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)	EMEA-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	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	
Metabolism and nutrition disorders			
Lactic acidosis			
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	

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	3 / 20 (15.00%)	0 / 21 (0.00%)	
occurrences (all)	3	0	
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 20 (15.00%)	1 / 21 (4.76%)	
occurrences (all)	3	1	
N-terminal prohormone brain natriuretic peptide increased			
subjects affected / exposed	0 / 20 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Vascular disorders			
Hypotension			
subjects affected / exposed	8 / 20 (40.00%)	4 / 21 (19.05%)	
occurrences (all)	8	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 20 (25.00%)	5 / 21 (23.81%)	
occurrences (all)	5	5	
Thrombocytopenia			

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	The main changes implemented with this amendment were: • 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	The main changes implemented with this amendment were: • 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	The main changes implemented with this amendment were: • 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: