Mean changes from baseline with addition of AC-052-352
Placebo subtracted mean changes for bosentan from baseline at last value, by dose and duration, is shown below.

Placebo subtracted change from baseline: hemoglobin (g/dl)

Duration of Rx	100 mg^	250-500 mg+	1000-1500 mg^^	2000 mg++	All doses combined!
2-12 weeks	-0.31 n=48	-0.29 n=45	-0.54 n=61	-0.93 n=95	-0.47 n=249
>12 weeks	-	-0.96 n=161	-0.93 n=208	-	-0.94 n=369

^n=48 bosentan, n=46 placebo
+2-12 wks n=45 bosentan, n=46 placebo; >12 wks n=161 bosentan, n=79 placebo
^^2-12 wks n=61 bosentan, n=53 placebo; >12 wks n=208 bosentan, n=116 placebo
++2-12 wks n=95 bosentan, n=67 placebo;
! 2-12 wks n=249 bosentan, n=74 placebo; >12 wks n=369 bosentan, n=195 placebo
From fax dated 6-01-01

There is a dose related mean decrease in hemoglobin that becomes more pronounced the longer the patient is on bosentan. For all doses combined and duration of treatment >12 weeks, the mean decrease from baseline is nearly 1 g/dl.

7.1.2.3 Markedly abnormal laboratory value (see appendix)
The incidence rates of patients reporting markedly abnormal hematology values (defined as a 15% change from baseline for hemoglobin and hematocrit) are shown below for patients in placebo controlled trials that had post baseline values.

Table 39 Incidence of marked laboratory abnormalities in all placebo-controlled studies

Table T44f / 23OCT00

		Placebo N=219 No.	%	Bosentan N=533 No.	%
HEMATOLOGY					
Hemoglobin	HH	0 /204		0 /497	
	LL	6 /204	2.9%	31 /497	6.2%
Hematocrit	HH	0 /204		0 /492	
	LL	6 /204	2.9%	41 /492	8.3%
Erythrocytes	HH	0 /196		0 /478	
	LL	0 /196		5 /478	1.0%
Leukocytes	HH	0 /205		0 /497	
	LL	2 /205	1.0%	4 /497	0.8%
Neutrophils	LL	0 /195		3 /473	0.6%
Eosinophils	HH	0 /195		2 /473	0.4%
Platelets	HH	0 /195		0 /458	
	LL	2 /195	1.0%	1 /458	0.2%

The rates of markedly low hemoglobin and/or hematocrit are higher for bosentan group than placebo. Reports of abnormalities for the other hematology values, however, were similar for the 2 groups.

7.1.2.4 Dose and duration

Marked decreases in hemoglobin and hematocrit by dose and duration

The reports of decreased hemoglobin by time in study and dose is shown below.

Percent of patients with markedly low^ hemoglobin

	100 mg		250-500 mg		1000-1500 mg		2000 mg		ALL doses	
WKS	B n=48	P n=46	B n=66	P n=57	B N=283	P n=172	B n=100	P n=69	B n=514	P n=212
2-12	0	0	0	0	11.1	1.9	4.0	1.5	4.3	2.7
>12	-	-	0	0	9.1	3.4	-	-	8.3	3.1
ALL wks	0	0	0	0	9.5	2.9	4.0	1.5	6.2	2.9

^15% decrease from baseline

n=total number of patients who received the dose and had labs measured

Appendix 61

In this limited database, doses of 1000 to 1500 mg were associated with a placebo subtracted percent incidence of 9.2% for markedly low hemoglobin within the first 12 weeks of treatment.

For all doses combined, the longer patients took bosentan, the higher the (placebo subtracted) incidence rate: 1.6% for patients taking bosentan 12 weeks or less and 5.2% for more than 12 weeks. This implies that the chances a patient will develop anemia increase the longer the patient is taking bosentan. This is supported by the figure shown below.

Percent of patients with low hemoglobin with addition of AC-052-352

Percents of bosentan patients (placebo subtracted) who had hemoglobin drop of 15% or more from baseline, by dose and duration, are shown below.

Percent of patients (placebo subtracted)

Duration of Rx	100 mg^	250-500 mg+	1000-1500 mg^^	2000 mg++	All doses combined!
2-12 weeks	2.0	2.3	18.4	18.0	4.4
>12 weeks	-	13.8	13.3	-	12.4

^n=48 bosentan, n=46 placebo

+2-12 wks n=45 bosentan, n=46 placebo; >12 wks n=163 bosentan, n=79 placebo

^^2-12 wks n=61 bosentan, n=53 placebo; >12 wks n=210 bosentan, n=117 placebo

++2-12 wks n=95 bosentan, n=67 placebo;

! +2-12 wks n=249 bosentan, n=74 placebo; >12 wks n=373 bosentan, n=196 placebo

from fax dated 6-01-01

The percent of patients (placebo subtracted) with a decrease in hemoglobin is shown below.

Percent of patients (placebo subtracted)

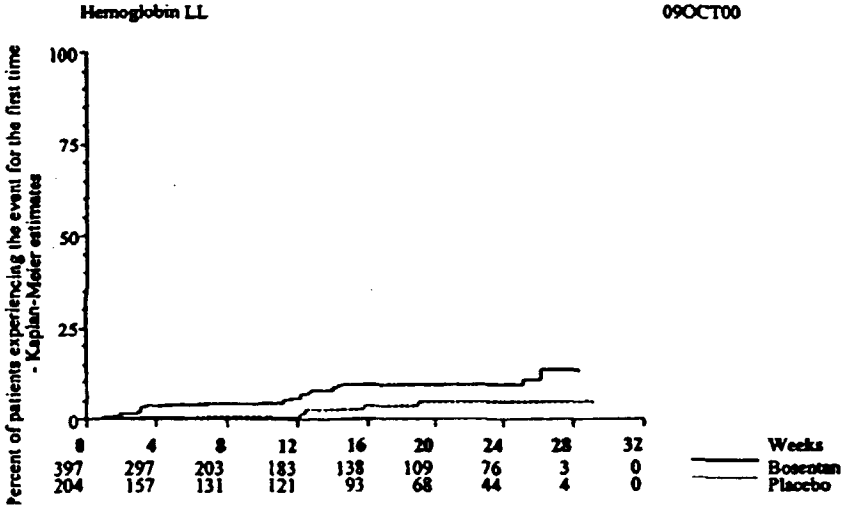
	Total dose of bosentan				
Decrease of hb	100 mg n=48	250-500 mg n=206	1000-1500 mg n=269	2000 mg n=95	All doses N=618
≥ 1.0 g/dl	7.6	31.2	31.7	42.9	27.8
To lower limit of normal	2.0	12.4	17.2	18.0	7.5
≥ 15% from baseline and < 11 g/l	0	1.6	6.6	2.5	3.1
≥ 15% from baseline and < 10 g/l	0	1.1	0.6	0	0

Numbers of patients are roughly the same for all categories
Fax dated 6-26-01

Overall, there is a dose related increase in the percent of patients with abnormally low hemoglobin. The longer the patients are on bosentan the greater the risk that they will have an abnormality.

The Kaplan-Meier estimate of the time to the first occurrence of marked decrease in hemoglobin concentration (decrease of 15% from baseline value) is shown in the figure below.

Figure 11 **Kaplan-Meier estimate of time to first appearance of marked decrease in hemoglobin**



Patients scheduled to receive the very high dose of Bosentan (2,000 mg/day) are excluded

As with the liver function test abnormalities, the longer patients take bosentan, the higher is the likelihood that they will have a marked decrease in hemoglobin.

7.1.3 REACH—NC15462

This 12 week placebo controlled trial in 370 CHF patients reported that hemoglobin, hematocrit, and RBCs were decreased by an average of 7-10% from baseline at week 3 in the bosentan group but unchanged in the placebo group. These changes in the bosentan group were present and of similar magnitude at weeks 12 and 26. There was a mean decrease in total leukocytes of 9%, 15% and 11% at weeks 3, 12, and 26, respectively. There were mean decreases in neutrophils and platelets as well.

The marked laboratory abnormalities in this study are shown below.

Percent of patients

		Bosentan (up to 500 mg bid)	
Hematology variable	Placebo n=119	slow titration n=109	fast titration n=111
Low hematocrit	4.2	11.9	16.2
Low hemoglobin	3.4	8.2	9.8
Low WBC	1.7	0	0.9
Low lymphocytes	10.9	17.4	12.5

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7.1.4 Anemia reported as serious adverse event

Of the 571 patients who received bosentan, 6 (1.1%) reported anemia (1 reported decreased hemoglobin) as a serious adverse event. In the placebo controlled trials, 2 (0.4%) bosentan patient and 2 (0.9%) placebo patient reported anemia (or decreased hemoglobin or secondary anemia) as a serious adverse event.

7.1.4.1 Reports of anemia

The bosentan patients listed below are those who reported anemia as a serious adverse event, needed a transfusion, and/or were discontinued from study drug for reasons that included anemia. N.B. hb=hemoglobin (units are g/dl); hct=hematocrit (units are %).

Hematoma, anemia requiring transfusion	Patient 20256/1481 bosentan 125 mg bid. This 90-year-old male patient with ischemic heart disease was hospitalized with hematoma and anemia on day 24. Medical history: atrial fibrillation , MI, and gout. Concomitant medications: warfarin, digoxin, furosemide and benazepril. Baseline hb/hct 12/33. Hct at hospitalization was 20 and he was transfused with two units of RBC. Hb/Hct 11.4/36 on day 31, 11.2/36 on day 88 and 12/35 last recorded value. Completed study.
Chest pain, atrial fibrillation, pulmonary edema, anemia requiring transfusion	Patient 20241/1061 bosentan 125 mg bid. This 78-year-old male patient with ischemic heart disease was hospitalized on day 649 with severe retrosternal chest pain with marked dyspnea and atrial fibrillation with rapid ventricular rate. Medical history: MI, CABG, CVA, Raynaud's disorders and hypothyroidism. Concomitant medications: losartan, furosemide, spironolactone, digoxin, glyceryl trinitrate, warfarin, quinine, cholestyramine and levothyroxine. In hospital, patient was treated with amiodarone, metoprolol, fentanyl and streptokinase was started but stopped immediately. Pulmonary edema was diagnosed. Hb was 8.6 (10.3 at baseline). Stool was positive for occult blood. Patient received 1 unit of blood. Hb was above 11 for the rest of the study. Other adverse events included edema, dizziness, and severe diarrhea for which drug was interrupted.
Anemia, heart failure, ventricular tachycardia	Patient 20097/1821 bosentan 125 mg bid. 70-year-old female with ischemic heart disease, diabetes mellitus, and idiopathic tbrombocytopenia and concomitant medications: cilazapril, bumetanide, carvedilol, spironolactone, digoxin, actrapid and insulin retards. Baseline hb/hct 13.5/43. She was diagnosed on day 57 with anemia (hb/hct 9.9/35); treated

	with iron supplementation. She was hospitalized on day 92 for worsening heart failure requiring diuretics. Last hb/hct on drug 10.7/not recorded. Study drug was stopped on day 133 because of ventricular tachycardia. Other reported events included CVA.
Chest pain, abdominal pain, anemia, transfusion, dyspnea, death	Patient 20081/0122 bosentan 125 mg. 76-year-old patient with ischemic heart disease was hospitalized because of chest pain on day 14. Medical history: MI, angina pectoris, diabetes, gastric vascular ectasia, gastric ulcer, gastric polyp and mild depression. Concomitant medication: captopril, furosemide, digoxin, metoprolol, glyceryl trinitrate, ticlopidine, glipizide, metformin, omeprazole, teniazepam, fluoxetine, paracetamol and iron supplement. Anti-anginal treatment based on glyceryl trinitrate was initiated and the pain resolved within 2 hours. He was rehospitalized on day 32 because of chest pain with T--wave inversion He was treated and discharged. He was re-hospitalized on day 65 because of chest and severe abdominal pain with shortness of breath. Hb was 9.2 (baseline hb/hct 11.7/34). Endoscopy was negative. He was discharged and rehospitalized on day 90 because of abdominal pain and dyspnea (hb/hct 10.3/30 day 89). The patient received 4 units of packed RBC and was discharged. On day 148 the patient was re-hospitalized with angina. On day 184 the patient was re-hospitalized suffering from musculoskeletal chest pain. He experienced sudden death on day 376 thought to be secondary to MI.
Active bleeding, anemia, transfusion, followed by septicemia. Death	Patient 20086/0041 bosentan 125 mg bid. This was a 65 year old male patient with a medical history ischemic heart disease, congestive cardiac failure, bacterial endocarditis, pacemaker insertion, NIDDM, gout and prostatic complaints. Concomitant medications: furosemide, spironolactone, digoxin, prazosin, isosorbide mononitrate, warfarin, glipazide, colchicine, allopurinol, omeprazole, temazepam, terbutaline, scopolamine, paracetamol and iron supplement. There were no baseline lab values. On day 27, he was hospitalized for bladder neck incision and reported hematuria and acute urinary retention with hematuria. On day 380, he was hospitalized because of malaise and increasing dyspnea. Clinical examination revealed pneumonia, anemia, renal failure, gout and worsening of cardiac failure. Colonoscopy showed blood in the caecum. Anemia (Hb 7.8 mg/l), melena and hematuria were noted and he was treated with 5 units of packed red blood cells, 5 units of plasma. He was treated with furosemide, antibiotics. The next day, fever was noted during blood transfusion and blood culture detected positive microbial growth. Bacterial endocarditis was suspected. The patient's condition gradually deteriorated and he died about 2 weeks later (day 398). While receiving placebo in the prior study (REACH), he was noted to have mild elevation of liver enzymes, including bilirubin, and raised creatinine and BUN.
Elevated LFTs, anemia, and worsening heart failure. Study drug discontinued	Patient 18233/8053 bosentan 250-500 mg bid. 67 year-old white male with coronary artery disease, NYHA class IV, ejection fraction 16%, NIDDM, peripheral artery disease, MI, TIA, coronary angioplasty, and renal failure, treated with acetylsalicylic acid, benazepril hydrochloride, ISMN, spironolactone, furosemide, and digoxin, was permanently discontinued from study drug on day 54 because of worsening heart failure, elevated liver enzymes and anemia. Day 43: ALT 82 U/l, GGT 230 U/l, alk phos 329 U/l (AST remained within the normal range throughout the study), and hb/hct 11.6/36 (baseline 14/41), eosinophils were elevated (.8810e9/l).LFTs normalized. Hb/hct were not followed.
Elevated LFTs, anemia. Fatigue, headache, flu-like sympomts. Study drug discontinued ;death secondary to CHF.	Patient 18197/9002 bosentan 125-250-500 mg bid. 82-year-old white female with valvular heart disease and pulmonary rales, history of coronary artery bypass surgery, gout and diabetes, treated with furosemide, enalapril, amiodarone, ISMN, glyceryl trinitrate, digoxin and warfarin, allopurinol, colchicine, oxazepam, metochlopramide, paracetamol, panadeine, coloxyl with senna, was anemic at baseline (hb/hct 10.2/30). Hb/hct continued to drop (9.7/28) day 24 and ALT started to rise (77 U/L) day 29. Alk phos was elevated at baseline but other LFTs were normal. Patient was pale and extremely fatigued and she reported headache and flu-like symptoms. Study drug was discontinued on day 70; she was not rechallenged because of ongoing heart failure and because "she felt better off study medication". Patient was transfused with 2 units of blood. Patient had 4 episodes of worsening CHF and died on day 157 after the last episode. LFTs were elevated 57 days (day 127) after bosentan had been discontinued. Other reported adverse events included headache, postural hypotension, back pain, and pruritic rash.
Elevated	Patient 18233/8053 bosentan 250-500 mg bid. 67 year-old white male with coronary

LFTs, anemia, and worsening heart failure. Study drug discontinued	artery disease, NYHA class IV, ejection fraction 16%, with a history of NIDDM, peripheral artery disease, MI, TIA, coronary angioplasty, and renal failure, treated with acetylsalicylic acid, benazepril hydrochloride, ISMN, spironolactone, furosemide, and digoxin, was permanently discontinued from study drug on day 54 because of worsening heart failure, elevated liver enzymes and anemia. ALT 82 U/l, GGT 230 U/l, alk phos 329 U/l , hb/hct 11.6/36, eosinophils were elevated. Baseline hb.hct13/41. LFTs normalized. Hb/hct were not followed up.
Elevated LFTs, anemia, lymphopenia . Hospitalized for a fib and developed ARF. Resolved. Study drug discontinued because of LFTs	Patient 18168/8001 bosentan 250-500 mg bid. 49 year old white male with coronary artery disease, NYHA Class IV, ejection fraction 26%, had a history of peripheral artery disease, coronary artery bypass surgery, chronic renal failure, diabetes mellitus and hyperlipidemia. Concomitant medications included captopril, furosemide, propranolol, isosorbide mononitrate, isophane insulin, insulin, simvastatin and acetylsalicylic acid. He was hospitalized on day 20 because of atrial fibrillation. He was cardioverted but 2 days later developed acute renal failure. He was discharged on day 30 with serum creatinine 2.1 md/dl. The patient was found to have an elevation of GGT 172 U/l and anemia, (hb/hct11.4/36). Study medication was discontinued on day 107. GGT 72 U/l and normal hb/hct more than 100 days after drug was discontinued.
Elevated LFTs and anemia. Study drug discontinued	Patient 18168/8004 bosentan 250-500 mg bid. 76-year-old white female with congestive dilated cardiomyopathy, NYHA class IV, ejection fraction 32%, history of hypertension, knee arthroplasty and hysterectomy, treated with enalapril and furosemide, developed both anemia and elevation of liver enzymes by day 34 with peak values between day 62 and 69 (AST 153 U/l, ALT 185 U/l, GGT 550 U/l, alk phos 387 U/l). Bosentan dose was reduced to 250 mg bid on day 62 and permanently discontinued on day 65.. Last values on drug: ALT 167 U/L, AST 153 U/L, GGT 520 U/L, alk phos 361 U/l. Hb/hct: 11.5/38. LFTs were normal 55 days after drug was discontinued. Hb/hct remained decreased. Hb/hct and LFTs were normal at baseline.
Anemia, blood transfusion, study drug withdrawal	Patient 18197/9007 bosentan 125-250-500 mg bid. 65-year-old white male with coronary artery disease, heart failure NYHA class IIIB, ejection fraction 28% and a history of COPD, peripheral artery disease, MI, stroke/TIA, peripheral neuropathy, peptic ulcer, coronary artery bypass surgery and NIDDM, treated with furosemide, enalapril, glibenclamide (glyburide), metformin, ranitidine, glyceryl trinitrate and acetylsalicylic acid, was hospitalized on day 22 with worsening heart failure. Hb/hct 10.6/30 at baseline (secondary to vitamin B12 deficiency). The patient was treated with diuretics, blood transfusion, ferrous sulfate, and hydroxycobalamine. He was discharged 2 days later. The patient reported weakness, unsteadiness on feet, constipation, and diarrhea and withdrew from the study on day 55. Last hb/hct on drug was 10.7/32. Patient remained anemia through follow up. Other events included nausea and flushing.
Anemia, worsening CHF, transfusion, study drug withdrawn	Patient 18113/6061 Bosentan 125-250-500 mg bid. 64-year-old female with CHF NYHA class IIIB and a history of iron-deficiency anemia (> 6 months), hypothyroidism, diabetes, previous MI and peripheral artery disease. Concomitant treatments included ferrous sulfate, beta-carotene, glibenclamide, metformin, captopril, furosemide, hydrochlorothiazide, digoxin. Hb/hct 10.5/33 baseline. After six weeks of treatment with study drug, patient reported worsening of CHF symptoms leading to hospitalization. Study medication was discontinued. Hb/hct 8.9/27. Patient received 2 units of RBC. Gastroscopy was negative for bleeding. Patient remained anemic through 127 days of follow up. Other events included edema, dizziness, diarrhea, epistaxis.
Anemia, transfusion	Patient 18199/9071 bosentan 500 mg bid. 63 year old male with CHF NYHA class IIIB and a history of diabetes, MI, diverticulum, hyperlipidemia and obstructive sleep apnea was randomized with baseline hb/hct (14.2/41). He was hospitalized around week 11 for worsening of CHF and his hb was 10.8. Patient received blood transfusion. Iron studies, B12/folate showed no abnormality. History of melena was reported. The patient completed the study (173 days) with hb/hct 14.1/41. Other events reported included flushing and

	nausea.
Anemia, low monocyte count. Study drug discontinued	Patient 18168/8006 Bosentan 250-500 mg bid. 75 year old male with CHF NYHA class IIIB and ejection fraction of 22% at baseline. Medical history included diabetes, hypertension, and hyperlipidemia. Concomitant medication included captopril, furosemide, atenolol, simvastatin, aspirin and nitrates. Treatment with study drug was discontinued on day 70 because of a decrease in hb/hct:10.8 g/dL/33 (hb/hct at baseline: 13.1 g/dL/39).There was also a rise in alk phos 277 U/L), ALT 59 U/L and AST (76 U/L) while patient was taking study drug. Laboratory values were back to baseline 84 days after drug was stopped.
Anemia, transfusion, study drug discontinued	Patient 18169/8021 bosentan 500 mg bid. 59-year-old male with CHF NYHA class IV and a history of diabetes, angina pectoris, MI and coronary bypass surgery. He was anemic at baseline hb/hct: 11.3/53. GTT at baseline was elevated (248 U/L). He was hospitalized on day 8 because of worsening heart failure and was discharged 4 days later. Hb/hct continued dropping (9.6/29). The patient was hospitalized again on day 30 for worsening of CHF. He
	was transfused with 2 units of RBC for symptomatic anemia, his condition improved and he was discharged one week later. Day 135 GGT 490 U/L with elevated ALT (86 U/L). Hb/hct 10.1/31 at study discontinuation. He was anemic with elevated, but falling, ALT and AST (51/52 U/L) at last follow up (39 days after drug was discontinued).
Anemia, transfusion, normal bone marrow biopsy	Patient 18202/9032 bosentan 500 mg bid. 82-year old male with CHF NYHA class IIIB and a history of angina pectoris, MI and gout was randomized with decreased hb/hct 12.5/38 and elevated ALT and AST (64/47 U/L). Anemia continued to worsen (hb/hct 9.6/27 day 81) but LFTs normalized. Results of bone marrow biopsy showed a normocellular marrow with adequate hematopoietic reserves and no significant diagnostic features. Iron stores were normal and no pathological ring sideroblasts were detected. Three weeks later the patient received 2 units of packed cells. Patient completed the study. Other reported events include positional vertigo, heart failure, dehydration.
Anemia, Study drug discontinued	Patient 20083/0022 bosentan 125 mg bid. 64-year-old white male with valvular heart disease. He had received placebo in the previous study during which he experienced five episodes of worsening of heart failure. Medical history: coronary artery bypass surgery, coronary angioplasty, NIDDM, and COPD, atrial flutter, Concomitant medications included lisinopril, digoxin, furosemide, isosorbide dinitrate, hydralazine, warfarin, chlorpropamide, simvastatin, ranitidine, salbutamol, tolbutamide, beclomethasone, and ketoprofen. Patient had low hb/hct at baseline (12.7/37) which worsened during the study . He has an episode of mild CHF on day 74. Anemia of 9.7/29 was reported and the study drug was discontinued on day 284.
Anemia reported with Safety update	
Anemia; transfusion	Patient No: AC-052-352 /10030. 67-year-old male with pulmonary hypertension secondary to systemic sclerosis receiving furosemide, spironolactone, aspirin, lisinopril, and omeprazole. Medical history included systemic hypertension, hiatal hernia, ischemic heart disease with CABG, prostate cancer, GERD, and CREST syndrome. He was diagnosed with anemia on day 28 (on day 36 hb/hct: 6.9/23). He received 4 units of blood over 2 days. He remained on study drug.

In comparison, there were 2 placebo patients (0.9%) in the clinical trials who received blood transfusions (fax 7-2-01). The one case of a normal bone marrow biopsy (#18202/9032) from a patient with anemia who received bosentan is reassuring.

7.1.5 Safety Update

7.1.5.1 ENABLE

This ongoing, still blinded, placebo controlled trial in patients with is using bosentan doses 62.5mg bid titrated to 125 mg bid.

As of the clinical cut-off, 16 (1.0%) reported anemia as a serious adverse event. A marked

decrease in hemoglobin of 15% from baseline was reported for 7.4% of patients (120/1613). Eight patients had hemoglobin of <8 g/dl.

Number and (percent) of all study patients

15% decrease in hemoglobin from baseline and hemoglobin			
<11 g/l but ≥ 10 g/l	<10 g/l but ≥ 9 g/l	<9 g/l but ≥ 8 g/l	< 8g/l
55 (3.4)	39 (2.4)	18 (1.1)	8 (0.5)

Table 17 of safety update

7.1.5.2 PAH ongoing blinded (AC-052-352)
There were 6 reports of anemia. One patient (10030) required transfusion.

7.2 White blood count

7.2.1 Mean changes
Mean changes from baseline at endpoint for various parameters are shown below by treatment group.

Means at baseline, mean change from baseline, % change from baseline

	Placebo			Bosentan		
	Baseline	Change	% change	Baseline	Change	% change
Leukocytes 10^9/L	7.6	7.5	0	7.1	-0.5	-7.0
Neutrophils 10^9/L	4.5	0.2	4.4	4.43	-0.4	-9
Lymphocytes 10^9/L	1.96	-0.04	-2	1.88	-0.13	-6.9
Monocytes 10^9/L	0.47	0	0	0.44	-0.01	-2.3
Eosinophils 10^9/L	0.19	0.01	5.3	0.18	0.06	27.3
Platelets 10^9/L	218	7	3.2	216	3	1.4

Fax sent 3-7-01

Overall, there tended to be a decrease in white blood cell parameters in the bosentan group compared to placebo except for eosinophils. However, the only consist finding was the increase in eosinophils. The placebo subtracted mean eosinophil count increased 22% over baseline suggesting a drug induced phenomenon. Changes in platelets were unremarkable.

8.0 All adverse events

8.1 All bosentan patients

APPEARS THIS WAY
ON ORIGINAL

Adverse events reported by at least 2% of the 571 patients who received bosentan are shown below.

Appendix 18 Summary of adverse events (including unrelated) in all bosentan-treated patients by frequency

Produced by sturlor on 26OCT00
Ro 47-0203, Protocols: AC-52351 AC-52353 BC-15064(I) BC-15064(II) BD-14884 BC-15018 BC-15020 NC-15462 NC-15464 NM-15031
Table T34: Summary of adverse events (including unrelated) by frequency
Population: Safety
All studies of oral Bosentan (including Open Label)

Body system / Adverse event	Bosentan N=571 No.	%
ALL BODY SYSTEMS		
Total pts with at least one AE	423	74.1%
Total number of AEs	1431	
CARDIAC FAILURE NOS	125	21.9%
HEADACHE NOS	81	14.2%
DIZZINESS (EXC VERTIGO)	75	13.1%
HYPOTENSION NOS	40	7.0%
DYSPNOEA	33	5.8%
FLUSHING	33	5.8%
HEPATIC FUNCTION ABNORMAL NOS	28	4.9%
CHEST PAIN NEC	27	4.7%
NAUSEA	27	4.7%
ANAEMIA NOS	25	4.4%
ANGINA PECTORIS	24	4.2%
DIARRHOEA NOS	24	4.2%
COUGH	23	4.0%
OEDEMA LOWER LIMB	22	3.9%
UPPER RESPIRATORY TRACT INFECTION NOS	21	3.7%
VISION BLURRED	19	3.3%
FATIGUE	17	3.0%
BACK PAIN	16	2.8%
BRONCHITIS NOS	16	2.8%
CONSTIPATION	16	2.8%
VOMITING NOS	16	2.8%
INFLUENZA	15	2.6%
PALPITATIONS	15	2.6%
GOUT	14	2.5%
POSTURAL HYPOTENSION	14	2.5%
URINARY TRACT INFECTION NOS	14	2.5%
ABDOMINAL PAIN NOS	12	2.1%
PYREXIA	12	2.1%

A majority of bosentan patients (74.1%) reported at least one adverse event. Cardiac failure was reported most often (21.9%), followed by headache (14.2%), dizziness excluding vertigo (13.1%), and hypotension (13.1%).

8.1.1 Dose

The table below shows all events reported by at least 2% of the all bosentan group, by the dose of bosentan.

Appendix 20 Summary of adverse events (including unrelated) in all bosentan-treated patients by frequency and dose

Produced by sterior on 26OCT00

Bo 67-0202, Protocols: AC-52351 AC-52352 BC-15064(I) BC-15064(II) BD-14884 MC-15018 MC-15020 MC-15462 MC-15464 MM-15031
Table T34d: Summary of adverse events (including unrelated) by frequency
Population: Safety

All studies of oral Bosentan (including Open Label)
Treatment: Bosentan

Body system / Adverse event	Bosentan 100 mg/d N=50 No.	%	Bosentan 250-500 mg/d N=101 No.	%	Bosentan 1000-1500 mg/d N=317 No.	%	Bosentan 2000 mg/d N=103 No.	%	All patients N=571 No.	%
ALL BODY SYSTEMS										
Total pts with at least one AE	21	42.0%	68	67.3%	271	85.5%	63	61.2%	423	74.1%
Total number of AEs	43		225		1014		149		1431	
CARDIAC FAILURE NOS	-		6	5.9%	110	34.7%	9	8.7%	125	21.9%
HEADACHE NOS	7	14.0%	16	15.8%	37	11.7%	21	20.4%	81	14.2%
DIZZINESS (EXC VERTIGO)	4	8.0%	8	7.9%	61	19.2%	2	1.9%	75	13.1%
HYPOTENSION NOS	-		2	2.0%	35	11.0%	3	2.9%	40	7.0%
DYSPNOEA	1	2.0%	10	9.9%	17	5.4%	5	4.9%	33	5.8%
FLUSHING	3	6.0%	8	7.9%	11	3.5%	11	10.7%	33	5.8%
HEPATIC FUNCTION ABNORMAL NOS	1	2.0%	-		27	8.5%	-		28	4.9%
CHEST PAIN NEC	1	2.0%	7	6.9%	15	4.7%	4	3.9%	27	4.7%
NAUSEA	-		3	3.0%	23	7.3%	1	1.0%	27	4.7%
ANAEMIA NOS	-		5	5.0%	20	6.3%	-		25	4.4%
ANGINA PECTORIS	-		6	5.9%	15	4.7%	3	2.9%	24	4.2%
DIARRHOEA NOS	1	2.0%	3	3.0%	18	5.7%	2	1.9%	24	4.2%
COUGH	2	4.0%	6	5.9%	12	3.8%	3	2.9%	23	4.0%
OEDEMA LOWER LIMB	1	2.0%	4	4.0%	7	2.2%	10	9.7%	22	3.9%
UPPER RESPIRATORY TRACT INFECTION NOS	-		6	5.9%	13	4.1%	2	1.9%	21	3.7%
VISION BLURRED	1	2.0%	3	3.0%	15	4.7%	-		19	3.3%
FATIGUE	-		4	4.0%	9	2.8%	4	3.9%	17	3.0%
BACK PAIN	2	4.0%	3	3.0%	7	2.2%	4	3.9%	16	2.8%
BRONCHITIS NOS	-		3	3.0%	12	3.8%	1	1.0%	16	2.8%
CONSTIPATION	-		1	1.0%	15	4.7%	-		16	2.8%
VOMITING NOS	-		1	1.0%	14	4.4%	1	1.0%	16	2.8%
INFLUENZA	3	6.0%	1	1.0%	5	1.6%	6	5.8%	15	2.6%
PALPITATIONS	1	2.0%	6	5.9%	4	1.3%	4	3.9%	15	2.6%
GOUT	-		1	1.0%	11	3.5%	2	1.9%	14	2.5%
POSTURAL HYPOTENSION	-		-		14	4.4%	-		14	2.5%
URINARY TRACT INFECTION NOS	-		-		11	3.5%	3	2.9%	14	2.5%
ABDOMINAL PAIN NOS	-		2	2.0%	9	2.8%	1	1.0%	12	2.1%
PYREXIA	-		1	1.0%	11	3.5%	-		12	2.1%

Since the sample sizes for the different dose groups are small and uneven, it is difficult to draw conclusions from this table. However, headache, flushing, lower limb edema were reported more often in the 2000 mg bosentan group and seem to be dose related.

8.1.1.1 Selected adverse events from NC15020 (hypertension)

This randomized, placebo controlled, parallel group, placebo and active controlled hypertension study used the widest dose range of all the bosentan studies. Duration of treatment was 4 weeks.

The percent of patients reporting at least of the selected adverse event, by treatment and dose group, is shown below.

Percent of patients

		bosentan				Enalapril
	Placebo n=49	100 mg n=50	500 mg n=49	1000 mg n=45	2000 mg n=50	20 mg n=50
Any event	57.1	42.0	49.0	51.1	56.0	50.0
Headache	18.4	14.0	14.3	20.0	24.0	12.0
Flushing	0	6.0	12.2	8.9	18.0	2.0
Edema+	0	6.0	10.2	4.4	24.0	0

+includes face and leg edema
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Although headache was reported at a high rate by the placebo group (18.4%), there was somewhat more headache reported in the 2000 mg bosentan group (24%). It is increasingly clear that flushing and various types of edema are related to bosentan use.

8.1.2 Duration in treatment

Reported adverse events, grouped by planned treatment duration (≤ 12 weeks and >12 weeks), are shown below.

Appendix 22 Summary of adverse events (including unrelated) in all bosentan-treated patients by frequency and planned treatment duration

Ro 47-0203, Protocols: AC-52351 AC-52353 BC-15064(I) BC-15064(II) BD-14884 NC-15018 NC-15020 NC-15462 NC-15464 NN-15031
Table T34p: Summary of adverse events (including unrelated) by frequency
Population: Safety
All studies of oral Bosentan (including Open Label)
Treatment: Bosentan

Body system / Adverse event	12 weeks or less N=275 No.	%	More than 12 weeks N=296 No.	%	All patients N=571 No.	%
ALL BODY SYSTEMS						
Total pts with at least one AE	156	56.7%	267	90.2%	423	74.1%
Total number of AEs	359		1072		1431	
CARDIAC FAILURE NOS	10	3.6%	115	38.9%	125	21.9%
HEADACHE NOS	48	17.5%	33	11.1%	81	14.2%
DIZZINESS (EXC VERTIGO)	8	2.9%	67	22.6%	75	13.1%
HYPOTENSION NOS	6	2.2%	34	11.5%	40	7.0%
DYSPNOEA	7	2.5%	26	8.8%	33	5.8%
FLUSHING	24	8.7%	9	3.0%	33	5.8%
HEPATIC FUNCTION ABNORMAL NOS	2	0.7%	26	8.8%	28	4.9%
CHEST PAIN NEC	5	1.8%	22	7.4%	27	4.7%
NAUSEA	5	1.8%	22	7.4%	27	4.7%
ANAEMIA NOS	3	1.1%	22	7.4%	25	4.4%
ANGINA PECTORIS	5	1.8%	19	6.4%	24	4.2%
DIARRHOEA NOS	8	2.9%	16	5.4%	24	4.2%
COUGH	8	2.9%	15	5.1%	23	4.0%
OEDEMA LOWER LIMB	14	5.1%	8	2.7%	22	3.9%
UPPER RESPIRATORY TRACT INFECTION NOS	3	1.1%	18	6.1%	21	3.7%
VISION BLURRED	2	0.7%	17	5.7%	19	3.3%
FATIGUE	5	1.8%	12	4.1%	17	3.0%
BACK PAIN	9	3.3%	7	2.4%	16	2.8%
BRONCHITIS NOS	1	0.4%	15	5.1%	16	2.8%
CONSTIPATION	3	1.1%	13	4.4%	16	2.8%
VOMITING NOS	4	1.5%	12	4.1%	16	2.8%
INFLUENZA	11	4.0%	4	1.4%	15	2.6%
PALPITATIONS	7	2.5%	8	2.7%	15	2.6%
GOUT	2	0.7%	12	4.1%	14	2.5%
POSTURAL HYPOTENSION	-		14	4.7%	14	2.5%
URINARY TRACT INFECTION NOS	7	2.5%	7	2.4%	14	2.5%
ABDOMINAL PAIN NOS	4	1.5%	8	2.7%	12	2.1%
PYREXIA	8	2.9%	4	1.4%	12	2.1%

As expected, the longer the patient is in a study, the higher the reporting of an adverse event (56.7% for patients in study 12 weeks or less compared to 90.2% for greater than 12 weeks). Therefore, without concurrent placebo groups, it is hard to draw conclusions about any findings. That said, while headache was reported at roughly the same rate regardless of length of planned treatment, dizziness and abnormal hepatic function were reported 10 times more often by patients who were on drug longer. Also, anemia was reported 7 times more often in patients with the longer planned treatment duration.

8.2 Placebo controlled trials

Adverse event reporting rates in the placebo controlled trials is shown below by treatment group.

Appendix 24 Summary of adverse events (including unrelated) in placebo-controlled trials by frequency

Produced by sturlor on 26OCT00
Ro 47-0203, Protocols: AC-52351 BC-15064(II) BD-14884 NC-15018 NC-15020 NC-15462 NN-15031
Table T31f: Summary of adverse events (including unrelated) by frequency
Population: Safety

Body system / Adverse event	Placebo N=219 No.	%	Bosentan N=533 No.	%
ALL BODY SYSTEMS				
Total pts with at least one AE	156	71.2%	393	73.7%
Total number of AEs	572		1079	
CARDIAC FAILURE NOS	60	27.4%	116	21.8%
HEADACHE NOS	23	10.5%	76	14.3%
DIZZINESS (EXC VERTIGO)	26	11.9%	65	12.2%
HYPOTENSION NOS	19	8.7%	36	6.8%
FLUSHING	2	0.9%	32	6.0%
HEPATIC FUNCTION ABNORMAL NOS	4	1.8%	26	4.9%
OEDEMA LOWER LIMB	-		20	3.8%
NAUSEA	22	10.0%	19	3.6%
DIARRHOEA NOS	13	5.9%	19	3.6%
COUGH	6	2.7%	19	3.6%
ANAEMIA NOS	2	0.9%	19	3.6%
CHEST PAIN NEC	13	5.9%	18	3.4%
DYSPNOEA	7	3.2%	18	3.4%
VISION BLURRED	7	3.2%	17	3.2%
UPPER RESPIRATORY TRACT INFECTION NOS	11	5.0%	16	3.0%
ANGINA PECTORIS	2	0.9%	15	2.8%
POSTURAL HYPOTENSION	14	6.4%	13	2.4%
INFLUENZA	9	4.1%	13	2.4%
VOMITING NOS	8	3.7%	13	2.4%
URINARY TRACT INFECTION NOS	8	3.7%	12	2.3%
BACK PAIN	5	2.3%	12	2.3%
PALPITATIONS	4	1.8%	12	2.3%
CONSTIPATION	4	1.8%	11	2.1%
PYREXIA	4	1.8%	11	2.1%
BRONCHITIS NOS	4	1.8%	10	1.9%
GOUT	6	2.7%	9	1.7%
OEDEMA NOS	1	0.5%	9	1.7%
FATIGUE	11	5.0%	8	1.5%
LOWER RESPIRATORY TRACT INFECTION NOS	3	1.4%	8	1.5%
PAIN IN LIMB	3	1.4%	8	1.5%
FACE OEDEMA	2	0.9%	8	1.5%
HYPOKALAEMIA	1	0.5%	8	1.5%
SYNCOPE	8	3.7%	7	1.3%
ABDOMINAL PAIN NOS	7	3.2%	7	1.3%
ARTHRALGIA	5	2.3%	7	1.3%
RENAL FAILURE NOS	5	2.3%	7	1.3%
DYSPEPSIA	3	1.4%	7	1.3%
ATRIAL FIBRILLATION	2	0.9%	7	1.3%
PRURITUS NOS	-		7	1.3%
NASOPHARYNGITIS	5	2.3%	6	1.1%
DERMATITIS NOS	4	1.8%	6	1.1%
INFLUENZA LIKE ILLNESS	1	0.5%	6	1.1%
PNEUMONIA NOS	1	0.5%	6	1.1%
VISUAL DISTURBANCE NOS	1	0.5%	6	1.1%
NASAL CONGESTION	-		6	1.1%
INSOMNIA	4	1.8%	5	0.9%
RHINITIS NOS	2	0.9%	5	0.9%

Slightly more bosentan patients reported at least one adverse event (73.7%) compared to the placebo patients (71.2%).

Adverse events of reported by at least 7 bosentan patients (2.8%) and were reported by at least 1% more bosentan patients than placebo patients are shown below.

No. and (percent) of patients

	Placebo N=219	Bosentan N=533	% Placebo subtracted
Flushing	2 (0.9)	32 (6.0)	5.1
Lower limb edema	0	20 (3.8)	3.8
Headache	23 (10.5)	76 (14.3)	3.8
Abnormal hepatic function	4 (1.8)	26 (4.9)	3.1
Anemia^	2 (0.9)	20 (3.7)	2.8
Angina	2 (0.9)	15 (2.8)	1.9
Pruritus	0	7 (1.3)	1.3
Edema NOS	1 (0.5)	9 (1.7)	1.2
Hypokalemia	1 (0.5)	8 (1.5)	1.0

^includes hemoglobin decreased

Bosentan use is associated with more reports of flushing, edema, headache, abnormal hepatic function, anemia, angina, pruritus and hypokalemia compared to placebo use.

8.2.1 Dose

Selected adverse events are shown in the following table, by dose.

Number and (%) of patients reporting

	placebo	bosentan			
Adverse event	n=219	<1000 mg n=120	1000-1500 mg n=310	2000 mg n=103	All bosentan n=533
Any event	156 (71.2)	65 (54.2)	265 (85.8)	63 (61.2)	393 (73.7)
Headache	23 (10.5)	20 (16.5)	35 (11.3)	21 (20.4)	76 (14.3)
Dizziness exc.vertigo	26 (11.9)	7 (5.8)	56 (18.1)	2 (1.9)	65 (12.2)
Flushing	2 (0.9)	11 (9.2)	10 (3.2)	11 (10.7)	32 (6.0)
Hepatic function abnormal	4 (1.8)	1 (0.8)	25 (8.1)	0	26 (4.9)
Lower limb edema	0	3 (2.5)	7 (2.3)	10 (9.7)	20 (3.8)
Cough	6 (2.7)	6 (5.0)	10 (3.2)	3 (2.9)	19 (3.6)
anemia	2 (0.9)	0	19 (6.1)	0	19 (3.6)
Angina	2 (0.9)	2 (1.7)	10 (3.2)	3 (2.9)	15 (2.8)

Although the numbers are small in some of the dosing groups, it looks like headache, flushing, and lower limb edema are dose related. Even though the pattern is not clear from this table, hepatic function abnormal and anemia are also dose related (see sections 6 and 7).

Reported adverse events with addition of AC-052-352

The numbers and percents of patients with an adverse event that was a) reported by at least 8 bosentan patients and b) at least 1% more bosentan patients reported the event compared to placebo patients are shown below.

No. and (percent) of patients

	Placebo N=288	Bosentan N=677	Placebo subtracted (%)
Any event	220 (76.4)	529 (78.1)	1.7
Flushing	5 (1.7)	45 (6.6)	4.9
Edema#	8 (2.8)	51 (7.5)	4.7
Abnormal hepatic function	6 (2.1)	40 (5.9)	3.8
Headache	37 (12.8)	107 (15.8)	3.0
Anemia^	3 (1.0)	25 (3.7)	2.7
Pruritus	0	12 (1.8)	1.8
Angina	3 (1.0)	15 (2.2)	1.2
Palpitations	5 (1.7)	18 (2.7)	1.0
Dry mouth	1 (0.3)	9 (1.3)	1.0

^includes hemoglobin decreased
#includes lower limb edema, edema NOS, peripheral edema
From fax dated 6-01-01

The reported events flushing, abnormal hepatic enzymes, anemia, edema, headache consistently show up in most of the lists of events.

9.0 Vital signs

Mean baseline and mean change from baseline at endpoint for blood pressure, heart rate, and weight, all doses combined and by treatment group, are shown below.

Table 58 Summary of vital sign findings in all placebo-controlled studies

Table T71f / 230CT00

		Placebo N=219			Bosentan N=533		
Parameter	Unit	N	BL	Change	N	BL	Change
SYS. BLOOD PRESSURE	(mmHg)	214	127.9	-1.8	521	134.0	-3.0
DIAS. BLOOD PRESSURE	(mmHg)	214	79.6	-0.7	521	83.5	-3.1
HEART RATE	(bpm)	214	77.6	-0.6	521	75.3	0.6
WEIGHT	(kg)	134	78.8	0.3	252	77.7	0.0

Bosentan, compared to placebo, produced a small mean decrease in systolic and diastolic blood pressure. Mean changes in heart rate and weight were similar in both groups.

Dose

The effects of bosentan on blood pressure by dose was examined in study NC15020, a 12 week hypertensive study. Results are shown for systolic and diastolic blood pressure and heart rate in the tables below.

Systolic blood pressure

Appendix 9B NC15020: Summary of changes in vital signs in patients with systemic hypertension

Produced by sturlor on 23OCT00

Ro 47-0203, Protocols: NC-15020
Table T70e_htn: Change to study end in vital signs
Population: Safety

Indication: HTN
SYSTOLIC BLOOD PRESSURE (mmHg)

	Placebo N=49	Bosentan 100 mg/d N=50	Bosentan 250-500 mg/d N=49	Bosentan 1000-1500 mg/d N=45	Bosentan 2000 mg/d N=50
Baseline					
n	49	50	49	45	50
Mean	154.1	164.5	158.1	160.3	160.5
SD	16.3	20.6	14.9	17.2	14.0
Stderr	2.3	2.9	2.1	2.6	2.0
Median	153.0	164.5	159.0	160.0	159.5
Q1 , Q3	140.0 , 167.5	150.0 , 178.0	145.0 , 169.0	150.0 , 171.0	151.0 , 170.0
Min , Max					
Study end					
n	49	50	49	45	50
Mean	150.4	159.4	153.5	151.9	153.6
SD	14.0	18.9	15.4	17.9	18.3
Stderr	2.0	2.7	2.2	2.7	2.6
Median	150.0	160.5	155.0	150.0	150.0
Q1 , Q3	143.0 , 159.0	145.0 , 173.0	141.0 , 162.0	140.0 , 161.0	140.0 , 161.0
Min , Max					
Absolute change					
n	49	50	49	45	50
Mean	-3.7	-5.1	-4.6	-8.4	-6.9
SD	15.6	17.3	16.3	13.1	16.6
Stderr	2.2	2.4	2.3	2.0	2.3
Median	-6.0	-4.5	-5.0	-7.0	-8.0
Q1 , Q3	-15.0 , 8.0	-18.0 , 6.0	-14.0 , 6.0	-15.0 , 0.0	-19.0 , 5.0
Min , Max					

Placebo subtracted changes from baseline at endpoint for bosentan total daily doses 100 mg, 250-500 mg, 1000-1500 mg, 2000 mg were -1.4 mmHg, -0.9 mmHg, -4.7 mmHg, and -3.2 mmHg, respectively.

Diastolic blood pressure

Appendix 98 NC15020: Summary of changes in vital signs in patients with systemic hypertension (cont.)

Produced by sturlor on 23OCT00

Bo 47-0203, Protocols: BC-15020
Table T70e_htn: Change to study end in vital signs
Population: Safety

Indication: HTN
DIASTOLIC BLOOD PRESSURE (mmHg)

	Placebo N=49	Bosentan 100 mg/d N=50	Bosentan 250-500 mg/d N=49	Bosentan 1000-1500 mg/d N=45	Bosentan 2000 mg/d N=50
Baseline					
n	49	50	49	45	50
Mean	101.1	102.5	100.3	103.4	103.0
SD	6.6	7.0	6.9	6.7	6.2
Stderr	0.9	1.0	1.0	1.0	0.9
Median	101.0	101.0	100.0	103.0	103.0
Q1 , Q3	96.0 , 106.0	99.0 , 107.0	95.0 , 105.0	99.0 , 109.0	100.0 , 105.0
Min , Max					
Study end					
n	49	50	49	45	50
Mean	95.8	98.6	95.1	96.3	97.2
SD	9.0	10.2	8.6	9.2	8.6
Stderr	1.3	1.4	1.2	1.4	1.2
Median	94.0	99.0	94.0	98.0	97.5
Q1 , Q3	90.0 , 102.0	91.0 , 105.0	90.0 , 101.0	90.0 , 103.0	90.0 , 104.0
Min , Max					
Absolute change					
n	49	50	49	45	50
Mean	-5.3	-3.9	-5.1	-7.1	-5.8
SD	10.1	10.8	8.3	7.3	8.0
Stderr	1.4	1.5	1.2	1.1	1.1
Median	-5.5	-4.5	-5.0	-6.0	-8.0
Q1 , Q3	-10.0 , 0.0	-11.0 , 5.0	-10.0 , 0.0	-11.0 , -2.0	-11.0 , 0.0
Min , Max					

Placebo subtracted changes from baseline at endpoint for bosentan total daily doses 100 mg, 250-500 mg, 1000-1500 mg, 2000 mg were +1.4 mmHg, +0.2 mmHg, -1.8 mmHg, and +0.5 mmHg, respectively.

Overall, bosentan has only a minor effect on blood pressure.

Heart rate

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Appendix 98 NC15020: Summary of changes in vital signs in patients with systemic hypertension (cont.)

Produced by sturlor on 23OCT00

Bo 47-0203, Protocols: BC-15020
Table T70e_htn: Change to study end in vital signs
Population: Safety

Indication: HTN
HEART RATE (bpm)

	Placebo N=49	Bosentan 100 mg/d N=50	Bosentan 250-500 mg/d N=49	Bosentan 1000-1500 mg/d N=45	Bosentan 2000 mg/d N=50
Baseline					
n	49	50	49	45	50
Mean	71.9	71.2	70.9	73.2	73.3
SD	10.0	9.3	9.5	7.6	8.6
Stderr	1.4	1.3	1.4	1.1	1.2
Median	72.0	69.0	72.0	73.0	74.0
Q1 , Q3	64.5 , 78.0	64.0 , 77.0	64.5 , 79.0	68.0 , 78.0	68.0 , 78.0
Min , Max					
Study end					
n	49	50	49	45	50
Mean	72.4	72.1	71.1	74.4	70.8
SD	8.1	8.6	11.9	8.6	9.1
Stderr	1.2	1.2	1.7	1.3	1.3
Median	72.5	71.3	72.0	74.0	71.0
Q1 , Q3	68.0 , 76.0	67.0 , 77.0	63.0 , 78.0	70.0 , 80.0	64.5 , 77.0
Min , Max					
Absolute change					
n	49	50	49	45	50
Mean	0.5	0.9	0.2	1.2	-2.5
SD	9.8	7.4	9.8	8.0	8.9
Stderr	1.4	1.0	1.4	1.2	1.3
Median	0.0	0.0	-1.0	0.0	-2.0
Q1 , Q3	-6.0 , 6.0	-4.0 , 4.0	-4.0 , 6.0	-4.0 , 6.5	-8.0 , 4.0
Min , Max					

Placebo subtracted changes from baseline at endpoint for bosentan total daily doses 100 mg, 250-500 mg, 1000-1500 mg, 2000 mg were +0.4 bpm, -0.3 bpm, +0.7 bpm, and –3.0 bpm, respectively. Bosentan probably has a minor effect on heart rate.

10.0 ECG changes

Treatment emergent ECG abnormalities reported in the placebo controlled trials are shown below.

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Table 41 Summary of treatment-emergent ECG findings in placebo-controlled studies

Table T65f / 31OCT00

ECG finding	Placebo N=219 No.	%	Bosentan N=533 No.	%
Total pts with at least one ECG	71	32.4%	119	22.3%
Total number of ECGs	110		172	
ATRIOVENTRICULAR BLOCK FIRST DEGREE	16	7.3%	21	3.9%
ST-T CHANGES	9	4.1%	20	3.8%
VENTRICULAR EXTRASYSTOLES	12	5.5%	15	2.8%
INTRA-VENTRICULAR CONDUCTION DEFECT	8	3.7%	15	2.8%
NON SPECIFIC ST-T CHANGES	5	2.3%	12	2.3%
EVIDENCE OF MYOCARDIAL INFARCTION	6	2.7%	8	1.5%
RIGHT AXIS DEVIATION	5	2.3%	8	1.5%
SINUS BRADYCARDIA	5	2.3%	8	1.5%
LEFT ANTERIOR HEMI-BLOCK	2	0.9%	7	1.3%
LEFT ATRIAL ENLARGEMENT (P MITRALE)	1	0.5%	7	1.3%
LEFT AXIS DEVIATION	-		7	1.3%
SINUS TACHYCARDIA	8	3.7%	6	1.1%
BUNDLE BRANCH BLOCK LEFT	6	2.7%	5	0.9%
SUPRAVENTRICULAR EXTRASYSTOLES	4	1.8%	5	0.9%
ATRIAL FLUTTER AND / OR FIBRILLATION	2	0.9%	5	0.9%
OTHER FINDINGS	1	0.5%	5	0.9%
LEFT VENTRICULAR HYPERTROPHY	9	4.1%	4	0.8%
SINUS RHYTHM	-		4	0.8%
RIGHT VENTRICULAR HYPERTROPHY	3	1.4%	3	0.6%
BUNDLE BRANCH BLOCK RIGHT	2	0.9%	2	0.4%
PROLONGED QT	1	0.5%	2	0.4%
BILATERAL ATRIAL ENLARGEMENT	1	0.5%	1	0.2%
PACEMAKER RHYTHM	1	0.5%	1	0.2%
RIGHT ATRIAL ENLARGEMENT (P PULMONALE)	-		1	0.2%
ATRIOVENTRICULAR BLOCK COMPLETE	1	0.5%	-	
BUNDLE BRANCH BLOCK BILATERAL	1	0.5%	-	
LEFT POSTERIOR HEMI-BLOCK	1	0.5%	-	

There was a higher incidence rate of placebo patients with an ECG finding compared to bosentan patients. Nearly all findings were more frequent in placebo group with the exception of left anterior hemiblock and left atrial enlargement. Nothing in the above table suggests that bosentan has a adverse effect on the heart.

ECG intervals

Table 42 Mean changes from baseline to end of treatment in ECG parameters in all placebo-controlled studies

Table T61f / 23OCT00

Parameter	Unit	Placebo N=219 N	BL	Change	Bosentan N=533 N	BL	Change
HEART RATE	(bpm)	176	77.4	-0.2	399	74.3	-0.7
PQ (PR)	(ms)	140	173.9	4.3	347	173.4	0.9
QRS	(ms)	74	97.7	1.2	239	93.3	0.0
QT	(ms)	171	384.0	3.0	396	390.7	0.0

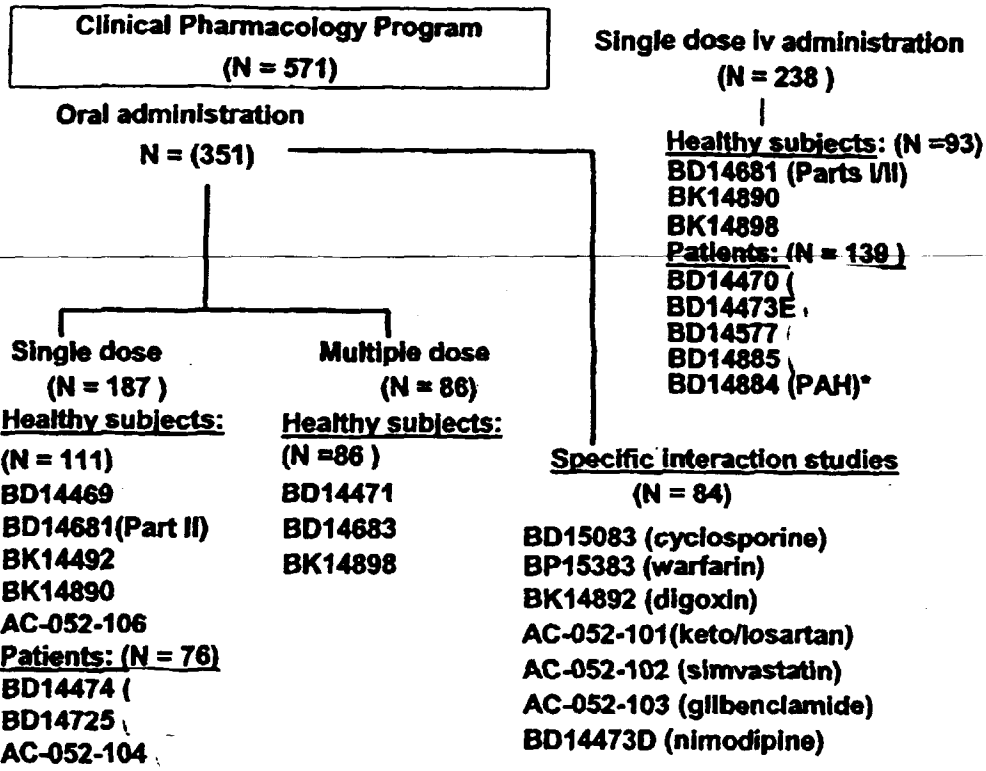
There is no indication that bosentan has an effect on ECG intervals. There was 1 report of torsades: Patient 18102/6162 Bosentan 125-250-500 mg bid. a 73-year-old white female with

heart failure NYHA class IIIB, treated with lisinopril, furosemide, digoxin, and levothyroxine, was hospitalized on day 43 for severe upper quadrant abdominal pain, elevated liver enzymes AST 64 U/l, ALT 149 U/l, and alkaline phosphatase (166 U/l). Cholelithiasis was diagnosed by ultrasound and the study drug was stopped. The patient developed ventricular tachycardia (described as torsades de pointe). After successful defibrillation, she was intubated and treated with lidocaine intravenously. Prolonged QT interval was identified. The patient was extubated and a laparoscopic cholecystectomy was performed. She was discharged and resumed the intake of study drug. Drug was again stopped because of elevation of LFTs and 2 weeks later LFTs were normal. Study drug was restarted and 2 weeks later LFTs increased (highest AST 161 U/l and ALT 283 U/l). Patient was permanently discontinued and LFTs became normal. The torsades event was probably unrelated to the use of bosentan.

11.0 Clinical Pharmacology

Summary
There were 23 clinical pharmacology studies. These are shown in the diagram below.

Figure 17 Diagram of the clinical pharmacology program



* Study BD 14884 is discussed in detail in Section 3.

Healthy volunteers

Single dose
There were 5 studies with healthy volunteers. Total daily doses ranged from 3 mg to 2400 mg.

There were no deaths in the clinical pharmacology studies. One subjects (#14219/0011) withdrew because of T wave abnormalities on ECG.

Adverse events
There was a dose response for headache/head discomfort with 100% of subjects reporting headache with the 2400 mg dose.

Multiple dose
There were 54 healthy volunteers who received between 100 mg and 1400 mg doses of bosentan for a mean of 6.3 days. There were no deaths, serious adverse events, or withdrawals for adverse events. Three subjects had increases in ALT (<3xULN).

Patients

Single dose
There were 53 patients who received a single oral dose of bosentan with total daily doses ranging from 125 to 2000 mg. There were no deaths, serious adverse events, or study withdrawals because of an adverse event.

Interaction studies
Age
Adverse events by age group: there is no study that evaluated this potential interaction. The table below shows the placebo subtracted incidence rate of selected adverse events by age.

Placebo subtracted incidence rate (%)

	<50 yrs n=117	50-74 yrs n=368	>74 yrs n=48
Any event	-5.8	-1.1	13.7
Headache	9.0	1.5	4.0
Flushing	7	4.3	4.2
Abnormal LFTs	0.1	3.8	4.2
Lower limb edema	3.4	3.5	6.3
Anemia	0.9	2.7	8.2

Table 60

The overall incidence rates of reporting adverse events were higher for placebo in the younger age groups. The rate, however, for patients above the age of 74 was nearly 14%. Of the events listed above, the higher rate of anemia in the oldest age group (8.2%) is disturbing.

Gender
Adverse events by gender group: there is no study that evaluated this potential interaction. The table below shows the placebo subtracted incidence rate of selected adverse events by gender.

Placebo subtracted incidence rate (%)

	Male N=383	Female N=150
Any event	1.2	6.7
Headache	2.2	8.0
Flushing	6.0	3.2
Abnormal LFTs	2.0	5.3
Lower limb edema	3.1	5.3
Anemia	3.0	3.3

Table 62

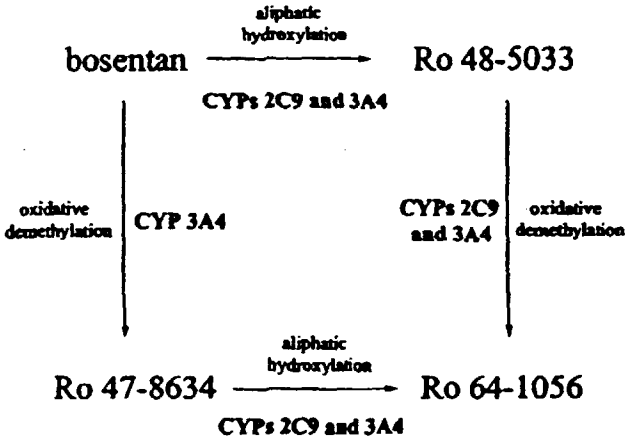
Of the 533 patients who received bosentan in a placebo controlled trial, 28% were female. A higher incidence of females on bosentan reported at least one adverse event (6.7%), compared to males (1.2%). Headache was reported nearly 4 times more in females on bosentan than the males.

Race
Adverse events by race: there is no study that evaluated this potential interaction. There were very few black patients in the bosentan studies: 26 (4.9%) received bosentan and 9 (4.1%) placebo in the placebo controlled trials. Any attempt to draw conclusions about a drug-race interaction is of no value.

Drug-drug
There were 7 studies that evaluated the effects of concomitant use of bosentan and cyclosporin, warfarin, digoxin, nimodipine, ketoconazole, losartan, simvastatin, or glibenclamide.

Bosentan metabolism is shown below

Figure 1 Metabolic pathways of bosentan metabolism



Drugs that inhibit CYP3A4 and/or CYP2C9 are expected to cause an increase in the plasma concentration of bosentan. Conclusions about the pharmacokinetics of the drugs were obtained from Dr. Gabriel Robbie's biopharmacology review.

Ketoconazole
Concomitant administration of ketoconazole significantly increases the Cmax and AUC of bosentan by 62% and 83%, respectively.

There were 12 study subjects. No adverse events were reported. One subject (#5) dropped out during the bosentan only phase; the sponsor gave no explanation. Five subjects had decreases from baseline in both hemoglobin and hematocrit.

Cyclosporin
Concomitant administration of bosentan and cyclosporin increased the trough concentration of bosentan by 30-fold. It is recommended that the concomitant use of bosentan and cyclosporin be contraindicated.

In the cyclosporin interaction study, 2 subjects receiving bosentan 2000 mg/d and cyclosporin reported severe headache and gastric disturbance resulting in dose reduction. Both completed the study. One subject receiving bosentan 1000 mg/d and cyclosporin reported severe nausea and vomiting. Subject continued to be symptomatic (myalgia, numbness of extremities, retrosternal burning and epigastric pain) even though dose was reduced. He was withdrawn from study drug.

Simvastatin
Coadministration of bosentan and simvastatin significantly decreased steady-state C_{max} and AUC of both simvastatin (31% and 49%, respectively) and its active metabolite, -hydroxy simvastatin, (by 33% and 60%, respectively). The concomitant use of bosentan and simvastatin could reduce the effectiveness of simvastatin.

There were 12 subjects: 4 male and 8 female. There were no serious events and no drop outs. Reported adverse events included flu (1) and headache (2). There were a few minor changes in LFTs. One subject had a decrease in hemoglobin/hematocrit from 12.6/36.9 at baseline to 10.6/31.5 at study end.

Digoxin
Bosentan 500-mg BID administered for 7 days slightly decreased the C_{max} and AUC of digoxin by 9% and 12%, respectively. Day 14 C_{min} of digoxin decreased by 30% in the presence of bosentan. Comparison of the pharmacokinetics of 500-mg BID bosentan from the present study with another study (B-159037) in healthy individuals indicated no effect of concomitant administration of digoxin on bosentan pharmacokinetics.

There were 19 subjects entered into the study. There were no deaths and no serious adverse events. One subject withdrew because of mild 2nd degree AV block after receiving digoxin alone and one subject withdrew because of bronchitis. The reporting of adverse events was similar for the 2 groups.

Warfarin
Steady-state bosentan increases the elimination of both R- and S-warfarin which, in turn, reduces the anticoagulation effect of warfarin as measured by prothrombin time and factor VII activity. Primary pharmacodynamic measures such as $PT_{max,cor}$ decreased by 23% and $AUC_{PT,cor}$ decreased by 38%. Consistent with the unaltered Cmax of R- and S-warfarin, the time to maximum effect and time course of warfarin effect on prothrombin time and factor VII activity were not altered by bosentan. The trough plasma concentration 12 hours after the warfarin dose were statistically

significantly lower compared to the predose concentrations. The concomitant use of bosentan and warfarin might reduce the effectiveness of warfarin. Prothrombin times should be checked more often.

Single-dose warfarin decreased the mean steady-state trough concentration of bosentan by 63%.

Safety
There were 12 subjects. No subject died, reported a serious adverse event, or dropped out of the study because of an adverse event. Of the subjects receiving warfarin plus bosentan, 92% reported headaches compared to 26% of subjects receiving warfarin alone. There is considerable concern regarding the reduction of the anticoagulation effect of warfarin when used in conjunction with bosentan.

Losartan
Concomitant administration of losartan lowered both Cmax and AUC of bosentan by 15%.

Glibenclamide
Coadministration of bosentan and glibenclamide significantly decreased steady-state C_{max} and AUC of both bosentan and glibenclamide. Steady-state Cmax and AUC of bosentan decreased by 24% and 29%, respectively, while that of glibenclamide decreased by 22% and 40%, respectively. The concomitant use of bosentan and glibenclamide could reduce the effectiveness of glibenclamide. Blood glucose should be checked more often.

Safety
There were 12 subjects. There were no reported deaths, serious adverse, or study withdrawals because of an adverse event. Four subjects reported adverse events: headache, headache and fatigue, abdominal pain and increased LFT, increased LFTs. No hematology values were obtained beyond screening.

Drug-disease
Mean C_{max} and AUC of bosentan were 37% and 11% lower in severe renal impairment patients compared to healthy subjects. Median Tmax and $T_{1/2}$, however, were similar in both groups. The concentrations of the active metabolite Ro 48-5033 increased in severe renal impairment patients but were <10% of parent drug concentrations. Concentrations of the other metabolites, Ro 47-8634 and Ro 64-1056, increased by 100% in severe renal impairment patients compared to normal subjects indicating that the renal route is a major route of elimination of the metabolites of bosentan. The use of bosentan in severe renally impaired patients should be discouraged. Its use in less impaired patients is probably acceptable.

Safety
There were no reported deaths or serious adverse events. The only subject reporting an adverse event was a healthy subject with headache and weakness. Blood pressure was lowered to a greater extent in the renally impaired subjects. However, it is not possible to drawn conclusions about blood pressure effects since the study was open label. There were no reports of hypotension.

There was no study evaluating the effect of bosentan in patients with liver impairment. It is reasonable to contraindicate the drug in patients with elevation of LFT > 3 times ULN, as was done in the protocols.

Appendix 1 Sponsor-defined critical values for laboratory parameters

Parameter	Standard Unit	Sponsor's Reference Range	Marked Reference Range	Significant Shift From Baseline	Outlying Values Treated as Missing
HEMATOLOGY					
Hemoglobin	g/dL	M: F:		15%	< 5
Hematocrit	Fraction	M: F:		15%	> 0.7
Erythrocytes	10E12/L			15%	< 0.5
Leucocytes (total)	10E9/L			30%	> 35
Neutrophils	10E9/L			Decrease 20%	> 30
Eosinophils	10E9/L			Increase 100%	
Platelets	10E9/L			Decrease 30% Increase 50%	
BIOCHEMISTRY					
AST	U/L			Increase 50%	
ALT	U/L			Increase 50%	
Gamma-GT	U/L			Increase 50%	
Bilirubin total	umol/L			Increase 50%	
Glucose fasting	mmol/L			75%	
Creatinine	umol/L			Increase 75%	> 500
Sodium	mmol/L			7%	
Potassium	mmol/L			Decrease 10% Increase 20%	
Chloride	mmol/L			7%	
Albumin	g/L			10%	
Alk.phosphatase	U/L			Increase 50%	
BUN / Urea	mmol/L			Increase 75%	
Cholesterol	mmol/L			Increase 50%	
Triglycerides	mmol/L			Increase 100%	
Protein Total	g/L			20%	

MEDICAL REVIEW OF EFFICACY

NDA#21,290
Drug Name: Bosentan (Tracleer™)
Sponsor: Acetlion
Date: June 29, 2001
Medical Reviewer: Maryann Gordon, M.D.

Summary of efficacy

Bosentan has been evaluated for efficacy in pulmonary arterial hypertension (PAH) in 3 studies, 2 with the oral formulation evaluating walking distance and 1 with the iv formulation evaluating acute hemodynamics. The latter trial was stopped prematurely for safety reasons and is included in the efficacy review only for completeness.

Study no.	Design/duration	Primary efficacy parameter	No. planned/ completed	doses	comments
AC 052-352	Double blind, randomized, placebo controlled for 16 weeks	6 min walk test	150/214	Oral 62.5 mg bid up titrated to 125 mg bid; 62.5 mg bid up titrated to 250 mg bid	Significant increase in walking distance compared to placebo.
AC 052-351	Double blind, randomized, placebo controlled for 12 weeks	6 min walk test	30/32	Oral 62.5 mg bid up titrated to 125 mg bid at week 4	Significant increase in walking distance compared to placebo.
BD14884	Open label iv dosing 1 day followed by oral dosing	Acute cardiac hemo-dynamics	30/7	iv: 50 mg, 150 mg, 300 mg. Oral: 1000 mg bid	Stopped for safety reasons

Demonstration of efficacy of bosentan
The walking distance was significantly increased in the bosentan groups compared to placebo in both study AC 052 352 (352) and study AC 052 351 (351). Compared to placebo, bosentan also delayed time clinical worsening, improved Borg dyspnea index, improved WHO functional class, and lessened the increase in therapy for PAH.

There was no evidence of loss of efficacy of bosentan up to 16 weeks of placebo controlled evaluation.

Study details

The studies were double blind, multicenter, parallel groups, placebo controlled. Bosentan doses used were 125 mg bid (both studies), 250 mg bid (352 only). Both studies included a starting dose of 62.5 mg bid for 4 weeks. Minimum duration on study drug was 12 weeks. Treatment could continue beyond the fixed efficacy timepoint[1].

Patient type

Patients were those:

- with PAH resulting from primary pulmonary hypertension (PPH) or connective tissue or autoimmune disease such as scleroderma or systemic lupus erythematosus;
- WHO functional class III-IV despite optimal therapy with vasodilators, cardiac glycosides, diuretics, and /or supplemental oxygen.
- receiving anticoagulants but not receiving prostacyclin therapy or scheduled to receive Flolan.
- walk between 150 m and 500 m, inclusive, on a 6-minute walk test. 352 reduced the maximum walk distance to 450 m.
- did not have ALT/AST greater than 3 times upper limit of normal or hemoglobin/hematocrit <30% below normal range.

Primary efficacy endpoint

The primary efficacy endpoint for both studies was change from baseline at endpoint in total walk distance (meters). The studies predefined how data would be handled for those patients who died or did not complete the study for other reasons.

Secondary endpoints

The secondary efficacy endpoints included time to clinical worsening, changes in Borg dyspnea index, changes in WHO functional class, and increase in therapy for PAH, number of days patient was known to be alive and out of hospital during first 28 weeks (study 352), and number of drop outs in the first 28 weeks.

[1] patients in study 352 who were recruited by 30 September 2000 were scheduled to be treated for up to an additional 12 weeks (Period 2). The study was completed when the last included patient completed Period 1. All patients had the opportunity to enter an open-label extension study after completion of this trial, if eligible. Patients recruited after 30 September 2000 could have entered the open-label extension upon completion of Period 1. Patients who were recruited up to and including on 30 September 2000 could have entered the open-label extension after completion of Period 2 or at any time during Period 2 if they met the predefined stopping criteria. Patients who were withdrawn during Period 1 were not eligible for the open-label extension trial.

Patients in study 351 who completed the 12 week double blind treatment phase as well as subjects who dropped out of the study prematurely had the option of entering an open label, uncontrolled phase.

Patient disposition

No. of patients

	Study 352			Study 351	
	Bos 125 mg bid	Bos 250 mg bid	Placebo bid	Bos 125 mg bid	Placebo bid
No. randomized	76	70	69	21	11
No. prematurely withdrawn	3	3	6	0	3

Reasons for premature withdrawal

No. of patients

	Study 352			Study 351	
	Bos 125 mg bid	Bos 250 mg bid	Placebo bid	Bos 125 mg bid	Placebo bid
No. prematurely withdrawn	3	3	6	0	3
Worsening of condition	2	1	3	0	1
Death	1	0	2	0	0
AE/ intercurrent illness	0	1	0	0	2
Increased LFTs	0	1	0	0	0
Lack of clinical/walk test improvement	0	0	1	0	0

Demographics

	Study 352			Study 351	
	Bos 125 mg bid	Bos 250 mg bid	Placebo bid	Bos 125 mg bid	Placebo bid
No. randomized	76	70	69	21	11
No. female	57	57	54	17	11
No. male	17	13	15	4	0
Mean age (yrs)	50.4	47.0	47.2	52.2	47.4
No. white	57	54	59	16	9
Mean time from diagnosis to randomization	898	893	843	634	1091

The most common concomitant medications in both studies were antithrombotic agents, diuretics, ca channel blocker, and cardiac glycosides.

6 minute walk test

Mean distances (m)

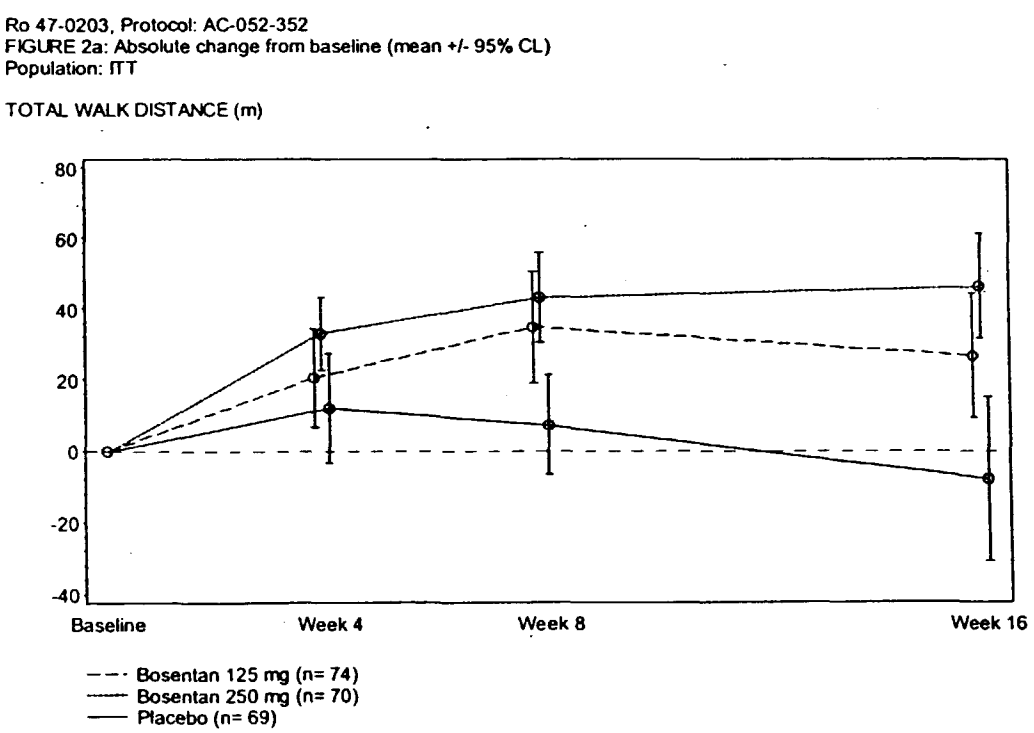
	Study 352			Study 351	
	Bos 125 mg bid N=74	Bos 250 mg bid N=70	Placebo bid N=69	Bos 125 mg bid N=21	Placebo bid N=11
Baseline	326.3	333.0	344.3	360.5	355.5
Endpoint^	353.1	379.5	336.5	430.5	349.6
Change from baseline	26.8	46.5	-7.8	70.1	-5.0
Placebo subtracted effect	34.6	54.3	-	75.9*	-

^ week 16 for study 352, week 12 for study 351
*p=0.0205 using t-test
***p=0.0002 using Mann-Whitney U test

Dose effect

Only study 352 used more than 1 dose of bosentan. The walking distance by dose is shown in the figure below

Walk distance: Change from baseline over time during Period 1 by dose, ITT population



Note: All bosentan patients received 62.5 m bid during the first 4 weeks of the study and then were up-titrated to the target dose (125 mg bid or 250 mg bid).

The 250 mg bosentan group was numerically superior to the 125 mg group at weeks 8 and 16 but the confidence limits overlapped at both time points.

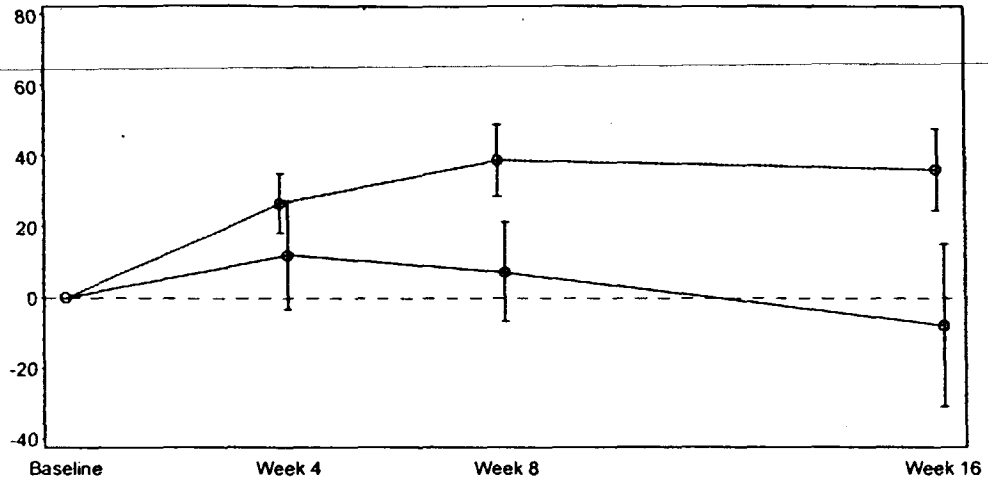
Walk distance by visit

The changes from baseline at weeks 4, 8 and 16 for the combined bosentan group and placebo in walk distance in study 352 and weeks 4, 6 and 12 for in study 351 are shown in the figures below.

Walk distance: Change from baseline over time during Period 1, ITT population

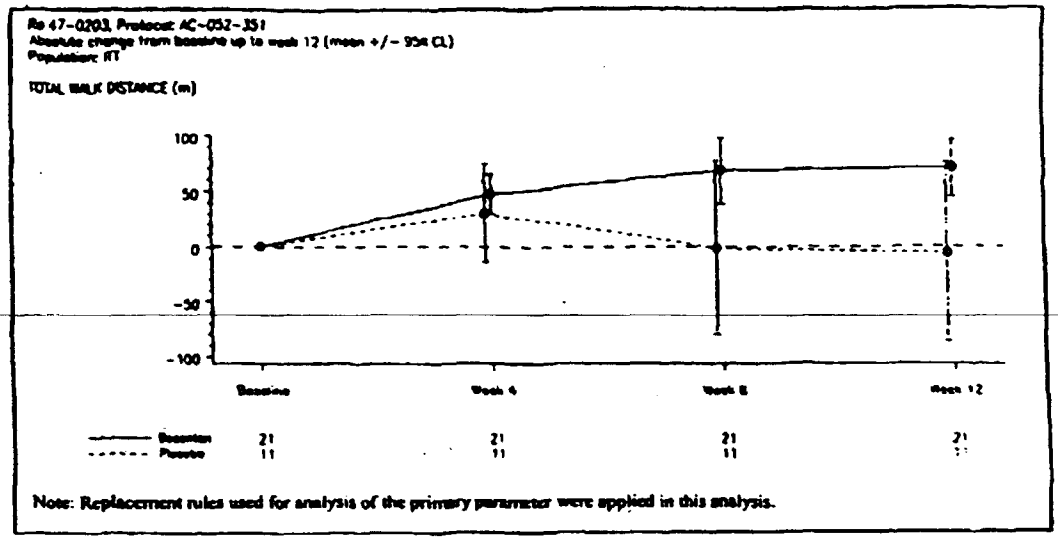
Ro 47-0203, Protocol: AC-052-352
FIGURE 2b: Absolute change from baseline (mean +/- 95% CL)
Population: ITT

TOTAL WALK DISTANCE (m)



APPEARS THIS WAY
ON ORIGINAL

Figure 3 Walk Distance: Change from Baseline to Week 12



Note: Replacement rules used for analysis of the primary parameter were applied in this analysis.

There is no evidence that the effect of bosentan on walk distance dissipates over 12-16 weeks of treatment.

Subgroups

Effect of bosentan by subgroups was only examined in study 352. Bosentan increase walk distance, compared to placebo, regardless of gender, age, weight, location, race, time from diagnosis, etiology (PPH vs. scleroderma), and baseline walk test. Patients who entered the study with lower mean PAP (< 50 mmHg) and/or higher cardiac index (≥ 2.3 l/min/m^2) had a smaller improvement with bosentan than did those who entered with a higher mean PAP and/or lower cardiac index.

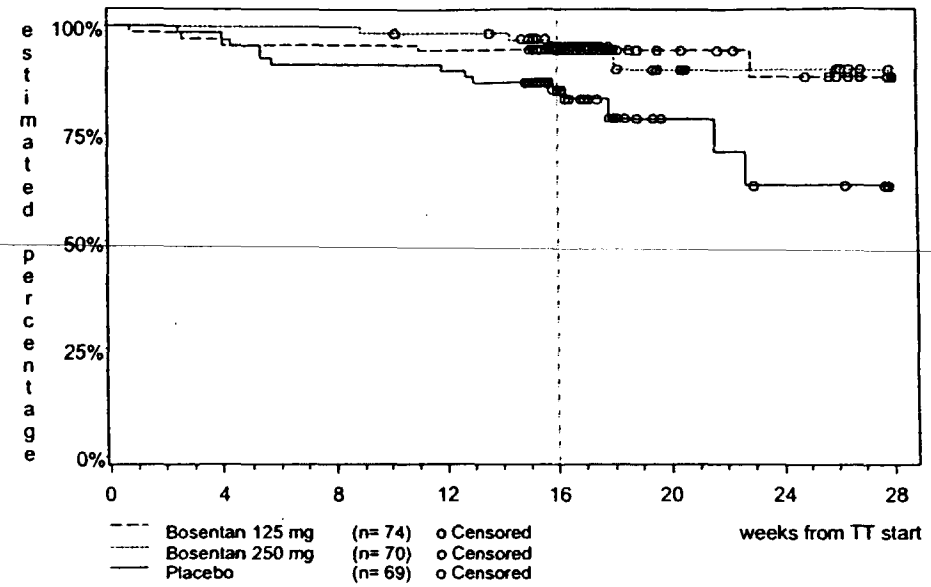
Secondary endpoints

Time to clinical worsening defined as the shortest time to death, lung transplantation, hospitalization or discontinuation due to worsening pulmonary arterial hypertension, start of prostacyclin therapy or septostomy

The figure below shows the results for 352, by dose of bosentan and placebo.

Time from randomization to clinical worsening by dose, ITT population

Ro 47-0203, Protocol: AC-052-352
FIGURE 3a Time from randomization to clinical worsening up to 28 weeks (Kaplan Meier estimates)
Population: ITT



There was an earlier time to deterioration by patients on placebo compared to those on either dose of bosentan.

There were 3 placebo and 0 bosentan patients who experienced clinical worsening in study 351.

Changes in Borg dyspnea index

Borg scale measures the levels of perceived exertion and the scale ranges from 0 (nothing at all) to 10 (maximal).

Means

	Study 352			Study 351	
	Bos 125 mg bid N=74	Bos 250 mg bin=70	Placebo bid N=69	Bos 125 mg bid N=21	Placebo bid N=11
Baseline	3.3	3.8	3.8	4.38	4.18
Endpoint^	3.3	3.3	4.2	4.19	5.55
Change from baseline	-0.1	-0.6	+0.3	-0.19	+1.36
Placebo subtracted effect	-0.4	-0.9	-	-1.55	-

^ week 16 for study 352, week 12 for study 351

At baseline patients in study 351 had a worse perception of their exertion compared to the patients in study 352. However, the bosentan patients in both studies had an improvement as measured by the scale compared to the placebo patients. The overall treatment effect was greater in the 351 study, which may mean that sicker patients have a greater perception of improvement with bosentan. This would have to be confirmed by additional studies.

Changes in WHO functional class

Only patients WHO functional classes III or IV at baseline were enrolled into the efficacy studies.

No. and (percent) of patients who improved

	Study 352			Study 351	
	Bos 125 mg bid N=74	Bos 250 mg bin=70	Placebo bid N=69	Bos 125 mg bid N=21	Placebo bid N=11
Improved from baseline	32 (43.2)	29 (41.1)	21 (30.4)	9 (42.9)	1 (9.1)

^ week 16 for study 352, week 12 for study 351

More bosentan patients improved in their functional class compared to placebo patients.

Increased therapy for PAH

The evaluation of the incidence of increased therapy for PAH was only evaluated in study 352. The results are shown below.

Table 1 Incidence of increased therapy for pulmonary arterial hypertension, ITT population

(Table T14 / 04MAY01)

	Bosentan 125 mg N=74	Bosentan 250 mg N=70	All Bosentan N=144	Placebo N=69
Period 1 (weeks 0 to 16)				
n	74	70	144	69
Patients with increase [n(%)]	18 (24.3%)	14 (20.0%)	32 (22.2%)	20 (29.0%)
95% confidence limits (%)	15.1 , 35.7	11.4 , 31.3	15.7 , 29.9	18.7 , 41.2
Treatment effect*				
Difference	-4.7%	-9.0%	-6.8%	
95% confidence limits (%)	-20.0 , 10.6	-24.3 , 5.9	-19.5 , 7.1	
Period 1+2 (weeks 0 to 28)†				
n	19	16	35	13
Patients with increase [n(%)]	6 (31.6%)	5 (31.3%)	11 (31.4%)	5 (38.5%)
95% confidence limits (%)	12.6 , 56.6	11.0 , 58.7	16.9 , 49.3	13.9 , 68.4
Treatment effect				
Difference	-6.9%	-7.2%	-7.0%	
95% confidence limits (%)	-41.0 , 27.5	-43.1 , 27.7	-36.5 , 25.4	

† Analyzed only in those patients who were scheduled to continue to period 2.

Compared to placebo, fewer bosentan patients had an increase in therapy for PAH and this remained true for the few patients who had up to 28 weeks of treatment.

Protocol AC 052-352

Because this study was submitted at end of the NDA review, its safety is discussed fully in this section. The safety from this trial was only partially integrated with the overall safety medical review.

1.0 Introduction

The protocol was dated March 28, 2000. The first patient's first visit was July 2000 and the last patient's last visit was October 2000.

1.1 Study Design

This was a double blind, multicenter, parallel, placebo controlled, randomized study in patients with pulmonary arterial hypertension (PAH). The study was conducted in Europe, North America, Israel, and Australia. Eligible subjects were those with either symptomatic severe primary pulmonary hypertension (PPH) or pulmonary hypertension secondary to scleroderma (SSc/PH), who were ambulatory and in functional class III-IV (1998 WHO classification).

1.2 Study Objective

The objective of this study was to evaluate the efficacy of 2 doses of bosentan compared to placebo on peak exercise capacity (6 minute walk test).

1.3. Patient Type

1.3.1. Inclusion Criteria

Eligible patients had to meet all of the following inclusion criteria at the initial screening visit of the study (visit 1) and at baseline for the 6-minute walk test (visit 1 and visit 2)

1. Male or female aged 12 years or more. Amendment #2 UK only: patients had to be $\geq$ 18 years of age.

2. Patients must have provided written informed consent to participate in the study. For a patient under the age of consent, written informed consent must be obtained from the patient's legal guardian.

3. PAH resulting from either:
- primary pulmonary hypertension (PPH) or
- Connective tissue or autoimmune diseases such as scleroderma (SSc/PH) or systemic lupus erythematosus (SLE).

In patients with SSc/PH and interstitial lung disease, total lung capacity (TLC) was to be >70 %. However, if TLC was between 60-70%, a high resolution CT scan should have been used to confirm the mild nature of disease with a total CT score $\leq$ 2. The diffusion lung capacity for carbon monoxide (DLCO) could be used to aid in the diagnosis. The CT scan was repeated at the end of the study.

4. PAH of WHO functional class III-IV despite optimal therapy with oral vasodilators, cardiac glycosides, diuretics and/or supplemental oxygen for at least one month. Patients had to be receiving oral anticoagulants unless there was a contraindication.

5. Hemodynamic documentation of PAH within 2 months prior to screening, i.e. a patient who has undergone invasive hemodynamics in the month preceding screening with the following results:
- Mean pulmonary arterial pressure (PAP) > 25 mmHg at rest

- Pulmonary capillary wedge pressure (PCWP) < 15 mmHg
- Pulmonary vascular resistance (PVR) > 3 mmHg/l/min.

If the capillary wedge pressure was not measured, an echocardiogram was acceptable to rule out left ventricular dysfunction.

6. Baseline 6-min walk test of ≥ 150 m and ≤ 500 m (Amendment #1 reduced this to ≤ 450 m). The difference between the screening and randomization walk tests had to be ≤ 15%. If the two tests differed by more than 15%, the patient underwent an additional walk test at least 1 day later, the results of which had to within 15% of the previous walk test. The definition of baseline as the average of the last 2 test results was added later (but not as an amendment).

7. women who were not pregnant and women who were postmenopausal, surgically sterile or using an acceptable method of contraception.

Exclusion Criteria

Eligible patients could not have any of the following exclusion criteria at the initial screening visit (visit 1) or at baseline (visit 1 or visit 2):

1. PAH of WHO functional class I or II.

2. PAH due to conditions other than PPH or connective tissue diseases, e.g.:
   congenital heart diseases (Eisenmenger's syndrome)
- pulmonary venous hypertension (e.g. left sided heart diseases)
- associated with disorders of the respiratory system (e.g. chronic obstructive pulmonary disease (COPD), sleep apnea, and patients with moderate to severe interstitial disease even of SSc origin)
- associated with chronic thrombotic or embolic diseases
- condition of inflammatory origin (HIV, schistosomiasis, sarcoidosis)
- portal pulmonary hypertension.

3. SSc/PH with moderate to severe interstitial disease or with TLC <60% or a CT scan total score (CT.Tot score) >2.

4. Patients who stopped treatment with oxygen, diuretics, oral vasodilators, cardiac glycosides within one month of screening.

5. Patients who started new treatment with oxygen, diuretics, oral vasodilators, cardiac glycosides within one month of screening.

6. Patients receiving prostacyclin therapy within 3 months of study screening. However patients who received acute prostacyclin at the time of a catheterization procedure to test pulmonary vascular reactivity could be included.

7. Patients scheduled to receive prostacyclin therapy.

8. Musculoskeletal or rheumatic disorders or any other condition that could limit his/her ability to perform the 6-minute walk tests.

9. Hypotension defined as systolic blood pressure < 85 mmHg.

10. Hemoglobin or hematocrit of less than 30% below the normal range (patients with secondary polycythemia were allowed).

11. AST and/or ALT values greater than 3 times the upper limit of normal.

12. Patients receiving cyclosporin-A, glibenclamide (glyburide), troglitazone, encainide, flecainide, disopyramide, propafenone, moricizine, pinacidil, minoxidil or oral positive inotropic agents other than digitalis at inclusion into the study or were expected to receive any of these drugs during the study period.

13. Patients who received therapy with an investigational drug in the month preceding screening.

14. Known drug or alcohol dependence or any other factors which could have interfered with conduct of the study or interpretation of the results.

15. Any illness other than PAH which might reduce life expectancy to less than 6 months.

1.4 Sample Size

Sample size, 80 patients for each of the 3 treatment arms, was based on an assumed change from baseline in walking distance of 45 m with standard deviation of 75 m.

1.5 Dose and duration

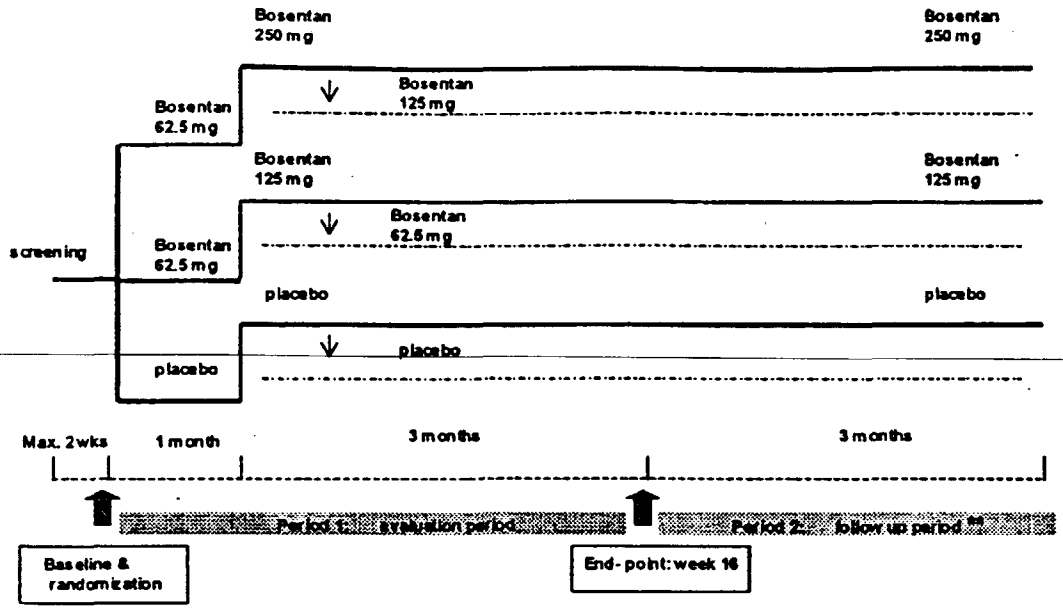
The 3 treatment arms were 1.) placebo bid for 16 weeks, 2.) bosentan 125 mg bid for 4 weeks titrated to 250 mg bid for 12 weeks, and 3.) bosentan 62.5 mg bid for 4 weeks titrated to 125 mg bid for 12 weeks. Down titrating to the starting dose was allowed if patient could not tolerate the higher dose. Amendment#1: patients with body weight < 40 kg were given half the randomized target dose. If patients had to be discontinued, they were weaned for 3-7 days.

Patients were instructed to take study drug at the time of or within 30 minutes after food intake.

Each subject received a minimum of 16 weeks of double blind treatment[2] and this period was used to determine efficacy. Patients recruited by 9-30-2000 took part in period 2 as well which was an additional 12 week treatment with double blind medication. This period was reviewed for efficacy but was not part of primary efficacy endpoint.

[2] meaning that all subjects received double blind treatment until the last enrolled subject, not prematurely withdrawn, completed week 16

All doses in the chart below are BD



Double blind period 1 and period 2/placebo controlled trial/ n= 80 patients per treatment group
Primary variable: change from baseline in a 6 min walk test

** the follow up period is maximum 3 months for the first half of the patients

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1.7 Study Procedure

The flow chart below outlines study procedures at each clinic visit.

Table 1: Schedule of Assessments

	Period 1							Period 2		
Treatment Week (Study day)	Screening [-14,-1]	Randomization a	1 [5-9] f	4 [21-35]	8 [49-63]	12 [77-91]	16 [105-119] end of period 1	Premature withdrawal	22 [147-161]	28 [189-283] end of study
Visit	1	2	3	4	5	6	7	-	8	9
Informed consent	X									
History	X									
Physical examination	X						X	X		X
Vital signs (blood pressure and heart rate)	X	X		X	X	X	X	X	X	X
Body weight	X	X					X	X		X
ECG (12-lead)	X						X	X		X
Laboratory tests	X[b]			X	X (only LFT)	X (only LFT)	X	X	X (only LFT)	X
Right heart cath.		X[c]								
High resolution CT scan[d]	X									X
Functional class	X	X	X	X	X	X	X	X	X	X
Exercise: 6-minute walk test, Borg dyspnea index	X[e]	X[e]		X	X		X	X		X
Dispense/Return study medication		X		X	X	X	X	X	X	X
Forced up-titration of study medication				X						
Optional down-titration of study medication					X	X	X		X	
Concomitant medications	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X

a: Visits 1 and 2 may be performed on the same day (see section 4.2/screening (Visit 1))
b: Includes a pregnancy test performed locally in women of childbearing potential; LFT: liver function tests
c: Invasive hemodynamics not requested if PHT hemodynamically documented within 2 months before screening, additional follow up catheterizations are optional
d: To be performed in patients with SSc and interstitial lung disease, see Appendix 1
e: Pulse oximetry to be performed before walk test
f: Visit 3 can be performed by phone

1.8 Protocol define study hypotheses and efficacy endpoints:

Primary endpoint of the study: the change from baseline (defined as the average of screening and randomization walk tests[3]) in exercise capacity at 16 weeks (6-minute walk test).

- Patients who died, underwent lung transplantation during the study, or discontinued study medication because of worsening of their PAH condition were analyzed using their last assessment if it was recorded at the time of premature withdrawal. If no assessment of walk distance was obtained at the time of premature withdrawal, these patients were assigned a walk distance of 0 meters at the 16-week time point.

- All other patients including those with serious adverse events not related to PAH worsening or lost to follow up without a week 16 assessment of the primary endpoint had their last assessment carried forward. If no assessment was obtained during the treatment period, the patient was assigned "no change" (zero change from baseline, equivalent to carrying forward the baseline value).

7.2 Secondary Endpoints[4]

1. Time from randomization to clinical worsening, defined as death from all causes, lung transplantation or discontinuation of therapy due to clinical deterioration due to PAH or need for prostacyclin or septostomy. Patients without documentation of any of the events listed above were

[3] This definition was added to the study report. It was not in the protocol.
[4] As defined by protocol

included in the analysis as censored observations from randomization to the last date the patient was known to be free of any of these events.

2. Changes from baseline in dyspnea index (Borg dyspnea index). Patients prematurely withdrawn from therapy and having had a "premature withdrawal" assessment will be included in the analysis using the last available assessment on treatment. Patients without any assessment during the treatment period were assigned worst rank (10) if the reason for premature withdrawal is death, lung transplantation or worsening of the patient's PAH condition. Patients without any assessment during the treatment period for reasons other than these were excluded from the analysis.

3. Changes from baseline in WHO functional class. Patients prematurely withdrawn from therapy and having had a "premature withdrawal" assessment were included in the analysis using the last available assessment on treatment. Patients without any assessment during the treatment period were assigned worst rank if the reason for premature withdrawal is death, lung transplantation or worsening of the patient's PAH condition. Patients without any assessment during the treatment period for reasons different than these were excluded from the analysis.

4. Increase in any therapy for PAH. Patients with missing data were analyzed as in item 3 above.

5. Number of days the patient is known to be alive and out of hospital in the first 28 weeks.

6. Number of dropouts in the first 28 weeks.

1.9 Disallowed concomitant medications

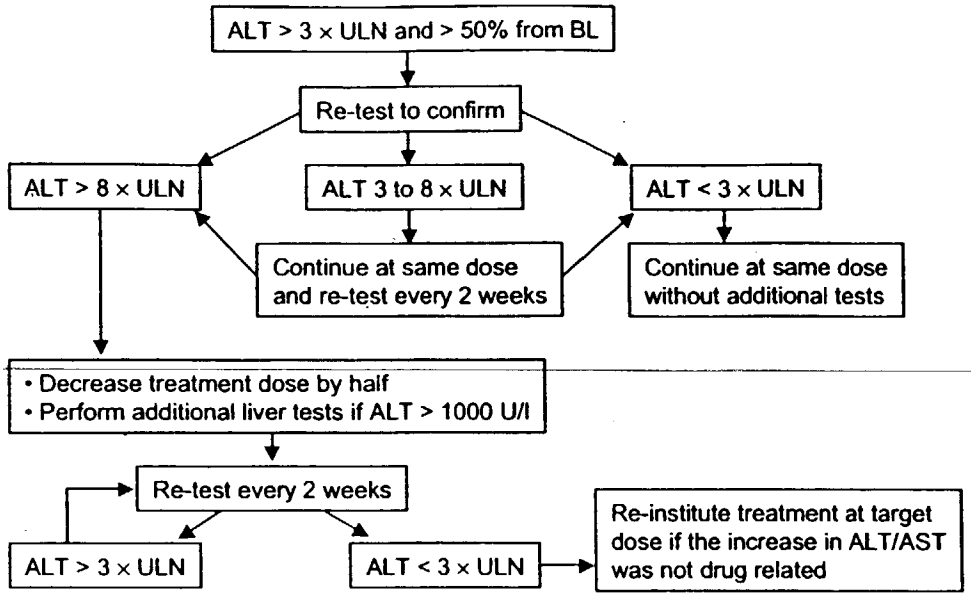
Prostacyclin and any investigational agent other than study drug intended for the treatment of PAH, cyclosporin-A, glibenclamide (glyburide), troglitazone, encainide, flecainide, disopyramide, propafenone, moricizine, pinacidil, minoxidil or oral positive inotropic agents other than digitalis.

1.10 Abnormal laboratory values

a) Liver function test (LFT)

Patients found to have abnormal LFTs during the study were treated according to the following outline.

Figure 1 **Guidelines for treatment of asymptomatic increases in liver enzymes**



b) Hemoglobin

- If hemoglobin decreased by at least 15% from baseline and was < 10 g/dl, and/or if hematocrit decreased by at least 15% from baseline and was < 0.30, a repeat test was performed to confirm the abnormality.

- If the abnormality was confirmed, the investigator was required to perform the following assessments using the local laboratory:

    - Complete blood count including reticulocytes, mean corpuscular volume, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, red cell distribution width, and direct inspection of blood smears
    - Bilirubin, direct and indirect
    - Serum iron, transferrin, iron-binding capacity, and serum ferritin

1.11 Major protocol amendments

Amendment 1, May 30, 2000: the hypothesis and analyses were simplified by changing from comparisons between each bosentan arm and placebo to a single comparison between pooled bosentan arms and the placebo arm. The change in analysis allowed a reduction in the number of patients required from 240 to 150 (50 per group) without affecting the power calculation and a consequent reduction in the number of centers from 40 to 30. The Mann-Whitney U-test replaced the Student's t-test as a more appropriate test with the non-normal data distribution due to zero introduced as a substitutive value. The dose-response relationship would only be analyzed descriptively. Primary and secondary parameters were to be analyzed descriptively in four groups: the bosentan 125-mg arm, the bosentan 250-mg arm, the pool of both bosentan arms, and the placebo arm.

The upper limit of the 6-minute walk test that determined eligibility was changed from < 500 m to ≤ 450 m. To avoid potential overdosing, patients with body weights of ≤ 40 kg were to be given half of the randomized target dose (i.e., 62.5 mg bid or 125 mg bid).

Amendment 2, June 30, 2000. This amendment applied only to centers in the UK. Local Institutional Review Boards (IRBs) for centers in the UK requested that only patients ≥ 18 years of age be included in the trial.

Amendment 3, July 19, 2000. This amendment applied only to centers in Austria. Local IRBs in Austria requested that only patients > 19 years of age be included in the trial and that pregnancy tests be performed every 4 weeks in all women of childbearing potential.

Amendment 4, August 22, 2000. This amendment introduced an echo/Doppler substudy that was to be conducted at 12 of the study centers (world wide) in a subset of study patients (29 in each treatment group) who were recruited into the substudy. Echo/Doppler imaging techniques were to be used to evaluate hemodynamic changes and alterations in right heart structure and function during the trial.

Amendment 5, September 4, 2000. This amendment applied only to centers in the UK. Local IRBs for centers in the UK requested that only patients over the age of 50 years and amenorrheic for at least 1 year be considered naturally sterile with regard to inclusion criteria. In addition, medication labels had been made for patients with body weight > 40 kg and could not be changed before the end of recruitment in the UK. Therefore, an inclusion criterion was added requiring patients in the UK to have a body weight of > 40 kg.

Amendment 6, 6 October 2000. Due to the delay in recruitment and in order to complete the study within the planned timelines, a recruitment date of September 30, 2000 was set as the cut-off for patients scheduled to continue randomized treatment past the first 16 weeks (i.e., participate in Period 2). Patients enrolling after September 30, 2000 were to participate in 16 weeks of randomized treatment only (Period 1), and the trial was to end when the last entered patient completed Period 1.

Some clarifications of study procedures were added and some changes were instituted to enhance patient safety (an inclusion criterion was changed so that hormone-based contraceptives alone were not acceptable forms of contraception; this change addressed concerns that an induction of CYP3A4 by bosentan would lead to a higher rate of metabolism of these compounds and possibly result in a loss of contraceptive efficacy; a pregnancy test at the end-of-study/premature-discontinuation visit in women of childbearing potential was added as a precautionary measure; and the procedures for use of weaning treatment upon temporary or permanent discontinuation of study medication were clarified for patients not entering the extension study; and study treatment was to be re-instituted within 15 days of a temporary discontinuation.

The management of patients with an increase in serum transaminases was changed at the request of the Data Safety and Monitoring Board The safety committee felt a reduction in the dose rather than temporary discontinuation of study medication would be more appropriate for asymptomatic patients with a confirmed transaminase concentration > 8 times the upper limit of normal. Following dose reduction or discontinuation, the patient could be re-challenged with study medication at the target dose (rather than half the target dose) provided that liver enzymes had returned to baseline values at two consecutive tests, and there was clear evidence that the reason for the increase was not related to study drug.

2.0 Results

A total of 258 patients were screened and 214 were enrolled into double blind treatment phase. There were 27 sites in Europe, North America, Israel, and Australia.

2.1 Patient disposition

Table below shows the outcome for all randomized subjects by treatment group.

	Bosentan 125 mg bid	Bosentan 250 mg bid	Placebo
No. randomized	76	70	69
No. who received study medication	75^	70	69
Included in safety and efficacy evaluations	74	70	69
No. prematurely withdrawn	3	3	6

^1 patient (206 20604) was randomized but did not receive study medication because he had an exclusion criterion (Eisenmenger's syndrome) and difficulty in keeping appointments because he lived in a remote location)

Patients who discontinued prematurely from the trial are shown below.

Appendix 1 Summary of premature discontinuations during Period 1, safety population

Produced by maddest on 04MAY01

Ro 47-0203, Protocol: AC-052-352
Table T02a: Summary of premature discontinuations in period 1
Population: Safety

Reason for premature discontinuation	Bosentan 125 mg N=74 No.	%	Bosentan 250 mg N=70 No.	%	All Bosentan N=144 No.	%	Placebo N=69 No.	%
Total pts with at least one reason	3	4.1%	3	4.3%	6	4.2%	6	8.7%
WORSENING OF PATIENT CONDITION	2	2.7%	1	1.4%	3	2.1%	3	4.3%
DEATH	1	1.4%	-		1	0.7%	2	2.9%
AE/INTERCURRENT ILLNESS	-		1	1.4%	1	0.7%	-	
INCREASED LIVER ENZYMES	-		1	1.4%	1	0.7%	-	
LACK OF CLINICAL/WALK TEST IMPROVEMENT	-		-		-		1	1.4%

Note: only the discontinuations in period 1 are considered
(Page 1/1)

There were 12 premature discontinuations in the first 16 weeks of treatment: 3 bosentan 125 mg, 3 bosentan 250 mg, and 6 placebo. Of the 6 who discontinued because of worsening condition, 3 were on bosentan and 3 were on placebo. There were 3 deaths: 1 on bosentan 125 mg and 2 on placebo. There was 1 drop out (bosentan 250 mg) for adverse event/intercurrent illness; 1 drop out (bosentan 250 mg) for increased liver enzymes, and 1 drop out (placebo) for lack of clinical/walk test improvement.

2.2 Demographics and baseline characteristics

Demographics for the study subjects, by treatment group, are shown below.

Table 2 Summary of patient demographics, ITT population

(Table T04 / 04MAY01)

	Bosentan 125 mg N=74	Bosentan 250 mg N=70	All Bosentan N=144	Placebo N=69
SEX [n (%)]				
n	74	70	144	69
Males	17 23.0%	13 18.6%	30 20.8%	15 21.7%
Females	57 77.0%	57 81.4%	114 79.2%	54 78.3%
AGE (years)				
n	74	70	144	69
Mean	50.4	47.0	48.7	47.2
Standard deviation	15.9	15.6	15.8	16.2
Median	50.5	48.0	49.0	50.0
Min , Max				
AGE [n (%)]				
n	74	70	144	69
12 - 20 years	3 4.1%	4 5.7%	7 4.9%	6 8.7%
21 - 40 years	13 17.6%	18 25.7%	31 21.5%	15 21.7%
41 - 60 years	38 51.4%	33 47.1%	71 49.3%	33 47.8%
> 60 years	20 27.0%	15 21.4%	35 24.3%	15 21.7%
WEIGHT (kg)				
n	74	70	144	69
Mean	71.6	70.5	71.0	73.7
Standard deviation	21.2	17.8	19.6	18.3
Median	67.0	69.7	68.0	73.0
Min , Max				
HEIGHT (cm)				
n	74	70	144	69
Mean	163.7	163.8	163.7	162.9
Standard deviation	10.2	8.3	9.3	9.0
Median	162.6	162.6	162.6	
Min , Max				
RACE [n (%)]				
n	74	70	144	69
Caucasian/white	57 77.0%	54 77.1%	111 77.1%	59 85.5%
Black	5 6.8%	7 10.0%	12 8.3%	1 1.4%
Asian	2 2.7%	1 1.4%	3 2.1%	-
Other	10 13.5%	8 11.4%	18 12.5%	9 13.0%
LOCATION [n (%)]				
n	74	70	144	69
US	41 55.4%	38 54.3%	79 54.9%	39 56.5%
Non-US	33 44.6%	32 45.7%	65 45.1%	30 43.5%

The majority of patients were female, in their late forties, weighed about 72 kg, and were white. More than half of the study patients resided in the U.S. The treatment groups were fairly well balanced.

2.2.1 Disease history

Summary of baseline disease characteristics is shown below.

Table 3 Summary of baseline disease characteristics, ITT population

(Table T05 / 04MAY01)

	Bosentan 125 mg N=74	Bosentan 250 mg N=70	All Bosentan N=144	Placebo N=69
Time from diagnosis of PAH (days)*				
n	73	70	143	69
Mean	898.4	892.5	895.5	843.4
Standard deviation	985.3	1144.2	1062.3	1442.4
Median	511.0	421.0	453.0	381.0
Min , Max				
Etiology of PAH [n (%)]				
n	74	70	144	69
PPH	57 77.0%	45 64.3%	102 70.8%	48 69.6%
SSc/PHT	13 17.6%	20 28.6%	33 22.9%	14 20.3%
Other	4 5.4%	5 7.1%	9 6.3%	7 10.1%
Presence of Raynaud's syndrome [n (%)]				
n	74	70	144	69
Yes	20 27.0%	21 30.0%	41 28.5%	19 27.5%
No	54 73.0%	49 70.0%	103 71.5%	50 72.5%
Presence of antinuclear antibody [n (%)]				
n	74	70	144	69
Yes	22 29.7%	18 25.7%	40 27.8%	24 34.8%
No	35 47.3%	28 40.0%	63 43.8%	29 42.0%
Unknown	17 23.0%	24 34.3%	41 28.5%	16 23.2%
Presence of rheumatoid factor [n (%)]				
n	74	70	144	69
Yes	4 5.4%	6 8.6%	10 6.9%	7 10.1%
No	35 47.3%	31 44.3%	66 45.8%	28 40.6%
Unknown	35 47.3%	33 47.1%	68 47.2%	34 49.3%
WHO grade at Baseline [n (%)]				
n	74	70	144	69
III	68 91.9%	62 88.6%	130 90.3%	65 94.2%
IV	6 8.1%	8 11.4%	14 9.7%	4 5.8%
Baseline oxygen saturation (%) †				
n	74	68	142	68
Mean	94.3	93.7	94.0	94.6
Standard deviation	3.8	4.5	4.1	3.7
Median	95.0	95.0	95.0	96.0
Min , Max				

(*) Reported number of days from diagnosis of pulmonary hypertension to randomization
(†) Last valid value between the visits 1 (Screening) and 2 (Randomization)
PAH=pulmonary arterial hypertension, PPH=primary pulmonary hypertension,
SSc/PHT=pulmonary hypertension due to scleroderma

The mean time to from time of diagnosis to randomization was about 2.5 years. The etiology of PAH for the majority of patients was PPH and the WHO grade at baseline was class II for 89%-94% of patients; somewhat more bosentan patients than placebo patients were identified as class IV. Mean oxygen saturation at baseline was about 94%. Again, the treatment groups were well balanced.

2.2.2 Baseline hemodynamics

Summary of baseline hemodynamics is shown below.

Table 4 Summary of baseline hemodynamics, ITT population

(Table T06 / 04MAY01)

	Bosentan 125 mg N=74	Bosentan 250 mg N=70	All Bosentan N=144	Placebo N=69
Mean PAP (mmHg)				
n	74	70	144	69
Mean	52.8	56.7	54.7	53.4
Standard deviation	14.5	16.8	15.8	16.6
Median	51.8	53.5	52.0	51.0
Min , Max				
PVR (dyn*sec/cm^5)				
n	73	62	135	65
Mean	884	1167	1014	880
Standard deviation	412	875	678	540
Median	857	962	888	800
Min , Max				
Cardiac index (l/min/m^2)				
n	74	70	144	68
Mean	2.46	2.24	2.35	2.43
Standard deviation	0.82	0.81	0.82	0.69
Median	2.41	2.06	2.23	2.33
Min , Max				
PCWP (mmHg)				
n	73	62	135	66
Mean	9.7	8.7	9.2	9.2
Standard deviation	4.1	3.6	3.9	4.1
Median	10.0	8.0	9.0	9.0
Min , Max				
Mean RAP (mmHg)				
n	74	69	143	67
Mean	9.7	9.9	9.8	8.9
Standard deviation	5.4	6.5	5.9	5.1
Median	8.3	8.0	8.0	8.0
Min , Max				

PAP = pulmonary arterial pressure, PCWP = pulmonary capillary wedge pressure, PVR = pulmonary vascular resistance, RAP = right atrial pressure.

Mean pulmonary arterial pressure, pulmonary capillary wedge pressure, and pulmonary venous resistance were approximately 53 mmHg, 9.2 mmHg, and 1000 dyn-sec/cm^5, respectively. The treatment groups were well balanced.

2.2.3 Concomitant diseases

Summary of previous and concomitant diseases is shown below.

Table 5 Summary of previous and concomitant diseases by class, safety population

(Table T07 / 04MAY01)

	Bosentan 125 mg N=74 No. %	Bosentan 250 mg N=70 No. %	All Bosentan N=144 No. %	Placebo N=69 No. %
ALL DISEASE CLASSES				
Total pts with at least one disease	63 85.1%	63 90.0%	126 87.5%	59 85.5%
Total number of diseases	324	290	614	297
GASTROINTESTINAL DISORDERS	28 37.8%	30 42.9%	58 40.3%	22 31.9%
METABOLISM AND NUTRITION DISORDERS	26 35.1%	25 35.7%	51 35.4%	30 43.5%
VASCULAR DISORDERS	27 36.5%	23 32.9%	50 34.7%	21 30.4%
MUSCULOSKELETAL, CONNECTIVE TISSUE AND BONE DISORDERS	23 31.1%	22 31.4%	45 31.3%	21 30.4%
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	22 29.7%	18 25.7%	40 27.8%	21 30.4%
CARDIAC DISORDERS	17 23.0%	23 32.9%	40 27.8%	16 23.2%
ENDOCRINE DISORDERS	14 18.9%	19 27.1%	33 22.9%	10 14.5%
PSYCHIATRIC DISORDERS	20 27.0%	8 11.4%	28 19.4%	17 24.6%
IMMUNE SYSTEM DISORDERS	14 18.9%	13 18.6%	27 18.8%	5 7.2%
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	13 17.6%	10 14.3%	23 16.0%	12 17.4%
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	12 16.2%	9 12.9%	21 14.6%	12 17.4%
NERVOUS SYSTEM DISORDERS	10 13.5%	10 14.3%	20 13.9%	14 20.3%
BLOOD AND LYMPHATIC SYSTEM DISORDERS	10 13.5%	5 7.1%	15 10.4%	9 13.0%
SKIN & SUBCUTANEOUS TISSUE DISORDERS	5 6.8%	6 8.6%	11 7.6%	8 11.6%
HEPATO-BILIARY DISORDERS	4 5.4%	5 7.1%	9 6.3%	7 10.1%
RENAL AND URINARY DISORDERS	7 9.5%	2 2.9%	9 6.3%	6 8.7%
EYE DISORDERS	2 2.7%	2 2.9%	4 2.8%	5 7.2%
SURGICAL & MEDICAL PROCEDURES	1 1.4%	1 1.4%	2 1.4%	2 2.9%
EAR AND LABYRINTH DISORDERS	2 2.7%	-	2 1.4%	1 1.4%
INFECTIONS AND INFESTATIONS	1 1.4%	-	1 0.7%	1 1.4%
INVESTIGATIONS	1 1.4%	-	1 0.7%	1 1.4%
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	-	1 1.4%	1 0.7%	1 1.4%
CONGENITAL AND FAMILIAL/GENETIC DISORDERS	-	1 1.4%	1 0.7%	-
NEOPLASMS BENIGN AND MALIGNANT (INCLUDING CYSTS AND POLYPS)	-	1 1.4%	1 0.7%	-
INJURY AND POISONING	-	-	-	1 1.4%

Most patients (85%-90%) had at least 1 concomitant disease. The most frequently reported diseases were GI disorders, followed by metabolism and nutritional disorders, vascular disorders, musculoskeletal/connective tissue/and bone disorders. The treatment groups were well balanced.

2.2.4 Concomitant medications

Summary of previous and concomitant treatments for PAH is shown below.

Table 6 Summary of previous and concomitant treatments for pulmonary arterial hypertension by class, safety population

(Table T08 / 04MAY01)

	Bosentan 125 mg N=74 No.	%	Bosentan 250 mg N=70 No.	%	All Bosentan N=144 No.	%	Placebo N=69 No.	%
ALL TREATMENT CLASSES								
Total pts with at least one TRT	65	87.8%	64	91.4%	129	89.6%	64	92.8%
Total number of TRTs	167		167		334		163	
ANTITHROMBOTIC AGENTS	51	68.9%	50	71.4%	101	70.1%	50	72.5%
HIGH-CEILING DIURETICS	34	45.9%	31	44.3%	65	45.1%	26	37.7%
CALCIUM CHANNEL BLOCKERS	33	44.6%	31	44.3%	64	44.4%	36	52.2%
POTASSIUM SPARING AGENTS	15	20.3%	16	22.9%	31	21.5%	17	24.6%
CARDIAC GLYCOSIDES	12	16.2%	16	22.9%	28	19.4%	13	18.8%
LOW CEILING DIURETICS, THIAZIDES	6	8.1%	6	8.6%	12	8.3%	5	7.2%
AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	5	6.8%	4	5.7%	9	6.3%	3	4.3%
MINERAL SUPPLEMENTS	1	1.4%	4	5.7%	5	3.5%	1	1.4%
BETA BLOCKING AGENTS	4	5.4%	-		4	2.8%	1	1.4%
HYDRAZINOPHTALAZINE DERIVATIVES	1	1.4%	1	1.4%	2	1.4%	2	2.9%
LOW-CEILING DIURETICS, EXCL. THIAZIDES	-		2	2.9%	2	1.4%	1	1.4%
ANTIARRHYTHMICS, CLASS I AND III	1	1.4%	1	1.4%	2	1.4%	-	
ANTI-ASTHMATICS	1	1.4%	-		1	0.7%	1	1.4%
ORGANIC NITRATES	-		1	1.4%	1	0.7%	1	1.4%
ANTIADRENERGIC AGENTS, PERIPHERALLY ACTING	-		1	1.4%	1	0.7%	-	
CORTICOSTEROIDS FOR SYSTEMIC USE	1	1.4%	-		1	0.7%	-	
OTHER VASODILATORS USED IN CARDIAC DISEASES	-		1	1.4%	1	0.7%	-	
ANTIADRENERGIC AGENTS, CENTRALLY ACTING	-		-		-		1	1.4%
IMMUNOSUPPRESSIVE AGENTS	-		-		-		1	1.4%

Note: only the medications reported during the visit 1 are included

Most patients (88%-93%) were taking at least 1 concomitant medication. The most common were antithrombotic agents followed by diuretics, calcium channel blockers, and cardiac glycosides. The treatment groups were well balanced.

2.3 Efficacy

2.3.1. Study discontinuations

The table below shows the number and percent of all premature study discontinuations in periods 1 and 2 (extension of the double blind phase).

Table 7 Summary of all premature discontinuations, safety population

(Table T02c / 04MAY01)

Reason for premature discontinuation	Bosentan 125 mg N=74 No.	%	Bosentan 250 mg N=70 No.	%	All Bosentan N=144 No.	%	Placebo N=69 No.	%
Total pts with at least one reason	10	13.5%	9	12.9%	19	13.2%	11	15.9%
ADMINISTRATIVE/OTHER	6	8.1%	3	4.3%	9	6.3%	3	4.3%
WORSENING OF PATIENT CONDITION	3	4.1%	2	2.9%	5	3.5%	5	7.2%
INCREASED LIVER ENZYMES	-		3	4.3%	3	2.1%	-	
DEATH	1	1.4%	-		1	0.7%	2	2.9%
AE/INTERCURRENT ILLNESS	-		1	1.4%	1	0.7%	-	
LACK OF CLINICAL/WALK TEST IMPROVEMENT	-		-		-		1	1.4%

Note: All the discontinuations in periods 1 and 2 are considered, including 7 patients who should not have had a period 2 and dropped for administrative reasons in period 2.

A slightly higher percentage of placebo patients (15.9%) discontinued the study compared to the all bosentan patients (13.2%). The most common reason was administrative (6.3% bosentan and 4.3% placebo) followed by worsening of the patient's condition (3.5% bosentan and 7.2% placebo). There were 3 bosentan patients (2.1%) who withdrew because of increased liver enzymes, 1 bosentan and 2 placebo patients who died, and 1 bosentan patient who withdrew because of an adverse event.

2.3.2 Primary endpoint (6 minute walk test)

The mean baseline (the average of the screening and randomization) walk test, the mean walk test at week 16, and the mean change from baseline at endpoint for the walk test for the intent to treat population are shown in the table below by treatment groups.

Table 8 Walk test: Change from baseline to Week 16, ITT population

(Table T09 / 09MAY01)

Walk test (m)	Bosentan 125 mg N=74	Bosentan 250 mg N=70	All Bosentan N=144	Placebo N=69
Use of supplemental oxygen during screening/randomization walk tests				
n	74	70	144	69
Yes	11 14.9%	12 17.1%	23 16.0%	16 23.2%
No	63 85.1%	58 82.9%	121 84.0%	53 76.8%
Baseline				
n	74	70	144	69
Mean	326.3	333.0	329.6	344.3
Standard deviation	73.2	75.4	74.1	76.4
95% CL of mean	309.3 , 343.2	315.0 , 351.0	317.4 , 341.8	326.0 , 362.7
Median	333.0	338.8	337.3	359.0
95% CL of median	306.5 , 357.5	316.0 , 369.0	320.0 , 357.0	344.0 , 382.5
Min , Max				
Week 16				
n	74	70	144	69
Mean	353.1	379.5	365.9	336.5
Standard deviation	115.0	101.2	109.0	129.2
95% CL of mean	326.4 , 379.7	355.3 , 403.6	348.0 , 383.9	305.4 , 367.5
Median	376.5	384.5	379.5	355.0
95% CL of median	338.0 , 396.0	363.0 , 417.0	363.0 , 396.0	333.0 , 378.0
Min , Max				
Change from baseline				
n	74	70	144	69
Mean	26.8	46.5	36.4	-7.8
Standard deviation	75.3	61.7	69.5	96.1
95% CL of mean	9.3 , 44.2	31.7 , 61.2	24.9 , 47.8	-30.9 , 15.2
Median	32.8	49.8	34.5	9.0
95% CL of median	19.5 , 40.0	19.5 , 66.0	26.0 , 48.5	-18.0 , 26.0
Min , Max				
TREATMENT EFFECT				
Mean	34.6	54.3	44.2	
95% CL of mean	6.2 , 63.1	27.3 , 81.4	21.4 , 67.0	
Median	28.2	45.0	36.7	
95% CL of median	7.5 , 51.5	23.1 , 67.1	17.9 , 55.9	
p-value Mann-Whitney U-test			0.0002	

CL=confidence limits.

The mean baseline walk tests were between 326.3 m and 344.3 m. Compared to the bosentan groups, the placebo group walked the longest at baseline by about 15 m.

Both bosentan groups, but not placebo, had a longer mean walk test at week 16 compared to baseline. The mean absolute changes from baseline (95% confidence limits) for the 125 mg and 250 mg bosentan groups were 26.8 m (9.3, 44.2) and 46.5 m (31.7, 61.2), respectively. The mean change[5] for the placebo group was –7.8 m (–30.9, 15.2).

The mean treatment effects (95% CL) for the 1.25 mg and 250 mg bosentan groups were 34.6 m (6.2, 63.1) and 54.3 (27.3, 81.4), respectively. The mean change in walk distance was significantly greater (p=0.0002 using the Mann-Whitney U test) for the all bosentan group (n=144) compared to the placebo group.

2.3.2.1 Mean walk distances by visit

The changes from baseline for the walk distance at baseline, weeks 4, 8, and 16 for the all bosentan group and the placebo group are shown in the figure below. N.B. all bosentan patients were receiving 62.5 mg bid for the first 4 weeks of treatment.

[5] median change was 9 m indicating that there was one really poor performer in the placebo group