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Publishing Title: Safety Endpoints and Thromboembolic Events for the First 250 Patients Enrolled in the Clot Lysis: Evaluation of Accelerated Resolution of Intraventricular Hemorrhage Trial (CLEAR III)

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Abstract Body:

Objective: The CLEAR III trial is a Phase III, randomized controlled trial comparing external ventricular drainage and either rt-PA or placebo in the management of subjects with small intracerebral hemorrhage (<30 cc) and large intraventricular hemorrhage (IVH) (blood obstruction of the 3rd or 4th ventricles). We report safety endpoints and use of heparin for the first 250 subjects.

Methods: We monitored pre-specified safety endpoint thresholds: symptomatic hemorrhage (i.e., hemorrhage extension, new hemorrhage, catheter tract hemorrhage) within 72 hours of study agent (35%) with daily CT scans; brain infections within 30 days of randomization (15%) with daily CSF cultures days 1-7; and 30-day mortality (30%) using systematic reporting of patient progress through day 30.

Results: Enrollment occurred over 34.63 months at 61 sites. Adjudicated safety events totaled three (1.2%) symptomatic hemorrhages within 72 hours of study agent, five (2.0%) cases of bacterial ventriculitis, 13 (5.2%) non-bacterial ventriculitis and 31 (12.4%) deaths at 30 days. At 30 days, brain hemorrhage had occurred in 48 subjects (19.2%)-- 6 (2.4%) were symptomatic; 42 (16.8%) were asymptomatic. Of the 48, there were 39 catheter tract, five ventricular, two parenchymal, and two subarachnoid hemorrhages. Of 35 intracranial hemorrhages within 72 hours post study agent, 23 (65.7%) occurred in the setting of prophylactic heparin; only one was symptomatic. There were 37 (14.8%) patients with DVT and eight (3.2%) with PE; in 16 patients (43.2%) prophylactic heparin had been started within an average of 231.04 hours of diagnosis. Of 213 patients without DVT, 151 (70.9%) received heparin; 62 (29.1%) did not. Additionally, there were 259 SAEs of which site investigators assessed 19 (7.3%) as possibly related to study agent. There were 13 ischemic strokes. Ventriculoperitoneal shunts were placed in 53 patients (21.2%).

Conclusion: None of the pre-specified safety thresholds have been crossed for the first 250 subjects. All three safety endpoints are lower than expected for patients with severe IVH and indicate that the study protocol is safe. The use of prophylactic heparin during and immediately post dosing may be associated with a higher risk of intracranial bleeding.

Author Disclosure Block:

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