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Pharmacokinetic and clinical profile of a novel formulation of bosentan in children with pulmonary arterial hypertension: the FUTURE-1 study

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Exposure to bosentan was lower in paediatric pulmonary arterial hypertension (PAH) patients treated with the marketed adult formulation at a dose of about 2 mg kg^{-1} when compared with adult PAH patients.
- In healthy adult subjects, bosentan pharmacokinetics are less than dose-proportional at doses of ≥500 mg.

WHAT THIS STUDY ADDS

- The pharmacokinetics of a new paediatric bosentan formulation were characterized in paediatric PAH patients.
- The level of exposure to bosentan as observed in adult PAH patients cannot be reached in paediatric patients with b.i.d. dosing.
- In paediatric PAH patients, nondose-proportional pharmacokinetics of bosentan occur at lower doses when compared with healthy adult subjects.

AIM

To show equivalent bosentan exposure in paediatric patients with pulmonary arterial hypertension (PAH) when compared with a cohort of historical controls of adult PAH patients using a newly developed paediatric formulation.

METHODS

Thirty-six paediatric PAH patients were enrolled in this multicentre, prospective, open-label, noncontrolled study and treated for 4 weeks with bosentan 2 mg kg^{-1} b.i.d. and then for 8 weeks with 4 mg kg^{-1} b.i.d. Blood samples were taken for pharmacokinetic purposes. Exploratory efficacy measurements included World Health Organization (WHO) functional class and parent's and clinician's Global Clinical Impression scales.

RESULTS

Comparing children with a historical group of adults, the geometric mean ratio (90% confidence interval) of the area under the plasma concentration–time curve was 0.54 (0.37, 0.78), i.e. children had lower exposure to bosentan than adults. Bosentan concentrations following doses of 2 and 4 mg kg^{-1} were similar. Improvements in WHO functional class and the Global Clinical Impression scales occurred mainly in bosentan-naive patients, whereas the rare worsenings occurred in patients already on bosentan prior to study initiation. The paediatric formulation was well accepted and bosentan well tolerated in this study. No cases of elevated liver enzymes or anaemia were reported.

CONCLUSIONS

Exposure to bosentan, as shown comparing the results from this study with those from a study in adults, was different in paediatric and adult PAH patients. Since FUTURE-1 and past studies suggest a favourable benefit–risk profile for bosentan at 2 mg kg^{-1} b.i.d., this dose is recommended for children with PAH. The new paediatric formulation was well tolerated.

Introduction

Pulmonary arterial hypertension (PAH) is a disease of the pulmonary arterioles characterized by progressive increases in pulmonary artery pressure and pulmonary vascular resistance, ultimately resulting in right ventricular failure and death [1, 2]. The definition of PAH in adults and children is the same: a mean pulmonary artery pressure >25 mmHg at rest or >30 mmHg during exercise with a normal pulmonary capillary wedge pressure, and an increased pulmonary vascular resistance index >3 Wood units m^2 [1]. While histopathology and pathophysiology of PAH are similar in adults and children [3, 4], the disease is often more aggressive and more rapidly progressive in paediatric patients than in adult patients, i.e. the median survival was 2.8 years in adults but only 10 months in children in the National Institutes of Health Patient Registry for the Characterization of Primary Pulmonary Hypertension [5]. In children, approximately 40% of cases of PAH are idiopathic [6] and approximately 6% are heritable [7], with the remainder mainly associated with congenital heart disease and few associated with connective tissue diseases, human immunodeficiency virus or portal hypertension. A number of drugs have been approved for the treatment of PAH in adults, including endothelin receptor antagonists, prostacyclin analogues, and phosphodiesterase type 5 inhibitors [8]. Although these drugs are used in paediatric patients [9, 10], none has been approved for the treatment of PAH in children.

Bosentan is an oral dual endothelin receptor antagonist with an approved dosing regimen for PAH in adults weighing >40 kg of 62.5 mg b.i.d. initially followed by uptitration to 125 mg b.i.d. after 4 weeks. After oral administration, maximum plasma concentrations of bosentan were attained within 3–5 h and the terminal elimination half-life ($t_{1/2}$) was about 5 h in healthy adult subjects, with a maximum plasma concentration (C_{max}) of approximately 1000 ng ml^{-1}. The metabolism of bosentan is dependent on the activity of CYP2C9 and 3A4 isoenzymes, and excretion of the metabolites via the bile constitutes the major pathway of elimination. Exposure to bosentan increased proportionally for doses of 3–600 mg [11].

Current regulatory guidelines consider that when a drug is to be used in the paediatric population for the same indication as that for which it is approved in adults, and if the disease process is not different in paediatric *vs.* adult patients, then the treatment effect is likely to be comparable and extrapolation from adult efficacy data is appropriate [12]. In such cases, the basis for regulatory approval is similar pharmacokinetics in children and adults. In a previous study, paediatric PAH patients were treated with the marketed (adult) formulation of bosentan at a dose of approximately 2 mg kg^{-1} and the improvement in haemodynamic variables in paediatric patients was similar to that demonstrated in adult patients [13]. Thereafter, a new formulation was developed providing more convenient dosing, facilitating administration and increasing acceptance for paediatric patients, and pediatric FormUlation of bosenTan in pUlmonary arterial hypeRtEnsion (FUTURE-1) was designed to evaluate its pharmacokinetic profile in the target population. Because it was shown in this previous study that bosentan plasma concentrations in children were about 50% lower than those measured in adult PAH patients [11, 13], in the present study a bosentan dose of 4 mg kg^{-1} was selected in an attempt to achieve similar plasma concentrations in paediatric PAH patients to those in adult PAH patients. In addition, tolerability, safety and efficacy of the new paediatric bosentan formulation were explored.

Patients and methods

Patients

Enrolled male or female patients (≥2 and <12 years old) had idiopathic or heritable PAH in World Health Organization (WHO) functional class (FC) II or III as diagnosed by right heart catheterization, and had a systemic arterial oxygen saturation at rest of >88%. Patients had to be in a stable condition regarding their disease and treatment. Treatments permitted included intravenous (i.v.) epoprostenol, inhaled or i.v. iloprost, calcium channel blockers, as well as bosentan treatment (with the marketed formulation) at the start of this study. Exclusion criteria included a body weight <4 kg and liver aminotransferases more than three times the upper limit of normal.

The study was conducted in conformity with the Declaration of Helsinki and in adherence to local guidelines for good clinical practice. The local ethics review committees approved the protocol. Written informed consent was obtained from a parent or legal guardian prior to the start of any study-related procedure. In addition, the patients were informed about the trial to an extent matching their capability to understand.

Study design

FUTURE-1 was a prospective, open-label, single-arm study consisting of a screening period, a 12-week treatment period, and a 28-day post-treatment follow-up period. The dose of bosentan was adjusted to the patient's body weight at study start. Patients with a body weight <30 kg received the initial dose of 2 mg kg^{-1} b.i.d. for 4 weeks, which was then uptitrated to the maintenance dose of 4 mg kg^{-1} b.i.d. for the remainder of the study. Patients with a body weight >30 kg received 64 mg b.i.d. for 4 weeks and then 120 mg b.i.d. as the maintenance dose. Those patients who prior to study entry were already on bosentan at a dose >2 mg kg^{-1} could, at the discretion of the investigator, immediately receive the maintenance dose. The new formulation of bosentan consists of a 32-mg tablet with quadrisecting score lines. These score lines allow for flexible dosing with 8-mg fractions, which can be dispersed

in water like the tablet as a whole. In addition, tablets also contain a flavour and a sweetener. Galenical tests have shown that the mass of both halved and quartered tablets is within the range of 85–115% of the theoretical mass and that broken tablets are stable at room temperature for up to 7 days. After study end and at the discretion of the treating physician, patients had the option to participate in an extension phase (FUTURE-2).

Pharmacokinetics

The primary objective of FUTURE-1 was to demonstrate that at the selected dose the exposure to bosentan obtained in this study in children with idiopathic or heritable PAH was similar to that in adults with PAH (historical control).

The pharmacokinetic assessment was performed ≥2 weeks after start of treatment with the maintenance dose, i.e. at steady state. Patients were hospitalized and an indwelling catheter was placed in an arm vein for repeated blood withdrawal. Blood samples of 1.2 ml were drawn predose and at 0.5, 1, 3, 7.5 and 12 h post dose in ethylenediamine tetraaceticacid-containing tubes. Plasma was separated and analysed for bosentan and its three metabolites, Ro 47-8634, Ro 48-5033 and Ro 64-1056, as described previously [14]. However, in order to minimize the amount of blood to be withdrawn from the patients, the volume of plasma to be extracted prior to the chromatographic analysis from each sample was divided by 4. As a consequence, the limits of quantification were raised fourfold to 4 and 8 ng ml^{-1} for bosentan and its metabolites, respectively. The day-to-day coefficients of variation varied between 6.8 and 9.0% for bosentan and its metabolites, and inaccuracy was <5.8%.

Plasma samples were analysed as they became available. Because the concentrations of bosentan were found to be lower than expected, it was decided to obtain more information on dose proportionality of bosentan pharmacokinetics. Thus, in a subset of patients the pharmacokinetics of bosentan were assessed both ≥2 weeks after study drug initiation and ≥2 weeks after uptitration to the maintenance dose.

The pharmacokinetic evaluation of bosentan and its metabolites was performed as described previously [13], in order to obtain values for the C_{max}, the time to C_{max} (t_{max}), and the area under the plasma concentration–time curve during a dose interval (AUC_t) using noncompartmental analysis.

Tolerability and safety

Tolerability and safety were evaluated by monitoring adverse events, vital signs, body weight, physical examination, premature discontinuations, laboratory tests (including monthly liver function tests), and 12-lead electrocardiogram.

Exploratory efficacy

WHO FC, a quality-of-life questionnaire (10-item Short Form survey for children, SF-10 [15]), and Global Clinical Impression scales [16] were completed by parents and investigators to assess clinical outcomes. Assessments were performed at baseline, at uptitration to the maintenance dose, during the pharmacokinetic visits, and at study end.

Statistical analysis

A sample size of 30 patients was chosen with the aim of rejecting the null hypothesis that the 90% confidence interval of the geometric mean ratio of AUC_t (primary end-point) in children and adult PAH patients (predefined historical control [11]) was outside the equivalence limits of 0.66 and 1.50 with a type I error of 0.05 and 80% power. The equivalence limits were chosen based on the AUC_t for bosentan and its variability as obtained in a previous study conducted in paediatric patients [13]. The geometric mean value [95% confidence limits (95% CL)] of AUC_t of bosentan in the historical control group of adult PAH patients was 8149 ng h^{-1} ml^{-1} (6021, 11 030).

The calculation of the geometric mean ratio and 90% two-sided CL (Student's *t*-distribution), comparing children and adults, was carried out using the per-protocol set. Patients were included in the per-protocol set when they were able to provide at least five of the six blood samples (including predose and 12-h samples) during the pharmacokinetic visit when they were on the maintenance dose and did not violate the protocol in a way that might have affected evaluation of the primary end-point. The pharmacokinetic parameters of bosentan following administration of 2 and 4 mg kg^{-1} were analysed descriptively, as were data for safety, tolerability and exploratory efficacy.

The effect of the covariates sex, age, body weight, WHO FC, concomitant treatment with i.v. epoprostenol, and treatment with bosentan at baseline on the pharmacokinetics of bosentan was graphically explored. For the exploratory efficacy parameters, subgroup analyses were based on treatment with bosentan at baseline.

Results

Patient characteristics and disposition

A total of 36 patients were enrolled at 11 centres in seven countries. The demographic and baseline disease characteristics of these patients are shown in Table 1. One patient was excluded from the per-protocol pharmacokinetic analysis set because of a dosing error, i.e. the evening dose on the day of pharmacokinetic assessments was taken prior to withdrawal of the 12-h blood sample. One patient was excluded from the exploratory efficacy set because the patient underwent a palliative procedure, i.e. atrial septostomy, not allowing reliable WHO FC and Quality of Life

assessments. An overview of the patient disposition and analysis sets is shown in Figure 1.

Pharmacokinetics

The pharmacokinetic profile of bosentan was characterized by a median t_{max} of 3 h followed by rapid disposition.

Table 1

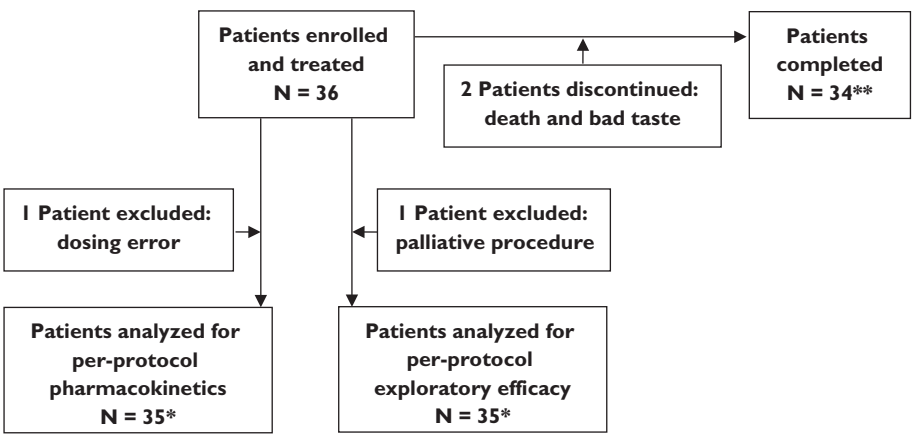
Patients' demographic and baseline disease characteristics

Characteristic*	All patients (n = 36)
Gender: male/female, *n* (%)	21 (58.3)/15 (41.7)
Age, years	7.0 (2.0–11.0)
Age, *n* (%)	
2–3 years	4 (11.1)
4–5 years	9 (25.0)
6–11 years	23 (63.9)
Weight, kg	20.7 (9.5–42.0)
Children below/above 30 kg, *n*	
<30 kg (4 mg kg^{-1} b.i.d.)	29
≥30 kg (adult dose, i.e. 125 mg b.i.d.)	7
Height, cm	119.0 (79.0–153.0)
Ethnicity, *n* (%)	
White	32 (88.9)
Black	1 (2.8)
Hispanic	2 (5.6)
Other	1 (2.8)
Aetiology, *n* (%)	
Idiopathic	31 (86.1)
Heritable	5 (13.9)
WHO FC, *n* (%)	
FC II	23 (63.9)
FC III	13 (36.1)

*Values are expressed as the median (range) or % when indicated. WHO, World Health Organization; FC, functional class.

Descriptive statistics of pharmacokinetic parameters of bosentan and its metabolites Ro 48-5033 and Ro 64-1056 after administration of a dose of 4 mg kg^{-1} are summarized in Table 2. No pharmacokinetic analysis could be performed for the metabolite Ro 47-8634 because in most plasma samples the concentration of this metabolite was below the limit of quantification. The ratio of the geometric means for AUC_t between paediatric and adult patients was 0.54 (95% CL 0.37, 0.78), indicating (i) that exposure to bosentan in children in the current study was half the exposure found in adult patients, and (ii) that the ratio was not within the predefined equivalence limits of 0.66–1.50. When comparing bosentan-naive patients at study start with those already on bosentan, it was noted that the AUC_t of bosentan was similar in both subgroups (4298 ng h^{-1} ml^{-1}, 95% CL 3497, 5282; and 4514 ng h^{-1} ml^{-1}, 95% CL 2594, 7855, respectively). Exposure to the metabolites Ro 48-5033 and Ro 64-1056 was low compared with that of bosentan, with Ro 48-5033 having the highest exposure of these two metabolites. WHO FC and the dichotomous covariates sex, i.v. epoprostenol treatment, and bosentan treatment at baseline did not affect the pharmacokinetics of bosentan (data not shown). In addition, analysis for the continuous variables age (Figure 2) and body weight did not show a trend for an effect on pharmacokinetics.

Figure 3 shows the plasma concentration–time profiles of bosentan following administration of doses of 2 and 4 mg kg^{-1} in the subgroup of patients who underwent two pharmacokinetic assessments. The two profiles overlap, yielding comparable pharmacokinetic parameters for both doses (Table 2).



*** Different patients were excluded from the 2 analysis sets**
**** Discontinuations occurred after the patients had completed their week 12 and pharmacokinetic assessments**

Figure 1

Analysis sets and patient disposition

Table 2

Pharmacokinetic parameters* of bosentan and its metabolites in paediatric pulmonary arterial hypertension patients after multiple-dose administration of bosentan at a dose of 2 and/or 4 mg kg^{-1} b.i.d.

Patient population/ analyte/dose	C_{max} (ng ml^{-1})	t_{max} (h)	AUC_t (ng h^{-1} ml^{-1})
All patients (n = 35)			
Bosentan (4 mg kg^{-1})	895 (699, 1146)	3.0 (0.0–8.5)	4383 (3461, 5552)
Ro 48-5033	91 (67, 123)	3.0 (0.0–12.0)	555 (431, 715)
Ro 64-1056	72 (56, 91)	3.0 (0.0–12.0)	501 (391, 643)
Patients with two pharmacokinetic assessments (n = 11)			
Bosentan			
2 mg kg^{-1}	583 (354, 961)	3.0 (1.0–7.5)	3577 (2294, 5577)
4 mg kg^{-1}	649 (444, 949)	3.0 (0.0–7.5)	3371 (2344, 4849)
Ro 48-5033			
2 mg kg^{-1}	71 (45, 112)	0.5 (0.0–7.5)	486 (305, 774)
4 mg kg^{-1}	57 (33, 97)	3.0 (0.0–7.5)	423 (247, 726)
Ro 64-1056			
2 mg kg^{-1}	76 (45, 130)	3.0 (0.0–12.0)	512 (295, 889)
4 mg kg^{-1}	61 (43, 85)	3.0 (0.0–7.5)	444 (279, 707)

*Data are expressed as geometric means (95% confidence limits) for C_{max} and AUC_t, and as median (range) for t_{max}.

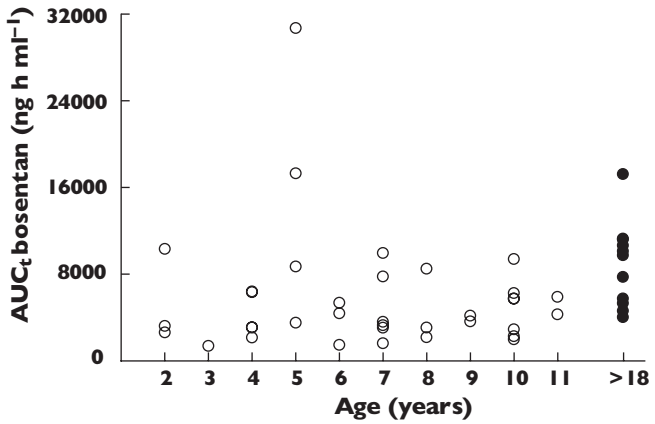


Figure 2

Individual AUC_t values of bosentan in paediatric (dose = 4 mg kg^{-1} b.i.d.; n = 35) and adult pulmonary arterial hypertension (dose ≈ 1.8 mg kg^{-1} b.i.d.; n = 11) patients by age

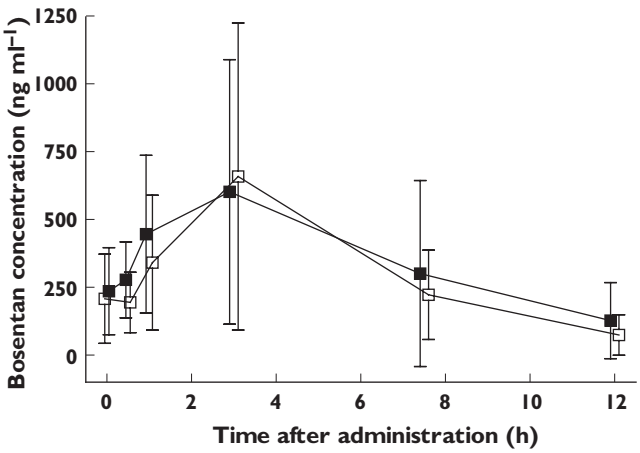


Figure 3

Arithmetic mean (±SD) plasma concentration *vs.* time profiles of bosentan in paediatric pulmonary arterial hypertension patients after multiple-dose administration of bosentan at a dose of 2 and 4 mg kg^{-1} b.i.d. (n = 11). 2 mg kg^{-1} (■); 4 mg kg^{-1} (⊟)

Tolerability and safety

Two patients prematurely withdrew from the study after the patients had completed the pharmacokinetic assessments at the maintenance dose. One child withdrew due to 'bad' taste of the medication and one died. Overall, four patients (11.1%) experienced eight serious adverse events, all requiring hospitalization. A 10-year old girl with heritable PAH died. She had a history of anaemia, 1p36 chromosomal deletion, encephalopathy, epilepsy, and patent ductus arteriosus and small ventricular septal defect, both having closed spontaneously. The patient died of right ventricular failure following development of an ear infection. This death was considered by the investigator to be unrelated to study treatment. There were six additional serious adverse events reported in three patients: preplanned adenoidectomy and bacterial infection in one patient; cough, fatigue, and an episode of systemic hypertension in another; and worsening of pulmonary hypertension in the third. Only the latter event was judged as related to study treatment by the investigator. Twenty-two patients (61%) experienced at least one adverse event. The most frequent (frequency >5%) individual adverse events were: abdominal pain (four events, 11.1%); vomiting (three events, 8.3%); upper abdominal pain, aggression, asthenia, bronchitis, chest pain, fatigue, flushing, headache, nasal congestion, pain in extremity, pulmonary hypertension, tonsillitis, viral infection (two events each, 5.6%). When

grouped as common clinical diagnoses, the most frequent were infections (mainly respiratory) and gastrointestinal disorders, which were reported in 12 and nine patients, respectively. All patients except one completed treatment with bosentan and the majority of adverse events resolved while bosentan was ongoing. The patient who discontinued bosentan initially developed an ear infection, which triggered right heart failure requiring hospitalization. The study drug was discontinued. The event resulted in death 1 day later. There were no cases of elevated liver enzymes, anaemia or any other clinically relevant abnormality. No changes in vital signs, body weight or ECG parameters were reported.

Exploratory efficacy

The changes from baseline to weeks 4, 8 and 12 in WHO FC showed that the majority of patients remained unchanged. At study end, of the 23 patients at baseline who were in FC II, only one worsened to FC III and two improved to FC I. The remaining 20 patients were stable at FC II. Of the 12 patients who were FC III at baseline, none worsened, and three improved to FC II. Results from the parents' and investigator's Global Clinical Impression scales at study end compared with baseline were available for 34 and 35 patients, respectively. In most cases, parents' responses were consistent with, or more favourable than, the physicians' assessments. Of the 17 patients whose condition the parents rated 'not good or bad' or 'bad' at baseline, nine were considered to be doing 'better' or 'significantly better' at week 12. Of the 17 patients whose condition the parents rated 'good' or 'very good' at baseline, only one was considered to be doing 'worse' or 'significantly worse' at week 12, with nine patients considered being either 'significantly better' or 'better' at week 12. Of 11 patients whose condition the physician rated 'not good or bad' or 'bad' at baseline, six were considered to be doing 'better' or 'significantly better' by week 12. Of 24 patients whose condition the physician rated 'good' or 'very good' at baseline, only two were considered to be doing 'worse' or 'significantly worse', with the majority of responses being 'no change' or 'better', at week 12. The SF-10 Physical Summary and Psychological Summary scores showed a clinically nonsignificant improvement (data not shown).

When comparing bosentan-naive patients at baseline with those previously treated with this drug, all patients who showed signs of worsening during the study were in the latter group. Furthermore, signs of clinical improvement were greater in bosentan-naive patients, irrespective of the instrument used to assess efficacy.

Discussion

In this study, the pharmacokinetics and clinical profile of a new paediatric formulation of bosentan were investigated in children with idiopathic or heritable PAH. The primary objective of demonstrating equivalent exposure to bosentan in paediatric and adult PAH patients was not met. Bosentan plasma concentrations in children were lower than those in adults despite doubling the dose from 2 to 4 mg kg^{-1}. Data from the subgroup of patients who underwent two pharmacokinetic assessments showed that the plasma concentration–time profiles of bosentan following administration of doses of 2 and 4 mg kg^{-1} overlapped, suggesting that an exposure plateau was reached at a dose of 2 mg kg^{-1}. In healthy adults, the pharmacokinetics of bosentan are dose-proportional up to a dose of 500 mg (approximately 7 mg kg^{-1} for a body weight of 70 kg) given once a day, but the AUC_t at a dose of 1000 mg was similar to that of 500 mg [17]. The FUTURE-1 findings in children are in accordance with the nondose-proportional pharmacokinetics of bosentan in adults, although the dose above which no further increase in exposure occurs appears to be lower in children.

To explain the observed exposure plateau in adults, it was suggested that the low solubility of bosentan may result in saturable absorption at higher doses [17]. However, this does not explain why in children the exposure plateau occurs at lower doses. A possible explanation in children could be the smaller size of their intestinal surface area and/or different absorption characteristics, resulting in a lower capacity for absorption. Given that the apparent elimination half-life of bosentan was similar in paediatric [13] and adult patients (Actelion Pharmaceuticals, data on file), it is unlikely that the observed exposure plateau is due to a difference in metabolic or excretory capacity between these patient populations. It is also unlikely that a difference in formulation is the reason for this, because it has been shown that the marketed formulation was bioequivalent to an oral suspension in healthy adults [18]. This oral suspension has similar physicochemical properties to the paediatric formulation when suspended in water.

Except for the difference in dose at which bosentan pharmacokinetics deviate from being proportional, the pharmacokinetic characteristics of bosentan in children and adults, in terms of time to maximum concentration and elimination, are comparable [11, 13]. Furthermore, there is a substantial overlap in exposure to bosentan, as shown in Figure 2. The plasma concentrations measured in this study are in the same range as those observed in a previous study with paediatric patients in which the marketed bosentan formulation at a dose of approximately 2 mg kg^{-1} was administered [13], further indicating that the marketed and the new paediatric formulations have similar pharmacokinetic profiles. In this previous study, treatment with bosentan resulted in an increase in cardiac index of 0.5 l min^{-1} m^{-2}, a decrease in mean pulmonary artery pressure of 8 mmHg and a decrease in pulmonary vascular resistance index of 3.8 Wood units m^2 after 12 weeks. These haemodynamic improvements were of

similar magnitude to those observed in adult patients [19] despite the lower bosentan plasma concentrations in children suggesting that efficacy is achieved with a dose of 2 mg kg^{-1}. This dose is used in clinical practice, and a number of clinicians have published their experience with bosentan in children. Rosenzweig *et al*. [9] reported on a cohort of 86 paediatric PAH patients, treated with bosentan monotherapy or added to treatment with prostacyclin analogue treatment, and of these patients 90% improved or remained unchanged in WHO FC after a median treatment duration of 14 months. The patients in the report by Rosenzweig *et al*. were also allowed to have additional PAH medications at the discretion of the clinical investigator. Comparable results were reported by Maiya *et al*. [20]. It thus appears that a dose of 2 mg kg^{-1} is an effective and safe dose for children. Based on the pharmacokinetic results of the current study, higher doses are unlikely to be more effective. Thus, based on an overall risk–benefit profile (including significant long-term observational data), we recommend treating children with PAH with bosentan at the 2 mg kg^{-1} dose b.i.d. regimen.

The covariates age and body weight had no effect on the pharmacokinetics of bosentan, indicating that dosing children on a mg kg^{-1} basis up to 30 kg is appropriate. Concomitant treatment with i.v. epoprostenol did not affect bosentan pharmacokinetics, consistent with what has been shown previously [13].

Treatment with the new formulation of bosentan was well tolerated by the children; one child discontinued treatment because of a bad taste. When compared with adult patients, no new safety findings were observed. Of note, no cases of elevated liver aminotransferases were observed. This could be due to the short duration of the trial, i.e. 12 weeks, plasma concentrations of bosentan being lower than in adults, and/or lack of right heart failure in the children as opposed to many adult patients. In placebo-controlled trials in adult PAH patients, elevations of liver aminotransferases (more than three times the upper limit of normal) occurred in 12.8% of the population (n = 258; median exposure time to bosentan 18.8 months) [21], and they appeared to be dose dependent [22]. In a paediatric cohort, such elevations occurred in only 3.5% of the patients (n = 86; median exposure time 14 months) [9]. A recent review of the safety data of bosentan, as captured in an internet-based post-marketing database of 4589 bosentan-naive PAH patients, showed a similar low incidence of elevated liver aminotransferases in children aged 2–11 years (2.7%; n = 146) compared with patients aged ≥12 years (7.8%; n = 4443) [6]. Together, these results appear to indicate that bosentan is better tolerated in children than in adults.

The exploratory efficacy and quality-of-life analyses indicated that most patients remained unchanged from baseline to end of study. Observations in bosentan-naive patients *vs.* patients previously treated with bosentan suggest a beneficial therapeutic effect following initiation of bosentan. The few patients who showed deterioration in these outcomes were all on bosentan at the time of study initiation, indicating progression of this severe disease although patients were on PAH-specific therapy. These exploratory efficacy results should be interpreted with caution due to the open-label nature of the study, the lack of a control group, and the relatively small number of patients. No double-blind, randomized trials have been performed with bosentan in children. Such trials are not feasible given the low patient numbers, and the severity and not infrequently rapidly progressive nature of idiopathic and heritable PAH in children compared with adult patients.

In conclusion, exposure to bosentan, as shown comparing the results from this study with those from a study in adults, was different in paediatric and adult PAH patients. An exposure plateau appears to be reached in children at the dose of 2 mg kg^{-1} b.i.d. Nevertheless, the pharmacokinetic profiles were similar between the marketed adult formulation and the new paediatric formulation. Since FUTURE-1, in accordance with previous studies, suggests a favourable benefit–risk profile for bosentan at 2 mg kg^{-1} b.i.d., this dose is recommended for children with PAH. The new paediatric formulation was well tolerated and may be better accepted by children due to its more convenient dosing and the sweet taste.

Competing interests

M.B. has served on advisory boards for Pfizer, Actelion, Bayer Schering Pharma, Encysive, GlaxoSmithKline, INO therapeutics, Eli Lilly and MondoBIOTECH and has received lecture fees from Actelion, Encysive and Bayer Schering Pharma. S.G.H. has served on advisory boards for Actelion, Encysive, Pfizer and GlaxoSmithKline, and has received grant support from Actelion, Encysive and GlaxoSmithKline. D.B. has served as consultant and has received lecture fees from Actelion. R.J.B. has served as a consultant/scientific advisor/educational speaker and/or received research support from: Actelion, Eli Lilly, Pfizer, Gilead, and United Therapeutics. P.A. has no competing interest to report. A.F. has been reimbursed by Actelion for attending a conference, has received a lecture fee from Actelion, and has received funds from Actelion for being a member and speaker in the French scientific committee for paediatric pulmonary hypertension. D.D.I. has served on advisory boards for Pfizer, Actelion, Gilead, and United Therapeutics, and has received a research grant from United Therapeutics. X.J. has been reimbursed to attend a symposium and has received lecture fees from Actelion, Pfizer and GlaxoSmithKline. I.S-N. has received lecture, consultant fees and educational and research support from Actelion, Pfizer, and Orion Pharma. N.G. has served on advisory boards of Pfizer, Actelion, Bayer Schering Pharma, Encysive, GlaxoSmithKline, Eli Lilly, Myogen, and MondoBIOTECH, and has been paid lecture

fees by Actelion and Bayer Schering Pharma. He reports his institute as having received grant support from Pfizer, Actelion, Bayer Schering Pharma, Encysive, United Therapeutics, Eli Lilly, MondoBIOTECH, and Myogen. J.D., A.K-P. and A.M. are employees of Actelion. R.M.F.B. has served on advisory boards of Actelion and GlaxoSmithKline, and has received lecture fees and grant support from Actelion.

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