CLINICAL TRIAL PROTOCOL

PLN-74809-IPF-205

Study Title:	A Phase 2a, randomized, double-blind, placebo-controlled evaluation of PLN-74809 on type 1 collagen deposition using ^{68}Ga-CBP8 PET/MRI imaging in participants with idiopathic pulmonary fibrosis (IPF)
Study Number:	PLN-74809-IPF-205
Study Phase:	2a
Product Name:	PLN-74809-000
IND Number:	139,998
Indication:	Treatment of idiopathic pulmonary fibrosis (IPF)
Sponsor:	Pliant Therapeutics Inc. 260 Littlefield Avenue South San Francisco, CA 94080, USA
Sponsor Study Director:	[redacted] Pliant Therapeutics Inc. [redacted]

	Date
Original Protocol (v1.0):	22 June 2021
Amendment 1:	4 October 2021

Confidentiality Statement

SYNOPSIS

Study Title:	A Phase 2a, randomized, double-blind, placebo-controlled evaluation of PLN-74809 on type 1 collagen deposition using ^{68}Ga-CBP8 PET/MRI imaging in participants with idiopathic pulmonary fibrosis (IPF)
Study Number:	PLN-74809-IPF-205
Study Phase:	2a
Number of Participants	Approx. 12 (8 receiving PLN-74809 and 4 receiving placebo)
Objectives:	**Primary:** • Quantification of type 1 collagen in the lung following 12 weeks of treatment with PLN-74809, as assessed by changes from Baseline in ^{68}Ga-CBP8 positron emission tomography (PET) / magnetic resonance imaging (MRI) tracer uptake patterns **Secondary:** • Assessment of the safety and tolerability of PLN-74809 in idiopathic pulmonary fibrosis (IPF) participants **Exploratory:** • Relationship between PLN-74809 systemic exposure and PET imaging and biomarkers in IPF participants • Forced vital capacity (FVC): absolute FVC volume and FVC as percent of predicted as assessed by spirometry • Patient-reported outcome (PRO): a visual analog scale (VAS) for cough severity
Study Design:	This is a Phase 2a, single-center, randomized, double-blinded, placebo-controlled study to evaluate type 1 collagen deposition in the lungs following once-daily (QD) treatment with 160 mg PLN-74809 for 12 weeks in participants with IPF. The study consists of an up to 28-day screening period, a 12-week treatment period, and a 2 week (±3 days) post treatment follow-up period. 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. Approximately 12 eligible participants will be randomized in a 2:1 ratio (160 mg PLN-74809 vs placebo; 8 receiving PLN-74809 and 4 receiving placebo) on Day 1 (Visit 3). Study treatment will be administered once daily for 12 weeks. Randomization will be stratified by use of standard of care (SoC) IPF therapy with pirfenidone or nintedanib (SoC use; yes or no). ^{68}Ga-CBP8 PET/MRI scans will be conducted within 7 days prior to baseline and at or within 7 days prior to Week 12, as indicated in the Schedule of Events. Participants who discontinue study drug for safety reasons prior to completion of 12 weeks of treatment will be encouraged 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. If a participant elects to withdraw from the study after the 6th week of randomization, an end of participation ^{68}Ga-CBP8 PET/MRI will be offered to the participant to enhance appropriate data capture. Potential acute exacerbations, respiratory-related hospitalizations, and/or respiratory-related deaths will be reviewed by an adjudication committee.

Study Population:	**Inclusion Criteria:** 1. Participants, aged 40 years or older 2. Diagnosis of IPF, within 8 years prior to screening, according to the American Thoracic Society (ATS)/ European Respiratory Society (ERS)/ Japanese Respiratory Society (JRS)/ Latin American Respiratory Society (ALAT) 2018 guidelines Note: If IPF diagnosis is within > 3 to ≤ 8 years at screening, the participant must have evidence of progression within the last 24 months, as defined by decline in FVC percent predicted based on a relative decline of ≥ 5% 3. FVC percent of predicted ≥ 45%; historical FVC for entry in the study is permitted if within 1 month of screening 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 either 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 9. 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. 10. 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 11. Able to understand the purpose of the study and its procedures and to sign a written informed consent form (ICF) **Exclusion Criteria:** 1. Hypersensitivity to PLN-74809 or to any of the excipients to PLN-74809 2. Not a suitable candidate or unlikely to comply with study requirements, in the opinion of the Investigator 3. Receiving any nonapproved agent intended for treatment of fibrosis in IPF 4. Forced expiratory volume during the first seconds of the forced breath (FEV1)/FVC ratio < 0.7 at screening 5. Clinical evidence of active infection, including but not limited to bronchitis, pneumonia or sinusitis that can affect FVC measurement during screening or at randomization 6. Any other condition that prevents the correct assessment of spirometry performance (e.g., a broken rib or chest pain of other origin that prevents adequate forced breathing) 7. Known acute IPF exacerbation or suspicion by the Investigator of such, within 6 months of screening

	8. Severe pulmonary hypertension 9. Smoking of any kind (not limited to tobacco) within 3 months prior to screening, as documented in the medical history, or unwilling to avoid smoking throughout the study 10. Lower respiratory tract infection requiring antibiotics within 4 weeks prior to screening and/or during the screening period 11. 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 12. End-stage liver disease 13. Renal impairment or end-stage kidney disease requiring dialysis 14. History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within the 6 months prior to screening, including but not limited to the following: a. Unstable angina pectoris or myocardial infarction b. Congestive heart failure requiring hospitalization c. Uncontrolled clinically significant arrhythmias (e.g., resulted in health care utilization or hospitalization) 15. Any clinically relevant electrocardiogram (ECG) abnormalities, including but not limited to, QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 msec for males or > 460 msec for females at the Screening Visit (including Day -1) or prior to administration of the initial dose of study drug 16. Any medical condition that, in the opinion of the Investigator, may make the candidate not suitable for the study 17. History of anaphylaxis to intravenous (IV) drugs 18. 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. 19. Any of the following at screening: hemoglobin < 10.0 g/dL, neutrophils < 1500 /mm3, or platelets < 100,000 /mL 20. Electrical implants such as cardiac pacemaker or perfusion pump 21. Ferromagnetic implants such as aneurysm clips, surgical clips, prostheses, artificial hearts, valves with steel parts, metal fragments, shrapnel, metallic tattoos anywhere on the body, tattoos near the eye, or steel implants, ferromagnetic objects such as jewelry or metal clips in clothing 22. Claustrophobic reactions 23. Research-related radiation exposure exceeds current Radiology Department guidelines (i.e. 50 mSv in the prior 12 months) 24. Unable to lie comfortably on a bed inside the PET/MRI 25. Body mass index (BMI) > 33 kg/m^2 (limit of the PET/MRI table) 26. Prior or current radiation to the thorax 27. Pregnant or lactating female participants 28. Male participants with pregnant female partners 29. A medical or surgical condition known to affect drug absorption (e.g., major

	gastric surgery) 30. Participation 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 trial, apart from PLN-74809 31. Currently receiving and expected to remain on treatment during the study with: potent and concomitant inhibitors or inducers of cytochrome P450 (CYP) 3A4, 2C9 or 2C19; potent inhibitors or inducers of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) or organic anion transporting polypeptide (OATP) 1B1/1B3 transporters; digoxin (a P-gp substrate with a narrow therapeutic window) 32. Daily use of phosphodiesterase-5 (PDE-5) inhibitor drugs (e.g., sildenafil, tadalafil, other) (Note: Intermittent use for erectile dysfunction is allowed.) 33. Surgical procedures planned to occur during the study period 34. Uncontrolled systemic arterial hypertension 35. Likely to have lung transplantation during the study (being on transplantation list is acceptable)
Test Product, Dose, and Mode of Administration:	PLN-74809 (80 mg immediate release tablets) 160 mg, oral, QD
Reference Therapy, Dose, and Mode of Administration:	Matching placebo - Oral, QD
PET Tracer, Dose, and Mode of Administration:	The ^{68}Ga-CBP8 PET/MRI tracer is not considered a study treatment but is an investigational tool used during the PET procedure for obtaining the images necessary for this trial. [68Ga]CBP8 is an intravenous injection given within 7 days prior to baseline and at or within 7 days prior to Week 12. The radiochemical dose is up to 12.9 mCi but in practice, the dose has averaged 5.5 mCi per subject.
Duration of Treatment:	12 weeks
Pharmacokinetic and Pharmacodynamic Assessments	**Pharmacokinetic Assessments** On Day 1, total and unbound plasma samples for PLN-74809 pharmacokinetic (PK) analysis will be obtained predose and at 2, 4, and 6 hours postdose. At steady-state, total and unbound plasma samples for PLN-74809 PK analysis will be obtained predose and at least 2 hours postdose at Weeks 4 and 12. **Pharmacodynamic Assessments** *PET/MRI Imaging for the Assessment of Type 1 Collagen Deposition* All PET/MRI will be performed at the Martinos Center for Biomedical Imaging at Massachusetts General Hospital. PET imaging will be performed at prespecified times as indicated in the Schedule of Events. Blood samples will be obtained prior to each PET/MRI and will be stored for future analyses. The total amount of radiation exposure from the PET/MRI is equal to a whole-body exposure up to 22 mSv (11 mSv per administration of ^{68}GaCBP8). *MRI for the Assessment of PET/MRI Relationship* All participants will undergo dynamic contrast-enhanced MRI during each PET/MRI session. This will be performed using gadoterate meglumine at a predefined weight-base dose and injection rate, as detailed in the study's Radiology Manual. *Biomarkers in Urine, Plasma, and Serum* Urine, plasma and serum samples will be obtained at predetermined times as indicated in the Schedule of Events. These samples will be used to measure specific proteins, peptides, metabolites and/or messenger ribonucleic acid (mRNA) transcripts that may

	be elevated in patients with inflammatory/fibrotic disease or act as pharmacodynamic (PD) markers that may change with inhibition of $\alpha_v\beta_6$. **Pharmacogenomic Assessments** A whole blood sample for deoxyribonucleic acid (DNA) isolation will be collected before dosing on Day 1 from each participant in the study.
Exploratory Efficacy Assessments:	**Spirometry** Absolute FVC volume and FVC percent of predicted will be assessed by spirometry at screening and at the timepoints specified in the Schedule of Events. FEV1 will be assessed by spirometry at screening. **Patient-reported Outcome (PRO)** Study participants will respond to a VAS for cough severity at the timepoints specified in the Schedule of Events.
Safety Assessments:	Open ended adverse event (AE) inquiry; clinical chemistry and hematology; vital signs; 12-lead ECG
Sample Size Justification:	The sample size of approximately 12 participants (8 participants receiving 160 mg PLN-74809 and 4 receiving placebo) is expected to provide a meaningful evaluation of PLN-74809 safety, tolerability and PK in the target population, and add to the data of approximately 21 participants planned to be evaluated at this dose level in an ongoing multicenter, dose ranging Phase 2a study (PLN-74809-IPF-202).
Statistical Methods:	**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 PET/MRI scan or PD assessment will be included in the PD analyses. **Primary Endpoint: PD** *Quantification of type 1 collagen in the lung following 12 weeks of treatment, as assessed by changes from Baseline in ^{68}Ga-CBP8 PET/MRI tracer uptake patterns.* PET/MRI scans will be interpreted by American Board of Nuclear Medicine (ABNM)-certified nuclear medicine physicians in an unblinded manner. Lung contours will be generated from baseline and post-treatment PET/MRI. Mean and maximum standardized uptake value (SUV) measurements of contoured lungs will be calculated using MIMS software, by analyzing the uptake values of ^{68}Ga-CBP8 PET/MRI within the lung, and by comparing values from the baseline and post-treatment scans. Numerical and graphical results will be presented by dose. In addition, relationships between PK and type 1 collagen deposition, as well as between MRI and PET imaging, may be evaluated in an exploratory fashion and presented in a graphical manner **Secondary Endpoint: Safety** Safety data from all participants who received at least one dose of study drug will be incorporated into the final safety analysis. **Exploratory Endpoints** *PK and PD* Plasma PLN-74809-versus-time profiles (with plasma concentrations on both a log and linear scale) will be plotted for each participant. Non-compartmental analysis will be used to calculate PK parameters as appropriate. Relationships between PK and type 1 collagen deposition, as well as between MRI and PET imaging, may be evaluated in an exploratory fashion and presented in a graphical manner.

	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, the relationship between these markers, and the level of PET tracer uptake (type 1 collagen deposition) in the lung. *Efficacy* Percent of predicted FVC and volume will be assessed using the standard spirometry procedure at the Chest Clinic at Massachusetts General Hospital and presented as absolute values and as percent of predicted values. Baseline FVC will be the average of the screening and Day 1 determinations. End-of-study FVC will be the average of Week 12 and Week 14 determinations. For PRO, cough VAS will be completed at the timepoints specified in the Schedule of Events.

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ABNM	American Board of Nuclear Medicine
ADL	activities of daily living
AE	adverse event
ALAT	Latin American Respiratory Society
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibody
anti-LC1	anti-liver cytosolic antigen type 1 (antibody)
anti-LKM1	anti-liver-kidney microsome type 1 (antibody)
anti-SMA	anti-smooth muscle antibody (antibody)
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
BMI	body mass index
BRCP	breast cancer resistance protein
C_{max}	maximum observed drug concentration
COL1A1	collagen type 1 alpha 1
COVID-19	coronavirus disease 2019
CRO	contract research organization
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
DILI	drug induced liver injury
DLco	diffusing capacity for carbon monoxide
DNA	deoxyribonucleic acid
ECG	electrocardiogram
eCRF	electronic case report form

EDC	electronic data capture
ERS	European Respiratory Society
ET	early termination
FDA	Food and Drug Administration
FEV1	forced expiratory volume during the first seconds of the forced breath
FSH	follicle-stimulating hormone
FVC	forced vital capacity
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
HIPAA	Health Information Portability and Accountability Act
HRCT	high-resolution computerized tomography
IC_{50}	50% inhibitory concentration
IC_{80}	80% inhibitory concentration
ICF	informed consent form
ICH	International Council on Harmonisation
IEC	independent ethics committee
IgG-1	immunoglobulin G1
INR	international normalized ratio
IPF	idiopathic pulmonary fibrosis
IRB	institutional review board
IRT	interactive response technology
IV	intravenous
JRS	Japanese Respiratory Society
MAD	multiple ascending dose
MATE1	multidrug and toxin extrusion transporter
mCI	millicurie
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
MRI	magnetic resonance imaging

mSv	millisievert
NOAEL	no observed adverse effect level
OATP	organic anion transporting polypeptide
P-gp	P glycoprotein
PCLS	precision cut lung slices
PD	pharmacodynamic(s)
PDE-5	phosphodiesterase -5
PET	positron emission tomography
PIPEDA	Personnel Information Protection and Electronic Documents Act
PK	pharmacokinetic(s)
PRO	patient-reported outcome
PSC	primary sclerosing cholangitis
QD	once daily
QLF	quantitative lung fibrosis
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
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
SUV	standardized uptake value
TEAE	treatment-emergent adverse event
TGF-β	transforming growth factor beta
ULN	upper limit of normal
US	United States
VAS	visual analog scale

1 INTRODUCTION

Pliant Therapeutics Inc. (Pliant) is developing PLN-74809 for the treatment of idiopathic pulmonary fibrosis (IPF), treatment of primary sclerosing cholangitis (PSC), and treatment of acute respiratory distress syndrome (ARDS) associated with at least severe coronavirus disease 2019 (COVID-19).

IPF is the most common interstitial lung disease usually observed in 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 (Lederer and Martinez, 2018). Although not completely understood, IPF appears to be a response to alveolar epithelial injury with the resultant fibrosis mediated by growth factors (Kreuter et al, 2015; Wilson and Raghu, 2015) and propagated by myofibroblasts. 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}) 5.7 nM and 3.4 nM, respectively, in an in vitro ligand-binding assay (protein-free); IC_{50} 30 nM and 19.5 nM (10.2 nM and 6.6 nM unbound), respectively, in an in vitro co-culture assay of transforming growth factor beta (TGF-β) activation. PLN-74809 reduced collagen synthesis in mice with bleomycin-induced lung injury, a commonly used experimental model for IPF (Moeller et al, 2008). In ex vivo human IPF lung tissue (precision cut lung slices), treatment with PLN-74809 significantly decreased collagen type 1 alpha 1 (*COL1A1*) 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 (Horan et al, 2008), suggesting that even full inhibition of such integrins is well tolerated.

1.1 Summary of Clinical Development

To date, 4 Phase 1 studies in healthy participants are completed. One Phase 1 and 4 Phase 2 studies are currently ongoing. All data from these studies are supportive of the continued clinical development of PLN-74809 across the current indications.

1.1.1 Completed Phase 1 Studies

In the first-in-human evaluation of PLN-74809 (PLN-74809-P1-01), a total of 71 healthy participants were exposed to PLN-74809 for up to 14 days, with single and multiple doses ranging from 10 to 75 mg. Overall, the study showed that single ascending dose (SAD) and multiple ascending dose (MAD) administration of PLN-74809 was well tolerated at all dose levels, with no apparent relationship between frequency or severity of adverse events (AEs) to PLN-74809 doses or to treatment duration.

In Study PLN-74809-P1-03, a total of 13 healthy participants were exposed to PLN-74809 at 20 and 40 mg for up to 7 days. Overall, the study showed that PLN-74809 was well tolerated and led to suppression of TGF-β signaling in the lung at the 40 mg dose.

In Study PLN-74809-106 (Relative Bioavailability Study), a total of 24 healthy participants were exposed to a single dose of 40 mg PLN-74809 in either oral solution or tablet formulation. There were no notable differences in the safety and tolerability of the 2 formulations.

In Study PLN-74809-107 (mass balance study), 12 healthy participants received a single 40 mg dose of ^{14}C-labelled PLN-74809. PLN-74809 was excreted mainly via the feces, and was safe and well tolerated. One minor metabolite was detected in plasma.

Overall, all the completed studies showed that SAD and MAD administration of PLN-74809 was safe and well tolerated.

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

1.1.2 Ongoing Phase 1 Study PLN-74809-104

Study PLN-74809-104 is a continued evaluation of higher single and multiple doses of PLN-74809 in healthy participants. To date, participants have received single doses of PLN-74809 up to 640 mg and multiple doses of PLN-74809 up to 320 mg.

PLN-74809 showed a favorable safety and tolerability profile after up to 7 days of treatment, with no new safety concerns observed during this dose-escalation study. There were no clinically significant alterations in vital signs, electrocardiogram (ECG) or laboratory parameters across either the SAD or MAD cohorts indicative of a safety signal. There were no deaths reported during or after the study period.

Please refer to the Investigator's Brochure for additional detailed information on this study. (Note that analysis of data from single doses greater than 320 mg and multiple doses greater than 160 mg is ongoing.)

1.1.3 Ongoing Phase 2 studies

Four Phase 2 studies evaluating doses of PLN-74809 are ongoing.

Study PLN-74809-IPF-201 is a Phase 2a open-label study to evaluate the effect of PLN-74809 on $\alpha_v\beta_6$ receptor occupancy using positron emission tomography (PET) imaging in participants with IPF evaluating single doses ranging from 60 to 320 mg. Evaluation of target engagement and the safety and tolerability of PLN-74809 is currently ongoing and no new safety concerns have been identified.

Study PLN-74809-IPF-202 is a Phase 2a, multicenter, 3-part, randomized, double-blind, dose-ranging, placebo-controlled evaluation of the safety, tolerability and pharmacokinetics (PK) of once daily treatment with PLN-74809 for 12 weeks in participants with IPF.

Study PLN-74809-PSC-203 is a Phase 2a, multicenter, 2-part, randomized, double-blind, dose-ranging, placebo-controlled evaluation of the safety, tolerability and PK of once daily treatment with PLN-74809 for 12 weeks in participants with PSC and suspected liver fibrosis.

Study PLN-74809-ARDS-204 is a Phase 2a, multicenter, 3-part, randomized, double-blind, dose-ranging, placebo-controlled evaluation of the safety, tolerability and PK of once daily treatment with PLN-74809 for 7-14 days in participants with ARDS associated with at least severe COVID-19.

At the time of protocol finalization, safety and tolerability data from these ongoing Phase 2 studies suggest no new safety concerns.

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

1.2 Study Rationale for PLN-74809-IPF-205

IPF is characterized by excessive type 1 collagen deposition in the lungs that replaces healthy parenchymal tissue with collagen-rich scar. As the disease advances, progressive architectural distortion and dysfunction ensues resulting in often subtle but limiting breathlessness, fatigue and cough. TGF-β is an important pleotropic cytokine that is a key regulator of tissue fibrogenesis in both normal wound repair and pathologic fibroproliferative diseases such as IPF. TGF-β is constitutively secreted and bound within the extracellular matrix in its latent or inactive form. Release or activation of latent TGF-β may occur with proteolytic cleavage via plasmin or matrix metalloproteinases, or interaction with several different integrins, namely $\alpha_v\beta_6$ (expressed on epithelial cells) and $\alpha_v\beta_1$ (expressed on fibroblasts) in the lung. In IPF, $\alpha_v\beta_6$ and $\alpha_v\beta_1$ expression are increased with a resultant increase in TGF-β signaling and its downstream pro-fibrotic targets, notably COL1A1.

PLN-74809 is an oral, once-daily, dual-selective inhibitor of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins in development for the treatment of IPF, with orphan drug designation granted by the US Food and Drug Administration (FDA). PLN-74809 was generally well tolerated in over 180 participants treated to date in clinical studies, with single doses up to 320 mg and multiple doses up to 160 mg once daily; additionally, single doses of up to 640 mg and multiple doses of 320 mg were evaluated and preliminary blinded data have not identified new safety concerns. The binding of PLN-74809 inhibits the interaction of these integrins with latency associated peptide and blocks the release of free TGF-β into the extracellular matrix for subsequent binding to its receptor and activation of profibrotic pathways, including collagen synthesis. 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 (200 nM or 1820 nM), collagen gene expression and SMAD2 phosphorylation (a marker of TGF-β signaling) in IPF patient PCLS were significantly reduced by approximately 50%. In vivo efficacy studies of PLN-74809 were also performed using the bleomycin mouse model of pulmonary fibrosis. In a prophylactic treatment study (PLN-74809 administered orally or via minipump from 1 to

14 days post-bleomycin challenge), PLN-74809 significantly decreased Ashcroft score, total hydroxyproline levels, new collagen synthesis, and phosphorylation of SMAD3 in lung tissue, confirming inhibition of collagen deposition via a reduction in TGF-β signaling. Similar effects were observed with therapeutic treatment with PLN-74809 in the bleomycin model (oral administration from 7 to 21 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. These data suggest that PLN-74809 is expected to decrease new collagen formation in the lungs of patients with IPF, which will be evaluated in this study.

^{68}Ga-CBP8, a PET radiotracer that binds specifically to type 1 collagen, has previously been shown to detect and quantify elevated collagen levels in patients with IPF compared to healthy individuals, particularly in the subpleural regions of the lung where fibrosis is known to be prominent (Montesi et al, 2019). Importantly, increased collagen tracer signal was also noted in radiographically normal areas on computerized tomography (CT) prior to architectural distortion, indicating the ^{68}Ga-CBP8 probe may be more sensitive than HRCT in detecting active and/or early fibrosis. Furthermore, ^{68}Ga-CBP8 uptake in mouse lungs has been shown to correlate with levels of fibrosis following injury, with data suggesting that the tracer more readily binds newly formed collagen in active disease than established mature collagen. PLN-74809 consistently, and in a dose-dependent manner, reduced *COL1A1* expression in murine models of bleomycin lung injury and PCLS. These findings suggest that ^{68}Ga-CBP8 may be an effective tool for measuring disease activity (e.g., recently deposited pulmonary collagen levels) and therefore a powerful tool for evaluating efficacy of anti-fibrotic agents such as PLN-74809 in clinical studies. Therefore, in the proposed 12-week study of PLN-74809, the measurement of ^{68}Ga-CBP8 PET ligand will serve two functions; changes over time will provide an exploratory endpoint of both pharmacodynamic (PD) activity and efficacy (reduced collagen levels) of PLN-74809.

To complement the evaluation of antifibrotic effects in the proposed PLN-74809-IPF-205 study, ongoing Phase 2 studies conducted in participants with IPF (PLN-74809-IPF-202) or PSC (PLN-74809-PSC-203) will assess the safety and tolerability of PLN-74809, along with exploratory endpoints relevant to fibrosis. In the PLN-74809-IPF-202 study, exploratory efficacy endpoints will be assessed, including change in forced vital capacity (FVC) and quantitative lung fibrosis (QLF) from baseline following 12 weeks of treatment with PLN-74809. These established (FVC) and exploratory assessments of progressive disease and collagen deposition in IPF will complement the current study, which will be first of its kind to quantify changes in type 1 collagen in the lungs of participants with IPF following 12 weeks of treatment with PLN-74809 using ^{68}Ga-CBP8 PET/ magnetic resonance imaging (MRI) tracer uptake.

2 STUDY OBJECTIVES

2.1 Primary Objective

- Quantification of type 1 collagen in the lung following 12 weeks of treatment with PLN-74809, as assessed by changes from Baseline in ^{68}Ga-CBP8 PET/MRI tracer uptake patterns

2.2 Secondary Objectives

- Assessment of the safety and tolerability of PLN-74809 in IPF participants

2.3 Exploratory Objectives

- Relationship between PLN-74809 systemic exposure and PET imaging and biomarkers in IPF participants
- FVC: absolute FVC volume and FVC as percent of predicted as assessed by spirometry
- Patient-reported outcome (PRO): a visual analog scale (VAS) for cough severity

3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This is a Phase 2a, single-center, randomized, double-blinded, placebo-controlled study to evaluate type 1 collagen deposition in the lungs following once-daily (QD) treatment with 160 mg PLN-74809 for 12 weeks in participants with IPF.

The study consists of an up to 28-day screening period, a 12-week treatment period, and a 2-week (±3 days) post treatment follow-up period.

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. Approximately 12 eligible participants will be randomized in a 2:1 ratio (160 mg PLN-74809 vs placebo; 8 receiving PLN-74809 and 4 receiving placebo) on Day 1 (Visit 3). Study treatment will be administered once daily for 12 weeks. Randomization will be stratified by use of standard of care (SoC) IPF therapy with pirfenidone or nintedanib (SoC use; yes or no).

^{68}Ga-CBP8 PET/MRI scans will be conducted within 7 days prior to baseline and at or within 7 days prior to Week 12, as indicated in the Schedule of Events (Appendix 1).

Participants who discontinue study drug for safety reasons prior to completion of 12 weeks of treatment will be encouraged 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. If a participant elects to withdraw from the study after the 6th week of randomization, an end of participation ^{68}Ga-CBP8 PET/MRI will be offered to the participant to enhance appropriate data capture.

Potential acute exacerbations, respiratory-related hospitalizations, and/or respiratory-related deaths will be reviewed by an adjudication committee.

3.2 Rationale for PLN-74809 Doses and Control Group

This study will quantify type 1 collagen expression in the lung following PLN-74809 exposure, as assessed by changes from baseline in ^{68}Ga-CBP8 PET/MRI tracer uptake patterns following 12 weeks of treatment with 160 mg of PLN-74809, administered once daily. Available safety, tolerability and PK data from Study PLN-74809-104 and Study PLN-74809-IPF-202 (i.e., Part B evaluating 40 mg once daily for 12 weeks; Part C has initiated and will evaluate doses of 80 or 160 mg once daily, in parallel groups) support evaluation of a dose of 160 mg, which is expected to achieve the target 80% inhibitory concentration (IC_{80}) for $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrin-mediated TGF-β1 activation (IC_{80} ~2300 ng/mL) for approximately 8 hours and the target IC_{50} (~500 ng/mL) for 24 hours. PLN-74809 160 mg is the highest dose evaluated in the ongoing dose ranging Study PLN-74809-IPF-202.

To complement prior and ongoing safety evaluations, the safety, tolerability and PK of PLN-74809 in participants with IPF, with or without co-administration with SoC (pirfenidone or nintedanib) will also be assessed. The proposed randomized, double-blind

study design allows a reduction in bias in the assessment of type 1 collagen expression and of drug safety and tolerability. Stratification for background treatment with SoC will ensure a similar proportion of participants on SoC in each treatment group. The proposed sample size and 12-week treatment duration are expected to provide meaningful PK information in the IPF population, comparing PLN-74809 to placebo. The proposed randomization strategy in this exploratory study, 2:1 (PLN-74809 : placebo), will allow for determination of change in type 1 collagen deposition over 3 months and the impact of PLN-74809, which is expected to lead to decreased type 1 collagen expression within the lung based on localized inhibition of TGF-β signaling.

The evaluation of PLN-74809 160 mg QD is supported by safety and PK data evaluating multiple doses of 160 mg from study PLN-74809-104. In Study PLN-74809-104, PLN-74809 showed a favorable safety and tolerability profile in healthy participants after single doses of up to 320 mg and after 7 days of treatment at doses of up to 160 mg, as described in the Investigator's Brochure; additionally, single doses of up to 640 mg and multiple doses of 320 mg were evaluated and preliminary blinded data have not identified new safety concerns (Section 1.1.2). The safety margins determined after single doses of up to 320 mg and multiple doses up to 160 mg were calculated using the no observed adverse effect level (NOAEL) observed in monkeys for both area under the plasma concentration-time curve from time zero to 24 hours (AUC_{0-24}) and maximum observed drug concentration (C_{max}) for the measured unbound concentrations of PLN-74809. At all dose levels studied, there was a substantial margin between the unbound AUC_{0-24} and the monkey NOAEL. See PLN-74809 Investigator's Brochure for more details.

The evaluation of PLN-74809 is also supported by safety and PK data from participants with IPF enrolled in study PLN-74809-IPF-202; in Part B, PLN-74809 showed a favorable safety and tolerability profile after daily doses of 40 mg for up to 12 weeks. No related treatment-emergent serious adverse events (SAEs) were reported, no new safety concerns were identified to date and the DSMB recommended continuation to Part C, evaluating PLN-74809 doses of 80 mg and 160 mg QD, without any modifications.

Taken together, the accumulating data from completed and ongoing Phase 1 and Phase 2 evaluations of PLN-74809 continue to highlight its favorable safety and tolerability profile and support the evaluation of the dose of 160 mg QD administered for 12 weeks in this study.

3.3 Study Duration

Participants will be on study for up to 18 weeks (4 weeks of screening, 12 weeks of treatment with study drug and 2 weeks of follow up).

4 STUDY POPULATION SELECTION

4.1 Study Population

This study intends to enroll participants with 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 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, within 8 years prior to screening, according to the American Thoracic Society (ATS)/ European Respiratory Society (ERS)/ Japanese Respiratory Society (JRS)/ Latin American Respiratory Society (ALAT) 2018 guidelines (Raghu et al, 2018)

   Note: If IPF diagnosis is within > 3 to ≤ 8 years at screening, the participant must have evidence of progression within the last 24 months, as defined by decline in FVC percent predicted based on a relative decline of ≥ 5%
3. FVC percent of predicted ≥ 45%; historical FVC for entry in the study is permitted if within 1 month of screening
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 either 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).
9. 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.

10. 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
11. Able to understand the purpose of the study and its procedures and to 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. Hypersensitivity to PLN-74809 or to any of the excipients to PLN-74809
2. Not a suitable candidate or unlikely to comply with study requirements, in the opinion of the Investigator
3. Receiving any nonapproved agent intended for treatment of fibrosis in IPF
4. Forced expiratory volume during the first seconds of the forced breath (FEV1)/FVC ratio < 0.7 at screening
5. Clinical evidence of active infection, including but not limited to bronchitis, pneumonia or sinusitis that can affect FVC measurement during screening or at randomization
6. Any other condition that prevents the correct assessment of spirometry performance (e.g., a broken rib or chest pain of other origin that prevents adequate forced breathing)
7. Known acute IPF exacerbation or suspicion by the Investigator of such, within 6 months of screening
8. Severe pulmonary hypertension
9. Smoking of any kind (not limited to tobacco) within 3 months prior to screening, as documented in the medical history, or unwilling to avoid smoking throughout the study
10. Lower respiratory tract infection requiring antibiotics within 4 weeks prior to screening and/or during the screening period
11. 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
12. End-stage liver disease
13. Renal impairment or end-stage kidney disease requiring dialysis
14. History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within the 6 months prior to screening, including but not limited to the following:
    a. Unstable angina pectoris or myocardial infarction
    b. Congestive heart failure requiring hospitalization
    c. Uncontrolled clinically significant arrhythmias (e.g., resulted in health care utilization or hospitalization)

15. Any clinically relevant ECG abnormalities, including but not limited to, QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 msec for males or > 460 msec for females at the Screening Visit (including Day -1) or prior to administration of the initial dose of study drug
16. Any medical condition that, in the opinion of the Investigator, may make the candidate not suitable for the study
17. History of anaphylaxis to intravenous (IV) drugs
18. 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.
19. Any of the following at screening: hemoglobin < 10.0 g/dL, neutrophils < 1500 /mm^3, or platelets < 100,000 /mL
20. Electrical implants such as cardiac pacemaker or perfusion pump
21. Ferromagnetic implants such as aneurysm clips, surgical clips, prostheses, artificial hearts, valves with steel parts, metal fragments, shrapnel, metallic tattoos anywhere on the body, tattoos near the eye, or steel implants, ferromagnetic objects such as jewelry or metal clips in clothing
22. Claustrophobic reactions
23. Research-related radiation exposure exceeds current Radiology Department guidelines (i.e. 50 mSv in the prior 12 months)
24. Unable to lie comfortably on a bed inside the PET/MRI
25. Body mass index (BMI) > 33 kg/m^2 (limit of the PET/MRI table)
26. Prior or current radiation to the thorax
27. Pregnant or lactating female participants
28. Male participants with pregnant female partners
29. A medical or surgical condition known to affect drug absorption (e.g., major gastric surgery)
30. Participation 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 trial, apart from PLN-74809
31. Currently receiving and expected to remain on treatment during the study with: potent and concomitant inhibitors or inducers of cytochrome P450 (CYP) 3A4, 2C9 or 2C19; potent inhibitors or inducers of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP) or organic anion transporting polypeptide (OATP) 1B1/1B3 transporters; digoxin (a P-gp substrate with a narrow therapeutic window)

32. Daily use of phosphodiesterase-5 (PDE-5) inhibitor drugs (e.g., sildenafil, tadalafil, other) (Note: Intermittent use for erectile dysfunction is allowed.)
33. Surgical procedures planned to occur during the study period
34. Uncontrolled systemic arterial hypertension
35. Likely to have lung transplantation during the study (being on transplantation list is acceptable)

5 STUDY DRUG AND ACCOUNTABILITY

5.1 Description of Study Drug

5.1.1 Study Drug

The zwitterion PLN-74809-000, and the phosphate salt PLN-74809-020 are derivatives of the parent form PLN-74809. Both are formulated as immediate-release tablets. In this study, the phosphate form will be tested, hereafter referred to as PLN-74809.

PLN-74809 drug product is supplied as 80-mg immediate release tablets. The PLN-74809 tablets are manufactured by dry granulation with standard excipients (microcrystalline cellulose, mannitol, crospovidone, magnesium stearate, and butylated hydroxytoluene), tablet compression, and spray coating of tablets.

5.1.2 Placebo

A corresponding matching placebo will be provided.

5.1.3 PET Tracer

The ^{68}Ga-CBP8 PET/MRI tracer is not considered a study treatment but is an investigational tool used during the PET procedure for obtaining the images necessary for this trial. [68Ga]CBP8 is given as an intravenous injection within 7 days prior to baseline and at or within 7 days prior to Week 12. The radiochemical dose is up to 12.9 mCi but in practice, the dose has averaged 5.5 mCi per subject.

5.2 Packaging and Labeling

The PLN-74809 oral tablets will be packaged in high-density polyethylene bottles with desiccant canisters. Details are provided in the Pharmacy Manual.

5.3 Storage and Accountability

The study drug should be stored refrigerated at 2°C to 8°C and protected from light, whether at the site pharmacy or at the participant's home.

All used and unused study medication bottles must be returned to the study site at the Week 4, 8, and 12 visits 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 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

160 mg of PLN-74809 or matching placebo administered orally QD (2 tablets)

PLN-74809 and matching placebo will be supplied by Pliant as a tablet for oral administration. 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 Sponsor 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 (e.g., liver enzyme elevation; see Section 9), in accordance with their corresponding prescribing information and in consultation with the Sponsor 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 the study drug on an empty stomach (no food for 2 hours before or 2 hours after dosing) and will drink up to 240 mL (~1 cup of water) after swallowing the study drug.

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

Approximately 12 eligible participants will be randomized in a 2:1 ratio (160 mg PLN-74809 vs placebo). Randomization will be stratified by use of SoC IPF therapy (pirfenidone or nintedanib) (SoC use; yes or no).

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 for tablet shape, size and color. This ensures that the participant, Investigator, clinical site study staff, and Sponsor study team directly involved in trial conduct 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 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.

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, no 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 Sponsor 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 systemic corticosteroids may induce CYP3A4 and reduce PLN-74809 concentrations; if such treatment is required, this must be discussed and approved by the Sponsor Study Director.

PLN-74809 is a moderate inhibitor of P-gp and multidrug toxin extrusion transporter (MATE1). Participants who receive substrates of these transporters should be monitored for potential tolerability issues.

This includes monitoring for signs and symptoms of lactic acidosis, which has been reported in patients receiving metformin, a substrate for MATE1. Symptoms of lactic acidosis include: malaise, myalgias, respiratory distress, somnolence, and abdominal pain. Laboratory abnormalities include elevated blood lactate levels, anion gap acidosis, increased lactate/pyruvate ratio; and metformin plasma levels generally >5 mcg/mL. If lactic acidosis is suspected or confirmed, metformin must be discontinued immediately, and the participant should undergo clinical evaluation and appropriate management. **The Sponsor Study Director should be notified within 24 hours of any suspected or confirmed onset of lactic acidosis.**

Coadministration of nintedanib with P-glycoprotein and CYP3A4 inhibitors or inducers may increase or decrease nintedanib exposure, respectively (see local prescribing information). **As PLN-74809 is a moderate inhibitor of P-gp (but not an inhibitor of CYP3A4), participants receiving nintedanib should be monitored for potential tolerability issues, including treatment-emergent elevations in liver enzymes (See Section 9)**.

6.6.2 Disallowed Medications

Treatment with potent inhibitors or inducers of CYP3A4, 2C9 or 2C19 or, potent inhibitors or inducers of P-gp, BCRP or OATP1B1/1B3 transporters is prohibited. This includes fluconazole (a strong inhibitor of 2C19 and a moderate inhibitor of 2C9 and 3A4), which is disallowed.

Treatment with digoxin, which has a narrow therapeutic window and is a substrate for P-gp, is not allowed since PLN-74809 is a moderate inhibitor of this transporter (IC_{50} 9.98 µM) and could increase digoxin exposures.

Use of rifampin (a potent inducer of CYP3A4) is not allowed, as it is expected to result in reduced PLN-74809 concentrations.

Grapefruit or grapefruit-containing foods and beverage are not allowed.

St. John's wort is not allowed.

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 on an empty stomach (no food for 2 hours before or 2 hours after dosing). 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, if that is their preferred and established lifestyle) 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.

Female and Male Participants

Highly effective methods of birth control are defined as those with a failure rate of < 1% per year (adapted from Trussell, 2004; CTFG 2014).

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 participant. 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.

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 ECGs, vital signs, etc. will be performed as close to the time point as possible.

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). 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 Electrocardiograms

Triplicate 12-lead ECGs will be obtained at the visits specified in the Schedule of Events (Appendix 1). ECG collection during the study will be performed using standardized equipment and centrally read. ECGs will be collected prior to a time-matched PK sample at

least 2 hours postdose). Additional 12-lead ECGs may be obtained at other times if clinically indicated, using unscheduled visits. All ECGs should be obtained after the participant has rested quietly in the supine position for at least 10 minutes with the triplicate ECGs recorded within ~ 5 to 10 minutes. The triplicate ECGs will be averaged and the mean values per time point (average of the 3 assessments) used to interpret the ECG tracings. QT correction will utilize the Fridericia Method (Fridericia 1920).

The Investigator (or designee) will evaluate the ECG tracings and will record 1 of the following interpretations on the electronic case report forms (eCRFs): normal; abnormal, not clinically significant; or abnormal, clinically significant. Clinically significant changes from baseline in ECG findings will be recorded as AEs. Refer to the ECG Manual for more information.

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. Results from these safety laboratory assessments will be recorded in the electronic data capture (EDC) as detailed in the Schedule of Events (Appendix 1).including at the end of treatment or at early termination. A detailed list of laboratory tests is provided in Table 1. Creatinine clearance will be calculated using the Cockcroft-Gault equation.

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

Table 1 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 **Other** Serum and urine human chorionic gonadotropin (hCG) (females)	**Serum Chemistry** - Alanine aminotransferase (ALT) - Albumin (ALB) - Alkaline phosphatase (ALP) - Alpha-1-acid-glucoprotein (AAG) - Amylase (reflex lipase if amylase ≥ 1.5 × ULN) - Aspartate aminotransferase (AST) - Bilirubin (total and direct) - Blood urea nitrogen (BUN) - Calcium (Ca) - Chloride (Cl) - Creatinine - Creatine kinase (CK) - Gamma-glutamyl transferase (GGT) - Glucose - High-sensitivity C-reactive protein (hsCRP) - Lactate dehydrogenase (LDH) - Phosphorus - Potassium (K) - Sodium (Na) - Total cholesterol - Total protein - Triglycerides - Troponins - Uric acid

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 (Appendix 1).

7.9 Pharmacokinetic Assessments

On Day 1, total and unbound plasma samples for PLN-74809 PK analysis will be obtained predose and at 2, 4, and 6 hours postdose.

At steady-state, total and unbound plasma samples for PLN-74809 PK analysis will be obtained predose and at least 2 hours postdose at Weeks 4 and 12, as indicated in the Schedule of Events (Appendix 1). 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.

If participants experience treatment-emergent elevations in liver enzymes or ECG abnormalities, additional PK samples will be collected at the time of repeat laboratory or ECG testing (See Sections 9 and 10).

7.10 Pharmacodynamic Assessments

7.10.1 PET/MRI Imaging for the Assessment of Type 1 Collagen Deposition

All PET/MRI will be performed at the Martinos Center for Biomedical Imaging at Massachusetts General Hospital. PET imaging will be performed at prespecified times according to the Schedule of Events (Appendix 1) using the collagen-targeted tracer, ^{68}Ga-CBP8 as synthesized at the Martinos Center for Biomedical Imaging, and following predefined instructions as detailed in the Radiology Manual for the study. The radiochemical dose is up to 12.9 mCi per administration; but in practice, the dose averages to 5.5 mCi per subject. The total amount of radiation exposure from the PET/MRI is equal to a whole-body exposure up to 22 mSv (11 mSv per administration of ^{68}GaCBP8). Blood samples will be obtained prior to each PET/MRI and will be stored for future analyses. Details for blood sample collection and processing are detailed in the Radiology Manual.

7.10.2 MRI for the Assessment of PET/MRI Relationship

All participants will undergo dynamic contrast-enhanced MRI during each PET/MRI session. This will be performed using gadoterate meglumine at a predefined weight-base dose and injection rate, as detailed in the study's Radiology Manual. Additional MRI sequences for anatomic assessment will be performed as detailed in the Radiology Manual.

7.10.3 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). 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 $\alpha_v\beta_6$.

The Sponsor may also use these samples to perform exploratory investigations using metabolomic, transcriptomic or proteomic methods to identify putative biomarkers for use in future studies in participants with fibrotic diseases. 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 PD value is presented below.

Category	Biomarker	Evidence of Prognostic or Pharmacodynamic Value
Epithelial Damage	Cytokeratin 19 fragment (CYFRA 21-1)	Higher levels of CYFRA 21-1 predict a worse prognosis among IPF patients; Change from baseline to 3 months predictive of mortality (Simpson 2017)
Fibrosis	ProC3, Pro C6 (Type III and type VI collagen synthesis neoepitopes)	Elevated serum levels in participants with progressive disease compared to those with stable disease (Organ 2019)
	Periostin (POSTN)	Prognostic for FVC in the test cohort (Effect size=-3.6, p<0.001) and replication cohort (Effect size=-2.5, p=0·186) (Neighbors 2018)
	Cartilage Oligomeric Matrix Protein (COMP)	Increased in serum of IPF; correlates with declines in FVC; colocalizes with pSMAD3 expressing cells by IHC (Vuga 2013)
Inflammation	CCL18	Prognostic for FVC in the test cohort (Effect size=-3.1, p=0·032) and replication cohort (Effect size=3.6, p=0·004) (Neighbors 2018)
Exploratory	Human Epididymis Protein 4 (HE4)	Elevated in IPF patient urine/plasma; significantly reduced in IPF patient plasma following lung transplant (Decaris 2019)

7.11 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.

7.12 Exploratory Efficacy Assessments

7.12.1 Spirometry

Absolute FVC volume and FVC percent of predicted will be assessed by spirometry at screening and at the timepoints specified in the Schedule of Events (Appendix 1). A historical value may be used if it has been completed within 1 month from the Baseline visit.

FEV1 will be assessed by spirometry at screening. A historical value may be used if it has been completed within 1 month from the Baseline visit.

7.12.2 Patient-reported Outcome (PRO)

Study participants will respond to a VAS for cough severity at the timepoints specified in the Schedule of Events (Appendix 1).

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

Collagen accumulation within the lungs of patients with fibrotic lung disease, particularly those with IPF, is the hallmark of disease progression and associated with substantial mortality. The changes in the PET ligand ^{68}Ga-CBP8 correlate with disease progression and may be a more sensitive measure of active disease, with ^{68}Ga-CBP8 preferentially binding to recently synthesized collagen over mature, organized collagen. Consistent with the mechanism of action of PLN-74809, changes in the PET ligand ^{68}Ga-CBP8 will support the role of ^{68}Ga-CBP8 as an important biomarker of disease activity, as well as evidence of PD effect and efficacy of PLN-74809 (decrease in collagen levels) in participants with IPF.

Collection of AEs, safety labs, vital signs, physical examinations and ECG recordings 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.

FVC is a standard measure collected according to current ATS guidelines for the measurement of IPF progression. The VAS scale for the assessment of cough will follow recommendations from the ERS Guidelines (Morice et al, 2007).

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/ serious adverse event [SAE]).
  Events that do not meet the definition of an AE include:
  - Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
  - Situations where an untoward medical occurrence did not occur (e.g., 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 (Version 5.0), 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.

Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Published: November 27, 2017
https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf

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 adverse event 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, 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, ECG, 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
- 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 meeting the criteria for suspected drug induced liver injury (DILI) or QT prolongation 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 per the Study Manual 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:

ctisafety@ctifacts.com

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 **ctisafety@ctifacts.com**.

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.

9 MONITORING AND MANAGEMENT OF ELEVATED LIVER BIOCHEMISTRY TESTS

Reference ranges for key liver biochemistry tests are shown in Table 2.

Table 2 Reference Ranges for Key Laboratory Liver Function Tests

Parameter	Reference Range
Alanine aminotransferase (ALT)	10 – 55 U/L
Aspartate aminotransferase (AST)	10 – 40 U/L
Alkaline phosphatase (ALP)	45 – 115 U/L
Total bilirubin	0.0 – 1.0 mg/dL

Participants who experience treatment-emergent elevations in serum ALT or AST that reach the thresholds listed below must be managed carefully:

- **ALT or AST ≥ 8 × ULN**
- **ALT or AST ≥ 5 × ULN** for more than 2 weeks
- **ALT or AST ≥ 3 × ULN** and (Total Bilirubin >2 × ULN or international normalized ratio [INR] >1.5)
- **ALT or AST ≥ 3 × ULN** with liver-related symptoms including the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (> 5%)

Participants must return to the study site for reevaluation within 48 to 72 hours after the abnormal laboratory results become available for confirmatory testing serum levels of ALT, AST, total and direct bilirubin, and INR. A PK sample must be obtained at the same time that the repeat clinical laboratory samples are drawn, and the date and time of the PK draw and the last dose of study drug (and that of pirfenidone or nintedanib, if applicable) must be recorded in the eCRF.

If prompt evaluation is not possible within 48 to 72 hours after receipt of the abnormal laboratory results, study drug should be interrupted immediately (date of last study drug dose [and that of pirfenidone or nintedanib, if applicable] must be recorded in the eCRF), and the participant must return to the study site as soon as possible for reevaluation. The Sponsor Study Director should be notified of laboratory abnormalities and any clinical symptoms within 48 hours of the availability of laboratory results and/or assessment of clinical symptoms.

Participants who experience treatment-emergent elevations in **ALT or AST ≥ 2 × ULN** (but < 3 × ULN) should be managed as follows:

- Participants must return to the study site for reevaluation within 48 to 72 hours after the abnormal laboratory results become available for confirmatory testing serum levels of ALT, AST, total and direct bilirubin.
- A PK sample must be obtained at the same time that the repeat clinical laboratory samples are drawn, and the date and time of the PK draw and the last dose of study drug (and that of pirfenidone or nintedanib, if applicable) must be recorded in the eCRF.

In the absence of liver-related symptoms and/or elevations in total bilirubin or INR, participants with confirmed treatment-emergent elevations in ALT or AST ≥ 2 × ULN (but < 3 × ULN), may continue dosing of study drug and be monitored closely with frequent (eg, at least once weekly) hepatic laboratory testing and clinical assessments using unscheduled visits, including a thorough causality evaluation and in consultation with the Sponsor Study Director.

Study drug must be permanently discontinued in the event of confirmed elevations in serum ALT or AST that meet the following criteria for suspected acute DILI, based on the Guidance for Industry on Drug-Induced Liver Injury: Premarketing Clinical Evaluation (FDA, 2009).

Criteria for permanent discontinuation of study drug for confirmed ALT or AST elevations:

- Confirmed ALT or AST ≥ 3× ULN with (Total Bilirubin > 2 × ULN or INR > 1.5) and/or, presence of liver-related symptoms, if no other etiology is suspected/confirmed and liver enzymes are sustained following interruption of study drug
- Confirmed ALT or AST ≥ 5× ULN for more than 2 weeks, if no other etiology is suspected/confirmed and liver enzymes are sustained following interruption of study drug
- Confirmed ALT or AST ≥ 8× ULN, if no other etiology is suspected/confirmed and liver enzymes are sustained following interruption of study drug

All elevations in serum ALT and/or AST that are confirmed upon repeat testing AND that meet the criteria for suspected DILI (as listed above) must be reported to the Sponsor Study Director within 48 hours. The participant must permanently discontinue study drug immediately and continue to be followed for close monitoring and causality and clinical evaluation as follows:

- Repeat liver enzyme and serum bilirubin tests at least once a week until abnormalities stabilize (i.e., levels are clinically comparable to baseline values or baseline grade of abnormality) and the participant is asymptomatic
- Obtain a detailed history of symptoms and prior or concomitant diseases

- Obtain a history of concomitant drug use (including nonprescription or over-the-counter medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets
- Rule out acute viral hepatitis types A, B, C, D, and E; alcoholic hepatitis; hypoxic/ischemic hepatopathy; and biliary tract disease
- Obtain immunoglobulin G1 (IgG-1), antinuclear antibody (ANA), anti-smooth muscle antibody (anti-SMA), anti-liver-kidney microsome type 1 (anti-LKM1), and anti-liver cytosolic antigen type 1 (anti-LC1) levels to be compared with baseline values, to rule out autoimmune hepatitis
- Obtain a history of exposure to environmental chemical agents
- Consider a gastroenterology or hepatology consultation, which may include a liver biopsy, for definite diagnosis

For participants with confirmed elevations in liver enzymes (as described above) warranting temporary interruption of study drug but not meeting permanent drug discontinuation criteria as stated above, more frequent hepatic laboratory testing and clinical assessments must be conducted using unscheduled visits, including a thorough causality evaluation and in consultation with the Sponsor Study Director.

Reinitiation of study drug can only be considered if another etiology is identified and confirmed and if liver abnormalities have returned to baseline values. **The decision to restart study drug must be discussed and approved in consultation with the Sponsor Study Director prior to reinitiation**.

Participants who permanently discontinue study drug due to potential liver toxicity must be followed for close monitoring until abnormalities stabilize to baseline levels or baseline grade of abnormality and the participant is asymptomatic. Participants should be encouraged to remain in the study and completed all scheduled visits and assessments. Long-term follow-up information should be provided for participants who permanently discontinue drug due to potential liver toxicity, including information on immunosuppressive therapy and new liver histology.

10 MONITORING AND MANAGEMENT OF ECG-RELATED ABNORMALITIES

The definition of a cardiac dysrhythmia characterized by a CTCAE Version 5 grading for electrocardiogram QT corrected interval prolonged is presented in Table 3.

Table 3 CTCAE Version 5 Grading for Electrocardiogram QT Corrected Interval Prolonged

CTCAE Term	Grade 1	Grade 2	Grade 3	Grade 4
Electrocardiogram (ECG) QT Corrected Interval Prolonged	Average QTc 450 – 480 msec	Average QTc 481 – 500 msec	Average QTc ≥ 501 msec ; or ≥60 msec change from baseline	Torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia

Any participant who experiences a treatment-emergent QT interval corrected for heart rate (QTc) prolongation of Grade 2 or higher must return to the study site for prompt clinical evaluation after the abnormal ECG results become available and to repeat the safety ECG assessment. A PK sample must be obtained at the same visit that the repeat ECG assessment is performed, and the date and time of the PK draw and the last dose of study drug (and that of pirfenidone or nintedanib, if applicable) must be recorded in the eCRF.

- Grade 2 QTcF interval > 480 but ≤ 500 msec; or increased > 30 to ≤ 60 msec from baseline value → **The participant must return to the study site within 48 to 72 hours.**
- Grade 3: QTcF interval > 500 msec or increased > 60 msec from baseline value → **The participant must return to the study site within 24 hours or, if not feasible, to a local clinic or hospital for immediate clinical evaluation.**

Clinical evaluation must include the following:

- Ruling out comorbidities and potential risk factors (eg, congestive heart failure, bradyarrhythmias)
- Evaluation of electrolyte disturbances (eg, potassium, calcium, and magnesium)
- Review of potential concomitant medications known to prolong the QTc interval (eg, serotonin receptor antagonists, anti-emetics)

If prompt evaluation is not feasible (as described above and based on severity of abnormality), study drug should be interrupted immediately (date of last study drug dose [and that of pirfenidone or nintedanib, if applicable] must be recorded in the eCRF), and the participant must return to the study site as soon as possible for

re-evaluation. The Sponsor Study Director should be notified within 48 hours of the availability of initial ECG results and/or assessment of clinical symptoms.

Study drug must be permanently discontinued in the event of QTc prolongation meeting the following criteria:

- Confirmed Grade 3 abnormality: QTcF interval > 500 msec or increased > 60 msec from baseline value
- Grade 4 abnormality (does not require confirmation): torsade de pointes; polymorphic ventricular tachycardia; signs/symptoms of serious arrhythmia

All treatment-emergent QTc abnormalities meeting the criteria for permanent discontinuation (as listed above) must be reported to the Sponsor Study Director within 48 hours. The participant must permanently discontinue study drug immediately and continue to be followed for close monitoring and causality and clinical evaluation as follows:

- Repeat ECG at least once weekly until abnormalities stabilize (ie, QTc interval is comparable to baseline value or baseline grade of abnormality, if applicable) and the participant is asymptomatic
- Correction of any electrolyte abnormalities, if applicable
- Obtain a detailed history of symptoms and comorbidities
- Obtain a history of concomitant drug use (including nonprescription or over-the-counter medications and herbal and dietary supplement preparations)
- Consider a cardiology consultation

For participants with confirmed QTc prolongation (as described below) warranting temporary interruption of study drug but not meeting permanent drug discontinuation criteria, more frequent ECG testing and clinical assessments (at least once weekly) must be performed using unscheduled visits, including a thorough causality evaluation and in consultation with the Sponsor Study Director.

- Confirmed Grade 2 QTcF interval >480 but ≤ 500 msec
- Confirmed increased > 30 to ≤ 60 msec from baseline value

Re-initiation of study drug can only be considered if a more likely etiology is identified and if ECG abnormalities have returned to baseline values. **The decision to restart study drug must be discussed and approved in consultation with the Sponsor Study Director prior to re-initiation**. More frequent clinical monitoring and ECG assessments (at least once weekly) after re-initiation of study drug, if applicable, should be performed through use of

unscheduled visits. **If the QTc prolongation reoccurs upon re-challenge, study drug must be permanently discontinued.**

Any participant who experiences a QTc prolongation not confirmed upon repeat ECG assessment may continue or resume administration of study drug and follow the scheduled study visits, if clinically appropriate. More frequent clinical evaluation and ECG monitoring through use of unscheduled visits is allowed, if clinically warranted.

Participants who permanently discontinue study drug due to potential QTc prolongation must be followed for close monitoring until abnormalities stabilize to baseline levels or baseline grade of abnormality and the participant is asymptomatic. Participants should be encouraged to remain in the study and completed all scheduled visits and assessments. Long-term follow-up information should be provided for participants who permanently discontinue drug due to confirmed QTc prolongation, including information on corrective therapy and cardiology consultation, if applicable.

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
- Confirmed elevations in serum ALT or AST meeting criteria for suspected acute DILI (see Section 9)
- Prolonged ECG QTc interval meeting criteria for permanent discontinuation (see Section 10)
- Male participants whose female partners become pregnant during the study must stop the medication immediately
- 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 (Appendix 1).

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

This is an exploratory 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. 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 12 participants (8 participants receiving 160 mg PLN-74809 and 4 receiving placebo) is expected to provide a meaningful evaluation of PLN-74809 safety, tolerability and PK in the target population, and add to the data of approximately 21 participants planned to be evaluated at this dose level in an ongoing multicenter, dose ranging Phase 2a study (PLN-74809-IPF-202).

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 PET/MRI scan or PD assessment will be included in the PD analyses.

12.4 Demographics and Baseline Characteristics

Data will be summarized using statistical summary methods.

12.5 Primary Endpoints

12.5.1 Primary Pharmacodynamic Endpoint

- Quantification of type 1 collagen in the lung following 12 weeks of treatment, as assessed by changes from Baseline in ^{68}Ga-CBP8 PET/MRI tracer uptake patterns.

If a participant elects to withdraw from the study after the 6th week of randomization, an end of participation ^{68}Ga-CBP8 PET/MRI will be offered to the participant to enhance appropriate data capture.

PET/ MRI

PET/MRI scans will be interpreted by American Board of Nuclear Medicine (ABNM)-certified nuclear medicine physicians in an unblinded manner. Lung contours will be generated from baseline and post-treatment PET/MRI. Mean and maximum standardized uptake value (SUV) measurements of contoured lungs will be calculated using MIMS software, by analyzing the uptake values of ^{68}Ga-CBP8 PET/MRI within the lung, and by comparing values from the baseline and post-treatment scans. Numerical and graphical results will be presented by dose.

In addition, relationships between PK and type 1 collagen deposition, as well as between MRI and PET imaging, may be evaluated in an exploratory fashion and presented in a graphical manner (see Section 12.7.1).

12.6 Secondary Endpoints

12.6.1 Secondary Safety Endpoint

- Assessment of the safety and tolerability of PLN-74809 in IPF participants

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 treatment.

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 the number and percentage of participants who withdraw due to an AE will be tabulated by study treatment and dose.

Clinical laboratory test parameters will be listed, using the CTCAE grading scale, for individual participants, with values outside the reference ranges flagged. The incidence of treatment-emergent laboratory abnormalities will be summarized by severity. Summary statistics will be calculated for each parameter.

Individual ECG results will be listed for each participant. Summaries of ECGs will include changes from baseline for each parameter. The number and percentage of participants with abnormal ECGs will be summarized by treatment.

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

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

12.7 Exploratory Endpoints

12.7.1 Exploratory Pharmacodynamic/Pharmacokinetic Endpoints

- Relationship between PLN-74809 systemic exposure and PET imaging and biomarkers in IPF participants

Pharmacokinetics

Plasma PLN-74809 concentrations at each sampling time point will be presented in listings and summarized with descriptive statistics. Plasma PLN-74809-versus-time profiles (with plasma concentrations on both a log and linear scale) will be plotted for each participant. Non-compartmental analysis will be used to calculate PK parameters as appropriate. Plasma PK parameters will be presented in listings and summarized with descriptive statistics. 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.

PET/MRI

Relationships between PK and type 1 collagen deposition, as well as between MRI and PET imaging, may be evaluated in an exploratory fashion and presented in a graphical manner. The analysis of PET/MRI imaging is described in Section 12.5.1.

Pharmacodynamics: Biomarkers

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, the relationship between these markers, and the level of PET tracer uptake (type 1 collagen deposition) in the lung. Results will be presented in listings and summarized with descriptive statistics and in graphical form.

12.7.2 Exploratory Efficacy Endpoints

12.7.2.1 Forced Vital Capacity (FVC)

- Absolute FVC volume and FVC as percent of predicted as assessed by spirometry

Percent of predicted FVC and volume (mL) will be assessed using the standard spirometry procedure at the Chest Clinic at Massachusetts General Hospital and presented as absolute

values and as percent of predicted values. Baseline FVC will be the average of the screening and Day 1 determinations. End-of-study FVC will be the average of Week 12 and Week 14 determinations.

12.7.2.2 Patient-reported Outcome (PRO)

- Patient-reported outcome (PRO): a VAS for cough severity

A cough VAS will be completed at the timepoints specified in the Schedule of Events (Appendix 1).

12.8 Other Assessments or Analyses

Unbound concentrations of PLN-74809 will be determined in plasma samples. Exploratory metabolite evaluation may be performed in plasma samples.

12.9 Interim Analysis

Not applicable

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 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 contract research organization (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 IRB/IEC/REB-approved ICF in his/her native language. The informed consent process should be recorded in the source documentation. The original copy of the signed and dated ICF must be retained in the institution's records and be available for inspection by representatives of the Sponsor, or representatives from regulatory agencies. The participant will be given a copy of the signed ICF.

Participants unable to sign the ICF may participate in the study if a legal representative or witness provides the consent (in accordance with the procedures of ICH-GCP and local regulations) and the participant confirms his/her interest in study participation.

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], Personnel Information Protection and Electronic Documents Act [PIPEDA], General Data Protection Regulation [GDPR]). Appropriate consent and authorizations for use and disclosure and/or transfer (if applicable) of protected information must be obtained.

14.5 Study Monitoring

The Investigator must allow the Study Monitors to periodically review, at mutually convenient times, during the study and after the study has been completed, all eCRFs and office, hospital, and laboratory records supporting the participation of each participant in the study. 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 Adjudication Committee

Potential acute exacerbations, respiratory-related hospitalizations, and/or respiratory-related deaths will be reviewed by an adjudication committee.

14.8 Retention of Data

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

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

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

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

14.9 Financial Disclosure

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

14.10 Publication and Disclosure Policy

The data generated in this clinical study are the exclusive property of the Sponsor and are confidential. Any publication of the results of this study must be authorized by the Sponsor. The Sponsor will have the opportunity to review any publications that arise from the

Investigators before submission for publication. Any such review and approval of publications related to the study shall be made pursuant to the process agreed between the parties in the site's clinical trial agreement with Sponsor. Authorship on any publication of the results from this study will be based on contributions to study design, data acquisition and analysis, and interpretation of results.

15 REFERENCE LIST

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APPENDIX 1 SCHEDULE OF EVENTS

	Screening		Treatment						EoS / ET
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7[a]	Visit 8[a]	Visit 9
	Day -28 to Day -1	Pre-Baseline Day -7 to Day -1	Baseline Day 1	Week 2 Day 14 (±2 days)	Week 4 Day 28 (±2 days)	Week 8 Day 56 (±3 days)	Day 84 (-7days)	Week 12 Day 84 (±3 days)	Week 14 Day 98 (±3 days)
Informed consent	**X**								
Medical history	**X**								
Demographics (age, sex, race)	X								
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						
FVC [b,c]	X		X		X	X		X	X
FEV1[c]	X								
DLco	X								
Cough VAS	X		X	X	X	X		X	X
Vital signs (post 3 minutes, supine; approx 2 hours post dose and around the time of the ECG)	X		X	X	X	X		X	X
Triplicate 12-lead ECG (post 10 minutes, supine; at least 2 hours post dose and prior to the PK sample)[d,e]	X		X	X	X	X		X	X
Hematology (post 8-hour fast)	X		X	X	X	X		X	X
Clinical chemistry (post 8-hour fast)[f]	X		X	X	X	X		X	X
Coagulation (post 8-hour fast)	X		X	X	X	X		X	X
PET/MRI scan		X					X		
Pharmacokinetic sample plasma [g]			X		X			X	X[e,f,,h]

	Screening		Treatment						EoS / ET
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7[a]	Visit 8[a]	Visit 9
	Day -28 to Day -1	Pre-Baseline Day -7 to Day -1	Baseline Day 1	Week 2 Day 14 (±2 days)	Week 4 Day 28 (±2 days)	Week 8 Day 56 (±3 days)	Day 84 (-7days)	Week 12 Day 84 (±3 days)	Week 14 Day 98 (±3 days)
Pharmacokinetic nintedanib/pirfenidone sample plasma x 2 (predose and at least 2 hours post dose to PLN-74809)[i]			X		X			X	X[e,f,h]
Pharmacogenomic sample			X						
Plasma biomarker samples			X		X			X	
Serum biomarker samples			X		X			X	
Urine biomarker samples			X		X			X	
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 (empty stomach: 2 hours predose and 2 hours postdose)[j]			←	—	—	—	—	→	
Study drug dispensing			X		X	X			
Study drug accountability					X	X		X	X

DL_{CO} = diffusing capacity for carbon monoxide; ECG = electrocardiogram; EoS = end of study; ET = early termination; FEV1 = forced expiratory volume during the first seconds of the forced breath; FVC = forced vital capacity; MRI = magnetic resonance imaging; PET = positron emission tomography; PK = pharmacokinetic; VAS = visual analog scale

[a] Visits 7 and 8 may be combined.

[b] Baseline FVC to be obtained both during screening and on Day 1.

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

[d] When time points for ECGs, vital sign assessment, and blood draws coincide, procedures should be carried out with blood draws last. ECGs should be collected postdose and close to the time of PK sample collection with the triplicate ECGs recorded within ~ 5 to 10 minutes. The triplicate ECGs will be averaged, and the mean values per time point (average of the 3 assessments) used to interpret the ECG tracings.

[e] ECG abnormality, then PK sample will be collected.

	Screening		Treatment						EoS / ET
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7[a]	Visit 8[a]	Visit 9
	Day -28 to Day -1	Pre-Baseline Day -7 to Day -1	Baseline Day 1	Week 2 Day 14 (±2 days)	Week 4 Day 28 (±2 days)	Week 8 Day 56 (±3 days)	Day 84 (-7days)	Week 12 Day 84 (±3 days)	Week 14 Day 98 (±3 days)

[f] Liver function test abnormality, then PK sample will be collected.

[g] Total and unbound PLN-74809 levels will be measured at the following timepoints:
Day 1: predose and 2, 4, and 6 hours postdose
Weeks 4 and 12: predose and at least 2 hours postdose
Actual PK sample collection time and dosing time will be recorded.

[h] If the participant discontinues the study early, a plasma sample for PK should be taken at the ET Visit if possible.

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

[j] Participants should be instructed to take study drug in the clinic on Visits 3, 5 and 8, and at the ET visit if applicable.

APPENDIX 2 SPONSOR SIGNATURE

Study Title:	A Phase 2a, randomized, double-blind, placebo-controlled evaluation of PLN-74809 on type 1 collagen deposition using ^{68}Ga-CBP8 PET/MRI imaging in participants with idiopathic pulmonary fibrosis (IPF)
Study Number:	PLN-74809-IPF-205
Version	Amendment 1
Final Date:	4 October 2021

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

Signed:_____ Date: 06 October 2021 | 10:24:20 AM PDT

[redacted]

Pliant Therapeutics, Inc.
260 Littlefield Avenue, South San Francisco, CA 94080, USA

APPENDIX 3 INVESTIGATOR'S SIGNATURE

Study Title:	A Phase 2a, randomized, double-blind, placebo-controlled evaluation of PLN-74809 on type 1 collagen deposition using ^{68}Ga-CBP8 PET/MRI imaging in participants with idiopathic pulmonary fibrosis (IPF)
Study Number:	PLN-74809-IPF-205
Version	Amendment 1
Final Date:	4 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:_____