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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for the Clinical Trial Net of the German Competence Network Stroke

82 cc is the key number within 6 hours
Pilot Study of Intravenous Glyburide in Patients With a Large Ischemic Stroke

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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

<table>
<thead>
<tr>
<th><strong>Design</strong></th>
<th>U.S., multi-center, prospective, randomized double-blinded study</th>
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</thead>
</table>
| **Population and Inclusion Criteria** | - 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
Within 10h of last known baseline neurological status

Screening MRI
Enrollment / Randomization

@ T=0 h

RP-1127

Placebo

Study Drug Bolus at T=0, 31 mL/hr infusion until 6h

@ 4-6 h

ECG

Study Drug infusion at 21 mL/hr from 6h to 72h

@ 24, 48, and 72 h

NIHSS and Safety Labs

@30±7 days

mRS, BI, SAEs

@90±14 days, 6, and 12 month±30 days

mRS, SAEs, quality of life measures
<table>
<thead>
<tr>
<th>Study Endpoints</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Safety</strong></td>
<td>Frequency of (significant) adverse events All cause mortality</td>
</tr>
<tr>
<td><strong>Primary Efficacy</strong></td>
<td>Frequency of composite – Avoidance of decompressive craniectomy AND modified Rankin ≤ 4 at 90 days</td>
</tr>
<tr>
<td><strong>Secondary Efficacy- Clinical</strong></td>
<td>Subjects undergoing DC and death</td>
</tr>
<tr>
<td><strong>Secondary Efficacy- Imaging</strong></td>
<td>Change between baseline and 72-96 hour ipsilateral hemisphere volume by MRI</td>
</tr>
<tr>
<td></td>
<td>Change between baseline and 72-96 hour swelling measurement by MRI</td>
</tr>
<tr>
<td><strong>Other key a priori analyses</strong></td>
<td>Midline shift between baseline and 72-96 hour imaging</td>
</tr>
</tbody>
</table>
Enrollment

- Post-treatment Scan (t = 76 hours)

Actual Enrollment vs. Projected Enrollment:

- May 2013: 2
- August 2013: 9
- November 2013: 11
- February 2014: 12
- May 2014: 16
- August 2014: 18

Study Month:
- May 2013
- August 2013
- November 2013
- February 2014
- May 2014
- August 2014
- November 2014
- February 2015
- May 2015
## Baseline Characteristics

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

<table>
<thead>
<tr>
<th></th>
<th>RP-1127</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EFFICACY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional Outcome Composite: Avoidance of DC AND mRS 0-4</td>
<td>17 (42%)</td>
<td>14 (39%)</td>
<td>0.77</td>
</tr>
<tr>
<td><strong>SAFETY</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serious Adverse Events</td>
<td>30 (68%)</td>
<td>28 (72%)</td>
<td>0.72</td>
</tr>
</tbody>
</table>
Blood Glucose & Hypoglycemia

<table>
<thead>
<tr>
<th>Trt</th>
<th>N</th>
<th>N (%) subjects with hypoglycemia blood glucose &lt;55 mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyb</td>
<td>44</td>
<td>4</td>
</tr>
<tr>
<td>Placbo</td>
<td>39</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>83</td>
<td>4 (4.8%)</td>
</tr>
</tbody>
</table>

p-value

pval=0.12 (Fishers)
Secondary and Tertiary Endpoints

90-day mRS Score

Placebo
- 0-4: 47%
- 8% (1), 17% (2), 22% (4), 17% (5), 36% (6)

Glyburide
- 0-4: 61%
- 2% (1), 10% (2), 22% (4), 27% (5), 22% (6), 17% (6)

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

<table>
<thead>
<tr>
<th>Placebo</th>
<th>Glyburide</th>
</tr>
</thead>
<tbody>
<tr>
<td>6%</td>
<td>2%</td>
</tr>
<tr>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>19%</td>
<td>12%</td>
</tr>
<tr>
<td>25%</td>
<td>22%</td>
</tr>
<tr>
<td>8%</td>
<td>24%</td>
</tr>
<tr>
<td>39%</td>
<td>17%</td>
</tr>
</tbody>
</table>

**SHIFT Analysis (p-value=0.13)**
Secondary and Tertiary Endpoints

54% subjects; 7% of DC

46% subjects; 93% of DC
DC and Decreased Level of Arousal

Change in NIHSS 1a subscore vs. Treatment

- Placebo, no DC
- Placebo, DC
- RP-1127, no DC
- RP-1127, DC

P=0.004
p=0.65
Secondary and Tertiary Endpoints

Product-Limit Survival Estimates

Survival Probability

DAYS

tx  Glyburide  Placebo

P=0.06
Adjudicated Neurological Deaths

Kaplan-Meier Survival Estimates

Days after Stroke

P=0.03

Placebo

RP-1127
Exploratory Analysis Under Age 70

3 Month mRS Score

Placebo (n=28)
- 7% (0)
- 18% (1)
- 25% (2)
- 21% (3)
- 29% (4)

Glyburide (n=35)
- 3% (0)
- 9% (1)
- 26% (2)
- 31% (3)
- 20% (4)
- 11% (5)

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
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Site Map
Thank you!

We look forward to GAMES 3!