Clinical trial results:
Multicenter, double-blind, placebo-controlled, randomized, prospective study of bosentan as adjunctive therapy to inhaled nitric oxide in the management of persistent pulmonary hypertension of the newborn (PPHN)

Summary

EudraCT number	2011-000203-41
Trial protocol	DE NL CZ GB FR BE PL Outside EU/EEA
Global end of trial date	05 December 2013

Results information

Result version number	v1 (current)
This version publication date	11 May 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	AC-052-391

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01389856
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 4123
Public contact	Clinical Trial Disclosure Desk, Actelion Pharmaceuticals Ltd, clinical-trials-disclosure@actelion.com
Scientific contact	Clinical Trial Disclosure Desk, Actelion Pharmaceuticals Ltd, clinical-trials-disclosure@actelion.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000425-PIP02-10
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	08 January 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 December 2013
Global end of trial reached?	Yes
Global end of trial date	05 December 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the efficacy of bosentan in neonates with persistent pulmonary hypertension of the newborn (PPHN) who were in need of continued inhaled nitric oxide (iNO) after at least 4 hours of continuous iNO treatment.

Protection of trial subjects:

This clinical study was conducted within the framework of the pediatric development program agreed with the Pediatric Committee at the European Medicines Agency, and designed in compliance with the EMA pediatric guidelines for PPHN, which recommend an add-on trials in patients failing treatment with iNO (EMA/CHMP/213972/2010)

Parent(s) or the legal representative(s) were asked if they agreed that their baby took part in the study.

Background therapy:

Inhaled nitric oxide (iNO) was administered concurrently with the study drug as per the standard care at the center, and as as per protocol requirements at randomization and weaning.
The following standard treatments for conditions associated with PPHN were permitted to be administered along with the study drugs:
• Milrinone
• Vasopressors (e.g., dopamine, dobutamine, terlipressin, epinephrine or norepinephrine)
• Neuromuscular blocking agents (e.g., Pancuronium/Pavulon)
• Surfactant
• Sodium bicarbonate or tromethamine to correct metabolic acidosis
• Other therapies to correct or avoid hypothermia, hypovolemia, hypoglycemia, hypocalcemia or anemia should have been applied as per best medical practice, including magnesium sulfate (MgSO4) if it was used to treat hypomagnesemia.

Evidence for comparator: -

Actual start date of recruitment	08 December 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	France: 1
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 3

Worldwide total number of subjects	21
EEA total number of subjects	17

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	21
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:

The study was conducted in expert pediatric centers with neonatal intensive care unit facilities at which inhaled nitric oxide (iNO) was used as standard of care for PPHN.
23 patients were randomized but 2 were not treated and not included in any analyses

Pre-assignment

Screening details:

Term or near-term (gestational age > 34 weeks) hypoxic newborns with respiratory distress refractory to supplemental oxygen were considered, provided they had no significant structural cardiac anomalies documented in the pre-natal period and no immediate need for extra corporeal membrane oxygenation.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

Only the members of the independent data monitoring committee reviewed data unblinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Bosentan

Arm description:

This arm includes neonates who received bosentan on top of iNO

Arm type	Experimental
Investigational medicinal product name	bosentan
Investigational medicinal product code	ACT-050088
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Nasogastric use

Dosage and administration details:

Quadrisectable 32 mg tablet of bosentan dispersed in sterile water and administered by nasogastric or orogastric tube at a dose of 2 mg/kg of weight at birth twice daily (b.i.d) for a minimum of 2 days and up to 14 days (planned duration)

Arm title	Placebo

Arm description:

This arm includes neonates who received matching placebo on top of iNO

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Nasogastric use

Dosage and administration details:

matching placebo tablets dispersed in sterile water and administered by nasogastric or orogastric tube according to the same schedule as the active compound

Number of subjects in period 1	Bosentan	Placebo
Started	13	8
Completed	13	8

Baseline characteristics

Reporting groups	
Reporting group title	Bosentan
Reporting group description:	
This arm includes neonates who received bosentan on top of iNO	
Reporting group title	Placebo
Reporting group description:	
This arm includes neonates who received matching placebo on top of iNO	

Reporting group values	Bosentan	Placebo	Total
Number of subjects	13	8	21
Age categorical			
Age at first dosing in all patients who received at least one dose of study drug			
Units: Subjects			
Newborns (0-27 days)	13	8	21
Age Continuous			
Median age at first dosing in all patients who received at least one dose of study drug			
Units: days			
median	1.4	1.7	
full range (min-max)	0.6 to 5.6	0.6 to 5.9	-
Gender categorical			
Units: Subjects			
Female	9	6	15
Male	4	2	6
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian/white	11	6	17
Asian	1	0	1
Hispanic	1	1	2
Other	0	1	1
Primary PPHN etiology			
Among the 9 patients reported to have neonatal aspiration in the Bosentan group, 4 also had another parenchymal lung disease: 3 had respiratory distress syndrome and one had sepsis. So, data reported in the table below for the Bosentan arm must be read as follows: neonatal aspiration n = 9, neonatal respiratory distress syndrome n = 4, pneumonia/sepsis n = 4 since these different conditions are not mutually exclusive			
Units: Subjects			
Idiopathic	0	3	3
Neonatal aspiration	9	3	12
Neonatal respiratory distress syndrome	1	0	1
Pneumonia / Sepsis	3	2	5
Gestational age			
Median gestational age in all patients who received at least one of study drug			
Units: weeks			
median	40	38.5	
full range (min-max)	36 to 41	36 to 42	-
Oxygenation index (OI) at first dosing			
OI is a measure of the severity of pulmonary dysfunction: The higher OI is, the more severe is the			

disease.			
Units: none			
median	18.3	13.2	
full range (min-max)	5.9 to 44.3	7.1 to 39.4	-

End points

End points reporting groups

Reporting group title	Bosentan
Reporting group description:	
This arm includes neonates who received bosentan on top of iNO	
Reporting group title	Placebo
Reporting group description:	
This arm includes neonates who received matching placebo on top of iNO	
Subject analysis set title	all-treated set
Subject analysis set type	Full analysis
Subject analysis set description:	
This set consists of all patients who received at least one dose of study drug (bosentan or matching placebo) and was used for the analysis of all efficacy endpoints. The "full analysis" set, the "safety" set and the "All -treated" set were identical. This set was used for the analysis of all efficacy endpoints.	
Subject analysis set title	pharmacokinetic set
Subject analysis set type	Per protocol
Subject analysis set description:	
This set comprised all bosentan-treated patients included in the all treated set who were able to provide at least 5 of the 7 blood samples requested for at least one evaluable profile of PK assessment and who did not violate the protocol in a way that might affect the evaluation of the PK endpoints. Pharmacokinetic analyses were performed using this set.	

Primary: Proportion of patients with treatment failure

End point title	Proportion of patients with treatment failure
End point description:	
Treatment failure was defined as the need for extra corporeal membrane oxygenation or initiation of alternative pulmonary vasodilator treatment	
End point type	Primary
End point timeframe:	
From the first dose of study drug up to end of study (maximum = 21 days)	

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: Percentage of patients				
number (not applicable)	7.7	0		

Statistical analyses

Statistical analysis title	Treatment comparison
Comparison groups	Bosentan v Placebo

Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 1
Method	Fisher exact

Notes:

[1] - No formal statistical hypothesis on expected treatment difference was defined

Primary: Time to complete weaning from iNO

End point title	Time to complete weaning from iNO

End point description:

Calculated from the time from first study drug administration to complete weaning from iNO. Weaning from iNO was considered complete if there was no requirement for the re-initiation of iNO within 24 h after stopping

End point type	Primary

End point timeframe:

From first study drug administration up to end of study (maximum = 21 days)

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: Days				
median (confidence interval 95%)	3.7 (1.17 to 6.95)	2.9 (1.26 to 4.23)		

Statistical analyses

Statistical analysis title	Treatment comparison
Comparison groups	Bosentan v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.3407
Method	Logrank

Notes:

[2] - No formal statistical hypothesis on expected treatment difference was defined

Primary: Time to complete weaning from mechanical ventilation

End point title	Time to complete weaning from mechanical ventilation

End point description:

Calculated from the time from first study drug administration to complete weaning from mechanical ventilation

End point type	Primary

End point timeframe:

From first study drug administration up to end of study (maximum = 21 days)

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: Days				
median (confidence interval 95%)	10.8 (3.21 to 12.21)	8.6 (3.71 to 9.66)		

Statistical analyses

Statistical analysis title	Treatment comparison
Comparison groups	Bosentan v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.2399
Method	Logrank

Notes:

[3] - No formal statistical hypothesis on expected treatment difference was defined

Secondary: Proportion of patients requiring re-initiation of iNO therapy

End point title	Proportion of patients requiring re-initiation of iNO therapy

End point description:

Re-initiation of iNO therapy following weaning from iNO therapy

End point type	Secondary

End point timeframe:

From first study drug administration up to end of study (maximum = 21 days)

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: percentage of participants				
number (not applicable)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of patients with pulmonary hypertension (PH) at end of treatment

End point title	Proportion of patients with pulmonary hypertension (PH) at end of treatment

End point description:

The presence of PH was assessed by echocardiography. PH was reported as 'present' if at least one of the following criteria was met: • Shunt through ductus arteriosus was either 'predominant right to left' or 'bidirectional' • Shunt through foramen ovale was either 'predominant right to left' or 'bidirectional' • Marked right ventricular dilation was ticked 'present' • Paradoxical shift of intraventricular septum was ticked 'present' • Right ventricular systolic pressure (mmHg) was > 2/3 of the reported systemic blood pressure

End point type	Secondary

End point timeframe:

From first study drug administraton up to end of treatment (maximum = 14 days)

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	8		
Units: Percentage of patients				
number (not applicable)	41.7	37.5		

Statistical analyses

Statistical analysis title	Treatment comparison

Statistical analysis description:

Treatment comparison 72 hours after first study drug administration

Comparison groups	Bosentan v Placebo
Number of subjects included in analysis	21
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 1
Method	Fisher exact

Notes:

[4] - No formal statistical hypothesis on expected treatment difference was defined.

Secondary: Change from baseline in oxygenation index (OI) over time

End point title	Change from baseline in oxygenation index (OI) over time

End point description:

OI was calculated as the mean airway pressure multiplied by the fraction of inspired oxygen (expressed in %), and the product was divided by the partial pressure of oxygen in arterial blood.
OI changed in a similar manner from baseline over time in the bosentan and placebo groups, with large inter-subject variability. So, only the statistical analysis for changes from baseline to 72 hours is reported here.
Note: one patient in the bosentan group was not analyzed after time 24 hours because of treatment failure.

End point type	Secondary

End point timeframe:

At baseline and at scheduled time points up to end of treatment. The data presented show changes from baseline to 72 hours because most patients were exposed at least 3 days and had measurements available during this period.

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: oxygenation index				
median (confidence interval 95%)				
Baseline for timepoint 72 hours	19.4 (8.2 to 35.4)	13.2 (7.9 to 39.4)		
Change from baseline to 72 hours	-8.9 (-23.1 to -1.8)	-9.4 (-17.7 to 2.2)		

Statistical analyses

Statistical analysis title	Treatment comparison

Statistical analysis description:

Treatment comparison 72 hours after first study drug administration

Comparison groups	Bosentan v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.1015
Method	Non-parametric ANCOVA

Notes:

[5] - No formal statistical hypothesis on expected treatment difference was defined

Secondary: Change from baseline in arterial pH over time

End point title	Change from baseline in arterial pH over time

End point description:

Arterial pH changed in a similar manner from baseline over time in the bosentan and placebo groups. So, only the statistical analysis for changes from baseline to 72 hours is reported here.
Note: one patient in the bosentan group was not analyzed after time 24 hours because of treatment failure.

End point type	Secondary

End point timeframe:

At baseline and at scheduled time points up to end of treatment. The data presented show changes from baseline to 72 hours because most patients were exposed at least 3 days and had measurements available during this period.

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: pH				
median (confidence interval 95%)				
baseline for timepoint 72 hours	7.37 (7.3 to 7.43)	7.31 (7.21 to 7.49)		

change from baseline to 72 hours	0.04 (-0.06 to 0.07)	0.02 (-0.09 to 0.19)		

Statistical analyses

Statistical analysis title	Treatment comparison

Statistical analysis description:

Treatment comparison 72 hours after first study drug administration

Comparison groups	Bosentan v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.0824
Method	Non-parametric ANCOVA

Notes:

[6] - No formal statistical hypothesis on expected treatment difference was defined

Secondary: Change from baseline in arterial blood oxygen saturation (SaO2) over time

End point title	Change from baseline in arterial blood oxygen saturation (SaO2) over time

End point description:

Arterial SaO2 changed in a similar manner from baseline over time in the bosentan and placebo groups. So, only the statistical analysis for changes from baseline to 72 hours is reported here.
Note: Data from 2 patients in the bosentan group were missing at time 72 hours and another one had no value available.

End point type	Secondary

End point timeframe:

At baseline and at scheduled time points up to end of treatment. The data presented show changes from baseline to 72 hours because most patients were exposed at least 3 days and had measurements available during this period.

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	8		
Units: percentage saturation				
median (confidence interval 95%)				
Baseline for timepoint 72 hours	95 (92 to 99)	95.5 (89 to 99)		
change from baseline to 72 hours	1 (0 to 8)	0 (-4 to 21)		

Statistical analyses

Statistical analysis title	Treatment comparison

Statistical analysis description:	
Treatment comparison 72 hours after first study drug administration	
Comparison groups	Bosentan v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.3863
Method	Non-parametric ANCOVA

Notes:

[7] - No formal statistical hypothesis on expected treatment difference was defined.

Secondary: Change from baseline in partial pressure of oxygen (PaO2) in arterial blood over time

End point title	Change from baseline in partial pressure of oxygen (PaO2) in arterial blood over time

End point description:

PaO2 changed in a similar manner from baseline over time in the bosentan and placebo groups, with both groups plateauing at 24 hours and retaining almost identical median values out to 72 hours. So, only the statistical analysis for changes from baseline to 72 hours is reported here.
Note: One patient in the bosentan group was not analyzed after time 24 hours because of treatment failure.

End point type	Secondary

End point timeframe:

At baseline and at scheduled time points up to end of treatment. The data presented show changes from baseline to 72 hours because most patients were exposed at least 3 days and had measurements available during this period.

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: mmHg				
median (confidence interval 95%)				
Baselin for timepoint 72 hours	61 (53 to 132)	69.5 (46 to 111)		
Change from baseline to 72 hours	18 (-13 to 32)	6 (-12 to 115)		

Statistical analyses

Statistical analysis title	Treatment comparison

Statistical analysis description:

Treatment comparison 72 hours after first study drug administration

Comparison groups	Bosentan v Placebo

Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.3936
Method	Nonparametric ANCOVA

Notes:

[8] - No formal statistical hypothesis on expected treatment difference was defined.

Secondary: Change from baseline in partial pressure of carbon dioxide (PaCO2) in arterial blood over time

End point title	Change from baseline in partial pressure of carbon dioxide (PaCO2) in arterial blood over time

End point description:

PaCO2 changed in a similar manner from baseline over time in the bosentan and placebo groups. So, only the statistical analysis for changes from baseline to 72 hours is reported here.
Note: one patient in the bosentan group was not analyzed after time 24 hours because of treatment failure.

End point type	Secondary

End point timeframe:

At baseline and at scheduled time points up to end of treatment. The data presented show changes from baseline to 72 hours because most patients were exposed at least 3 days and had measurements available during this period.

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: mmHg				
median (confidence interval 95%)				
Baseline for timepoint 72 hours	40.5 (31 to 47)	46 (35 to 57)		
Change from baseline to 72 hours	6 (-1 to 12)	8 (-8 to 21)		

Statistical analyses

Statistical analysis title	Treatment comparison

Statistical analysis description:

Treatment comparison 72 hours after first study drug administration

Comparison groups	Bosentan v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.2436
Method	Non-parametric ANCOVA

Notes:

[9] - No formal statistical hypothesis on expected treatment difference was defined.

Secondary: Change from baseline in pre-ductal peripheral oxygen saturation (SpO2) over time

End point title	Change from baseline in pre-ductal peripheral oxygen saturation (SpO2) over time

End point description:

Simultaneous pre- (right hand) and post-ductal (lower extremities) SpO2 were measured using pulse oximetry device.
Changes from baseline in SpO2 over time were similar in the bosentan and placebo groups. So, only the statistical analysis for changes from baseline to 72 hours is reported here.
Note: one patient in the bosentan group was not analyzed after time 24 hours because of treatment failure.

End point type	Secondary

End point timeframe:

At baseline and at scheduled time points up to end of treatment. The data presented show changes from baseline to 72 hours because most patients were exposed at least 3 days and had measurements available during this period.

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: percentage saturation				
median (confidence interval 95%)				
Baseline for time 72 hours	95 (91 to 99)	97 (91 to 99)		
Change from baseline to 72 hours	0.5 (-2 to 2)	-1 (-10 to 2)		

Statistical analyses

Statistical analysis title	Treatment comparison

Statistical analysis description:

Treatment comparison 72 hours after first study drug adminsitration

Comparison groups	Bosentan v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[10]
P-value	= 0.1756
Method	Non-parametric ANCOVA

Notes:

[10] - No formal statistical hypothesis on expected treatment difference was defined.

Secondary: Change from baseline in post-ductal peripheral oxygen saturation (SpO2) over time

End point title	Change from baseline in post-ductal peripheral oxygen saturation (SpO2) over time

End point description:

Simultaneous pre- (right hand) and post-ductal (lower extremities) SpO2 were measured using pulse oximetry device.
Changes from baseline in SpO2 over time were similar in the bosentan and placebo groups. So, only the statistical analysis for changes from baseline to 72 hours is reported here.
Note: one patient in the bosentan group was not analyzed after time 24 hours because of treatment failure.

End point type	Secondary

End point timeframe:

At baseline and at scheduled time points up to end of treatment. The data presented show changes from baseline to 72 hours because most patients were exposed at least 3 days and had measurements available during this period.

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: percentage saturation				
median (confidence interval 95%)				
Baseline for time 72 hours	96.5 (92 to 99)	96 (89 to 98)		
Change from baseline to 72 hours	0 (-2 to 3)	2 (1 to 12)		

Statistical analyses

Statistical analysis title	Treatment comparison

Statistical analysis description:

Treatment comparison 72 hours after first study drug administration

Comparison groups	Bosentan v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[11]
P-value	= 0.1155
Method	Non-parametric ANCOVA

Notes:

[11] - No formal statistical hypothesis on expected treatment difference was defined.

Secondary: Change from baseline in fraction of inspired oxygen (FiO2) over time

End point title	Change from baseline in fraction of inspired oxygen (FiO2) over time

End point description:

FiO2 was determined according to each study centers' standard procedure.
Changes from baseline in FiO2 over time were similar in the bosentan and placebo groups. So, only the statistical analysis for changes from baseline to 72 hours is reported here.
Note: one patient in the bosentan group was not analyzed after time 24 hours because of treatment failure.

End point type	Secondary

End point timeframe:

At baseline and at scheduled time points up to end of treatment. The data presented show changes from baseline to 72 hours because most patients were exposed at least 3 days and had measurements available during this period.

End point values	Bosentan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	12	8		
Units: percentage of oxygen				
median (confidence interval 95%)				
Baseline for time 72 hous	90 (62 to 97)	78 (60 to 100)		
Change from baseline to 72 hours	-33.5 (-50 to -15)	-35.5 (-60 to 0)		

Statistical analyses

Statistical analysis title	Treatment comparison

Statistical analysis description:

Treatment comparison 72 hours after first study drug administration

Comparison groups	Bosentan v Placebo
Number of subjects included in analysis	20
Analysis specification	Pre-specified
Analysis type	other[12]
P-value	= 0.14
Method	Non-parametric ANCOVA

Notes:

[12] - No formal statistical hypothesis on expected treatment difference was defined.

Secondary: Maximum whole blood concentration (Cmax) on Day 1 for bosentan and its metabolites (Ro 47-8634, Ro 48-5033, Ro 64-1056)

End point title	Maximum whole blood concentration (Cmax) on Day 1 for bosentan and its metabolites (Ro 47-8634, Ro 48-5033, Ro 64-1056)[13]

End point description:

This is the maximum concentration of bosentan or its metaboites measured directly from the whole blood samples (dried blood spot samples) scheduled to be taken immediately prior to study drug administration and 0.5, 1, 2, 3, 7.5, and 12 hours after first study drug administration on Day 1.
As the smallest dose unit was 8 mg (1/4 tablet), it was not possible to achieve the exact target dose of 2 mg/kg bosentan in all patients. Therefore Cmax was corrected to a dose of 2 mg/kg bosentan (Cmaxc = Cmax / actual dose x 2 mg/kg)

End point type	Secondary

End point timeframe:

Day 1

Notes:

[13] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Exploratory endpoint with only descriptive summary statistics provided

End point values	Bosentan			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: ng/mL				
geometric mean (confidence interval 95%)				
Bosentan	30.1 (2.4 to 372.2)			

Ro 47-8634	0.1 (0 to 1.1)			
Ro 48-5033	0.6 (0 to 18.3)			
Ro 64-1056	0.9 (0 to 16.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum whole blood concentration (Cmax) on Day 5 for bosentan and its metabolites (Ro 47-8634, Ro 48-5033, Ro 64-1056)

End point title	Maximum whole blood concentration (Cmax) on Day 5 for bosentan and its metabolites (Ro 47-8634, Ro 48-5033, Ro 64-1056)[14]

End point description:

This is the maximum concentration measured directly from the whole blood samples (dried blood spot samples) in patients still on study treatment on Day 5 and scheduled to be taken immediately prior to study drug administration on Day 5 and 0.5, 1, 2, 3, 7.5, and 12 hours thereafter.
As the smallest dose unit was 8 mg (1/4 tablet), it was not possible to achieve the exact target dose of 2 mg/kg bosentan in all patients. Therefore Cmax was corrected to a dose of 2 mg/kg bosentan (Cmaxc = Cmax / actual dose x 2 mg/kg)

End point type	Secondary

End point timeframe:

Day 5

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Exploratory endpoint with only descriptive summary statistics provided

End point values	Bosentan			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: ng/mL				
geometric mean (confidence interval 95%)				
Bosentan	880 (339.2 to 2282.7)			
Ro 47-8634	24.9 (9 to 69.1)			
Ro 48-5033	292.3 (115.8 to 738.1)			
Ro 64-1056	136 (77.4 to 238.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum whole blood concentration (tmax) for bosentan on Day 1

End point title	Time to maximum whole blood concentration (tmax) for

	bosentan on Day 1[15]

End point description:

tmax was measured directly from the whole blood samples (dried blood spot samples) scheduled to be taken immediately prior to study drug administration and 0.5, 1, 2, 3, 7.5, and 12 hours after first study drug administration on Day 1.

End point type	Secondary

End point timeframe:

Day 1

Notes:

[15] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Exploratory endpoint with only descriptive summary statistics provided

End point values	Bosentan			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: hours				
median (full range (min-max))	12 (7.5 to 12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum whole blood concentration (tmax) for Ro 47-8634 on Day 1

End point title	Time to maximum whole blood concentration (tmax) for Ro 47-8634 on Day 1[16]

End point description:

tmax was measured directly from the whole blood samples (dried blood spot samples) scheduled to be taken immediately prior to study drug administration and 0.5, 1, 2, 3, 7.5, and 12 hours after first study drug administration on Day 1.

End point type	Secondary

End point timeframe:

Day 1

Notes:

[16] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Exploratory endpoint with only descriptive summary statistics provided

End point values	Bosentan			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: hours				
median (full range (min-max))	12 (7.5 to 12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum whole blood concentration (tmax) for Ro 48-5033 on Day 1

End point title	Time to maximum whole blood concentration (tmax) for Ro 48-5033 on Day 1[17]

End point description:

tmax was measured directly from the whole blood samples (dried blood spot samples) collected within 12 hours after first study drug administration on Day 1.

End point type	Secondary

End point timeframe:

Day 1

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Exploratory endpoint with only descriptive summary statistics provided

End point values	Bosentan			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: hours				
median (full range (min-max))	12 (12 to 12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum whole blood concentration (tmax) for Ro 64-1056 on Day 1

End point title	Time to maximum whole blood concentration (tmax) for Ro 64-1056 on Day 1[18]

End point description:

Tmax was measured directly from the whole blood samples (dried blood spot samples) scheduled to be taken immediately prior to study drug administration and 0.5, 1, 2, 3, 7.5, and 12 hours after first study drug administration on Day 1.

End point type	Secondary

End point timeframe:

Day 1

Notes:

[18] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Exploratory endpoint with only descriptive summary statistics provided

End point values	Bosentan			
Subject group type	Reporting group			
Number of subjects analysed	8			
Units: hours				
median (full range (min-max))	12 (0.5 to 12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum whole blood concentration (tmax) for bosentan on Day 5

End point title	Time to maximum whole blood concentration (tmax) for bosentan on Day 5[19]

End point description:

tmax was measured directly from the whole blood samples (dried blood spot samples) in patients still on study treatment on Day 5. Samples were scheduled to be taken immediately prior to study drug administration on Day 5 and 0.5, 1, 2, 3, 7.5, and 12 hours thereafter.

End point type	Secondary

End point timeframe:

Day 5

Notes:

[19] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Exploratory endpoint with only descriptive summary statistics provided

End point values	Bosentan			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: hours				
median (full range (min-max))	7.5 (0.8 to 12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum whole blood concentration (tmax) for Ro 47-8634 on Day 5

End point title	Time to maximum whole blood concentration (tmax) for Ro 47-8634 on Day 5[20]

End point description:

tmax was measured directly from the whole blood samples (dried blood spot samples) in patients still on study treatment on Day 5. Samples were scheduled to be taken immediately prior to study drug administration on Day 5 and 0.5, 1, 2, 3, 7.5, and 12 hours thereafter.

End point type	Secondary

End point timeframe:

Day 5

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Exploratory endpoint with only descriptive summary statistics provided

End point values	Bosentan			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: hours				
median (full range (min-max))	6.5 (0.8 to 12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum whole blood concentration (tmax) for Ro 48-5033 on Day 5

End point title	Time to maximum whole blood concentration (tmax) for Ro 48-5033 on Day 5[21]

End point description:

tmax was measured directly from the whole blood samples (dried blood spot samples) in patients still on study treatment on Day 5. Samples were scheduled to be taken immediately prior to study drug administration on Day 5 and 0.5, 1, 2, 3, 7.5, and 12 hours thereafter.

End point type	Secondary

End point timeframe:

Day 5

Notes:

[21] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Exploratory endpoint with only descriptive summary statistics provided

End point values	Bosentan			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: hours				
median (full range (min-max))	7.5 (0.8 to 12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum whole blood concentration (tmax) for Ro 64-1056 on Day 5

End point title	Time to maximum whole blood concentration (tmax) for Ro 64-1056 on Day 5[22]

End point description:

tmax was measured directly from the whole blood samples (dried blood spot samples) in patients still on

study treatment on Day 5. Samples were scheduled to be taken immediately prior to study drug administration on Day 5 and 0.5, 1, 2, 3, 7.5, and 12 hours thereafter.

End point type	Secondary

End point timeframe:

Day 5

Notes:

[22] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Exploratory endpoint with only descriptive summary statistics provided

End point values	Bosentan			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: hours				
median (full range (min-max))	12 (7.5 to 12)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration-time curve over one dosing interval [AUC(0-12)] on Day 1 for bosentan and Its Metabolites (Ro 47-8634, Ro 48-5033, and Ro 64-1056)

End point title	Area under the concentration-time curve over one dosing interval [AUC(0-12)] on Day 1 for bosentan and Its Metabolites (Ro 47-8634, Ro 48-5033, and Ro 64-1056)[23]

End point description:

AUC(0-12) on Day 1 was calculated according to the trapezoidal rule using the measured concentration-time values above the limit of quantification (LOQ).
AUC(0-12) was determined on the basis of scheduled blood sampling time points (prior to study drug administration and 0.5, 1, 2, 3, 7.5, and 12 hours after first study drug administration on Day 1).

End point type	Secondary

End point timeframe:

Day 1

Notes:

[23] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Exploratory endpoint with only descriptive summary statistics provided

End point values	Bosentan			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: h*ng/mL				
geometric mean (confidence interval 95%)				
Bosentan	163.9 (9.6 to 2795.4)			
Ro 47-8634	0.1 (0 to 3.7)			
Ro 48-5033	1.4 (0 to 69.9)			
Ro 64-1056	2.2 (0.1 to 64.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration-time curve over a dosing interval at steady state (AUCtau)on Day 5 for Bosentan and Its Metabolites (Ro 47-8634, Ro 48-5033, and Ro 64-1056)

End point title	Area under the concentration-time curve over a dosing interval at steady state (AUCtau)on Day 5 for Bosentan and Its Metabolites (Ro 47-8634, Ro 48-5033, and Ro 64-1056)[24]

End point description:

AUCtau on Day 5 was calculated according to the trapezoidal rule using the measured concentration-time values above the limit of quantification.
AUCtau was determined on the basis of scheduled blood sampling time points (prior to study drug administration on Day 5 and 0.5, 1, 2, 3, 7.5, and 12 hours thereafter) in patients still on study treatment on Day 5.

End point type	Secondary

End point timeframe:

Day 5

Notes:

[24] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Exploratory endpoint with only descriptive summary statistics provided

End point values	Bosentan			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: h*ng/mL				
geometric mean (confidence interval 95%)				
Bosentan	6165.4 (2429.6 to 15645.3)			
Ro 47-8634	217.3 (75.3 to 626.8)			
Ro 48-5033	2839.5 (1155.2 to 6979.2)			
Ro 64-1056	1321.7 (729.5 to 2395)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration-time curve over a period of 24 h [AUC(0-

24c)] on Day 1 for Bosentan and Its Metabolites (Ro 47-8634, Ro 48-5033, and Ro 64-1056)

End point title	Area under the concentration-time curve over a period of 24 h [AUC(0-24c)] on Day 1 for Bosentan and Its Metabolites (Ro 47-8634, Ro 48-5033, and Ro 64-1056)[25]

End point description:

AUC(0-24c) on Day 1 was calculated as a multiple of AUC0-12 (2 × AUC0-12 for 2 times daily dosing) and corrected to 2 mg/kg (target dose).
AUC(0-24c) was determined on the basis of scheduled blood sampling time points (prior to study drug administration and 0.5, 1, 2, 3, 7.5, and 12 hours after first study drug administration on Day 1).

End point type	Secondary

End point timeframe:

Day 1

Notes:

[25] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Exploratory endpoint with only descriptive summary statistics provided

End point values	Bosentan			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: h*ng/mL				
geometric mean (confidence interval 95%)				
Bosentan	287.5 (15 to 5504.7)			
Ro 47-8634	0.1 (0 to 6.1)			
Ro 48-5033	2 (0 to 125.8)			
Ro 64-1056	3.4 (0.1 to 120.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the concentration-time curve over a period of 24 h [AUC(0-24hc)] on Day 5 for Bosentan and Its Metabolites (Ro 47-8634, Ro 48-5033, and Ro 64-1056)

End point title	Area under the concentration-time curve over a period of 24 h [AUC(0-24hc)] on Day 5 for Bosentan and Its Metabolites (Ro 47-8634, Ro 48-5033, and Ro 64-1056)[26]

End point description:

AUC(0-24c) on Day 5 was calculated as a multiple of AUCtau, (2 × AUCtau for 2 times daily dosing) corrected to 2 mg/kg (target dose).
[AUC(0-24c)] was determined on the basis of scheduled blood sampling time points (prior to study drug administration on Day 5 and 0.5, 1, 2, 3, 7.5, and 12 hours thereafter) in patients still on study treatment on Day 5.

End point type	Secondary

End point timeframe:

Day 5

Notes:

[26] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Exploratory endpoint with only descriptive summary statistics provided

End point values	Bosentan			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: h*ng/mL				
geometric mean (confidence interval 95%)				
Bosentan	11530.2 (4507 to 29497.5)			
Ro 47-8634	406.3 (139.8 to 1180.9)			
Ro 48-5033	5310.3 (2184.4 to 12908.9)			
Ro 64-1056	2471.9 (1386.1 to 4408)			

Statistical analyses

No statistical analyses for this end point

Secondary: Accumulation index (AI) for Bosentan

End point title	Accumulation index (AI) for Bosentan[27]

End point description:

AI was calculated as the ratio AUCtau / AUC(0-12) for the subjects having PK samples collected on both Day 1 and Day 5 and with AUC0-12 > 0 ng.h/mL.

End point type	Secondary

End point timeframe:

5 days

Notes:

[27] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Exploratory endpoint with only descriptive summary statistics provided

End point values	Bosentan			
Subject group type	Reporting group			
Number of subjects analysed	7			
Units: accumulation index				
geometric mean (confidence interval 95%)	61.6 (0.5 to 7813.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Events with onset up to 7 days after end of treatment

Adverse event reporting additional description:

For serious adverse events, a 60-day post-treatment safety follow-up was conducted by phone. During this follow-up period, hepatitis was reported in one bosentan-treated patient (8 days after study drug stop) and resolved within the 60-days follow-up period.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

This arm includes neonates who received matching placebo on top of iNO for a minimum of 2.5 days to a maximum duration of 6.5 days (i.e., until 24 hours after complete weaning from iNO) (median duration = 4.0 days).

Reporting group title	Bosentan

Reporting group description:

This arm includes neonates who received bosentan on top of iNO at least once to a maximum duration of 10 days (i.e., up to treatment failure or until 24 hours after complete weaning from iNO) (median duration = 4.5 days).

Serious adverse events	Placebo	Bosentan	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 8 (37.50%)	2 / 13 (15.38%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
CIRCULATORY COLLAPSE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
HEPATITIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
HYPERCAPNIA			

subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX			
subjects affected / exposed	2 / 8 (25.00%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
SEPSIS			
subjects affected / exposed	1 / 8 (12.50%)	0 / 13 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
METABOLIC ACIDOSIS			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Bosentan	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 8 (25.00%)	9 / 13 (69.23%)	
Investigations			
BILIRUBIN CONJUGATED INCREASED			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	2	
BODY TEMPERATURE INCREASED			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
C-REACTIVE PROTEIN INCREASED			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			

ENDOTRACHEAL INTUBATION COMPLICATION			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
PROCEDURAL COMPLICATION			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Cardiac disorders			
MITRAL VALVE INCOMPETENCE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	1 / 8 (12.50%)	3 / 13 (23.08%)	
occurrences (all)	1	3	
COAGULOPATHY			
subjects affected / exposed	1 / 8 (12.50%)	1 / 13 (7.69%)	
occurrences (all)	1	1	
METHAEMOGLOBINAEMIA			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
THROMBOCYTOPENIA			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	3	
General disorders and administration site conditions			
GENERALISED OEDEMA			
subjects affected / exposed	0 / 8 (0.00%)	3 / 13 (23.08%)	
occurrences (all)	0	3	
Gastrointestinal disorders			
VOMITING			
subjects affected / exposed	0 / 8 (0.00%)	2 / 13 (15.38%)	
occurrences (all)	0	2	
GASTRIC HAEMORRHAGE			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			

DYSPHONIA			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
PNEUMOMEDIASTINUM			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
PNEUMOTHORAX			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Infections and infestations			
INFECTIOUS DISEASE CARRIER			
subjects affected / exposed	0 / 8 (0.00%)	1 / 13 (7.69%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
HYPOGLYCAEMIA			
subjects affected / exposed	1 / 8 (12.50%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
HYPOKALAEMIA			
subjects affected / exposed	1 / 8 (12.50%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
HYPOPHOSPHATAEMIA			
subjects affected / exposed	1 / 8 (12.50%)	0 / 13 (0.00%)	
occurrences (all)	1	0	
METABOLIC ACIDOSIS			
subjects affected / exposed	1 / 8 (12.50%)	0 / 13 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 May 2012	Changes in the inclusion criteria Classification of objectives and endpoints into primary and secondary criteria
17 December 2012	Due to the slow recruitment, the eligibility criteria were adjusted to be less stringent, allowing inclusion of patients with less severe persistent pulmonary hypertension of the newborn (PPHN) and who were still in need of continuous inhaled nitric oxide (iNO) therapy and could benefit from additional therapy with bosentan

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Overall, the disease was more severe in the bosentan group than in the placebo group (higher oxygen index at baseline), which may have introduced a bias into the treatment comparison of the outcome "time to iNO weaning"

Notes: