Brief Overview of CLEAR, CLEAR-ER, CLEAR-FDR trials for acute ischemic stroke

CLEAR	The Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke
CLEAR-ER	The Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke - **E**nhanced **R**egimen
CLEAR-FDR	The Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke **F**ull **D**ose **R**egimen
sICH	symptomatic intracerebral hemorrhage
NCT#	clinicaltrials.gov identifier #

Intravenous (IV) recombinant tissue plasminogen activator (rt-PA) remains the only U.S. Food and Drug Administration (FDA)-approved and proven therapy for acute ischemic stroke. However, 50% of patients treated with rt-PA have physical disability at three months, and IV rt-PA alone opens only approximately 30-40% of occluded large arteries. The addition of glycoprotein IIb/IIIa antagonists to fibrinolytic regimens increases both the speed of arterial recanalization and the percentage of patients with open arteries in acute myocardial infarction.

As demonstrated in the AbESTT trial, full platelet inhibition at cardiac doses for 24 hours or longer may be unsafe in the setting of stroke. Our goal was to use the lowest possible combination of doses of rt-PA plus eptifibatide with the highest lytic efficacy and a shorter duration that is likely to affect early reperfusion but limit potential hemorrhagic complications over the first 24 hours.

Based on this rationale, we have completed 2 trials that have showed the combination of reduced dose IV rt-PA plus eptifibatide, a glycoprotein IIb/IIIa antagonist, was safe when administered within 3 hours of symptom onset in acute ischemic stroke.

CLEAR Trial (2003-2007) 94 patients (69 receiving combination drug therapy, 25 receiving standard treatment IV rt-PA)
NCT# 00250991

- Tier 1: 0.3mg/kg of IV rt-PA
- Tier 2 :0.45mg/kg of IV rt-PA
- In each tier, the IV eptifibatide dose was a 75mcg/kg bolus followed by a two hour infusion of 0.75mcg/kg/min.
- sICH occurred in 1 (1.4%) of the 69 patients in the combination treatment group

CLEAR-ER (2008-2012) 126 patients (101 receiving combination drug therapy, 25 receiving standard treatment IV rt-PA) NCT# 00894803

- 0.6mg/kg of IV rt-PA
- IV Eptifibatide dose of 135mcg/kg bolus followed by a two hour infusion at 0.75mcg/kg/min
- sICH occurred in two (2%) of 101 patients in the combination treatment group

CLEAR-FDR (2013-2015) single arm open label safety study (30 patients)

- 0.9mg/kg of IV rt-PA
- IV Eptifibatide dose of 135mcg/kg bolus followed by a two hour infusion at 0.75mcg/kg/min

Since 0.9mg/kg of rt-PA in the 3 hour window is a Class I recommendation by the American Stroke Association (ASA) and is the standard of care, determining whether combining eptifibatide with this standard full dose rt-PA regimen is safe would be clinically relevant, especially in the context of a planned Phase 3 trial where the 0.6mg/kg dosing regimen would present logistical challenges.