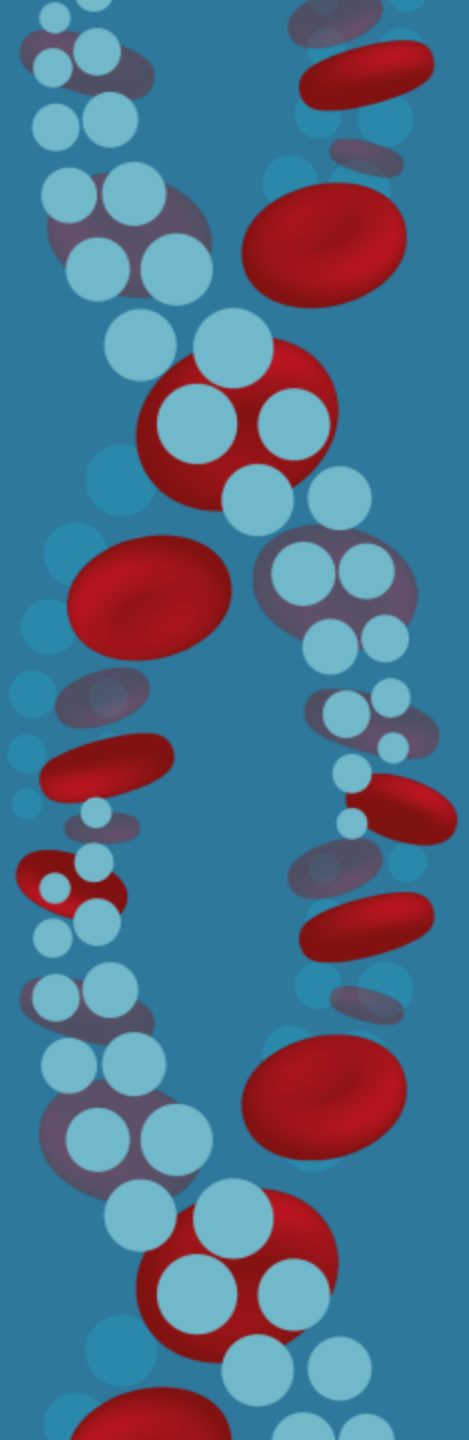
agios

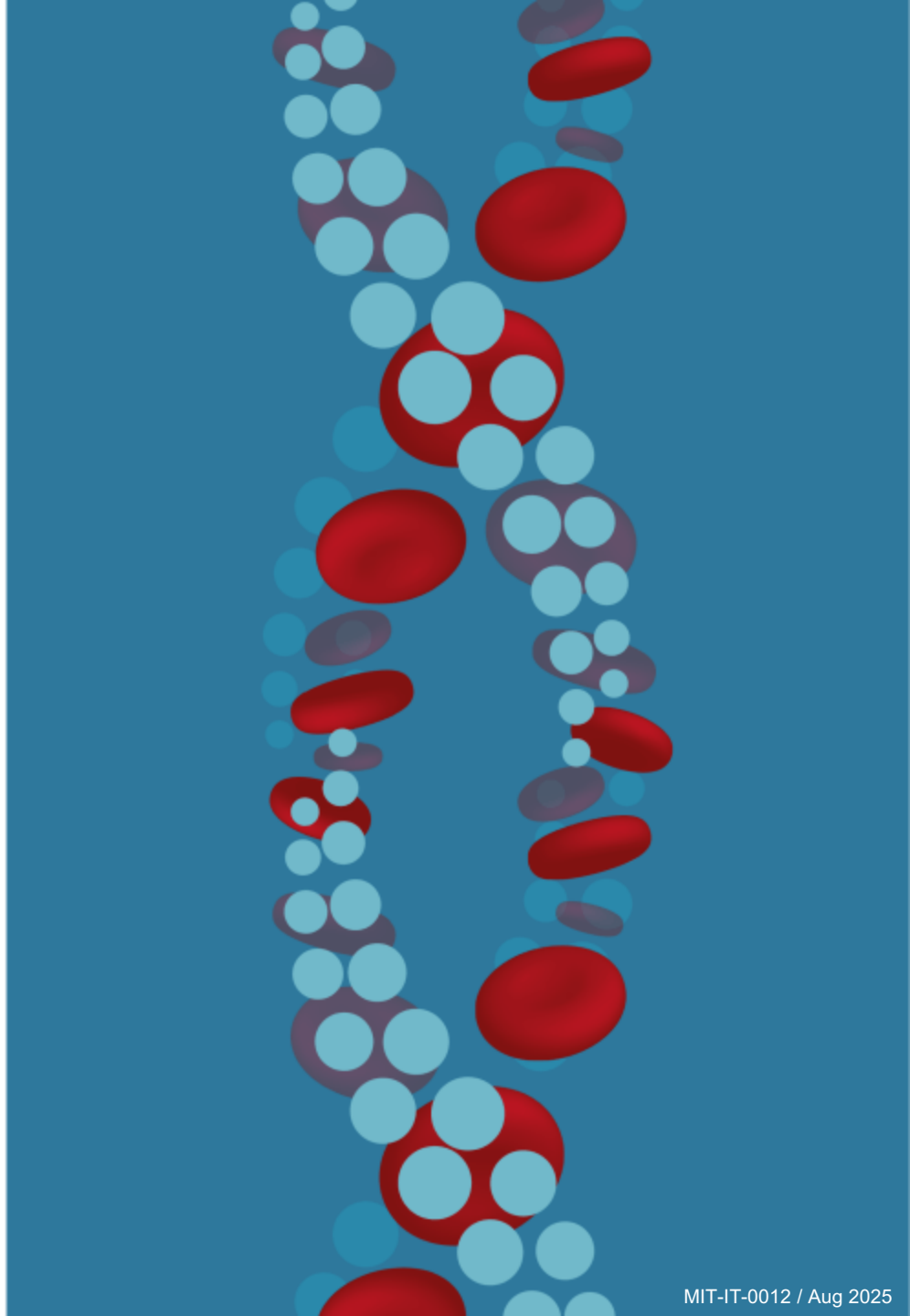
Pyruvate Kinase Activation in Thalassemia

SITE Congress 2025
Friday, September 12, 2025
15:30–16:00



Welcome and Introduction

Maria Domenica Cappellini, MD, FRCP, FACP
University of Milan, Ca’ Granda Foundation
IRCCS Maggiore Policlinico Hospital,
Milan, Italy



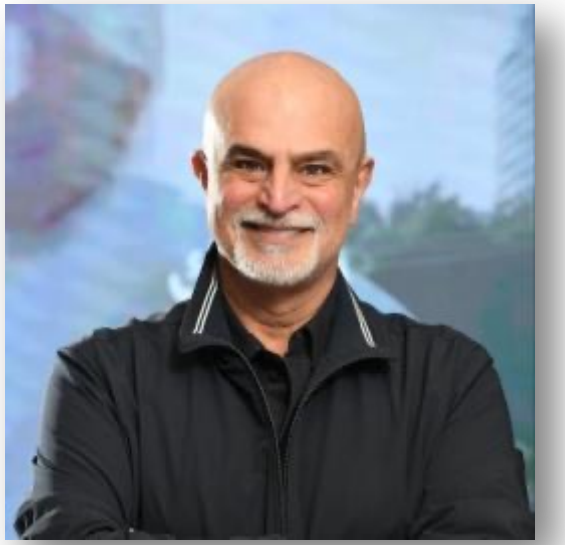
Disclaimer

- *This presentation is intended for scientific informational purposes only*
- *The speakers are presenting on behalf of Agios Pharmaceuticals, Inc.*
- *The ENERGIZE and ENERGIZE-T studies are funded by Agios Pharmaceuticals, Inc.*
- *Mitapivat is a first-in-class, allosteric activator of pyruvate kinase (PK) approved in the United States for the treatment of hemolytic anemia in adults with PK deficiency, and in the European Union and in the United Kingdom for the treatment of PK deficiency in adults; mitapivat is also approved in Saudi Arabia for the treatment of adult patients with non-transfusion-dependent and transfusion-dependent alpha- or beta-thalassemia. The safety and efficacy of mitapivat in other indications are under investigation and have not been established. There is no guarantee that mitapivat will receive health authority approvals or become commercially available in any country for the uses under investigation*

Disclosures

- Both speakers are receiving an honorarium for this presentation
- **Maria Domenica Cappellini, MD, FRCP, FACP:** Received advisory board fees from Celgene Corp (Bristol Myers Squibb), CRISPR Therapeutics, Novo Nordisk, Pharmacosmos, Sanofi Genzyme, and Vertex
- **Ali T. Taher, MD, PhD, FRCP:** Received consultancy fees and research funding from Agios Pharmaceuticals, Bristol Myers Squibb (Celgene), Pharmacosmos, and Vifor; and consultancy fees from Novo Nordisk

Faculty



ENERGIZE Study

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ENERGIZE-T Study

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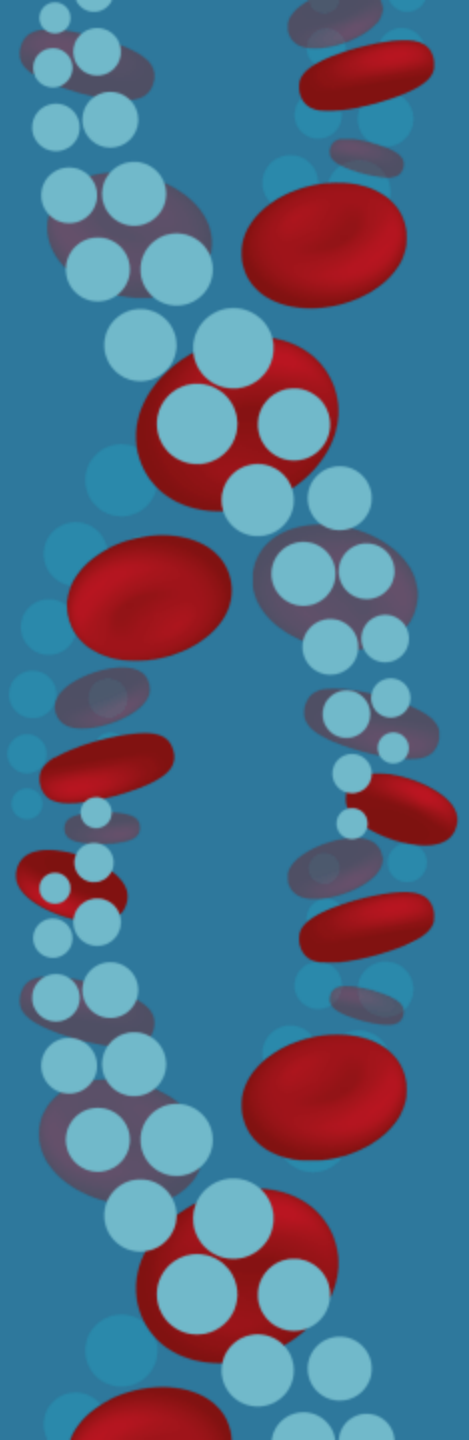
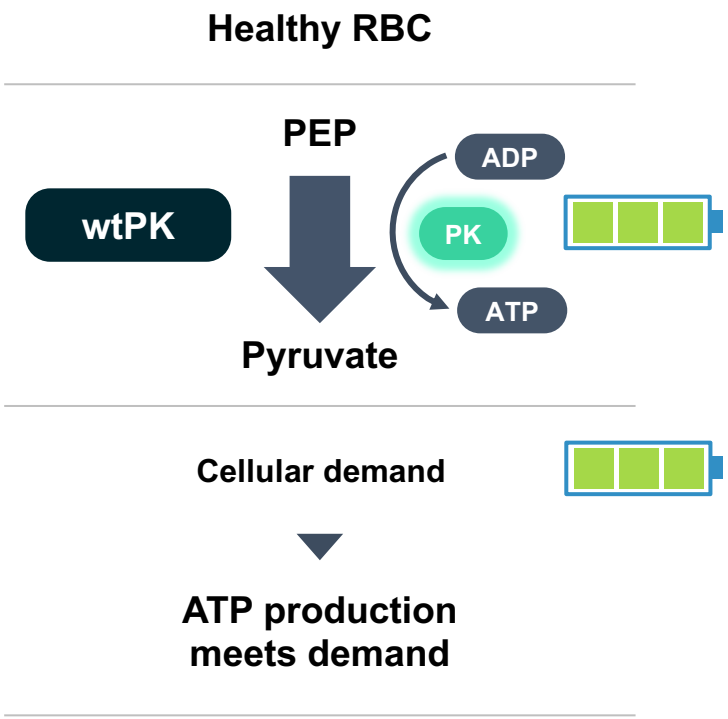
Activation of Pyruvate Kinase with Mitapivat

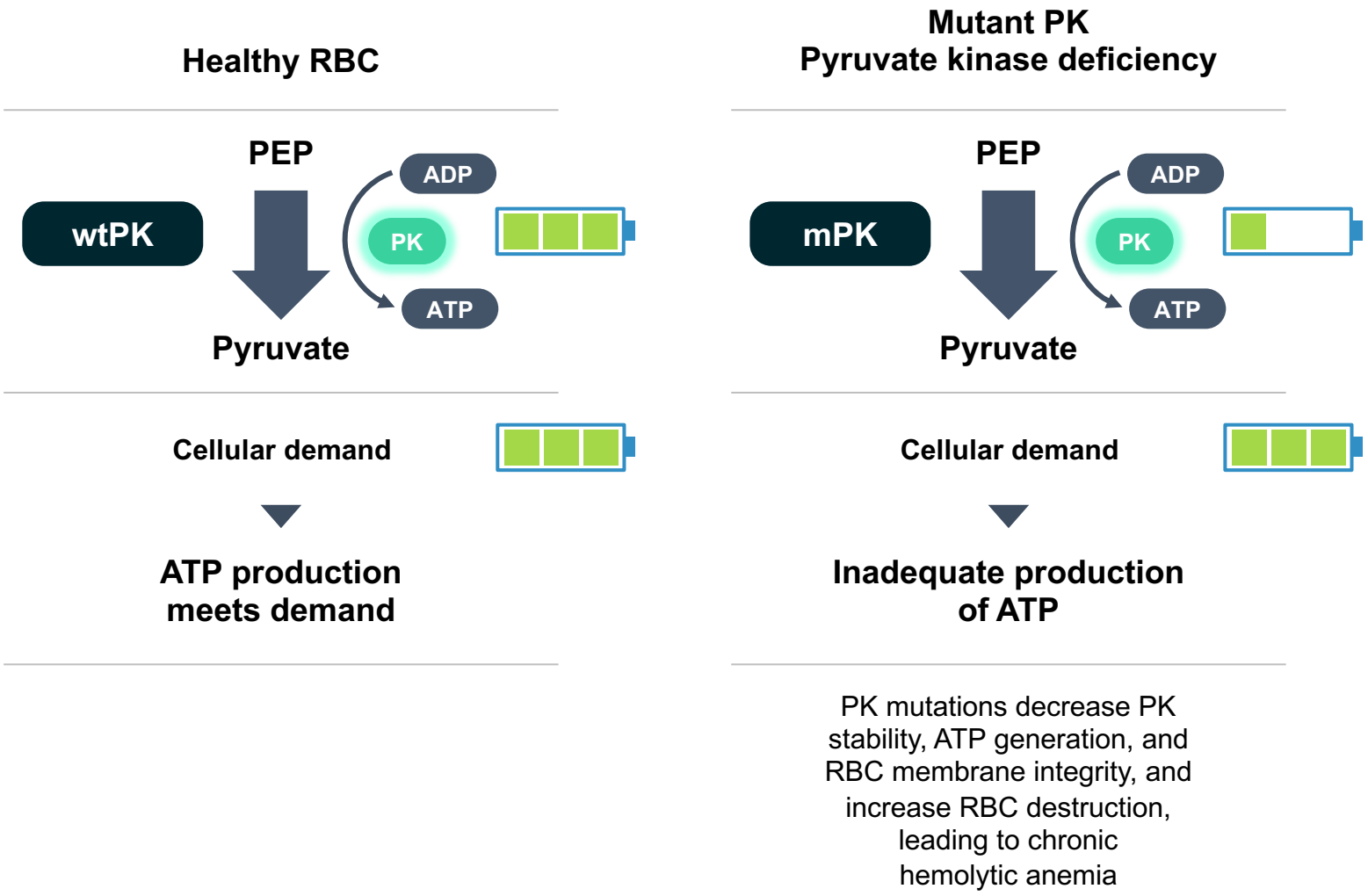


Pyruvate kinase (PK) activation represents a unique mechanism of action with the potential to address a broad range of hemolytic anemias



ADP, adenosine diphosphate; ATP, adenosine triphosphate; PEP, phosphoenolpyruvate; PK, pyruvate kinase; RBC, red blood cell; wt, wild-type.

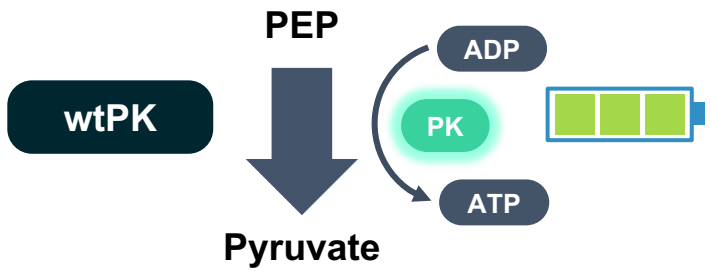
Pyruvate kinase (PK) activation represents a unique mechanism of action with the potential to address a broad range of hemolytic anemias



ADP, adenosine diphosphate; ATP, adenosine triphosphate; m, mutant; PEP, phosphoenolpyruvate; PK, pyruvate kinase; RBC, red blood cell; wt, wild-type.

Pyruvate kinase (PK) activation represents a unique mechanism of action with the potential to address a broad range of hemolytic anemias

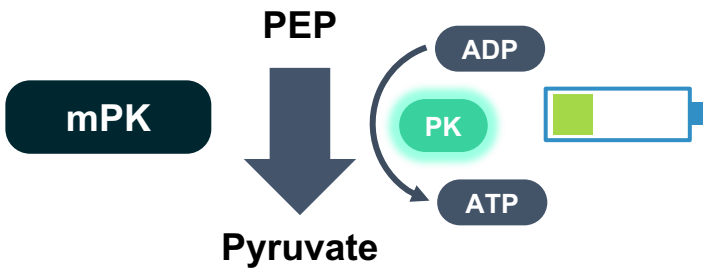
Healthy RBC



Cellular demand

ATP production meets demand

Mutant PK
Pyruvate kinase deficiency

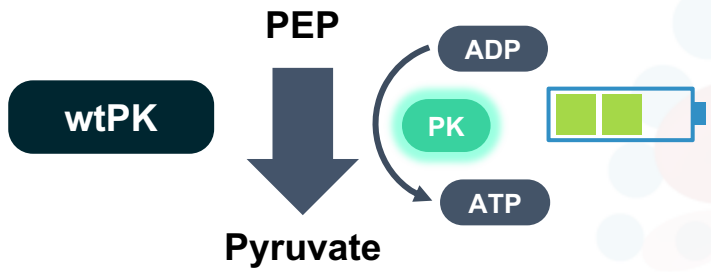


Cellular demand

Inadequate production of ATP

PK mutations decrease PK stability, ATP generation, and RBC membrate integrity and increase RBC destruction, leading to chronic hemolytic anemia

Wild-type PK
Other hemolytic anemias



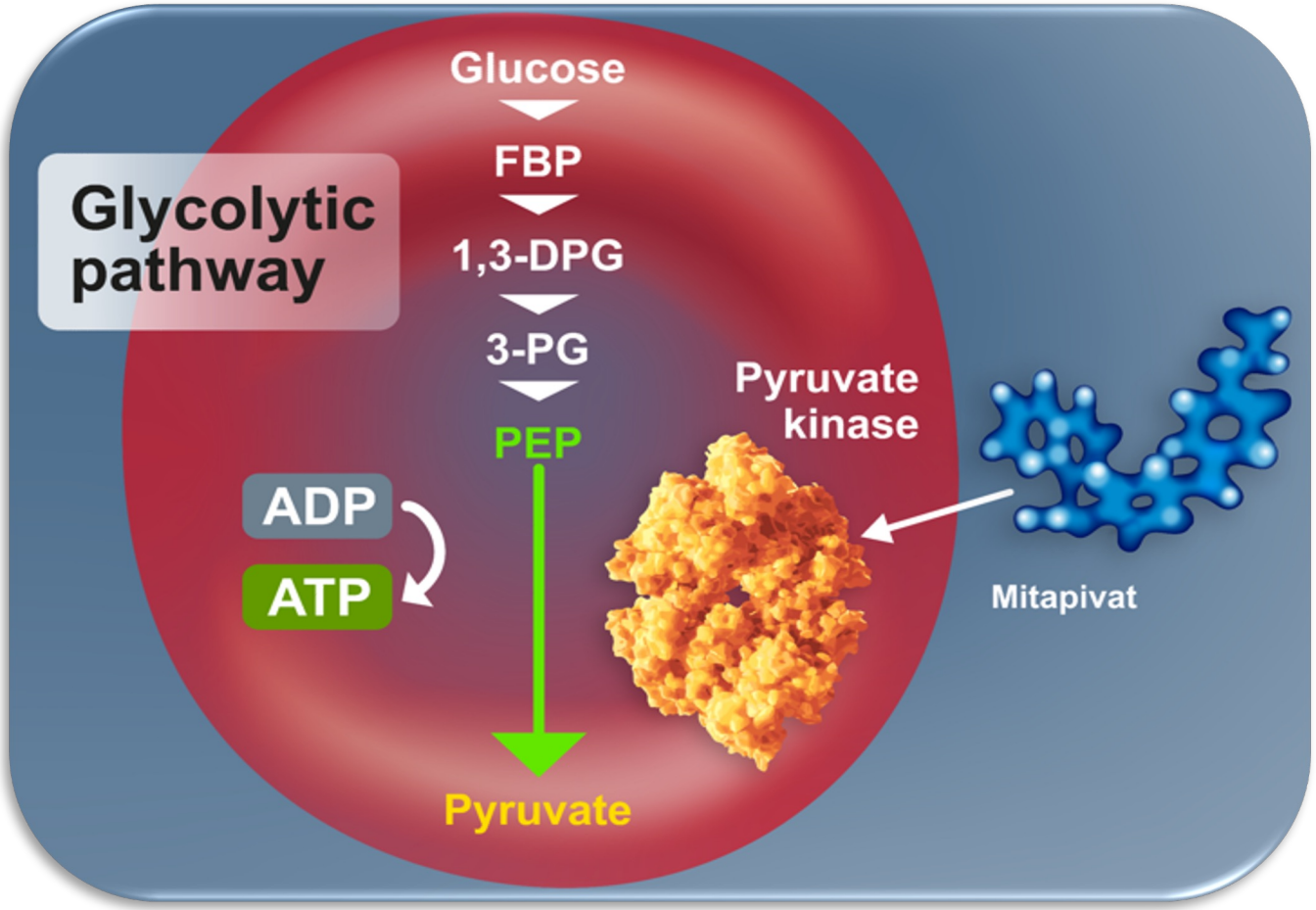
Cellular demand

Increased demand of ATP

In many other hemolytic anemias, there is an increase in ATP demand and impaired ATP production, leading to damage and premature death of RBCs, hemolysis, and anemia

ADP, adenosine diphosphate; ATP, adenosine triphosphate; m, mutant; PEP, phosphoenolpyruvate; PK, pyruvate kinase; RBC, red blood cell; wt, wild-type.

Mitapivat enhances cellular energy supply to support increased metabolic demands of thalassemic red blood cells (RBCs)

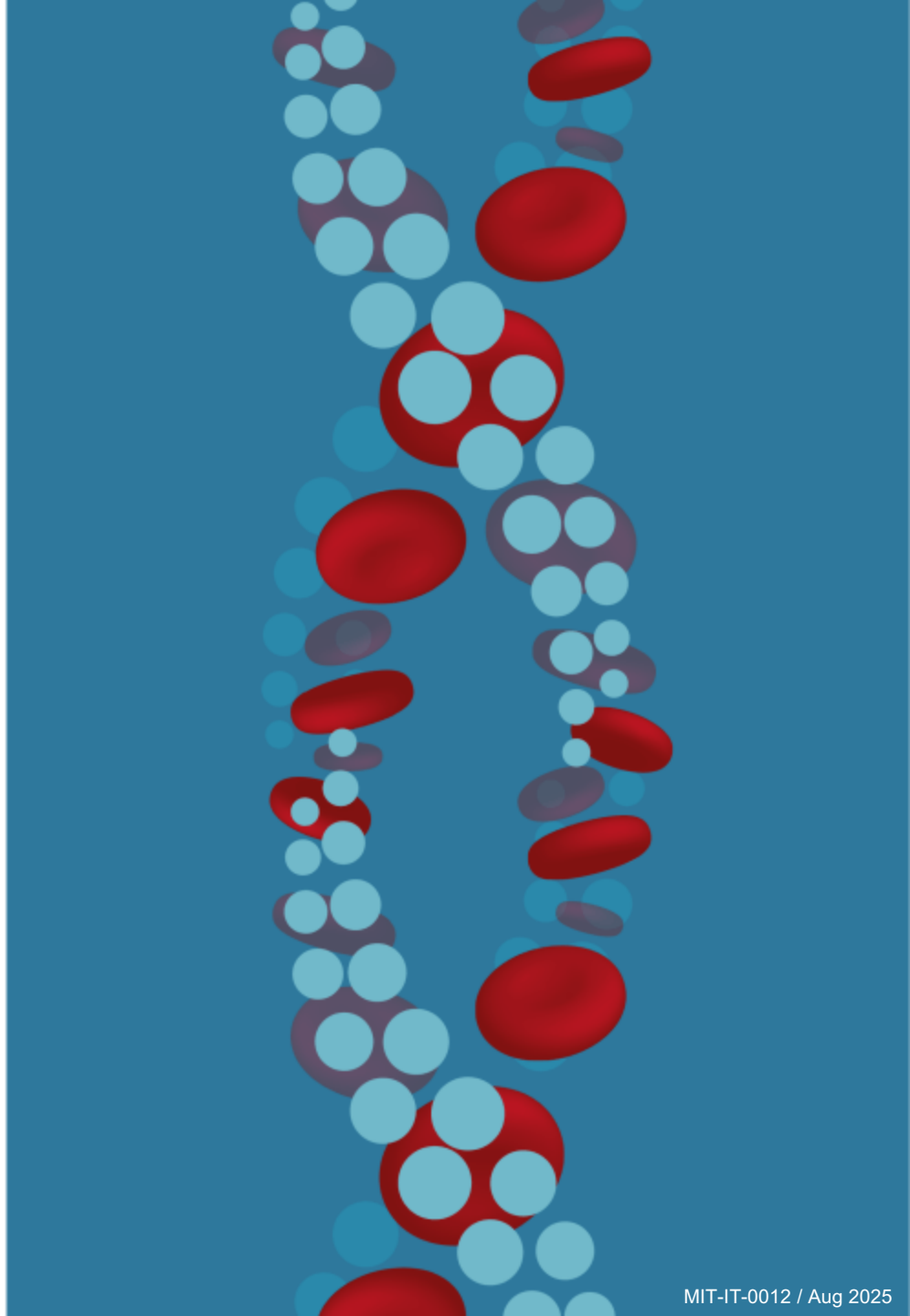


Mitapivat is an **allosteric activator** of **pyruvate kinase (PK)**, including the red cell-specific (PKR) and M2 (PKM2) isoforms, which act in glycolysis to generate ATP[1,2]

ADP, adenosine diphosphate; ATP, adenosine triphosphate; DPG, diphosphoglycerate; FBP, fructose bisphosphate; PEP, phosphoenolpyruvate; PG, phosphoglycerate; PK, pyruvate kinase; PKM2, pyruvate kinase muscle isoenzyme 2; PKR, pyruvate kinase R; RBC, red blood cell. 1. Kung C et al. Blood 2017;130:1347–56; 2. Matte A et al. J Clin Invest 2021;131:e144206.

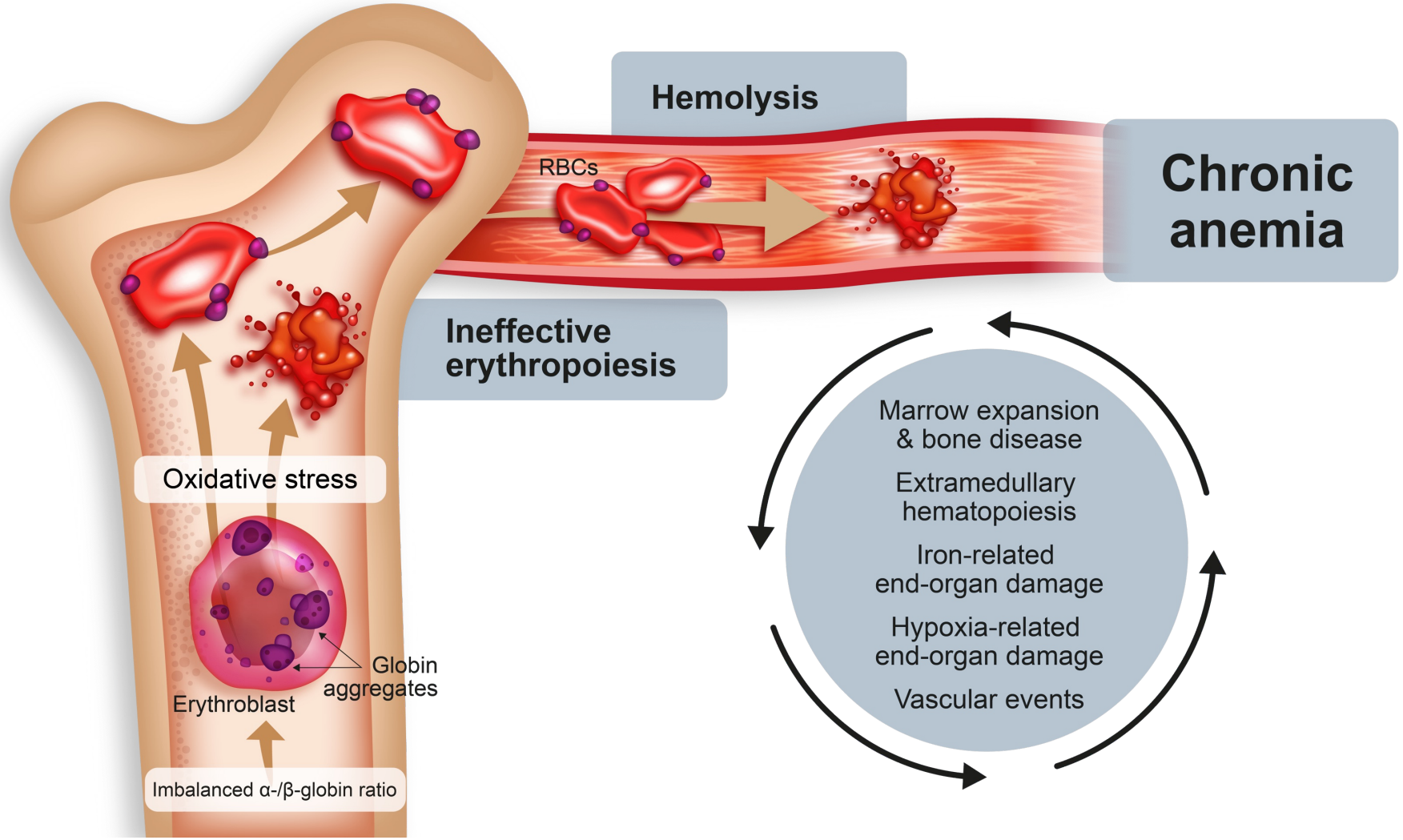
ENERGIZE Phase 3 Study

Ali T. Taher, MD, PhD, FRCP
American University of Beirut Medical Center,
Beirut, Lebanon



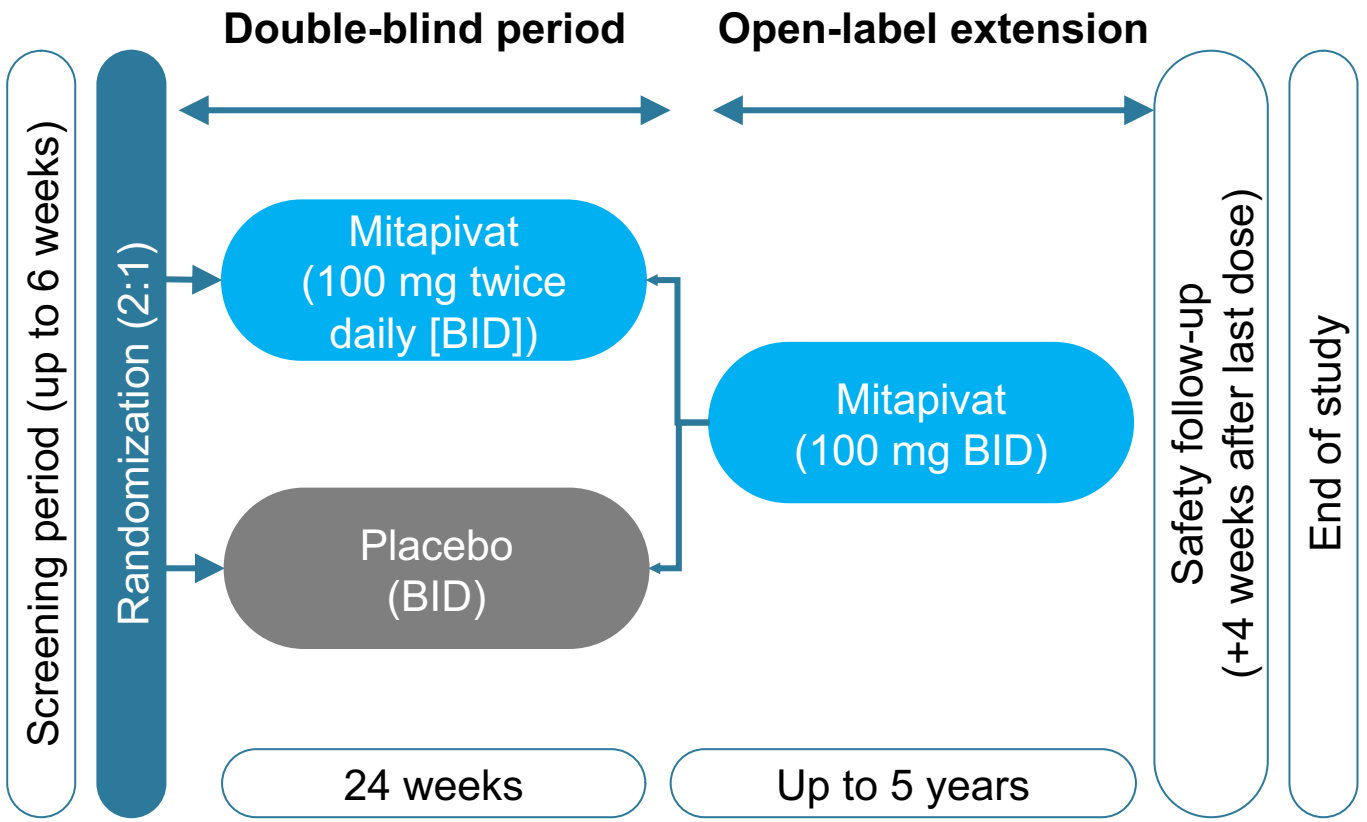
MIT-IT-0012 / Aug 2025

Pathophysiology of thalassemia



RBC, red blood cell. Taher A et al. N Engl J Med 2021;384(8):727–43.

ENERGIZE: A phase 3 study of mitapivat in adults with α- or β-NTDT



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

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)

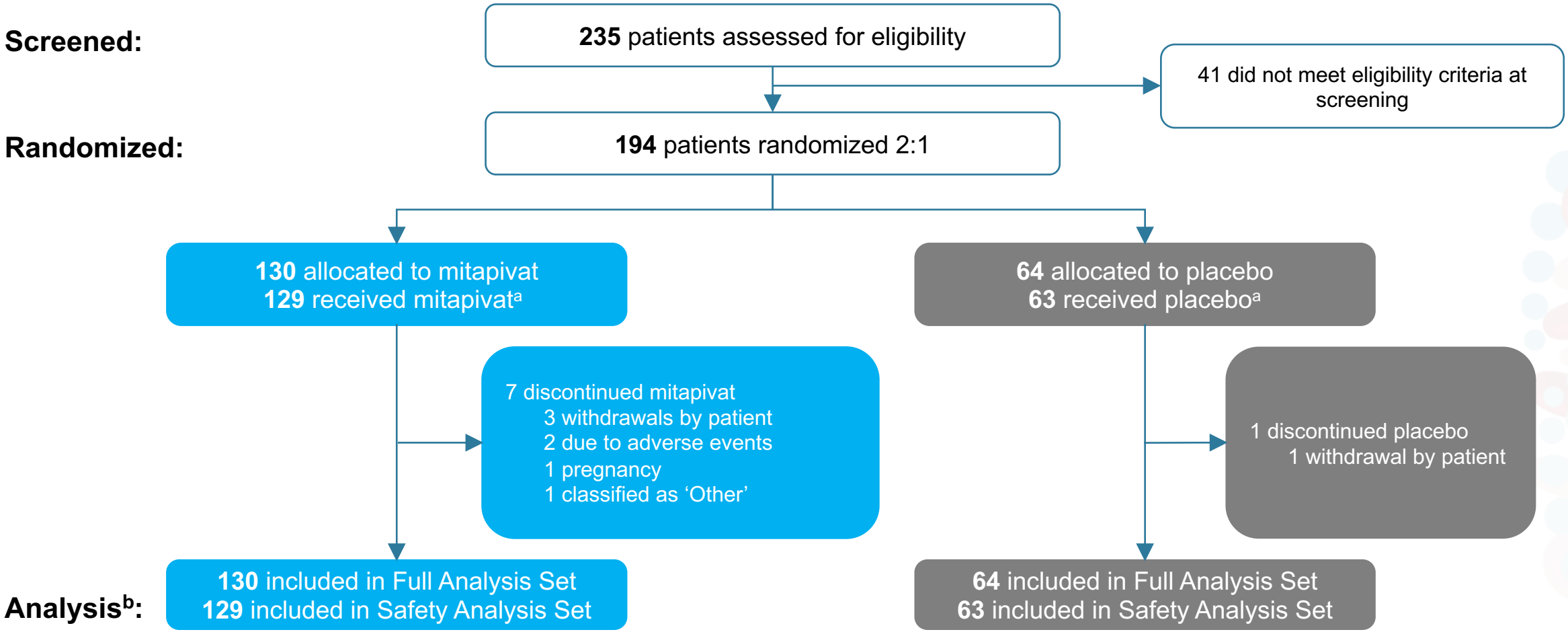
Randomization stratification factors

- 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; 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;406:33–42.

Patient flowchart: 194 patients were randomized in the study



Reprinted from The Lancet, Taher AT et al. Mitapivat in adult patients with non-transfusion-dependent α- or β-thalassaemia (ENERGIZE): a phase 3, international, randomised, double-blind, placebo-controlled trial, Copyright (2025), with permission from Elsevier. [a]One patient in each treatment arm was randomized but not dosed. [b]Full Analysis Set: all patients randomized. Patients are classified according to the randomized treatment group. Safety Analysis Set: all patients who received ≥1 dose of study treatment. If a patient randomized to placebo received ≥1 dose of mitapivat in the double-blind period, then the patient was classified to the mitapivat arm.

Taher AT et al. Lancet 2025;406:33–42.

Baseline demographics and disease characteristics were generally balanced between treatment arms

ENERGIZE

Demographics and disease characteristics	Mitapivat (N=130)	Placebo (N=64)
Age, years, mean (range)	42.4 (19–68)	38.9 (18–69)
Female, n (%)	84 (65)	39 (61)
Thalassemia type, n (%) α-thalassemia/HbH disease β-thalassemia	 42 (32) 88 (68)	 20 (31) 44 (69)
Transfusion burden[a], n (%) 0 1–2 3–5 >5	 114 (88) 10 (8) 6 (5) 0	 54 (84) 7 (11) 3 (5) 0
Previous splenectomy[b], n (%)	47 (36)	25 (39)
Previous cholecystectomy[b], n (%)	45 (35)	16 (25)
Received iron chelation[c], n (%)	46 (35)	22 (34)
Hb, mean (SD); n, g/dL	8.30 (1.08); n=130	8.39 (1.01); n=64
Indirect bilirubin, mean (SD); n, µmol/L	29.03 (24.57); n=130	27.28 (19.30); n=62
LDH, mean (SD); n, U/L	303.05 (157.16); n=130	309.15 (179.97); n=64
Haptoglobin[d], mean (SD); n, g/L	0.21 (0.26); n=127	0.29 (0.41); n=63
Reticulocyte percentage, mean (SD); n, %	7 (6); n=122	6 (5); n=58
Erythropoietin, mean (SD); n, IU/L	135.21 (222.63); n=118	197.05 (639.31); n=55

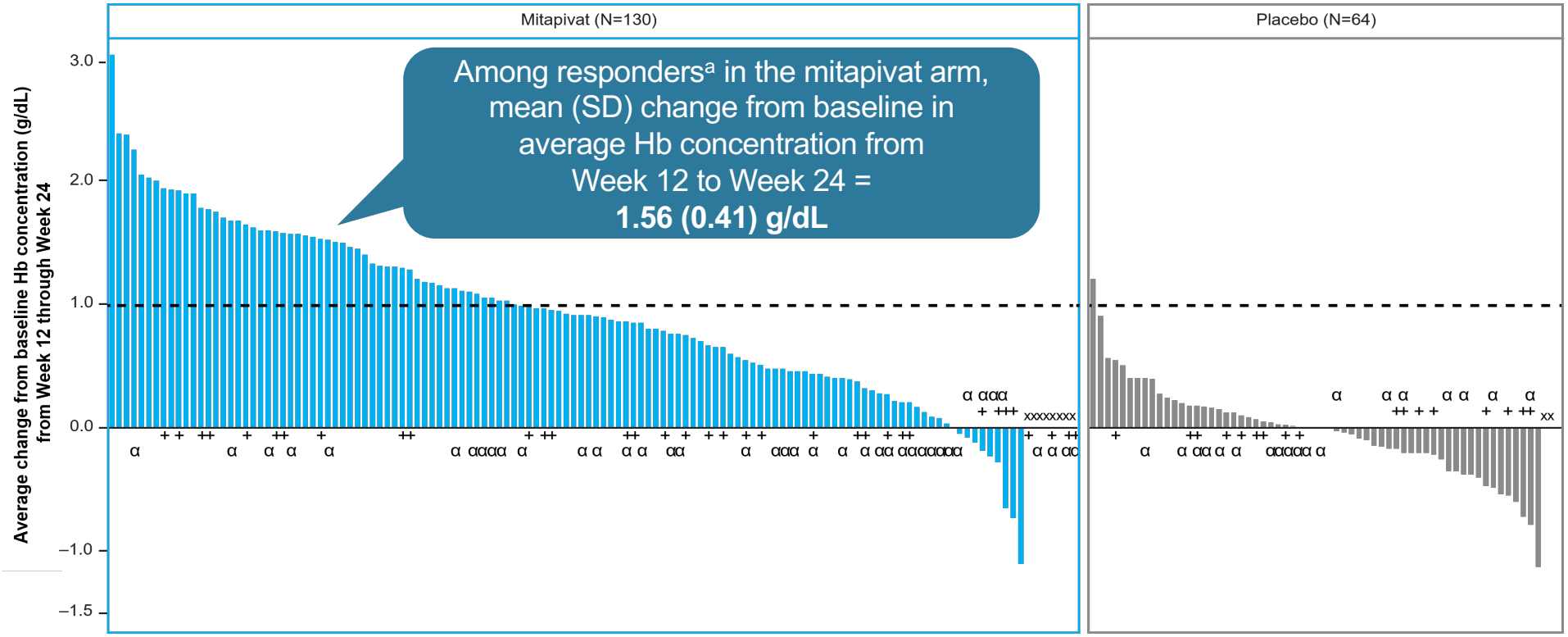
 [a]Total number of RBC units transfused in the 24-week period before randomization. [b]As recorded in medical/surgical history eCRF. [c]As recorded in disease characteristics eCRF. 'Yes' if a patient received chelation therapy within 1 year (365 days) before randomization. [d]For cases reported as '<0.1', a haptoglobin value of 0.099 was used for the summary. eCRF, electronic case report form; Hb, hemoglobin; HbH, hemoglobin H; LDH, lactate dehydrogenase; RBC, red blood cell; SD, standard deviation. Taher AT et al. Lancet 2025;406:33–42.

Mitapivat demonstrated a statistically significant improvement in Hb response[a] vs placebo

ENERGIZE

Primary endpoint

	Mitapivat N=130	Placebo N=64	2-sided p-value
Hb response, n (%)	55 (42)	1 (2)	p<0.0001



α = α-thalassemia/HbH disease

\+ = Baseline Hb category: 9.1–10 g/dL

x = Patient with missing baseline or with no assessments from Week 12 through Week 24

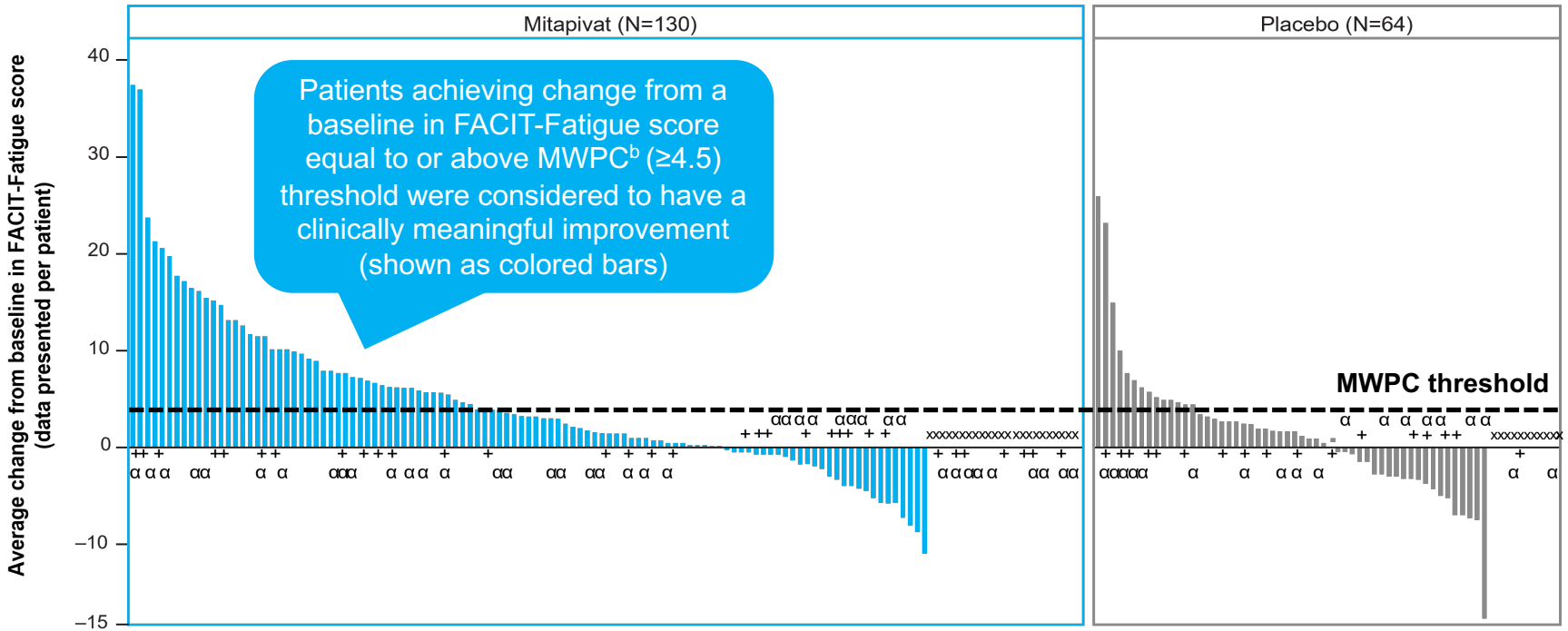
Reprinted from The Lancet, Taher AT et al. Mitapivat in adult patients with non-transfusion-dependent α- or β-thalassaemia (ENERGIZE): a phase 3, international, randomised, double-blind, placebo-controlled trial, Copyright (2025), with permission from Elsevier. Analysis conducted on Full Analysis Set. Each bar represents an individual patient in the Full Analysis Set who was randomly assigned to receive either mitapivat or placebo. [a]A Hb response was defined as an increase of ≥1.0 g/dL in average Hb concentration from Week 12 through Week 24, compared with baseline. Hb, hemoglobin; HbH, hemoglobin H; SD, standard deviation. Taher AT et al. Lancet 2025;406:33–42.

Mitapivat demonstrated a statistically significant improvement from baseline in average FACIT-Fatigue score from Weeks 12–24 vs placebo

ENERGIZE

Key secondary endpoint

	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



α = α-thalassemia/HbH disease

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x = Patient with missing baseline or with no assessments from Week 12 through Week 24

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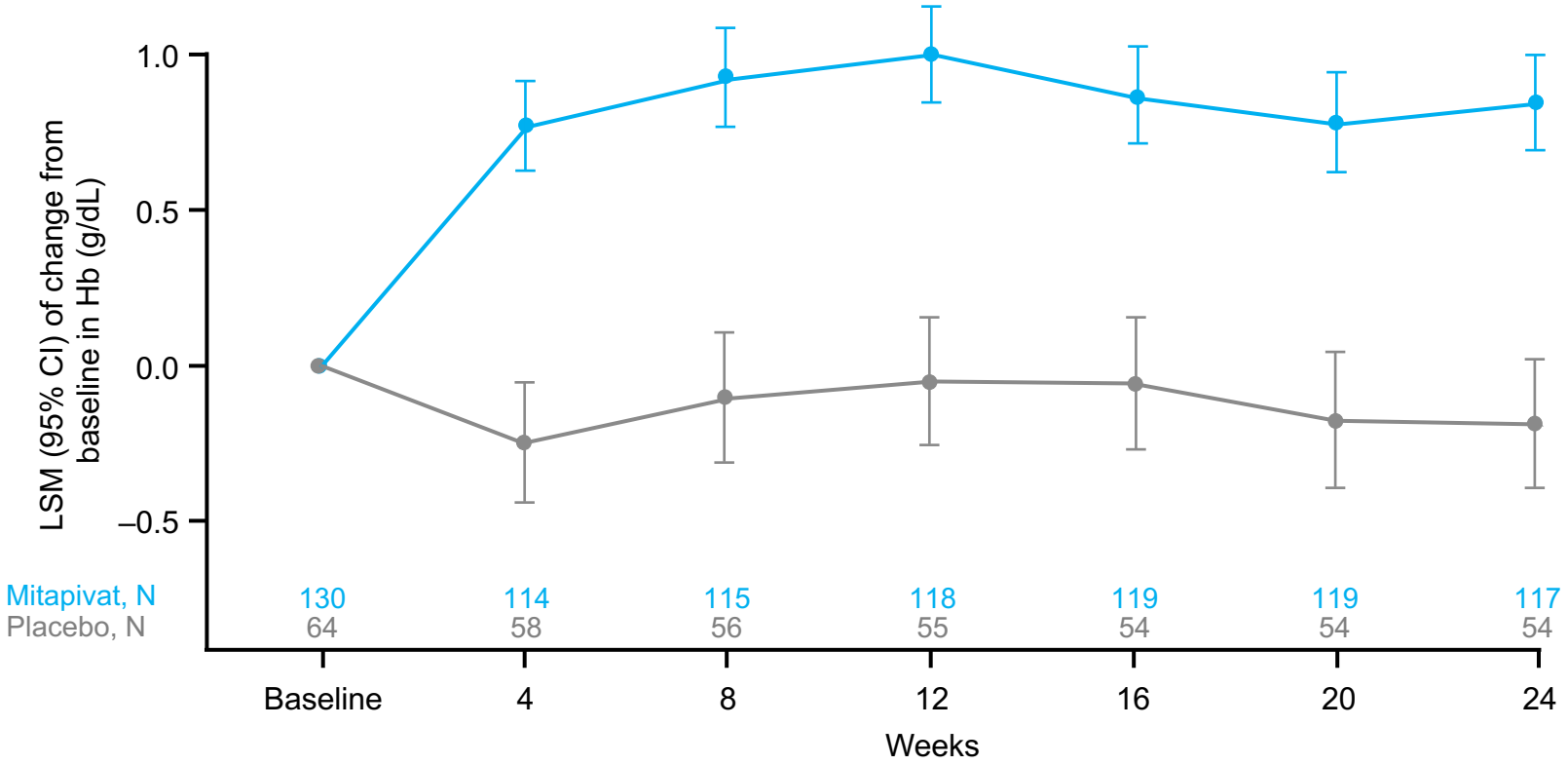
[a]In the general population, mean FACIT-Fatigue score reported in the literature was 43.6.[1] [b]Anchor-based analysis was conducted to define the threshold of FACIT-Fatigue score change associated with a meaningful change. A change of ≥4.5 points from Week 12 through Week 24 was considered clinically meaningful for a patient. CI, confidence interval; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue Scale; Hb, hemoglobin; HbH, hemoglobin H; LSM, least-squares mean; MWPC, meaningful within person change. 1. Cella D et al. Cancer 2002;94:528–38.
Taher AT et al. Lancet 2025;406:33–42.

Mitapivat demonstrated a statistically significant improvement in change from baseline in average Hb concentration from Weeks 12 to 24 vs placebo

ENERGIZE

Key secondary endpoint

	Mitapivat N=130	Placebo N=64	LSM difference	2-sided p-value
Hb, LSM (95% CI) change from baseline in average of Weeks 12 to 24, g/dL	0.86 (0.73, 0.99)	–0.11 (–0.28, 0.07)	0.96 (0.78, 1.15)	p<0.0001



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Taher AT et al. Lancet 2025;406:33–42.

Improvements in 6MWT were observed in the mitapivat arm vs placebo and exceeded minimal clinically important difference

ENERGIZE

Secondary endpoint

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[1,2]
- Patients in the mitapivat arm had greater improvements in the 6MWT than those in the placebo arm at Week 24

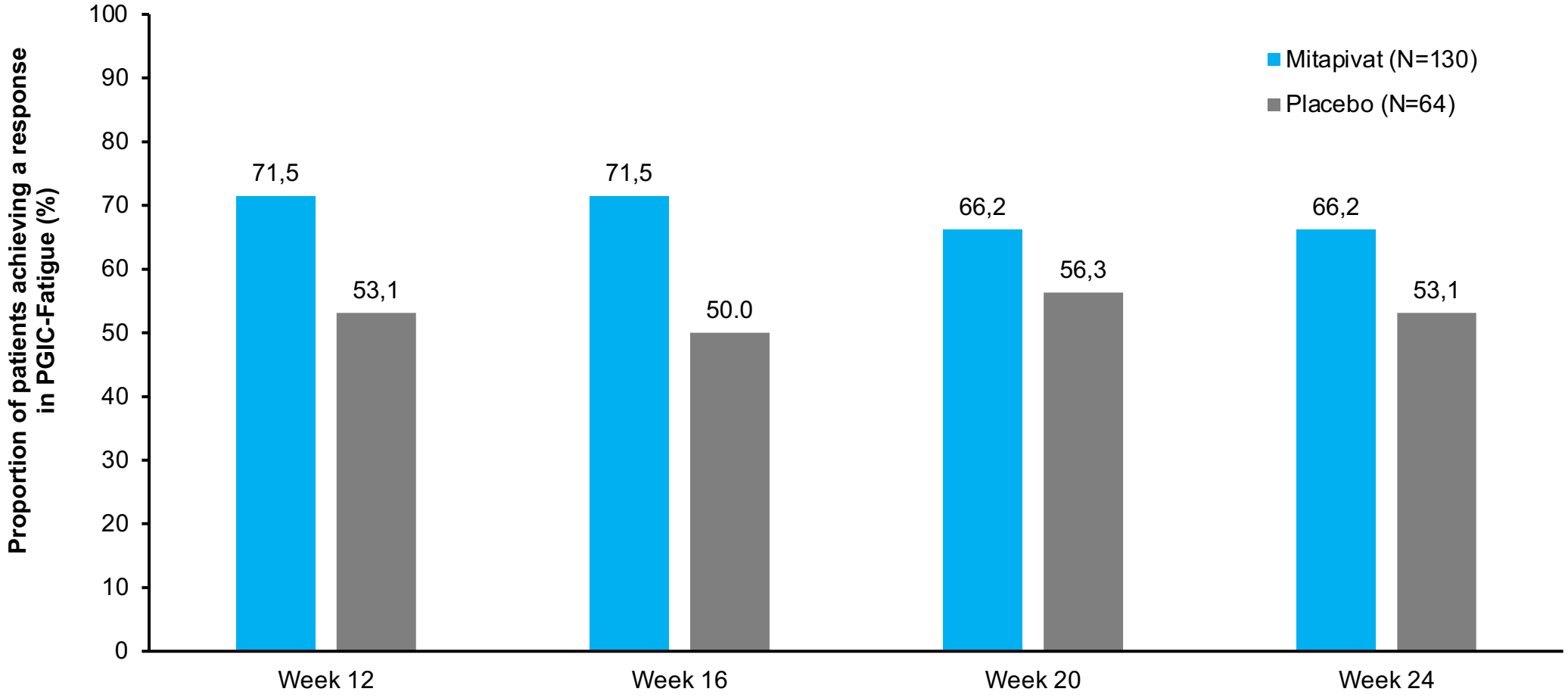
	Mitapivat (N=130)	Placebo (N=64)	LSM difference	Literature-reported MCID threshold[a]
6MWT distance at baseline, mean, m[b]	422.22	412.43	–	–
6MWT distance, LSM change from baseline to Week 24 (95% CI)[c]	30.48 (19.31, 41.64)	7.11 (–7.39, 21.62)	23.36 (6.90, 39.83)	≥20

[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.[2] [b]In healthy individuals aged 20–50 years, the mean (±SD) 6MWT distances reported in the literature were 593±57 m for females and 638±44 for males.[1] [c]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; CI, confidence interval; LSM, least-squares mean; MCID, minimal clinically important difference; SD, standard deviation. 1. St. Lezin E et al. Transfusion 2019;59:1934–43; 2. Chetta A et al. Respir Med 2006;100:1573–78.
Taher AT et al. Lancet 2025;406:33–42.

A higher proportion of patients receiving mitapivat reported improvements in fatigue as per PGIC vs those receiving placebo[a]

ENERGIZE

Secondary endpoint



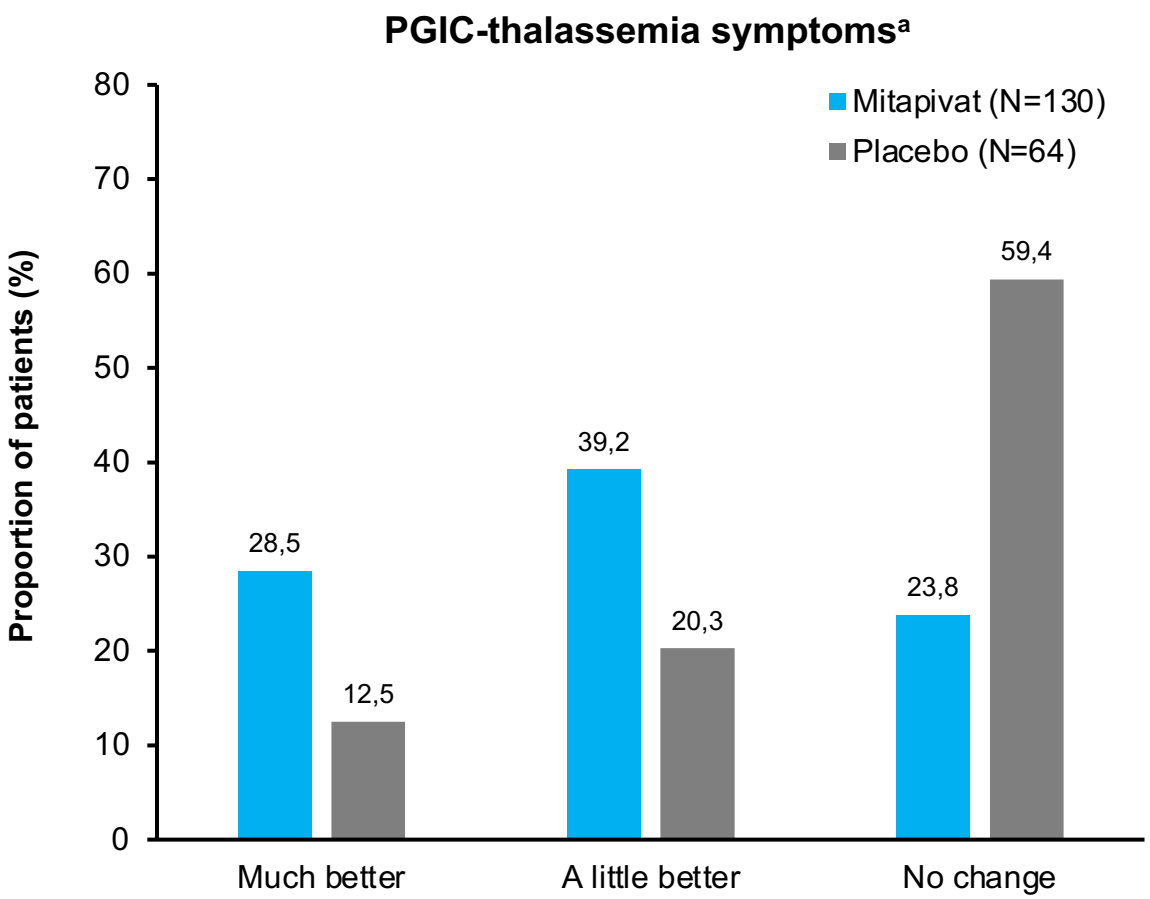
A patient was considered to have achieved a response at each visit if their baseline PGIS and corresponding PGIC met one of the following conditions: if the PGIS at baseline was 'None' or 'Mild', and PGIC at the visit was 'No Change', 'A Little Better', or 'Much Better'; if the PGIS at baseline was 'Moderate'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

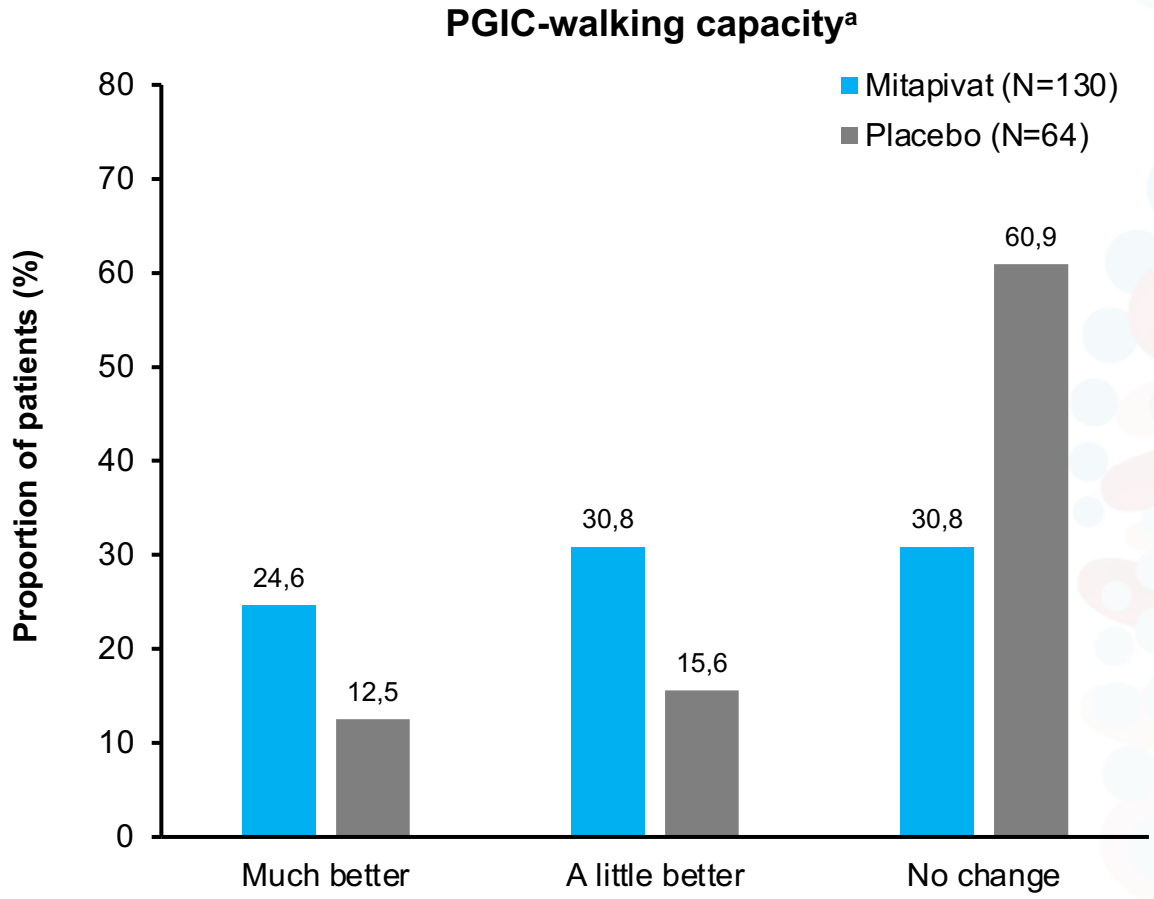
Kuo KHM et al. Poster presentation at the European Hematology Association Congress 2024, Madrid.

A higher proportion of patients receiving mitapivat reported improvements in thalassemia symptoms and walking capacity as per PGIC

ENERGIZE

Secondary endpoint





[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.
Kuo KHM et al. Poster presentation at the European Hematology Association Congress 2024, Madrid.

Summary of safety

Safety

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

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AE, adverse event; LDH, lactate dehydrogenase. Taher AT et al. Lancet 2025;406:33–42.

Most frequently reported (≥10%) AEs

Preferred term, n (%)	Mitapivat (N=129)	Placebo (N=63)
Headache		
Any Grade	29 (22)	6 (10)
Grade ≥3	0	0
Initial insomnia[a]		
Any Grade	18 (14)	3 (5)
Grade ≥3	1 (1)	0
Nausea		
Any Grade	15 (12)	5 (8)
Grade ≥3	0	0
Upper respiratory tract infection		
Any Grade	14 (11)	4 (6)
Grade ≥3	0	0

Reprinted from The Lancet, Taher AT et al. Mitapivat in adult patients with non-transfusion-dependent α- or β-thalassaemia (ENERGIZE): a phase 3, international, randomised, double-blind, placebo-controlled trial, Copyright (2025), with permission from Elsevier. Analysis conducted on Safety Analysis Set. Summarized in order of decreasing frequency of patients with events based on the frequencies observed in any Grade for the 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 AEs, 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 Event on a 5-point severity scale (Grades 1–5). [a]Initial insomnia refers to insomnia that occurs early during the course of a night (ie, difficulty initiating sleep). AE, adverse event.

Taher AT et al. Lancet 2025;406:33–42.

ENERGIZE[1]: Summary

- This was the first global phase 3 study to enroll patients with α-thalassemia in addition to β-thalassemia[1]
- The primary endpoint and key secondary endpoints were met, with statistically significant improvements in Hb and fatigue with mitapivat vs placebo[1]
- Functional improvement in patients with mitapivat, measured by the 6MWT, exceeded a previously reported meaningful change threshold from the literature[1–3]
- A higher proportion of patients reported improved fatigue, disease symptoms, and walking capacity via PGIC with mitapivat vs placebo[3]
- The most frequently reported AEs with mitapivat were headache, initial insomnia, nausea, and upper respiratory tract infection[1]
- Mitapivat was generally well tolerated in this study, with a low treatment discontinuation rate[1]

6MWT, 6-minute walk test; AE, adverse event; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue Scale; Hb, hemoglobin; PGIC, Patient Global Impression of Change.

1. Taher AT et al. Lancet 2025;406:33–42; 2. St. Lezin E et al. Transfusion 2019;59:1934–43;
3. Kuo KHM et al. Poster presentation at the European Hematology Association Congress 2024, Madrid.

ENERGIZE-T Phase 3 Study

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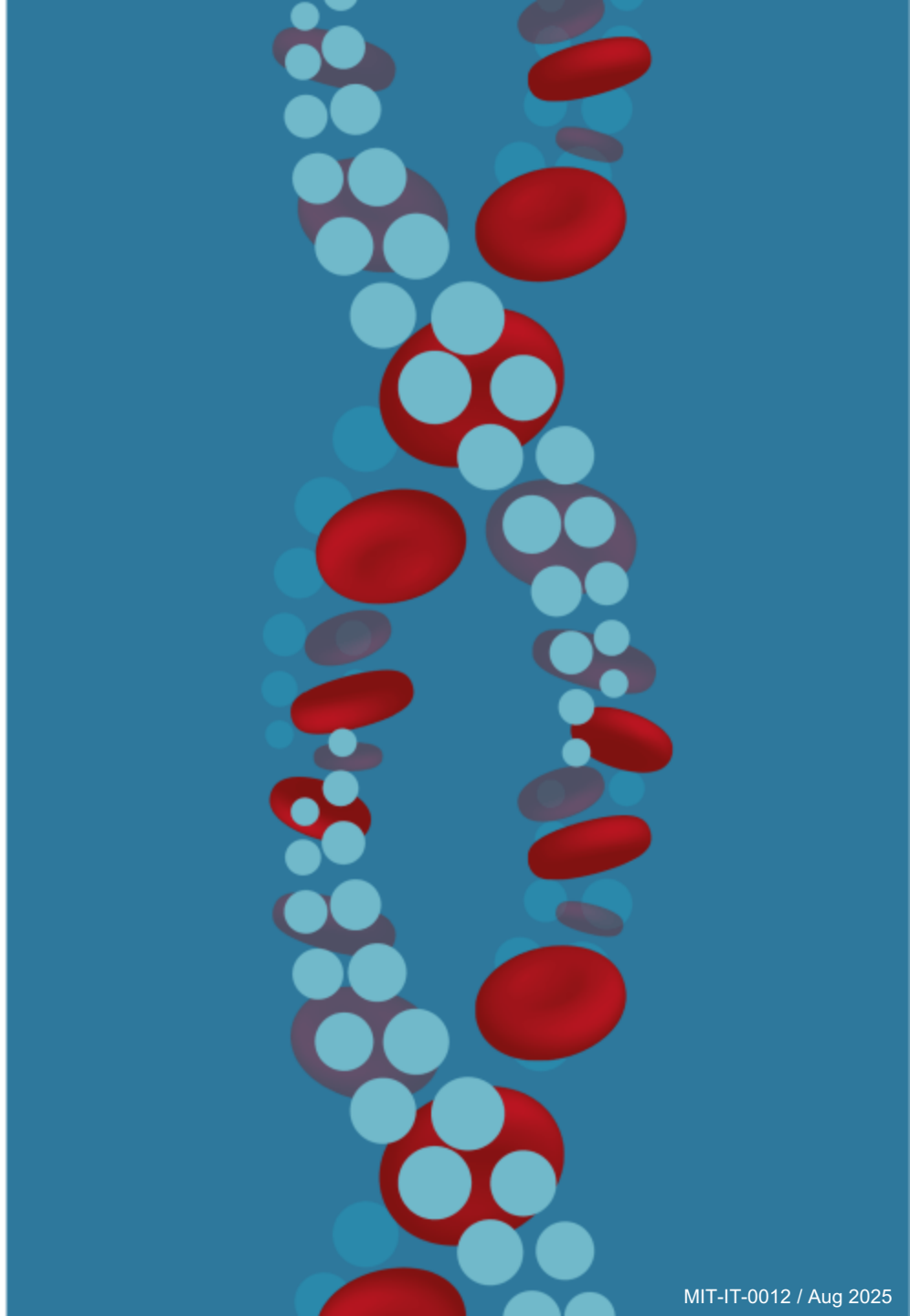
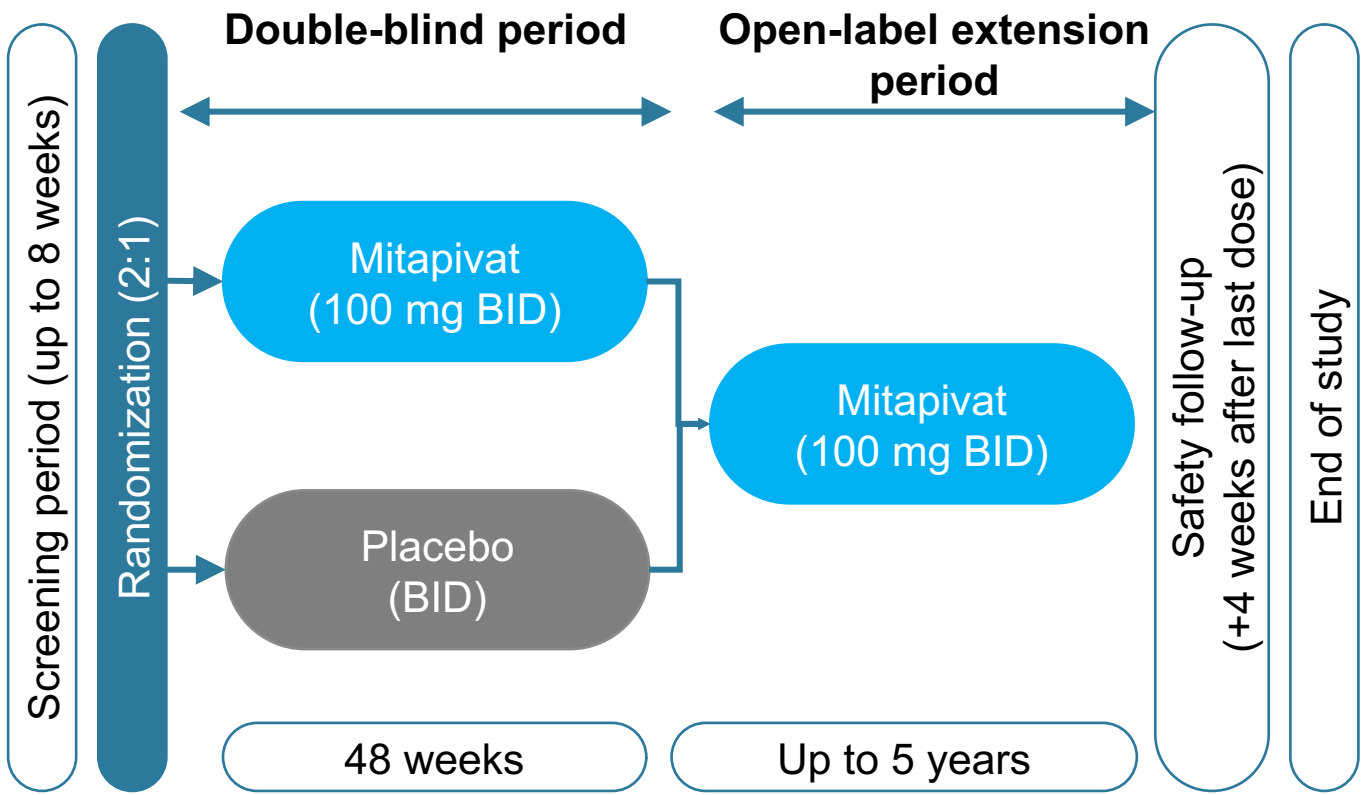


MIT-IT-0012 / Aug 2025

ENERGIZE-T: A phase 3 study of mitapivat in adults with transfusion-dependent α- or β-thalassemia



Primary endpoint: *Transfusion reduction response (TRR), defined as a ≥50% reduction in transfused RBC units and a reduction in ≥2 units of transfused RBCs in any consecutive 12-week period through Week 48 compared with baseline*

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)

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 the rest of the world)

BID, twice daily; Hb, hemoglobin; HbC, hemoglobin C; HbE, hemoglobin E; HbH, hemoglobin H; HbS, hemoglobin S; RBC, red blood cell; TRR, transfusion reduction response.

ClinicalTrials.gov: ENERGIZE-T (NCT04770779). Accessed Nov 2024. Cappellini MD et al. Oral presentation at the American Society of Hematology Annual Meeting and Exposition 2024, San Diego.

Endpoints

Primary endpoint:

- Transfusion reduction response (TRR), defined as a ≥50% reduction in transfused RBC units and a reduction in ≥2 units of transfused RBCs in any consecutive 12-week period through Week 48 compared with baseline

Key secondary endpoints:

- TRR2, defined as a ≥50% reduction in transfused RBC units in any consecutive 24-week period through Week 48 compared with baseline
- TRR3, defined as a ≥33% reduction in transfused RBC units from Week 13 through Week 48 (fixed 36-week period) compared with baseline
- TRR4, defined as a ≥50% reduction in transfused RBC units from Week 13 through Week 48 (fixed 36-week period) compared with baseline

Other secondary efficacy endpoints included:

- Transfusion independence, defined as transfusion-free for ≥8 consecutive weeks through Week 48

Safety endpoints:

- Type, severity, and relationship of adverse events and serious adverse events

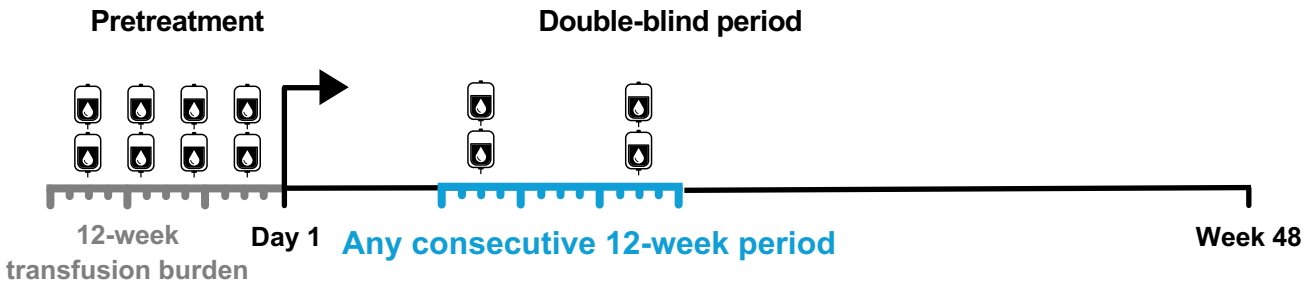
RBC, red blood cell; TRR, transfusion reduction response. Cappellini MD et al. Oral presentation at the American Society of Hematology Annual Meeting and Exposition 2024, San Diego.

Primary and key secondary endpoints[a]

KEY	
	= Units of RBCs transfused
	= Start of treatment

Primary endpoint:

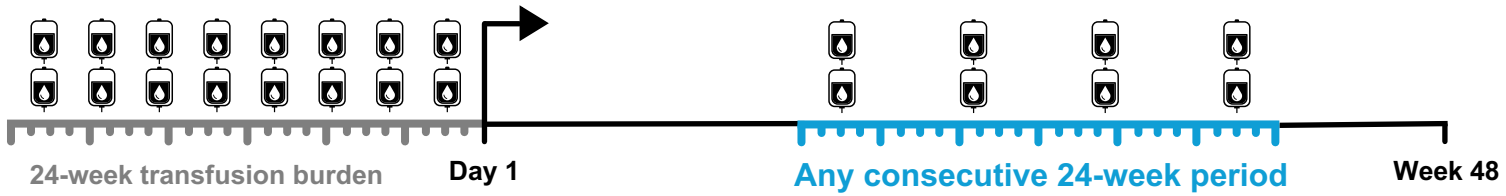
Transfusion reduction response (TRR)



≥50% reduction + ≥2 units reduction

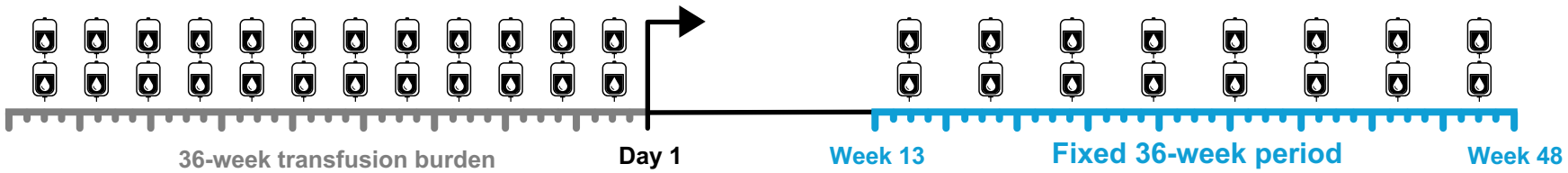
Key secondary endpoints:

TRR2



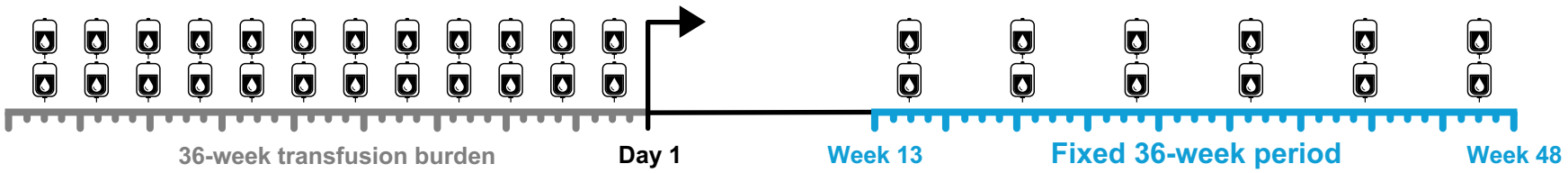
≥50% reduction

TRR3



≥33% reduction

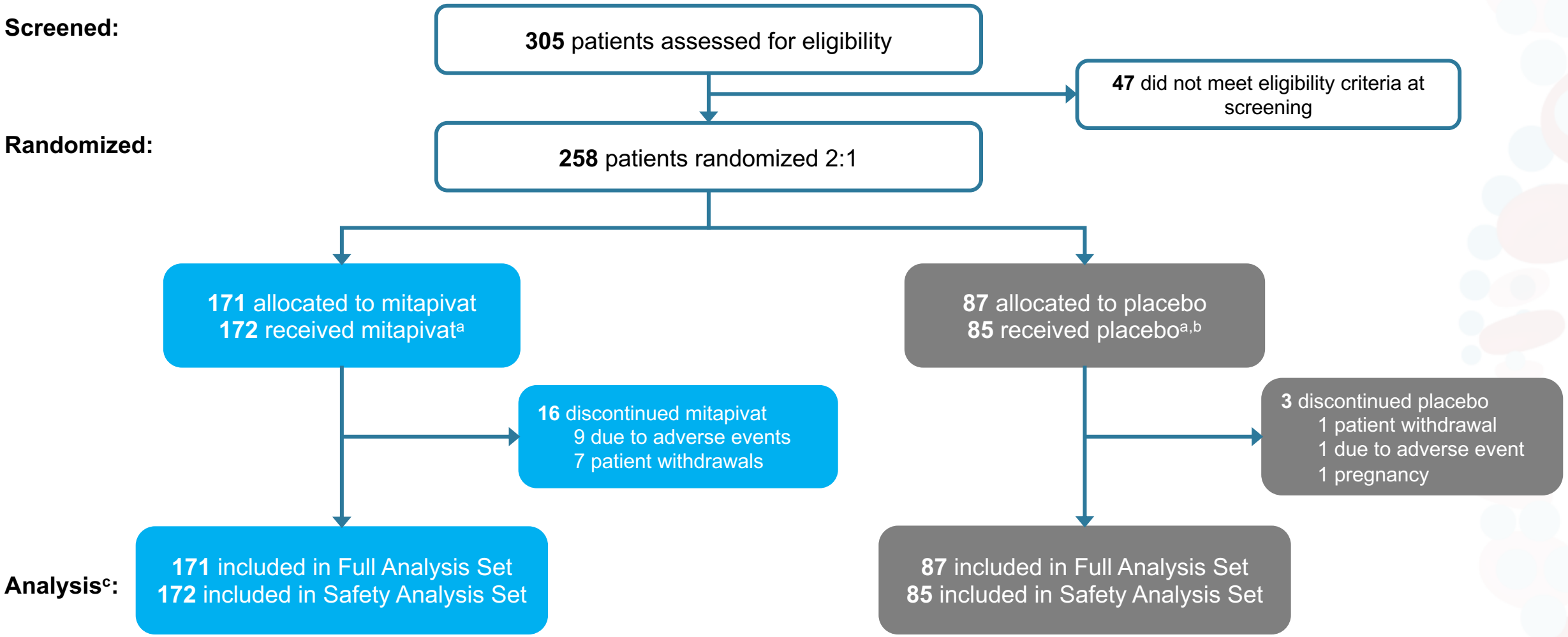
TRR4



≥50% reduction

[a]Visuals shown on this slide do not depict actual data and are shown for illustrative purposes only. RBC, red blood cell; TRR, transfusion reduction response.
Cappellini MD et al. Oral presentation at the American Society of Hematology Annual Meeting and Exposition 2024, San Diego.

Patient disposition: 258 patients were randomized in the study



[a]One patient, randomized to placebo, received mitapivat and was classified in the mitapivat group in the Safety Analysis Set. [b]One patient was randomized but not dosed. [c]Full Analysis Set: All patients randomized. Patients were classified according to the randomized treatment group. Safety Analysis Set: All patients who received ≥1 dose of study treatment. If a patient randomized to placebo received ≥1 dose of mitapivat in the double-blind period, then the patient was classified to the mitapivat group.

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Baseline demographics and disease characteristics

Demographics and disease characteristics	Mitapivat (N=171)	Placebo (N=87)
Age, mean (SD), years	35.8 (11.6)	34.7 (9.8)
Female, n (%)	93 (54.4)	43 (49.4)
Race, n (%)		
White	99 (57.9)	56 (64.4)
Asian	56 (32.7)	22 (25.3)
Black or African American	1 (0.6)	1 (1.1)
Multi-racial	2 (1.2)	0 (0.0)
Unknown	7 (4.1)	3 (3.4)
Not reported	6 (3.5)	5 (5.7)
Thalassemia genotype, n (%)		
Non-β^0/β^0 [a]	96 (56.1)	48 (55.2)
β^0/β^0 [b]	75 (43.9)	39 (44.8)
24-week transfusion burden[c], n (%)		
≤12 RBC units	54 (31.6)	21 (24.1)
>12 RBC units	117 (68.4)	66 (75.9)
Pretransfusion Hb threshold[d], median (range), g/dL	9.0 (5.1–11.8)	8.9 (5.1–10.9)
Prior splenectomy[e], n (%)	92 (53.8)	49 (56.3)
Received iron chelation in prior year[f], n (%)	165 (96.5)	87 (100.0)
Geographic region, n (%)		
North America and Europe	106 (62.0)	54 (62.1)
Asia-Pacific	31 (18.1)	16 (18.4)
Rest of the world[g]	34 (19.9)	17 (19.5)

No statistical comparisons were made between treatment groups for baseline demographics and disease characteristics. [a]Patients who do not have a β^0 mutation at both alleles of the β-globin gene including patients with HbE/β-thalassemia and α-thalassemia/HbH disease. [b]Patients who have a β^0 mutation at both alleles of the β-globin gene. [c]Total number of RBC units transfused in the 24-week period before randomization. [d]Pretransfusion Hb threshold was defined as the mean of all documented pretransfusion Hb concentration values recorded for the RBC transfusions administered during the 24-week period before randomization. [e]As recorded in medical/surgical history eCRF. [f]As recorded in disease characteristics eCRF. 'Yes' if a patient received chelation therapy within 1 year (365 days) before randomization. [g]Rest of the world included Latin America and the Middle East. eCRF, electronic case report form; Hb, hemoglobin; HbE, hemoglobin E; HbH, hemoglobin H; RBC, red blood cell; SD, standard deviation.

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Mitapivat met the primary endpoint and demonstrated a statistically significant reduction in transfusion burden vs placebo

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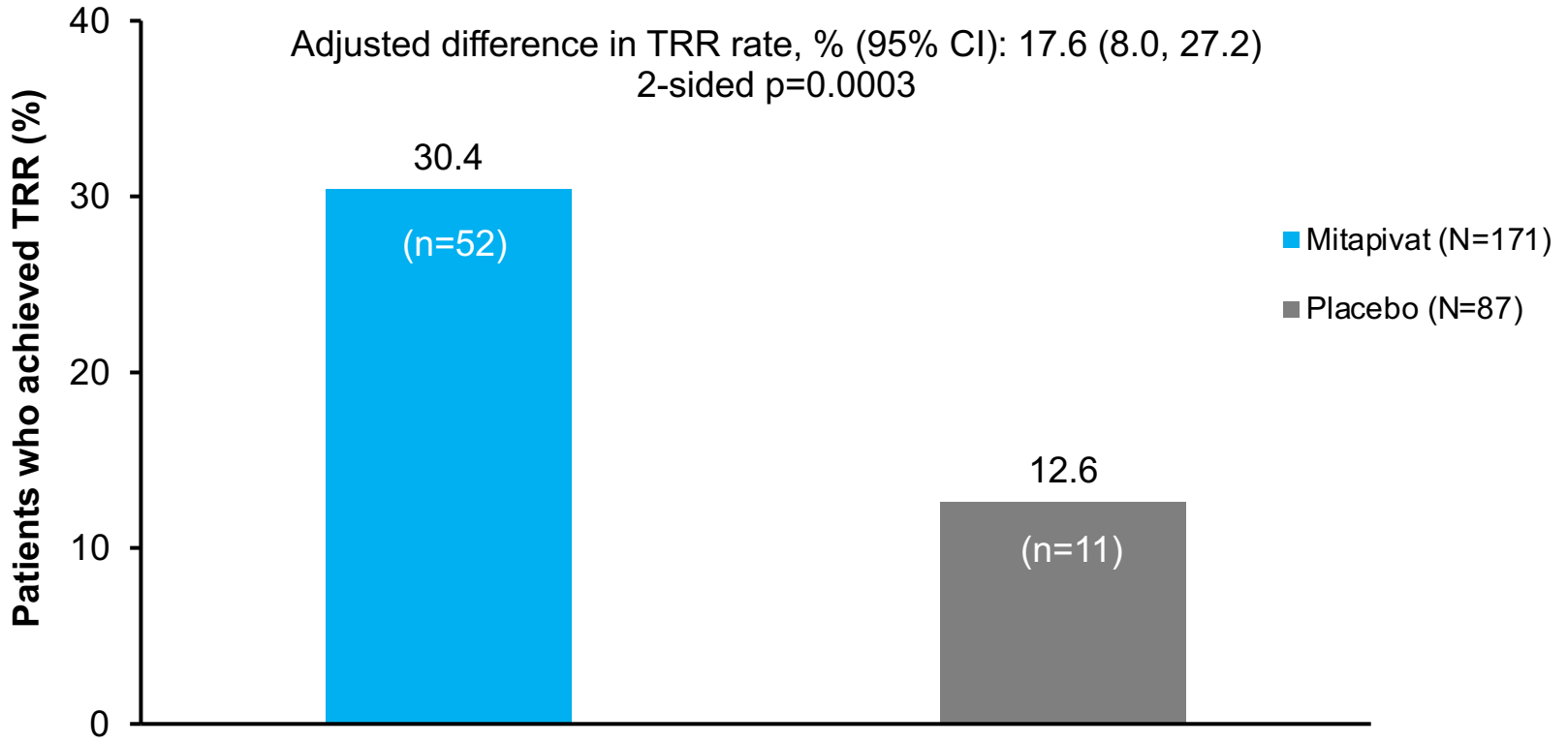
Primary endpoint



TRR was defined as a ≥50% reduction in transfused RBC units and a reduction in ≥2 units of transfused RBCs in any consecutive 12-week period through Week 48 compared with baseline

Analysis conducted on Full Analysis Set. Baseline transfusion burden standardized to 12 weeks=total number of RBC units transfused during the 24-week period (168 days) before 'reference date' ×12/24, where 'reference date' is the randomization date for subjects randomized and not dosed or the start of study treatment for subjects randomized and dosed. Subjects withdrawn from the study before Week 12 (Day 85) are considered non-responders. CI, confidence interval; RBC, red blood cell; TRR, transfusion reduction response.

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Mitapivat also demonstrated statistically significant reductions in transfusion burden vs placebo as measured by all key secondary endpoints

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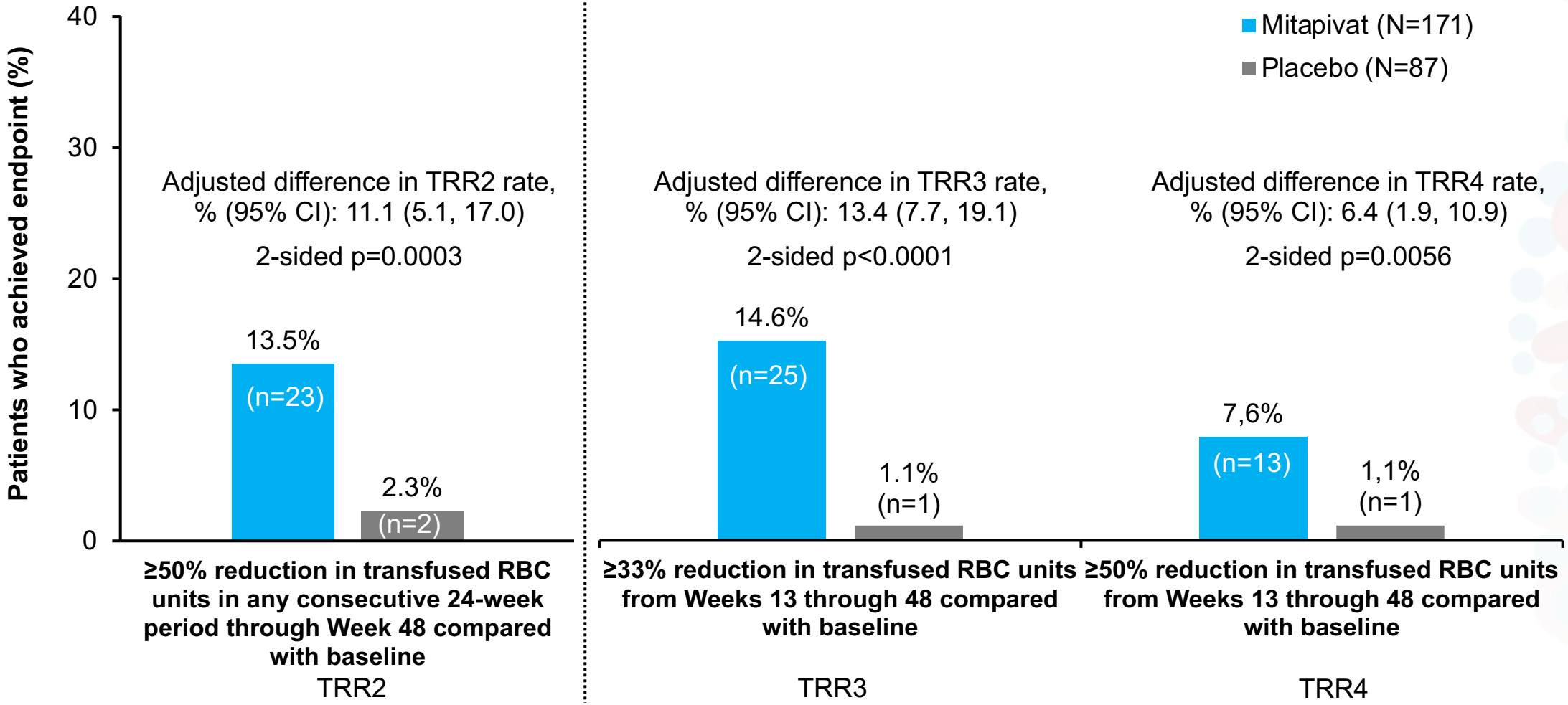
Key secondary endpoints



Analysis conducted on Full Analysis Set. 24-week baseline transfusion burden=total number of RBC units transfused during the 24-week period before 'reference date', where 'reference date' is the randomization date for patients randomized and not dosed or the start of study treatment for patients randomized and dosed. Patients withdrawn from the study before Week 24/Week 48 were considered non-responders for TRR2, TRR3, and TRR4, respectively (per protocol). CI, confidence interval; RBC, red blood cell; TRR, transfusion reduction response.

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A higher proportion of patients in the mitapivat group achieved transfusion independence vs placebo

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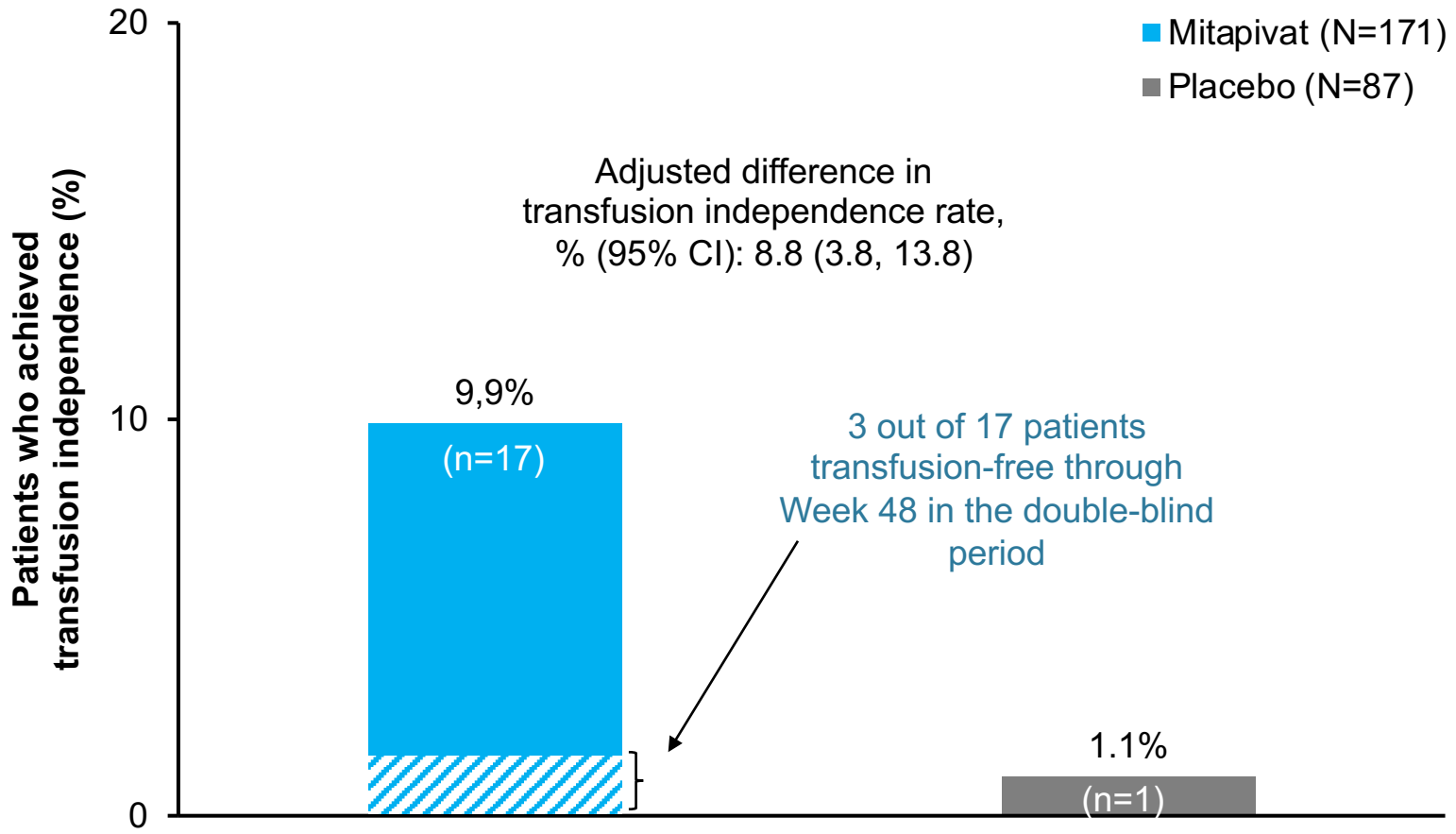
Secondary endpoint



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

Analysis conducted on Full Analysis Set. CI, confidence interval.

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Summary of safety

Safety

Patients, n (%)	Mitapivat (N=172)	Placebo (N=85)
Any TEAEs	155 (90.1)	71 (83.5)
Grade ≥3 TEAEs	32 (18.6)	12 (14.1)
Treatment-related TEAEs	65 (37.8)	16 (18.8)
Grade ≥3 treatment-related TEAEs	13 (7.6)	1 (1.2)
Serious TEAEs	19 (11.0)[a]	13 (15.3)[b]
Serious treatment-related TEAEs	4 (2.3)	1 (1.2)
TEAEs leading to discontinuation of study drug	10 (5.8)[c]	1 (1.2)[d]
TEAEs leading to dose reduction	20 (11.6)	2 (2.4)
TEAEs leading to interruption of study drug	13 (7.6)	5 (5.9)
TEAEs leading to death	0 (0.0)	0 (0.0)

Analysis conducted on Safety Analysis Set. CTCAE v4.03 used. [a]Serious TEAEs with mitapivat were gastroenteritis (in 2 patients), pneumonia, COVID-19 pneumonia, cellulitis, dengue fever, influenza, lower respiratory tract infection, hypersplenism, mesenteric lymphadenitis, pancytopenia, cholecystitis, acute cholecystitis, supraventricular arrythmia, supraventricular tachycardia, radius fracture, proctitis, asthenia, hepatic cancer, dizziness, renal mass, and ruptured ovarian cyst (all in 1 patient each). [b]Serious TEAEs with placebo were pneumonia (in 2 patients), viral infection, splenic hematoma, cholecystitis, acute cholecystitis, acute cholangitis, arrhythmia, left ventricular dysfunction, infusion-related reaction, cataract, increased blood creatine phosphokinase, limb deformity, spontaneous abortion, and pulmonary hypertension (all in 1 patient each). [c]The TEAEs leading to discontinuation of mitapivat, each of which occurred in 1 patient, were diarrhea, paresthesia oral, concurrent anxiety and insomnia, initial insomnia, supraventricular tachycardia, fatigue, hypertransaminasemia, hepatitis C, hepatic cancer, and renal mass. [d]The TEAE that led to discontinuation of the 1 patient on placebo was blood creatine phosphokinase increased. CTCAE, Common Terminology Criteria for Adverse Event; TEAE, treatment-emergent adverse event.

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Most frequently reported (≥10%) TEAEs

Safety

	Mitapivat (N=172)		Placebo (N=85)	
Preferred Term, n (%)	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Headache	46 (26.7)	0 (0.0)	10 (11.8)	0 (0.0)
Upper respiratory tract infection	27 (15.7)	0 (0.0)	14 (16.5)	0 (0.0)
Initial insomnia	24 (14.0)	3 (1.7)	4 (4.7)	0 (0.0)
Diarrhea	19 (11.0)	0 (0.0)	7 (8.2)	0 (0.0)
Fatigue	18 (10.5)	0 (0.0)	2 (2.4)	0 (0.0)

Analysis conducted on Safety Analysis Set. Summarized in order of decreasing frequency of patients with events based on the frequencies observed in any Grade for the mitapivat group. CTCAE v4.03 used. CTCAE, Common Terminology Criteria for Adverse Event; TEAE, treatment-emergent adverse event.

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ENERGIZE-T: Summary

- The primary and all key secondary endpoints of the study were met; mitapivat led to significant reductions in transfusion burden, with durability of response up to 36 weeks during the 48-week double-blind period
- A higher proportion of patients in the mitapivat group achieved transfusion independence compared with the placebo group; 3 patients in the mitapivat group were transfusion-free through Week 48 of the double-blind period
- The most frequently reported TEAEs with mitapivat were headache, upper respiratory tract infection, initial insomnia, diarrhea, and fatigue
- Mitapivat was generally well tolerated in this study, with a low treatment discontinuation rate

TEAE, treatment-emergent adverse event.

Cappellini MD et al. Oral presentation at the American Society of Hematology Annual Meeting and Exposition 2024, San Diego.

Closing Remarks

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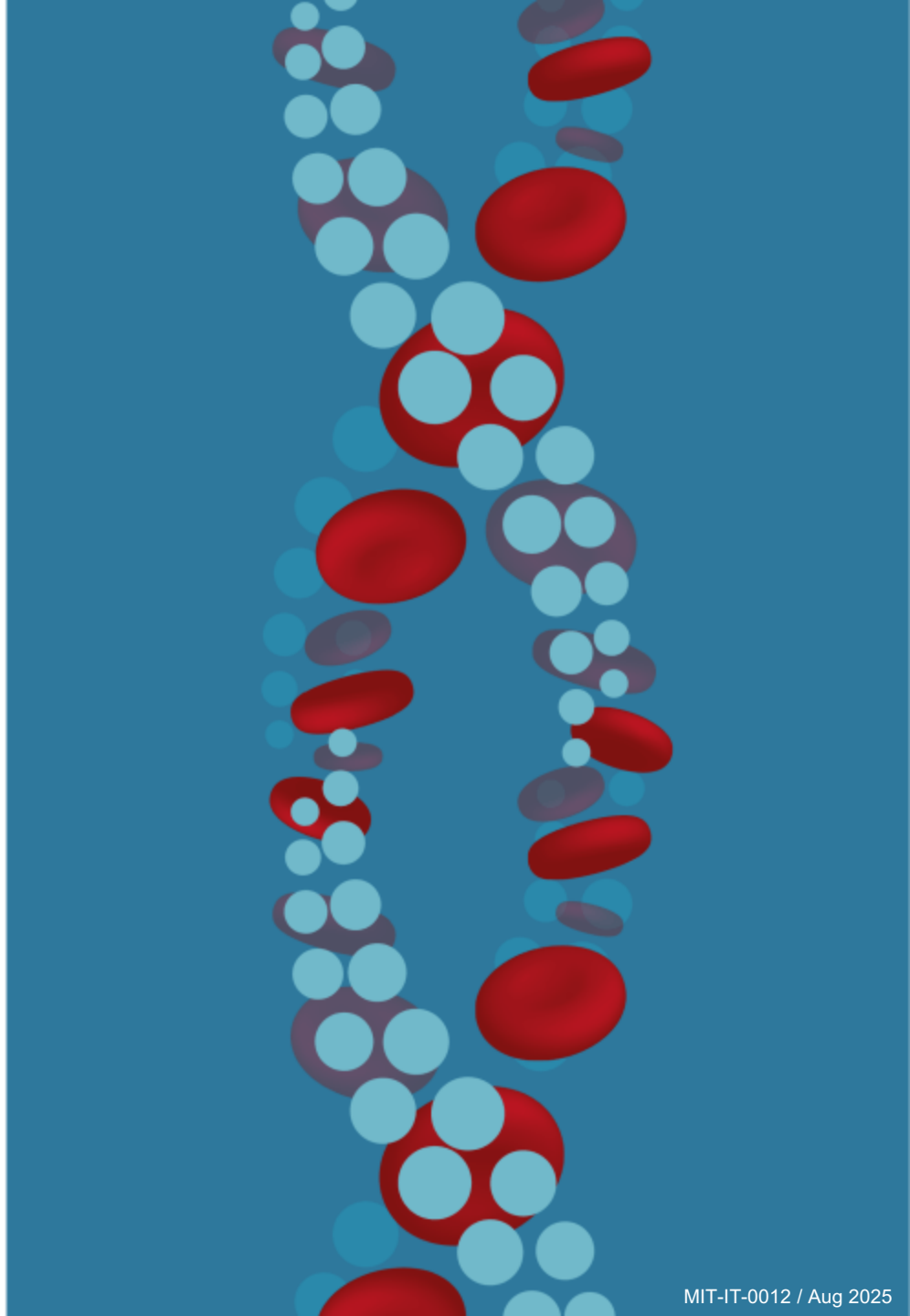


ENERGIZE and ENERGIZE-T summary

- The ENERGIZE and ENERGIZE-T program enrolled a population representative of the overall thalassemia population globally, encompassing thalassemia across genotypes and transfusion needs (total enrollment: N=452)[1–3]
- Both studies achieved the primary and all the key secondary endpoints, demonstrating benefit of mitapivat over placebo[1–3]
- Overall, the incidence of AEs was similar for patients on mitapivat and patients on placebo. There were 4.7% (n=14) of patients on mitapivat and 0.7% (n=1) of patients on placebo with TEAEs leading to treatment discontinuation across the 2 studies[1–3]
- During the double-blind periods, 2 patients on mitapivat experienced events of hepatocellular injury. During the open-label extension period, 3 patients experienced events of hepatocellular injury after switching from placebo to mitapivat[4]
  - All events occurred within the first 6 months of exposure. Liver tests improved following discontinuation of mitapivat[4]

Mitapivat may represent a disease-modifying therapy with the potential to impact the underlying drivers of thalassemia regardless of genotype or transfusion burden

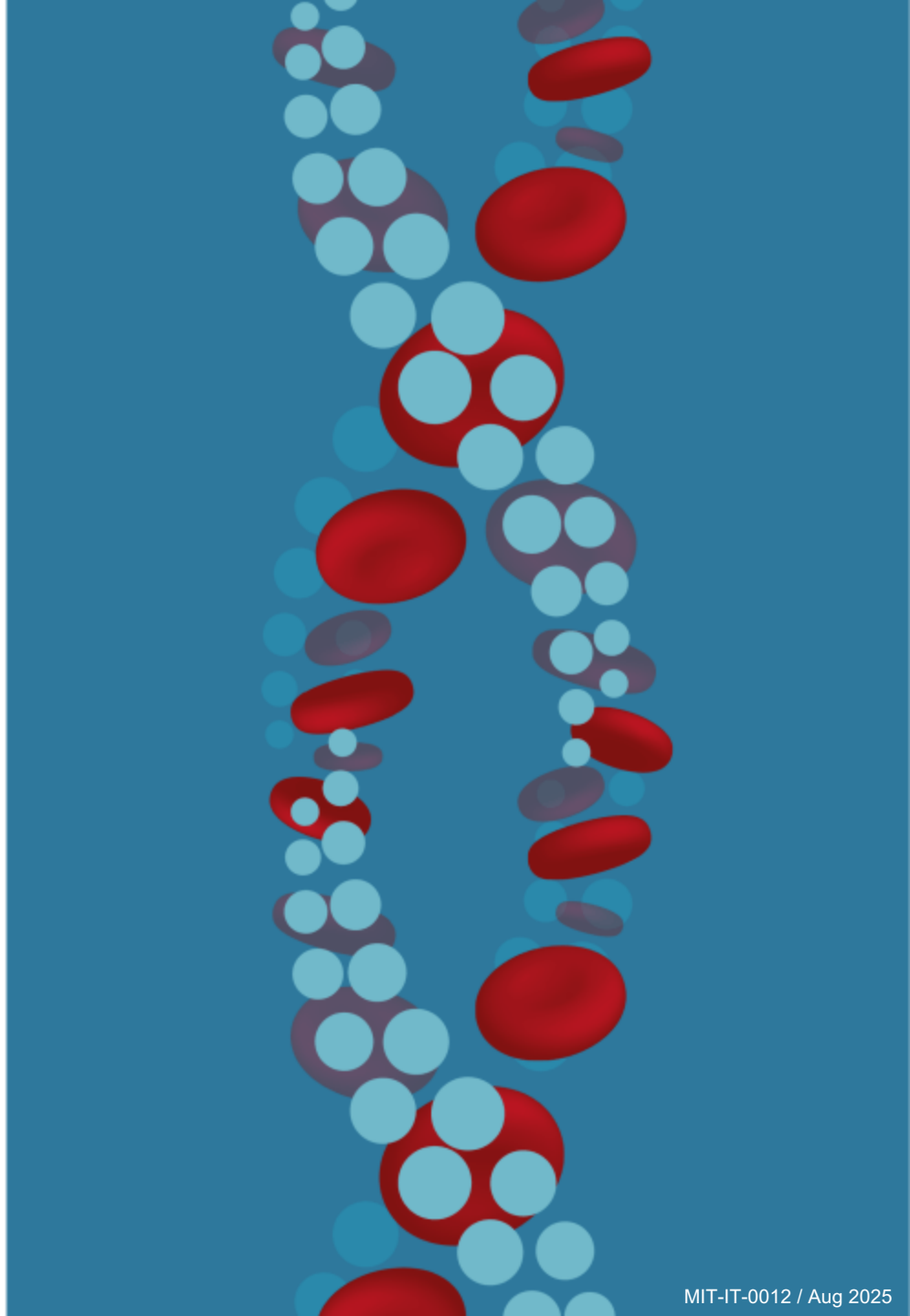
AE, adverse event; TEAE, treatment-emergent adverse event.

1. Taher AT et al. Lancet 2025;406:33–42; 2. Cappellini MD et al. Oral presentation at the American Society of Hematology Annual Meeting and Exposition 2024, San Diego; 3. Agios Industry Theater presentation during the American Society of Hematology Annual Meeting and Exposition 2024, San Diego; 4. Agios Pharmaceuticals Inc. Q4 2024 Financial Results and Business Update; Feb 13, 2025. https://investor.agios.com/static-files/abcd6895-8da1-4249-b216-15b6f1d3d01d. Accessed Jun 2025.

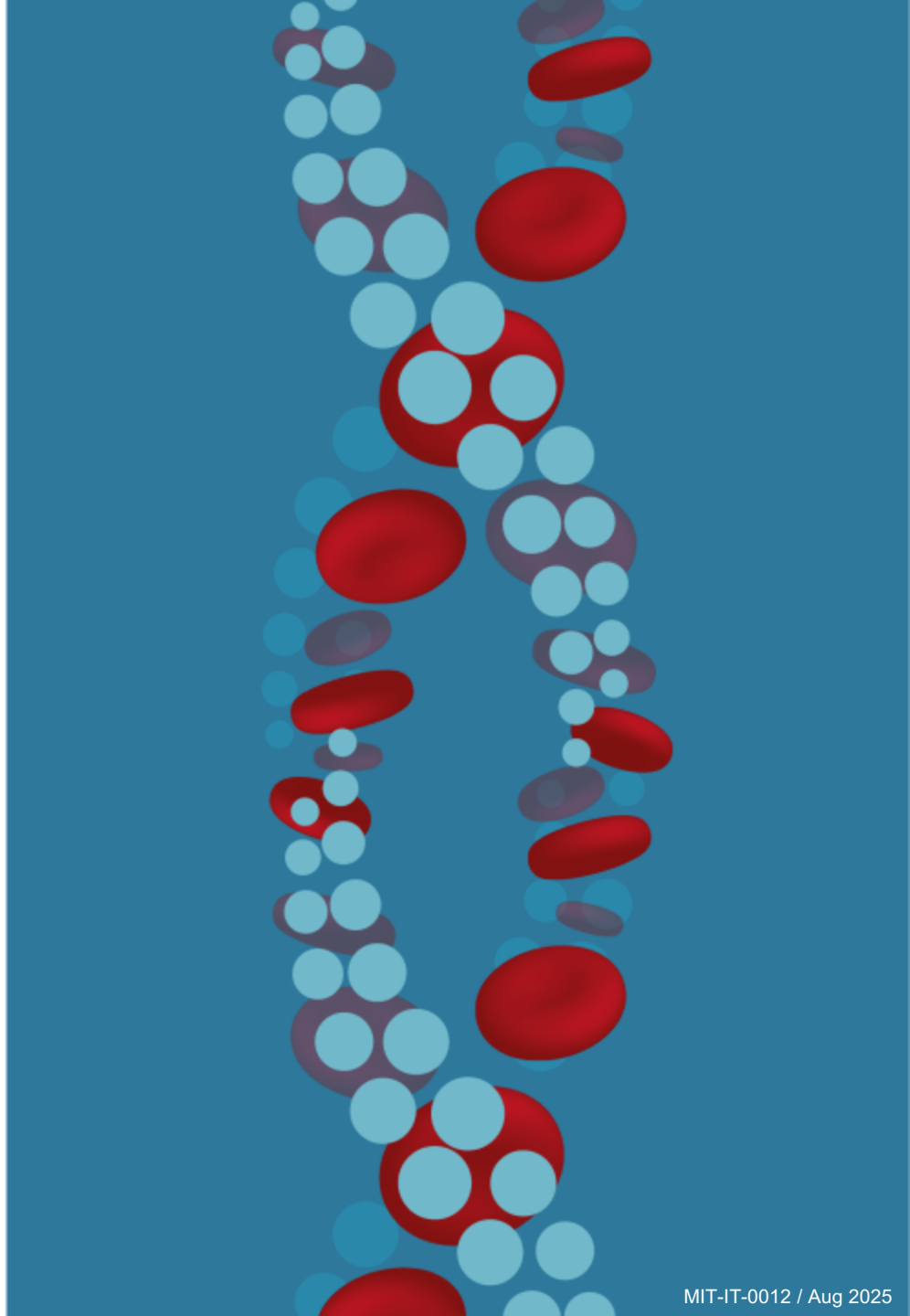
Thank you to all the patients, family, caregivers, investigators, and their teams for participation in the ENERGIZE and ENERGIZE-T studies

The full list of the study investigators can be found via the QR code:

SITE 2025



Supplemental Materials



ENERGIZE study investigators

Study countries	Principal study investigators	Study sites
Brazil	Sandra Loggetto	Banco de Sangue de Sao Paulo
	Vitor Mauad	Praxis Pesquisa Medica
	Sandra F. Menosi Gualandro	Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo
	Guilherme Rasia Bosi	Universidade de Caxias do Sul
	Viviani de Lourdes Rosa Pessoa	HEMORIO Instituto Nacional de Hematologia
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Study countries	Principal study investigators	Study sites
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	Tze S. Leong	Hospital Umum Sarawak
	Christopher C.K. Liam	Hospital Sultanah Aminah
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	Kittiphong Paiboonsukwong	Nakhon Pathom Hospital
	Adisak Tantiworawit	Maharaj Nakorn Chiang Mai Hospital
	Nattiya Teawtrakul	Srinagarind Hospital
	Noppacharn Uaprasert	King Chulalongkorn Memorial Hospital
	Vip Viprakasit	Siriraj Hospital
	Peerapon Wong	Naresuan University Hospital
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United States	Hanny Al-Samkari	Massachusetts General Hospital
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	Alexander Glaros	Children's Hospital of Michigan
	Srila Gopal	Moores Cancer Center at UC San Diego Health
	Ashutosh Lal	UCSF Benioff Children's Hospital Oakland
	Farzana Sayani	Perelman School of Medicine at the University of Pennsylvania
	Sujit Sheth	Weill Cornell Medicine – New York Presbyterian Hospital
	John Joseph Strouse	Duke University Medical Center

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Study countries	Principal study investigators	Study sites
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	Ana Silva Pinto	Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo, Ribeirao Preto
	Sandra Loggetto	Banco de Sangue de São Paulo, São Paulo
Bulgaria	Lachezar Bogdanov	University Multiprofile Hospital for Active Treatment “Dr. Georgi Stransk” EAD, Pleven
	Penka Ganeva	Specialized Hospital for Active Treatment of Hematological Diseases EAD, Sofia
	Pencho Georgiev	University Hospital for Active Treatment “Sveti Georgi,” Plovdiv
	Desislava Ilieva-Chiviyska	Multiprofile Hospital for Active Treatment “Dr. Nikola Vasilev” AD, Kyustendil
	Mariya Todorova	University Multiprofile Hospital for Active Treatment “Prof. Dr. Stoyan Kirkovich” AD, Stara Zagora
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Denmark	Andreas Glenthøj	Rigshospitalet, Copenhagen
France	Pablo Bartolucci	Hôpital Henri Mondor, Paris
	Giovanna Cannas	Hôpital Edouard Herroit – Hospices Civils de Lyon, Lyon
	Laure Joseph	Hôpital Necker, Paris
	Estelle Jean-Mignard	Hôpital de la Timone, APHM, Marseille
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Study countries	Principal study investigators	Study sites
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	Antonis Kattamis	Children's Hospital "Aghia Sophia," Pediatric Clinic of National and Kapodistrian University of Athens (NKUA), Athens
	Alexandra Kourakli-Symeonidis Vasiliki Labropoulou	University General Hospital of Patras, Rio
	Efthymia Vlachaki	General Hospital of Thessaloniki "IPPOKRATIO," Thessaloniki
Italy	Elena Cassinerio	Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milano
	Francesca Ferrara	Universitaria di Modena Policlinico di Modena, Modena
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