CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209279Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Office of Clinical Pharmacology Review

NDA Number	209279
Link to EDR	\\cdsesub1\evsprod\nda209279
Submission Date	08-05-2016
Submission Type	Standard review
Brand Name	Tracleer®
Generic Name	Bosentan
Dosage Form and Strength	Dispersible tablet, 32 mg
Route of Administration	Oral
Proposed Indication	Treatment of pulmonary arterial hypertension (PAH, WHO Group I)
Applicant	Actelion Clinical Research, Inc
Associated IND and NDA	*IND 058317 and NDA 021290*
OCP Review Team	Venkateswaran Chithambaram Pillai, MS(Pharm), PhD; Sudharshan Hariharan PhD;

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1. EXECUTIVE SUMMARY

Bosentan (Tracleer®), an oral endothelin receptor antagonist is approved as a film coated tablet for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) in adults under new drug application (NDA) 021290. In the current NDA, Actelion Clinical Research, Inc. is seeking approval for a dispersible tablet formulation (32 mg, double scored) intended to be available as an oral treatment option for pediatric patients with PAH via a 505 (b)(1) pathway.

The efficacy evaluation in this NDA is based on the 'bridging' of data between the adult and pediatric studies, with a primary focus on pulmonary vascular resistance (PVR). In that regard, BREATHE-3 study is considered pivotal for this submission which provides data on PVR following treatment with bosentan at approximately 2 mg/kg in pediatric PAH patients aged 3 to 15 years. In addition, this NDA contains pediatric pharmacokinetic information from studies BREATHE-3, FUTURE-1 and FUTURE-3. BREATHE-3 studied film coated tablets of bosentan whereas FUTURE-1 and FUTURE-3 studied the oral dispersible tablets. Finally, this submission also includes a relative bioavailability study in healthy adults comparing the pharmacokinetics of bosentan between film coated and oral dispersible tablets.

This review addresses (i) the relative bioavailability between the proposed bosentan oral dispersible tablet and approved film coated tablet in healthy adults, (ii) the pharmacokinetics of bosentan in pediatric patients relative to adult patients with PAH, and (iii) the pharmacokinetic bridge for the proposed dosing regimen using dispersible tablets to the exposures achieved in the pivotal efficacy study.

1.1 Recommendations

The Office of Clinical Pharmacology (OCP/DCP I) has reviewed the pharmacokinetic information submitted in this NDA. The review team proposes the following dosing table based on body weight bands that allow only bisection of the scored dispersible tablet to overcome any potential product issues that might arise with quadrisecting the tablet. For an evaluation of efficacy supporting this application, please refer to review by Drs. Garnet and Florian (NDA 209279, DARRTS date: 03/31/2017).

Patients ≤12 years of age	Initial 4 weeks	Maintenance (after 4 weeks)
≥4 to 8 kg	16 mg twice daily	16 mg twice daily
>8 to 16 kg	32 mg twice daily	32 mg twice daily
>16 to 24 kg	48 mg twice daily	48 mg twice daily
>24 to 40 kg	64 mg twice daily	64 mg twice daily

1.2 Post-Marketing Requirements and Commitments

None.

2. SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

2.1 Clinical Pharmacokinetics

- The average plasma exposure to bosentan at steady state ($AUC_{\tau, ss}$) in pediatric patients (age 3 to 15 years) treated with a mean dose of 2.2 mg/kg (range: 1.6-3.1 mg/kg) film coated tablets twice-daily in BREATHE-3 is approximately 37% lower than that observed in adult PAH patients receiving the approved maintenance dose of 125 mg twice-daily.
- Following oral administration of two 32 mg dispersible tablets (a total dose of 64 mg) of bosentan, the dose corrected total systemic exposures (C_{max}) [geometric mean ratio (GMR): 0.82 and 90% confidence interval (CI): 0.65-1.04] and area under the plasma concentration-time curve ($AUC_{0-\infty}$) [GMR: 0.87 and 90% CI: 0.78-0.97] of bosentan are slightly lower when compared to 62.5 mg film coated tablets in healthy subjects. For a chronic treatment such as bosentan, the total systemic exposure during the inter-dosing interval as reflected by AUC is likely to be more clinically relevant than C_{max}. Based on known pharmacokinetic variability for bosentan, a 13% lower AUC is likely not clinically significant.
- The mean steady state systemic exposures to bosentan ($AUC_{\tau, ss}$) following administration of a higher dose, 4 mg/kg twice-daily as evaluated in FUTURE-1, or a more frequent dosing regimen, 2 mg/kg thrice-daily as evaluated in FUTURE-3, resulted in similar exposures as achieved following administration of bosentan at 2 mg/kg twice-daily. However, the range of exposures achieved following 2 mg/kg twice-daily in FUTURE-1 and FUTURE-3 using the oral dispersible tablet spans the exposures achieved in BREATHE-3 providing an appropriate bridge to exposures achieved in the pivotal efficacy study.

2.2 Dosing and Therapeutic Individualization

2.2.1 General dosing

The recommended initial dose of bosentan for patients >12 years old and >40 kg weight is 62.5 mg and the dose is up-titrated to 125 mg after 4 weeks. The recommended initial and maintenance dose of bosentan for patients >12 years old and <40 kg weight is 62.5 mg. The Applicant proposed dosing for pediatric PAH patients in this submission is (b) (4) using oral dispersible tablets.

2.3 Outstanding Issues

None.

2.4 Summary of Labeling Recommendations

The review team recommends the following major labeling edits in the final package insert of Tracleer®:

- Dosing based on weight bands so as to not allow quadrisection of the dispersible tablet formulation in section 2 (Dosage and Administration)

- Presentation of CYP mediated drug interactions in a table format in section 7 (Drug Interactions)

3. COMPREHENSIVE CLINICAL PHARMACOLOGY REVIEW

Note: Tracleer®, a film coated tablet of bosentan, is approved for the treatment of PAH in adults. Please refer to the package insert of Tracleer® for prescribing information and clinical studies supporting the approved indication. For evaluation of clinical pharmacology information supporting the original submission, please refer to review by Drs. Robbie and Marroum (NDA 021290, DARRTS date: 07/18/2001). Therefore, an abridged version of the question based review is used to address the clinical pharmacology issues pertinent to the dispersible tablet formulation of bosentan for pediatric PAH patients.

3.1 Overview of the Product and Regulatory Background

Bosentan, an oral endothelin receptor antagonist is available as film coated tablets for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) in adults. Until now, no medication is approved for the treatment of PAH in pediatric patients.

NDA 021290 was approved by the FDA on November 2001 for the use of film coated tablets of bosentan for the treatment of adult PAH patients. The NDA was approved with boxed warning for hepatotoxicity and embryo-fetal toxicity. Later, Actelion requested the Division of Cardiovascular and Renal Products (b) (4) The Applicant later met with the Division to seek advice on the type of data that would be required to support an approval in pediatric patients. The Division agreed that a pediatric supplement could be submitted based on BREATHE-3 (ACT- 052-356), FUTURE-1 (AC-052-365) and its extension FUTURE-2 (AC-052-367), and FUTURE-3 (AC-052-373) and its extension AC-052-374 studies (IND 058317, Advice Letter dated 10/29/2015, DARRTS). Based on the feedback from the Division, the applicant is currently seeking approval for a dispersible tablet formulation (32 mg) of bosentan in pediatric PAH patients via a 505 (b)(1) pathway. Bosentan 32 mg dispersible tablet is currently approved in the European Union for the treatment of pediatric PAH patients above 2 years of age.

3.2 General Pharmacology and Pharmacokinetic Characteristics

Pharmacology	
Mechanism of action	Bosentan exerts vasodilatory effects through competitive inhibition of endothelin receptor types ET_A and ET_B. Bosentan has a slightly higher affinity for ET_A receptors than for ET_B receptors. ET-1 concentrations are elevated in plasma and lung tissue of patients with pulmonary arterial hypertension, suggesting a pathogenic role for ET-1 in this disease.
Pharmacokinetics	
Absorption	Absolute bioavailability in healthy subjects: 50% ; Food has no effect on the pharmacokinetics of bosentan; Time to reach maximum plasma concentrations (T_{max}): 3-5 h; Dispersible tablet formulation shows (b)(4)% and14% lower AUC and C_{max}, respectively, compared to film coated tablets.
Distribution	Protein binding: >98% (mainly albumin); Volume of distribution: 18 L
Metabolism	Metabolized by CYP3A4 and CYP2C9 to three metabolites, Ro 48-5033 (pharmacological activity is 10-20% of bosentan), Ro 47-8634 and Ro 64-1056. Bosentan is an inducer of CYP2C9, CYP3A4 and CYP2C19. Upon multiple oral dosing, plasma exposure at steady state (AUC_{ss}) in healthy adults decrease gradually to 50-65% of those seen after single dose administration, probably the effect of auto-induction of the metabolizing liver enzymes.
Excretion	Bosentan is primarily excreted through bile. Less than 3% of oral dose is excreted via urine. Total clearance (after single intravenous dose): 4 L/h ; Terminal elimination half-life: 5 h in healthy adults

3.3 Clinical Pharmacology Review Questions

3.3.1 What is the bioavailability of oral dispersible tablet compared to film coated tablet of bosentan in healthy subjects?

The total systemic exposures ($AUC_{0\text{-}inf}$) of bosentan and Ro 48-5033 are 13% and 9% lower, respectively, with the dispersible tablet compared to film coated tablet. The 90% CIs of the geometric mean ratio for $AUC_{0\text{-}inf}$ are within the conventional bioequivalence limits for Ro 48-5033, but marginally misses for bosentan (lower 90% CI: 0.78) [Table 1]. It should be noted that no formal sample size calculations were performed and the study with 16 subjects is likely underpowered to demonstrate bioequivalence given the pharmacokinetic variability of bosentan.

Table 1. Geometric mean ratios and 90% confidence intervals of the dose-corrected pharmacokinetic parameters of bosentan and Ro 48-5033 when administered either as film coated tablet or dispersible tablet in healthy adults

Parameter	Film coated tablet (A) 1 x 62.5 mg N = 16	Dispersible tablet (B) 2 x 32 mg N = 16	Geometric mean ratio [B/A] (90% CI)
Bosentan			
$AUC_{0\text{-}inf}$ (µg*h/L)	3494 (40)	3045 (46)	87 (78-97)
C_{max} (µg/L)	592 (41)	484 (44)	82 (65-104)
t_{max}# (h)	4 (2-5)	4 (3-5)	-
$t_{1/2}$ (h)	8.3 (53)	9.3 (44)	-
Ro 48-5033			
$AUC_{0\text{-}inf}$ (µg*h/L)	411 (43)	374 (57)	91 (81-101)
C_{max} (µg/L)	34 (41)	24 (44)	70 (55-88)
t_{max}# (h)	5 (4-16)	5 (4-12)	-
$t_{1/2}$ (h)	10 (29)	11 (55)	-

The peak concentration of bosentan and Ro 48-5033 are on an average 18% and 30% lower for the dispersible tablet when compared to film coated tablet. However, for a chronic treatment such as bosentan, the total systemic exposure during the inter-dosing interval as reflected by AUC is likely to be more clinically relevant than C_{max}. Based on known pharmacokinetic variability for bosentan, a 13% lower AUC is likely not clinically significant. The variability in pharmacokinetic measures between the two formulations are also similar. Therefore, the dispersible tablet is a viable alternative to film coated tablet for use in adults.

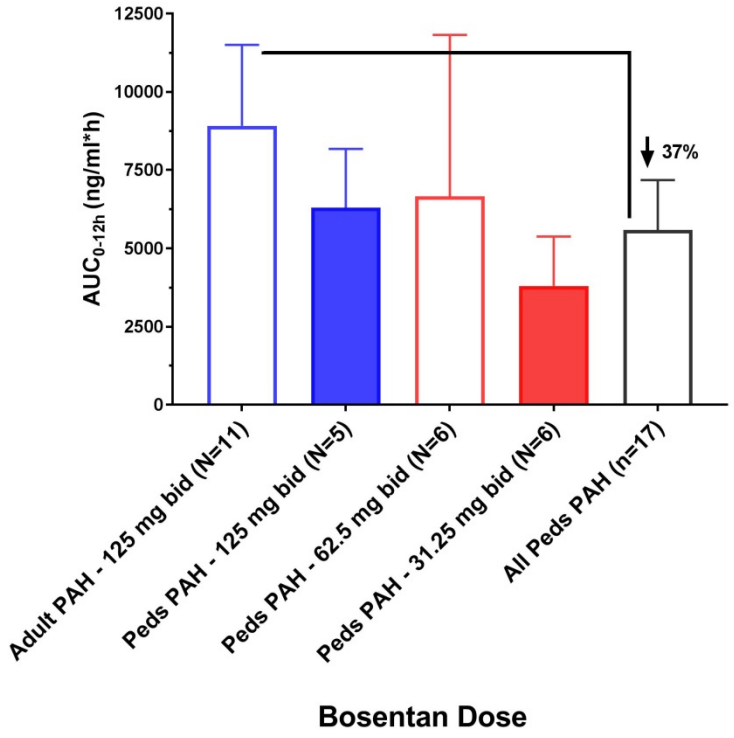
3.3.2 What is the systemic exposure to bosentan in pediatric patients relative to adult patients with PAH?

Pediatric data from BREATHE-3, which used film coated tablets of bosentan, is used for this comparison as this study provides primary evidence of efficacy in pediatric PAH patients. Pharmacokinetic assessments were performed after single and multiple-dose (week 12) administration of bosentan at 31.25 mg (1.6-2.3 mg/kg b.i.d), 62.5 mg (1.7-3 mg/kg b.i.d) and 125 mg b.i.d (1.6-3.1 mg/kg b.i.d) doses in pediatric PAH patients aged 3 to 15 years.

Data for adults is obtained from study AC-052-357 which evaluated pharmacokinetics of bosentan in a subset (N=13) of patients with PAH. Patients received 62.5 mg b.i.d. for the first 4 weeks and were then up titrated to receive 125 mg b.i.d. based on tolerability. Pharmacokinetics of bosentan and its metabolites were assessed at least 2 weeks after treatment with 62.5 mg and 125 mg twice-daily doses.

As seen from Figure 1, the average systemic exposures ($AUC_{0\text{-}12h}$) of bosentan at steady state in pediatric patients receiving 31.25, 62.5 or 125 mg b.i.d. (approximately 2.2 mg/kg, range: 1.6-3.1 mg/kg) is 37% lower than adults receiving the approved dose of 125 mg b.i.d. Although exposures in pediatric patients are lower than in adults, BREATHE-3 showed statistically significant reductions in PVR which are comparable to that observed in adults. Please refer to review by Drs. Garnett and Florian (NDA 209279, DARRTS: 03/31/2017) for details supporting the efficacy of bosentan in pediatric PAH patients.

Figure 1. Comparison of the average systemic exposures to bosentan between adult and pediatric patients with PAH following administration of film coated tablet formulation of bosentan. Data represents mean with 95% CI.

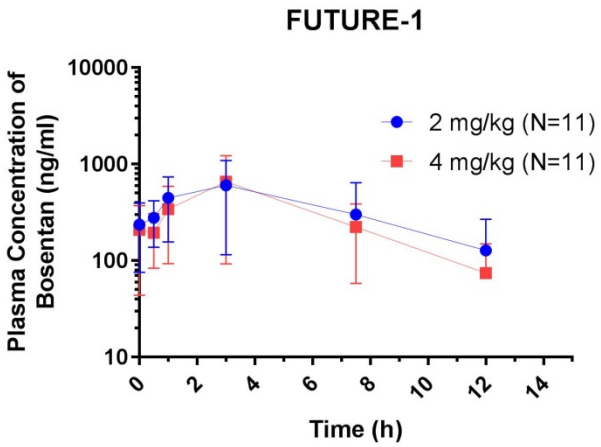


3.3.3 Does the proposed dose of (b) (4) b.i.d. with oral dispersible tablet provide an appropriate bridge to exposures achieved in the pivotal efficacy study, BREATHE-3?

As noted earlier [Figure 1], the systemic exposures to bosentan when administered at a dose of approximately 2 mg/kg twice daily using film coated tablet in BREATHE-3 was 37% lower compared to adults receiving the approved dose of 125 mg b.i.d. Moreover, the relative bioavailability of the intended pediatric dosage form i.e., oral dispersible tablet, was 13% lower compared to film coated tablets as observed from the relative bioavailability study in healthy adults [Table 1]. Therefore, with an aim to increase pediatric systemic exposures so as to match adult exposures as best as possible, the Applicant performed two additional studies, FUTURE-1 and FUTURE-3, to better characterize the pharmacokinetics of bosentan in pediatric patients. FUTURE-1 evaluated a higher dose (4 mg/kg versus 2 mg/kg b.i.d.) and FUTURE-3 evaluated a more frequent dosing regimen of bosentan (2 mg/kg t.i.d. versus 2 mg/kg b.i.d.). As seen from Figure 2, an increase in dose to 4 mg/kg b.i.d. did not result in any appreciable increase in systemic exposures to bosentan in comparison to exposures achieved following 2 mg/kg b.i.d. This observation is similar to that seen in adult PAH patients in study AC-052-357 where increase in dose from 62.5 mg b.i.d to 125 mg b.i.d. (approx. 1.87 mg/kg using the mean body weight of 66.9 kg) resulted in only about 40% increase in AUC_{τ}, indicating systemic exposures

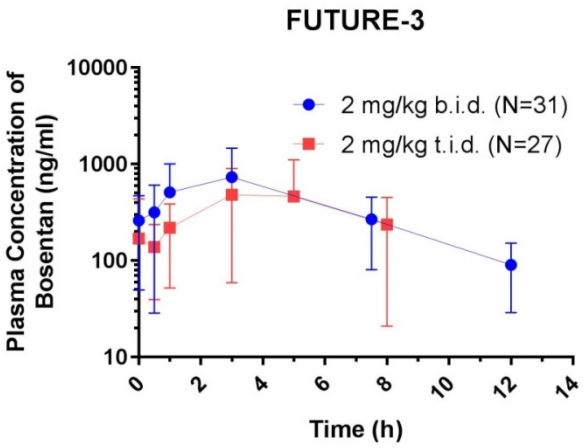
nearing a plateau. Such an observation has also been observed in healthy adults but at a higher dose where systemic exposures reached a plateau beyond 500 mg b.i.d. These results suggest similarity in pharmacokinetic characteristics between adults and pediatric patients such that increasing the dose beyond 2 mg/kg b.i.d. may not significantly increase systemic exposures to bosentan.

Figure 2. Plasma concentration-time profiles of bosentan following multiple-dose administration of 2 and 4 mg/kg b.i.d. in pediatric patients with PAH. Data represents mean ± SD.



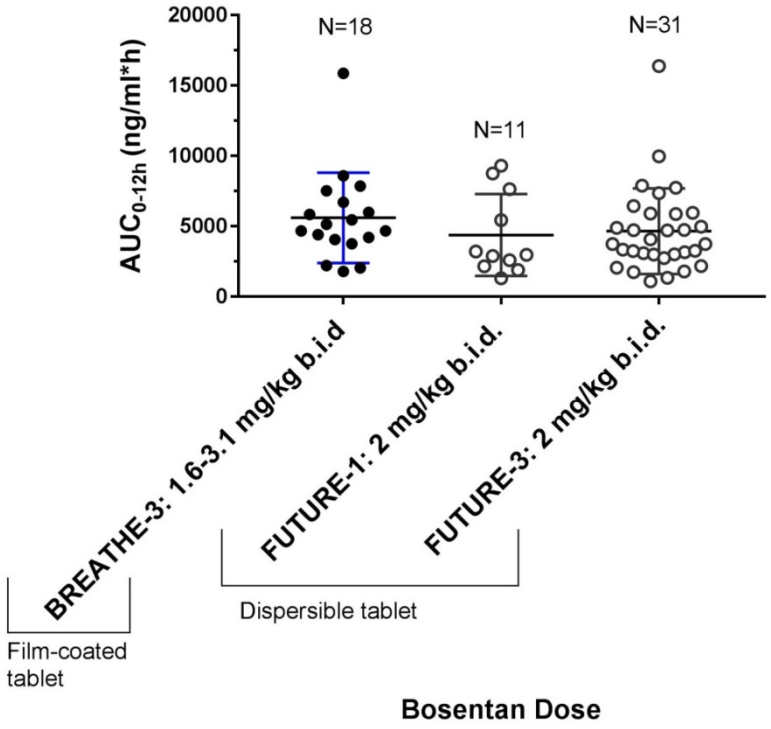
It was also observed from FUTURE-3 that increase in dosing frequency to 2 mg/kg t.i.d. did not increase systemic exposures to bosentan in comparison to exposures achieved following 2 mg/kg t.i.d. [Figure 3]. In fact, there is a modest reduction in exposures by about 15% when administered t.i.d. versus b.i.d. The reason for this modest decrease is not clearly understood. Nevertheless, there is a significant overlap in exposures between these two regimens due to the variability in bosentan pharmacokinetics. An evaluation in adults by administering bosentan more frequently than twice-daily has not been performed.

Figure 3. Plasma concentration-time profiles of bosentan following multiple-dose administration of 2 mg/kg b.i.d. and 2 mg/kg t.i.d. in pediatric patients with PAH. The plasma concentration-time profile of bosentan is shown in the following figure. Data represents mean ± SD.



With results from FUTURE-1 and FUTURE-3 suggesting that the systemic exposures to bosentan might have reached its maximum at 2 mg/kg b.i.d. in pediatric PAH patients, it is important to assess whether exposures achieved following administration of oral dispersible tablet at (b) (4) b.i.d. (the proposed dosage form and dosing regimen in pediatric patients) is similar to that achieved in BREATHE-3 (pivotal efficacy study). Due to small sample size and high variability in bosentan pharmacokinetics, it is best to compare the range of observed exposures between these studies than by using any measure of central tendency. As it can be seen from Figure 4, the range of exposures achieved following 2 mg/kg b.i.d. in FUTURE-1 and FUTURE-3 using the oral dispersible tablet spans the exposures achieved in BREATHE-3. Therefore, the proposed dosing regimen of (b) (4) b.i.d. with oral dispersible tablet represents an appropriate bridge to exposures achieved in the pivotal efficacy study, BREATHE-3.

Figure 4. Comparison of the systemic exposures to bosentan between film coated tablets and dispersible tablet formulations in pediatric patients with PAH. Data represents mean ± SD.



3.3.4 Is the recommended dose and dosing regimen appropriate for pediatric patients with PAH?

The review team agrees with the Applicant proposed dose of (b) (4) twice-daily using oral dispersible tablet for the treatment of PAH in pediatric patients. However, during review, the CMC team noted that the Applicant has not submitted data to ensure product quality of the dosage form when split into half and quarter parts (refer CMC IR sent 11/18/2016). Particularly, there were concerns that splitting the dosage form into four quarters could lead to greater variations in content mass between the quadrisected pieces leading to dosing errors. To address this concern, the review team assessed the pharmacokinetic variability in FUTURE-1 and FUTURE-3 studies that allowed quadrisection of dosage forms to achieve the intended doses based on body weight. It was observed that there was a higher variability in systemic exposure (AUC_{0-24h}) when quadrisected pieces of tablet were administered (CV: 86%) in comparison to administration of intact tablets (CV%: 56%) [Table 2]. Therefore, to avoid any potential product issues that might arise with quadrisecting the oral dispersible tablet, the review team proposes dosing based on body weight bands [Table 3] that allow only bisection of the scored dosage form. Since there is no appreciable change in systemic exposures when dosed beyond (b) (4)

the proposed body weight based dose range is optimal to address the potential product quality issue and also is within the clinical experience as evaluated in studies BREATHE-3, FUTURE-1 and FUTURE-3.

Table 2. Comparison of the systemic exposures (AUC_{0-24h}) to bosentan following administration of intact, quadrisected and the combination of intact and quadrisected tablets of dispersible formulation of bosentan in pediatric patients with PAH.

Dose: 2 mg/kg b.i.d.	Source of Data: FUTURE-1 and FUTURE-3		
PK Parameter	**Intact tablets (N=16)**	**QTR tablets (N=32)**	**Intact + QTR tablets (N=26)**
AUC_{24h} (ng/ml*h)	9035 ± 5049	8153 ± 6985	9396 ± 6361
% CV	56	86	68

Tablet splitting: Only quadrisection but not the bisection of the tablets were adopted in both FUTURE-1 and FUTURE-3 studies.

Table 3. Proposed weight-based dosing for pediatric PAH patients.

Target Dose: (b) (4)	Dose Adjustment Limit: 80-200% of Target Dose	(b) (4)
Weight band (kg)	**Initial Dose (mg), b.i.d.**	**Maintenance Dose (mg), b.i.d.**
≥4-8	16	16
≥8-16	32	32
≥16-24	48	48
≥24-40	64	64

4. APPENDICES

This section includes information on – (a) bioanalytical method validation and performance supporting all pharmacokinetic studies, and (b) brief description of study design and detailed pharmacokinetic results from the studies submitted in this application.

4.1 Summary of Bioanalytical Method Validation and Performance

Plasma concentrations of bosentan and its metabolites, Ro 48-5033, Ro 47-8634, Ro 64-1056 were measured by validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assay. It was found that:

- The precision and accuracy values (Table 4) of at least two-thirds of the overall QC samples from the supporting bioanalytical reports were equal to or better than 15% (20% at the LLOQ).

- Bosentan and its metabolites, Ro 48-5033, Ro 47-8634, Ro 64-1056 were found to be stable in plasma after at least three freeze-thaw cycles at -20˚ C, at room temperature storage over 6 h (short-term), at -20˚ C storage over 504 days (long term) and at auto-sampler storage at 4˚ C for at least 7 days.
- The QC sample accounting for dilution showed no bias. Although there were carry over effects observed for all the analytes, appropriate measures were taken to circumvent the carry over effects.
- More than two-thirds of the incurred sample reanalysis (ISR) fell within 20% deviation.

The bioanalytical methods satisfy the criteria for 'method validation' and 'application to routine analysis' set by the 'Guidance for Industry: Bioanalytical Method Development', and is acceptable.

Note: Bioanalysis of bosentan and its metabolites, Ro 48-5033, Ro 47-8634, Ro 64-1056 from Study AC-052-116, BREATHE-3, FUTURE-1 were performed at (b) (4) and FUTURE-3 at Actelion Pharmaceuticals Ltd, Switzerland. Because approval of the dispersible dosage form for adults would solely rely on Study AC-052-116, this relative BA study was considered important. Therefore, OCP requested a routine inspection of the bioanalytical site of Study AC-052-116 via Office of Study Integrity and Surveillance (OSIS) on 09/28/2016. It was later learnt that the bioanalytical site at (b) (4) closed its operations in 2012 and all the records relevant to Study AC-052-116 were transferred to the Applicant, Actelion Pharmaceuticals, Ltd. Since the bioanalytical site was closed, the routine inspection would be limited to a record audit and therefore no inspections were carried out by OSIS.

Table 4. Summary of bioanalytical methods and validation in each clinical study

Sponsor's study no	Bioanalytical study no	Facility	Analytical method	Analyte	Sample volume	Analytical range (ng/ml)	Precision (CV %)	Accuracy (%)
AC-052-116	(b) (4)	(b) (4)	LC-MS/MS	Bosentan	400 µl	1-4096	≤4.8%	99.6-105.3
				Ro 48-5033	400 µl	2-512	≤5.0%	97.5-101.1
				Ro 47-8634	400 µl	2-512	≤4.9%	98.7-106.4
				Ro 64-1056	400 µl	2-512	≤5.5%	94.8-98.4
BREATHE-3			LC-MS/MS	Bosentan	375 µl	1-4096	≤7.6%	95.4-103.3
				Ro 48-5033	375 µl	2-512	≤6.0%	98.1-102.3
				Ro 47-8634	375 µl	2-512	≤6.4%	96.9-100.8
				Ro 64-1056	375 µl	2-512	≤6.9%	97.8-101.4
FUTURE-1			LC-MS/MS	Bosentan	100 µl	1-4096	≤6.8%	97.6-105.8
				Ro 48-5033	100 µl	2-512	≤7.6%	99.3-103.2
				Ro 47-8634	100 µl	2-512	≤6.9%	98.4-101.8
				Ro 64-1056	100 µl	2-512	≤9.0%	100.4-102.3
FUTURE-3	BA-12.402	Actelion Pharmaceuticals Ltd	LC-MS/MS	Bosentan	10 µl	1-5000	≤5.4%	95.0-101.6
			(Batch I)	Ro 48-5033	10 µl	2-600	≤8.1%	95.5-108.7
				Ro 47-8634	10 µl	2-600	≤4.0%	100.2-102.5
				Ro 64-1056	10 µl	2-600	≤7.1%	98.8-104.1
FUTURE-3	BA-12.402	Actelion Pharmaceuticals Ltd	LC-MS/MS	Bosentan	50 µl	2-1000	≤9.0%	96.9-105.3
			(Batch II)	Ro 48-5033	50 µl	2-1000	≤5.0%	90.7-105.7
				Ro 47-8634	50 µl	2-1000	≤4.7%	94.1-103.1
				Ro 64-1056	50 µl	2-1000	≤5.0%	92.0-108.1

4.2 Clinical PK and/or PD Assessments

A) Study AC-052-116: Relative bioavailability of single dose bosentan administered orally as two 32 mg dispersible tablets (test) and as a 62.5 mg film coated tablet (reference)

This relative bioavailability study was conducted to test whether the pharmacokinetics of two 32 mg (a total of 64 mg) dispersible tablet formulation of bosentan is similar to that of 62.5 mg adult approved formulation, film coated tablet formulation in healthy adults.

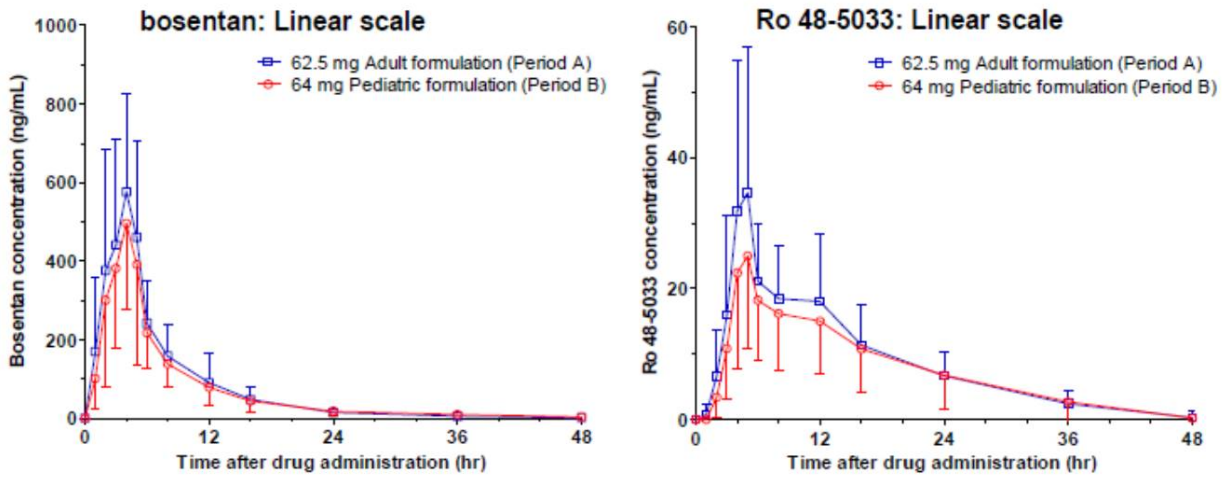
This was a single center, randomized, two treatment, two period crossover study in healthy male adults. A total of 16 subjects were randomized to treatment period sequence A/B or B/A (8 subjects per sequence). No formal sample size calculations were performed. All subjects completed the study and were included in pharmacokinetic evaluation.

Treatment A (Reference): a single oral 62.5 mg dose of bosentan given as one film coated tablet (adult formulation)

Treatment B (Test): a single oral 64 mg dose of bosentan given as two 32 mg dispersible tablets (adult formulation)

Plasma concentrations of bosentan and its active metabolite Ro 48-5033 were quantified.

Figure 5. Plasma concentration-time profile of bosentan and its active metabolite, RO 48-5033 following single oral administration of either 62.5 mg film coated tablet or two 32 mg (a total of 64 mg) dispersible tablets in healthy adults.

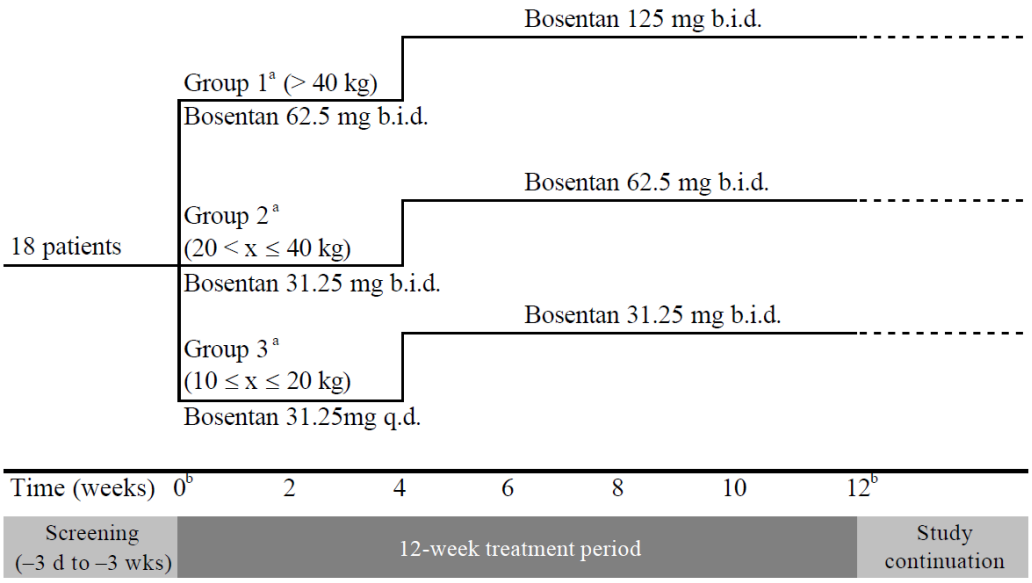


B) BREATHE-3 (AC-052-356): Pharmacokinetics of bosentan film coated tablet in pediatric PAH patients

The primary objective of this study was to evaluate the pharmacokinetics of bosentan film coated tablet formulation in pediatric patients with PAH. The secondary objectives of this study include assessment of tolerability and efficacy (i.e. change in exercise capacity, hemodynamics [PVR] and WHO functional classification).

Study design: Multicenter, open-label, non-controlled, parallel-group single- and multiple-dose study. Nineteen patients were enrolled (10-20 kg: 7 subjects, 20-40 kg: 6 subjects and >40 kg: 6 subjects) in the study. One patient was prematurely withdrawn after 7 days due to elevated liver aminotransferases, and 18 patients completed the week 12 assessments. One additional patient was withdrawn on Day 197 because of a recurrent increase in alanine aminotransferase (ALT).

Figure 6. Schematics of the study design adopted in BREATHE-3 study using film coated tablet in pediatric patients with PAH



[a] Each group included 3 patients on conventional vasodilator/anticoagulant therapy and 3 on epoprostenol therapy.

[b] Single-dose pharmacokinetic profiles were obtained on Day 1 and multiple-dose profiles at the Week-12 visit. Single doses given on Day 1 were 125 mg (Group 1), 62.5 mg (Group 2), and 31.25 mg (Group 3).

Pharmacokinetic assessments were performed after single and multiple-dose (week 12) administration of 31.25 mg (1.6-2.3 mg/kg b.i.d), 62.5 mg (1.7-3 mg/kg b.i.d) and 125 mg b.i.d (1.6-3.1 mg/kg b.i.d) doses in pediatric patients with PAH aged 3 to 15 years old. The pharmacokinetic samples were collected over a period of 24 h.

Figure 7. Average (± SEM) plasma concentration-time profiles of bosentan and its active metabolite (Ro 48-5033) in pediatric patients with PAH following single or multiple administration with three different doses (31.25 mg, 62.5 mg and 125 mg twice-daily).

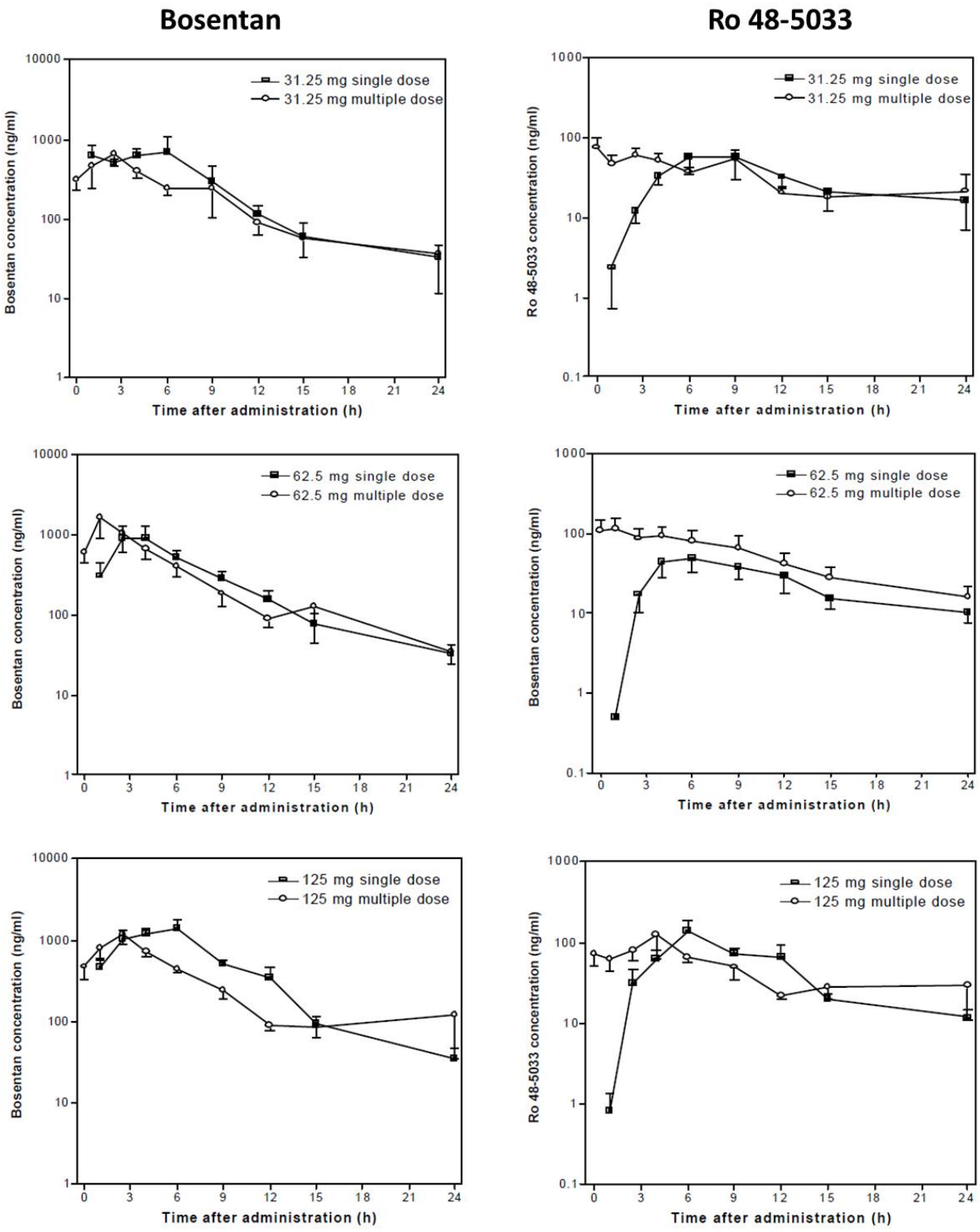


Table 5. Pharmacokinetic parameters of bosentan and its active metabolite (Ro 48-5033) following single or multiple-dose administration of bosentan film coated tablets in pediatric patients with PAH.

Bosentan					
Treatment	$AUC_{0-\infty}$ (ng•h/ml)	AUC_{τ} (ng•h/ml)	C_{max} (ng/ml)	t_{max} (h)	$t_{1/2}(\beta)$ (h)
31.25 mg SD	5453 (56)		959 (69)	1.0 (1.0 - 6.0)	4.7 (40)
31.25 mg MD		3496 (49)	685 (77)	2.5 (0.0 - 9.0)	6.0 (61)
62.5 mg SD	6118 (55)		815 (108)	2.5 (1.0 - 4.0)	5.3 (35)
62.5 mg MD		5428 (79)	1136 (85)	1.0 (0.0 - 2.5)	5.6 (25)
125 mg SD	10777 (32)		1709 (39)	4.0 (2.5 - 6.0)	4.2 (44)
125 mg MD		6124 (27)	1200 (50)	1.8 (1.0 - 6.0)	5.3 (38)
Ro 48-5033					
Treatment	AUC_{0-t} (ng•h/ml)	AUC_{τ} (ng•h/ml)	C_{max} (ng/ml)	t_{max} (h)	
31.25 mg SD	492 (80)		52.9 (73)	6.0 (4.0 - 12.3)	
31.25 mg MD		511 (41)	87.6 (46)	1.7 (0.0 - 9.2)	
62.5 mg SD	465 (86)		46.3 (110)	6.0 (4.0 - 15.0)	
62.5 mg MD		712 (115)	95.0 (103)	0.0 (0.0 - 3.8)	
125 mg SD	946 (60)		106 (89)	6.0 (4.0 - 6.9)	
125 mg MD		713 (53)	114 (86)	5.0 (0.0 - 9.0)	

Data expressed as geometric mean (CV%) and tmax as median (range). SD=Single dose; MD=Multiple dose

C) Study AC-052-357: Pharmacokinetics of bosentan in adult patients with PAH

Source: NDA 21-290/S-001, Clinical Pharmacology review dated on 02/05/2003; Dingemansse J et al., Clin Pharmacokinet. 2004; 43(15): 1089-1115)

In order to allow comparison of bosentan PK between pediatrics and adults, study AC-052-357 was used which evaluated PK in a subset of adult patients with PAH. This is a multicenter, open label, single arm, safety study of bosentan in adult patients with PAH. A pharmacokinetic sub-study was performed in 13 patients. The study used film coated tablet formulation. The patients received 62.5 mg dose of bosentan b.i.d. for the first 4 weeks and then were titrated to 125 mg b.i.d. based on tolerability. The pharmacokinetics of bosentan and its metabolites (Ro 48-5033, Ro 47-8634, Ro 64-1056) were determined at least 2 weeks after treatment with 62.5 mg and 125 mg twice-daily doses. The pharmacokinetic data were analyzed from 12 patients who completed the lower dose level and 11 patients who completed the higher dose level.

Figure 8. Average (± SEM) plasma concentration-time profile of bosentan following multiple dose administration of either 62.5 mg b.i.d. or 125 mg b.i.d. in adult patients with PAH.

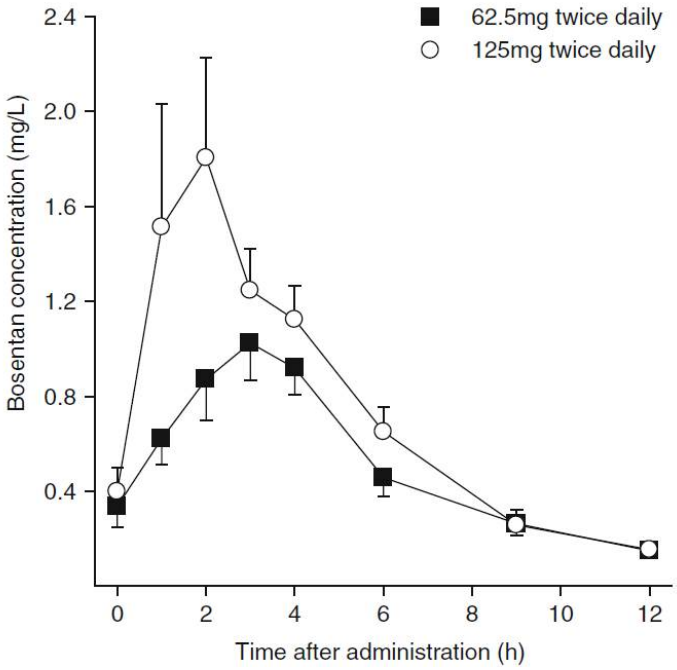


Table 6. The pharmacokinetic parameters of bosentan and its active metabolite (Ro 48-5033) following multiple dose administration of 62.5 mg and 125 mg twice-daily doses in adult patients with PAH.

Bosentan dose (mg)	C_{max} (µg/L)	t_{max} (h)	AUC_{τ} (µg • h/L)
Bosentan			
62.5	1190 (810, 1560)	3.0 (1.0–4.0)	6230 (4580, 7880)
125	2290 (1230, 3340)	2.3 (1.0–6.0)	8910 (6300, 11500)
Ro 48-5033			
62.5	356 (85.2, 627)	4.0 (0.0–9.0)	2460 (613, 4307)
125	429 (49.3, 808)	2.3 (0.0–6.0)	2573 (93, 5053)

Data are expressed as arithmetic mean (95% CIs), for t_{max} as median (range)

D) FUTURE-1 (AC-052-365): Pharmacokinetics of bosentan dispersible tablet formulation in pediatric patients with PAH following administration of 2 mg/kg b.i.d. and 4 mg/kg b.i.d.

The primary objective of the FUTURE-1 study is to evaluate the systemic exposure (week 12) to bosentan following administration of dispersible tablet formulation (initial dose: 2 mg/kg b.i.d. for 4 weeks and then up titrated to 4 mg/kg b.i.d.) in pediatric patients with idiopathic or familial PAH aged 2 to 11 years. In a PK sub-study, the objective was to compare the systemic exposure to bosentan following administration of 2 mg/kg and 4 mg/kg of dispersible tablet formulation.

A total of 36 patients were enrolled in this study. Twenty five patients were enrolled as per the original protocol which was intended to evaluate the pharmacokinetics of bosentan at least two weeks after up-titration of the dose to 4 mg/kg b.i.d. in pediatric patients with PAH. Eleven patients were enrolled as per the amended protocol which was aimed to evaluate the pharmacokinetics of bosentan at least two weeks after initiation of bosentan at 2 mg/kg b.i.d. and two weeks after up-titration of bosentan to 4 mg/kg b.i.d. in pediatric patients with PAH. One patient was excluded from the analysis due to major protocol violation.

Figure 9. Schematics of the study design adopted in FUTURE-1 study using film coated tablet in pediatric patients with PAH

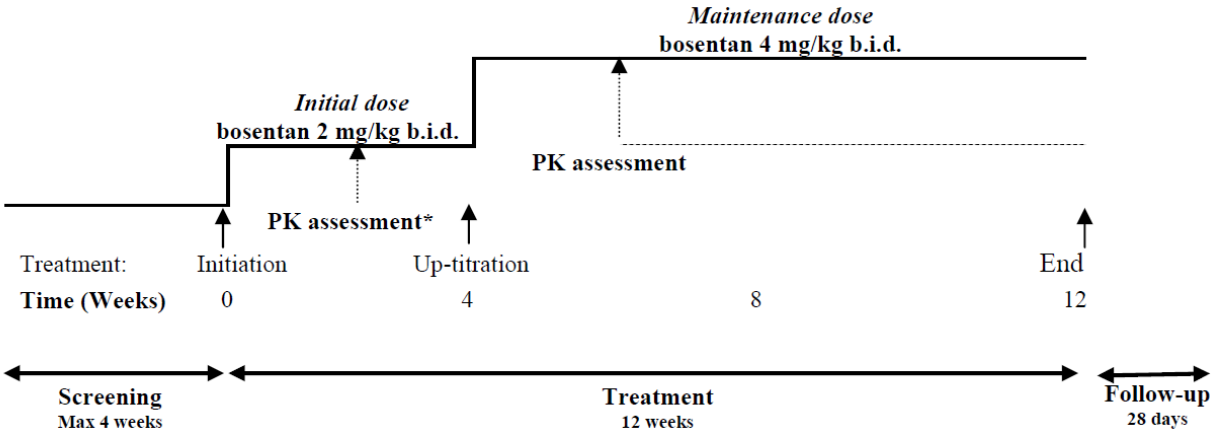


Table 7. The pharmacokinetic parameters of bosentan and its active metabolite (Ro 48-5033) following multiple dose administration of 2 mg/kg and 4 mg/kg twice-daily doses in pediatric patients with PAH.

Bosentan				
Dose	**N**	**AUC 0-12h (ng/ml*h)**	**Cmax (ng/ml)**	**Tmax (h)**
2 mg/kg, b.i.d.	11	2966 (67)	574 (66)	3 (1.0-7.5)
4 mg/kg, b.i.d.	11	2933 (58)	618 (68)	3 (0.0-7.5)
4 mg/kg, b.i.d.	35	3643 (55)	805 (72)	3 (0.0-8.5)
Ro 48-5033				
Dose	**N**	**AUC 0-12h (ng/ml*h)**	**Cmax (ng/ml)**	**Tmax (h)**
2 mg/kg, b.i.d.	11	522 (64)	77 (54)	0.5 (0.0-7.5)
4 mg/kg, b.i.d.	35	523 (92)	91 (135)	3 (0.0-12.0)

Data expressed as median (CV%), for Tmax as median (range)

E) FUTURE-3 (AC-052-373): Pharmacokinetics of bosentan dispersible tablet formulation in pediatric patients with PAH following administration of 2 mg/kg b.i.d. and 2 mg/kg t.i.d.

This was a prospective, multicenter, open-label, randomized, multiple dose phase 3 study intended to evaluate the pharmacokinetics, safety and tolerability of dispersible tablet formulation in pediatric patients with PAH from ≥ 3 months to ≤ 12 years of age. As increasing the dose of bosentan dispersible tablet from 2 mg/kg to 4 mg/kg b.i.d. did not result in an increase in systemic exposure to bosentan in FUTURE-1, this study assessed the pharmacokinetics of 2 mg/kg b.i.d. and 2 mg/kg t.i.d. in pediatrics PAH patients. A total of 64 patients were enrolled in this study. The patients were randomized to bosentan 2 mg/kg b.i.d. (n=33) and 2 mg/kg t.i.d. (n=31). Among the 64 randomized patients, 21 were < 2 years (10 b.i.d., 11 t.i.d.) and 43 were ≥ 2 years of age (23 b.i.d., 20 t.i.d.).

Figure 10. Schematics of the study design adopted in FUTURE-1 study using film coated tablet in pediatric patients with PAH

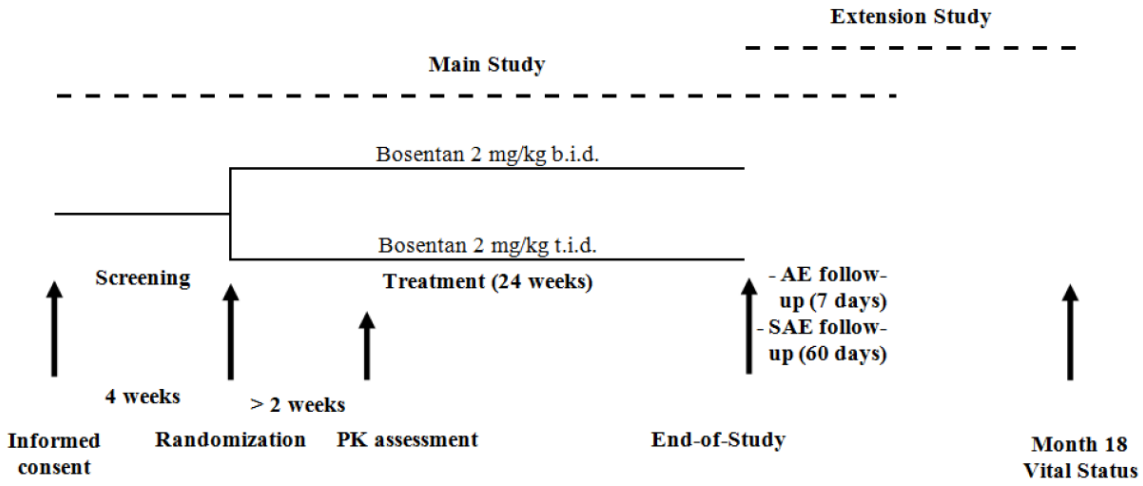


Table 8. The pharmacokinetic parameters of bosentan and its active metabolite (Ro 48-5033) following multiple dose administration of 2 mg/kg b.i.d. and 2 mg/kg t.i.d. in pediatric patients with PAH.

Bosentan				
Dose	**N**	**AUC 0-24h (ng/ml*h)**	**Cmax (ng/ml)**	**Tmax (h)**
2 mg/kg, b.i.d.	31	7453 (66)	762 (86)	3 (0.0-7.5)
2 mg/kg, t.i.d.	27	6845 (84)	446 (102)	3 (1.0-8.0)
Ro 48-5033				
Dose	**N**	**AUC 0-24h (ng/ml*h)**	**Cmax (ng/ml)**	**Tmax (h)**
2 mg/kg, b.i.d.	31	1132 (68)	91 (67)	3.0 (0.0-12.0)
2 mg/kg, t.i.d.	27	950 (81)	67 (115)	3 (0.0-8.0)

Data expressed as median (CV%), for Tmax as median (range)

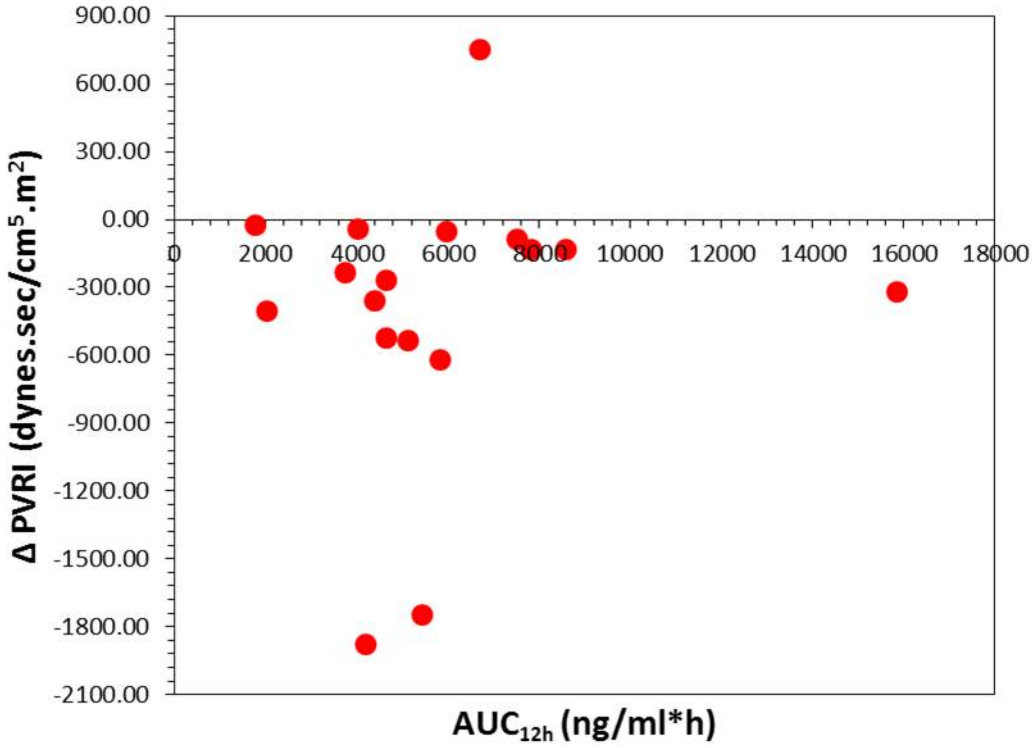
F) Covariates: Impact of age, gender and body weight on bosentan pharmacokinetics

Following administration of bosentan dispersible tablet (FUTURE-1 and FUTURE-3), the effect of covariates such as age, gender and body weight on the pharmacokinetics of bosentan were evaluated in pediatric patients with PAH. It was found that covariates such as age, gender and body weight did not affect the systemic exposures to bosentan in pediatric PAH patients.

G) Exposure-Response Analyses

The efficacy of bosentan in pediatric patients with PAH is primarily based on the change in pulmonary vascular resistance (PVR) on bosentan treatment. BREAHTE-3 is a pivotal trial in which the efficacy measures such as change in PVR was collected as secondary endpoint following administration of bosentan film coated tablet in pediatric patients with PAH. The relationship between steady state systemic exposure ($AUC_{0\text{-}12h}$) and change in PVR index (PVRI) from baseline to week 12 was evaluated.

Figure 11. Relationship between steady state systemic exposures ($AUC_{0\text{-}12h}$) to bosentan and change in PVRI from baseline to week 12 in pediatric patients with PAH treated with film coated tablet formulation. (Data source: BREATHE-3)



As seen from Figure 11, in general, there is a reduction in change from baseline PVRI in the range of exposures studied in BREATHE-3 with the exception of one patient who showed an increase upon treatment. Any formal assessment of exposure-response analysis with the extent of pharmacokinetic / pharmacodynamic information available from this study is limited.

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/s/

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