Clinical trial results:
A MULTI-CENTRE, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND, TWO-ARMED, PARALLEL GROUP STUDY TO EVALUATE EFFICACY AND SAFETY OF INTRAVENOUS (IV) SILDENAFIL IN THE TREATMENT OF NEONATES WITH PERSISTENT PULMONARY HYPERTENSION OF THE NEWBORN (PPHN) OR HYPOXIC RESPIRATORY FAILURE (HRF) AND AT RISK FOR PPHN, WITH A LONG TERM FOLLOW-UP INVESTIGATION OF DEVELOPMENTAL PROGRESS 12 AND 24 MONTHS AFTER COMPLETION OF STUDY TREATMENT

Summary

EudraCT number	2012-002619-24
Trial protocol	BE GB SE ES AT DE NO IT NL DK FR
Global end of trial date	28 September 2020

Results information

Result version number	v2 (current)
This version publication date	08 April 2021
First version publication date	17 July 2019
Version creation reason	• Correction of full data set Basic Results being posted with final data / end of global study date need to be added to results

Trial information

Trial identification

Sponsor protocol code	A1481316

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01720524
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer Inc.
Sponsor organisation address	235 E 42nd Street, New York, United States, NY 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer Inc., 001 8007181021, ClinicalTrials.gov_Inquiries@pfizer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000671-PIP01-09

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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 January 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 October 2018
Global end of trial reached?	Yes
Global end of trial date	28 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy and safety of IV sildenafil when added to inhaled nitric oxide (iNO) for the treatment of neonates with PPHN or HRF and at risk for PPHN.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy:

All subjects were treated with iNO.

Evidence for comparator: -

Actual start date of recruitment	05 August 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 1
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Denmark: 4
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 1
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Norway: 1
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Sweden: 8
Country: Number of subjects enrolled	United Kingdom: 10
Country: Number of subjects enrolled	United States: 19

Worldwide total number of subjects	59
EEA total number of subjects	27

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	59
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 in two parts Part A (double-blind phase) and Part B (long-term, non-interventional phase).

Pre-assignment

Screening details:

Neonates with PPHN or HRF and at risk of PPHN who were receiving iNO treatment were evaluated in this study.

Period 1

Period 1 title	Part A (Double-blind Phase)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Assessor, Carer, Subject, Monitor, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	IV Sildenafil

Arm description:

Subjects received sildenafil intravenously based on their body weight at a loading dose of 0.1 milligrams per kg (mg/kg) for 30 minutes on Day 1 followed by a maintenance dose of 0.03 milligrams per kg per hour (mg/kg/hr), for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

Arm type	Experimental
Investigational medicinal product name	Sildenafil Citrate
Investigational medicinal product code	UK-092,480
Other name	Revatio
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

IV sildenafil at a loading dose of 0.1 mg/kg, for 30 minutes, on Day 1, followed by maintenance dose of 0.03 mg/kg/hr, for a minimum of 2 days and maximum of 14 days.

Arm title	Placebo

Arm description:

Subjects received placebo (0.9 % normal saline or dextrose 10%) at a rate matched to sildenafil infusion, intravenously, based on subject's weight for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo (0.9 percent [%] normal saline or dextrose 10%) intravenously for a minimum of 2 days and maximum of 14 days.

Number of subjects in period 1	IV Sildenafil	Placebo
Started	29	30
Completed	22	18
Not completed	7	12
Consent withdrawn by subject	-	1
Missed 28 day follow-up visit	1	1
Other	-	1
Adverse event	2	2
Insufficient Clinical Response	2	4
Death (during follow-up)	-	1
Death (not completed study treatment)	2	-
Lost to follow-up	-	1
Protocol deviation	-	1

Period 2

Period 2 title	Part B (Non-Interventional Phase)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	IV Sildenafil

Arm description:

Subjects received sildenafil intravenously based on their body weight at a loading dose of 0.1 milligrams per kg (mg/kg) for 30 minutes on Day 1 followed by a maintenance dose of 0.03 milligrams per kg per hour (mg/kg/hr), for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Placebo

Arm description:

Subjects received placebo (0.9 % normal saline or dextrose 10%) at a rate matched to sildenafil infusion, intravenously, based on subject's weight for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	IV Sildenafil	Placebo
Started	22	18
Completed	22	17
Not completed	5	9
Death	-	2
No longer willing to participate in study	1	4
Unspecified	2	-
Lost to follow-up	2	3
Joined	5	8
Continued to follow-up	5	8

Baseline characteristics

Reporting groups	
Reporting group title	IV Sildenafil
Reporting group description:	
Subjects received sildenafil intravenously based on their body weight at a loading dose of 0.1 milligrams per kg (mg/kg) for 30 minutes on Day 1 followed by a maintenance dose of 0.03 milligrams per kg per hour (mg/kg/hr), for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo (0.9 % normal saline or dextrose 10%) at a rate matched to sildenafil infusion, intravenously, based on subject's weight for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.	

Reporting group values	IV Sildenafil	Placebo	Total
Number of subjects	29	30	59
Age Categorical			
Safety population included all subjects treated with study treatment.			
Units: Subjects			
Newborns (0-27 days)	29	30	59
Age Continuous			
Safety population included all subjects treated with study treatment.			
Units: days			
arithmetic mean	1.7	1.9	
standard deviation	± 0.90	± 0.75	-
Gender Categorical			
Safety population included all subjects treated with study treatment.			
Units: Subjects			
Female	13	13	26
Male	16	17	33
Race			
Safety population included all subjects treated with study treatment.			
Units: Subjects			
White	19	16	35
Black	1	7	8
Asian	2	5	7
Other	3	1	4
Unspecified	4	1	5

End points

End points reporting groups

Reporting group title	IV Sildenafil

Reporting group description:

Subjects received sildenafil intravenously based on their body weight at a loading dose of 0.1 milligrams per kg (mg/kg) for 30 minutes on Day 1 followed by a maintenance dose of 0.03 milligrams per kg per hour (mg/kg/hr), for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo (0.9 % normal saline or dextrose 10%) at a rate matched to sildenafil infusion, intravenously, based on subject's weight for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

Reporting group title	IV Sildenafil

Reporting group description:

Subjects received sildenafil intravenously based on their body weight at a loading dose of 0.1 milligrams per kg (mg/kg) for 30 minutes on Day 1 followed by a maintenance dose of 0.03 milligrams per kg per hour (mg/kg/hr), for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

Reporting group title	Placebo

Reporting group description:

Subjects received placebo (0.9 % normal saline or dextrose 10%) at a rate matched to sildenafil infusion, intravenously, based on subject's weight for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

Subject analysis set title	Part B (Non-Interventional Phase): IV Sildenafil
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received sildenafil intravenously based on their body weight at a loading dose of 0.1 milligrams per kg (mg/kg) for 30 minutes on Day 1 followed by a maintenance dose of 0.03 milligrams per kg per hour (mg/kg/hr), for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

Subject analysis set title	Part B (Non-Interventional Phase): Placebo
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects received placebo (0.9 % normal saline or dextrose 10%) at a rate matched to sildenafil infusion, intravenously, based on subject's weight for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

Primary: Time on Inhaled Nitric Oxide (iNO) Treatment After Initiation of Intravenous (IV) Study Drug For Subjects Without Treatment Failure

End point title	Time on Inhaled Nitric Oxide (iNO) Treatment After Initiation of Intravenous (IV) Study Drug For Subjects Without Treatment Failure

End point description:

Time in days, on iNO treatment, for subjects without iNO treatment failure, was calculated 14 days from the initiation of IV study drug or hospital discharge, whichever occurred first. iNO treatment failure was defined as need for additional treatment targeting PPHN, need for extra corporeal membrane oxygenation (ECMO), or death during the study. The intent-to-treat population (ITT) included all randomized subjects treated with study treatment. Here, "Number of Subjects Analyzed" signifies number of subjects without iNO treatment failure.

End point type	Primary

End point timeframe:

14 days from the initiation of IV study drug or hospital discharge, whichever occurs first

End point values	IV Sildenafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	21	24		
Units: days				
least squares mean (confidence interval 95%)	4.1 (2.58 to 5.58)	4.1 (2.70 to 5.50)		

Statistical analyses

Statistical analysis title	IV Sildenafil vs. Placebo

Statistical analysis description:

Field appearing in section: "Number of subjects included in analysis", is an auto populated field from database
(sum of number of subjects analyzed for the reporting arms selected to report statistical data): which may not be the actual number of subjects contributing to statistical analysis. Only subjects without treatment failure were included in the analysis.

Comparison groups	IV Sildenafil v Placebo
Number of subjects included in analysis	45
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.985
Method	ANCOVA
Parameter estimate	Least square (LS) mean difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.08
upper limit	2.04
Variability estimate	Standard error of the mean
Dispersion value	1.02

Primary: Treatment Failure Rate

End point title	Treatment Failure Rate

End point description:

Treatment failure rate was defined as percentage of subjects who needed additional treatment targeting PPHN, needed ECMO, or died during the study. The ITT population included all randomized subjects treated with study treatment.

End point type	Primary

End point timeframe:

14 days from the initiation of IV study drug or hospital discharge, whichever occurs first

End point values	IV Sildenafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	30		
Units: percentage of subjects				
number (confidence interval 95%)	27.6 (11.3 to 43.9)	20.0 (5.7 to 34.3)		

Statistical analyses

Statistical analysis title	IV Sildenafil vs. Placebo
Comparison groups	IV Sildenafil v Placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4935
Method	Chi-squared
Parameter estimate	Difference in percentage
Point estimate	7.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.1
upper limit	29.3

Secondary: Time From Initiation of Intravenous (IV) Study Drug to Final Weaning of Mechanical Ventilation

End point title	Time From Initiation of Intravenous (IV) Study Drug to Final Weaning of Mechanical Ventilation

End point description:

Time in days, from initiation of IV study drug to final weaning of mechanical ventilation among subjects achieving final weaning of mechanical ventilation for PPHN was evaluated. Kaplan-Meier method was used for estimation. For subjects with mechanical ventilation beyond 336 hours (14 days) from initiation of IV study drug, data is censored at 14 days. The ITT population included all randomized subjects treated with study treatment.

End point type	Secondary

End point timeframe:

14 days from the initiation of IV study drug or hospital discharge, whichever occurs first

End point values	IV Sildenafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	30		
Units: days				
median (confidence interval 95%)	8.3 (5.46 to 11.75)	7.3 (5.46 to 10.78)		

Statistical analyses

Statistical analysis title	IV Sildenafil vs. Placebo
Comparison groups	IV Sildenafil v Placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9885
Method	Logrank

Secondary: Time From Initiation of Intravenous (IV) Study Drug to First Treatment Failure

End point title	Time From Initiation of Intravenous (IV) Study Drug to First Treatment Failure

End point description:

Time in days, from initiation of IV study drug to first treatment failure (defined as need for additional treatment targeting PPHN, need for ECMO, or death) for subjects with treatment failure was evaluated. Kaplan-Meier method was used for estimation. For subjects without treatment failure by the endpoint assessment date, data is censored at the endpoint assessment date. The ITT population included all randomized subjects treated with study treatment. Due to low number of subjects with events, Kaplan-Meier estimates of median, upper and lower limit of CI could not be estimated/calculated and has been denoted by "99999", signifying data not available.

End point type	Secondary

End point timeframe:

14 days from the initiation of IV study drug or hospital discharge, whichever occurs first

End point values	IV Sildenafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	30		
Units: days				
median (confidence interval 95%)	99999 (-99999 to 99999)	99999 (-99999 to 99999)		

Statistical analyses

Statistical analysis title	IV Sildenafil vs. Placebo
Comparison groups	IV Sildenafil v Placebo

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.491
Method	Logrank

Secondary: Percentage of Subjects With Individual Components of Treatment Failure

End point title	Percentage of Subjects With Individual Components of Treatment Failure

End point description:

Percentage of subjects with individual components of treatment failure (need to start additional treatment targeting PPHN, need to start ECMO, or death) were evaluated. Some subjects could have had multiple qualifying events for treatment failure. The ITT population included all randomized subjects treated with study treatment.

End point type	Secondary

End point timeframe:

14 days from the initiation of IV study drug or hospital discharge, whichever occurs first

End point values	IV Sildenafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	30		
Units: percentage of subjects				
number (confidence interval 95%)				
Additional Treatment Targeting PPHN	13.8 (3.9 to 31.7)	10.0 (2.1 to 26.5)		
ECMO	10.3 (2.2 to 27.4)	10.0 (2.1 to 26.5)		
Death	6.9 (0.8 to 22.8)	0.0 (0.0 to 11.6)		

Statistical analyses

Statistical analysis title	IV Sildenafil vs. Placebo: Additional Treatment
Comparison groups	IV Sildenafil v Placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7065
Method	Fisher exact
Parameter estimate	Difference in Percentage
Point estimate	3.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.2
upper limit	22.9

Statistical analysis title	IV Sildenafil vs. Placebo: ECMO
Comparison groups	IV Sildenafil v Placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.999
Method	Fisher exact
Parameter estimate	Difference in Percentage
Point estimate	0.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.5
upper limit	18.5

Statistical analysis title	IV Sildenafil vs. Placebo: Death
Comparison groups	IV Sildenafil v Placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2373
Method	Fisher exact
Parameter estimate	Difference in Percentage
Point estimate	6.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	22.8

Secondary: Change From Baseline in Oxygenation Index (OI) at Hour 6, 12 and 24

End point title	Change From Baseline in Oxygenation Index (OI) at Hour 6, 12 and 24

End point description:

Oxygenation index was calculated as the product of fraction of inspired oxygen (FiO2) and mean airway pressure divided by partial pressure of oxygen dissolved in arterial blood (PaO2) [(FiO2*mean airway pressure)/PaO2] measured in centimeter of water per millimeter of mercury (cmH2O/mmHg). FiO2 is the measure of oxygen concentration that is breathed. Mean airway pressure is defined as an average of the airway pressure throughout the respiratory cycle. PaO2 is the measure of oxygen level dissolved in

the arterial blood. Here, 'n' = subjects evaluable for this endpoint at specified time points. The ITT population included all randomized subjects treated with study treatment.

End point type	Secondary

End point timeframe:

Baseline, Hour 6, 12 and 24 after start of infusion

End point values	IV Sildenafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	30		
Units: cmH2O/mmHg				
least squares mean (confidence interval 95%)				
Change at Hour 6 (n=29,22)	-4.2 (-11.64 to 3.34)	-8.0 (-16.63 to 0.57)		
Change at Hour 12 (n=28,22)	-4.1 (-10.51 to 2.23)	-8.2 (-15.42 to -1.04)		
Change at Hour 24 (n=18,17)	-11.6 (-15.40 to -7.83)	-9.5 (-13.36 to -5.57)		

Statistical analyses

Statistical analysis title	IV Sildenafil vs. Placebo: Hour 6

Statistical analysis description:

Field appearing in section: "Number of subjects included in analysis", is an auto populated field from database
(sum of number of subjects analyzed for the reporting arms selected to report statistical data): which may not be the actual number of subjects contributing to statistical analysis. Only subjects without treatment failure were included in the analysis.

Comparison groups	IV Sildenafil v Placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4984
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	3.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.5
upper limit	15.3

Statistical analysis title	IV Sildenafil vs. Placebo: Hour 12

Statistical analysis description:

Field appearing in section: "Number of subjects included in analysis", is an auto populated field from database
(sum of number of subjects analyzed for the reporting arms selected to report statistical data): which

may not be the actual number of subjects contributing to statistical analysis. Only subjects without treatment failure were included in the analysis.

Comparison groups	IV Sildenafil v Placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3956
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	4.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.5
upper limit	13.7

Statistical analysis title	IV Sildenafil vs. Placebo: Hour 24

Statistical analysis description:

Field appearing in section: "Number of subjects included in analysis", is an auto populated field from database
(sum of number of subjects analyzed for the reporting arms selected to report statistical data): which may not be the actual number of subjects contributing to statistical analysis. Only subjects without treatment failure were included in the analysis.

Comparison groups	IV Sildenafil v Placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4249
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-2.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.6
upper limit	3.3

Secondary: Change From Baseline in Differential Saturation at Hour 6, 12 and 24

End point title	Change From Baseline in Differential Saturation at Hour 6, 12 and 24

End point description:

Differential oxygenation saturation is a simple way to detect the right-to-left shunting at ductus arteriosus using 2 pulse oximeters. It is the difference between pre-ductal and post-ductal sites pulse oxygen saturation (SpO2). Where, pre-duct refers to right upper extremity and post-duct refers to lower limb. Oxygenation saturation is measured as percentage of hemoglobin binding sites occupied by oxygen in the blood. Here, 'n' = subjects evaluable for this endpoint at specified time points. The ITT population included all randomized subjects treated with study treatment.

End point type	Secondary

End point timeframe:

Baseline, Hour 6, 12 and 24 after start of infusion

End point values	IV Sildenafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	30		
Units: percentage of hemoglobin				
least squares mean (confidence interval 95%)				
Change at Hour 6 (n=26,19)	1.5 (-1.79 to 4.80)	0.8 (-3.10 to 4.62)		
Change at Hour 12 (n=25,19)	-1.2 (-7.65 to 5.21)	6.7 (-0.65 to 14.12)		
Change at Hour 24 (n=19,14)	1.2 (-7.15 to 9.49)	9.3 (-0.40 to 19.08)		

Statistical analyses

Statistical analysis title	IV Sildenafil vs. Placebo: Hour 6

Statistical analysis description:

Field appearing in section: "Number of subjects included in analysis", is an auto populated field from database
(sum of number of subjects analyzed for the reporting arms selected to report statistical data): which may not be the actual number of subjects contributing to statistical analysis. Only subjects without treatment failure were included in the analysis.

Comparison groups	IV Sildenafil v Placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7686
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.3
upper limit	5.8

Statistical analysis title	IV Sildenafil vs. Placebo: Hour 12

Statistical analysis description:

Field appearing in section: "Number of subjects included in analysis", is an auto populated field from database
(sum of number of subjects analyzed for the reporting arms selected to report statistical data): which may not be the actual number of subjects contributing to statistical analysis. Only subjects without treatment failure were included in the analysis.

Comparison groups	IV Sildenafil v Placebo

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1112
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.8
upper limit	1.9

Statistical analysis title	IV Sildenafil vs. Placebo: Hour 24

Statistical analysis description:

Field appearing in section: "Number of subjects included in analysis", is an auto populated field from database
(sum of number of subjects analyzed for the reporting arms selected to report statistical data): which may not be the actual number of subjects contributing to statistical analysis. Only subjects without treatment failure were included in the analysis.

Comparison groups	IV Sildenafil v Placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2089
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-8.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.2
upper limit	4.8

Secondary: Change From Baseline in Ratio of Partial Pressure of Oxygen in Arterial Blood to Fraction of Inspired Oxygen (P/F) at Hour 6, 12 and 24

End point title	Change From Baseline in Ratio of Partial Pressure of Oxygen in Arterial Blood to Fraction of Inspired Oxygen (P/F) at Hour 6, 12 and 24

End point description:

The ratio of partial pressure of arterial oxygen to fraction of inspired oxygen is a ratio between the oxygen level in the arterial blood and the oxygen concentration that is breathed. It helps to determine the degree of any problems with how the lungs transfer oxygen to the blood. Here, 'n' = subjects evaluable for this endpoint at specified time points. The ITT population consisted of all randomized subjects treated with study treatment.

End point type	Secondary

End point timeframe:

Baseline, Hour 6, 12 and 24 after start of infusion

End point values	IV Sildenafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	30		
Units: ratio				
least squares mean (confidence interval 95%)				
Change at Hour 6 (n=29,23)	45.3 (17.21 to 73.37)	8.1 (-23.48 to 39.60)		
Change at Hour 12 (n=28,24)	43.4 (16.76 to 70.13)	16.9 (-11.97 to 45.68)		
Change at Hour 24 (n=20,17)	94.6 (18.52 to 170.69)	14.7 (-67.83 to 97.25)		

Statistical analyses

Statistical analysis title	IV Sildenafil vs. Placebo: Hour 6

Statistical analysis description:

Field appearing in section: "Number of subjects included in analysis", is an auto populated field from database
(sum of number of subjects analyzed for the reporting arms selected to report statistical data): which may not be the actual number of subjects contributing to statistical analysis. Only subjects without treatment failure were included in the analysis.

Comparison groups	IV Sildenafil v Placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0829
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	37.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5
upper limit	79.5

Statistical analysis title	IV Sildenafil vs. Placebo: Hour 12

Statistical analysis description:

Field appearing in section: "Number of subjects included in analysis", is an auto populated field from database
(sum of number of subjects analyzed for the reporting arms selected to report statistical data): which may not be the actual number of subjects contributing to statistical analysis. Only subjects without treatment failure were included in the analysis.

Comparison groups	IV Sildenafil v Placebo

Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1802
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	26.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-12.7
upper limit	65.9

Statistical analysis title	IV Sildenafil vs. Placebo: Hour 24

Statistical analysis description:

Field appearing in section: "Number of subjects included in analysis", is an auto populated field from database
(sum of number of subjects analyzed for the reporting arms selected to report statistical data): which may not be the actual number of subjects contributing to statistical analysis. Only subjects without treatment failure were included in the analysis.

Comparison groups	IV Sildenafil v Placebo
Number of subjects included in analysis	59
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1576
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	79.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-32.5
upper limit	192.2

Secondary: Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point title	Number of Subjects With Treatment-Emergent Adverse Events (AEs) and Serious Adverse Events (SAEs)

End point description:

An AE was any untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. A SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly; medically important events. Treatment-emergent are events between first infusion of study drug and up to 31 days after end of study drug infusion (up to 45 days) that were absent before treatment or that worsened relative to pretreatment state. AEs included both SAEs and non-SAEs. The safety population included all subjects treated with study treatment.

End point type	Secondary

End point timeframe:

Baseline up to 31 days after end of study drug infusion (up to 45 days)

End point values	IV Sildenafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	30		
Units: subjects				
AEs	22	19		
SAEs	7	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Treatment-Emergent Adverse Events (AEs) According to Severity

End point title	Number of Treatment-Emergent Adverse Events (AEs) According to Severity

End point description:

AE: untoward medical occurrence in a subject who received study drug without regard to possibility of causal relationship. SAE: AE resulting in any of the following outcomes: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly; medically important events. Treatment-emergent are events between first infusion of study drug and up to 31 days after end of study drug infusion (up to 45 days) that were absent before treatment or that worsened relative to pretreatment state. AEs included both SAEs and non-SAEs. Severity criteria: mild=did not interfere with subject's usual function; moderate=interfered to some extent with subject's usual function and severe=interfered significantly with subject's usual function. Missing baseline severities were imputed as mild. The safety population included all subjects treated with study treatment.

End point type	Secondary

End point timeframe:

Baseline up to 31 days after end of study drug infusion (up to 45 days)

End point values	IV Sildenafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	30		
Units: events				
Mild	49	42		
Moderate	29	24		
Severe	12	17		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Laboratory Abnormalities

End point title	Number of Subjects With Laboratory Abnormalities

End point description:

Criteria for laboratory values: Hematology: hemoglobin, hematocrit, red blood cell count <0.8*lower limit of normal (LLN), platelets<0.5*LLN, >1.75*upper limit of normal (ULN), white blood cells count <0.6*LLN, >1.5*ULN; Liver function: total and direct bilirubin >1.5*ULN, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase >3.0*ULN, total protein <0.8*LLN, >1.2*ULN; Renal function: blood urea nitrogen, creatinine >1.3*ULN; Electrolytes: sodium <0.95*LLN, >1.05*ULN, potassium, chloride, calcium, bicarbonate (venous) <0.9*LLN, >1.1*ULN. Here, "number of subjects analyzed" signifies those subjects who were evaluable for this endpoint. The safety population included all subjects treated with study treatment.

End point type	Secondary

End point timeframe:

Up to 14 days from initiation of study drug infusion

End point values	IV Sildenafil	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	29	28		
Units: subjects	27	22		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Composite Scores of Cognitive, Language, and Motor Developmental Progress of Subjects as Assessed by Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III)

End point title	Part B: Composite Scores of Cognitive, Language, and Motor Developmental Progress of Subjects as Assessed by Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III)

End point description:

Bayley-III assesses infant and toddler development across five domains: cognitive, language, motor, social-emotional (SE), and adaptive behavior (AB). Assessments of the cognitive, language, and motor domains conducted using items administered to the child; assessments of the SE and AB domains conducted using the primary caregiver's responses to a questionnaire. Score ranges: cognitive scale 0-91, language scale 0-97 and motor scale 0-132, where higher scores indicated better cognitive function, communication and motor skills respectively. Raw scores of cognitive, language and motor domains were converted to composite scores. Composite scores of cognitive, language and motor developmental scales ranged from a scale of 40 to 160, where higher score indicated stronger skills and abilities. Part-B safety analysis set. Number Analysed =subjects evaluable for this end point, n =subjects evaluable for each specified rows.

End point type	Secondary

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

End point values	Part B (Non-Interventional Phase): IV Sildenafil	Part B (Non-Interventional Phase): Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	19	13		
Units: units on a scale				
arithmetic mean (standard deviation)				
Cognitive Development: Month 12 (n =19, 12)	97.5 (± 16.14)	94.5 (± 14.18)		
Cognitive Development: Month 24 (n =17, 13)	97.4 (± 18.12)	97.3 (± 14.95)		
Language Development: Month 12 (n =18, 12)	99.5 (± 16.86)	94.7 (± 10.25)		
Language Development: Month 24 (n =16, 11)	96.7 (± 21.91)	95.8 (± 17.70)		
Motor Development: Month 12 (n =19, 12)	93.1 (± 16.10)	88.2 (± 14.61)		
Motor Development: Month 24 (n =17, 12)	99.0 (± 19.59)	105.3 (± 24.00)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Composite Scores of Social-Emotional and Adaptive Behavior Questionnaire of Subjects as Assessed by Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III)

End point title	Part B: Composite Scores of Social-Emotional and Adaptive Behavior Questionnaire of Subjects as Assessed by Bayley Scales of Infant and Toddler Development Third Edition (Bayley-III)

End point description:

The Bayley-III assesses infant and toddler development across five domains: cognitive, language, motor, social-emotional (SE), and adaptive behavior (AB). Assessments of the cognitive, language, and motor domains conducted using items administered to the child; assessments of the SE and AB domains conducted using the primary caregiver’s responses to a questionnaire. The questionnaire comprises the SE scale (35 items) and the AB scale (241 items). Raw scores of SE and AB were converted to composite scores. Composite scores for SE and AB scale ranged from 40 to 160, where higher scores indicated better social-emotional skills and adaptive behavior in child. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. 'Number Analysed' = subjects evaluable for this end point.

End point type	Secondary

End point timeframe:

Month 24 after end of study treatment in Part A (Day 1 to 14)

End point values	Part B (Non-Interventional Phase): IV Sildenafil	Part B (Non-Interventional Phase): Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	15	8		
Units: units on a scale				
arithmetic mean (standard deviation)				
Social-Emotional Development	104.5 (± 21.40)	112.5 (± 18.13)		
Adaptive Behavior Development	91.6 (± 15.66)	98.3 (± 12.44)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Subjects With Eye Movement Disorders as Assessed by Eye Examination

End point title	Part B: Number of Subjects With Eye Movement Disorders as Assessed by Eye Examination

End point description:

Standard age-appropriate ophthalmological examinations of subjects were used to assess eye movement disorders (presence of amblyopia, strabismus, and nystagmus) at month 12 and 24. In this end point, data have been reported for right and left eye separately. Rows according to eye movement disorder categories at specified time points are reported in this end point, only when there was a non-zero data for at least 1 reporting arm. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and ‘n’ signifies number of subjects evaluable for each specified rows.

End point type	Secondary

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

End point values	Part B (Non-Interventional Phase): IV Sildenafil	Part B (Non-Interventional Phase): Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	14		
Units: subjects				
Strabismus Present,Right Eye: Month 12 (n =16, 14)	0	1		
Strabismus Present,Left Eye: Month 12 (n =16, 14)	0	1		
Strabismus Present,Right Eye: Month 24 (n =12, 12)	1	0		
Strabismus Present,Left Eye: Month 24 (n =12, 12)	1	0		
Nystagmus Present,Left Eye: Month 24 (n =12, 12)	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Visual Acuity of Verbal Subjects as Assessed by Ophthalmological Assessment

End point title	Part B: Visual Acuity of Verbal Subjects as Assessed by Ophthalmological Assessment

End point description:

Standard age-appropriate ophthalmological examinations were used to assess visual acuity (performed differently for children able of verbal interaction) through visual acuity chart (VAC) quantitative, counting finger (CF), hand motion (HM), light perception (LP), no light perception (NLP) and missing at month 12 and 24. In this end point, data have been reported for right and left eye separately. Rows according to visual acuity categories at specified time points are reported in this end point, only when there was a non-zero data for at least 1 reporting arm. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and ‘n’ signifies number of subjects evaluable for each specified rows.

End point type	Secondary

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

End point values	Part B (Non-Interventional Phase): IV Sildenafil	Part B (Non-Interventional Phase): Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	14		
Units: subjects				
VAC Quantitative, Right Eye: Month 12 (n =16, 14)	2	1		
HM, Right Eye: Month 12 (n =16, 14)	0	2		
LP, Right Eye: Month 12 (n =16, 14)	1	0		
Missing, Right Eye: Month 12 (n =16, 14)	13	11		
VAC Quantitative, Left Eye: Month 12 (n =16, 14)	2	1		
HM, Left Eye: Month 12 (n =16, 14)	0	2		
LP, Left Eye: Month 12 (n =16, 14)	1	0		
Missing, Left Eye: Month 12 (n =16, 14)	13	11		
VAC Quantitative, Right Eye: Month 24 (n =12, 12)	6	5		
HM, Right Eye: Month 24 (n =12, 12)	1	0		
Missing, Right Eye: Month 24 (n =12, 12)	5	7		
VAC Quantitative, Left Eye: Month 24 (n =12, 12)	6	5		

Missing, Left Eye: Month 24 (n =12, 12)	6	7		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Visual Acuity of Non-Verbal Subjects as Assessed by Ophthalmological Assessment

End point title	Part B: Visual Acuity of Non-Verbal Subjects as Assessed by Ophthalmological Assessment

End point description:

Standard age-appropriate ophthalmological examinations were used to assess visual acuity (performed differently for children unable of verbal interaction) through fixates and follows [F&F] (included central, steady and maintained), light perception [LP] (wince to light), no light perception [NLP], and missing at month 12 and 24. In this end point, data have been reported for right and left eye separately. Rows according to visual acuity categories at specified time points are reported in this end point, only when there was a non-zero data for at least 1 reporting arm. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and ‘n’ signifies number of subjects evaluable for each specified rows.

End point type	Secondary

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

End point values	Part B (Non-Interventional Phase): IV Sildenafil	Part B (Non-Interventional Phase): Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	14		
Units: subjects				
F&F, Right Eye: Month 12 (n =16, 14)	15	13		
LP, Right Eye: Month 12 (n =16, 14)	0	1		
Missing, Right Eye: Month 12 (n =16, 14)	1	0		
F&F, Left Eye: Month 12 (n =16, 14)	15	13		
LP, Left Eye: Month 12 (n =16, 14)	0	1		
Missing, Left Eye: Month 12 (n =16, 14)	1	0		
F&F, Right Eye: Month 24 (n =12, 12)	5	9		
Missing, Right Eye: Month 24 (n =12, 12)	7	3		
F&F, Left Eye: Month 24 (n =12, 12)	5	9		
Missing, Left Eye: Month 24 (n =12, 12)	7	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Visual Acuity of Verbal Subjects as Assessed by LogMAR Through Visual Acuity Chart

End point title	Part B: Visual Acuity of Verbal Subjects as Assessed by LogMAR Through Visual Acuity Chart

End point description:

Standard age-appropriate ophthalmological examinations were used to assess visual acuity (performed differently for children able of verbal interaction) at month 12 and 24. Visual acuity (VA) of verbal children was assessed for each eye using the Snellen method, where logarithm of minimum angle of resolution (logMAR) units were derived from the Snellen ratios. Subjects had to read letters from the chart at a distance of 20 feet/6 meter or 4 meter. VA (Snellen ratio) = distance between the chart and subject, divided by distance at which subject was able to see/read chart without impairment; expressed as decimal, logMAR = log10 (1/decimal VA). In this end point, data have been reported for right and left eye separately. Part B safety analysis. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and ‘n’ signifies number of subjects evaluable for each specified rows.

End point type	Secondary

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

End point values	Part B (Non-Interventional Phase): IV Sildenafil	Part B (Non-Interventional Phase): Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	6	6		
Units: LogMAR				
arithmetic mean (standard deviation)				
Right Eye: Month 12 (n =6, 3)	0.45 (± 0.394)	0.57 (± 0.513)		
Left Eye: Month 12 (n =6, 3)	0.47 (± 0.372)	0.57 (± 0.513)		
Right Eye: Month 24 (n =6, 4)	0.20 (± 0.155)	0.28 (± 0.299)		
Left Eye: Month 24 (n =6, 6)	0.20 (± 0.155)	0.35 (± 0.409)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Visual Status of Subjects With Abnormality as Assessed by Eye Examination of the Anterior and Posterior Segments

End point title	Part B: Visual Status of Subjects With Abnormality as Assessed by Eye Examination of the Anterior and Posterior Segments

End point description:

Standard age-appropriate ophthalmological examinations were used to assess examination of anterior and posterior chamber for abnormality in lids, conjunctiva, cornea, anterior chamber, lens, iris, pupil, extraocular muscle movement (EMM) and eye movements at month 12 and 24. In this end point, data have been reported for right and left eye separately. Rows according to visual status categories at specified time points are reported in this end point, only when there was a non-zero data for at least 1 reporting arm. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and ‘n’ signifies number of subjects evaluable for each specified rows.

End point type	Secondary

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

End point values	Part B (Non-Interventional Phase): IV Sildenafil	Part B (Non-Interventional Phase): Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	17	15		
Units: subjects				
Anterior (Lids), Right Eye: Month 12 (n =17, 15)	0	1		
Anterior (Lids), Left Eye: Month 12 (n =17, 15)	0	1		
Anterior (EMM), Right Eye: Month 24 (n =13, 11)	1	0		
Anterior (EMM), Left Eye: Month 24 (n =13, 11)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Audiological Status of Subjects as Assessed by Behavior Hearing Assessment Through Pure Tone Audiometry Test

End point title	Part B: Audiological Status of Subjects as Assessed by Behavior Hearing Assessment Through Pure Tone Audiometry Test

End point description:

Audiological evaluations of subjects were recorded and reported using behavior hearing assessment through pure tone audiometry test which included subjects with normal, abnormal, incomplete/inconclusive behavior at month 12 and 24. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point.

End point type	Secondary

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

End point values	Part B (Non-Interventional Phase): IV Sildenafil	Part B (Non-Interventional Phase): Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	16	12		
Units: subjects				
Normal Behavior: Month12	11	8		
Abnormal Behavior: Month 12	1	4		
Incomplete/Inconclusive Behavior: Month 12	4	0		

Normal Behavior: Month 24	13	8		
Abnormal Behavior: Month 24	0	2		
Incomplete/Inconclusive Behavior: Month 24	3	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Audiological Status of Subjects as Assessed by Bone Conduction Through Pure Tone Audiometry Test

End point title	Part B: Audiological Status of Subjects as Assessed by Bone Conduction Through Pure Tone Audiometry Test

End point description:

Audiological evaluations of subjects were recorded and reported by bone conduction assessment through pure tone audiometry test which included subjects with sensorineural hearing loss, conductive hearing loss, mixed hearing loss, neural, and unspecified. Rows according to bone conduction categories at specified time points are reported in this end point, only when there was a non-zero data for at least 1 reporting arm. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and ‘n’ signifies number of subjects evaluable for each specified rows.

End point type	Secondary

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

End point values	Part B (Non-Interventional Phase): IV Sildenafil	Part B (Non-Interventional Phase): Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	1	2		
Units: subjects				
Conductive Hearing Loss: Month 12 (n =1, 2)	0	1		
Unspecified: Month 12 (n =1, 2)	1	1		
Conductive Hearing Loss: Month 24 (n =0, 1)	0	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Audiological Status of Subjects as Assessed by Air Conduction via Phones/Headphones Through Pure Tone Audiometry Test

End point title	Part B: Audiological Status of Subjects as Assessed by Air Conduction via Phones/Headphones Through Pure Tone Audiometry Test

End point description:

Audiological evaluations of subjects were recorded and reported by air conduction via phones/headphones through pure tone audiometry test which included subjects with hearing loss ranged from less than or equal to (<=) 20 decibel hearing loss (DB HL), 21-40 DB HL, 41-70 DB HL, 71-90 DB HL, greater than (>) 90 DB HL or no response, and missing at frequencies ranged from 500 Hertz (Hz) to 8000 Hz at month 12 and 24. In this end point, data have been reported for right and left ear separately. Rows according to air conduction categories at specified time points are reported in this end point, only when there was a non-zero data for at least 1 reporting arm. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. 'Number of Subjects Analysed = subjects evaluable for this end point and ‘n’ = number of subjects evaluable for each specified rows.

End point type	Secondary

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

End point values	Part B (Non-Interventional Phase): IV Sildenafil	Part B (Non-Interventional Phase): Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	8	5		
Units: subjects				
Right Ear,500 Hz,<=20 DB HL: Month 12 (n =5, 5)	3	4		
Right Ear,500 Hz, 21-40 DB HL: Month 12 (n =5, 5)	2	1		
Right Ear,1000 Hz,<=20 DB HL: Month 12 (n =5, 5)	4	5		
Right Ear,1000 Hz,21-40 DB HL: Month 12 (n =5, 5)	1	0		
Right Ear,2000 Hz,<=20 DB HL: Month 12 (n =5, 5)	3	4		
Right Ear,2000 Hz,21-40 DB HL: Month 12 (n =5, 5)	2	0		
Right Ear,4000 Hz,<=20 DB HL: Month 12 (n =5, 5)	4	5		
Right Ear,4000 Hz,21-40 DB HL: Month 12 (n =5, 5)	1	0		
Right Ear,8000 Hz,<=20 DB HL: Month 12 (n =5, 5)	3	4		
Right Ear,8000 Hz, Missing: Month 12 (n =5, 5)	2	0		
Left Ear,500 Hz, <=20 DB HL: Month 12 (n =5, 5)	3	3		
Left Ear,500 Hz, 21-40 DB HL: Month 12 (n =5, 5)	2	1		
Left Ear,1000 Hz, <=20 DB HL: Month 12 (n =5, 5)	3	5		
Left Ear,1000 Hz, 21-40 DB HL: Month 12 (n =5, 5)	2	0		
Left Ear,2000 Hz, <=20 DB HL: Month 12 (n =5, 5)	3	4		
Left Ear,2000 Hz, 21-40 DB HL: Month 12 (n =5, 5)	2	0		
Left Ear,4000 Hz, <=20 DB HL: Month 12 (n =5, 5)	4	5		
Left Ear,4000 Hz, 21-40 DB HL: Month 12 (n =5, 5)	1	0		

Left Ear,8000 Hz, <=20 DB HL: Month 12 (n =5, 5)	3	4		
Left Ear,8000 Hz, Missing: Month 24 (n =5, 5)	2	1		
Right Ear,500 Hz, <=20 DB HL: Month 24 (n =8, 4)	5	3		
Right Ear,500 Hz, 21-40 DB HL: Month 24 (n =8, 4)	2	0		
Right Ear,1000 Hz, <=20 DB HL: Month 24 (n =8, 4)	5	2		
Right Ear,1000 Hz, 21-40 DB HL: Month 24 (n =8, 4)	1	0		
Right Ear,2000 Hz, <=20 DB HL: Month 24 (n =8, 4)	6	3		
Right Ear,2000 Hz, 21-40 DB HL: Month 24 (n =8, 4)	1	0		
Right Ear,4000 Hz, <=20 DB HL: Month 24 (n =8, 4)	7	3		
Right Ear,8000 Hz, <=20 DB HL: Month 24 (n =8, 4)	4	3		
Right Ear,8000 Hz, 21-40 DB HL: Month 24 (n =8, 4)	1	0		
Right Ear,8000 Hz, Missing: Month 24 (n =8, 4)	1	0		
Left Ear,500 Hz, <=20 DB HL: Month 24 (n =8, 4)	6	3		
Left Ear,500 Hz, 21-40 DB HL: Month 24 (n =8, 4)	1	0		
Left Ear,1000 Hz, <=20 DB HL: Month 24 (n =8, 4)	4	3		
Left Ear,1000 Hz, 21-40 DB HL: Month 24 (n =8, 4)	1	0		
Left Ear,2000 Hz, <=20 DB HL: Month 24 (n =8, 4)	6	2		
Left Ear,2000 Hz, 21-40 DB HL: Month 24 (n =8, 4)	1	0		
Left Ear,4000 Hz, <=20 DB HL: Month 24 (n =8, 4)	7	4		
Left Ear,8000 Hz, <=20 DB HL: Month 24 (n =8, 4)	3	3		
Left Ear,8000 Hz, 21-40 DB HL: Month 24 (n =8, 4)	1	0		
Left Ear,8000 Hz, Missing: Month 24 (n =8, 4)	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Audiological Status of Subjects as Assessed by Air Conduction via Soundfield Through Pure Tone Audiometry Test

End point title	Part B: Audiological Status of Subjects as Assessed by Air Conduction via Soundfield Through Pure Tone Audiometry Test

End point description:

Audiological evaluations of subjects were recorded and reported by air conduction via soundfield through pure tone audiometry test which included subjects with hearing loss ranged from <=20 DB HL, 21-40 DB HL, 41-70 DB HL, 71-90 DB HL, >90 DB HL or no response, and missing at frequencies ranged from 500 Hz to 4000 Hz at month 12 and 24. Rows according to air conduction categories at specified time

points are reported in this end point, only when there was a non-zero data for at least 1 reporting arm. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' = number of subjects evaluable for this end point and 'n' = number of subjects evaluable for each specified rows.

End point type	Secondary

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

End point values	Part B (Non-Interventional Phase): IV Sildenafil	Part B (Non-Interventional Phase): Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	13	9		
Units: subjects				
500 Hz, <=20 DB HL: Month 12 (n =13, 9)	6	2		
500 Hz, 21-40 DB HL: Month 12 (n =13, 9)	5	6		
500 Hz, 71-90 DB HL: Month 12 (n =13, 9)	1	0		
1000 Hz, <=20 DB HL: Month 12 (n =13, 9)	9	3		
1000 Hz, 21-40 DB HL: Month 12 (n =13, 9)	1	5		
1000 Hz, 71-90 DB HL: Month 12 (n =13, 9)	1	0		
2000 Hz, <=20 DB HL: Month 12 (n =13, 9)	7	2		
2000 Hz, 21-40 DB HL: Month 12 (n =13, 9)	3	4		
2000 Hz, Missing: Month 12 (n =13, 9)	1	0		
4000 Hz, <=20 DB HL: Month 12 (n =13, 9)	6	4		
4000 Hz, 21-40 DB HL: Month 12 (n =13, 9)	4	4		
4000 Hz, 71-90 DB HL: Month 12 (n =13, 9)	1	0		
500 Hz, <=20 DB HL: Month 24 (n =11, 9)	6	2		
500 Hz, 21-40 DB HL: Month 24 (n =11, 9)	2	5		
1000 Hz, <=20 DB HL: Month 24 (n =11, 9)	6	6		
1000 Hz, 21-40 DB HL: Month 24 (n =11, 9)	4	3		
2000 Hz, <=20 DB HL: Month 24 (n =11, 9)	6	3		
2000 Hz, 21-40 DB HL: Month 24 (n =11, 9)	2	4		
4000 Hz, <=20 DB HL: Month 24 (n =11, 9)	5	4		
4000 Hz, 21-40 DB HL: Month 24 (n =11, 9)	4	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Audiological Status of Subjects as Assessed by Tympanometry Assessment (Peak Pressure) Through Immittance Audiometry Test

End point title	Part B: Audiological Status of Subjects as Assessed by Tympanometry Assessment (Peak Pressure) Through Immittance Audiometry Test

End point description:

Audiological evaluations of subjects were recorded and reported by tympanometry assessment through immittance audiometry test which included subjects with peak pressure (PP) signs (+) and (-) at month 12 and 24. In this end point, data have been reported for right and left ear separately. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and ‘n’ signifies number of subjects evaluable for each specified rows.

End point type	Secondary

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

End point values	Part B (Non-Interventional Phase): IV Sildenafil	Part B (Non-Interventional Phase): Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	8		
Units: decapascals				
arithmetic mean (standard deviation)				
PP for Sign (+), Right Ear: Month 12 (n =7, 3)	51.89 (± 63.024)	27.33 (± 26.539)		
PP for Sign (+), Left Ear: Month 12 (n =3, 4)	5.07 (± 4.900)	73.75 (± 28.987)		
PP for Sign (+), Right Ear: Month 24 (n =3, 4)	44.00 (± 46.130)	33.50 (± 44.125)		
PP for Sign (+), Left Ear: Month 24 (n =7, 5)	42.71 (± 50.112)	35.00 (± 46.578)		
PP for Sign (-), Right Ear: Month 12 (n =6, 8)	149.3 (± 144.34)	67.75 (± 57.350)		
PP for Sign (-), Left Ear: Month 12 (n =9, 5)	79.89 (± 64.367)	46.80 (± 46.912)		
PP for Sign (-), Right Ear: Month 24 (n =8, 3)	98.00 (± 55.685)	83.67 (± 107.38)		
PP for Sign (-), Left Ear: Month 24 (n =6, 2)	102.2 (± 84.781)	135.0 (± 70.711)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Audiological Status of Subjects as Assessed by Tympanometry Assessment (Static Acoustic Admittance) Through Immittance Audiometry Test

End point title	Part B: Audiological Status of Subjects as Assessed by Tympanometry Assessment (Static Acoustic Admittance) Through Immittance Audiometry Test

End point description:

Audiological evaluations of subjects were recorded and reported by tympanometry assessment through immittance audiometry test which included subjects with static acoustic admittance at month 12 and 24. In this end point, data have been reported for right and left ear separately. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and ‘n’ signifies number of subjects evaluable for each specified rows.

End point type	Secondary

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

End point values	Part B (Non-Interventional Phase): IV Sildenafil	Part B (Non-Interventional Phase): Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	9	11		
Units: millimho				
arithmetic mean (standard deviation)				
Right Ear: Month 12 (n =9, 11)	0.241 (± 0.1403)	0.403 (± 0.1691)		
Left Ear: Month 12 (n =8, 9)	0.364 (± 0.1513)	0.330 (± 0.1595)		
Right Ear: Month 24 (n =6, 6)	0.273 (± 0.0784)	0.400 (± 0.1321)		
Left Ear: Month 24 (n =8, 6)	0.295 (± 0.0691)	0.585 (± 0.5558)		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Audiological Status of Subjects as Assessed by Ipsilateral Stapedial Reflex Through Immittance Audiometry Test

End point title	Part B: Audiological Status of Subjects as Assessed by Ipsilateral Stapedial Reflex Through Immittance Audiometry Test

End point description:

Audiological evaluations of subjects were recorded and reported by ipsilateral stapedial reflex through immittance audiometry test which included subjects with presence of ipsilateral stapedial reflex at frequencies ranged from 500 Hz to 2000 Hz at month 12 and 24. Ipsilateral stapedial reflex measures are used to assess the neural pathway surrounding the stapedial reflex, which occurs in response to a loud sound (70 to 90 decibel above threshold). In this end point, data have been reported for right and

left ear separately. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and ‘n’ signifies number of subjects evaluable for each specified rows.

End point type	Secondary

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

End point values	Part B (Non-Interventional Phase): IV Sildenafil	Part B (Non-Interventional Phase): Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	14	12		
Units: subjects				
500 Hz, Right Ear: Month 12 (n =14, 12)	5	1		
500 Hz, Left Ear: Month 12 (n =14, 12)	6	1		
1000 Hz, Right Ear: Month 12 (n =14, 12)	5	1		
1000 Hz, Left Ear: Month 12 (n =14, 12)	6	1		
2000 Hz, Right Ear: Month 12 (n =14, 12)	5	1		
2000 Hz, Left Ear: Month 12 (n =14, 12)	6	1		
500 Hz, Right Ear: Month 24 (n =13, 9)	4	2		
500 Hz, Left Ear: Month 24 (n =13, 9)	4	2		
1000 Hz, Right Ear: Month 24 (n =13, 9)	4	2		
1000 Hz, Left Ear: Month 24 (n =13, 9)	5	2		
2000 Hz, Right Ear: Month 24 (n =13, 9)	4	2		
2000 Hz, Left Ear: Month 24 (n =13, 9)	4	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Audiological Status of Subjects as Assessed by Transient Evoked Emission Through Otoacoustic Emissions Assessment

End point title	Part B: Audiological Status of Subjects as Assessed by Transient Evoked Emission Through Otoacoustic Emissions Assessment

End point description:

Audiological evaluations of subjects were recorded and reported by transient evoked emission through otoacoustic emissions assessment which included subjects with presence of transient evoked emissions at frequencies ranged from 1000 Hz to 4000 Hz at month 12 and 24. In this end point, data have been reported for right and left ear separately. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point.

End point type	Secondary

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

End point values	Part B (Non-Interventional Phase): IV Sildenafil	Part B (Non-Interventional Phase): Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	3		
Units: subjects				
1000 Hz, Right Ear: Month 12	3	2		
1000 Hz, Left Ear: Month 12	2	1		
1500 Hz, Right Ear: Month 12	3	2		
1500 Hz, Left Ear: Month 12	2	2		
2000 Hz, Right Ear: Month 12	5	2		
2000 Hz, Left Ear: Month 12	5	2		
3000 Hz, Right Ear: Month 12	4	2		
3000 Hz, Left Ear: Month 12	4	2		
4000 Hz, Right Ear: Month 12	6	2		
4000 Hz, Left Ear: Month 12	5	3		
1000 Hz, Right Ear: Month 24	3	2		
1000 Hz, Left Ear: Month 24	2	2		
1500 Hz, Right Ear: Month 24	2	3		
1500 Hz, Left Ear: Month 24	2	3		
2000 Hz, Right Ear: Month 24	7	3		
2000 Hz, Left Ear: Month 24	6	3		
3000 Hz, Right Ear: Month 24	6	3		
3000 Hz, Left Ear: Month 24	4	3		
4000 Hz, Right Ear: Month 24	7	3		
4000 Hz, Left Ear: Month 24	5	3		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Audiological Status of Subjects as Assessed by Distort Product Through Otoacoustic Emissions Assessment

End point title	Part B: Audiological Status of Subjects as Assessed by Distort Product Through Otoacoustic Emissions Assessment

End point description:

Audiological evaluations of subjects were recorded and reported by distort product through otoacoustic emissions assessment which included subjects with presence of distort product at frequencies ranged from 2000 Hz to 8000 Hz at month 12 and 24. Distortion-product otoacoustic emissions (DPOAEs) are generated in the cochlea in response to two tones of a given frequency and sound pressure level presented in the ear canal. Distort product otoacoustic emissions are an objective indicator of normally functioning cochlea outer hair cells. In this end point, data have been reported for right and left ear separately. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and ‘n’ signifies number of subjects evaluable for each specified rows.

End point type	Secondary

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

End point values	Part B (Non-Interventional Phase): IV Sildenafil	Part B (Non-Interventional Phase): Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	7		
Units: subjects				
2000 Hz, Right Ear: Month 12 (n =6, 6)	4	4		
2000 Hz, Left Ear: Month 12 (n =6, 6)	5	3		
3000 Hz, Right Ear: Month 12 (n =6, 6)	5	4		
3000 Hz, Left Ear: Month 12 (n =6, 6)	5	3		
4000 Hz, Right Ear: Month 12 (n =6, 6)	5	4		
4000 Hz, Left Ear: Month 12 (n =6, 6)	5	3		
6000 Hz, Right Ear: Month 12 (n =6, 6)	4	4		
6000 Hz, Left Ear: Month 12 (n =6, 6)	5	4		
8000 Hz, Right Ear: Month 12 (n =6, 6)	4	2		
8000 Hz, Left Ear: Month 12 (n =6, 6)	5	2		
2000 Hz, Right Ear: Month 24 (n =7, 7)	4	7		
2000 Hz, Left Ear: Month 24 (n =7, 7)	4	6		
3000 Hz, Right Ear: Month 24 (n =7, 7)	7	5		
3000 Hz, Left Ear: Month 24 (n =7, 7)	6	5		
4000 Hz, Right Ear: Month 24 (n =7, 7)	6	5		
4000 Hz, Left Ear: Month 24 (n =7, 7)	6	5		
6000 Hz, Right Ear: Month 24 (n =7, 7)	4	6		
6000 Hz, Left Ear: Month 24 (n =7, 7)	5	6		
8000 Hz, Right Ear: Month 24 (n =7, 7)	3	2		
8000 Hz, Left Ear: Month 24 (n =7, 7)	4	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Number of Subjects With Adverse Events (AEs), Serious Adverse Events (SAEs), and Deaths

End point title	Part B: Number of Subjects With Adverse Events (AEs), Serious Adverse Events (SAEs), and Deaths

End point description:

An AE was any untoward medical occurrence in a subject who received study medication without regard to possibility of causal relationship to it. SAE was an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/ incapacity; congenital anomaly. AEs included both serious and all non-serious AEs. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety.

End point type	Secondary

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

End point values	Part B (Non-Interventional Phase): IV Sildenafil	Part B (Non-Interventional Phase): Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	27	26		
Units: subjects				
AEs	17	17		
SAEs	9	6		
Deaths	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Part B: Neurological Progress of Subjects as Assessed by the Neurology Optimality Score

End point title	Part B: Neurological Progress of Subjects as Assessed by the Neurology Optimality Score

End point description:

The Hammersmith Infant Neurological Examination (HINE) was a standard scoring examination to assess development of cranial nerve; posture; movement; tone; and reflexes and reaction. HINE exam global score is a sum of subset (cranial nerve, posture, movement, tone, reflexes and reactions) scores, ranged from 0 to 78, where higher score represents better outcome. Here, the HINE global scores were reported at month 12 and 24. Part B safety analysis set included all subjects enrolled in Part B of the study for data analyses on developmental progress, audiological, neurological and ophthalmological assessment, and safety. Here 'Number of Subjects Analysed' signifies number of subjects evaluable for this end point and ‘n’ signifies number of subjects evaluable for each specified rows.

End point type	Secondary

End point timeframe:

Month 12 and 24 after end of study treatment in Part A (Day 1 to 14)

End point values	Part B (Non-Interventional Phase): IV Sildenafil	Part B (Non-Interventional Phase): Placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	12		
Units: units on a scale				
arithmetic mean (standard deviation)				
Month 12 (n =21, 12)	69.9 (± 14.97)	75.6 (± 3.45)		
Month 24 (n =17, 10)	65.6 (± 19.71)	76.5 (± 2.42)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Part A: Baseline up to 31 days after end of study drug infusion (up to 45 days); Part B: up to 24 months after end of study treatment in Part A (maximum up to 26 months)

Adverse event reporting additional description:

Same event may appear as both an AE and SAE. An event may be categorized as serious in one subject and as non-serious in another, or a subject may have experienced both a serious and non-serious event. Deaths (all causes) included only treatment emergent serious events. For Part-B (non-interventional) only SAEs and death data was collected.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Part A: IV Sildenafil

Reporting group description:

Subjects received sildenafil intravenously based on their body weight at a loading dose of 0.1 milligrams per kg (mg/kg) for 30 minutes on Day 1 followed by a maintenance dose of 0.03 milligrams per kg per hour (mg/kg/hr), for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

Reporting group title	Part A: Placebo

Reporting group description:

Subjects received placebo (0.9 % normal saline or dextrose 10%) at a rate matched to sildenafil infusion, intravenously, based on subject's weight for a minimum of 2 days and maximum of 14 days. Infusion continuation was upon investigator discretion in view of subjects' safety and well-being.

Reporting group title	Part B: IV Sildenafil

Reporting group description:

Subjects who started Part A (not necessarily completed Part A) and who were eligible and consented, continued to be followed up in part B of the study.

Reporting group title	Part B: Placebo

Reporting group description:

Subjects who started Part A (not necessarily completed Part A) and who were eligible and consented, continued to be followed up in part B of the study.

Serious adverse events	Part A: IV Sildenafil	Part A: Placebo	Part B: IV Sildenafil
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 29 (24.14%)	2 / 30 (6.67%)	9 / 27 (33.33%)
number of deaths (all causes)	1	1	0
number of deaths resulting from adverse events			
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural			

complications			
Skull fracture			
subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Pulmonary malformation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Congenital heart disease			
subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiomyopathy			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congestive cardiomyopathy			
subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Myoclonus			

subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Drug withdrawal syndrome			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroesophageal Reflux			
subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Apnoea			

subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension crisis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung disorder			
subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urosepsis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	2 / 27 (7.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchiolitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	2 / 27 (7.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			

subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	1 / 27 (3.70%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part B: Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 26 (23.08%)		
number of deaths (all causes)	2		
number of deaths resulting from adverse events			
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Skull fracture			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital, familial and genetic disorders			
Pulmonary malformation			

subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congenital heart disease			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiomyopathy			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Congestive cardiomyopathy			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Myoclonus			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Seizure			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Drug withdrawal syndrome			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Food allergy			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastroesophageal Reflux			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Apnoea			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary hypertension crisis			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Lung disorder			

subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Urosepsis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Bronchiolitis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory syncytial virus infection			
subjects affected / exposed	3 / 26 (11.54%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Upper respiratory tract infection			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Bronchopneumonia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			

subjects affected / exposed	1 / 26 (3.85%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Part A: IV Sildenafil	Part A: Placebo	Part B: IV Sildenafil
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 29 (68.97%)	19 / 30 (63.33%)	0 / 27 (0.00%)
Vascular disorders			
Haemodynamic instability			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Hypertension			
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Hypotension			
subjects affected / exposed	7 / 29 (24.14%)	3 / 30 (10.00%)	0 / 27 (0.00%)
occurrences (all)	7	3	0
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Drug withdrawal syndrome			
subjects affected / exposed	4 / 29 (13.79%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	4	0	0
Drug withdrawal syndrome neonatal			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Generalised oedema			

subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Infusion site extravasation			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Oedema			
subjects affected / exposed	1 / 29 (3.45%)	3 / 30 (10.00%)	0 / 27 (0.00%)
occurrences (all)	1	3	0
Secretion discharge			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Withdrawal syndrome			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Oedema genital			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	2 / 29 (6.90%)	2 / 30 (6.67%)	0 / 27 (0.00%)
occurrences (all)	2	2	0
Choking			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Hiccups			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Hypoxia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Lung disorder			

subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Neonatal asphyxia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Pneumothorax			
subjects affected / exposed	2 / 29 (6.90%)	4 / 30 (13.33%)	0 / 27 (0.00%)
occurrences (all)	2	4	0
Productive cough			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Pulmonary air leakage			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Pulmonary interstitial emphysema syndrome			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Pulmonary oedema			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Respiratory distress			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Respiratory failure			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Respiratory tract oedema			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Stridor			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0

Tachypnoea			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Selective eating disorder			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Blood albumin decreased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Blood calcium decreased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Blood magnesium decreased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Blood methaemoglobin present			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Blood urea increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
C-reactive protein increased			
subjects affected / exposed	0 / 29 (0.00%)	3 / 30 (10.00%)	0 / 27 (0.00%)
occurrences (all)	0	4	0
Haematocrit decreased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Hepatic enzyme increased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Oxygen saturation decreased			

subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
PCO2 decreased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Platelet count decreased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Staphylococcus test positive			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Thyroid function test abnormal			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Injury, poisoning and procedural complications			
Procedural hypertension			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Procedural hypotension			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Transfusion reaction			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Underdose			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Congenital, familial and genetic disorders			
Persistent foetal circulation			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Bradycardia			
subjects affected / exposed	3 / 29 (10.34%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	3	1	0
Bradycardia neonatal			

subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Junctional ectopic tachycardia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Myocardial ischaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Sinus bradycardia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Supraventricular tachycardia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Nervous system disorders			
Brain injury			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Cerebral ischaemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Hypertonia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Motor dysfunction			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Seizure			
subjects affected / exposed	2 / 29 (6.90%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	2	1	0
Vocal cord paralysis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	4 / 29 (13.79%)	3 / 30 (10.00%)	0 / 27 (0.00%)
occurrences (all)	5	3	0
Leukocytosis			
subjects affected / exposed	2 / 29 (6.90%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	2	1	0
Thrombocytopenia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Eye oedema			
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Periorbital oedema			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Pupil fixed			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 29 (3.45%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	1	1	0
Diarrhoea			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Gastric haemorrhage			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 29 (6.90%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	2	1	0
Intestinal perforation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Vomiting			

subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	2 / 29 (6.90%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	2	1	0
Hyperbilirubinaemia			
subjects affected / exposed	1 / 29 (3.45%)	3 / 30 (10.00%)	0 / 27 (0.00%)
occurrences (all)	1	3	0
Jaundice cholestatic			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	0 / 27 (0.00%)
occurrences (all)	0	2	0
Rash			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Rash erythematous			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Skin irritation			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Renal failure			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Infections and infestations			

Conjunctivitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Lung infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Nosocomial infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Pneumonia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Sepsis			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	0 / 27 (0.00%)
occurrences (all)	0	3	0
Tracheitis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Alkalosis hypochloraemic			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Feeding intolerance			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Fluid overload			
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	2	0	0
Fluid retention			
subjects affected / exposed	1 / 29 (3.45%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	1	1	0
Hyperchloraemia			

subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Hyperkalaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	0	0
Hypernatraemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminaemia			
subjects affected / exposed	1 / 29 (3.45%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	1	1	0
Hypocalcaemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Hypochloraemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	0 / 27 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	7 / 29 (24.14%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	8	0	0
Hypoproteinaemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0
Metabolic acidosis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	0 / 27 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Part B: Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 26 (0.00%)		
Vascular disorders			
Haemodynamic instability			

subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hypertension			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hypotension			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Drug withdrawal syndrome			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Drug withdrawal syndrome neonatal			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Generalised oedema			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Infusion site extravasation			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Malaise			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Oedema			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Secretion discharge			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Withdrawal syndrome			

subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Oedema genital			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Choking			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hiccups			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hypoxia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Lung disorder			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Neonatal asphyxia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Pneumothorax			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Productive cough			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Pulmonary air leakage			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Pulmonary interstitial emphysema syndrome			

subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Pulmonary oedema			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Respiratory distress			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Respiratory failure			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Respiratory tract oedema			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Stridor			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Tachypnoea			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Selective eating disorder			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Blood albumin decreased			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Blood calcium decreased			

subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Blood magnesium decreased			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Blood methaemoglobin present			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Blood urea increased			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
C-reactive protein increased			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Haematocrit decreased			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hepatic enzyme increased			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Oxygen saturation decreased			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
PCO2 decreased			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Platelet count decreased			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Staphylococcus test positive			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Thyroid function test abnormal			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Injury, poisoning and procedural			

complications			
Procedural hypertension			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Procedural hypotension			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Transfusion reaction			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Underdose			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Congenital, familial and genetic disorders			
Persistent foetal circulation			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Bradycardia neonatal			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Junctional ectopic tachycardia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Myocardial ischaemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Sinus bradycardia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Supraventricular tachycardia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		

Nervous system disorders			
Brain injury			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Cerebral ischaemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hypertonia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Motor dysfunction			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Seizure			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Vocal cord paralysis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Leukocytosis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Thrombocytopenia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Eye disorders			
Eye oedema			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Periorbital oedema			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Pupil fixed			

subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Diarrhoea			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Gastric haemorrhage			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Intestinal perforation			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Vomiting			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hyperbilirubinaemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Jaundice cholestatic			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Rash			

subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Rash erythematous			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Skin irritation			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Renal failure			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Lung infection			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Nosocomial infection			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Pneumonia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Sepsis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Tracheitis			

subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Metabolism and nutrition disorders			
Acidosis			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Alkalosis hypochloraemic			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Feeding intolerance			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Fluid overload			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Fluid retention			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hyperchloraemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hyperkalaemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hypernatraemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hypoalbuminaemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hypocalcaemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		
Hypochloraemia			
subjects affected / exposed	0 / 26 (0.00%)		
occurrences (all)	0		

Hypoglycaemia subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Hypokalaemia subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Hypoproteinaemia subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		
Metabolic acidosis subjects affected / exposed occurrences (all)	0 / 26 (0.00%) 0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported