Clinical trial results:
A Phase 2, Randomized, Double-Blind, Multicenter, Placebo-Controlled Study to Evaluate the Safety and Tolerability of Treprostinil Palmitil Inhalation Powder in Participants with Pulmonary Hypertension Associated with Interstitial Lung Disease

Summary

EudraCT number	2021-003294-66
Trial protocol	ES DE BE IT
Global end of trial date	13 March 2024

Results information

Result version number	v1 (current)
This version publication date	29 March 2025
First version publication date	29 March 2025

Trial information

Trial identification

Sponsor protocol code	INS1009-211

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT05176951
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Insmed Incorporated
Sponsor organisation address	700 US Highway 202/206, Bridgewater, United States, 08807-1704
Public contact	Insmed Medical Information, Insmed Incorporated, +1 1-844-446-7633, medicalinformation@insmed.com
Scientific contact	Insmed Medical Information, Insmed Incorporated, +1 1-844-446-7633, medicalinformation@insmed.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	13 March 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 March 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the safety and tolerability of Treprostinil Palmitil Inhalation Powder (TPIP) compared with placebo in participants with Pulmonary Hypertension with Interstitial Lung Disease.

Protection of trial subjects:

This study was conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP), including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 December 2022
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	Argentina: 4
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Spain: 12
Country: Number of subjects enrolled	United Kingdom: 3
Worldwide total number of subjects	39
EEA total number of subjects	30

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)	17
From 65 to 84 years	22
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in this multi-centre study at different investigative sites from 22 December 2022 to 14 March 2024.

Pre-assignment

Screening details:

A total of 39 participants with pulmonary hypertension associated with interstitial lung disease were enrolled in the study.

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	Treprostinil Palmitil

Arm description:

Participants received TPIP once daily (QD) at a starting dose of 80 micrograms (mcg), followed by dose titration from 80 mcg to maximum tolerated dose up to 640 mcg during the initial 3 weeks of dose-titration period. Additional up-titration was allowed at the Week 5 visit if the participant did not reach the target dose of 640 mcg. The participant's highest dose tolerated was continued for the remainder of the study until Week 16.

Arm type	Experimental
Investigational medicinal product name	Treprostinil Palmitil
Investigational medicinal product code	
Other name	INS1009
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received inhalation dry powder capsules containing 80 mcg, 160 mcg, 240 mcg, 320 mcg, 400 mcg, 480 mcg or 640 mcg of TPIP, QD.

Arm title	Placebo

Arm description:

Participants received placebo matching TPIP QD until Week 16.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

Participants received placebo matching TPIP QD until Week 16.

Number of subjects in period 1	Treprostinil Palmitil	Placebo
Started	29	10
Completed	24	8
Not completed	5	2
Adverse event, serious fatal	1	2
Physician decision	1	-
Adverse event, non-fatal	3	-

Baseline characteristics

Reporting groups	
Reporting group title	Treprostinil Palmitil
Reporting group description:	
Participants received TPIP once daily (QD) at a starting dose of 80 micrograms (mcg), followed by dose titration from 80 mcg to maximum tolerated dose up to 640 mcg during the initial 3 weeks of dose-titration period. Additional up-titration was allowed at the Week 5 visit if the participant did not reach the target dose of 640 mcg. The participant's highest dose tolerated was continued for the remainder of the study until Week 16.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matching TPIP QD until Week 16.	

Reporting group values	Treprostinil Palmitil	Placebo	Total
Number of subjects	29	10	39
Age Categorical Units: Subjects			
Age continuous Units:			
arithmetic mean	65.7	63.8	
standard deviation	± 7.65	± 10.55	-
Gender categorical Units: Subjects			
Female	9	2	11
Male	20	8	28
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	7	2	9
Not Hispanic or Latino	19	8	27
Unknown or Not Reported	3	0	3
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	24	9	33
More than one race	1	1	2
Unknown or Not Reported	4	0	4

End points

End points reporting groups

Reporting group title	Treprostinil Palmitil
Reporting group description:	
Participants received TPIP once daily (QD) at a starting dose of 80 micrograms (mcg), followed by dose titration from 80 mcg to maximum tolerated dose up to 640 mcg during the initial 3 weeks of dose-titration period. Additional up-titration was allowed at the Week 5 visit if the participant did not reach the target dose of 640 mcg. The participant's highest dose tolerated was continued for the remainder of the study until Week 16.	
Reporting group title	Placebo
Reporting group description:	
Participants received placebo matching TPIP QD until Week 16.	
Subject analysis set title	TPIP 80 mcg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants received TPIP 80 mcg QD until week 16.	
Subject analysis set title	TPIP 400 mcg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants received TPIP 400 mcg QD until week 16.	
Subject analysis set title	TPIP 480 mcg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants received TPIP 480 mcg QD until week 16.	
Subject analysis set title	TPIP 640 mcg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Participants received TPIP 640 mcg QD until week 16.	

Primary: Number of Participants Who Experienced Treatment Emergent Adverse Events (TEAEs) and Serious TEAEs

End point title	Number of Participants Who Experienced Treatment Emergent Adverse Events (TEAEs) and Serious TEAEs[1]
End point description:	
An AE is defined as any untoward medical occurrence in a participant or clinical investigation participant administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. A TEAE is defined as any AE that occurs after the first dose of study drug and within 30 days after the last dose of study drug. TEAEs included both serious and non-serious TEAEs. Safety analysis set included all randomised participants who had received at least 1 dose of study drug in the double-blind treatment period.	
End point type	Primary
End point timeframe:	
From signing the informed consent form up to Week 20	

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: Only descriptive analysis was planned for this endpoint.

End point values	Treprostinil Palmitil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	10		
Units: participants				
TEAEs	27	9		
Serious TEAEs	6	4		

Statistical analyses

No statistical analyses for this end point

Primary: Change From Baseline in Supplemental Oxygen Used During the 6-Minute Walk Test (6MWT) at Week 5, Week 10, and Week 16

End point title	Change From Baseline in Supplemental Oxygen Used During the 6-Minute Walk Test (6MWT) at Week 5, Week 10, and Week 16[2]

End point description:

Safety analysis set included all randomised participants who had received at least 1 dose of study drug in the double-blind treatment period. 'n' signifies number of participants analysed at the specified timepoint in this endpoint.

End point type	Primary

End point timeframe:

At Baseline, Week 5, Week 10, and Week 16

Notes:

[2] - 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: Only descriptive analysis was planned for this endpoint.

End point values	Treprostinil Palmitil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	10		
Units: litres per minute (L/min)				
arithmetic mean (standard deviation)				
Baseline (n=29,10)	3.3 (± 2.17)	2.3 (± 2.16)		
Change at Week 5 (n=25,9)	0.1 (± 1.19)	-0.4 (± 1.01)		
Change at Week 10 (n=25,8)	0.5 (± 1.69)	0.1 (± 0.83)		
Change at Week 16 (n=24,8)	0.0 (± 0.91)	0.6 (± 2.20)		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Peripheral Capillary Oxygen Saturation Measured by Pulse Oximetry (SpO2) Levels

End point title	Change from Baseline in Peripheral Capillary Oxygen Saturation Measured by Pulse Oximetry (SpO2) Levels[3]

End point description:

Lowest SpO2 was defined as the lowest SpO2 value during or after the 6MWT. Safety analysis set included all randomised participants who had received at least 1 dose of study drug in the double-blind treatment period. 'n' signifies number of participants analysed at the specified timepoint in this endpoint.

End point type	Primary

End point timeframe:

Pre, during, and post 6-minute walk test (6MWT) at Baseline, Week 5, Week 10, and Week 16

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: Only descriptive analysis was planned for this endpoint.

End point values	Treprostinil Palmitil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	10		
Units: percentage of oxygen saturation				
arithmetic mean (standard deviation)				
Baseline: Pre-test SpO2 (n=29,10)	94.6 (± 4.17)	96.1 (± 2.51)		
Baseline: Lowest SpO2 (n=29,10)	76.7 (± 11.71)	80.9 (± 9.96)		
Change at Week 5: Pre-test SpO2 (n=25,9)	0.1 (± 4.31)	-2.9 (± 7.79)		
Change at Week 5: Lowest SpO2 (n=25,9)	-2.7 (± 7.42)	-3.6 (± 5.17)		
Change at Week 10: Pre-test SpO2 (n=25,8)	0.7 (± 3.84)	-2.6 (± 5.60)		
Change at Week 10: Lowest SpO2 (n=25,8)	-3.5 (± 8.76)	-1.6 (± 6.19)		
Change at Week 16: Pre-test SpO2 (n=24,8)	-0.3 (± 5.64)	-0.9 (± 3.04)		
Change at Week 16: Lowest SpO2 (n=22,8)	-4.6 (± 11.65)	-1.3 (± 7.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Plasma Concentration (Cmax) of Treprostinil Palmitil (TP)

End point title	Maximum Plasma Concentration (Cmax) of Treprostinil Palmitil (TP)

End point description:

Pharmacokinetic (PK) analysis set included all participants who received one dose of TPIP and had at least one post-dose PK concentration datum available. Here 'Number of subjects analysed' is the number of participants with data available for analyses. 99999 indicates that coefficient of variation (CV) was not estimable as there was only 1 participant.

End point type	Secondary

End point timeframe:

Pre-dose and 0.5, 1, 2, 4 and 8 hours post-dose at Day 1 and Week 10

End point values	TPIP 80 mcg	TPIP 640 mcg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1	8		
Units: picogram per millilitre (pg/mL)				
geometric mean (geometric coefficient of variation)	13.40 (± 99999)	20.10 (± 45.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Cmax of Treprostinil (TRE)

End point title	Cmax of Treprostinil (TRE)

End point description:

PK analysis set included all participants who received one dose of TPIP and had at least one post-dose PK concentration datum available. Here 'Number of subjects analysed' is the number of participants with data available for analyses. 99999 indicates that CV was not estimable as there was only 1 participant.

End point type	Secondary

End point timeframe:

Pre-dose and 0.5, 1, 2, 4 and 8 hours post-dose at Day 1 and Week 10

End point values	TPIP 80 mcg	TPIP 400 mcg	TPIP 480 mcg	TPIP 640 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	28	1	3	20
Units: pg/mL				
geometric mean (geometric coefficient of variation)	107.3 (± 97.4)	535.0 (± 99999)	1129 (± 56.8)	1361 (± 60.2)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach Cmax (Tmax) of TP

End point title	Time to Reach Cmax (Tmax) of TP

End point description:

PK analysis set included all participants who received one dose of TPIP and had at least one post-dose PK concentration datum available. Here 'Number of subjects analysed' is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Pre-dose and 0.5, 1, 2, 4 and 8 hours post-dose at Day 1 and Week 10

End point values	TPIP 80 mcg	TPIP 640 mcg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1	8		
Units: hours				
median (full range (min-max))	4.33 (4.33 to 4.33)	3.06 (1.47 to 6.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Tmax of TRE

End point title	Tmax of TRE

End point description:

PK analysis set included all participants who received one dose of TPIP and had at least one post-dose PK concentration datum available. Here 'Number of subjects analysed' is the number of participants with data available for analyses.

End point type	Secondary

End point timeframe:

Pre-dose and 0.5, 1, 2, 4 and 8 hours post-dose at Day 1 and Week 10

End point values	TPIP 80 mcg	TPIP 400 mcg	TPIP 480 mcg	TPIP 640 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	28	1	3	20
Units: hours				
median (full range (min-max))	2.00 (0.47 to 6.00)	2.00 (2.00 to 2.00)	1.03 (0.50 to 2.00)	1.46 (0.47 to 6.00)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under Concentration-time Curve From Time 0 to 24 Hours Post-dose (AUCtau) of TP

End point title	Area Under Concentration-time Curve From Time 0 to 24 Hours Post-dose (AUCtau) of TP

End point description:

PK analysis set included all participants who received one dose of TPIP and had at least one post-dose PK concentration datum available. Here 'Number of subjects analysed' is the number of participants with data available for analyses. 9999 indicates that geometric mean and CV were not estimable because all samples were below level of quantification (BLQ).

End point type	Secondary

End point timeframe:

Pre-dose and 0.5, 1, 2, 4, 8 and 24 hours post-dose at Day 1 and Week 10

End point values	TPIP 80 mcg	TPIP 640 mcg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1	4		
Units: picograms*hours per millilitre (pg*h/mL)				
geometric mean (geometric coefficient of variation)	9999 (± 9999)	121.8 (± 48.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUCtau of TRE

End point title	AUCtau of TRE

End point description:

PK analysis set included all participants who received one dose of TPIP and had at least one post-dose PK concentration datum available. Here 'Number of subjects analysed' is the number of participants with data available for analyses. 9999 indicates that geometric mean and CV were not estimable because all samples were BLQ. 99999 indicates that CV was not estimable as there was only 1 participant.

End point type	Secondary

End point timeframe:

Pre-dose and 0.5, 1, 2, 4, 8 and 24 hours post-dose at Day 1 and Week 10

End point values	TPIP 80 mcg	TPIP 400 mcg	TPIP 480 mcg	TPIP 640 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	28	1	3	17
Units: pg*h/mL				
geometric mean (geometric coefficient of variation)	9999 (± 9999)	2625 (± 99999)	4590 (± 23.6)	7111 (± 35.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under Concentration-time Curve From 0 to Infinity (AUC0-inf) of TP

End point title	Area Under Concentration-time Curve From 0 to Infinity (AUC0-inf) of TP

End point description:

PK analysis set included all participants who received one dose of TPIP and had at least one post-dose PK concentration datum available. Here 'Number of subjects analysed' is the number of participants with data available for analyses. 9999 indicates that geometric mean and CV were not estimable because all samples were BLQ.

End point type	Secondary

End point timeframe:

Pre-dose and 0.5, 1, 2, 4, 8 and 24 hours post-dose at Day 1 and Week 10

End point values	TPIP 80 mcg	TPIP 640 mcg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1	4		
Units: pg*h/mL				
geometric mean (geometric coefficient of variation)	9999 (± 9999)	121.8 (± 48.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-inf of TRE

End point title	AUC0-inf of TRE

End point description:

PK analysis set included all participants who received one dose of TPIP and had at least one post-dose PK concentration datum available. Here 'Number of subjects analysed' is the number of participants with data available for analyses. 9999 indicates that geometric mean and CV were not estimable because all samples were BLQ. 99999 indicates that CV was not estimable as there was only 1 participant.

End point type	Secondary

End point timeframe:

Pre-dose and 0.5, 1, 2, 4, 8 and 24 hours post-dose at Day 1 and Week 10

End point values	TPIP 80 mcg	TPIP 400 mcg	TPIP 480 mcg	TPIP 640 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	28	1	3	17
Units: pg*h/mL				
geometric mean (geometric coefficient of variation)	9999 (± 9999)	2625 (± 99999)	4590 (± 23.6)	7111 (± 35.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under Concentration-time Curve From Time 0 to Last Measurable Concentration (AUClast) of TP

End point title	Area Under Concentration-time Curve From Time 0 to Last Measurable Concentration (AUClast) of TP

End point description:

PK analysis set included all participants who received one dose of TPIP and had at least one post-dose PK concentration datum available. Here 'Number of subjects analysed' is the number of participants with data available for analyses. 99999 indicates that CV was not estimable as there was only 1 participant.

End point type	Secondary

End point timeframe:

Pre-dose and 0.5, 1, 2, 4 and 8 hours post-dose at Day 1 and pre-dose and 0.5, 1, 2, 4, 8 and 24 hours post-dose at Week 10

End point values	TPIP 80 mcg	TPIP 640 mcg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1	8		
Units: pg*h/mL				
geometric mean (geometric coefficient of variation)	39.44 (± 99999)	62.04 (± 70.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: AUClast of TRE

End point title	AUClast of TRE

End point description:

PK analysis set included all participants who received one dose of TPIP and had at least one post-dose PK concentration datum available. Here 'Number of subjects analysed' is the number of participants with data available for analyses. 99999 indicates that CV was not estimable as there was only 1 participant.

End point type	Secondary

End point timeframe:

Pre-dose and 0.5, 1, 2, 4 and 8 hours post-dose at Day 1 and pre-dose and 0.5, 1, 2, 4, 8 and 24 hours post-dose at Week 10

End point values	TPIP 80 mcg	TPIP 400 mcg	TPIP 480 mcg	TPIP 640 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	28	1	3	20
Units: pg*h/mL				
geometric mean (geometric coefficient of variation)	306.7 (± 77.1)	2568 (± 99999)	4552 (± 24.1)	6356 (± 45.3)

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Total Clearance (CL/F) of TP

End point title	Apparent Total Clearance (CL/F) of TP

End point description:

PK analysis set included all participants who received one dose of TPIP and had at least one post-dose PK concentration datum available. Here 'Number of subjects analysed' is the number of participants with data available for analyses. 9999 indicates that geometric mean and CV were not estimable because all samples were BLQ.

End point type	Secondary

End point timeframe:

Pre-dose and 0.5, 1, 2, 4 and 8 hours post-dose at Day 1 and Week 10

End point values	TPIP 80 mcg	TPIP 640 mcg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1	4		
Units: litres per hour (L/h)				
geometric mean (geometric coefficient of variation)	9999 (± 9999)	5254 (± 48.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: CL/F of TRE

End point title	CL/F of TRE

End point description:

PK analysis set included all participants who received one dose of TPIP and had at least one post-dose PK concentration datum available. Here 'Number of subjects analysed' is the number of participants with data available for analyses. 9999 indicates that geometric mean and CV were not estimable because all samples were BLQ. 99999 indicates that CV was not estimable as there was only 1 participant.

End point type	Secondary

End point timeframe:

Pre-dose and 0.5, 1, 2, 4 and 8 hours post-dose at Day 1 and Week 10

End point values	TPIP 80 mcg	TPIP 400 mcg	TPIP 480 mcg	TPIP 640 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	28	1	3	17
Units: L/h				
geometric mean (geometric coefficient of variation)	9999 (± 9999)	152.4 (± 99999)	104.6 (± 23.6)	90.00 (± 35.1)

Statistical analyses

No statistical analyses for this end point

Secondary: Elimination Half-life (t1/2) of TP

End point title	Elimination Half-life (t1/2) of TP

End point description:

PK analysis set included all participants who received one dose of TPIP and had at least one post-dose PK concentration datum available. 9999 indicates that geometric mean and CV were not estimable because all samples were BLQ.

End point type	Secondary

End point timeframe:

Pre-dose and 0.5, 1, 2, 4 and 8 hours post-dose at Day 1 and Week 10

End point values	TPIP 80 mcg	TPIP 640 mcg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29	29		
Units: hours				
geometric mean (geometric coefficient of variation)	9999 (± 9999)	9999 (± 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: t1/2 of TRE

End point title	t1/2 of TRE

End point description:

PK analysis set included all participants who received one dose of TPIP and had at least one post-dose PK concentration datum available. Here 'Number of subjects analysed' is the number of participants with data available for analyses. 9999 indicates that geometric mean and CV were not estimable because all samples were BLQ. 99999 indicates that CV was not estimable as there was only 1 participant.

End point type	Secondary

End point timeframe:

Pre-dose and 0.5, 1, 2, 4, and 8 hours post-dose at Day 1 and Week 10

End point values	TPIP 80 mcg	TPIP 400 mcg	TPIP 480 mcg	TPIP 640 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	28	1	2	15
Units: hours				
geometric mean (geometric coefficient of variation)	9999 (± 9999)	11.16 (± 99999)	6.991 (± 42.3)	6.747 (± 34.0)

Statistical analyses

No statistical analyses for this end point

Secondary: Apparent Volume of Distribution After Terminal Phase (Vd/F) of TP

End point title	Apparent Volume of Distribution After Terminal Phase (Vd/F) of TP

End point description:

PK analysis set included all participants who received one dose of TPIP and had at least one post-dose PK concentration datum available. 9999 indicates that geometric mean and CV were not estimable because all samples were BLQ.

End point type	Secondary

End point timeframe:

Pre-dose and 0.5, 1, 2, 4 and 8 hours post-dose at Day 1 and Week 10

End point values	TPIP 80 mcg	TPIP 640 mcg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	29	29		
Units: litres				
geometric mean (geometric coefficient of variation)	9999 (± 9999)	9999 (± 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Vd/F of TRE

End point title	Vd/F of TRE

End point description:

PK analysis set included all participants who received one dose of TPIP and had at least one post-dose PK concentration datum available. Here 'Number of subjects analysed' is the number of participants with data available for analyses. 9999 indicates that geometric mean and CV were not estimable because all samples were BLQ. 99999 indicates that CV was not estimable as there was only 1 participant.

End point type	Secondary

End point timeframe:

Pre-dose and 0.5, 1, 2, 4 and 8 hours post-dose at Day 1 and Week 10

End point values	TPIP 80 mcg	TPIP 400 mcg	TPIP 480 mcg	TPIP 640 mcg
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	28	1	2	15
Units: litres				
geometric mean (geometric coefficient of variation)	9999 (± 9999)	2454 (± 99999)	1034 (± 84.2)	850.2 (± 50.8)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing the informed consent form up to Week 20

Adverse event reporting additional description:

Safety analysis set included all randomised participants who had received at least 1 dose of study drug in the double-blind treatment period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Participants received placebo matching TPIP QD until Week 16.

Reporting group title	Treprostinil Palmitil

Reporting group description:

Participants received TPIP once daily QD at a starting dose of 80 mcg, followed by dose titration from 80 mcg to maximum tolerated dose up to 640 mcg during the initial 3 weeks of dose-titration period. Additional up-titration was allowed at the Week 5 visit if the participant did not reach the target dose of 640 mcg. The participant's highest dose tolerated was continued for the remainder of the study until Week 16.

Serious adverse events	Placebo	Treprostinil Palmitil	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 10 (40.00%)	6 / 29 (20.69%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	2	2	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-small cell lung cancer			
subjects affected / exposed	0 / 10 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Subdural haematoma			
subjects affected / exposed	0 / 10 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac disorders			
Right ventricular failure			

subjects affected / exposed	1 / 10 (10.00%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 10 (10.00%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 10 (10.00%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 29 (6.90%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 10 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sepsis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Urosepsis			
subjects affected / exposed	0 / 10 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 10 (10.00%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 10 (0.00%)	1 / 29 (3.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	1 / 10 (10.00%)	0 / 29 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Placebo	Treprostinil Palmitil	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 10 (80.00%)	23 / 29 (79.31%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 10 (10.00%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Hot flush			
subjects affected / exposed	1 / 10 (10.00%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Flushing			
subjects affected / exposed	1 / 10 (10.00%)	3 / 29 (10.34%)	
occurrences (all)	1	9	
General disorders and administration site conditions			

Oedema			
subjects affected / exposed	1 / 10 (10.00%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	0 / 10 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Asthenia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Oedema peripheral			
subjects affected / exposed	1 / 10 (10.00%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Chest pain			
subjects affected / exposed	1 / 10 (10.00%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Cyanosis central			
subjects affected / exposed	1 / 10 (10.00%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	0 / 10 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Interstitial lung disease			
subjects affected / exposed	1 / 10 (10.00%)	2 / 29 (6.90%)	
occurrences (all)	1	2	
Productive cough			
subjects affected / exposed	0 / 10 (0.00%)	4 / 29 (13.79%)	
occurrences (all)	0	4	
Dyspnoea			
subjects affected / exposed	1 / 10 (10.00%)	4 / 29 (13.79%)	
occurrences (all)	2	5	
Cough			
subjects affected / exposed	2 / 10 (20.00%)	15 / 29 (51.72%)	
occurrences (all)	5	18	
Oropharyngeal pain			

subjects affected / exposed occurrences (all) Throat irritation subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1 0 / 10 (0.00%) 0	0 / 29 (0.00%) 0 2 / 29 (6.90%) 2	
Psychiatric disorders Post-traumatic stress disorder subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1	 0 / 29 (0.00%) 0	
Investigations Liver function test increased subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 3	 0 / 29 (0.00%) 0	
Injury, poisoning and procedural complications Craniofacial fracture subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1	 0 / 29 (0.00%) 0	
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	 0 / 10 (0.00%) 0	 2 / 29 (6.90%) 2	
Nervous system disorders Syncope subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 2 0 / 10 (0.00%) 0 0 / 10 (0.00%) 0	 0 / 29 (0.00%) 0 3 / 29 (10.34%) 3 4 / 29 (13.79%) 6	
Blood and lymphatic system disorders Lymphadenopathy subjects affected / exposed occurrences (all)	 1 / 10 (10.00%) 1	 0 / 29 (0.00%) 0	
Gastrointestinal disorders			

Abdominal pain upper			
subjects affected / exposed	1 / 10 (10.00%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	2 / 10 (20.00%)	7 / 29 (24.14%)	
occurrences (all)	2	8	
Vomiting			
subjects affected / exposed	0 / 10 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	5	
Nausea			
subjects affected / exposed	0 / 10 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	1 / 10 (10.00%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 10 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Back pain			
subjects affected / exposed	1 / 10 (10.00%)	3 / 29 (10.34%)	
occurrences (all)	1	3	
Pain in extremity			
subjects affected / exposed	1 / 10 (10.00%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 10 (0.00%)	2 / 29 (6.90%)	
occurrences (all)	0	2	
Infections and infestations			
Pneumonia serratia			
subjects affected / exposed	1 / 10 (10.00%)	0 / 29 (0.00%)	
occurrences (all)	1	0	
Pneumonia klebsiella			
subjects affected / exposed	1 / 10 (10.00%)	0 / 29 (0.00%)	
occurrences (all)	1	0	

Lower respiratory tract infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 29 (3.45%) 1	
COVID-19 subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0	2 / 29 (6.90%) 2	
Respiratory tract infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	2 / 29 (6.90%) 2	
Nasopharyngitis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	3 / 29 (10.34%) 3	
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1	1 / 29 (3.45%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 October 2021	The following changes were made as per Amendment 01 - 1. Updated the exclusion criteria. 2. Schedule of activities was updated. 3. Secondary objectives and endpoints were updated.
22 June 2022	The following changes were made as per Amendment 02 - 1. Updated inclusion and exclusion criteria. 2. Schedule of activities was updated.
26 April 2023	The following changes were made as per Amendment 03 - 1. Updated inclusion and exclusion criteria. 2. Schedule of activities was updated. 3. Secondary objectives and endpoints were updated.
15 May 2023	The following changes were made as per Amendment 04 - 1. Updated inclusion and exclusion criteria. 2. Schedule of activities was updated. 3. Secondary objectives and endpoints were updated.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported