



Clinical trial results:

A double blind controlled clinical study to investigate the efficacy and tolerability of subcutaneous Treprostinil sodium in patients with severe non-operable Chronic Thromboembolic Pulmonary Hypertension (CTREPH II)

Summary

EudraCT number	2008-006441-10
Trial protocol	AT CZ SK DE
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	25 April 2018
First version publication date	25 April 2018

Trial information

Trial identification

Sponsor protocol code	116-02
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01416636
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	SciPharm Sàrl
Sponsor organisation address	7, Fausermillen, Merttert, Luxembourg, 6689
Public contact	Clinical Trial Management, SciPharm Sàrl, +43 6649639319, b.tan@scipharm.eu
Scientific contact	Clinical Trial Management, SciPharm Sàrl, +43 6649639319, b.tan@scipharm.eu

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	Interim
Date of interim/final analysis	10 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 November 2016
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the effect of subcutaneous Treprostinil sodium on 6MWT distance after 24 weeks in patients with severe non-operable chronic thromboembolic pulmonary hypertension

Protection of trial subjects:

During their participation in the clinical trial the patients were insured as defined by legal requirements. The compensation of the patient in the event of study-related injuries complied with the applicable regulations.

Each subject had the right to withdraw the study at any timepoint without negative affect on subjects future health care.

The health status of trial subjects was assessed every 6 weeks during the study visits. All adverse events and adverse drug reactions had to be reported in the CRF. In addition, trial subject had to rate infusion site pain on a scale from 0 (no pain) to 10 (very severe pain).

If a subject did not tolerate an increase of the dose due to adverse drug reactions, the dose could be reduced. In the discretion of the investigator the dose was up titrated again after stabilization or recovery of the adverse drug reaction.

Furthermore, in case of deterioration of the underlying disease or the general health status, the subject had to be withdrawn from the study if withdrawal criteria were met.

Background therapy:

Patients were not allowed to receive any prostanoids within 30 days before Screening or be scheduled to receive any prostanoids during the participation in the study.

It was also prohibited to include patients who received any new type of chronic therapy (a different category of vasodilator or diuretic) for PH within 30 days prior to Randomization, except anticoagulants. If a patient received another type of vasodilator for PH for more than 30 days prior to Randomization the medication should be kept on stable doses throughout the blinded phase of its study participation.

Evidence for comparator:

Based on published clinical data (Skoro-Sajer, 2007) the CTREPH 116-02 trial was designed as a prospective randomized double-blind controlled study comparing high dose sc. Treprostinil (target dose ~ 30 ng/kg/min.) with low dose sc. Treprostinil (target dose ~ 3 ng/kg/min). A classical placebo controlled design was considered not feasible due to the characteristic smell of the Treprostinil solution and the anticipated local side reactions induced by subcutaneously administered Treprostinil. However earlier investigations with subcutaneous Treprostinil indicated that infusion site pain is not directly dependent on the rate of dose increase (Skoro-Sajer et al 2008). Therefore, a low dose comparator was determined to facilitate complete double blinding. Furthermore, this approach avoided 6 months placebo treatment of severely sick study participants which might be considered unethical.

The determination of target doses in low and high dose groups was based on published literature and the clinical experience of investigators with the use of Treprostinil in PAH patients, whose risk benefit profile was expected to be similar in the CTEPH population. Long-term data showed a positive outcome of exercise capacity after three years at an average dose of 40ng/kg/min. in PAH and CTEPH patients (Lang et al 2006). A significant increase of long term survival in IPAH patients was observed after one year at an average dose of 26 ng/kg/min. in another analysis (Barst et al 2006). In contrast doses of < 5ng/kg/min. showed no clinical improvement (Simonneau et al 2002).

Actual start date of recruitment	09 March 2009
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Ethical reason
Long term follow-up duration	100 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Austria: 54
Country: Number of subjects enrolled	Czech Republic: 34
Country: Number of subjects enrolled	Germany: 1
Worldwide total number of subjects	105
EEA total number of subjects	105

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)	42
From 65 to 84 years	62
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

First patient was enrolled on March 9, 2009 and the last patient completed the study on November 24, 2016.

Recruitment of subjects was performed continuously in all participating study centres.

Recruitment for the study was stopped due to planned interim analysis and restarted afterwards.

Pre-assignment

Screening details:

The selection of patients was performed according to inclusion and exclusion criteria defined in the study protocol CTREPH 116-02.

138 patients were assessed for eligibility, 33 did not qualify for enrollment (e.g. operable CTEPH, no consent given).

105 patients qualified for enrollment.

Period 1

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

Blinding implementation details:

For this clinical trial Treprostinil sodium was used in the strengths of 1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml. The drug was administered subcutaneously by an infusion pump.

The dose differences in the two groups (low dose & high dose) were induced due to the different strengths of Treprostinil vials. This means that patients in both arms always used the same infusion rates for the subcutaneous infusion pumps.

Arms

Are arms mutually exclusive?	Yes
Arm title	low dose

Arm description:

Dose was titrated to a target dose of 3ng/kg/min. Due to the predefined infusion rate setting schedule and the handling requirements of the infusion pump an interim dose of up to 6 ng/kg/min could be reached for few days at the end of the periods 1,2 and 3. This depended on the patient's exact weight and is caused by the limited infusion rate setting possibility of the infusion pump.

Arm type	Active comparator
Investigational medicinal product name	Treprostinil sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

The drug was administered subcutaneously by an infusion pump. Dose was titrated to a target dose of 3ng/kg/min. Due to the predefined infusion rate setting schedule and the handling requirements of the infusion pump an interim dose of up to 6 ng/kg/min could be reached for few days at the end of the periods 1,2 and 3. This depended on the patient's exact weight and is caused by the limited infusion rate setting possibility of the infusion pump.

The medication was provided in 20ml glas vials filled with 10ml solution for infusion. The vials for patients in the low dose group contained only solution with a dosage of 1mg/ml of Treprostinil sodium.

Arm title	high dose
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Arm description:

Dose were titrated to a target dose of 30ng/kg/min. Due to the predefined infusion rate setting schedule a dose of up to 33 ng/kg/min. could be reached.

Arm type	Experimental
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Investigational medicinal product name	Treprostinil sodium
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

The drug was administered subcutaneously by an infusion pump. Dose were titrated to a target dose of 30ng/kg/min. Due to the predefined infusion rate setting schedule a dose of up to 33 ng/kg/min. could be reached.

The medication was provided in 20ml glas vials filled with 10ml solution for infusion. The vials for patients in the high dose group contained solutions with a dosage of 1mg/ml, 2.5mg/ml, 5mg/ml and 10mg/ml of Treprostinil sodium. The strengths of the vials for the high dose group were raised continuously during the first 12 weeks (Period I – 1 mg/ml; Period II – 2.5 mg/ml; Period III – 5 mg/ml; Period IV-VIII – 10mg/ml).

Number of subjects in period 1	low dose	high dose
Started	52	53
Termination Visit	46	45
Completed	46	45
Not completed	6	8
Adverse event, serious fatal	1	2
Adverse event, non-fatal	3	1
progression of concomitant disease	-	2
Lack of efficacy	2	3

Baseline characteristics

Reporting groups

Reporting group title	low dose
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Reporting group description:

Dose was titrated to a target dose of 3ng/kg/min. Due to the predefined infusion rate setting schedule and the handling requirements of the infusion pump an interim dose of up to 6 ng/kg/min could be reached for few days at the end of the periods 1,2 and 3. This depended on the patient's exact weight and is caused by the limited infusion rate setting possibility of the infusion pump.

Reporting group title	high dose
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Reporting group description:

Dose were titrated to a target dose of 30ng/kg/min. Due to the predefined infusion rate setting schedule a dose of up to 33 ng/kg/min. could be reached.

Reporting group values	low dose	high dose	Total
Number of subjects	52	53	105
Age categorical			
Units: Subjects			
Adults (18-64 years)	27	15	42
From 65-84 years	25	37	62
85 years and over	0	1	1
Age continuous			
Units: years			
arithmetic mean	60.58	68.06	
standard deviation	± 14.59	± 11.16	-
Gender categorical			
Units: Subjects			
Female	30	19	49
Male	22	34	56
WHO NYHA functional class			
Units: Subjects			
Class II	3	3	6
Class III	44	47	91
Class IV	5	3	8
6MWD (6-Minute Walking Distance)			
Units: meter			
arithmetic mean	299.13	307.66	
standard deviation	± 85.7	± 68.77	-
Borg Dyspnoea Score			
Scale from 0-11			
Units: 0-11			
arithmetic mean	5.19	4.77	
standard deviation	± 2.25	± 2.05	-
Minnesota Living with Heart Failure Questionnaire			
There were 21 items to be scored between 0 and 5 (0=no / 5=very much) A score sum was calculated for each patient and visits Baseline, week 12 and week 24.			
Units: 0-105			
arithmetic mean	45.79	42.32	
standard deviation	± 23.16	± 21.16	-
pro-BNP			

Units: pg/ml arithmetic mean standard deviation	2040.29 ± 1650.63	2300.98 ± 2624.4	-
mPAP (mean Pulmonary Arterial Pressure) Units: mmHg arithmetic mean standard deviation	49.77 ± 10.79	49.92 ± 12.35	-
PVR (Pulmonary Vascular Resistance) Units: dyn.s.cm ⁻⁵ arithmetic mean standard deviation	809.01 ± 296.67	845.11 ± 385.5	-
CO (Cardiac Output) Units: L/min arithmetic mean standard deviation	4.36 ± 1.35	4.28 ± 1.32	-
CI (Cardiac Index) Units: L/min/m ² arithmetic mean standard deviation	2.28 ± 0.64	2.25 ± 0.67	-
mRAP (mean Right Artrial Pressure) Units: mmHg arithmetic mean standard deviation	10.25 ± 5.55	9.7 ± 5.99	-
mPCWP (mean Pulmonary Capillary Wedge Pressure) Units: mmHg arithmetic mean standard deviation	9.53 ± 4.3	10.42 ± 4.87	-

End points

End points reporting groups

Reporting group title	low dose
Reporting group description: Dose was titrated to a target dose of 3ng/kg/min. Due to the predefined infusion rate setting schedule and the handling requirements of the infusion pump an interim dose of up to 6 ng/kg/min could be reached for few days at the end of the periods 1,2 and 3. This depended on the patient's exact weight and is caused by the limited infusion rate setting possibility of the infusion pump.	
Reporting group title	high dose
Reporting group description: Dose were titrated to a target dose of 30ng/kg/min. Due to the predefined infusion rate setting schedule a dose of up to 33 ng/kg/min. could be reached.	

Primary: Change in 6MWT distance

End point title	Change in 6MWT distance
End point description:	
End point type	Primary
End point timeframe: 6MWT distance was assessed at baseline and termination	

End point values	low dose	high dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52 ^[1]	53 ^[2]		
Units: meter				
arithmetic mean (standard deviation)	3.83 (± 56.21)	45.43 (± 71.29)		

Notes:

[1] - Missing values at termination were imputed by LOCF

[2] - Missing values at termination were imputed by LOCF

Attachments (see zip file)	primary efficacy endpoint/primary efficacy endpoint.jpg
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Statistical analyses

Statistical analysis title	analysis of change in 6MWT
Statistical analysis description: The pooled data of both stages were also evaluated using an ANCOVA model resulting in a two-sided p-value of 0.002 (0.001 one-sided), so also significantly in favour of the high dose group. As the normality assumption of the ANCOVA model residuals was rejected (p value < 0.0001), the pooled stage I and stage II data were additionally analysed using the Mann-Whitney U test with a two-sided p value of 0.0003 (0.00015 one-sided) for the dose effect.	
Comparison groups	low dose v high dose

Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in 6MWT distance after 12 weeks

End point title	Change in 6MWT distance after 12 weeks
End point description:	baseline value compared to 6MWT distance after 12 weeks
End point type	Secondary
End point timeframe:	baseline vs. 12 weeks

End point values	low dose	high dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52 ^[3]	53 ^[4]		
Units: meter				
arithmetic mean (standard deviation)	27.31 (± 57.29)	32.7 (± 63.45)		

Notes:

[3] - Missing values at week 12 were imputed by LOCF

[4] - Missing values at week 12 were imputed by LOCF

Statistical analyses

Statistical analysis title	analysis of change in 6MWT after 12 weeks
Comparison groups	low dose v high dose
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.27 ^[5]
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - The ANCOVA model resulted in a two-sided p-value of 0.71 (0.355 one-sided). As the normality assumption of the ANCOVA model residuals was rejected (p value < 0.0001), the analysis after 12 weeks was additionally performed using Mann-Whitney U-test.

Secondary: Change in WHO NYHA functional class

End point title	Change in WHO NYHA functional class
End point description:	Change in WHO NYHA functional class was compared between baseline and termination
End point type	Secondary
End point timeframe:	baseline vs. termination

End point values	low dose	high dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: subjects				
improved	9	27		
no change	36	22		
worse	3	2		
not done	4	2		

Statistical analyses

Statistical analysis title	analysis of change in WHO NYHA FC
Comparison groups	low dose v high dose
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0019 ^[6]
Method	Chi-squared

Notes:

[6] - Additional evaluation was performed using Fisher Exact test resulting in a p-value of 0.0012

Secondary: Change in Borg Dyspnoe Score

End point title	Change in Borg Dyspnoe Score
End point description:	
Change in BDS Score (0-11) was compared between baseline and termination	
End point type	Secondary
End point timeframe:	
baseline vs. termination	

End point values	low dose	high dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	48	48		
Units: 0-11				
arithmetic mean (standard deviation)	0.13 (± 2.43)	0.44 (± 2.21)		

Statistical analyses

Statistical analysis title	analysis of change in Borg Dyspnoea Score
Comparison groups	low dose v high dose

Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.307
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in Minnesota Living with Heart Failure Questionnaire

End point title	Change in Minnesota Living with Heart Failure Questionnaire
End point description: Change in Quality of Life assessed with the Minnesota Living with Heart Failure Questionnaire was compared between baseline and termination. A score sum was calculated for each patient and visit baseline and termination.	
End point type	Secondary
End point timeframe: baseline vs. termination	

End point values	low dose	high dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	50		
Units: 0-105				
arithmetic mean (standard deviation)	-4.63 (± 19.34)	-6.36 (± 22.9)		

Statistical analyses

Statistical analysis title	analysis of change in MQoL
Comparison groups	low dose v high dose
Number of subjects included in analysis	96
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.557
Method	Wilcoxon (Mann-Whitney)

Secondary: Clinical Worsening

End point title	Clinical Worsening
End point description: Clinical worsening was defined as:	
<ul style="list-style-type: none"> Decrease of 6MWD from Baseline of more than 20% Decrease of NYHA functional class from Baseline Hospitalization due to CTEPH with the need of additional PH specific treatment (need of additional diuretic therapy was also rated as PH specific treatment) Death due to CTEPH 	

End point type	Secondary
End point timeframe: whole study duration	

End point values	low dose	high dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	52	53		
Units: subjects				
Hospitalization due to CTEPH worsening	6	4		
Death due to CTEPH worsening	0	2		
Reduction of 6MWD < 20% compared to baseline	7	2		
Worsening of WHO NYHA functional class	4	2		
At least one finding of Clinical Worsening	12	7		

Statistical analyses

Statistical analysis title	analysis of Clinical Worsening
Comparison groups	low dose v high dose
Number of subjects included in analysis	105
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.214 ^[7]
Method	Fisher exact

Notes:

[7] - P-value given is the result of the "at least one finding of clinical worsening" category as this was the main analysis.

Secondary: change in pro-BNP levels

End point title	change in pro-BNP levels
End point description: The individual percentage change in pro-BNP level were assessed between baseline and termination.	
End point type	Secondary
End point timeframe: baseline vs. termination	

End point values	low dose	high dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	46	46		
Units: pg/ml				
arithmetic mean (standard deviation)	41.68 (± 104.2)	0.84 (± 63.32)		

Statistical analyses

Statistical analysis title	analysis of change in pro-BNP level
Statistical analysis description: individual percentage change in pro-BNP level were assessed using Mann-Whitney U-test.	
Comparison groups	low dose v high dose
Number of subjects included in analysis	92
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in mPAP

End point title	Change in mPAP
End point description:	
End point type	Secondary
End point timeframe: change in mPAP between baseline and termination	

End point values	low dose	high dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	47		
Units: mmHg				
arithmetic mean (standard deviation)	-0.4 (± 6.87)	-3.36 (± 8.04)		

Statistical analyses

Statistical analysis title	analysis of change in mPAP
Comparison groups	low dose v high dose
Number of subjects included in analysis	94
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.04
Method	Wilcoxon (Mann-Whitney)

Secondary: Change in PVR

End point title	Change in PVR
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End point description:

End point type	Secondary
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End point timeframe:

change in PVR between baseline and termination

End point values	low dose	high dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	48		
Units: dyn.s.cm ⁻⁵				
arithmetic mean (standard deviation)	72.96 (± 284.95)	-214.23 (± 324.28)		

Statistical analyses

Statistical analysis title	analysis of change in PVR
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Comparison groups	low dose v high dose
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Number of subjects included in analysis	95
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Analysis specification	Pre-specified
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Analysis type	superiority
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P-value	< 0.001
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Method	Wilcoxon (Mann-Whitney)
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Secondary: change in CO

End point title	change in CO
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End point description:

End point type	Secondary
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End point timeframe:

change in CO between baseline and termination

End point values	low dose	high dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	48		
Units: L/min				
arithmetic mean (standard deviation)	-0.22 (\pm 1.06)	0.63 (\pm 1.47)		

Statistical analyses

Statistical analysis title	analysis of change in CO
Comparison groups	low dose v high dose
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: change in CI

End point title	change in CI
End point description:	
End point type	Secondary
End point timeframe: change in CI between baseline and termination	

End point values	low dose	high dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	48		
Units: L/min/m ²				
arithmetic mean (standard deviation)	-0.16 (\pm 0.54)	0.42 (\pm 0.9)		

Statistical analyses

Statistical analysis title	analysis of change in CI
Comparison groups	low dose v high dose
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Wilcoxon (Mann-Whitney)

Secondary: change in mRAP

End point title	change in mRAP
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End point description:

End point type	Secondary
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End point timeframe:

change in mRAP between baseline and termination

End point values	low dose	high dose		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	47	48		
Units: mmHg				
arithmetic mean (standard deviation)	2.87 (± 6.82)	0.65 (± 5.08)		

Statistical analyses

Statistical analysis title	analysis of change in mRAP
Comparison groups	low dose v high dose
Number of subjects included in analysis	95
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.227
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE and ADR were assessed regularly during the study visits every 6 weeks. The investigator had the possibility to contact the patient in between the visit to follow up on adverse events as well as the patient could contact the study team at any time.

Adverse event reporting additional description:

Patients were asked if new adverse events developed since the last study visit. All adverse events and adverse drug reactions had to be documented in source documents and in the CRF. It had to be assessed if the event was related to the study drug by the investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups

Reporting group title	safety population
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Reporting group description:

Safety population:

The safety population accounts for 105 patients (all patients randomized with post Baseline safety data).

Serious adverse events	safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 105 (18.10%)		
number of deaths (all causes)	3		
number of deaths resulting from adverse events	3		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Polycythaemia vera			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haematoma			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Worsening of Pulmonary Hypertension			
subjects affected / exposed	2 / 105 (1.90%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	2 / 105 (1.90%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Right ventricular failure			
subjects affected / exposed	5 / 105 (4.76%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 1		
Syncope			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
General physical health deterioration			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Incarcerated hernia			

subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Haemoptysis			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Escherichia bacteraemia			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			

subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 105 (0.95%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	safety population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	104 / 105 (99.05%)		
Vascular disorders			
Worsening of Pulmonary Hypertension			
subjects affected / exposed	13 / 105 (12.38%)		
occurrences (all)	14		
Cardiac disorders			
Oedema peripheral			
subjects affected / exposed	17 / 105 (16.19%)		
occurrences (all)	21		
Right ventricular failure			
subjects affected / exposed	6 / 105 (5.71%)		
occurrences (all)	8		
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 105 (15.24%)		
occurrences (all)	19		
General disorders and administration site conditions			
Decreased appetite			
subjects affected / exposed	7 / 105 (6.67%)		
occurrences (all)	7		
Flushing			

subjects affected / exposed	8 / 105 (7.62%)		
occurrences (all)	9		
Infusion site erythema			
subjects affected / exposed	38 / 105 (36.19%)		
occurrences (all)	42		
Infusion site pain			
subjects affected / exposed	81 / 105 (77.14%)		
occurrences (all)	96		
Infusion site pruritus			
subjects affected / exposed	10 / 105 (9.52%)		
occurrences (all)	10		
Infusion site swelling			
subjects affected / exposed	7 / 105 (6.67%)		
occurrences (all)	7		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	46 / 105 (43.81%)		
occurrences (all)	51		
Nausea			
subjects affected / exposed	8 / 105 (7.62%)		
occurrences (all)	10		
Vomiting			
subjects affected / exposed	6 / 105 (5.71%)		
occurrences (all)	8		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 105 (6.67%)		
occurrences (all)	7		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	6 / 105 (5.71%)		
occurrences (all)	7		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 105 (5.71%)		
occurrences (all)	6		

Pain in extremity subjects affected / exposed occurrences (all)	12 / 105 (11.43%) 14		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	14 / 105 (13.33%) 15		
Metabolism and nutrition disorders Hypokalaemia subjects affected / exposed occurrences (all)	9 / 105 (8.57%) 11		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 March 2009	<p>Protocol version 3.0 was submitted and approved before the initiation of the study and inclusion of the first patient.</p> <p>1) Exclusion criteria: The intake of phosphodiesterase inhibitors (PDEIs) before and/or during the study participation was not any more prohibited. In patients receiving stable doses of PDEIs but still fulfilling all inclusion and exclusion criteria the concomitant medication is not expected to impact the study outcome or interfere with the study drug. In addition, it would not have been possible to reach sample size with only including treatment naïve patients because of the rareness of the disease. From an ethical point of view, it would not be possible to stop any treatments the patient received prior to the inclusion into the study.</p> <p>2) Questionnaire: Camphor Questionnaire was replaced by Minnesota Living With Heart Failure Questionnaire (MLHFQ) because it was identified as more appropriate for the evaluation of the study outcome and the fulfilling of requirements for the clinical trial.</p> <p>3) Observational efficacy assessments: The percentage of patients showing clinical improvement at the end of study was added as an observational endpoint.</p>
11 May 2009	<p>Protocol version 4.0, 19.03.2009</p> <p>1) Change of the sponsor: The CTREPH 116-02 trial was initiated by Univ. Prof. Dr. Irene Lang, Medical University of Vienna in 2008 as an investigator initiated trial. In order to facilitate the achievement of the predefined sample size it was necessary to recruit patients in study centres in different countries. However, the Medical University of Vienna was not able to take over the sponsorship of a multinational/multicentre trial therefore the sponsorship for the non-commercial clinical trial was assigned to Medical Research Network GmbH.</p> <p>2) Right heart catheterization: The period prior to inclusion from which results from right heart catheterization of the patient could be accepted to serve as reference for the proof of inclusion and exclusion criteria was prolonged from three to six months.</p>
23 September 2009	<p>Protocol version 5.0, 27.08.2009</p> <p>1) Exclusion criteria: Serious liver problems (Child-Pugh, class C), such as active gastrointestinal ulcer, intrabdominal haemorrhaging were added as exclusion criteria.</p> <p>2) Hospitalization: The possibility to hospitalize patients for carrying out the Baseline examinations or to specify the training with the delivery system was added to the protocol.</p>
21 May 2010	<p>Protocol version 6.0, 21.04.2010</p> <p>1) Control dose: The information, that interim doses of up to 5 ng/kg/min. could temporarily be reached in the low dose group between Baseline and week 12, was added to the protocol. This could not be prevented as all patients need to follow the same up-titration schedule (depending on their weight) in order to guarantee blinding. Furthermore, the infusion pump only allows dose adaptations of a minimum of 0.002 ml/h. This could also lead to very slight dose variations which neither impact study outcome nor patients' safety.</p> <p>2) Stopping rules, withdrawal criteria and procedures: A passage about the criteria which could lead to premature termination of the clinical trial was added.</p> <p>3) Blinding: Following request from the German authorities a chapter describing the blinding and randomization procedures was added.</p>
10 December 2010	<p>Protocol version 7.0, 19.10.2010</p> <p>1) Safety evaluations: A procedure of monitoring infusion site pain during study participation was added in order to have a better overview about the occurrence of infusion site pain. The intensity of infusion site pain since last visit was assessed at each scheduled visit using a visual analogue scale (VAS) (1-10) which had to be completed by the investigator according to the patient's survey.</p>

12 December 2011	<p>Protocol version 8.0, 22.11.2011</p> <p>1) Blood chemistry: The parameter Bicarbonate/CO2 was deleted due to missing medicinal relevance for CTEPH.</p> <p>2) Coagulation times: The parameter PTT was added due to recommendation of the investigators.</p>
16 January 2013	<p>version 10.0, 30.11.2012</p> <p>1) Sponsor: Sponsorship was transferred from MRN-Medical Research Network GmbH to SciPharm Sàrl.</p> <p>2) Genetic sub-study: Genetic sub-study was not continued.</p> <p>3) Secondary objectives/endpoints: The criteria for clinical worsening were adapted according to internationally established approaches. Additionally, to the Borg score the heart rate and the oxygen saturation measurement during 6MWT were added as secondary endpoints.</p> <p>4) Exploratory objectives/endpoints: BNP and ADMA measurements and percentage of patients with clinical improvement were deleted as endpoints. The hemodynamic parameters to be evaluated were clearly defined and analysis of signs and symptoms of the CTEPH was added.</p> <p>5) Safety objectives/endpoints: Safety evaluations were adapted according to the international guidelines.</p> <p>6) Proof of non-operability assessment: A clearly defined evaluation process of the non-operability assessment of the patients was established</p> <p>7) Satellite centres: A process for including patients from foreign centres (not able to serve as study centres by their own) was defined. (This procedure was never established and is therefore not further explained in the CSR)</p> <p>8) Inclusion criteria: Adjusted to guarantee a proper selection with regard to the safety of the patients and the validity of data according to the GCP guideline.</p> <p>9) Exclusion criteria: Adjusted to guarantee a proper selection with regard to the safety of the patients and the validity of data according to the GCP guideline.</p> <p>10)Withdrawal criteria: Withdrawal criteria were defined and properly described. In the previous protocol versions, the withdrawal criteria were not specified in detail and explained in different sections of the protocol.</p> <p>was noch? AUSMISTEN!</p>
15 May 2013	<p>Protocol version 11.0, 12.03.2013</p> <p>1) Follow-up phase: A follow-up open label extension phase was added to the protocol in order to give the patient the possibility to be treated with Treprostinil sodium after finishing 24 weeks of the randomized, double-blinded phase of the clinical trial.</p> <p>2) Screening: It was added to the protocol that examinations which were already performed within 7 days prior to the Screening visit did not necessarily had to be repeated if the investigator considered that the results were still appropriate (e.g. laboratory testing, spirometry).</p> <p>3) Visit 3 & Visit 5: Under exceptional circumstances Visit 3 and Visit 5 could be performed by a phone call. It gave the patient the option to still participate in the study even though he/she was not able to come to the scheduled date of Visit 3 or Visit 5.</p> <p>4) Visit 4: A procedure was implemented if patient was not able to come to the visit on the scheduled date.</p>
04 December 2014	<p>Protocol version 12.0, 23.10.2014</p> <p>Following significant adaptations were included to the new protocol version:</p> <p>1) Biostatistician: Biostatistician was changed.</p> <p>2) Inclusion criteria: In order to follow the advice of medical experts it was defined that in case of recurrent PH after PEA, test results from before the surgery were acceptable if a typical specimen was harvested during PEA substantiating the diagnosis of CTEPH.</p> <p>3) Right heart catheterization: The measurement of SVR was deleted because the parameter was identified as not specific for CTEPH.</p> <p>4) Coagulation times: The measurement PT and PTT were deleted because the INR measurement is sufficient for monitoring the coagulation.</p> <p>5) Sample size recalculation: Based on the results of the interim analysis it was decided to continue the study and proceed with the originally planned sample size for stage II of n=23 per treatment group.</p> <p>6) Efficacy analysis: The statistical methods have been explained according to the expert review report from the medical University of Vienna.</p>

12 November 2015	<p>Protocol version 13.0, 29.09.2015</p> <p>1) Biostatistician: Biostatistician was changed as the Medical University of Vienna could not fulfil all requirements of a commercial trial.</p> <p>2) Treatment compliance: The defined compliance of 80-120% was changed to $\geq 80\%$.</p> <p>3) Intention to treat population: Data cleaning committee was implemented in order to decide about the validity of evaluation of the data after the end of trial.</p> <p>4) Sample size recalculation for stage II: It was defined that also data of the patients who did not reach the final visit were qualified for the analysis.</p>
09 February 2017	<p>Protocol version 14.0, 12.01.2017</p> <p>1) Efficacy assessments: In course of discussions with the consulting statistician it was decided not to evaluate the time to clinical worsening (in the blinded study phase) but only comparing the number of cases in the two different dosage groups. Since clinical worsening parameters were only assessed in course of planned visits or hospitalizations the number of measurements would not provide valid results for a time-to clinical worsening assessment.</p> <p>2) Intention to treat population: It was redefined that intention to treat set comprises all patients randomized who received at least one dose of study medication.</p> <p>The redefinition was done to comply with the "Full Analysis Set" as described in "International Conference on Harmonisation; Guidance on Statistical Principles for Clinical Trials".</p> <p>3) Per protocol population: As a result of the adaption of the ITT population it was redefined that the per protocol set comprises all patients from the full analysis set for whom valid data were available.</p> <p>The data cleaning committee decides about the validity of specific data for the per-protocol analysis.</p> <p>4) Modified per protocol: Because after redefining the ITT and PP populations a modified per protocol was not relevant anymore.</p> <p>5) Efficacy analysis: It was defined that in case the data are not normally distributed and/or the homogeneity of variances could not be assumed, non-parametric testing is performed (Wilcoxon-Mann-Whitney U- test) to ensure correctness and validity of the study results.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
15 April 2012	<p>Recruitment for the study was stopped due to planned interim analysis.</p> <p>As the result of the interim analyses led to continuation of the study recruitment was restarted again.</p>	20 February 2013

Notes:

Limitations and caveats

None reported