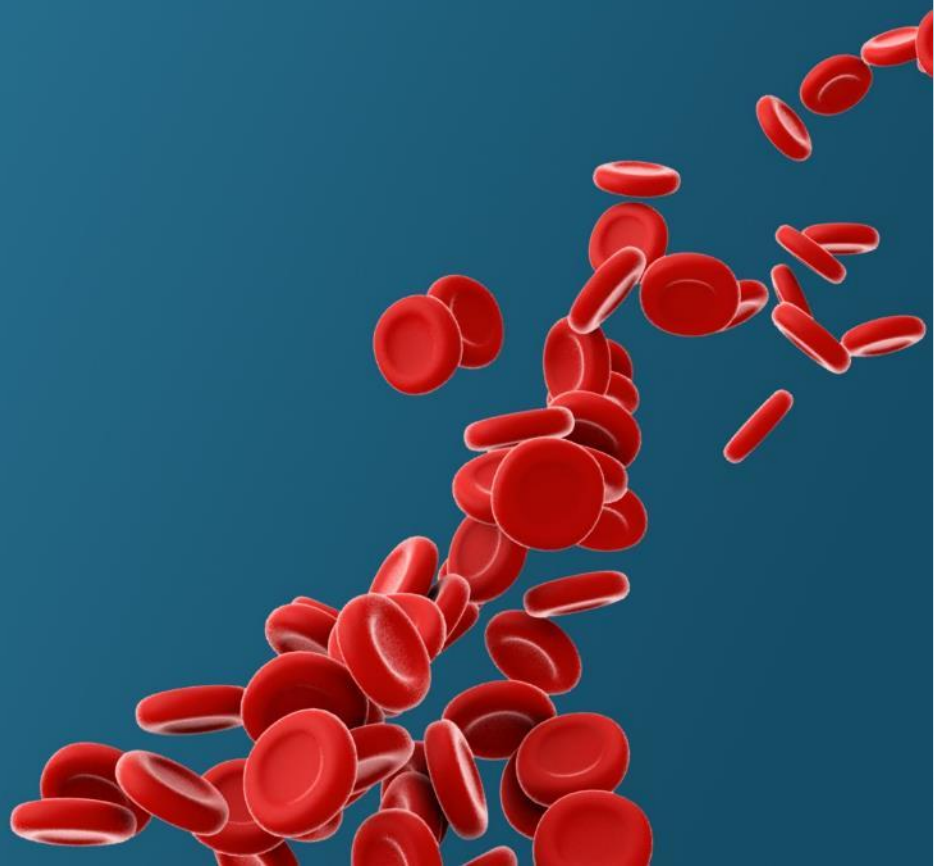
Agios at EHA 2024

June 16, 2024



Agios conference call participants

TOPIC	PARTICIPANT
Introduction	Chris Taylor, VP Investor Relations and Corporate Communications
Opening Remarks	Brian Goff, Chief Executive Officer
Mitapivat Phase 3 Development Program in Thalassemia	Sarah Gheuens, M.D., Ph.D., Chief Medical Officer, Head of Research and Development
ENERGIZE Data Overview	Ali Taher, M.D., Ph.D., Professor of Medicine, Hematology & Oncology and Director – Naef K. Basile Cancer Institute, American University of Beirut Medical Center
ENERGIZE Quality of Life and Patient-Reported Outcome Measures	Kevin Kuo, M.D., MSc, FRCPC; Division of Hematology, University of Toronto
Closing Remarks	Brian Goff, Chief Executive Officer
Q&A	All speakers, Cecilia Jones (CFO), and Tsveta Milanova (CCO)

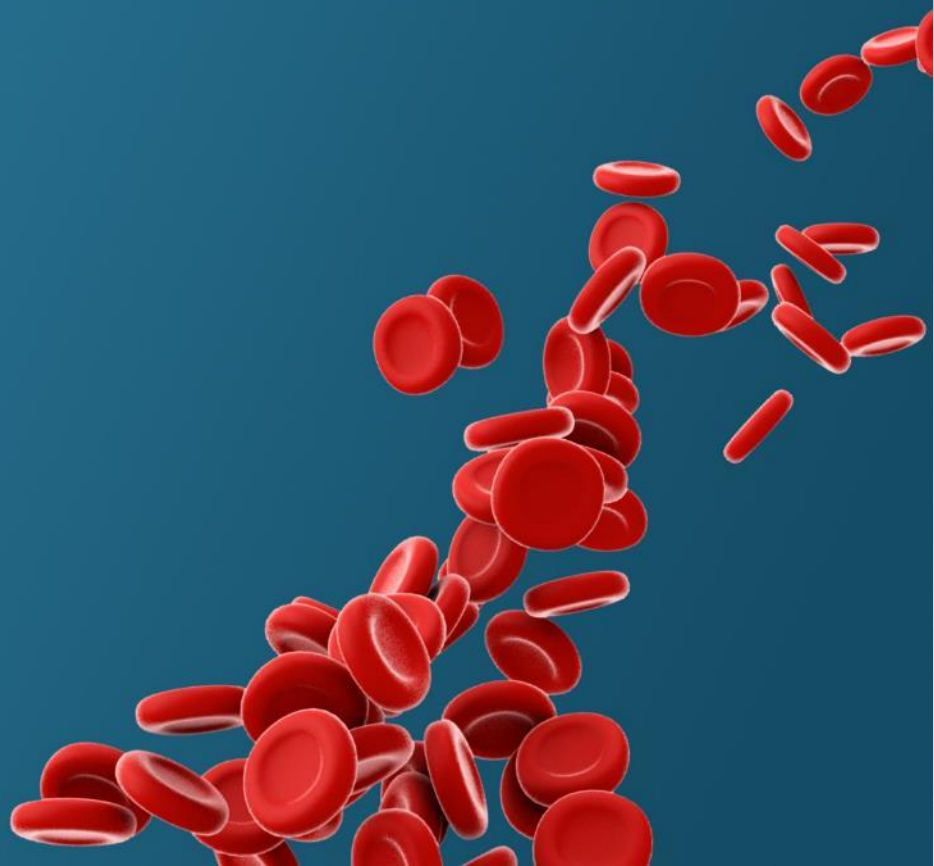
Forward-looking statements

This presentation and various remarks we make during this presentation contain forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding the potential benefits of mitapivat, Agios' plans for the future clinical development of mitapivat in alpha- and beta thalassemia; Agios' plans for future regulatory submissions; and Agios' strategic plans and prospects. The words "anticipate," "expect," "goal," "hope," "milestone," "opportunity," "plan," "potential," "possible," "strategy," "will," "vision," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Such statements are subject to numerous important factors, risks and uncertainties that may cause actual events or results to differ materially from Agios' current expectations and beliefs. For example, there can be no guarantee that any product candidate Agios is developing will successfully commence or complete necessary preclinical and clinical development phases, or that development of any of Agios' product candidates will successfully continue. There can be no guarantee that any positive developments in Agios' business will result in stock price appreciation. Management's expectations and, therefore, any forward-looking statements in this presentation and various remarks we make during this presentation could also be affected by risks and uncertainties relating to a number of other important factors, including, without limitation: risks and uncertainties related to the impact of pandemics or other public health emergencies to Agios' business, operations, strategy, goals and anticipated milestones, including its ongoing and planned research activities, ability to conduct ongoing and planned clinical trials, clinical supply of current or future drug candidates, commercial supply of current or future approved products, and launching, marketing and selling current or future approved products; Agios' results of clinical trials and preclinical studies, including subsequent analysis of existing data and new data received from ongoing and future studies; the content and timing of decisions made by the U.S. FDA, the EMA or other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies; Agios' ability to obtain and maintain requisite regulatory approvals and to enroll patients in its planned clinical trials; unplanned cash requirements and expenditures; Agios' ability to obtain, maintain and enforce patent and other intellectual property protection for any product candidates it is developing; Agios' ability to establish and maintain key collaborations; uncertainty regarding any milestone or royalty payments related to the sale of Agios' oncology business or its in-licensing of TMPRSS6 siRNA, and the uncertainty of the timing of any such payments; uncertainty of the results and effectiveness of the use of Agios' cash and cash equivalents; competitive factors; and general economic and market conditions. These and other risks are described in greater detail under the caption "Risk Factors" included in Agios' public filings with the Securities and Exchange Commission. Any forward-looking statements contained in this presentation and various remarks we make during this presentation speak only as of the date hereof, and Agios expressly disclaims any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

Opening Remarks

Brian Goff

Chief Executive Officer

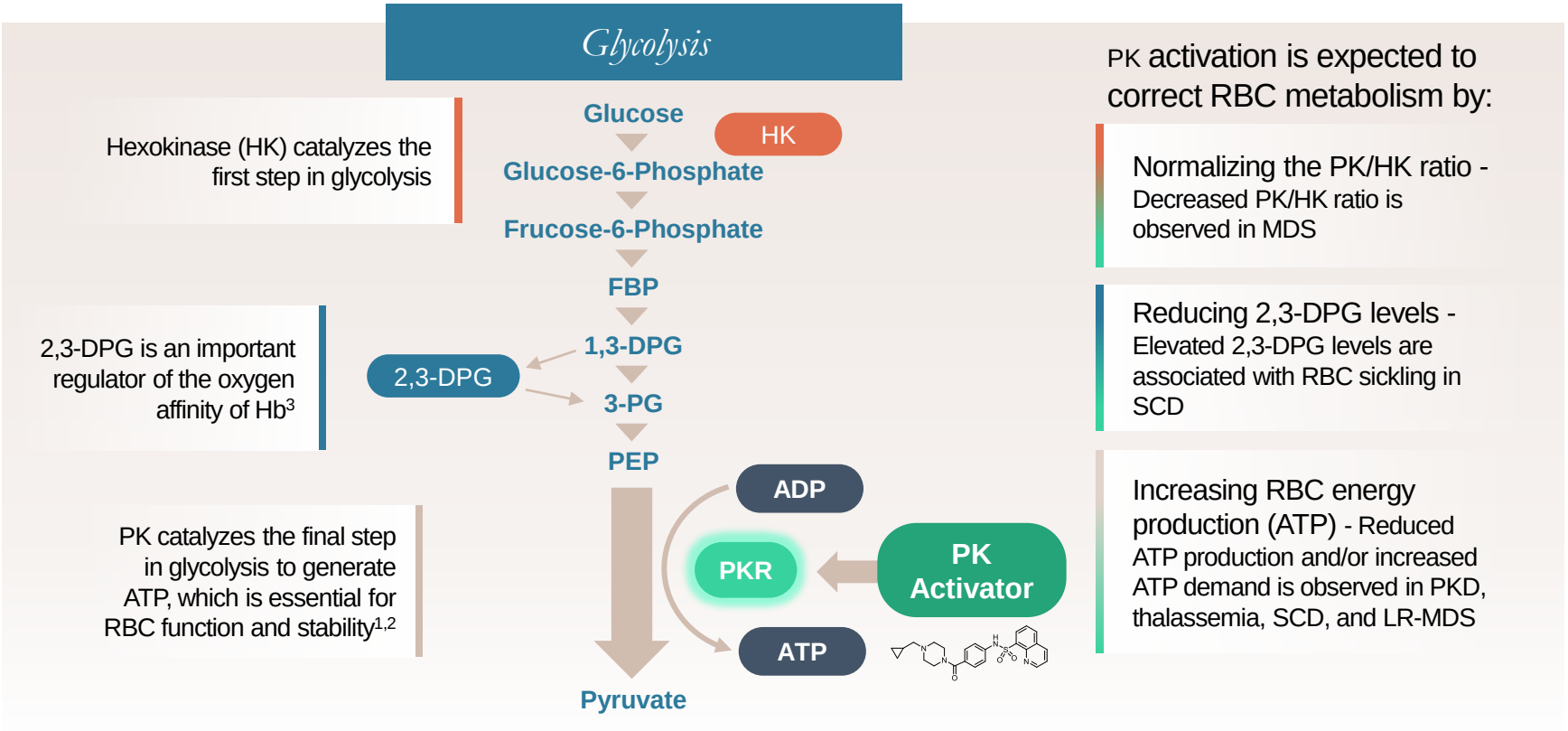


Mitapivat Phase 3 Development Program in Thalassemia

Sarah Gheuens, M.D., Ph.D.

Chief Medical Officer, Head of Research and Development

PYRUKYUND® (mitapivat) is an oral, small molecule allosteric activator of pyruvate kinase with the potential to correct RBC metabolism

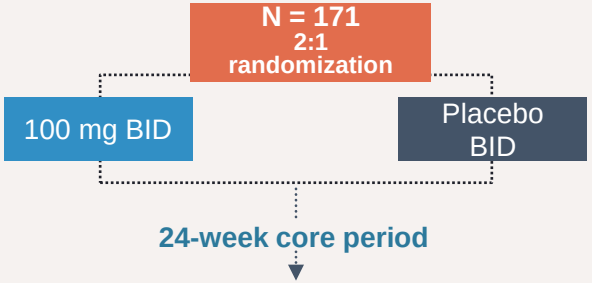


ADP = adenosine diphosphate; ATP = adenosine triphosphate; DPG = diphosphoglycerate; FBP = fructose bisphosphate; m = mutant; PEP = phosphoenolpyruvate; PG = phosphoglycerate; PK = pyruvate kinase; PKR = RBC-specific PK; RBC = red blood cell

1. Kung C et al. Blood 2017;130:1347; 2. Valentini G et al. J Biol Chem 2002;277:23807; 3. Rab MAE et al. Blood 2021;137:2997–3001

Two global, Phase 3, randomized controlled trials of PYRUKYND® in thalassemia encompass broad range of thalassemia patients

ENERGIZE



Primary endpoint

- Mean Hb ↑
  ≥ 1 g/dL from baseline

Secondary endpoints

- Fatigue, additional measures of Hb ↑, hemolysis, patient-reported outcomes, physical activity, iron metabolism, safety, PK/PD

Key inclusion criteria

- ≥ 18 years
- β-thalassemia ± α-globin mutations, HbE β-thalassemia, or α-thalassemia (HbH disease)
- Non-transfusion-dependent defined as ≤5 RBC units during the 24-week period before randomization and no RBC transfusions ≤8 weeks prior
- Hb ≤ 10.0 g/dL

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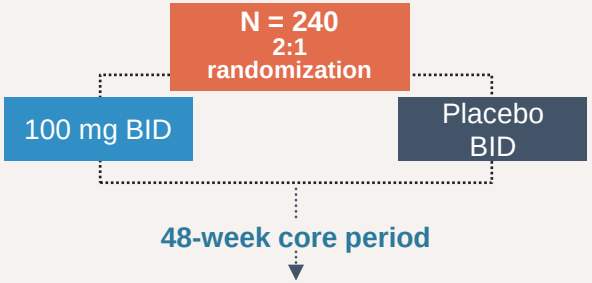


Primary endpoint

- 50% reduction in transfusion burden in any 12-week rolling period

Secondary endpoints

- Additional measures of transfusion reduction, safety, PK/PD

Key inclusion criteria

- ≥ 18 years
- β-thalassemia ± α-globin mutations, HbE β-thalassemia, or α-thalassemia (HbH disease)
- Transfusion-dependent defined as 6 to 20 RBC units transfused and ≤6-week transfusion-free period during the 24-week period before randomization

BID = twice daily; Hb = hemoglobin; HbE = hemoglobin E; HbH = hemoglobin H; PK = pharmacokinetics; PD = pharmacodynamics.

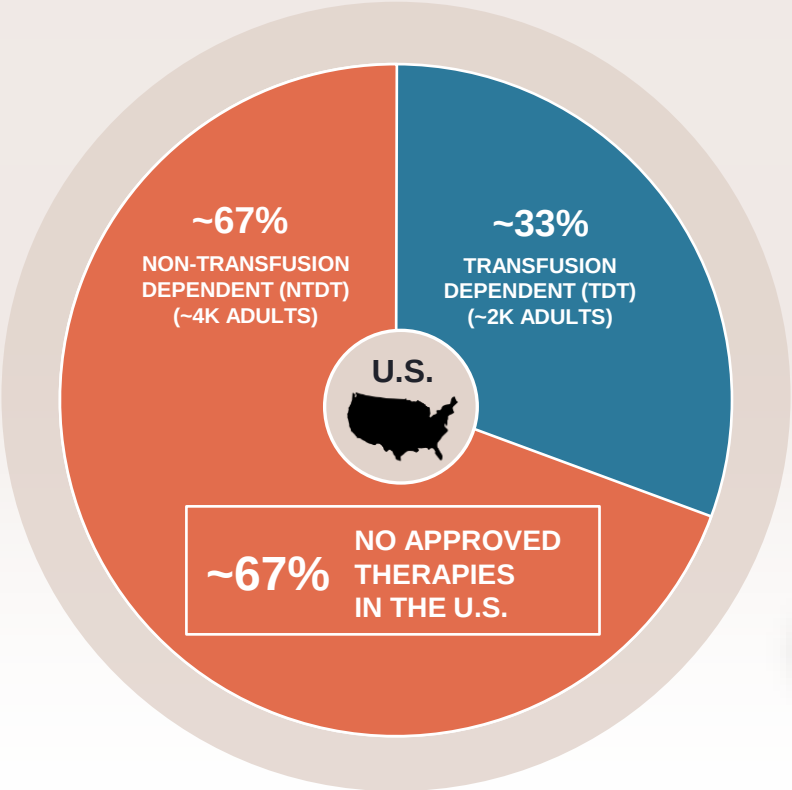
Based on strength of two pivotal Phase 3 trials, Agios has potential to deliver the first therapy for all thalassemia subtypes

Mitapivat Thalassemia Phase 3 program

ENERGIZE

- **Alpha- and Beta-thalassemia Non-transfusion dependent** patients
- Primary endpoint achieved: Hemoglobin (Hb) response

Data announced January 3, 2024



Mitapivat Thalassemia Phase 3 program

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- **Alpha- and Beta-thalassemia Transfusion dependent** patients
- Primary endpoint achieved: Transfusion Reduction Response

Data announced June 3, 2024

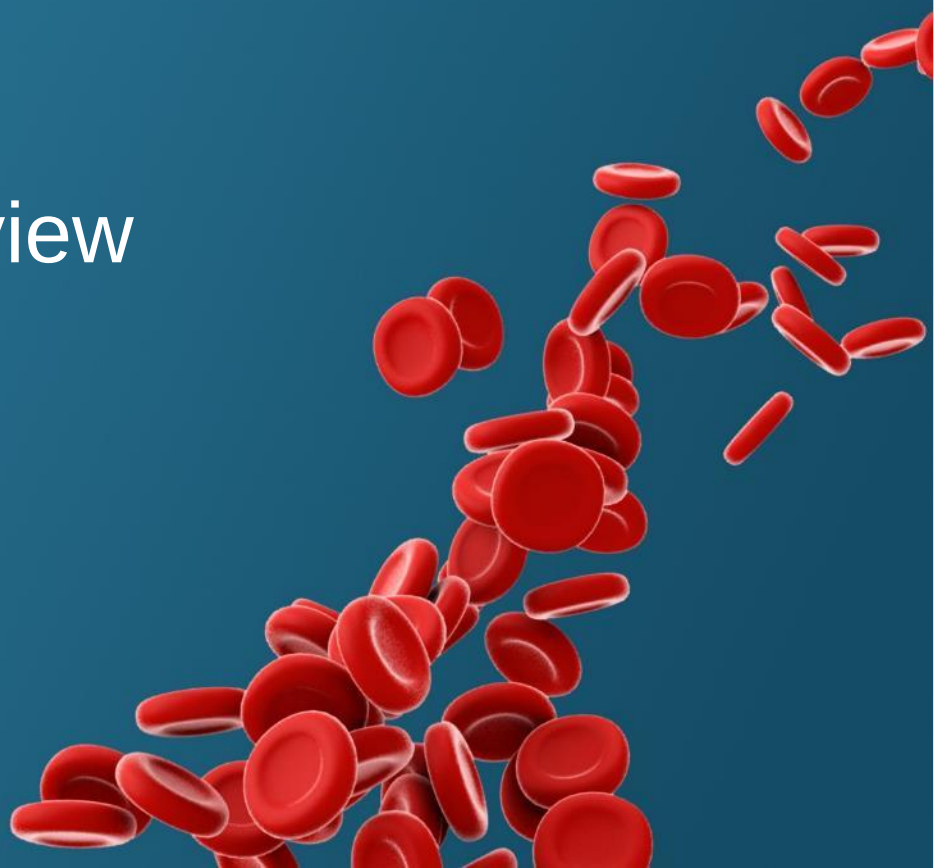
Beta-THAL prevalence: HEOR Global THAL Epidemiology SLE (XCENDA, 2021); US: Paramore, et.al; DE: Borchert, et.al; Alpha-THAL prevalence: Agios internal estimates; LEK Analysis | Beta-THAL TD/NTD split: Thuret, et.al., Haematologica 2010; Magnolia TPP MR, April 2020 | Alpha-THAL TD/NTD split; Taher, et.al., Vox Sanguinis, 2015; Magnolia TPP MR, April 2020.

PYRUKYND® is under investigation for thalassemia and is not approved anywhere for that use.

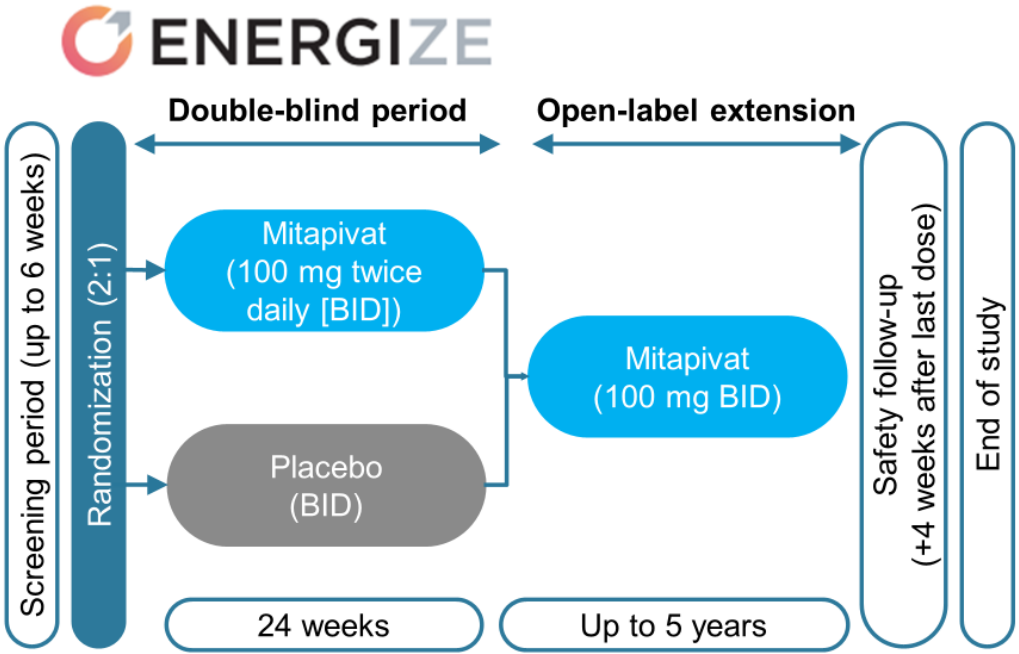
ENERGIZE Data Overview

Ali Taher, M.D., Ph.D.

Professor of Medicine, Hematology & Oncology and Director – Naef K. Basile Cancer Institute, American University of Beirut Medical Center



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 ± 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)

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

Kuo KHM et al. *Hemasphere* 2022;6:23–4.

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

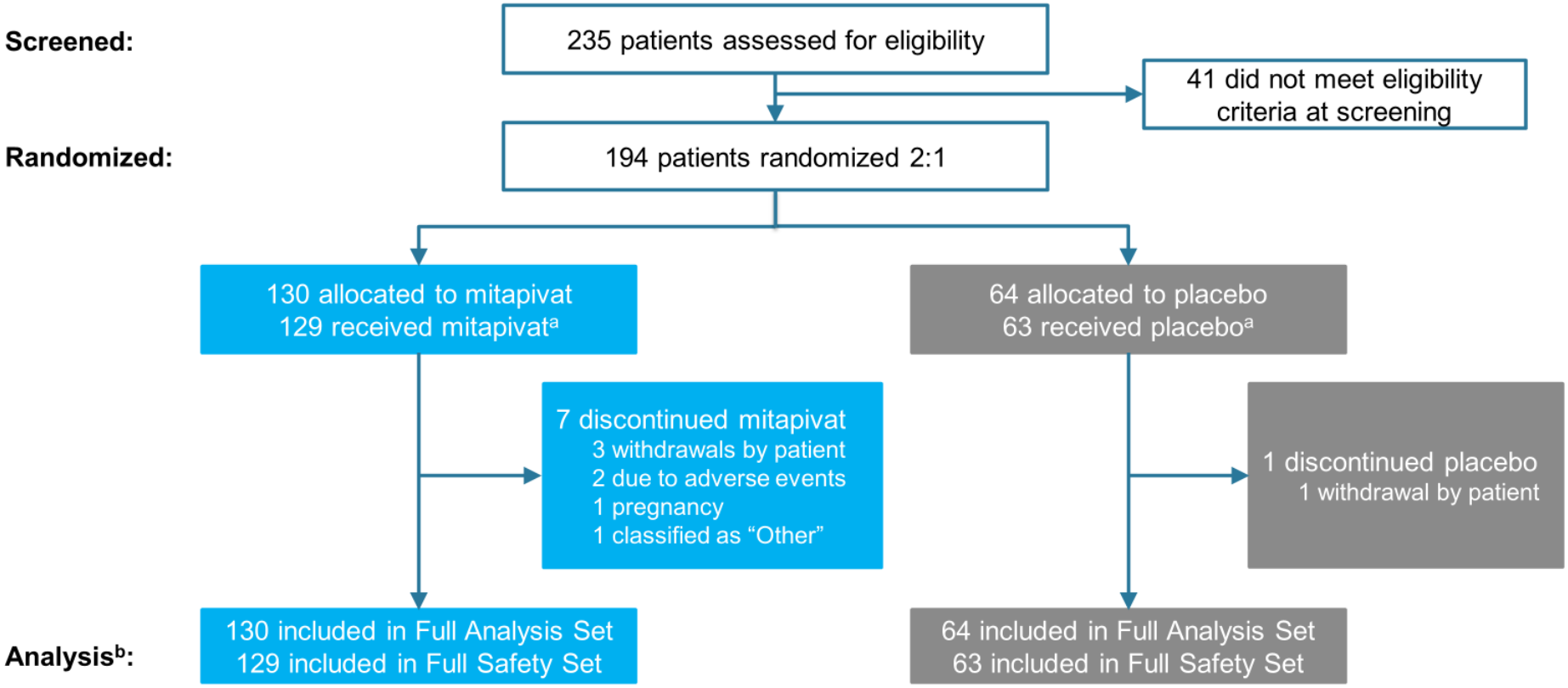
- Change from baseline in indirect bilirubin, lactate dehydrogenase (LDH), and haptoglobin at Week 24
- Change from baseline in reticulocytes and erythropoietin at Week 24

Safety endpoints

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

Hb, hemoglobin

Patient flowchart: 194 patients were randomized in the study



[a]1 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. Full Safety 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

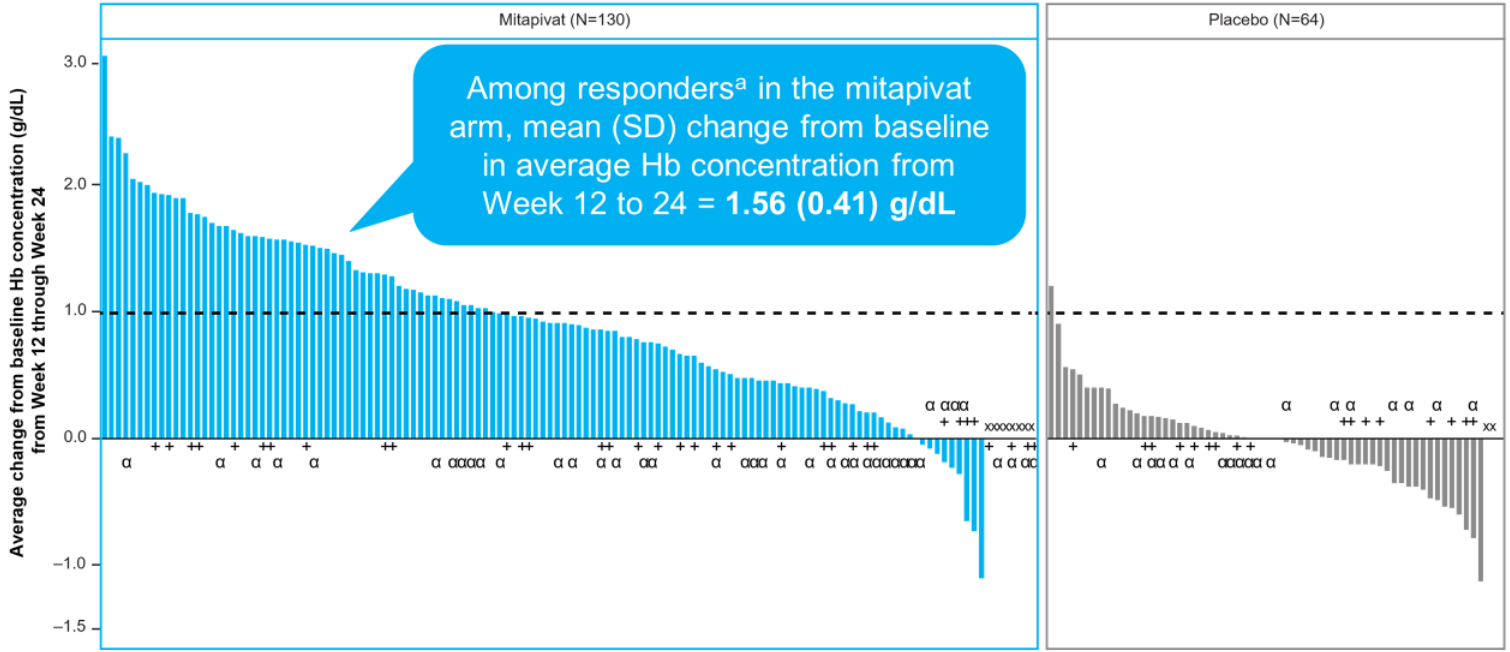
Demographics and disease characteristics	Mitapivat (N=130)	Placebo (N=64)
Age, mean (±SD), years	42.4 (13.0)	38.9 (13.0)
Female, n (%)	84 (64.6)	39 (60.9)
Thalassemia type, n (%)		
α-thalassemia/HbH disease	42 (32.3)	20 (31.3)
β-thalassemia	88 (67.7)	44 (68.8)
Transfusion burden,[a] n (%)		
0	114 (87.7)	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), µmol/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)

[a]Total number of RBC units transfused in the 24-week period before randomization. [b]As recorded in medical/surgical history electronic case report form (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.
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



α = α-thalassemia/HbH disease

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

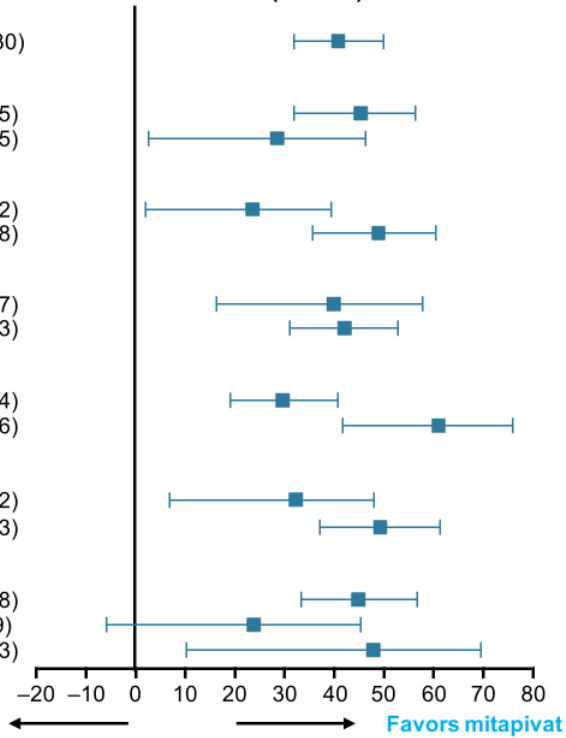
x = Patient with missing baseline or with no assessments from Week 12 through Week 24

Analysis conducted on Full Analysis Set. [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

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

Subgroup analysis of primary endpoint

Subgroup	Hb response rate, % (n/N) Placebo	Hb response rate, % (n/N) Mitapivat	Difference (95% CI)[b]
All patients (stratified)[a] (N=64 vs 130)	1.6 (1/64)	42.3 (55/130)	40.9 (32.0, 49.8)
Baseline Hb concentration			
≤9.0 g/dL (≤90 g/L)	2.1 (1/47)	47.4 (45/95)	45.2 (32.1, 56.2)
9.1–10.0 g/dL (91–100 g/L)	0 (0/17)	28.6 (10/35)	28.6 (2.6, 46.3)
Thalassemia genotype			
α-thalassemia/HbH disease	0 (0/20)	23.8 (10/42)	23.8 (2.2, 39.5)
β-thalassemia	2.3 (1/44)	51.1 (45/88)	48.9 (35.7, 60.2)
Age at screening (years)			
<35	3.7 (1/27)	43.2 (16/37)	39.5 (16.5, 57.6)
≥35	0 (0/37)	41.9 (39/93)	41.9 (31.1, 52.6)
Sex			
Female	0 (0/39)	29.8 (25/84)	29.8 (19.1, 40.7)
Male	4.0 (1/25)	65.2 (30/46)	61.2 (41.6, 75.7)
Race			
Asian	4.2 (1/24)	36.5 (19/52)	32.4 (7.1, 47.9)
White	0 (0/36)	49.3 (36/73)	49.3 (37.1, 61.3)
Geographic region			
North America and Europe	0 (0/39)	44.9 (35/78)	44.9 (33.4, 56.6)
Asia-Pacific	7.1 (1/14)	31.0 (9/29)	23.9 (–5.6, 45.3)
Rest of the world	0 (0/11)	47.8 (11/23)	47.8 (10.4, 69.4)

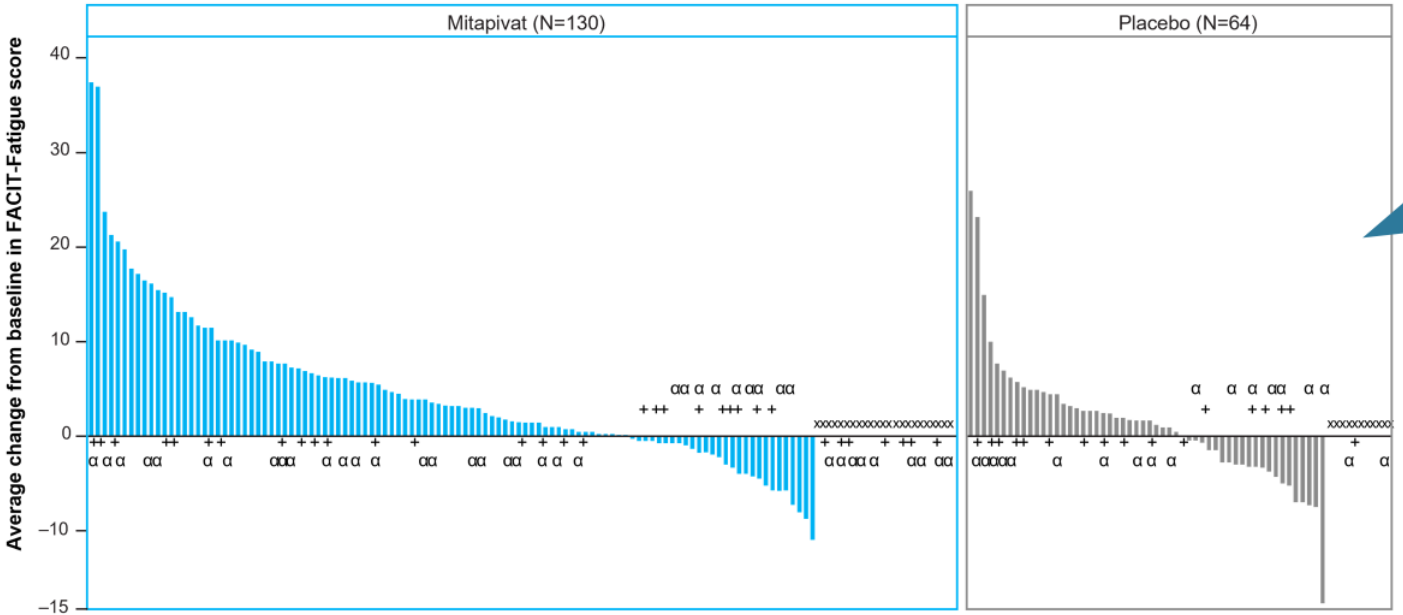


Analysis conducted on Full Analysis Set. [a]Stratified by baseline Hb concentration (≤9.0 g/dL or 9.1–10.0 g/dL) and thalassemia genotype (α-thalassemia/HbH disease or β-thalassemia). [b]For "All patients," the estimates for the difference and the 95% CIs are based on the Mantel–Haenszel stratum weighted 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

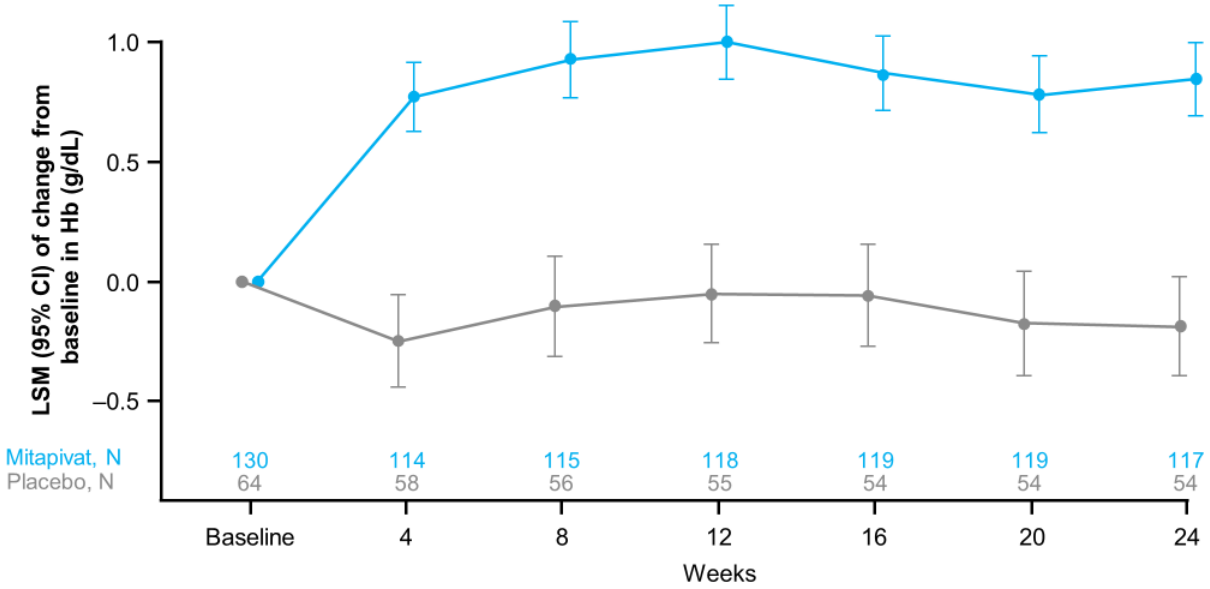
x = Patient with missing baseline or with no assessments from Week 12 through Week 24

Analysis conducted on Full Analysis Set.
FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue Scale; Hb, hemoglobin; HbH, hemoglobin H; HRQoL, health-related quality of life

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



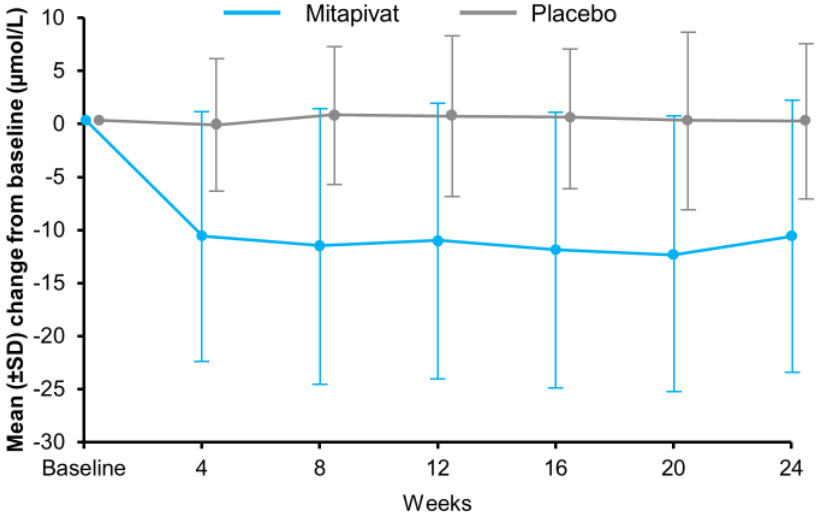
Analysis conducted on Full Analysis Set.
Hb, hemoglobin; LSM, least-squares mean

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

Secondary endpoints

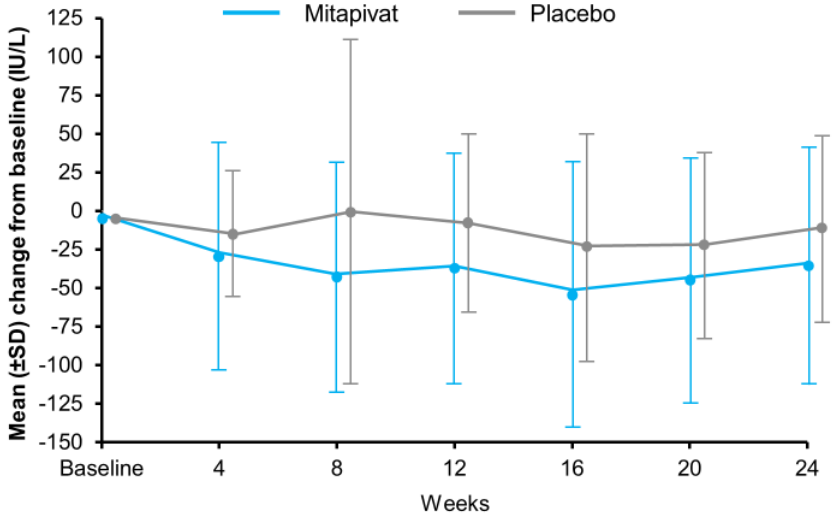
Indirect bilirubin

	Mitapivat N=116	Placebo N=54	LSM difference
Indirect bilirubin, LSM (95% CI) change from baseline at Week 24, µmol/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 (±SD)

Analysis conducted on Full Analysis Set.
LDH, lactate dehydrogenase; LSM, least-squares mean

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

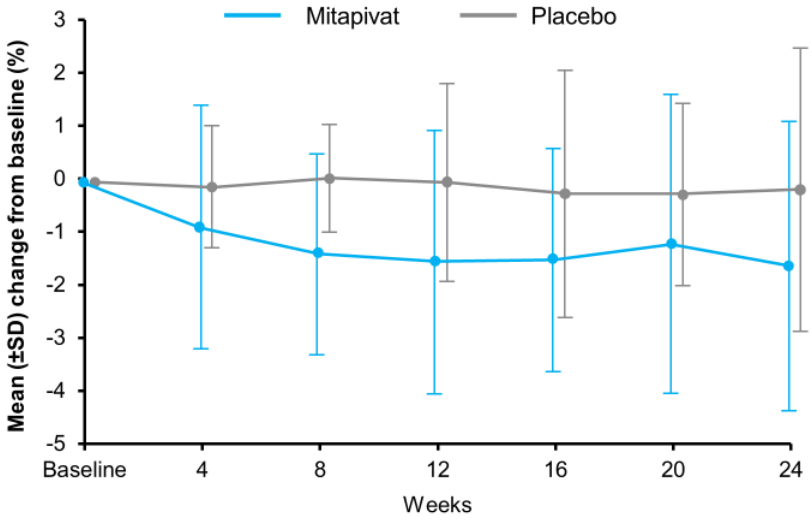
Secondary endpoints

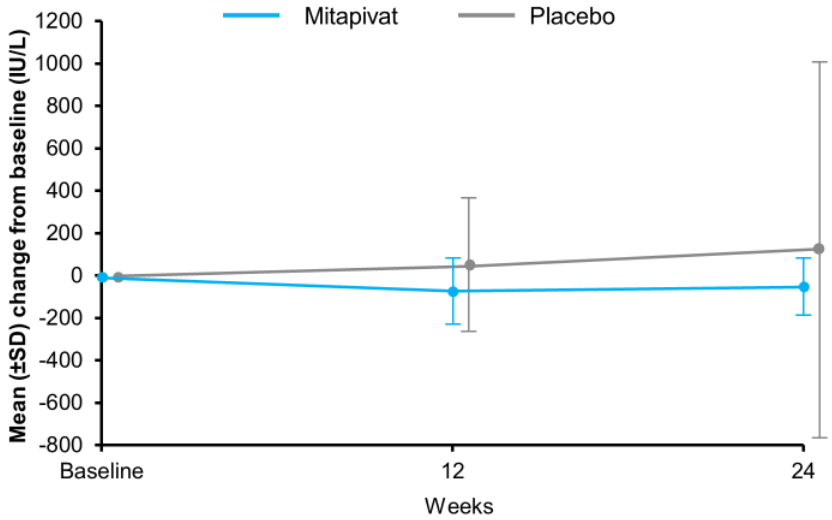
Reticulocyte percentage

	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)

Analysis conducted on Full Analysis Set.
LSM, least-squares mean

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)

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 Event on a 5-point severity scale (Grade 1–5).

Most frequently reported (≥10%) TEAEs

Secondary endpoint

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)

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 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 Event on a 5-point severity scale (Grade 1–5).
TEAE, treatment-emergent adverse event

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

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

1. Kung C et al. *Blood* 2017;130:1347–56; 2. Matte A et al. *J Clin Invest* 2021;131:e144206; 3. Kuo KHM et al. *Lancet* 2022;400:493–501; 4. Al-Samkari H et al. *NEJM* 2022;386:1432–42; 5. Glenthøj A et al. *Lancet Haematol* 2022;9:e724–32; 6. Idowu M et al. *Blood* 2023;142:271.

ENERGIZE Quality of Life and Patient-Reported Outcome Measures

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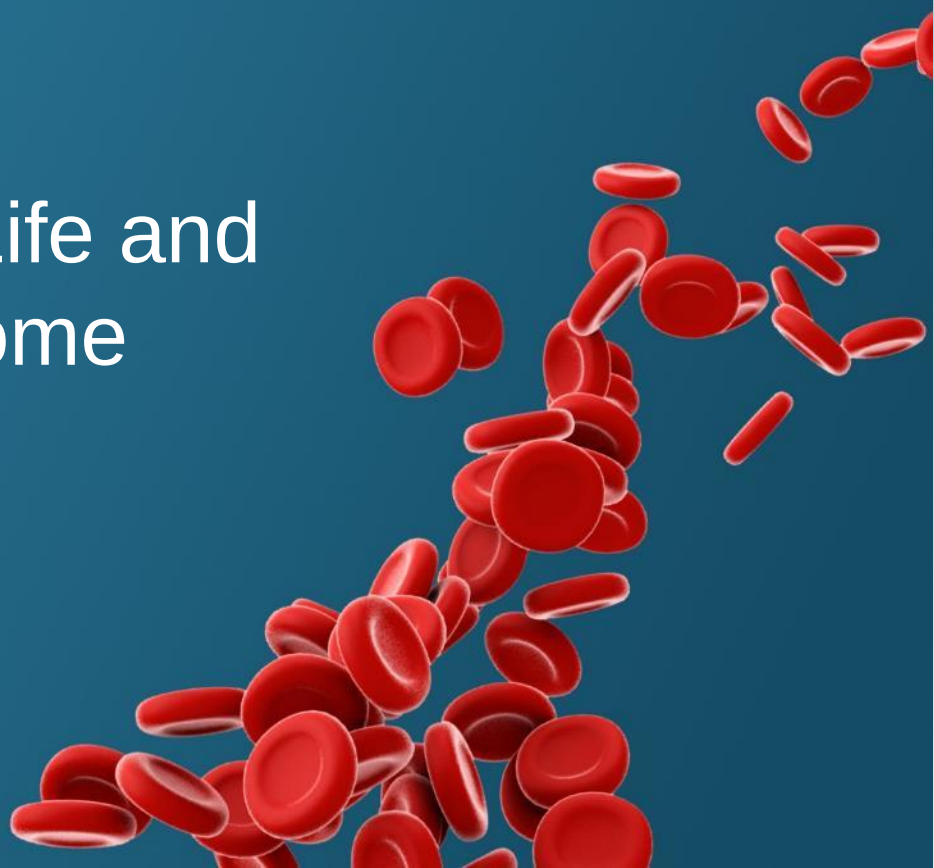


Background

Thalassemia and its impact on health-related quality of life (HRQoL)

- Thalassemia, a group of inherited disorders characterized by anemia due to chronic hemolysis and ineffective erythropoiesis, is associated with serious long-term complications[1,2]
- Anemia has been associated with increased symptom burden, such as fatigue, and poor HRQoL in patients with non–transfusion-dependent thalassemia (NTDT)[1,3]
- Patients with α- or β-thalassemia, regardless of transfusion status, report negative impacts on daily activities, physical functioning, and emotional/mental state[4–6]
- Some domains of HRQoL are reportedly worse or comparable in adult patients with NTDT vs those with transfusion-dependent thalassemia (TDT)[3–6]
- α-thalassemia has no approved therapies,[7,8] and β-thalassemia has no approved oral disease-modifying therapies[9]
  - No oral disease-modifying therapies for thalassemia have been shown to improve aspects of HRQoL[10]

HRQoL, health-related quality of life; NTDT, non–transfusion-dependent thalassemia; TDT, transfusion-dependent thalassemia. 1. Taher AT et al. Nicosia (Cyprus): Thalassaemia International Federation; 2023. https://ncbi.nlm.nih.gov/books/NBK599489. Accessed 21May2024; 2. Farmakis D, et al. Nicosia (Cyprus): Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/a-short-guide-for-the-management-of-transfusion-dependent-thalassaemia-2022/. Accessed 21May2024; 3. Cappellini MD et al. *Am J Hematol* 2019;94:E261–4; 4. Musallam KM et al. Poster presented at ASCAT 2022, London. October 2022; 5. Shah R, Badawy SM. Ann NY *Acad Sci* 2024;1532:50–62; 6. Bizri M et al. *Blood Rev* 2024:65:101181; 7. Amid A et al. Nicosia (Cyprus): Thalassaemia International Federation; 2023. https://thalassaemia.org.cy/publications/tif-publications/guidelines-for-the-management-of-%ce%b1-thalassaemia/. Accessed 21May2024; 8. Harewood J, Azevedo AM. In: StatPearls [Internet]. Treasure Island (FL); 2022. 9. Langer AL, Esrick EB. *Hematology Am Soc Hematol Educ Program* 2021:600–6; 10. Taher AT et al. *Expert Rev Hematol* 2021;14:897–909.

Methods

Study endpoints

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 secondary endpoint:

- Change from baseline in average Hb concentration from Week 12 through Week 24

Key secondary endpoint included here:

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

HRQoL-related secondary endpoints included here:

- Change from baseline in 6-minute walk test (6MWT) distance at Week 24
- Improvement in the Patient Global Impression of Change (PGIC)-Fatigue at Weeks 12, 16, 20, and 24, or “no change” if no or mild fatigue at baseline

HRQoL-related exploratory endpoints included here:

- HRQoL as assessed by PGIC-Thalassemia Symptoms and PGIC-Walking Capacity at Week 24

Refer to **plenary presentation S104** (Plenary Abstracts Session on Saturday, June 15 [14:45–16:15 CEST]) for outcomes

Focus of this poster

6MWT, 6-minute walk test; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue Scale; Hb, hemoglobin; HRQoL, health-related quality of life; PGIC, Patient Global Impression of Change

RESULTS

FACIT-Fatigue

- Patients were fatigued at baseline, with mean baseline FACIT-Fatigue scores lower than the general population (**Figure 3**)[21]
- Mitapivat demonstrated a statistically significant change from baseline in average FACIT-Fatigue score from Week 12 through Week 24 vs placebo (LSM difference (95% CI): 3.40 (1.21, 5.59) [2-sided p=0.0026]) (**Figure 3**)
- A higher proportion of those in the mitapivat arm (36.2%) met or exceeded the MWPC threshold compared with the placebo arm (21.9%) (**Figure 3 & Supplemental figure 2** [QR code])
- Mitapivat led to early and sustained improvements in FACIT-Fatigue score (**Figure 4**)

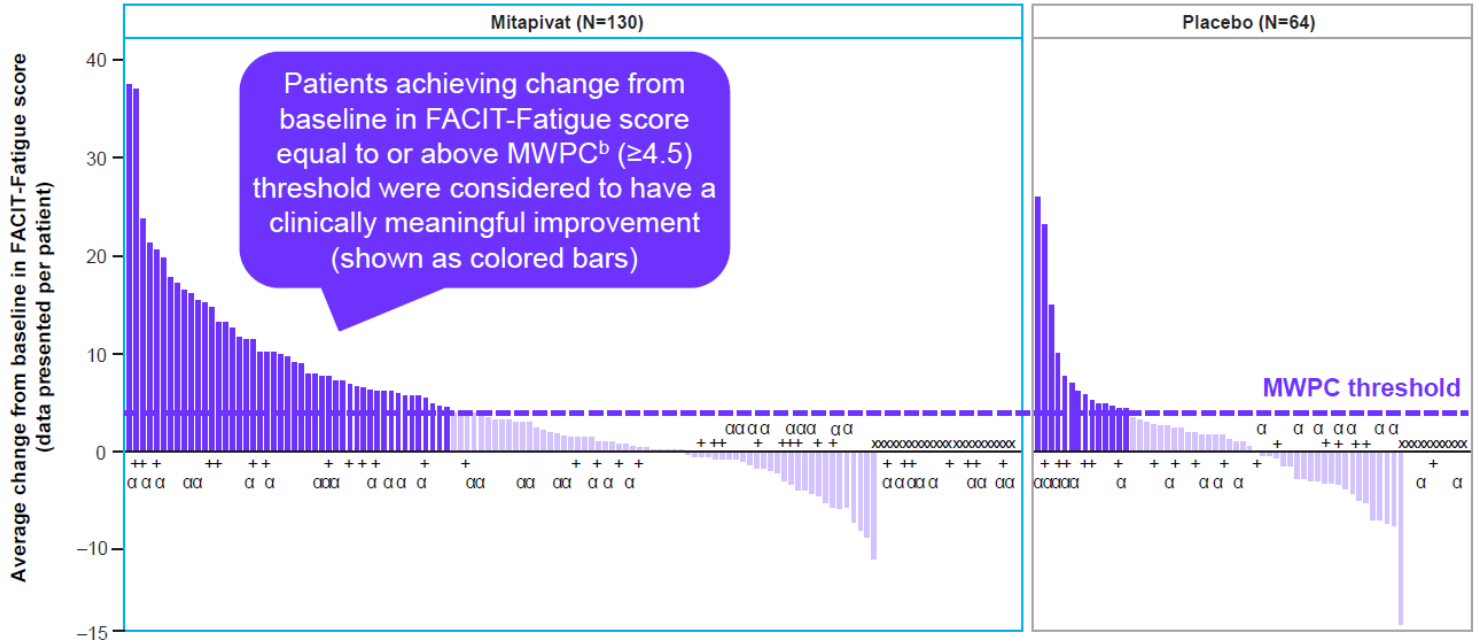
[a]In the general population, mean FACIT-Fatigue score reported in the literature was 43.6[21]

FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue Scale; LSM, least-squares mean.

21. Cella D et al. *Cancer* 2002;94:528–38.

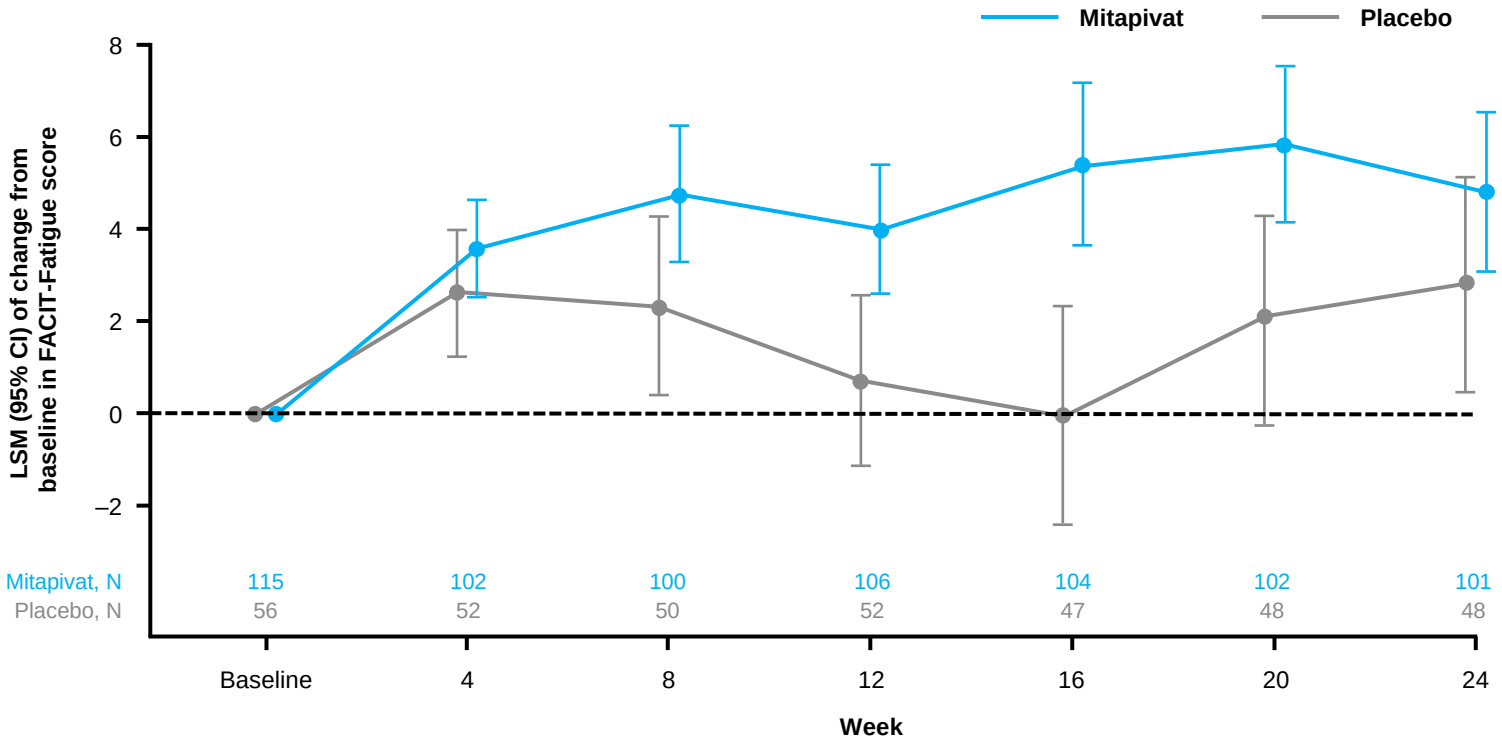
Figure 3. Average change from baseline in FACIT-Fatigue score from Week 12 through Week 24

	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



[a]In the general population, mean FACIT-Fatigue score reported in the literature was 43.6.[21] [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 was considered clinically meaningful for a patient. FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue Scale; Hb, hemoglobin; HbH, hemoglobin H; LSM, least-squares mean; MWPC, meaningful within-person change. 21. Cella D et al. *Cancer* 2002;94:528–38.

Figure 4. LSM (95% CI) of change from baseline in FACIT-Fatigue score over the 24-week double-blind period



FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue Scale; LSM, least-squares mean

Results

6MWT

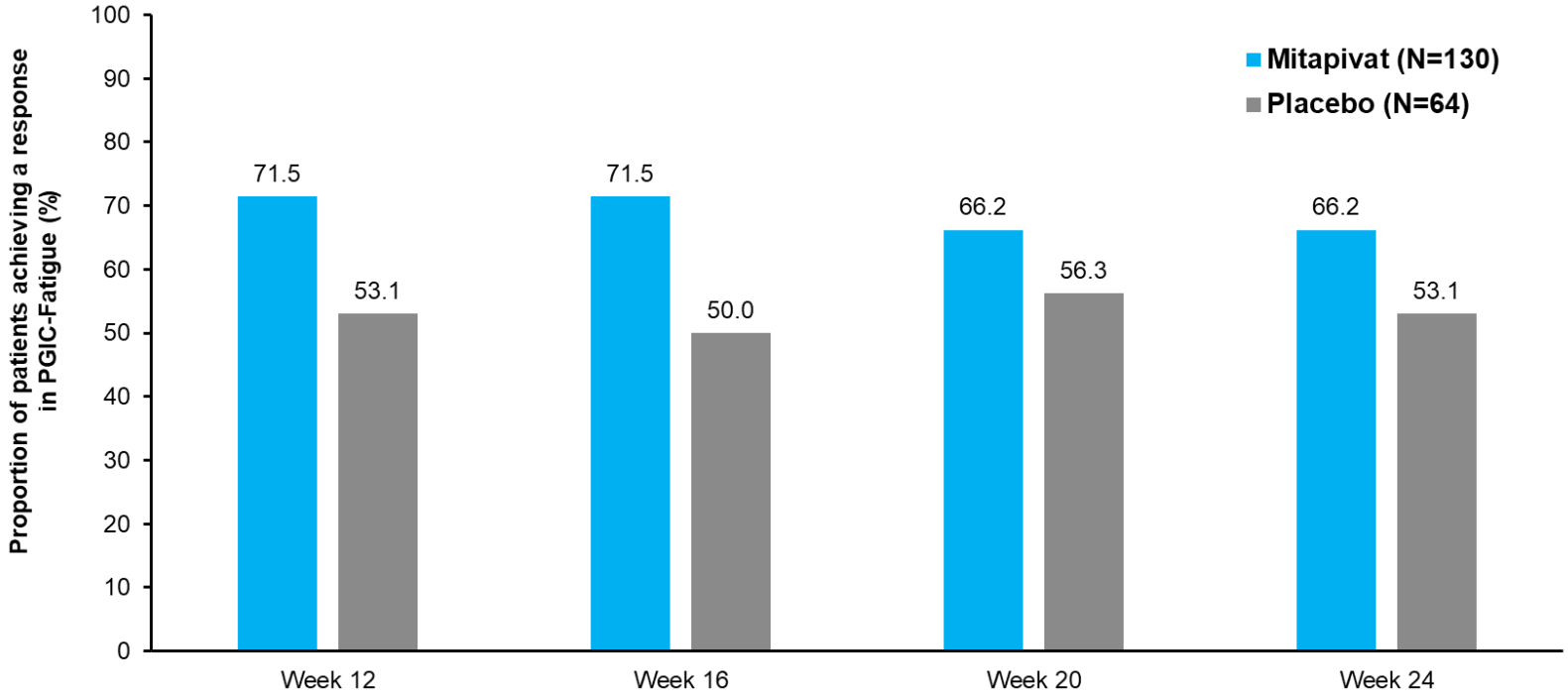
- In healthy individuals aged 20–50 years (a similar age range to the ENERGIZE cohort), mean (±SD) 6MWT distances reported in the literature are 593±57 m for females and 638±44 m for males[22]
  - Baseline 6MWT distances in the mitapivat and placebo arms were 422.22 m and 412.43 m, respectively, suggesting this population had reduced walking capacity at baseline compared with the general population (Table 2)
- Patients in the mitapivat arm had greater improvements in the 6MWT than those in the placebo arm at Week 24 (**Table 2**)
  - LSM change from baseline to Week 24 was 30.48 m in the mitapivat arm and 7.11 m in the placebo arm, with an LSM difference of 23.36 m between treatment arms; this exceeded the literature-reported MCID threshold of ≥20 m[18]

Table 2. LSM change from baseline to Week 24 for 6MWT distance

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

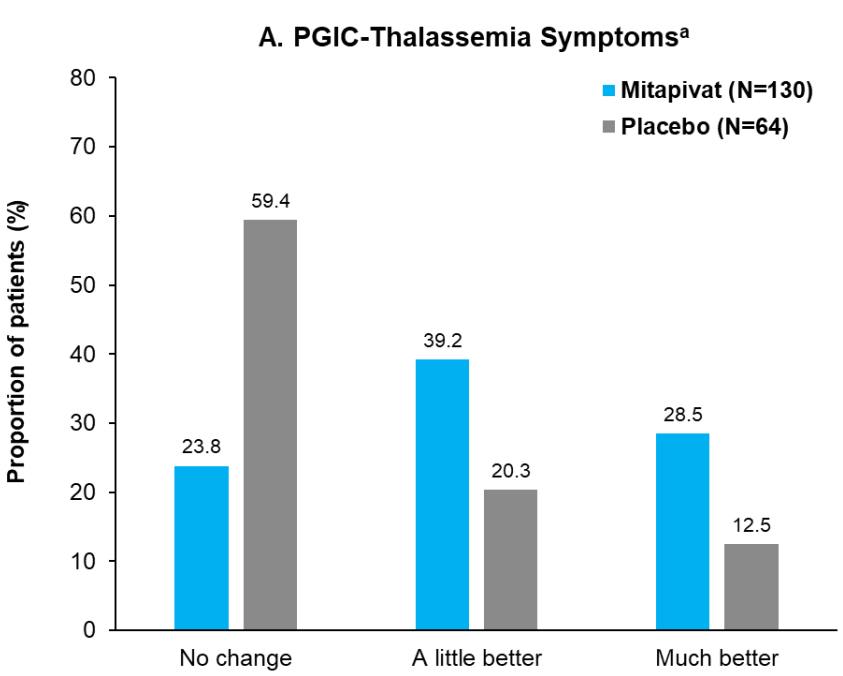
[a]MCID represents the smallest improvement considered valuable by a patient; in this case, MCID in 6MWT was measured by an increased ability to walk by 20 m or more, as reported in the literature.18 [b]In the mitapivat arm, 107 patients had 6MWT data at Week 24; in the placebo arm, 57 patients had 6MWT data at Week 24. 6MWT, 6-minute walk test; LSM, least-squares mean; MCID, minimal clinically important difference. 18. St. Lezin E et al. *Transfusion* 2019;59:1934–43; 22. Chetta A et al. *Respir Med* 2006;100:1573–8.

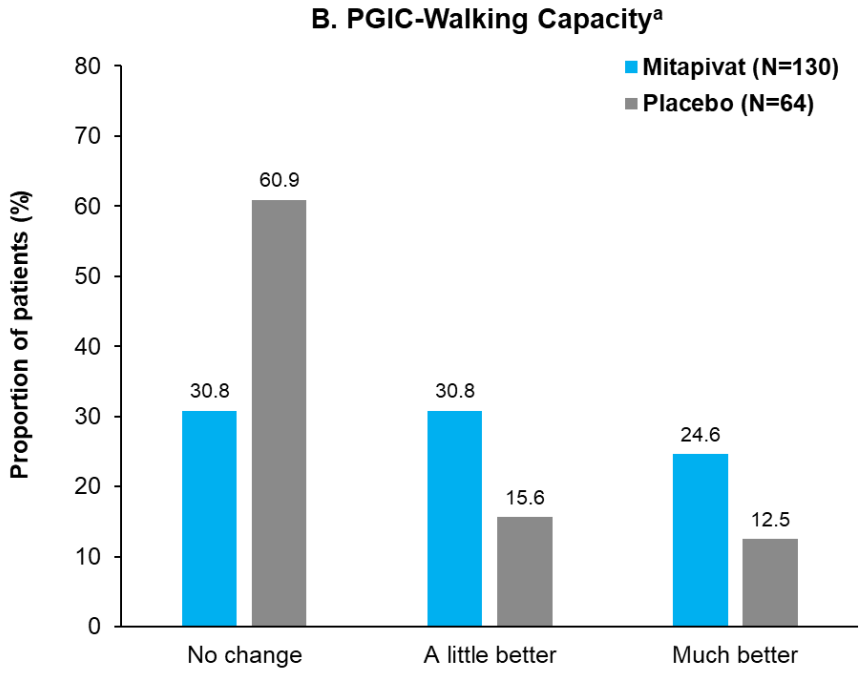
Figure 5. PGIC-Fatigue response by visit[a]



A patient was considered to have achieved a response at each visit if their baseline PGIS and corresponding PGIC met 1 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 was not calculated as part of the study analysis. PGIC, Patient Global Impression of Change; PGIS, Patient Global Impression of Severity

Figure 6. PGIC-Thalassemia Symptoms (A) and PGIC-Walking Capacity (B) at Week 24





[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

Conclusions

- In the 24-week double-blind period of ENERGIZE, significant improvements in fatigue, measured by FACIT-Fatigue, were demonstrated in the mitapivat arm compared with the placebo arm
  - A higher proportion of patients reported clinically meaningful improvements with mitapivat vs placebo
- Functional improvement in patients with mitapivat, measured by the 6MWT, exceeded a previously reported meaningful change threshold from the literature[18]
- A higher proportion of patients with mitapivat reported improved fatigue, disease symptoms, and walking capacity via PGIC with mitapivat vs placebo

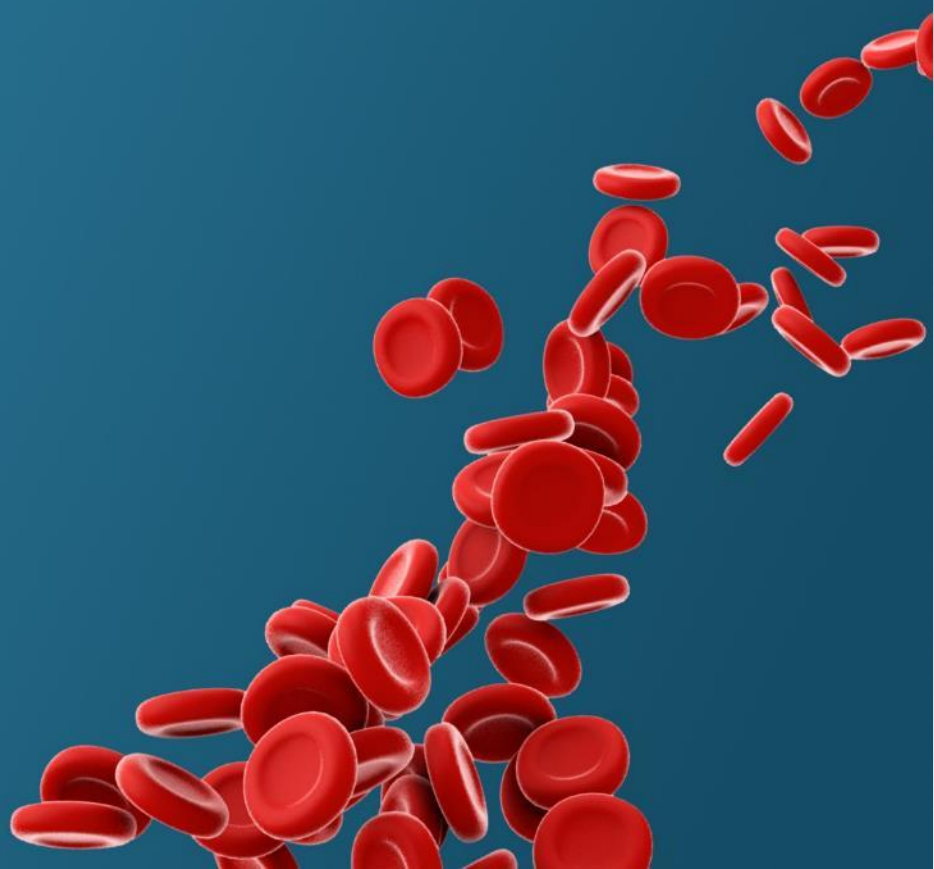
Mitapivat is the first oral, disease-modifying, investigational therapy to improve fatigue and walking capacity in patients with α- or β-NTDT

6MWT, 6-minute walk test; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy–Fatigue Scale; NTDT, non–transfusion-dependent thalassemia; PGIC, Patient Global Impression of Change

18. St. Lezin E et al. *Transfusion* 2019;59;1934–43.

Closing Remarks

Brian Goff
Chief Executive Officer



PYRUKYND® expansion into diseases with larger patient populations provides significant near-term growth potential for first- and best-in-class therapies

pyrukynd (mitapivat) tablets

3-8K patients
in the U.S./EU5

PK deficiency
2022
Approved for adults in the U.S., EU and Great Britain

OUR GOAL
Deliver the first approved therapy for pediatric PK deficiency

18-23K patients
in the U.S./EU5

~70K patients in GCC

>1M patients worldwide

Thalassemia
2025
Potential U.S. approval

OUR GOAL
Deliver the first therapy approved for all thalassemia subtypes

120-135K patients
in the U.S./EU5

~150K patients
in GCC

>3M patients
worldwide

Sickle cell disease
2026
Potential U.S. approval

OUR GOAL
Deliver a novel oral therapy that improves anemia and reduces VOCs

PYRUKYND® is approved in the U.S., EU, and Great Britain for adult pyruvate kinase (PK) deficiency and is under investigation for pediatric PK deficiency, thalassemia, and sickle cell disease.
Source: Agios internal estimates

Planning single regulatory filing incorporating data from ENERGIZE and ENERGIZE-T

ENERGIZE data readout January 3, 2024 

ENERGIZE-T data readout June 3, 2024 

Anticipated filing encompassing data from ENERGIZE and ENERGIZE-T by year-end 2024

Seeking broad indication for all thalassemia patients

Potential FDA approval in 2025

Strong beginning to 2024 with two positive Phase 3 readouts in thalassemia; three additional Phase 3 readouts expected by the end of 2025

2024

Thalassemia
PYRUKYND®
Phase 3 ENERGIZE readout

Thalassemia
PYRUKYND®
Phase 3 ENERGIZE-T readout

Pediatric PK Deficiency
PYRUKYND®
Phase 3 ACTIVATE kids-T readout

2025

Sickle Cell Disease
PYRUKYND®
Phase 3 RISE UP readout

Thalassemia
PYRUKYND®
Potential approval

Pediatric PK Deficiency
PYRUKYND®
Phase 3 ACTIVATE kids readout

2026

Sickle Cell Disease
PYRUKYND®
Potential approval

Pediatric PK Deficiency
PYRUKYND®
Potential approval

Well-positioned with multiple near-term catalysts to enter multi-billion-dollar markets and deliver significant value

PKa franchise with multi-billion-dollar potential	Differentiated mechanism of action	Increasing probability of success	Growing pipeline
Large opportunities with substantial value - potential for two additional **first and best-in-class** indications for PYRUKYND® by 2026	**Clearly differentiated** PK activation franchise targeting red blood cell health **beyond hemoglobin** increase	Proven track record supported by **compelling and consistent data** to date	Diversified pipeline addressing the underlying pathophysiology of **rare diseases with high unmet need**

- **Announced $905 million purchase agreement for vorasidenib royalty on May 28, 2024***
- **Retains rights to $200 million milestone payment from Servier upon FDA approval of vorasidenib**
- $714.3M in cash and equivalents as of March 31, 2024

PK = pyruvate kinase PKa = pyruvate kinase activation *Subject to FDA approval. Agios retains a 3% royalty on annual U.S. net sales greater than $1 billion

agios

Q&A