2 SYNOPSIS OF RESEARCH REPORT NO. D-06.141 (PROTOCOL BUILD 2-OL / AC-052-332)

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

TITLE OF THE STUDY	Abbreviated Final Study Report, BUILD 2-OL / AC-052-332. BUILD 2-OL: Bosentan Use in Interstitial Lung Disease (Open-Label) Long-term open-label study in patients with interstitial lung disease associated with systemic sclerosis who completed the protocol BUILD 2 /AC-052-330.		
STATUS OF STUDY / TYPE OF REPORT	Abbreviated Final Study Report		
INDICATION	Interstitial lung disease associated with systemic sclerosis		
INVESTIGATORS / CENTERS AND COUNTRIES	24 centers in 8 countries 3 centers in France: J. Cabane / Hopital St Antoine, Paris; L. Guillevin / Hopital Avicenne, Bobigny; E. Hachulla / CHRU, Lille 1 center in Germany: G. Riemekasten / Charité, Berlin 1 center in Israel: M. Kramer / Rabin Medical Center, Petach Tikva 3 centers in Italy: M. Matucci-Cerinic / Villa Monna Tessa, Firenze; R. Scorza / Ospedale Maggiore, Milano; S. Todesco / Policlinico Universitario, Padova 1 center in the Netherlands: F. van den Hoogen / Sint Maartenskliniek, Nijmegen 1 center in Sweden: A. Åkesson / University Hospital, Lund 2 centers in the U.K.: C. Black / Royal Free Hospital, London; P. Emery / General Infirmary, Leeds 12 centers in the U.S.A.: S. Chatterjee / Cleveland Clinic, Cleveland, OH; D.H. Collier / Denver Health Medical Center, Denver, CO; D. Furst / UCLA, Los Angeles, CA; R.W. Simms / University School of Medicine, Boston, MA; M. Mayes / University of Texas, Houston, TX; J. Molitor / Virginia Mason Medical Center, Seattle, WA; G. Raghu / University of Washington, Seattle, WA; V. Hsu / University of New Jersey, New Brunswick, NJ; L. Shapiro / The Center for Rheumatology, Albany, NY; R. M. Silver / Medical University of South Carolina, Charleston, SC; V. D. Steen / Georgetown University, Washington, DC; D. Schraufnagel / University of Illinois, Chicago, IL.		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	20-Jul-04 to 09-Feb-2006 (open-label period)	CLINICAL PHASE	2/3
OBJECTIVES	To collect long-term safety and efficacy data in patients with interstitial lung disease associated with systemic sclerosis, treated with bosentan.		

STUDY DESIGN	Multicenter, open-label, single arm, phase II/III study.
NUMBER OF SUBJECTS	100 patients in one group.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Only patients who completed the 12-month treatment period of the protocol AC-052-330/BUILD 2 were eligible for the open-label extension. Patients were excluded for any major violation of the protocol AC-052-330/BUILD 2. The main exclusion criteria in protocol AC-052-330/BUILD 2 (double-blind period) were: interstitial lung disease due to conditions other than systemic sclerosis, severe restrictive or obstructive lung disease, and significant pulmonary arterial hypertension. Other exclusion factors comprised severe co-morbidities, severe heart failure and treatment with high dose corticosteroids or immunosuppressive, cytotoxic or antifibrotic drugs. Patients who discontinued the BUILD 2 study prematurely for any reason, or failed to perform planned assessments, were not allowed to enter this Open-Label protocol.
TRIAL DRUG / BATCH No.	Oral bosentan (Ro 47-0203) 62.5 mg tablets, Batch No. FBP001 Batch No. C0407001 Oral bosentan (Ro 47-0203) 125 mg tablets, Batch No. FBR002 Batch No. FBR003
DOSE / ROUTE / REGIMEN / DURATION	Oral bosentan: - Initial dose 62.5 mg b.i.d. for 4 weeks. - Target dose 125 mg b.i.d., if the initial dose was well tolerated.
REFERENCE DRUG / BATCH No.	Not applicable; open-label extension study.
DOSE / ROUTE / REGIMEN / DURATION	Not applicable
CRITERIA FOR EVALUATION EFFICACY:	In light of AC-052-330/BUILD 2 double-blind period results, which failed to show a treatment effect in the primary endpoint (change from baseline to 12 months in 6-minute walk test), or consistent effects in secondary and exploratory efficacy endpoints, none of the efficacy endpoints were evaluated for the open-label extension.
SAFETY:	The safety endpoints included adverse events up to 24 hours after last dose of study medication, adverse events leading to permanent discontinuation of bosentan, and serious adverse events up to 28 days after last dose of study medication.

STATISTICAL METHODS:

No efficacy analysis was performed. Safety data were analyzed descriptively. No formal hypothesis testing was performed. Primarily descriptive methods were used and 95% confidence intervals were determined for key summary statistics.

Summary statistics for continuous variables included counts, mean, standard deviation, standard error, median, quartiles, minimum and maximum. Categorical variables were summarized using frequency and proportions.

The All-Enrolled set was used to describe patient disposition in the study, and the Safety set was used for the evaluation of demographic and safety data.

METHODOLOGY:

Following the End-of-Study visit in AC-052-330, all eligible patients started on oral bosentan 62.5 mg b.i.d. and were

up-titrated at Week 4 to achieve the target dose (125 mg b.i.d.) for the remainder of the treatment period, unless down-titrated for reasons of tolerability. Treatment duration was not defined in the open-label protocol. The sponsor decided to stop the study based on the absence of a treatment effect during the double-blind period. Patients were evaluated at enrollment and every three months thereafter. The 6-minute walk test (6MWT), pulmonary function tests (PFT), and other efficacy tests were performed at each visit. Adverse events and concomitant medications were monitored throughout the study; other safety parameters were assessed at enrollment and on an ongoing basis (monthly for the laboratory parameters).

PATIENT DISPOSITION:

100 patients were enrolled. A total of 16 patients did not complete the study.

EFFICACY RESULTS:

No efficacy analysis was performed.

SAFETY RESULTS:

Based on baseline characteristics, all patients had severe disease. Most patients experienced an adverse event (79.1% ex-bosentan and 80.7% ex-placebo). There was one death during the extension period. Thirty-one serious adverse events in 17 patients and 12 discontinuations due to adverse events were reported. The death was from cardiac arrest during treatment in the extension period and was assessed as not related to bosentan (ex-bosentan patient 551/570). One other death was reported after the follow-up period: it occurred in an ex-bosentan patient who had discontinued study medication since 60 days. The death was due to multi-organ failure and was assessed to be unrelated to bosentan. The overall incidences of liver enzyme abnormalities and anemia were 3.0% and 5.0%, respectively.

CONCLUSIONS:

The safety of bosentan as demonstrated in the open-label extension reported in this abbreviated study report was consistent with the known safety profile of bosentan: disease progression and AE rates in both ex-bosentan and ex-placebo groups were similar to those seen in previous trials. Study results in this limited set of patients with interstitial lung disease associated with systemic sclerosis do not materially affect the overall benefit/risk ratio of bosentan in other indications.

DATE OF THE REPORT:

14 January 2009