2 SYNOPSIS OF RESEARCH REPORT No. D-07.213 (PROTOCOL AC-054-201)

COMPANY:	TABULAR FORMAT REFERRING TO MODULE 5 OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
Actelion Pharmaceuticals Ltd	Type … *((ONLY DRA))*	
NAME OF FINISHED PRODUCT:	Volume:	
	Type … *((ONLY DRA))*	
NAME OF ACTIVE SUBSTANCE(S):	Page:	
Clazosentan (AXV-034343/VML 588/Ro 61-1790)	Type … *((ONLY DRA))*	

TITLE OF THE STUDY	A Phase IIb, multi-center, international, double-blind, randomized, placebo-controlled, parallel-group, dose-finding study for the prevention of cerebral vasospasm after aneurysmal subarachnoid hemorrhage (aSAH) by intravenous administration of clazosentan, a selective endothelin A (ET_A) receptor antagonist.		
INDICATION	Aneurysmal subarachnoid hemorrhage		
INVESTIGATORS / CENTERS AND COUNTRIES	Multicenter study in 52 centers including Austria (4), Canada (5), Finland (2), France (5), Germany (8), Israel (3), Italy (3), Sweden (4), Switzerland (2), the United Kingdom (3), and the United States (13). Coordinating Investigator: Dr R. Loch Macdonald		
PUBLICATION (REFERENCE)	None to date		
PERIOD OF TRIAL	10 January 2005 to 30 March 2006	CLINICAL PHASE	IIb
OBJECTIVES	The primary objective was to assess the efficacy of three dose levels (1 mg/h, 5 mg/h and 15 mg/h) of clazosentan in preventing the occurrence of cerebral vasospasm following aSAH. Secondary objectives of the study were to assess the ability of clazosentan to reduce the occurrence of a composite endpoint of mortality and vasospasm-related morbidity at 6 weeks, the effect of clazosentan on clinical outcome at 12 weeks and the safety [redacted] and tolerability of three dose levels of clazosentan.		
STUDY DESIGN	Multi-center, international, double-blind, randomized, placebo-controlled, parallel-group, dose-finding Phase IIb study. Randomization was stratified by center and procedure option, i.e., endovascular coiling versus surgical clipping.		
NUMBER OF SUBJECTS	Planned: Total of 400 patients, divided into 4 equal groups of 100 patients, in order to obtain a total of 316 evaluable patients. Recruited: 413, Treated: 409 Included in per-protocol set: 354		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	The main inclusion criteria were: female or male patients aged 18 to 70 years (inclusive); a ruptured saccular aneurysm that had been confirmed by digital subtraction angiography (DSA) and for which clipping or coiling was possible; a diffuse or localized thick subarachnoid clot on baseline computerized tomography (CT) scan; World Federation of Neurological Surgeons (WFNS) Grades I – IV, and those Grade V patients		

	who improved to Grade IV or less after ventriculostomy.
TRIAL DRUG / BATCH No.	Clazosentan: 10 mL, 25 mg/mL clazosentan in saline for i.v. use; Batch Number PD04056 (1 mg/h and 5 mg/h) and PD04057 (15 mg/h)
DOSE / ROUTE / REGIMEN / DURATION	Intravenous clazosentan 1 mg/h, 5 mg/h and 15 mg/h starting within 56 hours maximum after aneurysm rupture and continuing until Day 14 post-aneurysm rupture.
REFERENCE DRUG / BATCH No.	Intravenous placebo matching clazosentan: 10 mL saline for i.v. use; Batch Number PD04118.
DOSE / ROUTE / REGIMEN / DURATION	Intravenous placebo starting within 56 hours maximum after aneurysm rupture and continuing until Day 14 post-aneurysm rupture
CRITERIA FOR EVALUATION EFFICACY:	Primary efficacy endpoint: • Occurrence of moderate or severe vasospasm within 14 days post-aneurysm rupture confirmed by central assessment of post-baseline DSA(s). Secondary efficacy endpoints: • Occurrence of vasospasm-related morbidity and mortality of all causes defined as the occurrence of at least one of the following endpoints: death of any cause within the first 6 weeks post-aneurysm rupture; new cerebral infarct within first 6 weeks post-aneurysm rupture based on local investigator reading of post-baseline CT scans; delayed ischemic neurological deficits (DIND) due to vasospasm (based on investigator assessments) within 14 days post-aneurysm rupture; use of rescue medication due to vasospasm within 14 days post-aneurysm rupture. • Clinical outcome at 12 weeks post-aneurysm rupture as measured by the Glasgow Outcome Scale - Extended Version (GOSE) score and the Modified Rankin Scale (mRS) score. Exploratory endpoints: • [redacted]

	• [redacted] [redacted] [redacted] *Post-hoc* exploratory endpoints • Modified composite morbidity and mortality endpoint (up to 6 weeks post-aneurysm rupture) defined as the occurrence of at least one of the following endpoints: o death from any cause o new cerebral infarct excluding causes not related to vasospasm at any time post-procedure (central assessment) o DIND defined as neurological worsening due to confirmed post-baseline vasospasm (central assessment) o use of any rescue medication • Glasgow Outcome Scale Extended (GOSE) at Week 12 post-aSAH, dichotomized into good (score > 4) and poor (score ≤ 4) outcome.
SAFETY:	• Death and cause of death up to Week 12 post-aneurysm rupture. • Treatment-emergent adverse events (AEs) up to 24 hours after study drug discontinuation. • AEs leading to premature discontinuation of study drug. • Serious adverse events (SAEs) up to 28 days after study drug discontinuation. • Occurrence of treatment-emergent marked laboratory abnormalities (MLAs). • Occurrence of treatment-emergent vital signs abnormalities. • Occurrence of treatment-emergent electrocardiographic abnormalities at the end of the treatment period. • Occurrence of cerebral hemorrhage up to 24 hours after study drug discontinuation. • Occurrence of hypotension, hyponatremia, hypernatremia, anemia, lung complications up to 24 hours after study drug discontinuation.

STATISTICAL METHODS:

The treatment groups were compared using Fisher's exact test for the primary endpoint and the occurrence of morbidity/mortality (secondary endpoint), as well as for the *post hoc* defined exploratory endpoints (the modified morbidity/mortality endpoint and the dichotomized GOSE) . The mRS scores and the GOSE scores were compared using the Pitman Permutation test (scores = raw data).

Inferential methods were aimed at demonstrating the superiority of individual clazosentan dose groups over placebo. To adjust for multiple testing the Bonferroni-Holm rule was applied. Each clazosentan dose level was compared against placebo. Hypothesis testing to compare the effect of clazosentan versus placebo was performed using two-sided tests at a global significance level of 5%.

Seventy-nine evaluable patients per treatment group were required to have 90% power to detect a relative risk

reduction of 50% in the primary endpoint with an expected placebo rate of 60%, and using a two-sided type-I error of 0.0166 for each dose comparison against placebo.

The exact 95% (2-sided) confidence intervals were calculated for proportions using the Clopper-Pearson formula and for the differences in proportions using the Anderson-Hauck formula. For the relative risk ratios 95% (2-sided) confidence intervals using normal approximation were provided. The 95% confidence intervals for the means and the difference between two means were calculated with the quantile of the t-distribution.

The potential effects of clipping/coiling and US versus non-US were explored by fitting a linear logistic regression model by the method of maximum likelihood. P-values were derived from the Wald chi-square statistic.

The primary efficacy analysis was based on the per-protocol set. The all-treated set was used for the analyses of the secondary and exploratory endpoints as well as for supplemental primary endpoint analyses.

Treatment-emergent AEs, SAEs and marked laboratory abnormalities were summarized by frequencies and percentages.

No efficacy interim analyses were performed.

METHODOLOGY:

Screening was performed within 48 hours post-aneurysm rupture and study drug infusion began within 56 hours maximum post aneurysm rupture. The treatment procedure (coiling or clipping) started within the 68 hours post-aneurysm rupture and no later than 12 hours after initiation of the study drug infusion (if performed after start of infusion). Treatment continued until Day 14 post-aneurysm rupture. DSA was performed at screening and on Day 9 ± 2 post-aneurysm rupture; if there were clinical or sonographic changes suggestive of vasospasm prior to or after Day 9 ± 2 and until Day 14 post-aneurysm rupture, an angiogram was performed to confirm the vasospasm. If any follow-up angiogram was positive for moderate to severe vasospasm prior to the scheduled examination on Day 9 ± 2, there was no further need to perform the latter. Neurological scales (modified Glasgow Coma Scale [mGCS], abbreviated NIHSS [ab. NIHSS]), pupil size and reactivity were measured at randomization, during the treatment period up to Day 14 post-aneurysm rupture, and at the end of the infusion.

Follow-up was at 6 and 12 weeks post-aneurysm rupture. A CT scan was performed [redacted] was measured at 6 weeks. The [redacted] combined GOSE/mRS [redacted] were administered at 12 weeks. The GOSE/mRS [redacted] were administered via telephone by a central interviewer.

Vasospasm was assessed locally by the investigator, and also centrally to ensure consistency. The latter measurement was used for the primary efficacy analysis. Vasospasm was defined as none or mild 0–33%; moderate 34–66%; severe 67–100%.

PATIENT DISPOSITION and CHARACTERISTICS

Altogether, 413 patients were randomized: 96 to placebo; 108 to 1 mg/h; 111 to 5 mg/h; 98 to 15 mg/h. Of these, 96, 107, 110 and 96, respectively, received study drug and were included in the all-treated set and safety set. Treatment was discontinued prematurely by 11, 24, 25 and 19 patients, respectively; scheduled treatment was thus completed by 85 (88.5%), 83 (76.9%), 85 (76.6%) and 77 (78.6%) patients in the all-randomized set, respectively. [redacted] Of those randomized to placebo, 1 mg/h, 5 mg/h and 15 mg/h, 11 (11.5%), 8 (7.4%), 13 (11.7%) and 13 (13.3%) patients discontinued prematurely from the study. The main reason for premature study discontinuation was death (4, 5, 9 and 7 patients, respectively), followed by administrative/other (5, 3, 3 and 5 patients respectively).

The per-protocol set, which excluded major protocol violators, comprised 85 patients treated with placebo, 95 treated with 1 mg/h, 95 treated with 5 mg/h and 79 treated with 15 mg/h clazosentan.

Within the all-treated set, the numbers (%) of patients who were male in the placebo, 1 mg/h, 5 mg/h and 15 mg/h groups were 32 (33.3%), 28 (26.2%), 35 (31.8%) and 25 (26.0%). The mean (range) ages of the patients in each of the treatment groups were 52.2 (18–70), 50.9 (29–70), 51.2 (20–71) and 50.1 (19–70). The groups were comparable with regard to GCS at screening and admission blood pressure; the majority of patients (approximately 70% of each group) were of WFNS grades I or II. [redacted] Overall, 27.4% of patients were recruited from centers in the United States, with a similar distribution in all treatment arms. [redacted]

The aneurysm-securing procedure was surgical clipping in 45.2% of patients and endovascular coiling in 54.8% (all-treated set).

The treatment groups were generally well balanced with regard to the time from aneurysm rupture to start of treatment (mean 39.3–42.5 hours for clazosentan groups and 39.2 hours for placebo). The mean exposure to study treatment ranged from 12.2 to 13.0 days, with a median duration of 13.0 days in each group.

The per-protocol, all-randomized and all-treated sets were generally comparable with regard to baseline characteristics.

EFFICACY RESULTS:

The primary efficacy endpoint, the occurrence of moderate/severe vasospasm up to 14 days post-aneurysm rupture (central reading, per protocol set), is summarized in the table. A decrease in vasospasm incidence with clazosentan treatment was observed; the comparison with placebo was statistically significant at all doses. A dose-relationship was observed.

	Placebo	1 mg/h	5 mg/h	15 mg/h
Assessed	85	95	95	79
With moderate/severe vasospasm	56 (65.9%)	41 (43.2%)	37 (38.9%)	18 (22.8%)
Treatment effect		-22.7%	-26.9%	-43.1%
Adjusted p value		0.0027	0.0007	< 0.0001
Relative risk reduction		0.34	0.41	0.65

The results for the all-treated set were similar to those for the per-protocol set: the proportions of patients with moderate or severe vasospasm (central reading) were 66.7%, 47.7%, 40.9% and 31.3% for placebo and clazosentan 1, 5 and 15 mg/h groups, respectively. The effect of clazosentan on the incidence of vasospasm was statistically significant at all doses.

[redacted]

For the secondary efficacy endpoint of vasospasm-related morbidity and mortality of all causes within 6 weeks of aneurysm rupture, there was no evidence of benefit of clazosentan treatment: the proportions of patients (all-treated set) with morbidity or mortality were 31.3%, 37.4%, 30.9% and 37.5%, in the placebo, 1, 5, and 15 mg/h groups, respectively. This endpoint was analyzed using the local investigator assessments.

In a *post-hoc* analysis of morbidity/mortality, using a modified definition and blinded central assessments (performed after database lock), decreased incidences of morbidity/mortality were observed in the active treatment groups (37.1%, 28.3%, 29.0% in the 1, 5, and 15 mg/h groups respectively) versus placebo (39.1%). These results were obtained after excluding hypodensities on CT scans, which were unrelated to vasospasm. The relative risk reduction was similar with the 5 mg/h and 15 mg/h doses: 28% and 26%, respectively. The differences observed were not statistically significant at any dose.

In the clipped and coiled strata, benefits of active over placebo treatment were observed for the occurrence of morbidity or mortality (modified definition): in the clipped stratum, the incidence in the placebo group was 45.2% compared with 46.3%, 25.0% and 39.5% in 1 mg/h, 5 mg/h and 15 mg/h groups, respectively; in the coiled stratum, the incidence in the placebo group was 34.0% compared with 31.3%, 31.5% and 20.0% in 1 mg/h, 5 mg/h and 15 mg/h groups, respectively.

The percentage of patients with new cerebral infarcts occurring after post-procedure and up to Week 6 CT scan (centrally assessed CT scan, including all hypodensities such as encephalomalacia due to ventricular drains, procedure-related causes, and intracerebral hemorrhage) was similar between clazosentan-treated groups and placebo [redacted] In contrast, patients with cerebral infarcts due only to cerebral vasospasm showed occurrences of 12.6%, 8.6%, 4.5% in the 1, 5, 15 mg/h groups, compared with 18.7% in the placebo group. [redacted]

No relevant treatment effect on functional outcome, as measured by the Glasgow Outcome Scale (extended version), and the modified Rankin Scale, was observed on the overall population. [redacted]

SAFETY RESULTS:

[redacted] Pleural effusion, pulmonary edema, hypotension, acute respiratory distress syndrome, and hyperglycemia were more common at all doses of clazosentan than with placebo. Hyponatremia and hydrocephalus were less frequent with clazosentan treatment than placebo. Anemia was more common with clazosentan treatment than placebo, with the difference between active and placebo treatment being greatest at 1 and 5 mg/h. In the clipped population, the incidences of pulmonary complications, hypotension and anemia were lower in the 5 mg/h group than in the 15 mg/h group.

[redacted]

There were 25 deaths within 12 weeks after aneurysm rupture in the all-randomized set, 24 of which occurred in patients who had received treatment: 4 (4.2%) placebo patients, 4 (3.7%) 1 mg/h clazosentan patients, 9 (8.2%) 5 mg/h clazosentan patients and 7 (7.3%) 15 mg/h clazosentan patients. One death in the clazosentan group was considered by the investigator to be related to study treatment. In the all-randomized set, one patient randomized to 1 mg/h clazosentan died prior to receiving study drug. Of all fatal cases, 2 out of 4 in the placebo group and 12 out of 21 in the clazosentan groups occurred in patients suffering major intraoperative complications.

[redacted]

[redacted]

CONCLUSIONS:

The study met its primary objective: clazosentan significantly reduced the incidence of moderate to severe vasospasm at all tested doses and in an apparently dose-related manner from 65.9% in the placebo group to 43.2%, 38.9%, and 22.8% in the clazosentan 1, 5, and 15 mg/h groups, respectively. This represents a relative risk reduction of 65% versus placebo at the highest clazosentan dose.

[redacted]

There was no consistent effect on the number of new cerebral infarcts when all new hypodensities were considered as new infarcts. However, there was a trend towards a decrease in total infarct and hypodensity volume in the clazosentan groups. This prompted the *post-hoc* blinded reassessment of new infarcts based on their specific etiologies, which indicated a dose-related decrease in the incidence of vasospasm-related new infarcts in the clazosentan groups compared to placebo.

Based on local investigator assessments, no difference was observed in the occurrence of vasospasm-related morbidity or all-cause mortality between placebo and active treatment. The subsequent *post-hoc* central blinded assessment and analysis indicated that the incidence of the modified morbidity/mortality endpoint was lower in the groups treated with clazosentan. Analysis of the individual components of the modified endpoint suggested dose-related decreases in the incidences of new infarcts related to vasospasm, and DIND for patients treated with clazosentan. The administration of rescue therapy was also observed to be less frequent at the two highest doses of clazosentan, compared to placebo.

No effect of clazosentan treatment was observed on clinical outcome at 12 weeks post-aSAH, as measured by the GOSE in the overall study population. [redacted]

Treatment with clazosentan was associated with certain adverse effects; pulmonary complications, hypotension, anemia, and hyperglycemia were all more commonly reported with clazosentan than placebo. Hypotension was reported most frequently at doses of 5 and 15 mg/h and was apparent after 24 hours of treatment.

[redacted]

DATE OF THE REPORT:

07 August 2007