**Effects of AG-348, a pyruvate kinase activator, in patients with pyruvate kinase deficiency: Updated results from the DRIVE PK study**

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**BACKGROUND**

- Pyruvate kinase (PK) deficiency is an under-recognized hereditary disease caused by mutations in the PKLR gene, which results in blinding hereditary anemia.  
- Acute and chronic complications of supportive care (e.g., transfusions, splenectomy, or chelation) may additionally burden patients with PK deficiency.

**OBJECTIVE**

- To report updated data from the ongoing DRIVE PK study (ClinicalTrials.gov NCT02476916). An open-label, dose-ranging trial of AG-348 in adults with PK deficiency who are not receiving regular blood transfusions.

**METHODS**

- Open-label, global, phase 2 study: 16 centers in the US, Canada, and EU.
- PK-deficient adults who are not regularly transfused (ClinicalTrials.gov NCT02476916).

**RESULTS**

**Table 1. Demographic characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>50 mg BID (n=26)</th>
<th>300 mg BID (n=26)</th>
<th>50 mg  BID (n=15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males, n (%)</td>
<td>19 (73.1)</td>
<td>14 (53.8)</td>
<td>9 (60.0)</td>
</tr>
<tr>
<td>Age at randomization, median (range), years</td>
<td>26 (18–68)</td>
<td>30 (21–41)</td>
<td>26 (18–40)</td>
</tr>
<tr>
<td>Gender, n (%)</td>
<td>27 (100.0)</td>
<td>27 (100.0)</td>
<td>11 (73.3)</td>
</tr>
<tr>
<td>Hb baseline, median (range), g/dL</td>
<td>9.0 (5.9–12.2)</td>
<td>8.6 (5.5–12.0)</td>
<td>8.9 (5.5–12.3)</td>
</tr>
<tr>
<td>Spinal cord, n (%)</td>
<td>2 (7.7)</td>
<td>2 (7.4)</td>
<td>2 (13.3)</td>
</tr>
<tr>
<td>Hb change, median (range), g/dL</td>
<td>3.4 (1.1–5.8)</td>
<td>3.2 (0.4–7.8)</td>
<td>1.1 (0.0–3.1)</td>
</tr>
</tbody>
</table>

**Table 2. Most common AEs regardless of causality or grade (occurring in >15% of patients)**

<table>
<thead>
<tr>
<th>AE</th>
<th>Grade 1 (n=26)</th>
<th>Grade 2 (n=26)</th>
<th>Grade 3 (n=26)</th>
<th>Grade 4 (n=26)</th>
<th>Total (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>15 (57.7)</td>
<td>10 (38.5)</td>
<td>2 (7.7)</td>
<td>0</td>
<td>29 (100.0)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6 (22.2)</td>
<td>2 (7.7)</td>
<td>0</td>
<td>0</td>
<td>8 (30.8)</td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (57.7)</td>
<td>10 (38.5)</td>
<td>2 (7.7)</td>
<td>0</td>
<td>27 (100.0)</td>
</tr>
<tr>
<td>Cough</td>
<td>4 (15.4)</td>
<td>4 (15.4)</td>
<td>0</td>
<td>0</td>
<td>8 (30.8)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>4 (15.4)</td>
<td>4 (15.4)</td>
<td>0</td>
<td>0</td>
<td>8 (30.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (15.4)</td>
<td>4 (15.4)</td>
<td>0</td>
<td>0</td>
<td>8 (30.8)</td>
</tr>
<tr>
<td>Influenza</td>
<td>7 (26.9)</td>
<td>7 (26.9)</td>
<td>0</td>
<td>0</td>
<td>14 (53.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (11.1)</td>
<td>3 (11.1)</td>
<td>0</td>
<td>0</td>
<td>6 (23.1)</td>
</tr>
</tbody>
</table>

**Effect of AG-348 on sex hormones**

- Moderately elevated hormone changes from baseline in sex hormone levels were observed in males at planned protocol trial dose levels (50 mg BID).
- Data are consistent with mild aromatase inhibition.
- Mean sex hormone values remained within normal limits in females (data not shown).
- Interpretation is confounded by variability in menopausal status and contraceptive use.

**CONCLUSIONS**

- AG-348 is a novel, first-in-class, PK-R activator in clinical testing as a potential disease-altering therapy for patients with PK deficiency.
- Chronic daily dosing with AG-348 is well tolerated.
- There were 14 serious AEs in 11 patients.
- The mean maximum increase was 3.4 g/dL (range 1.1–5.8 g/dL).
- Most sex hormone values remained within normal limits in females (data not shown).
- Data are consistent with mild aromatase inhibition.
- Ongoing follow-up will continue to assess the clinical impact of mild aromatase inhibition.
- The mean maximum increase was 3.4 g/dL (range 1.1–5.8 g/dL).
- Patients were monitored for a median duration of 37.5 weeks.

**Figure 1. Study design**

- Enrollment is complete as of November 2016.
- Date cutoff: July 14, 2017.
- Primary safety and efficacy Secondary endpoint: Pharmacokinetics of AG-348: PK interactions, PK-R interactions, indication of clinical safety, pharmacodynamic and other pharmacological parameters.

**Figure 2. Patient disposition**

- Patients experiencing ≥1 AE, n (%)
- AE: adverse event.

**Figure 3. Sex hormone values over time in males**

- The mean maximum change was 3.4 g/dL (range 1.1–5.8 g/dL).
- Most sex hormone values remained within normal limits in females (data not shown).
- Data are consistent with mild aromatase inhibition.

**Figure 4. Maximum Hb increase observed during the Core period**

- The mean maximum increase was 3.4 g/dL (range 1.1–5.8 g/dL).
- Patients were monitored for a median duration of 37.5 weeks.

**Figure 5. Maximum Hb increase observed by genotype**

- The mean maximum increase was 3.4 g/dL (range 1.1–5.8 g/dL).
- Patients were monitored for a median duration of 37.5 weeks.

**Figure 6. Majority of Hb increases are rapid and sustained**

- The mean maximum increase was 3.4 g/dL (range 1.1–5.8 g/dL).
- Patients were monitored for a median duration of 37.5 weeks.

Acknowledgments

**DISCLOSURES**

- AG-348 is a novel, first-in-class, PK-R activator in clinical testing as a potential disease-altering therapy for patients with PK deficiency.
- Chronic daily dosing with AG-348 is well tolerated.
- There were 14 serious AEs in 11 patients.
- The mean maximum increase was 3.4 g/dL (range 1.1–5.8 g/dL).
- Most sex hormone values remained within normal limits in females (data not shown).
- Data are consistent with mild aromatase inhibition.
- Ongoing follow-up will continue to assess the clinical impact of mild aromatase inhibition.

**References**

- Optimized AG-348 dose
- Primary efficacy endpoint: Proportion of patients who achieve ≥1.5 g/dL increase in Hb from baseline at the end of the treatment period.

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