2 SYNOPSIS OF STUDY REPORT, No. D-08.136 (PROTOCOLS AC-052-368, AC-052-369, AND AC-052-371)

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:	Page:	
Ro 47-0203	Type … *(ONLY DRA)*	

TITLES OF THE STUDIES	**AC-052-368 and AC-052-369**: Randomized, placebo-controlled, double-blind, multicenter, parallel-group study to assess the efficacy, safety and tolerability of bosentan in patients with symptomatic pulmonary arterial hypertension or pulmonary hypertension associated with sickle cell disease (ASSET-1 and -2) **AC-052-371**: Long-term, open-label, multicenter extension study of bosentan in patients with pulmonary hypertension associated with sickle cell disease completing a double-blind ASSET study (AC-052-368 or AC-052-369) (ASSET-3)		
STATUS OF STUDY / TYPE OF REPORT	The ASSET-1 and -2 studies were stopped prematurely due to slow enrollment. Safety data from the few patients in both studies were integrated and are described in this abbreviated report along with safety data collected in the open-label extension study, ASSET-3.		
INDICATION	Pulmonary arterial hypertension (PAH) and pulmonary hypertension (PH) in sickle cell disease (SCD)		
INVESTIGATORS / CENTERS AND COUNTRIES	Conducted at 13 centers: France (1), UK (1), US (11). *Coordinating investigator:* Mark Gladwin, MD, Critical Care Medicine Dept, NIH Clinical Center, Bethesda, MD, USA		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	27 Mar 2006 to 29 Aug 2007	CLINICAL PHASE	III

	(first patient, first visit to last patient completed)		
OBJECTIVES	The primary objectives were to demonstrate that bosentan improves pulmonary vascular resistance (ASSET-1) and exercise capacity (ASSET-2) in patients with symptomatic PAH (ASSET-1) or PH (ASSET-2) associated with SCD. The objective of the open-label extension study (ASSET-3) was to collect long-term safety, tolerability, and efficacy data in patients with PH associated with SCD. Secondary objectives were to demonstrate that bosentan improves exercise capacity (ASSET-1 only) and to evaluate the effect of bosentan on the time to clinical worsening and the safety and tolerability of bosentan in these patients (both studies).		
STUDY DESIGN	Two prospective, randomized, double-blind, placebo-controlled, multicenter, parallel-group, Phase III studies consisting of a screening period (≤ 4 weeks), a 16-week treatment period, and a 28-day post-treatment safety follow-up (ASSET-1 and -2) Patients who completed the 16-week treatment period were offered open-label bosentan in the following extension study, ASSET-3, until the study was stopped by decision of sponsor.		
NUMBER OF PATIENTS	78 and 158 patients were planned and 14 and 12 were entered in the ASSET-1 and-2 studies, respectively. Eleven patients (4 and 7 from ASSET-1 and -2, respectively) continued in the extension ASSET-3.		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Males or females ≥ 12 years of age with a documented history of SCD and symptomatic PAH or PH associated with shortness of breath.		
TRIAL DRUG / BATCH No.	Oral bosentan (Ro 47-0203) 62.5-mg tablets, Batch No. C0407001, C0407002 Oral bosentan (Ro 47-0203) 125-mg tablets, Batch No. C0408001, C0408002		
TRIAL DRUG DOSE / ROUTE / REGIMEN / DURATION	**ASSET-1 and ASSET-2**: 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. **ASSET-3**: All patients started open-label bosentan at 62.5 mg b.i.d. and were to be up-titrated after 4 weeks to 125 mg b.i.d. (if ≥ 40 kg body weight) for the remainder of the study.
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 of ASSET-1 and ASSET-2.
CRITERIA FOR EVALUATION	
EFFICACY:	See section 9.5.2 for protocol-defined criteria. Efficacy was not evaluated for this abbreviated report.
PHARMACOECONOMICS:	See section 9.5.3 for protocol-defined criteria. Pharmacoeconomics were not evaluated for this abbreviated report.
SAFETY:	**ASSET-1 and ASSET-2**: Treatment-emergent adverse events and electrocardiographic (ECG) abnormalities up to 1 day after the end of study treatment Serious adverse events (SAEs) and marked laboratory abnormalities up to 28 days after the end of study treatment Adverse events leading to permanent discontinuation of study treatment Changes from baseline to the end of the treatment period in laboratory parameters, ECG variables, and vital signs Proportion of patients with alanine aminotransferase (ALT) greater than 3 × the upper limit of normal up to 1 day after the end of study treatment **ASSET-3**: Adverse events leading to discontinuation

	and treatment-emergent SAEs, treatment-emergent liver disease or symptoms, and elevated alanine aminotransferase (ALT) up to 1 day after discontinuation of study treatment

STATISTICAL METHODS:

Due to the low number of patients enrolled in the controlled studies, efficacy endpoints were not analyzed, and the hypotheses described in the protocols were not tested. Baseline, safety, and tolerability data were evaluated using appropriate descriptive statistics and comparison between treatment.

PATIENT DISPOSITION:

Only 26 patients were enrolled in the controlled studies (14 in ASSET-1, 12 in ASSET-2), and all were included in the safety analyses. Two patients in each study group for the pool studies were withdrawn prematurely (2 on bosentan due to an adverse event). Eleven patients (7 and 4 in the bosentan and placebo groups, respectively) participated in the extension study.

SAFETY RESULTS:

Bosentan was generally well tolerated in these patients. In the double-blind studies, adverse events (AEs) were reported for most patients in both treatment groups. No obvious difference between treatments was observed in the number or types of AEs and no relationship to treatment was evident in the number or type of AEs that were graded as severe or serious. Marked decreases in hemoglobin concentration occurred in four patients in each treatment group. No clinically relevant, treatment-emergent increases in liver function tests (i.e., ALT > 3 × the upper limit of the normal range) were observed. Asymptomatic decreases in mean systolic (–9.3 vs –7.3 mmHg on placebo) and diastolic blood pressures (–7.9 vs –0.9 mmHg) and a mean increase in body weight (0.8 vs –0.3 kg on placebo) were observed with bosentan treatment. No clinically meaningful differences between treatments were seen in clinical laboratory variables, heart rate, or ECG findings.

In the open-label extension, no deaths, discontinuations due to an AE, increases in ALT to > 3 × the upper limit of the normal range, or incidences or symptoms of liver disease occurred. Three patients experienced an SAE, which included sickle cell anemia with crisis in each case.

CONCLUSIONS:

Efficacy was not evaluated due to the few patients enrolled in the studies. Sixteen weeks of bosentan treatment revealed no unexpected safety issues in patients with pulmonary hypertension associated with sickle cell disease, and bosentan continued to be well tolerated during open-label treatment.

DATE OF THE REPORT: 14 July 2008