2 SYNOPSIS OF STUDY REPORT No. D-07.025 (PROTOCOL AC-052-364)

COMPANY:	TABULAR FORMAT REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
Actelion Pharmaceuticals Ltd		
NAME OF FINISHED PRODUCT:	Volume:	
Bosentan (Tracleer®)		
NAME OF ACTIVE SUBSTANCE(S):	Page:	
Ro 47-0203		

TITLE OF THE STUDY	A randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy, safety, and tolerability of bosentan in patients with mildly symptomatic pulmonary arterial hypertension (EARLY)		
STATUS OF STUDY / TYPE OF REPORT	This report is the final presentation of study data up to end of the double-blind treatment period (Period 1). Data collected during the open-label treatment period (Period 2) will be presented later, when all data have been collected.		
INDICATION	Mildly symptomatic pulmonary arterial hypertension (PAH)		
INVESTIGATORS / CENTERS AND COUNTRIES	Conducted at 52 centers worldwide. *Coordinating investigator:* Dr. N Galiè, Istituto di Cardiologia, Università di Bologna, Bologna, Italy		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	24 Sep 2004 to 09 Nov 2006 (first patient randomized to last patient completed Period 1)	CLINICAL PHASE	IIIb
OBJECTIVES	The primary objectives were to demonstrate that bosentan improves cardiac hemodynamics and exercise capacity in mildly symptomatic PAH patients. The secondary objectives were to evaluate the effect of bosentan on the time to clinical worsening; dyspnea, World Health Organization (WHO) functional class, and quality of life; and to demonstrate that bosentan is safe and well tolerated in this patient population. Further objectives were to evaluate the effects of bosentan on hemodynamics and exercise capacity in strata with or without concomitant sildenafil treatment at baseline.		
STUDY DESIGN	Prospective, randomized, double-blind, placebo-controlled, multicenter, parallel-group study. The study consisted of a		

	screening period (≤ 4 weeks), a 6-month double-blind treatment period (Period 1), a variable duration open-label extension (Period 2), and a 28-day post-treatment follow-up.
NUMBER OF PATIENTS	170 patients were planned (85/treatment group); 185 patients (93 bosentan and 92 placebo) were enrolled and treated.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Man or woman ≥ 12 years of age with mildly symptomatic (WHO functional class II) PAH, either idiopathic/familial or secondary to HIV infection, anorexigen intake, congenital heart defect, or connective tissue or autoimmune disease.
TRIAL DRUG / BATCH No.	Oral bosentan (Ro 47-0203) 62.5-mg tablets, Batch Numbers FBP001, C0407002 Oral bosentan (Ro 47-0203) 125-mg tablets, Batch Numbers FBR002, C0408002
DOSE / ROUTE / REGIMEN / DURATION	Initial dose: bosentan 62.5 mg twice daily (b.i.d.) for the first month Target dose: bosentan 125 mg b.i.d. for the rest of the double-blind treatment period, i.e., Period 1 (or 62.5 mg b.i.d. if body weight was < 40 kg) Down-titration to or maintenance at the 62.5-mg b.i.d. dose was available at any time for reasons of intolerability, with possible subsequent up-titration to the target dose.
REFERENCE DRUG / BATCH No.	Oral placebo tablets matching bosentan 62.5-mg tablets, Batch Numbers C0140001, C0405001 Oral placebo tablets matching bosentan 125-mg tablets, Batch Numbers C0020001,C0406001
DOSE / ROUTE / REGIMEN / DURATION	Same as for bosentan during the double-blind treatment period (Period 1).
CRITERIA FOR EVALUATION EFFICACY:	*Primary endpoints:* Pulmonary vascular resistance (PVR) at rest at Month 6, expressed as percent of the baseline value Change from baseline to Month 6 in 6-min walk distance *Secondary endpoints:* Time to clinical worsening (defined as death, hospitalization due to PAH complications, or symptomatic progression of PAH, i.e., appearance or worsening of right heart failure or ≥ 10% decrease from baseline [or ≥ 5% decrease with associated Borg dyspnea ≥ 2] in two 6-min walk tests

	performed ≥ 2 weeks apart) Change from baseline to Month 6 in WHO functional class Change from baseline to Month 6 in Borg dyspnea index Change from baseline to Month 6 in mean right atrial pressure (mRAP), mean pulmonary artery pressure (mPAP), cardiac index, total pulmonary resistance (TPR), and mixed venous oxygen saturation (SVO_2) at rest *Exploratory endpoint:* Change from baseline to Month 6 in plasma B-type natriuretic peptide (BNP) concentration
PHARMACOECONOMICS	Change from baseline to Month 6 in Medical Outcomes Survey Short-form Health Survey (SF-36) indices Change from baseline to Month 6 in Cambridge Pulmonary Hypertension Outcome Review scores Hospitalization for PAH complication up to Month 6
PHARMACOKINETICS	Maximum concentration (C_{max}), time to C_{max} (t_{max}), and area under the concentration-time curve (AUC_τ) with bosentan 62.5 mg b.i.d. (at Month 1) and 125 mg b.i.d. (at Month 3)
SAFETY:	Treatment-emergent adverse events (AEs), serious adverse events (SAEs), clinical laboratory test results, and vital signs up to 1 day after the end of double-blind treatment, premature discontinuation of double-blind treatment, and SAEs from 2 to 28 days after the end of study treatment

STATISTICAL METHODS:

With 85 patients per treatment group, a ≥ 20% reduction in the geometric mean PVR and a ≥ 35-meter increase in the mean 6-minute walk distance in the active vs placebo group could be determined with > 99% and 91% power, respectively.

The two primary endpoints were evaluated hierarchically, with the endpoint on walk distance tested only if the endpoint regarding PVR was significant, with both tested at a two-sided type-I error of 0.05. The main analysis was on the all-randomized analysis set. Treatment comparisons were performed using the two-sided Mann-Whitney U-test (main analysis) and a two-sided t-test (secondary analysis). Similar analyses were performed using different analysis sets, alternate substitution rules, in subgroups of the study population, and in strata with or without concomitant sildenafil treatment at baseline (stratified at randomization). Secondary and exploratory variables were analyzed on the all-randomized set only, with exploratory treatment comparisons performed. After applying the substitution rules, data were summarized descriptively, using location and scale statistics and frequency counts and proportions. Numerical variables were analyzed in the same manner as the primary endpoints. The time to clinical worsening was analyzed using the Kaplan-Meier method, with treatment effect evaluated using the hazard ratio

(from the Cox model) of the active vs placebo group and tested using the log-rank test; analyses of randomization strata and subgroups were similarly performed. The proportions of patients improved/worsened in functional class and SF-36 health transition index were compared using relative risk (active vs placebo) with the p-value from the Fisher exact test.

Safety data were summarized descriptively, with time-to-event analyses performed using the Kaplan-Meier method.

PATIENT DISPOSITION:

All 185 randomized functional class II patients received study treatment, 12.9% and 10.9% of patients on bosentan and placebo, respectively, discontinued prematurely. The study population consisted primarily of Caucasian females (mean age 44 to 45 years) with idiopathic/familial PAH and baseline mean 6-minute walk distances that indicated a relatively well preserved exercise capacity (438.1 and 431.0 meters in bosentan and placebo groups, respectively). The two treatment groups were well balanced except for a higher proportion of females in the bosentan than placebo group (76.3% vs 63.0%).

EFFICACY RESULTS:

After 6 months of bosentan treatment, the decrease in PVR with bosentan and increase with placebo resulted in a significant 22.6% reduction in PVR with bosentan compared with placebo ($P < 0.0001$, main co-primary endpoint). Similar significant improvements in PVR with bosentan were observed in all supportive analyses (different analysis sets, alternate substitution rules, excluding patients with unblinded treatment). Similar results were also observed in the strata of patients on or not on concomitant sildenafil at baseline (–20.4%, $P = 0.0478$ and –23.1%, $P < 0.0001$, respectively). Results of the main analysis were also supported by all subgroup analyses. The increase in 6-minute walk distance with bosentan and decrease with placebo resulted in +19.1-meter and +13.8-meter mean and median treatment effects, respectively. The effect did not reach full statistical significance ($P = 0.0758$ for median treatment effect; second co-primary endpoint). Similar results were obtained in all supportive analyses. A mean improvement from baseline in walk distance with bosentan was observed at Month 3 and was maintained at Month 6. A nominal median improvement in 6-minute walk distance at Month 6 was observed with bosentan compared with placebo in strata based on concomitant sildenafil treatment and in most subgroups evaluated.

Considering the predefined analysis strategy, no confirmatory conclusions could be based on other analyses. However, several important observations were made in secondary and exploratory endpoints (p-values provided to gauge the importance of the effect). A clinically relevant delay in time to clinical worsening (first seen primarily as symptomatic progression of PAH) was observed with bosentan compared with placebo (hazard ratio 0.227, $P = 0.0114$), which was apparent by Week 16 and consistent in strata based on sildenafil use at baseline and in most subgroups evaluated. Compared with placebo, bosentan treatment was also associated with a lower incidence of worsening of functional class (3.4% vs 13.2%, $P = 0.0285$), improvement in other hemodynamic variables (mPAP,

TPR, cardiac index, and SVO_2; $P < 0.05$), and small mean decreases in patient-rated dyspnea during the walk test and BNP concentration. The changes in the SF-36 health transition item indicated that more patients on bosentan than on placebo felt that their condition had improved (57.3% vs 38.3%, $P = 0.0244$).

PHARMACOKINETIC RESULTS:

The pharmacokinetics of bosentan in this patient population were characterized by a median t_{max} of 2 hours followed by rapid disposition. The exposure to bosentan was greater after 125 mg b.i.d. than after 62.5 mg b.i.d. but appeared to be less than dose proportional. Exposure to the three metabolites was low compared with that to bosentan. Results were similar to those previously seen with bosentan in the clinical trial program.

SAFETY RESULTS:

Safety findings with bosentan during the double-blind treatment period were similar to those previously seen with bosentan. Few patients experienced an SAE (12.9% and 8.7% in bosentan and placebo groups, respectively), two patients died (one during bosentan treatment and one as the outcome of a treatment-emergent event that led to discontinuation of placebo), and the most frequent events that led to discontinuation were abnormal liver function on bosentan (6.5% vs 0 on placebo) and worsening PAH on placebo (5.4% vs 1.1% on bosentan). Patients in both groups experienced AEs (69.9% and 65.2% with bosentan and placebo, respectively), but the incidence of severe events was higher on placebo (14.1% vs 10.8% on bosentan). Events more frequent on bosentan than placebo included events denoting elevated liver enzymes (11.8% vs 6.5%) and decreased hemoglobin concentration (6.5% vs 3.3%), but the incidences of events denoting edema were similar in the two groups (9.7% and 9.8%, respectively); pulmonary hypertension and headache were more frequent on placebo.

Clinically relevant elevations in liver aminotransferases (> 3 × upper limit of normal) occurred in 13.0% and 2.2% of patients on bosentan and placebo, respectively. Most of the elevations appeared during the first 20 weeks of bosentan treatment, were asymptomatic, and returned towards baseline without intervention or when bosentan was discontinued. However, in one patient diagnosed with autoimmune hepatitis and hepatic cirrhosis 3 months after study drug initiation, the first clinically relevant elevation in liver aminotransferases occurred after 67 weeks of bosentan treatment (and resolved after treatment discontinuation). Clinical features of this case suggested pre-existing liver disease. Most clinically relevant decreases in hemoglobin concentration (5 cases < 75% of the lower limit of normal) were associated with a bleeding event, trauma, or concomitant medication and resolved during the study. Small decreases from baseline in systolic and diastolic blood pressure were observed with bosentan treatment (–2.7 and –3.1 mmHg, respectively). Other changes in safety variables were not considered to be clinically meaningful.

CONCLUSIONS:

In this first clinical study dedicated to the evaluation of treatment effects in mildly symptomatic (functional class II) PAH patients, bosentan was associated with clinically

relevant improvements in hemodynamic, clinical, and quality-of-life parameters compared with placebo, with no evidence for new or unexpected safety concerns. Importantly, bosentan was observed to delay time to clinical worsening in this patient population, suggesting that treatment with bosentan should be started early, as it may alter the clinical course of the PAH disease.

DATE OF THE REPORT:

21 May 2007