Long-term hemoglobin improvements in non–transfusion-dependent α- or β-thalassemia: Results from the open-label extension of the ongoing phase 3 ENERGIZE trial

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Disclosures

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Management of anemia is critical for reducing risk of morbidity and mortality in patients with NTDT

- Hemolytic anemia in patients with NTDT is associated with increased risk of morbidity and mortality, including iron overload and organ damage[1,2]
- Optimal management of anemia throughout the disease course of NTDT is essential to reduce the risk of morbidity and mortality; therefore, long-term interventions to raise Hb level by ≥1 g/dL are recommended[2–4]

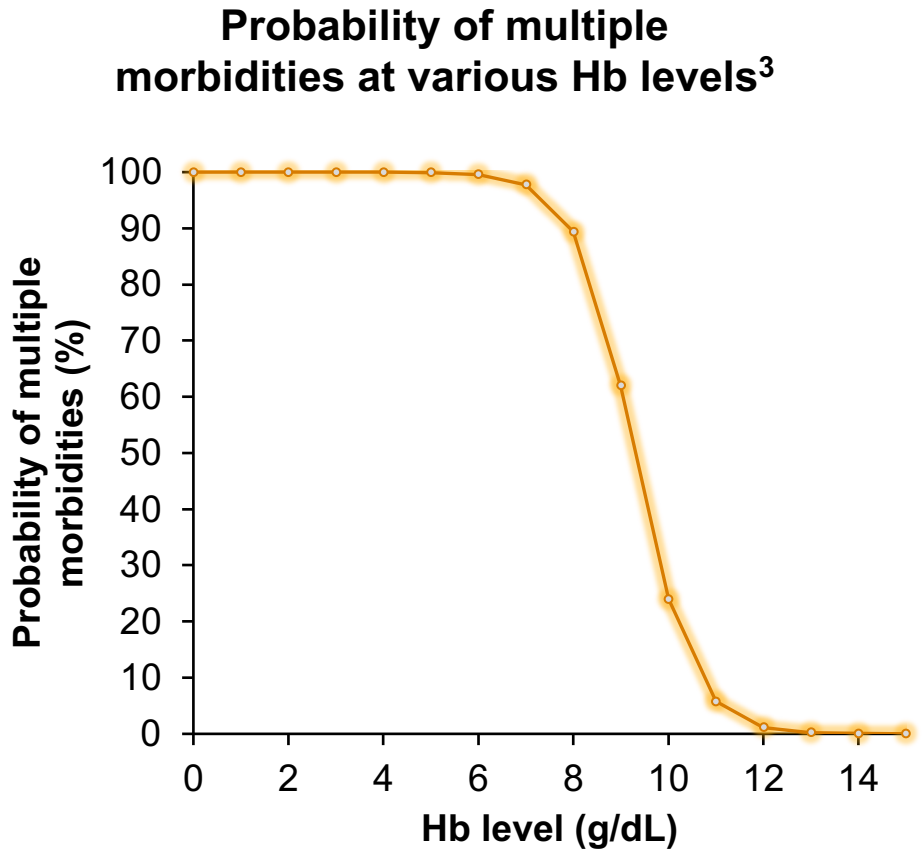
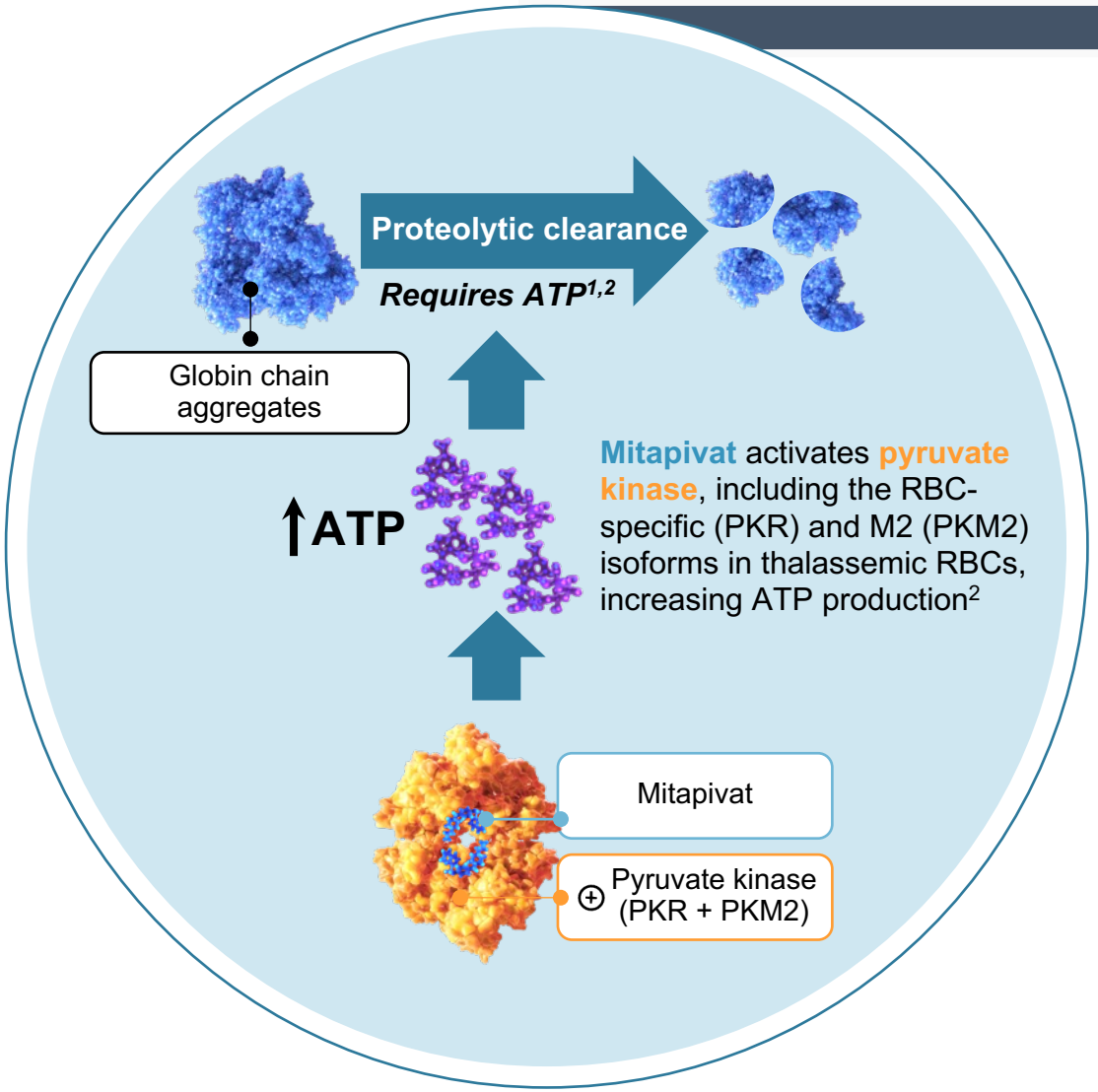


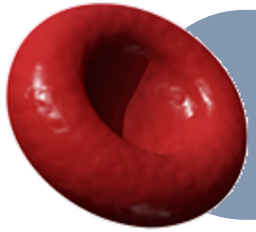
Figure adapted from Musallam KM et al. *Ann Hematol* 2021;100:1903–5.

Hb, hemoglobin; NTDT, non–transfusion-dependent thalassemia.

Figure adapted from Musallam KM, et al. *Ann Hematol*. 2021;100:1903–5. **1**. Kattamis A et al. *Lancet* 2022;399:2310–24. **2**. Taher AT et al. eds. *Guidelines for the Management of Non–Transfusion-Dependent β-Thalassaemia*. 3rd ed. Thalassaemia International Federation; 2023. **3**. Musallam KM et al. *Ann Hematol* 2021;100:1903–5. **4**. Musallam KM et al. *Br J Haematol* 2025;207:1578-88.

Mitapivat is an oral activator of PKR and PKM2 that targets the underlying pathophysiology of thalassemia by increasing cellular energy





Reduced oxidative stress and improved RBC membrane integrity[2,3]

Improved erythropoiesis, hemolysis, and anemia[2–5]

ATP, adenosine triphosphate; PKM2, M2 isoform of PK; PKR, red blood cell isoform of PK; RBC, red blood cell.

1. Shaeffer JR. *J Biol Chem* 1983;258(21):13172–7. **2.** Matte A et al. *J Clin Invest* 2021;131:e144206. **3.** Siciliano A et al. *Blood Adv* 2025;9(11):2818–30. **4.** Kuo KMH et al. *Lancet* 2022;400:493–501. **5.** Taher AT et al. *Lancet* 2025;406(10498):33–42.

Treatment with mitapivat demonstrates consistent and durable clinical benefits across hemolytic anemias

- The overall clinical development program for mitapivat encompasses:
  - >10 years of experience with consistent benefits across hemolytic anemias[1–8]
  - A well-defined safety profile with over 1300 patient-years of exposure in clinical trials
- Mitapivat is approved for 2 indications in adults:
  - PK deficiency in the US, EU, and UK[1,2]
  - Thalassemia in the US, EU, Saudi Arabia, and UAE[3–6]

PK, pyruvate kinase.

1. PYRUKYND (mitapivat) tablets, for oral use. Prescribing Information. Agios Pharmaceuticals; 2022; Accessed May 18, 2026. **2.** Pyrukynd. Summary of Product Characteristics. Agios Netherlands B.V.; 2022. **3.** AQVESME (mitapivat) tablets, for oral use. Prescribing information. Agios Pharmaceuticals, Inc.; 2025. **4.** PYRUKYND® (mitapivat) approved for adults with thalassemia in Saudi Arabia. 2025. Accessed March 18, 2026. **5.** PYRUKYND® (mitapivat) approved for adults with thalassemia in the United Arab Emirates. 2026. Accessed March 18, 2026. **6.** PYRUKYND® (mitapivat) approved in the European Union for adults with thalassemia. 2026. Accessed May 22, 2026. **7.** van Beers EJ et al. *Blood Adv* 2024;8(10):2433-41. **8.** Doeven T et al. *Blood* 2024;144 (Suppl. 1):3831.

The ENERGIZE trial demonstrated the efficacy and safety of oral mitapivat for the treatment of anemia in NTDT

ENERGIZE

- In the DBP of the phase 3 ENERGIZE trial investigating the efficacy and safety of oral mitapivat in adults with non–transfusion-dependent α- or β-thalassemia (NCT04770753; EudraCT: 2021-000211-23):[1]

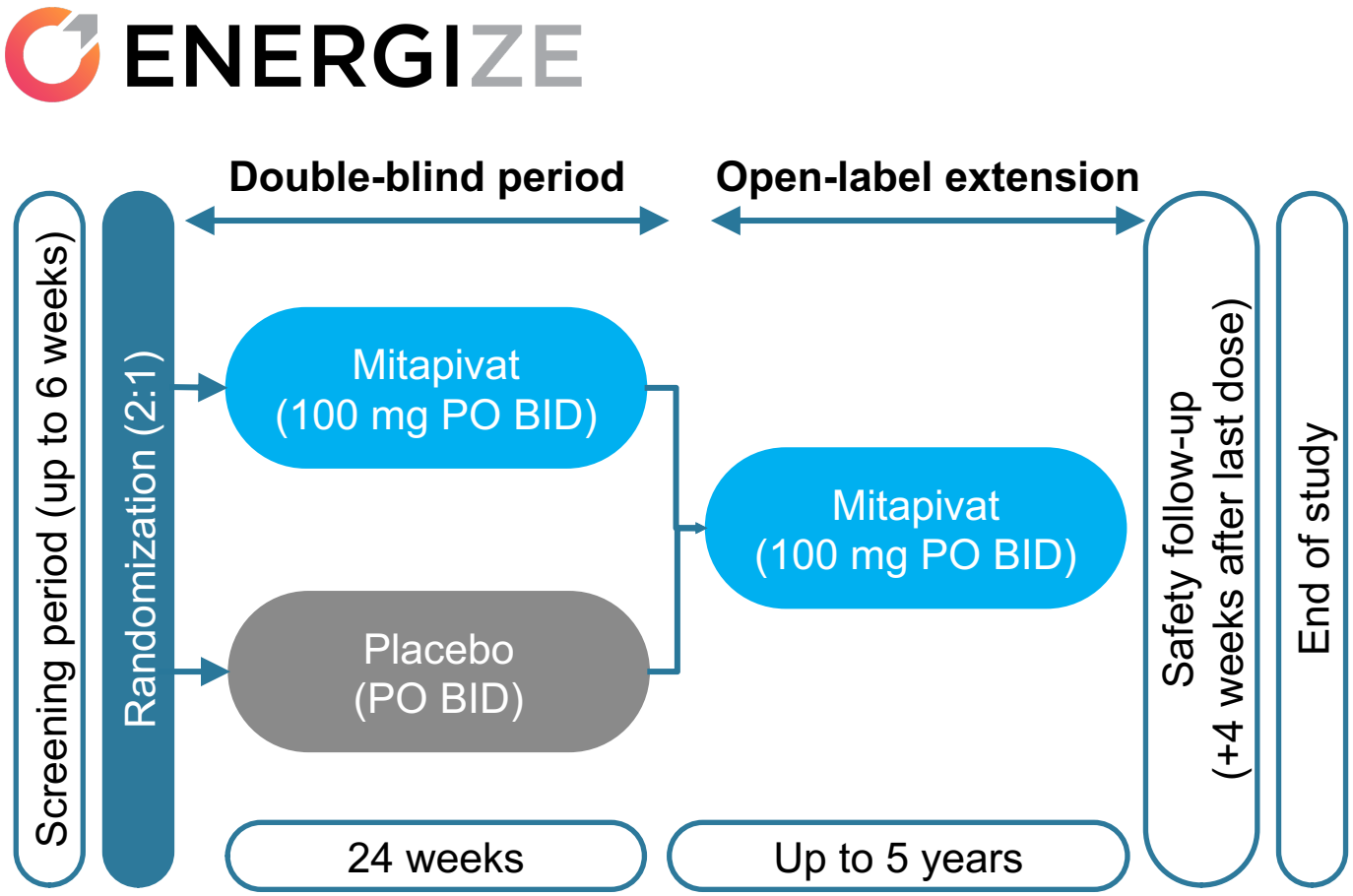
  - 42.3% of patients in the mitapivat arm achieved the primary endpoint of Hb response vs 1.6% in the placebo arm ($p<0.0001$)[a]
  - Statistically significant improvements in fatigue were demonstrated in the mitapivat arm vs the placebo arm[b]
  - Patients treated with mitapivat had improvements in markers of hemolysis (indirect bilirubin and LDH)
  - Mitapivat was generally well tolerated with a low treatment discontinuation rate

DBP, double-blind period; FACIT, Functional Assessment of Chronic Illness Therapy; Hb, hemoglobin; LDH, lactate dehydrogenase; NTDT, non–transfusion-dependent thalassemia.

[a]Hb response: ≥1.0 g/dL increase in average Hb concentration from Week 12 through Week 24 compared with baseline. [b]The least squares mean change from baseline in FACIT-Fatigue score over Weeks 12-24 was significantly greater for patients treated in the mitapivat arm vs placebo arm (between group difference, 3.4; p=0.0026).

1. Taher AT et al. *Lancet* 2025;406(10498):33–42.

ENERGIZE study design



Key inclusion criteria

- ≥18 years of age at time of informed consent
- Diagnosis of β-thalassemia ± α-globin mutations, HbE/β-thalassemia, or α-thalassemia (HbH disease)
- Non–transfusion-dependent (≤5 RBC units transfused during the 24-week period before randomization and no RBC transfusions ≤8 weeks before informed consent and during screening)
- Hb ≤10.0 g/dL

Key exclusion criteria

- Prior exposure to gene therapy or hematopoietic or stem cell transplantation
- Homozygous or heterozygous sickle Hb or HbC
- Receiving treatment with luspatercept or hematopoietic stimulating agents (last dose must have been ≥18 weeks before randomization)

Randomization stratification factors

- Baseline Hb (≤9.0 g/dL or 9.1-10.0 g/dL)
- Thalassemia genotype (α-thalassemia/HbH or β-thalassemia)

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

Post hoc long-term Hb analysis

Aim:

Assess longer-term Hb outcomes with mitapivat via a post hoc analysis of interim data from the ongoing OLE of the international, randomized, placebo-controlled, phase 3 ENERGIZE trial[1,2]

OLE, open-label extension.

1. Taher AT et al. *Lancet* 2025;406(10498):33-4. **2**. ClinicalTrials.gov. Accessed March 24, 2026. https://clinicaltrials.gov/study/NCT04770753

Datasets and Endpoints

Analyses were based on data from the DBP and OLE of the ENERGIZE trial as of the July 10, 2024, data cutoff

- This data cutoff represents 241 days (34.4 weeks) after the last patient's first dose in the OLE

Change in Hb and markers of hemolysis over time

- Mean change from baseline in Hb over Weeks 4-96 and in indirect bilirubin and LDH over Weeks 4-84[a]

Duration of Hb response

- Among primary endpoint responders, number of weeks from earliest data with Hb change from baseline of ≥1.0 g/dL through first date on which Hb change from baseline was <1.0 g/dL after the last Hb assessment in the DBP with a change from baseline of ≥1.0 g/dL
- Patients without loss of response were censored (+) at the end of the DBP or at the last assessment in the OLE, whichever occurred later

OLE Hb improvement of ≥1.0 g/dL

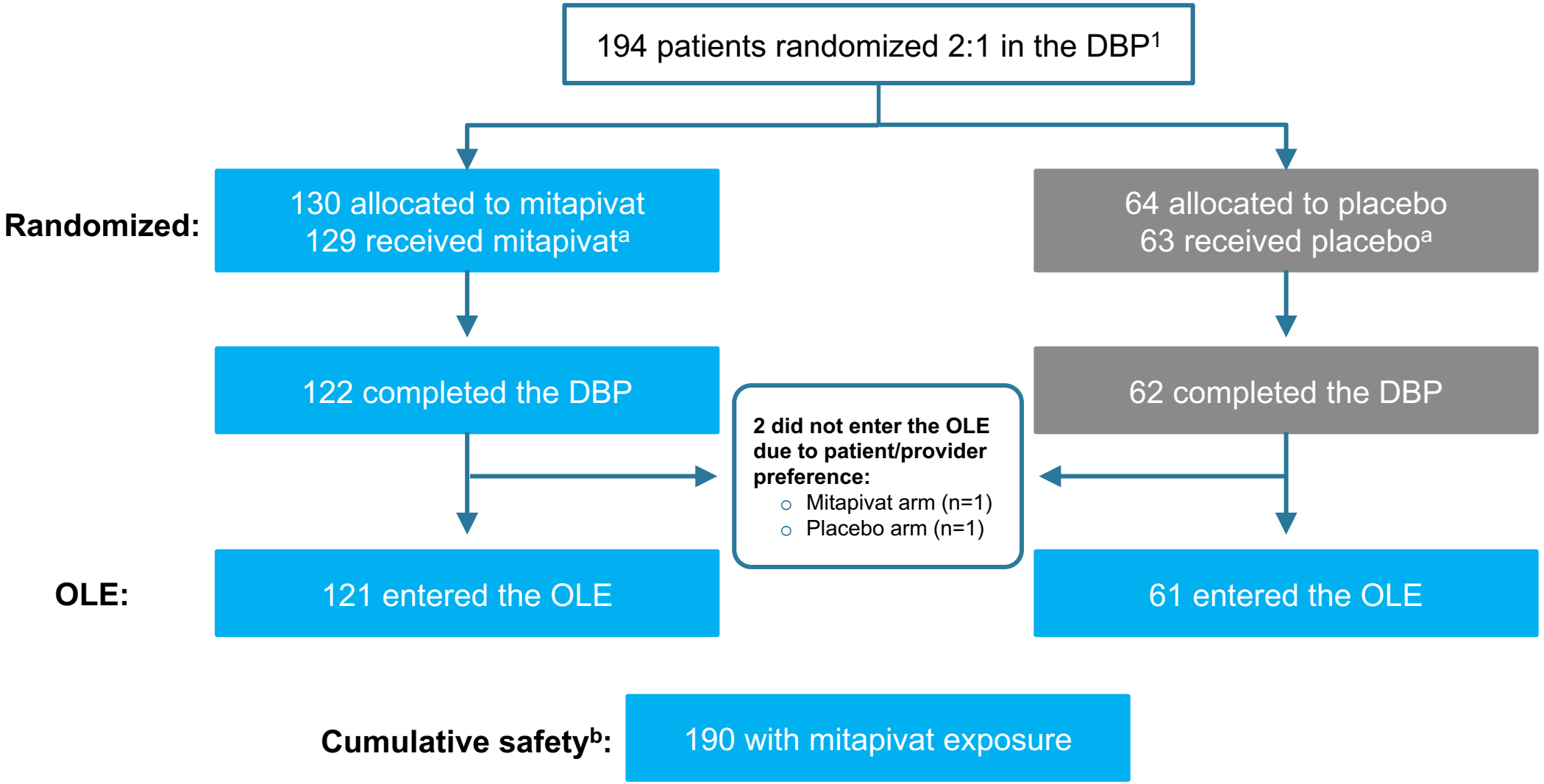
- Increase of ≥1.0 g/dL from baseline in average Hb over any 2 consecutive study visits in the OLE

Cumulative safety

- AEs and SAEs, including type, severity, and relationship to study drug

AE, adverse event; DBP, double-blind period; Hb, hemoglobin; LDH, lactate dehydrogenase; OLE, open-label expansion; SAE, serious adverse event.
[a]Hb, indirect bilirubin, and LDH were assessed every 4 weeks through Week 36 and every 12 weeks thereafter.

Patient disposition: 184 patients completed the DBP, of whom 182 enrolled in the OLE



DBP, double-blind period; OLE, open-label extension.
[a]One patient in each treatment arm was randomized but not dosed. [b]Cumulative safety assessed in all patients who received ≥1 dose of mitapivat in either the DBP or OLE. If a patient randomized to placebo received ≥1 dose of mitapivat in the DBP, then the patient was classified to the mitapivat arm.
1. Taher AT et al. *Lancet* 2025;406(10498):33-42.

Mitapivat exposure

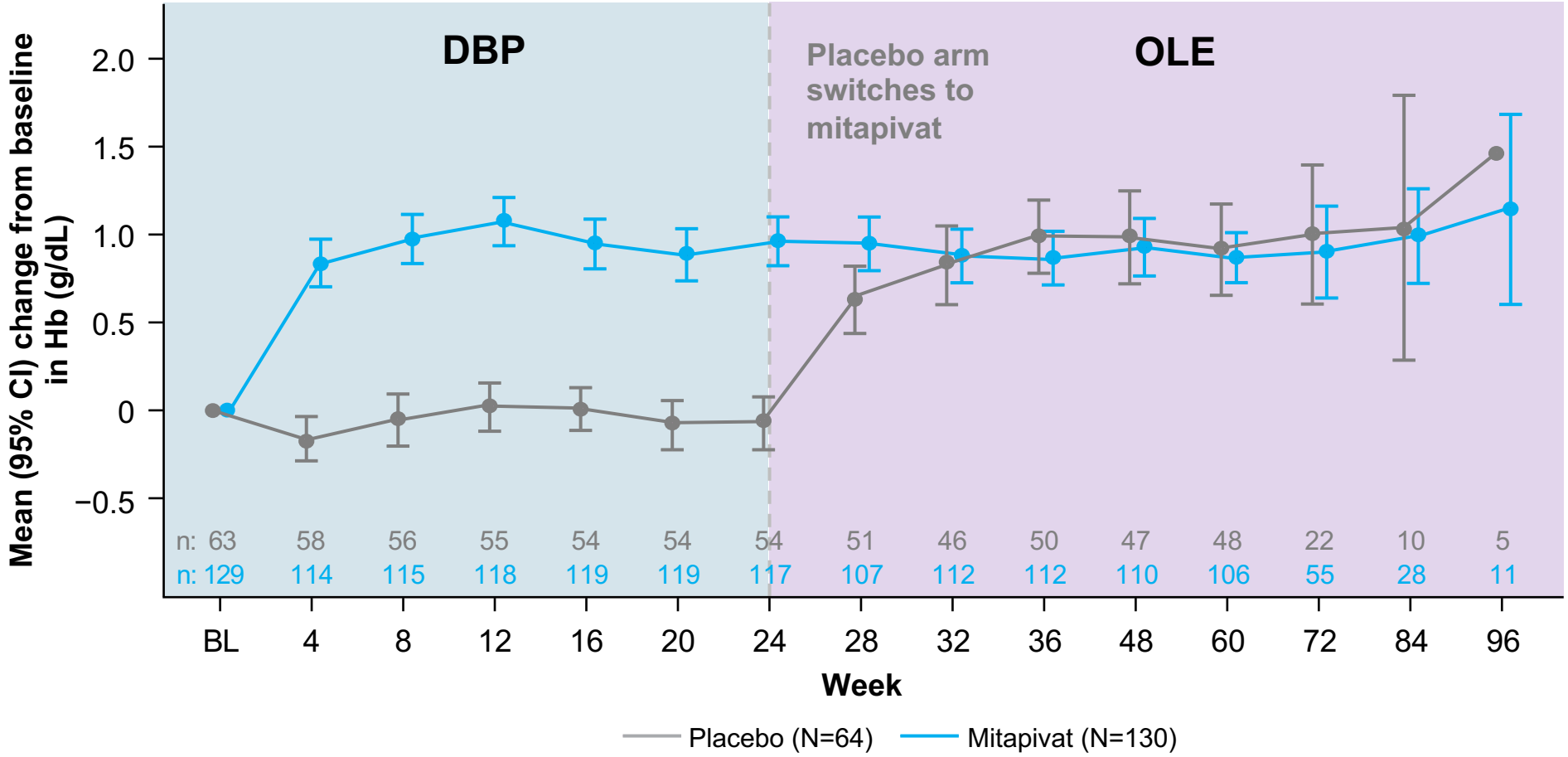
- Patients were exposed to mitapivat for a median duration of 64.4 weeks across the DBP and OLE

Mitapivat exposure	DBP+OLE
	Mitapivat (n=190)
Duration of exposure (weeks), median (min, max)	64.4 (1.1, 127.3)
Exposure (person-years)[a]	229.9

DBP, double-blind period; max, maximum; min, minimum; OLE, open-label extension.
[a]Exposure in person-years is the sum of duration of exposure for each patient in days within each treatment group divided by 365.25.

The mean Hb increase achieved with mitapivat in the DBP was sustained during the OLE

- Among patients who switched from placebo to mitapivat in the OLE, increases in Hb during the OLE were similar to those observed in patients who received mitapivat during the DBP



BL, baseline; CI, confidence interval; DBP, double-blind period; Hb, hemoglobin; OLE, open-label extension.
Data shown for all patients who received ≥1 dose of study treatment.

The duration of Hb response increased with continued exposure to mitapivat

- The mean duration of Hb response increased from 17.9 in the DBP to 43.6 weeks in the DBP+OLE among the 55 mitapivat-treated patients who achieved a Hb response in the DBP
  - At data cutoff, the maximum duration of Hb response was 93.3 weeks and ongoing

Duration of response (weeks)	DBP (n=55)	DBP+OLE (n=55)
Mean (SD)	17.9 (3.6)	43.6 (24.2)
Median (IQR)	19.6 (16.1-20.3)	32.9 (20.1-60.4)
Range (min, max)	4.0(+), 23.4(+)	15.4, 93.3(+)

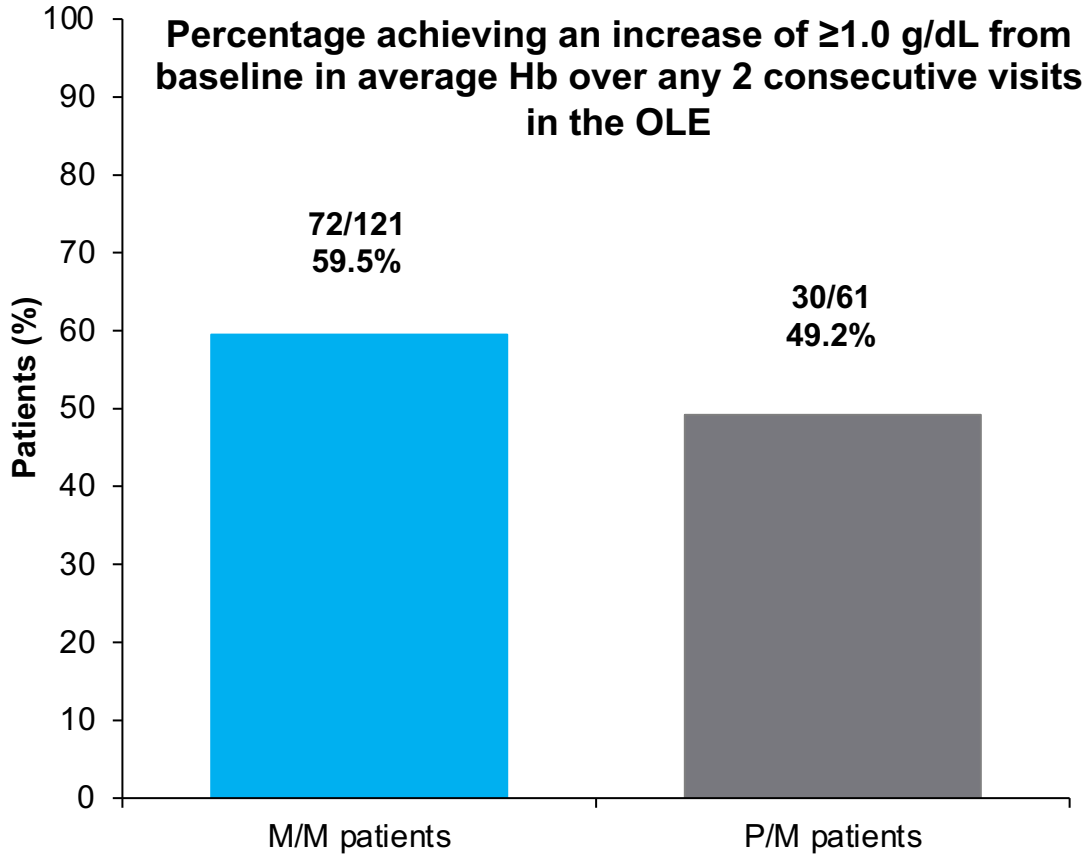
(+) indicates patients without loss of Hb response who were censored at the end of the 24-week DBP or the date of the last Hb assessment in the OLE with change from baseline ≥1.0 g/dL, whichever occurred later.

DBP, double-blind period; IQR, interquartile range; max, maximum; min, minimum; OLE, open-label extension; SD, standard deviation.
Patients who do not have at least 2 on-treatment Hb concentration assessments from Weeks 12 to 24 are considered non-responders. Hb concentrations assessed within 8 weeks after an RBC transfusion are excluded from the baseline derivation and from the analysis. For patients who achieved Hb response in the DBP, duration of Hb response is calculated as the number of weeks from start of Hb response (earliest data after treatment initiation with Hb change from baseline of ≥1 g/dL) through loss of Hb response (first date with Hb change from baseline of <1 g/dL after the last Hb assessment in the DBP with change from baseline of ≥1 g/dL).

Nearly 60% of M/M patients had an increase of ≥1.0 g/dL from baseline in average Hb over any 2 consecutive OLE study visits

- 23/68 patients (~1/3) who did not achieve a DBP Hb response with mitapivat met this threshold of Hb improvement in the OLE
- Nearly half of P/M patients had an increase of ≥1.0 g/dL from baseline in average Hb over any 2 consecutive OLE study visits

Among patients who achieved this threshold of Hb improvement, the **mean change from baseline in Hb across the OLE was 1.3 g/dL** for both the M/M and the P/M groups at data cutoff

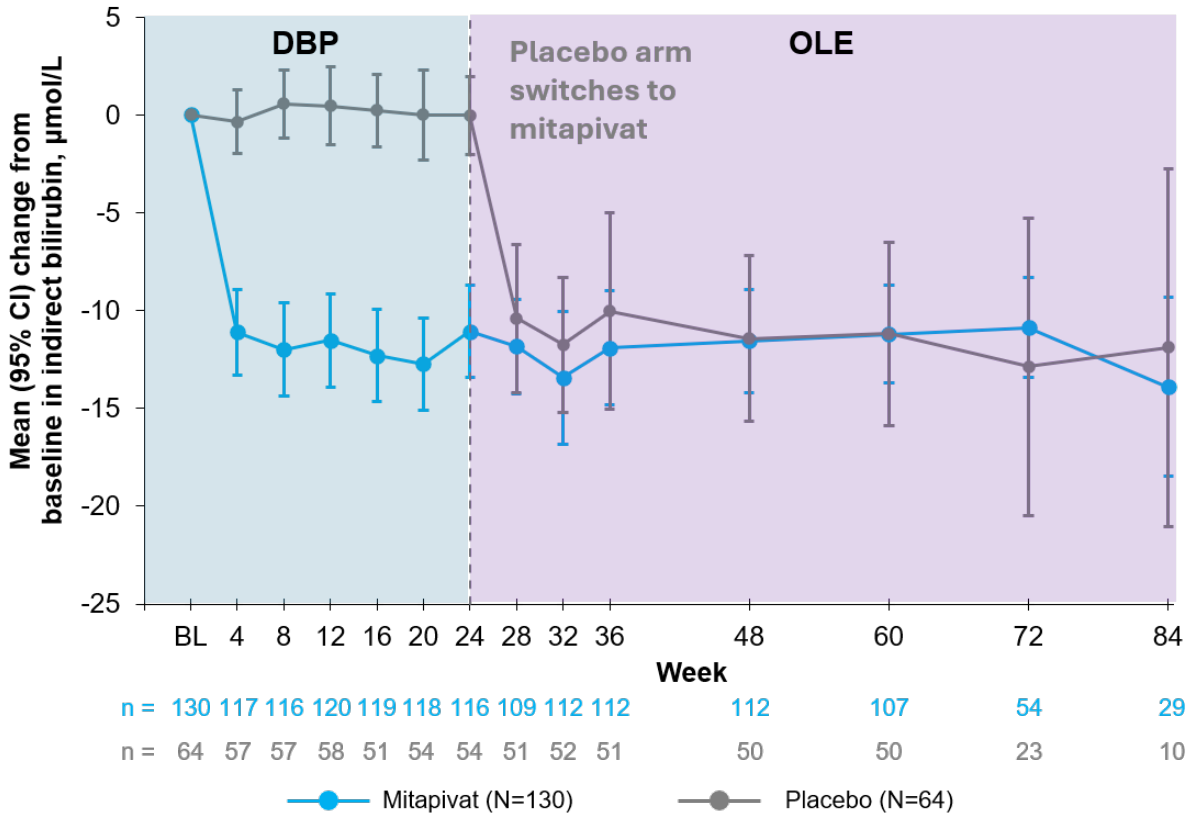


M/M: Patients who received mitapivat in the DBP and OLE
P/M: Patients who received placebo in the DBP and mitapivat in the OLE

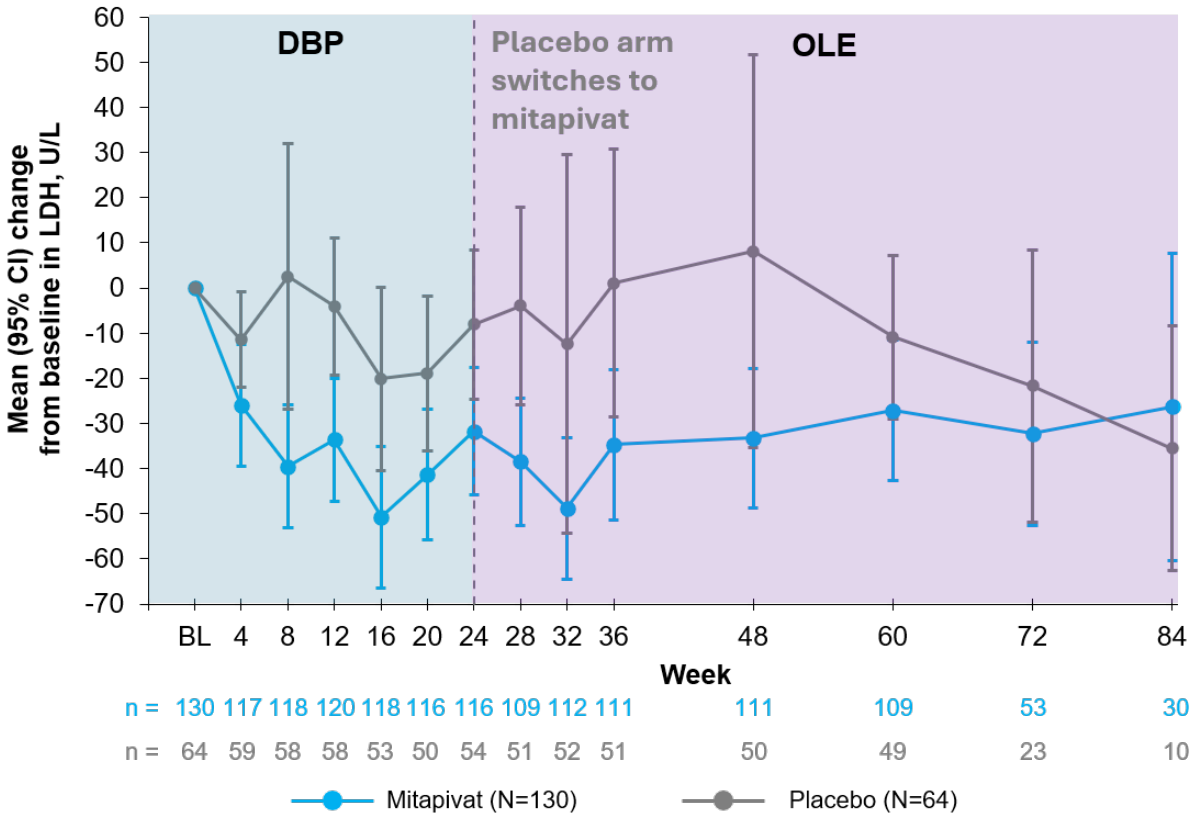
DBP, double-blind period; Hb, hemoglobin; OLE, open-label extension.
OLE Hb response: increase of ≥1.0 g/dL from baseline in average Hb during any 2 consecutive OLE study visits.

Improvements in markers of hemolysis were sustained over time with continued mitapivat treatment in the OLE

Indirect bilirubin



LDH



BL, baseline; CI, confidence interval; Hb, hemoglobin; DBP, double-blind period; LDH, lactate dehydrogenase; Hb, hemoglobin; OLE, open-label extension.

The safety profile of mitapivat remains consistent in the ENERGIZE trial

- Mitapivat was generally well tolerated and had a safety profile in the OLE that was consistent with that observed during the DBP
  - No new cases of hepatocellular injury have been reported beyond those previously disclosed

Patients, n (%)	DBP		DBP+OLE
	Mitapivat (N=129)	Placebo (N=63)	Mitapivat (N=190)
Any TEAEs	107 (82.9)	50 (79.4)	169 (88.9)
Grade ≥3 TEAEs	18 (14.0)	2 (3.2)	32 (16.8)
Treatment-related TEAEs	56 (43.4)	13 (20.6)	77 (40.5)
Grade ≥3 treatment-related TEAEs	5 (3.9)	0 (0.0)	10 (5.3)
Serious TEAEs	8 (6.2)	0 (0.0)	22 (11.6)
Serious treatment-related TEAEs	0 (0.0)	0 (0.0)	2 (1.1)
TEAEs leading to discontinuation of study drug	4 (3.1)	0 (0.0)	9 (4.7)
TEAEs leading to dose reduction	7 (5.4)	2 (3.2)	14 (7.4)
TEAEs leading to interruption of study drug	2 (1.6)	1 (1.6)	8 (4.2)
TEAEs leading to death	0 (0.0)	0 (0.0)	1 (0.5)

DBP, double-blind period; OLE, open-label extension; TEAE, treatment-emergent adverse event.

Analysis conducted on full safety set. The denominator used to calculate percentages is N, the number of patients in the safety analysis set within each treatment arm. The severity of all TEAEs, including clinically significant laboratory abnormalities, was graded by the investigator according to version 4.03 of the National Cancer Institute Common Terminology Criteria for Adverse Events on a 5-point severity scale (grade 1–5). Serious TEAEs were reported in 14 (23.0%) patients in the OLE; such events occurred in only 1 patient each except for for the events of pneumonia (3 patients), anemia (2 patients), and abdominal pain (2 patients). TEAEs leading to discontinuation of study drug were reported in 5 (8.2%) patients in the OLE; such events occurred in 1 only patient each except for the event of hypertransaminasemia (2 patients).

Most frequently reported TEAEs (≥10% of patients)

Preferred term, n (%)	DBP		DBP+OLE
	Mitapivat (N=129)	Placebo (N=63)	Mitapivat (N=190)
Headache			
Any grade	29 (22.5)	6 (9.5)	40 (21.1)
Grade ≥3	0 (0)	0 (0)	0 (0)
Upper respiratory tract infection			
Any grade	14 (10.9)	4 (6.3)	33 (17.4)
Grade ≥3	0 (0.0)	0 (0.0)	0 (0)
COVID-19			
Any grade	8 (6.2)	5 (7.9)	28 (14.7)
Grade ≥3	0 (0.0)	0 (0.0)	0 (0)
Initial insomnia			
Any grade	18 (14.0)	3 (4.8)	25 (13.2)
Grade ≥3	1 (0.8)	0 (0.0)	2 (1.1)
Nausea			
Any grade	15 (11.6)	5 (7.9)	22 (11.6)
Grade ≥3	0 (0.0)	0 (0.0)	0 (0)
Fatigue			
Any grade	12 (9.3)	4 (6.3)	19 (10.0)
Grade ≥3	1 (0.8)	0 (0.0)	3 (1.6)

COVID-19, coronavirus disease 2019; DBP, double-blind period; OLE, open-label extension; TEAE, treatment-emergent adverse event.
Analysis conducted on full safety set. Summarized in order of decreasing frequency of patients with events based on the frequencies observed in any grade for the cumulative mitapivat arm. The denominator used to calculate percentages is N, the number of patients in the safety analysis set within each treatment arm. The severity of all TEAEs, including clinically significant laboratory abnormalities, was graded by the investigator according to version 4.03 of the National Cancer Institute Common Terminology Criteria for Adverse Events on a 5-point severity scale (grade 1–5).

Conclusions

- Long-term mitapivat treatment resulted in sustained and clinically meaningful Hb improvements in patients with α- or β-NTDT, with Hb responses of up to 93.3 weeks and ongoing at data cutoff
- Approximately 60% of patients randomized to mitapivat and who continued into the OLE had a ≥1 g/dL increase from baseline in average Hb over at least 2 consecutive OLE study visits, including approximately 1/3 of those who did not achieve the primary endpoint in the DBP
- Improvements in markers of hemolysis, consistent with the mechanism of action of mitapivat, were sustained over time with continued treatment
- Mitapivat was generally well tolerated and safety was consistent with observations in the DBP

These long-term results support the sustained efficacy and consistent safety of mitapivat in adults with α- or β-NTDT, and suggest that patients may benefit from continued treatment regardless of initial response

DBP, double-blind period; Hb, hemoglobin; NTDT, non–transfusion-dependent thalassemia; OLE, open-label extension.

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