Efficacy of mitapivat in patients with non–transfusion-dependent α- or β-thalassemia with baseline hemoglobin ≥9.5 g/dL: Subgroup analysis from the phase 3 ENERGIZE trial

PF1281

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BACKGROUND

- Patients with α- or β-thalassemia experience a wide range of anemia severity, which correlates with the probability of developing morbidities (**Figure 1**)[1–3]
- Each hemoglobin (Hb) increase of 1.0 g/dL is associated with reduced morbidity risk,[1] and Thalassaemia International Federation guidelines recommend long-term therapy to raise Hb by ≥1.0 g/dL[2]
- Although the risk of morbidity is highest in patients with a Hb level of <10 g/dL, those at the highest end of this range are still at risk of complications but are often left untreated despite possibly benefiting from long-term therapy to raise Hb levels[1,3]
- Mitapivat, a first-in-class oral allosteric activator of the red blood cell (RBC)-specific isoform of pyruvate kinase (PKR) and pyruvate kinase M2 isoform (PKM2), is approved in adults with α- or β-thalassemia, regardless of transfusion needs, in the European Union, United States, Saudi Arabia, and United Arab Emirates[5–9]
- In the phase 3 ENERGIZE trial, the efficacy and safety of mitapivat was investigated in adults with non–transfusion-dependent (NTD) α- or β-thalassemia (NCT04770753; EudraCT: 2021-000211-23)[5]
  - In the 24-week double-blind period (DBP), the primary endpoint of Hb response was achieved in 42.3% of patients treated with mitapivat vs 1.6% of those who received placebo
  - The least squares mean change from baseline in Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue score was significantly greater from Week 12 to 24 in patients treated with mitapivat vs placebo
  - Mitapivat was generally well tolerated

Figure 1. Probability of multiple morbidities vs Hb level

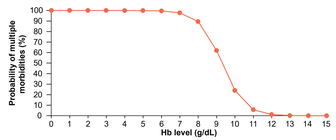


Figure adapted from Musallam KM, et al. *Ann Hematol* 2021;100:1903–5.
Hb, hemoglobin.

OBJECTIVE

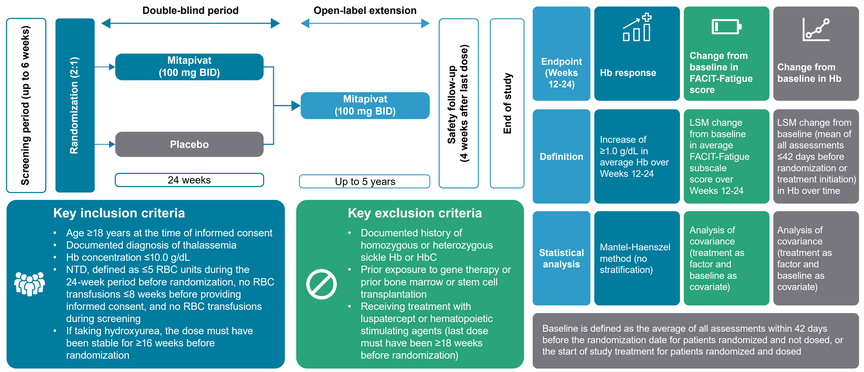
To assess efficacy of mitapivat in patients with NTD α- or β-thalassemia with baseline Hb ≥9.5 g/dL in a post hoc subgroup analysis of ENERGIZE

METHODS

Study Design

- This was a post hoc analysis of data from patients with α- or β-thalassemia and baseline Hb ≥9.5 g/dL in the DBP of the international, randomized, placebo-controlled, phase 3 ENERGIZE trial (**Figure 2**)[5,10]

Figure 2. ENERGIZE study design

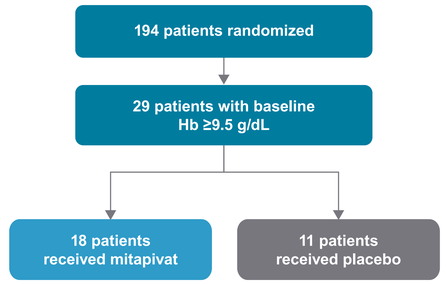


BID, twice daily; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, hemoglobin; LSM, least squares mean; NTD, non–transfusion-dependent; RBC, red blood cell.

RESULTS

- Of the 194 patients who were randomized in ENERGIZE, 29 had baseline Hb ≥9.5 g/dL (range: 9.5-10.7 g/dL; **Figure 3**)
- Baseline demographics and characteristics are presented in **Table 1**

Figure 3. Treatment allocation of patients with baseline Hb ≥9.5 g/dL



Hb, hemoglobin.

Table 1. Demographics and baseline characteristics of patients with baseline Hb ≥9.5 g/dL

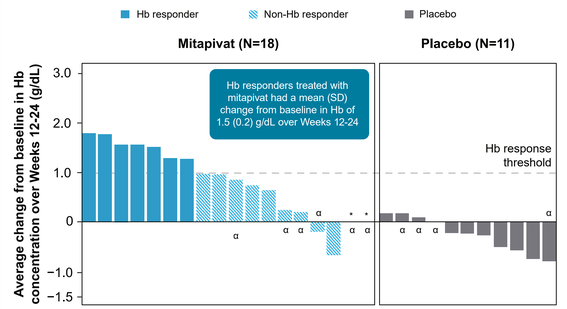
	Mitapivat (N=18)	Placebo (N=11)
Age, years, mean (SD)	42.7 (11.30)	44.3 (13.54)
Sex, n (%)		
Male	7 (38.9)	5 (45.5)
Female	11 (61.1)	6 (54.5)
Race, n (%)		
White	12 (66.7)	9 (81.8)
Asian	5 (27.8)	2 (18.2)
Black or African American	1 (5.6)	0
Hb, g/dL, mean (SD)	9.8 (0.2)	9.8 (0.4)
Transfusion burden, n (%)[a]		
0	17 (94.4)	11 (100)
1-2	1 (5.6)	0
Prior history of splenectomy, n (%)[b]	6 (33.3)	3 (27.3)
Prior history of cholecystectomy, n (%)[b]	7 (38.9)	0
Prior history of iron chelation, n (%)[c]	4 (22.2)	2 (18.2)
Prior history of hydroxyurea use, n (%)	0	1 (9.1)
Hepatic iron concentration, mg/g, mean (SD)[d]	5.4 (5.8)	1.7 (1.0)

[a]Total number of RBC units transfused in the 24-week period before randomization. [b]As recorded in medical/surgical history eCRF. [c]As recorded in disease characteristics eCRF and if a patient received chelation therapy within 1 year (365 days) before randomization. [d]As measured by MRI.
eCRF, electronic case report form; Hb, hemoglobin; MRI, magnetic resonance imaging; RBC, red blood cell; SD, standard deviation.

In the mitapivat arm, most patients had increased Hb levels, and 39% achieved an Hb response, compared with none in the placebo arm (**Figure 4**)

Figure 4. Achievement of Hb response (≥1.0 g/dL average increase over Weeks 12-24) in patients with baseline Hb ≥9.5 g/dL

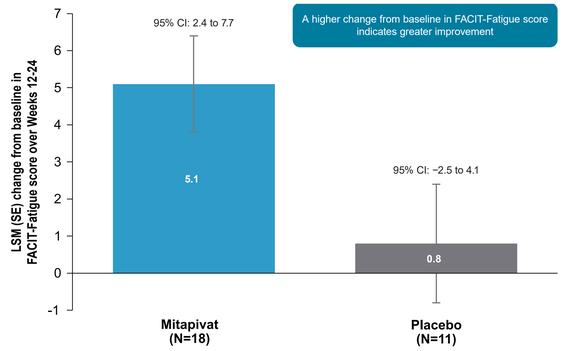
Hb response, n (%)		Response rate difference	95% CI of difference
Mitapivat (N=18)	Placebo (N=11)		
7 (38.9)	0 (0.0)	38.9%	16.4%-61.4%



α denotes a patient with α-thalassemia/HbH disease genotype; no label denotes a patient with β-thalassemia. *Patient with missing baseline or with no assessments over Weeks 12-24.
Hb response is defined as ≥1.0-g/dL increase in average Hb concentration over Weeks 12-24 compared with baseline. Patients who do not have at least 2 on-treatment Hb concentration assessments over Weeks 12-24 are considered non-responders. Hb concentrations assessed within 8 weeks after an RBC transfusion are excluded from the baseline derivation and the analysis.
CI, confidence interval; Hb, hemoglobin, RBC, red blood cell; SD, standard deviation.

Patients who received mitapivat had a greater change from baseline in FACIT-Fatigue score over Weeks 12-24 than patients who received placebo (**Figure 5**)

Figure 5. Change from baseline in average FACIT-Fatigue score over Weeks 12-24

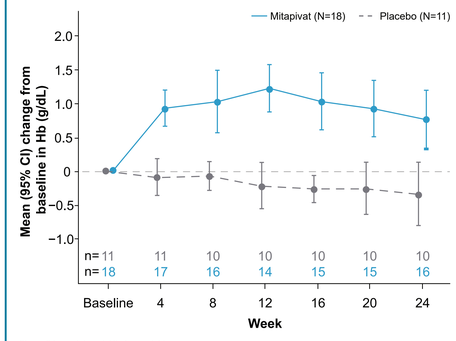


FACIT-Fatigue subscale scores (ranging from 0 to 52) assessed within 8 weeks after an RBC transfusion are excluded from the baseline derivation and the analysis. The FACIT-Fatigue subscale is scored on a 5-point Likert scale.
CI, confidence interval; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, hemoglobin; LSM, least square mean; RBC, red blood cell; SE, standard error.

Improvement in Hb level in the mitapivat arm was early and sustained throughout the DBP (**Figure 6**)

- The change from baseline in average Hb concentration was greater in the mitapivat arm than in the placebo arm as early as Week 4 and through Week 24

Figure 6. Change from baseline in Hb level



CI, confidence interval; Hb, hemoglobin.

CONCLUSIONS

- Among patients with baseline Hb ≥9.5 g/dL in ENERGIZE, 39% of mitapivat-treated patients achieved an Hb response vs 0 patients treated with placebo
- Patients treated with mitapivat also had greater improvements in fatigue relative to patients treated with placebo
- Improvement from baseline Hb level in patients treated with mitapivat was early and sustained through Week 24 (end of analysis)
- These findings align with results from the overall ENERGIZE population and suggest that mitapivat provides benefit for patients with higher baseline Hb as demonstrated by clinically meaningful improvements in both anemia and fatigue

References

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Disclosures

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