Safety and efficacy of intravenous glyburide on brain swelling after large hemispheric infarction (GAMES-RP): a randomised, double-blind, placebo-controlled phase 2 trial

Kevin N Sheth, Jordan J Elm, Bradley J Molyneaux, Holly Hinson, Lauren A Beslow, Gordon K Sze, Ann-Christin Ostwaldt, Gregory J del Zoppo, J Marc Simard, Sven Jacobson, W Taylor Kimberly**

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*Contributed equally

Department of Neurology, Division of Neurocritical Care and Emergency Neurology, Yale University School of Medicine, New Haven, CT, USA (K N Sheth MD, L A Beslow MD); Department of Public Health Sciences, Medical University of South Carolina, Charleston, SC, USA (J J Elm PhD); Department of Neurology, University of Pittsburgh, Pittsburgh, PA, USA (B J Molyneaux MD); Department of Neurology, Oregon Health Sciences University, Portland, OR, USA (H Hinson MD); Department of Pediatrics (L A Beslow) and Department of Radiology (G K Sze MD), Yale University School of Medicine, New Haven, CT, USA; Department of Neurology, Division of Neurocritical Care and Emergency Neurology, Massachusetts General Hospital, Boston, MA, USA (A-C Ostwaldt PhD, W T Kimberly MD); Division of Hematology, Department of Medicine, and Department of Neurology, University of Washington, Seattle, WA, USA (Prof G J del Zoppo MD); Department of Neurosurgery, University of Maryland, Baltimore, MD, USA (Prof J M Simard MD); and Remedy Pharmaceuticals, New York, NY, USA (S Jacobson BSE)

Correspondence to: Dr Kevin N Sheth, 15 York Street, LCI 1003, New Haven, CT 06510, USA
kevin.sheth@yale.edu

or

Dr W Taylor Kimberly, Lunder 644, 55 Fruit Street, Boston, MA 02114, USA
wtkimberly@mgh.harvard.edu

Summary

Background Preclinical models of stroke have shown that intravenous glyburide reduces brain swelling and improves survival. We assessed whether intravenous glyburide (RP-1127; glibenclamide) would safely reduce brain swelling, decrease the need for decompressive craniectomy, and improve clinical outcomes in patients presenting with a large hemispheric infarction.

Methods For this double-blind, randomised, placebo-controlled phase 2 trial, we enrolled patients (aged 18–80 years) with a clinical diagnosis of large anterior circulation hemispheric infarction for less than 10 h and baseline diffusion-weighted MRI image lesion volume of 82–300 cm³ on MRI at 18 hospitals in the USA. We used web-based randomisation (1:1) to allocate patients to the placebo or intravenous glyburide group. Intravenous glyburide was given as a 0·13 mg bolus intravenous injection for the first 2 min, followed by an infusion of 0·16 mg/h for the first 6 h and then 0·11 mg/h for the remaining 66 h. The primary efficacy outcome was the proportion of patients who achieved a modified Rankin Scale (mRS) score of 0–4 at 90 days without undergoing decompressive craniectomy. Analysis was by per protocol. Safety analysis included all randomly assigned patients who received the study drug. This trial is registered with ClinicalTrials.gov, number NCT01794182.

Findings Between May 3, 2013, and April 30, 2015, 86 patients were randomly assigned but enrolment was stopped because of funding reasons. The funder, principal investigators, site investigators, patients, imaging core, and outcomes personnel were masked to treatment. The per-protocol study population was 41 participants who received intravenous glyburide and 36 participants who received placebo. 17 (41%) patients in the intravenous glyburide group and 14 (39%) in the placebo group had an mRS score of 0–4 at 90 days without decompressive craniectomy (adjusted odds ratio 0·87, 95% CI 0·32–2·32; p=0·77). Ten (23%) of 44 participants in the intravenous glyburide group and ten (26%) of 39 participants in the placebo group had cardiac events (p=0·76), and four of 20 had serious adverse events (two in the intravenous glyburide group and two in the placebo group, p=1·00). One cardiac death occurred in each group (p=1·00).

Interpretation Intravenous glyburide was well tolerated in patients with large hemispheric stroke at risk for cerebral oedema. There was no difference in the composite primary outcome. Further study is warranted to assess the potential clinical benefit of a reduction in swelling by intravenous glyburide.

Funding Remedy Pharmaceuticals.

Introduction

Malignant cerebral oedema can develop as a complication of large hemispheric infarction and leads to abrupt neurological deterioration within 24–48 h after stroke onset.[1,2] Brain swelling, which is the mass-occupying consequence of cerebral oedema, can cause further ischaemic damage and, if left untreated, can result in brain herniation. The horizontal tissue shifts that occur as a consequence of brain swelling manifest clinically as a reduction in the level of arousal.[3] Medical treatment to reduce the brain volume includes supportive care and osmotic drugs. Nevertheless, herniation and death occur in up to 50% of patients with brain swelling.[1,4] Neurosurgical treatment with decompressive craniectomy can reduce mortality and might improve outcomes in patients younger than 60 years.[5] However, decompressive craniectomy is associated with substantial morbidity.[6] Moreover, surgery is done only after substantial tissue injury, brain shift, and neurological deterioration have already occurred.[1,3] Although treatment of oedema is reactive in clinical practice, no drug therapy has been assessed to prevent oedema.[7]

Results of preclinical studies[8,9] suggest that blockade of the inducible sulfonylurea receptor 1 (SUR1)-transient receptor potential melastatin 4 (TRPM4) channel in neurons, astrocytes, and endothelium substantially reduces cerebral oedema in rodent models of stroke. Further preclinical studies and retrospective studies in human beings have shown that a continuous parenteral infusion of the SUR1 inhibitor glyburide (glibenclamide) decreases water accumulation in the brain, improves survival, and facilitates neurological recovery in

Research in context

Evidence before this study

We searched PubMed for randomised controlled trials published in only English between Jan 1, 2000, and March 4, 2016, with the search terms "ischemic stroke", AND "brain edema", AND "glyburide", OR "glibenclamide", OR "sulfonylurea". We found 12 preclinical studies that showed that continuous glyburide administration led to a reduction in brain oedema and mortality in rodent models of stroke. A pilot trial of intravenous glyburide in patients with acute, large hemispheric stroke showed feasibility and initial safety of treatment of critically ill stroke patients at high risk for oedema. Interpretation of these retrospective and prospective pilot data is limited by the absence of double-blind, placebo controlled trials.

Added value of this study

To our knowledge, this is the first trial to assess the effect of early (within 10 h) and continuous administration of an intravenous glyburide for the prevention of brain oedema after a large hemispheric stroke in a randomised, double-blind, placebo-controlled trial. Treatment was well tolerated, hypoglycaemia was uncommon and successfully treated with a prespecified hypoglycaemia protocol. Although the percentage of people who had a modified Rankin Scale score of 0–4 at 90 days without decompressive craniectomy (primary endpoint) was not significantly different in the glyburide and placebo groups, and mortality was non-significantly reduced overall, functional outcome measured by the modified Rankin Scale was improved in patients treated with the active drug. There was an association with a reduction in midline shift of the brain and lower plasma matrix metalloproteinase-9 concentrations in patients treated with intravenous glyburide compared with placebo.

Implications of all the available evidence

Our findings suggest that the sulfonylurea receptor pathway is implicated in the formation of brain oedema after stroke in patients. Early and continuous intravenous administration of glyburide favourably affects markers of brain oedema and suggests that there might be a clinical effect on mortality and functional outcome at 90 days. These findings need to be replicated in a larger phase 3 trial in patients with large hemispheric infarction.

experimental settings.[10] This evidence suggests that the SUR1–TRPM4 channel is a candidate target for prevention of cerebral oedema after large hemispheric stroke in patients.[8] A phase 2A clinical trial showed the feasibility and safety of administering intravenous glyburide to critically ill stroke patients.[11,12]

The Glyburide Advantage in Malignant Edema and Stroke (GAMES-RP) trial was designed to test the safety and efficacy of intravenous glyburide in a critically ill, acute ischaemic stroke population at high risk for brain swelling.[13] On the basis of the GAMES-Pilot data,[11,12] we hypothesised that intravenous glyburide would safely diminish brain swelling, decrease the need for decompressive craniectomy, and improve clinical outcome.[11,12] An additional objective was to provide information for the design of a phase 3 trial of intravenous glyburide in patients at high risk for developing brain oedema.

Methods

Study design and participants

GAMES-RP was a double-blind randomised, phase 2 trial —done at 18 hospitals in the USA—of intravenous glyburide in patients with a large anterior circulation hemispheric infarction who were at risk to develop malignant oedema. The design of the GAMES-RP trial has been previously reported.[13] The study was done under an Investigational New Drug Application from the US Food and Drug Administration. The study was approved by the institutional review boards at all participating centres. All participants or their legally authorised representatives provided written informed consent at enrolment.

Participants were aged 18–80 years and had a clinical diagnosis of large anterior circulation hemispheric infarction for less than 10 h from the time last known to be neurologically healthy, confirmed by a baseline diffusion weighted image (DWI) lesion volume of 82–300 cm³. The ABC/2 method was used locally to assess the baseline DWI lesion volume for enrolment purposes.[14] Treatment with alteplase was permitted for up to 4·5 h after symptom onset.[15] Participants undergoing endovascular thrombectomy were not eligible, because the efficacy of this process is uncertain in strokes with a baseline DWI lesion volume of more than 70 cm³.[16] The full exclusion criteria are listed in the appendix.

See Online for appendix

Randomisation and masking

Eligible participants were randomly assigned to receive intravenous glyburide or placebo in a 1:1 ratio from a centralised, web-based randomisation algorithm. Patients were screened by clinical teams at each site and enrolled by site study personnel. Minimisation combined with biased coin were used to control for clinical site, age (≤60 years *vs* >60 years), and alteplase treatment. The funder, principal investigators, site investigators, patients, imaging core, and outcomes personnel were masked to treatment. Drug vials, preparation bags, and tubing were identical in appearance for both treatment groups.

Procedures

The bolus and the infusion concentrations of the study drug were both 5·3 µg/mL. A 0·13 mg bolus intravenous injection was given during the first 2 min of treatment. Subsequently, an intravenous infusion was administered

at a rate of 0·16 mg/h for the first 6 h, followed by a rate of 0·11 mg/h for the remaining 66 h (total daily dose on day 1 was 3·12 mg and on days 2 and 3 was 2·67 mg/day). This dosing schedule was based on preclinical studies, the maximum tolerated dose in a phase 1 study, and a safety analysis of the phase 2A study.[11] Treatment up to 10 h from stroke onset was selected because preclinical data indicated efficacy within this time.[17]

Concomitant treatments followed national practice guidelines from the American Heart Association and the American Stroke Association, codified into study-specific clinical guidelines.[1] Osmotherapy was recommended for patients who showed clinical deterioration with radiological evidence of substantial midline shift or mass effect. Decompressive craniectomy was standard-of-care for deterioration and its use was based on guidelines.[1,2] A 24 h hotline was maintained by the co-principal investigators and the medical safety monitor, who were available in real time for questions regarding the clinical protocol or standardisation guidelines.

Key baseline assessments were a physical examination, a National Institutes of Health Stroke Scale (NIHSS) assessment, and a screening brain MRI scan. The NIHSS score was assessed on days 1–4 and day 7 (or at discharge). The modified Rankin Scale (mRS) score was collected at day 30, day 90, 6 months, and 12 months. To ensure reliable scoring, qualified raters used a standardised questionnaire to assist site level determination in person or by telephone.[18] Clinical and outcomes scales, including NIHSS and mRS, were assessed by study personnel at the clinical sites. An electrocardiogram (ECG) and blood samples were obtained at baseline, 4–6 h after study drug bolus, and at 24 h, 48 h, and 60–72 h. An ECG was also obtained at 7 days or at discharge, whichever was first.

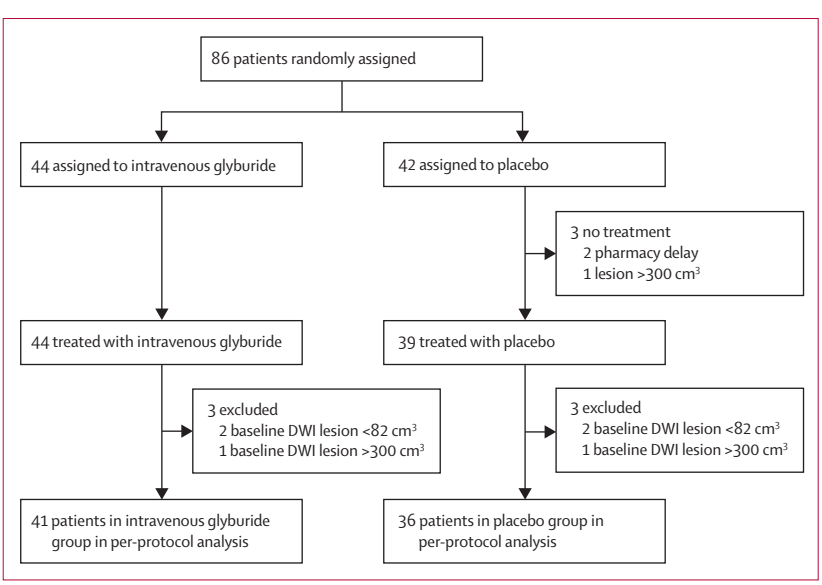


Figure 1: **Trial profile**
DWI=diffusion weighted MRI.

Point-of-care blood glucose concentrations were measured every hour during the first 24 h and then, in the absence of a value below 3·9 mmol/L, every 2 h for the next 24 h and every 4 h for the subsequent 40 h. A study-specific MRI scan was obtained at 72–96 h after the study drug bolus. Images were obtained on a 1·5 T or 3·0 T system with the following minimum sequences: axial fluid-attenuated inversion recovery, axial gradient echo, and axial DWI. Baseline vessel occlusion was determined by CT angiography or magnetic resonance angiography (MRA). An MRA was also obtained during the follow-up scan.

All imaging data were sent to a core laboratory (Yale University, New Haven, CT, USA) (GKS and LAB) for measurement of surrogate imaging measures of brain oedema (GKS and LAB)—ie, midline shift, change in hemisphere volume, and lesional swelling volume. Imaging measures were ascertained on baseline and follow-up scans with Analyze software (version 11.0) by the masked imaging core based on previous methods.[19–21] Previous inter-rater analyses have shown a concordance correlation of greater than or equal to 0·94.[19] Plasma samples were sent to a core biomarker laboratory (Massachusetts General Hospital, Boston, MA, USA) for measurement of total matrix metalloproteinase 9 (MMP-9) with a commercially available assay (Human MMP-9 Quantikine ELISA, R&D Systems, Minneapolis, MN, USA).

Outcomes

The primary outcome was the proportion of patients who achieved an mRS score of 0–4 at 90 days without undergoing decompressive craniectomy. The three secondary efficacy outcomes were the proportion of patients who underwent decompressive craniectomy or who died by day 14, change in ipsilateral hemispheric swelling from baseline to 72–96 h measured by MRI irrespective of decompressive craniectomy, and change in lesional swelling from baseline to 72–96 h measured by MRI.

Tertiary outcomes were the 90 day mRS (dichotomised at 0–4 *vs* 5 and 6), the frequency of decompressive craniectomy by day 7, time to death, all-cause mortality up to 90 days, midline shift from baseline to 72–96 h, and total concentration of MMP-9 (mean level of three daily samples collected during the study drug infusion).

An independent data monitoring committee conducted periodic prespecified safety reviews. Safety was assessed as the frequency and severity of adverse events and serious adverse events by organ system (Medical Dictionary for Regulatory Activities, version 15.0), with specific attention to the serious adverse events of all-cause mortality, cardiac mortality, and cardiac-related and blood glucose-related adverse events.

Statistical analysis

The study was initially planned with a two-stage design with a prespecified futility interim analysis. The funder

stopped further enrolment in the trial on April 30, 2015, at the first of the two stages, because of an absence of financial support for additional enrolment beyond the interim analysis. Therefore, the interim analysis was not done and the analysis plan was amended to a single stage, and finalised by the masked statistician on July 20, 2015, the details of which were published.[13] After all 90 day visits had been completed, the database was frozen on July 31, 2015, at 1345 h, and the study statistician was fully unmasked. Unmasking of the funder and leadership team was done on Aug 5, 2015, when the statistical analyses were provided by the study statistician. The data monitoring committee was fully unmasked to the results on Oct 29, 2015; before this timepoint, the committee had not identified any safety concerns. The decision to stop enrolment was made without knowledge of treatment assignment or outcome by the funder, leadership team, or data monitoring committee.

We calculated that 93 patients per group would be needed for 80% power to detect a 20 percentage point effect size (absolute difference in proportions) when the true placebo response proportion was 30% (one-sided test, α=0·025). The estimated effect size was smaller than in preliminary data from GAMES-Pilot,[11,12] when compared with matched historical controls[22,23] and was selected to maximise the likelihood of a clinically meaningful difference in a critically ill population expected to have substantial disability based on the index stroke. Because the placebo response rate was estimated, a sample size re-estimation was planned on the basis of the true placebo response rate, with a maximum total sample size of 240 patients. Simulations showed that the original two-stage design with a maximum total sample size of 240 would have 80% power to detect a 20 percentage point effect size (absolute difference in proportions) when the true placebo response proportion was 30% or higher. As described previously, the trial was stopped early for funding reasons before the interim analyses or sample size re-estimation. In the truncated study population, the existing sample had 80% power to detect a 30% percentage point absolute effect size (one-sided test, α=0·025) when the placebo response proportion was 30%.

The efficacy analyses for the primary, secondary, and tertiary outcomes were based on the per-protocol sample, which included participants who had a centrally read DWI baseline lesion volume of 82–300 cm³ and who received study drug. Sensitivity analysis of the primary, secondary, and tertiary outcomes was done on the modified intention-to-treat sample (which included all patients who were enrolled and received any study drug; appendix). After the database was frozen, an erroneous mRS value at 90 days was discovered because of a clerical error, which was monitor-verified, updated in the study database by the site, and manually corrected within the data freeze; an incorrect mRS score of 2 for a patient (identification number 1220) in the placebo group was corrected to 4. The primary efficacy hypothesis was assessed with a likelihood ratio test of the null hypothesis that the regression coefficient for treatment was equal to zero in a multiple logistic model that adjusted for baseline age, baseline DWI volume, and baseline internal carotid artery occlusion (complete *vs* partial, none, or unknown). If the baseline CT angiography or MRA was missing, but the internal carotid artery was occluded on a follow-up CT angiography or MRA, the baseline internal carotid artery occlusion was imputed as a complete occlusion.

	Intravenous glyburide (n=41)	Placebo (n=36)
Demographics		
Age (years)	58 (11)	63 (9)
Female	16 (39%)	10 (28%)
Ethnic origin		
Hispanic	3 (7%)	3 (8%)
Not Hispanic	38 (93%)	33 (92%)
Race		
White	35 (85%)	30 (83%)
Black	4 (10%)	4 (11%)
Asian	2 (5%)	2 (6%)
Medical history		
Ischaemic stroke or transient ischaemic attack	6 (15%)	4 (11%)
Carotid artery disease	7 (17%)	3 (8%)
Type 2 diabetes	8 (20%)	7 (19%)
Hypertension	31 (76%)	24 (67%)
Hyperlipidaemia	25 (61%)	20 (56%)
Coronary artery disease	8 (20%)	4 (11%)
Atrial fibrillation	13 (32%)	14 (39%)
Stroke characteristics		
Cause of stroke		
Large artery atherosclerosis	12 (29%)	9 (25%)
Cardio-aortic embolism	14 (34%)	18 (50%)
Small artery	1 (2%)	0 (0%)
Other	3 (7%)	4 (11%)
Unknown	11 (27%)	5 (14%)
Internal carotid artery occlusion	12 (29%)	13 (36%)
Left side of infarction	20 (49%)	20 (56%)
Baseline NIHSS	20 (16–22)	21 (17–23)
Baseline DWI lesion volume (cm³)	157 (53)	162 (49)
Baseline blood glucose (mg/dL)	6·7 (5·8–8·8)	7·0 (5·9–8·1)
Treatment		
Intravenous rtPA	25 (61%)	22 (61%)
Time intervals		
Symptom onset to intravenous rtPA (h)	2·2 (1·0)	2·2 (1·0)
Symptom onset to baseline MRI	6·0 (1·6)	5·7 (1·6)
Symptom onset to study drug bolus (h)	8·8 (1·3)	9·0 (1·4)

Data are mean (SD), n (%), and median (IQR). NIHSS=National Institutes of Health Stroke Scale Score. rtPA=recombinant tissue plasminogen activator. DWI=diffusion weighted imaging.

Table 1: **Demographics and baseline characteristics**

The NIHSS, blood glucose, and swelling variables were presented as median (IQR) because the distribution was expected to be skewed. Baseline characteristics were compared by treatment group with the χ^2 test or Wilcoxon rank-sum test. For imaging outcomes, missing data caused by comfort measures only, or decompressive craniectomy, or death were imputed with the largest observed value in that treatment group, because these outcomes were deemed a treatment failure. If a patient was unable to tolerate the MRI scan, imputation was done with a regression approach adjusting for age, baseline DWI lesion volume, and internal carotid artery occlusion. Additional sensitivity analyses were done for imputed values by measurement of the midline shift on the last available head CT scans (appendix).

The following test statistics were used to compare treatment groups for secondary and tertiary outcomes: χ^2 test and unadjusted odds ratio (for proportion of deaths, mRS score between 0 and 4, decompressive craniectomy, and composite proportions), Wilcoxon rank-sum test (for change in ipsilateral hemispheric swelling, lesional swelling, and midline shift), and two sample *t* test (for total concentration of MMP-9). Mean differences in treatment groups with 95% confidence intervals are provided for continuous variables. Shift analysis of the raw mRS scores at 90 days were compared with an unstratified Cochran-Mantel-Haenszel test.[24] A Kaplan-Meier curve, weighted log-rank test, and hazard ratios of all-cause deaths within 90 days were used to compare treatment groups. All tests were two-sided, and p values of less than 0·05 were significant, with no adjustment for multiplicity.

Safety analyses included all randomly assigned patients who received the study drug. The frequencies and percentages of safety events were reported by treatment group and comparisons were made with the Fisher's exact test or χ^2 test. SAS (version 9.3) was used for the statistical analyses, and figures were created with Graphpad Prism (version 6.0).

Role of the funding source

The funder of the study managed operational aspects of the trial, including drug distribution, site monitoring, and had a role in study design, data interpretation, and writing of the report. The co-principal investigators (KNS and WTK) and primary statistician (JJE) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

86 participants with a large anterior circulation hemispheric infarction were enrolled between May 3, 2013, and April 30, 2015. 44 participants were randomly

	Intravenous glyburide (n=41)	Placebo (n=36)	p value	Effect size (95% CI)
Primary outcome				
mRS 0–4 at 90 days without decompressive craniectomy	17 (41%)	14 (39%)	0·77	OR 0·87 (0·32 to 2·32)*
Secondary outcomes				
Decompressive craniectomy or death by day 14	15 (37%)	16 (44%)	0·48	OR 0·72 (0·29 to 1·80)
Change in ipsilateral hemispheric swelling 72–96 h (cm^3)	68 (36–105)	78 (52–133)	0·28	Mean difference −13·4 (−43·4 to 16·6)
Change in lesional swelling 72–96 h (cm^3)	58 (35–98)	78 (45–121)	0·41	−6·6 (−39·8 to 26·5)
Tertiary outcomes				
mRS 0–4 at 90 days†	25 (61%)	17 (47%)	0·23	OR 1·75 (0·71 to 4·32)
Decompressive craniectomy at 90 days†	13 (32%)	8 (22%)	0·35	OR 1·63 (0·58 to 4·53)
Midline shift of the brain from baseline to 72–96 h (mm)	4·6 (2·0–6·6)	8·5 (5·0–14·2)	0·0006	−4·3 (−6·3 to −2·4)
MMP-9 during study drug infusion (ng/mL) at 24–72 h‡	211·4 (138·1)	345·8 (250·7)	0·006	−134·4 (−224·8 to −43·9)
All cause mortality				
In-hospital deaths	3 (7%)	5 (14%)	0·46	..
7 day	4 (10%)	5 (14%)	0·73	..
30 day	6 (15%)	13 (36%)	0·03	..
90 day	7 (17%)	13 (36%)	0·06	HR 0·49 (0·21–1·13)
Post-hoc analysis				
Change in ipsilateral hemispheric swelling for patients without decompressive craniectomy (cm^3)§	49 (25–81)	77 (53–105)	0·04	−29·3 (−62·3 to 3·8)
Change in lesional swelling for subset of patients without decompressive craniectomy (cm^3)§	41 (27–69)	75 (37–100)	0·15	−21·1 (−56·7 to 14·5)

Data are n (%), median (IQR), and mean (SD). mRS=modified Rankin Scale. OR=odds ratio. MMP-9=matrix metalloproteinase-9. HR=hazard ratio. *Data were adjusted for baseline age, diffusion weighted imaging volume, and internal carotid artery. †Prespecified tertiary efficacy outcome. ‡MMP-9 collected at 24 h, 48 h, and 60–72 h was averaged for each patient. §Post-hoc analyses at 72–96 h, n=28 per group.

Table 2: **Efficacy outcome measures**

allocated to the intravenous glyburide group and 42 participants were randomly allocated to the placebo group. Three participants in the placebo group did not receive the study drug (two because of pharmacy delays and one because the lesion on the enrolling MRI was reassessed at the site before dosing and was >300 cm³), and were withdrawn from the study and excluded from the modified intention-to-treat sample. Six additional patients (three participants in each group) did not meet the criteria for inclusion after patients were randomly assigned because of DWI lesion volumes outside the prespecified range, as determined by the imaging core. A total of 77 participants remained in the per-protocol analysis (figure 1). Demographics and baseline characteristics were similar in the two treatment groups (table 1). In the per-protocol study population, the mean time from symptom onset to study drug bolus was 9 h (SD 1·4), the median NIHSS was 20 (IQR 16–22), and 61% of participants received intravenous glyburide.

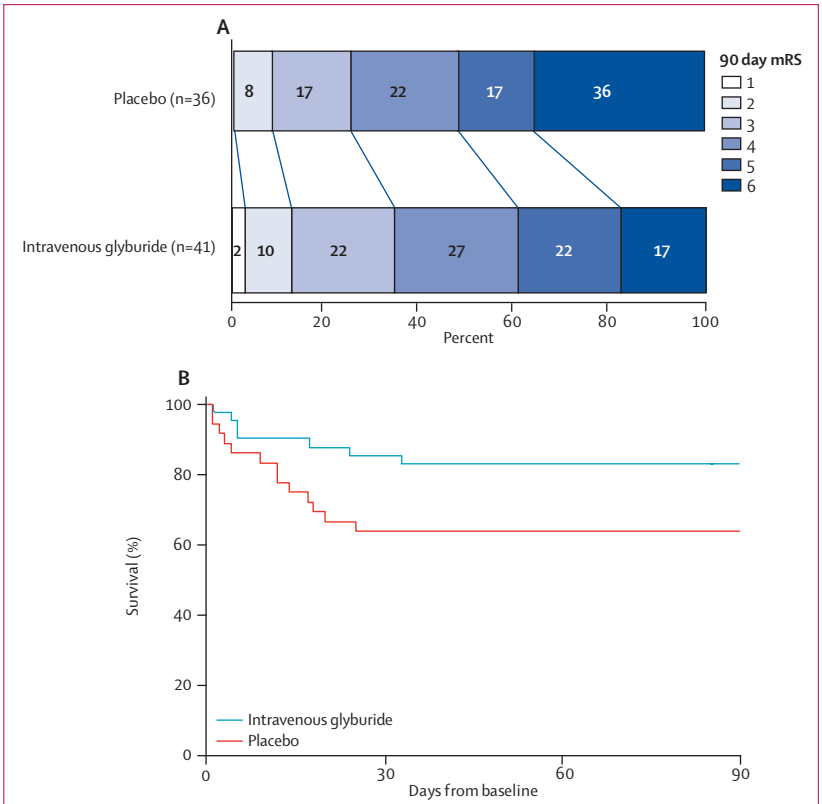
None of the patients in the per-protocol sample were missing a 90-day mRS score. Of the 77 per-protocol participants, there was no difference between the intravenous glyburide and placebo groups in the proportion of participants with the primary clinical outcome, mRS 0–4 without decompressive craniectomy (41% *vs* 39%; adjusted p value=0·77; table 2).

There were no differences between the intravenous glyburide and placebo groups in the three prespecified secondary short-term clinical endpoints (table 2). The results of the modified intention-to-treat analysis were similar, and are provided in the appendix.

In the shift analysis, the 90 day functional outcome (mRS scores) was not significantly improved in the intravenous glyburide group (p=0·12; figure 2A). The Kaplan-Meier survival curve suggested a survival benefit for patients treated with intravenous glyburide with and without decompressive craniectomy compared with placebo, but the time to death was not significantly different (weighted log-rank p=0·06; figure 2B). Compared with placebo, participants treated with intravenous glyburide with and without decompressive craniectomy had similar mortality at 7 days, significantly reduced mortality at 30 days, and non-significantly reduced mortality at 90 days (table 2). The median midline shift at the level of the septum pellucidum at 72–96 h was 4·6 mm in the intravenous glyburide group and 8·5 mm in the placebo group (p=0·0006; table 2 and figure 3A). The total MMP-9 concentration measured between 24 h and 72 h after initiation of the study drug infusion was lower in participants treated with intravenous glyburide compared those treated with placebo (mean 211 ng/mL *vs* 346 ng/mL; p=0·006; figure 3B; table 2). MMP-9 concentrations at individual timepoints were non-significantly lower in the intravenous glyburide group after the baseline measurement, and are shown in figure 3B.

No difference in decompressive craniectomy frequency (32% in the intravenous glyburide group *vs* 22% in the placebo group, p=0·35) or withdrawal of care (17% *vs* 25%, p=0·41) was observed (table 2). Patients in whom care was withdrawn during the index hospital admission had a greater midline shift (median 12·8 mm [IQR 8·1–14·7] *vs* 6·1 mm [3·9–10·2], p=0·01), and a lower level of consciousness (item 1A on the NIHSS subscore) that developed by day 2 (median 2 [IQR 2–2] *vs* 1 [IQR 0–1], p=0·0002; appendix) greater shift and lower consciousness than those who did not.

The percentages of participants with one or more serious adverse events in the intravenous glyburide and placebo groups were similar (table 3). No episodes of symptomatic hypoglycaemia were reported in either treatment group, and all low glucose levels resolved after implementation of the prespecified hypoglycaemia protocol (data not shown). Nine participants had hypoglycaemia (five mild, three moderate, and one severe), all in the intravenous glyburide group. Of these nine participants, four had a blood glucose concentration



	Enrolled	7 days	14 days	30 days	90 days ±7 days
Events (cumulative)					
Intravenous glyburide	..	4	4	6	7
Placebo	..	5	9	13	13
Number at risk					
Intravenous glyburide	41	37	37	35	34
Placebo	36	31	27	23	23

Figure 2: **Secondary clinical outcomes in the glyburide and placebo groups**
(A) Distribution of mRS scores in the per-protocol sample at 90 days (table 2). (B) A Kaplan-Meier survival curve for each treatment group. mRS=modified Rankin Scale.

of less than 3·1 mmol/L, which met the prespecified definition of a serious adverse event, during drug infusion and none were symptomatic (appendix). The proportion of patients with cardiac adverse events and cardiac serious adverse events were similar in the intravenous glyburide and placebo groups (table 3). One death from cardiac arrest 18 days after enrolment in the placebo group and one death from cardiac arrest 33 days after enrolment in the intravenous glyburide group were reported. Neither death was attributed to the study drug. Although 22 (27%) of 83 patients did not have any ECGs collected that were suitable for QTc analysis, the proportion of patients with a QTc of more than 500 ms was similar in each group (table 3). No clinically meaningful differences in vital signs or other laboratory variables were recorded between the active treatment and the control group (data not shown).

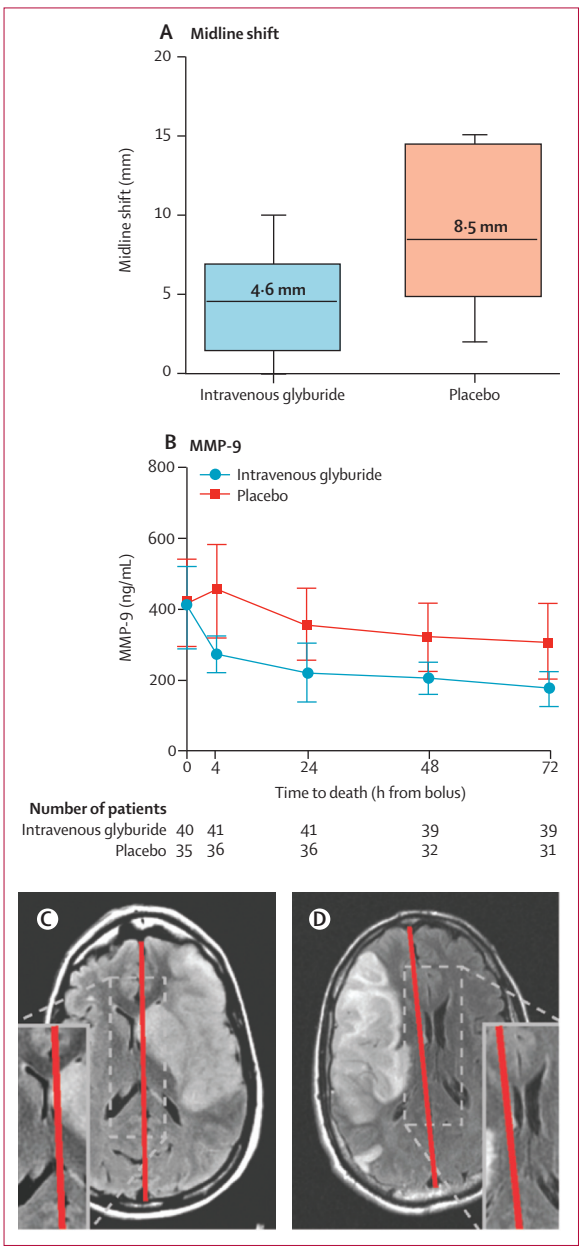


Figure 3: **Effect of glyburide on midline shift of the brain and plasma MMP-9**
(A) The median midline shift (horizontal bar) is shown for each treatment group in the per-protocol sample. The boxes represent IQR and whiskers are 10–90 percentiles. (B) Mean total plasma MMP-9 over time for the per-protocol sample. The error bars are 95% confidence intervals at baseline and 4 h, 24 h, 48 h, and 72 h from start of study drug. The number of patients represented at each timepoint is listed. (C) and (D) are examples of the median extent of midline shift on the follow-up brain MRI. (C) shows a patient treated with intravenous glyburide with midline shift of 5 mm. (D) shows a placebo-treated patient with 9 mm of midline shift. The red line indicates the midline of the brain. MMP-9=matrix metalloproteinase-9.

Because decompressive craniectomy or withdrawal of care could have confounded the outcome, several post-hoc analyses were done. First, the frequency of decompressive craniectomy by site was assessed. 19 [90%] of 21 decompressive craniectomies were done at eight clinical sites that enrolled about half of all participants (appendix). More decompressive craniectomies were done in the intravenous glyburide group than in the placebo group (13 [32%] of 41 participants *vs* eight [22%] of 36 participants), but the difference was not significant (p=0·35). To assess whether the difference in the treatment effect on mortality was due to the increased number of decompressive craniectomies in the intravenous glyburide group, a series of Cox proportional hazard regression models were fitted, and the hazard ratios (HR) for the risk of death in a given treatment group were compared with and without adjustment for decompressive craniectomy. When adjusting for this factor, the HR for death was 0·50 (95% CI 0·21–1·15) for the intravenous glyburide group compared with the placebo group (p=0·10), which was similar to the unadjusted HR of 0·49 (95% CI 0·21–1·13, p=0·095). There was no evidence for a treatment by decompressive craniectomy interaction (p=0·56). Finally, when the effect of decompressive craniectomy on survival was assessed ignoring the treatment effect, the unadjusted HR for death was 0·70 (95% CI 0·26–1·88) for those with compared with those without decompressive craniectomy (p=0·72). A reduction in level of consciousness (NIHSS item 1A) was intended to be a key trigger for proceeding to decompressive craniectomy. For patients treated with the placebo, the level of consciousness was reduced before the decompressive craniectomy but not with patients treated with intravenous glyburide (appendix p 7).

Sensitivity analyses of midline shift were done to establish the effect of imputation on the prespecified analysis. For patients who did not have a study-specific MRI scan because of withdrawal of care or who underwent decompressive craniectomy before the MRI, midline shift was measured on the CT closest to 72–96 h after study initiation. The effect of intravenous glyburide on midline shift was not affected by either decompressive craniectomy (p=0·014) or withdrawal of care (p=0·04; appendix). Post-hoc analysis of participants without

decompressive craniectomy (appendix) showed an effect of intravenous glyburide on hemispheric swelling (median 49 cm³ [IQR 23–84] for the glyburide group *vs* 77 cm³ [52–106] in the placebo group, p=0·04) but not lesional swelling (median 41 cm³ [IQR 26–71] *vs* 75 cm³ [36–102], p=0·15).

Discussion

The GAMES-RP trial showed that intravenous glyburide was safe in patients who are critically ill after an ischaemic stroke and have a large hemispheric infarction, but the trial was negative for the prespecified primary and secondary efficacy endpoints. However, intravenous glyburide administration resulted in a non-significant reduction in mortality and reduced brain swelling, as shown by the lower median midline shift compared with placebo, which is consistent with the preclinical effect of the drug—ie, reduced oedema formation.

A high mortality and frequent medical complications are characteristic of patients with large hemispheric infarction who routinely require intensive care unit admission.[1,25] Large territory infarction is the most specific predictor of neurological deterioration or malignant oedema.[23] Patients with a decreased level of consciousness and midline shift often receive neurological assessments, osmotherapy, and decompressive craniectomy.[3] In GAMES-RP, the baseline DWI lesion volume of 160 cm³ was considered large. In accord with a large infarction volume, overall proportions of adverse events were high but there was no difference between treatment groups. As in the previous phase 2A study of intravenous glyburide,[11] target blood glucose concentrations were managed with the glucose monitoring and treatment protocol developed. The intervention was safe and well tolerated in this study.

The primary efficacy outcome was the absence of decompressive craniectomy and a 90-day mRS score of 0–4. This outcome was chosen on the basis of the available preliminary data derived from the GAMES-Pilot trial and the use of decompressive craniectomy in other trials in similar patient populations.[5,25] In this context, we hypothesised that intravenous glyburide, if effective, would reduce the need for decompressive craniectomy. However, this premise was not supported by our trial, and was confounded by variation in practice, with 90% of the surgeries in GAMES-RP occurring in about half the participating sites. Additionally, decompressive craniectomy was not always preceded by a reduction in the level of consciousness. Although the clinical guidelines for decompressive craniectomy in the study were based on published recommendations,[1] the decision to proceed to decompressive craniectomy was left to individual centres and might have been applied inconsistently. We chose a clinical endpoint instead of an imaging endpoint as the primary outcome to assess swelling because available imaging endpoints had uncertain validity.[19]

Both frequency of decompressive craniectomies and mortality in GAMES-RP were lower than in earlier studies.[5,23] A contributing factor might be that GAMES-RP enrolled patients up to age 80 years, and decompressive craniectomy is infrequent in patients above the age of 60 years.[1] Previous studies have also shown that decompressive craniectomy reduces mortality.[5,25] Because there was an increased number of participants who received decompressive craniectomy in the intravenous glyburide group, this might have also confounded the reduction in mortality attributable to the study drug. However, patients who received intravenous glyburide either with or without decompressive craniectomy had a lower mortality than did those in the placebo group. Moreover, in sensitivity analyses, the hazard ratios for death were similar in models that were either unadjusted or adjusted for decompressive craniectomy, supporting the notion that the effect of treatment on mortality was independent of decompressive craniectomy. Nevertheless, we cannot exclude the possibility that the treatment effect was at least partly due to decompressive craniectomy.

GAMES-RP was also designed with prespecified outcomes related to brain swelling. In patients with an acute mass effect on the brain, midline shift is a marker of neurological deterioration and death.[3,26] The observed reduction in midline shift supports the conclusion that exposure to intravenous glyburide might have reduced oedema. The apparent discrepancy between midline shift and hemispheric and swelling volumes might be the result of the observed site-specific patterns of decompressive craniectomy use. Because decompressive craniectomy itself led to a large increase in the hemispheric and swelling volume measurements, interpretation of these imaging measures is unclear. However, the association between in-hospital withdrawal of care, increased midline shift, as well as a reduction in the level of consciousness, suggest that the mass effect might have been the proximate mechanism of neurological deterioration and death.

	Intravenous glyburide (n=44)	Placebo (n=39)	p value*
Serious adverse events	60 events in 30 patients (68%)	44 events in 28 patients (72%)	..
Blood glucose <3·1 mmol/L	4 (9%)	0 (0%)	0·12
Symptomatic hypoglycaemia	0 (0%)	0 (0%)	..
Cardiac serious adverse events	2 (5%)	2 (5%)	1·00
Cardiac events	10 (23%)	10 (26%)	0·76
Cardiac deaths	1 (2%)	1 (3%)	1·00
All cause deaths†	10 (23%)	15 (38%)	0·12
QTc >500 ms‡	3/37 (8%)§	2/24 (8%)¶	1·00
Abnormal, clinically significant ECGs after baseline	3 (7%)	4 (10%)||	0·70

Data are n (%). QTc=corrected QT interval on electrocardiogram. ECG=electrocardiogram. *Fisher's exact test or χ^2 test. †Two patients in the glyburide group and one in placebo group died beyond 90 days. ‡Excludes ECGs that were obtained, but not suitable for analysis. §Seven participants had ECGs that were not suitable for QTc analysis. ¶15 participants had ECGs collected that were not suitable for QTc analysis. ||Includes one participant in the placebo group who had a clinically significant finding at baseline.

Table 3: **Safety events**

Exposure to intravenous glyburide also led to a reduction in plasma MMP-9 levels. MMP-9 elevation is associated with several stroke-related complications,[27] including brain oedema after stroke.[28] More specific studies of glyburide administration in rodents and exploratory analysis in the GAMES-Pilot trial also suggested that intravenous glyburide might reduce MMP-9 antigen levels.[21,29] Taken together, these findings led us to measure the concentration of plasma MMP-9 in the GAMES-RP study population. Although our data showed a reduction of 39% (134 ng/mL) by intravenous glyburide, it is not known whether this finding reflects an effect within the brain, or derives from circulating inflammatory cells after stroke, or from other sources.[30] Thus, although these data support an effect of intravenous glyburide, they should be interpreted with caution in relation to attenuation of brain oedema.

Our trial had several strengths. It was a double-blind, randomised study done in a critically ill stroke population, where glucose levels were readily managed in the intensive care setting. There was no loss to follow-up for the primary endpoint, and any imputation for missing neuroimaging data was handled conservatively. The study design was informed by preclinical studies that clarified the molecular target, mode of delivery, and therapeutic time window for intravenous glyburide, with GAMES-RP closely mirroring the design of preclinical studies.[8,9] Endpoints were chosen to assess whether SUR1 was an appropriate target for the reduction of brain oedema. Finally, GAMES-RP studied a population of only patients with a large hemispheric infarction who were likely to experience substantial swelling, as shown in animal models.

There are several limitations to the GAMES-RP trial. The trial was terminated early because of limitations in funding. Although the decision to stop enrolment was not based on any knowledge of outcome or concern regarding safety, the sample size was smaller than originally planned. There is evidence that truncation of randomised clinical trials leads to overestimation of effect size.[31] In view of the exploratory nature of the trial, these analyses also relied on the per-protocol sample and there was no adjustment for the type I error rate for multiple endpoints. Further study is needed to confirm the results obtained for the tertiary endpoints. Also, decompressive craniectomy might not be an appropriate endpoint to assess medical treatments targeting swelling for reasons considered previously, and future study design will need to account for the potential for confounding. The drug was also started an average of 9 h after stroke onset and, in view of the time and efficacy interaction of intravenous glyburide in preclinical studies,[17] this comparatively late administration might have attenuated the observed effect size. Finally, it is possible that a higher dose of intravenous glyburide than that used in this study might have led to a more robust clinical effect. However, the maximum tolerated dose, established in a phase 1 study (NCT01132703), was safely used in this study.

There are several implications for future studies focusing on the prevention of brain oedema after stroke. The selection of surrogate imaging markers of oedema requires additional validation, although midline shift might be a reasonable choice for patients with a large hemispheric infarction. Future studies of intravenous glyburide should also consider minimising the time to administration of drug. Finally, these results might have implications for oedema prevention in other forms of stroke or acute brain injury in which swelling results in an adverse outcome.

The GAMES-RP study did not identify any new safety concerns for intravenous glyburide beyond what is already known for oral glyburide. Although the primary and secondary efficacy outcomes were not significant, in participants with large hemispheric stroke who are at risk for cerebral oedema, intravenous glyburide might reduce mortality, midline shift, and concentrations of plasma MMP-9. These findings identify a potential role of SUR1 in the pathogenesis of ischaemic brain swelling, and support further study of intravenous glyburide for this indication.

Contributors

KNS and WTK had full access to all of the data in the study, and take responsibility for the integrity of the data and the accuracy of the data analysis. KNS, WTK, JJE, and SJ planned the analysis, and JJE, the lead statistician, did the analysis. All four individuals had full access to the complete data set and output. KNS, WTK, SJ, and JJE were responsible for the study concept and design. JJE and the Data Coordination Unit at the Medical University of South Carolina managed the data. KNS, WTK, and JJE did the data analysis. KNS, WTK, JJE, SJ, JMS, GJdZ, LAB, GKS, CO, HH, and BJM interpreted the data. KNS, WTK, JJE, JMS, GJdZ, LAB, GKS, A-CO, SJ, HH, and BJM drafted the manuscript. All authors finalised and approved the final version of the paper.

GAMES-RP study investigators

Neuroimaging Core: *USA* Lauren A Beslow, Gordon K Sze (Yale University, New Haven, CT), Thomas Battey, Ann-Christin Ostwaldt (Massachusetts General Hospital, Boston, MA); *Biomarker Core*: *USA* Hannah Irvine (Massachusetts General Hospital, Boston, MA); *Data Monitoring Committee*: ***USA*** Don Easton (University of California, San Francisco, San Francisco, CA), Karen Johnston (University of Virginia, Charlottesville, VA), Michael Diringer (Washington University, St Louis, MO); *Medical Safety Monitor:* Eugene Means (Remedy Pharmaceuticals, New York, NY, USA); *GAMES-RP Site Investigators: USA* Bradley Molyneaux (University of Pittsburgh, Pittsburgh, PA), Paul Muscat (Maine Medical Center, Portland, ME), W Taylor Kimberly (Massachusetts General Hospital, Boston, MA), Kendra Drake (University of Arizona, Tucson, AZ), Jennifer Majersik (Salt Lake City, UT, USA), Edward Manno (Cleveland Clinic, Cleveland, OH), Raphael Carandang (University of Massachusetts, Boston, MA), Carolyn Cronin (University of Maryland, College Park, MD), Michel Torbey (Columbus, OH, USA), Shyam Prabhakaran (Northwestern, Evanston, IL), David Hwang (Yale University, New Haven, CT), Scott Silliman (University of Florida, Gainesville, FL), Osman Kozak (Abington, PA, USA), Holly Hinson (Oregon Health Sciences, Portland, OR), Igor Rybinnik (Rutgers, Brunswick, NJ), Wei Liu (University of Louisville, Louisville, KY), Gregory Albers (Stanford, Stanford, CA), Edward Jauch (Medical University of South Carolina, Charleston, SC); *GAMES-RP Advisors*: *USA* J Marc Simard, Barney J Stern (University of Maryland, Baltimore, MD, USA), Gregory del Zoppo (University of Washington, Seattle, WA, USA); *Adjudication Committee*: *Germany* Rüdiger von Kummer (Dresden); *USA* Javier Romero (Boston, MA); *Canada* Andrew Demchuk (Calgary, CA).

Declaration of interests

SJ is an employee, cofounder, and CEO of Remedy Pharmaceuticals. JMS has a patent related to the study and has shares in Remedy Pharmaceuticals. WTK, KNS, JJE, GKS, and LAB received grants from Remedy Pharmaceuticals during the conduct of this study. BJM and HH received grants from Remedy Pharmaceuticals outside of the submitted

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