2 SYNOPSIS OF STUDY REPORT, No. D-11.171 (AC-054-302)

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:	
Clazosentan	Type … *(ONLY DRA)*	
NAME OF ACTIVE SUBSTANCE(S):	Page:	
ACT-108475 (AXV-034343)	Type … *(ONLY DRA)*	

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 endovascular coiling.
STATUS OF STUDY	Following the results of the study AC-054-301 (CONSCIOUS-2), this study was prematurely terminated when 38% of the planned number of patients had been enrolled.
INDICATION	Aneurysmal subarachnoid hemorrhage
INVESTIGATORS / CENTERS AND COUNTRIES	Multicenter study in 106 centers in 27 countries: Argentina (2), Australia (5), Austria (4), Belgium (4), Brazil (5), Canada (8), Chile (3), Czech Republic (6), Denmark (3), Finland (2), France (5), Germany (9), Hong Kong (2), Hungary (3), India (1), Israel (3), Italy (1), Mexico (2), Norway (2), Poland (1), Singapore (2), Slovenia (1), Spain (5), Sweden (3), Switzerland (3), Taiwan (1) and USA (20). 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	10 July 2009 to 26 January 2011 (first patient first visit to last patient last visit)	CLINICAL PHASE	3
OBJECTIVES	The primary objective was to demonstrate that at least one dose (5 or 15 mg/h) of clazosentan reduces the incidence of cerebral vasospasm-related morbidity and all-cause mortality within 6 weeks post-aneurysmal subarachnoid hemorrhage (aSAH) in patients treated by endovascular coiling. Secondary objectives were: • To demonstrate that at least one dose (5 or 15 mg/h) of clazosentan improves clinical outcome at Week 12 post-aSAH in patients treated by endovascular coiling, 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 in patients treated by endovascular coiling, 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 endovascular coiling 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, clazosentan 15 mg/h or to matching placebo. Treatment allocation was stratified according to investigational study site and was designed to occur in a 1:1:1 ratio (clazosentan 5 mg/h: clazosentan 15 mg/h: 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 planned to include 1,470 treated patients in the study. Study recruitment was stopped after 577 patients had been randomized. Of these, 571 patients received study treatment. The All-treated and Safety sets were identical and included all 571 patients who received study treatment. Of those randomized, 82.8% (478/577) 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 endovascular coiling 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 SAH treatment, which may have included oral nimodipine.
TRIAL DRUG / BATCH No.	Clazosentan/ACT-108475 (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) or clazosentan [redacted] (15 mg/h) was started within 56 hours post-aSAH and was scheduled to continue during 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 up to Week 6 post-aSAH (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 or worsened 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 cm^3.
- The occurrence of death and the individual morbidity components of the primary composite endpoint.

PHARMACOECONOMICS:

Since the study was terminated prematurely, the health economic endpoints were not analyzed.

[redacted]

[redacted]

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 treatment-emergent AEs of specific interest up to 1 day after study drug discontinuation and up to Week 6 post-aSAH (i.e., lung complications, lung complications related to pulmonary edema, hypotension, anemia, cerebral hemorrhage, eye disorders, cardiac and cardiovascular events [rhythm and conduction disorders, cardiac ischemic events and vascular inflammation disorders]). Hepatobiliary events, only up to 1 day after study drug discontinuation.
- Time to specific AEs (i.e., death, lung complications, anemia and cardiac or cardiovascular events).
- Occurrence of new or worsened cerebral infarcts of all etiologies up to Week 6 post-aSAH, as assessed by the CEC.
- 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 (MLA) and predefined treatment-emergent abnormalities for selected laboratory variables. MLAs were defined for selected laboratory variables (centrally assessed) using the Actelion internal standard definitions.

- Change from baseline to end of study drug administration for laboratory variables.
- Shift from standard reference range comparing baseline to end-of-treatment (EOT) for selected laboratory variables.
- Average daily value and change from baseline up to Day 7, the hourly values up to 8 hours after start of treatment, and the change from baseline to EOT in systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP) and heart rate (HR).
- Occurrence of predefined treatment-emergent marked abnormalities in MAP and SBP.
- Occurrence of treatment-emergent ECG abnormalities based on central reading.
- Occurrence of new (i.e., not present at baseline) ECG abnormalities up to Week 6 and at Week 6 post-aSAH 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 infusion based on central reading.
- Occurrence of treatment-emergent increases of > 30 ms and > 60 ms in QT_CF or QT_CB based on central reading.
- Occurrence of treatment-emergent increases to > 450 ms, > 480 ms and > 500 ms in QT_CF or QT_CB based on central reading.

STATISTICAL METHODS:

The global primary null hypothesis was that the occurrence of vasospasm-related morbidity and all cause mortality in neither of the two active treatment groups differed from placebo. The alternative hypothesis was that at least one of the clazosentan groups differed from placebo. Based on the assumption of event rates of 0.35 with placebo and

0.245 with active treatment (odds ratio [OR] = 0.603), 1470 (490 per group) treated patients were required to have an approximate power of 90% to reject the null hypothesis at a comparison wise type I error rate of 2.5% (two-sided).

Since the study was terminated prematurely, formal testing was not performed. All statistical tests were of an exploratory nature.

For each dose of clazosentan, the treatment effect on the primary endpoint (occurrence of vasospasm-related morbidity and all cause mortality) and the main secondary endpoint (GOSE dichotomized into poor outcome [score ≤ 4] and good outcome [score > 4]) was tested by means of logistic regression adjusted for admission WFNS (≤ II, > II). The treatment effect was described by the OR and the corresponding 95% confidence limits (CLs). The OR is the ratio of the odds of an event occurring under treatment to the odds of it occurring under placebo.

In addition, the incidence within each treatment group was displayed together with the exact 95% CLs, and the relative risk reduction (defined as '1− relative risk') together with the 95% CLs (normal approximation) for both the primary and the main secondary endpoint. These supplementary analyses were performed for the total population, and the pre-specified subgroups.

PATIENT DISPOSITION:

A total of 577 patients, representing 38% of the planned sample size had been randomized at the time of premature termination of the study. Of these, 194 received clazosentan 5 mg/h, 188 patients received clazosentan 15 mg/h and 189 received placebo, resulting in 571 treated patients. A similar proportion of patients (92.2%–94.9%) in the three treatment groups completed the study up to Week 12.

The proportion of patients who received oral nimodipine concomitantly during the study was similar (93.7%–94.8%) for the three treatment groups.

The most frequently reported reason for premature discontinuation from the study was death. In the clazosentan 5 mg/h and 15 mg/h groups, 3.1% and 6.4% of the patients, respectively, discontinued the study due to death. In the placebo group, 5.7% of the patients discontinued the study due to death. Two patients each in the clazosentan 5 mg/h and placebo groups and one patient in the clazosentan 15 mg/h group withdrew consent.

On clazosentan 5 mg/h and 15 mg/h, 18.6% and 20.7% of patients, respectively, prematurely discontinued study treatment, compared to 13.8% on placebo. The main reasons for premature discontinuation of study treatment in all three treatment groups were AEs and administrative/other reasons. The most frequently reported AE leading to study treatment discontinuation was pulmonary edema in the clazosentan groups and cerebrovascular spasm in the placebo group.

DEMOGRAPHIC AND BASELINE CHARACTERISTICS:

The patient population treated in the study was predominantly female (69.9%) and Caucasian (81.1%), with a mean age of 53.1 years (range: 19–76 years). The demographic and baseline disease characteristics were similar for the three treatment groups.

According to central assessment, the majority of patients (60.5%) had a diffuse thick clot and 29.5% of the patients had a local thick clot on their baseline CT scan. WFNS grading (WFNS grade I [good] to WFNS grade V [poor]) measuring disease severity showed that, at admission, 52.6% of the patients were graded as WFNS grade I and 27.7% of the patients as WFNS II. WFNS grades at admission were generally similar for the three treatment groups.

EFFICACY RESULTS:

An independent CEC adjudicated whether or not patients met the primary endpoint and its individual morbidity components.

Treatment with clazosentan was associated with a decrease in the incidence of cerebral vasospasm-related morbidity and mortality of all causes within 6 weeks post-aSAH (primary endpoint) compared to placebo. In the clazosentan 5 mg/h and 15 mg/h groups, the incidence of the primary endpoint was 24.2% and 14.9%, respectively, compared to 26.5% in the placebo group. In the primary analysis (logistic regression analysis adjusted for WFNS), the treatment effect of clazosentan 15 mg/h compared to placebo was nominally statistically significant with an OR of 0.474 (95% CLs: 0.275, 0.818, P = 0.0073). The treatment effect of clazosentan 5 mg/h compared to placebo (OR) was 0.786 (95% CLs: 0.479, 1.289, P = 0.3395).

The observed incidence of poor outcome, i.e., GOSE score ≤ 4 at Week 12 post-aSAH (main secondary endpoint) was similar for the three treatment groups. In the clazosentan 5 mg/h and 15 mg/h groups, the incidence of GOSE score ≤ 4 was 25.3% and 27.7%, respectively, compared with 24.3% in the placebo group. The logistic regression analysis (adjusted for WFNS) did not indicate any statistically significant differences between either of the two clazosentan groups and placebo, with an OR of 0.918 (95% CLs: 0.546, 1.544, P = 0.7480) and 1.337 (95% CLs: 0.802, 2.227, P = 0.2655) for the clazosentan 5 mg/h and 15 mg/h groups, respectively.

Within 6 weeks post-aSAH, six patients (3.1%) in the clazosentan 5 mg/h group, 12 patients (6.4%) in the clazosentan 15 mg/h and nine patients (4.8%) in the placebo group had died, corresponding to a relative risk reduction of 0.35 (95% CLs: −0.79, 0.76) and −0.34 (95% CLs: −2.11, 0.42) with clazosentan 5 mg/h and 15 mg/h, respectively,

compared to placebo.

The incidences of new cerebral infarcts due to cerebral vasospasm up to Week 6 were 16.0%, 7.4% and 13.2% for the clazosentan 5 mg/h and 15 mg/h groups and placebo group, respectively, corresponding to a relative risk reduction of −0.21 (95% CLs: −0.97, 0.26) and 0.44 (95% CLs: –0.05, 0.70) with clazosentan 5 mg/h and 15 mg/h, respectively, compared to placebo.

The incidence of DIND due to cerebral vasospasm was 17.5% in the clazosentan 5 mg/h group and 9.6% in the clazosentan 15 mg/h group compared to 20.6% in the placebo group, corresponding to a relative risk reduction of 0.15 (95% CLs: −0.28, 0.44) and 0.54 (95% CLs: 0.22, 0.72) with clazosentan 5 mg/h and 15 mg/h, respectively, compared to placebo.

The incidence of valid rescue therapy was 14.9% in the clazosentan 5 mg/h group and 7.4% in the clazosentan 15 mg/h group compared to 21.2% in the placebo group, corresponding to a relative risk reduction of 0.29 (95% CLs: –0.09, 0.54) and 0.65 (95% CLs: 0.38, 0.80) with clazosentan 5 mg/h and 15 mg/h, respectively, compared to placebo.

The proportions of patients in the two clazosentan groups who experienced no new cerebral infarct (all causes) were 72.5% and 73.9% in the clazosentan 5 mg/h and 15 mg/h groups, respectively. In the placebo group, 77.2% of patients had no new cerebral infarct. Of those patients with new infarcts, there was no significant shift in the size of the total cerebral infarct volume for the patients who received clazosentan, compared with placebo.

[redacted]

SAFETY RESULTS:

Patients received study treatment for a median duration of 13.0 days, with 81.4%, 77.1% and 84.7% of the patients in the clazosentan 5 mg/h and 15 mg/h groups and placebo group, respectively, receiving the study treatment for > 10 days. Median exposure (excluding interruptions) was 11.8 days for the two clazosentan groups and 11.9 days for the placebo group.

During the study 86.1%, 91.5%, and 90.5% of the patients who received clazosentan 5 mg/h, clazosentan 15 mg/h and placebo, respectively, experienced at least one AE. The most frequently reported AEs that occurred at a higher incidence in the two clazosentan groups compared to placebo were hypotension (clazosentan 5 mg/h: 10.3%, clazosentan 15 mg/h: 15.4%, placebo: 6.3%), pleural effusion (clazosentan 5 mg/h: 11.9%, clazosentan 15 mg/h: 13.8%, placebo: 5.8%), pulmonary edema (clazosentan 5 mg/h: 13.4%, clazosentan 15 mg/h: 10.1%, placebo: 4.2%), anemia (clazosentan 5 mg/h: 12.4%, clazosentan 15 mg/h: 10.6%, placebo: 7.4%), atelectasis (clazosentan 5 mg/h:

6.2%, clazosentan 15 mg/h: 9.0%, placebo: 4.2%), and pneumonia (clazosentan 5 mg/h: 10.8%, clazosentan 15 mg/h: 9.6%, placebo: 6.3%). Cerebrovascular spasm was reported at a lower frequency in patients receiving clazosentan (clazosentan 5 mg/h: 22.2%, clazosentan 15 mg/h: 13.8%) than placebo (31.7%). The incidence of cerebral infarction reported as an AE (clazosentan 5 mg/h: 9.8%, clazosentan 15 mg/h: 8.0%) and as an SAE (clazosentan 5 mg/h: 8.8%, clazosentan 15 mg/h: 5.9%) was lower in the two clazosentan groups compared to placebo (12.2% and 11.6%, respectively). However, new or worsened cerebral infarcts of all etiologies as assessed by the CEC were experienced by a higher proportion of patients in the two clazosentan groups (clazosentan 5 mg/h: 27.5%, clazosentan 15 mg/h: 26.1%) compared to placebo (22.8%). Most of the AEs were considered to be of mild or moderate intensity. AEs considered as severe in intensity were experienced by 27.8%, 28.7% and 24.9% of the patients in the clazosentan groups 5 mg/h and 15 mg/h and placebo group, respectively.

Of the 571 treated patients, 7/194 (3.6%), 12/188 (6.4%) and 12/189 (6.3%) of the patients who received clazosentan 5 mg/h, clazosentan 15 mg/h and placebo, respectively, died during the study up to Week 12 post-aSAH. Cerebral infarction was the most frequently reported primary cause of death in the clazosentan 15 mg/h (3.2%) and placebo groups (2.1%).

A similar proportion of patients in the three treatment groups (clazosentan 5 mg/h: 40.7%, clazosentan 15 mg/h: 38.3%, placebo: 38.1%) experienced at least one SAE during the study. SAEs were mainly associated with the system organ classes (SOCs) Nervous system disorders (clazosentan 5 mg/h: 27.8%, clazosentan 15 mg/h: 26.1%, placebo: 34.9%), Respiratory, thoracic and mediastinal disorders (clazosentan 5 mg/h: 7.2%, clazosentan 15 mg/h: 9.6%, placebo: 5.3%), and Infections and infestations (clazosentan 5 mg/h: 6.2%, clazosentan 15 mg/h: 6.4%, placebo: 2.1%). Cerebrovascular spasm, the most frequently reported SAE, occurred at a lower incidence in the two clazosentan groups (clazosentan 5 mg/h: 17.0%, clazosentan 15 mg/h: 7.4%) than in the placebo group (23.3%).

A higher proportion of patients receiving clazosentan 5 mg/h (8.8%) and 15 mg/h (11.7%) discontinued study treatment due to AEs compared to patients who were receiving placebo (5.3%). AEs leading to discontinuation of treatment were mainly associated with the SOCs Respiratory, thoracic and mediastinal disorders (clazosentan 5 mg/h: 4.1%, clazosentan 15 mg/h: 6.4%, placebo: 1.6%) and Nervous system disorders (clazosentan 5 mg/h: 0.5%, clazosentan 15 mg/h: 4.3%, placebo: 3.2%). Pulmonary edema was the most frequently reported AE leading to discontinuation of treatment in the two clazosentan groups (clazosentan 5 mg/h: 2.6%, clazosentan 15 mg/h: 3.2%). Cerebrovascular vasospasm was the most frequent AE leading to discontinuation of treatment in the placebo group (2.1%).

Adverse events of specific interest

Adverse events of specific interest are groupings of AE preferred terms (PTs) that are associated with a particular medical condition of clinical relevance. AEs of specific interest were defined on the basis of the CONSCIOUS-1 study and preclinical toxicology findings. The subsequent paragraphs provide the incidence of treatment-emergent AEs of specific interest (AE onset during study drug treatment plus 1 day).

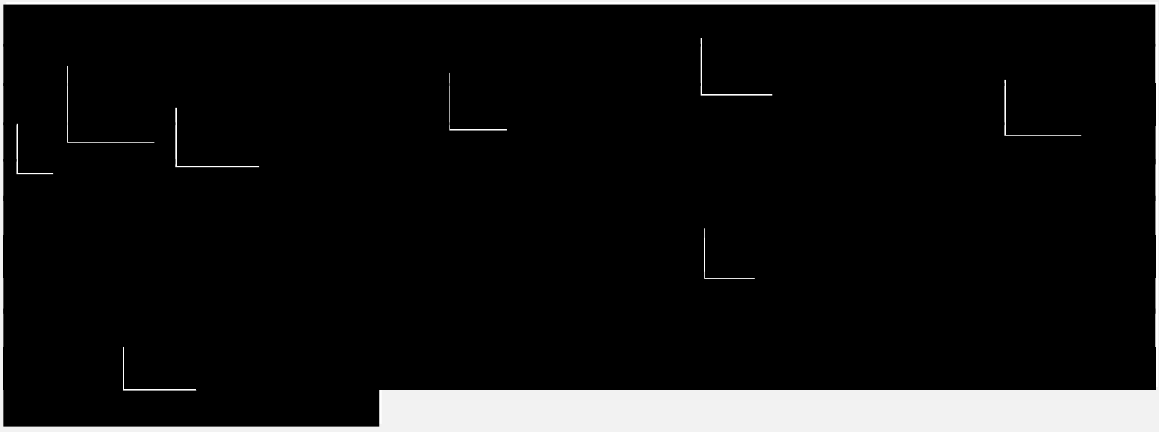
Adverse events associated with lung complications occurred at a higher incidence on clazosentan 5 mg/h (36.1%) and clazosentan 15 mg/h (37.2%) compared to placebo (21.2%). This was mainly due to a higher incidence of pleural effusion (clazosentan 5 mg/h: 11.9%, clazosentan 15 mg/h: 13.8%), pulmonary edema (clazosentan 5 mg/h: 13.4%, clazosentan 15 mg/h: 10.1%,) and pneumonia (clazosentan 5 mg/h: 10.8%, clazosentan 15 mg/h: 9.6%) on clazosentan compared to placebo (5.8%, 4.2% and 6.3% of the patients, respectively). The subset of lung complications related to pulmonary edema were also experienced by a higher proportion of patients on clazosentan 5 mg/h (19.1%) and clazosentan 15 mg/h (17.0%) compared to placebo (8.5%). For AEs associated with lung complications, the highest incidence was observed during the first four days of study treatment.

Anemia was reported at a higher incidence on clazosentan 5 mg/h (12.4%) and clazosentan 15 mg/h (10.6%) than on placebo (7.4%). Also, a higher proportion of patients on clazosentan 5 mg/h (40.4%) and clazosentan 15 mg/h (43.9%) experienced marked decrease (defined as < 11 g/dL and $\geq 15\%$ decrease from baseline) in their hemoglobin levels compared to placebo (22.2%). A similar proportion of patients receiving clazosentan 5 mg/h (8.8%), clazosentan 15 mg/h (8.5%) and placebo (6.9%) required (new) concomitant blood transfusion.

Adverse events associated with hepatobiliary events were reported for 20.1%, 14.9% and 18.5% of patients on clazosentan 5 mg/h, clazosentan 15 mg/h and placebo, respectively. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations $> 3 \times$ upper limit of normal (ULN) were experienced by 17.1% of the patients receiving clazosentan 5 mg/h compared to 10.6% of the patients receiving placebo. In the clazosentan 15 mg/h group, 9.0% of the patients experienced ALT or AST elevations $> 3 \times$ ULN. One patient in each of the two clazosentan groups experienced ALT or AST elevations $> 3 \times$ ULN with concurrent total bilirubin $> 2 \times$ ULN.

An AE of hypotension was reported in a higher proportion of patients on clazosentan 5 mg/h (10.3%) and clazosentan 15 mg/h (15.4%) compared to placebo (6.3%). This was in line with the effects observed on blood pressure. For SBP/DBP, a mean decrease of 4.6/4.0 mmHg and 7.3/5.5 mmHg was observed for clazosentan 5 mg/h (baseline: 140.3/70.3 mmHg) and clazosentan 15 mg/h (baseline: 141.2/70.4 mmHg), respectively, on Day 1, compared to 0.2/0.1 mmHg for placebo (baseline: 141.2/71.1 mmHg). Similar effect (decrease) on mean MAP was observed for the two clazosentan groups.

Adverse events associated with cardiac rhythm and conduction disorders were experienced by 8.2% and 10.6% of the patients on clazosentan 5 mg/h and 15 mg/h, respectively, compared to 12.2% of the patients on placebo. The incidence of bradycardia on clazosentan 5 mg/h and 15 mg/h was 2.1% and 1.6%, respectively, compared to placebo (6.3%). The incidence of sinus tachycardia reported as an ECG abnormality was higher on clazosentan 15 mg/h (17.6%) compared to clazosentan 5 mg/h (11.9%) and placebo (11.1%). Mean HR (ECG) increases of 8.0 bpm and 10.8 bpm were reported for clazosentan 5 mg/h and clazosentan 15 mg/h, respectively, at end-of-treatment (EOT) compared to 5.0 bpm for placebo. AEs associated with cardiac ischemic events were experienced by a higher proportion of patients on clazosentan 5 mg/h (4.1%) and clazosentan 15 mg/h (3.2%) compared to placebo (1.6%).



Adverse events associated with cerebral hemorrhage were reported in 3.6%, 3.7% and 2.6% of the patients receiving clazosentan 5 mg/h, clazosentan 15 mg/h and placebo, respectively. Cerebral hemorrhage reported as a preferred term occurred at a higher incidence on clazosentan 5 mg/h (2.6%) than on placebo (0.5%). In the clazosentan 15 mg/h, the incidence of cerebral hemorrhage reported as a preferred term was 0.5%.

Adverse events associated with Eye disorders were only reported in the clazosentan 15 mg/h group (3.2%). This was mainly due to the occurrence of dry eye (1.6%) and keratitis (1.6%).

DISCUSSION & CONCLUSIONS:

Following the results of Study AC-054-301 (CONSCIOUS-2), which could not demonstrate efficacy of clazosentan 5 mg/h in patients with aSAH having their aneurysm secured by surgical clipping, the present study was prematurely terminated at a point where enrollment was 38% complete. As protocol-mandated assessments were performed for all patients who had received study treatment up to the premature termination of the study, efficacy as well as safety were evaluated and are reported in full in this report. The treatment groups were well balanced in terms of baseline characteristics.

A nominally statistically significant reduction in cerebral vasospasm-related morbidity and mortality of all causes within 6 weeks post-aSAH (primary endpoint) was observed with clazosentan 15mg/h compared to placebo (OR of 0.474 [95% CLs: 0.275, 0.818, P = 0.0073]), despite a lower than anticipated event rate on placebo.

No statistically significant effect of clazosentan 15 mg/h compared to placebo was observed for the main secondary endpoint of clinical outcome as assessed by dichotomized GOSE at Week 12 post-aSAH (OR of 1.337 [95% CLs: 0.802, 2.227, P = 0.2655]). As rescue therapy was an allowed treatment option for established vasospasm, its increased use in the placebo group could have contributed to improved late outcome (GOSE). Under this assumption, rescue therapy constitutes a confounding factor for testing the outcome benefit of any preventative treatment strategy for vasospasm. A contribution of clazosentan to non-vasospasm related causes of poor clinical outcome cannot be excluded.

The AEs (such as lung complications, hypotension and anemia) experienced by the patients in this study were consistent with those observed in previous clinical trials with clazosentan.

Similar proportions of patients in the clazosentan 15 mg/h (6.4%) and placebo groups (6.3%) died during the study. In the clazosentan 5 mg/h, 3.6% died during the study. Cerebral infarction was the most frequently reported primary cause of death in the clazosentan 15 mg/h and placebo groups.

Similar proportions of patients in the three treatment groups experienced SAEs during the study. The most frequently reported SAEs were associated with the SOC Nervous system disorders. Due to the known pathology of aSAH, these findings were expected.

In summary, in this prematurely terminated study, a nominally statistically significant reduction in cerebral vasospasm-related morbidity and mortality of all causes within 6 weeks post-aSAH (primary endpoint) was observed for the clazosentan 15 mg/h dose vs placebo. No beneficial effect was seen on the main secondary endpoint of GOSE at 12 weeks post aSAH. The safety profile of clazosentan was consistent with that observed in previous studies.

DATE OF THE REPORT:

20 December 2011