A randomized, double-blind, dose-ranging, placebo-controlled Phase 2a evaluation of the safety, tolerability and pharmacokinetics of PLN-74809 in participants with idiopathic pulmonary fibrosis (IPF) (INTEGRIS-IPF)

Published: 06-08-2020
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Primary: • Assessment of the safety and tolerability of PLN-74809 Secondary:• Assessment of pharmacokinetics (PK) of PLN-74809 Exploratory:• Assessment of change from baseline in forced vital capacity (FVC) • Assessment of change from baseline in...

Ethical review	Approved WMO
Status	Completed
Health condition type	Immune disorders NEC
Study type	Interventional

Summary

ID

NL-OMON54907

Source
ToetsingOnline

Brief title
PLN-74809-IPF-202

Condition

- Immune disorders NEC

Synonym
idiopathic pulmonary fibrosis

Research involving

Human

Sponsors and support

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

Intervention

Keyword: Lung Disease, Pulmonary Fibrosis, Safety, Tolerability

Outcome measures

Primary outcome

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.
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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.

Secondary Pharmacodynamic Endpoints

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

Study description

Background summary

Idiopathic Pulmonary Fibriosis (IPF) is the most common interstital lung disease, a condition in which the tiny air sacs in the lungs become damaged. This causes scarring and the build-up of scar tissue (called fibrosis). The scar tissue causes the lungs to become stiffer, making breathing increasingly difficult. The symptoms of IPF can include shortness of breath, persistent dry cough, tiredness, weight loss, and rounded and enlarged fingertips.

Patients diagnosed with mild-to-moderate IPF and who do not present with other major health conditions that could affect the study drug or co-found the study outcomes will be recruited in the clinical study.

PLN-74809-000 is being developed for Idiopathic Pulmonary Fibriosis (IPF). PLN-74809 is a small molecule and is expected to exert anti-fibrotic effects through mechanisms that are different from those of current standards of care for IPF. The proposed trial is a randomised, double-blind, dose-ranging, placebo-controlled Phase 2a study evaluating he safety, tolerability and PK of 12 weeks treatment with PLN-74809 40mg or placebo.

Currently, treatment options for IPF are limited to 2 drugs approved for the treatment of IPF (nintedanib [OFEV] or pirfenidone [Esbriet]), and supportive treatments. In this study, PLN-74809 is being compared to a placebo (which looks like the investigational medication, but it contains no active ingredients) for the treatment of IPF. PLN-74809 has not been approved as a treatment for any condition in any country.

This is a placebo controlled, double-blind, randomized research study, which will be conducted in 3 parts (Parts A, B, C, and D). Part A has ended.

• Part B will evaluate the 40mg dose of PLN-74809.
• Part C will evaluate doses of 80mg and 160mg of PLN-74809
• Part D will evaluate 320 mg of PLN-74809

Study objective

Primary:
• Assessment of the safety and tolerability of PLN-74809
Secondary:
• Assessment of pharmacokinetics (PK) of PLN-74809
Exploratory:
• Assessment of change from baseline in forced vital capacity (FVC)
• Assessment of change from baseline in quantitative lung fibrosis (QLF) score
• Assessment of change from baseline in a visual analog scale (VAS) for cough
• Assessment of changes in selected biomarkers.

Study design

This is a Phase 2a, multicenter, 4-part, randomized, double-blind, dose-ranging, placebo-controlled study to evaluate the safety, tolerability, and PK of once-daily (QD) treatment with PLN-74809 in participants with idiopathic pulmonary fibrosis (IPF).
Each study part consists of an up to 28-day screening period, a 4-week (Part A), 12 week (Parts B and C), or at least 24-week (Part D) treatment period, and a 2-week (±3 days) post treatment follow-up period. Part A enrollment has been completed, so is not further described herein; no further participants will be enrolled or treated in this part of the study. Part B enrollment has been completed; no further participants will be enrolled or treated in this part of the study. Part C enrollment was initiated following review by the Data Safety Monitoring Board (DSMB) and Competent Authorities (if applicable) of the clinical data supporting the evaluation of 40 mg dosing. The DSMB and Competent Authorities (if applicable) recommended continuation of Study PLN 74809-IPF-202 to evaluate doses of 80 mg and 160 mg without modification. Part D enrollment will initiate following review by the DSMB and Competent Authorities (if applicable) of the 80 mg and 160 mg clinical data from Part C. The dose level of Part D is supported by the clinical data from study 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 28 days before administration of the first dose of study drug.
In Parts B, C and D, eligible participants will be randomized on Day 1 (Visit 2). Randomization will be stratified by use of standard of care (SoC) IPF therapy (pirfenidone or nintedanib) (SoC use; yes or no).
In Part B, 29 eligible participants were randomized in a 3:1 ratio (active:placebo) and treated for 12 weeks.
In Part C, approximately 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.
In Part D, an additional PLN-74809 dose of 320 mg is planned for evaluation based on the following criteria:
• Part C has been completely enrolled (i.e., 56 participants have been randomized
• Pending favorable review by the DSMB and Competent Authorities (if applicable) of:
o All available safety and PK data from this study (Part C)
o Safety and PK data from study PLN-74809-104, an ongoing Phase 1 study evaluating the safety, tolerability, and pharmacokinetics of PLN 74809 at multiple doses ranging from 80 to 320 mg in healthy participants, as described in the Investigator*s Brochure
In Part D, approximately 28 eligible participants will be randomized in a 3:1 ratio (320 mg PLN-74809:placebo) on Day 1 (Visit 2). Randomization will be stratified by use of SoC IPF therapy (pirfenidone or nintedanib) (SoC use; yes or no). Study treatment will be administered for at least 24 weeks. Treatment will continue for all participants in Part D until the last participant enrolled in Part D reaches Week 24. Participants who discontinue study drug for

safety reasons prior to completion of 12 weeks (Parts B and C) or at least 24 weeks (Part D) of treatment will be asked to remain in the study to complete all remaining assessments; if this is not feasible, they will be asked to return to the clinic for an Early Termination (ET) visit for follow-up evaluations.
The DSMB and Competent Authorities (if applicable) will assess participant safety at predetermined intervals during the study, including prior to initiating Part D and following the enrollment of the last participant in Part D. An adjudication committee will assess acute exacerbations, respiratory-related hospitalizations, and/or respiratory-related deaths.

Intervention

Part B: 40 mg of PLN 74809 or matching placebo administered orally QD
Part C: 80 mg or 160 mg of PLN-74809 or matching placebo administered orally QD
Part D: 320 mg of PLN-74809 or matching placebo administered orally QD
PLN-74809 will be supplied by Pliant as a tablet for oral administration. Study drug will be taken once daily at approximately 24-hour intervals. Participants will take the study drug on an empty stomach (no food for 2 hours before or 2 hours after dosing) and will drink up to 240 mL (~1 cup of water) after swallowing the study drug.

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.

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.

Placebo Risks
In the placebo group, there are no anticipated side effects* however, participants may experience side effects related to the study procedures. In addition, your symptoms of IPF may not improve or may even worsen.

Allergic Reactions
As with taking any medication, there is a risk of allergic reaction. Some symptoms of allergic reactions are: shortness of breath, itchy rash (hives) or swelling, flushing (feeling warm), low blood pressure, and slow heart rate.

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 about 110 mL (approximately half a cup).

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

High-resolution Computerzied Tomography (CT) Scan
When a CT scan is performed, you will be exposed to radiation. The radiation exposure during high resolution CT scan is 3-8 millisievert (mSv). This radiation exposure is 6 to 16 times less than the annual radiation limit for radiation workers.

Spirometry
Participants may experience lightheadedness, fainting, shortness of breath, or chest tightness.

Spirometery (DLco)
Participants may experience lightheadedness, fainting, shortness of breath, or chest tightness.

Fasting
Fasting could cause dizziness, headache, stomach discomfort, or fainting.

To ensure minimization of the above mentioned risks and discomforts during the study, health-care professional will be available 24-hours for participants to report any side-effects/adverse reactions and get immediate medical care.

Contacts

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Pliant Therapeutics Inc.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion Criteria:
1. Participants, aged 40 years or older
2. Diagnosis of IPF for up to 5 years prior to screening based on American Thoracic Society (ATS)/ European Respiratory Society (ERS)/ Japanese Respiratory Society (JRS)/ Latin American Respiratory Society (ALAT) 2018 guidelines (Raghu et al, 2018)
Note: If IPF diagnosis is within > 3 to <= 5 years at screening, the participant must have evidence of progression within the last 24 months, as defined by decline in FVC percent predicted based on a relative decline of >= 5%
3. FVC percent of predicted >= 45%; historical FVC for entry in the study is permitted if within 1 month of screening
4. Diffusing capacity for carbon monoxide (DLco) (hemoglobin-adjusted) >= 30%; historical DLco for entry in the study is permitted if within 1 month of screening
5. Participants currently receiving treatment for IPF with nintedanib or pirfenidone are allowed, provided these drugs have been given at a stable dose for at least 3 months before the Screening visit and are expected to remain unchanged during the study (stable dose is defined as the highest dose tolerated by the participant during >= 3 months)
6. Estimated glomerular filtration rate >= 50 mL/min, according to the Cockcroft-Gault equation

7. Female participants of non-childbearing potential must be surgically sterile or postmenopausal
8. Female participants of childbearing potential must use a contraceptive method with a failure rate of < 1% per year or remain abstinent (refrain from heterosexual intercourse) during the treatment period and for 1 month after the last dose of study treatment.
Male participants with female partners of childbearing potential must agree to use contraceptive measures or remain abstinent (refrain from heterosexual intercourse) during the treatment period and for at least 3 months after the last dose of study treatment.
9. Participants must agree to abstain from sperm or egg donation for the duration of the study, through to 3 months or 1 month, respectively, after administration of the last dose of study drug.
10. Able to read and sign a written informed consent form (ICF)

Exclusion criteria

Exclusion Criteria:
1. Receiving any nonapproved agent intended for treatment of fibrosis in IPF
2. Forced expiratory volume during the first second (FEV1) over the FVC ratio (FEV1/FVC ratio) < 0.7 at screening
3. Clinical evidence of active infection, including but not limited to bronchitis, pneumonia, or sinusitis that can affect FVC measurement during screening or at randomization
4. Any other condition that prevents the correct assessment of spirometry performance (for example a broken rib or chest pain of other origin that prevents adequate forced breathing)
5. Known acute IPF exacerbation or suspicion by the Investigator of such, within 6 months of screening
6. The extent of emphysema is greater than the extent of fibrotic changes on the most recent high-resolution computerized tomography (HRCT) scan (as determined by central reader); a) HRCT scan performed within 2 years of the screening date may be used
7. Severe pulmonary hypertension
8. Smoking of any kind (not limited to tobacco) within 3 months of screening or unwilling to avoid smoking throughout the study
9. Lower respiratory tract infection requiring antibiotics within 4 weeks prior to screening and/or during the screening period
10. History of malignancy within the past 5 years or ongoing malignancy other than basal cell carcinoma, resected noninvasive cutaneous squamous cell carcinoma, or treated cervical carcinoma in situ
11. End-stage liver disease
12. Renal impairment or end-stage kidney disease requiring dialysis
13. History of unstable or deteriorating cardiac or pulmonary disease (other than IPF) within the 6 months prior to screening, including but not limited to

the following:
a. Unstable angina pectoris or myocardial infarction
b. Congestive heart failure requiring hospitalization during the 6 months prior to screening
c. Uncontrolled clinically significant arrhythmias (e.g., potentially resulting in health care utilization or hospitalization)
d. Any clinically relevant electrocardiogram (ECG) abnormalities, including but not limited to, QT interval corrected for heart rate using Fridericia's formula (QTcF) > 450 msec for males or > 460 msec for females at the Screening visit (including Day -1) or prior to administration of the initial dose of study drug.
14. Any of the following liver function test criteria above specified limits: total bilirubin > 1.5 × the upper limit of normal (ULN); aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 3 × ULN; alkaline phosphatase > 2.5 × ULN.
Note: participants currently receiving nintedanib or pirfenidone as IPF SoC treatment, who have previously presented any liver function test elevations associated with nintedanib or pirfenidone treatment greater than that described above or resulting in dose reduction, treatment interruption, or discontinuation are not eligible.
15. Any of the following at screening: hemoglobin < 10.0 g/dL, or neutrophils < 1500 /mm3, or platelets < 100,000 /mL
16. Pregnant or lactating females
17. Daily use of phosphodiesterase-5 (PDE-5) inhibitor drugs (e.g., sildenafil, tadalafil, other) (Note: Intermittent use for erectile dysfunction is allowed)
18. A medical or surgical condition known to affect drug absorption (e.g., major gastric surgery)
19. Surgical procedures planned to occur during the study period
20. Uncontrolled systemic arterial hypertension
21. Has participated in a clinical study with an investigational agent in the 30 days prior to screening or 5 half-lives of the investigational drug, whichever is longer
22. Likely to have lung transplantation during the study (being on transplantation list is acceptable)
23. Any medical condition that, in the opinion of the Investigator, may make candidates not suitable for the study
24. Hypersensitivity to PLN-74809 or to any of the excipients, or placebo
25. Currently receiving and expected to remain on treatment during the study with: potent (i.e., strong) inhibitors or inducers of cytochrome P450 (CYP) 3A4 and P glycoprotein (P-gp) (e.g., itraconazole), breast cancer resistance protein (BCRP) or organic anion transporting polypeptide (OATP) 1B1/1B3 transporters

Study design

Design

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	03-03-2020
Enrollment:	9
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	PLN-74809-000
Generic name:	Not Applicable

Ethics review

Approved WMO Date:	06-08-2020
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-01-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-02-2021

Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-05-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-08-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-09-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-11-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-12-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-02-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-03-2022
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2019-002709-23-NL
ClinicalTrials.gov	NCT04396756
CCMO	NL74229.100.20

Study results

Date completed: 13-09-2022

Results posted: 06-10-2023

First publication
06-09-2023