13 October 2026

**AIEOP - Lecce**

# Mitapivat in Thalassemia: Latest Clinical Data



Prof. Raffaella Origa- Cagliari

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# Disclosures

**Consultancy fees:** Agios, Avanzanite, Novo Nordisk, Vertex.

**Speaker bureau:** Avanzanite, Bristol Myers Squibb (BMS), Vertex.

**Advisory board:** Agios, Avanzanite, BMS, Vertex.

# Disclaimer

*The presentation and the data presented are not intended for promotional purposes.*

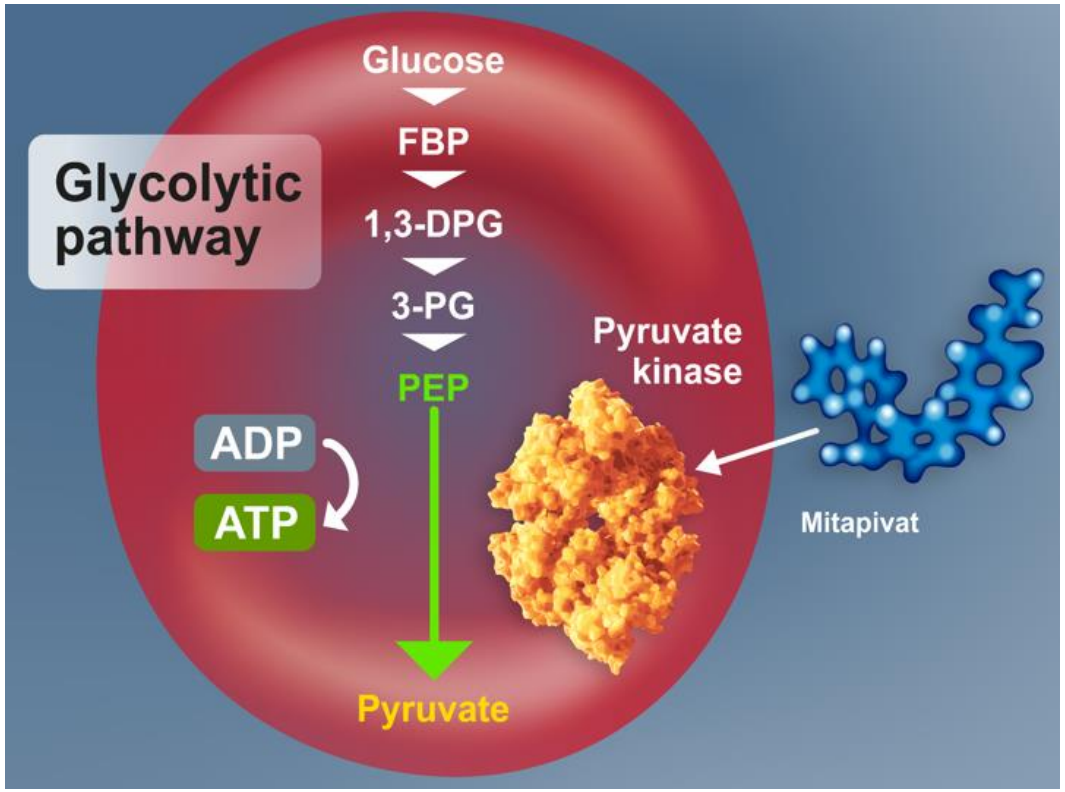
*Mitapivat (Pyrukynd®) is indicated in adults for the treatment of anaemia associated with transfusion-dependent and non-transfusion-dependent alpha- or beta-thalassaemia.*

*Mitapivat is indicated for the treatment of pyruvate kinase deficiency (PK deficiency) in adult patients.*

*Mitapivat is a pyruvate kinase (PK) activator.*

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# Mitapivat enhances cellular energy supply, supporting increased metabolic demands of thalassemic red blood cells

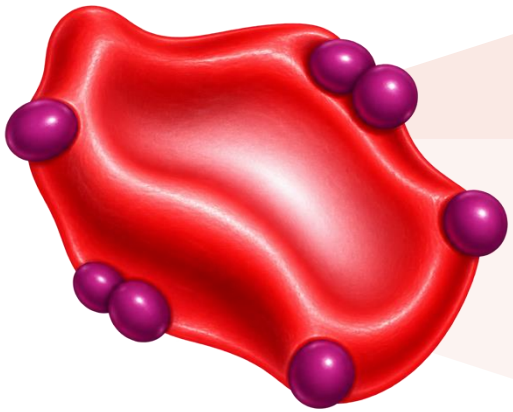


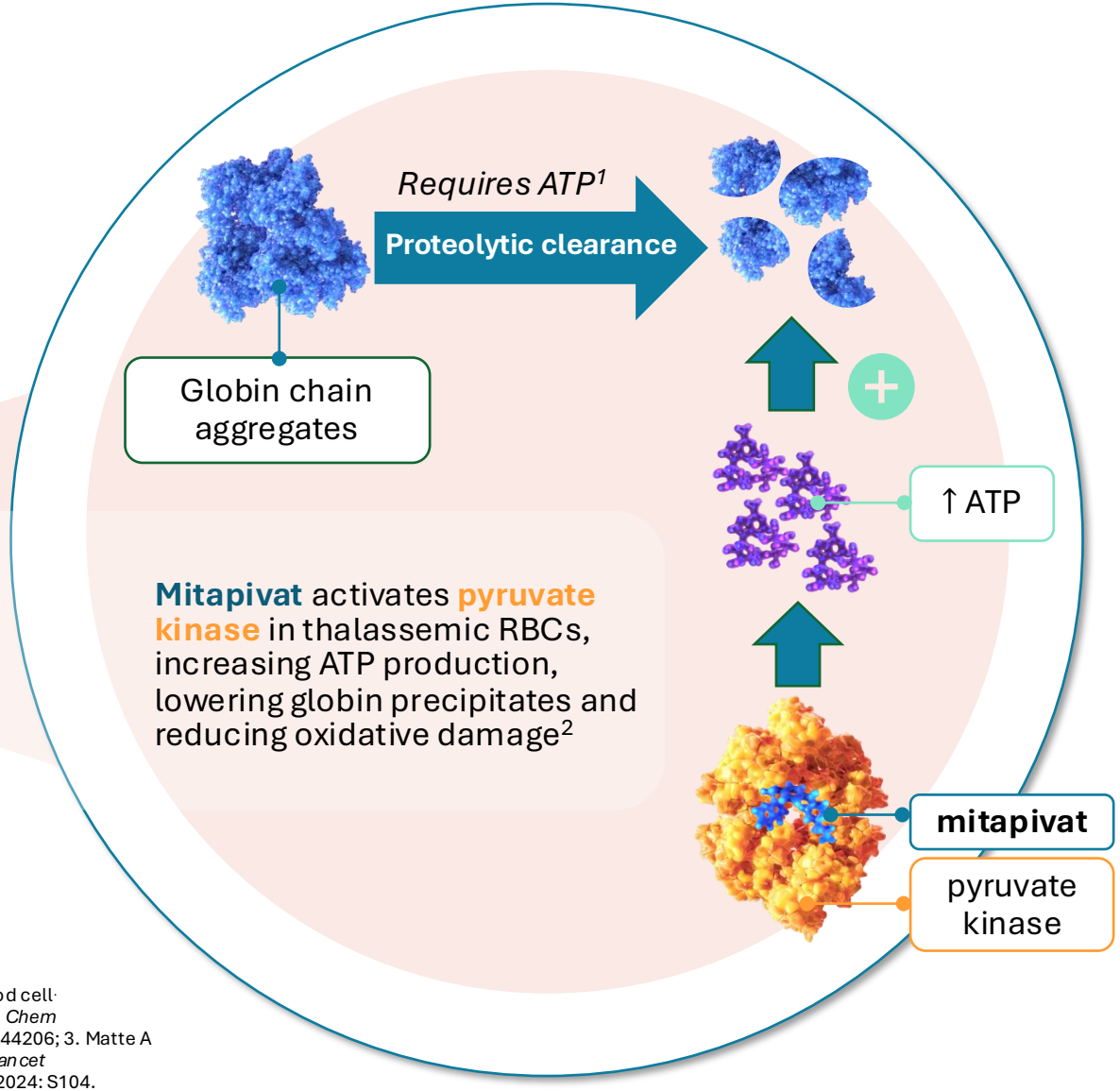

Mitapivat is an **allosteric activator** of **pyruvate kinase (PK)**, including the red cell-specific (PKR) and M2 (PKM2) isoforms, which act in glycolysis to generate ATP[1,2]

ADP, adenosine diphosphate; ATP, adenosine triphosphate; DPG, diphosphoglyceric acid; FBP, fructose biphosphate; PEP, phosphoenolpyruvate; PG, phosphoglycerate; PK, pyruvate kinase; PKM2, pyruvate kinase muscle isoenzyme 2; PKR, pyruvate kinase R. 1. Kung C et al. *Blood* 2017;130:1347; 2. Matte A et al. *J Clin Invest* 2021;131:e144206

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# Mitapivat targets the underlying pathophysiology of thalassemia by activating PK and increasing ATP production



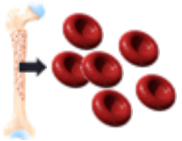



## Improved RBC Fitness

Improves multiple aspects of the disease pathophysiology



**Increased RBC half-life[2]**



**Improved erythroid maturation[2–5]**



**Reduced hemolysis[2,4,5]**



**Reduced iron overload and oxidative stress[2]**

**Improved cytoprotective systems[3]**

ATP, adenosine triphosphate; PK, pyruvate kinase; RBC, red blood cell·
[a]Preclinical data and clinical PK deficiency. 1. Shaeffer JR. *J Biol Chem* 1983;258(21):13172-7; 2. Matte A et al. *J Clin Invest* 2021;131:e144206; 3. Matte A et al. *Hemasphere* 2023;7(Suppl):e20723c9; 4. Kuo KMH et al. *Lancet* 2022;400:493–501; 5. Taher AT et al. *29th EHA Annual Congress* 2024: S104.

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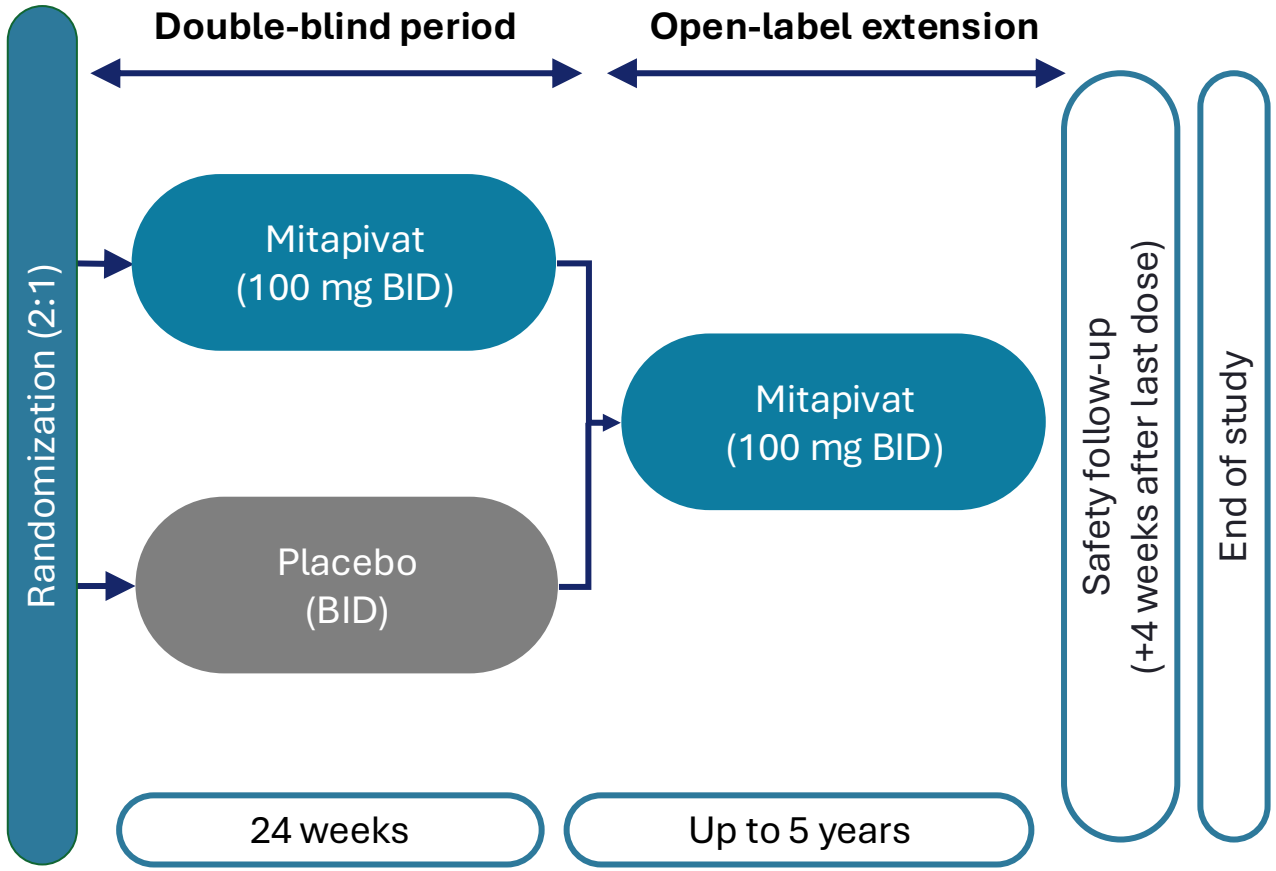
# Mitapivat in adults with non-transfusion-dependent α-thalassemia or β-thalassemia (ENERGIZE): A phase 3, international, randomized, double-blind, placebo-controlled trial

ENERGIZE: Phase 3 study primary data published in *The Lancet*[1]; Open Label Extension results presented at EHA 2026[2]


1. Taher AT et al. Lancet. 2025;406(10498):33–42
2. Al-Samkari H, et al. *EHA Library*. 2026;4206850:S296.


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# ENERGIZE study design




**Key inclusion criteria**

- ≥18 years of age at time of informed consent
- 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 stem cell transplant
- Homozygous or heterozygous for HbS or HbC
- Receiving treatment with luspatercept or a hematopoietic stimulating agent (last dose must be received ≥18 weeks before randomization)

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

BID, twice daily; Hb, hemoglobin; HbC, hemoglobin C; HbE, hemoglobin E; HbH, hemoglobin H; HbS, hemoglobin S; NTDT, non-transfusion-dependent thalassemia; RBC, red blood cell.

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

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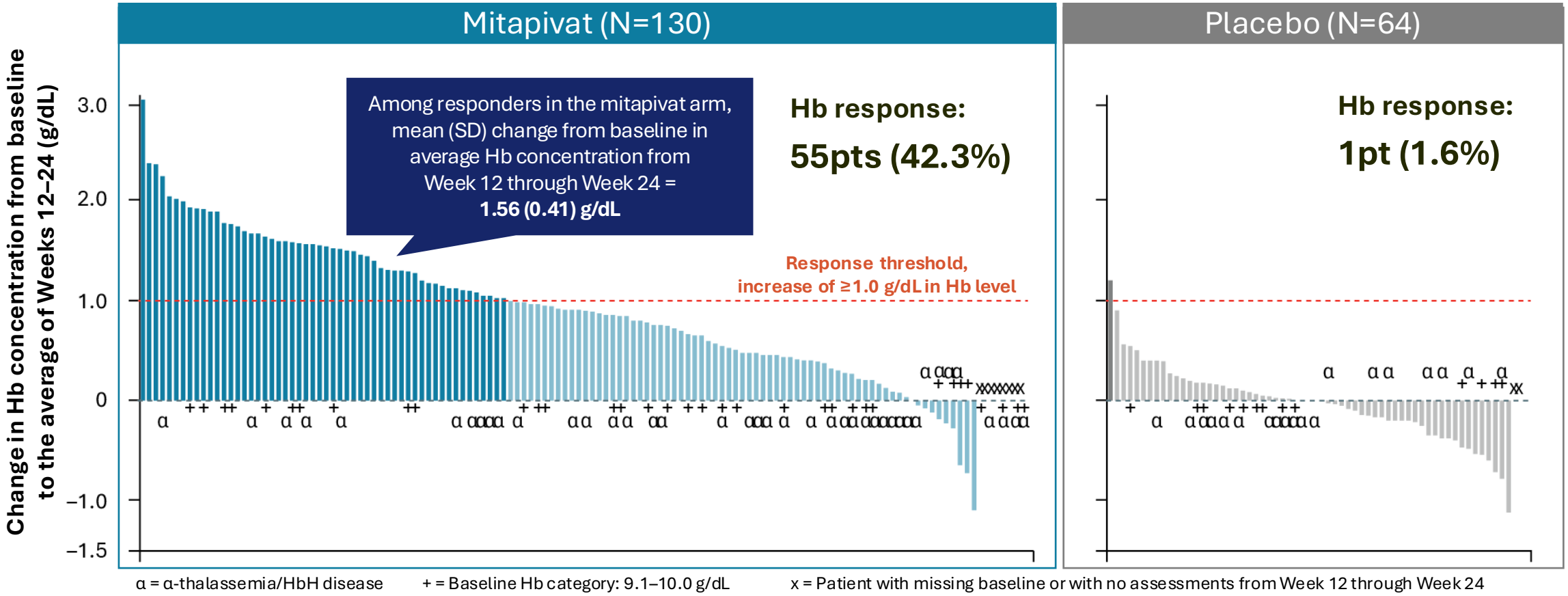
# Baseline characteristics (194 patients)

| Baseline and disease characteristics | Mitapivat N=130 | Placebo N=64 |
|---|---|---|
| Age (years), mean (range) | 42.4 (19–68) | 38.9 (18–69) |
| Sex, n (%) | | |
| Male | 84 (65) | 39 (61) |
| Female | 46 (35) | 25 (39) |
| Race, n (%) | | |
| White | 73 (56) | 36 (56) |
| Asian | 52 (40) | 24 (38) |
| Black or African American | 1 (1) | 1 (2) |
| American Indian or Alaska Native | 0 | 0 |
| Native Hawaiian or other Pacific Islander | 0 | 0 |
| Multiracial | 1 (1) | 0 |
| Unknown | 2 (2) | 2 (3) |
| Not reported | 1 (1) | 1 (2) |
| Ethnicity, n (%) | | |
| Hispanic or Latino | 11 (8) | 6 (9) |
| Not Hispanic or Latino | 118 (91) | 58 (91) |
| Not reported | 1 (1) | 0 |
| Thalassemia type, n (%) | | |
| α-thalassemia/HbH disease | 42 (32) | 20 (31) |
| β-thalassemia | 88 (68) | 44 (69) |
| Transfusion burden,[a] n (%) | | |
| 0 | 114 (88) | 54 (84) |
| 1–2 | 10 (8) | 7 (11) |
| 3–5 | 6 (5) | 3 (5) |
| >5 | 0 (0) | 0 (0) |

| Baseline and disease characteristics | Mitapivat N=130 | Placebo N=64 |
|---|---|---|
| Other characteristics | | |
| Prior splenectomy,[b] n (%) | 47 (36) | 25 (39) |
| Prior cholecystectomy,[b] n (%) | 45 (35) | 16 (25) |
| Received iron chelation in prior year,[c] n (%) | 46 (35) | 22 (34) |
| Laboratory values | | |
| Hb, mean (SD), g/dL | 8.30 (1.08) | 8.39 (1.01) |
| Indirect bilirubin, mean (SD), µmol/L | 29.03 (24.57) | 27.28 (19.30)[j] |
| LDH, mean (SD), U/L | 303.05 (157.16) | 309.15 (179.97) |
| Haptoglobin,[d] mean (SD), g/L | 0.21 (0.26)[e] | 0.29 (0.41)[k] |
| Reticulocyte percentage, mean (SD), % | 7 (6)[f] | 6 (5)[l] |
| Erythropoietin, mean (SD), IU/L | 135.21 (222.63)[g] | 197.05 (639.31)[m] |
| Function and quality of life | | |
| FACIT-Fatigue score, mean (SD) | 36.10 (11.12)[h] | 36.41 (9.41)[n] |
| 6-minute walk test score, mean (SD), m | 422.22 (76.64)[i] | 412.43 (88.12)[o] |

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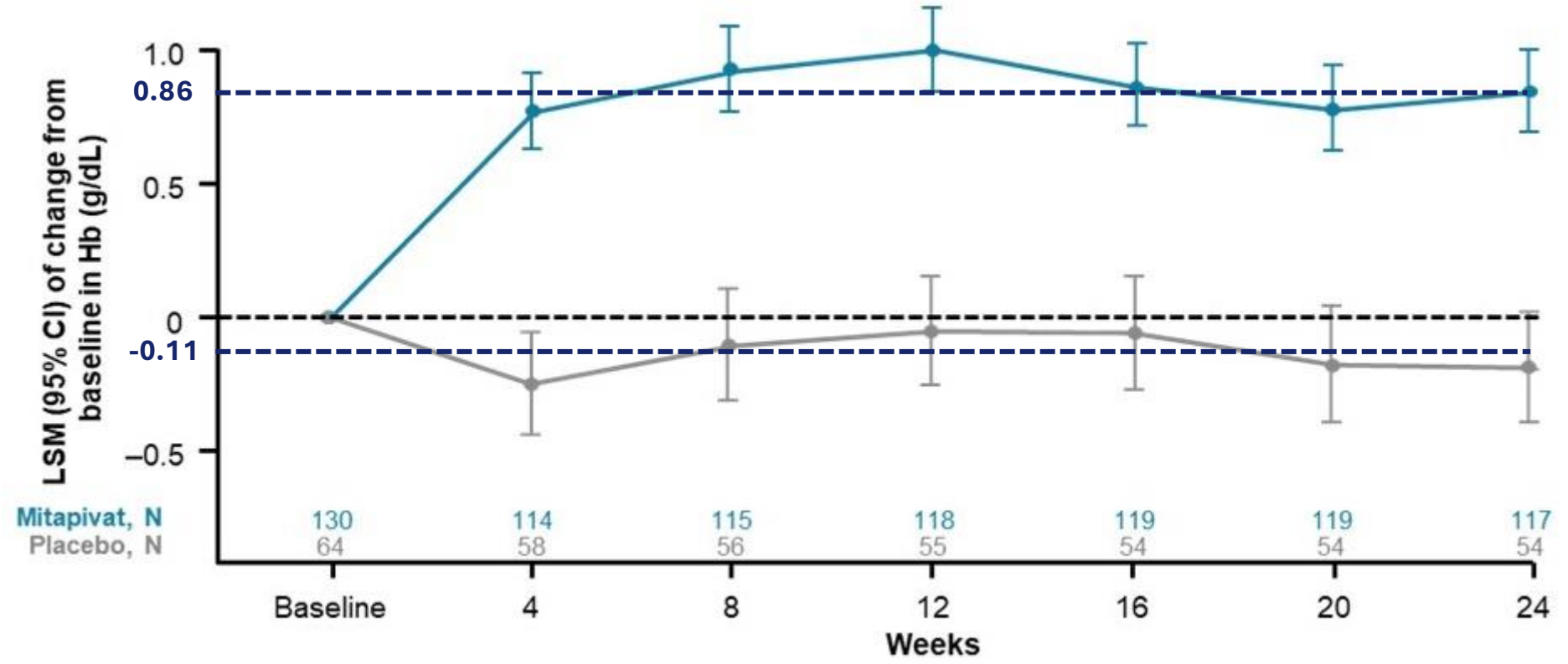
# Primary endpoint: Mitapivat demonstrated a significantly higher Hb response rate vs placebo




- **Hb response occurred in 55 patients** **42.3%** **treated with mitapivat vs 1 patient** **1.6%** **treated with placebo** (2-sided p<0.0001)
- **The effects of mitapivat on Hb response were robust and not driven by any individual subgroup**

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# ENERGIZE: Key secondary endpoints




CI, confidence interval; Hb, hemoglobin; LSM, least-squares mean.
Taher AT et al. *Lancet*. 2025;406(10498):33–42.

[a]In the general population, mean FACIT-Fatigue score reported in the literature was 43.61.

# Additional secondary endpoints

## Hemolysis and erythropoiesis markers

| | Mitapivat | Placebo | LSM difference |
|---|---|---|---|
| **Indirect bilirubin**, LSM (95% CI) change from baseline at Week 24, µmol/L | [N=116]<br>**–10.65**<br>(–12.72, –8.58) | [N=54]<br>**–0.03**<br>(–2.80, 2.74) | **–10.62**<br>(–13.74, –7.50) |
| **LDH**, LSM (95% CI) change from baseline at Week 24, U/L | [N=116]<br>**–30.07**<br>(–44.15, –15.99) | [N=54]<br>**–5.79**<br>(–24.43, 12.85) | **–24.28**<br>(–45.40, –3.15) |
| **Reticulocyte percentage**, LSM (95% CI) change from baseline at Week 24, % | [N=87]<br>**–1.59**<br>(–2.12, –1.07) | [N=40]<br>**–0.25**<br>(–0.97, 0.48) | **–1.35**<br>(–2.17, –0.53) |
| **Erythropoietin**, LSM (95% CI) change from baseline at Week 24, IU/L | [N=103]<br>**19.21**<br>(–55.45, 93.86) | [N=47]<br>**115.71**<br>(18.04, 213.37) | **–96.50**<br>(–209.59, 16.60) |

Patients in the mitapivat arm **showed improvements in two markers of hemolysis and a marker of erythropoiesis** (reticulocyte percentage) compared with the placebo group at Week 24

LSM: Least Square Mean

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# Additional secondary endpoints[1]

| | 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)[b] | **30.48** (19.31, 41.64) | **7.11** (–7.39, 21.62) | **23.36** (6.90, 39.83) | **≥20** |

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[2]

Patients on mitapivat had greater improvements in the **6-minute walk test (6MWT)** than those in the placebo arm at Week 24. **Improvements in 6MWT in the mitapivat arm exceeded the MCID[1]**

MCDI: Minimal Clinically Importance Difference, LSM: Least Square Mean

1. Taher AT et al. *Lancet*. 2025;406(10498):33–42. 2. Chetta A et al. *Respir Med* 2006;100:1573–1578.
3. St. Lezin E et al. *Transfusion* 2019;59:1934-1943.

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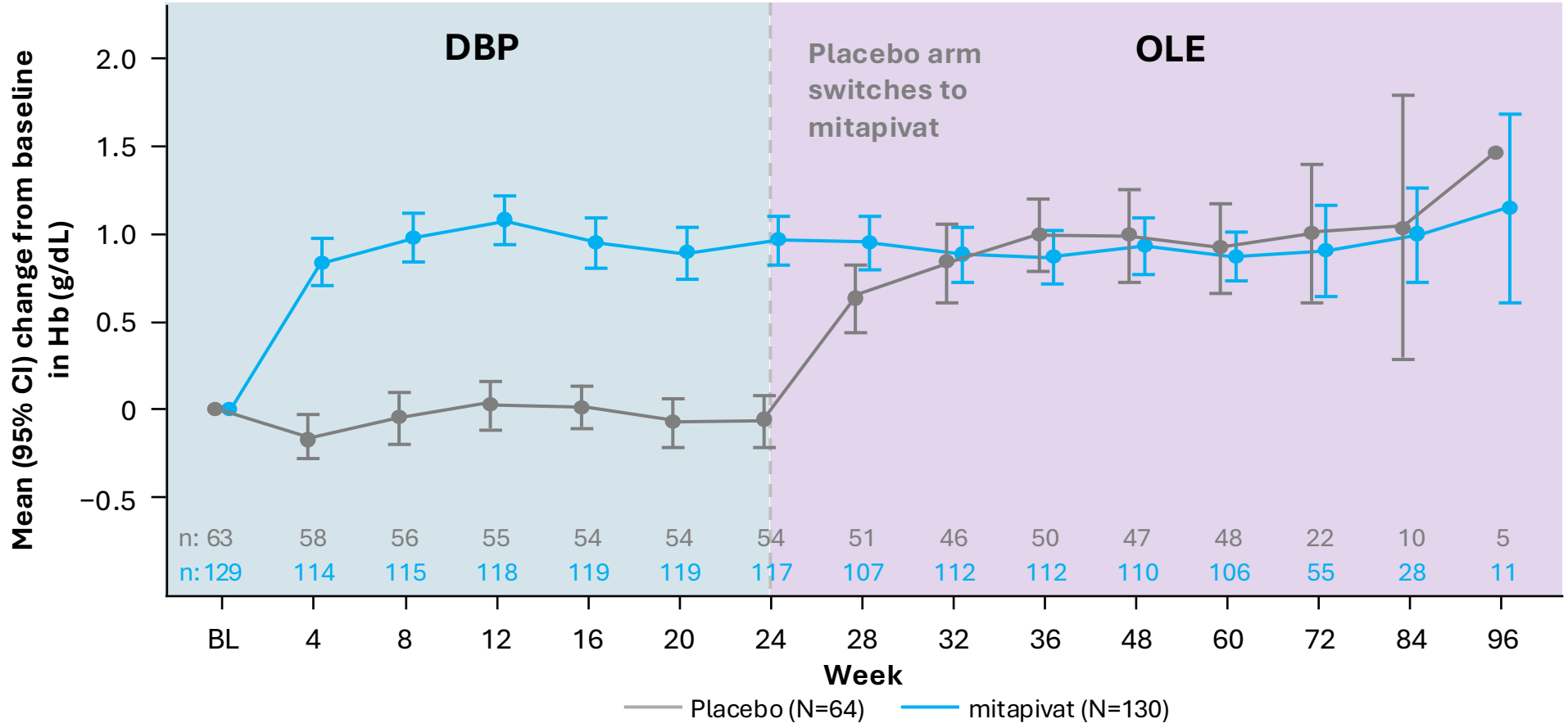
# ENERGIZE summary of safety

| Patients, n (%) | Mitapivat N=129 | Placebo N=63 |
|---|---|---|
| Any treatment-emergent adverse events (TEAEs) | 107 (83) | 50 (79) |
| Grade ≥3 TEAEs | 18 (14)[a] | 2 (3)[b] |
| Treatment-related TEAEs | 56 (43) | 13 (21) |
| Grade ≥3 treatment-related TEAEs[c] | 5 (4) | 0 (0) |
| Serious TEAEs | 8 (6) | 0 (0) |
| Serious treatment-related TEAEs | 0 (0) | 0 (0) |
| TEAEs leading to discontinuation of study drug[d] | 4 (3) | 0 (0) |
| TEAEs leading to dose reduction | 7 (5) | 2 (3) |
| TEAEs leading to interruption of study drug | 2 (2) | 1 (2) |
| TEAEs leading to death | 0 (0) | 0 (0) |

| Most frequently reported (≥10%) TEAEs, Preferred Term. Patients, n (%)[e] | Mitapivat N=129 | Placebo N=63 |
|---|---|---|
| Headache | | |
| Any grade | 29 (22) | 6 (10) |
| Grade ≥3 | 0 (0) | 0 (0) |
| Initial insomnia[f] | | |
| Any grade | 18 (14) | 3 (5) |
| Grade ≥3 | 1 (1) | 0 (0) |
| Nausea | | |
| Any grade | 15 (12) | 5 (8) |
| Grade ≥3 | 0 (0) | 0 (0) |
| Upper respiratory tract infection | | |
| Any grade | 14 (11) | 4 (6) |
| Grade ≥3 | 0 (0) | 0 (0) |

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# The mean Hb increase achieved with mitapivat in the DBP was sustained during the Open Label Extension



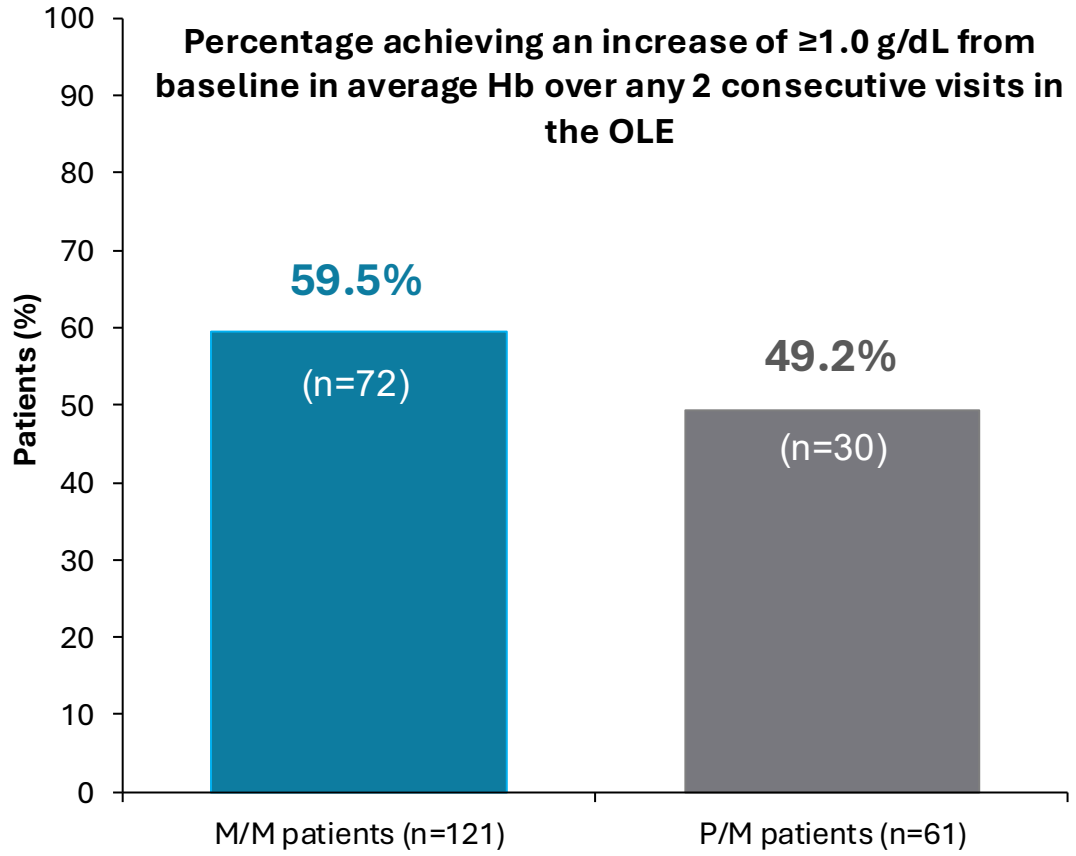

Among patients who switched from placebo to mitapivat in the OLE, increases in Hb during the OLE were similar to those observed in patients who received mitapivat during the DBP

OLE: Open Label Extension

Al-Samkari H, et al. *EHA Library*. 2026;4206850:S296

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# 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



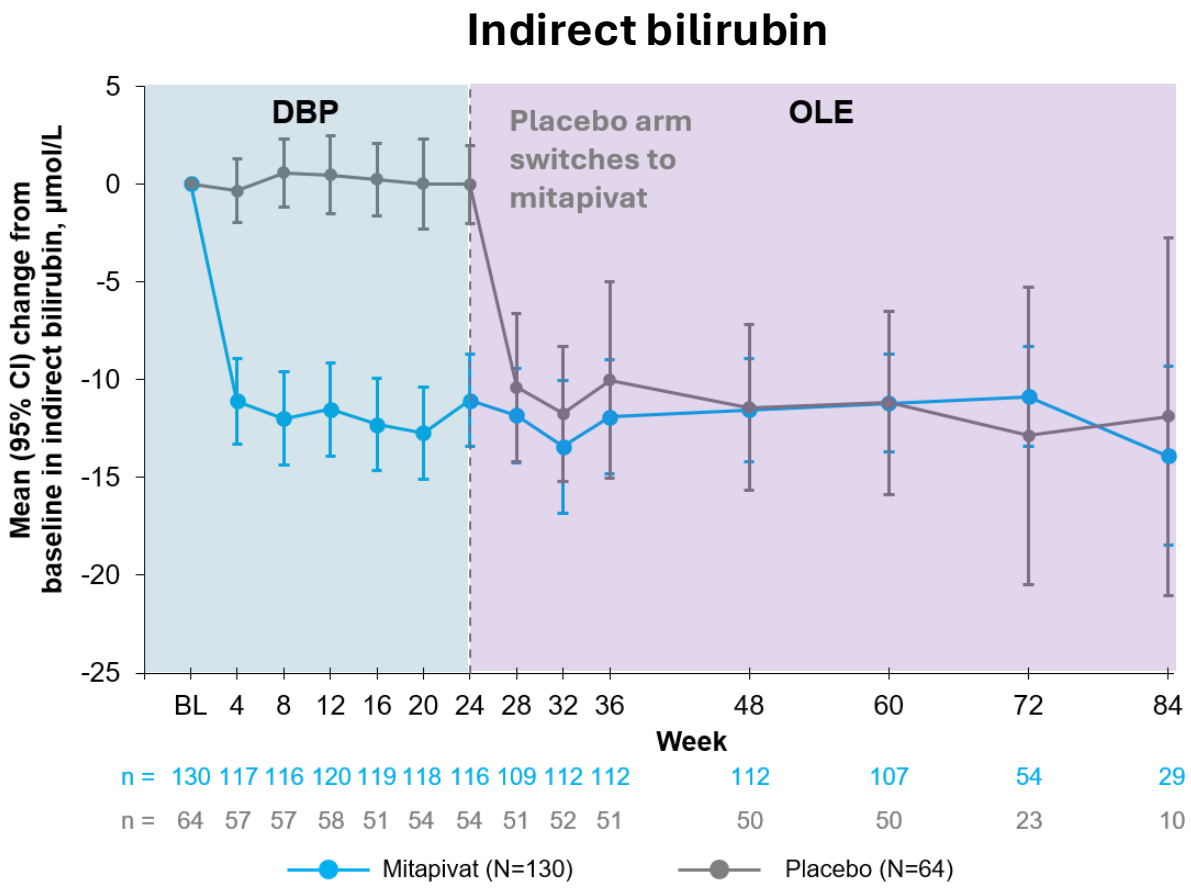

Among patients who achieved this threshold of Hb improvement, the **mean change from baseline in Hb across the OLE was 1.3 g/dL** for both the M/M and the P/M groups at data cutoff

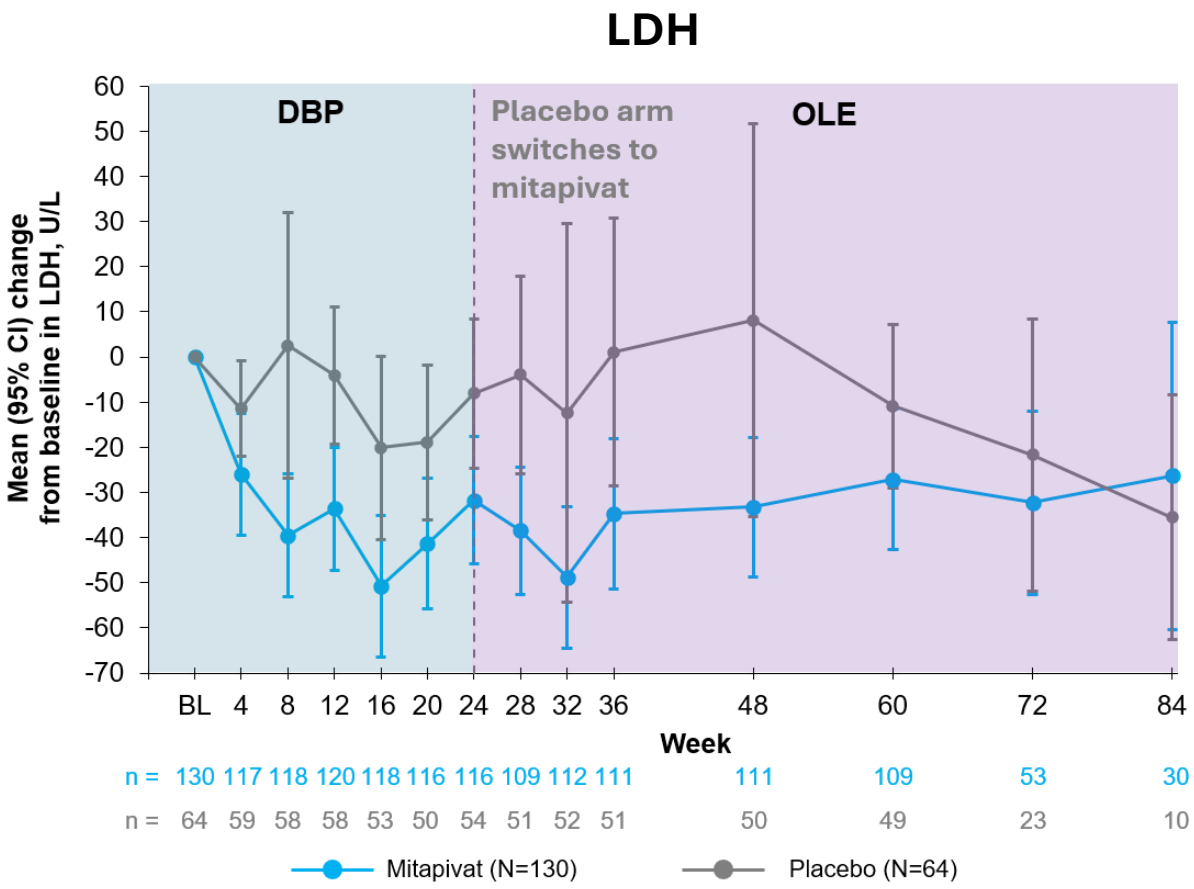
**M/M**: Patients who received mitapivat in the DBP and OLE
**P/M**: Patients who received placebo in the DBP and mitapivat in the OLE

Al-Samkari H, et al. *EHA Library*. 2026;4206850:S296.

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




Al-Samkari H, et al. *EHA Library*. 2026;4206850:S296.

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# ENERGIZE study summary

ENERGIZE is the **first phase 3 trial to demonstrate the efficacy of a disease-modifying therapy in α- and β-thalassemia,** with **significant improvements in anemia and fatigue**, and **improved walking capacity.**[1,2]

- Mitapivat significantly **improved both hemoglobin and fatigue**, with the primary and key secondary endpoint met[1]
- **Mitapivat reduced hemolysis and ineffective erythropoiesis markers**, including indirect bilirubin, LDH, and reticulocyte.[1]
- Mitapivat **improved functional capacity**, with **6MWT** changes exceeding the threshold for clinically meaningful improvement.[1–3]
- Mitapivat was **generally well tolerated**, with a **low treatment discontinuation rate** and headache, initial insomnia, nausea and upper respiratory tract infection as the most common TEAE[1]
- Long-term results support the **sustained efficacy** and **consistent safety** of mitapivat in **adults with α- or β-NTDT**.[4]

1. Taher AT et al. Lancet. 2025;406(10498):33–42. 2. Kuo KHM et al. 29th EHA Hybrid Congress 2024: P1529. 3. St. Lezin E et al. *Transfusion* 2019;59:1934-1943.
4. Al-Samkari H, et al. *EHA Library*. 2026;4206850:S296.

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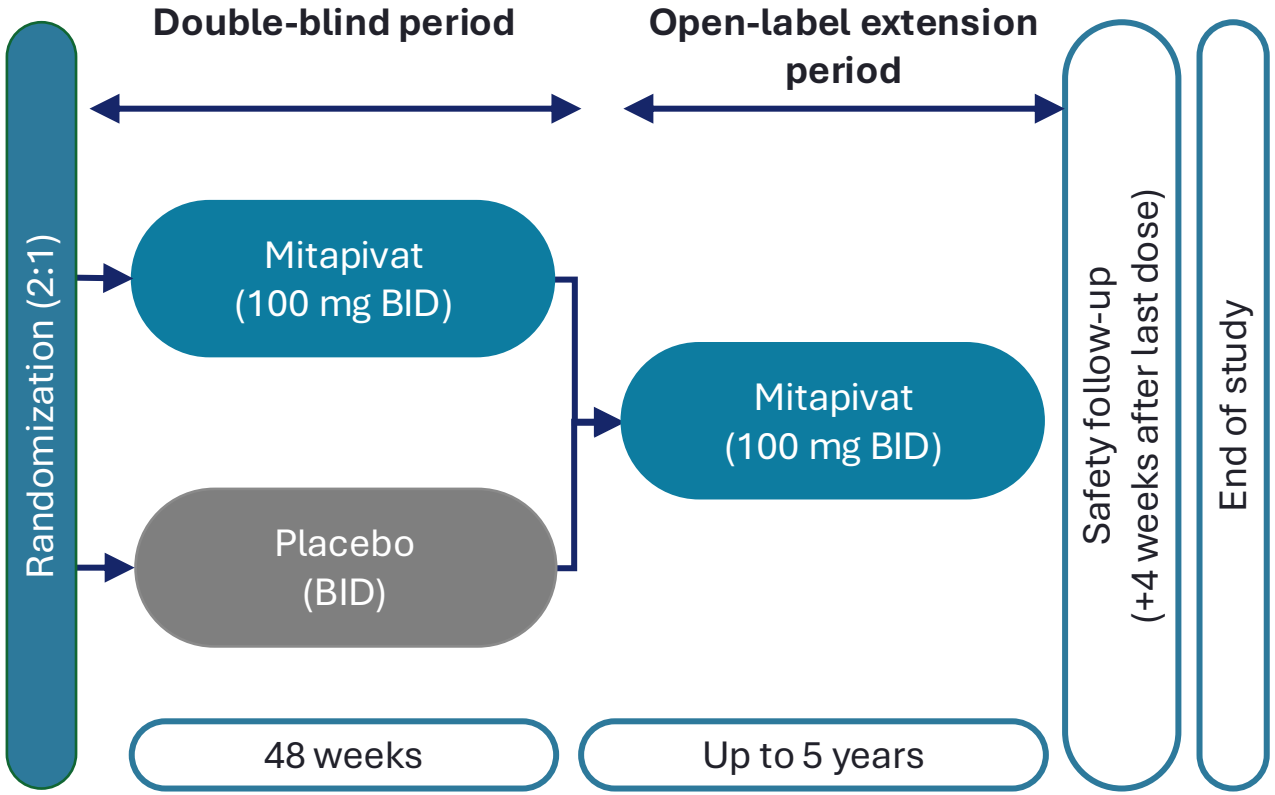
# ENERGIZE-T: A global, phase 3, double-blind, randomized, placebo-controlled study of mitapivat in adults with transfusion-dependent α-thalassemia or β-thalassemia

ENERGIZE-T: Phase 3 study primary data published in *The Lancet*[1];Open Label Extension results presented at ASH 2025[2]

1. Cappellini MD et al. Lancet. 2026;408(10559):1010–1018
2. Sheth S et al. 67th ASH Annual Meeting and Exposition. 2025; Abstract 146:4697–4698

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# 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 transplant
- Homozygous or heterozygous for HbS or HbC
- Receiving treatment with luspatercept or a hematopoietic stimulating agent (last dose must be received ≥36 weeks before randomization)

**Primary endpoint:** Transfusion reduction response (**TRR**)
Defined as 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**

Cappellini MD et al. Lancet. 2026;408(10559):1010–1018

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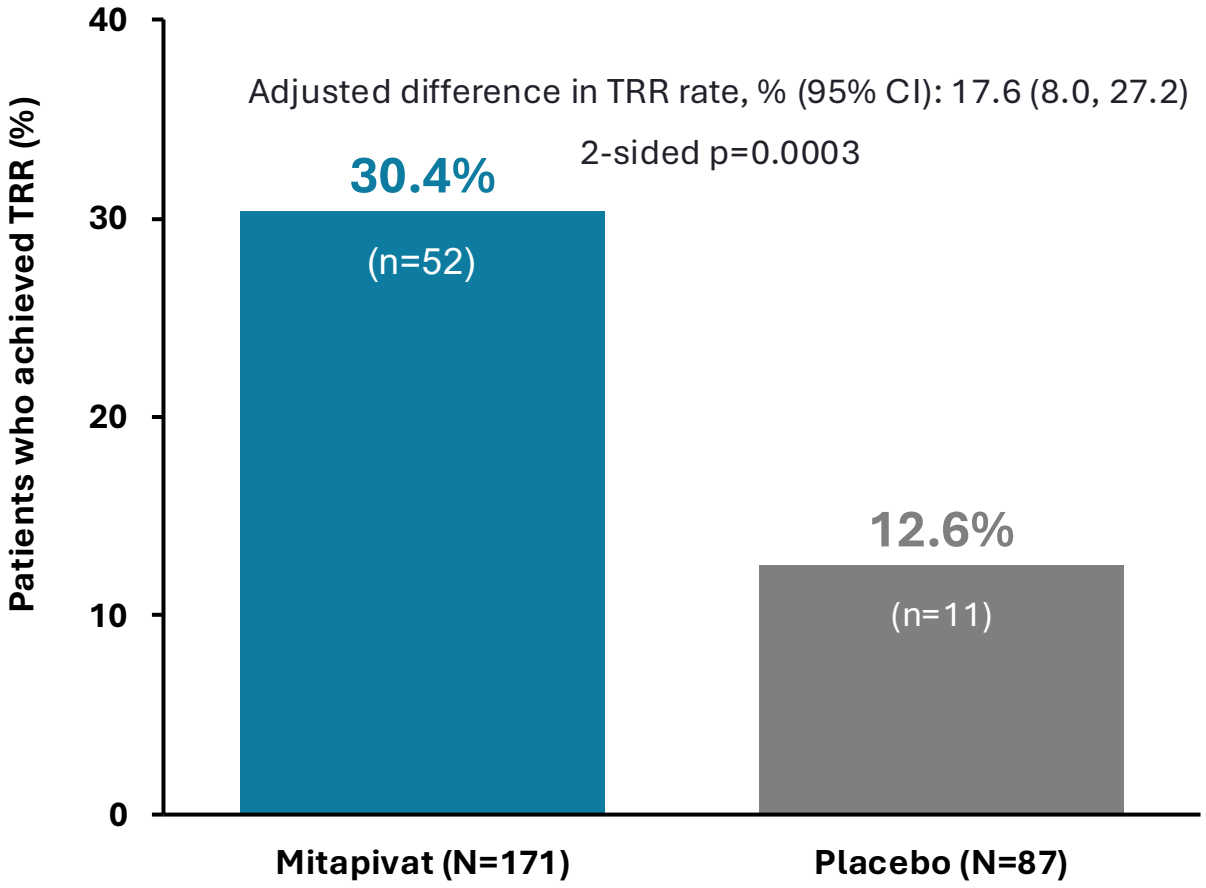
# Baseline demographics and disease characteristics (258 patients)

| Baseline and disease characteristics | Mitapivat N=171 | Placebo N=87 |
|---|---|---|
| Age, mean (SD), years | 36 (12) | 35 (10) |
| Female, n (%) | 93 (54) | 43 (49) |
| Race, n (%) | | |
| White | 99 (58) | 56 (64) |
| Asian | 56 (33) | 22 (25) |
| Black or African American | 1 (1) | 1 (1) |
| Multiracial | 2 (1) | 0 (0) |
| Unknown | 7 (4) | 3 (3) |
| Not reported | 6 (4) | 5 (6) |
| Thalassemia genotype, n (%) | | |
| Non-$\beta^0/\beta^0$ [a] | 96 (56) | 48 (55) |
| $\beta^0/\beta^0$ [b] | 75 (44) | 39 (45) |
| 24-week transfusion burden,[c] n (%) | | |
| ≤12 RBC units | 54 (32) | 21 (24) |
| >12 RBC units | 117 (68) | 66 (76) |
| Pretransfusion Hb threshold,[d] median (range), g/dL | 9.0 (5–12) | 8.9 (5–11) |
| Prior splenectomy,[e] n (%) | 92 (54) | 49 (56) |
| Received iron chelation in prior year,[f] n (%) | 165 (97) | 87 (100) |
| Geographic region, n (%) | | |
| North America and Europe | 106 (62) | 54 (62) |
| Asia-Pacific | 31 (18) | 16 (18) |
| Rest of the world[g] | 34 (20) | 17 (20) |

Cappellini MD et al. Lancet. 2026;408(10559):1010–1018

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# Primary endpoint: mitapivat demonstrated a statistically significant reduction in transfusion burden vs placebo




- **TRR** was defined as 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

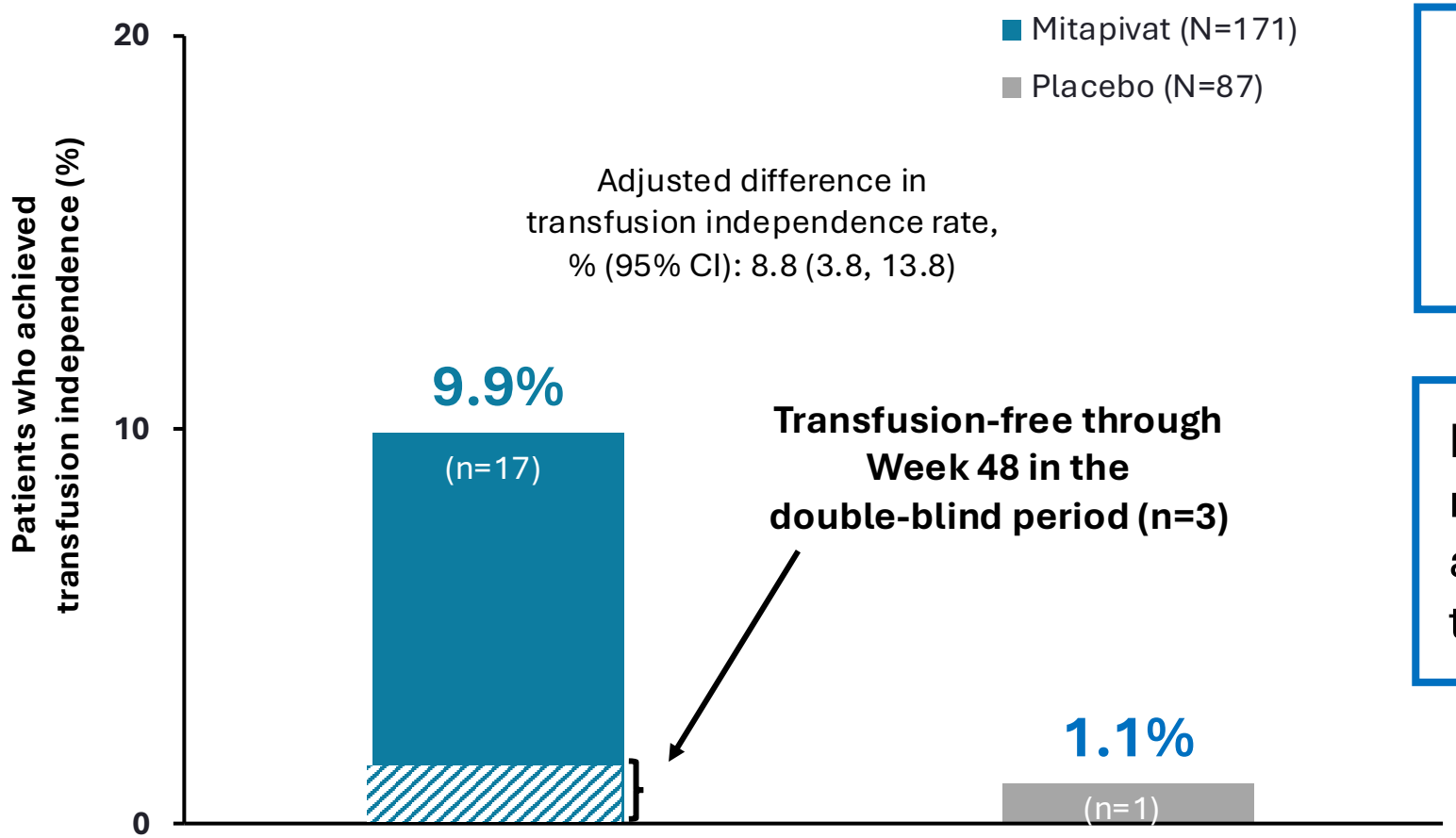
The effects of mitapivat on the reduction in transfusion burden were **not driven by any prespecified subgroup**

TRR: Transfusion Reduction Response
Cappellini MD et al. Lancet. 2026;408(10559):1010–1018

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# Additional secondary endpoint: a higher proportion of patients in the mitapivat group achieved transfusion independence vs placebo

**Transfusion independence** was defined as **transfusion-free for ≥8 consecutive weeks through Week 48** in the double-blind period




**6 of the 17** patients who achieved **transfusion independence** had a **$\beta^0/\beta^0$ genotype**

During transfusion-free periods, mean Hb was **maintained 1.4 g/dL** above the mean pre-study transfusion threshold of **8.1 g/dL.**

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# ENERGIZE-T summary of safety[1]

| Patients, n (%) | Mitapivat N=172 | Placebo N=85 |
|---|---|---|
| Any TEAEs | 155 (90) | 71 (84) |
| Grade ≥3 TEAEs | 32 (19) | 12 (14) |
| Treatment-related TEAEs | 65 (38) | 16 (19) |
| Grade ≥3 treatment-related TEAEs | 13 (8) | 1 (1) |
| Serious TEAEs | 19 (11) | 13 (15) |
| Serious treatment-related TEAEs | 4 (2) | 1 (1) |
| TEAEs leading to discontinuation of study drug | 10 (6) | 1 (1) |
| TEAEs leading to dose reduction | 20 (12) | 2 (2) |
| TEAEs leading to interruption of study drug | 13 (8) | 5 (6) |
| TEAEs leading to death | 0 (0) | 0 (0) |

| Most frequently reported (≥10%) TEAEs | Mitapivat N=172 | | Placebo N=85 | |
|---|---|---|---|---|
| Preferred Term. Patients, n (%) | Any grade | Grade ≥3 | Any grade | Grade ≥3 |
| Headache | 46 (27) | 0 (0) | 10 (12) | 0 (0) |
| Upper respiratory tract infection | 27 (16) | 0 (0) | 14 (17) | 0 (0) |
| Initial insomnia | 24 (14) | 3 (2) | 4 (5) | 0 (0) |
| Diarrhea | 19 (11) | 0 (0) | 7 (8) | 0 (0) |
| Fatigue | 18 (11) | 0 (0) | 2 (2) | 0 (0) |

The favorable safety profile was maintained during the Open Label Extension (OLE), with no new safety signals identified[2]

1. Cappellini MD et al. Lancet. 2026;408(10559):1010–1018
2. Steth S et al. 67th ASH Annual Meeting and Exposition 2025:146 (4697-4698)

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# ENERGIZE-T study summary

ENERGIZE-T demonstrated that mitapivat **significantly reduced transfusion burden** in adults with **transfusion-dependent α- or β-thalassemia.**[1]

The **primary and all key secondary endpoints were met**, including significant reductions in transfusion burden.[1]

A **higher proportion** of patients achieved **transfusion independence with mitapivat vs placebo**, with **3 patients** remaining **transfusion-free** through Week 48.[1]

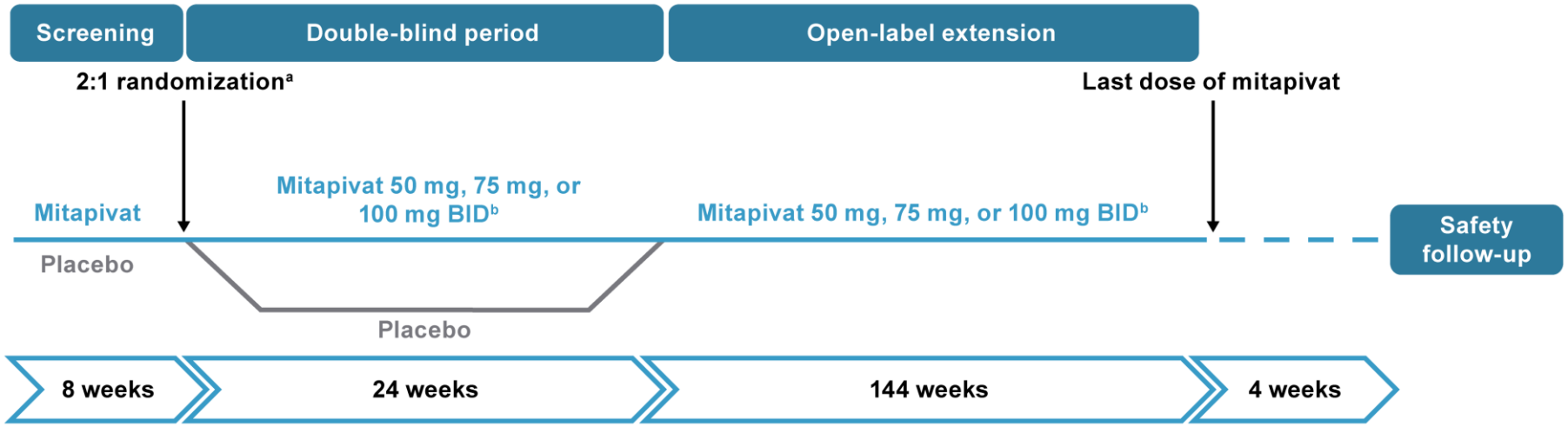
Oper Label Extension (OLE) data confirmed **sustained transfusion responses** with continued mitapivat treatment.[2]

Mitapivat was **generally well tolerated**, with a **low treatment discontinuation rate**. The most frequent TEAEs were headache, upper respiratory tract infection, initial insomnia, diarrhoea and fatigue. The safety profile remained consistent during the OLE, with no new safety signals[2].

1. Cappellini MD et al. Lancet. 2026;408(10559):1010–1018
2. Steth S et al. 67th ASH Annual Meeting and Exposition 2025:146 (4697-4698)

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# ENERGIZEkids: efficacy, pharmacokinetics (PK), and safety of mitapivat vs placebo in children with α- or β-NTDT




**Key inclusion criteria**

- Age 1 to <18 years and weight ≥7 kg
- Documented diagnosis of thalassemia
- Hb concentration ≤10.0 g/dL (≤100.0 g/L)
- Not transfusion dependent, defined as ≤5 transfusion episodes during 24-week period prior to randomization, no RBC transfusions <8 weeks before providing informed consent/assent, and no RBC transfusions during screening
- Hydroxyurea dose stable for ≥16 weeks before randomization

**Key exclusion criteria**

- Documented history of homozygous or heterozygous HbS or HbC
- Prior exposure to gene therapy or prior bone marrow or stem cell transplantation
- Currently receiving treatment with luspatercept
- Currently receiving treatment with hematopoietic stimulating agents

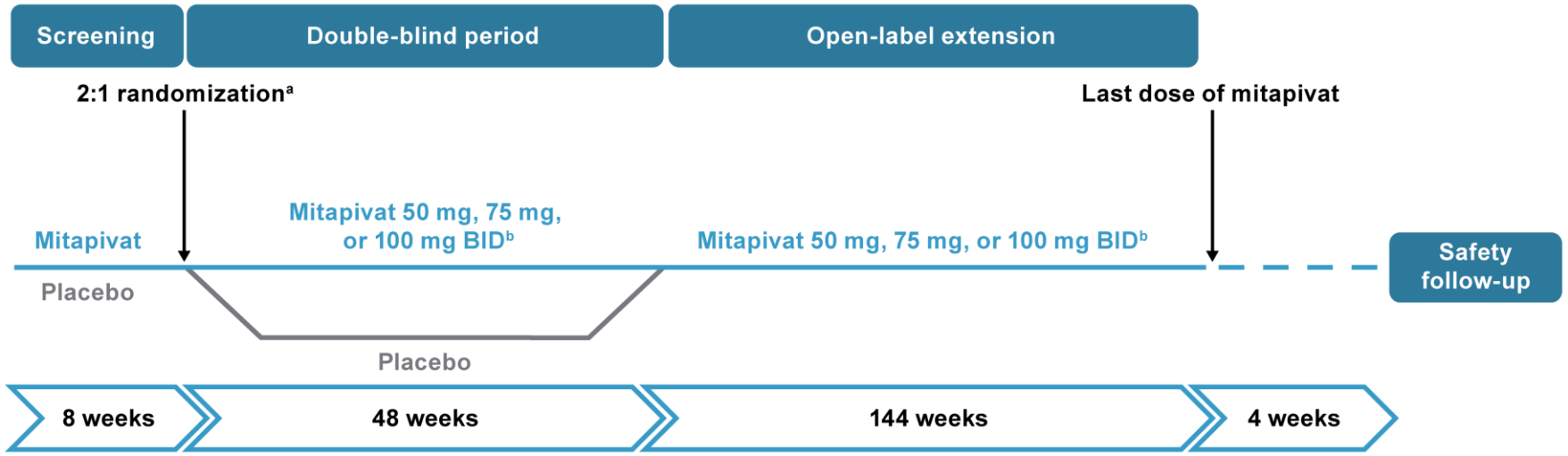
**Italian site:**

- Cagliari

Dickerson K, et al. EHA 2026. Abstract PB4160

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# ENERGIZEkids-T: Efficacy, pharmacokinetics (PK), and safety of mitapivat vs placebo in children with α- or β-TDT




**Key inclusion criteria**

- Age 1 to <18 years and weight ≥7 kg
- Documented diagnosis of thalassemia
- Transfusion dependent, defined as 6 to 20 transfusion episodes and ≤6-week transfusion-free period during the 24-week period prior to randomization
- Stable hydroxyurea dose for ≥16 weeks before randomization

**Key exclusion criteria**

- Documented history of homozygous or heterozygous HbS or HbC
- Prior exposure to gene therapy or prior bone marrow or stem cell transplantation
- Currently receiving treatment with luspatercept
- Currently receiving treatment with hematopoietic stimulating agents

**Italian sites:**

- Cagliari
- Padova

Kwiatkowski JL, et al. EHA 2026. Abstract PB4162.

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Thank you!

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