



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 (CAMPOR), 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/m ² /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/m ² /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) | 2 / 39 (5.13%) 2 | | |
| Tachycardia subjects affected / exposed occurrences (all) | 2 / 39 (5.13%) 2 | | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) | 27 / 39 (69.23%) 28 | | |
| Dizziness subjects affected / exposed occurrences (all) | 7 / 39 (17.95%) 7 | | |
| Presyncope subjects affected / exposed occurrences (all) | 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) | 28 / 39 (71.79%) 28 | | |
| Nausea subjects affected / exposed occurrences (all) | 18 / 39 (46.15%) 18 | | |
| Vomiting subjects affected / exposed occurrences (all) | 15 / 39 (38.46%) 16 | | |
| Abdominal distension subjects affected / exposed occurrences (all) | 3 / 39 (7.69%) 3 | | |

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

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 06 February 2012 | <p>Amendment 1:</p> <p>The following changes were made in line with Federal Institute for Drugs and Medical Devices (BfArM) request:</p> <ol style="list-style-type: none">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. <p>The following changes were made in line with Central Ethics Committee request:</p> <ol style="list-style-type: none">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 | <p>Amendment 2:</p> <ol style="list-style-type: none">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: