Pyruvate kinase (PK) deficiency is a congenital hemolytic anemia caused by deficiency of the PK enzyme in red blood cells. PK-R mutations lead to detectable hydrops fetus associated with reduced ATP levels and premature hemolysis of red cells. Small-molecule allosteric activators of PK-R have been shown to increase ATP and decrease 2,3-DPG, which results in enhanced red cell oxygen unloading and improved tissue oxygenation.

**METHODS**

Phase 1, single-center, open-label, randomized, double-blind, placebo-controlled study with MAD and MAD cohort. Doses and treatment schedules are shown in Table 1.

**RESULTS**

Participants: Healthy, non-smoking men and women (vitamin B12 deficiency potential) aged 18–60 years who provided written informed consent.

**Assessments:** Baseline, and multiple sample collections for PK/PD determination. Assessments included treatment emergent adverse events (AEs), laboratory parameters; results are summarized by AG-519 dose and by pooling AEs in pooled AG-519 group.

**Participant flow:** A total of 47 healthy volunteers (10 placebo, 6 each at 25, 50, 125, 250, 375 mg AG-519 q12hr for 14 days) were randomized for Part 1.”

**CONCLUSIONS**

- AG-519 is well tolerated in healthy subjects at doses ranging from 10 to 375 mg q12hr for 14 days.
- AG-519 demonstrated a tolerable pharmacokinetic profile.
- The robust dose-dependent increases in ATP and 2,3-DPG blood levels are consistent with increased activity of PK-R, the expected pharmacodynamic effect of AG-519.
- These data support the hypothesis that AG-519 may be able to enhance glycolytic activity in red cells.

Acknowledgments: Supported by MBC Pharma Solutions, New York, NY, USA; Agios Pharmaceuticals, Cambridge, MA, USA; Hua Yang, MBC Pharma Solutions, Newtown, PA, USA; and Lee Silverman, MBC Pharma Solutions, Newtown, PA, USA.

Figure 1. Study design

<table>
<thead>
<tr>
<th>Study phase</th>
<th>Dose (mg)</th>
<th>Treatment schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Part 1</td>
<td>Placebo</td>
<td>10 mg q12hr, n=10</td>
</tr>
<tr>
<td></td>
<td>AG-519</td>
<td>25 mg q12hr, n=6</td>
</tr>
<tr>
<td></td>
<td>AG-519</td>
<td>50 mg q12hr, n=6</td>
</tr>
<tr>
<td></td>
<td>AG-519</td>
<td>125 mg q12hr, n=6</td>
</tr>
<tr>
<td></td>
<td>AG-519</td>
<td>250 mg q12hr, n=6</td>
</tr>
<tr>
<td></td>
<td>AG-519</td>
<td>375 mg q12hr, n=6</td>
</tr>
<tr>
<td>Part 2</td>
<td>Placebo</td>
<td>10 mg q12hr, n=30</td>
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<tr>
<td></td>
<td>AG-519</td>
<td>125 mg q12hr, n=6</td>
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<tr>
<td></td>
<td>AG-519</td>
<td>250 mg q12hr, n=6</td>
</tr>
<tr>
<td></td>
<td>AG-519</td>
<td>375 mg q12hr, n=6</td>
</tr>
</tbody>
</table>

**Safety:**
- There were no unexpected safety observations.
- No drug-related serious adverse events (SAEs) were reported.
- The most common treatment-emergent AEs were related to the gastrointestinal system and were generally mild to moderate in severity.
- There was no premature hemolysis of red cells.

**Pharmacodynamics:**
- A dose-dependent decrease in blood 2,3-DPG concentration was observed following a single AG-519 oral dose, reaching steady state after 24 hr and remaining decreased throughout the dosing period (Figure 4).
- There were minimal increases in blood ATP levels after a single dose of AG-519.
- A dose-dependent increase in blood PK activity was observed following multiple doses of AG-519, reaching steady state before the morning dose on Day 12 and persisting throughout the dosing period.

**Pharmacokinetics:**
- Pharmacokinetic results on Day 14 following multiple doses of AG-519 showed a mean decrease in blood ATP concentration of 21.7 ng/mL from baseline (9.02 to 6.85 ng/mL).
- Pharmacokinetic results showed that AG-519 is well tolerated in healthy subjects at doses ranging from 10 to 375 mg q12hr for 14 days.
- AG-519 demonstrated a tolerable pharmacokinetic profile.
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**DISCUSSION**

- The PK/PD data from healthy subjects will inform dose selection for potential studies of AG-519 in patients with PK-R deficiency.
- The PK/PD data will also inform dose selection for potential studies of AG-519 in patients with PK-R deficiency.

**ACKNOWLEDGMENTS**

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