Results from a phase 1 study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of tebapivat (AG-946) in patients with sickle cell disease

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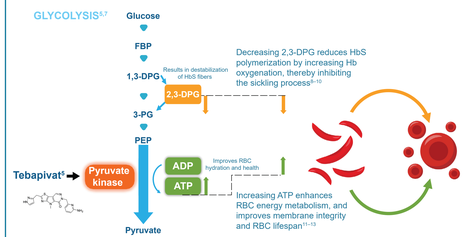
BACKGROUND

- In sickle cell disease (SCD), pyruvate kinase activation increases adenosine triphosphate (ATP), leading to improved membrane integrity and survival of red blood cells (RBCs), and decreases 2,3-diphosphoglycerate (DPG), preventing the polymerization of sickle hemoglobin (HbS) in its deoxygenated state[1]
- Mitapivat, an allosteric activator of the RBC-specific (PKR) and M2 (PKM2) isoforms of pyruvate kinase, demonstrated clinically meaningful improvements in hemoglobin (Hb) response and improvements in markers of hemolysis and erythropoiesis in phase 2 trials in SCD[2,3]
  - Mitapivat is currently being evaluated in a phase 3 trial in patients with SCD[4]
- Tebapivat (formerly AG-946) is an oral, once daily (QD), potent, allosteric activator of PKR and PKM2 (**Figure 1**)[5]; results from the randomized, double-blind, placebo-controlled single ascending dose (SAD) and multiple ascending dose (MAD) parts of a phase 1 study of tebapivat in healthy volunteers (HVs; NCT04536792) have been previously reported[6]

Figure 1. Tebapivat, a potent, oral activator of pyruvate kinase



ADP, adenosine diphosphate; ATP, adenosine triphosphate; DPG, diphosphoglycerate; FBP, fructose bisphosphate; Hb, hemoglobin; HbS, sickle hemoglobin; PEP, phosphoenolpyruvate; PG, phosphoglycerate; RBC, red blood cell

OBJECTIVE

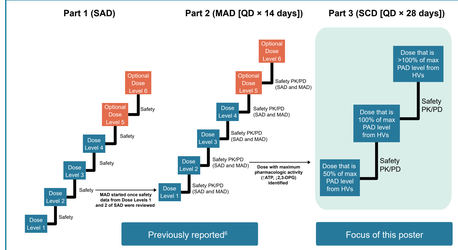
- **To understand the safety, tolerability, and pharmacokinetics/pharmacodynamics (PK/PD) of tebapivat in the non-randomized, open-label, third part of a phase 1 study in adult patients with SCD**

METHODS

Study design

- Adult patients (aged 18–70 years) with sickle cell anemia (homozygous for HbS [HbSS] or HbS/ß^0-thalassemia) and adequate organ function received 2 mg or 5 mg tebapivat QD for 28 days, with a further 28-day observational safety follow-up[14] (**Figure 2**)
- Further details of the study eligibility criteria can be found via the QR code

Figure 2. Study design[14]



ATP, adenosine triphosphate; DPG, diphosphoglycerate; HV, healthy volunteer; MAD, multiple ascending dose; PAD, pharmacologically active dose; PK/PD, pharmacokinetic/pharmacodynamic; QD, once daily; SAD, single ascending dose; SCD, sickle cell disease

Study endpoints

- The primary endpoints were:
  - Relationships between tebapivat dose, concentration, and safety endpoints
  - Relationships between tebapivat dose, concentration, and pharmacodynamic endpoints
- Secondary endpoints included:
  - Type, severity, and relationship of adverse events (AEs) and serious AEs (SAEs)
  - Plasma pharmacokinetic parameters after both single and multiple oral dose administration of tebapivat
  - Change over time in the whole blood concentrations of 2,3-DPG and ATP
  - Change from baseline in Hb
  - Change from baseline in markers of hemolysis (including total bilirubin and lactate dehydrogenase [LDH] levels) and erythropoiesis (including reticulocyte percentage and erythropoietin [EPO])

RESULTS

- Sixteen adult patients with SCD received ≥1 dose of either 2 mg QD (N=8) or 5 mg QD (N=8) oral tebapivat
- Fourteen patients (87.5%) completed the 28-day dosing period
  - One patient in the 2 mg QD cohort discontinued tebapivat due to an AE (sickle cell anemia with crisis), and 1 patient in the 5 mg QD cohort discontinued tebapivat due to increased Hb (but completed the study)
  - All 16 patients were included in the intention-to-treat analysis

Safety

- Two (25.0%) patients in the 2 mg QD cohort reported an SAE of sickle cell anemia with crisis; one patient reported two events, one during the treatment period and one during the safety follow-up, and the other patient experienced one event during the safety follow-up (**Table 2**)
- No TEAEs of sickle cell anemia with crisis were reported during the 5 mg QD treatment period; 1 (12.5%) patient in the 5 mg QD cohort reported an SAE of sickle cell anemia with crisis during the safety follow-up, which was the only AE/SAE of sickle cell anemia with crisis considered treatment-related by the Investigator

Table 1. Baseline demographics and disease characteristics

Demographics and disease characteristics	Tebapivat 2 mg QD (N=8)	Tebapivat 5 mg QD (N=8)
Age, median (range), years	28.0 (19.0–48.0)	37.5 (25.0–51.0)
Male, n (%)	4 (50.0)	4 (50.0)
Race, n (%)		
Black or African American	7 (87.5)	6 (75.0)
White	0 (0.0)	1 (12.5)
Multiracial	0 (0.0)	1 (12.5)
Not reported	1 (12.5)	0 (0.0)
Hb concentration, mean (SD), g/dL	7.8 (1.0)	8.1 (1.1)
VOC in the prior 12 months,[a] n (%)	4 (50.0)	3 (37.5)
Recieved prior SCD-related therapies,[b] n, (%)	4 (50.0)	6 (75.0)

[a]Includes VOCs that occurred within 12 months before informed consent and during screening; [b]Prior disease-modifying SCD-related therapies included hydroxyurea, crizanlizumab, L-glutamine, and voxelotor
Hb, hemoglobin; QD, once daily; SCD, sickle cell disease; SD, standard deviation; VOC, vaso-occlusive crisis

Table 2. Safety

Patients, n (%)	Tebapivat 2 mg QD (N=8)	Tebapivat 5 mg QD (N=8)
Any TEAEs	8 (100.0)	8 (100.0)
Grade ≥3 TEAEs	3 (37.5)	3 (37.5)
Treatment-related TEAEs	1 (12.5)	2 (25.0)
Grade ≥3 treatment-related TEAEs	0 (0.0)	1 (12.5)
Serious TEAEs	3 (37.5)	1 (12.5)
Serious treatment-related TEAEs	0 (0.0)	1 (12.5)
TEAEs leading to discontinuation of study drug	0(0.0)	0 (0.0)
TEAEs leading to dose reduction	0 (0.0)	0 (0.0)
TEAEs leading to interruption of study drug	2 (25.0)	0 (0.0)
TEAEs leading to death	0 (0.0)	0 (0.0)
Most frequently reported (≥10%) TEAEs		
Sickle cell anemia with crisis		
Any grade	4 (50.0)	3 (37.5)
Grade ≥3	2 (25.0)	1 (12.5)
Upper respiratory tract infection		
Any grade	1 (12.5)	2 (25.0)
Grade ≥3	0 (0.0)	1 (12.5)

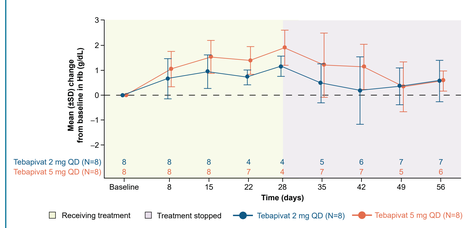
The severity of all TEAEs, including clinically significant laboratory abnormalities, was graded by the Investigator according to v5.0 of the National Cancer Institute Common Terminology Criteria for Adverse Event on a 5-point severity scale (Grade 1–5)
AE, adverse event; QD, once daily; TEAE, treatment-emergent adverse event

- All pain crises occurred in the setting of known triggers

Hb and markers of hemolysis and erythropoiesis

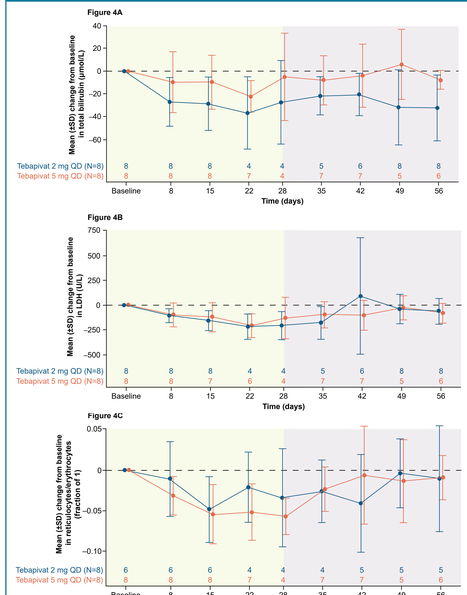
- At the end of the 28-day treatment period, the mean (SD) change from baseline for Hb was 1.2 g/dL (0.4) in the 2 mg QD cohort and 1.9 g/dL (0.7) in the 5 mg QD cohort (**Figure 3**)
- Overall decreases in markers of hemolysis (total bilirubin and LDH) and erythropoiesis (reticulocyte percentage) from baseline were observed at Day 28 in both cohorts (**Figure 4A–C**)

Figure 3. Mean (±SD) change from baseline in Hb concentration



Baseline was defined as the last assessment before start of study treatment
Hb, hemoglobin; QD, once daily; SD, standard deviation

Figure 4. Mean (±SD) change from baseline in (A) total bilirubin, (B) LDH, and (C) reticulocytes/erythrocytes (reticulocyte percentage)



Baseline was defined as the last assessment before start of study treatment
LDH, lactate dehydrogenase; QD, once daily; SD, standard deviation

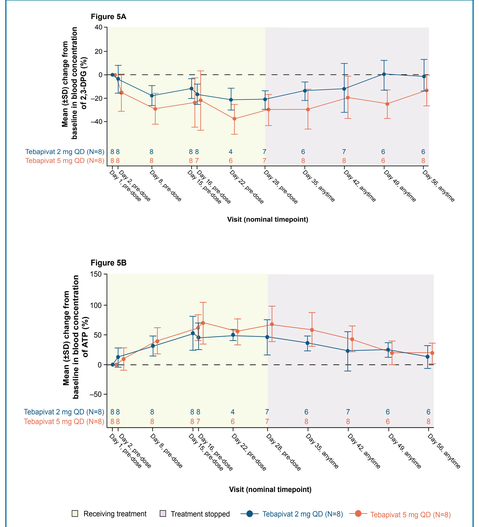
Pharmacokinetics

- Overall, tebapivat exposure increased with a higher dose (2 mg QD vs 5 mg QD)
- Tebapivat exposures in patients with SCD on both Day 1 (2 mg QD: 58 h·ng/mL; 5 mg QD: 197 h·ng/mL) and Day 15 (2 mg QD: 157 h·ng/mL; 5 mg QD: 447 h·ng/mL) were comparable to exposures in HVs[15]

Pharmacodynamics

- Dose-dependent pharmacodynamic effects on 2,3-DPG and ATP levels were demonstrated with tebapivat, with higher doses resulting in greater changes from baseline
- 2,3-DPG and ATP concentrations reached steady state after 2 weeks of QD dosing
- At Day 28 (pre-dose [sample collected ≤60 minutes before the administration of tebapivat]), mean (SD) percent reduction in 2,3-DPG from baseline was 20.9% (7.1) and 29.4% (12.7) for the 2 mg and 5 mg cohorts, respectively (**Figure 5A**)
- At Day 28 (pre-dose), mean (SD) percent increase in ATP from baseline was 46.3% (29.1) and 67.8% (30.9) for the 2 mg and 5 mg cohorts, respectively (**Figure 5B**)
- A sustained pharmacodynamic effect was observed up to 4 weeks after 28 days of QD dosing

Figure 5. Mean (±SD) percent change from baseline in (A) 2,3-DPG and (B) ATP



Baseline was defined as the pre-dose concentration on study Day 1. "Pre-dose" refers to samples collected ≤60 minutes before the administration of tebapivat. "Anytime" refers to samples collected at any point during that day
ATP, adenosine triphosphate; DPG, diphosphoglycerate; QD, once daily; SD, standard deviation

CONCLUSIONS

- **Tebapivat was well tolerated in patients with SCD receiving either 2 mg or 5 mg QD for 28 days**
- **Increases in Hb and trends towards improvements in hemolytic and erythropoietic markers were observed, and there was a sustained effect after tebapivat was stopped**
- **ATP levels were increased and 2,3-DPG levels decreased during the study, consistent with the proposed mechanism of action of tebapivat**
  - **A sustained pharmacodynamic effect was observed up to 4 weeks after the last dose**
- **Tebapivat will be further evaluated in different clinical studies**

Tebapivat is a potent pyruvate kinase activator with the potential to provide benefit in SCD

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References and supplemental materials are available via the QR code

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