

Glyburide Advantage in Malignant Edema and Stroke - RP

K.N. Sheth and W.T. Kimberly on behalf of the GAMES Investigators



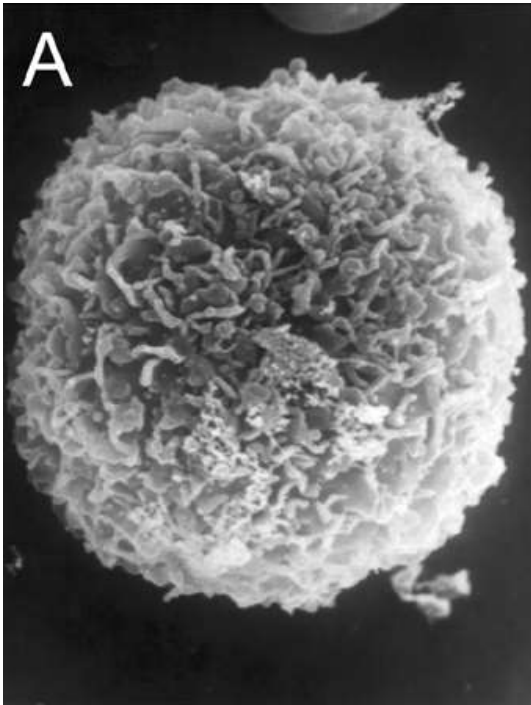
Disclosures

- Remedy Pharmaceuticals, Inc
- NIH/NINDS
- AHA/ASA
- Novartis
- Stryker

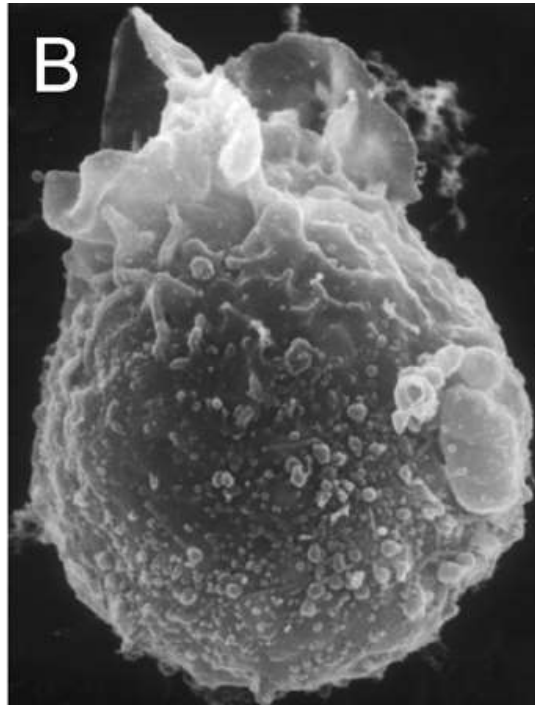
Background

- Large stroke with swelling occurs in 10-15% of all ischemic stroke
- There is no medical therapy to prevent swelling and death in malignant infarction
- Mortality rates are as high as 40-60% and the only proven therapy is decompressive craniectomy

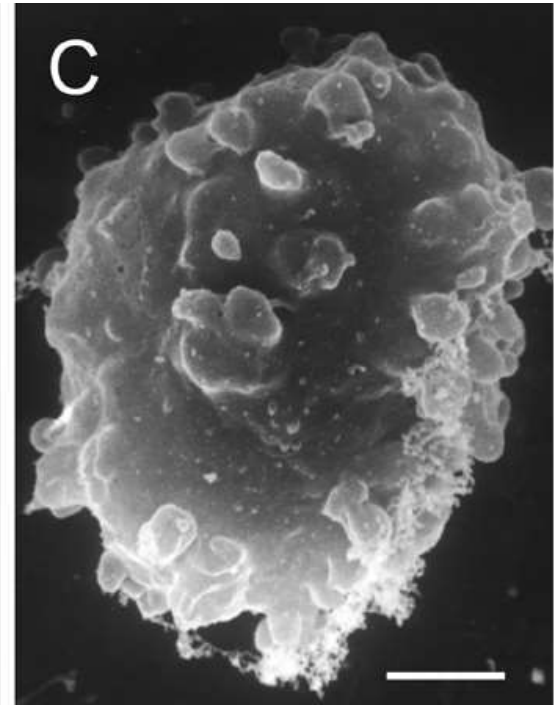
SUR1-TRPM4 Opening Causes Edema



Control

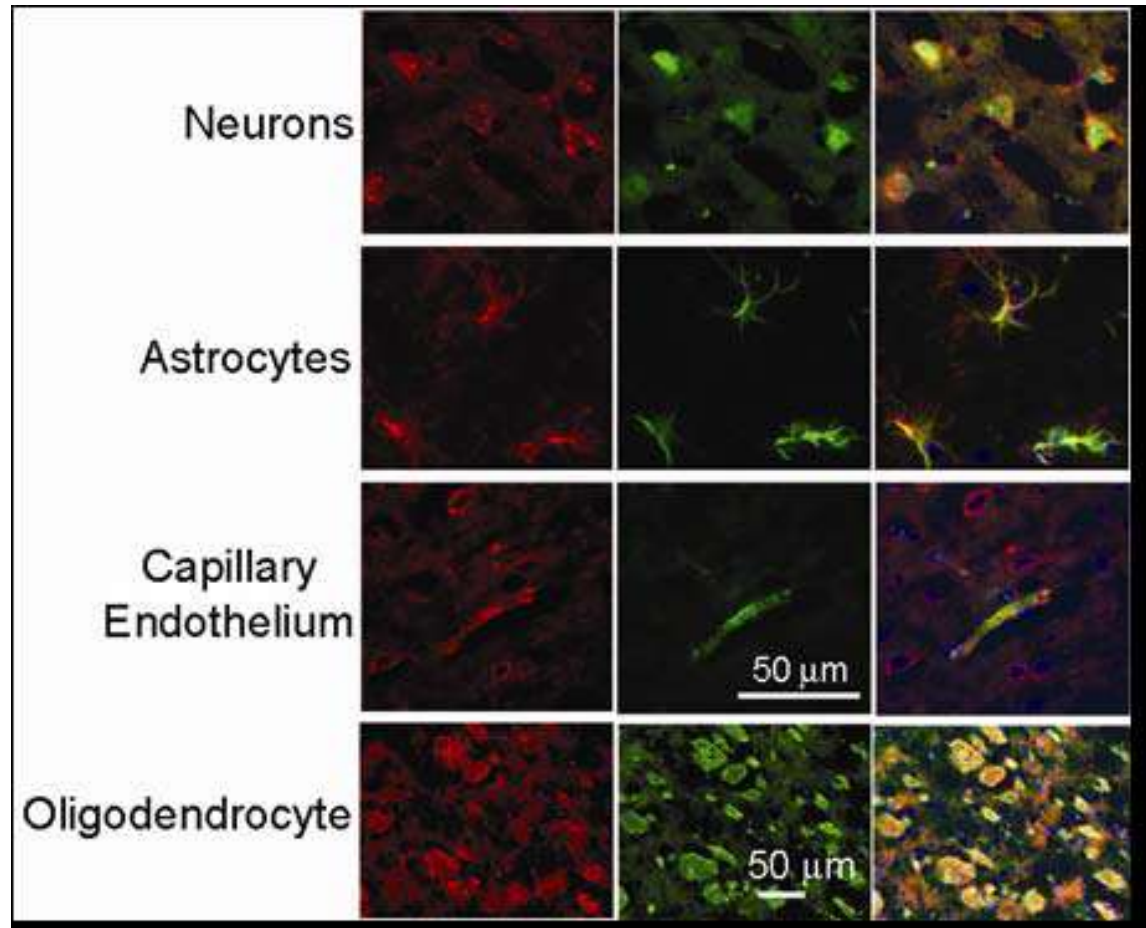


ATP depletion
5 min



ATP depletion
25 min

Multiple Cell Targets



Simard JM, Nature Medicine, 2006

Prediction of Malignant Middle Cerebral Artery Infarction by Magnetic Resonance Imaging Within 6 Hours of Symptom Onset: A Prospective Multicenter Observational Study

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82 cc is the key number within 6 hours

GAMES-Pilot

Stroke

JOURNAL OF THE AMERICAN HEART ASSOCIATION



American Heart Association | American Stroke Association®

Pilot Study of Intravenous Glyburide in Patients With a Large Ischemic Stroke

Kevin N. Sheth, W. Taylor Kimberly, Jordan J. Elm, Thomas A. Kent, Pitchaiah Mandava, Albert J. Yoo, Götz Thomalla, Bruce Campbell, Geoffrey A. Donnan, Stephen M. Davis, Gregory W. Albers, Sven Jacobson, J. Marc Simard and Barney J. Stern

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*Can a medical therapy be used to
PREVENT swelling before it occurs and
improve outcome in patients with large
infarction?*

Objectives

- To assess the **safety** of RP-1127 compared to placebo with a focus on mortality, cardiac-related, and blood glucose related outcomes
- To assess the **efficacy** of RP-1127 compared to placebo in patients who are likely to develop malignant edema and to provide information for a phase III trial

Study Design

| | |
|--|---|
| Design | U.S., multi-center, prospective, randomized double-blinded study |
| Population and Inclusion Criteria | <ul style="list-style-type: none">- Age 18-80- Large anterior circulation acute ischemic stroke- Able to undergo randomization within 10 hours- MRI DWI 82-300 cc- Patients exposed to IV tPA up to 4.5 hours, no TPA, endovascular patients excluded |
| Randomization | 1:1 IV RP-1127 vs. Placebo |
| Sites | 18 centers total |
| Sample Size | 83 patients enrolled and treated |
| Follow Up | Follow-up: Day 30 and 90, 6 and 12 months |

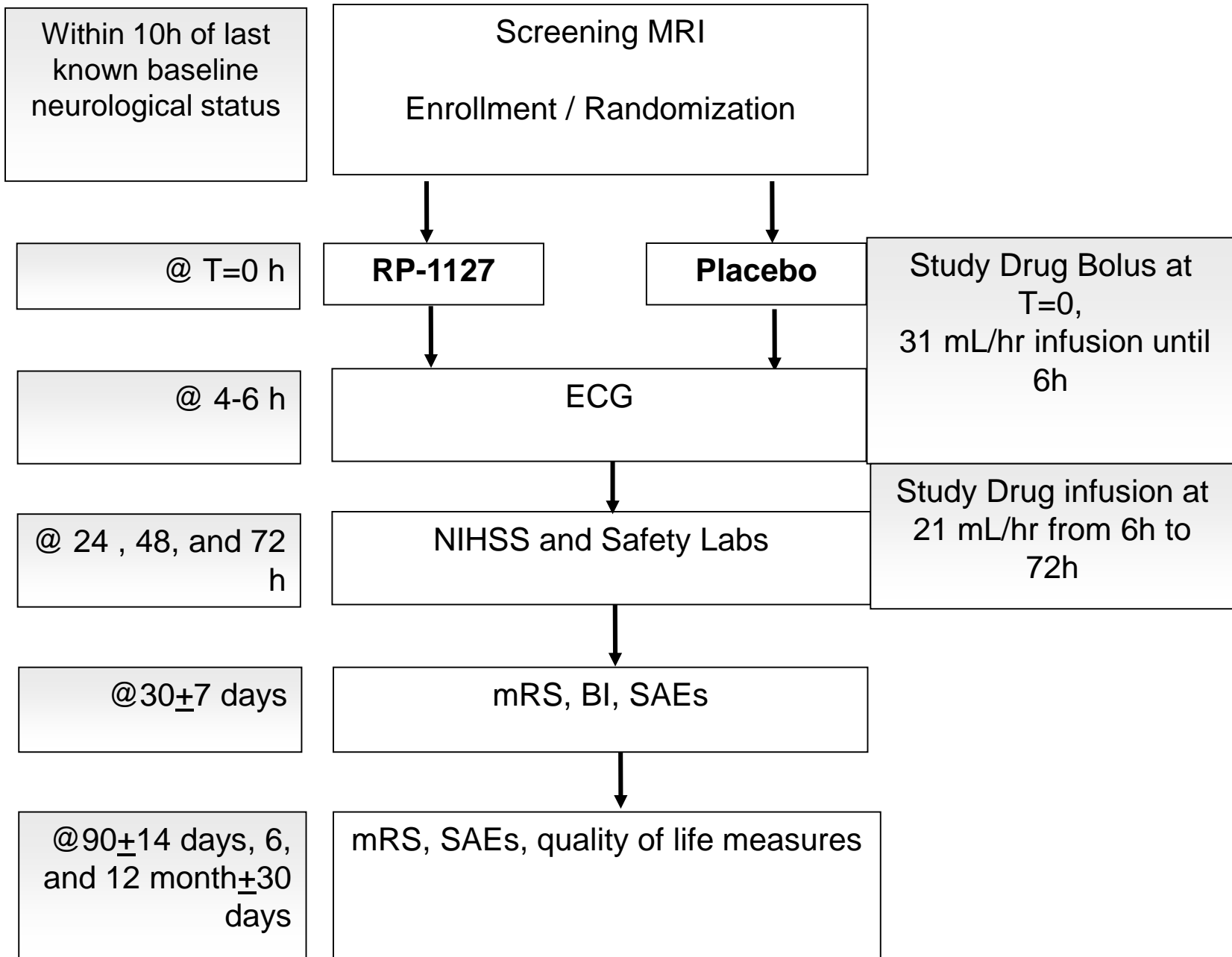
Analysis

Primary

- **Per protocol**
- Pre-specified lesion volume as determined by core imaging laboratory
- Subjects who received intervention within 11 hours

Secondary

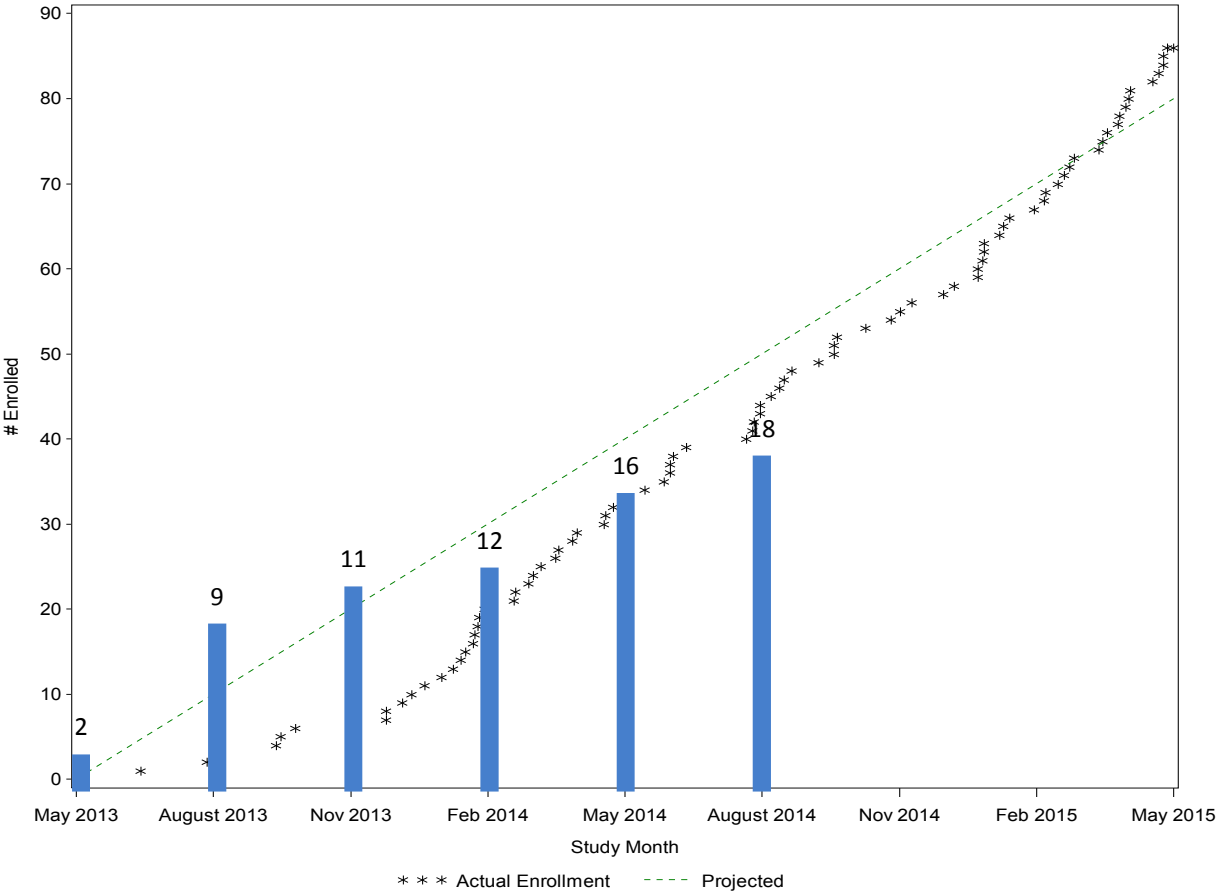
- Modified intention to treat
- All randomized patients for whom study drug was initiated



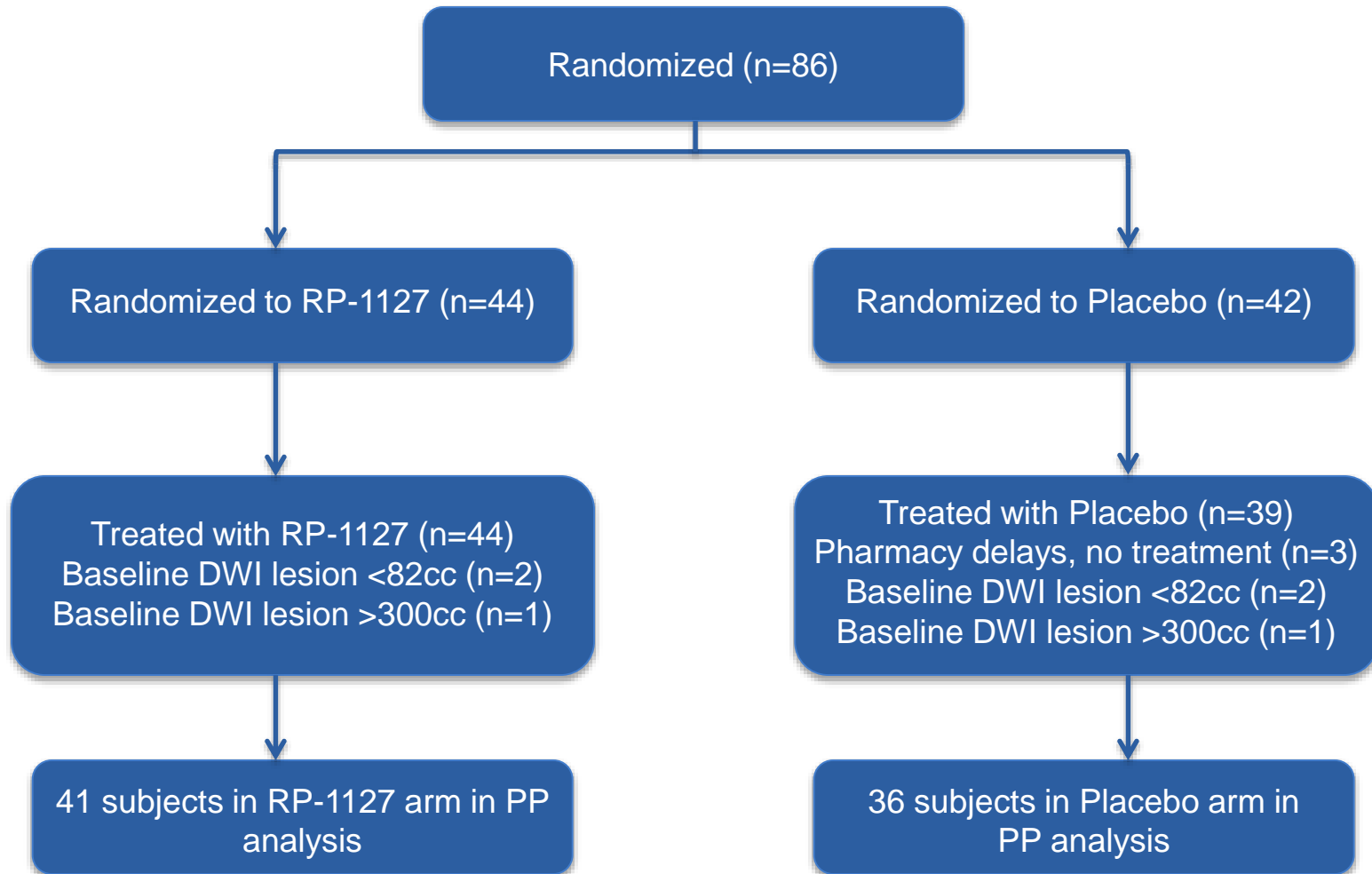
Study Endpoints

| | |
|-------------------------------------|---|
| Primary Safety | Frequency of (significant) adverse events All cause mortality |
| Primary Efficacy | Frequency of composite – Avoidance of decompressive craniectomy AND modified Rankin ≤ 4 at 90 days |
| Secondary Efficacy- Clinical | Subjects undergoing DC and death |
| Secondary Efficacy- Imaging | Change between baseline and 72-96 hour ipsilateral hemisphere volume by MRI Change between baseline and 72-96 hour swelling measurement by MRI |
| Other key a priori analyses | Midline shift between baseline and 72-96 hour imaging |

Enrollment



Randomization & Follow Up



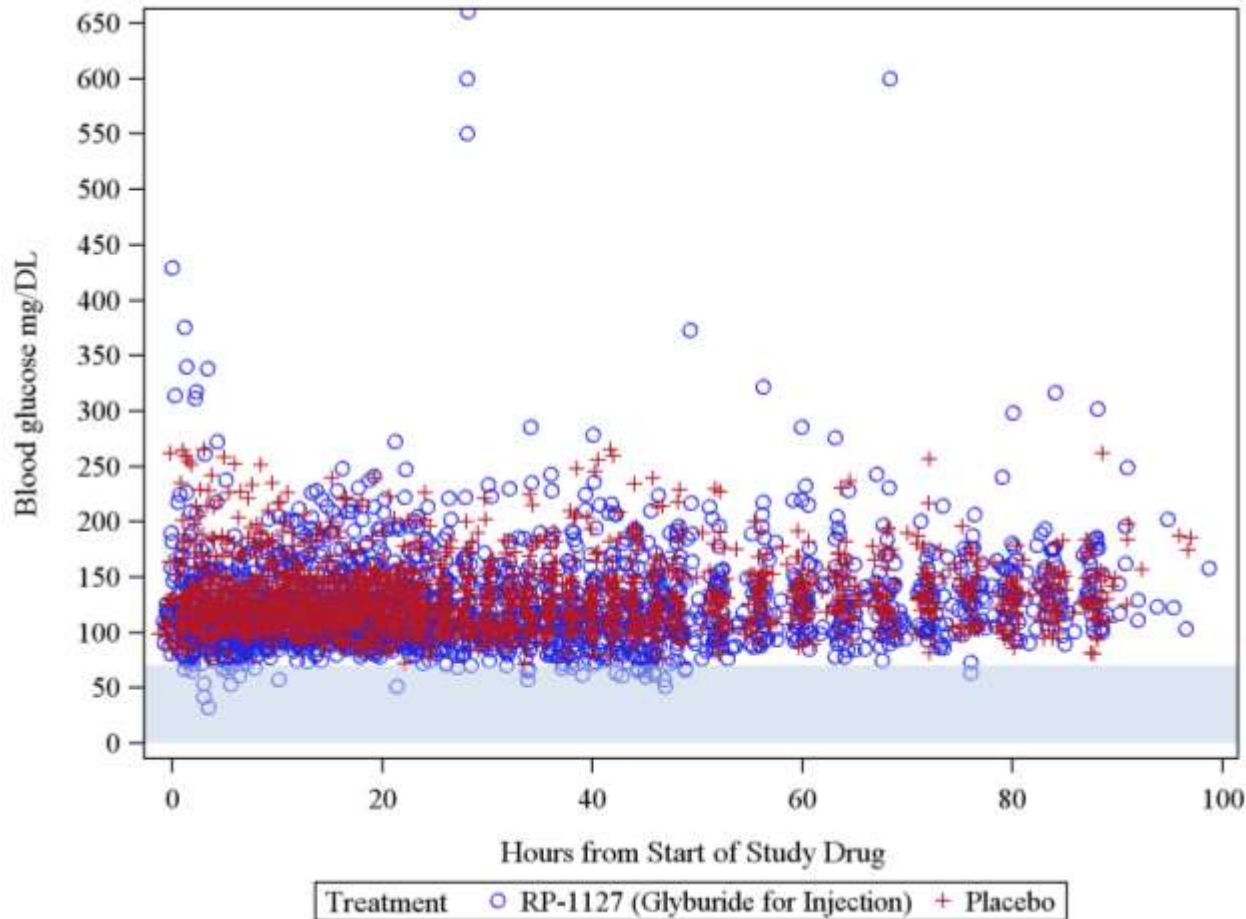
Baseline Characteristics

| Characteristics | RP-1127 (N=41) | Placebo (N=36) | p-value |
|---|----------------|----------------|-------------|
| Gender (Male) | 61% (25) | 72% (26) | 0.30 |
| Age (Mean) | 58 | 63 | 0.07 |
| Race (White) | 85% (35) | 83% (30) | 0.97 |
| Glucose (mg/dL) | 153 | 134 | 0.96 |
| NIHSS | 19 | 21 | 0.37 |
| IV TPA | 61% (25) | 61% (22) | 0.99 |
| Left side infarct | 49% (20) | 56% (20) | 0.55 |
| Time to study drug (h) | 8.8 | 9 | 0.55 |
| Mean baseline DWI (cm³) | 157 | 163 | 0.53 |

Primary Endpoint

| | RP-1127 | Placebo | p-value |
|--|----------|----------|---------|
| <u>EFFICACY</u> | | | |
| Functional Outcome Composite: Avoidance of DC AND mRS 0-4 | 17 (42%) | 14 (39%) | 0.77 |
| <u>SAFETY</u> | | | |
| Serious Adverse Events | 30 (68%) | 28 (72%) | 0.72 |

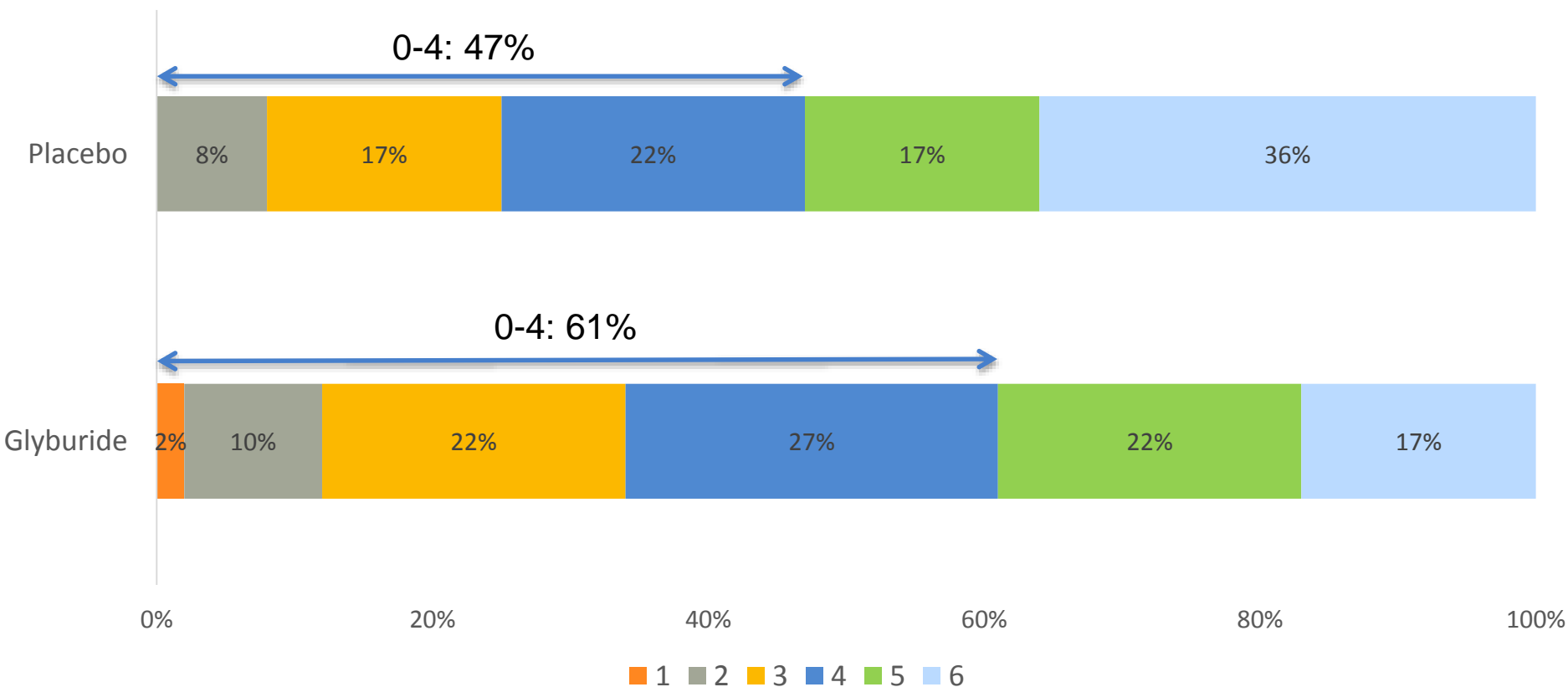
Blood Glucose & Hypoglycemia



| Trt | N | N (%) subjects with hypoglycemia blood glucose <55 mg/dL |
|---------|----|--|
| Glyb | 44 | 4 |
| Placbo | 39 | 0 |
| Total | 83 | 4 (4.8%) |
| p-value | | pval=0.12 (Fishers) |

Secondary and Tertiary Endpoints

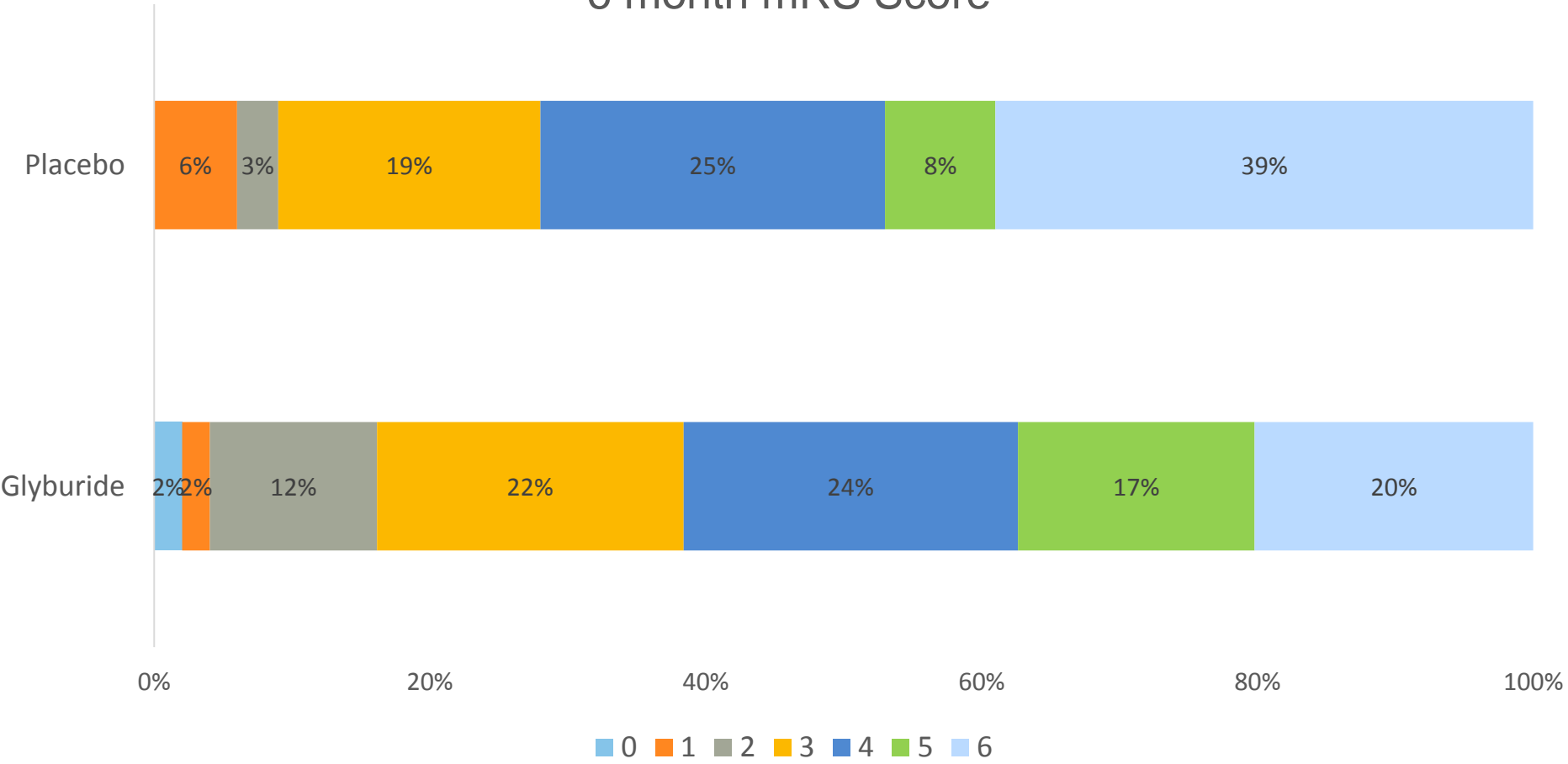
90-day mRS Score



Odds Ratio 1.7 for mRS 0-4 (p-value=0.23)
SHIFT Analysis (p-value=0.12)

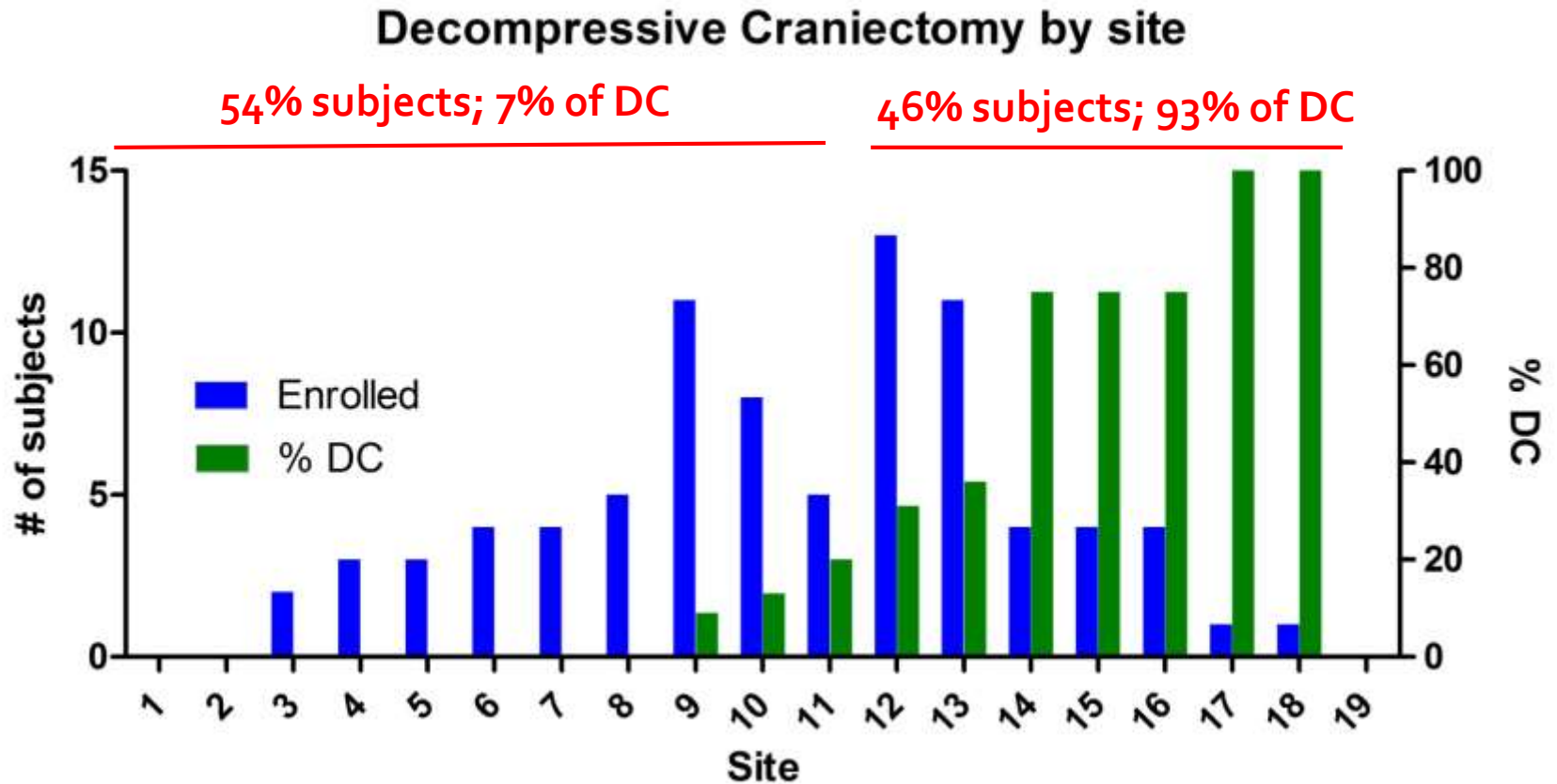
Secondary and Tertiary Endpoints

6 month mRS Score

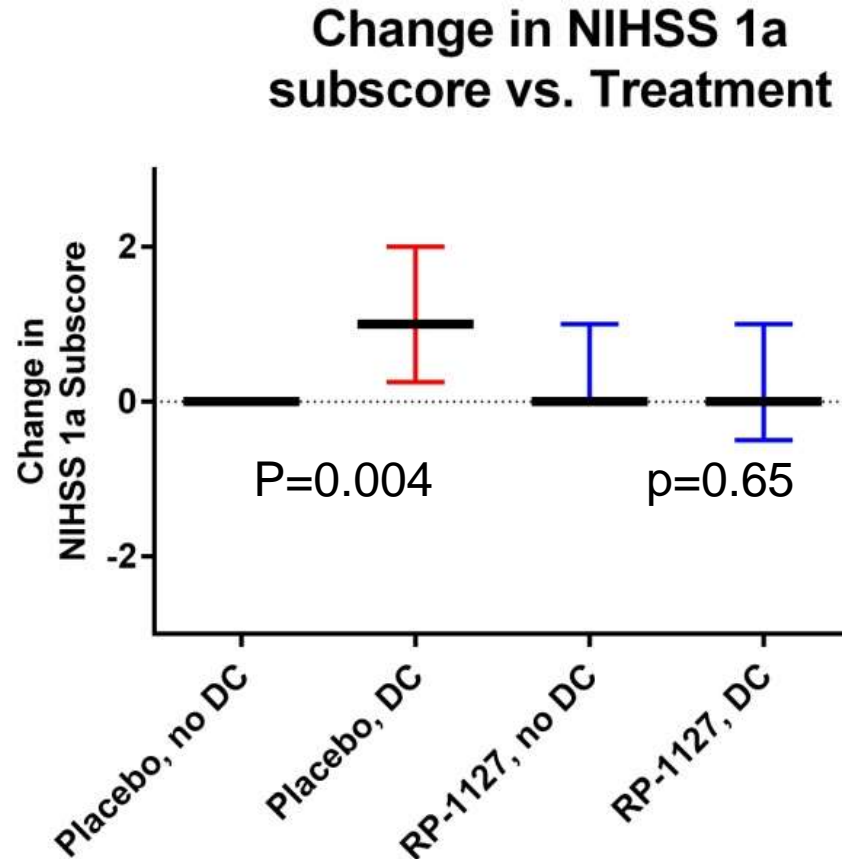


SHIFT Analysis (p-value=0.13)

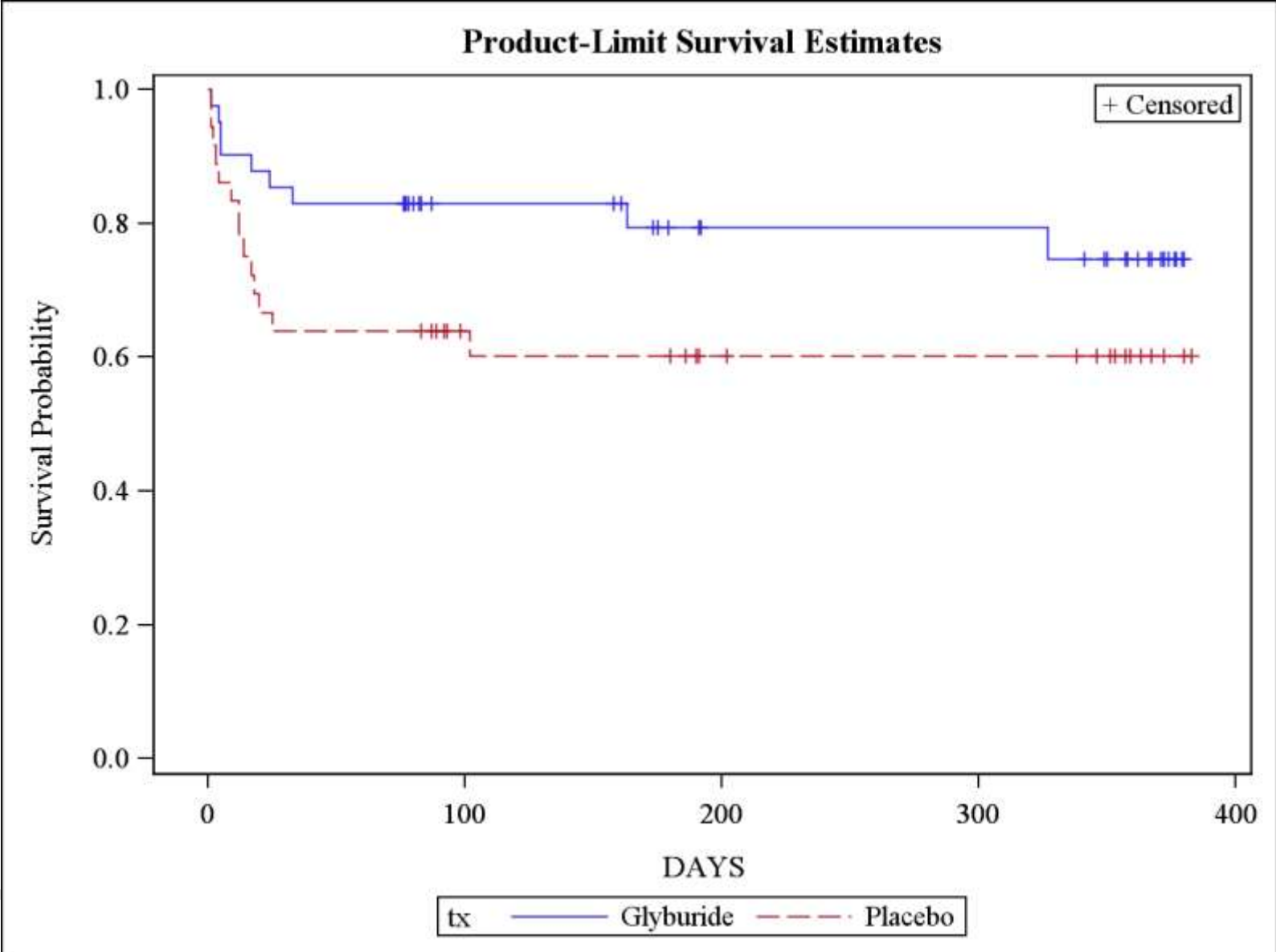
Secondary and Tertiary Endpoints



DC and Decreased Level of Arousal

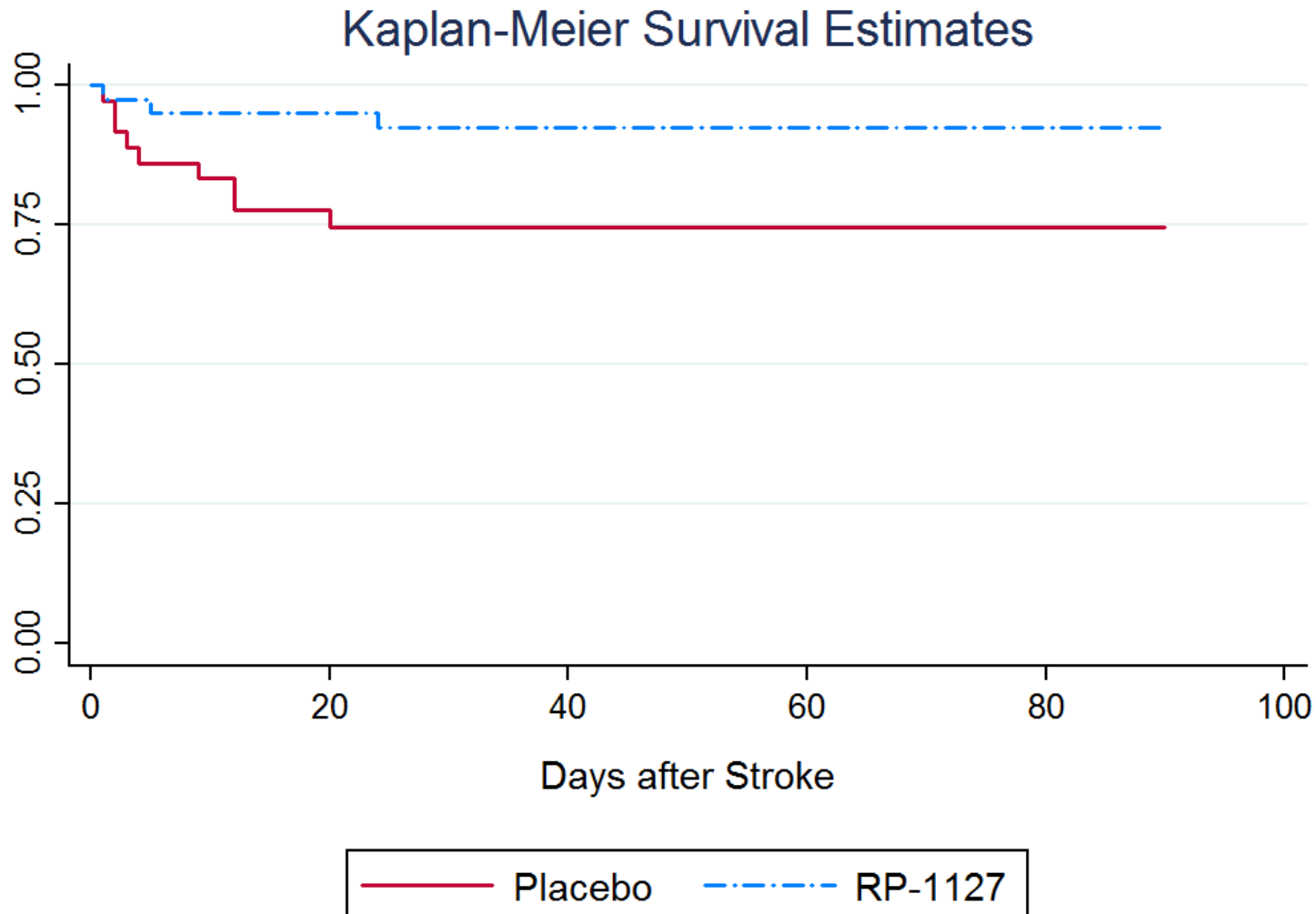


Secondary and Tertiary Endpoints



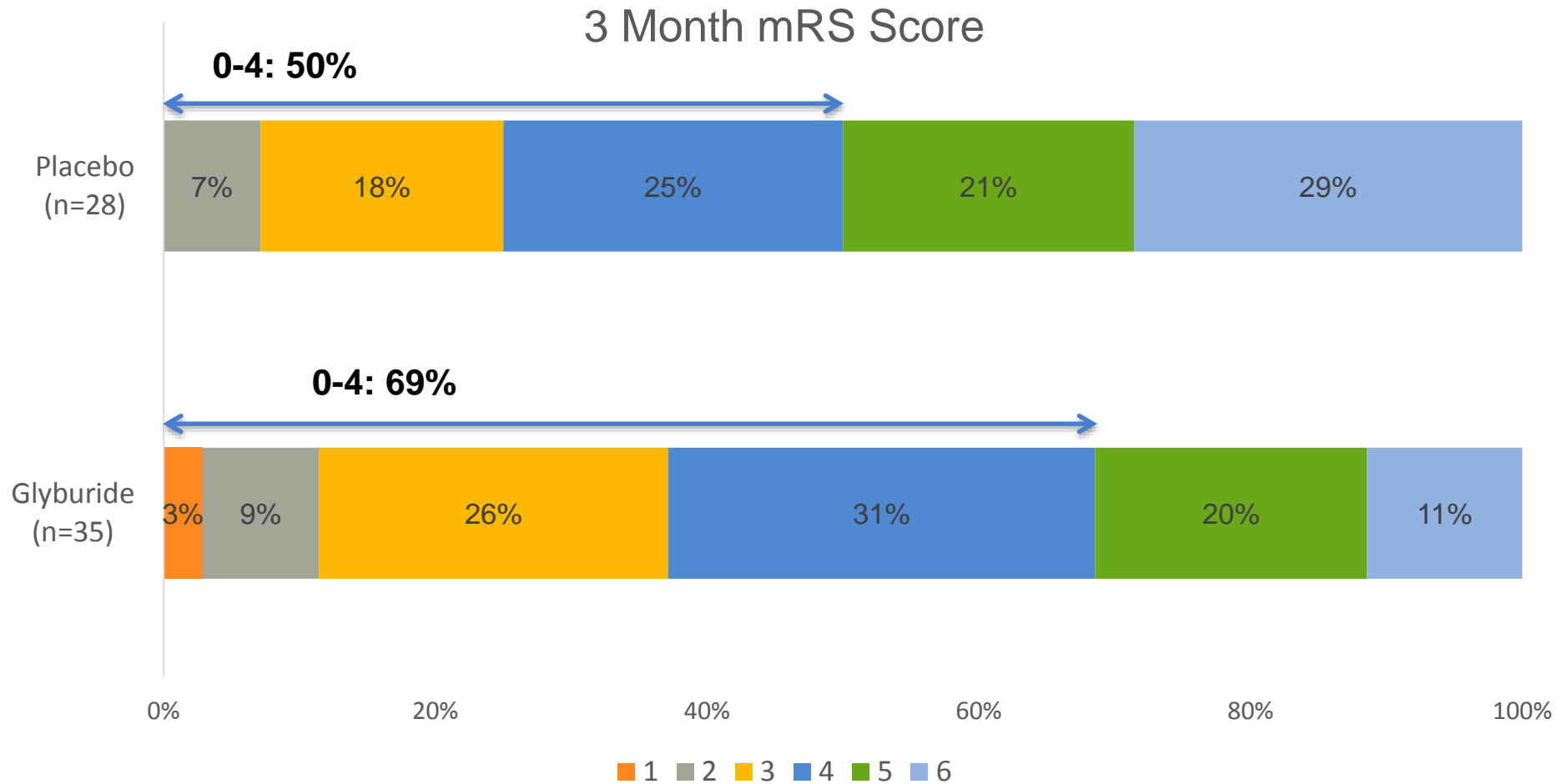
P=0.06

Adjudicated Neurological Deaths



P=0.03

Exploratory Analysis Under Age 70



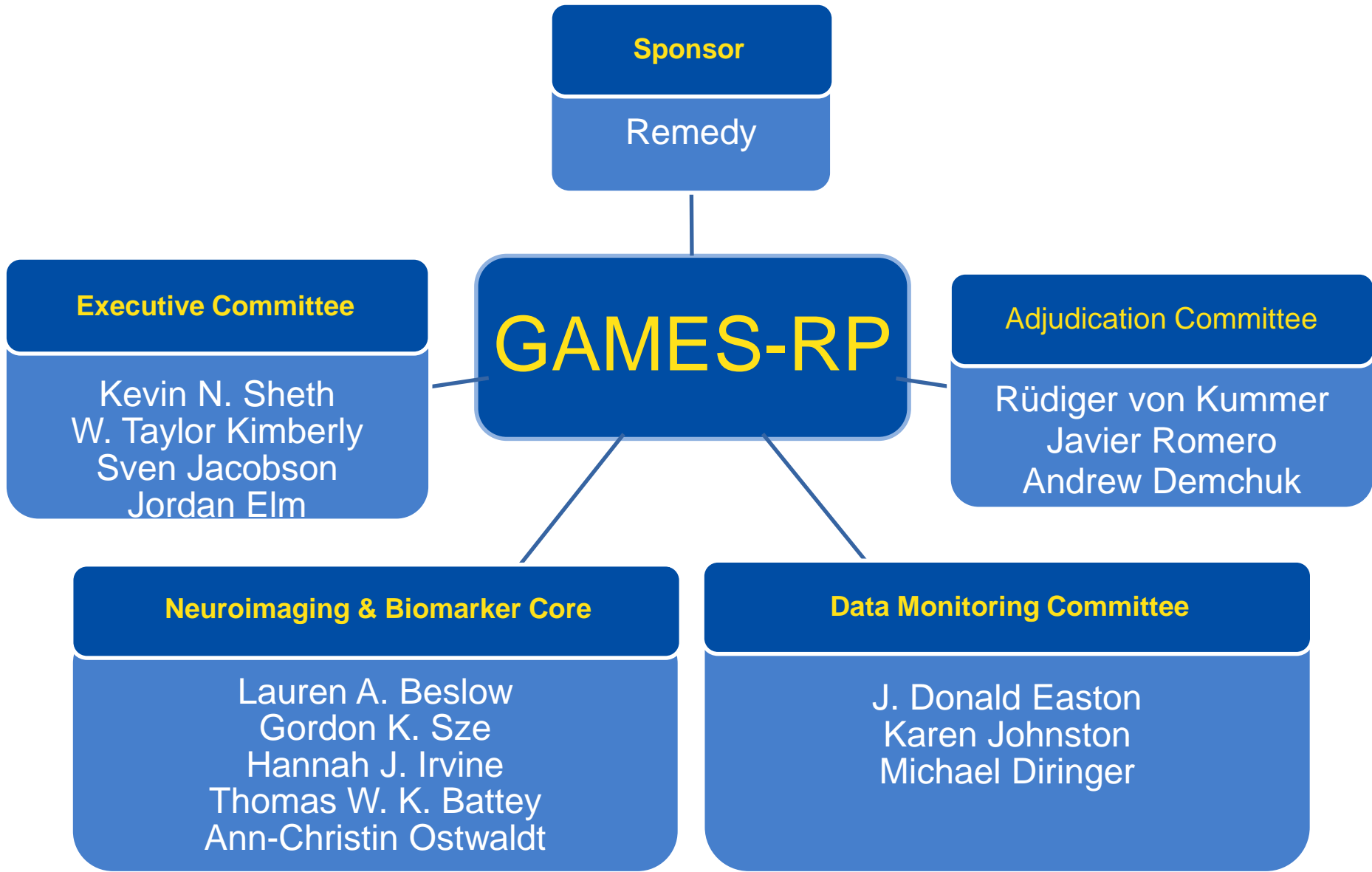
SHIFT Analysis (p-value=0.048)

Discussion

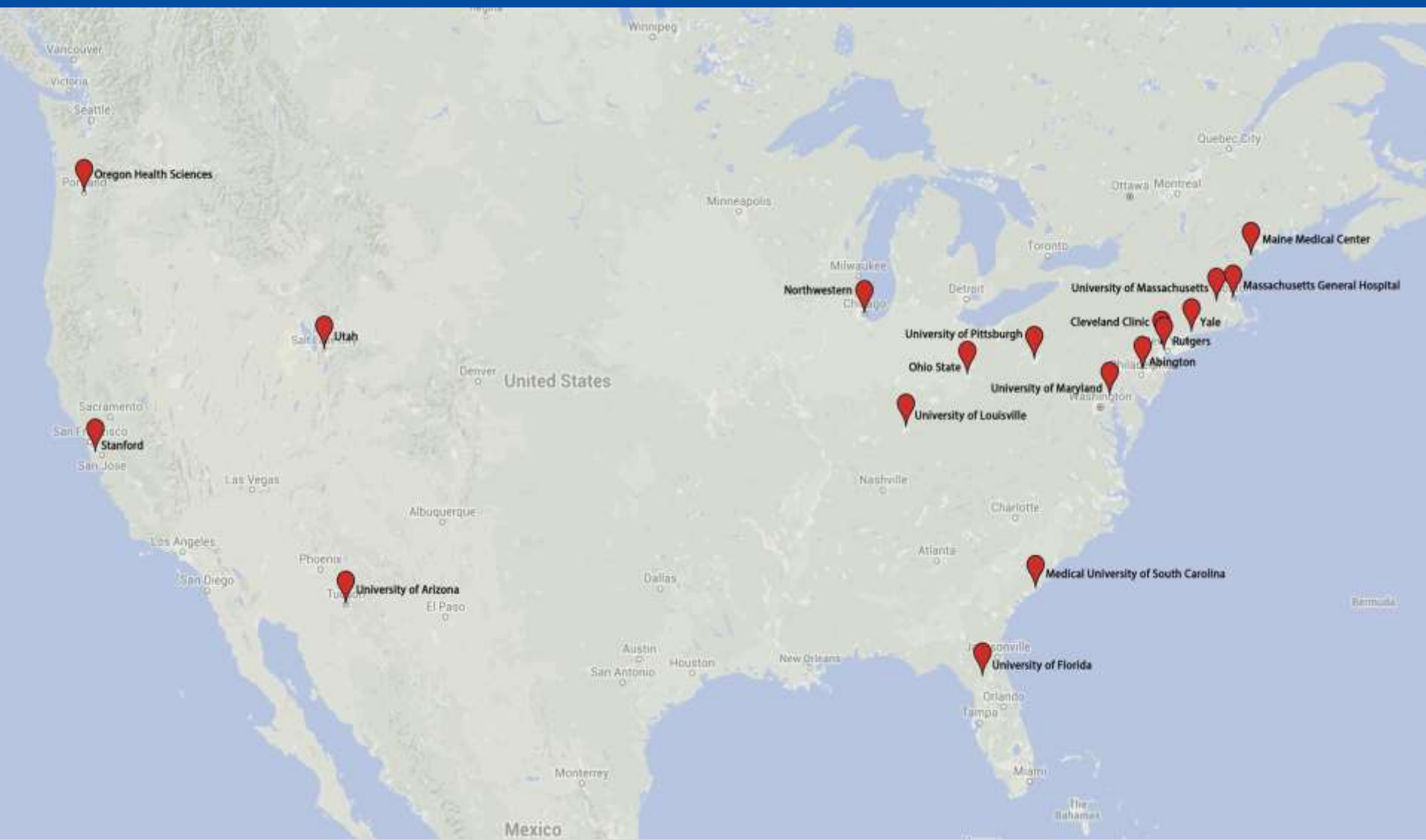
- RP-1127 is safe in patients with ischemic stroke, but it did not meet the primary pre-specified efficacy endpoint
- RP-1127 was associated with a trend towards reduced mortality
- RP-1127 reduces neurological deaths

Discussion

- DC rates varied across sites and standardization may be challenging. As a result, DC is not an ideal endpoint
- Patient age and earlier time to treatment may important factors in future studies
- Further analyses of intermediate endpoints related to brain swelling to be presented Friday



Site Map



Thank you!

We look forward to **GAMES 3!**