2 SYNOPSIS OF STUDY REPORT, No. D-06.138 (AC-052-366)

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

TITLE OF THE STUDY	Prospective, randomized, placebo-controlled, double-blind, multicenter, parallel group study to assess the efficacy, safety and tolerability of bosentan in patients with inoperable chronic thromboembolic pulmonary hypertension (BENEFIT)		
INDICATION	Chronic thromboembolic pulmonary hypertension (CTEPH)		
INVESTIGATORS / CENTERS AND COUNTRIES	Conducted at 26 centers: Australia (4), Austria (1), Belgium (1), Canada (3), Czech Republic (1), France (1), Germany (3), Italy (4), the Netherlands (2), Poland (1), Spain (1), the UK (2), and the US (2) *Coordinating investigator:* Gérald Simonneau, MD, Hôpital Antoine Béclère, Clamart, France		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	03 Oct 2005 to 07 Feb 2007 (first patient enrolled to last patient completed)	CLINICAL PHASE	III
OBJECTIVES	The primary objective was to demonstrate that bosentan improves exercise capacity and/or pulmonary vascular resistance (PVR) in patients with inoperable CTEPH. Secondary objectives were to evaluate the effect of bosentan on the time to clinical worsening, World Health Organization (WHO) functional class, and cardiac hemodynamics in patients with inoperable CTEPH and to evaluate the safety and tolerability of bosentan in this patient population.		

STUDY DESIGN	Prospective, randomized, double-blind, placebo-controlled, multicenter, parallel group, Phase III study The study consisted of a screening period (up to 3 weeks), randomization stratified by prior pulmonary endarterectomy (PEA), a 16-week treatment period, and a 28-day post-treatment safety follow-up. Patients were retrospectively evaluated for operability by the Operability Evaluation Committee (OEC). Those unanimously judged operable were excluded from the main analysis of the primary endpoints and were to be replaced. Patients who completed the 16-week treatment period were offered open-label bosentan in the following extension study, AC-052-370.
NUMBER OF PATIENTS	128 evaluable patients were planned and 157 patients (77 bosentan and 80 placebo) were entered; 137 patients (66 bosentan and 71 placebo), were evaluable for PVR and 140 (67 bosentan and 73 placebo) were evaluable for 6-min walk test (6MWT)
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Men or women ≥ 18 years and ≤ 80 years of age with pulmonary hypertension of WHO functional class II to IV due to CTEPH judged inoperable because of peripheral localization of thrombotic material or with persistent or recurrent pulmonary hypertension after PEA with no evidence of recurrent thromboembolism and not a candidate for repeated surgery
TRIAL DRUG / BATCH No.	Oral bosentan (Ro 47-0203) 62.5-mg tablets, Batch No. C0407002 Oral bosentan (Ro 47-0203) 125-mg tablets, Batch No. C0408002, FBR003
TRIAL DRUG DOSE / ROUTE / REGIMEN / DURATION	Initial dose: bosentan 62.5 mg twice daily (b.i.d.) for the first 4 weeks Target dose: bosentan 125 mg b.i.d. (or 62.5 mg b.i.d. if body weight was < 40 kg) for the rest of the 16-week treatment period 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 No. C0405001 Oral placebo tablets matching bosentan 125-mg tablets, Batch No. C0406001
REFERENCE DRUG DOSE / ROUTE / REGIMEN / DURATION	Same as for bosentan during the 16-week treatment period
CRITERIA FOR EVALUATION	
EFFICACY:	*Co-primary endpoints:* Change from baseline to Week 16 in 6MWT distance Change from baseline to Week 16 in PVR at rest, expressed as percent of the baseline value *Secondary endpoints:* Time to clinical worsening (defined as death, treatment-emergent adverse event that led to discontinuation of study treatment and with outcome death, lung transplantation, or hospitalization for worsening of pulmonary hypertension) Change from baseline to Week 16 in WHO class Change from baseline to Week 16 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 endpoints:* Change from baseline to Week 16 in Borg dyspnea index Change from baseline to Week 16 in N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP) and endothelin-1
PHARMACOECONOMICS:	Change from baseline to Week 16 in Medical Outcomes Survey Short-form Health Survey (SF-36) indices
SAFETY:	Treatment-emergent adverse events, serious adverse events (SAEs), marked laboratory abnormalities, and electrocardiogram abnormalities up to 1 day after the end of study treatment, premature discontinuations, adverse events that led to permanent discontinuation of study treatment, and for patients not entering the following extension study, SAEs occurring up to 28 days after the end of study treatment.

STATISTICAL METHODS:

The null hypothesis, composed of two subhypotheses testing the superiority of bosentan on each of the two co-primary endpoints, was to be rejected if either or both subhypotheses were rejected at their assigned proportion of the type-I error (0.01 two-sided for PVR and 0.04 two-sided for 6MWT distance). The type-I error split was applied to preserve the study-wise type-I error at 0.05 two-sided. A sample size of 128 evaluable patients (i.e., not unanimously judged operable by OEC) was based on the two co-primary endpoints, their assigned portion of type-I error, a 1:1 randomization ratio, treatment comparison carried out by Wilcoxon rank sum test (used for the primary analysis), and the following power considerations: 94% power to detect a 20% reduction in the geometric mean of PVR and 80% power to detect a 35-meter mean treatment effect in 6MWT.

The main analysis was on the all-randomized excluding operable analysis set (for PVR or 6MWT distance). Supplementary analyses were performed using different analysis sets and adjusting the treatment effect for the stratification factor at randomization (prior PEA or not). 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 data were analyzed in the same manner as the primary endpoints. The time to clinical worsening was summarized using the Kaplan-Meier method, with treatment effect evaluated using the hazard ratio (from the Cox model) of the active vs. placebo group. The proportions of patients improved/worsened in functional class and SF-36 health transition index were compared using relative risk (active vs. placebo). Safety data were summarized descriptively.

PATIENT DISPOSITION:

All randomized patients were treated, and the two treatment groups were well balanced except for a larger proportion of females in the bosentan group (71.4% vs 58.8%). Patients with a prior PEA constituted 28% of the study population. Eight patients were discontinued prematurely (3 on bosentan, 5 on placebo), and 11 were judged by the OEC to be operable (7 and 4 on bosentan and placebo, respectively).

EFFICACY RESULTS:

Compared with placebo, 16 weeks of bosentan treatment was associated with a statistically significant 24.1% decrease in PVR (95% CL: –31.5, –16.0; co-primary endpoint). Similar results were observed using alternate analysis sets ($P < 0.0001$). The decrease in PVR with bosentan compared with placebo was observed in patients with a prior PEA (–34.0%, 95% CL: –45.6, –20.0) and without a prior PEA (–19.5%, 95% CL: –28.7, –9.1), both $P < 0.0001$. The decrease in PVR was accompanied by a decrease in TPR (median treatment effect –157 dyn·sec/cm^5, 95% CL: –226, –89), an increase in cardiac index (0.29 L/min/m^2, 95% CL: 0.13, 0.45), and improvements in mPAP and SVO_2 with bosentan compared with placebo. There was no effect on mRAP.

Little change from baseline to Week 16 in 6MWT distance was observed in either treatment group (median treatment effect –4.8 meters, 95% CL: –21.2, 11.5; co-primary endpoint), but patients on bosentan showed a median decrease in Borg dyspnea index from baseline to Week 16, compared to placebo (–0.5 on the Borg scale, 95% CL: –1.2, –0.0). A larger proportion of patients on bosentan improved and a smaller proportion worsened in WHO functional class, or experienced clinical worsening (hazard ratio 0.63, 95% CL 0.15, 2.64), and greater improvements in many SF-36 evaluations of quality of life with bosentan than with placebo. There was a median 195-ng/L decrease (95% CL: –436, –61) in serum NT-pro-BNP concentration with bosentan compared with placebo. As expected, plasma endothelin-1 increased with bosentan treatment, while it changed little with placebo.

SAFETY RESULTS:

Safety findings with bosentan during the study were similar to those previously seen with bosentan. The overall incidence of treatment-emergent adverse events was higher with bosentan than placebo (67.5% vs 52.5%), but the incidence of severe events was similar in the two groups (10.4% and 11.3%, respectively). Individual events more frequent on bosentan than placebo were mainly those known to be associated with bosentan therapy, including headache (6.5% vs. 1.3%), events denoting abnormal liver function (13.0% vs. 5.0%), peripheral edema (13.0% vs. 7.5%), and decreased hemoglobin concentration (2.6% vs. none). Similar proportions of patients on bosentan and placebo experienced an SAE (9.1% and 12.5%, respectively) and fewer patients had treatment permanently discontinued because of an adverse event (2.6% and 5.0%, respectively). One patient in each treatment group died, with neither event considered related to study treatment by the investigator. The incidence of elevations in liver aminotransferases > 3 × upper limit of normal was higher on bosentan vs. placebo (14.5% vs. 3.8%). In all cases, the elevation was asymptomatic and resolved or improved without intervention, with a decrease in dose, or after treatment was stopped. No patient had a hemoglobin concentration < 75% of the lower limit of the normal range. Other changes in safety variables were not considered to be clinically meaningful.

CONCLUSIONS:

In patients with inoperable CTEPH, bosentan treatment was associated with statistically significant improvement in PVR and other aspects of cardio-pulmonary hemodynamics, as well as a decrease in dyspnea on the Borg scale, and a decrease in NT-pro-BNP. There was no effect on exercise capacity, which may be related to insufficient study duration or other factors.. The safety and tolerability profiles of bosentan in these patients were consistent with those observed in other patient populations.

DATE OF THE REPORT:

31 August 2007