2 SYNOPSIS OF STUDY REPORT, DOC NO D-11.516 (AC-051-206)

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:	
Tezosentan	Type … *(ONLY DRA)*	
NAME OF ACTIVE SUBSTANCE(S):	Page:	
ACT-050089/Ro 61-0612	Type … *(ONLY DRA)*	

TITLE OF THE STUDY	Multicenter, open-label, non-comparative, proof-of-concept, phase 2a study to evaluate the effect of a single infusion of tezosentan on pulmonary vascular resistance in patients with stable, chronic pulmonary arterial hypertension, currently not treated with endothelin receptor antagonists, phosphodiesterase-5 inhibitors or prostacyclins.		
STATUS OF STUDY / TYPE OF REPORT	Due to slow recruitment this study was prematurely discontinued and, thus, the results are provided in an abbreviated report.		
INDICATION	Pulmonary arterial hypertension		
INVESTIGATORS / CENTERS AND COUNTRIES	Adaani Frost, Houston, TX, USA **(**only recruiting investigator) Murali Chakinala, St. Louis, MO, USA Gerald Simonneau, Paris, France Michael Tamm, Basel, Switzerland Laurent Nicod, Lausanne, Switzerland		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	14-Aug-2010 to 10-May-2011 (FPFV – premature termination)	CLINICAL PHASE	2a, Proof of concept

OBJECTIVES	The primary objective was to evaluate the effect of a single infusion of tezosentan on pulmonary vascular resistance (PVR) in patients with stable, chronic pulmonary arterial hypertension (PAH).
STUDY DESIGN	Multicenter, open-label, non-comparative, single infusion, proof-of-concept phase 2a study. The study consisted of a Screening Visit (< 28 days) and Day 1, where 2.5 mg tezosentan was given as a 30-minute infusion, after which patients stayed in the clinic for up to 24 hours post treatment, followed by a 30-day safety follow-up period.
NUMBER OF PATIENTS	13 patients were planned, but only 3 were included into the study.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adult patients (≥18 years) with stable, chronic PAH and modified NYHA functional class II or III, having: – Resting mean pulmonary arterial pressure (mPAP) ≥ 25 mmHg – Resting mean PVR ≥ 240 dyn·s·cm^{-5} – Pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg (confirmed by right heart catheterization). Patients with a positive response to the vasoreactivity test were not to be included in the study.
TRIAL DRUG / BATCH No.	Tezosentan (ACT-050089/Ro 61-0612) as a 1% solution diluted with 0.9%NaCl – for intravenous use. Batch number: 89208G001.
TRIAL DRUG DOSE / ROUTE / REGIMEN / DURATION	Tezosentan was administered as one continuous intravenous infusion of 5 mg/h over 30 minutes corresponding to a total dose of 2.5 mg.
REFERENCE DRUG / BATCH No.	None
REFERENCE DRUG DOSE / ROUTE / REGIMEN / DURATION	None

CRITERIA FOR EVALUATION	

EFFICACY:	**Primary Endpoint**
	• Change in pulmonary vascular resistance (PVR) from Baseline to 30 minutes expressed as percent of the Baseline value.
	Exploratory Endpoints
	• Change from Baseline to 30 minutes in the following hemodynamic effects:
	  • mean right atrial pressure (mRAP)
	  • mean pulmonary arterial pressure (mPAP)
	  • total pulmonary resistance (TPR)
	  • pulmonary capillary wedge pressure (PCWP)
	  • cardiac output (CO)
	  • cardiac index (CI)

SAFETY:	• Treatment-emergent adverse events (AEs) until end of study (EoS) • AEs leading to permanent discontinuation of study drug • Treatment-emergent serious adverse events (SAEs) until EoS • Change from Baseline to end of treatment (EoT) in vital signs (heart rate, systolic and diastolic blood pressure)

STATISTICAL METHODS:

The primary endpoint of this study was the change in PVR from Baseline to 30 minutes expressed as percent of the Baseline value.

The null hypothesis was of no change, the alternative being that the change was not zero.

The two-sided type-1 error was set to 0.05 and the type-2 error was set to 10%.

As the primary parameter was expected to be normally distributed, the one-sample Student's t-test was considered appropriate and was to be used to test the null hypothesis.

Given the above-mentioned conditions, a sample of 13 patients was required to detect an average change of at least 20% from Baseline to 30 minutes, with the assumption that the standard deviation of this parameter was 20%.

The per-protocol set was to be used for the primary analysis of this study, supportive

analyses were to be performed using the all-treated set (with appropriate imputation rules) as well as using the log-transformation of the value of PVR at 30 minutes expressed as percent of the Baseline value. No correction for multiple testing was to be applied for the exploratory parameters. Due to the premature study termination, demographic characteristics, study drug exposure and adverse events are provided in listings only.
PATIENT DISPOSITION:
A total of 3 patients were recruited, found eligible, received tezosentan (as a 30-minute infusion) and completed the study.
EFFICACY RESULTS:
Not applicable: efficacy was not analyzed due to the premature study termination.
SAFETY RESULTS:
No deaths, no SAEs, and no discontinuations due to AEs were reported in this study.
CONCLUSIONS:
Due to the premature termination, no overall conclusions can be drawn from this study.
DATE OF THE REPORT:
30 September 2011