2 SYNOPSIS OF STUDY REPORT, No. D-09.038 (AC-054-301)

COMPANY: Actelion Pharmaceuticals Ltd NAME OF FINISHED PRODUCT: Clazosentan NAME OF ACTIVE SUBSTANCE(S): AXV-034343	TABULAR FORMAT REFERRING TO PART Enter Part OF THE DOSSIER Type … *(ONLY DRA)* Volume: Type … *(ONLY DRA)* Page: Type … *(ONLY DRA)*	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY	A prospective, multi-center, double-blind, randomized, placebo-controlled, parallel-group study to assess the efficacy and safety of clazosentan in reducing vasospasm-related morbidity and all-cause mortality in adult patients with aneurysmal subarachnoid hemorrhage treated by surgical clipping.		
INDICATION	Aneurysmal subarachnoid hemorrhage		
INVESTIGATORS / CENTERS AND COUNTRIES	Multicenter study in 102 centers including Australia (2), Austria (6), Belgium (1), Canada (7), China (5), Croatia (1), Czech Republic (4), Denmark (2), Finland (3), France (2), Germany (10), Hong Kong (2), India (6), Italy (5), Korea (9), New Zealand (1), Norway (3), Poland (6), Russia (1), Serbia (2), Singapore (1), Slovenia (1), Spain (3), Sweden (3), Switzerland (5), USA (10), and Ukraine (1). Coordinating Investigator: Dr R. Loch Macdonald.		
PUBLICATION (REFERENCE)	Macdonald RL, Higashida RT, Keller E, et al. Preventing vasospasm improves outcome after aneurysmal subarachnoid hemorrhage: rationale and design of CONSCIOUS-2 and CONSCIOUS-3 trials. Neurocritical Care 2010;13(3):416–24.		
PERIOD OF TRIAL	14 Dec 2007 to 13 Jul 2010 (first patient, first visit to last patient, last visit)	CLINICAL PHASE	3
OBJECTIVES	The primary objective was to demonstrate that clazosentan reduces the incidence of cerebral vasospasm-related morbidity and all-cause mortality within 6 weeks post-aneurysmal subarachnoid hemorrhage (aSAH) treated by surgical clipping.		

	Secondary objectives were: • To demonstrate that clazosentan improves clinical outcome at Week 12 post-aSAH treated by surgical clipping, as measured by the dichotomized GOSE (Glasgow Outcome Scale [extended version]). • To evaluate the impact of clazosentan on total infarct volume at Week 6 post-aSAH treated by surgical clipping, and on each individual component of the primary endpoint. • To evaluate the safety and tolerability of clazosentan.
STUDY DESIGN	Phase 3, prospective, multi-center, international, double-blind, randomized, placebo-controlled, parallel-group study. Screening was performed within a sufficient time window to allow for subsequent randomization and start of study drug infusion within 56 hours post-aSAH. Study-specific screening activities were permitted to start prior to the clipping procedure, provided that the informed consent had been signed. Once all screening procedures were completed and the entry criteria had been met, patients were randomized either to clazosentan 5 mg/h or to matching placebo. Treatment allocation was stratified according to investigational study site and was designed to occur in a 2:1 ratio (active treatment:placebo). Study treatment was scheduled to continue during the hospitalization until Day 14 post-aSAH, or at least until Day 10 post-aSAH for patients discharged before Day 14. Computed tomography (CT) scans, angiograms and electrocardiograms (ECGs) were sent to central laboratories for evaluation. Blood samples were collected and sent to a central laboratory for hematology, biochemistry, and pharmacokinetic (PK) assessment and analysis. There were two follow-up 'visits': a hospital visit at Week 6 post-aSAH, and a telephone contact and separate telephone interview at Week 12 post-aSAH (end of study). The total study duration for a given patient was 12 weeks.

NUMBER OF PATIENTS	It was estimated that 1,156 patients needed to be randomized, assuming that approximately 1% of the patients would not receive study drug. Randomization continued until 1,146 patients were treated, which resulted in the recruitment of a total of 1,157 patients. The All-treated and the Safety sets were identical and included all 1,147 patients who received study treatment. Of those randomized, 89.0% (1,030/1,157) were included in the Per-protocol analysis set.
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Male and female adult patients were included with aSAH secondary to rupture of a saccular aneurysm, secured by surgical clipping and without any major procedure-related complications. Patients with a recent aSAH confirmed by CT scan and angiography were considered for screening if it was judged possible to start study drug within 56 hours of the aneurysm rupture. Patients were to have a significant subarachnoid blood clot thickness as observed on baseline CT (investigator's assessment), and be categorized as World Federation of Neurosurgical Societies (WFNS) grades I–IV. Study drug was administered in addition to standard subarachnoid hemorrhage (SAH) treatment, which may have included oral nimodipine.
TRIAL DRUG / BATCH No.	Clazosentan/AXV-034343: clazosentan 25 mg/mL (2.5% w/v). Trial drug was supplied in several batches.
TRIAL DRUG DOSE / ROUTE / REGIMEN / DURATION	A continuous, [redacted] intravenous infusion of clazosentan [redacted] (5 mg/h) was started within 56 hours post-aSAH and was scheduled to continue during the hospitalization until Day 14 post-aSAH, or at least until Day 10 post-aSAH for patients discharged before Day 14.
REFERENCE DRUG / BATCH No.	Placebo: buffered normal saline (pH 8). The reference drug was supplied in several batches.
REFERENCE DRUG DOSE / ROUTE / REGIMEN / DURATION	A continuous, [redacted] intravenous infusion of placebo-matching clazosentan was started within 56 hours post-aSAH and was scheduled to continue during the hospitalization until Day 14 post-aSAH, or at least until Day 10 post-aSAH for patients discharged before Day 14.

CRITERIA FOR EVALUATION EFFICACY:	The primary efficacy endpoint of the study was the occurrence of cerebral vasospasm-related morbidity and mortality of all causes within 6 weeks post-aSAH. The primary endpoint was defined as the occurrence of one of the following: • Death (all causes) • New cerebral infarct(s) due to cerebral vasospasm as either the primary or relevant contributing cause, or not adjudicated to be entirely due to causes other than vasospasm • Delayed ischemic neurological deficit (DIND) due to cerebral vasospasm as either the primary or relevant contributing cause, or not adjudicated to be entirely due to causes other than vasospasm • Neurological signs or symptoms (depending on state of consciousness), in the presence of confirmed cerebral vasospasm on angiography, leading to the administration of a valid rescue therapy. An independent Critical Events Committee (CEC) adjudicated whether or not patients met the primary endpoint and its individual morbidity components. The secondary endpoints were: • GOSE at Week 12 post-aSAH, dichotomized into good (score > 4) and poor (score ≤ 4) outcomes. • Total volume of new cerebral infarcts of all etiologies at Week 6 post-aSAH, derived from the CEC assessment, and classified according to the following categories: 0 (no infarct), > 0–< 5 cm^3, 5–30 cm^3, > 30–70 cm^3, > 70–100 cm^3, > 100 cm^3. • The occurrence of death and the individual morbidity components of the primary composite endpoint.
PHARMACOKINETICS/ PHARMACODYNAMICS:	The PK/pharmacodynamic (PD) endpoints are provided in a separate report.
PHARMACOECONOMICS:	Since the study did not meet the primary and the main secondary efficacy endpoints, the health economic endpoints were not analyzed for this report.

SAFETY:

The main safety endpoints were:

- Occurrence of death up to Week 12 post-aSAH.
- Occurrence of treatment-emergent adverse events (AEs) up to 1 day after study drug discontinuation.
- Occurrence of AEs of special interest i.e., lung complications, lung complications related to pulmonary edema, hypotension, anemia, cerebral hemorrhage, eye disorders, hepatobiliary events, rhythm and conduction disorders and cardiac ischemic events, up to 1 day after study drug discontinuation, and up to Week 6 post-aSAH (excluding hepatobiliary events).
- Occurrence of new or worsened cerebral infarcts of all etiologies up to Week 6 post-aSAH, as assessed by the CEC.
- Average daily change from baseline during study drug infusion period in systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR).
- Occurrence of AEs leading to premature discontinuation of study drug.
- Occurrence of serious adverse events (SAEs) up to 28 days after study drug discontinuation.
- Occurrence of treatment-emergent marked laboratory abnormalities and change from baseline to end of study drug administration for selected centrally assessed laboratory variables.
- Occurrence of treatment-emergent ECG abnormalities based on central reading.
- Change in QT corrected for HR according to the methods of Fridericia (QT_CF) and Bazett (QT_CB), QRS, PR interval and HR from baseline to Day 3 ± 2 and Day 9 ± 2 of study drug infusion, and from baseline to end of study drug administration, based on central reading.
- Occurrence of a treatment-emergent increase of > 60 ms in QT_CF or QT_CB based on central reading.
- Occurrence of a treatment-emergent QT_CF or QT_CB > 500 ms based on central reading.

STATISTICAL METHODS:

The null hypothesis was that the primary endpoint of the occurrence of morbidity/mortality in patients treated with clazosentan 5 mg/h was not different from placebo. The alternative hypothesis was that the event rates were different between the treatment groups.

The treatment effect was tested by means of logistic regression adjusting for WFNS (I, II, > II).

The Wald Chi-Square test together with the 95% CLs (confidence limits) was used to determine the treatment effect.

The clinical outcome described by GOSE dichotomized into poor outcome, score (≤ 4) and good outcome, score (> 4) was analyzed using the same method as for the primary endpoint. A predefined hierarchical testing strategy was to be used. If the primary endpoint reached significance, the treatment effect of the main secondary endpoint of the dichotomized GOSE was determined at a two-sided nominal of 0.05.

Sample size consideration for the primary endpoint: With an experiment-wise two-sided type-I error set at 5%, a sample size of 1,146 treated patients (764 active treatment and 382 placebo) had a 90% power to detect a relative risk reduction of 30% in the occurrence of cerebral vasospasm related morbidity/all-cause mortality.

PATIENT DISPOSITION:

A total of 1,157 patients were randomized, 389 to placebo and 768 to clazosentan. Of these, 383 received placebo and 764 received clazosentan 5 mg/h, resulting in 1,147 treated patients. An equal proportion (92.0%) of the randomized patients in each of the two treatment arms completed the study up to Week 12 (i.e., Week 12 visit and/or interview performed).

The main reasons for premature discontinuation from the study were death and withdrawal of consent. In the clazosentan group, 42 patients (5.5%) discontinued the study due to death, and 11 patients (1.4%) withdrew consent. In the placebo group, 22 patients (5.7%) discontinued the study due to death, and eight patients (2.1%) withdrew consent. One patient in the clazosentan group was lost to follow-up. According to information received from the investigator, this patient was alive at Week 12 after aSAH.

More patients discontinued study treatment in the clazosentan group (16.1%) compared to placebo (11.2%). In the clazosentan group, 8.5% of patients discontinued treatment due to AEs compared to 5.2% on placebo.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS:

Enrolled patients were predominantly female (67.6%), Caucasian (71.4%) and aged between 18–75 years (median age: 52 years). The demographic and baseline disease characteristics were similar for the two treatment arms.

According to central assessment 50.1% patients had a diffuse thick clot and 34.5% patients had a local thick clot on baseline CT scan. Clinical neurological assessments measuring disease severity (WFNS grade I [good] to WFNS grade V [poor]) showed that a high proportion of patients were graded as good (WFNS grade I [50.4%] or II [27.5%]). There were no major imbalances in the two treatment arms with regards to WFNS grades at admission.

EFFICACY RESULTS:

The incidence of cerebral vasospasm-related morbidity and mortality of all causes within 6 weeks post-aSAH was 21.1% in the clazosentan group compared with 25.3% in the placebo group. The relative risk reduction (without adjustment for WFNS) with clazosentan was 17%. The primary analysis (logistic regression analysis adjusted for WFNS) comparing clazosentan and placebo for cerebral vasospasm-related morbidity and mortality of all causes within 6 weeks post-aSAH (primary endpoint) showed an odds ratio (OR) (clazosentan:placebo) of 0.783 (95% CLs 0.583–1.051, P = 0.1037).

The incidence of poor clinical outcome (main secondary endpoint), i.e., GOSE score ≤ 4 at 12 weeks post aSAH was 29.3% in the clazosentan group compared with 24.8% in the placebo group. The relative risk reduction was –18%. The logistic regression analysis comparing clazosentan and placebo for poor clinical outcome showed an OR (clazosentan:placebo) of 1.277 (95% CLs 0.950–1.716, P = 0.1048) The distribution of patients with GOSE score ranging from 1 (death) to 8 (good recovery) was similar between the two treatment groups.

In the subgroup analyses, the subgroups with admission WFNS grade > II, and diffuse thick clot suggested a treatment effect (upper 95% CL < 1.0) of clazosentan for the occurrence of morbidity/mortality events. However, clazosentan was not associated with a beneficial effect on the dichotomized GOSE score in these subgroups i.e., the event rate for poor clinical outcome (GOSE ≤ 4) was similar for the two treatment groups.

In the analysis of the individual components of the primary endpoint, treatment with clazosentan did not reduce the risk of death of all causes. Treatment with clazosentan was associated with a relative risk reduction of 12% for the occurrence of new cerebral infarct and 17% for DIND post-aSAH compared to placebo. Furthermore, a higher proportion of patients required rescue therapy due to cerebral vasospasm in the placebo group (16.4%) compared to the clazosentan group (10.5%). The relative risk reduction with clazosentan was 36%.

Treatment with clazosentan had no effect on total infarct volume. The proportion of patients in each pre-defined volume category was similar for the clazosentan and placebo groups, indicating no significant shift (P = 0.3149) in the size of the total infarct volume for patients who received clazosentan compared with placebo.

PHARMACOKINETIC/PHARMACODYNAMIC RESULTS:

Pharmacokinetic/pharmacodynamic results are provided in a separate report.

SAFETY RESULTS:

A total of 1,147 patients received study treatment for a median duration of 13.0 days, with 84.9% of the patients in the clazosentan group and 87.7% of the patients in the placebo group receiving the study treatment for > 10 days. Median total exposure to study treatment was same for both treatment groups (11.9 days).

During the study 92.0% of the patients in the clazosentan group and 90.9% of the patients in the placebo group experienced at least one AE. AEs that occurred at a higher incidence on clazosentan than on placebo included hypotension, pleural effusion, anemia, cerebral infarction and pulmonary edema. Cerebrovascular spasm occurred at a lower incidence in the clazosentan group than in the placebo group. The majority of AEs were mild or moderate in intensity and were not considered by the investigator to be related to study treatment.

In total, 43.6% and 39.9% of the patients who received clazosentan and placebo, respectively, experienced SAEs and 5.7% of patients in both treatment groups died. In both the clazosentan and placebo group, cerebrovascular spasm and cerebral infarction, were the most frequently reported SAEs as well as the most frequently occurring primary causes of death.

Adverse events resulting in the discontinuation of study treatment were reported for 8.6% and 5.5% of the patients in the clazosentan and placebo groups, respectively. Pulmonary edema, cerebrovascular vasospasm, and hypotension were the most frequently reported AEs leading to the discontinuation of treatment in both groups.

Adverse events of specific interest comprised specific groupings of AE preferred terms that are associated with a particular medical condition of clinical relevance (defined on the basis of the CONSCIOUS-1 study and preclinical toxicology findings). These AEs of specific interest were lung complications, lung complications related to pulmonary edema, anemia, hypotension, cerebral hemorrhage, hepatobiliary events, eye disorders, rhythm and conduction disorders and cardiac ischemic events.

Adverse events associated with lung complications occurred at a higher frequency on clazosentan (34.0%) than on placebo (17.8%). This finding was primarily due to a greater incidence of pleural effusion (10.5%), pulmonary edema (8.6%) and pneumonia (12.4%) in the clazosentan group compared to the respective placebo incidences of 2.9%, 4.7% and 8.6%. Lung complications related to pulmonary edema also showed a higher frequency on clazosentan (13.1%) than on placebo (7.3%).

Anemia was reported at a higher incidence on clazosentan than on placebo. The need for blood transfusion was higher in patients taking clazosentan as compared to placebo (17.1% vs 9.9%). Mean decreases in hemoglobin from baseline up to end-of-treatment (EOT) were greater on clazosentan (1.1 g/dL) than on placebo (0.1 g/dL).

Adverse events associated with hypotension showed a higher incidence in the clazosentan group (12.4%) than in the placebo group (4.4%). This observation is also consistent with the mean SBP decrease of 6.0 mmHg in the clazosentan group as compared to a decrease

of 1.2 mmHg in the placebo group on Day 1. Similar observations were made for mean arterial pressure. Consistent with the above is the observation that a higher proportion of patients in the clazosentan group (44.2%) were concomitantly treated with catecholamines than in the placebo group (33.7%).

In the clazosentan group, mean HR (ECG) increased from 72.3 bpm at baseline to 81.8 bpm at EOT (mean increase of 9.5 bpm). This compared to a smaller mean increase in the placebo group, from 72.9 bpm at baseline to 76.5 bpm at EOT (mean increase of 3.6 bpm). Sinus tachycardia was the most frequently reported ECG abnormality and occurred at a higher incidence in the clazosentan group (19.8%) than on placebo (14.4%). Overall, ECG abnormalities were reported for 50.3% and 44.9% of the patients in the clazosentan and placebo groups, respectively.

Adverse events denoting rhythm and conduction disorders were reported with higher incidence in the clazosentan group as compared to placebo (12% vs 8.9%). Cardiac ischemic event AEs were reported with higher incidence in placebo patients (2.9% vs 2.2%).

In the clazosentan group, QT_CF prolongations defined as absolute values of > 450 ms, > 480 ms, and > 500 ms, were reported for 20.3%, 5.7% and 1.5%, respectively, compared to 11.4%, 2.9% and 1.6% on placebo. Higher incidences of QT_CF increases from baseline of > 30 ms or > 60 ms were observed with clazosentan compared to placebo. These findings should be seen in the context of greater HR increases over the treatment period on clazosentan than on placebo.

The incidence of AEs associated with cerebral hemorrhage was similar in the clazosentan and placebo groups (3.9% and 3.1%, respectively). However, the preferred term ‘cerebral hemorrhage’ was only reported in the clazosentan-treated patients.

Adverse events associated with hepatobiliary events occurred at a slightly higher frequency on clazosentan (20.0%) than on placebo (17.0%). ALT or AST elevations > 3 × upper limit of normal (ULN) were reported for 14.9% of patients receiving clazosentan vs 10.7% on placebo.

Adverse events related to eye disorders were reported more frequently on clazosentan compared to placebo (1.4% vs 0.5%). In addition, the AE ‘conjunctival edema’ was reported at 1.3% in the clazosentan group, but did not occur in the placebo group.

CONCLUSIONS:

The primary objective of demonstrating that clazosentan reduces the incidence of cerebral vasospasm-related morbidity and all-cause mortality within 6 weeks post aSAH in patients treated with surgical clipping was not met. A treatment effect of clazosentan was observed on the primary endpoint, but it was not statistically significant. Treatment with clazosentan did not improve clinical outcome as assessed by dichotomized GOSE at 12 weeks post-aSAH. For this endpoint, the observed effect favored placebo.

An effect of clazosentan on the primary endpoint was observed in the subgroup of patients considered to be in poor neurological condition (WFNS grade > II, and diffuse

thick clot) at admission, but clazosentan was not associated with a beneficial effect on clinical outcome by dichotomized GOSE in these patients.

The observed safety profile of clazosentan, with AEs associated with fluid retention (edema) and systemic vasodilation (hypotension) is consistent with the known class effects of endothelin receptor antagonists (ERAs) and with the previously documented safety of clazosentan. Patient management guidelines for blood pressure and fluid management were implemented in this study but were not always strictly adhered to, based on frequently reported protocol deviations of non-adherence to these guidelines in both treatment groups. However, it remains difficult to ascertain if better compliance with guidelines would have decreased the incidence of fluid retention-related complications and hypotension in the clazosentan group.

Anemia and marked decreases in hemoglobin and hematocrit were more frequently observed on clazosentan compared to placebo, and were associated with a higher incidence of blood transfusion on clazosentan. Anemia is a known class effect of the ERAs.

The most frequently reported SAEs were associated with the system organ class (SOC) of Nervous system disorders, and many of these (cerebrovascular spasm, cerebral infarction, hydrocephalus, brain edema, intracranial pressure [ICP] and cerebral ischemia) are expected in aSAH.

The higher incidence of cerebrovascular spasm reported as an AE on placebo than on clazosentan supports the finding of the CONSCIOUS-1 study that clazosentan reduces the incidence of cerebrovascular spasm post-aSAH.

An equal proportion of patients in the two treatment groups died during the study. Cerebrovascular spasm and cerebral infarction were the two most commonly reported causes of death in both treatment groups, indicating that most cases of death were due to known consequences of aSAH. The cause of death in the clazosentan group appeared to be multifactorial for which among others, brain edema, brain herniation and increased ICP could have played a role.

The primary endpoint of cerebral vasospasm-related morbidity and mortality of all causes within 6 weeks post-aSAH was not met. No positive effect was seen on the main secondary endpoint of GOSE, and there was no reduction in total infarct volume with clazosentan. No new safety concerns were observed, i.e., the safety profile of clazosentan as previously assessed was confirmed.

The hypothesis that prevention of vasospasm reduces vasospasm-related morbidity and thereby improves clinical outcome was not confirmed by the results of the present study.

DATE OF THE REPORT:

10 March 2011