Proof of concept for the oral pyruvate kinase activator mitapivat in adults with non–transfusion-dependent thalassemia: Interim results from an ongoing, phase 2, open-label, multicenter study

Kevin H.M. Kuo, MD¹, D. Mark Layton, MB, BS², Ashutosh Lal, MD³, Hanny Al-Samkari, MD⁴, Feng Tai, PhD⁵, Megan Lynch, MSN⁵, Katrin Uhlig, MD⁵, Elliot P. Vichinsky, MD³

¹Toronto General Hospital, University Health Network, Toronto, Canada; ²Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, United Kingdom; ³UCSF Benioff Children’s Hospital Oakland, Oakland, CA, United States; ⁴Massachusetts General Hospital, Harvard Medical School, Boston, MA, United States; ⁵Agios Pharmaceuticals, Inc., Cambridge, MA, United States

This study was funded by Agios Pharmaceuticals, Inc.
Mitapivat (AG-348) is an oral, allosteric activator of PKR, which catalyzes the final step of glycolysis in RBCs\(^1,2\)

- Mitapivat increased whole blood ATP levels by 60% in healthy volunteers\(^3\)
- In a phase 2 study in adult patients with pyruvate kinase deficiency, BID dosing with mitapivat:
  - Increased Hb by > 1.0 g/dL in 50% of patients\(^4\)
  - Was well tolerated for up to 42 months\(^5\)

Mitapivat activates wild-type and mutant PKR enzymes\(^1\)

---

ADP = adenosine diphosphate; ATP = adenosine triphosphate; BID = twice daily; DPG = diphosphoglyceric acid; FBP = fructose 1,6–bisphosphate; Hb = hemoglobin; PEP = phosphoenolpyruvic acid; PG = phosphoglyceric acid; PK = pyruvate kinase; PKR = PK in RBCs; RBC = red blood cell.

Hypothesis: Mitapivat mechanism in thalassemia

Mitapivat increased PKR activity and ATP levels ex vivo in RBCs from patients with β-thalassemia¹
Mitapivat ameliorated ineffective erythropoiesis, iron overload, and anemia in the Hbb^{th3/+} mouse model of β-thalassemia²

ATP = adenosine triphosphate; PKR = PK in RBCs; RBC = red blood cell.
Study design: Open-label, phase 2, multicenter study

Key inclusion criteria
- β-thalassemia ± α-globin gene mutations, HbE β-thalassemia, or α-thalassemia (HbH disease)
- Hb ≤ 10.0 g/dL
- Non–transfusion-dependent

Primary endpoint
- Hb response, defined as increase of ≥ 1.0 g/dL from baseline at any time between Weeks 4–12, inclusive

Secondary/exploratory endpoints
- Sustained Hb response; delayed Hb response; markers of hemolysis; hematopoietic activity; safety

Mitapivat
- 50 mg BID orally
- 100 mg BID orally

Baseline
- Screening ≤ 42 days
- 24-week core period
  - 6 weeks
  - 18 weeks
- 10-year extension period
- Safety follow-up 28 days after last dose

N = 20

EudraCT 2018-002217-35; ClinicalTrials.gov: NCT03692052

a Fully enrolled.
b ≤ 5 RBC units transfused in the preceding 24 weeks and none in the 8 weeks prior to study drug.
c With the originally planned sample size of 17 patients enrolled, the study would have 80% power to reject a ≤ 30% response rate at a one-sided 0.05 type 1 error rate.

BID = twice daily; Hb = hemoglobin; RBC = red blood cell.
### Baseline characteristics

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Total (N = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median (range) duration of treatment, weeks</td>
<td>20.6 (1.1–50.0)</td>
</tr>
<tr>
<td>Male/female, n</td>
<td>5/13</td>
</tr>
<tr>
<td>Age at informed consent, median (range), years</td>
<td>43.5 (29–67)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>9 (50.0)</td>
</tr>
<tr>
<td>White</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>Native Hawaiian or other Pacific Islander</td>
<td>1 (5.6)</td>
</tr>
<tr>
<td>Other(^a)</td>
<td>4 (22.2)</td>
</tr>
<tr>
<td>Thalassemia type, n (%)</td>
<td></td>
</tr>
<tr>
<td>α</td>
<td>5 (27.8)</td>
</tr>
<tr>
<td>β</td>
<td>13 (72.2)</td>
</tr>
<tr>
<td>Hb baseline, median (range), g/dL</td>
<td>8.43 (5.6–9.8)</td>
</tr>
<tr>
<td>Indirect bilirubin, median (range), mg/dL</td>
<td>1.17 (0.31–5.52)</td>
</tr>
<tr>
<td>Lactate dehydrogenase, median (range), U/L</td>
<td>249 (126–513)</td>
</tr>
<tr>
<td>Erythropoietin, median (range), mU/mL</td>
<td>70.5 (15–11,191)</td>
</tr>
</tbody>
</table>

Splenectomy and prior transfusions were reported in two patients each at baseline.

\(^a\)Includes patients who reported more than one category, and one not reported.

Hb = hemoglobin.
Key efficacy results

- Primary endpoint was met in 92.3% of patients

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Genotype</th>
<th>n/N</th>
<th>%</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb responders during Weeks 4–12</td>
<td>All</td>
<td>12/13</td>
<td>92.3</td>
<td>68.4, 99.6</td>
</tr>
<tr>
<td>(completed 12 weeks)</td>
<td>α</td>
<td>4/4</td>
<td>100</td>
<td>47.3, 100</td>
</tr>
<tr>
<td></td>
<td>β</td>
<td>8/9</td>
<td>88.9</td>
<td>57.1, 99.4</td>
</tr>
<tr>
<td>Hb responders during Weeks 12–24</td>
<td>β⁹</td>
<td>8/9</td>
<td>88.9</td>
<td>57.1, 99.4</td>
</tr>
<tr>
<td>(completed 24 weeks)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sustained responders: primary</td>
<td>β⁹</td>
<td>7/8</td>
<td>87.5</td>
<td>52.9, 99.4</td>
</tr>
<tr>
<td>response and ≥ 2 Hb responses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>during Weeks 12–24</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Median (range) time to Hb increase of ≥ 1 g/dL among responders was 3.1 (1.4–7.1) weeks

Hb responder defined as a ≥ 1.0 g/dL Hb increase from baseline at least once.

⁹Only patients with β-thalassemia had completed 24 weeks of treatment at the time of data cut.

CI = confidence interval; Hb = hemoglobin.
Hb increases correlated with improvements in markers of hemolysis and erythropoiesis

- Mean ATP percent increase from baseline was similar to that previously observed with mitapivat in healthy volunteers

Dashed lines indicate upper limit of normal range. For α-thalassemia: N = 4 for lactate dehydrogenase and erythropoietin, for indirect bilirubin N = 3 at baseline, Weeks 2, 8, and 12, and N = 2 at Weeks 4 and 6; for β-thalassemia: N = 9 for erythropoietin, for lactate dehydrogenase N = 9 at baseline, Weeks 6, 8, 12, and 20 and N = 8 at Weeks 2, 4, 16, and 24, for indirect bilirubin N = 9 at baseline and N = 7 at the remaining times. ATP = adenosine triphosphate; Hb = hemoglobin; IQR = interquartile range (25th–75th centiles). 1. Yang H et al. Clin Pharmacol Drug Dev 2019;8:246–59.
Safety summary

- Dose escalation to 100 mg BID was well tolerated and not associated with an increase in AEs
- The most common AEs (> 25% of patients) were insomnia (8/18) and dizziness (5/18)
- There were no serious AEs and no AEs leading to treatment discontinuation
- 1 AE leading to treatment interruption (grade 3, postural vertigo, not treatment-related)
- 1 AE leading to treatment modification (grade 2, bloating and heartburn, treatment-related)
- A previously reported serious AE of renal dysfunction (grade 3) that occurred post-data cut was re-adjudicated by the investigator from treatment-related to not treatment-related

### AEs by maximum severity

<table>
<thead>
<tr>
<th>Grade</th>
<th>Patients, n (%)</th>
<th>Total (N = 18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>4 (22.2)</td>
<td></td>
</tr>
<tr>
<td>Grade 2</td>
<td>7 (38.9)</td>
<td></td>
</tr>
<tr>
<td>Grade 3</td>
<td>2 (11.1)</td>
<td></td>
</tr>
</tbody>
</table>

AEs coded using MedDRA, version 22.0.

*As of data cut of 03March2020. Neither were considered treatment-related in the opinion of the investigator. AE = adverse event; BID = twice daily; MedDRA = Medical Dictionary for Medical Regulatory Activities.
This is the first clinical study evaluating PKR activation as a therapeutic option in α- and β-thalassemia, and is the first drug trial aimed at treating α-thalassemia.

Proof-of-concept was demonstrated:
- > 90% of patients met the primary endpoint showing a clinically significant Hb increase.
- All 4 α-thalassemia patients and 8 of 9 β-thalassemia patients were responders.
- A sustained Hb response was observed over time in patients with longer follow-up.
- Improvements in markers of hemolysis and erythropoiesis were consistent with mitapivat’s mechanism of action.

Mitapivat was generally well tolerated; the safety profile was consistent with previous studies.

Summary:

These data indicate that activation of wild-type PKR by the oral agent mitapivat improved Hb and associated markers of hemolysis and erythropoiesis in patients with both α- and β-thalassemia, and that further investigation is warranted. Pivotal trials are in development.
Acknowledgments and disclosures

- We would like to thank the patients taking part in this study
- This study was funded by Agios Pharmaceuticals, Inc. These data were previously presented at the 25th European Hematology Association (EHA) Annual Meeting, June 11–21, 2020
- Kevin H.M. Kuo – Agios, Apellis, Bluebird Bio, Celgene, Pfizer – consultant; Alexion, Novartis – consultant, honoraria; Bioverativ – data safety monitoring board member; Pfizer – research support; D. Mark Layton – Agios, Novartis – consultant and advisory board member; Cerus – data safety monitoring board member; Ashutosh Lal – Bluebird Bio, Celgene, Insight Magnetics, La Jolla Pharmaceutical Company, Novartis, Protagonist Therapeutics, Terumo Corporations – research funding; Agios, Chiesi USA – consultancy; Celgene, Protagonist Therapeutics – membership on an entity's Board of Directors or advisory committees; Hanny Al-Samkari – Agios, Argenx, Dova, Rigel – consultant; Agios, Dova, Amgen – research funding; Feng Tai – Agios – employment and stockholder; Megan Lynch – Agios – employment and stockholder; Katrin Uhlig – Agios – employment and stockholder; Elliot P. Vichinsky – GBT, Pfizer, Novartis, Bluebird Bio, Agios – consultant and research funding
- Editorial assistance was provided by Julie B. Stimmel, PhD, Onyx Medica, London, UK, and supported by Agios Pharmaceuticals, Inc.