# 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