2 SYNOPSIS OF RESEARCH REPORT NO. D-07.041 (PROTOCOL AC-052-365)

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	An open-label, multicenter study to assess the pharmacokinetics, tolerability, and safety of a pediatric formulation of bosentan in children with idiopathic or familial pulmonary arterial hypertension (PAH).		
INDICATION	Pulmonary arterial hypertension in children		
INVESTIGATORS / CENTERS AND COUNTRIES	Coordinating Investigator: Maurice Beghetti, MD. 11 centers: France (4), Germany (1), Italy (1), The Netherlands (1), Switzerland (1), UK (1) and USA (2).		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	25 May 2005 to 14 December 2006	CLINICAL PHASE	III
OBJECTIVES	The primary objective was to demonstrate that the exposure to bosentan in children with idiopathic or familial PAH, using a pediatric formulation, is similar to that in adults with PAH. The secondary objective was to evaluate the tolerability and safety of the pediatric formulation of bosentan in this patient population. An implicit objective was added by protocol Amendment 2: to compare the bosentan AUC_{τ} at 2 and 4 mg/kg, in the subset of patients who have undergone two PK assessments of the bosentan pediatric formulation.		

STUDY DESIGN	Multicenter, open-label, single-arm, non-controlled, 12-week, prospective phase III study.
NUMBER OF SUBJECTS	Thirty evaluable patients were planned, preferably distributed within the following age groups: • Ten ≥ 2 and < 4 years • Ten ≥ 4 and < 6 years • Ten ≥ 6 and < 12 years Eight additional patients were planned to be included as per protocol Amendment 2. Non-evaluable patients, i.e., those not able to provide at least five of the six samples (including the pre-dose and 12h post-dose samples) for either pharmacokinetic (PK) analyses, were to be replaced.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Idiopathic PAH or familial PAH diagnosed by right heart catheterization (WHO functional class II or III). • Signed informed consent by the parents or legal representatives. • Male or female ≥ 2 and < 12 years of age. Females who were menstruating had to have a negative serum pregnancy test. A reliable method of contraception had to be considered, if appropriate. • Peripheral arterial oxygen saturation (SpO_2) ≥ 88%, (at rest, on room air). • PAH treatment-naïve patients or Patients already treated with either: – bosentan monotherapy – intravenous epoprostenol monotherapy – intravenous or inhaled iloprost monotherapy – combination of bosentan and intravenous epoprostenol – combination of bosentan and intravenous or inhaled iloprost • PAH therapy had to have been stable for at least 3 months prior to Screening.
TRIAL DRUG / BATCH No.	Oral bosentan dispersible tablets 32mg Batch No. C0457001

DOSE / ROUTE / REGIMEN / DURATION	Patients received the pediatric oral formulation of bosentan, i.e., 32 mg breakable and dispersable tablets. • The initial dose was 2 mg/kg b.i.d. for 4 weeks. • After 4 weeks, the dose was to be up-titrated to the maintenance dose of 4 mg/kg b.i.d. up to the end of the study treatment at Week 12. If the maintenance dose was not well tolerated, the dose was to be down-titrated to the initial dose. Children weighing 30 kg or above were to receive the maximum initial dose of 64 mg b.i.d., then 120 mg b.i.d. as the maintenance dose.
REFERENCE DRUG / BATCH No.	Not applicable
CRITERIA FOR EVALUATION	
PHARMACOKINETIC ENDPOINTS	The primary endpoint was defined as the area under the plasma concentration time curve during a dose interval (AUC_τ) of bosentan. Secondary endpoints were defined as the maximum plasma concentration (C_{max}) and time to reach the maximum plasma concentration (t_{max}) of bosentan and the C_{max}, t_{max}, and AUC_τ of its metabolites (Ro 47-8634, Ro 48-5033, Ro 64-1056).
TOLERABILITY/SAFETY ENDPOINTS:	• Adverse Events (AEs) up to 1 day after permanent discontinuation of study drug. • AEs leading to premature discontinuation of study drug. • Serious Adverse Events (SAEs) up to 28 days after permanent discontinuation of study drug. • Changes from Baseline to End of Treatment period (up to 1 day after treatment stop) in vital signs and body weight. • Treatment-emergent ECG abnormalities. • Treatment-emergent marked laboratory abnormalities. • Increase in ALT/AST > 3 times upper limit of normal range compared to Baseline.
EXPLORATORY EFFICACY AND QUALITY OF LIFE ENDPOINTS:	Exploratory efficacy and quality of life endpoints were defined as follows: • Change from Baseline to Week 12 in WHO

	functional class. • Change from Baseline to Week 12 in Quality of Life questionnaire (SF-10™). • Change from Baseline to Week 12 in Global Clinical Impression scale assessed by the parents and the physician.

STATISTICAL METHODS:

The main analysis of the primary endpoint was performed on the per-protocol pharmacokinetic set, which included all patients in the All-treated set who were able to provide at least five of the six blood samples (including the pre-dose and the 12h dose samples) requested at both PK visits and who did not violate the protocol in a way that might affect the evaluation of the primary endpoint. Missing data on the primary endpoint were not substituted. The similarity between the exposure to bosentan in children and adult PAH patients was tested using an equivalence hypothesis. The null hypothesis (of non equivalence) was to be rejected if both limits of the 90% confidence interval (based on Student's t-test) of the ratio of geometric means of AUC_τ between children and adults (pre-defined historical control group treated with bosentan 125 mg b.i.d.) were entirely within the pre-set equivalence limits of 0.66 to 1.5. The variable AUC_τ was assumed to be log-normally distributed with a common standard deviation of the log-transformed data of 0.45. With an overall two-sided type I error set to 0.05 and the mean of log-transformed AUC_τ in children assumed to be equal to that in adults, the study had 80% power to reject the null hypothesis with a sample size of 30 patients. The secondary PK endpoints were descriptively summarized.

A separate analysis of bosentan and its metabolites was performed on the subgroup of patients who performed both the 2- and 4-mg/kg PK assessments.

Safety and exploratory efficacy endpoints were descriptively evaluated. Post-hoc subgroup analysis of efficacy and safety was carried out on bosentan-naïve patients and patients previously treated with bosentan.

METHODOLOGY:

Pharmacokinetic visits / sampling

The PK assessment was to be performed at least 2 weeks after up-titration to the maintenance dose (i.e., between Weeks 6 and 12). For patients remaining on the initial dose (i.e., no up-titration to the maintenance dose at Week 4) or who started with the maintenance dose, the PK assessment was to be performed at any time after Week 4.

Initial evaluation of the PK results from the first 10 patients indicated lower than expected exposure to bosentan, and the protocol was therefore amended to require two PK assessments instead of one (protocol Amendment 2).

The new PK assessment (PK1) was performed at least 2 weeks after the initiation of study drug at 2 mg/kg b.i.d. (i.e., between Week 2 and Week 4). The second PK assessment (PK2) continued to be performed at least 2 weeks after up-titration to the

maintenance dose of 4 mg/kg b.i.d. (i.e., between Week 6 and Week 12).

Blood samples of 1.2 ml were taken immediately prior to drug administration (pre-dose), and then at 0.5h, 1h, 3h, 7.5h, and 12h post-dose. The blood volume for each PK assessment was approximately 7.2 ml. The total volume of blood to be withdrawn for both PK assessments was approximately 14.4 ml.

Study visits and other assessments

The exploratory clinical assessments (i.e., the WHO functional class, SF-10 for Children™ questionnaire, and parents and physician Global Clinical Impression scales) were to be performed 4-weekly, and standard ECG, physical examination, vital signs, and laboratory tests, were to be performed at the same time, as well as at the PK visits. Adverse events and concomitant medications were monitored throughout the study, and other safety parameters were assessed at each visit according to the Schedule of Assessments.

PATIENT DISPOSITION:

A total of 36 patients were enrolled in the study. Twenty-five patients were enrolled into the study as per the original protocol, while 11 patients were enrolled following implementation of protocol Amendment 2. Four patients were aged 2–3 years, 9 were aged 4–5 years and 23 were aged 6–11 years, and all patients received at least one dose of bosentan. Two patients did not complete the study. All patients were analyzed in the tolerability and safety analysis. One patient was excluded from the per-protocol pharmacokinetic analysis set and another patient was excluded from the per-protocol exploratory efficacy analysis set, which therefore comprised 35 patients each.

PHARMACOKINETIC RESULTS:

The primary objective of the study was not met: the geometric mean of the AUC_{τ} following treatment with the pediatric formulation of bosentan (and 95% confidence interval) was 4,383 ng.h/ml (3,461; 5,552). The ratio of the geometric means for AUC_{τ} (and 90% confidence interval) was 0.5 (0.4, 0.8), indicating that exposure to bosentan in adults was almost twice the exposure in children. The confidence interval around the ratio of the geometric means of AUC_{τ} was not entirely within the predefined equivalence limits of 0.66–1.5.

The median time to reach C_{max} (t_{max}) of bosentan was 3 hours. The exposure to the metabolites was low compared to the exposure to bosentan, with Ro 48-5033 being the most prominent.

In the 11 patients who underwent two PK assessments, the exposure to bosentan following both the initial dose of 2 mg/kg and the maintenance dose of 4 mg/kg was similar, i.e., there was no increase in exposure to bosentan after doubling of the dose.

EXPLORATORY EFFICACY RESULTS:

The exploratory efficacy and quality of life analysis showed that the majority of patients were maintained as stable from baseline to the end of study treatment, as expected given the short treatment period. Analysis of the subgroup of patients who were bosentan-naïve versus those previously treated revealed potentially clinically relevant differences in Parents' and Physicians' Global Clinical Impression and the SF-10 health-related quality of life survey. A beneficial therapeutic effect was consistently observed in all parameters in bosentan-naïve patients.

SAFETY RESULTS:

The pediatric dispersible formulation of bosentan was well tolerated. Only one child withdrew from the study due to 'bad' taste of the medication.

The overall safety profile of bosentan pediatric formulation was similar to that observed in other studies with the adult formulation. Four patients experienced a total of eight SAEs: adenoidectomy, bacterial infection, cough, ear infection, fatigue, hypertension, pulmonary hypertension worsening, and right ventricular failure, one of which (pulmonary hypertension worsening) was considered related to study treatment. Right heart failure triggered by ear infection had a fatal outcome 1 day after study treatment discontinuation. The death was considered by the investigator to be unrelated to study treatment. There were no other AEs leading to treatment discontinuation. Twenty-two patients (61.1%) experienced at least one AE, including those unrelated to study treatment. The most frequent treatment-emergent AEs were infections, experienced by 12 patients (33.3%), the vast majority being respiratory infections (9 patients, 25%), and abdominal pain/discomfort (7, 19.4%). No AEs of elevated liver enzymes or anemia were reported during the study or in the post-treatment period, and there were no clinically relevant changes in laboratory tests denoting liver function abnormalities or anemia. There were minor, not clinically relevant, changes in vital signs and ECG.

CONCLUSIONS:

- At a dose of 4 mg/kg b.i.d., the exposure to bosentan in pediatric PAH patients was not similar to that in adult PAH patients treated with bosentan 125 mg b.i.d (approximately 2 mg/kg b.i.d.). Based on the findings obtained at 2 mg/kg and 4 mg/kg, it is unlikely that increasing the dose of bosentan beyond 2 mg/kg in pediatric patients in a b.i.d. regimen will result in increased exposure to bosentan.
- Exploratory efficacy data were in line with findings in previous studies of bosentan in the pediatric PAH population.
- The pediatric formulation was well tolerated. AEs reported during this clinical trial were similar to those seen in previous trials. No new risks were identified in the pediatric patient population studied.

DATE OF THE REPORT:

15 November 2007