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Efficacy, safety, and pharmacokinetics of bosentan in portopulmonary hypertension

Short title: Bosentan in portopulmonary hypertension

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Abstract

Data on treatment of patients with portopulmonary hypertension (PoPH) are limited, as they are usually excluded from randomized controlled trials with pulmonary arterial hypertension (PAH) specific therapies. This study investigated short- and long-term efficacy/safety of bosentan in these patients, as well as pharmacokinetics.

All 34 consecutive patients with PoPH treated first-line with bosentan (December 2002 –July 2009) were retrospectively evaluated. Assessments included: New York Heart Association functional class (NYHA FC), blood tests, haemodynamics, 6-minute walk distance (6MWD) and event-free status. Pharmacokinetics of bosentan in 5 patients with Child-Pugh class B cirrhosis were compared with idiopathic PAH patients.

Significant improvements from baseline were observed in NYHA FC, 6MWD, and haemodynamics, and largely maintained during follow up. Patients with C-P class B cirrhosis (n=9) had significantly larger haemodynamic improvement after 5±2 months. Mean follow-up was 43±19 months; 4 patients died; seven patients had significant elevation of liver enzymes (annual rate 5.5%). Plasma concentrations of bosentan were higher in patients with cirrhosis C-P class B than observed in idiopathic PAH.

These data confirm the benefit of bosentan treatment for patients with PoPH. Haemodynamic improvements were particularly pronounced in patients with more severe cirrhosis. The safety profile of bosentan was consistent with previous studies.

Keywords: Hypertension, pulmonary – Portopulmonary hypertension – Endothelin receptor antagonists – Bosentan – Cirrhosis

Introduction

Portopulmonary hypertension (PoPH) is defined as pulmonary arterial hypertension (PAH) associated with portal hypertension, with or without advanced hepatic disease. The disease is classified as group I pulmonary hypertension (PH) in the current pulmonary hypertension (PH) classification [1]. Although it shares many characteristics with idiopathic PAH (IPAH), including pathophysiological changes in lung microvasculature, haemodynamics can be somewhat different at baseline with higher cardiac output and lower pulmonary vascular resistance.

According to estimates, 2–6% of patients with portal hypertension and approximately 1–2% of those with cirrhosis have PoPH [2-5]. PoPH is a relatively common cause of PH, representing 15% of patients enrolled in the French Registry of PAH [6]. Estimates of survival in patients with PoPH have varied widely among published studies [7-10]. The US Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) database, in which data from more than 2700 patients were collected, identified PoPH as an independent predictor of increased mortality among PAH patients (hazard ratio, 3.6; 95% confidence interval, 2.4 to 5.4) [11]. In contrast, Le Pavec *et al*. found that 1-, 3-, and 5-year survival rates among patients followed at the French National Referral Centre were 88%, 75%, and 68%, respectively, suggesting that these patients may in fact have less severe outcomes [7]. Poorer prognosis was associated with Child-Pugh class B or C cirrhosis, high right atrial pressure, and low cardiac index. Differences in the severity of liver disease at time of first assessment among the different series may in part explain the discordance of findings.

In contrast to other types of associated PAH, patients with PoPH have been excluded from the large clinical trials in PAH and there have been no controlled studies of PAH-specific therapies exclusively in PoPH. The majority of data on treatment of PoPH, therefore, derive from case series and case reports. A number of such reports suggest that the dual endothelin receptor antagonist (ERA) bosentan is well tolerated and effective in this population [12-18]. In a small study, treatment with bosentan proved to be efficacious and

well tolerated in patients with C-P class A cirrhosis [19, 20]. Furthermore, the pharmacokinetics of bosentan and its metabolites in patients with C-P class A did not differ to a relevant extent from those in healthy subjects [21]. However, to date there has been only one case report of treatment with bosentan in a single patient with more advanced liver disease [17]. This lack of data is mainly due to safety concerns associated with impaired metabolism and potentially increased risk of liver abnormalities in patients with advanced liver diseases. Indeed, bosentan is not approved for C-P B and C patients.

This present study provides data on both short- and long-term efficacy on the use of bosentan in patients with PoPH, as well as safety, tolerability, and some pharmacokinetic data. It is the first study to investigate the effect of treatment in patients with PoPH and cirrhosis, which included C-P class B patients.

Patients and Methods

Study subjects

This was a retrospective study, which aimed at describing the short- and long-term outcome of unselected patients with PoPH treated with first-line bosentan, including patients with non-cirrhotic portal hypertension and patients with C-P class A and B cirrhosis.

Data were analysed from a total of 34 consecutive patients with PoPH treated with first-line bosentan between December 2002 and July 2009 at the French Reference Center for severe PH in Clamart (France).

PAH was diagnosed by means of right heart catheterization (RHC) showing a mean pulmonary arterial pressure (mPAP) at rest of >25 mmHg, a pulmonary capillary wedge pressure <15 mmHg, and a pulmonary vascular resistance (PVR) of >3 Wood units [22]. Acute vasodilator testing with inhaled nitric oxide (10 ppm) was performed in all patients, as previously described [23]. The presence of primary lung disease and post-embolic pulmonary hypertension was excluded by performing pulmonary function tests, computed tomography of the chest, and ventilation/perfusion lung scan.

The diagnosis of portal hypertension was based on haemodynamic measurement of a hepatic venous pressure gradient of more than 5 mmHg or presence of oesophageal varices at endoscopy or portal vein thrombosis diagnosed by Doppler abdominal ultrasound. Cirrhosis was documented by history of liver biopsy findings or typical clinical and/or biological signs.

According to French legislation, ethics committee agreement and provision of informed consent are not required for retrospective collection of data corresponding to current practice. The database was, however, compiled anonymously within the restrictive requirements of the Commission Nationale Informatique et Liberté, the organisation dedicated to privacy, information technology, and civil rights in France. The present study was approved by the local institutional review board. For the pharmacokinetic (PK) study, informed consent was obtained. Five patients with C-P class B cirrhosis and 3 patients with IPAH were included in the PK sub-study (AC-052-114), which was approved by the ethics committee.

Treatment

All patients received non-specific supportive therapies in accordance with current guidelines, diuretics to control signs and symptoms of right heart failure (including peripheral oedema), and long-term oxygen therapy if hypoxaemia was present [24, 25]. Anticoagulants are not usually administered in the presence of severe hepatocellular insufficiency and/or thrombocytaemia due to hypersplenism.

Bosentan was prescribed according to the European Summary of Product Characteristics at 62.5 mg b.i.d. for 4 weeks, followed by 125 mg b.i.d. thereafter. All patients had liver enzymes < 3x upper limit of normal (ULN) before initiation of bosentan. For 7 patients (4 with C-P class B cirrhosis and 3 with C-P class A cirrhosis) the dosing regimen was maintained at 62.5 mg b.i.d. because of mildly increased liver enzymes <3x ULN at baseline. Liver function tests were performed every 2 weeks during the first 6 weeks and

monthly thereafter. In the event of elevated liver enzymes, bosentan was stopped or the dosage was reduced, in accordance with current recommendations [26].

Assessments

All patients underwent a complete baseline evaluation before starting bosentan therapy, including assessment of modified New York Heart Association Functional Class, physical examination, routine blood tests, non-encouraged 6-minute walk distance (6MWD), and resting haemodynamic variables measured by RHC. Patients were reassessed for all parameters at short and long term. Haemodynamic assessment was repeated 3-6 months after bosentan initiation, then every year or in case of clinical worsening. Non-invasive assessments were also repeated every 4–6 months. The first and last evaluation on bosentan monotherapy were analysed for the study.

Event-free status was defined as the survival time without introduction of prostacyclin analogues and/or phosphodiesterase type-5 inhibitors therapy, discontinuation of bosentan, or acute right heart failure requiring hospitalisation for intravenous diuretics and/or dobutamine infusion.

Pharmacokinetics

Five patients with C-P class B cirrhosis were included in a pharmacokinetic sub-study and compared with 3 patients with IPAH. Blood samples for the determination of plasma concentrations of bosentan and its three metabolites (Ro 47-8634, Ro 48-5033, and Ro 64-1056) were taken at regular intervals (predose, and 1, 2, 3, 4, 5, 6, 9, and 12 h after drug intake) over a dosing interval after patients had been on stable bosentan treatment for at least 14 days. Ro 48-5033 is the only pharmacologically active metabolite. Plasma concentrations were determined with a validated LC-MS/MS assay [27]. The pharmacokinetic variables were assessed by noncompartmental analysis (WinNonlin).

All patients with C-P class B cirrhosis were included in the pharmacokinetic sub-study 14 days after the start of treatment with bosentan at 62.5 mg b.i.d. Two patients with IPAH were treated with bosentan at 125 mg b.i.d. and one at 62.5 mg b.i.d. at the time of the pharmacokinetic sub-study. Pharmacokinetic variables were normalized to a dose of 125 mg b.i.d. This is justified in view of the small dose range investigated in this study and because the pharmacokinetics of bosentan are proportional to dose over a wide dose range [28].

Analysis

Results are expressed as mean ± standard deviation (SD) or as median. Baseline and post-baseline values for 6MWD, and haemodynamic variables were compared using a two-sided paired t-test. For the subgroup of patients for whom baseline data, data after 4 months, and data at last evaluation were available, comparisons were made using ANOVA. Changes in NYHA FC were compared using the Chi-squared test. A p-value <0.05 was to be considered statistically significant. Analyses of event-free status were performed using an intention-to-treat approach and the Kaplan–Meier method. The date of initiation of bosentan therapy was the starting point for determining the follow-up duration and estimating survival. Patients lost to follow-up were censored as of the date of the last bosentan prescription.

Results

Between December 2002 and July 2009, 77 patients with newly diagnosed PoPH were evaluated in our centre. Among them, 10 did not receive any PAH-specific therapy, 17 were treated with first-line sildenafil, 11 with i.v. epoprostenol, one with inhaled iloprost, and 4 with combination therapy (bosentan in association with sildenafil or epoprostenol). Finally, 34 patients were given first-line bosentan monotherapy and constituted the patient population of this study. Patient demographics at baseline as well as aetiologies of liver disease are shown in Table 1. Six patients had portal thrombosis without cirrhosis. Among the 28 patients with

cirrhosis, 19 were classified into C-P class A and 9 into class B. Five patients with C-P class B cirrhosis were included in the PK sub-study. No patient displayed positive acute vasodilator response to inhaled nitric oxide at first haemodynamic assessment.

Short-term efficacy

Short-term evaluation was performed after 5±2 months after bosentan initiation. Significant improvements from baseline were observed in 6MWD, NYHA FC, and haemodynamic variables (Table 2). Pulmonary haemodynamic data significantly improved with an increase in cardiac index (CI) and a decrease in PVR by a mean of 39% and 31%, respectively.

The short-term haemodynamic response was significantly better in patients with C-P class B cirrhosis, compared to those with C-P class A cirrhosis or with non-cirrhotic portal hypertension (PoH) (Figure 1). Individual data for patients with C-P class B cirrhosis after first evaluation of treatment are shown in Table 3. Notably, PVRs were near-normalized or normalized (<3 Wood units) in a subset of patients with cirrhosis C-P class B after 4 months of bosentan treatment.

After first evaluation, bosentan monotherapy was continued in 27 patients and sildenafil was added in 7. All these 7 patients had cirrhosis C-P class A.

Long-term efficacy

24 patients were assessed at least three times under bosentan monotherapy. The last evaluation of these patients was conducted 35±16 months (range 12-75 months) after bosentan initiation. The remaining 10 patients did not undergo long-term evaluation on monotherapy with bosentan for the following reasons: 7 patients received sildenafil in addition to bosentan after the first evaluation, sildenafil was introduced to replace bosentan in 1 patient because of liver toxicity, and 2 patients were receiving bosentan monotherapy but had only one evaluation at cut-off. In patients who were evaluated at least three times, improvements in haemodynamic variables observed at short term were largely maintained, with significant improvement of NYHA FC and increase over baseline in CI and PVR (Table

2). 6MWD significantly improved from baseline in this group of patients at final assessment. Individual data for patients with C-P class B after 37±25 months of treatment are shown in Table 3.

Effect of bosentan therapy on overall and event-free surviva

At the cut-off date (May 31, 2010), the mean follow-up period was 43±19 months. Event-free survival estimates were 82%, 63%, and 47% at 1, 2, and 3 years, respectively. Event-free survival curves were similar in patients with non cirrhotic PoH or C-P class A cirrhosis and patients with more severe C-P class B cirrhosis (Figure 2A).

Twelve patients required additional PAH-specific therapies during the follow-up period. All of them received sildenafil in combination with bosentan.

Four patients died during follow-up at 21, 36, 61, and 67 months, respectively. Three had cirrhosis C-P class A and 1 had cirrhosis C-P class B. The cause of death was right heart failure for 3 patients and hepatocellular carcinoma for one patient (Figure 2B).

Safety

A significant elevation of liver enzymes (>3xULN) was observed in 7 patients, corresponding to an annual rate of 5.5%. Among these 7 patients, bosentan was discontinued in 3 patients with C-P class A cirrhosis after 6, 15, and 33 months, and 2 others with C-P class B cirrhosis after 16 and 58 months due to increased liver enzymes. Bosentan was discontinued in 3 patients who received moderately high dosage (62.5 mg b.i.d.) because of a moderately elevated level of liver enzymes at baseline between 1 to 3x ULN. In all cases, sildenafil was introduced to replace bosentan. Annual rate of increase in liver enzymes was 4.1% (CI 95%, 0.2-8%) in patients with non-cirrhotic PoH and with cirrhosis CP class A, and 12.4% (CI 95%, 0.7-25.6%) in patients with cirrhosis C-P class B (not statistically significant). In 6 cases, normalization of hepatic transaminase levels was observed during the 3 months following

bosentan dose reduction or discontinuation. In one other case, persistently abnormal liver enzyme levels were attributed to underlying hepatocellular carcinoma.

Pharmacokinetics

Figure 3 presents the dose-normalized plasma concentration-time profiles of bosentan in 5 PoPH patients with C-P class B cirrhosis and 3 patients with IPAH. The profiles of the three bosentan metabolites measured showed a similar course and difference between the groups (data not shown). The pharmacokinetic variables derived from the individual plasma concentration-time profiles are presented in Table 4.

Discussion

There are currently few data on the use of PAH-specific therapies in PoPH, particularly in patients with more advanced hepatic disease. This study was one of the largest to date in this patient population and the first to include a significant number of patients in C-P class B. Treatment with bosentan was associated with short-term improvements in functional status, 6MWD, and haemodynamics that were maintained over the long-term. In patients with more advanced liver disease C-P class B, haemodynamic response was greater leading to a normalisation or near-normalisation of PVR in some patients. Moreover, long-term treatment with bosentan was well tolerated in patients with mild or more severe cirrhosis.

The mean treatment duration of 47±20 months enables an adequate evaluation of the potential long-term benefits of bosentan therapy in those patients. Significant improvement in haemodynamic variables between baseline and follow-up evaluations is encouraging since it is correlated with a better prognosis [7]. Indeed, patients with a lower CI are usually at higher risk of death [7]. Therefore, improvement in CI in this study suggests that bosentan may be beneficial and improve survival. In these patients with portal hypertension, bosentan seems at least as effective as previously observed in double-blind, placebo-controlled studies in patients with IPAH and PAH associated with connective tissue disease [29-31].

The pronounced improvements observed in patients with liver disease in C-P class B are of particular interest. This is an important result, because risk of mortality is higher for PoPH patients with more severe liver disease [7]. Despite the existence of a more severe liver dysfunction in patients with cirrhosis CP class B, known to be a poorer prognostic factor, the event-free survival is equivalent for patients with mild cirrhosis or non-cirrhotic portal hypertension and patients with more severe cirrhosis. Normalization or near-normalization of haemodynamics is exceptional with PAH-specific therapy in patients with either IPAH or PAH associated with concomitant disease. This type of response is generally observed in patients with PAH associated with inflammatory conditions such as HIV infection or connective tissue diseases [32, 33]. Inflammatory processes are more important in patients with more advanced hepatic disorders, which could explain pronounced improvement in these patients. In patients with portal hypertension, the development of portosystemic shunts, a decrease in liver phagocytic capacity, and increased frequency of bacterial translocation facilitate the circulation of pulmonary cytokines, proangiogenic factors or bacterial endotoxins, which probably induce pulmonary vascular endothelium dysfunction and increase production of endothelin. Data from this study also suggest a role of endothelin in the pathologic process of PoPH. In addition, there is evidence suggesting that ET-1 may be aetiologically relevant in portal hypertension and hepatic fibrotic remodelling [34-37].

Another hypothesis explaining differences of response in patients with more severe cirrhosis could be increased systemic exposure to bosentan and/or its active metabolite due to impaired metabolism in such patients. Results from the pharmacokinetic sub-study presented here suggest that this is indeed the case, as C_{max} was considerably higher in PoPH patients with cirrhosis C-P class B than those with IPAH although patients with cirrhosis were taking lower doses of bosentan at the time of the pharmacokinetic sub-study. The underlying mechanism for this difference is probably a decrease in the efficiency of organic anion transporter peptide (OATP), the transporter responsible for uptake of bosentan into hepatocytes, rather than enzymes responsible for bosentan metabolism in the liver (cytochrome P450 isoenzymes) because the extent of the increase in exposure was similar

for bosentan and its metabolites. Although only 3 patients with IPAH were included as comparators in this study, the pharmacokinetic results obtained were very similar to those obtained in a larger group of PAH patients [28]. More detailed pharmacokinetic studies are warranted to investigate the influence of more severe forms of liver cirrhosis on the disposition of ERAs.

The use of ERAs is associated with an increased frequency of elevated aminotransferase levels, and monthly liver function tests are required for all patients treated with them. Therefore, potential concerns exist regarding their safety in patients with cirrhosis/impaired liver function such as those analysed in this study. Liver damage could also change the metabolism of bosentan in such patients. However, the results presented here suggest that there is no difference between patients with PoPH and those with other forms of PAH. The annual rate of liver enzyme elevations observed in this study is similar to that previously reported in the post-marketing surveillance of bosentan [38] and in other trials in PAH [29-31]. They usually develop gradually, remain asymptomatic, and are generally reversible either spontaneously or after dose reduction or discontinuation. We observed a trend for higher annual rate of aminotransferases elevation and higher incidence of bosentan discontinuation in patients with more severe cirrhosis. In all cases, liver disturbance was reversible and without impact on liver disease evolution. However, close monitoring of liver enzymes should be conducted in patients with more severe cirrhosis C-P class B. Despite a good haemodynamic response observed in patients with advanced liver disease, bosentan should probably be used with caution in these patients and after having considered the use of alternative treatments without liver liability as first-line therapy. In addition, the results of the pharmacokinetic sub-study and responses to treatment observed in patients with more advanced liver disease may suggest that the use of bosentan at a dose of 62.5 mg b.i.d. may be sufficient.

A recently published observational study has reported on the effects of ambrisentan, a selective antagonist of the ET-1 A receptor subtype, in 13 patients with moderate to severe PoPH associated with mild cirrhosis (C-P class A). Treatment was associated with a

significant reduction in mPAP and PVR without adverse effects on liver function tests [39]. This drug, considering having a minimal effect on liver function, could also be an interesting option in patients with more severe cirrhosis. This option must be properly evaluated.

The main limitation of this study was its retrospective open-label design. Accordingly, data presented here should be interpreted with caution. Another limitation is the potential selection bias in the long-term data analysed in this study; it is possible that the patient population was enriched for patients who responded to treatment. This is especially true for the long-term analysis of 6MWD. Because of the small numbers, and the variability on dosing, the PK data have to be also interpreted with caution. It is unfortunate that bosentan plasma levels were not measured in all patients, especially as samples were obtained only from 3 control patients. However, the pharmacokinetic properties of bosentan in these control patients were in close accordance with those assessed in a larger historical control group [28]. Furthermore, the fact that bosentan plasma levels were not measured at least in some C-P A patients is also a limitation of the study. The pharmacokinetics of bosentan in C-P class A patients had been studied previously [21] but these patients were not diagnosed with PoPH. Finally, plasma levels may not necessary reflect tissular drug action on the receptor. Nevertheless, this study represents a considerable advance on previously available data and provides a rationale for further studies investigating this important patient population. It is unlikely that any future studies will be placebo-controlled given the poor prognosis of patients with PAH who do not receive treatment [40]. A prospective open-label trial would provide valuable data. Furthermore, pharmacological data should be enriched by a larger study comparing the pharmacokinetics of bosentan between patients with mild cirrhosis and more severe cirrhosis.

These data confirm the benefit of bosentan in the treatment of patients with PoPH, especially with regards to haemodynamic improvements. In particular, this study suggests greatest positive haemodynamic responses in patients with C-P stage B cirrhosis. The safety profile of bosentan in patients with PoPH was generally consistent with previous studies

including PAH patients without cirrhosis. However, special care must be taken with patients with more severe cirrhosis due to the potential liver toxicity of this treatment.

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Table 1. Baseline demographic, clinical, biological, and haemodynamic characteristics.

Patients, n	34
Demographics	
Age, yrs	50±12
Male/female, n	16/18
NYHA-FC I/II/III/IV, n	0/4/28/2
6-min walk distance, m	352±104
Hemodynamics	
RAP, mmHg	10±7
mPAP, mmHg	50±10
PCWP, mmHg	10±4
Cardiac Index, $L.min^{-1}.m^{-2}$	2.8±0.7
PVR, Wood units	8.7±3.3
SvO_2, %	63±9
Liver status	
Portal vein thrombosis, n	6
Cirrhosis Child-Pugh stage A/B, n	19/9
Aetiology of cirrhosis, n	
Alcoholic cirrhosis	20
Chronic hepatitis C infection	4
Mixed aetiology (alcohol + hepatitis C)	3
Autoimmune hepatitis	1

Biological data

AST, IU/L	42±16
ALT, IU/L	32±12
Total bilirubin, µmol/L	25±13
Platelet count, $x10^6$/L	108±49

Data are given as mean ± SD.
List of abbreviations: NYHA-FC: New York Heart Association functional class; 6MWD: 6-minute walk distance; RAP: Right atrial pressure; mPAP: mean pulmonary artery pressure;PCWP: Pulmonary capillary wedge pressure; PVR: Pulmonary vascular resistance; SvO_2: mixed venous oxygen saturation; AST: aspartate aminotransferase; ALT: alanine aminotransferase

Table 2. Functional class, exercise capacity, and haemodynamics at baseline and on bosentan monotherapy and follow-up evaluations in patients treated exclusively by bosentan monotherapy

	Patients evaluated more than once		**Patients evaluated at least three times**		
	Baseline	**First evaluation[$]**	**Baseline**	**First evaluation**	**Last evaluation[#]**
Patients, n	34		24		
NYHA-FC, I/II/III/IV	0/4/28/2	1/23/10/0***	0/3/19/2	1/16/7/0***	4/12/7/1**
6 MWD, m	352±104	403±86***	358±108	413±92	431±122*
RAP, mmHg	10±7	6±4*	8±6	5±4	6±5
mPAP, mmHg	50±10	43±13***	49±10	40±12*	43±14
CI, $L.min^{-1}.m^{-2}$	2.8±0.7	3.7±1***	2.7±0.6	3.8±0.8***	3.7±0.9***
PVR, Wood units	8.7±3.2	5.7±3***	8.7±3	4.9±1.9***	5.6±2.9***
SvO_2, %	63±9	69±6*	63±10	70±6*	67±10

Data are mean ± SD unless otherwise stated. NYHA-FC: New York Heart Association functional class; 6MWD: 6-minute walk distance; RAP: Right atrial pressure; mPAP: mean Pulmonary Artery Pressure; CI: Cardiac index; PVR: Pulmonary Vascular resistance

* p<0.05 versus baseline; ** p<0.01 versus baseline; *** p<0.001 versus baseline

$ first evaluation performed on bosentan monotherapy 5±2 months after treatment initiation (range 4-12 months)

last evaluation performed on bosentan monotherapy 35±16 months after treatment initiation (range 12-75 months)

Table 3. Functional class, exercise capacity, and haemodynamics at baseline and on bosentan therapy in patients with Child-Pugh class B cirrhosis and follow-up evaluations in patients with Child-Pugh class B cirrhosis treated exclusively with bosentan monotherapy

Patient	baseline				First evaluation					Last evaluation#			
	6MWD, m	mPAP, mmHg	CI, l.min.m^2	PVR, Wood units	Bosentan dose, mg	6MWD, m	mPAP, mmHg	CI, l.min.m^2	PVR, Wood units	bosentan dose, mg	6MWD, m	mPAP, mmHg	CI, l.min.m^2	PVR, Wood units
1	325	64	2.1	16.4	125 b.i.d.	465	29	5.9	2.7	125 b.i.d.	480	56	3.9	7.7
2	500	64	2.8	9.6	125 b.i.d.	512	34	5.4	2.3	125 b.i.d.	510	32	5.9	2.2
3	235	41	1.6	10.5	125 b.i.d.	453	29	3.9	3	125 b.i.d.	460	26	4.2	2.6
4	420	42	4.1	3.6	62.5 b.i.d.	373	31	7.2	1.5	62.5 b.i.d.	-	-	-	-
5	354	50	2.3	8.5	62.5 b.i.d.	410	37	4.5	3.1	62.5 b.i.d.	396	39	3.1	4.2
6	385	47	2.3	9.5	125 b.i.d.	443	46	3.4	5.4	125 b.i.d.	430	64	3.6	8.3
7	356	56	2.4	9.7	62.5 b.i.d.	418	52	3.4	7.8	62.5 b.i.d.	-	-	-	-
8	465	52	1.9	11.9	62.5 b.i.d	395	43	2.8	7.3	62.5 b.i.d.	465	43	2.5	8.4
9	412	42	2.4	6.8		-	-	-	-	125 b.i.d.	385	48	4.1	5.2
Mean± SD	384±79	51±9	2.5±0.7	9.6±3.5		433±44	38±9	4.6±1.5	4.1±2.4		446±45	44±13	3.9±1.1	5.5±2.6

6MWD: 6-minute walk distance; RAP: Right atrial pressure; mPAP: mean Pulmonary Artery Pressure; CI: Cardiac index; PVR: Pulmonary vascular resistance

last evaluation performed 37±25 months after bosentan initiation (range 12-75 months)

Table 4. Pharmacokinetic variables of bosentan and its metabolites in patients with PAH and portal hypertension (n = 5) and IPAH (n = 3)

	t_{max} (h)		C_{max} (ng/mL)		AUC_{τ} (ng/mL · h)	
	PoPH	IPAH	PoPH	IPAH	PoPH	IPAH
Bosentan	4 (2, 6)	4 (3, 4)	53.3 (22.4-127)	14.6 (1.27-168)	360 (212-613)	76.1 (9.07-638)
Ro 47-8634	6 (5, 6)	3 (3, 4)	0.753 (0.393-1.45)	0.351 (0.0439-2.81)	6.39 (3.21-12.7)	2.40 (0.427-13.5)
Ro 48-5033	2 (0, 9)	3 (0, 5)	13.2 (7.98-21.8)	1.46 (0.158-13.5)	106 (58.4-192)	8.57 (1.28-57.2)
Ro 64-1056	6 (5, 9)	4 (3, 5)	2.66 (1.43-4.97)	0.873 (0.170-4.48)	25.8 (14.7-45.1)	6.92 (1.59-30.0)

Data are expressed as geometric mean (95% confidence interval) or median for t_{max}.
To enable comparison, C_{max} and AUC_{τ} have been dose-normalized.
AUC_{τ}: Area under the curve for one dosing interval; C_{max}: maximum concentration; PoPH: portopulmonary hypertension; IPAH: idiopathic pulmonary arterial hypertension; t_{max}: time at the maximum concentration**.**

Figure1. Distribution of cardiac index, PVR, and 6MWD 4 months after initiation of bosentan according to the severity of the underlying liver disease.

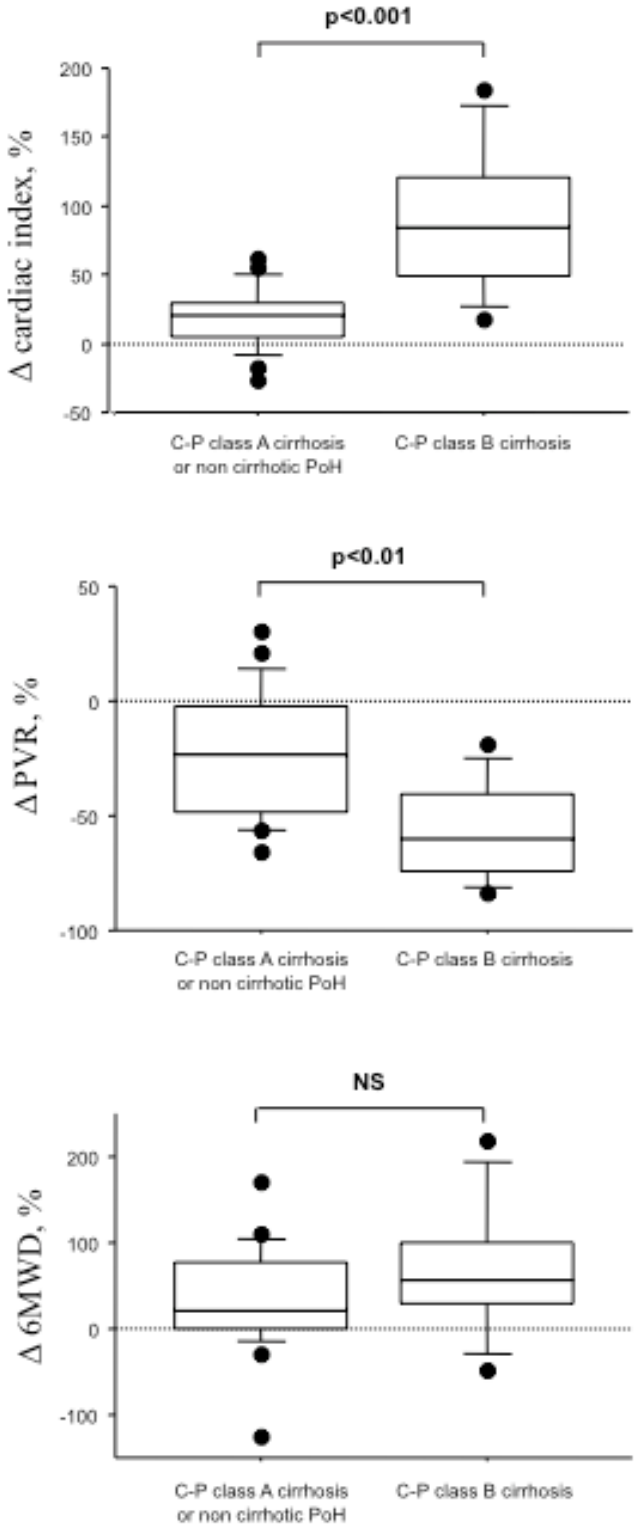


Figure 2A. Time to clinical worsening in patients with portopulmonary hypertension treated with bosentan according to the severity of the underlying liver disease.

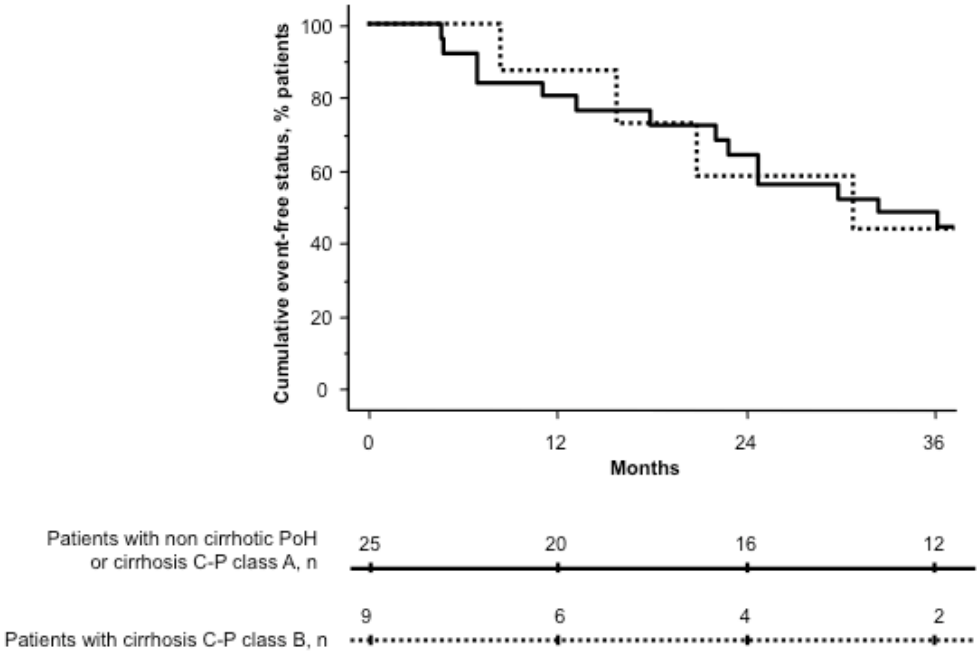


Figure 2B. Survival of patients with portopulmonary hypertension treated with bosentan according to the severity of the underlying liver disease.

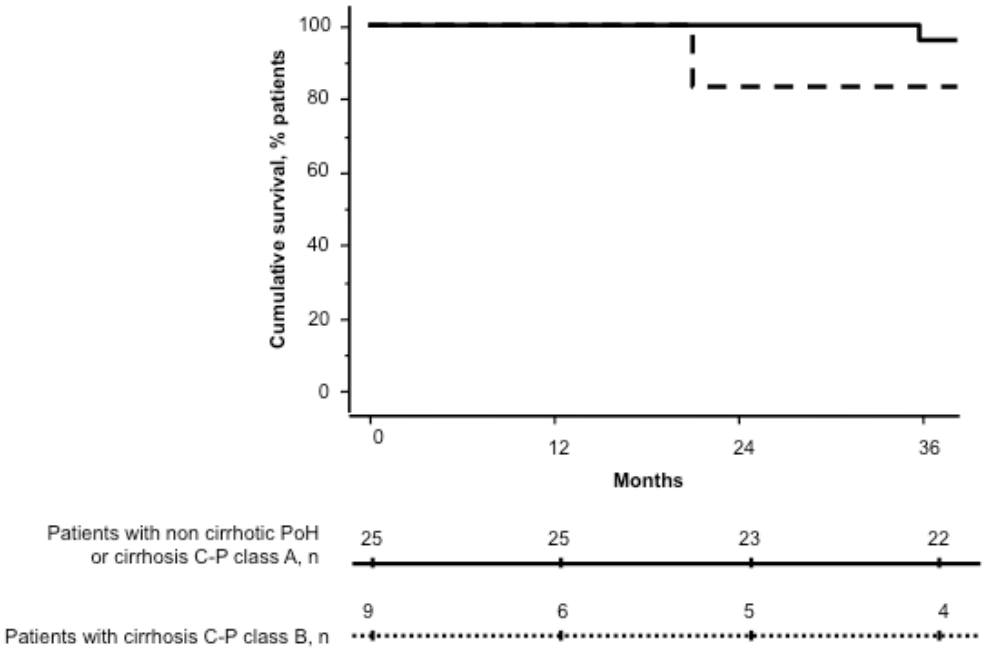
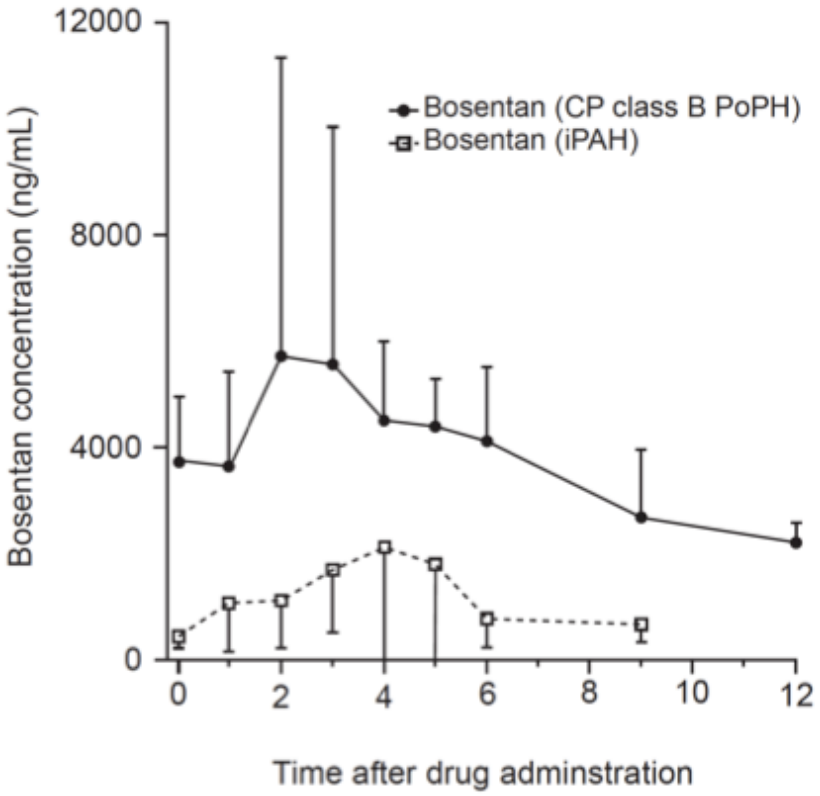


Figure 3. Pharmacokinetic profiles of bosentan in idiopathic PAH patients and those with Child-Pugh class B cirrhosis



Legends to figures

Figure 1:

Comparison of haemodynamic and functional parameters evolution between patients with non-cirrhotic portal hypertension or cirrhosis Child-Pugh class A (n=23) and patients with cirrhosis Child-Pugh class B (n=8). Results show that patients with Child-Pugh B cirrhosis have a greater haemodynamic improvement after 4 months of bosentan.

Figure 2.

Kaplan-Meier estimates of event-free status (A) and survival (B) in 34 patients with portopulmonary hypertension treated with first-line bosentan therapy according to the severity of the underlying liver disease.

Figure 3

Mean (± SD) plasma dose-normalized concentration-time profiles of bosentan in PoPH patients with Child-Pugh class B cirrhosis (n=5) or patients with IPAH without co-morbid portal hypertension (n=3). Concentrations from patients treated with doses of 62.5 mg b.i.d. were normalized to a dose of 125 mg.