Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension

Vallerie McLaughlin[1], Richard N. Channick[2], Hossein-Ardeschir Ghofrani[3], Jean-Christophe Lemarié[4], Robert Naeije[5], Milton Packer[6], Rogério Souza[7], Victor F. Tapson[8], Jonathan Tolson[9], Hikmet Al Hiti[10], Gisela Meyer[11] and Marius M. Hoeper[12]

Affiliations: [1]Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan, Ann Arbor, MI, USA. [2]Pulmonary and Critical Care, Massachusetts General Hospital, Boston, MA, USA. [3]University of Giessen and Marburg Lung Center, Giessen, Germany. [4]Department of Statistics, Effi-Stat, Paris, France. [5]Department of Cardiology, Erasme University Hospital, Brussels, Belgium. [6]Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, TX, USA. [7]Pulmonary Department, Heart Institute, University of São Paulo Medical School, São Paulo, Brazil. [8]Division of Pulmonary and Critical Care Medicine, Cedars-Sinai Medical Center, Los Angeles, CA, USA. [9]Global Medical Affairs, Actelion Pharmaceuticals Ltd, Allschwil, Switzerland. [10]Department of Cardiology, IKEM, Prague, Czech Republic. [11]Complexo Hospitalar Santa Casa De Porto Alegre, Pulmonary Vascular Research Institute, Porto Alegre, Brazil. [12]Department of Respiratory Medicine, Hannover Medical School and German Center of Lung Research (DZL), Hannover, Germany.

Correspondence: Vallerie McLaughlin, Department of Internal Medicine, Division of Cardiovascular Medicine, University of Michigan Health System, Ann Arbor, MI 48109-5853, USA. E-mail: vmclaugh@umich.edu

ABSTRACT   The safety and efficacy of adding bosentan to sildenafil in pulmonary arterial hypertension (PAH) patients was investigated.

In this prospective, double-blind, event-driven trial, symptomatic PAH patients receiving stable sildenafil ($\geqslant$20 mg three times daily) for $\geqslant$3 months were randomised (1:1) to placebo or bosentan (125 mg twice daily). The composite primary end-point was the time to the first morbidity/mortality event, defined as all-cause death, hospitalisation for PAH worsening or intravenous prostanoid initiation, atrial septostomy, lung transplant, or PAH worsening. Secondary/exploratory end-points included change in 6-min walk distance and World Health Organization functional class at 16 weeks, change in N-terminal pro-brain natriuretic peptide (NT-proBNP) over time, and all-cause death.

Overall, 334 PAH patients were randomised to placebo (n=175) or bosentan (n=159). A primary end-point event occurred in 51.4% of patients randomised to placebo and 42.8% to bosentan (hazard ratio 0.83, 97.31% CI 0.58–1.19; p=0.2508). The mean between-treatment difference in 6-min walk distance at 16 weeks was +21.8 m (95% CI +5.9–37.8 m; p=0.0106). Except for NT-proBNP, no difference was observed for any other end-point. The safety profile of bosentan added to sildenafil was consistent with the known bosentan safety profile.

In COMPASS-2, adding bosentan to stable sildenafil therapy was not superior to sildenafil monotherapy in delaying the time to the first morbidity/mortality event.

@ERSpublications
COMPASS-2: adding bosentan was not superior to sildenafil alone in delaying time to first morbidity/mortality event http://ow.ly/NiM65

Introduction

Pulmonary arterial hypertension (PAH) is a severe and progressive disease leading to right heart failure and death. Three major mechanistic pathways, the endothelin, prostacyclin and nitric oxide pathways, are known to be involved in the pathogenesis of PAH and therapies that target these pathways are available [1–3]. Combining agents that target more than one pathway is an attractive option for the treatment of PAH and may offer additional long-term benefits compared with monotherapy [4, 5]. The proceedings from the third World Symposium on Pulmonary Hypertension state that, despite the lack of supporting trial data, combination therapy could be considered an option for patients deteriorating on monotherapy [6]. In addition to the need for controlled data on the efficacy and safety of combination therapy in patients with PAH, it was also recognised at the time of the third World Symposium on Pulmonary Hypertension that future trial design would see a shift from short- to long-term studies and that composite primary end-points indicative of disease progression would be more useful than other end-points typically used in clinical trials at that time [7].

COMPASS-2 was designed as an event-driven study to evaluate the effect of bosentan on the long-term clinical course of patients with symptomatic PAH already receiving sildenafil, using a composite primary end-point of time to first confirmed morbidity/mortality event.

Methods

Study oversight

The steering committee designed and oversaw the conduct of the trial and data analysis in collaboration with the sponsor (Actelion Pharmaceuticals Ltd, Allschwil, Switzerland). The trial was conducted in compliance with good clinical practice and the principles of the Declaration of Helsinki, was approved by local institutional review boards or independent ethics committees, and was monitored by an independent data monitoring committee. Data were collected, managed and analysed by the sponsor according to a predefined statistical analysis plan. The manuscript was prepared by the authors, who had unrestricted access to the data, agreed to submit the manuscript for publication, and assume responsibility for the accuracy and completeness of the data and analyses.

Patients

Patients were ≥18 years old with symptomatic PAH confirmed by right heart catheterisation and included patients with idiopathic PAH, hereditary PAH, or PAH associated with connective tissue disease, repaired congenital heart defects (≥2 years repaired) or drugs and toxins. Patients were required to have a baseline 6-min walk distance (6MWD) of 150–480 m and to be receiving a stable dose of sildenafil ≥20 mg three times daily for at least 3 months prior to randomisation. PAH medications other than sildenafil could not be used within 3 months prior to randomisation (supplementary table 1). Written informed consent was obtained from all patients.

Study design and procedures

COMPASS-2 was a prospective, international, randomised, double-blind, placebo-controlled, event-driven trial (www.clinicaltrials.gov identifier number NCT00303459). Patients fulfilling the entry criteria were randomised, in a 1:1 ratio, to receive placebo or bosentan, initially at 62.5 mg twice daily for 4 weeks and then 125 mg twice daily, while sildenafil therapy was continued at an unchanged dose. Patients who could not tolerate the study medication at 125 mg twice daily could be down-titrated to 62.5 mg twice daily at any time. After 16 weeks, the dose of sildenafil could be adjusted or discontinued, or patients could be switched to tadalafil.

Clinical assessments, including 6-min walk test, World Health Organization (WHO) functional class and a seven-point patient global self-assessment (PGSA) scale for PAH symptoms (supplementary file 1), were performed every 4 months following randomisation until the end of the study; these assessments were also performed if the patient experienced worsening PAH. Adverse events (AEs) and serious adverse events (SAEs) were recorded while patients were taking the study medication, and up to 1 and 28 days after permanent discontinuation of study drug for an AE or SAE, respectively. Liver function tests and haemoglobin levels were measured monthly while patients were receiving double-blind treatment. Double-blind treatment could be discontinued for safety reasons or if the patient started open-label treatment with an endothelin receptor antagonist following the occurrence of a primary end-point event. The study was stopped when the target number of primary end-point events was reached.

Outcome measures

The composite primary efficacy end-point was time to the first morbidity/mortality event, defined as time to death from any cause, hospitalisation for worsening PAH or start of intravenous prostanoid therapy, atrial septostomy, lung transplant, or worsening PAH. Worsening PAH was defined as: 1) moderate or marked worsening of PAH symptoms on the PGSA together with the initiation of a subcutaneous or

inhaled prostanoid or use of open-label bosentan; or 2) no change or mild worsening of PAH symptoms accompanied by a decrease in 6MWD by more than 20% from the previous visit or by more than 30% from the baseline visit, together with the initiation of a subcutaneous or inhaled prostanoid or use of open-label bosentan. Patients reporting improvement in the PGSA were not considered to have experienced a worsening PAH event. All morbidity/mortality events were adjudicated in a blinded fashion by a clinical end-point committee and only confirmed first events were used in the analysis of the primary end-point.

The pre-specified secondary end-points were: 1) change in 6MWD at 16 weeks; 2) change in WHO functional class at 16 weeks; 3) time to the first occurrence of death from any cause, hospitalisation for PAH or start of intravenous prostanoid therapy, atrial septostomy, or lung transplant; and 4) death from any cause. Exploratory end-points included the change in N-terminal pro-brain natriuretic peptide (NT-proBNP).

Statistical analysis

The initial assumptions for the primary end-point were an annual rate of 21% on placebo with a risk reduced by 36% (hazard ratio (HR) 0.64) with bosentan and a negligible annual attrition rate. In addition, it was planned to conduct a single final analysis at 0.04 (two-sided), taking into account the existence of a co-primary end-point (change in 6MWD at 16 weeks) planned to be tested at 0.01 (two-sided). Over the course of the study, a number of amendments were introduced based on the evolution of knowledge in the field of PAH, as well as the rate of enrolment and blinded evaluation of the overall event rate. On implementation of an amendment in 2007, the 6MWD end-point was changed from a co-primary end-point to a secondary endpoint and the Type I error associated with the single remaining primary end-point was increased to 0.05 (two-sided). On implementation of the final amendment in 2010, the assumptions were that the annual rate of a primary end-point event would be 20% in the placebo group, that this risk would be reduced by 43% (HR 0.57) with bosentan, that the annual attrition rate would be 5.7%, and that two interim efficacy analyses would be performed at 50% and 75% of the target number of events. With an overall study-wise Type I error (α) set to 0.05 (two-sided) based on the log-rank test, when adjusted for two pre-planned blinded interim analyses at 50% and 75% of the target number of primary end-point events, the α for the final analysis of the primary end-point was 0.0269 and, thus, 97.31% confidence intervals were used in reporting the HRs. A total of 156 events were required to detect the pre-specified difference between the two groups with a power of 90%.

The primary analysis was based on data from all randomised patients following the intention-to-treat principle. All time-to-event end-point analyses were displayed using Kaplan–Meier plots and the difference between the groups was tested for significance using the log-rank test. The proportion of patients with missing data for the primary end-point was calculated in patient-years and expressed as a percentage of the total information expected if all patients having not experienced a primary end-point event would have completed the study as planned. Pre-specified subgroup analyses were performed for the primary end-point; interaction tests were performed without correction for multiple testing and evaluated for significance with a threshold of p=0.10. Change in 6MWD at 16 weeks was analysed with the Wilcoxon rank-sum test and the proportion of patients with an improved WHO functional class at 16 weeks was analysed with the Fisher's exact test. Missing assessments of 6MWD at 16 weeks and WHO functional class at 16 weeks were imputed with the use of either the last-observation-carried-forward method for patients who did not experience a primary end-point event within the first 16 weeks or a method that imputed data according to a worst-case scenario for patients who experienced a primary end-point event within the first 16 weeks (supplementary table 2). Repeated-measures analyses with the baseline value as a covariate were carried out for changes in NT-proBNP using mixed model techniques; assessments considered were those where ⩾60% patients with NT-proBNP sampling performed had available values.

Results

Patient disposition and duration of follow-up

Between May 2006 and June 2012, 334 patients were enrolled at 83 centres in 13 countries: 175 were randomised to placebo and 159 to bosentan (figure 1). Baseline characteristics were balanced between the two groups (table 1). The population was predominantly female, with a mean age of 53.9 years, mean body mass index (BMI) of 28.8 kg·m^{-2} and mean time from diagnosis of 25.7 months, and predominantly WHO functional class III and of idiopathic aetiology (63.8% of patients). The mean±SD duration of follow-up in the study was 39.7±22.6 months for the placebo group and 38.0±21.9 months for the bosentan group; >70% of patients in both treatment groups were followed for ⩾24 months. The median daily dose of sildenafil during the study was 60.0 mg for patients in the placebo and bosentan groups. Overall, 172 patients (placebo: 89 (50.9%); bosentan: 83 (52.2%)) did not complete the study: 77 patients died (placebo: 44; bosentan: 33) and 95 patients prematurely discontinued (placebo: 45; bosentan: 50), 58 of whom withdrew consent (placebo: 26; bosentan: 32) (figure 1). Of the 172 patients who did not complete the study, 63 did

not experience a primary end-point event, resulting in 20% missing information for the primary end-point and 22% for the secondary end-point of time to death from any cause.

Primary end-point

A primary end-point event occurred in 90 (51.4%) out of 175 patients and 68 (42.8%) out of 159 patients in the placebo and bosentan groups, respectively (table 2). The HR for the primary end-point in the bosentan group, as compared with the placebo group, was 0.83 (97.31% CI 0.58–1.19, p=0.2508) (figure 2). Approximately half of the primary end-point events were categorised as "worsening PAH" (placebo: 52 (57.8%) out of 90; bosentan: 32 (47.0%) out of 68). The overall treatment effect was consistent across all but two pre-specified groups; there were nominally significant interactions with 6MWD and geographical region (figure 3). The HR for the primary endpoint in the per-protocol set (n=270) was 0.88 (97.31% CI 0.60–1.29; p=0.4601).

Secondary and exploratory end-points

As the primary objective of the study was not met, all other efficacy analyses are considered exploratory. The mean 6MWD worsened by 14.6±80.4 m in the placebo group and improved at 16 weeks by 7.2±66.0 m in the bosentan group; the difference between the groups (21.8 m, 95% CI 5.9–37.8 m) was nominally

TABLE 1 Baseline characteristics in placebo and bosentan groups			
	Placebo	**Bosentan**	**All**
Patients n	175	159	334
Sex			
Female	128 (73.1)	125 (78.6)	253 (75.7)
Male	47 (26.9)	34 (21.4)	81 (24.3)
Age years			
Mean±SD	54.7±15.7	52.9±15.4	53.9±15.6
Median (interquartile range)	56.0 (41.0–68.0)	55.0 (40.0–65.0)	55.0 (40.0–66.0)
BMI# kg·m^{-2}			
Mean±SD	29.1±6.95	28.5±6.83	28.8±6.9
Median (interquartile range)	28.2 (24.5–32.8)	27.5 (23.9–32.2)	28.0 (24.1–32.8)
Geographical region			
USA	83 (47.4)	73 (45.9)	156 (46.7)
Europe	56 (32.0)	50 (31.4)	106 (31.7)
Brazil	35 (20.0)	36 (22.6)	71 (21.3)
Saudi Arabia	1 (0.6)		1 (0.3)
Time from PAH diagnosis months			
Mean±SD	26.2±51.2	25.3±47.3	25.7±49.4
Median (interquartile range)	11.4 (6.0–24.9)	12.2 (6.6–28.4)	12.1 (6.3–26.0)
Aetiology of PAH			
Idiopathic	114 (65.1)	99 (62.3)	213 (63.8)
Familial	2 (1.1)	3 (1.9)	5 (1.5)
Connective tissue disease	45 (25.7)	43 (27.0)	88 (26.3)
Repaired congenital shunts	11 (6.3)	9 (5.7)	20 (6.0)
Drugs and toxins	3 (1.7)	5 (3.1)	8 (2.4)
6-min walk distance m			
Mean±SD	357.6±73.1	363.1±78.5	360.3±75.7
Median (interquartile range)	372.0 (305–410)	385.0 (306–423)	375.5 (306–416)
WHO functional class			
II	69 (39.4)	71 (44.7)	140 (41.9)
III	104 (59.4)	88 (55.3)	192 (57.5)
IV	2 (1.1)		2 (0.6)
NT-proBNP¶ pmol·L^{-1}			
Mean±SD	170.1±239.4	189.7±384.0	179.6±317.2
Median (interquartile range)	56.6 (21.6–208.5)	54.3 (19.4–201.0)	54.9 (19.7–202.6)
Baseline sildenafil dose mg			
Mean±SD	81.1±45.1	77.8±48.5	79.6±46.7
Median (interquartile range)	60 (60–75)	60 (60–60)	60 (60–60)

Data are presented as n (%) unless otherwise stated. BMI: body mass index; PAH: pulmonary arterial hypertension; WHO: World Health Organization; NT-proBNP: N-terminal pro-brain natriuretic peptide. #: placebo, n=172; bosentan, n=157. ¶: placebo, n=117; bosentan, n=110.

TABLE 2 Primary end-point events in the placebo and bosentan groups

	Placebo	Bosentan
Patients n	175	159
Primary end-point event	90 (51.4)	68 (42.8)
Worsening of PAH[#]	52 (29.7)	32 (20.1)
Hospitalisation for PAH or start of *i.v.* prostanoid therapy	20 (11.4)	25 (15.7)
Death	18 (10.3)	10 (6.3)
Atrial septostomy	0 (0.0)	1 (0.6)
Lung transplantation	0 (0.0)	0 (0.0)

Data are presented as n (%) unless otherwise stated. Events listed are the first confirmed morbidity/ mortality events. PAH: pulmonary arterial hypertension. [#]: worsening PAH was 1) "moderately worse" or "markedly worse" symptoms and requirement for addition of PAH therapy (initiation of a subcutaneous or inhaled prostanoid, or transfer to open-label bosentan), or 2) "no change" or "mildly worse" symptoms, and requirement for addition PAH therapy and deterioration in 6-min walk distance >20% from the previous visit or >30% from the baseline visit.

significant (p=0.0106) (figure 4). There were no differences between the two groups in change in WHO functional class; time to first occurrence of death, hospitalisation for PAH or start of intravenous prostanoid therapy, atrial septostomy or lung transplantation; or time to death from any cause (table 3). NT-proBNP levels increased with placebo and generally remained stable with bosentan over 20 months of treatment, with a difference between the groups in favour of bosentan (p=0.0003) (supplementary figure 1).

Safety and tolerability

Of 334 randomised patients, all but one was included in the safety analyses; the excluded patient was randomly assigned to placebo but did not receive the study drug. Patients in the placebo and bosentan groups received double-blind treatment for a mean±SD duration of 30.7±24.31 and 26.4±20.99 months, respectively. During the double-blind phase of the trial, 22 (12.6%) out of 174 patients in the placebo group and 39 (24.5%) out of 159 patients in the bosentan group permanently discontinued the study drug due to an AE. The most common AEs experienced by patients receiving bosentan were related to the underlying disease (table 4). No new safety signals were observed.
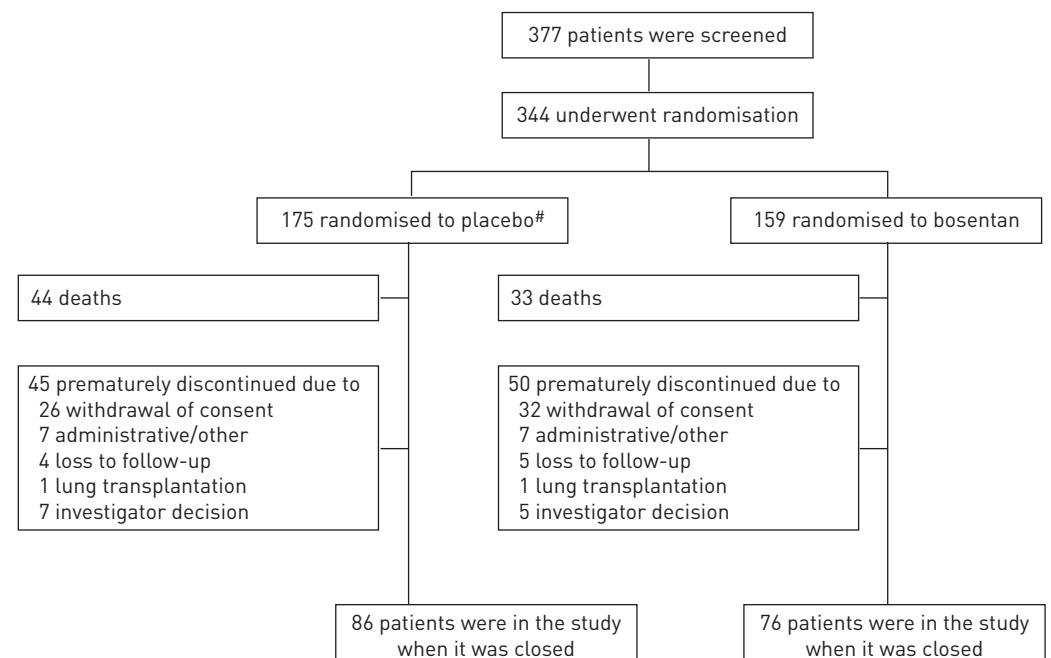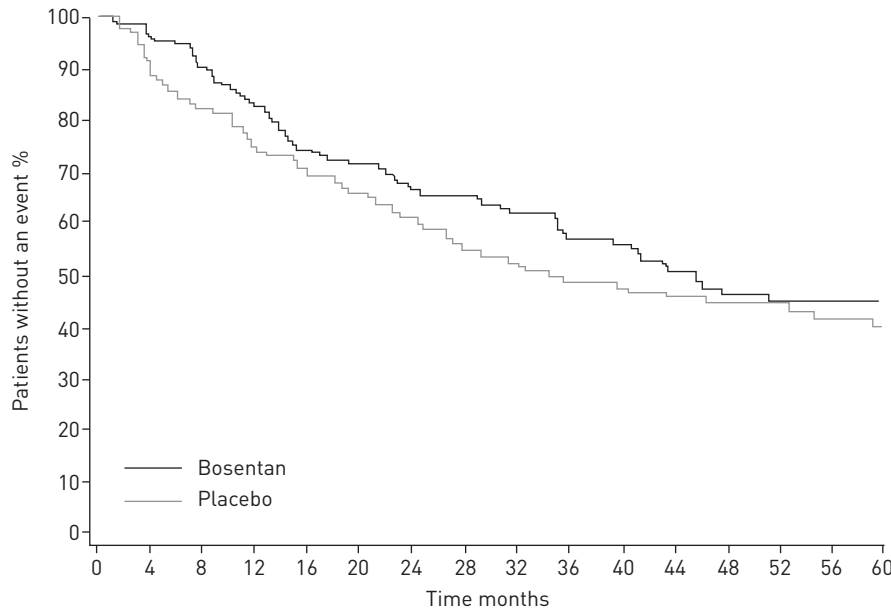

FIGURE 1 Patient disposition. [#]: one patient randomly assigned to receive placebo did not receive the study drug.

FIGURE 2 Time to primary end-point event up to the end of the study. Kaplan–Meier estimates for the time to first primary end-point event (death from any cause, hospitalisation for pulmonary arterial hypertension (PAH) or start of intravenous prostanoid therapy, atrial septostomy, lung transplantation, or worsening PAH) show a treatment effect in favour of bosentan versus placebo (hazard ratio 0.831, 97.31% CI 0.582–1.187; p=0.2508 by the log-rank test).

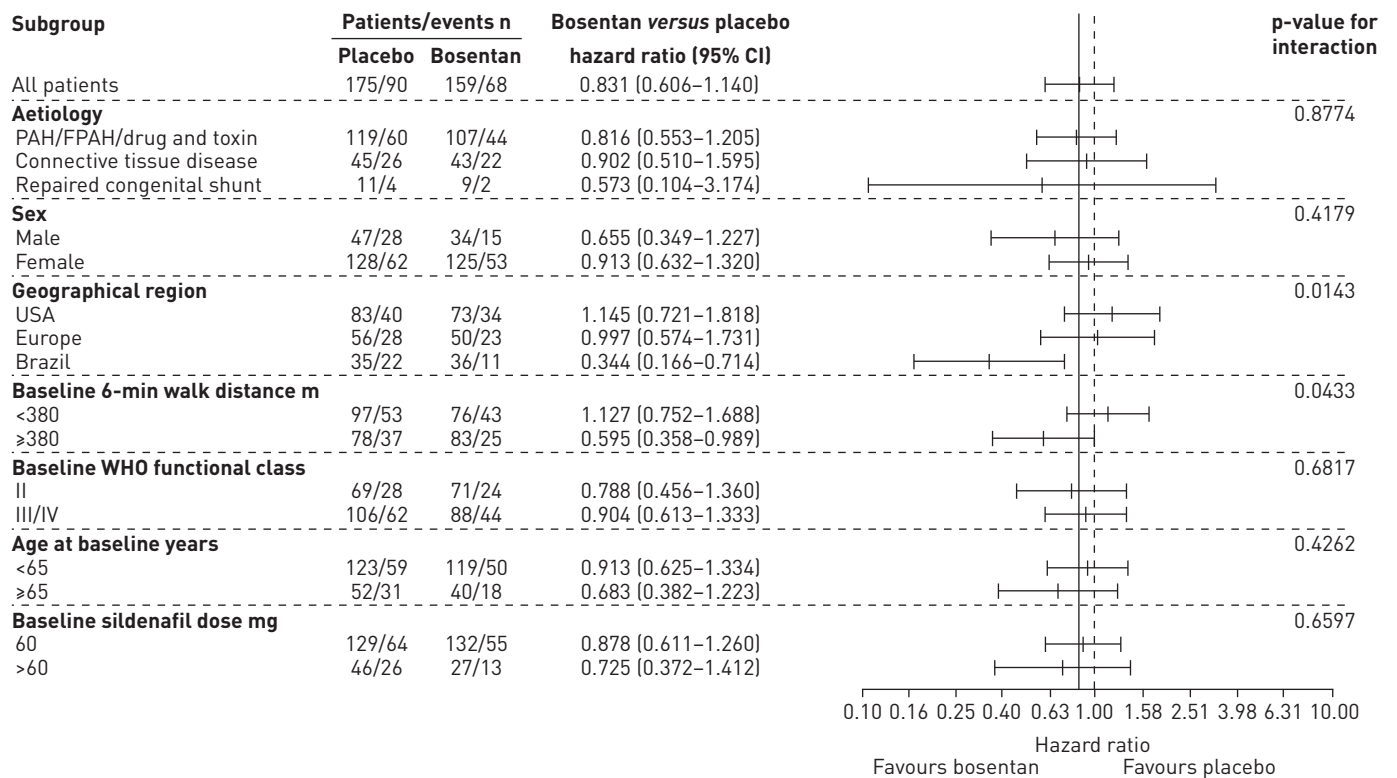| Subgroup	Patients/events n		Bosentan *versus* placebo	p-value for interaction
	Placebo	Bosentan	hazard ratio (95% CI)	
All patients	175/90	159/68	0.831 (0.606–1.140)	
Aetiology				0.8774
PAH/FPAH/drug and toxin	119/60	107/44	0.816 (0.553–1.205)	
Connective tissue disease	45/26	43/22	0.902 (0.510–1.595)	
Repaired congenital shunt	11/4	9/2	0.573 (0.104–3.174)	
Sex				0.4179
Male	47/28	34/15	0.655 (0.349–1.227)	
Female	128/62	125/53	0.913 (0.632–1.320)	
Geographical region				0.0143
USA	83/40	73/34	1.145 (0.721–1.818)	
Europe	56/28	50/23	0.997 (0.574–1.731)	
Brazil	35/22	36/11	0.344 (0.166–0.714)	
Baseline 6-min walk distance m				0.0433
<380	97/53	76/43	1.127 (0.752–1.688)	
⩾380	78/37	83/25	0.595 (0.358–0.989)	
Baseline WHO functional class				0.6817
II	69/28	71/24	0.788 (0.456–1.360)	
III/IV	106/62	88/44	0.904 (0.613–1.333)	
Age at baseline years				0.4262
<65	123/59	119/50	0.913 (0.625–1.334)	
⩾65	52/31	40/18	0.683 (0.382–1.223)	
Baseline sildenafil dose mg				0.6597
60	129/64	132/55	0.878 (0.611–1.260)	
>60	46/26	27/13	0.725 (0.372–1.412)	

FIGURE 3 Time to primary end-point event by subgroup. For geographical region, one patient from Saudi Arabia was excluded from the analysis. Error bars represent 95% confidence intervals. PAH: pulmonary arterial hypertension; FPAH: familial pulmonary arterial hypertension; IPAH: idiopathic pulmonary arterial hypertension; WHO: World Health Organization.
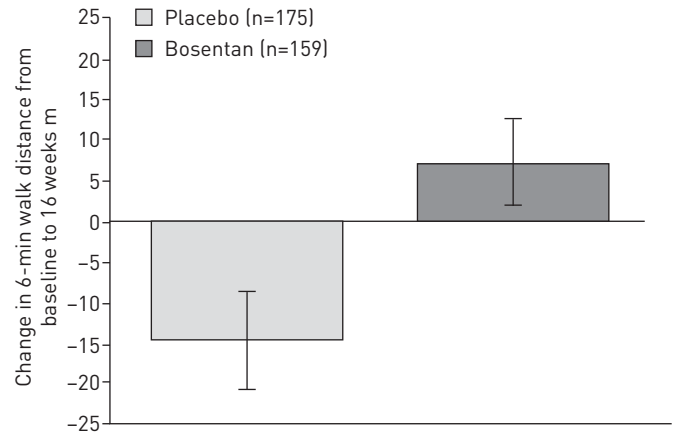
FIGURE 4 Change from baseline in 6-min walk distance at 16 weeks. The difference between the groups was 21.8 m (95% CI 5.9–37.8 m, p=0.0106) by Wilcoxon rank-sum test in favour of bosentan. Data are presented as mean±SEM.

The incidence of ALT or AST more than three times the upper limit of normal on double-blind treatment was 6.4% in the placebo group (n=11) and 21.8% in the bosentan group (n=34) (table 4). In the patients treated with bosentan, the majority of the ALT and AST elevations occurred within the first 12 months of treatment (17 (11.4%) at 4 months and 27 (18.9%) at 12 months). Similar proportions of patients in the placebo and bosentan groups experienced a decrease in haemoglobin levels to $\leqslant$10 g·dL^{-1} (8.8% and 9.0%, respectively).

Discussion

The COMPASS-2 study failed to demonstrate a statistically significant effect on the primary endpoint of time to first confirmed morbidity/mortality event, when adding bosentan therapy to sildenafil. There was a nominally significant difference between the treatment groups in favour of bosentan with regards to changes in 6MWD at week 16 and in NT-proBNP; however, no such differences were observed for any other efficacy endpoint. The safety profile of bosentan when added to sildenafil was consistent with the known safety profile of bosentan used as monotherapy. Specifically, the placebo-corrected incidence of liver aminotransferase elevations and haemoglobin decreases are consistent with other long-term bosentan data [8, 9], and no new safety signals were observed.

It was assumed that adding bosentan to sildenafil might improve the long-term outcome of PAH patients. This hypothesis was based on the observed effects of bosentan monotherapy on time to clinical worsening in earlier short-term trials [10–12], open-label uncontrolled reports [13] and preliminary data [14] that suggested a clinical benefit when bosentan was combined with sildenafil in patients with PAH.

There are several potential reasons why the COMPASS-2 study did not meet its primary end-point. First, the study was designed to detect a large treatment effect of >40%; the number of events was too few to allow the detection of smaller, but still potentially meaningful, effects (e.g. 20%).

TABLE 3 Secondary end-points

	Placebo	Bosentan	Treatment effect versus placebo
Patients n	175	159	
Change in WHO functional class from baseline to 16 weeks			Relative risk of improvement[#] 0.98 (95% CI 0.60–1.61, p=1.000[¶])
Worsened	17 (9.7)	13 (8.2)	
Unchanged	130 (74.3)	121 (76.1)	
Improved	28 (16.0)	25 (15.7)	
Time to death, hospitalisation for PAH, atrial septostomy or lung transplantation up to the end of the study			Hazard ratio 0.963 (95% CI 0.673–1.380, p=0.8385[+])
Patients	67 (38.3)	54 (34.0)	
Time to death from any cause up to the end of the study			Hazard ratio 0.855 (95% CI 0.544–1.344, p=0.4974[+])
Patients	44 (25.1)	33 (20.8)	

Data are presented as n (%) unless otherwise stated. WHO: World Health Organization; PAH: pulmonary arterial hypertension. [#]: versus no improvement; [¶]: Fisher's exact test; [+]: log-rank test.

TABLE 4 Exposure, safety and tolerability during double-blind treatment period

	Placebo	Bosentan
Patients n	174[#]	159
Exposure to double-blind study drug months		
Mean±SD	30.7±24.31	26.4±20.99
Median (interquartile range)	23.3 (0.3–85.7)	22.7 (0.0–86.7)
Variable		
Patients with adverse events	159 (91.4)	144 (90.6)
Patients with serious adverse events	102 (58.6)	73 (45.9)
Patients with adverse events leading to discontinuation of double-blind treatment	22 (12.6)	39 (24.5)
Patients with adverse events		
Worsening of pulmonary arterial hypertension	61 (35.1)	39 (24.5)
Oedema, peripheral	28 (16.1)	30 (18.9)
Dyspnoea	26 (14.9)	25 (15.7)
Headache	24 (13.8)	24 (15.1)
Upper respiratory tract infection	30 (17.2)	22 (13.8)
Cough	21 (12.1)	22 (13.8)
Chest pain	16 (9.2)	22 (13.8)
Diarrhoea	19 (10.9)	19 (11.9)
Pneumonia	13 (7.5)	18 (11.3)
Bronchitis	21 (12.1)	17 (10.7)
Dizziness	18 (10.3)	17 (10.7)
Anaemia	12 (6.9)	17 (10.7)
Nausea	22 (12.6)	16 (10.1)
Urinary tract infection	14 (8.0)	16 (10.1)
ALT increase	8 (4.6)	16 (10.1)
Back pain	23 (13.2)	15 (9.4)
Arthralgia	20 (11.5)	13 (8.2)
Fatigue	20 (11.5)	13 (8.2)
Syncope	12 (6.9)	8 (5.0)
Hypotension	7 (4.0)	0 (0)
Laboratory abnormality[¶]		
ALT or AST >3×ULN	11 (6.4)	34 (21.8)
ALT or AST >8×ULN	0 (0)	8 (5.1)
Haemoglobin ⩽10 g·dL^{-1}	15 (8.8)	14 (9.0)

Data are presented as n (%) unless otherwise stated. ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal. [#]: one patient randomly assigned to receive placebo did not receive the study drug and was excluded from the safety analyses. [¶]: placebo, n=171; bosentan, n=156.

Second, the extent of missing information for the primary end-point (calculated at 20%) as a result of patients discontinuing the study prematurely, without experiencing a primary end-point, was sizeable. The magnitude of missing data further reduced the statistical power and is an important factor when considering the study outcome. Although efforts were made, prior to study closure, to retrospectively collect additional data about these patients, this was not feasible due to patient privacy restrictions.

Third, the worsening PAH component of the primary end-point, which contributed most to the study outcome, differs from that used in recent PAH studies [5, 15, 16] in that it was determined using the PGSA score as the initial step, with subsequent consideration of 6MWD and the need for additional PAH therapy. Although the PGSA has not been validated in PAH and is associated with some limitations (*e.g.* it relies on the patient's recognition of worsening PAH symptoms), it was included in an attempt to ensure a patient-centric approach in conjunction with additional objective measures. At that time, validated PAH-specific patient-reported outcome tools were unavailable. Following the third World Symposium on Pulmonary Hypertension, recommendations regarding composite end-points have evolved and this is reflected in the design of more recent PAH studies, which have employed composite primary end-points with more objective criteria for assessing disease progression [5, 16].

Fourth, despite employing comparable inclusion and exclusion criteria to those used in PAH studies at the time of the start of COMPASS-2, the patient population observed in COMPASS-2 was slightly older and the patients had more comorbidities compared with those seen in contemporary PAH trials (key comorbidities are listed in table 3 of the supplementary material) [11, 17, 18]. Baseline characteristics,

such as older age, comorbidities, concomitant medications and higher BMI, may have affected the response to PAH-specific therapy in those patients and, thus, may have led to a diluted treatment effect. This is suggested by the observed improvement in the primary end-point in certain subgroups, such as the patients from Brazil (figure 3), whose baseline characteristics were more typical of patients enrolled in early PAH studies (*e.g.* low BMI, fewer comorbidities and younger age), and patients who were able to walk >380 m at baseline. Such subgroup effects must be interpreted with caution given the lack of statistical significance in the overall population, the absence of correction for multiple testing and the small number of patients in each subgroup. Nevertheless, this observation suggests that the evolution of inclusion/exclusion criteria in subsequent PAH trials, incorporating more stringent screening steps to minimise the enrolment of patients with confounding factors such as comorbidities, is warranted. The need for careful oversight of enrolled patients has been a key lesson from COMPASS-2 and has affected subsequent long-term event-driven trials in PAH [5, 16].

Fifth, co-administration of bosentan and sildenafil is known to reduce plasma levels of sildenafil and to increase the plasma levels of bosentan [19], and this pharmacokinetic interaction may have contributed to the lack of effect on the primary end-point. However, this remains speculative as plasma levels of both drugs were not measured during this study.

Finally, the trial recruited and followed patients over 7.5 years; the long duration of the trial was mainly due to the slow rate of patient enrolment. During this time, the management and treatment options of patients with PAH changed considerably; such changes may have affected the type of patients enrolled and the retention of patients in the trial.

Conclusion

COMPASS-2 did not demonstrate that adding bosentan to stable sildenafil therapy was superior to sildenafil monotherapy in delaying the time to the first morbidity/mortality event. Given the limitations of the study, the overall results of the COMPASS-2 study must be interpreted with caution.

References

1 Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med* 2004; 351: 1425–1436.
2 Sitbon O, Morrell N. Pathways in pulmonary arterial hypertension: the future is here. *Eur Respir Rev* 2012; 21: 321–327.
3 Sitbon O, Simonneau G. Optimal management of severe pulmonary arterial hypertension. *Eur Respir Rev* 2011; 20: 254–261.
4 Ghofrani HA, Humbert M. The role of combination therapy in managing pulmonary arterial hypertension. *Eur Respir Rev* 2014; 23: 469–475.
5 Pulido T, Adzerikho I, Channick RN, *et al.* Macitentan and morbidity and mortality in pulmonary arterial hypertension. *N Engl J Med* 2013; 369: 809–818.
6 Galiè N, Seeger W, Naeije R, *et al.* Comparative analysis of clinical trials and evidence-based treatment algorithm in pulmonary arterial hypertension. *J Am Coll Cardiol* 2004; 43: 81S–88S.
7 Hoeper MM, Oudiz RJ, Peacock A, *et al.* Endpoints and clinical trial designs in pulmonary arterial hypertension: clinical and regulatory perspectives. *J Am Coll Cardiol* 2004; 43: 48S–55S.
8 Simonneau G, Galiè N, Jansa P, *et al.* Long-term results from the EARLY study of bosentan in WHO functional class II pulmonary arterial hypertension patients. *Int J Cardiol* 2014; 172: 332–339.
9 Actelion Pharmaceuticals UK Ltd. Tracleer (bosentan) 62.5mg film-coated tablets. www.medicines.org.uk/emc/medicine/20422/SPC/Tracleer+(bosentan)+62%205mg+film-coated+tablets/ Date last accessed: September, 2014. Date last updated: January 2015.
10 Channick RN, Simonneau G, Sitbon O, Effects of the dual endothelin-receptor antagonist bosentan in patients with pulmonary hypertension: a randomised placebo-controlled study. *Lancet* 2001; 358: 1119–1123.
11 Rubin LJ, Badesch DB, Barst RJ, *et al.* Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002; 346: 896–903.
12 Galiè N, Rubin LJ, Hoeper MM, Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008; 371: 2093–2100.
13 Minai OA, Arroliga AC. Long-term results after addition of sildenafil in idiopathic PAH patients on bosentan. *South Med J* 2006; 99: 880–883.
14 Hoeper MM, Faulenbach C, Golpon H, Combination therapy with bosentan and sildenafil in idiopathic pulmonary arterial hypertension. *Eur Respir J* 2004; 24: 1007–1010.
15 EU Clinical Trials Register. EudraCT number: 2009-014490-41. www.clinicaltrialsregister.eu/ctr-search/trial/2009-014490-41/GB Date last accessed: September, 2014.
16 EU Clinical Trials Register. EudraCT number: 2009-011150-17. www.clinicaltrialsregister.eu/ctr-search/trial/2009-011150-17/GB Date last accessed: September, 2014.
17 Humbert M, Barst RJ, Robbins IM, Combination of bosentan with epoprostenol in pulmonary arterial hypertension: BREATHE-2. *Eur Respir J* 2004; 24: 353–359.
18 Galiè N, Ghofrani HA, Torbicki A, *et al.* Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med* 2005; 353: 2148–2157.
19 Paul GA, Gibbs JS, Boobis AR, Bosentan decreases the plasma concentration of sildenafil when coprescribed in pulmonary hypertension. *Br J Clin Pharmacol* 2005; 60: 107–112.