Clinical trial results:
An open label, prospective multicenter study to assess the pharmacokinetics, tolerability, safety and efficacy of the pediatric formulation of bosentan two versus three times a day in children with pulmonary arterial hypertension

Summary

EudraCT number	2010-021825-11
Trial protocol	NL HU DE ES CZ FR IT BG Outside EU/EEA
Global end of trial date	26 August 2013

Results information

Result version number	v1
This version publication date	03 June 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	AC-052-373

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01223352
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	25 September 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 August 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the pharmacokinetics (PK) of the dispersible tablet formulation of bosentan at doses of 2 mg/kg b.i.d. and 2 mg/kg t.i.d. in children with pulmonary arterial hypertension (PAH) from ≥ 3 months to < 12 years of age.

Protection of trial subjects:

This clinical study was designed and conducted in accordance with the ICH Harmonized Tripartite Guidelines for GCPs, with the ethical principles laid down in the 'Declaration of Helsinki' and with the laws and regulations of the countries in which the research was conducted.

Child's parents or legal representatives were asked if they agreed that their child took part in the study prior to any study procedure and after adequate explanation of the aims, methods, objectives, and potential hazards of the study.

Background therapy:

The following medications were allowed to be taken along with the study drug: anticoagulants, diuretics, digoxin, calcium channel blockers, prostanoids and phosphodiesterase-5 inhibitors.
All background PAH therapies were required to be maintained at a stable dose during the study. Intiation or dose increase of ongoing PAH-specific therapy (prostanoids and / or phosphodiesterase-5 inhibitors) was required to be associated with PAH progression, and this led to study discontinuation.

Patients receiving the commercial formulation of bosentan (adult tablet formulation) before entering the FUTURE 3 study had to stop it and instead take the study drug (dispersible tablet formulation).

Evidence for comparator: -

Actual start date of recruitment	08 March 2011
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	1 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Belarus: 3
Country: Number of subjects enrolled	China: 6
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	India: 3

Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	Serbia: 5
Country: Number of subjects enrolled	South Africa: 6
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Ukraine: 1
Worldwide total number of subjects	64
EEA total number of subjects	23

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	21
Children (2-11 years)	43
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:

patients were recruited from 45 expert pediatric centers in 20 countries worldwide

Pre-assignment

Screening details:

The screening period took place within 4 weeks prior to enrollment into the study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Bosentan 2mg/kg t.i.d.

Arm description:

2 mg/kg bosentan was administered three times a day (morning, afternoon, evening) for a planned duration of 24 weeks

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

Dosage and administration details:

32 mg quadrisected dispersible tablet. The dosage of bosentan was adjusted according to the patient's body weight at initiation of the study treatment and adminsitered after dispersion in a teaspoon of water. Dosage readjustment, by steps of 8 mg, was permitted after 12 weeks of treatment.

Arm title	Bosentan 2mg/kg b.i.d.

Arm description:

2 mg/kg bosentan was administered twice daily (morning and evening) for a planned duration of 24 weeks

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

Dosage and administration details:

32 mg quadrisected dispersible tablet. The dosage of bosentan was adjusted according to the patient's body weight at initiation of the study treatment and adminsitered after dispersion in a teaspoon of water. Dosage readjustment, by steps of 8 mg, was permitted after 12 weeks of treatment.

Number of subjects in period 1	Bosentan 2mg/kg t.i.d.	Bosentan 2mg/kg b.i.d.
Started	31	33
Completed	31	33

Baseline characteristics

Reporting groups	
Reporting group title	Bosentan 2mg/kg t.i.d.
Reporting group description:	
2 mg/kg bosentan was administered three times a day (morning, afternoon, evening) for a planned duration of 24 weeks	
Reporting group title	Bosentan 2mg/kg b.i.d.
Reporting group description:	
2 mg/kg bosentan was administered twice daily (morning and evening) for a planned duration of 24 weeks	

Reporting group values	Bosentan 2mg/kg t.i.d.	Bosentan 2mg/kg b.i.d.	Total
Number of subjects	31	33	64
Age categorical Units: Subjects			
Children (2-11 years)	20	23	43
Infants and toddlers (28 days-23 months)	11	10	21
Age continuous Units: years			
arithmetic mean	5.2	4.5	
standard deviation	± 3.81	± 3.35	-
Gender categorical Units:			
Female	10	18	28
Male	21	15	36
PAH etiology Units: Subjects			
Idiopathic	15	14	29
Heritable	0	2	2
Congenital heart disease associated w/ open shunts	2	6	8
Associated PAH	13	11	24
Missing data	1	0	1
WHO functional class (FC) Units: Subjects			
FC I	10	9	19
FC II	15	12	27
FC III	6	12	18
PAH-specifc therapy at baseline Units: Subjects			
Bosentan (adult tablet formulation)	4	3	7
Prostanoid	1	0	1
PDE-5 inhibitor	13	10	23
Bosentan / PDE-5 inhibitor combination	2	2	4
Bosentan / PDE-5 inhibitor/ prostanoid combination	2	5	7
None	9	13	22

Subject analysis sets

Subject analysis set title	Pharmacokinetic (PK) set
Subject analysis set type	Per protocol

Subject analysis set description:

This analysis set includes patients in the all-treated set without any major protocol violation and for whom at least 5 of the 6 blood samples requested for PK assessments were available. This set was used for the analysis of the pharmacokinetic data

Subject analysis set title	All-treated set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

This analysis set includes all randomized patients who received at least one dose of study drug. Because all randomized patients received study drug at least once, the all-randomized set and the all-treated set are identical. Baseline characteristics,safety data and exploratory endpoints were analyzed using this analysis set.

Reporting group values	Pharmacokinetic (PK) set	All-treated set	
Number of subjects	58	64	
Age categorical Units: Subjects			
Children (2-11 years)	41	43	
Infants and toddlers (28 days-23 months)	17	21	
Age continuous Units: years			
arithmetic mean	4.9	4.8	
standard deviation	± 3.47	± 3.57	
Gender categorical Units:			
Female	24	28	
Male	34	36	
PAH etiology Units: Subjects			
Idiopathic		29	
Heritable		2	
Congenital heart disease associated w/ open shunts		8	
Associated PAH		24	
Missing data		1	
WHO functional class (FC) Units: Subjects			
FC I		19	
FC II		27	
FC III		18	
PAH-specifc therapy at baseline Units: Subjects			
Bosentan (adult tablet formulation)		7	
Prostanoid		1	
PDE-5 inhibitor		23	
Bosentan / PDE-5 inhibitor combination		4	
Bosentan / PDE-5 inhibitor/ prostanoid combination		7	

None		22	

End points

End points reporting groups

Reporting group title	Bosentan 2mg/kg t.i.d.
Reporting group description:	
2 mg/kg bosentan was administered three times a day (morning, afternoon, evening) for a planned duration of 24 weeks	
Reporting group title	Bosentan 2mg/kg b.i.d.
Reporting group description:	
2 mg/kg bosentan was administered twice daily (morning and evening) for a planned duration of 24 weeks	
Subject analysis set title	Pharmacokinetic (PK) set
Subject analysis set type	Per protocol
Subject analysis set description:	
This analysis set includes patients in the all-treated set without any major protocol violation and for whom at least 5 of the 6 blood samples requested for PK assessments were available. This set was used for the analysis of the pharmacokinetic data	
Subject analysis set title	All-treated set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
This analysis set includes all randomized patients who received at least one dose of study drug. Because all randomized patients received study drug at least once, the all-randomized set and the all-treated set are identical. Baseline characteristics,safety data and exploratory endpoints were analyzed using this analysis set.	

Primary: Daily exposure to bosentan [AUC(0-24C)]

End point title	Daily exposure to bosentan [AUC(0-24C)]
End point description:	
AUC(0-24) is the area under the concentration-time curve over a period of 24 hours. AUC(0-24) was calculated as a multiple of AUCtau, the AUC over a dosing interval (AUCtau x 2 for the b.i.d. dosing regimen and AUCtau x 3 for the t.i.d. regimen). 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. Therefore, AUC(0-24) was corrected to 2 mg/kg (target dose) [AUC(0-24C)]	
End point type	Primary
End point timeframe:	
At Week 4, after at least 2 weeks of stable study drug treatment (scheduled blood sampling time point: prior to study drug administration and up to 12 hours or up to 8 hours post-dose for the b.i.d and t.i.d. dosing regimen, respectively)	

End point values	Bosentan 2mg/kg t.i.d.	Bosentan 2mg/kg b.i.d.	Pharmacokinetic (PK) set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	27	31	58	
Units: h*ng/mL				
geometric mean (confidence interval 95%)	7275.1 (5468.2 to 9679)	8535.4 (6936 to 10503.7)	7923.6 (6692.4 to 9381.3)	

Statistical analyses

Statistical analysis title	Treatment comparison of daily exposure

Statistical analysis description:

Ratio of geometric means between the t.i.d. and b.i.d. dosing regimen (b.i.d. bosentan regimen taken as reference)

Comparison groups	Bosentan 2mg/kg t.i.d. v Bosentan 2mg/kg b.i.d.
Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other[1]
Parameter estimate	Ratio of geometric means
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.2

Notes:

[1] - No statistical hypothesis tests were set for this study. The analysis of PK data was carried out descriptively.

Other pre-specified: Maximum plasma concentration of bosentan (Cmaxc)

End point title	Maximum plasma concentration of bosentan (Cmaxc)

End point description:

Cmaxc was directly obtained from the measured plasma concentrations and was dose-corrected to 2 mg/kg (target dose)

End point type	Other pre-specified

End point timeframe:

At Week 4, after at least 2 weeks of stable study drug treatment

End point values	Bosentan 2mg/kg t.i.d.	Bosentan 2mg/kg b.i.d.	Pharmacokinetic (PK) set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	27	31	58	
Units: ng/mL				
geometric mean (confidence interval 95%)	527.9 (386 to 721.9)	742.8 (572.8 to 963.2)	633.6 (518.7 to 774)	

Statistical analyses

Statistical analysis title	Ratio of geometric means for Cmax

Statistical analysis description:

Ratio of geometric means between the t.i.d. and b.i.d. dosing regimen (b.i.d. bosentan regimen taken as reference), unadjusted

Comparison groups	Bosentan 2mg/kg t.i.d. v Bosentan 2mg/kg b.i.d.

Number of subjects included in analysis	58
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	ratio of geometric means
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.05

Notes:

[2] - No statistical hypothesis tests were set for this study. The analysis of PK data was carried out descriptively.

Other pre-specified: Time to reach Cmax of bosentan (tmax)

End point title	Time to reach Cmax of bosentan (tmax)

End point description:

End point type	Other pre-specified

End point timeframe:

At Week 4, after at least 2 weeks of stable study drug treatment

End point values	Bosentan 2mg/kg t.i.d.	Bosentan 2mg/kg b.i.d.	Pharmacokinetic (PK) set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	27	31	58	
Units: hours				
median (full range (min-max))	3 (1 to 8)	3 (0 to 7.5)	3 (0 to 8)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Daily exposure to bosentan metabolites (Ro 47-8634, Ro 48-5033, Ro 64-1056)

End point title	Daily exposure to bosentan metabolites (Ro 47-8634, Ro 48-5033, Ro 64-1056)

End point description:

Daily exposure to the metabolites corresponds to the area under the concentration-time curve [AUC(0-24)c] of the corresponding metabolite over a period of 24 hours, and was calculated in the same manner as the primary endpoint.

End point type	Other pre-specified

End point timeframe:

At Week 4, after at least 2 weeks of stable study drug treatment (scheduled blood sampling time point: prior to study drug administration and up to 12 hours or up to 8 hours post-dose for the b.i.d and t.i.d. dosing regimen, respectively)

End point values	Bosentan 2mg/kg t.i.d.	Bosentan 2mg/kg b.i.d.	Pharmacokinetic (PK) set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	27	31	58	
Units: h*ng/mL				
geometric mean (confidence interval 95%)				
Ro 47-8634	173.2 (126.2 to 237.6)	200.4 (152.2 to 263.9)	187.2 (152.9 to 229.3)	
Ro 48-5033	968.8 (723.3 to 1297.7)	1352.5 (1073.4 to 1704)	1157.9 (964 to 1390.9)	
Ro 64-1056	716.2 (543.5 to 943.8)	1014.1 (801.2 to 1283.6)	862.5 (720.3 to 1032.9)	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline in WHO functional class at end of study

End point title	Change from baseline in WHO functional class at end of study

End point description:

Proportion of patients with improvement, worsening or no change in WHO functional class at end of study compared to baseline.

End point type	Other pre-specified

End point timeframe:

Baseline and end of study

End point values	Bosentan 2mg/kg t.i.d.	Bosentan 2mg/kg b.i.d.	All-treated set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	31	33	64	
Units: Percentage				
number (not applicable)				
Worsened	3.2	3	3.1	
Unchanged	87.1	75.8	81.3	
Improved	14.3	29.2	22.2	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline in Global clincial impression scale (GCIS) at end of study

End point title	Change from baseline in Global clincial impression scale (GCIS) at end of study

End point description:

The GCIS is an assessment tool to rate the patient's current overall clinical condition ("Very Good", "Good", "Neither Good or Bad", "Bad" and "Very Bad"). The assessment was performed both by the physician and the parents / legal representatives independently.
Proportion of patients with clinical condition (as measured by the GCIS) considered as worsened, improved or unchanged are reported here

End point type	Other pre-specified

End point timeframe:

Baseline and end of study

End point values	Bosentan 2mg/kg t.i.d.	Bosentan 2mg/kg b.i.d.	All-treated set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	31	33	64	
Units: Percentage				
number (not applicable)				
Worsened- Physician	6.7	6.5	6.6	
Unchanged- Physician	77.4	72.7	75	
Improved- Physician	19.2	26.9	23.1	
Worsened- Parents	13.3	10	11.7	
Unchanged- Parents	61.3	57.6	59.4	
Improved- Parents	32	45.8	38.8	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Proportion of treatment-emergent liver function abnormalities

End point title	Proportion of treatment-emergent liver function abnormalities

End point description:

Proportion of patients with increase in alanine aminotransferase (ALT) and / or aspartate aminotransferase (AST) above 3 x ULN (upper limit of normal) The worst post-baseline value was considered.

End point type	Other pre-specified

End point timeframe:

From baseline up to 7 days after end of treatment

End point values	Bosentan 2mg/kg t.i.d.	Bosentan 2mg/kg b.i.d.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31	33		
Units: percentage				
number (not applicable)				
ALT > 3 x ULN	3.3	0		
AST > 3 x ULN	0	0		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Proportion of treatmentemergent hemoglobin abnormalities

End point title	Proportion of treatmentemergent hemoglobin abnormalities

End point description:

Proportion of patients with marked hemoglobin decreases. The worst post-baseline value was considered.

End point type	Other pre-specified

End point timeframe:

From baseline up to 7 days after end of treatment

End point values	Bosentan 2mg/kg t.i.d.	Bosentan 2mg/kg b.i.d.		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	33		
Units: Percentage				
number (not applicable)				
Hemoglobin decrease with values < 100 g/dL	3.3	9.1		
Hemoglobin decrease with values < 80 g/L	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From baseline to 7 days after end of treatment	
Adverse event reporting additional description:	
Note: adverse events (AEs) with fatal outcome are not mutually exclusive. One death was reported during this time frame in the bosentan t.i.d group and was related to 2 Serious AEs (bronchopneumonia and pulmonary arterial hypertension)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups	
Reporting group title	Bosentan 2mg/kg t.i.d.
Reporting group description:	
2 mg/kg bosentan was administered 3 times a day for at least 0.4 week to a maximum duration of 28.7 weeks	
Reporting group title	Bosentan 2mg/kg b.i.d.
Reporting group description:	
Subjectsreceived 2 mg/kg bosentan twice daily for a at least 6 weeks to a maximum duration of 26.4 weeks	

Serious adverse events	Bosentan 2mg/kg t.i.d.	Bosentan 2mg/kg b.i.d.	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 31 (22.58%)	4 / 33 (12.12%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Body temperature increased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Atrial septal defect repair			

subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac operation			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Loss of consciousness			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multi-organ failure			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
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			
Pulmonary arterial hypertension			

subjects affected / exposed	1 / 31 (3.23%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection viral			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis adenovirus	Additional description: The investigator was informed about this event by the parents approximately 2 months after database closure		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 33 (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 disorder			
subjects affected / exposed	0 / 31 (0.00%)	1 / 33 (3.03%)	
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	Bosentan 2mg/kg t.i.d.	Bosentan 2mg/kg b.i.d.	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 31 (64.52%)	20 / 33 (60.61%)	
Vascular disorders			
Flushing			
subjects affected / exposed	2 / 31 (6.45%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	6 / 31 (19.35%)	4 / 33 (12.12%)	
occurrences (all)	7	7	
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	2 / 31 (6.45%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Diarrhea			
subjects affected / exposed	4 / 31 (12.90%)	2 / 33 (6.06%)	
occurrences (all)	5	2	
Vomiting			
subjects affected / exposed	4 / 31 (12.90%)	1 / 33 (3.03%)	
occurrences (all)	7	1	
Respiratory, thoracic and mediastinal disorders			
Cough			

subjects affected / exposed	3 / 31 (9.68%)	0 / 33 (0.00%)	
occurrences (all)	3	0	
Epistaxis			
subjects affected / exposed	3 / 31 (9.68%)	0 / 33 (0.00%)	
occurrences (all)	3	0	
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 31 (6.45%)	1 / 33 (3.03%)	
occurrences (all)	2	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 31 (3.23%)	2 / 33 (6.06%)	
occurrences (all)	1	2	
Nasopharyngitis			
subjects affected / exposed	3 / 31 (9.68%)	5 / 33 (15.15%)	
occurrences (all)	4	8	
Otitis media			
subjects affected / exposed	0 / 31 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Respiratory tract infection			
subjects affected / exposed	1 / 31 (3.23%)	2 / 33 (6.06%)	
occurrences (all)	2	3	
Upper respiratory tract infection			
subjects affected / exposed	11 / 31 (35.48%)	6 / 33 (18.18%)	
occurrences (all)	13	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 May 2012	Due to the difficulties in recruitment, inclusion criteria was modified as follows : Reduction of the proportion of patients < 2 years of age and possibility to include patients with pulmonary arterial hypertension associated with unrepaired congenital heart defect

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported