

**Clinical trial results:**

**Multi-center non-drug-interventional extension study to assess long-term safety and effects on growth in patients who received bosentan or placebo as adjunctive therapy to inhaled nitric oxide for persistent pulmonary hypertension of the newborn in FUTURE 4 (AC-052-391)**

**Summary**

EudraCT number	2012-001829-27
Trial protocol	BE CZ PL FR
Global end of trial date	05 December 2014

**Results information**

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	18 June 2015

**Trial information****Trial identification**

Sponsor protocol code	AC-052-392
-----------------------	------------

**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
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)	EMA-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	16 January 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	05 December 2014
Global end of trial reached?	Yes
Global end of trial date	05 December 2014
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

The main objective of this extension observational study (AC-052-392) was to assess long-term safety and effects on growth in patients who received bosentan or placebo as adjunctive therapy to inhaled nitric oxide (iNO) for persistent pulmonary hypertension of the newborn (PPHN) in the short-term interventional FUTURE 4 study (AC-052-391).

Protection of trial subjects:

This clinical study was designed and conducted in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations, including the European Directive 2001/20/EC, the US CFR Title 21, and with the ethical principles laid down in the Declaration of Helsinki.

Parent(s) or the legal representative(s) were asked if they agreed that their baby took part in the FUTURE 4 extension (AC-052-392) study.

Background therapy:

Not applicable

Evidence for comparator: -

Actual start date of recruitment	14 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Poland: 6
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	United States: 3
Worldwide total number of subjects	15
EEA total number of subjects	11

Notes:

### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	15

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:

Patients who received at least one dose of study drug (bosentan or placebo) in FUTURE 4 study (AC-052-391 / 2011-000203-41) were allowed to be enrolled in the FUTURE 4 extension study (AC-052-392).

### Pre-assignment

Screening details:

21 patients were randomized and received at least one dose of study drug in the FUTURE 4 study (AC-052-391), among whom 15 entered the FUTURE 4 extension study. 6 patients did not enter the extension study (3 parents could not be reached, 1 parent refused, 1 parent was lost to follow-up, 1 moved to another country)

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Bosentan 2 mg/kg

Arm description:

Only patients who participated in both the FUTURE 4 and FUTURE 4 extension study are reported here.

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:

Bosentan as add-on to iNO was administered twice daily by nasogastric or orogastric tube at a dose of 2 mg/kg of weight at birth for a maximum duration of 10 days during the FUTURE 4 study (AC-052-391).

<b>Arm title</b>	Placebo
------------------	---------

Arm description:

Only patients who participated in both the FUTURE 4 and FUTURE 4 extension study are reported here.

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:

Placebo as add-on to iNO was administered by nasogastric or orogastric tube for a maximum duration of 6.5 days during the FUTURE 4 study (AC-052-391).

<b>Number of subjects in period 1</b>	Bosentan 2 mg/kg	Placebo
Started	7	8
Completed	7	8

## Period 2

Period 2 title	Observational period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

## Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Ex-bosentan

### Arm description:

This arm includes patients who received bosentan at least once to a maximum of 10 days during neonatal age in the FUTURE 4 (AC-052-391) study and were followed for growth and adverse events during the first year of life (i.e., 12 months after the core FUTURE 4 end of study). They did not receive any study treatments during this observational period.

Arm type	No intervention
No investigational medicinal product assigned in this arm	
<b>Arm title</b>	Ex-placebo

### Arm description:

This arm includes patients who received placebo at least once to a maximum of 6.5 days during neonatal age in the FUTURE 4 (AC-052-391) study and were followed-up for growth and adverse events during the first year of life (i.e., 12 months after the core FUTURE 4 end of study). They did not receive any study treatments during this observational period.

Arm type	No intervention
No investigational medicinal product assigned in this arm	

<b>Number of subjects in period 2</b>	Ex-bosentan	Ex-placebo
Started	7	8
Completed	7	8

## Baseline characteristics

### Reporting groups

Reporting group title	Bosentan 2 mg/kg
-----------------------	------------------

Reporting group description:

Only patients who participated in both the FUTURE 4 and FUTURE 4 extension study are reported here.

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Only patients who participated in both the FUTURE 4 and FUTURE 4 extension study are reported here.

Reporting group values	Bosentan 2 mg/kg	Placebo	Total
Number of subjects	7	8	15
Age categorical			
Age at baseline during the core FUTURE 4 study			
Units: Subjects			
Newborns (0-27 days)	7	8	15
Age continuous			
Age at baseline in FUTURE 4 (AC-052-391) study			
Units: days			
median	1.1	1.7	-
full range (min-max)	0.6 to 2.6	0.6 to 5.9	-
Gender categorical			
Units: Subjects			
Female	4	6	10
Male	3	2	5
PPHN etiology			
Among the 6 patients reported to have neonatal aspiration in the Bosentan group, 1 also had respiratory distress syndrome. So, data reported in the table below for the Bosentan arm must be read as follows: neonatal aspiration: n = 6, neonatal respiratory distress syndrome: n = 2 since the conditions related to parenchymal lung disease are not mutually exclusive.			
Units: Subjects			
Idiopathic	0	3	3
Neonatal aspiration	6	3	9
Neonatal respiratory distress syndrome	1	0	1
Pneumonia / Sepsis	0	2	2

## End points

### End points reporting groups

Reporting group title	Bosentan 2 mg/kg
-----------------------	------------------

Reporting group description:

Only patients who participated in both the FUTURE 4 and FUTURE 4 extension study are reported here.

Reporting group title	Placebo
-----------------------	---------

Reporting group description:

Only patients who participated in both the FUTURE 4 and FUTURE 4 extension study are reported here.

Reporting group title	Ex-bosentan
-----------------------	-------------

Reporting group description:

This arm includes patients who received bosentan at least once to a maximum of 10 days during neonatal age in the FUTURE 4 (AC-052-391) study and were followed for growth and adverse events during the first year of life (i.e., 12 months after the core FUTURE 4 end of study). They did not receive any study treatments during this observational period.

Reporting group title	Ex-placebo
-----------------------	------------

Reporting group description:

This arm includes patients who received placebo at least once to a maximum of 6.5 days during neonatal age in the FUTURE 4 (AC-052-391) study and were followed-up for growth and adverse events during the first year of life (i.e., 12 months after the core FUTURE 4 end of study). They did not receive any study treatments during this observational period.

Subject analysis set title	all-enrolled set
----------------------------	------------------

Subject analysis set type	Safety analysis
---------------------------	-----------------

Subject analysis set description:

The all-enrolled set in the extension study comprises all patients included in the all-treated set of the FUTURE 4 (AC-052-391) study for whom parent(s) or the legal representative(s) signed the informed consent form for their baby to take part in the FUTURE 4 study extension (AC-052-392).

### Primary: Primary EP: none

End point title	Primary EP: none <sup>[1]</sup>
-----------------	---------------------------------

End point description:

This is an exploratory study in a small number of patients and no primary endpoint was defined

End point type	Primary
----------------	---------

End point timeframe:

0

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Not applicable as no primary efficacy endpoint was defined for this observational study designed to explore the long-term safety of bosentan in patients previously treated with bosentan as add-on therapy to iNO in the core FUTURE 4 study

<b>End point values</b>	all-enrolled set			
Subject group type	Subject analysis set			
Number of subjects analysed	0 <sup>[2]</sup>			
Units: not applicable				

Notes:

[2] - Not applicable (no primary endpoint was defined)

### Statistical analyses

No statistical analyses for this end point

---

**Other pre-specified: growth: body length and weight**

---

End point title	growth: body length and weight
-----------------	--------------------------------

End point description:

Per protocol, growth variables were to be summarized as changes from baseline to predefined time points. However, because of the small sample size and discrepancies in reporting growth across investigator sites, estimates of changes from baseline by treatment group would have been unreliable. Consequently, only individual absolute values were reported over time based on the standard WHO growth centiles by age.

Overall, subjects' growth curves (length and weight) remained within 5th to 95th WHO growth percentiles

End point type	Other pre-specified
----------------	---------------------

End point timeframe:

From birth up to the last available time point of the observational period

---

<b>End point values</b>	all-enrolled set			
Subject group type	Subject analysis set			
Number of subjects analysed	0 <sup>[3]</sup>			
Units: number				

Notes:

[3] - Due to the low number of subjects, no descriptive analysis was performed

---

**Statistical analyses**

---

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From baseline up to the end of the observation period in AC-052-392

Adverse event reporting additional description:

For non-serious adverse events, baseline is defined as end of treatment (EOT) + 7 days in FUTURE 4.

For serious adverse event, baseline is defined as EOT + 60 days in FUTURE 4.

Assessment type	Systematic
-----------------	------------

### Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	17.0
--------------------	------

### Reporting groups

Reporting group title	Ex-bosentan
-----------------------	-------------

Reporting group description:

This arm includes patients who received at least one dose of bosentan (2 mg/kg) during the FUTURE 4 (AC-052-391) study and followed-up for adverse events up to 14 months during the FUTURE 4 extension study

Reporting group title	Ex-Placebo
-----------------------	------------

Reporting group description:

This arm includes patients who received at least one dose of placebo during the FUTURE 4 (AC-052-391) study and followed-up for adverse events up to 14 months during the FUTURE 4 extension study

<b>Serious adverse events</b>	Ex-bosentan	Ex-Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 7 (0.00%)	0 / 8 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

<b>Non-serious adverse events</b>	Ex-bosentan	Ex-Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 7 (57.14%)	4 / 8 (50.00%)	
Injury, poisoning and procedural complications			
Scar			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			

Anaemia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 8 (0.00%) 0	
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	
Vomiting subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	
Respiratory, thoracic and mediastinal disorders Wheezing subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	
Dermatitis diaper subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	
Rash subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	
Seborrhoea subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	
Musculoskeletal and connective tissue disorders Positional plagiocephaly subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 8 (12.50%) 1	
Infections and infestations			

Bronchitis			
subjects affected / exposed	1 / 7 (14.29%)	1 / 8 (12.50%)	
occurrences (all)	2	1	
Croup infectious			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Ear infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis viral			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Respiratory tract infection viral			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Tonsillitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 8 (12.50%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	2 / 7 (28.57%)	0 / 8 (0.00%)	
occurrences (all)	4	0	
Urinary tract infection			
subjects affected / exposed	1 / 7 (14.29%)	0 / 8 (0.00%)	
occurrences (all)	1	0	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 July 2013	Global amendment includes the following main changes to the protocol: <ul style="list-style-type: none"><li>• Data collection was planned to occur via telephone call to a physician taking care of the patient outside of the investigational hospital. Because subjects were not followed by a physician in all countries, the protocol was amended to allow the patients to return for a site visit.</li><li>• Investigators were informed of the treatment assignment in the FUTURE 4 core study upon release of the study results. Hence, the wording 'investigator-blinded' was removed and the absence of drug intervention was added from the study design.</li><li>• Growth variables were planned to be assessed at the investigational site. The protocol was amended to allow assessment of growth variables by a healthcare professional.</li></ul>

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.

Limitations include: small number of subjects enrolled, lack of standardization of data collection including retrospective data collection.

Notes: