2 SYNOPSIS OF STUDY REPORT, No. D-08-131 (AC-051-350)

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:	
Ro 61-0612/ACT-050089	Type … *(ONLY DRA)*	

TITLE OF THE STUDY	Multicenter, double-blind, randomized, placebo-controlled, parallel-group study to assess the efficacy, safety and tolerability of tezosentan in patients with pre-operative pulmonary hypertension, due to left heart disease, undergoing cardiac surgery		
STATUS OF STUDY / TYPE OF REPORT	[redacted] esults for the primary and secondary efficacy endpoints are provided, as is a complete analysis of safety findings.		
INDICATION	Pulmonary hypertension associated with left heart disease in patients on cardiopulmonary bypass (CPB)		
INVESTIGATORS / CENTERS AND COUNTRIES	Conducted at 31 centers in 14 countries worldwide. *Coordinating investigator:* André Denault, MD, Montreal Heart Center, Montreal, QC, Canada		
PUBLICATION (REFERENCE)	None		
PERIOD OF TRIAL	17 Apr 2007 to 08 Feb 2008 (first patient, first visit to last 28-day follow-up visit)	CLINICAL PHASE	3
OBJECTIVES	*Primary objective* – to demonstrate that in patients undergoing cardiac surgery with CPB, tezosentan reduces the incidence of clinically relevant right ventricular (RV) failure resulting in difficult separation from or need for return to CPB or use of ventricular assist device or death.		

	Secondary objectives – to evaluate the effect of tezosentan on the incidence of major clinical events, the time to successful weaning off CPB, and the time to discharge from the Intensive Care Unit (ICU) as well as the tolerability and safety of tezosentan in this patient population. Secondary objectives were originally to be evaluated on data from both AC-051-350 and AC-051-351.
STUDY DESIGN	Prospective, multicenter, randomized, double-blind, placebo-controlled, parallel-group superiority study. The study consisted of a < 28-day screening phase, a 24-h treatment period (with potential for up to 72 h), variable duration of post-surgery hospital care, and a 28-day safety follow-up period.
NUMBER OF PATIENTS	270 patients (135/group) were planned, 284 were randomized (139 and 145 to tezosentan and placebo, respectively), and 274 (133 and 141, respectively) were treated.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Adults (≥ 18 years) who were: Undergoing complex* cardiac surgery on CPB and had a systolic pulmonary arterial pressure (PAP) > 40 mmHg or a mean PAP > 30 mmHg (measured by right heart catheterization or echocardiography at screening) OR Undergoing non-complex cardiac surgery on CPB and had a systolic PAP > 60 mmHg with mean PAP/mean arterial pressure > 0.5 or a systolic PAP > 60 mmHg with signs and/or symptoms of RV dysfunction. *Surgery on two valves, surgery on one valve plus revascularization, or re-operation of previous valve surgery.
TRIAL DRUG / BATCH No.	Tezosentan (Ro 61-0612, ACT-050089) as a 1% solution in 0.9% NaCl for intravenous (i.v.) use Batch numbers: AQ87, AQ85
TRIAL DRUG DOSE / ROUTE / REGIMEN / DURATION	Tezosentan was administered as a continuous i.v. infusion of 5 mg/h from the time of chest incision until end of surgery (chest closure) followed by 1 mg/h for up to 24 h (total infusion).

	The 5-mg/h infusion could be decreased to 1 mg/h if clinically relevant hypotension (i.e., not related to blood/fluid loss) did not respond to standard therapy. If pulmonary pressures increased after discontinuation of study treatment and the investigator found it warranted, study treatment could be reinstated and continued for up to 72 h (total infusion).
REFERENCE DRUG / BATCH No.	Placebo solution matching tezosentan Batch numbers: AQ90, AQ86
REFERENCE DRUG DOSE / ROUTE / REGIMEN / DURATION	Placebo was administered in the same manner as tezosentan and with the same dosing options.
CRITERIA FOR EVALUATION EFFICACY:	*Primary endpoint*: Proportion of patients who experienced clinically relevant RV failure* evaluated 30 min after the end of CPB or, for death, up to 24 h after the start of weaning from CPB *Absence or significant reduction of RV wall motion by visual inspection peri-operatively and/or severe reduction of RV fraction area change (> 20%) measured by 2-dimensional echocardiography, requiring the use of ≥ 3 inotropic/vasopressor treatments or 2 at high doses (as defined), return to CPB, use of rescue therapy for high PAP, use of ventricular assist device, or having a fatal outcome (all causes). *Secondary endpoints*: • Proportion of patients with a major clinical event† within 28 days • Time to weaning from CPB • Time from end of CPB to final discharge from ICU †Death, major cardiovascular event (acute pulmonary edema, myocardial infarction, stroke, ventricular arrhythmia requiring cardioversion, cardiogenic shock, or cardiac arrest), infection that prolonged the hospital stay or required readmission, or new onset of renal failure requiring renal replacement therapy Exploratory endpoints were not analyzed for this report.
PHARMACOECONOMICS:	Not analyzed for this report

PHARMACOKINETICS:	Not analyzed for this report
SAFETY:	• Treatment-emergent adverse events (AEs) and serious adverse events (SAEs) up to 48 h after the end of study treatment • Deaths up to 24 h after weaning from CPB and up to 28 days after initiation of study treatment • Premature discontinuations of study treatment

STATISTICAL METHODS:

With a sample size of 270 and a 1:1 randomization, the study had 90% power to detect a relative risk reduction of 40% in the incidence of clinically relevant RV failure in the active treatment group from the expected incidence of 50% with placebo.

The primary endpoint was analyzed by comparing the incidence of clinically relevant RV failure with tezosentan to placebo (relative risk reduction) by means of the Fisher's exact test at a 0.05 (2-sided) significance level without adjustment for covariates. The main analysis was on the all-treated set, with a supportive analysis on the per-protocol set. Secondary endpoints were analyzed on the all-treated set, with that regarding proportions analyzed similarly to the primary endpoint. Time-to-event endpoints were analyzed using the Kaplan-Meier technique, with treatment effect evaluated as the hazard ratio provided with the p-value from the log-rank test.

Safety and baseline data were summarized descriptively.

PATIENT DISPOSITION:

The treatment groups were generally well matched with regard to demographics, planned cardiac surgery, and baseline characteristics.In each treatment group, 15 patients had study treatment discontinued prematurely, including 9 due to an adverse event and 1 due to death in each group. All but 1 patient who was lost to follow-up after receiving 24 h of tezosentan completed the 28-day follow-up.

EFFICACY RESULTS:

The incidence of clinically relevant RV failure during CPB was low in both tezosentan and placebo groups (10.5% and 11.3%, respectively), and the small difference between groups was not statistically significant (treatment effect 0.07, 95% confidence limits –0.83, 0.53, P = 0.8491). Results were similar in supportive analyses, and the events that denoted clinically relevant RV failure were similar in the 2 treatment groups. No treatment effects with tezosentan compared with placebo were indicated in secondary endpoints.

SAFETY RESULTS:

During and up to 48 hours after study treatment, all treatment-emergent abnormalities were to be reported as adverse events, and the overall incidence of adverse events was similar in the two treatment groups (73.7% and 71.6% in tezosentan and placebo groups, respectively). In these patients undergoing cardiac surgery, SAEs (36.1% and 37.6%,

respectively) and severe adverse events (26.3% and 19.9%) were common, but only 6.8% and 7.1% of patients, respectively, had study treatment prematurely discontinued because of an adverse event. Adverse events with a higher incidence on tezosentan than placebo (> 3% difference) included hypotension, anemia, acute renal failure, atrial fibrillation, complete atrioventricular block, multi-organ failure, thrombocytopenia, and decreased oxygen saturation. Among tezosentan-treated patients, hypotension was the event most frequently considered severe (5.3% and 2.8% of patients, in the tezosentan and placebo groups, respectively), the reason for premature discontinuation (3.0% and 2.1%), and at least possibly related to study treatment (12.8% and 10.6%).

Deaths up to 24 hours after weaning from CPB included one patient on tezosentan (congestive cardiac failure) and two on placebo (operative hemorrhage, systemic inflammatory response syndrome). Over 28 days, 9.8% and 6.4% of patients in the tezosentan and placebo groups, respectively, died for a variety of reasons, the most frequent among tezosentan-treated patients being multi-organ failure (3.0% and 1.4%, respectively) and low cardiac output (2.3% and none). All but two deaths, one in each treatment group, were considered by the investigator to be unrelated to study treatment.

CONCLUSIONS:

In this study of patients undergoing cardiac surgery, a decrease in the relative risk of clinically relevant right ventricular failure during weaning from cardiopulmonary bypass was not observed with a 24-hour infusion of tezosentan compared with placebo. Safety findings were similar to those previously reported with higher tezosentan doses in patients with acute heart failure.

DATE OF THE REPORT:

9 October 2008