ARTICLE CLASS OF EVIDENCE

Effect of IV glyburide on adjudicated edema endpoints in the GAMES-RP Trial

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Abstract

Objective

In this secondary analysis of the Glyburide Advantage in Malignant Edema and Stroke (GAMES-RP) Trial, we report the effect of IV glyburide on adjudicated, edema-related endpoints.

Methods

Blinded adjudicators assigned designations for hemorrhagic transformation, neurologic deterioration, malignant edema, and edema-related death to patients from the GAMES-RP phase II randomized controlled trial of IV glyburide for large hemispheric infarct. Rates of these endpoints were compared between treatment arms in the per-protocol sample. In those participants with malignant edema, the effects of treatment on additional markers of edema and clinical deterioration were examined.

Results

In the per-protocol sample, 41 patients received glyburide and 36 received placebo. There was no difference in the frequency of hemorrhagic transformation (n = 24 [58.5%] in IV glyburide vs n = 23 [63.9%] in placebo, $p = 0.91$) or the incidence of malignant edema (n = 19 [46%] in IV glyburide vs n = 17 [47%] in placebo, $p = 0.94$). However, treatment with IV glyburide was associated with a reduced proportion of deaths attributed to cerebral edema (n = 1 [2.4%] with IV glyburide vs n = 8 [22.2%] with placebo, $p = 0.01$). In the subset of patients with malignant edema, those treated with IV glyburide had less midline shift ($p < 0.01$) and reduced MMP-9 (matrix metalloproteinase 9) levels ($p < 0.01$). The glyburide treatment group had lower rate of NIH Stroke Scale (NIHSS) increase of ≥4 during the infusion period (n = 7 [37%] in IV glyburide vs n = 12 [71%] in placebo, $p = 0.043$), and of change in level of alertness (NIHSS subscore 1a; n = 11 [58%] vs n = 15 [94%], $p = 0.016$).

Conclusion

IV glyburide was associated with improvements in midline shift, level of alertness, and NIHSS, and there were fewer deaths attributed to edema. Additional studies of IV glyburide in large hemispheric infarction are warranted to corroborate these findings.

ClinicalTrials.gov identifier

NCT01794182.

Level of evidence

This study provides Class II evidence that for patients with large hemispheric infarction, IV glyburide improves some edema-related endpoints.

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Criteria for rating therapeutic and diagnostic studies
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Glossary

DC = decompressive craniectomy; **DWI** = diffusion-weighted image; **GAMES-RP** = Glyburide Advantage in Malignant Edema and Stroke; **HT** = hemorrhagic transformation; **IQR** = interquartile range; **LHI** = large hemispheric infarction; **MCA** = middle cerebral artery; **MLS** = midline shift; **MMP-9** = matrix metalloproteinase 9; **NIHSS** = NIH Stroke Scale; **SUR1** = sulfonylurea receptor 1.

Large hemispheric infarction (LHI) is a subset of ischemic stroke that typically affects the total or near-total territory of the middle cerebral artery (MCA), with or without involvement of the adjacent (i.e., anterior or posterior cerebral artery) territories.[1] LHI is uniquely complicated by dramatic cerebral edema, which can ultimately lead to transtentorial herniation and death.[1–3]

The severe edema associated with LHI is often heralded by neurologic deterioration within 24 to 48 hours of stroke onset.[1,3] The subsequent brain swelling and mass effect can lead to secondary neurologic injury through tissue shifts and further ischemic damage. Current therapies are reactive rather than preventive, lagging behind progressive neurologic injury that has already occurred. Despite medical treatment with hyperosmolar agents, mortality from malignant edema ranges from 30% to 60%.[2,4,5] Decompressive craniectomy (DC) has a well-established effect on mortality, and provides a functional outcome benefit in some patients,[4,6] but comes at the risk of substantial morbidity.[7]

IV glyburide (RP-1127; BIIB093; glibenclamide) has emerged as a candidate agent for the prevention of edema. Glyburide targets the sulfonylurea receptor 1 (SUR1) protein, which regulates a number of ion channels including TRPM4, and is upregulated in the setting of neurologic injury, including acute stroke.[8,9] Inhibition of SUR1-TRPM4 limits cytotoxic cell death in vitro[10] and prevents edema in numerous animal models of stroke.[11–13] The Glyburide Advantage in Malignant Edema and Stroke (GAMES-RP) Trial was a phase 2 study designed to assess safety and to preliminarily evaluate whether IV glyburide prevents edema after LHI in humans.[14,15]

The objective of this secondary analysis was to determine the effect of IV glyburide on adjudicated endpoints related to edema in the GAMES-RP Trial. Prespecified outcome measures included hemorrhagic transformation (HT), malignant edema, and edema-related mortality.

Methods

Classification of evidence

This study seeks to address the following research questions, with the associated classification of evidence:

1. Does treatment with IV glyburide alter the rate of prespecified adjudicated endpoints, including HT, malignant edema, neurodegeneration from any cause, edema-related neurodeterioration, and edema-related death (Class II)?
2. In a post hoc analysis of the subgroup of patients with malignant edema, is IV glyburide treatment associated with a change in edema-related markers including midline shift (MLS) and matrix metalloproteinase 9 (MMP-9) levels (Class II)?
3. In a post hoc analysis of the subgroup of patients with malignant edema, is IV glyburide treatment associated with a change in rates of clinical deterioration as measured by change in total NIH Stroke Scale (NIHSS) or NIHSS item 1a (Class II)?

Standard protocol approvals, registrations, and patient consents

The GAMES-RP Trial was approved by the appropriate institutional review board at each participating center. All patients or their legally authorized representatives provided informed consent for participation in the trial. The trial is registered with ClinicalTrials.gov, identifier NCT01794182.

Patient characteristics

The patients for the study were enrolled in the GAMES-RP Trial. A full description of enrollment criteria and study design has been previously reported.[14,15] Briefly, the study enrolled patients aged 18 to 80 years within 10 hours of onset of anterior circulation stroke with diffusion-weighted image (DWI) lesion volume of 82 to 300 cm^3. Patients were randomized 1:1 to receive IV glyburide (approximately 3 mg per day for 72 hours) or placebo. In accordance with the primary study results, this analysis was conducted on the per protocol cohort (all patients with a baseline DWI lesion volume 82–300 cm^3 who received any study drug). The modified intention-to-treat sample, which included all participants who received any study drug, showed similar results (data available from Dryad, tables e-1 and e-2, doi.org/10.5061/dryad.d4vk706).

Adjudicated endpoints

A blinded adjudication committee (R.v.K., A.M.D., J.M.R.) evaluated neurologic deterioration, malignant edema, HT, and cause of death. Patients with neurologic deterioration were defined as having at least one of the following: (1) an increase of ≥1 on NIHSS subscore 1a, (2) a less brisk response to pain, (3) a new pupillary abnormality, or (4) an increase of ≥4 on the total NIHSS score. Neurologic deterioration was determined by individual sites. Based on brain imaging and clinical information, the committee assigned a cause for

neurologic deterioration by consensus, choosing from hemorrhage, edema, expansion of infarction, unknown, or other causes. Edema-related neurologic deterioration was examined for further analysis based on the proposed antiedema effect of IV glyburide; these results can be found in data available from Dryad (table e-3 and figure e-1, doi.org/10.5061/dryad.d4vk706).

Malignant edema was defined as clinical signs of large MCA infarction with an NIHSS score >18, a level of consciousness of ≥1 on item 1a of the NIHSS, a large space-occupying MCA infarction on the day 3–4 follow-up MRI or CT with compression of ventricles or MLS, and no other obvious cause for neurologic deterioration.[16] HT was defined using the European Cooperative Acute Stroke Study criteria and included petechial hemorrhagic infarction type 1, petechial hemorrhagic infarction type 2, or parenchymal hematoma 1 or 2.[17] Adjudication was based on review of all available follow-up CT (n = 43) and/or MRI (n = 33) scans obtained during the first 7 days. The average time from stroke onset to first detected HT was 3 ± 1 days. One patient did not have any follow-up imaging and could not be adjudicated for HT.

The cause of death was also determined by the committee on the basis of clinical and imaging data, and adverse-events reports within the first 30 days after stroke, and was classified as neurologic, cardiac, or other. For neurologic death, the cause of death was further classified as death due to edema, intracranial hemorrhage, recurrent stroke, or other. Classification of a death as edema-related relied on clinical reports of herniation syndrome or imaging evidence of swelling. If a patient died after goals of care were changed to focus on comfort only, the adjudicators considered the events leading up to the goals of care decision in determining cause of death.

Evaluation of intermediate and follow-up clinical endpoints

In patients who met the definition of malignant edema, the changes in total NIHSS score and in NIHSS 1a subscore were evaluated. The 1a subscore was examined because the level of consciousness is reported as the most specific clinical sign of brain swelling after stroke.[1,18] Additional clinical endpoints included the mortality rate by study visit.

The total NIHSS score and NIHSS 1a subscore were evaluated at baseline and on a daily basis throughout the study drug infusion (days 1–3). Thresholds for clinical deterioration were examined based on 3 different thresholds previously used: an increase in total NIHSS score of ≥2, an increase in total NIHSS score ≥4, or increase in NIHSS 1a subscore of ≥1 above baseline at any point in the first 3 days. For patients who died or underwent decompression before the end of the drug infusion period, NIHSS for subsequent days was imputed as the last recorded value prior to death or decompression. This was done to avoid bias introduced by either post-decompression sedation or dropout of the most severely injured patients at later time points.

Imaging and laboratory analysis

MLS and plasma total MMP-9 level were measured as part of the original trial, and the prespecified endpoint for each was used.[15] These endpoints were used to further examine the effects of IV glyburide in the neurologic deterioration and malignant edema subgroups. To determine the shift in millimeters, the midline was first established by laying a straight line between the anterior and posterior attachment of the falx cerebri to the inner table of the skull. MLS was quantified by drawing and measuring a second, perpendicular line at the point of maximal deviation from the midline, at the level of the septum pellucidum. If a day-4 MRI scan was missing because of death, the prespecified imputation was used (i.e., the worst value by treatment arm was imputed). Plasma total MMP-9 was measured with a commercially available assay (Human MMP-9 Quantikine ELISA; R&D Systems, Minneapolis, MN), and the average value during the infusion period (based on all measurements between 24 and 72 hours) was used.

Statistical analysis

Baseline characteristics are expressed as mean ± SD for normally distributed continuous variables or as median with interquartile range (IQR) for ordinal variables and continuous variables showing deviation from normality. Binary variables are represented as frequency and percentage. Differences between binary variables were analyzed using the Fisher exact or χ^2 test as appropriate (rates of neurologic deterioration and malignant edema). Survival analysis was conducted using the log-rank test. Continuous variables were compared between treatment arms using Wilcoxon rank sum test (MLS and MMP-9 level). Change in NIHSS over time was compared between treatment arms using a linear mixed-effects model, with the outcome of interest being the interaction between treatment group and time. All tests were 2-sided and performed with the threshold for significance set at $p < 0.05$. Statistical analysis was performed using JMP Pro 13 (SAS Institute, Cary, NC) and Stata software 14.2 (StataCorp LP, College Station, TX).

Data availability

The original trial protocol and the clinical guidelines used for the GAMES-RP Trial are published.[14] Patient-level data from the GAMES-RP clinical trial are not publicly available. Proposals for secondary analysis that have scientific merit will be reviewed by the study co–principal investigators and Biogen, Idec. If a proposal is approved, the mechanism to conduct the analysis will be established.

Results

Clinical characteristics and prespecified adjudicated endpoints

The initial study population consisted of 86 patients, 83 of whom received any amount of study drug and were part of the modified intention-to-treat group. Seventy-seven were treated per-protocol and are included in the present analysis. Results

in the modified intention-to-treat group were similar (data available from Dryad, tables e-1 and e-2, doi.org/10.5061/dryad.d4vk706). In the per-protocol group, 36 patients received placebo and 41 received glyburide. The baseline characteristics have been previously reported.[15] Briefly, in the IV glyburide treatment arm, the average age (±SD) was 58 ± 11 years, the average DWI lesion volume was 157 ± 53 cm^3, the average pretreatment sodium (±SD) was 138 ± 3 mEq/L, and the median NIHSS score (IQR) was 20 (16–22). In the placebo treatment arm, the average age was 63 ± 9 years, the average DWI lesion volume was 162 ± 49 cm^3, the average pretreatment sodium (±SD) was 139 ± 3 mEq/L, and the median NIHSS score was 21 (17–23). Time from last seen well to study drug bolus did not differ between groups (median 9.1 hours [IQR 8.3–9.8] for glyburide vs 9.5 hours [8.5–10] for placebo, $p = 0.54$). Rate of DC did not differ by treatment (n = 13 [32%] for glyburide vs n = 8 [22%] for placebo, $p = 0.35$), nor did time to craniectomy in those who underwent surgery (median 41 hours [IQR 33–62] for glyburide vs 54 hours [45–70] for placebo, $p = 0.19$).

Associations between treatment and the adjudicated endpoints are presented in table 1. There was no difference in rate of total HT or parenchymal hematoma between treatment groups. Similarly, there was no difference in the proportion of patients with malignant edema, neurologic deterioration from any cause, or neurologic deterioration due to edema.

It was determined that 9 patients had edema-related death at 30 days. In 7 of these, there were limitations to life-sustaining therapy instituted prior to death, with a median NIHSS score of 27 (IQR 26–31) at the last recorded examination. When examining all edema-related deaths at 30 days, treatment with IV glyburide was associated with a lower mortality (n = 1, 2.4% in IV glyburide group) compared to the placebo group (n = 8, 22%; $p = 0.010$, Fisher exact test). The rate of edema-related death in those without DC was 12.5% (n = 7), compared to a rate of 9.5% (n = 2) in those who had DC, which was not different ($p = 0.71$). IV glyburide treatment remained independently associated with a lower mortality when adjusting for DC (odds ratio = 0.09, 95% confidence interval 0.01–0.74, $p = 0.026$). Kaplan-Meier survival analysis suggested that patients treated with IV glyburide were less likely to die of edema-related causes compared to those in the placebo group within the first 30 days after stroke ($p = 0.009$; figure 1).

Post hoc analysis of edema-related endpoints

We sought to further investigate the effect of IV glyburide in the 36 patients who met the definition of malignant edema. We reasoned that more subtle clinical improvements from IV glyburide therapy may not be captured with the prespecified definition of malignant edema because of the uniformly severe stroke at baseline or the insensitivity of the outcome measure. We first assessed the effect of IV glyburide on MLS and plasma MMP-9 among those patients who experienced malignant edema (n = 36). IV glyburide was associated with approximately 50% reduction in MLS (4.6 vs 12.4 mm, $p = 0.001$; figure 2A). IV glyburide was also associated with approximately 50% lower plasma level of MMP-9 (161 vs 335 ng/mL, $p = 0.001$; figure 2B).

Table 1 Adjudicated outcomes in the GAMES-RP Trial

Adjudicated outcomes	Placebo (n = 36)	Glyburide (n = 41)	*p* Value
30-d mortality (all causes)[a]	13 (36)	6 (15)	0.036
Edema-related mortality	8 (22)	1 (2.4)	0.010
Mortality due to recurrent stroke	1 (2.8)	0 (0)	0.47
Hemorrhage-related mortality	0 (0)	2 (4.9)	0.50
Cardiac mortality	1 (2.8)	1 (2.4)	1.0
Mortality from other causes	3 (8.3)	2 (4.9)	0.66
Hemorrhagic transformation[b]			0.98
HI1	13 (36)	14 (35)	
HI2	8 (22)	9 (23)	
PH1	2 (5)	1 (2)	
PH2	0 (0)	0 (0)	
Hemorrhage outside the infarction[b]			
Intraventricular hemorrhage	3 (8)	3 (7)	0.89
Subarachnoid hemorrhage	0 (0)	2 (5)	0.18
Subdural hemorrhage	0 (0)	1 (2)	0.34
Neurologic deterioration (all causes)	23 (64)	23 (56)	0.49
Neurologic deterioration (edema-related)	18 (50)	18 (45)	0.66
Malignant edema	17 (47)	19 (46)	0.94

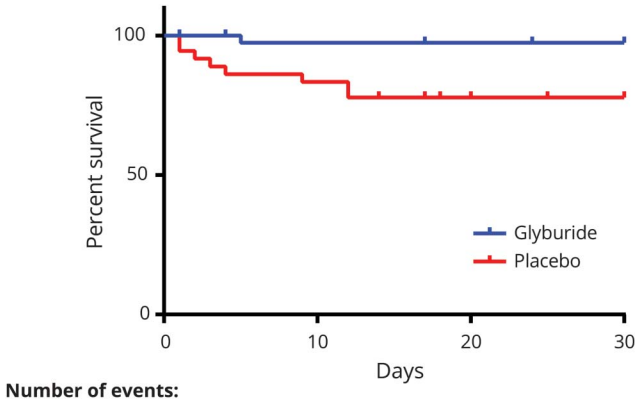
Abbreviations: GAMES-RP = Glyburide Advantage in Malignant Edema and Stroke; HI1 = hemorrhagic infarction type 1; HI2 = hemorrhagic infarction type 2; PH1 = parenchymal hematoma 1; PH2 = parenchymal hematoma 2. Data represent n (%).
[a] The cause of death through day 30 was assigned by the adjudication committee.
[b] One patient in the IV glyburide treatment arm did not have a follow-up scan available to evaluate hemorrhage.

Post hoc analysis of clinical deterioration

We next examined the change in total NIHSS from baseline over the 3 days of drug infusion. There was no difference in NIHSS over time when the entire cohort was examined ($p = 0.109$; figure 2C). However, for those patients who experienced malignant edema, there was an interaction of treatment with time, with a lower NIHSS score observed over time with IV glyburide ($p = 0.001$; figure 2D).

To further explore the possibility that clinically relevant change was occurring that the malignant edema definition did not capture, we examined several clinical thresholds for

Figure 1 Kaplan-Meier survival curve for edema-related mortality



Number of events:

	--	6	8	8
	--	1	1	1

Number at risk:

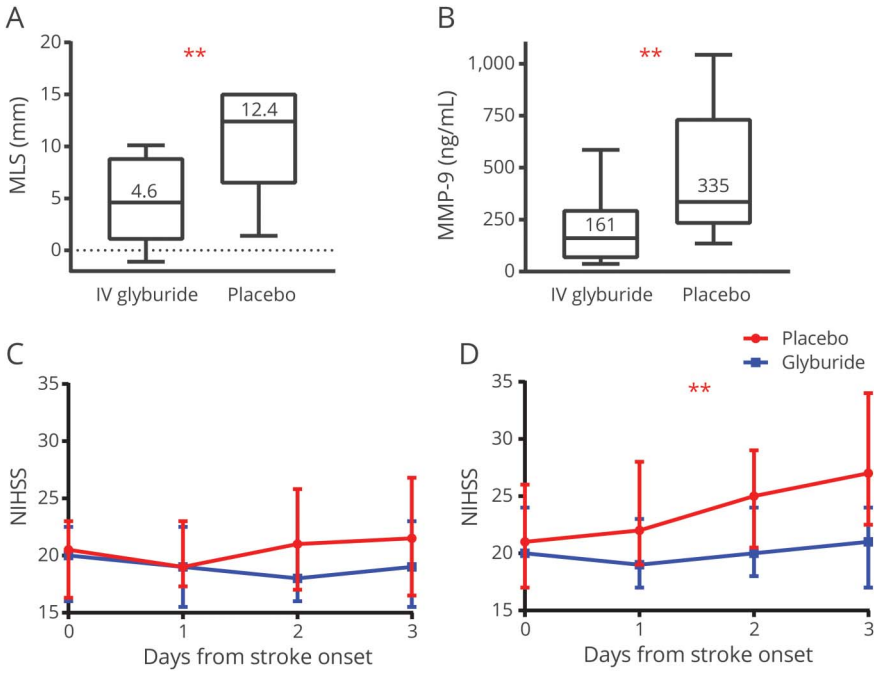
	36	30	25	23
	41	37	36	35

Mortality was lower in patients treated with IV glyburide (n = 1, 2%) as compared to placebo-treated patients (n = 8, 22%; log-rank test, $p = 0.009$).

neurologic deterioration that have been used in prior studies. These measures included an increase in total NIHSS score from baseline of ≥2 or ≥4,[19] or a change in level of consciousness as reflected by the NIHSS subscore 1a.[1,18] As expected, in the GAMES-RP study population, each of these subacute clinical thresholds was associated with reduced odds of good outcome, defined as modified Rankin Scale score 0–4 at 90 days (data available from Dryad, table e-4, doi.org/10.5061/dryad.d4vk706). When examining the entire study population, there was no effect of treatment on these clinical thresholds (table 2). However, in those with malignant edema, fewer patients treated with glyburide had an increase in NIHSS score of ≥2 (63% vs 94% with placebo, $p = 0.026$), an increase in NIHSS score ≥4 (37% vs 71%, $p = 0.043$), or increase in NIHSS 1a subscore of ≥1 (58% vs 94%, $p = 0.016$).

It is possible that DC could confound the interpretation of the change in NIHSS score during the first few days. Moreover, since there were a numerically greater number of DC cases in the IV glyburide arm (n = 13 vs n = 8, $p = 0.35$; table 3), we sought to differentiate the potential confounding effect of DC from study drug treatment. We first examined the change in total NIHSS score or NIHSS 1a subscore in the entire cohort, using the clinical scores collected just prior to surgery in those patients who underwent DC (table 3). Of note, fewer patients treated with IV glyburide had an increase in NIHSS score ≥4 prior to craniectomy or day 3 (n = 5 [12%] vs n = 11 [31%] in placebo, $p = 0.048$). There were also fewer patients with NIHSS increase of ≥2 or NIHSS 1a increase of ≥1, but these differences did not reach significance. When examining the patients who met the definition of malignant edema, there were lower rates of clinical deterioration based on all 3 measures (NIHSS increase of ≥2, NIHSS increase of ≥4, or NIHSS 1a increase of ≥1) in those treated with glyburide (all $p < 0.01$; table 3).

Figure 2 Changes in intermediate endpoints in patients with malignant edema



In the subgroup of patients who experienced malignant edema (n = 36), IV glyburide was associated with (A) less MLS (**$p = 0.001$) and (B) lower MMP-9 (**$p = 0.001$). For each panel, the median value is shown, the box plots define the interquartile range, and the whiskers the minimum and maximum values. (C) The time course of total NIHSS score over time was not different in the treatment arms in the overall cohort ($p = 0.11$). (D) In patients with malignant edema who were treated with IV glyburide, there was a reduction in NIHSS score relative to the placebo arm ($p = 0.001$) during the drug infusion. MLS = midline shift; MMP-9 = matrix metalloproteinase 9; NIHSS = NIH Stroke Scale.

Table 2 Markers of clinical deterioration before end of drug infusion

	Entire cohort			Malignant edema		
	Placebo (n = 36)	Glyburide (n = 41)	*p* Value	Placebo (n = 17)	Glyburide (n = 19)	*p* Value
NIHSS increase of ≥2	19 (53)	18 (44)	0.44	16 (94)	12 (63)	0.026
NIHSS increase of ≥4	12 (33)	9 (22)	0.26	12 (71)	7 (37)	0.043
NIHSS 1a increase of ≥1[a]	20 (57)	16 (39)	0.11	15 (94)	11 (58)	0.016

Abbreviation: NIHSS = NIH Stroke Scale.
Data represent n (%). One patient in the placebo group was missing day 3 NIHSS 1a data.

Discussion

We present the analysis of prespecified adjudicated endpoints from the GAMES-RP Trial, a phase 2 study that evaluated IV glyburide for the treatment of cerebral edema after LHI. Our analysis demonstrates that treatment with IV glyburide was associated with a reduction in edema-related deaths. However, there was no effect on rates of HT, or on the proportion of patients with malignant edema. In exploratory analyses, clinical, imaging, and laboratory biomarkers of edema were improved in patients with malignant edema who were treated with IV glyburide. Accordingly, IV glyburide was associated with reduced rates of NIHSS deterioration, less MLS, and lower levels of plasma MMP-9. IV glyburide was also associated with lower mortality from edema-related causes.

We also provide evidence that the designation of malignant edema—at least in a cohort of very severe stroke—may overlook clinically relevant changes related to edema formation. It is possible that the prespecified definition used, while based on preexisting literature,[16] may have been unable to discriminate an effect of IV glyburide, where a meaningful clinical improvement might not translate into a difference in the rate of malignant edema. This possibility is reinforced by the fact that many GAMES-RP patients met most of the malignant edema criteria at baseline, with the exception of "evidence of edema on imaging." While IV glyburide reduced MLS,[15] it did not eliminate mass effect completely. Furthermore, glyburide treatment was associated with a lower rate of edema-related death, suggesting that glyburide may have limited edema severity. Thus, a meaningful reduction in edema could be observed with IV glyburide while still meeting the prespecified criteria for malignant edema, indicating the insensitivity of this measure in this patient population.

To further assess whether IV glyburide may have a smaller, but clinically meaningful effect on edema that was not captured by the prespecified definitions, we conducted exploratory analyses of clinical and imaging biomarkers. The concordant effects on MLS, plasma MMP-9, NIHSS score, and level of consciousness suggest data that IV glyburide had a moderate but measurable effect on intermediate clinical and biomarker endpoints. Although these markers are not sufficient to demonstrate clinical efficacy, they lend support to the notion that a treatment effect may be present.

There are several limitations to this study. The GAMES-RP Trial consisted of a relatively small sample size, and while patients who experienced malignant edema accounted for slightly more than half of the participants, there was limited power to detect a difference in event rate. Furthermore, there are alternative definitions for malignant edema, including the original report of "malignant" infarction that was defined in part by mortality due to edema.[2] However, we did not examine this outcome since it was not prespecified, even though there was a reduction in edema-related mortality in patients treated with IV glyburide. The analyses presented in the current study were exploratory and do not demonstrate clinical efficacy of IV glyburide. However, the endpoints were adjudicated by a blinded committee and the analyses provide

Table 3 Markers of clinical deterioration by the end of drug infusion or before decompressive craniectomy

	Entire cohort			Malignant edema		
	Placebo (n = 36)	Glyburide (n = 41)	*p* Value	Placebo (n = 17)	Glyburide (n = 19)	*p* Value
Decompressive craniectomy	8 (22)	13 (32)	0.35	8 (44)	12 (67)	0.18
NIHSS increase of ≥2	19 (53)	13 (32)	0.061	16 (94)	8 (42)	<0.001
NIHSS increase of ≥4	11 (31)	5 (12)	0.048	11 (64)	3 (16)	0.003
NIHSS 1a increase of ≥1	20 (56)	14 (34)	0.059	15 (88)	9 (47)	0.009

Abbreviation: NIHSS = NIH Stroke Scale.
Data represent n (%)

some evidence that is consistent with the preclinical findings. Taken together, these studies identify SUR1 as a candidate mediator of postischemic brain edema and support further testing of IV glyburide in reducing edema formation.

Author contributions

W.T.K.: study concept and design, analysis and interpretation of data, drafting of manuscript, study supervision. M.B.B.: analysis and interpretation of data, drafting of manuscript. R.v.K.: study concept and design, critical revision of manuscript for intellectual content. A.M.D.: study concept and design, critical revision of manuscript for intellectual content. J.M.R.: study concept and design, critical revision of manuscript for intellectual content. J.J.E.: study concept and design, analysis and interpretation of data, critical revision of manuscript for intellectual content. H.E.H.: acquisition of data, critical revision of manuscript for intellectual content. B.J.M.: acquisition of data, critical revision of manuscript for intellectual content. J.M.S.: study concept and design, critical revision of manuscript for intellectual content. K.N.S.: study concept and design, analysis and interpretation of data, drafting of manuscript, study supervision.

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Disclosure

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Effect of IV glyburide on adjudicated edema endpoints in the GAMES-RP Trial

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