CLINICAL TRIAL PROTOCOL

PLN-74809-IPF-202

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 idiopathic pulmonary fibrosis (IPF) (INTEGRIS-IPF)
Study Number:	PLN-74809-IPF-202
Study Phase:	2a
Product Name:	PLN-74809-000
IND Number:	139,998
EUDRACT Number:	2019-002709-23
Indication:	Treatment of idiopathic pulmonary fibrosis (IPF)
Sponsor:	Pliant Therapeutics Inc. 260 Littlefield Avenue South San Francisco, CA 94080, USA
Sponsor Study Director:	[redacted]

	Date
Original Protocol (v1.0):	11 June 2019
Protocol Amendment 1 (v1.1):	08 April 2020
Protocol Amendment 2 (v2.0):	30 November 2020
Protocol Amendment 3 (v3.0):	19 October 2021

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 idiopathic pulmonary fibrosis (IPF) (INTEGRIS-IPF)
Study Number:	PLN-74809-IPF-202
Study Phase:	2a
Objectives:	**Primary:** • Assessment of the safety and tolerability of PLN-74809 **Secondary:** • Assessment of pharmacokinetics (PK) of PLN-74809 **Exploratory:** [redacted]
Study Design:	This is a Phase 2a, multicenter, 4-part, randomized, double-blind, dose-ranging, placebo-controlled study to evaluate the safety, tolerability, and PK of once-daily (QD) treatment with PLN-74809 in participants with idiopathic pulmonary fibrosis (IPF). Each study part consists of an up to 28-day screening period, a 4-week (Part A), 12-week (Parts B and C), or at least 24-week (Part D) treatment period, and a 2-week (±3 days) post-treatment follow-up period. Part A enrollment has been completed, so is not further described herein; no further participants will be enrolled or treated in this part of the study. Part B enrollment has been completed; no further participants will be enrolled or treated in this part of the study. Part C enrollment was initiated following Data Safety Monitoring Board (DSMB) review of the clinical data supporting the evaluation of 40 mg dosing. The DSMB recommended continuation of Study PLN-74809-IPF-202 to evaluate doses of 80 mg and 160 mg without modification. Part D enrollment will initiate following DSMB review of the 80 mg and 160 mg clinical data from Part C. The dose level of Part D is supported by the clinical data from study [redacted] and the duration is supported by the chronic toxicology data. Potential participants who provide written informed consent will be screened for study eligibility up to 28 days before administration of the first dose of study drug. In Parts B, C and D, eligible participants will be randomized on Day 1 (Visit 2). Randomization will be stratified by use of standard of care (SoC) IPF therapy (pirfenidone or nintedanib) (SoC use; yes or no). In Part B, 29 eligible participants were randomized in a 3:1 ratio (active:placebo) and treated for 12 weeks. In Part C, approximately 56 eligible participants will be randomized in a 3:3:2 ratio (80 mg PLN-74809:160 mg PLN-74809:placebo) and treated for 12 weeks in parallel treatment groups. In Part D, an additional PLN-74809 dose of 320 mg is planned for evaluation based on the following criteria: • Part C has been completely enrolled (i.e., 56 participants have been randomized

	• Pending favorable review by the DSMB of: o All available safety and PK data from this study (Part C) o Safety and PK data from study [redacted], an ongoing Phase 1 study evaluating the safety, tolerability, and pharmacokinetics of PLN-74809 at multiple doses ranging from 80 to 320 mg in healthy participants, as described in the Investigator's Brochure In Part D, approximately 28 eligible participants will be randomized in a 3:1 ratio (320 mg PLN-74809:placebo) on Day 1 (Visit 2). Randomization will be stratified by use of SoC IPF therapy (pirfenidone or nintedanib) (SoC use; yes or no). Study treatment will be administered for at least 24 weeks. Treatment will continue for all participants in Part D until the last participant enrolled in Part D reaches Week 24. Participants who discontinue study drug for safety reasons prior to completion of 12 weeks (Parts B and C) or at least 24 weeks (Part D) of treatment will be asked to remain in the study to complete all remaining assessments; if this is not feasible, they will be asked to return to the clinic for an Early Termination (ET) visit for follow-up evaluations. The DSMB will assess participant safety at predetermined intervals during the study, including prior to initiating Part D and following the enrollment of the last participant in Part D. [redacted]
Study Population:	Parts B, C and D of this study intend to enroll approximately 112 participants with mild-to-moderate IPF, who comply with the following eligibility criteria: **Inclusion Criteria:** 1. Participants, aged 40 years or older 2. Diagnosis of IPF for up to 5 years prior to screening based on American Thoracic Society (ATS)/ European Respiratory Society (ERS)/ Japanese Respiratory Society (JRS)/ Latin American Respiratory Society (ALAT) 2018 guidelines [redacted] **Note**: If IPF diagnosis is within > 3 to ≤ 5 years at screening, the participant must have evidence of progression within the last 24 months, [redacted] 3. [redacted] 4. Diffusing capacity for carbon monoxide (DLco) (hemoglobin-adjusted) ≥ 30%; historical DLco for entry in the study is permitted if within 1 month of screening 5. Participants currently receiving treatment for IPF with nintedanib or pirfenidone are allowed, provided these drugs have been given at a stable dose for at least 3 months before the Screening visit and are expected to remain unchanged during the study (stable dose is defined as the highest dose tolerated by the participant during ≥ 3 months) 6. Estimated glomerular filtration rate ≥ 50 mL/min, according to the Cockcroft-Gault equation 7. Female participants of non-childbearing potential must be surgically sterile or postmenopausal 8. Female participants of childbearing potential must use a contraceptive method with a failure rate of < 1% per year or remain abstinent (refrain from heterosexual intercourse) during the treatment period and for 1 month after the last dose of study treatment. Male participants with female partners of childbearing potential must agree to use contraceptive measures or remain abstinent (refrain from heterosexual intercourse) during the treatment period and for at least 3 months after the last dose of study treatment.

9. Participants must agree to abstain from sperm or egg donation for the duration of the study, through to 3 months or 1 month, respectively, after administration of the last dose of study drug.
10. Able to read and sign a written informed consent form (ICF)

Exclusion Criteria:

1. Receiving any nonapproved agent intended for treatment of fibrosis in IPF
2. [redacted]
3. [redacted]
4. Any other condition that prevents the correct assessment of spirometry performance (for example a broken rib or chest pain of other origin that prevents adequate forced breathing)
5. Known acute IPF exacerbation or suspicion by the Investigator of such, within 6 months of screening
6. The extent of emphysema is greater than the extent of fibrotic changes on the most recent high-resolution computerized tomography (HRCT) scan (as determined by central reader); a) HRCT scan performed within 2 years of the screening date may be used
7. Severe pulmonary hypertension
8. Smoking of any kind (not limited to tobacco) within 3 months of screening or unwilling to avoid smoking throughout the study
9. Lower respiratory tract infection requiring antibiotics within 4 weeks prior to screening and/or during the screening period
10. History of malignancy within the past 5 years or ongoing malignancy other than basal cell carcinoma, resected noninvasive cutaneous squamous cell carcinoma, or treated cervical carcinoma in situ
11. End-stage liver disease
12. Renal impairment or end-stage kidney disease requiring dialysis
13. History of unstable or deteriorating [redacted] or pulmonary disease (other than IPF) within the 6 months prior to screening, including but not limited to the following:
    a. [redacted]
    b. [redacted]
    c. [redacted]
    d. [redacted]
14. Any of the following liver function test criteria above specified limits: total bilirubin > 1.5 × the upper limit of normal (ULN); aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 × ULN; alkaline phosphatase > 2.5 × ULN.

    Note: participants currently receiving nintedanib or pirfenidone as IPF SoC treatment, who have previously presented any liver function test elevations associated with nintedanib or pirfenidone treatment greater than that described above or resulting in dose reduction, treatment interruption, or discontinuation are not eligible.

	15. Any of the following at screening: hemoglobin < 10.0 g/dL, or neutrophils < 1500 /mm^3, or platelets < 100,000 /mL 16. Pregnant or lactating females 17. Daily use of phosphodiesterase-5 (PDE-5) inhibitor drugs (e.g., sildenafil, tadalafil, other) (Note: Intermittent use for erectile dysfunction is allowed) 18. A medical or surgical condition known to affect drug absorption (e.g., major gastric surgery) 19. Surgical procedures planned to occur during the study period 20. [redacted] 21. Has participated in a clinical study with an investigational agent in the 30 days prior to screening or 5 half-lives of the investigational drug, whichever is longer 22. Likely to have lung transplantation during the study (being on transplantation list is acceptable) 23. Any medical condition that, in the opinion of the Investigator, may make candidates not suitable for the study 24. Hypersensitivity to PLN-74809 or to any of the excipients, or placebo 25. [redacted]
Test Product, Dose, and Mode of Administration:	Part B: 40 mg of PLN-74809 or matching placebo administered orally QD Part C: 80 mg or 160 mg of PLN-74809 or matching placebo administered orally QD Part D: 320 mg of PLN-74809 or matching placebo administered orally QD PLN-74809 will be supplied by Pliant as [redacted]. Study drug will be taken once daily at approximately 24-hour intervals. Participants will take the study drug [redacted] and will drink up to 240 mL (~1 cup of water) [redacted].
Duration of Treatment:	The duration for Parts B and C of the study will be up to 18 weeks each (up to 4 weeks of screening, 12 weeks of treatment with study drug, and 2 weeks of follow up). The duration for Part D of the study will be variable depending on the study enrollment rate; i.e. the time between enrolling the first and last participant. The minimum duration of participation will be up to 30 weeks for the last participant enrolled (up to 4 weeks of screening, 24 weeks of treatment with study drug, and 2 weeks of follow up) and a maximum of up to 54 weeks for the first participant enrolled (up to 4 weeks of screening, up to 48 weeks of treatment with study drug, and 2 weeks of follow up). The end of study will commence once the last participant reaches 24 weeks of treatment. At that time, all study participants will complete their next scheduled visit (End of Treatment [EoT]) and the 2 weeks of follow up (End of Study [EoS]).
Exploratory Efficacy Assessments:	[redacted]

Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Assessments	• PK: plasma samples for PK analysis ([redacted]) will be obtained • Biomarkers: urine, plasma, and serum samples will be obtained • Pharmacogenomics: a whole blood sample for deoxyribonucleic acid (DNA) isolation will be collected before dosing on Day 1 from each participant in the study
Safety Assessments:	Collection of adverse events (AEs), safety laboratory values, vital signs, physical examinations, and [redacted]
Statistical Methods:	This is a safety study, [redacted] In general, data will be summarized using statistical summary methods; graphic presentations of data may also be prepared.

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LIST OF ABBREVIATIONS

ADL	activities of daily living
AE	adverse event
ALAT	Latin American Respiratory Society
ALT	alanine aminotransferase
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
ATS	American Thoracic Society
AUC_{0-24}	area under the plasma concentration-time curve from time zero to 24 hours
BALF	bronchoalveolar lavage fluid
[redacted]	[redacted]
C_{max}	maximum observed drug concentration
COVID-19	coronavirus disease 2019
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
[redacted]	[redacted]
DLco	diffusing capacity for carbon monoxide
DNA	deoxyribonucleic acid
DSMB	Data Safety Monitoring Board
[redacted]	[redacted]
eCRF	electronic case report form
EDC	electronic data capture
EoS	end of study
ERS	European Respiratory Society

ET	early termination
[redacted]	[redacted]
FSH	follicle-stimulating hormone
[redacted]	[redacted]
GCP	Good Clinical Practice
HIPAA	Health Information Portability and Accountability Act
HRCT	high-resolution computerized tomography
IC_{50}	50% inhibitory concentration
IC_{80}	80% inhibitory concentration
IC_{90}	90% inhibitory concentration
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	independent ethics committee
[redacted]	[redacted]
INR	international normalized ratio
IPF	idiopathic pulmonary fibrosis
IRB	institutional review board
IRT	interactive response technology
ITT	intent-to-treat
JRS	Japanese Respiratory Society
MAD	multiple ascending dose
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
[redacted]	[redacted]
NOAEL	no observed adverse effect level
[redacted]	[redacted]
PCLS	precision cut lung slices
PD	pharmacodynamic(s)

PDE-5	phosphodiesterase -5
PET	positron emission tomography
PK	pharmacokinetic(s)
PRO	patient-reported outcome
PSC	primary sclerosing cholangitis
pSMAD2/3	phosphorylated SMAD2/3
QD	once daily
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
REB	research ethics board
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
SoC	standard of care
SMAD2/3	family of proteins similar to the gene products of the Drosophila gene 'mothers against decapentaplegic' (*Mad*) and the *C. elegans* gene Sma, 2 or 3
SpO_2	peripheral capillary oxygen saturation
TEAE	treatment-emergent adverse event
TGF-β	transforming growth factor beta
ULN	upper limit of normal
US	United States
[redacted]	[redacted]

1 INTRODUCTION

Pliant Therapeutics Inc. (Pliant) is developing PLN-74809 for the treatment of idiopathic pulmonary fibrosis (IPF) and primary sclerosing cholangitis (PSC).

IPF is a rare condition, usually of the elderly, characterized by dyspnea and progressive loss of lung function leading to death, with median survival of 3.8 years after diagnosis based on 2014 data in the United States (US). The hallmark honeycomb appearance of IPF on high-resolution computerized tomography (HRCT) is the result of extensive fibrosis [redacted]. Although not completely understood, IPF has been proposed to stem from ongoing microinjury to alveolar epithelial cells. Injured epithelium results in upregulation of profibrotic factors such as transforming growth factor beta (TGF-β), which promote fibroblast recruitment, proliferation, and differentiation into fibrogenic myofibroblasts [redacted]. As the disease progresses, actively proliferating fibroblasts and myofibroblasts organize into fibroblastic foci and produce excessive fibrillar collagen that results in scarring of the lung which, in turn, leads to distortion of the tissue architecture and loss of function [redacted].

As has also been indicated to be the case for other fibrotic conditions, signaling mediated by α_v integrins is central to the control of fibrosis in the lungs. Specific roles proposed for $\alpha_v\beta_6$ in epithelial cells and $\alpha_v\beta_1$ in myofibroblasts for induction of fibrosis are summarized in the Investigator's Brochure for PLN-74809.

PLN-74809 is a small molecule and a selective dual inhibitor of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins (50% inhibitory concentration [IC_{50}] [redacted], respectively). Additionally, integrin-ligand binding assays have demonstrated that PLN-74809 is highly selective for $\alpha_v\beta_6$ and $\alpha_v\beta_1$ over other integrin receptors, including those leukocyte-expressed integrins where therapeutic inhibition has previously been associated with significant toxicities (e.g., vedolizumab [$\alpha_4\beta_7$ inhibitor; increased risk of infections, potential risk of progressive multifocal leukoencephalopathy (PML); [redacted]] and natalizumab [$\alpha_4\beta_1$ and $\alpha_4\beta_7$ inhibitor; increased risk of PML; [redacted]]). PLN-74809 reduced collagen synthesis in mice with bleomycin-induced lung injury, a commonly used experimental model for IPF ([redacted]). In ex vivo human IPF lung tissue (precision cut lung slices), treatment with PLN-74809 significantly decreased collagen type 1α1 messenger ribonucleic acid (mRNA) expression levels after a 3-day incubation period, providing an indication of antifibrotic activity in IPF. Mice completely deficient for $\alpha_v\beta_6$ function live a normal lifespan ([redacted]), suggesting that even full inhibition of such integrins is well tolerated.

1.1 Summary of Clinical Development

PLN-74809 is currently being investigated for the treatment of IPF and PSC.

Seven Phase 1 clinical studies in healthy participants have completed clinical conduct (Including Part 1 of Study [redacted]), with safety data, pharmacokinetic (PK) data, and preliminary pharmacodynamic (PD) data available. [redacted]

[redacted]

1.1.1 Completed Phase 1 Studies (Completed Clinical Conduct)

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.1.2 Ongoing Phase 1 Studies

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.1.3 Completed Phase 2 Studies (Completed Clinical Conduct)

[redacted]

1.1.4 Ongoing Phase 2 Studies

[redacted]

1.2 Study Rationale for PLN-74809-IPF-202

PLN-74809 is a selective, small molecule antagonist of integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$, with antifibrotic activity. PLN-74809 prevents $\alpha_v\beta_6$ and $\alpha_v\beta_1$ from binding to the arginine-glycine-aspartate sequence of the latency associated peptide of the TGF-β precursor protein, thereby blocking the release of the activated form of TGF-β1 and preventing binding to its receptors and activation of pathways relevant to fibrogenesis. PLN-74809 was demonstrated to be a potent and selective inhibitor of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins (human and murine) exhibiting geometric mean 50% inhibitory concentration (IC_{50}) values of [redacted] and [redacted] against the human receptors, respectively.

Precision cut lung slices (PCLS) generated from IPF patient lungs collected during transplant were used to evaluate the ability of PLN-74809 to block TGF-β activation and collagen gene expression in fibrotic human lung tissue ex vivo. Following 7 days incubation with PLN-74809 ([redacted]), collagen gene expression and SMAD2 phosphorylation (a marker of TGF-β signaling) in IPF patient PCLS were significantly reduced by approximately [redacted]. Further studies with bleomycin-injured mouse PCLS also showed significant reductions in collagen gene expression observed at concentrations of PLN-74809 as low as [redacted].

In vivo efficacy studies of PLN-74809 were performed using the bleomycin mouse model of pulmonary fibrosis. In a prophylactic treatment study (PLN-74809 administered orally or via minipump from [redacted] post-bleomycin challenge), PLN-74809 significantly decreased Ashcroft score, total hydroxyproline levels in lung tissue, and phosphorylation of [redacted] in lung tissue, confirming inhibition of collagen deposition and TGF-β signaling. Similar effects were observed with therapeutic treatment with PLN-74809 in the bleomycin model (oral administration from [redacted] days post-bleomycin challenge). Lung hydroxyproline levels were significantly reduced and morphometric analysis of lung tissue showed a dose-dependent and significant reduction in interstitial fibrillar collagen deposition in mice treated with PLN-74809.

The main purpose of the current study is to confirm that PLN-74809 is well tolerated by participants with IPF, whether as monotherapy or as an add-on to standard of care (SoC), and that the drug concentrations are similar to those previously found in healthy participants. [redacted]

Part D of the study will evaluate approximately 28 participants at the 320 mg dose for at least 24 weeks to further characterize the safety profile of PLN-74809. In Part D, ongoing safety and [redacted] assessments will continue until the last participant reaches 24 weeks of the study; therefore, safety and [redacted] assessments may extend to 48 weeks in participants randomized earlier in the study. [redacted]

The extended duration of exposure at the highest dose planned to be evaluated in Part D

(320 mg QD) is consistent with the intended use of PLN-74809 to treat the chronic and progressive fibrosis that characterizes IPF.

2 STUDY OBJECTIVES (PARTS B, C, AND D)

2.1 Primary Objective

- Assessment of the safety and tolerability of PLN-74809

2.2 Secondary Objectives

- Assessment of PK of PLN-74809

2.3 Exploratory Objectives

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 2a, multicenter, 4-part, randomized, double-blind, dose-ranging, placebo-controlled study to evaluate the safety, tolerability, and PK of once-daily (QD) treatment with PLN-74809 in participants with IPF. The 4 parts of the study are summarized in Table 1.

Each study part consists of an up to 28-day screening period, a treatment period, and a 2-week post-treatment follow-up period; see study schematic in Figure 1 (Part B), Figure 2 (Part C), and Figure 3 (Part D).

Table 1 Overview of Parts A, B, and C of Study PLN-74809-IPF-202

Study Part	Duration (Weeks)	PLN-74809 Formulation	Randomization (active:placebo)	Dose (mg) Regimen (QD)
A	4	[redacted]	1:1:1 per treatment group	20/40/0
B	12	[redacted]	3:1 per treatment group	40/0
Following review of clinical data from Part B				
C	12	[redacted]	3:3:2 per treatment group	80/160/0
Following review of clinical data from Part C				
D	At least 24	[redacted]	3:1 per treatment group	320/0

QD = once daily

Part A enrollment has been completed, so is not further described herein; no further participants will be enrolled or treated in this part of the study.

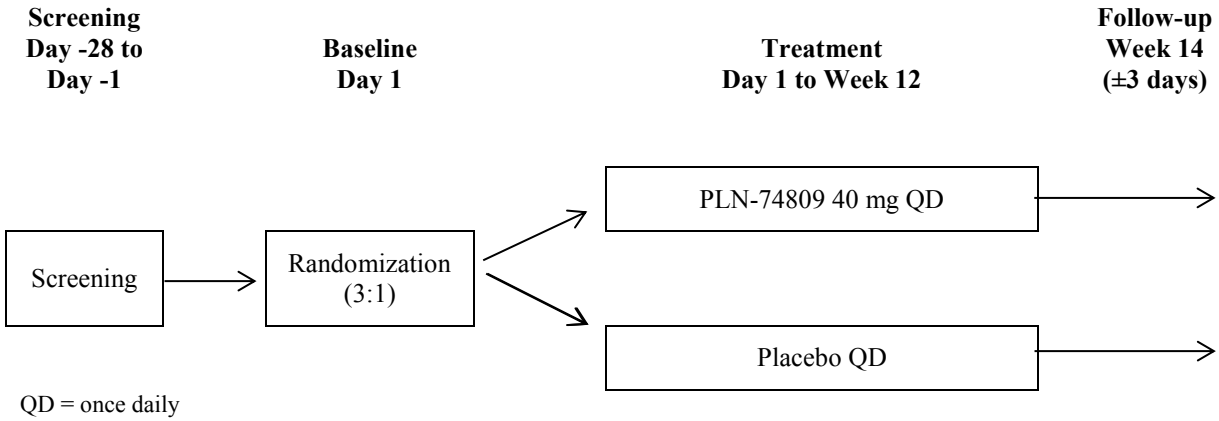
Part B enrollment has been completed; no further participants will be enrolled or treated in this part of the study.

Part C enrollment was initiated following Data Safety Monitoring Board (DSMB) review of the clinical data supporting the evaluation of 40 mg dosing. The DSMB recommended continuation of Study PLN-74809-IPF-202 to evaluate doses of 80 mg and 160 mg without modification.

Part D enrollment will initiate following DSMB review of the 80 mg and 160 mg clinical data from Part C. The dose level of Part D is supported by the clinical data from study [redacted] and the duration is supported by the chronic toxicology data.

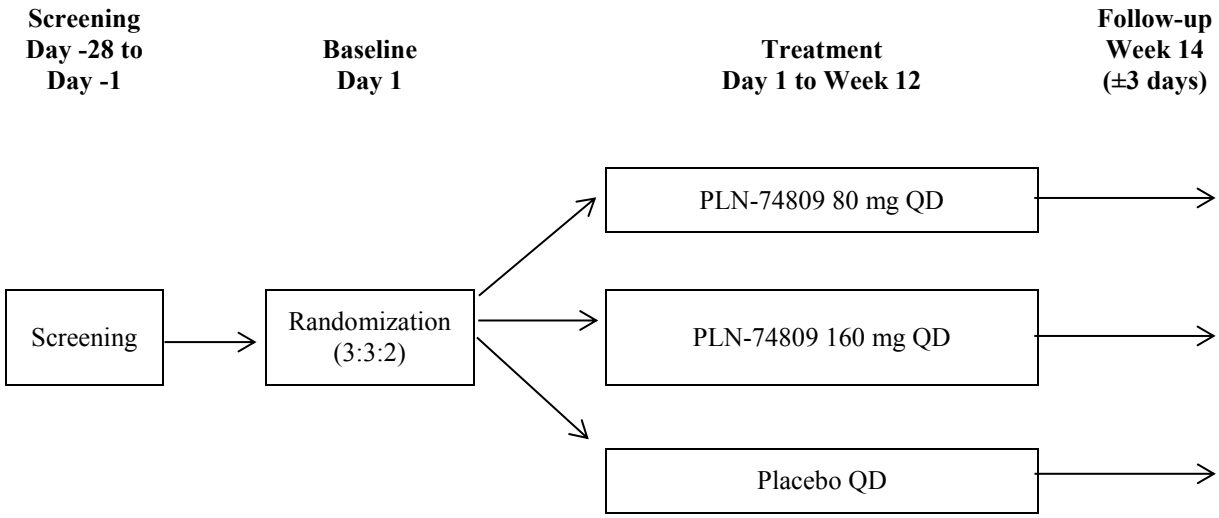
Please refer to the Investigator's Brochure for additional detailed information on chronic toxicology studies.

Figure 1 Study Schematic for Part B of Study PLN-74809-IPF-202



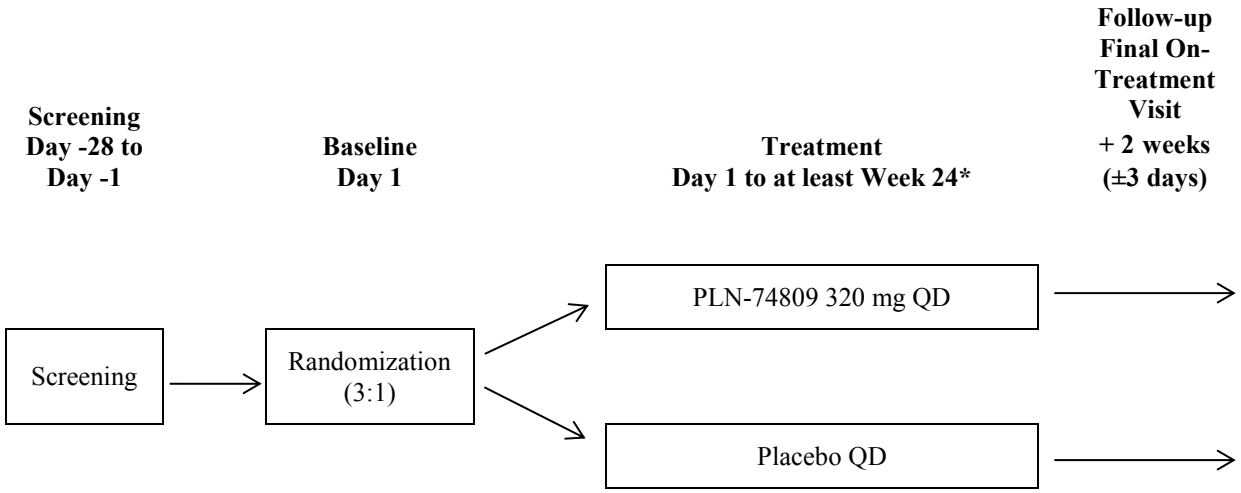
QD = once daily

Figure 2 Study Schematic for Part C of Study PLN-74809-IPF-202 (Parallel Dosing)



QD = once daily

Figure 3 Study Schematic for Part D of Study PLN-74809-IPF-202



QD = once daily

* Treatment will continue for all participants in Part D until the last participant enrolled in Part D reaches Week 24. All participants will complete visits every 8 weeks after the Week 24 visit until such time as the last participant enrolled has completed the Week 24 visit. At this time, all participants will be contacted to return and complete the Final On-Treatment Visit. All participants will have a Week 26 visit, which will be considered the End of Treatment Visit for the last participant to complete the Week 24 Visit.

Potential participants who provide written informed consent will be screened for study eligibility up to 28 days before administration of the first dose of study drug.

In Parts B, C and D, eligible participants will be randomized on Day 1 (Visit 2). Randomization will be stratified by use of SoC IPF therapy with pirfenidone or nintedanib (SoC use; yes or no).

In Part B, 29 eligible participants were randomized in a 3:1 ratio (active:placebo) and treated for 12 weeks.

In Part C, approximately 56 eligible participants will be randomized in a 3:3:2 ratio (80 mg PLN-74809:160 mg PLN-74809:placebo) and treated for 12 weeks in parallel treatment groups.

In Part D, an additional PLN-74809 dose of 320 mg is planned for evaluation based on the following criteria:

- Part C has been completely enrolled (ie, 56 participants have been randomized)
- Pending favorable review by the DSMB of:
  - All available safety and PK data from this study (Part C)
  - Safety and PK data from study [redacted], as described in the Investigator's Brochure

In Part D, approximately 28 eligible participants will be randomized in a 3:1 ratio (320 mg PLN-74809:placebo) on Day 1 (Visit 2). Randomization will be stratified by use of SoC IPF therapy (pirfenidone or nintedanib) (SoC use; yes or no). Study treatment will be administered for at least 24 weeks. Treatment will continue for all participants in Part D until the last participant enrolled in Part D reaches Week 24.

In Parts B and C, study drug will be administered at the investigational site on Day 1 and at Weeks 4 and 12. In Part D, study drug will be administered at the investigational site on Day 1 and at Weeks 4, 12, and 24. Participants will self-administer the study drug on an outpatient basis on all other days. In Parts B and C, participants will return to the study site for on-treatment evaluations on Day 1 and at Weeks 2, 4, 8, and 12 (see Schedule of Events in Appendix 1).

In Part D, participants will return to the study site for on-treatment evaluations on Day 1 and at Weeks 2, 4, 8, 12, 14, 20, 24, 26, and every 8 weeks after Week 24 until the last participant enrolled in Part D has completed this Week 24 visit. At this time, all participants will be contacted to return and complete the Final On-Treatment Visit (see Schedule of Events in Appendix 2). Blood and urine specimens for safety laboratory assessments will be collected after at least an 8-hour fast. A final study visit will be conducted 2 weeks ± 3 days after the last dose of study drug (Week 14 ± 3 days for Parts B and C; 2 weeks after the final On-Treatment Visit [± 3 days] for Part D), when participants will undergo a final [redacted] measurement, as well as follow-up end of study (EoS) evaluations.

Participants who discontinue study drug for safety reasons prior to completion of 12 weeks (Parts B and C) or at least 24 weeks (Part D) of treatment will be asked to remain in the study to complete all remaining assessments; if this is not feasible, they will be asked to return to the clinic for an Early Termination (ET) visit for follow-up evaluations.

[redacted] measurements will be obtained via spirometry and will be performed using study-standardized equipment and according to international guidelines (American Thoracic Society [ATS]/ European Respiratory Society [ERS]/ Japanese Respiratory Society [JRS]/ Latin American Respiratory Society [ALAT]). Spirometry reading will be centralized.

[redacted]

The DSMB will assess participant safety at predetermined intervals during the study, including prior to initiating Part D and following the enrollment of the last participant in Part D. [redacted]

The total number of participants enrolled in Parts B, C, and D of the study will be approximately 112, with approximately 84 receiving PLN-74809 and 28 receiving placebo.

3.2 Rationale for PLN-74809 Doses and Control Group

This study will be the first to characterize the safety, tolerability and PK of PLN-74809 in participants with IPF, with or without co-administration with SoC (pirfenidone or

nintedanib). The proposed randomized, double-blind study design allows a reduction in bias in the assessment of drug safety and tolerability. Stratification for background treatment with SoC will ensure a similar proportion of participants in each treatment group. The proposed sample size and 12-week treatment duration of Parts B and C are expected to provide meaningful PK information in the IPF population, as well as allow for preliminary evaluation of dose-dependent treatment effects on [redacted] study endpoints, comparing PLN-74809 to placebo.

The evaluation of PLN-74809 40 mg in Part B of this study is supported by the 13-week toxicology data, safety and PK data at these doses from study [redacted], as well as the PD findings from study [redacted], where this dose led to reduction of TGF-β activation in the lungs of healthy participants following 7 days of dosing, as assessed by reduction in phosphorylated SMAD2 (pSMAD2)/SMAD2 ratio in BALF (See PLN-74809 Investigator's Brochure for more details).

The evaluation of PLN-74809 80 mg and 160 mg doses in Part C is supported by all available safety and PK data from Parts A and B, as well as safety and PK data evaluating higher doses (80 and 160 mg) from study [redacted].

The evaluation of PLN-74809 320 mg in Part D is supported by all available safety and PK data from Parts B and C, as well as safety and PK data evaluating the higher dose (320 mg) from study [redacted].

In Study [redacted], PLN-74809 showed a favorable safety and tolerability profile in healthy participants after single doses of up to [redacted] mg and after 7 days of treatment at doses of up to [redacted] mg (Section 1.1.2). The safety margins determined after single doses of [redacted] mg and multiple doses of [redacted] mg were calculated using the NOAEL observed in toxicology studies in [redacted] for both area under the plasma concentration-time curve from time zero to 24 hours (AUC_{0-24}) and C_{max} for the measured [redacted] of PLN-74809. At all dose levels studied, there was a [redacted] between the unbound AUC_{0-24} and [redacted] no observed adverse effect level (NOAEL). See the PLN-74809 Investigator's Brochure for more details.

Comparison of the unbound AUC_{0-24} across all doses studied in the relevant dose escalation Phase 1 studies (i.e., [redacted]) demonstrates that doses ranging from [redacted] in the SAD and [redacted] in the MAD remain [redacted] the NOAEL established in the [redacted] toxicology studies.

The higher dose of 320 mg to be evaluated in Part D of this study provides a reasonable escalation and separation from the 80 and 160 mg doses evaluated in Part C, allowing for appropriate dose ranging [redacted] (please refer to the Investigator's Brochure for further details).

Emerging data indicate that a 320 mg QD dose of PLN-74809 achieves [redacted] exposure, expected to provide greater levels of $\alpha_v\beta_6$ target engagement, PD response and potential clinical benefit. Interim findings from an ongoing investigation measuring uptake kinetics of the $\alpha_v\beta_6$ knottin PET radiotracer in the IPF lung indicate > 90% target saturation

at single doses of [redacted] mg PLN-74809 (Study PLN-74809-201). In addition, preliminary data investigating PK and PD effects in BALF from healthy participants demonstrate a dose- and concentration- dependent reduction of SMAD2 phosphorylation (a marker of reduced TGF-β signaling) when PLN-74809 was dosed at [redacted] mg QD for 7 days (Study [redacted]). These dose-dependent PD responses were associated with [redacted] PLN-74809 concentrations that exceeded the cell-based $\alpha_v\beta_6$ IC_{50} (protein binding-corrected) for 6 hours (at [redacted] mg) or 24 hours (at [redacted] mg). A greater PD response is expected from a 320 mg dose, which is projected to achieve [redacted] concentrations that approach $\alpha_v\beta_6$ IC_{80} at steady-state. These higher [redacted] exposures achieved with a 320 mg QD dose are expected to elicit increased $\alpha_v\beta_6$ target engagement and additional PD response, leading to reduced TGF-β signaling in the lung and potentially slowing the clinical progression of pulmonary fibrosis.

Part D initiation will be contingent on DSMB review of the above-mentioned data from Part C.

Findings from this study will inform dose selection for future IPF studies.

3.3 Study Duration

The duration for Parts B and C of the study will be up to 18 weeks each (up to 4 weeks of screening, 12 weeks of treatment with study drug, and 2 weeks of follow up).

The duration for Part D of the study will be variable depending on the study enrollment rate; i.e. the time between enrolling the first and last participant. The minimum duration of participation will be up to 30 weeks for the last participant enrolled (up to 4 weeks of screening, 24 weeks of treatment with study drug, and 2 weeks of follow up) and a maximum of up to 54 weeks for the first participant enrolled (up to 4 weeks of screening, up to 48 weeks of treatment with study drug, and 2 weeks of follow up).

The end of study will commence once the last participant reaches 24 weeks of treatment. At that time, all study participants will complete their next scheduled visit (End of Treatment [EoT]) and the 2 weeks of follow up (End of Study [EoS]).

4 STUDY POPULATION SELECTION

4.1 Study Population

This study intends to enroll participants with mild-to-moderate IPF, with a life-expectancy of at least 6 months, who may or may not be receiving treatment with pirfenidone or nintedanib, and who otherwise do not present with other major health conditions that could affect the study drug or confound the study outcomes.

4.2 Inclusion Criteria

Each participant must meet the following criteria to be enrolled in this study:

1. Participants, aged 40 years or older
2. Diagnosis of IPF for up to 5 years based upon ATS/ERS/JRS/ALAT 2018 guidelines [redacted]

   Note: If IPF diagnosis is within > 3 to ≤ 5 years at screening, the participant must have evidence of progression within the last 24 months, [redacted]
3. [redacted]
4. Diffusing capacity for carbon monoxide (DLco) (hemoglobin-adjusted) ≥ 30%; historical DLco for entry in the study is permitted if within 1 month of screening
5. Participants currently receiving treatment for IPF with nintedanib or pirfenidone are allowed, provided these drugs have been given at a stable dose for at least 3 months before the Screening visit and are expected to remain unchanged during the study (stable dose is defined as the highest dose tolerated by the participant during ≥ 3 months)
6. Estimated glomerular filtration rate ≥ 50 mL/min, according to the Cockcroft-Gault equation
7. Female participants of non-childbearing potential must be surgically sterile or postmenopausal (refer to Section 6.7.4)
8. Female participants of childbearing potential must use a contraceptive method with a failure rate of < 1% per year or remain abstinent (refrain from heterosexual intercourse) during the treatment period and for 1 month after the last dose of study treatment (refer to Section 6.7.4).
   Male participants with female partners of childbearing potential must agree to use contraceptive measures (refer to Section 6.7.4) or remain abstinent (refrain from heterosexual intercourse during the treatment period and for at least 3 months after the last dose of study treatment.
9. Participants must agree to abstain from sperm or egg donation for the duration of the study, through to 3 months or 1 month, respectively, after administration of the last dose of study drug.
10. Able to read and sign a written informed consent form (ICF)

4.3 Exclusion Criteria

Participants who meet any of the following criteria will be excluded from the study.

1. Receiving any nonapproved agent intended for treatment of fibrosis in IPF.
2. [redacted]
3. [redacted]
4. Any other condition that prevents the correct assessment of spirometry performance (for example a broken rib or chest pain of other origin that prevents adequate forced breathing).
5. Known acute IPF exacerbation or suspicion by the Investigator of such, within 6 months of screening.
6. The extent of emphysema is greater than the extent of fibrotic changes on the most recent HRCT scan (as determined by central reader); a HRCT scan performed within 2 years of the screening date may be used.
7. Severe pulmonary hypertension.
8. Smoking of any kind (not limited to tobacco) within 3 months of screening or unwilling to avoid smoking throughout the study.
9. Lower respiratory tract infection requiring antibiotics within 4 weeks prior to screening and/or during the screening period.
10. History of malignancy within the past 5 years or ongoing malignancy other than basal cell carcinoma, resected noninvasive cutaneous squamous cell carcinoma, or treated cervical carcinoma in situ.
11. End-stage liver disease.
12. Renal impairment or end-stage kidney disease requiring dialysis.
13. [redacted]

14. Any of the following liver function test criteria above specified limits: total bilirubin > 1.5× the upper limit of normal (ULN); aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3× ULN; alkaline phosphatase > 2.5× ULN.

    Note: participants currently receiving nintedanib or pirfenidone as IPF SoC treatment, who have previously presented any liver function test elevations associated with nintedanib or pirfenidone treatment greater than that described above or resulting in dose reduction, treatment interruption, or discontinuation are not eligible.

15. Any of the following at screening: hemoglobin < 10.0 g/dL, or neutrophils < 1500 /mm^3, or platelets < 100,000 /mL.
16. Pregnant or lactating females.
17. Daily use of phosphodiesterase-5 (PDE-5) inhibitor drugs (e.g., sildenafil, tadalafil, other) (Note: Intermittent use for erectile dysfunction is allowed.).
18. A medical or surgical condition known to affect drug absorption (e.g., major gastric surgery).
19. Surgical procedures planned to occur during the study period.
20. [redacted]
21. Has participated in a clinical study with an investigational agent in the 30 days prior to screening or 5 half-lives of the investigational drug, whichever is longer.
22. Likely to have lung transplantation during the study (being on transplantation list is acceptable).
23. Any medical condition that, in the opinion of the Investigator, may make candidates not suitable for the study.
24. Hypersensitivity to PLN-74809 or to any of the excipients, or placebo.
25. Currently receiving and expected to remain on treatment during the study with: [redacted]

5 STUDY DRUG AND ACCOUNTABILITY

5.1 Description of Study Drug

5.1.1 Study Drug

[redacted]

Parts A, B and C of this study used the [redacted]. PLN-74809 drug product for Part B and Part C of the study is supplied as 40-mg [redacted]. These PLN-74809 [redacted]

In Part D of this study, [redacted]. PLN-74809 drug product for Part D of the study is supplied as 80-mg [redacted]. These PLN-74809 [redacted]

5.1.2 Placebo

A corresponding matching placebo will be provided.

5.2 Packaging and Labeling

The Part B portion of the study evaluating a dose of 40 mg QD has been completed.

For the Part C portion of the study evaluating doses of 80 mg and 160 mg QD, the PLN-74809 [redacted].

For the Part D portion of the study evaluating a dose of 320 mg QD, the PLN-74809 [redacted]

Details are provided in the Pharmacy Manual.

5.3 Storage and Accountability

For Parts B and C ([redacted]), the study drug should be stored [redacted], whether at the site pharmacy or at the participant's home.

For Part D (80-mg [redacted]), the study drug should be stored [redacted] whether at the site pharmacy or at the participant's home.

All used and unused study medication must be returned to the study site at the visits specified in the Schedule of Events (Appendix 1 [Parts B and C] and Appendix 2 [Part D]) in order to perform accountability.

5.4 Treatment Compliance

Dosing will be performed in the presence of site staff every time the participant is on site on dosing days. For offsite dosing, participants will be provided with a dosing log in which they will collect dosing information for PLN-74809 and, if applicable, nintedanib or pirfenidone doses taken at home. Participants should return all used and unused medication vials or bottles to the site at each site visit.

Treatment compliance will be calculated comparing the amount of drug dispensed and drug returned.

6 STUDY TREATMENTS

6.1 Description of Treatments

Part B: 40 mg of PLN-74809 or matching placebo administered orally QD

Part C: 80 mg or 160 mg of PLN-74809 or matching placebo administered orally QD

Part D: 320 mg of PLN-74809 or matching placebo administered orally QD

PLN-74809 will be supplied by Pliant [redacted]. Study drug will be taken once daily at approximately 24-hour intervals.

6.2 Dose Modifications and Interruptions

There will be no dose modifications of the study drug. If the study drug needs to be interrupted for safety or tolerability issues, this should happen, as feasible, in consultation with the Medical Monitor and Study Director, who together with the Investigator will assess and decide whether the study drug interruption should be temporary or permanent on a case-by-case basis. Participants who discontinue study drug for safety reasons prior to completion of 12 weeks of treatment will be asked to remain in the study to complete all remaining assessments; if this is not feasible, then they will be asked to return to the clinic for an early termination visit.

Dose modifications or interruptions of pirfenidone or nintedanib treatment may be implemented only for safety and tolerability reasons [redacted], in accordance with their corresponding prescribing information and in consultation with the Medical Monitor and Study Director. This should not affect the administration of the study drug or the continuation of participants in the study.

6.3 Selection and Timing of Dose for Each Participant

Participants will be encouraged to take their study drug at the same time of the day, each day. Participants will take [redacted]) and will drink up to 240 mL (~1 cup of water) [redacted].

A dose will be considered missed if the participant cannot take the dose within 12 hours of their regular dosing time.

- If a participant has missed a dose of study drug and is still within 12 hours of the time it is usually taken, the participant should take a dose of the missed drug as soon as possible. The participant may then continue the usual dosing schedule.
- If the participant has missed a dose of study drug more than 12 hours after the time it is usually taken, the participant should not take the missed dose and should resume the usual dosing at the next scheduled time. The participant should not take a double dose to make up for a missed dose.

6.4 Method of Assigning Participants to Treatment Groups

Up to approximately 112 participants may be enrolled in study Parts B (n = 28), C (n = 56) and D (n = 28). The randomization for each of the dose cohorts in Parts B, C, and D will be 3:1 (active:placebo). Randomization will be stratified by use of SoC IPF therapy (pirfenidone or nintedanib) (SoC use; yes or no).

- In Part B, 28 eligible participants were randomized on Day 1 (Visit 2) in a 3:1 ratio (40 mg PLN-74809:placebo).
- In Part C, 56 eligible participants will be randomized on Day 1 (Visit 2) in a 3:3:2 ratio (80 mg PLN-74809:160 mg PLN-74809:placebo).
- In Part D, 28 eligible participants will be randomized on Day 1 (Visit 2) in a 3:1 ratio (320 mg PLN-74809:placebo).

Assignment will be performed in a blinded manner using interactive response technology (IRT) based on a previously generated randomization code. Randomization will occur immediately prior to dosing on the morning of the first dose (Day 1).

6.5 Blinding

The placebo treatment will resemble the active treatment [redacted]. This ensures that the participant, Investigator, clinical site staff, and Sponsor are unaware of the treatment allocation during the conduct of the study. The PLN-74809 or placebo will be provided as blinded kits and will be assigned to participants using a randomization code.

Procedures will be in place to allow prompt breaking of the blind by the investigator if needed for the safety management of a participant. Unblinding at the study site for any other reason will be considered a protocol deviation. The investigator is strongly encouraged to contact the sponsor's Study Director before unblinding any participant's treatment assignment, but must do so within one working day after the event. A written explanation of the reason for unblinding should be provided to the sponsor within 24 hours of breaking the blind. Refer to the IRT User Guide for a description regarding how investigators may access treatment information via the IRT system.

6.6 Concomitant Therapy

6.6.1 Allowed Medications

During screening, all medications including over the counter medications and herbal supplements taken during the 30 days prior to screening will be recorded and reviewed by the Investigator in consultation with the sponsor Study Director to determine whether the participant is suitable for inclusion. For other concomitant medications needed during the study conduct, the Investigator should consult with the sponsor Study Director as soon as feasible.

Only treatment with approved SoC for IPF (nintedanib or pirfenidone) is allowed. These drugs must have been given at a stable dose for at least 3 months before initiation of screening and be expected to remain unchanged during the study. In addition, for participants receiving nintedanib or pirfenidone, the time of drug administration should be collected each day samples are obtained for assessing PLN-74809 PK. Treatments to address IPF disease symptoms, (e.g., cough, gastroesophageal reflux disease, etc.) are allowed.

Preliminary results from a [redacted].

Other medications to provide reasonable patient care of comorbidities are allowed during the study; however, these should only be used if necessary because, at this stage of development, limited formal drug-drug interaction studies with PLN-74809 have been performed. If used, all concomitant medications including both prescription and nonprescription drugs should first be discussed with the Investigator and Sponsor's Study Director before administration. This requirement does not apply in the case of urgent, necessary treatment of AEs. In all cases, medications, including over the counter medications and herbal supplements, taken by participants during the course of the study will be recorded using the generic name of the medication.

Prolonged treatment with high doses of [redacted]; if such treatment is required, this must be discussed and approved by the Medical Monitor.

In vitro, PLN-74809 [redacted]

[redacted] **The Medical Monitor and Sponsor Study Director should be notified within 24 hours of any suspected or confirmed onset of [redacted].**

As this will be the first study where multiple doses of PLN-74809 and nintedanib may be co-administered, **participants receiving nintedanib should be monitored for potential tolerability issues,** [redacted]

6.6.2 Disallowed Medications

Preliminary results from a [redacted].

Co-administration of PLN-74809 with [redacted]

Use of [redacted]

[redacted].

[redacted].

Treatment with a disallowed medication, other investigational drug or investigational device is prohibited within 30 days or, in the case of medications, 5 half-lives (whichever is longer) before screening.

6.7 Restrictions

6.7.1 Prior Therapy

Previous use of IPF SoC treatment (pirfenidone or nintedanib) is allowed for participation in this study.

6.7.2 Fluid and Food Intake

Participants should be dosed with the study drug [redacted]). Dosing should be accompanied by approximately 240 mL water (1 cup).

6.7.3 Participant Activity Restrictions

Smoking of any kind is not permitted within 3 months of screening and throughout the study.

6.7.4 Contraception

Female Participants of Childbearing Potential

Female participants of childbearing potential must agree to use a contraceptive method with a failure rate of <1% per year or remain abstinent (refrain from heterosexual intercourse) during the treatment period and for 1 month after the last dose of study treatment.

A woman is considered to be of childbearing potential if:

- She has not reached a postmenopausal state, defined as ≥12 continuous months of amenorrhea with no identified cause other than menopause or 6 months of spontaneous amenorrhea with serum follicle-stimulating hormone [FSH] levels >40 mIU/mL
- She has not undergone surgical sterilization, defined as hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy

Examples of contraceptive methods with a failure rate of < 1% per year include:

- Bilateral tubal ligation
- Male sterilization (>3 months from Day 1 or provide a zero sperm count)
- Hormonal contraceptives that inhibit ovulation (initiated >3 months from Day 1)
- Hormone-releasing intrauterine devices (initiated >3 months from Day 1)
- Copper intrauterine devices (initiated >3 months from Day 1)

Male Participants

Male participants, including those who are surgically sterile, must agree to use contraceptive measures as defined below, or alternately to remain abstinent (refrain from heterosexual intercourse)

- Male participants, with female partners of childbearing potential, must use a condom plus an additional contraceptive method that together result in a failure rate of < 1% per year or remain abstinent during the treatment period and for at least 3 months after the last dose of study treatment.
- Male participants with pregnant female partners are excluded from this study
- Male participants whose female partners become pregnant during the study must stop the medication immediately as outlined in Section 8.6

Highly effective methods of birth control are defined as those with a failure rate of < 1% per year [redacted]

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. Complete abstinence is considered a highly effective method when refraining from heterosexual intercourse during the entire period of risk associated with the study treatment.

7 STUDY PROCEDURES

The Schedule of Events with study activities is provided in Appendix 1 (Parts B and C) and Appendix 2 (Part D).

When several assessments are required at the same time point, evaluations should be completed so that the PK sample is collected at the required time. It is understood that other assessments such as [redacted], vital signs, etc. will be performed as close to the time point as possible.

Obtaining informed consent and acquisition of the HRCT must be conducted at the clinical site. All other study visits and procedures may be conducted by a qualified research nurse at the participant's home (per participant and site preference).

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 prior to any study-related procedures being performed.

7.2 Medical History

Medical history of the previous 5 years will be reviewed and recorded at screening. It should also include any relevant information or condition relevant to the purposes of this study, regardless of the timeframe.

7.3 Demographic Information

Date of birth, sex, ethnicity, and race will be recorded at screening.

7.4 Physical Examination

Complete and targeted physical examinations will be performed at the time points specified in the Schedule of Events (Appendix 1 [Parts B and C] and Appendix 2 [Part D]). Complete physical examinations include general appearance, head, ears, eyes, nose, throat, dentition, thyroid, chest (heart, lungs), abdomen, skin, neurological, extremities, back, neck, musculoskeletal, and lymph nodes. Targeted physical examination after screening will only be performed based on prior findings in the general exam, and includes head, ears, eyes, nose, throat, heart, lungs, abdomen, skin, musculoskeletal and lymph nodes, and any pertinent system based on any prior findings. Physical examinations may be performed at various unscheduled time points if deemed necessary by an Investigator.

7.5 Vital Signs

Blood pressure and heart rate will be recorded with participants having rested for at least 3 minutes in a supine position. Body temperature (preferably by ear) will be measured and peripheral capillary oxygen saturation (SpO_2) will be measured using a finger pulse oximeter.

7.6 [redacted]

[redacted]

7.7 Clinical Laboratory Tests

7.7.1 Laboratory Parameters

Participants will be in a seated or supine position during blood collection. Safety laboratory tests (hematology, serum chemistry and coagulation) will be collected from fasting (at least 8 hours) participants where appropriate. A detailed list of laboratory tests is provided in Table 2. Creatinine clearance will be calculated using the Cockcroft-Gault equation.

Table 2 List of Laboratory Tests

Hematology:

- 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

Coagulation:

- International normalized ratio (INR)

Urinalysis:

- Appearance
- Bilirubin
- Color
- Glucose
- Ketones
- Microscopic examination of sediment
- Nitrite
- Occult blood
- pH
- Protein
- Specific gravity
- Urobilinogen

Serum Chemistry:

- Alanine aminotransferase (ALT)
- Albumin (ALB)
- Alkaline phosphatase (ALP)
- [redacted]
- 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
- High-sensitivity C-reactive protein (hsCRP)
- Lactate dehydrogenase (LDH)
- Phosphorus
- Potassium (K)
- Sodium (Na)
- Total cholesterol
- Total protein
- Triglycerides
- [redacted]
- Uric acid

Serum and urine human chorionic gonadotropin (hCG) (females)

7.7.2 Sample Collection, Storage, and Shipping

Refer to the study manual for details regarding sample collection, storage, and shipping.

7.8 Dispensing Study Drug

Participants will receive study drug at the timepoints indicated in the Schedule of Events.

7.9 Exploratory Efficacy Assessments

[redacted]

7.10 Pharmacokinetic Assessments

[redacted] plasma samples for PLN-74809 PK analysis will be obtained predose and at least 2 hours postdose at the visits indicated in the Schedule of Events (Appendix 1 [Parts B and C] and Appendix 2 [Part D]). Samples will be obtained and stored as detailed in the study manual.

The actual collection time of each sample, as well as the dosing time, must be recorded in the source data and on the eCRF. If the participant discontinues the study early, a plasma sample for PK should be taken at the ET visit if possible.

Aliquots of these PK samples may be used to measure nintedanib and/or pirfenidone concentrations in those participants who are receiving background SoC.

[redacted] (See Sections 9 and 10).

7.11 Pharmacodynamic Assessments (Biomarkers in Urine, Plasma, and Serum

Urine, plasma and serum samples will be obtained at predetermined times as indicated in the Schedule of Events (Appendix 1 [Parts B and C] and Appendix 2 [Part D]). These samples

will be used to measure specific proteins, peptides, metabolites and/or mRNA transcripts that may be elevated in patients with inflammatory/fibrotic disease or act as PD markers that may change with inhibition of $\alpha_v\beta_6$. [redacted]
Details of sample collection, storage, and assay will be provided in the study manual.

A table of exploratory biomarkers of interest and evidence for their prognostic or pharmacodynamic value is presented below.

Category	Biomarker	Evidence of Prognostic or Pharmacodynamic Value
[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]

7.12 Pharmacogenomics

A whole blood sample for deoxyribonucleic acid (DNA) isolation will be collected before dosing on Day 1 from each participant in the study. The DNA samples will be analyzed to evaluate drug metabolic enzyme and transporter polymorphisms that may contribute to the variability in PK of PLN-74809. Detailed instructions for the handling and shipping of samples will be provided in the study manual.

7.13 Concomitant Medication and Adverse Event Assessments

At each study visit, participants will be asked about how they are feeling and what medications they are taking (have started/stopped, adjusted dose, etc.).

7.14 Missed Assessments

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

7.15 Appropriateness of Measurements

Collection of AEs, safety labs, vital signs, physical examinations and [redacted] are standard well-established parameters to assess the safety and tolerability of pharmacological agents.

PK samples will be analyzed according to predefined validated analytical methods to assess the concentrations of PLN-74809 in plasma. [redacted]

When available, appropriate standard guidelines will be used.

8 SAFETY ASSESSMENTS

8.1 Timing

In this study, AEs will be collected from the time the participant signs the ICF until the participant's last 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 (eg, endoscopy, appendectomy); the condition that leads to the procedure is an AE.
  - Situations where an untoward medical occurrence did not occur (eg, 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.
- 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 ([redacted] as described below. The clinical significance of the AE is determined by the Investigator. The Investigator is encouraged to consult with the Study Director.

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2 Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*.

Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.

Grade 4 Life-threatening consequences; urgent intervention indicated.

Grade 5 Death related to AE.

A semi-colon indicates 'or' within the description of the grade.

*Instrumental Activities of Daily Living (ADL) refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

[redacted]

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 the eCRF. Alternative causes, such as medical history, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drug should be considered and investigated, if appropriate. The following definitions are general guidelines to help assign grade of attribution.

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 (not related):	Evidence exists that the AE has an etiology other than the study drug. For SAEs, an alternative causality must be provided (eg, pre-existing condition, underlying disease, intercurrent illness, or concomitant medication).
Yes (related):	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 (not related):	Evidence exists that the AE has an etiology other than the study procedure.
Yes (related):	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 study participant becomes pregnant while enrolled in the study following administration of study drug and 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 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 the relevant information to the Sponsor using the Pregnancy Information Form to do so.

The pregnancy will be followed through delivery. If the pregnancy results in a congenital anomaly/birth defects/miscarriage, this will be considered and reported as an SAE as per definition detailed in Section 8.8.

8.7 Clinical Laboratory Adverse Events

Abnormal laboratory findings (eg, clinical chemistry, hematology and urinalysis) or other abnormal assessments (eg, [redacted], vital signs) per se are not reported as AEs. However, those abnormal findings that are deemed clinically significant or 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 of being serious, as described in Section 8.8). Clinically significant abnormal laboratory or other abnormal findings that are detected after consent or that are present at baseline and worsen after consent are included as AEs (and 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

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

- Is life-threatening
  - 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.
- Results in death
- Requires inpatient hospitalization (ie, admission) or prolongation of existing hospitalization. Except:
  - An emergency room visit without hospitalization is not considered fulfilling the serious criteria of hospitalization.

- Planned hospitalization or surgical procedures for an illness or disease which existed before the participant was enrolled in the clinical trial is not considered an SAE unless the condition deteriorated in an unexpected manner.

- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect/miscarriage
- Is an important medical event
  - An event that does not fulfill any of the serious criteria above, but is 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 but are not limited to: laboratory abnormalities [redacted] that lead to permanent study drug discontinuation, 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 Recording Adverse Events and Serious Adverse Events

All AEs and SAEs spontaneously reported by the participant and/or in response to an open question from study personnel or revealed by observation, physical examination or other diagnostic procedures will be recorded on the appropriate page of the eCRF. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE and must be recorded on the appropriate pages of the eCRF. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

8.8.3 Reporting Serious Adverse Events

In order to meet the requirements for expedited reporting of SAEs meeting specific requirements to applicable regulatory authorities and Institutional Review Boards (IRBs)/ Independent Ethics Committee (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 by completing the SAE form and emailing it to the below:

[redacted]

Initial notification of an SAE by telephone must be confirmed in writing within 24 hours by completing the SAE form. As further information regarding the SAE becomes available, such follow up information should be documented and sent to [redacted]

All SAEs must be followed by the Investigator to resolution or medical stabilization.

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

8.8.4 Reporting SAEs to Regulatory Authorities and IRB/IEC/REB

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 their regulations.

[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]

10 MONITORING AND MANAGEMENT OF [redacted] ABNORMALITIES

[redacted]

[redacted]

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

[redacted]

- [redacted]
- [redacted]

Clinical evaluation must include the following:

- Ruling out comorbidities and potential risk factors [redacted]
- [redacted]
- Review of potential concomitant medications [redacted]

[redacted]

[redacted]

11 EARLY DISCONTINUATION OF STUDY OR INDIVIDUAL PARTICIPANTS

In accordance with the Declaration of Helsinki, participants have the right to withdraw from the study at any time for any reason. The Investigator or Sponsor 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
- A serious or intolerable AE occurs
- Infection with COVID-19 that precludes safe participation in the study
- A clinically significant change in a laboratory parameter occurs
- [redacted]
- [redacted]
- The Sponsor or Investigator terminates the study
- The participant requests to be discontinued from the study

If a participant is withdrawn from the study or discontinues study drug, they will undergo early termination assessments; refer to the Schedule of Events for Parts B and C (Appendix 1) and Part D (Appendix 2).

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

This is a safety study with exploratory efficacy and biomarker assessments; 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. The contract research organization (CRO) will be responsible for the preparation of tables and listings and will assist in the preparation of figures, which may be done by Sponsor personnel. A statistical analysis plan (SAP), prepared and agreed before final database lock, will describe the analytic approach and methods in more detail.

12.2 Determination of Sample Size

The sample size of approximately 21 participants receiving PLN-74809 per dose level is expected to provide a meaningful evaluation of PLN-74809 safety, tolerability and PK in the target population.

12.3 Analysis Populations

Safety Population: All randomized participants who receive at least one dose of study drug will be included in the safety analyses.

PK Analysis Population: All randomized participants who have sufficient PLN-74809 concentration data for PK calculation will be included in the PK analyses.

PD Analysis Population: All randomized participants who receive any amount of study drug and who have results from Baseline and from at least one post-baseline PD assessment will be included in the PD analyses.

Efficacy Intent-to-Treat (ITT) Population: All randomized participants.

Efficacy Per Protocol Population: Subset of the ITT population who complete the study without any major protocol violations.

12.4 Demographics and Baseline Characteristics

Data will be summarized using statistical summary methods.

12.5 Primary Endpoints

12.5.1 Primary Safety Endpoint

- Nature and proportion of AEs 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 the last study visit. Treatment-emergent adverse events (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.

Individual [redacted] results will be listed for each participant. Summaries of [redacted] by treatment and dose will include changes from baseline for each parameter.

Vital sign measurements other laboratory tests, concomitant medications, medical history and changes in physical examinations at each time point will be listed by participant. The number and percentage of participants with abnormal [redacted] will be summarized by treatment and dose.

Concomitant medications will be coded using the most current World Health Organization drug dictionary available.

12.6 Secondary Endpoints

12.6.1 Secondary Pharmacokinetic Endpoints

Plasma PLN-74809 concentrations ([redacted]) 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.

12.6.2 Secondary Pharmacodynamic Endpoints

Urine, plasma and serum samples will be analyzed for biomarkers (presence or actual concentration). These samples will be used to determine the levels of these markers in participants and the relationship between these markers. Results will be presented by listings, descriptive summary statistics and in graphical form by treatment and dose and expressed as the relative change (and or absolute) for each participant.

In addition, relationships between PK and PD may be evaluated in an [redacted] and presented in graphical manner.

12.7 Exploratory Endpoints

12.7.1 Exploratory Efficacy Endpoints

[redacted]

12.8 Other Assessments or Analyses

[redacted]

12.9 Interim Analysis

Interim analyses will be conducted at the time points indicated below:

- Following full enrollment and 12-week treatment duration with 40, 80, or 160 mg PLN-74809 (completion of Parts B and C)
- Following 12-week treatment duration with 320 mg PLN-74809 (Part D)

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 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 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 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, 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 between the Sponsor and CRO, and then submitted to the IRB/IEC/REB for approval as well as 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 is 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 their 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 carried out 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 Parts 50, 54 56, 312 and Part 11 as well as International Council on Harmonisation (ICH) E6: Guideline for Good Clinical Practice (ICH GCP) consolidated guidelines (E6) and applicable regulatory requirements.

14.3 Participant Information and Consent

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

The participant should be given a copy of the ICF in their native language. The informed consent process should be recorded in the source documentation. The original copy of the signed and dated informed consent 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 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 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 CRF and other documents submitted to the Sponsor, participants will be identified by a participant study number only. Documents that are not submitted to the Sponsor (eg, 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 (eg Health Insurance Portability and Accountability Act [HIPAA]). 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 supporting the participation of each participant in the study (source data). The eCRFs and other documentation supporting 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 CRFs 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 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 Monitoring Committee

A DSMB will be established to assess participant safety at predetermined intervals during the study, and as needed. Refer to the DSMB Charter for further details. [redacted]

14.8 Data Generation and Analysis

The investigative site will use eCRFs to record all the protocol-specified data for each participant 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.

14.9 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.

14.10 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.

14.11 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, enrollment, data analysis, and interpretation of results.

15 REFERENCE LIST

[redacted]

APPENDIX 1 SCHEDULE OF EVENTS: PARTS B AND C

	Screening	Treatment					EoS / ET
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Day -28 to Day -1	Baseline Day 1	Week 2 Day 14 (±2 days)	Week 4 Day 28 (±2 days)	Week 8 Day 56 (±3 days)	Week 12 Day 84 (±3 days)	Week 14 Day 98 (±3 days)
Informed consent	**X**						
Medical history	**X**						
Demographics (age, sex, race)	X						
[redacted]	[redacted]					[redacted]	
Serum pregnancy test	X						
Check inclusion and exclusion criteria	X	X					
Complete physical examination (including height and weight)	X						
Targeted physical examination		X	X	X	X	X	X
Randomization		X					
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]						
DLco	X						
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vital signs (post 3 minutes, supine; approx 2 hrs post dose and around the time of the [redacted])	X	X	X	X	X	X	X
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hematology (post 8-hour fast)	X	X	X	X	X	X	X
Clinical chemistry (post 8-hour fast)[redacted]	X	X	X	X	X	X	X
Coagulation (post 8-hour fast)	X	X	X	X	X	X	X
Pharmacokinetic sample plasma × 2 (predose and at least 2 hours postdose) [g]		X		X		X	X[g]
Pharmacokinetic nintedanib/pirfenidone sample plasma x 2 (predose and at least 2 hours post dose to PLN-74809)[h]		X		X		X	X

	Screening	Treatment					EoS / ET
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	Day -28 to Day -1	Baseline Day 1	Week 2 Day 14 (±2 days)	Week 4 Day 28 (±2 days)	Week 8 Day 56 (±3 days)	Week 12 Day 84 (±3 days)	Week 14 Day 98 (±3 days)
Pharmacogenomic sample		X					
[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]		[redacted]	
[redacted]		[redacted]		[redacted]		[redacted]	
Urine pregnancy test (positive tests will be confirmed with a serum test)		X		X	X	X	X
Urinalysis (dipstick, followed up by micro if abnormal)	X	X		X	X		X
Adverse events	←	—	—	—	—	—	→
Concomitant medications	←	—	—	—	—	—	→
Study drug administration ([redacted])		X		X		X	
Study drug dispensing		X		X	X		
Study drug accountability		X		X	X	X	X

[redacted]; EoS = end of study; ET = early termination; [redacted]; HRCT = high resolution computerized tomography; PK = pharmacokinetic; [redacted]

[a] A HRCT scan performed within 2 years of the screening date may be used for emphysema vs. fibrotic changes. [redacted]

[redacted]

[c] A historical value may be used if it has been completed within 1 month from the Baseline visit.

[redacted]

[redacted].

[redacted]

[g] [redacted] PLN-74809 levels will be measured. Actual PK sample collection time and dosing time will be recorded. If the participant discontinues the study early, a plasma sample for PK should be taken at the ET Visit if possible.

[h] For participants receiving nintedanib/pirfenidone only; timed relative to PLN-74809 dosing.

APPENDIX 2 SCHEDULE OF EVENTS: PART D

The Schedule of Events for Part D is presented in 2 sections: Screening through the Week 12 Visit and the Week 14 Visit through End of Study.

Screening through Week 12 Visit

	Screening	Treatment				(continued)
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Day -28 to Day -1	Baseline Day 1	Week 2 Day 14 (±2 days)	Week 4 Day 28 (±2 days)	Week 8 Day 56 (±3 days)	Week 12 Day 84 (±3 days)
Informed consent	**X**					
Medical history	**X**					
Demographics (age, sex, race)	X					
[redacted]	[redacted]					[redacted]
Serum pregnancy test	X					
Check inclusion and exclusion criteria	X	X				
Complete physical examination (including height and weight)	X					
Targeted physical examination		X	X	X	X	X
Randomization		X				
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]	[redacted]
[redacted]	[redacted]					
DLco	X					
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vital signs (post 3 minutes, supine; approx 2 hrs post dose and around the time of the [redacted])	X	X	X	X	X	X
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hematology (post 8-hour fast)	X	X	X	X	X	X
Clinical chemistry (post 8-hour fast)[redacted]	X	X	X	X	X	X
Coagulation (post 8-hour fast)	X	X	X	X	X	X

	Screening	Treatment (continued)				
	Visit 1	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**	**Visit 6**
	Day -28 to Day -1	**Baseline Day 1**	**Week 2 Day 14 (±2 days)**	**Week 4 Day 28 (±2 days)**	**Week 8 Day 56 (±3 days)**	**Week 12 Day 84 (±3 days)**
Pharmacokinetic sample plasma × 2 (predose and at least 2 hours postdose) [g]		X		X		X
Pharmacokinetic nintedanib/pirfenidone sample plasma x 2 (predose and at least 2 hours post dose to PLN-74809)[h]		X		X		X
Pharmacogenomic sample		X				
[redacted]		[redacted]		[redacted]		[redacted]
[redacted]		[redacted]		[redacted]		[redacted]
[redacted]		[redacted]		[redacted]		[redacted]
Urine pregnancy test (positive tests will be confirmed with a serum test)		X		X	X	X
Urinalysis (dipstick, followed up by micro if abnormal)	X	X		X	X	
Adverse events	←	—	—	—	—	→
Concomitant medications	←	—	—	—	—	→
Study drug administration ([redacted])		X		X		X
Study drug dispensing		X		X	X	X
Study drug accountability		X		X	X	X

[redacted]; ET = early termination; [redacted]; HRCT = high resolution computerized tomography; PK = pharmacokinetic; [redacted]

[a] A HRCT scan performed within 2 years of the screening date may be used for emphysema vs. fibrotic changes. [redacted]

[redacted]

[c] A historical value may be used if it has been completed within 1 month from the Baseline visit.

[redacted]

[redacted]

[redacted]

g [redacted] PLN-74809 levels will be measured. Actual PK sample collection time and dosing time will be recorded. If the participant discontinues the study early, a plasma sample for PK should be taken at the ET Visit if possible.

h For participants receiving nintedanib/pirfenidone only; timed relative to PLN-74809 dosing.

Week 14 Visit through End of Study

(continued)	Treatment							EoS / ET
	Visit 7	Visit 8	Visit 9	Visit 10	Visit 11[a]	Visit 12[a]	Week 48 / Unscheduled / End of Treatment Visit EoT[a,b]	End of Study Visit EoS
	Week 14 Day 98 (±3 days)	Week 20 Day 140 (±3 days)	Week 24 Day 168 (±3 days)	Week 26 Day 182 (±3 days)	Week 32 Day 224 (±5 days)	Week 40 Day 280 (±5 days)	Final On-Treatment Visit	Final On-Treatment Visit + 2 weeks (±3 days)
[redacted]			[redacted]					
Targeted physical examination	X	X	X	X	X	X	X	X
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vital signs (post 3 minutes, supine; approx 2 hrs post dose and around the time of the [redacted])	X	X	X	X	X	X	X	X
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hematology (post 8-hour fast)	X	X	X	X	X	X	X	X
Clinical chemistry (post 8-hour fast)[redacted]	X	X	X	X	X	X	X	X
Coagulation (post 8-hour fast)	X	X	X	X	X	X	X	X
Pharmacokinetic sample plasma × 2 (predose and at least 2 hours postdose)[f, h][redacted]			X					
Pharmacokinetic nintedanib/pirfenidone sample plasma x 2 (predose and at least 2 hours post dose to PLN-74809)[g,h][redacted]			X					
[redacted]			[redacted]					
[redacted]			[redacted]					
[redacted]			[redacted]					

(continued)	Treatment							EoS / ET
	Visit 7	**Visit 8**	**Visit 9**	**Visit 10**	**Visit 11[a]**	**Visit 12[a]**	**Week 48 / Unscheduled / End of Treatment Visit EoT[a,b]**	**End of Study Visit EoS**
	Week 14 Day 98 (±3 days)	**Week 20 Day 140 (±3 days)**	**Week 24 Day 168 (±3 days)**	**Week 26 Day 182 (±3 days)**	**Week 32 Day 224 (±5 days)**	**Week 40 Day 280 (±5 days)**	**Final On-Treatment Visit**	**Final On-Treatment Visit + 2 weeks (±3 days)**
Urine pregnancy test (positive tests will be confirmed with a serum test)	X	X	X	X	X	X	X	X
Urinalysis (dipstick, followed up by micro if abnormal)			X	X				X
Adverse events	←	—	—	—	—	—	—	→
Concomitant medications	←	—	—	—	—	—	—	→
Study drug administration ([redacted])			X					
Study drug dispensing		X	X		X	X		
Study drug accountability	X	X	X	X	X	X	X	

[redacted]; EoS = end of study; ET = early termination; [redacted]; HRCT = high resolution computerized tomography; PK = pharmacokinetic; [redacted]

[a] All participants will complete visits every 8 weeks after the Week 24 visit until such time as the last participant enrolled has completed the Week 24 visit. At this time, all participants will be contacted to return and complete the Final On-Treatment Visit.

[b] EoT Visit not required for the last participant to complete the Week 24 Visit; the Week 26 visit will be considered the EoT visit for this participant. This participant will then be required to complete a final EoS visit.

[redacted]

[f] [redacted] PLN-74809 levels will be measured. Actual PK sample collection time and dosing time will be recorded.

[g] For participants receiving nintedanib/pirfenidone only; timed relative to PLN-74809 dosing.

[h] If the participant discontinues the study early, a plasma sample for PK should be taken at the ET Visit if possible (PK at ET visit can be collected at any point in visit).

[redacted]

APPENDIX 3 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 idiopathic pulmonary fibrosis (IPF)
Study Number:	PLN-74809-IPF-202 (INTEGRIS-IPF)
Version	Protocol Amendment 3 (v3.0)
Final Date:	19 October 2021

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

Signed:_____ Date:_____

[redacted]

APPENDIX 4 INVESTIGATOR'S 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 idiopathic pulmonary fibrosis (IPF)
Study Number:	PLN-74809-IPF-202 (INTEGRIS-IPF)
Version	Protocol Amendment 3 (v3.0)
Final Date:	19 October 2021

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

Signed:_____ Date:_____

Name:_____

Affiliation:_____

Site Number:_____