

Brief IMS III Trial Overview

The Interventional Management of Stroke (IMS III) Trial is a randomized, open-label multi-center study that will compare a combined intravenous (IV) and intra-arterial (IA) treatment approach to restoring blood flow to the brain to the current standard FDA approved treatment approach of giving IV rt-PA alteplase, Activase®/ Actilyse® alone. Both approaches must have treatment initiated within three hours of stroke onset. A projected 900 subjects with moderate to severe ischemic stroke will be enrolled at 50+ centers in the United States, Canada, Australia and potentially Europe. This summary reflects the current protocol version Amendment #4 (15-Oct-2009) The Trial Inclusion and Exclusion criteria are below:

Clinical Inclusion Criteria

- Age: 18 through 82 years (i.e., candidates must have had their 18th birthday, but not had their 83rd birthday)
- Initiation of intravenous rt-PA within 3 hours of onset of stroke symptoms. Time of onset is defined as the last time when the subject was witnessed to be at baseline
- An NIHSSS ≥ 10 at the time that intravenous rt-PA is begun or an NIHSSS >7 and <10 with an occlusion seen in M1, ICA or basilar artery on CTA at institutions where baseline CTA imaging is standard of care for acute stroke patients.
- Investigator verification that the subject has received/ is receiving the correct IV rt-PA dose for the estimated weight prior to randomization

Clinical Exclusion Criteria

- History of stroke in the past 3 months
- Previous intra-cranial hemorrhage, neoplasm, subarachnoid hemorrhage, or arteriovenous malformation
- Clinical presentation suggests a subarachnoid hemorrhage, even if initial CT scan is normal
- Hypertension at time of treatment; systolic BP > 185 or diastolic > 110 mm Hg) or aggressive measures to lower BP to below these limits are needed.
- Presumed septic embolus, or suspicion of bacterial endocarditis
- Presumed pericarditis, including pericarditis after acute MI
- Suspicion of aortic dissection
- Recent (within 30 days) surgery or biopsy of parenchymal organ
- Recent (within 30 days) trauma, with internal injuries or ulcerative wounds
- Recent (within 90 days) severe head trauma or head trauma with loss of consciousness
- Any active or recent (within 30 days) hemorrhage
- Pts with known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency or oral anticoagulant therapy require coagulation labs results prior to enrollment. Any subject with INR > 1.7 or institutionally equivalent prothrombin time is excluded. Patients without history or suspicion of coagulopathy do not require INR or prothrombin time lab results to be available prior to enrollment.
- Females of childbearing potential who are known to be pregnant and/or lactating or who have positive pregnancy tests
- Baseline lab values: glucose < 50 mg/dl or > 400 mg/dl, platelets $<100,000$, or Hct <25
- Subject who require hemodialysis or peritoneal dialysis, or who have a contraindication to an angiogram
- Subjects who have received heparin or a direct thrombin inhibitor (Angiomax™, argatroban, Refludan™) within 48 hours must have a normal partial thromboplastin time (PTT) to be eligible
- Subjects with an arterial puncture at a non-compressible site or a lumbar puncture in the previous 7 days
- Subjects with a seizure at onset of stroke
- Subjects with a pre-existing neurological or psychiatric disease that would confound the neurological or functional evaluations, mRS score at baseline must be < 2 . This excludes patients who live in a nursing home or who are not fully independent for activities of daily living (toileting, dressing, eating, cooking and preparing meals, etc.)
- Other serious, advanced, or terminal illness
- Any other condition that the investigator feels would pose a significant hazard to the subject if Activase®/ Actilyse® (Alteplase) therapy is initiated
- Current participation in another research drug treatment protocol
- Written Informed consent is not or cannot be obtained per regional regulatory requirements

CT Scan Exclusion Criteria

- High density lesion consistent with hemorrhage of any degree
- Significant mass effect with midline shift
- Large ($>1/3$ of the middle cerebral artery) regions of clear hypodensity on the baseline CT scan. (ASPECTS of < 4 can be used as a guideline) Sulcal effacement and/or loss of grey-white differentiation are not contraindications to tx
- CT evidence of intraparenchymal tumor

Subjects will be randomized in a 2:1 ratio with more subjects enrolled in the combined IV/IA group. The IV rt-PA alone group will receive the standard approved therapy dose of rt-PA or (0.9 mg/kg, 90 mg max) administered intravenously over an hour. The combined IV/IA group will have a lower dose of rt-PA (0.6 mg/kg, 60 mg max) administered intravenously over a half-hour. These IV/IA subjects will then undergo immediate angiography. If clot is not demonstrated, no more treatment is administered.

If clot is demonstrated, the neuro-interventionalist will then choose from currently available but trial defined intra-arterial treatment approaches; choosing the treatment they feel will be most effective in attempting to reopen the blocked artery. These approaches utilize local regulatory, US FDA and IMS III Executive Committee approved devices for the intra-arterial infusion of investigational rt-PA (maximum 2 mg bolus and 10 mg/hr) using standard microcatheter or the EKOS Micro-Infusion Catheter® (in US) or embolectomy devices including the Concentric Retriever Device® and the Penumbra System™. All devices must be used per the manufacturers instructions for use. Intra-arterial therapy, whether initially with the Merci® Retriever, EKOS Micro-Infusion Catheter, Penumbra System™, future device, or infusion of IA rt-PA via a standard microcatheter, must be started within 5 hours and completed within 7 hours of symptom onset. The maximum dose of IA rt-PA is 22mg. Use of tandem devices (i.e. EKOS Micro-Infusion Catheter, Merci Retriever® or Penumbra System™) in a single case is a protocol violation. Only standard microcatheter therapy may be administered following attempt with a device.

The primary measure of outcome in this trial is a favorable outcome in terms of functional independence as measured by a Modified Rankin Scale score of 0-2 at 3 months. The trial is designed to test whether there is an overall absolute difference of at least 10% in the proportion of a favorable outcomes for subjects treated with the combined IV/IA approach as compared to those treated with the IV rt-PA only approach. The IMS III Trial will also evaluate the effectiveness of the combined IV/IA approach compared to the IV rt-PA therapy alone by a number of secondary outcome measures. These include: 1) the Barthel Index, Glasgow Outcome Scale, NIHSS, EuroQol, and Trailmaking Test at 3 months, 2) an improved early response to treatment as determined by an NIHSS of 0-2 at 24 hours, 3) a CT angiography assessment of intracranial vascular patency at 24 hours (both treatment groups), 4) the volume of cerebral infarction as measured by a CT scan at 24 +/- 6 hours from onset. 5) We will also measure the rate of TICI Grade II or III perfusion flow and recanalization of the primary arterial occlusion at completion of angiography (combined IV/IA group only).

The IMS III Trial will compare the safety of a combined IV/IA approach to IV rt-PA alone. The primary measures of safety will be mortality at 3 months and symptomatic ICH within the first 24 hours after onset. All intracerebral hemorrhages will be classified radiographically using the ECASS criteria. The proportion of subjects with Type II parenchymal intracerebral hematomas within the first 24 hours after onset will be compared between the two treatment groups. The incidence of any asymptomatic hemorrhage within the first 24 hours will also be compared.

Finally, the IMS III Trial will determine the cost effectiveness of the combined IV/IA approach as compared to standard IV rt-PA as measured by differences in utilization of resources and quality of life over 12 months between the two arms of the trial. Collected resource data include hospitalizations, procedures, length of stay, diagnostic procedures, rehabilitation, outpatient visits, and personal patient costs. Quality of life will be measured by the EuroQol EQ-5D.

In summary the IMS III Trial will develop and maintain a network of interventional centers to test the efficacy and safety of a combined IV/IA approach to opening blocked vessel and restoring blood flow to the brain.