2 SYNOPSIS OF STUDY REPORT, No. D-09.493 (NS-304/-02)

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:	
ACT-293987 (NS-304)	Type … *(ONLY DRA)*	
NAME OF ACTIVE SUBSTANCE(S):	Page:	
ACT-293987 (NS-304)	Type … *(ONLY DRA)*	

TITLE OF THE STUDY	A multicenter, multinational, open-label, single-dose, acute hemodynamic study followed by a multicenter, multinational, randomized, double-blind, parallel-group, placebo-controlled study to assess the safety, tolerability, pharmacokinetics, and preliminary efficacy (proof-of-concept) of ACT-293987 (NS-304) in the treatment of pulmonary arterial hypertension in subjects aged 18 years and over		
INDICATION	Pulmonary arterial hypertension (PAH)		
INVESTIGATORS / CENTERS AND COUNTRIES	Conducted at seven centers in Europe (one center per country in Austria, Belgium, France, Germany, Hungary, Italy, and Poland) *Coordinating investigator:* G. Simonneau, Hôpital Antoine Béclère, Clamart, France		
PUBLICATION (REFERENCE)	None.		
PERIOD OF TRIAL	16 April 2008 to 23 June 2009 (first patient, first visit to last patient, last visit	CLINICAL PHASE	2a
OBJECTIVES	*Acute hemodynamic period:* The primary objective was to evaluate the effect of the drug on right heart catheterization parameters (pulmonary vascular resistance [PVR], systemic vascular resistance [SVR], and PVR/SVR) after a single oral dose of ACT-293987. The secondary objective was to assess safety and tolerability of a single oral dose of ACT-293987.		

	Double-blind treatment period: The primary objective was a proof-of-concept assessment of the efficacy (change in PVR from baseline at Week 17) of ACT-293987 as add-on therapy in PAH patients compared with placebo. The secondary objective was to assess efficacy using the 6-min walk test, proportion of patients with aggravation of PAH, and right heart catheterization parameters other than PVR. The tertiary objective was to assess efficacy using New York Heart Association (NYHA) functional class, Borg dyspnea score, plasma NT pro-brain natriuretic peptide (NT pro-BNP) concentration, and echocardiographic parameters. Exploratory analyses were to include preliminary assessment of the dose-effect relationship in the changes in the primary, secondary, and tertiary efficacy variables, the safety and tolerability of ACT-293987, and plasma concentrations of ACT-293987 and ACT-333679 at Weeks 5 and 17 in PAH patients.
STUDY DESIGN	A multicenter, multinational, Phase 2a study consisting of two periods: an open-label, single-dose, acute hemodynamic testing period followed by a randomized, double-blind, placebo-controlled, parallel-group treatment period. The study consisted of a screening visit, acute hemodynamic testing following a single dose of ACT-293987, and a 21-week double-blind treatment period. Patients had the option to continue in a following open-label extension study, and those who did not continue were followed-up 30 days after the last visit.
NUMBER OF PATIENTS	44 patients (33 ACT-293987, 11 placebo) were planned and 43 patients were randomized (33 were treated with ACT-293987, and 10 patients received placebo).
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Male or female, ≥ 18 years of age with symptomatic PAH despite treatment with anticoagulants, calcium channel blockers, diuretics, cardiac glycosides, supplemental oxygen, endothelin-receptor antagonists, and/or phosphodiesterase type-5 inhibitors and having a PVR > 400 dyn·s/cm^5 and two 6-min walk tests between

	150 and 500 m (inclusive) and within ± 15%.
TRIAL DRUG / BATCH No.	Tablets containing 200-µg ofACT-293987 (NS-304) (Batch number: S-200-(2)
TRIAL DRUG DOSE / ROUTE / REGIMEN / DURATION	*Acute hemodynamic period:* single dose of ACT-293987 (200 µg for the first 12 patients and 400 µg for remaining patients, based on safety assessment of the first 12 patients) *Double-blind treatment period:* Each patient was started at 200 µg b.i.d. and up-titrated in 200-µg increments to the final optimized dose by Day 35 with a maximum dose of 800 µg b.i.d. (i.e., up-titration to 400 µg b.i.d. on Day 3, 600 µg b.i.d. on Day 7, and 800 µg b.i.d. on Day 21 if well tolerated)
REFERENCE DRUG / BATCH No.	Placebo matching ACT-293987 200-µg tablets, batch number P-0-(2)
CRITERIA FOR EVALUATION EFFICACY:	*Primary endpoints:* Acute hemodynamic period – Change in PVR from baseline to 4 hours after the single ACT-293987 dose Double-blind treatment period – Change in PVR from baseline to Week 17 *Secondary endpoints:* Change in 6-min walk test from baseline to Week 17 Patients (proportion) with aggravation of PAH Changes in right heart catheterization parameters other than PVR from baseline to Week 17 *Tertiary endpoints:* Changes from baseline to Week 17 in – NYHA functional class – Borg dyspnea score – plasma NT pro-BNP concentration – echocardiography parameters
PHARMACOKINETICS:	Non-compartmental analysis of the plasma concentration-time profiles of ACT-293987 and ACT-333679 at Weeks 5 and 17 was performed and the following pharmacokinetic parameters derived: – The area under the plasma concentration-time curve from zero to 8 hours (AUC_{0-8}).

	– The maximum plasma concentration (C_{max}). – The time to reach maximum plasma concentration (t_{max}).
SAFETY:	Treatment-emergent adverse events, during the acute hemodynamic period and during the double-blind period Treatment-emergent ECG findings during the acute hemodynamic treatment period and during the double-blind treatment period Change in clinical laboratory tests, vital signs, and ECG variables from baseline to the last values on double-blind treatment period Change in vital signs from baseline to 4 hours after single oral administration of ACT-293987 Treatment-emergent marked laboratory abnormalities

STATISTICAL METHODS:

For the primary endpoint, change from baseline to Week 17 in PVR, assuming a 300-dyn·s/cm^5 difference in mean change between treatment groups, a 300-dyn·s/cm^5 common standard deviation, and a 3:1 (ACT-293987:placebo) allocation ratio, 44 patients (33 ACT-293987:11 placebo) would provide 80% power to detect a difference between the two treatment groups, based on a two-sided t-test at the 5% significance level.

The primary endpoints for both the acute hemodynamic and double-blind periods were summarized descriptively by treatment for the absolute values and the change from baseline using the subjects belonging to the corresponding per-protocol sets. Values at 4 hours (for the acute hemodynamic period) and at Week 17 (for the double-blind period) were additionally expressed as a percent of the baseline value and summarized using geometric means and 95% 2-sided confidence limits (CL). Treatment comparisons used the Wilcoxon rank-sum test (primary) and the t-test (secondary).

Secondary and tertiary endpoints were analyzed descriptively on the all-treated DB set, with the caveat that treatment comparisons had no confirmatory value.

Safety, tolerability, and baseline characteristics were analyzed descriptively by treatment group.

PATIENT DISPOSITION:

The study population was 81.4% female and 88.4% Caucasian, with a median age of 57.0 years (range 19 to 80 years). PAH was idiopathic in 72.1% of patients and related to collagen vascular disease in 14.0%. The two treatment groups were well balanced. All patients completed the acute hemodynamic period, with 12 receiving 200 μg and 31 receiving 400 μg ACT-293987. All patients started double-blind treatment;

2 (6.1%) patients on active treatment were discontinued prematurely (1 (3.0%) due to hospitalization for worsening of PAH and 1 (3.0%) due to adverse event) and 1 (10.0%) on placebo due to hospitalization for worsening of PAH. All patients were included in the all-treated and safety analysis sets; 10 (4 (40%) on placebo and 6 (18.2%) on active) and 8 (4 (40%) on placebo and 4 (12.1%) on active) patients were excluded from the per-protocol hemodynamic (HD) and double-blind (DB) sets, respectively.

EFFICACY RESULTS:

The single oral dose of ACT-293987 administered during acute hemodynamic testing was not associated with an effect on PVR, whether the patient received a 200- or 400-µg dose, and there were no relevant treatment effects on other right heart catheterization parameters, including SVR.

After 17 weeks of twice-daily treatment uptitrated to the patient's optimized dose, a statistically significant 30.3% geometric mean decrease in PVR (95% CL –44.7%, –12.2%; P = 0.0045, Wilcoxon rank-sum test) was observed in patients treated with ACT-293987 compared with placebo (main analysis, per-protocol DB set). Similar results were obtained in the supportive analysis on the all-treated DB set (–33.0%, 95% CL –47.0, –15.2; P = 0.0022, Wilcoxon rank-sum test). At Week 17, PVR (geometric mean and 95% CL) in the active and placebo groups, respectively, was 80.7% (72.8, 89.6; n = 29) and 115.9% (106.5, 126.1; n = 6) of baseline values. The decrease in PVR with ACT-293987 was associated with an increase in cardiac index (median treatment effect 0.41 L/min/m^2, 95% CL 0.10, 0.71), a decrease in SVR (median treatment effect –427 dyn·s/cm^5, 95% CL –668.3, –134.5). The other RHC parameters did not show clear treatment effects.

A median increase in 6-min walk distance from baseline to Week 17 was observed with ACT-293987 compared with placebo (treatment effect 18.0 meters, 95% CL –12.4, 61.4), with no changes observed in Borg dyspnea score. One patient on ACT-293987 had an event that qualified as aggravation of PAH (3.0%) vs 2 (20%) on placebo. In the placebo group two patients worsened from NYHA class III to IV, one patient improved from class III to II; in the active group one patient worsened from class III to IV and one from class II to III, five patients improved (one from class II to I and four from class III to II). No treatment effect was observed in plasma NT pro-BNP concentrations. The echocardiography results were inconclusive due to the lower than expected number of assessments.

PHARMACOKINETIC RESULTS:

The plasma concentration-time profiles of ACT-293987 and ACT-333679 after multiple-dose administrations of 200, 400, 600 and 800 µg ACT-293987 at Week 5 and Week 17 were characterized by a median t_{max} of 2.5 hours for ACT-293987 and by a median t_{max} of 2.5–4 hours for ACT-333679. Overall steady-state exposures to ACT-293987 and ACT-333679 both at Week 5 and Week 17 were similar within and across the 400- to 800-µg dose range (except for the mean ACT-293987 exposure in the

600-µg dose group at Week 5, which was approximately 3-fold higher as compared to the 400- and 800-µg dose group), which could be due to low patient numbers studied and high variability. Due to this variability no clear dose-proportionality was observed in patients. The exposure to ACT-333679 was approximately 3–4 times higher than that of ACT-293987. Due to the low number of evaluable patients in the 200-µg group these data have to be considered with caution and no comparison to the other dose groups was performed.

SAFETY RESULTS:

During the acute hemodynamic period, 58.1% of patients had at least one adverse event, most commonly headache (46.5%) regardless of the dose (200 or 400 µg). During the double-blind treatment period, adverse events reported more frequently with ACT-293987 than placebo (> 10% difference) were headache, pain in jaw, pain in extremity, nausea, flushing, dizziness, cough, and myalgia. Two patients on ACT-293987 and one patient on placebo reported adverse events leading to premature discontinuation of study treatment. SAEs were experienced by 6 (18.2%) and 4 (40.0%) patients on ACT-293987 and placebo, respectively, with headache the only SAE experienced by more than a single patient (i.e., 2 patients) on ACT-293987. There were no deaths and no changes in laboratory or ECG parameters that could be associated with ACT-293987 treatment. There were no clinically relevant changes in blood pressure and pulse rate observed at 4 hours after the single dose and no changes were observed after multiple-dose treatment with the optimized dose during the double-blind treatment period.

CONCLUSIONS:

A single oral dose of ACT-293987 had no relevant effect on PVR or SVR 4 hours after treatment.

The efficacy of ACT-293987 in the treatment of patients with PAH receiving PAH specific background therapy was demonstrated in this proof-of-concept study by the significant 30% reduction in PVR after 17 weeks of multiple-dose treatment compared with placebo. Results were supported by improvement in cardiac index, and an observed improvement in 6-minute walk distance. The compound was well tolerated, with no evidence for safety concerns.

DATE OF THE REPORT:

20 January 2010