A randomized, multi-center, prospective, double blind, Phase II trial of RP-1127 (Glyburide for Injection) in patients with a severe anterior circulation ischemic stroke who are likely to develop malignant edema.

**IND Holder:**
Remedy Pharmaceuticals, Inc.
IND 77,447

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26 May 2015
Protocol Signature Page

Principal Investigator
I agree to conduct the trial in compliance with this protocol and to adhere to all regulations that govern the conduct of the study.

Signature ___________________________ Date ____________
Name ________________________________
Institution ____________________________

Medical Monitor

Signature ___________________________ Date 26 May 2015
Eugene D. Means, M.D.

Sponsor
Protocol Approval and Authorization for Distribution

Signature ___________________________ Date 26 May 2015
Sven M. Jacobson, CEO
## STUDY ADMINISTRATION

| Lead Investigators: | Kevin N. Sheth, MD, FAHA  
Chief, Division of Neurocritical Care and Emergency Neurology  
Chief, Clinical Research, Department of Neurology, Yale School of Medicine  
Director, Neurosciences Intensive Care Unit, Yale New Haven Hospital  
Department of Neurology LCI 710  
15 York Street, PO Box 208018  
New Haven, CT 06520-8018  
Phone: 203-785-5947  
Fax: 203-737-4419  
Mobile: 443-615-4729  
Email: kevin.sheth@yale.edu |
|----------------------|--------------------------------------------------------------------------------|
|                      | W. Taylor Kimberly, M.D., Ph.D.  
Associate Director, Neuroscience Intensive Care Unit  
Massachusetts General Hospital  
Lunder 644  
55 Fruit St  
Boston, MA 02114  
Phone: 857-238-5644  
Fax: 857-238-5601  
Mobile: 617-429-4841  
Email: wtkimberly@mgh.harvard.edu |
| Sponsor’s Administrative Contact | Sven M. Jacobson  
Chief Executive Officer  
Remedy Pharmaceuticals, Inc.  
122 West 27th Street, 10th Floor  
New York, NY 10001  
Phone: 212 586 2226 x 225  
Fax: 212 586 2246  
Mobile: 646 258 3493  
Email: sven@remedypharmaceuticals.com |
| Sponsor’s Medical Contact / Medical Monitor | Eugene D. Means, M.D., F.A.A.N  
Remedy Pharmaceuticals, Inc.  
122 West 27th Street, 10th Floor  
New York, NY 10001  
Fax: 212 586 2246  
Mobile: (212) 620-3068  
Email: gene@remedypharmaceuticals.com |
| GAMES-RP 24/7 Hotline | 800 292 8141 |
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1 SYNOPSIS

Study Title
Glyburide Advantage in Malignant Edema and Stroke – Remedy Pharmaceuticals (GAMES-RP)

Design
This is a randomized, multi-center, prospective, double blind, Phase II trial of RP-1127 in patients with a severe anterior circulation ischemic stroke who are likely to develop malignant edema.

The study population consists of subjects with a clinical diagnosis of acute severe anterior circulation ischemic stroke, a baseline diffusion weighted image (DWI) lesion between 82 and 300 cm³, age 18-80 years, and time from symptom onset to start of study infusion of ≤10 hours. The study will enroll both patients that do not receive IV rtPA and those that receive IV rtPA within 4.5 hours of stroke, according to standard of care.

The study will enroll and treat 83 subjects.

Enrollment will be randomized controlling for site, age ≤60 (yes/no), and IV rtPA treatment at baseline (yes/no). Subjects will be randomized equally between RP-1127 and placebo.

Primary Objectives
Primary efficacy objective:
To assess the efficacy of RP-1127 (Glyburide for Injection) compared to placebo in subjects with a severe anterior circulation ischemic stroke who are likely to develop malignant edema. This objective will be addressed by comparing the proportion of RP-1127 treated patients and placebo treated patients with a Day 90 modified Rankin Scale (mRS) ≤ 4 without decompressive craniectomy (DC).

Primary safety objective:
To assess the safety of RP-1127 (Glyburide for Injection) compared to placebo in subjects with a severe anterior circulation ischemic stroke who are likely to develop malignant edema. This objective will be addressed by the statistical testing of frequency and severity of Adverse Events and Serious Adverse Events, with a specific focus on all cause mortality, cardiac mortality, and cardiac-related and blood glucose-related AE’s/SAE’s.

Secondary Objectives
To explore the efficacy of RP-1127 (Glyburide for Injection) compared to placebo in subjects with a severe anterior circulation ischemic stroke who are likely to develop malignant edema, as measured by:
• The proportion of subjects either undergoing DC or dead by Day 14
• The change between baseline and 72-96 hours in ipsilateral hemispheric swelling measured by MRI
• The change between baseline and 72-96 hours in lesional swelling measured by MRI
Additional exploratory outcome measures will be detailed in the Statistical Analysis Plan.

Sample Size Considerations:
The study will have a two-sided type I error rate at 0.05 and will have 80% power to detect a difference between the proportions of subjects with a modified Rankin Scale (mRS) ≤ 4 at 90 days without DC when the true placebo response rate is 30% and the true RP-1127 response rate is 60% (a 30 percentage point effect size).

Interventions and Duration
Subjects will be randomized to either RP-1127 or placebo, delivered as an IV bolus (0.13 mg over approximately 2 minutes) followed by an IV infusion for 72 hours (0.16 mg/hr for 6 hours, followed by 0.11 mg/hr for 66 hours).

Subjects will have a baseline (pretreatment) MRI scan, and one follow up MRI scan at 72-96 hours (as close to 72 hours as possible). A standard of care CTA, MRA or catheter angiography of the head and neck will be performed at baseline. Additionally, an MRA (head only) will be performed at the follow up MRI scan. The NIHSS will be collected at baseline, 24±12 hour, 48±12 hour, 72±12 hour and 7±1 days (or discharge, whichever is earlier). The mRS and Barthel Index will be assessed at Day 30±7, Day 90±14 and at 6 and 12 months ± 30 days. Beck Depression Inventory (BDI-II) and EuroQoL 5-D will be assessed at Day 90±14 and at 6 and 12 months ± 30 days. Safety labs will be assessed through Day 7 or discharge (whichever is earlier), and SAE’s will be assessed at Day 30±7, Day 90±14 and at 6 and 12 months ± 30 days.

Study participation is expected to last 12 months ± 30 days.
2 INTRODUCTION

2.1 Malignant Edema Background

Ischemic stroke afflicts 700,000 people in the United States annually (Sacco et al. 2006), and results in 412,000 hospitalizations per year (Russo et al. 2008). Life threatening edema ("malignant edema" or "malignant MCA infarction") complicates up to 10% of hospitalized stroke victims, and in anterior circulation strokes occurs exclusively in large strokes (Hacke et al. 1996). Such swelling can compromise arterial inflow to surrounding tissues causing further ischemic damage and enlargement of the infarct, and frequently results in brain herniation and death. Clinical characteristics comprise secondary deterioration of neurological symptoms, particularly a disturbance of consciousness and further clinical signs of brain stem herniation. The prognosis for these patients is frequently poor, with case fatality as high as 60–80% (Hacke et al. 1996, Berrouschot et al. 1998).

Decompressive craniectomy (DC) has improved the bleak outlook for these patients, and reduced mortality to 22% in a pooled analysis of DC studies (Vahedi et al. 2007). However, numerous factors limit the usefulness of DC, including limited eligibility for surgery among patients who are gravely ill and have important co-morbidities, and reduced efficacy of DC in patients >60 years of age (Arac et al. 2009). Moreover, from a physiologic standpoint, preventing swelling is preferable to decompressing the already swollen brain. There is a clear and urgent need for innovative non-surgical medical strategies to reduce edema formation in patients with a large stroke.

Various overlapping definitions of malignant edema have been used for inclusion in randomized DC studies, specifically:

- NIHSS ≥16, including a score ≥1 for item 1a (level of consciousness); CT ischemic signs involving > 50% of the MCA territory; and a diffusion-weighted imaging (DWI) infarct volume >145 cm³ (Vahedi et al. 2009).
- Clinical signs of infarction of the MCA territory with an NIHSS >18 for lesions of the nondominant hemisphere and >20 for lesions of the dominant hemisphere; Decrease in the level of consciousness to a score of ≥1 on item 1a of the NIHSS; and CT–documented unilateral MCA infarction, including at least 2/3 of the territory and including at least part of the basal ganglia, with or without additional ipsilateral infarction of the anterior or posterior cerebral artery (Juttler et al. 2007).

The definition used in this current study, that of Thomalla et al. (2010), is based on the definitions used in the randomized DC studies described above: Clinical signs of large MCA territory infarction with an NIHSS score >18 and a level of consciousness of ≥1 on item 1a of the NIHSS either on admission or after secondary deterioration; 2) large space-occupying MCA infarction on follow-up MRI or CT of at least 2/3 of the MCA territory with compression of ventricles or midline shift; and no other obvious cause for neurological deterioration.

There are currently no therapeutic approaches targeted at preventing the development of malignant edema early after the index stroke event. The ability to prevent the development of malignant edema would be a life saving intervention that would meaningfully reduce morbidity.
2.2 **Rationale for Glyburide in Preventing Malignant Edema**

Glyburide (5-chloro-N-(4-[N-(cyclohexylcarbamoyl) sulfamoyl]phenethyl)-2-methoxybenzamide) is an anti-diabetic medication in a class of medications known as sulfonylureas. Oral glyburide has been used successfully in the treatment of non-insulin-dependent diabetes mellitus (NIDDM) for more than 20 years. In treating NIDDM, the drug works by inhibiting ATP-sensitive potassium channels in pancreatic beta cells by antagonism of SUR1. This inhibition causes cell membrane depolarization, which causes voltage-dependent calcium channels to open, which in turn causes an increase in intracellular calcium in the beta cell, stimulating insulin release.

The NC\textsubscript{Ca-ATP} channel is a nonselective cation channel that is expressed in the central nervous system under conditions of ischemia, hypoxia, and trauma (Chen and Simard 2001; Chen et al. 2003; Simard et al. 2006). Channel opening, which is triggered by depletion of adenosine triphosphate (ATP), results in cytotoxic edema, onotic cell death and vasogenic edema (Simard et al. 2007). If the cell involved in the above pathophysiological sequence is a microvascular endothelial cell, these mechanisms result in formation of space-occupying edema (Simard et al. 2006; Simard et al. 2007) and secondary hemorrhage (Simard et al. 2007). Brain edema formation through this mechanism is a serious complication and can lead to mechanical compression of adjacent brain structures, herniation, and death. Additionally, it can impair regional cerebral blood flow, resulting in further ischemia.

Like the KATP channel in pancreatic beta cells, the NC\textsubscript{Ca-ATP} channel is regulated by sulfonylurea receptor 1 (SUR1) and is blocked by sulfonylureas such as glyburide. Glyburide thus specifically targets a mechanism involved in development of edema, reducing the formation of edema and secondary damage resulting from edema in multiple models of malignant infarction with treatment delays of up to 10 hours following stroke (Table 1).

<table>
<thead>
<tr>
<th>MODEL (Tx Delay)</th>
<th>EFFECTS of GLYBURIDE (all effects listed were statistically significant: 0.001 ≤ P &lt; 0.05)</th>
<th>SLP\textsuperscript{A}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simard et al. 2006 Malignant Edema (none)</td>
<td>reduced mortality from 65 to 24% at 7 d reduced excess brain water by 42% at 8 h</td>
<td>Yes\textsuperscript{A}</td>
</tr>
<tr>
<td>Simard et al. 2010 Malignant Edema (6 h)</td>
<td>reduced mortality from 67 to 5% at 24 h reduced hemispheric swelling from 21 to 8% at 24 h better preservation of watershed cortex and white matter, better neuroscores, Garcia scores, and the trajectory of weight gain compared to DC during 2 weeks post-insult</td>
<td>Yes\textsuperscript{B}</td>
</tr>
<tr>
<td>Simard et al. 2012a Malignant Edema + rtPA (4.5 &amp; 10 h)</td>
<td>reduced mortality from 53 to 17 or 12% at 48 h (Veh vs. Tx@4.5 or 10 h) reduced swelling from 14.7 to 8.1 or 8.8% at 24 h (same groups) improved Garcia scores from 3.8 to 7.6 or 8.4 at 48 h (same groups)</td>
<td>Yes\textsuperscript{A}</td>
</tr>
<tr>
<td>Simard et al. 2012b Malignant Edema + rtPA (6 h)</td>
<td>reduced hemispheric swelling from 26 to 12% at 24 h reduced hemorrhagic transformation scores from 2.4 to 0.6 at 24 h improved neuroscores from 7 to 3 at 2 weeks</td>
<td>Yes\textsuperscript{A}</td>
</tr>
</tbody>
</table>

\textsuperscript{1}SLP (STAIR laboratory practice), including monitoring LDF and blood gases, temperature control, random treatment allocation, and blinded outcome assessment, were: performed but not documented (Yes\textsuperscript{A}); or performed and documented (Yes\textsuperscript{B}).
Since the primary target for preventing edema formation is NCa-ATP channels expressed on the capillary endothelium, while glyburide has been shown to cross the blood brain barrier (Simard et al. 2006), this is not necessary for the agent’s anti-edema effect.

2.3 **RP-1127 in Stroke Patients at Risk for Malignant Edema (GAMES-Pilot Study)**

The GAMES-Pilot study (ClinicalTrials.gov Identifier: NCT01268683) was a 10-patient open label pilot study with inclusion/exclusion criteria, drug dosing, and assessments similar to those in this current protocol. Subjects were enrolled at two sites, the University of Maryland and Massachusetts General Hospital.

The primary objective was to assess the safety and feasibility of enrolling, evaluating, and treating with RP-1127 severe anterior circulation ischemic stroke patients, whether or not treated with IV rtPA.

The study enrolled patients with a baseline MRI DWI lesion between 82 - 210 cm³, age 18-80 years, and time from symptom onset to drug infusion of ≤ 10 hours. Patients who received intra-arterial reperfusion therapy, prophylactic DC, or were on sulfonylurea treatment at presentation were excluded. Upon enrollment, patients received a bolus and continuous infusion of RP-1127 for 72 hours, for a total dose of 8.33 mg glyburide. Baseline, on-treatment, and post-treatment clinical, imaging, and safety assessments were performed through Day 90.

rtPA was administered as standard of care to 9/10 patients. Of the 10 patients enrolled, 1 patient died, even after DC. One additional patient also required DC. The incidence of malignant edema was 20%, compared to 88% in a prospective observational study of patients with DWI ≥82 cm³ (Thomalla et al. 2010). Further, 8/10 patients did not require osmotherapy, intubation, or DC. There were no parenchymal hemorrhages seen with imaging, in contrast to parenchymal hematoma rates of ~30% in DEFUSE and EPITHET in patients with a malignant profile (Mlynash et al. 2011). There was no suggestion of delayed or “rebound” edema after the 72 hours of dosing.

The proportion of GAMES-Pilot patients with 30 day mRS ≤ 4 was 90% compared to 23.8% (at 12 months) in control patients from a pooled analysis of DC trials (Vahedi et al. 2007), 28.5% at 90 days (Sanak et al. 2006) for patients with DWI > 70 cm³, and 19% at 90 days in DEFUSE 2 patients with the malignant profile (Mlynash et al. 2012).

The number of patients enrolled in GAMES-Pilot was small and the study was open label, therefore necessitating cautious interpretation. However, the study’s findings in these large strokes suggest that RP-1127 may have a role in ameliorating swelling and the development of parenchymal hematoma, and improving clinical outcomes.
2.4 **RP-1127 Safety Profile**

Oral glyburide has been extensively used in the treatment of NIDDM for more than 20 years. Like all sulfonylureas, glyburide is capable of producing severe hypoglycemia, especially in patients with renal or hepatic impairment. Elderly, debilitated or malnourished patients, and those with adrenal or pituitary insufficiency, are particularly susceptible to the hypoglycemic action of glucose-lowering drugs. This hypoglycemic action can be enhanced by certain drugs including nonsteroidal anti-inflammatory agents and other drugs that are highly protein bound, salicylates, sulfonamides, chloramphenicol, probenecid, coumarins, monoamine oxidase inhibitors, and beta adrenergic blocking agents.

Oral glyburide, as with all sulfonylureas, carries a warning label of increased risk of cardiovascular mortality based on a study published in 1970 and conducted by the University Group Diabetes Program (UGDP) (Meinert et al. 1970). UGDP reported that patients treated for 5 to 8 years with diet plus a fixed dose of tolbutamide, a first generation sulfonylurea, had a rate of cardiovascular mortality approximately 2½ times that of patients treated with diet alone. However, glyburide was found not to increase cardiovascular mortality in a more recent study by the UK Prospective Diabetes Study Group (UKPDS 1998).

Treatment of patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency with sulfonylurea agents can lead to hemolytic anemia. In post marketing reports, hemolytic anemia has also been reported in patients who did not have known G6PD deficiency.

Sulfonylurea agents, including oral glyburide, have been reported to be safe prior to, and following stroke (Weih et al. 2001; Kunte et al. 2007; Silver et al. 2009; Favilla et al. 2011; Kunte et al. 2012). These studies have also reported a positive effect of sulfonylurea agents on stroke outcomes in patients taking sulfonylurea drugs prior to stroke and in the first 3 days (or more) following stroke.

Remedy has conducted a study of RP-1127 entitled “A Phase I Randomized, Double-blind, Placebo-controlled Study to Assess the Safety, Tolerability, and Pharmacokinetics of Escalating Doses of RP-1127 in Normal Male and Female Volunteers” (Study 101). The objectives of the study were to evaluate the safety and tolerability of different dose levels of RP-1127, administered as a bolus dose followed by a 3-day continuous infusion maintenance dose, and to assess the pharmacokinetics and pharmacodynamics of RP-1127.

Patients were dosed as indicated in Table 2:
<table>
<thead>
<tr>
<th>Dose</th>
<th>Number of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RP-1127</td>
</tr>
<tr>
<td>0.02 mg bolus + 0.40 mg/day</td>
<td>8</td>
</tr>
<tr>
<td>0.13 mg bolus + 3.00 mg/day</td>
<td>16</td>
</tr>
<tr>
<td>0.26 mg bolus + 6.00 mg/day</td>
<td>1</td>
</tr>
<tr>
<td>0.43 mg bolus + 10.00 mg/day</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>26</td>
</tr>
</tbody>
</table>

During the RP-1127 infusion, median blood glucose levels in the 3.00 mg/day dose group were generally lower than those in the placebo group. The incidence of blood glucose levels above 80 mg/dL was higher in the placebo group than in the 3.00 mg/day group while there was no difference in incidence of blood glucose levels below 70 mg/dL, implying a reduction in blood glucose at the 3.00 mg/day dose without hypoglycemia.

There were no serious adverse events during the study. Two patients (one each at 6.00 mg/day and 10.00 mg/day) discontinued the study because of persistent hypoglycemia, and one of these (at 6.00 mg/day) also experienced transient increases in ALT and AST beginning 3 days after study discontinuation. This patient was asymptomatic at all times. After peaking on Day 6, her liver enzyme levels decreased and were normal by Day 22. Liver function abnormalities, including elevations in liver enzymes, have been reported in patients taking oral glyburide, as described in package inserts for approved oral glyburide drug products. There were no other clinically significant adverse events.

2.5 Rationale for GAMES-RP Study

At present, no specific pharmacotherapy is available to prevent brain swelling secondary to stroke and no specific drug therapy has been rigorously investigated for patients with malignant edema or with a high risk of developing malignant edema.

The GAMES-RP Study is designed to enroll patients with a high probability of developing significant edema. MRI studies of large MCA infarcts have identified a DWI volume of 82 cm$^3$ as the optimum cutoff point for increased risk of significant swelling with a positive predictive values of 82% - 88% (Thomalla et al. 2003, Thomalla et al. 2010).

To facilitate enrollment the study recruits both patients that do not receive IV rtPA and those that receive IV rtPA up to 4.5 hours following stroke. The rationale for including patients with rtPA treatment up to 4.5 hr after time last known at baseline neurologic status (TLK@B) is as follows: The 3 hr window for IV rtPA is FDA approved. The 3–4.5 hr window, although not FDA approved, results in an increased rate of favorable outcome without adversely affecting mortality (Lansberg et al. 2009, del Zoppo et al. 2009).
The rationale for including subjects up to 10 hours following stroke is as follows: the preclinical data show that the treatment window for glyburide extends to 10 hours. In rats, herniation from malignant edema peaks at 12–24 hr, whereas in humans, herniation peaks at 2-3 days (Silver et al. 1984, Qureshi et al. 2003). In humans, midline shift is usually absent at 8 hours and becomes measurable only at 16 hours (Gerriets et al. 2001). Differences between species likely reflect differences in the sizes of the brain and skull – in humans, it takes longer to accumulate enough edema to cause herniation. Therefore, since glyburide is being used to arrest edema formation, it is thought that a 10 hour window is reasonable. The treatment period of 72 hours was selected because in humans with severe strokes, herniation peaks at 2-3 days.

2.6 Selection of Primary Efficacy Outcome Measure

2.6.1 mRS and Malignant Edema

In patients with malignant edema, a mRS of 0-4 is now widely defined in studies as a “good” or “favorable” outcome (Vahedi et al. 2007; Mlynash et al. 2011; Hofmeijer et al. 2009; Juttler et al. 2011; Mlynash et al. 2012). While a mRS of 4 is defined as “moderately severe disability” i.e. unable to attend to own bodily needs without assistance, and unable to walk unassisted, a systematic review of the currently available literature by Rahme et al (2012) suggests that, despite a high proportion of patients left with mRS 4 (46.8%) following DC, and a high rate of depression (56.1%), the vast majority of patients and/or caregivers (76.6%) are satisfied with life and had no regret for having undergone DC, supporting the notion that a mRS of 4 is a “good” or “favorable” outcome in these patients. Quinn et al. 2009 report that the mRS has the highest reliability (other than mRS 0 and 6) at mRS 4 and 5, which makes the distinction of mRS 0-4 robust. Janssen et al. 2010 report that telephone assessment of the mRS can be used reliably in the setting of a clinical trial.

In the absence of DC, it is expected that RP-1127 will increase the proportion of patients with “good” or “favorable” outcomes. Additionally RP-1127 is expected to reduce the incidence of DC by reducing edema formation and tissue displacement. DC has been shown to increase the incidence of mRS 0-4 in patients with malignant edema, but not the proportion of patients with mRS 0-3 (Vahedi et al. 2007). The prevalence of DC per 10,000 hospitalizations for ischemic stroke is low but has risen from 3.86 in 1999 to 14.46 in 2008 (Walcott et al. 2011). Thomalla et al. 2010 found that 55.6% of patients developing malignant edema underwent DC. For this reason, DC is a potential confounding factor in interpreting the effect of RP-1127 on the proportion of subjects with mRS 0-4. It is possible that a subject in the placebo arm of GAMES-RP may require DC, and be left with a mRS of 4 following DC. A similar patient in the RP-1127 group may have a mRS of 4, but not require DC due to the anti-edema effect of RP-1127. It should be noted that DC is a highly invasive procedure with adverse consequences including “sinking skin flap” syndrome and “paradoxical herniation” (Sarov et al. 2010), serious cardiac adverse events (Durga et al. 2011), and post-operative hydrocephalus (Waziri et al. 2007).

Thus, in the Study, a “responder” is defined as a subject that has a “good” or “favorable” outcome and does not require DC to attain such an outcome. As a result, a composite outcome measure of mRS 0-4 without DC was selected for the Study.
2.6.2 Potential Placebo Rates and Effect Size for mRS 0-4 without DC

Remedy has analyzed outcomes in subjects with baseline DWI > 82 cm³ from the EPITHET study (Davis et al. 2008) and from the MMI-MRI study (Thomalla et al. 2010). In both cases, the proportion of subjects that attained a mRS 0-4 without DC was 26.7% (4/15 for each dataset). In a pooled analysis of three DC studies (Vahedi et al. 2007), the proportion that attained a mRS 0-4 without DC in the control arm (there were by design no DC’s in the control) was 24%. In an unpublished analysis of the STOPStroke study, 38% (11/29) had mRS 0-4 without DC. In the GAMES-Pilot study, 80% (8/10) of subjects treated with RP-1127 attained a mRS 0-4 without DC. While there is practice variation surrounding the decision to go to DC, the Study Clinical Guidelines will assist in reducing this, and the assumed effect size of 30% appears to be appropriate.
3 STUDY OBJECTIVES

3.1 Primary Objectives

3.1.1 Primary efficacy objective
To assess the efficacy of RP-1127 (Glyburide for Injection) compared to placebo in subjects with a severe anterior circulation ischemic stroke who are likely to develop malignant edema.

This objective will be addressed by comparing the proportion of patients with a modified Rankin Scale (mRS) at Day 90 ≤ 4 without decompressive craniectomy (DC) in the RP-1127 and placebo groups.

3.1.2 Primary safety objective
To assess the safety of RP-1127 (Glyburide for Injection) compared to placebo in subjects with a severe anterior circulation ischemic stroke who are likely to develop malignant edema.

This objective will be addressed by comparing the frequency and severity of Adverse Events and Serious Adverse Events in the RP-1127 and placebo groups, with a specific focus on all cause mortality, cardiac mortality, and cardiac-related and blood glucose (BG)-related AE’s/SAE’s.

Specific outcome variables related to assessing BG-related safety of RP-1127 are:
- Hypoglycemia i.e. blood glucose (BG) < 55 mg/dL
- Symptomatic hypoglycemia i.e. Hypoglycemia with investigator-identified hypoglycemic symptoms.

Specific outcome variables related to assessing cardiac-related safety of RP-1127 are:
- Incidence of cardiac SAEs, cardiac mortality, and incidence / severity of cardiac AEs
- Incidence of QTc of > 500 ms
- Mean Heart Rate, mean QTc, and mean change in QTc from baseline.

3.2 Secondary Objectives
To explore the efficacy of RP-1127 (Glyburide for Injection) compared to placebo in subjects with a severe anterior circulation ischemic stroke who are likely to develop malignant edema, as measured by:
- The proportion of subjects either undergoing DC or dead by Day 14.
- The change between baseline and 72-96 hours in ipsilateral hemispheric swelling measured by MRI
- The change between baseline and 72-96 hours in lesional swelling measured by MRI

Additional exploratory outcome measures will be detailed in the Statistical Analysis Plan.
4 STUDY DESIGN

This is a randomized, multi-center, prospective, double blind, Phase II trial of RP-1127 in patients with a severe anterior circulation ischemic stroke who are likely to develop malignant edema.

The study population consists of subjects with a clinical diagnosis of acute severe anterior circulation ischemic stroke, a baseline diffusion weighted image (DWI) lesion between 82 and 300 cm³, age 18-80 years, and time from symptom onset to start of study infusion of ≤10 hours. Patients may receive IV rtPA in 0-4.5 hours from the onset of stroke as standard of care.

Eighty three (83) subjects will be randomized, treated and followed for 12 months at up to 20 sites.

Subjects will be randomized equally between RP-1127 and placebo controlling for site, age ≤60 (yes/no), and IV rtPA treatment at baseline (yes/no).

The dosing regimen is a bolus of 0.13 mg of Study Drug administered over approximately 2 minutes followed by a continuous infusion of 0.16 mg/hr for 6 hours and then 0.11 mg/hr for 66 hours, for a total dosing period of 72 hours. The total daily dose of Study Drug on Day 1, Day 2 and Day 3 will be 3.12 mg, 2.67 mg, and 2.67 mg respectively.

The imaging outcome measurements will be completed within 96 hours while the subjects are still in the hospital. Long-term (up to 12 months) clinical outcome measures and SAEs will be assessed. The primary analyses will be conducted after all patients have completed their Day 90 assessments. However, patients will continue to be followed through 12 months.

The following flowchart (Figure 1) provides an overview of the study procedures:
Figure 1. Overview of Study Procedures

Within 10 h of Time Last Known @ Baseline Neurological Status
rtPA (0-4.5 h) allowed as standard of care
Screening: NIHSS, MRI, Vascular Imaging, Safety Labs, ECG
Enrollment / Randomization

T=0 h
RP-1127
Placebo

@ 4-6 h
ECG PK (as close as possible to ECG)

@ 24 h
NIHSS and Safety Labs (±12h)
ECG (±6h), PK (close to ECG)

@ 48 h
NIHSS and Safety Labs (±12h)
ECG (±6h), PK (close to ECG)

@ 72 h
NIHSS and Safety Labs (±12h)
ECG (60-72h), PK (close to ECG)

@ 72-96 h
MRI and MRA (close to 72 h)
Safety Labs (96±12h)

@ 7±1 days or discharge
NIHSS, ECG, Safety Labs

@30±7 days
mRS, BI, SAEs

@90±14 days
mRS, BI, SAEs, BDI-II, EQ-5D

@6 and 12 month±30 days
mRS, BI, SAEs, BDI-II, EQ-5D

Study Drug Bolus at T=0 followed by 31 mL/hr infusion until 6 h
Continuous ECG Monitoring
BG Monitoring q2h (±30m) H25-48, q4h (±60m) H49-88

Study Drug infusion at 21 mL/hr from 6 h to 72 h
5 SELECTION AND ENROLLMENT OF SUBJECTS

5.1 Inclusion Criteria
1) A clinical diagnosis of acute ischemic stroke in the MCA territory (PCA and/or ACA territory involvement in addition to primary MCA territory stroke is acceptable).
2) Prior to stroke, no significant disability (able to carry out all usual duties and activities).
3) A baseline DWI lesion between 82 and 300 cm³ on MRI.
4) Patients treated with IV rtPA should meet established criteria for IV rtPA administration in the 0–3 and 3–4.5 hr time periods at the time of rtPA administration (if rtPA is administered in the 3-4.5 hr time window, the NIHSS must be ≤ 25 at the time of rtPA administration).
5) The time to the start of infusion of Study Drug must be ≤ 10 hours after time of symptom onset, if known, or the time last seen well [termed “time last known at neurologic baseline” (TLK@B)].
6) Age ≥ 18 years and ≤ 80 years.
7) Provision of written informed consent by patient or a legally authorized representative.

5.2 Exclusion Criteria
1) Commitment to decompressive craniectomy (DC) prior to enrollment, or following enrollment and prior to start of Study Drug.
2) Treatment with intra-arterial (IA) rtPA or by mechanical means for clot disruption.
3) Patients unable to tolerate MRI scanning, e.g. those with pacemakers or automatic defibrillators.
4) Evidence (clinical or imaging) of concurrent infarction in the contralateral hemisphere deemed by the investigator to be sufficiently serious so as to affect functional outcome.
5) Clinical signs of herniation, e.g. one or two dilated, fixed pupils; unconsciousness (i.e., ≥ 2 on item 1a on the NIHSS); and/or loss of other brain stem reflexes, attributable to edema or herniation according to the investigator’s judgment.
6) Brain hemorrhage (other than small petechial hemorrhages) on CT/MRI, or CT/MRI evidence of anteroseptal/pineal shift greater ≥ 2 mm prior to enrollment that is due to cerebral edema.
7) Severe renal disorder from the patient’s history (e.g. dialysis) or eGFR of < 30 mL/min/1.73 m².
8) Severe liver disease, or ALT > 3 times upper limit of normal or bilirubin > 2 times normal (subjects may be randomized if liver function tests have been drawn but are not yet available and the subject has no known history of liver disease; however treatment with Study Drug cannot commence until liver function tests are available and indicate ALT ≤ 3 times upper limit of normal and bilirubin ≤ 2 times upper limit of normal).
9) Blood glucose <55 mg/dL at enrollment or immediately prior to administration of Study Drug, or a clinically significant history of hypoglycemia.
10) Acute ST elevation myocardial infarction, and/or acute decompensated HF, and/or QTc>520 ms, and/or known history of cardiac arrest (PEA, VT, VF, asystole), and/or
admission for an ACS, MI, or coronary intervention (PCI or coronary artery surgery) within the past 3 months.

11) Known sulfonylurea treatment within 7 days. Sulfonylureas include glyburide/glibenclamide (Diabeta, Glynase); glyburide plus metformin (Glucovance); glimepiride (Amaryl); repaglinide (Prandin); nateglinide (Starlix); glipizide (Glucotrol, GlibeneseR, MinodiabR); gliclazide (DiamicronR); tolbutamide (Orinase, Tolinase); glibornuride (Glutril).

12) Known treatment with bosentan within 7 days.

13) Known allergy to sulfa or specific allergy to sulfonylurea drugs.

14) Known G6PD enzyme deficiency.

15) Pregnant women. Women must be either post-menopausal (as confirmed by the LAR), permanently sterilized or, if ≤ 50 years old must have a negative test for pregnancy obtained before enrollment.

16) Breast-feeding women who do not agree (or their LAR does not agree) to stop breast-feeding during Study Drug infusion and for 7 days following the end of Study Drug infusion.

17) Patients already enrolled in a non-observation-only stroke study, or with life-expectancy < 3 months not related to current stroke, or those unlikely to be compliant with follow up.

18) Patients currently receiving an investigational drug.

19) Patients in whom a peripheral IV line cannot be placed.

20) Mentally incompetent (prior to qualifying stroke) patients and wards of the state.

21) Patients who, in the opinion of the investigator, are not suitable for the study (reason to be documented).

5.3 Study Enrollment Procedures

5.3.1 Screening procedures

A screen failure log will be maintained at each site.

Because pertinent patient information will already be collected as part of standard of care, and to reduce additional study-specific procedures, baseline information may be taken from the patient’s medical records prior to obtaining informed consent. However, informed consent will be obtained prior to performing any study-specific procedures.

5.3.2 Consent procedure

The patient or a LAR (e.g. parent, legal guardian, designated healthcare proxy, or person with power of attorney) must sign the IRB-approved consent form. Determination of whether consent by a LAR is required (and if so, determination of the LAR) as well as specific details of the consenting process will be determined by state law and local IRB requirements.

Consent may be obtained any time prior to enrollment.
5.3.3 Procedure for enrolling and obtaining intervention group assignment

Patients should not be considered for enrollment if the baseline MRI scan cannot be completed within approximately 8.5 hours of TLK@B. This will permit time to enroll patients and to prepare and administer drug within 10 hours of stroke onset.

Enrollment and randomization will be concurrent. Subjects will be randomized 1:1 (RP-1127: placebo), controlling for site, age ≤ 60 (yes/no), and IV rtPA treatment at baseline (yes/no). When the subject is ready to be randomized, the study team member will be given a randomization number based on the randomization scheme. The randomization number will correspond to either RP-1127 or matching placebo that already will be at the clinical site.

The enrollment (baseline) NIHSS score (as free as possible of confounding drugs) will be obtained as close to enrollment as possible, and no more than 2 hours prior to enrollment.
6  STUDY INTERVENTIONS

6.1  Study Drug Description, Dose and Administration

6.1.1  Study Drug Description

Study Drug vials (i.e. RP-1127 or placebo) contain a white- to off-white lyophilized powder for IV administration after reconstitution; vials of RP-1127 and of placebo look identical. Each vial of RP-1127 contains 6 mg of glyburide, 180 mg of mannitol, and NaOH to adjust the pH during manufacture. Placebo vials contain only mannitol and NaOH. Vials of Study Drug will be reconstituted with water for injection (WFI) prior to further dilution for the bolus and continuous IV infusion with 0.9% normal saline.

Three vials of Study Drug will be assigned to each study subject, packaged into one kit. A new vial will be used for dosing on each day of the 3-day infusion. All vial labels will contain the FDA caution statement regarding investigational drug.

The site pharmacist or designee will prepare the Study Drug.

6.1.2  Handling of Study Drug

Sponsor, through its contract manufacturer and distributor, will be responsible for distribution of Study Drug to the clinical sites. The clinical site pharmacy will be responsible for reordering additional supplies of Study Drug if additional supplies are required.

Study Drug will be stored in a secure limited-access area. All vials of Study Drug will be stored refrigerated at 2-8°C until used, in accordance with labeled storage requirements. Storage temperature must be monitored and recorded.

Once reconstituted, the agent must not be refrigerated. Stability at room temperature of Study Drug in normal saline is 30 hours.

The Principal Investigator or designee at each site will keep an inventory of Study Drug received and dispensed during the conduct of this study. Study Drug inventory will be maintained in a drug accountability log. The investigator must notify Sponsor of any damaged or unusable study supplies that were supplied to the site.

Every effort should be made to commence Study Drug infusion as soon as possible after subject enrollment in the study. Enrollment, in turn, should be achieved as soon as possible upon arrival of the study subject at the hospital.

Please refer to the Pharmacy Manual for detailed instructions regarding the reconstitution of Study Drug.
6.1.3 **Study Drug Dose**
The bolus and the infusion concentrations are both 5.3 ug/mL. Once prepared, the 24 mL bolus injection will be given over approximately 2 minutes. The daily infusion will be administered at a rate of 31 mL/hr for the first 6 hours and then 21 mL/hr for 66 hours, for a total of 72 hours. The total volume of the continuous infusion will be 564 mL on Day 1, and 504 mL on Day 2 and on Day 3. The infusion will be prepared in 1,000 mL IV bags, which must be replaced every 24 hours. Table 3 provides a summary of the study dosing.

If dosing is reduced in accordance with Section 6.3.4, the dose reduction should be achieved by reducing the flow rates of 21 mL/hr and 31 mL/hr to 15 mL/hr and 22 mL/hr respectively.

<table>
<thead>
<tr>
<th></th>
<th>Bolus</th>
<th>Day 1 Infusion</th>
<th>Day 2 Infusion</th>
<th>Day 3 Infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Dose</strong></td>
<td>0.13 mg</td>
<td>2.99 mg</td>
<td>2.67 mg</td>
<td>2.67 mg</td>
</tr>
<tr>
<td><strong>Dose/hr</strong></td>
<td>N/A</td>
<td>0.16 mg/hr for 6 hours followed by 0.11 mg/hr for 18 hours</td>
<td>0.11 mg/hr for 24 hours</td>
<td>0.11 mg/hr for 24 hours</td>
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<tr>
<td><strong>Infusion Rate</strong></td>
<td>24 mL over approximately 2 minutes</td>
<td>31 mL/hr for 6 hours followed by 21 mL/hr for 18 hours</td>
<td>21 mL/hr (504 mL)</td>
<td>21 mL/hr (504 mL)</td>
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<tr>
<td><strong>Total Volume</strong></td>
<td>24 mL</td>
<td>564 mL</td>
<td>504 mL</td>
<td>504 mL</td>
</tr>
</tbody>
</table>

In the event administration of RP-1127 is halted due, for example, to insulin error or IV infiltration, Study Drug should be restarted by administering a bolus per Table 4 below and restarting the continuous infusion at the rate used prior to the Study Drug stoppage.

Note that the rebolus may be administered over approximately 2 minutes either by programming the infusion pump appropriately, or by withdrawing drug from the bag and injecting it by syringe through the peripheral IV, depending on site standards.
### Table 4. Rebolus Dose

<table>
<thead>
<tr>
<th>Study Drug interruption duration (hours)</th>
<th>Re-bolus dose (µg)</th>
<th>mL of infusate from bag (mL)</th>
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</thead>
<tbody>
<tr>
<td>&lt;0.5</td>
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<tr>
<td>≥0.5 &lt; 1.0</td>
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<tr>
<td>≥10</td>
<td>130</td>
<td>25</td>
</tr>
</tbody>
</table>

### 6.1.4 Study Drug Administration

Study Drug may stick to certain materials, and as such only specified components may be used in the fluid path. The infusion of Study Drug should only be through a dedicated peripheral IV line. The Study Drug may not be delivered through a central line or PICC line. No other medication may be administered in the same line as Study Drug, nor should the line be used for blood withdrawal. A calibrated infusion pump with a dedicated infusion line will be used to ensure infusion at the specified rates.
Only the following components may be in the fluid path:

- **B Braun EXCEL L8000 low sorbing saline bags.**
- Depending on the site’s pump system:
  - Alaris/Carefusion 2260-0500 low sorbing filterless administration sets, or
  - Hospira 11993-78 filterless low sorbing administration sets, or
  - Hospira 14248-28 filterless low sorbing administration sets, or
  - Baxter 1C8043 filterless low sorbing administration sets.
- **Alaris/Carefusion C20014 30" low sorbing filterless extension sets.**
- **Any peripheral IV BD catheter containing BD Vialon™ material may be used. However, no unauthorized extension sets may be attached to the catheter. Thus, the BD Nexiva catheter is recommended.**

The use of any bags, administration or extension sets, or any configuration of the components other than those specified above is strictly prohibited, unless permission to do so is provided by Sponsor in writing (email).

Study Drug infusion should not be stopped if an unscheduled MRI scan is required during infusion, other than to attach and position the administration/extension set through any portals leading to the MRI suite. Up to ten (10) approved extension sets may be connected to the administration set to allow the infusion pump to be outside of the MRI suite while continuing the infusion.

The infusion period will not be extended to account for any stoppages or reduction.

Study Drug should not be stopped if the patient goes to DC.

The date and time of the start and end of the infusion of each bag will be recorded in the CRF. At the end of the infusion of each bag, tubing, bags, and IV catheters must be visually inspected and confirmation that they consist of only the allowed components. If any components other than allowed components are found, these must be removed or replaced and recorded in the CRF.

The length of, and reason for, any stoppages of the infusion that last greater than 15 minutes must be recorded.

6.2 **Concomitant Interventions**

6.2.1 **Discouraged Interventions**

Specific treatment guidelines are provided in the Clinical Standardization Guidelines document. These guidelines are a template for the care of study subjects participating in the Study, and should be followed whenever clinically feasible. The attending clinician has ultimate responsibility and discretion for treating subjects. The clinician will use his/her best judgment in treating subjects based upon the specific clinical situation and in accordance with good clinical practices.
6.2.2 Prohibited Interventions
No sulfonylurea agents may be administered prior to the Day 4 (72-96 hour) MRI. After the Day 4 MRI, it is preferable that no sulfonylureas be administered through study completion.

No other investigational drugs may be administered during the 90-day follow up period.

Bosentan must not be administered until 24 hours after Study Drug administration is halted.

Treatment with intra-arterial (IA) rtPA, and treatment with IA thrombectomy devices are not permitted during the Study.

6.3 Interventions Related to Blood Glucose

6.3.1 Insulin
Insulin is not permitted during Study Drug administration when BG < 120 mg/dL. “Tight” BG control (80 – 110 mg/dL) is not permitted during administration of Study Drug.

6.3.2 Supplemental Fluids
Supplemental fluids are to be standard of care except that during Study Drug administration, D5NS or D10NS must be used instead of NS if necessary to maintain BG above 80 mg/dL. Total fluid volume, inclusive of Study Drug volume, must be consistent with site clinical practice and the clinical status of the Subject.

6.3.3 Hypoglycemia treatment
Any BG of < 70 mg/dL must be treated with a bolus of D50W at a volume (ml) of (100 – BG in mg/dL) x 0.4 as per Juneja et al. 2009. If D50W is not available, another concentration of dextrose fluid may be used as long as an equivalent amount of dextrose is delivered. If supplemental fluids are NS, D5NS must be started. If supplemental fluids are D5NS, D10NS must be substituted. While all BG < 70 mg/dL must be verified by laboratory test, the above treatment must occur prior to such verification. To avoid false readings, blood for the laboratory test must be drawn prior to treatment with D50W or switching supplemental fluids.

6.3.4 Study Drug Dose Reduction
The Study Drug dose must be reduced by 30% if subject is being administered D5NS or D10NS and (i) there is one lab confirmed BG < 55 mg/dL; or (ii) there are three lab confirmed BG < 70 mg/dL within a 12 hour period. This is achieved by reducing the flow rate by 30%. If (i) or (ii) above occurs and the Subject is on NS, D5NS or D10NS must be started.

Study Drug dosage must only be adjusted based on verified laboratory test values that are taken 15 minutes or more following the last administration of insulin.

6.3.5 Study Drug Discontinuation
The dose can only be reduced once; if (i) or (ii) above occurs a second time, Study Drug must be discontinued. Study Drug dosage must only be stopped based on verified laboratory test values that are taken 15 minutes or more following the last administration of insulin. When Study Drug is stopped as a result of low BG, D50W (or another concentration of dextrose, if D50W is not
available) should be administered by bolus in order to maintain BG > 80 mg/dL. Multiple boluses may be administered, the timing and volume of which are at the discretion of the clinician. BG monitoring is required every 15 (± 10) minutes until BG ≥ 80 for 3 consecutive readings without bolus glucose supplementation, then hourly (± 30 minutes) for the next 6 hours.
### 7 CLINICAL AND LABORATORY EVALUATIONS

#### 7.1 Schedule of Evaluations

<table>
<thead>
<tr>
<th>Screening/Enrollment</th>
<th>Day 1 (0–24h)</th>
<th>Day 2 (24–48h)</th>
<th>Day 3 (48–72h)</th>
<th>Day 4 (72–96h)</th>
<th>Days 5–6</th>
<th>Day 7±1 or Discharge</th>
<th>Days 30±7</th>
<th>Day 90±14</th>
<th>6 m ± 30 d</th>
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<tr>
<td>Concomitant medications</td>
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<tr>
<td>Concomitant procedures/therapies</td>
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<tr>
<td>Carbohydrates</td>
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<tr>
<td>Causative Classification System (CCS)</td>
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<td>X</td>
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<tr>
<td>mRS, Barthel</td>
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<td>X</td>
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<tr>
<td>BDI-II, EuroQoL</td>
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<td>-</td>
<td>X</td>
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<tr>
<td>Subject Status</td>
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<td>X</td>
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<td>X</td>
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<tr>
<td>Review safety data and record AE</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
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</tbody>
</table>

**Notes:**
- a Vital signs and O2 saturation as standard of care. BP and HR recorded in CRF approximately Q4 hours. Respiratory Rate, Temperature, O2 saturation recorded in CRF approximately Q8 hours.
- b MRI at screening (prior to enrollment) and DWI/FLAIR/GRE at 72-96 hours (as close to 72 hours as possible).
- c CTA, MRA or catheter angiography of the head and neck as standard of care prior to dosing. MRA (head only) at 72-96 hours.
- d At enrollment, 24±12 hours, 48±12 hours, and Day 7±1 (or discharge if earlier).
- e At 24±12 hours, evaluate since randomization. At 48±12 hours, 72±12 hours, 96±12 hours, and Day 7±1 (or discharge if earlier) evaluate since last assessment.
- f Prior to dosing, 24±12 hours, 48±12 hours, and 96±12 hours, and Day 7±1 (or discharge if earlier).
- g Prior to dosing, 4±12 hours, 48±12 hours, and 96±12 hours, and Day 7±1 (or discharge if earlier) evaluate since last assessment.
- h In the event of suspected hemolytic anemia sit-specific confirmatory tests should be performed. A G6PD deficiency test must be performed following resolution of anemia.
- i Infusion components inspected at start of each bag.
- j Mean (± 30 min) for H1-24, every 2 hours (± 30 min) for H25-48 and every 4 hours (± 60 min) for H49-88. If BG < 70 mg/dL, every 15 minutes (± 10 min) until BG ≥ 80 for 3 consecutive readings without exogenous glucose supplementation, then hourly (± 30 min) for the next 12 hours and every 2 hours (± 30 min) thereafter.
- k Prior to dosing, 4±6 hours, 48±6 hours, and 60-72 hours (prior to stopping Study Drug). All PK draws (other than prior to dosing) as close as possible to the ECG. Additional sample if QTc>550 ms or there is a cardiac-related SAE; or if there is a lab confirmed BG < 55mg/dL or hypoglycemia-related SAE during Study Drug administration.
- l One draw between 0 and 72 hours. At selected sites.
- m Prior to dosing, 4±6 hours, 48±6 and 60-72 hours (same timing as PK sampling). At selected sites.
- n Through Day 7±1 (or discharge if earlier) except osmotherapy (mannitol and hypertonic saline) which is recorded through discharge on a separate CRF.
- o Through Day 7±1 (or discharge if earlier) except tracheostomy and gastrostomy, recorded through discharge.
- p Record dextrose type (D5/D10/D50/Other), carrier (water, NS, ½ NS); rate (D5 and D10); volume (D50/Other). Record tube feed type and rate.
All AEs and SAEs through Day 7±1 (or discharge if earlier). Follow unresolved AEs present at discharge at Day 30 and 90. Record SAEs at Day 30 and 90 as determined by telephone and medical record review, as needed. Record only SAEs at 6 and 12 months determined by discussion with LAR and/or subject (no medical record review).
7.2  **Timing of Evaluations**

7.2.1  **Pre-Treatment Evaluations (Screening to Enrollment)**

These evaluations occur prior to the subject being enrolled:

- Time of stroke onset
- Standard of care vascular imaging (CTA, MRA or catheter angiography of the head and neck)
- Baseline MRI
  - Standard of care MRI sequence – DWI must be performed, as should FLAIR and GRE if available as standard of care. Every effort should be made to begin MRI scanning as soon as possible after the subject arrives at the hospital.
  - DWI lesion size assessment by local study team using the ABC/2 formula.
  - If the MRA/CTA/Angiography confirms an ICA/M1 occlusion and if the standard of care MRI sequence shows a DWI lesion volume \( \geq 60 \text{ cm}^3 \) and \(< 82 \text{ cm}^3 \), then, following informed consent, a study-specific baseline DWI sequence may be performed to determine whether at that point the DWI lesion volume is 82-300 cm\(^3\), in which case the subject will meet the DWI eligibility criteria.
  - In addition to the above, for sites where perfusion weighted imaging (PWI) is a standard of care, if the MRA/CTA/Angiography confirms an ICA/M1 occlusion and if the standard of care MRI sequence shows a DWI lesion volume \( \geq 40 \text{ cm}^3 \) and \(< 60 \text{ cm}^3 \), and shows a PWI \( T_{\text{max}} > 10 \) volume of \( > 85 \text{ cm}^3 \) Then, following informed consent, a study-specific baseline DWI sequence may be performed to determine whether at that point the DWI lesion volume is 82-300 cm\(^3\), in which case the subject will meet the DWI eligibility criteria.
- Demographics (age, race, gender)
- Pregnancy test for women of child-bearing potential
- Relevant medical history
- ECG (12-lead)
- Safety labs (to be done only after Informed Consent is obtained, if not standard of care)
  - Hematology: complete blood count
  - Chemistry: electrolytes (sodium, potassium, chloride, bicarbonate), BUN, creatinine, and glucose
  - Liver Function Tests: AST, ALT, bilirubin (total and direct), and alkaline phosphatase.
- Blood glucose
- Only patients with no significant disability (able to carry out all usual duties and activities) prior to TLK@B may be enrolled into the Study.
- Because pertinent patient information will already be collected as part of the standard of care, and to reduce additional study-specific procedures, screening and baseline information may be taken from the patient’s medical records prior to obtaining informed consent. **However, informed consent must be obtained prior to performing any study-specific procedures.**
- Once study eligibility has been confirmed (inclusion/exclusion criteria are met) and informed consent obtained, the patient will be enrolled into the study at randomization.
7.2.2 Pre-Treatment Evaluations (Enrollment to Treatment)

These evaluations occur following enrollment, prior to the subject receiving Study Drug:

- Enrollment (baseline) NIHSS (no more than 2 hours prior to enrollment). Every attempt should be made to collect NIHSS free of the effects of sedating and/or paralytic drugs.
- Physical examination, including height, weight, and vital signs (blood pressure, temperature, heart rate, and respiration rate). Body weight and height may be estimated if patient cannot be measured. Vitals signs are to be collected no more than 1 hour before beginning of drug infusion.
- Prior and concomitant medications, including all medications taken within 7 days prior to screening.
- Medical procedures since onset of symptoms.
- Adverse events, beginning at the time of enrollment.
- PK sampling.
- Blood sampling for additional laboratory tests to identify biomarkers at selected sites prior to dosing.
- Study Drug cannot commence until enrollment liver function tests are available and indicate ALT $\leq$ 3 times upper limit and bilirubin $\leq$ 2 times upper limit of normal.

7.2.3 Days 1-4 (0-96 hours)

Note: Study Drug must be started within 10 hours of TLK@B. Study Drug infusion will be stopped after 72 hours of infusion. Hard stop rules for Study Drug administration are listed in Section 8.

The following assessments will be performed and/or recorded:

- Vital signs and $O_2$ saturation will be assessed according to the standard of care, and will be recorded in the CRF according to the following schedule (Table 5):

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Frequency (Approximate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Pressure a</td>
<td>Every 4 hours</td>
</tr>
<tr>
<td>Heart Rate a</td>
<td>Every 4 hours</td>
</tr>
<tr>
<td>Respiratory Rate</td>
<td>Every 8 hours</td>
</tr>
<tr>
<td>Temperature</td>
<td>Every 8 hours</td>
</tr>
<tr>
<td>$O_2$ saturation</td>
<td>Every 8 hours</td>
</tr>
</tbody>
</table>

  a all attempts will be made to capture BP and HR on the above schedule; however, occasional assessments may be missed if the patient is not available.

- Safety labs (hematology, chemistry, and LFTs) at 24±12 hours, 48±12 hours 72±12 hours and 96±12 hours
  - Hematology: complete blood count
  - Chemistry: electrolytes (sodium, potassium, chloride, bicarbonate), BUN, creatinine, glucose
Liver Function Tests: AST, ALT, bilirubin (total and direct), and alkaline phosphatase.

- Blood glucose (BG) monitoring will be hourly (± 30 minutes) for H1-24, every 2 hours (± 30 minutes) for H25-48 and every 4 hours (± 60 minutes) for H49-88. If BG < 70 mg/dL, BG monitoring is required every 15 (± 10 minutes) minutes until BG ≥ 80 for 3 consecutive readings without exogenous bolus glucose supplementation, then hourly (± 30 minutes) for the next 12 hours and every 2 hours (± 30 minutes) thereafter.
- Continuous bedside cardiac telemetry monitoring from H0 through at least H72.
- ECG at 4-6 hours, 24±6, 48±6 and 60-72 hours (12-lead).
- Blood sampling for PK prior to dosing, at 4-6 hr (prior to reduction of infusion rate), 24±6, 48±6 and 60-72 hour (prior to infusion end). PK samples to be drawn as close as possible to ECGs. An additional PK sample will be drawn if QTc>550 or there is a cardiac-related SAE; or if there is a lab confirmed BG < 55mg/dL or hypoglycemia-related SAE during Study Drug administration.
- Start time of bolus, and start/stop times of each infusion bag of Study Drug. Record length of, and reason for, any stoppages of the infusion that last greater than 15 minutes.
- Visual inspection at the end of the daily infusion of tubing, bags, and IV catheters to confirm that they are allowed components. If any components other than allowed components are found, these must be replaced and recorded.
- Concomitant medications and procedures/therapies.
- Review safety and AEs.
- NIHSS at 24±12 hours, 48±12 hours, 72±12 hours. In the event of DC, an additional NIHSS must be recorded as close to DC as possible, preferably within 2 hours prior to surgery. Every attempt should be made to collect the NIHSS free of the effects of sedating and/or paralytic drugs.
- Neurological deterioration recorded at 24±12 hours, 48±12 hours, 72±12 hours, and 96±12 hours
- MRA (head only) and MRI (DWI, FLAIR, and GRE) sequences at 72-96 hours (as close to 72 hours as possible). Every attempt should be made to follow the imaging protocols in the Imaging Manual.
- Blood sampling for additional laboratory tests to identify biomarkers at selected sites prior to dosing, at 4-6 hr, 24±6, 48±6 and 60-72 hour.
- Blood sampling for pharmacogenetic analysis at selected sites between 0 and 72 hours.

7.2.4 Days 5-7

Post-treatment evaluations will be conducted on Days 5-7 or upon hospital discharge, whichever occurs first.

The following assessments will be performed and/or recorded:

- Vital signs and O₂ will be assessed according to the standard of care, and will be recorded in the CRF according to the following schedule (Table 6):
Table 6. Vital Signs and $O_2$ Saturation Assessments, Days 5-7

<table>
<thead>
<tr>
<th>Assessment</th>
<th>Frequency (Approximate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood Pressure a</td>
<td>Every 4 hours</td>
</tr>
<tr>
<td>Heart Rate a</td>
<td>Every 4 hours</td>
</tr>
<tr>
<td>Respiratory Rate</td>
<td>Every 8 hours</td>
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<tr>
<td>Temperature</td>
<td>Every 8 hours</td>
</tr>
<tr>
<td>$O_2$ saturation b</td>
<td>Every 8 hours</td>
</tr>
</tbody>
</table>

a all attempts will be made to capture BP and HR on the above schedule; however, occasional assessments may be missed if the patient is not available; further if subject is discharged from the ICU, assessments will be every 8 hours.
b Following discharge from the ICU, will be recorded only if available.

- Concomitant medications and procedures/therapies.
- Review safety and AEs.

Day 7 or discharge

The following evaluations and assessments will be performed at 7±1 days or at discharge, if earlier:

- Record the cholesterol labs closest to randomization in CRF if performed as standard of care, and not recorded previously.
- Record the drug screen test in the CRF if performed as standard of care, and not recorded previously.
- Subject status.
- NIHSS. Every attempt should be made to collect NIHSS free of the effects of sedating and/or paralytic drugs.
- Neurological deterioration assessment.
- CCS Stroke Subtype Classification.
- Concomitant medications through Day 7 or discharge, whichever is earlier, except osmotherapy (mannitol and hypertonic saline), which is recorded through discharge on a separate CRF.
- Safety labs:
  - Hematology: complete blood count
  - Chemistry: electrolytes (sodium, potassium, chloride, bicarbonate), BUN, creatinine, glucose
  - Liver Function Tests: AST, ALT, bilirubin (direct and total), and alkaline phosphatase.
- ECG (12-lead).
- Concomitant procedures and therapies through Day 7 or discharge, whichever is earlier, except tracheostomy and gastrostomy, recorded through discharge
- Review safety and AEs.
- Contact information for the subject (home and cellular telephone numbers, email addresses, home addresses, rehabilitation or nursing home information including fax and phone numbers); LAR (home and cellular telephone numbers, email addresses, home...
addresses); family members (home and cellular telephone numbers, email addresses, home addresses); and personal physician (phone and fax numbers).

All MRI, MRA, CT and CTA scans prior to Day 7 or discharge (whichever is earlier) must be sent to the Imaging Coordinating Center (see Imaging Manual).

7.2.5 Post-treatment Follow Up Evaluations

**Post-treatment Follow-up: Day 30**
The following assessments, which must be completed at 30±7 days, will be obtained:

- Subject status
- Review unresolved AEs present at discharge
- Record SAEs
- mRS
- Barthel Index

**Post-treatment Follow-up: Day 90**
The following assessments, which must be completed at 90±14 days, will be obtained:

- Subject status
- Review unresolved AEs present at discharge
- Record SAEs
- mRS
- Barthel Index
- Beck Depression Inventory (BDI-II)
- EuroQoL 5-D

**Post-treatment Follow-up: 6 and 12 month**
The following assessments, which must be completed at 6 months ± 30 days and 12 months ± 30 days, will be obtained:

- Subject status
- Record SAEs (only by discussion with LAR and/or subject)
- mRS
- Barthel Index
- Beck Depression Inventory (BDI-II)
- EuroQoL 5-D

7.3 Special Instructions and Definitions of Evaluations

7.3.1 Informed Consent and HIPAA Authorization
The potential study subject or a relevant LAR will provide informed consent and HIPAA Authorization by signing the local IRB approved document(s).

7.3.2 Documentation of Ischemic Stroke
Clinical diagnosis of ischemic stroke will be made by the stroke neurologist.
7.3.3 Medical History
Medical history will be recorded in the CRF and will include prior history of ischemic or hemorrhagic stroke, transient ischemic attack, hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, myocardial infarction, atrial fibrillation, congestive heart failure, baseline ejection fraction, heart valve replacement, carotid artery disease, carotid endarterectomy or stenting, malignancy, seizures, migraine headache, smoking use, alcohol, drug use, and family history of cardiovascular disease.

7.3.4 Treatment History
All medications used within 7 days prior to entry into the Study, including prescription as well as over-the-counter medications, dietary supplements, and systemic agents obtained from alternative medicine sources must be recorded in the CRF.

7.3.5 Concomitant Treatments and Procedures
All medications used through Day 7 or discharge (whichever is earlier) will be recorded in the CRF including but not limited to dextrose solutions (including concentration and flow rate/volume) and other concomitant medications e.g. paralytics, sedatives, vasoactive drugs. Osmotherapy [Mannitol (including dose) and hypertonic saline (including concentration and flow rate/volume)] will be recorded through discharge on a separate CRF. Medications that are ordered as standing orders for stroke patients but are not administered will not be recorded.

Concomitant treatments and procedures will be recorded through Day 7 or discharge, whichever is earlier, with the exception of tracheostomy and gastrostomy which will be recorded through discharge.

Note: when hypertonic saline is administered the reason for administration must be captured in the CRF so that administration for edema is clearly distinguished from other reasons for administration.

7.3.6 Safety/Laboratory Assessments

Vital Signs
Vital signs to be measured include blood pressure (supine position), heart rate (supine position at same time blood pressure is measured), respiratory rate (per minute), and temperature. Oxygen saturation will also be recorded.

Blood Glucose
BG concentrations are to be measured by point-of-care (POC) testing of capillary blood e.g. Accuchek. Alternately, blood from an arterial line may be used if one is in place. If blood from an arterial line is used, the line must be back-flushed with sufficient arterial blood to avoid falsely low BG readings from dilution with the arterial line carrier (i.e. heparinized saline). BG < 70 mg/dL measurements must be verified by laboratory test. The source of BG (capillary vs. arterial line) and whether the analysis was performed by POC or laboratory must be recorded in the CRF.
Hypoglycemia is defined as BG < 55 mg/dL. Symptomatic hypoglycemia is defined as investigator-identified hypoglycemic symptoms with a BG < 55 mg/dL. All instances of lab confirmed hypoglycemia, hypoglycemia symptoms, and treatment administered will be recorded in the CRFs.

Interventions related to BG are found in Section 6.3.

**Hemolytic Anemia**

In the event hemolytic anemia is suspected as a result of CBC, bilirubin, or any other laboratory value, sign or symptom, site-specific tests to confirm or rule out hemolytic anemia should be performed based on the clinical judgment of the treating clinicians. A G6PD deficiency test must be performed following resolution of anemia.

**ECG**

ECGs will be reviewed at the site and documented on the CRF. At each site, a study team physician (or if not available, the attending physician) must review each ECG strip within 12 hours of it being captured and indicate in writing (on the strip or in the patient’s medical file, with the reviewing physician’s initials or signature, and the time/date) whether any findings are clinically significant or not clinically significant. All clinically significant abnormal ECGs will be recorded as adverse events.

Additionally, continuous bedside cardiac telemetry monitoring will be performed from H0 through at least H72. Standard-of-care telemetry alarms must be activated. If an alarm is generated a rhythm strip must be printed and reviewed urgently by a physician caring for the patient. The rhythm strip must be further reviewed by a study team physician within 24 hours, and the strip initialed, dated, and timed by the reviewing study team physician. Telemetry events will be recorded on CRFs if determined by the study team physician to be clinically relevant.

Scheduled and unscheduled 12 lead ECGs will be centrally read for safety analyses. The ECG Manual provides information how to capture and transmit ECGs to the central reader.

7.3.7 Clinical Assessments Performed by Site

**Mortality**

If a patient death occurs during the Study, the primary cause of death, secondary cause (if any), and date and time of death will be determined and recorded. Brain Death, consistent with the American Academy of Neurology 2010 guideline (Wijdicks et al. 2010), and death by withdrawal of care must be documented. Where life sustaining interventions are withdrawn, the patient will remain in the Study unless specifically withdrawn per Section 12.1.

**Decompressive Craniectomy**

Decompressive craniectomy, surgical treatment for edema, that is performed prior to Day 7 or discharge (whichever is earlier) will be recorded in the CRF. Reasons for decompressive craniectomy and any complications resulting from the procedure will also be recorded.
NIHSS Score
The NIHSS will be performed by study team members with NIHSS training and certification.

Every attempt should be made to collect the NIHSS score free of the effects of sedating and/or paralytic drugs.

Neurological Deterioration
Details of neurological deterioration experienced by the subject, if any, will be recorded.

Causative Classification System (CCS) for Ischemic Stroke
The stroke subtype will be classified using the CCS system, per https://ccs.mgh.harvard.edu/ccs_title.php.

Subject Status
Alive, dead, nursing home with rehabilitation, nursing home without rehabilitation, rehabilitation facility, home with rehabilitation, home without rehabilitation, hospice.

Day 30/90 and Month 6/12 Assessments
Scripts to assess mRS, Barthel Index, Beck Depression Inventory (BDI-II), EuroQoL 5-D are to be followed per the Follow Up Clinical Outcomes Manual.

Potential sources of follow up information will include subject medical records, the subject, LAR, family members, and personal physician. In addition, information may be collected by contacting the rehabilitation facility/nursing home, or accessing a shared healthcare database or publicly available death records. If all attempts to collect the follow up assessments are unsuccessful, the subject will be classified as “lost to follow up.” The subject should not be classified as “lost to follow up” until the final assessment has been missed and a certified letter has been sent to both the LAR and subject with no response within 30 days of sending.

7.3.8 Imaging Evaluations Performed by the Site
Baseline MRI DWI Lesion Volume Assessment
Baseline MRI DWI lesion volume assessments will be performed by the study team using the ABC/2 methodology. A worksheet will be provided, with instructions as to how to calculate the lesion volume using ABC/2. Investigators and study coordinators will be trained in performing the ABC/2 assessment.

CT / Other Scans
It is anticipated that CT or additional MRI scans may be performed as standard of care either as routine, or in the presence of neurological deterioration.

7.3.9 Pharmacokinetic Studies
Blood will be drawn for measurement of plasma levels of glyburide. The blood draw should be done as close as possible to the ECG time. The 4-6 hour PK must be done prior to the scheduled change in Study Drug dosing at 6 hours. The 60-72 hours PK must be done prior to stopping Study Drug. An additional PK sample will be drawn if QTc>550 ms or there is a cardiac-related
SAE; or if there is a lab confirmed BG < 55mg/dL or hypoglycemia-related SAE during Study Drug administration.

PK samples should be taken from the arm contralateral to the arm in which the Study Drug is being infused or from an arterial line if one is in place (where PK samples are drawn from an arterial line, this must be recorded in the CRF).

Detailed collection, processing, tracking, storage and shipping instructions may be found in the PK and Biomarker Study Manual.

7.3.10 Other Laboratory Studies
Additional laboratory tests to identify biomarkers may be performed at selected sites. Candidates may include markers such as SUR1, MMP-9 and circulating metabolites. Detailed collection, processing, tracking, storage and shipping instructions may be found in the PK and Biomarker Study Manual.

An additional blood sample for pharmacogenetics may be drawn at selected sites. Genetic material will be identified only by assigned Study patient number. DNA samples may be sent to a third party for genomic analysis, in which case samples will be sent out coded and completely anonymous. Pharmacogenetic analyses will be for research purposes and no information will be shared with study participants and no record of participation will be entered in the medical record. Candidate single nucleotide polymorphisms (SNPs) that may be explored include TRPM4 and ABCC8. Detailed collection, processing, tracking, storage and shipping instructions may be found in the PK and Biomarker Study Manual.

7.3.11 Unblinding
If a study team member believes it is necessary for the site to be unblinded to the study treatment assignment, the study team member must first call the GAMES-RP 24/7 hotline, and select the item corresponding to subject safety. They will be routed to a Sponsor representative to discuss the reason for unblinding. If it is determined that unblinding is necessary, then the Sponsor representative will either give the study team member a numeric unblinding code to be used for unblinding the subject through the randomization system, or activate the unblinding process within WebDCU.
8 CRITERIA FOR INTERVENTION DISCONTINUATION

If possible, the Medical Safety Monitor (MSM) should be contacted before early discontinuation of Study Drug. The MSM must be informed within 24 hours of early drug discontinuation.

8.1 Blood Glucose
Study Drug must be discontinued if Study Drug Dose has already been reduced in accordance with Section 6.3.4 and following the reduction of Study Drug Dose (i) there is one lab confirmed BG < 55 mg/dL; OR (ii) there are three lab confirmed BG < 70 mg/dL within a 12 hour period. When Study Drug is stopped as a result of BG, D50W or an equivalent amount of dextrose using D5W, D10W, D25W, or D70W (or other concentration) should be administered by bolus in order to maintain BG > 80 mg/dL. Multiple such boluses may be administered, the timing and volume of which are at the discretion of the clinician. BG monitoring is required every 15 (± 10) minutes until BG ≥ 80 for 3 consecutive readings without bolus glucose supplementation, then hourly (± 30 minutes) for the next 6 hours.

8.2 Cardiac
Study Drug must be halted if:
1. A life threatening cardiac-related SAE occurs, whether or not believed by the clinician to be related to Study Drug, and/or
2. Subject experiences QTc of > 550 ms (Bazett’s formula) for 15 minutes, whether or not believed by the clinician to be related to Study Drug. Before a decision to stop Study Drug is made, ECG leads must be repositioned and must be confirmed to be in the correct position, following which the ECG must be repeated in order to confirm QTc > 550 ms.

8.3 Hemolytic Anemia
Study Drug must be discontinued if hemolytic anemia, which in the judgment of the Investigator is severe, is detected. In the event of hemolytic anemia, a G6PD deficiency test should be performed following resolution of anemia. This test generally has a multi-day turnaround and will be used for information purposes only.

8.4 Liver Function
Study Drug must be discontinued if ALT rises to greater than 8 x the upper limit of normal. Study Drug must be discontinued if the subject develops cholestatic jaundice or hepatitis.
9  **BLINDED CENTRAL READINGS**

9.1  **Imaging Outcomes**

All MRI, MRA, CT and CTA scans prior to Day 7 or discharge (whichever is earlier) must be sent to the Imaging Coordinating Center (see Imaging Manual). The Imaging Coordinating Center will be blinded to treatment group. Specifically, the Imaging Coordinating Center will determine:

9.1.1  **Volumetric Data on MRI**

Lesion volume data will be based on a manual outline of the infarct on baseline (DWI) and 72-96 hour scans (DWI and FLAIR).

9.1.2  **Midline shift on MRI and CT**

Midline shift will be assessed on baseline and 72-96 hour FLAIR (or if not available, DWI) scans and CT scans by measuring the distance between the septum pellucidum and the midline, defined by a line drawn from the insertions of the falx anteriorly and posteriorly.

9.1.3  **Hemispheric Volumes on MRI**

The method described by Yoo et al. 2012 will be used to determine ipsilateral hemisphere volume at baseline and 72-96 hours. Briefly, the cerebral hemisphere ipsilateral to the infarct will be outlined on all relevant slices on baseline and 72-96 hour MRI, ensuring that whole brain coverage is achieved. Outlines will be performed on DWI sequences. Sulci that are at least 2 mm or more in width and extend from the brain surface, major cisterns, and ventricles will be excluded.

9.1.4  **Lesional Swelling Volumes on MRI**

The method described by Battey et al. 2014 will be used to determine swelling volume measurements. Briefly, baseline and follow-up DWI images will be co-registered, and the change in total lesional volume (ΔDWI) will be calculated by subtracting the baseline from the follow-up region of interest (ROI). The baseline and follow-up lesional ROIs will then be superimposed on each other and the infarct growth volume, parenchymal hematoma volume and/or edema volume will be assigned using slice-by-slice review in three orthogonal planes.

9.1.5  **Angiography (MRA/CTA/Angiography)**

Side (left/right) and site of occlusion (ICA/M1/M2/ACA/PCA) will be determined at baseline and 72-96 hours. The DEFUSE classification for vessel patency (complete occlusion, partial obstruction, and normal) will be used (Mlynash et al. 2011).

9.1.6  **Other**

Other analyses e.g. CSF sulcal displacement, ADC intensity ratio, GRE intensity ratio, and FLAIR intensity ratio, may be performed.

9.2  **ECGs**

Scheduled and unscheduled 12 lead ECGs will be centrally read for safety analyses by one or
more blinded reviewer(s). QTc (Bazett and Fridericia) along with other relevant parameters will be assessed.
10 STATISTICAL CONSIDERATIONS

The Data Coordination Unit (DCU) will coordinate all data and statistical services for the Study.

10.1 Outcome Measures

10.1.1 Safety Outcomes

Safety will be assessed by the frequency and severity of Adverse Events and Serious Adverse Events, with a specific focus on all cause mortality, and cardiac-related and BG-related AE’s/SAE’s.

Specific outcome variables related to assessing BG-related safety of RP-1127 are:

- Hypoglycemia i.e. blood glucose (BG) < 55 mg/dL
- Symptomatic hypoglycemia i.e. Hypoglycemia with investigator-identified hypoglycemic symptoms.

Specific outcome variables related to assessing cardiac-related safety of RP-1127 include:

- Incidence of cardiac SAEs, cardiac mortality, and incidence / severity of cardiac AEs
- Incidence of QTc of > 500 ms
- Mean Heart Rate, mean QTc, and mean change in QTc from baseline.

10.1.2 Efficacy Outcomes

The primary outcome measure is a modified Rankin Scale (mRS) at Day 90 ≤ 4 without decompressive craniectomy (DC).

The secondary outcomes are:

- The proportion of subjects either undergoing DC or dead by Day 14
- The change between baseline and 72-96 hours in ipsilateral hemispheric swelling measured by MRI
- The change between baseline and 72-96 hours in lesional swelling measured by MRI

Other outcomes will be described in the Statistical Analysis Plan and will include:

- Proportion of subjects that develop malignant edema by day 7
- Proportion of subjects undergoing DC, and DC-associated AEs and SAEs
- Proportion of subjects that experience an increase in the NIHSS score by ≥4 points between baseline and 72 hours
- Proportion of subjects that develop parenchymal hematomas by day 7
- Proportion of subjects with 90 day mRS 0-3 and 0-4
- Barthel Index at 90 days
- All-cause mortality at 90 days
- Incidence of intubation, tracheostomy, gastrostomy, and osmotherapy
- Length of ICU stay
- Proportion of subjects that develop symptomatic hemorrhage by day 7
- Mortality at day 7 and day 30
- Proportion of subjects that experience an increase in the NIHSS score by ≥4 points between baseline and day 7 (or discharge if earlier)
• MRI-derived midline shift and changes in lesion volume
• Quantitative T2/FLAIR, GRE and ADC ratios of lesion to unaffected hemisphere
• Shift analysis of mRS at 30 days, 90 days, 6 months and 12 months
• Proportion of subjects with 30 day, 6 month and 12 month mRS 0-3, 0-4, and mRS 0-4 without DC
• Day 90, 6 month and 12 month Beck Depression Inventory (BDI-II) and EuroQoL 5-D

10.2 Sample Size and Powering
The study was initially planned with a two-stage design. Stage 1 was to be comprised of 50 subjects (25 per arm) randomized and treated and meeting the Per Protocol definition, and Stage 2 was to be comprised of up to 190 subjects (95 per arm). Once Stage 1 was complete, i.e. 50 patients had been randomized and treated Per Protocol, and had completed the Day 90 evaluation, an interim analysis was planned (with enrollment continuing during the interim analysis). The interim analysis was to examine futility and re-estimate sample size. The final analysis was to be tested at the two-sided significance level of 0.05. Simulation had demonstrated that the design would have had 80% power to detect a 20-percentage-point effect size. However, due to administrative reasons, the interim analysis was not performed, and study enrollment was stopped after 83 subjects were enrolled and treated. The design was changed to conduct a single primary analysis once all subjects complete the Day 90 evaluation, with no unblinding prior to this analysis. With this number of subjects, the study has 80% power when the true placebo response rate is 30% and the true RP-1127 response rate is 60% (a 30 percentage point effect size, absolute difference of proportions) with a two-sided, two-sample test of proportions. Although the detectable difference (30%) is larger than originally stated (20%), it is still considerably smaller than observed with preliminary data (see Section 2.6.1).

10.3 Randomization
Randomization will take place centrally. Subjects will be randomized 1:1 (RP-1127: placebo), controlling for clinical site, age ≤ 60 (yes/no), and IV rtPA treatment at baseline (yes/no) using minimization (biased coin randomization).

10.4 Statistical Analysis Plan
A detailed statistical analysis (SAP) plan will be prepared prior to the analysis. It is expected to follow the analyses below, however, where differences occur, the SAP will be followed.

10.4.1 Primary Efficacy Analysis
The primary efficacy analysis will be conducted when all patients have completed the Day 90 assessment. A logistic regression model will be fit. The logistic model will include terms for treatment group, baseline age (continuous), baseline DWI volume (continuous), and baseline ICA occlusion (‘yes’ vs. partial/none/unknown) (SAS Proc GenMod). The likelihood ratio test will be used to test the null hypothesis that the coefficient for the treatment group is equal to zero (1=RP-1127 to 0=placebo). The analysis will be tested at the two-sided significance level of 0.05.

The primary efficacy analysis will be a Per Protocol analysis that will include all subjects in whom study drug was initiated, with a centrally read DWI lesion of 82-300 cm³, and treated with
their assigned study drug. An Intent-to-Treat analysis will be conducted as a secondary analysis and will include all randomized patients for whom study drug was initiated regardless of the treatment actually received. Patients will be analyzed according to the group to which they were randomized.

Missing mRS data on Day 90 will be imputed using last observed carried forward (LOCF; Day 30 mRS). If the patient is missing both the 30 and 90 day mRS, the primary outcome will be imputed via a regression method adjusting for clinical characteristics at baseline.

10.4.2 Primary Safety Analysis
All subjects who receive study drug will be included in the Safety Analysis. All adverse events and serious adverse events will be summarized in terms of frequency, severity and relatedness to the Study Drug using the MedDRA code. Frequency of adverse experiences will be compared using chi-square tests or Fisher’s exact tests. Mortality will be compared using Kaplan Meier curves and a log-rank test. All safety analyses, including mortality, will be tested at the two-sided 0.05 significance level.

10.4.3 Secondary and Other Efficacy Analyses
For continuous and ordinal outcomes, Wilcoxon rank-sum tests will be used to assess group differences. For binary and categorical outcomes, Pearson’s chi-square test or Fisher’s exact test will be used. Retention rates of the two groups will also be compared using chi-square test. All secondary/other efficacy analyses will be two-sided at the 0.05 level. A trend will be defined as a two-sided P-value of ≤ 0.20.

10.4.4 Population pharmacokinetic/pharmacodynamic modeling
Population pharmacokinetic/pharmacodynamic modeling will be employed to examine the effects of glyburide plasma levels on blood glucose and ECG parameters, including QT interval.
11 ADVERSE EVENT COLLECTING AND REPORTING

11.1 Adverse Event Collection

An adverse event (AE) is any symptom, sign, illness or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as adverse events. Abnormal results of diagnostic procedures are considered to be adverse events if the abnormality:

- results in study withdrawal, or
- is associated with a serious adverse event, or
- is associated with clinical signs or symptoms, or
- leads to additional treatment or to further diagnostic tests, or
- is considered by the investigator to be of clinical significance.

For this study, all AE’s whether reported, observed, or elicited by direct or indirect questioning will be recorded from the time of drug administration through Day 7 or discharge, whichever is earlier. Minimum information required for each AE includes type of event, duration (start and end dates), severity, seriousness, causality to Study Drug, action taken, and outcome.

All unresolved adverse events will be followed, whenever possible, until the events are resolved or stabilized, the subject is lost to follow-up, and/or it has been determined that the study treatment or participation in the study is not the cause. At the last scheduled assessment, the investigator should instruct each subject to report any subsequent event(s) that the subject, the LAR, or the subject’s personal physician, believes might reasonably be related to participation in this study.

Information on adverse events should be recorded in the source document, and also in the appropriate adverse event module of the CRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be grouped under one diagnosis in the CRF.

11.2 Adverse Event Reporting

11.2.1 Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be reported as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

11.2.2 Abnormal Laboratory Values

A clinical laboratory abnormality should be reported as an adverse event if the following conditions are met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality, and
- The abnormality suggests a disease and/or organ toxicity, and
- The abnormality is of a degree that requires active management; e.g. change of dose, discontinuation of the drug, more frequent follow-up assessments, further diagnostic investigation, etc.
However:
- Electrolyte imbalances that are asymptomatic and not considered clinically significant by the investigator should not be reported as AEs even if they are treated; and
- The following table defines which blood glucose values should be reported as AEs:

<table>
<thead>
<tr>
<th>BG Value</th>
<th>Report as AE?</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 70-79 mg/dL</td>
<td>Mandatory AE reporting not required; may be reported as an AE or an SAE if the event meets the protocol-defined definitions.</td>
</tr>
<tr>
<td>2 55-69 mg/dL</td>
<td>Must be reported as an AE if confirmed by lab value retest (not point of care); may be considered an SAE if it results in an AE that meets the protocol definition of serious.</td>
</tr>
<tr>
<td>3 &lt;55 mg/dL</td>
<td>Must be reported as an SAE if confirmed by lab value retest (not point of care).</td>
</tr>
</tbody>
</table>

11.2.3 Hospitalization, Prolonged Hospitalization or Surgery
Any adverse event that results in hospitalization or prolonged hospitalization, according to the judgment of the clinical investigator, should be documented and reported as a serious adverse event unless specifically instructed otherwise in this protocol.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an adverse event in the following circumstances:
- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should not be reported as an outcome of an adverse event if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

11.3 Evaluating Adverse Events
All AEs must be evaluated by the Investigator for severity and relationship to Study Drug.

11.3.1 Adverse Event Severity
Severity of AEs will be graded by the Investigator using the following criteria as guidelines:
1. Mild: Nuisance, barely noticeable. No medical intervention/therapy required.
2. Moderate: Uncomfortable, troublesome symptoms not significantly interfering with daily activities. No or minimal medical intervention/therapy required.
3. Severe: Symptoms significantly interfere with daily activities. Medical intervention/therapy required.
4. Life-threatening: Urgent intervention is indicated
5. Death
11.3.2 **Relationship to Study Drug**

The relationship of the AE to the Study Drug should be specified by the Investigator as Unrelated, Possibly/Probably related, and Definitely related.

When assessing the relationship of an AE to Study Drug, the Study Investigators and Sponsor should consider the following list of events that are anticipated in the stroke population, in the absence of Study Drug:

- Atrial fibrillation
- Brain death
- Cardiac arrest
- Cerebral edema
- Cerebral hemorrhage
- Recurrent (second) ischemic stroke
- Death
- Deep vein thrombosis
- Brain/brainstem herniation
- Hydrocephalus
- Myocardial infarction
- QT prolongation
- Pneumonia
- Pulmonary embolism
- Renal failure
- Seizures
- Sepsis
- Systemic hemorrhage
- Urinary tract infection

In patients who undergo decompressive craniectomy, the following are potential complications:

- surgical site infection
- hemorrhagic at operative site
- contralateral subdural effusion
- subdural hematoma
- sinking flap syndrome
- extra-axial hygroma
- hydrocephalus
- ventriculomegaly (asymptomatic)
- CSF fluid diversion (external drain)

11.4 **Serious Adverse Event Collection and Expedited Reporting**

All SAEs will be recorded through Day 90. SAEs disclosed through telephone interviews with LAR and/or subject will be recorded at 6 and 12 months.
A **serious adverse event** is any AE that is:

- fatal, or
- life-threatening, or
- requires or prolongs hospital stay, or
- results in persistent or significant disability or incapacity, or a congenital anomaly or birth defect, or
- an important medical event. Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, drug overdose or abuse, a seizure that did not result in in-patient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

11.4.1 Reporting of Serious Adverse Events

SAEs and unanticipated problems posing risks to subjects or others should be reported by the study sites within 24 hours of occurrence. Submission of an SAE report will trigger an alert to the Medical Safety Monitor.

Investigators are responsible for complying with local IRB reporting requirements. Copies of each report and documentation of IRB notification and receipt will be kept in the investigator’s study file.

The Sponsor will notify the FDA of any unexpected drug-related fatal or life-threatening experience as soon as possible but no later than 7 calendar days from Sponsor’s original receipt of the information. All other unexpected drug-related serious adverse events will be reported no later than 15 calendar days after Sponsor’s determination that the event qualifies for reporting.

If a previous adverse event that was not initially deemed reportable is later found to fit the criteria for reporting, the Sponsor will submit the adverse event in a written report to the FDA as soon as possible, but no later than 15 calendar days from the time the determination is made.
12 PROCEDURAL, REGULATORY, AND ETHICAL REQUIREMENTS

12.1 Subject Withdrawal

Subjects may voluntarily withdraw from the study at any time for any reason, and without prejudice to further treatment. Subject participation in the study may be terminated at any time at the discretion of the Investigator.

Possible reasons for discontinuation include, but are not limited to, the following:

- The subject’s health would be jeopardized by continued participation (e.g., the patient required restricted medication, or alternative treatment seems to be in the subject’s best interest.)
- Occurrence of a significant or intolerable clinical or laboratory adverse event that, in the opinion of the investigator, requires early termination.
- Withdrawal of subject/LAR consent. Subject withdrawal may occur any time the subject or LAR wishes to no longer continue with the study. Every attempt must be made to obtain information about the reason(s) for discontinuation, and any possible adverse events.
- Subject is randomized but does not receive study drug, due (for example) to insufficient time to prepare and administer study drug, or elevated liver enzymes at screening.

The date the subject is discontinued from the clinical investigation and the reason for discontinuation will be recorded in the case report form (CRF). Subjects whose study therapy is discontinued for any reason should be treated and followed according to established medical practice.

Whenever possible, the Day 30, Day 90 and 6 and 12 month assessments should be performed.

Note that if a site learns, while a patient is receiving Study Drug, that the patient had taken sulfonylureas within 7 days of study enrollment, this will not be a cause for automatic discontinuation of Study Drug, or of withdrawal from the study.

12.2 Data Monitoring Committee (DMC)

An independent DMC will meet at regular intervals to review partially unblinded study data provided by study statistician. The DMC may also provide the Sponsor with recommendations on study modification. The DMC will be comprised of individuals that are experienced in the care of stroke patients, and in the conduct of clinical trials. The frequency and format of DMC meetings, and the specific data and format of the data that will be reviewed, will be described in a DMC charter.

12.3 Adjudication Committee

An adjudication committee appointed by the Sponsor and comprising 1 to 3 members blinded to treatment group will assess/adjudge:

- Malignant edema through Day 7 or discharge, whichever is earlier. Malignant Edema is defined as:
  1) clinical signs of large middle cerebral artery (MCA) territory infarction with an NIHSS
score >18 and a level of consciousness of ≥1 on item 1a of the NIHSS after secondary deterioration; AND
2) large space-occupying MCA infarction on follow-up MRI or CT of at least two-thirds of the MCA territory with compression of ventricles or midline shift; AND
3) no other obvious cause for neurological deterioration.

- Cause of death through Day 7 or discharge, whichever is earlier.

- Hemorrhage type according to ECASS criteria (Hacke et al. 1995) i.e. HI types 1 and 2 and PH types 1 and 2. HI 1 is defined as small petechiae along the margins of the infarct while HI 2 represents more confluent petechiae within the infarcted area, but without space occupying effect. PH 1 is defined as blood clot not exceeding 30% of the infarcted area with some mild space-occupying effect, and PH 2 represents dense blood clot(s) exceeding 30% of the infarct volume with significant space occupying effect.

- Whether neurological worsening is the result of hemorrhage, edema, other, or unknown cause.

12.4 **Project Management**
The Sponsor will be responsible for project management of the Study.

12.5 **Data Management**
Data entry will occur at the enrolling sites and at the imaging center using a web-based data entry system, WebDCU™. Data quality assurance and analyses will be performed by the Data Coordinating Unit (DCU).

12.6 **Data Monitoring**
All aspects of the study will be monitored at regular intervals by qualified individuals designated by the Sponsor. Monitoring will be conducted in accordance with FDA and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines, and will be described in a Data Monitoring Plan. The investigators must agree to allow monitors, FDA, or other relevant health authorities to inspect facilities and records relevant to this study.

Safety monitoring, which will be described in a Safety Monitoring Plan, will include careful assessment and appropriate reporting of adverse events as noted above. Medical monitoring will include a regular assessment of the number and type of serious adverse events.

12.7 **Medical Safety Monitor (MSM)**
A medical monitor is required to review all unanticipated problems involving risk to subjects or others, serious adverse events and all deaths associated with the protocol.

12.8 **Institutional Review Board (IRB) Review and Informed Consent**
This protocol and the informed consent document and any subsequent modifications will be reviewed and approved by the IRB or ethics committee responsible for oversight of the study. A signed and dated consent form will be obtained from the subject or subject’s LAR.

Confidential. Remedy Pharmaceuticals, Inc.
12.9 **Record Retention**

Investigators must retain all study records required by the applicable regulations in a secure and safe facility. The investigator must consult with Sponsor before disposal of any study records, and must notify the Sponsor of any change in the location, disposition, or custody of the study files. All records are to be retained by the Investigator for at least 2 years after the United States Food and Drug Administration/local health authority approves the New Drug Application (NDA); or a minimum period of 2 years following the termination or withdrawal of the health regulatory agency exemption (e.g., Investigational New Drug (IND) or clinical trial application) under which the study was conducted, or for a period consistent with the record retention policies of the country where the study is being conducted. The Investigator must contact the Sponsor prior to the destruction of any study records, and in cases of accidental loss or destruction.

12.10 **Subject Confidentiality**

All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the site will be identified only by the Study Patient Number (SPN) to maintain subject confidentiality. All records will be kept in a locked file cabinet. All computer entry and networking programs will be done using SPNs only. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the IRB, the Sponsor or Sponsor’s designee, the FDA, or other relevant health authority representative.

12.11 **Study Modification/Discontinuation**

The study may be modified or discontinued at any time by the IRB, the Sponsor (Remedy Pharmaceuticals), the FDA, or other government agencies as part of their duties to ensure that research subjects are protected.

12.12 **Publication Of Research Findings**

Publication of the results of this trial will be at the discretion of the Lead Investigators. Any presentation, abstract, or manuscript will be made available for review by the Sponsor prior to submission. The results of the primary and secondary objectives will be posted on Clinicaltrial.gov.
13 REFERENCES


### Summary of Changes

A summary of changes other than minor edits is provided below:

<table>
<thead>
<tr>
<th>Location of Change</th>
<th>Description of Change</th>
<th>Reason for Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study Administration</td>
<td>Added GAMES-RP hotline number.</td>
<td>Hotline has been established.</td>
</tr>
<tr>
<td>1, 4, 4</td>
<td>Changed wording around Stage 1 so that 50 subjects can be enrolled and treated “per protocol”. The protocol allows for up to 60 subjects to be enrolled to yield these 50 “per protocol” subjects.</td>
<td>From a power perspective, it is important to have 50 evaluable subjects, treated per protocol.</td>
</tr>
<tr>
<td>1, 2.6.1, 3.3.1, 10.1.2</td>
<td>Removed “the need for”.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>1, 3.2, 10.1.2</td>
<td>Added “by day 7”.</td>
<td>Clarification, consistency throughout protocol.</td>
</tr>
<tr>
<td>1</td>
<td>Added “the effect... to placebo on”.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>1, 3.3, 10.1.2</td>
<td>Changed feeding tube placement to gastrostomy.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>1, 3.3, 10.1.2</td>
<td>Removed definition of NIHSS $\geq$ 4 points as early neurological deterioration.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>1, 3.3, 10.1.2</td>
<td>Added GRE.</td>
<td>An additional tertiary analysis</td>
</tr>
<tr>
<td>1, 3.3</td>
<td>Changed “sooner” to “earlier”.</td>
<td>Consistency.</td>
</tr>
<tr>
<td>1</td>
<td>Removed “standard of care” prior to MRI.</td>
<td>Enrolling MRI may not always be standard of care.</td>
</tr>
<tr>
<td>1</td>
<td>Clarified follow up MRA as head only.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>4</td>
<td>Changed 12 to 15 sites.</td>
<td>Flexibility to recruit at additional sites.</td>
</tr>
<tr>
<td>4 (Figure 1)</td>
<td>Updated to reflect changes to protocol and include BG monitoring.</td>
<td>To reflect protocol changes and clarify BG monitoring.</td>
</tr>
<tr>
<td>5.1.1</td>
<td>Clarified language to indicate that MCA plus PCA and/or ACA is acceptable.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>5.1.2, 7.2.1</td>
<td>Removed reference to mRS, focusing instead on general disability level prior to stroke.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>5.2.2</td>
<td>Removed hypothermia</td>
<td>While hypothermia is not proven, it</td>
</tr>
<tr>
<td>Location of Change</td>
<td>Description of Change</td>
<td>Reason for Change</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>5.2.4</td>
<td>Added exclusion for bilateral infarcts.</td>
<td>Exclusion added to prevent futile cases from being enrolled.</td>
</tr>
<tr>
<td>5.2.5 (old 5.2.4)</td>
<td>Clarified that ≥ 2 on item 1a on the NIHSS is only an exclusion when related to edema</td>
<td>Clarification.</td>
</tr>
<tr>
<td>5.2.6 (old 5.2.5)</td>
<td>Added “brain”.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>5.2.8 (old 5.2.7)</td>
<td>Changed the ALT/AST exclusion to ALT &gt; 3 times ULN.</td>
<td>AST is not specific to liver and should not be used as a liver injury exclusion. 3 X ULN is an accepted cutoff for ALT – 2 X is considered unnecessarily restrictive.</td>
</tr>
<tr>
<td>5.2.8 (old 5.2.7)</td>
<td>Allowed randomization BUT NOT TREATMENT of a subject prior to establishing enzyme levels.</td>
<td>A logistical improvement – prevents delays due to getting liver enzymes from affecting enrollment while still requiring that the criteria be met in order to treat.</td>
</tr>
<tr>
<td>5.3.3</td>
<td>Changed “initial” to “baseline”.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>5.3.3</td>
<td>Removed specific reference to IVRS.</td>
<td>Randomization will be by IVRS or web.</td>
</tr>
<tr>
<td>6.1.3</td>
<td>Modified Study Drug interruption duration ranges so they are always “greater than or equal to” on the lower end and “less than” on the upper end.</td>
<td>Minor correction.</td>
</tr>
<tr>
<td>6.1.4</td>
<td>Added allowed administration sets.</td>
<td>Administration sets with similar compositions to those initially tested are now allowed.</td>
</tr>
<tr>
<td>6.2.2</td>
<td>Removed hypothermia.</td>
<td>Hypothermia will be standardized in the clinical guidelines in the same way as DC is.</td>
</tr>
<tr>
<td>6.2.2</td>
<td>Removed use of glucocorticoids</td>
<td>The use of glucocorticoids will be standardized in the clinical guidelines in the same way as DC is.</td>
</tr>
<tr>
<td>6.3.3, 6.3.5, 8.1</td>
<td>Added alternatives to D50W.</td>
<td>There are intermittent D50 shortages so the range of concentrations was widened.</td>
</tr>
<tr>
<td>7.1, 7.2.3, 7.3.7</td>
<td>Added neurological deterioration evaluation.</td>
<td>For completeness.</td>
</tr>
<tr>
<td>7.1</td>
<td>Added Carbohydrate evaluation.</td>
<td>For completeness.</td>
</tr>
<tr>
<td>7.1</td>
<td>Removed pre-morbid mRS assessment.</td>
<td>Disability assessment is part of the inclusion/exclusion criteria assessment.</td>
</tr>
<tr>
<td>Location of Change</td>
<td>Description of Change</td>
<td>Reason for Change</td>
</tr>
<tr>
<td>--------------------</td>
<td>------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>7.1, 7.2.3, 7.2.4</td>
<td>Added “approximately” for vital signs. Allow q8 if discharged from ICU.</td>
<td>To comply with the standard of care.</td>
</tr>
<tr>
<td>7.1, 7.2.3</td>
<td>Allow ECG and PK to be captured in 4-6 instead of 5-6 hours.</td>
<td>A wider window is provided to accommodate the difficulty in collecting these at what may be the early hours of the morning.</td>
</tr>
<tr>
<td>7.1</td>
<td>Added text to the AE/SAE footnote.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>7.2.1</td>
<td>Added text to allow a protocol-specified MRI to be performed for enrollment if the standard of care MRI DWI is “close” to 82cm³ or, at sites that do PWI as standard of care, there is a large PWI volume and a medium DWI volume.</td>
<td>To allow rescanning of the patients to see if the lesion meets inclusion criteria at a slightly later timepoint – to facilitate enrollment.</td>
</tr>
<tr>
<td>7.2.1, 7.2.3, 7.2.4</td>
<td>Edits to safety labs.</td>
<td>To standardize with later text. Also, CBC includes platelet count.</td>
</tr>
<tr>
<td>7.2.2</td>
<td>Added text re: starting Study Drug after confirming ALT and Bilirubin meet required thresholds.</td>
<td>See note related to 5.2.8.</td>
</tr>
<tr>
<td>7.2.3</td>
<td>Clarified that the follow up MRI must follow the imaging protocols in the Imaging Manual. It is not important that the same scanner is used.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>7.2.4</td>
<td>Inserted text about capturing cholesterol and drug screen tests, if done.</td>
<td>For completeness.</td>
</tr>
<tr>
<td>7.2.4, 7.3.5</td>
<td>Harmonized con procedures and therapies with con meds, other than tracheostomy and gastrostomy which are captured at discharge.</td>
<td>Standardization.</td>
</tr>
<tr>
<td>7.3.6</td>
<td>Added that testing for hemolytic anemia is per clinician’s judgment.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>7.3.6, 9.2</td>
<td>Added “twelve lead”.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>7.3.7, 12.3</td>
<td>Moved assessment of malignant edema from site to adjudicators.</td>
<td>For consistency.</td>
</tr>
<tr>
<td>7.3.7</td>
<td>Added “prior to Day 7 or discharge” phrase to DC.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>7.3.7</td>
<td>Added text to lost to follow up description.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>7.3.8</td>
<td>Removed ABC/2 instructions</td>
<td>A detailed worksheet is provided</td>
</tr>
<tr>
<td>7.3.8</td>
<td>Removed requirement for site to comment on scans.</td>
<td>Adjudication committee does not require this, and deterioration is captured in the neurological deterioration assessment.</td>
</tr>
<tr>
<td>7.3.9</td>
<td>Moved PK/PD to statistical section.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>7.3.9, 7.3.10</td>
<td>Changed to “PK and Biomarker Study”</td>
<td>The manual is combined PK and</td>
</tr>
<tr>
<td>Location of Change</td>
<td>Description of Change</td>
<td>Reason for Change</td>
</tr>
<tr>
<td>-------------------</td>
<td>-----------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>7.3.11</td>
<td>Added section on unblinding.</td>
<td>Previously omitted from protocol.</td>
</tr>
<tr>
<td>8</td>
<td>Modified wording in regards to contacting MSM.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>8.4</td>
<td>Removed AST as a stopping rule and changed the ALT to 8 X ULN.</td>
<td>AST is not specific to liver damage; 8 X is a more usual stopping threshold.</td>
</tr>
<tr>
<td>9.1, 12.3</td>
<td>Removed brain hemorrhage from central readings and moved to adjudicators.</td>
<td>This will be determined by adjudicators, not central readers.</td>
</tr>
<tr>
<td>9.1.2</td>
<td>Added CT. Added DWI if FLAIR not available.</td>
<td>Midline shift can accurately be measured on MRI (FLAIR or DWI) or CT.</td>
</tr>
<tr>
<td>9.1.3</td>
<td>Added ability to use DWI if FLAIR is not available.</td>
<td>In case the DWI is not of acceptable quality.</td>
</tr>
<tr>
<td>9.1.4</td>
<td>Added ACA/PCA.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>9.1.5</td>
<td>Add other analyses.</td>
<td>Exploratory analyses have been added.</td>
</tr>
<tr>
<td>10.2-10.4</td>
<td>Various statistical changes.</td>
<td>Clarifications, simplifications.</td>
</tr>
<tr>
<td>11.2</td>
<td>Added specifics on defining BG-related AE’s and electrolyte AE’s.</td>
<td>Clarification for consistency.</td>
</tr>
<tr>
<td>11.3.2</td>
<td>Added QT prolongation.</td>
<td>QT prolongation is a common event in severe stroke.</td>
</tr>
<tr>
<td>11.4.1</td>
<td>Removed the requirement for SAE reporting to be by WebDCU.</td>
<td>Flexibility in the event of problems with WebDCU.</td>
</tr>
<tr>
<td>12.1</td>
<td>Added wording on withdrawal from study</td>
<td>Clarification</td>
</tr>
<tr>
<td>12.3</td>
<td>Added through day 7 or discharge phrasing to Cause of death.</td>
<td>Clarification</td>
</tr>
<tr>
<td>12.3</td>
<td>Tightened up how to score the relationship between neurological worsening and the various potential clauses.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>12.3</td>
<td>Removed the need to adjudicate adherence to DC guidelines.</td>
<td>Adjudicators not in a position to adjudicate this, and it has limited value.</td>
</tr>
</tbody>
</table>
# SCHEDULE 2 – VERSION 3 REVISIONS

## SUMMARY OF PROTOCOL REVISIONS

**Protocol History:**
- Version 1, 9 January 2013
- Version 2, 2 October 2013
- Version 3, 19 November 2013

### Summary of Changes

A summary of changes other than minor edits is provided below:

<table>
<thead>
<tr>
<th>Location of Change</th>
<th>Description of Change</th>
<th>Reason for Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Synopsis, 4, 5.1.</td>
<td>Changed maximum age to 80 years.</td>
<td>To facilitate recruitment.</td>
</tr>
<tr>
<td>Synopsis, 5.1, 7.2.1, 10.4.1</td>
<td>Changed maximum lesion size to 300 cm³</td>
<td>To facilitate recruitment. Reviewed Vahedi et al. 2007 and determined that for untreated patients infarct volumes beyond 210 cm³ portend a dire prognosis; however, this was modified by treatment with DC, with the majority of subjects with &gt;210 cm³ lesions who underwent DC surviving. Since RP-1127 may reduce the requirement for DC, it is not automatically futile to treat these patients and so they are now included. Introduced a cap of 300 cm³ to exclude the very largest lesions.</td>
</tr>
<tr>
<td>4</td>
<td>Changed 15 to 20 sites.</td>
<td>Flexibility to recruit at additional sites in order to facilitate recruitment.</td>
</tr>
<tr>
<td>4</td>
<td>Limited the number of subjects 76-80 to 10 in Stage 1.</td>
<td>In the event there is an interaction between advanced age and outcome, this will prevent excessive impact of such an interaction.</td>
</tr>
<tr>
<td>7.1</td>
<td>Added Day 4 assessment for Neurological Deterioration</td>
<td>Correction – is now consistent with footnote and protocol.</td>
</tr>
<tr>
<td>7.1</td>
<td>Changed footnote “m” describing first biomarker assessment to 4-6 hours.</td>
<td>Correction – is now consistent with PK draws.</td>
</tr>
<tr>
<td>7.1, 7.3.5</td>
<td>Changed osmotherapy (mannitol and hypertonic saline) to be recorded through discharge on its own CRF.</td>
<td>Osmotherapy may in rare cases be administered beyond 7 days and given the focus of the protocol on edema formation, it will be helpful to record all uses of osmotherapy. Clarified that osmotherapy is captured in a separate CRF to other concomitant medications.</td>
</tr>
<tr>
<td>Location of Change</td>
<td>Description of Change</td>
<td>Reason for Change</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------------------------------------------------</td>
<td>--------------------------------------------------------</td>
</tr>
<tr>
<td>7.2.4</td>
<td>Added “neurological deterioration assessment”</td>
<td>Correction – is now consistent with schedule of events.</td>
</tr>
</tbody>
</table>
16 SCHEDULE 3 – VERSION 4 REVISIONS

SUMMARY OF PROTOCOL REVISIONS

Protocol History:  
Version 1, 9 January 2013  
Version 2, 2 October 2013  
Version 3, 19 November 2013  
Version 4, 19 December 2013

Summary of Changes

A summary of changes other than minor edits is provided below:

<table>
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</tr>
</thead>
<tbody>
<tr>
<td>5.1, 5.3.2, 7.3.1, 12.8</td>
<td>Determination of whether consent by a LAR is required is determined by state law and local IRB requirements.</td>
<td>Some subjects may be able to self-consent.</td>
</tr>
<tr>
<td>5.2</td>
<td>Patients on bosentan within 7 days of stroke may not be enrolled.</td>
<td>Coadministration of glyburide and bosentan is contraindicated. Given the short half-life of bosentan (5 hours), bosentan would be eliminated well within 7 days.</td>
</tr>
<tr>
<td>6.2.2</td>
<td>Bosentan must not be administered until 24 hours after Study Drug administration is halted.</td>
<td>Co-administration of glyburide and bosentan is contraindicated. Given the short half-life of intravenous glyburide (4 hours), 24 hours is sufficient time to substantially reduce or eliminate plasma glyburide.</td>
</tr>
</tbody>
</table>
**Summary of Changes**

A summary of changes other than minor edits is provided below:

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Front page, 1; 2.6.2; 4; 10.2; 10.4.1; 12.2</td>
<td>References to “Two stage” design deleted; description of two stage design deleted and replaced with a single primary analysis once all 83 enrolled and treated patients complete their 90 day follow up; Powering changed from 20% to 30%; References to the interim analysis and its review by the DSMB were removed.</td>
<td>Due to administrative reasons, study enrollment was stopped prior to the interim analysis, after 83 subjects were enrolled and treated. No interim analysis was performed. The design was changed to conduct only a single analysis once all subjects completed the Day 90 evaluation with no unblinding prior to this analysis. With this number of subjects, the study has 80% power when the true placebo response rate is 30% and the true RP-1127 response rate is 60% (a 30 percentage point effect size) using a two-sided test. Although the detectable different (30%) is larger than originally stated (20%), it is still considerably smaller than observed with preliminary data (see Section 2.6.1). The decision was not related to safety or any knowledge of outcomes (the study team and sponsor remain blinded per the protocol), but rather was made for administrative reasons. Per the original plan, further analyses will take place when 6 month and 12 month follow up data becomes available for all subjects.</td>
</tr>
<tr>
<td>10.4.1</td>
<td>The “per protocol” analysis was made the primary analysis and the definition of per protocol was loosened to</td>
<td>Given the smaller sample size of the revised design, the “per protocol” analysis, which is expected to be more</td>
</tr>
<tr>
<td>Location of Change</td>
<td>Description of Change</td>
<td>Reason for Change</td>
</tr>
<tr>
<td>--------------------</td>
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</tr>
<tr>
<td>include subjects treated beyond 10 hours 15 minutes.</td>
<td>include subjects treated beyond 10 hours 15 minutes.</td>
<td>homogenous than the “intention to treat” analysis was chosen as the primary analysis and patients treated beyond 10 hours were included to maximize the sample size.</td>
</tr>
<tr>
<td>10.4.1</td>
<td>The WALD test was replaced with the Likelihood ratio test.</td>
<td>Given the smaller sample size of the new design, the Likelihood ratio test was selected as it performs better than WALD in small samples.</td>
</tr>
<tr>
<td>1; 3.2; 10.1.2; 10.4.3</td>
<td>List of secondary objectives reduced. Introduced shorter-term secondary endpoints that are more proximal to the initial event and related to the anticipated mechanism of action. Previous Secondary and Tertiary endpoints moved into Statistical Analysis Plan.</td>
<td>Given the smaller sample size of the new design, secondary outcome measures more closely aligned to the expected mechanism of action and temporally closer to the initial stroke were introduced.</td>
</tr>
<tr>
<td>9.1.2</td>
<td>A more detailed description of measuring midline shift was introduced.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>9.1.3</td>
<td>Clarified that volume calculations are to be performed on DWI sequences.</td>
<td>Clarification.</td>
</tr>
<tr>
<td>9.1.4</td>
<td>Details of how to measure lesional swelling (introduced as a secondary outcome measure) were included.</td>
<td>To accommodate introduction of lesional swelling as an outcome measure.</td>
</tr>
</tbody>
</table>