A phase 2a/2b multicenter study of AG-946 in anemia with patients due to lower-risk myelodysplastic syndromes

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BACKGROUND

Myelodysplastic syndromes

- Myelodysplastic syndromes (MDS) are a heterogeneous group of hematologic neoplasms characterized by ineffective erythropoiesis, dysplasia, and progression to acute leukemia.2
- MDS occurs with an incidence of 4.5/100,000 people per year, with 21,000 new cases per year in the USA.3
- Overall survival and risk of progression from MDS to acute myeloid leukemia can be characterized using the Revised International Prognostic Scoring System (IPSS-R) criteria (Table 1).1

Table 1. IPSS-R featuresa,b,5

<table>
<thead>
<tr>
<th>Score</th>
<th>Clinical features</th>
<th>Myelodysplastic features</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>Good performance</td>
<td>Good cytopenias</td>
</tr>
<tr>
<td>2</td>
<td>Intermediate PS</td>
<td>Intermediate cytopenias</td>
</tr>
<tr>
<td>3–4</td>
<td>Poor performance</td>
<td>Poor cytopenias</td>
</tr>
</tbody>
</table>

Anemia due to LR-MDS

- Anemia is the most common cytopenia of MDS, with >90% of patients with MDS experiencing anemia at diagnosis or during the course of the disease.4
- Anemia in LR-MDS is linked to multiple complications, contributing to a negative health-related quality of life, such as transfusion-related iron overload and anemia-related fatigue.4
- Half of patients with LR-MDS develop transfused red blood cell (RBC) transfusion (T1B) dependence.4
- Anemia and T1B dependence in MDS has also been associated with shorter survival.4
- Iron overload due to transfusions carries rare risks, such as cardiac iron deposition, which can precipitate a patient’s cardiomyopathy, arrhythmias, and possible sudden death.5
- Therapeutic options targeting anemia are limited, and there is a continued need for new treatments.4

AG-946

- AG-946 is an investigational, once-daily activator of pyruvate kinase, and results in low numbers of differentiated mature erythroblasts.4
- AG-946 induces red blood cell production of ATP, according to a pharmacokinetic–pharmacodynamic modeling and was considered safe and tolerable upon completion of phase 1 studies.4

OBJECTIVE

- To report the design of a phase 2 multicenter study consisting of an open-label, proof-of-concept study of AG-946 in adult patients with lower-risk myelodysplastic syndromes and anemia due to LR-MDS (NCT05944446).

METHODS

- Study design: Phase 2a/2b multicenter study evaluating proof of concept and the efficacy and safety of AG-946 in adult patients with LR-MDS with anemia (Figure 2).
- Phase 2a is a single-arm, open-label, proof-of-concept study—Following a 4-week screening period, patients will enter a 24-week double-blind period.
- Patients who complete the phase 2a core period or the phase 2b double-blind period are eligible to receive AG-946 in a 3-year (ie, 156-week) extension period from the respective phase.

RESULTS

- A phase 2a study endpoint: Change from baseline in total transfused RBC units from Week 8 through Week 24 (Dose level 1: 10 mg QD; Dose level 2: 15 mg QD; Dose level 3: 20 mg QD).
- A phase 2b study endpoint: Maximum duration of RBC transfusion independence in those who reach RBC transfusion independence during the double-blind period.

CONCLUSIONS

- This phase 2a/2b global study aims to provide proof of concept and evaluate the efficacy and safety of AG-946 in patients with anemia due to LR-MDS.

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