Clazosentan to overcome neurological ischemia and infarction occurring after subarachnoid hemorrhage (CONSCIOUS-1): randomized, double-blind, placebo-controlled phase 2 dose-finding trial.

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.