Clinical trial results:
A 16 Week, Open Label, Multi-Centre, Study to Evaluate the Safety, Tolerability and Pharmacodynamic Effects of a Rapid Dose Titration Regimen of Subcutaneous Remodulin® Therapy in Subjects with Pulmonary Arterial Hypertension.

Summary

EudraCT number	2011-004631-31
Trial protocol	DE
Global end of trial date	20 March 2014

Results information

Result version number	v1 (current)
This version publication date	21 October 2016
First version publication date	21 October 2016

Trial information

Trial identification

Sponsor protocol code	REM-PH-416

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02847260
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	United Therapeutics Corporation
Sponsor organisation address	55 TW Alexander Drive, Research Triangle Park, United States, NC 27709
Public contact	Medical Information, United Therapeutics Corporation, +44 1932573848, druginfo@unither.com
Scientific contact	Medical Information, United Therapeutics Corporation, +44 1932573848, druginfo@unither.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	22 September 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 March 2014
Global end of trial reached?	Yes
Global end of trial date	20 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the safety and tolerability of a rapid dose titration regimen of subcutaneous (SC) Remodulin® therapy in patients with Pulmonary Arterial Hypertension (PAH).
Safety and tolerability of the rapid dose titration regimen was considered to be demonstrated by those clinical trial subjects that completed the 16 week treatment period of the study without experiencing any serious adverse events (SAEs) considered by the investigator to be possibly related to Remodulin.

The secondary objectives of the study were to assess the effect of SC Remodulin on exercise capacity using the six minute walk test (6MWT), N-terminal pro-brain natriuretic peptide (NT-proBNP), World Health Organisation (WHO) Functional Class, Borg dyspnoea score, quality of life (CAMPHOR), right ventricular function, haemodynamics, Patient Reported Site Pain Questionnaire (PRSPQ), symptoms of PAH and safety.

Protection of trial subjects:

The objective of this study was to evaluate safety, tolerability and clinical effects of a rapid up-titration dosing regimen of SC treprostinil using pro-active infusion site pain management.
> Subjects were hospitalised for a minimum of 72 hours upon initiation of SC Remodulin therapy.

> Subjects were fully trained on self-administration of SC Remodulin during hospitalisation. Training included the preparation of Remodulin, the operation and programming of the micro infusion pump, the connection and care of the infusion system, and management of SC infusion site.

> Subjects could not be discharged from hospital until fully competent with the infusion set and Remodulin dosing.

> Subjects and Medical staff were provided with a site pain management brochure. This brochure was a guide for subjects to use if they experienced any site pain. It detailed techniques to limit site pain and provided information on changing the infusion site, canula and drug reservoir.

> Every time a subject changed their infusion site they had to complete a PRSPQ. The PRSPQ was a self assessment and a means to measure the magnitude and longevity of the subject's site pain. The PRSPQ was reviewed at each study visit by trained site personnel with any persistent and untoward events recorded and managed by medics.

Background therapy:

Subjects were either treatment naive or receiving approved therapy for PAH (endothelin receptor antagonist (ERA) and/or phosphodiesterase (PDE)-5 inhibitor) for a minimum duration of 60 days and on a stable dose for at least 30 days prior to screening. All subjects were to remain on the same medication and doses from screening until study completion at the week 16 visit, unless the subject's safety was a concern and events experienced by the subject were deemed causally related to the background therapy (e.g. liver function test abnormality due to Bosentan therapy).

Conventional PAH therapies were permitted (e.g., oral vasodilators, digoxin and/or oxygen) provided the dose administered was stable at least 14 days before the start of the screening phase (i.e. date of obtaining written informed consent), with the exception of diuretics and anticoagulants which could be adjusted throughout the study as required. Unless they were considered essential to ensure subject safety, no dose adjustments or new vasodilator therapies were to be added to treatment of pulmonary hypertension during the course of the study. All conventional therapies were to remain constant for all study assessments.

Evidence for comparator:

No comparators were used for this study.

Actual start date of recruitment	16 April 2012
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	Germany: 39
Worldwide total number of subjects	39
EEA total number of subjects	39

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)	29
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Single territory (Germany), 10 centre study.
First site initiation April 2012 and first patient recruited on the 16th April 2012.
Enrollment ran for two years with the last patient/last visit on the 20th March 2014.
40 patients screened, 39 enrolled and 32 completed the 16 week study.
7 patients withdrew prematurely.

Pre-assignment

Screening details:

At screening, the following assessments were conducted: 6MWT, NT-proBNP, WHO Functional Class, Borg dyspnoea score, cardiopulmonary haemodynamics (RAP; mPAP; CI; PVR; PVRI; PCWP), TAPSE and TRJV, PAH symptoms and history, safety (vital signs, physical exam, local lab samples, medical history, serum pregnancy test, Adverse Events (AE))

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

N/A Open Label

Arms

Arm title	Overall Trial - Intent to treat

Arm description:

The overall trial arm included all subjects enrolled to the study. As this was an open label study, all enrolled subjects received study drug.

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

Dosage and administration details:

Remodulin was administered by continuous SC infusion using an ambulatory micro infusion pump and microbore infusion tubing connected to a cannula. The treatment phase consisted of 16 weeks of SC Remodulin therapy, which was initiated at baseline whilst subjects were hospitalised (minimum of 72 hours) and under medical supervision. The dose of SC Remodulin was optimised prior to the subject's discharge. Treatment was initiated at approximately 2.0 ng/kg/min with dose increments of 1-2 ng/kg/min applied approximately every 12 hours according to clinical response and tolerability. Following discharge, dose rate increments were permitted at 1-2 ng/kg/min with a minimum of 24 hours between each dose titration. Once a dose rate of 20 ng/kg/min was achieved the dose could be increased by 4 ng/kg/min again with each dose increment separated by at least 24 hours.

Number of subjects in period 1	Overall Trial - Intent to treat
Started	39
Completed	39

Period 2	
Period 2 title	Week 4
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Overall Trial - Intent to treat

Arm description:

The overall trial arm included all subjects enrolled to the study who completed all assessments up to and including Week 4. As this was an open label study, all enrolled subjects received study drug.

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

Dosage and administration details:

Treatment was continuous with up titrations made throughout the duration of the study. Dose rate increments were permitted at 1-2 ng/kg/min with a minimum of 24 hours between each dose titration. Once a dose rate of 20 ng/kg/min was achieved the dose could be increased by 4 ng/kg/min again with each dose increment separated by at least 24 hours.

Number of subjects in period 2	Overall Trial - Intent to treat
Started	39
Completed	39

Period 3

Period 3 title	Week 8
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Overall Trial - Intent to treat

Arm description:

The overall trial arm included all subjects enrolled to the study who completed all assessments up to and including Week 8. As this was an open label study, all enrolled subjects received study drug.

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

Dosage and administration details:

Treatment was continuous with up titrations made throughout the duration of the study. Dose rate increments were permitted at 1-2 ng/kg/min with a minimum of 24 hours between each dose titration. Once a dose rate of 20 ng/kg/min was achieved the dose could be increased by 4 ng/kg/min again with each dose increment separated by at least 24 hours.

Number of subjects in period 3	Overall Trial - Intent to treat
Started	39
Completed	35
Not completed	4
Adverse event, non-fatal	3
Clinical deterioration	1

Period 4

Period 4 title	Week 12
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Overall Trial - Intent to treat

Arm description:

The overall trial arm included all subjects enrolled to the study who completed all assessments up to and including Week 12. As this was an open label study, all enrolled subjects received study drug.

Arm type	Experimental

Investigational medicinal product name	Treprostinil
Investigational medicinal product code	
Other name	Remodulin
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Treatment was continuous with up titrations made throughout the duration of the study. Dose rate increments were permitted at 1-2 ng/kg/min with a minimum of 24 hours between each dose titration. Once a dose rate of 20 ng/kg/min was achieved the dose could be increased by 4 ng/kg/min again with each dose increment separated by at least 24 hours.

Number of subjects in period 4	Overall Trial - Intent to treat
Started	35
Completed	32
Not completed	3
Consent withdrawn by subject	2
Implantable Pump	1

Period 5

Period 5 title	Week 16
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Overall Trial - Intent to treat

Arm description:

The overall trial arm included all subjects enrolled to the study who completed all assessments up to and including Week 16. As this was an open label study, all enrolled subjects received study drug.

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

Dosage and administration details:

Treatment was continuous with up titrations made throughout the duration of the study. Dose rate increments were permitted at 1-2 ng/kg/min with a minimum of 24 hours between each dose titration. Once a dose rate of 20 ng/kg/min was achieved the dose could be increased by 4 ng/kg/min again with each dose increment separated by at least 24 hours.

Number of subjects in period 5	Overall Trial - Intent to treat
Started	32
Completed	32

Baseline characteristics

Reporting groups	
Reporting group title	Baseline

Reporting group description:

The reporting group included the entire study population. This was all subjects enrolled into the study who received study drug. As this was an open label study, all study subjects enrolled were included in this group.

Reporting group values	Baseline	Total	
Number of subjects	39	39	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	29	29	
85 years and over	10	10	
Gender categorical Units: Subjects			
Female	29	29	
Male	10	10	
Race Units: Subjects			
Black or African American	1	1	
White	38	38	
Ethnicity Units: Subjects			
Hispanic or Latino	0	0	
Non Hispanic or Latino	39	39	

End points

End points reporting groups

Reporting group title	Overall Trial - Intent to treat
Reporting group description:	
The overall trial arm included all subjects enrolled to the study. As this was an open label study, all enrolled subjects received study drug.	
Reporting group title	Overall Trial - Intent to treat
Reporting group description:	
The overall trial arm included all subjects enrolled to the study who completed all assessments up to and including Week 4. As this was an open label study, all enrolled subjects received study drug.	
Reporting group title	Overall Trial - Intent to treat
Reporting group description:	
The overall trial arm included all subjects enrolled to the study who completed all assessments up to and including Week 8. As this was an open label study, all enrolled subjects received study drug.	
Reporting group title	Overall Trial - Intent to treat
Reporting group description:	
The overall trial arm included all subjects enrolled to the study who completed all assessments up to and including Week 12. As this was an open label study, all enrolled subjects received study drug.	
Reporting group title	Overall Trial - Intent to treat
Reporting group description:	
The overall trial arm included all subjects enrolled to the study who completed all assessments up to and including Week 16. As this was an open label study, all enrolled subjects received study drug.	

Primary: Number of subjects that tolerated the rapid dose titration

End point title	Number of subjects that tolerated the rapid dose titration[1]
End point description:	
Patients were deemed to tolerate the dose if they completed the 16 week treatment phase without experiencing a study drug related SAE. No statistical analyses were performed, data were descriptively summarised.	
End point type	Primary
End point timeframe:	
Measured from initiation of study drug dose at baseline through to the Week 16 visit.	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No analysis was conducted because the end point was qualitative not quantitative.

End point values	Overall Trial - Intent to treat	Overall Trial - Intent to treat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	39	32		
Units: subjects	39	26		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Six Minute Walk Test distance

End point title	Change in Six Minute Walk Test distance

End point description:

Comparison of Six Minute Walk Test distance after 16 weeks of Remodulin therapy. Subjects presented are those that completed the 6MWT at both the Baseline and Week 16 visits only.
No statistical analyses were performed, data were descriptively summarised.

End point type	Secondary

End point timeframe:

Collected at Baseline and Week 16 visit.

End point values	Overall Trial - Intent to treat	Overall Trial - Intent to treat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: metres				
median (inter-quartile range (Q1-Q3))	351 (294 to 420)	419 (309 to 468)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Borg Dyspnoea Score

End point title	Change in Borg Dyspnoea Score

End point description:

Comparison of Borg Dyspnoea Scores after 16 weeks of Remodulin therapy. Subjects presented are those that completed the Borg Dyspnoea assessment at both the Baseline and Week 16 visits only.
No statistical analyses were performed, data were descriptively summarised.

End point type	Secondary

End point timeframe:

Borg Dyspnoea Score was measured at Baseline and Week 16.

End point values	Overall Trial - Intent to treat	Overall Trial - Intent to treat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: Score				
median (inter-quartile range (Q1-Q3))	4.5 (3 to 5)	3.5 (3 to 5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in NT-proBNP

End point title	Change in NT-proBNP

End point description:

Comparison of NT-proBNP after 16 weeks of Remodulin therapy. Subjects presented are those that completed the NT-proBNP assessment at both the Baseline and Week 16 visits only.
No statistical analyses were performed, data were descriptively summarised.

End point type	Secondary

End point timeframe:

Collected at Baseline and Week 16 visit.

End point values	Overall Trial - Intent to treat	Overall Trial - Intent to treat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	32		
Units: pg/mL				
median (inter-quartile range (Q1-Q3))	998.7 (521.5 to 2537.5)	701.5 (375.5 to 1377)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in WHO Functional Class

End point title	Change in WHO Functional Class

End point description:

Comparison of WHO Functional Class categorisation after 16 weeks of Remodulin therapy. Data presented is for those subjects that completed the 16 week study.
No statistical analyses were performed, data were descriptively summarised.

End point type	Secondary

End point timeframe:

WHO Functional Class data was collected throughout the study and shift data from Baseline to Week 16 generated.

End point values	Overall Trial - Intent to treat			
Subject group type	Reporting group			
Number of subjects analysed	32			
Units: subjects				
WHO Functional Class II to II	4			
WHO Functional Class II to III	1			
WHO Functional Class III to II	8			
WHO Functional Class III to III	18			
WHO Functional Class III to IV	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Pulmonary Vascular Resistance Index (PVRI)

End point title	Change in Pulmonary Vascular Resistance Index (PVRI)

End point description:

Comparison of Pulmonary Vascular Resistance Index after 16 weeks of Remodulin therapy. Subjects presented are those that completed the PVRI assessment at both the Baseline and Week 16 visits only. No statistical analyses were performed, data were descriptively summarised.

End point type	Secondary

End point timeframe:

Collected at Baseline and Week 16 visit.

End point values	Overall Trial - Intent to treat	Overall Trial - Intent to treat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	29		
Units: mmHg/min/m2/L				
median (inter-quartile range (Q1-Q3))	20.7 (16.1 to 24.7)	16.3 (12 to 21.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Systemic Vascular Resistance Index (SVRI)

End point title	Change in Systemic Vascular Resistance Index (SVRI)

End point description:

Comparison of Systemic Vascular Resistance Index after 16 weeks of Remodulin therapy. Subjects presented are those that completed the SVRI assessment at both the Baseline and Week 16 visits only. No statistical analyses were performed, data were descriptively summarised.

End point type	Secondary

End point timeframe:

Collected at Baseline and 16 Week visit.

End point values	Overall Trial - Intent to treat	Overall Trial - Intent to treat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	25	27		
Units: mmHg/min/m2/L				
median (inter-quartile range (Q1-Q3))	36.1 (30.8 to 42.1)	29.7 (24.7 to 36.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Cardiac Index (CI)

End point title	Change in Cardiac Index (CI)

End point description:

Comparison of Cardiac Index after 16 weeks of Remodulin therapy. Subjects presented are those that completed the CI assessment at both the Baseline and Week 16 visits only.
No statistical analyses were performed, data were descriptively summarised.

End point type	Secondary

End point timeframe:

Collected at Baseline and Week 16 visit.

End point values	Overall Trial - Intent to treat	Overall Trial - Intent to treat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	29		
Units: L/min/m2				
median (inter-quartile range (Q1-Q3))	2.2 (1.9 to 2.5)	2.6 (2.2 to 2.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Pulmonary Artery Pressure (PAPm)

End point title	Change in Pulmonary Artery Pressure (PAPm)

End point description:

Comparison of Pulmonary Artery Pressure after 16 weeks of Remodulin therapy. Subjects presented are those that completed the PAPm assessment at both the Baseline and Week 16 visits only.
No statistical analyses were performed, data were descriptively summarised.

End point type	Secondary

End point timeframe:

Collected at Baseline and Week 16 visit.

End point values	Overall Trial - Intent to treat	Overall Trial - Intent to treat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	29		
Units: mmHg				
median (inter-quartile range (Q1-Q3))	52 (47 to 62)	49 (44 to 60)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Tricuspid Annular Plane Systolic Excursion (TAPSE)

End point title	Change in Tricuspid Annular Plane Systolic Excursion (TAPSE)

End point description:

Comparison of TAPSE after 16 weeks of Remodulin therapy. Subjects presented are those that completed the TAPSE assessment at both the Baseline and Week 16 visits only.
No statistical analyses were performed, data were descriptively summarised.

End point type	Secondary

End point timeframe:

Collected at Baseline and Week 16

End point values	Overall Trial - Intent to treat	Overall Trial - Intent to treat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	31		
Units: cm				
median (inter-quartile range (Q1-Q3))	1.6 (1.3 to 1.8)	1.8 (1.6 to 2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Tricuspid Regurgitant Jet Velocity (TRJV)

End point title	Change in Tricuspid Regurgitant Jet Velocity (TRJV)

End point description:

Comparison of TRJV after 16 weeks of Remodulin therapy. Subjects presented are those that completed the TRJV assessment at both the Baseline and Week 16 visits only.
No statistical analyses were performed, data were descriptively summarised.

End point type	Secondary

End point timeframe:

Collected at Baseline and Week 16 visit.

End point values	Overall Trial - Intent to treat	Overall Trial - Intent to treat		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	27		
Units: m/sec				
median (inter-quartile range (Q1-Q3))	4.33 (3.94 to 4.74)	3.9 (3.4 to 4.53)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All serious adverse events (SAEs) were reported to the Sponsors Global Drug Safety department with a 24 hour reporting timeline & were coded according to MedDRA V.17.0. All SAEs were followed until resolution, death, or the subject was lost to follow up.

Adverse event reporting additional description:

Disease related events were assessed at Baseline and throughout the treatment phase by means of a brief physical examination and vital signs assessment (weight, blood pressure, heart rate and respiratory rate) with the subjects PAH symptoms (fatigue, dyspnoea, oedema, dizziness, syncope, chest pain, orthopnoea) rated as mild, moderate or severe.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	Overall Trial - Intent to treat

Reporting group description:

The overall trial - Intent to treat group included all subjects enrolled to the study. As this was an open label study, all enrolled subjects received study drug and adverse events were reported for these subjects throughout the study.

Serious adverse events	Overall Trial - Intent to treat		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 39 (28.21%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Rib fracture			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Right ventricular failure			

subjects affected / exposed	3 / 39 (7.69%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Headache				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Dizziness				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Syncope				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Infusion site pain				
subjects affected / exposed	2 / 39 (5.13%)			
occurrences causally related to treatment / all	2 / 2			
deaths causally related to treatment / all	0 / 0			
Fatigue				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Non-cardiac chest pain				
subjects affected / exposed	1 / 39 (2.56%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Abdominal pain			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal Impairment			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia, bacterial			

subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 39 (2.56%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Fluid overload			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Overall Trial - Intent to treat		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 39 (100.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	3 / 39 (7.69%)		
occurrences (all)	3		
Flushing			
subjects affected / exposed	2 / 39 (5.13%)		
occurrences (all)	2		
General disorders and administration site conditions			
Infusion site pain			
subjects affected / exposed	36 / 39 (92.31%)		
occurrences (all)	39		
Infusion site erythema			
subjects affected / exposed	10 / 39 (25.64%)		
occurrences (all)	10		
Oedema peripheral			
subjects affected / exposed	6 / 39 (15.38%)		
occurrences (all)	6		

Infusion site haemorrhage subjects affected / exposed occurrences (all)	5 / 39 (12.82%) 6		
Fatigue subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3		
Infusion site irritation subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 4		
Infusion site swelling subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 4		
Local swelling subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 4		
Injection site inflammation subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Oedema subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea subjects affected / exposed occurrences (all)	8 / 39 (20.51%) 8		
Cough subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3		
Epistaxis subjects affected / exposed occurrences (all)	4 / 39 (10.26%) 4		
Psychiatric disorders			
Sleep disorder subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2		
Cardiac disorders			

Angina pectoris subjects affected / exposed occurrences (all) Tachycardia subjects affected / exposed occurrences (all)	2 / 39 (5.13%) 2 2 / 39 (5.13%) 2		
Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Presyncope subjects affected / exposed occurrences (all)	 27 / 39 (69.23%) 28 7 / 39 (17.95%) 7 2 / 39 (5.13%) 4		
Blood and lymphatic system disorders Iron deficiency anaemia subjects affected / exposed occurrences (all)	 2 / 39 (5.13%) 2		
Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all)	 8 / 39 (20.51%) 8		
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Abdominal distension subjects affected / exposed occurrences (all)	 28 / 39 (71.79%) 28 18 / 39 (46.15%) 18 15 / 39 (38.46%) 16 3 / 39 (7.69%) 3		

Abdominal pain upper subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all)	 3 / 39 (7.69%) 3 1 / 39 (2.56%) 1		
Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all)	 3 / 39 (7.69%) 3 2 / 39 (5.13%) 2		
Musculoskeletal and connective tissue disorders Pain in jaw subjects affected / exposed occurrences (all) Rheumatic disorder subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all) Myalgia subjects affected / exposed occurrences (all) Arthralgia subjects affected / exposed occurrences (all) Back pain subjects affected / exposed occurrences (all) Bone pain subjects affected / exposed occurrences (all) Groin pain	 9 / 39 (23.08%) 9 7 / 39 (17.95%) 7 6 / 39 (15.38%) 7 6 / 39 (15.38%) 6 3 / 39 (7.69%) 3 2 / 39 (5.13%) 2 3 / 39 (7.69%) 3		

subjects affected / exposed occurrences (all)	3 / 39 (7.69%) 3		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Infusion site infection subjects affected / exposed occurrences (all) Infusion site abscess subjects affected / exposed occurrences (all)	 6 / 39 (15.38%) 8 4 / 39 (10.26%) 4 2 / 39 (5.13%) 2		
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) Hypokalaemia subjects affected / exposed occurrences (all)	 4 / 39 (10.26%) 4 4 / 39 (10.26%) 4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 February 2012	Amendment 1: The following changes were made in line with Federal Institute for Drugs and Medical Devices (BfArM) request: 1)The trial phase was changed from IV to Phase III (b). 2)Exclusion criterion 8 was revised to include all contraindications listed in the product information for Remodulin. 3)Local blood sampling was added to the screening visit. 4)Section 3.3.2.3 of the protocol, was revised to include "new" events so these could be captured alongside those that were serious, unusual, or there was a reasonable possibility that the event was caused by Remodulin therapy. 5)Further findings from the paper Skoro-Sajer N et al, Clin Pharmacokinet; 2008; 47 (9) were added to the protocol to provide further information on the risk/benefit rationale of the study. 6)The word "approximately" was added ahead of the starting dose of 2.0 ng/kg/min of study medication due to study drug dose being dependent on the weight of the subject and the flow rate of the infusion pump. The following changes were made in line with Central Ethics Committee request: 1)The protocol was updated to prospectively define the criteria that will be considered to demonstrate safety and tolerability of the rapid dose titration regimen. 2)Descriptive statistics were more specifically defined. 3)The subject coding and identifiers were simplified and outlined. 4)The entry for Patient initials in the "Patient reported site pain questionnaire" was removed.
11 October 2012	Amendment 2: 1) Exclusion criterion 2 was changed to allow subjects on inhaled prostacyclins into the study, given that the wash out time for this route of administration is minimal. 2) The window for accepting right heart catheterisation (RHC) data obtained prior to screening was increased from 4 weeks to 8 weeks due to the invasive nature of the assessment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The main limitations of the study were the small sample size and the study duration of 16 weeks. The study was an investigation of the titration phase thus there was no long-term follow up conducted.

Notes: