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Improvements in fatigue and 6-minute walk test in adults with α- or β-non–transfusion-dependent thalassemia: The phase 3 ENERGIZE trial of mitapivat

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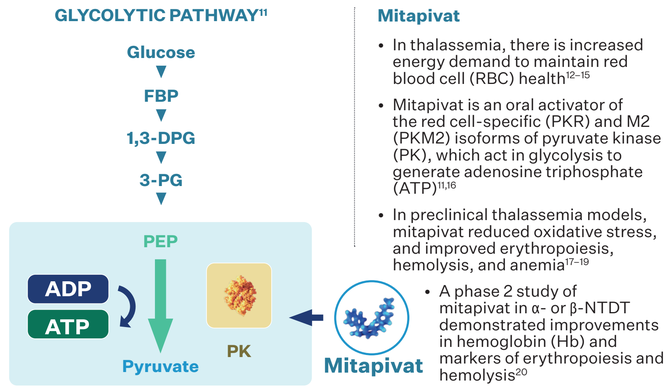
BACKGROUND

Thalassemia and its impact on health-related quality of life (HRQoL)

- Thalassemia, a group of inherited disorders characterized by anemia due to chronic hemolysis and ineffective erythropoiesis, is associated with serious long-term complications[1,2]
- Anemia has been associated with increased symptom burden, such as fatigue, and poor HRQoL in patients with non–transfusion-dependent thalassemia (NTDT)[1,3]
- Patients with α- or ß-thalassemia, regardless of transfusion status, report negative impacts on daily activities, physical functioning, and emotional/mental state[4–6]
- Some domains of HRQoL are reportedly worse or comparable in adult patients with NTDT vs those with transfusion-dependent thalassemia[3–6]
- α-thalassemia has no approved therapies,[7,8] and ß-thalassemia has no approved oral disease-modifying therapies[9]
- No oral disease-modifying therapies for thalassemia have been shown to improve aspects of HRQoL[10]

Figure 1. Mechanism of mitapivat



Mitapivat

- In thalassemia, there is increased energy demand to maintain red blood cell (RBC) health[12–15]
- Mitapivat is an oral activator of the red cell-specific (PKR) and M2 (PKM2) isoforms of pyruvate kinase (PK), which act in glycolysis to generate adenosine triphosphate (ATP)[11,16]
- In preclinical thalassemia models, mitapivat reduced oxidative stress, and improved erythropoiesis, hemolysis, and anemia[17–19]
- A phase 2 study of mitapivat in α- or β-NTDT demonstrated improvements in hemoglobin (Hb) and markers of erythropoiesis and hemolysis[20]

ADP, adenosine diphosphate; DPG, diphosphoglycerate; FBP, fructose bisphosphate; PEP, phosphoenolpyruvic acid; PG, phosphoglycerate; PK, pyruvate kinase

OBJECTIVE

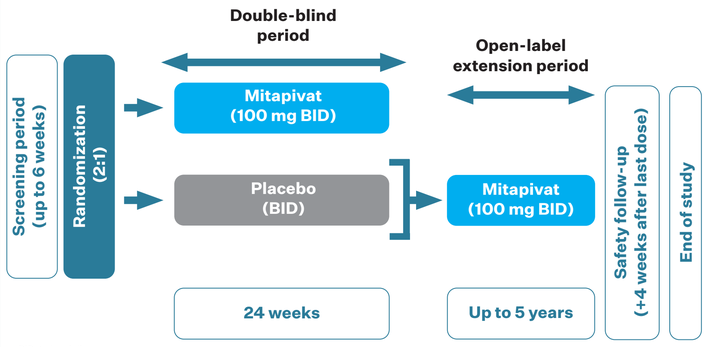
To evaluate the impact of mitapivat vs placebo on fatigue, physical function, and other thalassemia symptoms in adults with α- or ß-NTDT in ENERGIZE (NCT04770753),[21] a phase 3, double-blind, randomized, placebo-controlled, global trial

METHODS

Study design

- During the 24-week double-blind period of ENERGIZE, adults (≥18 years) with NTDT were randomly assigned in a 2:1 ratio to treatment with mitapivat 100 mg or matched placebo, administered orally twice daily (**Figure 2**)
- Patients who completed the double-blind period could receive mitapivat for an additional 5 years in an open-label extension period
- Key inclusion and exclusion criteria for ENERGIZE can be found in **Supplemental figure 1** (QR code)

Figure 2. ENERGIZE study design[22]



BID, twice daily

Study design

Primary endpoint: Hb response, defined as an increase of ≥1.0 g/dL in average Hb concentrationfrom Week 12 through Week 24, compared with baseline

Key secondary endpoint: Change from baseline in average Hb concentration from Week 12 through Week 24

Key secondary endpoint included here: Change from baseline in average Functional Assessment of Chronic Illness Therapy–Fatigue Scale (FACIT-Fatigue) score from Week 12 through Week 24

HRQoL-related secondary endpoints included here: Change from baseline in 6-minute walk test (6MWT) distance at Week 24 and improvement in the Patient Global Impression of Change (PGIC)-Fatigue at Weeks 12, 16, 20, and 24, or "No change" if no or mild fatigue at baseline

HRQoL-related exploratory endpoints included here: HRQoL as assessed by PGIC-Thalassemia Symptoms and PGIC-Walking Capacity at Week 24

Refer to the **ENERGIZE oral presentation** (Abstract ID: 6421798) for outcomes (Oral Abstract Presentations Session Thursday, October 3rd, 2024; 9:30 am)

Focus of this poster

Statistical analyses

- **FACIT-Fatigue:** 7-day recall period and scored on a 5-point Likert scale: 0 (not at all) to 4 (very much) (see full list of questions in **Supplemental appendix 1** [QR code])[23]
  - The least-squares means (LSMs) of the key secondary endpoint (change from baseline in average FACIT-Fatigue score for Week 12 through Week 24) for the mitapivat and placebo arms, and the difference between arms, were provided with the associated 95% CIs and 2-sided p-value (based on analysis of covariance [ANCOVA])
  - The meaningful within-person change (MWPC) threshold for FACIT-Fatigue was estimated to be a **≥4.5-point** change from baseline in average score from Week 12 through Week 24, using an anchor-based method
- **6MWT:** Measured the distance patients can walk on a hard, flat surface in 6 minutes
  - The LSMs of the change from baseline at Week 24 in 6MWT for the mitapivat and placebo arms, and the difference between arms, were provided with the associated 95% CI (based on ANCOVA)
  - The minimal clinically important difference (MCID) threshold reported in literature for the 6MWT is **≥20 m**[24]
- **PGIC-Fatigue, -Thalassemia Symptoms, and -Walking Capacity:** Patients rated the overall change in these aspects of their disease since the start of the study on a 5-point scale ranging from "Much better" to "Much worse" (full list of questions in **Supplemental appendices 2–4** [QR code])[25,26]
  - Improvements in PGIC-Fatigue at Weeks 12, 16, 20, and 24 were compared between the mitapivat arm and the placebo arm using the Mantel–Haenszel stratum weighted method, where improvement was defined as improving by at least 1 category compared with baseline, or "No change" if patients had no or mild fatigue at baseline
  - The proportions of patients in each response level of the PGIC-Thalassemia Symptoms and -Walking Capacity at Week 24 were summarized by treatment arm

RESULTS

Baseline demographics and disease characteristics

- Baseline demographics and disease characteristics were balanced between treatment arms (**Table 1**)

Table 1. Baseline demographics and disease characteristics

Demographic/characteristic	Mitapivat (N=130)	Placebo (N=64)
Age, mean (±SD), years	42.4 (13.0)	38.9 (13.0)
Female, n (%)	84 (64.6)	39 (60.9)
Thalassemia type, n (%) α-thalassemia/HbH disease ß-thalassemia	42 (32.3) 88 (67.7)	20 (31.3) 44 (68.8)
Transfusion burden,[a] n (%) 0 1–2 3–5 >5	114 (87.7) 10 (7.7) 6 (4.6) 0 (0.0)	54 (84.4) 7 (10.9) 3 (4.7) 0 (0.0)
Hb, median (range), g/dL	8.4 (5.3–10.4)	8.4 (5.9–10.7)

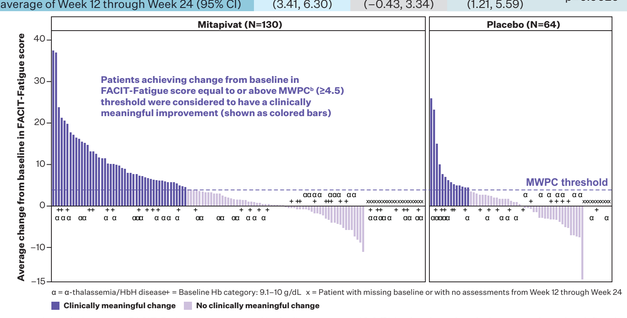
[a]Total number of RBC units transfused in the 24-week period before randomization
Hb, hemoglobin; HbH, hemoglobin H; RBC, red blood cell

FACIT-Fatigue

- Patients were fatigued at baseline, with mean baseline FACIT-Fatigue scores lower than the general population (**Figure 3**)[27]
- Mitapivat demonstrated a statistically significant change from baseline in average FACIT-Fatigue score from Week 12 through Week 24 vs placebo (LSM difference (95% CI): 3.40 (1.21, 5.59) [2-sided p=0.0026]) (**Figure 3**)
- A higher proportion of those in the mitapivat arm (36.2%) met or exceeded the MWPC threshold compared with the placebo arm (21.9%) (**Figure 3 & Supplemental figure 2** [QR code])
- Mitapivat led to early and sustained improvements in FACIT-Fatigue score (**Figure 4**)

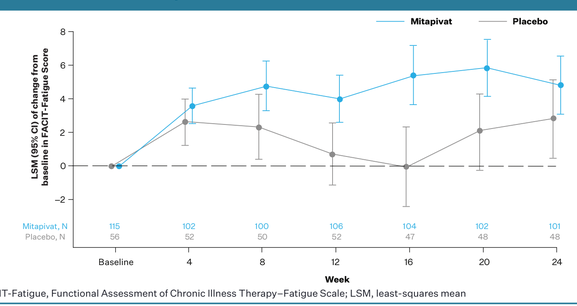
Figure 3. LSM change from baseline in average FACIT-Fatigue score from Week 12 through Week 24

	Mitapivat (N=130)	Placebo (N=64)	LSM difference	2-sided p-value
FACIT-Fatigue score at baseline, mean[a]	36.10	36.41	–	–
FACIT-Fatigue score, LSM change from baseline in average of Week 12 through Week 24 (95% CI)	4.85 (3.41, 6.30)	1.46 (−0.43, 3.34)	3.40 (1.21, 5.59)	p=0.0026



[a]In the general population, mean FACIT-Fatigue score reported in the literature was 43.6.[27] [b]Anchor-based analysis was conducted to define the threshold of FACIT-Fatigue score change associated with a meaningful change. A change of ≥4.5 points was considered clinically meaningful for a patient. FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue Scale; Hb, hemoglobin; HbH, hemoglobin H; LSM, least-squares mean; MWPC, meaningful within-person change

Figure 4. LSM (95% CI) of change from baseline in FACIT-Fatigue score over the 24-week double-blind period



FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue Scale; LSM, least-squares mean

6MWT

- In healthy individuals aged 20–50 years (a similar age range to the ENERGIZE cohort), mean (±SD) 6MWT distances reported in the literature are 593±57 m for females and 638±44 m for males[28]
  - Baseline 6MWT distances in the mitapivat and placebo arms were 422.22 m and 412.43 m, respectively, suggesting this population had reduced walking capacity at baseline compared with the general population (**Table 2**)
- Patients in the mitapivat arm had greater improvements in the 6MWT than those in the placebo arm at Week 24 (**Table 2**)
  - LSM change from baseline to Week 24 was 30.48 m in the mitapivat arm and 7.11 m in the placebo arm, with an LSM difference of 23.36 m between treatment arms; this exceeded the literature-reported MCID threshold of ≥20 m[24]

Table 2. LSM change from baseline to Week 24 for 6MWT distance

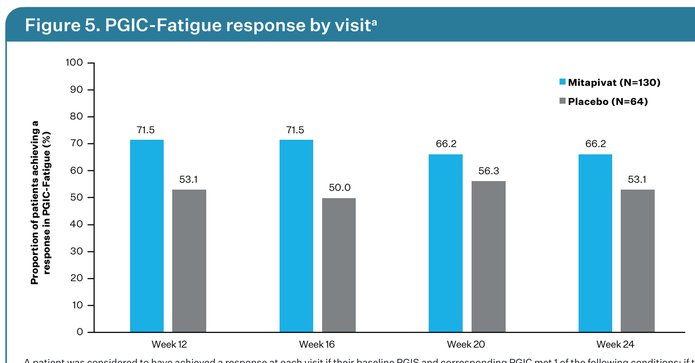
	Mitapivat (N=130)	Placebo (N=64)	LSM difference	Literature-reported MCID threshold[a]
6MWT distance at baseline, mean, m	422.22	412.43	–	–
6MWT distance, LSM change from baseline to Week 24 (95% CI), m[b]	30.48 (19.31, 41.64)	7.11 (−7.39, 21.62)	23.36 (6.90, 39.83)	≥20

[a]MCID represents the smallest improvement considered valuable by a patient; in this case, MCID in 6MWT was measured by an increased ability to walk by 20 m or more, as reported in the literature.[24] [b]In the mitapivat arm, 107 patients had 6MWT data at Week 24; in the placebo arm, 57 patients had 6MWT data at Week 24. 6MWT, 6-minute walk test; LSM, least-squares mean; MCID, minimal clinically important difference

PGIC

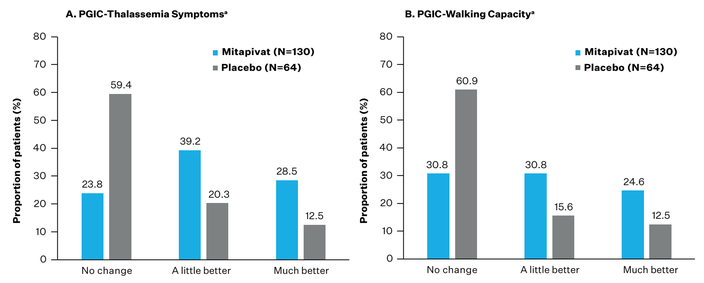
- A higher proportion of patients in the mitapivat arm reported improvements in fatigue as per PGIC vs those in the placebo arm at Weeks 12, 16, 20, and 24 (**Figure 5**)
  - At Week 24, the adjusted difference in response rate (95% CI) between the mitapivat and placebo arms for PGIC-Fatigue was 12.0% (−2.9, 26.9)
- A higher proportion of patients in the mitapivat arm reported improvements in thalassemia symptoms and walking capacity at Week 24 (as per the PGIC) vs those in the placebo arm (**Figure 6**)

Figure 5. PGIC-Fatigue response by visit[a]



A patient was considered to have achieved a response at each visit if their baseline PGIS and corresponding PGIC met 1 of the following conditions: if the PGIS at baseline was "None" or "Mild," and PGIC at the visit was "No change," "A little better," or "Much better;" if the PGIS at baseline was "Moderate" or "Severe," and PGIC at the visit was "A little better" or "Much better." [a]Statistical significance of PGIC-Fatigue score vs baseline was not calculated as part of the study analysis. PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity

Figure 6. PGIC-Thalassemia Symptoms (A) and PGIC-Walking Capacity (B) at Week 24



[a]Data for the PGIC categories "A little worse," "Much worse," and "Missing" are not shown on this chart owing to low reporting rates
PGIC, Patient Global Impression of Change

CONCLUSIONS

- **In the 24-week double-blind period of ENERGIZE, significant improvements in fatigue, measured by FACIT-Fatigue, were demonstrated in the mitapivat arm compared with the placebo arm**
  - **A higher proportion of patients reported clinically meaningful improvements with mitapivat vs placebo**
- **Functional improvement in patients with mitapivat, measured by the 6MWT, exceeded a previously reported meaningful change threshold from the literature[24]**
- **A higher proportion of patients reported improved fatigue, disease symptoms, and walking capacity via PGIC with mitapivat vs placebo**

Mitapivat is the first oral, disease-modifying, investigational therapy to improve fatigue and walking capacity in patients with α- or β-NTDT

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References and supplemental materials are available via the QR code

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