Clinical trial results:
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)

Summary

EudraCT number	2019-002709-23
Trial protocol	GB DE NL BE IT
Global end of trial date	15 February 2023

Results information

Result version number	v1 (current)
This version publication date	08 May 2024
First version publication date	08 May 2024

Trial information

Trial identification

Sponsor protocol code	PLN-74809-IPF-202

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04396756
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pliant Therapeutics Inc.
Sponsor organisation address	331 Oyster Point Boulevard, South San Francisco, United States, CA 94080
Public contact	Gregory P. Cosgrove, MD, Pliant Therapeutics Inc., +1 650-481-6770, GCosgrove@pliantrx.com
Scientific contact	Gregory P. Cosgrove, MD, Pliant Therapeutics Inc., +1 650-481-6770, GCosgrove@pliantrx.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 February 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is the assessment of the safety and tolerability of PLN-74809.

Protection of trial subjects:

The Investigator documented approval from the Institutional Review Board (IRB), Independent Ethics Committee (IEC), or Research Ethics Board (REB), as appropriate, for the study protocol, any amendments, informed consent forms (ICFs) and any revised ICFs, participant recruitment documents (eg, advertisements, video and/or video script), and any other study documentation provided to participants.

Background therapy:

Participants who were receiving treatment for IPF with nintedanib or pirfenidone were allowed, provided these drugs had been given at a stable dose for at least 3 months before the Screening Visit and were expected to remain unchanged during the study.

Evidence for comparator: -

Actual start date of recruitment	21 February 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Italy: 2
Country: Number of subjects enrolled	United States: 89
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	New Zealand: 4
Worldwide total number of subjects	120
EEA total number of subjects	14

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0

Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	16
From 65 to 84 years	102
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

Participants were screened at 37 sites in 7 countries (Australia, Belgium, Canada, Italy, the Netherlands, New Zealand, and the United States) between Feb 2020 and Feb 2023. This study was divided into 4 parts, each part comprised a screening period of up to 28 days, a double-blind treatment period, and a 2-week post-treatment follow-up period.

Pre-assignment

Screening details:

Out of 168 participants who were screened, 10 participants were re-screened, 49 participants failed screening and 119 participants were enrolled and assigned to one of four treatment arms. One participant received both placebo and PLN-74809 320 mg due to incorrect study drug dispensation.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Part A: PLN-74809 40 mg

Arm description:

PLN-74809 (Part A): Consists of an up to 28-day screening period, a 4-week treatment period, and a 2-week (+/- 3 days) post-treatment follow-up period.

Participants took either PLN-74809 40mg or a matching placebo with 100ml water after fasting.

Arm type	Experimental
Investigational medicinal product name	PLN-74809
Investigational medicinal product code	
Other name	Bexotegrast
Pharmaceutical forms	Oral liquid
Routes of administration	Oral use

Dosage and administration details:

PLN-74809 administered orally.

Arm title	Part B: PLN-74809 40 mg

Arm description:

PLN-74809 (Part B): Consists of an up to 28-day screening period, a 12-week treatment period, and a 2-week (+/- 3 days) post-treatment follow-up period.

Participants took either PLN-74809 40mg or a matching placebo with 240ml water after fasting.

Arm type	Experimental
Investigational medicinal product name	PLN-74809
Investigational medicinal product code	
Other name	Bexotegrast
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

PLN-74809 tablet administered orally.

Arm title	Part C: PLN-74809 80 mg

Arm description:

PLN-74809 (Part C): Consists of an up to 28-day screening period, a 12-week treatment period, and a 2-week (+/- 3 days) post-treatment follow-up period.
Participants took either PLN-74809 80mg or a matching placebo with 240ml water after fasting.

Arm type	Experimental
Investigational medicinal product name	PLN-74809
Investigational medicinal product code	
Other name	Bexotegrast
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

PLN-74809 tablet(s) administered orally.

Arm title	Part C: PLN-74809 160 mg

Arm description:

PLN-74809 (Part C): Consists of an up to 28-day screening period, a 12-week treatment period, and a 2-week (+/- 3 days) post-treatment follow-up period.

Participants took either PLN-74809 160mg or a matching placebo with 240ml water after fasting.

Arm type	Experimental
Investigational medicinal product name	PLN-74809
Investigational medicinal product code	
Other name	Bexotegrast
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

PLN-74809 tablets administered orally.

Arm title	Part D: PLN-74809 320 mg

Arm description:

PLN-74809 (Part D): Consists of an up to 28-day screening period, at least 24-week treatment period, and a 2-week (+/- 3 days) post-treatment follow-up period.

Participants took either PLN-74809 320 mg or a matching placebo with 240ml water after fasting.

Arm type	Experimental
Investigational medicinal product name	Part D: PLN-74809 320 mg
Investigational medicinal product code	
Other name	Bexotegrast
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

PLN-74809 tablet administered orally

Arm title	Placebo

Arm description:

Participants took a matching placebo with water after fasting.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Matching placebo tablets administered orally.

Number of subjects in period 1	Part A: PLN-74809 40 mg	Part B: PLN-74809 40 mg	Part C: PLN-74809 80 mg
Started	1	22	23
Completed	1	21	23
Not completed	0	1	0
Adverse event, serious fatal	-	-	-
Physician decision	-	1	-
Consent withdrawn by subject	-	-	-
Adverse event, non-fatal	-	-	-
Not specified	-	-	-

Number of subjects in period 1	Part C: PLN-74809 160 mg	Part D: PLN-74809 320 mg	Placebo
Started	22	21	31
Completed	20	15	25
Not completed	2	6	6
Adverse event, serious fatal	-	1	-
Physician decision	-	-	-
Consent withdrawn by subject	2	3	3
Adverse event, non-fatal	-	2	2
Not specified	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Part A: PLN-74809 40 mg

Reporting group description:

PLN-74809 (Part A): Consists of an up to 28-day screening period, a 4-week treatment period, and a 2-week (+/- 3 days) post-treatment follow-up period.

Participants took either PLN-74809 40mg or a matching placebo with 100ml water after fasting.

Reporting group title	Part B: PLN-74809 40 mg

Reporting group description:

PLN-74809 (Part B): Consists of an up to 28-day screening period, a 12-week treatment period, and a 2-week (+/- 3 days) post-treatment follow-up period.

Participants took either PLN-74809 40mg or a matching placebo with 240ml water after fasting.

Reporting group title	Part C: PLN-74809 80 mg

Reporting group description:

PLN-74809 (Part C): Consists of an up to 28-day screening period, a 12-week treatment period, and a 2-week (+/- 3 days) post-treatment follow-up period.
Participants took either PLN-74809 80mg or a matching placebo with 240ml water after fasting.

Reporting group title	Part C: PLN-74809 160 mg

Reporting group description:

PLN-74809 (Part C): Consists of an up to 28-day screening period, a 12-week treatment period, and a 2-week (+/- 3 days) post-treatment follow-up period.

Participants took either PLN-74809 160mg or a matching placebo with 240ml water after fasting.

Reporting group title	Part D: PLN-74809 320 mg

Reporting group description:

PLN-74809 (Part D): Consists of an up to 28-day screening period, at least 24-week treatment period, and a 2-week (+/- 3 days) post-treatment follow-up period.

Participants took either PLN-74809 320 mg or a matching placebo with 240ml water after fasting.

Reporting group title	Placebo

Reporting group description:

Participants took a matching placebo with water after fasting.

Reporting group values	Part A: PLN-74809 40 mg	Part B: PLN-74809 40 mg	Part C: PLN-74809 80 mg
Number of subjects	1	22	23
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			

Age continuous			
Units: years			
arithmetic mean	64	69.2	74.2
standard deviation	± 999	± 7.11	± 4.70
Gender categorical			
Units: Subjects			
Female	0	4	4
Male	1	18	19

Reporting group values	Part C: PLN-74809 160 mg	Part D: PLN-74809 320 mg	Placebo
Number of subjects	22	21	31
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	71.5	70.6	72.1
standard deviation	± 6.63	± 7.31	± 6.20
Gender categorical			
Units: Subjects			
Female	6	1	4
Male	16	20	27

Reporting group values	Total		
Number of subjects	120		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous			
Units: years			
arithmetic mean			
standard deviation	-		

Gender categorical Units: Subjects			
Female	19		
Male	101		

End points

End points reporting groups

Reporting group title	Part A: PLN-74809 40 mg

Reporting group description:

PLN-74809 (Part A): Consists of an up to 28-day screening period, a 4-week treatment period, and a 2-week (+/- 3 days) post-treatment follow-up period.

Participants took either PLN-74809 40mg or a matching placebo with 100ml water after fasting.

Reporting group title	Part B: PLN-74809 40 mg

Reporting group description:

PLN-74809 (Part B): Consists of an up to 28-day screening period, a 12-week treatment period, and a 2-week (+/- 3 days) post-treatment follow-up period.

Participants took either PLN-74809 40mg or a matching placebo with 240ml water after fasting.

Reporting group title	Part C: PLN-74809 80 mg

Reporting group description:

PLN-74809 (Part C): Consists of an up to 28-day screening period, a 12-week treatment period, and a 2-week (+/- 3 days) post-treatment follow-up period.
Participants took either PLN-74809 80mg or a matching placebo with 240ml water after fasting.

Reporting group title	Part C: PLN-74809 160 mg

Reporting group description:

PLN-74809 (Part C): Consists of an up to 28-day screening period, a 12-week treatment period, and a 2-week (+/- 3 days) post-treatment follow-up period.

Participants took either PLN-74809 160mg or a matching placebo with 240ml water after fasting.

Reporting group title	Part D: PLN-74809 320 mg

Reporting group description:

PLN-74809 (Part D): Consists of an up to 28-day screening period, at least 24-week treatment period, and a 2-week (+/- 3 days) post-treatment follow-up period.

Participants took either PLN-74809 320 mg or a matching placebo with 240ml water after fasting.

Reporting group title	Placebo

Reporting group description:

Participants took a matching placebo with water after fasting.

Primary: Parts A,B,C, and D - Number of Participants With Treatment-emergent Adverse Events (TEAEs)

End point title	Parts A,B,C, and D - Number of Participants With Treatment-emergent Adverse Events (TEAEs)[1]

End point description:

An AE was any untoward medical occurrence in a clinical study participant administered a study drug that does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and/or unintended sign, symptom, or disease temporally associated with the use of a study drug, whether or not the AE is considered related to the study drug. TEAEs were defined as any AEs with an onset date on or after the study drug start date and no later than 14 days after permanent discontinuation of study drug.

Safety Population: All participants who took at least 1 dose of study drug.

Values of 9999 indicate that data are not available for the specified time point.

End point type	Primary

End point timeframe:

Up to 4 weeks for Part A, 12 weeks for Part B-C, and up to week 12 and 48 for Part D

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No additional statistical analyses were pre-specified for this endpoint.

End point values	Part A: PLN-74809 40 mg	Part B: PLN-74809 40 mg	Part C: PLN-74809 80 mg	Part C: PLN-74809 160 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	22	23	22
Units: Number of Participants				
Up to 4 weeks	1	9999	9999	9999
Up to 12 weeks	9999	16	15	14
Up to 48 weeks	9999	9999	9999	9999

End point values	Part D: PLN-74809 320 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	31[2]		
Units: Number of Participants				
Up to 4 weeks	9999	9999		
Up to 12 weeks	17	21		
Up to 48 weeks	20	7		

Notes:

[2] - N=31 for Placebo (Part B, C, D) "Up to 12 week" data
N=8 for Placebo (Part D) "Up to 48 week" data

Statistical analyses

No statistical analyses for this end point

Primary: Parts A,B,C, and D - Number of Participants With Serious TEAEs

End point title	Parts A,B,C, and D - Number of Participants With Serious TEAEs[3]

End point description:

A serious adverse event (SAE) was defined as an event that, at any dose, results in the following: death, a life-threatening situation; in-patient hospitalization or prolongation of existing hospitalization, persistent or significant disability/incapacity, a congenital anomaly/birth defect or a medically important event or reaction.

Safety Population: All participants who took at least 1 dose of study drug.

Value of 9999 indicate that data are not available for the specified time point.

End point type	Primary

End point timeframe:

Up to 4 weeks for Part A, 12 weeks for Part B-C, and up to week 12 and 48 for Part D

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No additional statistical analyses were pre-specified for this endpoint.

End point values	Part A: PLN-74809 40 mg	Part B: PLN-74809 40 mg	Part C: PLN-74809 80 mg	Part C: PLN-74809 160 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	22	23	22
Units: Number of Participants				
Up to 4 weeks	0	9999	9999	9999
Up to 12 weeks	9999	1	0	2
Up to 48 weeks	9999	9999	9999	9999

End point values	Part D: PLN-74809 320 mg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	31[4]		
Units: Number of Participants				
Up to 4 weeks	9999	9999		
Up to 12 weeks	1	3		
Up to 48 weeks	2	1		

Notes:

[4] - N=31 for Placebo (Part B, C, D) "Up to 12 week" data
N=8 for Placebo (Part D) "Up to 48 week" data

Statistical analyses

No statistical analyses for this end point

Secondary: Parts A,B, C, and D - PLN-74809 Total Plasma Concentrations

End point title	Parts A,B, C, and D - PLN-74809 Total Plasma Concentrations[5]

End point description:

PK Analysis Population: All randomized participants who had sufficient PLN-74809 concentration data for PK calculation were included in the PK analyses.
Values of "9999.99" indicate mean and standard deviation could not be calculated.

End point type	Secondary

End point timeframe:

Part A: week 4, 1-hour post-dose; Part B-D: week 12, 2 hours post-dose; Part D: week 24, 2 hours post-dose

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: NA

End point values	Part A: PLN-74809 40 mg	Part B: PLN-74809 40 mg	Part C: PLN-74809 80 mg	Part C: PLN-74809 160 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	1	20	23	21
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 4, 1 hour post-dose	829 (± 9999.99)	9999.99 (± 9999.99)	9999.99 (± 9999.99)	9999.99 (± 9999.99)
Week 12, 2-hours post-dose	9999.99 (± 9999.99)	921.45 (± 549.103)	1731.70 (± 875.776)	2733.71 (± 1038.402)
Week 24, 2 hours post-dose	9999.99 (± 9999.99)	9999.99 (± 9999.99)	9999.99 (± 9999.99)	9999.99 (± 9999.99)

End point values	Part D: PLN-74809 320 mg			
Subject group type	Reporting group			
Number of subjects analysed	18[6]			
Units: ng/mL				
arithmetic mean (standard deviation)				
Week 4, 1 hour post-dose	9999.99 (± 9999.99)			
Week 12, 2-hours post-dose	3742.78 (± 1383.345)			
Week 24, 2 hours post-dose	4120.63 (± 1866.606)			

Notes:

[6] - N=16 for Part D (320 mg) - "Week 24, 2 hours post-dose"

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

ACM: Randomization up to 190.1 days +14 days. AEs: First dose date up to 29 days +14 (Part A 40 mg), 83.6 days +14 (Part B 40 mg), 86.0 days +14 (Part C 80 mg), 82.7 days +14 (Part C 160 mg), 190.1 days +14 (Part D 320 mg), and 107.6 days +14 (Placebo).

Adverse event reporting additional description:

Safety population included all participants who took at least 1 dose of study drug.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Part A: PLN-74809 40 mg

Reporting group description:

PLN-74809 (Part A): Consists of an up to 28-day screening period, a 4-week treatment period, and a 2-week (+/- 3 days) post-treatment follow-up period.

Participants took either PLN-74809 40mg or a matching placebo with 100ml water after fasting.

Reporting group title	Part B: PLN-74809 40 mg

Reporting group description:

PLN-74809 (Part B): Consists of an up to 28-day screening period, a 12-week treatment period, and a 2-week (+/- 3 days) post-treatment follow-up period.

Participants took either PLN-74809 40mg or a matching placebo with 240ml water after fasting.

Reporting group title	Part C: PLN-74809 80 mg

Reporting group description:

PLN-74809 (Part C): Consists of an up to 28-day screening period, a 12-week treatment period, and a 2-week (+/- 3 days) post-treatment follow-up period.

Participants took either PLN-74809 80mg or a matching placebo with 240ml water after fasting.

Reporting group title	Part C: PLN-74809 160 mg

Reporting group description:

PLN-74809 (Part C): Consists of an up to 28-day screening period, a 12-week treatment period, and a 2-week (+/- 3 days) post-treatment follow-up period.

Participants took either PLN-74809 160mg or a matching placebo with 240ml water after fasting.

Reporting group title	Part D: PLN-74809 320 mg

Reporting group description:

PLN-74809 (Part D): Consists of an up to 28-day screening period, at least 24-week treatment period, and a 2-week (+/- 3 days) post-treatment follow-up period.

Participants took either PLN-74809 320 mg or a matching placebo with 240ml water after fasting.

Reporting group title	Placebo

Reporting group description:

Participants took a matching placebo with water after fasting.

Serious adverse events	Part A: PLN-74809 40 mg	Part B: PLN-74809 40 mg	Part C: PLN-74809 80 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	1 / 22 (4.55%)	0 / 23 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Congenital, familial and genetic disorders			
Haemorrhagic arteriovenous malformation			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			

subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 1 (0.00%)	1 / 22 (4.55%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Idiopathic pulmonary fibrosis/Pulmonary fibrosis			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder dilatation			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			

subjects affected / exposed	0 / 1 (0.00%)	1 / 22 (4.55%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperlactacidaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part C: PLN-74809 160 mg	Part D: PLN-74809 320 mg	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 22 (9.09%)	2 / 22 (9.09%)	3 / 31 (9.68%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	1	0
Congenital, familial and genetic disorders			
Haemorrhagic arteriovenous malformation			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute left ventricular failure			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Gastric ulcer haemorrhage			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileus			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Idiopathic pulmonary fibrosis/Pulmonary fibrosis			
subjects affected / exposed	1 / 22 (4.55%)	0 / 22 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder dilatation			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	1 / 31 (3.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperlactacidaemia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	0 / 31 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Part A: PLN-74809 40 mg	Part B: PLN-74809 40 mg	Part C: PLN-74809 80 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	8 / 22 (36.36%)	8 / 23 (34.78%)
Investigations			
Amylase increased			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0

Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	0 / 1 (0.00%)	2 / 22 (9.09%)	2 / 23 (8.70%)
occurrences (all)	0	2	2
Oedema peripheral			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	1 / 1 (100.00%)	0 / 22 (0.00%)	1 / 23 (4.35%)
occurrences (all)	1	0	1
Diarrhoea			
subjects affected / exposed	1 / 1 (100.00%)	2 / 22 (9.09%)	5 / 23 (21.74%)
occurrences (all)	1	2	5
Vomiting			
subjects affected / exposed	1 / 1 (100.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	1 / 1 (100.00%)	1 / 22 (4.55%)	1 / 23 (4.35%)
occurrences (all)	1	1	1
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	1 / 23 (4.35%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	0 / 1 (0.00%)	1 / 22 (4.55%)	1 / 23 (4.35%)
occurrences (all)	0	1	2
Idiopathic pulmonary fibrosis/Pulmonary fibrosis			

subjects affected / exposed	0 / 1 (0.00%)	1 / 22 (4.55%)	0 / 23 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
COVID-19			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0
Pneumonia			
subjects affected / exposed	0 / 1 (0.00%)	1 / 22 (4.55%)	1 / 23 (4.35%)
occurrences (all)	0	1	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 1 (0.00%)	1 / 22 (4.55%)	0 / 23 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 1 (0.00%)	0 / 22 (0.00%)	0 / 23 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Part C: PLN-74809 160 mg	Part D: PLN-74809 320 mg	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	10 / 22 (45.45%)	18 / 22 (81.82%)	14 / 31 (45.16%)
Investigations			
Amylase increased			
subjects affected / exposed	0 / 22 (0.00%)	2 / 22 (9.09%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Injury, poisoning and procedural complications			
Skin abrasion			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	2 / 31 (6.45%)
occurrences (all)	0	0	2
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 22 (0.00%)	2 / 22 (9.09%)	2 / 31 (6.45%)
occurrences (all)	0	2	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	0 / 31 (0.00%)
occurrences (all)	1	2	0
Headache			

subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	2 / 31 (6.45%)
occurrences (all)	0	1	2
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 22 (4.55%)	2 / 22 (9.09%)	2 / 31 (6.45%)
occurrences (all)	1	3	2
Oedema peripheral			
subjects affected / exposed	0 / 22 (0.00%)	2 / 22 (9.09%)	0 / 31 (0.00%)
occurrences (all)	0	3	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	0 / 22 (0.00%)	1 / 22 (4.55%)	1 / 31 (3.23%)
occurrences (all)	0	1	1
Diarrhoea			
subjects affected / exposed	5 / 22 (22.73%)	7 / 22 (31.82%)	4 / 31 (12.90%)
occurrences (all)	8	11	5
Vomiting			
subjects affected / exposed	2 / 22 (9.09%)	0 / 22 (0.00%)	0 / 31 (0.00%)
occurrences (all)	2	0	0
Nausea			
subjects affected / exposed	2 / 22 (9.09%)	0 / 22 (0.00%)	3 / 31 (9.68%)
occurrences (all)	5	0	4
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 22 (9.09%)	5 / 22 (22.73%)	1 / 31 (3.23%)
occurrences (all)	2	6	1
Cough			
subjects affected / exposed	1 / 22 (4.55%)	3 / 22 (13.64%)	3 / 31 (9.68%)
occurrences (all)	1	3	3
Idiopathic pulmonary fibrosis/Pulmonary fibrosis			
subjects affected / exposed	1 / 22 (4.55%)	4 / 22 (18.18%)	3 / 31 (9.68%)
occurrences (all)	2	4	3
Infections and infestations			
COVID-19			

subjects affected / exposed	2 / 22 (9.09%)	2 / 22 (9.09%)	0 / 31 (0.00%)
occurrences (all)	2	3	0
Pneumonia			
subjects affected / exposed	0 / 22 (0.00%)	2 / 22 (9.09%)	0 / 31 (0.00%)
occurrences (all)	0	2	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 22 (0.00%)	2 / 22 (9.09%)	1 / 31 (3.23%)
occurrences (all)	0	2	1
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 22 (0.00%)	3 / 31 (9.68%)
occurrences (all)	0	0	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 March 2020	Version 1.1: Part A was no longer described in the protocol. -Part B was introduced as a randomized, double-blind, placebo controlled cohort in which 28 participants with IPF were to be randomized in a 3:1 ratio to receive PLN-74809 40 mg or placebo once daily for 28 days. -Part C was introduced following favorable DSMB review and completion of enrollment in Part B, to proceed with randomized, double-blind, placebo-controlled cohorts introducing doses above 40 mg. -The sample size was changed to capture the increased number of participants to be enrolled in the study.
30 November 2020	Version 2.0: A description and rationale for the 80 and 160 mg doses studied in Part C was added. -Clarified that participants in Part C were to be allocated in a 3:3:2 ratio (parallel randomization) to receive once daily PLN-74809 80 mg or 160 mg, or placebo. Participants in Part C were enrolled under protocol v2.0 in Australia, Canada, and the United States.
02 December 2020	Version 2.1: Clarified that participants in Part C were to be allocated in a 3:1 ratio (sequential randomization) to receive once daily PLN-74809 80 mg or placebo (sequential Cohort 1) or 160 mg or placebo (sequential Cohort 2). Participants in Part C were enrolled under protocol v2.1 in Italy, the Netherlands, New Zealand, and the United States. -Inclusion criteria 7, 8, and 9 regarding contraception were revised in alignment with feedback from various competent authorities. Contraception was also updated. -Exclusion criterion 6 (HRCT scan) was clarified and refined based on feedback from competent authorities. - “Diagnosis” was removed from exclusion criterion 7 in relation to severe pulmonary hypertension to simplify PI assessment for eligibility. -Hepatic impairment was removed from exclusion criterion 11 as it was covered by the exclusion of both end-stage liver disease and liver function tests above the specified limits. -Clarified that participation in a previous clinical study should be the linger of either 30 days prior to screening OR 5 half-lives in exclusion criterion 21. -Added standardized guidance for the management of missed or delayed study drug administration in Section 6.3 Selection and Timing of Dose for Each Participant. -Global guidance for procedures that were to be followed should unblinding have occurred was added. -Grapefruit, grapefruit-containing foods and beverages, and St. John’s Wort were added as disallowed medications as they can affect the concentration of PLN-74809. -Study Procedures was updated to allow a home health care vendor to conduct some of the study visits. -Language describing triplicate ECGs and how they were to be captured and measured was added. -Historical FVC and FEV1 could be used for eligibility assessments. -Clarified that Investigators or the Sponsor could discontinue participants with COVID-19 if their continued study involvement posed a safety risk.

02 December 2020	02-Dec-2020 continued: - The schedule of assessments was revised for consistency. - The definition of SAEs was clarified to include examples of important medical events, including laboratory abnormalities consistent with drug-induced liver injury, QT prolongation that results in study drug discontinuation, allergic bronchospasm requiring intensive treatment, blood dyscrasias, convulsions, and the development of drug dependency or abuse. - The determination of sample size was clarified to explain that 21 participants per dose level pertained only to those who would receive PLN-74809.
19 October 2021	Version 3.0: Timepoints specific to Part B and C were removed from the objectives to account for the different duration in Parts B and C and Part D.
20 October 2021	Version 3.1: A description and rationale for the 320 mg once daily dose for Part D was added following DSMB evaluation of the 80 and 160 mg doses from Part C. -Updated on the progress of Part C to explain that the DSMB had evaluated the 40 mg dose and recommended to continue without modification. -Digoxin (a P-gp substrate) was removed from exclusion criterion 25 following completion of the drug-drug interaction study PLN-74809-110. -Additional data was added to Section 6.6.1 Allowed Medications to describe drug-drug interaction studies between PLN-74809 and fluconazole and digoxin. Additional data was also added to Section 6.6.2 Disallowed Medications to describe the drug-drug interactions studies between PLN-74809 and itraconazole. -The phosphate salt formulation of PLN-74809 used in Part D was described, and storage conditions were revised. -Added language to provide direction as to how AEs and SAEs were to be reported. The process for reporting SAEs was revised to align with pharmacovigilance vendor reporting procedures. -Interim Analysis was updated to include a description of additional interim analyses. -Assessments and visits were added to the schedules of assessments for Parts B, C, and D to align with the revised study design and objectives.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported