CLINICAL STUDY PROTOCOL
TITLE PAGE

Protocol Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate Safety and Antiviral Activity of BLD-2660 in Hospitalized Subjects with Recently Diagnosed COVID-19 Compared to Standard of Care Treatment
Protocol Number:	B-2660-204
Study Drug:	BLD-2660
Study Indications	Coronavirus disease 2019 (COVID-19)
Study Phase:	2
Study Sites	Multiple US sites
Sponsor Name:	Blade Therapeutics, Inc.
Legal Registered Address:	442 Littlefield Avenue, South San Francisco, CA 94080, United States
Sponsor Representative:	Gary Patou, MD Chief Medical Officer
Regulatory Agency Identifier Number(s):	IND: 149130
Approval Date:	08 May 2020
Version:	3.0
Amendment	2.0

SPONSOR SIGNATORY

Gary Patou

5/8/2020

Gary Patou, MD
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Date

Sponsor's Designated Medical Monitor contact details will be provided separately in the study reference manual.

PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Protocol Title:	A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Antiviral Activity of BLD-2660 in Hospitalized Subjects with Recently Diagnosed COVID-19 Compared to Standard of Care Treatment
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Amendment No.	2.0
IND Number:	149130

I, the undersigned, have read this protocol and agree to personally supervise conduct of this protocol in accordance with ethical principles as outlined in the International Council for Harmonisation (ICH) guidelines on Good Clinical Practice, any applicable laws and requirements (including Part 54: Financial Disclosure by Clinical Investigators) and any additional conditions mandated by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I acknowledge that I am responsible for the overall study conduct; I approve of and will comply with all conditions, instructions and restrictions described in this protocol. I am aware that my adherence to the above protocol is mandatory and that any changes in the protocol or consent form, except those necessary to eliminate apparent immediate hazards to human subjects, must first be approved in writing by <company> and the respective IRB/IEC.

I also agree that all information provided to me by the Sponsor, including this document, Investigator's Brochure, case report form, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting the study. It is recognized that this information may be related in confidence to the IRB/IEC. I also understand that reports of information about the study or its progress will not be provided to anyone not involved in the study other than to the Principal Investigator, or in confidence to the IRB/IEC or to the FDA or other legally constituted authority.

Todd W. Rice — May 8, 2020

Principal Investigator Signature — Date

Todd W. Rice, MD, MSc — Vanderbilt University Medical Ctr Nashville, TN USA

Printed Name — Institution City, Country

PROTOCOL AMENDMENT SUMMARY OF CHANGES TABLE

DOCUMENT HISTORY	
Document	**Date**
Protocol V3.0, Amendment 2	08 May 2020
Protocol V2.0, Amendment 1	23April 2020
Original Protocol V1	05 April 2020

Amendment 2, 08 May 2020

Overall Rationale for the Amendment:

Blade has introduced the following modifications to protocol V3.0, these changes are presented in order of appearance:

Section # and Name	**Description of Change**	**Brief Rationale**
1.1 Synopsis 2.1 Study rationale	• Update rationale	• To reflect emerging data
1.1 Synopsis 3.0 Objectives and Endpoints	• Revise primary endpoints and add new co-primary endpoint (time to recovery) • Add an endpoint regarding remdesivir use • Move anti-viral endpoints to exploratory endpoints	• To reflect emerging data
1.2 Schedule of Activities	• Update per changes in the protocol • Add D-dimer assessment on Day 5	• To ensure accuracy and consistency
2.2 Background 2.3.2 Benefit	• Update text regarding approved EUA medications	• To reflect emerging data
5.1.1 Inclusion criteria	• Delete SARS-CoV-2 infection confirmation by PCR • Update oxygenation requirements to match remdesivir ($SpO_2 \leq 94\%$) • Temperature clarification	• To reflect emerging data and change in COVID treatment management • Typo correction
5.1.2 Exclusion criteria	• Correct exclusion criterion no. 5 to ≥ 0.75 FiO_2 • Delete exclusion of antiviral agents (e.g. remdesivir)	• Typo correction • To reflect change in COVID treatment management

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 4.1 Overall design 6.4 Measure to minimize bias: randomization and blinding	• Change stratification to remdesivir use at study entry	• To reflect change in COVID treatment management
6.6 Concomitant therapy	• Allow remdesivir as concomitant medication • Move anti-IL, IL-6 receptor antagonist or use of JAKi from restricted to prohibited medication during the study • Add EUA agent or compassionate use as restricted medication	• To reflect change in COVID treatment management • To reflect change in primary endpoint
8.1 Efficacy Assessments	• Reorganize subsections to match endpoint order.	• For consistency across the protocol
8.3 AEs and SAEs	• Add that SAEs will also be collected for remdesivir	• Per FDA request
9 Statistical consideration	• Update to reflect changes to objectives/endpoints	• For consistency across the protocol
General	• Corrected typos, formatting, style • Aligned changes across protocol • Updated Abbreviation (Appendix 6)	• For clarity and readability

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1. PROTOCOL SUMMARY

1.1. Synopsis

Protocol Title

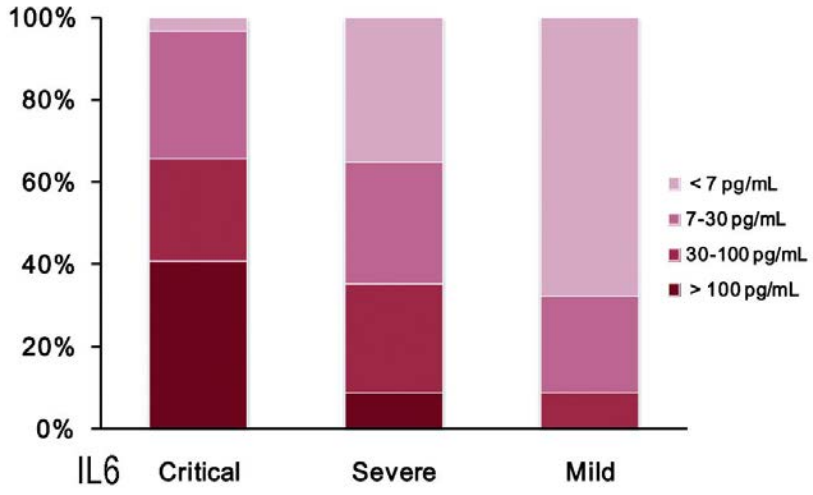
A Phase 2, Randomized, Double-blind, Placebo-controlled Study to Evaluate the Safety and Antiviral Activity of BLD-2660 in Hospitalized Subjects with Recently Diagnosed COVID-19 Compared to Standard of Care Treatment

Rationale

BLD-2660 is a novel, synthetic, orally active, small molecule inhibitor of calpain (CAPN) 1, 2, and 9 that is selective over the cathepsins as well as other protease families, displays good metabolic stability and permeability, oral bioavailability and low cytochrome P450 (CYP) inhibition. It is under development for the treatment of coronavirus disease-19 (COVID-19) resulting from infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), where there is significant unmet medical need.

Interleukin 6 (IL-6), a proinflammatory cytokine, is a key driver of a cytokine storm that plays a significant role in clinical complications and acute lung injury (Dinarello, 2000). Emerging data indicate that serum levels of IL-6 are elevated in COVID-19 patients and are predictive of respiratory failure (Coomes, 2020; Herold, 2020; McGonagle, 2020) and mortality (Gong, 2020) (Figure 1). IL-6 has been shown to contribute to lung damage during SARS-CoV infection and the virus itself is capable of directly inducing its expression (Bozym, 2011; Yoon, 2008). Suppression of pro-inflammatory IL-6 have been shown to have a therapeutic effect in many inflammatory diseases, including viral infections (Conti, 2020).

Figure 1 Comparison of IL-6 levels among mild, severe and critical patients with COVID-19 Pneumonia



Source: (Gong, 2020)

In a mouse model of lung injury employing bleomycin, BLD-2660, at therapeutic doses of 30 and 100 mg/kg twice per day (BID), reduced IL-6 levels in bronchoalveolar lavage (BAL) fluid (Figure 2). BLD-2660 also attenuated fibrosis damage as measured by significant reductions in the alpha smooth muscle actin and collagen 1 in lung tissue (Figure 3). BLD-2660 also demonstrated target engagement by inhibiting cleavage of one of its substrates, spectrin, in bronchoalveolar cells.

Figure 2 A Mouse Bleomycin (bleo) Pulmonary Fibrosis Model Assessing IL-6 in Bronchoalveolar Lavage (BAL) Fluid

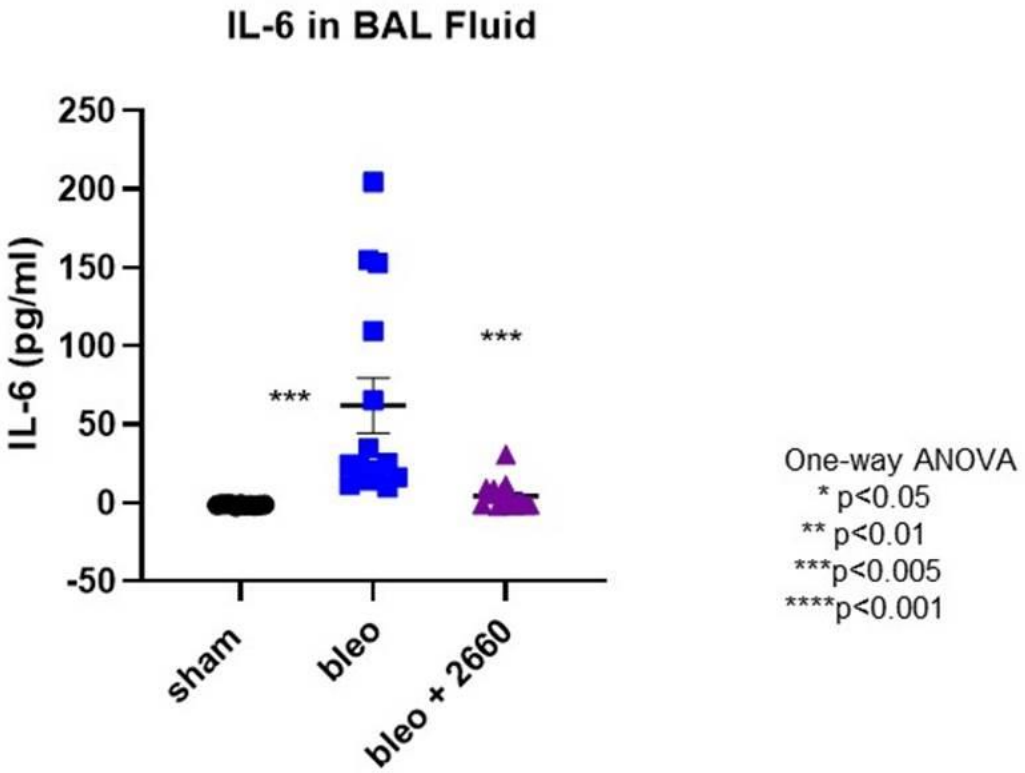
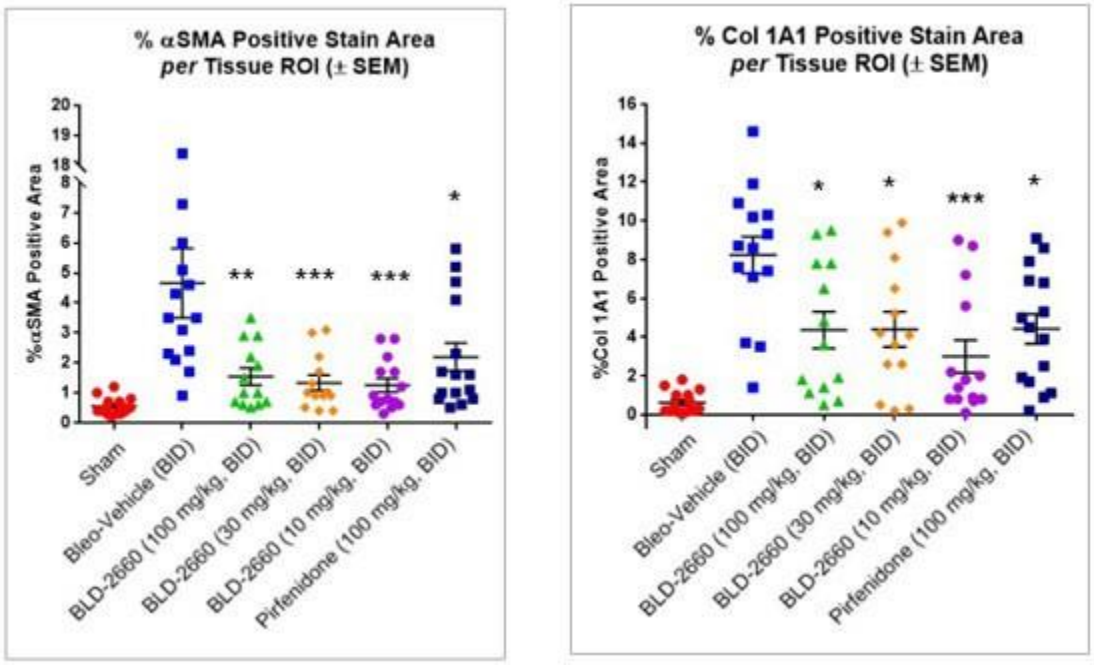


Figure 3: BLD-2660 Attenuates Fibrosis Damage in a Mouse Bleomycin (bleo) Pulmonary Fibrosis Model



One-way ANOVA
* p< 0.05
** p< 0.01
*** p< 0.005

BLD-2660 was also evaluated in a mouse model of NASH fibrosis, demonstrating an anti-fibrotic effect. A significant decrease in IL-6 transcription was also observed. This suggests that the effect of BLD-2660 on IL-6 is independent of the injury, or the affected organ.

It has been shown that the receptor for SARS-CoV-1 and -2 entry into the cell is angiotensin-converting enzyme 2 (ACE-2) (Kuba, 2010). ACE-2 and the dimeric calpains (data on file) are co-expressed in respiratory epithelial cells, the site of both viral entry and predominant early lung injury in COVID-19. Inhibition of dimeric calpain activity has not been associated with impairment of normal immune function. The safety and tolerability of BLD-2660 has been demonstrated in the recently completed Phase 1 single ascending dose (SAD)/multiple ascending dose (MAD) B-2660-101 study.

As BLD-2660 has been demonstrated to (1) reduce tissue IL-6 levels and (2) attenuate lung fibrosis damage, it could therefore, potentially reduce the nonproductive IL-6 mediated host-response to infection, which contribute to morbidity and mortality in COVID-19. In addition, data suggest that survivors of SARS-CoV-2 infection are at risk for chronic impairment of pulmonary function, likely attributable to pulmonary fibrosis secondary to lung injury and inflammation. Although there is not yet available data documenting numbers of patients infected with SARS CoV2 pneumonia who progress to pulmonary fibrosis, epidemiology, viral immunology, and current clinical evidence support that pulmonary fibrosis may become

one of the serious long-term complications of survivors of COVID-19 related pneumonia (Wang, 2020b).

Thus, BLD-2660 could not only potentially downregulate the nonproductive host-response to infection, which contributes to morbidity and mortality in COVID-19 but also could reduce potential long-term fibrosis and loss of pulmonary function resulting from SARS-CoV pneumonia (Wang, 2020a, Ong, 2005). This study will evaluate BLD-2660 as an add-on therapy to standard of care (SOC) in hospitalized subjects with recent diagnosis of COVID-19.

Objectives and Endpoints (Primary and Secondary)

Objectives	Endpoints
Primary	
• To evaluate clinical benefit of BLD-2660 in hospitalized adults with recently diagnosed SARS-CoV-2 infection	• Time to recovery as defined by no longer requiring oxygen support or hospital discharge, whichever occurs first
• To evaluate improvement in oxygenation in hospitalized adults with COVID-19 treated with BLD-2660	• Change from baseline to Day 10 or hospital discharge, if sooner, in the ratio of peripheral hemoglobin oxygen saturation to fraction of inspired oxygen (SpO_2/FiO_2)
Secondary	
• To evaluate the safety and tolerability of BLD-2660 in the same population	• Incidence of TEAEs and serious adverse events (SAEs)
• To evaluate improvement in oxygenation	• Improvement from baseline to Days 10, 14, 21 and 28 as measured by the ratio of hemoglobin oxygen saturation to inspired oxygen fraction (SpO_2/FiO_2), categorized on the 4--point ordinal scale (Table 4) • Time to discontinuation of oxygen supplementation requirement • Mean SpO_2 for subjects not requiring oxygen supplementation at Days 5, 10, 21 and 28 • Number of O_2 supplementation free days during hospitalization

Objectives	Endpoints
	• Proportion of subjects who do not require oxygen supplementation (sustained for at least 24 hours) during hospitalization *Note, criteria for removal of oxygen supplementation is defined as resting (5 minutes of rest) room air saturation >90%*
• Additional efficacy outcomes	• Mortality rate during the 28-day study period following enrollment • Time to hospital discharge readiness • Proportion of subjects ready to be discharged from the hospital during the 28-day study period following enrollment • Proportion of subjects with resolution of fever below entry criteria for 24 hours (as defined in Section 5.1.1) by Day 10 in subjects with fever at baseline • Time to resolution of fever below entry criteria for 24 hours (as defined in Section 5.1.1) in subjects with fever at baseline • Duration (in days) of remdesivir use in subjects starting remdesivir within 24 hours of first dose of BLD-2660 • Change from baseline to Days 10, 14, 21 and 28 in clinical status outcome using a 6-point ordinal scale (Section 8.1.3) • Proportion of subjects reporting each 6--point ordinal scale of the clinical status outcome assessment • Change from baseline to Days 5, 10, 14, 21 and 28 in NEWS score • Change from baseline to Days 10, 14, 21 and 28 in IL-6 and D-dimer

Overall Design

This is a Phase 2 randomized, double-blind, placebo-controlled multicenter study designed to evaluate BLD-2660 as add-on to standard of care (SOC) therapy in hospitalized subjects with recently diagnosed COVID-19 compared to SOC treatment.

The study will include a Screening period, a Treatment period, and a Follow-up period.

After signing informed consent form (ICF), potential candidates who are hospitalized for confirmed infection with SARS-CoV-2 will undergo additional screening procedures.

On Day 1, eligible subjects will be randomized in 2:1 ratio to one of 2 treatment groups, as shown in Table 1. Randomization will be stratified by remdesivir use at study entry. All subjects will receive study drug in combination with SOC over 10 days (through Day 10/end of treatment) or until hospital discharge, if sooner. Subjects will be followed for at least 18 days after the last dose of study drug on Days 14, 21 and 28. Subjects will be contacted 60 days post-study to collect information on mortality and forced vital capacity (FVC).

Subjects will be evaluated as specified in the Schedule of Activities (SoA; Section 1.2).

Number of Subjects, Intervention Groups and Duration

Intervention Groups

Table 1: Treatment Groups

Treatment Group	Dose Level, Schedule and Route of administration	Number of subjects
Active	BLD-2660 900 mg twice per day (BID), oral + SOC	80
Control	Matching placebo, BID, oral + SOC	40

Duration

For each subject the study is expected to last as follows:

Study Period	Duration
Screening period	Up to 3 days
Treatment period	10 days
Follow-up period	18 days
Post study follow-up	60 days

Data Monitoring Committee: Yes

1.2. Schedule of Activities (SoA)

Table 2: Schedule of Activities

General Notes:

- In case of natural disasters or pandemics, some visits/study procedures can be done via virtual visits (e.g., telemedicine or telephone) or at home visits after hospital discharge. Refer to study reference manual for more details.
- Assessments completed as part of standard of care within the protocol defined windows, will not need to be repeated specifically for the protocol.

Procedure	**Screening**	**Treatment Period**			**Follow-up**			**Post-study visit**	**Notes**
		BL	**Daily visits‡**	**EOT/ET***			**EOS**		Baseline (BL); End of Treatment (EOT), Early termination (ET); End of study (EOS) ‡ If a subject is discharged prior to Day 10, they will complete Day 5 and Day 10 visits assessments * This visit will be conducted at hospital discharge, if subject is discharged prior to Day 10
Study Day	**-3 to -1**	**1**	**2-9**	**10**	**14**	**21**	**28**	+60 days from EOS	
Visit window (days)				±1	±2	±2	±2	±10	
Informed consent	X								
Inclusion and exclusion criteria	X	X							
Demography	X								
Medical history	X								
Current medical conditions	X	X							Including time from onset of symptoms (fever, cough, etc.) to study entry, COVID-19 severity for each subject
Comprehensive physical exam	X			X					
Height and weight	X			X*					*Weight only

Procedure	Screening	Treatment Period			Follow-up			Post-study visit	Notes
		BL	Daily visits‡	EOT/ET*			EOS		Baseline (BL); End of Treatment (EOT), Early termination (ET); End of study (EOS) ‡ If a subject is discharged prior to Day 10, they will complete Day 5 and Day 10 visits assessments * This visit will be conducted at hospital discharge, if subject is discharged prior to Day 10
Study Day	**-3 to -1**	**1**	**2-9**	**10**	**14**	**21**	**28**	+60 days from EOS	
Visit window (days)				±1	±2	±2	±2	±10	
Limited physical exam		X	Day 5		X	X	X		Physical exam will be symptom-directed exam
Hematology	X	X	Day 5	X	X	X	X		Refer to Section 10.2
Clinical chemistries	X	X	Day 5	X	X	X	X		Refer to Section 10.2
INR	X						X		International normal ratio (INR)
Urinalysis	X						X		Refer to Section 10.2
Sputum samples and nasopharyngeal swab for SARS-CoV-2 PCR		X	Day 5	X	X	X	X		Samples to be frozen as specified in the laboratory manual for viral quantification.
Serum hsCRP and ferritin		X	Day 5	X	X	X	X		High sensitivity c-reactive protein (CRP)
Reserve blood sample for biomarker analyses		X	Day 5	X	X	X	X		Date and times to be recorded when samples were collected.
IL-6		X	X	X	X	X	X		Interleukin 6 (IL-6)
Serum troponin		X	X	X	X	X	X		
D-dimer		X	Day 5	X	X	X	X		
Pharmacokinetics plasma*			Day 5						Predose and 1-2 hours postdose *if naso-gastic tube (NGT) is inserted, PK samples will also be collected 2 hours postdose after the first NGT use.

Procedure	Screening	Treatment Period			Follow-up			Post-study visit	Notes
		BL	Daily visits‡	EOT/ET*			EOS		Baseline (BL); End of Treatment (EOT), Early termination (ET); End of study (EOS) ‡ If a subject is discharged prior to Day 10, they will complete Day 5 and Day 10 visits assessments * This visit will be conducted at hospital discharge, if subject is discharged prior to Day 10
Study Day	**-3 to -1**	**1**	**2-9**	**10**	**14**	**21**	**28**	+60 days from EOS	
Visit window (days)				±1	±2	±2	±2	±10	
Serum Pregnancy test (WOCBP only)	X								Women of childbearing potential (WOCBP)
12-lead ECG	X	X	Day 5	X			X		Electrocardiogram (ECG) Can be done more frequently if clinically indicated (e.g., elevated troponin post baseline level) per safety cardiac monitoring (Section 10.5)
	X								If subjects are on telemetry, ECG is only required at screening.
Vital signs	X	X	X	X	X	X	X		Temperature should be collected twice per day (morning and night) while hospitalized; same method for temperature measurement should be used throughout the study
Chest x-ray or CT scan of lungs (if conducted as SOC)	X						X		Computed tomography (CT), standard of care (SOC) Same modality to be used throughout the study, where possible

Procedure	Screening	Treatment Period			Follow-up			Post-study visit	Notes
		BL	Daily visits‡	EOT/ET*			EOS		Baseline (BL); End of Treatment (EOT), Early termination (ET); End of study (EOS) ‡ If a subject is discharged prior to Day 10, they will complete Day 5 and Day 10 visits assessments * This visit will be conducted at hospital discharge, if subject is discharged prior to Day 10
Study Day	**-3 to -1**	**1**	**2-9**	**10**	**14**	**21**	**28**	+60 days from EOS	
Visit window (days)				±1	±2	±2	±2	±10	
SpO_2%	X	X	X	X	X	X	X		Peripheral capillary oxygen saturation (SpO_2) is to be recorded morning and night while hospitalized (coinciding with body temperature)
Record FiO_2	X	X	X	X	X	X	X		Fraction of inspired oxygen (FiO_2) at each SpO_2 assessment (morning and night while hospitalized)
FVC							*	X*	Forced vital capacity (FVC) *Subjects will be requested to conduct FVC post study, approximately 50 to 70 days after last follow-up visit
APACHE II score		X							APACHE (acute physiology and chronic health evaluation)
Hospital discharge readiness assessment		X	X	X	X	X	X		Refer to Section 8.1.5
Clinical status 6-point ordinal scale	X	X	X	X	X	X	X		Refer to Section 8.1.2
State of consciousness	X	X	X	X	X	X	X		Level of consciousness: alert (A), arousable only to voice (V), or pain (P) and unresponsive (U)

Procedure	Screening	Treatment Period			Follow-up			Post-study visit	Notes
		BL	Daily visits‡	EOT/ET*			EOS		Baseline (BL); End of Treatment (EOT), Early termination (ET); End of study (EOS) ‡ If a subject is discharged prior to Day 10, they will complete Day 5 and Day 10 visits assessments * This visit will be conducted at hospital discharge, if subject is discharged prior to Day 10
Study Day	**-3 to -1**	**1**	**2-9**	**10**	**14**	**21**	**28**	+60 days from EOS	
Visit window (days)				±1	±2	±2	±2	±10	
Randomization		X							
Study drug administration		X	X	X					Treatment to be administered during hospitalization only
Study drug accountability			X	X					
AE and SAE review		X	X	X	X	X	X		Adverse event (AEs), Serious AE (SAEs)
Prior and concomitant medication	X	X	X	X	X	X	X		
Survival status					X	X	X	X	

2. INTRODUCTION

2.1. Study Rationale

BLD-2660 is a novel, synthetic, orally active, small molecule inhibitor of calpain (CAPN) 1, 2, and 9 that is selective over the cathepsins as well as other protease families, displays good metabolic stability and permeability, oral bioavailability and low cytochrome P450 (CYP) inhibition. It is under development for the treatment of coronavirus disease-19 (COVID-19) resulting from infection with Severe Acute Respiratory Syndrome Coronavirus 2 (SARSCoV2), where there is significant unmet medical need.

Interleukin 6 (IL-6), a proinflammatory cytokine, is a key driver of a cytokine storm that plays a significant role in clinical complications and acute lung injury (Dinarello, 2000). Emerging data indicate that serum levels of IL-6 are elevated in COVID-19 patients and are predictive of respiratory failure (Coomes, 2020; Herold, 2020; McGonagle, 2020) and mortality (Gong, 2020) (Figure 1). IL-6 has been shown to contribute to lung damage during SARS-CoV infection and the virus itself is capable of directly inducing its expression (Bozym, 2011; Yoon, 2008). Suppression of pro-inflammatory IL-6 have been shown to have a therapeutic effect in many inflammatory diseases, including viral infections (Conti, 2020).

In a mouse model of lung injury employing bleomycin, BLD-2660, at therapeutic doses of 30 and 100 mg/kg twice per day (BID), reduced IL-6 levels in bronchoalveolar lavage (BAL) fluid (Figure 2). BLD-2660 also attenuated fibrosis damage as measured by significant reductions in the alpha smooth muscle actin and collagen 1 in lung tissue (Figure 3). BLD-2660 also demonstrated target engagement by inhibiting cleavage of one of its substrates, spectrin, in bronchoalveolar cells.

BLD-2660 was also evaluated in a mouse model of NASH fibrosis, demonstrating an anti-fibrotic effect. A significant decrease in IL-6 transcription was also observed. This suggests that the effect of BLD-2660 on IL-6 is independent of the injury, or the affected organ.

It has been shown that the receptor for SARS-CoV-1 and -2 entry into the cell is angiotensin-converting enzyme 2 (ACE-2) (Kuba, 2010). ACE-2 and the dimeric calpains (data on file) are co-expressed in respiratory epithelial cells, the site of both viral entry and predominant early lung injury in COVID-19. Inhibition of dimeric calpain activity has not been associated with impairment of normal immune function. The safety and tolerability of BLD-2660 has been demonstrated in the recently completed Phase 1 single ascending dose (SAD)/multiple ascending dose (MAD) B2660-101 study.

As BLD-2660 has been demonstrated to (1) reduce tissue IL-6 levels and (2) attenuate lung fibrosis damage, it could therefore, potentially reduce the nonproductive IL-6 mediated host-response to infection, which contribute to morbidity and mortality in COVID-19. In addition, data suggest that survivors of SARS-CoV-2 infection are at risk for chronic impairment of pulmonary function, likely attributable to pulmonary fibrosis secondary to lung injury and inflammation. Although there is not yet available data documenting numbers of patients infected with SARS CoV2 pneumonia who progress to pulmonary fibrosis, epidemiology, viral

immunology, and current clinical evidence support that pulmonary fibrosis may become one of the serious long-term complications of survivors of COVID-19 related pneumonia (Wang, 2020b).

Thus, BLD-2660 could not only potentially downregulate the nonproductive host-response to infection, which contributes to morbidity and mortality in COVID-19 but also could reduce potential long-term fibrosis and loss of pulmonary function resulting from SARS-CoV pneumonia (Wang, 2020a, Ong, 2005). This study will evaluate BLD-2660 as an add-on therapy to standard of care (SOC) in hospitalized subjects with recent diagnosis of COVID-19.

2.2. Background

SARS-CoV-2, a positive-sense single-stranded RNA virus of zoonotic origin, is highly contagious in humans and is the cause of the ongoing worldwide pandemic of COVID-19. As of April 4, 2020, the SARS-CoV-2 has been responsible for more than 1.2 million infections and 70,000 deaths worldwide (data from https://coronavirus.jhu.edu/).

SARS-CoV-2 is transmitted via respiratory droplets (fomites infectious particles) within a range of about 2 meters and direct contact with contaminated surfaces. The median incubation period was estimated to be 4-5 days, and the majority (97.5%) developed symptoms within 11.5 days (CI, 8.2 to 15.6 days) of infection (Guan, 2020; Lauer, 2020). Higher viral loads are detected soon after symptom onset, with higher viral loads detected in the nose than in the throat (Zou, 2020). The mean viral load of severe cases was around 60 times higher than that of mild cases, suggesting that higher viral loads might be associated with severe clinical outcomes (Liu, 2020).

Clinical symptoms of COVID-19 include fever, cough, and dyspnea (Guan, 2020; Jiang, 2020; Rodriguez-Morales, 2020; Rothan, 2020); a small population of patients also may suffer from gastrointestinal symptoms (Guan, 2020; Guo, 2020). Radiologic features in the lungs include bilateral ground glass opacities on chest x-ray or computed tomography (CT) (Guan, 2020). COVID-19 appears to be more prevalent in males than females (Adhikari, 2020). The population most at risk are immune-compromised patients such as the elderly, and subjects with co-morbid diseases (e.g., diabetes, cardiovascular, cancer). This population is prone to serious outcomes, which may be associated with acute respiratory distress syndrome (ARDS) and cytokine storm (Adhikari, 2020; Guo, 2020). Approximately 14% (95%CI 6.2–21.5%) of hospitalized patients had fatal outcomes (case fatality rate, CFR) (Rodriguez-Morales, 2020).

Initially, the SARS-CoV-2 predominantly infects lower airways and binds to ACE-2 on alveolar epithelial cells (Guo, 2020; Kuba, 2010). It is a potent inducer of inflammatory cytokines. The "cytokine storm" or "cytokine cascade" is the postulated mechanism for organ damage. The virus activates immune cells and induces the secretion of inflammatory cytokines and chemokines into pulmonary vascular endothelial cells (Jiang, 2020).

The FDA has recently approved an emergency use authorization (EUA) for remdesivir to treat patients with severe COVID-19. There are no other approved treatments for COVID-19, or vaccines against SARS-CoV-2. Treatment management is mainly focused on symptomatic and respiratory support. There are few specific antiviral strategies, but several potent candidates of antivirals and repurposed drugs are under urgent investigation (Guo, 2020). Chloroquine phosphate, a drug for treatment of malaria, was shown to have apparent efficacy against COVID-

19 associated pneumonia in multicenter clinical trials conducted in China (Gao, 2020), however, these studies were not well controlled. A recent French study showed no benefit with hydroxychloroquine in hospitalized patients with COVID-19 infections requiring oxygen (Mahevas, 2020), and another retrospective study in US veterans hospitalized with COVID-19 showed that hydroxychloroquine increased mortality rate (Magagnoli, 2020). In addition, IL-6 or IL-6-receptor blocking antibodies like tocilizumab (Actemra, Roche-Genentech), sarilumab (Kevzara, Regeneron), and siltuximab (Sylvant, EUSA Pharma) which are FDA-approved for various conditions, including cytokine release syndrome (CRS), are being investigated in critically ill patients with COVID-19-induced hypoxia (Ascierto, 2020; Conti, 2020). Other treatments and therapies include antibiotics, corticosteroids, mechanical ventilation, extracorporeal membrane oxygenation (ECMO), oxygen therapy, and continuous renal replacement techniques (CRRT) (Jiang, 2020).

A detailed description of the chemistry, pharmacology, efficacy, and safety of BLD-2660 is provided in the Investigator's Brochure (IB).

2.3. Benefit/Risk Assessment

More detailed information about the known and expected benefits and risks and reasonably expected adverse events of BLD-2660 may be found in the IB.

2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Potential Risk for Study Drug BLD-2660	Mitigation Strategy
Elevated troponin	Transient, asymptomatic mild troponin elevation was observed in 2 healthy volunteers in Phase 1; there were no associated clinical, electrocardiographic or imaging findings and these changes resolved without sequalae despite continued dosing. Biologically, calpain inhibition has not been associated with cardiac toxicity in animal models, and there was no evidence of cardiac toxicity in acute and chronic toxicology studies.	Safety cardiac monitoring protocol (see Section 10.5)

2.3.2. Benefit Assessment

The FDA has recently approved an emergency use authorization (EUA) for remdesivir to treat patients with severe COVID-19. There are no other approved medical therapies for COVID-19. BLD-2660 is a candidate for treating COVID-19 due to the potential protection from lung damage which occurs during SARS-CoV-2 infection by reducing IL-6 levels.

2.3.3. Overall Benefit: Risk Conclusion

By implementing measures to minimize risk to subjects participating in this study, the potential risks identified in association with BLD-2660 are justified by the anticipated benefits that may be afforded to subjects with COVID-19.

3. OBJECTIVES AND ENDPOINTS

Objectives	Endpoints
Primary	
• To evaluate clinical benefit of BLD-2660 in hospitalized adults with recently diagnosed SARS-CoV-2 infection	• Time to recovery as defined by no longer requiring oxygen support or hospital discharge, whichever occurs first
• To evaluate improvement in oxygenation in hospitalized adults with COVID-19 treated with BLD-2660	• Change from baseline to Day 10 or hospital discharge, if sooner, in the ratio of peripheral hemoglobin oxygen saturation to fraction of inspired oxygen (SpO_2/FiO_2)
Secondary	
• To evaluate the safety and tolerability of BLD-2660 in the same population	• Incidence of TEAEs and serious adverse events (SAEs)
• To evaluate improvement in oxygenation	• Improvement from baseline to Days 10, 14, 21 and 28 as measured by the ratio of hemoglobin oxygen saturation to inspired oxygen fraction (SpO_2/FiO_2), categorized on the 4-point ordinal scale (Table 4) • Time to discontinuation of oxygen supplementation requirement • Mean SpO_2 for subjects not requiring oxygen supplementation at Days 5, 10, 21 and 28 • Number of O_2 supplementation free days during hospitalization • Proportion of subjects who do not require oxygen supplementation (sustained for at least 24 hours) during hospitalization *Note, criteria for removal of oxygen supplementation is defined as resting (5 minutes of rest) room air saturation >90%*

Objectives	Endpoints
• Additional efficacy outcomes	• Mortality rate during the 28-day study period following enrollment • Time to hospital discharge readiness • Proportion of subjects ready to be discharged from the hospital during the 28-day study period following enrollment • Proportion of subjects with resolution of fever below entry criteria for 24 hours (as defined in Section 5.1.1) by Day 10 in subjects with fever at baseline • Time to resolution of fever below entry criteria for 24 hours (as defined in Section 5.1.1) in subjects with fever at baseline • Duration (in days) of remdesivir use in subjects starting remdesivir within 24 hours of first dose of BLD-2660 • Change from baseline to Days 10, 14, 21 and 28 in clinical status outcome using a 6-point ordinal scale (Section 8.1.3) • Proportion of subjects reporting each 6-point ordinal scale of the clinical status outcome assessment • Change from baseline to Days 5, 10, 14, 21 and 28 in NEWS score • Change from baseline to Days 10, 14, 21 and 28 in IL-6 and D-dimer
Exploratory	
• Other efficacy outcomes	• Proportion of subjects who require mechanical ventilation after study entry • Number of ventilator-free days to Day 21 • Proportion of subjects with ICU transfer and/or ventilator dependence during the 28-day study period following enrollment

Objectives	Endpoints
	• The time to a NEWS of ≤ 2 and maintained for 24 hours • Change in NEWS from baseline to Days 3, 5, 8, 10, 14, 21 and 28 in NEWS
• To evaluate antiviral activity of BLD-2660 in the same population	• Proportion of subjects who are SARS--CoV-2 virus free by Day 10/EOT or hospital discharge, whichever is sooner • Time to eradication of SARS-CoV-2 • Change from baseline in SARS-CoV-2 viral load at Days 5, 10, 14, and 28
• Other safety outcomes	• Clinically relevant changes from baseline in electrocardiogram (ECG), and clinical laboratory values at each post baseline timepoint • Proportion of subjects with clinically significant drug-related troponin elevations that have repeat elevation upon confirmatory testing as adjudicated by the DMC while continuing on study drug during the 10-day treatment period
• To assess population pharmacokinetics (PK) characteristics of BLD-2660	• BLD-2660 plasma concentrations

4. STUDY DESIGN

4.1. Overall Design

This is a Phase 2 randomized, double-blind, placebo-controlled multicenter study designed to evaluate BLD-2660 as add-on to standard of care (SOC) therapy in hospitalized subjects with recently diagnosed COVID-19 compared to SOC treatment.

The study will include a Screening period, a Treatment period, and a Follow-up period.

After signing informed consent form (ICF), potential candidates who are hospitalized for confirmed infection with SARS-CoV-2 will undergo additional screening procedures.

On Day 1, eligible subjects will be randomized in 2:1 ratio to one of 2 treatment groups, active or control, as shown in Table 1. Randomization will be stratified by remdesivir at study entry. All subjects will receive study drug in combination with SOC over 10 days (through Day 10/end of treatment) or until hospital discharge, if sooner. Subjects will be followed for at least 18 days after the last dose of study drug on Days 14, 21 and 28. Subjects will be contacted 60 days post-study to collect information on mortality and forced vital capacity (FVC).

Subjects will be evaluated as specified in the Schedule of Activities (SoA; Section 1.2).

4.2. Scientific Rationale for Study Design

This Phase 2, randomized, double-blind, placebo-controlled study compares 2 treatment groups, active and control. The study drug will be administered as add-on therapy to SOC as currently there are no approved treatments for this potentially lethal disease.

4.3. Justification for Dose

The BLD-2660 dose selected for this study is 900 mg BID is based on nonclinical and clinical studies as follows:

- No maximum tolerated dose has been established due to saturation of absorption at doses above 900 mg. After a single 900 mg dose or 900 mg BID for 2 weeks, BLD-2660 was well-tolerated.
- A threshold plasma concentration ≥ 400 ng/mL was associated with efficacy in the mouse bleomycin model of idiopathic pulmonary fibrosis (IPF). Based upon the similarity of the IC_{50} of BLD-2660 in mice and humans (474 nM and 170 nM, respectively) and similar pharmacokinetics (PK) curves, the anticipated threshold exposure in humans for target engagement is likely to be similar to that seen in the mouse. The 900mg dose demonstrated plasma exposure (C_{max}) at or above the 400 ng/ml for up to 60 minutes on Day 1 and exposures were lower at Day 7 and 14.
- BID dosing is also proposed to maximize the time above the plasma concentration associated with efficacy in the animal models.
- The 900 mg BID dosing has a wide safety margin with respect to the no observed adverse effects level (NOAEL) doses administered in the rat and dog with a 10-fold

safety profile when comparing C_{max} and AUC values from the two chronic Good Laboratory Practice (GLP) repeated dose toxicology studies.

For additional details, refer to the Investigator Brochure.

4.4. Study Duration

For each subject the study is expected to last as follows:

Study Period	Duration
Screening period	Up to 3 days
Treatment period	10 days
Follow-up period	11 days
Post study follow-up	60 days

4.5. End of Study Definition

A subject is considered to have completed the study if he/she has completed all phases of the study including the last visit on Day 28. The end of the study is defined as the date of the last visit of the last subject in the study.

5. STUDY POPULATION

5.1. Eligibility Criteria

5.1.1. Inclusion Criteria

To be eligible for participation in this study, subjects must meet all the following:

Age

1. At least 18 years of age at the time of signing the ICF.

Type of Subject and Disease Characteristics

2. Hospitalized for COVID-19.
3. Diagnosed with COVID-19 as defined by having at least 2 of the following signs or symptoms within the past 2 days:
    a. Fever defined as a body temperature of ≥ 38.0 °C oral, or ≥ 38.3 °C rectal, ≥37.7 °C forehead or ≥38.7°C aural (axillary temperatures are not allowable);
    b. Cough;
    c. Fatigue;
    d. Shortness of breath.
4. Radiographic evidence (chest x-ray or CT scan) of one the following:
    a. Ground-glass opacities, or
    b. Local or bilateral patchy infiltrates, or
    c. Interstitial pulmonary infiltrates.
5. Oxygen requirements:
    a. $SpO_2 \leq 94\%$ on ambient air

    OR

    b. Requires supplemental oxygen administration by nasal cannula, simple face mask, or other similar oxygen delivery device.

Sex

6. Male and/or female subjects.

Contraception use by men or women should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies.

7. All subjects (male or female) who are of childbearing potential must agree to use highly effective contraception during the study. Female subjects and male partners of female subjects must continue to use highly effective contraception for 30 days after the last dose of study drug. Female subjects should not donate oocytes during this time. Male subjects and female partners of male subjects must continue to use highly effective contraception for 90 days. Male subjects must agree not to donate sperm during this time.

Note: Abstinence is acceptable if this is the usual lifestyle and preferred contraception for the subject.
Note: Ethinyl estradiol is the primary estrogen used in hormonal contraceptives. The progestin component consists of norethindrone, levonorgestrel, norgestrel, norethindrone acetate, ethynodiol diacetate, norgestimate, desogestrel, and drospirenone. As BLD-2660 is a weak CYP3A4 inducer, exposure to both the estrogen and progestin components in hormonal contraceptives may be decreased, resulting in an increased risk of pregnancy. As such, it is recommended that subjects who are on hormonal contraceptives for birth control should use an alternate means of contraception (condoms, diaphragms, intrauterine device (IUD), other barrier methods, sexual abstinence, etc.) during participation in the study.

8. Women of childbearing potential must have a negative serum pregnancy test at Screening within 72 hours prior to first administration of study drug.
9. Women not of childbearing potential must be postmenopausal (defined as cessation of regular menstrual periods for at least 1 year

Informed Consent

10. Capable of giving signed informed consent which includes compliance with the requirements and restrictions listed in the ICF and in this protocol.

5.1.2. Exclusion Criteria

Subjects will be excluded from study participation if they meet any of the following:

Medical Conditions

1. Active bacterial pneumonia infection
2. Known active tuberculosis (TB).
3. History of Child-Pugh B or C cirrhosis.
4. History of ischemic heart disease or myocardial infarction or acute coronary syndrome.
5. Subjects requiring supplemental oxygen ≥0.75 FiO_2.
6. It is not in the best interest of the subjects to participate, in the opinion of the treating Investigator.
7. Female subjects who are pregnant or breastfeeding or expecting to conceive within the projected duration of the study, starting with the screening visit through 90 days after the last dose of study drug.

Diagnostic Assessments

8. The following laboratory parameters are excluded:
    - Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5 x upper limit of normal (ULN);

- Creatinine clearance < 50 mL/min.

Prior Therapy (refer to Section 6.6 for allowed, prohibited and restricted therapy during the study)

9. Requiring, or expected to require mechanical ventilation at screening.
10. Treatment with chloroquine or hydroxychloroquine at study entry.
11. Treatment with anti-IL-6, anti-IL-6 receptor antagonists, or with Janus kinase inhibitors (JAKi) in the past 30 days or plans to receive during the study period.

Prior/Concurrent Clinical Study Experience

12. Participation in any other clinical study of an experimental drug treatment for COVID-19 within 6 half-lives of the experimental treatment.
13. Current participation or have participated in a study of an investigational agent or has used an investigational device within 4 weeks prior to the first dose of study drug.

Note: Subjects participating in an observational study are an exception to this criterion and may qualify for the study with Sponsor approval.

Note: Subjects who have entered the follow-up phase of an investigational study may participate as long as it has been 4 weeks after the last dose of the previous investigational agent.

Other Exclusions

14. Unable to swallow solid oral medication or known malabsorption disorder.
15. Subjects who have allergy to BLD-2660 or inactive components of BLD-2660.

5.2. Screen Failures

Screen failures are defined as subjects who consent to participate in the clinical study but are not subsequently randomized. A minimal set of screen failure information is required to ensure transparent reporting of screen failure subjects to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes screening number, demography, reason for screen failure and eligibility criteria.

Rescreening requests will be on a case-by-case basis and will require Medical Monitor approval.

6. STUDY DRUG

6.1. Study Drugs Administered

For more details on specific indications refer to the BLD-2660 Investigator Brochure (IB).

Table 3: Study Drug Administered

	Active	**Control**
Drug Name	BLD-2660	Placebo
Type	Drug (small molecule)	Drug
Dose Formulation	Capsules, Hard gelatin size '00'	Capsules, Hard gelatin size '00'
Unit Dose Strength(s)	150 mg	NA
Dosage Level(s)	900 mg BID (6 capsules BID) for a total of 1800 mg per day	NA
Route of Administration	Oral (PO); naso-gastric tube (NGT) may be used in special cases as detailed in Administration instruction below.	
Administration instruction	Study drug to be taken orally BID: • Morning dose to be taken at least one hour before food • Evening dose to be taken at least 2 hours after food In the case where a subject needs mechanical ventilation, study drug can be administered via an NGT by opening the study drug capsules and suspending the contents in the required amount of water as described in the Pharmacy Manual, then administering through the tube. Lavage with additional 20-30 mL of water to ensure study drug does not stick to the tubing. Do not attempt to administer through a feeding tube.	
Sourcing	Study drug will be provided to the site centrally by the Sponsor or designated representative.	
Packaging and Labeling	Drug product, both active and placebo, will be supplied in bulk packaging (40 capsules/bottle). Label text will at a minimum include the protocol number, lot number, storage conditions, and Sponsor name and address. Labels comply with regulatory requirements for study drugs.	

6.2. Standard of Care

In both study groups, subjects should receive appropriate supportive care measures as deemed necessary by the treating Investigator.

6.3. Preparation/Handling/Storage/Accountability

- Drug product will be shipped refrigerated at 2-8°C with a temperature monitor. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study drug received and any discrepancies are reported and resolved before use of the study drug.
- Only subjects enrolled in the study may receive study drug and only authorized site staff may supply or administer study drug. All study drugs must be stored in a secure, refrigerated (2-8°C), and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff.
- The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study drug accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records). Clinical supplies including study drug and inventory records must be made available upon inspection by Sponsor/FDA upon request. The site monitors will review the records along with other study records during monitoring visits.
- Further guidance and information for the final disposition of unused study drug is provided within the Pharmacy Manual.

6.4. Measures to Minimize Bias: Randomization and Blinding

All subjects will be centrally assigned to randomized study drug using an Interactive Response Technology (IRT). Before the study is initiated, the log in information & directions for the IRT will be provided to each site.

Randomization will be stratified by remdesivir use at study entry (yes/no)

Study drug will be dispensed by the unblinded pharmacy staff to the study staff/research nurse in a blinded manner per the schedule summarized in the SoA (Section 1.2).

The IRT will be programmed with blind-breaking instructions. Subject 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 contact the Sponsor prior to unblinding a subject's drug assignment unless this could delay emergency treatment of the subject. If a subject's drug assignment is unblinded, the Sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and case report form, as applicable.

6.5. Study Drug Compliance

Compliance with study drug will be assessed by the study staff by documenting that at all 6 capsules per dose are administered. Unused capsules that have been dispensed to the subject but not administered should be documented as such in the source documents and CRF. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

A record of the number of BLD-2660 capsules dispensed to and taken by each subject must be maintained and reconciled with study drug and compliance records. Drug start and stop dates, including dates for drug delays will also be recorded in the eCRF.

6.6. Concomitant Therapy

All medications including over -the -counter medications and herbal supplements taken during the 30 days prior to the first study drug administration will be recorded and reviewed by the Investigator (or designee) to determine whether the subject is eligible for inclusion.

Treatment with another study drug, investigational device, or approved therapy for investigational use within 30 days (or five half-lives, whichever is longer) before anticipated dosing is prohibited.

Allowed medications during the study:

- Remdesivir

Note, for subjects receiving remdesivir therapy, BLD-2660 is to be administered at least an hour before remdesivir administration**.**

6.6.1. Prohibited Medications and Herbal Supplements:

Below is a list of medications that are prohibited **during the study.**

- Anti-IL-6, IL-6 receptor antagonists, or JAKi

6.6.2. Restricted Medications

Restricted medications are defined as medications which should be avoided, if possible; however, **they are not necessarily prohibited during this study**. If such medications are required, consider switching to another medication in the class that is not restricted. If a restricted medication is required, seek approval of the Medical Monitor and use with caution per approved product label.

- FDA EUA or compassionate use agent(s) (to be discussed with Medical Monitor)
- Chloroquine, hydroxychloroquine, azithromycin (***Note: prior to prescribing these medications, must seek approval of the Sponsor's Medical Monitor***)
- HIV anti-viral drugs
- H2 blockers and antacids will be allowed as long as they are administered 2 hours before or after administration of study drug.

BLD-2660 as a Perpetrator

CYP3A4

The following are examples of some CYP3A4 substrates whose exposure could be reduced due to induction of that enzyme; however, it is not all inclusive and subjects should be monitored for adverse effects of these and CYP3A4 substrates in general.

- HMG CoA reductase inhibitors: atorvastatin, cervistatin, lovastatin, and simvastatin. *Note: Subjects taking the above statins can be switched to any of the following medications: pravastatin (Pravachol), rosuvastatin (Crestor), pitavastatin (Livalo), and fluvastatin (Lescol). If subject is unable to switch statin medications for any reason, the investigator to consult with Sponsor's Medical Monitor.*
- Benzodiazepines
- Immune modulators
- Cyclosporine
- Tacrolimus
- Calcium channel blockers
- Hormonal contraceptives (refer to Section 10.4.2)

CYP1A2

The following are examples of some CYP1A2 substrates whose exposure could be reduced due to induction of that enzyme; however, it is not all inclusive and subjects should be monitored for adverse effects of these and CYP1A2 substrates in general.

- Non-steroidal anti-inflammatory drugs (NSAIDs): Acetaminophen, phenacetin, naproxen
- Anticoagulants: Warfarin
- Antiemetics: Ondansetron
- Tricyclic antidepressants: Clomipramine, doxepin, imipramine
- Selective serotonin and norepinephrine reuptake inhibitors (SSNRIs): Duloxetine, fluvoxamine
- Antipsychotics: Olanzapine
- Bronchodilators: Theophylline
- Calcium channel blockers: Verapamil

CYP2B6

The following are examples of some CYP2B6 substrates whose exposure could be altered due to inhibition or induction of that enzyme; however, it is not all inclusive and subjects should be monitored for adverse effects of these and CYP2B6 substrates in general.

- Antidepressants: Bupropion, selegiline
- Anesthetics and analgesics: Ketamine, meperidine, propofol, tramadol

BLD-2660 as a Victim

BLD-2660 has been shown *in vitro* to be a substrate of CYP3A4. Consequently, drugs that inhibit or induce CYP3A4 have the potential to increase or decrease exposure to BLD-2660.

The following are examples of some CYP3A4 inhibitors; however, it is not all inclusive and subjects should be monitored for adverse effects when any CYP3A4 inhibitor is coadministered with BLD-2660.

- Azole antifungals: Fluconazole, itraconazole, ketoconazole
- Macrolide antibiotics: clarithromycin, erythromycin,
- Quinoline antibiotics: ciprofloxacin, norfloxacin
- Proton pump inhibitors: esomeprazole, omeprazole, pantoprazole
- Calcium channel blockers: Verapamil
- Others: Grapefruit juice, starfruit

The following are examples of some CYP3A4 inducers; however, it is not all inclusive and subjects should be monitored for adverse effects when any CYP3A4 inducer is coadministered with BLD-2660.

- Barbiturates
- Anticonvulsants: Carbamazepine, oxcarbazepine, phenytoin
- Rifabutin and rifampin
- Glucocorticoids
- St. John's Wort

Transporter Interactants

The following are examples of some P-glycoprotein inhibitors; however, it is not all inclusive and subjects should be monitored for adverse effects when any P-glycoprotein inhibitor is coadministered with BLD-2660.

- amiodarone, carvedilol, clarithromycin, dronedarone, itraconazole, lapatinib, lopinavir and ritonavir, propafenone, quinidine, ranolazine, ritonavir, saquinavir and ritonavir, telaprevir, tipranavir and ritonavir, verapamil

The following are examples of some breast cancer resistance protein (BCRP) inhibitors; however, it is not all inclusive and subjects should be monitored for adverse effects when any BCRP inhibitor is coadministered with BLD-2660.

- curcumin, cyclosporine A, elthrombopag

6.7. Dose Modification

Dose modifications are not planned in this study.

6.8. Treatment of Overdose

For this study, any dose of study drug greater than the prescribed daily dose will be considered an overdose. There is no specific treatment recommended to treat an overdose of study drug and the subject should receive treatment directed towards any symptoms manifested.

In the event of an overdose, the Investigator should:

1. Contact the Medical Monitor as soon as possible.
2. Closely monitor the subject for any AE/SAE and laboratory abnormalities.
3. Document the quantity of the excess dose as well as the duration of the overdose.

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the subject

6.9. Intervention after the End of the Study

No additional intervention is planned beyond the end of the study.

7. DISCONTINUATION OF STUDY DRUG AND SUBJECT DISCONTINUATION/WITHDRAWAL

7.1. Stopping Rules

Given severity of illness in COVID-19, there are no pre-specified stopping rules for this study as a whole. Instead there will be close oversight by the Sponsor and DMC reviews for safety as specified in Section 9.5.1.

7.1.1. Pregnancy

A subject must permanently discontinue study drug if she becomes pregnant. See Appendix 4 (Section 10.4) and Section 8.3.5 for additional details.

See the SoA (Section 1.2) for data to be collected at the time of study drug discontinuation and follow-up, and for any further evaluations that need to be completed.

7.2. Discontinuation of Study Drug

In some instances, it may be necessary for a subject to permanently discontinue study drug. Please also refer to stopping rules described in Section 7.1.

Permanent discontinuation of study drug does not mean withdrawal from the study, and the subject will be encouraged to remain in the study and continue to complete all study visits. See the SoA (Section 1.2) for data to be collected at the time of drug discontinuation and follow-up and for any further evaluations that need to be completed.

Subjects may discontinue or be discontinued from study drug at any time. A subject may discontinue study drug for reasons including but not limited to:

- Adverse event
- Death
- Lost to follow-up
- Non-compliance with study drug
- Physician decision
- Pregnancy
- Lack of efficacy
- Protocol deviation
- Study terminated by Sponsor
- Withdrawal by subject* (*only for discontinuing study drug, but will remain in study)

The reason for subject discontinuation from study drug will be recorded in the eCRF. At the time of treatment completion or study drug discontinuation, the EOT/ET visit should be completed as shown in the SoA (Section 1.2). Subjects should continue to be followed for safety even if they discontinue study drug prematurely unless they withdraw consent.

Pregnancy is a mandatory criterion for permanent discontinuation of study drug (see Section 7.1.1).

7.3. Withdrawal from the Study

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the Investigator or at the institution. A subject may withdraw from the study for reasons including but not limited to:

- Death
- Withdrawal by subject
- Lost to follow-up
- Study terminated by Sponsor

The reason for subject withdrawal from the study will be recorded in the eCRF.

At the time of withdrawal from the study, the end of study visit should be completed, as shown in the SoA (Section 1.2).

If the subject withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.

If a subject withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

7.4. Lost to Follow up

A subject will be considered lost to follow-up if he or she repeatedly fails to return to the study site or be contacted remotely for scheduled outpatient visits post hospital discharge.

The following actions must be taken if a subject fails to return to the clinic and/or be available for remote contact for a required study visit:

- The site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the subject (where possible, 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods). These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1.8).

8. STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA (Section 1.2). Protocol waivers or exemptions are not allowed.
- Immediate safety concerns should be discussed with the Sponsor immediately upon occurrence or awareness to determine if the subject should continue or discontinue study drug.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential subjects meet all eligibility criteria. The Investigator will maintain screening information including details of all subjects screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Missed visits should be avoided if at all possible; if a visit is missed and cannot be rescheduled, the subject should resume their original visit schedule at the next scheduled visit. In case of natural disasters or pandemics, some visits/study procedures can be done via virtual visits or at home visits when discharged. Refer to study reference manual for more details.

8.1. Efficacy Assessments

8.1.1. Oxygenation Measures

Peripheral capillary oxygen saturation (SpO_2) with pulse oximeter will be used as surrogate for arterial blood oxygen saturation. While hospitalized, the SpO_2 will be measured twice a day (morning and night). Measurement is to be done with the subject laying supine or with the head of the bed inclined, unless indicated otherwise; the same position should be used throughout the study and the subject's position will be captured in the eCRF. The FiO_2 at the time of each SpO_2 measurement (morning and night while hospitalized) must also be recorded in the eCRF.

Peripheral hemoglobin oxygen saturation to inspired oxygen fraction (SpO_2/FiO_2) will also be measured. Oxygenation will be assessed using the categories in Table 4.

Table 4: A 4-Point Oxygen Ordinal Scale for Severity Categories by SpO_2/FiO_2 Ratio

Score	Severity	SpO_2/FiO_2 (mmHg)
0	None	> 315
1	Mild	> 235 to 315
2	Moderate	> 150 to 235
3	Severe	≤ 150

8.1.2. Measure of Clinical Support

At each study day while hospitalized, the following measure of clinical support should be assessed:

- Oxygen requirement
- Non-invasive mechanical ventilation (via mask)
- Mechanical ventilator requirement (via endotracheal tube or tracheostomy tube) or Extracorporeal membrane oxygenation (ECMO) requirement
- Level of consciousness: alert vs. (arousable only to voice or pain or unresponsive)

In addition, date of hospital discharge readiness or date of hospital discharge (if different) will be collected.

8.1.3. Clinical Status Ordinal Score

Clinical status will be assessed using the 6-point ordinal score (Table 5). The ordinal scale is an assessment of the clinical status at the first assessment of a given study day. Each day, the worse score for the previous day will be recorded. i.e. on day 3, day 2 score is obtained and recorded as day 2. This scale has been used successfully as an endpoint for evaluation of treatments for severe influenza requiring hospitalization (Peterson, 2017).

Table 5: A 6-Point Ordinal Score for Assessing Clinical Status

Score	Description
1	Not hospitalized
2	Hospitalized, not requiring supplemental oxygen
3	Hospitalized, requiring supplemental oxygen
4	Hospitalized, on non-invasive ventilation or high flow oxygen devices
5	Hospitalized, on invasive mechanical ventilation or ECMO
6	Death

8.1.4. National Early Warning Score (NEWS)

The NEWS has demonstrated an ability to discriminate subjects at risk of poor outcomes. (Smith, 2016; Williams, 2019). This score is based on 7 clinical parameters, vital signs (respiratory rate, temperature, blood pressure, and heart rate), SpO_2, breathing room air or supplemental oxygen, and consciousness (Table 6). The NEWS is being used as an efficacy measure.

NEWS will be derived from other parameters to be collected during the study as specified in SoA (Section 1.2).

Table 6: NEW Score

PHYSIOLOGICAL PARAMETERS	3	2	1	0	1	2	3
Respiration Rate	≤8		9 - 11	12 - 20		21 - 24	≥25
Oxygen Saturations	≤91	92 - 93	94 - 95	≥96			
Any Supplemental Oxygen		Yes		No			
Temperature	≤35.0		35.1 - 36.0	36.1 - 38.0	38.1 - 39.0	≥39.1	
Systolic BP	≤90	91 - 100	101 - 110	111 - 219			≥220
Heart Rate	≤40		41 - 50	51 - 90	91 - 110	111 - 130	≥131
Level of Consciousness				A			V, P, or U

Level of consciousness: alert (A), arousable only to voice (V), or pain (P) and unresponsive (U)

8.1.5. Hospital Discharge Readiness Criteria

The subject's readiness for hospital discharge will be evaluated based on the following criteria (must meet all):

- Normal O_2 saturation on room air or a return to pre-morbid status
- Afebrile
- Able to ambulate (or use commode) without assistance or a return to pre-morbid mobility (for non-ambulatory subjects)
- Able to dress self or a return to pre-morbid status
- Eating pre-morbid full diet or a return to pre-morbid status

Date of actual hospital discharge and date of any readmission during the study period should be captured. Subjects' oxygen supplementation status at hospital discharge will also be captured (with vs. without oxygen supplementation).

8.1.6. Antiviral Activity

Quantitative viral load using nasopharyngeal swab/sputum SARS-CoV-2 PCR will be used to monitor disease status during the study. For more details refer to the laboratory manual.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the SoA (Section 1.2).

8.2.1. Physical Examinations

- Physical examinations will be performed by the principal investigator, a designated sub-investigator or a qualified hospital care staff member.
- A complete physical examination will include, at a minimum, assessments of the skin, cardiovascular system, respiratory system, abdomen (gastrointestinal, liver and spleen) and neurological system. Height and weight will also be measured and recorded.
- A symptom-directed physical examination will include, at a minimum, assessments of the skin, respiratory system, cardiovascular system, and abdomen (liver and spleen).

8.2.2. Vital Signs

- Blood pressure, heart rate, and respiratory rate will be measured after the subject has been resting for 5 minutes.
- Temperature will be recorded twice daily while hospitalized (morning and evening)
- Vital signs will be measured prior to any blood draw that occurs at the same timepoint

8.2.3. Electrocardiograms

12-lead ECG will be obtained while subject is in supine position using an ECG machine that automatically calculates the heart rate and measures PR, QRS, and QT (QTcF), intervals. Subject to be resting for at least 2 minutes prior to ECG.

8.2.4. Clinical Safety Laboratory Assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically significant adverse changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents.
- All laboratory tests with values considered clinically significantly during participation in the study or within 11 days after the last dose of study drug should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Sponsor's Medical Monitor/designee.
  - If such clinically significant values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified, and the Sponsor notified.

- All protocol-required laboratory assessments, as defined in Appendix 2, must be conducted in accordance with the laboratory manual and the SoA.
- If laboratory values from non-protocol specified laboratory assessments performed at the institution's local laboratory require a change in subject management or are considered clinically significant by the Investigator (e.g., SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and SAE can be found in Appendix 3 (Section 10.3).

All AEs will be reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of AE, SAE.

All AEs will be classified for severity using the common terminology criteria for AEs (CTCAE) V.5.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

Table 7 below summarizes the different reporting periods for AEs and SAEs.

Table 7: Adverse Event Reporting Periods

Type of Event	Adverse Event	Serious Adverse Event
Reporting period	From consent until Day 28 visit (at least 18 days after last dose of study drug).	From consent until Day 28 visit (at least 18 days after the last dose of study drug). SAEs will be recorded for study drug and for remdesivir.
Reporting Timelines to the Sponsor	Entered into the clinical database on an ongoing basis	Within 24 hours of site awareness

Medical occurrences that begin before the start of study drug but after obtaining informed consent will be recorded on the Adverse Events section of the case report form (CRF) and will be identified in the analysis as non-treatment-emergent adverse events (non-TEAEs).

All SAEs (for study drug and for remdesivir) will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours from site awareness, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a subject has been discharged from the study, and he/she considers the event to be related to the study drug or study participation, the Investigator must promptly notify the Sponsor or designee.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in Appendix 10.3.

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the subject is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the Investigator is required to proactively follow each subject at subsequent visits/contacts. All SAEs, will be followed until resolution, stabilization, the event is otherwise explained, or the subject is lost to follow-up (as defined in Section 7.4). Further information on follow-up procedures is provided in Appendix 10.3.

8.3.4. Regulatory Reporting Requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of a SAE is essential so that legal obligations and ethical responsibilities towards the safety of subjects and the safety of a study drug under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study drug under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- For all studies must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- An Investigator who receives an Investigator safety report describing a SAE or other specific safety information (e.g., summary or listing of SAEs) from the Sponsor will review and then file it along with the IB and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5. Pregnancy

- Details of all pregnancies in female subjects and of female partners of male subjects will be collected as outlined in Section 10.4 (Appendix 4).
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4.
- Abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6. Deaths

All deaths will be recorded in the eCRF. As deaths are always considered SAEs, they should be reported to the Sponsor within 24 hours of site awareness.

8.4. Pharmacokinetics

PK assessment of BLD-2660 will be analyzed using a population PK approach based upon sparse sampling to be obtain at designated timepoints as specified in the SoA (Section 1.2). Note, if NGT is inserted, PK samples will also be collected 2 hours postdose after the first NGT use.

- Instructions for the collection and handling of biological samples will be provided by the Sponsor. The actual date and time (24-hour clock time) of each sample will be recorded.
- Samples will be used to evaluate the PK of BLD-2660. Samples collected for analyses of BLD-2660 serum concentration may also be used to evaluate safety, efficacy and/or pharmacodynamic aspects related to concerns or questions arising during or after the study.
- Subject confidentiality will be maintained. At visits during which blood samples for the determination of PK, and PD related to BLD-2660 will be taken, 1 sample of sufficient volume can be used.
- Any changes in the timing or addition of time points for any planned study assessments must be documented and approved by the relevant study team member and then archived in the Sponsor and site study files but will not constitute a protocol amendment. The IRB/IEC will be informed of any safety issues that require alteration of the safety monitoring scheme or amendment of the ICF.

8.5. Pharmacodynamics and Biomarker Assessments

Blood samples will be collected and analyzed for biomarker analysis as specified in the SoA (Section 1.2) including IL-6 and D-dimers. Additional blood sample for future biomarker analyses will also be collected and stored.

The Sponsor or designee will supply complete written instructions for handling, processing, storage, and shipping of biomarker samples in the Laboratory Manual.

Samples may be stored for a maximum of 15 years after the last subject's last visit for the study, at a facility selected by the Sponsor, to enable further analysis of biomarker responses to BLD2660.

9. STATISTICAL CONSIDERATIONS

9.1. Statistical Hypothesis

Two primary hypotheses will be tested. The study will be declared a success if either of the hypotheses are statistically significant.

Hypothesis 1: Will evaluate clinical benefit in hospitalized adult subjects with recent SARS-CoV-2 infection. The primary endpoint is time to recovery as defined by no longer requiring oxygen support or hospital discharge, whichever occurs first. The null hypothesis is the hazard ratio is = 1 and the alternative hypothesis is the hazard ratio does not equal 1.

Hypothesis 2: Will evaluate improvement in oxygenation in hospitalized adult subjects with recent SARS-CoV-2 infection at the time of discharge, or Day 10, if they are still hospitalized. The primary endpoint is the change from baseline to Day 10 or hospital discharge if sooner in the ratio of hemoglobin oxygen saturation to inspired oxygen fraction (SpO_2/FiO_2). The null hypothesis is the mean treatment difference equals 0 and the alternative hypothesis is the mean treatment difference does not equal 0.

9.2. Sample Size Determination

Time to clinical improvement

A randomized, double-blind, placebo-control study evaluating remdesivir in 1063 hospitalized patients with COVID-19 reported 606 recoveries, with a median time to recovery of 11 days and 15 days in the remdesivir and placebo groups, respectively (remdesivir package insert). Recovery was defined as the first day on which the subject satisfies one of the following 3 categories from the ordinal scale: 1) Hospitalized, not requiring supplemental oxygen - no longer requires ongoing medical care; 2) Not hospitalized, limitation on activities and/or requiring home oxygen; 3) Not hospitalized, no limitations on activities (https://clinicaltrials.gov/ct2/show/NCT04280705).

Assuming the median time to clinical improvement, defined as no longer requiring oxygen support or hospital discharge whichever occurs first, will be 12-15 days in the placebo group, and that at least 75 of the planned 120 subjects enrolled meet the clinically improved criteria, the study will have at least 80% power to detect a 50% reduction in the time to clinical improvement, (i.e., hazard ratio of 0.5).

Change from baseline to Day 10 or hospital discharge if sooner in the ratio of hemoglobin oxygen saturation to inspired oxygen fraction (SpO_2/FiO_2).

A prospective observational cohort study of non-intubated moderate to severe ARDS patients (Ding, 2020) reported the partial pressure of oxygen (PaO_2)/FiO_2 ratio for 10 patients, which gave a mean and standard deviation of 147 ± 46 mm Hg. Converting to a $Sp0_2/FiO_2$ ratio gives a mean and standard deviation of 192 ± 39 using the equation reported by Rice et al. (2007) (Rice, 2007).

Assuming a standard deviation of 40 in the SpO_2/FiO_2 ratio, a sample size of 120 subjects (80 active, vs 40 control) will provide approximately 90% power to detect a treatment difference in

the SpO_2/FiO_2 ratio of 25 or greater, based on a two-sample t-test with a two-sided 5% significance level

9.3. Population Analysis Set

For purposes of analysis, the following populations are defined:

Population	Description
Full Analysis Set (FAS)	All randomized subjects who receive at least one dose of study drug. This population will be used for all efficacy analyses
Modified Intent to Treat (MITT)	All randomized subjects who receive at least one dose of study drug and one post baseline assessment of the SpO_2/FiO_2 ratio. This population will be used for the primary and secondary endpoints related to improvement in SpO_2/FiO_2 ratio.
Per Protocol Analysis Set	All randomized subjects who receive at least one dose of study drug without any major protocol violations that would impact the assessment of the primary efficacy endpoints. This population will be used for efficacy analyses of the primary efficacy endpoints
Safety Analysis Set	All enrolled subjects who receive any study drug
PK Analysis Set	All enrolled subjects who receive any study drug and have plasma concentration data

9.4. Statistical Methods

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan (SAP), which will be maintained by the Sponsor. The SAP may modify the plans outlined in the protocol; however, any major modifications will also be reflected in a protocol amendment. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1. General

In general, summary tabulations will be presented that display the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent (of non-missing values) per category for categorical data.

9.4.2. Efficacy Analyses

The primary efficacy endpoint of time to clinical improvement will be presented using the Kaplan-Meier estimator. Subjects will be censored at Day 28 or earlier, if they discontinue the study prior to observing the event. A Cox proportional hazards model with treatment, remdesivir use (yes/no) and age as covariates will be used to estimate the hazard ratio and compare treatment groups.

The primary efficacy endpoint of change from baseline to Day 10 or hospital discharge if sooner, in the ratio of hemoglobin oxygen saturation to inspired oxygen fraction (SpO_2/FiO_2) will be analyzed a mixed measures repeated model (MMRM). The Kenward-Roger method will be used to calculate the denominator degrees of freedom for the test of fixed effects and adjusted standard errors. The model will contain treatment, time and the treatment by time interaction as fixed effects and baseline score, age, and remdesivir drug use (yes vs no) as covariates. An unstructured covariance matrix will be assumed to model the within-participant errors.

Sub-group analyses for the two primary endpoints will also be conducted for the following sub-groups: Chloroquine or hydroxychloroquine use (yes vs no), HIV anti-viral drug use (yes vs no) and azithromycin use (yes vs no). If warranted, these effects may be included in the primary model.

No adjustment for multiplicity among the two primary endpoints will be made, as this is a Phase 2 study. Secondary endpoints will be analyzed without adjustment for multiplicity. All efficacy analyses will use the FAS analysis set, and MITT analysis set if applicable.

Secondary endpoints that are defined as time to event endpoints will be analyzed using survival analysis methods. Data will be presented using the Kaplan-Meier. Subjects will be censored at Day 28 or earlier, if they discontinue the study prior to observing the event. A Cox proportional hazards model with treatment, remdesivir use (yes/no), and age as covariates will be used to estimate the hazard ratio and compare treatment groups.

Secondary endpoints that are defined as proportions will be summarized using frequency counts and proportions. Treatment groups will be compared using a Cochran–Mantel–Haenszel (CMH) test stratified by remdesivir use (yes vs no). Additional covariates may be included if warranted.

Change from baseline in SARS-CoV-2 viral load at Day 10/EOT (or hospital discharge, whichever is sooner and end of study (Day 28) will be analyzed using an MMRM model.

The proportion of patients reporting each of the categories using the 6-point ordinal scale will be compared between treatment groups using the CMH test.

The change from baseline in the NEWS score will be summarized at each time point. A comparison between treatment groups will be made using an MMRM model.

The following secondary endpoints: number of O_2 supplementation free days, change from baseline in clinical status using 6-point ordinal scale (Table 5), and improvement (i.e., change) from baseline as measured by the ratio of hemoglobin oxygen saturation to inspired oxygen fraction (SpO_2/FiO_2) using the 4-point ordinal scale (Table 4) will be summarized using descriptive statistics and comparisons between treatment groups made using appropriate statistical methods.

The mean SpO_2 for subjects not requiring oxygen supplementation at Days 5, 10, 21 and 28 will be summarized using descriptive statistics.

9.4.3. Safety and Tolerability Analyses

All safety analyses will be performed on the Safety Analysis Set. AEs will be coded using the most current Medical Dictionary for Regulatory Activities (MedDRA®). The number of subjects

experiencing TEAEs) and number of individual TEAEs will be summarized by treatment, system organ class and preferred term. TEAEs will also be summarized by severity and by relationship to study drug. Serious TEAEs (SAEs) and TEAEs leading to discontinuation of study drug will be summarized by treatment, system organ class and preferred term.

Laboratory evaluations, vital signs assessments and ECG parameters will be summarized by treatment and protocol specified collection time point.

9.4.4. Other Analyses

BLD-2660 plasma concentrations will be summarized using descriptive statistics. Pharmacokinetic parameters will be estimated using a population PK approach.

Change from baseline in IL6 and D-dimer will be analyzed using a repeated measure mixed effects model. Missing data will be assumed to be missing at random. The model will include fixed effects for treatment group, and remdesivir use (yes vs no). Additional covariates may be included if warranted. Subjects will be treated as random, with an unstructured covariance structure. The least square (LS) means, and 95% confidence intervals within treatment and for the treatment difference will be reported at each timepoint.

9.5. Interim Analysis

Interim analyses are planned when approximately 25%, 50% and 75% of subjects have completed the study for the purpose of early stopping for efficacy or futility. The timing of these interim analyses may change based on the rate of recruitment. If recruitment is extremely quick these interim analyses may not be conducted.

The Lan-DeMets spending function analog of the O'Brien-Fleming boundaries will be used to monitor each of the primary endpoints as a guide for the DMC for an overall two-sided type-I error rate of 5%, for each endpoint.

Conditional power will be used as an additional guide to the DMC to assess futility. Conditional power allows computation of the probability of obtaining a statistically significant result by the end of the study given the data accumulated thus far. If the conditional power is less than 20% under the original study assumptions, consideration should be given to stopping the study.

At the interim analysis when approximately 50% of the subjects have completed the study, a sample size re-estimation step will occur using the promising zone approach and method of Chen, DeMets and Lan, based on the observed effect size at this interim analysis. The promising zone is defined as a conditional power of between 50% and 90%. If the conditional power falls into this region the sample size may be increased. Further statistical details surrounding the interim analysis, including the stopping boundaries, will be included in the statistical analysis plan.

The study will not stop enrolment awaiting these DMC reviews, though the DMC may recommend temporary or permanent cessation of enrolment based on their safety reviews.

A separate unblinded statistical team will prepare the above information for the DMC to review and make recommendations to the Sponsor.

9.5.1. Data Monitoring Committee

The DMC, a specific independent committee for the study with external representation, will meet when approximately 25%, 50% and 75% of subjects have been recruited and on an ad hoc basis to review safety results. The DMC may recommend stopping the study if at any time during the study there are unacceptable AEs or safety concerns. The members of the DMC will be listed in a separate DMC Charter, the governing document that will supersede this section of the protocol.

10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH Good Clinical Practice (GCP) Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (e.g., advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study subjects.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2. Financial Disclosure

Investigators and sub-investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3. Informed Consent Process

- The Investigator or his/her representative will explain the nature of the study to the subject or his/her legally authorized representative and answer all questions regarding the study.
- Subjects must be informed that their participation is voluntary. Subjects will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before any study-specific procedures were performed and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Subjects must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the signed ICF(s) must be provided to the subject or the subject's legally authorized representative.
- Subjects who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The investigator or authorized designee will explain to each subject the objectives of the exploratory research. Subjects will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a subject's agreement to allow any remaining specimens to be used for exploratory research. Subjects who decline to participate in this optional research will not provide this separate signature.

10.1.4. Data Protection

- Subjects will be assigned a unique identifier by the Sponsor. Any subject records or datasets that are transferred to the Sponsor will contain the identifier only; subject names or any information which would make the subject identifiable will not be transferred.
- The subject must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

10.1.5. Dissemination of Clinical Study Data

A clinical study report will be developed by the Sponsor at completion of data analysis. This report will be a clinical and statistical integrated report, according to the ICH E3 guidelines.

Sponsor will register the study and post study results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

10.1.6. Data Quality Assurance

- All subject data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (e.g., laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (e.g., risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in the Clinical Monitoring Plan. Due to the infectious nature of COVID-19, the Sponsor (or designees) will work with clinical sites to implement remote monitoring procedures with a focus on review and source data verification (SDV) of safety data.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (e.g., Contract Research Organizations).
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator per ICH-GCP and local regulations or institutional policies. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.7. Source Documents

- Source documents provide evidence for the existence of the subject and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical

and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

10.1.8. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of subjects.

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

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

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

- Failure of the Investigator to comply with the protocol, the requirements of the IRB/IEC or local health authorities, the Sponsor's procedures, or GCP guidelines
- Inadequate recruitment of subjects by the Investigator
- Discontinuation of further study drug development

If the study is prematurely terminated or suspended, the Sponsor shall promptly inform the Investigators, the IECs/IRBs, the regulatory authorities, and any contract research organization(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The Investigator shall promptly inform the subject and should assure appropriate subject therapy and/or follow-up.

10.1.9. Publication Policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2. Appendix 2: Clinical Laboratory Tests

- The clinical laboratory tests detailed in Table 8 will be performed by a local laboratory, except where specified below, at the timing/frequency detailed in the SoA.
- Protocol-specific requirements for inclusion or exclusion of subjects are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations
- Investigators must document their review of each laboratory safety report.

Table 8: Protocol-Required Laboratory Assessments

Hematology	
White blood cell count (WBC) with absolute differential (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils) Hemoglobin Platelet count	Red blood cell (RBC) with indices (mean corpuscular volume [MCV] and mean corpuscular hemoglobin [MCH]) Hematocrit
Clinical Chemistries	
Alanine aminotransferase (ALT) Alkaline phosphatase Total and direct bilirubin (fractionated) Albumin Calcium Sodium Glucose Chloride	Aspartate aminotransferase (AST) Gamma-glutamyl transferase (GGT) Blood urea nitrogen (BUN) L-lactate dehydrogenase (LDH) Creatinine Potassium Total protein Bicarbonate
Urinalysis	
Basic Urinalysis (dipstick, including macroscopic appearance, bilirubin, blood, color, glucose, ketones, leukocyte esterase, nitrite, pH, protein, specific gravity, urobilinogen)	
Other Laboratory Assessments	
• Troponin (serum) • IL-6 (to be analyzed at central laboratory) • D-dimer • Coagulation panel: International normalized ratio (INR) • Serum ferritin • Serum high sensitivity C-reactive protein (hsCRP) • Serum pregnancy test • SARS-COV-2 (COVID-19) test (RT-PCR via nasopharyngeal swab)	

10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition

- An AE is any untoward medical occurrence in a patient or clinical study subject, temporally associated with the use of study drug, whether or not considered related to the study drug.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study drug.

Events Meeting the AE Definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (e.g., ECG, radiological scans, vital signs measurements), including those that worsen from baseline (see bullet below), considered clinically significant in the medical and scientific judgment of the Investigator (i.e., not related to progression of underlying disease).
- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- 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 drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

Events NOT Meeting the AE Definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the subject's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition.

- Medical or surgical procedure (e.g., endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

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

A SAE is defined as any untoward medical occurrence that, at any dose:
Results in death
Is life-threatening The term 'life-threatening' in the definition of 'serious' refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death, if it were more severe.
Requires inpatient hospitalization or prolongation of existing hospitalization • In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious. • Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.
Results in persistent disability/incapacity • The term disability means a substantial disruption of a person's ability to conduct normal life functions. • This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.
Is a congenital anomaly/birth defect

Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical drug to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

10.3.3. Recording and Follow-Up of AE and/or SAE

AE and SAE Recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (e.g., hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the Investigator to send photocopies of the subject's medical records to the Sponsor or designee in lieu of completion of the AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or designee. In this case, all subject identifiers, with the exception of the subject number, will be redacted on the copies of the medical records before submission to the Sponsor or designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Severity

AE severity will be evaluated by the Investigator in accordance with the NCI CTCAE v5. 0 [1]. For AEs that are not adequately addressed in the NCI CTCAE, the Investigator should classify the intensity of the AE using the following guidelines:

Grade 1: Mild: Aware of sign or symptom, but easily tolerated; no intervention needed

Grade 2: Moderate: Discomfort enough to cause interference with usual activity, minimal non-invasive intervention indicated (e.g., short course of antibiotics)

Grade 3: Severe: Medically significant but not immediately life-threatening; incapacitation with inability to work or do usual activity

Grade 4: Life-threatening: Refers to an event in which the subject was at risk of death at the time of the event, as judged by the Investigator; urgent/emergent drug indicated. This category should not be used for an event that hypothetically might have caused death if it were more severe.

Grade 5: Fatal outcome.

An event is defined as 'serious' when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention (investigational drug and/or study procedures) each occurrence of each AE/SAE according to the categories below.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.
- The investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.

[1] Please refer to the CTCAE v5 at: https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.
Accessed April 19, 2019

- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality in terms of whether the AE/SAE may be related to study intervention and/or study procedures.
- There may be situations in which 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 always assess causality for every event before the initial transmission of the SAE data to the Sponsor**
- The investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Causality Categories:

Related: The AE follows a reasonable temporal sequence from the time of study drug administration and/or follows a known response to the study drug and cannot be reasonably explained by other factors such as the subject's clinical state or other therapeutic interventions, or concomitant drugs administered to the subject.

Not related: The AE is clearly related to other factors such as the subject's clinical state, therapeutic interventions or concomitant drugs administered to the subject. There is no temporal relationship between the study drug and event onset. This is especially so when an event occurs prior to the commencement of treatment with the study drug.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a subject dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor with a copy of any postmortem findings including histopathology, if available.
- New or updated information will be recorded in the originally completed CRF.
- The Investigator will submit any updated SAE data to the Sponsor or designee within 24 hours of receipt of the information.

10.3.4. Reporting of SAEs

SAE Reporting to Medical Monitor via an Electronic Data Collection Tool
• The primary mechanism for initial reporting of an SAE to Sponsor or designee will be the electronic case report form (eCRF). • If the eCRF is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours. • The site will enter the SAE data into the eCRF as soon as it becomes available. • After the study is completed at a given site, the eCRF will be taken off-line to prevent the entry of new data or changes to existing data. • If a site receives a report of a new SAE from a study subject or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Medical Monitor by telephone. • Contacts for SAE reporting can be found in the relevant site manual.

10.4. Appendix 4: Contraceptive Guidance and Collection of Pregnancy Information

10.4.1. Definitions

Woman of Childbearing Potential (WOCBP)

A woman is considered fertile following menarche and until becoming post-menopausal unless permanently sterile (see below).

If fertility is unclear (e.g., amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study drug, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

For individuals with permanent infertility due to a medical cause other than the above, (e.g., Mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

Note: Documentation can come from the site personnel's review of the subject's medical records, medical examination, or medical history interview.

Postmenopausal female

- A postmenopausal state is defined as having had no menses for 1 year without an alternative medical cause.
  - A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy (HRT). However, in the absence of 1 year of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the non-estrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

10.4.2. Contraception Guidance

Male Subjects:

Male subjects are eligible to participate if they agree to the following from informed consent, during the treatment period and for 90 days after the last dose of study drug:

- Refrain from donating sperm

PLUS, either**:**

- Be abstinent from heterosexual intercourse as their preferred and usual lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent

OR

- Must agree to use contraception/barrier as detailed below
  - Agree to use a male condom

Female Subjects:

- A female subject is eligible to participate if she is not pregnant or breastfeeding, and at least one of the following conditions applies:
  - Is not a woman of childbearing potential (WOCBP)

OR

  - Is a WOCBP and using a contraceptive method that is highly effective (with a failure rate of < 1% per year), preferably with low user dependency (see table below), at least 28 days prior to Screening, during the intervention period, and for 30 days after the last dose of study drug, and agrees not to donate eggs (ova, oocytes) for the purpose of reproduction during this period. The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study drug.
  - A WOCBP must have negative serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of human chorionic gonadotropin [HCG]) within 72 hours prior to receiving the first administration of study drug.
  - If a urine test cannot be confirmed as negative (e.g., an ambiguous result), a serum pregnancy test is required, and results must be negative. In such cases, the subject must be excluded from participation if the serum pregnancy result is positive.

Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for those participating in clinical studies.

Note: Ethinyl estradiol is the primary estrogen used in hormonal contraceptives. The progestin component consists of norethindrone, levonorgestrel, norgestrel, norethindrone acetate, ethynodiol diacetate, norgestimate, desogestrel, and drospirenone. As BLD-2660 is a weak CYP3A4 inducer, exposure to both the estrogen and progestin components in hormonal contraceptives may be decreased, resulting in an increased risk of pregnancy. As such, it is recommended that subjects who are on hormonal contraceptives for birth control should use an

alternate means of contraception (condoms, diaphragms, IUD, other barrier methods, sexual abstinence, etc.) during participation in the study.

10.4.3. Collection of Pregnancy Information

- In the event of a pregnancy, the female subject or partner of a male study subject should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.
- The Investigator will follow the female subject or partner of a male study subject until completion of the pregnancy
- The Investigator must notify the Sponsor's Medical Monitor of the outcome within 5 days.
- The Investigator will provide this information as a follow-up to the initial report.
- If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (e.g., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), then the Investigator should report it as such.
- All neonatal deaths that occur within 30 days of birth are to be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the in-utero exposure to the study drug should also be reported.

10.5. Appendix 5: Cardiac Monitoring Protocol

All troponin elevations and cardiac AEs and SAEs will be reviewed by the DMC.

Subjects with elevated troponins will be questioned regarding occurrence of any cardiac symptoms. The symptoms will be evaluated by a study investigator and a consulting physician independent of the investigator team who will recommend whether any additional studies should be performed. In addition, during the evaluation period:

1. Study drug could be withheld, at the discretion of the investigator
2. Serum troponin, Creatine Kinase-Myocardial Band (CK-MB), myoglobin, comprehensive metabolic panel (including AST) will be obtained and echocardiogram and ECG performed and interpreted
3. Detailed history of potential causes of troponin elevation should be obtained
4. Additional work up will be initiated per the Investigator's discretion and cardiology consultant

If work up is negative, as determined by Investigator and/or Medical Monitor, no further action is required and, if the study drug had been stopped, it may be restarted.

If work up is positive for a cardiac source, the DMC will review and determine whether the study drug should be permanently discontinued and advise on any next steps, if any.

10.6. Appendix 6: Abbreviations

Abbreviation Term	Description
ACE-2	Angiotensin-converting enzyme 2
AE	Adverse event
ALT	Alanine aminotransferase
APACHE	Acute physiology and chronic health evaluation
ARDS	Acute respiratory distress syndrome
AST	Aspartate aminotransferase
BCRP	Breast cancer resistance protein
BID	Twice per day
BUN	Blood urea nitrogen
CAPN	Small molecule inhibitor of calpain
CFR	Case fatality rate
CIOMS	Council for International Organizations of Medical Sciences
CMH	Cochran–Mantel–Haenszel
COVID-19	Coronavirus disease 2019
CRP	C-reactive protein
CRRT	Continuous rental replacement technique
CRS	Cytokine release syndrome
CT	Computed tomography
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome P450
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
eCRF	Electronic case report form
EOS	End of Study
EOT	End of Treatment
ET	Early termination
EUA	Emergency use authorization
FAS	Full analysis set

Abbreviation Term	Description
FiO_2	Fraction of inspired oxygen
FVC	Forced vital capacity
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
HC	Hormonal contraceptives
Hgb	Hemoglobin
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
hsCRP	high sensitivity C-reactive protein
IB	Investigator's brochure
ICF	Informed consent form
IEC	Independent Ethics Committees
INR	International normalized ratio
IPF	Idiopathic pulmonary fibrosis
IRT	Interactive Response Technology
ITT	Intent-treat Set
IUD	Intrauterine device
JAKi	Janus kinase inhibitor
LAM	Lactational amenorrhoea method
LDH	Lactate dehydrogenase
LS	Least square
MAD	Multiple ascending dose
MedDRA	Medical Dictionary for Regulatory Activities
MITT	Modified intent-to-treat sect
MMRM	Mixed measures repeated model
NEWS	National Early Warning Score
NGT	Naso-gastric tube
NOAEL	No observed adverse effects level

Abbreviation Term	Description
NSAID	Non-steroidal anti-inflammatory drug
PaO_2	Partial pressure of oxygen
PCR	Polymerase chain reaction
PK	Pharmacokinetics
PO	Oral
PP	Per protocol
PPAR	peroxisome proliferator-activated receptor
RBC	Red blood cell
SAD	Single ascending dose
SAE	Serious adverse events
SAP	Statistical analysis plan
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
siRNA	Small interfering RNA
SoA	Schedule of Activities
SOC	Standard of care
SpO_2	Peripheral capillary oxygen saturation
SSNRI	Selective serotonin and norepinephrine reuptake inhibitor
SUSAR	Suspected unexpected serious adverse reactions
TB	Tuberculosis
TEAE	Treatment emergent adverse event
ULN	Upper limit of normal
WBC	White blood cell count
WOCBP	Women of childbearing potential

10.7. Appendix 7: Protocol Amendment History

Prior Amendments

Blade has introduced the following modifications to Protocol Version 2.0. These changes are presented in order of appearance:

Amendment 1, 23 April 2020

Overall Rationale for the Amendment:

Section # and Name	Description of Change	Brief Rationale
1.1 Synopsis 3.0 Objectives and endpoints	• Reorganize objectives and endpoints • For oxygenation endpoints, added definition for medically fit for removal of oxygen • Changed mortality rate to be a secondary endpoint • Added Day 28 to relevant endpoints	• Per FDA request
1.1 Synopsis 1.2 Schedule of Activities 4.0 Study Design 8.3.1 Time Period and Frequency of Collection of AEs	• Extended the study follow-up to Day 28 • Added 60 days post-study to collect mortality, safety data and forced vital capacity	• Per FDA request
5.1.1 Inclusion Criteria	• Added oxygen requirements inclusion criteria	• Per FDA request
5.1.2 Exclusion Criteria	• Modified supplement oxygen exclusion criteria • Added cross reference to the Concomitant Medication section of the protocol • Clarified excluded COVID therapies prior to study entry	• Based on Investigator's input • For clarity and safety measure
6.6 Concomitant Therapy	• Updated restricted medications section to include azithromycin • Clarified to consult with Sponsor's Medical Monitor prior to prescribing chloroquine, hydroxychloroquine and azithromycin • Expanded section to include medications affected by potential interactions with BLD-2660	• Per FDA request • Safety precaution

Section # and Name	Description of Change	Brief Rationale
1.2 Schedule of Activities 8.1.2 Oxygenation Measures	• Clarified procedures for collecting oxygen saturation	• Per Investigator feedback
1.2 Schedule of Activities 8.1.4 Clinical Status Ordinal Score	• Changed to 6-point ordinal scale by collapsing 'not hospitalized' into 1 category	• Per FDA request
8.1.6 Hospital Discharge Readiness Criteria	• Clarified normal oxygen saturation criteria • Clarified oxygen supplementation status will be captured in the database	• Per FDA request
8.2.1 Physical examinations	• Clarified text	• For clarity
1.2 Schedule of Activities 8.4 Pharmacokinetics (PK)	• Clarified that PK samples will also be collected after first naso-gastric tube (NGT) is inserted	• To allow characterization of BLD-2660 using NGT route of administration
1.2 Schedule of Activities	• Update visit window • Remove biomarker blood sampling at screening as well as INR, urinalysis and chest x-ray/CT on Day 21 • Add overall survival check • Other updates as reflected above (e.g., adding Day 28)	• To update per changes to protocol and to ensure consistency throughout protocol
9 Statistical Consideration	• Added azithromycin use to efficacy analyses • Updated to 6-point ordinal scale • Updated to reflect Day 28 as EOS • Revised interim analysis to include efficacy boundaries and sample size re-estimation when 50% of subjects completed the study	• Per FDA request
General	• Corrected typos, formatting, style • Aligned changes across protocol • Updated Abbreviation (Appendix 6)	• For clarity and readability

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