Progressive edema and tissue swelling after large anterior circulation stroke are the leading cause of death in malignant infarction. \textsuperscript{1-3} The formation of rapidly accumulating cerebral edema after infarction compromises arterial inflow to surrounding tissue, culminating in further ischemic damage, enlargement of the infarct, herniation, and death. Despite the great morbidity and mortality that are a direct consequence of brain swelling, novel approaches to the prevention of cerebral edema have not been previously explored and are lacking. The prognosis for these patients is poor, with case fatality rates as high as 60% to 80\%. \textsuperscript{4,5} A significant barrier to progress in managing patients with a large stroke is identifying safe and effective pharmacotherapy to minimize the brain swelling that produces such devastating consequences.

Recent preclinical experiments have identified ischemia-induced transcriptional upregulation of SUR1-regulated NC\textsubscript{Ca-ATP} channels in capillary endothelial cells, neurons, astrocytes, and oligodendrocytes, which are implicated in the formation of brain swelling. \textsuperscript{6} When microvascular endothelial cells are affected, the consequence is space-occupying edema and hemorrhagic transformation. \textsuperscript{7} Blocking the channel by constant infusion of low-dose glyburide results in robust benefit in several clinically relevant animal models of stroke, including thromboemboli, permanent occlusion, and transient occlusion times up to 6 hours followed by recanalization/reperfusion, and cotreatment with recombinant tissue-type plasminogen activator.

We initiated an open-label, prospective, phase IIa study to assess the feasibility of enrolling, evaluating, and treating with RP-1127 (bolus followed by 72-hour infusion) patients with severe ischemic stroke at high risk for experiencing clinically significant brain swelling.

From a physiological and clinical perspective, preventing swelling is preferable to decompressing the already swollen brain. This study examined a potential treatment strategy for preventing cerebral edema in patients with large stroke at high risk for malignant infarction so as prevent the need for surgical decompression. Further research regarding the mechanism, detection and surveillance, and treatment of brain swelling should be an urgent priority.

Disclosures
Glyburide Advantage in Malignant Edema and Stroke (GAMES) Pilot was funded by Remedy Pharmaceuticals, Inc. Dr Sheth received the American Heart Association Robert Siekert Award for this work and as the principal investigator is responsible for all aspects of the study.

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Novel Approaches to the Primary Prevention of Edema After Ischemia
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