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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-290/S-001

Medical Review(s)

Safety and efficacy review
NDA #21,290
Drug Name: Bosentan (Tracleer™)
Sponsor: Actelion

Introduction

This is a safety and efficacy review of additional studies to be used to change labeling for bosentan, an approved agent for the treatment of primary pulmonary hypertension. There were 3 additional studies the sponsor is using to support the new product label:

- 1) protocol AC-052-356, a small uncontrolled trial with 16 patients between the ages of 3 and 16, inclusive.
- 2) Protocol AC-052-301/302, two large placebo controlled trials with a total of 1613 patients with congestive heart failure (this was a combined medical/statistical review).
- 3) Protocol AC-052-355, a small placebo controlled trial evaluating the combined use of bosentan and epoprostenol in patients with primary pulmonary hypertension.

Protocol ID: AC-052-356

Conclusions

In this small, uncontrolled study bosentan was administered to 19 patients age 3 to 16 years with (mostly) WHO grade II pulmonary hypertension from either primary pulmonary hypertension or congenital heart disease. The primary objective was to investigate the pharmacokinetics of bosentan in pediatric patients with PAH. The study also attempted to obtain preliminary data on changes in exercise capacity, Borg dyspnea index, hemodynamics, and WHO functional class. Current medications being used in this population include prostacyclin, endothelin receptor blockers, sildenafil and nitric oxide.

Without a control group, no conclusions can be drawn from the pharmacodynamic results. That said, hemodynamics were improved after 12 weeks of bosentan treatment with decreases in PAP, PVR, and SVR and increased in cardiac output and stroke index. There was no change in the walk test exercise test or any of the other parameters from baseline at week 12. By Week 12, one of the 15 patients who was class II at baseline deteriorated to class III and 2 improved to class I; the majority (12) stayed the same. Of the 4 who were class III at baseline, 3 improved to class II and 1 stayed the same.

There were no deaths. All but 1 patient completed the 12 week study. Serious events were reported by 2 patients: patient #2021 had prolonged hospitalization because of tachycardia, hypertension, tremor, and dizziness on day 1; patient #2026 had marked increase in ALT (up to 131 U/L) that resulted in the patient's premature discontinuation on Day 7. Both patients recovered without sequelae. An additional patient discontinued bosentan on day 197 because of an elevation in ALT.

The most frequent adverse events were flushing (4 patients), headache, and abnormal hepatic function (3 patients each). Fluid retention/edema was reported by 3 patients.

Summary

Protocol title: Pharmacokinetics and tolerability of Tracleer (bosentan) in pediatric patients with pulmonary arterial hypertension: single and multiple oral doses.

Period of trial: May 11,2001 to February 13, 2002

The primary objective was to investigate the pharmacokinetics of bosentan in pediatric patients with PAH. Other objectives were to evaluate the tolerability and safety of single and multiple oral doses of

bosentan and to obtain preliminary data on changes in exercise capacity, Borg dyspnea index, hemodynamics, and WHO functional class.

This was a multicenter, open-label, uncontrolled, parallel-group single- and multiple-dose study. Patients were stratified by weight and epoprostenol use.

A total of 19 patients were studied. Patients equally divided into 3 body-weight groups:

6 patients > 40 kg (3 on epoprostenol, 3 not on epoprostenol)

6 patients >20 kg but ≤ 40 kg (3 on epoprostenol, 3 not on epoprostenol)

7 patients >10 kg but ≤ 20kg (4 on epoprostenol, 3 not on epoprostenol)

Patients were male or female patients with PAH (primary or related to scleroderma or congenital heart defects and of WHO class II-III) on conventional vasodilators/anticoagulant therapy or epoprostenol therapy

The dosage of oral bosentan tablets was adjusted to the patient's body weight (shown below).

Body weight	Single dose (Day 1 and at Week-12 visit)	Initial dose (Day 2 through Week-4 visit)	Target dose (starting Week 5)
> 40 kg	125 mg	62.5 mg b.i.d.	125 mg b.i.d.
20 < x ≤ 40 kg	62.5 mg	31.25 mg b.i.d.	62.5 mg b.i.d.
10 ≤ x ≤ 20 kg	31.25 mg	31.25 mg q.d.	31.25 mg b.i.d.

Note: 31.25 mg doses were obtained by cutting 62.5 mg tablets in half.

Patients received a single dose on Day 1, started daily treatment with the initial dose on Day 2, and had treatment up-titrated to the target dose at the Week-4 visit. At the Week-12 visit, patients received a single dose in the morning and if they elected to continue treatment, resumed daily treatment at the target dose the following day.

If the target dose was not tolerated, the dose could be down-titrated to the initial dose. Patients continued treatment until the study was stopped and bosentan was commercially available.

Pharmacokinetic evaluations included C_{max}, t_{max}, AUC, and t_{1/2} for bosentan, Ro 48-5033, Ro 47-8634, and Ro 64-1056 following single and multiple doses of bosentan

Efficacy evaluations included change from baseline to Week 12 in cardiopulmonary hemodynamics, 6-minute walk test, Borg dyspnea index, cycle ergometry test, and WHO functional class.

Pharmacokinetic parameters were analyzed descriptively. Hemodynamic and exercise parameters were summarized descriptively as the change from baseline to Week 12. Hemodynamic parameters in subgroups defined by whether or not the patient was on concomitant epoprostenol were analyzed descriptively. Changes in WHO functional class were presented as numbers of patients and proportions.

Following a screening period of 3 to 21 days, eligible patients were assigned to one of three parallel bosentan treatment arms based on body weight. On Day 1, patients were treated with a single dose of oral bosentan determined by body weight, and blood samples for pharmacokinetic profiles were taken periodically for the following 24 hours. On Day 2, patients began daily treatment with the initial dose determined by body weight for 4 weeks, upon which the dosage was up-titrated to twice the initial dose (target dose). At the Week-12 visit, patients were again treated with a single morning bosentan dose

determined by body weight, and blood samples for multiple-dose pharmacokinetic profiles were taken periodically for the following 24 hours. Pharmacodynamic assessments (hemodynamics, 6-minute walk test, Borg dyspnea index, and cycle ergometry test) were performed at baseline and at Week 12 prior to pharmacokinetic assessments (exercise tests were held only in patients ≥ 8 years of age), and WHO functional class was assessed periodically.

Patients were hospitalized for 3 days at each pharmacokinetic assessment for right heart catheterization (to measure hemodynamic parameters) and for pharmacokinetic assessments beginning the following day. Patients who completed the 12-week pharmacokinetic evaluation were eligible to continue open-label treatment until bosentan became available commercially. Safety parameters and WHO functional class were assessed regularly throughout continued treatment until the end of the study.

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Table 2 Schedule of assessments

Treatment Schedule (Study day)	Pharmacokinetic Study Period					Extended Treatment Period						End of treatment or premature withdrawal
	Screening [-21:-3]	Initiation [1]	Week 4 [24-33]	Week 8 [52-61]	Week 12 [80-89]	Month 4 [108-117] Phone	Month 6 [170-179]	Month 8 [230-250] Phone	Month 10 [290-310] Phone	Month 12 [350-370]	Every 3 months	
Visit number	1	2	3	4	5	6	7	8	9	10	11	12
Informed consent	X											
History	X											
Physical examination	X											X
Tanner assessment	X											
ECG (12 lead)	X	X			X							X
Laboratory tests ²	X	X	X	X	X	X	X	X	X	X	X	X
Exercise tests and Borg dyspnea index		X			X							
WHO functional class	X	X	X	X	X		X			X	X	X
Hemodynamic measurements ³		X			X							
BP, HR, body weight and height	X	X	X		X		X			X	X	X
Pharmacokinetic evaluation		X			X							
Dispense/return medication		X	X		X		X			X	X	X
Adverse events/ intercurrent illness		X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X

¹ The screening and treatment initiation visits may have been combined if the patient had documented laboratory test results that met the screening eligibility criteria within 3 weeks prior to treatment initiation.

² Laboratory tests performed at each visit included hematology, biochemistry, and liver function tests. Qualitative urinalysis was performed only at screening, baseline (initiation), the Week-12 visit, and at end of study/premature withdrawal (added with Amendment 1).

³ Involved right heart catheterization.

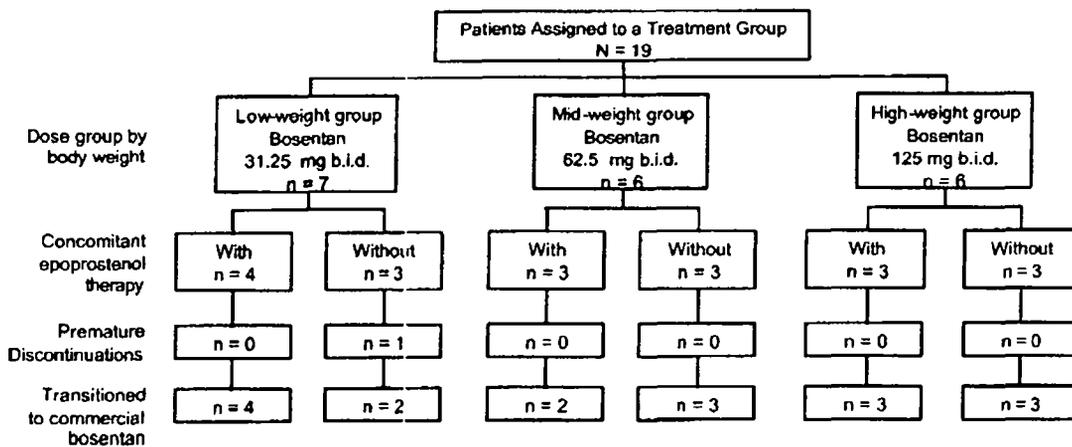
BP = blood pressure, ECG = electrocardiogram, HR = heart rate, WHO = World Health Organization.

Results

Patient disposition

Nineteen patients were enrolled in the study, 7 in the low-weight group and 6 each in the mid- and high-weight groups. One patient was prematurely withdrawn after 7 days because of elevated liver aminotransferases, and 18 patients completed the Week-12 assessments. One additional patient was withdrawn on Day 197 because of a recurrent increase in alanine aminotransferase (ALT). The remaining 17 patients were started on commercial bosentan at the end of the study.

Figure 3 Disposition of patients



A total of 19 subjects were entered into the study. Dosing with bosentan was based on body weight. Ten subjects were receiving concomitant epoprostenol therapy. There was 1 premature discontinuation (elevated liver enzymes). Seventeen patients continued with commercial bosentan treatment after study was finished.

Demographics

Table 4 Summary of patient demographics – all enrolled patients

(Table DEM01: 03APR02 - Data 03APR02)

	Patients 10 - 20 kg N=7	Patients >20 - 40 kg N=6	Patients > 40 kg N=6	All N=19
SEX [n (%)]				
n	7	6	6	19
Males	4 57.1%	2 33.3%	3 50.0%	9 47.4%
Females	3 42.9%	4 66.7%	3 50.0%	10 52.6%
AGE (years)				
n	7	6	6	19
Mean	5.7	10.0	14.2	9.7
Standard deviation	1.9	2.4	1.2	4.0
Median	6.0	10.5	14.5	10.0
Min , Max	[]
AGE [n (%)]				
n	7	6	6	19
< 8 years	5 71.4%	1 16.7%	-	6 31.6%
8 - 12 years	2 28.6%	4 66.7%	1 16.7%	7 36.8%
13 - 17 years	-	1 16.7%	5 83.3%	6 31.6%
WEIGHT (kg)				
n	7	6	6	19
Mean	17.1	31.0	46.5	30.8
Standard deviation	2.5	6.4	5.5	13.3
Median	16.0	33.3	47.3	33.1
Min , Max	[]
HEIGHT (cm)				
n	7	6	6	19
Mean	108.8	135.9	156.8	132.5
Standard deviation	8.0	11.2	6.1	22.0
Median	108.0	136.4	157.8	133.1
Min , Max	[]
RACE [n (%)]				
n	7	6	6	19
Caucasian/white	6 85.7%	6 100%	3 50.0%	15 78.9%
Other	1 14.3%	-	3 50.0%	4 21.1%

The sample size is too small to determine if there are differences between treatment groups.

Baseline Characteristics

Table 5 Summary of baseline characteristics— all enrolled patients

(Table BAS01: 03APR02 - Data 03APR02)

	Patients 10 - 20 kg N=7	Patients >20 - 40 kg N=6	Patients > 40 kg N=6	All N=19
Time from diagnosis of PAH (months) *				
n	7	6	6	19
Mean	35.3	46.1	113.2	64.0
Standard deviation	36.2	48.0	53.7	55.0
Median	28.6	19.5	102.2	61.1
Min , Max				
Etiology of PAH [n (%)]				
n	7	6	6	19
Primary Pulmonary Hypertension	3 42.9%	4 66.7%	3 50.0%	10 52.6%
Congenital Heart Defect	4 57.1%	2 33.3%	3 50.0%	9 47.4%
WHO grade at Baseline [n (%)]				
n	7	6	6	19
II	7 100%	5 83.3%	3 50.0%	15 78.9%
III	-	1 16.7%	3 50.0%	4 21.1%
Baseline oxygen saturation (%) †				
n	7	6	6	19
Mean	95.7	94.8	95.3	95.3
Standard deviation	2.2	0.8	3.7	2.4
Median	96.0	95.0	95.5	95.0
Min , Max				
FiO2 (%) †				
n	3	2	3	8
Mean	23.7	24.0	23.5	23.7
Standard deviation	3.8	0.0	0.9	2.1
Median	22.0	24.0	24.0	24.0
Min , Max				
Patients using supplemental oxygen [n (%)] †				
n	7	6	6	19
Never	5 71.4%	4 66.7%	3 50.0%	12 63.2%
At any time	2 28.6%	2 33.3%	3 50.0%	7 36.8%
PRN	2 28.6%	2 33.3%	2 33.3%	6 31.6%
During night time	-	-	1 16.7%	1 5.3%

(*) Reported number of days from diagnosis of pulmonary hypertension to the screening visit.

(†) Last valid value between the visits 1 (Screening) and 2 (Initiation).

PAH = pulmonary arterial hypertension, PRN = as circumstances require, WHO = World Health Organization.

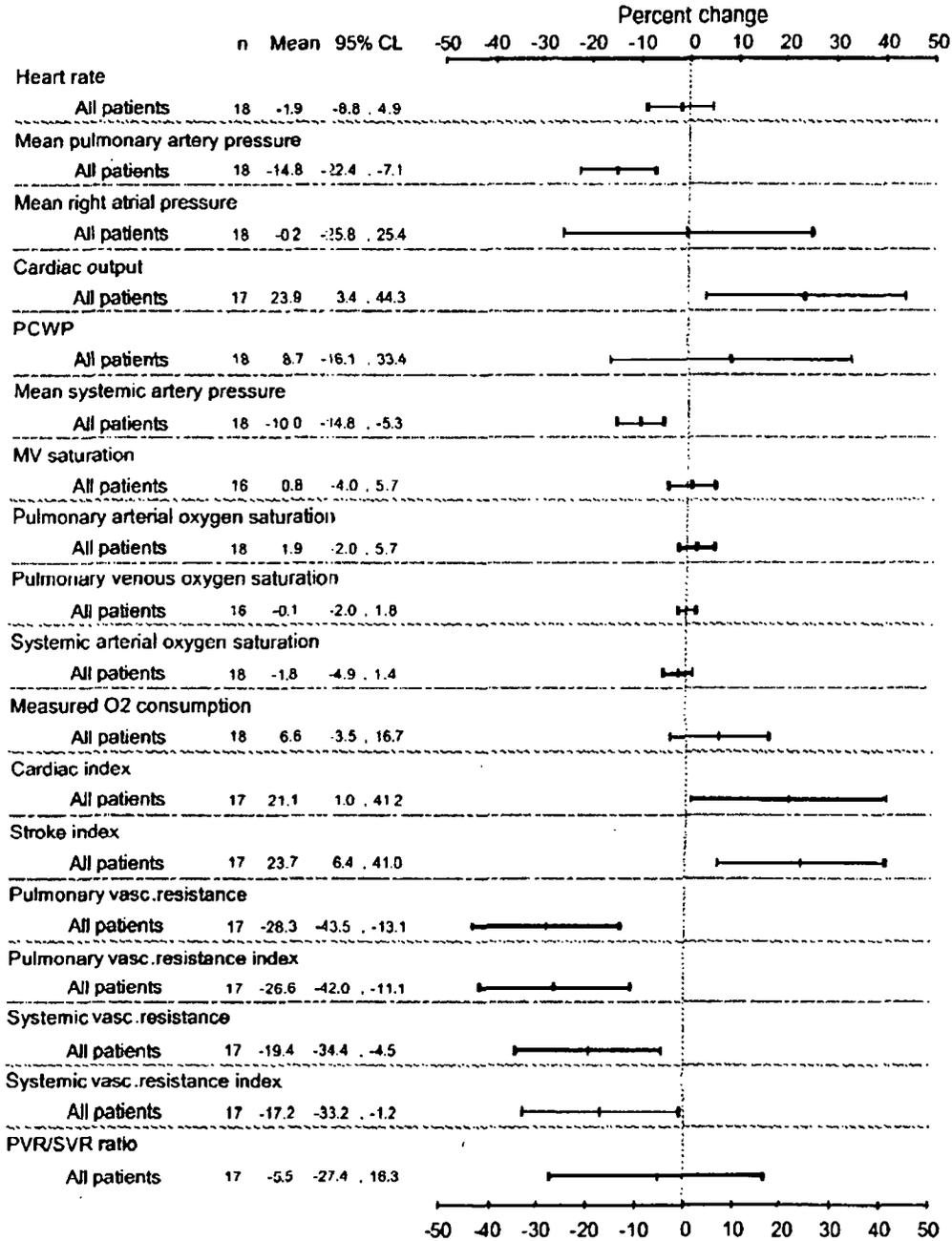
The mean time from time of diagnosis to study enrollment was about 65 months. The etiology of PAH was either primary pulmonary hypertension (52.6%) or congenital heart defect (47.4%). The majority of patients (78.9%) were WHO grade II at baseline and the majority (62.3%) had never used supplemental oxygen.

Efficacy

Overall, hemodynamics were improved after 12 weeks of bosentan treatment.

Figure 13 Hemodynamics: Percent change from baseline to Week 12
- all enrolled patients

(Figure hem_g: 03APR02 - Data 03APR02)



Mean and mean changes were observed in

- pulmonary artery pressure (-8.0 and -7.0 mmHg),
- pulmonary vascular resistance index (-300 and -274 dynsecm²/cm⁵),
- systemic artery pressure (-8.6 and -7.0 mmHg), and
- systemic vascular resistance index (-426 and -384 dynsecm²/cm⁵),

- cardiac output (0.61 and 0.50 L/min),
- stroke index (0.006 and 0.009 ml/m²).

There was no overall effect on heart rate (-2.4 and 0.3 bpm).

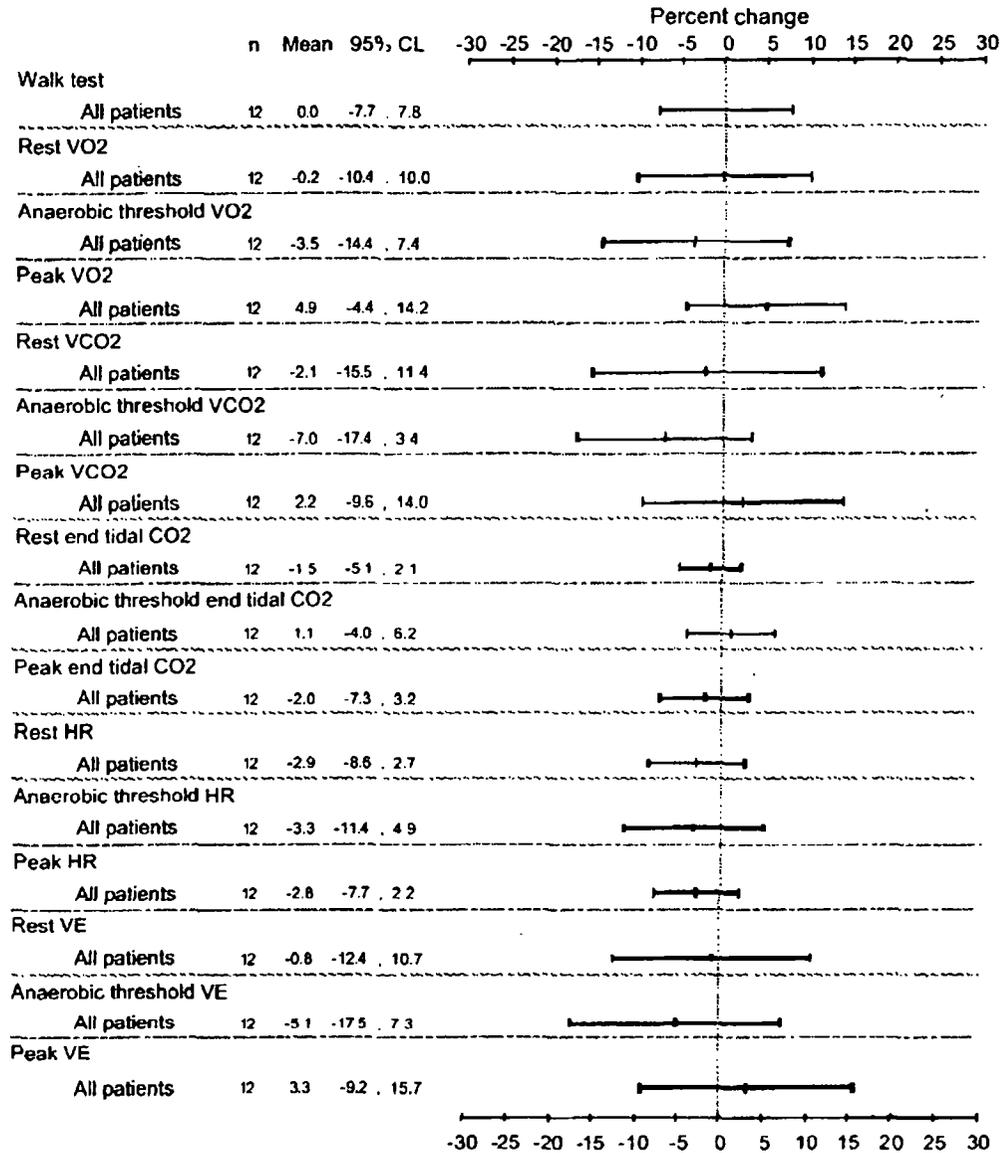
Exercise testing was limited to children 8 years of age or older. Mean changes in the parameters for the 12 children meeting this criterion are shown below.

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Figure 14 Exercise parameters: Percent change from baseline to Week 12 - all enrolled patients

(Figure wlk_erg_g1: 03APR02 - Data 03APR02)



There was no change in the walk test exercise test or any of the other parameters from baseline at week 12.

Functional class

By Week 12, one of the 15 patients who was class II at baseline deteriorated to class III and 2 improved to class I; the majority (12) stayed the same. Of the 4 who were class III at baseline, 3 improved to class II and 1 stayed the same.

Table 10 Summary of pharmacodynamic outcomes

Patient number (wt group)	Diagnosis	WHO class (BL / Wk 12)	Change in mean PAP / cardiac index	6-min walk distance (meters)		Peak VO ₂ (ml/min)	
				BL	Week 12	BL	Week 12
With epoprostenol							
1001 (H)	CHD	III / III	↓ / ↑	438	371	682	648
1004 (M)	PPH	III / II	↓ / ↓	397	339	367	311
1005 (L)	CHD	II / II	↓ / ↓	—	—	—	—
1007 (L)	PPH	II / I	↑ / ↑	—	—	—	—
1009 (H)	PPH	II / II	↑ / ↑	456	450	1353	1515
1010 (L)	CHD	II / III	↓ / na	424	429	279	288
2023 (H)	PPH	II / II	↓ / ↑	416	500	926	783
2024 (M)	PPH	II / II	↓ / ↑	523	462	770	751
2027 (L)	PPH	II / II	↓ / ↓	—	—	—	—
2028 (M)	PPH	II / II	↓ / ↑	—	—	—	—
Without epoprostenol							
1002 (M)	CHD	II / II	↓ / ↑	487	505	324	389
1003 (M)	CHD	II / II	↓ / ↓	569	512	908	884
1008 (H)	CHD	III / II	↓ / ↓	485	498	813	797
2021 (M)	PPH	II / II	↑ / ↑*	604	638	993	1299
2022 (H)	PPH	II / I	↓ / ↓	527	643	1602	1887
2025 (L)	CHD	II / II	↓ / ↑	—	—	—	—
2026 (L)	CHD	II / II	na	—	—	—	—
2029 (H)	CHD	III / II	↓ / ↑	573	560	560	660
2030 (L)	PPH	II / II	↓ / ↑	—	—	—	—

↓ Values decreased from baseline to Week 12.

↑ Values increased from baseline to Week 12.

* Improvement seen with bosentan at Week 12; addition of i.v. epoprostenol at 6 months.

— Missing values indicate patient was <8 years; per protocol, no exercise test was performed.

BL = baseline, CHD = congenital heart defect, H = high-weight group, L = low-weight group, M = mid-weight group, na = not available, PPH = primary pulmonary hypertension, WHO = World Health Organization, wt = weight.

Safety

There were no deaths. Two serious adverse events were reported.

Serious events were reported by 2 patients. Both patients recovered without sequelae. One patient (2021) had prolonged hospitalization because of tachycardia, hypertension, tremor, and dizziness on day 1. The other patient (2026) had marked increase in ALT (up to 131 U/L) that resulted in the patient's premature discontinuation on Day 7.

All adverse events: those events that were reported by at least 2 patients are shown below.

Table 12 Summary of treatment-emergent adverse events (including unrelated) - all enrolled patients

(Table AES01A2: 03APR02 - Data 03APR02)

Body system / Adverse event	Patients 10 - 20 kg N=7		Patients >20 - 40 kg N=6		Patients > 40 kg N=6		All N=19	
	No.	%	No.	%	No.	%	No.	%
ALL BODY SYSTEMS								
Total pts with at least one AE	6	85.7%	6	100%	5	83.3%	17	89.5%
Total number of AEs	16		27		14		57	
FLUSHING	2	28.6%	2	33.3%	-		4	21.1%
HEADACHE NOS	-		3	50.0%	-		3	15.8%
HEPATIC FUNCTION ABNORMAL NOS	1	14.3%	2	33.3%	-		3	15.8%
DIZZINESS (EXC VERTIGO)	-		2	33.3%	-		2	10.5%
FLUID RETENTION	1	14.3%	-		1	16.7%	2	10.5%
IMPLANT INFECTION	1	14.3%	1	16.7%	-		2	10.5%
PHARYNGITIS STREPTOCOCCAL	1	14.3%	1	16.7%	-		2	10.5%
PNEUMONIA NOS	1	14.3%	1	16.7%	-		2	10.5%
PULMONARY HYPERTENSION NOS AGGRAVATED	-		2	33.3%	-		2	10.5%
PYREXIA	1	14.3%	1	16.7%	-		2	10.5%
SORE THROAT NOS	-		1	16.7%	1	16.7%	2	10.5%
UPPER RESPIRATORY TRACT INFECTION NOS	1	14.3%	1	16.7%	-		2	10.5%

The most frequent adverse events were flushing (4 patients), headache, and abnormal hepatic function (3 patients each). Other adverse events known to be associated with bosentan treatment included edema (late onset fluid retention in two patients, edema in one) and anemia (not reported in this study).

An additional patient discontinued bosentan on day 197 because of an elevation in ALT. The incidences of marked abnormalities in liver function tests are categorized below.

Table 16 Incidence of special marked laboratory abnormalities - all enrolled patients

(Table LMA02b: 03APR02 - Data 03APR02)

Laboratory Abnormality	Patients 10 - 20 kg N=7		Patients >20 - 40 kg N=6		Patients > 40 kg N=6		All N=19	
	No.	%	No.	%	No.	%	No.	%
ALT > 3*upper std	1 / 7	14.3%	1 / 6	16.7%	0 / 6		2 / 19	10.5%
AST > 3*upper std	0 / 7		0 / 6		0 / 6		0 / 19	
ALT or AST > 3*upper std	1 / 7	14.3%	1 / 6	16.7%	0 / 6		2 / 19	10.5%
Hemoglobin < 10g/dl and LL ... with decrease from baseline	0 / 7		0 / 6		0 / 6		0 / 19	

Values given are the number of patients with at least one abnormality/number of patients (%). HH and LL denote values above or below the marked reference range and having a clinically relevant change in the same direction.

ALT = alanine aminotransferase, AST = aspartate aminotransferase.

The presence of blood in the urine of one patient (1005) in the low-weight group was observed on Day 98 of the study. It did not result in an adverse event report.

Changes in blood pressure, heart rate, and body weight are shown in the table below.

Table 17 Change from baseline to Week 12 in vital signs, body weight, and height - all enrolled patients

(Table VIT01a: 03APR02 - Data 03APR02)

	Patients 10 - 20 kg N=7		Patients >20 - 40 kg N=6		Patients > 40 kg N=6		All N=19	
Pulse Rate supine (bpm)								
n	7		6		6		19	
Baseline	112.3 ± 8.5	85.0 ± 10.9	80.5 ± 8.7	89.9 ± 13.3				
Last up to week 12	104.6 ± 6.8	79.5 ± 18.5	77.3 ± 6.5	84.4 ± 13.7				
Change from baseline	-7.7 ± 11.2	-5.5 ± 12.4	-3.2 ± 7.6	-5.6 ± 10.2				
% Change from baseline	-7.0 ± 11.0	-6.9 ± 15.1	-3.3 ± 10.1	-5.8 ± 11.6				
Pulse Rate standing (bpm)								
n	6		6		6		18	
Baseline	106.5 ± 5.8	98.2 ± 20.1	87.2 ± 10.5	97.3 ± 15.1				
Last up to week 12	102.7 ± 8.3	91.7 ± 16.0	85.3 ± 11.9	93.2 ± 13.9				
Change from baseline	-3.8 ± 9.1	-6.5 ± 11.3	-1.8 ± 15.4	-4.1 ± 11.7				
% Change from baseline	-3.4 ± 8.4	-5.7 ± 10.2	-0.9 ± 18.1	-3.4 ± 12.3				
Systolic BP supine (mmHg)								
n	7		6		6		19	
Baseline	93.6 ± 9.8	103.2 ± 13.4	107.2 ± 10.6	102.7 ± 11.3				
Last up to week 12	97.1 ± 10.3	103.5 ± 8.5	108.3 ± 9.2	102.7 ± 10.1				
Change from baseline	-1.4 ± 8.1	0.3 ± 17.1	1.2 ± 8.0	-0.1 ± 11.1				
% Change from baseline	-1.2 ± 7.8	1.8 ± 16.1	1.4 ± 7.1	0.6 ± 10.4				
Systolic BP standing (mmHg)								
n	6		6		6		18	
Baseline	99.2 ± 6.2	100.8 ± 12.0	107.2 ± 11.4	102.4 ± 10.2				
Last up to week 12	96.3 ± 11.8	99.7 ± 7.7	105.2 ± 8.8	100.4 ± 9.7				
Change from baseline	-2.8 ± 11.6	-1.2 ± 10.9	-2.0 ± 10.4	-2.0 ± 10.3				
% Change from baseline	-2.7 ± 11.9	-0.3 ± 11.2	-1.3 ± 9.2	-1.5 ± 10.2				
Diastolic BP supine (mmHg)								
n	7		6		6		19	
Baseline	60.0 ± 5.6	61.0 ± 5.8	63.5 ± 8.1	61.4 ± 6.4				
Last up to week 12	57.4 ± 10.1	63.3 ± 8.0	56.5 ± 4.5	59.0 ± 8.2				
Change from baseline	-2.6 ± 13.0	2.3 ± 11.2	-7.0 ± 8.6	-2.4 ± 11.2				
% Change from baseline	-3.1 ± 21.7	4.9 ± 18.3	-9.8 ± 13.7	-2.7 ± 18.4				
Diastolic BP standing (mmHg)								
n	6		6		6		18	
Baseline	62.7 ± 12.3	63.2 ± 8.1	68.2 ± 5.9	64.7 ± 9.0				
Last up to week 12	54.7 ± 9.5	64.5 ± 6.2	56.8 ± 8.5	58.7 ± 8.8				
Change from baseline	-8.0 ± 15.7	1.3 ± 9.2	-11.3 ± 12.2	-6.0 ± 13.1				
% Change from baseline	-9.5 ± 27.3	3.4 ± 14.8	-15.7 ± 16.9	-7.3 ± 20.8				
Weight (Kg)								
n	7		6		6		19	
Baseline	17.0 ± 2.7	31.0 ± 6.4	46.4 ± 5.4	30.7 ± 13.3				
Last up to week 12	17.4 ± 2.9	32.4 ± 7.0	47.4 ± 6.1	31.6 ± 13.7				
Change from baseline	0.4 ± 0.6	1.4 ± 1.2	1.0 ± 2.3	0.9 ± 1.5				
% Change from baseline	2.2 ± 4.1	4.3 ± 3.1	2.0 ± 5.3	2.8 ± 4.2				
Height (cm)								
n	6		6		6		18	
Baseline	107.5 ± 7.6	135.7 ± 10.9	156.4 ± 5.5	133.2 ± 22.1				
Last up to week 12	108.8 ± 7.6	137.9 ± 11.5	159.3 ± 6.4	135.3 ± 22.8				
Change from baseline	1.4 ± 1.4	2.2 ± 1.4	2.9 ± 3.0	2.2 ± 2.0				
% Change from baseline	1.3 ± 1.3	1.6 ± 1.0	1.8 ± 1.9	1.6 ± 1.4				

Note: Values are mean ± standard deviation.

Without a control group, the relevance of any of the changes cannot be determined.

Protocol AC-052-301/302

Medical Reviewer: Maryann Gordon, M.D.

Statistical Reviewer: John Lawrence, Ph.D.

Conclusions:

This review summarizes, primarily, the safety results of a congestive heart failure trial with 1613 randomized patients followed for a mean of approximately 70 weeks. Overall, bosentan was not

statistically different from placebo in the improvement in time to death or hospitalization for CHF or in clinical status. However, numerically more patients in the bosentan group in both studies who were reported as "improved". When both studies are pooled together, a point estimate for the difference in the proportion of patients who were "improved" is 3% and the confidence interval is (-1.3%, 7.2%). This means that it is questionable whether there is any difference in the rates and a difference of as much as 7.2% can be ruled out. On the other hand, patients on bosentan compared to those on placebo, tended to have a greater rate of worsening in both studies. The point estimate for the difference in rates is 5.3% and the confidence interval is (0.8%, 9.8%). This apparent difference was the result of increased incidence of hospitalization for CHF rather than a difference in death rates.

The leading adverse events reported in this trial are similar to those identified in the NDA (anemia/decreased hemoglobin, abnormal hepatic function, headache, edema, URI). There were 2 reports of jaundice (both patients recovered with drug discontinuation and without rechallenge) and no reports of liver failure. There was one report of liver failure in MedWatch that was most likely the result of septic shock.

In summary, nothing reported in this study prompts a change in the package label with the exception of a statement about patients with NYHA class IIIb-IV heart failure becoming clinically worse (and needing hospitalization) when starting bosentan. It should be added that there was no adverse effect on mortality.

A double-blind, randomized, placebo-controlled study to assess the effects of bosentan on the morbidity and mortality of patients with chronic heart failure (also known as ENABLE).

The study was conducted in Europe, Australia, Israel, and North America between June 29, 1999 and January, 2002

The primary objectives were to evaluate the effects of bosentan on clinical status in each study and on morbidity and mortality in the combined study population of patients with chronic heart failure.

Two identical multicenter, double-blind, placebo-controlled, randomized studies of oral bosentan given twice daily (bid) until all randomized patients have been followed for at least 9 months and at least 600 events (death or hospitalization for CHF) have occurred in the pooled ENABLE population from both studies.

A total of 1613 patients were enrolled (816 in AC-052-301 and 797 in AC-052-302). Patients had left ventricular systolic dysfunction (ejection fraction 35%) and NYHA class IIIb-IV CHF for at least 2 months, despite therapy with diuretics and ACE-inhibitors (unless contraindicated) with or without other agents

The initial dose of oral bosentan was 62.5 mg b.i.d. for the first 4 weeks followed by 125mg bid for the remainder of the study if tolerated. Back titration to 62.5 mg bid was allowed.

Primary efficacy was clinical status (worse, unchanged, or improved) after 9 months follow-up in each study population and time to death from all causes or hospitalization for CHF assessed in the pooled ENABLE population.

RESULTS

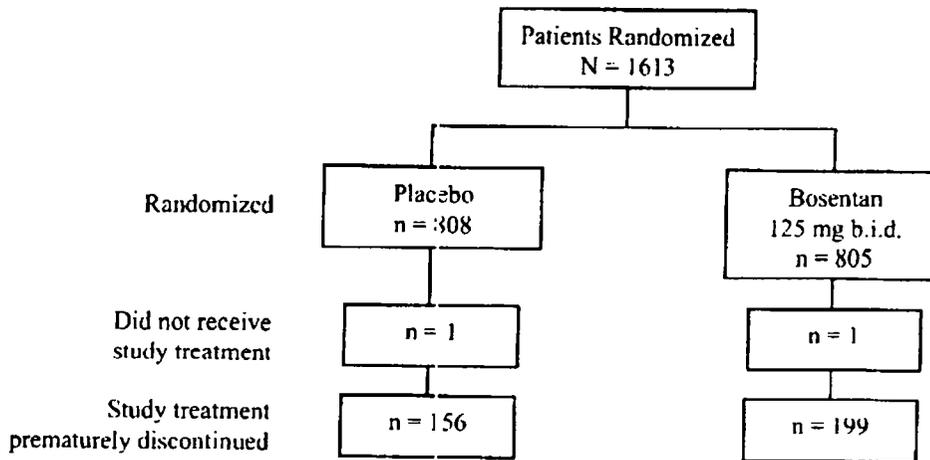
Number of patients

A total of 1613 patients were enrolled into Enable. Two patients (1 bosentan and 1 placebo) did not receive study drug and 355 patients (199 bosentan (24.7%) and 156 placebo (19.3%) did not complete the study.

Disposition of patients

The outcome for the randomized patients is shown in the figure below.

Figure 3 Disposition of patients



Duration of treatment

Table 16 Summary of exposure to trial treatment, ITT/safety population

Protocols: ENABLE-1 ENABLE-2 (Table EXPC1: 01FEB02 - Data dump of 01FEP02)

	Placebo N=807	Bosentan N=804
Exposure (weeks) *		
n	807	804
Mean	72.6	68.7
Standard deviation	33.3	35.8
95% CL of mean	70.3, 74.9	66.2, 71.1
Median	81.0	75.4
95% CL of median	79.1, 83.1	76.0, 81.1
Min, Max	[]
PATIENTS EXPOSED (n (%)) *	807	804
At least 4 weeks	781 96.8%	763 94.9%
At least 12 weeks	735 91.1%	710 88.3%
At least 26 weeks	689 85.4%	643 80.0%
At least 52 weeks	614 76.1%	567 70.5%
At least 78 weeks	446 55.3%	408 50.7%
At least 104 weeks	140 17.3%	141 17.5%

(*): From start of trial treatment to end of trial treatment
CL = confidence limit.

The mean duration of treatment was 68.7 days for the bosentan patients which was slightly shorter than for the placebo patients (72.6 days).

Premature discontinuations

Table 6 Summary of premature discontinuations, ITT/safety population

Protocols: ENABLE-1 ENABLE-2 (Table PWD01: 25APR02 - Data dump of 24APR02)

Reason for premature discontinuation	Placebo		Bosentan	
	No.	%	No.	%
Total pts with at least one reason	156	19.3%	199	24.8%
AE/INTERCURRENT ILLNESS	69	8.4%	96	11.9%
REFUSED TREATMENT/DID NOT COOPERATE/ WITHDREW CONSENT	51	6.3%	52	6.5%
CARDIAC FAILURE NOS	18	2.2%	37	4.6%
ADMINISTRATIVE/OTHER	14	1.7%	9	1.1%
STUDY TERMINATION	4	0.5%	2	0.2%
PROTOCOL VIOLATION	2	0.2%	2	0.2%
ELECTIVE HEART TRANSPLANT	-		1	0.1%

AE = adverse event, NOS = not otherwise specified.

Of the 807 placebo patients randomized, 19.3% were discontinued for any reason and 8.4% were discontinued for an adverse event. Of the 804 bosentan randomized, 24.8% were discontinued for any reason and 11.9% were discontinued for an adverse event. More than twice as many bosentan patients discontinued for cardiac failure (37, 4.6%) compared to placebo patients (18, 2.2%).

Demographics

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Table 8 Summary of patient demographics, ITT/safety population

Protocols: ENABLE-1 ENABLE-2 (Table DEM(1: 26FEB02 - Data dump of C1FEB02)

	Placebo N=807	Bosentan N=804
SEX n (%)		
n	807	804
Males	602 74.6%	595 74.0%
Females	205 25.4%	209 26.0%
AGE (years)		
n	807	804
Mean	66.9	67.5
Standard deviation	11.0	11.0
Median	69.0	69.0
Min , Max	<]	>
AGE n (%)		
n	807	804
21 - 40 years	13 1.6%	15 1.2%
41 - 60 years	205 25.4%	178 22.1%
> 60 years	589 73.0%	616 76.6%
WEIGHT (kg)		
n	806	804
Mean	80.8	81.6
Standard deviation	19.0	19.1
Median	78.6	79.3
Min , Max	<]	>
HEIGHT (cm)		
n	804	798
Mean	170.0	170.2
Standard deviation	10.2	10.1
Median	170.2	170.0
Min , Max	<]	>
RACE n (%)		
n	807	804
Caucasian/white	734 91.0%	723 89.9%
Black	47 5.8%	55 6.6%
Japanese	2 0.2%	-
Asian other than Japanese	10 1.2%	11 1.4%
Hispanic	13 1.6%	14 1.7%
Other	1 0.1%	3 0.4%
LOCATION n (%)		
n	807	804
US	398 49.3%	399 49.6%
Non-US	409 50.7%	405 50.4%

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Approximately 75% of patients were male, almost all were white and the mean age was about 67 years. The groups were well balanced.

Disease characteristics

Table 9 Summary of baseline disease characteristics, ITT/safety population

Protocols: ENABLE-1 ENABLE-2 (Table BAS: 14FEB02 - Data dump of 01FEB02)

	Placebo N=807	Bosentan N=804
NYHA class at Baseline 1 [n (%)]		
n	807	804
III b	734 91.0%	730 90.8%
IV	73 9.0%	74 9.2%
Ejection fraction (%)		
n	806	803
Mean	25.2	24.8
Standard deviation	6.3	6.3
95% CI of mean	24.8 , 25.7	24.4 , 25.3
Previous hospitalization for CHF within last 12 months (yes/no) [n (%)]		
n	806	803
No	473 58.7%	476 59.3%
Yes	333 41.3%	327 40.7%
Etiology [n (%)]		
n	807	804
Ischemic heart disease	572 70.9%	542 67.4%
Non-ischemic dilated cardiomyopathy	219 27.1%	249 31.0%
Primary valvular disease	16 2.0%	13 1.6%
Patient history of cardiovascular disease [n (%)]		
n	807	804
MYOCARDIAL INFARCTION	520 64.4%	499 60.8%
CORONARY ARTERY DISEASE NOS	344 42.6%	370 46.0%
CORONARY ARTERY SURGERY	236 29.2%	235 29.4%
CORONARY REVASCUARISATION	155 19.2%	153 19.0%
ANGINA UNSTABLE	140 17.3%	145 18.0%
CARDIAC PACEMAKER INSERTION	112 14.0%	148 18.3%
CEREBROVASCULAR ACCIDENT NOS	118 14.6%	126 15.7%
VENTRICULAR FIBRILLATION	62 7.7%	72 9.0%
VENTRICULAR TACHYCARDIA	62 7.7%	72 9.0%
IMPLANTABLE DEFIBRILLATOR INSERTION	45 5.6%	66 8.2%
HYPOTENSION NOS	45 5.6%	45 5.6%
RESUSCITATION	42 5.2%	34 4.2%
VALVULAR HEART DISEASE NOS	36 4.5%	34 4.2%
HEART VALVE REPLACEMENT NOS	31 3.8%	27 3.4%
ARRHYTHMIA NOS	17 2.1%	15 1.9%

(†) Last valid value between visits 1 (Screening) and 2 (Randomization).
 CI = confidence limit, NOS = not otherwise specified, NYHA = New York Heart Association.

Almost all patients had NYHA class IIIb heart failure and mean ejection fraction was 25%. The groups were well balanced.

Concomitant medication at baseline

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Table 11 Summary of most frequent ($\geq 20\%$ on bosentan) classes of concomitant medication at baseline, ITT/safety population

Protocols: ENABEL-1 ENABEL-2 (Table CME01); 01FEB02 - Data dump of 01FEB02)

Class / Preferred Term	Placebo N=807 No. %	Bosentan N=804 No. %
ALL TREATMENT CLASSES		
Total pts with at least one TRT	807 100%	804 100%
Total number of TRTs	6821	6960
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM		
Total pts with at least one TRT	773 95.8%	772 96.0%
Total number of TRTs	793	789
HIGH-CEILING DIURETICS		
Total pts with at least one TRT	769 95.3%	767 95.4%
Total number of TRTs	774	771
ANTITHROMBOTIC AGENTS		
Total pts with at least one TRT	661 81.9%	651 81.0%
Total number of TRTs	725	752
CARDIAC GLYCOSIDES		
Total pts with at least one TRT	460 57.0%	468 58.2%
Total number of TRTs	461	469
BETA BLOCKING AGENTS		
Total pts with at least one TRT	404 50.1%	417 51.9%
Total number of TRTs	404	419
ORGANIC NITRATES		
Total pts with at least one TRT	357 44.2%	358 44.5%
Total number of TRTs	417	416
SERUM LIPID REDUCING AGENTS		
Total pts with at least one TRT	374 46.3%	316 39.3%
Total number of TRTs	391	358
MINERAL SUPPLEMENTS		
Total pts with at least one TRT	258 32.0%	269 33.5%
Total number of TRTs	290	314
POTASSIUM SPARING AGENTS		
Total pts with at least one TRT	225 27.6%	241 30.0%
Total number of TRTs	223	245
DRUGS USED IN DIABETES		
Total pts with at least one TRT	212 26.3%	218 27.1%
Total number of TRTs	278	284
ANTACIDS, DRUGS FOR TREATMENT OF PEPTIC ULCER AND FLATULENCE		
Total pts with at least one TRT	177 21.9%	194 24.1%
Total number of TRTs	195	214

Abstracted from Appendix 6.
TRT = treatment.

At least 80% of patients were taking an ACE inhibitor/ARB, diuretic, and/or antithrombotic agent.

EFFICIACY AND SAFETY

Clinical status at 9 months

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Table 12 Clinical status at 9 months in AC-052-301 and AC-052-302 (adjudicated), ITT population

(Table CLSS 1 and CLSS 2: 01FEB02 - Data dump of 01FEB02)

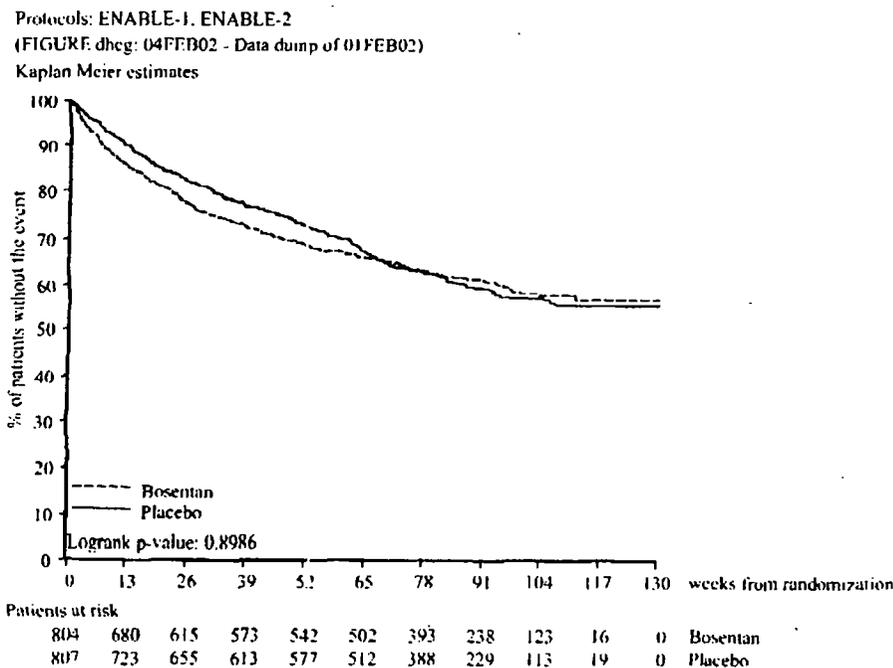
	AC-052-301		AC-052-302	
	Placebo N=409	Bosentan N=405	Placebo N=398	Bosentan N=399
Clinical status at 9 month FU				
n	409	405	398	399
IMPROVED	79 19.3%	97 24.0%	93 23.4%	98 24.6%
UNCHANGED	231 56.5%	194 47.9%	203 51.0%	172 43.1%
WORSE	99 24.2%	114 28.1%	102 25.6%	129 32.3%
TREATMENT EFFECT				
p-value Mann-Whitney U-test		0.9264		0.2626

FU = follow-up.

Statistically, there was no difference between drug and placebo for clinical status at 9 months. However, more bosentan patients became worse compared to placebo patients in both studies (28.1% versus 24.2% in study 301 and 32.2% versus 25.6% in study 302).

The primary endpoint for the pooled studies was the time from randomization to death from all causes or hospitalization associated with heart failure (adjudicated). The log rank p-value for the treatment difference was 0.8986 (312 events for bosentan versus 321 for placebo).

Figure 4 Time to death or hospitalization for CHF (adjudicated) in the pooled ENABLE population, ITT population

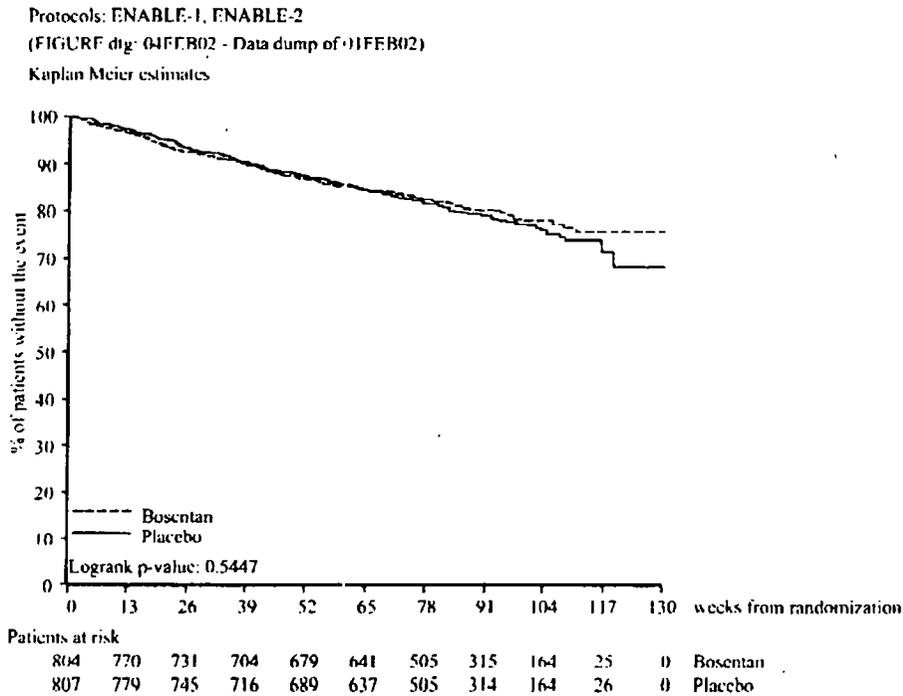


From Table 12, it can be seen that there are numerically more patients in the bosentan group in both

studies who are "improved". When both studies are pooled together, a point estimate for the difference in the proportion of patients who are "improved" is 3% and the confidence interval is (-1.3%, 7.2%). This means that it is questionable whether there is any difference in the rates and a difference of as much as 7.2% can be ruled out. On the other hand, patients on bosentan, compared to those on placebo, tended to have a greater rate of worsening in both studies. The point estimate for the difference in rates is 5.3% and the confidence interval is (0.8%, 9.8%). This apparent difference was the result of increased incidence of hospitalization for CHF rather than a difference in death rates.

The time to death from all causes is shown below.

Figure 6 Time to death from all causes up to study end, ITT population



There was no difference in the death rates between bosentan and placebo at any timepoint.

The causes of death for patients (≥ 3) who died during the randomized period or within 28 days of the treatment end are shown below.

Table 20 Most frequent (≥ 3 patients on bosentan) reasons for death during randomized treatment or within 28 days of treatment end, safety population

Protocols: ENABLE-1 ENABLE-2 (Table DEAM1d: 01FEB02 - Data dump of 01FEB02)

Cause of death	Placebo		Bosentan	
	N=807		N=804	
	No.	%	No.	%
Total pts with at least one cause	139	17.2%	119	14.8%
CARDIAC FAILURE NOS	50	6.2%	42	5.2%
SUDDEN CARDIAC DEATH	33	4.1%	35	4.4%
VENTRICULAR FIBRILLATION	8	1.0%	6	0.8%
MYOCARDIAL INFARCTION	4	0.5%	5	0.6%
SUDDEN DEATH UNEXPLAINED	10	1.2%	5	0.6%
RENAL FAILURE NOS	6	0.7%	5	0.6%
CARDIOGENIC SHOCK	5	0.6%	4	0.5%
CORONARY ARTERY DISEASE NOS	2	0.2%	4	0.5%
PNEUMONIA NOS	1	0.1%	4	0.5%
RESPIRATORY FAILURE (EXC NEONATAL)	1	0.1%	4	0.5%
CARDIAC ARREST	6	0.7%	3	0.4%
SEPSIS NOS	4	0.5%	3	0.4%
CARDIO-RESPIRATORY ARREST	3	0.4%	3	0.4%
MULTI-ORGAN FAILURE	2	0.2%	3	0.4%

Abstracted from Appendix 56.

NOS = not otherwise specified, SAE = serious adverse event.

Nothing seems unusual.

Adverse events

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Table 17 Most frequent (≥ 5% on bosentan) treatment-emergent adverse event (including unrelated), safety population

Protocols: ENABLE-1 ENABLE-2 (Table AES01A3: 25APR02 - Data dump of 24APR02)

Body system / Adverse event	Placebo N=807 No. %	Bosentan N=804 No. %
ALL BODY SYSTEMS		
Total pts with at least one AE	772 95.7%	764 95.0%
Total number of AEs	5383	5167
CARDIAC FAILURE NOS	317 39.3%	304 37.8%
DYSPIAEA NOS	200 24.8%	233 29.2%
DIZZINESS (EXC VERTIGO)	146 18.1%	142 17.7%
CHEST PAIN NEC	133 16.5%	130 16.3%
FATIGUE	124 15.4%	109 13.5%
HYPOTENSION NOS	88 10.9%	98 12.2%
OEDEMA LOWER LIMB	66 8.2%	93 11.6%
ANAEMIA NOS	42 5.2%	81 10.1%
COUGH	93 11.5%	79 9.8%
HEADACHE NOS	55 6.8%	71 8.8%
NAUSEA	63 7.8%	66 8.2%
UPPER RESPIRATORY TRACT INFECTION NOS	45 5.6%	62 7.7%
HEPATIC FUNCTION ABNORMAL NOS	27 3.3%	60 7.5%
RENAL FAILURE NOS	73 9.0%	57 7.1%
DIARRHOEA NOS	69 8.6%	54 6.7%
ANGINA PECTORIS	49 6.1%	54 6.7%
PNEUMONIA NOS	62 7.7%	52 6.5%
URINARY TRACT INFECTION NOS	41 5.1%	51 6.3%
WEAKNESS	63 7.8%	50 6.2%
RENAL IMPAIRMENT NOS	70 8.7%	49 6.1%
ARTHRALGIA	40 5.0%	40 5.0%
ATRIAL FIBRILLATION	47 5.8%	46 5.7%
NASOPHARYNGITIS	45 5.6%	46 5.7%
BRONCHITIS NOS	42 5.2%	45 5.6%
BACK PAIN	43 5.3%	43 5.3%
HAEMOGLOBIN DECREASED	21 2.6%	43 5.3%
PULMONARY OEDEMA NOS	33 4.1%	42 5.2%
MYOCARDIAL INFARCTION	42 5.2%	41 5.1%
OTHER	710 88.0%	682 84.8%

Note: All AEs with a bosentan incidence < 5% are pooled under 'Other'.
 Adapted from Appendix 3.7.
 AE = adverse event, NEC = not elsewhere classified, NOS = not otherwise specified.

Events in the above table that were reported at least 2% more often by the bosentan group compared to the placebo group include lower limb edema.

Percent of patients who reported an event

Event	Placebo	Bosentan	Placebo subtracted
Anemia nos	5.2	10.1	4.9
Abnormal hepatic function	3.3	7.5	4.2
Decreased hemoglobin	2.1	5.3	3.2
URI nos	5.3	7.7	2.4
Headache nos	6.6	8.8	2.2
Lower limb edema	8.2	10.3	2.1

Anemia, abnormal hepatic function, and decreased hemoglobin were reported at least 3% more often by the bosentan group compared to the placebo group.

Serious adverse events

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Table 22 Most frequent ($\geq 1\%$ on bosentan) SAEs (excluding censored) during randomized treatment or within 28 days of treatment end, safety population

Protocols: ENABLE-1 ENABLE-2 (Table SAE(2D2: 01FEB02 - Data dump of 01FEB02)

Body system / Adverse event	Placebo N=607 No.	Bosentan N=804 No.
ALL BODY SYSTEMS		
Total pts with at least one SAE	338 45.6%	336 41.9%
Total number of SAEs	1005	906
CHEST PAIN NEC	30 3.7%	43 5.3%
PNEUMONIA NOS	37 4.6%	40 5.0%
ANGINA UNSTABLE	23 2.9%	32 4.0%
RENAL FAILURE NOS	33 4.1%	28 3.5%
CORONARY ARTERY DISEASE NOS	21 2.6%	20 2.5%
SYNCOPE	25 3.1%	19 2.4%
DYSPNOEA NOS	28 3.5%	17 2.1%
CEREBROVASCULAR ACCIDENT NOS	26 3.2%	17 2.1%
CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	17 2.1%	16 2.0%
ELECTIVE TREATMENT	15 1.9%	16 2.0%
ANGINA PECTORIS	16 2.0%	15 1.9%
ANAEMIA NOS	13 1.6%	15 1.9%
DEHYDRATION	22 2.7%	12 1.5%
ABDOMINAL PAIN NOS	8 1.0%	12 1.5%
GASTROINTESTINAL HAEMORRHAGE NOS	9 1.1%	11 1.4%
WEARINESS	9 1.1%	11 1.4%
DIZZINESS (EXC VERTIGO)	9 1.1%	10 1.2%
RENAL IMPAIRMENT NOS	14 1.7%	9 1.1%
HYPERCALCAEMIA	11 1.4%	9 1.1%
CELLULITIS	7 0.9%	9 1.1%
DIABETES MELLITUS NOS	12 1.5%	8 1.0%
SEPSIS NOS	10 1.2%	9 1.0%
PYREXIA	7 0.9%	8 1.0%
CHOLELITHIASIS	4 0.5%	8 1.0%
HAEMATURIA	4 0.5%	8 1.0%

Note: only SAEs with onset from start of treatment to 28 calendar days after end of treatment are included.
 NOS = not otherwise specified, SAE = serious adverse event.
 Abstracted from Appendix 71.

Chest pain nec and unstable angina were reported at least 1% more by bosentan patients than by placebo patients.

Discontinuations for adverse events

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Table 23 Most frequent (≥ 3 patients on bosentan) adverse events that led to discontinuation of randomized treatment, safety population

Protocols: ENABLE-1 ENABLE-2 (Table AED01: 01FEB02 - Data Dump of 01FEB02)

Body system / Adverse event	Placebo N=807 No.	Bosentan N=804 No.
ALL BODY SYSTEMS		
Total pts with at least one AE	86 10.7%	154 16.7%
Total number of AEs	145	254
CARDIAC FAILURE NOS	25 3.1%	39 4.9%
HEPATIC FUNCTION ABNORMAL NOS	1 0.1%	19 2.4%
DYSPINOEA NOS	6 0.7%	10 1.2%
FATIGUE	2 0.2%	10 1.2%
NAUSEA	3 0.4%	9 1.1%
DIZZINESS (EXC VERTIGO)	2 0.2%	9 1.1%
ANAEMIA NOS	5 0.6%	2 1.0%
HEADACHE NOS	3 0.4%	8 1.0%
HYPOTENSION NOS	5 0.6%	6 0.7%
WEAKNESS	2 0.2%	6 0.7%
PULMONARY OEDEMA NOS	2 0.2%	5 0.6%
VOMITING NOS	3 0.4%	4 0.5%
DIARRHOEA NOS	1 0.1%	3 0.4%
HAEMOGLOBIN DECREASED	-	3 0.4%
MYOCARDIAL INFARCTION	-	3 0.4%

Abstracted from Appendix 74.
AE = adverse event, NOS = not otherwise specified.

Adverse events from the above table and leading to discontinuation more often in the bosentan group compared to the placebo group are shown below.

Percent of patients

	Placebo	Bosentan	Placebo subtracted
Any event	10.7	16.7	6.0
cardiac failure	3.1	4.9	1.8
abnormal hepatic function	0.1	2.4	2.3
fatigue	0.2	1.2	1.0
nausea	0.4	1.1	0.7
dizziness (exc vertigo),	0.2	1.1	0.9
decreased hemoglobin	0	0.4	0.4
MI	0	0.4	0.4

Laboratory parameters

Incidence of markedly abnormal laboratory values reported during or within 28 days of receiving study drug.

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Table 25 Incidence of marked laboratory abnormalities occurring during randomized treatment or within 28 days after treatment end, safety population

Protocols: ENABLE-1 ENABLE-2 (Table ID: 01FEB02 - Data dump of 01FEB02)

Laboratory Abnormality (*)		Placebo N=807		Bosentan N=804	
		No.	%	No.	%
HEMATOLOGY					
Hemoglobin	HH	3 / 762	0.4%	0 / 776	
	LL	69 / 782	8.8%	158 / 776	20.0%
Hematocrit	HH	1 / 781	0.1%	0 / 775	
	LL	82 / 781	10.5%	190 / 775	23.2%
Leukocytes	HH	18 / 780	2.3%	16 / 775	2.1%
	LL	8 / 780	0.6%	7 / 775	0.9%
Neutrophils	LL	9 / 779	1.0%	11 / 771	1.4%
	HH	7 / 765	0.9%	2 / 764	0.3%
Platelets	HH	0 / 778		2 / 775	0.3%
	LL	12 / 778	1.5%	20 / 775	2.6%
CLINICAL CHEMISTRY					
ALT	HH	41 / 784	5.2%	104 / 771	13.5%
	LL	35 / 775	4.5%	76 / 770	9.9%
AST	HH	27 / 774	3.5%	17 / 762	2.2%
	LL	17 / 782	2.2%	30 / 773	3.9%
Bilirubin	HH	1 / 781	0.1%	1 / 775	0.1%
	LL	12 / 781	1.5%	13 / 775	1.7%
Alkaline Phosphatase	HH	84 / 786	10.7%	67 / 779	8.6%
	LL	4 / 784	0.5%	4 / 777	0.5%
Albumin	LL	27 / 784	3.4%	13 / 771	1.7%
	HH	5 / 768	0.7%	5 / 767	0.7%
Potassium	HH	37 / 785	4.7%	23 / 777	3.0%
	LL	10 / 785	1.3%	13 / 775	1.7%
Glucose	HH	93 / 781	11.9%	98 / 772	12.7%
	LL	3 / 781	0.4%	4 / 772	0.5%
Triglycerides	HH	91 / 763	11.9%	75 / 765	9.8%
	LL	137 / 782	17.5%	116 / 779	14.9%
URINE					
Urine Protein	HH	38 / 770	4.9%	24 / 759	3.2%
	LL	31 / 772	4.0%	38 / 762	5.0%

Values given are the number of patients with at least one abnormality/number of patients (n). HH and LL denote values above or below the marked reference range and having a clinically relevant change in the same direction.

ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen.

As expected, there were more bosentan patients with abnormally low hemoglobin and hematocrit compared to placebo patients (20% versus 8.8%, respectively, and 23.2% versus 10.5%, respectively) and more bosentan patients with abnormally high ALT and AST compared to placebo patients (13.5% versus 5.2%, respectively, and 9.9% versus 4.5%, respectively). While abnormally high Alk phos values were somewhat more common in bosentan patients compared to placebo patients (3.9% versus 2.2%, respectively), there were more placebo patients with abnormally high bilirubin compared to bosentan patients.

The table below shows those patients who had ALT and/or AST > 3 times upper limit of normal as well those patients with hemoglobin < 10 g/dl.

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Table 26 Incidence of marked abnormalities in hemoglobin and liver aminotransferases to a clinically meaningful cut-off, safety population

Protocols: ENABLE-1 ENABLE-2 (Table LMA03d: 01FEB02 - Data dump of 01FEB02)
Abnormalities up to 28 days after the end of study treatment

Laboratory Abnormality	Placebo		Bosentan	
	No.	%	No.	%
ALT > 3*upper std	23 / 784	2.9%	69 / 771	8.9%
AST > 3*upper std	19 / 775	2.5%	56 / 773	7.3%
ALT or AST > 3*upper std	26 / 784	3.3%	76 / 776	9.8%
Hemoglobin < 10g/dL and LL ... with decrease from baseline	40 / 779	5.1%	100 / 772	13.0%

Values given are the number of patients with at least one abnormality/number of patients (%).
HE and LL denote values above or below the marked reference range and having a clinically relevant change in the same direction.
ALT = alanine aminotransferase, AST = aspartate aminotransferase.

The percents of patients with ALT and/or AST by various degrees of abnormality are shown below.

Table 27 Incidence of marked increases in ALT or AST by magnitude, safety population

Protocols: ENABLE-1 ENABLE-2 (Table LMA03i: 01FEB02 - Data dump of 01FEB02)
Abnormalities up to 28 days after the end of study treatment

Laboratory Abnormality	Placebo		Bosentan	
	No.	%	No.	%
ALT or AST > 3*upper std	26 / 784	3.3%	76 / 776	9.8%
ALT or AST >= 5*upper std	14 / 784	1.8%	49 / 776	6.3%
ALT or AST >= 8*upper std	9 / 784	1.1%	29 / 776	3.7%

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

The percents of patients with increases in bilirubin and ALT and/or AST > 3 times upper limit of normal are shown below.

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Table 29 Incidences of increases in bilirubin and ALT and/or AST to > 3 x ULN, safety population

Protocols: ENABLIF-1 FNABLIF-2 (Table LMA04d: 04FEB02 - Data dump of 01FEB02)
Abnormalities up to 28 days after the end of study treatment

Laboratory Abnormality	Placebo		Bosentan	
	No.	%	No.	%
ALT or AST > 3*upper std	26 /764	3.3%	76 /776	9.8%
BILIRUBIN >= 2*upper std	35 /774	4.5%	24 /762	3.1%
BILIRUBIN >= 3*upper std	9 /774	1.2%	9 /762	1.2%
ALT or AST > 3*upper std and ... BILIRUBIN >= 2*upper std	6 /774	0.8%	9 /761	1.2%
ALT or AST > 3*upper std and ... BILIRUBIN >= 3*upper std	3 /774	0.4%	3 /761	0.4%

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

There seems to be little difference between patients on bosentan and patients on placebo.

Outcomes of patients with abnormal ALT and or AST are shown below.

Table 32 Outcomes of patients with ALT and/or AST > 3 x ULN, safety population

	Number of patients	Transient*	Treatment interruption / successful reintroduction†	Prematurely discontinued treatment‡	Death (with elevated ALT/AST)	Others (NA or concomitant disease)
Bosentan 125 mg b.i.d.	76	36	11	20	7	2
Placebo	26	8	3	1	10	4

Note: The sponsor's upper limit of the normal range was 30 U/l for ALT and 25 U/l for AST.

* Transient value = liver function tests decreased to $\leq 2 \times$ ULN while on treatment (target or reduced dose).

† Successful reintroduction of treatment after ALT and/or AST returned to baseline.

‡ Prematurely discontinued randomized treatment (initially or upon re-introduction)

ALT = alanine aminotransferase, AST = aspartate aminotransferase, NA = not applicable, ULN = upper limit of normal.

A total 10 placebo patients and 7 bosentan patients died of cardiac failure or Myocardial infarction while aminotransferases were > 3 x ULN but none were associated with a report of "liver failure.

There were 2 bosentan patients who reported jaundice compared to 0 placebo patients. These were:

Patient 50511

This patient with ischemic heart disease, CHF NYHA class IIIb and an ejection fraction of 27% at study start, developed an increase in liver aminotransferases during the course of the study. She had a medical history of osteoporosis, insulin-dependent diabetes mellitus, urinary tract infection, myocardial infarction, hypertension, congestive heart failure, cerebrovascular accident, hypothyroidism and colon cancer. Concomitant medication at study entry included atenolol, isosorbide mononitrate, cilazapril, oxazepam, vitamin E, and famotidine. Liver aminotransferases were elevated on day 58 (ALT and AST were 70 U/l and 44 U/l, respectively), but normalized by day 63. On day 170, the patient complained of weakness (105/55 mmHg). After a one-day interruption and subsequent dose reduction of study drug, her blood

pressure increased, but weakness persisted, along with nausea, abdominal pain and jaundice, and an increase in liver tests were noted: total bilirubin 115.4 $\mu\text{mol/l}$, direct bilirubin 48.2 $\mu\text{mol/l}$, AST 341 U/I, ALT 183 U/I, and alkaline phosphatase 217 U/L. The patient was hospitalized on day 176, and the study drug was stopped at that time. Liver and spleen were normal sized, and a CT of the abdomen showed a small amount of ascites. A gastroscopy revealed severe esophagitis and duodenitis. The patient's condition improved and she was discharged on day 177 with a diagnosis of 'drug-induced jaundice'. Eosinophil count remained normal throughout the event. On day 218 transaminases were normal and bilirubin was 16.4 $\mu\text{mol/l}$. The patient was rehospitalized on days 316-318 with chest pain and dyspnea, and was treated with furosemide. Liver function tests remained normal through day 626 (end of study visit).

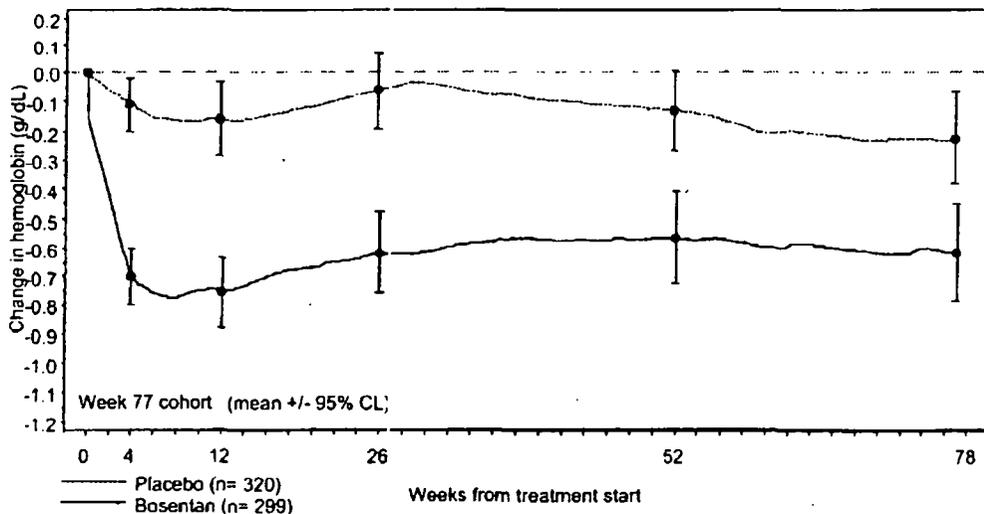
Patient 92806

This patient with ischemic heart disease, CHF NYHA class IIIb, ejection fraction 21%, was prematurely discontinued from the study because of increased liver aminotransferases. She had a medical history of myocardial infarction, coronary angioplasty, coronary artery bypass surgery, unstable angina, and hypercholesterolemia. Concomitant medication included captopril, hydrochlorothiazide, digoxin, warfarin, carvedilol, atorvastatin and estrogen. Between days 24-33, the patient developed dizziness, nausea, vomiting and mild jaundice. Study medication was permanently stopped on day 40. Liver function tests were found to be elevated on day 29 (ALT and AST were 231 and 130 U/L, respectively, AP was 254 U/I, and total bilirubin was 19.5 $\mu\text{mol/l}$). Values increased on day 33 (ALT-295, AST-130 U/I, AP-362 U/I and bilirubin-22 $\mu\text{mol/l}$). Eosinophil count was also increased (from 0.13 at baseline to 0.77 $10^9/l$). Clinical symptoms completely resolved on day 54 without treatment. Laboratory values returned to baseline by day 79.

The absolute changes from baseline in hemoglobin over time for the 2 treatment groups are shown in the figure below.

Figure 16 Absolute changes from baseline in hemoglobin concentration over time by cohorts, safety population

Protocols: ENABLE-1, ENABLE-2
(FIGURE hemog: 11FEB02 - Data dump of 01FEB02)



Protocol AC-052-355.

Summary

This study is too small to draw any conclusions about the combined use of epoprostenol+bosentan except that there is no indication that these drugs are excessively harmful if used together.

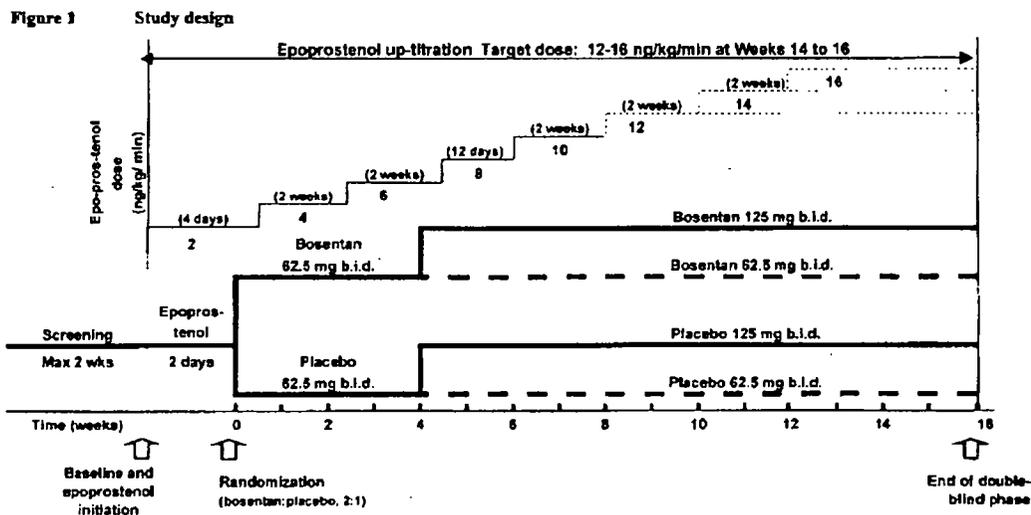
A double-blind, randomized, placebo-controlled study to assess the effect of Tracleer™ (bosentan) in combination with the initiation of epoprostenol therapy on cardiopulmonary hemodynamics in patients with severe pulmonary arterial hypertension (PAH).

This document reports data from the double-blind study up to the 28-day safety follow-up. There is an ongoing open-label extension.

The primary objective of this study was to determine the effects of bosentan on hemodynamics when combined with the initiation of epoprostenol in patients with severe primary pulmonary hypertension (PPM) or pulmonary hypertension due to scleroderma (SSc/P11) or scleroderma spectrum disorders in need of epoprostenol.

Secondary objectives were to evaluate the effects of bosentan combined with epoprostenol on exercise capacity, dyspnea-fatigue rating and functional classification as well as to assess the safety and tolerability of the epoprostenol/bosentan combination.

This study was multicenter, randomized, double-blind, placebo-controlled with two parallel groups. Patients were randomized in a 2:1 ratio to receive oral bosentan (62.5 mg bid for first 4 weeks followed by 125 mg bid for last 16 weeks, if tolerated) or placebo in addition to epoprostenol (initiation at 2 ng/kg/min for 4 days and increased to 4 ng/kg/min. Thereafter, increased at rate of 2ng/kg/min at 2 week intervals for a target dose of 12 to 16 ng/kg/min between weeks 14 and 16.



Safety

Disposition of patients

	Epoprostenol+bosentan	Epoprostenol+placebo
No. randomized	22	11
No. discontinued	4	1
Discontinued for death	2+	0
Discontinued for AE	1	1
Worsening condition	1	0

+a 3rd patient died 36 days after being withdrawn from trial although the patient remained on bosentan.

Of the 22 patients randomized to epoprostenol+bosentan, 4 discontinued early (2 died, 1 withdrew for adverse events and 1 withdrew for worsening condition). Of the 11 patients randomized to epoprostenol+placebo, 1 discontinued early (for adverse event).

The majority of patients in both groups were female, mean ages were about 45 years, and nearly all were white. The mean times from diagnosis of PAH to enrollment were about 14 months, the majority of etiology of PAH was primary, most had of WHO grade of III at baseline, and the majority did not have clinical signs of right heart failure.

Deaths

There were no deaths in the epoprostenol+placebo and 2 deaths in the epoprostenol+bosentan. One patient (208 40065) died of cardiopulmonary failure on Day 15 and one patient 208 40067 died of cardiac failure on Day 111 after randomization. The third bosentan-treated patient (101 40031) died 36 days after being withdrawn from the study. Treatment was unblinded on Day 47 because of his worsening condition. The patient, however, continued unblinded bosentan on a compassionate use basis. The patient's condition grew worse, and on Day 83, died of cardiac failure.

Serious adverse events

There was little difference between the 2 treatment groups regarding the reporting of serious events. Only cardiac failure was reported by more than 1 patient in epoprostenol+placebo group (2, 18.2%) and epoprostenol+bosentan group (2, 9.1%). This difference in reporting rates is probably irrelevant.

Discontinuations for adverse events

There were 2 discontinuations for adverse events, both the result of abnormal hepatic function. One patient receiving epoprostenol+placebo developed elevated LFTs on day 3; the study drug then was discontinued and reintroduced with a resurgence of LFT levels. The patient was then permanently discontinued and later had decreasing LFT values. This patient had elevated LFTs at baseline. The other patient was receiving epoprostenol+bosentan when she developed increased LFTs on day 36. She was discontinued and LFTs returned to normal.

Adverse events

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Table 16 Summary of adverse events (including unrelated) reported for $\geq 5\%$ of patients on bosentan, safety population

Protocol: AC-052-355 (Table AESS03: 26JUL02 - Data 19JUL02)

Body system / Adverse event	Placebo		Bosentan	
	N=11 No.	%	N=22 No.	%
ALL BODY SYSTEMS				
Total pts with at least one AE	11	100%	22	100%
Total number of AEs	67		123	
PAIN IN JAW	10	90.9%	13	59.1%
DIARRHOEA NOS	3	27.3%	12	54.5%
FLUSHING	5	45.5%	6	27.3%
HEADACHE NOS	4	36.4%	6	27.3%
OEDEMA LOWER LIMB	1	9.1%	6	27.3%
PAIN IN LIMB	2	18.2%	5	22.7%
NAUSEA	2	18.2%	4	18.2%
DERMATITIS NOS	1	9.1%	4	18.2%
CARDIAC FAILURE NOS	2	18.2%	3	13.6%
UPPER RESPIRATORY TRACT INFECTION NOS	1	9.1%	3	13.6%
HEPATIC FUNCTION ABNORMAL NOS	2	18.2%	2	9.1%
COUGH	1	9.1%	2	9.1%
DIZZINESS (EXC VERTIGO)	1	9.1%	2	9.1%
DYSPNOEA NOS	1	9.1%	2	9.1%
EPISTAXIS	1	9.1%	2	9.1%
MYALGIA	1	9.1%	2	9.1%
ANAEMIA NOS	-		2	9.1%
BLOOD IN STOOL	-		2	9.1%
FATIGUE	-		2	9.1%
IMPLANT INFECTION	-		2	9.1%
OEDEMA NOS	-		2	9.1%
TOOTH ABSCESS	-		2	9.1%
VISUAL DISTURBANCE NOS	-		2	9.1%
OTHER	9	81.8%	14	63.6%

Note: Only AEs with onset from start of study treatment to 1 calendar day after end of study treatment are included.
 All AEs with a bosentan incidence $< 5\%$ are pooled under 'Other'.
 All patients in the study are treated with epoprostenol in addition to randomized treatment (placebo or bosentan).
 AE = adverse event, EXC = excluding, NOS = not otherwise specified, pts = patients.

The adverse event reported most frequently in either treatment group was jaw pain, an event associated with the use of epoprostenol. The incidence rate was higher in the epoprostenol+placebo group compared to epoprostenol+bosentan.

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/s/

Maryann Gordon
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