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CLINICAL REVIEW(S)

CLINICAL AND CLINICAL PHARMACOLOGY EFFICACY REVIEW

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Established Name	Bosentan
(Proposed) Trade Name	TRACLEER
Applicant	Actelion
Formulation(s)	Oral dispersible tablets
Dosing Regimen	(b) (4)
Applicant Proposed Indication(s)/Population(s)	Treatment of pulmonary arterial hypertension in pediatrics

1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following two questions related to the efficacy of bosentan in pediatric patients with pulmonary arterial hypertension (PAH).

1.1.1 Can the relationship between Δ PVR and Δ 6MWD developed using data from intervention trials in adult patients with PAH be used to extrapolate efficacy to pediatric patients?

The relationship between Δ PVR and Δ 6MWD was evaluated using linear regression analysis of pooled patient-level data from 12 randomized, placebo-controlled trials in adults of 9 drugs approved for the treatment of PAH. The relationship is based on pooling both treatment and placebo arms. The slope is -0.055 (-0.62, -0.047) m per dyne*sec/cm⁵, p-value=<0.0001 (Figure 1). The slope is consistent in magnitude across drug classes (Figure 3) and individual drugs (Figure 5) as shown by the overlapping 95% confidence intervals.

For bosentan, patient-level data from 3 randomized, placebo-controlled trials in adults were used to evaluate how much of the treatment effect on 6MWD could be explained by the treatment effect on Δ PVR. The magnitude of the bosentan treatment effect on the Δ 6MWD that can be explained by Δ PVR was determined in 3 sequential steps: 1) determined the magnitude of the treatment effect on 6MWD using regression analysis with treatment as covariate; 2) tested whether including Δ PVR in the model modifies the treatment effect; and 3) computed the proportion of the treatment effect on 6MWD explained by Δ PVR when treatment is removed from model.

- Bosentan treatment had a significant effect on $\Delta 6\text{MWD}$ and ΔPVR (Table 9). After adjusting for placebo, the mean increase in 6MWD from baseline was +33 m (p-value 0.0005) and the mean change in PVR from baseline was -249 dyne*sec/cm⁵ (p-value <0.0001).
- When ΔPVR was included in the regression model of the relationship between treatment (bosentan vs. placebo) and $\Delta 6\text{MWD}$, the treatment effect decreased from 35 m to 18 m, and was not statistically significant at alpha of 0.05 (p-value =0.056, Table 11). Approximately 49% of bosentan's treatment effect is explained by ΔPVR [$100\%*(1-18/35)$].

Overall, the relationship between relationship between ΔPVR and $\Delta 6\text{MWD}$ support the use of ΔPVR to bridge efficacy between adult and pediatric PAH patients for bosentan.

1.1.2 Do pediatric patients with PAH achieve a sufficient decrease in ΔPVR with bosentan treatment to establish clinical efficacy?

After administration of 2 mg/kg bid bosentan (film-coated tablets) to pediatric PAH patients in AC-052-356, the mean ΔPVR was -389 (95% CI: -682, -96) dyne*sec/cm⁵ (Table 13). This mean effect was similar to the mean ΔPVR in adult PAH patients treated with bosentan 125 mg bid [-158 (95% CI: -256, -60) dyne*sec/cm⁵] and was significantly decreased (p-value=0.003) compared to ΔPVR in adults treated with placebo [+138 (95% CI: 54, 222) dyne*sec/cm⁵]. This mean effect was also decreased (p-value=0.06) compared to the mean ΔPVR in pediatrics taking placebo for 16 weeks in study A1481131 [+6 (95% CI: -255, 268) dyne*sec/cm⁵; Clinical Pharmacology Review by Dr. Brar, 4/27/2012].

Stochastic simulations were performed using the regression model in adults to assess whether the change in ΔPVR in pediatrics would result in increases in mean $\Delta 6\text{MWD}$ that excluded zero. The simulations included 1) uncertainty in mean ΔPVR for bosentan and placebo treatments by sampling from a parametric distribution of ΔPVR values; 2) a random effect for study on model parameters to account for any heterogeneity across studies; and 3) uncertainty in the regression estimates by sampling from variance-covariance matrix of parameter estimates. The predicted treatment effect of bosentan on 6MWD in pediatrics was 14 m (95% CI: 3–31 m) for a mean decrease in ΔPVR of -212 dyne*sec/cm⁵ for bosentan and -27 dyne*sec/cm⁵ for placebo (Table 14).

Based on the relationship between ΔPVR and $\Delta 6\text{MWD}$ in adults, the observed mean decrease in ΔPVR with bosentan treatment in pediatric patients with PAH would result in an improvement in the 6MWD to establish efficacy.

1.2 Recommendation

Adult data from 12 clinical trials (9 approved PAH drugs from 5 drug classes) identified and quantified the relationship between $\Delta 6\text{MWD}$ and ΔPVR . This relationship combined with the PVR data from BREATHE-3 establishes clinical efficacy for bosentan in pediatric patients with PAH.

Since the completion of BREATHE-3 study, invasive procedures such as the right heart catheterization (RHC) to obtain PVR measurements have been deemed unethical in pediatric patients because of a small, but unacceptable risk of death from this procedure. Therefore, our modeling approach to bridge the clinical efficacy using PVR obtained by RHC is limited to bosentan and is not intended to be generalized to other drugs.

2 PERTINENT REGULATORY BACKGROUND

TRACLEER (bosentan) was approved for the treatment of pulmonary arterial hypertension (PAH) in adults on November 20, 2001.

The Tracleer 32 mg dispersible tablet was approved in the EU in 2009, and dose recommendations were included in the Summary of Product Characteristics for pediatric PAH patients above 2 years of age. In November 2014, the CHMP granted a positive opinion on a variation to include the data generated in the pediatric PAH studies with bosentan 32 mg dispersible tablets conducted as a part of the agreed EU Pediatric Investigation Plan [EMA-000425-PIP02-10-M04] in the EU SmPC. The dose recommendations were extended to pediatric PAH patients above 1 year of age.

(b) (4)

In an Advice Letter dated 10/29/2015, the FDA agreed that a NDA for pediatrics could be based on completed data from 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.

3 REVIEWER'S ANALYSIS

3.1 Introduction

PAH is a chronic syndrome characterized by progressive deterioration of cardiopulmonary hemodynamics and right ventricular function, leading to impaired exercise capacity and premature death. PAH patients become symptomatic mainly because of the inability of their right ventricular to overcome the increased right ventricular afterload, and thus they are unable to adequately increase pulmonary blood flow (cardiac output) for exercise demand. RHC with measurements of cardiopulmonary hemodynamics quantifies both the disease process (pulmonary vascular resistance [PVR]) and its main functional consequence (cardiac output [CO] limitation). Hemodynamic measurements have not been considered as primary endpoints in randomized controlled trials of new pharmacological approaches to PAH therapy because improvements of hemodynamics observed in randomized clinical trials correlate with exercise capacity changes but have not shown to predict clinical events (e.g., mortality/morbidity).^{1,2}

¹ Ventetuolo CE, Gabler NB, Fritz JS, et al. Are hemodynamics surrogate endpoints in pulmonary arterial hypertension? *Circulation* 2014.

To date, the 6-minute walk distance (6MWD) has been used in a number of drug development programs to establish the efficacy of new therapies for PAH in adults (Table 1). Recent approvals of macitentan (OPSUMIT, 2013) and selexipag (UPTRAVI, 2015) used a composite efficacy endpoint of death, morbidity and disease progression as the primary endpoint. The 6-minute walk test may not be appropriate for children with PAH at all ages for reasons of compliance or reliability. Peak oxygen consumption (VO₂, maximal exercise test) was used (b) (4) to evaluate pharmacologic intervention with sildenafil.

Table 1. Drugs Approved for Treatment of PAH WHO Group 1

Treatment (date of approval)	Primary Efficacy Endpoint
Epoprostenol (FLOLAN, 1995)	6MWD at 12 weeks
Bosentan (TRACLEER, 2001)	6MWD at 16 weeks
Treprostinil (TYVASO, 2002)	6MWD at 12 weeks
Treprostinil (REMODULIN, 2002)	6MWD at 12 weeks
Tadalafil (ADCIRCA, 2003)	6MWD at 16 weeks
Iloprost (VENTAVIS, 2004)	Clinical response at 12 weeks (composite of 6MWD, NYHA functional class, death or disease progression)
Sildenafil (REVATIO, 2005)	6MWD at 12 weeks
Ambrisentan (LETAIRIS, 2007)	6MWD at 12 weeks
Riociguat (ADEMPAS, 2013)	6MWD at 12 weeks
Macitentan (OPSUMIT, 2013)	Composite endpoint (time to death, significant morbidity event, or other worsening of PAH)
Selexipag (UPTRAVI, 2015)	Composite endpoint (time to death, hospitalization for PAH, PAH worsening, initiation of parenteral prostanoid therapy or chronic oxygen therapy, or other disease progression)

Abbreviations: 6MWD, 6-minute walk distance

The Office of Clinical Pharmacology in collaboration with the DCRP performed a systematic investigation of the relationship between hemodynamic measures and exercise capacity in adult patients with PAH in order to extrapolate efficacy of approved PAH treatments in pediatric population based on PVRI. The analysis supported a theoretical concept that change in hemodynamic measures can predict change in exercise capacity in adult patients using data from 13 trials (n=1096 subjects). A significant relationship was observed between the change in hemodynamic measures (Δ CI, Δ mPAP, Δ RAP, Δ SVRI, and Δ PVRI) and exercise capacity, Δ 6MWD (univariate, p-value all < 0.05). The estimated slope [-0.032 (-0.039, -0.024) m per dyn*s/cm⁵*m²] between Δ PVRI and Δ 6MWD was consistent across all trials of drug classes. A multivariate analysis showed

² Savarese G, Musella F, D'Amore C, et al. Haemodynamics, exercise capacity and clinical events in pulmonary arterial hypertension. Eur Respir J 2013;42(2):414-24.

that the combination of Δ PVRI and Δ RAP were significant predictors of Δ 6MWD in adult patients with PAH.

This analysis was presented on July 29, 2010 to the Cardiovascular and Renal Drugs Advisory Committee when discussing Revatio (sildenafil) for the treatment of pediatric PAH. The Committee Members agreed that there seems to be a relationship between PVRI and exercise capacity in adults with PAH; however, many questioned the extent and conditions under which it is reliable. Overall the committee was not in favor of using PVRI to extend the indication (improved exercise in adults) to another subpopulation of adults, stating that there are disparities in the type, etiology, pathogenesis and pathophysiology of PAH in adults. Although the etiologies of PAH are different in children than adults, and the clinical course has some inconsistencies, the committee agreed that they were similar enough, with the caveat of subgroups. The committee members agreed that it is technically feasible. Most of the members did not feel that the risk of collecting hemodynamic data in children raised ethical issues. Some members expressed that in children with PAH the benefits could outweigh the risk. The Committee had a split vote (Yes 7, No 6 and Abstain 0) on the question on whether PVRI can be used to demonstrate effectiveness to derive dosing information in pediatric PAH population for a product with an approved indication in adults with PAH. Committee members voting “no” agreed that more work is needed to validate the proposed hemodynamic endpoint using the data available in adults. It was suggested that the available data be used to determine if the result of a study could be predicted. Others stated that the validation model under development is the right one to use, but that the information provided to the committee was incomplete and needs more complete characterization. Suggestions from the committee members included looking at: (1) concordance of 6 minute walk data with peak oxygen consumption (VO_{2peak}), (2) time to clinical worsening, and 3) a combination of right atrial pressure and PVRI to determine a more suitable endpoint. In addition, it was suggested that effort should be given to developing a physical performance measure for children. One member suggested that there may be a class effect, and that one endpoint may not be suitable for all agents.

3.2 Objectives

Analysis objectives are to determine whether:

1. there is a consistent relationship between change in PVR and change in 6MWD across drugs and drug classes in adult patients with PAH;
2. bosentan treatment has a significant effect on change in PVR and change in 6MWD in adults;
3. bosentan treatment effect on 6MWD is explained by PVR; and
4. bosentan treatment has a significant effect on change in PVR in pediatrics with a magnitude similar to the treatment effect in adults.

3.3 Methods

3.3.1 Adult Clinical Trials

The 12 randomized, double-blinded, placebo-controlled adult trials used in the pooled analysis are summarized in Table 2. Trials were selected for inclusion in the database if the trial collected PVR and 6MWD data. For studies in which multiple assessments of 6MWD were obtained, the measure corresponding to the time of the PVR measure was used. Imputation methods for missing 6MWD endpoint data were based on individual study protocols. The most common imputation method was last-observation-carried-forward for missing data or when a patient crossed over from placebo to active treatment. In the bosentan trials, patients who had missing data on disease progression were assigned the worst value in the treatment cohort.

Datasets from 9 of the 12 studies were checked against source documents to confirm that the datasets were error free. For 3 studies (Iloprost/ME97218 and Treprostinil/P01:04 and P01:05) the database could not be verified because there were insufficient information in either the electronic datasets or source documents to reproduce study findings.

Table 2. Pooled Randomized, Placebo-Controlled Clinical Trials of Drugs Used to Treat PAH

Drug/Study ID	Efficacy Duration	Therapy	Patients	Number (Active/Placebo) with 6MWD or PVR assessments	Location of Data
Bosentan/AC-052-351/Phase 2	12 weeks	Bosentan 62.5 mg b.i.d. or matching placebo for 4 weeks, followed by bosentan 125 mg b.i.d. or matching placebo for the duration of study.	≥ 18 years WHO Group I FC III PAH , either PPH or PAH secondary to scleroderma or other CTD. (N=32)	Total: 21(active) / 11(placebo) 6MWD: 21(active) / 11(placebo) PVR: 19(active) / 10(placebo)	\\FDSWA150\NONECTD\N21290\N_000\2008-04-04 (database QC against source document)
Bosentan/AC-052-364 (EARLY)/Phase 3	24 weeks	Bosentan 62.5 mg b.i.d. or matching placebo for 4 weeks, followed by bosentan 125 mg b.i.d. or matching placebo for the duration of study.	≥ 12 years with mildly symptomatic PAH (WHO Group 1 FC II), either idiopathic/familial or secondary to HIV infection, anorexigen intake, CHD, CTD, or autoimmune disease. (N=185)	Total: 93(active)/92(placebo) 6MWD: 86(active)/91(placebo) PVR: 80(active)/88(placebo)	\\FDSWA150\NONECTD\N21290\S_012\2007-08-03 (database QC against source document)
Bosentan/AC-052-405 (BREATHE-5)/Phase 3	16 weeks	Bosentan 62.5 mg b.i.d. or matching placebo for 4 weeks, followed by bosentan 125 mg b.i.d. or matching placebo for the duration of study.	≥ 12 years with body weight ≥ 40 kg with WHO FC III PAH related to Eisenmenger Physiology (N=54)	Total: 37(active)/17(placebo) 6MWD: 34(active)/15(placebo) PVR: 34(active)/15(placebo)	\\Fdswa150\nonectd\N21290\N_000\2008-09-17\AC-052-405\ (database QC against source document)
Epoprostenol/BW46/Phase 3	12 weeks	Chronic Flolan Infusions plus conventional therapy to conventional therapy alone for 12 weeks	≥ 6 years with severe PAH (Class III or IV). (N = 81)	Total: 41(active)/40(placebo) 6MWD: 41(active)/32(placebo) PVR: 29(active)/23(placebo)	\\Cdsub1\EVSPROD\NDA020444\0003\m5\datasets\bw-study-46\analysis\ (database QC against source document)
Iloprost/ME97218/Phase 3	12 weeks	Patients were randomized (1:1) to iloprost (101 patients) by inhalation or placebo (102 patients).	≥18 years with primary or secondary PHT (FC III/IV).	Total: 101(active)/102(placebo) 6MWD: 95(active)/85(placebo) PVR: 70(active)/77(placebo)	\\Fdswa150\NONECTD\N21779\N_000\2004-06-30\crt\datasets\A02997 (database not QC against

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Drug/Study ID	Efficacy Duration	Therapy	Patients	Number (Active/Placebo) with 6MWD or PVR assessments	Location of Data
					source document)
Macitentan/ AC-055-302 (SERAPHIN) / Phase 3	24 weeks	742 patients were randomized (1:1:1 ratio) to macitentan 3 mg (250 patients), macitentan 10 mg (242 patients) or placebo (250 patients).	≥ 12 years with symptomatic PAH (WHO FC II/IV). The PAH etiology was required to be within groups 1.1 to 1.3 of the Venice classification. (Sub-study N=187)	Total: 492(active)/250(placebo) 6MWD: 248(3mg)/ 242(10mg)/ 249(placebo) PVR: 62(3mg)/ 57(10mg) /67(placebo)	\\Cdsub1\EVSPROD\NDA204410\0000\m5\datasets\ac-055-302\analysis\legacy\databases (database QC against source document)
Riociguat/12934 PATENT-1)/ Phase 3 (N=443)	12 weeks	Riociguat titrated up to 1.5 mg (n=63), 2.5 mg (n=254) or placebo (n=126) three times a day.	≥ 18 years with symptomatic PAH (WHO FC I/IV). The PAH etiology was group 1 of the Venice classification. (N=443)	Total: 317(active)/126(placebo) 6MWD: 254(active)/126(active) PVR: 232(active)/107(active)	\\Cdsub1\EVSPROD\NDA204819\0000\m5\datasets\12934 (database QC against source document)
Selexipag/ NS-304-02/ Phase 2 (N=43)	17 weeks	Selexipag titrated to 800 mcg bid or placebo	≥ 18 years with symptomatic PAH (WHO FC II/III). Idiopathic PAH, familial PAH, or PAH associated with CVD, corrected congenital vitium or anorexigen use.	Total: 33(active)/10(placebo) 6MWD: 32(active)/10(placebo) PVR: 29(active)/6(placebo)	\\cdsub1\evsprod\NDA207947\0000\m5\datasets\ns-304-02\tabulations\sdtm (database QC against source document)
Sildenafil/ A1481140/ Phase 3	12 weeks	Patients randomized 1:1:1:1 to Sildenafil 20, 40, 80 mg TID or Placebo (60 per group)	≥ 18 years with primary PPH, PAH with connective tissue disease, or PAH with surgical repair.	Total: 200(active)/66(placebo) 6MWD: 67(20mg)/ 64(40mg)/ 69(80mg)/ 66(placebo) PVR: 65(20mg)/ 63(40mg)/ 65(80mg)/ 64(placebo)	\\Fdswa150\NONECTD\N21845\N_000\2004-12-02\crt\datasets\1140 (database QC against source document)

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Tracleer (bosentan) dispersible tablets

Drug/Study ID	Efficacy Duration	Therapy	Patients	Number (Active/Placebo) with 6MWD or PVR assessments	Location of Data
Tadalafil/LVGY/ Phase 3	16 weeks	405 patients randomized 1:1:1:1 to Tadalafil 2.5, 10, 20, 40 mg QD or Placebo	≥ 12 years with PAH that was idiopathic, related to CVD, related to anorexigen use, related to HIV infection, associated with an atrial septal defect, or associated with surgical repair of at least 1 year in duration of a congenital systemic-to-pulmonary shunt	Total: 323(active)/82(placebo) 6MWD: 82 (2.5mg)/ 80(10mg)/ 82(20mg)/ 79(40mg)/ 82(placebo) PVR: 24(2.5mg)/ 18(10mg)/ 17(20mg)/ 18(40mg)/16(placebo)	\\Cdsesub1\evsprod\NDA\022332\0000\m5\datasets\h6d-mc-lvgy\analysis\ (database QC against source document)
Treprostinil/P01:04 and P01:05/ Phase 3	12 weeks	448 patients (224 in each of Study 04 and Study 05) randomized to treprostinil IV or placebo	≥ 8 years with symptomatic PPH (FC II/III/IV) associated with CTD or congenital systemic-to-pulmonary shunt.	Total: 232(active)/ 236(placebo) 6MWD: 232(active)/ 236(placebo) PVR: 163 (active) / 182 (placebo)	\\cdsnas\pharmacometrics\ Disease Modeling and Database Projects\PulmonaryHypertension\Database\PAHProjectData\Treprostinil\Derived\ (database not QC against source document)

Abbreviations: QD, once daily; BID, twice daily; PAH, pulmonary arterial hypertension; IPAH, idiopathic PAH; CTD, connective tissue disease; HIV, human immunodeficiency virus; WHO, World Health Organization; FC, functional class; CVD, collagen vascular disease; PPH, primary pulmonary hypertension

3.3.2 Pediatric Clinical Trials

Bosentan was administered to pediatric subjects with PAH in 6 clinical trials. A total of 119 PAH patients across the pediatric age range (3 months to 15 years) were treated and evaluated, including 100 pediatric patients treated with the 32 mg dispersible tablet for treatment durations up to 5 years (Table 3). All trials were open label and uncontrolled, and primarily designed to evaluate the pharmacokinetics, safety and tolerability. PVR data were collected in BREATHE-3, FUTURE-3 and Japanese studies. Given the low number of patients contributing PVR data in the FUTURE 3 hemodynamic sub-study (n = 4) and in the Japanese pediatric study (n = 6), these studies were not used for bridging analysis.

Table 3. Pediatric Clinical Trials

Study ID	Design	Treated	Patients
AC-052-356 (BREATHE-3)	Open label, single arm 12-week study Bosentan film-coated tablet: 2mg/kg bid Primary: PK; Secondary: Efficacy, hemodynamics, safety	N=19	3-15 years WHO FC II or III PPH or associated PAH-CHD
AC-052-365 (FUTURE 1 and 2)	Open label, single arm 13-week study Bosentan 32mg dispersible tablet: 2mg/kg bid to 120 mg bid Primary: PK; Secondary: Safety Future 2: Open-label, extension to Future 1	N=36	≥ 2 and < 12 years WHO FC II or III IPAH or familial PAH
AC-052-373 (FUTURE-3 and FUTURE-3 extension)	Open label, 24-week study Bosentan 32mg dispersible tablet: 2mg/kg bid or 2mg/kg tid Primary: PK; Secondary: Secondary: hemodynamics, WHO FC and PAH worsening	N=64	≥ 3 months and < 12 years WHO FC I, II or III IPAH, heritable PAH, or associated PAH-CHD
AC-052-377 (Japanese)	Open label, 12-week study 32mg dispersible tablet: 2mg/kg bid Primary: PK; Secondary: Secondary: hemodynamics (6/6), WHO FC	N=6	≥ 1 year and < 14 years WHO FC II, III or IV IPAH, heritable PAH, or associated PAH-CHD

Abbreviations: bid, twice daily; PAH, pulmonary arterial hypertension; IPAH, idiopathic PAH; CTD, connective tissue disease; WHO, World Health Organization; FC, functional class; CVD, collagen vascular disease; PPH, primary pulmonary hypertension

3.3.3 Software

R version 3.2.2 (2015-08-14) was used for all analyses.

3.3.4 Statistical Methods and Models

Analysis variables were change from baseline PVR (Δ PVR) and change from baseline 6MWD (Δ 6MWD). In the previous evaluation by Dr. Satjit Brar, PVRI was used as the analysis variable. PVRI is PVR adjusted for a patient's body surface area (BSA). PVR was selected for this investigation because there was less missing data with PVR (i.e., if a patient did not have BSA measurement then PVRI would be missing even though PVR was measured). Given that Δ PVR was used as the analysis variable and Δ PVR is highly correlated with Δ PVRI ($R^2=0.98$), there should be no impact on the relationship with Δ 6MWD.

Continuous variables are expressed as mean $\pm$ standard deviation (95% confidence interval) and categorical variables as percentages. Treatment assignment was designated as either active treatment or placebo.

Linear regression analysis using pooled data from adult clinical trials was used to evaluate the following 3 hypotheses which are based on Prentice's criteria³ for surrogate endpoints:

- (1) Δ PVR has a significant association with Δ 6MWD across drugs and drug classes approved for the treatment of PAH in adults;
- (2) Bosentan treatment has a significant effect on Δ PVR and Δ 6MWD in adults; and
- (3) Bosentan treatment on Δ 6MWD is explained by Δ PVR in adults.

To extrapolate clinical efficacy in pediatric patients, the distribution of Δ PVR in pediatrics was compared to adults using descriptive summaries. Stochastic simulations were performed to compute the 6MWD in pediatric patients based observed Δ PVR and the adult Δ PVR- Δ 6MWD model (see Section 4.2). The median and 95th predictive intervals were computed from 10,000 simulation replicates as follows:

1. Sampled from truncated Cauchy distribution of Δ PVR values for bosentan (peds: location=-237, scale=187) and placebo (peds: location= -24, scale=233). Mean Δ PVR was computed by treatment for each replicate (see section 4.3).
2. Sampled from a multivariate normal distribution of model parameters (estimates, variance-covariance matrix of estimates) from the linear mixed-effect regression model with random effect term for study. Each replicate had new values of model parameters.
3. Computed the Δ 6MWD for bosentan and placebo treatments for each replicate using the mean Δ PVR values obtained in step (1) and model parameters in step

³ Prentice RL. Surrogate endpoints in clinical trials: definition and operational criteria. Stat Med. 1989;8(4): 431-40.

- (2). $\Delta\Delta 6\text{MWD}$ was computed as the difference between $\Delta 6\text{MWD}$ for bosentan and $\Delta 6\text{MWD}$ for placebo.
4. Obtained the 50th, 2.5th and 97.5th percentiles of the 10,000 values for ΔPVR , $\Delta 6\text{MWD}$ and $\Delta\Delta 6\text{MWD}$.

3.4 Results

3.4.1 Relationship between ΔPVR and $\Delta 6\text{MWD}$ for Drugs Used to Treatment PAH

3.4.1.1 Pooled PAH Database

The final database includes 2028 patients from 12 adult clinical trials of 9 drugs (bosentan [n=271, 13%], epoprostenol [n=73, 4%], iloprost [n=142, 7%], macitentan [n=187, 9%], riociguat [n=443, 22%], selexipag [n=43, 2%], sildenafil [n=270, 13%], tadalafil [n=392, 19%] and treprostinil [n=207, 10%]). Characteristics of the study population and those assigned to active treatment (n=1343, 66%) or placebo (n=685, 34%) are shown in Table 4.

Table 4. Baseline Characteristics of Pooled Adult PAH Trials

	Active Treatment (N=1343)	Placebo (N=685)
Age	49.3±16.0	48.5±15.4
Sex		
Males	312 (23%)	175 (26%)
Females	1031 (77%)	510 (74%)
NYHA functional class		
1	56 (4%)	53 (8%)
2	497 (37%)	282 (41%)
3	760 (57%)	332 (48%)
4	30 (2%)	21 (2%)
Baseline 6MWD, m	355±84	360±93
Baseline PVR, dyne*sec/cm ⁵	1006±734	1008±619

Abbreviations: PVR, pulmonary vascular resistance; 6MWD, 6-minute walk distance; NYHA, New York Heart Association. Source: Efficacy.Rmd

The means and 95% confidence intervals for ΔPVR and $\Delta 6\text{MWD}$ endpoints by study and treatment arm are shown in Table 5. The weighted average ΔPVR values are -160 dyne*sec/cm⁵ for pooled active treatments and +119 dyne*sec/cm⁵ for pooled placebo. For the majority of studies, the placebo treatment arms showed a worsening (i.e., increase) of ΔPVR . The weighted average $\Delta 6\text{MWD}$ values are +30 m for pooled active treatments and -3 m for pooled placebo.

Table 5. Summary of 6MWD and PVR Endpoints Across Adult PAH Clinical Trials

Study ID	Treatment	Δ PVR, dyne*sec/cm ⁵				Δ 6MWD, m			
		N	Mean	95% UCL	95% UCL	N	Mean	95% UCL	95% UCL
AC2405	Bosentan	36	-317	-588	-46	37	43.4	27.5	59.4
AC2405	Placebo	17	155	-108	418	17	-9.7	-53.5	34.1
AC-052-364	Bosentan	80	-69	-173	35	86	11.2	-4.4	26.8
AC-052-364	Placebo	88	128	31	225	91	-7.9	-24.1	8.3
AC-052-351	Bosentan	19	-223	-333	-113	21	70.1	46.1	94.1
AC-052-351	Placebo	10	191	46	337	11	-5.8	-77.0	65.4
BW46	Epoprostenol	27	-274	-386	-161	41	34.1	13.4	54.9
BW46	Placebo	17	122	-71	314	32	-7.8	-44.3	28.8
ME97218	Iloprost aerosol	69	-27	-88	35	69	26.5	11.6	41.4
ME97218	Placebo	73	81	20	143	73	3.5	-10.7	17.7
A1481140	Sildenafil 20mg TID	47	-122	-214	-29	67	41.3	28.2	54.4
A1481140	Sildenafil 40mg TID	47	-143	-216	-71	63	44.3	29.2	59.4
A1481140	Sildenafil 80mg TID	55	-261	-363	-159	69	46.8	30.1	63.6
A1481140	Placebo	51	49	-52	150	65	-3.9	-16.8	9.1
LVGY	Tadalafil 2.5mg	18	-65	-171	40	79	21.8	8.4	35.2
LVGY	Tadalafil 10mg	12	-140	-307	26	78	28.6	14.8	42.4
LVGY	Tadalafil 20mg	13	-254	-375	-134	80	36.2	25.8	46.6
LVGY	Tadalafil 40mg	14	-209	-387	-31	76	41.1	30.0	52.2
LVGY	Placebo	12	11	-141	163	79	9.2	-4.0	22.4
P01:04	Treprostinil	42	-195	-288	-101	42	5.3	-10.3	20.9
P01:04	Placebo	51	37	-62	136	51	-11.4	-30.1	7.3
P01:05	Treprostinil	56	-128	-204	-53	56	28.8	9.1	48.4
P01:05	Placebo	58	54	-2	109	58	7.3	-10.1	24.7
12934	Placebo	107	-9	-69	51	126	-5.6	-20.5	9.4
12934	Riociguat 1.5 mg	58	-168	-250	-85	63	31.1	11.6	50.7
12934	Riociguat 2.5 mg TID	232	-223	-257	-190	254	29.6	21.5	37.7
NS-304/-02	Selexipag	32	-130	-237	-22	32	23.2	-2.4	48.7
NS-304/-02	Placebo	10	224	3	444	10	0.4	-17.0	17.8
AC-055-302	Macitentan 10 mg	57	-25	-204	153	57	8.4	-12.1	28.9
AC-055-302	Macitentan 3 mg	62	-122	-198	-45	62	18.4	-4.6	41.4

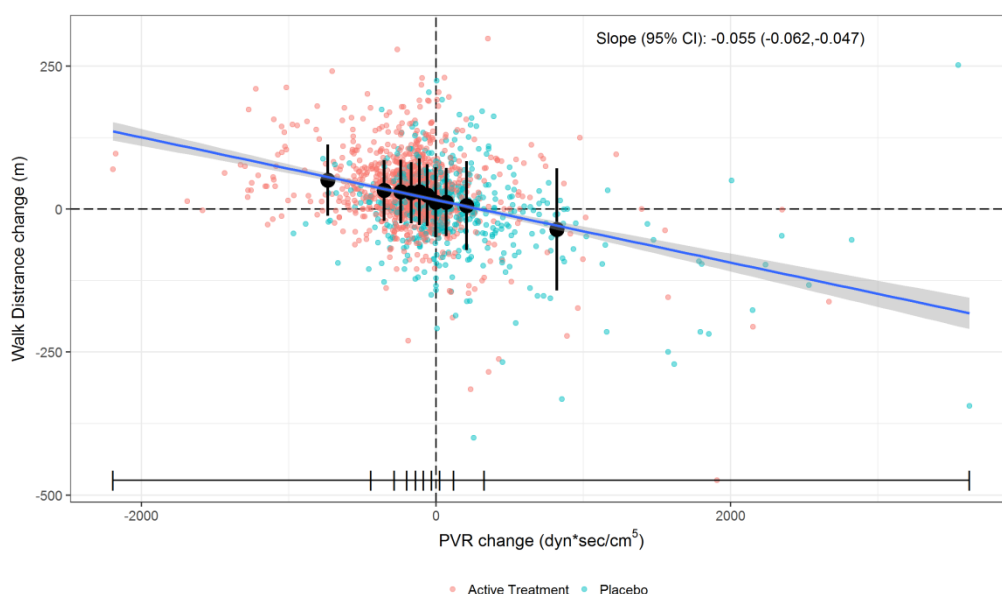
Study ID	Treatment	Δ PVR, dyne*sec/cm ⁵				Δ 6MWD, m			
		N	Mean	95% UCL	95% UCL	N	Mean	95% UCL	95% UCL
AC-055-302	Placebo	67	504	284	724	68	-13.0	-32.6	6.7

Abbreviations: PVR, pulmonary vascular resistance; 6MWD, 6-minute walk distance; UCL, upper confidence interval. Source: Efficacy.Rmd

3.4.1.2 Relationship between Δ PVR and Δ 6MWD

There is an association between improvement in 6MWD and a decrease in Δ PVR (Figure 1) using pooled patient-level data for active and placebo treatments. The mean regression slope (95% CI) is -0.055 (-0.062, -0.047) m per dyne*sec/cm⁵, p-value=<0.0001. The adjusted R-squared value is low (0.121), indicating there is high unexplained variability in the individual responses. This would be important if the goal is to precisely predict 6MWD from PVR for individual patients. Because the goal of this analysis is to understand the population response to PAH treatments, the R-squared value is not important for the intended purpose.

Figure 1. Relationship between Δ PVR and Δ 6MWD by Treatment Assignment



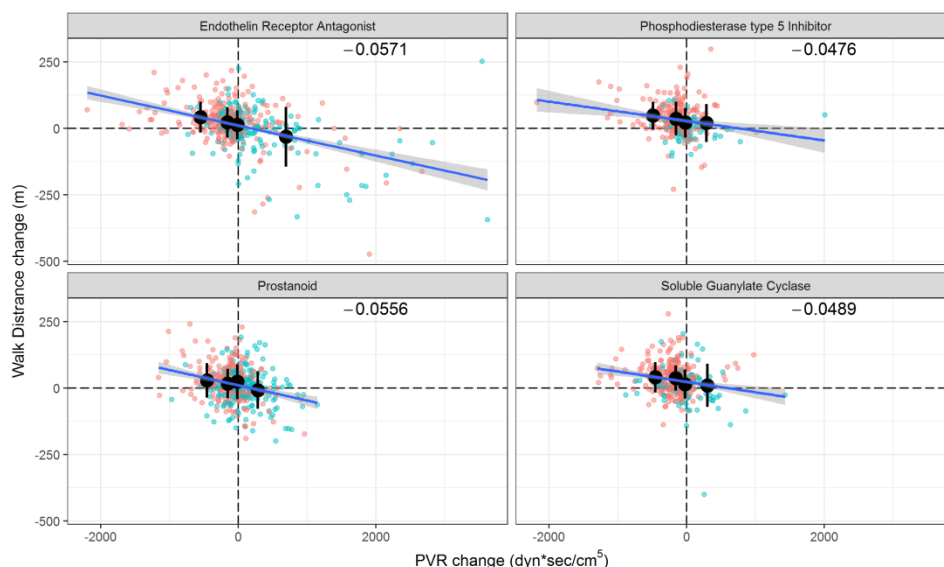
Shown are the observed data by treatment assignment overlaid with regression slope and 95% confidence interval. Black error bars represent mean and standard deviation Δ 6MWD within each decile of Δ PVR. Source: Quant.plot.png.

The relationship between Δ PVR and Δ 6MWD using pooled treatment and placebo arms is consistent across drug classes (Figure 2) and the slope is statistically significant for each class (Figure 3) with p-values <0.0001.

For individual drugs, the relationship between Δ PVR and Δ 6MWD using pooled treatment and placebo arms is consistent for all drugs (Figure 4), but does not reach statistical significance for selexipag (p-value=0.065). The lack of statistical significance

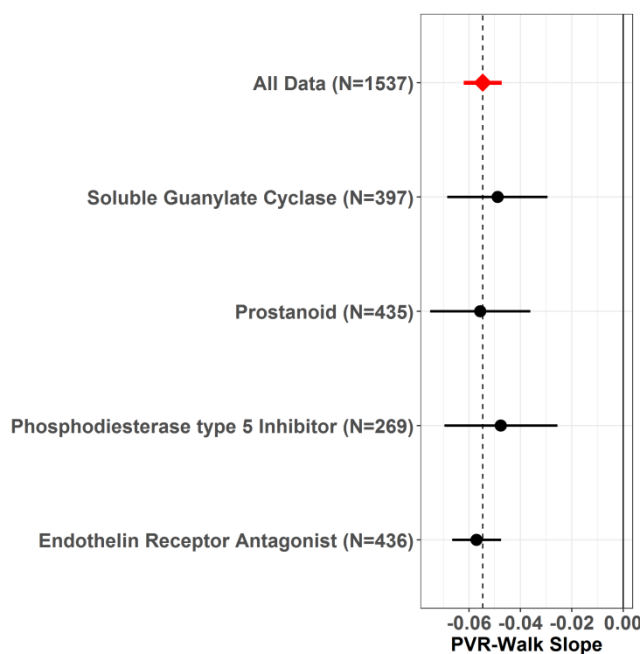
could be related to small sample size for selexipag (N=42) since this drug has demonstrated efficacy in larger clinical trials and the mean slope is similar to other drugs.

Figure 2. Relationship between Δ PVR and Δ 6MWD by Treatment Assignment and Drug Class



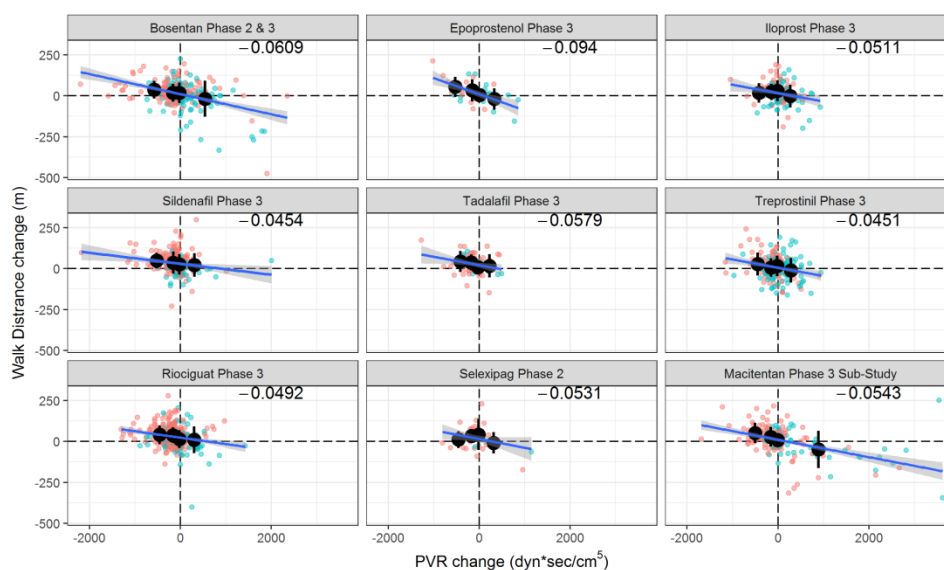
Shown are the observed data by treatment assignment (red=active treatment; blue=placebo) overlaid with regression slope and 95% confidence interval. Black error bars represent mean and standard deviation Δ 6MWD within each quartile of Δ PVR. Source: *Quant.plot.class.png*.

Figure 3. Forest Plot of Mean (95% CI) Regression Slopes for Drug Classes (Pooled Treatment and Placebo Arms)



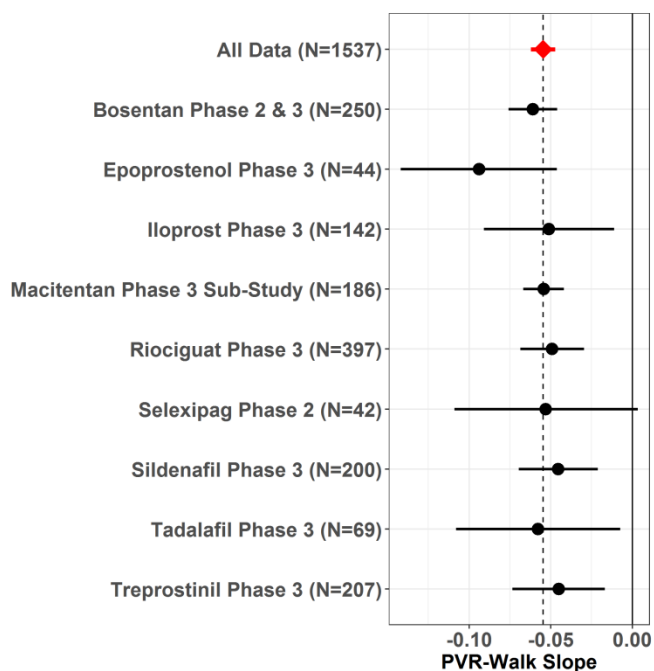
Analysis removed subjects with missing PVR or 6MWD data. Source: *p.forest.slope.class.png*

Figure 4. Relationship between Δ PVR and Δ 6MWD by Treatment Assignment and Individual Drug



Shown are the observed data by treatment assignment (red=active treatment; blue=placebo) overlaid with regression slope and 95% confidence interval. Black error bars represent mean and standard deviation Δ 6MWD within each quartile of Δ PVR. Source: [Quant.plot.grp.png](#).

Figure 5. Forest Plot of Mean (95% CI) Regression Slopes for Individual Drugs Pooled Treatment and Placebo Arms)



Analysis removed subjects with missing PVR or 6MWD data. Source: [p.forest.slope.png](#)

3.4.2 Bosentan Treatment Effects

3.4.2.1 Bosentan in Adults

3.4.2.2 Database

The adult bosentan database includes 271 patients from three placebo-controlled clinical trials: AC-052-351 (Phase II), AC-052-364 (EARLY) and AC-052-405 (BREATHE-5). Eight subjects had missing 6MWD; therefore, the analysis dataset consisted of 263 subjects.

Table 6. Analysis Population

	Bosentan	Placebo	Total
Pooled ITT Population	151	120	271
Analysis population <i>Exclude patients with missing Δ6MWD</i>	144 Missing (by study): AC-052-364: 7	119 Missing (by study): AC-052-364: 1	263
Complete population <i>Excludes patients with missing Δ6MWD and ΔPVR</i>	134 Missing (by study): AC-052-351: 2 AC-052-364: 13 AC-052-405:1	115 Missing (by study): AC-052-351: 1 AC-052-364: 4 AC-052-405:0	249

Characteristics of the study population assigned to bosentan (n=144, 55%) or placebo (n=119, 45%) are shown in **Table 7**.

Table 7. Baseline Characteristics of Pooled Bosentan Trials

	Bosentan (N=144)	Placebo (N=119)
Age	43.6±16.2	44.5±15.4
Sex		
Males	38 (26%)	41 (34%)
Females	106 (74%)	78 (66%)
NYHA Functional Class		
2	86 (60%)	91 (76%)
3	58 (40%)	28 (24%)
Baseline 6MWD, m	402±97	415±92
Baseline PVR, dyne*sec/cm5	1508±1399	1113±919

Abbreviations: PVR, pulmonary vascular resistance; 6MWD, 6-minute walk distance; NYHA, New York Heart Association. Source: Efficacy.Rmd.

Quality control of the database was assessed by comparing Δ PVR and Δ 6MWD values computed from the database to those presented in source documents (Table 8). The internal database has good agreement with source document study results across all treatment arms.

Table 8. QC of Bosentan Adult Database

Study	Treatment	Descriptive Summary of Database ¹		Descriptive Summary in Source Document	
		Δ PVR N=250	Δ 6MWD N=263	Δ PVR N=250	Δ 6MWD N=263
AC-052-351 (Phase II)	Bosentan	n=19 -223.5±245	n=21 70.1±56.2	n=19 ² -223±245	n=21 ² 70±56
	Placebo	n=10 191±234.8	n=11 -5.8±120.5	n=10 ² 191±235	n=11 ² -6±121
AC-052-364 (EARLY)	Bosentan	n=80 83.2%	n=86 11.2 (95%CI: -4.4; 27.0)	n=80 ³ 83.2% (95%CI: 73.8, 93.7)	n=86 ³ 11.2 (95%CI: -4.6; 27.0)
	Placebo	n=88 107.5%	n=91 -7.9 (95%CI: -24.1, 8.3)	n=88 ³ 107.5% (95%CI: 97.6, 118.4)	n=91 ³ -7.9 (95%CI: -24.3, 8.5)
AC-052-405 (BREATHE-5)	Bosentan	n=36 -316.9±830	n=37 43.4±49.5	n=36 ⁴ -316.9±830	n=37 ⁴ 43.4±49.5
	Placebo	n=17 155±553	n=17 -9.71±92.1	n=17 ⁴ 155±552	n=17 ⁴ -9.7±92.1

Sources: ¹Adult.Data.Rmd; ²TRACLEER label; ³Galie et al. Lancet.2008; ⁴AC-052-405FSR/Report No D-05.131

3.4.2.3 Bosentan Treatment

Bosentan has a significant effect on Δ PVR and Δ 6MWD in Table 9. For the pooled analysis, mean change from baseline in the 6MWD was 28 m for bosentan compared to -7 m for placebo. After adjusting for placebo, the mean increase in 6MWD from baseline was +35 m (p-value 0.0005). The mean change from baseline in PVR was -137 dyne*sec/cm⁵ for bosentan compared to +113 dyne*sec/cm⁵ placebo. After adjusting for placebo, the mean change in PVR from baseline was -250 dyne*sec/cm⁵ (p-value <0.0002). Bosentan treatment effects within individual studies are presented in Table 8.

Table 9. Treatment effect of Bosentan of 6MWD and PVR (Pooled Data from 3 Clinical Trials in Adults)

	LSMean (95% CI) Bosentan (n=134)	LSMean (95% CI) Placebo (n=115)	LSMean Difference (Bosentan-Placebo)
Δ 6MWD, m =TRT+baseline 6MWD	28 (15, 41)	-7 (-22, 7)	35 (19, 51); p-value: 0.0005
Δ PVR, dyne*sec/cm ⁵ =TRT+baseline PVR	-137 (-225, -49)	113 (18.6, 208)	-250 (-359, -141); p-value=<0.0002

Abbreviations: LSMean, least square mean; CI, confidence intervals; 6MWD, 6-minute walk distance; PVR, pulmonary vascular resistance; Δ , change from baseline.
Source: Efficacy.Rmd.

3.4.2.4 Δ PVR as Predictor for Δ 6MWD

Age, sex, baseline 6MWD, baseline PVR, New York Heart Association functional class, treatment and Δ PVR were tested individually as covariates in the regression model (Table 10). Significant factors ($p < 0.05$) were baseline 6MWD, baseline PVR, New York Heart Association functional class, treatment and Δ PVR. A correlation plot of individual predictors (Figure 6) showed that NYHA functional class is highly correlated with baseline PVR ($R^2 = 0.612$) and baseline 6MWD ($R^2 = -0.436$). Therefore, NYHA functional class was not included in the multivariate analysis.

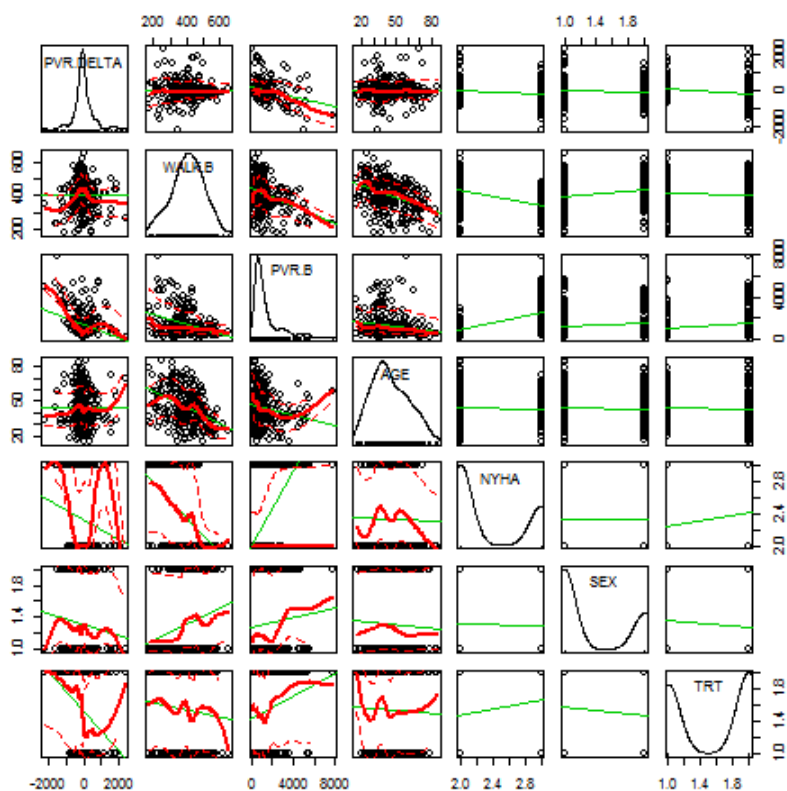
All significant predictors from the univariate analysis (excluding NYHA functional class) were included in a multivariate model. Covariates were retained in the model if the AIC increased upon their removal in a stepwise fashion. Baseline PVR was the only covariate removed. Based on AIC, the final model included Δ PVR, baseline 6MWD and treatment. However, the estimate for treatment was not significant at an alpha of 0.05 ($p = 0.056$) suggesting that Δ PVR explains some of the effect of treatment (Table 11).

Table 10. Stepwise Multivariate Regression Analysis of Covariates

Covariate	Estimate	P-value	AIC	Change in AIC
Step 1: univariate analysis of individual covariates				
None			2185	0
Sex	8.4	0.443	2186	+1
Age	-0.1898	0.561	2186	+1
Baseline PVR	0.0082	0.0473	2183	-2
Baseline 6MWD	-0.131	0.01392	2180	-5
NYHA functional class	32.7	0.00233	2177	-8
Treatment	36.7	0.000271	2173	-12
Δ PVR	-0.061	<0.0001	2139	-46
Step 2: Stepwise removal of covariates from full model based on AIC				
Baseline PVR + Baseline 6MWD + Treatment + Δ PVR			2132	
-Baseline PVR			2132	0
-Treatment			2135	+3
-Baseline 6MWD			2138	+6
- Δ PVR			2172	+40

Abbreviations: Δ , change from baseline; AIC, Akaike information criterion; PVR, pulmonary vascular resistance; 6MWD, 6-minute walk distance; NYHA, New York heart association. Source: Efficacy.Rmd

Figure 6. Correlation Plot of Covariates



Abbreviations: PVR, pulmonary vascular resistance; PVR.Delta, change from baseline PVR; PVR.B, baseline PVR; 6MWD, 6-minute walk distance; WALK.B, baseline 6MWD; NYHA, New York heart association functional class. Source: Efficacy.Rmd

Table 11. Predictors of Change from Baseline 6-Minute Walk Distance

Parameter	Estimate	95% CI	P-value
Intercept, m	63	23.5, 103	0.0019
Δ PVR, m per dyne*sec/cm ⁵	-0.061	-0.078, -0.045	<0.00001
Baseline 6MWD, m	-0.129	-0.224, -0.035	0.0076
Model with Treatment and the Above Predictors (0, placebo; 1, bosentan)			
Treatment	18	-0.44, 37	0.0556

Abbreviations: Δ , change from baseline, PVR, pulmonary vascular resistance; 6MWD, 6-minute walk distance. Source: Efficacy.Rmd

To assess what percentage of the bosentan treatment effect on 6MWD could be explained by changes in PVR, the final regression model was used to predict 6MWD in studie (b) (4)

The results are presented in Table 12 and show that in the pooled studies, Δ PVR explained approximately 50% of the bosentan treatment effects. Within each study, Δ PVR explained 29% to 62% of the treatment effect on Δ 6MWD.

Table 12. Bosentan Treatment Effects by Pooled Data and Individual Studies

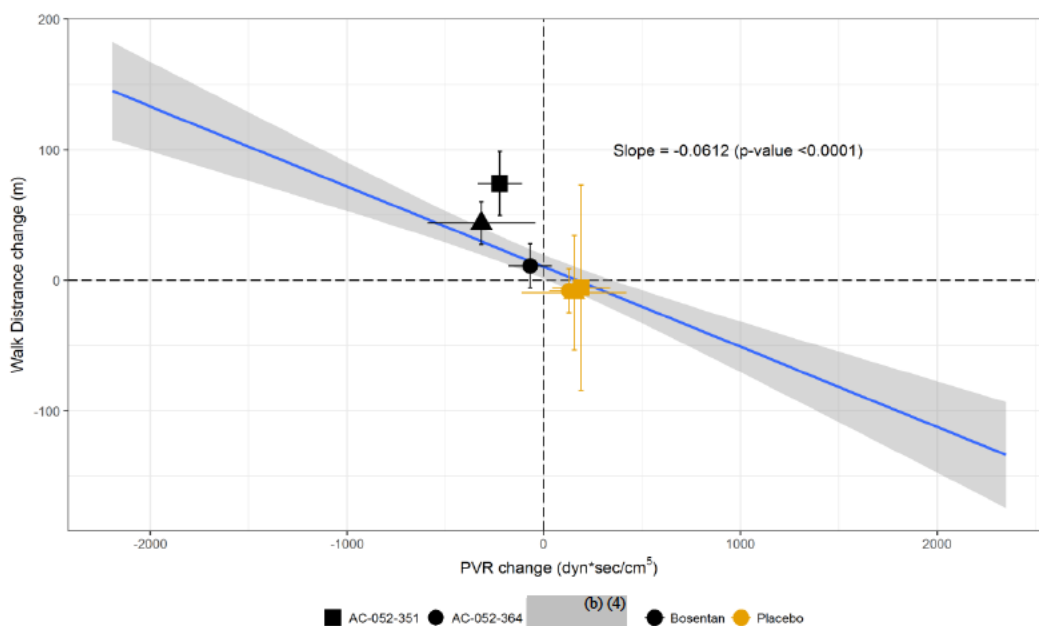
Study		Δ 6MWD, m		
		LSMean (95% CI)	LSMean (95% CI)	LSMean Difference (Bosentan-Placebo)
		Bosentan	Placebo	
Internal Validation (data used for model development)				
Pooled Studies	Model-predicted Δ PVR placebo = +138 Δ PVR bosentan= -158	20 (11, 29)	1.9 (-7.5, 11)	18 (14, 22)
	Model: <i>TRT+baseline 6MWD</i>	n=134 28 (15, 41)	n=115 -7.3 (-22, 6.9)	35 (19, 51)
AC-052-351 (Phase II)	Model-predicted Δ PVR placebo = +191 Δ PVR bosentan= -223	25 (15, 35)	-0.35 (-10, 9.3)	25 (20, 31)
	Model: <i>TRT+baseline 6MWD</i>	n=19 77 (38, 116)	n=10 -9 (-63, 45)	87 (31, 143)
AC-052-364 (EARLY)	Model-predicted Δ PVR placebo = +128 Δ PVR bosentan= -69	11 (1.4, 20)	-1.2 (-11, 8.5)	12 (9.3, 15)
	Model: <i>TRT+baseline 6MWD</i>	n=79 11 (-6, 28)	n=88 -8 (-25, 8)	19.5 (-0.64, 39.7)

(b) (4)

(b) (4)

Abbreviations: Δ , change from baseline; PVR, pulmonary vascular resistance; CI, confidence interval; LS, least square; TRT, indicator variable for treatment (1, bosentan; 0, placebo); 6MWD, 6-minute walk distance. Source: Efficacy.Rmd

Figure 7. Bosentan Δ PVR vs. Δ Walk Plot



Shown are the mean $\pm$ SD of observed data by treatment assignment and Study ID overlaid with regression slope and 95% confidence interval. Source: Quant.plot.png.

3.4.3 Bosentan in Pediatrics

3.4.3.1 Efficacy Data

PVR data supporting pediatric clinical efficacy primarily came from AC-052-356 (Figure 8). This study was a PK, efficacy and tolerability study in 19 pediatric patients with PAH, WHO function class II/III. 53% patients were taking stable epoprostenol before and during bosentan treatment.

Figure 8. Pediatric PVR Data

PEDIATRIC STUDIES				
AC-052-356 ¹ (BREATHE-3) 12 weeks	17/19	-389.2 (-706.0, -72.4)	II 15/19 III 4/19	None 9/19 (47%) Stable epoprostenol 10/19 (53%)
AC-052-373 ^{2,3} (FUTURE 3) ^a 24 weeks	4/10	-107.7 ± 151.33	I 2/4 II 2/4	None 2/4 (50%) PDE5i 2/4 (50%)
AC-052-377 (Japanese) ^{2,3} 12 weeks	6/6	-4.0 ± 258.6	II 4/6 ^b	None 1/6 (17%) Stable sildenafil/tadalafil and/or beraprost 5/6 (83%)

¹ Study with film-coated tablet

² Study with 32 mg dispersible tablet

^a PVRi evaluated

^{*}Results to be interpreted considering the fact that the start of bosentan was concomitant to epoprostenol administration in the study

^b 2 patients with no WHO FC evaluation

Source: Module 2.7.3, Table 3-26.

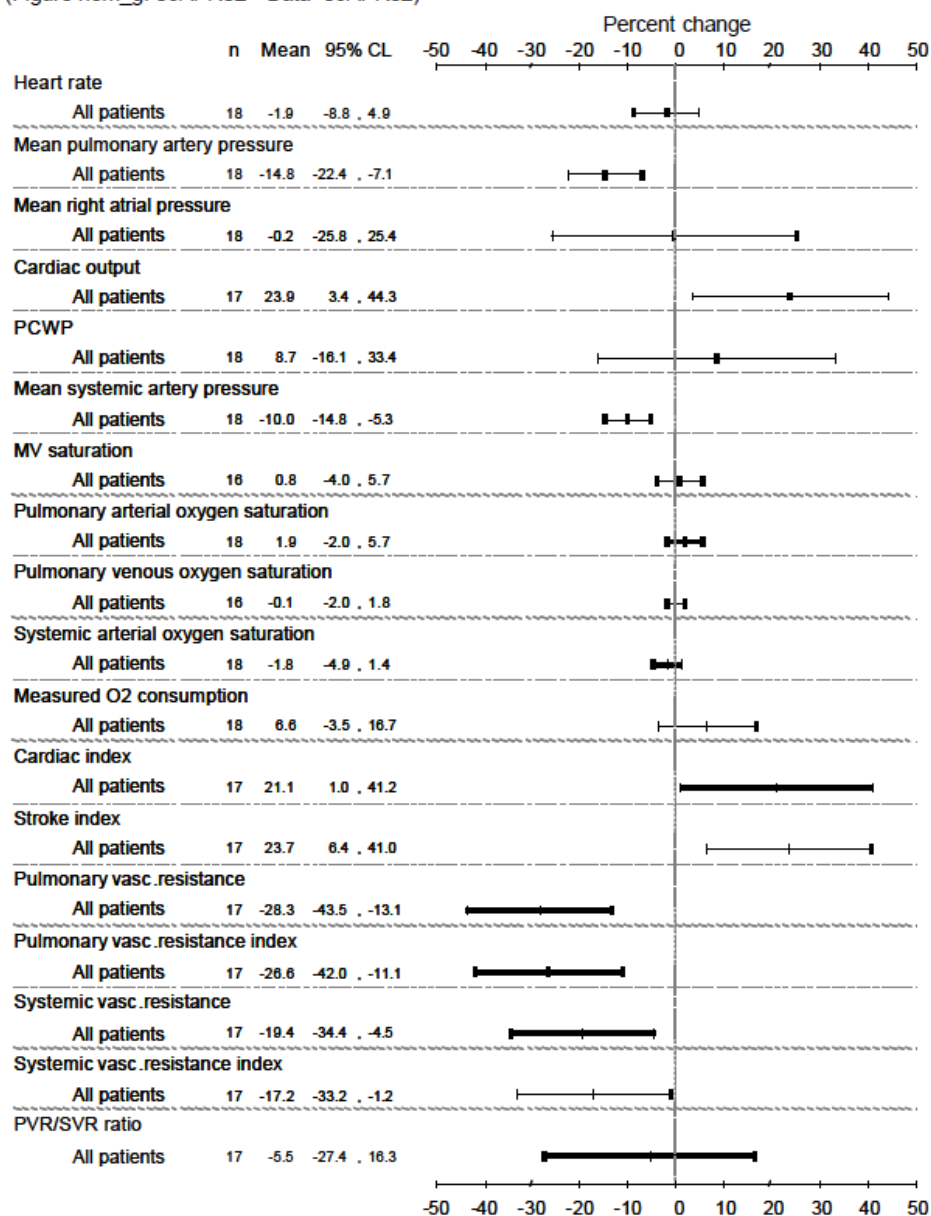
CL = confidence limits; PAH = pulmonary arterial hypertension; PDE5i = phosphodiesterase type-5 inhibitor;
PVR = pulmonary vascular resistance; PVRi = pulmonary vascular resistance index; SD = standard deviation;
WHO FC = World Health Organization functional class.

Reference: Sponsor's Figure 12 in AC-052-356 Final Study Report

After 12 weeks of bosentan treatment, there were significant improvement in hemodynamic parameters of pulmonary artery pressure, PVR, mean systemic artery pressure, systemic vascular resistance, cardiac output and stroke index (Figure 9). Assessments of 6MWD were available in 12 patients ≥ 8 years in this study. No significant changes were seen in 6MWD [0.7 m (95% CI: -36, 38)]. This is not unexpected given the poor reproducibility inherent in exercise testing in pediatric patients.

Figure 9. Percent Change from Baseline in Hemodynamic Parameters

(Figure hem_g: 03APR02 - Data 03APR02)



Reference: Sponsor's Figure 12 in AC-052-356 Final Study Report

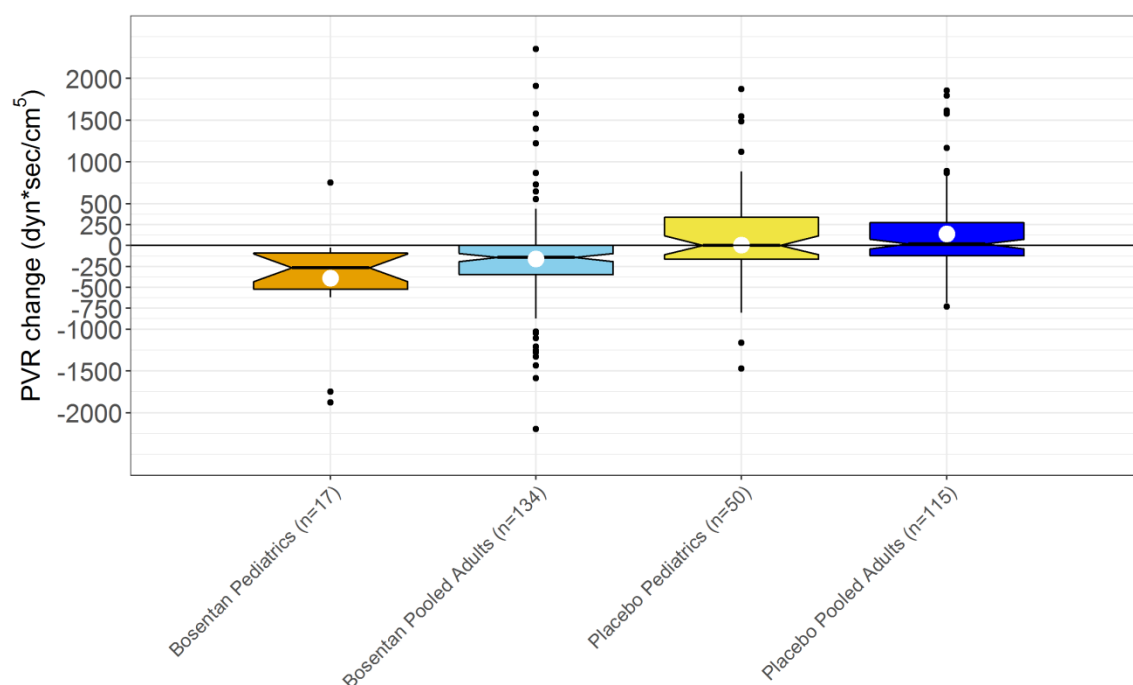
3.4.3.2 Comparison of Δ PVR in Adults and Children

The distributions of Δ PVR in children taking bosentan (AC-052-356) or placebo (A1481131) were compared to the Δ PVR in adults (Figure 10, Table 13)—the differences in the lengths of treatment duration is not accounted for in the comparison. The PVR data in pediatrics taking placebo for 16 weeks were obtained from study A1481131, a Phase 3, placebo controlled parallel group, dose ranging study in patients

aged 1 to 17 years with primary PAH, PAH secondary to congenital heart disease, or collagen vascular disease (Clinical Pharmacology Review by Dr. Brar, 4/27/2012).

After administration of 2 mg/kg bid bosentan (film-coated tablets) to pediatric PAH patients in AC-052-356, the decrease in mean Δ PVR was -389 (95% CI: -682, -96) $\text{dyne}\cdot\text{sec}/\text{cm}^5$ at Week 12 (Table 13). This mean effect was similar to the mean Δ PVR measured at 12 to 24 Weeks in adult PAH patients treated with bosentan 125 mg bid and was significantly decreased (p-value=0.003) compared to the Δ PVR in adults treated with placebo. This mean effect was also decreased (p-value=0.06) compared to the mean Δ PVR in pediatrics taking placebo for 16 weeks in study A1481131 (Clinical Pharmacology Review by Dr. Brar, 4/27/2012).

Figure 10. Distribution of Δ PVR in Pediatrics and Adult PAH Patients



Box plot show the mean (white circles), median (notch); 95% CI of median (width of notch); 5th and 75th percentile (with of box); 1.5* interquartile range (whiskers); and outliers (filled circles). Data were obtained from AC-052-356 (bosentan pediatrics), A1481131 (placebo pediatrics), and pooled studies in adults (Table 8).

Table 13. Summary of Δ PVR in Adults and Pediatrics

	Δ PVR, dyne*sec/cm ⁵			
	Pediatrics		Adults	
	Bosentan (AC-052-356)	Placebo (A1481131)	Bosentan (Pooled data)	Placebo (Pooled data)
N	17	50	134	115
Mean	-389	6.3	-158	138
Median	-266	-8.5	-143	19
SD	616	944	579	461
95% CI	-682, -96	-255, 268	-256, -60	54, 222

Data were obtained from AC-052-356 (bosentan pediatrics), A1481131 (placebo pediatrics), and pooled studies in adults (Table 6). Abbreviations: Δ , change from baseline; PVR, pulmonary vascular resistance; SD, standard deviation; N, number of subjects; CI, confidence interval. Source: Efficacy.Rmd

3.4.3.3 Model-Predicted $\Delta\Delta$ 6MWD in Pediatrics

Model-based predictions for $\Delta\Delta$ 6MWD based solely on PVR changes account for both the uncertainty in mean Δ PVR in both bosentan and placebo arms as well as the uncertainty in regression model parameters. To account for potential heterogeneity across bosentan adult studies, the standard errors in the slope and intercept parameters in the regression model were adjusted by including study as random effect.

Based on the model, the predicted treatment effect of bosentan on 6MWD in pediatrics is 14 m (95% CI: 3–31 m) for a mean decrease in PVR of -212 dyne*sec/cm⁵ for bosentan and -27 dyne*sec/cm⁵ for placebo (Table 14). The prediction does not account for between-study variability in responses across the adult clinical trials.

Table 14. Predicted 6MWD in Adults and Pediatrics

Population	Treatment	Median (95% Confidence Intervals)		
		Δ PVR, dyne*sec/cm ⁵	Δ 6MWD, m	$\Delta\Delta$ 6MWD, m
Adults	Bosentan	-137 (-221, -53)	27 (10, 46)	19 (4, 40) ¹
	Placebo	139 (58, 219)	8 (-12, 27)	
Pediatrics	Bosentan	-212 (-244, -180)	34 (15, 54)	14 (2.5, 31)
	Placebo	-27 (-119, 70)	20 (2.7, 36)	

¹Because the Δ PVR explains approximately 50% of the treatment effect on 6MWD in adults, the model-predicted values are lower than those observed in pooled studies.

Listing of Analyses Codes and Output Files

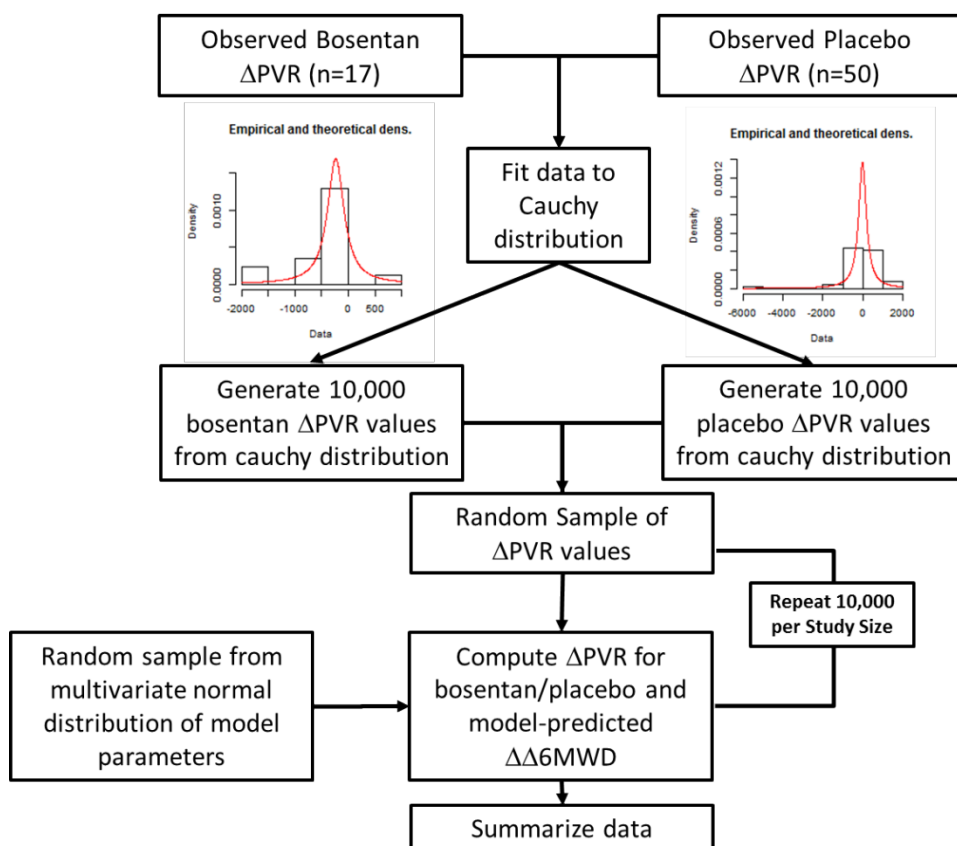
File Name	Description	Location in \\cdsnas\pharmacometrics\
Adult.Data.Rmd	R code that generated the adult database.	\\cdsnas\pharmacometrics\Reviews\Ongoing PM Reviews\Bosentan_NDA209279_GC\
Efficacy.Rmd	R code for all analyses and graphs.	

4 APPENDICES

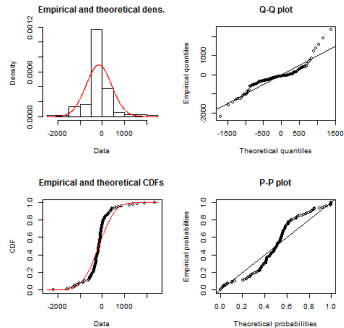
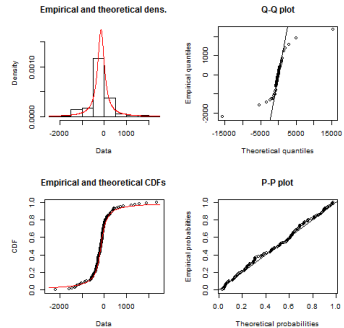
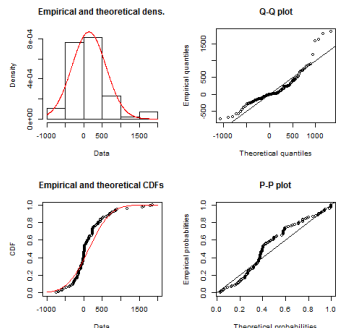
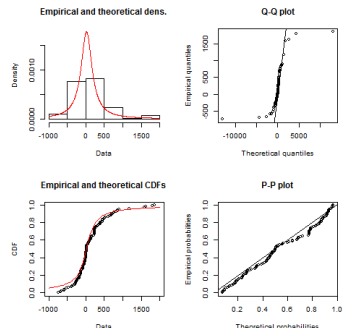
4.1 Pediatric subjects enrolled in Studies AC-052-356 (bosentan) and A1481131 (placebo)

Bosentan Study AC-052-356	Sildenafil Study A1481131
Male or female subjects aged from 2 to 17 years PAH in WHO functional class II or III with or without <u>epoprostenol therapy</u>, were eligible for the trial. Pulmonary arterial hypertension could have been: • Primary PAH; • PAH associated with scleroderma or congenital heart defects such as ventricular/atrial septal defect (VSD/ASD), transposition of the great vessels, patent ductus arteriosus, partial anomalous pulmonary venous return, and aortopulmonary window.	Male or female subjects aged from 1 to 17 years Subjects who had symptomatic PAH due to 1 of the following conditions: • Primary PAH; • PAH in the presence of a small or hemodynamically insignificant congenital systemic to pulmonary shunt lesion that in the opinion of the investigator was not the cause of PH; • PAH associated with collagen vascular disease (eg, scleroderma); • PAH associated with congenital systemic-to-pulmonary shunts with a baseline resting room air oxygen saturation (SaO₂) $\geq$ 88%. If the defect was repaired, it should have been repaired $\geq$ 6 months prior to screening (repairs could be either surgical or via interventional cardiac catheterization (eg, atrial septal defect closure device or coil of patent ductus arteriosus); • PAH associated with d-transposition of the great arteries repaired within the first 30 days of life; • PAH in subjects who had undergone surgical repair of other congenital heart lesions $\geq$ 6 months prior to screening and did not have clinically significant residual left-sided heart disease consistent with the exclusion criteria
Patients allowed to take epoprostenol	Prohibited medications: prostacyclins

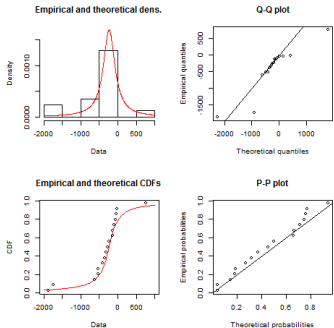
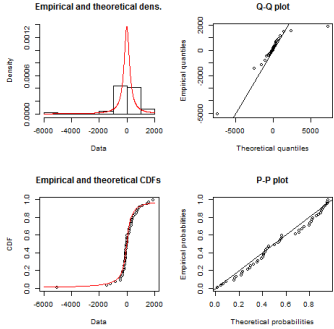
4.2 Schematic of Simulation Methods for Pediatrics Using Parametric Simulations



4.3 Distributions of Δ PVR following bosentan and placebo in adults and pediatrics

Treatment	Statistic	Normal Distribution	Cauchy Distribution
Adults			
Bosentan	AIC/BIC	2088/2094	2031/2037
	Estimated distribution parameters	mean (SE): -158 (50) SD (SE): 577 (35)	location (SE): -151 (23) scale (SE): 183 (22)
	Goodness-of-fit		
Placebo	AIC/BIC	1740/1745	1725/1730
	Estimated distribution parameters	mean (SE): 138 (43) SD (SE): 459 (30)	location (SE): 19 (24) scale (SE): 179 (24)
	Goodness-of-fit		
Cauchy Distribution Applied to Pediatric Data			
Bosentan	Estimated distribution parameters	<i>not determined</i>	location (SE): -237 (73) scale (SE): 187 (59)

Clinical/Clinical Pharmacology Efficacy Review
NDA0209279
Tracleer (bosentan) dispersible tablets

Treatment	Statistic	Normal Distribution	Cauchy Distribution
	Goodness-of-fit	<i>not determined</i>	
Placebo	Estimated distribution parameters	<i>not determined</i>	location (SE): -24 (47) scale (SE): 233 (48)
	Goodness-of-fit	<i>not determined</i>	

Abbreviations: AIC, Aikake Information Criterion; BIC, Bayesian Information Criterion; SD; standard deviation; SE, standard error. Source: Efficacy.Rmd

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/s/

CHRISTINE E GARNETT
03/30/2017

JEFFRY FLORIAN
03/31/2017

CLINICAL REVIEW

Application Type NDA
Application Number 209279
Priority or Standard S

Submit Date 08/05/2016
Received Date 08/05/2016
PDUFA Goal Date 06/05/2017
Division / Office DCRP

Reviewer Name Maryann Gordon, M.D.
Review Completion Date

Established Name bosentan
Trade Name Tracleer®
Therapeutic Class endothelin receptor antagonist
Applicant Actelion

Formulation dispersible tablet

Dosing Regimen patients $\leq$ 12 years of age: dosage is (b) (4)
(b) (4) with or without food twice daily

Indication treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening.

Intended Population(s) Pediatric patients

Template Version: March 6, 2009

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Bosentan dispersible tablet should not be approved for use in children with PAH because there is no demonstration of clinical benefit in adequate and well controlled trials.

All efficacy trials for this indication were uncontrolled. While there were changes in cardiac hemodynamics generally viewed as improvements, these changes are insufficient to be used as proof of efficacy for any PAH drug, especially the first one to have such an indication. There were few changes in functional class and the Global Clinical Impression Scales in these trials.

In regard to safety, bosentan use in children can cause

- 1) a dose-related decrease in hemoglobin and hematocrit. The decreases tend to be mild and rarely require intervention.
- 2) an elevation in liver aminotransferases. The elevations are usually reversed when drug is discontinued. No link between use of bosentan and subsequent liver impairment in the pediatric population can currently be made. However, a link cannot be ruled about.
- 3) fluid retention/edema.

The safety outlined in the pediatric studies is not obviously different from that reported in adults with PAH receiving bosentan.

1.2 Risk Benefit Assessment

Because proof of clinical benefit is lacking, the risk/benefit of bosentan use in children is unfavorable.

2 Introduction and Regulatory Background

2.1 Product Information

Tracleer is an endothelin receptor antagonist indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability and to decrease clinical worsening.

2.2 Currently Available Treatments for Proposed Indication

None

2.3 Availability of Proposed Active Ingredient in the United States

Available

2.4 Important Safety Issues With Consideration to Related Drugs

Labeling information concerning serious safety associated with Tracleer is shown below.

CONTRAINDICATIONS

- Pregnancy (4.1)
- Use with Cyclosporine A (4.2)
- Use with Glyburide (4.3)
- Hypersensitivity (4.4)

WARNINGS AND PRECAUTIONS

- Pre-existing hepatic impairment: Avoid use in moderate and severe impairment (5.3).
- Fluid retention: May require intervention (5.4).
- Pulmonary veno-occlusive disease (PVOD): If signs of pulmonary edema occur, consider the diagnosis of associated PVOD and consider discontinuing Tracleer (5.5).
- Decreased sperm counts (5.6).
- Decreases in hemoglobin and hematocrit: Monitor hemoglobin levels after 1 and 3 months of treatment, then every 3 months thereafter (5.7).
-  (b) (4)

3 Ethics and Good Clinical Practices

3.1 Compliance with Good Clinical Practices

Regarding right heart catheterization (RHC) as part of study design, the following is a response to pediatrics ethic consultation¹.

The individual risks of interventions or procedures in a research protocol must be evaluated as part of the risk assessment of a protocol at the time of initial review. If there is no direct benefit to pediatric patients (21 CFR 50.52), the risk of these procedures must either minimal (21 CFR 50.51) or a minor increase over minimal risk (21 CFR 50.53). In the BREATHE-3 trial, the initial RHC was done for diagnostic purposes, is considered to be standard of care, and therefore the procedure directly benefits the patient. However a second RHC done solely for research purposes does not directly benefit the patient and thus must constitute a minor increase over minimal risk in order to be performed as part of a research protocol.

Data collected in the BREATHE-3 trial were collected prior to substantive published literature and the generation of pediatric clinical trial data that described the serious adverse events that

¹ Author: Donna L. Snyder, M.D., consult dated 1-12-2017

may occur with RHC. Consequently, the FDA considered the procedure allowable as a research outcome at the time these studies were conducted.

Additionally, until data surfaced in the sildenafil trials calling into question the risk of the procedure, DCRP had allowed repeat RHC as a research outcome to be included in study protocols. We would argue that use of these data is ethical given that at the time the data was collected, the available evidence of risk permitted IRBs to consider RHC to present no more than a minor increase over minimal risk.

3.3 Financial Disclosures

There is no indication that the reported disclosures raise any concern of any clinical study being compromised.

Form 3454 was signed by most investigators for studies AC-052-116, -365—373, -374, as well as adult study AC-052-356. The sponsor submitted information regarding the five investigators who signed form 3455 and is discussed below.

ATTACHMENT TO FORM FDA 3455

Protocol AC-052-365

FUTURE 1: An open-label, multicenter study to assess the pharmacokinetics, tolerability, and safety of a pediatric formulation of bosentan in children with idiopathic or familial pulmonary arterial hypertension

Protocol AC-052-367

FUTURE 2: An open-label, long-term, safety and tolerability extension study using the pediatric formulation of bosentan in the treatment of children with idiopathic or familial pulmonary arterial hypertension who completed FUTURE 1

(b) (6) who served as a Principal Investigator and a Subinvestigator at (b) (6) for the above referenced trials, has identified that (b) (6) received significant payments from Actelion for consultancy work. (b) (6) never provided the exact amount of payments.

(b) (6) relinquished (b) (6) duties as Principal Investigator on (b) (6) and assigned (b) (6) as the PI. (b) (6) became a Subinvestigator in the study. (b) (6) eventually left (b) (6) took over the complete oversight of all patients enrolled in the study until the site was closed in 2008.

Steps taken to minimize bias:

A total of (b) (6) patients participated in study AC-052-365 in 7 countries and in 11 centers.

Patients who completed AC-052-365 were eligible to participate in AC-052-367.

In a trial of this size, conducted in multiple countries and sites, it was determined that (b) (6), as an investigator at one site with (b) (6) patients, and whose responsibilities were finished prior to the end of the study, would not have sufficient influence or independent ability to impact or influence the overall conduct of the study or its outcomes. (b) (6) was no longer actively involved in the study during the analysis of the results and the finalization of the study reports.

ATTACHMENT TO FORM FDA 3455

Protocol AC-052-373

FUTURE 3: An open-label, randomized multicenter, multiple dose trial to evaluate the pharmacokinetics, tolerability, safety and efficacy of the pediatric formulation of bosentan two versus three times a day in children from 3 months to less than 12 years of age with pulmonary arterial hypertension

Protocol AC-052-374

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

(b) (6) who served as a Principal Investigator at (b) (6) for the above referenced trials, has identified that (b) (6) received approximately \$25,000 to \$50,000 from Actelion for consultancy work and honoraria.

Steps taken to minimize bias:

A total of 64 patients participated in study AC-052-373 in 20 countries and in 45 centers.

Patients who completed AC-052-373 were eligible to participate in AC-052-374.

In a trial of this size, conducted in multiple countries and sites, it was determined that (b) (6), as an investigator at one site with (b) (6) patients, would not have sufficient influence or independent ability to impact or influence the overall conduct of the study or its outcomes.

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FUTURE 3: An open-label, randomized multicenter, multiple dose trial to evaluate the pharmacokinetics, tolerability, safety and efficacy of the pediatric formulation of bosentan two versus three times a day in children from 3 months to less than 12 years of age with pulmonary arterial hypertension

Protocol AC-052-374

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

(b) (6) who served as a Principal Investigator at (b) (6) for the above referenced trials, has identified that (b) (6) received approximately \$25,000 - \$50,000 from Actelion for consultancy fees, grants and honoraria.

Steps taken to minimize bias:

A total of 64 patients participated in study AC-052-373 in 20 countries and in 45 centers.

Patients who completed AC-052-373 were eligible to participate in AC-052-374.

In a trial of this size, conducted in multiple countries and sites, it was determined that (b) (6) as an investigator at one site (b) (6) would not have sufficient influence or independent ability to impact or influence the overall conduct of the study or its outcomes.

ATTACHMENT TO FORM FDA 3455

Protocol AC-052-365

FUTURE 1: An open-label, multicenter study to assess the pharmacokinetics, tolerability, and safety of a pediatric formulation of bosentan in children with idiopathic or familial pulmonary arterial hypertension

Protocol AC-052-367

FUTURE 2: An open-label, long-term, safety and tolerability extension study using the pediatric formulation of bosentan in the treatment of children with idiopathic or familial pulmonary arterial hypertension who completed FUTURE 1

(b) (6) who served as a Subinvestigator at the (b) (6) for the above referenced trials, has identified (b) (6) was funded by a research grant from Actelion in a different hospital.

Steps taken to minimize bias:

A total of 36 patients participated in study AC-052-365 in 7 countries and in 11 centers.

Patients who completed AC-052-365 were eligible to participate in AC-052-367.

In a trial of this size, conducted in multiple countries and sites, it was determined that (b) (6) as a Subinvestigator at one site with (b) (6) patients, would not have sufficient influence or independent ability to impact or influence the overall conduct of the study or its outcomes.

ATTACHMENT TO FORM FDA 3455

Protocol AC-052-373

FUTURE 3: An open-label, randomized multicenter, multiple dose trial to evaluate the pharmacokinetics, tolerability, safety and efficacy of the pediatric formulation of bosentan two versus three times a day in children from 3 months to less than 12 years of age with pulmonary arterial hypertension

Protocol AC-052-374

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

(b) (6) who served as a Principal Investigator a (b) (6) for the above referenced trials, has identified (b) (6) received education and research support of approximately (b) (6) from Actelion, which is equivalent to approximately \$ 151,900 USD.

Steps taken to minimize bias:

A total of 64 patients participated in study AC-052-373 in 20 countries and in 45 centers.

Patients who completed AC-052-373 were eligible to participate in AC-052-374.

In a trial of this size, conducted in multiple countries and sites, it was determined that (b) (6) as an investigator at one site with (b) (6) patients, would not have sufficient influence or independent ability to impact or influence the overall conduct of the study or its outcomes.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 1 Listing of clinical studies

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Comparative bioavailability and bioequivalence study	AC-052-116	5.3.1.2	- To evaluate the relative PK properties of two different formulations of bosentan after single-dose administration - Safety and tolerability	Prospective, single-center, Open-label, two-period, two-treatment, randomized, crossover, uncontrolled Phase 1 study	Period A: single oral dose of 62.5 mg bosentan as 1 tablet of 62.5 mg (adult formulation) Period B: single oral dose of 64 mg bosentan as 2 tablets of 32 mg (pediatric formulation)	16	Healthy male subjects	2 single-dose administrations	Completed Final study report
Patient PK and initial tolerability study	AC-052-365 (FUTURE 1)	5.3.3.2	Primary objective: To demonstrate that exposure to bosentan in pediatric patients with IPAH or familial PAH, using a pediatric formulation, is similar to that in adults with PAH Secondary objective: Safety and tolerability	Open-label, single-arm, uncontrolled Phase 3 study	Bosentan 32 mg oral dispersible tablets administered as an aqueous dispersion Weeks 1 to 4 < 30 kg: 2 mg/kg b.i.d. ≥ 30 kg: 64 mg b.i.d. Weeks 5 to 12 < 30 kg: 4 mg/kg b.i.d. ≥ 30 kg: 120 mg b.i.d.	36	Patients aged ≥ 2 and < 12 years WHO FC II or III, IPAH or familial PAH	13.1 weeks (median)	Completed Final study report

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Patient PK and initial tolerability study	AC-052-373 (FUTURE 3)	5.3.3.2	Primary objective: To investigate the PK of the dispersible tablet formulation of bosentan at doses of 2 mg/kg b.i.d. and 2 mg/kg t.i.d. in children with PAH aged from ≥ 3 months to < 2 years and from 2 years to < 12 years Secondary objectives: Efficacy and safety	Open-label, randomized, comparative, parallel group, uncontrolled Phase 3 study	Bosentan 32 mg oral dispersible tablets administered as an aqueous dispersion at target bosentan doses of 2 mg/kg b.i.d. and 2 mg/kg t.i.d.	64	Patients aged ≥ 3 months and < 12 years WHO FC I, II or III, IPAH, or heritable PAH, or associated PAH, or PAH-CHD	24.2 weeks (median)	Completed Final study report
Supplementary data analysis	Echocardiographic change analysis (D-15.315)	5.3.3.2	- To complement the echocardiographic data presented in the FUTURE 3 clinical study report - To evaluate the prognostic value of changes in different echocardiographic parameters, or their combinations, after 24 weeks of bosentan treatment in the FUTURE 3 core study, versus clinical outcomes at the end of the 18-month observation period (end of FUTURE 3 extension study).	NA	NA	NA	NA	NA	Completed Echocardiographic analysis report

Clinical review
Maryann Gordon, M.D.
NDA#209279
Tracleer® (bosentan)

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Population PK study	AC-052-373 (FUTURE 3) (D-14.035)	5.3.3.5	1. To describe population PK characteristics of bosentan and its metabolites, including inter- and intra-individual variability in children with PAH 2. To quantify the influence of subject-specific factors on PK parameters 3. To perform simulations based on population PK results to investigate the relevance of identified covariates	NA	NA	NA	NA	NA	Completed Modeling and simulation report - Population PK of bosentan in children with PAH

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PBPK modeling report	PBPK modeling report (D-11.250)	5.3.3.5	1. To develop a human PBPK model for bosentan in adults and children 2. To compare model predictions with observed data in adults and children 3. To use the PBPK model to simulate PK in different age ranges (including neonates) in order to support further pediatric drug development	NA	NA	NA	NA	NA	Completed Modeling and simulation report - PBPK modeling of bosentan with application to pediatric patients

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Patient PK and PK/PD study	AC-052-356 (BREATHE-3)	5.3.4.2	Primary objective: To investigate the PK of bosentan given as single and multiple oral doses in pediatric patients with PAH Secondary objective: Safety and tolerability	Open-label, parallel-group single- and multiple-dose, uncontrolled Phase 3 study	Bosentan 62.5 mg and 125 mg oral tablets Single dose Day 1 10 to 20 kg: 31.25 mg > 20 to 40 kg: 62.5 mg > 40 kg: 125 mg Day 2 through Week 4 10 to 20 kg: 31.25 mg once daily > 20 to 40 kg: 31.25 mg b.i.d. > 40 kg: 62.5 mg b.i.d. Weeks 5 to 12+ 10 to 20 kg: 31.25 mg b.i.d. > 20 to 40 kg: 62.5 mg b.i.d. > 40 kg: 125 mg b.i.d. Optional extension up to commercial availability of bosentan	19	Patients aged 3 to 15 years WHO FC II or III, IPAH, PAH associated to scleroderma, or PAH-CHD	23.9 weeks (median)	Completed Final study report

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Patient PK and PK/PD study	AC-052-377	5.3.4.2	Primary objective: To evaluate the effect of bosentan based on change from baseline to Week 12 in PVRI in pediatric patients with PAH Secondary objectives: - To evaluate the effect of bosentan in pulmonary hemodynamic variables other than PVRI, and WHO FC - To evaluate the plasma PK of bosentan and its metabolites - To evaluate the safety and tolerability of bosentan	Open-label, uncontrolled Phase 3 study	Bosentan 32 mg oral dispersible tablets administered as an aqueous dispersion at target bosentan dose of 2 mg/kg b.i.d., with a maximal dose of 120 mg b.i.d.	6	Japanese patients aged < 15 years WHO FC II-IV, IPAH, heritable PAH, or PAH-CHD	84.0 days (median)	Completed Final study report

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Open-label uncontrolled study	AC-052-367 (FUTURE 2)	5.3.5.2	Long-term safety and efficacy	Open-label, uncontrolled extension to FUTURE 1	Bosentan 32 mg oral dispersible tablets administered as an aqueous dispersion at target bosentan doses of 4 mg/kg b.i.d. (down-titration to 2 mg/kg if dose not tolerated) Patients ≥ 30 kg, total dose of 120 mg b.i.d. (down-titrated to 64 mg b.i.d. if not tolerated)	36	Patients from core FUTURE 1 study entering extension: aged ≥ 2 and < 12 years WHO FC II or III, IPAH or familial PAH	119.9 weeks (median)	Completed Final study report
Open-label uncontrolled study	AC-052-374 (FUTURE 3 extension)	5.3.5.2	Long-term safety, tolerability and efficacy	Open-label, double-arm, uncontrolled extension to FUTURE 3	Bosentan 32 mg oral dispersible tablets administered as an aqueous dispersion at target bosentan doses of 2 mg/kg b.i.d. and 2 mg/kg t.i.d.	58	Patients from core FUTURE 3 study entering extension: aged ≥ 3 months and < 12 years WHO FC I, II or III, IPAH, or heritable PAH, or associated PAH, or PAH-CHD	72.2 weeks (median cumulative exposure)	Completed ¹ Final study report

¹ The AC-052-374 open-ended Exceptional Use Treatment Period is ongoing, allowing treatment of patients beyond the 12-month treatment period in cases where bosentan is not available commercially or via compassionate use or similar programs.

b.i.d. = twice daily; CHD = congenital heart disease; FC = functional class; NA = not applicable; IPAH = idiopathic pulmonary arterial hypertension; PAH = pulmonary arterial hypertension; PAH-CHD = PAH associated with congenital heart disease; PBPK = Physiologically-based pharmacokinetic(s); PD = pharmacodynamics(s); PK = pharmacokinetic(s); PVRI = pulmonary vascular resistance index; t.i.d. = three times daily; WHO = World Health Organization.

6 Review of Efficacy

Reviewer's conclusions regarding efficacy

Bosentan should not be approved for use in children with PAH because there is no demonstration of clinical benefit in adequate and well controlled trials.

All efficacy trials for this indication were uncontrolled. While there were changes in cardiac hemodynamics generally viewed as improvements, these changes are insufficient to be used as proof of efficacy for any PAH drug, especially the first one to have such an indication. There were few changes in functional class and the Global Clinical Impression Scales in these trials.

Reviewer's summary

The determination of efficacy of bosentan in children is based on three open label, uncontrolled studies, one using the film-coated tablet (BREATHE 3) and two using the 32 mg dispersible tablet (FUTURE 1/2 AND 3).

The study subjects were similar across the three studies. Most patients had a disease etiology of primary pulmonary hypertension (PPH)/idiopathic, with the remaining having PAH related to congenital systemic-to-pulmonary shunts, or familial. Ages ranged from 4.5 to 14.2 years.

The sponsor chose to establish efficacy primarily on the change in pulmonary vascular resistance obtained during right heart catheterization. No formal hypothesis testing was pre-defined in any study.

Pulmonary vascular resistance (PVR)

The BREATHE-3 study in 19 pediatric PAH patients showed improvement in PVR (mean change from baseline to Week 12 was $-389 \text{ dyn}\cdot\text{sec}/\text{cm}^5$) after administration of bosentan film-coated tablets at approximately 2 mg/kg b.i.d. The mean change from baseline in PVR in the BREATHE-2 study (WHO FC III or IV patients) was $-563.5 \text{ dyn}\cdot\text{sec}/\text{cm}^5$. There is a limitation to the interpretation of these results without a control group.

This effect is similar in magnitude to the PVR improvement in the bosentan treatment arms of two placebo-controlled adult PAH studies. Mean changes from baseline were $-223 \text{ dyn}\cdot\text{sec}/\text{cm}^5$ for AC-052-351, and $-253.6 \text{ dyn}\cdot\text{sec}/\text{cm}^5$ for BREATHE-5. There was less change for the EARLY trial ($-69 \text{ dyn}\cdot\text{sec}/\text{cm}^5$).

WHO functional class (WHO FC)

Table 4-4 WHO FC: Change from baseline to Month 12 in pediatric studies (dispersible tablets)

FUTURE 1 and FUTURE 2 (N = 36)	FUTURE 3 and FUTURE 3 extension (N = 64)
Improved: 34.6% (9/26)	Improved: 15.6% (10/64)
Stable: 65.0% (17/26)	Stable: 73.4% (47/64)
Worsened: 0	Worsened: 10.9% (7/64)
WHO FC = World Health Organization functional class. Source: Module 2.7.3, Table 3-28.	

At month 12, the majority of patients were unchanged from baseline in their WHO functional class score.

Global Clinical Impression Scale (GCIS)

Table 4-5 Global Clinical Impression Score: Change from baseline to Month 12 in pediatric studies (dispersible tablets)

FUTURE 1 and FUTURE 2 (N = 36)	FUTURE 3 and FUTURE 3 extension (N = 64)
<i>Physicians' GCIS:</i>	
Improved: 46.1% (12/26)	Improved: 31.4% (16/51)
Stable: 50% (13/26)	Stable: 62.7% (32/51)
Worsened: 3.8% (1/26)	Worsened: 5.9% (3/51)
<i>Parents' GCIS</i>	
Improved: 50% (11/22)	Improved: 39.2% (20/51)
Stable: 36.3% (8/22)	Stable: 54.9% (28/51)
Worsened: 13.6% (3/22)	Worsened: 5.9% (3/51)
GCIS = Global Clinical Impression Scale. Source: Module 2.7.3, Table 3-28.	

Similar to the WHO FC scores, the GCIS rated both by physicians and parents showed that the majority of patients in FUTURE 1 and 2, and in FUTURE 3 and its extension remained stable compared to baseline scores.

PAH worsening

Table 4-6 PAH worsening at Month 12 in pediatric studies (dispersible tablets)

FUTURE 1 and FUTURE 2 (N = 36)	FUTURE 3 core and its extension (N = 64)
No. of patients with PAH worsening events at Month 12	
Worsening of PAH ¹ : 7	Worsening of PAH ¹ : 9
Worsening of PAH ² : 12	Worsening of PAH ² : 11
KM estimate at Month 12	
No worsening of PAH ¹ : 78.9%	No worsening of PAH ¹ : 84.7%
No worsening of PAH (broader definition) ² : 65.8%	No worsening of PAH (broader definition) ² : 81.4%
¹ Time to first occurrence of death, transplantation, or hospitalization for PAH worsening	
² Time to first occurrence of death, transplantation, hospitalization for PAH worsening, initiation of new therapy for PAH or new/worsening of right heart failure	
KM = Kaplan-Meier; PAH = pulmonary arterial hypertension.	

PAH worsening at month 12 was somewhat worse for Future 1 and Future 2 compared to Future 3.

Background

The three studies used to support efficacy are discussed below in detail.

AC-052-356 (BREATHE-3)

Title: Pharmacokinetics and Tolerability of Tracleer™ (Bosentan) in Pediatric Patients with Pulmonary Arterial Hypertension: Single and Multiple Oral Doses

This was a 12-week, open-label, single- and multiple-dose study conducted at 2 centers in the USA in pediatric male or female PAH patients aged between 3–15 years (primary or related to scleroderma or congenital heart defects and of WHO FC II–III) on conventional vasodilator/anticoagulant therapy or epoprostenol therapy.

First patient first visit: May 11, 2001

Last patient completed: February 13, 2002

The main objective was to investigate the PK of bosentan given as single and multiple oral doses in pediatric patients with PAH. Other objectives were to evaluate the tolerability and safety of single and multiple oral doses of bosentan and to obtain preliminary data on changes in exercise capacity, hemodynamics, and WHO FC.

Following the screening period (up to 21 days), eligible patients were assigned to one of three parallel bosentan treatment arms on the basis of body weight, and treated as shown in the table below.

Table 2-1 Bosentan treatment by body weight in the BREATHE-3 study

Table 2-1 Bosentan treatment by body weight in the BREATHE-3 study			
Body weight	Single dose (Day 1 and at Week 12 visit)	Initial dose (Day 2 through Week 4 visit)	Target dose (starting Week 5)
> 40 kg	125 mg	62.5 mg b.i.d.	125 mg b.i.d.
20–40 kg	62.5 mg	31.25 mg b.i.d.	62.5 mg b.i.d.
10–20 kg	31.25 mg	31.25 mg q.d.	31.25 mg b.i.d.

Note: 31.25 mg doses were obtained by cutting 62.5 mg tablets in half.
b.i.d. = twice daily; q.d. = once daily.

On Day 1, patients were treated with a single dose of oral bosentan determined by body weight, and blood samples for PK profiles were taken periodically for the following 24 h.

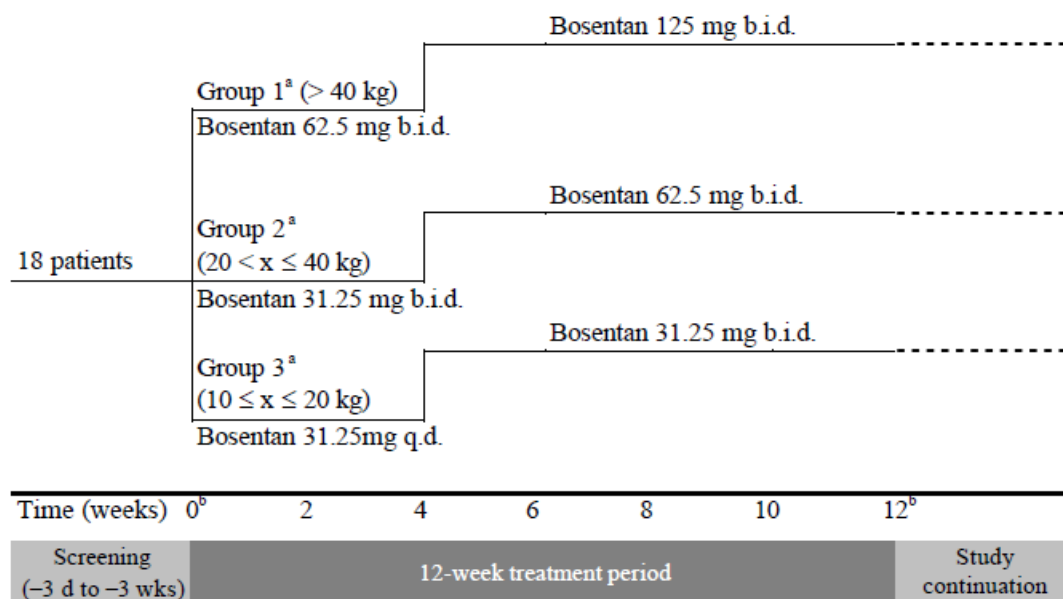
On Day 2, patients began daily treatment with the initial dose determined by body weight for 4 weeks, which was thereafter up-titrated to the target dose. At the Week 12 visit, patients were again treated with a single morning bosentan dose determined by body weight, and blood samples for multiple-dose PK profiles were taken periodically for the following 24 h. Patients who completed the 12-week PK evaluation were eligible to continue open-label treatment until bosentan became available commercially.

Study design

Multicenter, open-label, non-controlled, parallel-group single- and multiple-dose study, with stratification for weight and epoprostenol use

The study design is shown below.

Figure 1 Study design



^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).

Inclusion criteria

Male or female patients with PAH (primary or related to scleroderma or congenital heart defects and of WHO class II-III) on conventional vasodilator/anticoagulant therapy or epoprostenol therapy.

Male or female pediatric patients with PAH in WHO functional class II or III, with or without epoprostenol therapy, were eligible for the trial. Pulmonary arterial hypertension could have been primary or associated with scleroderma or congenital heart defects such as ventricular/atrial septal defect (VSD/ASD), transposition of the great vessels, patent ductus arteriosus, partial anomalous pulmonary venous return, and aortopulmonary window.

- Age: 2 to 17 years at screening
- Body weight ≥ 10 kg
- Oxygen saturation ≥ 88% (at rest and room air)
- Negative results from drug screening (cocaine, cannabinoids, opiates, benzodiazepines)
- Negative results from pregnancy test (for females, except those with documented surgical sterilization or hysterectomy)
- For epoprostenol-treated patients: stable clinical status on epoprostenol for at least 3 months prior to screening (modified from 6 months by Amendment 1 to the protocol)
- For patients on conventional vasodilator therapy: stable for at least 3 months prior to screening
- Written informed consent given by parent or legal guardian (modified to include parent by Amendment 1 to the protocol)

- Gave assent (if required)

Exclusion criteria

Patients were not included in the study if one of the following exclusion criteria was fulfilled at the screening visit and/or prior to study medication initiation:

- Pregnant or nursing (for female patients)
- Cardiac index < 2 l/min /m²
- Hypotension, defined as systolic blood pressure < 80 mmHg
- Left ventricular dysfunction. Patients should have had an echocardiogram within 3 months prior to screening, unless pulmonary capillary wedge pressure (PCWP) was measured, to rule out left ventricular dysfunction.
- Hemoglobin and/or hematocrit below 30% of the normal range (patients with secondary polycythemia were permitted in the study)
- Aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) values greater than two times the upper limit of the normal range ($> 2 \times \text{ULN}$)
- Clinically relevant intercurrent medical conditions (*e.g.*, liver impairment) that might have interfered with the evaluation of the safety of the study medication or any other objective of the study
- Clinical, biochemical, or serological signs that indicated active hepatitis
- Positive results from HIV serology, hepatitis B, or hepatitis C
- History of drug abuse
- History of clinically relevant hypersensitivity or severe adverse reactions to any drug
- Symptoms of a clinically relevant illness (*e.g.*, acute uncontrolled bacterial, viral, or fungal infection) in the 4-week period preceding the screening examination for the study
- Started or stopped treatment for PAH within 1 month of screening, excluding anticoagulation with warfarin
- Use at inclusion or expected use during the study of glibenclamide, cyclosporine A, tacrolimus (FK506), inhibitors/inducers of CYP3A4 and/or CYP2C9 (*e.g.*, ketoconazole, erythromycin, omeprazole, or fluvoxamine [see Appendix 8 of the protocol])

Efficacy endpoints

Hemodynamic endpoints

Change from baseline to Week 12 in the following hemodynamic variables:

- PVR and PVRI.

Other hemodynamic variables including systolic, diastolic and mPAP, RAP, PCWP, pulmonary arterial and venous oxygen saturation, SVO₂, cardiac index, stroke index, cardiac output, SVR and SVR index, PVR/SVR.

Other efficacy endpoints

Change from baseline to Week 12 in:

- 6MWD
- Borg dyspnea index score

- Cycle ergometry test variables measured at rest and at peak exercise.
- WHO FC.

Statistical analyses

No formal hypothesis testing was defined. All analyses (hemodynamic and efficacy) were performed descriptively (any p-values presented being of exploratory nature) using the All-enrolled population.

Study subjects

A total of 19 pediatric patients were enrolled in the study and were assigned to one of three dosing regimens on the basis of body weight: 7 patients on bosentan 31.25 mg b.i.d., 6 patients on 62.5 mg b.i.d., and 6 patients on 125 mg b.i.d.

One of the 19 patients 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).

Table 3-5 AC-052-356 (BREATHE-3): Summary of demographic and baseline characteristics – All-enrolled patients

	Patients 10 - 20 kg N=7	Patients >20 - 40 kg N=6	Patients > 40 kg N=6	All N=19
SEX [n (%)]				
n	7	6	6	19
Males	4 57.1%	2 33.3%	3 50.0%	9 47.4%
Females	3 42.9%	4 66.7%	3 50.0%	10 52.6%
AGE (years)				
n	7	6	6	19
Mean	5.7	10.0	14.2	9.7
Standard deviation	1.9	2.4	1.2	4.0
Median	6.0	10.5	14.5	10.0
Min , Max	3.0 , 8.0	6.0 , 13.0	12.0 , 15.0	3.0 , 15.0
AGE [n (%)]				
n	7	6	6	19
< 8 years	5 71.4%	1 16.7%	-	6 31.6%
8 - 12 years	2 28.6%	4 66.7%	1 16.7%	7 36.8%
13 - 17 years	-	1 16.7%	5 83.3%	6 31.6%
RACE [n (%)]				
n	7	6	6	19
Caucasian/white	6 85.7%	6 100%	3 50.0%	15 78.9%
Other	1 14.3%	-	3 50.0%	4 21.1%
Time from diagnosis of PAH (months)*				
n	7	6	6	19
Mean	39.3	46.1	113.2	64.8
Standard deviation	26.2	48.0	53.7	55.0
Median	28.6	19.5	102.2	61.1
Min , Max	0.5 , 105.2	12.9 , 126.1	61.1 , 184.5	0.5 , 184.5
Etiology of PAH [n (%)]				
n	7	6	6	19
Primary Pulmonary Hypertension	3 42.9%	4 66.7%	3 50.0%	10 52.6%
Congenital Heart Defect	4 57.1%	2 33.3%	3 50.0%	9 47.4%
WHO grade at Baseline [n (%)]				
n	7	6	6	19
II	7 100%	5 83.3%	3 50.0%	15 78.9%
III	-	1 16.7%	3 50.0%	4 21.1%

Source: Appendix 5, Table 1 and Table 2.

The majority of patients were female (53%), white (79% overall), and had a median age of 10 years (range: 3–15 years). The median time from diagnosis to enrollment was 61.1 months (range: 0.5–184.5 months). All patients belonged to either WHO FC II (79%) or FC III (21%) at baseline. Ten out of the 19 enrolled patients were on stable epoprostenol therapy at baseline.

Of the 19 patients, 10 had a disease etiology of PPH, and the remaining had PAH related to congenital systemic-to-pulmonary shunts.

The median (range: min–max) duration of exposure to bosentan was on 23.9 weeks (1–39 weeks).

Change in PVR

Table 3-17 AC-052-356 (BREATHE-3): PVR change from baseline to Week 12, All-enrolled patients

All N=19	
Baseline	
n	17
Mean	1194.5
Standard deviation	754.7
Standard error	183.0
95% CL of mean	806.5 , 1582.5
Median	1194.0
95% CL of median	613.3, 1437.7
Q1 , Q3	613.3, 1437.7
Min , Max	282.8, 3100.0
Week 12	
n	17
Mean	805.3
Standard deviation	504.9
Standard error	122.5
95% CL of mean	545.7 , 1064.9
Median	793.9
95% CL of median	467.1 , 927.5
Q1 , Q3	467.1 , 927.5
Min , Max	106.0 , 2173.3
Change from Baseline to Week12	
n	17
Mean	-389.2
Standard deviation	616.2
Standard error	149.5
95% CL of mean	706.0 , -72.4
Median	-266.5
95% CL of median	523.4 , -90.2
Q1 , Q3	523.4 , -90.2
Min , Max	1675.8 , 751.1
Percent ratio Week 12/Baseline	
n	17
Geometric Mean	66.1
95% CL of geometric mean	53.2 , 82.2

CL=confidence limits. Geometric mean is obtained from back transformation of the mean calculated from log-transformed data;
Source: Appendix 5, Table 5.

Mean PVR (95% CLs) declined from baseline to Week 12 ($-389.2 \text{ dyn}\cdot\text{sec}/\text{cm}^5$, -706.0 , -72.4)).

Change in WHO FC status

Table 3-18 AC-052-356: WHO functional class change from baseline to Week 12, All-enrolled analysis set

Treatment	n	Baseline WHO class	n	Week 12							
				I		II		III		IV	
				No.	%	No.	%	No.	%	No.	%
All	19	I	-	-	-	-	-	-	-	-	-
		II	15	2	10.5%	12	69.2%	1	5.9%	-	-
		III	4	-	-	3	15.8%	1	5.9%	-	-
		IV	-	-	-	-	-	-	-	-	-
All											
N=19											
Change at week 12											
n			19								
Improved [n (%)]			5 (26.3%)								
95% confidence limits (%)			9.1 , 51.2								

Source: Appendix 5, Table 9 and Table 10.

During the 12 weeks of treatment, 5 patients (26%) improved by one WHO FC: 3 patients improved from WHO FC III to II, and 2 improved from WHO FC II to I. One patient worsened from WHO FC II to III.

Studies conducted with 32 mg bosentan dispersible tablets in pediatric patients

AC-052-365 (FUTURE 1) and its extension AC-052-367 (FUTURE 2)

Study	Patient population: age and etiology of PAH	Study objectives	Patients treated / evaluable	Median treatment duration on bosentan	Treatment / regimen Mean daily dose	Type of control / blinding / design	Efficacy endpoints
Studies conducted with bosentan 32 mg oral dispersible tablet formulation in pediatric population							
AC-052-365 (FUTURE 1) [D-07.041]*	≥ 2 and < 12 years WHO FC II or III IPAH or familial PAH	PK, safety and tolerability	Treated: 36 patients Evaluable efficacy: 36 patients	13.1 weeks (range: 8.4–21.1)	2 mg/kg b.i.d. to 120 mg b.i.d. Up-titration after 4 weeks from 2 to 4 mg/kg b.i.d.	Open-label, single-arm, uncontrolled 12-week study	Changes in WHO FC, QoL and parents' and physicians' GCIS Time to worsening (composite)

FUTURE 1 was a 12-week, multicenter, prospective, open-label, single-arm study designed to evaluate the PK and safety of the dispersible tablet formulation of bosentan in male and female patients aged ≥ 2 and < 12 years of age with WHO FC II or III idiopathic or familial PAH. The study was conducted at 11 centers in 7 countries (Europe and USA).

The objective of FUTURE 1 was to demonstrate that the exposure to bosentan in pediatric patients with idiopathic or familial PAH, using a pediatric formulation, was similar to that in adults with PAH. Other objectives were to evaluate the tolerability and safety of a pediatric formulation of bosentan in pediatric PAH patients.

Patients were either PAH-treatment naïve, or were already treated with bosentan monotherapy, intravenous epoprostenol monotherapy, intravenous or inhaled iloprost monotherapy, a

combination of bosentan and intravenous epoprostenol, or a combination of bosentan and intravenous or inhaled iloprost.

Patients initially received bosentan as an aqueous dispersion at a dose of 2 mg/kg b.i.d. for 4 weeks, which was up-titrated to a maintenance dose of 4 mg/kg b.i.d., provided that tolerability was acceptable. If the dose was not well tolerated, it was down-titrated to 2 mg/kg b.i.d. Patients weighing 30 kg or more received a maximum total dose of 120 mg b.i.d. of bosentan unless down-titration was necessary, in which case they received 64 mg b.i.d. Patients who completed the study per protocol, and for whom the investigator considered treatment with bosentan to be beneficial, were eligible for enrollment into open label extension study FUTURE 2.

Efficacy endpoints (Future 1)

- Change from baseline to end of study or premature study drug discontinuation in:
 - WHO functional class
 - QoL questionnaire score (10-item short form health survey for children)
 - GCIS according to the parents/legal representatives
 - GCIS according to the physician
- PAH worsening endpoints:
 - Worsening of PAH: time to first occurrence of death, transplantation, or hospitalization for PAH worsening.
 - Worsening of PAH (broader definition): time to first occurrence of worsening of PAH (as defined above), or initiation of new therapy for PAH, or new right heart failure, or worsening of right heart failure.

Statistical analyses

No formal hypothesis testing was defined. Descriptive efficacy analyses were performed for all patients. All patients who received at least one dose of study medication were included in the efficacy analyses.

Demographics

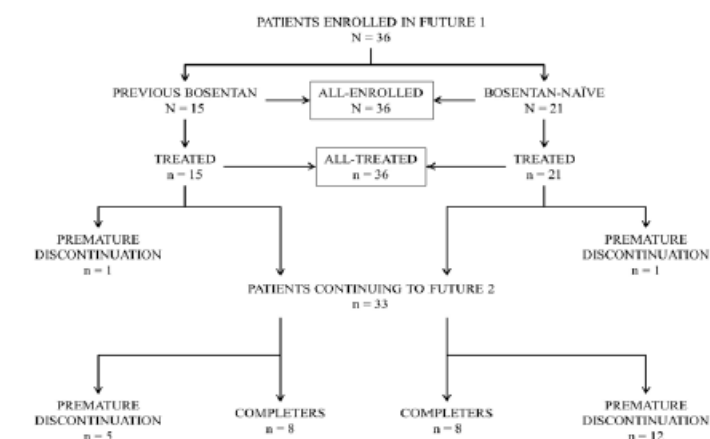
Table 3-6 FUTURE 1 and FUTURE 2: Summary of patient demographics and baseline characteristics, All-treated set

	All patients N=36	Patients with previous Bosentan N=15	Patients Bosentan naïve N=21
SEX [n (%)]			
n	36	15	21
Males	21 58.3%	10 66.7%	11 52.4%
Females	15 41.7%	5 33.3%	10 47.6%
AGE (years)			
n	36	15	21
Mean	6.8	6.9	6.6
Standard deviation	2.72	2.05	3.15
Median	7.0	7.0	7.0
Q1, Q3	4.5, 9.5	5.0, 8.0	4.0, 10.0
Min, Max	2.0, 11.0	3.0, 10.0	2.0, 11.0
AGE [n (%)]			
n	36	15	21
2 - 3 years	4 11.1%	1 6.7%	3 14.3%
4 - 5 years	9 25.0%	3 20.0%	6 28.6%
6 - 11 years	23 63.9%	11 73.3%	12 57.1%
RACE [n (%)]			
n	36	15	21
Caucasian/white	32 88.9%	14 93.3%	18 85.7%
Black	1 2.8%	-	1 4.8%
Hispanic	2 5.6%	-	2 9.5%
Other	1 2.8%	1 6.7%	-
DURATION OF PAH (months)			
n	36	15	21
Mean	21.8	38.3	26.9
Standard deviation	21.03	24.41	34.80
Median	25.8	37.6	14.0
Q1, Q3	4.1, 49.8	22.7, 52.4	0.4, 39.3
Min, Max	0.0, 133.5	1.2, 82.6	0.0, 133.5
ETIOLOGY OF PAH [n (%)]			
n	36	15	21
Idiopathic	31 86.1%	12 80.0%	19 90.5%
Familial	5 13.9%	3 20.0%	2 9.5%

Most of the patients were female, around age 7 years (range 2–11 years), white and had idiopathic PAH. The median time since PAH diagnosis was 25.8 months (range: 0.0–133.5 months). At baseline, patients were in WHO FC II (64%) or III (36%), and the majority was on stable prostanoids and/or commercial bosentan treatment (64%).

Study Disposition

Figure 3-1 Disposition of patients in FUTURE 1 and FUTURE 2



Note: One additional patient in the previous bosentan subgroup completed FUTURE 1 but did not enroll in FUTURE 2

Of the 36 patients treated in FUTURE 1, two prematurely discontinued the study:
-one death resulting from right ventricular failure following development of an ear infection, and
-one administrative reason (difficulty in administering pediatric formulation).

Of the remaining 34 patients, 33 continued bosentan treatment in the extension study FUTURE 2. Overall, a total of 19 patients (53%) discontinued prematurely from the core or extension study because of administrative reasons or withdrawal of consent (n = 10), disease progression, adverse events, transplant or treatment failure (n = 5), or death caused by PAH or infection (n = 4).

The median (range: min–max) cumulative duration of exposure to bosentan treatment was 119.9 weeks (8.4–258.0 weeks).

Change in WHO FC status

Table 3-19 FUTURE 1 and 2: WHO functional class change from baseline to EOS, All-treated set

	n	Baseline	End of Study/Premature Discontinuation of Study Drug visit				
			n	I	II	III	IV
All patients	28	I	-	-	-	-	-
		II	17	6 21.4%	10 35.7%	1 3.6%	-
		III	11	2 7.1%	9 30.7%	5 17.9%	1 3.6%
		IV	-	-	-	-	-

From baseline to end of study or premature discontinuation of study drug (FUTURE 1 or 2), WHO FC improved in 11/28 patients (39%). Worsening was reported for two patients who discontinued because of death (treated for 265 days) or disease progression (treated for 168 days).

Change in global clinical impression scale (GCIS)

Table 3-20 FUTURE 1 and 2: GCIS change from baseline to EOS, All-treated set

		End of Study/ Premature Discontinuation of Study Drug visit									
		n	Baseline	n	Significantly Better	Better	No change	Worse	Significantly Worse		
PARENT'S GCIS											
All patients	16	Very good	1	1	6.3%	-	-	-	-		
		Good	7	4	25.0%	2	12.5%	1	6.3%	-	
		Neither good or bad	6	2	12.5%	3	18.8%	1	6.3%	-	
		Bad	2	1	6.3%	-	-	1	6.3%	-	
PHYSICIAN'S GCIS											
All patients	26	Very good	1	-	-	-	1	3.8%	-		
		Good	16	2	7.7%	8	30.8%	5	19.2%	1	3.8%
		Neither	6	3	11.5%	3	11.5%	-	-	-	
		Bad	3	1	3.8%	-	-	1	3.8%	1	3.8%

GCIS = Global clinical impression scale

In 13 (81%) out of 16 patients with available data, GCIS, as rated by the parents, improved from baseline to end of study or premature discontinuation of study drug. Two patients remained unchanged and one was rated as worse.

In 17 (65%) out of 26 patients with available data, GCIS, as rated by the physician, improved from baseline to end of study or premature discontinuation of study drug. Seven remained unchanged and two were rated as worse.

Time to disease worsening

Table 13 Time to worsening of PAH (Kaplan Meier estimates), All-treated set

Ro 47-0208, Protocol: AC-052-867
Time to worsening of PAH (Kaplan Meier estimates)
Analysis set: All treated

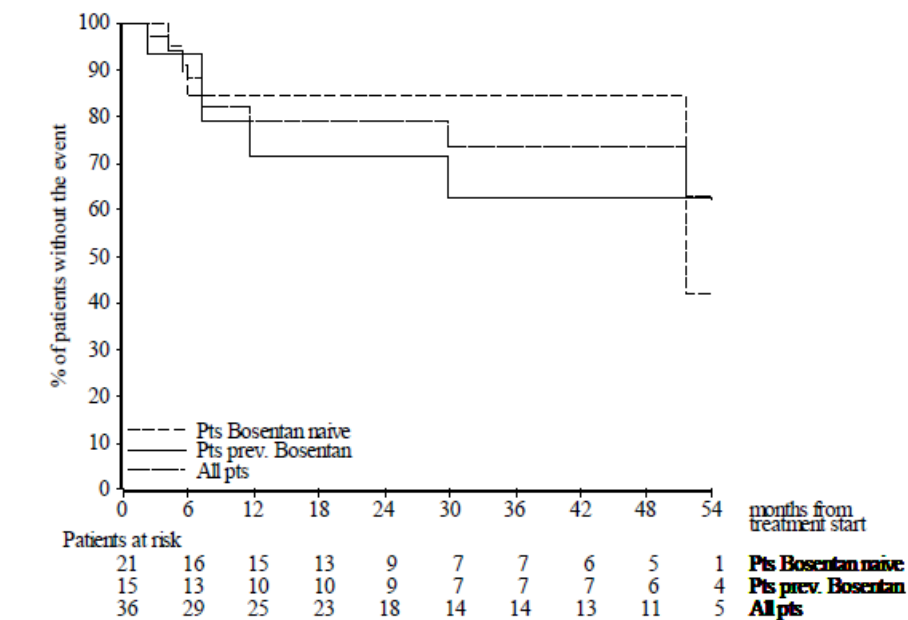
K-M estimate of the event-free rate %	All patients N=36	Patients with previous Bosentan N=15	Patients Bosentan naïve N=21
At month 6 (183 days)			
Patients at risk	29	13	16
Patients censored	3	1	2
Patients with event	4	1	3
K-M estimate (%)	88.1	93.3	84.4
95% confidence interval (%)	71.4, 95.4	61.3, 99.0	59.1, 94.7
At month 12 (366 days)			
Patients at risk	25	10	15
Patients censored	4	1	3
Patients with event	7	4	3
K-M estimate (%)	78.9	71.8	84.4
95% confidence interval (%)	60.7, 89.3	41.1, 88.4	59.1, 94.7
At month 24 (732 days)			
Patients at risk	18	9	9
Patients censored	11	2	9
Patients with event	7	4	3
K-M estimate (%)	78.9	71.8	84.4
95% confidence interval (%)	60.7, 89.3	41.1, 88.4	59.1, 94.7
At month 36 (1098 days)			
Patients at risk	14	7	7
Patients censored	14	3	11
Patients with event	8	5	3
K-M estimate (%)	73.6	62.8	84.4
95% confidence interval (%)	53.1, 86.2	31.8, 82.8	59.1, 94.7
At month 48 (1464 days)			
Patients at risk	11	6	5
Patients censored	18	4	14
Patients with event	8	5	3
K-M estimate (%)	73.6	62.8	84.4
95% confidence interval (%)	53.1, 86.2	31.8, 82.8	59.1, 94.7
At month 60 (1830 days)			
Patients at risk	-	-	-
Patients censored	27	10	17
Patients with event	9	5	4
K-M estimate (%)	63.1	62.8	42.2
95% confidence interval (%)	35.3, 81.6	31.8, 82.8	1.3, 84.4

K-M = Kaplan-Meier.
Table PAH13.T - Produced by saslogm on 25SEP12 - Data dump of 25SEP12
(Page 1/1)

The KM event-free estimates for worsening of PAH (defined as time to first occurrence of death, lung transplantation or hospitalization for PAH worsening) were 79% (95% confidence interval [CI] 60.7%, 89.3%) at 2 years and 74% (95% CI 53.1%, 86.2%) at four years.

Figure 2 Time to death, lung transplantation, hospitalization for PAH-progression, All-treated set

Ro 47-0203, Protocol AC-052-367
Time to worsening of PAH (Kaplan-Meier Estimate)
Analysis set: All treated



Note: Pts - Patients. prev. - previous. Survival plots are presented up to 54 months, time at which more than 10% of the patients are still at risk.
Figure PAH1G_T - Produced by ameglm on 29APR13 - Data dump of 25SEP12

Table 14 Time to worsening of PAH or initiation of new therapy for PAH or new right heart failure or worsening of right heart failure (Kaplan-Meier Estimate), All-treated set

Bo 47-0203, Protocol: AC-052-367

Time to worsening of PAH or initiation of new therapy for PAH or new right heart failure or worsening of right heart failure (Kaplan-Meier Estimate)

Analysis set: All treated

K-M estimate of the event-free rate %	All patients N=36	Patients with previous Bosentan N=15	Patients Bosentan naive N=21
At month 6 (183 days)			
Patients at risk	26	10	16
Patients censored	1	-	1
Patients with event	9	5	4
K-M estimate (%)	74.4	66.7	80.0
95% confidence interval (%)	56.6 , 85.8	37.5 , 84.6	55.1 , 92.0
At month 12 (366 days)			
Patients at risk	22	9	13
Patients censored	2	-	2
Patients with event	12	6	6
K-M estimate (%)	65.8	60.0	70.0
95% confidence interval (%)	47.7 , 78.9	31.8 , 79.7	45.1 , 85.3
At month 24 (732 days)			
Patients at risk	15	9	6
Patients censored	6	-	6
Patients with event	15	6	9
K-M estimate (%)	56.2	60.0	51.7
95% confidence interval (%)	38.0 , 71.0	31.8 , 79.7	27.1 , 71.7
At month 36 (1098 days)			
Patients at risk	12	7	5
Patients censored	8	1	7
Patients with event	16	7	9
K-M estimate (%)	51.9	52.5	51.7
95% confidence interval (%)	33.4 , 67.5	25.2 , 74.0	27.1 , 71.7
At month 48 (1464 days)			
Patients at risk	10	6	4
Patients censored	11	2	9
Patients with event	16	7	9
K-M estimate (%)	51.9	52.5	51.7
95% confidence interval (%)	33.4 , 67.5	25.2 , 74.0	27.1 , 71.7
At month 60 (1830 days)			
Patients at risk	-	-	-
Patients censored	19	8	11
Patients with event	17	7	10
K-M estimate (%)	44.5	52.5	25.8
95% confidence interval (%)	24.2 , 62.9	25.2 , 74.0	1.9 , 62.1

K-M = Kaplan-Meier.

Table PAH25 T - Produced by sasolm on 25SEP12 - Data date of 25SEP12

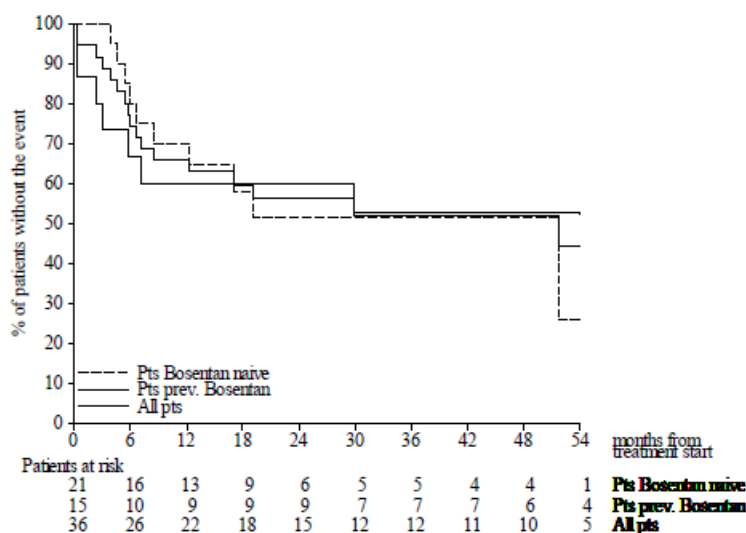
For the broader definition of worsening of PAH (defined as time to first occurrence of death, lung transplantation, hospitalization for PAH worsening or initiation of new therapy for PAH, or new/worsening right heart failure), the KM event-free estimates were 56% (95% CI 38.0%, 71.0%) at 2 years and 52% (95% CI 33.4%, 67.5%) at 4 years.

Figure 3 Time to first occurrence of death, lung transplantation, hospitalization for PAH-progression, initiation of new therapy for PAH, new right heart failure or worsening of right heart failure (FUTURE 2) – All-treated set

Ro 47-0203, Protocol AC-052-367

Time to worsening of PAH or initiation of new therapy for PAH or new right heart failure or worsening of right heart failure (Kaplan-Meier Estimate)

Analysis set: All treated



Note: Pts - Patients; prev. - previous. Survival plots are presented up to 54 months, time at which more than 10% of the patients are still at risk.
Figure PAH2G_T - Produced by amegim on 12MAR14 - Data dump of 25SEP12

PAH = pulmonary arterial hypertension; Pts = patients; prev. = previous.

AC-052-373 (FUTURE 3 core) and its extension AC-052-374 (FUTURE 3 extension)

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
Patient PK and initial tolerability study	AC-052-373 (FUTURE 3)	5.3.3.2	Primary objective: To investigate the PK of the dispersible tablet formulation of bosentan at doses of 2 mg/kg b.i.d. and 2 mg/kg t.i.d. in children with PAH aged from ≥ 3 months to < 2 years and from 2 years to < 12 years Secondary objectives: Efficacy and safety	Open-label, randomized, comparative, parallel group, uncontrolled Phase 3 study	Bosentan 32 mg oral dispersible tablets administered as an aqueous dispersion at target bosentan doses of 2 mg/kg b.i.d. and 2 mg/kg t.i.d.	64	Patients aged ≥ 3 months and < 12 years WHO FCI, II or III, IPAH, or heritable PAH, or associated PAH, or PAH-CHD	24.2 weeks (median)	Completed Final study report

The FUTURE 3 core study was a prospective, open-label, randomized study to investigate the PK of the dispersible tablet formulation of bosentan at doses of 2 mg/kg b.i.d. and 2 mg/kg t.i.d.

in children with PAH from ≥ 3 months to < 2 years of age and from 2 years to < 12 years of age. The study also evaluated the efficacy, tolerability, and safety of bosentan in this patient population.

The study was conducted at 45 pediatric PAH centers across 20 countries in Europe, North America, Latin America, Australia, Asia, and Africa. The children included in this study were required to have WHO FC I, II or III idiopathic PAH heritable PAH, or associated PAH persisting after complete repair of a CHD, or PAH-CHD associated with systemic-to-pulmonary shunts, including Eisenmenger syndrome, with the diagnosis confirmed by RHC.

Patients were randomized in a 1:1 ratio to receive oral doses of bosentan as an aqueous dispersion at doses of 2 mg/kg b.i.d. or 2 mg/kg t.i.d., stratified for baseline bosentan treatment as well as other PAH-specific treatment including prostanoids (epoprostenol, iloprost), phosphodiesterase type-5 (sildenafil, tadalafil) or their combination (hierarchically as bosentan, prostanoid or PDE-5 inhibitor).

The bosentan dosage could be adjusted to the patient's body weight, if required, 12 weeks after start of treatment.

Patients were considered study completers if they completed the 24-week treatment period or, in case of premature discontinuation of study treatment, provided end of study assessments. Patients had the option of participation in a one-year follow-up extension study. Those patients who did not enter the extension study had a 60-day post-treatment follow-up period for serious adverse event reporting. Vital status was to be assessed for all patients 18 months after randomization.

Hemodynamic endpoints

The following endpoint was defined for the FUTURE 3 core study only:

- Change from baseline to end of study in hemodynamic variables for the hemodynamics subgroup (patients who had results for at least one post-baseline RHC assessment):
 - PVRI
 - Other hemodynamic variables: pulmonary arterial systolic, diastolic and mean pressure, mRAP, PCWP or left atrial pressure, SVO₂, cardiac index, cardiac output.

Efficacy endpoints

The following efficacy endpoints were defined for the FUTURE 3 core study only:

- Change from baseline to Weeks 12 and 24, and change from baseline to EOS in echocardiography/ Doppler variables, including indices of left and right size and function.
- Change from baseline to Weeks 12 and 24, and to end of study in plasma NT-proBNP.

The following exploratory efficacy endpoints were defined for all patients across the FUTURE 3 core and its extension study, with the baseline being the FUTURE 3 core study:

- Change from baseline to 3, 6, 9, 12, 15, and 18 months of treatment over FUTURE 3 core and extension study in WHO FC

• PAH worsening endpoints:

– Worsening of PAH: time to death, lung transplantation or hospitalization for PAH progression¹ up to End-of-Treatment (EOT) + 7 days².

¹ ‘PAH-progression’ was defined as a definite/irreversible change in the patient’s clinical condition related to PAH. This excludes transient changes of the patient’s condition caused by, for example, intercurrent infection (e.g., pneumonia), surgery (e.g., adenoidectomy), trauma, etc.

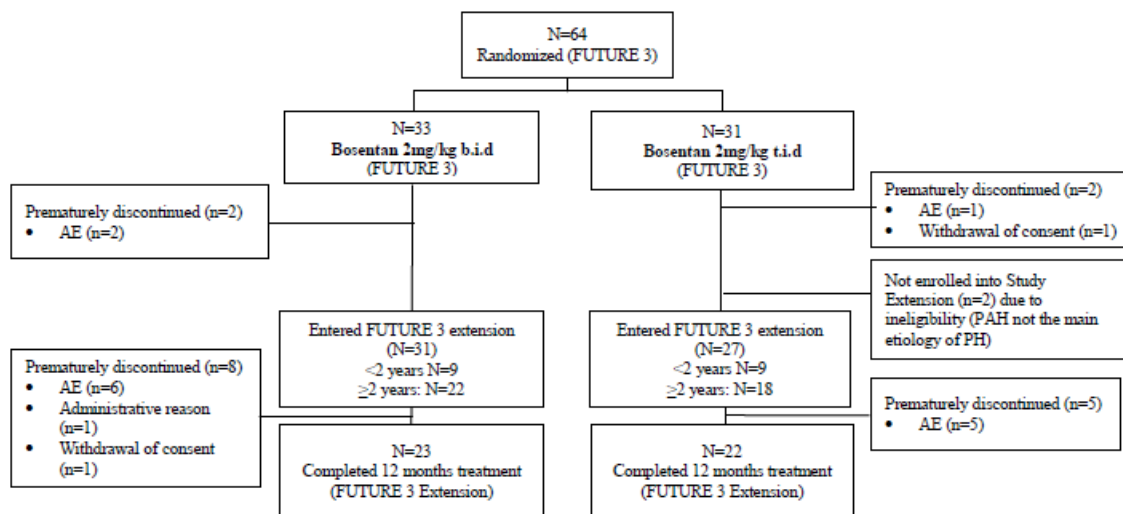
² For time-to-event endpoints, the start was defined as initiation of bosentan treatment in the FUTURE 3

Statistical analyses

No formal hypothesis testing was defined. Analyses of all endpoints were performed descriptively.

Study subject disposition

Figure 3-2 Disposition of patients in FUTURE 3 core and its extension



Of the 64 patients randomized in the FUTURE 3 core study, 6 did not enter the extension study: one patient withdrew consent and permanently discontinued the study, three patients died after experiencing worsening of PAH, and 2 patients were ineligible based on their disease etiology (PAH not the main etiology of patients’ pulmonary hypertension, as assessed after enrollment into FUTURE 3 core study).

Most patients (91%) entered the FUTURE 3 extension study and continued receiving 2 mg/kg bosentan b.i.d. (n = 31) or t.i.d. (n = 27).

Overall, 45 (70%) patients (23 b.i.d and 22 t.i.d.) completed the 12-month treatment period in the extension study. A total of 13 (20%) patients prematurely discontinued study treatment (8 b.i.d., 5 t.i.d.), primarily due to AEs (6 b.i.d., 5 t.i.d.). There were 2 patients (b.i.d) who withdrew either for administrative reasons or withdrawal of consent.

Demographics

Table 3-7 FUTURE 3 core and its extension: Summary of demographic and baseline characteristics overall and by dose regimen, All-randomized set

	b.i.d. N=33	t.i.d. N=31	Total N=64
GENDER [n (%)]			
n	33	31	64
Males	15 45.5%	21 67.7%	36 56.3%
Females	18 54.5%	10 32.3%	28 43.8%
AGE (years)			
n	33	31	64
Mean	4.5	5.2	4.8
Standard error	0.58	0.68	0.45
95% CI of mean	3.3 , 5.7	3.8 , 6.6	3.9 , 5.7
Median	3.7	4.8	3.8
Q1 , Q3	1.8 , 5.6	1.2 , 8.7	1.7 , 7.8
Min , Max	0.3 , 11.0	0.3 , 11.4	0.3 , 11.4
RACE [n (%)]			
n	33	31	64
Caucasian/white	25 75.8%	23 74.2%	48 75.0%
Black	1 3.0%	2 6.5%	3 4.7%
Asian	6 18.2%	4 12.9%	10 15.6%
Hispanic	-	1 3.2%	1 1.6%
Other	1 3.0%	1 3.2%	2 3.1%
PAH specific medications			
Total patients with at least one medication	20 60.6%	22 71.0%	42 65.6%
PDE-5 inhibitor	10 30.3%	13 41.9%	23 35.9%
Bosentan	3 9.1%	4 12.9%	7 10.9%
Bosentan & Prostanoid	-	-	-
PDE-5 inhibitor & Bosentan	5 15.2%	2 6.5%	7 10.9%
PDE-5 inhibitor & Prostanoid	2 6.1%	2 6.5%	4 6.3%
Prostanoid	-	1 3.2%	1 1.6%
Etiology of PAH			
n	33	30	63
Idiopathic (iPAH)	14 42.4%	15 50.0%	29 46.0%
Heritable (hPAH)	2 6.1%	-	2 3.2%
Associated (aPAH)	11 33.3%	13 43.3%	24 38.1%
PAH-CHD (open shunt)	6 18.2%	2 6.7%	8 12.7%
Time from first observed/assumed PAH symptoms* (days*)			
n	33	18	40
Mean	601.5	800.0	690.8
Standard deviation	735.71	933.44	825.38
Median	392.0	371.0	377.5
Q1 , Q3	101.0 , 788.0	239.0 , 1056.0	193.5 , 896.5
Min , Max	5.0 , 3341.0	20.0 , 2812.0	5.0 , 3341.0
Time from diagnosis of PAH by RHC (days*)			
n	32	30	62
Mean	470.4	622.1	543.8
Standard deviation	888.74	910.02	894.96
Median	76.0	111.5	87.5
Q1 , Q3	7.0 , 610.5	6.0 , 1226.0	6.0 , 755.0
Min , Max	-15.0 , 3766.0	0.0 , 2780.0	-15.0 , 3766.0
WHO functional Class [n (%)]			
n	33	31	64
I	9 27.3%	10 32.3%	19 29.7%
II	12 36.4%	15 48.4%	27 42.2%
III	12 36.4%	6 19.4%	18 28.1%

CI=confidence limits.

*Time from PAH symptoms excludes patients with a-PAH etiology

* Calculated in relation to the date of screening

Source: Appendix 7, Table 3 and Table 5; D-14.491, Table 10-3.

The majority of patients were male (56%), white (75%), and had a median age of 3.8 years (range: 0.3–11.4 years).

Etiology of PAH was mainly idiopathic PAH (46%), associated PAH (38%), and PAH-CHD associated with systemic-to-pulmonary shunts (12.7%). The percentages of patients with WHO FC II and III were 42% and 28%, respectively.

The majority of patients were on stable commercial bosentan and/or PDE-5 inhibitor and/or prostanoid treatment (66%).

The median (range) time since diagnosis of PAH by RHC in the overall population was 87.5 days (–15 to 3766 days).

The majority of patients (58% b.i.d., 55% t.i.d.) had at least 72 weeks of exposure to bosentan. The cumulative median (range: min–max) exposure duration to bosentan was 72.1 weeks (6.0–90.1 weeks) in the b.i.d. group and 72.6 weeks (0.4–81.1 weeks) in the t.i.d. group.

Hemodynamic results (FUTURE 3 core only)

Changes in hemodynamics were analyzed in the hemodynamics subgroup, which included patients who had at least one post-baseline RHC assessment. Only patients with the assessment scheduled as per standard hospital practice were to be included.

There were ten patients (four b.i.d. and six t.i.d.) who were included in the hemodynamic substudy. Not all variables were obtained in all patients.

Mean change ($\pm$ standard deviation [SD]) from baseline to 24 weeks in PVRI ($\text{dyn}\cdot\text{sec}\cdot\text{m}^2/\text{cm}^5$) -55.0 ± 77.71 and -160.5 ± 226.98 in the b.i.d. and t.i.d. groups, respectively. There were only four patients (two b.i.d. and two t.i.d.) who had this data for this variable.

Table 3-21 FUTURE 3 core study: Summary of changes in hemodynamics from baseline to EOS– Hemodynamics subgroup, overall age groups, All-randomized set

Variable	n	b.i.d. (N=4)	n	t.i.d. (N=6)
Mean $\pm$ SD				
Pulmonary vascular resistance index ($\text{dyn}\cdot\text{s}\cdot\text{m}^2/\text{cm}^5$)	2	-55.0 ± 77.71	2	-160.5 ± 226.98
Systolic pulmonary arterial pressure (mmHg)	4	-16.8 ± 3.30	6	-4.7 ± 4.18
Diastolic pulmonary arterial pressure (mmHg)	4	-12.3 ± 6.24	6	-1.7 ± 2.25
Mean pulmonary arterial pressure (mmHg)	4	-15.9 ± 5.33	6	-2.8 ± 2.53
Mean right atrial pressure (mmHg)	4	-1.8 ± 3.19	5	0 ± 1.87
Pulmonary capillary wedge pressure (mmHg)	4	-0.5 ± 1.91	6	2.7 ± 4.32
Mixed venous oxygen saturation (%)	4	2.0 ± 5.60	5	-3.8 ± 11.30
Cardiac index ($\text{L}/\text{min}/\text{m}^2$)	2	-3.1 ± 1.13	2	0.2 ± 0.27
Cardiac output (L/min)	2	-2.8 ± 1.13	2	0.2 ± 0.27
Total pulmonary vascular resistance ($\text{dyn}\cdot\text{s}/\text{cm}^5$)	2	-9.9 ± 186.75	2	125.5 ± 177.48
Systemic vascular resistance index ($\text{dyn}\cdot\text{s}\cdot\text{m}^2/\text{cm}^5$)	2	4.2 ± 1.75	1	-3.6
Heart rate (beats/min)	4	-23.3 ± 19.70	6	-10.0 ± 7.92
Systolic systemic arterial pressure (mmHg)	4	1.5 ± 5.07	5	-1.4 ± 4.98
Diastolic systemic arterial pressure (mmHg)	4	-4.0 ± 19.71	5	-0.4 ± 0.89
Mean systemic arterial pressure (mmHg)	4	-0.9 ± 3.12	3	-1.7 ± 2.89

b.i.d. = twice daily; EOS = End-of-Study; SD = standard deviation; t.i.d. = three times daily.

WHO FC

Including data from the extension study, the majority (78%) of patients had no change from baseline at month 18 in functional class.

Table 3-22 FUTURE 3 core and its extension: Change in WHO functional class over time, All-treated set

Time point*	Response	b.i.d. N = 33	t.i.d. N = 31	Total N = 64
Month 6	Stable	25 (75.8%)	27 (87.1%)	52 (81.3%)
	Improved	7 (21.2%)	3 (9.7%)	10 (15.6%)
	Worsened	1 (3.0%)	1 (3.2%)	2 (3.1%)
Month 12	Stable	22 (66.7%)	25 (80.6%)	47 (73.4%)
	Improved	7 (21.2%)	3 (9.7%)	10 (15.6%)
	Worsened	4 (12.1%)	3 (9.7%)	7 (10.9%)
Month 18	Stable	25 (75.8%)	25 (80.6%)	50 (78.1%)
	Improved	3 (9.1%)	3 (9.7%)	6 (9.4%)
	Worsened	5 (15.2%)	3 (9.7%)	8 (12.5%)

b.i.d. = twice daily; FC = functional class; t.i.d. = three times daily; WHO = World Health Organization.

GCIS (physicians and parents)

Table 3-23 FUTURE 3 core and its extension: Summary of shift in physicians' and parents' GCIS from baseline to EOS, All-randomized set

Time point	Response	b.i.d. N = 33	t.i.d. N = 31	Total N = 64
Physicians' GCIS				
Month 6	Stable	23 (74.2%)	23 (79.3%)	46 (76.7%)
	Improved	7 (22.6%)	6 (20.7%)	13 (21.7%)
	Worsened	1 (3.2%)	0 (0.0%)	1 (1.7%)
Month 12	Stable	16 (57.1%)	16 (69.6%)	32 (62.7%)
	Improved	10 (35.7%)	6 (26.1%)	16 (31.4%)
	Worsened	2 (7.1%)	1 (4.3%)	3 (5.9%)
Month 18	Stable	9 (47.4%)	12 (66.7%)	21 (56.8%)
	Improved	6 (31.6%)	5 (27.8%)	11 (29.7%)
	Worsened	4 (21.1%)	1 (5.6%)	5 (13.5%)
Parents' GCIS				
Month 6	Stable	16 (51.6%)	15 (51.7%)	31 (51.7%)
	Improved	12 (38.7%)	11 (37.9%)	23 (38.3%)
	Worsened	3 (9.7%)	3 (10.3%)	6 (10.0%)
Month 12	Stable	16 (57.1%)	12 (52.2%)	28 (54.9%)
	Improved	9 (32.1%)	11 (47.8%)	20 (39.2%)
	Worsened	3 (10.7%)	0 (0.0%)	3 (5.9%)
Month 18	Stable	8 (42.1%)	7 (38.9%)	15 (40.5%)
	Improved	6 (31.6%)	10 (55.6%)	16 (43.2%)
	Worsened	5 (26.3%)	1 (5.6%)	6 (16.2%)

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

b.i.d. = twice daily; GCIS = Global Clinical Impression Scale; t.i.d. = three times daily.

Source: Appendix 7, Table 16 and Table 18.

At Month 18, physicians' GCIS remained unchanged for 57% of patients, improved for 30% of patients, and worsened for 14% of patients.

The results for the parents' / legal representatives' GCIS rating were similar to those for the physicians' GCIS rating.

Time to disease worsening

Events of death, lung transplantation, hospitalization for PAH progression, or initiation of new therapy for PAH or new/worsening right heart failure (broader definition) were reported for 15 patients (10 b.i.d., 5 t.i.d.), 4 reported during the FUTURE 3 core study and 11 during the extension study.

Table 3-24 FUTURE 3 core and its extension: Summary of PAH-worsening components (all occurrences up to EOT + 7 days): death, lung transplant, hospitalization due to PAH progression, initiation of new therapy for PAH or new/worsening right heart failure - Analysis set: All-treated set

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

There were 11 reports of new/worsening right heart failure, 10 reports of death, seven reports of hospitalizations because of PAH, and 4 initiations for PAH related new therapy.

AC-052-377

This was an open-label, multicenter study to assess the efficacy, safety, tolerability, and pharmacokinetics of bosentan in Japanese children with pulmonary arterial hypertension.

Trial start date June 2013 and concluded June 2014

This was a 12-week, multicenter, open-label, uncontrolled Phase 3 study conducted in Japan. The objective of the study was to assess the efficacy, PK, safety and tolerability of the 32 mg dispersible tablet formulation of bosentan in Japanese male or female patients ≥ 1 and < 14 years of age with PAH (idiopathic, heritable or associated with CHD, and in WHO FC II, III or IV). All patients enrolled in the study were naïve to PAH-specific treatment.

Patients received bosentan as an aqueous dispersion at a dose of 2 mg/kg b.i.d. for 12 weeks. Patients weighing 59 kg or more received a maximum total dose of 120 mg b.i.d. of bosentan.

The efficacy of bosentan was evaluated on the basis of pulmonary hemodynamic variables and WHO FC (≥ 4 years of age) by comparing the Week 12 values to baseline..

Primary Objective

To evaluate the effect of bosentan based on change from baseline to Week 12 in pulmonary vascular resistance index (PVRI) in pediatric patients with PAH.

Secondary Objectives

- To evaluate the effect of bosentan based on change from baseline to Week 12 in pulmonary hemodynamic variables other than PVRI, and WHO functional class (WHO FC).
- To evaluate the plasma pharmacokinetics (PK) of bosentan and its metabolites.
- To evaluate the safety and tolerability of bosentan up to Week 12.

Number of patients

Five patients planned, 6 patients enrolled and treated.

Inclusion criteria

- Idiopathic PAH, heritable PAH, and PAH associated with congenital heart disease (CHD)
- WHO FC II to IV
- Japanese male or female pediatric patients < 15 years of age at first study drug administration

Primary endpoint

- Change from baseline (immediately before drug intake) to Week 12 in pulmonary vascular resistance index (PVRI)

Secondary endpoints:

- Change from baseline (immediately prior to drug intake) to Week 12 in:
 - Pulmonary hemodynamic variables other than PVRI
 - Cardiac index
 - Mean right atrial pressure (mRAP)
 - Mean pulmonary arterial pressure (mPAP)
 - Systemic vascular resistance index (SVRI)
 - Pulmonary vascular resistance (PVR)

Systemic vascular resistance (SVR) ratio

- Mixed venous oxygen saturation (SvO₂)

– WHO FC (Only in pediatric patients aged 4 years or older) at the start of study drug administration

Statistical methods

All statistical evaluations were exploratory in nature.

Patient disposition and key demographic data:

Six patients (4 boys and 2 girls) were enrolled into the study and treated with the study drug. Mean age was 6.7 ± 4.8 years, four patients had idiopathic PAH, 1 had heritable PAH and 1 had PAH associated with congenital heart disease. At the time of the first study drug administration, 5 patients were concomitantly receiving PAH treatment (sildenafil citrate: 2 patients, tadalafil: 3 patients and beraprost sodium: 3 patients).

Efficacy results

All six patients underwent right heart catheterization at baseline and after 12 weeks of treatment with the study drug.

Primary endpoint

The mean change $\pm$ standard deviation (SD) from baseline at Week 12 in PVRI was -4.0 ± 258.6 dyn·sec·m²/cm⁵.

Secondary endpoints

The mean change $\pm$ SD from baseline to Week 12 in mPAP was -4.7 ± 10.9 mmHg, mean change $\pm$ SD from baseline to Week 12 in cardiac index, mRAP, SVRI, PVR/SVR ratio, and SvO₂ were -0.4 ± 0.71 L/min/m², 1.3 ± 2.5 mmHg, 142.8 ± 288.6 dyn·sec·m²/cm⁵, $-5.88 \pm 13.63\%$, and $-3.97 \pm 2.93\%$, respectively.

All 4 patients ≥ 4 years old at the time of the first study drug administration were in WHO FC II at baseline and at Week 12. One patient had improved from WHO FC II to I at Week 8.

7 Review of Safety

Safety Summary

There are safety data submitted on 125 pediatric subjects collected during uncontrolled PAH studies. The following conclusions can be reached based on the results of both the studies including children and the studies including adults.

- 1) No death in the pediatric PAH program can be conclusively linked to the use of bosentan.
- 2) As in adults, bosentan use in children can cause a dose-related decrease in hemoglobin and hematocrit. The decreases tend to be mild and rarely require intervention.
- 3) As in adults, the use of bosentan in children can cause an elevation in liver aminotransferases. The elevations are usually reversed when drug is discontinued. No link between use of bosentan and subsequent liver impairment in the pediatric population can currently be made. However, a link cannot be ruled about.
- 4) As in adults, the use of bosentan in children can cause fluid retention/edema.
- 5) The safety is not obviously different from that reported in adults with PAH receiving bosentan.
- 6) The safety update presents no additional safety concerns not reported in the original NDA.
- 7) A review of pediatric post-marketing experience reinforces the known safety profile of bosentan in the adult/elderly population.
- 8) I recommend approval for the use of this drug in children only if it has been shown to be unequivocally beneficial in well controlled clinical trials.

Background

Definitions of variables (as provided in appendix 1 of the integrated summary of safety)

Treatment-emergent adverse events were defined by the applicant as any adverse events starting on or after study treatment start date. To account for differences in reporting time periods across studies and to harmonize data presentations, the summaries and analyses of AEs were conducted using AEs reported up to 7 days after end-of-treatment (EOT).

Sources of safety data

There are 6 completed clinical studies in pediatric PAH. There is one study (BREATHE 3²) conducted with the approved film coated tablet and the remaining five used the 32 mg dispersible tablet.

Safety data were collected on a total of 100 patients ranging in age from 3 months to 12 years. This 100-patient group is referred to as the pooled analysis set and includes patients from FUTURE 1 and FUTURE 2 (n=36), and FUTURE 3 and its extension (n=64). The patients who are not in the pooled analysis set but are examined separately are from BREATHE-3 (n=19) and from the Japanese study AC-052-377 (n=6).

There is one ongoing study in pediatric patients with PAH, AC-052-374 EUTP, which included 10 of the 64 patients from FUTURE 3 extension. This study is ongoing in four countries (Belarus, Ukraine, Russia and China).

Duration of exposure

The duration of treatment for the pooled analysis set is shown below as is the weight adjusted daily dose.

Table 1-3 Duration of exposure in the pooled safety analysis set

Bosentan N=100	
Duration of Study Treatment (months)	
n	100
Mean	21.0
Median	17.0
Q1, Q3	14.2, 22.8
Min, Max	0.1, 59.3
Cumulative duration of Study Treatment [n (%)]	
At least 6 months	87 87.0%
At least 12 months	77 77.0%
At least 18 months	32 32.0%
At least 24 months	23 23.0%
At least 30 months	17 17.0%
At least 36 months	16 16.0%
At least 42 months	15 15.0%
At least 48 months	12 12.0%
At least 54 months	6 6.0%
Mean planned weight-adjusted daily dose (mg/kg/day)	
n	100
Mean	5.4
Median	5.3
Q1, Q3	3.8, 6.9
Min, Max	2.1, 26.1
Total Subject year exposure*	
n	100
Cumulative exposure (years)	174.7

* Based on the total days on study drug/365.25 for subjects who have taken study drug for at least one day.
Source: Appendix 2, Table 4.

The mean duration of treatment was 21 months with minimum treatment 0.1 month and maximum 59 months. Only 77 were treated for at least a year. The mean weight adjusted daily dose was 5.4 mg/kg/day. The approved starting dose in adults is 62.5 mg twice daily (1.8

² Data from BREATHE-3 (shorter treatment duration) and the Japanese study AC-052-377 are presented separately

mg/kg/day for 70 kg adult) for 4 weeks and then increased to the maintenance dose of 125 mg twice daily (3.6 mg/kg/day for 70 kg adult).

In BREATHE-3 (n = 19), the mean duration of treatment was 24 weeks. The six patients in the Japanese study were treated for a minimum of ten weeks.

Demographics

Select demographics of the pooled analysis set are shown below.

Table 1-5 Demographic characteristics of the pooled safety analysis set

	Bosentan N=100
Age (years)	
n	100
Mean	5.7
Standard deviation	3.49
Median	5.2
Min , Max	0.3 , 11.7
Age (Categories) [n (%)]	
n	100
Age < 2 years	21 21.0%
Age ≥ 2 years	79 79.0%
Gender [n (%)]	
n	100
Males	57 57.0%
Females	43 43.0%
Race [n (%)]	
n	100
Caucasian/white	80 80.0%
Black	4 4.0%
Asian	10 10.0%
Other	6 6.0%
Weight (kg)	
n	100
Mean	18.4
Standard deviation	3.49
Median	17.0
Min , Max	3.6 , 42.0
Height (cm)	
n	100
Mean	107.8
Standard deviation	24.60
Median	109.5
Min , Max	54.0 , 152.0
BMI (kg/m ²)	
n	100
Mean	15.0
Standard deviation	2.28
Median	14.8
Min , Max	7.2 , 23.5

BMI = Body Mass Index
Source: Appendix 2, Table 7.

The mean age was 5.7 years (range 0.3-11.7 years), the majority was male and white. Mean BMI was 15 kg/m².

In BREATHE-3, the population tended to be slightly more female (54%), white (79%) and with a mean age of 10 years (range: 3–15 years). In the Japanese study AC-052-377, there were four males and two females. The median age was 5.5 years (range: 1–13 years).

Baseline disease characteristics

Select disease characteristics of the pooled analysis set are shown below.

Table 1-7 Baseline disease characteristics in the pooled analysis set

	Bosentan N=100
PAH Etiology [n (%)]	
n	99
Idiopathic	60 60.6%
Heritable	7 7.1%
Associated***	24 24.2%
PAH-CHD (open shunt)	8 8.1%
WHO Functional Class at Baseline [n (%)]	
n	100
I	16 16.0%
II	53 53.0%
III	31 31.0%
Bosentan use at Baseline [n (%)]	
n	100
Yes	33 33.0%
No	67 67.0%
Duration of Bosentan use prior to Baseline* (months)	
n	33
Mean	24.2
Standard deviation	19.55
Median	23.8
Min , Max	1.1 , 78.5
Time since diagnosis** (months)	
n	98
Mean	23.0
Standard deviation	30.64
Median	7.7
Min , Max	0.0 , 134.2
Current Baseline PAH-specific Treatment [n (%)]	
n	100
No PAH-specific therapy	42 42.0%
Bosentan only	7 7.0%
PDE-5 inhibitors only	22 22.0%
Prostanoid only	17 17.0%
Bosentan and PDE-5i	1 1.0%
Bosentan and Prostanoid	1 1.0%
PDE-5i and Prostanoid	7 7.0%
Bosentan, PDE-5i, Prostanoid	3 3.0%
REGION [n (%)]	
n	100
US	9 9.0%
non-US	91 91.0%

* Calculated in relation to the start of Treatment

** Calculated in relation to the date of Screening

*** Associated PAH includes CHD associated PAH (post-surgery for CHD)

Some Subjects had their PAH confirmed at or after screening. Their time from PAH diagnosis

Values were imputed to 0

Source: Appendix 2, Table 10.

The etiology of PAH for the 100 pooled safety patients was predominantly idiopathic (61%) and post-surgery CHD associated PAH (24%). Other less common reasons included heritable PAH (7%) and PAH resulting from open shunt (8%). The mean time since PAH diagnosis was nearly 2 years with the range from 0 to 134 months.

Most patients were WHO FC II (53%) or FC III (31%). There were 16% with FC I and none with FC IV.

In patients < 2 years of age (n = 21), the majority were WHO FC II (33%) or III (43%), with approximately a quarter of the patients in WHO FC I (24%).

In patients ≥ 2 years of age (n = 79), the majority were WHO FC II (58%) or III (28%), with a smaller proportion in WHO FC I (14%).

The majority of patients (67%) had not received previous bosentan therapy.

The majority of patients (58%) were receiving drug therapy for PAH. Use of PDE-5 inhibitor monotherapy was the most common (22%) followed by prostanoids monotherapy (17%) and bosentan monotherapy (7%). The remaining patients used combination therapy or none at all.

In the BREATHE-3 study (n=19), patients had either IPAH (n = 10) or PAH-CHD (n = 9) in WHO FC II (79%) or III (21%).

In the Japanese study AC-052-377 (n=6), there were 4 patients with IPAH and 1 each with heritable PAH and PAH-CHD. At the time of the study start, 5 were concomitantly treated with beraprost sodium and/or a PDE-5 inhibitor.

Patient disposition

Table 1-9 Patient disposition in the pooled safety analysis set

	Bosentan N=100	
	n	%
Safety Analysis Set	100	100%
Subjects who completed Treatment	56	56.0%
Subjects who prematurely discontinued Treatment	37	37.0%
Subjects still under treatment*	7	7.0%

* Subjects still under treatment in EUTP: Exceptional Use Treatment Period, as of 01MAR15

Of the 100 patients included in the pooled safety analysis set, 37 prematurely discontinued study treatment. The table below shows the number of patients who discontinued study prematurely by reason and study.

Number of patients

	Adverse event including death	Administrative reason	Withdrawal of consent	other
Future 1	1	0	0	1#
Future 2	5	5	5	4^
Future 3	3	0	1	1
Future 3 ext	11	1	1	0

#unable to administer drug

^2 disease progression, 1 transplant, 1 treatment failure

As of March 1, 2015 (data cut-off), 7 patients were still receiving bosentan treatment under the EUTP.

Of the 19 enrolled patients in Breathe-3, two patients prematurely discontinued the study because of elevated liver aminotransferases. The remaining 17 patients were switched to commercial bosentan at the end of the study.

All 6 enrolled patients in the Japanese study completed the 12-week evaluation period and were subsequently enrolled in the extension study AC-052-378.

Safety results

The overall safety data from the pooled set is shown below.

Table 2-1 Overview of treatment-emergent adverse events, pooled safety analysis set

Characteristic	Bosentan N=100		n*
	n	%	
Patients with at least one AE	87	87.0%	50.4
Patients with at least one serious AE	46	46.0%	26.6
Patients with at least one fatal AE	15	15.0%	8.7
Patients with at least one related AE	25	25.0%	14.5
Patients with at least one related serious AE	3	3.0%	1.7
Patients with an AE leading to drug discontinuation	18	18.0%	10.4
Total patient-year exposure	172.8		

AE = Treatment Emergent Adverse Event

n=number of events, n=number of cases

n*= n / total patient-year exposure * 100

AC-052-374 exceptional treatment use period cut-off date 01MAR15

Most patients (87) reported at least one adverse event, there were 46 patients reporting at least one serious adverse event, there were 15 fatal events (plus three from long-term follow up), and 18 patients who withdrew for an adverse event.

Reported adverse events (at least 3% incidence rate) reported by the pooled set are shown below.

Table 2-2 Treatment-emergent adverse events (at least 3.0% incidence), by frequency, pooled safety analysis set

Preferred Term	Bosentan		
	n	N=100 %	n*
Total patients with at least one AE	87	87.0%	50.4
UPPER RESPIRATORY TRACT INFECTION	27	27.0%	15.6
PULMONARY ARTERIAL HYPERTENSION	16	16.0%	9.3
PYREXIA	16	16.0%	9.3
NASOPHARYNGITIS	14	14.0%	8.1
VOMITING	14	14.0%	8.1
BRONCHITIS	11	11.0%	6.4
DIARRHOEA	11	11.0%	6.4
ABDOMINAL PAIN	10	10.0%	5.8
COUGH	10	10.0%	5.8
PNEUMONIA	9	9.0%	5.2
VIRAL UPPER RESPIRATORY TRACT INFECTION	9	9.0%	5.2
GASTROENTERITIS	8	8.0%	4.6
EPISTAXIS	7	7.0%	4.1
SYNCOPE	7	7.0%	4.1
VIRAL INFECTION	7	7.0%	4.1
CONSTIPATION	6	6.0%	3.5
FLUSHING	6	6.0%	3.5
HEADACHE	6	6.0%	3.5
PULMONARY HYPERTENSION	6	6.0%	3.5
CHEST PAIN	5	5.0%	2.9
FATIGUE	5	5.0%	2.9
NASAL CONGESTION	5	5.0%	2.9
OTITIS MEDIA	5	5.0%	2.9
BLOOD BILIRUBIN INCREASED	4	4.0%	2.3
CATARH	4	4.0%	2.3
EAR INFECTION	4	4.0%	2.3
INFLUENZA	4	4.0%	2.3
PHARYNGITIS	4	4.0%	2.3
TONSILLITIS	4	4.0%	2.3
ABDOMINAL PAIN UPPER	3	3.0%	1.7
ASTHENIA	3	3.0%	1.7
BRONCHOPNEUMONIA	3	3.0%	1.7
CONJUNCTIVITIS	3	3.0%	1.7
CYANOSIS	3	3.0%	1.7
DEVICE RELATED INFECTION	3	3.0%	1.7
DIZZINESS	3	3.0%	1.7
GASTROINTESTINAL VIRAL INFECTION	3	3.0%	1.7
HAEMOGLOBIN DECREASED	3	3.0%	1.7
LOWER RESPIRATORY TRACT INFECTION	3	3.0%	1.7
PAIN IN EXTREMITY	3	3.0%	1.7
PALPITATIONS	3	3.0%	1.7
RASH	3	3.0%	1.7
RESPIRATORY TRACT INFECTION	3	3.0%	1.7
RESPIRATORY TRACT INFECTION VIRAL	3	3.0%	1.7
RHINITIS	3	3.0%	1.7
RHINORRHOEA	3	3.0%	1.7

n* = n / total patient-year exposure * 100
AC-052-374 exceptional treatment use period cut-off date 01MAR15

According to the system organ classification (appendix 2, table 37), the most commonly reported events included various infections (70 patients) such as URI (27 patients) and PAH/PH (22 patients), expected events in this population.

There were 7 reports of syncope, 4 reports of elevated bilirubin, and 3 reports of decreased hemoglobin.

In BREATHE-3, 17 of the 19 patients experienced at least one treatment-emergent adverse event. The most frequently reported adverse events were flushing (4 patients), headache (3 patients), and abnormal hepatic function (3 patients).

In the Japanese study AC-052-377, 5 of the 6 patients experienced at least one adverse event. The most frequently reported AE was nasopharyngitis, reported in 2 patients.

Deaths

Deaths reported by the pooled safety set are summarized below.

Table 2-4 Summary of all deaths in the pooled safety analysis set

Cause of Death	Bosentan	
	N=100	%
	n	%
Total number of deaths	18	
PULMONARY ARTERIAL HYPERTENSION	7	7.0%
PNEUMONIA	3	3.0%
CARDIO-PULMONARY FAILURE	2	2.0%
RIGHT VENTRICULAR FAILURE	2	2.0%
BRONCHOPNEUMONIA	1	1.0%
CARDIAC ARREST	1	1.0%
CARDIAC FAILURE	1	1.0%
CARDIAC FAILURE ACUTE	1	1.0%
CATHETERISATION CARDIAC	1	1.0%
DEATH	1	1.0%
EAR INFECTION	1	1.0%
METABOLIC DISORDER	1	1.0%
MUCOPOLYSACCHARIDOSIS	1	1.0%
MULTI-ORGAN FAILURE	1	1.0%
PULMONARY EMBOLISM	1	1.0%
PULMONARY HYPERTENSION	1	1.0%
RESPIRATORY FAILURE	1	1.0%
SYNCOPE	1	1.0%
SYSTEMIC-PULMONARY ARTERY SHUNT	1	1.0%

AC-052-374 exceptional treatment use period cut-off date 01MAR15
Source: Appendix 2, Table 46.

Of the 18 reported deaths, 15 occurred during the study period (or resulted from events reported during the treatment period) and three deaths occurred during the follow up treatment. There were eight deaths attributed to PAH/PH and three to pneumonia.

Details of the 18 deaths are shown in the table below, by study.

Table 9-1 Tabular listing of death cases in the pooled safety analysis set

Patient No.	Age Sex	PAH etiology	WHO FC at baseline	Baseline Bosentan use (days)	PAH-specific therapy at baseline	Reported cause of death (PT)	No. days after EOT
FUTURE 1							
(b) (6)	10.8 Years Female	Familial	III	Yes (147)	Bosentan only	Ear infection, right ventricular failure	1
FUTURE 2							
(b) (6)	5.7 years Male	Idiopathic	III	Yes (432)	Bosentan only	Syncope, PH, cardiac arrest	38
	2.6 years Male	Idiopathic	III	No	No PAH-specific therapy	Cardiac catheterization	327
	5.1 years Male	Familial	II	No	No PAH-specific therapy	Systemic-pulmonary artery shunt, PAH, right ventricular failure	0
	8.8 years Female	Idiopathic	II	Yes (302)	Bosentan only	Pneumonia, respiratory failure	1
	7.4 years Male	Idiopathic	III	No	Prostanoid only	Cardiac failure	0
FUTURE 3							
(b) (6)	4.9 years Male	Idiopathic	III	Yes (122)	Bosentan and PDE-5 inhibitors and prostanoid	PAH	112
	0.3 years Female	Heritable	III	No	PDE-5 inhibitors only	Metabolic disorder, multi-organ failure	89
	1.2 years Male		I	No	No PAH-specific therapy	Bronchopneumonia, PAH	0
FUTURE 3 extension							
(b) (6)	3.7 years Male	Heritable	I	Yes (316)	Bosentan and PDE-5 inhibitors and prostanoid	PAH	0
	3.4 years Female	Idiopathic	II	No	PDE-5 inhibitors only	PAH	0
	6.7 years Male	Idiopathic	II	No	PDE-5 inhibitors only	Acute cardiac failure mucopolysaccharidosis	0
	3.5 years Female	Idiopathic	III	No	No PAH-specific therapy	Pulmonary embolism	1
	0.6 years Male	Associated	III	No	PDE-5 inhibitors only	Cardiopulmonary failure, pneumonia	0
	1.8 year Female	Idiopathic	II	No	No PAH-specific therapy	Cardiopulmonary failure, pneumonia	1
	4.8 years Male	Idiopathic	III	No	Prostanoid only	PAH	0
	10.1 years Female	Idiopathic	III	No	No PAH-specific therapy	PAH	0
	11 year Male	Idiopathic	III	No	No PAH-specific therapy	unknown death*	0

* Indicated by the investigator as related to PAH progression; persistent cough, parent refused hospitalization.

EOT = End-of-Treatment; FC = functional class; PAH = pulmonary arterial hypertension; PDE-5 = phosphodiesterase type-5; PH = pulmonary hypertension; WHO = World Health Organization.

Additional details are given for each of the reported deaths.

Patient (b) (6) (Future 1) was a ten-year-old white female with a medical history of familial PAH (WHO FC III), anemia, 1p36 chromosomal deletion, encephalopathy, epilepsy, and patent ductus arteriosus and small ventricular septal defect, both spontaneously closed. Medication included fluindione, furosemide, spironolactone, iron and bosentan (62.5 mg bid). She was started on study drug at dose of 104 mg bid. The patient was allegedly doing well until Day (b) (6) she reported fever and otitis was suspected but not definitively diagnosed. Treatment with antibiotic was started and she was sent home. The patient was hospitalized two days later (day (b) (6)) because of fever, low cardiac output and right ventricular failure. She was aggressively treated but had several episodes of cardiac arrest during the night and died the next day. No

autopsy was performed. As stated above, the patient had been previously treated with 62.5 mg b.i.d.

Patient (b) (6) (Future I and Future 2) was a five-year-old white male with a medical history of idiopathic PAH (WHO FC III) treated with bosentan, amblyopia, cerebellar ataxia and cerebellar hypoplasia, rhinitis, otitis, adenoidal hypertrophy and bacterial infection secondary to adenoidectomy, gastrostomy, and thrombocytopenia. The patient reported bacteremia around day (b) (6) which resolved one month later. He presented with fever and cough on day (b) (6) and was hospitalized with a diagnosis of pulmonary infection. He was treated and discharged on the same day.

On Day (b) (6), the patient was found to have worsening of pulmonary hypertension on echocardiogram performed during routine examination. He reported symptoms of fatigue and near syncope and given supplemental oxygen. Sildenafil was started on day (b) (6) in the hospital. The event did not resolve and the patient was discharged two days later. On Day (b) (6), the patient was hospitalized because of dyspnea and cyanosis. Two weeks earlier, the patient reported syncope. He was treated with subcutaneous treprostinil and the event resolved.

On Day (b) (6) the patient was hospitalized because of clinical worsening with right heart failure and pericardial effusion as well as pain at infusion site. He was started on iv epoprostenol and the events resolved.

On Day (b) (6), consent for the study was withdrawn and the patient was prematurely discontinued from FUTURE 2. He died on day (b) (6) after study drug was stopped with the cause given as “syncope related to pulmonary hypertension followed by cardiac arrest”.

Patient (b) (6) (Future I and Future 2) was a two-year-old white male with a medical history of idiopathic pulmonary hypertension (WHO FC III) without drug treatment, osteoarthritis and syncope. The patient was treated with bosentan for (b) (6) days, completed the FUTURE 1 study and entered FUTURE 2. No adverse events were reported during the bosentan study drug treatment period and patient’s condition appeared to be stable. The patient’s caregiver withdrew consent (not further discussed) and the patient prematurely discontinued the study on day (b) (6). The 3-year long-term vital status check revealed that the patient died on Day (b) (6). The investigator confirmed that the child died during right heart catheterization in another hospital with no prior worsening of PAH.

Patient (b) (6) (Future I and Future 2) was a five-year-old Hispanic male with a medical history of untreated familial pulmonary hypertension WHO FC II. He was treated with bosentan for (b) (6) days, completed the FUTURE 1 study and entered FUTURE 2. The patient developed a serious adverse event of right heart failure after Potts anastomosis (day (b) (6)) and was hospitalized for worsening of pulmonary hypertension on Day (b) (6). He died less than one week later as a result of refractory right ventricular failure with worsening of PAH.

Patient (b) (6) (Future I and Future 2) was an eight year old white female with a medical history of idiopathic pulmonary hypertension WHO FC II treated with bosentan and Noonan’s

Syndrome. Concomitant medication included acenocoumarol. The patient completed the FUTURE 1 study and then entered FUTURE 2. On Day (b) (6), the patient was hospitalized for pneumonia and respiratory insufficiency. Reported symptoms included dyspnea, tachypnea and epistaxis. Acenocoumarol was discontinued but bosentan remained ongoing. On Day (b) (6), while still hospitalized, the patient experienced severe hemoptysis and decreased oxygen levels. Resuscitation was unsuccessful. An autopsy showed necrotic arteritis and vasculitis in both lungs. Death was attributed to pneumonia.

Patient (b) (6) (Future I and Future 2) was a seven-year-old white male patient with medical history of idiopathic pulmonary hypertension WHO FC III, asthma and atrial septal defect (surgically corrected at age 4) who received bosentan for (b) (6) days, completed the FUTURE 1 study and then entered FUTURE 2. Concomitant medication included acetylsalicylic acid, fluticasone, furosemide, salmeterol and oxygen. On Day (b) (6), the patient reported cough and fever of 38.5 °C and was diagnosed with viral rhinobronchitis. He was hospitalized on day (b) (6) and discharged two days later. Study drug remained unchanged. On Day (b) (6), the patient was hospitalized because of worsening of pulmonary hypertension. He was treated with iv epoprostenol. Death, attributed to cardiac failure, occurred on day (b) (6).

Patient (b) (6) (Future 3 core) was a 4 year 11 month old white male with a medical history of balloon atrial septostomy and IPAH (WHO FC III) treated with 64 mg bosentan (for 2.5 years), acetylsalicylic acid, sildenafil, and treprostinil as well as past treatment with epoprostenol. He was randomized to the bid treatment arm. On Day (b) (6), the patient reported an increase of dyspnea at minimal exercise and episodes of cyanosis after physical activity, suggesting progression of PAH. A bidirectional shunt at the atrial septostomy level was observed and the patient was hospitalized for a dose increase of treprostinil. This event was reported as a serious adverse event PAH-progression and the patient was discontinued from the study on the same day. Treatment with commercial bosentan treatment continued. The patient was transferred to another hospital to undergo surgery (Pott's surgery) 16 weeks after study treatment was discontinued. He died 4 days later and prior to surgery from "PAH-progression". N.B. The patient reported thrombocytopenia on day (b) (6) ($44 \times 10^9/L$) requiring repeated transfusion after the study discontinuation. Values at baseline and day 29 were above $120 \times 10^9/L$.

Patient (b) (6) (Future 3) was a 3-month-old white female with a medical history of heritable PAH (WHO FC III) and unresolved mitral valve and tricuspid valve incompetence. Concomitant medications included captopril, furosemide, sildenafil and spironolactone. The patient was hospitalized with signs of heart failure and infection including elevated C-reactive protein, fever (negative blood cultures). Study drug was discontinued on day (b) (6). She went on to develop multiorgan failure, including global heart failure and respiratory insufficiency. Restrictive cardiomyopathy was diagnosed on MRI and a congenital metabolic disease was suspected but not confirmed. Her condition continued to deteriorate and she did not respond to CPR on day (b) (6). Cause of death was listed as heart failure and restrictive cardiomyopathy.

Patient (b) (6) (Future 3) was a 14-month-old Asian male with a medical history of trisomy 21, ventricular septal defect, patent ductus arteriosus and PAH-CHD associated with systemic-to-pulmonary shunts (WHO FC I). He was not receiving concomitant medication at baseline.

The patient developed cough and cold-like symptom on day (b) (6) and two days later developed fever and was hospitalized with a diagnosis of bronchopneumonia. PAH was reported as worsening and he discontinued the study and died on day (b) (6). Cause of death was reported as bronchopneumonia and worsening PAH.

Patient (b) (6) (Future 3 and extension) was a 3.7-year-old male patient with a medical history of mental retardation, a failed attempt of ductus arteriosus stenting, and heritable PAH (WHO FC I). Concomitant medication included bosentan, sildenafil, treprostinil and oxygen. He was randomized to the bid treatment arm and started treatment. The patient completed the 24-week treatment period and enrolled in the FUTURE 3 study extension. He was diagnosed with lower airway infection caused by respiratory syncytial virus on Day (b) (6) and was admitted the following day to the hospital. At admission, the patient was febrile and had poor oxygenation. Chest X-ray showed an initial infection of right lower lung lobe. Increasing pulmonary arterial pressures and desaturation were reported. On Day (b) (6), he experienced a significant deterioration in respiratory status related to a probable sepsis. He was aggressively treated but died on Day (b) (6) from worsening PAH.

Patient (b) (6) (Future 3 extension) was a 3.4-year-old white female with a medical history of IPAH (WHO FC II) diagnosed 25 weeks prior to baseline. Concomitant medications included sildenafil, furosemide and oxygen. She was randomized to the t.i.d. treatment arm and completed the 24-week treatment period and was enrolled in the FUTURE 3 study extension. The patient was admitted to hospital on day (b) (6) with right heart failure resulting from progression of PAH with dyspnea, fatigue, edema, cyanosis, markedly elevated NT-proBNP and mild liver transaminases elevation. Symptoms of right heart failure improved with treatment until day (b) (6) when the patient developed acute right heart failure and bradycardia without arrhythmia was observed. The patient died and right heart failure was reported as the cause of death.

Patient (b) (6) (Future 3 extension) was a 6.7-year-old white male patient with a medical history of mucopolysaccharidosis type I, secondary cardiomyopathy, hepatosplenomegaly, chondrodysplasia, acquired corneal dystrophy, Dandy-Walker syndrome, hydrocephalus, psychomotor development impaired and speech disorder, umbilical hernia, adenoidal hypertrophy and chronic bilateral ethmoiditis as well as IPAH (WHO FC II) diagnosed 4.3 weeks prior to baseline. Concomitant medication included sildenafil, spironolactone, hydrochlorothiazide, captopril and laronidase. He was randomized to the t.i.d treatment arm and started treatment with bosentan. The patient completed the 24-week treatment period and was enrolled in the FUTURE 3 study extension despite being reclassified as WHO FC III (Day (b) (6)). According to the patient's mother, the child lived in a hospice for approximately a month and then returned home on Day (b) (6). He had unwitnessed death on Day (b) (6) despite going to bed with no unusual symptoms or complaints. The cause of death was assessed as acute heart failure resulting from mucopolysaccharidosis.

Patient (b) (6) (Future 3 extension) was a 3.5-year-old white female patient with a medical history of IPAH (WHO Class III) diagnosed about 13 weeks prior to baseline. Concomitant medication included spironolactone and captopril. She completed the 24-week treatment period with signs of disease worsening (reported by echocardiographic assessments and an increase in

NT-proBNP) and was enrolled in the FUTURE 3 extension. On Day (b) (6), 16 days after enrollment in the extension study, the patient experienced sudden death (no reports of symptom before going to bed, but she cried out during the night). Cause of death was reported as thromboembolism of the pulmonary artery. No autopsy was performed.

Patient (b) (6) (Future 3 extension) was a 0.6-month-old white male patient with a medical history of circulatory failure, Down syndrome, patent ductus arteriosus repair, patent foramen ovale, malabsorption syndrome, IPAH (WHO Class III) diagnosed 4.4 weeks prior to the study. Concomitant medication included sildenafil, spironolactone, captopril, furosemide, and magnesium aspartate/potassium aspartate. He completed the 24-week treatment period (with some signs of disease worsening as suggested by an increase in NT-proBNP) and was enrolled in the FUTURE 3 study extension. On Day (b) (6) the patient started to cough but was afebrile and had an appetite. He was hospitalized the next day for severe shortness of breath and increased cyanosis and cough. He did not recover and cause of death, supported by autopsy findings, was cardio-respiratory failure due to acute pneumonia.

Patient (b) (6) (Future 3 extension) was a 22-month-old white female with a medical history of Down's syndrome, partial suture of the patent ductus arteriosus and IPAH (WHO FC II) diagnosed about 3 months prior to baseline. Concomitant medication included captopril and spironolactone. The patient completed the 24-week treatment period and was enrolled in the FUTURE 3 study extension on Day (b) (6). The patient reported an upper respiratory infection on day (b) (6) and her FC was downgraded to class III. FC was later upgraded to class II. On Day (b) (6) the patient was hospitalized with a high body temperature, cough, headache and muscle pain. Acute bronchitis was diagnosed and treatment for it began. She was sent to ICU on day (b) (6) because of cardio-respiratory worsening. On Day (b) (6), X-ray showed pneumothorax and pneumonia. The patient was intubated on day (b) (6) and bosentan was discontinued. The patient died that day with cardio-respiratory failure and pneumonia reported as the cause of death. No autopsy was performed.

Patient (b) (6) (Future 3 extension) was a 4 year 10 month old white male subject with a medical history of epilepsy and IPAH (FC III) diagnosed 2 years prior to study enrollment. Concomitant medication included prostanoïd, acetylsalicylic acid, furosemide, valproic acid and oxygen. The patient reported two episodes of loss of consciousness and cyanosis lasting for under 1 minute on day (b) (6) and he was hospitalized on day (b) (6) for possible seizures. During hospitalization, the patient experienced repeated episodes of loss of consciousness and an EEG revealed light epileptical changes. A 24-hour monitoring of arterial blood pressure was normal. Lamotrigine for epilepsy was started and the patient was discharged. The patient reported fever and a sore throat on day (b) (6) and skin rash and aphthous stomatitis on day (b) (6) resulting in hospitalization. Signs of severe allergic reactions were reported and lamotrigine was discontinued on day (b) (6). The symptoms resolved and the patient was discharged. He completed the 24-week treatment period and was enrolled in the FUTURE 3 study extension. The patient was hospitalized on day (b) (6) for severe deterioration of PAH. Signs and symptoms included tachypnea, cyanosis, tachycardia, mild pulses and cold extremities. Echocardiogram showed extremely enlarged right heart and high right ventricle pressure. Laboratory findings showed

severe metabolic cyanosis. He started mechanical ventilation. A cardiac arrest was reported with unsuccessful CPR. Cause of death was reported as PAH progression. No autopsy was performed.

Patient (b) (6) (Future 3 extension) was a 10.1-year-old Asian female patient with a medical history that included complaints of bilateral pedal edema, dyspnea, mild jaundice and IPAH (WHO III). Concomitant medication was limited to furosemide and digoxin. She completed the 24-week treatment period and enrolled in the FUTURE 3 study extension. During the study her WHO FC was upgraded to class II and then class I. On day 294 she reported mild dyspnea and palpitation and spironolactone was added. On Day 426 pedal edema was noted and her functional status was downgraded to class III. Persistent vomiting was reported and digoxin was discontinued. Further deterioration of PAH (to class IV) was noted and development of heart failure were diagnosed. The patient was not able to walk for short distances, with swelling of legs and vomiting. Laboratory values showed total bilirubin at $1.8 \times \text{ULN}$, direct bilirubin at $2.0 \times \text{ULN}$, and blood glucose at 5.8 mmol/L. Echocardiogram showed severe right ventricular dysfunction, moderate-severe tricuspid regurgitation, severe right ventricular peak systolic pressure and mild pericardial effusion. The patient and her family refused hospitalization and further treatment. Sudden death occurred on day (b) (6) with cause of death being listed as worsening PAH. No autopsy was performed.

Patient (b) (6) (Future 3 extension) was an 11-year-old Asian male patient with a medical history that included reports of exertional dyspnea, generalized edema, elevated NT-proBNP and IPAH (WHO FC III) diagnosed 1.9 weeks before study start. Concomitant medication included furosemide and spironolactone. The patient completed the 24-week treatment period and was enrolled in the FUTURE 3 study extension. By week 12, the study the patient's FC improved to class II (Day 170) and he remained stable until day (b) (6) when he reported episodes of cough. He was unable to attend the clinic although he showed no improvement. The family was advised to hospitalize the patient on day (b) (6) which was refused. The patient died the next day with a presumptive cause of death listed by the investigator as worsening PAH. No autopsy was performed.

N.B. The following patient was not included in table 9-1 because the death was reported beyond the data cut-off of March 1, 2015 for the pooled safety analysis set. The patient was ongoing in the EUTP.

Patient (b) (6) was a 20-month-old white female with a medical history of lymphocyte abnormality, atrial septal defect and IPAH (WHO FC II) diagnosed 1 year prior to study entry. Concomitant medication included enalapril and sildenafil. The patient completed the 24-week treatment period and was enrolled in the FUTURE 3 study extension. During the 12-month treatment period the patient experienced two episodes of non-serious viral upper respiratory tract and one gastrointestinal tract infection. The patient was hospitalized because of symptomatic nasal hemorrhage on day (b) (6). The event resolved without sequelae and the patient was discharged. The patient completed the 12-month treatment period and continued receiving bosentan during the EUTP study. On Day (b) (6) she was hospitalized for acute respiratory viral infection / lobar pneumonia, further complicated by respiratory failure. The event resolved.

On day 1039 the patient developed cyanosis, dyspnea, circulatory collapse and poor exercise capacity. On Day (b) (6), the patient came to a routine monthly visit and had sudden collapse. CPR was unsuccessful. An autopsy was not performed.

The 3 deaths that occurred during long-term follow-up (and end of treatment) are briefly discussed below.

- Patient (b) (6) (FUTURE 3) died (b) (6) days after EOT because of multi-organ failure related to an unspecified congenital metabolic disease.
- Patient (b) (6) (FUTURE 3) died (b) (6) days after EOT because of worsening PAH (reported during the long-term vital status follow-up).
- Patient (b) (6) (FUTURE 2) died because of complications associated with cardiac catheterization (b) (6) days after EOT.

Survival rate in the pooled PAH safety set

Kaplan Meier survival estimates, by baseline WHO FC, at years 1 and 2 are shown below.

KM survival estimate

Baseline WHO FC	At 1 year	At 2 years
I/II	94.0%	90.9%
III	77.1%	73.3%

There were no reported deaths in study AC-052-356 (BREATHE-3) or in the Japanese study AC-052-377 and the ongoing extension study AC-052-378.

Serious adverse events

The table below shows the serious events with a frequency $\geq 2\%$ reported by patients in the pooled safety set.

³ According to the sponsor, the catheterization procedure was not related to the study and was not performed on behalf of Actelion or in relation to any Actelion supported clinical trial; it was reported in the long-term vital status follow-up.

Table 2-5 Treatment-emergent serious adverse events, by frequency (at least 2% incidence), pooled PAH safety analysis set

Preferred Term	Bosentan N=100				
	n	%	e	n*	e*
Total patients with at least one SAE	46	46.0%	115	26.6	66.0
PULMONARY ARTERIAL HYPERTENSION	10	10.0%	12	5.8	6.9
PNEUMONIA	5	5.0%	5	2.9	2.9
PULMONARY HYPERTENSION	3	3.0%	3	1.7	1.7
DEVICE RELATED INFECTION	3	3.0%	7	1.7	4.1
SYNCOPE	3	3.0%	4	1.7	2.3
BRONCHOPNEUMONIA	2	2.0%	2	1.2	1.2
CATHETERISATION CARDIAC	2	2.0%	2	1.2	1.2
CARDIAC FAILURE	2	2.0%	3	1.2	1.7
CARDIOPULMONARY FAILURE	2	2.0%	2	1.2	1.2
FATIGUE	2	2.0%	2	1.2	1.2
RIGHT VENTRICULAR FAILURE	2	2.0%	2	1.2	1.2
SEIZURE	2	2.0%	5	1.2	2.9
RESPIRATORY TRACT INFECTION VIRAL	2	2.0%	2	1.2	1.2
SYSTEMIC-PULMONARY ARTERY SHUNT	2	2.0%	2	1.2	1.2
VIRAL INFECTION	2	2.0%	2	1.2	1.2

e=number of events, n=number of cases

n*= n / total patient-year exposure * 100

e*= events / total patient-year exposure * 100

Pooled analysis includes AC-052-374 exceptional treatment use period (cut-off date 01MAR15)

Source: Appendix 2, Table 50.

According to the system organ classification (appendix 2, table 50), there were 22 patients reporting various infections and 13 patients reporting PAH/PH. None of the reported events are unusual in this type of patient population.

Patients in the pooled safety dataset reporting serious adverse event not usually associated with PAH or childhood illnesses are discussed below.

One patient reported autoimmune hepatitis and was discontinued from study drug. **Patient** (b) (6) was a 2-year-old white female patient with a medical history that included Down Syndrome, bronchopulmonary dysplasia, hypothyroidism, strabismus, pneumonia, sepsis, atrial septal defect, and IPAH. Concomitant medication included levothyroxine, furosemide, and oxygen.

The patient was treated with bosentan for 85 days, completed the FUTURE 1 study and entered FUTURE 2. On Day (b) (6) a diaphragmatic hernia was diagnosed and she was underwent surgery to repair the hernia. The study drug was temporarily interrupted. The event resolved without sequelae. On Day 273, the patient had abnormal LFTs. Laboratory tests on that date showed markedly increased AST (51 U/L) and ALT (125 U/L). The study drug was reduced from 48 mg b.i.d. to 24 mg b.i.d. On Day 287, laboratory tests were positive for F-Actin antibody and anti-smooth muscle immunoglobulin G (IgG) antibody, both consistent with autoimmune hepatitis or chronic active hepatitis. Hepatitis panel was negative. Epstein-Barr virus IgG was positive. The study drug was interrupted. Follow-up laboratory tests showed improvement and the study drug was restarted on Day 330. On Day 341, elevated AST (95 U/L) and ALT (219 U/L) values led to study drug discontinuation and the patient was prematurely discontinued from the study on the same day. Bilirubin values remained normal. Follow-up information confirmed that the hepatitis resolved without sequelae on Day 448.

In study AC-052-356 (BREATHE-3), two patients reported a total of 6 serious adverse events either during treatment or within 28 days after end of treatment.

Table 7 Summary of serious adverse events during study treatment or within 28 days of treatment end - all enrolled patients

(Table SAE02: 03APR02 - Data 03APR02)

Body system / Adverse event	Patients 10 - 20 kg N=7		Patients >20 - 40 kg N=6		Patients > 40 kg N=6		All N=19	
	No.	%	No.	%	No.	%	No.	%
ALL BODY SYSTEMS								
Total pts with at least one SAE	1	14.3%	1	16.7%	-	-	2	10.5%
Total number of SAEs	1		5		-		6	
CENTRAL LINE PLACEMENT	-		1	16.7%	-		1	5.3%
DIZZINESS (EAC VERTIGO)	-		1	16.7%	-		1	5.3%
HYPERTENSION NOS	-		1	16.7%	-		1	5.3%
TACHYCARDIA NOS	-		1	16.7%	-		1	5.3%
TREMOR NEC	-		1	16.7%	-		1	5.3%
HEPATIC FUNCTION ABNORMAL NOS	1	14.3%	-		-		1	5.3%

Note: only SAEs with onset from start of treatment to 28 calendar days after end of treatment are included.

NEC = not elsewhere classified, NOS = not otherwise specified, SAE = serious adverse event.

Two patients experienced a serious adverse event and both recovered without sequelae. They are discussed below. A third (b) (6) not included in the above table is also discussed.

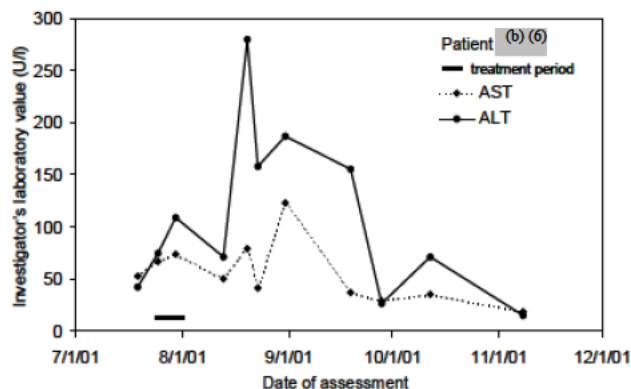
Patient (b) (6) (abnormal hepatic function) was an eight year old white male with a medical history of previously operated ASD and severe PAH. Concomitant medication included furosemide, digoxin, acetylsalicylic acid, fluoride with iron, and multivitamins. Liver function tests were above upper limit of normal at screening. The patient started bosentan 31.25 mg q.d. Additional liver enzyme monitoring showed a further increase, and bosentan was permanently stopped on Day 7. Further follow-up by the investigator showed that liver enzymes in this patient remained high for about 8 weeks. Liver core biopsy performed 2 months following the first dose of bosentan showed severe portal and early bridging fibrosis (suggesting preexisting disease), bile ductule proliferation, and patchy lymphocytic inflammation. No evidence of viral infection was present. Following additional tests, ulcerative colitis and associated sclerosing cholangitis were diagnosed. The patient's original diagnosis of PAH was reassessed as pulmonary hypertension associated with the liver disease, which subsequently improved on immune-suppressive therapy.

Investigator-supplied liver function test results for Patient (b) (6)

	AST (U/l)	ALT (U/l)	GGT (U/l)	Alkaline phosphatase (U/l)	Total bilirubin (mg/dl)
Investigator reference values	(10 - 40)	(5 - 25)	(0 - 51)	(175 - 420)	(0 - 1.1)
Date:					
08/25/00	26	14	—	124	0.6
07/19/01 (D-7)	53	42	31	188	0.5
07/25/01 (D-1)	67	75	43	181	0.4
07/30/01 (D5)	74	109	72	203	0.4
08/13/01 (D19)	50	71	120	237	0.5
08/20/01 (D26)	79	280	309	388	0.4
08/23/01	41	158	322	320	0.5
08/31/01*	123	187	—	240	0.6
09/19/01	37	155	472	396	0.7
09/28/01	29	26	198	166	0.6
10/12/01	35	71	180	228	0.7
11/08/01	18	15	—	75	0.7

* Local laboratory was used.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, D = study day, GGT = gamma glutamyltransferase.



- Patient (b) (6) was a 10-year-old female with a medical history of severe familial PPH (WHO class III) treated epoprostenol at the age of 9. By Week 12 of treatment, there was evidence to suggest worsening exercise tolerance (–15% in both 6-minute walk test and peak VO₂ from cycle ergometry tests), but she remained stable clinically and hemodynamically. After the 12-week evaluation, the patient's liver function tests showed elevated ALT to $> 3 \times \text{ULN}$. Bosentan was withheld (Days (b) (6)) until aminotransferase levels returned to $< 3 \times \text{ULN}$ and then re-instituted at half the dose. Subsequently, the liver aminotransferases increased again, and bosentan was permanently discontinued. According to the investigator, the liver aminotransferases were within the normal range at the time of this report. LFT values are shown below.

Laboratory: ALT, AST, BILIRUBIN TOTAL, ALKALINE PHOSPHATASE;
Treatment: Patients >20 - 40 kg

Center	Pro	Sex	Age	Date	T.Day	Days	Com-	men-	Inves	AST	Std.	Inves	ALT	Std.	Bilirubin	Std.	Alkaline	Phosphat.
						off	ment		value	value		value	value		value	value	value	value
						trt.	ts											
									U/L	U/L		U/L	U/L		mg/dL	umol/L	U/L	U/L
1	(b) (6)	F	10	23JUL01	-3				29	18		20	20		0.5	7.8	161	29
				25JUL01	-1				27	17		18	18		0.6	9.3	149	27
				27AUG01	33				25	16		18	18		0.5	7.8	175	31
				09SEP01	46		Yes		COMMENTS			COMMENTS			COMMENTS		COMMENTS	
				04OCT01	71		Yes		24	15		18	18		0.3	4.7	176	31
				24OCT01	91				99	62	HH	166	166	HH	0.3	4.7	187	33
				26OCT01	93		Yes		93	58	HH	158	158	HH	0.4	6.2	169	30
				07NOV01	105				43	27	H	75	75	HH	0.5	7.8	189	34
				19NOV01	117		Yes		34	21		35	35	H	0.3	4.7	198	35
				11DEC01	139		Yes		55	34	H	82	82	HH	0.4	6.2	160	38
				12FEB02	202	5	Yes		92	58	HH	173	173	HH	0.6	9.3	218	52

Note: H and L denote values above or below the standard reference range.

HH and LL denote values above or below the marked reference range and having a clinically relevant change in the same direction.

(Page 2/2)

-Patient (b) (6) was a 13-year-old male patient with PPH who had his initial per-protocol hospitalization prolonged due to an onset of moderate hypertension, tachycardia, tremor, and dizziness 2.5 hours after the first dose of 62.5 mg bosentan. The patient had a medical history of reactive airways disease. Concomitant medication included nifedipine, warfarin, dipyridamole, albuterol, salmeterol, and fluticasone. According to the investigator, he experienced milder dizziness and stomach ache with the next two doses of bosentan (31.25 mg each), and pulse and blood pressure were in the normal range. The events were not reported again with subsequent dosing. Two months into the extended treatment phase, the patient was hospitalized for placement of a Broviac catheter for initiation of epoprostenol therapy.

Serious adverse events in Japanese AC-052-377 and the ongoing extension study AC-052-378.

One patient reported a serious adverse event (described as upper respiratory infection).

-Patient (b) (6) reported adenovirus upper respiratory infection in the base study and then reported pneumonia during the extension study.

Adverse events leading to discontinuation of study treatment in the pooled safety analysis set

There were 18 patients who reported at least one adverse event that led to study drug discontinuation. The table below shows the adverse event that led to drop out for these patients, by frequency.

Table 2-6 Treatment emergent adverse events leading to premature study drug discontinuation by frequency, pooled safety analysis set

Preferred Term	Bosentan		
	n	%	N=100 n*
Total patients with at least one AE	18	18.0%	10.4
PULMONARY ARTERIAL HYPERTENSION	5	5.0%	2.9
CARDIAC FAILURE	2	2.0%	1.2
CARDIOPULMONARY FAILURE	2	2.0%	1.2
LIVER FUNCTION TEST ABNORMAL	2	2.0%	1.2
PNEUMONIA	2	2.0%	1.2
RIGHT VENTRICULAR FAILURE	2	2.0%	1.2
AUTOIMMUNE HEPATITIS	1	1.0%	0.6
BRONCHOPNEUMONIA	1	1.0%	0.6
CARDIAC FAILURE ACUTE	1	1.0%	0.6
DEATH	1	1.0%	0.6
DYSPNOEA EXERTIONAL	1	1.0%	0.6
EAR INFECTION	1	1.0%	0.6
MUCOPOLYSACCHARIDOSIS	1	1.0%	0.6
PULMONARY EMBOLISM	1	1.0%	0.6
PULMONARY HYPERTENSION	1	1.0%	0.6
SYSTEMIC-PULMONARY ARTERY SHUNT	1	1.0%	0.6

e=number of events, n=number of cases
n*= n / total patient-year exposure * 100
AC-052-374 exceptional treatment use period cut-off date 01MAR15

According to the system organ classification (appendix 2, table 55), there were six patients reporting PAH/PH and four reporting cardiac failure/cardiopulmonary failure. Other reports indicating worsening disease included right ventricular failure, acute cardiac failure, exertional dyspnea, pulmonary hypertension. There were two patients reporting pneumonia and one reporting bronchopneumonia. There was one report of pulmonary embolism and one report of systemic pulmonary artery shunt. These events are not inconsistent findings in a PAH population.

There were two reporting abnormal LFTs.

-Patient (b) (6) was a 10.8-year-old white female patient with PAH persisting after complete repair of congenital heart defect. The patient completed the 24-week treatment period and was enrolled in the FUTURE 3 study extension. On day (b) (6), the patient reported an isolated ALT/AST increase (ALT 204 U/L, AST 114 U/L) leading to permanent discontinuation from the

extension study on day (b) (6). Liver aminotransferases values were within normal limits at screening and baseline. The event was considered resolved on day (b) (6).

-Patient (b) (6) (also discussed in serious adverse event section for viral infection) was an 8 year and 3 month white male subject with IPAH treated with sildenafil. On Day (b) (6), the patient was diagnosed with a viral infection and he was hospitalized on Day (b) (6) for fever and arthralgia.

This patient's LFTs were within normal limits at baseline. On Day 145 the local laboratory assessment of LFTs showed ALT 159 U/L and AST 84 U/L. The study drug was interrupted from Day 145–159. On day 171, values were ALT 44 U/L and AST 35 U/L. The study drug was then stopped on day 193 because of elevated LFTs. This event was reported to be resolved 4 weeks later.

In study AC-052-356 (BREATHE-3), two patients reported abnormal hepatic function adverse events which resulted in discontinued study drug.

-Patient (b) (6) (low-weight group) reported severe ulcerative colitis and sclerosing cholangitis prior to start of drug. The ALT and AST elevations on Day 5 (both $> 3 \times \text{ULN}$) were reported as a serious adverse event and study treatment was discontinued. Nineteen days after bosentan discontinuation, ALT remained elevated (336 U/L) and elevations continued for about eight weeks.

-Patient (b) (6) (mid-weight group) had ALT $> 3 \times \text{UL}$ that resulted in bosentan discontinuation. Bosentan was withheld until ALT and AST returned to $< 3 \times \text{ULN}$ (about two weeks later) and was then re-started at half the dose. An ALT value increase led to permanently discontinued of bosentan on day 197.

In Japanese study AC-052-377 and ongoing extension study AC-052-378 (up to March 1, 2015), there were no adverse events leading to study drug discontinuation.

Drug specific abnormalities

Anemia/hemoglobin decrease

This is an adverse event associated with bosentan use. The current package label states

“Treatment with Tracleer can cause a dose-related decrease in hemoglobin and hematocrit. There have been postmarketing reports of decreases in hemoglobin concentration and hematocrit that have resulted in anemia requiring transfusion. It is recommended that hemoglobin concentrations be checked after 1 and 3 months, and every 3 months thereafter. If a marked decrease in hemoglobin concentration occurs, further evaluation should be undertaken to determine the cause and need for specific treatment.”

In adult clinical trials, 3% of patients treated with Tracleer 125-250 mg twice daily (n=258) reported anemia compared to 0% of patients treated with placebo (n=172).

Pooled safety set

Analyses focused on changes in laboratory values and reported adverse events. The PTs (narrow and broad) relating to the following sub-SMQs within the Hematopoietic cytopenias (SMQ) were included in the applicant's adverse event analyses:

- Hematopoietic erythropenia (SMQ)
- Hematopoietic cytopenias affecting more than one type of blood cell (SMQ) along with any PT containing "anaemia".

Mean hemoglobin values decreased 3.3 g/dL from baseline to end of treatment as did mean hematocrit (0.86%) and erythrocyte count ($0.1 \times 10^{12}/L$). No patients in this safety set had a decrease in hemoglobin to < 8 g/dL.

There were five patients with reports of hemoglobin as an adverse event. There was one patient (b) (6) who reported iron deficiency anemia. He was hospitalized, transfused, and discharged on day (b) (6). He discontinued the study because of withdrawal of consent on day 820. The other four remained on study drug.

Table 2-7 Anemia / decreased hemoglobin, pooled safety analysis set

Bosentan
Preferred Term
N=100
n %
ANEMIA/HGB DECREASES
Total patients with at least one AE 5 5.0%
HAEMOGLOBIN DECREASED 3 3.0%
HAEMATOCRIT DECREASED 2 2.0%
ANAEMIA 1 1.0%
IRON DEFICIENCY ANAEMIA 1 1.0%
AC-052-374 exceptional treatment use period cut-off date 01MAR15

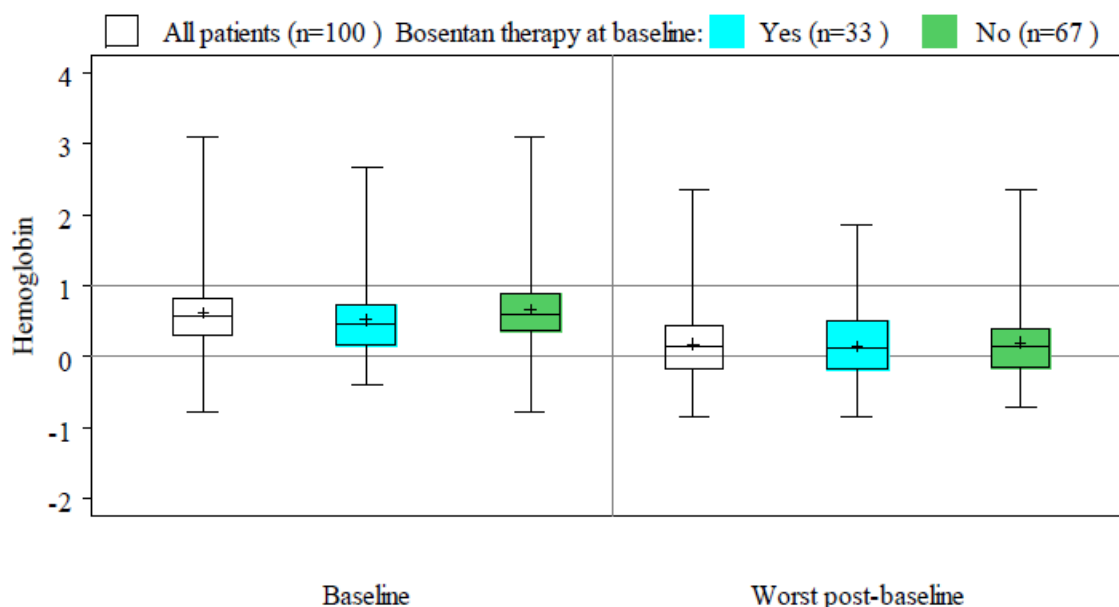
There were five patients reporting at least one anemia/HGB decrease, nothing unexpected with bosentan use.

The figure below shows hemoglobin value at baseline and the worst post baseline value. Data are shown for all patients (n=100) as well as split into those who had been on bosentan at baseline (n=33) and those who had not (n=67).

Figure 9 Box plot of hemoglobin at baseline and worst post-baseline value,
Safety set

Pooled Bosentan Studies (ISS): AC-052-365, AC-052-367, AC-052-373, AC-052-374

Figure F_BLHA_S: Box Plots of Hemoglobin (Standardized) at Baseline and Worst Post Baseline Value
Analysis Set: Safety Set



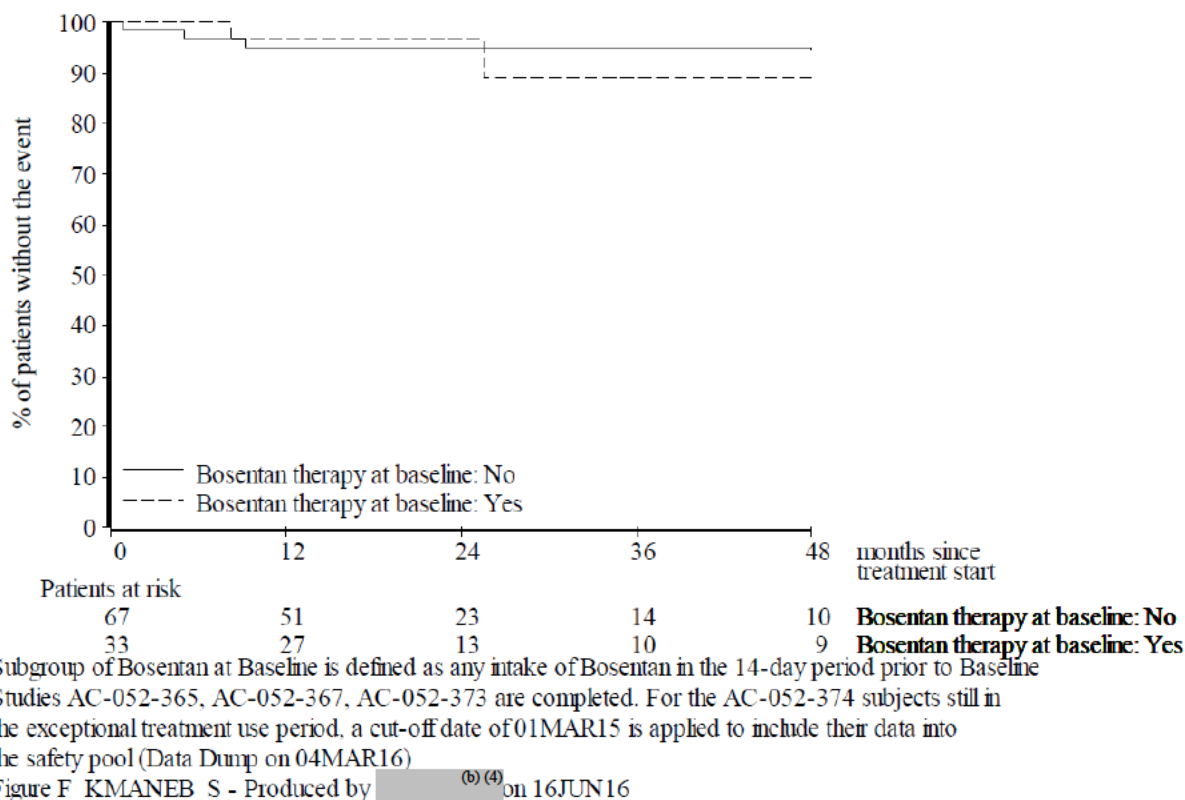
Mean (plus), median (solid line), minimum, maximum, Q1 (25th percentile) and Q3 (75th percentile) statistics are displayed.

Studies AC-052-365, AC-052-367, AC-052-373 are completed. For the AC-052-374 subjects still in the exceptional treatment use period, a cut-off date of 01MAR15 is applied to include their data into the safety pool (Data Dump on 04MAR16)

Patients tended to see a drop in hemoglobin from baseline, whether they had been receiving bosentan at baseline or not.

Figure 3 Time to first anemia event: Kaplan-Meier estimates by baseline bosentan use, Safety set

Pooled Bosentan Studies (ISS): AC-052-365, AC-052-367, AC-052-373, AC-052-374
Figure F_KMANEB_S: Time to First Anemia Event, Kaplan-Meier Estimates by Baseline Bosentan Use.
Analysis Set: Safety Set



Anemia events started to be reported by 12 months of treatment, regardless of whether patients had received bosentan at baseline or not. More events were reported as patients progressed in the studies.

A total of 11 patients (11%) had a hemoglobin decrease to < 10 g/dL (all ≥ 2 years of age). These patients are shown in the table below by study.

Table 9-2 Tabular listing of hemoglobin cases < 10 g/dL, pooled safety analysis set

Patient No.	Age Sex	Hemoglobin values (g/dL)			Death/AE reported (Onset/ event day)	Outcome (value at resolution)	Blood transfusion during the study (Yes/No)	Baseline Bosentan use (Yes/No), duration)	Other information/ remarks
		Baseline	Time point* of values < 10 g/dL	Reference range (g/dL)					
FUTURE 1									
(b) (6)	3.2 years Male	10.8	9.9 (Day 29)	10.5–14.5	None	Resolved, 12 (Day 64)	No	Yes, 678 days	Concomitant iron treatment Hemoglobin decrease to 8.3 g/dL with simultaneous decrease in leukocyte and platelet count known 1 year prior to enrolment (all values normalized within 4 months of onset).
FUTURE 2									
(b) (6)	8.8 years Female	12.2	8.86 (Day 894) 9.99 (Day 910)	7.5–9.9	Death (Day (b) (6))	Unresolved at the time of last follow up	Yes	Yes, 302 days	Noonan's Syndrome (and associated bleeding diathesis and platelet count) and on concomitant acenocoumarol. Hemoglobin decrease was noted at the time of hospitalization for pneumonia and respiratory failure. Acenocoumarol was discontinued as the patient also had epistaxis and hemoptysis. Several transfusions of packed RBCs were administered for anemia, with resulting improved hemoglobin two days before death due to pneumonia.
FUTURE 3									
(b) (6)	7.2 years Male	12.2	8.88 (Day (b) (6))	11.5–15.5	SAEs decreased hemoglobin. Iron deficiency anemia (Day (b) (6))	Resolved, 13.8 (Day (b) (6))	Yes	Yes, 1109 days	Concomitant warfarin treatment. Hospitalized due to iron deficiency anemia, decreased hemoglobin and fatigue. The patient was transfused and discharged the following day (no values provided).
(b) (6)	11.3 years Male	16.2	9.5 (Day 724. EOS / premature discontinuation)	11.5–15.5	None	Unresolved at the time of last follow up	No	No	Discontinued study same day as hemoglobin decrease to 9.5 g/dL due to lung transplant.
FUTURE 3 extension									
(b) (6)	3.6 years Male	10	9.6 (Day 148)	11–14.5	None	Resolved 11.3 (Day 169)	No	Yes, 39 months	
(b) (6)	2.8 years Male	9.5	9 (Day 1) 8.5 (Day 29) 9 (Day 60) 9.2 (Day 87) 9 (Day 115)	11–14.5	AE decreased hemoglobin (Day 30)	Resolved 10.1 (Day 143)	No	No	Concomitant ferrous sulphate treatment at baseline. Hemoglobin fluctuated between 10.5 and 9.7 g/dL throughout the 16 months study participation while study drug was ongoing.
(b) (6)	2.1 years Male	10.9	9.5 (Day 169)	11–14.5	None	Resolved 11.3 (Day 253)	No	No	Fluctuating baseline hemoglobin (Hgb of 10.9 at screening and 11.7 at randomisation 1 month later).
FUTURE 3 extension									
(b) (6)	2.3 years Female	10.8	9.8 (Day 332) 9.7 (Day 395) 9.6 (Day 428)	11.8–14.7	None	Resolved 10.2 (Day 500)	No	Yes, 140 days	
(b) (6)	3.2 years Male	12.5	9.9 (Day 511)	11–14.5	None	Unresolved at the time of last follow up	No	No	Medical history iron-deficiency anemia, concomitant ferrous sulphate treatment at baseline, repeated AEs of epistaxis prior to haemoglobin decrease.
(b) (6)	3.8 years Male	12.5	9.9 (Day 22) 9.4 (Day 211) 8.8 (Day 350) 9.8 (Day 434)	11–14.5	None	Status unknown	No	No	Over the 12.5 months of the study, hemoglobin fluctuated between 10.9 and 8.8g/dL while study drug was ongoing.
(b) (6)	4 years Male	13.8	9.5 (Day 1268)	11.2–15.5	None	Resolved 10.6 (Day 1292)	No	No	

* Time point = Days after treatment start

AE = adverse event; EOS = End-of-Study; Hgb = hemoglobin; RBC = red blood cell; SAE = serious adverse event.

Of the eleven patients, two patients (105/145) received blood transfusion during the study.

-**Patient** (b) (6) had history of bleeding diathesis and platelet abnormality. She died on day (b) (6) reportedly of pneumonia.

-**Patient** (b) (6) was hospitalized for iron deficiency anemia needing transfusion on day (b) (6). He was receiving concomitant warfarin and permanently discontinued from study drug on day (b) (6).

In BREATHE-3, no adverse events of anemia or hemoglobin decrease were reported.

In study AC-052-377, there was one patient who reported mild anemia as an adverse event and one patient had a transient hemoglobin decrease from 10.9 g/dL at baseline to 7.6 g/dL at Week 8 (and 11.2 g/dL at week 12).

Liver abnormalities (AEs and laboratory data)

This is an adverse event associated with bosentan use. The current package label states

“In clinical studies, Tracleer caused at least 3-fold upper limit of normal (ULN) elevation of liver aminotransferases (ALT and AST) in about 11% of patients, accompanied by elevated bilirubin in a small number of cases. Because these changes are a marker for potential serious hepatotoxicity, serum aminotransferase levels must be measured prior to initiation of treatment and then monthly [see Dosage and Administration (2.2), Warnings and Precautions (5.1)]. In the postmarketing period, in the setting of close monitoring, rare cases of unexplained hepatic cirrhosis were reported after prolonged (> 12 months) therapy with Tracleer in patients with multiple comorbidities and drug therapies. There have also been reports of liver failure. The contribution of Tracleer in these cases could not be excluded.

In at least one case, the initial presentation (after > 20 months of treatment) included pronounced elevations in aminotransferases and bilirubin levels accompanied by non-specific symptoms, all of which resolved slowly over time after discontinuation of Tracleer. This case reinforces the importance of strict adherence to the monthly monitoring schedule for the duration of treatment and the treatment algorithm, which includes stopping Tracleer with a rise of aminotransferases accompanied by signs or symptoms of liver dysfunction [see Dosage and Administration (2.2)].

Elevations in aminotransferases require close attention [see Dosage and Administration (2.2)]. Tracleer should generally be avoided in patients with elevated aminotransferases (> 3 x ULN) at baseline because monitoring for hepatotoxicity may be more difficult. If liver aminotransferase elevations are accompanied by clinical symptoms of hepatotoxicity (such as nausea, vomiting, fever, abdominal pain, jaundice, or unusual lethargy or fatigue) or increases in bilirubin ≥ 2 x ULN, treatment with Tracleer should be stopped. There is no experience with the reintroduction of Tracleer in these circumstances.”

Pooled safety set

Analyses focused on change in laboratory values and reported adverse events. The PTs (narrow and broad) relating to the following sub-SMQs within the “Hepatic disorders” SMQ and within the “Drug related hepatic disorders - comprehensive search” SMQ included in the applicant’s analyses of adverse events:

- Cholestasis and jaundice of hepatic origin (SMQ)
- Drug related hepatic disorders - severe events only (SMQ)
 - o Hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions (SMQ)
 - o Hepatitis, non-infectious (SMQ)
 - o Liver neoplasms, benign (incl. cysts and polyps) (SMQ)
 - o Liver neoplasms, malignant and unspecified (SMQ)
 - Liver malignant tumours (SMQ)
 - Liver tumours of unspecified malignancy (SMQ)
- Liver-related investigations, signs and symptoms (SMQ)

Of note: the “Liver-related coagulation and bleeding disturbances” SMQ was not included due to the use of anticoagulant medications in the majority of patients in this PAH patient population.

There were two subjects who discontinued study drug because of liver function test abnormality and one for autoimmune hepatitis (see table 2-6). One subject reported autoimmune hepatitis as a serious adverse event (appendix 2 table 50).

The table below shows the number of patients in the pooled safety set who reported at least one liver abnormality as an adverse event.

Table 2-8 Liver abnormalities, pooled safety analysis set

Preferred Term	Bosentan	
	N=100	
	n	%
LIVER ABNORMALITIES		
Total patients with at least one AE	11	11.0%
BLOOD BILIRUBIN INCREASED	4	4.0%
HEPATIC FUNCTION ABNORMAL	2	2.0%
LIVER FUNCTION TEST ABNORMAL	2	2.0%
ALANINE AMINOTRANSFERASE INCREASED	1	1.0%
ASPARTATE AMINOTRANSFERASE INCREASED	1	1.0%
AUTOIMMUNE HEPATITIS	1	1.0%
HEPATOSPLENOMEGALY	1	1.0%

AC-052-374 exceptional treatment use period cut-off date 01MAR15
Source: Appendix 2, Table 58.

There were 11 patients who reported at least one liver abnormality as an adverse event. (Of these 11, only two had been receiving bosentan prior to study start.) There was one additional case of ALT > 3 × ULN which was not reported as an adverse event because the patient (b) (6) had ALT value reported as 144 U/L at baseline which was recognized two days after treatment started. Bosentan was interrupted and re-started when the levels of ALT had returned to the normal range (about one month). ALT remained within normal range throughout the treatment period with bosentan. Only the report of autoimmune hepatitis was identified as serious.

Details of the 12 patients are shown in the table below.

9.1.3 Liver abnormalities

Table 9-3 Tabular listing of liver abnormalities (based on pre-defined laboratory abnormality categories and/or AEs), pooled safety analysis set

Patient No.	Age Sex	Variables with abnormality based on pre- defined categories ¹	Baseline	Abnormal value (Time point ^{2,3})	Reference range on the event day	Fold increase	AE reported (duration)	Outcome (value at resolution) ³	Baseline Bosentan use (Yes/No), duration	Other information/ remarks
FUTURE 2										
(b) (6)	11.7 years Male						Increased hepatospleno- megaly (Day 167)	Unresolved	No	ALT, AST and TBIL normal. Event associated with PAH progression to FC III.
	21 years Female	ALT ≥ 3 × ULN ALT ≥ 5 × ULN to < 8 × ULN AST ≥ 3 × ULN	ALT: 28 U/L AST: 36 U/L	171 U/L (Day 273) 299 U/L (Day 341) 144 U/L (Day 341)	7-41 U/L 7-41 U/L 12-38 U/L	4.2 × ULN 7.3 × ULN 3.8 × ULN	SAE autoimmune hepatitis (Days 273-448)	Resolved 2.5 months after study drug discontinuation	No	TBIL normal. Positive for F-Actin antibody and anti-smooth muscle IgG antibody. Medical history included Down's syndrome, hypothyroidism, (predisposition to immunological dysregulation).
	4.6 years Female		32 U/L	107 U/L (Day 284)	30-65 U/L	1.6 × ULN	ALT increased (Days 284-315)	Resolved 36 U/L (Day 368)	No	AST and TBIL normal. Onset 5 days after central line infection and Bactrim and cefalexin administration.
	4.2 years Male		40 U/L	50 U/L (Day 321) 48 U/L (Day 689)	10-40 U/L Unknown	1.3 × ULN	AST increased (Days 321-353, Days 689-752)	Resolved 40 U/L (Day 353, 752)	No	All other scheduled LFT assessments remained normal throughout the 1167 days of study drug use.

Patient No.	Age Sex	Variables with abnormality based on pre- defined categories ¹	Baseline	Abnormal value (Time point ^{2,3})	Reference range on the event day	Fold increase	AE reported (duration)	Outcome (value at resolution) ³	Baseline Bosentan use (Yes/No), duration	Other information/ remarks
FUTURE 3										
(b) (6)	1 year Male	ALT $\geq 3 \times$ ULN	ALT 35 U/L	144 U/L (baseline Day 1)	6-34 U/L	4.2 $\times$ ULN		Resolved 23 U/L (Day 44)	No	ALT value (35 U/L) close to ULN at screening. ALT/AST elevation occurred prior to study drug administration but only discovered the following day; bosentan was therefore interrupted from Day 2 to Day 25. TBIL remained normal. Re-started on Day 26 when ALT, AST and TBIL were normal.
			AST 43 U/L	120 U/L (baseline Day 1)	10-69 U/L	1.7 $\times$ ULN		Resolved 45 U/L (Day 44)		
	9.8 years male	TBIL $\geq 2 \times$ ULN	20.5 μ mol/L	61.6 μ mol/L (Day 56)	3-21 μ mol/L	2.9 $\times$ ULN	Blood bilirubin increased (Day 56-65)	Resolved 20.5 μ mol/L (Day 64)	Yes, 2388 days	6.5 years of prior bosentan therapy without liver abnormality. Isolated increased bilirubin, which resolved within 9 days without change in bosentan dosing frequency. ALT and AST normal.
	10.8 years Female	ALT $\geq 5 \times$ ULN to $< 8 \times$ ULN	ALT: 14 U/L	ALT: 204 U/L (Day 169)	6-34 U/L	6 $\times$ ULN	Abnormal liver function test (Days 169-186)	Resolved ALT: 17 U/L (Day 200)	No	TBIL normal. Event led to study drug discontinuation.
			AST: 27 U/L	AST: 112 U/L (Day 169)	10-40 U/L	2.8 $\times$ ULN		AST: 30 U/L (Day 200)		

Patient No.	Age Sex	Variables with abnormality based on pre-defined categories ¹	Baseline	Abnormal value (Time point ^{2,3})	Reference range on the event day	Fold increase	AE reported (duration)	Outcome (value at resolution) ³	Baseline Bosentan use (Yes/No), duration	Other information/ remarks
(b) (6)	8.3 years male		ALT: 11 U/L	ALT: 159 U/L (Day 145)	13-69 U/L	2.3 × ULN	Hepatic function abnormal (Day 143-171) Abnormal liver function test (Day 192-220)	Resolved Day 171: ALT: 44 U/L AST: 35 U/L Total bilirubin: 8.6 U/L	No	TBIL normal. Onset following 10 days of clindamycin given for viral infection (NOS). Abnormal liver function test AE led to study drug discontinuation
			AST: 26 U/L	AST: 84 U/L (Day 145)	10-40 U/L	2.1 × ULN				
FUTURE 3 extension										
(b) (6)	1.8 years Female	TBIL ≥ 2 × ULN	TBIL 20.5 μmol/L	80.4 μmol/L (Day 239)	3.4-20.5 μmol/L	3.9 × ULN	Blood bilirubin increased (Day 239-245)	Resolved (value unavailable from listing)	No	ALT and AST normal. First isolated TBIL elevation was on Day 138 with gradual increase until Day 239 when it was reported as an AE immediately following a viral respiratory tract infection. Within 6 days, TBIL was 1.2 × ULN on Day 239.
	10.6 years Female		TBIL 25.7 μmol/L	25.7 μmol/L	3.4-20.5 μmol/L		Blood bilirubin increased (Day 213)	Unresolved	No	Medical history of Gilbert's syndrome. TBIL values were already above ULN at screening and Day 1 and remained above ULN.

Patient No.	Age Sex	Variables with abnormality based on pre-defined categories ¹	Baseline	Abnormal value (Time point ^{2,3})	Reference range on the event day	Fold increase	AE reported (duration)	Outcome (value at resolution) ³	Baseline Bosentan use (Yes/No), duration	Other information/ remarks
(b) (6)	4.5 years Male		TBIL 10.3 μmol/L	TBIL 72 μmol/L	3-21 μmol/L		Blood bilirubin increased (Day 1236-1431)	Resolved 39 μmol/L (last available value Day 1333)	No	Indirect hyperbilirubinemia after 3 years of uneventful bosentan treatment, resolving after drug rechallenge
	0.8 years Female		ALT: 28 U/L AST: 51 U/L	ALT: 52 U/L AST: 60 U/L	ALT: 6-34 U/L AST: 10-56 U/L		Hepatic function abnormal (Day 694-730)	Resolved	No	ALT and AST slightly elevated (< 2 × ULN). TBIL normal

¹ Categories defined in the SAP: ALT or AST ≥ 3 × ULN, ≥ 5 × ULN, ≥ 8 × ULN, bilirubin ≥ 2 × ULN

² Time point = Days after treatment start

³ Value from laboratory listings may or may not coincide with the reported AE onset/resolution date. In case no laboratory values were available on the day of AE onset/resolution from the listings, the closest available value is provided.

AE = adverse event; ALT = Alanine aminotransferase; AST = aspartate aminotransferase; EUTP = exceptional use treatment period; FC = functional class; LFT = liver function test; NOS = not otherwise specified; PAH = pulmonary arterial hypertension; SAE = serious adverse event; SAP = statistical analysis plan; TBIL = total bilirubin; ULN = upper limit of normal.

Source: Appendix 2, Listing 5, Listing 6, Listing 10, Listing 11, Listing 12, and Listing 13.

-Patient (b) (6) had ALT 204 U/L and AST 112 U/L reported on Day 169. Bilirubin remained within the normal range. These elevations were reported as an adverse events and the study drug was discontinued. ALT was reported as normal one month later.

-Patient (b) (6) reported autoimmune hepatitis as a serious adverse event resulting in premature discontinuation of study treatment and study.

Liver test abnormalities reported during a study are shown below.

Table 64 Post-baseline liver function abnormalities, Safety set

Pooled Bosentan Studies (ISS): AC-052-365, AC-052-367, AC-052-373, AC-052-374

Table T LFA S: Post-Baseline Liver Function Abnormalities
Analysis Set: Safety Set

Laboratory abnormality	Bosentan	
	N=100	
	n	%
ALT or AST $\geq$ 3*ULN	2 / 99	2.0%
ALT or AST $\geq$ 3*ULN - < 5*ULN	1 / 99	1.0%
ALT or AST $\geq$ 5*ULN - < 8*ULN	2 / 99	2.0%
ALT or AST $\geq$ 8*ULN	0 / 99	
ALT or AST $\geq$ 3*ULN and total bilirubin $\geq$ 2*ULN (1)	0 / 99	

ALT = Alanine Aminotransferase, AST = Aspartate Aminotransferase, ULN = Upper Limit of Normal
(1) Only when total bilirubin $\geq$ 2*ULN is concomitant to ALT or AST $\geq$ 3*ULN
Values given are the number of patients with at least one abnormality/number of patients (%)
Based on any post-Baseline value up to end of treatment
One subject can be reported in two separate categories if his AST and ALT levels fall in two distinct categories
Studies AC-052-365, AC-052-367, AC-052-373 are completed. For the AC-052-374 subjects still in the exceptional treatment use period, a cut-off date of 01MAR15 is applied to include their data into the safety pool (Data Dump on 04MAR16)

These results show infrequent LFT elevations, similar to that seen in adults receiving bosentan.

Table 71 Shift table of liver function abnormalities (standardized) from baseline to worst high post-baseline value, Safety set

Pooled Bosentan Studies (ISS): AC-052-365, AC-052-367, AC-052-373, AC-052-374

Table T LFA S: Shift Table of Liver Function Abnormalities (Standardized) from Baseline to Worst High Post-Baseline Value
Analysis Set: Safety Set

AST (U/L)

	n	Baseline	n	worst high case up to EOT + 7 days							
				No marked abnormalities		H		HH		HHH	
				n	%	n	%	n	%	n	%
Bosentan (N= 100)	97	No marked abnormalities	84	65	77.4%	16	21.4%	1	1.2%	0	0
		H	13	2	15.4%	11	84.6%	0	0	0	0
		HH		0	0	0	0	0	0	0	0
		HHH		0	0	0	0	0	0	0	0

EOT is defined as the last available value while on treatment
Studies AC-052-365, AC-052-367, AC-052-373 are completed. For the AC-052-374 subjects still in the exceptional treatment use period, a cut-off date of 01MAR15 is applied to include
Table T LFA S - Produced by (b) (4) on 16JUN16
(Data: 17/1)

Pooled Bosentan Studies (ISS): AC-052-365, AC-052-367, AC-052-373, AC-052-374

Table T_LFA_S: Shift Table of Liver Function Abnormalities (Standardized) from Baseline to Worst High Post-Baseline Value
Analysis Set: Safety Set

ALT (U/L)	n	Baseline	n	worst high case up to EOT + 7 days							
				No marked abnormalities		H		HH		HHH	
				n	%	n	%	n	%	n	%
Bosentan (N= 100)	97	No marked abnormalities	91	75	82.4%	14	15.4%	0		2	2.2%
		H	6	4	66.7%	2	33.3%	0		0	
		HH		0		0		0		0	
		HHH		0		0		0		0	

EOT is defined as the last available value while on treatment
Studies AC-052-365, AC-052-367, AC-052-373 are completed. For the AC-052-374 subjects still in the exceptional treatment use period, a cut-off date of 01MAR15 is applied to include
Table T_LFA_S - Produced by (b) (4) on 16JUN16
(Page 272)

There are uncommon increases in LFTs.

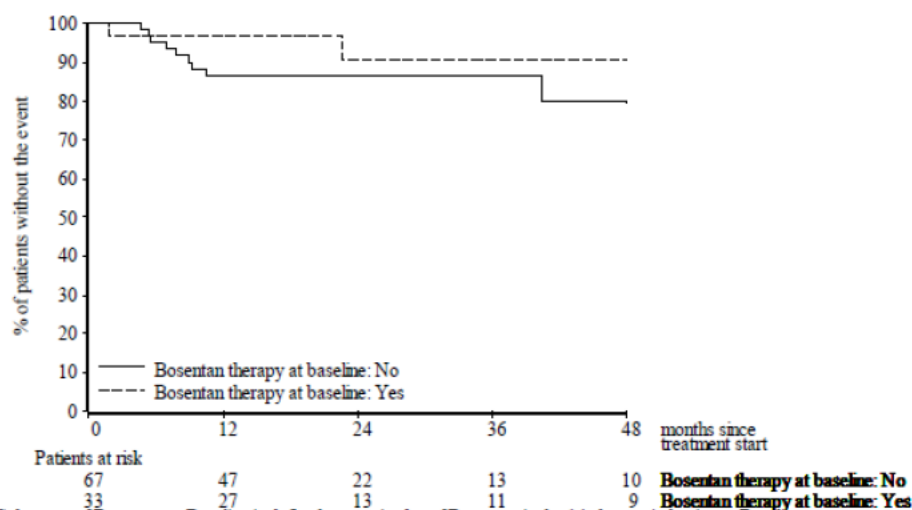
The figure below shows the time to first reported liver abnormality event, by baseline bosentan use.

Figure 5 Time to first liver abnormality event: Kaplan-Meier estimates by baseline bosentan use, Safety set

Pooled Bosentan Studies (ISS): AC-052-365, AC-052-367, AC-052-373, AC-052-374

Figure F_KMLIVB_S: Time to First Liver Abnormality Event, Kaplan-Meier Estimates by Baseline Bosentan Use.

Analysis Set: Safety Set



Subgroup of Bosentan at Baseline is defined as any intake of Bosentan in the 14-day period prior to Baseline

Studies AC-052-365, AC-052-367, AC-052-373 are completed. For the AC-052-374 subjects still in

the exceptional treatment use period, a cut-off date of 01MAR15 is applied to include their data into

the safety pool (Data Dump on 04MAR16)

Figure F_KMLIVB_S - Produced by (b) (4) on 16JUN16

Time to first reported liver abnormality was somewhat earlier for subjects who were not taking bosentan at baseline. Most likely, those who were taking bosentan before study start and had elevated LFTs were not enrolled.

In AC-052-356 (BREATHE-3), three patients reported abnormal hepatic function as adverse events.

-Patient (b) (6) reported serious adverse events of severe ulcerative colitis and sclerosing cholangitis. The patient's ALT and AST elevations on Day 5 (both $> 3 \times \text{ULN}$) were reported as a serious adverse event and study treatment was discontinued. On Day 26, the patient had ALT value 336 U/L 19 days after study drug discontinuation. The LFT abnormalities started resolving about 8 weeks later.

-Patient (b) (6) reported elevated ALT value 166 U/L Day 91 that resulted in study drug discontinuation. Bosentan was withheld about 2 weeks until ALT and AST normalized and it was restarted at half the dose. Elevated ALT was again reported and study drug was permanently discontinued on Day 197.

-Patient (b) (6) reported mild, transient ALT elevations as an adverse event.

In the Japanese study AC-052-377, one patient reported mildly increased AST as an adverse event. There were no reported clinically significant liver function laboratory abnormalities (AST and/or ALT $> 3 \times \text{ULN}$).

Edema

This is an adverse event associated with bosentan use. The current package label states

Peripheral edema is a known clinical consequence of PAH and worsening PAH and is also a known effect of Tracleer and other endothelin receptor antagonists. In PAH clinical trials with Tracleer, combined adverse events of fluid retention or edema were reported in 1.7 percent (placebo-corrected) of patients. In addition, there have been numerous post-marketing reports of fluid retention in patients with pulmonary hypertension occurring within weeks after starting Tracleer. Patients required intervention with a diuretic, fluid management, or hospitalization for decompensating heart failure.

Edema in the pooled safety analysis set

Adverse events related to edema were reported for three patients (two peripheral edema and one pericardial edema).

-Patient (b) (6) reported pedal edema (preferred term was peripheral edema) on day (b) (6). The patient was experiencing PAH progression and died 17 days later.

-Patient (b) (6) reported pedal edema (preferred term was peripheral edema) on day 1. The patient's medical history included generalized edema along with dyspnea. Edema resolved 4 months later and WHO FC improved from Class III at baseline to Class II. The patient completed the 24-week treatment period and was enrolled in the FUTURE 3 study extension (Day 170). He died of what was reported as worsening PAH on day (b) (6).

-Patient (b) (6) reported pericardial effusion along with disease worsening and right-heart failure. The patient was hospitalized and the event resolved with subcutaneous treprostinil and intravenous epoprostenol.

In AC-052-356 (BREATHE-3), two patients reported mild fluid retention and one reported moderate edema. These cases were reported as not severe, occurring late during treatment, and unrelated to the initiation of bosentan treatment.

In the Japanese study AC-052-377, there were no reports of edema.

Clinical labs⁴

Pooled studies

There were no clinically significant changes from baseline at end of treatment in mean alkaline phosphatase, platelets, leukocytes, albumin, glucose, sodium, potassium, creatinine and BUN.

Vital signs, height/length, BMI, body weight⁵

Pooled studies

The mean increases in height, weight and BMI were 11.7 cm, 4.8 kg and 2 kg/m², respectively. Both systolic and diastolic blood pressure showed no change. There was a decrease in pulse rate (about 6 bpm).

Safety in subpopulations

The numbers of patients in subgroups (tid vs bid dosing regimens, age, sex, race, PAH treatment prior to study start) were small and unlikely to show a difference in safety even if a difference exists.

There was no obvious difference between tid and bid dosing regimens concerning the number of patients reporting adverse events, including serious safety.

POST-MARKETING SURVEILLANCE

Non-interventional post-authorization safety studies in the pediatric population

AC-052-516 – Systematic review of pediatric registries

Disease characteristics and outcomes of pulmonary arterial hypertension in children and adolescents in real-world clinical settings: systematic review of four prospective, observational registries.

Background

Following the approval of Tracleer 32 mg dispersible tablets on July 1, 2009 by the European Commission, the Marketing Authorization Holder for Tracleer, Actelion Registration Ltd, committed to collect long-term data on safety and outcomes from pediatric PAH patients treated with Tracleer in a systematic review of four prospective, observational registries. This commitment was a follow-up measure requested by the Committee for Medicinal Products for Human Use at the time of the marketing authorization for Tracleer 32 mg dispersible tablets.

⁴ From appendix 2 table 70

⁵ From appendix 2 table 72

The systematic review used aggregated data from four prospective observational (non-interventional) disease registries initiated to study the disease course and long-term outcomes of PAH in children and adolescents in real-world clinical settings. The following four pediatric registries contributed to the systematic review:

- Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) Registry
- Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL) (US)
- Dutch National Pediatric PAH registry (NL)
- French Registry ItinerAIR Pédiatrie part 2 (FR).

Table 8-1 Registries that contribute data to the systematic review of pediatric registries (AC-052-516)

Registry name	Description	Enrollment/Database closure	Registry population ^a	Data owner
Terminated registries				
The Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension (TOPP) Registry ^b	Multi-national prospective registry in 34 centers / 20 countries [Berger 2012]	January 2008 to May 2009 for 'prevalent' patients (patients enrolled more than 3 months after diagnosis) January 2008 until registry termination for 'incident' patients (patients enrolled within 3 months of diagnosis) Database closure: 9 July 2015	WHO Group 1, 3, 4 and 5 patients aged ≥ 3 months to ≤ 18 years; diagnosis confirmed by RHC after 1 January 2001 ^d	Association for Pediatric Pulmonary Hypertension. Supported by Actelion with a research grant.
Registry to Evaluate Early And Long-Term PAH Disease Management (REVEAL) ^c	Multi-center prospective registry with 54 centers in the US (25 centers with pediatric patients) [Barst 2012]	March 2006 to December 2009 Database closure: 31 December 2012	Both adult and pediatric WHO Group 1 PAH patients aged ≥ 3 months with diagnosis confirmed by RHC	Actelion
Ongoing registries				
Dutch National Pediatric PAH Registry (NL) ^c	Single-reference-center prospective registry in the Netherlands	From December 2006	WHO Group 1 PAH patients aged ≥ 1 month to ≤ 18 years with diagnosis confirmed by RHC ^d	Dutch Network for Children with Pulmonary Hypertension. Supported by Actelion with a research grant.

ItinerAIR Pédiatrie part 2 Registry (FR) ^c	Multi-center prospective registry with 16 centers in France	September 2010 to present	WHO Group 1 PAH patients aged ≥ 28 days to ≤ 18 years with diagnosis confirmed by RHC or echocardiogram (PAH-CHD patients are included only if the PAH is not the result of the underlying CHD) ^e	Actelion
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^a Of each registry population, only patients prospectively followed on or after 15 October 2009 who were aged ≤ 17 years (i.e., up to but excluding the date of the patient's 18th birthday) at diagnosis and at enrollment in each registry, and categorized as WHO Group 1 PAH are included in the systematic review.

^b As some centers contributed to more than one registry, a subset of patients are enrolled in both the TOPP registry and one of the other 3 registries. These patients are included in data summaries of the TOPP registry but are excluded from the analysis of the other registries in the systematic review.

^c Patients also enrolled in TOPP are excluded from the analysis of the registry data in the systematic review.

^d Includes both 'incident' (enrolled within 3 months of PAH diagnosis) and 'prevalent' (enrolled more than 3 months after PAH diagnosis) patients.

^e Includes only 'prevalent' (enrolled more than 3 months after PAH diagnosis) patients.

CHD = congenital heart disease; PAH = pulmonary arterial hypertension; PAH-CHD = PAH associated with CHD; RHC = right-heart catheterization; WHO = World Health Organization.

The TOPP and REVEAL registries have been terminated; however, the NL and FR registries are ongoing.

The Sixth Annual Report was issued on January 26, 2016, presenting cumulative data from 15 October 15, 2009 to September 15, 2015 for ongoing registries or to the last available information at database closure for the terminated registries. The objective of the systematic review was to describe patient demographics, disease characteristics and outcomes, and additional safety experience in Tracleer-treated pediatric patients. Tracleer patients may have received either the immediate release tablet or dispersible tablet of Tracleer.

Overall, median Tracleer exposure time since the start of the systematic review was 28.0 months in the TOPP registry, 24.8 months in REVEAL, and 30.3 months in the NL registry.

Across all four registries, there were 79 deaths, the majority of which (61) were considered related to PAH. 34 of the deaths occurred in 'Tracleer patients' (29 related to PAH). In TOPP, where the majority of deaths were recorded, the event rates in 'Tracleer patients' and 'All patients' were similar.

Across the four registries, discontinuation of Tracleer treatment was reported for a total of 53 'Tracleer patients' (49 patients [19%] in the TOPP registry and 4 patients [21%] in the REVEAL registry).

For safety topics of special interest, elevations in liver aminotransferases (≥ 3 to $\leq 5 \times$ ULN and $> 5 \times$ ULN) were reported for 'Tracleer patients' both in the TOPP (7 and 2 events, respectively) and the REVEAL (1 and 0 events, respectively) registry.

Events of hemoglobin < 9 g/dL in 'Tracleer patients' were reported only in the TOPP registry (5 events).

Safety Update

Pooled analysis set

The applicant submitted updated safety data from 7 of the 100 pediatric PAH patients who are part of the ongoing FUTURE 3 extension EUTP⁶. Data are presented for up to the analysis cut-off date of August 31, 2016.

Japanese studies

Full data from study AC-052-378, the extension to study AC-052-377, is presented up to the analysis cut-off date of April 13, 2015 ($n = 6$). Patients entering the extension study continued to receive the dose of bosentan they were receiving at the end of AC-052-377.

Overall extent of exposure

EUTP

⁶ An open-ended EUTP of the FUTURE 3 extension study has been implemented to allow for the treatment of patients in cases where bosentan is not commercially available or where compassionate use or similar programs are not feasible. The EUTP is currently ongoing in four countries (Belarus, Ukraine, Russia, and China)

The median cumulative exposure for the 7 patients in the EUTP up to the data analysis cut-off (August 31, 2016) was 17.6 months (16.7–59.9 months). For the NDA, the median duration of exposure to bosentan treatment in the pooled safety analysis set (n = 100) was 17 months (range: 0.1–59.3 months).

Up to the data analysis cut-off (August 31, 2016), 1 of the 7 patients (Patient (b) (6)) withdrew consent and discontinued EUTP, and 1 patient died (Patient (b) (6)).

AC-052-378 Japanese study

While all 6 patients were treated for at least 29 weeks, two of the six prematurely discontinued study treatment:

-Patient (b) (6) withdrew consent because of difficulties visiting the hospital every 4 weeks according to the study schedule, and

-Patient (b) (6) discontinued study treatment as alternative treatment with Flolan® was planned.

Serious safety

Deaths

EUTP

There was one death (patient (b) (6)) reported after the NDA cut-off date but included in the NDA and discussed earlier in this review.

AC-052-378 Japanese study

There were no reported deaths during study AC-052-378 up to April 13, 2015.

Serious adverse events including discontinuations because of adverse events

EUTP

A total of two patients reported serious adverse events in the EUTP during the reporting period.

-Patient (b) (6) experienced progressive PAH worsening with fatal outcome (discussed above).

-Patient (b) (6) experienced a PAH crisis (about 2.5 years after the start of study drug) with complications resulting from the right heart catheterization. The episode resolved without sequelae within 8 days.

No discontinuations because of adverse events were reported.

AC-052-378 Japanese study

Serious adverse events were reported in two patients.

-Patient (b) (6) with adenovirus upper respiratory infection during study AC-052-377 study reported pneumonia during study AC-052-378.

-Patient (b) (6) reported reduction in eyesight in his right eye on day 358. The ophthalmologic examination revealed retinal vein occlusion affecting the subauricular region. Study drug was continued.

One subject, who reported liver function test abnormal, was discontinued after the cut-off for interim report date (April 13, 2015). This subject had begun concomitant treatment with beraprost sodium after week 52 and the reported abnormality was attributed to this.

POST-MARKETING DATA

Cumulative post-marketing exposure

Cumulatively (from the international birthday (IBD) to August 31, 2016), an estimated 167,030 patients were exposed to commercial bosentan worldwide. During the previous Periodic Safety Update Report/Periodic Benefit-Risk Evaluation Report review period (November 20, 2014 to November 19, 2015), cumulatively in the US, 4.9% of exposed patients were below the age of 18 years (8134 patients, 3.7% < 12 years, and 1.2% ≥ 12 and < 18 years), 50.8% were adults and 44.3% were elderly (≥ 65 years). The age group was unknown for 0.01% of patients.

The majority of adverse events reported cumulatively (from the IBD to August 31, 2016) from pediatric case (60.6%) and from adult/elderly cases (57.3%) were reported in the following System Organ Classes (SOC):

- respiratory, thoracic and mediastinal disorders' (16.4% and 15.8% in pediatric and adult/elderly, respectively),
- investigations (15.9% and 14.3% in pediatric and adult/elderly, respectively),
- general disorders and administration site conditions (including death and lack of efficacy; 15.1% and 19.7% in pediatric and adult/elderly, respectively), and
- infections and infestations (13.2% and 7.5% in pediatric and adult/elderly, respectively).

The cumulative overall reporting rate for hepatobiliary events or liver abnormalities (reported as the primary event or as a secondary event) was 5.8% (9719 cases/167,030 patients exposed). In the pediatric population, the cumulative reporting rate for liver abnormalities was 5.4% (439 cases/8134 patients exposed). For 368 cases, age or age group was not provided.

There were 36 new initial pediatric cases with hepatic events reported during the interval (November 20, 2015 to August 31, 2016). These events are shown below.

Table 7-3 120-Day Safety Update: summary tabulation of PTs denoting hepatic events from pediatric cases (< 18 years) (20 November 2015 to 31 August 2016)

Preferred terms		Interval
		Total
Aspartate aminotransferase increased	22	27.8%
Alanine aminotransferase increased	17	21.5%
Liver function test increased	13	16.5%
Hepatic enzyme increased	8	10.1%
Liver function test abnormal	2	2.5%
Transaminases increased	2	2.5%
Blood bilirubin increased	2	2.5%
Blood alkaline phosphatase increased	2	2.5%
Gamma-glutamyltransferase increased	2	2.5%
Hepatic function abnormal	1	1.3%
Hepatotoxicity	1	1.3%
Bilirubin conjugated increased	1	1.3%
Liver disorder	1	1.3%
Liver injury	1	1.3%
Biopsy liver	1	1.3%
Feeding tube complication	1	1.3%
Ocular icterus	1	1.3%
Blood bilirubin decreased	1	1.3%

According to the sponsor, all hepatic events received during the reporting interval were extensively reviewed. In 1 case, a 4-year-old male patient with porto-pulmonary hypertension and medical history of pre-existing hepato-pulmonary syndrome underwent a liver biopsy to assess the patient's eligibility for a lung transplant; the liver biopsy confirmed the presence of intrapulmonary portal vein without fibrosis, and a definitive diagnosis of congenital extrahepatic portosystemic shunt Type 2 (intrahepatic portal vein patency) was made. Tracleer remained ongoing. The nature of hepatic events received during this review interval for pediatric patients was similar to adult/elderly patients, and consistent with those received cumulatively as presented in the summary of clinical safety. No unexpected safety concerns were identified.

The estimated cumulative reporting rate of events denoting anemia or hemoglobin decrease was similar between pediatric (1.2%) and adult/elderly (1.8%) patients.

Table 7-4 120-Day Safety Update: reported incidence of events of anemia in the overall exposed patient population and in pediatric patients from IBD up to 19 November 2015

Bosentan-treated patients	Adult/elderly patients	Pediatric patients (age < 18 years)
Estimated exposure to bosentan	158,879	8134
Number of cases in Argus (related and unrelated)	83,492	4168
Number of cases (reporting rate) of anemia or hemoglobin decreased	2929 (1.8%)	97 (1.2%)

IBD = International Birth Date.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MARYANN GORDON
03/22/2017

ALIZA M THOMPSON
03/22/2017
CDTL memo to follow containing my perspective on the data supporting efficacy.