



Clinical trial results:

Intravenous Remodulin (Treprostinil) as Add-on Therapy for the Treatment of Persistent Pulmonary Hypertension of the Newborn: A Randomized, Placebo-Controlled, Safety and Efficacy Study Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2023-001028-40 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 17 May 2023 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 17 February 2024 |
| First version publication date | 17 February 2024 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | RIV-PN-201 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02261883 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | United Therapeutics Corp. |
| Sponsor organisation address | 55 TW Alexander Drive, North Carolina, United States, 14186 |
| Public contact | Clinical Trials Information, United Therapeutics Corp, +1 9014258167, |
| Scientific contact | Clinical Trials Information, United Therapeutics Corp, +1 9014258167, |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000207-PIP01-08 |
| 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 | 25 September 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 17 May 2023 |
| Global end of trial reached? | Yes |
| Global end of trial date | 17 May 2023 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

To explore the safety and treatment effect of intravenous (IV) Remodulin as add on therapy in neonates with PPHN compared to placebo. Efficacy will be assessed by a composite endpoint of clinical worsening through Day 14 as defined by one of the following:

- Death
- Initiation of extracorporeal mechanical oxygenation (ECMO) per institutional policies
- Need for additional treatment (initiation of an additional targeted pulmonary vasodilator therapy [e.g., phosphodiesterase-5 inhibitor [PDE-5i], endothelin receptor antagonist [ERA], prostanoid, L-citrulline]).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and the ICH E6 GCP guidance.

The parent(s) or legal guardian(s) of each subject enrolled in the study were provided with information related to the clinical study, including specifics related to subject participation. This was documented in a written ICF that was approved by the same IRB/IEC responsible for approval of the protocol at the clinical study site. Each ICF included the elements required by the FDA regulations in 21 CFR Part 50. Informed consent was obtained from each subject's parent(s) or legal guardian(s) prior to initiating any study-specific procedures in accordance with Title 21 CFR, Part 50 and ICH GCP guidance. A copy of the signed ICF was given to the subject's parent(s) or legal guardian(s), and the original was retained in the study site's records.

Subjects could have voluntarily withdrawn or been withdrawn from the study and/or study drug by the Investigator at any time for reasons including, but not limited to, the following:

- The subject's parent or legal guardian wished to withdraw the subject from further participation.
- A serious or life-threatening adverse event (AE) occurred, or the Investigator considered it necessary to discontinue study drug to protect the safety of the subject.
- The subject did not initiate study drug.

Background therapy:

None.

Evidence for comparator:

Placebo was the comparator in the Treatment period.

| | |
|---|--------------|
| Actual start date of recruitment | 29 July 2015 |
| 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 | United States: 42 |
| Worldwide total number of subjects | 42 |
| EEA total number of subjects | 0 |

Notes:

| Subjects enrolled per age group | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 42 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 23 centers in the US. 59 subjects were screened and 42 were enrolled in the study. 41 received study treatment: 20 subjects in the Remodulin group and 21 subjects in the placebo group. One subject assigned to Remodulin required ECMO prior to study drug administration and was not included in the ITT population.

Pre-assignment

Screening details:

Eligible subjects had 2 consecutive oxygenation indexes (OIs) of ≥ 15 , separated by at least 30 minutes, after having received inhaled nitric oxide (iNO) for at least 3 hours. All neonates underwent a screening echocardiogram (ECHO) to confirm the presence of pulmonary hypertension (PH).

Period 1

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

Blinding implementation details:

Investigators, research staff, attending clinicians, neonatal intensive care unit staff, parent(s)/guardian(s), and Sponsor were not aware of the treatment allocation. Once prepared, the appearance of active and placebo doses was identical. The site personnel were not unblinded to the treatment assignment of subjects unless required for safety reasons.

Arms

| | |
|------------------------------|-----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Remodulin |

Arm description:

Subjects received Remodulin as a continuous intravenous (IV) infusion. Venous access (preferred via central line [eg, umbilical venous catheter or peripherally inserted central venous catheter]) was required for the IV administration of study drug. Administration as a continuous subcutaneous (SC) infusion could be used in subjects when a dedicated central venous access could not be established, when subjects were too unstable to attempt to establish a dedicated central venous access line for IV administration of study drug, or for subjects initiated on an IV infusion of study drug who lost venous access.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | treprostinil |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Remodulin was supplied as 20-mL clear glass multi-dose vials sealed with a rubber-coated stopper and fitted with a cap containing 20 mg (1 mg/mL) of treprostinil as sterile solutions in water for injection. Composition: 1 mg/mL treprostinil. Each mL also contains 5.3 mg sodium chloride, 3 mg metacresol, 6.3 mg sodium citrate, and water for injection. Sodium hydroxide and hydrochloric acid may be added to adjust pH between 6.0 and 7.2.

Remodulin was delivered via continuous IV or SC infusion. Study drug was diluted to the appropriate concentration based upon the subject weight, dose, fluid constraints in this neonate patient population, and infusion pump flow rate capabilities. Study drug was diluted with 0.9% sodium chloride injection, sterile water for injection, or high-pH glycine diluent (sterile diluent for Flolan or sterile diluent for epoprostenol sodium) prior to IV administration as a continuous infusion using an infusion pump designed for IV drug delivery.

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Subjects received placebo as a continuous intravenous (IV) infusion. Venous access (preferred via central line [eg, umbilical venous catheter or peripherally inserted central venous catheter]) was required for the IV administration of study drug. Administration as a continuous subcutaneous (SC) infusion could be used in subjects when a dedicated central venous access could not be established, when subjects were too unstable to attempt to establish a dedicated central venous access line for IV administration of study drug, or for subjects initiated on an IV infusion of study drug who lost venous access.

| | |
|--|-----------------|
| Arm type | Placebo |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Placebo was supplied as 20-mL clear glass multi-dose vials sealed with a rubber-coated stopper and fitted with a cap containing 20 mg (1 mg/mL) of placebo as sterile solutions in water for injection.

Composition: sodium citrate USP/EP/JP, sodium chloride USP/EP/JP, sodium hydroxide pellets, metacresol, and citric acid (anhydrous). The pH was adjusted, if needed, with 1M citric acid and 1N sodium hydroxide.

Placebo was delivered via continuous IV or SC infusion. Study drug was diluted to the appropriate concentration based upon the subject weight, dose, fluid constraints (ie, flow rate/total daily volume) in this neonate patient population, and infusion pump flow rate capabilities. Study drug was diluted with 0.9% sodium chloride injection, sterile water for injection, or high-pH glycine diluent (sterile diluent for Flolan or sterile diluent for epoprostenol sodium) prior to IV administration as a continuous infusion using an infusion pump designed for IV drug delivery.

| Number of subjects in period 1^[1] | Remodulin | Placebo |
|---|-----------|---------|
| Started | 20 | 21 |
| Completed | 15 | 18 |
| Not completed | 5 | 3 |
| Physician decision | 1 | - |
| Consent withdrawn by subject | - | 1 |
| Death | 3 | 2 |
| Visit completed out of window | 1 | - |

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Subject 387001 was assigned to the Remodulin group but required ECMO prior to study drug administration. This subject was not included in the ITT Population.

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Remodulin |
|-----------------------|-----------|

Reporting group description:

Subjects received Remodulin as a continuous intravenous (IV) infusion. Venous access (preferred via central line [eg, umbilical venous catheter or peripherally inserted central venous catheter]) was required for the IV administration of study drug. Administration as a continuous subcutaneous (SC) infusion could be used in subjects when a dedicated central venous access could not be established, when subjects were too unstable to attempt to establish a dedicated central venous access line for IV administration of study drug, or for subjects initiated on an IV infusion of study drug who lost venous access.

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received placebo as a continuous intravenous (IV) infusion. Venous access (preferred via central line [eg, umbilical venous catheter or peripherally inserted central venous catheter]) was required for the IV administration of study drug. Administration as a continuous subcutaneous (SC) infusion could be used in subjects when a dedicated central venous access could not be established, when subjects were too unstable to attempt to establish a dedicated central venous access line for IV administration of study drug, or for subjects initiated on an IV infusion of study drug who lost venous access.

| Reporting group values | Remodulin | Placebo | Total |
|--|-----------|-----------|-------|
| Number of subjects | 20 | 21 | 41 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 20 | 21 | 41 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: days | | | |
| median | 2.0 | 3.0 | |
| full range (min-max) | 1 to 6 | 1 to 6 | - |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 10 | 10 | 20 |
| Male | 10 | 11 | 21 |
| Baseline OI | | | |
| Units: unit(s) | | | |
| median | 25.5 | 22.0 | |
| full range (min-max) | 4 to 46 | 6 to 46 | - |
| Baseline FiO2 | | | |
| Units: percent | | | |
| median | 100.0 | 100.0 | |
| full range (min-max) | 75 to 100 | 35 to 100 | - |

| | | | |
|---|-------------------------|--------------------------|---|
| Baseline PaO2 (mmHG) Units: millimetre(s) median full range (min-max) | 51.0 33 to 153 | 57.0 32 to 286 | - |
| Baseline PaO2/FiO2 Units: unit(s) median full range (min-max) | 0.57 0.4 to 1.6 | 0.69 0.4 to 2.9 | - |
| Inhaled nitric oxide Units: part per million median full range (min-max) | 20.0 20 to 20 | 20.0 20 to 20 | - |
| Baseline NT-proBNP Units: unit(s) median full range (min-max) | 11194.0 792 to 31366 | 16646.0 1011 to 70000 | - |

End points

End points reporting groups

| | |
|---|-----------|
| Reporting group title | Remodulin |
| Reporting group description: | |
| Subjects received Remodulin as a continuous intravenous (IV) infusion. Venous access (preferred via central line [eg, umbilical venous catheter or peripherally inserted central venous catheter]) was required for the IV administration of study drug. Administration as a continuous subcutaneous (SC) infusion could be used in subjects when a dedicated central venous access could not be established, when subjects were too unstable to attempt to establish a dedicated central venous access line for IV administration of study drug, or for subjects initiated on an IV infusion of study drug who lost venous access. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Subjects received placebo as a continuous intravenous (IV) infusion. Venous access (preferred via central line [eg, umbilical venous catheter or peripherally inserted central venous catheter]) was required for the IV administration of study drug. Administration as a continuous subcutaneous (SC) infusion could be used in subjects when a dedicated central venous access could not be established, when subjects were too unstable to attempt to establish a dedicated central venous access line for IV administration of study drug, or for subjects initiated on an IV infusion of study drug who lost venous access. | |

Primary: Clinical Worsening from Baseline to Day 14

| | |
|---|--|
| End point title | Clinical Worsening from Baseline to Day 14 |
| End point description: | |
| Due to the early termination of the study, interpretation of the efficacy endpoints was limited as the number of subjects analyzed was not sufficient to provide meaningful statistical analysis. | |
| End point type | Primary |
| End point timeframe: | |
| The primary endpoint in this study was if Remodulin reduced the incidence of clinical worsening in subjects with PPHN from Baseline to Day 14 compared to placebo. | |

| End point values | Remodulin | Placebo | | |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 | 21 | | |
| Units: Number | | | | |
| Clinical worsening: Yes | 8 | 12 | | |
| Clinical worsening: No | 12 | 9 | | |

Statistical analyses

| | |
|----------------------------|---------------------|
| Statistical analysis title | Chi-square test |
| Comparison groups | Remodulin v Placebo |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.2723 ^[1] |
| Method | Chi-squared |

Notes:

[1] - Not statistically significant.

Secondary: Change in Oxygenation Index (OI)

| | |
|-----------------|----------------------------------|
| End point title | Change in Oxygenation Index (OI) |
|-----------------|----------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change in OI from Baseline to Hours 12, 24, and 72; Days 7 and 14; and/or prior to study drug discontinuation/weaning.

| End point values | Remodulin | Placebo | | |
|-------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 ^[2] | 21 ^[3] | | |
| Units: unit(s) | | | | |
| median (full range (min-max)) | | | | |
| 12 hours | -2.0 (-41 to 37) | -3.5 (-29 to 34) | | |
| 24 hours | -8.5 (-40 to 23) | -5.5 (-30 to 58) | | |
| 72 hours | -7.0 (-40 to 65) | -10.0 (-41 to 83) | | |
| Day 7 | -9.5 (-40 to 36) | -11.0 (-43 to 42) | | |
| Day 14 | -12.0 (-40 to 36) | -14.0 (-35 to 42) | | |

Notes:

[2] - Corresponds to the ITT population.

[3] - Corresponds to the ITT population.

12 hours: N=20

24 hours: N=20

72 hours: N=20

Day 7/14: N=21

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Group t-test comparing change from baseline values |
|----------------------------|--|

Statistical analysis description:

Change from baseline to 12 hours

| | |
|-------------------|---------------------|
| Comparison groups | Remodulin v Placebo |
|-------------------|---------------------|

| | |
|---|---------------------------------------|
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.9235 ^[4] |
| Method | T-test comparing change from baseline |

Notes:

[4] - Not statistically significant

| | |
|-----------------------------------|--|
| Statistical analysis title | Group t-test comparing change from baseline values |
|-----------------------------------|--|

Statistical analysis description:

Change from baseline to 24 hours

| | |
|---|---------------------------------------|
| Comparison groups | Remodulin v Placebo |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.5977 ^[5] |
| Method | T-test comparing change from baseline |

Notes:

[5] - Not statistically significant.

| | |
|-----------------------------------|--|
| Statistical analysis title | Group t-test comparing change from baseline values |
|-----------------------------------|--|

Statistical analysis description:

Change from baseline to 72 hours

| | |
|---|---------------------------------------|
| Comparison groups | Remodulin v Placebo |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.7643 ^[6] |
| Method | T-test comparing change from baseline |

Notes:

[6] - Not statistically significant.

| | |
|-----------------------------------|--|
| Statistical analysis title | Group t-test comparing change from baseline values |
|-----------------------------------|--|

Statistical analysis description:

Change from baseline to day 7

| | |
|---|---------------------------------------|
| Comparison groups | Remodulin v Placebo |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.7458 ^[7] |
| Method | T-test comparing change from baseline |

Notes:

[7] - Not statistically significant.

| | |
|-----------------------------------|--|
| Statistical analysis title | Group t-test comparing change from baseline values |
|-----------------------------------|--|

Statistical analysis description:

Change from baseline to day 14

| | |
|-------------------|---------------------|
| Comparison groups | Remodulin v Placebo |
|-------------------|---------------------|

| | |
|---|---------------------------------------|
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.7795 ^[8] |
| Method | T-test comparing change from baseline |

Notes:

[8] - Not statistically significant.

Secondary: Change in PaO2/FiO2

| | |
|-----------------|---------------------|
| End point title | Change in PaO2/FiO2 |
|-----------------|---------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change in PaO2/fraction of inspired oxygen (FiO2) (P/F ratio) from Baseline to Hours 12, 24, and 72.

| End point values | Remodulin | Placebo | | |
|-------------------------------|---------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 ^[9] | 21 ^[10] | | |
| Units: unit(s) | | | | |
| median (full range (min-max)) | | | | |
| 12 hours | 0.11 (-0.5 to 10.5) | 0.10 (-2.3 to 4.1) | | |
| 24 hours | 0.35 (-0.4 to 9.3) | 0.27 (-2.3 to 7.1) | | |
| 72 hours | 0.50 (-0.4 to 4.8) | 0.65 (-2.3 to 7.5) | | |

Notes:

[9] - Corresponds to the ITT population.

[10] - Corresponds to the ITT population.

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Group t-test comparing change from baseline values |
|----------------------------|--|

Statistical analysis description:

Change from baseline to 12 hours

| | |
|---|---------------------------------------|
| Comparison groups | Remodulin v Placebo |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.1992 ^[11] |
| Method | T-test comparing change from baseline |

Notes:

[11] - Not statistically significant

| | |
|----------------------------|--|
| Statistical analysis title | Group t-test comparing change from baseline values |
|----------------------------|--|

Statistical analysis description:

Change from baseline to 24 hours

| | |
|-------------------|---------------------|
| Comparison groups | Remodulin v Placebo |
|-------------------|---------------------|

| | |
|---|---------------------------------------|
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.282 ^[12] |
| Method | T-test comparing change from baseline |

Notes:

[12] - Not statistically significant

| | |
|-----------------------------------|--|
| Statistical analysis title | Group t-test comparing change from baseline values |
|-----------------------------------|--|

Statistical analysis description:

Change from baseline to 72 hours

| | |
|---|---------------------------------------|
| Comparison groups | Remodulin v Placebo |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.6955 ^[13] |
| Method | T-test comparing change from baseline |

Notes:

[13] - Not statistically significant

Secondary: Change in pre- and post-ductal SpO2

| | |
|-----------------|-------------------------------------|
| End point title | Change in pre- and post-ductal SpO2 |
|-----------------|-------------------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change in pre- and post-ductal oxygen saturation of peripheral capillary oxygenation (SpO2) from Baseline to Hours 6, 12, 24, and 72.

| End point values | Remodulin | Placebo | | |
|-------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 ^[14] | 21 ^[15] | | |
| Units: unit(s) | | | | |
| median (full range (min-max)) | | | | |
| 6 hours | 3.0 (-6 to 13) | 1.0 (-10 to 7) | | |
| 12 hours | 3.0 (-7 to 17) | 0.5 (-7 to 12) | | |
| 24 hours | 3.0 (-12 to 15) | 1.0 (-17 to 11) | | |
| 72 hours | 0.0 (-4 to 16) | 1.5 (-21 to 8) | | |

Notes:

[14] - Corresponds to the ITT population.

6 hours: N=17

12 hours: N=17

24 hours: N=18

72 hours: N=18

[15] - Corresponds to the ITT population.

6 hours: N=20

12 hours: N=20

24 hours: N=20

72 hours: N=20

Statistical analyses

| | |
|--|--|
| Statistical analysis title | Group t-test comparing change from baseline values |
| Statistical analysis description: Change from baseline to 6 hours | |
| Comparison groups | Remodulin v Placebo |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.0247 ^[16] |
| Method | T-test comparing change from baseline |
| Notes: [16] - Statistically significant | |

| | |
|---|--|
| Statistical analysis title | Group t-test comparing change from baseline values |
| Statistical analysis description: Change from baseline to 12 hours | |
| Comparison groups | Remodulin v Placebo |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.0914 ^[17] |
| Method | T-test comparing change from baseline |
| Notes: [17] - Not statistically significant | |

| | |
|---|--|
| Statistical analysis title | Group t-test comparing change from baseline values |
| Statistical analysis description: Change from baseline to 24 hours | |
| Comparison groups | Remodulin v Placebo |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.1886 ^[18] |
| Method | T-test comparing change from baseline |
| Notes: [18] - Not statistically significant | |

| | |
|---|--|
| Statistical analysis title | Group t-test comparing change from baseline values |
| Statistical analysis description: Change from baseline to 72 hours | |
| Comparison groups | Remodulin v Placebo |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.1825 ^[19] |
| Method | T-test comparing change from baseline |
| Notes: [19] - Not statistically significant | |

Secondary: Change in NT-proBNP

| | |
|-----------------|---------------------|
| End point title | Change in NT-proBNP |
|-----------------|---------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Change in N-terminal pro-brain natriuretic peptide (NT-proBNP) at day 1, day 2, day 3, day 7 and day 14.

| End point values | Remodulin | Placebo | | |
|-------------------------------|--------------------------------|---------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 20 ^[20] | 21 ^[21] | | |
| Units: unit(s) | | | | |
| median (full range (min-max)) | | | | |
| Day 1 | -1577.00 (-21322.0 to 43388.0) | -1378.00 (-23203.0 to 17923.0) | | |
| Day 2 | -1955.00 (-24637.0 to 34599.0) | -4090.00 (-37390.0 to 14163.0) | | |
| Day 3 | -252.00 (-24623.0 to 30629.0) | -4090.00 (-49200.0 to 13550.0) | | |
| Day 7 | 484.00 (-24623.0 to 19970.0) | -11312.00 (-65387.0 to 12299.0) | | |
| Day 14 | -719.00 (-26283.0 to 56529.0) | -9003.00 (-65387.0 to 12299.0) | | |

Notes:

[20] - Corresponds to the ITT population.

Day 1: N=13

Day 2: N=15

Day 3: N=15

Day 7: N=15

Day 14: N=15

[21] - Corresponds to the ITT population.

Day 1: N=19

Day 2: N=21

Day 3: N=21

Day 7: N=21

Day 14: N=21

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | Group t-test comparing change from baseline values |
|----------------------------|--|

Statistical analysis description:

Change from baseline to day 1

| | |
|-------------------|---------------------|
| Comparison groups | Remodulin v Placebo |
|-------------------|---------------------|

| | |
|---|---------------------------------------|
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.3133 ^[22] |
| Method | T-test comparing change from baseline |

Notes:

[22] - Not statistically significant

| | |
|-----------------------------------|--|
| Statistical analysis title | Group t-test comparing change from baseline values |
|-----------------------------------|--|

Statistical analysis description:

Change from baseline to day 2

| | |
|---|---------------------------------------|
| Comparison groups | Remodulin v Placebo |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.1244 ^[23] |
| Method | T-test comparing change from baseline |

Notes:

[23] - Not statistically significant

| | |
|-----------------------------------|--|
| Statistical analysis title | Group t-test comparing change from baseline values |
|-----------------------------------|--|

Statistical analysis description:

Change from baseline to day 3

| | |
|---|---------------------------------------|
| Comparison groups | Remodulin v Placebo |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.0378 ^[24] |
| Method | T-test comparing change from baseline |

Notes:

[24] - Statistically significant

| | |
|-----------------------------------|--|
| Statistical analysis title | Group t-test comparing change from baseline values |
|-----------------------------------|--|

Statistical analysis description:

Change from baseline to day 7

| | |
|---|---------------------------------------|
| Comparison groups | Remodulin v Placebo |
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.0219 ^[25] |
| Method | T-test comparing change from baseline |

Notes:

[25] - Statistically significant

| | |
|-----------------------------------|--|
| Statistical analysis title | Group t-test comparing change from baseline values |
|-----------------------------------|--|

Statistical analysis description:

Change from baseline to day 14

| | |
|-------------------|---------------------|
| Comparison groups | Remodulin v Placebo |
|-------------------|---------------------|

| | |
|---|---------------------------------------|
| Number of subjects included in analysis | 41 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.0483 ^[26] |
| Method | T-test comparing change from baseline |

Notes:

[26] - Statistically significant

Secondary: Time to Clinical Worsening

| | |
|-----------------|----------------------------|
| End point title | Time to Clinical Worsening |
|-----------------|----------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to clinical worsening

| End point values | Remodulin | Placebo | | |
|-------------------------------|-------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 8 ^[27] | 12 ^[28] | | |
| Units: day | | | | |
| median (full range (min-max)) | 3.0 (1 to 8) | 3.0 (1 to 13) | | |

Notes:

[27] - Corresponds to the ITT population.

[28] - Corresponds to the ITT population.

Statistical analyses

| | |
|---|--------------------------|
| Statistical analysis title | Log-rank test |
| Comparison groups | Remodulin v Placebo |
| Number of subjects included in analysis | 20 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.3327 ^[29] |
| Method | Logrank |

Notes:

[29] - Not statistically significant

Secondary: Time to initiation of ECMO

| | |
|-----------------|----------------------------|
| End point title | Time to initiation of ECMO |
|-----------------|----------------------------|

End point description:

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline to ECMO initiation

| End point values | Remodulin | Placebo | | |
|-------------------------------|-------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 6 ^[30] | 7 ^[31] | | |
| Units: day | | | | |
| median (full range (min-max)) | 2.5 (1 to 8) | 3.0 (1 to 5) | | |

Notes:

[30] - Corresponds to the ITT population.

[31] - Corresponds to the ITT population.

Statistical analyses

| Statistical analysis title | Log-rank test |
|---|--------------------------|
| Comparison groups | Remodulin v Placebo |
| Number of subjects included in analysis | 13 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.8894 ^[32] |
| Method | Logrank |

Notes:

[32] - Not statistically significant

Secondary: Time to Discontinuation of iNO

| | |
|---|--------------------------------|
| End point title | Time to Discontinuation of iNO |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline to discontinuation of iNO | |

| End point values | Remodulin | Placebo | | |
|-------------------------------|--------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 12 ^[33] | 15 ^[34] | | |
| Units: day | | | | |
| median (full range (min-max)) | 7.5 (1 to 12) | 7.0 (1 to 11) | | |

Notes:

[33] - Corresponds to the ITT population.

[34] - Corresponds to the ITT population.

Statistical analyses

| Statistical analysis title | Log-rank test |
|----------------------------|---------------------|
| Comparison groups | Remodulin v Placebo |

| | |
|---|---------------|
| Number of subjects included in analysis | 27 |
| Analysis specification | Pre-specified |
| Analysis type | equivalence |
| P-value | = 0.4791 |
| Method | Logrank |

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Subjects with ongoing AEs at the time of hospital discharge were followed for their AEs until resolution. All SAEs were followed until resolution, death, or the subject was lost to followup, even if they were ongoing more than 4 weeks after last dose.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 26.0 |

Reporting groups

| | |
|-----------------------|-----------|
| Reporting group title | Remodulin |
|-----------------------|-----------|

Reporting group description: -

| | |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events | Remodulin | Placebo | |
|---|-----------------|-----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 8 / 20 (40.00%) | 3 / 21 (14.29%) | |
| number of deaths (all causes) | 3 | 2 | |
| number of deaths resulting from adverse events | | | |
| Congenital, familial and genetic disorders | | | |
| Congenital diaphragmatic hernia | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pyloric stenosis | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardio-respiratory arrest | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Laryngeal stenosis | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatobiliary disorders | | | |
| Liver disorder | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 1 / 21 (4.76%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 20 (5.00%) | 0 / 21 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------------------------|----------------------------------|--|
| Infections and infestations Sepsis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 1 / 20 (5.00%) 0 / 1 0 / 0 | 0 / 21 (0.00%) 0 / 0 0 / 0 | |
| Metabolism and nutrition disorders Lactic acidosis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 20 (0.00%) 0 / 0 0 / 0 | 1 / 21 (4.76%) 0 / 1 0 / 0 | |

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

| Non-serious adverse events | Remodulin | Placebo | |
|---|---|---|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 19 / 20 (95.00%) | 17 / 21 (80.95%) | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) Aspartate aminotransferase increased subjects affected / exposed occurrences (all) N-terminal prohormone brain natriuretic peptide increased subjects affected / exposed occurrences (all) | 3 / 20 (15.00%) 3 3 / 20 (15.00%) 3 0 / 20 (0.00%) 0 | 0 / 21 (0.00%) 0 1 / 21 (4.76%) 1 2 / 21 (9.52%) 2 | |
| Vascular disorders Hypotension subjects affected / exposed occurrences (all) | 8 / 20 (40.00%) 8 | 4 / 21 (19.05%) 4 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Thrombocytopenia | 5 / 20 (25.00%) 5 | 5 / 21 (23.81%) 5 | |

| | | | |
|---|----------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 4 / 20 (20.00%) 4 | 1 / 21 (4.76%) 1 | |
| Gastrointestinal disorders Oedema subjects affected / exposed occurrences (all) | 0 / 20 (0.00%) 0 | 2 / 21 (9.52%) 2 | |
| Respiratory, thoracic and mediastinal disorders Pneumothorax subjects affected / exposed occurrences (all) | 1 / 20 (5.00%) 1 | 2 / 21 (9.52%) 2 | |
| Skin and subcutaneous tissue disorders Dermatitis diaper subjects affected / exposed occurrences (all) | 3 / 20 (15.00%) 3 | 1 / 21 (4.76%) 1 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 29 August 2014 | <p>The main changes implemented with this amendment were:</p> <ul style="list-style-type: none">• Revised study design from an uncontrolled, open-label, single arm design to a controlled, blinded, comparator study.• Clarified the maximum amount of time a subject randomized to study drug would be enrolled in the study was 56 days.• Increased number of centers from up to 20 to up to 30.• Revised secondary objectives to identify time points for comparison between treatment arms.• Added change in P/F ratio, change in pre- and post-ductal SpO₂, and change in NT proBNP as secondary objectives.• Identified procedures for randomization and unblinding.• Revised safety sections to include definitions for unexpected AE, suspected adverse reaction, and disease-related AEs.• Updated the window for continued safety follow-up of subjects in the study to reflect the change in study duration. |
| 30 October 2015 | <p>The main changes implemented with this amendment were:</p> <ul style="list-style-type: none">• Increased number of centers to approximately 40.• Updated study duration description to include time of study withdrawal as an end of study participation.• Clarified end of study participation for a subject continuing on commercial Remodulin beyond Day 28.• Clarified sample size of approximately 70 subjects to be randomized.• Increased allowed number of subjects with congenital diaphragmatic hernia.• Added Chi-square test to test for treatment differences. Added efficacy analyses in the ITT Population. Revised analysis plan to include Group t-test analysis of secondary endpoints, Kaplan Meier estimate for time to event variables, and log-rank tests of treatment differences.• Added a second pre-planned DSMB review.• Updated administration description to allow continuous SC infusion. Added dosing guidelines for initiation of study drug as a SC infusion.• Clarified text regarding dilution of study drug and added information regarding acceptable diluents.• Added language regarding management of subjects on active study drug who needed to continue therapy beyond Day 28.• Revised text to clarify blinding in the study.• Added clarification that subjects should not be automatically unblinded upon initiation of ECMO, unless required for purposes of medically managing the subject.• Clarified timing of Day 7 and Day 14 assessments.• Allowed use of a recently performed historic ECHO.• Added that study drug should be initiated as soon as possible after randomization.• Clarified timing of assessments in a subject who would be continuing on commercial Remodulin and not weaning prior to Day 28.• Clarified when End of Study assessments should be performed.• Added that if withdrawal from study drug was warranted, then the dose of study drug was to be weaned until discontinued.• Clarified timing of FiO₂, NT-proBNP, and vital sign assessments.• Clarified AE reporting requirements. |

| | |
|---------------|--|
| 15 April 2016 | <p>The main changes implemented with this amendment were:</p> <ul style="list-style-type: none"> • Updated to identify the overall End of Study event. • Clarified access to treatment assignment. • Clarified that some Screening and Baseline assessments could be combined if conducted within 3 hours of randomization. • Added caution statements regarding use of Remodulin with CYP450 2C8 inhibitors/inducers, and other blood pressure lowering agents and anticoagulants. • Clarified that symptoms of the underlying disease under study were recorded in the eCRF and identified as disease-related events. |
|---------------|--|

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.

Due to the early termination of the study, interpretation of the efficacy endpoints was limited as the number of subjects analyzed was not sufficient to provide meaningful statistical analysis.

Notes: