Long-term efficacy and safety of the oral pyruvate kinase activator mitapivat in adults with non–transfusion-dependent alpha- or beta-thalassemia

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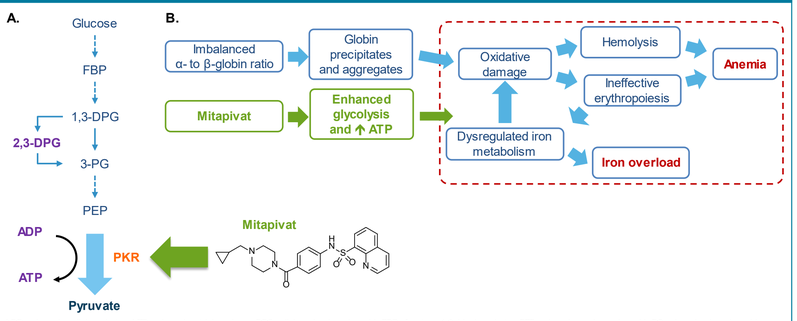
BACKGROUND

- Thalassemia is a red blood cell (RBC) disorder in which ineffective erythropoiesis and hemolysis occur due to imbalanced globin production and precipitation of excess globin chains[1,2]
- Thalassemic RBCs have insufficient levels of adenosine triphosphate (ATP) to meet increased energy demands associated with globin chain precipitation, protein degradation, and cellular oxidative stress responses[3,4]
- Thalassemia can result in complications including[1,2]
  - Anemia, bone marrow expansion, extramedullary hematopoiesis, osteoporosis and bone deformities, iron overload, gallstones, and splenomegaly
- Treatment options for non–transfusion-dependent thalassemia (NTDT) are supportive only, highlighting an unmet need for disease-modifying therapies[5]
- Mitapivat is a first-in-class, oral, small-molecule allosteric activator of pyruvate kinase (PK), a key glycolytic enzyme that regulates ATP production[6]
- Mitapivat activates PK, which catalyzes the final step of glycolysis in RBCs[7] (**Figure 1A**)
  - ATP generation is essential for RBC function and stability[6,8]
- Mitapivat increased PKR activity and ATP levels *ex vivo* in RBCs from patients with β-thalassemia[9] (**Figure 1B**)
- Mitapivat ameliorated ineffective erythropoiesis, iron overload, and anemia in the Hbb$^{th3/+}$ mouse model of β-thalassemia[10] (**Figure 1B**)

Figure 1. Proposed mitapivat mechanism of action in thalassemia

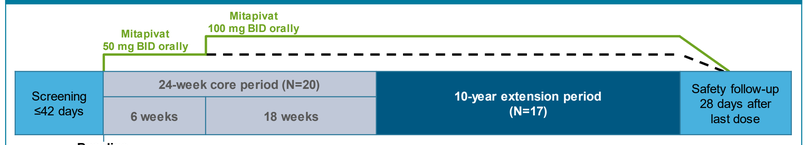


ADP, adenosine diphosphate; ATP, adenosine triphosphate; DPG, diphosphoglyceric acid; FBP, fructose 1,6–bisphosphate; PEP, phosphoenolpyruvic acid; PG, phosphoglyceric acid; PKR, RBC-specific form of pyruvate kinase; RBC, red blood cell

METHODS

- This is a phase 2, open-label, study to determine the efficacy, safety, pharmacokinetics, and pharmacodynamics of AG-348 in adult subjects with α- or β-NTDT (**Figure 2**)

Figure 2. Design of phase 2 study of mitapivat in adults with α- or β-NTDT[a]



Core period[11] – key inclusion criteria
- β-thalassemia ± α-globin gene mutations, hemoglobin E (HbE) β-thalassemia, or α-thalassemia (hemoglobin H [HbH] disease)
- Hemoglobin (Hb) ≤10.0 g/dL
- Non–transfusion-dependent

Long-term extension – key inclusion criteria
- Completed 24-week core period
- Achieved a primary Hb response, or achieved a delayed Hb response (Hb increase of ≥1.0 g/dL at ≥1 assessment after Week 12)
- No ongoing grade ≥3 treatment-emergent adverse events related to study drug

[a]EudraCT 2018-002217-35, ClinicalTrials.gov: NCT03692052.
BID, twice daily; NTDT, non–transfusion-dependent thalassemia

Results from core period (previously presented)[11,a]
- The primary endpoint of Hb response was met in 80.0% (16/20) of patients
  - Hb response defined as: ≥1.0 g/dL increase in Hb concentration from baseline at 1 or more assessments between Weeks 4–12, inclusive
- Improvements in markers of hemolysis and ineffective erythropoiesis were also observed
- Mean ATP percent increase from baseline was similar to that previously observed with mitapivat in healthy volunteers
- Mitapivat was generally well tolerated, and the safety profile was consistent with that of previously published mitapivat studies

Long-term extension period[a]

Here, we report on long-term efficacy and safety of mitapivat in patients who continue treatment in the ongoing extension period (up to Week 72; data cutoff 27Mar2021)

- Change in Hb from baseline
- Markers of hemolysis
- Markers of ineffective erythropoiesis
- Safety

[a]EudraCT 2018-002217-35, ClinicalTrials.gov: NCT03692052.

RESULTS

Table 1. Patient demographics and baseline[a] characteristics for patients who entered the long-term extension period

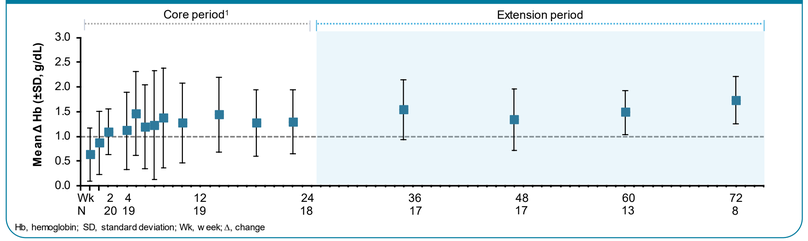
Patient demographics and baseline[a] characteristics	All patients (N=17)
Median (range) duration of treatment, weeks	70.9 (54.7, 105.6)
Sex, n (%)	
Male	5 (29.4)
Female	12 (70.6)
Age, median (range), years	44 (29, 67)
Race, n (%)	
Asian	8 (47.1)
White	4 (23.5)
Native Hawaiian or other Pacific Islander	1 (5.9)
Other	3 (17.6)
Not reported	1 (5.9)
Thalassemia type, n (%)	
α-thalassemia	4 (23.5)
β-thalassemia	13 (76.5)
Hb baseline, median (range), g/dL	8.5 (5.6, 9.8)
Total bilirubin, median (range), µmol/L	32.0 (8.6, 90.0)
LDH, median (range), U/L	245.0 (126.0, 513.0)
Erythropoietin, median (range), IU/L	70.5 (15.0, 11191.0)

Genotype	Patients (N = 16)[b]
β-thalassemia, n (%)	
Intermedia	5 (31.3)
Intermedia + α duplication	3 (18.8)
Trait/phenotypic β-thalassemia intermedia	2 (12.5)
HbE/β-thalassemia, n (%)	
HbE/β^0	2 (12.5)
α-thalassemia, n (%)	
Deletional	1 (6.3)
Non-deletional	3 (18.8)

[a]Baseline is defined as the last assessment on or before the start of study treatment in core period. [b]17 patients entered the extension, genotype data are unknown for 1 patient; Hb, hemoglobin; HbE, hemoglobin E; LDH, lactate dehydrogenase; U, units

- Durable improvements in Hb concentration were observed in the extension period (**Figure 2**)[11]
- Mean Hb (standard deviation) increase from baseline to Week 60 (α-thalassemia, n=4; β-thalassemia, n=9) and Week 72 (β-thalassemia, n=8) were 1.5 (0.4) g/dL and 1.7 (0.5) g/dL, respectively

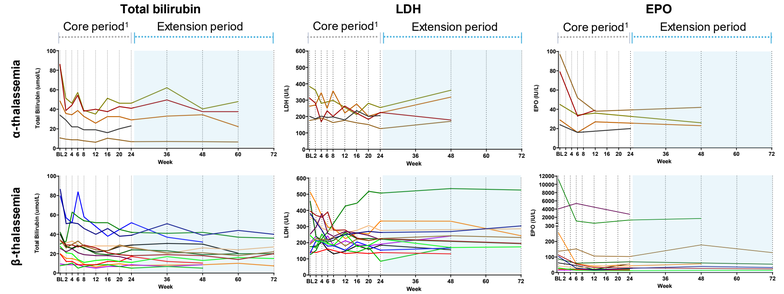
Figure 2. Mean Hb change from baseline over time



Hb, hemoglobin; SD, standard deviation; Wk, week; Δ, change

- Improvements in markers of hemolysis and ineffective erythropoiesis observed in the core period were maintained in the extension period up to Week 72 (**Figure 3**)

Figure 3. Markers of hemolysis and ineffective erythropoiesis



EPO, erythropoietin; IU, international units; LDH, lactate dehydrogenase; U, units

- The majority of events occurred earlier in the study and were transient in nature
- There were no treatment-related serious AEs during the extension period (**Table 2**)

Table 2. Safety summary for the core and extension periods

Category	Core period, n (%)[a][11] (N=20) Weeks 0–24	Extension period, n (%)[a] (N=17)[b] Weeks 25–72
Treatment-related TEAEs	13 (65.0)	2 (11.8)
Grade ≥ 3 TEAEs	5 (25.0)	2 (11.8)
Grade ≥ 3 treatment-related TEAEs	1 (5.0)	0
Serious TEAEs	1 (5.0)	2 (11.8)
TEAEs leading to study drug:		
Dose reduction	3 (15.0)	1 (5.9)
Interruption	1 (5.0)	0
Discontinuation	1 (5.0)[c]	1 (5.9)[c]

[a]TEAEs listed in the extension period are new AEs that occurred after entering the extension period. [b]16 patients received 100 mg BID mitapivat and 1 received 50 mg BID. [c]1 patient discontinued during the core period as a result of an AE. 1 further patient discontinued during the extension period (patient decision) as of the cutoff date (27March2021)
AE, adverse event; BID, twice daily; TEAE, treatment-emergent adverse event

- The safety profile was consistent with that observed during the core period
- AEs occurring in ≥15% of patients during the extension period were headache (5/17) and back pain (3/17), none of which were grade ≥3 (**Table 3**)
- No new safety findings were reported in the extension period

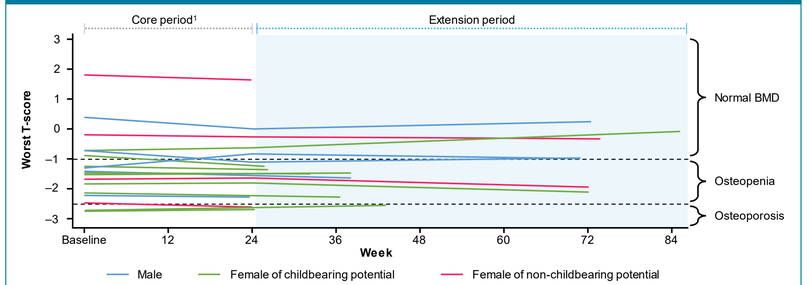
Table 3. Most common TEAEs occurring during the core and extension periods

Most common TEAEs (any grade in ≥15% of patients)	Core period (N=20)[11] Weeks 0–24 Any grade, n (%)	Extension period (N=17)[a] Weeks 25–72 Any grade, n (%)
Patients with events	17 (85.0)	13 (76.5)
Initial insomnia	10 (50.0)	0
Dizziness	6 (30.0)	1 (5.9)
Headache	5 (25.0)	5 (29.4)
Cough	4 (20.0)	0
Dyspepsia	4 (20.0)	1 (5.9)
Fatigue	4 (20.0)	0
Nasal congestion	4 (20.0)	0
Upper respiratory tract infection	4 (20.0)	0
Abdominal pain	3 (15.0)	1 (5.9)
Diarrhea	3 (15.0)	2 (11.8)
Ocular icterus	3 (15.0)	0
Pain	3 (15.0)	0
Pain in extremity	3 (15.0)	2 (11.8)
Abdominal distension	3 (15.0)	0
Nausea	3 (15.0)	1 (5.9)
Oropharyngeal pain	3 (15.0)	0
Back pain	2 (10.0)	3 (17.6)

[a]TEAEs listed in the extension period are new AEs that occurred after entering the extension period
AE, adverse event; TEAE, treatment-emergent adverse event

- No trends for decreases in bone mineral density were observed (**Figure 4**)

Figure 4. Plot of individual patient BMD by worst DXA T-scores[a] over time



[a]Adjusted spine and femoral total were used to determine worst DXA T-scores; assessed at baseline, Week 24, and Week 72
BMD, bone mineral density; DXA, dual-energy X-ray absorptiometry

CONCLUSIONS

- A favorable efficacy-safety profile was observed with long-term treatment with mitapivat in patients with either α- or β-thalassemia
- Consistent and durable improvements in Hb concentration, and markers of hemolysis and ineffective erythropoiesis, were observed with up to 72 weeks of treatment in a cohort with heterogeneity of globin genotypes
- There were no new safety findings
  - Bone mineral density remained stable over time
- Mitapivat, through its unique mechanism of action, may represent a novel therapeutic approach for this condition
- 2 phase 3 trials of mitapivat in α- and β-thalassemia, 1 in patients who are non–transfusion-dependent (ENERGIZE; NCT04770753) and 1 in patients who are transfusion-dependent (ENERGIZE-T; NCT04770779), are enrolling

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