Clinical Trial Protocol

PLN-74809-PSC-203

Study Title:	A randomized, double-blind, dose-ranging, placebo-controlled, Phase 2a evaluation of the safety, tolerability, and pharmacokinetics of PLN-74809 in participants with primary sclerosing cholangitis (PSC) and suspected liver fibrosis (INTEGRIS-PSC)
Study Number:	PLN-74809-PSC-203
Study Phase:	2a
Product Name:	PLN-74809-000
IND Number:	145,730
EudraCT Number:	2020-001428-33
Indication:	Treatment of primary sclerosing cholangitis
Sponsor:	Pliant Therapeutics Inc. 260 Littlefield Avenue South San Francisco, CA 94080, USA
Sponsor Study Director:	[redacted]

Document ID	Date
[redacted]	[redacted]

SYNOPSIS

Study Title: A randomized, double-blind, dose-ranging, placebo-controlled, Phase 2a evaluation of the safety, tolerability, and pharmacokinetics of PLN-74809 in participants with primary sclerosing cholangitis (PSC) and suspected liver fibrosis (INTEGRIS-PSC)

Study Number: PLN-74809-PSC-203

Study Phase: 2a

Primary Objective:

- To assess the safety and tolerability of PLN-74809 in participants with PSC and suspected liver fibrosis

Secondary Objective:

- To assess the pharmacokinetics (PK) of PLN-74809 in participants with PSC and suspected liver fibrosis

Exploratory Objectives:

- To assess changes from Baseline in liver fibrosis biomarkers, [redacted] PRO-C3 and Enhanced Liver Fibrosis (ELF) score
- To assess changes from Baseline in alkaline phosphatase (ALP)
- To assess changes from Baseline in magnetic resonance (MR)-based liver imaging
- To assess changes from Baseline in patient-reported outcomes (PROs)

Study Design:

This is a Phase 2a, multicenter, 3-part, randomized, double-blind, dose-ranging, placebo-controlled, parallel-group study to evaluate the safety, tolerability, and PK of once-daily treatment with PLN-74809 in male and female participants aged 18 to 75 years with an established diagnosis of large duct PSC and suspected liver fibrosis. Participants with stable inflammatory bowel disease (IBD) may be eligible. Each study part will include an up to 42-day screening period, followed by a treatment period of either 12-weeks (Parts 1 and 2) or at least 24 weeks (Part 3), and finally a 4-week post-treatment follow-up period. The treatment period for Part 3 will be at least 24 weeks and up to 48 weeks.

Part 1 (40 mg PLN-74809 for up to 12 weeks [Cohort 1]) enrollment has been completed; no further participants will be enrolled or treated in this part of the study. Part 2 (2 cohorts: 80 and 160 mg PLN-74809 for up to 12 weeks [Cohorts 2 and 3]) enrollment was initiated following review by the Data Safety Monitoring Board (DSMB) of the clinical data supporting the evaluation of 40 mg dosing. The DSMB recommended continuation of Study PLN-74809-PSC-203 to evaluate doses of 80 mg and 160 mg without modification. Part 3 (320 mg PLN-74809 for at least 24 weeks and up to 48 weeks [Cohort 4]) enrollment will initiate following review by the DSMB of the 80 mg and 160 mg clinical data from Part 2. The dose level of Part 3 is supported by the clinical data from Study PLN-74809-104 and the duration is supported by the chronic toxicology data.

Potential participants who provide written informed consent will be screened for study eligibility up to 42 days before administration of the first dose of study drug. Individuals who are deemed to be eligible for the study based on the Screening visit (Visit 1) will be scheduled for a Prebaseline visit (Visit 2) to confirm eligibility prior to Day 1 (Visit 3). Eligible participants will be randomized on Day 1 (Visit 3). Randomization will be stratified by use of ursodeoxycholic acid (UDCA; yes/no).

In Part 1, 28 eligible participants were planned to be randomized (3:1 ratio) to receive 40 mg PLN-74809 once daily (N=21) or matching placebo once daily (N=7) for 12 weeks.

In Part 2, approximately 28 eligible participants per cohort (56 in total) will be randomized in a 3:1 ratio (active:placebo) and treated for 12 weeks in sequential treatment cohorts. PLN-74809 doses of 80 mg and 160 mg will be evaluated.

In Part 3, an additional PLN-74809 dose of 320 mg is planned for evaluation based on the following criteria:

- Part 2 has been completely enrolled (i.e., 56 participants have been randomized)
- DSMB has reviewed and provided a favorable opinion on the following data:
    - All available safety and PK data from this study (Parts 1 and 2)
    - Safety and PK data from study PLN-74809-104, a completed Phase 1 study evaluating the safety, tolerability, and pharmacokinetics of PLN-74809 at multiple doses ranging from 80 to 320 mg in healthy participants

If Part 3 is initiated, approximately 28 eligible participants will be randomized in a 3:1 ratio (320 mg PLN-74809:placebo) on Day 1 (Visit 3). Randomization will be stratified by use of UDCA (yes/no). Study treatment will be administered for at least 24 weeks. Treatment will continue for all participants in Part 3 until the last participant enrolled in Part 3 reaches Week 24. At this time, all participants will be contacted to return and complete the End of Treatment (EoT) Visit. The maximum treatment duration will be 48 weeks.

The total number of participants enrolled in Parts 1 and 2 and treated for 12 weeks will be approximately 84, with approximately 63 receiving PLN-74809 and 21 receiving placebo. Approximately 28 additional participants will be enrolled in Part 3, with approximately 21 receiving PLN-74809 and 7 receiving placebo.

Study drug will be administered at the investigational site on Day 1, at Weeks 4 and 12 (Parts 1, 2, and 3), and additionally at Week 24 in Part 3. Participants will self-administer the study drug on an outpatient basis on all other days. In Parts 1 and 2, participants will return to the study site for on-treatment evaluations on Day 1 and at Weeks 2, 4, 8, and 12. In Part 3, participants will return to the study site for on-treatment evaluations on Day 1 and at Weeks 2, 4, 8, 12, 18, 24, and every 8 weeks after Week 24 until the last participant enrolled in Part 3 has completed this Week 24 visit. At this time, all participants will be contacted to return and complete the EoT Visit. The maximum treatment duration will be 48 weeks. Blood and urine specimens for safety laboratory assessments will be collected [redacted]. A final study visit will be conducted 4 weeks after the last dose of study drug.

Participants who discontinue study drug for safety reasons prior to completion of 12 weeks (Parts 1 and 2) or at least 24 weeks (Part 3) of treatment will be asked to remain in the study to complete all remaining assessments; if this is not feasible, they will be asked to return to the clinic for an Early Termination (ET) visit for follow-up evaluations.

The DSMB will assess participant safety at predetermined intervals during the study, including prior to initiating Part 3, following the enrollment of the last participant in Part 3, and as needed.

[redacted]

Study Population:

Approximately 112 participants with PSC who meet the following eligibility criteria may be enrolled.

Inclusion Criteria:

General and Administrative

1. Aged 18 to 75 years, inclusive.
2. 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 drug.

   Male participants with female partners of childbearing potential must agree to use contraceptive measures or remain abstinent (refrain from heterosexual intercourse) during screening and the treatment period and for at least 3 months after the last dose of study drug.
3. Female participants of nonchildbearing potential must be surgically sterile or postmenopausal.
4. Participants must agree to abstain from sperm or egg donation for the duration of the study, through 3 months or 1 month, respectively, after administration of the last dose of study drug.
5. Able to understand the purpose and procedures that are involved in the study and willing to sign a written informed consent form.

Primary Sclerosing Cholangitis Diagnosis

6. Established clinical diagnosis of large duct PSC based on an abnormal cholangiography as assessed by magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and/or percutaneous transhepatic cholangiopancreatography (PTC) in the context of elevated cholestatic liver chemistries.
7. Serum alkaline phosphatase concentration within normal ranges or > 1 × the upper limit of normal (ULN).
8. Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) concentration ≤ 5 × ULN.
9. Serum total bilirubin ≤ 1.5 × ULN, in the absence of hemolysis.

   Participants with serum total bilirubin > 1.5 × ULN may be enrolled if they have Gilbert's Syndrome and a direct bilirubin ≤ 0.6 mg/dL. In participants with Gilbert's syndrome, stable direct bilirubin during the screening period will be confirmed by measurements ≥2 weeks apart with a ≤30% increase observed with the follow-up value. This will only be applied to values that are outside the normal range at Screening Visit 2.
10. Suspected liver fibrosis, as defined by any of the following:
    - Liver stiffness measurement (LSM) ≥ 8 kPa but ≤ 14.4 kPa, assessed by FibroScan® **OR**
    - Enhanced Liver Fibrosis (ELF) Score ≥ 7.7 at Screening **OR**
    - Historical liver biopsy showing fibrosis without cirrhosis (by any scoring system) **OR**
    - Magnetic resonance elastography (MRE) ≥ 2.4 kPa but ≤ 4.9 kPa
11. Platelet count ≥ 140,000/mm^3.

12. Albumin ≥ 3.3 g/dL.
13. International normalized ratio (INR) ≤ 1.3 in the absence of anticoagulant therapy.
14. Serum carbohydrate antigen 19-9 (CA19-9) value ≤ 130 U/mL.

Prior and Concomitant Medications

15. If receiving treatment with UDCA, therapy is at a dose of < 25 mg/kg/day, has been stable for at least 3 months before screening, will remain stable from screening through Day 1 (baseline), and is expected to remain stable for the duration of the study.
16. If receiving allowed concomitant medications for the treatment of IBD, therapy must be stable from screening and expected to remain stable for the duration of the study.

Medical History and Comorbid Conditions

17. Participants with IBD must have had a colonoscopy showing no evidence of dysplasia within no more than 18 months before screening.
18. Participants with IBD must have no evidence of active disease and a partial Mayo score of < 2, with a score of < 1 on the Rectal Bleeding domain, between screening through Day 1.
19. Participants with IBD who are receiving treatment with biologics, including tumor necrosis factor-alpha (TNF-α) inhibitors and/or vedolizumab, immunosuppressive agents, or corticosteroids must have been receiving a stable dose for at least 3 months before screening. The dose must remain stable from screening through Day 1 (baseline) and be expected to remain stable for the duration of the study.
20. Estimated glomerular filtration rate ≥ 60 mL/min, according to the Cockcroft-Gault equation.

Exclusion Criteria:

Primary Sclerosing Cholangitis Diagnosis

1. Other causes of liver disease, including secondary sclerosing cholangitis or viral, metabolic, or alcoholic liver disease, as assessed clinically.
2. Known or suspected overlapping clinical and histologic diagnosis of autoimmune hepatitis.
3. Small duct PSC with no evidence of large duct involvement (evidence of PSC on historical liver histology, with normal bile ducts on cholangiography).

Liver Disease Status

4. Presence of a clinically significant dominant stricture based on the combination of radiological, biochemical, and clinical features.
5. Presence of a percutaneous drain or bile duct stent.
6. Serum alkaline phosphatase (ALP) concentration > 10 times ULN.

7. Worsening of liver disease, [redacted]
8. Ascending cholangitis within 60 days of screening, as assessed clinically or use of antibiotics for acute cholangitis within 60 days of screening.
9. IgG4-associated cholangitis.
10. Positive anti-mitochondrial antibody.
11. Presence of liver cirrhosis as assessed by historical liver histology, ultrasound-based liver stiffness measurement (FibroScan® value > 14.4 kPa), MRE > 4.9 kPa, and/or signs and symptoms of hepatic decompensation (including, but not limited to, jaundice, ascites, variceal hemorrhage, and/or hepatic encephalopathy).
12. Presence of hepatic impairment, end-stage liver disease, and/or a model for end-stage liver disease (MELD) score ≥ 15.
13. Prior or planned liver transplantation during the study.

Medical History and Comorbid Conditions

14. Presence of end-stage renal disease that requires dialysis.
15. History, current clinical or radiological suspicion, or diagnosis of cholangiocarcinoma, other hepatobiliary malignancy, colorectal cancer, or other abdominal malignancy at any time.
16. Human immunodeficiency virus (HIV), hepatitis A virus, hepatitis B virus, and/or hepatitis C virus infection, with the exception of those who have been successfully treated for hepatitis C infection and have achieved sustained virologic response for ≥ 1 year.
17. 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.
18. Clinical evidence of active bacterial, viral, or fungal infection within 30 days before screening.
19. History of unstable or deteriorating cardiac disease within the previous 6 months, including, but not limited to:
    a. Unstable angina pectoris or myocardial infarction.
    b. Congestive heart failure requiring hospitalization.
    c. Uncontrolled clinically significant arrhythmias.
    d. [redacted]
20. Surgery within the 4 weeks before administration of study drug.

Prior and Concomitant Medications

21. [redacted]

22. Current treatment or anticipated need for treatment with immunomodulating agents (such as interleukins and interferons), radiation therapy, or cytotoxic or chemotherapeutic agents.

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

Screening Assessments

24. Pregnancy or breastfeeding or male participant whose female partner is pregnant.

25. History of weekly alcohol consumption > 21 units for male participants or > 14 units for female participants (1 unit = 1 oz/30 mL of alcohol contained in 12 oz/360 mL of beer, 4 oz/120 mL of wine, or 1 oz/30 mL of 40% proof alcohol).

26. Positive urine drug screen at screening unless the positive result is due to a medical treatment for a comorbid condition.

27. Any other clinically significant disorders or prior therapy that, in the opinion of the Investigator, would make the participant unsuitable for the study or unable to comply with the dosing and protocol requirements.

28. Prior use of an investigational drug within 5 half-lives or 30 days before screening, whichever time is longer, or the use of an investigational device within 30 days before screening.

29. Participation in an earlier part of the current study.

Test Product, Dose, and Mode of Administration:

Part 1: 40 mg of PLN-74809 or matching placebo administered orally once daily
Part 2: 80 mg or 160 mg of PLN-74809 or matching placebo administered orally once daily
Part 3: 320 mg of PLN-74809 or matching placebo administered orally once daily

PLN-74809 will be supplied by Pliant Therapeutics as a tablet for oral administration. Study drug will be taken once daily at approximately 24-hour intervals. Participants will take the study drug [redacted]

Reference Therapy, Dose, and Mode of Administration:

Placebo will be supplied by Pliant Therapeutics as a tablet. The placebo tablet will be identical in appearance to the PLN-74809 tablet and will be taken as described above for PLN-74809.

Duration of Treatment:

The duration of Parts 1 and 2 of the study will be up to 22 weeks each (up to 6 weeks of screening, 12 weeks of treatment with study drug, and 4 weeks of follow up).

The duration for Part 3 of the study will be variable depending on the study enrollment rate; i.e., the time between enrolling the first and last participant. The duration of participation will be up to approximately 34 weeks for the last participant enrolled (up to 6 weeks of screening, 24 weeks of treatment with study drug, and 4 weeks of follow up) and up to approximately 58 weeks for the first participant enrolled (up to 6 weeks of screening, up to 48 weeks of treatment with study drug, and 4 weeks of follow up). The end of Part 3 will commence once the last participant reaches 24 weeks of treatment. At that time, all study participants will complete their next scheduled visit (EoT) and the 4 weeks of follow up (End of Study [EoS]).

Safety Assessments:

Safety assessments will include adverse events (AEs), as determined by open-ended questioning; laboratory parameters; vital sign measurements; [redacted] and physical examinations.

Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic Assessments:

- PK: plasma samples for PK analysis [redacted] will be obtained.
- Biomarkers: plasma, and serum (Parts 1, 2, and 3), [redacted] samples will be obtained.
- [redacted]

Statistical Methods:

[redacted]

In general, data will be summarized using statistical summary methods; graphic presentations of data may also be prepared.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ADL	activities of daily living
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
ARDS	acute respiratory distress syndrome
AST	aspartate aminotransferase
AUC	area under the plasma concentration-time curve
AUC_{0-24}	area under the plasma concentration-time curve from time zero to 24 hours
BALF	bronchoalveolar lavage fluid
[redacted]	[redacted]
C_{max}	maximum plasma drug concentration
CA19-9	carbohydrate antigen 19-9
CCA	cholangiocarcinoma
CFR	Code of Federal Regulations
COVID-19	coronavirus disease 2019
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
[redacted]	[redacted]
[redacted]	[redacted]
DSMB	Data Safety Monitoring Board
[redacted]	[redacted]
eCRF	electronic case report form
ELF	Enhanced Liver Fibrosis (score)
EoS	end of study

EoT	end of treatment
ERCP	endoscopic retrograde cholangiopancreatography
ET	early termination
FDA	Food and Drug Administration
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GGT	gamma-glutamyl transferase
HIPAA	Health Information Portability and Accountability Act
HIV	human immunodeficiency virus
IBD	inflammatory bowel disease
IC_{50}	50% inhibitory concentration
IC_{80}	80% inhibitory concentration
IC_{90}	90% inhibitory concentration
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	independent ethics committee
[redacted]	[redacted]
INR	international normalized ratio
IRB	institutional review board
IRT	interactive response technology
kPa	kilopascal
[redacted]	[redacted]
LDH	lactic dehydrogenase
[redacted]	[redacted]
LSM	liver stiffness measurement
MAD	multiple ascending dose
[redacted]	[redacted]
MedDRA	Medical Dictionary for Regulatory Activities
MELD	model for end stage liver disease

MR	magnetic resonance
MRCP	magnetic resonance cholangiopancreatography
NCI	National Cancer Institute
NOAEL	no observed adverse effect level
[redacted]	[redacted]
OHP	hydroxyproline
PD	pharmacodynamic(s)
[redacted]	[redacted]
PIPEDA	Personnel Information Protection and Electronic Documents Act
PK	pharmacokinetic, pharmacokinetics
PROs	patient-reported outcomes
PSC	primary sclerosing cholangitis
pSMAD2/3	phosphorylated SMAD2/3
PTC	percutaneous transhepatic cholangiography
REB	research ethics board
SAD	single ascending dose
SAE	serious adverse event
[redacted]	[redacted]
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
TE	transient elastography
TEAE	treatment-emergent adverse event
TGF-β	transforming growth factor-beta
TNF-α	tumor necrosis factor-alpha
UDCA	ursodeoxycholic acid
ULN	upper limit of normal

Abbreviations used only in tables and figures are defined in the footnotes of the respective tables and figures and are not included in the List of Abbreviations.

1 INTRODUCTION

1.1 Background

Pliant Therapeutics, Inc. (Pliant) is developing PLN-74809 for the treatment of primary sclerosing cholangitis (PSC) and idiopathic pulmonary fibrosis (IPF). PSC is a rare, idiopathic, cholestatic liver disease that is characterized by biliary inflammation and progressive fibrosis. Over time, this biliary and hepatic inflammation progresses to serious and often fatal liver complications such as cirrhosis, portal hypertension and end-stage liver disease (Toy et al, 2011; Goode & Rushbrook, 2016). More than 50% of patients require liver transplantation within 10 to 15 years after diagnosis; however, disease recurrence after transplantation is common (Hirschfield et al, 2013). Patients with PSC are at greater risk of developing certain cancers in the hepatobiliary regions, with cholangiocarcinoma (CCA), the most prevalent form, having a lifetime risk ranging from 5% to 20% (Horsley-Silva et al, 2017). Once diagnosed with CCA, the 5-year overall survival is poor, ranging from 20% to 68% (Ali et al, 2018). Although the progression of PSC is generally slow, the disease exhibits a highly variable natural history associated with age at diagnosis, sex, and ductal and inflammatory bowel disease (IBD) subtypes (Weismüller et al, 2017).

Although the etiology of PSC is largely unknown, strong associations have been made with both environmental and genetic risk factors. The characteristic biliary inflammation and injury seen in PSC may be the result of environmental exposures and gut microbial trauma triggering predisposed genetic pathways, which contribute to persistent injury of cholangiocytes, the cells that line the bile ducts (Lazaridis & LaRusso, 2016). Concurrent autoimmune disease in patients with PSC is also common. The majority of cases of PSC are associated with IBD, mainly ulcerative colitis, and IBD is a major risk factor for the development of PSC (Toy et al, 2011; Hirschfield et al, 2013; Goode & Rushbrook, 2016). In an analysis of high-density genotype data from tens of thousands of individuals of European ancestry, many of the genetic risk variants for PSC were found to be shared with ulcerative colitis (Ellinghaus et al, 2016). Patients with PSC also have a high lifetime risk of developing gastrointestinal malignancies (Bambha et al, 2003).

There are currently no widely approved medical treatments for PSC. Disease management is confined to supportive measures, which fail to address disease progression. Ursodeoxycholic acid (UDCA), an established treatment for primary biliary cirrhosis (PBC), is commonly used for the management of PSC and is approved in a few countries. However, clinical studies of its use in patients with PSC have produced meager and inconclusive results (Eaton et al, 2013; Hirschfield et al, 2013). Moreover, long-term use of UDCA is controversial due to increased rates of serious adverse events (SAEs), including death and need for liver transplantation when given at high doses (Lindor et al, 2009; Chapman et al, 2010). High-dose UDCA has also been associated with the development of colorectal neoplasia in patients with ulcerative colitis or PSC (Eaton et al, 2011).

Thus, there remains a significant unmet medical need for effective therapies for PSC.

The profibrotic cytokine transforming growth factor beta (TGF-β)1 is synthesized as a precursor molecule that is associated with LAP, a protein derived from the same gene

product which keeps it in a quiescent state. The binding of integrins, transmembrane proteins responsible for cell-extracellular matrix protein interactions, to the arginine-glycine-aspartate amino acid sequence present in LAP has been identified as a major TGF-β1 activation pathway in PSC, driving progression of fibrotic tissue remodeling.

PLN-74809 is a small molecule and a selective dual inhibitor of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins [redacted]. Additionally, integrin-ligand binding assays have demonstrated that PLN-74809 is highly selective for $\alpha_v\beta_6$ and $\alpha_v\beta_1$ over other integrin receptors, including those leukocyte-expressed integrins where therapeutic inhibition has previously been associated with significant toxicities (e.g., vedolizumab [$\alpha_4\beta_7$ inhibitor; increased risk of infections, potential risk of progressive multifocal leukoencephalopathy (PML); ENTYVIO PI, 2021; ENTYVIO SmPC, 2021] and natalizumab [$\alpha_4\beta_1$ and $\alpha_4\beta_7$ inhibitor; increased risk of PML; TYSABRI PI, 2020; TYSABRI SmPC, 2021]). PLN-74809 reduced collagen synthesis and improved liver parameters in a mouse model of sclerosing cholangitis (see Section 1.3). In ex vivo human PSC liver tissue (precision cut liver slices), treatment with PLN-74809 dose-dependently decreased collagen gene expression, providing an indication of antifibrotic activity in PSC. 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.

1.2 Summary of Clinical Development

PLN-74809 is currently being investigated for the treatment of IPF and PSC; a study in participants with acute respiratory distress syndrome (ARDS) associated with at least severe coronavirus disease 2019 (COVID-19) has been discontinued. An overview and discussion of the clinical development program is available in the Investigator's Brochure. An updated list of studies and current statuses is provided in Table 1.

Table 1. Overview of Clinical Development Program

Study Number	Type of Study	Dose(s)[a] and Duration	Participants planned, enrolled, or completed	Status
PLN-74809-PSC-203 (INTEGRIS-PSC)	Randomized, double-blind, dose-ranging, placebo-controlled evaluation of the safety, tolerability, and PK of PLN-74809 in participants with PSC and suspected liver fibrosis	Part 1: 0, 40 mg once daily (12 weeks)	28 participants with primary sclerosing cholangitis enrolled; 27 completed	Part 1: clinical conduct completed
		Part 2: 0, 80, 160 mg once daily (12 weeks)	56 participants with primary sclerosing cholangitis planned	Part 2: ongoing
		Part 3: 0, 320 mg once daily (24 to 48 weeks)	28 participants with primary sclerosing cholangitis planned	Part 3: planned
[redacted]				

[a] Placebo is denoted as a dose of 0 mg/mL.

[redacted]

1.3 Rationale for Study

PLN-74809 is a selective, small molecule antagonist of integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$, two heterodimeric cell surface proteins that potentiate TGF-β-driven fibrosis in biliary liver disease. PLN-74809 prevents $\alpha_v\beta_6$ and $\alpha_v\beta_1$ from binding to the arginine-glycine-aspartate sequence of the latency associated peptide of the TGF-β precursor protein, thereby blocking the release of the activated form of TGF-β and preventing binding to its receptors and activation of pathways relevant to fibrogenesis (e.g. collagen synthesis). PLN-74809 was demonstrated to be a potent and selective inhibitor of $\alpha_v\beta_6$ and $\alpha_v\beta_1$ integrins (human and murine) exhibiting geometric mean [redacted] against the human receptors, respectively.

Preliminary evidence of the potential anti-fibrotic benefits of PLN-74809 for the treatment of PSC is provided by the results of an in vivo pharmacology study in the [redacted] murine model of sclerosing cholangitis. Starting at 6 weeks of age, PLN-74809 was administered [redacted] PLN-74809 for 6 consecutive weeks dose-dependently inhibited the deposition of collagen, as measured by hydroxyproline (OHP), a principal amino acid of collagen, with the [redacted]. PLN-74809 dose-dependently inhibited [redacted], indicating improvement in liver parameters in [redacted] mice. The greatest improvement was seen at the [redacted] PLN-74809 ($p <$ [redacted]). Additional evidence of potential therapeutic effectiveness comes from an ex vivo study using precision cut liver slices generated from PSC patient tissue explant. A two-day treatment of precision cut PSC liver slices with PLN-74809 at doses of [redacted] resulted in a dose-dependent reduction in the expression of [redacted] (see the PLN-74809 Investigator's Brochure for further details).

This Phase 2a, multicenter, randomized, double-blind, placebo-controlled, 3-part study will evaluate the safety, tolerability, and pharmacokinetics (PK) of PLN-74809 in individuals with PSC and suspected liver fibrosis. The main purpose of the current study is to confirm that PLN-74809 is well tolerated by participants with PSC and that drug concentrations achieved are similar to those previously observed in healthy participants. In addition, Parts 1, 2, and 3 of the study will evaluate, in an exploratory manner, changes in liver fibrosis biomarkers (including PRO-C3 and Enhanced Liver Fibrosis [ELF] score), alkaline phosphatase (ALP), magnetic resonance (MR)-based liver imaging, and patient-reported outcomes (PROs).

Part 3 of the study will evaluate approximately 28 participants at the 320 mg dose or placebo for at least 24 weeks and up to 48 weeks to further characterize the safety profile of PLN-74809. In Part 3, ongoing safety and liver assessments will continue until the last participant reaches 24 weeks of the study; therefore, safety and liver assessments may extend up to 48 weeks in participants randomized earlier in the study.

1.4 Benefit-Risk Assessment

This is the first study in individuals with PSC and suspected liver fibrosis; thus, it is unknown whether the participants in this study will benefit from their participation in the study. Nonclinical data in a murine model of sclerosing cholangitis suggest that PLN-74809 has the potential to provide anti-fibrotic benefits and improve liver injury markers ([redacted]) in individuals with PSC (Section 1.3). This study will evaluate the safety, tolerability, and PK of PLN-74809 in individuals with PSC and suspected liver fibrosis when administered once daily for 12 weeks (Parts 1 and 2) or at least 24 weeks and a maximum of 48 weeks (Part 3).

The dose evaluated in Part 1 of this study (40 mg once daily) was within the range of doses that were well tolerated by the healthy male and female participants who received multiple doses of PLN-74809 for 14 days in the MAD part of Phase 1 Study [redacted]. The doses to be studied in Parts 2 and 3 of this study (80 mg, 160 mg, and 320 mg) are supported by the SAD and MAD data from the [redacted] study in healthy participants, which demonstrated a favorable safety and tolerability profile. At all dose levels studied, there is a substantial margin between the human plasma [redacted]. The extended duration of exposure in Part 3 is supported by chronic toxicology studies of PLN-74809, which are completed and have not identified [redacted]). The extended duration of exposure at the highest dose planned to be evaluated in Part 3 (320 mg once daily) is consistent with the intended use of PLN-74809 to treat the chronic and progressive fibrosis that characterizes PSC.

The participants with PSC in this study will be closely monitored (by review of the type and severity of adverse events [AEs], laboratory tests, vital signs, [redacted], and physical examinations) at each scheduled visit during the conduct of the study.

2 STUDY OBJECTIVES

2.1 Primary Objective

The primary objective of this study is to assess the safety and tolerability of PLN-74809 in participants with PSC and suspected liver fibrosis.

2.2 Secondary Objective

The secondary objective of this study is to assess the PK of PLN-74809 in participants with PSC and suspected liver fibrosis.

2.3 Exploratory Objectives

The exploratory objectives of this study are as follows:

- To assess changes from Baseline in liver fibrosis biomarkers, [redacted] PRO-C3 and Enhanced Liver Fibrosis (ELF) score.
- To assess changes from Baseline in ALP.
- To assess changes from Baseline in magnetic resonance (MR)-based liver imaging.
- To assess changes from Baseline in patient-reported outcomes (PROs).

3 INVESTIGATIONAL PLAN

3.1 Study Duration

The duration for Parts 1 and 2 of the study will be up to approximately 154 days (22 weeks) each (up to 6 weeks of screening, 12 weeks of treatment with study drug, and 4 weeks of follow up).

The duration for Part 3 of the study will be variable depending on the study enrollment rate; i.e., the time between enrolling the first and last participant. The duration of participation will be up to approximately 34 weeks for the last participant enrolled (up to 6 weeks of screening, 24 weeks of treatment with study drug, and 4 weeks of follow up) and up to approximately 58 weeks for the first participant enrolled (up to 6 weeks of screening, up to 48 weeks of treatment with study drug, and 4 weeks of follow up). The end of Part 3 will commence once the last participant reaches 24 weeks of treatment. At that time, all study participants will complete their next scheduled visit (End of Treatment [EoT]) and the 4 weeks of follow up (End of Study [EoS]).

The End of Study is defined as the last visit of the last participant.

3.2 Overall Study Design and Plan

This is a Phase 2a, multicenter, 3-part, randomized, double-blind, dose-ranging, placebo-controlled, parallel-group study to evaluate the safety, tolerability, and PK of once-daily treatment with PLN-74809 in male and female participants aged 18 to 75 years with an established diagnosis of large duct PSC and suspected liver fibrosis. Participants with stable IBD may be eligible. Each study part will include an up to 42-day screening period, followed by a treatment period of either 12 weeks (Parts 1 and 2) or at least 24 weeks (Part 3), and finally a 4-week post-treatment follow-up period. The treatment period for Part 3 will be at least 24 weeks and up to 48 weeks. See study schematics in Figure 1 (each cohort in Parts 1 and 2) and Figure 2 (Part 3). The sequential dosing scheme across all study parts and cohorts is shown in Figure 3.

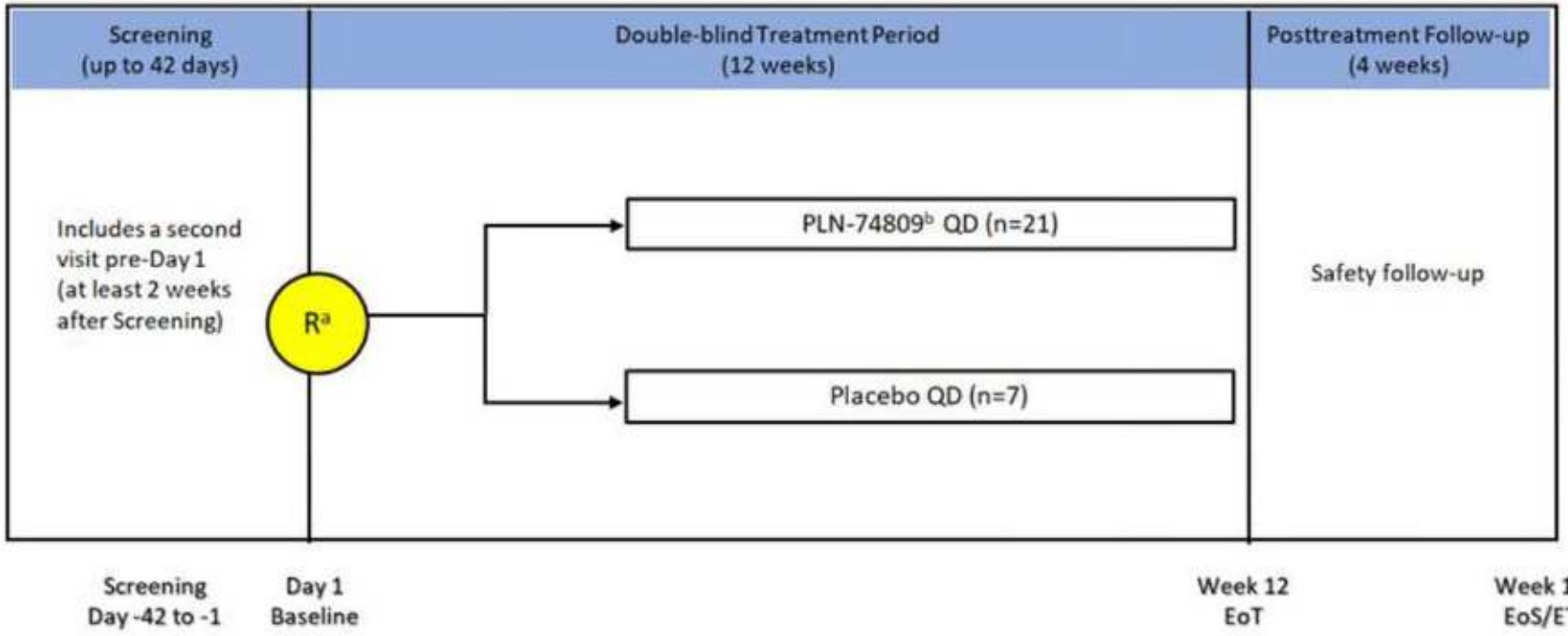
Part 1 (40 mg PLN-74809 for up to 12 weeks [Cohort 1]) enrollment has been completed; no further participants will be enrolled or treated in this part of the study.

Part 2 (2 cohorts: 80 and 160 mg PLN-74809 for up to 12 weeks [Cohorts 2 and 3]) enrollment was initiated following review by the Data Safety Monitoring Board (DSMB) of the clinical data supporting the evaluation of 40 mg dosing. The DSMB recommended continuation of Study PLN-74809-PSC-203 to evaluate doses of 80 mg and 160 mg without modification (Figure 2).

Part 3 (320 mg PLN-74809 for at least 24 weeks and up to 48 weeks [Cohort 4]) enrollment will initiate following review by the DSMB of the 80 mg and 160 mg clinical data from Part 2. The dose level of Part 3 is supported by the clinical data from study PLN-74809-104 and the duration is supported by the chronic toxicology data.

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

Figure 1. Study Design For Each Treatment Cohort: Parts 1 and 2

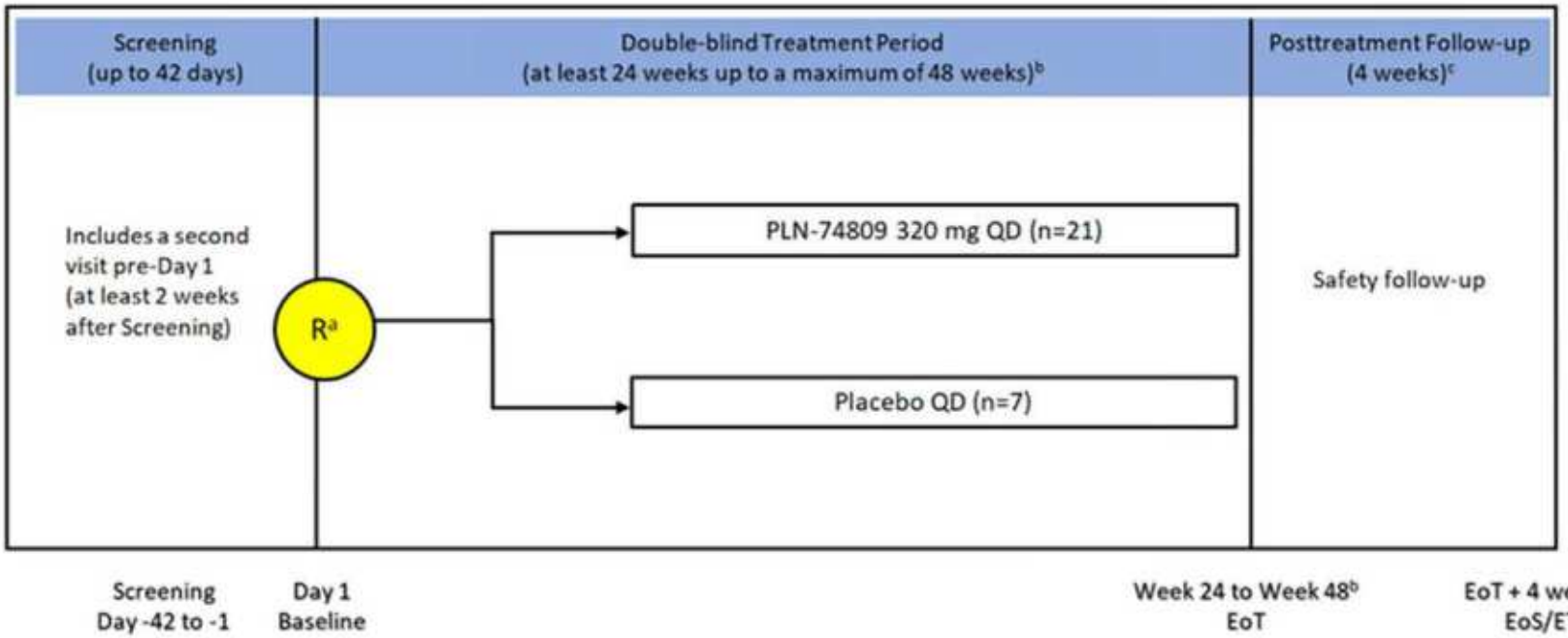


EoS = end of study, EoT = end of treatment, ET = early termination, PSC = primary sclerosing cholangitis, QD = once daily, R = randomization; UDCA = ursodeoxycholic acid

[a] Randomization will be stratified by use of UDCA (yes/no) at Baseline

[b] Part 1, Cohort 1: 40 mg PLN-74809
Part 2, Cohort 2: 80 mg PLN-74809
Part 2, Cohort 3: 160 mg PLN-74809

Figure 2. Study Design: Part 3



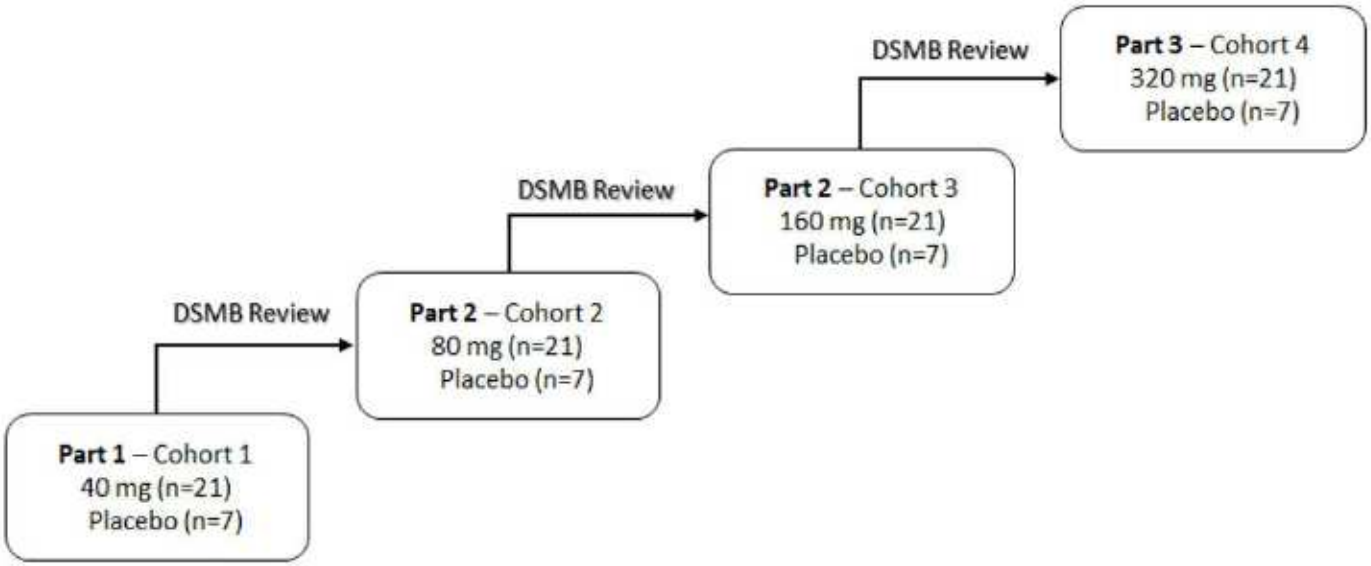
EoS = end of study, EoT = end of treatment, ET = early termination, PSC = primary sclerosing cholangitis, QD = once daily, R = randomization; UDCA = ursodeoxycholic acid

[a] Randomization will be stratified by use of UDCA (yes/no) at Baseline

[b] Treatment will continue for all participants in Part 3 until the last participant enrolled in Part 3 reaches Week 24. All participants will complete visits every 8 weeks after the Week 24 visit until such time as the last participant enrolled has completed the Week 24 visit. At this time, all participants will be contacted to return and complete the EoT Visit. The maximum treatment duration will be 48 weeks.

[c] The EoS visit will take place 4 weeks (±3 days) after the EoT Visit.

Figure 3. Study Schematic – Sequential Dosing



Potential participants who provide written informed consent will be screened for study eligibility up to 42 days before administration of the first dose of study drug. Individuals who are deemed to be eligible for the study based on the Screening visit (Visit 1) will be scheduled for a Prebaseline visit (Visit 2) to confirm eligibility prior to Day 1 (Visit 3). Eligible participants will be randomized on Day 1 (Visit 3). Randomization will be stratified by use of UDCA (yes/no).

In Part 1, 28 eligible participants were planned to be randomized (3:1 ratio) to receive 40 mg PLN-74809 once daily (N=21) or matching placebo once daily (N=7) for 12 weeks.

In Part 2, approximately 28 eligible participants per cohort (56 in total) will be randomized in a 3:1 ratio (active:placebo) and treated for 12 weeks in sequential treatment cohorts. PLN-74809 doses of 80 mg and 160 mg will be evaluated.

In Part 3, an additional PLN-74809 dose of 320 mg is planned for evaluation based on the following criteria:

- Part 2 has been completely enrolled
- DSMB has reviewed and provided a favorable opinion on the following data:
  - All available safety and PK data from this study (Parts 1 and 2)
  - Safety and PK data from study PLN-74809-104, a completed Phase 1 study evaluating the safety, tolerability, and pharmacokinetics of PLN-74809 at multiple doses ranging from 80 to 320 mg in healthy participants.

If Part 3 is initiated, approximately 28 eligible participants will be randomized in a 3:1 ratio (320 mg PLN-74809:placebo) on Day 1 (Visit 3). Randomization will be stratified by use of UDCA (yes/no). Study treatment will be administered for at least 24 weeks. Treatment will continue for all participants in Part 3 until the last participant enrolled in Part 3 reaches Week 24. At this time, all participants will be contacted to return and complete the EoT Visit. The maximum treatment duration will be 48 weeks.

The total number of participants enrolled in Parts 1 and 2 and treated for 12 weeks will be approximately 84, with approximately 63 receiving PLN-74809 and 21 receiving placebo. Approximately 28 additional participants will be enrolled in Part 3, with approximately 21 receiving PLN-74809 and 7 receiving placebo.

Study drug will be administered at the investigational site on Day 1, at Weeks 4 and 12 (Parts 1, 2, and 3), and additionally at Week 24 in Part 3. Participants will self-administer the study drug on an outpatient basis on all other days. In Parts 1 and 2, participants will return to the study site for on-treatment evaluations on Day 1 and at Weeks 2, 4, 8, and 12 (see Schedule of Events in Appendix 1). In Part 3, participants will return to the study site for on-treatment evaluations on Day 1 and at Weeks 2, 4, 8, 12, 18, 24, and every 8 weeks after Week 24 until the last participant enrolled in Part 3 has completed this Week 24 visit. At this time, all participants will be contacted to return and complete the EoT Visit (see Schedule of Events in Appendix 2). The maximum treatment duration will be 48 weeks. [redacted]

[redacted] A final study visit will be conducted 4 weeks after the last dose of study drug.

Participants who discontinue study drug for safety reasons prior to completion of 12 weeks (Parts 1 and 2) or at least 24 weeks (Part 3) of treatment will be asked to remain in the study to complete all remaining assessments; if this is not feasible, they will be asked to return to the clinic for an Early Termination (ET) visit for follow-up evaluations.

Whole liver MRI may be obtained but is not required. All MRI acquisitions obtained will be standardized across participating sites, and the MRI will be centrally read for quality.

The DSMB will assess participant safety at predetermined intervals during the study, including prior to initiating Part 3, following the enrollment of the last participant in Part 3, and as needed. [redacted]

The total number of participants enrolled in Parts 1, 2, and 3 of the study will be approximately 112, with approximately 84 receiving PLN-74809 and 28 receiving placebo.

3.3 Rationale for Study Treatments

3.3.1 Rationale for PLN-74809 Doses

This study will be the first to characterize the safety, tolerability, and PK of PLN-74809 in participants with PSC and suspected liver fibrosis, with or without co-administration with UDCA. The proposed randomized, double-blind, placebo-controlled, parallel-group study design allows a reduction in bias in the assessment of drug safety and tolerability (US FDA, 2001). [redacted] The proposed sample size and treatment duration are expected to provide meaningful safety and PK information in the PSC population, as well as allow for preliminary evaluation of potential treatment effects across a dose range on exploratory study endpoints, comparing PLN-74809 to placebo.

The evaluation of PLN-74809 40 mg for 12 weeks in Part 1 of this study is supported by the 13-week toxicology data, as well as safety and PK data at this dose from Study [redacted] (See PLN-74809 Investigator's Brochure for more details).

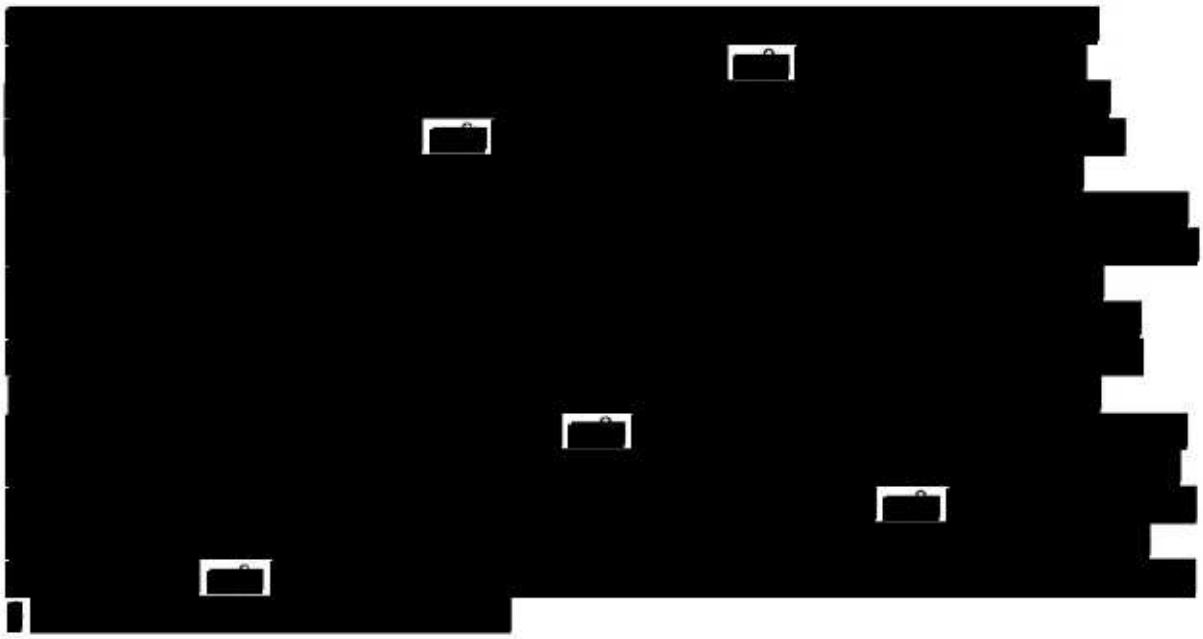
The evaluation of PLN-74809 80 mg and 160 mg doses for 12 weeks in Part 2 is supported by all available safety and PK data from Part 1, as well as safety and PK data evaluating higher single and multiple doses (80 and 160 mg) from [redacted].

The evaluation of PLN-74809 320 mg in Part 3 of this study will be supported by all available safety and PK data from Parts 1 and 2, as well as safety and PK data evaluating [redacted]
The treatment duration (24 to 48 weeks) is supported by the chronic toxicology studies of PLN-74809, which are completed and [redacted].

In Study [redacted], PLN-74809 showed a favorable safety and tolerability profile in healthy participants after single doses of up to [redacted] and after [redacted] days of treatment at doses of up to [redacted]. The safety margins determined after single doses of [redacted] and multiple doses of [redacted] were calculated using the NOAEL observed in toxicology studies in [redacted] for both area under the plasma concentration-time curve from time zero to 24 hours (AUC_{0-24}) and C_{max} for the [redacted] of PLN-74809. At all dose levels studied, there was a substantial margin between the human [redacted] AUC_{0-24} and the [redacted] AUC_{0-24} NOAEL in [redacted]. See the PLN-74809 Investigator's Brochure for more details.

Comparison of the [redacted] AUC_{0-24} across all doses studied in the relevant dose escalation Phase 1 studies [redacted] demonstrates that doses ranging from [redacted] mg to [redacted] mg in the SAD and [redacted] mg to [redacted] mg in the MAD remain far below the NOAEL established in the [redacted] toxicology studies.

The higher dose of 320 mg to be evaluated in Part 3 of this study provides a reasonable escalation and separation from the 80 and 160 mg doses evaluated in Part 2, allowing for appropriate dose ranging while remaining within the safety margins (please refer to the Investigator's Brochure for further details).



Initiation of Part 3 dosing will be contingent on approval by the DSMB of the above-mentioned data from Part 2.

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

3.3.2 Rationale for Control Group

This study incorporates the use of a placebo comparator arm as it is the most rigorous test of treatment efficacy and safety for evaluating an experimental therapy in complex patient populations. Currently, there are no widely approved pharmacologic therapies for the treatment of PSC patients. UDCA, an established treatment for PBC, is commonly used for the management of PSC and is approved in a few countries. Multiple prospective trials have studied UDCA in PSC patients and have demonstrated varying degrees of pharmacologic response. However, the current guidelines from both the European Association for the Study of the Liver (EASL) and American Association for the Study of Liver Disease (AASLD) currently do not make a recommendation for the general use of UDCA in PSC. Therefore, the vast majority of recent and current trials of experimental therapies for PSC utilize placebo as the comparator arm, independent of whether UDCA is co-administered or not, as there is not an acceptable standard of care comparator.

4 STUDY POPULATION AND SELECTION

4.1 Study Population

4.1.1 Inclusion Criteria

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

General and Administrative

1. Aged 18 to 75 years, inclusive.
2. 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 drug (refer to Section 6.7.4).

   Male participants with female partners of childbearing potential must agree to use contraceptive measures (refer to Section 6.7.4) or remain abstinent (refrain from heterosexual intercourse) during screening and the treatment period and for at least 3 months after the last administration of study drug.
3. Female participants of nonchildbearing potential must be either surgically sterile or postmenopausal (refer to Section 6.7.4).
4. Participants must agree to abstain from sperm or egg donation for the duration of the study, through 3 months or 1 month, respectively, after administration of the last dose of study drug.
5. Able to understand the purpose and procedures that are involved in the study and willing to sign a written informed consent form.

Primary Sclerosing Cholangitis Diagnosis

6. Established clinical diagnosis of large duct PSC based on an abnormal cholangiography as assessed by magnetic resonance cholangiopancreatography (MRCP), endoscopic retrograde cholangiopancreatography (ERCP), and/or percutaneous transhepatic cholangiopancreatography (PTC) in the context of elevated cholestatic liver chemistries.
7. Serum ALP concentration within normal ranges or > 1 × the upper limit of normal (ULN).
8. Serum aspartate aminotransferase (AST) and serum alanine aminotransferase (ALT) concentration ≤ 5 ULN.
9. Serum total bilirubin ≤ 1.5 × ULN, in the absence of hemolysis.
   Participants with serum total bilirubin > 1.5 × ULN may be enrolled if they have Gilbert's Syndrome and a direct bilirubin ≤ 0.6 mg/dL. In participants with Gilbert's syndrome, stable direct bilirubin during the screening period will be confirmed by measurements ≥2 weeks apart with a ≤30% increase observed with the follow-up value. This will only be applied to values that are outside the normal range at Screening Visit 2.

10. Suspected hepatic fibrosis, as determined by any of the following:
    - Liver stiffness measurement (LSM) ≥ 8 kPa but ≤ 14.4 kPa, assessed by FibroScan® **OR**
    - Enhanced Liver Fibrosis (ELF) Score ≥ 7.7 at Screening **OR**
    - Historical liver biopsy showing fibrosis without cirrhosis (by any scoring system) **OR**
    - Magnetic resonance elastography ≥ 2.4 kPa but ≤ 4.9 kPa
11. Platelet count ≥ 140,000/mm^3.
12. Albumin ≥ 3.3 g/dL.
13. International normalized ratio (INR) ≤ 1.3 in the absence of anticoagulant therapy.
14. Serum carbohydrate antigen 19-9 (CA19-9) value ≤ 130 U/mL.

Prior and Concomitant Medications

15. If receiving treatment with UDCA, therapy is at a dose of < 25 mg/kg/day, has been stable for at least 3 months before screening, will remain stable from screening through Day 1 (baseline), and is expected to remain stable for the duration of the study.
16. If receiving allowed concomitant medications for the treatment of IBD, therapy must be stable from screening and expected to remain stable for the duration of the study.

Medical History and Comorbid Conditions

17. Participants with IBD must have had a colonoscopy showing no evidence of dysplasia within no more than 18 months before screening.
18. Participants with IBD must have no evidence of active disease and a partial Mayo score of < 2, with a score of < 1 on the Rectal Bleeding domain, between screening through Day 1.
19. Participants with IBD who are receiving treatment with biologics, including tumor necrosis factor-alpha (TNF-α) inhibitors and/or vedolizumab, immunosuppressive agents, or corticosteroids must have been receiving a stable dose for at least 3 months before screening. The dose must remain stable from screening through Day 1 (baseline) and expected to remain stable for the duration of the study.
20. Estimated glomerular filtration rate ≥ 60 mL/min, according to the Cockcroft-Gault equation.

4.1.2 Exclusion Criteria

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

Primary Sclerosing Cholangitis Diagnosis

1. Other causes of liver disease, including secondary sclerosing cholangitis or viral, metabolic, or alcoholic liver disease, as assessed clinically.
2. Known or suspected overlapping clinical and histologic diagnosis of autoimmune hepatitis.
3. Small duct PSC with no evidence of large duct involvement (evidence of PSC on historical liver histology, with normal bile ducts on cholangiography).

Liver Disease Status

4. Presence of a clinically significant dominant stricture based on the combination of radiological, biochemical, and clinical features.
5. Presence of a percutaneous drain or bile duct stent.
6. Serum ALP concentration > 10 times ULN.
7. Worsening of liver disease, [redacted]
8. Ascending cholangitis within 60 days of screening, as assessed clinically or use of antibiotics for acute cholangitis within 60 days of screening.
9. IgG4-associated cholangitis.
10. Positive anti-mitochondrial antibody.
11. Presence of liver cirrhosis as assessed by historical liver histology, ultrasound-based liver stiffness measurement (FibroScan® value > 14.4 kPa), MRE >4.9 kPa, and/or signs and symptoms of hepatic decompensation (including, but not limited to, jaundice, ascites, variceal hemorrhage, and/or hepatic encephalopathy).
12. Presence of hepatic impairment, end-stage liver disease, and/or a model for end-stage liver disease (MELD) score ≥ 15.
13. Prior or planned liver transplantation during the study.

Medical History and Comorbid Conditions

14. Presence of end-stage renal disease that requires dialysis.
15. History, current clinical or radiological suspicion, or diagnosis of cholangiocarcinoma, other hepatobiliary malignancy, colorectal cancer, or other abdominal malignancy at any time.

16. Human immunodeficiency virus (HIV), hepatitis A virus, hepatitis B virus, and/or hepatitis C virus infection, with the exception of those who have been successfully treated for hepatitis C infection and have achieved sustained virologic response for ≥ 1 year.
17. 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.
18. Clinical evidence of active bacterial, viral, or fungal infection within 30 days before screening.
19. History of unstable or deteriorating cardiac disease within the previous 6 months, including, but not limited to:
    a. Unstable angina pectoris or myocardial infarction.
    b. Congestive heart failure requiring hospitalization.
    c. Uncontrolled clinically significant arrhythmias.
    d. [redacted]
20. Surgery within the 4 weeks before administration of study drug.

Prior and Concomitant Medications

21. [redacted]
22. Current treatment or anticipated need for treatment with immunomodulating agents (such as interleukins and interferons), radiation therapy, or cytotoxic or chemotherapeutic agents.
23. Hypersensitivity to PLN-74809 or to any of the excipients or placebo.

Screening Assessments

24. Pregnancy or breastfeeding or male participant whose female partner is pregnant.
25. History of weekly alcohol consumption > 21 units for male participants or > 14 units for female participants (1 unit = 1 oz/30 mL of alcohol contained in 12 oz/360 mL of beer, 4 oz/120 mL of wine, or 1 oz/30 mL of 40% proof alcohol).
26. Positive urine drug screen at screening (Table 2) unless the positive result is due to a medical treatment for a comorbid condition.

27. Any other clinically significant disorders or prior therapy that, in the opinion of the Investigator, would make the participant unsuitable for the study or unable to comply with the dosing and protocol requirements.
28. Prior use of an investigational drug within 5 half-lives or 30 days before screening, whichever time is longer, or the use of an investigational device within 30 days before screening.
29. Participation in an earlier part of the current study.

5 STUDY DRUG AND ACCOUNTABILITY

5.1 Description of Study Drug

5.1.1 PLN-74809

PLN-74809 will be supplied by Pliant Therapeutics as a [redacted] for oral administration.

[redacted]

5.1.2 Placebo

A corresponding matching placebo will be provided.

5.2 Packaging and Labeling

[redacted]

5.3 Storage and Accountability

[redacted]

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

5.4 Treatment Compliance

Dosing will be performed in the presence of site staff at visits on which scheduled PK blood samples are obtained (Baseline, Weeks 4 and 12 in Parts 1, 2, and 3; additionally at Week 24 in Part 3). [redacted]

Participants will be instructed to bring dosing logs, and all used and unused [redacted] and [redacted] to each clinic visit. Treatment compliance will be assessed by comparing the amount of drug dispensed and returned.

6 STUDY TREATMENTS

6.1 Description of Treatments

Participants will receive double-blind treatment with PLN-74809 or matching placebo.

Part 1: 40 mg of PLN-74809 or matching placebo administered orally once daily for 12 weeks

Part 2: 80 mg or 160 mg of PLN-74809 or matching placebo administered orally once daily for 12 weeks

Part 3: 320 mg of PLN-74809 or matching placebo administered orally once daily for at least 24 weeks and up to a maximum of 48 weeks.

6.2 Dose Modifications and Interruptions

No modifications in dosing are allowed. Study drug may be temporarily or permanently discontinued if it is not well tolerated or is associated with clinically significant AEs that warrant it. These circumstances will be assessed and decided by the Investigator in consultation with the study Medical Monitor and Sponsor Study Director.

Study drug may be temporarily interrupted for clinical evaluation and safety management. [redacted]

6.3 Selection and Timing of Dose for Each Participant

Doses of study drug will be taken at the investigative site at visits on which scheduled PK blood samples are obtained (Baseline, Weeks 4 and 12 in Parts 1, 2, and 3; additionally at Week 24 in Part 3). All other doses will be taken on an outpatient basis.

Participants will be instructed to take their study drug once daily at approximately the same time each day (at approximately 24-hour intervals). [redacted] Participants should drink approximately 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 112 participants may be enrolled in Parts 1 (N=28), 2 (N=56), and 3 (N=28). Participants will be centrally randomized to each of the treatment arms at the baseline visit using an interactive response technology (IRT) system in a blinded manner, according to a computer-generated randomization scheme. Randomization will occur immediately prior to dosing on the morning of the first dose (Day 1). Randomization will be stratified by use of UDCA (yes/no).

- In Part 1, 28 eligible participants were planned to be randomized on Day 1 (Visit 3) in a 3:1 ratio (40 mg PLN-74809:placebo).
- In Part 2, 28 eligible participants per cohort (56 in total) will be randomized on Day 1 (Visit 3) in a 3:1 ratio (PLN-74809:placebo). PLN-74809 doses administered in each cohort will be 80 mg or 160 mg. Cohort 3 (160 mg PLN-74809 and placebo) treatment assignments will be initiated after Cohort 2 (80 mg PLN-74809 and placebo) has completed enrollment and approved by the DSMB.
- In Part 3, 28 eligible participants will be randomized on Day 1 (Visit 3) in a 3:1 ratio (320 mg PLN-74809:placebo).

6.5 Blinding

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

Procedures will be in place to allow prompt breaking of the blind by the Principal Investigator if needed for the safety management of a participant. Unblinding at the study site for any other reason will be considered a protocol deviation and the investigator is strongly encouraged to contact the sponsor's Study Director before unblinding a 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

Prior and concomitant use of the following is allowed:

- Biologics (including TNF-α inhibitors and/or vedolizumab), immunosuppressive agents, or corticosteroids for the treatment of IBD, if the dose has been stable for at least 3 months before screening and is expected to remain stable from screening through the end of study visit. Prednisone doses >10 mg or equivalent must be approved by the Pliant Study Director.
- UDCA at a dose of <25 mg/kg/day, at a stable dose for at least 3 months before screening and is expected to remain stable from screening through the end of study visit.
- Supportive therapies for PSC (e.g., antibiotics, antihistamines) or for comorbid conditions (e.g., depression, anxiety), unless the therapy is included among the prohibited classes of medications.

[redacted]

Other medications to provide reasonable care of comorbidities are allowed during the study; however, these should only be used if necessary [redacted] If used, all concomitant medications including both prescription and nonprescription drugs should first be discussed with the Investigator and Sponsor's Study Director before administration. This requirement does not apply in the case of urgent, necessary treatment of AEs. In all cases, medications, including over the counter medications and herbal supplements, taken by participants during the course of the study will be recorded using the generic name of the medication.

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

[redacted]

[redacted]

6.6.2 Disallowed Medications

Use of any of the following is prohibited:

- [redacted]
  - [redacted]
  - [redacted]
  - [redacted]
- [redacted]
- Other investigational drugs, including those under evaluation for treatment of PSC (e.g., vancomycin, fibrates, obeticholic acid).
- Immunomodulating agents (such as interleukins and interferons).
- Cytotoxic or chemotherapeutic agents or radiation therapy.
- Treatment with a disallowed medication, other investigational drug within 5 half-lives or 30 days before screening, whichever time is longer, or the use of an investigational device within 30 days before screening is prohibited.

6.7 Restrictions

6.7.1 Prior Therapy

Prior use of an investigational drug within 5 half-lives or 30 days before screening, whichever time is longer, or the use of an investigational device within 30 days before screening is prohibited. Individuals who have received any of these therapies must not be enrolled in the study.

6.7.2 Fluid and Food Intake

Participants will be required to fast for at least 4 hours before ultrasound-based transient elastography (FibroScan®) and the optional MR-based liver imaging performed at the Screening visit and Week 12 (Parts 1, 2, and 3) and at Week 24 (Part 3 only). [redacted] Dosing should be accompanied by approximately 240 mL of water (~1 cup).

6.7.3 Participant Activity Restrictions

No restrictions on activity will be imposed.

6.7.4 Contraception

Female Participants of Childbearing Potential

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

A woman is considered to be of childbearing potential if:

- She has not reached a postmenopausal state, defined as ≥12 continuous months of amenorrhea with no identified cause other than menopause
- She has not undergone surgical sterilization, defined as hysterectomy, bilateral salpingectomy, and/or bilateral oophorectomy

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 screening and 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 (Refer to Section 8.6).

Highly Effective Methods of Birth Control

Highly effective methods of birth control are defined as those with a failure rate of < 1% per year (adapted from Trussell, 2004; CTFG 2020). 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)

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or post-ovulation 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 for the study is presented in Appendix 1 (Parts 1 and 2) and Appendix 2 (Part 3).

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

Obtaining informed consent as well as acquisition of MR-based liver imaging and FibroScan® must be conducted by the clinical site. All other study visits and procedures may be conducted by a qualified research nurse at the participant's home (per participant and site preference).

Retesting of a screening laboratory test(s) and/or FibroScan® may be permitted once and must be at least 7 days from initial testing if there are reasons to believe that the retest value(s) will be within protocol specified parameters.

Screening procedures and results for a screen failure participant in a cohort may be transferred to the participant's Re-screening visit for a subsequent cohort if completed within the 42-day screening window.

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 Inclusion/Exclusion Criteria

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

7.3 Demographic Information

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

7.4 Medical History

A complete medical history will be obtained at the screening visit. Conditions that are relevant and/or clinically significant should be recorded, with at least a start date and whether the condition is ongoing or resolved. All surgeries should be reported. The most recent

MRCP may be collected for exploratory analyses of PSC-associated changes to the biliary tract, if applicable.

7.5 Height and Weight

Height (in centimeters) and weight (in kilograms) will be recorded at the screening visit. Weight will be measured on a calibrated scale, with the participant in light clothing.

7.6 Ultrasound-Based Transient Elastography (FibroScan®)

Each participant will undergo an ultrasound-based transient elastography (FibroScan®) assessment at the screening and Week 12 study visits (Parts 1, 2, and 3) and at Week 24 (Part 3 only). FibroScan® is a noninvasive technique that uses ultrasound-based transient elastography (TE) to assess liver stiffness measurement (LSM) and determine likelihood of clinically meaningful liver fibrosis. In the TE assessment, a controlled 50-Hz frequency shear wave is mechanically induced, and the propagation speed of the shear wave is measured with ultrasound.

The LSM, as assessed by TE, is expressed in kilopascals (kPa). Larger values (normal range approximately between 2 and 7 kPa) indicate a greater likelihood of clinically meaningful liver fibrosis (Corpechot, 2014, Ehlken, 2016). Participants with LSM values ≥ 8 kPa at screening will be eligible for the study, if all other eligibility criteria are met. Those with LSM values > 14.4 kPa at screening will not be eligible for the study due to increased likelihood of having liver cirrhosis (Muir, 2019).

7.7 Liver Imaging (optional)

Imaging of the whole liver may be performed by MRI prior to Baseline and at Week 12 (Parts 1, 2, and 3) and at Week 24 (Part 3 only), and read centrally. This may be performed utilizing dynamic liver imaging in combination with the contrast agent gadoxetate disodium (if meets local approval requirements) and 4-hour fast (no food or drink, except water) will be required. Participants may complete all or partial imaging procedures based on availability and eligibility for the procedures. Only procedures completed at Baseline should be completed at Week 12 (Parts 1, 2, and 3) and at Week 24 (Part 3 only).

Liver images will be read centrally by a medically qualified radiologist, with incidental findings reported to the Principal Investigator for review and documentation. The central read will serve as the official report for the study. Any clinically significant incidental findings will be evaluated as potential adverse events.

Refer to the Radiology Manual for more information.

7.8 Patient-Reported Outcomes (PROs)

Questionnaires to assess PROs will be administered at Baseline, Weeks 4 and 12 (Parts 1, 2, and 3) and at Week 24 (Part 3 only), and include the [redacted]

[redacted] the Partial Mayo Score (PMS), when available for use (Younossi 1999, Naegeli 2015, Lewis 2008).

7.9 Prior and Concomitant Medication Assessments

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

7.10 Physical Examinations

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

Targeted physical examinations will be performed at the time points specified in the Schedule of Events (Appendix 1 [Parts 1 and 2] and Appendix 2 [Part 3]). A targeted physical examination will be performed based on prior findings in the general exam, as well as evaluation of any pertinent system based on any previous findings.

7.11 Vital Signs

Vital signs (blood pressure, pulse rate and body temperature (preferably ear) will be recorded at each clinic visit. Blood pressure and pulse rate will be obtained after the participant has rested supine for at least 3 minutes.

[redacted]

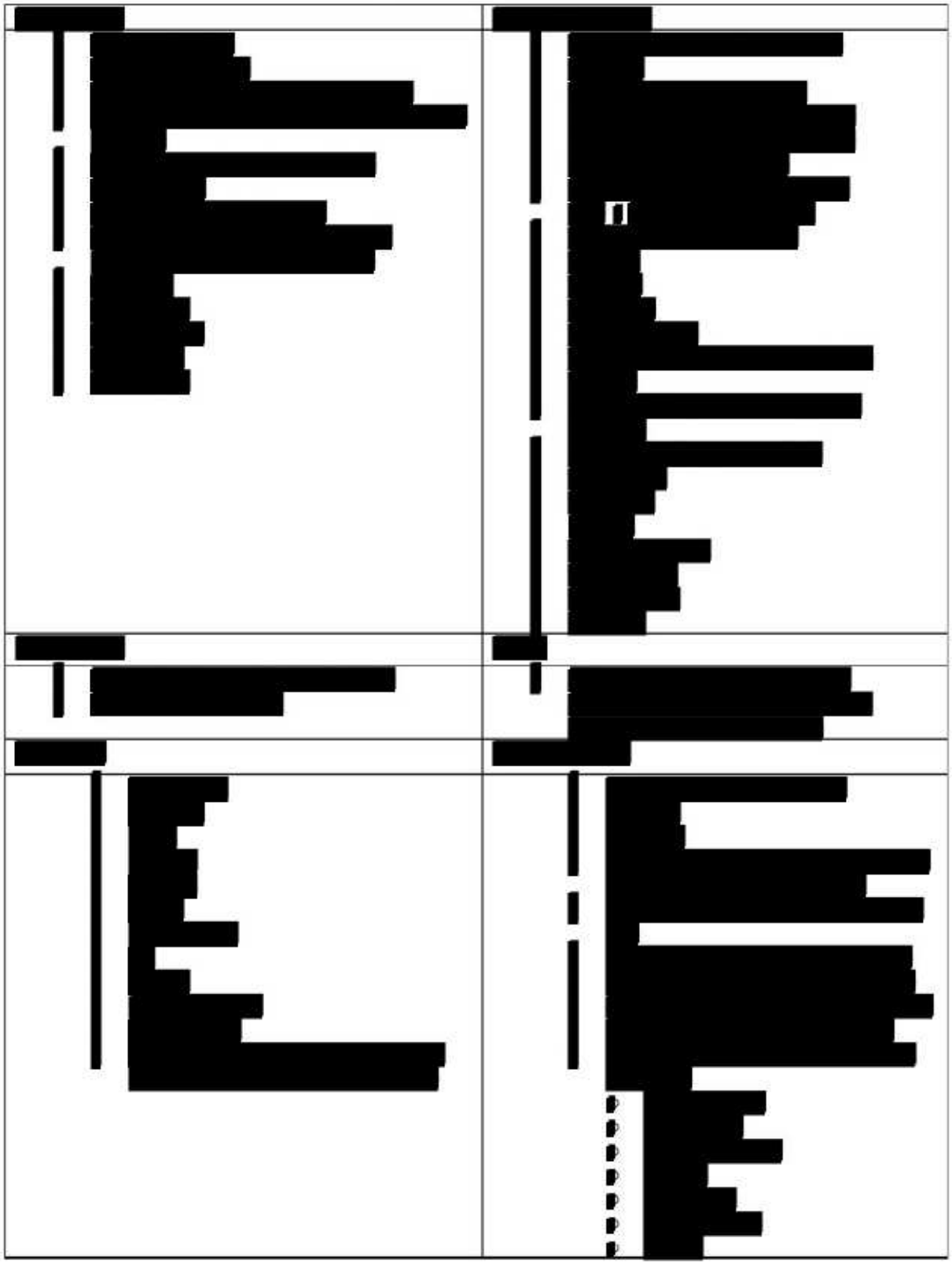
7.13 Clinical Laboratory Tests

7.13.1 Laboratory Parameters

Fasting blood and urine specimens for safety laboratory assessments will be obtained at the time points specified in the Schedule of Events (Appendix 1 [Parts 1 and 2] and Appendix 2 [Part 3]). Specimens will be obtained after at least an 8-hour fast. Participants will be in a seated or supine position during blood collection. The required clinical laboratory tests are listed in Table 2.

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

Table 2. List of Laboratory Tests



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

7.13.2 Sample Collection, Storage, and Shipping

Information on sample collection, processing, storage, and shipping will be provided in the Laboratory Manual.

7.14 Adverse Event Assessments

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

7.15 Pharmacokinetic Assessments

Blood samples for determination of plasma concentrations of PLN-74809 will be obtained [redacted] of study drug on Day 1, at Weeks 4 and 12 (Parts 1, 2, and 3), Week 24 (Part 3 only), and at early termination (if possible, for any participant who prematurely discontinues from the study). The actual time dosing and the actual time of blood collection will be recorded. [redacted] (see also Section 5.4). Aliquots of these samples may be used to measure concentrations of commonly used medications for PSC in subjects who are receiving such medications concomitantly.

[redacted]

Information on the collection, processing, storage, and shipping of PK samples will be provided in the Laboratory Manual.

7.16 Pharmacodynamic Assessments

In Parts 1 and 2, plasma, serum, [redacted] will be obtained at predetermined times as indicated in the Schedule of Events (Appendix 1). In Part 3, plasma and serum biomarker samples will be obtained at predetermined times as indicated in the Schedule of Events (Appendix 2). These samples will be used to measure specific [redacted], [redacted] that may be [redacted] in patients with fibrosis, and/or pharmacodynamic markers that may change with inhibition of integrins $\alpha_v\beta_6$ and $\alpha_v\beta_1$. The samples may also be used to perform exploratory investigations using [redacted] for use in future studies in participants with fibrotic diseases.

The main purpose of the current study is to confirm that PLN-74809 is well tolerated by participants with PSC and that drug concentrations are similar to those previously found in healthy participants. In addition, the study will test, in an exploratory manner, [redacted] A table of exploratory biomarkers of interest and evidence for their potential prognostic or pharmacodynamic value is presented below. Discovery efforts to identify novel PSC biomarkers, which may also be measured in this study, are ongoing.

Table 3. PSC Exploratory Biomarkers

Biomarker	Evidence of Prognostic or Pharmacodynamic Value
Collagen neo-epitope serum markers: (e.g. PRO-C3 and [redacted])	PSC patients with high baseline serum levels of PRO-C3 and [redacted]) had shorter survival compared to patients with low baseline serum levels (Nielsen et al, 2018); Significant reductions in PRO-C3 observed in the NGM282 treatment groups compared with the placebo (Hirschfield et al, 2019).
ELF [redacted])	ELF levels predict transplant-free survival in patients with PSC (de Vries et al, 2017); NGM282 significantly reduced serum ELF levels in PSC patients compared with placebo (Hirschfield et al, 2019).
[redacted]	[redacted]
[redacted]	[redacted]

Information on the collection, processing, storage, and shipping of biomarker samples will be provided in the Laboratory Manual.

[redacted]

7.18 Dispensing Study Drug

Participants will be dispensed study drug at the timepoints indicated in the Schedule of Events (Appendix 1 [Parts 1 and 2] and Appendix 2 [Part 3]). Participants will be instructed on how to store and use the medication and to bring all used, partially used, and unused bottles or blister cards/kits back to the clinic at the next scheduled visit.

7.19 Missed Assessments

Participants should be reminded of the importance of adhering to the protocol-required clinic visits.

Missed clinic visits and clinic visits outside of the allowed window will be recorded as protocol deviations. No imputation of missing data will be performed.

7.20 Appropriateness of Measurements

The safety and tolerability measures (AEs, laboratory parameters, vital sign measurements, [redacted] and physical examinations) are those that are commonly used to assess the safety and tolerability of an investigational medicinal product.

8 ADVERSE EVENTS

8.1 Timing

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

8.2 Definition of an Adverse Event

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

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

8.3 Severity of an Adverse Event

Grading the severity of AEs will use the Common Terminology Criteria for Adverse Events (CTCAE) grading system, Version 5.0 (NCI, 2017), 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[a]	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2[a]	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL[b]
Grade 3[a]	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL[c]
Grade 4[a]	Life-threatening consequences; urgent intervention indicated
Grade 5[a]	Death related to AE

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

8.4 Causal Relationship of an Adverse Event

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

No (not related):	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 (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 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 female participant or the female partner of a male study participant will be followed through the outcome of the pregnancy. The Investigator is required to provide all relevant information to the Sponsor using the Pregnancy Information Form to do so.

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

8.7 Clinical Laboratory Adverse Events

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

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

8.8 Serious Adverse Events

8.8.1 Definition of Serious Adverse Events

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

- Is life-threatening
  - 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 (i.e., admission, overnight stay) or prolongs existing hospitalization
  - An emergency room visit without hospitalization is not considered fulfilling the serious criteria of hospitalization.
  - Planned hospitalization or surgical procedures for an illness or disease which existed before the participant was enrolled in the clinical trial is not considered an SAE unless the condition deteriorated in an unexpected manner.
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect/miscarriage
- Is an important medical event:
  - An event that does not fulfill any of the serious criteria above, but is considered to be clinically significant and may jeopardize the participant, or when medical or surgical intervention may be required to prevent one of the outcomes listed above.
    - Examples of such events include, but are not limited to: [redacted] 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

To meet the requirements for expedited reporting of SAEs that meet specific requirements to applicable regulatory authorities and IRBs/IECs/REBs, all SAEs must be reported to the Sponsor within 24 hours from the time site personnel first become aware of the event by completing the SAE form and emailing it to the below:

[redacted]

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

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

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

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 relevant regulations.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

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

[redacted]

- [redacted]
- [redacted] n.

[redacted]

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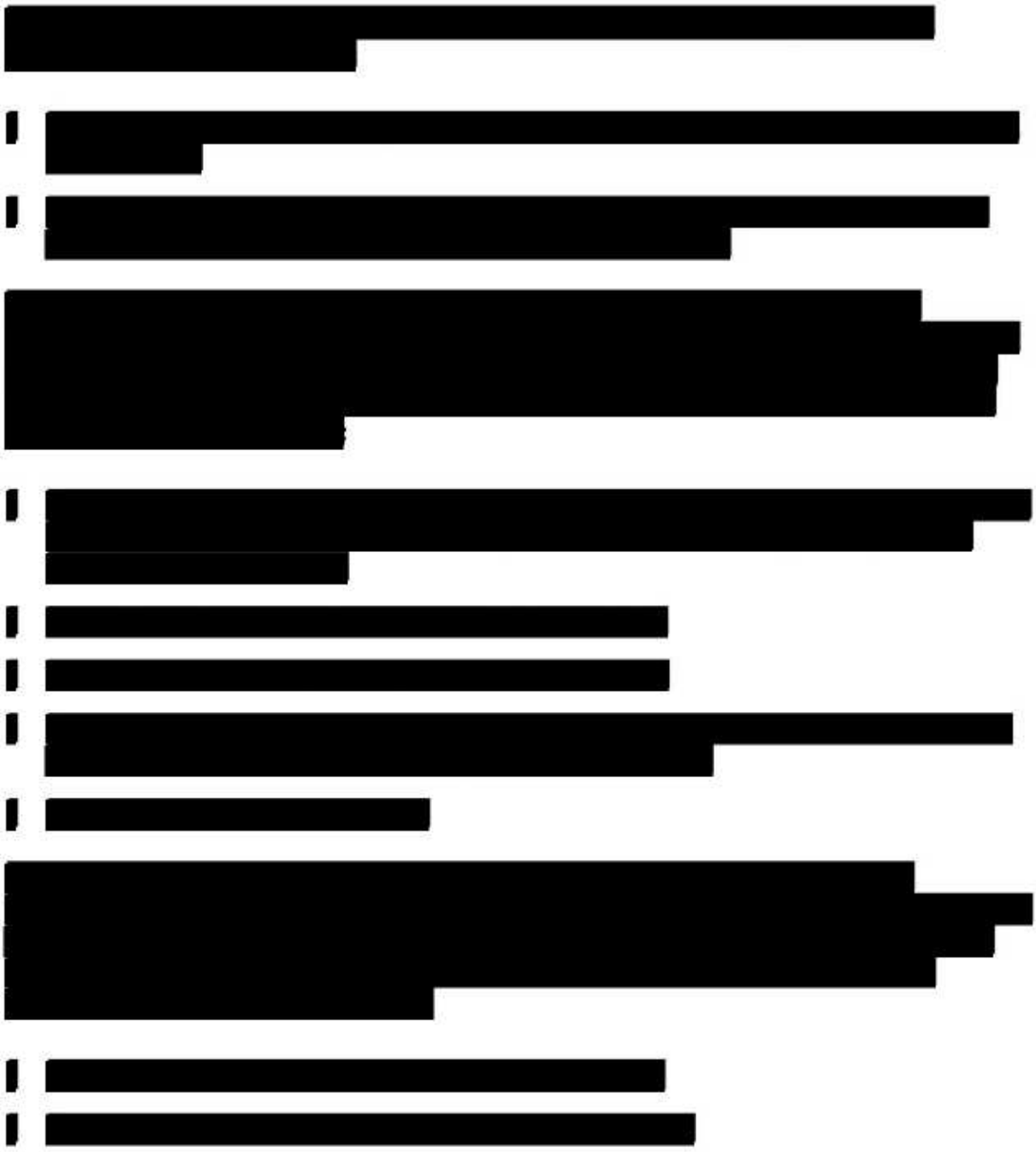

11 EARLY DISCONTINUATION OF STUDY OR INDIVIDUAL PARTICIPANTS

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

- Noncompliance with protocol procedures, including those relating to administration of study drug
- Occurrence of an SAE or intolerable AE
- Occurrence of a clinically significant change in a laboratory parameter
- [redacted]
- [redacted]
- Infection with COVID-19 that precludes safe participation in the study

A participant may elect to discontinue study drug or withdraw from the study at any time.

Participants who discontinue study drug for safety reasons before completing 12 weeks (Parts 1 and 2) or at least 24 weeks (Part 3) of treatment will be asked to remain in the study to complete all remaining assessments. If this is not feasible, the participant will be asked to return to the clinic for an early termination visit. All assessments that are required at the last study visit (EoS), as shown in the Schedule of Events for Parts 1 and 2 (Appendix 1) and Part 3 (Appendix 2), should be completed for any participant who discontinues study drug and does not agree to complete all remaining assessments.

The study may be terminated at the discretion of the Sponsor.

12 PLANNED STATISTICAL METHODS

12.1 General Considerations

[redacted] Data will be summarized with descriptive statistics. Graphic presentations may also be prepared. All data will be listed by treatment group and participant.

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

12.2 Determination of Sample Size

[redacted] A sample size of approximately 21 participants per treatment group exposed to PLN-74809 is expected to provide a meaningful evaluation of the safety, tolerability, and PK of PLN-74809 in the target population.

12.3 Analysis Populations

Three analysis populations will be defined:

- Safety Population: all randomized participants who receive at least 1 dose of study drug.
- PK Concentration Population: all participants in the safety population who have any measurable PLN-74809 concentration data.
- PD Analysis Population: all participants in the safety population who have evaluable baseline and at least 1 evaluable postbaseline PD measurement.

12.4 Demographics and Baseline Characteristics

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

12.5 Primary Endpoint

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

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

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

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

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

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

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

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

12.6 Secondary Endpoints

12.6.1 Secondary Pharmacokinetic Endpoints

Plasma PLN-74809 concentrations [redacted] at each sampling timepoint will be presented in listings and descriptive summary statistics by dose and visit. The data will also be presented graphically.

[redacted]

12.7 Exploratory Endpoints

12.7.1 Exploratory Endpoints

Absolute and relative changes from Baseline in liver fibrosis biomarkers (including PRO-C3 and ELF) and in ALP will be presented in numerical and graphical forms by treatment and dose utilizing data from the timepoints specified in the Schedule of Events (Appendix 1 and Appendix 2). Changes from Baseline to Week 12 (Parts 1 and 2) and Week 24 (Part 3) in magnetic resonance (MR)-based liver imaging will also be evaluated, as well as changes in PROs. More details will be provided in the statistical analysis plan.

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

In addition, relationships between PK and PD may be evaluated in an exploratory fashion and presented in graphical manner.

12.8 Interim Analysis

Interim analyses (safety and tolerability) will be conducted at the time points indicated below:

- Following full enrollment and completion of the 12-week treatment duration with 40, 80, or 160 mg PLN-74809 (completion of Parts 1 and 2)
- Following full enrollment and completion of the 12-week treatment duration with 320 mg PLN-74809 (Part 3)

[redacted]

[redacted]

12.9 Final Analysis

Final analyses (safety and tolerability) will be conducted once the last randomized participant in Part 3 has completed 24 weeks of treatment, including the follow up visit.

13 QUALITY CONTROL AND ASSURANCE

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

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

14 ADMINISTRATIVE CONSIDERATIONS

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

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

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

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

14.2 Ethical Conduct of the Study

The study will be conducted in accordance with the current version of the Declaration of Helsinki, concerning medical research in humans. The study will be conducted in adherence to the study protocol and Good Clinical Practice (GCP), as defined in Title 21 of the US Code of Federal Regulations (CFR) Parts 50, 54 56, 312 and Part 11 and in International Council for Harmonisation E6 (R2): Guideline for Good Clinical Practice Consolidated Guidelines (ICH-GCP), and applicable regulatory requirements.

14.3 Participant Information and Consent

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

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.

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

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

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

14.5 Study Monitoring

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

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

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

14.6 Case Report Forms and Study Records

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

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

14.7 Data Safety Monitoring Board

A DSMB will be established to assess participant safety at predetermined intervals during the study, and as needed. Further details will be provided in the DSMB Charter.

[redacted]

14.8 Retention of Data

The Investigator must ensure that all records pertaining to the conduct of the clinical study, ICFs, drug accountability records, source documents, and other study documentation are adequately maintained for a period of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the study drug or for 25 years per local requirements.

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.

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Appendix 1. Schedule of Events: Parts 1 and 2

Schedule of Events – Protocol PLN-74809-PSC-203: Parts 1 and 2								
	Screening		Treatment					EoS/ET
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	(Visit 2 separated by ≥2 weeks from Visit 1)		Baseline	Week 2	Week 4	Week 8	Week 12	Week 16
Evaluation	Day -42 to -1		Day 1	Day 14±2	Day 28±3	Day 56±3	Day 84±3	Day 112±3
Entrance and General Assessments								
Informed consent	X							
Inclusion/exclusion criteria	X		X					
Randomization			X					
Demographic information	X							
Medical history	X							
Height and weight	X							
Urine drug screen	X							
Urine pregnancy test (women of childbearing potential)[a]	X		X		X	X	X	X
FSH test (women only)	X							
ELF Test	X							
Serology (HBsAg, HCVAb, HIV)	X							
Concomitant medications	→							
Safety Assessments								
Complete physical examination	X							
Targeted physical examination			X	X	X	X	X	X
Vital signs (blood pressure, pulse rate, temperature)	X		X	X	X	X	X	X

Schedule of Events – Protocol PLN-74809-PSC-203: Parts 1 and 2								
	Screening		Treatment					EoS/ET
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
	(Visit 2 separated by ≥2 weeks from Visit 1)		Baseline	Week 2	Week 4	Week 8	Week 12	Week 16
Evaluation	Day -42 to -1		Day 1	Day 14±2	Day 28±3	Day 56±3	Day 84±3	Day 112±3
[redacted]	X		X	X	X	X	X	X
Hematology[b]	X		X	X	X	X	X	X
Coagulation (INR only)[b]	X		X	X	X	X	X	X
Serum chemistry[b]	X	X	X	X	X	X	X	X
Urinalysis (macro panel)[b,c]	X		X	X	X	X	X	X
Adverse events	→	→	→	→	→	→	→	→
Pharmacokinetic Assessments								
[redacted]			X		X		X	X
Pharmacodynamic Assessments								
MR-based liver imaging[h]		X					X	
FibroScan® (to be done after at least a 4 hour fast)	X						X	
Patient-Reported Outcomes (PROs)[i]			X		X		X	
Plasma biomarker sample			X		X	X	X	X
Serum biomarker sample			X	X	X	X	X	X
[redacted]			X		X		X	
[redacted]			X					
Study Drug Administration and Compliance								
Study drug administration onsite			X		X		X	
Dispense study drug			X		X	X		
Treatment compliance					X	X	X	

[redacted], EoS = end of study, ET = early termination, FSH = follicle-stimulating hormone, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HIV = human immunodeficiency virus, INR = international normalized ratio, PK = pharmacokinetics

a Positive urine pregnancy tests will be confirmed with a serum pregnancy test.

b Samples will be collected after at least an 8-hour fast.

c A microscopic examination will be done if the results of the macro panel analysis are abnormal.

[redacted]

e The actual time of sample collection and dosing will be recorded. Participants will record the time of their last meal before taking their dose of study drug and the time of their first meal after taking their dose of study drug in their dosing diary.

[redacted]

[redacted] Optional and may be completed after Visit 1 for eligible participants only. Only for participants who have completed an MRI scan at Visit 2.

i PROs will be administered at Baseline, Weeks 4, and 12 and include [redacted] and the Partial Mayo Score (PMS), when available for use.

Appendix 2. Schedule of Events: Part 3

The Schedule of Events for Part 3 is presented in 2 sections: Screening through the Week 12 Visit and the Week 18 Visit through End of Study.

Screening through Week 12 Visit

Schedule of Events – Protocol PLN-74809-PSC-203: Part 3 (Screening through Week 12 Visit)							
	Screening		Treatment				(continued)
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	(Visit 2 separated by ≥2 weeks from Visit 1)		Baseline	Week 2	Week 4	Week 8	Week 12
Evaluation	Day -42 to -1		Day 1	Day 14±2	Day 28±3	Day 56±3	Day 84±3
Entrance and General Assessments							
Informed consent	X						
Inclusion/exclusion criteria	X		X				
Randomization			X				
Demographic information	X						
Medical history	X						
Height and weight	X						
Urine drug screen	X						
Urine pregnancy test (women of childbearing potential)[a]	X		X		X	X	X
FSH test (women only)	X						
ELF Test	X						
Serology (HBsAg, HCVAb, HIV)	X						
Concomitant medications	[redacted]						
Safety Assessments							
Complete physical examination	X						
Targeted physical examination			X	X	X	X	X
Vital signs (blood pressure, pulse rate, temperature)	X		X	X	X	X	X
[redacted]	X		X	X	X	X	X

Schedule of Events – Protocol PLN-74809-PSC-203: Part 3 (Screening through Week 12 Visit)							
	Screening		Treatment				(continued)
	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
	(Visit 2 separated by ≥2 weeks from Visit 1)		Baseline	Week 2	Week 4	Week 8	Week 12
Evaluation	Day -42 to -1		Day 1	Day 14±2	Day 28±3	Day 56±3	Day 84±3
Hematology[b]	X		X	X	X	X	X
Coagulation (INR only)[b]	X		X	X	X	X	X
Serum chemistry[b]	X	X	X	X	X	X	X
Urinalysis (macro panel)[b,c]	X		X	X	X	X	X
Adverse events	→	→	→	→	→	→	→
Pharmacokinetic Assessments							
[redacted]			X		X		X
Pharmacodynamic Assessments							
MR-based liver imaging[g]		X					X
FibroScan® (to be done after at least a 4 hour fast)	X						X
Patient-Reported Outcomes (PROs)[h]			X		X		X
Plasma biomarker sample			X		X	X	X
Serum biomarker sample			X	X	X	X	X
[redacted]			X				
Study Drug Administration and Compliance							
Study drug administration onsite			X		X		X
Dispense study drug			X		X	X	
Treatment compliance					X	X	X

[redacted] FSH = follicle-stimulating hormone, HBsAg = hepatitis B surface antigen, HCVAb = hepatitis C virus antibody, HIV = human immunodeficiency virus, INR = international normalized ratio, PK = pharmacokinetics

[a] Positive urine pregnancy tests will be confirmed with a serum pregnancy test.

[b] Samples will be collected after at least an 8-hour fast.

[c] A microscopic examination will be done if the results of the macro panel analysis are abnormal.

d [redacted]

e The actual time of sample collection and dosing will be recorded. Participants will record the time of their last meal before taking their dose of study drug and the time of their first meal after taking their dose of study drug in their dosing diary.

f [redacted]

g Optional and may be completed after Visit 1 for eligible participants only. Only for participants who have completed an MRI scan at Visit 2.

h PROs will include [redacted] and the Partial Mayo Score (PMS), when available for use.

Week 18 Visit through End of Study

Schedule of Events – Protocol PLN-74809-PSC-203: Part 3 (Week 18 Visit through End of Study)						
continued	**Treatment**					**EoS/ET**
	Visit 8	**Visit 9**	**Visit 10[a]**	**Visit 11[a]**	**EoT[a]**	**EoS**
	Week 18	**Week 24**	**Week 32**	**Week 40**	**Week 48 / Unscheduled / End of Treatment Visit**	**End of Study Visit**
Evaluation	**Day 126±3**	**Day 168±3**	**Day 224±5**	**Day 280±5**	**EoT Visit**	**EoT Visit +4 weeks (±3 days)**
General Assessments						
Urine pregnancy test (women of childbearing potential)[b]	X	X	X	X	X	X
Concomitant medications	→	→	→	→	→	→
Safety Assessments						
Targeted physical examination	X	X	X	X	X	X
Vital signs (blood pressure, pulse rate, temperature)	X	X	X	X	X	X
[redacted]	X	X	X	X	X	X
Hematology[c]	X	X	X	X	X	X
Coagulation (INR only)[c]	X	X	X	X	X	X
Serum chemistry[c]	X	X	X	X	X	X
Urinalysis (macro panel)[c,d]	X	X	X	X	X	X
Adverse events	→	→	→	→	→	→
Pharmacokinetic Assessments						
[redacted]		X				X[g]
Pharmacodynamic Assessments						
MR-based liver imaging[i]		X				
FibroScan® (to be done after at least a 4 hour fast)		X				
Patient-Reported Outcomes (PROs)[j]		X				
Plasma biomarker sample		X			X	X

Schedule of Events – Protocol PLN-74809-PSC-203: Part 3 (Week 18 Visit through End of Study)						
continued	**Treatment**					**EoS/ET**
	Visit 8	**Visit 9**	**Visit 10[a]**	**Visit 11[a]**	**EoT[a]**	**EoS**
	Week 18	**Week 24**	**Week 32**	**Week 40**	**Week 48 / Unscheduled / End of Treatment Visit**	**End of Study Visit**
Evaluation	**Day 126±3**	**Day 168±3**	**Day 224±5**	**Day 280±5**	**EoT Visit**	**EoT Visit +4 weeks (±3 days)**
Serum biomarker sample		X			X	X
Study Drug Administration and Compliance						
Study drug administration onsite		X				
Dispense study drug	X	X	X	X		
Treatment compliance	X	X	X	X	X	

[redacted], EoS = end of study, EoT = end of treatment, ET = early termination, INR = international normalized ratio, PK = pharmacokinetics

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

[b] Positive urine pregnancy tests will be confirmed with a serum pregnancy test.

[c] Samples will be collected after at least an 8-hour fast.

[d] A microscopic examination will be done if the results of the macro panel analysis are abnormal.

[redacted]

[f] The actual time of sample collection and dosing will be recorded. Participants will record the time of their last meal before taking their dose of study drug and the time of their first meal after taking their dose of study drug in their dosing diary.

[redacted]

[redacted]

i Optional and may be completed after Visit 1 for eligible participants only. Only for participants who have completed an MRI scan at Visit 2.

j PROs will include [redacted] and the Partial Mayo Score (PMS), when available for use.

Appendix 3. Sponsor Signature

Study Title:	A randomized, double-blind, dose-ranging, placebo-controlled, Phase 2a evaluation of the safety, tolerability, and pharmacokinetics of PLN-74809 in participants with primary sclerosing cholangitis (PSC) and suspected liver fibrosis (INTEGRIS-PSC)
Study Number:	PLN-74809-PSC-203
Version:	[redacted]
Final Date:	09 February 2023

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

Signed: [redacted] Date: [redacted]

Appendix 4. Investigator Signature

Study Title:	A randomized, double-blind, dose-ranging, placebo-controlled, Phase 2a evaluation of the safety, tolerability, and pharmacokinetics of PLN-74809 in participants with primary sclerosing cholangitis (PSC) and suspected liver fibrosis (INTEGRIS-PSC)
Study Number:	PLN-74809-PSC-203
Version:	[redacted]
Final Date:	09 February 2023

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:_____