London, 20 August 2015
EMA/554571/2015
Committee for Medicinal Products for Human Use (CHMP)

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006, as amended

Tracleer

International non-proprietary name: Bosentan

Procedure no.: EMA/H/C/000401/P46

Note

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

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7418 8613
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

Administrative information

Rapporteur's contact person:	**Name: Marie COULON** Tel: +33 1 55 87 38 71 Email: marie.coulon@ansm.sante.fr
Name of the Assessor:	**Name: Benjamin BURRUS** Email: benjamin.burrus@ansm.sante.fr
Procedure Manager:	**Name: Anne-Marie van Nederkassel** Email: Anne-Marie.Vannederkassel@ema.europa.eu

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1. Introduction

On 04/06/2015, the MAH submitted the final study report FUTURE 4 extension (AC-052-392), 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 has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that *FUTURE 4 Extension (*Study AC-052-392): *Multicenter, non-drug-interventional extension study to assess long-term safety and effects on growth in patients who received bosentan or placebo as adjunctive therapy to inhaled nitric oxide (iNO) for persistent pulmonary hypertension of the newborn (PPHN) in FUTURE 4 ((AC-052-391),* is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

FUTURE 4 Extension was a non-drug-interventional study.

During the core study FUTURE 4, 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 FUTURE 4 pediatric studies in PPHN patients was conducted as part of the PIP:

- FUTURE 4 study (AC-052-391): 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." (FUTURE 4).
- FUTURE 4-extension study (AC-052-392): Multicenter, non-drug-interventional extension study to assess long-term safety and effects on growth in patients who received bosentan or placebo as adjunctive therapy to iNO for PPHN in FUTURE 4 (FUTURE 4 Extension).

Background:

Core FUTURE 4 (AC-052-391) was submitted as part of a Type II variation in April 2014 (EMEA/H/C/000401/II/0066). 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.

FUTURE 4 (AC-052-391) was the 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.

Subjects with persistent pulmonary hypertension of the newborn (PPHN) had been treated in the FUTURE 4 core study for a maximum of 10 days with bosentan (2 mg/kg body weight twice a day [b.i.d.]) or placebo as adjunctive treatment to inhaled nitric oxide (iNO) therapy. Results of the FUTURE 4 core study did not indicate additional benefit of an endothelin receptor antagonist in this setting. 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). The median age (days, 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 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. 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.

The MAH now submits a final report(s) for:

- FUTURE 4 Extension (AC-052-392);

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

2.3.2. Clinical study

FUTURE 4 Extension (AC-052-392)

Description

Methods

Objectives

To assess long-term safety and effects on growth in subjects who received bosentan or placebo in the FUTURE 4 core study

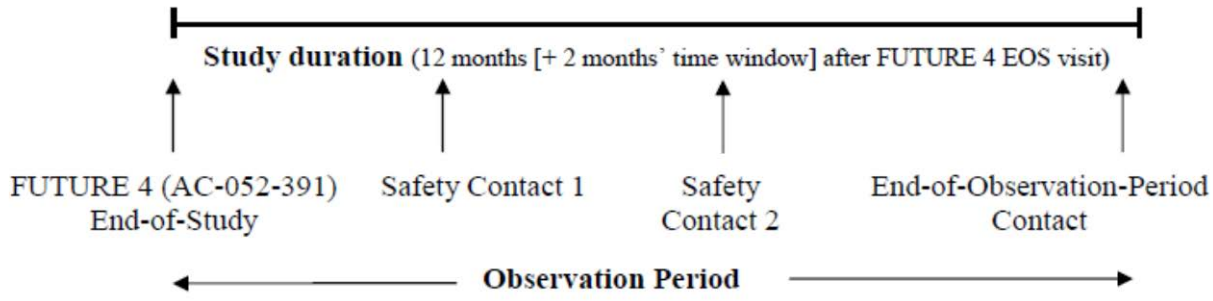
Study design

This was a multi-center, non-drug-interventional, exploratory, Phase 3, extension study, which enrolled the subjects from the FUTURE 4 core study who had received at least one dose of study drug (bosentan 2 mg/kg twice a day [b.i.d.] dispersible tablet formulation or matching placebo).

The enrollment in FUTURE 4 extension study was performed after the FUTURE 4 core End-of-Study (EOS) visit and within 6 months after approval of the FUTURE 4 study extension protocol at the respective study site. The observation period for all subjects enrolled into the FUTURE 4 extension study started from the FUTURE 4 core EOS and lasted up to 12 months (+ 2 months' time window) thereafter. The observation period concluded with an End-of-observation period (EoOP) assessment visit, which included collection of growth variables.

At Month 4 (± 1 month) and at Month 8 (± 1 month) after the FUTURE 4 core EOS, subjects were either brought to the site or the investigator contacted the health professional (e.g., pediatrician) taking care of the subject to record AEs or SAEs (if any), and to collect other data (i.e., bosentan administration).

Figure 9-1 Study design



For prospective data collection safety contacts (either site visit or telephone contact between investigator and health professional taking care of the subject) were conducted at 4 and 8 months (± 1 month) after EOS visit of FUTURE 4.
EOS = End-of-Study.

CHMP's comment:

Actelion and the investigator remained blinded to the treatments administered in the FUTURE 4 core study until the closure of the FUTURE 4 core study database i.e. before the end of FUTURE 4 extension.

Study population /Sample size

The study included male and female subjects who had received at least one dose of study drug (bosentan 2 mg/kg b.i.d. dispersible tablet formulation or matching placebo) in the FUTURE 4 core study. Subjects treated in the FUTURE 4 core study were term or near-term newborns (gestational age > 34 weeks) between ≥ 12 h and < 7 days of age with idiopathic PPHN (100% bosentan, 62.5% n=5 placebo) or PPHN secondary to parenchymal lung diseases (n= 3 patients placebo) with no or insufficient response to inhaled nitric oxide (iNO) therapy.

CHMP's comment:

The median exposure (days, min–max) in FUTURE 4 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.

Treatments

No study drug was administered.

Outcomes/endpoints

The safety endpoints of the study were the following:

- Serious adverse events (SAEs) occurring more than 60 days after the End-of-Treatment (EOT) in the FUTURE 4 core study and up to EoOP.
- Non-serious adverse events (AEs) occurring during the observation period (i.e., from EOS of FUTURE 4 core study and up to EoOP).
- Change from baseline (birth weight and length) to EoOP in growth variables (i.e., weight and length).

Statistical Methods

There was no hypothesis testing and all statistical analyses were descriptive in nature.

Results

Recruitment/ Number analysed

Of the 23 randomised neonates, 21 patients received the study drug, 20 (12 bosentan, 8 placebo) completed the study treatment.

In total, 15 of the 21 subjects treated in the FUTURE 4 core study were enrolled into the FUTURE 4 extension study; 6 were not enrolled due to refusal or inability to participate (n = 5) or lost contact (n = 1).

All 15 subjects enrolled into the FUTURE 4 extension study completed the 12-month observation period.

Baseline data

Of the 21 subjects treated in the FUTURE 4 core study, 20 were successfully weaned from iNO at study completion (i.e., EOS); 1 subject was on extra-corporeal membrane oxygenation but recovered within 60 days. 15 of these 21 subjects entered the extension study.

In these 15 subjects (7 ex-bosentan, 8 ex-placebo), median gestational age (median, min-max) was 41 weeks (37.0-41.0 weeks) in the ex-bosentan group and 38.5 weeks (36.0-42.0 weeks) in the ex-placebo group. The median age (days, min-max) at first dosing with the study treatment was 1.1 days (0.6-2.6 days) in the ex-bosentan group and 1.7 days, (0.6-5.9 days) in the ex-placebo group.

Median baseline oxygenation index (OI) (min-max) for the 21 subjects of the FUTURE 4 core study indicated that the disease condition was more severe in the bosentan group (OI=18.3 [5.9-44.3]) than in the placebo group (OI=13.2 [7.1-39.4]). However, in the 15 subjects who entered the extension

study, median baseline OI values (min-max) were similar in the ex-bosentan (14.0 [7.6, 37.8]) and ex-placebo groups (13.2 [7.1, 39.4]).

Table 2 Overview of the demographic and background characteristics of the FUTURE 4 extension safety analysis set

	Ex-Bosentan N=7	Ex-Placebo N=8	All patients N=15
GESTATIONAL AGE (weeks)			
n	7	8	15
Mean	39.9	38.6	39.2
Standard deviation	1.57	2.00	1.86
Median	41.0	38.5	39.0
Q1 , Q3	39.0 , 41.0	37.0 , 40.0	37.0 , 41.0
Min , Max	37.0 , 41.0	36.0 , 42.0	36.0 , 42.0
PPHN etiology [n (%)]*			
n	7	8	15
Idiopathic	-	3 37.5%	3 20.0%
Due to parenchymal lung disease	7 100%	5 62.5%	12 80.0%
NEONATAL ASPIRATION	6 85.7%	3 37.5%	9 60.0%
NEONATAL RESPIRATORY DISTRESS SYNDROME	2 28.6%	-	2 13.3%
PNEUMONIA	-	2 25.0%	2 13.3%
SEPSIS	-	1 12.5%	1 6.7%
AGE at 1st dosing (days)			
n	7	8	15
Mean	1.3	2.2	1.7
Standard deviation	0.65	1.64	1.32
Median	1.1	1.7	1.3
Q1 , Q3	0.9 , 1.5	1.3 , 2.5	1.0 , 2.3
Min , Max	0.6 , 2.6	0.6 , 5.9	0.6 , 5.9
SEX [n (%)]			
n	7	8	15
Males	3 42.9%	2 25.0%	5 33.3%
Females	4 57.1%	6 75.0%	10 66.7%
CRF BIRTH WEIGHT (kg)			
n	7	8	15
Mean	3.39	3.20	3.29
Standard deviation	0.556	0.445	0.491
Median	3.20	3.10	3.15
Q1 , Q3	2.90 , 4.02	2.91 , 3.31	2.90 , 3.78
Min , Max	2.84 , 4.09	2.80 , 4.20	2.80 , 4.20
BIRTH LENGTH (cm)			
n	5	6	11
Mean	55.20	52.63	53.80
Standard deviation	3.347	4.734	4.181
Median	54.00	50.40	53.00
Q1 , Q3	53.00 , 55.00	50.00 , 53.00	50.00 , 55.00
Min , Max	53.00 , 61.00	50.00 , 62.00	50.00 , 62.00
RACE [n (%)]			
n	7	8	15
Caucasian/white	5 71.4%	6 75.0%	11 73.3%
Asian	1 14.3%	-	1 6.7%
Hispanic	1 14.3%	1 12.5%	2 13.3%
Other	-	1 12.5%	1 6.7%
Baseline OI			
n	7	8	15
Mean	21.2	17.3	19.1
Standard deviation	13.79	11.37	12.25
Median	14.0	13.2	14.0
Q1 , Q3	8.2 , 35.4	8.5 , 24.2	8.2 , 34.0
Min , Max	7.6 , 37.8	7.1 , 39.4	7.1 , 39.4

* conditions leading to parenchymal lung disease are not mutually exclusive
CRF: Case report form; OI: Oxygenation index; PPHN: Persistent pulmonary hypertension of the newborn
Source: D-14.580, Table 15-3

Efficacy results

Not applicable

Growth curves

Subjects' growth curves (length and weight) remained within 5th to 95th WHO growth percentiles, which indicated sustained growth.

Safety results

Overall adverse event profile:

The FUTURE 4 extension study protocol allowed prospective and retrospective data collection: 7 subjects were enrolled within the observation period (i.e., within 12 + 2 months after FUTURE 4 core EOS) and had both prospective and retrospective data. In 8 subjects, enrollment was after the end of observation period, and thus data obtained were fully retrospective.

A total of 8 subjects (4 each, ex-bosentan and ex-placebo) experienced AEs during the 12-month (+ 2 months) observation period (i.e., from FUTURE 4 core EOS up to FUTURE 4 extension end of observation period) [Table 3]. Overall, AEs reported were of the nature that was expected for infants. Respiratory infections were the most frequently reported AEs, whose incidence was similar in the ex-bosentan and ex-placebo groups (3 subjects, each).

In the ex-bosentan group, 4 subjects experienced AEs. Upper respiratory tract infection was reported in 2 subjects. 1 of these subjects also experienced urinary tract infection and anemia. Bronchitis and ear infection was reported in 1 subject each.

In the ex-placebo group, 4 subjects experienced AEs. 1 subject who simultaneously experienced respiratory tract infection and wheezing also experienced vomiting, had rash and was further reported with viral gastroenteritis and tonsillitis without any temporal association to the earlier infections. 1 subject who experienced bronchitis was also reported with constipation, seborrhea, alopecia, gastroesophagal reflux disease and diaper dermatitis. 1 subject experienced croup infection and had a scar on the right heel. 1 subject experienced positional plagiocephaly.

Anemia in 1 subject was assessed by the investigator as unrelated to previous bosentan administration. All AEs resolved except anemia, scar and positional plagiocephaly.

Table 3 Summary of treatment-emergent adverse events, FUTURE 4 extension safety analysis set

Preferred Term	Ex-Bosentan N=7		Ex-Placebo N=8	
	N	%	N	%
ALL SYSTEM ORGAN CLASSES				
Total subjects with at least one AE	4	57.1%	4	50.0%
Total number of AEs	6		15	
Upper Respiratory Tract Infection	2	28.6%	-	
Bronchitis	1	14.3%	1	12.5%
Respiratory Tract Infection Viral	-		1	12.5%
Croup Infectious	-		1	12.5%
Tonsillitis	-		1	12.5%
Ear Infection	1	14.3%	-	
Urinary Tract Infection	1	14.3%	-	
Gastroenteritis Viral	-		1	12.5%
Anaemia	1	14.3%	-	
Alopecia	-		1	12.5%
Constipation	-		1	12.5%
Dermatitis Diaper	-		1	12.5%
Gastrooesophageal Reflux Disease	-		1	12.5%
Positional Plagiocephaly	-		1	12.5%
Rash	-		1	12.5%
Scar	-		1	12.5%
Serborrhoea	-		1	12.5%
Vomiting	-		1	12.5%
Wheezing	-		1	12.5%

Source: D-14.580, appendix 16.2.7.2

Death and other serious adverse events:

No deaths occurred during the observational period and there were no serious adverse events (SAEs) reported. The vital status of the 6 subjects who did not participate in this study is also known: 4 subjects are alive and 2 subjects have no death records in a publicly available registry.

Safety topics of special interest:

AEs known to be associated with bosentan treatment, such as abnormal liver tests data, anemia or edema, are not expected to occur once the treatment is terminated and the drug is eliminated from the body. In the FUTURE 4 extension study, mild anemia was reported 7 months after discontinuation of bosentan treatment, following repetitive infections. However, the AE was considered by the investigator as unrelated to the study drug.

Safety topics of special interest:

The change from baseline to end of observation period in growth variables (i.e., weight and length) did not indicate any apparent difference between ex-bosentan and ex-placebo subjects. Overall subject

growth curves (length and weight) remained within 5th to 95th WHO growth percentiles, which indicated sustained growth.

CHMP comment:

Results of this extension phase study did not raised any new safety concern.

2.3.3. Discussion on clinical aspects

Bosentan is not indicated in PPHN and the development of bosentan in PPHN is no longer ongoing due to lack of benefit in this population. The results from the 12 months observational period of the FUTURE 4 extension study, though with limitations, did not suggest safety concerns or growth impairment during a 1-year follow-up.

3. Rapporteur's overall conclusion and recommendation

In the variation EMEA/H/C/000401/II/0066 assessing the study reports of FUTURE 3 and FUTURE 4, it was concluded that Tracleer PIP could be considered fulfilled.

☒ **Fulfilled:**

No regulatory action required.

☐ **Not fulfilled:**

4. Additional clarification requested

None

Annex

Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Non clinical studies

Product Name: Active substance:

Study title	Study number	Date of completion	Date of submission of final study report

Clinical studies

Product Name: Active substance:

Study title	Study number	Date of completion	Date of submission of final study report
FUTURE 3	AC-052-373	February 2015	April 2014 (please see variation II/66)
FUTURE 4	AC-052-391	26/02/2014	April 2014 (please see variation II/66)
FUTURE 3 extension	AC-052-374	03/02/2015	March 2015 (please see CHMP assessment
FUTURE 4 extension	AC-052-392	May 2015	June 2015