Phase 1 Multiple Ascending Dose Study of Safety, Tolerability, and Pharmacokinetics/Pharmacodynamics of Mitapivat (AG-348) in Subjects with Sickle Cell Disease

NCT04000165; Investigator-initiated trial; Principal Investigator: Swee Lay Thein

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Abstract #681

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Pyruvate Kinase R (PKR): A new disease modifying target in SCD?

Polymerization of deoxy-Hb S results in vaso-occlusion and hemolytic anemia and is the root cause of sickle cell disease (SCD) complications.

- Elevated 2,3-DPG levels promote polymerization.

Mitapivat (AG-348) is an oral PKR activator that decreases 2,3-DPG and increases ATP levels\(^1\) and improves anemia in PK deficiency and thalassemia.\(^2,3\)

\[\text{Mitapivat} \quad \text{PKR} \quad \text{Improved RBC hydration and health}\]

ATP, adenosine triphosphate; DPG, diphosphoglycerate; Hb, hemoglobin; O\(_2\), oxygen; PKR, red-cell pyruvate kinase; RBC, red blood cell.

\(^1\) Yang et al. Clin Pharmacol Drug Dev. 2018,00(0)1–14; \(^2\) Grace et al. NEJM. 2019;5;381(10):933-944; \(^3\) Kuo et al. Abstract, EHA 2020.
Study Design: Dose Escalation of Mitapivat in SCD

- Nonrandomized, open-label, Phase 1 study; N ≈ 15–25
- Adults (age ≥ 18 years) with stable Hb SS disease eligible
- No transfusions or changes in hydroxyurea/L-glutamine within 90 days

**Primary endpoints:**
- Safety and tolerability
- Changes in Hb and hemolytic markers

**Secondary endpoints:**
- Pharmacokinetics
- 2,3-DPG and ATP levels
- O₂ dissociation and sickling tendency

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*100 mg dose level added to protocol with amendment #6. BID, twice daily.
** Data is incomplete due to disruptions related to COVID-19 pandemic.
### Demographics, Disease Characteristics, and Disposition

<table>
<thead>
<tr>
<th>Baseline Characteristics at Enrollment</th>
<th>N=12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (range), years</td>
<td>40.2 (27-55)</td>
</tr>
<tr>
<td>Male, N (%)</td>
<td>8 (66.7)</td>
</tr>
<tr>
<td>African or African-American, N (%)</td>
<td>12 (100)</td>
</tr>
<tr>
<td>Hydroxyurea use, N (%)</td>
<td>8 (66.7)</td>
</tr>
<tr>
<td>L-glutamine use, N (%)</td>
<td>1 (8.3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Baseline Laboratory Measures</th>
<th>N=11*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin, mean (SD), g/dL</td>
<td>9.5 (1.0)</td>
</tr>
<tr>
<td>Abs reticulocyte count, mean (SD), K/µL</td>
<td>191.0 (109.3)</td>
</tr>
<tr>
<td>Total bilirubin, mean (SD), mg/dL</td>
<td>2.2 (0.9)</td>
</tr>
<tr>
<td>Lactate dehydrogenase, mean (SD), U/L</td>
<td>374.6 (140.9)</td>
</tr>
<tr>
<td>Hemoglobin F % by HPLC, mean (SD), %</td>
<td>18.3 (10.7)</td>
</tr>
</tbody>
</table>

#### Subjects # 1-12
- Enrolled by 6 October 2020 (N=12)
- Escalated to 100 mg (N=5)
- Withdrawal of #4 on day 4 per investigator decision*
- Completed 50 mg dose level (N=11)
- Completed study per protocol (N=6)

#### Subjects # 8-12
- Completed 100 mg dose level (N=3)
- 1. Withdrawal of #10 on day 76 due to other (per patient)**
- 2. Subject #12 ongoing

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* #4 withdrawn due to need for medical interventions for an AE unrelated to drug and lost to follow-up; not evaluable for laboratory response.
** #10 self-discontinued therapy due to an AE unrelated to drug; in safety follow-up.
AE, adverse event; Abs, absolute; HPLC, high-performance liquid chromatography; SD, standard deviation; Data cut date: Oct 6, 2020.
### Adverse Events

<table>
<thead>
<tr>
<th>Adverse Events</th>
<th>N=12 (%)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Grades (≥10%)</td>
<td>Grade ≥ 3</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>4 (30.8%)</td>
<td>2 (15.4%)</td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>4 (30.8%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Vaso-occlusive crisis (VOC)</td>
<td>3 (23.1%)</td>
<td>3 (23.1%)</td>
<td></td>
</tr>
<tr>
<td>Anemia</td>
<td>3 (23.1%)</td>
<td>2 (15.4%)</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (23.1%)</td>
<td>1 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>3 (23.1%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Heart rate increased</td>
<td>3 (23.1%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>AST increased</td>
<td>2 (15.4%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Blood bicarbonate decreased</td>
<td>2 (15.4%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>2 (15.4%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Sore throat</td>
<td>2 (15.4%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Upper respiratory infection</td>
<td>2 (15.4%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (7.7%)</td>
<td>1 (7.7%)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1 (7.7%)</td>
<td>1 (7.7%)</td>
<td></td>
</tr>
</tbody>
</table>

### Serious Adverse Events (SAEs)

<table>
<thead>
<tr>
<th>Serious Adverse Events (SAEs)</th>
<th>N=12 (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>5 (41.7)</td>
<td></td>
</tr>
<tr>
<td>VOC*</td>
<td>3 (25)</td>
<td></td>
</tr>
<tr>
<td>Pain (shoulder)</td>
<td>1 (8.3)</td>
<td></td>
</tr>
<tr>
<td>Pulmonary embolism (PE)**</td>
<td>1 (8.3)</td>
<td></td>
</tr>
</tbody>
</table>

**Summary of VOCs:**
- No VOC during dose escalation
- 2 VOCs during 28-day safety follow-up post drug exposure due to known VOC triggers
- 1 VOC during drug taper, improved with extended dosing†

* Regardless of relationship to study treatment.
** Pre-existing PE discovered 4 days after study drug initiation; patient withdrawn (subject #4).
† Triggered protocol amendment to extend length of taper.
AST, aspartate aminotransferase.
Data cut date: Oct 6, 2020.
Mitapivat Decreases 2,3-DPG and Increases ATP in SCD

- Linear PK was observed up to 50 mg BID.
- After 100 mg BID, CYP3A auto-induction effect resulted in ~20% reduction in exposure.

Mitapivat Increases Hemoglobin Level

**Mean Change from Baseline (g/dL)**

<table>
<thead>
<tr>
<th>Dose Level</th>
<th>N=11</th>
<th>N=11</th>
<th>N=11</th>
<th>N=3</th>
<th>N=8</th>
<th>N=8</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg BID</td>
<td>1.3 (0.8)</td>
<td>1.3 (0.8)</td>
<td>1.3 (0.8)</td>
<td>1.9 (0.7)</td>
<td>1.9 (0.7)</td>
<td>1.9 (0.7)</td>
</tr>
<tr>
<td>20 mg BID</td>
<td>1.3 (0.8)</td>
<td>1.3 (0.8)</td>
<td>1.3 (0.8)</td>
<td>1.9 (0.7)</td>
<td>1.9 (0.7)</td>
<td>1.9 (0.7)</td>
</tr>
<tr>
<td>50 mg BID</td>
<td>1.3 (0.8)</td>
<td>1.3 (0.8)</td>
<td>1.3 (0.8)</td>
<td>1.9 (0.7)</td>
<td>1.9 (0.7)</td>
<td>1.9 (0.7)</td>
</tr>
<tr>
<td>100 mg BID</td>
<td>1.3 (0.8)</td>
<td>1.3 (0.8)</td>
<td>1.3 (0.8)</td>
<td>1.9 (0.7)</td>
<td>1.9 (0.7)</td>
<td>1.9 (0.7)</td>
</tr>
<tr>
<td>End of taper</td>
<td>1.3 (0.8)</td>
<td>1.3 (0.8)</td>
<td>1.3 (0.8)</td>
<td>1.9 (0.7)</td>
<td>1.9 (0.7)</td>
<td>1.9 (0.7)</td>
</tr>
<tr>
<td>End of study</td>
<td>1.3 (0.8)</td>
<td>1.3 (0.8)</td>
<td>1.3 (0.8)</td>
<td>1.9 (0.7)</td>
<td>1.9 (0.7)</td>
<td>1.9 (0.7)</td>
</tr>
</tbody>
</table>

**Response parameter N=11**

- Maximal Hb increase, mean (SD), g/dL: 1.3 (0.8)
- Hb increase ≥ 1g/dL, N (%): 6 (54.5)
- Maximal Hb increase in subjects with ≥ 1g/dL response*, mean (SD), g/dL: 1.9 (0.7)

* N=6.
Mitapivat Decreases Markers of Hemolysis

**Mean Change from Baseline (mg/dL)**

- **Total Bilirubin**
  - Dose Level: 5 mg BID, 20 mg BID, 50 mg BID, 100 mg BID, End of taper, End of study
  - N=11, N=11, N=11, N=3, N=8, N=8

- **Lactate Dehydrogenase**
  - Dose Level: 5 mg BID, 20 mg BID, 50 mg BID, 100 mg BID, End of taper, End of study
  - N=11, N=11, N=11, N=3, N=8, N=8

- **Absolute Reticulocyte Count**
  - Dose Level: 5 mg BID, 20 mg BID, 50 mg BID, 100 mg BID, End of taper, End of study
  - N=11, N=11, N=11, N=3, N=8, N=8

Mitapivat, an oral, twice daily PKR activator was well tolerated in subjects with SCD. Pharmacokinetic and safety profile in SCD resembles results from previous studies in PK deficiency and thalassemia.

This study provides proof of concept:
- Mitapivat reduces 2,3-DPG and increases in ATP in patients with SCD.
- During a short period (6-8 weeks) of dose escalation, mitapivat increased Hb by ≥ 1g/dl in 6/11 evaluable subjects and decreased hemolytic markers, signaling its potential to improve clinical outcomes in SCD.

An extension study (ClinicalTrials.gov NCT04610866) will evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics of long-term mitapivat dosing in SCD subjects enrolled on NCT04000165.

Summary
Acknowledgments

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