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	

Results information

Result version number	v1
This version publication date	17 July 2019
First version publication date	17 July 2019

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	Interim
Date of interim/final analysis	24 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 October 2018
Global end of trial reached?	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	37

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 is planned to be conducted in two parts Part A (double-blind phase) and Part B (long-term, non-interventional phase). Currently reported final results are only for Part A, since the last subject last visit for Part B is expected at the end of 2020.

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 (overall period)
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

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.

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

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

Same event may appear as both an AE and SAE. However, what is presented are distinct events. 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. Total number of deaths (all causes) included only treatment emergent serious events.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

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.

Serious adverse events	IV Sildenafil	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 29 (24.14%)	2 / 30 (6.67%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events			
Congenital, familial and genetic disorders			
Pulmonary malformation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			

subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiomyopathy			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Myoclonus			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Drug withdrawal syndrome			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Infections and infestations			
Urosepsis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			

subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

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

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

subjects affected / exposed	2 / 29 (6.90%)	4 / 30 (13.33%)	
occurrences (all)	2	4	
Productive cough			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Pulmonary air leakage			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Pulmonary interstitial emphysema syndrome			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Pulmonary oedema			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Respiratory distress			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Respiratory failure			
subjects affected / exposed	0 / 29 (0.00%)	2 / 30 (6.67%)	
occurrences (all)	0	2	
Respiratory tract oedema			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Stridor			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Tachypnoea			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Selective eating disorder			

subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Blood albumin decreased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Blood calcium decreased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Blood magnesium decreased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Blood methaemoglobin present			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Blood urea increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
C-reactive protein increased			
subjects affected / exposed	0 / 29 (0.00%)	3 / 30 (10.00%)	
occurrences (all)	0	4	
Haematocrit decreased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Hepatic enzyme increased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Oxygen saturation decreased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
PCO2 decreased			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	

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

Myocardial ischaemia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Sinus bradycardia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Supraventricular tachycardia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Brain injury			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Cerebral ischaemia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Hypertonia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Motor dysfunction			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Seizure			
subjects affected / exposed	2 / 29 (6.90%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Vocal cord paralysis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 29 (13.79%)	3 / 30 (10.00%)	
occurrences (all)	5	3	
Leukocytosis			
subjects affected / exposed	2 / 29 (6.90%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Thrombocytopenia			

subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Eye disorders			
Eye oedema			
subjects affected / exposed	2 / 29 (6.90%)	0 / 30 (0.00%)	
occurrences (all)	2	0	
Periorbital oedema			
subjects affected / exposed	1 / 29 (3.45%)	0 / 30 (0.00%)	
occurrences (all)	1	0	
Pupil fixed			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 29 (3.45%)	1 / 30 (3.33%)	
occurrences (all)	1	1	
Diarrhoea			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Gastric haemorrhage			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	2	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 29 (6.90%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Intestinal perforation			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	0 / 29 (0.00%)	1 / 30 (3.33%)	
occurrences (all)	0	1	
Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	2 / 29 (6.90%)	1 / 30 (3.33%)	
occurrences (all)	2	1	
Hyperbilirubinaemia			

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

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

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