CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-290

Medical Review(s)

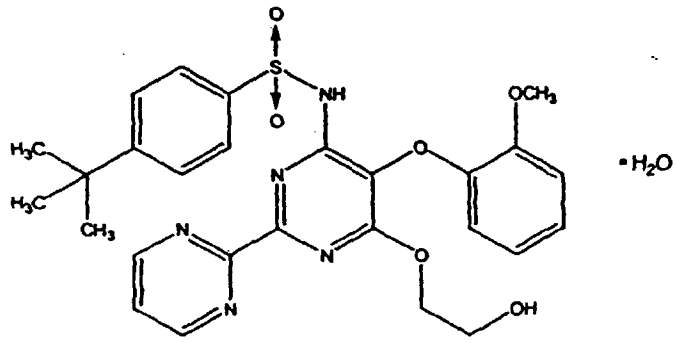
MEDICAL REVIEW OF SAFETY AND EFFICACY
CONCLUSIONS

NDA #: 21,290
Drug Name: bosentan
Type of Document: new drug application
Date Completed: July 6, 2001

Sponsor: Actelion

Medical Reviewer: Maryann Gordon, M.D.

General Information:
Name of Drug
Generic: bosentan
Trade: Tracleer™
~~Structural Formula:~~



Pharmacological Category: endothelin receptor antagonist
Proposed Indication: treatment of pulmonary arterial hypertension
Dosage Form: 62.5 mg and 125 mg tablets
Route of Administration: oral

Summary

Benefits

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 full efficacy review only for completeness.

Study no.	Design/ duration	Primary efficacy parameter	No. planned/ completed	doses	Patient types
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	-with PAH resulting from primary pulmonary hypertension -WHO functional class III-IV despite optimal therapy with vasodilators, cardiac glycosides, diuretics, and /or supplemental oxygen; -receiving anticoagulants -neither receiving nor scheduled to receive epoprosternol (Flolan); -can walk between 150 m and 500 m, inclusive, on a 6-minute walk test. (reduced to 450 m for 352)
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	Same as above

6 minute walking distance

Bosentan, compared to placebo significantly increased mean walking distance in both study AC 052 352 (352) and study AC 052 351 (351).

Mean distances ± SD (m)

	Study 352			Study 351	
	Bos 125 mg bid N=74	Bos 250 mg bid=70	Placebo bid N=69	Bos 125 mg bid N=21	Placebo bid N=11
Baseline	326±73	333±75	344±76	360±86	355±82
Endpoint^	353±115	380±101	336±130	430±66	350±147
Change from baseline	27±75	46±62	-8±96	70±56	-6±120
Placebo subtracted effect	35***	54***	-	76*	-

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

*p=0.020 using Student's t-test

*** p=0.0002 for combined bosentan effect using Wilcoxon test.

Dose effect

Only study 352 used more than 1 dose of bosentan in a parallel group design. In this study, the 250 mg bid bosentan group was numerically superior in walking distance to the 125 mg bid group at weeks 8 and 16, but there was overlapping of confidence limits at both time points. Although 62.5 mg bid was the starting dose for both studies, it was never adequately evaluated for efficacy.

Walk distance by visit

In both studies, after an initial increase from baseline (at week 4), the placebo groups walking distance was similar to their baseline distance. The bosentan groups, on the other hand, had an increase in walking distance that was maintained for 12 and 16 weeks.

Secondary endpoints

Time to clinical worsening was 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 placebo group in 352 was significantly worse at week 16 compared to the bosentan groups. In 351, there were 3 placebo and 0 bosentan patients who deteriorated during the 12 week study.

Changes in Borg dyspnea index measures the levels of perceived exertion. In both studies, there were (small) improvements in the Borg scale in the bosentan groups (ranging from( ) compared to a worsening in the placebo groups (ranging from( )

Changes in WHO functional class showed that more bosentan patients improved in their functional class compared to placebo patients.

Need for increased therapy for PAH occurred less often in the bosentan groups compared to placebo.

Risks

The safety of oral bosentan has been tested in just over 1000 patients/subjects (includes second efficacy trial and clinical pharmacology trials).

Mortality

The combined death rates for patients with PAH who participated in studies 351 and 352 were 2.4% for bosentan (4/165) and 2.5% for placebo (2/80).

Liver toxicity (black box warning)

Approximately 10% to 11% of patients who took bosentan during the clinical program experienced increases in ALT or AST at least 3 times upper limit of normal and 4% had values greater than 8 times upper limit of normal. One patient had an elevated ALT that was 73 times higher than his baseline value. It appears that the higher the dose and the longer a patient takes any dose, the higher the risk of having an elevated LFT. Some, but not all patients with elevated LFTs also reported symptoms of abdominal pain, fever, fatigue, flu-like syndrome.

There are reports of patients with elevated bilirubin as well as two reports of jaundice[1] plus an additional report from (ENABLE).

Understanding that there is only a small population from which to draw conclusions, there is no indication at this time that the increase in liver enzymes will not be reversible with discontinuation of bosentan, at least in the majority of patients. There is no indication that bosentan was tied to any death and there were no reports of liver failure or need for liver transplant.

In addition to patients being discontinued from bosentan for rising LFTs, patients complaining of fever and/or abdominal pain should be discontinued as well before more aggressive tactics (exploratory laparotomy, for example) are taken.

The protocols routinely excluded patients with AST/ALT > 3 times upper limit of normal and this should remain a contraindication.

[1] patient 110 10037 in study AC 052 352 (see summary of efficacy) and 20060 0084 in study RO15464

MEDICAL REVIEW OF SAFETY

NDA#21,290
Drug Name: Bosentan (Tracleer™)
Sponsor: Actelion
Date: July 6, 2001
Medical Reviewer: Maryann Gordon, M.D.

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Drug interactions with CYP3A4 inhibitors (black box warning)
Medications whose concomitant use with bosentan is to be contraindicated include cyclosporin (bosentan concentration increased 30 fold) and ketoconazole.

Anemia
There is a dose related mean decrease in hemoglobin in patients taking bosentan for more than 12 weeks. About 3% of patients reported serious anemia requiring withdrawal and/or transfusion. There was evidence in some, but not all, of these patients of blood loss that would account for such a drop in hb/hct. The one case of bone marrow biopsy[2] reported as normal is reassuring. Reticulocyte count[3] and erythropoietin levels were not measure. The sponsor's explanation that this is all the result of hemodilution seems unlikely.

There is no indication that there is irreversible harm done to patients who develop anemia when taking bosentan. Thus far, it appears that by stopping bosentan when patients show an unacceptable drop in hemoglobin/hematocrit results in patients returning to baseline levels. The protocols routinely excluded patients with hemoglobin and/or hematocrit <30% below normal limits.

Other adverse events
Adverse events that were reported by at least 8 bosentan patients and reported by at least 1% more in the bosentan group compared to placebo include flushing, edema, headache, pruritus, angina, palpitations, and dry mouth. Although there was no evidence that bosentan is associated with hypotension, the protocols routinely exclude patients with systolic blood pressure < 85 mmHg.

Although there was one report of torsades de pointes, there is no indication that bosentan affects the electrical activity in the heart.

Other drug interactions
Bosentan can be expected to decrease the concentrations (and may be the effect) of CYP3A4 and CYP2C9 substrates.

Other drugs that the sponsor prohibited study patients from taking include glibenclamide, encainide, flecainide, disopyramide, propafenone, moricizine, pinacidil, minoxidil and oral positive inotropic agents other than digitalis.

Patients receiving warfarin and bosentan must be monitored for decreases in prothrombin time. There are no safety data supporting the concomitant use of bosentan and prostacyclin therapy.

Conclusion
Bosentan should be approved for improving walking distance in patients with WHO functional class III or IV, who are not responding adequately to conventional therapy, and are not taking Flolan. Because of the toxic effects on the liver and the serious drug-drug interactions, it is recommended that a patient registry with education for physicians who treat patients with PAH be implemented prior to the marketing of bosentan.

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[2] patient 18202/9032
[3] sponsor reports that in the ongoing ENABLE trials, mean reticulocyte count decreased by 6.4 x10^9/l in the 285 patients with baseline and on treatment measurements, and the 26 patients with markedly decreased hemoglobin also had a decrease in mean reticulocyte count (fax dated 6-26-01).

Summary of safety

The safety of oral bosentan has been tested in just over 1000 patients[1]. The indications that have been studied include pulmonary arterial hypertension (for which this application has been submitted), [redacted]. Bosentan has been studied over a fairly wide dosing range (total daily doses 100 mg to 2000 mg). Twenty-nine patients with pulmonary hypertension have been treated for at least 1 year.

Adverse events leading to premature withdrawal occurred more frequently in the bosentan group (11.1%) compared to placebo (9.4%) and the most common reason for discontinuation in the bosentan group was abnormal hepatic function (3.4% placebo subtracted). Events leading to withdrawal but reported only in the bosentan group include anemia, hypotension, diarrhea, dyspnea, flushing, lower limb edema, pyrexia, vomiting, abdominal pain, face edema, and myocardial infarction.

Bosentan provokes elevation of LFTs, primarily ALT and AST (ALT for one patient[2] was increased 73 times over his baseline value), with examples of positive drug rechallenge. The increases in alkaline phosphatase tended to be less striking. Approximately 10 to 13% of bosentan patients had LFTs at least 3 times upper limit of normal and 4% had values greater than 8 times upper limit of normal. Overall, the higher the dose and the longer a patient takes any dose, the higher the risk of having an elevated LFT.

There are reports of patients with elevated bilirubin as well as two reports of jaundice[3] (plus an additional report of jaundice from the [redacted] (ENABLE)). There are examples of patients with elevated LFTs reporting abdominal pain, fever, flu-like syndrome.

Understanding that there is only a small population from which to draw conclusions, there is no indication at this time that the increase in liver enzymes will not be reversible, at least in the majority of patients, with discontinuation of bosentan, or an attempt to lower the dose. There is no indication that bosentan was tied to any death (with the possible exception of the REACH study that had an increase in deaths in the fast titration group). As of June 19, 2001, the sponsor has not received a report (s) of liver failure, liver transplant, or a death because of liver impairment in any patient who has received bosentan[4]. The protocols routinely excluded patients with AST/ALT > 3 times upper limit of normal and this should continue to be a contraindication if the drug receives approval.

In addition to the elevation of LFTs, there is a dose related mean decrease in hemoglobin of nearly 1 g/dl in patients taking bosentan for more than 12 weeks. About 3% of patients reported serious anemia requiring withdrawal and/or transfusion. (In comparison, there were 2 placebo patients (0.9%) who received blood transfusion and none was withdrawn for anemia.) The one case of bone marrow biopsy[5] reported as normal is reassuring. The cause of the anemia is unknown. The sponsor's explanation that it is all the result of hemodilution seems unlikely.

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[1] Total = 1066 (571 from therapeutic trials+144 from 352 trial+351 from clinical pharmacology trial)
[2] 18164/6331
[3] patient 110 10037 in study AC 052 352 (see summary of efficacy) and 20060 00841 in study RO15464
[4] fax dated June 19, 2001.
[5] patient 18202/9032

Although anemia can be a serious side effect, there is no indication that there is irreversible harm done to patients who develop anemia when taking bosentan. Thus far, it appears that by stopping bosentan when patients show an unacceptable drop in hemoglobin/hematocrit results in patients returning to baseline levels. The protocols routinely excluded patients with hemoglobin and/or hematocrit <30% below normal limits.

Additional dose related adverse events include headache, flushing and edema (definitely peripheral and perhaps face as well). Although there was no evidence that bosentan is associated with hypotension, the protocols routinely exclude patients with systolic blood pressure < 85 mmHg.

Although there was one report of torsade de pointes in a patient receiving bosentan, there is no indication that bosentan affects electrical activity in the heart.

Medications whose concomitant use with bosentan is to be contraindicated include cyclosporin and ketoconazole. Great care should be used when bosentan is coadministered with any CYP3A4 inhibitors, especially with the first bosentan dose. This drug-drug interaction does present a predicament since there are so many drugs that inhibit CYP3A4. Bosentan also can be expected to decrease the concentrations (and may be the effect) of CYP3A4 and CYP2C9 substrates.

Other drugs that the sponsor prohibited study patients from taking include glibenclamide, encainide, flecainide, disopyramide, propafenone, moricizine, pinacidil, minoxidil and oral positive inotropic agents other than digitalis.

Patients receiving warfarin and bosentan must be monitored for decreases in prothrombin time. There are no data supporting the concomitant use of bosentan and Flolan therapy.

1.0 Overall Clinical Program

The bosentan program contains both completed and ongoing safety and efficacy studies involving There are also various clinical pharmacology studies.

The indication currently being pursued are pulmonary arterial hypertension (PAH)

1.1 Completed studies

- 3 studies in PAH: 2 double blind, randomized efficacy trials and 1 open label safety study;
- 7 studies (≥ 2 weeks duration) in patients
- 23 clinical pharmacology studies and studies with special objectives (< 2 weeks duration).

1.1.1 PAH

The efficacy and safety of bosentan in the treatment of patients with PAH are based on the following studies:

- randomized, placebo-controlled, double-blind trial (AC-052-351) using doses of 62.5 mg bid up to 125 mg bid for 12 weeks. A total of 32 patients were enrolled.
- AC-052-352 (BREATHE-1): double blind, placebo controlled randomized 16-week efficacy study using 62.5 mg bid up to 250 mg bid that enrolled 214 patients. The study was submitted for review on May 18, 2001. There was a complete medical review of efficacy and safety of

doses (62.5 mg bid to 125 mg bid).

b) trial

NC15020 double blind, placebo controlled, 4 week efficacy trial that was stopped prematurely because of increased incidence of elevated liver enzymes. A total of 293 patients entered the study with doses of 100 mg qd to 1000 mg bid.

1.2 Ongoing studies

Interim reports containing data collected up to the clinical cut-off for the following ongoing, open-label or blinded studies:

PAH

- AC-052-353: small, ongoing open-label extension study of AC-052-351 (base study) using doses of 62.5 mg bid up to 125 mg bid in patients with PAH;

- NC15464B: ongoing open-label extension study of NC15462 in patients

- AC-052-301 and AC-052-302 (The ENABLE Trials): ongoing, large, still blinded morbidity/mortality trials in patients

1.3 Clinical pharmacology studies

There are 23 studies with healthy volunteers and various patient populations designed to characterize the pharmacokineties of bosentan and to assess potential interactions with other medications. These include:

- 3 single-dose i.v. studies in healthy volunteers;
- 5 single-dose i.v. studies in patient populations;
- 6 single-dose oral studies in healthy volunteers;
- 3 single-dose oral studies in patient populations;
- 3 multiple-dose oral studies in healthy volunteers;
- 7 drug-drug interaction studies.

1.4 Safety update

Data from the studies shown below have been added to the safety update.

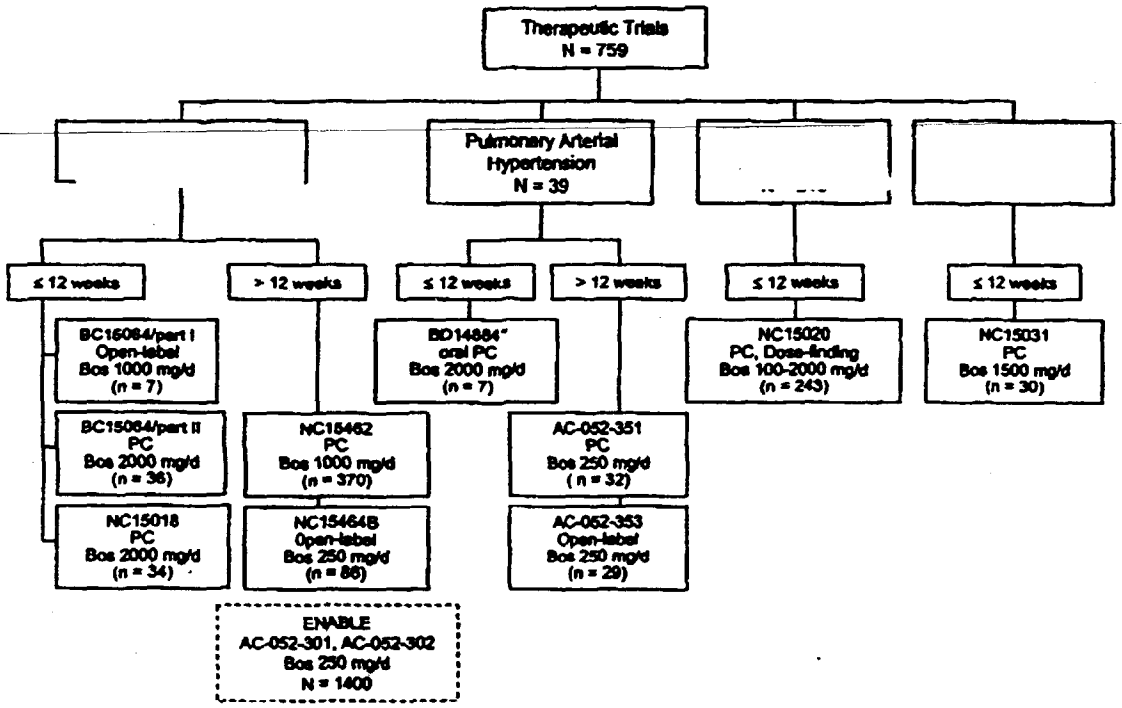
2.0 Demographics

2.1 Numbers of patients

2.1.1 All bosentan patients

Total number of all subjects[7] in bosentan database (regardless of treatment group) at the time of the NDA submission is 759. The number of patients studied for the various indications are shown in the following chart.

Figure 3 Therapeutic studies in the integrated safety database



* = Each of the 7 patients received on day 1 bosentan 500 mg i.v., bos = bosentan, PC = placebo-controlled

There were 447 patients 39 patients with PAH, 243 patients with nd 30 patients in a total of 10 studies (limited to those with a duration ≥ 2 weeks).

The numbers of patients in the various types of trials are shown below.

[7] this total does not include AC 052 352

Table 9 Summary of populations within the integrated database

• Number of patients in the 10 therapeutic trials	759
Number of patients treated with bosentan	571
• Number of patients in the 7 placebo-controlled trials	752
Number of patients treated with bosentan	533
Number of patients treated with placebo	219
• Number of patients in the 3 open-label trials	122
Extension trials (NC15464B and AC-052-353)	115
– Ex-bosentan patients	84
– Ex-placebo patients	31
Non extension trials (BC15064 Part I)	7
• Number of patients in the 23 clinical pharmacology trials	571
Number of patients treated with bosentan	434
• Number of patients in the still blinded ENABLE trials (AC-052-301and AC-052-302), randomized 1:1 to bosentan and placebo	1400

A total of 571 patients received bosentan in 1 of 10 clinical trials.

2.1.2 All Placebo controlled trials

A total of 533 patients[8] received bosentan and 219 patients received placebo in the 7 placebo controlled clinical trials. There were 38 bosentan patients (who are not part of the 533) in open label extension trials. The 23 clinical pharmacology trials enrolled 571 subjects with 434 of these having received bosentan. This is a very small safety data base.

At the time of the NDA submission, the ongoing ENABLE trials ( ) had 1400 patients enrolled which increased to 1613 at the time of the submission of the safety update. The ENABLE trials remain blinded and are expected to be completed November 2001.

2.1.3 Safety update

There are 29 PAH patients in the open label extension study AC-052-353. These patients are carry overs from study AC-052-351.

A total of 427 new patients have been added to the bosentan safety database: 214 patients were recruited into the ongoing BREATHE-1 trial (AC-052-352, the second efficacy trial in PAH) and 213 patients were added to the 1,400 patients of the ongoing ENABLE trials ( ) for a total of 1613.

[8] this total does not include study AC 052 352

2.2 Demographics and duration of exposure

2.2.1 All bosentan patients

Demographics and characteristics of the 571 patients who received bosentan in 1 of the 10 therapeutic trials are shown in the table below.

Table 10 Summary of demographic and baseline clinical characteristics of all bosentan-treated patients in the therapeutic studies

Table T02 / 23OCT00

	Bosentan N=571
SEX	
n	571
Males	408 71.5%
Females	163 28.5%
AGE (years)	
n	571
Mean	59.6
SD	12.0
Std err	0.5
Median	61.0
Q1 , Q3	51.0 , 68.0
Min , Max	
WEIGHT (kg)	
n	544
Mean	79.6
SD	15.4
Std err	0.7
Median	78.2
Q1 , Q3	70.0 , 88.4
Min , Max	
LOCATION	
n	571
US	124 21.7%
Non-US	447 78.3%
RACE	
n	571
BLACK	28 4.9%
CAUCASIAN	523 91.6%
OTHER	20 3.5%
INDICATION	
n	571
[redacted]	323 56.6%
	194 34.0%
PAH	33 5.8%
	21 3.7%
PLANNED DURATION	
n	571
12 weeks or less	275 48.2%
More than 12 weeks	296 51.8%
TREATMENT DOSE	
n	571
Bosentan 100 mg/d	50 8.8%
Bosentan 250-500 mg/d	101 17.7%
Bosentan 1000-1500 mg/d	317 55.5%
Bosentan 2000 mg/d	103 18.0%

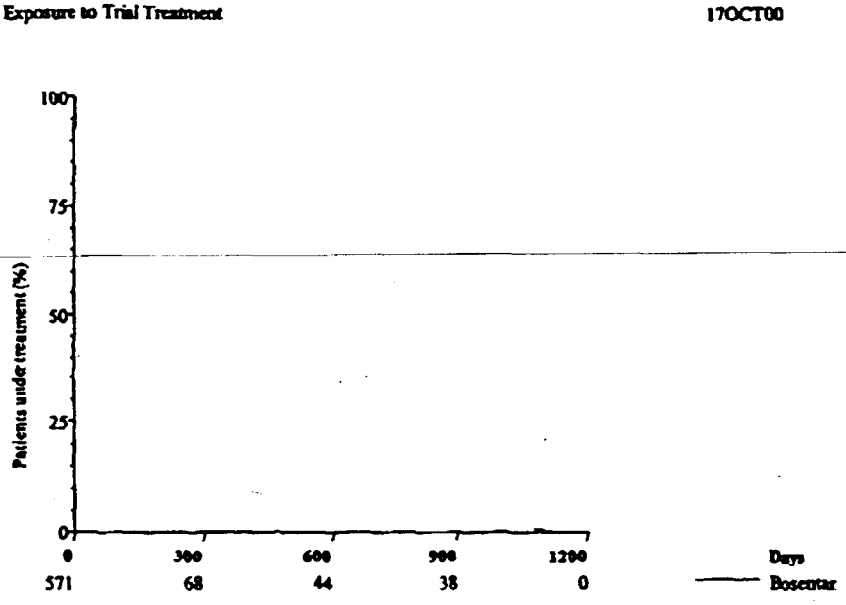
PAH = pulmonary arterial hypertension;

= SD = standard deviation

Most patients were male (71.5%) and white (91.6%), with a mean age of 59.6 years (range 25 to 90 years). Over half of the study patients were [redacted] patients, about one third were [redacted] patients and a minority (5.8%) were PAH patients. Total daily doses ranged from 100 mg to 2000 mg. Nearly two thirds of study patients received daily doses of $\geq$ 1000 mg.

A figure showing the duration of exposure is displayed below.

Figure 4 **Duration of exposure for all bosentan-treated patients in the therapeutic studies***



Approximately 50 % of patients received bosentan for around 4 weeks or less. According to the above figure, at least 68 patients have received bosentan for 300 days.

2.2.2 PAH

a) Demographics

The table below displays information on the 31 patients who participated in the efficacy study and the 29 patients who entered into the extension study.

Table 16 AC-051-351 and AC-051-353: Patient demographics and disease characteristics

	Study AC-052-351		Study AC-052-353
	Bosentan	Placebo	All patients
	N=21	N=11	N=29
SEX [n(%)]			
Males	4 19.0%	-	4 13.8%
Females	17 81.0%	11 100%	25 86.2%
AGE (years)			
Mean ± SD	52.2 ± 12.2	47.4 ± 14.0	50.2 ± 13.3
Std err	2.7	4.2	2.5
Median	52.0	53.0	51.0
Min , Max			
WEIGHT (kg)			
Mean ± SD	85.9 ± 22.8	87.1 ± 17.7	87.3 ± 20.1
Std err	5.0	5.3	3.7
Median	78.5	89.8	83.0
Min , Max			
RACE [n(%)]			
CAUCASIAN/WHITE	16 76.2%	9 81.8%	22 75.9%
BLACK	3 14.3%	2 18.2%	5 17.2%
OTHER	2 9.5%	-	2 6.9%
Etiology of PAH [n(%)]			
PRIMARY PHT	17 81.0%	10 90.9%	24 82.8%
PRIMARY PHT WITH SYSTEMIC SCLEROSIS	4 19.0%	1 9.1%	5 17.2%
Time from diagnosis to randomization (days)			
Mean ± SD	634 ± 528	1091 ± 1032	-
Median	455	909	-
Min, Max			

PAH = pulmonary arterial hypertension; PHT = pulmonary hypertension; SD = standard deviation; std err = standard error.

Most patients were white and female with a mean age around 50 years. Primary pulmonary hypertension was a more common etiology than primary pulmonary hypertension with systemic sclerosis. Mean amount of time from PAH diagnosis to randomization was less than 2 years.

b) Duration of exposure

All patients randomized to bosentan in study AC-052-351 completed the 12 week double blind phase and these patients were allowed to continue taking bosentan past the 12 weeks. Patients who had been randomized to placebo were allowed to receive bosentan after completing the double blind part of the study. The extension study AC-052-353 accepted patients who had been enrolled into and completed AC-052-351. All patients who entered the extension study received open label bosentan. The mean duration of treatment was 227± 35 days for the 21 patients who had received bosentan in the base study and 98± 8 days for the 9 patients who had received placebo in the base study.

2.3 Numbers of patients who stopped treatment for any reason

2.3.1 Placebo controlled trials

The table below shows the number and percent of patients who dropped out of a trial, by reason and treatment group (from fax sent 5-23-01).

TABLE 1

All Placebo controlled	Bosentan N=533		Placebo N=219	
Administrative / Other	6	1.1%	2	0.9%
Sponsor's decision	124	23.3%	56	25.6%
Patient's decision	13	2.4%	4	1.8%
Worsening	10	1.9%	5	2.3%
Death	21	3.9%	10	4.6%
AE	66	12.4%	22	10.0%
of these: LFT	25	4.7%	2	0.9%
All Withdrawals	240	45.0%	99	45.2%

Approximately equal incidence rates were reported for all study withdrawals: bosentan 45.0% and placebo 45.2%. The most common reason was administrative/other, which is puzzling. Adverse event was also common. It can usually be assumed that a patient's decision to withdraw results from an (unreported) adverse event.

2.3.2 Open label trials

The incidence rates for patients in open label bosentan treatment are shown below by reason.

TABLE 2

Open label studies	Bosentan N=122	
Administrative / Other	8	6.6%
Sponsor's decision	0	0.0%
Patient's decision	7	5.7%
Worsening	4	3.3%
Death (1)	15	12.3%
AE	15	12.3%
of these: LFT	4	3.3%
All Withdrawals	49	40.2%

(1) Pts 20081/123,20082/64, 20088/41, 20254/1462, were reported as withdrawals for AE/Intercurrent illness, but no AE leading to discontinuation was given, they all died within 10 days of the end of study treatment

Death and adverse events were the most common reasons for withdrawing from bosentan treatment in the open label trials. The 7 patients who decided to stop probably did so because of an adverse event. The incidence rate for withdrawal for elevated LFTs was 3.3%.

3.0 Deaths

3.1 All bosentan patients

The deaths reported for the all bosentan population (n=571) are shown below by cause of death. The mean duration of exposure to bosentan for this group was 154 days (range from days).

Table 44 Summary of all deaths in bosentan-treated patients

Table T92 / 25OCT00

Cause of death	Bosentan (All) N=571 No.	%
Total pts with at least one cause	51	8.9%
SUDDEN DEATH UNEXPLAINED	9	1.6%
CARDIAC FAILURE NOS	7	1.2%
MYOCARDIAL INFARCTION	6	1.1%
PULMONARY OEDEMA NOS	4	0.7%
CARDIAC ARREST	3	0.5%
CARDIOGENIC SHOCK	3	0.5%
CEREBROVASCULAR ACCIDENT	3	0.5%
RENAL FAILURE NOS	3	0.5%
UNKNOWN	3	0.5%
MULTI-ORGAN FAILURE	2	0.4%
CARDIO-RESPIRATORY ARREST	1	0.2%
CORONARY ARTERY DISEASE NOS	1	0.2%
DEATH NOS	1	0.2%
HYDROCEPHALUS ACQUIRED	1	0.2%
METASTASES NOS	1	0.2%
METASTASES TO BRAIN	1	0.2%
PNEUMONIA NOS	1	0.2%
RESPIRATORY FAILURE (EXC NEONATAL)	1	0.2%
SEPTICAEMIA NOS	1	0.2%
VENTRICULAR FIBRILLATION	1	0.2%
VENTRICULAR TACHYCARDIA	1	0.2%

NOS = not otherwise specified; pts = patients.

A total of 51 (8.9%) deaths were reported: 50 deaths occurred in patients participating in NYHA class III-IV trials (26 in placebo controlled trial NC15462B, REACH, and 24 in open label ongoing extension NC15464B) and 1 death occurred . (death attributed to cerebral infarction).

Most of the causes of death appear to be related to underlying cardiac disease: sudden death (9 patients, 17.6%), cardiac failure (7 patients, 13.7%), and myocardial infarction (6 patients, 11.8%). Two patients died of multi-organ failure and there were 3 deaths for which the cause was unknown/not reported.

There were 24 deaths in the bosentan 250 mg and 27 in the bosentan 1000-1500 mg daily dose groups.

Three deaths occurred in patients who were or had received iv bosentan (patient #806 died with bronchopneumonia, patient #03 died with hypotension, oliguria, thrombocytopenia, and patient #107 died with hydrocephalus and CVA). The deaths occurred either during or shortly after drug was administered. The iv formulation is no longer being developed.

3.2 All placebo controlled trials

There are 7 placebo controlled studies with a total of 219 placebo patients and 533 bosentan patients. Deaths reported for patients who participated in these trials are shown below.

Appendix 73 Summary of deaths in placebo-controlled studies

Produced by sturlor on 25OCT00
Ro 47-0203, Protocols: AC-52351 BC-15064(II) BD-14884 NC-15018 NC-15020 NC-15462 NN-15031
Table T90f: Summary of deaths
Population: Safety

Cause of death	Placebo N=219 No.	%	Bosentan N=533 No.	%
Total pts with at least one cause	13	5.9%	27	5.1%
SUDDEN DEATH UNEXPLAINED	5	2.3%	3	0.6%
CARDIAC FAILURE NOS	1	0.5%	4	0.8%
CARDIAC ARREST	-		3	0.6%
CARDIOGENIC SHOCK	1	0.5%	2	0.4%
CEREBROVASCULAR ACCIDENT	1	0.5%	2	0.4%
MYOCARDIAL INFARCTION	-		3	0.6%
DEATH NOS	1	0.5%	1	0.2%
PULMONARY OEDEMA NOS	-		2	0.4%
RENAL FAILURE NOS	-		2	0.4%
ARRHYTHMIA NOS	1	0.5%	-	
CARDIO-RESPIRATORY ARREST	-		1	0.2%
CORONARY ARTERY DISEASE NOS	-		1	0.2%
HEPATORENAL SYNDROME	1	0.5%	-	
HYDROCEPHALUS ACQUIRED	-		1	0.2%
MALIGNANT HEPATIC NEOPLASM	1	0.5%	-	
MULTI-ORGAN FAILURE	-		1	0.2%
PULMONARY THROMBOSIS	1	0.5%	-	
SEPSIS NOS	1	0.5%	-	
VENTRICULAR FIBRILLATION	-		1	0.2%

(1/1)

The incidence rates for death are similar for the 2 treatment groups: 5.9% for placebo and 5.1% for bosentan. The most common causes of death for placebo and bosentan groups were sudden death and cardiac failure. Most deaths were attributed to cardiovascular causes, which is to be expected in this predominantly CHF population.

There were 2 bosentan deaths attributed to renal failure:

-subject 18111/6022 was a 64 year old with ischemic heart disease, NYHA class IV, ejection fraction 15%, post MI and post CABG received bosentan 500-1000 mg daily for 12 days. The study medication was discontinued because of worsening heart failure. He made a temporary recovery but then developed acute renal failure secondary to low cardiac output. The patient had steady deterioration followed by sudden death.

-subject 18195/9068 was a 66 year old with ischemic heart disease, NHYA class IV, ejection fraction 29% and a history of COPD, MI, stroke and coronary artery bypass surgery received bosentan 500-1000 mg daily until day 44 when he was discontinued on day 44 because of worsening CHF and chronic renal failure. His death, on day 70, was attributed described as acute renal failure. No autopsy was performed.

Deaths with addition of AC-052-352

The numbers and percents of patients who died in the placebo controlled trials (including AC-0520352) are shown below.

Produced by sturlor on 17MAY01

Ro 47-0203, Protocols: AC-52351 AC-52352 BC-15064(II) BD-16894 NC-15018 NC-15020 NC-15462 NH-15031
Table T90f: Summary of deaths
Population: Safety

Cause of death	Placebo N=289 No.	%	Bosentan N=677 No.	%
Total pts with at least one cause	15	5.2%	31	4.6%
SUDDEN DEATH UNEXPLAINED	5	1.7%	3	0.4%
CARDIAC FAILURE NOS	1	0.3%	6	0.9%
CARDIAC ARREST	-		3	0.4%
CARDIOGENIC SHOCK	1	0.3%	2	0.3%
CEREBROVASCULAR ACCIDENT NOS	1	0.3%	2	0.3%
MYOCARDIAL INFARCTION	-		3	0.4%
PULMONARY HYPERTENSION NOS AGGRAVATED	2	0.7%	-	
DEATH NOS	1	0.3%	1	0.1%
PULMONARY OEDEMA NOS	-		2	0.3%
RENAL FAILURE NOS	-		2	0.3%
SEPSIS NOS	1	0.3%	1	0.1%
ARRHYTHMIA NOS	1	0.3%	-	
CARDIO-RESPIRATORY ARREST	-		1	0.1%
CORONARY ARTERY DISEASE NOS	-		1	0.1%
HEPATORENAL SYNDROME	1	0.3%	-	
HYDROCEPHALUS ACQUIRED	-		1	0.1%
MALIGNANT HEPATIC NEOPLASM	1	0.3%	-	
MULTI-ORGAN FAILURE	-		1	0.1%
PNEUMONIA NOS	-		1	0.1%
PULMONARY HAEMORRHAGE	-		1	0.1%
PULMONARY THROMBOSIS	1	0.3%	-	
VENTRICULAR FIBRILLATION	-		1	0.1%

(Pag 1/1)

from fax dated 6-04-01

There is a slightly higher death rate in the placebo group (5.2%) compared to the bosentan group (4.6%). Most deaths were cardiovascular in nature.

3.3 REACH--Protocol NC15462B

This was a large placebo controlled trial with NYHA class III-IV patients. There were 370 patients randomized to placebo, bosentan fast titration to 500 mg bid or slow titration to 500 mg bid. Patients were followed for 26 weeks. The numbers of deaths per group are shown below:

Number and (percent) of patients

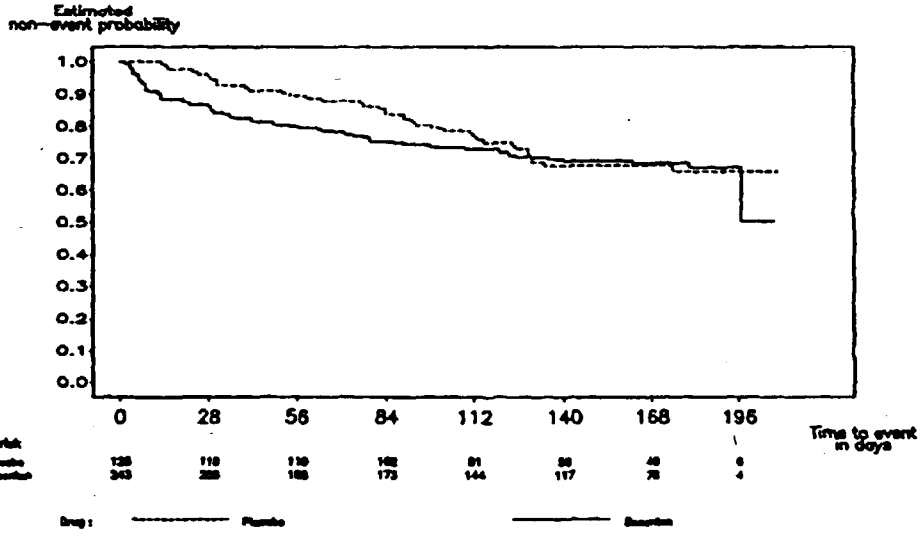
	Placebo N=126	Bosentan slow titration N=121	Bosentan fast titration N=123	Total bosentan N=244
Death	11 (8.7)	9 (7.4)	17 (13.8)	26 (10.7)

Table 18 vol 40.

The death rates were similar for placebo (8.7%) and the bosentan slow titration group (7.4%) but higher for the bosentan fast titration group (13.8%). Overall, there is a small imbalance in the death rate favoring placebo.

The figure below is the Kaplan-Meier plot of time to death or heart failure morbidity for study NC15462B.

Figure 5. Kaplan-Meier Plot of Time to Death or Heart Failure Morbidity: Whole Population



The break down by reason for the deaths is shown below.

Table 18. Summary of Deaths by Trial Treatment (All Patients)

REASON FOR DEATH	Placebo N = 126		Ro 125-250-500 N = 121		Ro 250-500 N = 123	
	No.	(%)	No.	(%)	No.	(%)
Total of patients with death	11	(8.7)	9	(7.4)	17	(13.8)
Total of all reasons	11		9		17	
SUDDEN DEATH UNEXPLAINED	5	(4.0)	2	(1.7)	1	(0.8)
CARDIAC ARREST	-		2	(1.7)	1	(0.8)
CARDIAC FAILURE NOS	-		1	(0.8)	2	(1.6)
CARDIOGENIC SHOCK	1	(0.8)	-		2	(1.6)
CEREBROVASCULAR ACCIDENT	1	(0.8)	-		2	(1.6)
MYOCARDIAL INFARCTION	-		1	(0.8)	2	(1.6)
*DEATH CAUSE UNKNOWN	1	(0.8)	-		1	(0.8)
PULMONARY EDEMA	-		1	(0.8)	1	(0.8)
RENAL FAILURE NOS	-		-		2	(1.6)
ARRHYTHMIA NOS	1	(0.8)	-		-	
CARDIAC FAILURE AGGRAVATED	-		1	(0.8)	-	
CARDIO-RESPIRATORY ARREST	-		-		1	(0.8)
CORONARY ARTERY DISEASE NOS	-		-		1	(0.8)
HEPATORENAL SYNDROME	1	(0.8)	-		-	
MALIGNANT HEPATIC NEOPLASM	1	(0.8)	-		-	
MULTI-ORGAN FAILURE	-		1	(0.8)	-	
VENTRICULAR FIBRILLATION	-		-		1	(0.8)

NOTE: Percentages are based on N. If N < 10 percentages are omitted.

The deaths do not seem unexpected in a heart failure population, but the imbalance is not reassuring.

There is no evidence that bosentan adversely affects mortality, at least in patients, but there is no convincing evidence that it does not. The analysis of mortality from the large ENABLE trials may clarify this issue.

3.4 Safety update

3.4.1 PAH

a) ongoing, open label trial

There are 29 patients in the extension study AC-052-351. No deaths have been reported.

b) ongoing, blinded trial (AC-052-352)

A total of 214 patients have been randomized to bosentan 62.5mg-250 mg bid or placebo. At the time of the safety update, 2 deaths have been reported:

Patient 10014 was a 48-year-old white female with pulmonary hypertension due to systemic sclerosis. Medical history included cardiac failure, anemia, thrombocytopenia, lupus erythematosus, Raynaud's syndrome, rectal bleeding, urinary tract infection, cholelithiasis, hip arthroplasty and constipation. Concomitant medication included prednisone, acetylsalicylic acid, omeprazole, fluorazepam, paracetamol, docusate, and calcium. The patient reported nausea treated with promethazine on day 1, dyspepsia on day 6, tinnitus on day 31, and arthralgia on day 87. LFTs were found to be severely increased on day 99 (AST 659 U/L, ALT 554 U/L, alk phos 275 U/I). Total and direct bilirubin were high (22 and 36 mmol/1) Study drug was permanently discontinued on day 116. Hepatic function tests returned to normal by day 141. The patient reported to her local pneumologist on day 145 with symptoms of worsening pulmonary hypertension. After admission to the local hospital, epoprostenol therapy was initiated. Inotropic

drugs were started and mechanical ventilation was needed. Three days later the patient died. The cause of death was reported as right heart failure secondary due to worsening pulmonary hypertension. No autopsy was performed.

Patient 10070 was a 50-year-old white female with PPH. Medical history included monoclonal gammopathy, irritable bowel syndrome, and anxiety. Concomitant medication included furosemide, spironolactone, digoxin, warfarin, fluticasone, salmeterol, promethazine, clonazepam, diazepam, paracetamol, codeine, dicycloverine, diphenydramine and estrogens. She collapsed at home on day 19 with cardiac arrest. CPR was unsuccessful. An autopsy was performed and the death was attributed to worsening PPH.

3.4.2 CHF

a) ongoing open label

There are 27 ongoing patients and 3 additional deaths. Overall, there have been 26 deaths in this long term extension study with severe heart failure patients.

Patient 20252/1283 had worsening heart failure and renal function. He continued to deteriorate, all medication was discontinued and he died 3 days later.

Patient 20266/1641 complained of abdominal pain with nausea and vomiting and was found unresponsive the next day. Resuscitation was unsuccessful. He died on study day 848. Patient was anemic (hb: 11.4 g/dl and hct: 36.5%). GTT was elevated (76 U/L). History included diabetes with worsening renal failure and excised melanoma.

Patient 20086/42 was a 79-year-old white male patient with ischemic heart disease, NYHA class IIIb-IV enrolled into the open-label study. Concomitant medication included enalapril, furosemide, digoxin, perhexiline, metoprolol, isosorbide mononitrate, acetylsalicylic acid, indomethacin, diclofenac, imipramine, temazepam, and ferrous supplements. He reported 2 episodes of gout, 2 vasovagal episodes that resolved spontaneously, and blurred vision resolved without treatment, upper respiratory tract infection that resolved with treatment. He had 2 episode of shortness of breath treated with readjustment of diuretic or rest. These events were reported months prior to his sudden collapse and death at home. He had been on study drug for about 2 years. No autopsy was performed.

b) ongoing, double blind (ENABLE trials)

There have been a total of 187 deaths in 1613 study patients. The reasons given for the deaths are shown below.

Table 9 **Summary of the most frequent (≥ 3) reasons of deaths (ENABLE studies, all events)**

Reason	No random code N=1613 No.	%
Total pts with at least one reason	187	11.6%
CARDIAC FAILURE NOS	68	4.2%
SUDDEN DEATH UNEXPLAINED	32	2.0%
CARDIAC ARREST	20	1.2%
CORONARY ARTERY DISEASE NOS	14	0.9%
RENAL FAILURE NOS	9	0.6%
VENTRICULAR FIBRILLATION	9	0.6%
CARDIO-RESPIRATORY ARREST	8	0.5%
UNKNOWN REASON	7	0.4%
CARDIOGENIC SHOCK	6	0.4%
MYOCARDIAL INFARCTION	6	0.4%
ACUTE MYOCARDIAL INFARCTION	5	0.3%
ARRHYTHMIA NOS	5	0.3%
CARDIOMYOPATHY NOS	5	0.3%
DEATH NOS	5	0.3%
PULMONARY OEDEMA NOS	5	0.3%
RESPIRATORY FAILURE (EXC NEONATAL)	5	0.3%
CEREBROVASCULAR ACCIDENT NOS	4	0.2%
PNEUMONIA NOS	3	0.2%
SEPSIS NOS	3	0.2%
SEPTICAEMIA NOS	3	0.2%
VENTRICULAR ARRHYTHMIA NOS	3	0.2%

Until the study is completed and analyzed, it is difficult to draw conclusions about the deaths in patients with advanced heart failure.

3.5 Abrupt bosentan withdrawal

Reviewing the 4 deaths reported for PAH patients receiving bosentan (AC 052 352) discloses no evidence that abruptly stopping bosentan leads to death.

4.0 Serious adverse events

Clinical adverse events are included that were reported during or up to 28 days after treatment was stopped. Those events identified as part of the efficacy endpoint of a particular trial (e.g., worsening heart failure in studies), however, were not consistently reported in safety so some numbers are unreliable.

4.1 All bosentan patients

Ten studies were conducted with bosentan in various indications with a total of 571 bosentan patients. Serious adverse events reported by at least 0.5% (3) of all bosentan patients are shown below, by indication as well as for the total bosentan population.

Table 48 Summary of SAEs (including unrelated) occurring in ≥ 0.5% of patients in the pool of all bosentan-treated patients by frequency and indication

Table T24I / 23OCT00

Body system / Adverse event	PAH				All patients	
	N=323	N=194	N=33	N=21	N=571	
	No. %	No. %	No. %	No. %	No. %	
ALL BODY SYSTEMS						
Total pts with at least one SAE	88 27.2%	1 0.5%	4 12.1%	3 14.3%	96 16.8%	
Total number of SAEs	163	1	8	9	181	
ATRIAL FIBRILLATION	8 2.5%	-	-	-	8 1.4%	
PNEUMONIA NOS	8 2.5%	-	-	-	8 1.4%	
CARDIAC FAILURE NOS	5 1.5%	-	1 3.0%	1 4.8%	7 1.2%	
CEREBROVASCULAR ACCIDENT	6 1.9%	-	-	-	6 1.1%	
CHEST PAIN NEC	6 1.9%	-	-	-	6 1.1%	
DYSPNOEA	4 1.2%	-	1 3.0%	1 4.8%	6 1.1%	
RENAL FAILURE NOS	6 1.9%	-	-	-	6 1.1%	
ANAEMIA NOS	5 1.5%	-	-	-	5 0.9%	
ABDOMINAL PAIN NOS	4 1.2%	-	-	-	4 0.7%	
BRONCHITIS NOS	4 1.2%	-	-	-	4 0.7%	
MYOCARDIAL INFARCTION	2 0.6%	1 0.5%	-	1 4.8%	4 0.7%	
ANGINA PECTORIS	3 0.9%	-	-	-	3 0.5%	
ANGINA UNSTABLE	3 0.9%	-	-	-	3 0.5%	
DIABETES MELLITUS NOS	3 0.9%	-	-	-	3 0.5%	
GASTROENTERITIS NOS	2 0.6%	-	1 3.0%	-	3 0.5%	
HEPATIC FUNCTION ABNORMAL NOS	3 0.9%	-	-	-	3 0.5%	
PYREXIA	3 0.9%	-	-	-	3 0.5%	
SYNCOPE	3 0.9%	-	-	-	3 0.5%	

Note: only treatment-emergent SAEs are included.

: NOS = not otherwise specified; PAH = pulmonary arterial hypertension; pts = patients; SAE = serious adverse event;

Overall, 16.8% of bosentan patients reported at least 1 serious event. For the indication with the largest number of patients (with 323 patients), 27.2% reported at least one event.

The most commonly reported serious events were atrial fibrillation, pneumonia, cardiac failure, and cerebrovascular accident. Renal failure was reported by 1.1%, anemia 0.9%, abdominal pain by 0.7%, and abnormal hepatic function 0.5% of the total bosentan population.

4.2 All placebo controlled trials

There were 7 placebo controlled studies with a total of 219 placebo patients and 533 bosentan patients. Serious adverse events reported by at least 2 bosentan patients are shown below.

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Appendix 83 Summary of serious adverse events (including unrelated) in placebo-controlled studies by frequency

Produced by sturlor on 23OCT00
Ro 47-0203, Protocols: AC-52351 BC-15064(II) BD-14884 NC-15018 NC-15020 NC-15462 NN-15031
Table T21f: Summary of serious 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	35	16.0%	64	12.0%
Total number of AEs	63		95	
RENAL FAILURE NOS	3	1.4%	4	0.8%
CARDIAC FAILURE NOS	2	0.9%	4	0.8%
ATRIAL FIBRILLATION	1	0.5%	4	0.8%
DYSPNOEA	1	0.5%	4	0.8%
PNEUMONIA NOS	-		4	0.8%
CHEST PAIN NEC	3	1.4%	3	0.6%
GASTROENTERITIS NOS	1	0.5%	3	0.6%
MYOCARDIAL INFARCTION	1	0.5%	3	0.6%
HEPATIC FUNCTION ABNORMAL NOS	-		3	0.6%
CEREBROVASCULAR ACCIDENT	4	1.8%	2	0.4%
ANGINA UNSTABLE	1	0.5%	2	0.4%
SYNCOPE	1	0.5%	2	0.4%
ABDOMINAL PAIN NOS	-		2	0.4%
BRONCHITIS NOS	-		2	0.4%
HYPERGLYCAEMIA NOS	-		2	0.4%
HYPERKALAEMIA	-		2	0.4%
PYREXIA	-		2	0.4%

More serious events were reported for the placebo patients (16%) compared to the bosentan patients (12%). The incidence rate for reporting serious hepatic function, in this table, is 0.6% for the bosentan patients compared to 0 for the placebo patients. However, there were many more bosentan patients with abnormal hepatic function than the 3 reported here (see section 6). Also, anemia, sometimes requiring transfusions, were reported but not classified as a serious event (see section 7.0).

4.3 Serious events by dose

Most events were reported for patients on the higher doses, in part because most study patients were taking least 1000 mg daily.

There were 54 patients (17.4%) who received bosentan 1000-1500mg daily and reported at least 1 event compared to 31 placebo patients (16.8%). Events reported by at least 3 bosentan patients included renal failure (4 reports), pneumonia (4 reports), atrial fibrillation (3 reports), and abnormal hepatic function (3 reports).

There were 8 patients (7.8%) who received bosentan 2000 mg daily and reported at least 1 event compared to 3 patients (4.1%) who received placebo. Events reported by at least 2 patients included cardiac failure (3 reports) and dyspnea (2 reports). There were no reports of abnormal hepatic function with this bosentan dose.

4.3.1 REACH--Protocol NC15462B

This was a large placebo controlled trial with [redacted] patients. There were 370 patients randomized to placebo, bosentan fast titration to 500 mg bid or slow titration to 500 mg bid. Patients were followed for 26 weeks. The table below briefly discusses events reported by bosentan patients

Patient no.	Adverse event
18102/6162	Abdominal pain, elevated LFTs, diagnosis of cholelithiasis, torsades de pointe (discussed in section 6.0)
18106/6072	Abnormal hepatic function (discussed in section 6.0)
18108/6003	Postural changes on day 7, 3 episodes of syncope day 42 with SBP 68 mmHg. Received pacemaker day 48.
18120/2051	Vomiting, watery stools, syncope day 169
18122/2001	Pyrexia, elevated LFTs (discussed in section 6.0)
18127/8085	Duodenal ulcer and transfusion
18136/8143	Severe abdominal pain with diarrhea possible resulting from gastroenteritis
18141/6263	Severe abdominal pain with metastatic carcinoma
18149/6374	Fever, malaise, and elevated LFTs (discussed in section 6.0)
18166/6473	Severe abdominal pain, diaphragmatic hernia, worsening heart failure
18197/9006	Severe elevation of LFTs and mild dermatitis (discussed in section 6.0)
18197/9007	Decreased hemoglobin requiring transfusion (discussed in section 7.0)
18199/9071	Anemia requiring transfusion (discussed in section 7.0)
18207/4031	Flushing, lightheadedness, palpitations, tremor day 15
18219/3020	Asthenia, diarrhea, fever, elevated LFTs, hepatomegaly (discussed in section 6.0)
18229/3081	Syncope

Reported serious 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 2 bosentan patients and b) reported more often by bosentan patients than placebo patients are shown below.

No. and (percent) of patients

	Placebo N=288	Bosentan N=677	Placebo subtracted (%)
Any event	51 (17.7)	92 (13.6)	-4.1
Pneumonia	1 (0.3)	6 (0.9)	0.6
Pyrexia	0	3 (0.4)	0.4
Abdominal pain	1 (0.3)	4 (0.6)	0.3
Pneumothorax	0	2 (0.3)	0.3
Intestinal obstruction	0	2 (0.3)	0.3
Myocardial infarction	1 (0.3)	4 (0.6)	0.3
Gastroenteritis	1 (0.3)	3 (0.4)	0.1
Abnormal hepatic function	1 (0.3)	3 (0.4)	0.1

from fax dated 6-01-01

Overall, there were more patients in the placebo group who reported serious adverse events. The events with the highest placebo subtracted incidence rates included pneumonia, abdominal pain and pyrexia, all less than 1%.

4.4 Safety update

4.4.1 PAH

a) ongoing, open label trial

There are 29 patients in the extension study AC-052-351. Two serious adverse events have been reported:

Patient 10202 reported cramping abdominal pain and fever and was hospitalized on day 190. She also had new onset atrial fibrillation. Laboratory values were reported to be within normal limits except prothrombin time (elevated but INR was low). Patient was taking warfarin.

b) ongoing, blinded trial

A total of 214 patients have been randomized to bosentan 62.5mg to 250 mg bid or placebo. At the time of the safety update, there were 16 reports of serious adverse events: bronchitis (2), intestinal obstruction, renal failure, syndrome of malaise (with fever, chills, and elevated LFTs),worsening pulmonary hypertension leading to death, anemia needing transfusion, hyperkalemia, abdominal pain thought to be attributed to diverticulitis, hypokalemia, abdominal pain and diarrhea, atrial fibrillation/flutter, vomiting and abdominal pain with normal liver and renal function, gall bladder disease and abdominal pain, abdominal distension of unknown etiology, hypotension and bradycardia.

4.4.2 ___

a) ongoing open label (NC 15464)

There are 27 ongoing patients out of 86 enrolled. The dose in this long term, open label study is 125 mg bid.

There were 41 patients with reports of serious adverse events at the time of the ISS cut off date (n=86). The events are listed below:

Acute bronchitis, CVA
CVA, death
Unstable angina
Atrial fibrillation, ventricular fibrillation, respiratory failure, death
Right ventricular failure
Pneumonia, cardiac failure (x2), atrial fibrillation
Atrial fibrillation, diabetes mellitus
Head trauma, subdural hematoma
Abdominal pain, jaundice (20060/00841, discussed in section 6.0)
Septicemia
Abdominal angiogram for aneurysm
Thyroidectomy
Chest pain (x5), anemia requiring transfusion, death (discussed in section 7.0)
Renal failure, death
CVA, death
Metastatic melanoma, anemia requiring transfusion
Cataract extraction, foot ulcer, amputation, wound infection,
COPD, death
Loin pain, angina, pneumonia, renal failure, cardiac failure, death
Hemorrhage, anemia requiring transfusion, hematuria after bladder surgery, abdominal pain, urinary retention, pnemonia, death (see section 7.0)

Skin carcinoma
Anemia, cardiac failure, ventricular tachycardia
Chest pain, dyspnea, pulmonary edema, atrial fibrillation, anemia requiring transfusion
Unstable angina
Cellulitis, muscle weakness, pneumonia
Pyrexia, dehydration, hypotension, chest pain, abdominal pain with laparoscopic cholecystectomy, fever, chills, pneumonia
Arthralgia, death resulting from worsening heart failure, metastatic carcinoma
Shortness of breath, weakness, chills, worsening heart failure, cellulitis
Epigastric abdominal pain, urinary retention, fecal impaction
Chest pain, shortness of breath, hypovolemia, acute MI, death
Fever, dyspnea, bronchitis, worsening heart failure, hypotension
Hematoma, anemia requiring transfusion, elbow pain (see section 7.0)
Cardiac arrest, death
Heat stroke, dizziness, syncope, hypoglycemia
Bilateral leg pain with lumbar laminectomy
Diabetes, gangrene requiring saphenous vein bypass
Pulmonary tumor, survived sudden death, bronchospasm, acute pulmonary edema, anemia, death
Epistaxis, ventricular tachycardia

There were 4 additional serious adverse events (and 2 were not reported previous). The 4 new ones include vomiting and palpitations, cardiac arrest and death, dental extraction, infection in pacemaker pouch and thyroid carcinoma.

The 2 additional reports include peripheral edema requiring hospitalization and cardiac failure followed by sudden death.

b) ongoing, double blind (ENABLE trials)
The bosentan doses used in these trials are 62.5 mg with titration to 125 mg bid.

There have been a total of 336 patients reporting a serious adverse event at the time of the safety update. The events reported by at least 5 of the patients are shown below.

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Appendix 6 Summary of the most frequent (≥ 0.5%) serious adverse events (ENABLE studies, all events)

Table T07 / 07MAR01

Body system / Adverse event N=1613	No random code No.	%
ALL BODY SYSTEM		
Total pts with at least one AE	474	29.4%
Total number of AEs	924	
CARDIAC FAILURE NOS	79	4.9%
CHEST PAIN NEC	52	3.2%
PNEUMONIA NOS	48	3.0%
CEREBROVASCULAR ACCIDENT NOS	31	1.9%
RENAL FAILURE NOS	31	1.9%
ANGINA UNSTABLE	26	1.6%
SYNCOPE	22	1.4%
ABDOMINAL PAIN NOS	17	1.1%
ANAEMIA NOS	16	1.0%
DEHYDRATION	16	1.0%
DYSPNOEA NOS	16	1.0%
CORONARY ARTERY DISEASE NOS	13	0.8%
MYOCARDIAL INFARCTION	13	0.8%
ANGINA PECTORIS	12	0.7%
PULMONARY OEDEMA NOS	10	0.6%
SUDDEN DEATH UNEXPLAINED	10	0.6%
CHRONIC OBSTRUCTIVE AIRWAYS DISEASE	9	0.6%
DIGOXIN TOXICITY	9	0.6%
HYPERKALAEMIA	9	0.6%
HYPOTENSION NOS	9	0.6%
WEAKNESS	9	0.6%
GASTROINTESTINAL HAEMORRHAGE NOS	8	0.5%
VENTRICULAR TACHYCARDIA	8	0.5%
BRADYCARDIA NOS	7	0.4%
DEATH NOS	7	0.4%
SEPSIS NOS	7	0.4%
CELLULITIS	6	0.4%
COLLAPSE	6	0.4%
LOWER RESPIRATORY TRACT INFECTION NOS	6	0.4%
UNKNOWN	6	0.4%
ATRIAL FIBRILLATION	5	0.3%
BACK PAIN	5	0.3%
BRONCHITIS NOS	5	0.3%
CARDIAC ARREST	5	0.3%
CARDIO-RESPIRATORY ARREST	5	0.3%
CORONARY ARTERY SURGERY	5	0.3%
DIZZINESS (EXC VERTIGO)	5	0.3%
HAEMATURIA	5	0.3%
PLEURAL EFFUSION	5	0.3%
PYREXIA	5	0.3%
VOMITING NOS	5	0.3%

A total of 474 patients (29.4%) reported a serious adverse event thus far. There are 21 reports of abdominal pain (including 4 upper abdominal pain), 16 reports of serious anemia and 4 reports of serious LFT elevations in this table. Study drug assignment remains blinded.

5.0 Premature withdrawals because of adverse events

All adverse events including laboratory and ECG abnormalities as well as clinical events leading to study discontinuation were reviewed.

5.1 All bosentan patients

Events leading to discontinuation in the 10 therapeutic studies (571 bosentan patients) for at least 3 patients are shown below.

Table 53 Summary of most frequent (≥ 3 patients) adverse events (including unrelated) leading to withdrawal in all bosentan-treated patients

Table T56 / 300CT00

Body system / Adverse event	Bosentan N=571 No.	%
ALL BODY SYSTEMS		
Total pts with at least one AE	81	14.2%
Total number of AEs	128	
HEPATIC FUNCTION ABNORMAL NOS	29	5.1%
HEADACHE NOS	9	1.6%
ANAEMIA NOS	6	1.1%
HYPOTENSION NOS	6	1.1%
CARDIAC FAILURE NOS	5	0.9%
NAUSEA	4	0.7%
DIARRHOEA NOS	3	0.5%
DYSPNOEA	3	0.5%
FATIGUE	3	0.5%
FLUSHING	3	0.5%
OEDEMA LOWER LIMB	3	0.5%
PYREXIA	3	0.5%
VOMITING NOS	3	0.5%

AE = adverse event; NOS = not otherwise specified; pts = patients.

This table includes patients listed in appendix 88

A total of 81 (14.2%) of the 571 bosentan patients withdrew for a safety reason. Abnormal hepatic function was the leading cause of these discontinuations (35.8%, 29/81), followed by headache (11.1%, 9/81), anemia (7.4%, 6/81), hypotension (7.4%, 6/81). Lower limb edema led to drop out in 3 patients.

In addition to the above list, reasons for study withdrawal reported by 2 bosentan patients were abdominal pain, CVA, face edema, MI.

The number of patients and subjects who withdrew for unclear reasons include #5 who did not return after 4.5 days receiving bosentan 125 mg bid. No adverse events were reported.

Descriptions of selected withdrawals for abdominal pain, fever, flushing, and edema are discussed below.

report 165230 Patient 16321/1305. 43 year old female withdrew for precordial sensations, not further discussed. Other events include flushing and gastritis. Narrative erroneously describes dropout because of flushing.
report 165230 Patient 16324/1424. 40 year old female reported periorbital edema reported on day 13 and then discontinued study. LFTs were increasing while hemoglobin was decreasing. She was treated with furosemide
report 165230 Patient 16325/1530. 59 year old male discontinued study drug on day 8 because of lower limb edema. A 3 pound weight gain was reported as was an increasing ALT.
report 165230 Patient 16339/1608. 70 year old male discontinued study drug because of "feeling strange," face edema, leg edema, headache, insomnia. He had strongly positive hematuria, his hemoglobin was dropping and eosinophil count was elevated.
report 165230 Patient 16818/1802. 56 year old male reported headache, pain in limbs, dysuria, decreased appetite, and hot flushes. LFTs were increased, as were eosinophils. RBCs in urine.
Report b165230 patient 16309/0308 70 year old female was discontinued because of myocardial

infarction. Also reported leg swelling. LFTs were increasing and hemoglobin was decreasing
Report b165231 patient 16945/1003 68 year old reported severe headache, nausea, fatigue about 4 hours after the first dose of study drug. He discontinued study drug.
Report b165231 patient 16945/1004. 70 year old male reported headache about 2 hours after the first dose. He was discontinued from study drug. In the follow up he reported nausea, fatigue, coughing up blood and body aches.
Report b166849 patient 18209/4082 76 year old male discontinued study drug on day 14 because of diarrhea, vomiting, fatigue, leg edema, cough, and insomnia.
Report b166849 patient 18106/6474 64 year old male discontinued study drug on day 53 because of diarrhea, nausea, vomiting that had started on day 15.
Report b166849 patient 18134/
Report 166849 patient 18223/3032. 76 year old female patient discontinued study medication ~~because of a serious hypotensive episode at home. Her blood pressure was 65/40 mmHg at the clinic~~ and she was treated with iv fluids.
Report 18223/3036 71 year old patient reported worsening of his gastritis with persistent itching. He had no post baseline laboratory values.
Study NC15464 patient 20045/00323. 65 year old female with CAD was hospitalized for ventricular fibrillation. "Patient was slow to respond to resuscitation efforts" and drug was discontinued. She died 4 months later from respiratory failure.
Study NC15464 patient 20251/01262. 69 year old male with CAD reported 2 episodes of light headedness, hypotension, leg muscle fatigue, and chest tightness. He withdrew from study for groin pain.
Report 166849 patient 18120/2051. 44 year old male experienced several episodes of vomiting and watery stool with syncope. He could not tolerate oral fluids and had a presyncopal episode. He recovered with iv fluids.

5.2 All placebo controlled trials

There are 7 placebo controlled studies with a total of 219 placebo patients and 533 bosentan patients. Serious adverse events reported by at least 2 bosentan patients are shown below.

Appendix 94 Summary of adverse events (including unrelated) leading to withdrawal in placebo-controlled studies by frequency

Produced by sturlor on 30OCT00
Ro 47-0203, Protocols: AC-52351 BC-15064(II) BD-14884 NC-15018 NC-15020 NC-15462 NN-15031
Table TS1f: Summary of adverse events (including unrelated) leading to withdrawal 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	22	10.0%	66	12.4%
Total number of AEs	31		109	
HEPATIC FUNCTION ABNORMAL NOS	2	0.9%	25	4.7%
HEADACHE NOS	2	0.9%	8	1.5%
ANAEMIA NOS	-		5	0.9%
HYPOTENSION NOS	-		5	0.9%
CARDIAC FAILURE NOS	-		4	0.8%
FATIGUE	2	0.9%	3	0.6%
NAUSEA	2	0.9%	3	0.6%
DIARRHOEA NOS	-		3	0.6%
DYSPNOEA	-		3	0.6%
FLUSHING	-		3	0.6%
OEDEMA LOWER LIMB	-		3	0.6%
PYREXIA	-		3	0.6%
VOMITING NOS	-		3	0.6%
ABDOMINAL PAIN NOS	-		2	0.4%
FACE OEDEMA	-		2	0.4%
MYOCARDIAL INFARCTION	-		2	0.4%

The incidence of withdrawal for adverse events was higher in bosentan patients (12.4%) compared to placebo patients (10.0%). The leading reason for withdrawal, abnormal hepatic function, was reported by 4.7% of the bosentan patients compared to 0.9% of placebo patients. Other events reported by at least 4 bosentan patients and occurring more often in these patients than in the placebo group included headache (1.5% versus 0.9%), followed by anemia (0.9% versus 0), and hypotension (0.9% versus 0).

Premature withdrawals with addition of AC-052-352

The reasons for withdrawal (limited to reasons given by 2 or more bosentan patients) are shown below by treatment group.

Produced by sturlor on 17MAY01
Ro 47-0203, Protocols: AC-52351 AC-52352 NC-15064(II) BD-14884 NC-15018 NC-15020 NC-15462 NN-15031
Table T51f: Summary of adverse events (including unrelated) leading to withdrawal by frequency
Population: Safety

Body system / Adverse event	Placebo N=288 No.	%	Bosentan N=677 No.	%
ALL BODY SYSTEMS				
Total pts with at least one AE	27	9.4%	75	11.1%
Total number of AEs	30		121	
HEPATIC FUNCTION ABNORMAL NOS	2	0.7%	28	4.1%
HEADACHE NOS	2	0.7%	8	1.2%
CARDIAC FAILURE NOS	1	0.3%	6	0.9%
ANAEMIA NOS	-		5	0.7%
HYPOTENSION NOS	-		5	0.7%
FATIGUE	2	0.7%	3	0.4%
NAUSEA	2	0.7%	3	0.4%
DIARRHOEA NOS	-		3	0.4%
DYSPNOEA NOS	-		3	0.4%
FLUSHING	-		3	0.4%
OEDEMA LOWER LIMB	-		3	0.4%
PYREXIA	-		3	0.4%
VOMITING NOS	-		3	0.4%
PULMONARY HYPERTENSION NOS AGGRAVATED	6	2.1%	2	0.3%
ABDOMINAL PAIN NOS	-		2	0.3%
FACE OEDEMA	-		2	0.3%
MYOCARDIAL INFARCTION	-		2	0.3%

from fax dated 6-01-01

There was a higher rate of withdrawal for the bosentan group (11.1%) compared to placebo (9.4%). The most common reason in the bosentan group (placebo subtracted) was abnormal hepatic function (3.4%). Events leading to withdrawal but reported only in bosentan group include anemia, hypotension, diarrhea, dyspnea, flushing, lower limb edema, pyrexia, vomiting, abdominal pain, face edema, and myocardial infarction.

5.2.1 REACH--Protocol NC15462B

Discontinuations because of increased LFTs or anemia reported for this large trial are shown below:

Number and (percent) of patients

	Placebo N=126	Total bosentan 500 mg bid N=244
Any event	13^ (8.7)	52+ (21.3)
Increased LFTs	1 (0.8)	32 (13.1)
Anemia	0	4 (1.6)

^includes 2 who dropped out for liver enzyme increase
+includes 7 bosentan patients who dropped out for an adverse event but were recorded as refusal to continue, and 16 who dropped out for adverse event including cardiac transplantation (3) and liver enzyme increase (6).
Table 21 vol 40.

5.3 Safety update

5.3.1 PAH

a) ongoing, open label trial
There are 29 patients in the extension study AC-052-351. One patient (10503) was discontinued from study drug on day 105 because of worsening pulmonary hypertension.

b) ongoing, blinded trial (AC-052-352)
A total of 214 patients have been randomized to bosentan 62.5mg-250 mg bid or placebo. There have been 4 discontinuations, all attributed to worsening of the patient's underlying condition.

5.3.2

a) ongoing open label
There are 27 ongoing patients with a total of 5 being discontinued prematurely from study drug. The 4 drop outs not previous discussed include 3 who refused to continue and 1 who withdrew for an unknown reason.

6.0 Liver toxicity

Bosentan provokes elevation of LFTs, primarily ALT and AST (ALT was reported up to 3000 U/L), including reports of positive rechallenge. There are few reports of patients with elevated bilirubin as well as two reports of jaundice[9]. Some of the patients with elevated LFTs are also reporting symptoms such as nausea, vomiting, abdominal pain, flu like syndrome.

6.1 All bosentan patients

The number and percent of patients in 3 categories of ALT and/or AST elevation (greater than 3 times but less than 5 times upper limit of normal[10], greater than 5 times but less than 8 times upper limit of normal, and greater than 8 times upper limit of normal) for all patients who took bosentan and had post baseline laboratory data (n=550) are shown below.

Number and (percent) of bosentan patients

	>x 3 but <x 5	> x 5 but <x 8	>x 8	total
ALT (n=550)	19 (3.5)	15 (2.7)	22 (4.0)	56 (10.2)
AST (549)	18 (3.3)	5 (0.9)	10 (1.8)	33 (6.0)
ALT and/or AST (n=550)	19 (3.5)	15 (2.7)	22 (4.0)	56 (10.2)

corrected fax dated 3-13-01

A total of 56 (10.2%) of all bosentan patients had LFT abnormalities; 22 (39%) of these patients had values greater than 8 times upper limit of normal. The most extreme ALT value reported was 2838 U/L (an increase of 73 times the baseline value of 39 U/l, patient 18164/6331).

Abnormal LFTs with addition of AC 052 352

The number and percent of patients with abnormal LFTs by category are shown below for patients with baseline and post baseline data including study AC 052 352.

Number and (percent) of patients

	>x 3 but <x 5	> x 5 but <x 8	>x 8	total
ALT (n=693)	28 (4.0)	18 (2.6)	29 (4.2)	75 (10.8)
AST (692)	27 (3.9)	6 (0.9)	15 (2.2)	48 (6.9)
ALT and/or AST (n=693)	29 (4.2)	18 (2.6)	29 (4.2)	76 (11.0)

Fax dated 6-26-01

The incidence rates for abnormal LFTs were roughly the same with the addition of the second PAH study even though the doses of bosentan were somewhat lower in this study than doses used in the entire clinical program.

The incidences of marked laboratory abnormalities (above 50 U/L for ALT, 60 U/L for AST, and 34.2 umol/l for bilirubin plus increase of 50% from baseline) in all bosentan patients are shown below.

[9] patient 110 10037 in study AC 052 352 (see summary of efficacy) and 20060 0084 in study RO15464

[10] Upper limits of normal for ALT and AST were 30 U/l and 25 U/l, respectively.

Appendix 56 Incidence of marked laboratory abnormalities in all bosentan-treated patients

Produced by sturlor on 23OCT00

Ro 47-0203, Protocols: AC-52351 AC-52353 BC-15064(I) BC-15064(II) HD-14884 MC-15018 MC-15020 MC-15462 MC-15464 MN-15031

Table T44: Incidence of marked laboratory abnormalities
Population: Safety

All studies of oral Bosentan (including Open Label)

		Bosentan N=571 No.	%
CLINICAL CHEMISTRY			
ALT	HH	77 /550	14.0%
AST	HH	53 /549	9.7%
Bilirubin	HH	3 /551	0.5%
Alkaline Phosphat.	HH	13 /551	2.4%
Albumin	HH	0 /488	
	LL	2 /488	0.4%
Creatinine	HH	5 /537	0.9%
Chloride	HH	1 /261	0.4%
	LL	0 /261	
Sodium	HH	2 /536	0.4%
	LL	4 /536	0.7%
Cholest. Total	HH	0 /167	
Potassium	HH	3 /533	0.6%
	LL	2 /533	0.4%
Gamma GT	HH	66 /449	14.7%
Glucose	HH	18 /527	3.4%
	LL	0 /527	
Phosphate	HH	2 /242	0.8%
	LL	7 /242	2.9%
Protein Total	HH	0 /242	
	LL	0 /242	
Blood urea	HH	22 /534	4.1%
Uric Acid	HH	0 /242	
URINE			
Urine Protein	HH	11 /471	2.3%
Urine Blood	HH	17 /495	3.4%

(Pag 1/1)

ALT and GGT were markedly increased in 14% and 14.7 % of patients, respectively; AST and alk phos were increased in 9.7% and 2.4% of patients, respectively; bilirubin was high in 0.5%.

6.2 Placebo controlled trials

6.2.1 Mean changes

Mean changes from baseline for ALT in the placebo controlled trials are shown below by treatment group.

Produced by stuclac on 07MAR01
Bo 47-0003, Protocols: AC-52351 BC-15064(II) Mo-14904 MC-15018 MC-15020 MC-15462 MM-15031
Table T45f_1: Change from baseline to study end in laboratory parameters
Population: Safety

CLINICAL CHEMISTRY - ALT (U/l)

	Placebo N=219	Bosentan N=533
Baseline		
n	209	501
Mean	19	20
SD	10	11
Stderr	1	0
Median	17	17
Q1 , Q3	12 , 22	12 , 25
Min , Max		
Study end		
n	209	501
Mean	21	34
SD	25	61
Stderr	2	3
Median	16	19
Q1 , Q3	12 , 23	13 , 28
Min , Max		
Change		
n	209	501
Mean	2	14
SD	21	60
Stderr	1	3
Median	0	1
Q1 , Q3	-3 , 3	-5 , 7
Min , Max		

Study end value is last valid value after baseline up to and including the day after end of randomized treatment
(Pag 10/27)

The group who took bosentan had a mean increase in ALT of 14 U/l from baseline (70%, 14/20) compared to placebo that had a 2 U/l increase (10.5%, 2/19). The increases for AST were less striking (37.5%, 6/16 for bosentan and 6.7%, 1/15 for placebo). This table shows mean changes in bilirubin and alk phos as being unremarkable.

6.2.2 Markedly abnormal values (see appendix)

Incidence rates for markedly abnormal clinical chemistry values are shown below, by treatment groups.

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

Table T44f / 23OCT00

		Placebo N=219		Bosentan N=533	
		No.	%	No.	%
CLINICAL CHEMISTRY					
ALT	HH	8 /212	3.8%	71 /514	13.8%
AST	HH	7 /212	3.3%	48 /513	9.4%
Bilirubin	HH	5 /212	2.4%	2 /515	0.4%
Alkaline Phosphat.	HH	4 /212	1.9%	10 /515	1.9%
Albumin	HH	0 /197		0 /477	
	LL	3 /197	1.5%	2 /477	0.4%
Creatinine	HH	4 /209	1.9%	3 /502	0.6%
Chloride	HH	0 / 76		1 /255	0.4%
	LL	2 / 76	2.6%	0 /255	
Sodium	HH	0 /207		2 /501	0.4%
	LL	2 /207	1.0%	3 /501	0.6%
Cholest. Total	HH	0 / 44		0 /167	
Potassium	HH	0 /206		2 /498	0.4%
	LL	4 /206	1.9%	2 /498	0.4%
Gamma GT	HH	15 /172	8.7%	56 /426	13.1%
Glucose	HH	12 /204	5.9%	11 /493	2.2%
	LL	1 /204	0.5%	0 /493	
Phosphate	HH	0 / 68		1 /236	0.4%
	LL	0 / 68		5 /236	2.1%
Protein Total	HH	0 / 68		0 /236	
	LL	1 / 68	1.5%	0 /236	
Blood urea	HH	12 /207	5.8%	16 /499	3.2%
Uric Acid	HH	1 / 68	1.5%	0 /236	
URINE					
Urine Protein	HH	6 /183	3.3%	8 /444	1.8%
Urine Blood	HH	13 /192	6.8%	15 /468	3.2%

ALT = alanine aminotransferase; AST = aspartate aminotransferase; GT = glutamyl transferase.

The placebo subtracted incidence rate of marked ALT, AST, GGT elevations (HH defined as a 50 % increase from the baseline value and above range) in the bosentan group were 10%, 6.1%, and 4.4%, respectively. Remarkable differences between drug and placebo were not seen for bilirubin or alkaline phosphatase.

Bosentan was similar to placebo for the other chemistry values.

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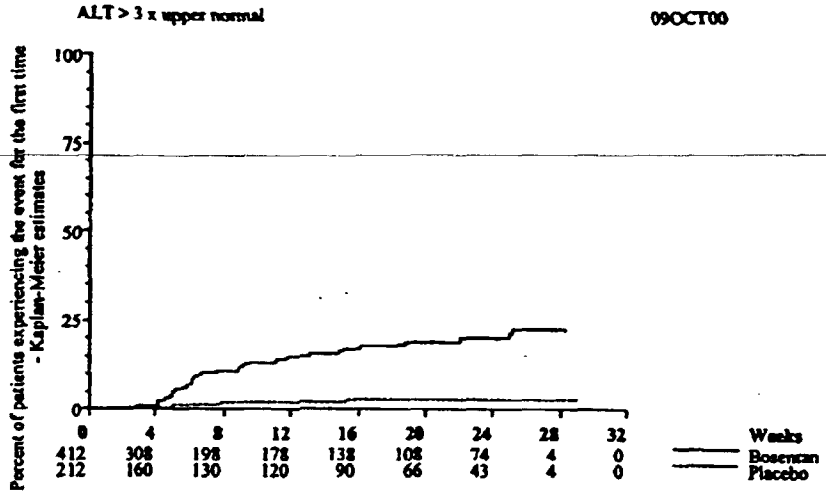
Time of occurrence of liver abnormalities (ALT > 3xULN) is shown in the figure below. There were 412 bosentan patients (figure does not include 102 patients who received 2000 mg/day and 19 patients with no post baseline data) and 212 placebo patients included in the figure at time 0.

Figure 13 Kaplan-Meier estimate of time to first appearance of ALT > 3 x ULN



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

Abnormal ALT started being reported about 4 weeks after start of bosentan treatment. By week 12, roughly 15% of patients who were still on drug were reporting abnormalities and by week 28, nearly 25% of patients had abnormalities. The effect does not level off: the longer patients are treated with the bosentan, the greater is the chance that they will develop high LFTs. The crude incidence rate of ALT elevation was 11.4% when the high dose is excluded and 10.5% when the high dose is included (fax March 6, 2001).

6.2.3 Dose

Of the bosentan patients who withdrew for abnormal hepatic function or anemia, 24/25 were receiving 1000-1500 mg/d; all 5 withdrawals for anemia occurred in this dose group as well. This was the dose range that was received by the majority (58.2%, 310/533) of bosentan patients who participated in placebo controlled trials. Only 19.3% (103/533) received the higher doses (2000 mg). Elevated LFTs occurs at low as well as high bosentan doses.

The number of occurrences of high ALT values by time in study and dose is shown below.

Incidence (%) of patients with high ALT (3xULN)

	100 mg		250-500 mg		1000-1500 mg		2000 mg		ALL doses	
WKS	B n=48	P n=47	B n=67	P n=58	B N=297	P n=179	B n=102	P n=69	B n=514	P n=212
2-12	2.1	0	4.3	0	9.5	1.8	6.9	0	6.2	1.3
>12	-	-	4.8	0	15.8	2.4	-	-	14.9	2.2
ALL wks	2.1	0	4.5	0	14.5	2.2	6.9	0	10.5	1.9

n=total number of patients who received the dose and had labs measured
Appendix 62

Overall, the higher the dose and the longer a patient takes any dose, the higher the risk of having an elevated ALT.

Percent of patients with ALT or AST > 3ULN with addition of AC-052-352
Percents of bosentan patients (placebo subtracted) who had elevated ALT or AST when the recently completed PAH study is included are shown below by dose and study duration.

Percent of patients (placebo subtracted)

Duration of Rx	100 mg^	250-500 mg+	1000-1500 mg^^	2000 mg++	All doses combined!
2-12 weeks	0	2.2	5.9	5.4	3.6
>12 weeks	-	12.7	13.4	-	13.1

^n=48 bosentan, n=47 placebo
+2-12 wks n=46 bosentan, n=47 placebo; >12 wks n=165 bosentan, n=79 placebo
^^2-12 wks n=63 bosentan, n=55 placebo; >12 wks n=234 bosentan, n=124 placebo
++2-12 wks n=102 bosentan, n=69 placebo;
from fax dated 6-04-01
! +2-12 wks n=259 bosentan, n=77 placebo; >12 wks n=399 bosentan, n=203 placebo

The longer the patients are on bosentan the greater the risk that they will have an abnormal ALT or AST.

Percent of patients with Abnormal LFT reported as an AE, with addition of AC-052-352

Percents of bosentan patients (placebo subtracted) who reported an abnormal LFT when the recently completed PAH study is included are shown below by dose and study duration.

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	0	1.5	0	0.7
>12 weeks	-	6.0	6.7	-	6.4

^n=50 bosentan, n=49 placebo
+2-12 wks n=49 bosentan, n=49 placebo; >12 wks n=165 bosentan, n=80 placebo
^^2-12 wks n=66 bosentan, n=58 placebo; >12 wks n=244 bosentan, n=126 placebo
++2-12 wks n=103 bosentan, n=73 placebo;
! 2-12 wks n=268 bosentan, n=82 placebo; >12 wks n=409 bosentan, n=206 placebo
from fax dated 6-04-01

Approximately 6% of patients in a study with bosentan given for >12 weeks reported an abnormal LFT as an adverse event.

Associated symptoms
There were 29 bosentan patients (5.1%) who reported abdominal complaints including abdominal pain, abdominal cramps, abdominal distention, and/or abdominal discomfort. Of these, 14 had a ALT value that was at least 15% above baseline value and 13 had low hemoglobin value. There were 8 patients with abdominal complaints and both high ALT and low hemoglobin values (from database).

6.3 Individual cases of abnormal hepatic function

The patients listed below are some of the bosentan patients who had liver enzyme elevations and/or bilirubin elevations. Many, but not all, had at least 1 report of a adverse event, sometimes serious, and many, but not all, were discontinued for an adverse event, usually, but not necessarily, suggestive of liver abnormality and/or elevated LFTs. Upper limit of normal (ULN) was 60 U/l for ALT and 50 U/L for AST for the purposes of this review.

Jaundice, vomiting, edema. Died from end stage cardiac failure.	Patient 110 10037 (study 352) 43 year old white female with pulmonary hypertension (class IV) systemic sclerosis gastro-esophageal reflux disease, calcinosis, Raynaud's syndrome, sclerodactyly and telangiectasis and concomitant medication including digoxin, furosemide, omeprazole, metolazone, spironolactone, thyroid, hydrocodone, phenyltoloxamine, guafenesin, metoclopramide, triamcinolone, warfarin, and azithromycin. During the course of the study, the patient experienced vomiting, dehydration, edema, respiratory tract infection, alopecia, drying of mucus membranes, and jaundice. On day 127, the patient's pulmonary hypertension worsened (indicated by a decrease in walking performance) and the patient was treated with i.v. epoprostenol. The study medication was permanently discontinued on day 147 due to worsening of the condition. Highest bilirubin 64.3 umol/l; baseline was elevated (26.1 umol/l). ALT and AST remained within normal limits but alk phos was elevated (120 U/L). After bosentan was discontinued, bilirubin remained elevated. She was started on epoprostenol but continued to deteriorate, was hospitalized with multiorgan failure secondary to endstate cardiac failure, and died on day 36 of open label bosentan. (fax dated 6-21-2001)
Jaundice,	Patient 20060/00841 bosentan 125 mg bid. A 81-year old male with ischemic heart disease

vomiting and abdominal pain, anemia, increased LFTs, study drug withdrawal	and CHF NYHA class IV, previous MI, COPD, previous episode of epigastric pain and flatulence with raised liver enzymes and impaired renal function tests, and anemia and concomitant medications including furosemide, perindopril, digoxin, warfarin, acetylsalicylic acid, ISMN, salbutamol, ipratropium, gliclazide and ferrous sulphate was hospitalized on day 559 with one-week history of persistent vomiting, lower abdominal pain and weight loss. He was jaundiced, his abdomen was bloated and tender over the epigastrium with a palpable mass, and his urine was dark. Highest ALT 392 U/L and bilirubin 91 umol/l (normal bilirubin range 3-15 umol/l). Pleural effusion was observed. Biopsies of the gastric mucosa demonstrated chemical (reactive) gastritis. Questionable evidence of pancreatitis, inflammatory gall bladder or cholelithiasis were found. Bosentan was stopped 9 days after the start of the symptoms. Approximately 2 months later he was improved but with jaundice and an enlarged liver that was tender on palpation[11]. Laboratory values were normal except for total bilirubin (21 umol/l). Patient was reported to be doing well about 8 months later. The sponsor states that there was an episode of elevated ALT and alk phos with epigastric pain 1 year prior to study (fax dated 6-21-2001).
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 mg/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. Study drug discontinued	Patient 18140/6251 bosentan 125-250-500 mg bid. This 51 year old male patient had increased LFTs. Highest ALT: 457 U/L, AST: 255 U/L. Dose of study drug was decreased to 250 mg bid on day 115, and LFTs continued to rise. Study drug was discontinued on day 120 and within 72 days (sponsor states 35 days), LFTs were normal. Reported hypotension and cardiac failure.
Elevated LFTs with diarrhea, abdominal pain. Study drug discontinued	Patient 18134/8174 bosentan 125-250-500 mg bid. This 82 year old white female patient with coronary artery disease, NYHA class IV, ejection fraction 20%, with a history of angina pectoris, pacemaker insertion, polymyalgia rheumatica, and osteoporosis, treated with enalapril, furosemide, digoxin, carvedilol, omeprazole, cortisone, paracetamol, dextropropoxyphene, isosorbide dinitrate, and pravastatin, experienced diarrhea from days 20 to 29. The study drug was temporarily stopped on day 25. Study treatment was re-started on day 33. On day 43, AST and ALT were elevated (80 U/l and 97 U/l, respectively). The study medication was again temporarily stopped on day 50. After re-starting the study drug on day 84, the patient reported abdominal pain of approx. 1 h duration following the second and third doses. The patient stated he was afraid of the study drug and requested to be taken off the study. The study drug was permanently discontinued on day 85 and AST and ALT eventually become normal. Other reported adverse events included dizziness and postural hypotension.
Elevated LFTs, anemia. Fatigue, headache, flu-like sympomts. Study drug	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

[11] Letter to Prof. Barker dated 12-2-99

discontinued ;death secondary to CHF.	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 LFTs, abdominal pain and angina. Study drug was stopped for admini-strative reasons.	Patient 18147/6523 Bosentan 250-500 mg bid. This 61-year-old white male with coronary artery disease, NYHA class IIIB, ejection fraction 34%, history of MI, coronary artery bypass surgery, coronary angioplasty, hypertension and ongoing hypercholesterolemia and diabetes, treated with captopril, metoprolol, digoxin, furosemide, pravastatin, glibenclamide (glyburide), acetylsalicylic acid and potassium chloride. Patient was discontinued on day 43 because of elevated liver enzymes (AST 321 U/l, ALT 406 U/l, GGT 595 U/l, alk phos 131 U/l, total bilirubin 1.7 mg/dl). Baseline values were normal except for elevated bilirubin (1.6 mg/dl). LFTs started to decrease after bosentan had been stopped. Six weeks later, on day 87, patient presented with mild right upper quadrant pain, rated as of non-cardiac origin. HIDA scan, sonogram and CT scan were performed, results unknown. LFTs were again elevated 49 days (day 92) after drug had been discontinued for administrative reasons (AST 172 U/l, ALT 396 U/l, GGT 413 U/l, alk phos 134 U/l and total bilirubin 1.7 mg/dl), but again normalized (except mild ALT and GGT) after two weeks without further intervention. Patient reported recurrent chest pain diagnosed as angina on day 127. Metoprolol dose was increased. LFTs were at or below baseline levels.
Elevated LFTs, study drug withdrawn. Reported flushing, headache, pain on limbs, coughing, dysuria, and decrease of appetite	Patient 16818/1802 bosentan 1000 mg bid. This 56-year-old male patient with hypertension, treated with fish skin oils showed markedly elevated values for LFTs by day 15 (highest recorded ALT: 265 U/L, AST 144 U/L). Baseline values were normal. Drug was discontinued on day 18. Patient reported flushing, headache, pain on limbs, coughing, dysuria, and decrease of appetite beginning day 9. Follow-up evaluations after study medication discontinuation showed all LFTs except GGT returned to baseline levels by 34 days.
Elevated LFTs, flushing edema, headache, dizziness	Patient 16317/0907 bosentan 1000 mg bid. This 47-year-old female patient with hypertension and a history of dyspepsia, treated with ranitidine, showed markedly elevated LFTs by day 29 (highest ALT: 200 U/l, AST: 112 U/L). Baseline values were normal. LFTs with the exception of GGT returned to baseline by 16 days after study drug was stopped. Reported adverse events included dizziness, leg and face edema, flushing, headache. Completed study.
Elevated LFTs.	Patient 16317/0905 bosentan 1000 mg bid. This 43-year-old female patient with hypertension and a history of hypercholsterolemia showed markedly elevated LFTs by day 15 (highest ALT: 239 U/l, AST: 203 U/L). Baseline ALT was slightly above normal (37 U/L). Study drug was discontinued on day 29. Evaluations during active treatment showed LFTs returned to baseline levels by day 29 except. GGT which returned to baseline within 7 days after drug was stopped. Completed study. Reported adverse event was headache.
Elevated LFTs, study drug withdrawal for administrativ e reasons. Reported cystitis, headache, renal	Patient 16315/0523 bosentan 1000 mg qd. This 37-year-old female patient with hypertension treated with medroxyprogesterone, showed markedly elevated values for LFTs by day 8 (highest ALT: 161U/l, AST 82 U/L). Baseline ALT was slightly high (55 U/L). Follow-up evaluation showed return to baseline levels by 2 weeks. Reported adverse events included cystitis, headache, renal calculus, abdominal pain. Study drug was discontinued for administrative reasons.

calculus, abdominal pain	
Elevated LFTs Reported headache and influenza	Patient 16312/0707 bosentan 1000 mg qd. This 53-year-old female patient with hypertension showed markedly elevated values for LFTs by day34 (highest ALT: 256 U/l), AST 170 U/L. Pretreatment values were normal. Completed study. There was persistent abnormality for ALT levels and partial return to baseline levels for AST within six days of drug discontinuation. Reported adverse events included headache and influenza.
Elevated LFTs. Reported nosebleed, influenza, and rash.	Patient 16309/0311 bosentan 100 mg qd. This 70-year-old female patient with hypertension and history of asthma, treated with salbutamol, beclomethazone showed markedly elevated values for LFTs on starting on day 14 (highest ALT 566 U/l, AST 242 U/l). Pretreatment values for LFTs were above normal (ALT 163 U/l). Completed study. LFTs were returning to baseline levels within 20 days. Reported adverse events included nosebleed, influenza, and rash.
Elevated LFTs. Reported abdominal pain and feeling strange.	Patient 16306/0235 bosentan 500 mg qd. This 50-year-old male patient with hypertension and a history of lactose intolerance showed markedly elevated LFTs starting on day 29. Pretreatment ALT and GGT values were above normal (99 U/l and 274 U/L, respectively). Highest ALT (860 U/L) and AST (480 U/l) on day 29. Completed study. LFTs returned to baseline levels within 43 days. Reported adverse events included abdominal pain and feeling strange.
Elevated LFTs. Abdominal pain , edema	Patient 16306/0216 bosentan 1000 mg bid. This 52-year-old female patient with hypertension and a history of unspecified menopausal and postmenopausal disorder and treated with vitamin B complex, multivitamin combination, and estradiol, showed markedly elevated values for LFTs starting on day 16 (highest ALT: 120 U/l). Pretreatment values for ALT, AST, GGT, and bilirubin were above the normal range. Completed study. Eosinophils were markedly elevated (2.2x 10^9/L). The patient complained of mild abdominal pain on day 33. Follow-up evaluations showed return to baseline levels within 32 days. Reported adverse events included chest pain, coughing, dyspnea, headache, edema, flushing, abdominal pain.
Elevated LFTs. Blurred vision, headache	Patient 16306/0207 bosentan 500 mg qd. This 47-year-old male patient with hypertension had markedly elevated LFTs by day 29 of treatment. (highest ALT: 600 U/l, AST 360 U/l) Baseline values for AST and ALT were normal. Completed study and follow-up evaluations showed a return to baseline levels within 28 days. Reported adverse events included blurred vision, headache, ocular disorder.
Elevated LFTs, study drug withdrawal	Patient 18106/6072 bosentan 125-250-500 mg bid. This 61-year-old white male with ischemic heart disease, NYHA class III, ejection fraction 10% and a history of peripheral and coronary artery disease, MI, coronary artery bypass surgery and diabetes, hyperlipidemia, esophageal reflux and pain in limb, treated with digoxin, metoprolol, metolazone, captopril, furosemide, omeprazole, lovastatin, insulin, acetylsalicylic acid and potassium chloride developed asymptomatic elevation of liver enzymes on day 41: ALT 155 U/l, AST 116 U/l, GGT 1039 U/l, alk phos 240 U/l. Study drug was permanently discontinued and LFTs returned to baseline values except AST (38 U/L) and GGT (168 U/L). Reported adverse events included lymphoma, constipation, anemia.
Elevated LFTs	18184/7074 This patient was reported as having an adverse event of elevated liver enzymes (reported as <3xULN). The dose of study drug was decreased by half. The enzymes had started to decrease while the patient was on drug. Study drug was stopped for administrative reasons and LFTs were normal less than a month later (fax dated 3-6-01)
Elevated LFTs, study drug withdrawal. Bronchitis, influenza	Patient 16945/1014 Bosentan 1000 mg bid. This 64-year-old female had elevated LFTs (ALT: 387 U/L, AST 159 U/L) starting day 29. Baseline values were normal.. She was withdrawn on day 76 and within 40 days values were normal except ALT (47 U/l). TSH was abnormally high on day 8. Reported adverse events included bronchitis and influenza.

Elevated LFTs, abdominal pain, surgery (cholelithiasis), positive rechallenge, study drug withdrawn. Report of tdp	Patient 18102/6162 Bosentan 125-250-500 mg bid. This 73-year-old white female with congestive (dilated) cardiomyopathy with heart failure NYHA class IIIB, ejection fraction 30%, and hypothyroidism, currently 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 torsade 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; 2 weeks later LFTs were reported as 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 returned to normal. Other reported adverse events included diarrhea, dizziness, cough
Elevated LFTs, study drug withdrawn	18119/2014 bosentan 125-250-500 mg bid. This 67-year-old male developed elevated LFTs on day 27. Highest ALT values 850 U/L, GGT 440 U/l, and AST 460 U/L and alk phos 871 U/l. Bilirubin was elevated but it was elevated at baseline as were alk phos and GGT.
Fever, chills, elevated LFTs, positive re-challenge, drug withdrawal	Patient 18122/2001 bosentan 125-250-500 mg bid. This was a 67-year-old white male with congestive (dilated) cardiomyopathy, NYHA class IIIB, ejection fraction 25% and a history of diabetes, stroke, coronary angioplasty, Parkinson's disease and healing gastric ulcer. Ongoing medications included quinapril, hydrochlorothiazide, digitoxin, furosemide, isosorbide dinitrate, molsidomine, phenprocoumon, memantin, glyburide, ranitidine, levodopa. The patient presented on day 63 with fever and chills and elevated ALT (118 U/l). He had been hospitalized previously (day 8 to day 39) because of pulmonary congestion, peripheral edema, and pneumonia and had been treated with ampicillin, ceftriaxone and imipenem. Highest ALT 820 U/l and AST 460 U/l. GGT, alk phos, total bilirubin, urea, and were elevated at baseline. Study medication was discontinued on day 27. ALT and AST normalized by day 56 and other values normalized in the following weeks. Study drug was restarted on day 63 (250 mg bosentan). Elevated ALT and fever were reported 8 hours after dosing. Study medication was permanently discontinued and LFTs became normal.
Elevated LFTs, drug withdrawal	Patient 18128/8122 (Bosentan 125-250-500 mg bid.). This 67-year-old male patient withdrew on day 65. Highest ALT: 174 U/L. Withdrew on day 65 and LFTs became normal. Reported adverse events included dizziness, cardiac failure, gout and eczema.
LFTs increased; study drug dis continued	Patient 18148/6363 bosentan 250--500 mg bid. This 48-year-old black female patient with CHF NYHA class IIIB, ejection fraction 15%, had a history of MI, diabetes, hepatitis C, chronic renal insufficiency, hypercholesterolemia, pancytopenia and secondary pulmonary hypertension. She received treatment with furosemide, losartan, digoxin, ISMN, suoralfate and alprazolam. At baseline liver function tests were above normal and were increased by study day 44. Study drug was reduced 250 mg bid and then discontinued on day 101 (AST 65 U/l, ALT 74 U/l, GGT 450 U/l. LFTs had decreased slightly 40 days later.
Dyspnea, urticaria, elevated LFTs, study drug dis continued	Patient 18149/6373 (bosentan 250-500 mg bid). This 64-year-old black female patient with congestive (dilated) cardiomyopathy with heart failure NYHA class IIIB, ejection fraction 20%, and a history of hyperlipidemia and mitral valve incompetence, treated with lisinopril, terazosin, digoxin, furosemide and metoprolol, was hospitalized because of dyspnea on day 114. Resolved in 1 day. She had received penicillin by her dentist at some unknown earlier time point Study drug was permanently discontinued on day 133 because of elevated LFTs (highest ALT 380 U/l, AST 111 U/l, GGT 97 U/l). Values returned to normal by 50 days. Reported adverse events included hearing impaired and tooth repair.
Fever, edema, elevated LFTs, study drug dis continued	Patient 18149/6374 bosentan 125-250-500 mg bid. This 58-year-old black male with congestive, dilated cardiomyopathy, NYHA class IIIB, ejection fraction 20% and a history of ongoing NIDDM, hypertension and lymphocytic leukemia, concomitant treatments of losartan, furosemide, digoxin, and glipizide, presented with fever and 'achy all over' on day 23. Ceftibuten was given on days 30 and 31. Hospitalized on Day 34 because of ongoing fever and concomitant elevation of liver enzymes: ALT 833 U/L and AST 385 U/L.

	Bilirubin rose from 0.5 mg/dl at baseline to 1.1 mg/dl day 61. Gall bladder sepsis was ruled out. Permanent discontinuation of study medication on day 34. LFTs normal within 110 days. Reported adverse events included bradycardia, blurred vision, dizziness, headache, diabetes, cardiac failure, ventricular extrasystoles, edema.
Extremely elevated ALT. Study drug discontinued	Patient 18164/6331 Bosentan 250-500 mg bid. This 44-year-old black male patient who was also taking glienclamide, was discontinued around day 50 because of elevated LFTs. ALT 2838 U/l, AST 846 U/L on day 40. Recovered within 50 days.
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.
Fever[12], elevated LFTs, study drug discontinued	Patient 18169/8025 bosentan 125-250-500 mg bid. This was a 73 year old male. On day 80, he reported pyrexia, his LFTs were elevated (ALT: 272 U/L, AST 118 U/l), and he was discontinued. LFTs were normal within 33 days.
Abnormal GGT and alk phos and weight gain. Study drug discontinued	Patient 18169/8027 bosentan 250-500 mg bid. This 45-year-old white female with coronary artery disease, NYHA class IV, ejection fraction 32%, with a history of NIDDM, stroke, and hypertension, treated with benazepril, furosemide, spironolactone, ISMN, atenolol, digoxin, propranolol, bezafibrate, warfarin, glibenclamide (glyburide), and metformin, permanently discontinued the study medication on day 23 because of elevated GGT: 274 U/l) alk phos (573 U/). ALT and AST were normal throughout the study. The patient gained 6 kg of weight in two weeks. On day 43, GGT: 101 U/l and normal alk phos and loss of the 6 kgs.
Elevated LFTs. Sustained ventricular tachycardia. Study drug discontinued	Patient 18170/8064 bosentan 250-500 mg bid. This 51-year-old white female with congestive (dilated) cardiomyopathy, NYHA class IIIB, ejection fraction 27%, was taking furosemide, enalapril and propranolol. Dose of study drug was reduced on day 43 because of elevated LFTs. Highest ALT: 135 U/L, AST 80 U/L Patient was hospitalized because of palpitations, dizziness and general weakness on day 72 and diagnosed with atrial fibrillation, and then 3 hours later with sustained ventricular tachycardia. Sinus rhythm was restored. Study drug was discontinued. The next day, ventricular tachycardia recurred and was successfully treated. LFTs normal within 84 days. Low blood pressure was also reported.
Elevated LFTs. UTI and brain tumor. Study drug discontinued	Patient 18171/8017 bosentan 125-250-500 mg bid. This 72-year-old white female with coronary artery disease, NYHA class IV, ejection fraction 22%, had a history of MI, arterial hypertension, anemia, NIDDM and chronic renal failure. Concomitant medications included captopril, furosemide, digoxin, acetylsalicylic acid, ISMN, ferrous sulfate, isophane insulin and glibenclamide (glyburide). The patient was hospitalized on day 8 for severe dehydration. She recovered with treatment by day 13. The patient was re-hospitalized on day 55 because of general deterioration, weakness, and dyspnea and evidence of worsening renal function. A urinary culture was positive for *E. coli*. She was discharged on day 65. The following day she was discontinued from study drug because of elevated hepatic enzymes: ALT 141 U/L, GGT 170 U/l. She was re-hospitalized on day 122 (56 days after study discontinuation) and CT scan of the brain revealed a meningioma. ALT and AST were within normal limits by 33 days.
Elevated	Patient 18172/8042 bosentan 250-500 mg bid. This was a 57-year-old male with ALT 264

[12] Sponsor states that fever was erroneously listed (fax dated 3-27-01).

LFTs. Study drug discontinued	U/L and AST 219 U/L on day 53. Dose was reduced to 250 mg bid on day 60 and discontinued on day 64. LFTs normal within 66 days.
Lethargy, elevated LFTs, anemia. Study drug discontinued	Patient 18207/4032 bosentan 250-500 mg bid. This was a 64 year old male with ALT 203 U/L and AST 77 /l on day 65. He was discontinued that day and LFTs were within normal range by 62 days. Reported adverse events included lethargy, gout, cardiac failure, hematuria, hypokalemia
Elevated LFTs. Rash. Study drug discontinuation.	Patient 18197/9006 bosentan 250-500 mg bid. This 61 year old white male with coronary artery disease with heart failure NYHA class IIIB, ejection fraction 25%, and a history of angina, essential hypertension, atrial fibrillation, hypercholesterolemia and osteoarthritis, treated with atenolol, digoxin, furosemide, fosinopril, warfarin, piroxicam, roxithromycin, and simvastatin, was withdrawn from the study on day 29 for mild dermatitis and severe liver function abnormalities (ALT 713 U/l, AST 399 U/l, GGT 93 U/l). All values had returned to baseline within 56 days. Reported adverse events included sinusitis, dermatitis, rash.
Elevated LFTs. Study drug discontinuation.	Patient 18219/3019 bosentan 125-250-500 mg bid. This was a 57 year old male with ALT 350 U/L and AST 115 U/L on day 106. He was discontinued and LFTs were within normal limits by 42 days.
Fever, hepatomegaly, elevated LFTs, anemia. Hospitalized. Study drug discontinued	Patient 18219/3020 bosentan 125-250-500 mg bid. This was a 66-year-old white female with non-ischemic dilated cardiomyopathy, NYHA class IV, ejection fraction 23% and active herpes zoster, treated with torsemide, enalapril, captopril and phenprocoumon. She was hospitalized on day 6 because of asthenia and mild diarrhea and treated with cyanocobalamin and paracetamol. Patient was discharged without sequelae on Day 14. The patient developed fever on day 19 and was hospitalized on day 21. LFTs were elevated (ALT 118 U/l, AST 84 U/l, GGT 226 U/l, alk phos 719 U/l, total bilirubin 28 umol/l). LFTs at baseline were normal. Hepatomegaly was diagnosed on ECHO. Hepatitis, cancer, and immune disease were ruled out. Study drug was discontinued. Fever resolved and LFTs were within normal limits by about 42 days. Reported adverse events included asthenia, viral infection, cardiac failure.
Elevated LFTs. Study drug discontinued	Patient 18221/3025 bosentan 125-250-500 mg bid. This 58 year old female was down-titrated to 250 mg bid on day 49 because of elevated LFTs. The 500 mg bid was restarted, LFTs continued to rise (ALT: 130 U/L and AST: 62). She was discontinued from study drug and LFTs eventually normalized. Reported dizziness.
Elevated LFTs. Syncope. Study drug discontinued	Patient 18229/3081 (bosentan 125-250-500 mg bid). A 53-year-old with male with non-ischemic dilated cardiomyopathy, NYHA class IV., ejection fraction 20%, a history of TIA with syncope, active diabetes, hyperuricemia and hypertension, treated with digoxin, furosemide, enalapril, carvedilol, mexileline, potassium, L-camitine, ticlopidine, chlorpropamide, phenformin, allopurinol and ranitidine, experienced an episode of syncope on day 30 which resolved within 10 minutes. He was hospitalized and brain CT showed no change from when he had had a previous syncopal event (prior to start of study). He remained on same dose of study medication until day 70 when he was down titrated to 250 mg because of low blood pressure. Metformin and glibenclamide (glyburide) were started on day 77. Highest ALT 280 U/l and AST 168 U/l, bilirubin 24 umol/l. GGT had been elevated at baseline. He was discontinued on day 135. ALT was still elevated (163 U/l) and there was no follow up. Reported adverse events included UTI, paraesthesia, chest pain, cough, cardiac failure.
Elevated LFTs, anemia, and worsening heart failure.	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

Study drug discontinued	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. LFTs normalized. Hb/hct were not followed.
Elevated LFTs, study drug discontinued	Patient 20068/00862 bosentan 125 mg bid. This 65-year-old white male with ischemic heart disease, previous MI, and gout discontinued study drug because of elevated liver enzymes. ALT and AST were 600 and 972 U/l. Bosentan was stopped and values dropped to normal. In a previous study, patient had developed atrial fibrillation, was cardioverted, and had 3 episodes of ventricular tachycardia. Bosentan was temporarily discontinued and a defibrillator was inserted. Concomitant medications included digoxin, ISMN, captopril, furosemide, bendrofluazide, allopurinol, acetylsalicylic acid, warfarin and codydramol tablets. Reported adverse events included epistaxis, blurred vision, dyspnea, anorexia.
Elevated LFTs, positive rechallenge, nausea, study drug discontinued	Patient 20082/00063 bosentan 125 mg bid. This 73-year-old white female with non-ischemic dilated cardiomyopathy and previous MI experienced an increase in LFTs that resulted in study discontinuation. She had received bosentan 500 mg bid in a previous study without apparent abnormalities. Concomitant medications included lisinopril, digoxin, carvedilol, bumetanide, ISMN, simvastatin, naproxen, colchicine and metformin. Glibenclamide (glyburide) was started on day 149. ALT and AST were 763 and 381 U/l, respectively, by day 284. Alk phos and GGT were 218 and 432 U/l, respectively. Bosentan was stopped between days 285 and 369 and 4 weeks later, liver enzymes returned to baseline levels. Bosentan was restarted. Nausea and with elevated LFTs were reported on day 383 and bosentan was discontinued on day 389. Simvastatin was also discontinued. Reported adverse events included gout, hypotension, diabetes, diarrhea, dyspnea.
LFTs increased. Reported various adverse events. Positive rechallenge, discontinued study drug	Patient 20257/1502 bosentan 125 mg bid. This 61-year-old white male with heart failure, ischemic heart disease, angina, previous MI, CABG, and angioplasty discontinued study drug because of increased LFTs. ALT: 489 U/l and AST 263 U/l. Bosentan was stopped and enzymes normalized. Other reported adverse events included fatigue, bronchitis, irritability and vertigo. Patient had participated in a previous study during which he received bosentan 500 mg bid. He reported headaches, nightmares, palpitations, worsening heart failure, allergic drug rash, and increased LFTs during this first study. LFTs normalized when drug was stopped. Concomitant medications included furosemide, ISMN, acebutolol and acetylsalicylic acid.
Elevated LFTs, positive rechallenge, study drug discontinued	Patient 20273/1122 bosentan 125 mg bid. This 70-year-old white male patient with ischemic heart disease, NIDD discontinued study drug increased in LFTs. Concomitant medications included glibenclamide (glyburide) and metformin, lisinopril, furosemide, metoprolol, prinivil and simvastatin. ALT and AST increased to 238 and 119 U/l, respectively. LFTs normalized after bosentan was discontinued. Patient had received bosentan 500 mg bid in a previous study with ALT and AST peaking at 262 U/L and 98 U/l. Study drug was stopped and LFTs returned to baseline.
Elevated LFTs with positive rechallenge.	Patient 18127/8082 bosentan 250-500 bid. 71 year old female had ALT peak of 1420 U/L on day 47. AST was 840, alk phos 317. She was termporarily discontinued from drug with decrease in LFTs. A rechallenge caused re-elevation of LFTs (ALT to 161). Permanently discontinued.
	Patients added from safety update
Malaise, fever, chills, elevated LFTs, elevated bilirubin. Study drug discontinued	AC-052-352 Patient 106/10008. This 53-year-old black female with pulmonary hypertension secondary to systemic sclerosis was receiving prednisone, hydrochloroquine, lorazepam, zolpidem, and panadeine. Her medical history included systemic lupus erythematosus with previous hepatic involvement, systemic hypertension, and obesity. She presented to the emergency room with fever, chills, and malaise on day 143. The patient had reported a recent history of URI treated with multiple antibiotics. ALT 433 U/l, AST 298 U/l, AP 164 U/l, total bilirubin 17.9 umol/l). Study drug was stopped. The consulted local rheumatologist reported that the event occurring on study drug is consistent with patient's previous pattern of flares in liver function abnormalities due to auto-immune hepatitis (lupus), cessation of hydrochloroquine, and a 2-day cessation of prednisone. The study medication was discontinued.

Elevated LFTs and bilirubin; nausea, fatigue, anorexia. Study drug discontinued. Died of worsening PAH.	Patient AC-052-352/105 10014. Bosentan 250 mg bid. 48-year-old white female with pulmonary arterial hypertension due to systemic lupus erythematosus. Reported adverse events included loss of appetite, nausea and fatigue with increases in LFTs (AST 659 U/l, ALT 554 U/l, alk phos 275 U/l, bilirubin 36 umol/l). Study drug was discontinued on day 116 followed by a return to baseline levels about 24 days later. Patient died of worsening of underlying condition 32 days after drug was stopped.
Elevated LFTs and bilirubin. Study drug discontinued	Patient AC-052-352/10050. 59-year-old white male with increase in LFTs (ALT 900 U/L, AST 596 U/L and bilirubin 1.9 mg/dl. Drug was discontinued and values were normal by about 4 weeks. Remained asymptomatic.

There were a few reports of very high elevations of ALT and most patients were discontinued when their LFTs started to increase. There were 2 reports of jaundice[13]. Adverse events of fever, nausea, vomiting, flu or flu-like symptoms were reported in some patients while other patients remained asymptomatic. The cases of rechallenge usually resulted in elevation of LFTs (noted as early as 8 hours after the rechallenge dose). At this time, there is no evidence of a liver related fatality or need for liver transplantation in this small sample of patients. It seems so far that stopping bosentan results in patients returning to baseline status.

There is a concern that patients who develop fever and abdominal pain could be having a drug reaction but be taken (mistakenly) to surgery for an acute abdominal event.

6.4 Ongoing ENABLE trials

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

As of the clinical cut-off date, increases of ALT and/or AST to $\geq$ 3 x ULN have been reported in 40 patients, with 11 reporting increases of 8 times upper limit of normal or higher. Of the 40 patients, 24 continued taking the study drug, at least for a while longer. The patients of note are discussed below. Although the blind remains intact, these are more likely to be bosentan than placebo patients:

-patient 50511: LFTs were starting to rise by week 8. By week 26, increases in ALT (262 U/L, AST 546 U/l), total bilirubin (6.75 mg/dl), and alkaline phosphatase (374 U/L) associated with nausea, jaundice, abdominal pain and weakness were reported. Treatment was stopped and within 10 days, LFTs had decreased markedly (ALT was not reported). Gastroscopy revealed severe esophagitis and duodenitis.

-patient 71114: After 4 weeks of treatment, ALT increased to 1485 U/l and total bilirubin to 40 mg/dl with reports of abdominal pain. Treatment was stopped 8 days later and LFTs fell to normal values by around 2 weeks. Patient is being re-challenged with the low dose. Results of this re-challenge are pending.

[13] And a second patient reported jaundice from the recently concluded study AC 052 352 (see medical review of efficacy).

-patient 92806: LFTs at week 4 were elevated: ALT 442 U/L, AST 213 U/L, bilirubin (1.8 mg/dl, and alkaline phosphatase 622 with reports of nausea, vomiting and dizziness. Study drug was stopped and symptoms disappeared. All laboratory parameters returned to baseline values within 4 weeks.

There are 8 patients who stopped receiving the target dose and were re-challenged with the low dose after their transaminases returned to baseline values. Rechallenge with the low dose has resulted in 3 patients (40405, 71114, 96001) with no follow up information, 1 patient (93403) with no increase in transaminases, 2 patients (30302, 41103) with transient increases in ALT and/or AST, and 2 patients (50317, 95201) with recurrent increases in transaminases and permanently discontinued.

One patient (50427) had an increase in ALT and AST reported on day 59. Bilirubin was elevated (21.9 mg/dl) on day 243. Evidence for acute hepatitis A was reported. Study drug was bilirubin gradually decreased and was 5.5 mg/dl 2 weeks later (day 299). After 3 additional weeks, treatment with study medication (low dose) was restarted.

6.5 Safety Update

6.5.1 PAH

a) ongoing, blinded trial (AC-052-352)

A total of 214 patients have been enrolled and 7 of these had ALT/AST >3 times ULN. Of the 7, 3 had ALT/AST >8 times. Total bilirubin increased in 5 patients. Three of the 7 are discussed in the abnormal LFT list. The remaining 4 were not symptomatic and did not discontinue study drug.

The reporting of elevated LFTs, sometimes higher than 8xULN with and without elevations in bilirubin and with or without symptoms continues unabated.

b) ENABLE: 1613 patients have been randomized and treated with bosentan 125 mg or placebo for a minimum of 16 weeks. At the time of the Safety update, there have been 69 patients (4.3%) who have had increases in ALT and/or AST at least 3 times upper limit of normal. Three patients had study drug discontinued.

No. of patients

	Category of AST and/or ALT elevations			
	≥3 but <5 times ULN	≥ 5 but < times ULN	> 8 times ULN	≥ 3 times ULN
Any elevation	31	15	23	69

A total of 23 patients (1.4%) have had elevations of LFTs of greater than 8 times ULN. Although the study is still blinded, it is certain that most of the 69 patients are in the bosentan group taking doses ≤ 125 mg bid.

7.0 Hematology

7.1 Anemia

7.1.1All bosentan patients

7.1.1.1 Adverse event

Of the 571 patients who received bosentan, 27 (4.7%) reported anemia as an adverse event.

7.1.1.2 Markedly abnormal laboratory value (see appendix)

The incidence rates of patients with markedly abnormal hematology values defined as a significant shift from baseline for and outside a reference range are shown below for all patients who received bosentan or placebo and had post baseline values.

Appendix 56 Incidence of marked laboratory abnormalities in all bosentan-treated patients

Produced by sturlox on 23OCT00

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 T44: Incidence of marked laboratory abnormalities

Population: Safety

All studies of oral Bosentan (including Open Label)

		Bosentan N=571 No.	%
HEMATOLOGY			
Hemoglobin	HH	1 /532	0.2%
	LL	42 /532	7.9%
Hematocrit	HH	0 /527	
	LL	53 /527	10.1%
Erythrocytes	HH	2 /513	0.4%
	LL	8 /513	1.6%
Leukocytes	HH	1 /532	0.2%
	LL	4 /532	0.8%
Neutrophils	LL	4 /507	0.8%
Eosinophils	HH	3 /507	0.6%
Platelets	HH	0 /493	
	LL	2 /493	0.4%

Forty two (7.9%) bosentan patients had a markedly low hemoglobin[14] and 53 had markedly low hematocrit[15].

Other parameters including platelets and white blood cells were abnormal for less than 2% of bosentan patients. A markedly high eosinophil count[16] was reported in 0.6% of bosentan patients.

7.1.2 Placebo controlled trials

7.1.2.1 Adverse event

Of the patients who received bosentan in a placebo controlled trial, 3.7% (20/533) reported anemia (1 reported hemoglobin decreased) as an adverse effect compared to 0.9% (2/219) patients who received placebo.

7.1.2.2 Mean changes

[14] defined as 15% decrease from baseline value and less than 11 g/dl

[15] defined as 15% decrease from baseline value and less than 36%

[16] defined as 100% increase from baseline value and less than 1.5 10^9/L

Mean changes from baseline for hemoglobin in the placebo controlled trials are shown below by treatment group.

Produced by stuzler on 07MAR01
Rq 17-0703, Protocols: AC-52351 MC-15064(II) MD-14884 MC-15018 MC-15020 MC-15462 MN-15031
Table T45f_1: Change from baseline to study end in laboratory parameters
Population: Safety

HEMATOLOGY : Hemoglobin (g/dl)

	Placebo N=219	Bosentan N=333
Baseline		
n	201	478
Mean	14.4	14.7
SD	1.7	1.6
Stderr	0.1	0.1
Median	14.3	14.9
Q1 , Q3	13.2 , 15.5	13.9 , 15.8
Min , Max		
Study end		
n	201	478
Mean	14.2	13.8
SD	1.9	1.8
Stderr	0.1	0.1
Median	14.0	14.0
Q1 , Q3	13.1 , 15.5	12.7 , 15.1
Min , Max		
Change		
n	201	478
Mean	-0.2	-0.9
SD	1.2	1.2
Stderr	0.1	0.1
Median	-0.2	-0.9
Q1 , Q3	-0.8 , 0.6	-1.5 , -0.2
Min , Max		

Study end value is last valid value after baseline up to and including the day after end of randomized treatment
(Pag 1/27)

The bosentan group had a mean decrease from baseline in hemoglobin of 0.9 g/dl (6.1%) compared to 0.2 g/dl (1.4%) in the placebo group. Similar decreases were shown for the hematocrit (0.03, 6.8% decrease for bosentan and 0.01, 2.3% decrease for placebo).