Clinical trial results:
A single center, open-label, two-period, non-randomized, paired-design study to compare steady-state plasma levels following switch from a 10 mg/ml treprostinil formulation to a 20 mg/ml treprostinil formulation in patients with pulmonary arterial hypertension (PAH)

Summary

EudraCT number	2021-004002-21
Trial protocol	AT
Global end of trial date	21 December 2021

Results information

Result version number	v1 (current)
This version publication date	03 March 2023
First version publication date	03 March 2023

Trial information

Trial identification

Sponsor protocol code	Bio-Eq-20

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	AOP Orphan Pharmaceuticals GmbH
Sponsor organisation address	Leopold-Ungar-Platz 2, Vienna, Austria, 1190
Public contact	Clinical Project Manager, AOP Orphan Pharmaceuticals GmbH, bio-eq-20@aoporphan.com
Scientific contact	Clinical Project Manager, AOP Orphan Pharmaceuticals GmbH, bio-eq-20@aoporphan.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	07 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 December 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the interchangeability of 20 mg/ml treprostinil compared to a 10 mg/ml treprostinil formulation by using pharmacokinetic (PK) endpoints.

Protection of trial subjects:

The Investigator obtained a freely given signed ICF, with name and date and time noted by the patient before the patient was exposed to any study-related procedure. The study was carried out in compliance with the principles of Good Clinical Practice (GCP), data protection and confidentiality were handled in compliance with local laws.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 November 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 12
Worldwide total number of subjects	12
EEA total number of subjects	12

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)	9
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients aged 18 years at screening or above with confirmed PAH diagnosis and who met all inclusion and exclusion criteria, were invited to participate in the study.

Pre-assignment

Screening details:

Patients who fulfill inclusion and exclusion criteria were enrolled into the study after giving their informed consent. A total of 12 patients was screened and were enrolled into the study.

Period 1

Period 1 title	Non-IMP - 10 mg/ml treprostinil
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Non-IMP - 10 mg/ml treprostinil

Arm description: -

Arm type	Non-IMP - 10 mg/ml treprostinil
Investigational medicinal product name	Non-IMP - 10 mg/ml treprostinil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Patients who were already receiving 10 mg/ml treprostinil as continuous SC infusion via an ambulatory infusion pump as standard treatment for their PAH disease and on a stable dose of at least 15 ng/kg/min since at least 2 weeks.

Number of subjects in period 1	Non-IMP - 10 mg/ml treprostinil
Started	12
Completed	12

Period 2

Period 2 title	IMP - 20 mg/ml treprostinil
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	IMP - 20 mg/ml treprostinil

Arm description:

The patients started with period 2 in the morning at 09:00 hours clock time after non-IMP was switched to the 20 mg/ml treprostinil formulation.

Arm type	20 mg/ml treprostinil
Investigational medicinal product name	20 mg/ml treprostinil
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered as continuous subcutaneous infusion via an ambulatory infusion pump.
Dosage and regimen: Each patient was administered 20 mg/ml treprostinil formulation for 24 hours maintaining the same dose used for at least 2 weeks prior to study start.

Number of subjects in period 2	IMP - 20 mg/ml treprostinil
Started	12
Completed	12

Baseline characteristics

Reporting groups

Reporting group title	Non-IMP - 10 mg/ml treprostinil

Reporting group description:

Number of subjects at baseline: 12

Reporting group values	Non-IMP - 10 mg/ml treprostinil	Total	
Number of subjects	12	12	
Age categorical Units: Subjects			
aged 18 years or above	12	12	
Gender categorical Units: Subjects			
male	7	7	
female	5	5	

Subject analysis sets

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS included all patients who have signed the informed consent (i.e., including screening failures plus subject enrolled). The FAS is the primary set used for patient disposition and baseline characteristics, analyses of the secondary endpoint and safety data.

Reporting group values	FAS		
Number of subjects	12		
Age categorical Units: Subjects			
aged 18 years or above	12		
Gender categorical Units: Subjects			
male	7		
female	5		

End points

End points reporting groups

Reporting group title	Non-IMP - 10 mg/ml treprostinil
Reporting group description: -	
Reporting group title	IMP - 20 mg/ml treprostinil

Reporting group description:

The patients started with period 2 in the morning at 09:00 hours clock time after non-IMP was switched to the 20 mg/ml treprostinil formulation.

Subject analysis set title	FAS
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS included all patients who have signed the informed consent (i.e., including screening failures plus subject enrolled). The FAS is the primary set used for patient disposition and baseline characteristics, analyses of the secondary endpoint and safety data.

Primary: Average concentration of treprostinil at steady-state (Cavg.ss)

End point title	Average concentration of treprostinil at steady-state (Cavg.ss)

End point description:

To evaluate the primary endpoint a two-way ANOVA model was fitted using the ln-transformed Cavg,ss as output variable including Patient N° and period as categorical covariates.
The point estimate, geometric mean ratio was obtained by back transformation from the ln-scale of the estimated treatment covariate coefficient (i.e., difference of ln(Cavg,ss) between periods). The two-sided 90% confidence interval of the point estimate was obtained by back transformation from the ln-scale of the two-sided 90% confidence interval of the estimated treatment covariate coefficient. Bioequivalence was to be concluded if the 2-sided 90% CI is contained within the closed interval [0.8, 1.25].

End point type	Primary

End point timeframe:

Two 24h periods - one 24h period on non-IMP (10 mg/ml TRE) followed by 24h period on IMP (20 mg/ml TRE)

End point values	Non-IMP - 10 mg/ml treprostinil	IMP - 20 mg/ml treprostinil		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	12		
Units: pg/ml				
arithmetic mean (standard deviation)	10.3850 (± 5.89362)	9.2863 (± 6.11273)		

Statistical analyses

Statistical analysis title	Primary Endpoint Analysis

Statistical analysis description:

The point estimate of the ratio of the geometric mean of IMP to the geometric mean of the non-IMP for Cavg,ss was obtained from the ANOVA model by back transformation from the ln-scale of the estimated treatment covariate coefficient (i.e., difference of ln(Cavg,ss) between periods). The corresponding two-sided CI90% of the point estimate was obtained from the ANOVA model by back transformation from the ln-scale of the two-sided CI90% of the estimated treatment covariate coefficient.

Comparison groups	Non-IMP - 10 mg/ml treprostinil v IMP - 20 mg/ml treprostinil
Number of subjects included in analysis	24
Analysis specification	Pre-specified
Analysis type	equivalence[1]
Method	ANOVA
Parameter estimate	GMR
Point estimate	0.88
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.81
upper limit	0.97

Notes:

[1] - In total, 12 subjects were analyzed in period 1 and period 2, which are automatically calculated and displayed as "Number of subjects included in analysis: *24"

Secondary: Average pain scale score

End point title	Average pain scale score

End point description:

The pain scale was designed as a 5-scale intensity score (ranging from 1 no pain to 5 extreme pain) (score 1 = no pain; score 2 = slight pain; score 3 = moderate pain; score 4 = severe pain; score 5 = extreme pain).
The secondary endpoint analysis was performed using descriptive statistics.

End point type	Secondary

End point timeframe:

The local infusion site tolerability was assessed per patient by a non-validated pain scale at screening in period 1 (4 h, 24h) and in period 2 (28h, 48h).

End point values	FAS			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: NA				
arithmetic mean (standard deviation)				
Screening	1.4 (± 0.51)			
Period P1-4h	1.6 (± 0.51)			
Period P1-24h	1.3 (± 0.49)			
Period P2-28h	1.4 (± 0.51)			
Period P2-48	1.2 (± 0.39)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were recorded throughout the study from screening until the subject completed the study.	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.0
Reporting groups	
Reporting group title	Period 1
Reporting group description: -	
Reporting group title	Period 2
Reporting group description: -	
Reporting group title	Overall
Reporting group description: -	
Reporting group title	AE over both Periods
Reporting group description:	
AEs reported as overlapping from Period 1 to Period 2	

Serious adverse events	Period 1	Period 2	Overall
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)	0 / 12 (0.00%)	0 / 12 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			

Serious adverse events	AE over both Periods		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 12 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Period 1	Period 2	Overall
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 12 (58.33%)	7 / 12 (58.33%)	9 / 12 (75.00%)

Vascular disorders Flushing subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0	1 / 12 (8.33%) 1	1 / 12 (8.33%) 1
General disorders and administration site conditions Infusion Site Pain subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	7 / 12 (58.33%) 7 0 / 12 (0.00%) 0	6 / 12 (50.00%) 6 1 / 12 (8.33%) 1	8 / 12 (66.67%) 8 1 / 12 (8.33%) 1

Non-serious adverse events	AE over both Periods		
Total subjects affected by non-serious adverse events subjects affected / exposed	2 / 12 (16.67%)		
Vascular disorders Flushing subjects affected / exposed occurrences (all)	0 / 12 (0.00%) 0		
General disorders and administration site conditions Infusion Site Pain subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all)	2 / 12 (16.67%) 2 0 / 12 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 November 2021	Following inclusion and exclusion criteria were adjusted to ensure fast enrolment of the patients: • Inclusion of patients aged 18 years and older • Patients on a stable dose of at least 15 ng/kg/min instead of 30 ng/kg/min • No limitations regarding the BMI • Infusion site pain not > 3 (5-scale intensity score) at the time of screening.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported