CLINICAL TRIAL PROTOCOL

PLN-74809-IPF-201

Study Title:	A Phase 2a evaluation of PLN-74809 on $\alpha_v\beta_6$ receptor occupancy using PET imaging in participants with IPF
Study Number:	PLN-74809-IPF-201
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
Medical Monitor:	[redacted]
GCP Statement:	This trial will be conducted in compliance with this protocol, Good Clinical Practices and applicable regulatory requirements.

Version	Date
Original Protocol (v1.0):	29 April 2019
Protocol Amendment 1 (v2.0):	14 May 2019
Protocol Amendment 2 (v3.0):	20 November 2019
Protocol Amendment 3 (v4.0):	16 March 2020
Protocol Amendment 4 (v5.0):	25 January 2021
Protocol Amendment 5 (v6.0):	26 October 2021

SYNOPSIS

Name and Address of Sponsor:	Pliant Therapeutics Inc., 260 Littlefield Avenue, South San Francisco, CA 94080, USA.
Name of Test Product:	PLN-74809-000, [redacted] (hereafter referred to as PLN-74809)
Name of Active Ingredient:	PLN-74809
Study Center:	Stanford Medical Center 300 Pasteur Dr, Stanford, CA 94305
Title of Study:	A Phase 2a evaluation of PLN-74809 on $\alpha_v\beta_6$ receptor occupancy using PET imaging in participants with IPF
Study Number:	PLN-74809-IPF-201
Study Phase	2a
Objectives:	**Primary:** • Evaluation of $\alpha_v\beta_6$ receptor occupancy by PLN-74809 in the lungs, as assessed by changes from Baseline in $\alpha_v\beta_6$ PET tracer uptake patterns following a single dose **Secondary:** • Assessment of the safety and tolerability of PLN-74809 in idiopathic pulmonary fibrosis (IPF) participants **Exploratory:** • [redacted]
Number of Participants Planned:	Up to 12 participants with IPF.
Study Design:	This is an open-label study in which up to 12 participants with IPF will receive up to two doses of PLN-74809, starting at 60 mg [redacted] or 80 mg ([redacted]). Higher planned doses, including 120 mg, 240 mg and 320 mg, will also be evaluated [redacted] All participants will undergo PET imaging at Baseline and on the day of PLN-74809 dosing. Eligible participants consenting to receive a maximum of four single doses (on different occasions) of PLN-74809 (e.g., 60 mg and 120 mg) will need to undergo a ≥14-day washout between doses and will not need to repeat the Baseline PET imaging. Additionally, if in the opinion of the Investigator, there is no clinical decline within 60 days only hematology and clinical chemistry assessments should be completed; other Screening and Baseline procedures are not required. If the PET ligand cannot be successfully synthetized on the scheduled day, participants will wait at least 1 week until another dose of PLN-74809 is administered. Participants will undergo no more than 3 PET imaging scans (Baseline and up to 2 scans post PLN-74809 dosing). All PET imaging will be performed using the R_01 Knottin tracer, as generated by the radiology department at Stanford Medical Center. Post-dose PET imaging for the assessment of $\alpha_v\beta_6$ receptor occupancy will be performed > 4 hours postdose, to coincide with PLN-74809 time to maximum observed drug concentration (T_{max}; ~ 4 hours after the administration of study drug).

	Blood samples for PLN-74809 pharmacokinetics (PK) will be obtained before and at 0.5, 1, 2, 3 and 4 hours postdose on Day 1 (prior to administration of the PET ligand) and at 24 hours postdose (Day 2). Biomarker blood samples will be collected as per the Schedule of Assessments. Forced vital capacity (FVC) and diffuse capacity for carbon monoxide (DLco) will be performed on all participants at Screening for inclusion/exclusion purposes; a historical FVC and DLco within 1 month of screening may be used. For those participants whose travel to the study center would prohibit study participation, housing accommodation may be provided by the Sponsor. Except for the previously described periods, participants will be allowed to return to their homes between study visits.
Duration of Participant Participation/Study Duration:	Screening for all participants will be up to 35 days prior to dosing (dosing will be on Day 1). The Baseline Visit (including PET) will be performed on Day -7 to allow a washout of the PET ligand between PET procedures. Screening and Baseline visit may occur on the same day, if appropriate. Participants will receive PLN-74809 on Day 1 and will attend a Follow-Up Visit 7 days (±2 days) after administration of the single dose. For participants consenting to receive 2 different single doses of PLN-74809, at least 14 days will be added to the study duration due to the required washout period.
Study Population:	**Inclusion Criteria** Each participant must meet the following criteria to be enrolled in this study: 1. Participants aged 40 or older 2. Confident diagnosis of IPF, within 8 years prior to Screening, according to the Fleischner Guidelines criteria; specifically either high-resolution computed tomography (HRCT) imaging showing a pattern of typical or probable usual interstitial pneumonia (UIP) or a histopathology specimen demonstrating a UIP pattern in the correct clinical context and confirmed by multidisciplinary conference review at study site 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. 6. Female participants of non-childbearing potential must be either surgically sterile (hysterectomy, bilateral tubal ligation, salpingectomy, and/or bilateral oophorectomy at least 26 weeks before the Screening Visit) or post-menopausal, defined as spontaneous amenorrhea for at least 2 years. 7. Female participants must have a negative pregnancy test at Baseline. 8. Female participants of childbearing potential (i.e., ovulating, pre-menopausal, and not surgically sterile) and all male participants with sexual partners of childbearing potential must agree to use highly effective methods of birth control during their participation in the study and for 30 and 90 days, respectively, after the last administration of study drug. Highly effective methods of birth control are defined as those with 99% or greater efficacy

	9. Participants must agree to abstain from egg or sperm donation through 30 or 90 days, respectively, after administration of the last dose of study drug. 10. Able to understand the purpose of the study and its procedures and to sign a written informed consent form **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. Currently receiving or planning to initiate treatment for IPF (fibrosis) during the study with pharmacological agents not approved for that indication by the Food and Drug Administration (FDA) 4. Forced expiratory volume during the first seconds of the forced breath (FEV1)/FVC ratio <0.7 5. Suspicion of an interstitial lung disease (ILD) different from IPF according to the Investigator 6. Clinical evidence of active infection, including but not limited to bronchitis, pneumonia, sinusitis that can affect FVC measurement or IPF progression 7. Any other condition that prevents the correct assessment of spirometry performance (e.g., a broken rib or chest pain of other origin that prevent adequate forced breathing) 8. Known acute IPF exacerbation or suspicion by the Principal Investigator (PI) of such, within 6 months of Screening 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. Any ongoing known malignancy, except for localized cancers (e.g., basal cell carcinoma) 11. [redacted] 14. Any medical condition that, in the opinion of the Investigator, may make the candidate not suitable for the study 15. History of anaphylaxis to intravenous (IV) drugs 16. 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 17. Hemoglobin <10.0 g/dL at Screening 18. Pregnant or lactating females 19. Medical or surgical condition known to affect drug absorption

	20. Participation in a clinical trial with another investigational agent in the 30 days prior to Screening apart from PLN-74809 21. [redacted]
Test Product; Dose; and Mode of Administration:	[redacted]
Reference Therapy; Dose; and Mode of Administration:	Not applicable
Duration of Treatment:	Single dose
R_{01} Knottin PET Tracer	The Knottin PET tracer is not considered a study treatment but is an investigational tool used during the PET procedure for obtaining the computerized images necessary for this trial.
Study Assessments:	**Pharmacokinetic and Pharmacodynamic Assessments:** • Plasma sample collection for measurement of PLN-74809 concentration. • PET imaging for the assessment of target engagement. • HRCT for the assessment of PET/HRCT relationship. • [redacted] • Spirometry testing for FVC measurement • [redacted] **Safety Assessments:** • Open-ended adverse event (AE) inquiry, hematology, clinical chemistry, vital signs; [redacted] and physical examinations.
Sample Size Justification:	The sample size was determined empirically. Up to 12 participants should provide proof of concept on the ability of the study to assess target engagement ($\alpha_v\beta_6$ receptor occupancy by PLN-74809).
Analytic Methods:	**Pharmacokinetic and Pharmacodynamic Data:** **PK Data:** 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 the PK parameters T_{max}, C_{max}, area under the drug concentration-time curve from time zero to the time of the last measurable concentration (AUC_{last}), AUC from time zero to 4 hours ($AUC_{(0-4)}$) and from time zero to 24 hours ($AUC_{(0-24)}$) after dosing, and average drug concentration (C_{avg}), if applicable. Plasma PK parameters will be presented in listings and summarized with descriptive statistics. **PET/computerized tomography (CT):** PET-CT scans will be interpreted by American Board of Nuclear Medicine (ABNM)-certified Nuclear Medicine physicians in a unblinded manner. Lung contours will be generated from baseline and post-treatment PET-CTs. Mean and maximum standardized

	uptake value (SUV) measurements of contoured lungs will be calculated using MIMS software, by analyzing the uptake values of [^{18}F]FP-R01-MG-F2 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 PET receptor occupancy, as well as between HRCT and PET receptor imaging, may be evaluated in an exploratory fashion and presented in a graphical manner. **FVC:** Percent of predicted and volume (mL) will be assessed using the standard spirometry procedure at the Chest Clinic at Stanford Medical Center and presented as absolute values and as percent of predicted values. [redacted] **HRCT:** Visual results will be presented in listings and summarized with descriptive statistics by dose to support the inclusion criteria. Quantitative volumetric HRCT results will be analyzed and presented individually and in relationship to the PET findings. Results will be presented in tabular and graphical form.

	Safety Data: Safety data from all participants who received at least one dose of study drug will be incorporated into the final safety analysis. AEs will be collected from the time the participant signs the informed consent form (ICF) until the last study visit. All AEs will be graded for severity per the Common Terminology Criteria for Adverse Events (CTCAE) grading scale and will be listed by participant and summarized. The incidence of AEs, the incidence of treatment-emergent AEs (TEAEs), the incidence of treatment-related AEs, and the severity of AEs will be summarized by system organ class (SOC), preferred term, and maximum severity. In cases in which 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 serious adverse events (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. [redacted] Vital sign measurements, other laboratory tests, concomitant medications, medical history and changes in physical examinations at each time point will be listed by participant.
Original Protocol (v1.0):	29 April 2019
Amendment 1 (v2.0):	14 May 2019
Amendment 2 (v3.0)	20 November 2019
Amendment 3 (v4.0)	16 March 2020
Amendment 4 (v5.0)	25 January 2021
Amendment 5 (v6.0)	26 October 2021

PROTOCOL AMENDMENT SUMMARY OF CHANGES

Document History

Document	Date
Protocol Amendment 5 (v6.0)	26 October 2021
Protocol Amendment 4 (v5.0)	25 January 2021
Protocol Amendment 3 (v4.0)	16 March 2020
Protocol Amendment 2 (v3.0)	20 November 2019
Protocol Amendment 1 (v2.0)	14 May 2019
Original Protocol (v1.0)	29 April 2019

Protocol Amendment 5 (v6.0): 26 October 2021

This protocol amendment will introduce the flexibility for participants to receive up to four doses of PLN-74809 (on different occasions) to account for the potential $R_0$1 Knottin tracer synthesis failure. Participants will undergo no more than 3 PET imaging scans (Baseline and up to 2 scans post PLN-74809).

Updates to inclusion/exclusion criteria include:

- Increase of diagnosis of IPF within 8 years prior to Screening.
- [redacted]

Minor editorial and grammatical corrections were incorporated.

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LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ABNM	American Board of Nuclear Medicine
ADL	Activities of Daily Living
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
ATS	American Thoracic Society
$AUC_{(0-4)}$	area under the drug concentration-time curve from time zero to 4 hours after dosing
$AUC_{(0-24)}$	area under the drug concentration-time curve from time zero to 24 hours after dosing
AUC_{last}	area under the drug concentration-time curve from time zero to the time of the last measurable concentration
BALF	bronchoalveolar lavage fluid
[redacted]	[redacted]
C_{max}	maximum observed drug concentration
C_{avg}	average drug concentration
COL1A1	collagen type 1α1 (human)
CRO	contract research organization
CT	computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
DLco	diffusing capacity for carbon monoxide
[redacted]	[redacted]
[redacted]	[redacted]
eCRF	electronic case report form
EoS	End of Study (visit)
ET	Early Termination (visit)
FDA	Food and Drug Administration
FEV1	forced expiratory volume during the first seconds of the forced breath
FIH	first-in-human
FP-$R_0$1-MG-F2	$R_0$1 cystine knot peptide
FVC	forced vital capacity
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act
HRCT	high-resolution computerized tomography
IC_{50}	50% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation

ILD	interstitial lung disease
IPF	idiopathic pulmonary fibrosis
IRB	Institutional Review Board
IV	intravenous
IWRS	interactive web response system
MAD	multiple ascending dose
MATE1	multidrug and toxin extrusion transporter
MedDRA	Medical Dictionary for Regulatory Activities
mRNA	messenger ribonucleic acid
[redacted]	[redacted]
PD	pharmacodynamics(s)
PET	positron emission tomography
PI	Principal Investigator
PK	pharmacokinetic(s)
PLN	Pliant
$R_0$1 Knottin	[^{18}F]FP-R01-MG-F2, aka Knottin, radiotracer for PET imaging of $\alpha_v\beta_6$ receptor
SAD	single ascending dose
SAE	serious adverse event
SAP	statistical analysis plan
[redacted]	[redacted]
SOC	system organ class
SOP	standard operating procedure
SpO_2	peripheral capillary oxygen saturation
SUV	standardized uptake value
T_{max}	time to maximum observed drug concentration
TEAE	treatment-emergent adverse event
[redacted]	[redacted]
[redacted]	[redacted]
UIP	usual interstitial pneumonia
ULN	upper limit of normal
US	United States
WHO	World Health Organization

1 INTRODUCTION

Pliant Therapeutics Inc is developing PLN-74809-000 (hereafter referred to as PLN-74809) for the treatment of idiopathic pulmonary fibrosis (IPF), the most common interstitial lung disease. IPF is a condition that is usually observed in the elderly and that is 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. The hallmark honeycomb appearance of IPF on high-resolution computerized tomography (HRCT) is the result of extensive fibrosis [redacted].

Although not completely understood, IPF appears to be a response to alveolar epithelial injury with the resultant fibrosis mediated by growth factors [redacted] 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). PLN-74809 reduced collagen synthesis in mice with bleomycin-induced lung injury, a commonly used experimental model for IPF [redacted]. In ex vivo human IPF lung tissue (precision cut lung slices), treatment with PLN-74809 significantly decreased collagen type 1α1 (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 [redacted] suggesting that even full inhibition of such integrins is well tolerated.

Integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$ mediate the release of activated transforming growth factor beta (TGF-β)1, leading to binding of TGF-β1 to its receptor (TGFβR)I/II and induction of SMAD2 and SMAD3 phosphorylation [redacted]. Measurement of SMAD phosphorylation in lung lysates and in cells from bronchoalveolar lavage fluid (BALF) has, therefore, been proposed to serve as a pharmacodynamic (PD) measure of $\alpha_v\beta_6$ integrin engagement [redacted] PLN-74809 treatment of mice exposed to bleomycin via oropharyngeal aspiration to induce lung injury and fibrosis was shown to inhibit phosphorylation of SMAD3 in lung tissue and in cells isolated from BALF, confirming PLN-74809-mediated inhibition of the release of activated TGF-β1 in the mouse lung. PLN-75068 (a tool compound with similar potency/integrin selectivity to PLN-74809) was also shown to inhibit the phosphorylation of SMAD2 in BALF cells isolated from the lungs of healthy cynomolgus monkeys. In both mouse and non-human primate studies, the plasma concentrations of $\alpha_v\beta_6/\alpha_v\beta_1$ integrin inhibitors correlated with reduced SMAD phosphorylation levels, demonstrating a clear pharmacokinetic (PK)/PD relationship.

The present positron-emission tomography (PET) study described here is designed to address a relevant clinical question in participants with IPF. The dose- and exposure-response interaction of PLN-74809 with $\alpha_v\beta_6$ integrin will be investigated by performing PET imaging

with a competitive $\alpha_v\beta_6$-binding probe at or near the maximum observed drug concentration (C_{max}) of PLN-74809. Evaluation of PLN-74809 receptor occupancy of $\alpha_v\beta_6$ will be analyzed by the use of an $\alpha_v\beta_6$-specific PET probe ([^{18}F]FP-R$_0$1-MG-F2; R$_0$1), also known as the Knottin tracer. Previous work conducted in collaboration with Stanford Medical Center demonstrated the utility of in vivo imaging of IPF patients for the detection of increased $\alpha_v\beta_6$ protein expression in the lung [redacted] The R$_0$1 cystine knot peptide (FP-R$_0$1-MG-F2) is a 36-amino acid peptide which has been shown to bind selectively and specifically to $\alpha_v\beta_6$, in vivo and in vitro, with nanomolar affinity [redacted] The ^{18}F radiotracer decays in the body with a short half-life of ~110 minutes (refer to the Radiology Manual for details about the Knottin tracer). Pliant has previously conducted studies in tissue and purified proteins demonstrating the ability of PLN-74809 to block the binding of a fluorescently tagged R$_0$1 peptide to $\alpha_v\beta_6$.

The present study will characterize the effect of PLN-74809 on $\alpha_v\beta_6$ receptor occupancy using PET imaging in participants with IPF. This study will also characterize the safety, tolerability, PK, and PD of PLN-74809 in participants with IPF.

1.1 Summary of Clinical Development

[redacted]

1.1.1 Completed Phase 1 Studies

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.1.1.1 Overview of Treatment Emergent Adverse Events (TEAEs) for completed Phase 1 Studies

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.1.2 Ongoing Phase 1 Studies

[redacted]

1.1.3 Ongoing Phase 2 Studies

[redacted]

2 STUDY OBJECTIVES

The primary objective of this study is:

- Evaluation of $\alpha_v\beta_6$ receptor occupancy by PLN-74809 in the lungs, as assessed by changes from baseline in $\alpha_v\beta_6$ PET tracer uptake patterns following a single dose.

The secondary objective is:

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

The exploratory objective is:

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3 INVESTIGATIONAL PLAN

3.1 Overall Study Design and Plan

This study is an open-label study in which up to 12 participants with IPF will receive up to two doses of PLN-74809, starting at 60 mg [redacted] or 80 mg [redacted] Higher planned doses, including 120 mg, 240 mg, and 320 mg, will also be evaluated [redacted] All participants will undergo PET imaging at the Baseline Visit and on the day of PLN-74809 dosing.

Eligible participants consenting to receive a maximum of 4 different doses of PLN-74809 (e.g., 60 mg and 120 mg) will need to undergo a ≥14-day washout between doses, and not have to repeat Baseline PET imaging. Additionally, if in the opinion of the Investigator, there is no clinical decline, the other Screening and Baseline procedures do not have to be repeated. If the PET ligand cannot be successfully synthetized on the scheduled day, participants will wait at least 1 week before another dose of PLN-74809 is administered.

All PET imaging will be performed using the $R_0$1 Knottin tracer, as generated by the radiology department at Stanford Medical Center. Post-dose PET imaging, for the assessment of $\alpha_v\beta_6$ receptor occupancy, will be performed to coincide with PLN-74809 time to maximum observed drug concentration (T_{max}; ~4 hours after the administration of study drug). Participants will undergo no more than 3 PET imaging scans (Baseline and up to 2 scans post PLN-74809 dosing).

Blood samples for PLN-74809 PK will be obtained before and at 0.5, 1, 2, 3, and 4 hours after dosing on Day 1 and at 24 hours after dosing (Day 2). [redacted]

Forced vital capacity (FVC) will be performed on all participants at Screening for inclusion/exclusion purposes. [redacted]

Except for the previously described periods, participants will be allowed to return to their homes between study visits.

3.2 Rationale for Study Design and Control Group

[redacted]

[redacted]

[redacted]

[redacted]

3.3 Dose Rationale

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3.4 Study Duration and Dates

Screening for all participants will be performed up to 35 days prior to dosing (dosing will be on Day 1). The Baseline Visit (including PET) will be performed on Day -7 to allow for washout of the PET ligand between PET procedures. Screening & Baseline visit may occur on the same day, if appropriate.

Participants will receive PLN-74809 on Day 1 and will attend a Follow-Up Visit 7 days (±2 days) after administration of the single dose. The study duration will be approximately 43 days for participants testing 1 dose of PLN-74809.

For participants consenting to receive up to four single doses of PLN-74809, at least 14 days will be added to the study duration due to the required washout period. Refer to Section 5.5 for further information.

4 STUDY POPULATION

4.1 Inclusion Criteria

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

1. Participants aged 40 or older.
2. Confident diagnosis of IPF, within 8 years prior to Screening, according to the Fleischner Guidelines criteria; specifically either HRCT imaging showing a pattern of typical or probable usual interstitial pneumonia (UIP) or a histopathology specimen demonstrating a UIP pattern in the correct clinical context (and confirmed by multidisciplinary conference review at study site.
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.
6. Female participants of nonchildbearing potential must be either surgically sterile (hysterectomy, bilateral tubal ligation, salpingectomy, and/or bilateral oophorectomy at least 26 weeks before the Screening Visit) or postmenopausal, defined as spontaneous amenorrhea for at least 2 years.
7. Female participants must have a negative pregnancy test at Baseline.
8. Female participants of childbearing potential (i.e., ovulating or premenopausal and not surgically sterile) and all male participants with sexual partners of childbearing potential must agree to use highly effective methods of birth control during their participation in the study and for 30 and 90 days, respectively, after the last administration of study drug. Hormonal contraceptives are not allowed. Highly effective methods of birth control are defined as those with 99% or greater efficacy
9. Participants must agree to abstain from sperm or egg donation through 90 or 30 days, respectively, after administration of the last dose of study drug.
10. Able to understand the purpose of the study and its procedures and to sign a written informed consent form.

4.2 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. Currently receiving or planning to initiate treatment for IPF (fibrosis) during the study with pharmacological agents not approved for that indication by the Food and Drug Administration (FDA).
4. Forced expiratory volume during the first seconds of the forced breath (FEV1)/FVC ratio <0.7.
5. Suspicion of an interstitial lung disease (ILD) different from IPF according to the Investigator.
6. Clinical evidence of active infection, including but not limited to bronchitis, pneumonia, sinusitis that can affect FVC measurement or IPF progression.
7. Any other condition that prevents the correct assessment of spirometry performance (e.g., a broken rib or chest pain of other origin that prevent adequate forced breathing).
8. Known acute IPF exacerbation or suspicion by the Investigator of such within 6 months of Screening.
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. Any ongoing known malignancy, except for localized cancers (e.g., basal cell carcinoma).

14. Any medical condition that, in the opinion of the Investigator, may make the candidate not suitable for the study.
15. History of anaphylaxis to intravenous (IV) drugs.
16. 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.

17. Hemoglobin <10.0 g/dL at Screening.
18. Pregnant or lactating females.
19. Medical or surgical condition known to affect drug absorption.
20. Participation in a clinical trial with an investigational agent in the 30 days prior to Screening apart from PLN-74809.

5 STUDY TREATMENTS

5.1 Description of Treatments

5.1.1 Study Drug

5.1.2 Placebo or Control

Not applicable.

5.1.3 R_01 Knottin PET tracer

The Knottin PET tracer is not considered a study treatment but is an investigational tool used during the PET procedure for obtaining the computerized images necessary for this trial.

The Knottin tracer, also known as [^{18}F]FP-$R_0$1-MG-F2 is formulated in a sterile and pyrogen-free isotonic solution and is administered as a single slow IV injection. Refer to the Radiology Manual for details.

5.2 Treatments Administered

Participants will receive a single dose of 60 mg or 80 mg 120, 240 or 320 mg of PLN-74809. Eligible participants consenting to participate will receive up to four single doses of PLN-74809 (on different occasions). Study drug will be dispensed by the site pharmacist. Refer to the Pharmacy Manual for details.

5.3 Selection and Timing of Dose for Each Participant

[redacted]

5.4 Method of Assigning Participants to Treatment Groups

[redacted]

5.5 For Participants Receiving an Additional Single Dose

[redacted]

5.6 Blinding

This is an open-label study.

5.7 Concomitant Therapy

Treatment with current standard of care (nintedanib or pirfenidone) for IPF is allowed provided these drugs have been given at a stable dose for at least 3 months before initiation of Screening and are expected to remain unchanged during the study.

Treatment for IPF (fibrosis) with any other non-FDA-approved agent is not permitted during the study. Treatments to address IPF disease symptoms, (cough, gastroesophageal reflux disease, etc) are allowed.

[redacted]

[redacted]

Treatment with another investigational drug, investigational device, or approved therapy for investigational use within 30 days or 5 half-lives (whichever is longer) before anticipated dosing is prohibited apart from PLN-74809.

Other medications to provide reasonable patient care of IPF or other 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.

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 Principal Investigator (PI) in consultation with the Medical Monitor to determine whether the participant is suitable for inclusion. For other concomitant medications that are needed during the study conduct, the PI should consult with the Medical Monitor as soon as feasible.

If used, all concomitant medications, including both prescription and nonprescription drugs, should first be discussed with the PI and Medical Monitor before administration. This requirement does not apply in the case of urgent, necessary treatment of adverse events (AEs). In all cases, all medications, including over-the-counter medications and herbal supplements, that are taken by participants during the course of the study will be recorded using the generic name of the medication. In addition, for participants who are receiving nintedanib or pirfenidone, the time of drug administration should be collected on each day on which samples are obtained for assessing PLN-74809 PK.

5.8 Restrictions

5.8.1 Prior Therapy

Previous use of IPF standard-of-care treatment (pirfenidone or nintedanib) is allowed for participation in this study. Prohibited medications (see Section 5.7, Concomitant Therapy) should be stopped at least 5 half-lives before dosing on Day 1.

5.8.2 Fluid and Food Intake

[redacted]

5.8.3 Participant Activity Restrictions

Smoking of any kind is not permitted within 3 months of Screening or during the study.

5.8.4 Contraception

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

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

- Complete abstinence from sexual intercourse if this is the participant's usual and preferred lifestyle
- Implanted contraceptives
- Oral hormonal contraceptives if using for 1 year or more
- Dual method of contraception:
  - Condom in conjunction with use of an intrauterine device
  - Condom in conjunction with use of a diaphragm
  - Oral hormonal contraceptives with less than 1 year of use in conjunction with condom
- Sexual partner with surgical sterilization (e.g., vasectomy, tubal ligation, hysterectomy and/or bilateral oophorectomy).

Females who are using hormonal contraceptives should have started use at least 12 weeks before Screening.

Participants must agree to abstain from egg or sperm donation and to continue condom use through 30 or 90 days, respectively, after administration of the last dose of study drug.

5.8.5 Diet and Other Restrictions

There are no specific dietary restrictions.

Smoking and vaping are not permitted during the study. Use of recreational drugs and/or abuse of alcohol consumption are not permitted during the study.

5.9 Treatment Compliance

Dosing will be performed in the presence of site staff. Site staff will ensure the full dose amount is taken. Participants who are receiving nintedanib or pirfenidone will be provided with a dosing log in which they will collect dosing information on the day before and the day of study drug dosing.

5.10 Packaging and Labeling

[redacted]

5.11 Storage and Accountability

6 STUDY PROCEDURES

6.1 Informed Consent

An informed consent form (ICF) describing the study and all anticipated risks of participation will be prepared and submitted to the institutional review board (IRB) for approval. Written and dated informed consent will be obtained from each study participant prior to any study-related procedures being performed.

6.2 Medical History

Medical history will be reviewed and recorded at Screening.

6.3 Demographic Information

Date of birth, sex, ethnicity, and race will be recorded at Screening. Body weight and height will be measured with the participant in light clothing. Weight will be recorded in kilograms and height will be recorded in centimeters.

6.4 Physical Examination

Complete and directed 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. Directed physical examination 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.

6.5 Vital Signs

Blood pressure and heart rate will be recorded after participants have rested for at least 3 minutes in a supine position. Ear temperature will be measured and peripheral capillary oxygen saturation (SpO_2) will be measured using a finger pulse oximeter.

6.6 [redacted]

[redacted]

6.7 Clinical Laboratory Tests

Participants will be in a seated or supine position during blood collection. Clinical laboratory tests will include hematology, clinical chemistry, and urinalysis. Safety laboratory tests (hematology and clinical chemistry) will be collected from fasting (at least 2 hours) participants where appropriate.

Urine pregnancy tests will be performed on all women at Baseline prior to the dose of study drug and, if positive, will be confirmed by a blood pregnancy test.

A detailed list of laboratory tests is provided in Appendix 2.

6.8 Pharmacokinetic Assessments

Plasma samples for PK analysis will be obtained before and at 0.5, 1, 2, 3, and 4 hours after dosing on Day 1 (prior to receiving the $R_0$1 Knottin tracer) and at 24 hours after dosing (Day 2). A collection window of ±5 minutes will be allowed for samples up to 1-hour post-dose and a collection window of ±10 minutes will be allowed for samples that are collected at 2 hours post-dose and after. Samples will be obtained and stored as detailed in the study PK Manual.

The actual collection time of each sample 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 Early Termination (ET) Visit if possible.

Aliquots of these PK samples may be used to measure nintedanib and or pirfenidone concentrations in participants receiving these drugs.

6.9 Pharmacodynamic Assessments

6.9.1 PET Imaging

All PET imaging will be performed at prespecified times according to the Schedule of Events (see Appendix 1), using the $R_0$1 Knottin tracer as synthetized by the Radiology Department at Stanford Medical Center, and following predefined instructions as detailed in the study Radiology Manual.

PET imaging that is performed following administration of PLN-74809 on Day 1 will be conducted as much as possible to coincide with PLN-74809 T_{max} (at least 4 hours post-dose and no more than 30 minutes after the 4 hour PK timepoint) to assess $\alpha_v\beta_6$ receptor occupancy.

Blood samples for radiotracer PK will be obtained at the following time points: 1, 3, 5, 10, 30, and 60 minutes after completion of radiotracer injection for PET-computed tomography (CT) to obtain blood time activity measurements. Each collection time point has a +4-minute window. During some PET-CT scans, sample collection may not be possible or may be obviated due to staffing availability or scientific considerations. Refer to the Radiology Manual for details, including definitive information regarding the allowed sample collection windows.

6.9.2 HRCT

An HRCT will be performed at Screening only if a scan meeting the quality necessary for diagnosis purposes is not already available. If an HRCT is performed at Screening, a second one is not needed during PET-CT. An HRCT during PET-CT may be performed if the entry HRCT is not adequate for the assessment of HRCT-PET relationship.

6.9.3 [redacted]

[redacted]

6.9.4 Spirometry Testing for FVC Measurement

Spirometry will be performed according to American Thoracic Society (ATS) guidelines and using the Chest Clinic equipment at Stanford Medical Center. FVC will be assessed for all participants at Screening for inclusion criteria purposes.

6.9.5 [redacted]

[redacted]

6.10 Adverse Events Assessments

6.10.1 Timing

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

6.10.2 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 preexisting 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 preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.
- If there is evidence of an AE through report or observation, the Investigator or designee will evaluate further and record the following information:
  - Time of onset and resolution
  - Severity
  - Causality/relation to study treatment
  - Action taken regarding study drug
  - Outcome

6.10.3 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 Medical Monitor.

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 refers to bathing, dressing and undressing, feeding self, using the toilet, or 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

6.10.4 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 relationship or association of the AE to a study drug (PLN-74809 or placebo) should be assessed using clinical judgment and the following considerations:

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

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

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

No: Evidence exists that the AE has an etiology other than the study procedure

Yes: The AE occurred as a result of protocol-mandated procedures.

6.10.5 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

6.10.6 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 or within 90 days after last dose, the Sponsor must be notified within 24 hours of the Investigator learning of the pregnancy. 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.

6.10.7 Clinical Laboratory Adverse Events

Abnormal laboratory findings (e.g., clinical chemistry, hematology, urinalysis) or other abnormal assessments [redacted] per se are not reported as AEs. However, those abnormal findings that are deemed clinically significant or that are associated with signs and/or symptoms must be recorded as AEs if they meet the definition of an AE (or recorded as an SAE if they meet the criteria of being serious), as described in Section 6.10.2. 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.

6.10.8 Serious Adverse Events

6.10.8.1 Definition of Serious Adverse Events

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

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

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

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

6.10.8.2 Reporting Serious Adverse Events

In order to meet the requirements for expedited reporting of SAEs meeting specific requirements to applicable regulatory authorities and IRBs, all SAEs must be reported to the Sponsor within 24 hours from the time site personnel first become aware of the event. This may be initially achieved by telephone or by completing an SAE report form and e-mailing it to the email address, as provided on the form.

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

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.

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 by the Investigator in accordance with their regulations.

6.11 Removal of Participants from the Study or Discontinuation of Study Drug

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 adverse event occurs.
- A clinically significant change in a laboratory parameter occurs.
- 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, he or she will undergo ET assessments (refer to the Schedule of Evaluations in Appendix 1).

6.12 Appropriateness of Measurements

All PK, PD, and safety assessments are typical of those that are usually employed in studies aiming to establish a PK/PD relationship. When available, appropriate standard guidelines will be used.

We [redacted] and others have previously demonstrated that the density of $\alpha_v\beta_6$ integrin receptor can be measured utilizing PET probes in IPF patients. The evaluation of receptor occupancy of an investigational compound with PET imaging has been a well-established method in the study of neurological receptors for many years. We are applying both approaches to evaluate the PK/PD relationship of PLN-74809 in IPF patients. Assessment of the primary endpoint will be made using standard methods for quantifying the amount of PET tracer bound to the $\alpha_v\beta_6$ integrin receptor in the lungs before and after administration of study drug. Standard mathematical and analytical tools will be used to determine if the presence of PLN-74809 reduces the binding of the PET tracer. Tracer uptake before and after treatment will be quantified to estimate changes in receptor density.

7 STUDY ACTIVITIES

The Schedule of Events with study activities is provided in Appendix 1.

When multiple study procedures are scheduled at the same time point, the suggested order of procedures is as follows but may be adjusted by the site staff to allow flexibility in the study flow: [redacted] obtain vital signs, collect urine sample, and collect blood sample. 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. [redacted] When samples for PK purposes are scheduled for collection around a PET procedure, the PK samples should be obtained as close as possible to the prescheduled timing while minimizing interference with the PET procedure, which has priority.

8 QUALITY CONTROL AND ASSURANCE

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

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

9 PLANNED STATISTICAL METHODS

9.1 General Considerations

This is an exploratory study; as such, no statistical hypotheses are being tested. In general, data will be summarized using statistical summary methods; graphic presentations of data may also be prepared. The contract research organization (CRO) will be responsible for the preparation of tables and listings and will assist in the preparation of figures, which may be done by Sponsor personnel. A statistical analysis plan (SAP), prepared and agreed before final database lock, will describe the analytic approach and methods in more detail.

9.2 Determination of Sample Size

The sample size has been set empirically. Up to 12 participants should provide proof of concept on the ability of the study to assess target engagement ($\alpha_v\beta_6$ receptor occupancy by PLN-74809). Pharmacodynamic, PK, and safety/tolerability evaluation of PLN-74809 will be assessed in the target population.

9.3 Analysis Populations

Safety Population: All participants who receive one dose of study drug will be included in the Safety Population.

PET Population: All participants with at least a baseline PET will be included in the PET Population.

PK Concentration Population: All participants who receive one dose of study drug and have any measurable PLN-74809 concentration data will be included in PK Concentration Population.

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

[redacted]

9.4 Pharmacokinetic Analysis

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 the PK parameters T_{max}, C_{max}, area under the drug concentration-time curve from time zero to the time of the last measurable concentration (AUC_{last}), AUC from time zero to 4 hours ($AUC_{(0-4)}$) and from time zero to 24 hours ($AUC_{(0-24)}$) after dosing, and average drug concentration (C_{avg}), if applicable. Plasma PK parameters will be presented in listings and summarized with descriptive

statistics. Further details of the analyses will be provided in the SAP, which will 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.

9.5 Pharmacodynamic Analysis

9.5.1 $\alpha_v\beta_6$ Receptor Occupancy from PET Imaging

PET-CT 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-CTs. Mean and maximum standardized uptake value (SUV) measurements of contoured lungs will be calculated using MIMS software, by analyzing the uptake values of [^{18}F]FP-R$_0$1-MG-F2 within the lung, and comparing values from the Baseline and post-treatment scans. Numerical and graphical results will be presented by dose.

In addition, relationships between PK and PET receptor occupancy, as well as between HRCT and PET receptor imaging, may be evaluated in an exploratory fashion and presented in a graphical manner.

9.5.2 FVC from Spirometry

FVC, percent of predicted and volume (mL), will be assessed using the standard spirometry procedure at the Chest Clinic at Stanford Medical Center and presented as absolute values and as percent of predicted values.

9.5.3 [redacted]

[redacted]

9.5.4 HRCT

Visual results will be presented in listings and summarized with descriptive statistics by dose to support the inclusion criteria. Quantitative volumetric HRCT results will be analyzed and presented individually and in relationship to the PET findings. Results will be presented in tabular and graphical form.

9.6 Safety Analysis

Safety data from all participants who receive 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. AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA®).

All AEs will be listed by participant and summarized in a table. The incidence of AEs, the incidence of treatment-emergent AEs (TEAEs), the incidence of treatment-related AEs, and the severity of AEs will be summarized by system organ class (SOC), preferred term, and maximum severity. In cases in which 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.

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.

[redacted]

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

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

9.7 [redacted]

[redacted]

10 ADMINISTRATIVE CONSIDERATIONS

10.1 Institutional Review Board Approval

It is the responsibility of the Investigator to assure that all aspects of the study are conducted in accordance with the Declaration of Helsinki as described in the International Council for Harmonisation (ICH) E6: Guideline for Good Clinical Practice (GCP), and/or local laws, whichever provides the greatest level of protection for the study participants. The protocol and any information supplied to the participant to obtain informed consent, including written ICF(s), participant recruitment procedures (e.g., advertisements), and written information to be provided to participants (information leaflets), must be reviewed and approved by a qualified IRB prior to enrollment of participants in the study. Prior to initiation of the study, the Sponsor must receive documentation of the IRB approval, which specifically identifies the study/protocol, and a list of the committee members.

Amendments to the protocol and revisions to the informed consent must also be submitted to and, if required, approved by the IRB.

The Investigator must submit progress reports to the IRB in accordance with the IRB requirements. Annual re-approval of the study must be obtained. Copies of progress reports and Annual re-approvals must be sent to the Sponsor.

When the Sponsor provides the Investigator with a safety report, the Investigator must promptly forward a copy to the IRB.

After completion or termination of the study, the Investigator must submit a final report to the IRB and to the Sponsor.

The Investigator, as part of the records retention requirements for the study, must maintain documentation of all submissions, correspondence, and approvals to and from the IRB.

Each clinical Investigator is responsible to conduct the study in accordance with the protocol, all applicable laws, regulations, and GCP according to ICH guidelines.

10.2 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 (recommendations guiding physicians in biomedical research involving human participants). The study will be conducted in adherence to the study protocol and GCPs, as defined in Title 21 of the US Code of Federal Regulations Parts 50, 54 56, and 312 and Part 11, as well as ICH E6: Guideline for Good Clinical Practice (ICH GCP) consolidated guidelines (E6) and applicable regulatory requirements.

10.3 Participant Information and Consent

Preparation of the ICF is the responsibility of the Investigator and the Sponsor or designee. It must include all elements required by the ICH, GCP, and applicable regulatory requirements

and must adhere to GCP and to the ethical principles that have their origin in the Declaration of Helsinki.

The Sponsor or designee must review and approve the ICF before submission to the IRB.

The ICF must include a statement that the Sponsor or designee and regulatory authorities have direct access to participant records. Prior to the beginning of the study, the Investigator must have the IRB's written approval/favorable opinion of the written ICF and any other information to be provided to the participants.

Before being enrolled in the clinical study, participants must consent to participate after the nature, scope, and possible consequences of the study have been explained in a form understandable to them.

An ICF that includes both information about the study and the consent form will be prepared and given to the participant. This document will contain all the elements required by the ICH E6 Guideline for Good Clinical Practice and any additional elements required by local regulations. The document must be in a language understandable to the participant and must specify who informed the participant. Where required by local law, the person who informs the participant must be a physician.

A copy of the signed and dated consent document must be given to the participant. The original signed and dated consent document will be retained by the Investigator.

The Investigator will not undertake any measures specifically required only for the clinical study until valid consent has been obtained.

10.4 Participant Confidentiality

Participant names will not be supplied to the Sponsor. Only the participant number will be recorded in the eCRF, and if the participant name appears on any other document (e.g., laboratory report), it must be obliterated on the copy of the document to be supplied to the Sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. The participants will be informed that representatives of the Sponsor, IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

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

10.5 Study Monitoring

Qualified representatives designated by the Sponsor ("study monitors") will monitor the study. Monitoring visits provide the Sponsor with the opportunity to:

- Evaluate the progress of the study.
- Verify the accuracy and completeness of eCRFs.
- Ensure that all protocol requirements, applicable laws and/or regulations, and Investigator's obligations are being fulfilled.
- Resolve any inconsistencies in the study records.

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

The Study Monitor will review the various records of the study (eCRFs, participant medical and laboratory records, and other pertinent data). The Study Monitor will verify the eCRF data against original source documentation for accuracy and completeness. The Study Monitor will identify data discrepancies and collaborate with the Investigator and research staff to resolve the discrepancies in a timely manner. Protocol deviations will also be identified and recorded on a Protocol Deviation Log and reviewed in accordance with the monitoring plan.

10.6 Case Report Forms and Study Records

The investigative site will use eCRFs to record all the protocol-specified data for each participant 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 to verify that the information is true and correct.

Queries generated by Data Management will be sent to the study site for resolution.

10.7 Protocol Violations/Deviations

Participants must meet eligibility requirements to be enrolled in the study. Deviations must be reported to the IRB in accordance with the IRB requirements. During the course of the study, the monitor must notify the Sponsor of participants found not to have met eligibility

criteria. The Medical Monitor in collaboration with the Investigator will determine if the participant should be withdrawn from the study.

10.8 Data Generation and Analysis

Data management will be performed using eCRFs with data entry being performed by the research site staff into a validated clinical database. Laboratory data will be captured in a separate validated database.

All data entry and verification will be performed in accordance with the standard operating procedures (SOP) of the CRO.

10.9 Retention of Data

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

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

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

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

10.10 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, enrolment, data analysis, and interpretation of results.

11 REFERENCE LIST

Appendix 1 Schedule of Events

Study Period	Screening[m,n]	Baseline[m,n]	Dosing Day						Day 2 (or Day 9)	EoT/EoS/ET
Study Day	Day -35 to Day -8	Day -7	Day 1 (or Day 8[a])							Day 8 (or Day 15) (±2 days)
Hours after Dose			0[b]	0.5	1	2	3	4		
Informed consent, medical history, demographics	●									
Check inclusion exclusion criteria	●	●								
Physical examination[c]	●	●	●							●
Vital signs (post 3 minutes, supine)	●	●	●							●
[redacted]										
Hematology and clinical chemistry[d]	●	●	●						●	●[o]
Urinalysis[e]	●	●	●							●
Urine pregnancy test (females only)		●								
FVC	●									
DLco	●									
Volumetric HRCT (quantitative)[f]	●									
PET imaging		●						●[g]		
Blood samples for radiotracer PK		●						●[h]		
[redacted]										
Study drug administration (PLN-74809)[i]			●							
Blood sample for PLN-74809 PK [d]			●	●	●	●	●	●	●[j]	
[redacted]										
Adverse events[l]	●	●	●	●	●	●	●	●	●	●
Concomitant medications [l]	●	●	●	●	●	●	●	●	●	●

[redacted]; EoT = end of treatment; EoS = end of study; ET = early termination; FVC = forced vital capacity; HRCT = high-resolution computerized tomography; PET = positron emission tomography; PK = pharmacokinetic.

[a] In case the PET ligand cannot be successfully synthetized on the scheduled day, participants will wait at least 1 week and then be dosed again for a second attempt at PET synthesis and imaging.

[b] Time 0 refers to immediately pre-dose.

[c] Complete physical examination at Screening and directed physical examination thereafter.

[d] A table of blood volumes is provided in Appendix 3.

[e] Urinalysis: dipstick followed up by microscopic examination if needed.

[f] An HRCT at Screening may not be needed if a scan that weeks the quality necessary for diagnosis purposes exists. If an HRCT is performed at Screening, a second one is not needed during PET. An HRCT during PET may be performed if the Screening HRCT is not adequate for the assessment of HRCT-PET relationship.

[g] PET to be performed at least 4 hours post-dose and no more than 30 minutes after the 4 hour PK timepoint.

[h] Blood samples for radiotracer PK to be taken 1, 3, 5, 10, 30, and 60 minutes after completion of radiotracer injection for PET-CT. Each collection time point has a +4-min window. Refer to the Radiology Manual for details of sample collection including definitive information about allowable windows.

[i] Dosing to occur in connection to PET synthesis and availability.

[j] Day 2 plasma PK sample to be collected 24 hours post-dose.

[k] [redacted]

[l] Adverse events and concomitant medications to be collected at each visit.

[m] For participants testing 2 different doses of PLN-74809, the Baseline PET scan will be based on the first single dose screening and not repeated. Additionally, if in the opinion of the Investigator, there is no clinical decline, the other Screening and Baseline procedures do not have to be repeated. Participants must washout of PLN-74809 for at least 14 days prior to testing the second dose level of PLN-74809.

[n] Screening & Baseline visit may occur on the same day, duplicative assessments will not need to be repeated

[o] Hematology and clinical chemistry may be conducted outside of study institution for EOS visit, if appropriate.

Appendix 2 List of Laboratory Tests

Hematology:

- Hematocrit (Hct)
- Hemoglobin (Hgb)
- Mean corpuscular hemoglobin (MCH)
- Mean corpuscular hemoglobin concentration (MCHC)
- Mean corpuscular volume (MCV)
- Platelet count
- Red blood cell (RBC) count
- White blood cell (WBC) count with differential (absolute counts only)
- Basophils
- Eosinophils
- Lymphocytes
- Monocytes
- Neutrophils

Urinalysis:

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

Urine pregnancy test for all female participants

Clinical Chemistry:

- Alanine aminotransferase (ALT; SGPT)
- Albumin (ALB)
- Alkaline phosphatase (ALP)
- Alpha-1-acid-glucoprotein (AAG)
- Aspartate aminotransferase (AST; SGOT)
- Bilirubin (total and direct)
- Amylase (reflex lipase if amylase ≥ 1.5 × ULN)
- Blood urea nitrogen (BUN)
- Calcium (Ca)
- Chloride (Cl)
- Creatinine
- Creatine kinase
- Gamma-glutamyl transferase (GGT)
- Glucose
- Lactate dehydrogenase (LDH)
- Phosphorus
- Potassium (K)
- Sodium (Na)
- Total bilirubin
- Total cholesterol
- Total protein
- Triglycerides
- Total protein
- Uric acid

Safety laboratory tests (hematology and clinical chemistry) will be collected from fasting (at least 4 hours) participants where appropriate.

Appendix 3 Table of Blood Volumes

Per participant

Type of sample	Blood volume per sample (mL)	Number of samples	Total blood volume (mL)
[redacted]			
Plasma PK	4	8	32
Hematology and clinical chemistry	10	5	50
[redacted]			
Radiotracer PK	3	12	36
Total			138.5

[redacted] PK = pharmacokinetic.

Appendix 4 Exposure to Radiation

Volumetric HRCT*:* The amount of radiation from one procedure is 3-8 milliSieverts (mSv) per Stanford volumetric HRCT protocol, depending on participant's body size.

PET-CT*:* The amount of radiation from one Knottin PET-CT scan is 9.5 mSv (2.5 mSv from 7.5 mCi of Knottin radiotracer and 7 mSv from 3 localizer and low dose attenuation correction CT scans).

The amount of radiation from 3 Knottin PET-CT and one possible HRCT is less than the 50 mSv annual limit for radiation workers set by the United State Nuclear Regulatory Commission.

Appendix 5 Sponsor Signature

Study Title:	A Phase 2a evaluation of PLN-74809 on $\alpha_v\beta_6$ receptor occupancy using PET imaging in participants with IPF
Study Number:	PLN-74809-IPF-201
Original Protocol Final Date:	29 April 2019
Protocol Amendment 1 Date:	14 May 2019
Protocol Amendment 2 Date:	20 November 2019
Protocol Amendment 3 Date:	16 March 2020
Protocol Amendment 4 Date:	25 January 2021
Protocol Amendment 5 Date:	26 October 2021

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

Signed:_____ Date: 27 October 2021 | 1:57:14 PM PDT

Appendix 6 Investigator's Signature

Study Title:	A Phase 2a evaluation of PLN-74809 on $\alpha_v\beta_6$ receptor occupancy using PET imaging in participants with IPF
Study Number:	PLN-74809-IPF-201
Original Protocol Final Date:	29 April 2019
Protocol Amendment 1 Date:	14 May 2019
Protocol Amendment 2 Date:	20 November 2019
Protocol Amendment 3 Date:	16 March 2020
Protocol Amendment 4 Date:	25 January 2021
Protocol Amendment 5 Date:	26 October 2021

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

I agree to comply with the International Council for Harmonisation (ICH), Tripartite Guideline on Good Clinical Practice (ICH, GCP) and the provisions of the Helsinki Declaration.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical study without the prior written consent of Pliant Therapeutics Inc.

The Sponsor or its designee will have access to source documentation from which case report forms have been completed.

Signed:_____ Date:_____

Signed:_____ Date:_____