# Long-term transfusion-free duration and impact on transfusion-related burdens: Results from the ongoing ENERGIZE-T open-label extension study of mitapivat in transfusion-dependent alpha- or beta-thalassemia

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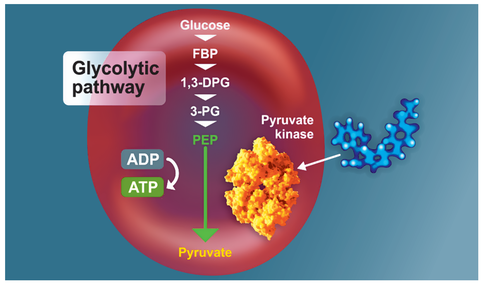
## BACKGROUND

- People with transfusion-dependent thalassemia require regular, lifelong red blood cell (RBC) transfusions for survival[1]
- Transfusions improve survival and outcomes but come with many disadvantages, including the risk of potentially life-threatening reactions, iron overload requiring treatment with potentially toxic drugs, and major burdens on quality of life[1–3]
- There remains an unmet need for novel therapies that can address the underlying pathophysiologic drivers of ineffective erythropoiesis and hemolysis to potentially reduce transfusion burden and associated negative outcomes
- In thalassemia, there is increased energy demand to maintain RBC health[4–7]
- Mitapivat is an activator of the RBC-specific form of pyruvate kinase (PKR) and pyruvate kinase (PKM2), which act in glycolysis to generate adenosine triphosphate (ATP; **Figure 1**)[8,9]

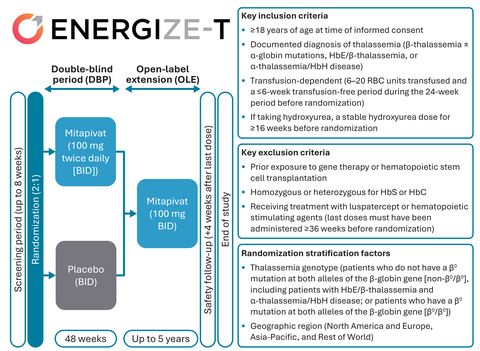
### Figure 1. Mitapivat mechanism of action




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

- ENERGIZE-T is a global, phase 3, double-blind, randomized, placebo-controlled study of mitapivat in transfusion-dependent α- or β-thalassemia (NCT04770779; **Figure 2**)[10]

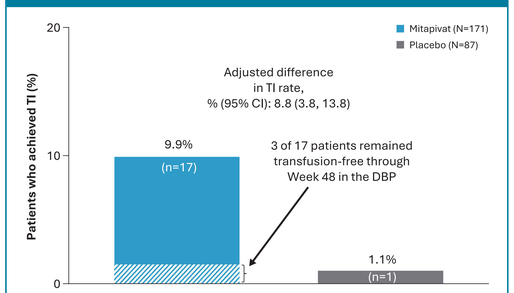
### Figure 2. ENERGIZE-T study design[10,11]




BID, twice daily; DBP, double-blind period; Hb, hemoglobin; OLE, open-label extension; RBC, red blood cell.

- In the double-blind period (DBP), the primary and key secondary endpoints were met; these endpoints assessed the impact of mitapivat on transfusion reduction response at different intervals[1]
- Transfusion independence (TI) was a secondary endpoint in ENERGIZE-T and was defined in the protocol as a transfusion-free interval of ≥8 consecutive weeks through Week 48 of the DBP[10]
  - 17 (9.9%) patients in the mitapivat group achieved protocol-defined TI vs 1 (1.1%) in the placebo group (adjusted difference [95% confidence interval], 9% [4%, 14%]; **Figure 3**)[10]
  - 3 of the 17 patients were transfusion-free through Week 48 in the DBP

### Figure 3. A higher proportion of patients in the mitapivat group achieved protocol-defined TI during the DBP vs the placebo group




CI, confidence interval; DBP, double-blind period; TI, transfusion independence.

## OBJECTIVE

This post hoc exploratory analysis assessed the duration of transfusion-free periods in the long term and the potential real-world impact on transfusion burdens for patients in the mitapivat arm who achieved protocol-defined TI during the 48-week DBP of ENERGIZE-T

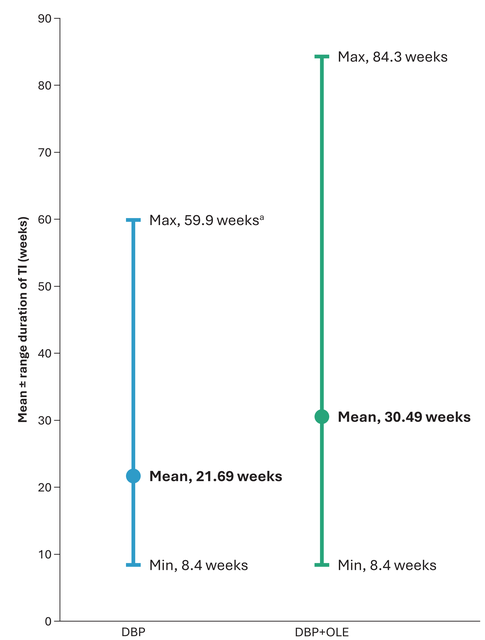
## METHODS

- The longest transfusion-free period was evaluated for each of the 17 patients in the mitapivat arm who achieved protocol-defined TI in the DBP using longer term cumulative data from the DBP and open-label extension (OLE) as of a data cutoff 90 days after the last patient's first dose in the OLE; this evaluation period is referred to throughout as the **DBP+OLE**
- Transfusion-free duration was calculated as the number of weeks in the longest transfusion-free period starting on or after the first dose of mitapivat through the end of the DBP+OLE evaluation period
- A transfusion visit was defined as the day when a transfusion was given; transfusions (≥1 packed RBC [PRBC] unit) given on consecutive days were counted separately as visits for each day
- The total number of transfusion visits and PRBC units received in the evaluation period for each patient were annualized and compared with their respective annualized baseline values
- The impact on transfusion-related burdens in terms of annualized reductions in the number of hours and transfusional iron intake per year were calculated with the following assumptions:
  - 7 hours per transfusion visit[12]
  - An intake of 200 mg of iron per transfused PRBC unit[1,13]

## RESULTS

- The 17 patients who achieved protocol-defined TI in the DBP had a median (minimum, maximum) mitapivat exposure of 72.0 (47.3, 99.3) weeks in the DBP+OLE
- The mean (standard deviation [SD]) duration of the longest transfusion-free period in the 17 patients was 21.69 (16.892) weeks in the 48-week DBP (**Figure 4**)
  - The maximum transfusion-free period in the DBP was 59.9 weeks[a]
- The mean (SD) duration of the longest transfusion-free period increased to 30.49 (27.087) weeks during the DBP+OLE (**Figure 4**)
  - The maximum transfusion-free period increased to 84.3 weeks through the DBP+OLE
  - The 3 patients who did not receive any transfusions during the 48-week DBP remained transfusion-free through the DBP+OLE

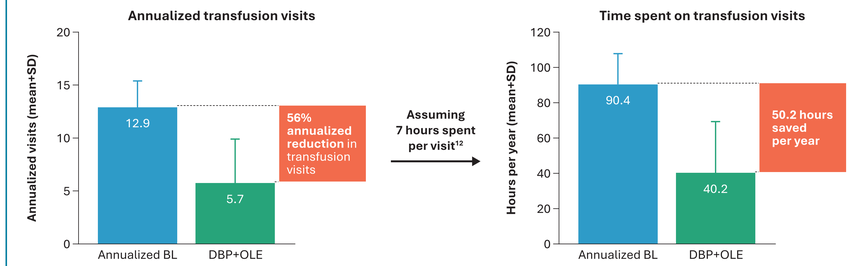
### Figure 4. Mean duration of longest transfusion-free period for mitapivat-treated patients who achieved protocol-defined TI




[a]Patient did not receive any RBC transfusions and had several visits beyond the DBP. Duration of TI is the number of weeks in the longest transfusion-free period starting on or after study treatment through the end of the evaluation period.
DBP, double-blind period; DBP+OLE, double-blind period and open-label extension evaluation period as of a data cutoff 90 days after the last patient's first dose in the open-label extension; max, maximum; min, minimum; RBC, red blood cell; TI, transfusion independence.

- For the 17 patients who achieved protocol-defined TI in the DBP, a mean (SD) of 7.17 (4.163) fewer annualized transfusion visits was observed in the DBP+OLE compared to an annualized baseline, representing a **56.0% (29.00%) reduction in transfusion visits** and approximately **50.2 (29.14) hours saved in visits per year** (assuming 7 hours spent per visit[12]; **Figure 5**)

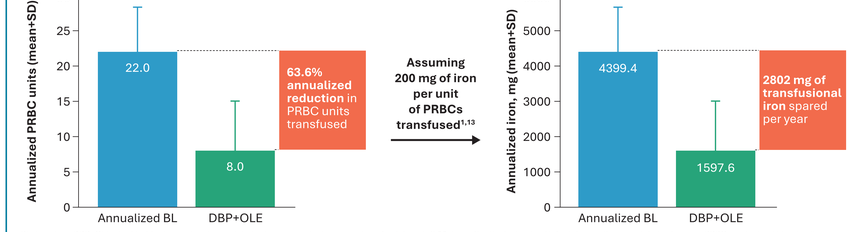
### Figure 5. Transfusion-related burden of transfusion visits in the DBP+OLE




BL, baseline; DBP+OLE, double-blind period and open-label extension evaluation period as of a data cutoff 90 days after the last patient's first dose in the open-label extension; SD, standard deviation.

- For the 17 patients who achieved protocol-defined TI in the DBP, a mean (SD) of 14.01 (7.543) fewer PRBC units transfused per year was observed in the DBP+OLE compared to an annualized baseline, representing a 63.6% (27.45%) reduction in transfused PRBC units and approximately **2802 mg (1508.5 mg) less transfusional iron loading per year** (assuming 200 mg of iron per unit of PRBCs transfused[1,13]; **Figure 6**)

### Figure 6. Transfusion-related burden of transfusional iron intake in the DBP+OLE




BL, baseline; DBP+OLE, double-blind period and open-label extension evaluation period as of a data cutoff 90 days after the last patient's first dose in the open-label extension; PRBC, packed red blood cell; SD, standard deviation.

## CONCLUSIONS

- **The mean duration of transfusion-free period increased in the DBP+OLE compared to the DBP for the 17 patients who achieved protocol-defined TI in the DBP of ENERGIZE-T**
- **This long-term duration of prolonged transfusion-free periods of up to 84.3 weeks shows the potential of mitapivat to improve clinical and humanistic transfusion-related burdens, as suggested by improvements in the annualized number of transfusion visits, time saved on visits, and transfusional iron intake**
- **These results further support the potential use of mitapivat as an effective oral disease-modifying therapy for adults with transfusion-dependent α- or β-thalassemia**

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