20 November 2014
EMA/168487/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Tracleer

International non-proprietary name: BOSENTAN

Procedure No. EMEA/H/C/000401/II/0066

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AE	Adverse event
ALT	Alanine aminotransferase
AR	Assessment Report
Argus	Argus Safety™; Actelion Global Drug Safety database
AST	Aspartate aminotransferase
AUC_{0-24}	Area under the plasma concentration-time curve from 0 to 24 hours
b.i.d.	Twice daily
BREATHE	**B**osentan **R**andomized trial of **E**ndothelin **A**ntagonist **THE**rapy for pulmonary hypertension
BSEP	Bile salt export pump
CHD	Congenital heart disease
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence interval
CL/f	Apparent systemic clearance after oral dosing
C_{max}	Maximum concentration
CSR	Clinical study report
CTD	Connective tissue disease
CYP	Cytochrome P450
DDI	Drug-drug interaction
DIC	Disseminated intravascular dissemination
eCTD	Electronic Common Technical Document
EMA/EMEA	European Medicines Agency
ERA	Endothelin receptor antagonist
Eur. Pharm.	European Pharmacopeia
FC	Functional class
FDA	Food and Drug Administration
FUM	Follow-up measures
FUTURE	Pediatric **F**orm**U**lation of bosen**T**an in p**U**lmonary arterial hype**R**t**E**nsion
HD	Hemodynamic
HLGT	High-level group terms
HLT	High-level terms
IBD	International Birth Date
iPAH	Idiopathic pulmonary arterial hypertension
ITT	Intention-to-treat
k_m	Elimination rate constant
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Affairs
mPAP	Mean pulmonary arterial pressure
mRNA	Messenger ribonucleic acid
NCA	Non-compartmental analysis
NOEL	No-observed-effect level
NOS	Not otherwise specified
PAH	Pulmonary arterial hypertension

PAH-CHD	PAH due to congenital heart disease
PBPK	Physiologically based pharmacokinetic
PCWP	Pulmonary capillary wedge pressure
PDCO	Paediatric Committee
PDE-5	Phosphodiesterase type 5
PH	Pulmonary hypertension
PIL	Patient information leaflet
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PMS	Post-marketing surveillance
PopPK	Population pharmacokinetic(s)
PPHN	Persistent Pulmonary Hypertension of the Newborn
PPSR	Proposed paediatric study request
PSUR	Periodic Safety Update Report
PT	Preferred Term
PVR	Pulmonary vascular resistance
Qp/Qs	Pulmonary-Systemic Flow Ratio
REVEAL	Registry to Evaluate Early and Long-term PAH Disease Management
RHC	Right heart catheterisation
RHF	Right heart failure
RMP	Risk management plan
RSE	Relative standard error
SAE	Serious adverse event
SmPC	Summary of product characteristics
SOC	System organ class
SVR	Systemic vascular resistance
TAP	Tracleer Access Program
t.i.d.	Three times a day
t_{max}	Time to maximum concentration
TTCW	Time to Clinical Worsening
ULN	Upper limit of normal
V	Volume of distribution
WBC	White blood cells
WHO	World Health Organization

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Actelion Registration Ltd. submitted to the European Medicines Agency on 7 April 2014 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product: **For presentations: See Annex A**	**International non-proprietary name:**
Tracleer	BOSENTAN

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

The MAH applied for an extension of the indication to include treatment of symptomatic pulmonary arterial hypertension in paediatric patients aged from 3 months to 2 years. The MAH proposed to update the SmPC in order to include the data generated in studies conducted according to the agreed Paediatric Investigation Plan for bosentan (EMEA-000425-PIP02-10-M04). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, 5.3 and 6.6 of the SmPC were proposed to be updated and the Package Leaflet was proposed to be updated accordingly. In addition, taking into account the new data in the paediatric population, an updated version of the RMP (version 5) was provided as part of the application.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0090/2013 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0090/2013 was completed.

The PDCO issued an opinion on compliance for the PIP P/0090/2013.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the application included a critical report addressing the possible similarity with authorised orphan medicinal products.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Pierre Demolis Co-Rapporteur: Kristina Dunder

Timetable	Dates
Submission date:	7 April 2014
Start of procedure:	25 April 2014
The CHMP adopted a report on similarity of Tracleer with Volibris(ambrisentan), Revatio(sildenafil), Ventavis(iloprost), Opsumit(macitentan) and Adempas(riociguat) on (Appendix 1):	28 May 2014
CHMP Rapporteur's preliminary assessment report circulated on:	25 June 2014
PRAC Rapporteur's preliminary RMP assessment report circulated on:	1 July 2014
PRAC Rapporteur's updated RMP assessment report circulated on:	4 July 2014
Adoption of PRAC Assessment Overview and Advice:	10 July 2014
CHMP Rapporteur's updated assessment report circulated on:	18 July 2014
Request for supplementary information and extension of timetable adopted by the CHMP on:	24 July 2014
MAH's responses submitted to the CHMP on:	17 September 2014
PRAC Rapporteur's preliminary assessment report on the MAH's responses circulated on:	24 October 2014
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	28 October 2014
PRAC RMP advice and assessment overview adopted by PRAC:	6 November 2014
CHMP opinion:	20 November 2014

2. Scientific discussion

2.1. Introduction

In February 2002, the CPMP recommended the granting of a Marketing Authorisation (MA) for the medicinal products Tracleer 62.5 mg and 125 mg film-coated tablet. In April 2009, Tracleer 32 mg quadrisectable dispersible tablets were approved by CHMP as a line extension for patients who cannot take the film coated tablets (registration procedure EMEA/H/C/000401/X/0039)

The active substance of Tracleer is bosentan which is an oral, dual endothelin(ET)-receptor antagonist with affinity for both ETa and ETb receptors. Bosentan competes with the binding of ET-1 to both receptors.

The current indication for the 3 strengths is:
Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with WHO functional class III. Efficacy has been shown in:

- *Primary (idiopathic and familial) PAH*
- *PAH secondary to scleroderma without significant interstitial pulmonary disease*
- *PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology*

Some improvements have also been shown in patients with PAH WHO functional class II (see section 5.1).

Tracleer is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease (see section 5.1).

The current SMPCs include recommendations for pediatric patients above 2 years of age informing on pharmacokinetics results from PK studies AC-052-356/BREATHE-3 and AC-052-365/FUTURE-1 which showed that bosentan plasma concentrations in children were on average lower than in adult patients and were not increased by increasing the dose of Tracleer above 2 mg/kg body weight twice daily (based on PK results as described in section 5.2 of the SMPC). Subsequently, section 4.2 of the SMPC states that in children above 2 years of age, the dose of 2 mg/kg b.i.d. is recommended as starting and maintenance doses since higher doses are considered unlikely to be more effective while higher rate of undesirable effects cannot be excluded (see below for background in pediatrics). In children below 2 years of age, the SMPC states that there is only limited clinical experience in pediatric patients below 2 years of age.

The main safety concerns with bosentan relate to its effect in decreasing the haemoglobin, hepatoxicity and potential teratogenicity.

In April 2014, Actelion submitted a Type II variation to amend the Product information with the aim to extend the indication to children above 3 months of age:
The wording claimed for paediatric patients in section 4.1 is:

Paediatric population
Treatment of symptomatic PAH in paediatric patients aged from 3 months to 18 years old (see section 5.1)."

The posology claimed by the MAH for children 3 months to 18 years is worded as "*2 mg/kg twice daily morning and evening up to a maximum dose of 125 mg twice daily".*

Further amendments in relation to paediatrics are also claimed by the MAH in Sections 4.2, 4.5, 4.8., 5.1. 5.2. and 5.3. of the SMPC and accordingly in the patient leaflet :

- Amend the posology and information in PAH children but no dosing recommendation for neonates with PPHN,
- Update the undesirable effects section to reflect the additional safety information obtained in paediatric studies,
- Update the pharmacodynamic properties to include summaries of the completed paediatric studies not included in the current SmPC,
- Update the section on pharmacokinetic properties with the PK data from the newly submitted paediatric studies FUTURE 3 and FUTURE 4,
- Update the nonclinical safety data to include information on the toxicity studies conducted in juvenile rats.

2.2. Background information regarding paediatric data with bosentan

In 2002, since no data had been initially provided to document neither the pharmacokinetic (PK) nor the clinical use in children and patients with low body weight, the SMPC, section 4.2 initially stated
"Safety and efficacy in patients under the age of 12 years have not been established." and "*There is limited experience in patients with a body weight below 40 kg."*

In February 2003, the MAH provided the paediatric pharmacokinetic study BREATHE-3 (AC-052-356) studying 19 children less than 15 years and less than 40 kg. This study showed a lower systemic exposure in young children using film coated tablets 2 mg/kg b.i.d as compared to the exposure in adults treated with 125 mg b.i.d. Thus the PK information was added in the section 4.2 in order to inform on the

specificity of the pharmacokinetics in children with special attention to the lack of data to establish the optimal dose in this population.

Indeed, the scarcity of the clinical paediatric study (the sole clinical study being BREATHE-3) did not allow to establish the optimal dose in children less than 15 years bearing in mind that, in one hand, a lower systemic exposure could lead to a suboptimal treatment in children (as compared to adult) and, on the other hand, that safety concerns could not be excluded when the dose would be increased to reach a higher effect.

In May 2008, the MAH applied for a line extension for Tracleer 32 mg dispersible tablets (EMEA/H/C/401/X/0039) based on clinical data focusing on paediatrics including: a new paediatric PK study: AC-052-365 (FUTURE-1) using 32 mg dispersible tablets and the preliminary results from its open-label extension study AC-052-367 (FUTURE-2) (Cut-off 1 March 2008).

FUTURE-1 included 36 paediatric PAH patients 2 to 11 years old and showed no difference in AUC after administration of doses of 2 and 4 mg/kg b.i.d. and available paediatric pharmacokinetic data showed that bosentan plasma concentrations in children were on average lower than in adult patients again and were not increased by increasing the dose of Tracleer above 2 mg/kg body weight twice daily.

These short term PK studies suggested that children were stabilised (based on WHO functional status and hemodynamics) with 2 mg/kg for short term periods (12 weeks maximum in BREATHE-3 including 19 patients) and maintenance dose of 4 mg/kg in the available longer term data (FUTURE-1/2).

These studies had limitations as they were short terms, uncontrolled, conducted in a limited number of patients, of whom a significant part was receiving concomitant epoprostenol (25% in FUTURE-1).
From an efficacy point of view, the observed plateau in systemic concentration would suggest that increasing the dose of bosentan beyond 2 mg/kg in paediatric patients in a b.i.d. regimen will unlikely result in any increased exposure to bosentan and subsequent increased effect on pulmonary vasculature. No clinical study primarily well-designed for efficacy/safety assessment was performed in children especially comparing the two maintenance regimen 2 mg/kg b.i.d. versus 4 mg/kg b.i.d. on safety/efficacy grounds.

In conclusion, the CHMP considered that information on these specific results were warranted in the SmPC (EMEA/H/C/401/X/0039 and EMEA/H/C/401/X/41) but further long term safety and clinical data should be collected in paediatric patients. The CHMP agreed on the proposal of the MAH for these data to be collected in a Systematic Review. The Systematic Review uses aggregated data from a number of prospective disease registries initiated to study the disease course and long-term outcomes of PAH in children and adolescents in current real-world clinical settings:

- Tracking Outcomes and Practice in Paediatric Pulmonary Hypertension (TOPP), an international prospective disease registry
- The French paediatric PAH registry (FR).
- The Dutch national paediatric PAH Registry (NL).
- REVEAL (Registry to EVvaluate Early And Long-term PAH Disease Managment), an American PAH disease registry including both adult and pediatric PAH patients.

The systematic review protocol (AC-052-516) "*Disease characteristics and outcomes for PAH in children and adolescents in real world settings: systematic review of four prospective observational registries"* was submitted by the MAH on 01 July 2009. The systemic review started on 15 October 2009. As a comment, the MAH was requested to consider ways to follow-up PAH children up to puberty in order to get information on sexual maturity.

As follow-up measure (FUM 062), the MAH has provided 4 annual reports of systemic review of the four registries. Respectively, Rapporteur's assessment reports were circulated on May 2011, May 2012, June 2013, and October 2014. The fourth annual report has been provided by the MAH during this procedure upon request.

In October 2010, the MAH submitted Study AC-052-116 comparing the bioavailability of the 32 mg dispersible tablet and the marketed film-coated tablet in healthy male adults as a follow-up measure (FUM-061) requested by CHMP following approval of Tracleer 32 mg dispersible tablets. This study showed that the 62.5 mg film coated tablet and the 32 mg dispersible tablet could not be considered bioequivalent as lower bioavailability was observed with the 32 mg dispersible tablet. Results of this study were included in section 5.2. of the SMPCs of Tracleer 32 mg dispersible tablets under subheading

"Comparison between formulations". Recommendations were included in the SmPC for the dispersible tablets to be used only in patients not able to use film coated tablets.

Meanwhile, a paediatric investigation plan (PIP) for bosentan was agreed by the EMA under Article 8 of the Paediatric Regulation (EMEA-000425-PIP02-10-M04). The latest modification acceptance from EMA is dated on 29 April 2013.

The PIP that was agreed by PDCO consisted of the 6 following measures :

Quality :
Measure 1: Study on nasogastric tube administration of the bosentan dispersible tablet.
Non-clinical:
Measure 2: 24 days dose-range-finding toxicity study in juvenile rats.
Measure 3: 94 days toxicity study in juvenile rats.
Measure 4: Safety and efficacy study in a model of chronic pulmonary hypertension in newborn sheep.

Clinical:
Measure 5: Open-label, randomised multicentre, multiple dose trial to evaluate pharmacokinetics, safety of bosentan in children from 3 months to less than 12 years of age with Pulmonary Arterial Hypertension (PAH) (so cold FUTURE 3).
Measure 6: Double blind, randomised multicentre, add-on, placebo controlled, trial to evaluate pharmacokinetics, safety, efficacy, of bosentan in neonates with persistent pulmonary hypertension of the newborn (PPHN).

A partial waiver was granted for the treatment of PAH. This waiver applied to infants aged from 28 days to less than 3 months and to adolescents aged from 12 years to less than 18 years based on consideration agreed by PDCO that "a diagnosis of PAH cannot be consistently made before the age of 3 months and that adolescent PAH patients were included in the pivotal clinical trials with bosentan as well as in the first paediatric study [BREATHE-3]."

2.3. Quality aspects

2.3.1. Introduction

As part of the agreed Paediatric Investigation Plan, the MAH committed to conduct a study on nasogastric tube administration of the Tracleer 32 mg dispersible tablet. The goal of this study was to explore the acceptability of the Tracleer 32 mg dispersible tablet as an age-appropriate formulation for infants and children with pulmonary arterial hypertension (PAH), and for neonates with persistent pulmonary hypertension of the newborn (PPHN), for whom the administration of bosentan via an orogastric or nasogastric tube would be necessary.

The study investigated the administration of the Tracleer 32 mg dispersible tablet via a nasogastric tube in vitro for doses ranging from 4 mg to 16 mg (covering the anticipated needs for paediatric patients with body weights from 2–8 kg at a dose per administration of 2 mg/kg body weight). The objective of the study was to provide data on the accuracy of the dosage by nasogastric tube administration of the Tracleer 32 mg dispersible tablet.

For each dose, an amount of Tracleer 32 mg (one quarter tablet, one half tablet) was dispersed in a volume of water. A volume, depending on the dose, was collected with a graduated syringe to administer through the nasogastric tube. To control the content of bosentan, for each dose, which is delivered, the dispersion was collected at the end of the tube to be analyzed - tests have been performed in duplicate.

All mean values obtained were within 79–96% of the targeted delivered dose (see table hereafter). The Applicant explains there may be some losses of substance during the sample preparation as error for dividing the quadrisected Tracleer 32 mg dispersible tablet, the non-homogeneous dispersion and delivery through the syringe and tubing as precision of syringe, potential adsorption on plastic materials.

Targeted delivered dose	Test number	Recovery rate* (in %)	Mean value (%)
4 mg dose	1	97.5	95.9
	2	94.4	
6 mg dose	1	74.2	84.8
	2	95.4	
8 mg dose	1	73.1	79.4
	2	85.6	
12 mg dose	1	85.8	94.6
	2	103.3	
16 mg dose	1	79.1	88.6
	2	98.1	
Average for all doses			88.7

* One set of material was used for each sample.

The MAH has estimated that approximately 10% loss of substance would be expected when delivering the Tracleer 32 mg dispersible tablet via an orogastric or nasogastric tube.
Consequently, the MAH states that to compensate for the loss of substance observed in the study, the patient's body weight should always be rounded up to the next 0.5Kg step when calculating the dose.

2.3.2. Discussion

The Applicant has provided an *in vitro* study testing different doses (4, 6, 8, 12 and 16 mg) from one quarter or one half tablet dispersed in appropriate volume of water.in order to know the accuracy of the dosage by nasogastric tube administration of Tracleer 32 mg dispersible tablet.

Experimental tests have been performed in duplicate leading to a high variability of data. Even if, a 10% loss of substance is expected, the results presented are not justified since all mean values obtained were within 79–96% of the targeted delivered dose. In this context, data are considered as non-sufficient to evaluate the accuracy of the dosage. Further data (more than duplicate) should be provided in order to demonstrate the accuracy of the dosage.

The Applicant described that the 10% loss of the active substance could be due to the subdivision of tablets, the non-homogeneous dispersion of the tablet, the precision of the syringe as well as the potential adsorption of the substance on the plastic materials. However, data provided do not allow confirming that estimation of approximately 10% loss of the substance.

The MAH provided further clarification mentioned below:

A second study performed in 2011, investigated the administration of the Tracleer 32 mg dispersible tablet via a nasogastric tube for doses ranging from 6 mg to 12 mg.

In this study the volume of water in which the dispersible tablet or sub-part of dispersible tablet is dispersed was reduced to 4–5 mL (instead of 8 mL in the previous study). In addition, the administered volume was reduced to 1.5 mL. These lower administered volumes were considered to be more in line with common practices. Triplicate testing was performed to increase the robustness of the methodology.

The results are summarised in Table 1.

Table 1 Analytical results - Second study

Targeted delivered dose	Test number	Recovery* (in %)	Mean value and standard deviation (%)
6 mg dose (1.5 mL of 1/2 tablet in 4 mL)	1	84.7	78.0 ± 5.6
	2	71.0	
	3	78.3	
7 mg dose (1.5 mL of 3/4 tablet in 5 mL)	1	73.3	83.2 ± 12.5
	2	75.3	
	3	100.8	
8 mg dose (1.5 mL of 3/4 tablet in 4.5 mL)	1	51.3**	73.7 ± 17.3
	2	93.3	
	3	76.5	
9 mg dose (1.5 mL of 3/4 tablet in 4 mL)	1	57.8**	73.5 ± 11.1
	2	82.0	
	3	80.7	
10 mg dose (1.5 mL of one tablet in 5 mL)	1	78.9	80.6 ± 1.3
	2	81.0	
	3	82.0	
11 mg dose (1.5 mL of one tablet in 4.5 mL)	1	78.7	87.0 ± 9.0
	2	99.5	
	3	82.7	
12 mg dose (1.5 mL of one tablet in 4 mL)	1	79.2	76.5 ± 8.9
	2	64.6	
	3	85.8	
Average for all doses			78.9 ± 11.4

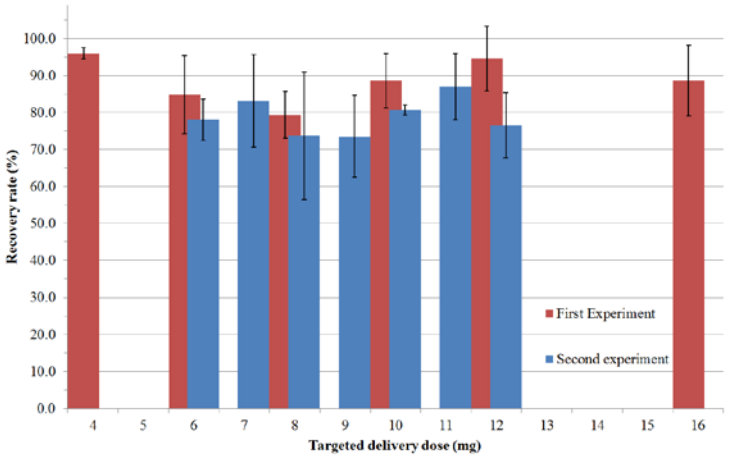
*One set of material was used for each sample.** Bosentan dispersion clogged into the tubes.

This additional study confirmed that the administration of bosentan dispersible tablets 32 mg via a nasogastric tube produced variable results (average standard deviation of approximately 10%). Moreover, accuracy of the delivered dose was not achieved as the recovery rate deviated substantially from the target (on average, 80% of the dose was delivered), as shown in

Figure **1**. In addition, two administrations failed (50–60% of dose delivered) due to clogging in the tubes, representing approximately 10% of the experiments.

The higher concentration of the suspension (tablets are dispersed in 4–5 mL of water in the second study instead of 8 mL in the first study) might explain this increase in losses and clogging within the tubing.

Figure 1 Summary of results from administration via nasogastric tubes



According to the MAH, to overcome these losses and avoid clogging, an excess of 20% of the delivered dose by nasogastric tube administration would need to be recommended, as well as the use of tubes with an inner diameter no narrower than 1.5 mm. This may raise difficulties in usual practice.

Based on these results, the MAH withdrew the proposed recommendation to administer Tracleer dispersible tablets through a nasogastric tube.

2.3.3. Conclusion

In summary, the accuracy of the delivered dose is not achieved when Tracleer dispersible tablets is dispersed in appropriate volume of water and administered per a nasogastric tube due to losses and clogging, notably. Based on the results presented above, an excess of 20% of the dose should be required. The Applicant explained that the lack of accuracy could be due in part to the precision of the syringe (graduation) and potential adsorption of the substance on its surface and on the tubing might also be a cause for loss of substance. However no data are provided to support this explanation.

Nevertheless, as the PPHN indication is not claimed and as the MAH withdrew the recommendation regarding the administration of Tracleer dispersible tablets through a nasogastric tube, the issue can be considered solved.

2.4. Non-clinical aspects

2.4.1. Introduction

Three nonclinical studies were conducted to support the paediatric development of bosentan: an efficacy study in a model of persistent pulmonary hypertension of the newborn (PPHN), and toxicity studies in juvenile rats (a dose-range finding study followed by a pivotal study).

2.4.2. Pharmacology

Since endothelin-1 (ET-1) is elevated in neonates with severe PPHN, treatment with bosentan, a dual ETA and ETB receptor antagonist, was expected to cause pulmonary dilation. To support this hypothesis, an experimental model of persistent pulmonary hypertension of the newborn (PPHN) was used. This model has been established through partial ligation of the ductus arteriosus (DA) in utero in late-gestation foetal sheep, i.e. between 120-128 days of gestation (term=147 days). This procedure is known to cause a marked elevation of pulmonary vascular resistance (PVR) at delivery despite ventilation with high fraction of inspired oxygen (FiO2), thereby mimicking severe human PPHN.

Practically, nine animals were used in this study, 5 with chronic DA ligation (PPHN) and 4 controls. When surgery was performed, catheters and a flow transducer were placed in the left pulmonary artery (LPA) to allow the administration of bosentan to foetal lambs and measurement of various physiological responses. The range of gestational ages at the time of study was 130-142, 131-140 days for control and PPHN group, respectively. Control and PPHN animals were studied between 3-8 and 3-12 days after foetal surgery, respectively. The haemodynamic effects of acute infusion of bosentan (10 or 50 mg over 30 min into the LPA), were assessed by measuring the following physiologic responses in foetal lambs: mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), LPA blood flow (Qipa), mean aortic pressure (mAoP), heart rate, and arterial blood gases at baseline and during the infusion period.

There were no changes in heart rate, pH, PO2 or pCO2 in control and PPHN animals treated with bosentan. As shown in Table 2, bosentan lowered PVR by 25% ($p<0.02$) vs. baseline in PPHN animals and tended to decrease PVR in the normal foetus (control) by 16% ($p=0.47$).

Table 2: hemodynamics in control and PPHN animals at baseline and after bosentan administration (mean±SEM)

		Baseline	Post bosentan	% reduction
PVR	Control	0.69±0.16	0.58±0.11	16%
(mmHg/ml/min)	PPHN	1.00±0.19	0.74±0.14 *	25%
mPAP	Control	44.8±4.1	42.5±4.1	
(mmHg)	PPHN	64.4±7.5	63.8±6.7	
mAoP	Control	42.8±3.9	40.5±4.4	
(mmHg)	PPHN	43.2±2.7	41.0±3.5	
Q_{lpa}	Control	68.5±5.7	78.5±12.7	
(ml/min)	PPHN	74.6±19.2	100.4±23.8 (p=0.06)	

* $p<0.02$ versus baseline

The applicant concluded that pulmonary arterial infusion of bosentan caused pulmonary vasodilation without adversely affecting systemic haemodynamics in experimental PPHN, suggesting that bosentan could provide therapeutic benefit in children with PPHN.

2.4.3. Toxicology

As specified before, a dose-range finding juvenile toxicity study in rats followed by a pivotal study were performed to support the extension of the therapeutic indication of bosentan to the treatment of symptomatic PAH in paediatric patients aged 3 months and above. The results of these two studies are summarised below.

2.4.3.1. Dose -range finding juvenile toxicity study

The summary of the results of the dose range finding study are provided below

Species Study ID GLP status	**Route / Dose / Duration**	**Major findings**
Rats HanRcc^{TM}: WIST(SPF) 6 /sex/group 2 /sex/group for TK Study N° T-10.181 GLP: no	Oral (gavage) **0, 60, 300, 1500 mg/kg/d** PND4 to PND28	**<u>At 1500 mg/kg bw/d</u>** - One F died during blood sampling - One F and one M smaller and lighter than the control group (71% and 74% reduced body weights, respectively) - ↓ body weight gain in M (-43%) and F (-40%) - ↓ locomotor activity in M and F **<u>At 300 mg/kg bw/d</u>** - One M died during blood sampling - Sacrifice of one F on day 18 post partum - ↓ body weight gain in M (-29%) and F (-14%) - ↓ locomotor activity in M **<u>At 60 mg/kg bw/d</u>** - ↓ body weight gain in M (-13%) and F (-7%) - ↓ locomotor activity in M

PND = Post Natal Day

2.4.3.2. Pivotal juvenile toxicity study

- **Methods**

The purpose of this study was to determine effects of bosentan on growth and development of the neonatal/juvenile Han Wistar rat.

Rat pups were treated orally once daily by gavage beginning at 4 days of age. The within litter design was used. Each litter contained 8 pups and one male and one female pup was used per dose group, respectively. After weaning the treated animals were group housed by dose group and sex. Dams (F0 Generation) were not treated; they only fostered the juvenile rats.

The study was divided into three subsets: histopathology (subset I), behavior and fertility (subset II), and toxicokinetic (subset III). Subset I and III were administered until 69 days of age and subset II until mating (at least 84 days old). Subset I and II consisted of 20, and subset III of 9 litters. In parallel to subset I, 4 control litters were treated (total 16 males and 16 females) with the vehicle only (between-litter-design) to supplement the control group with histology information due to the lack of historical control data at the corresponding age.

Mortality, clinical signs, food consumption and body weight were recorded in all subsets. Food consumption was recorded after weaning, from 21 days of age on.

Subset I animals were used for clinical laboratory investigations, long bone length, organ weights and histopathology and on day 21 and 70 post-partum (n = 10 per group/sex/day).

Subset II animals were used for recording developmental indices, behavioral tests and fertility incl. estrus length, mating performance, reproduction data, and seminology and spermatid count.

Subset III animals were used for toxicokinetic evaluations on days 4, 21 and 69 post-partum. On day 4 post-partum, blood samples were collected at 1 h, 3 h or 6 h after application by decapitation, from pups, which were selected for culling. On days 21 and 69, each pup was sampled at two time points sublingually under isoflurane anaesthesia.

- **Results**

Table 3: summary of the pivotal juvenile toxicity study

Species (number) Study ID GLP status	Route / Dose / Duration	Major findings	NOAEL
Rats HanRcc™: WIST(SPF) Control group: 20/sex + 16/sex to generate historical data Treated groups: - Subset I (histopathology): 20/sex/group - Subset II (behaviour & fertility): 20/sex/group - Subset III (toxicokinetic): 9/sex/group Study N° T-10.407 GLP: yes	Oral gavage **0, 15, 45, 135 mg/kg/d** PND4 to PND69 for subset I and III PND4 to PND84 for subset II	**<u>At 135 mg/kg bw</u>** - ↓ food consumption - ↓ body weight gain during the first two weeks of the treatment period until PND18 - ↓ body weight up to 6 weeks in F - ↑ heart weight in M and F (+47% and 50% respectively relative to body weight) - ↑ thymus weight in M and F (+20% and +28%, respectively relative to body weight) - ↓ absolute and relative testis weight - ↓ number of sperms and reduced epididymides weights - ↓ long bone length in M on PND21 only (-4%), not on PND70 - ↓ long bone length in F on PND21 and 70 (-7% and -4%, respectively) **<u>At 45 mg/kg bw</u>** - ↓ food consumption - ↓ body weight gain during the first two weeks of the treatment period until PND18 in M - ↓ body weight up to 6 weeks in F - ↑ phosphorus level - ↑ heart weight in M and F (+18% and 50% respectively relative to body weight) - ↓ long bone length in F on PND21 and 70 (-4% on each occasion)	**15 mg/kg/d** **AUC_{0-24} = 65500 ng.h/mL**

PND = Post Natal Day

The applicant concluded that no new target organ toxicity was identified in juvenile rats.

2.4.3.3. toxicokinetics

The results are provided in Table 4.

Table 4: animal-to-human exposure ratios

Time	Dose (mg/kg bw/d)	AUC0-24h (ng.h/mL) in juvenile rats		Safety margins based on AUC_{0-24} in children at 2 mg/kg bid < 2years*		Safety margins based on AUC_{0-24} in children at 2 mg/kg bid > 2years**	
		M	F	M	F	M	F
PND21	**15**	**59700**	**168000**	**7.6**	**21.3**	**6.8**	**19.0**
	45	185000	270000	23.5	34.3	21.0	30.6
	135	282000	191000	35.8	24.2	32.0	21.7
PND69	**15**	**11800**	**22500**	**1.5**	**2.9**	**1.3**	**2.6**
	45	23100	53700	2.9	6.8	2.6	6.1
	135	49900	78100	6.3	9.9	5.7	8.9

* 7879 ng.h/mL ** 8820 ng.h/mL

Data at the NOAEL

It should be noted that data on day 4 post-partum were not used as the AUC measured covers a period of 0 to 6 hours vs. 0 to 24 hours for day 20 and 69 post-partum.

2.4.4. Discussion on non-clinical aspects

Assessment of paediatric data on non-clinical aspects

The PIP specified that a "PK/safety and efficacy study in a model of chronic pulmonary hypertension in newborn sheep" should be performed. Originally, a study was performed to assess the effects of oral bosentan at the time of cesarean section delivery of newborn sheep that had undergone surgical ligation of the ductus arteriosus (DA) in utero 7-10 days before delivery. However, no measureable effects with oral administration was detected due to problems with absorption after c-section delivery and the need for continuous anaesthesia and sedation to the lamb at the time of birth and throughout the acute study period (which further impairs GI motility and absorption). Therefore, the study detailed above was conducted to check whether lack of efficacy was due to the route of administration (oral versus intravenous). The technique used, i.e. intravenous dosing of foetal lambs during the development of pulmonary hypertension prior to birth, was already used in the past by different scientific teams as argued by the MAH, including an ETA receptor antagonist.
The results of the juvenile study showed that infusions of bosentan induce pulmonary vasodilatation in chronically-prepared foetal lambs. However, the clinical relevance of this study may be viewed as limited since the pulmonary function of newborn lambs was not reproduced in this experimental model. In addition, further studies are needed to assess the effects of more prolonged infusions after birth of animals with PPHN and to determine how the response to bosentan compares with the response to other agents, especially inhaled NO (iNO), and whether bosentan therapy can augment inhaled NO-induced pulmonary vasodilatation or blunt the effects of rebound after iNO withdrawal. Importantly, clinical studies in children with PPNH do not show any efficacy of bosentan associated to iNO compared to "placebo" group (only treated with iNO).
The major findings reported in juvenile rats were reduced body weight, increased heart weight, reduced long bone length, and reduced testis weight associated with reduced number of sperms and reduced epididymides weights (only observed at high dose).

The effects reported above were only observed at mid and high dose levels, i.e. at ≥45 mg/kg/d. Indeed, no effect was noted at 15 mg/kg/d. In addition, no effect on developmental indices, clinical pathology, histology, or reproductive performance, was reported. The reduced long bone length was in accord with the reduced body weights as:

- the long bone length and body weights were reduced on day 21 post-partum but not on day 69 post-partum in males,
- the long bone length and body weights were reduced on day 21 and 69 post-partum in females.

The MAH argued that no new target organ toxicity was detected compared to rat toxicity studies in adult animals. However, effects on testis and heart weights (observed only at high dose) were not reported in adult rats.

- Heart-weight

As mentioned by the MAH, a treatment-related effect on heart weight cannot be excluded although there was no histopathological heart finding (the reported increase in heart weight may indicate an increased workload). Some effects were reported on the male reproductive tissues (decreased testis and epididymides weights, reduced number of sperms, decreased epididymal sperm count). Unfortunately, neither discussed the potential causes underlying these findings nor their clinical relevance. It should be noted that effects on testis were observed with other molecules of this pharmacological class (e.g. macitentan and ambrisentan) in adult rats. Corresponding findings were reported in SmPC sections 5.3 and 4.6.

The CHMP agreed with the MAH that only the relative heart weights (to body and brain weights) was increased and not the absolute relative heart weights. However, relative heart weights increases were not only observed at that dose (135 mg/kg bw/d.) as this was also reported in females at the dose of 45 mg/kg bw/d. on day 21 post-partum (pp). Therefore, the NOAEL for females at day 21 pp is 15 mg/kg bw/d. and corresponding safety margins for children under 2 years and above 2 years are, 21 and 19, respectively, which are still considered acceptable.

Considering that only relative heart weights were increased at the top dose (135 mg/ kg bw/d.) and not absolute heart weights, no histopathological findings were observed, safety margins could be considered acceptable, increased relative heart weights in the juvenile toxicity study in rats is no more considered as a concern and the CHMP agreed for not amending the RMP with heart findings reported in the juvenile rat toxicity study.

- *Testicular toxicity*

The MAH states *that "testicular toxicity of other endothelin receptor antagonists (ERAs) typically includes tubular dilatation up to subchronic treatment leading to tubular atrophy after chronic treatment*" and considers that neither tubular dilatation, nor tubular atrophy was observed with bosentan and then considers that these effects are only related to a class-effect of ERAs.

The CHMP did not agree with the MAH and concluded that there is enough evidence showing testicular effects with bosentan itself in animals considering:

- decreased absolute weights of testes and epididymis, and reduced number of sperm in epididymis in the newly provided juvenile rat toxicity study conducted with bosentan,
- slight increased incidence of testicular tubular atrophy (effect also observed with other ERAs) in a toxicity study in rats after 2 years of treatment with bosentan (as mentioned by the MAH in the new labelling proposed in section 5.3 of the SmPC),

Additionally, the MAH has provided the study report of a clinical study investigating the effects of bosentan treatment on testicular function in male PAH patients (Study AC-052-402). In this study, 8 out of 24 male patients treated had a decreased sperm concentration from baseline of at least 42% after 3 or 6 months of treatment with bosentan. Two of these 8 patients showed a sperm concentration lower than 15×106/ml which is the lower reference limit of sperm concentration, for the fifth centiles (with 95th percent confidence intervals), generated from men whose partners had time to pregnancy ≤ 12 months, according to WHO (2010)1

In conclusion, based on the results observed in the juvenile rat toxicity study, and on the data from clinical study AC-052-402 in humans to assess testicular effects of bosentan, it cannot be excluded that bosentan has an effect on spermatogenesis in human. Upon request from the PRAC/CHMP, testicular disorders and male infertility and decrease of sperm count are included as an important potential risk and important identified risk, respectively in the RMP and sections 4.6 (fertility) and 5.3 of the SmPC are amended as follows:

section 4.6. of SmPC:

" Fertility-

~~*The development of testicular tubular atrophy in male animals was observed after treatment with other ERAs (see section 5.3). The relevance of this finding to humans is unknown, but a deterioration of*~~ ***Animals studies showed testicular effects (see section 5.3). In a study investigating the effects of bosentan on testicular function in male PAH patients, 8 out of 24 patients showed a***

[1] World Health Organization (2010). Who laboratory manual for the examination and processing of human semen. Fifth Edition. Available online: http://whqlibdoc.who.int/publications/2010/9789241547789_eng.pdf?ua=1

***decreased sperm concentration from baseline of at least 42% after 3 or 6 months of treatment with bosentan. Based on these findings and preclinical data, it cannot be excluded that bosentan may have a detrimental effect on spermatogenesis in men. In male children , a long term impact on fertility after treatment with bosentan cannot be excluded*.**

section 5.3 of the SmPC:
[….]

Development of testicular tubular atrophy and impaired fertility has been linked with chronic administration of endothelin receptor antagonists in rodents.

In fertility studies in male and female rats a~~t plasma concentrations 21 and 43 times, respectively, the expected therapeutic level in humans~~, no effects on sperm count, motility and viability, or on mating performance or fertility were observed **at exposures that were 21 and 43 times the expected therapeutic level in humans, respectively**; nor was there any adverse effect on the development of the pre-implantation embryo or on implantation.

Slightly increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as 125 mg/kg/ day (about 4 times the maximum recommended human dose (MRHD) and the lowest doses tested) for two years but not at doses as high as 1500 mg/kg/day (about 50 times the MRHD) for 6 months. In a juvenile rat toxicity study, where rats were treated from Day4 post partum up to adulthood, decreased absolute weights of testes and epididymides, and reduced number of sperm in epididymides were observed after weaning. The NOAEL was 21 times (at Day 21 post partum) and 2.3 times (Day 69 post partum) the human therapeutic exposure, respectively.

However, no effects on general development, growth, sensory, cognitive function and reproductive performance were detected at 7 (males) and 19 (females) times the human therapeutic exposure at Day 21 *post partum.* At adult age (Day 69 *post partum*) no effects of bosentan were detected at 1.3 (males) and 2.6 (females) times the therapeutic exposure in children with PAH.

Toxicokinetics was evaluated on PND4, 21, and 69. The MAH specified that bosentan does not induce CYP in rat based on toxicokinetic data available and therefore suggested that only differences in enzyme maturation is involved for bosentan metabolism of adult versus juvenile rats. As shown in Table 4, exposure levels were higher on PND21 than on PND69, which the CHMP considered probably due to in part the maturation of enzymes involved in the metabolism of bosentan and therefore, an age effect on kinetics is observed.

The MAH determined safety margins ranging from 7 to 8, taking into account exposure levels reached in juvenile rats and in children below and above 2 years of age. More precisely, an exposure level of 65,500 ng.h/mL in juvenile rats was used, and obtained by averaging sex combined animal data on PND21 ([59,700+168,000]/2=113,850 ng.h/mL) and on PND69 ([11800+22500]/2=17150 ng.h/mL), respectively – please see Table 4. This is not endorsed by the CHMP. As shown in Table 4, exposure levels decreased over time and were 6.8 and 19 fold higher in juvenile rats and 1.3- to 2.9-fold higher in adult rats compared to children. Therefore, it is concluded that the course of exposure needs to be taken into consideration for the safety margins which is considered weak.

In conclusion, the labelling of the SmPC (section 4.6 and 5.3) are amended as above mentioned.

2.4.5. Conclusion on the non-clinical aspects

Based on the submitted non-clinical data, no major concern was raised regarding juvenile toxicity. However, reduced testis weight associated with reduced number of sperms and reduced epididymides weights were observed with bosentan (only observed at high dose). These effects were not observed adult toxicity studies. Of note, effects on testis were observed in adult toxicity studies with other ERAs (i.e. macitentan and ambrisentan) and the relevance of these findings in humans is unknown.

The SmPC sections 4.6 and 5.3. were updated to reflect the above findings and the RMP is updated to reflect testicular disorders and male infertility as an important potential risk.

2.5. Clinical aspects

2.5.1. Introduction

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

In support of the present application, the MAH submitted two pharmacokinetic (PK) studies summarized in a tabular overview and a PKPD modelling in accordance with paediatric investigation plan,

- STUDY AC-052-373 (FUTURE 3)
- STUDY AC-052-391 (FUTURE 4)
- Physiologically-based pharmacokinetic (PBPK) modeling of bosentan with application to pediatric patients. The Applicant did not use the PBPK study to update the SmPC. Therefore, it was not assessed in this report.

• Tabular overview of clinical studies

2.5.2. Pharmacokinetics

2.5.2.1. Study AC-052-373 (FUTURE 3)

- ***Methods/study design***

study AC-052-373 : *An open-label, prospective randomized multicenter, multiple dose trial study to evaluate assess the pharmacokinetics, tolerability, safety and efficacy of the pediatric formulation of bosentan two versus three times a day in children from 3 months to less than 12 years of age with pulmonary arterial hypertension.*

Investigators / centers and countries. 45 expert pediatric centers in 20 countries across Europe, North America, Latin America, Australia, Asia, and Africa

Period of trial. 8 March 2011 to 19 August 2013

Study design/ Objective

The primary objective was to investigate the pharmacokinetics (PK) of the dispersible tablet formulation of bosentan at doses of 2 mg/kg twice daily (b.i.d.) and 2 mg/kg three times daily (t.i.d.) in children with pulmonary arterial hypertension (PAH) from ≥ 3 months to < 2 years of age and from 2 years to < 12 years of age.
Secondary objectives were to evaluate the efficacy, tolerability, and safety of bosentan in children with PAH from ≥ 3 months to < 2 years of age and from 2 years to < 12 years of age.

This was a prospective, multicenter, open-label, randomized, multiple dose (two dose regimens) Phase 3 study in children aged ≥ 3 months to < 12 years of age. At least 16 patients in the study were required to be below 2 years of age.

Following the screening period (4 weeks' duration), patients were randomized in a 1:1 ratio to receive oral doses of bosentan as dispersible tablets of 2 mg/kg b.i.d. or 2 mg/kg t.i.d., stratified for baseline bosentan treatment as well as other PAH-specific treatments. At randomization, bosentan dosage was adjusted according to the patient's body weight. The treatment period lasted for 24 weeks.

Number of patients included
64 patients were planned to be randomized in a 1:1 ratio to bosentan 2 mg/kg b.i.d. and 2 mg/kg t.i.d. Patients were required to be ≥ 3 months and < 12 years of age.
64 patients were actually randomized to bosentan 2 mg/kg b.i.d. (n=33) and 2 mg/kg t.i.d. (n=31). Of the 64 randomized patients, 21 were < 2 years (10 b.i.d., 11 t.i.d.) and 43 were ≥ 2 years of age (23 b.i.d., 20 t.i.d.).

Trial drug dose / Route / Regimen / Duration 32 mg dispersible tablets dispersed for oral administration (b.i.d. or t.i.d.)

Criteria for pharmacokinetic evaluation
The main PK endpoint was defined as the daily exposure to bosentan, i.e., area under the concentration-time curve (AUC) over a period of 24 h (AUC_{0-24}), and calculated as a multiple of the exposure over a dosing interval (AUC_{τ}), 3 × AUC_{τ} and 2 × AUC_{τ} for t.i.d. and b.i.d regimens, respectively. Other PK endpoints were maximum plasma concentration (C_{max}) of bosentan, time to reach the maximum plasma concentration (t_{max}) of bosentan, and daily exposure (AUC_{0-24}), C_{max}, t_{max} of bosentan metabolites (Ro 47-8634, Ro 48-5033, Ro 64-1056).

Statistical methods
No formal hypothesis testing was defined for this study. Analyses of PK endpoints were performed for the overall population and by age groups < 2 years or ≥ 2 years.

The statistical analyses of the PK parameters were performed using the All-randomized set (= intention-to-treat population) and using the PK set. In the analysis of primary interest performed using the All-randomized set, it was noted that this analysis set included subjects who did not have reliable PK profiles due to protocol deviations. Therefore, to reflect the PK properties of this population more correctly, all PK analyses were also performed using the PK set.

All subjects did not receive an exact dose of 2 mg/kg, as the smallest dosage unit was 8 mg (quarter tablet), therefore AUC_{0-24} and C_{max} were corrected to the target dose of 2 mg/kg (AUC_{0-24C} and C_{maxC}). All AUC and C_{max} values were assumed to be log-normally distributed. The comparison of the b.i.d. and the t.i.d. dosing regimens of bosentan was based on the ratio of geometric means of the daily exposures (AUC_{0-24C}) and of C_{maxC} of bosentan and its metabolites: test treatment (t.i.d.): reference treatment (b.i.d.) and their 95% confidence intervals (CI). The linear fixed-effects model with dosing regimen as fixed effect was used for generation of 95% CIs for the ratios of the geometric means. The influence of the WHO FC, body weight, gender and age at study entry (baseline covariates) on the main analysis was assessed in *post hoc* sensitivity analyses. The linear fixed-effects model used for the main analysis was used to produce baseline covariate-adjusted treatment effect estimates.

Patient disposition
Of 87 screened patients, 64 were randomized 1:1 to bosentan 2 mg/kg b.i.d. (N=33) and 2 mg/kg t.i.d. (N=31) treatment groups (hereafter referred to as b.i.d. and t.i.d.). Of the 64 randomized patients, 21 were < 2 years (10 b.i.d., 11 t.i.d.) and 43 were ≥ 2 years of age (23 b.i.d., 20 t.i.d.). A total of 4 patients (2 each in b.i.d. and t.i.d. groups) discontinued the study treatment prematurely either due to AEs (n=3) or by withdrawal of consent (n=1). Of the 4 patients who discontinued study drug prematurely, 3 were < 2 years of age. All 64 randomized patients completed the study as per protocol. No patient was lost to follow-up.
All 64 randomized patients were included in the All-treated set. The Per-protocol set included 56 of the randomized patients (87.5%), and the Per-protocol PK set (hereafter referred to as PK set) included 58 of the randomized patients (90.6%). Finally, PK data in children less than 2 years were available for 9 children from the b.i.d. and 8 children from the t.i.d. group (less than one year was n= 2 in b.i.d. group and 2 in the t.i.d group).

2.5.2.1.1. Pharmacokinetics results

The study compared the PK properties of two dosing regimens of bosentan: t.i.d. (as 3 × 2 mg/kg per day) vs b.i.d. (as 2 × 2 mg/kg per day), with b.i.d. as the dosing regimen of reference.
The PK profiles for bosentan and its three metabolites Ro 47-8634, Ro 48-5033, and Ro 64-1056 at steady-state were comparable for the t.i.d. and b.i.d. dosing regimens. PK profiles of bosentan for both dosing regimens were characterized by rapid absorption, with a median t_{max} of 3 h.
Taking into account the inter-subject variability and despite an observed 15% lower daily exposure (AUC_{0-24C}) and a 29% lower C_{maxC} with t.i.d. vs b.i.d. dosing regimens, the exposure to bosentan was considered to be comparable with both dosing regimens in the overall pediatric population, as the 95 % CI of the geometric mean ratio included 1.00.

Summary of main statistical analysis of the effect of the dosing regimen (t.i.d. vs b.i.d.) on bosentan PK parameters, PK set:

PK parameter	Ratio of geometric means	95% confidence interval for ratio of means
AUC_{0-24C} [h·ng/mL]	0.85	(0.61–1.20)
C_{maxC} [ng/mL]	0.71	(0.48–1.05)

AUC_{0-24C} = dose-corrected area under the concentration-time curve over a period of 24 h;C_{maxC} = dose-corrected maximum observed plasma concentration; PK = pharmacokinetic

The point estimates of the geometric mean ratios of AUC_{0-24C} and C_{maxC} for bosentan and its metabolites were comparable across the age groups, and the systemic exposure to bosentan was also comparable between patients aged < 2 years and those ≥ 2 years, and this was observed for both b.i.d. and t.i.d. dosing regimens.

Summary of the effect of the dosing regimen (t.i.d. vs b.i.d.) on bosentan PK parameters per age group, PK set:

PK parameter		Ratio of geometric means	95% confidence interval for ratio of means
AUC_{0-24C} [h·ng/mL]	< 2 years	0.86	(0.43–1.72)
	≥ 2 years	0.85	(0.57–1.28)
C_{maxC} [ng/mL]	< 2 years	0.78	(0.36–1.69)
	≥ 2 years	0.68	(0.42–1.11)

AUC_{0-24C} = dose-corrected area under the concentration-time curve over a period of 24 h; C_{maxC} = dose-corrected maximum observed plasma concentration; PK = pharmacokinetic.

Overall, the study showed that t.i.d. dosing in the pediatric PAH population did not increase the exposure to bosentan compared to b.i.d. dosing.

2.5.2.1.2. Conclusion on Pharmacokinetics results

The results of the study FUTURE 3 showed that the overall daily systemic exposure to bosentan for children with PAH appears to be almost similar with both dosing regimen (b.i.d. vs t.i.d.) in both groups of age. These results confirmed that an increase in dose frequency of bosentan from 2 mg/kg b.i.d. to 2 mg/kg t.i.d. did not result in increased daily systemic exposure in pediatric PAH patients.

In PAH study FUTURE-3, PK parameters of bosentan and its metabolites in patients < 2 years appeared consistent with those in patients ≥ 2 years. However, due to the limited PK data in children below 2 years of age (b.i.d. n=9 ; t.i.d. n= 8), pharmacokinetics remains not well characterised in this age category.

The MAH justification regarding the difficulty in enrolling PAH children in the study FUTURE 3 less than 2 years in relation to the low frequency of the disease in this age group is acceptable, however due to the very limited number of children less than one year (i.e. n= 2 in b.i.d. group and n= 2 in the t.i.d. group) and high variability in PK results (see also PK results from FUTURE 4 study below), no clear information can be made on this age group of less than 1 year. In summary, the section 5.2. of the SmPC has been updated accordingly.

2.5.2.1.3. Population PK analysis

A population pharmacokinetic (PopPK) analysis of bosentan in pediatric patients with PAH was performed on data from study AC-052-373, pediatric FormUlation of bosenTan in pUlmonary arterial hypertension (FUTURE 3), a prospective study with bosentan in children with PAH investigating the pharmacokinetics of 2 mg/kg b.i.d. versus three times per day (t.i.d.).

The objectives of the PopPK analysis were:

1. To describe population PK characteristics (i.e., population-typical PK parameters) of bosentan and its metabolites (Ro 47-8634, Ro 48-5033, Ro 64-1056), including inter- and intra-individual variability in children with PAH.
2. To quantify the influence of subject-specific factors (i.e., covariates such as age, body weight, dosing regimen [exposure]) on PK parameters.
3. To perform simulations based on PopPK results to investigate the relevance of identified covariates.

The data were analyzed in accordance with the FDA Guidance for Industry on Population Pharmacokinetics and the EMA/CHMP guideline on PopPK analyses.
Nonlinear mixed-effects modeling and simulations were performed using the computer programs Monolix (Stand-alone Version 4.2) and R (Version 2.14.1).
PK assessments were performed at Week 4. Blood samples for PK were drawn at the following times:

- Bosentan b.i.d. dosing regimen: immediately before administration of the study medication dose in the morning (pre-dose) and at 0.5 h, 1 h, 3 h, 7.5 h, and 12 h post-dose
- Bosentan t.i.d. dosing regimen: immediately before administration of the study medication dose in the morning (pre-dose) and at 0.5 h, 1 h, 3 h, 5 h, and 8 h post-dose

Concentrations of bosentan and its metabolites (i.e., Ro 47-8634, Ro 48-5033, Ro 64-1056) in plasma were determined using a validated LC-MS/MS method. The lower limit of quantification in plasma was set at 1 ng/mL for bosentan and at 2 ng/mL for its metabolites.

The following parameters were tested as candidate covariates for model inclusion:

- Age (years)
- Body weight (kg)
- Dosing regimen (b.i.d., t.i.d.)

Plasma concentration data from 63 subjects were available. Five subjects were excluded from the PK set due to protocol violations. In addition, 6 subjects were excluded since their profiles were implausible and not compatible with a model, i.e., their concentrations were increasing or decreasing over the entire dosing interval or had high trough values with lower values in between. Out of these 6 subjects, 5 were on t.i.d. treatment. Finally, 52 subjects were included in the analysis (30 subjects with b.i.d. dosing, 22 subjects with t.i.d. dosing). Out of the 52 subjects, 14 subjects were below 2 years of age.

Estimation method and settings

The parameters of the population PK analysis were estimated using the stochastic approximation expectation maximization (SAEM) algorithm in Monolix. The option “auto” was selected for the number of iterations in the two stages of the population parameter estimation algorithm: the algorithm determined automatically if it could move from one stage to the next and when to terminate the iteration. The simulated annealing version of SAEM was used to estimate the population parameters. The Monte-Carlo sizes, i.e., the number of simulated samples to compute prediction distributions, the normalized prediction distribution errors (NPDE), and the visual predictive checks (VPC), were 100, 500, and 20,000, respectively.

Model building

The model building process was performed as a two-step approach (development of the base model and covariate selection) to determine the inclusion of candidate covariates.

Model selection

The simplest structural model was selected based on knowledge of the PK of bosentan from previous clinical studies. In addition, the most appropriate between-subject variability model and the residual error model were identified and the resulting model was used as a base model.
The base model consisted of the PK parameters, inter-individual variability (random effects) and residual variability in drug concentrations (random variability). Covariates were not included in the base model.

Covariate selection

The inclusion of the covariates was tested according to the following relationship, e.g.,

- for continuous covariates such as age: $TV = THETA(1) \times EXP(THETA(2) \times AGE)$
- for binary categorical variables such as dosing regimen (ARM):
  $TV = THETA(1) \times EXP(THETA(2) \times ARM)$ with ARM = 0 for b.i.d and ARM = 1 for t.i.d.

The model was run with one covariate added on one parameter at a time. The selection of the best model was based on the log-likelihood ratio test (LRT) that follows a Chi-square (χ^2) distribution. If the decrease in objective function value (OFV) was significant (decrease in OFV > 3.84 for 1 degree of freedom with 1-p = 0.05), the covariate was included in the model.

Full model and final model

Following the univariate covariate selection, all statistically significant covariates were added to obtain the full model.
The full model was subsequently used for backward elimination. The covariate leading to the smallest increase in OFV if omitted from the model was determined. If the difference in the OFV with and without the covariate was less than 7.88 (based on the log-likelihood ratio test for one degree of freedom for 1-p = 0.005), this covariate was removed from the model. The reduced model became the new reference model. This procedure was repeated until no further covariate had to be removed from the model. The resulting model was declared the final model.

Model qualification

The graphical analyses consisted of goodness-of-fit plots (observed versus predicted concentrations, weighted residuals versus predicted concentrations and time), individual predicted and observed concentration-time profiles, *post-hoc* parameter distributions and graphical evaluation of covariate effects using *post-hoc* estimated parameters.
A VPC was employed to verify that the model predicted both the population-typical profile and the variability in the observed data. In this approach, the final model parameter estimates were used to simulate the setup of the dataset observed (doses, covariates, and variability). The median, 5^{th} and 95^{th} percentiles of the observed concentration data over time were superimposed graphically on the corresponding quantiles and 90% confidence intervals of the simulated concentration values over time. If the data could arise from the model, they should generally fall into the confidence interval range of the simulated data (visual judgment).

Simulations

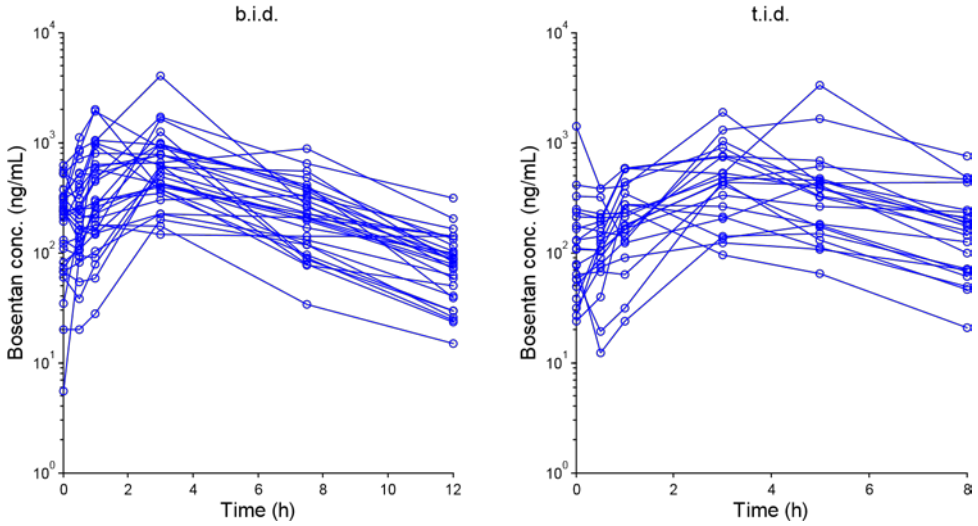
Monte-Carlo simulations (n = 250) were performed based on the final model, to investigate the relevance of the identified covariates on bosentan plasma concentrations. The resulting simulated concentration-time curves were summarized and plotted, and split by the covariates.

Results

The raw PK data are displayed in Figure 1 for bosentan.

Figure 1 Individual bosentan concentration-time profiles by dosing regimen

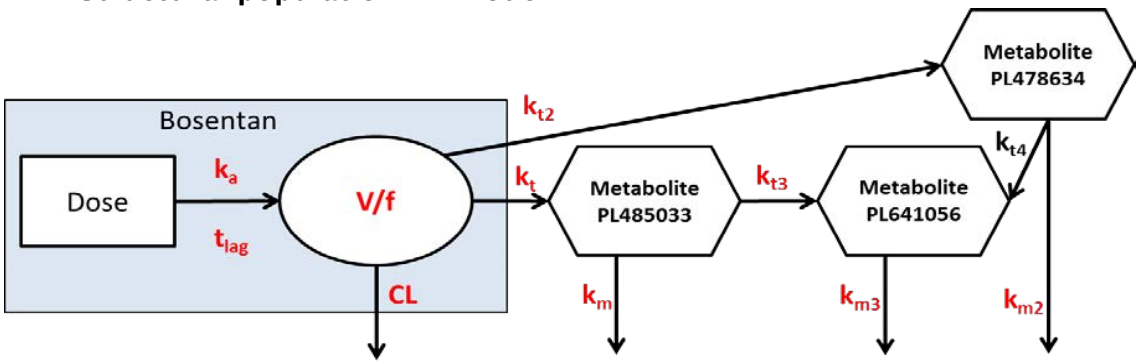
(b.i.d.: n = 30, t.i.d.: n = 22)



Base model development

Based on prior knowledge and data available, the best structural model for bosentan was a one-compartment model (with V/f as apparent volume of distribution) with first order absorption (with absorption rate constant k_a), lag-time (t_{lag}), and first order elimination (with CL/f as apparent total body clearance). Bosentan and its metabolites were fit simultaneously. The metabolism from bosentan to Ro 48-5033 was modeled with a transfer (or conversion) rate constant k_t and the elimination of Ro 48-5033 with an elimination rate constant k_m. The metabolism from bosentan to Ro 47-8634 was modeled with a transfer rate constant k_{t2} and the elimination of Ro 47-8634 with an elimination rate constant k_{m2}. The metabolism from Ro 48-5033 to Ro 64-1056 was modeled with a transfer rate constant k_{t3} and the elimination of Ro 48-5033 with an elimination rate constant k_{m3}. The metabolism from Ro 47-8634 to Ro 64-1056 (with transfer rate constant k_{t4}) was not modeled initially, but final results are provided with and without k_{t4}. The structural model is illustrated in figure 5.

Figure 5 Structural population PK model



It was assumed that the individual parameters followed a log-normal distribution for the between-subject variability. Proportional, combined (additive + proportional), and exponential error models were tested and the best error model was an exponential error model for bosentan and a proportional error model for the 3 metabolites.

Covariate selection

The covariate testing was performed on the base model. The covariates dosing regimen, age, and body weight were tested as covariates on all model parameters. The statistically significant covariates based on the LRT (their inclusion led to a significant decrease in OFV of 3.84 or more for one degree of freedom and 1-p = 0.05) were dosing regimen on tlag, ka, CL/f, kt, kt3, km, and km3, age on CL/f and kt, and body weight on tlag, CL/f, and km3.

Full model, backward elimination, and final model

The full model was built by including all statistically significant covariates. Thus, the full model included all 12 covariate effects identified in the previous step.
During the backward elimination process, 8 covariate effects out of the 12 initially present in the model were removed. The resulting model (BACKREF8) was declared to be the final model. The final model contained 4 covariate effects: dosing regimen on k_a, CL/f, and k_t, and body weight on CL/f. Parameter estimates for the final model are given in Table 3.

Table 3 Final model: population PK parameters

Parameter	Estimate	SE	RSE %
k_a	0.12	0.011	9
arm on k_a	0.628	0.14	22
tlag	0.956	0.1	11
V/f	2.05	0.21	10
CL/f	1.78	0.42	24
arm on CL/f	0.55	0.18	33
weight on CL/f	0.0419	0.011	27
k_t	0.0832	0.0092	11
arm on k_t	-0.406	0.11	27

k_{t2}	0.0931	0.01	11
k_{t3}	0.65	0.038	6
k_m	1.87e-010	4.2e-009	2.26e+003
k_{m2}	6.85	0.9	13
k_{m3}	1.18	0.061	5
Omega k_a	0.4	0.057	14
Omega t_{lag}	0.71	0.079	11
Omega V/f	0.0996	0.12	117
Omega CL/f	0.577	0.063	11
Omega k_t	0.258	0.055	21
Omega k_{t2}	0.158	0.12	79
Omega k_{t3}	0.256	0.044	17
Omega k_m	1.97	2.8e+002	1.4e+004
Omega k_{m2}	0.102	0.19	185
Omega k_{m3}	0.214	0.039	18
Exponential error bosentan	0.586	0.028	5
Proportional error Ro 48-5033	0.469	0.021	5
Proportional error Ro 47-8634	0.59	0.03	5
Proportional error Ro 64-1056	0.345	0.016	5

Source: Appendix 11.4.3
RSE = Relative standard error, SE = Standard error

Model qualification

Goodness-of-fit plots are employed in the following to qualify the model. In order to verify that the model predicted both the central tendency and the variability in the observed data, VPCs were employed. The VPCs show that the model was able to reproduce both the typical profile and the variability in the observed data. This analysis shows that the random effects were approximately normally distributed and that the population distribution of the individual parameters were log-normally distributed (as assumed in the model specification).

Simulation

In this section, the simulations split by covariates were investigated for their relevance regarding bosentan plasma concentrations. The simulations are the result of the Monte-Carlo simulation (n = 250 complete datasets) based on the final model. Simulation results performed for the metabolites are shown in Appendix 11.10. The dose regimen was identified as statistically significant covariate on k_a, CL/f, and k_t. The differences in bosentan concentrations between the 2 dosing regimens were very small with similar maximum concentrations and slightly faster elimination (higher CL/f) for the t.i.d. dosing regimen. These simulations show that the concentration-time profiles differ between the different body weights. Children with higher body weights receive higher total doses (2 mg/kg). On the other hand, children with higher body weight have higher clearances: the parameter for the body weight effect on clearance was estimated as 0.0419 such that the estimated clearance for a body weight of 4 kg is exp (0.0419*4)*1.78 = 2.1 while the estimated clearance for a body weight of 32 kg is exp(0.0419*32)*1.78 = 6.8, or more than 3 times as high. Since the dose increases from 8 mg to 64 mg (8-fold), the resulting exposure is higher in children with higher body weight. Body weight and age are highly correlated and both covariates alone showed significant influence on the PK of bosentan during individual covariate testing. During backward deletion, age was dropped and body weight resulted as the covariate which can better explain differences in PK in children. This effect of body weight on bosentan exposure was already observed previously (FUTURE 1, BREATHE 3, and the physiologically-based PK model for bosentan) [D-07.041, B-02.003, D-11.250].

Discussion

The Methodology for model building and validation was well described.
The population PK characteristics of bosentan and its metabolites in children with PAH could be adequately described by a population PK model. Bosentan was modeled as a one-compartment model with first order absorption (including lag-time) and first order elimination. Simultaneously, its 3 metabolites were modeled with different transfer (conversion) and elimination rates. The relationship between the subject-specific factors dosing regimen, age, and body weight and the different PK parameters were investigated and the following statistically significant covariates were identified: dosing regimen on k_a, CL/f, and k_t, and body weight on CL/f. The model qualification of the final model including all significant covariates showed that the model can adequately fit the observed data. The different VPCs verified that the model predicted both the population-typical PK and the variability in the observed data. Subsequent simulations showed that the overall variability of bosentan concentrations in children is high. The influence of body weight on bosentan exposure is in accordance with previous studies (FUTURE 1, BREATHE 3) and with physiologically-based PK modeling results for bosentan.

Regarding the results of the base model and final model, some parameters (e.g. km) were estimated with a huge imprecision (high value of RSE close to 100% or much more). If these parameters should be in the model, usually a fixed value is assigned to these parameters. The Applicant should explain the reason of keeping these parameters to be estimated in the selected model. Maybe a simple model with bosentan data only should be built and results from both models should be compared.

The final model contained 4 covariate effects: dosing regimen on ka, CL/f, and kt, and body weight on CL/f. Simulations split by covariates were investigated for their relevance regarding bosentan plasma concentrations. According to the Applicant, the differences in bosentan concentrations between the 2 dosing regimens were very small with similar maximum concentrations and slightly faster elimination (higher CL/f) for the t.i.d. dosing regimen. The Applicant did not provide adequate justification for the estimation of the values of bosentan PK parameters from the popPK model (i.e. summary of the effect of the dosing regimen (t.i.d. vs b.i.d) and the summary of the effect of the dosing regimen (t.i.d. vs b.i.d.) on bosentan PK parameters per age group). As the claimed indication was withdrawn by the MAH, this issue was not pursued further.

2.5.2.2. Study AC052-391- Future 4

Methods/ study design

study AC-052-391: multicenter, double-blind, randomized, placebo-controlled, prospective study to evaluate pharmacokinetics, safety and efficacy of bosentan as add-on therapy to inhaled nitric oxide in the management of persistent pulmonary hypertension of the newborn.

Investigators/ centers and countries: Patients were randomised in 9 centers across 6 countries (Czech Republic, France, South Korea, Poland, UK and USA).

Period of trial: 08 December 2011 to 05 December 2013

Study design/ Objective

The primary objective was to assess the efficacy of bosentan in neonates with PPHN who were in need of continued iNO after at least 4 h of continuous iNO treatment. The secondary objectives were to evaluate the PK, tolerability, and safety of bosentan in this patient population.

Term or near-term (gestational age > 34 weeks) hypoxic newborns with refractory respiratory distress due to parenchymal lung disease who requiredhigher than 10 ppm iNO and with fraction of inspired oxygen (FiO2) ≥ 50% under mechanical ventilation despites at least 4 hour of iNO were included. (see complete description below)

Number of patients included

It was planned to enroll 30 evaluable patients into the study and randomize them in a 2:1 ratio to either receive bosentan 2mg/kg b.i.d. or matching placebo.

Of the 23 randomized patients (15 bosentan, 8 placebo), 21 patients (13 bosentan, 8 placebo) were evaluable. Recruitment was terminated early because of unforeseen rarity of the study population.

Trial drug dose / Route / Regimen / Duration Bosentan 32 mg dispersible tablets dispersed in water prior to oral administration of 2 mg/kg birth weight (b.i.d) by nasogastric or orogastric tube administered until 24 h after complete weaning from iNO or until treatment failure or a maximum of 14 days.

PK data were analyzed descriptively using the All-treated set (patients who received bosentan) and the PK analysis set, i.e., all treated patients for whom at least 5 of the 7 requested blood samples (including the pre-dose, the 2 h and 12 h post-dose samples) were available on Day 1 and/or Day 5 (i.e., had at least one evaluable profile) and who did not violate the protocol in a way that might have affected the evaluation of the PK endpoints. AUC0-24 and Cmax were corrected to a dose of 2 mg/kg (AUC0-24C and CmaxC). All AUC and Cmax values were assumed to be log-normally distributed.

Patient Disposition

A total of 23 patients were randomized in a 2:1 ratio to bosentan 2 mg/kg b.i.d. (N = 15) or placebo (N = 8). A total of 21 patients received study drug. Two patients randomized to the bosentan group did not receive study treatment due to low birth weight (1 patient) and due to a transient increase in ALT (1 patient). A total of 20 patients (12 bosentan, 8 placebo) completed study treatment (i.e., 2 doses after successful weaning). One patient in the bosentan group discontinued study treatment prematurely due to treatment failure (need for ECMO [protocol-defined]). A total of 21 patients (13 bosentan, 8 placebo) completed the study The gestational age (median, min–max) was similar for patients in the bosentan (40.0 weeks, 36.0–41.0 weeks) and placebo groups (38.5 weeks, 36.0–42.0 weeks). The median age (days, min–max) at first dosing with the study treatment was similar in the bosentan (1.4 days, 0.6–5.6 days) and placebo groups (1.7 days, 0.6–5.9 days). The majority of patients were female (69.2% bosentan, 75.0% placebo).

2.5.2.2.1. Pharmacokinetics results

As the PK parameters estimated using the popPK analysis were estimated with a very high imprecision, the results of the NCA were considered more reliable. On Day 1, the geometric mean AUC0-24C for bosentan was 287.5 ng.h/mL (95% CI: 15.0, 5504.7). The bosentan PK profile, on Day 1, was characterised by a slow absorption rate which can be explained by slower gastric emptying in neonates. On Day 5 (at steady-state), geometric mean AUC0-24C had increased to 11530.2 ng.h/mL (95% CI: 4507.0, 29497.5), which was approximately 40 times higher than on Day 1. The geometric mean CmaxC for bosentan on Day 1 was 30.1 ng/mL (95% CI: 2.4, 372.2) and at steady-state was approximately 30 times higher (880 ng/mL [95% CI 339.2, 2282.7]). Comparing Day 5 to Day 1, AUC0-24 and Cmax for bosentan were respectively 40 times and 30 times lower at Day 1. Therefore the pharmacokinetic profiles of bosentan in newborns were substantially different between Day 1 and Day 5. But the substantial

difference in exposure observed between Day 1 and Day 5 could have been driven by very low exposures to bosentan after the first dosing rather than by high exposure on Day 5.

2.5.2.2.2. Methodology- Pop PK

This part describes the results of the population pharmacokinetic (popPK) analysis of bosentan in pediatric patients with persistent pulmonary hypertension of the newborn (PPHN) from study AC-052-391, pediatric FormUlation of bosenTan in pUlmonary arterial hypeRtEnsion (FUTURE 4).

Objectives.

The objectives of the popPK analysis were:

1. To describe popPK characteristics (i.e., population-typical pharmacokinetic parameters) of bosentan, including inter- and intra-individual variability in neonates with PPHN.
2. To quantify the influence of subject-specific factors (i.e., covariates such as age and body weight, dose [exposure]) on PK parameters.

The study AC-052-391 (FUTURE 4) was a Phase 3, exploratory, multicenter, double-blind, randomized, placebo-controlled, parallel-group, prospective study of bosentan as adjunctive therapy to inhaled nitric oxide in the management of PPHN.

General considerations

The data were analyzed in accordance with the FDA Guidance for Industry on Population Pharmacokinetics and the EMA/CHMP guideline on PopPK analyses [FDA 1999, EMA 2007].
PK assessments were performed at Day 1 and at Day 5 (if study drug was discontinued prior to Day 5, PK was not assessed on Day 5). Whole blood samples for PK for the preparation of dried blood spot samples were drawn at the following timepoints:

- On Day 1: the pre-dose blood sample was to be drawn immediately prior to the first study drug administration, and then at 0.5 h, 1 h, 2 h, 3 h, 7.5 h, 12 h after the first study drug administration. The 12 h sample was to be drawn before the second study drug administration.
- On Day 5 (if applicable): the pre-dose blood sample was to be drawn immediately prior to study drug administration. Post-dose samples were to be drawn 0.5 h, 1 h, 2 h, 3 h, 7.5 h, and 12 h after study drug administration. The 12 h sample was to be drawn before the next study drug administration. Time of drug administration and time of blood samplings were to be in line with those of Day 1.

All assessments had to be scheduled in such a way that the actual timepoint of PK sampling did not deviate by more than ± 5% from the scheduled timepoint of PK sampling. Concentrations of bosentan in blood were determined using a validated liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS method). The lower limit of quantification for bosentan in plasma was set at 2 ng/mL.

Covariates

The following parameters were tested as candidate covariates for model inclusion:

- Age (days) at start of treatment.
- Body weight (kg) at start of treatment.

The covariate “exposure”, i.e., the actual dose based on body weight, was finally not considered as a separate covariate, since body weight and dose based on body weight are highly correlated by definition and the limited amount of data would not allow to differentiate these two covariates.

Data programming.

Blood concentration data from 21 subjects were available (all-treated set). Eight out of the 21 subjects were placebo patients with blood concentrations below the limit of quantification (BLQ).

The remaining 13 subjects with measurable blood concentrations were used for further analysis (6 subjects with concentration data on Day 1 only, 1 subject with concentration data on Day 5 only [at Day 1 all samples were BLQ], and 6 subjects with concentration data on Day 1 and Day 5 = 12 subjects with data on Day 1 and Day 7 subjects with data on Day 5).

Bosentan profiles were atypical on Day 1. For most of the patients the concentrations were continuously increasing over the first dosing interval. On Day 5, the 7 patients who were still under bosentan treatment showed more common profiles.
The analysis was therefore split in Day 1 and Day 5: at Day 1, for one subject all blood concentrations were BLQ and only the remaining 12 subjects were used for further analysis; at Day 5, data from only 7 subjects were available, since in some cases drug treatment was discontinued prior to Day 5 and PK was then not assessed at Day 5. Furthermore, 5 individual data points were excluded because plasma concentrations were extremely high (implausible) or second peaks were observed being not compatible with standard PK models (excluded data points are shown in Table 1).
The split between Day 1 and Day 5 was motivated by the fact that the observed plasma concentration-time profiles differed substantially. This suggested that the PK parameters change dramatically during the first days of life and therefore it was reasonable to assess the PK parameters separately for Day 1 and Day 5.

Table 1 Data points excluded from analysis

Subject no.	Excluded data point	Reason
10303	Day 5, 12 h	Second peak, increase at 12 h
10401	Day 5, 7.5 h	Second peak (highest conc. at 7.5 h)
30251	Day 5, 12 h	Extremely high + increase at 12 h
30458	Day 5, 12 h	Extremely high + increase at 12 h
30552	Day 5, 7.5 h	Second peak at 7.5 h

Model selection

The base model consisted of the PK parameters, inter-individual variability (random effects) and residual variability in drug concentrations (random variability). Covariates were not included in the base model.

Covariate selection

The inclusion of the covariates was tested according to the following relationship, e.g., for continuous covariates such as age:

$$TV = THETA(1) \times \left(\frac{AGE}{meanAGE} \right)^{THETA(2)}$$

with TV = typical value, THETA(1) = population parameter value, and THETA(2) = covariate effect. The model was run with one covariate added on one parameter at a time. The selection of the best model was based on the log-likelihood ratio test (LRT) that follows a Chi-square (χ^2) distribution. If the decrease in objective function value (OFV) was significant (decrease in OFV > 3.84 for 1 degree of freedom with p = 0.05), the covariate was included into the model.

Full model and final model

Following the univariate covariate selection, all statistically significant covariates were added to obtain the full and final model.

Model qualification

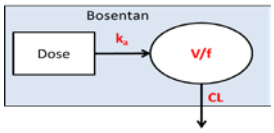
The graphical analyses consisted of goodness-of-fit plots (observed versus predicted concentrations, weighted residuals versus predicted concentrations and time), individual predicted and observed concentration-time profiles, post-hoc parameter distributions and graphical evaluation of covariate effects using post-hoc estimated parameters.

Results

Base model development

Based on prior knowledge and data available, the selected structural model for bosentan was a one-compartment model (with V/f as apparent volume of distribution) with first order absorption (with absorption rate constant ka), and first order elimination (with CL/f as apparent total body clearance). The structural model is illustrated in Figure 4.

Figure 4 Structural population PK model



It was assumed that the individual parameters (random effects) characterizing the between-subject variability followed a log-normal distribution. Since the exploratory data analysis showed a significant difference between Day 1 and Day 5, model parameters were estimated for both days individually. Table 2 shows the estimated population parameters for the base model on Day 1 and Table 3 on Day 5.

Table 2 Base model Day 1: popPK parameters

Parameter	**Estimate**	**SE**	**RSE %**
k_a	0.0417	0.047	112
V/f	17.8	21	117
CL/f	0.615	0.54	88
Omega k_a	0.67	1.3	189
Omega V/f	1.42	0.66	47
Omega CL/f	1.75	0.82	47
Exponential error	0.494	0.049	10

(Source: Appendix 11.1.1.1) CL/f = apparent total body clearance: k_a = absorption rate constant; PK = pharmacokinetic; RSE = relative standard error (relative to the mean); SE = standard error; V/f = apparent volume of distribution.

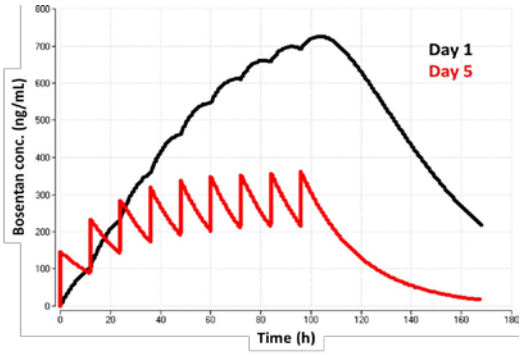
Table 3 Base model Day 5: popPK parameters

Parameter	**Estimate**	**SE**	**RSE %**
k_a	0.0428	0.012	27
V/f	0.0101	9.9	9.77e+04
CL/f	1.69	1.1	66
Omega k_a	0.325	0.41	126
Omega V/f	3.6	1.4e+05	3.92e+06
Omega CL/f	1.32	0.4	30
Exponential error	0.297	0.038	13

(Source: Appendix 11.1.2.1) CL/f = apparent total body clearance: k_a = absorption rate constant; PK = pharmacokinetic; RSE = relative standard error (relative to the mean); SE = standard error; V/f = apparent volume of distribution.

As visualized in Figure 5, the two base popPK models at Day 1 and Day 5 differ substantially. Given the Day 5 data, the model based on the Day 1 data seems implausible.

Figure 5 Visualization of the base popPK models at Day 1 (black) and Day 5 (red)



Covariate selection

The covariate testing was performed on the base model. The results of the covariate testing are given in Table 4 (Day 1) and Table 5 (Day 5). The covariates age and body weight (at birth) were tested as covariates on all model parameters. For Day 1, none of the covariates was significant. For Day 5, the statistically significant covariates based on the LRT (their inclusion led to a significant decrease in OFV of 3.84 or more for one degree of freedom and p = 0.05) were body weight on V/f and CL/f.

Table 4 Covariate testing on Day 1: all models tested and numerical results. Green color indicates statistical significance, red color indicates non-significance at the 5% level

Name	Project name	Info	OFV	Delta OFV	LRT
BASE	**BASE_day1**	**no covariate**	**634.23**		
TEST_COV1	test_Covariate_20140123.txt	AGE on k_a	634.15	−0.08	0.7810
TEST_COV2	test_Covariate_20140123_1.txt	AGE on V/f	634.13	−0.1	0.7507
TEST_COV3	test_Covariate_20140123_2.txt	AGE on CL/f	633.67	−0.56	0.4547
TEST_COV4	test_Covariate_20140123_3.txt	WEIGHT on k_a	634.32	0.09	1.0000
TEST_COV5	test_Covariate_20140123_4.txt	WEIGHT on V/f	632.91	−1.32	0.2509
TEST_COV6	test_Covariate_20140123_5.txt	WEIGHT on CL/f	634.26	0.03	1.0000

(Source: Appendix 11.1.1.2) CL/f = apparent total body clearance: k_a = absorption rate constant; LRT = log-likelihood ratio test; OFV = objective function value; V/f = apparent volume of distribution.

Table 5 Covariate testing on Day 5: all models tested and numerical results. Green color indicates statistical significance, red color indicates non-significance at the 5% level

Name	Project name	Info	OFV	Delta OFV	LRT
BASE	**BASE_day5**	**no covariate**	**569.11**		
TEST_COV1	test_Covariate_20140204.txt	AGE on k_a	568.86	−0.25	0.6162
TEST_COV2	test_Covariate_20140204_1.txt	AGE on V/f	568.28	−0.83	0.3607
TEST_COV3	test_Covariate_20140204_3.txt	AGE on CL/f	568.58	−0.53	0.4641
TEST_COV4	test_Covariate_20140204_4.txt	WEIGHT on k_a	570.31	1.2	1.0000

TEST_COV5	test_Covariate_20140204_5.txt	WEIGHT on V/f	554.76	−14.35	0.0002
TEST_COV6	test_Covariate_20140204_6.txt	WEIGHT on CL/f	564.00	−5.11	0.0238

(Source: Appendix 11.1.2.2) CL/f = apparent total body clearance: k_a = absorption rate constant; LRT = log-likelihood ratio test; OFV = objective function value; V/f = apparent volume of distribution.

Final model

The final model for Day 1 is equivalent to the base model [see Table 2], since no covariate had a statistically significant influence on the PK parameters. For Day 5, body weight was a significant covariate on V/f and CL/f. Due to the limited amount of data, no backward deletion was performed and both terms were therefore added to the base model to obtain the final model [Table 6].

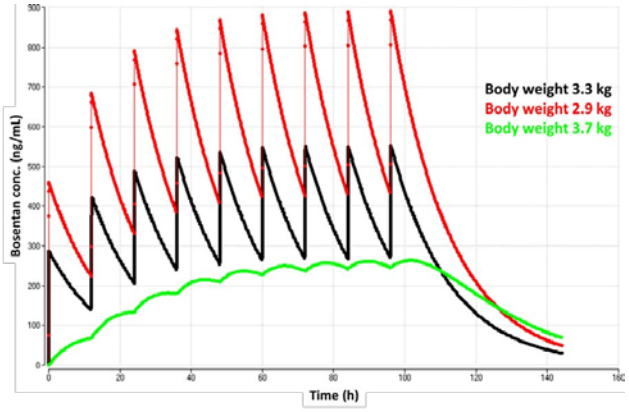
Table 6 Final model Day 5: popPK parameters

Parameter	Estimate	SE	RSE %
k_a	0.0606	0.013	21
V/f	0.0188	0.031	165
Weight on V/f	66.4	10	16
CL/f	1.39	0.56	40
Weight on CL/f	4.66	3.1	67
Omega k_a	0.142	0.46	323
Omega V/f	0.123	0.31	248
Omega CL/f	0.914	0.27	29
Exponential error	0.279	0.035	13

(Source: Appendix 11.1.2.3) CL/f = apparent total body clearance: k_a = absorption rate constant; PK = pharmacokinetic; RSE = relative standard error (relative to the mean); SE = standard error; V/f = apparent volume of distribution.

The effect of body weight on V/f and CL/f might be explained by the dramatic physiologic changes during the first days of life in neonates and the differences in gestational age between neonates with different body weights. Figure 6 visualizes the effect of body weight on the PK in neonates based on the final popPK model. Predictions of the effect of body weight should be interpreted with caution due to the limited size and high variability of the data.

Figure 6 Visualization of the effect of body weight in the final popPK model at Day 5 (black = body weight 3.3 kg, red = body weight 2.9 kg, green = body weight 3.7 kg)



Model qualification.
Goodness-of-fit plots are employed in the following to qualify the model.

2.5.2.2.3. Discussion

The methodology for model building and validation was well described.
Bosentan was modeled as a one-compartment model with first-order absorption and first-order elimination. Since the exploratory data analysis showed a significant difference between Day 1 and Day 5, model parameters were estimated for both days individually.
The relationship between the subject-specific factors age and body weight and the different PK parameters were investigated and the covariate effects body weight on V/f and CL/f were identified to be statistically significant (on Day 5 only). Higher body weight resulted in higher V/f and a higher CL/f, but these results should be interpreted with caution due to the limited amount of data and high variability observed.
The qualification of the final models showed that the models can adequately fit the observed data. Predictions of unobserved data and simulations should be interpreted with caution though due to the limited amount of data and high variability observed.
According to the MAH, the differences between Day 1 and Day 5 can be explained by substantial physiologic changes during the first days of life in neonates, e.g., changes in absorption (i.e., gastric pH, gastric emptying), and clearance pathways. The model parameter estimates on Day 5 are closer to population parameter estimates for bosentan in older children (above 3 months of age) [D-14.035] than to the model parameter estimates on Day 1, including the observed influence of body weight on the PK of bosentan.

2.5.3. Discussion on clinical pharmacokinetics

The popPK characteristics of bosentan in neonates with PPHN could be described by popPK models with the caveat that only limited data with high variability were available. The PK parameters were estimated with a very high imprecision (base and final model). Therefore, it is difficult to consider these estimations reliable. A noncompartmental analysis seems to be needed to compare PK parameters on Day 1 and Day 5.
Furthermore, the estimated values of the primary PK parameters (CL, V and Ka) are very different between FUTURE 3 and FUTURE 4 studies.

As the pharmacokinetic profiles of bosentan in newborns were substantially different between Day 1 and Day 5, model parameters were estimated for both days separately. According to the Applicant, this suggested that the PK parameters change dramatically during the first days of life. However bearing in mind that bosentan PK is subject to autoinduction, it is not clear if that deep change in PK is linked to the maturity of the enzymatic system or to autoinduction phenomenon.
This observation of dramatic change in PK highlights the need of further investigation of bosentan PK in the claimed subgroup of children (3 months to *2 years).*

Pharmacokinetics of bosentan on this subgroup cannot be considered as well characterized due to the limited data. Looking at demographic data of patients included in FUTURE 3, of the 64 randomized patients, 21 were < 2 years (33%) with only 4 patients < 1 year with PK data and 43 were ≥ 2 years. The PK analysis was performed on 58 subjects including only 4 patients < 1 year. In summary, data collected on the subgroup of interest (i.e. children aged from 3 months to 2 years) were too limited to adequately characterize the PK profile of bosentan in children from 3 months to 1 year. However for children above 1year, further recommendations can be made and the section 4.2 is updated accordingly.

2.5.4. Conclusions on clinical pharmacology

The data collected on the subgroup of interest (children aged from 3 months to 2 years) were too limited to adequately characterize the PK profile of bosentan in children from 3 months to 1 year.

Nevertheless updated information is inserted in the SmPC section 5.2. For children above 1year, updated information is inserted in the posology section.

2.6. Clinical efficacy

2.6.1. Main study(ies)

Efficacy data provided in support of this application are based on exploratory endpoints from the open-label, not controlled studies conducted with the 32mg dispersible tablet formulation of bosentan in pediatric patients with PAH: FUTURE 1 (AC-052-365) and its extension (FUTURE 2 ; AC-052-367), and the recently completed FUTURE 3 (AC-052-373).

The final study report of FUTURE 1 (D-07.041) and preliminary analysis from its extension FUTURE 2 with data cut-off of 1 March 2008 were previously submitted and assessed through procedure EMEA/H/C/401/X/0039 that ended on April 2009. The present application provided cumulative final data up to end of FUTURE 2 study (last patient visit 28 October 2011).

No efficacy data are presented for the ongoing FUTURE 3 extension study.

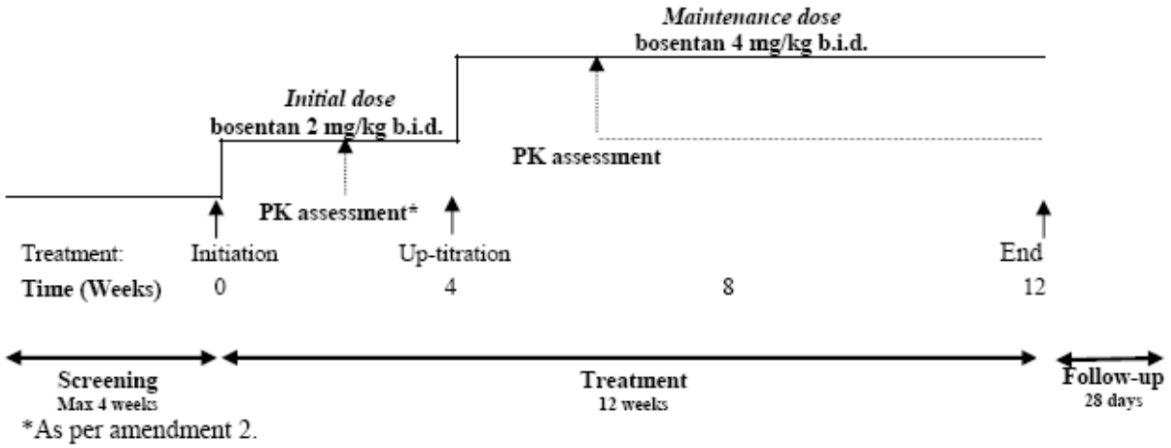
In addition, data are presented for a placebo controlled study newly conducted with 32 mg dispersible tablets in patients with persistent pulmonary hypertension of the newborn (PPHN; FUTURE 4 ; AC-052-391).
No patients were enrolled in FUTURE 4 extension at the time of completion of FUTURE 4 study, hence no data is available.

2.6.1.1. FUTURE 1 study (AC-052-365)

This study was an open-label, multicenter, uncontrolled, 12-week (3 months) study to assess the pharmacokinetics (as primary objective) and tolerability and safety (as secondary objective) of bosentan orally administered with 32 mg dispersible tablets in children with idiopathic or familial pulmonary arterial hypertension.

The study consisted of a screening period of a maximum of 4 weeks, a treatment period of 12 weeks, and a post-treatment follow-up period of 28 days (see Figure 1). Patients were to receive the bosentan with a 32 mg dispersible tablet formulation orally for 12 weeks, with the dosage adjusted to the patient's body weight at study start. After 4 weeks of treatment, the initial dose of 2 mg/kg b.i.d. was to be up-titrated to the maintenance dose of 4 mg/kg b.i.d. All patients were to start the study drug at the 2 mg/kg b.i.d. dose, whether or not they were previously treated with bosentan.
Patients weighing 30 kg or more were to receive a maximum of 120 mg b.i.d. of bosentan, unless down-titration was necessary, in which case they were to receive 64 mg b.i.d.

Figure 1 Study design



*As per amendment 2.

Demographics at baseline and disposition:

In this study 36 children aged from 2 to 11 years (mean age = 6.7 ± 2.7 years; mean weight: 22.4 ± 8.1 kg) were included. One patient was excluded due to the development of confounding condition.

The greatest proportion of patients were 6 to 11 years old (63.9% = 23 patients) and the lowest proportion of patients was between 2-3 years (11.1 % = 4 patients) and 9 patients were 4 to 5 years old. Thirty one patients (86.1%) were diagnosed as idiopathic PAH and 5 (13.9%) as familial PAH.

A total of 15 patients/36 (41.7%) had "previous bosentan" intake prior to study treatment start (9 in WHO class II, 5 in WHO class III) and 21 patients/36 (58.3%) were identified as "bosentan naïve" patients (14 in WHO class II, 7 in WHO class III).
The most common treatments reported at baseline by frequency were epoprostenol (9 patients, 25.0%), furosemide (8 patients, 22.2%), and oxygen (7 patients, 19.4%).

Efficacy results :

Efficacy was assessed only exploratory based on WHO functional status measurement, patients' and physicians' clinical impression rate, and SF10 questionnaire.

The changes from baseline to week 4, 8, and 12 in the WHO functional class showed the majority of patients were stable. At Week 12, out of the 23 patients at baseline who were diagnosed class II, one worsened to class III and two improved to class I (the remaining 20 patients were stable at class II), and out of the 12 patients at baseline who were diagnosed class III, none worsened, and three improved to class II. The improvements were mainly observed in bosentan naïve patients while in contrast patients previously treated with bosentan remained largely stable with one patient worsening from class II to class III.

Table 44 WHO functional class – changes from baseline to week 12

Produced by madesu on 24SEP07 - Data dump of 24SEP07
Ro 47-0203, Protocol: AC-052-365
Table WHOS12_T: WHO functional class change from baseline to week 12 in treatment period
Analysis set: All treated

Treatment: Bosentan

			Endpoint							
	n	Baseline	n	I		II		III		IV
Week 12	35	I	-	-		-		-		-
		II	23	2	5.7%	20	57.1%	1	2.9%	-
		III	12	-		3	8.6%	9	25.7%	-
		IV	-	-		-		-		-

(Page 1/1)

Out of the 24 patients whose condition the physician rated as 'good' or 'very good' at baseline, two were considered to be doing 'worse' or 'significantly worse', with the majority of responses being 'no change' or 'better', at Week 12.

Parents and physician global clinical impression
Out of the 17 patients whose condition the parents rated 'not good or bad' or 'bad' at baseline, 9 patients were considered to be doing 'better' or 'significantly better' at Week 12.
Out of the 17 patients whose condition the parents rated 'good' or 'very good' at baseline, only 1 patient was considered to be doing 'worse' or 'significantly worse' at Week 12, with 9 patients considered being either 'significantly better' or 'better' at Week 12.

For the majority of cases, parents' responses were consistent with, or more positive than, the physician's assessment at each timepoint. Out of 11 patients whose condition the physician rated 'not good or bad' or 'bad' at baseline, 6 patients were considered to be doing 'better' or 'significantly better' by Week 12. Out of 24 patients whose condition the physician rated 'good' or 'very good' at baseline, only 2 patients were considered to be doing 'worse' or 'significantly worse', with the majority of responses being 'no change' or 'better', at Week 12.

Neither any exercise capacity tests nor pulmonary hemodynamic measurements were performed in this study.

Clinical worsening occurred in 2 patients leading to discontinuation and one of them died during the study (suspected infection otitis triggering right ventricular failure).

CHMP discussion

This study was previously assessed in the procedure EMA/HC/401/X/039. PK results from this study showed that the systemic exposures with 2 mg/kg b.i.d. and with 4 mg/kg b.i.d. were similar and approximately half lower than in adults (historical controls) when treated with 125 mg b.i.d. (corresponding to the dose of 2 mg/kg b.i.d. in adults weighing around 60 kg).

Efficacy was only exploratory. The majority of patients remained stable after 12 weeks treatment with the maintenance dose of 4 mg/kg b.i.d. based on WHO functional class assessment. 9/36 patients (25.0%), were receiving concomitant epoprostenol. No hemodynamic measurement were performed. Clinical worsening during the 12-week period leading to discontinuation occurred in 2 patients and one of them died. No pulmonary hemodynamic measurements were performed nor any exercise capacity tests.

Table 1. Summary of Efficacy for trial AC-052-365 (FUTURE 1)

Title: Pediatric FormUlation of bosenTan in pUlmonary arterial hypeRtEnsion: An open-label, multicentre study to assess the pharmacokinetics, tolerability, and safety of a pediatric formulation of bosentan in children with idiopathic or familial pulmonary arterial hypertension (FUTURE 1)	
Study identifier	AC-052-365

Design	Multicenter, open-label, single-arm, non-controlled, 12-week, prospective Phase III study.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12-weeks treatment period not applicable Maximum exposure of 258 weeks in the OL extension study of AC-052-365 (AC-052-367, FUTURE 2)
Hypothesis	Equivalence between AUC_{τ} of 4 mg/kg b.i.d. bosentan paediatric formulation in paediatric PAH patients and adult PAH patients having received 125 mg b.i.d. bosentan as marketed tablet (historical data of 11 patients from study AC-052-357 identified in the study protocol).		
Treatments groups	Bosentan group		Bosentan 2 mg/kg b.i.d.: initiation to Week 4. Bosentan 4 mg/kg b.i.d. (maintenance dose): Week 4 up to Week 12. Children weighing 30 kg or above were to receive the maximum initial dose of 64 mg b.i.d., then 120 mg b.i.d. as the maintenance dose. 36 patients were enrolled
Endpoints and definitions	Primary endpoints	PK	Area under the plasma concentration time curve during a dose interval (AUC_{τ}) of bosentan
	Secondary endpoints	PK	Maximum plasma concentration (C_{max}) and time to reach the maximum plasma concentration (t_{max}) of bosentan and the C_{max}, t_{max}, and AUC_{τ} of its metabolites (Ro 47-8634, Ro 48-5033, Ro 64-1056)
	Exploratory endpoint	Efficacy	Exploratory efficacy and quality of life endpoints were defined as follows: • Change from Baseline to Week 12 in WHO functional class • Change from Baseline to Week 12 in Quality of Life questionnaire (SF-10™) • Change from Baseline to Week 12 in Global Clinical Impression scale assessed by the parents and the physician
Database closure	23FEB07 ((Re-opened and re-closed: 25SEP07)		

Results and Analysis

Analysis description	**Primary Analysis**	
Analysis population and time point description	Per protocol set Between Week 6 and Week 12	
Descriptive statistics and estimate variability	Treatment group	4 mg/kg b.i.d. bosentan
	Number of subjects	35

	Bosentan AUC_{τ} [ng.h/ml] (geometric mean)	4383
	95% confidence limit of geometric mean	3461, 5552
Analysis description	**Secondary analysis**	
Analysis population and time point description	Per protocol set Between Week 6 and Week 12	
Descriptive statistics and estimate variability	Treatment group	4 mg/kg b.i.d. bosentan
	Number of subject	35
	Bosentan C_{max} [ng/mL] (geometric mean)	895
	95% confidence limit of geometric mean	699, 1146
	Bosentan t_{max} [h] (median)	3.0
	min, max	0.0, 8.5
Analysis population and time point description	Per protocol set Between Week 2 and Week 4	
Descriptive statistics and estimate variability	Treatment group	2 mg/kg b.i.d. bosentan
	Number of subjects	11
	Bosentan AUC_{τ} [ng.h/ml] (geometric mean)	3577
	95% confidence limit of geometric mean	2294, 5577
	Bosentan C_{max} [ng/mL] (geometric mean)	583
	95% confidence limit of geometric mean	354, 961
	Bosentan t_{max} [h] (median)	3.0
	Min, max	1.0, 7.5
Analysis description	**Exploratory Analysis**	

Analysis population and time point description	All treated set From baseline (last assessment before study treatment start) up to Week 12					
Descriptive statistics and estimate variability	Treatment group	Bosentan group				
	Change from Baseline to Week 12 in WHO functional class (35 patients)	Baseline	I (%)	II (%)	III (%)	IV(%)
		I	-	-	-	-
		II	5.7	57.1	2.9	-
		III	-	8.6	25.7	-
		IV	-	-	-	-
	Change from Baseline to Week 12 in Quality of Life questionnaire (SF-10™) (median, 35 patients) Min, Max	Physical Summary Score: 1.3 Psychological Summary Score: 0.0 Physical Summary Score: -53.2, 33.6 Psychological Summary Score: -24.0, 20.6				
	Change from Baseline to Week 12 in Global Clinical impression scale assessed by the parents (34 patients)	Baseline	Sign. Better (%)	Better (%)	No change (%)	Worse (%)	Sign. Worse (%)
		V. good	2.9	-	5.9	-	-
		Good	8.8	14.7	14.7	-	2.9
		Neither good or bad	5.9	11.8	11.8	2.9	-
		Bad	2.9	5.9	5.9	-	2.9
	Change from Baseline to Week 12 in Global Clinical Impression scale assessed by the physician (35 patients)	Baseline	Sign. Better (%)	Better (%)	No change (%)	Worse (%)	Sign. Worse (%)
		V. good	-	-	2.9	-	-
		Good	-	25.7	34.3	2.9	2.9
		Neither good or bad	5.7	5.7	8.6	-	-
		Bad	-	5.7	5.7	-	-

2.6.1.2. Study AC-052-367 (FUTURE-2): cumulative analysis from FUTURE-1 and FUTURE-2

FUTURE-2 is the extension of FUTURE-1.

It was open-labelled, not-controlled with the primary objective to collect additional and longer than 12 weeks safety data and additional exploratory efficacy and outcome data (i.e.: PAH worsening, time to initiation of new therapy for PAH, time to new onset or worsening of right heart failure, vital status,

functional capacity, QoL, and physicians' and parents' GCI) in paediatric patients with IPAH or familial PAH using 32 mg dispersible tablets.

Of the 36 patients enrolled in FUTURE-1, 33 patients entered in FUTURE-2.

An interim cumulative efficacy analysis was presented through procedure EMEA/H/C/401/X/0039 in May 2008 based upon data collected from May 2005 (FUTURE-1 beginning) to 1er March 2008.

The present submission provides the cumulative analysis for all patients in FUTURE 1 and its extension (FUTURE 2) from the start of bosentan study treatment up to end of study of FUTURE 2 (first patients first visit on 23 August 2005 to last patient, last visit: 28 October 2011). The final study report (D-12.790) is dated on 17 December 2012.

Patients continuing into FUTURE-2 were to continue receiving the 4 mg/kg b.i.d. maintenance dose they were receiving at the end of FUTURE-1 unless this dose was not tolerated. In such cases, patients were down titrated to 2 mg/kg b.i.d. The dosage was adjusted to the patient's body weight at each visit throughout the study. Doses were dispensed by step of 8 mg delivered using ¼ of the 32 mg dispersible tablets.
Patients weighing 30 kg or over were to receive a maximum dose of 120 mg b.i.d., and a maximum of 64 mg b.i.d. if down-titration was necessary.

Baseline demographics and disposition of patients :
Two of the 36 patients included prematurely discontinued the study FUTURE-1. Of the remaining 34 patients, 33 agreed to continue bosentan treatment in FUTURE 2 (one refusal).

Treatment was to be discontinued in patients who reached the age of 12 years during the study, as the upper limit of the included age range was < 12 years of age. Six patients reached the age of 12 during the FUTURE 2 study and remained in the study for a further 23 to 489 days (around 17,5 months) after reaching this age.

Summary of the demographic characteristics of all treated patients at baseline of FUTURE-1 study has been detailed in the above description of FUTURE-1.

Overall, a total of 19 patients (52.8%) (6 (40.0%) of them in the subgroup with previous bosentan and 13 (61.9%) in the bosentan-naïve subgroup) discontinued prematurely from the core or extension study due to administrative reasons or withdrawal of consent (n = 10), disease progression, AEs, transplant or treatment failure (n = 5), or death caused by PAH or infection (n = 4).
Given the evolving treat-to-target treatment approach, the MAH speculates that the administrative reasons might have included addition of new PAH-specific therapy without prior worsening of PAH. One patient who prematurely discontinued due to administrative/other reasons reached adult weight and was switched to the adult formulation of bosentan.
The MAH considers that this rate of discontinuation can be expected in this population of PAH patient and for a study of this duration. However as it is open-label, no comparison can be made.

Table 3 Summary of all premature study discontinuations

Ro 47-0203, Protocol: AC-052-367
Summary of all premature study discontinuations
Analysis set: All treated

Reason for premature discontinuation	All patients N=36 n	%	Patients with previous Bosentan N=15 n	%	Patients Bosentan naive N=21 n	%
Total patients with at least one reason	19	52.8%	6	40.0%	13	61.9%
ADMINISTRATIVE/OTHER	5	13.9%	-		5	23.8%
WITHDRAWAL OF CONSENT	5	13.9%	4	26.7%	1	4.8%
DEATH	4	11.1%	2	13.3%	2	9.5%
DISEASE PROGRESSION	2	5.6%	-		2	9.5%
ADVERSE EVENT	1	2.8%	-		1	4.8%
TRANSPLANT	1	2.8%	-		1	4.8%
TREATMENT FAILURE	1	2.8%	-		1	4.8%

Table PWDSS_T - Produced by ameglim on 25SEP12 - Data dump of 25SEP12
(Page 1/1)

Duration of exposure to bosentan

Duration of exposure to bosentan throughout FUTURE-1 and FUTURE-2 studies ranged from 8.4 weeks to 258.0 weeks (60 months i.e. 5 years) with overall median duration of exposure of 119.9 weeks (i.e 28 months = 2,3 years).

6 patients received 5 years treatment, 8 patients received between 4 years to 5 years treatment, 7 patients received between 3 to 4 years treatment, 8 patients received between 2 to 3 years treatment. At the end of study (EOS), a total of 16 patients completed the FUTURE 2 study

Concomitant PAH-specific medications :
Specific PAH medication such as calcium channel blockers, intravenous epoprostenol intravenous or inhaled iloprost were permitted at inclusion and during the study but not sildenafil. Addition of any PAH medication including sildenafil was only permitted in the case of documented worsening PAH worsening. If the initiation of an ET receptor antagonist other than bosentan was considered, the study drug was discontinued.

At baseline, 9 patients took epoprostenol (25.0%). 2 patients took sildenafil or other PAH-specific drugs in the absence of PAH worsening (protocol violation).
Among the 36 initially included patients, a total of 9 patients were newly initiated PAH-specific therapy during FUTURE 1/2 study and were all rated as clinical worsening event before (7 patients) or at the time of the start of the new PAH-medication (2 patients) in the time to clinical worsening analysis.

Efficacy results :

Exploratory efficacy end point were analysed on the cumulative data from FUTURE 1 and FUTURE 2. All patients from FUTURE-1 except one refusal and 2 discontinuation with FUTURE-1 were included in FUTURE-2 and continued their treatment (33/36 patients). The analysis based on cumulative review from FUTURE-1 and 2 was considered acceptable. .

WHO functional class :
Of the 33 patients entered in FUTURE-2, data for WHO functional class at baseline and end of study or premature discontinuation of study drug (FUTURE 1 or 2) were available for 28 patients.

Among 28 subjects with available data, data (among the 36 patients initially included in FUTURE 1), the WHO FC remained unchanged at End-of-Study or premature discontinuation of study drug (FUTURE 1 or 2) as compared to baseline, in 15 subjects (53.6%).

Among the remaining 8 patients initially included in FUTURE1, 3 patients died, 1 worsened, no worsening is reported in the 4 other cases.

Thus, it could be concluded that of the 36 patients included in FUTURE 1, at the time of the last reported WHO class assessment, 11 + 1 improved in WHO FC, 2 + 4 worsened or died, and 15 + 3 remained unchanged during the bosentan treatment administration (but it is unclear how many patients were finally using bosentan as monotherapy.

All patients were symptomatic at baseline (class II or III) allowing some room to assess any change. A higher rate of patients improved in the naïve bosentan group as compared to the group of patient treated with bosentan before the start of the study suggesting that bosentan introduction had some effect. However, as this study was single arm not controlled no comparison can be made or would be limited.

WHO functional class has been established for adults and may not be readily appropriate for the assessment of functional status or effect of a drug in PAH children. But it is acknowledged that a disease classification to assess functional status in children was not available at the time when the study was conducted.

Quality of life:

SF-10 physical (PHS) and psychosocial (PSS) summary scores (range: 0–100) were available for 15/36 (42%) and 16/36 patients (45%), respectively, at baseline and EOS or premature discontinuation of study drug (FUTURE 1 or 2). In this sample the mean physical summary score improved by 10.2 (median 4.7) over the course of the study. The mean psychosocial summary score decreased slightly by – 4.4. (median – 4.0).

The Short Form Health Survey has been designed for children, SF-10 and can be used in children with pulmonary hypertension, but it is not disease specific. Nor does it help assess children less than 5 five years of age.

Parents' and physicians' assessment of global clinical conditions (CGI):

In 13 (81.3%) out of 16 patients with available data, GCIS as rated by the parents improved from baseline to end of study or premature discontinuation of study drug (FUTURE 1 or 2). It remained unchanged in 2 patients and worsened in 1 patient (6.3%).

In 17 (65.4%) out of 26 patients with available data, GCIS as rated by the physician improved from baseline to EOS or premature discontinuation of study drug (FUTURE 1 or 2). It remained unchanged in 7 patients and worsened in 2 patients (7.7%).

After 6 months of treatment in the FUTURE 1 and 2 study, approximately 27% of patients remained stable according to physicians' and parents' / legal representatives' GCIS ratings. The proportion of patients who improved was approximately 59% according to both physicians' ratings and parents' / legal representatives' ratings. Approximately 13% of patients were rated as having worsened according to both groups of raters.

Time to worsening of PAH:

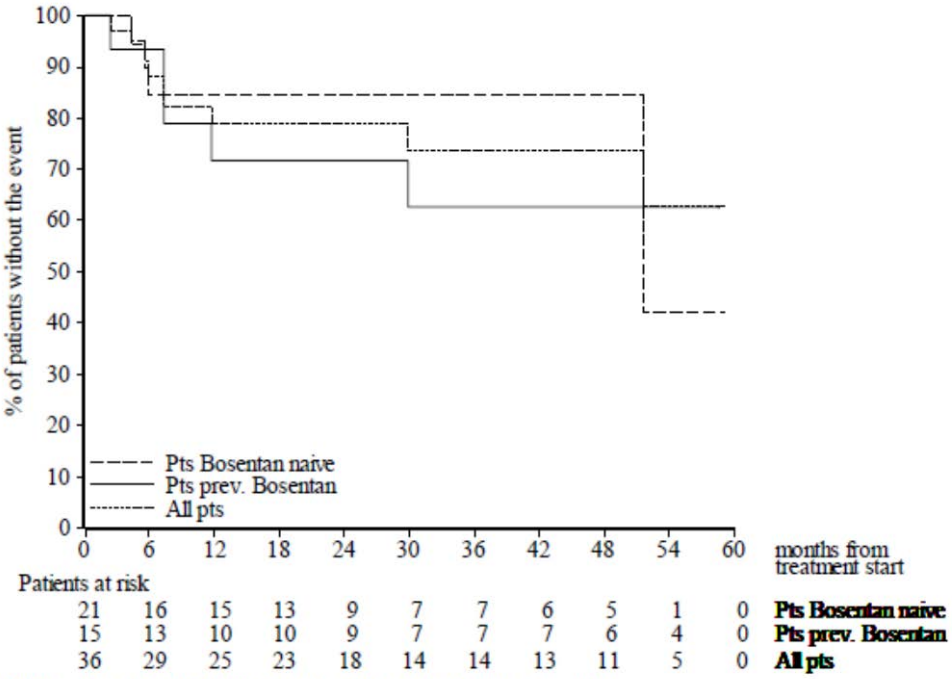
Time to worsening of PAH was assessed based on the 2 following definitions :

- time to the first occurrence of death, transplantation, or hospitalization for PAH worsening (from baseline in FUTURE 1).
- time to first occurrence of worsening of PAH (as defined above), or initiation of new therapy for PAH, or new right heart failure, or worsening of right heart failure (from baseline in FUTURE 1) (broader definition).

FUTURE 1 and 2: Kaplan-Meier estimates for time to worsening of PAH defined as defined as the first occurrence of death, transplantation, or hospitalization for PAH worsening (from baseline in FUTURE 1). – All-treated set

Ro 47-0203, Protocol: AC-052-367
Time to worsening of PAH (Kaplan Meier estimates)
Analysis set: All treated

K-M estimate of the event-free rate *	All patients N=36	Patients with previous Bosentan N=15	Patients Bosentan naive N=21
At month 60 (1830 days)			
Patients at risk	-	-	-
Patients censored	27	10	17
Patients with event	9	5	4
K-M estimate (%)	63.1	62.8	42.2
95% confidence interval (%)	35.3 , 81.6	31.8 , 82.8	1.3 , 84.4



PAH = pulmonary arterial hypertension; Pts = patients; prev. = previous
Figure PAH1G_T - Produced by ameglim on 25SEP12

The KM event-free estimate for worsening of PAH was 88.1% at 6 months, 78.9% (95% CI 60.7%, 89.3%) at 2 years, 73.6% (95% CI 53.1%, 86.2%) at 4 years and 63.1% (95% CI 35.3%, 81.6%) at 5 years.

The MAH provided Kaplan-Meier estimates for time to worsening of PAH (defined as the first occurrence of death, transplantation, or hospitalization for PAH worsening), initiation of new therapy for PAH, new right heart failure or worsening of right heart failure (from baseline in FUTURE 1) – All-treated set (broader definition).

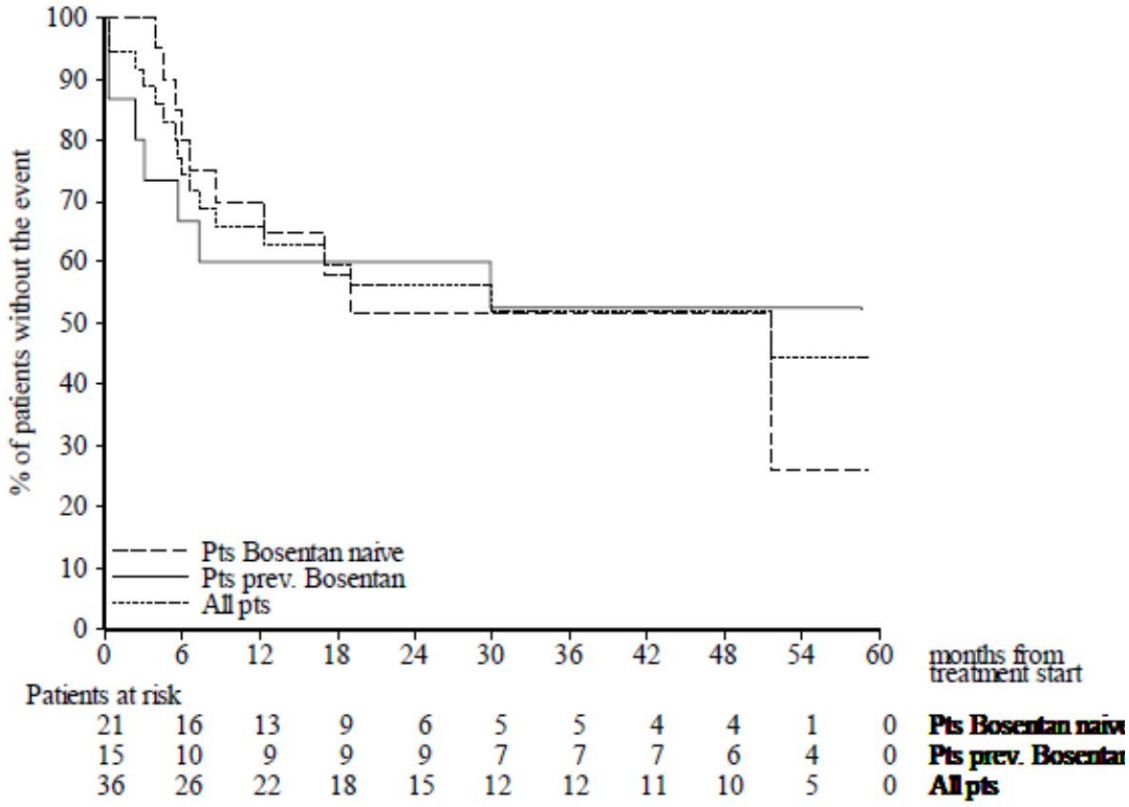
FUTURE 1 and 2: Kaplan-Meier estimates for time to worsening of PAH (defined as defined as the first occurrence of death, transplantation, or hospitalization for PAH worsening), initiation of new therapy for PAH, new right heart failure or worsening of right heart failure (from baseline in FUTURE 1). – All-treated set (broader definition)

Ro 47-0203, Protocol: AC-052-367
Time to worsening of PAH or initiation of new therapy for PAH or new right heart failure or worsening of right heart failure (Kaplan-Meier Estimate)
Analysis set: All treated

K-M estimate of the event-free rate ¥	All patients N=36	Patients with previous Bosentan N=15	Patients Bosentan naive N=21
At month 60 (1830 days)			
Patients at risk	-	-	-
Patients censored	19	8	11
Patients with event	17	7	10
K-M estimate (¥)	44.5	52.5	25.8
95¥ confidence interval (¥)	24.2 , 62.9	25.2 , 74.0	1.9 , 63.1

K-M = Kaplan-Meier.
Table PAH28 T - Produced by ameglim on 25SEP12 - Data dump of 25SEP12

The KM estimate of not having experienced worsening of PAH, initiation of new therapy for PAH, new right heart failure or worsening of right heart failure (broader definition) was 74.4% (95% CI 56.6%; 85.8%), 56.2% (95% CI 38.0%, 71.0%) at 2 years and 51.9% (95% CI 33.4%, 67.5%) at 4 years and 44.5% (95% CI 24.2%, 62.9%) at 5 years.



PAH = pulmonary arterial hypertension; Pts = patients; prev. = previous
Figure PAH2G_T - Produced by ameglim on 25SEP12

In conclusion, the Summary of FUTURE 1 and 2 efficacy results are as follows : All-treated set

	Change from baseline to EOS / premature discontinuation of study drug
WHO FC	Improved: 39.3% (11/28) Stable: 53.6% (15/28) Worsened: 7.1% (2/28)
SF-10 n, mean ± SD	*Physical summary score:* 10.2 ± 16.56 (15/36) *Psychosocial summary score:* –4.4 ± 9.56 (16/ 36)
GCIS	*Physicians' GCIS*: Improved: 65.4% (17/26) Stable: 26.9% (7/26) Worsened: 7.7% (2/26) *Parents' GCIS* Improved: 81.3% (13/16) Stable: 12.5% (2/16) Worsened: 6.3% (1/16)
KM event-free estimates	
at 2 years	78.9% (7 patients had worsening of PAH) 56.2% (15 patients had worsening of PAH [broader definition]
at 4 years	73.6% (8 patients had worsening of PAH) 51.9% (16 patients had worsening of PAH [broader definition])

EOS = end of study; FC = functional class; GCIS = global clinical improvement scale; KM = Kaplan-Meier; PAH = pulmonary arterial hypertension; SD = standard deviation; SF-10 = 10-item short form health survey; WHO = World Health Organization

Table 2. Summary of Efficacy for trial AC-052-367 (FUTURE 2)

Title: An open-label, long-term, safety, and tolerability extension study using the pediatric formulation of bosentan in the treatment of children with idiopathic or familial pulmonary arterial hypertension who completed FUTURE 1 (FUTURE 2: Pediatric FormUlation of bosenTan in pUlmonary arterial hypeRtEnsion).		
Study identifier	AC-052-367	
Design	Multicenter, multinational, open-label, non-comparative, Phase 3 extension study (FUTURE 2) of a 12-week open-label, single-arm study (FUTURE 1).	
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Median exposure of 119.9 weeks (range: 8.4–258.0 weeks) not applicable not applicable
Hypothesis	No statistical hypothesis was set for the study	

Treatments groups	All patients		Bosentan 4 mg/kg b.i.d. until the end of the study (if the dose was not well tolerated, it could be down-titrated to 2 mg/kg b.i.d.). Patients weighing 30 kg or over were to receive a maximum dose of 120 mg b.i.d. and a maximum of 64 mg b.i.d. if down-titration was necessary. 33 of 34 patients who completed FUTURE 1 continued in FUTURE 2.
Endpoints and definitions	Primary endpoint		Not applicable; All efficacy analysis were exploratory.
	Secondary endpoint		Not applicable; All efficacy analysis were exploratory.
	Exploratory endpoint	Efficacy	• Change from baseline in FUTURE 1 to study end or premature study drug discontinuation FUTURE 1 or FUTURE 2) in: o World Health Organization (WHO) functional class o QoL questionnaire score (SF-10 for children™) o GCI scale according to the parents/legal representatives o GCI scale according to the physician • Time to worsening of PAH, defined as the first occurrence of death, transplantation, or hospitalization for PAH worsening (from baseline in FUTURE 1) • Time to first occurrence of worsening of PAH (as defined above), or initiation of new therapy for PAH, or new right heart failure, or worsening of right heart failure (from baseline in FUTURE 1)
Database closure	4APR12 (Re-opened and re-closed: 21SEP12)		

Results and Analysis

Analysis description	**Primary/Secondary Analysis**	
Analysis population and time point description	N/A	
Descriptive statistics and estimate variability	Treatment group	N/A
	Number of subject	N/A
	Endpoint	N/A
	variability	N/A
Notes	Exploratory efficacy endpoints only	

Analysis description	**Exploratory analysis**						
Analysis population and time point description	All-treated set (This analysis set comprised all subjects included in the "All-treated" set of study AC-052-365 / FUTURE 1, i.e., N = 36). Time point specified in individual endpoints.						
Descriptive statistics and estimate variability	Treatment group	All patients					
	Change from baseline in FUTURE 1 to study end or premature study drug discontinuation FUTURE 1 or FUTURE 2) in World Health Organization (WHO) functional class (End of Study, 28 patients)	Baseline (n)	I (%/n)	II (%/n)	III (%/n)	IV (%/n)	
		I (-)	-/-	-/-	-/-	-/-	
		II (17)	21.4/6	35.7/10	3.6/1	-	
		III (11)	7.1/2	10.7/3	17.9/5	3.6/1	
		IV (-)	-/-	-/-	-/-	-/-	
	o QoL questionnaire score (SF-10 for children™) (End of Study, median, 15 patients) Min, Max	Physical Summary Score: 4.7 Psychological Summary Score: -4.0 Physical Summary Score: -10.2 , 48.5 Psychological Summary Score: -18.3, 13.7					
	o GCI scale according to the parents/legal representatives (End of Treatment, 26 patients)	Baseline	Sign. Better (%)	Better (%)	No change (%)	Worse (%)	Sign. Worse (%)
		V. good	6.3	-	-	-	-
		Good	25.0	12.5	6.3	-	-
		Neither good or bad	12.5	18.8	6.3	-	-
		Bad	6.3	-	-	6.3	-
	o GCI scale according to the physician (End of Study, 26 patients)	Baseline	Sign. Better (%)	Better (%)	No change (%)	Worse (%)	Sign. Worse (%)
		V. good	-	-	3.8	-	-
		Good	7.7	30.8	19.2	3.8	-
		Neither good or bad	11.5	11.5	-	-	-

		Bad	3.8	-	3.8	3.8	-
	Time to worsening of PAH, defined as the first occurrence of death, transplantation, or hospitalization for PAH worsening (from baseline in FUTURE 1) (K-M estimate, %)	At month 6 (183 days) - 88.1 At month 12 (366 days) - 78.9 At month 24 (732 days) - 78.9 At month 36 (1098 days) - 73.6 At month 48 (1464 days) - 73.6 At month 60 (1830 days) - 63.1					
	95% confidence interval (%)	At month 6 (183 days) - 71.4, 95.4 At month 12 (366 days) - 60.7, 89.3 At month 24 (732 days) - 60.7, 89.3 At month 36 (1098 days) - 53.1, 86.2 At month 48 (1464 days) - 53.1, 86.2 At month 60 (1830 days) - 35.3, 81.6					
	Time to first occurrence of worsening of PAH (as defined above), or initiation of new therapy for PAH, or new right heart failure, or worsening of right heart failure (from baseline in FUTURE 1)	At month 6 (183 days) - 74.4 At month 12 (366 days) - 65.8 At month 24 (732 days) - 56.2 At month 36 (1098 days) - 51.9 At month 48 (1464 days) - 51.9 At month 60 (1830 days) - 44.5					
	95% confidence interval (%)	At month 6 (183 days) - 56.6, 85.8 At month 12 (366 days) - 47.7, 78.9 At month 24 (732 days) - 38.0, 71.0 At month 36 (1098 days) - 33.4, 67.5 At month 48 (1464 days) - 33.4, 67.5 At month 60 (1830 days) - 24.2, 62.9					

2.6.1.3. Study AC-052-373 (FUTURE 3)

Study title

Pediatric FormUlation of bosenTan in *pUlmonary arterial hypeRtEnsion an open-label, randomized multicenter, multiple dose trial to evaluate the pharmacokinetics, tolerability, safety and efficacy of the pediatric formulation of bosentan two versus three times a day in children from 3 months to less than 12 years of age with pulmonary arterial hypertension."*

The study was conducted by Actelion from 8 March 2011 to 19 August 2013. The study was conducted at 45 expert pediatric PAH centers across 20 countries in Europe, North America, Latin America, Australia, Asia and Africa.

Study design

This study was a prospective, multicenter, open-label, randomized parallel-group study primarily designed to investigate the PK of the dispersible tablet formulation of bosentan at doses of 2mg/kg b.i.d. and 2 mg/kg t.i.d. in children from ≥ 3 months to < 2 years of age and from 2 years to < 12 years of age with stable PAH (idiopathic or persistent for at least 6 months after complete surgical repair of a congenital heart defect, or PAH-CHD associated with open systemic-to-pulmonary shunts, including Eisenmenger syndrome, with PVR > 8 Wood Units and Qp/Qs < 2).

The secondary objectives were to evaluate the efficacy, tolerability, and safety of bosentan in children from ≥ 3 months to < 2 years of age and from 2 years to < 12 years of age with PAH as described above.

CHMP comments:

This study was primarily designed as a PK study and further explore the PK profile in children bearing in mind the plateau of systemic exposure that was observed with 4 mg.kg b.i.d. in the previous FUTURE-1 study. However, efficacy and subsequent benefit of increasing the dose higher than 2 mg/kg b.i.d. was

also a missing information that needed to be addressed. For more accurate evaluation it would have been possible to conduct in a double blinded design but this was not the choice of the sponsor.

The dosage of bosentan was adjusted according to the patient's body weight at initiation of the study treatment (Visit 2) and may have been readjusted after 12 weeks of treatment (Visit 4) if necessary. The body weight dose-adjustment was performed by steps of 8 mg, corresponding to a quarter of a 32 mg dispersible tablets.

Patients who completed the 24 week treatment period had the option of participation in a one-year follow-up extension study (FUTURE-3 extension is on-going, no efficacy data are provided in the present submission).

Demographics:

64 patients were randomized in a 1:1 ratio to bosentan 2 mg/kg b.i.d. (N=33) or 2 mg/kg t.i.d. (N=31) treatment groups. The overall population was predominantly male (56.3%) and Caucasian (75.0%),
The median age was 3.8 years (range: 0.3–11.4 years) sligtly higher in the t.i.d. group (median age 4.8 years) as compared to the b.i.d. (median age 3.7 years).
Of the 64 randomized patients 43 (67%) were ≥ 2 years of age (23 b.i.d., 20 t.i.d.) and 21 (33%) were < 2 years (10 b.i.d., 11 t.i.d.). Among them 6 were less than 1 year (2 b.i.d. and 4 t.i.d.) and 15 (8 b.i.d. and 7 t.i.d.) were between 1 to 2 years old.
The etiology of PAH was mainly idiopathic PAH (46.0%), associated PAH (38.1%) and PAH-CHD associated with systemic-to-pulmonary shunts (12.7%).

CHMP comments

On average, based on the WHO FC (used for adults), the disease condition at baseline was more severe in patients in the b.i.d. group (WHO FC I/II: 63.6%, III: 36.4%) than in the t.i.d. group (WHO FC I/II: 80.6%, III: 19.4%).

In comparison to the profile of WHO FC in FUTURE 1 and 2 patients (II 63.9%, III 36.1%), the disease condition was less severe in FUTURE 3 patients (I 25.0%, II 46.9%, III 28.1%). The mean (± SD) time since diagnosis of PAH in FUTURE 2 (32.2 months) was longer than in the FUTURE 3 study (approximately 18 months).

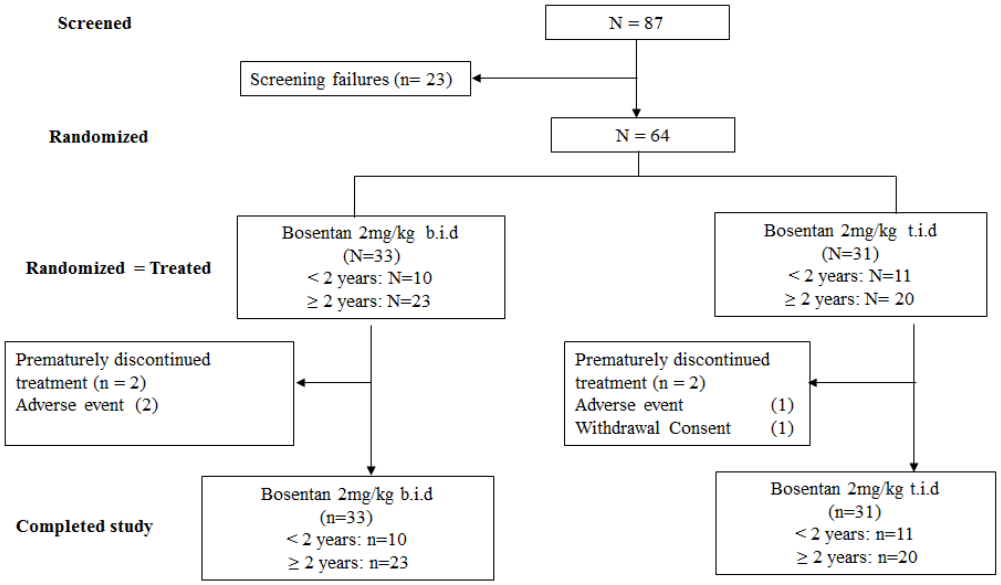
In summary, 18/64 patients received bosentan at baseline before starting of the study, 46/64 were bosentan naïve at baseline.
At baseline, PDE-5 inhibitors were present in 53 % (34/64) of patients: 51.5% (17/33) in b.i.d. group and 54.8 % (17/31) in the t.i.d group of whom 10.9% (7/64) also received prostanoids (15.2% (5/33) in the b.i.d group and 6.5 % (2/31) in the t.i.d group. In total, 12.5 % (8/64) received prostanoids: 15.2% (5/33) patients in the b.i.d. group and 9.7% (3/31) in the t.i.d group. In other words, a total of 54.7% (35/64) of patients (b.i.d: 51.5% (17/33); t.i.d.: 58 % (18/31) received at least one PAH-specific medication other than bosentan.

As only 4 patients discontinued the treatment prematurely, it is considered that no more than 45.3% (b.i.d : 48.5%; t.i.d: 41.9%) were treated with bosentan alone during the study as more than half of the patients received bosentan combined with another PAH-specific medication.

Disposition:
In total, 4 patients (2 in the 2 mg/kg b.i.d. group and 2 in the t.i.d. group, respectively) discontinued the study treatment prematurely either due to AEs (n = 3 worsening of PAH, which in one case was associated with bronchopneumonia) or withdrawal of consent (n = 1). Of the 4 patients who discontinued the study prematurely, 3 were < 2 years of age (1 b.i.d. and 2 t.i.d.).

The mean exposure duration to bosentan was similar in the b.i.d. group (23.6 ± 3.71 weeks) and t.i.d. group (23.3 ± 5.02 weeks). 72.7% in the b.i.d. group and 77.4% in the t.i.d. group had at least 24 weeks of exposure.
The mean (± SD) exposure duration (weeks) to bosentan in patients < 2 years of age (22.8 ± 5.98 weeks b.i.d., 21.8 ± 8.29 weeks t.i.d.) and ≥ 2 years of age (24.0 ± 2.22 weeks b.i.d., 24.1 ± 1.35 weeks t.i.d.) were similar.

Figure 2 Disposition of patients in the FUTURE 3 study



In total, 58 patients were enrolled in the FUTURE 3 study extension after 24 weeks of treatment in the FUTURE 3 core study.
FUTURE-3 extension is on-going. No efficacy data are provided in the present submission.

Exploratory efficacy analysis Results and discussion

No formal hypothesis testing was defined. Efficacy was assessed only exploratory.

Patients were considered study completers if they completed the 24-week treatment period, or in case of premature discontinuationof study treatment, provided relevant End of Study (EOS)
Global EOS was defined as the date on which the last randomized patient, for whom study treatment was not prematurely discontinued, completed the 24-week treatment and a 7-day adverse event (AE) follow-up period.

WHO functional class (WHO FC):
At start of treatment, 19 subjects were in class I, 27 subjects in class II and 18 subjects in class III.During the study, the majority of patients (82.8%) remained clinically stable, i.e.: without change in WHO FC status from baseline to the last post-baseline value up to end of treatment (EOT) + 7 days (75.8% in the b.i.d. group versus 90.3% in the t.i.d. group).

A greater proportion of patients improved from baseline to the last post-baseline value up to EOT + 7 days in the b.i.d. group (7 patients, 29.2%) than in the t.i.d. group (3 patients 14.3%).
In the b.i.d.: 5 patients improved from WHO FC III to II, and 2 improved from WHO FC II to I.
In the t.i.d. group, 3 patients improved from WHO FC II to I.
Improvement in WHO class was reported in 7 out of 10 patients newly exposed to bosentan.
Of the 10 patients who had improvement in WHO FC, 7 patients (4 b.i.d., 3 t.i.d) were bosentan naïve (4 of whom were naïve to any PAH-specific treatment) and 3 were non-bosentan naïve (all b.i.d.).

Worsening was reported for 1 patient in the b.i.d. group.

FUTURE-3 : Change (shift) in WHO functional class from baseline to last post-baseline value up to EOT + 7 days and proportion worsened / unchanged / improved; overall age group, All-randomized set

ACT-050088, Protocol: AC-052-373
Change (shift) in WHO functional class from baseline to last post-baseline value up to EOT + 7 days and proportion worsened/unchanged/improved; overall age groups
Analysis set: All-randomized set

Overall age groups

	n	Baseline	n	Last post-baseline value up to EOT + 7 days: I No.	I %	II No.	II %	III No.	III %	IV No.	IV %
b.i.d (N=33)	33	I	9	9	27.3%	-		-		-	
		II	12	2	6.1%	10	30.3%	-		-	
		III	12	-		5	15.2%	6	18.2%	1	3.0%
		IV	-	-		-		-		-	
t.i.d (N=31)	31	I	10	10	32.3%	-		-		-	
		II	15	3	9.7%	12	38.7%	-		-	
		III	6	-		-		6	19.4%	-	
		IV	-	-		-		-		-	
Total (N=64)	64	I	19	19	29.7%	-		-		-	
		II	27	5	7.8%	22	34.4%	-		-	
		III	18	-		5	7.8%	12	18.8%	1	1.6%
		IV	-	-		-		-		-	

	b.i.d	t.i.d	Total
n	33	31	64
Worsened	1 3.0%	-	1 1.6%
Unchanged	25 75.8%	28 90.3%	53 82.8%
Improved	7 29.2%	3 14.3%	10 22.2%
Imputation for missing values			
n	0	1	1
Carry-forward	-	1 3.2%	1 1.6%
n	33	31	64
Worsened	1 3.0%	0	1 1.6%
Exact 95% CLs*	0.1%, 15.8%	0.0%, 11.2%	0.0%, 8.4%
TREATMENT EFFECT:			
Risk Ratio			
95% CLs			
n	24	21	45
Improved	7 29.2%	3 14.3%	10 22.2%
Exact 95% CLs*	12.6%, 51.1%	3.0%, 36.3%	11.2%, 37.1%
TREATMENT EFFECT:			
Risk Ratio		0.49	
95% CLs		0.14, 1.66	

* Clopper-Pearson formula
Table WHOLVS R - Produced by petratd on 23DEC13 - Data dump of 29NOV13

Based on WHO classification, the greater proportion of patients remained stable during the study. Only one patient worsened while a greater proportion of patients improved in the b.i.d. group as compared to the t.i.d.group. Since more than half of the patients received combined PAH-specific medications (PDE-5 inhibitors and/or prostanoids), it cannot be excluded that the apparent majority of clinical stability in WHO class is related to the high proportion of patients stable at baseline continuing their therapy but this render difficult the assessment of the true effect of bosentan. It would be interesting to know the evolution in patients treated with bosentan alone.

40.6% (26/64) of subjects remained on bosentan monotherapy during the 24 weeks of study treatment without experiencing PAH worsening."

Functional status (so called WHO functional status) was measured using the Dana Point pulmonary hypertension specific classification (based on NYHA classification) for adults. This classification is not readily appropriate to pediatric disease especially because, physical growth and maturation achieved influences the way in which the functional effects of a disease are expressed.
The Experts considered that the adult classification would be appropriate for children aged >16 years.

The Functional Classification of Pulmonary Hypertension in Children proposed by the members of the Pediatric Task Force during the Annual Meeting of the Pulmonary Vascular Research Institute (PVRI) February 2011 follows the same pattern as the adult classification with four classes of disease severity, Class IV being the most severe and Class III has been subdivided into a) and b).
Five different age groups were determined of whom 3 dealt with children less than two years of age when the most rapid physical development and maturation occurs (i.e. : 0-0.5; 0.5-1; 1-2; 2-5 and 5-16 years of age).
It is acknowledged that disease specific classification to assess functional status in children with pulmonary hypertension was not available before this consensus (i.e. at the time FUTURE 3 was designed). However, the functional assessment based on the classification for children newly defined in February 2011 and published in April 2011 could have been introduced via a protocol amendment after the study started (first patient enrolled in March 2011).

A subgroup analysis was performed in the subgroups of patients bosentan-naïve at baseline (n= 46 patients = 71.9%) and patients previously treated with bosentan before starting the study (n=18 patients= 28.1 %).

The percentage of patients who improved on WHO FC functional class, was quite similar in patients who were already treated with bosentan as compared to those bosentan naïve patients (i.e. 23.1% (n= 3/18) versus 21.9% (n= 7/46) respectively) with a tendency for less patients improved in the bosentan naïve group. The same proportion of patients remained unchanged in each subgroup whether they were bosentan-naïve or previously treated with bosentan (i.e. 82.6% versus 83.3% respectively). One bosentan naïve patient worsened.

CHMP comments:
It is not surprising that stable patients (as defined in protocol) previously treated with bosentan were mainly unchanged after the start of the study, but as newly treated with bosentan, the introduction of bosentan in naïve bosentan patients should have resulted in a higher rate of improvement as compared to the bosentan treated patients. Conversely, the rate of patients who improved were lower in the newly treated patients group as compared to those previously treated with bosentan. These results would suggest no clinically significant effect relating to the introduction of bosentan, except if patients were asymptomatic and then did not require to be treated with bosentan.

The MAH referred to the lower severity of the naïve bosentan sub-group as compared to the bosentan non naïve sub-group at baseline (WHO class III: 21.7% versus 44.4%, respectively) allowing less room for improvement in the naïve bosentan group. This could be only a partial explanation since it is noticed that in the bosentan naïve subgroup there was a higher rate of class II that could have been improved to class I (52.2%) than in the bosentan non naïve subgroup (33.3%).

It is acknowledged that the heterogeneity of the groups may have impaired the comparison between bosentan naïve patients and non-bosentan naïve patients. However, it remains that the present data did not demonstrate that the introduction of bosentan exerted an improvement in WHO FC status in bosentan naïve patients.
As the study is not controlled it cannot be established whether the stabilisation of the WHO FC functional status during the short term period of the study can be related to the true effect of bosentan alone.

Echocardiography/Doppler

The echocardiography/Doppler subgroup included a total of 56 patients (27 b.i.d., 29 t.i.d) i.e. all patients except those 8 patients with a derived etiology called “PAH-CHD”[open shunt].

The changes from baseline to the last post-baseline value up to EOT + 7 days (i.e. : observed data and without worst imputation value) in the echocardiography/Doppler variables were small and overlapping in both b.i.d. and t.i.d. groups.
However, in the b.i.d. group, the mean change in inferior vena cava size collapse was greater than in the t.i.d. group (13.12% vs –0.71%).
Pericardial effusion, assessed by categories of severity, remained stable during the study for the majority of patients of the echo/Doppler subgroup (45 patients), worsened in 5 patients, and improved in 4 patients.

The mean changes in the echocardiography/Doppler variables were similar in the b.i.d. and t.i.d. groups among patients < 2 years and ≥ 2 years of age

According to the MAH, no conclusion could be drawn from the echocardiography/Doppler assessments due to high variability in data collected between the centers. However, as the majority of patients had their successive assessments within the study performed in the same investigation center, the analysis based on the rate of patients who improved/stabilised/deteriorated should have been possible.
For completion of the analysis, the MAH will provide the echocardiographic change analysis in relation to the clinical outcomes at the end of the 18 months observation period following the completion of the CSR of the FUTURE 3 extension study. The MAH will provide this analysis in Q2 2015. This can be considered acceptable.

Hemodynamics:

The right heart catheter (RHC) subgroup comprised a low number of 10 patients (4 b.i.d., 6 t.i.d.) as only patients with the assessment scheduled as per standard hospital practice were to be included for this assessment Additionally, only bosentan-naïve patients without open cardiac shunt, and who had no diagnosis of Down syndrome, and no serious complication with previous right heart catheterization were considered.

Overall, the results of changes in echocardiography/Doppler variables and hemodynamic variables considered together showed no consistent indication of effects favoring either the b.i.d or t.i.d. dose regimen although *apparent* better results in the b.i.d. group as compared to the t.i.d. group could be observed. However, the sample size is very limited precluding reliable conclusion.

Time to PAH worsening:

PAH worsening was defined with the 2 following definition :

- Time to first occurrence of death, lung transplantation or hospitalization for PAH-progression.[1]

- (broader definition): Time to first occurrence of death, lung transplantation, hospitalization for PAH-progression[1], initiation of new therapy for PAH or new/worsening right heart failure.

  1* PAH-progression' was defined as a definite/irreversible change in the patient's clinical condition related to PAH. This excludes transient changes of the patient's condition caused by, for example, intercurrent infection (e.g. : pneumonia), surgery (e.g., adenoidectomy), trauma etc. No further requirements were imposed in the protocol, and the qualification of AEs as "PAH-progression" remained at the investigator's discretion.

During the 24 week duration of the study, 'PAH-worsening' (broader definition) was reported for a total of 4 patients: 3 in the b.i.d. group and one in the t.i.d. Group.

According to the broader definition, the KM event-free estimate for the worsening of PAH, initiation of new therapy for PAH, new right heart failure or worsening of right heart failure at Week 25 was 93.1% i.e. 89.7% and 96.7% in the b.i.d. and t.i.d. groups, respectively.

FUTURE 3: Time to worsening of PAH (both definition) All-randomized set

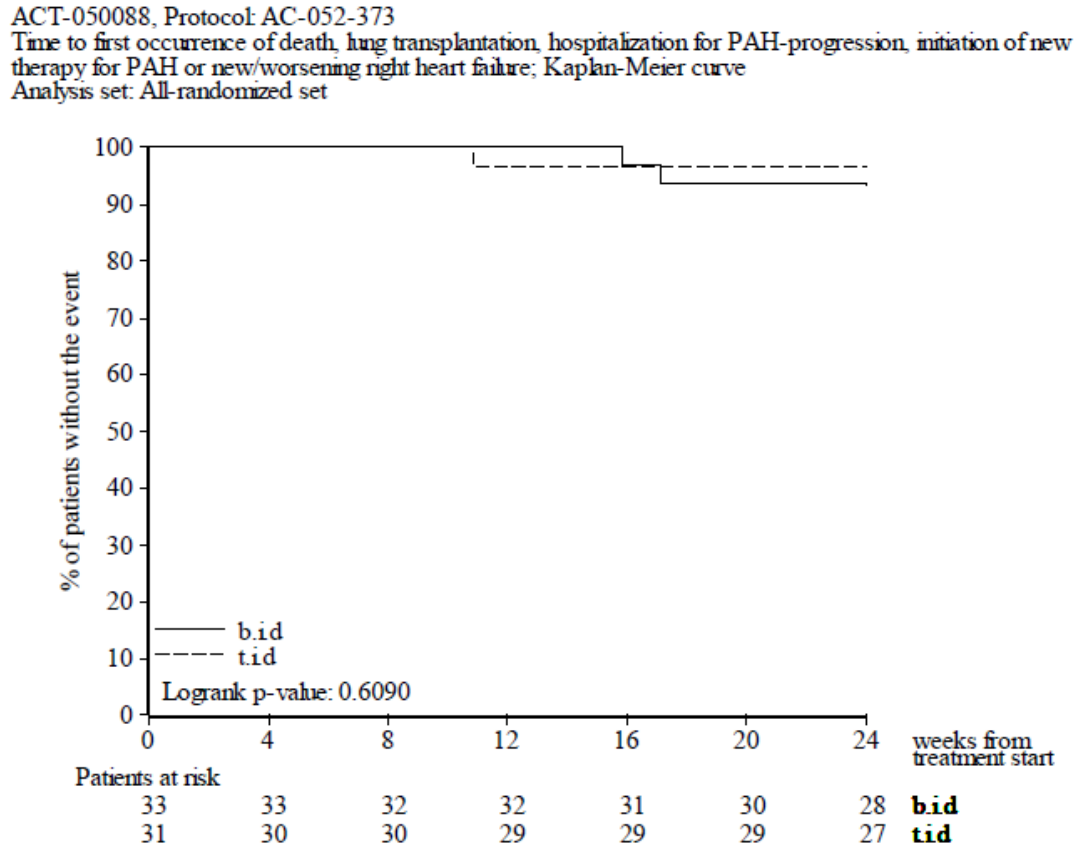


Figure TDLHIG_R - Produced by petratd on 10OCT13 - Data dump of 25SEP13

There were no relevant differences between the b.i.d. and t.i.d. groups for time to occurrence of events defined within the 'PAH-worsening cap'. However, the number of worsening events is very low: only 4 patients: 3 in the b.i.d. group and one in the t.i.d. group experienced a worsening event. This could relate to the low severity at baseline i.e.WHO FC I/II 63.6% in the b.i.d. group and 80.6% in the t.i.d group and the short term duration of the study (6 months). Moreover, as concomitant treatment with PAH-specific medications were present in more than 54.7% of patients, it is difficult to assess the proper effect of bosentan.

NT-proBNP

The NT-pro-BNP ratio of geometric means (expressed as percent ratio) of the 'last post-baseline value up to EOT + 7 days to baseline' was similar in the b.i.d. (88.94%, 95% confidence limits [CLs] 62.40, 126.78) and t.i.d. groups (83.65%, 95% CLs 57.88, 120.87), i.e., 1.12 and 1.20-fold decrease (= improvement) in the b.i.d. and t.i.d. groups, respectively.
Similar results were observed across the age groups.

The MAH has provided a synthetic table of efficacy results in FUTURE-3.

Summary of FUTURE 3 efficacy results, All-randomized set

	Bosentan 2 mg/kg b.i.d. (n=33)	Bosentan 2 mg/kg t.i.d. (n=31)
	Change from baseline to EOT + 7 days	
WHO FC	Improved: 21.2% (7/33) Stable: 75.8% (25/33) Worsened: 3% (1/33)	Improved: 9.7% (3/31) Stable: 84.8% (28/33) Worsened: 0
	Change from baseline to EOS/premature discontinuation of study drug	
GCIS	Physicians' GCIS: Improved: 21.2% (7/33) Stable: 72.7% (24/33) Worsened: 6.1% (2/33) Parents' GCIS Improved: 33.3% (11/33) Stable: 57.6% (19/33) Worsened: 9.1% (3/33)	Physicians' GCIS: Improved: 16.1% (5/31) Stable: 77.4% (24/31) Worsened: 6.5% (2/31) Parents' GCIS Improved: 25.8% (8/31) Stable: 61.3% (19/31) Worsened: 12.9% (4/31)
KM event-free estimate at Week 25 (approximately 6 months)	96.9% (1 patient had worsening of PAH) 89.7% (3 patients worsening of PAH) [broader definition])	96.7% (1 patient had worsening of PAH) 96.7% (1 patient had worsening of PAH [broader definition])
NT-pro-BNP1	88.9% (95% CLs 62.4, 126.8)	83.7% (95% CLs 57.9, 120.9)

b.i.d. = twice daily; CL = confidence limit; EOS = end of study; EOT = end of treatment; FC = functional class; GCIS = global clinical impression scale; KM = Kaplan-Meier; NT-pro-BNP = N-terminal prohormone brain natriuretic peptide; PAH = pulmonary arterial hypertension; t.i.d. = thrice daily; WHO = World Health Organization

1 Geometric means (expressed as percent ratio) of the 'last post-baseline value up to EOT + 7 days to baseline'

Efficacy was only exploratory. However, clinical worsening appeared similar in both groups with apparently a slightly greater proportion of patients in the b.i.d. group with improvement in WHO FC and in Global Clinical Impression Scale (GCIS) as compared to t.i.d. group. However, slightly more patients worsened in the b.i.d. group as compared to t.i.d. group. The MAH states that this could be explained by the less severe condition at baseline in the t.i.d. group as compared to the t.i.d. group. This explanation cannot be firmly confirmed as this analysis is only exploratory and the present data do not show a benefit in increasing the dose from 2 mg/kg b.i.d. to 2mg/kg t.i.d. in children.

Subgroup analysis in children < 2 years or ≥ 2 years :

Of the 64 randomized patients, 21 patients were < 2 years and 43 patients were ≥ 2 years of age. The median age was 1.2 years (range: 0.3–1.9 years) in patients < 2 years and 6 years (range: 2.1–11.4 years) in patients ≥ 2 years of age.

The etiology of PAH (< 2 years vs ≥ 2 years) was idiopathic PAH (38.1% vs 50%), associated PAH (28.6% vs 42.9%) and PAH-CHD associated with systemic-to-pulmonary shunts (28.6% vs 4.8%).

The disease condition at baseline (WHO FC) was on average more severe in patients < 2 years (I/II: 57.1%, III: 42.9%) than those ≥ 2 years (I/II: 79.1%, III: 20.9%).

The MAH has provided a synthetic table of efficacy from FUTURE-3 study:

Efficacy variable		
	< 2 years (N=21)	≥ 2 years (N=43)
WHO FC Change from baseline to the last post-baseline value up to EOT + 7 days	Improved: 19% (4/21) Stable: 76.2% (16/21) Worsened: 4.8% (1/21)	Improved: 14.0% (6/43) Stable: 86% (37/43) Worsened: 0
GCIS Change from baseline to EOS / premature discontinuation of study drug	Physicians' GCIS: Improved: 19% (4/21) Stable: 76.2% (16/21) Worsened: 4.8% (1/21) Parents' GCIS: Improved: 33.3% (7/21) Stable: 52.4% (11/21) Worsened: 14.3% (3/21)	Physicians' GCIS: Improved: 18.6% (8/43) Stable: 74.4%% (32/43) Worsened: 7.0% (3/43) Parents' GCIS Improved: 27.9% (12/43) Stable: 62.8% (27/43) Worsened: 9.3% (4/43)
No. of patients with PAH worsening events	Worsening of PAH1: 1 Worsening of PAH2: 2	Worsening of PAH1: 1 Worsening of PAH2: 2
KM estimate of not experiencing an event at 6 months	Worsening of PAH: 94.7% Worsening of PAH (broader definition): 89.5%	Worsening of PAH: 97.7% Worsening of PAH (broader definition): 94.5%

NT-pro-BNP :

NT-pro BNP was available in 19/21 patients < 2 years and in 39/43 patients > 2 years. Geometric mean at baseline was 112.21 UI [range 6-3286] and 45.46 UI [range 4 to 1025].

The NT-pro-BNP ratio of geometric means (expressed as percent ratio) of the 'last post-baseline value up to EOT + 7 days to baseline' was 72.33%, 95% CLs 40.34, 129.67, in patients < 2 years of age and 94.3%, 95% CLs 73.15, 121.51 in patients ≥ 2 years of age.

No statistical analysis has been provided., the results are similar in patients less than 2 years old and those older than 2 years. However, the subgroup of patients less than 2 years finally only dealt with 21 patients from FUTURE-3 study.

Survival estimates based on pooled analysis of studies performed in children.

In PAH safety analysis, the overall KM survival estimate was 86.4% at one year and 83.4% at 2 years. An analysis by WHO FC showed that survival was influenced by baseline disease severity. In baseline FC II patients, the KM survival estimate was 95.8% at one year and 92.9% at 2 years. In FC III patients, the KM survival estimate was 69.9% at one year and 65.2% at 2 years.

It is considered that the interpretation of the survival estimate should be cautious as survival was not collected at the same time.

Table 3. Summary of Efficacy for trial AC-052-373 (FUTURE 3)

Title: FUTURE 3 - Pediatric FormUlation of bosenTan in pUlmonary arterial hypeRtEnsion: An open-label, randomized multicenter, multiple dose trial to evaluate the pharmacokinetics, tolerability, safety and efficacy of the pediatric formulation of bosentan two versus three times a day in children from 3 months to less than 12 years of age with pulmonary arterial hypertension			
Study identifier	AC-052-373		
Design	A prospective, multicenter, open-label, randomized, multiple dose (two dose regimens) Phase 3 study in children aged ≥ 3 months to < 12 years of age. At least 16 patients in the study were required to be below 2 years of age.		
	Duration of main phase:		24-weeks treatment period
	Duration of Run-in phase:		not applicable
	Duration of Extension phase:		1 year follow-up extension study (AC-052-374 / FUTURE 3 study extension); ongoing
Hypothesis	Exploratory: no formal hypothesis testing was defined for this study		
Treatments groups	Bosentan 2 mg/kg b.i.d.		Bosentan 2 mg/kg b.i.d. 24 weeks, 33 patients
	Bosentan 2 mg/kg t.i.d.		Bosentan 2 mg/kg t.i.d. 24 weeks , 31 patients
Endpoints and definitions	Primary endpoint	PK	The main PK endpoint was defined as the daily exposure to bosentan, i.e., area under the concentration-time curve (AUC) over a period of 24 h (AUC_{0-24}), and calculated as a multiple of the exposure over a dosing interval (AUC_{τ}), 3 × AUC_{τ} and 2 × AUC_{τ} for three times and two times daily dosing, respectively. The main PK endpoint was investigated on exposure corrected to the 2mg/kg target dose.
	Other endpoint	PK	• Maximum plasma concentration (C_{max}) of bosentan • Time to reach the maximum plasma concentration (t_{max}) of bosentan
	Exploratory endpoint	Efficacy	• Change (shift) from baseline to EOT plus 7 days and proportion of patients worsened/unchanged/improved in WHO FC. • Time to first occurrence of death, lung transplantation or hospitalization for PAH-progression up to EOT + 7 days. • Time to first occurrence of death, lung transplantation, hospitalization for PAH-progression, initiation of new therapy for

			PAH or new/worsening right heart failure progression up to EOT + 7 days. • Change (shift) from baseline to EOS and proportion of patients worsened/unchanged/improved in Global Impression Scale (GCIS) assessed by the physician and parents • Change from baseline to EOT + 7 days in plasma NT-proBNP (log_e-transformed). • Change from baseline to EOT +7 days in the following echocardiography/Doppler variables: – Right ventricular fractional area change – Inferior vena cava size collapse (%) – Right ventricular systolic pressure (mmHg) – Tricuspid annular plane systolic excursion (BSA normalized, cm/m^2) – Left ventricular eccentricity index (diastolic) – Left ventricular eccentricity index (systolic) – E/A ratio mitral valve flow
Note	***The above listed exploratory efficacy endpoints are those meaningful (e.g. Hemodynamic data not presented, only performed in a small subset of patients, 10/64)***		
Database closure	25 September 2013 (re-opened and re-closed on 27NOV2014).		
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	The analysis was done on the Per-protocol PK set (n=58)		
Descriptive statistics and estimate	Treatment group	PK set	
	Number of subjects	58	

variability	Ratio of geometric means between treatment groups of bosentan daily exposures (t.i.d./b.i.d.,) (Geometric mean ratio)	0.85
	95% CI	0.61 , 1.20

Analysis description	**Secondary Analysis**				
Descriptive statistics and estimate variability	Treatment group	Bosentan 2 mg/kg b.i.d. overall population		Bosentan 2 mg/kg t.i.d. overall population	
	Patients included in PK set	31		27	
	Bosentan AUC_{0-24c} [h*ng/mL] (Geometric mean)	8535		7275	
	95% CI of geometric mean	6936 , 10504		5468 , 9679	
	Bosentan C_{maxc} [ng/mL] (Geometric mean)	742.8		527.9	
	95% CI of geometric mean	572.8 , 963.2		386.0 , 721.9	
	Bosentan t_{max} [h] (median)	3.0		3.0	
	Min, max	0.0 , 7.5		1.0, 8.0	
	Treatment group	Bosentan 2 mg/kg b.i.d. < 2 years		Bosentan 2 mg/kg t.i.d. < 2 years	
	Patients included in PK set	9		8	

	Bosentan AUC_{0-24c} [h*ng/mL] (Geometric mean)	7879	6756
	95% CI of geometric mean	4783 , 12979	3761 ,12135
	Bosentan C_{maxc} [ng/mL] (Geometric mean)	622.2	487.1
	95% CI of geometric mean	350.1 , 1105.7	262.2 , 905.0
	Bosentan t_{max} [h] (median)	3.0	4.0
	Min, max	0.0 , 3.0	1.0 , 8.0
	Treatment group	Bosentan 2 mg/kg b.i.d. ≥ 2 years	Bosentan 2 mg/kg t.i.d. ≥ 2 years
	Patients included in PK set	22	19
	Bosentan AUC_{0-24c} [h*ng/mL] (Geometric mean)	8820	7506
	95% CI of geometric mean	6939 ,11210	5236 , 10759
	Bosentan C_{maxc} [ng/mL] (Geometric mean)	798.6	546.1
	95% CI of geometric mean	586.6 , 1087.4	366.3 , 814.1
	Bosentan t_{max}[h] (median)	3.0	3.0
	Min, max	0.0 , 7.5	1.0 , 8.0
Analysis description	**Exploratory Analysis** **The efficacy analyses in this study were neither statistically powered, nor stratified for the factors known to influence them (e.g. disease severity)**		
Analysis population and time	Intent to treat (All-randomized set) From baseline (last assessment prior to randomization) up to End of Treatment (EOT) plus 7 days From baseline up to week 24 for Global Clinical Condition		

point description			
	Treatment group	Bosentan 2 mg/kg b.i.d.	Bosentan 2 mg/kg t.i.d.
	Change (shift) from baseline to EOT plus 7 days and proportion of patients worsened/unchanged/improved in WHO FC	Baseline I (%) II (%) III (%) IV (%) I (9) 27,3 II (12) 6,1 30,3 III (12) 15,2 18,2 3,0 IV Worsened 3% Unchanged 75,8% Improved 29,2%	Baseline I (%) II (%) III (%) IV (%) I (10) 32,3 II (15) 9,7 38,7 III (6) 19,4 IV Worsened - Unchanged 90,3% Improved 14,3%
	Time to first occurrence of death, lung transplantation or hospitalization for PAH-progression up to EOT + 7 days	**N=33**	**N=31**
	At Week 4 Patients at risk Patients with event KM estimate (%)	**33** **-** **100**	**30** **-** **100**
	At Week 12 Patients at risk Patients with event KM estimate (%)	**32** **-** **100**	**29** **1** **96.7**

	At Week 24 Patients at risk Patients with event KM estimate (%)	**24** **1** **96.9**	**21** **1** **96.7**
	Time to first occurrence of death, lung transplantation or hospitalization for PAH-progression, initiation of new therapy for PAH or new/worsening right heart failure up to EOT + 7 days	**N=33**	**N=31**
	At Week 4 Patients at risk Patients with event KM estimate (%)	**33** **-** **100**	**30** **-** **100**
	At Week 12 Patients at risk Patients with event KM estimate (%)	**32** **-** **100**	**29** **1** **96.7**
	At Week 24 Patients at risk Patients with event KM estimate (%)	**22** **1** **89.7**	**21** **1** **96.7**
	Change (shift) from baseline to EOS in Global Impression Scale (GCIS) assessed by the physician and proportion of patients worsened/unchanged/improved in WHO FC	Baseline: Very good (%): Very good: 18,2; Good: - / Good (%): 3,0 / 36,4 / Neither good or bad (%): - / - / Bad (%): - / 3,0 / Very bad (%): - / -	Baseline: Very good (%): Very good: 16,1; Good: 3,2; Neither good or bad: - / Good (%): - / 45,2 / 9,7 / Neither good or bad (%): - / 9,7 / 6,5 / Bad (%): - / - / - / Very bad (%): - / - / -

		Neither good or bad - 12,1 3,0 - - Bad - 3,0 3,0 12,1 - Very bad - - - 3,0 3,0 Worsened 6,5% Unchanged 72,7% Improved 26,9%	Bad - 3,2 - 3,2 - Very bad - - - - 3,2 Worsened 6,7% Unchanged 77,4% Improved 19,2%
	Change (shift) from baseline to EOS in Global Impression Scale (GCIS) assessed by the parents and proportion of patients worsened/unchanged/improved in WHO FC	Baseline / Very good (%) / Good (%) / Neither good or bad (%) / Bad (%) / Very bad (%) Very good 21,2 6,1 - - - Good 12,1 24,2 - - - Neither good or bad - 12,1 3,0 3,0 - Bad - - 3,0 6,1 - Very bad - - 6,1 - 3,0 Worsened 10,0% Unchanged 57,6% Improved 45,8%	Baseline / Very good (%) / Good (%) / Neither good or bad (%) / Bad (%) / Very bad (%) Very good 12,9 6,5 - - - Good 12,9 38,7 6,5 - - Neither good or bad - 12,9 3,2 - - Bad - - - 3,2 - Very bad - - - - 3,2 Worsened 13,3% Unchanged 61,3% Improved 32,0%

	Change from baseline to EOT + 7 days in plasma NT-proBNP (loge-transformed)	**N=33**	**N=31**
	NT-pro-BNP percent ratio of the last post-baseline value (up to EOT + 7 days) to the baseline 95% Confidence Limits	**88.94%** **62.40, 126.78**	**83.65** **57.88, 120.87**
	Changes in echocardiography/Doppler variables from baseline to last post-baseline value up to EOT + 7 days	**N=27**	**N=29**
	Right ventricular fractional area change (mean±SD)	N=14 -0.79 ± 15.954	N=20 -0.78 ± 12.954
	Inferior vena cava size collapse (%)	N=22 13.12 ± 22.925	N=21 -0.71 ± 18.734
	Right ventricular systolic pressure (mm Hg)	N=24 7.95 ± 23.271	N=18 -3.37 ± 25.301
	Tricuspid annular plane systolic excursion (BSA normalized, cm/m2)	N=21 -0.25 ± 0.666	N=19 -0.33 ± 0.834
	Left ventricular eccentricity index (diastolic)	N=22 -0.09 ± 0.542	N=24 -0.08 ± 0.356

	Left ventricular eccentricity index (systolic)	N=22 -0.03 ± 0.983	N=24 -0.03 ± 0.677
	E/A ratio mitral valve flow	N=14 0.13 ± 0407	N=20 0.32 ± 0.722

2.6.1.4. Study AC-052-391 (FUTURE 4)

Study title : *"Pediatric FormUlation of bosenTan in pUlmonary arterial hypeRtEnsion: 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."*

Study design

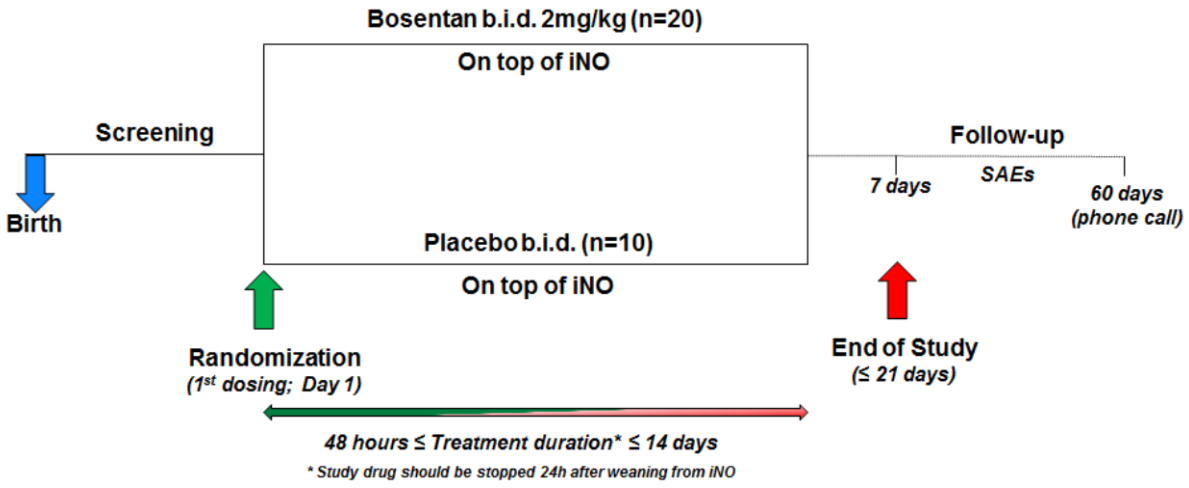
This was a multicenter, double-blind, randomized, placebo-controlled, parallel-group study. Patients were randomised in 9 centers across 6 countries (Czech Republic, France, South Korea, Poland, UK and USA).

The primary objective was to assess the efficacy of bosentan in neonates with PPHN who were in need of continued iNO after at least 4 h of continuous iNO treatment. The secondary objectives were to evaluate the PK, tolerability, and safety of bosentan in this patient population.

Term or near-term (gestational age > 34 weeks) hypoxic newborns with respiratory distress refractory to supplemental oxygen due to parenchymal lung disease (e.g. respiratory distress syndrome, meconium aspiration syndrome, pneumonia, sepsis without multi-organ failure) were eligible for randomization only if they were mechanically ventilated and had been continuously treated with iNO for at least 4 h, and if after 4 h of treatment, the requirement for iNO exceeded 10 ppm with fraction of inspired oxygen (FiO2) ≥ 50% under mechanical ventilation. In addition, in order to additionally substantiate sub-optimal response to iNO therapy prior to study drug start, two OI values, recorded at least 30 min. apart, were required to be ≥ 12 within 12 h prior to randomization, while the patient was receiving iNO treatment.

Newborns with PPHN secondary to congenital diaphragmatic hernia, with congenital cyanotic heart disease or immediate need for extra corporeal membrane oxygenation (ECMO) were excluded.

Patients who met the eligibility criteria were randomized in a 2:1 ratio to receive, on top of inhaled nitric oxide (iNO), either bosentan 2 mg/kg b.i.d. dispersible tablet formulation or matching placebo.



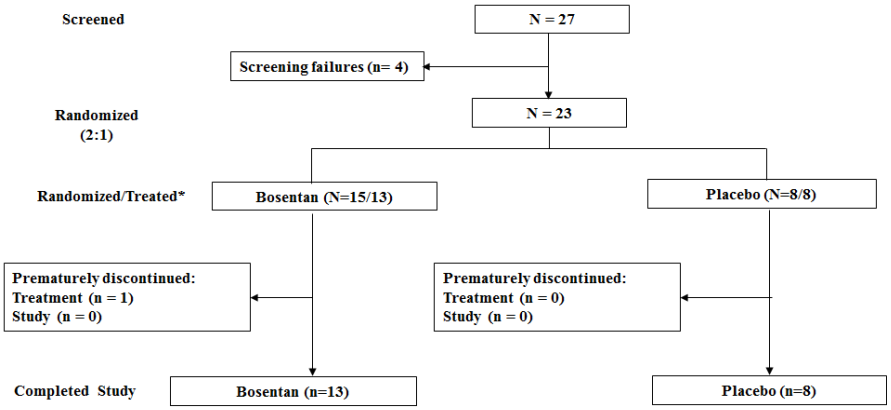
Study drug was prepared extemporaneously and was administered as a 1.5 mL aqueous dispersion of the dispersible tablets, as soon as a nasogastric or orogastric tube placement was possible, but not within the first 12 h of the baby's life. The age was restricted to at least 12 h after birth as patients younger than 12 h may not be able to absorb study drug.

Thereafter, study drug was administered approximately every 12 h for a minimum of 2 consecutive days (i.e., 4 administrations over 48 h) and may have continued according to the same regimen until 24 h (i.e. 2 doses) after complete weaning of iNO or until treatment failure (defined as need for ECMO or initiation of alternative pulmonary vasodilator). The maximum permitted duration of treatment with bosentan for an individual patient was 14 days (regardless of whether there was a need for continued iNO treatment).

Patients disposition
A sample size of 30 evaluable patients was planned based on feasibility considerations.
However, due to the rarity of the targeted population, a total of 23 patients were randomized in a 2:1 ratio to bosentan 2 mg/kg b.i.d. (N = 15) or placebo (N = 8).

In 2 (bosentan group) of the 23 randomized patients, study treatment was not administered due to low birth weight and transient increase in alanine aminotransferase (ALT).
Of the 21 patients who received the study drug, 20 (12 bosentan, 8 placebo) completed the study treatment (i.e.: two doses after successful iNO weaning). One patient in the bosentan group discontinued study treatment prematurely due to treatment failure on Day 1 (need for ECMO [protocol-defined]).

Figure 3 Disposition of patients in the FUTURE 4 study



*For two patients bosentan treatment was not administered: One due to low birth weight and one due to transient ALT increase

Demographics:

The demographics were balanced between bosentan and placebo groups. The population was predominantly female (69.2% bosentan, 75.0% placebo) and Caucasian (84.6% bosentan, 75.0% placebo). The length and weight at birth were similar in both groups

The etiology of PPHN was predominantly parenchymal lung disease in both groups (100% bosentan (13 patients), 62.5% placebo (5patients)). Idiopathic PPHN was diagnosed for 3 patients in the placebo group (37.5%).

The gestational age (median, min–max) was similar between bosentan (40.0 weeks, 36.0–41.0 weeks) and placebo (38.5 weeks, 36.0-42.0 weeks).

The age (median, min–max) at first dosing with the study treatment was similar in the bosentan group (1.4 days, 0.6–5.6 days) and in the placebo group (1.7 days, 0.6–5.9 days). The age (median, min–max) at PPHN diagnosis was 13.1 h (2.0–33.9 h) in the bosentan group and 18.1 h (4.0–43.0 h) in the placebo group.

FUTURE-4: Summary of PPHN-related data, Safety analysis set

ACT-050088, Protocol: AC-052-391
Summary of PPHN related data
Analysis set: Safety analysis set

	Bosentan N=13	Placebo N=8
PPHN etiology [n (%)]*		
n	13	8
Idiopathic	-	3 37.5%
Due to parenchymal lung disease	13 100%	5 62.5%
NEONATAL ASPIRATION	9 69.2%	3 37.5%
NEONATAL RESPIRATORY DISTRESS SYNDROME	4 30.8%	-
PNEUMONIA	2 15.4%	2 25.0%
SEPSIS	2 15.4%	1 12.5%
AGE at PPHN diagnosis (hrs)		
n	13	8
Mean	14.9	19.4
Standard deviation	9.3	13.8
Standard error	2.6	4.9
Median	13.1	18.1
Q1 , Q3	7.5 , 19.4	6.6 , 29.3
Min , Max	2.0 , 33.9	4.0 , 43.0
Time since diagnosis at first study drug administration (hrs)		
n	13	8
Mean	32.9	34.0
Standard deviation	28.1	38.1
Standard error	7.8	13.5
Median	26.0	18.8
Q1 , Q3	14.9 , 32.0	12.2 , 41.1
Min , Max	8.0 , 100.1	6.3 , 121.4

* conditions leading to parenchymal lung disease are not mutually exclusive
Source: Appendix 3, Table 50

FUTURE-4:

Summary of oxygenation and pulmonary pressure related data, FUTURE 4 PPHN Safety analysis set

	Bosentan N=13	Placebo N=8
Second to last OI prior to randomization**		
n	9	6
Mean	23.0	18.5
Standard deviation	8.67	6.47
Standard error	2.89	2.64
Median	22.0	17.5
Q1 , Q3	15.0 , 27.0	13.0 , 23.0
Min , Max	15.0 , 39.0	12.0 , 28.0
Last OI prior to randomization**		
n	9	6
Mean	29.0	21.2
Standard deviation	19.23	6.88
Standard error	6.41	2.81
Median	16.0	20.5
Q1 , Q3	16.0 , 49.0	16.0 , 28.0
Min , Max	13.0 , 62.0	12.0 , 30.0
Baseline OI		
n	13	8
Mean	21.1	17.3
Standard deviation	12.95	11.37
Standard error	3.59	4.02
Median	18.3	13.2
Q1 , Q3	11.5 , 34.0	8.5 , 24.2
Min , Max	5.9 , 44.3	7.1 , 39.4
Baseline AaDO2 (mmHg)		
n	13	8
Mean	468.5	421.4
Standard deviation	132.50	139.72
Standard error	36.75	49.40
Median	481.0	429.0
Q1 , Q3	405.2 , 577.6	283.9 , 535.0
Min , Max	177.8 , 606.9	255.8 , 619.3
Right ventricular systolic pressure (RVSP) (mmHg)		
n	8	7
Mean	43.0	48.1
Standard deviation	23.93	19.10
Standard error	8.46	7.22
Median	44.5	51.0
Q1 , Q3	28.0 , 55.5	38.0 , 58.0
Min , Max	6.0 , 82.0	13.0 , 75.0
Systemic systolic blood pressure (SSBP) (mmHg)*		
n	12	8
Mean	70.3	67.8
Standard deviation	16.89	12.89
Standard error	4.88	4.56
Median	70.0	67.5
Q1 , Q3	58.5 , 76.5	57.5 , 73.5
Min , Max	48.0 , 113.0	52.0 , 93.0

*SSBP measured during echocardiography (RVSP estimation)
**The last 2 OI values while on iNO treatment prior to randomization were only reported following the first protocol amendment
OI = Oxygenation Index
Appendix 4, Table 5

Baseline OI (median [min–max]) values indicated that the disease condition was more severe in patients randomized to bosentan (18.3 [5.9–44.3]) than in patients randomized to placebo (13.2 [7.1–39.4]). Consistently, median baseline alveolar-arterial oxygen difference (AaDO2; min–max) was 481.0 mmHg (177.8–606.9 mmHg) in the bosentan group and 429.0 mmHg (255.8–619.3 mmHg) in the placebo group.

The median time (min–max) from iNO initiation to start of study treatment was 20.7 h (7.9–115.5 h) in the bosentan group versus 23.5 h (6.0–118.2 h) in the placebo group.
The median dose of iNO (min–max) at study drug initiation was 20 ppm in both groups (Bosentan: 20 ppm [13–20 ppm], placebo: 20 ppm [10–20 ppm]).

FUTURE-4 Efficacy results:

Median duration on bosentan was 4.5 days (range: 0.5–10.0 days) and median duration on placebo was 4.0 days (range: 2.5–6.5 days).

The efficacy endpoints of the study were exploratory. No formal hypothesis testing was predefined.

- Primary endpoints:
  - Proportion of patients with treatment failure defined as the need for ECMO or initiation of alternative pulmonary vasodilator
  - Time to complete weaning from iNO
  - Time to weaning from mechanical ventilation.
- The secondary efficacy endpoints included proportion of patients requiring re-initiation of iNO therapy, change from baseline to various time points in OI, arterial blood gas (ABG) values, pulse oximetry (SpO_2), FiO_2, $AaDO_2$ and the presence of pulmonary hypertension.

Treatment failures:

One patient in the bosentan group had treatment failure (need for ECMO as per protocol definition), which was declared based on increasing OI values within 8 h after the first dose of study drug. This patient with PPHN due to parenchymal lung disease (neonatal aspiration) had been on iNO therapy for 8 h at study drug start (initial dose 10 ppm, dose at study drug start 16 ppm). All other patients were successfully weaned from iNO. No patient required reinitiation of iNO.

Time to complete weaning from iNO:

The median time to complete weaning from iNO was 3.7 days (95% CLs 1.17, 6.95 days) on bosentan and 2.9 days (95% CLs 1.26, 4.23 days) on placebo; p-value = 0.3407 (log-rank test).

FUTURE 4: Time to complete weaning from iNO, Full analysis set

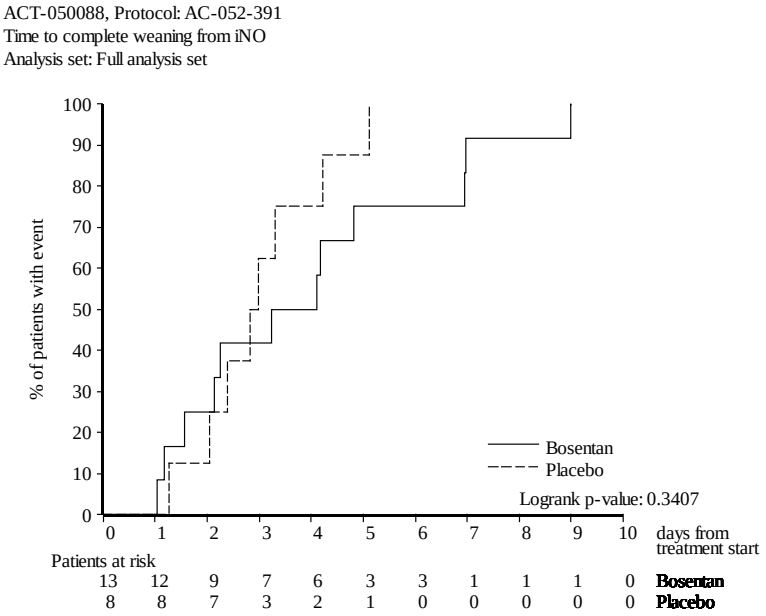


Figure TINOG_F - Produced by petratd on 14JAN14 - Data dump of 08JAN14

Time to weaning from mechanical ventilation: The median time to complete weaning from mechanical ventilation was 10.8 days (95% CLs 3.21, 12.21 days) on bosentan and 8.6 days (95% CLs 3.71, 9.66 days) on placebo; p-value = 0.2399 (log-rank test).

FUTURE 4: Time to complete weaning from mechanical ventilation, Full analysis set

ACT-050088, Protocol: AC-052-391
Time to complete weaning from mechanical ventilation
Analysis set: Full analysis set

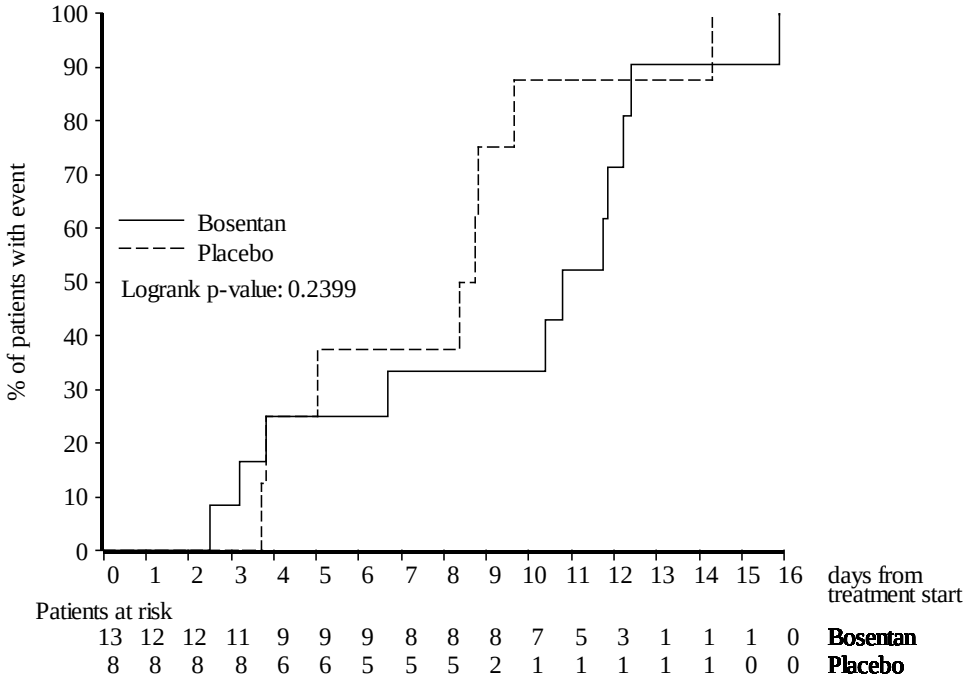


Figure TMECG_F - Produced by petratd on 14JAN14 - Data dump of 08JAN14

Even though treatment comparisons for both weaning-related primary endpoints resulted in p-values greater than 0.05 it was observed that 3 patients randomized to bosentan had longer iNO and mechanical ventilation weaning times than all other patients, resulting in longer median times to weaning in the bosentan randomized group.

Secondary efficacy endpoints:

Changes in oxygen index (OI), arterial blood gas (ABG) variables, SpO2, FiO2 and alveolar-arterial oxygen difference (AaDO2) over time were similar in the bosentan and placebo groups.
The proportion of patients with pulmonary hypertension at end of treatment (EOT) was comparable between treatment groups (41.7% bosentan, 37.5% placebo).
No patients had re-initiation of iNO.

CHMP comments:
In this first randomized, placebo-controlled trial performed to investigate the effect of bosentan as add-on therapy to inhaled nitric oxide (iNO) in neonates with PPHN and who did not adequately respond to iNO, no additional benefit of bosentan treatment was observed.
Although not statistically different between the 2 groups, the mean time to complete weaning from iNO and from mechanical ventilation appeared longer in the bosentan group as compared to the placebo group.
This study was well conducted although sample size is limited (only 13 patients treated with bosentan less than 14 days). The design of this study as add-on therapy to the iNO, the mainstay treatment of PPHN, was well appropriate and efficacy assessments in this study were standard assessments performed for patients with PPHN.

The median baseline OI and AaDO2 indicated that the disease condition was slightly more severe in patients randomized to bosentan than in patients randomized to placebo in this study (OI: 18.3 in bosentan-group versus 13.2 on placebo; AaDO2: 481.0 mmHg in the bosentan group versus 429.0 mmHg on placebo). Based on a post hoc exploratory analyses where baseline OI was found to be strongly related to time to weaning from iNO, influencing the treatment effect for this endpoint, the study report states that the difference in baseline OI between the bosentan and placebo groups could explain the

apparent difference in point estimates for time to iNO weaning. Larger population studied would be needed to allow reliable assessment. It is pointed out that 3 patients randomized to bosentan had longer iNO and mechanical ventilation weaning times than all other patients.

Table 4. Summary of Efficacy for trial AC-052-391 (FUTURE 4)

FUTURE 4- Pediatric FormUlation of bosenTan in pUlmonary arterial hypeRtEnsion: Exploratory, multicenter, double-blind, placebo-controlled, randomized, prospective study to evaluate pharmacokinetics, safety and efficacy of bosentan as add-on therapy to inhaled nitric oxide in the management of persistent pulmonary hypertension of the newborn			
Study identifier	AC-052-391		
Design	This was a Phase 3, exploratory, multi-center, international, double-blind, randomized, placebo-controlled, parallel-group study conducted in expert pediatric centers in the USA, Europe, Australia and Asia to evaluate PK, safety and efficacy of bosentan as add-on therapy to inhaled nitric oxide in the management of persistent pulmonary hypertension of the newborn (PPHN).		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		Maximum of 14 days treatment period. Not applicable 1 year follow-up, non-drug interventional extension study AC-052-392 (FUTURE 4 extension); ongoing
Hypothesis	Exploratory		
Treatments groups	Bosentan 2 mg/kg b.i.d.		Bosentan 2 mg/kg b.i.d. maximum of 14 days or until 1 day after iNO weaning completion or until treatment failure if less than 14 days, 15 patients randomized
	Placebo		Placebo. maximum of 14 days or until 1 day after iNO weaning completion or until treatment failure if less than 14 days, 8 patients randomized
Endpoints and definitions	Primary endpoint	Efficacy	All primary efficacy endpoints were analyzed up to 1 week after end of treatment, i.e. up to end-of-study (EOS) • Proportion of patients with treatment failure defined as: – Need for Extra Corporeal Membrane Oxygenation (ECMO) – Initiation of alternative pulmonary vasodilator • Time to complete weaning from iNO[1] • Time to weaning from mechanical ventilation[1] [1] Calculated from the time of first study drug administration to complete weaning from iNO or mechanical ventilation, respectively.

	Secondary endpoint	Efficacy	• Proportion of patients requiring re-initiation of iNO therapy (up to EOS). • Change from baseline to 3 h, 5 h, 12 h, and 24 h following the first drug administration; and thereafter every day until end-of-treatment (EOT) for: – Oxygenation index (OI) – Arterial blood gas (ABG) values (pH, arterial oxygen saturation [SaO_2], partial pressure of oxygen [PaO_2], partial pressure of carbon dioxide [$PaCO_2$]) – Pulse oximetry (SpO_2) – Fraction of inspired oxygen (FiO_2) – Alveolar-arterial oxygen difference ($AaDO_2$) Values for OI and $AaDO_2$ were derived from ABG values and mechanical ventilation parameters at matching time points. • Presence of pulmonary hypertension (assessed by echocardiography) at 24 h (Day 2) and at EOT.
	Endpoint	PK	• C_{max} and t_{max} (Days 1 and 5), AUC_{0-12} (Day 1), AUC_{τ} [1] (Day 5), and AUC_{0-24} (Days 1 and 5) for bosentan and its metabolites (Ro 48-5033, Ro 47-8634, Ro 64-1056) following administration of bosentan • Accumulation index (AI), defined as the ratio between AUC_{τ} [1] (Day 5) and AUC0-12 (Day 1) for patients who had PK assessments performed on Days 1 and 5, provided that AUC0-12 was > 0 ng.h/mL [1]AUC_{τ} - Area under the concentration-time curve during a dosing interval.
Database lock	8 January 2014		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set = All-treated set		
Descriptive statistics and estimate variability	Treatment group	Bosentan 2 mg/kg b.i.d on top of iNO	Matching placebo on top of iNO
	Number of patients	13	8
	Proportion of patients with need for Extra Corporeal Membrane Oxygenation (ECMO) (up to End of Study)	7.7%	-
	Exact 95% Confidence Limits (Clopper-Pearson formula)	0.002, 0.360	N/A

Proportion of patients with initiation of alternative pulmonary vasodilator (up to End of Study)	-	-
95% Confidence Limits	N/A	N/A
Median time to complete weaning from iNO (up to End of Study)	3.7 days	2.9 days
95% Confidence Limits of median	1.17 - 6.95 days	1.26 - 4.23 days
Median time to weaning from mechanical ventilation (up to End of Study)	10.8 days	8.6 days
95% Confidence Limits of median	3.21 - 12.21 days	3.71 - 9.66 days
Proportion of patients requiring re-initiation of iNO therapy (up to End of Study)	-	-
95% Confidence Limits	N/A	N/A
Median change in Oxigenation Index (72h)	-8.9	-9.4
95% Confidence Limits of median	-23.1, -1.8	-17.7, 2.2
Median change in blood gas variables (from baseline to 72h): pH SaO2 (%) PaO2 (mmHg) PaCO2 (mmHg)	 0.04 1.0 18.0 6.0	 0.02 0.0 6.0 8.0
95% Confidence Limits of median pH SaO2 (%) PaO2 (mmHg) PaCO2 (mmHg)	 -0.06, 0.07 0.0, 8.0 -13.0, 32.0 -1.0, 12.0	 -0.09, 0.19 -4.0, 21.0 -12.0, 115.0 -8.0, 21.0
Median change in pulse oximetry (from baseline to 72h): Pre-ductal (%) Post-ductal (%)	 0.50 0.0	 -1.00 2.0
95% Confidence Limits of median Pre-ductal (%) Post-ductal (%)	 -2.00, 2.00 -2.0, 3.0	 -10.00, 2.00 1.0, 12.0
Median change in fraction of inspired oxygen (from baseline to 72h) (%)	-33.5	-35.5
95% Confidence Limits of median	-50.0, -15.0	-60.0, 0.0

	Median change in alveolar-arterial oxygen difference (from baseline to 72h) (mmHg)	-235.5	-316.6
	95% Confidence Limits of median	-384.9, -148.0	-417.9, 0.3
	Proportion of patients with pulmonary hypertension (assessed by echocardiography at EOT (%)	41.7	37.5
	Exact 95% Confidence Limits (Clopper-Pearson formula)	0.152, 0.723	0.085, 0.755
Effect estimate per comparison		Bosentan 2 mg/kg b.i.d on top of iNO	Matching placebo on top of iNO
	Proportion of patients with need for Extra Corporeal Membrane Oxygenation (ECMO) Odds Ratio Exact 95% CLs P-value Fisher Exact Test	 infinity 0.032, Infinity 1	
		Bosentan 2 mg/kg b.i.d on top of iNO	Matching placebo on top of iNO
	Proportion of patients with initiation of alternative pulmonary vasodilator Odds Ratio Exact 95% CLs P-value Fisher Exact Test	 N/A N/A N/A	
		Bosentan 2 mg/kg b.i.d on top of iNO	Matching placebo on top of iNO
	Time to complete weaning from iNO Log-Rank statistics P-value	 0.9079 0.3407	
		Bosentan 2 mg/kg b.i.d on top of iNO	Matching placebo on top of iNO
	Time to weaning from mechanical ventilation Log-Rank statistics P-value	 1.3812 0.2399	
		Bosentan 2 mg/kg b.i.d on top of iNO	Matching placebo on top of iNO
	Proportion of patients requiring re-initiation of iNO therapy Odds Ratio Exact 95% CLs P-value Fisher Exact Test	 N/A N/A N/A	
		Bosentan 2 mg/kg b.i.d on top of iNO	Matching placebo on top of iNO

Change in Oxygenation Index (from baseline to 72h) Median 95% CLs of median P-value (non-parametric ANCOVA)	-1.2 -10.7, 12.6 0.1015	
	Bosentan 2 mg/kg b.i.d on top of iNO	Matching placebo on top of iNO
Change in blood gas variables (72h): pH SaO_2 (%) PaO_2 (mmHg) $PaCO_2$ (mmHg)	Median 0.01 1.0 -1.0 -1.0	
	95% CLs of median -0.09, 0.11 -7.0, 6.0 -54.0, 30.0 -9.0, 8.0	
	P-value (non-parametric ANCOVA) 0.0824 0.3863 0.3936 0.2436	
	Bosentan 2 mg/kg b.i.d on top of iNO	Matching placebo on top of iNO
Change in pulse oximetry (from baseline to 72h): Pre-ductal (%) Post-ductal (%)	Median 1.0 -2.0	
	95% CLs of median -2.00, 6.00 -6.0, 1.0	
	P-value (non-parametric ANCOVA) 0.1756 0.1155	
	Bosentan 2 mg/kg b.i.d on top of iNO	Matching placebo on top of iNO
Change in fraction of inspired oxygen (from baseline to 72h) (%) Median	5.0	
95% CLs of median	-21.0, 26.0	
P-value (non-parametric ANCOVA)	0.1400	
	Bosentan 2 mg/kg b.i.d on top of iNO	Matching placebo on top of iNO

	Change in alveolar-arterial oxygen difference (72h) (mmHg) Median	31.3	
	95% CLs of median	-148.2, 184.4	
	P-value (non-parametric ANCOVA)	0.1316	
		Bosentan 2 mg/kg b.i.d on top of iNO	Matching placebo on top of iNO
	Proportion of patients with pulmonary hypertension (assessed by echocardiography) at EOT (%) Odds ratio	1.1905	
	Exact 95% Confidence Limits (Clopper-Pearson formula)	0.138, 11.40	
	P-value Fisher Exact Test	1.000	
Analysis description	**Exploratory Analysis**		
Analysis population and time point description	Per protocol PK set		
Descriptive statistics and estimate variability	Treatment group	Bosentan 2 mg/kg b.i.d on top of iNO	
	Number of patients	11	7
	Bosentan (whole blood) C_{maxc} (ng/mL) Geometric mean (n)	Day 1 30.1 (11)	Day 5 880.0 (7)
	95% confidence intervals	2.4, 372.2	339.2, 2282.7
	Bosentan t_{max} (hour) Median (n)	Day 1 12.0 (10)	Day 5 7.5 (7)
	Range	7.5, 12.0	0.8, 12.0
	Bosentan (whole blood) Day 1 AUC_{0-12} (h*ng/mL) Geometric mean (n)	163.9 (11)	
	95% Confidence Intervals of Geometric mean	9.6, 2795.4	
	Bosentan (whole blood) Day 5 AUC_{T} (h*ng/mL) Geometric mean (n)	6165.4 (7)	
	95% Confidence Intervals of Geometic mean	2429.6,15645.3	

	Bosentan (whole blood) AUC_{0-24c} (h*ng/mL) Geometric mean (n)	Day 1 287.5 (11)	Day 5 11530.2 (7)
	95% Confidence Interval of Geometric mean	15.0, 5504.7	4507.0, 29497.5
	Bosentan (whole blood) Accumulation Index Geometric mean (n)	61.6 (7)	
	95% Confidence Intervals of Geometric mean	0.5, 7813.9	

AI = Accumulation Index; CI = Confidence Interval; CL = Confidence Limit

2.6.2. Discussion and conclusion on clinical efficacy

The efficacy data in children less than 12 years provided in support of this application are derived from FUTURE 1 (AC-052-365) and its extension (FUTURE 2 ; AC-052-367), and the recently completed FUTURE 3 (AC-052-373).
In addition, data are presented for a placebo controlled study newly conducted with 32 mg dispersible tablets in neonates with persistent pulmonary hypertension of the newborn (PPHN; FUTURE 4 ; AC-052-391).

PAH and PPHN are considered separately as their clinical features, etiology and outcome are different.

PAH in children :
In PAH children less than 12 years, efficacy was assessed exclusively based on exploratory endpoints in 2 open label and not controlled studies. They present several limitations with regards to the efficacy endpoints which were exploratory and their appropriateness to properly assess bosentan effect (open label, important proportion of patients with combined associated treatment, doubt on lack of sensitivity). Moreover, data in children less than 2 years are limited (21 children with PK data only for 4 patients).

The newly provided FUTURE-3 study did not show any clinical benefit when using a dose higher than 2 mg/kg b.i.d. (i.e.: 2 mg/kg t.i.d.) over the 24 weeks period, which is consistent with the systemic exposure remaining similar in both b.i.d. and t.i.d. groups, comparable to the 4mg/kg b.i.d. dosing.
The clinical studies using the 32 mg dispersible tablets are not robust to document the efficacy in paediatric pulmonary hypertension. The limit of age where PK profile differs from adults and where it could be considered as similar to adults remains undetermined.

In this context, informing prescribers on the data available in children (especially with regards to the specificity of PK and plateau dosings as compared to adults) appears justified.

Persistent pulmonary hypertension of the newborn

Treatment with iNO is the mainstay for PPHN with proven efficacy. In the majority of infants, an acute improvement in oxygenation can be expected within 30 to 60 min of initiation of iNO at a dose of around 20 ppm regardless of the severity of the illness. Inhaled NO is recommended as the first line treatment of PPHN. In some cases, infants may not exhibit improved oxygenation or a satisfactory and sustained response to iNO.

FUTURE-4 is the first double-blind, randomized, placebo-controlled study investigating the effect of bosentan (2 mg/kg b.i.d.) as add-on therapy to inhaled nitric oxide (iNO) in neonates with PPHN and suboptimal response to inhaled NO.

Future 4 study was well conducted and used an appropriate design assessing bosentan as add-on therapy to the iNO, the mainstay treatment of PPHN. However the sample size of 21 patients (13 treated with bosentan, 8 with placebo) is limited.

The pharmacokinetics of bosentan in neonates with PPHN were characterized by variable exposure, which was low after the first dose and attained apparent steady-state within 5 days. The systemic concentrations at steady-state of bosentan and its metabolites were higher than those studied previously in older pediatric PAH patients ≥ 3 months of age, but similar to those observed in adult PAH patients treated with 125 mg b.i.d.

Overall, this study showed that there was no benefit in adding bosentan on top of inhaled NO in neonates who did not adequately respond to inhaled NO. The mean time to complete weaning from iNO and from mechanical ventilation appeared longer in the bosentan group as compared to the placebo group. In conclusion, based on this study, the use of bosentan cannot be recommended in the standard care of PPHN.

Bosentan appeared well tolerated but the number of patients contributing to the safety data in the PPHN safety set was low (13 bosentan vs 8 placebo), and bosentan exposure was very short-term (≤ 10 days treatment; median exposure 4.5 days ranging from 0.5 to 10 days). AEs and laboratory data were consistent with the known safety profile of bosentan. Anemia, including anemia requiring transfusion, was the most commonly reported treatment-emergent adverse effect. There were no aminotransferase elevations > 2 × ULN during the treatment-emergent period (i.e. from first study drug dose until 7 days after last study drug dose).

The section 4.2. of the SmPC is amended to mention that no recommendation on a posology can be made in neonates with PPHN and key data from FUTURE-4 are added in section 5.2.

Due to the major objection on efficacy raised, the claim for indication in section 4.1. in children from 3 months to 2 years was subsequently withdrawn by the MAH.

2.7. Clinical safety

The safety data provided by the MAH in support of this application consist of:
- an integrated safety analysis for the 100 paediatric PAH patients, aged 3 months to 12 years who took at least one dose of bosentan using dispersible tablets throughout the 2 open label studies:
    - FUTURE-1 (12 weeks, single arm, 36 patients included) with its completed extension FUTURE 2,
    - FUTURE 3 (24 weeks, 64 patients included) with data from its ongoing extension with cut-off date up to 19 August 2013.

- the safety data in neonates from the placebo-controlled FUTURE 4 study conducted in patients with persistent pulmonary hypertension of the newborn (PPHN) (13 Tracleer patients versus 8 placebo included).

- a review of post-marketing data, including spontaneous reports (including those from regulatory authorities and literature) and solicited reports (including named patient / compassionate use, investigator-initiated/-sponsored trials (cut-off date: 19 November 2013).

a- Safety data from clinical trials

The designs of studies FUTURE-1/2, FUTURE-3 and FUTURE-4 are described individually and in details in the above section Efficacy

Exposure in the pooled PAH safety analysis set:

Given the limited number of PAH children from the individual studies, the applicant has presented the analysis of safety data cumulatively over the core and extension periods, based on the start of study treatment in the core study.

The pooled PAH safety analysis set comprising 100 children from 3 months to 11.4 years at baseline (57 male; 43 females).

The median age of the patients was 5.2 years (ranging from 0.3 to 11.7 years), with 21 patients < 2 years of age (all issued from FUTURE-3).

Overview of the demographic and background characteristics of the pooled PAH safety analysis set

Characteristic	
Age, median (range)	5.2 years (0.3–11.7 years)
Sex	Male 57%, Female 43%
Race/ethnicity	80% Caucasian, 10% Asian, 4% Black, 3% Hispanic, 3% Other
PAH etiology	61% idiopathic, 24% associated, 8% PAH-CHD, 7% heritable/familial
WHO FC	FCI 16%, FCII 53%, FCIII 31%
Time since diagnosis	8.2 months (0.1–135.9 months)
Bosentan use at baseline	33%

FC = functional class; PAH-CHD = pulmonary arterial hypertension associated with congenital heart disease; WHO = World Health Organization
Source: Module 2.7.4, Table 5 and Table 7

Dosings were different in FUTURE ½ (4 mg/kg b.i.d.) and FUTURE 3 (i.e. 2 mg/kg b.i.d. or 2 mg/kg t.i.d.). As similarity in systemic exposure was observed in the PK analysis, pooling the data for safety assessment can be considered acceptable. FUTURE-3 allow direct safety comparison of increasing the dosings above 2 mg/kg b.i.d. i.e. 2 mg/kg t.i.d. in children. The sample size is however limited to 100 patients.

The median duration of exposure to bosentan treatment in the pooled PAH population was 71.8 weeks i.e. 16.8 months (ranging from 0.4 weeks to 258 weeks i.e. 5.0 years), with 64 of patients exposed for at least 12 months and 33 exposed for at least 18 months.

The median duration of exposure to bosentan treatment was 27.1 weeks i.e. 6.3 months (ranging from 0.4 weeks to 77.1 weeks i.e.18.0 months) in patients < 2 years of age and 73.9 weeks i.e. 17.2 months (ranging from 8.4 weeks to 258 weeks i.e. 5.0 years) in patients ≥ 2 years of age.

Exposure in PPHN patients (FUTURE 4)

13 neonates (9 females and 4 males) received bosentan 2 mg/kg b.i.d. and 8 neonates (6 females and 2 males) received placebo.

The gestational age (median, min–max) was similar for bosentan (40.0 weeks ranging from 36 to 41 weeks) and placebo (38.5 weeks ranging from 36 to 42 weeks).

The etiology of PPHN was predominantly parenchymal lung disease in both groups (100% bosentan (13 patients), 62.5% placebo (5patients)). Idiopathic PPHN was diagnosed for 3 patients in the placebo group (37.5%).

The median exposure (days, min–max) in this short-term study was similar in the bosentan (4.5 days, 0.5–10.0 days) and placebo groups (4.0 days, 2.5–6.5 days). Approximately 60.0% of patients in the bosentan and placebo groups had at least 4 days of exposure to study treatment.

It is considered that the safety analysis set from these clinical studies using the 32 mg dispersible tablet doesn't allow assessment of the safety profile in patients with the exclusion criteria applied e.g., patients with severe renal function impairment, patients with moderate or severe hepatic impairment (missing information).

B) Overall AE profile

Pooled PAH safety analysis set

The most frequently reported AEs in the pooled PAH safety analysis set were associated with disorders of the respiratory system (69.0%), particularly upper respiratory tract infection (RTI; 25%). Other AEs

associated with infections of the upper respiratory tract/system included nasopharyngitis (17%), viral upper RTI (5%), pharyngitis (4%), and tonsillitis (3.0%). Regarding other RTIs, bronchitis was reported for 10% of patients, pneumonia for 7%, viral RTI for 5%, influenza and RTI were reported for 4% of patients each, and bronchopneumonia for 3%.

Worsening of PAH or pulmonary hypertension (PH) were reported for 14% and 6% patients, respectively. Cough was reported for 9% of patients, most frequently in association with an RTI. Two patients each experienced dyspnea and wheezing, and one patient experienced exertional dyspnea.

CHMP comments

From this pooled analysis, AEs are similar in nature to that generally seen in adults. However, a higher rate of AEs associated with the infections and infestations system organ class, with upper respiratory tract infections being the most frequently reported, was observed (adulte around 41.3% reported in pooled clinical studies). The MAH considered that this may in part be due to the longer median exposure in the pediatric set (71.8 weeks, range: 0.4–258.0 weeks) compared to the adult set (17.4 weeks, range: 0.7–74 weeks) and the higher incidence of acute respiratory infections in children compared to adults in the general population. This explanation is plausible, but as the studies were not controlled, this explanation cannot be confirmed and a specific effect of bosentan cannot be formally excluded.

PPHN safety analysis set

In this short-term study, the most frequently reported AEs in patients treated with bosentan were anemia and generalized oedema. Anemia was reported as an AE for 3 bosentan-treated patients and one placebo-treated patient. Anemia and/or laboratory hemoglobin decreases to below the lower limit of normal were reported for a total of 7 patients on bosentan (53.8%) and 2 patients on placebo (25.0%).

Generalized edema was reported in 3 patients on bosentan, all of whom had received multiple plasma expanders / intravenous (i.v.) fluid supplementation on days preceding the event onset.

No treatment-emergent AEs of aminotransferase elevations (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) were reported.

c) Deaths, other serious adverse events and AEs leading to treatment discontinuation

Deaths- Pooled PAH safety analysis set

The analysis of deaths in the pooled PAH safety set included those that occurred up to 2 years after the End of Treatment (EOT) for patients in FUTURE 2. Overall, 17 patients (17%) died, with 14 of these deaths occurring during the study treatment period, or resulting from an AE that commenced during the study treatment period. In addition, there were 3 deaths that occurred during long-term follow-up.

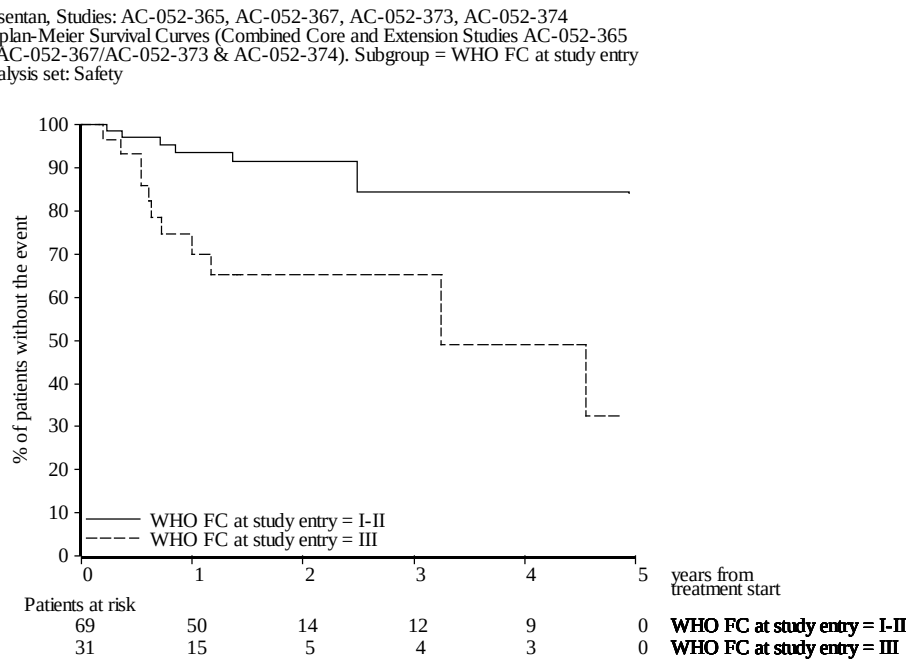
The causes of death were consistent with what has been previously reported in bosentan studies conducted in pediatric and adult PAH populations, i.e., were predominantly associated with events related to progression of PAH. Other causes of death were represented by single patients, and none were associated with hepatobiliary events, anemia or edema. In addition, there were no cases that indicated the occurrence of any previously unrecognized potentially fatal AEs associated with bosentan treatment. Of the 3 deaths that occurred during the long-term follow-up period, one was due to worsening of the underlying disease. Of the other 2 deaths, one resulted from multi-organ failure related to unspecified congenital metabolic disease, and the third was due to complications associated with cardiac catheterization.

Survival rate in the pooled PAH safety analysis set

The MAH has provided KM survival estimate for the pooled PAH safety analysis. The KM estimate survival was 86.4% at one year and 83.4% at 2 years

Survival was influenced by baseline severity. In baseline FC II patients, the KM survival estimate was 95.8% at one year and 92.9% at 2 years. In FC III patients, the KM survival estimate was 69.9% at one year and 65.2% at 2 years.

Figure: Kaplan-Meier survival curve for the pooled PAH safety analysis set by WHO FC at study entry



Studies AC-052-365, AC-052-367, AC-052-373 are completed. For the ongoing study AC-052-374 interim data up to 19AUG13 (Data Dump on 23JAN14)
Figure KMSC_WG_S - Produced by Saccoa on 05FEB14

CHMP comments :

This KM estimates from the PAH studies using the dispersible tablets (FUTURE 1/2 and FUTURE 3) showed an improvement in survival as compared to prior to the introduction of vasodilator therapy where mean survival time for children after diagnosis of IPAH was less than 12 months. However, it is noticed that more than 50 % of the patients were receiving combined treatment associated to bosentan in FUTURE 3. Moreover, it includes the collection up to 2 years after the End of Treatment (EOT) for patients in FUTURE 2. In most of them combined therapy including sildenafil will have been introduced. Therefore, these results may be overoptimistic but not solely relating to the use of bosentan.

PPHN safety analysis set

No deaths were reported in the FUTURE 4 study.

d) Serious adverse events

Pooled PAH safety analysis set

A total of 44 (44%) of the patients experienced at least 1 serious adverse event (SAE) in the pooled PAH safety analysis set. The most frequently reported SAE was worsening of PAH, reported as the PTs PAH (9.0%), PH (3.0%) and right ventricular failure (2.0%). Other frequently reported SAEs were broncho-pneumonia / pneumonia / viral pneumonia (7.0%), device-related infection and syncope (3.0% each).

SAEs associated with cardiac disorders (other than right ventricular failure) included cardiac failure (2 patients), cardiac arrest, acute cardiac failure, cardiopulmonary failure, and pericardial effusion (1 patient each).

SAEs of iron deficiency anemia and decreased hemoglobin were reported in 1 patient. The patient prematurely discontinued the FUTURE 2 study by withdrawal of consent.

An SAE of autoimmune hepatitis was reported that resulted in premature discontinuation of study treatment, as well as discontinuation from the study. The patient had ALT > 3 × upper limit of normal (ULN) on Day 273 (171 U/L) and ALT > 5 × ULN accompanied by AST > 3 × ULN on Day 341 (299 U/L and 144 U/L, respectively). Bilirubin remained within the reference range. The event was reported as resolved on follow-up approximately 2.5 months after permanent discontinuation of study drug. The investigator assessed the event as related to study drug administration.

The majority of the treatment-emergent SAEs were reported as resolved on follow-up and assessed by the investigator as unrelated to study drug administration

The CHMP noted that as immune hepatitis were also reported in adults, a review of immune hepatitis cases has been requested in the next PSUR.

PPHN safety analysis set

A total of 2 (15.4%) patients on bosentan and 3 (37.5%) patients on placebo experienced treatment-emergent SAEs. In one bosentan-treated patient, the SAEs were ongoing conditions of circulatory collapse, hypercapnia and metabolic acidosis that led to permanent discontinuation of study drug within one day of study drug initiation (considered as treatment failure as per protocol and likely reflecting worsening of the underlying PPHN). A treatment-emergent abnormality on hepatic ultrasound (reported as unspecified reactive hepatitis) was reported in the second bosentan-treated patient 3 days after EOT; ALT and AST remained < 2 × ULN. Two patients on placebo had SAEs of pneumothorax, and one patient had sepsis reported as an SAE. All treatment-emergent SAEs were reported as resolved on follow-up and assessed by the investigator as unrelated to study drug administration.

During the follow-up period, 8 days after EOT, neonatal hepatitis was reported for a patient who had been on bosentan treatment for 5.5 days. Peak ALT elevations (10.7 × ULN) were reached on the 17th day after study drug discontinuation with total bilirubin of 1.2 × ULN. The event resolved without sequelae 6 weeks later. The investigator assessed the event as related to study drug administration.

The CHMP noted that the sample size of neonates is limited to 13 patients to draw reliable conclusion on safety in neonates.

e) AEs leading to discontinuation of treatment

Pooled PAH safety analysis set

A total of 17 patients (17%) had at least one AE that resulted in discontinuation of study treatment, and the AEs were also reported as SAEs for 14 of these patients.

The AEs leading to discontinuation that were not reported as SAEs were abnormal liver function test (2 patients) and exertional dyspnea (one patient).

PPHN safety analysis set

One patient discontinued study treatment in the FUTURE 4 study. The patient discontinued due to 3 AEs that were also reported as SAEs (circulatory collapse, hypercapnia and metabolic acidosis). The AEs satisfied the protocol-defined criteria for treatment failure and automatically led to permanent discontinuation of study treatment.

f) Safety topics of special interest

Anemia / hemoglobin decrease, Liver abnormalities and Edema in the pooled PAH safety analysis set were evaluated on the basis of treatment-emergent AEs

- ***Anemia/hemoglobin decrease***

Pooled PAH safety analysis set :

Hemoglobin concentrations < 10 g/dL were reported for 10 patients (5 of whom were bosentan naïve), and were reported as AEs in 2 cases, one of which was an SAE and was associated with an SAE of iron deficiency anemia. The patient subsequently withdrew consent. No patient had a decrease in hemoglobin to a concentration < 8 g/dL.

PPHN safety analysis set

AEs of anemia and/or laboratory hemoglobin decreases to below the lower limit of the normal range were reported for a total of 7 patients on bosentan (53.8%) and 2 patients on placebo (25.0%). Four of the 7 bosentan-treated patients, and one of the 2 placebo-treated patients received blood transfusions. Of the 7 bosentan-treated patients, 2 had generalized edema concomitantly and one had thrombocytopenia concomitantly (this patient had ongoing anemia and thrombocytopenia at baseline). For 5 of the 7 bosentan-treated patients, the anemia / decreased hemoglobin occurred following administration of human albumin as a plasma volume expander. It is notable that prior to study drug administration, 6 of the 21 patients (3 subsequently on bosentan and 3 on placebo) received a red-blood-cell transfusion.

- ***Liver abnormalities***

Pooled PAH safety analysis set

Liver abnormality AEs were reported for a total of 9 patients, and were associated with treatment–emergent increases in ALT to > 3 × ULN in 2 cases (one case 7.3 × ULN associated with an SAE of autoimmune hepatitis). None of these elevations were accompanied by bilirubin elevations. Three patients had isolated/intermittent hyperbilirubinemia, which was not associated with an aminotransferase increase or other hepatic event. With the exception of autoimmune hepatitis (considered by the investigator to be unrelated to study treatment), none of the liver abnormality AEs were reported as SAEs.

PPHN safety analysis set

No aminotransferase elevations > 3 × ULN were reported during study treatment. In 3 patients (1 bosentan, 2 placebo), total bilirubin increased from within the reference range at baseline to values above ULN (worst post-baseline); all were < 2 × ULN, and none were associated with elevated ALT.

After discontinuation of bosentan treatment, there were 2 reports of hepatitis. One of these was transient unspecified reactive hepatitis reported on Day 8, 3 days after treatment discontinuation. The diagnosis was based on an abnormal hepatic ultrasound appearance associated with increased C-reactive protein, and was not supported by liver test results. Ultimately, the abnormal hepatic ultrasound appearance was suspected to be associated with the umbilical line placement. The event was reported as resolved with sequelae 2 weeks later.

The second case was reported as neonatal hepatitis with maximum aminotransferase elevations of approximately 10 × ULN and bilirubin slightly above the ULN (1.2 × ULN) 17 days after the end of bosentan treatment. The event was reported as resolved without sequelae 6 weeks later, when aminotransferases were approximately 2 × ULN and bilirubin was within the reference range. The investigator assessed the event as related to study drug administration.

- ***Edema***

Pooled PAH safety analysis set

Peripheral edema was reported in 2 patients, one in the context of PAH progression leading to death and the other was an ongoing AE that was reported in the patient's medical history. One patient had face edema reported concurrently with AEs of worsening chest pain and abdominal pain.

PPHN safety analysis set

Generalized edema was reported in 3 patients on bosentan, all of whom had received multiple plasma expanders / intravenous. fluid supplementation on days preceding the event onset.

g) Intrinsic factors

- Age

In the pooled PAH analysis set, the overall proportion of patients with AEs was similar in patients aged < 2 years and those aged ≥ 2 years. There were some apparent differences in the pattern of events between the age groups, although the smaller number of patients aged < 2 years and the difference in the developmental stage of the children in the two groups makes it difficult to accurately compare the findings.

The main differences between the age groups were in relation to liver abnormalities and anemia / decreased hemoglobin. Of the 9 patients with liver abnormality AEs, 8 were aged ≥ 2 years. In the patients aged < 2 years, there was one AE of increased bilirubin, and this was not associated with an aminotransferase increase. All cases of decreased hemoglobin, decreased hematocrit and anemia were reported in patients ≥ 2 years of age. Gastroenteritis AEs were reported more frequently in the younger patients (19.0%) compared to those aged ≥ 2 years (7.6%).

CHMP comments: The sample size of patients less than 2 years is limited to 21 patients precluding firm conclusion.

- Sex

No clinically relevant influence of sex on exposure to bosentan has been observed in pharmacokinetic studies in adults, particularly when corrected for body weight. Due to the small number of (predominantly female) neonates in the FUTURE 4 PPHN safety analysis set, and the high variability seen in the PK parameters, a subgroup analysis by sex was not performed.

- Race/ethnicity

In the pooled PAH safety analysis, the vast majority (80%) of the patients were Caucasian. Of the remaining patients, 10% were Asian, 4% were Black, 3% were Hispanic and 3% were 'Other'. In the FUTURE 4 PPHN safety analysis set, 11/13 of the bosentan group were Caucasian, and 6/8 of the placebo group were Caucasian. Therefore, given the small number of patients from any particular racial/ethnicity category (other than Caucasian), it was considered that evaluation on the basis of race/ethnicity would not be meaningful for either analysis set.

- Growth

The mean and median changes from baseline in the height Z-scores were small, and the direction of change was generally positive. Mean height-for-age Z-scores were slightly below 0 both at baseline and EOS / premature discontinuation of study drug, indicating a somewhat lower height for age than expected in healthy children.

The growth profiles were consistent with the underlying disease condition of patients, an observation consistent with the data from the systematic review of PAH registries conducted by the sponsor.

CHMP comments: Growth is an indicator of health in children with PAH but the available data presented from this pooled analysis are limited. Based on the presentation of the MAH, no detrimental effect of bosentan is shown.

- Dose frequency (t.i.d vs b.i.d)

The effect of increasing the dose frequency from b.i.d. to t.i.d. was assessed in FUTURE 3. No additional clinical benefit was observed.

h) Post marketing

Non-interventional post-authorisation safety studies in the pediatric population

AC-052-516 – Systematic review of pediatric registries

Disease characteristics and outcomes of pulmonary arterial hypertension in children and adolescents in real-world clinical settings: systematic review of four prospective, observational registries.

The Fourth Annual Report of this systematic review was completed on 17 December 2013 and was submitted in parallel to this procedure.

CHMP comment:

As a reminder, the third annual report referred to cumulative data from 15 October 2009 to 15 September 2012. A total of 547 patients had been included in the 4 registries constituting the Enrolled analysis set (EAS). At least one follow-up visit was available for 458 of them (constituting the Full analysis Set (FAS) among which 218 were treated with Tracleer.

On average, patients had been exposed to Tracleer for at least 20 months with a quarter of patients having been exposed to Tracleer for more than 30 months (2.5 years). Approximately half the children treated with Tracleer received more than the dose recommended in the SmPC (i.e. ≥ 4 mg/kg). Thirty-two patients had been treated with Tracleer 32 mg dispersible tablet formulation.

Data on sexual maturation was mainly reported from TOPP registry (158 patients with Tracleer having reached sexual maturation). The available data suggested that Tracleer had few, if any, impact on general development and sexual maturation. Conclusions of the AR was that no new safety signal emerged from the data collected in these registries. A higher event rate was observed in comparison to previous reports

but this may be explained by the change in definition of end of observation leading to a shorter follow-up period and consequently to a higher rate. This should be confirmed within the next annual reports.

It is considered premature to stop the long-term collection of safety and clinical data with bosentan. Enrollment is still ongoing in TOPP, NL and FR registries, and it was agreed that PAH children should be followed-up until puberty, in order to get information on sexual maturity.

Consequently, the CHMP is of opinion that the MAH should continue the registries to monitor PAH children patients and provide additional systematic review of paediatric registries annually. The frequency of submission of systematic review of paediatric registries may be amended following the assessment report of the fifth report.
The MAH is requested to submit the fifth annual report within 3 months of the CHMP opinion. The following issues should be addressed in the next annual report:

- All events and first event rates of PAH related and non-PAH related hospitalisation in the Tracleer are higher than in the whole registry population, for both TOPP and NL registries. This was already observed in the previous periods. A higher rate of PAH retaled events might reflect a non-optimal treatment of the PAH with Tracleer in the paediatric population as well as the non-PAH related events might reflect a lower tolerance of the product compared to other PAH treatment. The MAH should discuss this finding in the next report.

- Regarding events of hepatic disorders and haemoglobin decreased, the MAH should provide additional data (e.g. patients' age, Tracleer dose, Tracleer treatment duration, outcome, time to onset…).

- During the reviewed period, 42/233 (18% of patients) in the TOPP registry discontinued Tracleer treatment. The MAH states that reasons are provided for 38 patients but only provides the 2 most common specific reasons (i.e. PAH improvement (8 patients) and cost or access (6 patients)). The MAH should provide more details regarding reasons for discontinuing treatment with Tracleer. In addition, 7 patients in the TOPP registry (including 2 Tracleer patients) died from known reasons not PAH-related. Details of these cases should be provided.

Post-marketing safety experience in paediatric patients with PAH

The number of patients exposed to bosentan during the post-marketing period (for all age groups) is estimated via controlled distribution systems or from the number of packages sold in USA.

Cumulatively, the proportional distribution of events per SOC was generally similar for both groups, adults elderly and paediatric patients .The majority of AEs arose from the following four SOCs: General Disorders and administration site conditions (including 'death' and lack of efficacy), Infections and infestations, Respiratory, thoracic and mediastinal disorders, and Investigations (60.6% in the paediatric population vs 58.4% in the adult/elderly population). The distribution of AEs by SOC in pediatric patients revealed a higher proportion of Infections and infestations (11.8% vs 6.8%), and Surgical and medical procedures (6.0% vs 2.9%), compared to the adult/elderly population. Regarding events from the Infections and infestations SOC, respiratory tract infections were the most predominant. Cumulatively, both upper (8.8% of pediatric cases vs 4.3% of adult/elderly cases) and lower respiratory tract infections (7.9% of pediatric cases vs 6.2% of adult/elderly cases) appeared more frequent in the pediatric population.

Overall, the reporting rate for hepatobiliary events/investigations in the pediatric population from IBD (20 November 2001) to 19 November 2013 was 5.5% . The overall estimated reporting rate for hepatobiliary events/investigations in the non-paediatric population was 6.0%. All hepatic events were extensively reviewed, and the findings were consistent with the conclusions of the completed European Tracleer post-marketing surveillance (PMS) programme (with data to 19 November 2004), namely that the pediatric population did not seem to be at increased risk of developing liver injury while on bosentan treatment compared to the adult/elderly population (incidence of abnormal liver tests 2.7% in 2–12 year olds, 7.8% in patients > 12 years). A lower incidence of liver injury in pediatric PAH patients was supported by the medical literature [Beghetti 2009a, Beghetti 2009b, Moledina 2010].

The cumulative reporting rate of events denoting anemia was similar between pediatric (1.2%) and adult/elderly patients (1.9%).

Since IBD, 18,557 reports of death (regardless of causality) were received and entered into Argus. The cumulative number of reported deaths expressed as a percentage of treated pediatric patients [11.6%] is similar to that of all ages (13.8%) and to adult/elderly patients [13.71%]. These cumulative estimated reporting rates of death are also comparable with the overall rate of 17% seen in the pooled analysis of children with PAH aged 3 months to 12 years.

Overall conclusion of post-marketing data:
There was no increase in the proportion of reported events in pediatric patients from any events of special interest compared to adults.

The analysis of the cumulative data shows that the safety profile of bosentan in pediatric PAH patients is consistent with the known safety profile of bosentan in adult/elderly PAH patients. A similar safety profile in children and adults was also supported in an overview of three clinical studies including 423 pediatric patients treated with bosentan for PAH [Beghetti 2009a, Beghetti 2009b, Carter 2010], and in the pooled analysis of children with PAH aged 3 months to 12 years.

The CHMP agreed with the MAH that the reporting ratio and the distribution of event per SOC are consistent between pediatric and adult/elderly population.
The reporting rate of serious cases is globally similar between paediatric and adult/elderly populations (overall reporting rate of serious events: 30% or 1 per 3.3 paediatric subjects and 28.9% or 1 per 3.5 adult/elderly subjects).

The overall proportion of serious and non-serious cases in paediatric and adult/elderly populations was comparable with a slightly higher ratio of serious case in the paediatric population (63.2% and 56.5% of cases reported as serious, respectively), with a higher proportion of serious cases in patients < 2 years old (infants/neonates: 76.1%; 507/666), compared with paediatric subjects above 2 years (58.8%; 1143/1944),

The higher differences between these 2 populations is observed in the SOC Respiratory, thoracic and mediastinal disorders (66,7% events reported in this SOC are serious in the paediatric population vs 48% in the adult/elderly population). As mentioned by the MAH, respiratory conditions are the most frequent reason for admission to the hospital in the children population (Hao 2009), this may explain this discrepancy between the populations.

Reporting ratios of fatal outcome are consistent between children aged form 3 month to 2 years (12%), overall paediatric (11,6%) and adult/elderly population (13,8%). When it is known, the cause of death in the paediatric population is more probably related to the underlying disease and conditions than to the treatment with bosentan, and this is as well observed in the adult/elderly population.

Regarding the analysis in children aged from 3 months to 2 years provided by the MAH, the available data do not show specific safety concern in this population.

In summary, no specific risk emerged from post marketing data in children as compared to adults related to the use of bosentan.

2.7.1. Discussion and conclusions on clinical safety

The pooled pediatric safety analysis set from FUTURE-1/2 and FUTURE 3 in 100 PAH patients showed similar AEs in nature to that generally seen in adults. However, a higher rate of AEs associated with the infections and infestations system organ class, with upper respiratory tract infections being the most frequently reported appeared more frequent in the pediatric population as compared to adults.

This may in part be due to the longer median exposure in the pediatric set (71.8 weeks, range: 0.4–258.0 weeks) compared to the adult set (17.4 weeks, range: 0.7–74 weeks) and the higher incidence of acute

respiratory infections in children compared to adults in the general population. This explanation is acceptable for CHMP, however given that the studies were not controlled; a specific effect of bosentan cannot be formally excluded.

Based on post marketing data, bosentan appeared to be used frequently in children (out of label). The reporting ratio and the distribution of event per SOC are consistent between paediatric and adult/elderly population.

The safety data in children aged from 3 months to 2 years do not show specific safety concern in this population.

No specific safety risk emerged from the safety data provided in neonates and in older children as compared to adults related to the use of bosentan.

Reduced testis weight associated with reduced number of sperms and reduced epididymides weights were observed in the newly provided non clinical study conducted in juvenile rats. A slight increased incidence of testicular tubular atrophy (effect also observed with the other ERAs macitentan and ambrisentan) was shown in a toxicity study in rats after 2 years of treatment with bosentan. A clinical study designed to specifically investigate the effects of bosentan treatment on testicular function in male PAH human patients (Study AC-052-402) showed no changes in sperm morphology, sperm motility but 8 out of 24 male patients had a decreased sperm concentration of at least 42% from baseline after 3 or 6 months of treatment with bosentan. Two of these 8 patients showed a sperm concentration lower than 15×10^6/ml which is the lower reference limit of sperm concentration, for the fifth centiles (with 95th percent confidence intervals), generated from men whose partners had time to pregnancy ≤ 12 months, according to WHO (2010). Based on this global it cannot be excluded that bosentan has a proper effect on spermatogenesis in human.
In summary, three new risks are added in the RMP, based on non-clinical and clinical safety data as follows : testicular disorders and male infertility (important potential risk), decrease of sperm count (important identified risk) and respiratory tract infection in children (important potential risk) and the SmPC section 4.8 is amended to reflect additional ADR from the updated safety data set.

The MAH should continue to submit the following safety data,

- systematic review of paediatric registries annually.
- Fifth report of systematic review within 3 months of this CHMP opinion.

2.7.2. The PSUR cycle

The PSUR cycle remains unchanged.

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.8. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 6 could be acceptable if the applicant implements the changes to the RMP as described in the PRAC endorsed PRAC Rapporteur assessment report.

The following amendments were requested:

- Testicular disorders and male infertility should be considered as an important potential risk, the RMP should clearly mention the effect observed in non-clinical studies (i.e. decreased absolute weights of testes and epididymis, increased incidence of testicular tubular atrophy) with bosentan itself.

- Decrease of sperm count should be considered as an important identified risk in accordance with the data from study AC-052-402.
- Respiratory tract infection in children should be considered as an important potential risk.
- The public summary should be updated with rapporteur's comment on issue n°7 and issue n°8. It should also be updated to include the requested additional important potential/identified risks.

An updated RMP version 7 dated 10 November 2014 was received as a result of the list of outstanding issues and the meeting with the MAH taken on 7 November 2014.

The revised RMP contained the following elements:

Summary of safety concerns

• Important identified risks	• Hepatotoxicity • Teratogenicity • Decrease in haemoglobin concentration • Decrease of sperm count
• Important potential risks	• Pulmonary oedema associated with PVOD • Interactions with substrates, inducers or inhibitors of cytochrome P450 isoenzymes CYP3A4 and CYP2C9 (including hormonal contraceptives, sildenafil and antiretrovirals) • Testicular disorders and male infertility • Respiratory tract infection in children
• Important missing information	• Use of bosentan with addition of sildenafil • Use in children with renal function impairment

Table of ongoing and planned additional pharmacovigilance studies/activities in the Pharmacovigilance Plan

Study/activity Type, title and category (1–3)	**Objectives**	**Safety concerns addressed**	**Status (planned, started)**	**Date for submission of interim or final reports (planned or actual)**
DUO Registry*	To document adherence to SmPC requirements for liver function, pregnancy testing	Hepatotoxicity, teratogenicity	Ongoing	Yearly submission cycle with PSUR
Study AC-052-516*: "disease characteristics and outcomes of PAH in children and adolescents in real world clinical settings: Systematic review of four prospective observational registries"	Collect further data on long-term safety and outcomes in paediatric patients with PAH.	Long-term safety and outcomes in paediatric patients with PAH.	Ongoing	Yearly submission cycle

* Classified as Category 3

Summary table of risk minimisation measures

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hepatotoxicity	Information in SmPC section 4.4 (Special warnings and precautions for use) on liver function: *"Elevations in liver aminotransferases, i.e., aspartate and alanine aminotransferases (AST and/or ALT), associated with bosentan are dose-dependent. Liver enzyme changes typically occur within the first 26 weeks of treatment, but may also occur late in treatment (see section 4.8)."* Information on possible mechanisms for liver aminotransferases provided and warning that the risk may be increased if inhibitors of bile export pumps are co-administered (see sections 4.3 and 4.5 of the SmPC). Warning that: *"Liver aminotransferase levels must be measured prior to initiation of treatment and subsequently at monthly intervals for the duration of treatment with Bosentan"* (see further recommendations for dose adjustments in case of ALT/AST elevations and treatment re-introduction under section 4.4 of the SmPC). • Labelled in section 4.8 of the SmPC • This information is also reflected in the PIL. • Restricted medical prescription	Controlled distribution system to identify all prescribers in the EEA in order that they can be informed about the appropriate use of bosentan. Educational material supplied to prescribers (as Prescriber Kit) and patients (patient brochure and reminder card). Patient Reminder Card specifically aimed at facilitating patient's awareness of the need for regular blood tests for liver function. LFT monitoring reminders through DUO registry case report form, newsletters and investigator meetings.
Teratogenicity	• Contraindication in section 4.3 of the SmPC: – *"Pregnancy (see sections 4.4 and 4.6)* – *Women of child-bearing potential who are not using reliable methods of contraception" (see sections 4.4, 4.5, and 4.6)."* • Warning in section 4.4 of the SmPC that: *"Bosentan treatment must not be initiated in women of*	Controlled distribution system to identify all prescribers in the EEA in order that they can be informed about the appropriate use of bosentan. Educational material supplied to prescribers (as Prescriber Kit) and patients (patient brochure and reminder card), as detailed in Pregnancy Action Plan. Patient Reminder Card specifically aimed at informing patients of the need to avoid pregnancy and to

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	child-bearing potential unless they practice reliable contraception (see section 4.5 [Interaction with other medicinal products and other forms of interaction]) *and the result of the pre-treatment pregnancy test is negative (see section 4.6* [Pregnancy and lactation, Use in women of child-bearing potential]*).”* • Sections 4.4 and 4.6: *“Before the initiation of Bosentan treatment in women of child-bearing potential, the absence of pregnancy should be checked, appropriate advice on reliable methods of contraception provided, and reliable contraception initiated.”* • Sections 4.4 and 4.6: *“Patients and prescribers must be aware that, due to potential pharmacokinetic interactions, Bosentan may render hormonal contraceptives ineffective (see section 4.5). Therefore, women of child-bearing potential must not use hormonal contraceptives (including oral, injectable, transdermal, and implantable forms) as the sole method of contraception but should use an additional or an alternative reliable method of contraception. If there is any doubt on what contraceptive advice should be given to the individual patient, consultation with a gynaecologist is recommended.”* • Section 4.5 (interaction with other medicinal products and other forms of interaction): *“…hormone-based contraceptives alone, regardless of the route of administration (i.e., oral, injectable, transdermal, and implantable forms), are not considered as*	ensure effective contraceptive measures are used. Reminders of the need to avoid pregnancy through DUO registry case report form, newsletters and investigator meetings.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	reliable methods of contraception." • This information is also reflected in the PIL. • Restricted medical prescription	
Decrease in haemoglobin concentration	Warning in section 4.4 that treatment with bosentan is associated with a dose-related decrease in haemoglobin concentration and proposals for monitoring. This information is also reflected in the PIL.	Controlled distribution system to identify all prescribers in the EEA in order that they can be informed about the appropriate use of bosentan. Educational material supplied to prescribers (as Prescriber Kit) and patients (patient brochure).
Decrease of sperm count	Information in section 4.6 of the SmPC: *"Animal studies showed testicular effects (see section 5.3). In a study investigating the effects of bosentan on testicular function in male PAH patients, 8 out of 24 patients showed a decreased sperm concentration from baseline of at least 42% after 3 or 6 months of treatment with bosentan. Based on these findings and preclinical data, it cannot be excluded that bosentan may have a detrimental effect on spermatogenesis in men. In male children, a long-term impact on fertility after treatment with bosentan cannot be excluded."* Recommendation in the PIL: "*If you are a man taking Tracleer, it is possible that this medicine may lower your sperm count. It cannot be excluded that this may affect your ability to father a child. Talk to your doctor if you have any questions or concerns about this."*	Controlled distribution system to identify all prescribers in the EEA in order that they can be informed about the appropriate use of bosentan. Educational material supplied to prescribers (as Prescriber Kit) and patients (patient brochure).
Pulmonary oedema associated with veno-occlusive disease	Warning in section 4.4 that pulmonary oedema has been reported with vasodilators (mainly prostacyclins) when used in patients with PVOD disease and to consider PVOD if pulmonary oedema occurs. This information is also reflected in the PIL.	Controlled distribution system to identify all prescribers in the EEA in order that they can be informed about the appropriate use of bosentan. Educational material supplied to prescribers (as Prescriber Kit).
Interaction with	Information in section 4.5 and 4.6 of	Controlled distribution system to

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
hormonal contraceptives	the SmPC.	identify all prescribers in the EEA in order that they can be informed about the appropriate use of bosentan. Educational material supplied to prescribers (as Prescriber Kit) and patients (patient brochure and reminder card), as detailed in Pregnancy Action Plan. Patient Reminder Card specifically aimed at informing patients of the need to avoid pregnancy and to ensure effective contraceptive measures are used. Reminders of the need to avoid pregnancy through DUO registry case report form, newsletters and investigator meetings.
Interaction with sildenafil	Information in section 4.5 of the SmPC.	Controlled distribution system to identify all prescribers in the EEA in order that they can be informed about the appropriate use of bosentan. Educational material supplied to prescribers (as Prescriber Kit).
Drug interaction with antiretrovirals	Warnings in section 4.4 regarding the use of bosentan in patients with PAH associated with HIV infection, treated with antiretrovirals, and in section 4.5 regarding interactions with lopinavir + ritonavir (and other ritonavir-boosted protease inhibitors) and other antiretroviral agents. Recommendation in the PIL: *It is especially important to tell your doctor if you are taking. medicines for the treatment of HIV infection.*	Controlled distribution system to identify all prescribers in the EEA in order that they can be informed about the appropriate use of bosentan. Strengthening of prescriber and patient information through Prescriber Kit, Patient brochure. Educational material supplied to prescribers (as Prescriber Kit) and patients.
Testicular disorders and male infertility	Information in section 4.6 of the SmPC: *"Animal studies showed testicular effects (see section 5.3). In a study investigating the effects of bosentan on testicular function in male PAH patients, 8 out of 24 patients showed a decreased sperm concentration from baseline of at least 42% after 3 or 6 months of treatment with bosentan. Based on these findings and preclinical data, it*	N/A

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	cannot be excluded that bosentan may have a detrimental effect on spermatogenesis in men. In male children, a long-term impact on fertility after treatment with bosentan cannot be excluded." Recommendation in the PIL: "*If you are a man taking Tracleer, it is possible that this medicine may lower your sperm count. It cannot be excluded that this may affect your ability to father a child. Talk to your doctor if you have any questions or concerns about this".*	
Respiratory tract infection in children	Information in section 4.8 of the SmPC: *"The safety profile in this pooled analysis of uncontrolled paediatric studies was similar to that observed in the pivotal trials in adult patients with PAH except for infections that were more frequently reported than in adults (69.0% vs 41.3%).This difference in infection frequency may in part be due to the longer median treatment exposure in the paediatric set (median 71.8 weeks) compared to the adult set (median 17.4 weeks)."*	N/A
Missing information - use in children with renal impairment	Routine pharmacovigilance	N/A
Missing information - use of bosentan in addition with sildenafil	Routine pharmacovigilance COMPASS studies (Safety of combined bosentan and sildenafil treatment)	N/A

The CHMP, having considered the data submitted in the version 7, was of the opinion that the risk management plan can be agreed.

2.9. Update of the Product information

Update of SmPC sections 4.2, 4.5, 4.6, 4.8, 5.1, 5.2 and 5.3 to reflect non-clinical and clinical data generated in studies conducted according to the agreed Paediatric Investigation Plan for bosentan (EMEA-000425-PIP02-10-M04). The Annex II and the Package Leaflet have been updated accordingly. In addition, the MAH took the opportunity to make editorial changes in the SmPC and to update the contact details of the local representatives in the Package Leaflet.

Please refer to Attachment 1 for the final agreed product information adopted by the CHMP on 20 November 2014.

3. Benefit-Risk Balance

Benefits

Beneficial effects

PAH and PPHN are to be considered separately as their clinical features, etiology and outcome are different.

PAH in children :

In PAH children less than 12 years, efficacy was assessed exclusively based on exploratory endpoints in 2 open label and not controlled studies which present several limitations with regards to the efficacy endpoints which were exploratory and their appropriateness to properly assess bosentan effect. Data in children less than 2 years are limited (21 children with PK data only for 4 patients).

FUTURE-1/2, FUTURE-3 did not show any additional clinical benefit when using a dose higher than 2 mg/kg b.i.d. (i.e.: 2 mg/kg t.i.d.) over the 24 weeks period, which is consistent with the systemic exposure remaining similar in both b.i.d. and t.i.d. groups, and also in the 4mg/kg b.i.d. group.

The clinical studies FUTURE-1/2, FUTURE-3 with the 32 mg dispersible tablets are not robust to support the inclusion of children 3 months and older in section 4.1 of the SmPC. Several limitations have been identified with the studies (i.e. open label, important proportion of patients with combined associated treatment, doubt on lack of sensitivity).

Therefore, the definite benefit/risk to support full indication in children remains not fully demonstrated,with uncertainties which prevent from mentioning any specific age group in the indication. However the CHMP agreed to amend the posology section (section 4.2 of the SmPC) to reflect available paediatric data.

The submitted data confirm that higher systemic exposure could not be reached with higher dosing than 2 mg/kg b.i.d. per day. The key study results of the studies have been included in SmPC sections 5.1 and 5.2.

Due to the major objection on efficacy raised, the claim for indication in children from 3 months to 18 years section 4.1. of the SmPC has been withdrawn by the MAH.

Persistent pulmonary hypertension of the newborn

Treatment with iNO is the mainstay for PPHN with proven efficacy. In the majority of infants, an acute improvement in oxygenation can be expected within 30 to 60 min of initiation of iNO at a dose of around 20 ppm regardless of the severity of the illness. Inhaled NO is recommended as the first line treatement of PPHN. In some cases, infants may not exhibit improved oxygenation or a satisfactory and sustained response to iNO.

Future 4 study was well conducted with a well appropriate design as add-on therapy to the iNO, the mainstay treatment of PPHN. However the sample size of 13 patients creates limitation in the overall efficacy assessment.

Overall, there was no benefit in adding bosentan on top of inhaled NO in infants who did not adequately respond to inhaled NO. The mean time to complete weaning from iNO and from mechanical ventilation appeared longer in the bosentan group as compared to the placebo group. In conclusion, the use of bosentan cannot be recommended in PPHN.

Uncertainty about benefits

FUTURE 1/2 were single arm studies. Bosentan was used in combination with prostanoids in 33% of patients. The Future 3 study is the first and sole clinical study including PAH children less than 2 years old (excluding PPHN). It included 21 children less than 2 years treated with bosentan.

This study has several limitations with respect to assessment of efficacy as discussed below. First, this study was open label. It could have been conducted in a double blinded, double dummy design to provide more “robustness” of the subjective parameter WHO functional class and GCIS.

Relevant indicators such as whether children are thriving, the need for supplemental feeds and the records of school nursery attendance assessment would have contributed to a more accurate evaluation of efficacy criteria. However, at the time of protocol finalization (30 August 2010) or FPFV (8 March 2011) this (Panama) classification comprising these indicators was not published.

No conclusion could be drawn from hemodynamics, known to have robustness in PAH, due to the limited sample size of 10 patients.

No conclusion could be drawn from the echocardiography/doppler due to high variability in data collected between the centers.

In Future 3 eligible patients were to be clinically stable. Around 55% of the patients included received PAH-specific medications before starting the study (i.e. PDE-5 inhibitors and/or prostanoids) and continued their treatment in combination to bosentan study treatment. As such, it is difficult to evaluate what was the proper effect of bosentan in those patients. The large part of associated PAH-specific medications in this study introduces a confounding factor in the assessment of the proper effect of bosentan in children.

The same uncertainty regarding the magnitude of the effect of bosentan is raised when looking at bosentan-naïve patients as compared to non-naïve bosentan patients at baseline (i.e.: 82.6% (38/46) and 83.3% (15/18), respectively) with a slightly lower rate of improvement in the bosentan naïve group (improved : 21.9 % (7/46) and 23.1% (3/18) respectively. It is not surprising that stable bosentan non naïve patients, while maintain on their bosentan treatment, were mainly unchanged after the start of the study. But the introduction of bosentan in naïve bosentan patients should have result in a higher rate of improvement as compared to the non-naïve patients. Conversely, the rate of improvement was lower in bosentan-naïve patients as compared to those previously stable with bosentan (alone or combined) suggesting no clinically significant effect relating to the introduction of bosentan, except if patients were asymptomatic and then did not require to be treated with bosentan. If this is the case, the study lacks of sensitivity to assess the effect of bosentan.

WHO functional status was measured using the Dana Point pulmonary hypertension specific classification (based on NYHA classification) for adults. The adult classification would be appropriate for children aged 16 years onwards. It is not appropriate in younger children because physical growth and maturation achieved, influenced the way in which the functional effects of a disease are expressed. Indeed, in February 2011, a consensus on how to define a functional classification in children with pulmonary hypertension was reached by the Paediatric Task Force during the Annual Meeting of the Pulmonary Vascular Research Institute (PVRI). In younger children objective indicators such as thriving, need for supplemental feeds and the record of school or nursery attendance would be necessary.

It is also noted that data from a well conducted clinical study that, in line with the current standard of care, comparing sildenafil+bosentan versus bosentan alone and eventually versus sildenafil alone would be beneficial and are still lacking.

Risk

The safety data provided by the MAH in support of this application consist of an integrated safety analysis for the 100 paediatric PAH patients, aged 3 months to 12 years: - FUTURE-1/2 (12 weeks, 36 patients), FUTURE 3/Extension (72 weeks, 64 patients) and post marketing data.

Additionally, safety data in neonates from the placebo-controlled FUTURE 4 study conducted in patients with persistent pulmonary hypertension of the newborn (PPHN) (13 patients treated with bosentan).

In neonates (Future 4), bosentan appeared well tolerated, however the safety data are not sufficient to conclude given the limited number of PPHN patients and the short-term duration (median exposure 4.5 days ranging from 0.5 to 10 days). The safety was consistent with the known safety profile of bosentan in older patients.

In PAH children, the pooled pediatric safety analysis set from FUTURE-1/2 and FUTURE 3/Extension in 100 PAH patients showed similar AEs in nature to that generally seen in adults. However, a higher rate of AEs associated with the infections and infestations system organ class, with upper respiratory tract infections being the most frequently reported, compared to adults was observed (adult around 41.3% reported in pooled clinical studies).

This may in part be due to the longer median exposure in the pediatric set (71.8 weeks, range: 0.4–258.0 weeks) compared to the adult set (17.4 weeks, range: 0.7–74 weeks) and the higher incidence of acute respiratory infections in children compared to adults in the general population. This explanation is acceptable for CHMP, however given that the studies were not controlled, a specific effect of bosentan cannot be formally excluded.

Regarding post marketing data, bosentan appeared to be used frequently in children (out of label). The reporting ratio and the distribution of event per SOC are consistent between paediatric and adult/elderly population.

The safety data in children aged from 3 months to 2 years do not show specific safety concern in this population (Future 3).

A slight increased incidence of testicular tubular atrophy (effect also observed with other ERAs macitentan and ambrisentan) was shown in a toxicity study in rats after 2 years of treatment with bosentan. A clinical study designed to specifically investigate the effects of bosentan treatment on testicular function in male PAH human patients (Study AC-052-402) showed a decreased sperm concentration (8/24 patients) of at least 42% from baseline after 3 or 6 months of treatment with bosentan. Two of the 8 patients showed a sperm concentration lower than the reference limit of sperm concentration. No changes in sperm morphology, sperm motility were observed. Based on this global it cannot be excluded that bosentan has a proper effect on spermatogenesis in human. This information has been included in the SPC and patient leaflet.

In summary, three new risks are added in the RMP, based on non-clinical and clinical safety data as follows: testicular disorders and male infertility (important potential risk), decrease of sperm count (important identified risk) and respiratory tract infection in children (important potential risk).

Discussion about benefit and risks

In PAH children less than 12 years, efficacy was assessed exclusively based on exploratory endpoints in 2 open label and not controlled studies which present several limitations with regards to the efficacy endpoints which were exploratory and their appropriateness to properly assess bosentan effect (open label, important proportion of patients with combined associated treatment, doubt on lack of sensitivity). Moreover, data in children less than 2 years are limited (21 children with PK data only for 4 patients).

FUTURE-1 showed that in children, systemic exposure with bosentan 2 mg/kg was on average lower as compared to adults and was not increased with 4 mg/kg b.i.d. Similar results were observed in FUTURE 3 study, where the systemic exposure (also lower compared to adults) could not be increased with a more frequently dosing of 2 mg/kg t.i.d.

Following the major objections raised by CHMP with respect to the limitations of the newly provided clinical studies to have a reliable conclusion on efficacy in children, the MAH has withdrawn the claim for changing the wording of the indication in section 4.1.
In conclusion, the available clinical studies in children with PAH have several limitations and do not support to extend the indication in children from 3 months and older.

However, updated information is provided in the SmPC, to inform prescribers on the data available in children (especially with regards to the specificity of PK and exposure plateaus as compared to adults).

Persistent pulmonary hypertension of the newborn

Overall, this study showed that there was no benefit in adding bosentan on top of inhaled NO in infants who did not adequately respond to inhaled NO. The mean time to complete weaning from iNO and from mechanical ventilation appeared longer in the bosentan group as compared to the placebo group.

Based on the available data, the use of bosentan cannot be recommended in PPHN.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following changes:

Variation accepted		**Type**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II

Update of SmPC sections 4.2, 4.5, 4.6, 4.8, 5.1, 5.2 and 5.3 to reflect non-clinical and clinical data generated in studies conducted according to the agreed Paediatric Investigation Plan for bosentan (EMEA-000425-PIP02-10-M04). The Annex II and the Package Leaflet have been updated accordingly. Further, the MAH took the opportunity to make editorial changes in the SmPC and to update the contact details of the local representatives in the Package Leaflet. In addition, taking into account the results observed on testis and spermatogenesis and the new data in the paediatric population, an updated version of the RMP (version 7) was agreed.

The requested variation proposed amendments to the SmPC, Annex II and Package Leaflet.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0090/2013 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.