25 June 2015
EMA/CHMP/473644/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Tracleer

International non-proprietary name: Bosentan

Procedure no.: EMEA/H/C/000401 P46 081

Note

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

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1. Introduction

On 13 February 2015, the MAH submitted a completed paediatric study for FUTURE 3 (AC-052-373) and FUTURE 3 extension (AC-052-374) study in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

These data are also submitted as part of the post-authorisation measure(s)

A short critical expert overview dated 31 March 2014, has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that Study AC-052-374: A prospective, multicenter, open label extension of FUTURE 3 to assess the safety, tolerability and efficacy of the pediatric formulation of bosentan two versus three times a day in children with pulmonary arterial hypertension (FUTURE 3 Extension), is a stand alone study.

2.2. Information on the pharmaceutical formulation used in the study

Study drug was bosentan at doses of 2 mg/kg b.i.d. and 2 mg/kg t.i.d., provided as a 32 mg dispersible tablet for oral administration. Each tablet was quadrisectible, clover shaped, and breakable into 4 parts of 8 mg each. (Tracleer 32 mg dispersible tablets, batches FP014, CXFC, DTHD, and GTXF).

2.3. Clinical aspects

2.3.1. 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 quadrisecable 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 core FUTURE 3 pediatric study in PAH patients was conducted as part of the PIP:

• AC-052-373: Open-label, randomized, multicenter, multiple dose trial to evaluate PK, 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 PAH (FUTURE 3)

The 6-month core study was followed by a 12-month extension study, which was not part of the PIP:

• AC-052-374: A prospective, multicenter, open-label extension of FUTURE 3 to assess the safety, tolerability and efficacy of the pediatric formulation of bosentan two versus three times a day in children with pulmonary arterial hypertension (FUTURE 3 extension).

The 6 month core FUTURE 3 including cumulative safety data from the FUTURE 3 core and its extension, up to a cut-off date of 19 August 2013, was submitted as part of a Type II variation in April 2014 (EMEA/H/C/000401/II/0066) with the aim to amend the SPC and patient information leaflet of Tracleer 62.5 mg and 125 mg film-coated tablet and Tracleer 32 mg dispersible tablets especially with regards to children information. The Day 80 and Day 150 Rapporteur's Assessment reports were circulated in June 2014 and October 2014 respectively with final CHMP opinion on November 2014.

Actelion now submits the final study report for clinical study AC-052-374 entitled "A prospective, multicenter, open label extension of FUTURE 3 to assess the safety, tolerability and efficacy of the pediatric formulation of bosentan two versus three times a day in children with pulmonary arterial hypertension (FUTURE 3 Extension)" in accordance with Article 46 of Regulation (EC) No 1901/2006.

The present submission complies with Article 46 of Regulation (EC) No. 1901/2006 (the ‘Paediatric Regulation’).

2.3.2. Clinical study

AC-052-374: A prospective multicenter, open-label extension of FUTURE 3 to assess the safety, tolerability and efficacy of the pediatric formulation of bosentan two versus three times a day in children with pulmonary arterial hypertension.

The final study report AC-052-374 is dated on 3th February 2015 and provides the analysis of cumulative data from the start of bosentan treatment in the 6 month FUTURE 3 core study (AC-052-373) up to the end of the 12 months FUTURE 3 extension study, i.e., for a period of up to 18 months.

First patient was included in March 2011 (FUTURE 3) and last patient visit of FUTURE 3 extension was on 13 august 2014.

Description

Methods

Objective(s)

The aim of study AC-052-374 was to evaluate the long-term safety, tolerability and efficacy of the 32 mg dispersible tablet formulation of bosentan at doses of 2 mg/kg, twice daily (b.i.d.) versus three times daily (t.i.d.) in PAH children.

Study design

This study was a prospective, multicenter, multinational, open-label, parallel double-arm, and exploratory one-year extension to FUTURE 3 core study (AC-052-373).

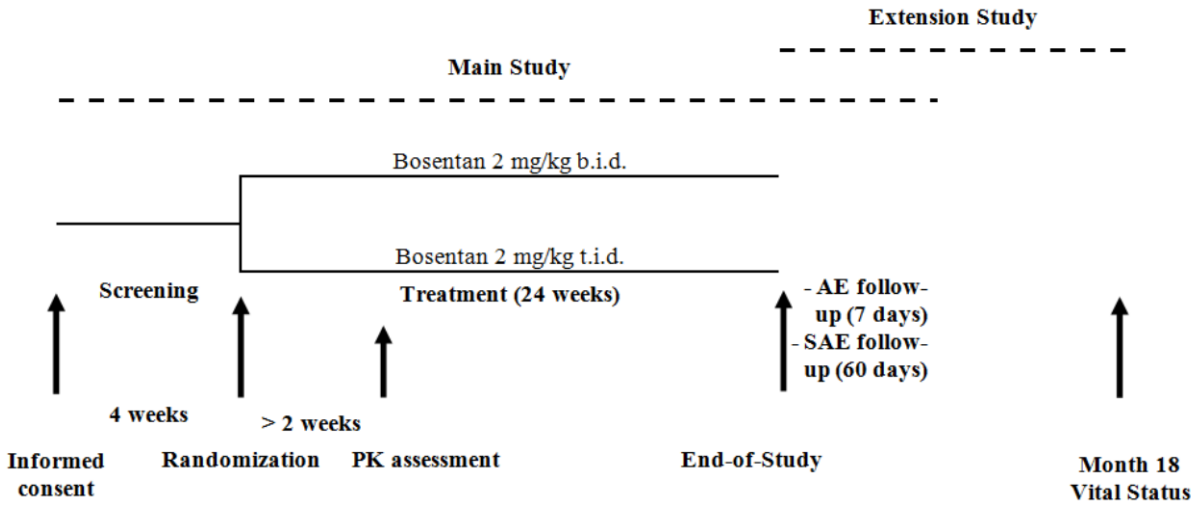
The 6-month FUTURE 3 core study was designed as a PK, efficacy, tolerability, and safety study to investigate two dosing regimens of bosentan (2 mg/kg body weight b.i.d. and t.i.d.) in pediatric PAH patients ≥ 3 months and < 12 years of age. The extension study was planned to continue bosentan treatment for a further 12 months (48 weeks) in addition to the core study.

The patient population in this extension study included pediatric PAH patients who completed the FUTURE 3 core study, either per protocol or who prematurely discontinued study treatment due to PAH progression, and had performed relevant End of Study (EOS) assessments. In addition, patients were required to have tolerated treatment with the bosentan dispersible tablet formulation during the FUTURE 3 core study and were considered by the investigator to benefit from continued bosentan treatment.

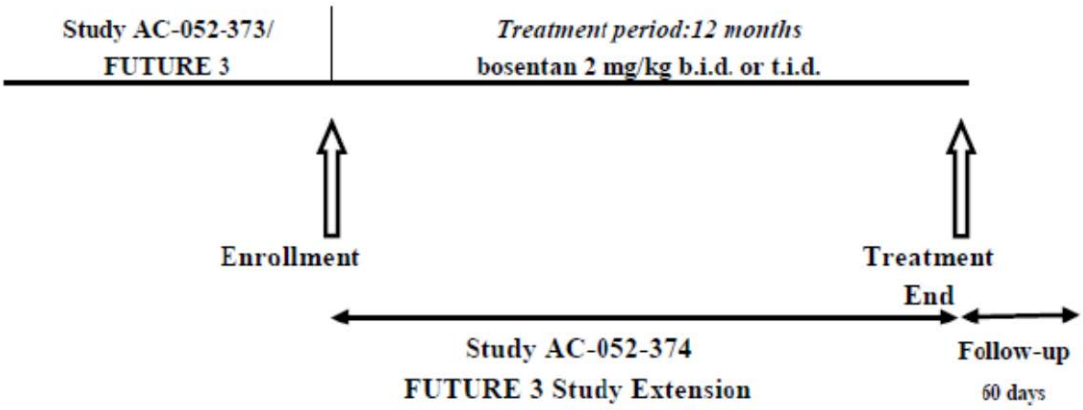
Treatment groups assigned at randomization of FUTURE 3 core study were continued in the extension study. Patients received 32 mg dispersible tablet formulation of bosentan, adjusted to their body weight at each visit (if required), according to the same dosing regimen as in the FUTURE 3 core study (i.e., 2 mg/kg either twice daily [b.i.d.] or three times daily [t.i.d.]).

Following the end of treatment, there was a 60-day post-treatment follow-up period for each patient and reported only SAES.

FUTURE 3 design (AC-052-373)



FUTURE 3 extension (AC-052-374)



b.i.d. = twice daily; t.i.d. = three times daily.

The sequence of the assessment of efficacy (except hemodynamics, echocardiography and n-terminal prohormone brain natriuretic peptide [NT-proBNP]) and safety variables was applied uniformly throughout the FUTURE 3 core and FUTURE 3 extension studies.

Table 9-2: Schedule of visits and assessments

Periods	Name	Treatment			Follow-up	
	Duration	12 months			60 days[4]	
Visit	Time	Enrollment (FUTURE 3 core study EOS visit)	Months 3, 6 & 9 (± 1 week)	Month 12: EOS or Premature Study Discontinuation (± 1 week)	Phone call: 7 days	Phone call: 60 days
	Number	1	2, 3 & 4	5		
Informed consent		X				
▪ Physical examination ▪ Vital signs ▪ Body weight ▪ Height/length ▪ WHO FC ▪ GCIS (physician & parents) ▪ Concomitant medications		X[5]	X	X		
Laboratory tests[1, 2]		X[5]	X	X		
			Liver tests[3]: Monthly until one month after treatment discontinuation **Hemoglobin**: Monthly during the first 6 months since treatment start in FUTURE 3 core study (AC-052-373) and quarterly thereafter			
AEs		X				
SAEs		X				
Study medication dispense/adjustment/return		X	X	X		

1 Laboratory tests included hematology and biochemistry.
2 Included monthly serum pregnancy test for female patients of childbearing potential.
3 Liver function tests included AST, ALT, AP, TBIL and direct bilirubin.
4 SAEs that occurred more than 7 days after study drug discontinuation were reported to Drug Safety and recorded in the Drug Safety database only.
5 These assessments did not have to be repeated if already performed and recorded within 2 weeks of the FUTURE 3 core study (AC-052-373) "Visit 5: EOS per protocol / Premature Study Discontinuation".

AEs = adverse event(s); ALT = alanine aminotransferase; AP = alkaline phosphatase; AST = aspartate aminotransferase; EOS = end of study; FC = functional class; GCIS = global clinical impression scale; SAEs = serious adverse events; TBIL = total bilirubin; WHO = World Health Organizazion.

Assessor comments:
FUTURE 3 and FUTURE 3 extension studies were both open labelled. Treatment groups assigned at randomization of FUTURE 3 core study were continued in the extension study. Assessments at visits were performed at 3-monthly intervals consistently in the FUTURE 3 core and FUTURE 3 extension studies. This enabled a cumulative analysis of the data collected continuously over both periods.

Study population /Sample size

There was no sample size calculation specifically for the extension study.

Treatments

Treatment groups assigned at randomization of FUTURE 3 core study in open label were continued in the extension study according to the same dosing regimen as in the FUTURE 3 core study (i.e., 2 mg/kg either twice daily [b.i.d.] or three times daily [t.i.d.]) adjusted to their body weight at each visit (if required) and using the 32 mg dispersible breakable into 4 parts of 8 mg each.

Outcomes / endpoints

No primary endpoint was defined for FUTURE 3 and FUTURE 3 extension.

All efficacy endpoints defined were exploratory:
• Change from baseline (i.e. the last valid assessment performed prior to first study drug intake in the FUTURE 3 core study) to permanent discontinuation (FUTURE 3 study extension EOS for those patients that participated in the extension study, or FUTURE 3 core study EOS for those patients that did not participate in the FUTURE 3 study extension) of study drug in WHO functional class (FC).
• Time to death, lung transplantation or hospitalization for PAH-progression up to EOT + 7 days4.
• Time to death, lung transplantation, hospitalization for PAH-progression or initiation of new therapy for PAH or new/worsening right heart failure up to EOT + 7 days.
Notes:

* For time-to-event endpoints, the start was defined as initiation of bosentan treatment in the FUTURE 3 core study.
** time to initiation of new therapy for PAH encompassed PAH-progression requiring initiation or dose increase of PAH-specific therapy.

• Overall survival: Time to death (any cause) up to EOS.
• Change from baseline1 to 3, 6, 9, 12, 15, and 18 months of treatment over FUTURE 3 core and extension studies in Global Clinical Impression scale (GCIS) assessed by the physician and parents.
• Change from baseline to 3, 6, 9, 12, 15, and 18 months of treatment over FUTURE 3 core and extension studies in WHO FC.

Safety assessment:

Treatment-emergent period was defined as AEs with onset from study treatment start up to 7 days after permanent study drug discontinuation (limits included).
SAEs were also collected from 7 up to 60 days after permanent discontinuation of study drug (from Actelion's Drug Safety database Argus Safety).

Statistical Methods

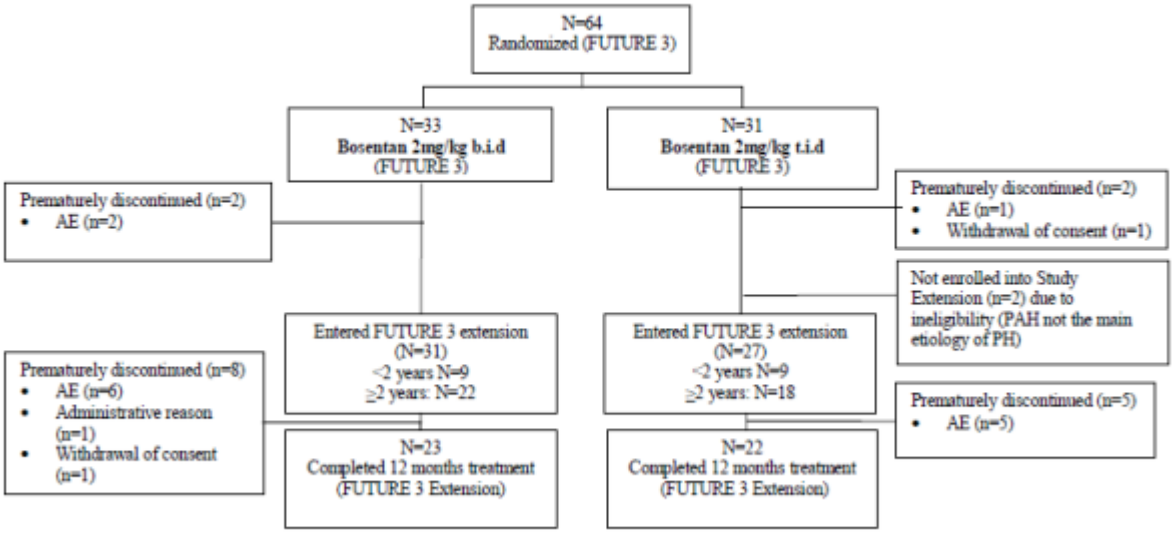
All analyses were performed on the pooled data of the FUTURE 3 and the extension study.
No hypothesis test was performed. Comparisons between the treatment groups were Descriptive.
All efficacy and safety analyses were performed descriptively using the 'All Treated' analysis set (Safety analysis set) , which included all patients in the FUTURE 3 study who received at least one dose of the study drug.

Results

Recruitment / Number analysed

Of the **64** patients (33 b.i.d., 31 t.i.d.) randomized in the FUTURE 3 core study and who received at least one dose of the study treatment, **58** (31 b.i.d., 27 t.i.d.) entered the extension study, 18 of whom were < 2 years of age (9 each, b.i.d. and t.i.d.) and 40 were ≥ 2 years of age (22 b.i.d., 18 t.i.d.).

Figure 10-1: Disposition of patients



Six patients did not enter the extension study: one patient withdrew consent and permanently discontinued the study, 3 patients died after experiencing worsening of PAH, and 2 patients were ineligible based on their disease etiology (PAH not the main etiology of patients' PH) at the time of enrolment into FUTURE 3 core study.

Of the 58 patients who entered the FUTURE 3 extension study, 13 patients prematurely discontinued study treatment, due to AEs (6 b.i.d. and 5 t.i.d.), administrative reasons and withdrawal of consent (1 patient each, b.i.d.) and 45 patients (23 b.i.d. and 22 t.i.d.) completed the 12-month treatment period in the extension study. Of the 13 patients who discontinued during the extension study, 3 (out of 18, 16.7%) were < 2 years of age (2 b.i.d., 1 t.i.d.) and 10 (out of 40, 25%) were ≥ 2 years of age (6 b.i.d., 4 t.i.d.)

Baseline data

All 64 patients who were randomized in the FUTURE 3 core study received at least one dose of the study drug and were included in the 'All Treated' and safety analysis sets.

At inclusion, 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, 21 (33%) were < 2 years (10 b.i.d., 11 t.i.d.) and 43 (67%) were ≥ 2 years of age (23 b.i.d., 20 t.i.d.). The overall mean age was sligtly higher ranging from 0.3 to around 11 years in both groups.

The overall population was predominantly male (56.3%) and Caucasian (75.0%). In the b.i.d. group, the majority of patients were female (54.5%); however, males predominated in the t.i.d. group (67.7%). The majority of patients in each group were Caucasian (75.8% b.i.d., 74.2% t.i.d.).

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%).

FUTURE 3: Summary of demographic and baseline characteristics, All-randomized set

	b.i.d N=33	t.i.d N=31	Total N=64
GENDER [n (%)]			
n	33	31	64
Males	15 45.5%	21 67.7%	36 56.3%
Females	18 54.5%	10 32.3%	28 43.8%
AGE (years)			
n	33	31	64
Mean	4.5	5.2	4.8
Standard deviation	3.35	3.81	3.57
Standard error	0.58	0.68	0.45
95% CL of mean	3.3 , 5.7	3.8 , 6.6	3.9 , 5.7
Median	3.7	4.8	3.8
95% CL of median	2.1 , 4.9	1.7 , 7.8	2.8 , 5.6
Q1 , Q3	1.8 , 5.6	1.2 , 8.7	1.7 , 7.8
Min , Max	0.3 , 11.0	0.3 , 11.4	0.3 , 11.4
RACE [n (%)]			
n	33	31	64
Caucasian/white	25 75.8%	23 74.2%	48 75.0%
Black	1 3.0%	2 6.5%	3 4.7%
Asian	6 18.2%	4 12.9%	10 15.6%
Hispanic	-	1 3.2%	1 1.6%
Other	1 3.0%	1 3.2%	2 3.1%
Etiology of PAH			
n	33	30	63
Idiopathic (iPAH)	14 42.4%	15 50.0%	29 46.0%
Heritable (hPAH)	2 6.1%	-	2 3.2%
Associated (aPAH)	11 33.3%	13 43.3%	24 38.1%
PAH-CHD (open shunt)	6 18.2%	2 6.7%	8 12.7%
WHO functional Class			
n	33	31	64
I	8 24.2%	8 25.8%	16 25.0%
II	13 39.4%	17 54.8%	30 46.9%
III	12 36.4%	6 19.4%	18 28.1%
Global Clinical Impression Scale (Physician) [n (%)]			
n	33	31	64
Very bad	2 6.1%	1 3.2%	3 4.7%
Bad	6 18.2%	2 6.5%	8 12.5%
Neither good or bad	5 15.2%	6 19.4%	11 17.2%
Good	13 39.4%	17 54.8%	30 46.9%
Very good	7 21.2%	5 16.1%	12 18.8%
Global Clinical Impression Scale (Parent/Legal Representative) [n (%)]			
n	33	31	64
Very bad	3 9.1%	1 3.2%	4 6.3%
Bad	3 9.1%	1 3.2%	4 6.3%
Neither good or bad	6 18.2%	5 16.1%	11 17.2%
Good	12 36.4%	18 58.1%	30 46.9%
Very good	9 27.3%	6 19.4%	15 23.4%

CL=confidence limits.

Assessor's comment: In general, demographic characteristics were similar in the b.i.d. and t.i.d. groups in the overall population and mean age was balanced between the two treatment groups (years ± standard error, 4.5 ± 0.58 b.i.d., 5.2 ± 0.68 t.i.d.).

Following the response of the MAH to questions raised during the type II variation EMEA/H/C/401/II/066 (see AR), it was clarified that 6 children less than 1 year were included in the FUTURE 3 study (2 b.i.d. and 4 t.i.d.) and 15 children were between 1 to 2 years old. This reflected the current practice for diagnosis of PAH. However, it was noticed that this limited sample doesn't help to document the benefit/risk in the youngest children for whom concerns are raised with respect to PK profile different between adults and children.

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%).

Of note : according to the response of the MAH provided in the initial assessment report of FUTURE 3 core study (See day 150 AR EMEA/H/C/401/II/066), at Visit 1 : 16 subjects were in WHO functional class I, 30 subjects in class II and 18 subjects in class III. At Visit 2 (4 weeks later) 19 subjects were in class I, 27 subjects in class II and 18 subjects in class III. Based on the clarification provided by the MAH, it was noticed that 3 patients "spontaneously" improved from class II to class I throughout this 4 weeks period.
This doesn't change the results from the subsequent analysis as it was performed using visit 2 as baseline.

PAH-specific medication at baseline :

Table 10-3: Summary of baseline (FUTURE 3 definition) PAH-specific medications including combinations by Frequency, All-treated/randomized set

Class / Preferred Term	b.i.d N=33 n	b.i.d N=33 %	t.i.d N=31 n	t.i.d N=31 %	Total N=64 n	Total N=64 %
PAH specific medications						
Total patients with at least one medication	20	60.6%	22	71.0%	42	65.6%
PDE-5 inhibitor	10	30.3%	13	41.9%	23	35.9%
Bosentan	3	9.1%	4	12.9%	7	10.9%
Bosentan & Prostanoid & PDE-5 inhibitor	5	15.2%	2	6.5%	7	10.9%
Bosentan & PDE-5 inhibitor	2	6.1%	2	6.5%	4	6.3%
Prostanoid	-		1	3.2%	1	1.6%

All background PAH treatments were required to be maintained at a stable dose during the study.

Initiation or dose-increase of an ongoing PAH-specific therapy (i.e., prostanoid and/or PDE-5 inhibitor) was required to be associated with 'PAH-progression', and this was reported in the CRF AE page.

Anticoagulants, diuretics, digoxin, calcium channel blockers were permitted.

Assessor's comment: Overall, 42 patients (65.6%) were reported to be taking at least one PAH-specific medication at baseline. During EMEA/H/C/401/II/66 procedure, the MAH confirms that 45.3% (29 among 64) of subjects were on bosentan monotherapy during the study FUTURE 3.

Efficacy results

Efficacy was assessed on an exploratory basis in the FUTURE 3 core and its extension study.

Assessor's comment: The results for all exploratory efficacy variables were presented up to 24 weeks (approximately 6 months) in the FUTURE 3 core study. In order to focus on the changes in the efficacy variables during long-term treatment with bosentan in the extension study, results are specifically described for Month 12 and Month 18 time points.

The MAH has presented all exploratory efficacy results by b.i.d. and t.i.d. groups as assigned in FUTURE 3 and continued into the extension study without any comparisons drawn between the 2 groups.

WHO functional class

Table 3 Change in WHO FC over time, All-treated set

Time point*	Response	b.i.d. N=33	t.i.d. N=31	Total N=64
Month 12	Stable	22 (66.7%)	25 (80.6%)	47 (73.4%)
	Improved	7 (21.2%)	3 (9.7%)	10 (15.6%)
	Worsened	4 (12.1%)	3 (9.7%)	7 (10.9%)
Month 18	Stable	25 (75.8%)	25 (80.6%)	50 (78.1%)
	Improved	3 (9.1%)	3 (9.7%)	6 (9.4%)
	Worsened	5 (15.2%)	3 (9.7%)	8 (12.5%)

Post-hoc imputation accounting for the worst values substitution. Source: D-14.491 Table 15-31
b.i.d. = twice daily; FC = functional class; t.i.d. = three times daily; WHO = World Health Organization.

Cumulatively over the FUTURE 3 core and extension study, the majority of patients remained clinically stable (i.e., without change in WHO FC status from baseline at Month 12: 73.4%, Month 18: 78.1%).

WHO FC remained unchanged for 66.7% (b.i.d.) vs 80.6% (t.i.d.) of patients at Month 12, and 75.8% (b.i.d.) vs 80.6% (t.i.d.) of patients at Month 18.

Improvements were reported for 21.2% (b.i.d.) vs 9.7% (t.i.d.) of patients at Month 12, and 9.1% (b.i.d.) vs 9.7% (t.i.d.) of patients at Month 18.

Worsening was reported for 12.1% (b.i.d.) vs 9.7% (t.i.d.) of patients at Month 12, and 15.2% (b.i.d.) vs 9.7% (t.i.d.) of patients at Month 18.

Assessor's comment: cumulatively and based on WHO classification, the greater proportion of patients remained stable during the study (without change in WHO FC from baseline (Month 12: 73.4%, Month 18: 78.1%). As discussed in EMEA/H/C401/II/066 AR for the 6 month core FUTURE 3 study, as patients were to be stable at entry and that more than half of them received combined PAH-specific medications (PDE-5 inhibitors and/or prostanoids), the proper effect of bosentan is difficult to assess and 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.
Moreover, as already discussed in the previous EMEA/H/C401/II/066 AR, the 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 influence the way in which the functional effects of a disease are expressed.

A slightly higher proportion of patients worsened in the b.i.d. group than in t.i.d. group.

Global Clinical Impression Scale

Table 4 **Global clinical impression score: Change in physician GCIS over time, All-treated set**

Time point	Response	b.i.d. N=33	t.i.d. N=31	Total N=64
Month 12	Stable	16 (57.1%)	16 (69.6%)	32 (62.7%)
	Improved	10 (35.7%)	6 (26.1%)	16 (31.4%)
	Worsened	2 (7.1%)	1 (4.3%)	3 (5.9%)
Month 18	Stable	9 (47.4%)	12 (66.7%)	21 (56.8%)
	Improved	6 (31.6%)	5 (27.8%)	11 (29.7%)
	Worsened	4 (21.1%)	1 (5.6%)	5 (13.5%)

*Note n is different across the different assessment time points, *no imputations performed*, see Source: D-14.491 Table 15-33
b.i.d. = twice daily; GCIS = global clinical impression scale; t.i.d. = three times daily.

Table 5 **Global clinical impression score: Change in parents / legal representatives GCIS over time, All-treated set**

Time point	Response	b.i.d. N=33	t.i.d. N=31	Total N=64
Month 12	Stable	16 (57.1%)	12 (52.2%)	28 (54.9%)
	Improved	9 (32.1%)	11 (47.8%)	20 (39.2%)
	Worsened	3 (10.7%)	0 (0.0%)	3 (5.9%)
Month 18	Stable	8 (42.1%)	7 (38.9%)	15 (40.5%)
	Improved	6 (31.6%)	10 (55.6%)	16 (43.2%)
	Worsened	5 (26.3%)	1 (5.6%)	6 (16.2%)

*Note n is different across the different assessment time points, see Source: D-14.491 Table 15-35
b.i.d. = twice daily; GCIS = global clinical impression scale; t.i.d. = three times daily.

The majority of patients remained stable over time according to the Physician's GCIS (Month 12: 62.7%, Month 18: 56.8%). Physician's GCIS remained unchanged for 57.1% (b.i.d.) vs 69.6% (t.i.d.) of patients at Month 12, and 47.4% (b.i.d.) vs 66.7% (t.i.d.) of patients at Month 18.
Physician's GCIS was rated as improved for 35.7% (b.i.d.) vs 26.1% (t.i.d.) of patients at Month 12, and 31.6% (b.i.d.) vs 27.8% (t.i.d.) of patients at Month 18.
The proportion of patients rated as having worsened was 7.1% (b.i.d.) vs 4.3% (t.i.d.) at Month 12 and 21.1% (b.i.d.) vs 5.6% (t.i.d.) at Month 18.

The overall results for the parents' / legal representatives' GCIS rating was consistent with those for the Physician's GCIS rating.
The majority of patients remained stable over time (Month 12: 54.9%, Month 18: 40.5%). Parents' / legal representatives' GCIS remained unchanged for 57.1% (b.i.d.) vs 52.2% (t.i.d.) of patients at Month 12, and 42.1% (b.i.d.) vs 38.9% (t.i.d.) of patients at Month 18.
The proportion of patients rated as having worsened was for 10.7% (b.i.d.) vs 0 (t.i.d.) at Month 12 and 26.3% (b.i.d.) vs 5.6% (t.i.d.) at Month 18.

Assessor's comment : consistent with the results on WHO functional class, the majority of patients remained stable or improved over the 18 month assessment period of the Future 3 core study and its extension based on the Global clinical impression scale (GCIS) rated both by physicians and by parents.
A higher proportion of patients worsened in the b.i.d. group than in t.i.d. group.

PAH-worsening

Death, lung transplant or hospitalization due to PAH-progression was reported for a total of 13 patients (8 b.i.d., 5 t.i.d.), 4 reported during the FUTURE 3 core study and 9 during the extension study. Of the 13 patients, 4 (out of 21, 19.0%) were < 2 years of age and 9 (out of 43, 20.9%) were ≥ 2 years of age

The broader definition including initiation of new therapy for PAH or new/worsening right heart failure (reported for 2 patients) resulted in a total of 15 patients (10 b.i.d., 5 t.i.d.) with such events (i.e. death, lung transplantation, hospitalization for PAH-progression, or initiation of new therapy for PAH or new/worsening right heart failure); 4 were reported during the FUTURE 3 core study and 11 during the extension study. Of the 15 patients, 5 (out of 21, 23.8%) were < 2 years of age and 10 (out of 43, 23.3%) were ≥ 2 years of age.

Cumulatively over 12 and 18 months of treatment in the FUTURE 3 core and extension studies, the Kaplan-Meier (KM) estimate of the event-free rate for PAH worsening based on death, lung transplantation or hospitalization for PAH worsening was 84.7% (95% confidence limits [CLs]: 72.6%, 91.7%) and 77.4% (95% CLs: 64.2%, 86.2%), respectively. For the broader definition that included initiation of new therapy for PAH and new/worsening right heart failure, the estimated event-free rate was 81.4% (95% CLs: 69.0%, 89.3%) at Month 12 and 74.1% (95% CLs: 60.8%, 83.6%) at Month 18.

Table 11-4: Summary of PAH-worsening components (all occurrences up to EOT + 7 days): death, lung transplant, hospitalization due to PAH-progression, initiation of new therapy for PAH or new/worsening right heart failure - Analysis set: All-treated/randomized set

	b.i.d N=33		t.i.d N=31		Total N=64	
	n	%	n	%	n	%
Total patients with at least one event	10	30.3%	5	16.1%	15	23.4%
NEW/WORSENING RIGHT HEART FAILURE	8	24.2%	3	9.7%	11	17.2%
DEATH	6	18.2%	4	12.9%	10	15.6%
HOSPITALIZATION DUE TO PAH-PROGRESSION	4	12.1%	3	9.7%	7	10.9%
INITIATION OF NEW THERAPY FOR PAH	2	6.1%	2	6.5%	4	6.3%

Source: Table 15-45

Assessor's comment: consistent with the changes observed in WHO FC and GCIS, a higher proportion of patients worsened in the b.i.d. group than in t.i.d. group: 30.3 % vs 16.1 % respectively.

Survival:

Two survival analyses were performed.

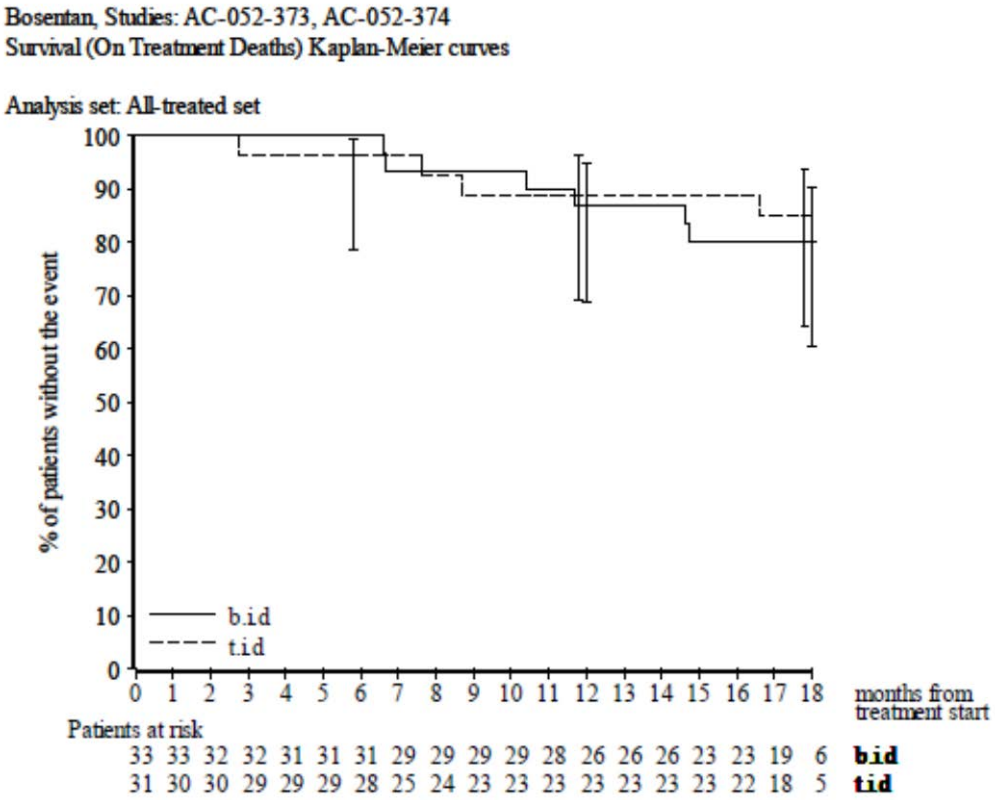
In the survival analysis for all deaths up to EOS (regardless of whether the patient was on study treatment), the overall KM estimates of survival was 85.7% (95% CLs: 74.3, 92.3) at Month 12 and 80.9% (95% CLs: 68.7, 88.6) at Month 18.
In the analysis for 'on-treatment deaths' (on study treatment in either FUTURE 3 or its extension study up to 7 days post treatment discontinuation), the overall KM estimates for survival were 87.9% (95% CLs: 76.2, 94.0) at Month 12 and 82.3% (95% CLs: 69.5, 90.1) at Month 18.

Table 6 Survival at Month 12 and Month 18, All-treated set (N=64)

	KM survival estimates (95% CLs):	
	All deaths up to EOS	On-treatment deaths
Month 12	85.7% (74.3%, 92.3%)	87.9% (76.2%, 94.0%)
Month 18	80.9% (68.7%, 88.6%)	82.3% (69.5%, 90.1%).

CL = confidence limit; EOS = end of study; KM = Kaplan-Meier. Source: D-14.491 Table 15-49 and Table 15-51

Figure 11-1: Survival (On Treatment Deaths) Kaplan-Meier curves - Analysis set: All-treated set



Survival analysis according to WHO FC showed that in baseline FC I/II patients, the KM survival estimate was 93.2% at Month 12 and 88.1% at Month 18.
In baseline FC I/II patients, the KM survival estimate was 93.2% at Month 12 and 88.1% at Month 18.
In FC III patients, the KM survival estimate was 71.4% at Month 12 and 64.3% at Month 18.

Assessor's comment: Survival estimates were slightly lower in the b.i.d. group than in the t.i.d. group, consistent with the higher rate of PAH worsening in the b.i.d. group (consistently denoted by all relevant clinical changes, i.e., WHO FC, GCIS, and per protocol PAH worsening).

Post hoc analysis:

Due to an imbalance disease severity (in terms of WHO FC) at baseline in the treatment groups, post-hoc Cox proportional hazards model analyses (univariate and multivariate) adjusted for baseline

covariates (WHO FC I/II versus III) were performed for the time to event endpoints of worsening (defined as death, transplantation, hospitalization for PAH-progression) up to EOT + 7 days, death up to EOT + 7 days, and death up to EOS (Month 18).

Time to PAH worsening:

Table 11-5: Multivariate model for Time to PAH worsening up to EOT + 7 including treatment (bid vs tid) and WHO FC (III vs I/II) factors - Analysis set: All-treated set

Model Covariates	HR	95% CL		p-value
Treatment (b.i.d. vs t.i.d.)	1.169	0.371	3.681	0.7899
WHO FC (III vs I/II)	2.845	0.928	8.72	0.0674

b.i.d. = twice daily; CL = confidence limit; FC = functional class; HR = heart rate; t.i.d. = three times daily; WHO = World Health Organization.

In the univariate model, the treatment effect (b.i.d. vs t.i.d.) hazard ratio was 1.438. In the multivariate model, the treatment effect (b.i.d. vs t.i.d.) hazard ratio was approximately 19% lower compared to that for the univariate model (1.169), indicating a neutral effect.
Such reductions (multivariate vs univariate) were not seen in the remaining covariate adjusted Models.

Time to death:

The data show that the addition of the WHO FC (III vs I/II) covariate to the treatment only model resulted in a lower treatment effect hazard ratio in both the time to PAH worsening and time to death endpoints up to EOT + 7 days. The hazard ratio for the treatment effect (b.i.d. vs t.i.d.) in the multivariate model (1.17) compared to that for the univariate model (1.44) for time to PAH worsening, and for the time to death endpoint was 1.04 compared to 1.33.

Table 11-6: Multivariate model for Time to death up to EOT + 7 including treatment (b.i.d. vs t.i.d.) and WHO FC (III vs I/II) factors - Analysis set: All-treated set

Model Covariates	HR	95% CL		p-value
Treatment (b.i.d. vs t.i.d.)	1.037	0.283	3.799	0.9559
WHO FC (III vs I/II)	3.48	0.975	12.425	0.0548

b.i.d. = twice daily; CL = confidence limit; FC = functional class; HR = heart rate; t.i.d. = three times daily; WHO = World Health Organization.

For the endpoint, time to death up to EOS, the treatment effect hazard ratio was lower in the multivariate model at 1.49, compared to 1.94 in the univariate model), which in both cases, was in favor of the bosentan t.i.d. group. With the addition of the covariate non-death-related worsening up to EOT + 7 days to the treatment only model, the hazard ratio was lower in the multivariate model at 1.08 compared to 1.94 in the univariate model. It was predicted using the univariate model that subjects who experienced non-fatal worsening prior to EOT + 7 days were over 9 times more likely to die. In addition, subjects randomized to the b.i.d. group were more likely to die than those randomized to the t.i.d. group (24.2% vs 9.7%).
As it was observed that WHO FC and clinical worsening were collinear, it was not considered appropriate to include them together as covariates in a multivariate model.

Table 11-7: Multivariate model for Time to death up to EOS including treatment (b.i.d. vs t.i.d.) and WHO FC (III vs I/II) and worsening up to EOT + 7 as factors - Analysis set: All-treated set

Model	Model Covariates	HR	95% CL		p-value
1	Treatment (b.i.d. vs t.i.d.)	1.487	0.437	5.052	0.5252
	WHO FC (III vs I/II)	4.348	1.348	14.027	0.0139
2	Treatment (b.i.d. vs t.i.d.)	1.084	0.304	3.860	0.9015
	Worsening to EOT + 7 days (Yes/No)	9.439	2.765	32.220	0.0003

b.i.d. = twice daily; CL = confidence limit; EOT = end of treatment; FC = functional class; HR = heart rate; t.i.d. = three times daily; WHO = World Health Organization.

Taken together, these results indicate that the baseline imbalance in the WHO FC status influences the treatment effect on time to PAH worsening and death. Adjusting for this imbalance in these models led to a neutral treatment effect.

Assessor's comment:
Survival estimates were slightly lower in the b.i.d. group than in the t.i.d. group, consistent with the higher rate of PAH worsening in the b.i.d. group (consistently denoted by all relevant clinical changes, i.e., WHO FC, GCIS, and per protocol PAH worsening).

To allow further assessment of these results, the MAH performed post hoc analyses. The KM survival estimate was shown to be lower in the FC III patients (71.4% at Month 12 and 64.3% at Month 18) as compared to the FC I/II sous group of patients (93.2% at Month 12 and 88.1% at Month 18). Furthermore, results from post-hoc Cox proportional hazards model analyses for the time to PAH worsening and time to death up to End of Treatment (EOT) + 7 days and time to death up to End of Study (EOS) (Month 18), showed that the addition of the baseline WHO FC (III vs I/II) covariate to the treatment only model resulted in a lower treatment effect hazard ratio for both endpoints indicating that the baseline imbalance in the WHO FC status influences the treatment effect on time to PAH worsening and subsequent death. Adjusting for this imbalance in these models led to a neutral treatment effect.

It can be agreed with the MAH that a plausible reason for the observed imbalance in disease severity observed at baseline, with a higher proportion of more severely sick patients in the b.i.d. group than in the t.i.d. group (i.e. b.i.d. WHO FC I/II: 63.6%, III: 36.4%; t.i.d. group : WHO FC I/II: 80.6%, III: 19.4%) can explain the lower results and lower rate of survival in the 2 mg/kg b.i.d. group as compared to the 2 mg/kg t.i.d. group. Overall, consistent to the absence of increase in systemic exposure with t.i.d. over b.i.d. dosing these results do not change the recommendation that there is no evidence of increase efficacy with dosing higher than 2 mg/kg b.i.d.

Subgroup analysis of exploratory efficacy according to age

Table 7 **Summary of efficacy data in the age subgroups (< 2 years and ≥ 2 years) in the FUTURE 3 core and its extension study, All-treated set**

	< 2 years (N=21)	≥ 2 years (N=43)
WHO FC* Change from baseline to		
Month 12	Improved: 19% (4/21) Stable: 67% (14/21) Worsened: 14% (3/21)	Improved: 14% (6/43) Stable: 77% (33/43) Worsened: 9 (4/43)
Month 18	Improved: 14% (3/21) Stable: 67% (14/21) Worsened: 19% (4/21)	Improved: 7% (3/43) Stable: 84% (36/43) Worsened: 9% (4/43)
GCIS Change from baseline**		
Physicians´ GCIS: Month 12	Improved: 35% (6/17) Stable: 53% (9/17) Worsened: 12% (2/17)	Improved: 29% (10/34) Stable: 68% (23/34) Worsened: 3% (1/34)
Month 18	Improved: 31% (4/13) Stable: 54% (7/13) Worsened: 15% (2/13)	Improved: 29% (7/24) Stable: 58% (14/24) Worsened: 12% (3/24)
Parents´ GCIS: Month 12	Improved: 53% (9/17) Stable: 41% (7/17) Worsened: 6% (1/17)	Improved: 32% (11/34) Stable: 62% (21/34) Worsened: 6% (2/34)
Month 18	Improved: 38% (5/13) Stable: 46% (6/13) Worsened: 15% (2/13)	Improved: 46% (11/24) Stable: 37% (9/24) Worsened: 17% (4/24)
No. of patients with PAH worsening events		
Occurrence of death, transplantation, or hospitalization for PAH worsening	19% (4/21)	21% (9/43)
Occurrence of death, transplantation, hospitalization for PAH worsening, initiation of new therapy for PAH or new/worsening of right heart failure	24% (5/21)	23% (10/43)
Event-free KM estimate (95% CLs)		
Occurrence of death, transplantation, or hospitalization for PAH worsening:		
Month 12 Month 18	89.5% (64.1%, 97.3%) 78.3% (51.9%, 91.3%)	82.4% (66.5%, 91.2%) 76.9% (60.2%,87.3%)
Occurrence of death, transplantation, hospitalization for PAH worsening, initiation of new therapy for PAH or new/worsening of right heart failure		
Month 12 Month 18	84.2% (58.7%, 94.6%) 73.0% (46.7%, 87.8%)	80.0% (63.9%, 89.5%) 74.6% (57.8%, 85.5%)

CL = confidence limit; FC = functional class; GCIS = global clinical impression scale; KM = Kaplan-Meier; PAH = pulmonary arterial hypertension; WHO = World Health Organization. **Post-hoc* imputation accounting for the worst values substitution.

** Note n is different across the different assessment time points for the observed values, no imputations performed.

Source: D-14.491 Table 15-32, Table 15-34, Table 15-36, Table 15-38, Table 15-42, Table 15-44, and Table 15-48

For WHO FC, the majority of patients remained stable or improved over the FUTURE 3 core and extension study periods in the subgroup of patients aged < 2 years (85.7% at Month 12 and 81.0% at Month 18), and in the subgroup ≥ 2 years (90.7% at Month 12 and 90.7% at Month 18). The GCIS rated both by physicians and parents also showed that the majority of patients were either stable or improved in both subgroups.

The incidence of PAH worsening was consistent in both age groups: 23.8% in < 2 years and 23.3% in ≥ 2 years of age; as well as the KM event-free rate estimates at Month 12 and Month 18, respectively: 84.2% and 73.0% in < 2 years, and 80.0% and 74.6% in ≥ 2 years of age.

Assessor's comment: Based on the presentation of results, patients aged < 2 years showed a similar treatment response to those aged ≥ 2 years suggesting that no specific concern is raised. However, it should be emphasized that the sample size of patients less than 2 years of age is small i.e. 21 children among whom 6 children were less than 1 year (2 b.i.d. and 4 t.i.d.) and 15 children were between 1 to 2 years old at inclusion in the FUTURE 3 study. As already concluded in the initial assessment report in EMEA/H/C/401/II/0066, the sample size is too small to document the benefit/risk in the youngest children for whom concerns are still pending with respect to PK profile different between adults and children.

Safety results

Patient exposure

The final study report (AC-052-374) provides cumulative analysis of data from the FUTURE 3 core study (AC-052-373) and FUTURE 3 extension study. The pooled PAH safety analysis set comprised 64 pediatric patients less than 12 years.

Table 12-1: Summary of exposure to study drug - duration and dose - Analysis set: Safety set

	b.i.d N=33	t.i.d N=31	Total N=64
DURATION:			
Exposure (weeks)			
n	33	31	64
Mean	64.1	60.4	62.3
Standard error	3.38	4.20	2.67
95% CL of mean	57.2 , 71.0	51.9 , 69.0	57.0 , 67.7
Median	72.1	72.6	72.2
Q1 , Q3	62.6 , 75.4	37.3 , 74.9	59.6 , 74.9
Min , Max	6.0 , 90.1	0.4 , 81.1	0.4 , 90.1
Patients exposed* [n (%)]			
n	33	31	64
At least 4 weeks	33 100%	30 96.8%	63 98.4%
At least 8 weeks	32 97.0%	30 96.8%	62 96.9%
At least 12 weeks	32 97.0%	30 96.8%	62 96.9%
At least 16 weeks	32 97.0%	29 93.5%	61 95.3%
At least 20 weeks	31 93.9%	29 93.5%	60 93.8%
At least 24 weeks	31 93.9%	29 93.5%	60 93.8%
At least 28 weeks	31 93.9%	25 80.6%	56 87.5%
At least 32 weeks	29 87.9%	25 80.6%	54 84.4%
At least 36 weeks	29 87.9%	24 77.4%	53 82.8%
At least 40 weeks	29 87.9%	23 74.2%	52 81.3%
At least 44 weeks	29 87.9%	23 74.2%	52 81.3%
At least 48 weeks	27 81.8%	23 74.2%	50 78.1%
At least 52 weeks	26 78.8%	23 74.2%	49 76.6%
At least 56 weeks	26 78.8%	23 74.2%	49 76.6%
At least 60 weeks	25 75.8%	23 74.2%	48 75.0%
At least 64 weeks	23 69.7%	23 74.2%	46 71.9%
At least 68 weeks	23 69.7%	21 67.7%	44 68.8%
At least 72 weeks	19 57.6%	17 54.8%	36 56.3%
At least 76 weeks	7 21.2%	4 12.9%	11 17.2%
At least 80 weeks	1 3.0%	1 3.2%	2 3.1%
DOSE:			
Mean daily dose (mg/kg/day)			
n	33	31	64
Mean	3.7	6.1	4.8
Standard error	0.04	0.67	0.36
95% CL of mean	3.6 , 3.8	4.7 , 7.5	4.1 , 5.6
Median	3.7	5.5	4.0
Q1 , Q3	3.5 , 3.9	5.2 , 5.7	3.7 , 5.5
Min , Max	3.1 , 4.0	4.5 , 26.1	3.1 , 26.1

* Information on exposure is taken from the drug log pages of the CRF.
Some treated patients currently have no drug log records available.
CL=confidence limits.

The median duration of exposure to bosentan treatment in the pooled PAH population was 72.2 weeks (range: 0.4–90.1 weeks).

N= 49 patients (76.6% of patients: 76.8 % b.i.d (n=26). and 74.2% t.i.d.(n= 23) were exposed for at least 52 weeks and N= 36 patients (56.3% patients : 57.6% b.i.d. (n=19), 54.8% t.i.d. (n=17) were exposed for at least 72 weeks

Over the FUTURE 3 and the extension study, the cumulative mean (± SD) exposure duration to bosentan was 64.1 ± 3.38 weeks in the b.i.d. group and 60.4 ± 4.20 weeks in the t.i.d. group.

The mean (± SD) duration of exposure (weeks) to bosentan in patients < 2 years of age (63.3 ± 7.01 b.i.d., 57.1 ± 8.46 t.i.d.) and ≥ 2 years of age (64.5 ± 3.89 b.i.d., 62.3 ± 4.69 t.i.d.) were similar.

The mean daily dose (± SD) was 3.7 ± 0.04 mg/kg/day in the b.i.d. group and 6.1 ± 0.67 mg/kg/day in the t.i.d. group.

Assessor's comment: The final study report (AC-052-374) provides cumulative analysis of data from the FUTURE 3 core study (AC-052-373) and FUTURE 3 extension study which extend the observation period as compared to EMEA/H/C/401/II/006 AR.

Overall AE profile :

In the FUTURE 3 core study, the proportions of patients in the overall population who experienced at least one treatment-emergent AE were 66.7% in the b.i.d. group and 67.7% in the t.i.d. group.

Cumulatively over the FUTURE 3 and the extension study, the proportions were 87.9% in the b.i.d. group and 83.9% in the t.i.d. group.

Cumulatively in the age groups, the proportions were 80.0% (b.i.d.), 81.8% (t.i.d.) in patients < 2 years of age, and 91.3% (b.i.d.), 85.0% (t.i.d.) in patients ≥ 2 years of age.

Upper respiratory tract infection was the most frequently reported AE (FUTURE 3 core: 6 patients [18.2%] b.i.d., 11 patients [35.5%] t.i.d. groups; cumulatively: 9 patients [27.3%] b.i.d.,13 patients [41.9%] t.i.d. group).

Worsening of PAH as AE was reported for a total of 4 patients (6.3%) in the FUTURE 3 core study and for 8 patients (12.5%) cumulatively.

In the FUTURE 3 core study and cumulatively over both studies, pyrexia / increased body temperature (11 patients, 17.2% and 13 patients, 20.3%, respectively), were in many cases associated with AEs of the respiratory tract infections.

The majority of AEs were mild or moderate intensity.

Table 9 **Summary of treatment-emergent adverse events reported up to EOT + 7 days for at least 2 patients overall by frequency - Analysis set: Safety set**

Treatment-emergent adverse events by frequency up to EOT + 7 days
Analysis set: Safety set

System Organ Class / Preferred Term	b.i.d N=33 n	b.i.d N=33 %	t.i.d N=31 n	t.i.d N=31 %	Total N=64 n	Total N=64 %
ALL SYSTEM ORGAN CLASSES						
Total patients with at least one AE	29	87.9%	26	83.9%	55	85.9%
Total number of AEs	129		152		281	
UPPER RESPIRATORY TRACT INFECTION	9	27.3%	13	41.9%	22	34.4%
PYREXIA	5	15.2%	8	25.8%	13	20.3%
NASOPHARYNGITIS	6	18.2%	5	16.1%	11	17.2%
VOMITING	4	12.1%	6	19.4%	10	15.6%
DIARRHOEA	2	6.1%	6	19.4%	8	12.5%
PULMONARY ARTERIAL HYPERTENSION	6	18.2%	2	6.5%	8	12.5%
VIRAL UPPER RESPIRATORY TRACT INFECTION	5	15.2%	3	9.7%	8	12.5%
COUGH	4	12.1%	3	9.7%	7	10.9%
GASTROENTERITIS	3	9.1%	4	12.9%	7	10.9%
BRONCHITIS	4	12.1%	2	6.5%	6	9.4%
PNEUMONIA	1	3.0%	4	12.9%	5	7.8%
CONSTIPATION	1	3.0%	3	9.7%	4	6.3%
EPISTAXIS	1	3.0%	3	9.7%	4	6.3%
VIRAL INFECTION	2	6.1%	2	6.5%	4	6.3%
ABDOMINAL PAIN	1	3.0%	2	6.5%	3	4.7%
BLOOD BILIRUBIN INCREASED	2	6.1%	1	3.2%	3	4.7%
BRONCHOPNEUMONIA	1	3.0%	2	6.5%	3	4.7%
LOWER RESPIRATORY TRACT INFECTION	1	3.0%	2	6.5%	3	4.7%
OTITIS MEDIA	2	6.1%	1	3.2%	3	4.7%
RASH	1	3.0%	2	6.5%	3	4.7%
RESPIRATORY TRACT INFECTION	2	6.1%	1	3.2%	3	4.7%
RESPIRATORY TRACT INFECTION VIRAL	1	3.0%	2	6.5%	3	4.7%
RHINORRHOEA	3	9.1%			3	4.7%
SYNCOPE	2	6.1%	1	3.2%	3	4.7%
ACCIDENTAL OVERDOSE			2	6.5%	2	3.1%
ARTHRALGIA	1	3.0%	1	3.2%	2	3.1%
BLOOD GLUCOSE INCREASED	1	3.0%	1	3.2%	2	3.1%
CARDIOPULMONARY FAILURE	1	3.0%	1	3.2%	2	3.1%
DERMATITIS ALLERGIC			2	6.5%	2	3.1%
EAR INFECTION	2	6.1%			2	3.1%
FLUSHING			2	6.5%	2	3.1%
GASTROINTESTINAL VIRAL INFECTION	1	3.0%	1	3.2%	2	3.1%
HEADACHE	1	3.0%	1	3.2%	2	3.1%
INFLUENZA			2	6.5%	2	3.1%
LARYNGITIS	2	6.1%			2	3.1%
LIVER FUNCTION TEST ABNORMAL			2	6.5%	2	3.1%
N-TERMINAL PROHORMONE BRAIN NATRIURETIC PEPTIDE INCREASED	1	3.0%	1	3.2%	2	3.1%
NASAL CONGESTION			2	6.5%	2	3.1%
OEDEMA PERIPHERAL	2	6.1%			2	3.1%
OTITIS MEDIA CHRONIC	2	6.1%			2	3.1%
OXYGEN SATURATION DECREASED			2	6.5%	2	3.1%
PHARYNGITIS	2	6.1%			2	3.1%
RHINITIS			2	6.5%	2	3.1%
SEASONAL ALLERGY			2	6.5%	2	3.1%
THROMBOCYTOPENIA	2	6.1%			2	3.1%
TONSILLITIS			2	6.5%	2	3.1%
TOOTH EXTRACTION	1	3.0%	1	3.2%	2	3.1%
URTICARIA			2	6.5%	2	3.1%

A patient having experienced the same event (preferred term) more than once is counted only once for that AE.
AE = adverse event

Assessor's comment: Overall, the nature of AEs reported during the FUTURE 3 extension study were consistent with those reported during the FUTURE 3 core study. It is agreed with the MAH that the increased incidences of AEs reported cumulatively over both studies compared to FUTURE 3 core study alone, are a reflection of the longer observation period during the extension study (approximately 2 times longer compared to FUTURE 3 core study) in these children. Respiratory tract infection is the most frequently reported adverse events with a slightly higher rate in the t.i.d. as compared to b.i.d.

Deaths:

The MAH states that the analysis of deaths in the pooled PAH safety set included all those that occurred up to 18 months.

Over the cumulative FUTURE 3 and extension study periods, a total of 12 deaths (18.8%) were reported (10 within and 2 beyond EOT + 7 days), 3 of which occurred during the FUTURE 3 core study and 9 occurred during the extension study. Death was reported in 8 patients 24.2% in the b.i.d. group and 4 patients, 12.9% in the t.i.d. group.

Table 10 Summary of all deaths - Analysis set: Safety set

Cause of death	b.i.d N=33 No.	%	t.i.d N=31 No.	%	Total N=64 No.	%
Total patients with at least one cause	8	24.2%	4	12.9%	12	18.8%
PULMONARY ARTERIAL HYPERTENSION	4	12.1%	2	6.5%	6	9.4%
CARDIOPULMONARY FAILURE	1	3.0%	1	3.2%	2	3.1%
PNEUMONIA	1	3.0%	1	3.2%	2	3.1%
BRONCHOPNEUMONIA	-		1	3.2%	1	1.6%
CARDIAC FAILURE ACUTE	-		1	3.2%	1	1.6%
DEATH	1	3.0%	-		1	1.6%
METABOLIC DISORDER	1	3.0%	-		1	1.6%
MUCOPOLYSACCHARIDOSIS	-		1	3.2%	1	1.6%
MULTI-ORGAN FAILURE	1	3.0%	-		1	1.6%
PULMONARY EMBOLISM	1	3.0%	-		1	1.6%

The causes of death [Table 10] 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 reported in individual 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 2 deaths that occurred during the long-term follow-up period, one was due to worsening of the underlying disease and one resulted from multi-organ failure related to unspecified congenital metabolic disease.All deaths occurred in the context of underlying disease worsening, cardiopulmonary disorders, and infections and none were a consequence of hepatobiliary events, anemia or edema.

Of the 12 patients who died, 4 patients were < 2 years of age and 8 patients were ≥ 2 years of age.

Assessor's comment: it can be agreed with the MAH that the numerical difference in deaths in the b.i.d. (8 patients 24.2%) and t.i.d. groups (4 patients, 12.9%) reflected the difference in disease severity at baseline concurring to the post-hoc survival analysis models described above.

Serious adverse events (SAEs)

Cumulatively, 28 patients (43.8%) experienced at least one serious adverse events (SAEs), 4 of whom experienced SAEs during both the FUTURE 3 core and the extension study.

Of the 28 patients with SAEs, 12 (57.1%, 4 b.i.d., 8 t.i.d.) were < 2 years of age and 16 (37.2%, 11 b.i.d., 5 t.i.d.) were ≥ 2 years of age.

The most frequently reported SAE was worsening of PAH, reported as the PTs PAH (9.4%) and associated events of cardiopulmonary failure and syncope (3.1% each).

Other frequently reported SAEs were pneumonia (6.3%) and broncho-pneumonia (3.1%), while the remaining events were single PT occurrences.

SAEs associated with cardiac disorders (other than cardiopulmonary failure) included cardiac arrest, cardiac failure, acute cardiac failure, and cyanosis (1 patient each).

Overall, infections, respiratory disorders, and cardiac disorders were the most frequently reported SAEs (within respective System organ class [SOC]), accounting for approximately half of the observed SAEs (20.3%, 17.2% and 9.4%, respectively).

There were no SAEs denoting anemia / hemoglobin decrease, liver abnormality or edema.

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

AEs leading to discontinuation of treatment

A total of 12 patients (18.8%; 7 b.i.d., 5 t.i.d.) had at least one AE that resulted in discontinuation of study treatment, 3 during the FUTURE 3 core and 9 during the extension study.

Of the 12 patients who prematurely discontinued study treatment, 4 were < 2 years of age and 8 were ≥ 2 years of age.

The AEs leading to discontinuation of treatment were also reported as SAEs for 10 patients, most frequently worsening of PAH (n = 4) with other reasons being cardiopulmonary failure, liver abnormalities, and pneumonia (2 patients each). The two AEs that were non-serious were both abnormal liver tests (2 patients). (see below for discussion on liver abnormality).

Safety topics of special interest:

Anemia/hemoglobin decrease:

Cumulatively, 6 patients experienced marked decreases in hemoglobin values to < 10 g/dL (4 b.i.d., 2 t.i.d.), all ≥ 2 years, No patients had decreases in hemoglobin to values < 8 g/dL.

Liver abnormalities:
Three AEs of elevated aminotransferases were reported for 2 patients (both t.i.d. and ≥ 2 years of age). In one patient, the AE was associated with an increase in alanine aminotransferase (ALT) to 6 × upper limit of normal (ULN) after 5.5 months of treatment. In the second patient, the increase was less pronounced (2.3 × ULN, after 4.7 months of treatment) but reoccurred after study drug restart following an interruption of 7 weeks. These events ultimately led to treatment discontinuation, and resolved 4 weeks later.

3 patients had AEs of isolated/intermittent hyperbilirubinemia (2 b.i.d., 1 t.i.d.; 2 patients ≥ 2 years and 1 patient < 2 years of age), none of which was associated with an aminotransferase increase or other hepatic event.

All events resolved and none resulted in study drug discontinuation. It should be noted that one of the patients had Gilbert's disease and had elevated total bilirubin (TBIL) at baseline. Intermittent TBIL

elevations were reported during study treatment, but none were clinically relevant (> 2 × ULN), and none exceeded the baseline value. In addition, one of the other 2 patients had been on commercial bosentan for 6.5 years prior to the study start and had a negative rechallenge following interruption of bosentan due to the elevation in TBIL.
None of the liver abnormality AEs were reported as SAEs.
There were no cases of ALT or aspartate aminotransferase (AST) elevations > 3 × ULN with concomitant TBIL > 2 × ULN and AP ≤ 2 × ULN, and there were no new cases of ALT and/or AST > 3 × ULN during the FUTURE 3 extension study.

Oedema

Peripheral edema was reported in 2 patients (1 each in the FUTURE core and in the extension study, both b.i.d.), one in the context of PAH progression leading to death and the other an ongoing event (generalized edema reported in the medical history), resolving on diuretic therapy.

Intrinsec 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: 81.0% and 88.4%, respectively.
Infections were the most frequently reported AEs in both age groups (SOC: infections and infestations), 76.2% and 69.8%, respectively.

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.
It is of note that no AEs of special interest were observed in patients aged < 2 years, except for one AE of increased bilirubin, and this was not associated with an aminotransferase increase.
No notable differences were observed between the age groups for the change (shift) in height/length z-scores.

Sex:

No clinically relevant influence of sex on exposure to bosentan has been observed in PK studies in adults, particularly when corrected for body weight. Other processes commonly causing sex-related differences generally result from post-pubertal effects, none of which are considered of relevance in the population included in the pooled PAH safety analysis set of predominantly pre-pubertal children. Therefore, no subgroup analysis by sex was performed.

Race/ethnicity
In the pooled PAH safety analysis, the vast majority (75%) of the patients were Caucasian. Of the remaining patients, 15.6% were Asian, 4.7% were Black, 1.6% were Hispanic, and 3.1% were 'Other'. 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
In the pooled PAH safety analysis, no detrimental growth effect was observed based on height Z-scores groups. 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.

Extrinsic factors
Dose frequency (t.i.d. vs b.i.d.)
No clinically relevant differences were apparent in the safety profiles of the two dose regimens.

2.3.3. Discussion on clinical aspects

The new data from the 12 months FUTURE 3 extension study of the 6 month open label FUTURE 3 core study provided further safety and exploratory efficacy evaluation of longer-term outcomes with the 2 mg/kg b.i.d. and 2 mg/kg t.i.d. dosings in PAH children less than 12 years. The results from the open labelled 6 month FUTURE 3 core study was assessed in the EMEA/H/C/401/II/066 AR (CHMP final opinion on November 2014).
58 of the 64 patients (91%) initially included in the FUTURE 3 core study were included in the FUTURE 3 extension.

Over the FUTURE 3 and the extension study, the cumulative mean exposure was 62.3 ± 2.67 weeks, similar in the b.i.d. and t.i.d. groups (64.1 ± 3.38 weeks and 60.4 ± 4.20 weeks, respectively). The median duration of exposure was 72 weeks with 36 patients/64 (n=19 patients from the b.i.d. group and n= 17 patients from the t.i.d.) who were exposed at least 72 weeks (18 months).

On safety grounds, in line with the longer observation period, the proportions in the overall population who experienced at least one treatment-emergent AE was increased in the cumulative analysis over the FUTURE 3 and the extension study (87.9% in the b.i.d. group and 83.9% in the t.i.d. group as compared 66.7% in the b.i.d. group and 67.7% in the t.i.d. group in the FUTURE 3 core study).

The nature of the AEs observed remained consistent with those reported in the core FUTURE 3 study and with that generally seen adults.

Cumulatively, 43.8% of patients (28 patients) experienced SAEs of which the vast majority was associated with cardiopulmonary disorders and infections. Of the 28 patients with SAEs, 12 (57.1%, 4 b.i.d., 8 t.i.d.) were < 2 years of age and 16 (37.2%, 11 b.i.d., 5 t.i.d.) were ≥ 2 years of age.

Respiratory tract infections, particularly the upper respiratory tract infection, was the most frequently reported AE (with a slightly higher rate in t.i.d. as compared to b.i.d.)
The MAH considers that this was not surprising as the respiratory tract infections are the most common causes of morbidity and mortality in children under age of 5. It is probable that this explanation would be plausible, but as emphasizes in the EMEA/H/C/401/II/066 AR, this study was not placebo (nor other PAH-medication) controlled precluding confirmation that a specific effect of bosentan could be formally excluded. The risk of respiratory tract infections was therefore added as potential risk in the RMP.

No patients had decreases in hemoglobin to values < 80 g/L. There were no new cases in the number of patients who experienced marked decrease in platelets (LLL, i.e., < 50 × 109/L) and no new cases of ALT and/or AST > 3 × ULN during the FUTURE 3 extension study.
There were no cases of ALT or AST elevations > 3 × ULN with total bilirubin > 2 × ULN and alkaline phosphatase ≤ 2 × ULN altogether in the cumulative reporting period.

In terms of AEs of special interest for bosentan (anemia / decreased hemoglobin, liver abnormalities, and edema), there was no indication that children exposed beyond 1 year of treatment are at a higher risk than adults of either experiencing such an event or experiencing such an event more severely. Cumulatively in the age groups, the proportions of patients with AEs were 80.0% (b.i.d.), 81.8% (t.i.d.) in patients < 2 years of age, and 91.3% (b.i.d.), 85.0% (t.i.d.) in patients ≥ 2 years of age. There is no indication that would suggest a higher rate of adverse effects in children less than 2 years as compared to > 2 years but rather some slight higher rate in children > 2 years. However, no reliable conclusion can be drawn as the sample size is limited as only 21 children less than 2 years were included in the FUTURE 3 study with 6 children less than 1 year and 15 children between 1 to 2 years old.

Cumulatively over the FUTURE 3 and the extension study, a total of 12 deaths (18.8%) were reported (10 within and 2 beyond EOT + 7 days). All deaths occurred in the context of underlying disease worsening, cardiopulmonary disorders, and infections and none were a consequence of hepatobiliary events, anemia or edema. It can be agreed that the numerical difference of deaths in the b.i.d. (8 patients 24.2%) and t.i.d. groups (4 patients, 12.9%) reflected the difference in disease severity at baseline, further confirmed by the post-hoc survival analysis models see below.

In the pooled PAH analysis set, the overall number of patients who had decreases in hemoglobin concentrations to < 10 g/dL was 6 (9.4%), and there were no cases of decreases to < 8 g/dL. In the subset of patients aged < 2 years, no cases of decreased hemoglobin were reported. One patient had a

treatment emergent aminotransferase elevation of > 3 × ULN, but it was not associated with elevated bilirubin. Three patients had isolated events of increased bilirubin, none of which was associated with an aminotransferase increase or other hepatic event. Cases of edema were reported for 2 (3.1%) of the pediatric population, and no cases of fluid retention were reported.

On efficacy grounds:
All efficacy analyses were of exploratory nature in the open-label 6 month FUTURE 3 core study and the 12 month extension.
The exploratory efficacy results showed that the greater proportion of patients remained stable or improved during the study on the basis of WHO FC (without change in WHO FC from baseline up to Month 18: 78.1%) and GCIS (parent- and investigator-rated).
However, the proper effect of bosentan is difficult to assess as more than half of them receiving combined PAH-specific medications (PDE-5 inhibitors and/or prostanoids) at entry. To be included in FUTURE 3 extension, patients were required to have tolerated treatment with the bosentan dispersible tablet formulation during the FUTURE 3 core study and were considered by the investigator to benefit from continued bosentan treatment. As discussed in the initial assessment report EMEA/H/C/401/II/066, 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 PAH therapy.

PAH condition deteriorates more frequently in the b.i.d. group as compared to the t.i.d. group. At Month 18, WHO FC deteriorates in 15.2% (b.i.d.) vs 9.7% (t.i.d.) of patients. This was also observed on CGSI. Cumulatively, death, lung transplantation, hospitalization for PAH-progression, or initiation of new therapy for PAH or new/worsening right heart failure was reported more frequently in the b.i.d. group as compared to t.i.d. group: 30.3 % (b.i.d.) vs 16.1 % (t.i.d.). Consistently denoted by all relevant clinical changes, i.e., WHO FC, GCIS, and per protocol PAH worsening, survival estimates were slightly lower in the b.i.d. group than in the t.i.d. group.
It can be agreed with the MAH that a plausible reason for the observed imbalance in disease severity observed at baseline, with a higher proportion of more severely sick 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%) can explain the lower rate of survival in the 2 mg/kg b.i.d. group as compared to the 2 mg/kg t.i.d. group. Post hoc analyses performed by the MAH showed that the addition of the baseline WHO FC (III vs I/II) covariate to the treatment only model resulted in a lower treatment effect hazard ratio for PAH worsening and time to death indicating that the baseline imbalance in the WHO FC status influences the treatment effect on both endpoints. Adjusting for this imbalance in these models led to a neutral treatment effect. Overall, these results do not allow to conclude that 2 mg/kg t.i.d. improved the efficacy of bosentan.
Consistent with the PK data from 6 month FUTURE 3 core study (see EMEA/H/C401/II/066 AR) that showed that the alternative approach of increasing the frequency of dosing to 2 mg/kg t.i.d. did not result in greater exposure than was achieved using the 2 mg/kg b.i.d. regimen as confirmed with PK data, there is no reliable indication from this study that would change the recommendation that there is no evidence of increase efficacy with dosing higher than 2 mg/kg b.i.d. in children.

Similar efficacy results were observed across both age groups (< 2 years and ≥ 2 years). However, as clarified in EMEA/H/C/401/II/066, only 21 children less than 2 years were included in the FUTURE 3 study with 6 children less than 1 year (2 b.i.d. and 4 t.i.d.) and 15 children were between 1 to 2 years old. This reflected the current practice for diagnosis of PAH. However, this limited sample of patients doesn't help to document the benefit/risk in the youngest children for whom concerns are raised with respect to PK profile different between adults and children.

3. Rapporteur's overall conclusion and recommendation

Consistent with the PK data showing that higher systemic exposure could not be reached with higher than 2 mg/kg b.i.d. per day dosing in children, there was no evidence of efficacy or safety differences between the two regimen 2 mg/kg b.i.d. or 2 mg/kg t.i.d. from the longer term cumulative analysis of FUTURE-3 core and extension data.

There is no evidence that the current recommendation that no benefit has been evidenced with higher than 2 mg/kg b.i.d. should be changed.

The data submitted do not change the benefit-risk balance for TRACLEER as initially assessed therefore do not require further regulatory action on the marketing authorisation to be taken.

It is reminded that as part of procedure EMEA/H/C/00401/II/0066, Actelion agreed to undertake the post Approval Measure requested by the CHMP, and commits to submit the report on the echocardiographic change analysis performed in FUTURE 3 study in relation to the long-term clinical outcomes at the end of FUTURE 3 extension study (overall 18 months observation period) in June 2015.

4. Additional clarification requested

None