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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- Hassan Yaish – study investigator
- Yaddanapudi Ravindranath – study investigator
- Kevin HM Kuo – study investigator
- Sujit Sheth – study investigator
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Pyruvate kinase (PK) deficiency: a severe congenital anemia

- **Description**
  - Presents in childhood with severe hemolytic anemia

- **Etiology**
  - Caused by mutations in the PK-LR gene coding for erythrocyte pyruvate kinase (PK-R)

- **Disease Burden**
  - Lifelong hemolytic anemia
  - Iron overload and jaundice
  - Infection risk post-splenectomy

- **Diagnosis/Treatment**
  - PK-R enzyme activity and/or genetic testing
  - Supportive treatment: transfusions, splenectomy, iron chelation

**Type of PK-LR mutations found in 74 unrelated cases enrolled in the PK deficiency natural history study**

- Missense/misserse 53%
- Non-missense/non-missense 25%
- Missense/non-missense 22%

Study design

Open-label, global phase 2 study: 14 centers in the US, Canada, and EU

Transfusion-independent PK-deficient adults
(ClinicalTrials.gov NCT02476916) n=25 in each arm

Randomization
Stratified by PK-R genotype (none excluded)

Arm 1
300 mg BID

Arm 2
50 mg BID

6 month core
dosing period

1 2 3 6 9 12 16 20 24
Assessment points
(weeks)

Primary endpoints:
• Safety and tolerability

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

Extension arm

Transfusion independence = no more than 3 units of red blood cells transfused in 12 months prior to the first day of study dosing and no transfusions within 4 months of first day of study dosing

Fully enrolled as of November, 2016

All patients provided written informed consent. BID = twice daily; PD = pharmacodynamic
## Demographics

<table>
<thead>
<tr>
<th>Characteristicsa</th>
<th>50 mg BID, n=27</th>
<th>300 mg BID, n=25</th>
<th>Total, N=52</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n (%)</td>
<td>18 (66.7)</td>
<td>14 (56.0)</td>
<td>32 (61.5)</td>
</tr>
<tr>
<td>Age at randomization in years, median (range)</td>
<td>29 (18, 58)</td>
<td>40 (21, 62)</td>
<td>34 (18, 62)</td>
</tr>
<tr>
<td>Race whiteb, n (%)</td>
<td>22 (81.5)</td>
<td>20 (80.0)</td>
<td>42 (80.8)</td>
</tr>
<tr>
<td>Hemoglobin (Hb) baseline, median (range)</td>
<td>9.6 (6.9, 12.3)</td>
<td>8.6 (6.5, 12.0)</td>
<td>8.9 (6.5, 12.3)</td>
</tr>
<tr>
<td>Duration of treatment, weeks, median (range)</td>
<td>23.0 (13.0, 76.9)</td>
<td>26.3 (12.9, 70.9)</td>
<td>24.9 (12.9, 76.9)</td>
</tr>
<tr>
<td>Splenectomized, n (%)</td>
<td>23 (85.2)</td>
<td>20 (80.0)</td>
<td>43 (82.7)</td>
</tr>
<tr>
<td>Iron chelation prior to enrolment, n (%)</td>
<td>14 (51.9)</td>
<td>11 (44.0)</td>
<td>25 (48.1)</td>
</tr>
<tr>
<td>Cholecystectomy, n (%)</td>
<td>19 (70.4)</td>
<td>19 (76.0)</td>
<td>38 (73.1)</td>
</tr>
</tbody>
</table>

aData cut-off March 27, 2017; bNot reported in 3 patients, 3 patients were Asian, and 4 were “other”
Safety summary

- AG-348 was generally well tolerated
- The majority of adverse events (AEs) were grade 1–2
- Treatment related AEs leading to discontinuation, n=3
  - Chest discomfort/pleural effusion, pharyngitis/nausea, anemia
- 13 serious AEs in 10 patients
  - Six drug-related SAEs in 5 patients: Withdrawal hemolysis followed by anemia; anemia; osteoporosis; hypertriglyceridemia; pharyngitis
    - Grade 4 hypertriglyceridemia at Week 24, resolved upon AG-348 discontinuation (Grade 1 at baseline)

<table>
<thead>
<tr>
<th>Patient disposition by study period</th>
<th>Ongoing, N</th>
<th>Completed, N</th>
<th>Discontinued&lt;sup&gt;a&lt;/sup&gt;, N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Core</td>
<td>15</td>
<td>29&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8</td>
</tr>
<tr>
<td>Extension</td>
<td>21</td>
<td>0</td>
<td>3</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reasons for discontinuation: AEs (3), investigator decision (4), and withdrew consent (4)
<sup>b</sup>Five subjects completing the Core period did not enter the Extension
## Safety summary: Most common AEs

<table>
<thead>
<tr>
<th>AEs, regardless of causality (occurring in &gt;5 patients)</th>
<th>50 mg BID n=27</th>
<th>300 mg BID n=25</th>
<th>Total N=52</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All grades</td>
<td>Grade ≥3</td>
<td>All grades</td>
</tr>
<tr>
<td>Patients experiencing at least 1 AE, n (%)</td>
<td>25 (92.6)</td>
<td>7 (25.9)</td>
<td>25 (100.0)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (33.3)</td>
<td>0</td>
<td>14 (56.0)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>5 (18.5)</td>
<td>1 (3.7)</td>
<td>15 (60.0)</td>
</tr>
<tr>
<td>Nausea</td>
<td>10 (37.0)</td>
<td>0</td>
<td>9 (36.0)</td>
</tr>
<tr>
<td>Viral upper respiratory tract infection</td>
<td>7 (25.9)</td>
<td>0</td>
<td>2 (8.0)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>5 (18.5)</td>
<td>0</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (14.8)</td>
<td>0</td>
<td>4 (16.0)</td>
</tr>
<tr>
<td>Back pain</td>
<td>4 (14.8)</td>
<td>0</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>Cough</td>
<td>4 (14.8)</td>
<td>0</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>4 (14.8)</td>
<td>0</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (11.1)</td>
<td>0</td>
<td>4 (16.0)</td>
</tr>
<tr>
<td>Hot flush</td>
<td>1 (3.7)</td>
<td>0</td>
<td>6 (24.0)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>3 (11.1)</td>
<td>0</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>Influenza</td>
<td>5 (18.5)</td>
<td>1 (3.7)</td>
<td>1 (4.0)</td>
</tr>
</tbody>
</table>

Grade 3 AEs not reported in previous slide or table above: colitis (n=1), thrombosis (n=1), pharyngitis (n=1), post procedural hemorrhage (n=1), hypertension (n=1)

AEs graded using National Cancer Institute Common Terminology Criteria, version 4.03
Dose titration in DRIVE PK

- Patients randomized to 50 mg or 300 mg BID AG-348 starting dose
  - Dose decreased:
    - AEs (e.g. insomnia)
    - Hb exceeding midpoint of normal range (Male: Hb >15.0 g/dL; Female >13.5 g/dL)
  - Dose increased:
    - Lack of Hb response

- Range of doses (5 mg QD–300 mg BID) used
- Efficacy and steroid hormone levels analyzed by the dose received for the longest duration in the Core period
Effect of AG-348 on hormones: total testosterone in men

- Preliminary findings are consistent with aromatase inhibition by AG-348 across multiple dose levels in men
  - Most testosterone values remained within the normal range
  - DEXA scan data inconclusive
  - Longer follow up required to assess clinical impact

Normal reference low and high limits shown as horizontal dotted lines; DEXA = dual energy X-ray absorptiometry
Clinical activity results
Maximum Hb increase observed during the Core period

- 25/52 (48%) patients had a maximum Hb increase of >1.0 g/dL
  - The mean maximum increase was 3.5 g/dL (range 1.1-5.8 g/dL)

The baseline value is the average of all central assessments within the screening period (42 days prior to Day 1)
Maximum Hb increase observed by genotype

- 25/52 (48%) patients had a max increase in Hb >1.0 g/dL
  - 24/42 (57%) patients who had ≥1 missense mutation had Hb increase >1.0 g/dL

The baseline value is the average of all central assessments within the screening period (42 days prior to Day 1)
Majority of Hb increases are rapid and sustained

- Median time to the first observation of a Hb increase >1.0 g/dL above baseline was 10 days (range 7–141 days)
  - Median baseline Hb in subjects who experienced a maximum Hb increase of >1.0 g/dL was 9.7 g/dL (range 7.5–12.3 g/dL) vs. 8.0 g/dL (range 6.5–10.1) in subjects who did not

- In 8 patients, the dose had to be held or reduced due to rapid rise in Hb
Hemolysis markers improve in patients with Hb increase of >1.0 g/dL

- Rapid decreases in reticulocytes and LDH in the first weeks of dosing
- Steady increase in haptoglobin

Only visits with ≥5 subjects included. Figure shows central laboratory results. LDH = lactate dehydrogenase
Hb response with improvements in hemolysis parameters: Single subject experience with AG-348

- 35 yo female, white, missense/missense genotype (T384M/R479H)
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
- Clinical significance of AG-348 aromatase inhibition is unclear
- One grade 4 serious AE of elevated triglycerides was observed

25 of 52 (48%) subjects had a maximum Hb increase of >1.0 g/dL
- Responses are rapid in onset and durable
- Other parameters (reticulocytes, LDH and haptoglobin) indicate decreased hemolysis in responders
- Some genotype–Hb response correlations were observed

These data highlight the potential of AG-348 as the first disease-altering treatment for patients with PK deficiency, providing rationale for pivotal studies
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