Phase 1 Multiple Ascending Dose Study of the Safety, Tolerability and Pharmacokinetics/Pharmacodynamics of AG-348, a First-in-Class Allosteric Activator of Pyruvate Kinase R, in Healthy Subjects

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6th EUROPEAN SYMPOSIUM ON RARE ANAEMIAS
1st Dutch-Belgian meeting for patients and health professionals

21st - 22nd November 2015
Amsterdam - The Netherlands
## Disclosures

<table>
<thead>
<tr>
<th>Company name</th>
<th>Research support</th>
<th>Employee</th>
<th>Consultant</th>
<th>Stockholder</th>
<th>Speakers bureau</th>
<th>Advisory board</th>
<th>Other</th>
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<tbody>
<tr>
<td>Agios</td>
<td></td>
<td>X</td>
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### This talk is applicable for:

<table>
<thead>
<tr>
<th></th>
<th>Definite</th>
<th>Probable</th>
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<tr>
<td>Thalassemia’s</td>
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<td>Sickle cell disease</td>
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<tr>
<td>Membrane disorders (e.g. sferocytosis)</td>
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<tr>
<td>Enzyme defects (e.g. PKD, G6PD)</td>
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<td>X</td>
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<tr>
<td>PNH</td>
<td></td>
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<tr>
<td>Other forms of hemolytic disease</td>
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Disclosures

- This study was funded by Agios Pharmaceuticals
- Hua Yang, Elizabeth Merica, Yue Chen, Hyeryun Kim, Penelope A Kosinski, Charles Kung, Meredith Goldwasser, Luke Utley, Sam Agresta, Ann Barbier: Agios – employees and stockholders
- Marvin Cohen, Bruce Silver: Agios – consultants
- Ronald Goldwater: Parexel International – employee
- Editorial assistance was provided by Christine Tomlins, PhD, Excel Scientific Solutions, Horsham, UK, and supported by Agios
Key Points

- Pyruvate Kinase (PK) deficiency is a serious, rare, genetic disease.

- AG-348 is a PK-R activator intended to correct the glycolytic pathway defect in patients with PK deficiency.

- Healthy volunteer study has established a safety profile at pharmacodynamically active doses that may be relevant to patients with PK deficiency.

- DRIVE PK, a global phase 2 study in patients, is now open and enrolling
AG-348: Allosteric Activator of Wild-Type and Mutant PK-R

PK-R enzyme: active tetramer
AG-348 binds at the PK-R dimer-dimer interface

Kung C et al. 55th ASH Annual meeting 2013, Abstract 2180
AG-348 activates PK-R wild type and nearly all mutant enzymes tested

Kung C et al. 56th ASH Annual meeting 2014, Abstract 4010
### AG-348 Restores the Glycolytic Pathway in Models

**PK Deficient**

**Patient Red Blood Cell Samples**

<table>
<thead>
<tr>
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<tbody>
<tr>
<td><strong>PK Activity (relative to DMSO)</strong></td>
<td><strong>PK Activity (relative to DMSO)</strong></td>
<td><strong>PK Activity (relative to DMSO)</strong></td>
</tr>
<tr>
<td>DMSO</td>
<td>1.0 ± 0.2</td>
<td>DMSO</td>
</tr>
<tr>
<td>AG-348</td>
<td>4.5 ± 0.3</td>
<td>AG-348</td>
</tr>
<tr>
<td><strong>2,3-DPG (relative to DMSO)</strong></td>
<td><strong>2,3-DPG (relative to DMSO)</strong></td>
<td><strong>2,3-DPG (relative to DMSO)</strong></td>
</tr>
<tr>
<td>DMSO</td>
<td>1.0 ± 0.2</td>
<td>DMSO</td>
</tr>
<tr>
<td>AG-348</td>
<td>0.5 ± 0.1</td>
<td>AG-348</td>
</tr>
<tr>
<td><strong>ATP (relative to DMSO)</strong></td>
<td><strong>ATP (relative to DMSO)</strong></td>
<td><strong>ATP (relative to DMSO)</strong></td>
</tr>
<tr>
<td>DMSO</td>
<td>1.0 ± 0.2</td>
<td>DMSO</td>
</tr>
<tr>
<td>AG-348</td>
<td>2.5 ± 0.3</td>
<td>AG-348</td>
</tr>
</tbody>
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**Kung C et al. 56th ASH Annual meeting 2014, Abstract 4010**

*6th European Symposium on Rare Anaemias - 1st Dutch-Belgian meeting for patients and health professionals*
Objective: Establish the safety, tolerability and PD effects of AG-348

Randomized, double-blind, placebo controlled study
14 days of continuous dosing

Healthy men and postmenopausal women
(age 18–60 years)

In-patient period

Dosing

Day: –1 1 8 14 19 22 29

Multiple sample collections for PK/PD evaluation up to 120 hr after last dose

Final follow-up

n=8 per cohort
AG-348 → n=6
Placebo → n=2

Single ascending dose safety data informed dose selection for the study

120 mg q12hr
360 mg q12hr
700 mg q24hr
120 mg q24hr
60 mg q12hr
15 mg q12hr

q12hr = twice daily
q24hr = once daily

PK/PD = pharmacokinetic/pharmacodynamic

CT02149966
Demographics and Disposition

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo n=12</th>
<th>AG-348 n=36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>9 (75)</td>
<td>33 (92)</td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>3 (25)</td>
<td>3 (8)</td>
</tr>
<tr>
<td>Age in years, mean (SD)</td>
<td>37.8 (11.4)</td>
<td>42.8 (12.2)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>—</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Black</td>
<td>6 (50)</td>
<td>18 (50)</td>
</tr>
<tr>
<td>White</td>
<td>6 (50)</td>
<td>17 (47)</td>
</tr>
<tr>
<td>Body mass index in kg/m², mean (SD)</td>
<td>27.4 (2.3)</td>
<td>26.5 (2.0)</td>
</tr>
</tbody>
</table>

- 12 placebo treated and 32 of 36 AG-348 treated patients completed study:
  - Two withdrew due to AEs: Drug eruption (60 mg q12hr), grade 3 liver function test abnormalities at the highest dose explored (700 mg q12hr)
  - Two withdrew consent due to nausea and vomiting at the highest dose explored (700 mg q12hr)

AE = adverse event; SD = standard deviation

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AG-348 was well tolerated up to 360 mg oral q12 hr

- Drug-related events were grade 1 and 2
- One grade 3 event at 700 mg q12h (increased LFTs – DLT)

<table>
<thead>
<tr>
<th>AE, n (%)</th>
<th>Placebo n=12</th>
<th>15–360 mg q12hr n=30</th>
<th>700 mg q12hr n=6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>4 (33)</td>
<td>10 (33)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Most common treatment-related AEs (≥2 subjects):</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>—</td>
<td>—</td>
<td>5 (83)</td>
</tr>
<tr>
<td>Headache</td>
<td>1 (8)</td>
<td>1 (3)</td>
<td>4 (67)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>1 (8)</td>
<td>—</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Feeling hot</td>
<td>1 (8)</td>
<td>—</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>—</td>
<td>2 (7)</td>
<td>1 (17)</td>
</tr>
<tr>
<td>Restlessness</td>
<td>—</td>
<td>—</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>—</td>
<td>—</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (8)</td>
<td>—</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>1 (8)</td>
<td>—</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Drug eruption</td>
<td>—</td>
<td>2 (7)</td>
<td>—</td>
</tr>
<tr>
<td>Abdominal discomfort</td>
<td>2 (17)</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

AEs were graded using National Cancer Institute Common Terminology Criteria, version 4.03
- Changes in serum androgens and estrogens were observed
- Most changes remained within normal reference ranges for age and sex
- Levels recovered to baseline
- Endocrine/physiologic significance to be evaluated in phase 2 study
Pharmacokinetic and Pharmacodynamic Results
Pharmacokinetics

- AG-348 displayed low to moderate pharmacokinetic variability
- Plasma exposure increased dose-proportionally
  - At higher doses, exposure at Day 14 was lower than on Day 1
  - AG-348 is a moderate inducer of CYP3A4, the main clearance pathway for AG-348

Exposure to AG-348 measured by $\text{AUC}_{0-\tau}$ after single and multiple oral doses

Geometric mean ± SD
n=6 at each dose level except:
- n=5 for Day 14 of 60 mg q12hr
- n=3 for Day 14 of 700 mg q12hr
A ~50% increase from Baseline was observed with ≥60 mg AG-348

Levels remained elevated through 120 hours after the final dose
A ~50% decrease from Baseline was observed with ≥120 mg AG-348.

The concentration returned to Baseline 72 hours after the final dose.

Day 0 = Baseline value. Day 14 is the final day of dosing.
Transfusion-independent PK-deficient adults  
\( n=25 \) in each arm

**Primary endpoints:**
- Safety and tolerability

**Secondary endpoints:**
- Pharmacokinetics of AG-348
- PD response: ATP, 2,3-DPG
- **Indicators of clinical activity:** hemoglobin, hematocrit, reticulocyte count, and other hematologic parameters.

**Randomization**
- Arm 1: 300 mg q12hr
- Arm 2: 50 mg q12hr
- Optional 3\(^{rd}\) Arm

Screening

6-month dosing period

Natural History Study collaboration with Boston Children’s Hospital ongoing

Open, global phase 2 study: 14 centers in the US, Canada, and EU
## Visit Schedule

<table>
<thead>
<tr>
<th>Screening</th>
<th>Month 1</th>
<th>Months 2 &amp; 3</th>
<th>Months 4, 5 &amp; 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening 1</td>
<td>Day 1</td>
<td>Week 6</td>
<td>Week 16</td>
</tr>
<tr>
<td>Screening 2</td>
<td>Week 1</td>
<td>Week 9</td>
<td>Week 20</td>
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<tr>
<td></td>
<td>Week 2</td>
<td>Week 12</td>
<td>Week 24</td>
</tr>
<tr>
<td></td>
<td>Week 3</td>
<td></td>
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</tbody>
</table>

- Most visits are 1 – 2 hours on average.
- The first and last visits (Screening 1 and Week 24) may be an additional 1 – 2 hours for additional testing.
What happens during the Screening Period?

• The doctor and nurse will explain the study requirements and provide an informed consent document
  – the doctor and nurse have obligations to make sure that patients are treated safely during the study
  – Patients have an obligation to determine is this the right study for them

• Patients who sign the consent form will have certain tests performed to see if they are eligible for the study
  – The doctor and nurse will explain these results and tell the patient if they can join the study

• The patient makes the final decision about participating
  – Discuss this with their family
  – Ask any questions to feel more comfortable with their decision
DRIVE PK : Current Status

- The trial has been open in USA since June 2015
- Half of the sites are open for enrollment, with more coming soon
- For further information, please check [www.clinicaltrials.gov](http://www.clinicaltrials.gov) and type in “pyruvate kinase deficiency” or “NCT02476916” in the search window
- Investigator for Belgium and The Netherlands: Dr. E. De Beers (Utrecht)
Summary and Conclusions

- PK deficiency is a serious hematologic disorder
- AG-348 is a novel, first-in-class, PK-R activator that is intended to restore the glycolytic pathway defect in patients with PK deficiency
- Healthy volunteer study:
  - Established a clear range of well tolerated doses over 14 days and demonstrated maximal PD effects
- PD data are consistent with preclinical and ex-vivo data demonstrating:
  - Sustained concomitant increases in ATP
  - Decreases in 2,3-DPG
- Data overall provide compelling evidence to initiate global phase 2 study in PK deficiency
We would like to thank the volunteers who agreed to participate in this study and the PK-Deficiency patients who are participating in the DRIVE PK study, as well as the Clinical Site Staff and Investigators.