

Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage (CONSCIOUS-1)

Randomized, Double-Blind, Placebo-Controlled Phase 2 Dose-Finding Trial

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Background and Purpose—This randomized, double-blind, placebo-controlled, dose-finding study assessed efficacy and safety of 1, 5, and 15 mg/h intravenous clazosentan, an endothelin receptor antagonist, in preventing vasospasm after aneurysmal subarachnoid hemorrhage.

Methods—Patients (n=413) were randomized to placebo or clazosentan beginning within 56 hours and continued up to 14 days after initiation of treatment. The primary end point was moderate or severe angiographic vasospasm based on centrally read, blinded evaluation of digital subtraction angiography at baseline and 7 to 11 days postsubarachnoid hemorrhage. A morbidity/mortality end point, including all-cause mortality, new cerebral infarct from any cause, delayed ischemic neurological deficit due to vasospasm, or use of rescue therapy, was evaluated by local assessment. Clinical outcome was assessed by the extended Glasgow Outcome Scale at 12 weeks.

Results—Moderate or severe vasospasm was reduced in a dose-dependent fashion from 66% in the placebo group to 23% in the 15 mg/h clazosentan group (risk reduction, 65%; 95% CI, 47% to 78%; $P<0.0001$). No significant effects were seen on secondary end points. Post hoc analysis using a centrally assessed morbidity/mortality end point that included death and rescue therapy but only cerebral infarcts and delayed ischemic neurological deficit due to vasospasm on central review showed a trend toward improvement with clazosentan (37%, 28%, and 29% in the 1, 5, and 15 mg/h groups versus 39% in the placebo group, nonsignificant). Clazosentan was associated with increased rates of pulmonary complications, hypotension, and anemia.

Conclusions—Clazosentan significantly decreased moderate and severe vasospasm in a dose-dependent manner and showed a trend for reduction in vasospasm-related morbidity/mortality in patients with aneurysmal subarachnoid hemorrhage when centrally assessed. Overall, the adverse effects were manageable and not considered serious. (*Stroke*. 2008;39:3015-3021.)

Key Words: cerebral infarction ■ outcome ■ subarachnoid hemorrhage ■ vasospasm

Despite advances in treatment, outcome after aneurysmal subarachnoid hemorrhage (SAH) remains poor.¹ Much of the death and disability is related to the admission neurological condition and amount of bleeding from the aneurysm. Vasospasm is probably the most preventable complication in these patients and remains a leading cause of mortality and morbidity.²⁻⁴ There are, however, few treatments available for vasospasm and evidence for efficacy of most of them is limited.⁵

Endothelin is a potent, long-lasting endogenous vasoconstrictor that has been implicated in the pathogenesis of vasospasm.^{6,7} Endothelin concentrations may be increased in the cerebrospinal fluid and there is increased sensitivity of the cerebral arteries to endothelin after SAH. Endothelin receptor antagonists reduce experimental vasospasm.⁷⁻¹⁰ Specifically, clazosentan, a nonpeptide endothelin receptor A antagonist, reduced vasospasm after experimental SAH.^{11,12} A Phase 2a blinded, placebo-controlled trial in 34 patients with SAH

Received March 12, 2008; accepted March 26, 2008.

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Stroke is available at <http://stroke.ahajournals.org>

DOI: 10.1161/STROKEAHA.108.519942

undergoing aneurysm surgery reported that clazosentan significantly reduced the incidence and severity of angiographic vasospasm.¹³ This result led us to conduct CONSCIOUS-1, a larger trial designed to identify the safest and most effective dose of clazosentan for prevention of angiographic cerebral vasospasm in patients with SAH undergoing clipping or coiling of a ruptured aneurysm.

Patients and Methods

Study Design

This was a Phase 2b randomized double-blind, placebo-controlled, dose-finding study of clazosentan (1, 5, or 15 mg/h [1:1:1]) conducted at 52 centers in 11 countries (see the Appendix). Patients were enrolled between January 2005 and March 2006. Patients were stratified by site and procedure (coiling or clipping). The ethics committee at each institution reviewed and approved the protocol before study initiation and the study was conducted in compliance with the Declaration of Helsinki or with laws and regulations of the country in which the research was conducted. The trial was registered (<http://clinicaltrials.gov/ct/show/NCT00111085>). The authors designed the trial and wrote the article. The sponsor collected the data. Radiology images and data were collected by Perceptive Informatics (Berlin, Germany). With the exception of the pharmacist and an independent pharmacy monitor who was not involved in other study tasks, all investigators, patients, and individuals responsible for conduct, monitoring, and analysis of the study were blinded to treatment. Drug and placebo were clear and colorless with no obvious acute effects that would compromise blinding. A data safety monitoring board reviewed the safety data set on a monthly basis throughout the study.

Study Population

Eligible patients were 18 to 70 years old with aneurysmal SAH due to a ruptured saccular aneurysm confirmed by digital subtraction catheter angiography (DSA). SAH had to be diffuse (long axis ≥ 20 mm) or localized (long axis < 20 mm) thick (short axis ≥ 4 mm) subarachnoid clot on CT scan within 48 hours of SAH. Patients had a World Federation of Neurological Surgeons Grade 1 to 4 on admission or were Grade 5 patients who had improved to Grade 4 or less after resuscitation and ventriculostomy.¹⁴

Exclusion criteria were: (1) SAH from a lesion other than a ruptured saccular aneurysm; (2) intraventricular or intracerebral blood in the absence of localized thick or diffuse SAH; (3) no or localized thin SAH on CT; (4) cerebral vasospasm on admission DSA; (5) hypotension (systolic blood pressure ≤ 90 mm Hg) refractory to fluid therapy; (6) neurogenic pulmonary edema or cardiac failure requiring inotropic support; (7) severe or unstable concomitant condition or disease or chronic condition, which, in the opinion of the investigator, could affect assessment of the safety or efficacy of the study drug; (8) kidney (plasma creatinine ≥ 177 $\mu\text{mol/L}$) and/or liver disease (total bilirubin > 51.3 $\mu\text{mol/L}$); and (9) prior cerebral damage on CT scan such as stroke (> 2 cm maximum diameter), traumatic brain injury, previously treated cerebral aneurysm, arterial venous malformation, or pre-existing cerebrovascular disorder that would affect diagnosis and evaluation of SAH. Women of childbearing potential had negative pretreatment serum pregnancy tests.

Study Interventions

Placebo or clazosentan was started intravenously within 56 hours of SAH and continued for 14 days. Aneurysmal clipping or coiling was performed before or within 12 hours after initiation of treatment. Oral nimodipine (60 mg every 4 hours) and intravenous fluids of ≥ 3 L/day were recommended. If symptomatic vasospasm was diagnosed, the investigators initiated treatment, which could include induced hypertension, hypervolemia, hemodilution, and endovascular balloon dilation or vasodilator infusion. Prophylactic intravenous nimodipine, nicardipine, magnesium, other endothelin receptor an-

tagonists, antifibrinolytics, or intrathecal thrombolytics were prohibited.

Clinical Assessments and Radiology

All patients had baseline DSA within 48 hours of SAH before the aneurysm-securing procedure and on day 9 ± 2 postaneurysm rupture. DSA also was performed if patients showed signs of symptomatic vasospasm at any time unless vasospasm had already occurred and there was no other medical indication for DSA. CT scan was performed on admission within 48 hours of SAH, 24 to 48 hours after the aneurysm-securing procedure, 6 weeks after SAH, and whenever there was neurological worsening. The images were submitted to Perceptive and reviewed centrally by 2 independent, blinded reviewers. CT scans were assessed for SAH using the Hijdra scale,¹⁵ hydrocephalus by ventriculocranial ratio,¹⁶ volume of intracerebral hemorrhages and hypodense areas quantified by planimetric analysis, intraventricular hemorrhage by the Graeb scale,¹⁷ and presence or absence of midline shift and extraaxial hematoma. The diameters of proximal cerebral arteries were measured on DSA and corrected for magnification using metal rings of known diameter that were taped to the scalp during DSA or by measuring diameters of the extracranial arteries.^{18,19} Vasospasm was quantified as the percent reduction in arterial diameter between baseline and day 9 ± 2 DSA. A global assessment of vasospasm was then made and classified as none/mild (0% to 33%), moderate (34% to 66%), or severe (67% to 100%).

Efficacy and Safety

The primary efficacy end point was moderate or severe vasospasm within 14 days of SAH based on central assessment. The main secondary end point was morbidity and mortality (M/M) within 6 weeks of SAH assessed by local investigators. M/M was defined as at least one of the following: death within 6 weeks of SAH from any cause; new cerebral infarct within 6 weeks of SAH compared with postprocedure CT scan; delayed ischemic neurological deficit (DIND) due to vasospasm within 14 days of SAH; and rescue therapy for DSA or transcranial Doppler vasospasm within 14 days of SAH.

DIND was defined as locally defined vasospasm on DSA or transcranial Doppler associated with neurological worsening lasting for at least 2 hours. Neurological worsening was defined as a decline of at least 2 points in the modified Glasgow Coma Scale or an increase of at least 2 points in the abbreviated National Institutes of Health Stroke Scale.^{20–22} When patients were not evaluable neurologically, DIND was defined as clinical signs of vasospasm (eg, unexplained fever, new neurological deficit) with vasospasm on DSA or transcranial Doppler or when a new hypodensity was observed on a postprocedure CT scan. Transcranial Doppler criteria for vasospasm were a Lindegaard ratio ≥ 3 , a mean middle or anterior cerebral artery flow velocity > 200 cm/s, or an increase > 50 cm/s/24 hours.²³ Other causes of neurological worsening had to be excluded.

Rescue therapy was defined as the start of either hemodynamic therapy or angioplasty within 14 days of SAH in the presence of vasospasm on DSA or transcranial Doppler. Clinical outcome was measured by the extended version of Glasgow Outcome Scale assessed by a centrally administered telephone interview at 12 weeks.²⁴

The protocol-defined assessment of M/M included all new infarcts and hypodensities, including those unrelated to vasospasm. We subsequently modified this end point by performing a central, blinded review of the cause of infarcts in patients who had any postbaseline CT scan. A centrally assessed M/M end point was defined as: death from any cause within 6 weeks of SAH; new cerebral infarct due to vasospasm within 6 weeks of SAH; DIND due to vasospasm on centrally reviewed DSA; and any rescue therapy within 14 days of SAH.

Adverse events of specific interest were hypotension, pulmonary complications, anemia, and death occurring at any time within 24 hours of study treatment discontinuation.

Table 1. Demographics and Baseline Characteristics for All Treated Patients*

Characteristic	Clazosentan				Total (n=409)
	Placebo (n=96)	1 mg/hour (n=107)	5 mg/hour (n=110)	15 mg/hour (n=96)	
Female	64 (67)	79 (74)	75 (68)	71 (74)	289 (71)
Mean age, years (range)	52±11 (18–70)	51±10 (29–70)	51±11 (20–71)	51±11 (19–70)	51±11 (18–71)
Aneurysm clipping	45 (47)	42 (39)	53 (48)	45 (47)	185 (45)
World Federation of Neurological Surgeons admission grade					
Grade 1	47 (49)	46 (43)	45 (41)	44 (46)	182 (45)
Grade 2	19 (20)	35 (33)	35 (32)	28 (29)	117 (29)
Grade 3–5	30 (31)	26 (24)	30 (27)	24 (25)	110 (27)
Baseline CT scan	94	106	110	95	405
Thick diffuse	74 (79)	78 (74)	81 (74)	74 (78)	307 (76)
Thick local	4 (4)	6 (6)	6 (6)	2 (2)	18 (4)
Thin diffuse	16 (17)	22 (21)	23 (21)	19 (20)	80 (20)
Thin local	1 (1)	0	0	2 (2)	3 (1)
Intraventricular hemorrhage	35 (37)	40 (38)	37 (34)	34 (35)	146 (36)
Hydrocephalus	25 (27)	29 (27)	37 (34)	30 (31)	121 (30)
Intraparenchymal hemorrhage	11 (12)	14 (13)	8 (7)	12 (13)	45 (11)

*Values are n (%)± SD where appropriate. Baseline CT scans results are based on local assessment.

Statistics

Sample size was estimated from the Phase 2a study.¹³ The expected frequency of moderate and severe angiographic vasospasm in the placebo group was 60%. Seventy-nine evaluable patients per group were required to detect a relative risk reduction of 50% reduction in the primary end point using a 2-sided Type 1 error of 0.0166 for each dose comparison against placebo.

The all-randomized data set included all patients randomized and the all-treated set included all randomized patients who received at least one dose of treatment. The safety set was all randomized patients who received at least one dose of study treatment and for whom any safety assessment was reported. The per-protocol set comprised all randomized patients excluding major protocol violators. Major protocol violations were defined as no study drug administration (n=4); study treatment discontinuation or interruption for >12 hours during the 2 days before angiographic moderate or severe vasospasm (n=9); treatment from another treatment group received before angiographic moderate or severe vasospasm or before day 9±2 DSA (n=4); no baseline or day 9±2 DSA (n=37); World Federation of Neurological Surgeons Grade 5 (n=1); no ruptured aneurysm or no or local thin clot on admission CT scan based on central reading; or SAH due to a cause other than aneurysm rupture (n=7).

The primary end point was analyzed using the per-protocol set (primary analysis) and the all-treated set. Secondary and exploratory end points were analyzed using the all-treated set. For patients in whom the end point could not be determined due to missing data or loss to follow-up, occurrence of the end point has been assumed unless the patient completed the treatment period and had no signs of neurological worsening or reported symptomatic vasospasm. Safety analysis was on the all-treated set and summarized by frequencies and percents. Treatment groups were compared using Fisher exact test for the primary and secondary end points. Inferential methods were aimed at demonstrating the superiority of individual clazosentan dose groups over placebo using a studywide 2-sided significance level of 5%. The Bonferroni-Holm rule was applied to adjust for multiple testing. The exact 95% (2-sided) CIs were calculated for proportions. For the relative risk ratios, 95% (2-sided) CIs using normal approximation were calculated. Safety analyses were based on the all-treated set and summarized by frequencies and percents. All analyses were performed using SAS 8.2 software.

Results

Patient Characteristics

The 30 centers that kept screening logs screened 702 patients and recruited 248 (35% screened patients, 60% of recruited patients from these centers) of the 413 randomized patients. Four hundred thirteen patients were randomized to placebo (n=96) or 1 (n=108), 5 (n=111), or 15 mg/h (n=98) clazosentan. Twenty-seven percent of patients were recruited from the United States. The all-treated and safety sets excluded no placebo patients and one patient in each of the clazosentan 1 and 5 mg/h and 2 in the 15 mg/h groups. The per-protocol set excluded 11 (12%), 13 (12%), 16 (14%), and 19 (19%) patients, respectively.

There were no significant differences between groups in demographics (Table 1). Eighty-three percent to 94% of patients were white (overall, 365 of 409 [89%]) and the majority were World Federation of Neurosurgical Societies Grades 1 or 2. There was a trend for more patients with thick and diffuse clots in the 3 clazosentan groups. Study treatment was completed by 85 (89%), 83 (77%), 85 (77%), and 77 (79%) patients in the all-randomized set, respectively (Figure 1). Reasons for discontinuation from the study were death (4%, 5%, 8%, and 7%), administrative or other reason (5%, 3%, 3%, and 5%), adverse event (1%, 0%, 1%, and 0%), and lost to follow-up (1%, 0%, 0%, and 1%) in the placebo and 1, 5, and 15 mg/h clazosentan groups, respectively.

Efficacy

Moderate or severe angiographic vasospasm in the per-protocol set assessed by central reading occurred in 56 patients (66%; 95% CI, 55% to 76%) in the placebo group compared with 41 (43%; 95% CI, 33% to 54%), 37 (39%; 95% CI, 29% to 50%), and 18 (23%; 95% CI, 14% to 34%)

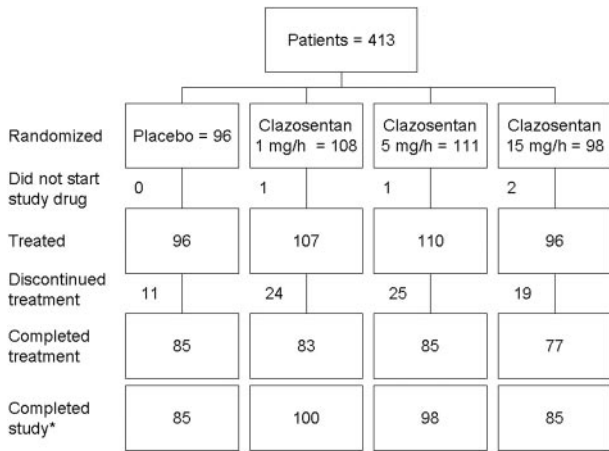


Figure 1. Disposition of patients (n). *Patients for whom Week 12 visit was completed regardless of study drug discontinuation.

patients in the 1, 5, and 15 mg/h clazosentan groups, respectively ($P < 0.02$ for each group compared with placebo; Figure 2). Compared with placebo, the relative risk reductions were 34% (95% CI, 14% to 50%; $P = 0.0027$), 41% (95% CI, 21% to 56%; $P = 0.0003$), and 65% (95% CI, 47% to 78%; $P < 0.0001$) in the 1, 5, and 15 mg/h groups clazosentan, respectively. In the all-treated set, all doses of clazosentan also were associated with significant reductions compared with placebo in moderate or severe vasospasm ($P < 0.02$ for each group compared with placebo). In the placebo group, 64 patients (67%; 95% CI, 56% to 76%) had moderate or severe vasospasm compared with 51 (48%; 95% CI, 38% to 58%), 45 (41%; 95% CI, 32% to 51%), and 30 (31%; 95% CI, 22% to 42%) patients in the 1, 5, and 15 mg/h clazosentan groups, respectively.

There was no significant difference in the proportion of patients in the all-treated set who developed M/M assessed by the local investigator (30 [31%] in the placebo and 40 [37%], 34 [31%], and 36 [38%] in the 1, 5, and 15 mg/h clazosentan groups, respectively; $P > 0.1$ for all comparisons; Figure 3). A trend toward decreased M/M was observed using the centrally assessed end point (37%, 28%, and 29% with 1, 5, and 15 mg/h, respectively) versus placebo (39%; $P > 0.1$ for all comparisons). Discrepancies between investigator and central assessment of M/M were due mainly to differences in

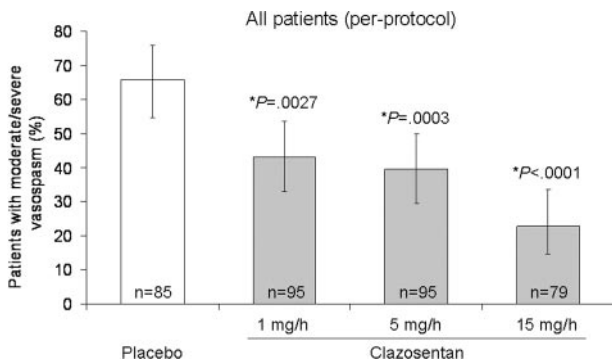


Figure 2. Occurrence of moderate or severe vasospasm measured by DSA at day 9 \pm 2 postaneurysm rupture, centrally read, per-protocol set. Percents are based on n. Exact 95% CIs are shown. *Fisher exact test.

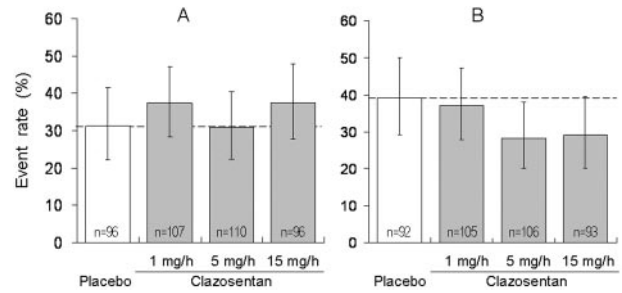


Figure 3. Occurrence of vasospasm-related morbidity and mortality within 6 weeks postaneurysm rupture (A) All-treated set, based on local investigator assessments; 95% CIs. B, All-treated set based on central assessment and using the modified definition; 95% CIs.

vasospasm-related cerebral infarction and DIND. In patients with available CT scans, the incidence of vasospasm-related new cerebral infarcts was 19% in the placebo group compared with 13%, 9%, and 5% in the 1, 5, and 15 mg/h groups, respectively. DIND showed a similar treatment effect trend (24%, 19%, 17%, and 12% in the placebo, 1, 5, and 15 mg/h groups, respectively). Rescue therapy showed no relation to treatment, being used in 24%, 27%, 17%, and 19% for the same groups. There was no effect of clazosentan on GOSE (Table 2).

The protocol specified stratification by site and mode of aneurysm treatment (clipping or coiling). There was some interaction between mode of treatment and moderate to severe angiographic vasospasm when tested on the all-treated set ($P < 0.05$, χ^2 test), which requires detailed description because patients were not randomized to treatment modality and those who underwent clipping differed from those treated by coiling and word limitations preclude description of the analysis here.

Safety

Hypotension, anemia, and pulmonary complications were more frequent in the clazosentan groups (Table 3). Most pulmonary complications occurred during the first 7 days of study drug infusion and included pneumonia, pleural effusion, pulmonary edema, and acute respiratory distress syndrome. Three patients (1%) discontinued the study drug due to hypotension; all were treated with clazosentan.

There were 25 deaths within 12 weeks postaneurysm rupture in the randomized set, 24 of which occurred in the all-treated set. One death occurred in the 1 mg/h clazosentan group after randomization but before the start of treatment. Mortality was 4 (4%) placebo patients and 4 (4%), 9 (8%), and 7 (7%) patients in the 1, 5 and 15 mg/h clazosentan groups, respectively. Causes of death included cerebral infarction, pulmonary embolism, cardiac arrest, SAH, brain edema, sepsis, and rebleeding. Fourteen of 21 deaths were due primarily to intraoperative complications with a preponderance in the clazosentan groups.

Discussion

We designed this Phase 2b trial with a primary end point of angiographic vasospasm based on the notion that vasospasm leads to cerebral infarction and poor outcome after SAH.²⁵

Table 2. Extended Glasgow Outcome Scale for the All-Treated Set*

Characteristic	Placebo (n=96)	Clazosentan		
		1 mg/hour (n=107)	5 mg/hour (n=110)	15 mg/hour (n=96)
Death, vegetative, or severe disability	30 (31)	28 (26)	30 (27)	33 (34)
Exact 95% CI	22–42%	18–36%	19–37%	25–45%
Absolute risk reduction		–5%	–4%	3%
Exact 95% CI		–18–8%	–17–9%	–11–17%
<i>P</i> value (Fisher exact test)		0.44	0.54	0.76
Relative risk reduction		0.16	0.13	–0.10
95% CI (normal approximation)		–0.29–0.46	–0.34–0.43	–0.65–0.27

*Values are n (%). CIs calculated by Clopper-Pearson formula for death, vegetative, or severe disability on the extended Glasgow Outcome Scale and by Anderson-Hauck formula for the differences in rates.

This is the largest clinical trial thus far to use this end point and the first to show that angiographic vasospasm can be significantly reduced. All 3 doses of clazosentan statistically significantly reduced the frequency and severity of moderate to severe angiographic vasospasm in a dose-dependent fashion. The highest dose (15 mg/h) was associated with a 65% relative risk reduction in vasospasm. This study confirms the results of Vajkoczy and colleagues who reported that 0.2 mg/kg clazosentan per hour significantly reduced the incidence and severity of angiographic vasospasm in 15 patients compared with 17 treated with placebo.¹³ For the average 70-kg person, the dose in that study would be 14 mg/h. The relative risk reduction observed by Vajkoczy et al was similar to that observed with the 15-mg/h dose in this study.¹³

Most clinical trials of treatments to prevent vasospasm after SAH used symptomatic as opposed to angiographically documented vasospasm as an end point.⁵ Nimodipine is the only proven treatment. Meta-analysis of the randomized trials showed that it improved outcome, reduced symptomatic vasospasm, and probably reduced cerebral infarction after SAH.²⁶ In the subgroups of patients in the nimodipine studies who had catheter angiography, however, it did not reduce angiographic vasospasm.²⁷ This in part led to controversy about whether nimodipine was beneficial or whether trial design problems led to the observed benefits. Use of angiographic vasospasm as the primary end point in this study removes this concern and provides strong evidence of the role of endothelin in the pathogenesis of vasospasm.^{6–12}

Table 3. Adverse Events More Frequently Reported With Clazosentan Compared With Placebo

Characteristic	Placebo (n=96)	Clazosentan		
		1 mg/hour (n=107)	5 mg/hour (n=110)	15 mg/hour (n=96)
Hypotension	3 (3)	6 (6)	13 (12)	11 (12)
Anemia	16 (17)	27 (25)	32 (29)	19 (20)
Lung complications	26 (27)	47 (44)	48 (44)	37 (39)
Pulmonary edema	1 (1)	11 (10)	14 (13)	10 (10)
Acute respiratory distress syndrome	2 (2)	6 (6)	8 (7)	8 (8)
Pleural effusion	5 (5)	13 (12)	14 (13)	13 (14)
Pneumonia	14 (15)	21 (20)	25 (23)	13 (14)

Despite the marked beneficial effect on angiographic vasospasm, no difference between groups was observed for the vasospasm-related M/M end point when based on investigator assessment. We investigated this further by central blinded review of the components of the M/M end point and found a trend toward decreased incidence of M/M using this modified end point. This was due primarily to a decrease in infarcts related to vasospasm in patients treated with clazosentan. Investigator assessment included more hypodense areas from periprocedural and other causes. Also, there was a decrease in patients who had DIND in the presence of angiographic vasospasm based on central review apparently because investigators sometimes attributed DIND to vasospasm that was measured as only mild by central review. In support of the central review opinion, the incidence of new infarcts related to vasospasm in the placebo group was similar to that reported in the literature.²⁵ These findings support the notion that decreasing vasospasm will improve clinical outcome. They emphasize the need to assess the etiology of CT-based hypodensities in a consistent manner to avoid confounders unrelated to vasospasm and is in agreement with the assessments made in some but not all previous SAH trials.^{13,28,29}

Clazosentan treatment had no obvious effect on functional outcome measured by the GOSE. This study, however, was not powered to detect a treatment effect on clinical outcome. Sample size calculations suggest that thousands of patients need to be randomized to detect a change in the Glasgow Outcome Scale even if vasospasm is completely prevented by treatment.³⁰ This may be because the Glasgow Outcome Scale categories focus on physical changes and are not very sensitive to subtle neurological changes such as those occurring after SAH.^{24,31} From a practical perspective, until more sensitive outcome scales are developed and validated, alternative outcome measures focused on vasospasm-related outcomes may reduce sample size requirements.

Pulmonary complications, hypotension, and anemia were more common at all doses of clazosentan than with placebo. Pulmonary adverse events may have been related to fluid retention, which is postulated to be a class effect of endothelin receptor antagonists.^{32,33} Anemia may also be dilutional secondary to fluid retention. Overall, the adverse events were generally manageable and not considered serious. The causes of death were not unexpected in this patient population and

for the most part could be attributed either to patients' underlying condition or major intraoperative complications, which tended to be higher in the clazosentan-treated groups.

Conclusions

This study shows that 1, 5, and 15 mg/h intravenous clazosentan significantly reduces moderate and severe angiographic vasospasm when compared with placebo. The results of the centrally assessed M/M end point showed a trend toward reduction in clinically relevant vasospasm-related events. They also suggest that evaluations of the effects of treatments for vasospasm should avoid confounders such as hypodensities on CT unrelated to vasospasm. Clazosentan increased the incidence of pulmonary complications, anemia, and hypotension. Overall the results support conduct of a Phase 3 clinical trial (CONSCIOUS-2) to evaluate effects of clazosentan on vasospasm-related M/M using central clinical and radiological assessment and with attention to avoidance of excess fluid administration and hypotension.

Appendix

CONSCIOUS-1 Investigators included 52 centers in Israel, Europe, and North America, 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)—Austria: Hans Tritthart, LKH Graz, Neurochirurgische, Universitätsklinik, Auenbruggerplatz 29, A-8036 Graz; Erich Schmutzhard, Medizinische Universität Innsbruck, Universitätsklinik für Neurologie, Anichstrasse 35, A-6020 Innsbruck; Bernd Riehling, Christian-Doppler-Klinik Salzburg, Neurochirurgie, Ignaz-Harrer-Strasse 79, A-5020 Salzburg; and Andreas Gruber, AKH University of Vienna, Neurosurgery, Währinger Gürtel 18–20, A-1090, Vienna. Canada: Michel Bojanowski, 245 Plamondon Street, Repentigny, Quebec J6A 7E3; Jay Max Findlay, University of Alberta Hospital, Room 2D1.02 MacKenzie Sciences Centre, 8440 112 Street NW, Edmonton, Alberta T6G 2B7; Gary J. Redekop, University of British Columbia, Interventional Neuroradiology 323c-700, West 10th Avenue, Vancouver, BC V5Z 4E5; Niall Ferguson, Toronto Western Hospital, Edith Cavell, Wing 2–026, 399 Bathurst Street, Toronto, Ontario M5T 2S8; and Ian Fleetwood, QEII Health Sciences Centre Division of Neurosurgery, Halifax Infirmary, 1796 Summer Street, Room 3809, Halifax, NS B3H 3A7. Finland: Juha Öhman, Helsinki University Central Hospital, Töölö Hospital, Department of Neurosurgery, Box 266, FIN-00029 HUS; and Juha Öhman, Tampere University Central Hospital, Department of Neurosurgery, Teiskonkatie 35, Box 2000, Tampere 33521. France: Laurent Beydon, Centre Hospitalier Universitaire d'Angers, Hôpital Larrey, Service de Réanimation Chirurgicale B, 4 Rue Larrey, F-49033 Angers; Nicolas Bruder, Département d'Anesthésie Réanimation, Hôpital de la Timone, CHU de Marseille, 264 Rue St Pierre, 13385 Marseille Cedex 10; Marie-Reine Lossier, Didier Payen de la Garanderie, Département d'Anesthésie Réanimation, Hôpital Lariboisière, 2 rue Ambroise, Paré, 75475 Paris cedex 10; Frédérique Dailler, SIPO, Hôpital Neurologique et Neurochirurgical Pierre Wertheimer, 59 Blvd Pinel, 69677 Bron cedex; and François Proust, Département de Neurochirurgie, Hôpital Charles Nicolle, CHU de Rouen, 1 rue de Germont, 76031 Rouen cedex. Germany: Bernhard Meyer, Karl Schaller, Rheinische Friedrich-Wilhelms-Universität Bonn, Neurochirurgische Klinik, Sigmund-Freud-Str 25, 53105 Bonn; Dietmar Stolke, Universitätsklinikum Essen, Neurochirurgische Klinik, Hufelandstrasse 55, 45122 Essen; Andreas Raabe, Klinik für Neurochirurgie, Johann-Wolfgang-Goethe-Universität Frankfurt, Schleusenweg 2 to 16, 60528 Frankfurt/Main; Peter Schmiedek, Universitätsklinikum Mannheim gGmbH, Mannheim, Neurochirurgische Klinik, Theodor-Kutzer-Ufer 1 to 3, 68135 Mannheim; Maximilian Mehdorn, Universitätsklinikum Schleswig-Holstein, Campus Kiel, Klinik für Neurochirurgie, Schittenhelmstr 10, D-24105 Kiel; Jürgen Meix-

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Acknowledgments

We thank the principal investigators of the CONSCIOUS-1 study.

Source of Funding

This study was supported by Actelion Pharmaceuticals.

Disclosures

R.L.M., N.F.K., S.M., D.R., P.S., S.W., and A.P. are consultants for Actelion Pharmaceuticals.

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