Efficacy of mitapivat in patients with transfusion-dependent alpha-thalassemia: Subgroup analysis from the ENERGIZE-T trial

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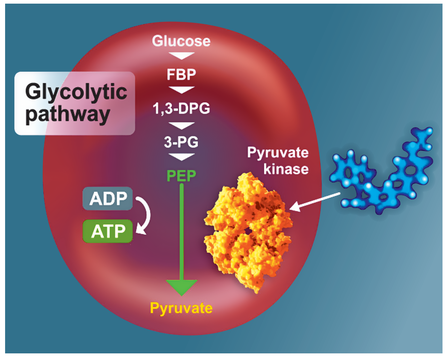
BACKGROUND

- In thalassemia, globin aggregates cause cellular oxidative stress, ineffective erythropoiesis, and hemolysis, resulting in chronic anemia and downstream complications[1–3]
- Thalassemic red blood cells (RBCs) have insufficient energy production to meet the high energy demands necessary to repair cellular damage and maintain RBC health[4]
- Mitapivat is a first-in-class oral allosteric activator of pyruvate kinase (PK), including the RBC-specific (PKR) and M2 isoforms (PKM2), that enhances glycolytic production of adenosine triphosphate to support the increased energetic needs of thalassemic RBCs (**Figure 1**)[5,6]

Figure 1. Mitapivat mechanism of action



ADP, adenosine diphosphate; ATP, adenosine triphosphate; DPG, diphosphoglyceric acid; FBP, fructose biphosphate; PEP, phosphoenolpyruvate; PG, phosphoglycerate.

- In the phase 3 ENERGIZE-T trial (NCT04770779)—which included patients with transfusion-dependent (TD) α- and β-thalassemia—the primary and all key secondary endpoints were met in the overall population: mitapivat led to significant reductions in transfusion burden, with durability of response up to 36 weeks during the 48-week double-blind period[7]
  - Three patients in the mitapivat group were transfusion-free through Week 48 of the double-blind period
  - Mitapivat was generally well tolerated with a low treatment discontinuation rate
- The disease burden of α-thalassemia is historically underrecognized, and patients experience serious complications and early mortality[8]
- There are no approved disease-modifying treatments for α-thalassemia

OBJECTIVE

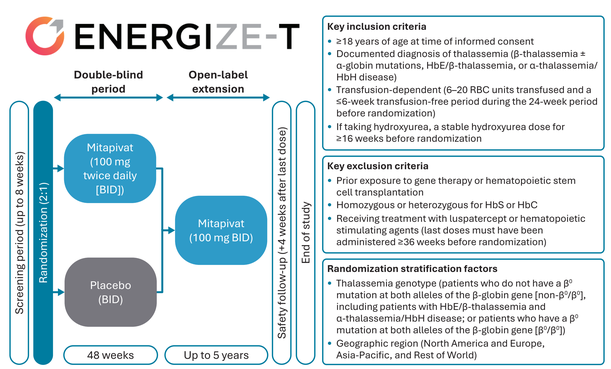
This post hoc exploratory subgroup analysis assessed the impact of mitapivat on transfusion burden in adults with TD α-thalassemia in ENERGIZE-T

METHODS

Study design[7,9]

- This was a post hoc analysis of patients with α-thalassemia in the ENERGIZE-T trial (**Figure 2**)

Figure 2. ENERGIZE-T study design



Key inclusion criteria
- ≥18 years of age at time of informed consent
- Documented diagnosis of thalassemia (β-thalassemia ± α-globin mutations, HbE/β-thalassemia, or α-thalassemia/HbH disease)
- Transfusion-dependent (6–20 RBC units transfused and a ≤6-week transfusion-free period during the 24-week period before randomization)
- If taking hydroxyurea, a stable hydroxyurea dose for ≥16 weeks before randomization

Key exclusion criteria
- Prior exposure to gene therapy or hematopoietic stem cell transplantation
- Homozygous or heterozygous for HbS or HbC
- Receiving treatment with luspatercept or hematopoietic stimulating agents (last doses must have been administered ≥36 weeks before randomization)

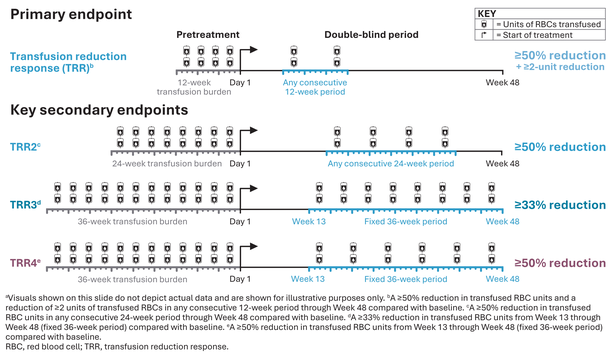
Randomization stratification factors
- Thalassemia genotype (patients who do not have a β^0 mutation at both alleles of the β-globin gene [non-β^0/β^0], including patients with HbE/β-thalassemia and α-thalassemia/HbH disease; or patients who have a β^0 mutation at both alleles of the β-globin gene [β^0/β^0])
- Geographic region (North America and Europe, Asia-Pacific, and Rest of World)

BID, twice daily; Hb, hemoglobin; RBC, red blood cell.

Endpoints assessed

- **Transfusion reduction response (TRR)**: a ≥50% reduction in transfused RBC units and a reduction of ≥2 units of transfused RBCs in any consecutive 12-week period through Week 48 compared with baseline (**Figure 3**)
- **TRR2**: a ≥50% reduction in transfused RBC units in any consecutive 24-week period through Week 48 compared with baseline
- **TRR3**: a ≥33% reduction in transfused RBC units from Week 13 through Week 48 (fixed 36-week period) compared with baseline
- **TRR4**: a ≥50% reduction in transfused RBC units from Week 13 through Week 48 (fixed 36-week period) compared with baseline
- **TI**: transfusion free for ≥8 consecutive weeks through Week 48 in the double-blind period

Figure 3. Endpoint depiction[a]



[a]Visuals shown on this slide do not depict actual data and are shown for illustrative purposes only. [b]A ≥50% reduction in transfused RBC units and a reduction of ≥2 units of transfused RBCs in any consecutive 12-week period through Week 48 compared with baseline. [c]A ≥50% reduction in transfused RBC units in any consecutive 24-week period through Week 48 compared with baseline. [d]A ≥33% reduction in transfused RBC units from Week 13 through Week 48 (fixed 36-week period) compared with baseline. [e]A ≥50% reduction in transfused RBC units from Week 13 through Week 48 (fixed 36-week period) compared with baseline.
RBC, red blood cell; TRR, transfusion reduction response.

Statistics

- Outcomes are presented with descriptive summary statistics

Transfusion modification guidelines

- A pre-transfusion hemoglobin (Hb) threshold was determined for each patient based on their transfusion history and was defined as the mean of all documented pre-transfusion Hb concentrations for RBC transfusions administered during the 24 weeks prior to randomization
- During the study, investigators monitored changes in Hb concentration and modified each patient's transfusion schedule accordingly (**Table 1**)
- Patients could receive transfusions at the discretion of the investigator for acute symptoms related to anemia or other comorbidities requiring immediate treatment (eg, infection or cardiopulmonary compromise)

Table 1. Per-protocol transfusion modification guidance

Pre-transfusion Hb concentration[a]	RBC transfusion modification
Hb concentration ≥1 g/dL above the pre-transfusion Hb threshold and ≤ULN (by sex)	Delay RBC transfusion or decrease the number of RBC units to be transfused
>ULN (by sex)	Delay RBC transfusion • Recheck Hb concentration within 28 days • If Hb concentration remains >ULN (by sex) for ≥4 weeks in the absence of RBC transfusions, modify the dose

[a]The pre-transfusion Hb concentration is the Hb concentration obtained before a planned transfusion event to guide its transfusion prescription, irrespective of whether a transfusion is subsequently delivered or deferred.
Hb, hemoglobin; RBC, red blood cell; ULN, upper limit of normal.

Patients

- In ENERGIZE-T, a total of 258 adult patients were randomized (mitapivat, N=171; placebo, N=87)
- Twelve patients had a confirmed diagnosis of TD α-thalassemia (mitapivat, N=9; placebo, N=3; **Table 2**)

Table 2. Demographics and baseline characteristics of adult patients diagnosed with α-thalassemia[a]

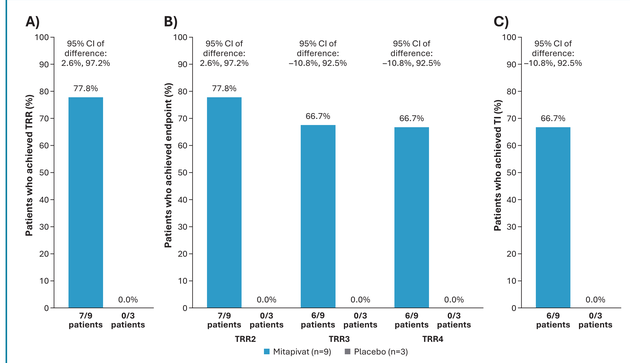
Demographics and disease characteristics	Mitapivat (N=9)	Placebo (N=3)
Age, median (range), years	44.0 (25–62)	36.0 (26–49)
Female, n (%)	5 (55.6)	2 (66.7)
Race, n (%)		
White	3 (33.3)	0 (0.0)
Asian	5 (55.6)	2 (66.7)
Unknown	1 (11.1)	1 (33.3)
Geographic region, n (%)		
North America and Europe	6 (66.7)	2 (66.7)
Asia-Pacific	3 (33.3)	1 (33.3)
24-week transfusion burden,[b] n (%)		
≤12 RBC units	8 (88.9)	1 (33.3)
>12 RBC units	1 (11.1)	2 (66.7)
Pre-transfusion Hb threshold,[c] median (range), g/L	81.00 (58.7–91.9)	78.00 (72.2–82.0)
Prior splenectomy,[d] n (%)	3 (33.3)	0 (0.0)
Received iron chelation in prior year,[e] n (%)	9 (100.0)	3 (100.0)

[a]Documented diagnosis of thalassemia (β-thalassemia with or without α-globin gene mutations, HbE/β-thalassemia, or α-thalassemia/HbH disease) based on DNA analysis from the patient's medical record. If this information is not available from the patient's medical record, DNA analysis can be performed by a local laboratory during the screening period. If a local laboratory is unable to perform the test, results from the comprehensive α- and β-globin genotyping performed by the study central laboratory can be used. [b]Total number of RBC units transfused in the 24-week period before randomization. [c]Pre-transfusion Hb threshold was defined as the mean of all documented pre-transfusion Hb concentration values recorded for the RBC transfusions administered during the 24-week period before randomization. [d]As recorded in the medical/surgical history eCRF. [e]As recorded in the disease characteristics eCRF: "Yes" if a patient received chelation therapy within 1 year (365 days) before randomization.
eCRF, electronic case report form; Hb, hemoglobin; RBC, red blood cell.

RESULTS

- 77.8% of patients with α-thalassemia in the mitapivat group met the primary endpoint vs none in the placebo group (**Figure 4A**)
- 77.8%, 66.7%, and 66.7% of patients with α-thalassemia in the mitapivat group met the key secondary endpoints of transfusion reduction response TRR2, TRR3, and TRR4, respectively, vs none in the placebo group (**Figure 4B**)
- 66.7% of patients with α-thalassemia in the mitapivat group achieved transfusion independence (TI) vs none in the placebo group (**Figure 4C**)

Figure 4. Proportion of patients with α-thalassemia who achieved A) TRR, B) key secondary endpoints, and C) TI



Analysis conducted on patients with α-thalassemia in the full analysis set. The 24-week baseline transfusion burden was the total number of RBC units transfused during the 24-week period (168 days) before the start of study treatment for patients randomized and dosed. Baseline for TRR was standardized to 12 weeks based on the 24-week baseline. Baseline for TRR3 and TRR4 was standardized to 36 weeks based on the 24-week baseline. Patients who withdrew from the study before Week 24/Week 48 were considered nonresponders for TRR2, TRR3, and TRR4.
CI, confidence interval; RBC, red blood cell; TI, transfusion independence; TRR, transfusion reduction response.

CONCLUSIONS

- **Mitapivat reduced the transfusion burden of patients with TD α-thalassemia compared with placebo**
  - **Large proportions of patients treated with mitapivat achieved the primary and key secondary endpoints (TRR, TRR2, TRR3, and TRR4) and the additional secondary endpoint of protocol-defined TI compared with no patients treated with placebo**
- **These data are consistent with results from the overall ENERGIZE-T population and support the beneficial effects of mitapivat in transfusion reduction in patients with α-thalassemia**

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