

ENERGIZE: A global, phase 3 study of mitapivat demonstrating efficacy and safety in adults with alpha- or beta-non-transfusion-dependent thalassemia

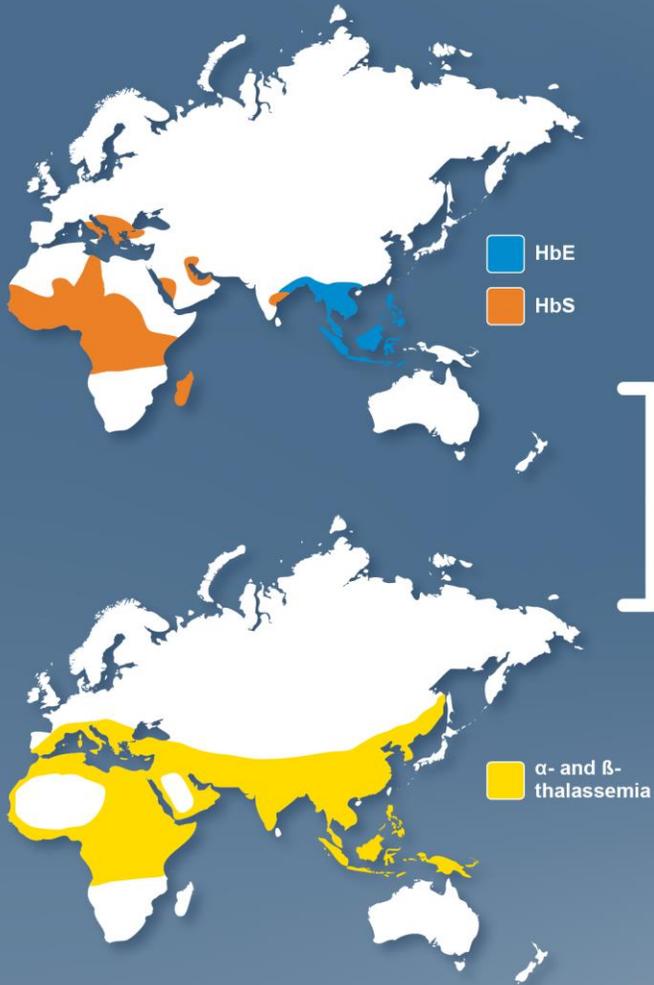
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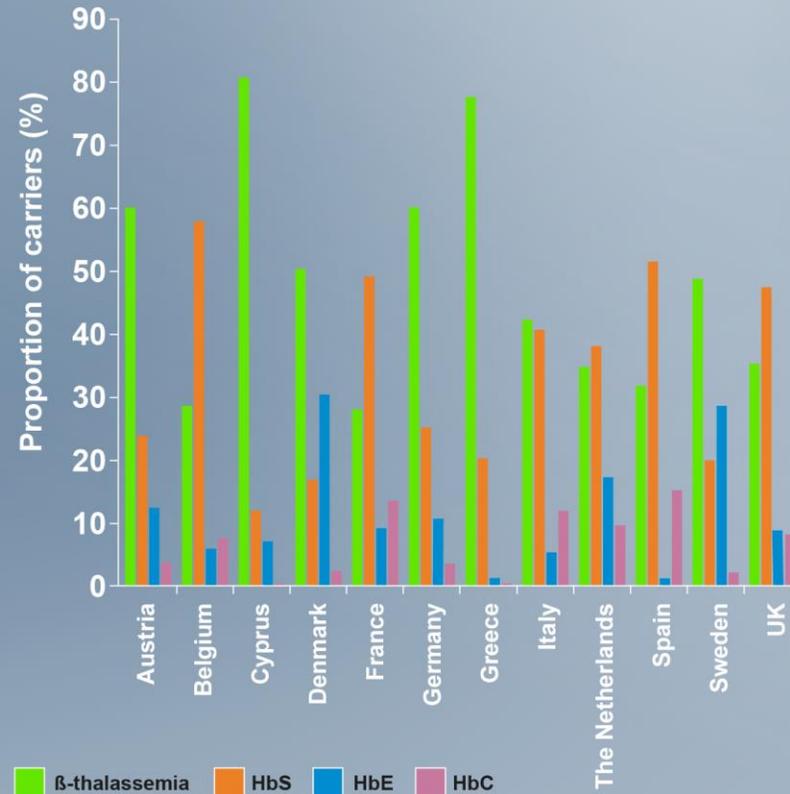
Conflict of interest disclosures

- **This study was funded by Agios Pharmaceuticals, Inc.**
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 - **Ali T Taher, MD, PhD, FRCP**
 - Agios (consultancy, research funding);
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Changing epidemiology of thalassemia^{1,2}



Relative proportion of carriers of hemoglobin (Hb) disorders among immigrant populations

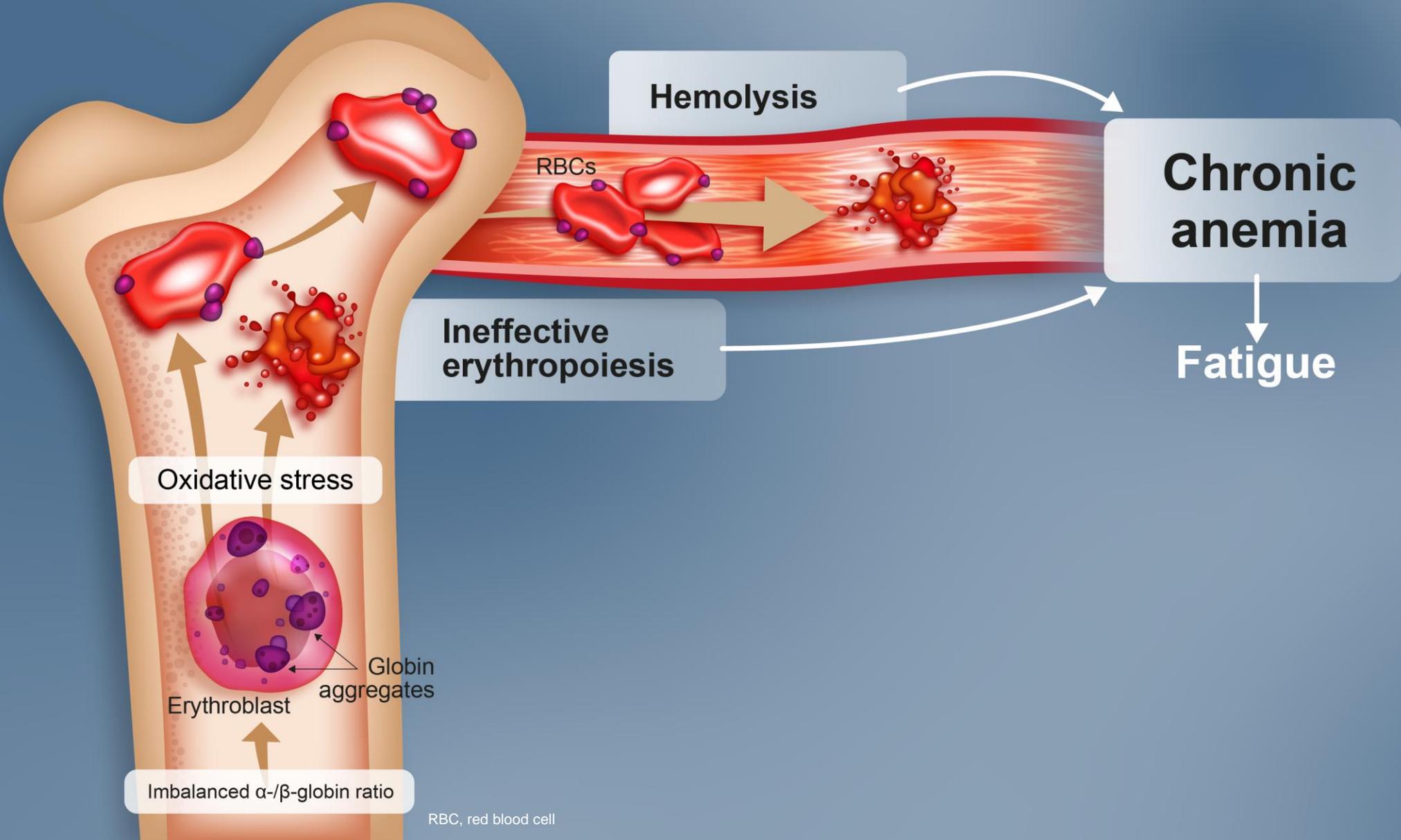


- The evolutionary association between the thalassemia carrier state and resistance to *malaria* explains its high prevalence in the area extending from sub-Saharan Africa, the Middle East, and the Mediterranean basin to Southeast Asia¹
- Population *migrations* have also introduced thalassemia to Europe and the Americas, where the disease was previously relatively rare²⁻⁴

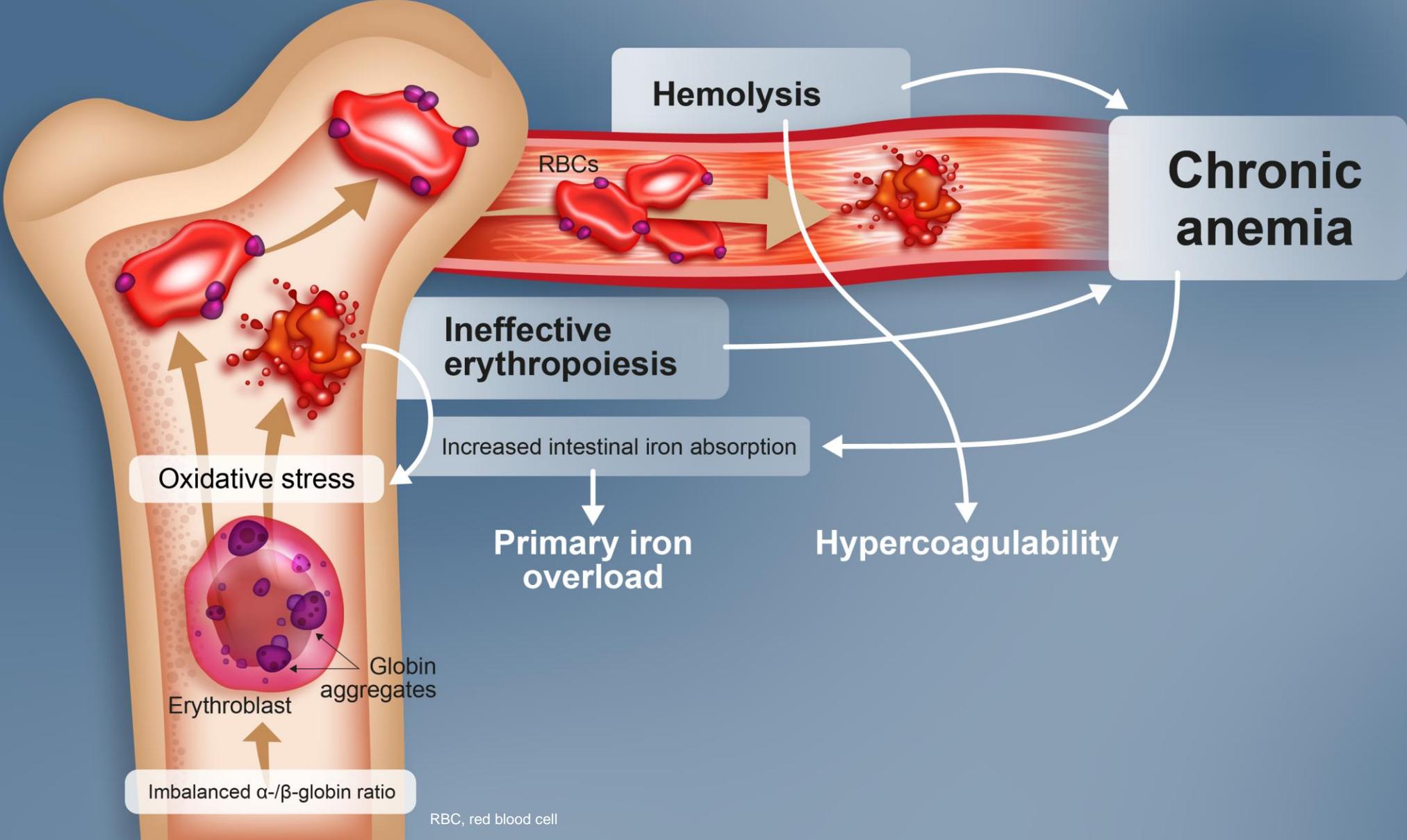
HbC, hemoglobin C; HbE, hemoglobin E; HbS, hemoglobin S

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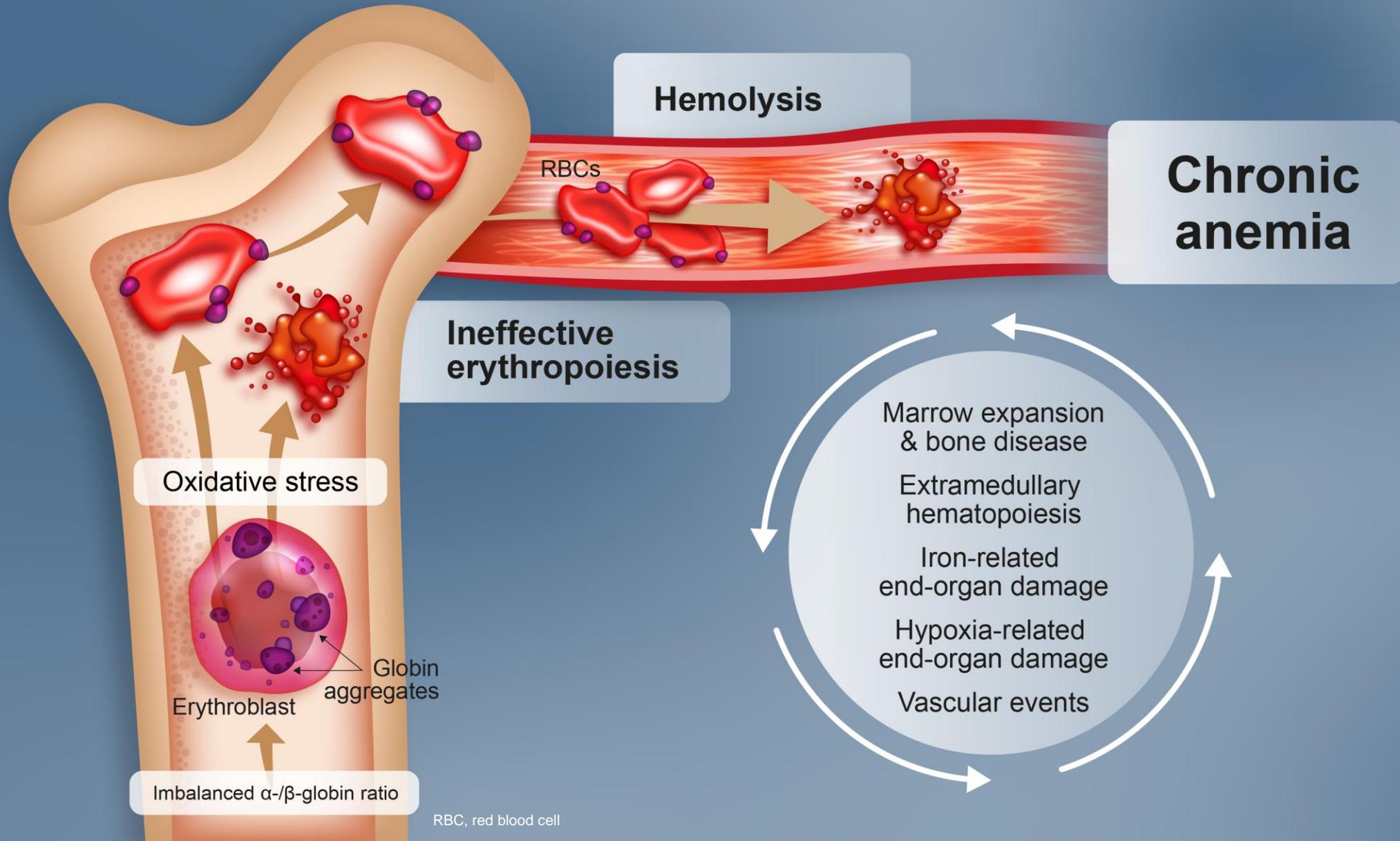
Pathophysiology of thalassemia



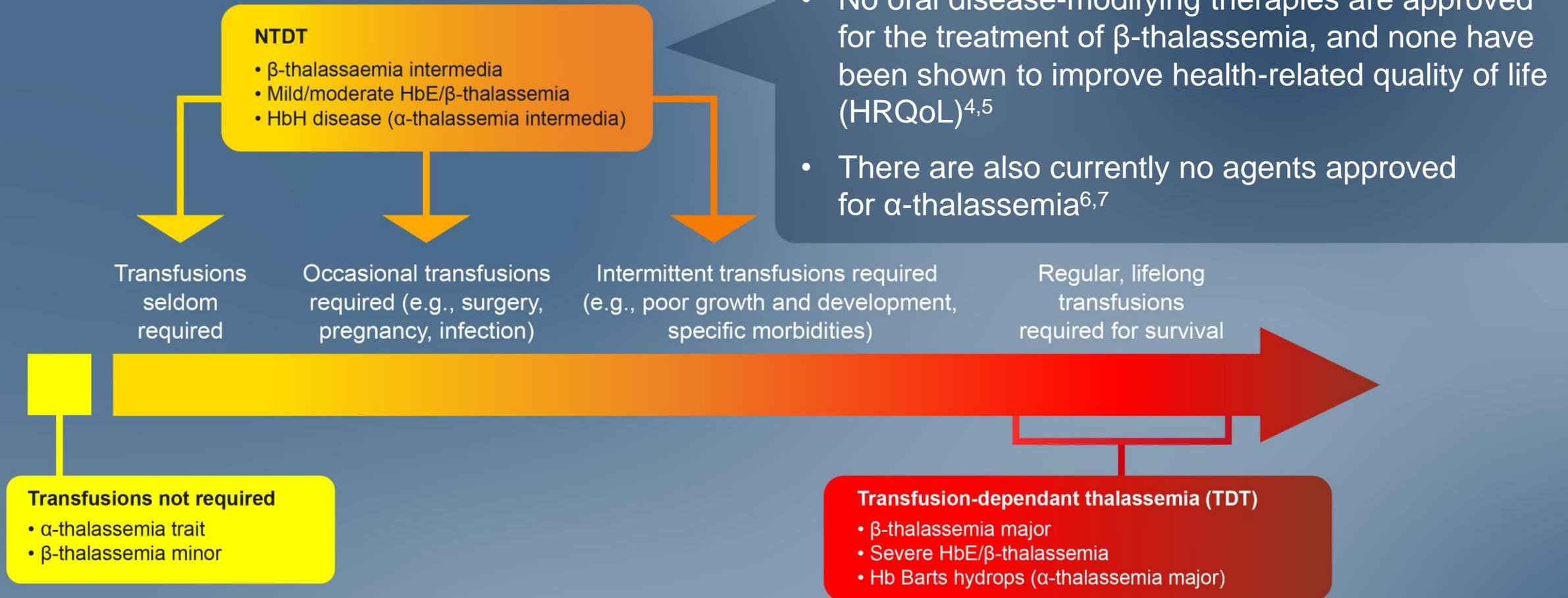
Pathophysiology of thalassemia



Pathophysiology of thalassemia



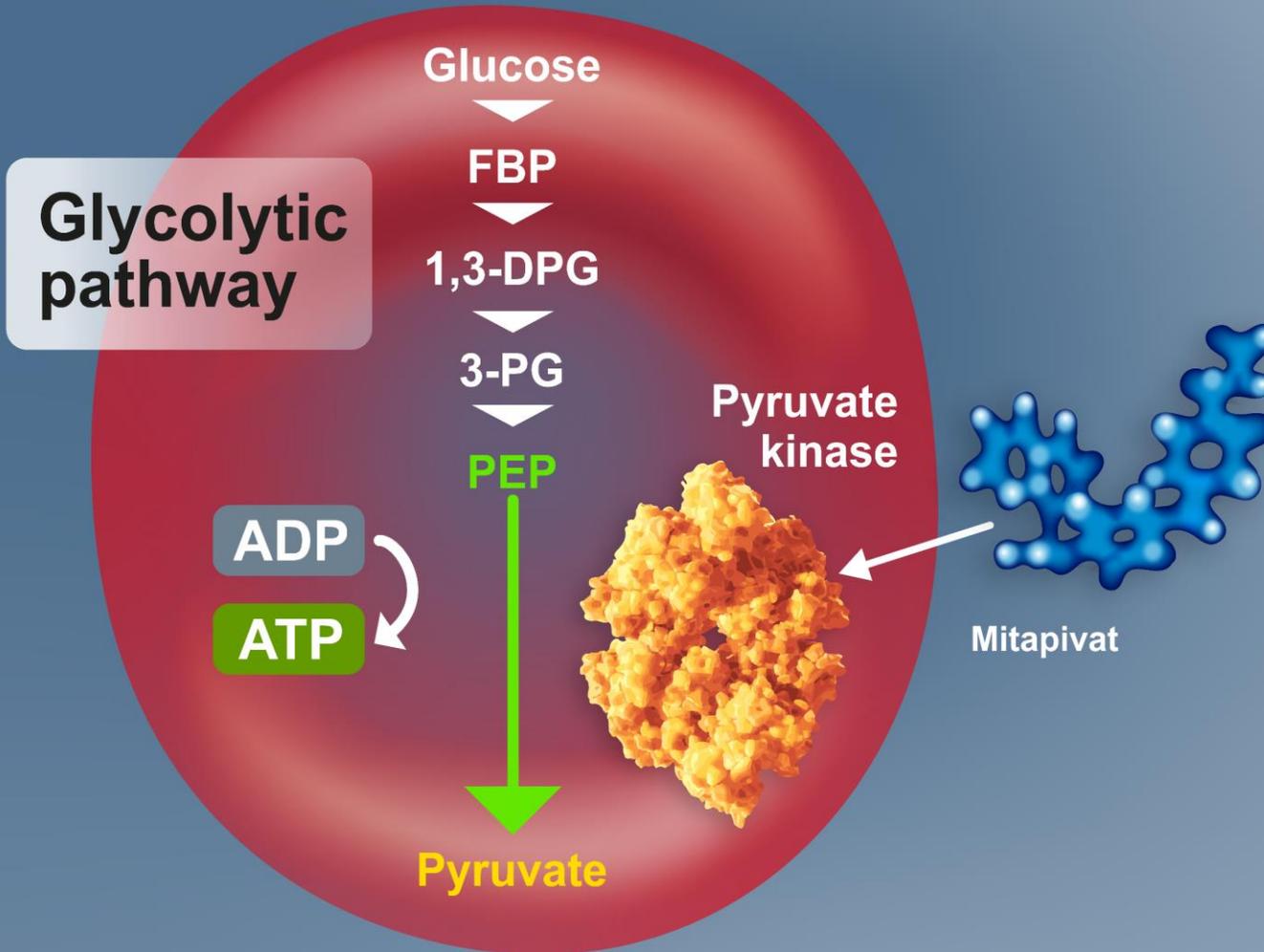
Non-transfusion-dependent thalassemia (NTDT) and unmet needs¹



Hb, hemoglobin; HbE, hemoglobin E; HbH, hemoglobin H

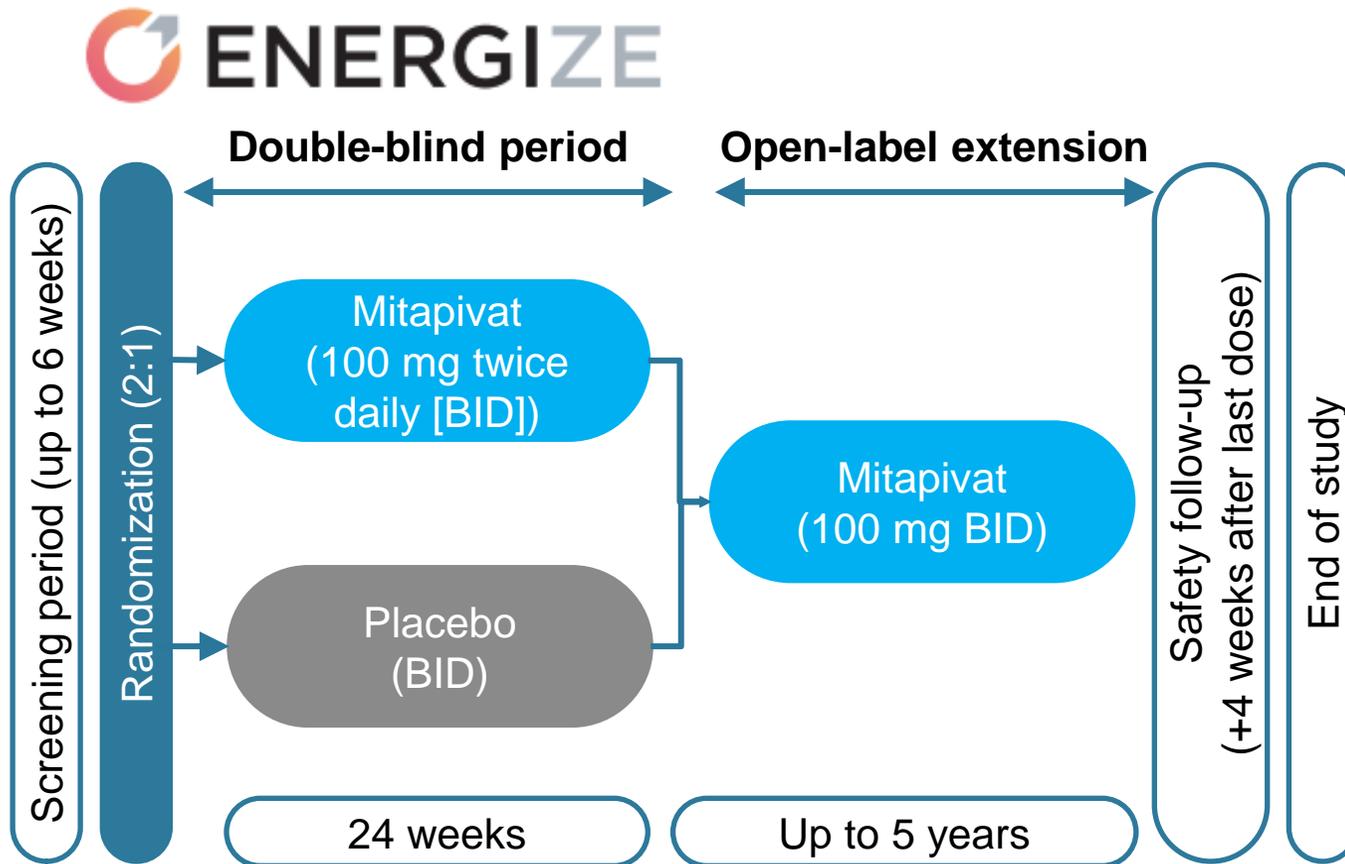
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Mitapivat enhances cellular energy supply to support increased metabolic demands of thalassemic red cells



- In thalassemia, there is increased energy demand to maintain RBC health^{1–4}
- Mitapivat is an activator of the red cell-specific form of pyruvate kinase (PKR) and pyruvate kinase M2 (PKM2) isoforms of pyruvate kinase (PK), which acts in glycolysis to generate adenosine triphosphate (ATP)^{5,6}
- In preclinical thalassemia models, mitapivat reduced oxidative stress, and improved erythropoiesis, hemolysis, and anemia^{7–9}
- A phase 2 study of mitapivat in α - or β -NTDT demonstrated improvements in Hb and markers of erythropoiesis and hemolysis¹⁰

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



Key inclusion criteria

- ≥ 18 years of age at time of informed consent
- β -thalassemia \pm 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)

Endpoints

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

Key secondary endpoints

- Change from baseline in average Functional Assessment of Chronic Illness Therapy–Fatigue Scale (FACIT-Fatigue) score from Week 12 through Week 24
- Change from baseline in average Hb concentration from Week 12 through Week 24

Secondary efficacy endpoints associated with hemolysis and erythropoietic activity

- Change from baseline in indirect bilirubin, lactate dehydrogenase (LDH), and haptoglobin at Week 24
- Change from baseline in reticulocytes and erythropoietin at Week 24

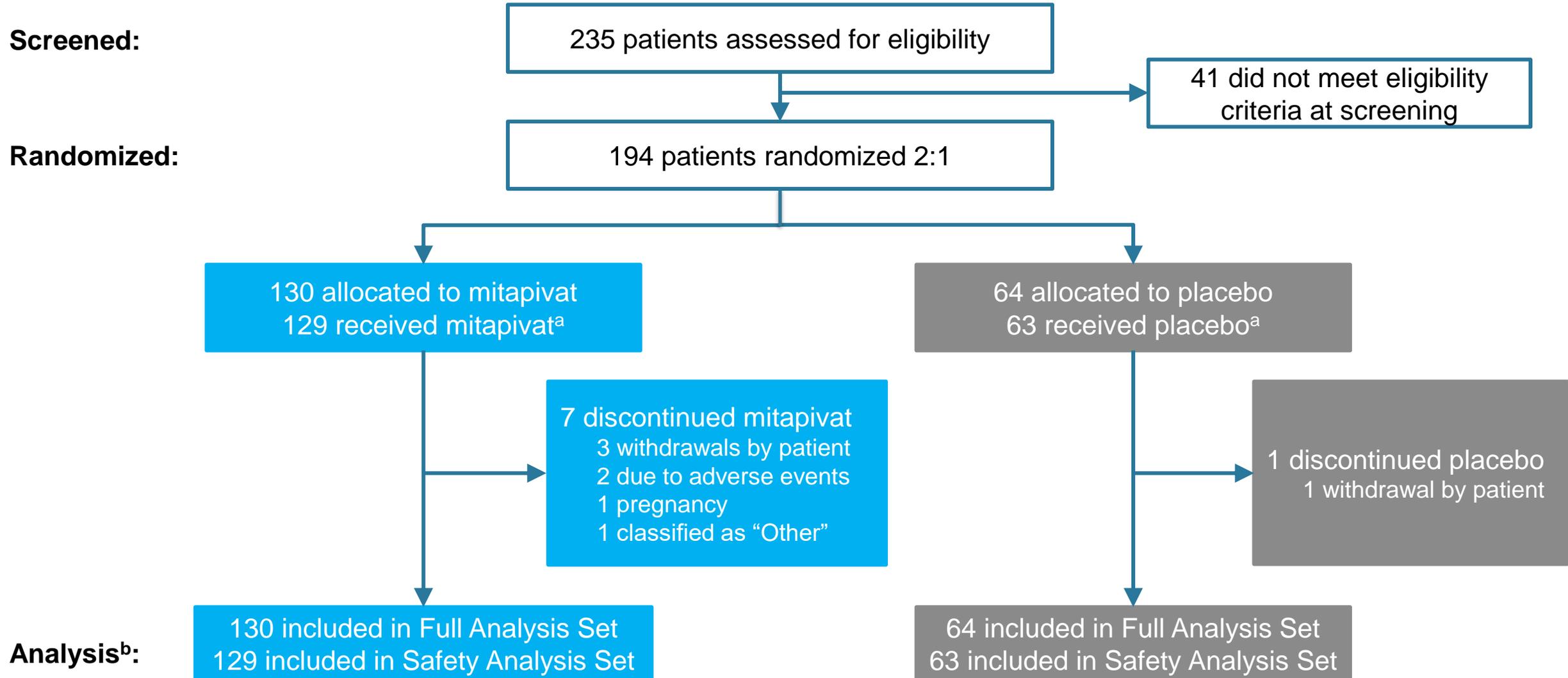
Safety endpoints

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

Statistical methods

- The primary endpoint of Hb response was tested using the Mantel–Haenszel stratum weighted method, after adjusting for randomization stratification factors
- The key secondary endpoints were compared between the mitapivat and placebo arms using an analysis of covariance model
 - The secondary endpoints of change from baseline in indirect bilirubin, LDH, and haptoglobin at Week 24 and change from baseline in reticulocytes and erythropoietin at Week 24 were compared between the mitapivat and placebo arms using this method
- The primary and key secondary endpoints were tested using a fixed-sequence statistical testing procedure and were also assessed in prespecified subgroups
- Descriptive statistics were reported for the safety endpoint

Patient flowchart: 194 patients were randomized in the study



^a1 patient in each treatment arm was randomized but not dosed. ^bFull 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.

Baseline demographics and disease characteristics were balanced between treatment arms

Demographics and disease characteristics	Mitapivat (N=130)	Placebo (N=64)
Age, mean (\pm SD), years	42.4 (13.0)	38.9 (13.0)
Female, n (%)	84 (64.6)	39 (60.9)
Thalassemia type, n (%)		
α -thalassemia/HbH disease	42 (32.3)	20 (31.3)
β -thalassemia	88 (67.7)	44 (68.8)
Transfusion burden, ^a n (%)		
0	114 (87.7)	54 (84.4)
1–2	10 (7.7)	7 (10.9)
3–5	6 (4.6)	3 (4.7)
>5	0 (0.0)	0 (0.0)
Prior splenectomy, ^b n (%)	47 (36.2)	25 (39.1)
Prior cholecystectomy, ^b n (%)	45 (34.6)	16 (25.0)
Received iron chelation in prior year, ^c n (%)	46 (35.4)	22 (34.4)
Hb, median (range), g/dL	8.4 (5.3–10.4)	8.4 (5.9–10.7)
Indirect bilirubin, median (range), μ mol/L	23.4 (2.2–155.8)	22.6 (2.7–81.6)
LDH, median (range), U/L	264 (108–1208)	267 (110–1009)
Haptoglobin, ^d median (range), g/L	0.1 (0.1–1.7)	0.1 (0.1–2.8)
Reticulocyte percentage, median (range), %	4.6 (0.3–29.8)	4.4 (0.0–21.9)
Erythropoietin, median (range), IU/L	65.1 (8.3–1587.0)	64.1 (15.7–4710.0)

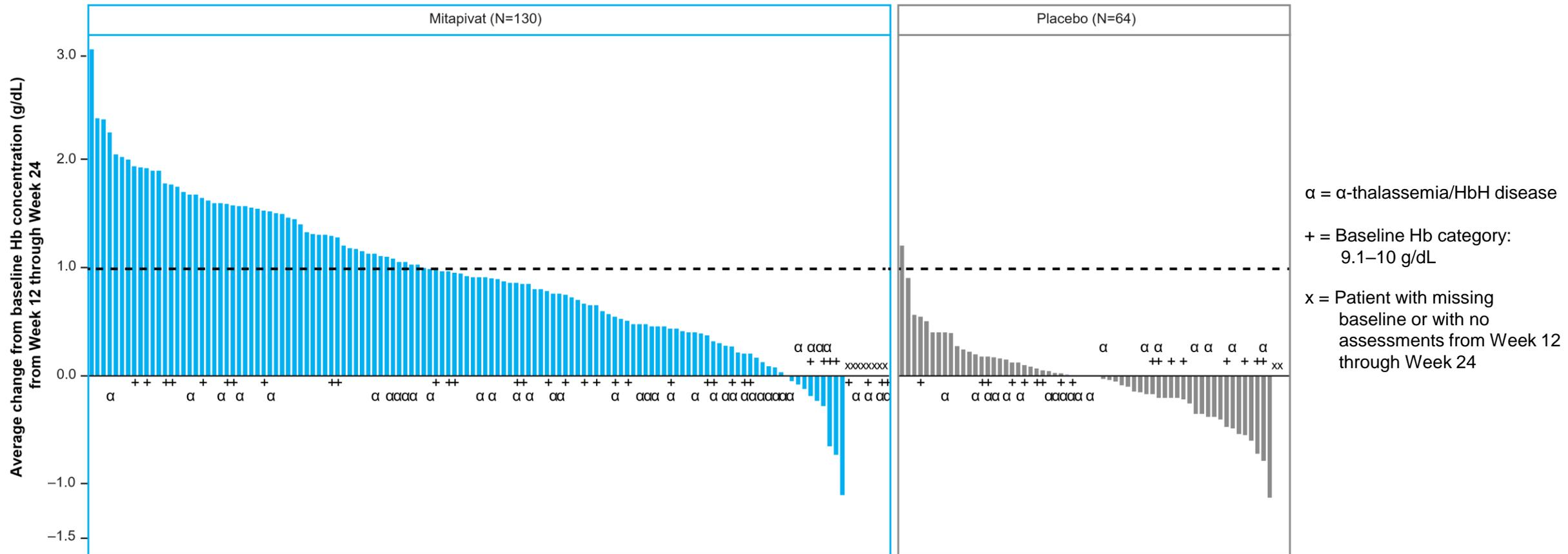
^aTotal number of RBC units transfused in the 24-week period before randomization. ^bAs recorded in medical/surgical history electronic case report form (eCRF). ^cAs recorded in disease characteristics eCRF. "Yes" if a patient received chelation therapy within 1 year (365 days) before randomization. ^dFor cases reported as "<0.1," a haptoglobin value of 0.099 was used for the summary.

Hb, hemoglobin; HbH, hemoglobin H; LDH, lactate dehydrogenase; RBC, red blood cell

Mitapivat demonstrated a statistically significant improvement in Hb response vs placebo

Primary endpoint

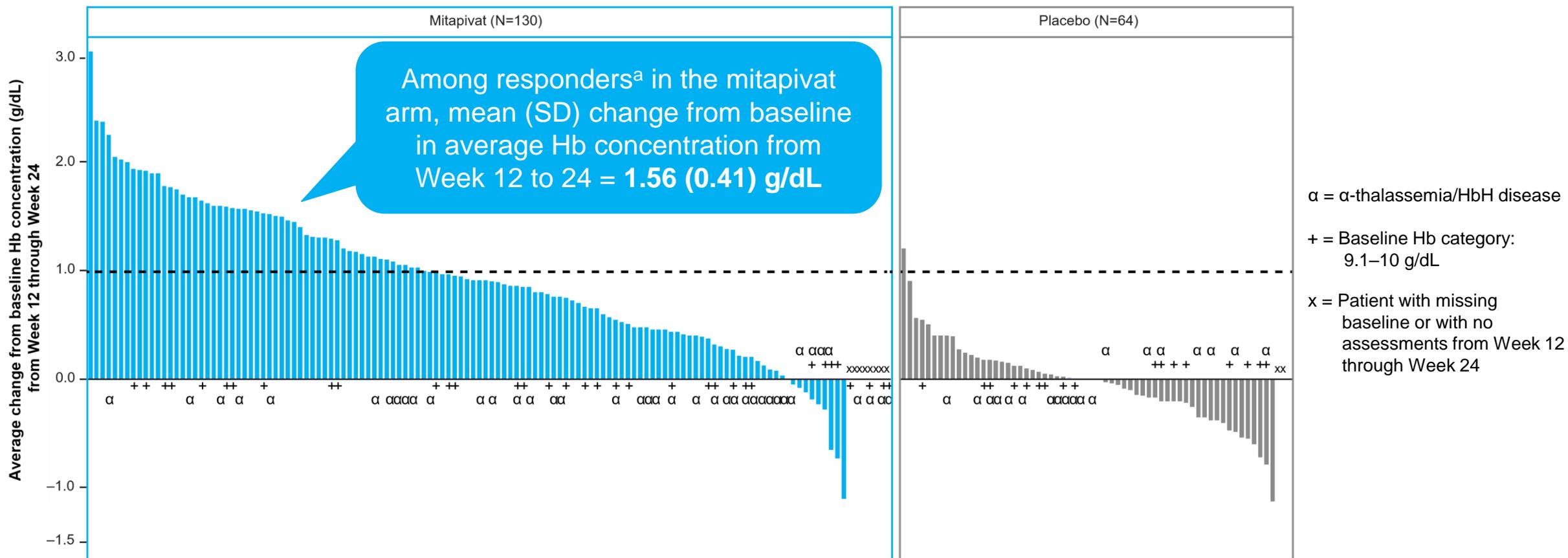
	Mitapivat N=130	Placebo N=64	2-sided p-value
Hb response, ^a n (%)	55 (42.3)	1 (1.6)	p<0.0001



Mitapivat demonstrated a statistically significant improvement in Hb response vs placebo

Primary endpoint

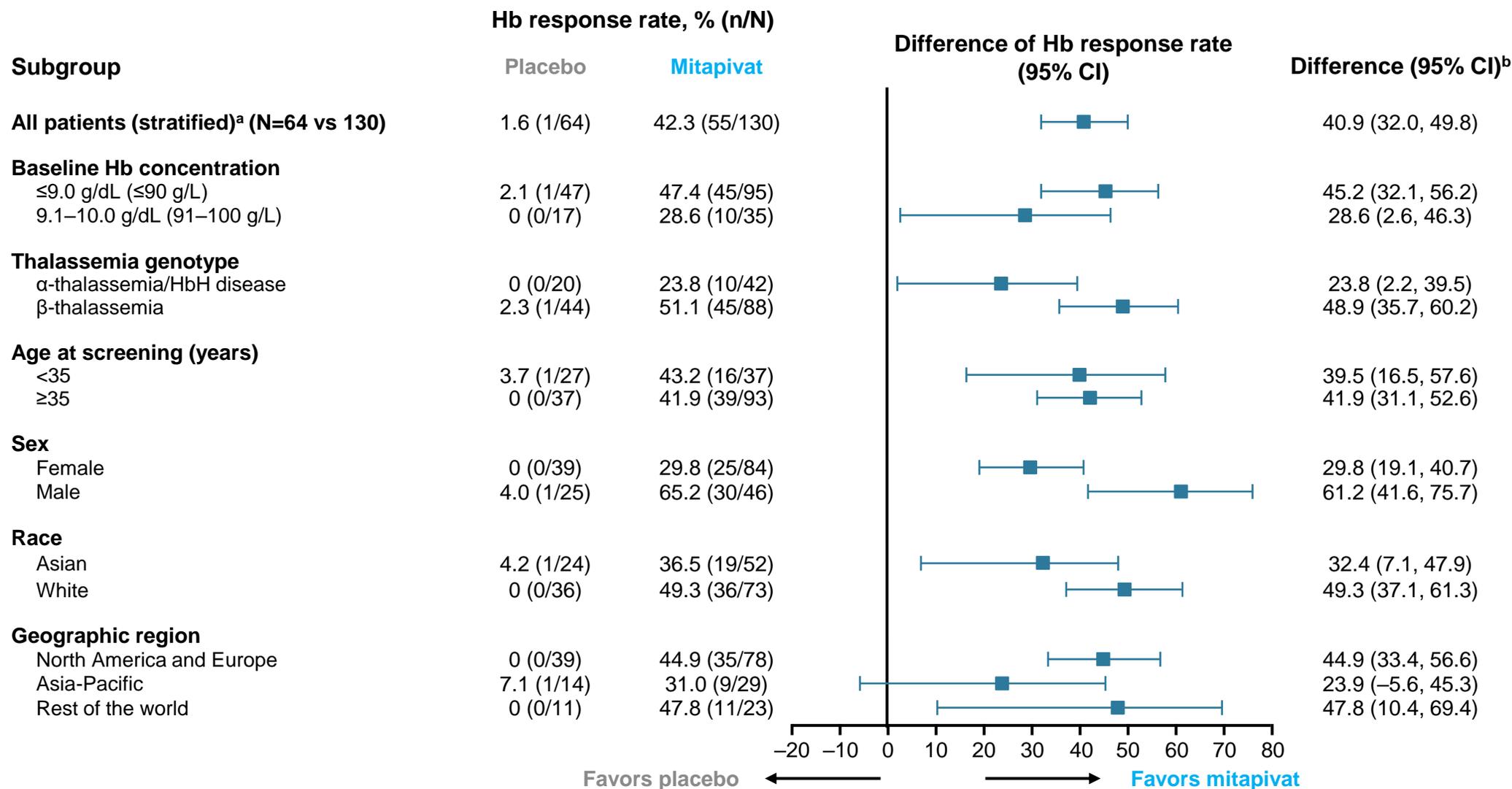
	Mitapivat N=130	Placebo N=64	2-sided p-value
Hb response, ^a n (%)	55 (42.3)	1 (1.6)	p<0.0001



Analysis conducted on Full Analysis Set. ^aA 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

Hb response rates were higher for mitapivat vs placebo across all prespecified subgroups

Subgroup analysis of primary endpoint

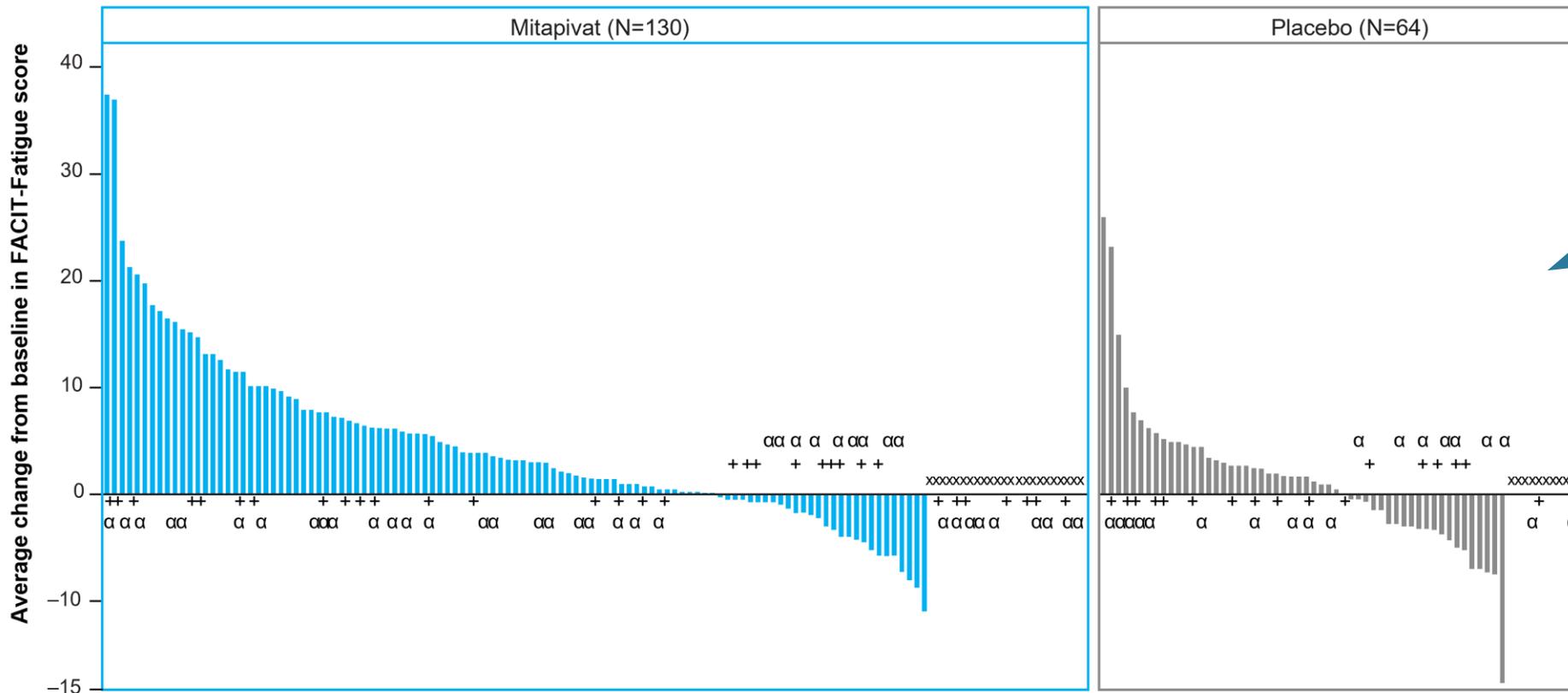


Analysis conducted on Full Analysis Set. ^aStratified by baseline Hb concentration (≤9.0 g/dL or 9.1–10.0 g/dL) and thalassemia genotype (α-thalassemia/HbH disease or β-thalassemia). ^bFor "All patients," the estimates for the difference and the 95% CIs are based on the Mantel–Haenszel stratum weighted method adjusting for the randomization stratification factors. For subgroups, the estimates for the difference and the 95% CIs are based on unstratified analyses. Hb, hemoglobin; HbH, hemoglobin H

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

Key secondary endpoint

	Mitapivat N=130	Placebo N=64	LSM difference	2-sided p-value
FACIT-Fatigue score, least-squares mean (LSM) (95% CI) change from baseline in average of Weeks 12–24	4.85 (3.41, 6.30)	1.46 (-0.43, 3.34)	3.40 (1.21, 5.59)	p=0.0026



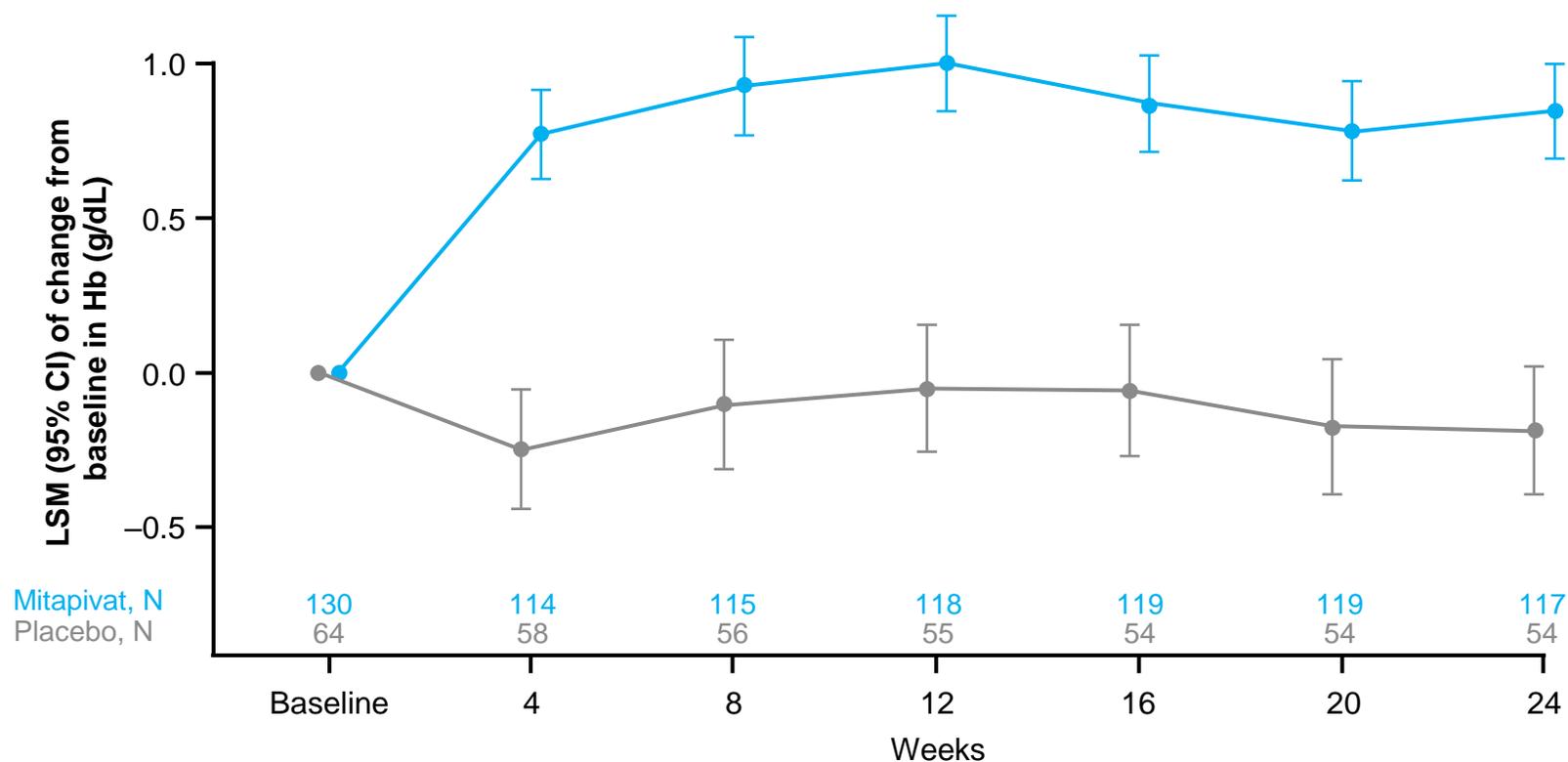
See poster P1529 for further details on HRQoL-related data

- 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

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

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 12–24, g/dL	0.86 (0.73, 0.99)	-0.11 (-0.28, 0.07)	0.96 (0.78, 1.15)	p<0.0001

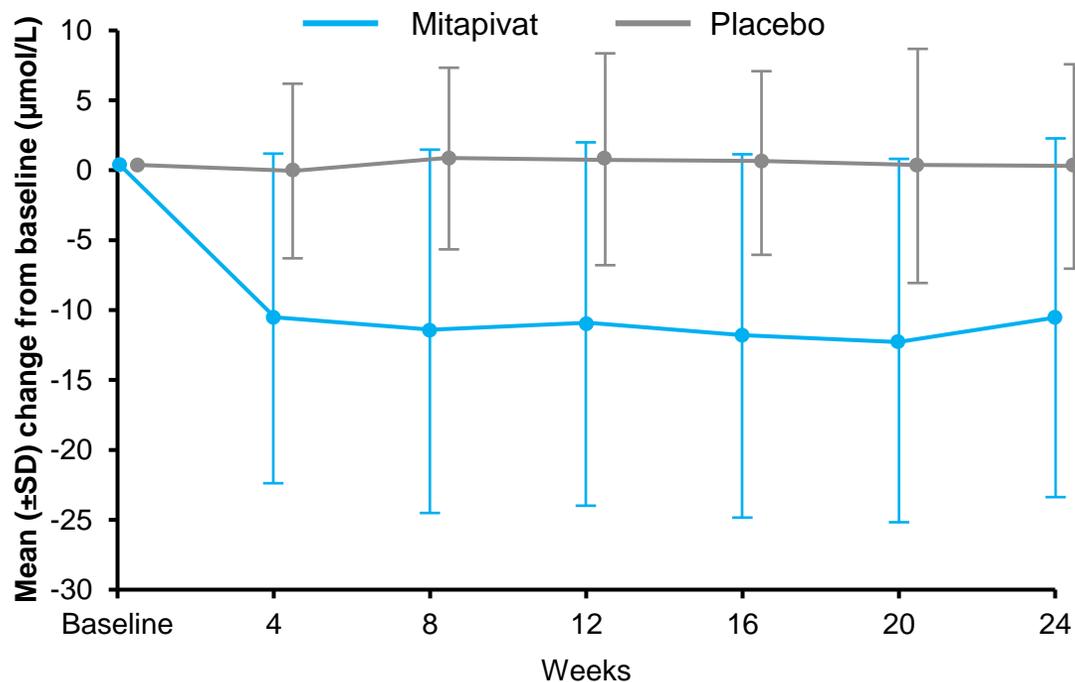


Improvements in markers of hemolysis were observed in the mitapivat arm vs placebo

Secondary endpoints

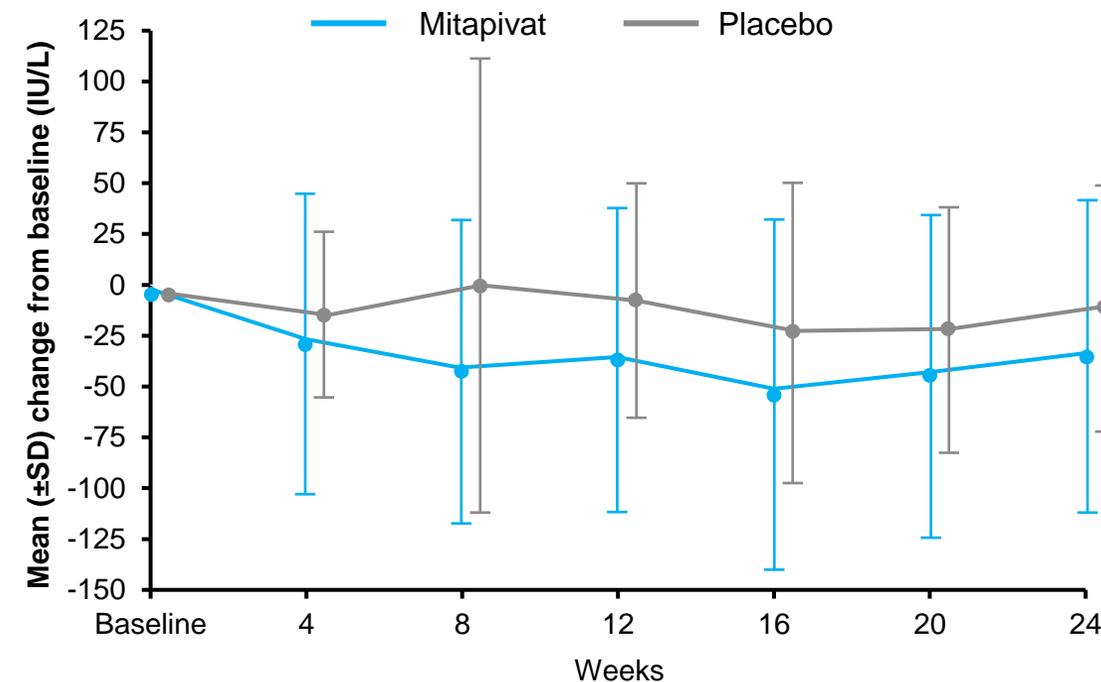
Indirect bilirubin

	Mitapivat N=116	Placebo N=54	LSM difference
Indirect bilirubin, LSM (95% CI) change from baseline at Week 24, $\mu\text{mol/L}$	-10.65 (-12.72, -8.58)	-0.03 (-2.80, 2.74)	-10.62 (-13.74, -7.50)



LDH

	Mitapivat N=116	Placebo N=54	LSM difference
LDH, LSM (95% CI) change from baseline at Week 24, U/L	-30.07 (-44.15, -15.99)	-5.79 (-24.43, 12.85)	-24.28 (-45.40, -3.15)



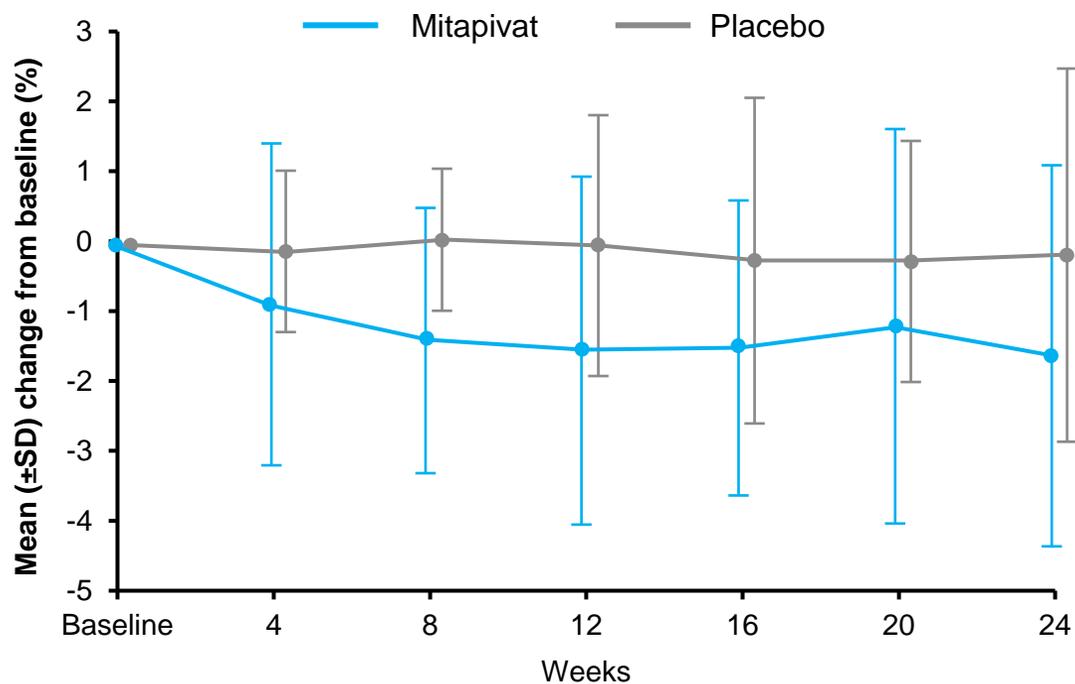
Note: numeric data are reported as LSM (95% CI) and figures are plotted with mean (\pm SD)

Improvements in markers of erythropoietic activity were observed in the mitapivat arm vs placebo

Secondary endpoints

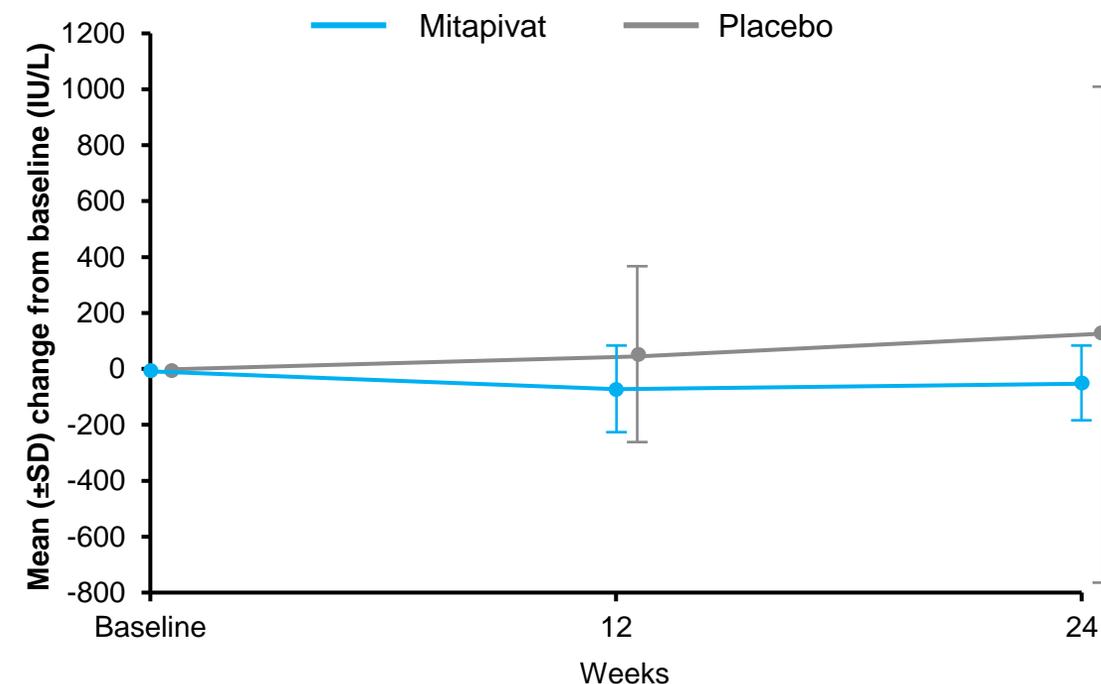
Reticulocyte percentage

	Mitapivat N=87	Placebo N=40	LSM difference
Reticulocyte percentage, LSM (95% CI) change from baseline at Week 24, %	-1.59 (-2.12, -1.07)	-0.25 (-0.97, 0.48)	-1.35 (-2.17, -0.53)



Erythropoietin

	Mitapivat N=103	Placebo N=47	LSM difference
Erythropoietin, LSM (95% CI) change from baseline at Week 24, IU/L	19.21 (-55.45, 93.86)	115.71 (18.04, 213.37)	-96.50 (-209.59, 16.60)



Note: numeric data are reported as LSM (95% CI) and figures are plotted with mean (±SD)

Summary of safety

Secondary endpoint

Patients, n (%)	Mitapivat (N=129)	Placebo (N=63)
Any treatment-emergent adverse events (TEAEs)	107 (82.9)	50 (79.4)
Grade ≥3 TEAEs	18 (14.0)	2 (3.2)
Treatment-related TEAEs	56 (43.4)	13 (20.6)
Grade ≥3 treatment-related TEAEs	5 (3.9)	0 (0.0)
Serious TEAEs	8 (6.2)	0 (0.0)
Serious treatment-related TEAEs	0 (0.0)	0 (0.0)
TEAEs leading to discontinuation of study drug	4 (3.1)	0 (0.0)
TEAEs leading to dose reduction	7 (5.4)	2 (3.2)
TEAEs leading to interruption of study drug	2 (1.6)	1 (1.6)
TEAEs leading to death	0 (0.0)	0 (0.0)

Most frequently reported ($\geq 10\%$) TEAEs

Preferred Term, n (%)	Mitapivat (N=129)	Placebo (N=63)
Headache		
Any grade	29 (22.5)	6 (9.5)
Grade ≥ 3	0 (0.0)	0 (0.0)
Initial insomnia		
Any grade	18 (14.0)	3 (4.8)
Grade ≥ 3	1 (0.8)	0 (0.0)
Nausea		
Any grade	15 (11.6)	5 (7.9)
Grade ≥ 3	0 (0.0)	0 (0.0)
Upper respiratory tract infection		
Any grade	14 (10.9)	4 (6.3)
Grade ≥ 3	0 (0.0)	0 (0.0)

Summary

- This global study was the first to enroll patients with α -thalassemia in addition to β -thalassemia
- The primary and key secondary endpoints were met, with statistically significant improvements in Hb and fatigue with mitapivat vs placebo
 - All prespecified subgroup analyses favored mitapivat vs placebo
- Improvements in markers of hemolysis and erythropoietic activity were observed, consistent with the mechanism of mitapivat^{1–3}
- Mitapivat was generally well tolerated in this study, with a low treatment discontinuation rate and a safety profile consistent with other studies^{3–6}

ENERGIZE demonstrated efficacy of mitapivat, a disease-modifying therapy, with significant improvements in both Hb and fatigue across the full range of NTDT, including both α - and β -thalassemia

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- We would like to thank all the patients, their families, and the ENERGIZE study investigators and teams who participated in this study
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**Supplemental data are
available via the QR code**