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TAKE CLOSER LOOK AT TRIALS

Glyburide Advantage in Malignant Edema and Stroke (GAMES-RP) Trial: Rationale and Design

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Abstract
Background Patients with large territory infarction are at high risk of cerebral edema and neurological deterioration, including death. Preclinical studies have shown that a continuous infusion of glyburide blocks edema formation and improves outcome. We hypothesize that treatment with RP-1127 (Glyburide for Injection) reduces formation of brain edema in patients after large anterior circulation infarction.
Methods GAMES-RP is a prospective, randomized, double-blind, multicenter trial designed to evaluate RP-1127 in patients at high risk for the development of malignant cerebral edema. The study population consisted of subjects with a clinical diagnosis of acute severe anterior circulation ischemic stroke with a baseline diffusion-weighted image lesion between 82 and 300 cm^3 who are 18–80 years of age. The target time from symptom onset to start of study infusion was $\leq$10 h. Subjects were randomized to RP-1127 (glyburide for injection) or placebo and treated with a continuous infusion for 72 h.
Results The primary efficacy outcome was a composite of the modified Rankin Scale and the incidence of decompressive craniectomy, assessed at 90 days. Safety outcomes were the frequency and severity of adverse events, with a focus on cardiac- and glucose-related serious adverse events.
Conclusions GAMES-RP was designed to provide critical information regarding glyburide for injection in patients with large hemispheric stroke and will inform the design of future studies.

Keywords Ischemic stroke · Cerebral edema · Malignant infarction · Large stroke · Clinical trials · MRI

The GAMES-RP Study Team members are listed in the Appendix.

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Introduction

Ischemic stroke afflicts 700,000 people in the United States annually and is the fifth leading cause of death [1]. Life-threatening edema ["malignant edema" or "malignant middle cerebral artery (MCA) infarction"] is a complication in up to 10 % of hospitalized stroke victims, and most commonly occurs in large strokes [2]. Such swelling can compromise arterial inflow to surrounding tissues causing further ischemic damage and frequently results in brain

herniation and death [3]. Clinical characteristics include a disturbance of consciousness and further clinical signs of brain herniation. The prognosis for these patients is frequently poor, with case fatality being as high as 60–80 % [2, 4]. Decompressive craniectomy (DC) has improved the bleak outlook for these patients, and reduced mortality to 22 % in pooled analyses of DC studies [5]. However, numerous factors limit the usefulness of DC, including limited eligibility for surgery, and reduced efficacy of DC in patients >60 years of age [6]. Moreover, from a physiological standpoint, preventing swelling is preferable to decompressing the already swollen brain [7]. There is a clear and urgent need for innovative nonsurgical medical strategies to reduce edema formation in patients with a large stroke.

Glyburide (5-chloro-*N*-(4-[*N*-(cyclohexylcarbamoyl)-sulfamoyl]phenethyl)-2-methoxybenzamide) is an antidiabetic sulfonylurea medication that inhibits the action of the sulfonylurea receptor 1 (SUR1) and adenosine triphosphate (ATP)-sensitive potassium channels in pancreatic beta cells], leading to the release of insulin. An analogous channel complex composed of SUR1-Transient Receptor Potential Melastatin-4 (TRPM4) is a nonselective cation channel that is expressed in the central nervous system under conditions of ischemia, hypoxia, and trauma [8–10]. Channel opening, which is triggered by depletion of ATP, results in the unregulated flow of ions leading to edema and oncotic cell death [10, 11]. Like the KATP channel in pancreatic beta cells, the SUR1-TRPM4 channel is regulated by SUR1 and is blocked by sulfonylureas such as glyburide. In preclinical models of malignant infarction, glyburide prevents the development of edema and reduces secondary damage with treatment delays of up to 10 h following stroke [12].

In order to translate these findings into clinical practice, we completed GAMES-Pilot, a phase IIa open label study of 10 subjects with large anterior circulation ischemic stroke at high risk of malignant edema and poor outcome [13, 14]. Drug administration was safe and well tolerated, and compared to historical controls, mortality and functional outcomes were improved [13, 14]. We now describe the design of a phase II clinical trial, underline the rationale, and present the primary components of the statistical plan.

Methods

Design

GAMES-RP was designed as a randomized, multicenter, double-blind, and phase II trial of RP-1127 in subjects with a severe anterior circulation ischemic stroke who were likely to develop malignant edema. The GAMES-RP Protocol is included in Supplemental Table 1.

The primary objective was 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, and to provide information for the design of a phase III multicenter trial. 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 DC. The primary safety objective was to assess the safety of RP-1127 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 comparing the frequencies and severities of Adverse Events and Serious Adverse Events, with a specific focus on all-cause mortality, cardiac mortality, and cardiac-related and blood glucose-related safety outcomes. Additional secondary objectives explore the efficacy of RP-1127 on neurological deterioration attributable to cerebral edema, including early death, DC, and imaging evidence of swelling. The GAMES-RP trial is registered with clinicaltrials.gov (NCT0179482).

Patient Population

Eligibility criteria are presented in Table 1. Eligible subjects had a clinical diagnosis of acute severe anterior circulation ischemic stroke, a baseline diffusion-weighted image (DWI) lesion between 82 and 300 cm^3, 18–80 years of age, and time from symptom onset to start of study infusion of ≤10 h. The baseline stroke lesion volume, a key eligibility criterion for predicting risk of malignant edema [15], was calculated in real time using the ABC/2 method to minimize time delays [16]. Stroke volume was later calculated on DWI using computer-assisted manual segmentation techniques using Analyze 11.0 (Mayo Clinic). The standard for Per Protocol inclusion was the volumetric measurement. Although intravenous rtPA-treated were eligible to participate, endovascular thrombectomy patients were not, since this treatment was considering investigation at the start of the trial and efficacy in large strokes was not established [17]. Furthermore, available evidence suggested that endovascular reperfusion in large infarction may be detrimental [18].

Rationale for Treatment Window of 10 h

In human patients, midline shift usually becomes measurable at 16 h [2, 19]. Our strategy was to achieve steady-state drug levels prior to significant brain swelling. Furthermore, the inducible SUR1-TRPM4 channel becomes manifest as early as 3–4 h, but increasingly upregulated over 8 h in rats

Table 1 Inclusion and exclusion criteria for the GAMES-RP trial

Inclusion criteria
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)
Prior to stroke, no significant disability (able to carry out all usual duties and activities)
A baseline DWI lesion between 82 and 300 cm^3 on MRI
Patients treated with IV rtPA should meet established criteria for IV rtPA administration in the 0–3- and 3–4.5-h time periods at the time of rtPA administration (if rtPA is administered in the 3–4.5-h time window, the NIHSS must be $\leq$25 at the time of rtPA administration)
The time to the start of infusion of Study Drug must be $\leq$10 h after time of symptom onset, if known, or the time last seen well [termed "time last known at neurologic baseline" (TLK@B)]
Age $\geq$18 and $\leq$80 years
Provision of written informed consent by patient or a legally authorized representative
Exclusion criteria
Commitment to decompressive craniectomy (DC) prior to enrollment, or following enrollment and prior to start of Study Drug
Treatment with intra-arterial (IA) rtPA or by mechanical means for clot disruption.
Patients unable to tolerate MRI scanning, e.g., those with pacemakers or automatic defibrillators
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
Clinical signs of herniation, e.g., one or two dilated, fixed pupils; unconsciousness (i.e., $\geq$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
Brain hemorrhage (other than small petechial hemorrhages) on CT/MRI, or CT/MRI evidence of anteroseptal/pineal shift greater $\geq$2 mm prior to enrollment that is due to cerebral edema
Severe renal disorder from the patient's history (e.g., dialysis) or eGFR of $<$30 mL/min/1.73 m^2
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 $\leq$3 times upper limit of normal and bilirubin $\leq$2 times upper limit of normal)
Blood glucose $<$55 mg/dL at enrollment or immediately prior to administration of study. Drug, or a clinically significant history of hypoglycemia
Acute ST elevation myocardial infarction, and/or acute decompensated heart failure, and/or *Tc* $>$ 520 ms, and/or known history of cardiac arrest (PEA, VT, VF, asystole), and/or admission for an acute coronary syndrome, myocardial infarction, or coronary intervention within the past 3 months
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)
Known treatment with bosentan within 7 days
Known allergy to sulfa or specific allergy to sulfonylurea drugs
Known G6PD enzyme deficiency
Pregnant women. Women must be either postmenopausal (as confirmed by the LAR), permanently sterilized or, if $\leq$50 years old must have a negative test for pregnancy obtained before enrollment
Breast-feeding women who do not agree (or their LAR does not agree) to stop breastfeeding during Study Drug infusion and for 7 days following the end of Study Drug infusion
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 followup
Patients currently receiving an investigational drug
Patients in whom a peripheral IV line cannot be placed
Mentally incompetent (prior to qualifying stroke) patients and wards of the state
Patients who, in the opinion of the investigator, are not suitable for the study (reason to be documented)

via sequential gene activation, consistent with an extended treatment window that is physiologically based [12]. Preclinical data show that the treatment window for glyburide extends to 10 h [20], and in the GAMES Pilot study, subjects treated with RP-1127 as late as 10 h appeared to benefit [13]. A 10-h window would have a meaningful public health impact, and all site investigators were urged to begin study drug as soon as possible after stroke onset.

Rationale for Lesion Size

The use of a high-specificity predictor of significant edema after ischemia is a cornerstone of the GAMES-RP design. The prevention of edema is the primary anticipated mechanism of protection of RP-1127. Therefore, targeting a population where clinically significant swelling is likely to be very common should maximize the likelihood of observing a beneficial effect of the intervention. We use 82 cm^3 to identify patients at high risk of malignant infarction (positive predictive value, 0.88), as it is the only high-specificity DWI threshold that has been prospectively verified [15]. Vahedi et al. 2007 report that for patients not undergoing DC, infarct volumes beyond 210 cm^3 portend a dire prognosis; however, this was modified by treatment with DC, with the majority of subjects with >210 cm^3 lesions who underwent DC surviving [5]. Since RP-1127 may reduce the requirement for DC, it may not be futile to treat these patients. However, an upper limit of the baseline lesion volume was set at 300 cm^3 to exclude the very largest lesions, in which treatment is likely to be futile.

Rationale for Exclusion of Subjects Exposed to Endovascular Therapy

Evidence suggests that intra-arterial therapy (IAT) is futile in patients with large DWI lesion volumes. Yoo et al. demonstrated that patients with a baseline DWI volume >70 cm^3 had a poor outcome, despite a 50 % recanalization rate [21]. Furthermore, when early reperfusion was achieved in patients with a DWI volume ≥ 70 cm^3, it was not associated with better outcome [18]. PH1/PH2 rates in these patients were 44 % [18]. These data suggest that IAT above the GAMES DWI threshold of 82 cm^3 is unlikely to be beneficial. Since our protocol requires a baseline MRI to be performed prior to enrollment, site investigators will be aware of the DWI volume. Clinical sites have been selected for their ability to consistently obtain screening MRI's and their willingness, as standard of care, to defer IA in patients with large DWI lesions.

Randomization and Treatment

A centralized, web-based 1:1 randomization process was employed. Enrollment was controlled for site, age ≤ 60, and IV rtPA treatment at baseline using a combination of minimization and biased coin. The bolus and the infusion concentrations of the study drug were both 5.3 μg/mL. In order to rapidly achieve a steady-state concentration, a 24 bolus injection was given over approximately 2 min. A daily infusion followed at a rate of 31 mL/h for the first 6 h and then 21 mL/h for the remaining 66 h, for a total of infusion period of 72 h.

An overview of the study flowchart is presented in Fig. 1. Neurologicallogic statuses were assessed at enrollment and at 24, 48, 72 h and 7 days (or discharge). Electrocardiograms were obtained at baseline, 6 h after study drug bolus, and at 24, 48, 72 h, and 7 days. Blood glucose levels were measured every hour during the first 24 h with the increasing increments to every 4 h in the absence of any decline below 70 mg/dL. Vital signs were monitored frequently during the infusion period. Safety labs were assessed through Day 7. A study-specific MRI was obtained at 72–96 h poststroke.

Study participants receive standard of care therapy for stroke, intensive care, and other appropriate therapy according to clinical standardization guidelines (Supplemental Table 2) developed by a multidisciplinary team of vascular and critical care neurologists, emergency physicians, and neurosurgeons, based on guidelines from the American Heart Association/American Stroke Association [3]. Avoidance of hyponatremia was encouraged, and continuous 3 % saline infusions were permitted for this purpose. Bolus osmotherapy was reserved for clinical deterioration or radiological evidence of significant midline shift and/or mass effect. DC was performed if there was evidence of clinical deterioration due to mass effect, including a decrease in the level of arousal [5].

Outcome Assessments

As a phase II trial, GAMES-RP was designed with both clinical and imaging outcomes to provide information about mechanism of action and relevant clinical outcomes. Subjects were followed for 90 days, with additional follow-up extending for 1 year. The mRS was assessed at Day 30, Day 90 (the primary end-point), and at 6 and 12 months. The Barthel Index was assessed at similar time points. Beck depression inventory (BDI-II) and EuroQoL 5-D were assessed at Day 90 and at 6 and 12 months.

In patients with malignant edema, a mRS of 0-4 is widely defined in studies as a "good" or "favorable" outcome [5, 18, 22]. While a mRS of 4 is defined as "moderately severe disability," a recent systematic review [23] suggests that, despite a high proportion of patients left with mRS 4 (46.8 %) following DC, 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.

In addition, if RP-1127 is effective, it would be expected to reduce the incidence of DC by reducing edema formation and tissue displacement. DC has been shown to increase the incidence of mRS of 0–4 in patients with malignant edema, but not the proportion of patients with mRS of 0–3 [5]. The prevalence of DC per 10,000

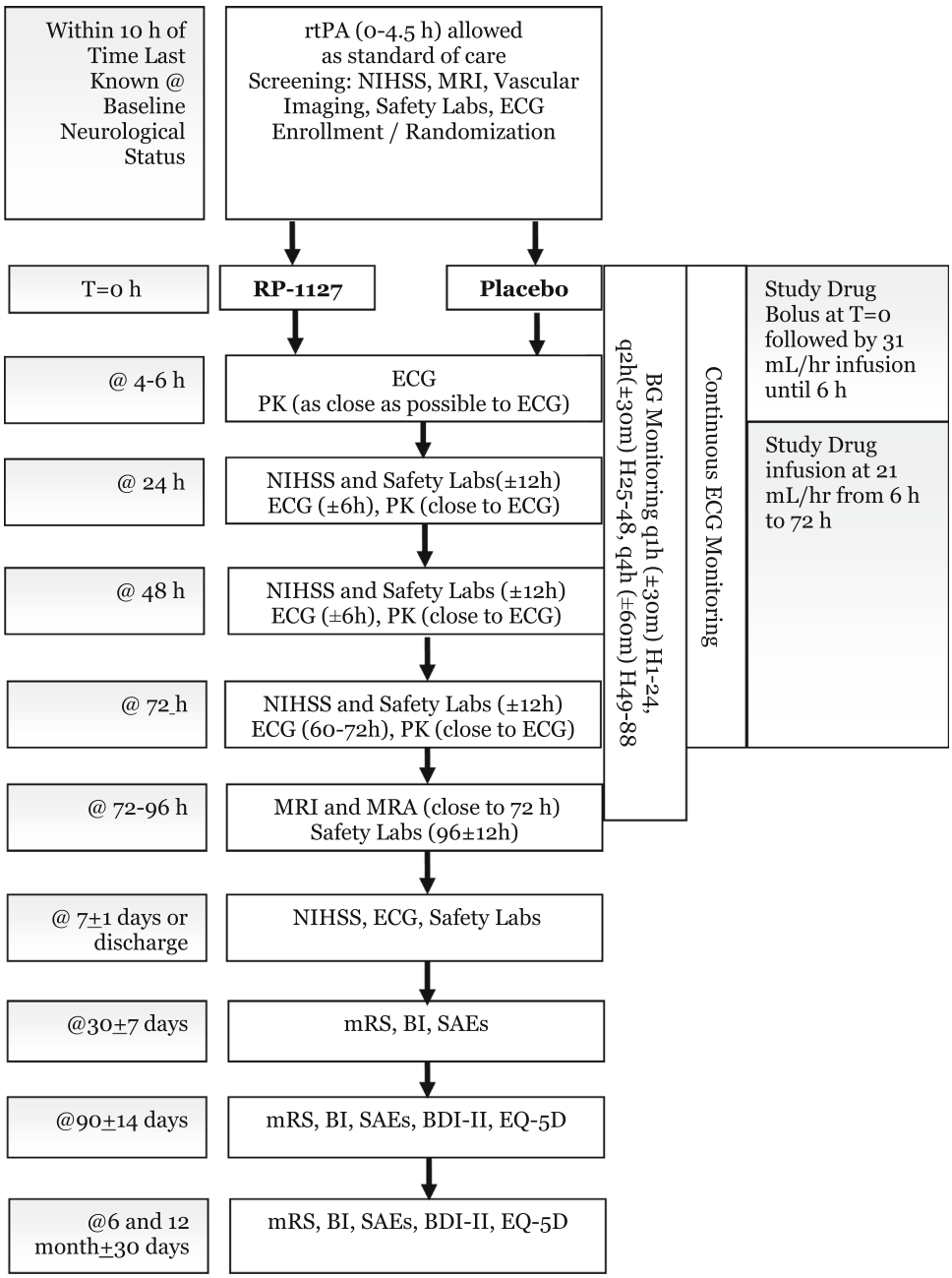

Fig. 1 Overview of study procedures

hospitalizations for ischemic stroke is low but has risen from 3.86 in 1999 to 14.46 in 2008 [24]. Thomalla et al. 2010 found that 55.6 % of patients developing malignant edema underwent DC [15]. For these reasons, DC is a potential confounding factor in interpreting the effect of RP-1127 on the proportion of subjects with mRS of 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. Thus, in GAMES-RP, a "responder" is defined as a subject that has a "good" or "favorable" outcome and does not require DC to attain such an outcome.

A study-specific MRI was performed at 72–96 h. The baseline and follow-up MRIs, MR angiography (MRA) as well as all computerized tomography (CT) and CTA studies through day 7 are sent to the central imaging core. Blinded evaluators performed measurement of the key secondary imaging outcomes that are surrogate measures of brain edema, including the changes in hemisphere volume [25] and swelling volume [26]. In brief, for hemisphere volumes, the entire outline of the hemisphere ipsilateral to the stroke will be outlined at baseline and at follow-up, and a volume will be derived. The change in hemisphere volume will be the difference between these two volumes. For swelling volume, baseline and follow-up diffusion-weighted images

(DWI) will be coregistered within each subject. The baseline and follow-up lesional will be outlined using region-of-interest (ROI) maps. The ROIs will then be superimposed on each other. The difference in lesional volumes will be assigned to infarct growth, hemorrhage, or edema using slice-by-slice review in three orthogonal planes. Each subject's assignments will be reviewed by two members, with final assignment decided by consensus. Additional exploratory analyses that assess blood–brain barrier breakdown by neuroimaging [27] and circulating level of matrix metalloproteinase-9 [27, 28] are prespecified.

Posttreatment follow-up was performed in person or by telephone to assess subject status, adverse events, and clinical outcomes at day 30, 90, and at 6 and 12 months.

Statistical Analyses

The study was initially planned with a two-stage design. Enrollment was stopped by the sponsor prior to a planned interim analysis, after 83 subjects were enrolled and treated. This decision, as well as the development of the final statistical analysis plan, were made prior to any unblinding or knowledge of treatment assignment by the sponsor, leadership team, neuroimaging core, and the primary statistician. There were no safety considerations and the decision to cease enrollment was made after consultation with and approval from the independent data-monitoring committee. Accordingly, the design was changed to a single analysis once all subjects completed the Day 90 evaluation with no unblinding until all subjects had reached this endpoint. 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 with alpha 0.05.

Efficacy

The primary outcome will compare the proportion of "responders" in the RP-1127-treated group to the placebo group. A "responder" is defined as a patient with a Day 90 mRS of $\leq$4 without DC.

The primary efficacy analysis will be conducted when all patients have completed the Day 90 assessment. A logistic model will be fit which will include terms for treatment group, baseline age (continuous), baseline DWI volume (continuous), and baseline ICA occlusion (categorized as complete, partial, none, or unknown'). The likelihood ratio test will be used to test the null hypothesis that $H_0 : \beta_1 = 0$ versus $H_1 : \beta_1 \neq 0$, where β_1 is the regression coefficient for $x_1 =$ treatment assignment (0 = placebo, 1 = RP-1127) in a logistic model that also includes baseline covariates. The analysis will be tested using a two-sided significance test with alpha 0.05. The adjusted odds ratio and 95 % CI will be reported.

Safety

The primary safety analysis will be conducted when all patients have completed the Day 90 assessment. To assess the safety of RP-1127 compared with placebo, all adverse events and serious adverse events, including deaths, will be summarized by body systems in terms of frequency, severity, and relatedness to the study drug using the MedDRA codes. Of specific focus is all-cause mortality, cardiac mortality, and cardiac-related and blood glucose-related AEs/SAEs. Frequencies of adverse events will be compared using Chi-square tests or Fisher's exact tests. All safety analyses, including mortality, will be tested at the two-sided 0.05 significance level.

A cornerstone of the GAMES Pilot and GAMES-RP designs was to target patients who are at the highest risk for developing malignant edema after stroke, based on initial infarct volume. Baseline infarct volume is a highly specific predictor for the development of subsequent malignant edema [15]. For this reason, the primary analysis includes subjects whose baseline infarct volume meet the prespecified lesion inclusion criterion (82–300 cm^3), as determined by the blinded, central core imaging laboratory. Further details of the Per Protocol analysis are

1. Subjects for whom study drug was started within 11 h of TLK@B.
2. Subjects will be analyzed according to the treatment that was actually received.

A modified Intent-to-Treat analysis will be conducted as a secondary analysis and which 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 in which they were randomized. This sample would include patients who were randomized, but did not actually meet the eligibility criteria or for whom protocol violations occurred.

Prespecified Secondary and Other Analyses

In this phase II study of an intervention aimed at preventing cerebral edema after ischemic stroke, secondary analyses will facilitate an improved understanding of whether there is an effect of the drug on edema and clinical outcome. The secondary efficacy analyses are outlined in Table 2. Additional prespecified exploratory analyses will assess the effect of the study drug on hemorrhagic transformation, blood–brain barrier breakdown, and alternative clinical outcomes to the modified Rankin Scale.

Table 2 Secondary efficacy analyses

Proportion of subjects either undergoing DC or dead by Day 14
Change between baseline and 72–96 h in ipsilateral hemispheric swelling measured by MRI
Change between baseline and 72–96 h in lesional swelling measured by MRI

Discussion

"Malignant infarction" occurs in 10–12 % of stroke victims, or ~70,000 patients per year [2], and is characterized by the formation of rapidly accumulating cerebral edema. Despite the great morbidity and mortality that are a direct consequence of brain swelling, novel approaches to the prevention of cerebral edema are lacking [29]. A significant barrier to progress in managing patients with a large stroke is identifying safe and effective pharmacotherapy to minimize the brain swelling that produces such devastating consequences. Managing patients with a large stroke includes neurointensive care for management of sedation, strict blood pressure and temperature control, mechanical ventilation, osmotherapy, and DC in the event of imminent herniation [3]. However, numerous factors limit the usefulness of DC, including limited eligibility for surgery among patients who are gravely ill and have serious comorbidities [30].

Current practice in large hemispheric stroke is characterized by reactive medical management (e.g., mannitol, hypertonic saline) and surgical decompression. There is a significant unmet medical need for preventive medical treatment, and GAMES-RP is the first trial to test a therapy designed to prevent malignant swelling.

Our approach selects a relatively homogenous group of patients at high risk of malignant infarction, using a prospectively validated, high-specificity parameter (baseline DWI lesion volume $\geq$82 cm^3) [15]. Furthermore, we are studying the impact of RP-1127 through the use of neuroimaging and plasma biomarkers of cerebral edema. Since the treatment effect of glyburide results, in part, from decreased edema formation, the application of intermediate neuroimaging biomarkers of edema are an essential component of this phase II trial. It is expected that the combination of clinical and imaging outcomes will assist in the design of future studies a phase III trial that will test clinical efficacy.

Compliance with Ethical Standards

Conflict of interest The authors received research Grants from the sponsor of the study to conduct study activities. No author has received speaking honoraria, nor owns stock in the sponsoring company.

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