European Medicines Agency

ASSESSMENT REPORT
FOR
TRACLEER

International non-proprietary name/Common name:
bosentan

Procedure No.EMEA/H/C/000401/II/0037

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

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1. Introduction

Tracleer (bosentan) is an endothelin receptor (ET_A and ET_B) antagonist and thus competes with the binding of ET-1 and other ET peptides to both ET_A and ET_B receptors. Bosentan decreases both pulmonary and systemic vascular resistance resulting in increased cardiac output without increasing heart rate.

The Marketing Authorisation of Tracleer was granted by the European Commission on 15 May 2002.

Tracleer is currently indicated for:
Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients with grade III functional status. Efficacy has been shown in:

- *primary PAH*
- *PAH secondary to scleroderma without significant interstitial pulmonary disease.*
- *PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology*

Tracleer is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

In the present application, the Marketing Authorisation Holder (MAH) of Tracleer applied for an extension of indication for the treatment of patients with pulmonary arterial hypertension (PAH) categorised as WHO functional Class II with subsequent changes in sections 4.4, 4.8 and 5.1 of Summary of Product Characteristics (SPC).

2. Clinical aspects

Severity of the pulmonary arterial hypertension is usually assessed using the World Health Organisation (WHO) classification of pulmonary hypertension as modified from the New York Heart Association functional classification. Four categories are defined according to the following criteria:

Class I: Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity did not cause undue dyspnoea or fatigue, chest pain, or near syncope.

Class II: Patients with pulmonary hypertension resulting in slight limitation of physical activity. They were comfortable at rest. Ordinary physical activity caused undue dyspnoea or fatigue, chest pain, or near syncope.

Class III: Patients with pulmonary hypertension resulting in marked limitation of physical activity. They were comfortable at rest. Less than ordinary activity caused undue dyspnoea or fatigue, chest pain, or near syncope.

Class IV: Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifested signs of right heart failure. Dyspnoea and/or fatigue may even have been present at rest. Discomfort was increased by any physical activity.

The efficacy and safety of bosentan for the treatment of moderately to severely symptomatic PAH was initially shown in two placebo-controlled trials conducted in patients with PAH disease of WHO functional class III and IV. In both studies, bosentan treatment resulted in a statistically significant increase in the 6-minute walk distance and a significant delay in the time to clinical worsening, compared with placebo. These improvements were accompanied by a decrease in patient-rated dyspnoea during exercise, improved functional class in a substantial proportion of patients, and improvements in cardiac haemodynamics.

The marketing authorisation of Tracleer was based on the demonstration of a favourable benefit/risk ratio to improve exercise capacity and symptoms in patients with grade III functional status severity in

primary/familial pulmonary arterial hypertension, PAH secondary to scleroderma and PAH associated with congenital systemic-to-pulmonary shunts and Eisenmenger's physiology.

WHO Class I or II PAH patients have not been adequately studied in previous clinical trials. PAH is a rare disease, and only about 25% of PAH patients seen in the clinic are in functional class II or less at the time of diagnosis.

In support of the present application to extend the indication in PAH patients with mildly symptomatic disease (WHO functional class II), the MAH has now submitted an additional clinical phase III study, the EARLY trial (Endothelin Antagonist Trial in Mildly Symptomatic PAH Patients, Study AC-052-364). This study was designed to determine if initiating treatment with bosentan earlier in the course of the disease would not only affect haemodynamics and exercise capacity over a 6-month treatment period, but also delay clinical worsening.

2.1 Clinical efficacy

2.1.1 Pivotal study: Study AC-052-364 (EARLY)

- Methods

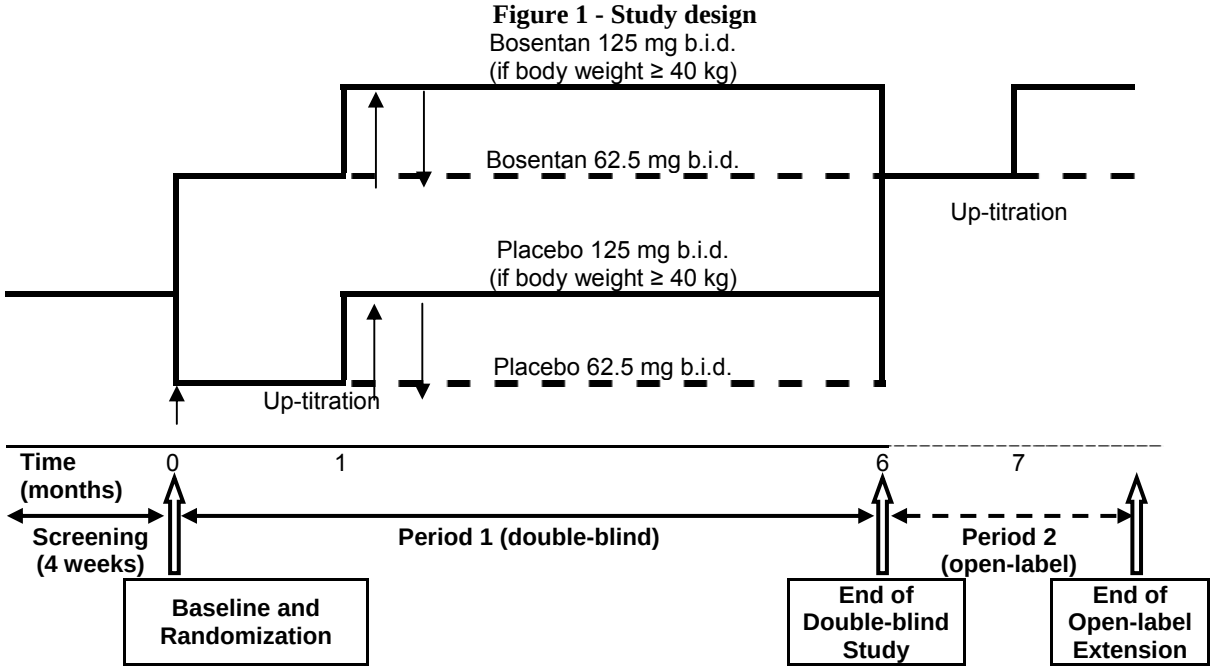
Study AC-052-364 (EARLY) was a multicentre, randomized, double-blind, placebo-controlled, parallel-group, Phase IIIb study designed to assess the efficacy and safety of bosentan in patients with mildly symptomatic PAH (WHO functional class II). The study was conducted in a total of 185 patients at 52 centres worldwide.

The primary objectives were to demonstrate that bosentan improves cardiac haemodynamics and exercise capacity in mildly symptomatic PAH patients. The secondary objectives were to evaluate the effect of bosentan on the time to clinical worsening; dyspnoea, WHO functional class, and quality of life; and to demonstrate that bosentan is safe and well tolerated in this patient population. Further objectives were to evaluate the effects of bosentan on haemodynamics and exercise capacity in strata with or without concomitant sildenafil treatment at baseline.

Study design

The study design is described in Figure 1. After a 4-week screening, the 6 months treatment period consisted of an initial dosing phase (administration of bosentan 62.5 mg b.i.d. or matching placebo for 4 weeks), followed by a target dose treatment phase: bosentan 125 mg b.i.d. for patients with body weight ≥40 kg (62.5 mg b.i.d. for patients with body weight < 40 kg) or matching placebo for 5 additional months. Patients who did not tolerate the 125 mg b.i.d. target dose could be down titrated to the starting dose (62.5 mg b.i.d.).

Figure 1 - Study design



With the approval of sildenafil in the United States for the treatment of PAH (regardless of functional class), the study design was modified to allow up to 50% of patients to be on concomitant sildenafil at entry. Patients were stratified according to use or non-use of sildenafil at entry, with patients in each stratum randomized in a 1:1 ratio to receive bosentan or placebo.

Allowed concomitant treatments for PAH included calcium channel blockers (if present for at least 1 month before randomization and remained constant during the study), sildenafil (if present for at least 2 months before randomization at a stable dose ≥ 20 mg three times daily and remained constant during the study), and anticoagulants.

All patients who completed Period 1 were given the option of ending their participation in the study or switching to open-label bosentan until the study was ended (Period 2). The main objective of the open-label treatment period was to collect longer-term safety data. During Period 2, the dosing regimen for all patients was to be the initial low dose of bosentan followed by up-titration after 1 month, and concomitant PAH therapy was allowed. The results of the double-blind Period 1 were submitted in this application. Further to the request from the CHMP, a progress report on the open-label extension was submitted by the MAH and is discussed in section 3.2.1.3.

Study participants

The main inclusion criteria were:

- Man or woman ≥ 12 years of age (≥ 18 years in Denmark, Germany, Ireland, Norway, Sweden, and the United Kingdom).
- WHO functional class II PAH (either idiopathic/familial (primary pulmonary hypertension), secondary to HIV, secondary to intake of anorexigens, secondary to atrial septum defect of < 2 cm, ventricular septum defect of < 1 cm or patent ductus arteriosus, secondary to connective tissue or autoimmune diseases).
- A 6-minute walk test distance < 80% of the normal predicted value or < 500 meters associated with a Borg dyspnoea index score of ≥ 2.
- Mean pulmonary artery pressure (mPAP) ≥ 25 mmHg and pulmonary capillary wedge pressure (PCWP) < 15 mmHg and PVR ≥ 320 dyn.sec.cm−5 at rest.

Patients were excluded if they had significant vasoreactivity during right heart catheterization (i.e., could benefit from calcium channel blockers) or had PAH associated with other conditions or severe obstructive lung disease. Patients were also excluded if they had previously received treatment for PAH (except calcium channel blockers, sildenafil, and anticoagulants) within 1 month or an ET-

receptor antagonist or prostanoid (excluding acute administration during a catheterization procedure to test vascular reactivity) within 3 months of randomization. Other exclusion criteria were to protect patient safety.

Primary endpoints

The efficacy of bosentan in class II patients was assessed using two co-primary endpoints sequentially:

- PVR at rest at Month 6 expressed as a percent of the baseline value.
- Change from baseline to Month 6 in 6-minute walk distance.

Secondary endpoints

- Time to clinical worsening, defined as:
  - Death (during treatment or as the outcome of a treatment-emergent adverse event that led to discontinuation of study treatment).
  - Hospitalization due to PAH complications.
  - Symptomatic progression of PAH (at least one of the following: Appearance or worsening of right heart failure; ≥ 10% decrease from baseline in two 6-minute walk tests performed ≥ 2 weeks apart; ≥ 5% decrease from baseline in two 6-minute walk tests performed ≥ 2 weeks apart associated with a ≥ 2-point increase in Borg dyspnea index).
- Change from baseline to Month 6 in WHO functional class.
- Change from baseline to Month 6 in Borg dyspnoea index.
- Change from baseline to Month 6 in mean right atrial pressure (mRAP), mean pulmonary artery pressure (mPAP), cardiac index, TPR and mixed venous oxygen saturation (SVO_2) at rest.

Exploratory endpoints

- Change from baseline to Month 6 in B-type natriuretic peptide (BNP) concentration.
- Change from baseline to Month 6 in percent change from value at rest to each workload level for mPAP, TPR, cardiac index, and SVO_2 during exercise (cycle ergometry).
- Change from baseline to Month 6 in mean peripheral oxygen saturation (SpO_2), time to desaturation (as defined by a ≥ 4% decrease in SpO_2), trough SpO_2, and area under the curve during exercise (6-minute walk test).
- Change from baseline to Month 6 in mean heart rate during exercise (6-minute walk test).

Safety endpoints

Treatment-emergent adverse events (AEs) and serious adverse events (SAEs) in the double-blind treatment period, clinical laboratory test results (i.e., changes from baseline to the end of double-blind treatment period, incidence of marked and special laboratory abnormalities), and changes from baseline in vital signs and body weight up to 1 day after the end of double-blind treatment, premature discontinuation of double-blind treatment, and SAEs from 2 to 28 days after the end of double-blind treatment.

Statistical methods

With 85 patients per treatment group, a ≥ 20% reduction in the geometric mean PVR and a ≥ 35-meter increase in the mean 6-minute walk distance in the active vs placebo group could be determined with > 99% and 91% power, respectively.

The two primary endpoints were evaluated hierarchically, with the endpoint on walk distance tested only if the endpoint regarding PVR was significant, with both tested at a two-sided type-I error of 0.05. The main analysis was on the all-randomized analysis set.

Treatment comparisons were performed using the two-sided Mann-Whitney U-test (main analysis) and a two-sided t-test (secondary analysis). Similar analyses were performed using different analysis sets, alternate substitution rules, in subgroups of the study population, and in strata with or without concomitant sildenafil treatment at baseline (stratified at randomization). Secondary and exploratory variables were analyzed on the all-randomized set only, with exploratory treatment comparisons performed. After applying the substitution rules, data were summarized descriptively, using location

and scale statistics and frequency counts and proportions. Numerical variables were analyzed in the same manner as the primary endpoints. The time to clinical worsening was analyzed using the Kaplan-Meier method, with treatment effect evaluated using the hazard ratio (from the Cox model) of the active vs placebo group and tested using the log-rank test; analyses of randomization strata and subgroups were similarly performed. The proportions of patients improved/worsened in functional class and SF-36 health transition index were compared using relative risk (active vs placebo) with the p-value from the Fisher exact test.

Safety data were summarized descriptively, with time-to-event analyses performed using the Kaplan-Meier method.

Randomization

Patients were randomized to bosentan or placebo in a 1:1 ratio, with randomization stratified by the presence or absence of stable sildenafil therapy at baseline. This stratification allowed for the additional objective of the evaluation of bosentan's effects on hemodynamics and exercise capacity in resulting strata.

Handling of missing values: Substitution rules

Substitution rules to replace any missing assessments were in place before the study was unblinded. Missing values for either PVR or walk distance at Month 6 were replaced by carrying forward the last available post-baseline value in the treatment period unless the patient died during treatment, permanently discontinued due to an adverse event which resulted in death, or the patient remained alive but experienced clinical worsening during the treatment period. In these cases, the worst value was used to replace the missing value.

Missing values for other hemodynamic parameters were replaced in the same manner as for PVR. Missing values at Month 6 for WHO functional class or Borg dyspnea index were replaced by carrying forward the last available post-baseline value in the treatment period unless the patient experienced clinical worsening, in which case the worst value (the maximum value or if the patient died, class IV and score of 10, respectively) was used for the missing value.

For the co-primary endpoints, robustness analyses were performed on the all-randomized set, using alternate rules for imputation of missing values at Month 6 (end of double-blind treatment period). Table 1 shows the criteria for inclusion of patients in these analyses.

Table 1 - Handling of patients without a valid Month-6 (end of double-blind treatment) or other valid post-baseline assessment in the different robustness analyses

Patient with:		Alternate substitution rules used in robustness analyses				
Clinical worsening	Post-tmt assessment	Including post-tmt values only for missing (derived) values	Including post-tmt values only for missing (derived) values + carry forward from BL	Including post-tmt values	Including post-tmt values + carry forward from BL	No worst substitution (only carry forward)
No	No	Excluded	BL carried forward	Excluded	BL carried forward	Excluded
Yes	No	Worsening substitution	Worsening substitution	Worsening substitution	Worsening substitution	Excluded
No	Yes	Used post-tmt value	Used post-tmt value	Used post-tmt value	Used post-tmt value	Excluded
Yes	Yes	Worsening substitution	Worsening substitution	Used post-tmt value	Used post-tmt value	Excluded

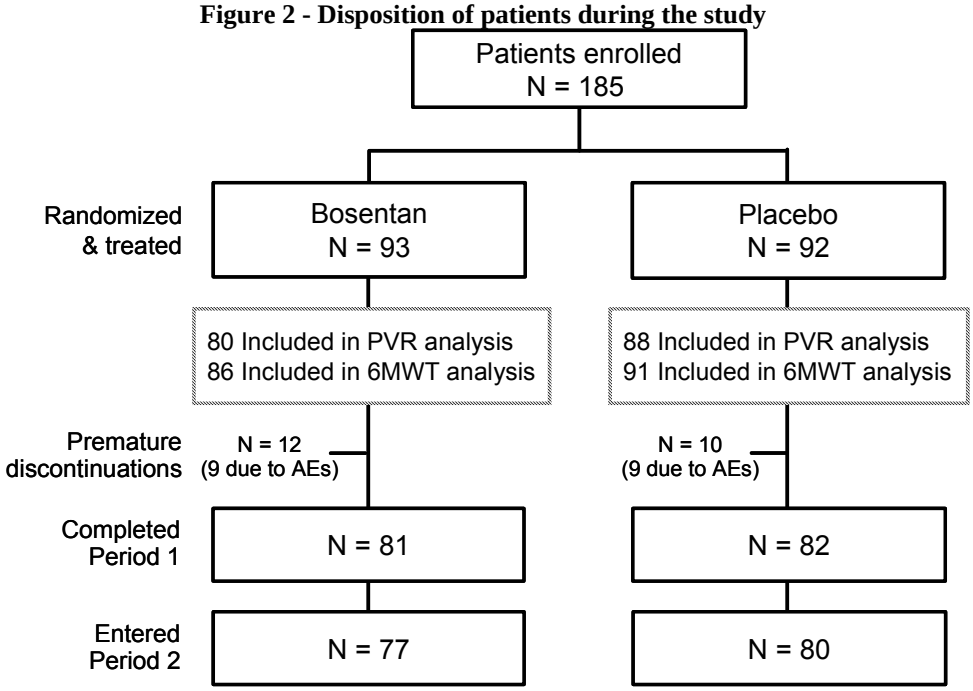
BL = baseline, tmt = treatment.

- Results

Disposition of patients

As described in Figure 2 below, a total of 185 patients were enrolled in the study and randomized in a 1:1 ratio to bosentan (n = 93) and placebo (n = 92).

Figure 2 - Disposition of patients during the study



Period 1 = 6-month double-blind treatment period.
Period 2 = variable open-label treatment period.
AE = adverse event, PVR = pulmonary vascular resistance, 6MWT = 6-minute walk test.

During the double-blind treatment period, 12.9% and 10.9% of bosentan- and placebo-treated patients, respectively, had study treatment prematurely discontinued. The most frequent reason for treatment discontinuation was an AE in bosentan-treated patients (6.5%, mainly increased liver aminotransferases) and aggravated pulmonary hypertension (6.5%) in placebo-treated patients. The term aggravated pulmonary hypertension denoted the occurrence of symptomatic progression of PAH as defined per protocol and may have been based on an AE.

Patients with a missing value at Month 6 for the primary endpoints are identified in the patient listings and are summarized in Table 2. The numbers of patients with missing values at Month 6 after applying the substitution rules and hence missing in the main analysis should not have greatly affected the power since more than the recommended number of patients (i.e., 85 per treatment group) was enrolled.

Table 2 - Numbers of patients with missing or substituted values in the main analysis of the primary endpoints

	PVR		**Walk test**	
	Placebo (n = 92)	**Bosentan (n = 93)**	**Placebo (n = 92)**	**Bosentan (n = 93)**
Total patients with a missing valid value at baseline or Month 6	7	16	6	14
Worst substituted at Month 6	3	3	5	2
Carry forward at Month 6	—	—	0	5
No substitution available for the main analysis	4	13	1	7

PVR = pulmonary vascular resistance.

The primary analysis did not include the cases with missing End of Study data in accordance with the pre-specified protocol. Further to the request from the CHMP, the applicant clarified that except for one case with baseline missing PVR, the End of Study missing data were mainly due to adverse events leading to premature discontinuation and delay in End of Study assessment (in the period defined by the protocol) or not performed if judged ethically not justified (i.e. treatment exposure too short to perform a end of treatment invasive right heart catheterisation). The applicant provided graphical presentations of analysis with alternative substitution rules applied to all randomised set (either with or without worst substitution). The presentation showed consistency in the results on co-primary endpoint with the primary analysis.

Demographics and baseline characteristics

A summary table describing the characteristics of patients in the EARLY study and in the pivotal registration study BREATHE-1 is presented below. The study population consisted primarily of Caucasian females and the mean age of subjects was 44 to 45 years. The two treatment groups were well balanced with regard to age, race, weight, and height. The placebo group had a higher proportion of males than did the bosentan group (37.0 % vs 23.7 %, respectively) (Table 3).

Table 3 - Patient characteristics in the EARLY and BREATHE-1 studies in pulmonary arterial hypertension

	BREATHE-1		**EARLY**	
	Placebo (n = 69)	**Bosentan 125mg b.i.d (n = 74)**	**Placebo (n = 92)**	**Bosentan 125mg b.i.d (n = 93)**
WHO class II (%)	—	—	100	100
class III/IV	94 / 6	92 / 8	—	—
Gender (male/female, %)	22 / 78	23 / 77	37 / 63	24 / 76
Mean age (y)	47 ± 16	50 ± 16	44 ± 16	45 ± 18
Range	12 – 80	15 – 89	19 – 79	15 – 85
Mean weight (kg)	74 ± 18	72 ± 21	69 ± 16	67 ± 16
Mean height (cm)	164 ± 9	164 ± 10	166 ± 9	165 ± 10
Race (white/other, %)	86 / 14	77 / 23	88 / 12	94 / 6
Location (Europe/other, %)	26 / 74	28 / 72	58 / 42	63 / 37
Etiology (%)				
idiopathic/familial	70	77	63	58
CTD or autoimmune	30	18	17	19
CHD or HIV	—	5	19	22
Mean time from diagnosis (y)	2.3 ± 3.9	2.5 ± 2.7	3.7 ± 6.5	2.9 ± 5.5
Range	0.0 – 27.2	0.0 – 10.7	0.0 – 32.5	0.0 – 27.0

Mean values are provided ± standard deviation.
BREATHE-1 = Study AC-052-352, CHD = congenital heart disease, CTD = connective tissue disease, EARLY = Study AC-052-364, HIV = human immunodeficiency virus, WHO = World Health Organization.

Within the group of patients with connective tissue disease, 9.7 % (9 patients) in the bosentan group and 5.4 % (5 patients) in the placebo group had scleroderma. The HIV patients constituted 2.2 % (2 patients) and 5.4 % (5 patients) in the placebo and bosentan group, respectively. None of the enrolled patients had PAH associated with anorexigen use. The mean time from diagnosis was longest for the patients with congenital heart disease and shortest for patients with HIV etiology. Overall, the mean time from diagnosis to randomization was shorter among patients in the bosentan than placebo group (2.9 vs 3.7 years), regardless of etiology. However, median values often differed markedly from mean values, and results differed among analysis sets. This high variability is common with the difficult identification and lack of standard definition of the start of the disease.

Overall, 15.7% of the study population was on sildenafil at baseline, and the stratification procedure resulted in balanced treatment groups (14 patients on sildenafil in the bosentan group and 15 in the placebo group).

Treatments at baseline other than PAH treatments were relatively well balanced between the two treatment groups with the exception of the lower incidence of digoxin use (7.5% vs 17.4%) and the higher incidence of ethinylestradiol use (5.4% vs none) in the bosentan than placebo group.

Baseline characteristics are summarised in the Table 4 below.

Table 4 - Functional measures at baseline in the EARLY and BREATHE 1 studies in pulmonary arterial hypertension

	BREATHE-1		**EARLY**	
	Placebo (n = 69)	**Bosentan 125mg b.i.d (n = 74)**	**Placebo (n = 92)**	**Bosentan (n = 93)**
PVR (dyn·sec/cm^5)	n = 65	n = 74	n = 92	n = 92
Mean ± SD	880 ± 540	884 ± 412	805 ± 369	839 ± 531
Median	800	888	728	665
Range	133 – 3727	196 – 2067	171 – 2097	140 – 2922
mPAP (mmHg)	n = 69	n = 74	n = 89	n = 81
Mean ± SD	53.4 ± 16.6	52.8 ± 14.5	52.4 ± 16.0	53.7 ± 19.0
Median	51	52	53	51
Range	26 – 109	28 – 92	25 – 98	26 – 115
mRAP (mmHg)	n = 67	n = 74	n = 88	n = 81
Mean ± SD	8.9 ± 5.1	9.7 ±5.4	7.7 ± 5.1	7.0 ± 4.6
Median	8	8	7	6
Range	0.5 – 20	1 – 27	0 – 28	0 – 25
Cardiac index (L/min/m^2)	n = 68	n = 74	n = 87	n = 81
Mean ± SD	2.43 ± 0.69	2.46 ± 0.82	2.66 ± 0.62	2.75 ± 0.77
Median	2.33	2.41	2.69	2.55
Range	1.35 – 4.16	1.19 – 5.84	1.57 – 4.29	1.66 – 5.32
6-min walk distance (m)	n = 69	n = 74	n = 92	n = 93
Mean ± SD	344 ± 76	326 ± 73	431 ± 91	438 ± 86
Median	359	333	436	440
Range	150 – 449	159 – 465	178 – 660	251 – 598
Patients using supplemental O_2 during the walk test (%)	23.0	15.0	5.5	2.3

BREATHE-1 = Study AC-052-352, EARLY = Study AC-052-364, mPAP = mean pulmonary artery pressure, mRAP = mean right atrial pressure, PVR = pulmonary vascular resistance, SD =standard deviation.

When compared with the functional class III and IV patients enrolled in the pivotal BREATHE-1 trial, patients in EARLY were clearly different with regard to objective functional measures. At baseline, the class II patients in EARLY were characterized by a greater 6-minute walk distance (6-MWD) and cardiac index and a lower PVR and mean right atrial pressure (mRAP) than seen in the class III/IV patients in BREATHE-1. Mean PAP was similar in both studies.

Co-primary efficacy endpoint: Pulmonary Vascular Resistance (PVR)

Results from the main analysis of the co-primary endpoint on PVR demonstrated a statistically significant 22.6% reduction in PVR with bosentan compared with placebo (95% CL −33.5, −10.0, P < 0.0001, Mann-Whitney U-test) as shown in Table 5. After 6 months of treatment, mean PVR was decreased from baseline in the bosentan group (−69 ± 53 dyn.sec.cm^{-5}, ± standard error (SEM)) and increased in the placebo group (128 ± 50 dyn.sec.cm^{-5}). Similar results were observed in all other analyses as shown in the table below.

Table 5 - EARLY: Analyses of PVR percent of baseline at Month 6

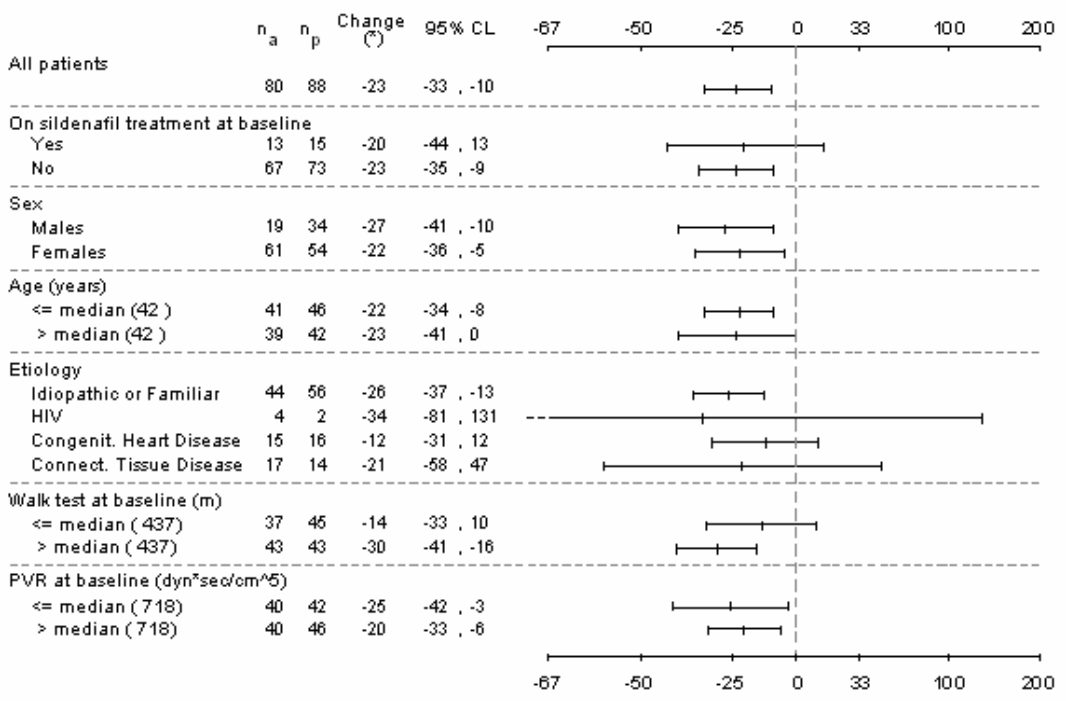
Analysis	Treatment effect: % change *vs* placebo (95% CL of % change)	P value*
All randomized set (main analysis)	–22.6 (–33.5, –10.0)	< 0.0001
Alternate analysis sets		
All randomized for PVR set	–22.6 (–33.5, –10.0)	< 0.0001
All treated set	–22.6 (–33.5, –10.0)	< 0.0001
Per protocol for PVR set	–24.5 (–34.5, –12.9)	< 0.0001
Alternate substitution rules (all-randomized set)		
No worst substitution (only carry forward)	–25.3 (–33.5, –16.0)	< 0.0001
Including post-treatment values	–20.4 (–31.0, –8.2)	< 0.0001
Including post-treatment values for only missing (derived) values	–21.3 (–32.0, –9.0)	< 0.0001
Including post-treatment values + carry forward from baseline	–19.3 (–29.5, –7.5)	< 0.0001
Including post-treatment values for only missing (derived) values + carry forward from baseline	–20.1 (–30.5, –8.3)	< 0.0001
All randomized excluding unblinded patients	–21.0 (–32.1, –8.1)	< 0.0001

*p value determined using the Mann-Whitney U-test.
PVR = pulmonary vascular resistance.

Baseline PVRs were similar between treatment groups in each stratum of the stratification factor (i.e., presence or absence of stable sildenafil therapy at baseline), but were higher in patients on concomitant sildenafil (1006 and 951 dyn.sec.cm^{-5} mean in bosentan and placebo groups, respectively) than in those not taking sildenafil (821 and 772 dyn.sec.cm^{-5}, respectively). However, the bosentan treatment effect was similar in the two subgroups (–20.4%, P = 0.0478 on sildenafil and –23.1%, P < 0.0001 not on sildenafil; Mann-Whitney U-test). The treatment effect remained statistically significant when adjusted for the stratification factor at randomization (p<0.0001 using van Elteren's test).

Subgroup analyses defined by patient gender, age, disease aetiology, and baseline values for PVR and walk distance showed a consistent benefit with bosentan treatment in all subgroups analyzed (gender and age were planned, disease aetiology and baseline values for PVR and walk distance were added post-hoc, Figure 3). The placebo-corrected percent changes in PVR in subgroups ranged from −12.3% to −34.2%, with P < 0.05 (Mann-Whitney U-test) for all comparisons between treatments except in the small subgroups of patients with an aetiology other than idiopathic/familial PAH.

Figure 3 - EARLY: Placebo-corrected percent of baseline at Month 6 for PVR in strata of the stratification factor and subgroups, all randomized set



(*) Percent change over placebo = (ratio of geometric means - 1)*100

CL = confidence limits, HIV = human immunodeficiency virus, n_a = number on active treatment, n_p = number on placebo PVR = pulmonary vascular resistance.

Further to the request from the CHMP, the MAH provided statistical analyses of PVR adjusted for the baseline values of PVR and 6-minute walk distance. The influence of the stratification factor at randomization (presence/absence of sildenafil treatment at baseline), of selected covariates anticipated at blind in the statistical analysis plan (gender, age, pooled site), and of *post-hoc* selected covariates (aetiology, baseline 6MWT and PVR) on treatment effect for 6MWT and PVR was explored by introducing, one at a time, each of the quoted variables as a stratification factor in a stratified Wilcoxon-Mann-Whitney test.

Similarly to the main analysis, the p-values resulting from adjusted statistical testing were < 0.0001, confirming that the conclusions of the study are not sensitive to the inclusion of the selected covariates.

Co-primary efficacy endpoint: 6-minute walk test

Because a statistically significant treatment effect was observed in the first co-primary endpoint regarding PVR, hypothesis testing for the second co-primary endpoint on 6-minute walk distance was undertaken. The comparison between treatments did not reach statistical significance (Median +13.8m, 95% CL −1.4, 29.4, P = 0.0758, Mann-Whitney U-test).

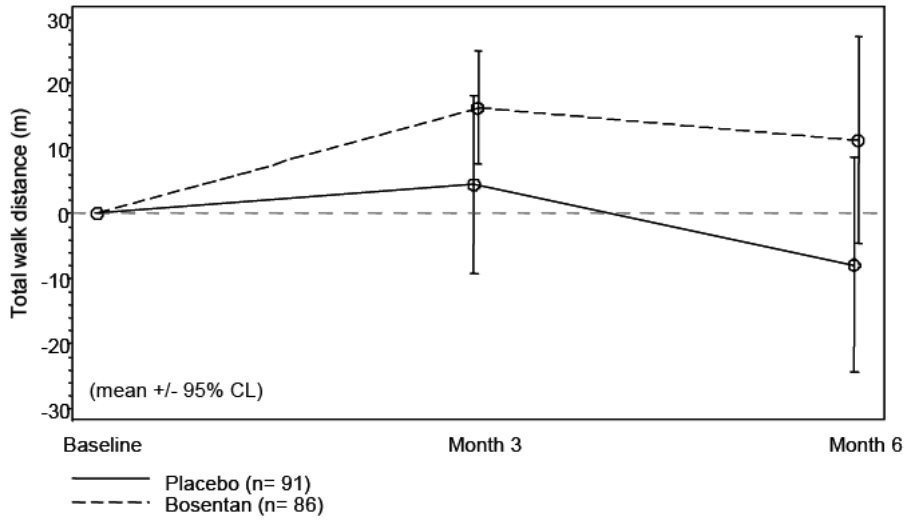
Table 6 - EARLY: Analyses of the change from baseline to Month 6 in 6-minute walk distance

Analysis	Median treatment effect in meters (95% CL)	P value*
All-randomized set (main analysis)	13.8 (–1.4, 29.4)	0.0758
Alternate analysis sets		
All randomized for 6MWT	13.8 (–1.4, 29.4)	0.0758
All treated	13.8 (–1.4, 29.4)	0.0758
Per protocol for 6MWT	15.0 (–0.2, 30.7)	0.0548
Alternate substitution rules (all-randomized set)		
No worst substitution (only carry forward)	11.1 (–3.0, 25.3)	0.1257
Including post-treatment values	14.8 (–0.4, 29.6)	0.0571
Including post-treatment values for only missing (derived) values	15.3 (0.7, 30.6)	0.0421
Including post-treatment values + carry forward from baseline	14.2 (–0.8, 28.9)	0.0627
Including post-treatment values for only missing (derived) values + carry forward from baseline	14.8 (0.3, 29.7)	0.0466
All randomized excluding unblinded patients	12.3 (–2.5, 27.7)	0.1057

* p values determined using the Mann-Whitney U-test.
6MWT = 6-minute walk test.

An increase from baseline in walk distance with bosentan was observed at the Month-3 assessment (median +14.5m; 95% CL 5.0, 24.0), and the increase was maintained at the 6-month assessment.

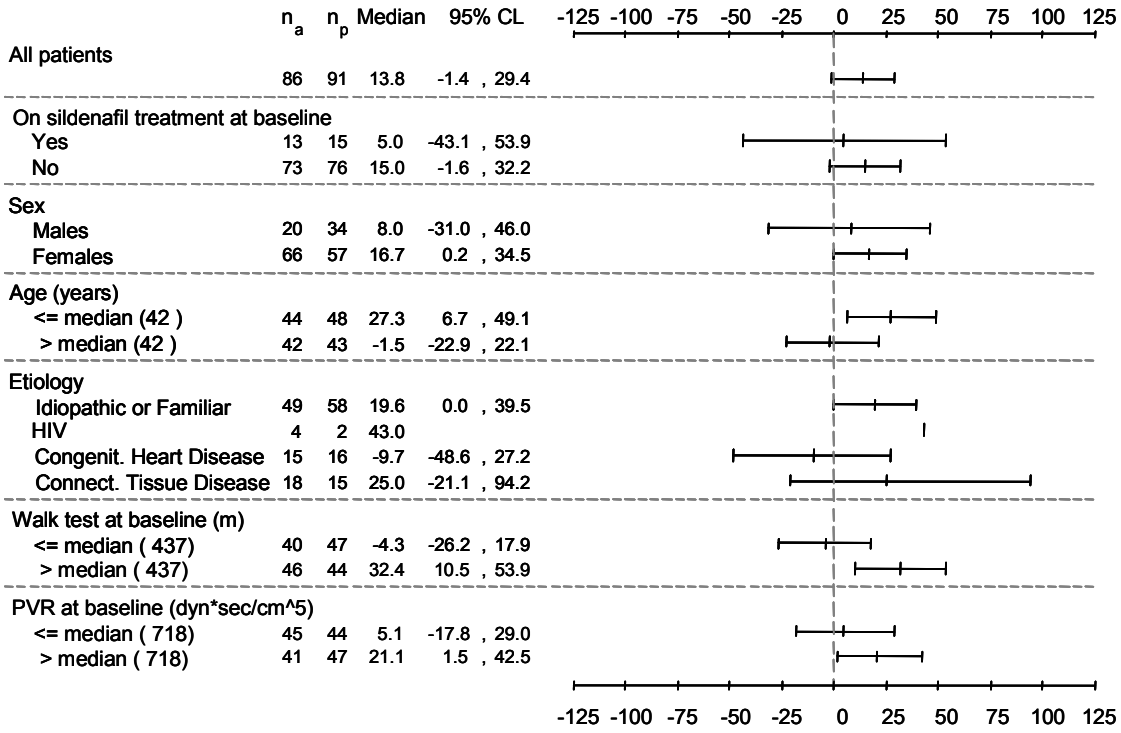
Figure 4 - Walk test: Change from baseline to Month 6, all-randomized set



When classifying patients according to the stratification factor at randomization, after 6 months of treatment, the median bosentan treatment effect was +5.0m for patients on sildenafil and +15.0m for those not on sildenafil at baseline (95% CL −43.1, 53.9, P = 0.8551 and 95% CL −1.6, 32.2, P=0.0795, respectively).

In subgroup analyses an improved median walk distance with bosentan compared with placebo was observed in most subgroups evaluated (Figure 5). An improved median walk distance with bosentan compared with placebo reached $P < 0.05$ in females, patients below the median age (42 years), and patients with a baseline walk distance or PVR above the median (437 meters and 718 dyn.sec.cm^{-5}).

Figure 5 - EARLY: Placebo-corrected median changes in 6-minute walk distance from baseline to Month 6 in strata of the stratification factor and subgroups, all-randomized set



CL = confidence limits, HIV = human immunodeficiency virus, n_a = number on active treatment, n_p = number on placebo, PVR = pulmonary vascular resistance.

As requested by the CHMP, the MAH provided statistical analyses of the 6-minute walk distance adjusted for the baseline values of PVR and 6-minute walk distance. The influence of the stratification factor at randomization (presence/absence of sildenafil treatment at baseline), of selected covariates anticipated at blind in the statistical analysis plan (gender, age, pooled site), and of *post-hoc* selected covariates (aetiology, baseline 6MWT and PVR) on treatment effect for 6MWT and PVR was explored by introducing, one at a time, each of the quoted variables as a stratification factor in a stratified Wilcoxon-Mann-Whitney test.

Results are presented in Table 7 and showed that the conclusions of the study are not sensitive to the inclusion of the selected covariates.

Table 7 - 6MWT: Adjusted statistical analysis of the change from baseline to Month 6, all randomized set

Analysis set: All randomized
Van Elteren's test (stratified Wilcoxon-Mann-Whitney)
Factors one at a time

Stratum	n	p-value
Sildenafil treatment at baseline	177	0.0868
Sex	177	0.0585
Age <= / > median	177	0.0704
Pooled sites	177	0.1029
Etiology	177	0.0899
6MWT at BL (<=/> median)	177	0.0635
PVR at BL (<=/> median)	177	0.0743

An exploratory analysis of the change in 6MWT vs WHO/NYHA functional class at Month 6 was performed (see Table 8 below).

Table 8 - AC-052-364 (EARLY, double-blind phase): Change in 6MWT vs WHO/NYHA functional class at Month 6

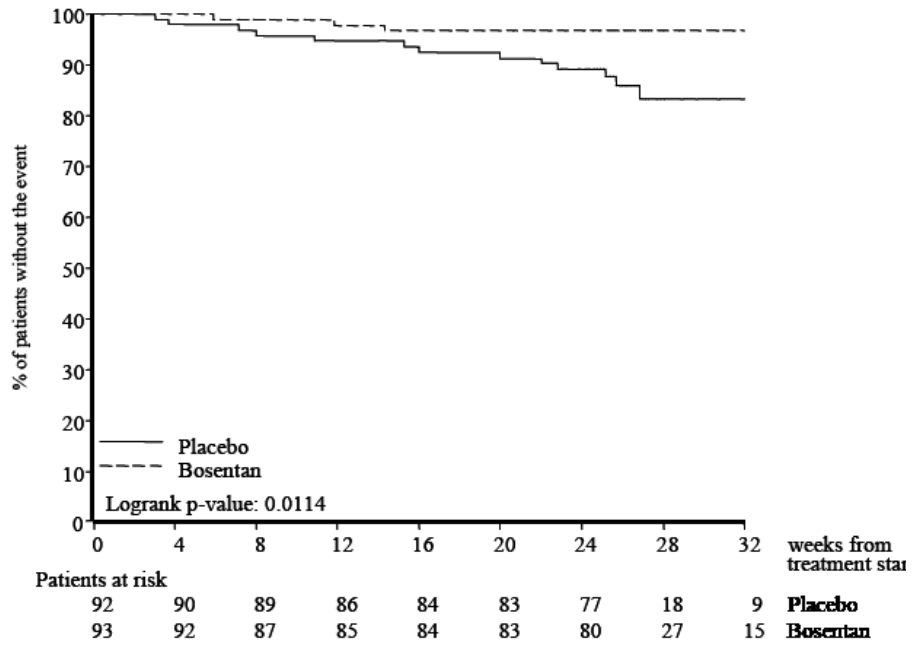
Analysis set: All randomized

				NYHA at month 6							
	n	Change in walk test to month 6	n	I		II		III		IV	
				No.	%	No.	%	No.	%	No.	%
Placebo	91	<0 m	41	1	1.1%	32	35.2%	5	5.5%	3	3.3%
		>=0 m	50	4	4.4%	42	46.2%	4	4.4%	-	
Bosentan	86	<0 m	31	-		28	32.6%	1	1.2%	2	2.3%
		>=0 m	55	6	7.0%	49	57.0%	-		-	

Secondary endpoint: Time to clinical worsening

The time from treatment start to clinical worsening was the main secondary endpoint, and results over the duration of double-blind treatment are presented in Figure 6. A delay in the time to clinical worsening was observed with bosentan compared with placebo, which could be discerned before 16 weeks of treatment. The hazard ratio was 0.227, corresponding to a proportional risk reduction of 77% (95% CI 20%–94%, P = 0.0114 log-rank test).

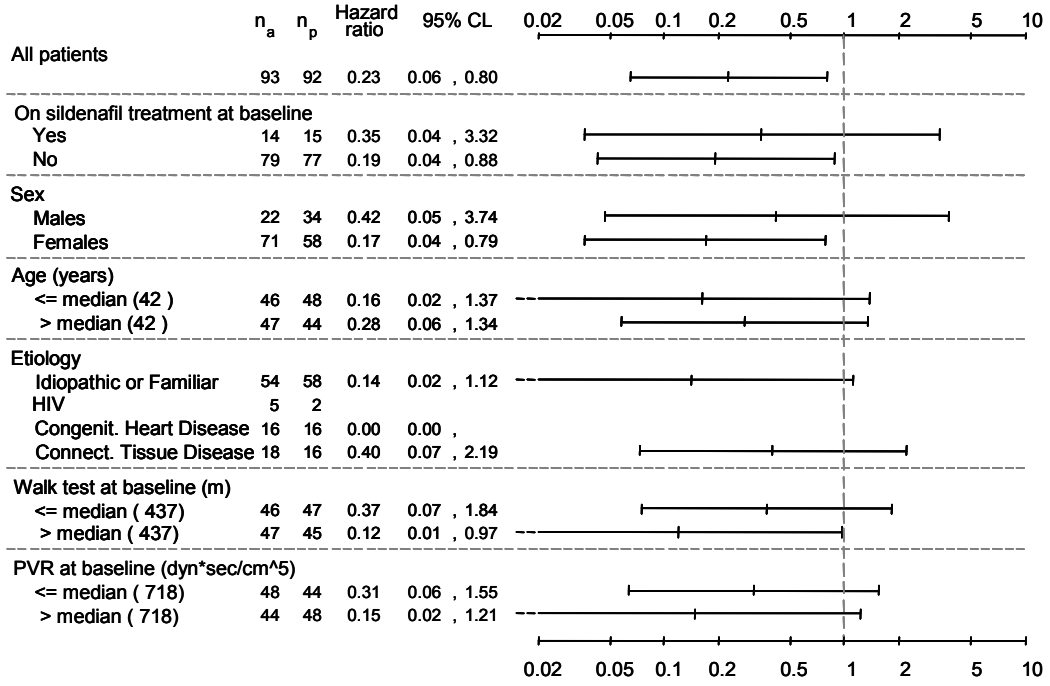
Figure 6 - EARLY: Kaplan-Meier estimates of time to clinical worsening, all-randomized set



Patients are censored at the end of the treatment period.

As with the co-primary endpoints, the time to clinical worsening was evaluated in strata based on sildenafil use at baseline and in a variety of subgroups of the all-randomized set (Figure 7).

Figure 7 - EARLY: Hazard ratios for clinical worsening for bosentan vs placebo in strata of the stratification factors and subgroups, all-randomized set



CL = confidence limits, HIV = human immunodeficiency virus, n_a = number on active treatment, n_p = number on placebo, PVR = pulmonary vascular resistance.

The causes of clinical worsening are summarised in the table below.

Table 9 - Summary of causes of clinical worsening, all-randomized set

Cause	Placebo N=92 No.	%	Bosentan N=93 No.	%
Total pts with at least one cause	13	14.1%	3	3.2%
SYMPTOMATIC PROGRESSION OF PAH*	12	13.0%	2	2.2%
HOSPITALIZATION FOR PAH	3	3.3%	1	1.1%
DEATH	1	1.1%	1	1.1%

DEATH includes 'DEATH' and 'AE LEADING TO DISCONTINUATION AND DEATH'.
HOSPITALIZATION FOR PAH includes hospitalization occurring at any time during clinical worsening.

Out of the 12 patients in the placebo group that experienced symptomatic progression of PAH, three patients had increased dyspnea as the only symptom of clinical worsening. Three patients presented with decreased 6-MWD. The remaining eight patients which presented with clinical symptoms were later either hospitalized due to worsening or prematurely discontinued study treatment due to worsening. In the bosentan treated group, one of the patients with symptomatic progression was hospitalized and the other patient prematurely discontinued medication due to worsening of PAH.

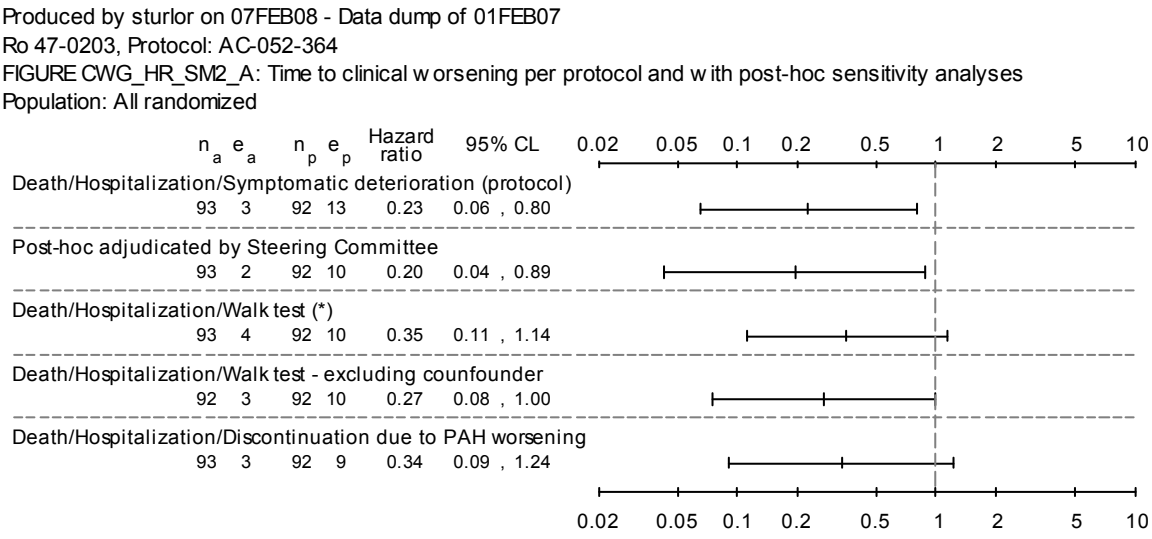
In addition, exploratory sensitivity analyses of clinical worsening were performed as follows:

- Analysis excluding events in 4 worsening patients (3 on placebo and 1 on bosentan) considered by post hoc expert review as incomplete or not convincing enough for a final diagnosis of clinical worsening.
- Analyses excluding symptomatic progression, using alternative definitions of worsening, as follows:
  - Death, hospitalisation due to PAH, or ≥ 20% decrease from baseline in 6MWT, including all patients who stopped the walk test prematurely for any reason.
  - Death, hospitalisation due to PAH, or ≥ 20% decrease from baseline in 6MWT, excluding patients who stopped the walk test prematurely due to limitations not associated with PAH.

- Death, hospitalisation due to PAH, or early treatment escape, i.e., premature discontinuation of study drug due to PAH worsening.

Results of these sensitivity analyses and of the analysis predefined in the protocol are presented in **Figure 8** below. The point estimates (hazard ratios) for time to clinical worsening and their 95% confidence boundaries were consistent across analyses.

Figure 8 - AC-052-364 (EARLY, double-blind phase): Time to clinical worsening, per protocol and post hoc sensitivity analyses, all randomized set



n_a = number of exposed patients in active treatment; e_a = number of events in active treatment
n_p = number of exposed patients in placebo; e_p = number of events in placebo
(*) 6MWT decrease must not be invalidated by a subsequent change from baseline greater then -10%

Secondary endpoint: WHO functional class

All patients were WHO class II at baseline and at Month 6 improvement to class I was observed in 6.9% and 5.5% of bosentan- and placebo-treated patients, respectively (P = 0.7629). 3.4% of patients on bosentan worsened to class III or IV compared with 13.2% of patients on placebo (P = 0.0285, Fisher exact test).

Secondary endpoint: Borg dyspnoea index

The small increase in patient-rated dyspnoea in the placebo group and the small decrease with bosentan treatment resulted in a mean treatment effect of – 0.4 on the Borg scale from 0 to 12 (P= 0.2599, Mann-Whitney U-test).

Secondary endpoint: haemodynamic parameters (mRAP, mean pulmonary artery pressure, SVO_2)

In addition to PVR, the haemodynamic variables mRAP, mPAP, TPR, cardiac index, and SVO_2 were also evaluated at rest, and the changes from baseline to Month 6 analyzed. As with PVR, a treatment effect with bosentan compared with placebo was observed in each of the haemodynamic variables and in SVO_2. The decreases in mPAP and TPR and the increases in cardiac index and SVO_2 with bosentan were associated with P-values < 0.05 (Mann-Whitney U-test).

Exploratory endpoint: BNP concentration

BNP, a known biomarker of disease severity in PAH, was measured in this study as an indicator of disease progression. During double-blind treatment, a small mean decrease from baseline in serum BNP concentration was observed with bosentan compared with a small mean increase with placebo, which resulted in a mean –26 ng/L (95% CL –79, 26) and median –4 ng/L (95% CL –23, 10) treatment effect (P = 0.4391, Mann-Whitney U-test). Due to the central laboratory's concern about the

reliability of the BNP assay in serum, existing serum samples were reanalyzed using a validated assay for N-terminal-pro-BNP, the more stable precursor of BNP. As with BNP, a mean decrease was observed with bosentan and a mean increase with placebo, resulting in mean and median treatment effects of −471 ng/L (95% CL −749, −192) and −150 ng/L (95% CL −289, −61), respectively (P = 0.0003, Mann-Whitney U-test).

Exploratory endpoint: SF-36 questionnaire

The changes in patients' quality of life over the 6-month treatment period were assessed using the generic SF-36 questionnaire. In the SF-36 domains, higher scores indicate a better condition, and increases with bosentan compared with placebo were observed in all but the role emotional domain. The changes in the SF-36 health transition item indicated that more patients on bosentan than on placebo felt their condition had improved (57.3% vs 38.3%; relative risk 1.5 (95% CL 1.07, 2.10)). The proportion of patients reporting worsening in this domain did not differ between groups (18.7 % vs 18.5 % for bosentan and placebo, respectively).

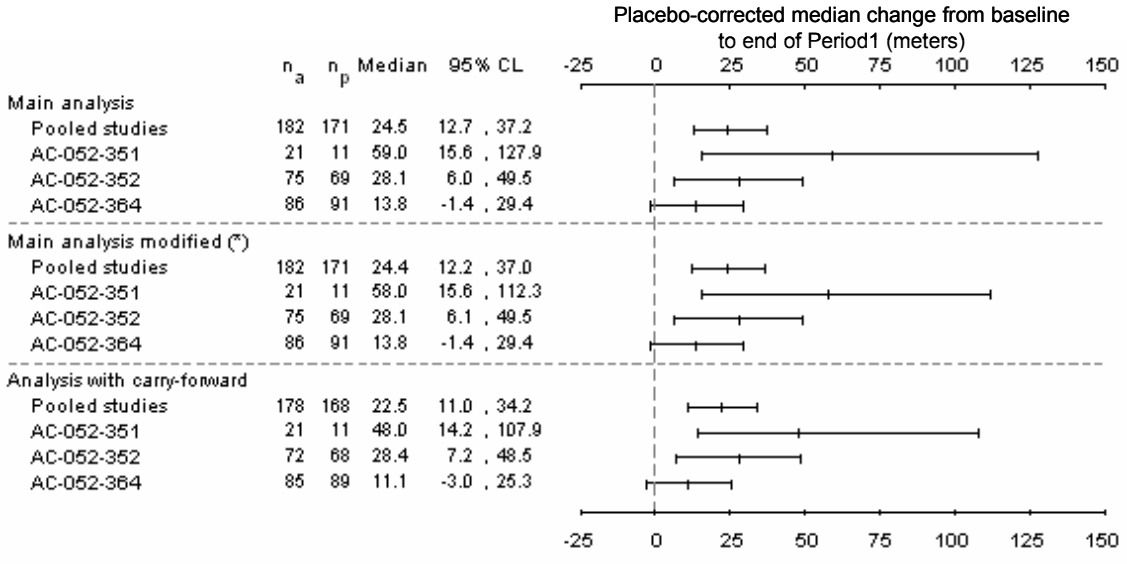
2.1.2 Analysis performed across trials (pooled analyses and meta-analysis)

Data from the two previously conducted phase III trials in class III/IV PAH (BREATHE-1, AC-051-351) and from the EARLY trial in class II PAH were pooled to evaluate the efficacy of bosentan as assessed by the 6-minute walk test over a broad spectrum of PAH patients. The methods of analysis introduced for pooled data were also applied to the individual studies.

The two treatment groups of the pool were well matched with regard to patient demographics except for a higher proportion of females in the bosentan group (76.7% vs 71.5% on placebo, with a concomitantly smaller proportion of males), which was due to the imbalance between treatment groups in the EARLY trial. Most patients of "other" race were Hispanic (9 and 10 patients in the bosentan and placebo groups, respectively). Approximately 51% of patients in the pool were class II, 46% class III, and 3% class IV at study entry.

Results are presented in Figure 9 below.

Figure 9 - Pooled and individual studies: Placebo-corrected median change from baseline to end of Period 1 in 6-minute walk distance, main and alternate analyses on the all-randomized set (AC-052-351, BREATHE-1 and EARLY)



* Worst percent change in place of 0 substitution for patients who were alive.

Note: Period 1 was to Week 12 in AC-052-351, to Week 16 in AC-052-352 (BREATHE-1), and to Month 6 in AC-052-364 (EARLY).

2.1.3 Open-label extension of EARLY study: Study AC-052-364-OL

Further to a request for supplementary information from the CHMP, the MAH provided a progress report on the open-label extension period of the EARLY study, based on data collected as of 14 December 2007.

Overall, 157 patients were enrolled into the open-label extension to the EARLY study, out of 185 included in the double-blind phase. The main reason for discontinuation from the double-blind study and consequently not rolling over to the open-label extension was PAH worsening for placebo patients, and elevated LFTs for bosentan patients.

The following exploratory efficacy and safety data are collected during the open-label treatment period: 6-monthly assessments of the 6MWT and NYHA/WHO functional class, new PAH-specific treatments, reasons for premature discontinuation, AEs leading to discontinuation, occurrences of pre-defined LFT and haemoglobin (Hb) changes.

In the progress report submitted, summaries were provided for the data collected continuously, i.e., for all parameters except new/concomitant PAH-specific treatment and occurrences of LFT/Hb changes which will be collected only at study end.

- Exposure results

Exposure data as per the cut-off date are given in Table 10. Data in patients randomized to bosentan cover a mean/median treatment duration of almost 2 years.

Table 10 - AC-052-364-OL (EARLY open-label extension): Summary of exposure to study drug, safety set

	Ex-Placebo N=80	Ex-Bosentan N=93	All patients N=173
Exposure (months) (*)			
n	80	93	173
Mean	15.8	20.9	18.5
Standard deviation	7.0	9.1	8.6
Standard error	0.8	0.9	0.7
Median	15.2	21.4	19.5
Q1 , Q3	13.2 , 22.0	19.0 , 27.9	13.8 , 24.4
Min , Max	0.1 , 26.7	0.2 , 37.9	0.1 , 37.9
Patients exposed [n (%)]			
n	80	93	173
At least 6 months	69 86.3%	81 87.1%	150 86.7%
At least 12 months	67 83.8%	77 82.8%	144 83.2%
At least 18 months	29 36.3%	74 79.6%	103 59.5%
At least 24 months	13 16.3%	34 36.6%	47 27.2%

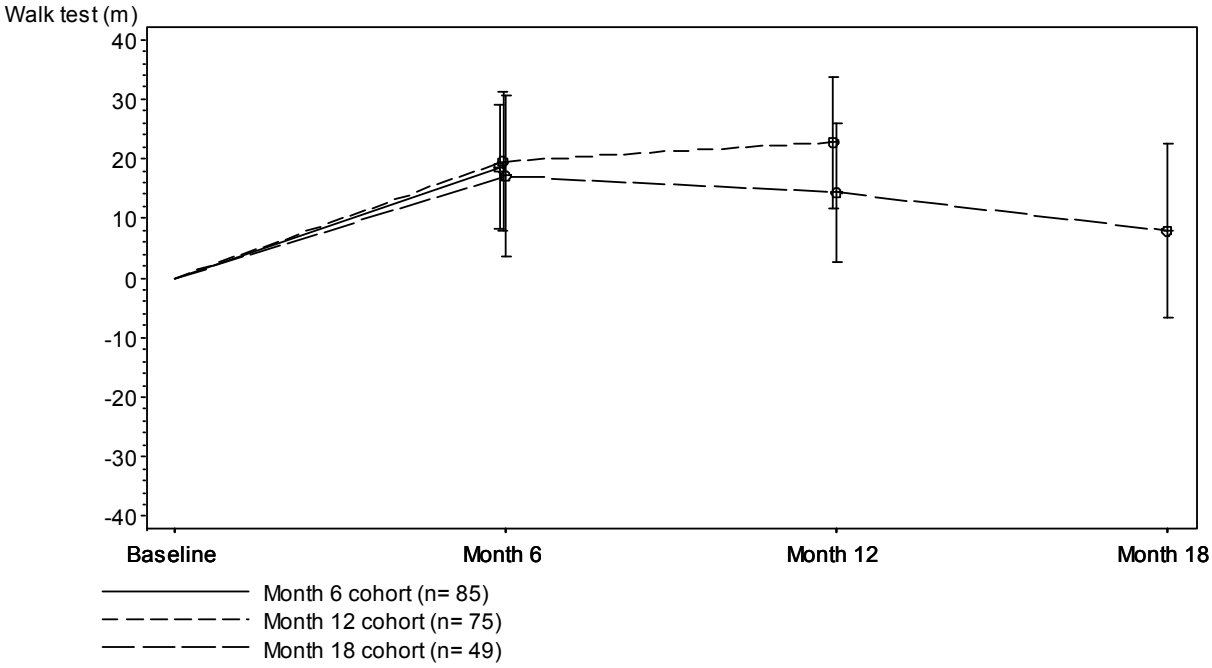
(*) From study treatment start date to study treatment discontinuation or death or cutoff date

- Changes in the 6MWT

Available data are in favour of the maintenance of the response to bosentan on exercise capacity after one year of treatment in the WHO functional class II population (Figure 10). It should be noted that data beyond Month 12 are not yet complete.

Figure 10 - AC-052-364-OL (EARLY open-label extension): Long-term effect of bosentan on 6MWT

Produced by sturlor on 24JAN08 - Data dump of 18DEC07 - Cutoff date: 14DEC07
Ro 47-0203, Protocol: AC-052-364 AC-052-364-OL
FIGURE WTCG_T: Change from baseline in walk test to scheduled timepoints by cohorts (mean ± 95% CL)
Analysis set: All treated
Treatment: Ex-Bosentan



- Changes in NYHA/WHO functional class

The proportions of patients who showed improvement or worsening, respectively, in functional class during open-label treatment are summarised in Table 11 and Table 12.

Table 11 - AC-052-364-OL (EARLY open-label extension): WHO/NYHA functional class – improved patients to scheduled timepoints by cohorts, all treated set

Produced by sturlor on 18DEC07 - Data dump of 18DEC07 - Cutoff date: 14DEC07
Ro 47-0203, Protocol: AC-052-364 AC-052-364-OL
Table NYHACS_T: NYHA functional class: improved patients to scheduled timepoints by cohorts
Analysis set: All treated

	Ex-Placebo N=80	Ex-Bosentan N=93	All patients N=173
Month 6 cohort			
n	71	87	158
Improved to month 6	10 14.1%	6 6.9%	16 10.1%
Month 12 cohort			
n	47	79	126
Improved to month 6	6 12.8%	5 6.3%	11 8.7%
Improved to month 12	7 14.9%	5 6.3%	12 9.5%
Month 18 cohort			
n	20	55	75
Improved to month 6	2 10.0%	2 3.6%	4 5.3%
Improved to month 12	2 10.0%	3 5.5%	5 6.7%
Improved to month 18	2 10.0%	6 10.9%	8 10.7%
Month 24 cohort			
n	5	23	28
Improved to month 6	0	1 4.3%	1 3.6%
Improved to month 12	0	2 8.7%	2 7.1%
Improved to month 18	0	3 13.0%	3 10.7%
Improved to month 24	0	4 17.4%	4 14.3%

Table 12 - AC-052-364-OL (EARLY open-label extension): WHO/NYHA functional class – worsened patients to scheduled timepoints by cohorts, all treated set

Produced by sturlor on 01FEB08 - Data dump of 18DEC07 - Cutoff date: 14DEC07
Ro 47-0203, Protocol: AC-052-364 AC-052-364-OL
Table NYHAWCS_T: NYHA functional class: worsened patients to scheduled timepoints by cohorts
Analysis set: All treated

	Ex-Placebo N=80		Ex-Bosentan N=93		All patients N=173	
Month 6 cohort						
n	71		87		158	
Worsened to month 6	5	7.0%	2	2.3%	7	4.4%
Month 12 cohort						
n	47		79		126	
Worsened to month 6	3	6.4%	0		3	2.4%
Worsened to month 12	3	6.4%	4	5.1%	7	5.6%
Month 18 cohort						
n	20		55		75	
Worsened to month 6	1	5.0%	0		1	1.3%
Worsened to month 12	1	5.0%	3	5.5%	4	5.3%
Worsened to month 18	3	15.0%	3	5.5%	6	8.0%
Month 24 cohort						
n	5		23		28	
Worsened to month 12	0		2	8.7%	2	7.1%
Worsened to month 18	1	20.0%	2	8.7%	3	10.7%
Worsened to month 24	2	40.0%	3	13.0%	5	17.9%

2.1.4 Discussion on clinical efficacy

The inclusion and exclusion criteria were adequate in selecting a less deteriorated group than studied in the previous trials, representative of the target population. Both primary endpoints of the EARLY study have been used in previous studies on bosentan and are considered relevant endpoints for evaluating treatment effect.

A number of different substitution rules were applied to handle missing data. The choice of rules is judged to be appropriate and sufficiently conservative. The imputation rules for handling missing values seem to have been established in relation with the baseline value of the primary endpoints PVR and 6MWT, for which thresholds were part of the inclusion criteria. Despite that, some patients have been excluded from the main analysis, with a higher rate of patients excluded in the bosentan group than in the placebo group. However, the applicant provided graphical presentations of analyses with alternative substitution rules applied to all randomised sets (either with or without worst substitution). The presentation showed consistency in the results on co-primary endpoints with the main analysis.

The patients enrolled in the study appear to be representative of the target population. No apparent differences were seen between the placebo and bosentan groups in the EARLY study. The only exception is the higher percentage of males enrolled in the placebo group. This differs, not only from the bosentan group in the present study, but also from the previous BREATHE-1 trial. Furthermore, 7 patients with PAH secondary to HIV were included in this study whereas PAH secondary to HIV is not an approved indication of Tracleer. The additional analyses on the co-primary endpoints conducted at the request of the CHMP, respectively excluding PAH-HIV patients and adjusting for pre-specified covariates including gender, showed results consistent with those of the main analysis.

Results of the EARLY study showed a statistically significant reduction of the PVR with bosentan compared to placebo. The effect was of similar magnitude as compared to that observed in studies with grade III populations. Changes in PVR are accepted as a marker of treatment effect in PAH and have been shown to be of prognostic importance.

At baseline, mean and median values of the 6MWD were similar in the bosentan and placebo groups and indicated that exercise capacity was relatively well preserved in both groups, reflecting grade II severity assessment. Based on the main analysis, no statistically significant effect was seen on the

6MWD between bosentan and placebo groups. Furthermore, the change in 6MWD remained under the threshold of clinically relevant improvement initially defined as > 35 meters.

The MAH provided supplementary analyses of change in 6-MWD in different subgroups with variable cut off baseline 6MWD values: > and < median 437 meters; > and < 400 meters; > and < 450 meters. The analysis of 6MWD in patients with a baseline value > 400 meters, corresponding to 64% of the EARLY study population, showed a clinically relevant, albeit not dramatic, effect of approximately 30 meters with borderline statistical significance. The consistency of the findings regarding clinical worsening and WHO functional class transition further supports the robustness of the results.

In the pooled analysis, the effect on exercise capacity (6MWD) is statistically significant due to the strong effect in the studies on patients in WHO class III-IV. All the point estimates are in favour of bosentan treatment, with a positive trend also seen in patients of WHO class II. However, no conclusion can be drawn based on the available data.

The time to clinical worsening was used as a secondary endpoint in this study. The definition of clinical worsening is somewhat different to the one used in the previous studies and was adjusted to better fit the less deteriorated subjects in the target group. This endpoint is a composite of objective and subjective variables which is debatable as it highly depends on investigator assessment. Especially, the evaluation of worsening of right heart failure could be difficult to standardise. An effect on the time to worsening in favour of bosentan was observed in the subgroup analysis, although not statistically significant (except for patients not treated with sildenafil and for females). The number of events is low and a longer observation time would have been preferable. Only weak differences were observed, driven by symptomatic criteria relating to functional capacity. The use of 'soft' symptoms and signs to characterise an outcome is of course debatable. However, when reviewing the data of the individual patients, it appears that the results in clinical worsening are clinically relevant since the first symptomatic event of clinical worsening in most cases was associated with or followed by more severe events. The analysis made by the MAH, using alternative definitions of clinical worsening resulted in consistent findings. This supports the assumption that the results on clinical worsening are robust and clinically relevant.

There was one hospitalisation related to PAH worsening in the bosentan group and 3 hospitalisations in the placebo group. Only one death occurred in each treatment group during the 6-month double-blind study period, therefore no conclusion can be drawn on survival.

The use of a supportive endpoint such as change in function in WHO class is adequate and clinically relevant. However, it is subject to variability depending on the investigator assessment and despite the clarifications from the MAH on missing values, it cannot be recognized as a robust criterion for assessment of efficacy.

The change in Borg dyspnoea class (which is a more objective parameter) as a supportive secondary endpoint does not add much to the information since this is already included in the main secondary endpoint.

The supportive data on quality of life tend to be in favour of bosentan treatment, however, not statistically significant. The results observed are in line with the improvement in symptoms but do not support any other claim.

The open-label extension data currently are in favour of the maintenance of the treatment effect of bosentan in functional class II PAH after one year.

2.2 Clinical safety

2.2.1 Study AC-052-364 (EARLY) safety results

- Patient exposure

The safety population used in the analysis included all 185 randomised patients. Patients were to be treated for at least 6 months and were exposed to bosentan treatment for a mean of 27.9 weeks (median 26.1 weeks) and up to 74.0 weeks. The duration of treatment was similar for those patients on placebo (mean 26.8 weeks, median 26.1 weeks). All safety data collected during double-blind treatment, regardless of duration, were included in the analysis.

The exposure to study treatment was quite similar in the two treatment groups, with 86.0% and 88.0% of patients receiving a full 24 weeks of bosentan and placebo treatment, respectively. Because the original study design continued double-blind treatment after the Month-6 visit, some patients received up to 74 weeks of double-blind treatment.

The majority of patients were treated per protocol and the mean daily dose did not differ between treatment groups (224 and 221 mg daily for the placebo and bosentan group, respectively).

- Adverse events

An overview of the AEs that occurred during the double-blind treatment period shows that, in general, the incidence of AEs was similar in the two treatment groups (Table 13).

Most events were considered by the investigator to be unrelated to study treatment. Only 33.3% and 28.3% of patients on bosentan and placebo, respectively, experienced an AE considered to be related to study drug. The events that were most often considered related to study treatment in both treatment groups were those known to be associated with bosentan therapy, including investigations denoting an elevation in liver aminotransferases or decrease in haemoglobin concentration, vascular disorders (e.g., flushing), headache, and peripheral oedema.

Table 13 - EARLY: Overall summary of treatment-emergent adverse events

	Number of patients (%)	
	Placebo (n = 92)	**Bosentan (n = 93)**
Patients with ≥ 1 AE	60 (65.2)	65 (69.9)
Patients with a treatment-related AE	26 (28.3)	31 (33.3)
Patients with a severe AE	13 (14.1)	10 (10.8)
Deaths*	1 (1.1)	1 (1.1)
Patients with a serious AE	8 (8.7)	12 (12.9)
Patients with an AE that led to discontinuation of study treatment	9 (9.8)	9 (9.7)
Patients discontinued due to abnormal liver function	0 (—)	6 (6.5)†

Note: Includes events that occurred during and up to 1 day after the end of double-blind treatment.
* Patients who died during double-blind treatment or experienced a treatment-emergent adverse event that led to permanent discontinuation of double-blind treatment and resulted in death.
† Included four patients with an adverse event of liver function test abnormal, one with ALT increased/AST increased, and one with hepatitis C/hepatitis.
AE = adverse event.

Adverse events experienced during or up to 1 day after the end of double-blind treatment are summarized in Table 14.

Table 14 - EARLY: Summary of treatment-emergent adverse events (including unrelated) during the double-blind treatment period, safety set

System Organ Class / Preferred Term	Placebo N=92 No.	%	Bosentan N=93 No.	%
ALL SYSTEM ORGAN CLASSES				
Total patients with at least one AE	60	65.2%	65	69.9%
Total number of AEs	220		182	
NASOPHARYNGITIS	8	8.7%	7	7.5%
LIVER FUNCTION TEST ABNORMAL	3	3.3%	7	7.5%
OEDEMA PERIPHERAL	7	7.6%	6	6.5%
NAUSEA	8	8.7%	5	5.4%
DIZZINESS	5	5.4%	5	5.4%
CHEST PAIN	4	4.3%	5	5.4%
OTHER	57	62.0%	57	61.3%

All AEs with an overall bosentan incidence < 5% are pooled under 'Other'.
AE = adverse event.

At least one AE was reported for 69.9% and 65.2% of bosentan- and placebo-treated patients, respectively. The most frequent events in the bosentan group were nasopharyngitis (7.5% vs 8.7% in the placebo group) and an abnormal liver function test (7.5% vs 3.3%), and that in the placebo group was headache (9.8% vs 4.3% in the bosentan group). Because of an association with bosentan treatment, events that could denote an elevation in liver enzymes, decreased haemoglobin concentration, or oedema were summarized together to obtain a better estimate of these adverse experiences. In this combined analysis, events denoting elevated liver enzymes were more frequent with bosentan than placebo (11.8% vs 6.5%), as were events denoting a decrease in haemoglobin (6.5% vs 3.3%). The incidences of events denoting oedema were similar in the two treatment groups (9.7% and 9.8% with bosentan and placebo, respectively) as was the individual component event of peripheral oedema (6.5% and 7.6%, respectively).

Individual events that were more frequent on placebo than bosentan (≥ 4% difference) included pulmonary hypertension, headache, diarrhoea, rhinitis, upper abdominal pain, and dyspepsia.

Nine patients in each treatment group had study treatment discontinued because of a variety of adverse events. An event denoting abnormal liver function led to the discontinuation of six bosentan-treated patients (6.5% vs none on placebo), and pulmonary hypertension led to the discontinuation of five placebo-treated patients (5.4% vs 1.1% on bosentan).

- Serious adverse events and deaths

Deaths

Only deaths that occurred on double-blind treatment or were the outcome of a treatment-emergent event that led to the permanent discontinuation of double-blind treatment were reported for Period 1 of the study. Two such events occurred, one in each treatment group.

One patient in the bosentan group died on Day 101 while on double-blind treatment. The sudden death (following a fall with subsequent headache) was possibly due to the underlying disease, antiphospholipid syndrome and systemic lupus erythematosus, but an autopsy was not performed. The investigator considered the events to be related to study treatment and to sildenafil treatment.

One patient in the placebo group experienced the SAEs of respiratory failure and spinal cord hemorrhage on Day 27, was hospitalized and discontinued study treatment. Despite the investigator breaking the treatment blind to better evaluate the event and an emergency operation, the patient continued to deteriorate and died on Day 31. The investigator judged these events to be unrelated to study treatment.

Serious adverse events

Serious adverse events were experienced by 12.9% and 8.7% of bosentan- and placebo-treated patients, respectively. No individual SAE was reported by more than two patients in either treatment group. Events reported by two patients included syncope in bosentan-treated patients and pulmonary arterial hypertension and right ventricular failure in placebo-treated patients.

One patient on bosentan had a history of CREST syndrome and was diagnosed with autoimmune hepatitis and hepatic cirrhosis, which were considered by the investigator to be unrelated to study treatment. Clinical features and laboratory abnormalities already present at baseline were suggestive of pre-existing liver disease. On the day of completion, the patient had an AE of abnormal liver function test, which was judged by the investigator to be serious and related to study treatment. Consequently, open-label bosentan treatment was not started as planned, and the abnormality resolved.

A similar proportion of patients in both bosentan and placebo groups had double-blind treatment permanently discontinued because of an AE (9.7% and 9.8%, respectively).

One of the 28 patients who permanently discontinued study treatment (either prematurely or at the end of the double-blind treatment period) and were followed for 28 days post treatment experienced an SAE during the safety follow-up. The patient (placebo) was hospitalized with menorrhagia during the study, and 6 days after completing the double-blind treatment period, she had a hysterectomy and oophorectomy. The events resolved without sequelae and were not considered by the investigator to be related to study treatment.

In addition, one patient (placebo) had a positive pregnancy test on Day 34 of the study, with conception estimated on Day −11 and a missed abortion diagnosed on Day 35. The events resolved without sequelae and were judged by the investigator to be not related to study treatment.

- Laboratory findings

The incidences of marked laboratory abnormalities are summarized in Table 15. The incidences of marked decrease in hemoglobin concentration and marked increases in ALT and AST were greater with bosentan than with placebo.

Table 15 - Incidence of special treatment-emergent laboratory abnormalities during the double blind treatment period, safety set

Laboratory abnormality	Placebo N=92 No.	%	Bosentan N=93 No.	%
ALT > 3*upper std	2 / 91	2.2%	10 / 92	10.9%
AST > 3*upper std	0 / 91		8 / 92	8.7%
ALT or AST > 3*upper std	2 / 91	2.2%	12 / 92	13.0%
ALT > 3*upper std and <= 5*upper std	2 / 91	2.2%	3 / 92	3.3%
ALT > 5*upper std and <= 8*upper std	0 / 91		2 / 92	2.2%
ALT > 8*upper std	0 / 91		5 / 92	5.4%
AST > 3*upper std and <= 5*upper std	0 / 91		5 / 92	5.4%
AST > 5*upper std and <= 8*upper std	0 / 91		1 / 92	1.1%
AST > 8*upper std	0 / 91		2 / 92	2.2%
Hemoglobin < 75% of standard lower limit	0 / 91		5 / 92	5.4%
Hemoglobin <= 8 g/dl	0 / 91		3 / 92	3.3%
Hemoglobin > 8 g/dl and <= 10g/dl	1 / 91	1.1%	2 / 92	2.2%
Creatinine with increase from baseline greater than 50%	2 / 74	2.7%	0 / 72	

Values given are the number of patients with at least one abnormality/number of patients (%).
ALT = alanine aminotransferase, AST = aspartate aminotransferase, std = standard.

An increase in liver aminotransferase to > × 3 the upper limit of normal (ULN) during the double-blind treatment period was observed in 12 (13.0%) patients on bosentan compared with two (2.2%) on placebo. Among bosentan-treated patients, the increase in ALT and/or AST was to

> 8 × ULN in five patients. The elevations were asymptomatic in all cases. There was one case of an additional liver abnormality in a patient who had an associated increase in alkaline phosphatase to > 3 × ULN.

Most of the elevations first appeared during the first 20 weeks of bosentan treatment, although in one case (patient with autoimmune hepatitis), the elevation first appeared after 67 weeks of treatment.

The two cases with hepatitis (one with autoimmune hepatitis and one with hepatitis C) were SAEs and for the patient with hepatitis C, hospitalization was required. With this exception, none of the elevations in liver enzymes led to hospitalization, liver transplant, or death during the double-blind treatment period.

A decrease in haemoglobin concentration to < 75% of the lower limit of normal (LLN) was observed in five (5.4%) patients on bosentan and none on placebo. Two patients on bosentan with a marked decrease in haematocrit also had a marked decrease in haemoglobin concentration. Few marked abnormalities in other haematology and clinical chemistry variables were observed in either treatment group.

2.2.2 Open-label extension of EARLY study: Study AC-052-364-OL

Overall, 157 patients were enrolled into the open-label extension to the EARLY study, out of 185 included in the double-blind phase. The main reason for discontinuation from the double-blind study and consequently not rolling over to the open-label extension was PAH worsening for placebo patients, and elevated LFTs for bosentan patients. Exposure data as per the cut-off date of 14 December 2007 are presented in Table 10 above.

- Deaths and other SAEs

Forty-four (44) SAEs (8 related, 36 not related) were reported to Actelion Global Drug Safety during the open-label extension period of the EARLY study (from the start of the open-label study up to 20 December 2007). A fatal outcome was reported in 9 patients (5 previously exposed to placebo and 4 to bosentan; 2 from related cases and 7 from unrelated cases). Of the 5 ex-placebo patients, 4 died due to or in association with possible worsening of the underlying disease.

With the exception of a suspected allergic reaction to allopurinol, the spectrum of events seen is consistent with the nature of the clinical progression of this severe underlying disease and associated conditions and the known safety profile of bosentan as established in the pivotal clinical trials and in the post marketing experience.

- Premature study treatment discontinuation

Overall 34 patients (19.7%) discontinued open-label study treatment, 16 (20%) ex-placebo and 18 (19.4%) ex-bosentan patients. The most frequent reason for premature discontinuation was an AE other than PAH (12.5 and 9.7%, respectively) and death of any cause (5% and 3.2%, respectively). Data are summarised in Table 16.

Table 16 - AC-052-364-OL (EARLY open-label extension): Summary of reasons for premature discontinuations of study treatment

Reason for premature discontinuation	Ex-Placebo N=80 No.	%	Ex-Bosentan N=93 No.	%	All patient N=173 No.	%
Total pts with at least one reason	16	20.0%	18	19.4%	34	19.7%
ADVERSE EVENT	10	12.5%	9	9.7%	19	11.0%
DEATH	4	5.0%	3	3.2%	7	4.0%
ADMINISTRATIVE/OTHER	1	1.3%	3	3.2%	4	2.3%
PULMONARY HYPERTENSION AGGRAVATED NOS	-		2	2.2%	2	1.2%
LOST TO FOLLOW-UP	-		1	1.1%	1	0.6%
**OTH:NO COMPLIANT PATIENT	1	1.3%	-		1	0.6%

NOS = not otherwise specified, pts = patients

- Adverse events leading to premature treatment discontinuation

Overall 24 patients (13.9%) discontinued bosentan treatment due to AE: 10 (12.5%) ex-placebo and 14 (15.1%) ex-bosentan patients. The most frequent were events denoting liver dysfunction 4 (5.0%) ex-placebo and 9 (9.7%) ex-bosentan patients (see Table 17).

Table 17 - AC-052-364-OL (EARLY open-label extension): Summary of adverse events denoting liver dysfunction

System Organ Class / Preferred Term	Ex-Placebo N=80 No.	%	Ex-Bosentan N=93 No.	%	All patient N=173 No.	%
AEs DENOTING LIVER DYSFUNCTION						
Total pts with at least one AE	4	5.0%	9	9.7%	13	7.5%
Total number of AEs	4		11		15	
LIVER FUNCTION TEST ABNORMAL	4	5.0%	7	7.5%	11	6.4%
ALANINE AMINOTRANSFERASE INCREASED	-		1	1.1%	1	0.6%
ASPARTATE AMINOTRANSFERASE INCREASED	-		1	1.1%	1	0.6%
HEPATITIS	-		1	1.1%	1	0.6%
HEPATITIS C	-		1	1.1%	1	0.6%

AE = adverse event, pts = patients

2.2.3 Overall clinical trial and post-marketing experience with Tracleer

The safety profile of bosentan in the EARLY study in WHO functional class II PAH patients was consistent with that demonstrated in class III and IV PAH patients in the pivotal registration trials for Tracleer, as well as with what has been documented for bosentan in trials in other indications.

Accordingly, the long-term safety and, especially, the long-term hepatic safety of Tracleer is an important issue. Data on this are available from clinical trials and post-marketing use.

- Clinical trial experience

The longest-term, placebo-controlled clinical trials with bosentan were the AC-052-301/302 ENABLE studies in 804 bosentan-treated patients with congestive heart failure, in which most patients were treated with bosentan 125 mg b.i.d. for at least 1 year (mean duration of exposure 68.7 weeks, median exposure 78.4 weeks). These studies did not provide indications of increasing liver toxicity of bosentan over time of exposure.

In placebo-controlled trials, elevations reaching at least 3 × ULN have been observed in about 10% to 14% of patients, generally within the first 26 weeks of therapy.

As currently stated in the SPC, liver enzyme changes typically occur within the first 26 weeks of treatment. In a few cases they may also occur late in treatment, as reported in post-marketing experience and as reflected in the section 4.8 of the approved SPC.

- Post-marketing experience

Data are available to reflect the experience with Tracleer in approximately 55,000 patients who have been exposed to bosentan between 20 November 2001 and 19 November 2007. Data of particular interest are available from surveillance programmes, the Tracleer Post-marketing Surveillance (PMS) in the EU, and the Tracleer Access Program (T.A.P.) in the USA.

Tracleer PMS

In the EU, the Tracleer PMS database gathered solicited adverse drug reaction (ADR) data from 4,994 patients with a mean exposure time of 38.6 weeks. Of these 4,994 patients, 4,623 were naïve to bosentan at the time of database entry, and 11.8% were reported as having WHO/NYHA functional

class II PAH. The data from this source corroborate the findings from the EARLY study in patients with functional class II PAH that the risk for hepatotoxicity, as assessed by the incidence of LFT elevations, is not higher than that in patients within WHO/NYHA functional class III or IV.

T.A.P. program in the USA

In order to ascertain whether there was any increased risk over time of liver function abnormalities occurring in patients who take Tracleer, data from the Actelion global drug safety database regarding US Tracleer patients was reviewed. The results showed that patients in the first 6 months of exposure were more likely to have a liver event (8% of patients) than those who were exposed for 6 years (2% of exposed patients). The results do not provide information as to how many patients discontinued Tracleer as a result of their liver event.

Overall, the data support the conclusion that within the US exposure of 28,679 patients over the last 6 years, 1,920 or 7%, had a liver event reported to Actelion GDS, and that the chance of this happening was higher in the first 6 months of use, and gradually went down over time.

2.2.4 Discussion on clinical safety

During the EARLY Study, the majority of patients were treated according to the protocol and reached the target dose. No new safety concerns were observed from these data. Safety findings with bosentan during the double-blind treatment period were similar to those previously observed with bosentan. Elevated liver enzymes and anaemia, which are well known side effects of bosentan, were seen more frequently in the bosentan treated group, whereas worsening of PAH was more frequently seen in the placebo group.

There is no apparent difference in the risk of hepatic side effects in the grade II population compared to patients with grade III functional status. As described by the MAH, the majority of hepatic AEs appear within the first six months of treatment and their incidence then decreases.

Data currently available from the ongoing open-label extension to the EARLY study show no new safety concerns with bosentan. Clinically relevant elevations in liver enzymes were of expected frequency and were all manageable. Deaths associated with PAH worsening, already observed within 4 months into the open-label extension, were more frequent in patients previously exposed to placebo (4) than treated with bosentan (2). These deaths confirm the serious prognosis of WHO functional class II PAH patients despite initial presentation with mild symptoms.

The experience from treatment of functional class III patients has shown that the hepatic events can be managed by repeated control of liver function tests as part of the risk management plan and could be handled in a safe way. Furthermore, elevated liver values have been shown to normalise after discontinuation of therapy.

The MAH committed to prolong the open-label extension to the EARLY study until at least half of the randomised patients have been followed for five years. Data on several outcomes (death, transplantation, atrial septostomy, start of intravenous or subcutaneous prostanoids) will be collected in addition to safety and exploratory efficacy information. Annual progress reports will be submitted to the CHMP. The Final study report will be submitted as soon as available.

3. Summary of the Risk Management Plan

The MAH submitted an updated risk management plan which included a risk minimisation plan:

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimisation activities (routine and additional)
Teratogenicity	Routine Pharmacovigilance	• Contraindication in section 4.3. of the SPC: "Pregnancy, Woman of child bearing potential who are not using reliable methods of contraception" (see sections 4.4, 4.5, and 4.6). • Warning in sections 4.4 that: "Tracleer must not be initiated in women of childbearing potential unless they practise reliable contraception (see section 4.5 Interaction with other medicinal products and other forms of interaction) and the result of the pre-treatment pregnancy test is negative. (See section 4.6 Pregnancy and lactation, Use in women of child-bearing potential)." • Sections 4.4 and 4.6: "Before the initiation of Tracleer treatment in women of child-bearing potential, the absence of pregnancy should be checked, appropriate advice on reliable methods of contraception provided, and reliable contraception initiated." • Sections 4.4 and 4.6: Patients and prescribers must be aware that, due to potential pharmacokinetic interactions, Tracleer may render hormonal contraceptives ineffective (see section 4.5). Therefore, women of child-bearing potential must not use hormonal contraceptives (including oral, injectable, transdermal, and implantable forms) as the sole method of contraception but should use an additional or an alternative reliable method of contraception. If there is any doubt on what contraceptive advice should be given to the individual patient, consultation with a gynaecologist is recommended. • Section 4.5 (interaction with other medicinal products and other forms of interaction): "…hormone-based contraceptives alone, regardless of the route of administration (i.e. oral, injectable, transdermal, and implantable forms), are not considered as reliable methods of contraception." • Educational material as Prescriber Kit for prescribers. • Patient Reminder Card specifically aimed at informing patients of the need to avoid pregnancy and to ensure effective contraceptive measures are used.

		• Sending a 'Reminder Letter' to all Tracleer prescribers identified via the controlled distribution system to reinforce these messages.
Hepatotoxicity	Routine Pharmacovigilance	• Information in sections 4.4 (Special warnings and precautions for use) on Liver function: Elevations in liver aminotransferases, i.e., aspartate and alanine aminotransferases (AST and/or ALT), associated with bosentan are dose-dependent. Liver enzyme changes typically occur within the first 26 weeks of treatment, but may also occur late in treatment (see section 4.8). • Information on possible mechanisms for liver aminotransferases provided and warning that the risk may be increased if inhibitors of bile export pumps are co-administered (see sections 4.3 and 4.5). • Warning that: Liver aminotransferase levels must be measured prior to initiation of treatment and subsequently at monthly intervals for the duration of treatment with Tracleer (see further recommendations for dose adjustments in case of ALT/AST elevations and treatment re-introduction under section 4.4 of SPC). • Labelled in section 4.8 • Educational material as Prescriber Kit for prescribers. • Patient Reminder Card specifically aimed at facilitating patient's awareness of the need for regular blood tests for liver function.
Decrease in haemoglobin concentration, thrombocytopenia	Routine Pharmacovigilance	• Warning in section 4.4 that treatment with bosentan associated with a dose-related decrease in haemoglobin concentration and proposals for monitoring. • Labelled in section 4.8
Fluid retention	Routine Pharmacovigilance	• Warning in section 4.4 of the SPC that, in patients with severe chronic heart failure, treatment with bosentan resulted in an increased incidence of hospitalisation during the first 4-8 weeks which could have been due to fluid retention. Recommendation that patients should be monitored for signs of fluid retention and appropriate treatment given. • Peripheral oedema and oedema labelled in section 4.8
Pulmonary oedema associated with veno-occlusive disease (PVOD)	Routine Pharmacovigilance	• Warning in section 4.4 that pulmonary oedema has been reported with vasodilators (mainly prostacyclins) when used in patients with pulmonary veno-occlusive (PVOD) disease and to consider PVOD if pulmonary oedema occurs

Interaction with substrates, inducers or inhibitors of cytochrome (CYP) P450 isoenzymes CYP3A4 and CYP2C9 (including hormonal contraceptives)	Routine Pharmacovigilance	• Warnings in section 4.4 regarding concomitant use with glibenclamide, fluconazole and rifampicin and warning against concomitant administration of both a CYP3A4 inhibitor and a CYP2C9 inhibitor. • Information about specific interactions (including hormonal contraceptives) in section 4.5 of the SPC.
Interaction with sildenafil	Routine Pharmacovigilance COMPASS studies	• Information in section 4.5 of the SPC
Long term safety and efficacy in digital ulcer population	Routine Pharmacovigilance Digital ulcer registry	
Possible interaction with anti-retroviral compounds	Routine Pharmacovigilance Interaction study of bosentan and Kaletra in healthy volunteers.	• Warning in section 4.4 of the SPC that because bosentan is a CYP450 inducer, there is a potential for interaction and decreased efficacy of antiretroviral therapy and that the risk of hepatic toxicity and haematological adverse events may be increased. • Information in section 5.1
Possible seminiferous tubule atrophy	Routine Pharmacovigilance Results of Study 052-402 (Testicular study)	
Possible Vasculitis	Routine Pharmacovigilance	

The current risk minimisation activities described in the conditions or restrictions with regard to the safe and effective use of the medicinal product in Annex II of the Product information are considered adequate for the proposed extension of indication.

However, as a follow-up measure, the RMP should be revised with the next PSUR to take into account the following comments:

- The post-marketing experience section should be updated in accordance with the EU template.
- Data on patients exposed in the post marketing setting should be provided, if possible, for each indication and broken down into EU country or sales area.
- The applicant should make efforts to better present the data on pregnancies and try to document as often as possible information on the root of contraception failure through the pregnancy reporting forms implemented. These forms should also be appended to the RMP.
- The Pregnancy Action Plan appended to the RMP should be updated in accordance to the conclusions from the CHMP during procedure II/34.

4. Orphan Medicinal Products

Bosentan was granted an orphan designation (EU/3/01/019) by the European Commission on 14 February 2001 for the treatment of pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension.

Due to the overlap of the extension of indication in PAH WHO functional class II proposed by the MAH of Tracleer with that approved for Volibris (ambrisentan), the MAH was requested to submit a critical report addressing the possible similarity with this authorised orphan medicinal product.

Having considered the arguments presented by the MAH of Tracleer on 18 April 2008, it is concluded that bosentan and ambrisentan do not share the same principal molecular structural features and the differences in molecular structure are not only minor. Bosentan is regarded as structurally not similar to ambrisentan. As defined in Art. 3 of Commission Regulation (EC) No 847/2000), Tracleer and Volibris are considered as non-similar.

Therefore, with reference to article 8 of Regulation (EC) No. 141/2000, the existence of any market exclusivity for Volibris in Pulmonary Hypertension (PAH) including WHO functional class II, does not prevent the granting of the extension of indication of Tracleer in PAH WHO functional class II which can be considered as significantly overlapping with the indication approved for Volibris. This finding is without prejudice to the outcome of the scientific assessment of the extension of indication application.

5. Benefit-Risk Assessment

Pulmonary arterial hypertension is a rare disease, and only about 25% of PAH patients seen in the clinic are in functional class II or less at the time of diagnosis. PAH is a serious progressive disease with a mean survival of 3.5 years in WHO Class II-III, 4.9 years in WHO Class I/II. There is no available cure but lung transplantation. Available pharmacological treatment aims at providing relief of symptoms and to maintain productivity and quality of life. Another aspect of pharmacological treatment is to delay clinical worsening.

The EARLY trial was designed to evaluate treatment effects in PAH patients with mildly symptomatic disease (WHO functional class II). The objectives were to determine if initiating treatment with bosentan earlier in the course of the disease would not only affect haemodynamics and exercise capacity over a 6-month treatment period, but also delay clinical worsening. The study managed to recruit a representative group of patients with clinical and objective findings characteristic of WHO functional class II. The chosen endpoints have previously been used to evaluate the effects of treatment of PAH and they are well established.

Based on the main analysis, no statistically significant effect was seen on the 6MWD between bosentan and placebo groups. Furthermore, the change in 6MWD remained under the threshold of clinically relevant improvement initially defined as > 35 meters. Therefore, the results are not sufficient to grant an indication to improve exercise capacity.

However, a significant effect on PVR has been convincingly shown in the submitted study and the effect was of the similar magnitude to that observed in studies with grade III populations. The magnitude of the effects is therefore judged to be relevant and is supported by the observed effects on exercise capacity, clinical symptoms worsening and functional status improvement, although they were not as statistically convincing as the haemodynamic results. Therefore, it can be concluded that some improvements have also been shown in patients with PAH grade II functional status treated with Tracleer.

No new safety concerns were raised during the EARLY study. Since the target population is rather young and would be exposed to the drug for a longer time, the safety aspects are important. Severe adverse reactions would be more difficult to accept in a population that is less severely affected by the disease. The severe adverse effects are, however, well known and could be dealt with through the current recommendations in the product information and risk management plan.

In addition, the current risk minimisation activities described in the conditions or restrictions with regard to the safe and effective use of the medicinal product in Annex II of the Product information are considered adequate for the proposed extension of indication.

Therefore, the CHMP considers that the benefit of Tracleer in patients with PAH WHO functional class II outweighs the risks.