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Survival in patients with class III idiopathic pulmonary arterial hypertension treated with first-line oral bosentan compared with an historical cohort of patients started on i.v. epoprostenol

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ABSTRACT

Background. The oral, dual endothelin receptor antagonist bosentan improves exercise capacity and delays clinical worsening in patients with pulmonary arterial hypertension, but its use could delay starting intravenous epoprostenol, a life-saving therapy.

Methods. Survival in patients with functional class III idiopathic pulmonary arterial hypertension treated with bosentan in clinical trials was compared with historical data from similar patients treated with epoprostenol in the clinic. Statistical methods were used to adjust for possible underlying differences between the two groups.

Results. Baseline factors for the 139 bosentan- and 346 epoprostenol-treated patients suggested that the epoprostenol cohort had more severe disease, i.e., lower cardiac index (2.01 *vs* 2.39 L/min/m^2) and higher pressures and resistance. After 1 and 2 years, Kaplan-Meier survival estimates were 97% and 91%, respectively, in the bosentan cohort and 91% and 84% in the epoprostenol cohort. Cox regression analyses adjusting for differences in baseline factors showed a greater probability of death in the epoprostenol cohort (hazard ratio 2.2 with 95% confidence interval of 1.2–4.0 in the model adjusted for hemodynamics). Alternate regression analyses and analyses to adjust for different data collection dates gave consistently similar results. When matched cohorts of 83 patients each were selected, survival estimates were similar. In the bosentan cohort, 87% and 75% of patients followed 1 and 2 years remained on monotherapy.

Conclusions. No evidence was found to suggest that initial therapy with oral bosentan, followed by or with the addition of other treatment if needed, adversely affected long-term outcome compared with initial intravenous epoprostenol in class III idiopathic PAH patients.

INTRODUCTION

Several treatments of pulmonary arterial hypertension (PAH) are now approved in North America (intravenous [i.v.] epoprostenol, subcutaneous treprostinil, oral bosentan) and Europe (i.v. epoprostenol, i.v. or inhaled iloprost, oral bosentan). With the exception of recent data from patients receiving prolonged epoprostenol therapy,[1][2] long-term treatment effects of these therapies are unknown. There is a need for long-term observational studies evaluating the different treatments in terms of survival, side effects, quality of life, and costs. Ideally, head-to-head comparisons of approved therapies are the most appropriate way to compare treatments. However, in the absence of such data, the choice of optimal treatment is currently dictated by clinical experience and drug availability, as well as patient preference.

Two 12-week open-label, randomized studies have shown that continuous i.v. infusion of epoprostenol (Flolan®) improves exercise capacity, quality of life, and hemodynamics in patients with functional class III-IV idiopathic PAH[3] and PAH related to scleroderma.[4] In addition, analyses of large cohorts of idiopathic PAH patients have demonstrated that long-term survival is improved in epoprostenol-treated patients compared with either predicted survival[1] or an historical control group.[2] These data have led to the suggestion of initiating therapy in functional class III and IV patients with continuous i.v. epoprostenol.

Bosentan (Tracleer®), an ET_A and ET_B receptor antagonist, is the first oral therapy approved for the treatment of PAH. In clinical studies, bosentan therapy improved hemodynamics and functional class, increased exercise capacity, and delayed clinical worsening compared with placebo in primarily functional class III idiopathic PAH and PAH related to connective tissue diseases.[5][6] Furthermore, the improvement in functional class with bosentan was often stable for at least 1 year.[7] A recent prospective, uncontrolled study of observed survival in idiopathic PAH patients initially treated with bosentan, followed by other therapy if needed, supports an improved survival compared with their predicted survival in the absence of targeted treatment.[8] A possible long-term effect of bosentan is suggested by experimental evidence that bosentan can block and may reverse the pathological processes resulting from the excessive endothelin present in pulmonary and cardiac tissue.[9] By blocking both ET_A and ET_B receptor subtypes, bosentan may alleviate abnormal vasoconstriction, prevent and reverse vascular hypertrophy and cardiac remodeling, attenuate pro-fibrotic and inflammatory effects, and blunt neurohormonal activation. These effects may contribute to an improved survival in PAH patients.

Considering its demonstrated efficacy and oral availability, bosentan may be favored as first-line therapy before initiating epoprostenol therapy, especially in patients with less severe disease. However, it is unclear if a delay in starting epoprostenol therapy is detrimental to patients' long-term outcome. The aim of the present study was to evaluate if initiating therapy with bosentan, followed by other therapy if needed, has any negative long-term consequences compared with epoprostenol therapy. In order to achieve this, recently available long-term data from patients who received bosentan in clinical trials were compared with historical data from patients who were initially treated with epoprostenol at some of the same centers that participated in the bosentan studies.

METHODS

The study was conducted using two cohorts of patients with class III idiopathic PAH, one that received bosentan as first-line therapy in clinical trials (followed prospectively), and one that received epoprostenol as the initial treatment in the clinic (historical records). The analyses were confined to those patients with functional class III idiopathic PAH to reduce selection bias due to differences between the treatments.

Bosentan cohort. Patients included in the analyses were enrolled in two placebo-controlled trials of bosentan in PAH.[5][6] At entry, patients were ≥ 12 years old and had severe symptomatic (World Health Organization [WHO] functional class III or IV) PAH, with a resting mean pulmonary arterial pressure (mPAP) > 25 mmHg, pulmonary vascular resistance (PVR) > 3 mmHg/L/min, and pulmonary capillary wedge pressure (PCWP) < 15 mmHg as measured by right heart catheterization, and 6-minute walk distance of 150-450 meters. Patients who completed a placebo-controlled study were eligible to continue in an open-label extension study. All patients gave written informed consent, and the studies were conducted in accordance with the amended Declaration of Helsinki.

Of the 245 patients enrolled in the studies, 139 had class III idiopathic PAH and received bosentan therapy, either during a placebo-controlled study or its extension. Patients had no previous exposure to epoprostenol or prostacyclin analogs, and the treating physician determined other treatments. During the placebo-controlled studies, bosentan was discontinued in patients starting on prostanoid therapy, but this was not required during the extensions. Data on vital status and alternative treatments were collected from September 1999 (start of the first bosentan study) to December 31, 2002 (data cut-off).

Epoprostenol cohort. Records of 785 patients started on epoprostenol from April 1987 to May 2002 were available from five referral centers (Clamart, France; Chicago, IL; Denver, CO; New York, NY; and San Diego, CA). The 346 patients who had class III idiopathic PAH at the start of epoprostenol treatment, more than zero survival time, a known vital status, and who started epoprostenol on or after January 1995 (considered contemporary) were included in the analyses. Data from only the first 36 months of treatment for each patient were included to parallel that available for bosentan-treated patients. Where patient consent was not obtained, local Institutional Review Boards provided exempt approval for use of historical data, provided patient anonymity was maintained.

Analyses. Baseline and follow-up information were summarized as mean and standard deviation or frequency counts and proportions for patients with available data. Baseline comparisons were performed using Fisher's exact test (gender) and the student's t-test (all others). Treatments at 12 and 24 months for bosentan-treated patients were expressed as the proportions of patients followed for at least 12 and 24 months, respectively, omitting patients with an insufficient observation period.

Survival was assessed from the start of treatment to death or data cut-off if on bosentan and to death, loss to follow-up, or data cut-off if on epoprostenol. All bosentan-treated class III idiopathic PAH patients were included in the analyses (intent to treat), with

patients lost to follow-up counted as dead at the last known contact. In contrast, patients on epoprostenol who were lost to follow-up were censored at the last known contact. Observed survival data up to 36 months were reported as Kaplan-Meier estimates; the log-rank test was used to explore the significance of the difference between treatments.

In order to explore possible underlying differences between the two treatment groups, two additional methods were used to compare long-term outcome of the different treatment regimens. The Cox proportional hazard regression model,[10] a statistical method used to model survival data in the presence of covariates and censoring, was used to adjust for differences between treatment groups at baseline. In order to confirm the results obtained with the Cox regression, a matched-patient analysis was used. The objective of the analyses was to determine whether or not starting therapy with bosentan negatively influenced the long-term outcome of class III idiopathic PAH patients compared to starting with epoprostenol.

Cox proportional hazard regression model. Treatment effect on survival was analyzed using the Cox proportional hazard regression model adjusting for known prognostic factors, such as relevant baseline factors identified empirically and/or in the literature.[11] The stepwise variable selection procedure provided by the SAS® procedure PHREG was used as a supportive approach and included age, gender, and baseline values of cardiac index, mPAP, mean right atrial pressure (mRAP), and PVR, with and without 6-minute walk distance as explanatory factors in the model. To address biases related to the dissimilar time periods of data collection in the two cohorts, the analyses were also performed on subsets of the epoprostenol cohort consisting of patients who started epoprostenol treatment on or after September 1999 (corresponding to bosentan-treated patients) and between January 1995 and September 1999 (before bosentan was available as a treatment option). In all Cox regression analyses, hazard ratios represent the risk of death in the epoprostenol cohort versus the bosentan cohort and are presented with the associated 95% confidence limits and p-value; a hazard ratio greater than one indicated that no negative influence of bosentan treatment was observed.

Matched-patient analysis. The rules used to select two matched cohorts of class III patients can be found online. In brief, patients in each treatment group were matched using the baseline hemodynamic variables of cardiac index, mPAP, and mRAP. The procedure used strict matching criteria and conservative rules for eliminating unmatched patients. If within the match criteria there was an excess of bosentan patients, those with the best outcome were removed to equalize the number of patients in each treatment group. Conversely, if the excess was in the epoprostenol group, those with the worst outcome were removed. This resulted in an equal number of patients in each cohort and closely matched baseline hemodynamics; any bias introduced by the procedure was against the bosentan cohort. Kaplan-Meier survival estimates and hazard ratio with 95% confidence limits were computed for the resulting matched cohorts. As with the Cox regression analysis, a hazard ratio greater than one indicated that no negative influence of bosentan treatment was observed.

RESULTS

Several baseline factors differed between the 139 bosentan- and 346 epoprostenol-treated class III idiopathic PAH patients in the database (Table 1), and the epoprostenol cohort had more severe disease, i.e., lower baseline cardiac index (2.01 *vs* 2.39 L/min/m^2), higher PVR, mPAP, and mRAP, and a shorter time between diagnosis and initial treatment (13 *vs* 32 months).

Table 1 Demographics and baseline characteristics of class III idiopathic PAH patients in the study

	n	Bosentan cohort (N = 139)	n	Epoprostenol cohort (N = 346)	p-value*
Gender (male / female, %)	139	20 / 80	346	26 / 74	0.240
Age (years)					
Mean [SD]	139	46 [16]	341	41 [14]	< 0.001
Range		13 – 80		10 – 75	
Time from diagnosis of PAH to start of therapy (months)*					
Mean [SD]	138	32 [42]	100	13 [21]	< 0.001
Range		0.3 – 326		0 – 135	
Hemodynamics (mean [SD])†					
Cardiac index (L/min/m^2)	138	2.4 [0.8]	317	2.0 [0.6]	< 0.001
PVR (Wood units)	132	12 [6]	207	18 [10]	< 0.001
mPAP (mm Hg)	139	56 [15]	333	66 [18]	< 0.001
mRAP (mm Hg)	136	9 [5]	330	11 [5]	< 0.001
Walk test (meters)					
Mean [SD]	139	351 [80]	171	335 [106]	0.136

* P-values were determined using the Fisher's exact test (gender) and the student's t- test (all others).

† For most bosentan-treated patients, time from diagnosis and hemodynamic data were available only at the start of the placebo-controlled study.

Abbreviations: mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; SD, standard deviation

Kaplan-Meier survival analysis. The Kaplan-Meier estimates of survival after 1 and 2 years of treatment were 97% and 91%, respectively, in the bosentan cohort and 91% and 84% in the epoprostenol cohort (log-rank p-value = 0.022, Figure 1). Since the difference in survival may have been influenced by baseline differences, several methods were used to adjust the treatment effect for possible underlying differences between the two groups.

Cox regression analysis. The Cox regression was used to adjust for baseline factors that may cause the observed difference. Three different types of analyses using Cox regression were performed in the whole database (Table 2) with the following results. 1) When the model included no adjustment, the hazard ratio was 1.9 (p = 0.025). 2) When the model used the *a priori* defined set of clinically meaningful hemodynamic variables

suggested by the literature,[11] the treatment effect persisted (hazard ratio = 2.2, p = 0.014). Tests for variables such as the walk test or selected combinations (i.e., walk test + cardiac index, walk test + mRAP) produced similar results (hazard ratios of 1.7–1.8, data not shown). 3) Finally, when the step-wise variable selection was used, mPAP was selected by the model as a relevant explanatory variable, but treatment effect again persisted with a hazard ratio of 2.3 (p = 0.006). When the step-wise model was used on those patients with walk test results, both mPAP and walk test were selected as relevant explanatory variables, and still the treatment effect persisted (hazard ratio = 2.7, p = 0.005). In all of the Cox regression analyses performed, the probability of death was never higher in the bosentan cohort, regardless of the factors used for adjustment.

Table 2 **Main Cox regression analyses on mortality for class III idiopathic PAH patients treated with bosentan or epoprostenol**

	Bos (n)	Epo (n)	Number of events	Hazard ratio	95% CL	p-value
Entire database*						
No adjustment	139	346	85	1.9	1.1, 3.5	0.025
Model adjusted for hemodynamics§	136	314	76	2.2	1.2, 4.0	0.014
Stepwise model†: mPAP	136	314	76	2.3	1.3, 4.2	0.006
Stepwise model‡: mPAP, walk test	136	169	46	2.7	1.4, 5.4	0.005
Patients treated during same time period*						
No adjustment	139	81	26	2.5	1.1, 5.6	0.022
Model adjusted for hemodynamics§	136	78	25	2.3	0.9, 5.6	0.073
Stepwise model†: none	136	78	25	2.4	1.1, 5.4	0.033
Stepwise model‡: walk test	136	29	18	2.1	0.7, 6.6	0.206
Patients treated during different time periods*						
No adjustment	139	217	67	1.9	1.0, 3.5	0.035
Model adjusted for hemodynamics§	136	196	60	2.2	1.2, 4.3	0.016
Stepwise model†: mPAP, mRAP	136	196	60	2.3	1.2, 4.3	0.012
Stepwise model‡: mPAP, mRAP	136	117	39	2.7	1.3, 5.7	0.007

* In the entire database, patients started bosentan on/after Sept 1999 and epoprostenol on/after Jan 1995. For the same time period, all patients started treatment on/after September 1999, and for different time periods, patients started bosentan on/after Sept 1999 and started epoprostenol Jan 1995–Sept 1999.
† Using the parameters age, gender and baseline cardiac index, mPAP, mRAP, pulmonary vascular resistance, and World Health Organization functional class.
‡ Using the stepwise model parameters given in the footnote above + walk test.
§ Parameters of cardiac index, mPAP, and mRAP suggested by the literature.[11]
Abbreviations: Bos, bosentan; CL, confidence limits; Epo, epoprostenol; mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure.

In order to address any bias resulting from the different time periods of data collection between the two cohorts (e.g., different standards of care or a skewing of disease severity due to a new treatment option), the same analyses were performed on subgroups of

epoprostenol-treated patients (Table 2). The bosentan cohort was compared with those patients who started epoprostenol on or after September 1999 (as in the bosentan cohort) and with those who started epoprostenol between January 1995 and September 1999 (before bosentan was a treatment option). Results from all analyses using both subsets of the epoprostenol cohort support the results of the main analyses, i.e., the hazard ratios for mortality ranged from 1.6 to 2.7 (including analyses not shown), with the greater risk consistently in the epoprostenol-treated patients.

Matched-patient analysis. A more empirical alternative method was used to reduce any underlying differences between the two groups. This required the identification of matched cohorts of patients that were selected based on hemodynamic variables and using exclusion rules consistently biased against bosentan. The selected analysis set contained two 83-patient cohorts (60% of bosentan patients and 24% of epoprostenol patients) that were well matched for demographics and baseline hemodynamic and exercise variables (Table 3). Kaplan-Meier survival estimates in the two matched cohorts were nearly identical (Figure 2, hazard ratio = 1.03).

Table 3 Demographics and baseline characteristics of class III idiopathic PAH patients in matched cohorts

	Bosentan matched cohort		Epoprostenol matched cohort		
	n	(N = 83)	n	(N = 83)	p-value*
Gender (male / female, %)	83	24 / 76	83	28 / 72	0.723
Age (years)					
Mean [SD]	83	46 [16]	83	43 [13]	0.136
Range		13 – 76		15 – 74	
Time from diagnosis (months)*					
Mean [SD]	83	29 [36]	26	11 [19]	0.014
Range		1 – 173		0 – 92	
Hemodynamics (mean [SD])†					
Cardiac index (L/min/m^2)	83	2.2 [0.6]	83	2.1 [0.6]	0.610
PVR (Wood units)	79	13 [6]	53	14 [6]	0.553
mPAP (mm Hg)	83	57 [15]	83	59 [15]	0.397
mRAP (mm Hg)	83	10 [5]	83	10 [5]	0.893
Walk test (meters)					
Mean [SD]	83	355 [76]	41	350 [110]	0.762

NB: Patients were matched using baseline cardiac index, mPAP, and mRAP and 6^3 cells (see methods).

* P-values were determined using the Fisher's exact test (gender) and the student's t- test (all others).

† For most bosentan-treated patients, time from diagnosis and hemodynamic data were available only at the start of the placebo-controlled study.

Abbreviations: mPAP, mean pulmonary artery pressure; mRAP, mean right atrial pressure; PAH, pulmonary arterial hypertension; PVR, pulmonary vascular resistance; SD, standard deviation.

Overall outcomes. Over the entire data collection period, overall outcomes in the two cohorts of class III idiopathic PAH patients were different. The mean [standard deviation] duration of observation in the epoprostenol cohort was 3.1 [2.4] years. Over this period of time, 71 of the 346 patients died, and 22 underwent lung transplantation. The bosentan cohort was followed for a shorter mean time period (2.2 [0.5] years) and had fewer deaths (13/139) and lung transplantations (2/139) than the epoprostenol cohort. Furthermore, patients in the bosentan cohort had the option of being transferred to or given in addition other drug therapies at the discretion of the investigator. However, after 1 year of follow-up, 87% of all bosentan-treated patients remained on bosentan monotherapy (Table 4). Epoprostenol had been added to bosentan therapy in five patients and replaced it in two others. After 2 years, 75% of the 116 patients who were followed for a full 2 years were still treated with bosentan alone. By this time, an additional two patients had been transferred to epoprostenol therapy; other changes in therapy were infrequent but included added treatments (i.v. or inhaled iloprost, subcutaneous treprostinil, or oral sildenafil), replacement therapy (subcutaneous treprostinil or oral sitaxsentan), and discontinuation of bosentan without replacement.

Table 4 Vital status and treatment at 12 and 24 months of follow-up in class III idiopathic PAH patients in the bosentan cohort

	Status at 12 months (N = 139)	Status at 24 months (N = 139)
Dead	4 (2.9%)*	13 (9.4%)*
Alive	135 (97.1%)	103 (74.1%)
Insufficient observation	—	23 (16.5%)
Patients with sufficient observation time‡	(n = 139)	(n = 116)
Bosentan alone	121 (87%)	87 (75%)
Bosentan + other treatment	7 (5%)	8 (7%)
Other or no treatment	7 (5%)†	8 (7%)†
Dead	4 (3%)*	13 (11%)*

* Includes one patient lost to follow-up.
† Includes patients with missing information.
‡ Percentages are based on the total number of patients with sufficient observation at the given time point.
Abbreviations: PAH, pulmonary arterial hypertension.

DISCUSSION

Long-term treatment with epoprostenol is known to improve symptoms, quality of life, exercise capacity, hemodynamics, and survival in patients with class III or IV idiopathic PAH.[1] [3] [7] Despite its efficacy, epoprostenol remains a complicated, inconvenient and costly therapy. In addition, it has several drawbacks, including complications related to its delivery system (indwelling venous catheter-related infections, portable pump dysfunction) as well as side effects, including headache, jaw pain, diarrhea, and rash. In contrast, the side-effect profile of oral bosentan includes increased incidences of edema and elevated liver enzymes.[6][7] Bosentan has been approved in North America and Europe for the treatment of PAH (WHO functional class III–IV), and for many clinicians bosentan provides an appealing alternative to epoprostenol as first-line therapy. However, clinicians are faced with the difficult decision of choosing between an agent that may be more convenient for the patient (e.g., bosentan) and one that has demonstrated improved survival (e.g., epoprostenol).

The best way to compare the long-term effects of different therapeutic approaches is a prospective, randomized, controlled study comparing the two interventions. However, conducting a parallel-arm, randomized trial of i.v. epoprostenol versus oral bosentan would be difficult due to the inability to blind the study, bias introduced by patient preferences, and the poorly defined target population at the present time (i.e., epoprostenol is most often administered to patients with more severe disease, while bosentan may be started in less ill patients). Therefore, a comparison of existing survival data from two cohorts of patients, one initially treated with bosentan and one initially started on epoprostenol, was considered an appropriate approach to address the question.

Due to the retrospective nature of the study, several analyses were performed to adjust for any inherent differences between the cohorts that may bias the results. The Cox regression was used to control for explanatory variables other than treatment effect. Like other regression models (e.g., multiple linear regression), the Cox proportional hazard regression model provides an adjustment of the treatment effect based on known prognostic factors, thus allowing a correct interpretation of the results even in the presence of an imbalance of the prognostic factors. Baseline hemodynamics suggested that the epoprostenol cohort had more severe disease. Results of the regression analysis that adjusted for this difference were consistent; the probability of death was never greater in the bosentan cohort than in the epoprostenol cohort. Since epoprostenol was available for therapeutic use before bosentan, the standard of care might have been different in the two cohorts. This bias was addressed by comparing patients treated during the same time period (from September 1999 to data cut-off). Also, the availability of bosentan as an investigational drug after September 1999 might have influenced treatment decisions, with epoprostenol proposed for only the most severe patients. This was addressed by comparing the bosentan cohort with those epoprostenol patients treated before September 1999. These analyses showed similar results in that the probability of death was never greater in the bosentan cohort than the epoprostenol cohort. To address differences in patient selection in the two cohorts (clinical studies vs the clinic), matched cohorts were selected using rules intentionally biased against the bosentan cohort. Survival estimates of these matched cohorts were nearly identical, with a hazard ratio of 1.03.

In summary, Kaplan-Meier estimates of survival in the bosentan cohort were not inferior to those of the epoprostenol cohort. Cox regression analyses to adjust for prognostic factors and time periods confirmed this result, regardless of the factor or time period considered. Kaplan-Meier estimates of survival for the conservatively biased matched cohorts were very similar (hazard ratio of 1.03). Since this was a retrospective study, the significance of the findings must be interpreted with caution. The different statistical approaches were successively more conservative and even biased against bosentan. They resulted in a reduction of the difference initially seen between the two cohorts. However, in no case was the probability of survival in the bosentan cohort less than in the epoprostenol cohort. Since epoprostenol was a treatment option in the bosentan cohort, the results of this study might have been biased by the early use of epoprostenol in bosentan patients. However, 2 years after treatment initiation, 75% of the bosentan cohort remained on bosentan monotherapy. In addition, the longer time from diagnosis to initial treatment in the bosentan cohort may indicate more stable disease and slower progression compared with the epoprostenol cohort.

There are a number of limitations to this type of analysis. Data from the two treatment cohorts were obtained under different conditions, i.e., protocol-guided studies in the case of bosentan and needs-based treatment in the clinic in the case of epoprostenol. This difference not only affects the type of treatment administered but also the type of patient included in each cohort. Treatment with epoprostenol was based on practices at each center, which vary center to center, and data were not systematically collected at these centers in the manner specified for the clinical trials. Statistical methods were used to address many of the possible resulting biases, but 6-minute walk test was not included in the identification of matched cohorts, since the assessment was available for only 42% of epoprostenol patients. Fewer patients in the bosentan than epoprostenol cohort were followed for 3 years, and arguably the long-term effect of treatment would be more in evidence with even longer follow-up. With long-term data collection, some of the data from both the epoprostenol and bosentan cohorts included in this study have been previously reported in other analyses.[1][2] [7]

The use of bosentan as first-line therapy in PAH patients could delay the initiation of epoprostenol, a treatment that has been demonstrated to confer a survival benefit in this disease. No evidence was found in the present study to suggest that initial therapy with oral bosentan, followed by or with the addition of other treatment if clinically indicated, adversely affected long-term outcome compared with initial i.v. epoprostenol in class III idiopathic PAH patients. Decisions regarding treatment initiation for individual idiopathic PAH patients should take into account a number of factors, including ease of administration, side-effect profile, and long-term outcomes associated with each treatment option. Ideally, prospective comparison studies are warranted in order to provide treating physicians with additional information.

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Competing interests: OS, VVM, DBB, RJB, CB, NG, LJR, and GS have been remunerated consultants for Actelion Pharmaceuticals Ltd, the manufacturer of bosentan; MR is an employee of Actelion Pharmaceuticals Ltd.

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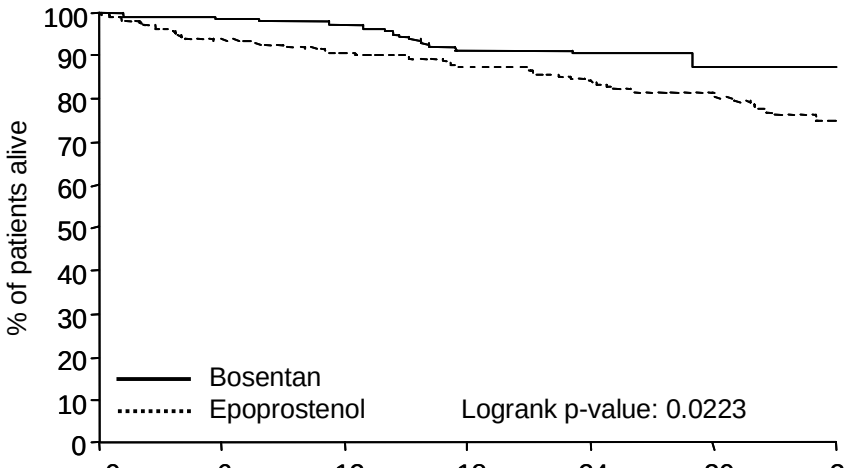
FIGURE LEGENDS

Figure 1 Kaplan-Meier (K-M) survival curves for class III idiopathic PAH patients treated with bosentan (solid line) or epoprostenol (dashed line)

Figure 2 Kaplan-Meier survival curves for matched cohorts of class III idiopathic PAH patients treated with bosentan (solid line) or epoprostenol (dashed line)
CL, confidence limits

Figure 1 Kaplan-Meier (K-M) survival curves for class III idiopathic PAH patients treated with bosentan (solid line) or epoprostenol (dashed line)



K-M survival estimates (%)

100	**99**	**97**	**91**	**91**	**87**	**87**	Bosentan
100	**94**	**91**	**87**	**84**	**81**	**75**	Epoprostenol

Patients at risk

139	137	135	127	103	22	16	Bosentan
346	307	281	256	221	187	159	Epoprostenol

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