GAMES – RP Trial

Analysis of intermediate endpoints

W Taylor Kimberly MD PhD and Kevin N Sheth MD
for the GAMES-RP investigators
Disclosures

- Sponsor of the trial is Remedy Pharmaceuticals, Inc.
- AHA / ASA
- NIH / NINDS
Introduction

The GAMES-RP trial was a phase II study that evaluated intravenous glyburide (RP-1127) for the prevention of brain edema after large hemispheric stroke.

The prevention of brain edema represents a new therapeutic strategy.

As a consequence, there is uncertainty about what the appropriate clinical endpoints are for this indication.
Introduction

An important goal of GAMES-RP was to include intermediate endpoints to:

1) learn as much about the disease as possible
2) guide interpretation of clinical outcomes and
3) inform future trial design
# GAMES-RP Study Design

<table>
<thead>
<tr>
<th>Design</th>
<th>A multi-center, prospective, randomized double-blind study</th>
</tr>
</thead>
</table>
| Population      | - Large hemispheric stroke  
                 |  - IV tPA up to 4.5 hours was permitted  
                 |  - Patients treated with endovascular thrombectomy were excluded |
| Randomization   | RP-1127 (intravenous glyburide) vs. Placebo              |
| Sites           | 18 centers across the U.S.                               |
| Sample Size     | 83 patients enrolled and treated                         |
GAMES-RP Study Design

STUDY ACTIVITIES

stroke onset

study drug bolus

10 hr

Day 1

Day 2

Day 3

CT scans

Day 4

blood sampling for biomarker analysis

study MRI
## 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 (hr)</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 Outcomes

<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>Composite Outcome: mRS 0-4 and avoidance of DC</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>
Other Clinical Endpoints

Kaplan-Meier Survival Curve

Cumulative Probability of Survival

RP-1127 vs Placebo

Days from Baseline

N  %

RP-1127  6  (17%)
Placebo  13  (36%)

P=0.06

50% reduction
Other Clinical Endpoints

Adjudicated Neurological deaths

Cumulative Probability of Survival

Days from Baseline

P = 0.03

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP-1127</td>
<td>3</td>
<td>7%</td>
</tr>
<tr>
<td>Placebo</td>
<td>9</td>
<td>25%</td>
</tr>
</tbody>
</table>

Adjudicated Edema deaths

Cumulative Probability of Survival

Days from Baseline

P = 0.008

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP-1127</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Placebo</td>
<td>8</td>
<td>22%</td>
</tr>
</tbody>
</table>
Other Clinical Endpoints

Cochran-Mantel-Haenszel p=0.12
Intermediate Endpoints

The trial did not meet its primary efficacy endpoint

However, there was improved survival and a trend toward improved functional outcome

Therefore, we evaluated intermediate endpoints to determine whether there was additional evidence to support a potential effect of RP-1127
Intermediate Endpoints

The GAMES program was built on a foundation of preclinical evidence that informed the selection of intermediate endpoints.

**Neuroimaging biomarker:** Midline shift

**Plasma biomarker:** Total MMP-9
## Intermediate Endpoints

<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>Time to BL MRI (hr)</td>
<td>6.0 ± 1.6</td>
<td>5.8 ± 1.6</td>
<td>0.50</td>
</tr>
<tr>
<td>Time to FU MRI (days)</td>
<td>3.4 ± 0.8</td>
<td>3.5 ± 0.6</td>
<td>0.48</td>
</tr>
<tr>
<td>Baseline DWI volume (mL)</td>
<td>157 ± 62</td>
<td>163 ± 64</td>
<td>0.59</td>
</tr>
<tr>
<td>Baseline MMP-9 (ng/mL)</td>
<td>413 ± 377</td>
<td>427 ± 357</td>
<td>0.88</td>
</tr>
<tr>
<td>Midline shift (mm)</td>
<td>4.6 ± 3.6</td>
<td>8.4 ± 4.9</td>
<td>0.0006</td>
</tr>
<tr>
<td>Average MMP-9 (ng/mL)</td>
<td>211 ± 138</td>
<td>345 ± 251</td>
<td>0.006</td>
</tr>
</tbody>
</table>
Midline Shift

- 5mm
- 9mm

RP-1127

Placebo
Midline Shift

LEVEL OF CONSCIOUSNESS

Post hoc Sensitivity Analysis

72-96 hr or prior to DC

72-96 hr, prior to DC or last scan prior to death

**Midline Shift**

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Midline shift (mm)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP-1127</td>
<td>6.0 mm</td>
<td>p=0.014</td>
</tr>
<tr>
<td>Placebo</td>
<td>9.0 mm</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Midline shift (mm)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RP-1127</td>
<td>6.0 mm</td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>8.5 mm</td>
<td>p=0.040</td>
</tr>
</tbody>
</table>
• Plasma MMP-9 level is elevated after stroke

• Higher MMP-9 has been associated with brain edema

• Preclinical studies and preliminary studies in GAMES-Pilot suggested that RP-1127 may reduce MMP-9
Massachusetts General Hospital

Total MMP-9

**,** $P=0.006$
Total MMP-9 and Edema

\[ P = 0.024 \]
Limitations

• GAMES-RP was a phase II trial and further study is needed to evaluate clinical efficacy.

• Imaging endpoints are susceptible to missing data, which may introduce bias. Sensitivity analyses evaluated the robustness of the findings.

• There is uncertainty about the role of MMP-9 and what it may reflect (what cellular sources and biological processes). Pharmacologic intervention provides an opportunity to clarify those uncertainties.
• RP-1127 treatment led to a reduction in midline shift, a marker of brain edema
• RP-1127 also reduced plasma total MMP-9 level
• Plasma MMP-9 was associated with edema in this study
Summary

• Taken together, these analyses suggest that RP-1127 reduces brain edema in large stroke patients

• This effect is consistent with the proposed mechanism based on experimental animal models

• The planned GAMES-3 trial will address whether RP-1127 improves clinical outcome
GAMES-RP sites
Acknowledgments

**Executive Committee**
Kevin N. Sheth
W. Taylor Kimberly
Jordan J. Elm
Sven Jacobson

**Neuroimaging Core**
Lauren A. Beslow
Gordon K. Sze
Tom W. K. Battey
Ann-Christin Ostwaldt

**Biomarker Core**
Hannah Irvine

**Data Monitoring Committee**
J. Donald Easton
Karen C. Johnston
Michael Diringer

**Adjudication Committee**
Rüdiger von Kummer
Javier Romero
Andrew Demchuk

**Other Contributors**
J. Marc Simard
Gregory J. del Zoppo
Barney Stern
Holly Hinson
Bradley Molyneaux
Thank you