EG-1962

https://clinicaltrials.gov/ct2/show/NCT02790632

A sustained release microparticle formulation of nimodipine (EG-1962) was developed for treatment of patients with aneurysmal subarachnoid hemorrhage (aSAH).

To assess safety, tolerability, and pharmacokinetics of intracisternal EG-1962 in an open-label, randomized, phase 2 study of up to 12 subjects.

Subjects were World Federation of Neurosurgical Societies grading for subarachnoid hemorrhage grades 1 to 2, Modified Fisher scale grades 2 to 4, and underwent aneurysm clipping within 48 h of aSAH. EG-1962, containing 600 mg nimodipine, was administered into the basal cisterns. Outcome on the extended Glasgow Outcome Scale (eGOS), pharmacokinetics, delayed cerebral ischemia and infarction, rescue therapy, and safety were evaluated.

The study was halted when a phase 3 study of intraventricular EG-1962 stopped because that study was unlikely to meet its primary endpoint. Six subjects were randomized (5 EG-1962 and 1 oral nimodipine). After 90-d follow-up, favorable outcome on the eGOS occurred in 1 of 5 EG-1962 and in the single oral nimodipine patient. Four EG-1962 and the oral nimodipine subject had angiographic vasospasm. One EG-1962 subject had delayed cerebral ischemia, and all subjects with angiographic vasospasm received rescue therapy except 1 EG-1962 patient. One subject treated with EG-1962 developed right internal carotid and middle cerebral artery narrowing 5 mo after placement of EG-1962, leading to occlusion and cerebral infarction. Pharmacokinetics showed similar plasma concentrations of nimodipine in both groups.

Angiographic vasospasm and unfavorable clinical outcome still occurred after placement of EG-1962. Internal carotid artery narrowing and occlusion after placement of EG-1962 in the basal cisterns has not been reported [1)].

In 2018 Edge Therapeutics released an update on its interim analysis of Phase 3 of the NEWTON 2 study of EG-1962 in aneurysmal subarachnoid hemorrhage (aSAH), stating its current data indicates the study (if fully enrolled) has a low probability of achieving a statistically significant difference compared to the standard of care in the study's primary endpoint. Based on the independent Data Monitoring Committee's (DMC) recommendation the study be stopped, Edge Therapeutics decided to terminate the study.

aSAH is the rupture of a brain aneurysm, causing bleeding in the space between the brain and tissue covering the brain.

EG-1962 is a novel polymeric microparticle that contains nimodipine suspended in a diluent of sodium hyaluronate, which is designed to be administered through an external ventricular drain (EVD).1 In relation to aSAH, it attempts to improve patients' outcomes following aSAH. While EG-1962 has not shown efficacy in Phase 3 of its study, it was granted Fast Track designation by the U.S. Food and Drug Administration (FDA) and orphan drug designation by the FDA and European Commission.

Phase 3 of the NEWTON 2 study sought to compare the safety and efficacy of EG-1962 (nimodipine micoparticles) to the standard of care of oral nimodipine in adult patients with aSAH. In the experimental arm, participants were administered a 600 mg intraventricular injection of EG-1962 plus placebo capsules or tablets that were given for up to 21 days. In the active comparator, participants were administered a single dose of intraventricular normal saline and oral nimodipine capsules or tablets for up to 21 days.1

The proportion of patients with a favorable outcome of 6 to 8 on the Extended Glasgow Outcome Scale (GOSE) at the day 90 visit was the primary outcome measure. Health economic endpoints, safety (including delayed cerebral infraction at day 30), and neurocognitives outcomes were secondary outcomes.

Data from the 210 subjects on the day 90 visit indicates the EG-1962 treatments in adults with aSAH had a low probability of achieving a greater standard of care than the current standard.

Brian A. Leuthner, Edge's President and Chief Executive Office, expressed his disappointment with the drug's inefficacy. "We are very disappointed that the NEWTON 2 study did not demonstrate evidence of improved outcomes with EG-1962, given the positive findings demonstrated on this measure in our randomized, open-label Phase 1/2 NEWTON study of EG-1962 in a similar patient population."

While the NEWTON 2 study has proven to be unsuccessful, Edge will analyze the unblinded data from the study for a better understanding of the outcome [2)].

In 2015 Edge Therapeutics Received FDA Orphan Drug Designation for EG-1962 for the Treatment of Patients with Subarachnoid Hemorrhage [3)].

Hänggi et al. described a Phase 1/2a multicenter, controlled, randomized, open-label, dose escalation study to determine the maximum tolerated dose (MTD) and assess the safety and tolerability of EG-1962 in patients with aSAH. The study will comprise two parts: a dose escalation period (Part 1) to determine the MTD of EG-1962 and a treatment period (Part 2) to assess the safety and tolerability of the selected dose of EG-1962. Patients with a ruptured saccular aneurysm treated by neurosurgical clipping or endovascular coiling will be considered for enrollment. Patients will be randomized to receive either EG-1962 (study drug: nimodipine microparticles) or oral nimodipine in the approved dose regimen (active control) within 60 h of aSAH.

Primary objectives were to determine the MTD and the safety and tolerability of the selected dose of intraventricular EG-1962 as compared to enteral nimodipine. The secondary objective was to determine release and distribution by measuring plasma and CSF concentrations of nimodipine. Exploratory objectives are to determine the incidence of delayed cerebral infarction on computed tomography, clinical features of delayed cerebral ischemia, angiographic vasospasm, and incidence of rescue therapy and clinical outcome. Clinical outcome will be determined at 90 days after aSAH using the extended Glasgow outcome scale, modified Rankin scale, Montreal cognitive assessment, telephone interview of cognitive status, and Barthel index [4)].

References

1)

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2) https://www.hcplive.com/view/phase-3-of-the-newton-2-study-of-eg1962-in-asah-is-unlikely-to-meet-primary-endpoint-

3) https://www.businesswire.com/news/home/20150605005277/en/Edge-Therapeutics-Receives-FDA-Orphan-Drug-Designation

4) Hänggi D, Etminan N, Macdonald RL, Steiger HJ, Mayer SA, Aldrich F, Diringer MN, Hoh BL, Mocco J, Strange P, Faleck HJ, Miller M. NEWTON: Nimodipine Microparticles to Enhance Recovery While Reducing Toxicity After Subarachnoid Hemorrhage. Neurocrit Care. 2015 Oct;23(2):274-84. doi: 10.1007/s12028-015-0112-2. PMID: 25678453.