A phase 2a/2b multicenter study of AG-946 in patients with anemia 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 progressive cytopenias[1–4]
- MDS occur with an incidence of 4.5/100,000 people per year, with 21,000 new cases per year in the US[1,3]
  - Approximately two-thirds of patients with MDS present with lower-risk MDS (LR-MDS)[3]
  - An estimated 25% of patients with LR-MDS die within 2 years[3]
- Overall survival and risk of progression from MDS to acute myeloid leukemia can be categorized using Revised International Prognostic Scoring System (IPSS-R) criteria (**Table 1**)[2,5]

Table 1. IPSS-R features[a,b,5]

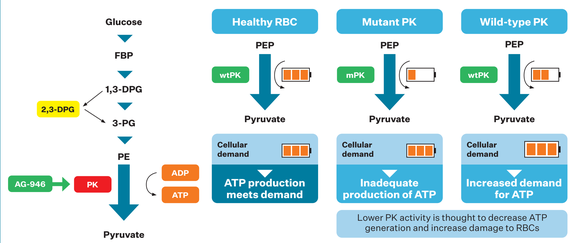
Score	Cytogenetics	BM blast, %	Hb, g/dL	Platelets, x 10^9/L	ANC, x 10^9/L
0	Very good	≤2	≥10	≥100	≥0.8
0.5	--	--	--	50–<100	<0.8
1	Good	>2–<5	8–<10	<50	--
1.5	--	--	<8	--	--
2	Intermediate	5–10	--	--	--
3	Poor	>10	--	--	--
4	Very poor	--	--	--	--

[a]IPSS-R risk categories are very low (score ≤1.5), low (score >1.5–3), intermediate (score >3–4.5), high (score >4.5–6), and very high (score >6)[5]
[b]LR-MDS includes very low, low, and some cases of intermediate IPSS-R risk[2]
ANC, absolute neutrophil count; BM, bone marrow; Hb, hemoglobin; IPSS-R, Revised International Prognostic Scoring System; LR-MDS, lower-risk myelodysplastic syndrome

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[6–8]
- Anemia in LR-MDS is linked to multiple complications, contributing to a negative health-related quality of life, such as transfusional iron overload and debilitating fatigue[9]
- Half of patients with LR-MDS develop red blood cell (RBC) transfusion (TF) dependence[10]
- Anemia and TF dependence in MDS have also been associated with shorter survival[1]
- Iron overload due to TF also carries rare risks, such as cardiac iron deposition, which can predispose a patient to cardiomyopathy, arrhythmias, and possible sudden death[7]
- Therapeutic options targeting anemia are limited, and there continues to be a tremendous need for novel therapies[1,8]
- Acquired pyruvate kinase (PK) deficiency has been observed in MDS, suggesting potential for direct involvement of RBC-specific PK in the pathogenesis of MDS-associated anemia[11–13]
- AG-946 is an investigational, potent, small-molecule, allosteric activator of PK that has the potential to (**Figure 1**)[14]:
  - Enhance RBC functionality and survival by increasing glycolysis and adenosine triphosphate (ATP) production[13,14]
  - Improve differentiation of erythroid cells in bone marrow (BM), potentially improving anemia caused by ineffective erythropoiesis in MDS[13]
- In a phase 1 study in healthy volunteers, treatment with 5 mg of AG-946 once daily was associated with near-maximal pharmacodynamic activity (predicted to provide ~95% of the maximal effect in increasing ATP, according to a pharmacokinetic–pharmacodynamic modeling) and was considered safe and tolerable[13]

Figure 1. AG-946, an investigational, oral activator of PK[11–17]



1,3-DPG, 1,3-diphosphoglycerate; 2,3-DPG, 2,3-diphosphoglycerate; 3-PG, 3-phosphoglycerate; ADP, adenosine diphosphate; ATP, adenosine triphosphate; FBP, fructose 1,6-bisphosphate; mPK, mutant pyruvate kinase; PEP, phosphoenolpyruvate; PK, pyruvate kinase; RBC, red blood cell; wtPK, wild-type pyruvate kinase

OBJECTIVE

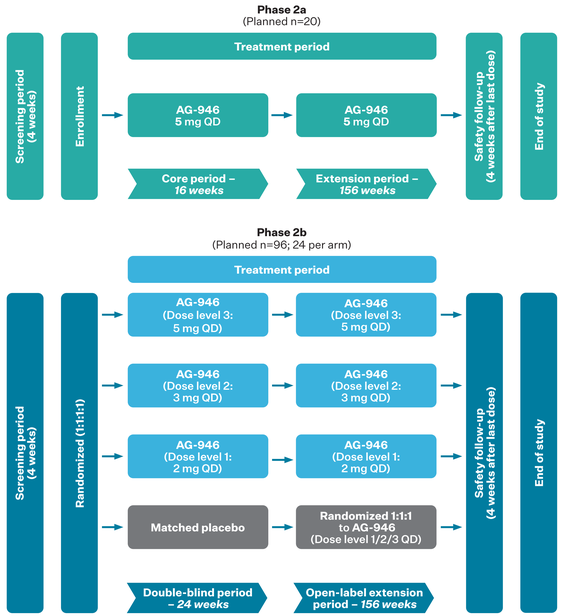
- Report the design of a phase 2 multicenter study consisting of an open-label, proof-of-concept (phase 2a) study and a double-blind, randomized, placebo-controlled (phase 2b) study evaluating the efficacy and safety of AG-946 in adult patients with anemia due to LR-MDS (NCT05490446)

METHODS

Study design

- Phase 2a/2b multicenter study evaluating proof of concept and the efficacy and safety of AG-946 in adult (≥18 years) 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 16-week core period
  - 20 patients are expected for enrollment and will receive AG-946 at a dose of 5 mg once daily
- Phase 2b is a double-blind, randomized, placebo-controlled evaluation of the efficacy and safety of AG-946 vs placebo
  - Following a 4-week screening period, patients will enter a 24-week double-blind period
  - 96 patients will be randomized 1:1:1:1 to receive AG-946 (2 mg, 3 mg, or 5 mg once daily) or placebo
    - Randomization will be stratified by baseline TF burden category
- 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 of the respective phase

Figure 2. Phase 2a/2b study design



Key inclusion criteria

- Age ≥18 years
- Documented LR-MDS with an IPSS-R score of ≤3.5 and <5% BM blasts per biopsy during the screening period
- Hb level <11.00 g/dL during the screening period
- ECOG PS of 0, 1, or 2

Phase 2a	Phase 2b
• NTD or LTB status	• NTD, LTB, or HTB status • ≤2 prior therapies, including ESAs (eg, EPO ± G-CSF) and/or luspatercept

Key exclusion criteria

- History of AML
- Secondary MDS
- Phase 2a platelet count ≤75,000/μL (75 × 10^9/L) or Phase 2b platelet count <50,000/μL (50 × 10^9/L)
- Absolute neutrophil count <500/μL (0.5 × 10^9/L)
- Prior exposure to PK activator, disease-modifying agents, or treatment for high-risk MDS
- Treatment of EPO or G-CSF must have been stopped for ≥28 days and luspatercept for ≥65 days before administration of the first dose of AG-946

AML, acute myeloid leukemia; BM, bone marrow; ECOG PS, Eastern Cooperative Oncology Group Performance Status; EPO, erythropoietin; ESA, erythropoietin-stimulating agent; G-CSF, granulocyte colony-stimulating factor; Hb, hemoglobin; HTB, high transfusion burden; IPSS-R, Revised International Prognostic Scoring System; LR-MDS, lower-risk myelodysplastic syndrome; LTB, low transfusion burden; MDS, myelodysplastic syndrome; NTD, non–transfusion-dependent; PK, pyruvate kinase; QD, once daily

- Categorization by TF burden: Patients will be grouped throughout the study by the following categories of TF burden, using International Working Group (IWG) 2018 criteria and based on patient history according to medical records[16]:
  - Non–TF-dependent (NTD): <3 RBC units within 16 weeks and 0 RBC units within 8 weeks prior to first dose
  - Low TF burden (LTB): 3–7 RBC units within 16 weeks and <4 RBC units within 8 weeks prior to first dose
  - High TF burden (HTB): ≥8 RBC units within 16 weeks and ≥4 RBC units within 8 weeks prior to first dose (included in phase 2b only)
- Study endpoint examples are shown in **Figure 3**

Figure 3a. Phase 2a study endpoints

Phase 2a primary endpoints[a]

- Hb response, defined as a ≥1.5 g/dL increase from baseline in the average Hb concentration from Week 8 through Week 16
- In patients with LTB: TF independence, defined as being TF-free for ≥8 consecutive weeks

Phase 2a select secondary endpoints

- Safety during the core period, as measured by AEs, serious AEs, discontinuations due to AEs, and laboratory abnormalities
- Change in Hb concentration during the core period, compared to baseline
- Hb 1.0+ response, defined as a ≥1.0 g/dL increase from baseline in the average Hb concentration from Week 8 through Week 16
- Change in total transfused RBC units during the core period, compared to baseline
- ≥50% reduction in total transfused RBC units for ≥8 consecutive weeks during the core period, compared to baseline
- Pharmacokinetics and pharmacodynamics during the core period

[a]Primary endpoints in this study are defined per IWG 2018 criteria
AE, adverse event; Hb, hemoglobin; IWG, International Working Group; LTB, low transfusion burden; RBC, red blood cell; TF, transfusion

Figure 3b. Phase 2b study endpoints

Phase 2b primary endpoints[a]

- Modified hematologic improvement-erythroid (mHI-E) response during the double-blind period, ie:
  - In NTD patients, a ≥1.5 g/dL increase in Hb concentration over baseline for ≥8 consecutive weeks during the double-blind period
  - In patients with LTB, transfusion independence (TI), defined as being TF-free for ≥8 consecutive weeks during the double-blind period
  - In patients with HTB, ≥50% reduction in total transfused RBC units, compared to baseline, for ≥8 consecutive weeks during the double-blind period

Phase 2b select secondary endpoints

- Safety during the double-blind period, as measured by AEs, serious AEs, discontinuations due to AEs, and laboratory abnormalities
- TI, defined as being TF-free for ≥8 consecutive weeks during the double-blind period
- Time to first mHI-E response during the double-blind period
- Maximum duration of mHI-E response in those who reach mHI-E response during the double-blind period
- Change in Hb during the double-blind period
- Change from baseline in total transfused RBC units from Week 8 through Week 24
- Exposure–response (or pharmacokinetic–pharmacodynamic) relationship between relevant pharmacokinetic parameters and endpoints that are indicators of clinical activity and safety during the double-blind period
- Additional pharmacokinetics and pharmacodynamics during the double-blind period

[a]Primary endpoints in this study are defined per IWG 2018 criteria
AE, adverse event; Hb, hemoglobin; HTB, high transfusion burden; IWG, International Working Group; LTB, low transfusion burden; mHI-E, modified hematologic improvement-erythroid; NTD, non–transfusion-dependent; RBC, red blood cell; TF, transfusion; TI, transfusion independence

Analyses

- **Phase 2a**
  - Proportions of participants achieving hemoglobin (Hb) response and transfusion independence will be summarized respectively, with 2-sided 95% exact CIs calculated by the Clopper-Pearson method
  - Hb concentrations assessed within 14 days after an RBC TF will be excluded from the analyses of the primary endpoint; once this exclusion is applied, participants who do not have any Hb concentration assessments from Week 8 through Week 16 will be considered non-responders
- **Phase 2b**
  - The proportion of modified hematologic improvement-erythroid responders will be analyzed using logistic regression
  - The multiple comparison procedure-modeling (MCP-Mod) method will be used to assess the dose-response relationship while controlling multiplicity
    - A planned sample size of 96 participants is powered to detect a dose-response relationship
  - Hb concentrations assessed within 14 days after an RBC TF will be excluded from the analyses of the primary endpoint; once this exclusion is applied, participants who are NTD and participants with LTB will be considered as nonresponders if the participants do not have at least 2 Hb concentration assessments separated by ≥8 weeks through Week 24

RESULTS

Planned sites

- Global site recruitment is in progress
- Geographic distribution of planned study sites is shown in **Figure 4**

Figure 4. Planned study sites

CONCLUSIONS

- **Anemia is the most common cytopenia of MDS, occurring in up to 90% of patients[6–8]**
- **Although genetically different, there are similarities in the features of ineffective erythropoiesis for both MDS and thalassemia; ineffective erythropoiesis is characterized by proliferation of precursor cells, but high levels of apoptosis results in low numbers of differentiated mature erythroblasts[4]**
- **Decreased glycolytic activity, observed as reduced PK activity and ATP in RBCs from patients with LR-MDS, indicates an overall lack of energy in MDS-RBCs[11–13,19]**
- **AG-946 is an investigational, once-daily activator of PK, and it has the potential to improve anemia caused by ineffective erythropoiesis in LR-MDS[13]**

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

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