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FUTURE-2: Results from an open-label, long-term safety and tolerability extension study using the pediatric FormUlation of bosenTan in pUlmonary arterial hypeRtEnsion

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ABSTRACT

Background: A novel formulation of bosentan was evaluated in children with pulmonary arterial hypertension (PAH) in FUTURE-1, which characterized its pharmacokinetic and clinical profile. The subsequent phase III, open-label, long-term extension study, FUTURE-2, aimed to provide long-term tolerability, safety and exploratory efficacy data.

Methods: Children (≥2 and <12 years) with idiopathic or heritable PAH, who completed 12-week treatment in FUTURE-1 and for whom bosentan was considered beneficial were enrolled, and continued to receive bosentan 4 mg/kg twice-daily, which could be down-titrated to 2 mg/kg if not tolerated. Safety and tolerability were evaluated via treatment-emergent adverse events (AEs), serious AEs, growth, and laboratory measurements. Exploratory efficacy endpoints included time to PAH worsening and long-term survival. All analyses were conducted on pooled data of both studies.

Results: 36 patients were enrolled in FUTURE-1 and 33 continued in FUTURE-2. The overall median duration of exposure to bosentan was 27.7 (range 1.9–59.6) months. Treatment-emergent AEs occurred in 32 (88.9%) patients; AEs considered treatment-related in 15 (41.7%) patients. Of 51 serious AEs, three were considered treatment-related: two incidences of reported PAH worsening and one of autoimmune hepatitis. Six deaths occurred; none were considered treatment-related. Kaplan–Meier event-free estimates of PAH worsening were 78.9% and 73.6% at 2 and 4 years, respectively.

Conclusions: The pediatric bosentan formulation was generally well tolerated, its safety profile comparable to that of the adult formulation when used in children. The results are in line with the efficacy profile of bosentan in previous pediatric and adult PAH studies of shorter duration.

1. Introduction

Pulmonary arterial hypertension (PAH) is a progressive disease characterized by an increase in both pulmonary arterial pressure and pulmonary vascular resistance, ultimately resulting in right ventricular failure and death [1]. Pediatric PAH is diagnosed using the same criteria as for adults and defined as the presence of a mean pulmonary arterial

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pressure greater than 25 mm Hg at rest, measured by right heart catheterization, with a pulmonary arterial wedge pressure less than 15 mm Hg [2–4]. In addition, a prolonged preservation of right heart function in children may reflect the delay in onset of symptoms of PAH in this age group [4,5].

The prognosis of children with PAH has improved due to new therapies and aggressive treatment strategies; however, the use of these therapies is based primarily on adult studies rather than trials carried out in pediatric patients [4]. Data from the Registry to Evaluate Early and Long-Term Pulmonary Arterial Hypertension Disease Management (REVEAL) gave 1-, 3-, and 5-year estimated survival rates of 96 ± 4%, 84 ± 5%, and 74 ± 6% for childhood onset PAH [6,7]. Retrospective analysis of survival data of pediatric PAH from three patient cohorts showed overall 1-, 3-, 5-, and 7-year transplant-free survival rates of 96%, 89%, 81%, and 79%, respectively [8]. The observed differences in unadjusted survival rates between the individual cohorts were considered a result of differing diagnoses and measures of disease severity. Despite this apparent overall improvement in survival with the availability of PAH-specific therapies, certain patient populations such as those with repaired congenital heart disease and pulmonary hypertensive vascular disease remain at increased risk [9–11]. When using any therapeutic regimen to treat PAH in children, the detection of long-term side effects needs to be taken into consideration when planning clinical studies for new PAH therapies due to the physiological changes that occur as children grow and develop [12].

Bosentan is an oral dual endothelin receptor antagonist (ERA) approved for the treatment of PAH. Studies have indicated that bosentan may be effective in the treatment of pediatric PAH [13–17]. The recommended dose for adults >40 kg is 62.5 mg b.i.d. (twice daily) for 4 weeks, which is then increased to 125 mg b.i.d. FUTURE-1 was a prospective, open-label study in which 36 children with idiopathic or heritable PAH, previously naïve to bosentan or treated with its adult tablet formulation, were treated with a 32 mg dispersible pediatric formulation of bosentan; initial doses of 2 mg/kg b.i.d were administered for 4 weeks and then uptitrated to 4 mg/kg b.i.d. as maintenance dose for 8 weeks [18]. This study showed that in children with PAH similar plasma concentrations of bosentan are achieved following administration of 2 and 4 mg/kg doses and that the systemic exposure to bosentan plateaued at 2 mg/kg. Overall, exposure in children was lower than that seen in adult patients treated with 125 mg b.i.d. doses of bosentan using the 125 mg tablet formulation. Improvements in World Health Organization (WHO) functional class (FC) and Global Clinical Impression scales (GCIS) were seen primarily in pediatric patients who were bosentan-naive at baseline compared with patients who had already received bosentan treatment at the start of the study. The pediatric formulation of bosentan was generally well tolerated and FUTURE-1 results support a dose recommendation of 2 mg/kg b.i.d. for children with PAH.

The primary objective of FUTURE-2 was to assess the long-term safety and tolerability of the 32 mg dispersible pediatric formulation of bosentan with main secondary objectives being an exploratory evaluation of efficacy parameters and long-term vital status of the participants. We present the analysis of pooled data from both the FUTURE-1 study and its extension, the FUTURE-2 study, including safety, tolerability, and exploratory efficacy endpoints.

2. Methods

2.1. Study design

FUTURE-2 (NCT00319020) was an open-label extension of FUTURE-1, a 12-week, multicenter, open-label, non-comparative, phase III study which assessed the pharmacokinetics, safety, and tolerability of a 32 mg dispersible pediatric formulation of bosentan in children with idiopathic or heritable PAH. The main objective of FUTURE-2 was to assess the long-term safety and tolerability of this pediatric formulation. Details of FUTURE-1, including patient disposition, study design, and the analyses carried out have been described previously [18]. All patients who were bosentan-naive or previously treated with bosentan at baseline and who completed the 12-week treatment period of FUTURE-1 were eligible to continue their treatment in FUTURE-2. The FUTURE-2 treatment period extended until the investigator or patient decided to permanently discontinue the study drug, or until bosentan was commercially available as a pediatric formulation in the country of the study patient, or until the patient reached the age of 12 years.

2.2. Patient population

Eligible patients were aged ≥2 years and <12 years, with idiopathic or heritable PAH in WHO FC II or III at the start of FUTURE-1; had previously completed the FUTURE-1 study and in whom bosentan treatment was considered beneficial by their treating physician. The use of calcium channel blockers, IV epoprostenol, IV or inhaled iloprost, anticoagulants, diuretics, and digoxin was permitted on entry to FUTURE-2 provided their use had remained stable during FUTURE-1. Addition of PAH therapies, other than ERAs or sildenafil, was permitted during FUTURE-2 in the case of PAH worsening, as determined by the investigator. The study was conducted in accordance with the Declaration of Helsinki and local guidelines for good clinical practice. The local ethics review committees approved the protocol. Written informed consent was obtained from the patients' parent or guardian; patients were informed about the trial to an extent that they could understand.

2.3. Study procedure

The study drug consisted of a flavored 32 mg bosentan dispersible tablet with quadrisecting score lines to allow flexible dosing. During the FUTURE-2 extension study, a 4 mg/kg b.i.d. maintenance dose of bosentan was administered to patients, which could be down-titrated to 2 mg/kg b.i.d. if not tolerated.

2.4. Outcomes measures

Safety and tolerability were evaluated by treatment-emergent adverse events (AEs; up to 1 day following discontinuation of the study drug), serious AEs (up to 28 days following discontinuation of the study drug), growth, and laboratory assessments.

An AE was defined as any adverse change from the patient's baseline condition that occurred during the course of the study; AEs were not adjudicated. Serious AEs were defined according to the International Conference on Harmonisation (ICH) guidelines [19]. Treatment-emergent AEs were AEs reported during the treatment period, possible interruption(s) in the drug intake were considered as part of the treatment period. Each treatment-emergent AE was assessed by the investigator and reported as either related or unrelated to study medication (bosentan-related AE vs bosentan-unrelated AE); AEs with missing relationship were considered as related.

In the context of safety events reporting, investigators used the terms PAH worsening or pulmonary hypertension (PH) worsening at their discretion.

Long-term mortality was followed up annually in all patients that entered FUTURE-2, irrespective of discontinuation of study drug, for the entire duration of the study.

In the context of efficacy assessment, worsening of PAH was defined strictly as the time to first occurrence of death, transplantation, or hospitalization for PAH worsening from baseline in FUTURE-1. Efficacy was assessed in an exploratory manner by time to worsening of PAH, changes from baseline in WHO FC, in the 10-item short form health survey (SF-10) and GCIS [18] which were completed by physicians, patients and caregivers.

2.5. Statistical methods and analyses

Statistical analyses were conducted on pooled data from all patients in FUTURE-1 and FUTURE-2, who received ≥1 dose of bosentan from the start of FUTURE-1.

Patients were grouped as 'all patients' and by sub-groups depending on whether they had received bosentan prior to entry into FUTURE-1 as 'previously bosentan-treated' or 'previously bosentan-naive'.

Kaplan–Meier event-free estimates (95% two-sided confidence intervals [CIs]) were calculated for time to worsening of PAH.

Patients without an event during the treatment period were right-censored at the earliest between treatment end date + 1 day (i.e., end date in either FUTURE-1 or FUTURE-2) and date of last contact or discontinuation.

3. Results

3.1. Patient disposition

Of 36 patients enrolled in FUTURE-1, 15 were previously bosentan-treated and 21 were previously bosentan-naive at baseline (Fig. 1). All 36 patients received ≥1 dose of bosentan, however two patients did not complete FUTURE-1 and one patient elected not to enroll in FUTURE-2; therefore, 33 patients continued into FUTURE-2.

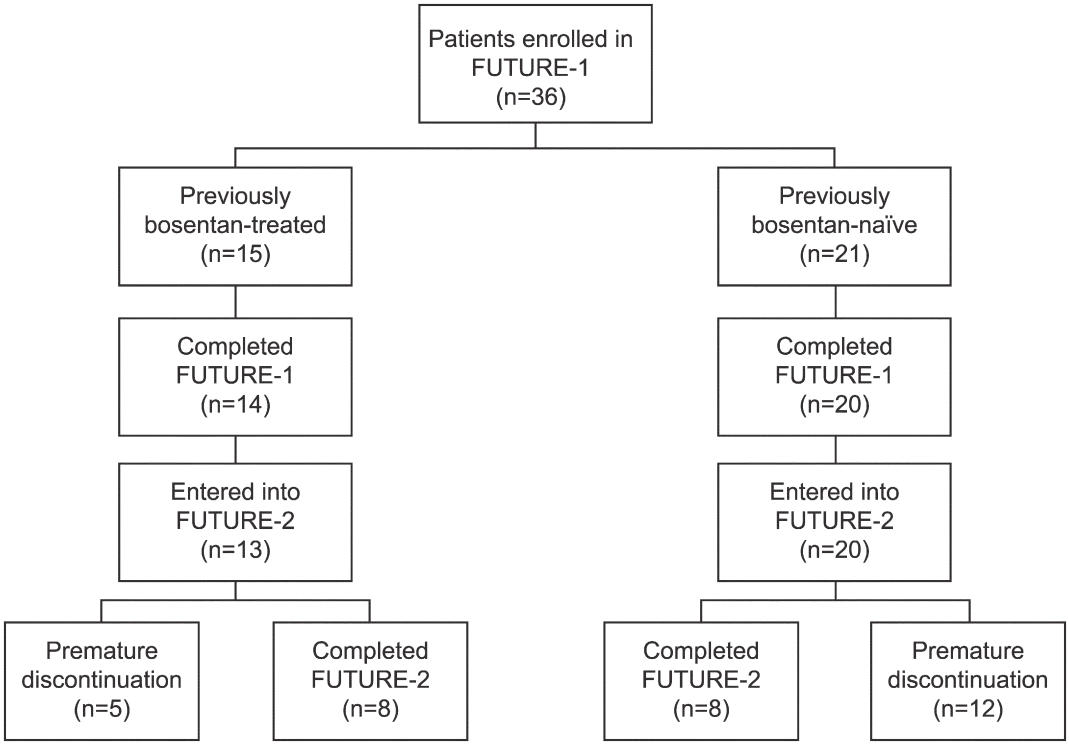

Fig. 1. Disposition of patients in FUTURE-1 and FUTURE-2.

3.2. Patient demographics

At baseline of the FUTURE-1 study, more females than males were enrolled (58.3% vs. 41.7%) and the mean ± standard deviation (SD) age was 6.8 ± 2.7 years. Weight and height were similar across the groups (Table 1). The majority of patients (86.1%) had idiopathic PAH, and the mean duration of PAH from time of diagnosis was 31.6 ± 31.0 months. At baseline, previously bosentan-treated patients had a longer duration of PAH (mean of 38.3 ± 24.4 months) compared with previously bosentan-naive patients (mean of 26.9 ± 34.8 months). At baseline, 75.0% of patients were treated with at least one concomitant medication (Table 1).

3.3. Exposure to bosentan

The overall median (range) duration of exposure to bosentan during the study (from study treatment start date in FUTURE-1 to study treatment end in FUTURE-2) was 27.7 (1.9–59.6) months; and the mean duration was 31.1 ± 19.8 months.

Table 1
Demographics and baseline characteristics of all patients at the start of FUTURE-1.

	Previously bosentan-treated (n = 15)	Previously bosentan-naive (n = 21)	All patients (n = 36)
Sex — female, n (%)	10 (66.7)	11 (52.4)	21 (58.3)
Age (years)[a]	6.9 ± 2.1	6.6 ± 3.2	6.8 ± 2.7
Weight (kg)[a]	21.3 ± 4.7	23.1 ± 9.8	22.3 ± 8.0
Height (cm)[a]	119.5 ± 11.7	119.5 ± 22.5	119.5 ± 18.9
Duration of PAH (months)[a]	38.3 ± 24.4	26.9 ± 34.8	31.6 ± 31.0
Etiology of PAH, n (%)			
Idiopathic	12 (80.0)	19 (90.5)	31 (86.1)
Familial	3 (20.0)	2 (9.5)	5 (13.9)
WHO FC, n (%)			
I	0	0	0
II	6 (54.5)	5 (71.4)	17 (60.7)
III	5 (45.5)	2 (28.6)	11 (39.3)
IV	0	0	0
Concomitant medications at baseline,[b] n (%)	12 (80.0)	12 (71.4)	27 (75.0)
Epoprostenol	3 (20.0)	6 (28.6)	9 (25.0)
Furosemide	4 (26.7)	4 (19.0)	8 (22.2)
Oxygen	3 (20.0)	4 (19.0)	7 (19.4)
Acenocoumarol	3 (20.0)	3 (14.3)	6 (16.7)
Warfarin	2 (13.3)	4 (19.0)	6 (16.7)
Acetylsalicylic acid	2 (13.3)	3 (14.3)	5 (13.9)
Digoxin	1 (6.7)	4 (19.0)	5 (13.9)

FC = functional class; PAH = pulmonary arterial hypertension; WHO = World Health Organization.
[a] Values are displayed as means ± SD.
[b] Most common concomitant medications at baseline were used in >10% of patients in both groups.

3.4. Safety and tolerability

3.4.1. Adverse events

Thirty-two (88.9%) patients experienced one or more treatment-emergent AEs (Table 2). Overall, the most common AEs were abdominal pain and nasopharyngitis. Bosentan-related AEs occurred in 15 (41.7%) patients. Six (16.7%) patients experienced AEs that led to premature discontinuation of bosentan treatment; five patients due to investigator reported PAH/PH worsening (including triggered by infection in one patient and after Potts' anastomosis in another patient) and in one patient due to autoimmune hepatitis. AEs which led to premature discontinuation were considered bosentan treatment-related in two patients; one experiencing autoimmune hepatitis and one investigator reported PAH/PH worsening.

3.4.2. Serious adverse events

Fifty-one serious AEs occurred in 18 (50.0%) patients; 60.0% of previously bosentan-treated patients vs 42.9% of previously bosentan-naive patients (Table 3). Worsening of PAH/PH, including a change from FC II to FC III, was reported in two patients as being related to the study drug. One of the patients had previously received treatment with the commercial adult formulation of bosentan for 3 years but experienced investigator reported worsening of PAH/PH whilst on the study drug. The investigator reported that non-compliance with intake of the study drug may have contributed to the worsening. Following completion of the study, this patient resumed treatment with the adult bosentan formulation and showed some signs of hemodynamic improvement and the patient's condition ultimately stabilized following hospitalization and the initiation of treatment with IV milrinone and sildenafil. Following the patient's recovery, commercial bosentan was reinstated.

In the other patient, the investigator stopped the study drug in response to investigator reported PAH/PH worsening and treated the patient with nitric oxide and oxygen during a hospitalization together with initiation of sildenafil 20 mg three times daily. Despite resolution of symptoms in this instance, this patient subsequently prematurely discontinued the study treatment due to further PAH/PH worsening.

Autoimmune hepatitis was experienced by one patient in the study who was previously bosentan-naive. This patient was on bosentan treatment for 9 months, since the start of the FUTURE-1 study, and presented at a regular study visit with an increase in liver enzymes (>3 times the upper limit of normal), which remained elevated following a subsequent dose reduction of bosentan. Additional laboratory testing (F-actin antibody and anti-smooth muscle IgG positive, CMV, and Epstein–Barr virus IgG negative) were consistent with autoimmune hepatitis. Upon this diagnosis, administration of the study drug was interrupted. The subject showed improvement in follow-up testing, after which bosentan was reinstated. However, 10 days later an increase in liver enzymes and alkaline phosphatase levels occurred, which led to the permanent discontinuation of bosentan. Following this, the autoimmune hepatitis resolved without sequelae 108 days later.

In the 33 patients who entered FUTURE-2, six deaths occurred during the study period; all were reported as unrelated to bosentan. Four deaths occurred during the treatment period or up to 28 days after discontinuation of bosentan. Of these four, three deaths were due to investigator reported worsening of the underlying PAH and subsequent cardiac complications, cardiac failure, and right ventricular failure related to suspected otitis (not proven microbiologically), and one was due to respiratory failure following pneumonia. Two deaths occurred after the 28-day period following discontinuation of bosentan. One death occurred due to PAH and cardiac complications at 38 days after discontinuation, and one death occurred during cardiac catheterization approximately 11 months after discontinuation without PAH worsening.

Table 2
Treatment-emergent adverse events occurring in >10% of patients.

AE up to 1 day after permanent discontinuation of the study drug, n (%)	Previously bosentan-treated (n = 15)	Previously bosentan-naive (n = 21)	All patients (n = 36)
Total of patients with ≥1 AE	13 (86.7)	19 (90.5)	32 (88.9)
Abdominal pain	2 (13.3)	5 (23.8)	7 (19.4)
Nasopharyngitis	3 (20.0)	4 (19.0)	7 (19.4)
Pulmonary arterial hypertension[a]	4 (26.7)	2 (9.5)	6 (16.7)
Pulmonary hypertension[a]	1 (6.7)	5 (23.8)	6 (16.7)
Bronchitis	2 (13.3)	3 (14.3)	5 (13.9)
Upper respiratory tract infection	1 (6.7)	4 (19.0)	5 (13.9)
Chest pain	1 (6.7)	3 (14.3)	4 (11.1)
Fatigue	1 (6.7)	3 (14.3)	4 (11.1)
Flushing	1 (6.7)	3 (14.3)	4 (11.1)
Headache	1 (6.7)	3 (14.3)	4 (11.1)
Pneumonia	2 (13.3)	2 (9.5)	4 (11.1)
Syncope	3 (20.0)	1 (4.8)	4 (11.1)
Vomiting	0	4 (19.0)	4 (11.1)

AE = adverse event.
[a] Both terms indicate worsening of the underlying condition.

Table 3
Serious treatment-emergent adverse events.

Serious AE up to 28 days after permanent discontinuation of the study drug	Previously bosentan-treated (n = 15)	Previously bosentan-naive (n = 21)
Total of patients with ≥1 serious AE, n (%)	9 (60.0)	9 (42.9)
Total number of serious AEs, n	26	25
Device related infection	1	2
Pulmonary arterial hypertension[a]	2	1
Pulmonary hypertension[a]	1	2
Fatigue	1	1
Right ventricular failure	1	1
Potts shunt	1	1
Abdominal pain	1	
Adenoidectomy	1	
Arterial catheterization		1
Autoimmune hepatitis		1
Bacteremia	1	
Balloon atrial septostomy		1
Bronchial obstruction	1	
Bronchitis viral		1
Cardiac failure		1
Catheter site infection	1	
Catheterization cardiac		1
Cellulitis		1
Chest pain	1	
Convulsion	1	
Cough		1
Diaphragmatic hernia		1
Dystonia		1
Ear infection	1	
Flank pain	1	
Hemoglobin decreased	1	
Hypertension		1
Injection site nodule		1
Iron deficiency anemia	1	
Lobar pneumonia		1
Lung infection	1	
Medical device complication		1
Pericardial effusion	1	
Pneumonia	1	
Pneumonia viral	1	
Pulmonary arterial pressure		1
Pulmonary vein stenosis		1
Respiratory failure	1	
Syncope	1	
Viral infection	1	
Viral rhinitis		1
Wheezing	1	

If a patient had ≥2 occurrences of the same serious AE (as qualified by its preferred term[s]), such an event was counted only once.
AE = adverse event.
[a] Both terms indicate worsening of the underlying condition.

3.4.3. Additional measurements

Laboratory abnormalities (see Table 4), body weight, height, and vital signs were carried out to further characterize safety, and did not reveal new safety concerns. In particular, increase in aminotransferases was observed in one patient only, the one who experienced autoimmune hepatitis.

3.5. Exploratory efficacy endpoints

A summary of the exploratory efficacy endpoint results is shown in Table 5. At end of study or premature discontinuation of study drug (FUTURE-1 or 2) the WHO FC had improved in 39.3% of patients overall (compared to baseline); only 2/28 patients (7.1%) showed a worsening in FC. Overall, there was an improvement in the mean ± SD change from baseline to end of study or premature discontinuation of study drug (FUTURE-1 or 2) in SF-10 physical summary score (10 ± 17 [15/36]). However, there was a slight decrease in the mean change from baseline to end of study or premature discontinuation of study drug (FUTURE-1 or 2) for SF-10 psychosocial summary score (−4.4 ± 9.6 [16/36]) in 13 (81.3%) patients. GCIS (as rated by the parents) improved from baseline to end of study or premature discontinuation of study drug (FUTURE-1 or 2) in 13 (81.3%) patients, remained unchanged in two (12.5%) patients and worsened in one (6.3%). GCIS (as rated by the physician) improved in 17 (65.4%) of patients, remained unchanged in seven (26.9%) patients and worsened in two (7.7%).

The Kaplan–Meier estimate of not having experienced defined clinical worsening of PAH was 78.9% (95% CI 60.7–89.3%) at 2 years and 73.6% (95% CI 53.1–86.2%) at 4 years (Table 5, Fig. 2). Estimated long-term survival at 2 and 4 years after start of treatment in FUTURE-1 were 91.2% (95% CI 75.0–97.1%) and 84.0% (95% CI 65.5–93.1%), respectively (Fig. 3).

Table 5
Summary of FUTURE-1 and FUTURE-2 efficacy results, all-treated set.

	Change from baseline to end of study or to premature discontinuation of study drug	
WHO FC, % (n)[a]	Improved	39.3% (11/28)
	Stable	53.6% (15/28)
	Worsened	7.1% (2/28)
SF-10, mean ± SD (n)[a]	Physical summary score	10 ± 17 (15/36)
	Psychosocial summary score	−4 ± 10 (16/36)
Physicians' GCIS, % (n)[a]	Improved	65.4% (17/26)
	Stable	26.9% (7/26)
	Worsened	7.7% (2/26)
Parents' GCIS, % (n)[a]	Improved	81.3% (13/16)
	Stable	12.5% (2/16)
	Worsened	6.3% (1/16)
Kaplan–Meier event-free estimates		
At 2 years	78.9% (7 patients had study defined worsening of PAH)	
	56.2% (15 patients had investigator reported worsening of PAH/PH)	
At 4 years	73.6% (8 patients had study defined worsening of PAH)	
	51.9% (16 patients had investigator reported worsening of PAH/PH)	

FC = functional class; GCIS = Global Clinical Impression Scale; PAH = pulmonary arterial hypertension; PH = pulmonary hypertension; SD = standard deviation; SF-10 = 10-item short form health survey; WHO = World Health Organization.
[a] n Values expressed as number with changes/total number evaluated.

4. Discussion

The FUTURE-2 study represents an extension of FUTURE-1, a prospective trial in which 36 pediatric patients were treated with bosentan doses of 2 mg/kg and 4 mg/kg b.i.d. using a 32 mg dispersible formulation. Benefits of the pediatric formulation include the administration of a more precise dose due to its dispersible nature, and the flavored taste could be more acceptable to children. FUTURE-2 examined the long-term safety and tolerability of bosentan, in addition to exploratory efficacy endpoints including Kaplan–Meier estimates of time to PAH worsening.

The majority of patients in this study experienced AEs; however, these included those that would be expected in a pediatric population; for example respiratory tract infections and vomiting, those due to the underlying PAH (i.e., chest pain, fatigue, and syncope [20]), or those consistent with the known safety profile of bosentan [18,21–25]. Autoimmune hepatitis has been previously observed with bosentan. As elevation of liver enzymes due to treatment with bosentan can occur, monthly monitoring of liver function is mandatory. In the BREATHE-3 trial, one patient had to discontinue bosentan because of unknown primary sclerosing cholangitis that was diagnosed when the liver function tests increased [17], and in this series one patient had to stop bosentan because of autoimmune hepatitis. These observations warrant that if a child has to discontinue bosentan because of elevated liver enzymes >3× the upper limit of normal, a complete evaluation of other liver diseases be undertaken. Discontinuation from elevated liver tests in children is an uncommon event, and when developed, should lead to further evaluation. There were no clinically significant changes in laboratory measurements including hemoglobin, hematocrit and vital signs. These results support the conclusion that bosentan has a safety profile consistent with previous findings, and is generally well tolerated.

While this trial was primarily aimed at investigating the safety and tolerability of long-term bosentan administration, efficacy was also examined. However, as FUTURE-1 had been initially designed as a pharmacokinetic trial, the conclusions from these efficacy results must not be overstated. It is not clear how many patients with PAH experienced worsening of their disease prior to the commencement of the study. Direct comparisons between patients who were previously bosentan-naive or previously bosentan-treated cannot be made. Nevertheless, favorable exploratory efficacy results were seen as WHO FC improved or remained stable in the majority of patients, as did both physician and parent GCIS scores. Overall, parent GCIS scores were higher than those from physicians, indicating differences in perception of treatment efficacy. Reasons for this discrepancy may include differences in stress levels and treatment expectation between patients' parents and their physicians; these differences highlight the need to design more appropriate patient-reported outcomes for future studies.

The overall survival data were consistent with recent trials that have been performed in pediatric patients with PAH; current era trials with second-generation therapies including combinations of epoprostenol, bosentan and sildenafil have reported survival rates of ~70–95% at two years [10,24,26], and have been shown to improve predicted survival rates in pediatric patient cohorts who switched to these therapies during their disease course [26–29].

The FUTURE-1 trial [18] highlighted the challenges with determining a dose beneficial for pediatric patients; increasing the dose from

Table 4
Laboratory abnormalities.

Laboratory abnormalities, patients with abnormality n/total patients n (%)	Previously bosentan-treated[a]	Previously bosentan-naive[a]	All patients
Alanine aminotransferase or aspartate aminotransferase > 3× ULN	0/15 (0.0%)	1/21 (4.8%)	1/36 (2.8%)
Bilirubin > 2× ULN	0/15 (0.0%)	0/21 (0.0%)	0/36 (0.0%)
Hemoglobin ≤ 8 g/dL	2/15 (13.3%)	2/21 (9.5%)	4/36 (11.1%)

ULN = upper limit of normal.
[a] At entry to FUTURE-1.

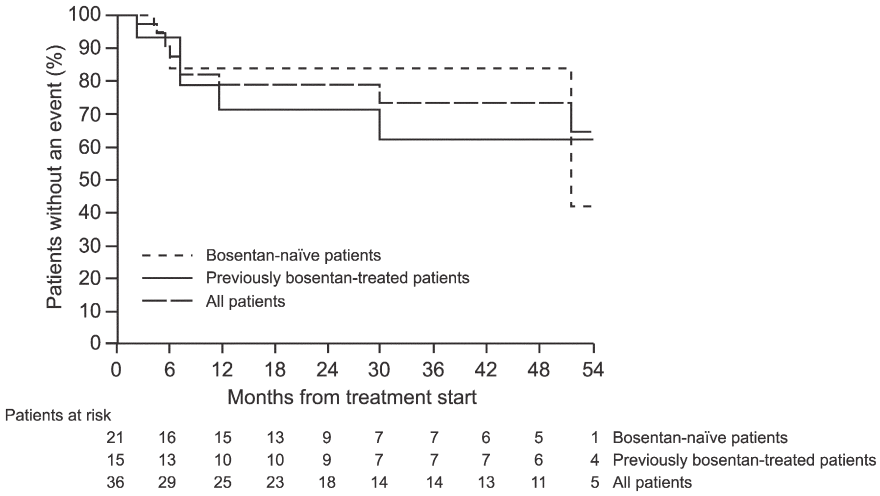

Fig. 2. Kaplan–Meier estimates for defined time to worsening of PAH.

2 mg/kg to 4 mg/kg using the 32 mg dispersible tablet did not result in increased systemic bosentan exposure, which appeared to remain lower than that reported in adult patients treated with the 125 mg tablet. Despite this, the exposure achieved was (apparently) associated with prolonged efficacy as observed in the FUTURE-2 study.

The FUTURE-1 and FUTURE-2 studies reflect on the challenges of performing pediatric clinical trials for diseases such as PAH in which patient numbers are low. An additional challenge of performing studies in children, following the identification of sufficient treatment-naive patients, is to ensure adequate retention levels in the context of changing treatment standards [12,20]. Although the TOPP [30] and REVEAL (pediatric cohort only) [7] registries have generated important data on the symptoms, diagnosis, and clinical outcome of PAH-specific therapies in a real-life setting, there is still a paucity of data for these treatments in pediatric patients with PAH.

The main challenges in designing clinical studies include the use of appropriate study endpoints and high enough patient numbers to test PAH-specific therapies adequately. Furthermore, endpoints in pediatric clinical trials are required that are validated but also acceptable, reproducible, without elevated risks for the patient, and feasible considering the often lower number of patients in such trials. It has been proposed that the use of long-term trials is warranted to ensure adequate measurement of endocrine status and neurodevelopment in such a diverse and changing patient population [12]. The generation of data on PAH-specific therapies for a pediatric population, such as those presented here, would potentially lead to improved guidelines for the clinical management of this patient population.

5. Study limitations

This was an open-label extension study with no control arm and this should be considered when interpreting the safety and in particular the exploratory efficacy data. A number of patients prematurely discontinued the trial; most were classified as administrative discontinuations. However, these patients were still followed up for vital status for the duration of the study and contributed to the long-term survival analyses.

6. Conclusions

This study demonstrated that long-term use of the pediatric formulation of bosentan was generally well tolerated. The safety profile of bosentan was comparable to that of the adult formulation when used in children, and no unexpected safety events were observed. The study results are in agreement with the efficacy profile of bosentan seen in previous pediatric and adult PAH studies of shorter duration, with improvements seen across different efficacy parameters over long-term observation.

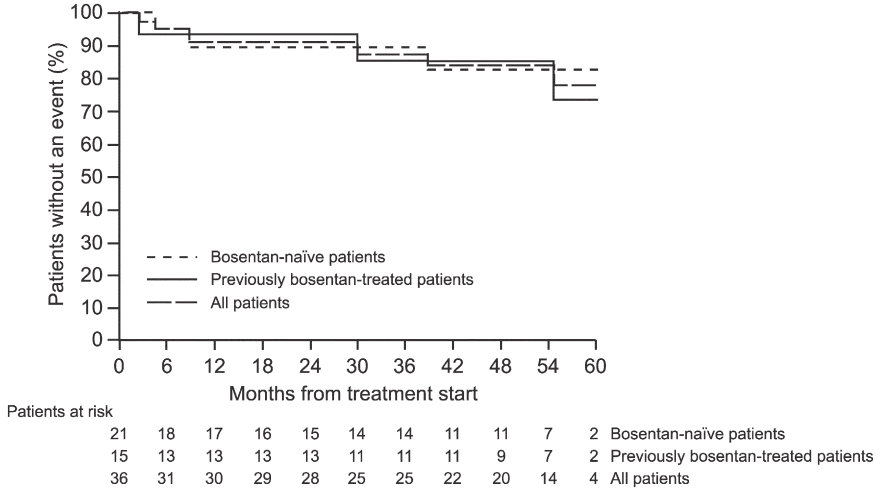

Fig. 3. Kaplan–Meier estimates for long-term survival of PAH.

Disclosures

The University Medical Center Groningen has received consulting fees from Actelion, Bayer, GlaxoSmithKline, Eli Lilly and Co, Novartis, and Pfizer for consultancy activities performed by Rolf M.F. Berger for these companies. Sheila G. Haworth has no disclosures. Damien Bonnet has received consulting fees and research support from Actelion Pharmaceuticals Ltd, Bayer HealthCare, Eli Lilly and Co, and Pfizer. Yves Dulac has received speaking fees from Actelion Pharmaceuticals Ltd. Alain Fraisse has received speaking fees from Actelion Pharmaceuticals Ltd and Pfizer. Nazzareno Galiè has received consulting fees and research support from Actelion Pharmaceuticals Ltd, Bayer HealthCare, Eli Lilly and Co, GlaxoSmithKline and Pfizer Ltd. The University of Colorado contracts with Actelion Pharmaceuticals Ltd, Bayer HealthCare, Gilead, Eli Lilly and Co, and United Therapeutics for D. Dunbar Ivy to be a consultant. Xavier Jaïs has received speaking fees and consulting fees from Actelion Pharmaceuticals Ltd, GlaxoSmithKline and Pfizer. Oliver Miera received speaker's fees from Actelion Pharmaceuticals Ltd and Bayer HealthCare. Erika B. Rosenzweig has received honoraria from Actelion Pharmaceuticals Ltd, Gilead Science, and United Therapeutics as an advisor on Scientific Advisory Board Panels and Ikaria for a study oversight committee in the past three years. Michela Efficace and Andjela Kusic-Pajic are employees of Actelion Pharmaceuticals Ltd and hold stock and stock options in Actelion Pharmaceuticals Ltd. Maurice Beghetti has served as a consultant or advisory board member for Actelion Pharmaceuticals Ltd, Bayer, Eli Lilly and Co, GlaxoSmithKline, Novartis, and Pfizer; has received grants from Actelion Pharmaceuticals Ltd and Bayer HealthCare, lecture fees from Actelion Pharmaceuticals Ltd, Bayer HealthCare, and Pfizer and has developed educational materials for Actelion Pharmaceuticals Ltd and Pfizer.

Contributions

All authors made substantial contributions to the conception or design of the work, or to the acquisition, analysis or interpretation of data. Rolf M F Berger, Maurice Beghetti, Sheila G Haworth (Steering Committee), Michela Efficace (Statistician) and Andjela Kusic-Pajic (International Clinical Trial Leader) drafted or critically revised the work for intellectual content. All authors reviewed the manuscript and approved the final version for publication and agreed to be accountable for all aspects of the work.

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This study was sponsored by Actelion Pharmaceuticals Ltd, Allschwil, Switzerland. The study investigators in collaboration with the study sponsor designed the trial and supervised its conduct. The data were collected by the investigators and their staff at the study sites. The study sponsor performed the monitoring of the study, data management, statistical analyses, and clinical study report writing. All investigators had unrestricted access to the data and participated in their interpretation. This article was the sole responsibility of the authors and was approved by all authors before submission.

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