Clinical Trial Protocol
PLN-74809-ARDS-204

Study Title:	A randomized, double-blind, dose-ranging, placebo controlled, Phase 2a evaluation of the safety, tolerability, and pharmacokinetics of PLN-74809 in participants with acute respiratory distress syndrome (ARDS) associated with at least severe COVID-19 (INTEGRIS-ARDS)
Study Number:	PLN-74809-ARDS-204
Study Phase:	2a
Product Name:	PLN-74809-000
IND Number:	150,181
EudraCT Number:	Not applicable
Indication:	Treatment of acute respiratory distress syndrome (ARDS) associated with at least severe COVID-19
Sponsor:	Pliant Therapeutics Inc. 260 Littlefield Avenue South San Francisco, CA 94080, USA
Sponsor Study Director:	[redacted]

Document ID	Date
Original Protocol	24 June 2020
Amendment 1	31 July 2020
Amendment 2	23 October 2020

SYNOPSIS

Study Title: A randomized, double-blind, dose-ranging, placebo controlled, Phase 2a evaluation of the safety, tolerability, and pharmacokinetics of PLN-74809 in participants with acute respiratory distress syndrome (ARDS) associated with at least severe COVID-19 (INTEGRIS-ARDS)

Study Number: PLN-74809-ARDS-204

Study Phase: 2a

Primary Objective:

- To assess the safety and tolerability of PLN-74809

Secondary Objective:

- To evaluate the pharmacokinetics of PLN-74809 following multiple doses using sparse sampling

Exploratory Objectives:

[redacted]

Study Design:

This is a Phase 2a, multicenter, randomized, double-blind, dose-ranging, placebo-controlled, study to evaluate the safety, tolerability, and PK of treatment with PLN-74809 for at least 7 and up to 14 days in participants with ARDS associated with at least severe COVID-19. The study will include an up to 3-day screening period, a 7- to 14-day (or day of hospital discharge, whichever one is sooner) treatment period, and a 90-day follow-up period.
Approximately 36 participants will be enrolled sequentially into 3 cohorts. Within each cohort of 12 participants, 9 will be randomized to PLN-74809 and 3 will be randomized to placebo (3:1 ratio).

- In Part 1, approximately 12 participants will be randomized to 40 mg PLN-74809 or placebo QD
- In Part 2, approximately 12 participants will be randomized to 80 mg PLN-74809 or placebo QD
- In Part 3, approximately 12 participants will be randomized to 160 mg PLN-74809 or placebo QD

A data safety monitoring board (DSMB) will be established to assess participant safety at predetermined intervals during the study, and as needed. [redacted]

Commencement of Part 2 and Part 3 will occur only following favorable DSMB review of the previous study part. The 160 mg cohort will only be dosed following favorable DSMB review of the 80 mg cohort. The DSMB will review PK from the preceding dose cohort to ensure doses administered in Parts 2 and 3 are not expected to exceed the daily exposure limit (i.e., area under

the plasma concentration-time curve from time zero to 24 hours [AUC_{0-24}] of unbound PLN-74809 of 800 ng*h/mL).

[redacted] Once participants are discharged from the hospital, they will no longer be administered study drug.

Successful treatment of ARDS associated with COVID-19 will likely require co administration of drugs with complementary mechanisms of action targeting different components of the disease, such as antiviral compounds to control viral replication (e.g., remdesivir) combined with drugs with the potential to address the pathophysiology of ARDS, in addition to respiratory support measures. Therefore, treatment with investigational COVID-19 therapies available under EUA by the FDA may be allowed, pending review and approval by the Medical Monitor and Sponsor Study Director. Key considerations for allowing co-administration of PLN-74809 with investigational COVID-19 therapies under EUA will include the potential for drug interactions and adverse drug reactions. Treatment with off-label use of any other drugs, devices, or interventions that might be used to manage COVID-19 may also be allowed, pending review and approval by the Medical Monitor and Sponsor Study Director.

Participants who discontinue study drug (regardless of reason) prior to completion of up to 14 days of treatment will be encouraged to remain in the study to complete all remaining assessments until hospital discharge or Day 28, whichever is sooner. If this is not feasible, they will be asked to perform an Early Termination (ET) visit for follow-up evaluations.

Study Population:

Participants with ARDS associated with at least severe COVID-19 who meet with the following eligibility criteria may be enrolled.

Inclusion Criteria:

General and Administrative

1. Ages 18 years and older.
2. Able to provide consent either on their own behalf or through a legally authorized representative.
3. Female participants of childbearing potential (ovulating or premenopausal and not surgically sterile) and male participants with sexual partners of childbearing potential must agree to use highly effective methods of birth control during their participation in the study and for 30 days for female participants and 90 days for male participants and female partners of male participants after the last administration of study drug. Highly effective methods of birth control are defined as those with 99% or greater efficacy (see Section 6.7.4).
4. Female participants of nonchildbearing potential must be either surgically sterile (defined as hysterectomy, bilateral tubal ligation, salpingectomy and/or bilateral oophorectomy at least 6 months prior to screening) or postmenopausal (defined as 12 months of spontaneous amenorrhea without an alternative medical cause or 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone [FSH] levels >40 mIU/mL).
5. Agree to abstain from sperm or egg donation through 90 days or 30 days, respectively, after administration of the last dose of study drug.
6. [redacted]

ARDS Diagnosis

7. Clinical diagnosis of ARDS, as defined by Berlin criteria, including:
    a. Chest imaging (radiography or CT scan): bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules
    b. Origin of edema: respiratory failure not fully explained by cardiac failure or fluid overload
    c. Acute hypoxemia defined by partial pressure of arterial oxygen (PaO_2)/ fraction of inspired oxygen (FiO_2):
        i. Mild hypoxemia: 200 mm Hg < $PaO_2/FiO_2 \leq$ 300 mm Hg with positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) $\geq$ 5 cm H_2O
        ii. Moderate hypoxemia: 100 mm Hg < $PaO_2/FiO_2 \leq$ 200 mm Hg with PEEP $\geq$ 5 cm H_2O
        iii. Severe hypoxemia: $PaO_2/FiO_2 \leq$ 100 mm Hg with PEEP $\geq$ 5 cm H_2O

    Note: If a reliable estimation of FiO_2 is not possible in non-ventilated participants, those meeting inclusion Criteria 9 and 10 will be eligible if all other criteria are met.
8. The radiological and hypoxemia inclusion criteria (i.e., 7a and 7c) must be met within the same 24-hour period. The time of onset of ARDS is defined as the time when these two criteria are met.
9. Receiving support for acute lung injury/respiratory distress via supplemental oxygen (e.g., high flow nasal cannula [HFNC], face mask [i.e., non-rebreather]), non-invasive ventilation, or via intubation and mechanical ventilation.

<u>Medical History and Comorbid Conditions</u>

10. Hospitalized with at least severe COVID-19 [redacted])
    a. Positive testing by standard reverse transcription polymerase chain reaction (RT-PCR) assay (or an equivalent COVID-19 test authorized under EUA)
    b. Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress
    c. Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate $\geq$ 30 per minute, heart rate $\geq$ 125 per minute, oxygen saturation (SpO_2) $\leq$ 93% on room air at sea level or PaO_2/FiO_2 < 300 mm Hg
11. Serum aspartate aminotransferase (AST) concentration $\leq$ 120 U/L and serum alanine aminotransferase (ALT) concentration $\leq$ 150 U/L (approximately 3 × ULN for both parameters)
12. Serum total bilirubin $\leq$ 1.8 mg/dL, in the absence of Gilbert's syndrome or hemolysis.
13. Platelet count $\geq$120,000/mm^3
14. Albumin $\geq$ 3.3 g/dL
15. International normalized ratio (INR) $\leq$1.5 in the absence of anticoagulant therapy or other coagulopathies

Exclusion Criteria

ARDS Status

1. Greater than 72 hours since time of onset of ARDS.
2. Greater than 7 days since start of mechanical ventilation.
3. Unwillingness to follow lung protective ventilation strategy (i.e., tidal volume of 6 mL/kg of predicted body weight and prone positioning) and fluid management protocol (Fluids and Catheters Treatment Trial [FACTT] Conservative or Lite) per local institutional standards.
4. Currently receiving or anticipated to receive extracorporeal life support (ECLS), extracorporeal membrane oxygenation (ECMO) or high-frequency oscillatory ventilation (HFOV).

Medical History and Comorbid Conditions

5. History of severe chronic respiratory disease with a partial pressure of arterial carbon dioxide ($PaCO_2$) > 50 mm Hg or the use of home oxygen.
6. Major trauma in the prior 5 days.
7. Presence of severe renal impairment, as defined by creatinine clearance < 30 mL/min.
8. Prior or planned lung, liver or bone marrow transplantation.
9. [redacted]
10. Suspected or confirmed acute liver failure, as defined by elevations in liver biochemistry, INR or other laboratory markers, with or without clinical symptoms associated with impaired liver function.
11. Suspected or confirmed cirrhosis (compensated or decompensated) as assessed by historical liver histology, imaging, laboratory markers and/or signs and symptoms of portal hypertension and/or hepatic decompensation.

Prior and Concomitant Medications

12. [redacted]
13. Current treatment or anticipated need for treatment with radiation therapy, cytotoxic or chemotherapeutic agents.

14. Hypersensitivity to PLN-74809 or to any of the excipients, or placebo.

Screening Assessments

15. Pregnancy or breastfeeding.
16. Any other clinically significant disorders (e.g., resulting in health care utilization or hospitalization), pre-existing condition, or prior therapy that, in the opinion of the Investigator, would make the participant unsuitable for the study or unable to comply with the dosing and protocol requirements.

Administrative

17. Participation in a clinical trial with an investigational agent within 30 days before screening. **Note**: Treatment with investigational COVID-19 therapies available under EUA by the FDA and/or off-label use of any other drugs, devices, or interventions that might be used to manage COVID-19 may be allowed, pending review and approval by the Medical Monitor and Sponsor Study Director.
18. Incarceration.

Test Product, Dose, and Mode of Administration:

[redacted]

- Part 1: 40 mg of PLN-74809 or matching placebo QD
- Part 2: 80 mg of PLN-74809 or matching placebo QD
- Part 3: 160 mg of PLN-74809 or matching placebo QD

Reference Therapy, Dose, and Mode of Administration:

A corresponding matching placebo will be provided. The placebo tablet will be identical in appearance to the PLN-74809 tablet and will be taken as described above for PLN-74809.

Duration of Treatment:

The planned duration of treatment is at least 7 days and up to 14 days or until day of hospital discharge, whichever is less. Once participants are discharged from the hospital, they will no longer be administered study drug.

Each participant will participate in the study for up to approximately 107 days, including screening, treatment, and post-treatment follow-up.

Safety Assessments:

[redacted]

Pharmacokinetic and Pharmacodynamic Assessments:

- PK: plasma samples for PK analysis will be obtained.

• Biomarkers: plasma and serum samples will be obtained.
Statistical Methods: This is a safety and PK study, with exploratory endpoints; as such, no statistical hypotheses are being tested. In general, data will be summarized using statistical summary methods; graphic presentations of data may also be prepared.

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AAG	alpha-1 acid glycoprotein
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC_{0-24}	area under the plasma concentration-time curve from time zero to 24 hours
BALF	bronchoalveolar lavage fluid
[redacted]	[redacted]
CFR	Code of Federal Regulations
COVID-19	coronavirus disease
CPAP	continuous positive airway pressure
CRO	contract research organization
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
DDI	drug-drug interaction
[redacted]	[redacted]
DSMB	Data Safety Monitoring Board
[redacted]	[redacted]
eCRF	electronic case report form
ECLS	extracorporeal life support
ECMO	extracorporeal membrane oxygenation
EDC	electronic data capture
EoT	end of treatment
ET	early termination
EUA	Emergency Use Authorization (by the FDA)

FACTT	Fluids and Catheters Treatment Trial
FDA	Food and Drug Administration
FiO_2	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HFNC	high flow nasal cannula
HFOV	high-frequency oscillatory ventilation
HIPAA	Health Information Portability and Accountability Act
IC_{50}, IC_{80}	50%, 80% inhibitory concentration
ICF	informed consent form
ICH	International Conference on Harmonisation
ICU	intensive care unit
IEC	independent ethics committee
IL	interleukin
INR	international normalized ratio
IPF	idiopathic pulmonary fibrosis
IRB	institutional review board
LAP	latency-associated peptide
MATE1	multidrug toxin extrusion transporter 1
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East Respiratory Syndrome
NE	nasoenteric
NG	nasogastric
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
$PaCO_2$	partial pressure of arterial carbon dioxide
PaO_2	partial pressure of arterial oxygen

PD	pharmacodynamics(s)
PEEP	positive end-expiratory pressure
PIPEDA	Personnel Information Protection and Electronic Documents Act
PK	pharmacokinetic(s)
PPB	plasma-protein binding
PSC	primary sclerosing cholangitis
QD	once daily
[redacted]	[redacted]
REB	research ethics board
RT-PCR	reverse transcription polymerase chain reaction
SAE	serious adverse event
SAP	statistical analysis plan
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMA	smooth muscle antibody
SMAD	family of proteins similar to the gene products of the Drosophila gene 'mothers against decapentaplegic' (*Mad*) and the *C. elegans* gene *Sma*
[redacted]	[redacted]
SpO_2	oxygen saturation
TEAE	treatment-emergent adverse event
TGF-β	transforming growth factor-beta
ULN	upper limit of normal
WHO	World Health Organization

1 INTRODUCTION

1.1 Background

Disease Background

Pliant Therapeutics, Inc. (Pliant) is developing PLN-74809-000 (hereafter referred to as PLN-74809) for the treatment of acute respiratory distress syndrome (ARDS) associated with at least severe coronavirus disease (COVID-19). ARDS is a major cause of mortality in patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes COVID-19. Infection by SARS-CoV-2 can cause a range of symptoms from mild fever and cough to severe respiratory illness, including ARDS, respiratory failure and death. ARDS is characterized by persistent pulmonary edema which is a result of impaired fluid and ion transport in the alveolar space.

In a recent study of 201 patients with confirmed COVID-19 pneumonia hospitalized at Jinyintan Hospital in Wuhan (China), risk factors associated with the development of ARDS and progression from ARDS to death included older age, neutrophilia, and organ and coagulation dysfunction ([redacted]). In this study, the median age of patients was 51 years and 63.7% patients were men. Eighty-four patients (41.8%) went on to develop ARDS, and of those 84 patients, 44 (52.4%) died.

In an observational database including 8910 patients from 169 hospitals in Asia, Europe, and North America, the relationship between cardiovascular disease and in-hospital death among hospitalized patients with COVID-19 was evaluated. This investigation confirmed previous reports of the independent relationship of older age, underlying cardiovascular disease (coronary artery disease, heart failure, and cardiac arrhythmias), current smoking, and chronic obstructive pulmonary disease with death due to COVID-19 ([redacted]). Although the mortality rate in patients with ARDS and COVID-19 was not reported in this analysis, older age and comorbidities continue to be strongly associated with increased risk of death.

Available ARDS/COVID-19 Therapies

Various supportive therapies have been found to reduce mortality in patients with ARDS; however, mortality remains high at 20% to 40% ([redacted]). Effective supportive therapies are lung-protective mechanical ventilation and a fluid conservative strategy, alongside neuromuscular blockade and prone positioning in more severe cases. Lung-protective ventilation, using a tidal volume of 6 mL per kg of predicted bodyweight and a plateau airway pressure of < 30 cm H_2O, has had a major effect in reducing mortality from ARDS. Neuromuscular blockade and prone positioning have further reduced mortality in more severely hypoxemic ARDS patients; probably by extending the therapeutic effects of lung protective ventilation. In addition, fluid-conservative therapy has increased ventilator-free days.

However, no effective pharmacological therapies have been found to improve clinical outcome in ARDS ([redacted]). The lack of availability of drugs to treat ARDS remains a significant medical challenge. Many large multicenter clinical trials with various drug therapies, including glucocorticoids (methylprednisolone), nitric oxide, surfactant, β_2-agonists, statins (simvastatin and rosuvastatin), antioxidants, ketoconazole, lisofylline, omega 3 supplementation, activated protein C, liposomal prostaglandin, granulocyte-macrophage stimulating factor, sivelestat, and factor VIIai, have failed to show any clear benefit.

One pharmacological intervention has been allowed under Emergency Use Authorization (EUA) by the Food and Drug Administration (FDA): remdesivir, for treatment of suspected or laboratory confirmed COVID-19 in adults and children hospitalized with severe disease.

Pathophysiology of ARDS

ARDS is characterized by persistent pulmonary edema, which is a result of impaired fluid and ion transport in the alveolar space. Transforming growth factor beta (TGF-β) is a pluripotent cytokine with established roles in ARDS and pulmonary fibrosis ([redacted]). TGF-β levels are significantly increased in lung tissue and bronchoalveolar lavage fluid (BALF) from ARDS patients and TGF-β is implicated in early lung injury as well as promotion of the fibroproliferative phase of ARDS ([redacted]). Thrombin as well as interleukin (IL)-1β, early mediators of acute lung injury, activate TGF-β in an $\alpha_v\beta_6$ integrin-specific manner, promoting epithelial damage, alveolar leak and collagen synthesis and fibrosis ([redacted]).

Integrin $\alpha_v\beta_6$, expressed on lung epithelial cells, binds to the arginine-glycine-aspartate sequence of latency-associated peptide (LAP) and upon stimulation by a variety of signals (e.g. proteinase-activated receptor-1 and lysophosphatidic acid) releases TGF-β from the latent complex and initiates TGF-β driven processes ([redacted]). In the lung, $\alpha_v\beta_6$ is the key regulator of TGF-β activity ([redacted]). In healthy lungs, $\alpha_v\beta_6$ is expressed at low levels and primarily functions to suppress alveolar macrophage activation. In lung injury in mice and humans, the expression of $\alpha_v\beta_6$ on epithelial cells and activation of TGF-β is dramatically increased and TGF-β driven tissue injury and repair effects dominate while anti-inflammatory effects are overcome by other pro-inflammatory mediators. In adults, $\alpha_v\beta_6$ expression is limited to epithelial cells and is expressed at low levels in healthy tissues, suggesting that pharmacological inhibition of $\alpha_v\beta_6$ may provide a tissue-targeted and potentially safer approach for TGF-β inhibition.

Similarly, integrin $\alpha_v\beta_1$ is expressed by lung fibroblasts and, like $\alpha_v\beta_6$ on epithelial cells, regulates TGF-β activity through binding to LAP and release of active TGF-β ([redacted]). Pharmacological inhibition of $\alpha_v\beta_1$ attenuates fibrosis in the bleomycin mouse model of pulmonary fibrosis ([redacted]), implicating $\alpha_v\beta_1$ in TGF-β-driven lung injury. In ARDS a subset of patients develop fibrotic disease that results in reduced lung function after recovery from acute injury, including approximately 30% of Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS) survivors ([redacted]). While it is too early to know the long term impact of COVID-19 ARDS on lung health and function

in surviving patients, there are several reports of fibrosis on computed tomography (CT) scans in COVID-19 patients ([redacted]), with one study reporting 17.5% of patients showing fibrous stripes on CT scan ([redacted]). For these reasons, pharmacological blockade of $\alpha_v\beta_1$ on lung fibroblasts in addition to $\alpha_v\beta_6$ on injured lung epithelial cells may provide clinical benefits in patients with ARDS.

Mechanism of Action of PLN-74809

[redacted]

1.2 Summary of Clinical Development

[redacted]

[redacted]

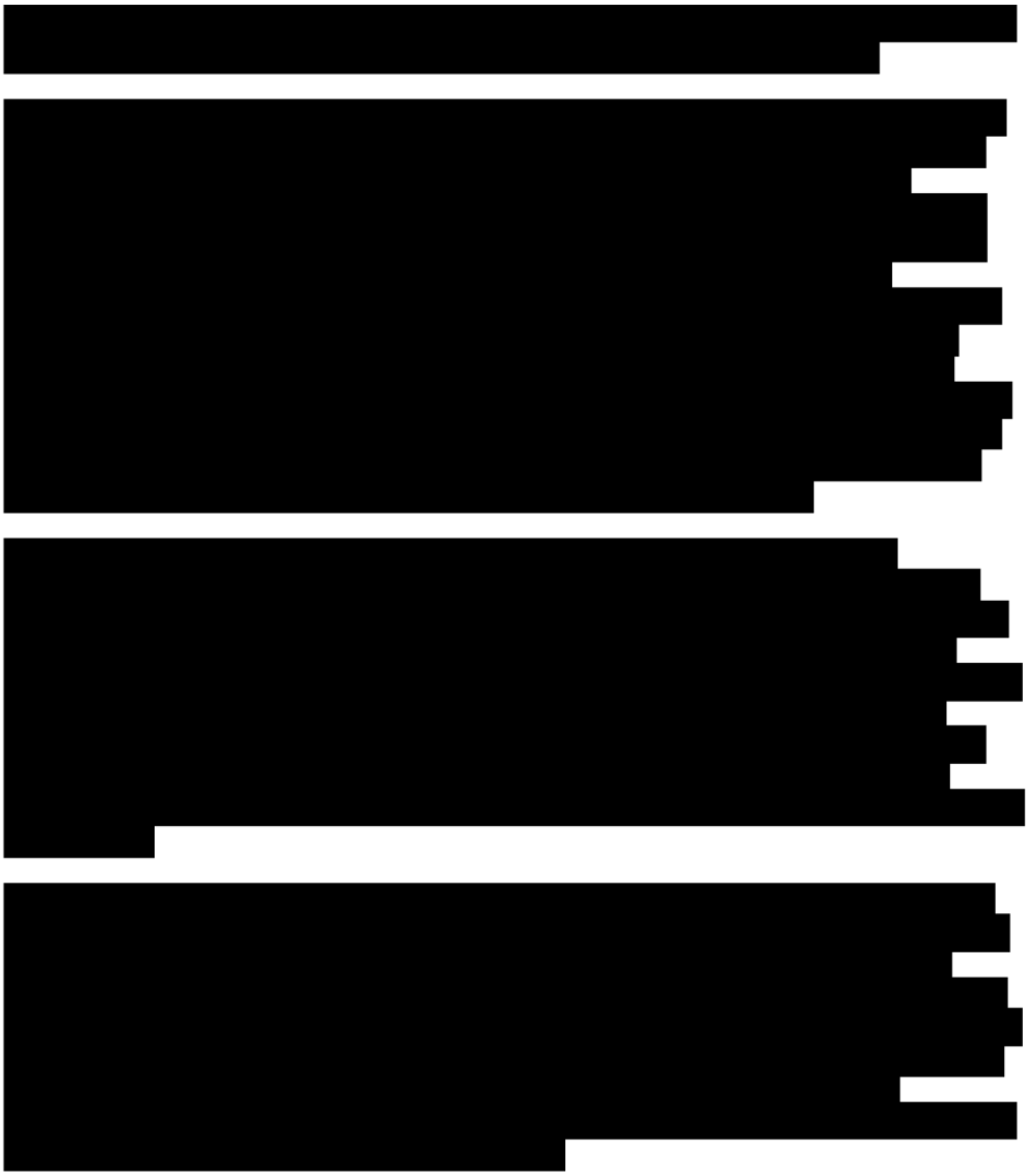
1.3 Rationale for Study

[redacted]

[redacted]

1.4 Benefit-Risk Assessment

[redacted]



2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the safety and tolerability of PLN-74809.

2.2 Secondary Objective

The secondary objective of this study is to evaluate the pharmacokinetics of PLN-74809 following multiple doses using sparse sampling.

2.3 Exploratory Objectives

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 2a, multicenter, randomized, double-blind, dose-ranging, placebo-controlled, study to evaluate the safety, tolerability, and PK of treatment with PLN-74809 for at least 7 and up to 14 days in participants with ARDS associated with at least severe COVID-19. The study will include an up to 3-day screening period, a 7- to 14-day (or day of hospital discharge, whichever one is sooner) treatment period, and a 90-day follow-up period (Figure 1).

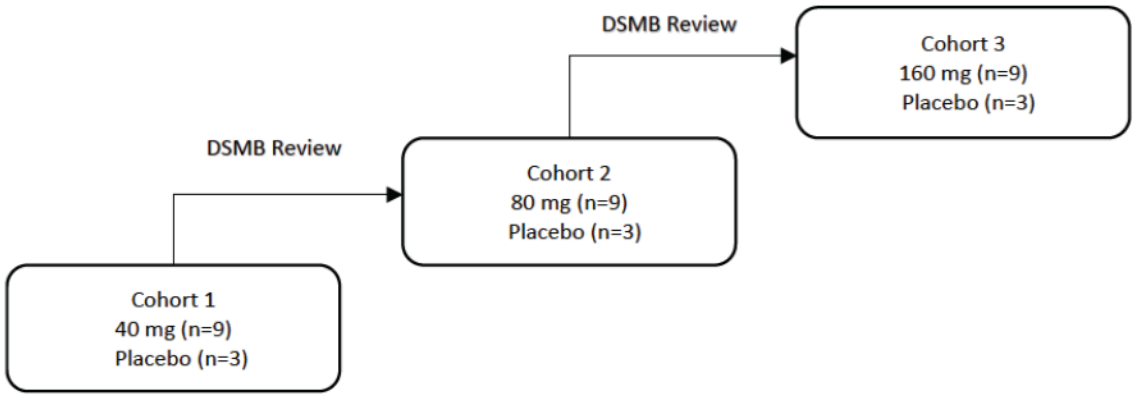
Approximately 36 participants will be enrolled sequentially into 3 cohorts. Within each cohort of 12 participants, 9 will be randomized to PLN-74809 and 3 will be randomized to placebo (3:1 ratio).

- In Part 1, approximately 12 participants will be randomized to 40 mg PLN-74809 or placebo QD
- In Part 2, approximately 12 participants will be randomized to 80 mg PLN-74809 or placebo QD
- In Part 3, approximately 12 participants will be randomized to 160 mg PLN-74809 or placebo QD

A DSMB will be established to assess participant safety at predetermined intervals during the study, and as needed (refer to Section 14.7). [redacted]

Commencement of Part 2 and Part 3 will occur only following favorable data safety monitoring board (DSMB) review of the previous study part. The 160 mg cohort will only be dosed following favorable DSMB review of the 80 mg cohort. [redacted]

Figure 1. Study Schematic



Non-ventilated participants will take study drug orally. Ventilated participants will receive study drug through a nasogastric (NG) or nasoenteric (NE) tube. Once participants are discharged from the hospital, they will no longer be administered study drug.

Successful treatment of ARDS associated with COVID-19 will likely require co-administration of drugs with complementary mechanisms of action targeting different components of the disease, such as antiviral compounds to control viral replication (e.g., remdesivir) combined with drugs with the potential to address the pathophysiology of ARDS, in addition to respiratory support measures. Therefore, treatment with investigational COVID-19 therapies available under EUA by the FDA may be allowed, pending review and approval by the Medical Monitor and Sponsor Study Director. Key considerations for allowing co-administration of PLN-74809 with investigational COVID-19 therapies under EUA will include the potential for drug interactions and adverse drug reactions. Treatment with off-label use of any other drugs, devices, or interventions that might be used to manage COVID-19 may also be allowed, pending review and approval by the Medical Monitor and Sponsor Study Director.

Participants who discontinue study drug for regardless of reason prior to completion of up to 14 days of treatment will be encouraged to remain in the study to complete all remaining assessments until hospital discharge or Day 28, whichever is sooner. If this is not feasible, they will be asked to perform an Early Termination (ET) visit for follow-up evaluations.

3.2 Rationale for Study Design and Control Group

[redacted]

[redacted]

3.3 Study Duration

Each participant will participate in the study for up to approximately 107 days, including screening, treatment, and post-treatment follow-up. The end of study is defined as the last visit of the last randomized participant.

The planned duration of treatment is at least 7 days and up to 14 days or until day of hospital discharge, whichever is less. Once participants are discharged from the hospital, they will no longer be administered study drug.

4 STUDY POPULATION AND SELECTION

4.1 Study Population

Participants with ARDS associated with at least severe COVID-19 who meet with the following eligibility criteria may be enrolled.

Treatment with investigational COVID-19 therapies available under EUA by the FDA and/or off-label use of any other drugs, devices, or interventions that might be used to manage COVID-19 may be allowed, pending review and approval by the Medical Monitor and Sponsor Study Director.

4.1.1 Inclusion Criteria

Each participant must meet all the following criteria to be enrolled in the study.

General and Administrative

1. Ages 18 years and older.
2. Able to provide consent either on their own behalf or through a legally authorized representative.
3. Female participants of childbearing potential (ovulating or premenopausal and not surgically sterile) and male participants with sexual partners of childbearing potential must agree to use highly effective methods of birth control during their participation in the study and for 30 days for female participants and 90 days for male participants and female partners of male participants after the last administration of study drug. Highly effective methods of birth control are defined as those with 99% or greater efficacy (see Section 6.7.4).
4. Female participants of nonchildbearing potential must be either surgically sterile (defined as hysterectomy, bilateral tubal ligation, salpingectomy and/or bilateral oophorectomy at least 6 months prior to screening) or postmenopausal (defined as 12 months of spontaneous amenorrhea without an alternative medical cause or 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone [FSH] levels >40 mIU/mL)
5. Agree to abstain from sperm or egg donation through 90 days or 30 days, respectively, after administration of the last dose of study drug.
6. [redacted]

ARDS Diagnosis

7. Clinical diagnosis of ARDS, as defined by Berlin criteria (refer to Appendix 2), including:
    a. Chest imaging (radiography or CT scan): bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules
    b. Origin of edema: respiratory failure not fully explained by cardiac failure or fluid overload
    c. Acute hypoxemia defined by partial pressure of arterial oxygen (PaO_2)/ fraction of inspired oxygen (FiO_2):
        i. Mild hypoxemia: 200 mm Hg < $PaO_2/FiO_2 \leq$ 300 mm Hg with positive end-expiratory pressure (PEEP) or continuous positive airway pressure (CPAP) $\geq$ 5 cm H_2O
        ii. Moderate hypoxemia: 100 mm Hg < $PaO_2/FiO_2 \leq$ 200 mm Hg with PEEP $\geq$5 cm H_2O
        iii. Severe hypoxemia: $PaO_2/FiO_2 \leq$ 100 mm Hg with PEEP $\geq$ 5 cm H_2O

    Note: If a reliable estimation of FiO_2 is not possible in non-ventilated participants, those meeting inclusion Criteria 9 and 10 will be eligible if all other criteria are met.
8. The radiological and hypoxemia inclusion criteria (i.e., 7a and 7c) must be met within the same 24-hour period. The time of onset of ARDS is defined as the time when these two criteria are met.
9. Receiving support for acute lung injury/respiratory distress via supplemental oxygen (e.g., high flow nasal cannula [HFNC], face mask [i.e., non-rebreather]), non-invasive ventilation, or via intubation and mechanical ventilation.

Medical History and Comorbid Conditions

10. Hospitalized with at least severe COVID-19 ([redacted])
    a. Positive testing by standard reverse transcription polymerase chain reaction (RT-PCR) assay (or an equivalent COVID-19 test authorized under EUA)
    b. Symptoms suggestive of severe systemic illness with COVID-19, which could include any symptom of moderate illness or shortness of breath at rest, or respiratory distress
    c. Clinical signs indicative of severe systemic illness with COVID-19, such as respiratory rate $\geq$ 30 per minute, heart rate $\geq$ 125 per minute, oxygen saturation (SpO_2) $\leq$ 93% on room air at sea level or PaO_2/FiO_2 < 300 mm Hg
11. Serum aspartate aminotransferase (AST) concentration $\leq$ 120 U/L and serum alanine aminotransferase (ALT) concentration $\leq$ 150 U/L (approximately 3 × ULN for both parameters)
12. Serum total bilirubin $\leq$ 1.8 mg/dL, in the absence of Gilbert's syndrome or hemolysis

13. Platelet count ≥120,000/mm^3
14. Albumin ≥ 3.3 g/dL
15. International normalized ratio (INR) ≤1.5 in the absence of anticoagulant therapy or other coagulopathies

4.1.2 Exclusion Criteria

Potential participants will be excluded from the study for any of the following reasons:

ARDS Status

1. Greater than 72 hours since time of onset of ARDS.
2. Greater than 7 days since start of mechanical ventilation.
3. Unwillingness to follow lung protective ventilation strategy (i.e., tidal volume of 6 mL/kg of predicted body weight and prone positioning) and fluid management protocol (Fluids and Catheters Treatment Trial [FACTT] Conservative or Lite) per local institutional standards. See Appendix 3 for further details.
4. Currently receiving or anticipated to receive extracorporeal life support (ECLS), extracorporeal membrane oxygenation (ECMO) or high-frequency oscillatory ventilation (HFOV).

Medical History and Comorbid Conditions

5. History of severe chronic respiratory disease with a partial pressure of arterial carbon dioxide ($PaCO_2$) > 50 mm Hg or the use of home oxygen.
6. Major trauma in the prior 5 days.
7. Presence of severe renal impairment, as defined by creatinine clearance < 30 mL/min.
8. Prior or planned lung, liver or bone marrow transplantation.
9. [redacted]
10. Suspected or confirmed acute liver failure, as defined by elevations in liver biochemistry, INR or other laboratory markers, with or without clinical symptoms associated with impaired liver function.

11. Suspected or confirmed cirrhosis (compensated or decompensated) as assessed by historical liver histology, imaging, laboratory markers and/or signs and symptoms of portal hypertension and/or hepatic decompensation.

Prior and Concomitant Medications

12. [redacted]

13. Current treatment or anticipated need for treatment with radiation therapy, cytotoxic or chemotherapeutic agents.

14. Hypersensitivity to PLN-74809 or to any of the excipients, or placebo.

Screening Assessments

15. Pregnancy or breastfeeding.

16. Any other clinically significant disorders (e.g., resulting in health care utilization or hospitalization), pre-existing condition, or prior therapy that, in the opinion of the Investigator, would make the participant unsuitable for the study or unable to comply with the dosing and protocol requirements.

Administrative

17. Participation in a clinical trial with an investigational agent within 30 days before screening.
    Note: Treatment with investigational COVID-19 therapies available under EUA by the FDA and/or off-label use of any other drugs, devices, or interventions that might be used to manage COVID-19 may be allowed, pending review and approval by the Medical Monitor and Sponsor Study Director.

18. Incarceration.

5 STUDY DRUG AND ACCOUNTABILITY

5.1 Description of Study Drug

5.1.1 PLN-74809

[redacted]

5.1.2 Placebo

A corresponding matching placebo will be provided.

5.2 Packaging and Labeling

[redacted]

5.3 Storage and Accountability

[redacted]

The Investigator (or designee) will maintain accurate records of receipt of all investigational drug supplies, including dates of receipt and the amount of study drug that is dispensed and used by each participant. Reasons for departure from the expected dispensing regimen must be recorded. At the completion of the study, all study drugs will be reconciled and destroyed, according to applicable regulations, to satisfy regulatory requirements regarding drug accountability.

5.4 Treatment Compliance

Study staff will perform the dosing of the study drug.

6 STUDY TREATMENTS

6.1 Description of Treatments

- Part 1: 40 mg of PLN-74809 or matching placebo QD
- Part 2: 80 mg of PLN-74809 or matching placebo QD
- Part 3: 160 mg of PLN-74809 or matching placebo QD

[redacted]

6.2 Dose Modifications and Interruptions

[redacted]

[redacted]

6.3 Selection and Timing of Dose for Each Participant

[redacted]

6.4 Method of Assigning Participants to Treatment Groups

Approximately 36 participants are planned to be enrolled and centrally randomized according to a computer-generated randomization scheme.

6.5 Blinding

The PLN-74809 and placebo tablets will be identical in appearance and will be packaged identically to ensure that the participant, Investigator and clinical site staff are unaware of the treatment assignments.

The Sponsor will remain blinded until dosing is completed (i.e., after the last participant enrolled in each study part completes the end of treatment or early termination visit, whichever applies). Selected Sponsor representatives with no direct interactions with clinical sites will subsequently be unblinded to allow for a more comprehensive review and assessment of the safety and PK data by the DSMB before proceeding to subsequent parts of the study.

Procedures will be in place to allow prompt breaking of the blind by the Principal Investigator if needed for the safety management of a participant in the event of a serious adverse event (SAE).

6.6 Concomitant Therapy

6.6.1 Allowed Medications

[redacted]

Treatment with investigational COVID-19 therapies available under EUA by the FDA and/or off-label use of any other drugs, devices, or interventions that might be used to manage COVID-19 may be allowed, pending review and approval by the Medical Monitor and Sponsor Study Director.

[redacted]

[redacted]

6.6.2 Disallowed Medications

[redacted]

6.7 Restrictions

6.7.1 Prior Therapy

For prior and/or concomitant treatment with COVID-19 investigational treatments or device, see Section 6.6.1. Prior treatment with an investigational treatment within 30 days for other indications is prohibited. Prior radiation therapy is prohibited. Individuals who have received any of these therapies must not be enrolled in the study.

6.7.2 Fluid and Food Intake

[redacted]

6.7.3 Participant Activity Restrictions

No restrictions on activity will be imposed.

6.7.4 Contraception

Female participants of nonchildbearing potential must be either surgically sterile (defined as hysterectomy, bilateral tubal ligation, salpingectomy, and/or bilateral oophorectomy at least 6 months prior to screening) or postmenopausal (defined as 12 months of spontaneous amenorrhea without an alternative medical cause or 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone [FSH] levels >40 mIU/mL).

Female participants of childbearing potential (i.e., ovulating, premenopausal, and not surgically sterile) and all male participants with sexual partners of childbearing potential must use highly effective methods of birth control during their participation in the study and for 30 for female participants and 90 days for male participants and female partners of male participants after the last administration of study drug. Highly effective methods of birth control are defined as those with 99% or greater efficacy ([redacted]).

Acceptable methods of contraception for female and male participants who are enrolled in the study include:

- Complete abstinence from sexual intercourse if this is the participant's usual and preferred lifestyle
- Implanted contraceptives
- Oral hormonal contraceptives if using for 1 year or more
- Hormonal intrauterine device
- Dual method of contraception, defined as:
  - Condom in conjunction with use of a non-hormonal intrauterine device

  - Oral hormonal contraceptives with less than 1 year of use in conjunction with condom

- Sexual partner with surgical sterilization (e.g., vasectomy, tubal ligation, hysterectomy and/or bilateral oophorectomy)

Female participants who are using hormonal contraceptives must have been using the hormonal contraceptive for at least 12 weeks before screening. Participants must agree to abstain from sperm or egg donation for at least 90 days or 30 days, respectively, after administration of the last dose of study drug.

7 STUDY PROCEDURES

The schedule of events for the study is presented in Appendix 1. Additional safety assessments may be conducted per ICU standards.

[redacted]

7.1 Informed Consent

Written and dated informed consent, describing the study and all anticipated risks of participation must be obtained from each study participant, or the participant's legally authorized representative, prior to any study-related procedures being performed.

7.2 Inclusion/Exclusion Criteria

The inclusion/exclusion criteria will be reviewed at the screening and baseline (Day 1) visits. Potential participants must meet all of the inclusion criteria (Section 4.1.1) and none of the exclusion criteria (Section 4.1.2) to be enrolled in the study.

7.3 Demographic Information

Demographic information, including date of birth, sex, race, and ethnicity, will be recorded at the screening visit.

7.4 Medical History

A medical history will be obtained at the screening visit. Conditions that are considered relevant for the safety evaluation and/or clinically significant (e.g., resulting in health care utilization or hospitalization) should be recorded, with at least a start date and whether the condition is ongoing or resolved. All surgeries within the past 4 weeks should be recorded.

7.5 Height and Weight

Height (in centimeters) and weight (in kilograms) will be recorded at the screening visit.

7.6 Exploratory Efficacy Assessments

7.6.1 [redacted]

[redacted]

7.6.2 [redacted]

[redacted]

7.6.3 [redacted]

[redacted]

7.7 Prior and Concomitant Medication Assessments

All medications and therapies (including over-the-counter or prescription medications, vitamins, and herbal supplements) that are used by participants at the screening visit through the end of study or at early termination will be recorded, along with the indication for use, the dose, the frequency of administration, the route of administration, and the start and end dates. Generic names should be used.

7.8 Physical Examinations

Physical examinations may be performed if can be done safely. Otherwise nursing assessment or verbal review of systems may be performed.

A complete physical examination will be performed at the screening visit. A complete physical examination includes evaluation of general appearance; the head, ears, eyes, nose, throat, and dentition; the thyroid; the chest (heart and lungs); the abdomen; the skin; a neurological examination; the extremities; the back and neck; a musculoskeletal examination; and the lymph nodes.

Targeted physical examinations will be performed as detailed in the Schedule of Events (Appendix 1), including at the end of treatment or at early termination. A targeted physical examination includes evaluation of the head, ears, eyes, nose, throat, heart, lungs, abdomen,

skin, musculoskeletal system, and lymph nodes, as well as evaluation of any pertinent system based on any previous findings.

7.9 Vital Signs

[redacted] Additional assessments may be conducted per ICU standards and at least daily. Confirmation of the performance of these daily assessments will be recorded in the electronic case report form (eCRF).

7.10 [redacted]

[redacted]

7.11 Clinical Laboratory Tests

7.11.1 Laboratory Parameters

Local laboratory assessments will be conducted per ICU standards and at least daily. Confirmation of the performance of these daily assessments will be recorded in the eCRF.

Results from these safety laboratory assessments will be recorded in the electronic data capture (EDC) as detailed in the Schedule of Events (Appendix 1), including at the end of treatment or at early termination. The required clinical laboratory tests are listed in Table 2.

Creatinine clearance will be calculated using the Cockcroft-Gault equation:

$$\text{Creatinine clearance} = \frac{(140 - age) \times body\ weight\ (kg)}{serum\ creatinine\ \left(\frac{mg}{dL}\right) \times 72} \times 0.85\ (if\ female)$$

Table 2. Laboratory Tests, as Listed, or per Local Standards

Hematology	**Serum Chemistry**
- Hematocrit (Hct) - Hemoglobin (Hgb) - Mean corpuscular hemoglobin (MCH) - Mean corpuscular hemoglobin concentration (MCHC) - Mean corpuscular volume (MCV) - Platelet count - Red blood cell (RBC) count - White blood cell (WBC) count with differential	- Alanine aminotransferase (ALT) - Albumin (ALB) - Alkaline phosphatase (ALP) - Alpha-1-acid-glucoprotein (AAG) - Amylase (reflex lipase if amylase ≥1.5 × ULN) - Aspartate aminotransferase (AST) - Bilirubin (total and direct) - Blood urea nitrogen (BUN) - Calcium (Ca) - Chloride (Cl) - Creatinine - Creatine kinase (CK) - Gamma-glutamyl transferase (GGT) - Globulin - Glucose - Lactate dehydrogenase (LDH) - Phosphorus (P) - Potassium (K) - Sodium (Na) - Total protein - Total cholesterol - Triglycerides - Troponins - Uric acid
Coagulation	
- International normalized ratio (INR)	
Urinalysis	
- Appearance - Bilirubin - Color - Glucose - Ketones - Microscopic examination of sediment - Nitrite - Occult blood - pH - Protein - Specific gravity - Urobilinogen	
Other	**Screening Only**

- Serum human chorionic gonadotropin (hCG) (females)	- Follicle-stimulating hormone (FSH) – to confirm postmenopausal status
	- Hepatitis A IgM antibody (HAV-IgM Ab)
	- Hepatitis B surface antigen (HbsAg)
	- Hepatitis C virus antibody (HCVAb)
	- Human immunodeficiency virus (HIV)
	- SARS-CoV-2 PCR (or COVID-19 tests authorized under EUA)
	- Urine drug screen, including, but not limited to:
	  o amphetamines
	  o barbiturates
	  o benzodiazepines
	  o cocaine
	  o methadone
	  o phencyclidine
	  o opiates

The Investigator will review the results of all laboratory tests as they become available and will ascertain if any laboratory value is abnormal or represents a clinically significant change from baseline for the individual participant. If a laboratory value is determined to be abnormal and to represent a clinically significant change from baseline for the participant, the Investigator will determine if it qualifies as an AE. If "yes," the abnormality will be reported on the AE eCRF. All clinically significant laboratory abnormalities that occur during the study and that were not present at baseline should be followed and evaluated with additional tests, if necessary, until diagnosis of the underlying cause or resolution.

7.11.2 Sample Collection, Storage, and Shipping

Information on sample collection, processing, storage, and shipping will be provided in a laboratory manual.

7.12 Adverse Event Assessments

All AEs observed by the Investigator, volunteered by the participant, or elicited through open-ended questioning of the participant from the time the informed consent form (ICF) is signed at the screening visit through Day 28 are to be recorded. Any SAEs must be reported to the Sponsor within 24 hours of Investigator first awareness of the event. All AEs, including SAEs, must be followed to resolution or until the Investigator determines that there is not an anticipated resolution. Definitions of AEs and the procedures for documenting and reporting AEs and SAEs are described in Section 8.

7.13 Pharmacokinetic Assessments

Blood samples for determination of plasma levels of PLN-74809 will be obtained at the following timepoints:

- Day 1: 0.5 hours (±15 min), 3 hours (±60 min), and 10 hours (± 120 min) postdose
- Day 7: predose, 3 hours (±60 min), and 24 hours (±60 min) postdose
- Day 14: predose for participants on study drug

If the participant is no longer being treated with study drug, discontinues the study early, or is not treated with study drug on Day 14, a single plasma sample for PK should be taken at the Day 14/ end of treatment (EoT)/ early termination (ET) visit, if possible. Actual PK sample collection time and dosing time will be recorded. The PK sampling schema may be modified based on emerging data.

[redacted]

Information on the collection, processing, storage, and shipping of PK samples will be provided in a laboratory manual.

7.14 Pharmacodynamic Assessments

Plasma and serum biomarker samples will be obtained as detailed in the Schedule of Events (Appendix 1).

The study will test, in an exploratory manner, a panel of biomarkers with potential to assess drug effects. A table of key exploratory biomarkers of interest and evidence for their prognostic or pharmacodynamic value is presented in Table 3.

Information on the collection, processing, storage, and shipping of biomarker samples will be provided in a laboratory manual.

Table 3. Key Exploratory Biomarkers of Interest and Evidence for Their Prognostic or Pharmacodynamic Value

Category	Biomarker	Evidence of Prognostic or Pharmacodynamic Value (Reference)
Epithelial Damage	Receptor for advanced glycation end-products (RAGE)	Higher levels increase odds of ARDS diagnosis in at risk patients ([redacted]) and predict mortality in ARDS patients with high-tidal volume ventilation ([redacted])
	Krebs von den Lungen-6 (KL-6)	Higher levels in patients with ARDS than ventilated and healthy controls and, within ARDS patients, higher levels in non-survivors than survivors ([redacted])
	Surfactant protein D (SP-D)	Higher baseline levels of SP-D were associated with worse outcomes and increased mortality in ARDS ([redacted])
Fibrinolysis	Plasminogen activator inhibitor 1 (PAI-1)	Higher baseline levels of PAI-1 in ARDS patients and predictor of mortality ([redacted])
	D-dimer	Higher levels of D-dimer may predict in-hospital mortality in COVID-19 patients ([redacted])
Inflammation	Interleukin 6 (IL-6)	Higher baseline levels of IL-6 predict more severe COVID-19 and a significant decrease in IL-6 was observed in recovering patients ([redacted]). Higher levels were observed in patients who died versus those who were discharged ([redacted]).
	Interleukin 8 (IL-8)	Higher levels are a predictor of mortality in patients with ARDS ([redacted])
	C-reactive protein (CRP)	Higher levels observed in patients with severe COVID-19 ([redacted]) and in patients who died versus those who were discharged ([redacted])
Fibrosis	ProC3 (Type III collagen synthesis neoepitope)	Higher levels of related N-terminal peptide for type III procollagen were observed in serum of patients with biopsy-confirmed fibroproliferative ARDS ([redacted])

7.15 Dispensing Study Drug

Participants will receive study drug at the timepoints indicated in the Schedule of Events (Appendix 1).

7.16 Missed Assessments

Missed assessments will reported as such and will not be imputed.

7.17 Appropriateness of Measurements

[redacted]

PK samples will be analyzed according to predefined validated analytical methods to assess the total and unbound levels of PLN-74809 in plasma.

[redacted]

When available, appropriate standard guidelines will be used.

8 ADVERSE EVENTS

8.1 Timing

In this study, AEs will be collected from the time the participant signs the ICF until the Day 28 study visit.

8.2 Definition of an Adverse Event

An AE is any event, side effect, or other untoward medical occurrence that occurs in conjunction with the use of a study drug in humans, whether or not considered to have a causal relationship to this treatment. An AE can, therefore, be any unfavorable and unintended sign (that could include a clinically significant abnormal laboratory finding), symptom, or disease temporally associated with the use of a study drug, whether or not considered related to the study drug. Events meeting the definition of an AE include:

- 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 prior to the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study drug or a concomitant medication (overdose per se will not be reported as an AE/SAE). Events that do not meet the definition of an AE include:
  - Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE.
  - Situations in which an untoward medical occurrence did not occur (e.g., social and/or convenience admission to a hospital).
  - Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- If there is evidence of an AE through report or observation, the Investigator or designee will evaluate further and record the following information:
  - Time of onset and resolution
  - Severity
  - Causality/relation to study treatment
  - Action taken regarding study drug
  - Outcome

8.3 Severity of an Adverse Event

Grading the severity of AEs will use the Common Terminology Criteria for Adverse Events (CTCAE) grading system, version 5.0 ([redacted]), as described below. The clinical significance of the AE is determined by the Investigator. The Investigator is encouraged to consult with the Medical Monitor. For AEs or laboratory abnormalities not listed in the CTCAE grading system, please use the grading scale as described below.

Grade 1[a]	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2[a]	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[b]
Grade 3[a]	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[c]
Grade 4[a]	Life-threatening consequences; urgent intervention indicated
Grade 5[a]	Death related to AE

a. A semi-colon indicates 'or' within the description of the grade.
b. Instrumental activities of daily living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
c. Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

8.4 Causal Relationship of an Adverse Event

The Investigator will assess the relationship between study drug and the occurrence of each AE. The Investigator's assessment of the relationship of each AE to study drug will be recorded in the source documents and on the eCRF. Alternative causes, such as medical history, concomitant therapy, or other risk factors, and the temporal relationship of the event to the study drug should be considered and investigated, if appropriate. The relationship or association of the AE to a study drug (PLN-74809 or placebo) should be assessed using clinical judgment and the following considerations:

No: Evidence exists that the adverse event has an etiology other than the study drug. For SAEs, an alternative causality must be provided (e.g., preexisting condition, underlying disease, intercurrent illness, or concomitant medication).

Yes: A temporal relationship exists between the AE onset and administration of the study drug that cannot be readily explained by the participant's clinical state or concomitant therapies. Furthermore, the AE appears with some degree of certainty to be related, based on the known therapeutic and pharmacologic actions or AE profile of the study drug. In case of cessation

or reduction of the dose, the AE abates or resolves and reappears upon re-challenge.

The relationship to study procedures (such as venipuncture) should be assessed using the following considerations:

No: Evidence exists that the AE has an etiology other than the study procedure.
Yes: The AE occurred as a result of protocol-mandated procedures

8.5 Outcome

The outcome of an AE will be recorded on the AE eCRF as follows:

- Recovered/Resolved
- Recovering/Resolving
- Recovered/Resolved with Sequelae
- Not Recovered/Not Resolving
- Fatal
- Unknown

8.6 Pregnancy

A pregnancy is not an AE. If a female participant or the female partner of a male participant becomes pregnant within 30 or 90 days, respectively, after administration of the last dose of study drug, the Sponsor must be notified within 24 hours of the Investigator learning of the pregnancy. Administration of study drug will be discontinued immediately, and the female participant or the female partner of a male study participant will be followed through the outcome of the pregnancy. The Investigator is required to provide all relevant information to the Sponsor using the Pregnancy Information Form to do so.

If the pregnancy results in a congenital anomaly/birth defects, this will be considered and reported as an SAE as per definition detailed in Section 8.8.1.

8.7 Clinical Laboratory Adverse Events

Abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments ([redacted]) per se are not reported as AEs. However, those abnormal findings that are deemed clinically significant or that are associated with signs and/or symptoms must be recorded as AEs if they meet the definition of an AE, as described in Section 8.2 (or recorded as an SAE if they meet the criteria for serious, as described in Section 8.8.1). Clinically significant abnormal laboratory findings or other abnormal findings that are detected after the ICF is signed or that are present at baseline and worsen after the ICF is signed are included as AEs (and as SAEs if serious).

The Investigator should exercise his/her medical and scientific judgment in deciding whether an abnormal laboratory finding or other abnormal assessment is clinically significant. Usually, the abnormality should be associated with a clinically evident sign or symptom or be likely to result in an evident sign or symptom in the near term to be considered clinically significant. A clinically significant laboratory abnormality in the absence of clinical symptoms may jeopardize the participant and may require intervention to prevent immediate consequences. For example, a markedly low serum glucose concentration may not be accompanied by coma or convulsions yet be of a magnitude to require glucose administration to prevent such sequelae.

8.8 Serious Adverse Events

8.8.1 Definition of Serious Adverse Events

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

- Is life-threatening
- Results in death
- Requires inpatient hospitalization (i.e., admission, overnight stay) or prolongs existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect

An AE is considered life-threatening if, in the opinion of either the Investigator or the Sponsor, its occurrence places the participant at immediate risk of death. It does not include an AE that, had it occurred in a more severe form, might have caused death.

Important medical events that are not one of the above may be considered to be SAEs by the Investigator when, based upon appropriate medical judgement, they are considered to be clinically significant and may jeopardize the participant or when medical or surgical intervention may be required to prevent one of the outcomes listed above. (Examples of such events include allergic bronchospasm requiring intensive treatment at an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)

8.8.2 Reporting Serious Adverse Events

To meet the requirements for expedited reporting of SAEs that meet specific requirements to applicable regulatory authorities and institutional review boards (IRBs)/ independent ethics committees (IECs)/ research ethics boards (REBs), all SAEs must be reported to the Sponsor within 24 hours from the time site personnel first become aware of the event. This may initially be achieved by telephone or by completing an SAE report form and emailing the form to the email address, as provided on the form.

Initial notification of an SAE by telephone must be confirmed in writing within 24 hours from the time the site personnel first become aware of the event using the SAE report form as described above. As further information regarding the SAE becomes available, such follow-up information should be documented on a new SAE report form, marked as a follow-up report, scanned, and emailed to the address provided.

Withdrawal from the study in the event of an SAE and the therapeutic measures that are taken shall be at the discretion of the Investigator. A full explanation for the discontinuation from the study should be made in the eCRF.

The reporting of any SAEs to applicable regulatory authorities will be the responsibility of the Sponsor in compliance with applicable country regulations. All SAEs must be reported to the IRB/IEC/REB by the Investigator in accordance with relevant regulations.

9 [redacted]

[redacted]

10 [redacted]

[redacted]

[redacted]

[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

11 EARLY DISCONTINUATION OF STUDY OR INDIVIDUAL PARTICIPANTS

The Investigator may withdraw a participant from the study or discontinue study drug for any of the following reasons:

- Noncompliance with protocol procedures, including those relating to administration of study drug
- Occurrence of an SAE or intolerable AE
- Occurrence of a clinically significant change in a laboratory parameter
- [redacted]
- [redacted]
- Termination of the study by the Sponsor or Investigator
- The participant requests to be discontinued from the study

Participants who discontinue study drug (regardless of reason) will be asked to remain in the study to complete all remaining assessments until hospital discharge or Day 28, whichever is sooner, unless they withdraw consent or are lost to follow-up. If this is not feasible, the participant will be assessed for an early termination visit. All assessments that are required at the last study visit, as shown in Appendix 1, should be completed for any participant who is withdrawn from the study or prematurely discontinues study drug and does not agree to complete all remaining assessments.

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

No statistical hypotheses will be tested. Data will be summarized with descriptive statistics. Graphic presentations may also be prepared. All data will be listed by treatment group and participant.

A statistical analysis plan (SAP), which will provide a detailed analysis plan, will be prepared and approved before database lock. Where different, the analyses described in the statistical analysis plan will supersede those described in the protocol.

12.2 Determination of Sample Size

[redacted]

12.3 Analysis Populations

Two analysis populations will be defined:

- Safety Population: all randomized participants who receive at least 1 dose of study drug.
- PK Concentration Population: all randomized participants who receive at least 1 dose of study drug and have any measurable PLN-74809 concentration data.

12.4 Demographics and Baseline Characteristics

Demographic data will be summarized descriptively (n, mean, standard deviation, median, minimum, and maximum) by treatment group. Medical history and prior and concomitant medication data will be listed by treatment group and participant.

12.5 Primary Endpoint

The primary endpoint is the nature and proportion of TEAEs between PLN-74809 and placebo groups (descriptive).

Safety data from all participants who received at least one dose of study drug will be incorporated into the final safety analysis. Further details of the safety analyses will be provided in the SAP. AEs will be collected from the time the participant signs the ICF until Day 28. TEAEs are defined as AEs that emerged or worsened in severity after the first administration of study drug.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®). All AEs will be graded for severity per the CTCAE grading scale and listed by participant and summarized by last treatment taken at onset of AE. All AEs will be listed by participant and summarized by last treatment taken at onset of AE.

The incidence of AEs, the incidence of TEAEs, the incidence of treatment-related AEs, and the severity of AEs will be summarized by system organ class, preferred term, and maximum severity. In cases where a participant reports multiple occurrences of the same event (preferred term), the greatest severity will be included in the summary. The number and percentage of participants with SAEs and treatment-related SAEs and participants who withdraw prematurely due to an AE will be tabulated by study treatment and dose.

Clinical laboratory test parameters will be graded using the CTCAE grading scale for individual participants and values outside the reference ranges will be flagged. The incidence of treatment-emergent laboratory abnormalities will be summarized by severity and treatment group. For each parameter, summary statistics will be calculated for each measure and summarized by treatment and dose.

[redacted]

Vital sign measurements, other laboratory tests, concomitant medications, medical history and changes in physical examinations at each time point will be listed by participant. [redacted]

Concomitant medications will be coded using the most current WHO drug dictionary available.

12.6 Secondary Endpoints

12.6.1 Secondary Pharmacokinetic Endpoints

Plasma PLN-74809 concentrations (total and unbound concentrations) at each sampling timepoint will be presented in listings and descriptive summary statistics by dose and visit. The data will also be presented graphically.

Further details of the analyses will be provided in the SAP to be prepared and agreed prior to final 'database lock' at the end of the study. The PK analysis plan and report may be prepared separately from the SAP as appropriate.

12.7 Exploratory Endpoints

[redacted]

12.8 Interim Analysis

No interim analyses are planned.

13 QUALITY CONTROL AND ASSURANCE

During the study, the Sponsor and/or representatives of the Sponsor may visit the site to conduct an audit of the study. The purpose of this visit will be to determine the Investigator's adherence to the protocol, applicable regulations, and the Sponsor's procedures, in addition to assessing the accuracy of the study data. Prior to initiating this audit, the Investigator will be contacted by the Sponsor to arrange a convenient time for this visit. The Investigator and staff are expected to cooperate with the auditors and to allow access to all participant records supporting the eCRFs and other study-related documents.

At some point during the development program for the study drug, a regulatory authority may visit the Investigator to conduct an inspection of the study and the site. The Investigator and staff are expected to cooperate with the inspectors and to allow access to all source documents supporting the eCRFs and other study related documents. The Investigator must immediately notify the Sponsor when contacted by any regulatory authority for purposes of conducting an inspection.

14 ADMINISTRATIVE CONSIDERATIONS

14.1 Institutional Review Board, Independent Ethics Committee Approval, or Research Ethics Board Approval

The Investigator must inform and obtain approval from the IRB/IEC/REB for the conduct of the study at named sites, for the protocol, for the participant ICF and any other written information that will be provided to the participants, and any advertisements that will be used. Written approval must be obtained prior to recruitment of participants into the study and shipment of investigational agent.

Proposed amendments to the protocol and aforementioned documents must be discussed among the Sponsor and contract research organization (CRO) personnel, submitted to the IRB/IEC/REB for approval, and then submitted to regulatory authorities for approval prior to implementation. Amendments may be implemented only after a copy of the local IRB/IEC/REB approval letter has been transmitted to the Sponsor. Amendments that are intended to eliminate an apparent immediate hazard to participants may be implemented prior to receiving Sponsor or IRB/IEC/REB approval. However, in this case, approval must be obtained as soon as possible after implementation.

The Investigator will be responsible for reporting protocol deviations to the IRB/IEC/REB as required by local requirements. The Investigator will be responsible for ensuring that an annual update is sent to the IRB/IEC/REB to facilitate continuing review of the trial (if needed) and that the IRB/IEC/REB is informed about the end of the study. Copies of the update, subsequent approvals, and final letter must be sent to the Sponsor.

14.2 Ethical Conduct of the Study

The study will be conducted in accordance with the current version of the Declaration of Helsinki, concerning medical research in humans. The study will be conducted in adherence to the study protocol and Good Clinical Practice (GCP), as defined in Title 21 of the US Code of Federal Regulations (CFR) Parts 50, 54 56, 312 and Part 11 and in International Conference on Harmonisation (ICH) E6: Guideline for Good Clinical Practice Consolidated Guidelines (ICH-GCP), and applicable regulatory requirements.

14.3 Participant Information and Consent

It is the Investigator's responsibility to obtain written informed consent from the participant, or the participant's legally authorized representative, after adequate explanation of the objectives, methods, anticipated benefits, and potential hazards of the study and before any study procedures commence.

The participant, or the participant's legally authorized representative, should be given a copy of the IRB/IEC/REB-approved ICF in his/her native language. The informed consent process should be recorded in the source documentation. The original copy of the signed and dated ICF must be retained in the institution's records and be available for inspection by

representatives of the Sponsor or representatives from regulatory agencies. The participant, or the participant's legally authorized representative, will be given a copy of the signed ICF.

The participant, or the participant's legally authorized representative, will be informed that he/she can freely withdraw consent and stop participation in the study at any time with no prejudice to further treatment. It is the participant's, or the participant's legally authorized representative responsibility to communicate this decision to the Investigator.

14.4 Participant Confidentiality

The Investigator must ensure that the participant's privacy is maintained. On the eCRF and other documents that are submitted to the Sponsor, participants will be identified by a participant study number only. Documents that are not submitted to the Sponsor (e.g., signed ICF) should be kept in a strictly confidential file by the Investigator.

The Investigator shall permit authorized representatives of the Sponsor, regulatory agencies, and IRBs/IECs/REBs to review the portion of the participant's medical record that is directly related to the study. As part of the required content of informed consent, the participant must be informed that his/her records will be reviewed in this manner.

Applicable data privacy laws and regulations must be adhered to. The Investigator and the Sponsor are responsible for ensuring that sensitive information is handled in accordance with local requirements (e.g., Health Insurance Portability and Accountability Act [HIPAA], Personnel Information Protection and Electronic Documents Act [PIPEDA], General Data Protection Regulation [GDPR]). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

14.5 Study Monitoring

The Investigator must allow the Study Monitors to periodically review, at mutually convenient times, during the study and after the study has been completed, all eCRFs and office, hospital, and laboratory records that support the participation of each participant in the study (source data). The eCRFs and other documentation that support the study must be kept up-to-date by the Investigator and the research staff at the investigative site. These study materials must be available for review by the Study Monitor and/or other qualified representatives of the Sponsor, at each monitoring visit.

It is the monitor's responsibility to inspect the eCRFs at regular intervals throughout the trial to verify adherence to the protocol; the completeness, accuracy and consistency of the data; and adherence to GCP guidelines.

The Investigator agrees to cooperate with the monitor to ensure that any problems detected during the course of these monitoring visits are resolved.

14.6 Case Report Forms and Study Records

The investigative site will use eCRFs to record all the protocol-specified data for each participant who is enrolled in this study. Entries made in the eCRF must be verifiable against source documents. Data reported in the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained.

The Investigator will be responsible for reviewing all data and eCRF entries and will sign and date the designated pages in each participant's eCRF, verifying that the information is accurate.

14.7 Data Safety Monitoring Board

A DSMB will be established to assess participant safety at predetermined intervals during the study, and as needed. The DSMB will formally assess and review all available safety and PK data and will issue recommendations pertaining to the conduct of the study and the dose escalation from Part 1 to Part 2 and from Part 2 to Part 3. Further details will be provided in the DSMB Charter.

[redacted]

14.8 Retention of Data

The Investigator must ensure that all records pertaining to the conduct of the clinical study, ICFs, drug accountability records, source documents, and other study documentation are adequately maintained for a period of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug.

The Investigator must not destroy any records associated with the study without receiving approval from the Sponsor. The Investigator must notify the Sponsor in the event of accidental loss or destruction of any study records.

Whenever possible, an original recording of an observation must be retained as the source document. However, a photocopy of a record is acceptable provided it is legible and is a verified copy of the original document.

All eCRF data entered by the site (including audit trail), as well as computer hardware and software (for accessing the data), will be maintained or made available at the site in compliance with applicable record retention regulations. The CRO will retain the original eCRF data and audit trail.

14.9 Financial Disclosure

Financial Disclosure statements will be handled in a separate agreement apart from the protocol, kept on file, and submitted as applicable with any subsequent license application.

14.10 Publication and Disclosure Policy

The data generated in this clinical study are the exclusive property of the Sponsor and are confidential. Any publication of the results of this study must be authorized by the Sponsor. The Sponsor will have the opportunity to review any publications that arise from the Investigators before submission for publication. Any such review and approval of publications related to the study shall be made pursuant to the process agreed between the parties in the site's clinical trial agreement with Sponsor. Authorship on any publication of the results from this study will be based on contributions to study design, data acquisition and analysis, and interpretation of results.

15 REFERENCE LIST

[redacted]

[redacted]

[redacted]

APPENDIX 1. SCHEDULE OF EVENTS

	Screening	Treatment Period[a]						EoT/ET	Phone Call[b]	Phone Call[b]
	Day -3 to Day -1	Baseline Day 1	Day 3	Day 5	Day 7	Day 10[c]	Day 14	Day of Hospital Discharge	Day 28	Day 90
Informed consent	X									
Medical history	X									
Demographics (age, sex, race)	X									
SARS-CoV-2 infection by RT-PCR or COVID-19 tests authorized under EUA	X									
Serum pregnancy test (for women only)	X	X					X	X		
Check inclusion and exclusion criteria	X	X								
Complete physical examination (including height and weight)[d]	X									
Targeted physical examination[d]		X	X	X	X	X	X	X		
Randomization		X								
[redacted]	X	X	X	X	X	X	X	X		
Ventilator utilization[e]	←	—	—	—	—	—	—	→		
[redacted]	X	X	X		X		X	X		
[redacted]	←	—	—	—	—	—	—	—	—	→
Vital signs[g]	X	X	X	X	X	X	X	X		
[redacted]	X	X	X	X	X	X	X	X		
Confirm daily conduct of vital signs and safety labs[h]		←	—	—	—	—	→			
Hematology[g,h]	X	X	X	X	X	X	X	X		
Clinical chemistry[g,h]	X	X	X	X	X	X	X	X		
Coagulation (INR)[g,h]	X	X	X	X	X	X	X	X		
Pharmacokinetic sample plasma[i]		X			X		X	X		

	Screening	Treatment Period[a]						EoT/ET	Phone Call[b]	Phone Call[b]
	Day -3 to Day -1	Baseline Day 1	Day 3	Day 5	Day 7	Day 10[c]	Day 14	Day of Hospital Discharge	Day 28	Day 90
Plasma biomarker samples		X	X		X		X	X		
Serum biomarker samples		X	X		X		X	X		
Urinalysis (dipstick, followed up by micro if abnormal)	X	X	X	X	X	X	X	X		
Adverse events	←	—	—	—	—	—	—	—	→	
Concomitant medications	←	—	—	—	—	—	—	—	→	
Study drug administration [redacted]		←	—	—	—	—	→			
Hospital and ICU utilization[e]	←	—	—	—	—	—	—	—	—	→
Vital status								X	X	X

eCRF = electronic case report form; EUA = emergency use authorization; [redacted]; EoT = end of treatment; ET = early termination; ICU = intensive care unit; INR = international normalized ratio; [redacted]; PK = pharmacokinetic; RT-PCR = reverse transcription polymerase chain reaction; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; [redacted]

[a] The treatment duration will be a minimum of 7 days and up to 14 days or day of hospital discharge, whichever one is sooner. Once participants are discharged from the hospital, they will no longer be administered study drug.

[b] Additional information will be obtained from medical records.

[c] If participant is no longer being treated with study drug and has been discharged from the hospital, the remaining assessments may be omitted, except for the Day 28 and 90 phone calls and/or medical records.

[d] Physical examinations may be performed if can be done safely. Otherwise nursing assessment or verbal review of systems may be performed.

[e] [redacted]

[f] [redacted]

[g] [redacted]

[h] Vital signs and local laboratory assessments will be conducted per ICU standards and at least daily. Results from these safety laboratory assessments will be recorded on the days specified.

[i] Samples will be collected at the following timepoints:
Day 1: 0.5 hours (±15 min), 3 hours (±60 min), and 10 hours (± 120 min) postdose

Day 7: predose, 3 hours (±60 min), and 24 hours (±60 min) postdose
Day 14: predose for participants on study drug

If the participant is no longer being treated with study drug, discontinues the study early, or is not treated with study drug on Day 14, a single plasma sample for PK should be taken at the Day 14/EoT/ET Visit if possible. Actual PK sample collection time and dosing time will be recorded.

[j] For participants on hemodialysis, the study drug will be administered after the participant has completed the hemodialysis.

APPENDIX 2. BERLIN DEFINITION OF ARDS

	ARDS
Timing	Within 1 week of a known clinical insult or new or worsening respiratory symptoms
Chest imaging[a]	Bilateral opacities – not fully explained by effusions, lobar/lung collapse, or nodules
Origin of edema	Respiratory failure not fully explained by cardiac failure or fluid overload Need objective assessment (e.g., echocardiography) to exclude hydrostatic edema if no risk factor present
Oxygenation[b]	
Mild	200 mm Hg < $PaO_2/FiO_2 \leq$ 300 mm Hg with PEEP or CPAP ≥5 cm H_2O[c]
Moderate	100 mm Hg < $PaO_2/FiO_2 \leq$ 200 mm Hg with PEEP ≥5 cm H_2O
Severe	$PaO_2/FiO_2 \leq$ 100 mm Hg with PEEP ≥ 5 cm H_2O

CPAP = continuous positive airway pressure; FiO_2 = fraction of inspired oxygen; PaO_2 =partial pressure of arterial oxygen; PEEP = positive end-expiratory pressure.

[a] Chest radiograph or CT scan

[b] If altitude is higher than 1000 m, the correction factor should be calculated as follows: [$PaO_2/FiO_2 \times$ (barometric pressure/760)]

[c] This may be delivered noninvasively in the mild ARDS group

Source: [redacted]

APPENDIX 3. VENTILATION PROTOCOL AND FLUID MANAGEMENT PROTOCOL

May be modified per local institutional standards

ARDS Ventilation Protocol ([redacted])

Low tidal volume ventilation in patients with acute respiratory distress syndrome

Initial Ventilator Settings

Calculate predicted body weight (PBW)

Male = 50 + 2.3 [height (inches) – 60] or 50 + 0.91 [height (cm) – 152.4]
Female = 45.5 + 2.3 [height (inches) – 60] or 45.5 0.91 [height (cm) – 152.4]

Set mode to volume assistant-control

Set initial tidal volume to 6 mL/kg PBW

Set initial ventilator rate ≤ 35 breaths/min to match baseline minute ventilation

Subsequent tidal volume adjustment

Plateau pressure goal: Pplat ≤ 30 cm H_2O

Check inspiratory plateau pressure with 0.5 second inspiratory pause at least every 4 hours and after each change in PEEP or tidal volume

If Pplat > 30 cm H_2O, decrease tidal volume in 1 mL/kg PDW steps to 5 or if necessary to 4 mL/kg PWB

If Pplat < 25 cm H_2O and tidal volume < 6 mL/kg, increase tidal volume by 1 mL/kg PBW until Pplat > 25 cm H_2O or tidal volume = 6 mL/kg

If breath stacking (AutoPEEP) or severe dyspnea occurs, tidal volume may be increased to 7 or 8 mL/kg PDW if Pplat remains ≤ 30 cm H_2O

Arterial Oxygenation and PEEP

Oxygenation goal: PaO_2 55 to 80 mm Hg or SpO_2 88% to 95%

Use these FiO_2/PEEP combinations to achieve oxygenation goal:

FiO_2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
PEEP	5	5 to 8	8 to 10	10	10 to 14	14	14 to 18	18 to 24

PEEP should be applied starting with the minimum value for a given FiO_2
Pplat: plateau pressure. PaO_2: arterial oxygen tension. SpO_2: oxyhemoglobin saturation. PEEP: positive end-expiratory pressure. FiO_2: fraction of inspired oxygen.
Adapted from [redacted].

Fluid Management Protocol: FACTT-Lite ([redacted])

Central Venous Pressure (Recommended)	Pulmonary Artery Occlusion Pressure (Optional)	Mean Arterial Pressure ≥ 60 mm Hg and Off Vasopressors ≥ 12 hours	
		Urine output < 0.5 mL/kg/h	Urine output ≥ 0.5 mL/kg/h
> 8	> 12	Furosemide[a]; reassess in 1 h	Furosemide[a]; reassess in 4 h
4–8	8–12	Give fluid bolus; reassess in 1 h	Furosemide[a]; reassess in 4 h
< 4	< 8	Give fluid bolus; reassess in 1 h	No intervention; reassess in 4 h

[a] Recommended furosemide dosing = begin with 20 mg bolus or 3 mg/h infusion or last known effective dose. Double each subsequent dose until goal achieved (oliguria reversal or intravascular pressure target) or maximum infusion rate of 24 mg/h or 160 mg bolus reached. Do not exceed 620 mg/d. Also, if patient has heart failure, consider treatment with dobutamine.

Initiate this protocol within 4 hours of randomization in enrolled participants and continue until unassisted breathing or study Day 14, whichever occurs first.

Protocol Meta-rules:

1. Discontinue maintenance fluids
2. Continue medications and nutrition
3. Manage electrolytes and blood products per usual practice
4. For shock, use any combination of fluid boluses (recommended fluid bolus = 15 mL/kg crystalloid [round to nearest 250 mL] or 1 unit packed red cells or 25 g albumin) and vasopressor(s) to achieve mean arterial pressure ≥ 60 mm Hg as fast as possible. Wean vasopressors as quickly as tolerated beginning 4 hours after blood pressure has stabilized
5. Withhold diuretic therapy in renal failure (defined as dialysis dependence, oliguria with serum creatinine > 3 mg/dL, or oliguria with serum creatinine 0 – 3 with urinary indices indicative of acute kidney injury) and until 12 hours after last fluid bolus or vasopressor given

Please refer to the following table for the FACTT Conservative Fluid Management Protocol.

Supplemental Table: Fluid and Catheter Treatment Trial (FACTT) Conservative and Liberal Fluid Management Protocols ([redacted])

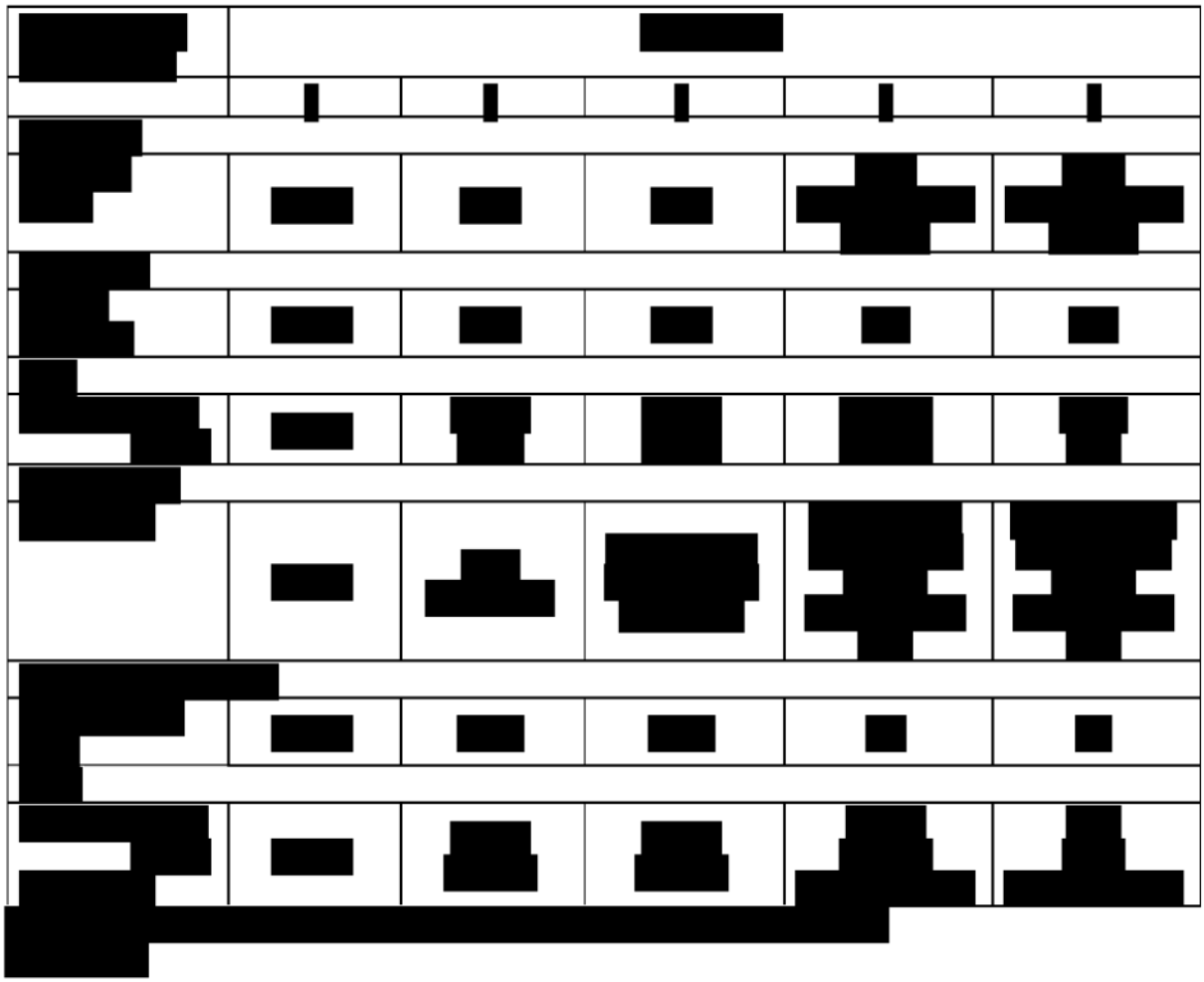
Measured intravascular pressure (mm Hg)				MAP < 60 mm Hg or a need for any vasopressor	MAP ≥ 60 mm Hg without vasopressors (except dopamine ≤ 5 µg/kg/min)			
CVP		PAOP			Average urinary output < 0.5 mL/kg/h		Average urinary output ≥ 0.5 mL/kg/h	
Conservative	Liberal	Conservative	Liberal		Ineffective Circulation§	Effective Circulation#	Ineffective Circulation§	Effective Circulation#
Range 1				vasopressor fluid bolus	KVO IV Dobutamine Furosemide	KVO IV Furosemide	KVO IV Dobutamine Furosemide	KVO IV Furosemide
> 13	> 18	> 18	> 24					
Range 2					KVO IV Dobutamine	KVO IV Furosemide	KVO IV Dobutamine	KVO IV Furosemide
9-13	15-18	13-18	19-24					
Range 3				fluid bolus vasopressor	Fluid bolus	Fluid bolus	Fluid bolus	Liberal KVO IV
4-8	10-14	8-12	14-18					Conservative Furosemide
Range 4					Fluid bolus	Fluid bolus	Fluid bolus	Liberal Fluid bolus
< 4	< 10	< 8	< 14					Conservative KVO IV

CVP = central venous pressure; IV = intravenous; KVO = keep vein open; PAOP = pulmonary artery occlusion pressure

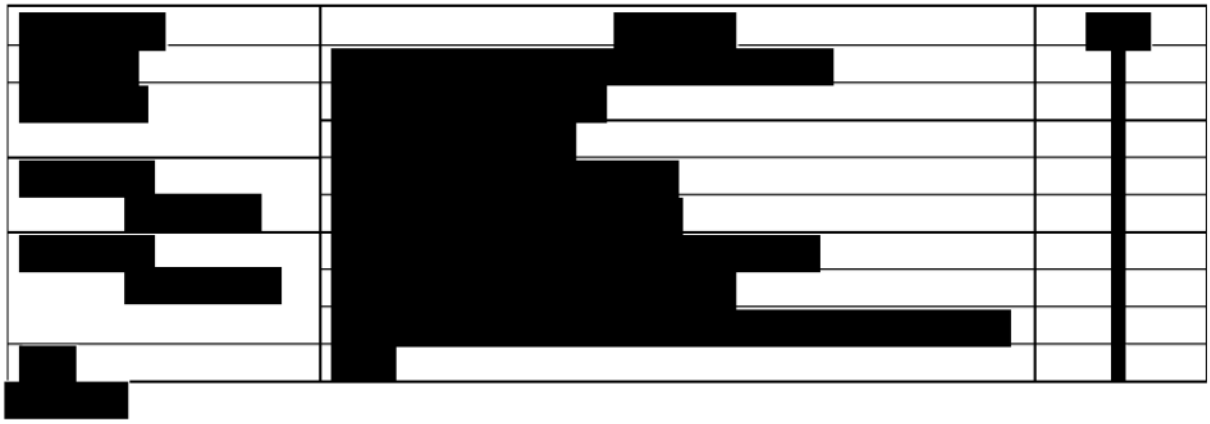
§ Ineffective circulation: Cardiac index < 2.5 L/min/m^2 or cold, mottled skin with capillary-refilling time > 2 seconds

Effective circulation: Cardiac index ≥ 2.5 L/min/m^2 or absence of criteria for ineffective circulation

APPENDIX 4. [redacted]



APPENDIX 5. [redacted]



APPENDIX 6. SPONSOR SIGNATURE

Study Title:	A randomized, double-blind, dose-ranging, placebo-controlled, Phase 2a evaluation of the safety, tolerability, and pharmacokinetics of PLN-74809 in participants with acute respiratory distress syndrome (ARDS) associated with at least severe COVID-19 (INTEGRIS-ARDS)
Study Number:	PLN-74809-ARDS-204
Final Date:	23 October 2020

This clinical study protocol was subject to critical review and has been approved by the Sponsor.

Signed: [redacted] Date: 23 OCT 2020

APPENDIX 7. INVESTIGATOR SIGNATURE

Study Title:	A randomized, double-blind, dose-ranging, placebo-controlled, Phase 2a evaluation of the safety, tolerability, and pharmacokinetics of PLN-74809 in participants with acute respiratory distress syndrome (ARDS) associated with at least severe COVID-19 (INTEGRIS-ARDS)
Study Number:	PLN-74809-ARDS-204
Final Date:	23 October 2020

I have read the protocol described above. I agree to comply with all applicable regulations and to conduct the study as described in the protocol.

Signed:_____ Date:_____

Name: _____

Affiliation:_____

Site Number:_____