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REACT: a randomized trial to assess the efficacy and safety of clazosentan for preventing clinical deterioration due to delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage

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OBJECTIVE Ischemic complications account for significant patient morbidity following aneurysmal subarachnoid hemorrhage (aSAH). The Prevention and Treatment of Vasospasm with Clazosentan (REACT) study was designed to assess the safety and efficacy of clazosentan, an endothelin receptor antagonist, in preventing clinical deterioration due to delayed cerebral ischemia (DCI) in patients with aSAH.

METHODS REACT was a prospective, multicenter, randomized, double-blind, phase 3 study. Eligible patients had aSAH secured by surgical clipping or endovascular coiling, and had presented with thick and diffuse clot on admission CT scan. Patients were randomized (1:1 ratio) to 15 mg/hour intravenous clazosentan or placebo within 96 hours of the aSAH for up to 14 days, in addition to standard of care treatment including oral or intravenous nimodipine. The primary efficacy endpoint was the occurrence of clinical deterioration due to DCI up to 14 days after initiation of the study drug. The main secondary endpoint was the occurrence of clinically relevant cerebral infarction at day 16 after study drug initiation. Other secondary endpoints included clinical outcome assessed on the modified Rankin Scale (mRS) and the Glasgow Outcome Scale–Extended (GOSE) at week 12 post-aSAH. Imaging and clinical endpoints were centrally adjudicated.

RESULTS A total of 409 patients were randomized between February 2019 and May 2022 across 74 international sites. Three patients did not start study treatment and were not included in the analysis set. The occurrence of clinical deterioration due to DCI was 15.8% (32/202 patients) in the clazosentan group and 17.2% (35/204 patients) in the placebo group, and the difference was not statistically significant (relative risk reduction [RRR] 7.2%, 95% CI –42.6% to 39.6%, p = 0.734). A nonsignificant RRR of 34.1% (95% CI –21.3% to 64.2%, p = 0.177) was observed in clinically relevant cerebral infarcts treated with clazosentan (7.4%, 15/202) versus placebo (11.3%, 23/204). Rescue therapy was less frequently needed for patients treated with clazosentan compared to placebo (10.4%, 21/202 vs 18.1%, 37/204; RRR 42.6%, 95% CI 5.4%–65.2%). A nonsignificant relative risk increase of 25.4% (95% CI –10.7% to 76.0%, p = 0.198) was reported in

ABBREVIATIONS aSAH = aneurysmal subarachnoid hemorrhage; CONSCIOUS = Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage; CVS = cerebral vasospasm; DCI = delayed cerebral ischemia; DIND = delayed ischemic neurological deficit; ET = endothelin; GOSE = Glasgow Outcome Scale–Extended; IV = intravenous; MedDRA = Medical Dictionary for Regulatory Activities; mRS = modified Rankin Scale; REACT = Prevention and Treatment of Vasospasm with Clazosentan; RRR = relative risk reduction; TEAE = treatment-emergent adverse event; WFNS = World Federation of Neurosurgical Societies.

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the risk of poor GOSE and mRS scores with clazosentan (24.8%, 50/202) versus placebo (20.1%, 41/204) at week 12 post-aSAH. Treatment-emergent adverse events were similar to those reported previously.

CONCLUSIONS Clazosentan administered for up to 14 days at 15 mg/hour had no significant effect on the occurrence of clinical deterioration due to DCI.

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EU clinical trial registration no.: 2018-000241-39 (clinicaltrialsregister.eu)

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KEYWORDS aneurysm; cerebral ischemia; cerebral vasospasm; clazosentan; endothelin-1; subarachnoid hemorrhage; vascular disorders

Aneurysmal subarachnoid hemorrhage (aSAH) is a neurological emergency caused by the rupture of an intracranial aneurysm, which carries a high risk of death and of persistent disability in survivors.[1–4] Rebleeding is prevented by securing the ruptured aneurysm with either surgical clipping or endovascular coiling, but the patient remains at risk for secondary neurological deterioration due to cerebral vasospasm (CVS) or other causes of delayed cerebral ischemia (DCI) during the first 2 weeks following the acute bleeding event.[5] DCI is a clinical syndrome of neurological deterioration that is observed in approximately 30% of patients after aSAH.[6] It can progress to cerebral infarction and death,[7] and it is a major predictor of cognitive impairment, quality of life deterioration, and poor long-term outcome.[8–12] The mechanisms involved in the pathophysiology of DCI remain poorly understood, but interdependent pathways are likely to include CVS, macro- and microcirculatory dysfunction, inflammation, and cortical spreading depolarization.[13]

Current management of DCI is based on the restoration of cerebral perfusion by using induced hypertension or endovascular therapy with intraarterial vasodilators and/or transluminal balloon angioplasty, but treatment efficacy is limited.[14] The only evidence-based strategy currently available for the prevention of DCI and improvement of clinical outcomes remains the calcium channel blocker nimodipine,[2,15] which has no significant effect on angiographic CVS.[16]

Clazosentan is a parenteral endothelin (ET) receptor antagonist that selectively inhibits the binding of ET-1, a potent vasoconstrictor,[17] to the ET_A receptors[18] primarily expressed in vascular smooth-muscle cells and pericytes, including those located in the cerebral arteries.[19,20] Increased ET-1 levels in the CSF have been associated with vasospasm and DCI in patients with aSAH,[21] which supported the investigation of clazosentan in this condition. In several phase 2 and 3 clinical trials,[22–25] continuous intravenous (IV) infusion of clazosentan consistently decreased the incidence of angiographic CVS in patients with aSAH. More recently, two phase 3 studies performed in Japanese patients with aSAH—secured by endovascular coiling in one study and surgical clipping in the other[25]—reported a significant decrease in the combined incidence of vasospasm-related morbidity (e.g., DCI or new cerebral infarct) and all-cause mortality in patients treated with 10 mg/hour clazosentan compared with those treated with placebo.

In the Prevention and Treatment of Vasospasm with Clazosentan (REACT) study described here, the main objective was to investigate the efficacy of 15 mg/hour clazosentan in preventing clinical deterioration due to DCI in a population at high risk for developing vasospasm-related ischemic complications post-aSAH.

Methods

Study Design

REACT was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 study. It was designed to assess the safety and efficacy of clazosentan in preventing clinical deterioration due to DCI in patients with aSAH. The study was conducted in 74 ICUs in 15 countries (Austria, Belgium, Canada, Czechia, Denmark, Finland, France, Germany, Hungary, Israel, Italy, Poland, Spain, Sweden, and the US). It included a double-blind treatment period (maximum 14 days), followed by a safety follow-up period (24 hours) (Fig. 1). The extended follow-up period included an on-site visit 12 weeks post-aSAH and a telephone interview 24 weeks post-aSAH. The study protocol has been previously published.[26] This study was registered with the ClinicalTrials.gov database (clinicaltrials.gov) and the EudraCT database (clinicaltrialsregister.eu), and its registration nos. are NCT03585270 and 2018-000241-39, respectively.

Written informed consent to participate in the study was provided by all patients or their legal representative. The study protocol and amendments were approved by an institutional review board or ethics committee at each site. The study was conducted in compliance with the International Conference on Harmonization Good Clinical Practice Guideline, the principles laid down in the Declaration of Helsinki, and local laws and regulations. An independent data monitoring committee monitored unblinded safety and efficacy data during the study. The results are reported in compliance with the Consolidated Standards of Reporting Trials (CONSORT) statement.

Participants

Eligible patients in our study were adults (aged 18–70 years) with an angiographically confirmed ruptured saccular aneurysm, which was successfully secured within 72 hours of rupture by surgical clipping or endovascular coiling. Patients could have a World Federation of Neurosurgical Societies (WFNS) grade of 1–5 at admission, but were required to have a WFNS grade of 1–4 after recovery from the aneurysm-securing procedure and after external ventricular drainage for hydrocephalus, if required. An additional key inclusion criterion was the presence of a thick and diffuse clot on the admission CT scan, defined

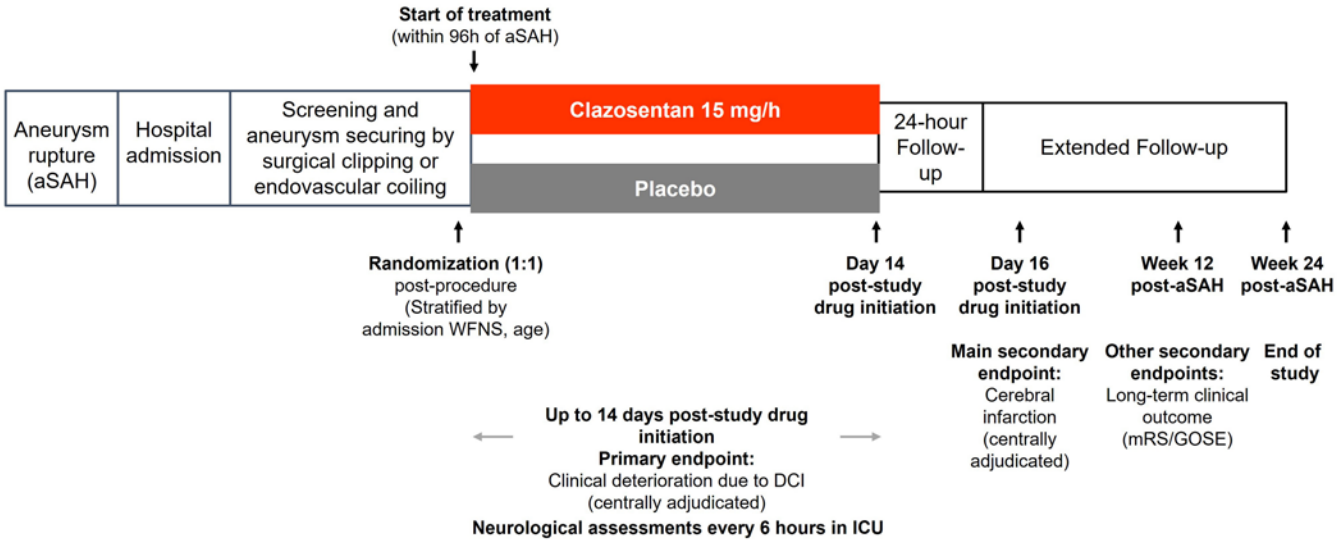

FIG. 1. REACT study design. h = hour.

as a thick confluent clot > 4 mm in thickness, involving ≥ 3 basal cisterns.

Randomization and Masking

Patients were randomly assigned (1:1) to clazosentan or placebo within 96 hours of the aSAH symptom onset or time last known to be well. Randomization was stratified by WFNS grade (1–2 vs 3–5), age at hospital admission (≤ 60 years vs > 60 years), and patient recruitment group (high-risk prevention vs early treatment: see definition in the *Statistical Analyses* section). Treatment was assigned using an interactive response technology system. Study drug kits were similarly packaged, rendering the investigational treatment indistinguishable from its matching placebo. Patients, investigators, and site personnel stayed blinded to the study treatment until study closure. In case of medical emergency, the study treatment could be unblinded by the investigator.

Procedures

In the double-blind treatment phase, patients received clazosentan (15 mg/hour) or placebo as a continuous IV infusion for a maximum of 14 days and a minimum of 10 days,[26] as well as the usual standard of care treatment, including oral or IV nimodipine.

Outcomes

The primary endpoint was the occurrence of clinical deterioration due to DCI, from study drug initiation up to 14 days after study drug initiation. Clinical deterioration due to DCI was defined as a worsening of ≥ 2 points on the modified Glasgow Coma Scale or the abbreviated National Institutes of Health Stroke Scale that lasted for ≥ 2 hours, and that could not be entirely attributed to causes other than CVS. Patients were also considered as meeting the primary endpoint if they died during the 14-day period after study drug initiation; if they were not evaluable for neurological status (e.g., due to sedation) and rescue therapy was administered for relevant vasospasm (or the reason for the patient not being evaluable was vasospasm-related); and finally, if they were discharged prior to day 14 and rehospitalized for possible or probable symptomatic vasospasm. Rescue therapy was defined as an escalation of medical therapy beyond standard hemodynamic augmentation for the treatment of refractory vasospasm. Refractory vasospasm was characterized by a minimum of a ≥ 2-point worsening on either the modified Glasgow Coma Scale or the abbreviated National Institutes of Health Stroke Scale and no response to hemodynamic therapy. Rescue therapies included balloon angioplasty or intraarterial/intrathecal/intracisternal/intraventricular administration of vasodilators. IV vasodilators (e.g., nicardipine or milrinone) qualified as rescue therapy if they were preceded by intraarterial administration of a vasodilator. The primary endpoint was adjudicated by an independent clinical event committee.

The main secondary endpoint was the occurrence of clinically relevant cerebral infarction at day 16 after study drug initiation based on CT images. This endpoint included all-cause cerebral infarction ≥ 5 cm^3 (first component) or cerebral infarction < 5 cm^3 in patients who experienced clinical deterioration due to DCI (second component). Cerebral infarction referred to new or worsened infarcts reported after comparing the total volume of infarcts on the day 16 CT scan to the CT scan performed just before randomization. Infarct size was centrally assessed by an independent radiology committee, and the first component of the secondary endpoint was adjudicated by the independent clinical event committee.

Other secondary endpoints included long-term clinical outcome, assessed at week 12 post-aSAH using a structured interview to assign scores on the modified Rankin Scale (mRS) and the Glasgow Outcome Scale–Extended (GOSE). Scores were dichotomized into poor outcome (score ≥ 3 for mRS, ≤ 4 for GOSE) and good outcome

(score < 3 for mRS, and > 4 for GOSE). Adverse events were defined using the Medical Dictionary for Regulatory Activities (MedDRA; version 25).

Statistical Analyses

It was estimated that a sample size of 176 patients in each group would be needed to demonstrate that clazosentan was superior to placebo with 90% power at a 5% two-sided significance level. This calculation was made using Pearson's chi-square test and assumed a true incidence of clinical deterioration due to DCI of 28% in the placebo group and 14% in the clazosentan group. These values were based on observations from the Clazosentan to Overcome Neurological Ischemia and Infarction Occurring After Subarachnoid Hemorrhage (CONSCIOUS) 2 and CONSCIOUS 3 studies in the subgroup of patients with thick and diffuse clots. Taking into consideration a study dropout rate of 10%, the overall sample size for study enrollment was estimated to be 400 patients (200 patients in each treatment group).

The primary and secondary endpoints were analyzed on the full analysis set that comprised all randomized patients who had initiated the study treatment, and the Cochran-Mantel-Haenszel test was used with stratification by WFNS grade (1–2 vs 3–5) and age at hospital admission (≤ 60 years and > 60 years). The primary and secondary endpoints were tested using a hierarchical procedure, at the two-sided significance level of 0.05 until first nonrejection. A supportive analysis included repetition of the primary analysis after adding administration of rescue therapy to the definition of the primary endpoint to account for the impact of rescue therapy administered prior to any neurological deterioration.

No missing data were expected for the primary endpoint and for the first component of the secondary endpoint, because all patients had these adjudicated by the clinical event committee. If the second component of the main secondary endpoint could not be derived due to a missing CT scan, then the patients meeting the primary endpoint were considered as meeting the main secondary endpoint.

The changes to the protocol that occurred after the study started have been reported previously.[26] In particular, a second group of high-risk patients, which included patients who had already developed moderate to severe vasospasm with no significant neurological deterioration was initially planned by protocol. However, recruitment into this so-called early treatment group was discontinued because inclusion rates were low, making the contribution of these patients to the overall study futile. The 11 patients enrolled in the early treatment group (6 treated with clazosentan and 5 with placebo) are included in the analyses presented here.

Results

Overall, 409 patients were randomized between February 2019 and May 2022. Three patients did not start the study treatment and 406 patients were included in the full analysis set: 202 in the clazosentan group and 204 in the placebo group (Fig. 2).

Patient demographic and disease characteristics were similar across the two treatment groups (Table 1). The mean patient age (± SD) was 53.3 ± 10.2 years, and approximately two-thirds of the patients were women. An imbalance in geographical region was observed, with more patients in the clazosentan than in the placebo group from the US (17.3% vs 11.8%) and from non-European countries (24.3% vs 21.1%). Most patients (78.6%) had good clinical WFNS grades (grade 1–2) at admission, and the most severe (grade 5; allowed by protocol at admission but not after the securing procedure) was reported for 8.6% of all patients. Overall, the aneurysm securing procedure was more likely to be endovascular coiling (70.0%) than surgical clipping (30.0%); surgical clipping was more frequent in the clazosentan than in the placebo group (35.6% vs 24.5%).

Patients received study treatment for a median duration of 12.0 days (min–max = 0.0–15.0 days) in the clazosentan group and 12.9 days (min–max = 1.8–15.0 days) in the placebo group, and treatment was started 68.3 hours (min–max = 9.3–99.3 hours) and 70.9 hours (min–max = 20.4–100.8 hours) after the aSAH in the clazosentan and placebo groups, respectively. Oral or IV nimodipine was administered concomitantly to 193 (95.5%) participants receiving clazosentan and 203 (99.5%) receiving placebo. Reasons for premature treatment discontinuation prior to day 14 are presented in Fig. 2.

The occurrence of clinical deterioration due to DCI up to 14 days after study drug initiation was 15.8% (32/202 patients) in the clazosentan group and 17.2% (35/204 patients) in the placebo group, and the difference was not statistically significant (relative risk reduction [RRR] 7.2%, 95% CI –42.6% to 39.6%, p = 0.734). In the sensitivity analysis that included any administration of rescue therapy in the definition of the primary endpoint, the RRR for clinical deterioration due to DCI was 26.7% (95% CI –8.5% to 50.5%), with an occurrence of 16.8% (34/202 patients) in the clazosentan group and 23.0% (47/204 patients) in the placebo group, which remained nonsignificant. A nonsignificant relative risk reduction of 34.1% (95% CI –21.3% to 64.2%) was observed with regard to clinically relevant cerebral infarcts with clazosentan versus placebo (7.4%, 15/202 vs 11.3%, 23/204).

Rescue therapy (up to hospital discharge) was less frequently needed for patients treated with clazosentan than for those treated with placebo (10.4%, 21/202 vs 18.1%, 37/204; RRR 42.6%, 95% CI 5.4%–65.2%). The median duration of rescue therapy was also shorter in the clazosentan arm (1 day, min–max = 1–7 days vs 2 days, min–max = 1–10 days).

Over the treatment period, 87.9% (182/207) of patients in the clazosentan group and 82.9% (165/199) in the placebo group experienced at least one treatment-emergent adverse event (TEAE) (Table 2). The rate of TEAE considered to be related to study treatment was 28.0% and 18.1%, respectively. Severe adverse events were reported for 15.9% of the clazosentan-treated patients and 13.1% of the placebo-treated patients. A higher proportion of patients receiving clazosentan (13.0%) prematurely discontinued treatment compared with patients receiving placebo (5.5%). The incidence of TEAEs of specific inter-

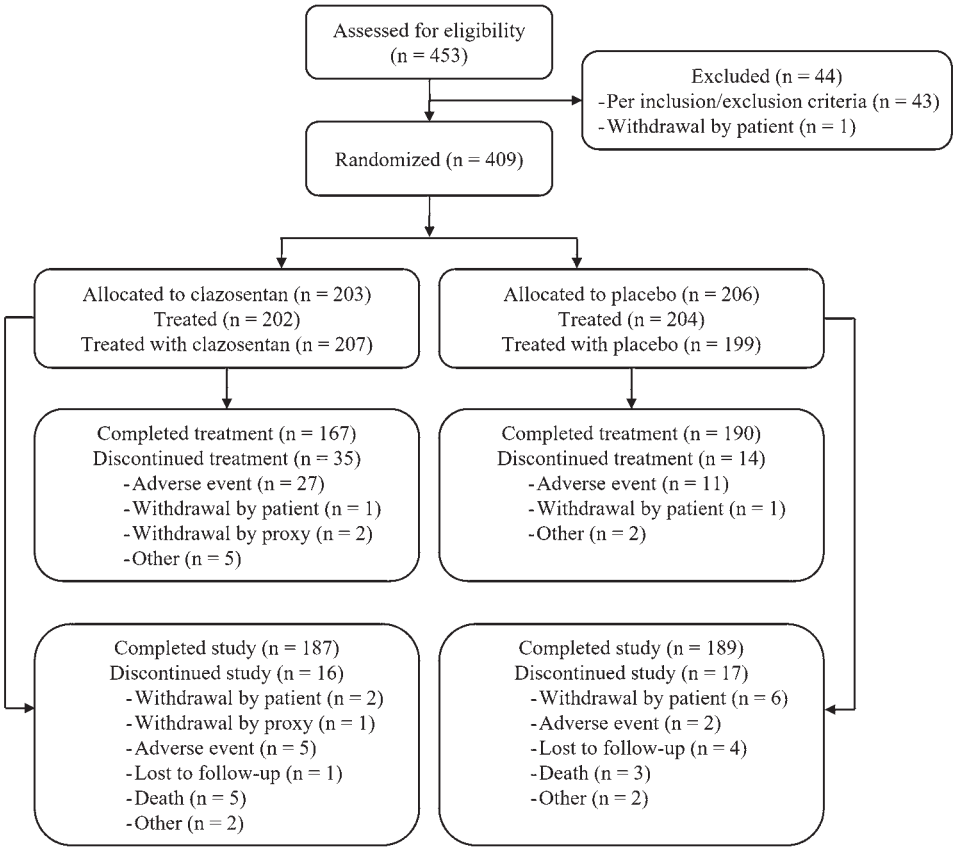

FIG. 2. REACT study profile. Efficacy analyses were performed by allocated treatment groups and safety analyses by received treatment groups. Data added to the CONSORT template (from Schulz KF, Altman DG, Moher D, CONSORT Group. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. BMJ. 2010;340:c332) under the terms of the Creative Commons Attribution Noncommercial (CC BY-NC 2.0) License (https://creativecommons.org/licenses/by-nc/2.0/).

est is shown in Table 3. Events that occurred more frequently with clazosentan than placebo included lung complications (25.6% vs 10.6%), edema/fluid retention (19.8% vs 4.0%), hypotension (10.1% vs 4.0%), and brain edema (13.0% vs 9.0%).

Regarding clinical outcome at week 12 post-aSAH, a nonsignificant relative risk increase of 25.4% (95% CI –10.7% to 76.0%) was reported in patients with poor GOSE and mRS scores, with clazosentan (24.8%, 50/202) versus placebo (20.1%, 41/204) (Fig. 3). At the end of the study, 15 patients had died or were in a vegetative state: 3.4% (7/207) in the clazosentan group and 4.0% (8/199) in the placebo group (Table 4). Among these, 10 patients died within 24 weeks of aSAH: 3.4% (7/207) in the clazosentan group and 1.5% (3/199) in the placebo group. Of the 6 deaths occurring during the treatment period, 5 were attributed to the underlying medical conditions and 1 (caused by brain edema) was potentially related to clazosentan.

Discussion

The REACT study did not demonstrate a significant effect of clazosentan—administered by continuous IV infusion for up to 14 days at 15 mg/hour—on the occurrence of clinical deterioration due to DCI in an aSAH population at high risk of developing vasospasm-related ischemic complications. The reduction in cerebral infarcts during the 16 days following clazosentan initiation did not reach statistical significance, and no benefit was shown on clinical outcome at 3 months. These results were unexpected given the established effect of clazosentan on angiographic CVS reported in previous studies,[23,24] and given the observed reduction of vasospasm-related morbidity/mortality, including a composite endpoint of death, DCI, or cerebral infarction in two recent phase 3 Japanese studies (Table S1).[25]

The REACT study was developed using similar standardized definitions and time frames for the assessment of DCI, vasospasm, infarction, and long-term outcome,[26] but some differences with the previous positive Japanese studies[25] could explain the present results. Although specific patient management guidelines were implemented across all study centers to standardize patient medical care to the extent possible, in particular with regard to blood pressure control and fluid management, some variability in local patient care was unavoidable given the large number of participating countries.

The primary endpoint of REACT, which assessed clinical deterioration due to DCI, was derived from pre-

TABLE 1. Patient demographic and disease characteristics at admission (all-treated population)

Characteristic	Clazosentan 15 mg/hr, n = 202	Placebo, n = 204	All Pts, n = 406
Age in yrs*	53.0 ± 10.4	53.7 ± 10.0	53.3 ± 10.2
18 to ≤64	171 (84.7)	175 (85.8)	346 (85.2)
65 to ≤84	31 (15.3)	29 (14.2)	60 (14.8)
Female sex	138 (68.3)	137 (67.2)	275 (67.7)
Geographic area			
Europe	153 (75.7)	161 (78.9)	314 (77.3)
USA	35 (17.3)	24 (11.8)	59 (15)
Canada	8 (4.0)	12 (5.9)	20 (4.9)
Israel	6 (3.0)	7 (3.4)	13 (3.2)
Race			
White	176 (87.1)	169 (82.8)	345 (85.0)
Black/African American	6 (3.0)	5 (2.5)	11 (2.7)
Asian	4 (2.0)	6 (2.9)	10 (2.5)
Other	1 (0.5)	4 (2.0)	5 (1.2)
Unknown/not permitted	15 (7.4)	20 (9.8)	35 (8.6)
Motor deficit†	23 (11.5)	29 (14.4)	52 (13.0)
WFNS grade assessed by investigator			
Grade 1	105 (52.0)	100 (49.0)	205 (50.5)
Grade 2	56 (27.7)	58 (28.4)	114 (28.1)
Grade 3	8 (4.0)	7 (3.4)	15 (3.7)
Grade 4	18 (8.9)	19 (9.3)	37 (9.1)
Grade 5	15 (7.4)	20 (9.8)	35 (8.6)
Clot size			
Thick & diffuse	196 (97.0)	198 (97.1)	394 (97.0)
Other	6 (3.0)	5 (2.4)	11 (2.7)
Unable to assess	0	1 (0.5)	1 (0.2)
Common CT findings‡			
Intraventricular hemorrhage	184 (91.1)	188 (92.6)	372 (91.9)
Hydrocephalus	123 (60.9)	131 (64.5)	254 (62.7)
Intraparenchymal hemorrhage	31 (15.3)	32 (15.8)	63 (15.6)
Ventricular drainage	6 (3.0)	10 (4.9)	16 (4.0)
Extraaxial hematoma	10 (5.0)	4 (2.0)	14 (3.5)
Midline shift	6 (3.0)	4 (2.0)	10 (2.5)
Location of ruptured aneurysm			
ACoA	81 (40.1)	81 (39.7)	162 (39.9)
MCA	40 (19.8)	34 (16.7)	74 (18.2)
Supraclinoid ICA	27 (13.4)	32 (15.7)	59 (14.5)
PCoA	22 (10.9)	21 (10.3)	43 (10.6)
ACA	15 (7.4)	16 (7.8)	31 (7.6)
BA	11 (5.4)	9 (4.4)	20 (4.9)
Distal VA	3 (1.5)	6 (2.9)	9 (2.2)
PCA	3 (1.5)	4 (2.0)	7 (1.7)
Other	0	1 (0.5)	1 (0.2)
Size of ruptured aneurysm			
≤5 mm	100 (49.5)	104 (51.2)	204 (50.4)
>5 mm	102 (50.5)	99 (48.8)	201 (49.6)
Missing	0	1	1

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TABLE 1. Patient demographic and disease characteristics at admission (all-treated population)

Characteristic	Clazosentan 15 mg/hr, n = 202	Placebo, n = 204	All Pts, n = 406
No. of aneurysms secured (ruptured & unruptured)			
1	179 (88.6)	194 (95.1)	373 (91.9)
2	17 (8.4)	10 (4.9)	27 (6.7)
3	5 (2.5)	0	5 (1.2)
5	1 (0.5)	0	1 (0.2)
Aneurysm-securing procedure			
Surgical clipping	72 (35.6)	50 (24.5)	122 (30.0)
Endovascular coiling	130 (64.4)	154 (75.5)	284 (70.0)

ACA = anterior cerebral artery; ACoA = anterior communicating artery; BA = basilar artery; ICA = internal carotid artery; MCA = middle cerebral artery; PCA = posterior cerebral artery; PCoA = posterior communicating artery; pts = patients; VA = vertebral artery.
Values are expressed as the mean ± SD for continuous variables, and as the number (%) for categorical variables.
* Age ranges are standard; the actual range in this study was 18–70 years.
† For motor deficits, n = 200 for the clazosentan group, n = 201 for the placebo group, and n = 401 for the all-patient group.
‡ In entries for common CT findings, n = 202 for the clazosentan group, n = 203 for the placebo group, and n = 405 for the all-patient group.

vious observations suggesting that the treatment effect of clazosentan on the composite vasospasm-related morbidity and all-cause mortality endpoint[24,25,27] was largely driven by a reduction in vasospasm-related delayed ischemic neurological deficit (DIND). The primary endpoint definition in REACT was expected to capture the immediate clinical manifestations of post-aSAH cerebral ischemia preventable by an antivasospastic strategy, with the main secondary endpoint of clinically relevant cerebral infarction complementing the primary endpoint with radiological evidence of ischemia.

Yet, the occurrence of the primary endpoint in the placebo group (17.2%) was considerably lower than expected. A much higher rate (28%) had been previously observed for vasospasm-related DIND in a post hoc analysis of the CONSCIOUS 2 and 3 studies,[28] focusing on similar patients with thick and diffuse clot at hospital admission and therefore at high risk of ischemic complications. Improved standards of care in the decade following the CONSCIOUS trials, differences in the definition of DCI for patients who are not assessable on neurological scales, in particular removing the criteria of pressor use in the definition of rescue therapy, might explain the observed low rates of DCI. An overview of efficacy data from the large phase 2 and 3 studies is provided in Table S1. The recent phase 3 Japanese studies[25] also reported a higher

TABLE 2. TEAEs reported for ≥ 4% of patients treated with clazosentan (safety population)

	Clazosentan 15 mg/hr, n = 207	Placebo, n = 199
No. of pts w/ at least 1 event	182 (87.9)	165 (82.9)
Pyrexia	42 (20.3)	35 (17.6)
Cerebral vasoconstriction	33 (15.9)	50 (25.1)
Hyponatremia	33 (15.9)	29 (14.6)
Constipation	32 (15.5)	28 (14.1)
Headache	31 (15.0)	23 (11.6)
Hypokalemia	25 (12.1)	31 (15.6)
Urinary tract infection	25 (12.1)	24 (12.1)
Gamma-glutamyltransferase increased	24 (11.6)	20 (10.1)
Hypotension	18 (8.7)	7 (3.5)
Nausea	17 (8.2)	6 (3.0)
Vomiting	17 (8.2)	6 (3.0)
Pleural effusion	16 (7.7)	3 (1.5)
Alanine aminotransferase increased	15 (7.2)	14 (7.0)
Insomnia	14 (6.8)	11 (5.5)
Intracranial pressure increased	14 (6.8)	6 (3.0)
Pneumonia	14 (6.8)	6 (3.0)
Aspartate aminotransferase increased	13 (6.3)	9 (4.5)
Pulmonary edema	13 (6.3)	2 (1.0)
Anemia	12 (5.8)	8 (4.0)
Hypertension	10 (4.8)	26 (13.1)
Brain edema	10 (4.8)	2 (1.0)

Values are expressed as the numbers of patients with at least 1 event (%).
Events are individual MedDRA (version 25) terms.

TABLE 3. TEAEs of specific interest (safety population)

	Clazosentan 15 mg/hr, n = 207	Placebo, n = 199
Lung complications	53 (25.6)	21 (10.6)
Edema & fluid retention	41 (19.8)	8 (4.0)
Hypotension	21 (10.1)	8 (4.0)
Brain edema	27 (13.0)	18 (9.0)
Anemia	17 (8.2)	12 (6.0)
Tachyarrhythmia	21 (10.1)	19 (9.5)
Hepatic disorders	42 (20.3)	42 (21.1)
Cerebral hemorrhage	3 (1.4)	5 (2.5)

Values are expressed as the numbers of patients with at least 1 event (%).
Events are groupings of MedDRA (version 25) terms.

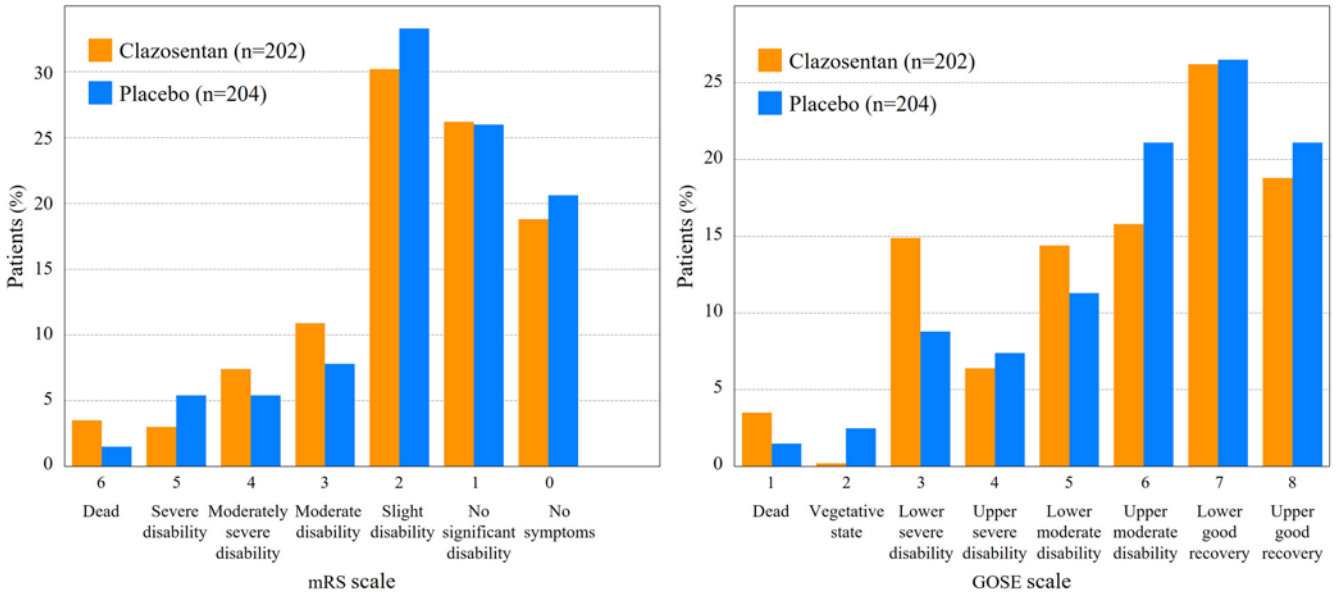

FIG. 3. Patient distribution on the mRS and GOSE at week 12 post-aSAH.

event rate for vasospasm-related DIND in the placebo group (19.6%) than in the REACT study, despite a less severely affected patient population. This endpoint differed in definition from the REACT primary endpoint by the inclusion of hemodynamic therapy (induced hypertension, hypervolemia, and hemodilution) and inotropes (hyperdynamic therapy with dobutamine) as rescue therapies, in addition to intraarterial vasodilators and angioplasty. This may have increased the number of patients potentially eligible to meet the endpoint. The design of the Japanese studies also required an angiogram on day 9 post-aSAH for all patients and allowed additional imaging modalities, which may have resulted in a more standardized and complete set of clinical data being used in central adjudication. As a result, the identification of vasospasm as a factor contributing to the observed clinical deterioration may have been facilitated and therefore may be more homogeneous in the Japanese studies, especially in complex cases with concomitant medical complications. In contrast, the REACT study's primary endpoint appeared to have been more dependent on clinical judgment, resulting in some cases not qualifying for the endpoint despite the presence of vasospasm, and others qualifying in the absence of vasospasm. The causes for the low event rates reported in the REACT study remain uncertain, and it is not entirely clear if marginal differences in study design between REACT and the Japanese studies may have contributed to the observed discrepancy in treatment effect.

TABLE 4. Primary cause of death by preferred term (safety population)

	Clazosentan 15 mg/hr, n = 207	Placebo, n = 199
Pts in vegetative state, from GOSE	0	5 (2.5)
Total deaths	7 (3.4)	3 (1.5)
Deaths during treatment period		
Brain death	1 (0.5)	0
Brain edema	1 (0.5)	0
Cardiorespiratory arrest	1 (0.5)	0
Cerebral ischemia	1 (0.5)	0
Stress cardiomyopathy	1 (0.5)	0
SAH	0	1 (0.5)
Deaths during follow-up		
Cardiac arrest	1 (0.5)	0
Subdural hematoma	1 (0.5)	0
Cerebral hemorrhage	0	1 (0.5)
Cerebral vasoconstriction	0	1 (0.5)

Values are expressed as the number of patients (%).

Rescue therapy may have been a relevant confounding factor in the evaluation of the effects of clazosentan. In line with the CONSCIOUS 2 and 3 studies,[27,29] both of which showed that clazosentan as add-on therapy to nimodipine reduced the requirement for rescue therapy, a 42.6% relative risk reduction in rescue therapy administration was observed in the REACT study with clazosentan compared with placebo. This illustrates an antivasospasm effect of clazosentan when added to nimodipine, given that rescue therapy is usually initiated in response to observed vasospasm on imaging and to clinical symptoms of DCI. In REACT, the impact of rescue therapy in the time frame between study drug initiation and day 14 was investigated in a preplanned supportive analysis. When the primary analysis was repeated after including any administration of rescue therapy in the definition of the primary endpoint, the RRR for death or vasospasm-related morbidity with clazosentan compared to placebo increased from 7.2% to

26.7%. Like the primary analysis, the supportive analysis did not reach statistical significance, but it indicates that rescue therapy administered outside of the protocol guidelines may have had an impact on treatment effect.

An association between short-term prevention of vasospasm-related morbidity/mortality with clazosentan and long-term functional outcome has not been consistently observed in the clazosentan development program,[24,27] but positive trends have been reported recently supporting an improvement in clinical outcome evaluated 12 weeks after aSAH with the GOSE and the mRS.[25] In the REACT study the relative risk for poor outcome was increased nonsignificantly by 25.4% with clazosentan compared with placebo. Post hoc analyses indicated that this increased risk could be partly associated with a baseline imbalance in patient geographical location and aneurysm-securing procedure. After adjustment for both variables, the relative risk increase for poor GOSE became 14.0% (95% CI –64.6% to 21.1%), suggesting some impact of study group imbalance on the long-term outcome results.

An important difference between REACT and the two phase 3 Japanese trials is that clazosentan was given in addition to oral or IV nimodipine, whereas use of systemic vasodilators was strictly avoided in the Japanese studies. Surprisingly, the frequency of TEAEs in the REACT active treatment group (pulmonary edema, pleural effusion, and hypotension) was comparable between those studies. In REACT, adverse events were consistent in nature with those observed in previous studies and were even less frequent than in previous studies.[23–25,27,29] No clear association between adverse events specific to clazosentan and long-term outcome could be identified in initial post hoc analyses, but further investigations would be required to fully explore this topic.

Numerous confounding factors in addition to CVS are expected to affect the long-term clinical outcome following aSAH, including the severity of early brain injury, iatrogenic and medical complications, and personal characteristics including frailty and concomitant medical conditions. Moreover, nonvasospasm-related mechanisms, such as microcirculatory dysfunction, microvascular thrombosis, and cortical spreading depolarization have been hypothesized to contribute to DCI. As such, the debate regarding the level of relevance of large-vessel angiographic vasospasm to long-term outcome is still ongoing.[5,30–32] Finally, the choice of the mRS and GOSE tools to assess long-term outcome, although widely used in patients with aSAH,[33] may be criticized given these tools' lack of reliability to discriminate between fully recovered patients and those with cognitive deficits.[34] Improved tools are needed to characterize the long-term functional and psychological outcome of patients who have experienced aSAH.

Conclusions

The REACT study could not demonstrate the efficacy of clazosentan in reducing the occurrence of clinical deterioration due to DCI. Some of the differences with previous studies, notably the primary endpoint and rescue therapy definitions, and methodological differences in the adjudication process may partially explain the lack of demonstrable efficacy on the primary endpoint in REACT. The safety profile of clazosentan was not different from previous studies, but the efficacy results reported in the REACT study were inconclusive.

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Disclosures

Dr. Mayer reported personal fees from Idorsia during the conduct of the study. Dr. Bruder reported personal fees from Idorsia related to study monitoring board during the conduct of the study. Dr. Citerio reported consulting fees from Idorsia during the conduct of the study. Ms. Dubois reported being an employee of Idorsia Pharmaceuticals outside the submitted work. Dr. Gupta reported consulting fees from Idorsia, Inc., and from Medtronic, Inc.; expert witness fees from US Attorney's Office, District of Colorado; grant to his institution from Samsung Healthcare; a speaker honorarium from Siemens Medical Solutions, USA; personal fees for work on the Scientific Advisory Boards of Bayer HealthCare LLC, BrainTale, Inc., and Agfa HealthCare, Inc.; and he also reported grants to his institution from the NIH and from the DoD for his work as a PI during the conduct of the study. Dr. Higashida reported consulting for Idorsia during the conduct of the study. Mrs. Marr reported being an employee and owning shares of Idorsia Pharmaceuticals Ltd. outside the submitted work. Dr. Nguyen reported being on the Advisory Boards of Idorsia and Brainomix; and being an associate editor for *Stroke* outside the submitted work. Dr. Aldrich reported consulting fees ("$400/hr/11 hr") from Idorsia Pharmaceutical during the conduct of the study.

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Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

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