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)

Published: 31-08-2020
Last updated: 08-04-2024

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

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON56399

Source
ToetsingOnline

Brief title
PLN-74809-PSC-203

Condition

- Hepatic and hepatobiliary disorders

Synonym
Primary Sclerosing Cholangitis (PSC) and suspected liver fibrosis

Research involving
Human

Sponsors and support

Primary sponsor: Pliant Therapeutics Inc.,
Source(s) of monetary or material Support: Pliant Therapeutics INC.

Intervention

Keyword: Primary Sclerosing cholangitis, Safety, Tolerability

Outcome measures

Primary outcome

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

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

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

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

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

Individual ECG results will be listed for each participant. Summaries of ECGs 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 ECGs will be summarized by treatment
and dose.

Concomitant medications will be coded using the most current World Health

Organization drug dictionary available.

Secondary outcome

Secondary Pharmacokinetic Endpoints

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

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

Exploratory Endpoints

Absolute and relative changes from Baseline to Week 12 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 of the protocol version 1.0 dated 14 December 2020).

Changes from Baseline to Week 12 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.

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

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

Study description

Background summary

Pliant Therapeutics, Inc. (Pliant) is developing PLN-74809 for the treatment of primary sclerosis cholangitis (PSC), 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. More than 50% of patients require liver transplantation within 10 to 15 years after diagnosis; however, disease recurrence after transplantation is common. 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%. Once diagnosed with CCA, the 5-year overall survival is poor, ranging from 20% to 68%. 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. 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. 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 .

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. Patients with PSC also have a high lifetime risk of developing gastrointestinal malignancies. There is currently no approved medical treatment 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 also commonly used for the management of PSC. However, clinical studies of its use in patients with PSC have produced meager and inconclusive results. 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. High-dose UDCA has also been associated with the development of colorectal neoplasia in patients with ulcerative colitis or PSC. Thus, there remains a significant unmet medical need for effective therapies for PSC.

Study objective

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

Study design

This is a Phase 2a, multicenter, randomized, double-blind, dose-ranging, placebo-controlled, parallel-group study to evaluate the safety, tolerability, and PK of once-daily (QD) 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. The study will include an up to 42-day screening period, a 12-week treatment period (Part 1 and 2) or 24-48 week treatment period (part 3), and a 4-week post-treatment follow-up period.

Intervention

Part 1: Participants will receive 40 mg PLN-74809 or matching placebo once a day for 12 weeks

Part 2: Participants will receive 80 or 160 mg or matching placebo once a day for 12 weeks

Part 3: Participants will receive 320 mg or matching placebo once a day for at least 24 weeks and up to 48 weeks.

Study burden and risks

Side Effects of PLN-74809

The investigational study medication PLN-74809 is at a research stage, so it may have adverse effects (side effects) that are not known at this time. As with any new medication there is a risk that unexpected adverse effects may occur. Almost all medications, both old and new, can cause severe reactions. In a previous first-in-human research study, healthy participants received PLN-74809 at doses of up to 75 mg (as a single dose) and 40 mg (as multiple doses). The investigational study medication was well tolerated and had an acceptable safety profile. To date, PLN-74809 has been given to 84 healthy participants in 2 completed clinical studies, either as single doses (one time) between 15 and 75 mg, or multiple doses (up to two weeks) between 10 and 40 mg. One (1) serious adverse event (SAE) has been reported in an ongoing clinical study. The SAE was a severe
intravenous catheter site infection.

As the safety and tolerability of PLN-74809 is still being researched* not all side effects and risks are known. If participants are in a group that receives PLN-74809, there is no guarantee that they will experience the above side effects and it is possible participants may have other side effects which may be more severe. In addition, symptoms of PSC may not improve or may even worsen.

Placebo Risks
If participants are in the group that is assigned to the placebo, there are no anticipated side effects* however, they may experience side effects related to the study procedures. In addition, their symptoms of PSC may not improve or may even worsen.

Allergic Reactions
As with taking any medication, there is a risk of allergic reaction. If participants have a very serious allergic reaction, they may be at risk of death. Some symptoms of allergic reactions are: shortness of breath, itchy rash (hives) or swelling, flushing (feeling warm), low blood pressure, and slow heart rate. If they are having an allergic reaction,they should tell the study doctor or study staff right away.

Blood Sampling
The risks of taking blood include fainting and pain, bruising, swelling, or rarely infection where the needle was inserted. These discomforts are brief and transient. The total volume to be collected during your participation in this research study will be approximately 243 mL (approximately 1 cup).

Electrocardiogram
Skin irritation from the ECG electrode pads or pain when removing the pads are possible side effects.

Fasting
Participants will be asked to fast (no food or drink except water) for at least 8 hours before study visits where blood is to be collected for laboratory

testing, and for 4 hours before undergoing the FibroScan® and MR-based liver imaging. Fasting could cause dizziness, headache, stomach discomfort, or fainting. If they feel faint, they should tell the study doctor or study staff right away.

FibroScan®
The Fibroscan® device is used on the surface of participant skin and is painless. They may feel light pressure where the device is pressed on skin. They cannot have a Fibroscan® if they have an implantable device, such as a pacemaker.

MRI-based liver imaging
MRI scanners use a large magnet and radio waves to take pictures of participants liver. There are no known risks from being exposed to the magnetic fields in an MRI. Participants should not have an MRI if you have a pacemaker, metallic cardiac valve(s), or certain types of metallic aneurysm clips. Participants should not have an MRI if they have implanted electronic infusion pumps or other metallic pieces in body, head, or eyes. During the MRI, they will lie flat on a table that will move into a horizontal tube that is within a large magnet. This may make them feel *closed in*. Participants will receive a contrast dye (an MRI imaging material) to help get a clearer picture of liver. This material is
administered through vein. The contrast dye they will receive is used routinely for MRI exams. Participants will not get the MRI contrast dye if they have abnormal kidney function. It is uncommon, but they may feel warmth, pain, or bruising in the area where the needle was inserted. Participant may also have dizziness, nausea, vomiting, or headache. Serious allergic reactions to the contrast material that may be life threatening are very rare.

Unknown Risks
There may be risks that are currently not known or cannot be predicted. Participants condition may worsen, remain the same, or improve as a result of participating in this research study. Participants have to seek treatment immediately and tell the study doctor and study staff if they have any of the symptoms or any other side effects, during the study (even if they think they are not related to participation in this study).

Contacts

Public
Pliant Therapeutics Inc.,

Littlefield Avenue 260
South San Francisco CA 94080

US
Scientific
Pliant Therapeutics Inc.,

Littlefield Avenue 260
South San Francisco CA 94080
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

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.
10. Suspected liver fibrosis, as defined by any of the following:
- Enhanced Liver Fibrosis (ELF) Score >= 7.7 at Screening OR
- Liver stiffness measurement (LSM) >= 8 kPa but <= 14.4 kPa, assessed by FibroScan® 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/mm3.
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.

Exclusion criteria

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, defined as 2 consecutive ALP, ALT, or AST measurements obtained >= 2 weeks apart during the screening period that increase by > 30% and represent either a Common Terminology Criteria for Adverse Events (CTCAE) Grade 1 that is associated with new or worsening symptoms or a CTCAE Grade 2 with or without new or worsening symptoms, as defined by CTCAE Version 5.0.
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 that

required antibiotic or antifungal therapy 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. Clinically significant electrocardiogram (ECG) abnormalities, including but not limited to, QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 msec for males or > 460 msec for females at Screening Visit 1 or prior to administration of the initial dose of study drug.
20. Surgery within the 4 weeks before administration of study drug.
Prior and Concomitant Medications
21. Currently receiving and expected to remain on treatment during the study with: potent (i.e., strong) inhibitors or inducers of cytochrome P450 (CYP) 3A4, 2C9 or 2C19; potent inhibitors or inducers of and P-glycoprotein (P-gp) (e.g., itraconazole), breast cancer resistance protein (BCRP) or OATP1B1organic anion transporting polypeptide (OATP) 1B1/1B3 transporters P-gp substrates with a narrow therapeutic window should also be excluded.
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 (ie, Part 1 or 2) within 6 months of dosing for a subsequent part (ie, Part 2 or 3).

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-09-2022
Enrollment:	5
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	PLN-74809
Generic name:	PLN-74809

Ethics review

Approved WMO Date:	31-08-2020
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-07-2021
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-10-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-12-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-03-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-05-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-06-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-11-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-11-2022
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam) Kamer G4-214 Postbus 22660

	1100 DD Amsterdam
	020 566 7389
	mecamc@amsterdamumc.nl
Approved WMO Date:	14-12-2022
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam)
	Kamer G4-214
	Postbus 22660
	1100 DD Amsterdam
	020 566 7389
	mecamc@amsterdamumc.nl
Approved WMO Date:	16-01-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam)
	Kamer G4-214
	Postbus 22660
	1100 DD Amsterdam
	020 566 7389
	mecamc@amsterdamumc.nl
Approved WMO Date:	11-06-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam)
	Kamer G4-214
	Postbus 22660

	1100 DD Amsterdam
	020 566 7389
	mecamc@amsterdamumc.nl
Approved WMO Date:	23-08-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam)
	Kamer G4-214
	Postbus 22660
	1100 DD Amsterdam
	020 566 7389
	mecamc@amsterdamumc.nl
Approved WMO Date:	18-09-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam)
	Kamer G4-214
	Postbus 22660
	1100 DD Amsterdam
	020 566 7389
	mecamc@amsterdamumc.nl
Approved WMO Date:	06-11-2023
Application type:	Amendment
Review commission:	MEC Academisch Medisch Centrum (Amsterdam)
	Kamer G4-214
	Postbus 22660

1100 DD Amsterdam

020 566 7389

mecamc@amsterdamumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-001428-33-NL
ClinicalTrials.gov	NCT04480840
CCMO	NL74849.018.20