected intranasally with influenza A virus (A/PR/8/34). Starting 3 days after infection, mice were treated daily with PBS (n = 7) or Bruton tyrosine kinase (Btk) inhibitor (Inh, n = 10) administered intranasally. Animals were monitored until death (4 mice) or weight loss of >30%, at which point they were euthanized and counted as dead (3 mice). Values for weight loss are means ± SE. Statistical significance of weight loss for *days 4–9* of PBS-treated mice (n = 7) and Btk inhibitor-treated mice (n = 10) was determined by 2-way repeated-measures ANOVA with post hoc Bonferroni's t-test: $^{**}P < 0.01$.

Figure 5: Inflammatory Cells Observed in BAL Fluids, and Cytokine Levels From Lung Homogenates in Mice Treated With PBS or Ibrutinib Following Lethal Intranasal Challenge With Mouse-Adapted H1N1 Influenza



Source: Figures and legend taken from Florence et al 2018.
Abbreviations: BAL, bronchoalveolar lavage; Btk Inh, Bruton tyrosine kinase inhibitor; Flu, influenza A virus; IL, interleukin; KC, keratinocyte chemoattractant; PBS, phosphate buffered saline; TNFα, tumor necrosis factor alpha; MCP-1, monocyte chemoattractant protein-1; WBC, white blood cell.
A: bronchoalveolar lavage (BAL) protein concentration, total white blood cell (WBC) count, and number of neutrophils in BAL fluids at 7 days after influenza A virus (Flu) infection. Values are means ± SD; $n = 10$ and 4 mice for PBS- and Bruton tyrosine kinase (Btk) inhibitor (Inh)-treated groups, respectively, for BAL protein concentration and 10 and 5 mice for PBS- and Btk inhibitor-treated groups, respectively, for cell counts. $^{**}P < 0.01$ (by Mann-Whitney rank sum test); $^{***}P < 0.001$ (by Student's *t*-test).
B: inflammatory cytokine/chemokine concentrations in lung homogenates from mice at 7 days after influenza A virus infection. Values are means ± SD; $n = 10$ and 5 mice for PBS- and Btk inhibitor-treated groups, respectively. $^{*}P < 0.001$ (by Student's *t*-test).

The above findings support the rationale that an exaggerated cytokine response triggered by ATII cells and resident macrophages in response to SARS-CoV-2 is etiological for the pulmonary injury and respiratory failure associated with COVID-19. The importance of inflammatory cytokines to lung injury in SARS-CoV-2 infected patients has been suggested by reports of benefit with IL-6 and IL-6-receptor-blocking antibodies, and clinical trials to examine their use have been initiated (ClinicalTrials.gov IDs: NCT04317092, NCT04306705,

NCT04315298). The ability to block inflammatory cytokine production to limit pulmonary injury has been observed in patients with severe COVID-19 who received treatment with the IL-6 blocking antibody tocilizumab.

Ibrutinib blocks TLR signaling, and cytokines associated with SARS-CoV-2, including those found in ATII cells. Importantly, in a relevant experimental mouse model, ibrutinib protected mice subjected to lethal intranasal inoculums of mouse adapted H1N1 influenza and suppressed inflammatory cell recruitment and pathological cytokines that overlapped with many of those observed in SARS-CoV-2 infected patients. Ibrutinib and the BTK inhibitor class may therefore protect against lung injury in patients with COVID-19 related pulmonary distress.

1.4. Zanubrutinib

Zanubrutinib is a potent, specific, and irreversible BTK inhibitor that was designed to be more specific than ibrutinib; similar to ibrutinib, zanubrutinib potently inhibited BTK kinase in biochemical assays, with an IC_{50} of 0.3 nM, and in vitro cellular assays also show that zanubrutinib inhibited BTK signaling and cellular growth in several mantle cell lymphoma cell lines.

Zanubrutinib is more selective than ibrutinib for the inhibition of kinase activity of BTK versus EGFR, FGR, FRK, HER2, HER4, ITK, JAK3, LCK, and TEC. Cellular assays also confirmed that zanubrutinib is significantly less active than ibrutinib in inhibiting ITK (10-fold) and EGFR (> 6-fold). Zanubrutinib was shown to be at least 10-fold weaker than ibrutinib in inhibiting rituximab-induced antibody-dependent cell-mediated cytotoxicity. In a randomized clinical trial comparing zanubrutinib versus ibrutinib in patients with Waldenström macroglobulinemia, fewer adverse events (AEs) were noted in the zanubrutinib arm. Adverse events > Grade 3 occurred in 58.4% of patients in the zanubrutinib arm and 63.3% of patients in the ibrutinib arm of the study. Four percent of zanubrutinib-treated patients discontinued therapy because of AEs, and 1% had a Grade 5 event; 9.2% of ibrutinib-treated patients discontinued because of an AE, and 4.1% had Grade 5 events. For zanubrutinib and ibrutinib, respectively, the rates of all-grade atrial fibrillation/flutter were 2% and 15.3%, of minor bleeding were 48.5% and 59.2%, of major hemorrhage were 5.9% and 9.2%, and of diarrhea were 20.8% and 31.6%. Neutropenia was more common with zanubrutinib (29.7%) than with ibrutinib (13.3%) (Tam et al 2020).

2. STUDY OBJECTIVES

2.1. Primary Objectives (Cohort 1)

- To compare the efficacy of zanubrutinib plus supportive care versus placebo plus supportive care as measured by respiratory failure-free survival rate at Day 28
- To evaluate if the addition of zanubrutinib to supportive care reduces time to breathing room air

2.2. Secondary Objectives (Cohort 1)

- To compare the efficacy of zanubrutinib plus supportive care versus placebo plus best supportive care as measured by:
  - Proportion of patients experiencing respiratory failure or death;
  - All-cause mortality;
  - Proportion of patients discharged alive;
  - Proportion of patients discharged from the ICU alive;
  - Median reduction in days spent on supplemental oxygen;
  - Mechanical ventilation-free survival;
  - Days on mechanical ventilation;
  - Duration of hospitalization;
  - Time to discharge;
  - Change in World Health Organization (WHO) 8-point scale from baseline;
  - P_{AO_2}:F_{IO_2} and/or oxygenation index, for patients on mechanical ventilation;
  - Safety and tolerability of zanubrutinib as an adjuvant therapy to standard of care as assessed by treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), related AEs, TEAEs by grade, and abnormal laboratory findings;
  - Clinical status assessed using an ordinal scale at a pre-specified timepoint;
  - Time to objective measure of recovery.
- To compare the safety of zanubrutinib plus supportive care versus placebo plus best supportive care

2.3. Exploratory Objectives

- [redacted]
- [redacted]

3. STUDY DESIGN

3.1. Summary of Study Design

There is currently no standard of care for hospitalized patients experiencing COVID-19 beyond supportive care. Numerous studies examining various study interventions are underway. Discovering/providing treatment options for patients with moderate or severe COVID-19 is a high priority, particularly for those with respiratory distress. Exaggerated cytokine response triggered by ATII cells and resident macrophages in response to SARS-CoV-2 appears etiological for the pulmonary injury and respiratory failure associated with COVID-19. The BTK inhibitor, ibrutinib, blocks TLR signaling and cytokines associated with SARS-CoV-2, including those found in ATII cells. Importantly, in a relevant experimental mouse model, ibrutinib protected mice subjected to lethal intranasal inoculums of mouse adapted H1N1 influenza and suppressed inflammatory cell recruitment and pathological cytokines that overlapped with many of those observed in SARS-CoV-2 infected patients. Based on this, it is hypothesized that inhibitors of BTK may potentially provide protection against lung injury.

Zanubrutinib is an oral BTK inhibitor approved by the FDA for the treatment of adult patients with mantle cell lymphoma who have received at least one prior therapy. Accelerated approval was granted for this indication based on overall response rate.

This study will enroll patients who meet inclusion/exclusion criteria and sign an associated consent form. Patients will be enrolled [redacted] based on mechanical ventilation requirements at screening:

- Cohort 1 - no mechanical ventilation (N = 63)
- [redacted]

Patients not requiring mechanical ventilation (Cohort 1) will be randomized 1:1 to receive zanubrutinib plus supportive care or placebo plus supportive care. Patients will be stratified by age (< 65 years or ≥ 65 years) and use of antiviral therapy (yes or no) on the date of randomization. The first dose of study drug should be given ≤ 12 hours after randomization. Study drug (zanubrutinib 320 mg once daily or placebo 4 capsules once daily) will be administered for up to 28 days. Approximately 63 patients will be enrolled in Cohort 1.

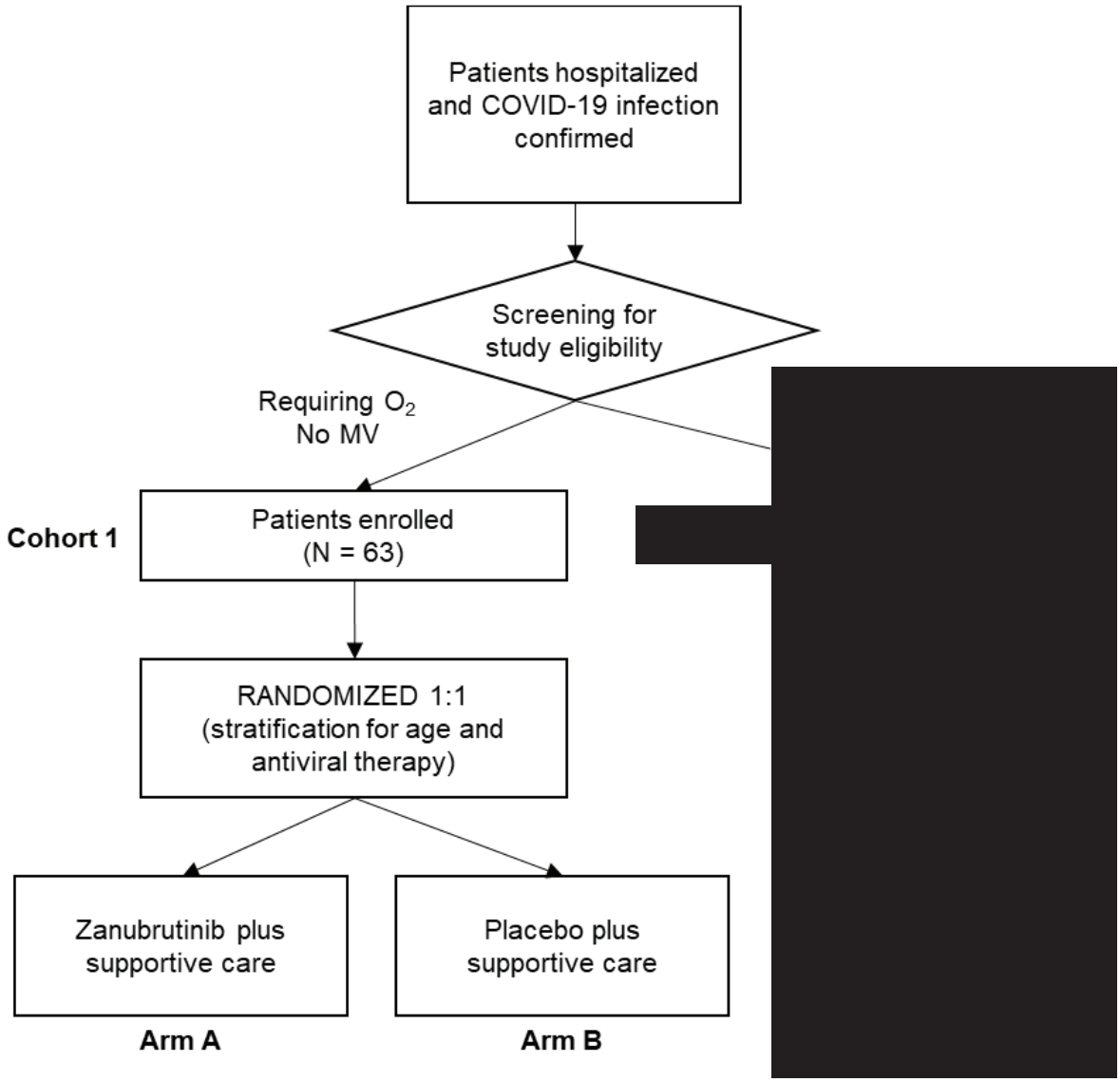
[redacted]

The coprimary endpoints for this study are the respiratory failure-free survival rate at Day 28 and the time to breathing room air. The respiratory failure-free survival rate at Day 28 can also be described as the proportion of patients who have not had respiratory failure nor died any time ≤ 28 days from randomization.

Participating clinical trial sites must have the capability of implementing appropriate infection control measures to prevent infection of study staff and others who share the clinical site space.

3.2. Study Schema

Figure 6: Study Schema



Abbreviation: MV, mechanical ventilation.

4. ELIGIBILITY CRITERIA

4.1. Inclusion Criteria

Each patient eligible to participate in this study must meet all of the following criteria:

1. Age ≥ 18 years
2. Willing and able to provide consent prior to study therapy, including by virtual consenting per hospital policy
3. Patient requires hospitalization for COVID-19
4. Patient has SARS-CoV-2 infection confirmed by polymerase chain reaction (PCR) Documented SARS-CoV-2 infection confirmed by PCR within 10 days prior to screening is acceptable
5. For Cohort 1, patient requires supplemental oxygen, but not mechanical ventilation, for pulmonary distress related to COVID-19, and has been on supplemental oxygen for no more than 96 hours from time of screening. [redacted]
6. C-reactive protein ≥ 8.0 mg/L at time of screening
7. Adequate hematologic function defined as:
   a. Absolute neutrophil count > 750 cells/mm^3 (0.75 x 10^9/L)
   b. Platelet count > 50,000 cells/mm^3 (50 x 10^9/L)
8. Adequate hepatic and renal function defined as:
   a. Estimated Creatinine Clearance ≥ 30 mL/min (Cockcroft-Gault)
   b. Bilirubin ≤ 2.0 x upper limit of normal (ULN) unless bilirubin rise is due to Gilbert's syndrome or of non-hepatic origin.
   c. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3 x ULN
9. Female patients of childbearing potential must practice highly effective methods (Section 5.2.2) of contraception initiated before first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of study drug
10. Male patients are eligible if vasectomized; otherwise they must agree to the use of barrier contraception combined with other highly effective methods described in Section 5.2.2 during the study treatment period and for ≥ 90 days after the last dose of study drug
11. Prothrombin time/International normalized ratio < 1.5 x ULN and activated partial thromboplastin time < 1.5 x ULN

4.2. Exclusion Criteria

Each patient eligible to participate in this study must not meet any of the following exclusion criteria prior to initiation of study drug:

1. Malabsorption syndrome, disease significantly affecting gastrointestinal function, or resection of the stomach or small bowel, symptomatic inflammatory bowel disease or ulcerative colitis, or partial or complete bowel obstruction
2. Patient has a "Do Not Intubate" order at time of screening
3. On a BTK inhibitor
4. Planned or concurrent use of host modifiers/immune-based therapies. Treatment with intravenous immunoglobulin or convalescent plasma is allowed. See Appendix 7 for guidance.
5. Prior therapy or planned on-study treatment with an anti-CD20 monoclonal antibody treatment (eg, rituximab, obinutuzumab, ofatumumab), and/or an immune checkpoint inhibitor (eg, pembrolizumab, nivolumab)
6. Current use of therapeutic anticoagulation or combined use of an anti-platelet agent with an anticoagulant. Anticoagulation to prevent thrombosis is allowed
7. Known bleeding disorders (eg, von Willebrand's disease or hemophilia)
8. Major surgery ≤ 4 weeks before first dose of study drug
9. Patients in whom surgery is anticipated to be necessary within 72 hours.
10. History of stroke or intracranial hemorrhage ≤ 6 months before first dose of study drug
11. Known history of human immunodeficiency virus (HIV) or active with hepatitis C virus (HCV) or hepatitis B virus (HBV). Patients who are positive for hepatitis B core antibody (HBcAb), hepatitis B surface antigen (HBsAg), or HCV antibody must have a negative PCR result before enrollment. Those who are PCR positive will be excluded.
12. Currently active, clinically significant cardiovascular disease, such as uncontrolled arrhythmia or Class 3 or 4 congestive heart failure as defined by the New York Heart Association Functional Classification; or a history of myocardial infarction, unstable angina, or acute coronary syndrome within 6 months prior to randomization.
13. Asymptomatic arrythmias (eg, nonsustained ventricular tachycardia , bradycardia heart rate < 50 bpm, or atrioventricular block, or any other atrial or ventricular arrythmia) and/or known history ejection fraction < 40%.
14. Patients receiving a strong cytochrome P450 (CYP) 3A4 inhibitor with the exception of those receiving anti-fungal therapy/prophylaxis or antiviral therapy (Appendix 3).
15. Patients with chronic liver disease and hepatic impairment meeting Child-Pugh Class C.
16. Female patients who are pregnant, or breastfeeding, or planning to become pregnant while enrolled in this study or within 3 months of last dose of study drug. Male patients who plan to father a child while enrolled in this study or within 3 months after the last dose of study drug.

17. Underlying medical conditions that, in the investigator's opinion, will render the administration of study drug hazardous or obscure the interpretation of toxicity or AEs.
18. Unwilling or unable to participate in all required study evaluations and procedures
19. Unable to understand the purpose and risks of the study and to provide a signed and dated informed consent form (ICF) and authorization to use protected health information (in accordance with national and local patient privacy regulations), except to the extent that surrogate consents and assents are obtained in accordance with national and local laws and regulations. For clarity, the surrogate consents and assents may include, but are not limited to, the following: court-appointed guardians, healthcare proxies, durable powers of attorney, or family members/next-of-kin.
20. Vaccinated with a live, attenuated vaccine ≤ 4 weeks before first dose of study drug
21. Hypersensitivity to zanubrutinib or its formulation excipients
22. Uncontrolled hypertension (systolic blood pressure ≥ 150 mmHg and diastolic blood pressure ≥ 90 mmHg)
23. History of interstitial lung disease
24. Prior or current hematologic malignancy, or solid tumor malignancy with treatment consisting of chemotherapy, immunotherapy, and/or radiation therapy within 6 months prior to study entry or planned use of any of these treatments in the next 3 months

5. ENROLLMENT AND STUDY PROCEDURES

Study enrollment and procedures are summarized in the following subsections. The timing of all study procedures is provided in the Schedule of Assessments (Appendix 5).

5.1. Visit Windows

Study visits are daily for patients that are admitted. A ± 1-day window for outpatient visits on Days 7, 14, and 21 is permitted (Appendix 6). There is a ± 3-day window for the End of Treatment visit and ± 7-day window for each of the follow-up visits.

5.2. Screening

5.2.1. Informed Consent

Study site personnel must explain to potential study participants all aspects of the study, including all scheduled visits and activities. A copy of the ICF will be given to the patient to read, and the patient must have adequate time to understand the content and ask questions.

Study site personnel must obtain signed informed consent before any study specific assessments or procedures are conducted unless part of routine standard of care. The informed consent process must be documented in the patient's clinical record. Consent must be obtained using the most current version of the form approved by the Independent Review Board (IRB)/Independent Ethics Committee (IEC).

All screening procedures must be completed within 14 days before the first dose of study drug. Repeating screening procedures or tests are allowed once within the protocol-specified screening window if the patient did not previously meet the inclusion and exclusion criteria or if needed to have a documented acceptable result. Screening procedures performed within 2 days before date of first dose need not be repeated on Day 1.

For patients who provide informed consent and subsequently do not meet eligibility criteria or withdraw consent before initiation of study drug, study site personnel should document the screen failure in the patient's source documents. Patients may be rescreened once.

5.2.2. Females of Childbearing Potential and Contraception

A woman is considered of childbearing potential (ie, fertile) after menarche and until becoming postmenopausal unless surgically sterilized. Surgical sterilization methods include hysterectomy, bilateral salpingectomy, and bilateral oophorectomy.

Contraception methods include the following:

- Combined (estrogen- and progestogen-containing) hormonal contraception associated with the inhibition of ovulation
  - Oral, intravaginal, or transdermal
- Progestogen-only hormonal contraception associated with the inhibition of ovulation
  - Oral, injectable, or implantable
- An intrauterine device

- Intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Vasectomized partner (provided that the vasectomized partner is the sole sexual partner of the woman of childbearing potential study participant and that the vasectomized partner has received medical assessment of surgical success)
- Sexual abstinence (defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatment, starting the day before first dose of study drug, for the duration of the study, and for ≥ 90 days after the last dose of study drug).

  Total sexual abstinence should only be used as a contraceptive method if it is in line with the patients' usual and preferred lifestyle. Periodic abstinence (eg, calendar, ovulation, symptothermal, postovulation methods), declaration of abstinence for the duration of exposure to investigational medicinal product, and withdrawal are not acceptable methods of contraception.

Of note, barrier contraception (including male and female condoms with or without spermicide) is not considered a highly effective method of contraception, and, if used, this method must be used in combination with another acceptable method listed above.

If a woman of childbearing potential is using hormonal contraceptives such as birth control pills or devices, a second barrier method of contraception (eg, condoms) must also be used.

A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. A high follicle-stimulating hormone level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 12 months of amenorrhea, a single follicle-stimulating hormone measurement is insufficient.

5.2.3. Patient Numbering

After obtaining informed consent, study site personnel will record in Interactive Response Technology (IRT) and a unique patient number will be assigned to the potential study participant. Patient number will be assigned in chronological order by site starting with the lowest number. Once a patient number has been assigned to a patient, it cannot be re-assigned to any other patient.

5.2.4. Medical History

After obtaining informed consent, a review of the medical history will be conducted, most notably the onset of signs and symptoms related to COVID-19. Clinically significant medical history (ie, previous diagnoses, diseases, or surgeries) that does not pertain to the study indication, will be captured in the electronic case report form (eCRF). "Clinically significant" is defined as any event, diagnosis, or laboratory value requiring treatment or follow-up or the presence of signs or symptoms that require medical intervention. Concurrent medical signs and symptoms must be documented to establish baseline severities. All medical conditions ongoing at the time of first study drug dose and all relevant conditions that may have resolved prior to the

first dose of study drug should be recorded. The reason for current hospitalization will be recorded.

Other background information to be collected include prior medications/significant nondrug therapies and demographic data (gender, year of birth [or age], and race/ethnicity) will also be collected.

New onset SAEs that occur during the Screening period will be reported on the AE eCRF. Any new or continuing non-SAEs during Screening will be recorded on the medical history eCRF.

5.2.5. Confirmation of Eligibility

The investigator will assess and confirm the eligibility of each patient. Should the investigator have any concerns while determining if a patient is eligible, the investigator or designee can discuss with the medical monitor.

5.3. Randomization

For patients in Cohort 1, site personnel will access the IRT system to randomize to treatment assignment (Arm A or Arm B). Study drug should be administered ≤ 12 hours after randomization/treatment assignment. Randomization will be stratified by age (< 65 years or ≥ 65 years) and use of antiviral therapy (yes or no). [redacted]

5.4. Study Drug Dispensation

For hospitalized patients, study drug will be administered by qualified staff. For patients discharged from the hospital, study drug will be self-administered, and participants will be instructed to write in a diary daily, documenting that the drug was taken, and AEs were experienced. Patients should be instructed to take the study drug with a glass of water at approximately the same time each day. Patients taking study drug at home will be instructed on how to complete the diary by study staff prior to discharge. If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. The patient should not take extra capsules to make up a missed dose. The patient will be instructed to document missed study drug doses in the study diary. Furthermore, they will be instructed to call their provider, the principal investigator, or research nurse if vomiting occurs or they have recurrence of their COVID-19 symptoms or any other AEs consistent with the product label. If the pills are vomited, this should be noted on the patient diary, but a replacement dose should not be taken that day. All dosages prescribed and dispensed to the patient, and all dose changes during the study should be recorded. Diaries will be collected at the end of the treatment period. In the event of circumstances that prevent a discharged patient from returning to clinic, a telehealth visit is permitted. Study staff will collect or coordinate with patient in the event of a telehealth visit for the return of any unused drug and the study diary. Unused drug will be counted and returned to the pharmacy to be destroyed. A prescription for dispensing study drug for at home use, as detailed above, will be filled by the study pharmacy. Medication labels will comply with U.S. legal requirements and be printed in English. The storage conditions for study drug will be described on the medication label. Study drug (zanubrutinib or placebo) will be provided by BeiGene, Ltd. Zanubrutinib is formulated as capsules for oral administration and will be available for this study in 80-mg capsules. Placebo

is formulated as capsules with the same appearance as zanubrutinib 80-mg capsules for this study.

5.5. Safety Assessments

5.5.1. Physical Examination and Vital Signs

Physical examination and vital signs (blood pressure, heart rate, body temperature, and weight), will be performed daily while hospitalized as well at the end of treatment and follow up visits. Height (cm) is determined at Screening only.

A complete physical examination includes an assessment of organ systems per standard of care at the study site and as clinically indicated for evaluation of new onset signs or symptoms.

5.5.2. Electrocardiogram

A 12-lead electrocardiogram (ECG) will be performed at Screening for all patients. During the study, an ECG will be conducted on Days 1 through 3, Day 7, and then weekly if patient remains hospitalized (Appendix 5).

5.5.3. Adverse Events Review

Record all new or worsening, non-SAEs from the time of first dose of study drug through the Safety Follow-up Visit. Information on all SAEs will be collected from the time of informed consent through screen failure or safety follow-up. The AE reporting period is defined in Section 8.4.1.

Data related to any new infection will be reported in the AE case report form (CRF). Information related to the infection such as infecting agent, site of infection, and source of culture will also be collected on the CRF.

All TEAEs and SAEs will be followed until resolution or stabilization. The regulatory definition for an AE is provided in Section 8.1, and the definition of an SAE is provided in Section 8.2.1. Important additional requirements for reporting SAEs are explained in Section 8.

5.6. Efficacy Assessments

5.6.1. Oxygenation

Oxygen saturation and documentation of supplemental oxygen (if any) will be assessed daily while in the hospital, and at the end of treatment and follow up visits as specified per the Schedule of Assessments (Appendix 5).

Data related to delivery techniques and modes of mechanical ventilation including the clinical decisions to implement or discontinue mechanical ventilation will be documented in the CRF, including changes in goals of care, and impacts due to changes in allocation of resources.

5.6.2. Radiographic Evaluation

A chest computed tomography or similar radiographic studies will be performed at Screening. A similar modality of study may be used for follow-up as clinically indicated. All imaging studies will be reviewed locally at each respective study site as part of the assessments.

5.7. Laboratory Assessments

Laboratory studies will be assessed in a local laboratory unless otherwise indicated. Laboratory assessments will be performed at the timepoints specified in the Schedule of Assessments (Appendix 5) and may also be performed at other timepoints as medically necessary.

5.7.1. Hematology

Complete blood count including hemoglobin, hematocrit, platelet count, red blood cell count, and white blood cell count with differential (neutrophil, lymphocyte, monocyte, eosinophil, and basophil) will be performed at timepoints specified in the Schedule of Assessments. Patients who develop marked and persistent lymphocytosis should have an analysis (ie, flow cytometry) to rule out an underlying hematologic malignancy disorder.

5.7.2. Serum chemistries

Serum chemistries including sodium, potassium, glucose, blood urea nitrogen, creatinine, calcium, total bilirubin, total protein, albumin, ALT, AST, alkaline phosphatase, and LDH will be performed at the timepoints specified in the Schedule of Assessments (Appendix 5).

5.7.3. Inflammatory and Cardiac Markers

C-reactive protein, serum ferritin, and cardiac troponin will be drawn at Screening and timepoints noted in Schedule of Assessments (Appendix 5).

5.7.4. SARS-CoV-2 Testing

Based on Emergency Use Authorization by the FDA, only qualitative PCR is feasible for nasopharyngeal sampling. Blood and stool sampling has not been validated given its unknown clinical utility. In a study by Wang et al (Wang et al 2020), viremia related to SARS-CoV-2 was only observed in 3 of 307 (1%) patients. Stool samples also had a low (44/153; 29%) rate of positivity. Serial follow-up after discharge may also be complicated due to limited testing resources, and potential of exposure of uninfected individuals. We also note anecdotal reports of detectable virus by RT-PCR in the absence of symptoms after patient discharge, which may be due to remnant virus. These limitations in the current landscape of viral load determination have prompted us to limit qualitative SARS-CoV-2 testing to baseline assessment.

Clinical samples for SARS-CoV-2 diagnostic testing will be obtained according to WHO guidelines. For each patient, a sampling strategy will be implemented in which samples are obtained at screening. Samples will be tested for viral load using a qualitative RT-PCR assay.

5.7.5. Coagulation

The coagulation profile includes prothrombin time/international normalized ratio, activated partial thromboplastin time, and D-dimer. With the exception of D-dimer, the coagulation

profile will be performed at Screening and only as clinically indicated thereafter (see Appendix 5).

5.7.6. Hepatitis B and C testing

Viral hepatitis B and C serologic markers and/or viral load will be tested at Screening. HBV and HCV testing will be performed in a local laboratory. The HBV panel includes HBsAg, HBcAb, and hepatitis B surface antibody (HBsAb), as well as quantitative HBV DNA by PCR, if the patient is negative for HBsAg but HBcAb positive (regardless of HBsAb status). The HCV panel includes HCV antibody as well as quantitative HCV RNA by PCR if the patient is HCV antibody positive.

Patients positive for HBsAg and/or with detectable levels of HBV DNA are not eligible for the study.

Patients who are HBsAg negative, HBcAb positive, and HBV DNA negative must undergo at least monthly HBV DNA screening by PCR. These patients should be considered for prophylactic antiviral treatment in consultation with a local HBV expert. If a patient is receiving prophylactic antiviral treatment, HBV DNA screening by PCR must be done at least every 90 days.

HBV DNA values between 20 and 100 IU/mL should be rechecked within 2 weeks. Study drug should be interrupted, and antiviral therapy initiated if, on repeat testing, this level of HBV DNA is confirmed. If the HBV DNA level is 100 IU/mL or higher, study drug should be interrupted, and antiviral therapy initiated or continued. Resumption of study drug in patients whose HBV reactivation resolves should be discussed with, and approved by, the medical monitor and physicians with expertise in managing chronic HBV infection.

Patients positive for HCV antibody, but negative for HCV RNA, must undergo monthly HCV RNA screening. Patients with HCV RNA ≥ 15 IU/mL should stop study drug and antiviral therapy should be initiated. Resumption of study drug in patients whose HCV reactivation resolves should be discussed with, and approved by, the medical monitor and physicians with expertise in managing HCV infection.

All patients with a history of hepatitis B and C viral infection and baseline negative PCR that develop elevations in liver function tests should be evaluated for viral hepatitis reactivation.

The medical monitor should be informed of any suspected HBV or HCV reactivation. Table 2 describes how the results for HBV and HCV testing at Screening relate to study eligibility.

Table 2: Active Hepatitis B or Hepatitis C Infection (Detected Positive by Polymerase Chain Reaction)

Screening assessment	Meets inclusion criteria	To be excluded
HBV	HBsAg (-) and HBcAb (-)	HBsAg (+)
	HBsAg (-) and HBcAb (+) and HBV DNA "Not detected" *Perform monthly monitoring of HBV DNA*	HBsAg (-) and HBcAb (+) and HBV DNA detected
HCV	Antibody (-)	Antibody (+) and HCV RNA detected
	Antibody (+) and HCV RNA "Not detected" *Perform monthly monitoring of HCV RNA*	

Abbreviations: HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, viral hepatitis B; HCV, viral hepatitis C.

5.7.7. Pregnancy Test

Any female patient who is pregnant is not eligible for the study. In women of childbearing potential, a serum pregnancy test will be performed within 7 days before first dose of study drug. Additional β-HCG testing will be performed as described in Appendix 5 and Appendix 6. A patient who has a positive pregnancy test result at any time after the first administration of study drug will immediately discontinue study treatment and withdraw from the study.

5.8. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.8.1. [redacted]

[redacted]

5.9. [redacted]

[redacted]

5.10. Hospital Discharge

Patients may be discharged from the hospital prior to completion of the full 28-day treatment course. Discharge may be considered if:

- Patient is clinically stable on room air with an O_2 saturation ≥ 94%
- Patient is NOT receiving oxygen therapy
- Patient is afebrile (body temperature ≤ 38.0ºC)

- Patient is not on receiving intravenous antibiotics, excluding antibiotics for a central venous catheter infection

5.11. Outpatient Visits

In the event a patient is discharged from the hospital prior to Day 28, outpatient visits should be conducted at Days 7, 14, 21, and 28 as described in Appendix 6. A safety follow-up visit should be conducted 30 ± 7 days and 56 ± 7 days after last dose for all patients who discontinue the study drug, as described in Appendix 5 and Appendix 6. A telehealth visit with coordinated diary collection and/or return of zanubrutinib is permitted after discharge from hospital if circumstances prevent a clinic visit. Lab draws and other assessments that may be clinically indicated should be performed through outpatient laboratory or radiology services unless it is not medically safe.

5.12. Unscheduled Visits

Unscheduled visits may be performed at any time as necessary for evaluation of treatment or disease-related complications. If an unscheduled visit is necessary to assess toxicity or for suspected worsening of pulmonary function, diagnostic tests may be performed as directed by the investigator, and the results of the assessments should be entered on the unscheduled visit eCRF.

5.13. End of Treatment Period

The treatment period starts with the first day of study treatment and ends 30 days after the date of permanent study drug discontinuation.

Patients may discontinue study drug for any of the reasons listed in Section 6.5.

Patients may voluntarily withdraw consent for treatment at any time.

5.14. Safety Follow-up

All patients who permanently discontinue study drug will have Safety Follow-up Visits 30 ± 7 days and 56 ± 7 days after the last dose of study drug. Refer to the Schedule of Assessments (Appendix 5) for the assessments to be performed at the Safety Follow-up Visits.

5.15. End of Study

Reasons for withdrawal from the study may include the following:

- Patient withdrew consent
- Death
- Lost to follow-up
- Investigator decision
- Study termination by sponsor
- Other (specify)

5.16. Lost to Follow-up

Every reasonable effort should be made to contact any patient lost to follow-up during the study to complete study related assessments, record outstanding data, and retrieve study drug.

After unsuccessful telephone contact, an effort to contact the patient by mail using a method that provides proof of receipt should be attempted. Alternate contacts are permissible if the patient is not reachable (eg, primary care providers, referring physician, relatives). Such efforts should be documented in the patient's source documents.

If all efforts to establish contact with the patient fail, the patient will be considered lost to follow-up, which will be documented in the patient's source documents and CRF.

6. STUDY TREATMENT

6.1. Study Treatment Preparation and Dispensation

6.1.1. Packaging and Labeling

Study drug (either zanubrutinib 80-mg capsules or placebo capsules) will be provided in a child-resistant, high-density polyethylene bottle with induction seal and bottle label.

The contents of the label will be in accordance with all applicable local regulatory requirements.

Study drug (either zanubrutinib 80-mg capsules or placebo capsules) is formulated as hard gelatin capsules with the same appearance.

6.1.2. Handling and Storage

The study drug will be dispatched to a study center only after receipt of the required documents in accordance with applicable regulatory requirements and the sponsor's procedures. The investigator or pharmacist/designated personnel is responsible for maintaining the drug supply inventory and acknowledging receipt of all study drug shipments. All study drug must be stored in a secure area, with access limited to the investigator and authorized study center personnel and kept under physical conditions that are consistent with study drug-specific requirements. The study drug must be kept at the temperature condition as specified on the labels.

Study drug bottles must be stored at room temperature 15ºC to 30ºC (59ºF to 86ºF).

Study drug must be dispensed or administered according to procedures described herein. Only patients enrolled in the study may receive study drug, in accordance with all applicable regulatory requirements. Only sponsor authorized study center personnel may supply or administer study drug.

6.1.3. Compliance and Accountability

Compliance will be assessed by the investigator and/or study personnel at each patient visit and information provided by the patient and/or guardian.

The investigator and/or study personnel will keep accurate records of the quantities of study drug dispensed and used by each patient. This information must be captured in the source document at each patient visit. The investigator is responsible for study drug accountability, reconciliation, and record maintenance. In accordance with all applicable regulatory requirements, the investigator or designated study center personnel must maintain study drug accountability records throughout the course of the study. This person will document the amount of study drug received from the sponsor, the amount supplied, and/or the amount administered to and returned by patients, if applicable.

6.1.4. Disposal and Destruction

After completion of the study and after final drug inventory reconciliation by the monitor, the study site, upon sponsor's election, will destroy or return all unused study drug supplies to sponsor. The inventoried supplies can be destroyed on site or at the depot according to institutional policies after receiving prior written sponsor approval.

6.2. Dosage and Administration

6.2.1. Study Drug

Study drug for this study is zanubrutinib or placebo administered orally once daily. The capsules are to be taken around the same time each day with a glass of water. Study drug can be taken with or without food. The capsules should be swallowed intact and patients should not attempt to open capsules or dissolve them in water. For patients who require nasogastric or feeding tube placement while on study, study drug may be administered by qualified site staff by opening the capsules, mixing with the recommended dosing solution, and flushing down the nasogastric or feeding tube (see guidance for nasogastric/feeding tube administration in Appendix 2). Though the use of strong CYP3A inhibitors/inducers (see Appendix 3) and grapefruit and Seville oranges should be avoided for the duration of treatment, treatment with antifungal prophylaxis (eg, voriconazole, posaconazole) and antiviral therapy is permitted; however, dose reductions of study drug are necessary (see Table 4). If a dose is not taken at the scheduled time, it can be taken as soon as possible on the same day with a return to the normal schedule the following day. Extra capsules to make up the missed dose should not be dispensed.

Dose reductions for toxicity will be permitted (Section 6.4).

Patients should be instructed that if a dose of the study drug is not taken at the scheduled time, they should skip the dose if the time to next dose is ≤ 8 hours and return to normal dosing intervals with the next dose thereafter. If a patient vomits after a dose of study drug, that dose should not be repeated.

6.2.2. Dispensation for Outpatient Administration

Study drug will be dispensed to patients who, upon discharge (see Section 5.10), do not meet the criteria for study drug discontinuation for clinical benefit described in Section 6.5.2.

6.3. Overdose

Any dose of study drug in excess of that specified in this protocol is considered to be an overdose. AEs associated with an overdose or incorrect administration of study drug will be recorded on the AE eCRF. Any SAEs associated with an overdose or incorrect administration are required to be reported within 24 hours via the SAE reporting process as described in Section 8.4.2.1. There is no specific antidote for an overdose of zanubrutinib. In the event of an overdose, patients should be closely monitored and given appropriate supportive treatment.

6.3.1. Minor Surgical Procedures

For minor procedures (eg, central venous catheter, arterial line placement) that are urgently needed and could result in bleeding, immediately stop study drug and consider transfusion with platelets just prior to procedure. Study drug should be held for 24 hours after procedure. If there is ongoing bleeding after the procedure, additional platelet transfusions can be administered, and study drug held to 24 hours after bleeding stops. No drug hold or platelet transfusions are needed for routine venipunctures or peripheral IV placement.

6.3.2. Elective Major Surgical Procedures

For any elective surgery or invasive procedure requiring sutures or staples for closure, study drug should be held at least 3 to 7 days prior to the intervention (except for emergency procedures) and should be held at least 3 to7 days after the procedure and restarted at the discretion of the treating physician when the surgical site is reasonably healed without serosanguineous drainage or the need for drainage tubes. For less than 7 days hold prior to the procedure, consider a transfusion of platelets just prior to the procedure to decrease risk of bleeding.

6.3.3. Emergency Major Surgical Procedures

For emergency procedures that could result in bleeding and require sutures or staples for closure, transfusion with platelets prior to the procedure should be given and study drug held after the procedure for at least 3 days after the surgical procedure. Consider additional platelet transfusions peri- and post-operatively to reduce bleeding risk or active bleeding.

6.4. Dose Modifications

The guidelines below (Table 3) should be followed for modification of study drug dosing for non-COVID-19 hematologic and nonhematologic toxicities (other than hypertension adequately controlled with oral medication or asymptomatic laboratory events). Laboratory events indicating liver or renal dysfunction will not be considered asymptomatic laboratory events and should compel adherence to dose modification guidelines provided below.

Lymphocytosis is considered as an expected manifestation of treatment with zanubrutinib and therefore may not be an AE; clinical correlates should be present if reporting lymphocytosis as an AE.

Table 3: Study Drug Dose Reduction Levels

Toxicity occurrence	Dose level	Study drug dose
First	-1 dose level	Restart at 160 mg once daily
Second	-2 dose level	Restart at 80 mg once daily
Third	Discontinue study drug	Discontinue study drug

Any patient experiencing a ≥ Grade 3 hematologic or nonhematologic toxicity should have their dose held. The dose hold should start on the day that the above occurrence is noted. Study drug may be restarted at the next lower dose level upon resolution of toxicity if interrupted for up to 7 consecutive days, per the investigator's discretion. A maximum of 2 dose reductions will be allowed before study drug is allowed.

6.5. Discontinuation from Study Treatment

6.5.1. Discontinuation for Adverse Events

Any 1 or more of the following will require permanent discontinuation of study drug:

- All study drug-related Grade 4 AEs (hematologic and/or nonhematologic)

- The following changes in liver function tests:
  - ALT or AST > 8 x ULN
  - ALT or AST > 5 x ULN for more than 2 weeks
  - ALT or AST > 3 x ULN and (total bilirubin > 2 x ULN or international normalized ratio > 1.5)
  - ALT or AST > 3 x ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)
- Hemorrhage/bleeding AEs meeting the following criteria:
  - Any ≥ Grade 3 hemorrhagic/bleeding AE, regardless of underlying condition
  - Any grade serious bleeding AE
  - Any grade intracranial hemorrhage/hematoma
- ≥ Grade 3 atrial fibrillation
- Any patient with a baseline history of mild and/or moderate chronic hepatic impairment should discontinue study drug for worsening liver disease (eg, progression from Class A to Class B or C, etc).
- Withdrawal of consent for further study participation (see Section 5.15)
- Pregnancy
- The investigator or sponsor determines it is in the best interest of the patient
- Intercurrent illness that compromises the patient's ability to participate in the study
- Need for prohibited concomitant medication
- Study drug interruption > 7 days
- Significant, persistent, or recurrent AEs
- For all patients discontinuing therapy, the reason for discontinuation should be recorded in the medical record.

All patients that discontinue study treatment for an AE should be followed through resolution and study completion.

6.5.2. Discontinuation for Clinical Benefit

Patients who are discharged and are clinically stable on room air for ≥ 24 hours with an O_2 saturation ≥ 94% should discontinue the use of study drug.

6.6. Blinding

Patients in Cohort 1 will be randomized to receive zanubrutinib or matched placebo in a double-blind fashion in Arm A and Arm B (Figure 6). It is imperative to maintain the blind such that neither the investigator, nor the patient, nor medical or ancillary medical staff will know

which drug is being administered in addition to supportive care. Due to the ongoing need to assess safety, the sponsor staff will not be blinded to patient treatment assignment.

Every effort should be made to avoid unblinding the patient's treatment assignment in Cohort 1 unless necessary. Unblinding may be indicated and permissible only in specific situations as described below and, if necessary, for the patient's welfare.

[redacted]

6.6.1. Emergency Unblinding

In case of an emergency, such as when a patient has an AE suspected to be related to the investigational drug product and for which management of the AE with one or more drug products with substantial toxicity or invasive procedures is being considered, unblinding can occur in Cohort 1. The investigator has the sole responsibility for determining if unblinding of a patient's treatment assignment is warranted. Patient safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to inform the medical monitor of their intent before unblinding a patient's treatment assignment unless this could delay emergency treatment of the patient. If a patient's treatment assignment is unblinded, the sponsor must be notified immediately.

The investigator performs the emergency unblinding for AEs through an IRT System as per the instructions in the IRT site user manual. Unblinded patients may remain on study treatment at the discretion of the investigator in consultation with the medical monitor and only as permissible per definitions in the study protocol.

6.6.2. Inadvertent Unblinding

Every effort will be made to blind both the patient and the investigator to the identity of the treatment assignment in Cohort 1 (ie, zanubrutinib or placebo), but the inadvertent unblinding of a patient may occur. If an investigator, site personnel (eg, those performing assessments), or patient is unblinded, the unblinding will not be sufficient cause (in and of itself) for that patient to be discontinued from study therapy or excluded from any safety or efficacy analyses.

Additionally, there may be ethical reasons to have the patient remain on the study treatment. For patients to continue study treatment in the event of unblinding, the investigator must obtain specific approval from the medical monitor.

7. CONCOMITANT THERAPY

7.1. Concomitant Therapy

All concomitant medications and herbal supplements taken during the study will be recorded in the eCRF, including indications and dates of administration.

7.1.1. Permitted Medications

The following treatments are allowed (per institutional standards of care):

- Blood product transfusions and growth factor support
- Myeloid growth factors to manage neutropenia
- Therapy to reduce symptoms
- Infection prophylaxis
- Antiviral treatment
- Dexamethasone
- Intravenous immunoglobulin
- Convalescent plasma
- Anticoagulation to prevent thrombosis

In patients with a high risk for opportunistic infections, including *Pneumocystic jirovecii pneumonia* , prophylaxis should be considered as per institutional standards.

7.1.2. Prohibited Medications

In all arms, the concomitant use of the following agents is prohibited during the study:

- BTK inhibitors
- Host modifiers or immune-based therapies (see Appendix 7)
- Therapy with anti-CD20 monoclonal antibody treatment (eg, rituximab, obinutuzumab, ofatumumab), and/or immune checkpoint inhibitor (eg, pembrolizumab, nivolumab)
- Therapeutic anticoagulation including warfarin
- Combined use of antiplatelet + anticoagulation (low molecular weight heparin or direct-acting oral anticoagulants)

7.2. Potential Interactions Between the Study Drugs and Concomitant Medications

7.2.1. Effects of Cytochrome P450 (CYP)-Inhibiting/Inducing Drugs on Exposure of Zanubrutinib

Administration of study drug with strong/moderate CYP3A inhibitors or inducers (refer to Appendix 3 for a list of these medications), grapefruit juice, or Seville oranges should be done with caution because they may affect the metabolism of zanubrutinib. If at all possible, patients are encouraged not to administer concurrent strong/moderate CYP3A inhibitors and inducers and consider using alternative agents. If these agents will be used, follow the dose modification table instructions in Table 4. The medical monitor should be consulted in these situations. Please refer to http://medicine.iupui.edu/clinpharm/ddis/main-table/ for a more complete list. A list of potential agents used for the management of COVID-19 and potential dose modifications is shown in Appendix 4.

Table 4: Dose Modification for Study Drug when Co-Administered with Strong/Moderate CYP3A Inhibitors or Inducers

CYP3A	Co-administered Drug	Recommended use
Inhibition	Strong CYP3A inhibitor (eg, ketoconazole, conivaptan, clarithromycin, indinavir, itraconazole, lopinavir, ritonavir, telaprevir, posaconazole, voriconazole)	80 mg once daily
	Moderate CYP3A inhibitor (eg, erythromycin, ciprofloxacin, diltiazem, dronedarone, fluconazole, verapamil, aprepitant, imatinib, grapefruit products)	160 mg once daily
Induction	Strong CYP3A inducer (eg, carbamazepine, phenytoin, rifampin, St. John's wort)	Avoid concomitant use; consider alternative agents with less induction potential.
	Moderate CYP3A inducer (eg, bosentan, efavirenz, etravirine, modafinil, nafcillin)	320 mg once daily, use with caution; monitor for potential lack of efficacy.

Abbreviations: CYP3A, cytochrome P450, family 3, subfamily A.

7.2.2. Effects of zanubrutinib on exposure of other concomitant medications

A clinical drug-drug interaction study (Study BGB-3111-108) indicated that zanubrutinib is a mild inducer of CYP3A4 and CYP2C19. Narrow therapeutic index drugs that are metabolized by CYP3A4 (alfentanil, cyclosporine, dihydroergotamine, ergotamine, fentanyl, pimozide, quinidine, sirolimus and tacrolimus), and CYP2C19 (eg, S-mephenytoin) should be used with caution, as zanubrutinib may decrease the plasma exposures of these drugs.

Because ethinylestradiol (a key ingredient in a variety of combined oral contraceptives) is partly metabolized by CYP3A4, patients using hormonal contraceptives (eg, birth control pills or devices) must use a barrier method of contraception (eg, condoms) as well (Section 5.2.2).

Repeated dosing of zanubrutinib increased exposure of digoxin (P-gp substrate) with a mean increase of 11% for AUC_{0-t} and 34% for C_{max}. The coadministration of oral P-gp substrates with a narrow therapeutic index (eg, digoxin) should be used with caution as zanubrutinib may increase their concentrations.

8. SAFETY MONITORING AND REPORTING

The investigator is responsible for the detection and documentation of events meeting the definition of an AE or SAE as provided in this protocol. In addition, a separate Safety Monitoring Committee (Section 8.7) will be formed to monitor the safety (including lack of efficacy) of the study on a periodic basis.

8.1. Adverse Events

8.1.1. Definitions and Reporting

An AE is defined as any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a study drug, whether considered related to study drug or not.

Examples of AEs include the following:

- Worsening of a chronic or intermittent pre-existing condition, including an increase in severity, frequency, duration, and/or has an association with a significantly worse outcome
- New conditions detected or diagnosed after study drug administration even though it may have been present before the start of the study
- Signs, symptoms, or the clinical sequelae of a suspected interaction
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concurrent medication (overdose per se should not be reported as an AE or SAE)

When an AE or SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory results, and diagnostics reports) relative to the AE or SAE. The investigator will then record all relevant information regarding an AE or SAE in the eCRF. However, there may be instances when copies of medical records for certain cases are requested by the sponsor. In these instances, all patient identifiers will be blinded on the copies of the medical records before submission to the sponsor. When a new infection is reported, the site of infection and the diagnostic test used to make the diagnosis will be recorded.

8.1.1.1. Assessment of Severity

The investigator will assess the severity for each AE and SAE reported during the study. AEs and SAEs should be assessed and graded based upon the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI-CTCAE v5.0).

Toxicities that are not specified in the NCI-CTCAE v5.0 will be defined as follows:

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

- Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living
- Grade 4: Life-threatening consequences; urgent intervention indicated
- Grade 5: Death related to AE

Note: The terms "severe" and "serious" are not synonymous. Severity is a measure of intensity (eg, grade of a specific AE, mild [Grade 1], moderate [Grade 2], severe [Grade 3], or life-threatening [Grade 4]), whereas seriousness is classified by the criteria based on the regulatory definitions. Seriousness serves as the guide for defining regulatory reporting obligations from the sponsor to applicable regulatory authorities as described in Section 8.2.

8.1.1.2. Assessment of Causality

The investigator is obligated to assess the relationship between the study drug and the occurrence of each AE or SAE, using best clinical judgement. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the AE or SAE to the study drug should be considered and investigated. The investigator should consult the IB in the determination of his/her assessment.

There may be situations when an SAE has occurred, and the investigator has minimal information to include in the initial report to the sponsor. However, it is very important that the investigator assesses causality for every SAE before transmission of the SAE report to the sponsor because the causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator may change his/her opinion of causality in light of follow-up information and amend the SAE report accordingly.

The causality of each AE should be assessed and classified by the investigator as "related" or "not related." An AE is considered related if there is "a reasonable possibility" that the AE may have been caused by the study drug (ie, there are facts, evidence, or arguments to suggest possible causation). A number of factors should be considered in making this assessment, including the following:

- Temporal relationship of the AE to the administration of study treatment/study procedure
- Whether an alternative etiology has been identified
- Mechanism of action of the study drug
- Biological plausibility

An AE should be considered "related" to study drug if any of the following criteria are met, otherwise the event should be assessed as not related:

- There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out.
- There is evidence to suggest a causal relationship, and the influence of other factors is unlikely.

- There is some evidence to suggest a causal relationship (eg, the AE occurred within a reasonable time after administration of the study drug). However, the influence of other factors may have contributed to the AE (eg, the patient's clinical condition or other concomitant AEs).

8.1.1.3. Follow-up of Adverse Events and Serious Adverse Events

After the initial AE or SAE report, the investigator is required to proactively follow each patient and provide further information to the sponsor on the patient's condition.

All AEs and SAEs documented at a previous visit/contact and designated as ongoing will be reviewed at subsequent visits/contacts.

All AEs and SAEs will be followed until resolution, the condition stabilizes or is considered chronic, the AE or SAE is otherwise explained, the patient is lost to follow-up, or the patient withdraws consent. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, radiographic imaging, or consultation with other health care professionals.

The sponsor may request that the investigator perform or arrange for the conduct of supplemental measurements and/or evaluations to elucidate as fully as possible the nature and/or causality of the AE or SAE. The investigator is obligated to assist. If a patient dies during participation in the study or during a recognized follow-up period, the sponsor will be provided with a copy of any postmortem findings, including histopathology.

New or updated information should be reported to the sponsor according to the SAE instructions provided by the sponsor within the time frames outlined in Section 8.4.2.1.

8.1.2. Laboratory Test Abnormalities

Abnormal laboratory findings (eg, clinical chemistry, complete blood count, coagulation, or urinalysis) or other abnormal assessments (eg, ECGs, X-rays, or vital signs) that are judged by the investigator as clinically significant will be recorded as AEs or SAEs. This includes clinically significant abnormal laboratory findings or other abnormal assessments that are present at baseline and significantly worsen during the study. The definition of clinically significant is left to the judgment of the investigator; in general, these are laboratory test abnormalities that are associated with clinical signs or symptoms, require active medical intervention, or lead to dose interruption or discontinuation, require close observation, more frequent follow-up assessments, or further diagnostic investigation.

Lymphocytosis is considered as an expected manifestation of treatment with zanubrutinib and therefore may not be an AE; clinical correlates should be present if reporting lymphocytosis as an AE. Patients who develop marked and persistent lymphocytosis should have an analysis (ie, flow cytometry) to rule out an underlying hematologic malignancy disorder.

For information on procedures for the monitoring and prevention of hepatitis B and hepatitis C, see Section 5.7.6.

8.1.3. Lack of Efficacy

Lack of efficacy will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfill the AE or SAE definition (including clarifications).

8.2. Serious Adverse Events

8.2.1. Definitions

An SAE is any untoward medical occurrence that, at any dose:

- Results in death
- Is life-threatening

  Note: the term "life-threatening" in the definition of "serious" refers to an AE in which the patient was at risk of death at the time of the AE. It does not refer to an AE, which hypothetically might have caused death, if it was more severe.
- Requires hospitalization or prolongation of existing hospitalization

  Note: In general, hospitalization signifies that the patient was admitted (usually involving at least an overnight stay) to the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting.
- Results in disability/incapacity

  Note: The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance, such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle), which may interfere or prevent everyday life functions, but do not constitute a substantial disruption.
- Is a congenital anomaly/birth defect
- Is considered a significant medical AE by the investigator based on medical judgment (eg, may jeopardize the patient or may require medical/surgical intervention to prevent one of the outcomes listed above)

The following are NOT considered SAEs:

- Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline
- Hospitalization for social/convenience considerations
- Scheduled therapy for the target disease of the study, including admissions for transfusion support or convenience

8.3. Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction is a serious adverse reaction that is both unexpected (ie, not present in the product's Reference Safety Information) and meets the definition of a serious adverse drug reaction, the specificity or severity of which is not consistent with those noted in the IB.

8.4. Timing, Frequency, and Method of Capturing Adverse Events and Serious Adverse Events

8.4.1. Adverse Event Reporting Period

After informed consent has been signed but prior to the administration of the study drug, only SAEs should be reported.

After initiation of study drug, all AEs and SAEs, regardless of relationship to study drug, will be reported until 56 days after the last dose of study drug. The investigator should report any SAEs that are assessed as related to study-drug treatment, at any time after treatment discontinuation.

8.4.2. Prompt Reporting of Serious Adverse Events

8.4.2.1. Timeframes for Reporting Serious Adverse Events

As soon as the investigator determines that an AE meets the protocol definition of an SAE, the event must be reported promptly (within 24 hours) to the sponsor or designee as described in Table 5.

Table 5: Timeframes and Documentation Methods for Reporting Serious Adverse Events to the Sponsor or Designee

	Timeframe for Making Initial Report	Documentation Method	Timeframe for Making Follow-up Report	Documentation Method	Reporting Method
All SAEs	Within 24 hours of first knowledge of the AE	SAE Report	As expeditiously as possible	SAE Report	Email or fax SAE form

Abbreviations: AE, adverse event; SAE, serious adverse event.

8.4.2.2. Completion and Transmission of the Serious Adverse Event Report

Once an investigator becomes aware that an SAE has occurred in a patient, he/she is to report the information to the sponsor within 24 hours as outlined above in Section 8.4.2.1. The SAE report will always be completed as thoroughly as possible with all available details of the event and forwarded to the sponsor or designee within the designated time frames.

If the investigator does not have all information regarding an SAE, he/she is not to wait to receive additional information before notifying the sponsor or designee of the SAE and completing the form. The form will be updated when additional information is received.

The investigator must always provide an assessment of causality at the time of the initial report as described in Section 8.1.1.2.

The sponsor will provide contact information for SAE report submission.

8.4.2.3. Regulatory Reporting Requirements for Serious Adverse Events

The investigator will report all SAEs to the sponsor in accordance with the procedures detailed in Section 8.4.2.1. The sponsor has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation.

The investigator, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the IRB/IEC.

All suspected unexpected serious adverse reaction (as defined in Section 8.3) will be submitted to all applicable regulatory authorities and investigators for zanubrutinib studies.

When a study center receives an initial or follow-up safety report or other safety information (eg, revised IB) from the sponsor, the investigator or designated responsible person is required to promptly notify his/her IRB or IEC. The investigator should place copies of safety reports from the sponsor in the Investigator Site File.

8.4.3. Eliciting Adverse Events

The investigator or designee will ask about AEs by asking the following standard questions:

- How are you feeling?
- Have you had any medical problems since your last visit?
- Have you taken any new medicines since your last visit?

8.4.4. Death

Death is an outcome and not usually considered an event. If the only information available is death and the cause of death is unknown, then the death is reported as an event (eg, "death," "death of unknown cause," or "death unexplained").

8.5. Pregnancy Reporting

If a female patient or the partner of a male patient becomes pregnant while receiving investigational therapy or within 90 days after the last dose of study drug, a pregnancy report form is required to be completed and expeditiously submitted to the sponsor to facilitate outcome follow-up. Information on the status of the mother and child will be forwarded to the sponsor. Generally, follow-up will be no longer than 6 to 8 weeks after the estimated delivery date. Any premature termination of the pregnancy will be reported.

While pregnancy itself is not considered to be an AE, any pregnancy complication or elective termination of a pregnancy for medical reasons will be recorded as an AE or SAE.

An abortion, whether accidental, therapeutic, or spontaneous, should always be reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a patient exposed to the study drug should be recorded and reported as an SAE.

8.6. Expedited Reporting to Health Authorities, Investigators, Institutional Review Boards, and Independent Ethics Committees

The sponsor will promptly assess all SAEs against cumulative study drug experience to identify and expeditiously communicate new safety findings to regulatory authorities, investigators, IRBs, and IECs based on applicable legislation. To determine the reporting requirements for individual SAEs, the sponsor will assess the expectedness of the SAEs using the Zanubrutinib Investigator's Brochure.

8.7. Safety Monitoring Committee

Due to the critically ill nature of these patients and the potential impact of blunting an immune response during an active infection, a Safety Monitoring Committee (SMC) will be established. An SMC will review and monitor toxicity and accrual data from this study on an ongoing basis, [redacted]. The committee will meet at least weekly until the study is fully accrued and all patients have completed at least 28 days of treatment. All active patients will be reviewed at least weekly until the final patient has completed active therapy. Thereafter, the SMC will continue at a frequency that is dependent upon the patterns that have been seen to date. All deaths will be reviewed and patterns of SAEs will be discussed at the weekly meeting. A decision will be made to continue as planned, modify the protocol for safety reasons or discontinue the protocol if significant safety concerns are identified. The SMC will consist of at least the following: 3 physician consultants, the medical monitor, an internal medical chair, a biostatistician, and a safety representative from BeiGene. The SMC may have access to unblinded information to assess safety and efficacy on an ongoing basis.

9. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

A statistical analysis plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives. Any deviations in the planned analysis as stated in the protocol will be delineated in the SAP. Any deviations from the SAP will be reported in the clinical study report. A data review will be conducted prior to database lock. This review will assess the accuracy and completeness of the study database, participant evaluability, and appropriateness of the planned statistical methods.

9.1. Randomization Methods

As discussed in Section 5.3, patients in Cohort 1 will be randomized 1:1 to zanubrutinib plus supportive care (Arm A) versus placebo plus supportive care (Arm B). Patients will be stratified by age (< 65 years or ≥ 65 years) and the use of antiviral therapy (yes or no). As no standard for treatment in patients with COVID-19 in pulmonary distress currently exists and new treatment options are urgently needed, this study will be exploratory in nature, and following the assessment of efficacy and safety results from the first 42 patients the study may continue to enroll based on review of the trial outcomes by study amendment. [redacted]

9.2. Study Endpoints

The coprimary endpoints for this study are the respiratory failure-free survival rate at 28 days and the time to breathing room air, both in Cohort 1.

Respiratory failure-free survival is defined as the time to the first occurrence of either respiratory failure or death. The rate of respiratory failure-free survival at 28 days is the proportion of patients who have not had respiratory failure nor died at any time ≤ 28 days after randomization.

Respiratory failure is defined by a clinical diagnosis of respiratory failure and initiation of one of the following therapies:

1. Endotracheal intubation and mechanical ventilation,
2. Extracorporeal membrane oxygenation,
3. Clinical diagnosis of respiratory failure with initiation of none of these measures only when clinical decision-making driven is driven solely by resource limitation or change in goals of therapy (these events will be formally collected in the CRF and flagged, for purposes of sensitivity analyses).

Time to breathing room air is defined as the time from randomization to the earliest time when the patient is stable on room air. If a patient is on room air for several hours and subsequently receives oxygen, the patient is not considered stable on room air and will not be considered back to room air for purposes of calculating the endpoint.

If a patient dies before breathing room air, time to breathing room air will be treated as censored at Day 28 in the analysis. If a patient is lost to follow-up before breathing room air, they will be

censored at the time they are lost to follow-up. All patients who take longer than 28 days to breathe room air will be censored at Day 28.

The respiratory failure-free survival rate at Day 28 will be compared between the two arms using simple proportions. The proportions will be compared by Fisher's exact test. If the 1-sided p-value is less than 0.10, the addition of zanubrutinib to best supportive care will be considered to increase the respiratory failure-free survival rate at 28 days.

The impact of adding zanubrutinib to best supportive care on the time to breathing room air will be described by the "hazard ratio" from a Cox model with treatment as an explanatory variable. The Cox model will include the stratification factors as explanatory variables as well as the WHO 8-point score at baseline. The p-value for testing the effect of zanubrutinib will come from the Wald test on the treatment parameter in the model.

Because testing will be carried out at the 0.10 one-sided level of significance for both of the coprimary endpoints instead of the traditional 0.05 two-sided level, a positive result will not be considered definitive evidence of zanubrutinib's effectiveness. Two analyses (interim and final) will be performed for the coprimary endpoints in Cohort 1, with the interim analysis performed when the first 42 randomized patients complete 28 days of follow-up. The type 1 error increase due to the interim and final analyses will be controlled by the O'Brien Fleming alpha spending function. The boundary for efficacy stop will be based on the p-value controlled from the Fisher's exact test for the respiratory failure-free survival rate at Day 28 and the p-value from the Cox model for the time to breathing room air.

The respiratory failure-free survival rate will also be assessed on an exploratory basis using a Cox proportional hazards regression approach, treating the occurrence of respiratory failure or death as an event. The stratification variables of age category (< 65 or ≥ 65), and use of antivirals (yes or no), as well as a time-dependent variable for the amount the dose was reduced compared to the full dose during their treatment course will be added to the Cox proportional hazards model as explanatory variables.

Secondary endpoints will include:

- Proportion of patients experiencing respiratory failure or death on Study Days 7, 14 and 21
- All-cause mortality at Study Days 7, 14, 21, and 28
- Proportion of patients discharged alive at Days 7, 14, 21, and 28
- Proportion of patients discharged from the ICU alive at Days 7, 14, 21 and 28
- Median reduction in days spent on supplemental oxygen, with time on supplemental oxygen imputed to the maximum number of days on oxygen observed in the study + 1 for patients who died. Testing to compare the two groups will be done with the Wilcoxon rank sum test.
- Mechanical ventilation-free survival
- Days on mechanical ventilation. Death will be assigned the maximum value observed in the trial + 1 and comparison between the two arms will be done using the Wilcoxon rank sum test.

- Duration of hospitalization. Death will be assigned the maximum value observed in the trial + 1 and comparison between the two arms will be done using the Wilcoxon rank sum test.
- Time to discharge. Death will be assigned the maximum value observed in the trial + 1 and comparison between the two arms will be done using the Wilcoxon rank sum test.
- Proportion of patients discharged alive [redacted]
- Change in WHO 8-point scale from baseline. Comparison between the two arms will be done using the Wilcoxon rank sum test. The WHO 8-point scale is defined as in Table 6.

Table 6: Ordinal Scale for Clinical Improvement

Patient State	Descriptor	Score
Uninfected	No clinical or virologic evidence of disease	0
Ambulatory	No limitation of activity	1
	Limitation of activities	2
Hospitalized, Mild disease	Hospitalized, no oxygen therapy	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, ECMO	7
Dead	Death	8

Abbreviations: ECMO, extracorporeal membrane oxygenation; RRT, registered respiratory therapist.

- P_{AO_2}:F_{IO_2} and/or oxygenation index, for patients on mechanical ventilation. Death will be assigned the maximum value observed in the trial + 1 and comparison between the two arms will be done using the Wilcoxon rank sum test.
- Clinical status assessed using an ordinal scale at a pre-specified timepoint
- Time to objective measure of recovery (eg, return to baseline oxygen requirement, as appropriate)
- Safety and tolerability of zanubrutinib as an adjuvant therapy to standard of care as assessed by TEAEs, SAEs, related AEs, TEAEs by grade, and abnormal laboratory findings. Frequency, seriousness and relatedness of TEAEs will be analyzed according to Medical Dictionary for Regulatory Activities (MedDRA). Laboratory abnormalities will be analyzed according to NCI CTCAE v5.0.

Time to event data will be assessed using survival curves, and the Cox proportional hazard model may be utilized to determine predictors of response and to control for patient variability. Time will be measured starting from the randomization date. For patients who were randomized and not treated, time to an event will be measured from the day of randomization.

Demographic and baseline disease characteristics will be assessed by randomization group to identify any factors in which there was an imbalance between the treatment groups. Should an imbalance exist in spite of randomization, the variable in which an imbalance is noted, may be added as an explanatory variable to adjust for the imbalance in the efficacy interpretation. Sensitivity analyses that include age, gender, and other demographic and baseline characteristics will be conducted to assess robustness of the trial results.

9.3. Sample Size, Accrual Rate and Study Duration

The study will enroll approximately 67 to 73 patients with 63 patients in Cohort 1 randomized to either zanubrutinib and supportive care (Arm A) or placebo and supportive care (Arm B).

[redacted]Enrollment is anticipated to be complete within 3 to 6 months. The study is expected to be complete within 6 to 9 months after activation.

The standard of care for treating COVID-19 patients with respiratory distress is changing rapidly and as a result the rate of respiratory failure or death anticipated in the sample size calculations below may be higher than what will actually be seen in the study. If the rate of respiratory failure or death in Cohort 1 is substantially less than what was anticipated for the trial per advice from the SMC, the sample size for the study may be increased to ensure there is adequate power for the primary endpoints. Further, the change in standard of care may make a small study with respiratory failure-free survival at Day 28 as a primary endpoint not feasible because of a low rate of such events.

From the standard of care arm of the lopinavir-ritonavir study (n = 100) (Cao et al 2020), we have the following statistics regarding respiratory failure and death (Table 7).

Table 7: Respiratory Failure and Death in the Standard Care Arm of Lopinavir-Ritonavir Study

Time point	Respiratory failure n (%)	Death n (%)	Respiratory failure or death n (%)
Baseline	16 (16)		16 (16)
Day 7	25 (25)	7 (7)	32 (32)
Day 14	11 (11)	17 (17)	28 (28)
Day 28		25(25)	NA

Abbreviation: NA, not available.

The maximum observed rate of respiratory failure or death is 32%. In Cohort 1 of the current study under consideration, patients in respiratory failure are not enrolled. However, in the study by Cao et al, there were patients in respiratory failure at baseline. Removing patients in the Cao et al study in respiratory failure at baseline from our estimate of the respiratory failure--free survival rate at Day 28, we estimate the respiratory failure or death rate to be 16% on Day 28 for the population in Cohort 1 of this study, or an 84% respiratory failure-free rate.

Myers et al (Myers et al 2020) identified of 377 patients treated for COVID-19 as inpatients at Kaiser Permanente Northern California. The following statistics on the highest level of respiratory support were presented.

Table 8: Highest Level of Respiratory Support in Kaiser Permanente Study

Respiratory support	n (%)
Nasal cannula/face mask	150 (39.8)
High-flow oxygen	12 (3.2)
Noninvasive ventilation	8 (2.1)
Invasive ventilation	110 (29.2)

Forty-six percent, (110 + 8 + 12) / (110 + 8 + 12 + 150), of patients who received some sort of respiratory support were in what the current protocol defines as respiratory failure. Unfortunately, we cannot decipher how many were in respiratory failure when they were admitted to the hospital. Thus, the maximum respiratory failure rate expected in this study is 46%. If we assume the same baseline rate that was observed in the Lopinavir-Ritonavir trial, (Cao et al 2020), then we would come up with a respiratory failure rate of 46% - 16% = 30%.

Assuming a 10% dropout prior to Day 28, unrelated to efficacy, 42 patients total in Cohort 1will provide approximately 81% power to detect an increase in the respiratory failure-free survival rate from 70 to 95% under a z-test for proportions with type 1 error of 0.10 1-sided (see Section 9.3.2 for the update to these sample size considerations). It will also provide 77% power for detecting an increase from 80 to 99% and 64% power for detecting an increase from 85 to 99% both with type 1 error of 0.10 one sided.

Table 9: Power for the Primary Endpoint of Respiratory Failure-Free Survival at Day 28

Respiratory Failure-Free Survival Rate		
Control	**Zanubrutinib**	**Power Alpha = 0.10 one-sided n = 19 per group**
0.85	0.90	0.208
0.85	0.95	0.405
0.85	0.99	0.642
0.80	0.90	0.341
0.80	0.95	0.561
0.80	0.99	0.767
0.70	0.80	0.286
0.70	0.90	0.622
0.70	0.98	0.897

Respiratory Failure-Free Survival Rate		
Control	**Zanubrutinib**	**Power** **Alpha = 0.10 one-sided** **n = 19 per group**
0.70	0.95	0.807

9.3.1. [redacted]

[redacted]

Table 10: [redacted]

[redacted]							

[redacted]

9.3.2. Update to the Statistical Considerations for Cohort 1

During the execution of this study, the RECOVERY study (RECOVERY Collaborative Group et al 2020) reported that the use of dexamethasone reduced the percentage of patients who died by a factor of 0.82 in those patients who received oxygen but not mechanical ventilation. The original analysis plan for Cohort 1 and the data that were used to determine the size of Cohort 1 did not reflect these published data. As a result, the sample size for Cohort 1 will be increased by a factor of 1/0.82**2, which represents an approximately 50% increase in the size of Cohort 1.

The incidence of respiratory failure is similarly assumed to be reduced by a factor of 0.82. In addition, an interim/futility analysis will be performed in Cohort 1 at the point when the final analysis for Cohort 1 was previously planned to occur, specifically when 42 patients reach an event of respiratory failure or complete 28 days of treatment, whichever occurs later. Table 11 summarizes the planned interim and final analyses for Cohort 1 that will preserve the overall type 1 error at the 0.10, 1-sided level and provide 81% power to detect an increase in respiratory failure-free survival at Day 28 from 70% to 91%. The study was initially designed to detect an increase in the respiratory failure-free survival rate from 70% to 95%.

Table 11: Power, Sample Size, and Type 1 Error for the Interim Analysis Plan

Parameter	Interim analysis	Final analysis
Total number of patients	42	63
p-value boundary for efficacy (reject the null)	0.044	0.087
p-value boundary for futility (reject the alternative)	0.15 favoring control	0.087
Cumulative power	0.53	0.807
Cumulative type 1 error (1-sided)	0.044	0.100
Cumulative probability of stopping for futility (alternative)	0.002	0.193
Cumulative probability of stopping for futility (null)	0.15	0.90

There is 81% power overall to detect the treatment benefit described above. There is a 53% chance that the study will stop at the interim analysis for efficacy. If the study drug is not effective, the study has a 15% chance to stop for futility at the interim analysis, where futility is defined as a p-value of 0.15 favoring control.

If the respiratory failure-free survival rate at Day 28 is ≤ 0.547 on zanubrutinib compared with 0.700 on control, then the study will be stopped for futility (per an approximation using the z-test).

In Amendment 4.0, time to breathing room air has been made a coprimary endpoint. From the first stage of the Adaptive Covid-19 trial (ACTT-1) which investigated the use of remdesivir, patients on oxygen who received remdesivir took a median of 7 days to recover. Assuming that the treatment effect of zanubrutinib corresponds to hazard ratio of 0.50 (the event is breathing room air), then 38 events will provide 80% power with a type 1 error of 0.10 one-sided. A hazard ratio of 0.57 will require 59 events for 80% power with a type 1 error of 0.10 one-sided.

10. STUDY COMMUNICATION

10.1. Provision of Study Results and Information to Investigators

When the clinical study report is completed, the sponsor will provide the major findings of the study to the investigator.

In addition, details of the study drug assignment will be provided to the investigator to enable him/her to review the data to determine the outcome of the study for his/her patient(s).

The sponsor will not routinely inform the investigator or patient of the test results, because the information generated from this study will be preliminary in nature, and the significance and scientific validity of the results would be undetermined at such an early stage of research.

11. INVESTIGATOR AND ADMINISTRATIVE REQUIREMENTS

11.1. Regulatory Authority Approval

The sponsor will obtain approval to conduct the study from the appropriate regulatory agency in accordance with any applicable country specific regulatory requirements or file the protocol to an appropriate regulatory agency before the study is initiated at a study center in that country.

11.2. Investigator Responsibilities

11.2.1. Good Clinical Practice

The investigator will ensure that this study is conducted in accordance with the principles of the "Declaration of Helsinki" International Council on Harmonisation guidelines and that the basic principles of "Good Clinical Practice," as adopted by and outlined in 21 Code of Federal Regulations 312, Subpart D, "Responsibilities of Sponsors and Investigators," 21 Code of Federal Regulations, Part 50, and 21 Code of Federal Regulations, Part 56, are adhered to.

11.2.2. Ethical Conduct of the Study and Ethics Approval

This study will be conducted by the investigator and the study center in accordance with GCP and all applicable regulatory requirements, including, where applicable, the current version of the Declaration of Helsinki.

The sponsor's sample ICF will be provided to each investigator who shall adapt it, subject to sponsor's approval, for use at his/her site. The investigator (or sponsor, where applicable) is responsible for ensuring that: 1) this protocol, 2) the study center's ICF, and 3) any other information or forms that will be presented to potential patients (eg, advertisements, Health Insurance Portability and Accountability Act of 1996 authorization, or information that supports or supplements the informed consent) are reviewed and approved by the appropriate Independent Ethics Committee/Institutional Review Board (IEC/IRB). The IEC/IRB must be constituted in accordance with all applicable regulatory requirements. The sponsor will provide the investigator with relevant document(s)/data that are needed for IEC/IRB review and approval of the study. Before the study drug(s) can be shipped to the study center, the sponsor or its authorized representative must receive copies of the IEC/IRB approval, the approved ICF, and any other information that the IEC/IRB has approved for presentation to potential patients.

11.2.2.1. Protocol Amendments

Protocol modifications, except those intended to reduce immediate risk to study patients, may be initiated only by BeiGene, Ltd. All protocol modifications must be submitted by the investigator (or sponsor, where applicable) to competent authorities according to local requirements and to the IRB/IEC together with, if applicable, a revised model ICF in accordance with local requirements. Written documentation from competent authorities (according to local requirements) and from the IRB/IEC and required site approval must be obtained – before changes can be implemented.

Information on any change in risk and/or change in scope must be provided to patients already actively participating in the study, and they must read, understand, and sign each revised ICF, confirming willingness to remain in the trial.

If the protocol, the ICF, or any other information that the IRB/IEC has approved for presentation to potential patients is amended during the study, the investigator (or sponsor, where applicable) is responsible for ensuring the IRB/IEC reviews and approves, where applicable, these amended documents. The investigator must follow all applicable regulatory requirements pertaining to the use of an amended ICF including obtaining IRB/IEC approval of the amended form before new patients can consent to take part in the study using this version of the form. Copies of the IRB/IEC approval of the amended ICF/other information and the approved amended ICF/other information must be forwarded to the sponsor promptly.

11.2.3. Informed Consent

The investigator is responsible for obtaining written informed consent from each individual participating in this study after an adequate explanation of the aims, methods, objectives, and potential hazards of the study and before undertaking any study-related procedures. The investigator must utilize an IRB/IEC-approved ICF for documenting written informed consent. Each ICF will be appropriately signed and dated by the patient or the patient's legally authorized representative and the person obtaining consent.

Informed consent must be obtained before the patient can participate in the study. Virtual consenting will be allowed per hospital policy. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

In the event that the ICF or other form signed by the patient is amended during their participation in the study, patients must be reconsented to the most current version of the ICFs or form. For any updated or revised ICFs or forms, the case history or clinical records for each patient shall document the informed consent process and that written informed consent was reobtained using the updated/revised ICFs for continued participation in the study.

A copy of each signed ICF must be provided to the patient or the patient's legally authorized representative. All signed and dated ICFs must remain in each patient's study file or in the site master study file and must be available for verification by study monitors at any time.

11.2.4. Investigator Reporting Requirements

As indicated in Section 8.4.1, the investigator (or sponsor, where applicable) is responsible for reporting SAEs to the IRB/IEC, in accordance with all applicable regulations. Furthermore, the investigator may be required to provide periodic safety updates on the conduct of the study at his/her study center and notification of study closure to the IRB/IEC. Such periodic safety updates and notifications are the responsibility of the investigator and not of the sponsor.

11.2.5. Confidentiality

The investigator and sponsor will maintain confidentiality and privacy standards by following applicable data privacy laws covering the collection, storage, transmission, and processing of patients' personal and medical information.

Patient medical information obtained during this study is confidential and may be disclosed only to third parties as permitted by the signed ICF (or a separate authorization for the use and disclosure of personal health information that has been signed by the patient), unless permitted or required by law.

In the event of a breach of the confidentiality of a patient's personal and medical information, the investigator and sponsor, as appropriate, shall fulfill all mediation steps and reporting obligations under applicable data privacy laws.

Information on maintaining patient confidentiality in accordance with individual local and national patient privacy regulations must be provided to each patient as part of the ICF process, either as part of the ICF or as a separate signed document (for example, in the United States, a site specific Health Insurance Portability and Accountability Act of 1996 consent may be used).

The investigator must assure that patients' anonymity will be strictly maintained and that their identities are protected from unauthorized parties. The investigator shall code the medical information obtained during the study with a unique patient identification number assigned to each patient enrolled in the study. This approach ensures that patients' identifiable information is not included in any data set transmitted to any sponsor location. Only date of independent central review and an identification code (ie, not names) should be recorded on any form or biological sample submitted to the sponsor, IRB, or laboratory. The investigator must keep a screening log showing codes, names, and addresses for all patients screened and for all patients enrolled in the trial.

The investigator agrees that all information received from the sponsor, its affiliates, or representatives, including but not limited to the IB, this protocol, eCRFs, the investigational drug, and any other study information, remain the sole and exclusive property of the sponsor during the conduct of the study and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the study or as required by law) without prior written consent from sponsor. The investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the study site to any third party or otherwise into the public domain.

If the written contract for the conduct of the study includes confidentiality provisions regarding sponsor's confidential information inconsistent with this section, that contract's provisions shall apply to the extent they are inconsistent with this section.

11.2.6. Data Collection

Data required by the protocol should be entered into the electronic data capture (EDC) system promptly, unless otherwise indicated in the written contract for the conduct of the study. Data collection in the CRF should follow the instructions described in the eCRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered in the eCRF. The investigator or designee as identified on Statement of Investigator Form must sign the completed casebooks to attest to its accuracy, authenticity, and completeness.

Data contained in the eCRFs are the sole property of sponsor and should not be made available in any form to third parties without prior written permission from sponsor, except for authorized representatives of BeiGene or appropriate regulatory authorities.

11.2.7. Data Management/Coding

All final patient data, both eCRF and external data (eg, laboratory data), collected according to the protocol, will be stored at sponsor at the end of the study.

Standard procedures (including following data review guidelines, computerized validation to produce queries, and maintenance of an audit file which includes all database modifications) will be followed to support accurate data collection. Data will be reviewed for outliers, logic, data inconsistencies, and completeness.

During the course of the study, a study monitor (clinical research associate) will make site visits to review protocol compliance, compare eCRFs against individual patient's medical records, and ensure that the study is being conducted according to pertinent regulatory requirements.

Electronic CRF entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained. Checking the eCRFs for completeness, clarity, and cross-checking with source documents is required to monitor the progress of the study. Direct access to source data is also required for inspections and audits and will be carried out giving due consideration to data protection and medical confidentiality.

Adverse events will be coded using the MedDRA. Concomitant medications will be coded using the WHO Drug Dictionary. Concomitant diseases/medical history will be coded using the MedDRA.

11.2.8. Drug Accountability

The investigator or designee (ie, pharmacist) is responsible for ensuring adequate accountability of all used and unused study drug. This includes acknowledgment of receipt of each shipment of study product (quantity and condition), patient drug dispensation records, and returned or destroyed study product. Dispensing records will document quantities received from sponsor, quantities dispensed to patients, and quantities destroyed or returned to sponsor, including lot number, date dispensed, patient identifier number, and the initials of the person dispensing the medication.

At study initiation, sites should have an appropriate standard operating procedure for study drug disposal/destruction. At the end of the study, after final drug inventory reconciliation by the monitor, the study site will dispose of and/or destroy all unused study drug supplies, including empty containers, according to these procedures and applicable law, including that regarding disposal of hazardous waste. If the site cannot meet BeiGene's requirements for disposal, arrangements will be made between the site and BeiGene or its representative for destruction or return of unused study drug supplies.

All drug supplies and associated documentation will be periodically reviewed and verified by the study monitor over the course of the study.

11.2.9. Inspections, Audits, and Monitoring Visits

The investigator must ensure the facilities used for this trial and all the source documents for this trial should be made available to appropriately qualified personnel from BeiGene or its representatives, to IRBs/IECs, or to regulatory authority or health authority inspectors.

11.2.10. Protocol Adherence

The investigator is responsible for ensuring that the study is conducted in strict accordance with the procedures and evaluations described in this protocol. Investigators assert that they will apply due diligence to avoid protocol deviations.

The investigator is to document and explain any deviations from the approved protocol. The investigator must promptly report any major deviations that might impact patient safety and/or data integrity to the sponsor and, if applicable, to the IRB/IEC, in accordance with established IRB/IEC policies and procedures.

11.2.11. Financial Disclosure

Investigators and Sub-investigators (as designated on the Form FDA1572) are required to provide the sponsor with sufficient, accurate financial information in accordance with regulations to allow the sponsor to submit complete disclosure or certification to the absence of certain financial interest of clinical investigators and/or disclose those financial interests, as required by the appropriate health authorities. This is intended to ensure financial interests and arrangements of clinical investigators with BeiGene that could affect reliability of data submitted to health authorities are identified and disclosed by the sponsor. Investigators and Sub-investigators are responsible for providing information about their financial interests before participation in the study, and to update this information if any relevant changes occur during the study and for 1 year after completion of the study (ie, last patient, last visit).

11.3. Study Report and Publications

A clinical study report will be prepared and provided to the regulatory agency(ies). Sponsor will ensure that the report meets the standards set out in the International Conference on Harmonisation Guideline for Structure and Content of Clinical Study Reports (International Conference on Harmonisation E3). Note that an abbreviated report may be prepared in certain cases.

The results of this study will be published or presented at scientific meetings in a timely, objective, and clinically meaningful manner that is consistent with good science, industry, and regulatory guidance, and the need to protect the intellectual property of BeiGene (sponsor), regardless of the outcome of the trial. The data generated in this clinical trial are the exclusive property of the sponsor and are confidential. As this is a multicenter study, the first publication or disclosure of study results shall be a complete, joint multicenter publication or disclosure coordinated by the sponsor. Thereafter, any secondary publications will reference the original publication(s). Authorship will be determined by mutual agreement, and all authors must meet the criteria for authorship established by the International Committee of Medical Journal Editors Uniform Requirements for Manuscripts or stricter local criteria (International Committee of Medical Journal Editors, 2019).

Each investigator agrees to submit all manuscripts, abstracts, posters, publications, and presentations (both oral and written) to the sponsor for review before submission or presentation in accordance with the clinical study agreement. This allows the sponsor to protect proprietary information, to provide comments based on information from other studies that may not yet be available to the investigator, and to ensure scientific and clinical accuracy. The details of the

processes of producing and reviewing reports, manuscripts, and presentations based on the data from this trial will be presented in the clinical study agreement. Each investigator agrees that, in accordance with the terms of the clinical study agreement, a further delay of the publication/presentation may be requested by the sponsor to allow for patent filings in advance of the publication/presentation.

11.4. Study and Study Center Closure

Upon completion of the study, the monitor will conduct the following activities in conjunction with the investigator or study center personnel, as appropriate:

- Return of all study data to the sponsor
- Resolve and close all data queries
- Accountability, reconciliation, and arrangements for unused study drug(s)
- Review of study records for completeness

In addition, the sponsor reserves the right to suspend or prematurely discontinue this study either at a single study center or at all study centers at any time for any reason; some reasons include, but are not limited to, safety or ethical issues or noncompliance with this protocol, GCP, sponsor written instructions, the clinical study agreement, or applicable laws and regulations. If the sponsor determines such action is needed, the sponsor will discuss this with the investigator (including the reasons for taking such action) at that time. When feasible, the sponsor will provide advance notification to the investigator of the impending action before it takes effect.

The sponsor will promptly inform all other investigators and/or institutions conducting the study if the study is suspended or terminated for safety reasons and will also inform the regulatory authorities of the suspension or termination of the study and the reason(s) for the action. If required by applicable regulations, the investigator must inform the IRB/IEC promptly and provide the reason for the suspension or termination.

If the study is prematurely discontinued, all study data must still be provided to the sponsor. In addition, arrangements will be made for all unused study drug(s) in accordance with the applicable sponsor procedures for the study.

Financial compensation to investigators and/or institutions will be in accordance with the clinical study agreement established between the investigator and/or institutions and the sponsor.

11.5. Records Retention and Study Files

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into at least the following 2 categories: (1) investigator's study file and (2) patient clinical source documents.

The investigator's study file will contain the protocol/amendments, eCRF and queries within the EDC System, IRB/IEC, and governmental approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, and other appropriate documents and correspondence.

Patient clinical source documents (usually defined by the project in advance to record key efficacy/safety parameters independent of the eCRFs) would include (although not be limited to) the following:

- Patient hospital/clinic records
- Physician's and nurse's notes
- Appointment book
- Original laboratory reports
- ECG
- Electroencephalogram
- Imaging assessments
- Pathology
- Special assessment reports
- Consultant letters
- Screening and enrollment log

After closure of the study, the investigator must maintain all study records in a safe and secure location. The records must be maintained to allow easy and timely retrieval when needed (eg, audit or inspection), and, whenever feasible, to allow any subsequent review of data in conjunction with assessment of the facility, supporting systems, and personnel. Where permitted by local laws/regulations or institutional policy, some or all of these records can be maintained in a format other than hard copy (eg, microfiche, scanned, electronic); however, caution needs to be exercised before such action is taken. The investigator must assure that all reproductions are legible, are a true and accurate copy of the original, and meet accessibility and retrieval standards, including re-generating a hard copy, if required. Furthermore, the investigator must ensure there is an acceptable back up of these reproductions and that an acceptable quality control process exists for making these reproductions.

The sponsor will inform the investigator of the time period for retaining these records to comply with all applicable regulatory requirements. The minimum retention time will meet the longer of the strictest standard applicable to that study center for the study, as dictated by local laws or regulations or the sponsor's standards/procedures; otherwise, or 15 years.

The investigator must notify the sponsor of any changes in the archival arrangements, including, but not limited to, the following: archival at an off-site facility, transfer of ownership of or responsibility for the records in the event the investigator leaves the study center.

If the investigator cannot guarantee this archiving requirement at the study site for any or all of the documents, special arrangements must be made between the investigator and BeiGene to store these in sealed containers outside of the site so that they can be returned sealed to the investigator in case of a regulatory audit. When source documents are required for the continued care of the patient, appropriate copies should be made for storage outside of the site.

Biological samples remaining after this study may be retained in storage by the sponsor for the shorter of a period of up to 20 years or as allowed by the IRB/IEC. A longer storage period may apply in the event that patients consent to BeiGene retaining remaining samples for future research.

11.6. Information Disclosure and Inventions

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) are the sole property of the sponsor.

All rights, title, and interests in any inventions, know-how or other intellectual or industrial property rights, whether or not patentable, which are conceived or reduced to practice by the study center personnel during the course of or because of the study are the sole property of the sponsor, and are hereby assigned to the sponsor.

If a written contract for the conduct of the study that includes ownership provisions inconsistent with this statement is executed between the sponsor and the study center and/or investigator, that contract's ownership provisions shall apply rather than this statement.

All information provided by the sponsor and all data and information generated by the study center as part of the study (other than a patient's medical records) will be kept confidential by the investigator and other study center personnel. This information and data will not be used by the investigator or other study center personnel for any purpose other than conducting the study and as allowed herein for publications and presentations.

These restrictions do not apply to the following:

- Information that becomes publicly available through no fault of the investigator or study center personnel
- Information that is necessary to disclose in confidence to an IRB/IEC solely for the evaluation of the study
- Information that is necessary to disclose to provide appropriate medical care to a patient
- Study results that may be published as described in Section 11.3.

If a written contract for the conduct of the study which includes provisions inconsistent with this Section 11.6 is executed, that contract's provisions shall apply rather than this statement.

11.7. Joint Investigator/Sponsor Responsibilities

11.7.1. Access to Information for Monitoring

In accordance with International Conference on Harmonisation GCP guidelines, the study monitor must have direct access to the investigator's source documentation to verify the data recorded in the eCRFs for consistency.

The monitor is responsible for routine review of the eCRFs at regular intervals throughout the study to verify adherence to the protocol and the completeness, consistency, and accuracy of the

data being entered on them. The monitor should have access to any patient records needed to verify the entries on the eCRFs. The investigator agrees to cooperate with the monitor to ensure that any problems detected or queries raised in the course of these monitoring visits are resolved.

11.7.2. Access to Information for Auditing or Inspections

Representatives of regulatory authorities or of sponsor may conduct inspections or audits any time during or after completion of this clinical study. If the investigator is notified of an inspection by a regulatory authority, the investigator agrees to notify the sponsor or its designee immediately. The investigator agrees to cooperate with representatives of a regulatory agency and sponsor and to provide them access to records, facilities, and personnel for the effective conduct of any inspection or audit.

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APPENDIX 1. SIGNATURE OF INVESTIGATOR

PROTOCOL TITLE: A Phase 2, Randomized, Double-Blind, Placebo-Controlled Study of Zanubrutinib Treatment in Patients Hospitalized for COVID-19 Infection and Pulmonary Distress

PROTOCOL NO: BGB-3111-219

This protocol is a confidential communication of BeiGene, Ltd. and its subsidiaries. I confirm that I have read this protocol, I understand it, and I will work according to this protocol and the terms of the clinical study agreement governing the study. I will also work consistently with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with good clinical practices and the applicable laws and regulations. Acceptance of this document constitutes my agreement that no unpublished information contained herein will be published or disclosed without prior written approval from BeiGene, Ltd. or one of its subsidiaries.

Instructions to the investigator: Please SIGN and DATE this signature page prior to implementation of this sponsor-approved protocol. PRINT your name, title, and the name of the center in which the study will be conducted.

I have read this protocol in its entirety and agree to conduct the study accordingly:

Signature of Investigator: _____ Date: _____

Printed Name: _____

Investigator Title: _____

Name/Address of Center: _____

_____

_____

_____

APPENDIX 2. NASOGASTRIC/FEEDING TUBE ADMINISTRATION FOR ZANUBRUTINIB

For patients who require nasogastric (NG) or feeding tube placement while on study, zanubrutinib/placebo may be administered by opening the capsules, mixing with the recommended dosing solution, and flushing the suspension down the NG or feeding tube. Additional guidance regarding preparation of zanubrutinib/placebo suspension is detailed in the Pharmacy Manual. The zanubrutinib/placebo capsule(s) should be gently squeezed/massaged to break cakes before opening the capsules. The zanubrutinib/placebo suspension should be drawn into a syringe and administered via the NG or feeding tube.

[redacted]

If your local site's practices are to formulate the zanubrutinib/placebo suspension within the Pharmacy, **please consider for all patients (regardless of Cohort or Arm assignment) retaining all study drug bottles at the Pharmacy for daily dispensation** in lieu of dispensing both bottles to the patient for self-administration.

APPENDIX 3. CYP3A INHIBITORS AND INDUCERS

Note: The list of drugs in this table is not exhaustive. Please refer to the prescribing information and Summary of Product Characteristics to check for CYP3A inhibition or induction risks or contact the medical monitor of the protocol.

Strong CYP3A Inhibitors
Antibiotics: clarithromycin, telithromycin, troleandomycin
Antifungals: itraconazole, ketoconazole, posaconazole, voriconazole
Antivirals: boceprevir, telaprevir
Other: cobicistat, conivaptan, elvitegravir, mibefradil, nefazodone, idelalisib
Protease inhibitors: indinavir, lopinavir, nelfinavir, ritonavir, saquinavir, tipranavir
Moderate CYP3A Inhibitors
CYP3A4, CYP3A5, CYP3A7
Antibiotics: ciprofloxacin, erythromycin
Antifungals: fluconazole, clotrimazole
Protease inhibitors: amprenavir, atazanavir, darunavir/ritonavir, fosamprenavir
Calcium channel blockers: diltiazem, verapamil
Tyrosine kinase inhibitors (anticancer): imatinib, crizotinib
Food products: grapefruit juice (*citrus paradisi* juice), Seville oranges
Herbal medications: Schisandra sphenanthera
Others: amiodarone, aprepitant, casopitant, cimetidine, cyclosporine, dronedarone, tofisopam
Strong/Moderate CYP3A Inducers
Avasimibe, carbamazepine, mitotane, phenobarbital, phenytoin, rifabutin, rifampin (rifampicin), St. John's wort (hypericum perforatum), enzalutamide, mitotane, bosentan, efavirenz, etravirine, modafinil

Abbreviations: CYP3A, cytochrome P450, family 3, subfamily A.
Source: Food and Drug Administration Drug Development and Drug Interactions: Table of Substrates, Drug Development and Drug Interactions and Inducers: https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers
For a more complete list, please refer to the Flockhart Table: http://medicine.iupui.edu/clinpharm/ddis/main-table

APPENDIX 4. GUIDANCE ON POSSIBLE DRUG INTERACTIONS FOR ZANUBRUTINIB AND MEDICATIONS THAT MAY BE IN USE TO TREAT COVID-19

Drug name	Interaction	Recommended study drug dose
Antivirals		
Atazanavir	Potent CYP450 3A4 Inhibitor	80 mg once daily
Cobistat	Potent CYP450 3A4 Inhibitor	80 mg once daily
Darunavir	Moderate CYP450 3A4 Inhibitor	160 mg once daily
Lopinavir/Ritonavir (Kaletra)	Potent CYP450 3A4 Inhibitor	80 mg once daily
Remdesivir	None	No dose adjustment necessary
Blood product		
Immune globulin-IV	None	No dose adjustment necessary
Statins		
Atorvastatin	None	No dose adjustment necessary
Pitavastatin	None	No dose adjustment necessary
Pravastatin	None	No dose adjustment necessary
Rosuvastatin	None	No dose adjustment necessary

Abbreviation: CYP450 3A, cytochrome P450, family 3, subfamily A.

APPENDIX 5. SCHEDULE OF ASSESSMENTS

	Baseline (Screening)	**Day 1 (Predose)**	**Treatment Period Days 1 to 28 Study Drug**	**End of Treatment (0 ± 3 days after the last dose)**	**Follow-up Visit (30 days ± 7 days after the last dose)**	**Follow-up Visit (56 days ± 7 days after the last dose)**
Informed consent	X					
Demographics	X					
Medical history including onset of COVID-19 symptoms	X					
Concurrent Medications[a]	X		X	X	X	X
Physical Exam including vitals[a]	X		Daily while in hospital; weight if feasible	X	X	X
O_2 saturation and documentation of supplemental O_2[a]	X		Daily while in hospital	X	As clinically indicated	As clinically indicated
CBC with differential[a,b]	X		Weekly and as clinically indicated	X	As clinically indicated	As clinically indicated
Serum Chemistries, BUN, Cr, LDH[a]	X		Weekly and as clinically indicated	X	As clinically indicated	As clinically indicated
PT/aPTT	X					
C-reactive protein, ferritin, D-dimer	X		X (Day 2, Day 7)			
Cardiac troponin	X		X (Day 2, Day 7)			
Viral RNA (SARS-CoV-2)	X					
[redacted]	X		[redacted]	[redacted]	[redacted]	

	Baseline (Screening)	Day 1 (Predose)	Treatment Period Days 1 to 28 Study Drug	End of Treatment (0 ± 3 days after the last dose)	Follow-up Visit (30 days ± 7 days after the last dose)	Follow-up Visit (56 days ± 7 days after the last dose)
[redacted]			X			
ECG[e]	X		X	As clinically indicated	As clinically indicated	As clinically indicated
β-HCG[f]	X		X	X		
Hepatitis serologies[g]	X					
Radiological evaluation[h]	X		As clinically indicated	As clinically indicated	As clinically indicated	As clinically indicated
Survival[a]	X		X	X	X	X
Adverse events related or possibly related to study drug[a]			X	X	X	X
Randomization		X				
Study drug dispensation		X				
Study drug administration[i]			X			

Abbreviations: aPTT, activated partial thromboplastin time; β-HCG, beta-human chorionic gonadotropin; BUN, blood urea nitrogen; CBC, complete blood count; Cr, creatinine; CT, computed tomography; ECG, electrocardiogram; EDTA, ethylenediamine tetra acetic acid; FT, feeding tube; HBcAb, hepatitis B core antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; LDH, lactate dehydrogenase; MTM, molecular transport medium; NG, nasogastric; PCR, polymerase chain reaction; PK, pharmacokinetic; PT, prothrombin time; SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.
Note: Screening procedures performed within 2 days before date of first dose need not be repeated on Day 1.

[a] A telehealth visit with coordinated diary collection and/or return of study drug at end of study is permitted if circumstances prevent a clinic visit. Laboratory draws and other studies that may be clinically indicated will be performed through outpatient laboratory or radiology services or other accessible facilities determined by the treating physician or study team unless it is not medically safe.

[b] Patients who develop marked and persistent lymphocytosis should have an analysis (ie, flow cytometry) to rule out an underlying hematologic malignancy disorder.

[c] Unless patient is unstable or blood draw is not possible, blood samples for serology (1 x 10 mL, red top) will be collected at screening, Day 2, Day 7, Day 28, and at the first follow-up visit. Additionally, if possible, blood samples for the following assessments will be collected at screening, Day 2, and Day 7: blood (1 x 10 mL) for the assessment of cytokines in EDTA tubes, blood (2 x 2.5 mL) for the NanoString transcriptome analysis, and blood (4 x 10 mL, heparin) for single cell RNA analysis (Section 5.8). Additionally, a swab will be collected on Day 1 in an MTM tube for the confirmation of SARS-CoV-2. For details for the correct procedures for collection, labelling and shipment of all samples, please refer to the study Laboratory Manual.

[d] [redacted]

[e] An ECG will be performed daily for Days 1 through 3, Day 7, and then weekly thereafter while the patient is hospitalized.

[f] β-HCG should be performed in all women of child-bearing potential at screening, Week 2, Week 4, and the End-of-Treatment Visit.

[g] Patients who are HBsAg negative, HBcAb positive, and HBV DNA negative must undergo at least monthly HBV DNA screening by PCR. If a patient is receiving prophylactic antiviral treatment, HBV DNA screening by PCR must be done at least every 90 days.

[h] Chest CT or radiographic studies will be performed at screening. A similar modality of study may be used for follow-up unless medical resources are limited.

[i] The first dose of study drug should be given ≤ 12 hours after randomization.

APPENDIX 6. SCHEDULE OF ASSESSMENTS - OUTPATIENT VISITS (DISCHARGE PRIOR TO DAY 28)

	Day 7 (± 1 day)	Day 14 (± 1 day) Day 21 (± 1 day)	End of Treatment (0 ± 3 days after the last dose)	Follow-up Visit (30 days ± 7 days after the last dose)	Follow-up Visit (56 days ± 7 days after the last dose)
Concurrent medications[a]	X	X	X	X	X
CBC with differential[a,b]	X	X	X	As clinically indicated	As clinically indicated
Serum chemistries, BUN, Cr, LDH[a]	X	X	X	As clinically indicated	As clinically indicated
C-reactive protein, ferritin, D-dimer[a]	X				
Cardiac troponin[a]	X				
[redacted]	[redacted]		[redacted]	[redacted]	
β-HCG[d]		X	X		
Radiological evaluation[a,e]	As clinically indicated	As clinically indicated	X	As clinically indicated	As clinically indicated
Survival[a]	X	X	X	X	X
Adverse events related or possibly related to study drug[a]	X	X	X	X	X
Study drug administration	Daily until Day 28 or until discontinuation for clinical benefit criteria are met (Section 6.5.2)				

Abbreviations: β-HCG, beta-human chorionic gonadotropin; BUN, blood urea nitrogen; CBC, complete blood count; Cr, creatinine; EDTA, ethylenediamine tetra acetic acid; LDH, lactate dehydrogenase.

Note: Unless otherwise specified the visit window for outpatient visits is ± 1 day of the nominal visit date.

[a] A telehealth visit with coordinated diary collection and/or return of study drug at end of study is permitted if circumstances prevent a clinic visit. Laboratory draws and other studies that may be clinically indicated will be performed through outpatient laboratory or radiology services or other accessible facilities determined by the treating physician or study team unless it is not medically safe.

[b] Patients who develop marked and persistent lymphocytosis should have an analysis (ie, flow cytometry) to rule out an underlying hematologic malignancy disorder.

[c] Unless patient is unstable or blood draw is not possible, blood samples for serology (1 x 10 mL, red top) will be collected on Day 7, Day 28, and at the first follow-up visit. Additionally, if possible, blood samples for the following assessments will be collected on Day 7: blood (1 x 10 mL) for the assessment of cytokines in EDTA tubes, blood (2 x 2.5 mL) for the NanoString transcriptome analysis, and blood (4 x 10 mL, heparin) for single cell RNA analysis (Section 5.8). For details for the correct procedures for collection, labelling and shipment of all samples, please refer to the study Laboratory Manual.

[d] β-HCG should be performed in all women of child-bearing potential at screening, Week 2, Week 4, and the End-of-Treatment Visit.

[e] Chest CT or radiographic studies will be performed at screening. A similar modality of study may be used for follow-up unless medical resources are limited.

APPENDIX 7. PROHIBITED HOST MODIFIERS/IMMUNE-BASED THERAPIES

Planned or concurrent use of the following host-based modifiers and immune-based therapies are prohibited during the study:

- Allogeneic HB-adMSCs (stem cell therapy)
- Anti-CCR5 (T-cell therapy)
- CD24Fc (checkpoint inhibitor)
- Colchicine
- Estrogen used as therapy to treat COVID-19
- FT516 (NK cell product)
- Anti-GM-CSF
- Hydroxychloroquine
  - Hydroxyquinone plus antibiotic (eg, azithromycin)
- INO-4800 (vaccine)
- Interferons (eg, interferon-α, interferon-β)
  - Peg-interferon-λ 1a
- Interleukin-1 inhibitors (eg, anakinra)
- Interleukin-6 inhibitors (eg, sarilumab, siltuximab, tocilizumab)
- Interleukin-8 inhibitors
- Jason kinase inhibitors (eg, baricitinib)
- Leflunomide
- Immunomodulation with naltrexone/ketamine
- Progesterone used as therapy to treat COVID-19
- Sirolimus
- Anti-TNF therapy
- Umbilical stem cell therapy
- Low dose whole body XRT

Adapted from: https://covid19treatmentguidelines.nih.gov/therapeutic-options-under-investigation/host-modifiers-immunotherapy/