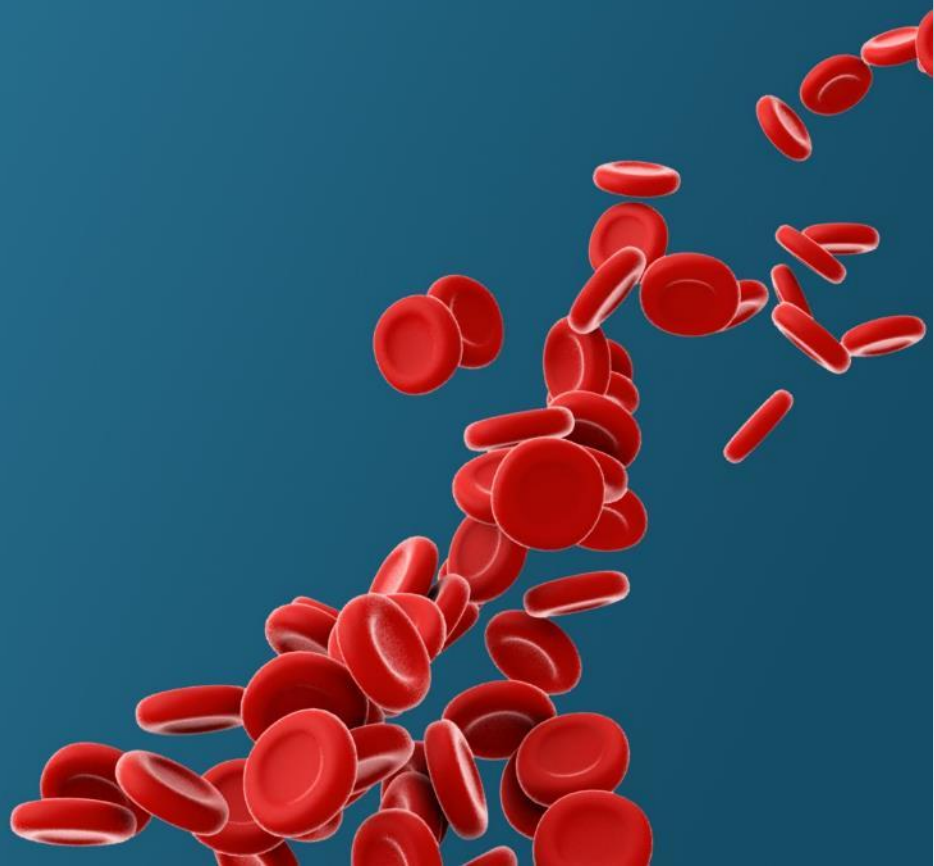
Agios at ASH 2024

December 9, 2024



Agios ASH Investor Breakout Session

TOPIC	PARTICIPANT
Opening Remarks	Brian Goff, Chief Executive Officer
ENERGIZE-T Phase 3 Data Overview	Kevin Kuo, M.D., MSc, FRCPC; Division of Hematology, University of Toronto
Mitapivat Phase 3 Development Program in Thalassemia	Sarah Gheuens, M.D., Ph.D., Chief Medical Officer, Head of Research and Development
Tebapivat Phase 1 SCD Data Overview	Julia Xu, M.D., MScGH, Assistant Professor of Medicine, Division of Classical Hematology and Vascular Medicine Institute, University of Pittsburgh
Tebapivat Development Program in SCD and MDS	Sarah Gheuens, M.D., Ph.D., Chief Medical Officer, Head of Research and Development
Closing Remarks	Brian Goff, Chief Executive Officer
Q&A	All speakers, Cecilia Jones (CFO), and Tsveta Milanova (CCO)

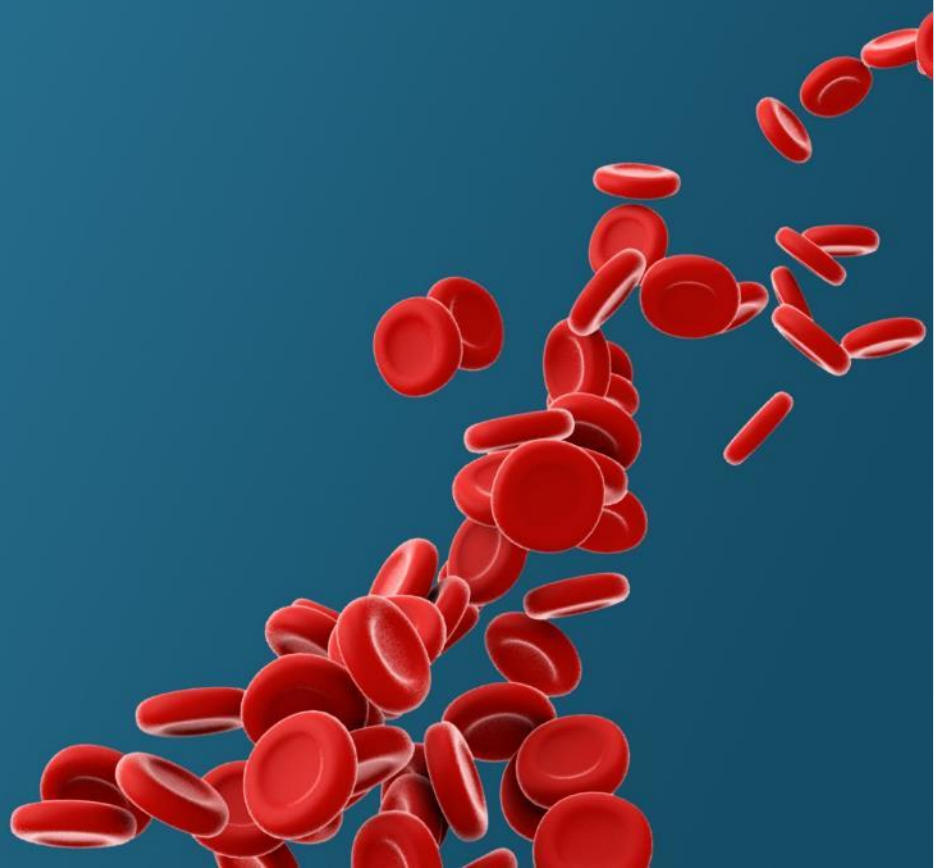
Forward-looking statements

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 PYRUKYND® (mitapivat), tebapivat (AG-946), TMPRSS6 siRNA and AG-181, Agios' PAH stabilizer; Agios' plans, strategies and expectations for its preclinical, clinical and commercial advancement of its drug development, including PYRUKYND®, tebapivat and AG-181; the submission of PYRUKYND to regulators for approval in alpha-and-beta thalassemia; Agios' strategic vision and goals, including its key milestones for 2024; and the potential benefits of Agios' strategic plans and focus. 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; competitive factors; 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 royalty payments related to the sale of its oncology business or any milestone or royalty payments related to 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; 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



ASH 2024 data continues to validate PK activation mechanism and showcase clinical benefits across rare disease portfolio

In total, 16 presentations/publications led by Agios and external collaborators shared at ASH 2024

Thalassemia

- ENERGIZE-T: A Global, Phase 3, Double-Blind, Randomized, Placebo-Controlled Study of Mitapivat in Adults with Transfusion-Dependent Alpha- or Beta-Thalassemia

Sickle Cell Disease

- Results From A Phase 1 Study To Assess The Safety, Tolerability, Pharmacokinetics, And Pharmacodynamics Of Tebapivat (AG-946) In Patients With Sickle Cell Disease

Lower-risk MDS

- A Phase 2B, Open-Label Multicenter Study of Tebapivat (AG-946), a Potent Pyruvate Kinase Activator, in Patients with Anemia due to Lower-Risk Myelodysplastic Syndromes

Additional datasets available as publication only in the Blood November 2024 supplementary edition

ENERGIZE-T Data Overview

Kevin Kuo, M.D., MSc, FRCPC;

Division of Hematology, University of Toronto

#409

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

Maria Domenica Cappellini, MD[1], Sujit Sheth, MD[2], Ali T Taher, MD, PhD, FRCP[3], Hanny Al-Samkari, MD[4], Ali Bülent Antmen, MD, PhD[5], David Beneitez, MD[6], Giovanna Cannas, MD[7], Thomas Coates, MD[8], Lauren Czapla, ANP[9], Jayme L Dahlin, MD, PhD[9], Jeremie H Estepp, MD[9], Elizabeth Feenstra, MD[9], Pencho Georgiev, MD, PhD[10], Sarah Gheuens, MD, PhD[9], Keely S Gilroy, PhD[9], Andreas Glenthøj, MD, PhD[11], Khaled M Musallam, MD, PhD[2,12,13], Kareem Osman, MD[9], John B Porter, MD[14], Hui Shao, PhD[9], Katrin Uhlig, MD, MS[9], Eduard J van Beers, MD, PhD[15], Vip Viprakasit, MD, Dphil (Oxon)[16], Kevin HM Kuo, MD, MSc, FRCPC[17], Antonis Kattamis, MD[18]

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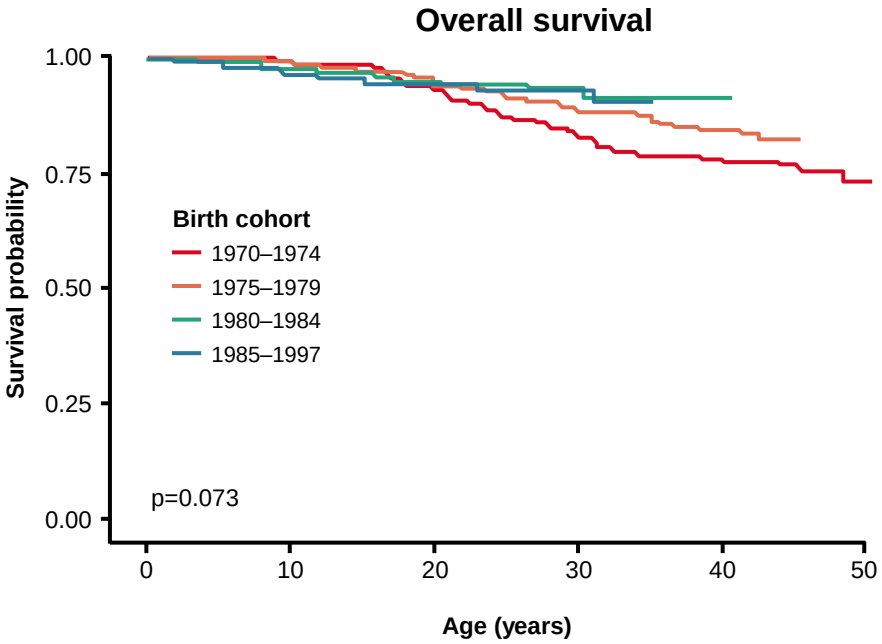
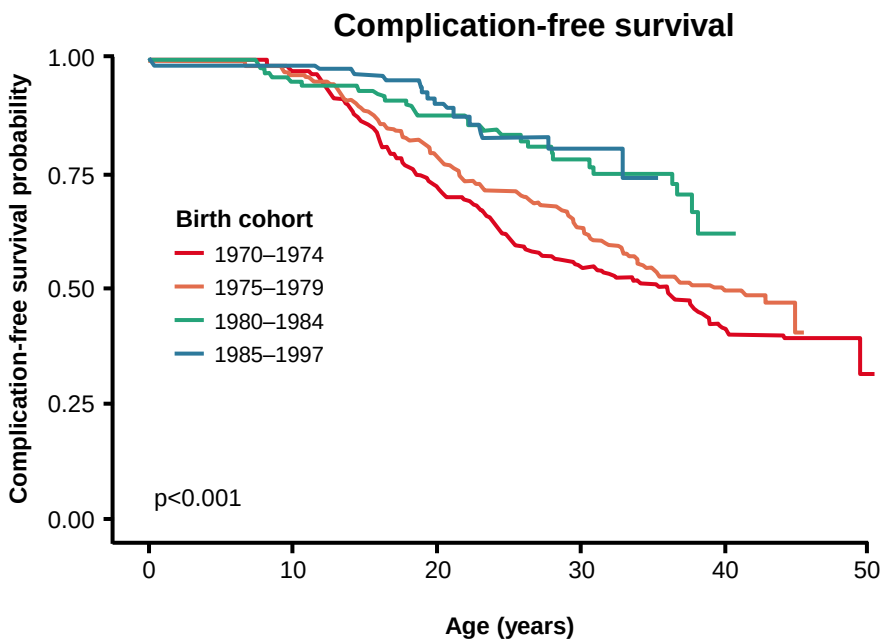
This study was funded by Agios Pharmaceuticals, Inc.
Presented at the 66th American Society of Hematology (ASH) Annual Meeting and Exposition, December 7–10, 2024, San Diego, CA, and online

Although survival and clinical outcomes in patients with transfusion-dependent thalassemia (TDT) have improved over past decades, there remains an unmet need

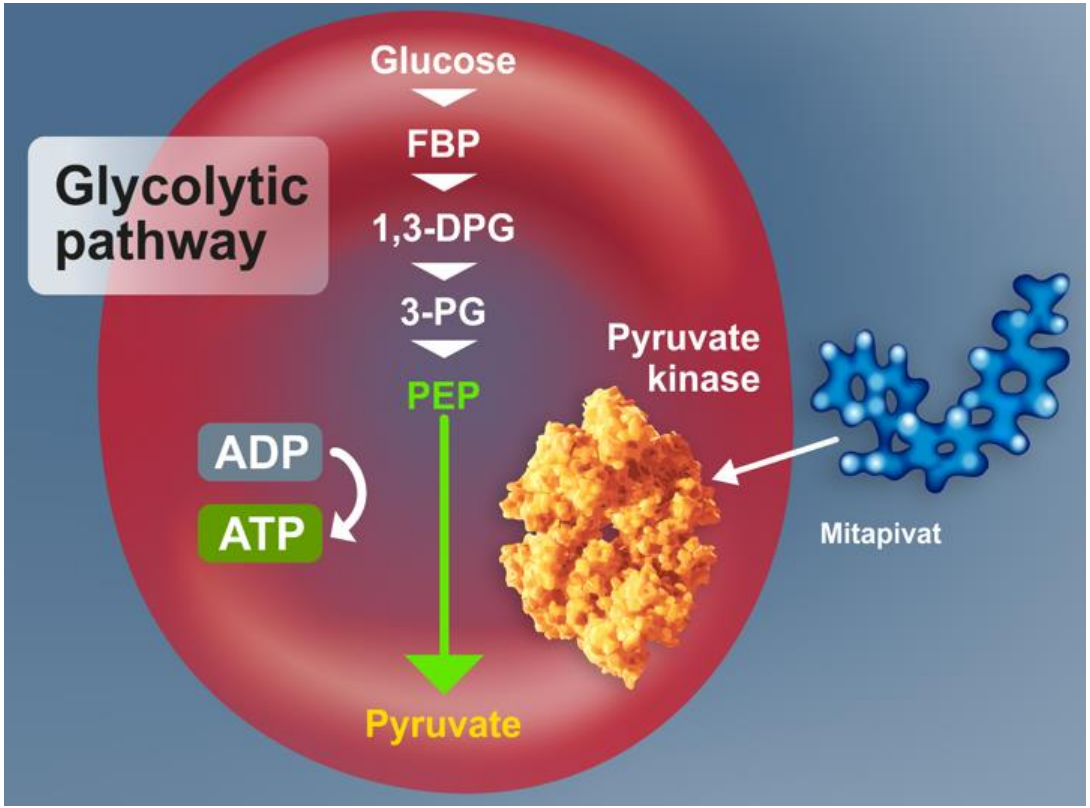
Survival and complications in patients with TDT by birth cohort (N=709)





- The introduction of transfusion and iron chelation therapy in the management of TDT contributed to these improved outcomes

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

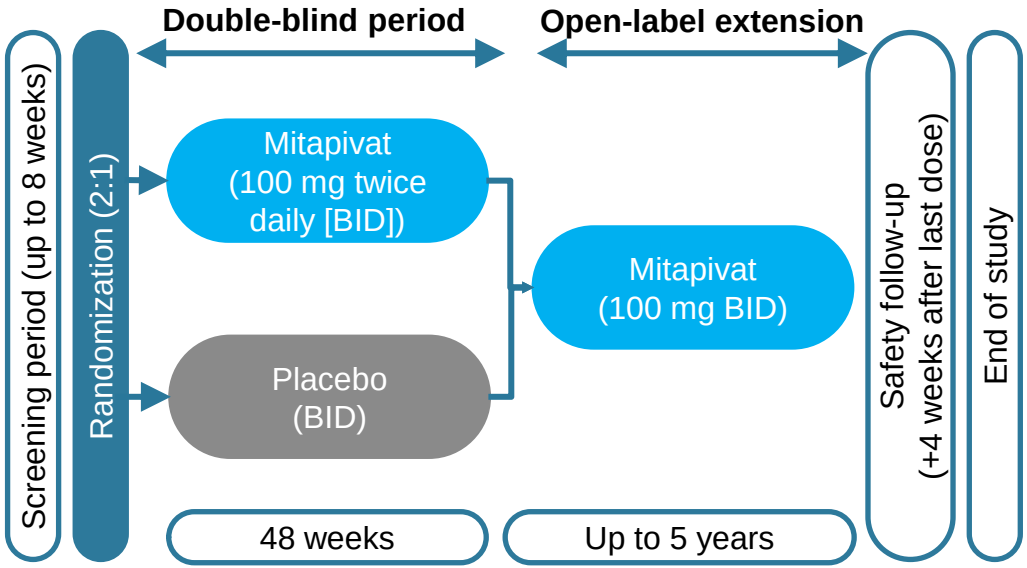


- In thalassemia, there is increased energy demand to maintain RBC health[1–4]
- Mitapivat is an activator of pyruvate kinase (PK), including the red cell-specific (PKR) and M2 (PKM2) isoforms, which act in glycolysis to generate ATP[5,6]
- In the phase 3 ENERGIZE study of patients with non–transfusion-dependent α- or β-thalassemia (NCT04770753), mitapivat increased Hb and improved fatigue vs placebo[7]

ADP, adenosine diphosphate; ATP, adenosine triphosphate; DPG, diphosphoglyceric acid; FBP, fructose biphosphate; Hb, hemoglobin; PEP, phosphoenolpyruvate; PG, phosphoglycerate; RBC, red blood cell. 1. Chakraborty I et al. *Arch Med Res* 2012;43:112–6; 2. Ting YL et al. *Br J Haematol* 1994;88:547–54; 3. Shaeffer JR. *J Biol Chem* 1983;258:13172–7; 4. Khandros E, Weiss MJ. *Hematol Oncol Clin North Am* 2010;24:1071–88; 5. Kung C et al. *Blood* 2017;130:1347; 6. Yang H et al. *Clin Pharmacol Drug Dev* 2019;8:246; 7. Taher AT et al. 2024. EHA 2024, Madrid, Spain: Abstract S102.

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

ENERGIZE-T



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 transplantation
- Homozygous or heterozygous for HbS or HbC
- Receiving treatment with luspatercept or hematopoietic stimulating agents (last doses must have been administered ≥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 Rest of World)

Hb, hemoglobin; HbC, hemoglobin C; HbE, hemoglobin E; HbH, hemoglobin H; HbS, hemoglobin S; RBC, red blood cell. Clinicaltrials.gov. https://clinicaltrials.gov/study/NCT04770779. Accessed November 2024.

Endpoints

Primary endpoint

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

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

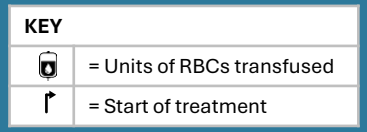
- Transfusion independence, defined as transfusion-free for ≥8 consecutive weeks through Week 48

Safety endpoints

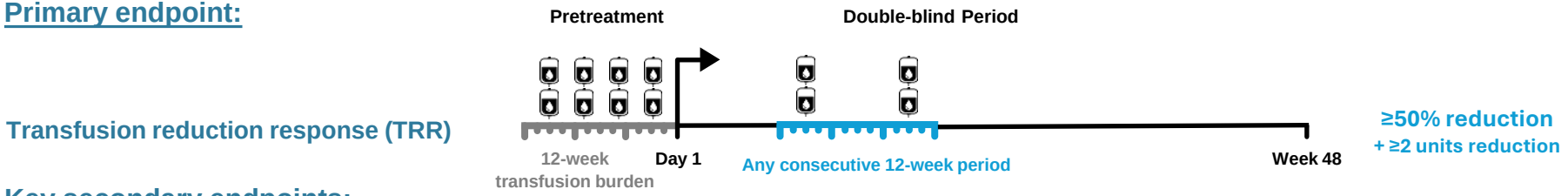
- Type, severity, and relationship of adverse events and serious adverse events

RBC, red blood cell.

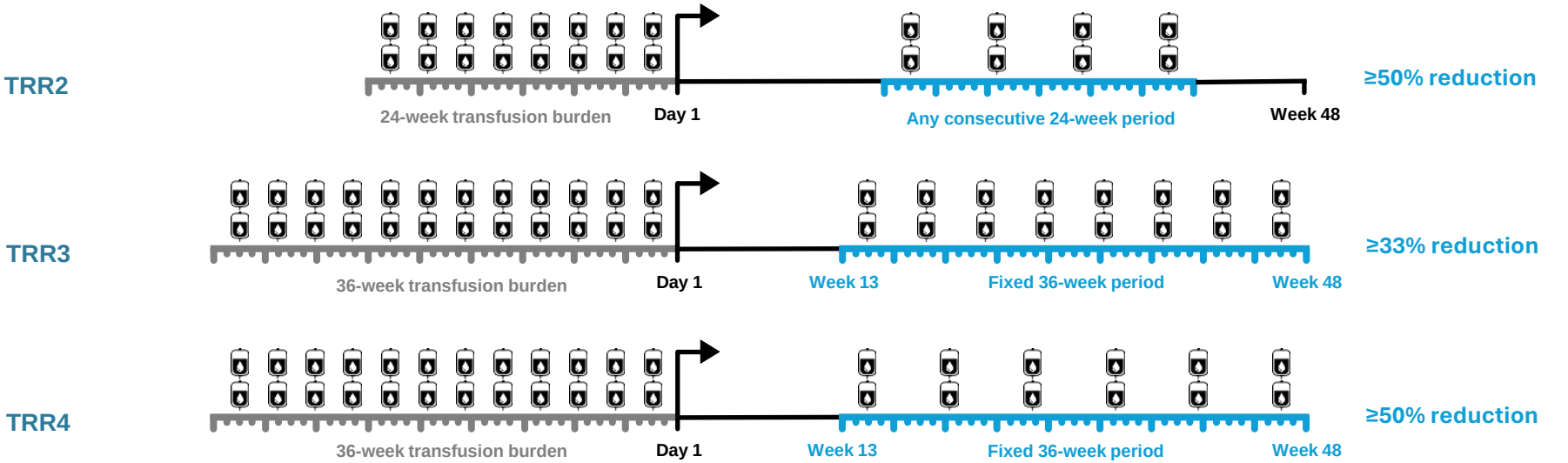
Depiction of endpoint concept[a]



Primary endpoint:

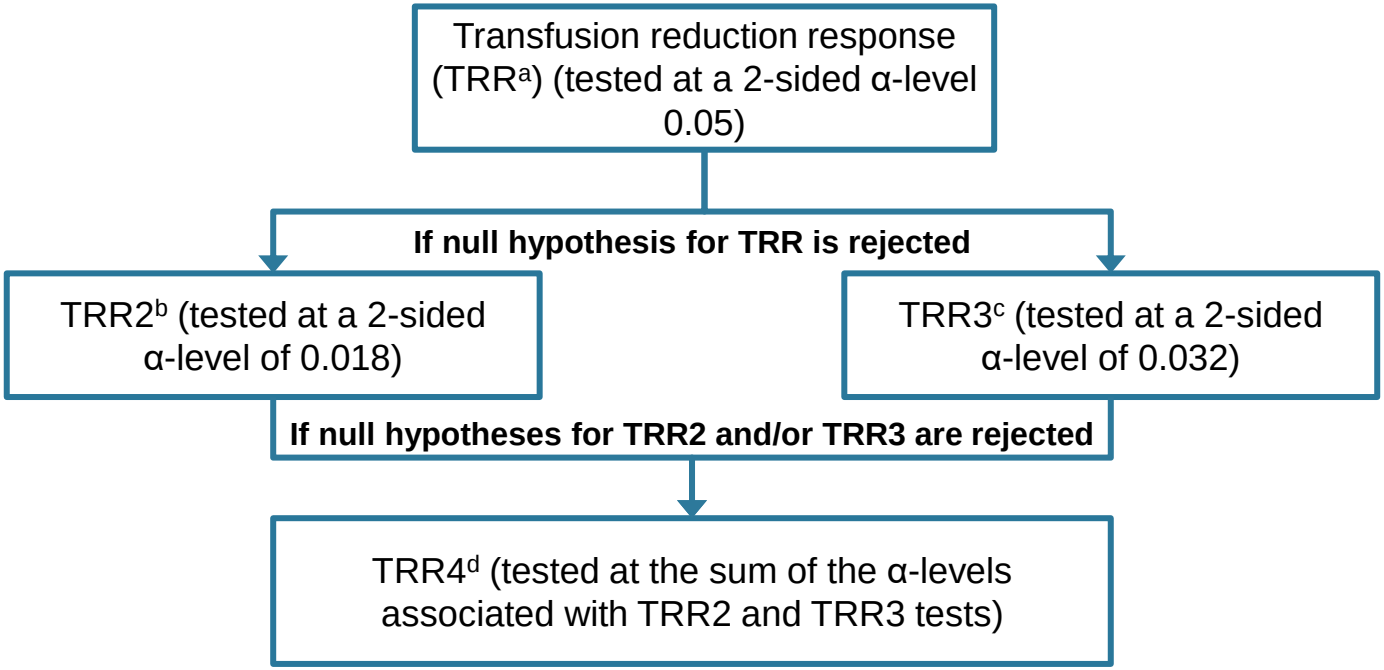


Key secondary endpoints:



[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.

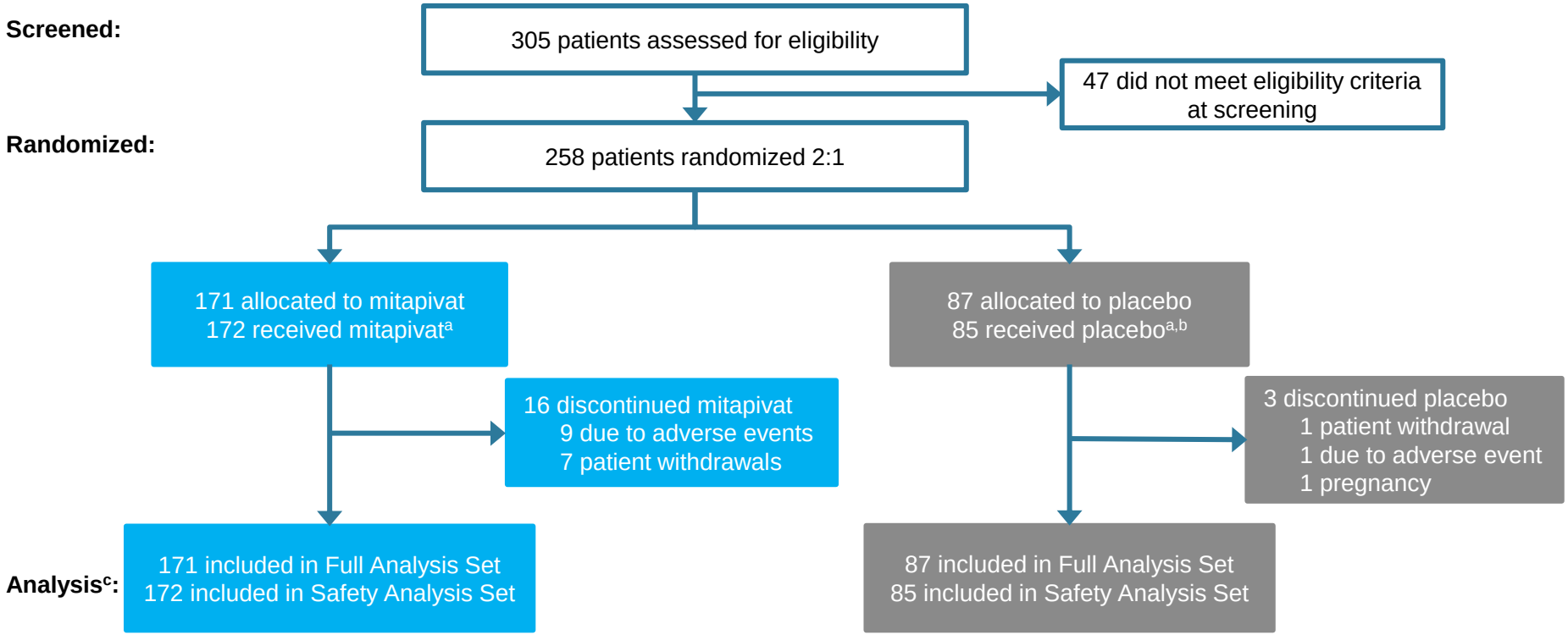
Statistical testing strategy



Primary and key secondary endpoints were tested using the Mantel–Haenszel stratum weighted method adjusting for randomization stratification factors[e]

[a]TRR was defined as a ≥50% reduction in transfused RBC units and a reduction of ≥2 units of transfused RBCs in any consecutive 12-week period through Week 48 compared with baseline. [b]TRR2 was defined as a ≥50% reduction in transfused RBC units in any consecutive 24-week period through Week 48 compared with baseline. [c]TRR3 was defined as a ≥33% reduction in transfused RBC units from Week 13 through Week 48 compared with baseline. [d]TRR4 was defined as a ≥50% reduction in transfused RBC units from Week 13 through Week 48 compared with baseline. [e]Additional information on the statistical methodology is included in the Supplemental Materials.

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.

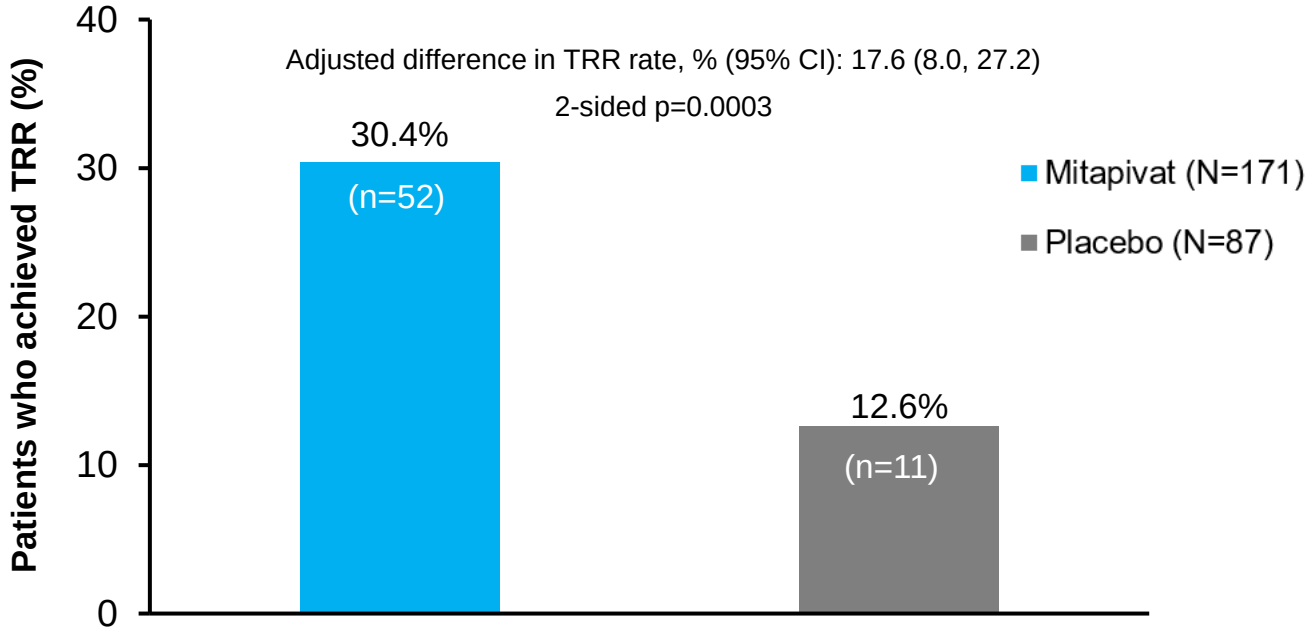
Baseline demographics and disease characteristics

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)
Multiracial	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 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 electronic case report form (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 world included Latin America and the Middle East. Hb, hemoglobin; RBC, red blood cell; SD, standard deviation.

Mitapivat demonstrated a statistically significant reduction in transfusion burden vs placebo

Primary endpoint



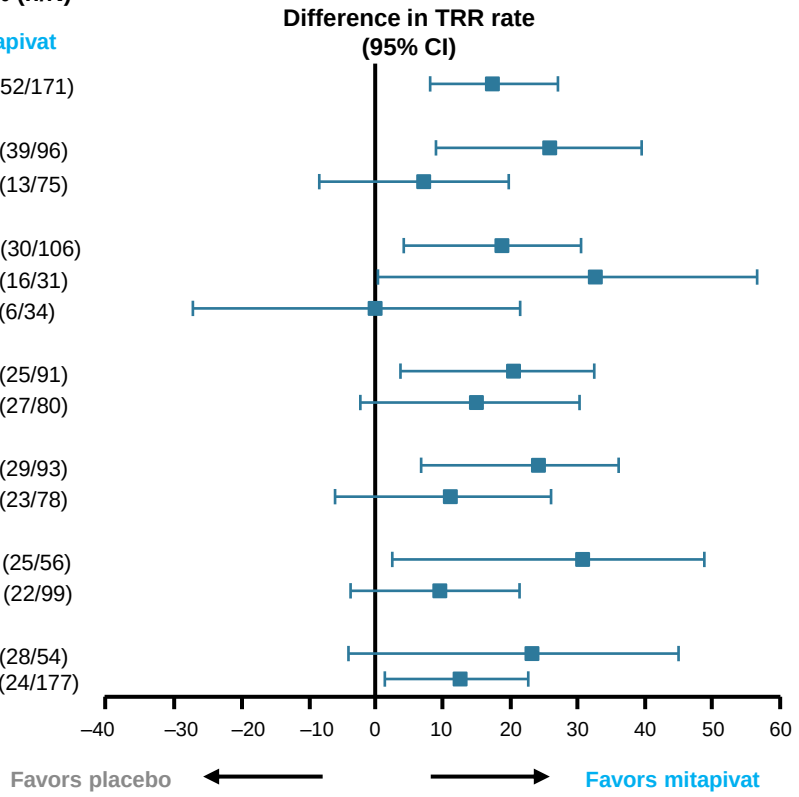
Transfusion reduction response (TRR) was defined as a ≥50% reduction in transfused RBC units and a reduction of ≥2 units of transfused RBCs in any consecutive 12-week period through Week 48 compared with baseline

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.

Reduction in transfusion burden by prespecified subgroups

Subgroup analysis of primary endpoint

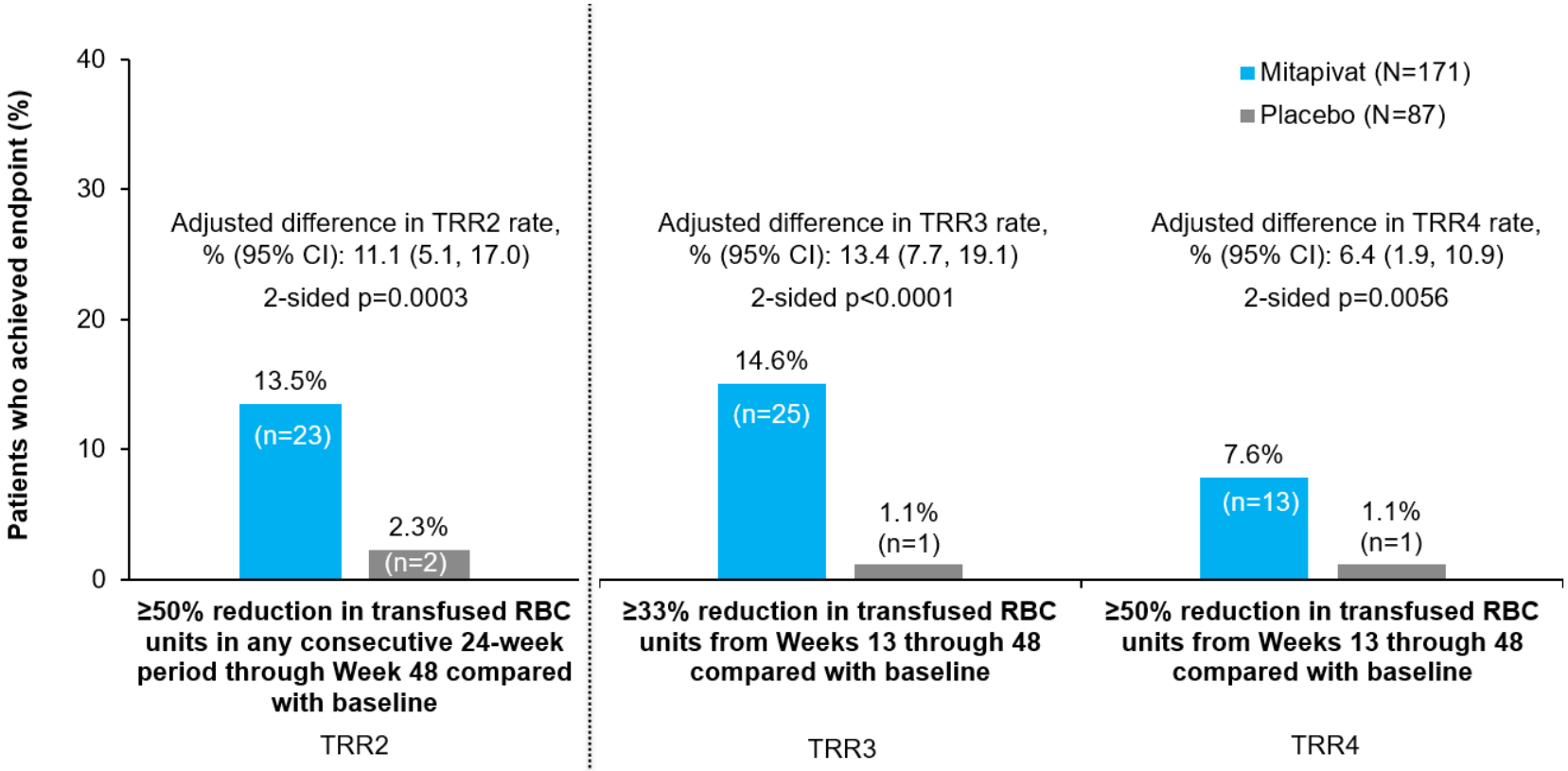
Subgroup	TRR response rate, % (n/N) Placebo	Mitapivat	Difference (95% CI)[b]
All patients (stratified)[a]	12.6 (11/87)	30.4 (52/171)	17.6 (8.0, 27.2)
Thalassemia genotype			
Non-β^0/β^0	14.6 (7/48)	40.6 (39/96)	26.0 (8.9, 39.6)
β^0/β^0	10.3 (4/39)	17.3 (13/75)	7.1 (–8.3, 19.7)
Geographic region, n (%)			
North America and Europe	9.3 (5/54)	28.3 (30/106)	19.0 (4.2, 30.5)
Asia-Pacific	18.8 (3/16)	51.6 (16/31)	32.9 (0.3, 56.6)
Rest of world	17.6 (3/17)	17.6 (6/34)	0.0 (–27.1, 21.5)
Age at screening (year)			
<35	6.8 (3/44)	27.5 (25/91)	20.7 (3.8, 32.4)
≥35	18.6 (8/43)	33.8 (27/80)	15.1 (–2.3, 30.3)
Sex			
Female	7.0 (3/43)	31.2 (29/93)	24.2 (6.8, 36.1)
Male	18.2 (8/44)	29.5 (23/78)	11.3 (–6.0, 26.0)
Race			
Asian	13.6 (3/22)	44.6 (25/56)	31.0 (2.5, 48.8)
White	12.5 (7/56)	22.2 (22/99)	9.7 (–3.7, 21.4)
24-week baseline transfusion burden			
≤12 RBC units	28.6 (6/21)	51.9 (28/54)	23.3 (–4.0, 45.0)
>12 RBC units	7.6 (5/66)	20.5 (24/177)	12.9 (1.4, 22.7)



Analysis conducted on Full Analysis Set. TRR was defined as a ≥50% reduction in transfused RBC units and a reduction of ≥2 units of transfused RBCs in any consecutive 12-week period through Week 48 compared with baseline. [a]Stratified by thalassemia genotype and geographic region. [b]For "All patients," the estimates for the difference and the 95% CI 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. CI, confidence interval; RBC, red blood cell; TRR, transfusion reduction response.

Mitapivat also demonstrated statistically significant reductions in transfusion burden vs placebo as measured by all 3 key secondary endpoints

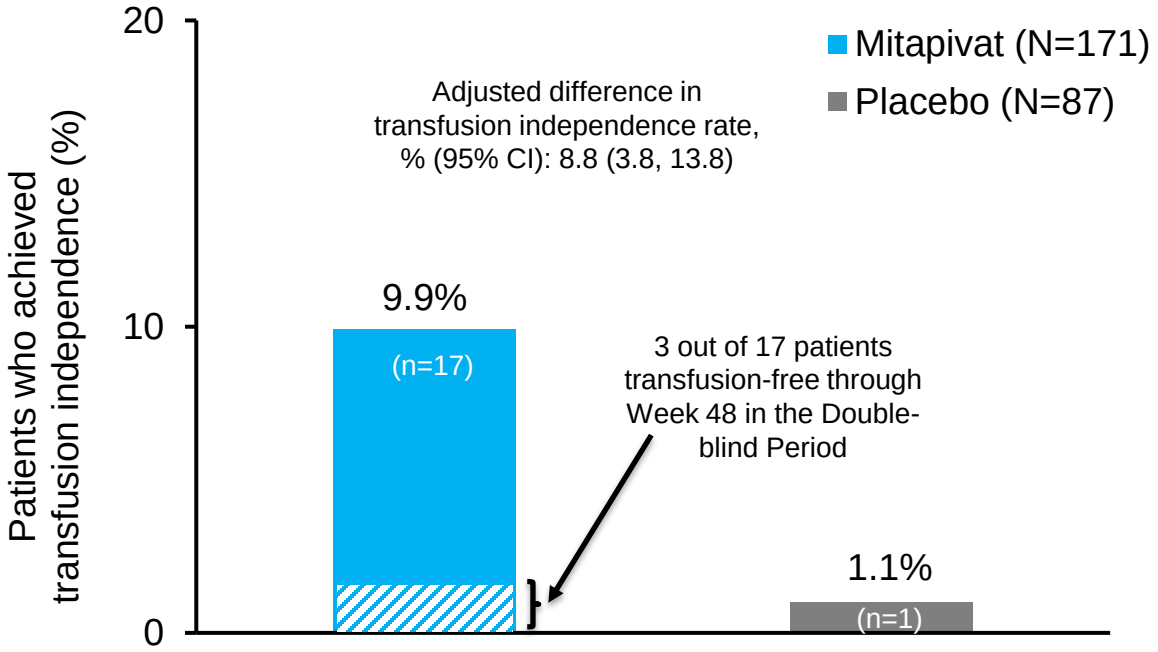
Key secondary endpoints



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.

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

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.

Summary of safety

Safety

Patients, n (%)	Mitapivat (N=172)	Placebo (N=85)
Any treatment-emergent adverse events (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

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 one 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 one patient on placebo was blood creatine phosphokinase increased. CTCAE, Common Terminology Criteria for Adverse Events.

Most frequently reported (≥10%) TEAEs

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

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
  - Efficacy was not driven by any prespecified subgroups
- 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
- Mitapivat was generally well tolerated in this study, with a low treatment discontinuation rate

In ENERGIZE-T, treatment with mitapivat, a disease-modifying therapy, was effective and resulted in significant reductions in transfusion burden in a globally representative population of patients with TDT, including both α- and β-thalassemia

TDT, transfusion-dependent thalassemia.

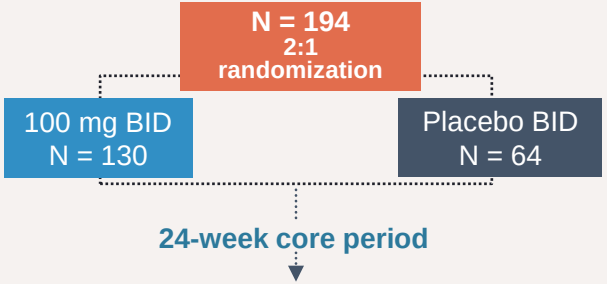
Thalassemia Clinical & Regulatory Update

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

Chief Medical Officer, Head of Research and Development

Two global, Phase 3, randomized controlled trials of PYRUKYND® in thalassemia across full range of thalassemia patients

ENERGIZE



Primary endpoint

- Mean Hb ↑ ≥ 1 g/dL from baseline

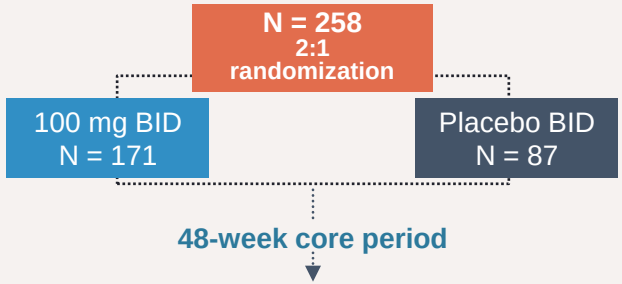
Secondary endpoints

- 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

ENERGIZE-T



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

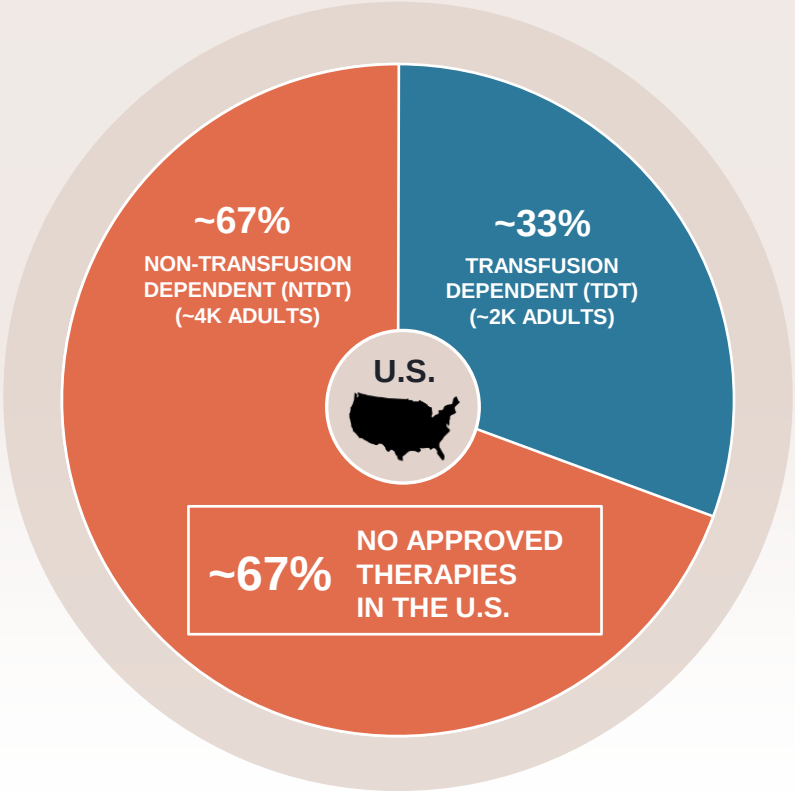
BID = twice daily; Hb = hemoglobin; HbE = hemoglobin E; HbH = hemoglobin H; PK = pharmacokinetics; PD = pharmacodynamics.

Agios aims to deliver the first therapy for all thalassemia subtypes

Mitapivat Thalassemia Phase 3 program

ENERGIZE

- Topline data announced January 3, 2024
- Data set presented during plenary session at EHA June 15, 2024



Mitapivat Thalassemia Phase 3 program

ENERGIZE-T

- Topline data announced June 3, 2024
- Data set presented during oral session at ASH December 8, 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.

Established favorable benefit / risk profile – **efficacy summary**

ENERGIZE

- **Achieved primary endpoint of Hb response,** defined as an increase of ≥1.0 g/dL in average Hb concentration from Week 12 through Week 24, compared with baseline
    - **Statistically significant improvement in Hb response** observed in the mitapivat arm (42.3%) compared to placebo (1.6%)
- **Improvements in markers of hemolysis and erythropoiesis** observed compared to placebo
- Mitapivat demonstrated **statistically significant improvement from baseline in average FACIT-Fatigue score** from weeks 12-24
- Patients in the mitapivat arm had **greater improvements in the 6MWT** than those in the placebo arm at Week 24

ENERGIZE enrollment: (N=194)

ENERGIZE-T

- **Achieved primary endpoint of Transfusion Reduction Response (TRR),** defined as a ≥50% reduction in transfused RBC units and a reduction of ≥2 units of transfused RBCs in any consecutive 12-week period through Week 48 compared with baseline
    - **Statistically significant transfusion reduction response** observed in the mitapivat arm (30.4%) compared to placebo (12.6%)
- **Transfusion independence achieved** in a higher proportion of patients in the mitapivat arm (9.9%) compared to placebo (1.1%). Transfusion independence was defined as transfusion-free for ≥8 consecutive weeks through Week 48 in the double-blind period
- Mitapivat also demonstrated **statistically significant reductions in transfusion burden vs placebo as measured by the 3 key secondary endpoints**

ENERGIZE-T enrollment: (N=258)

Established favorable benefit / risk profile – **safety summary**

ENERGIZE

- Overall, during the 24-week double-blind period, incidence of **adverse events was similar across mitapivat and placebo arms,** with 82.9% (n=107) of patients in the mitapivat arm and 79.4% (n=50) of patients in the placebo arm experiencing treatment-emergent adverse events (TEAEs).
- In mitapivat arm, **3.1%** (n=4) **of the patients experienced a TEAE leading to discontinuation**, compared to zero in the placebo arm,
- TEAEs that led to discontinuation of mitapivat, **each of which occurred in one patient**, were thrombocytopenia, arthralgia, abdominal distension, and 5 concurrent laboratory adverse events (alanine aminotransferase increase, aspartate aminotransferase increase, blood bilirubin increase, blood LDH increase, and international normalized ratio increase)

ENERGIZE enrollment: (N=194)

ENERGIZE-T

- Overall, during the 48-week double-blind period, **incidence of adverse events (AEs) was similar** across the mitapivat and placebo arms. The proportion of patients with any treatment-emergent adverse events (TEAEs) was 90.1% (n=155) in patients on mitapivat and 83.5% (n=71) in patients on placebo.
- In mitapivat arm, **5.8%** (n=10) **of the patients experienced a TEAE leading to discontinuation,** compared to 1.2% (n=1) in the placebo arm.
- TEAEs leading to discontinuation of mitapivat, **each of which occurred in one patient**, were diarrhea, paresthesia oral, concurrent anxiety and insomnia, initial insomnia, supraventricular tachycardia, fatigue, hypertransaminasemia, hepatitis C, hepatic cancer, and renal mass. The TEAE that led to discontinuation of the one patient on placebo was blood creatine phosphokinase increased.

ENERGIZE-T enrollment: (N=258)

Phase 3 ENERGIZE and ENERGIZE-T studies established a favorable benefit-risk profile

Established an overall favorable benefit-risk profile in all subtypes of thalassemia

- 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)
- Both studies achieved the primary and all the key secondary endpoints, demonstrating benefit of mitapivat over placebo
- 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 two studies.
- Two of 301 patients (0.66%) on mitapivat experienced AEs of hepatocellular injury within the first six months of exposure leading to treatment discontinuation. Liver tests improved following discontinuation of mitapivat.
- Based on the data from the ENERGIZE and ENERGIZE-T studies, Agios included, in its regulatory applications, hepatocellular injury as an important potential risk of mitapivat in patients with thalassemia and proposed monthly monitoring of liver tests for the first six months of treatment with mitapivat. In addition, mitapivat clinical trial protocols across all indications have been updated to incorporate similar monitoring.

Regulatory submissions filed in four priority regions, including United States

Based on the favorable benefit/risk profile, Agios has filed sNDA with FDA

Completed additional regulatory submissions for:

- European Union
- Kingdom of Saudi Arabia
- United Arab Emirates

Anticipated approval decision and potential US launch in 2025

EU = European Union; KSA = Kingdom of Saudi Arabia; UAE = United Arab Emirates

Mitapivat has potential to transform the thalassemia treatment landscape

- **FIRST** Phase 3 program to include **Alpha- & Beta-thalassemia**
- **FIRST oral treatment candidate** to show potential for benefits in pivotal Phase 3
- **FIRST to demonstrate Quality-of-Life improvements** in non-transfusion dependent patients
- **FIRST to demonstrate up to 36 weeks durability** of effect on reduction of transfusion burden

Results from a Phase 1 Trial of Tebapivat in Sickle Cell Disease

Julia Xu, M.D., MScGH

Assistant Professor of Medicine, Division of Classical Hematology and Vascular Medicine Institute, University of Pittsburgh

Results from a phase 1 study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of tebapivat (AG-946) in patients with sickle cell disease

Julia Z Xu, MD, MS[1,2], Enrico M Novelli, MD, MS[1,2], Jean Antoine Ribeil, MD, PhD[3], Andreas Glenthøj, MD, PhD[4], Srila Gopal, MD[5], Hanny Al-Samkari, MD[6], Modupe Idowu, MD[7], Jenny Despotovic, DO[8], Spurthi Patil, MS[8], Xiaoshu Dai, PhD[8], Abdullah Al Masud, PhD[8], Mike Callaghan, MD[8], Fuad El-Rassi, MD[9,10]

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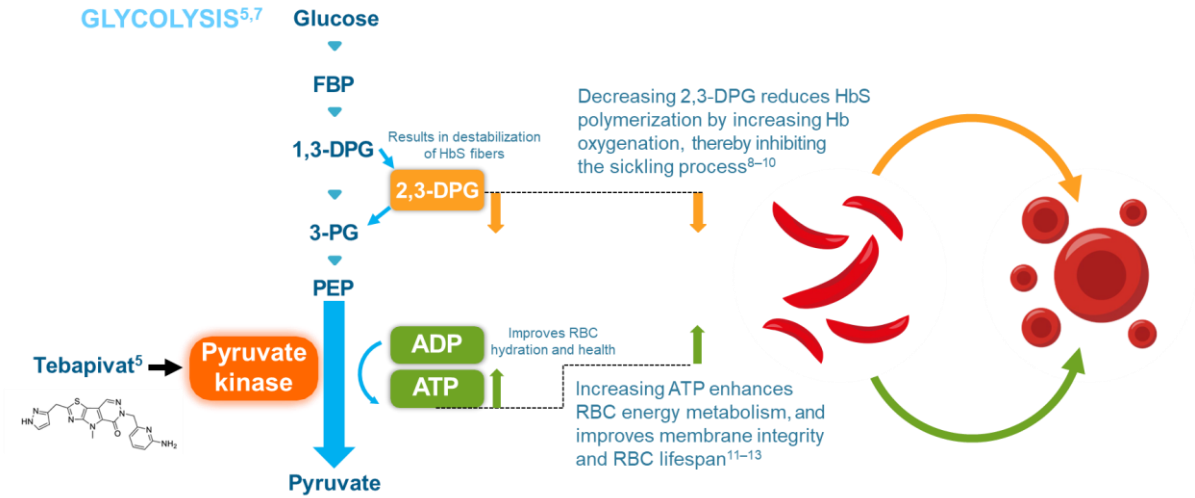
This study was funded by Agios Pharmaceuticals, Inc.
Presented at the 66th American Society of Hematology (ASH) Annual Meeting and Exposition, December 7–10, 2024, San Diego, CA, USA, and virtual

Background

Figure 1. Tebapivat, a potent, oral activator of pyruvate kinase



- In sickle cell disease (SCD), pyruvate kinase activation increases adenosine triphosphate (ATP), leading to improved membrane integrity and survival of red blood cells (RBCs), and decreases 2,3-diphosphoglycerate (DPG), preventing the polymerization of sickle hemoglobin (HbS) in its deoxygenated state[1]
- Mitapivat, an allosteric activator of the RBC-specific (PKR) and M2 (PKM2) isoforms of pyruvate kinase, demonstrated clinically meaningful improvements in hemoglobin (Hb) response and improvements in markers of hemolysis and erythropoiesis in phase 2 trials in SCD[2,3]
  - Mitapivat is currently being evaluated in a phase 3 trial in patients with SCD[4]
- Tebapivat (formerly AG-946) is an oral, once daily (QD), potent, allosteric activator of PKR and PKM2[5]; results from the randomized, double-blind, placebo-controlled single ascending dose (SAD) and multiple ascending dose (MAD) parts of a phase 1 study of tebapivat in healthy volunteers (HVs; NCT04536792) have been previously reported[6]

ADP, adenosine diphosphate; FBP, fructose bisphosphate; PEP, phosphoenolpyruvate; PG, phosphoglycerate. 1. Xu JZ, Vercellotti GM. *Hematology Am Soc Hematol Educ Program* 2023;1:107–13; 2. Idowu M et al. *Blood* 2023;142(Suppl 1):271; 3. van Dijk R et al. *Am J Hematol* 2022;97:226–80; 4. Andemariam B et al. *HemaSphere* 2024;8(S1):4142–43; 5. Liu T et al. *ChemMedChem* 2024;19:e202300559; 6. Dai Gurov X et al. *Blood* 2022;140(Suppl 1):5426–27 7. Idowu M et al. *65th ASH Annual Meeting and Exposition* 2023: Poster 271; 8. Adebeyi MG et al. *Blood Adv* 2019;3:1347–55; 9. Eaton WA, Bunn HF. *Blood* 2017;129:2719–26; 10. Poillon WN et al. *Blood* 1995;85:3289–96; 11. Kung C et al. *Blood* 2017;130:1347–56; 12. Yang H et al. *Clin Pharmacol Drug Dev* 2019;8:246–59; 13. Valentini G et al. *J Biol Chem* 2002;277:23807–14

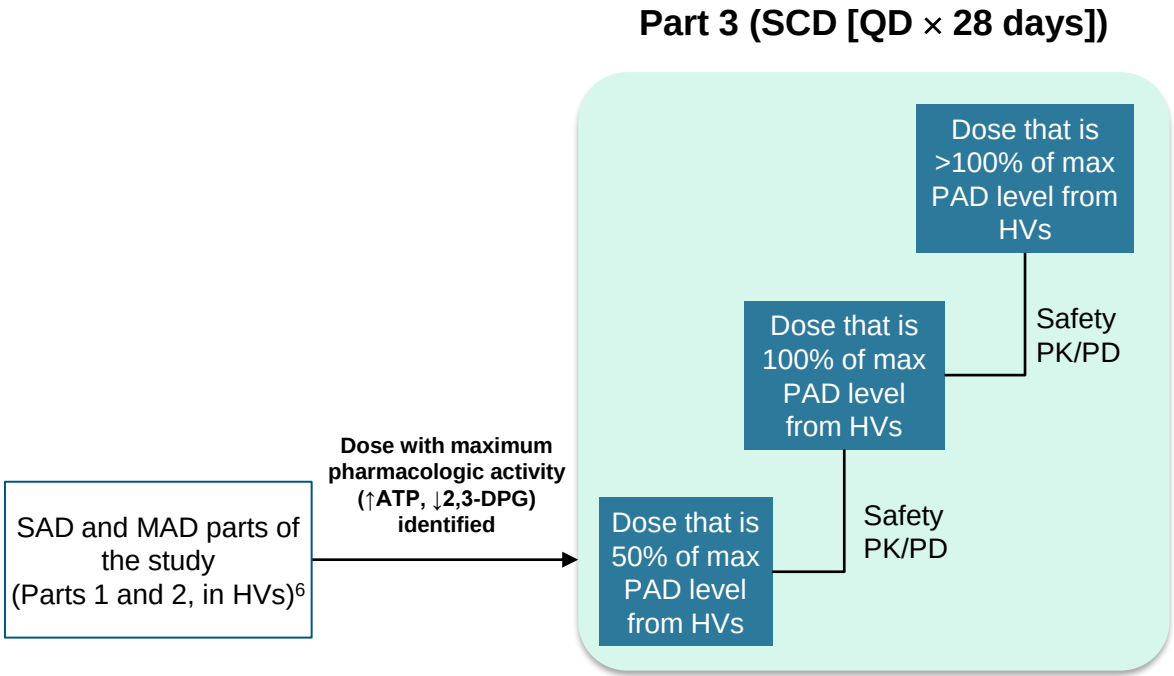
Objective

To understand the safety, tolerability, and pharmacokinetics/pharmacodynamics (PK/PD) of tebapivat in the non-randomized, open-label, third part of a phase 1 study in adult patients with SCD

SCD, sickle cell disease

Methods

Figure 2. Study design[14]



Study design

- Adult patients (aged 18–70 years) with sickle cell anemia (homozygous for HbS [HbSS] or HbS/β^0-thalassemia) and adequate organ function received 2 mg or 5 mg tebapivat QD for 28 days, with a further 28-day observational safety follow-up[14]
- Further details of the study eligibility criteria can be found via the QR code

ATP, adenosine triphosphate; DPG, diphosphoglycerate; HV, healthy volunteer; MAD, multiple ascending dose; PAD, pharmacologically active dose; PK/PD, pharmacokinetic/pharmacodynamic; QD, once daily; SAD, single ascending dose; SCD, sickle cell disease. 6. Dai Gurov X et al. *Blood* 2022;140(Suppl 1):5426–27; 14. Clinicaltrials.gov. Available at: https://clinicaltrials.gov/study/NCT04536792 (accessed October 2024)

Methods

Study endpoints

- The primary endpoints were:
  - Relationships between tebapivat dose, concentration, and safety endpoints
  - Relationships between tebapivat dose, concentration, and pharmacodynamic endpoints

- Secondary endpoints included:
  - Type, severity, and relationship of adverse events (AEs) and serious AEs (SAEs)
  - Plasma pharmacokinetic parameters after both single and multiple oral dose administration of tebapivat
  - Change over time in the whole blood concentrations of 2,3-DPG and ATP
  - Change from baseline in Hb
  - Change from baseline in markers of hemolysis (including total bilirubin and lactate dehydrogenase [LDH] levels) and erythropoiesis (including reticulocyte percentage)

ATP, adenosine triphosphate; DPG, diphosphoglycerate; Hb, hemoglobin

Results

- Sixteen adult patients with SCD received ≥1 dose of either 2 mg QD (N=8) or 5 mg QD (N=8) oral tebapivat
- Fourteen patients (87.5%) completed the 28-day dosing period
  - One patient in the 2 mg QD cohort discontinued tebapivat due to an AE (sickle cell anemia with crisis), and 1 patient in the 5 mg QD cohort discontinued tebapivat due to increased Hb (but completed the study)
  - All 16 patients were included in the intention-to-treat analysis

AE, adverse event; Hb, hemoglobin; QD, once daily; SCD, sickle cell disease

Results

Table 1. Baseline demographics and disease characteristics

Demographics and disease characteristics	Tebapivat 2 mg QD (N=8)	Tebapivat 5 mg QD (N=8)
Age, median (range), years	28.0 (19.0–48.0)	37.5 (25.0–51.0)
Male, n (%)	4 (50.0)	4 (50.0)
Race, n (%) Black or African American White Multiracial Not reported	 7 (87.5) 0 (0.0) 0 (0.0) 1 (12.5)	 6 (75.0) 1 (12.5) 1 (12.5) 0 (0.0)
Hb concentration, mean (SD), g/dL	7.8 (1.0)	8.1 (1.1)
VOC in the prior 12 months,[a] n (%)	4 (50.0)	3 (37.5)
Received prior SCD-related therapies,[b] n (%)	4 (50.0)	6 (75.0)

[a]Includes VOCs that occurred within 12 months before informed consent and during screening; [b]Prior disease-modifying SCD-related therapies included hydroxyurea, crizanlizumab, L-glutamine, and voxelotor
Hb, hemoglobin; QD, once daily; SCD, sickle cell disease; SD, standard deviation; VOC, vaso-occlusive crisis

Results

Table 2. Safety

Patients, n (%)	Tebapivat 2 mg QD (N=8)	Tebapivat 5 mg QD (N=8)
Any TEAEs	8 (100.0)	8 (100.0)
Grade ≥3 TEAEs	3 (37.5)	3 (37.5)
Treatment-related TEAEs	1 (12.5)	2 (25.0)
Grade ≥3 treatment-related TEAEs	0 (0.0)	1 (12.5)
Serious TEAEs	3 (37.5)	1 (12.5)
Serious treatment-related TEAEs	0 (0.0)	1 (12.5)
TEAEs leading to discontinuation of study drug	0 (0.0)	0 (0.0)
TEAEs leading to dose reduction	0 (0.0)	0 (0.0)
TEAEs leading to interruption of study drug	2 (25.0)	0 (0.0)
TEAEs leading to death	0 (0.0)	0 (0.0)
Most frequently reported (≥10%) TEAEs		
Sickle cell anemia with crisis		
Any grade	4 (50.0)	3 (37.5)
Grade ≥3	2 (25.0)	1 (12.5)
Upper respiratory tract infection		
Any grade	1 (12.5)	2 (25.0)
Grade ≥3	0 (0.0)	1 (12.5)

Safety

- Two (25.0%) patients in the 2 mg QD cohort and 1 (12.5%) patient in the 5 mg QD cohort experienced an SAE of sickle cell anemia with crisis; these events occurred during the safety follow-up period after tebapivat was discontinued (**Table 2**)
  - The SAE reported in the 5 mg QD cohort was the only AE/SAE of sickle cell anemia with crisis considered treatment-related by the Investigator
- No TEAEs of sickle cell anemia with crisis were reported during the 5 mg QD treatment period
- All pain crises occurred in the setting of known triggers

The severity of all TEAEs, including clinically significant laboratory abnormalities, was graded by the Investigator according to v5.0 of the National Cancer Institute Common Terminology Criteria for Adverse Event on a 5-point severity scale (Grade 1–5). AE, adverse event; QD, once daily; SAE, serious adverse event; TEAE, treatment-emergent adverse event

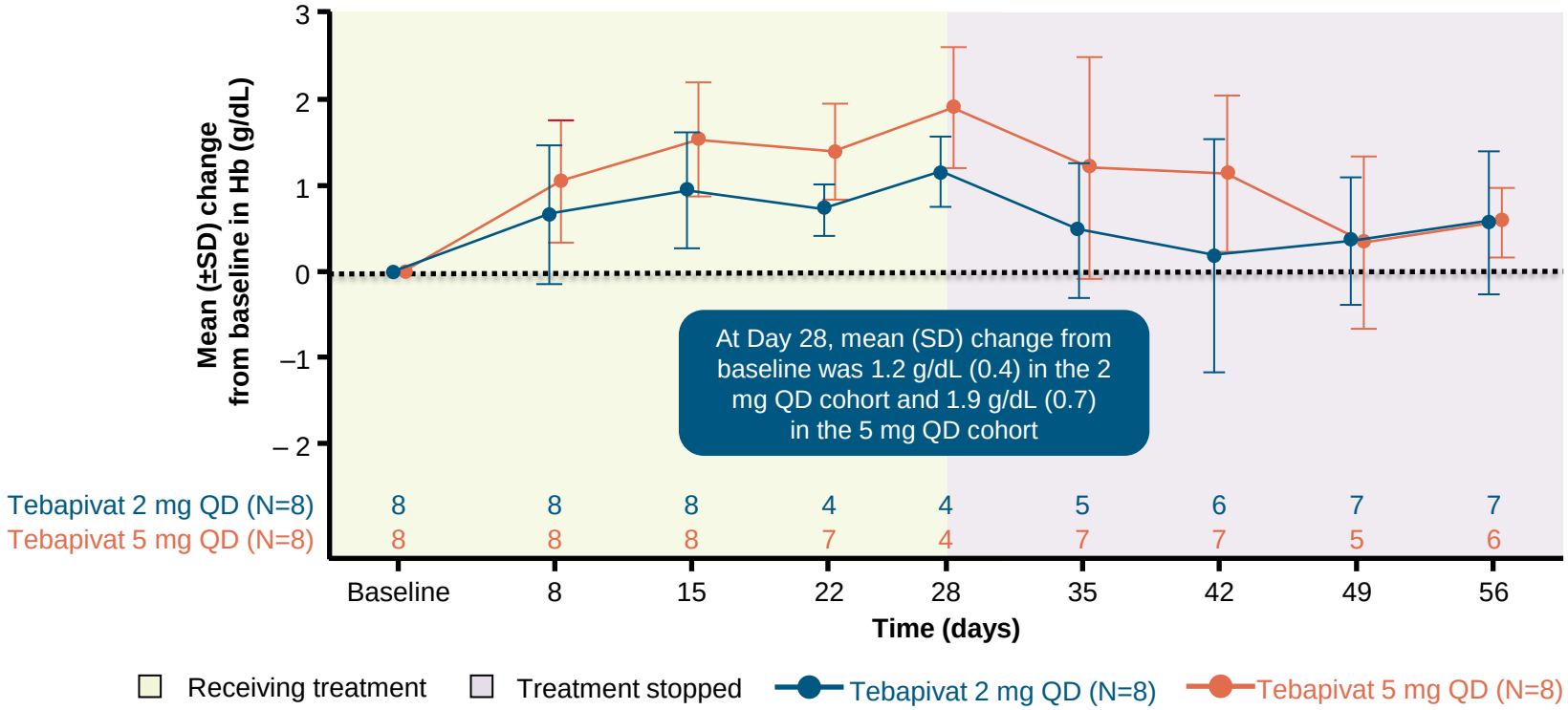
Results

Hb and markers of hemolysis and erythropoiesis

- At the end of the 28-day treatment period, the mean (SD) change from baseline for Hb was 1.2 g/dL (0.4) in the 2 mg QD cohort and 1.9 g/dL (0.7) in the 5 mg QD cohort (**Figure 3**)
- Overall, decreases in markers of hemolysis (total bilirubin, LDH, and reticulocyte percentage) from baseline were observed at Day 28 in both cohorts (**Figure 4A–C**)

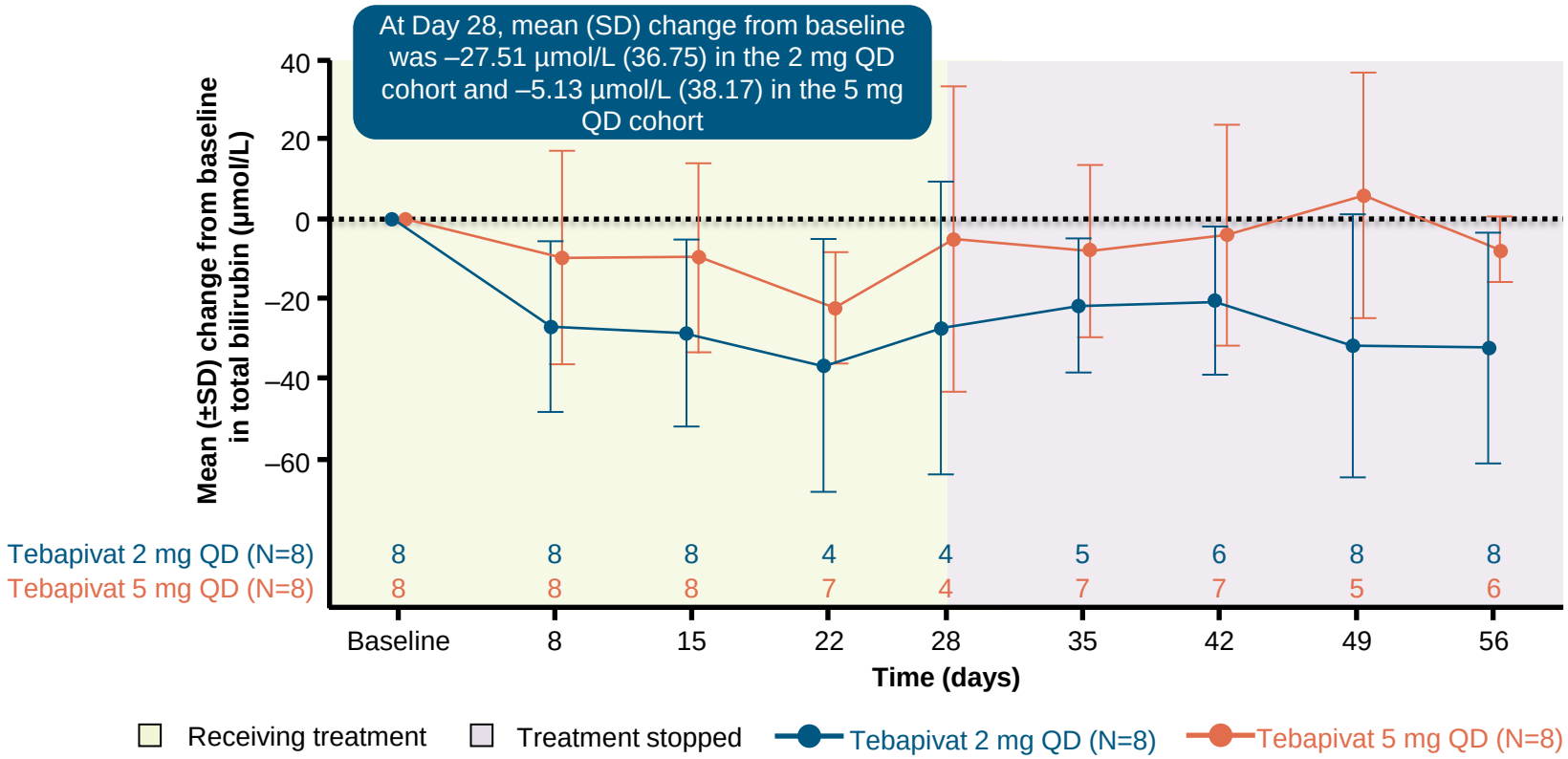
Hb, hemoglobin; LDH, lactate dehydrogenase; QD, once daily; SD, standard deviation

Figure 3. Mean (±SD) change from baseline in Hb concentration



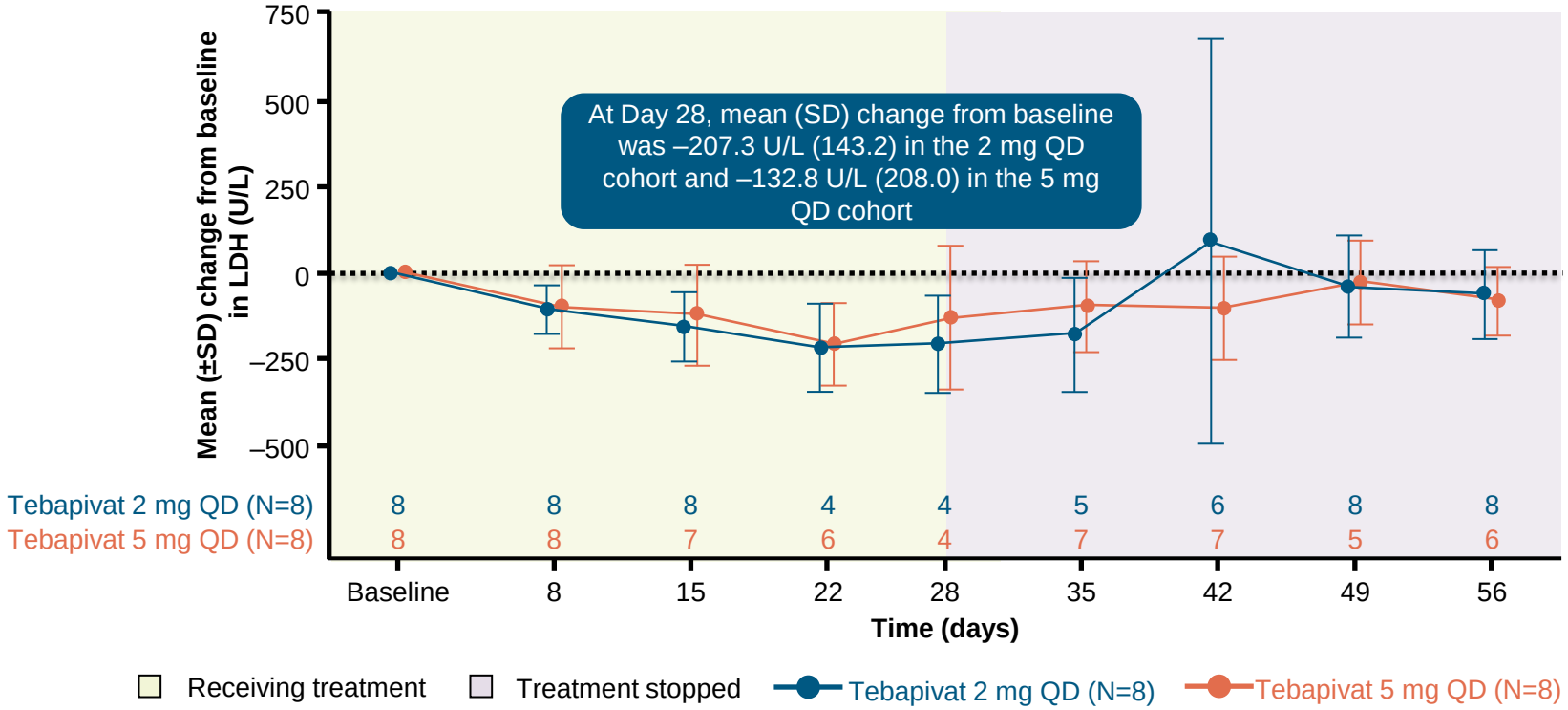
Baseline was defined as the last assessment before start of study treatment
Hb, hemoglobin; QD, once daily; SD, standard deviation

Figure 4A. Mean (±SD) change from baseline in total bilirubin



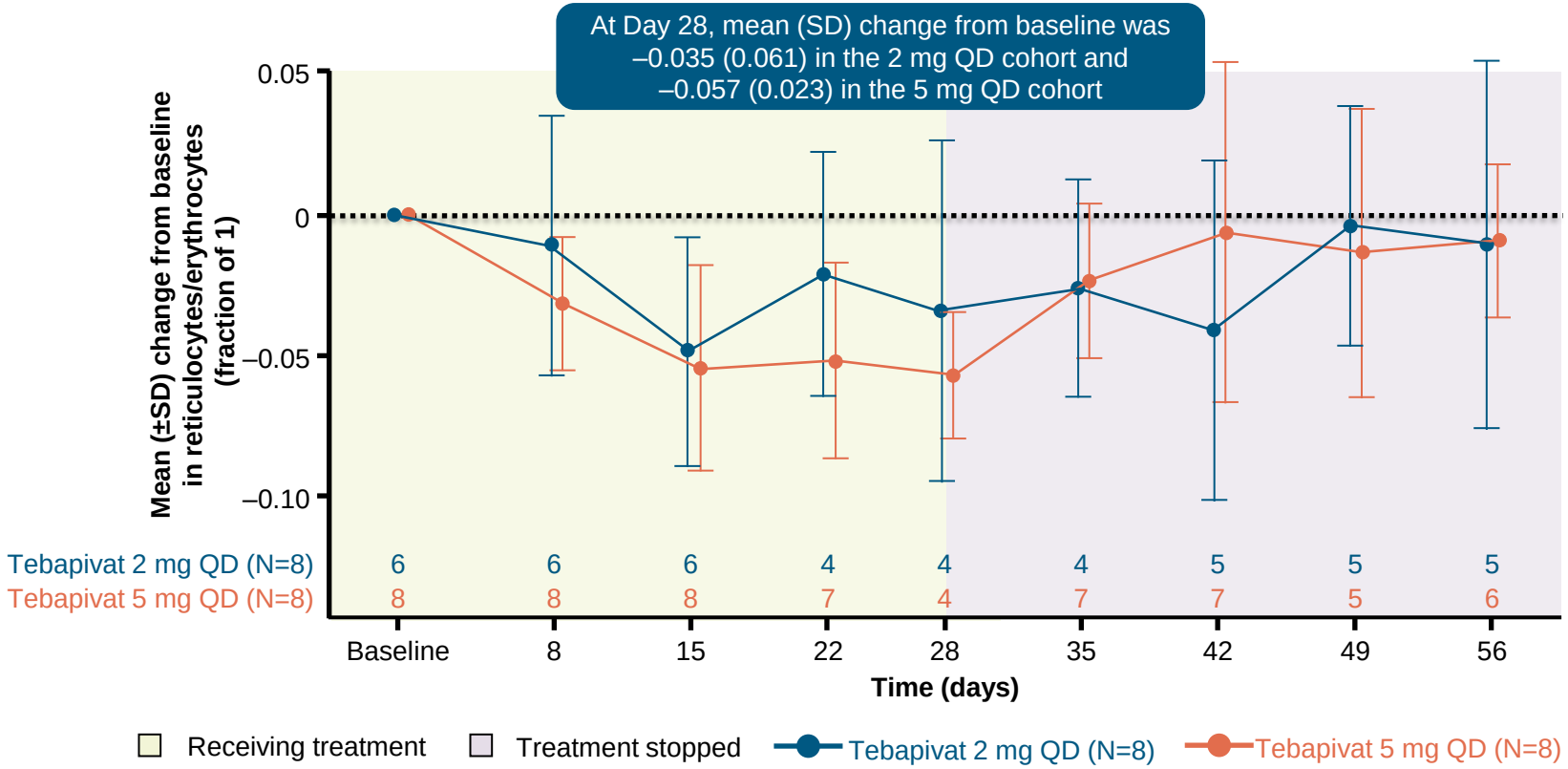
Baseline was defined as the last assessment before start of study treatment
QD, once daily; SD, standard deviation

Figure 4B. Mean (±SD) change from baseline in LDH



Baseline was defined as the last assessment before start of study treatment
LDH, lactate dehydrogenase; QD, once daily; SD, standard deviation

Figure 4C. Mean (±SD) change from baseline in reticulocytes/erythrocytes (reticulocyte percentage)



Baseline was defined as the last assessment before start of study treatment
QD, once daily; SD, standard deviation

Results

Pharmacokinetics

- Overall, tebapivat exposure increased with a higher dose (2 mg QD vs 5 mg QD)
- Tebapivat exposures in patients with SCD on both Day 1 (2 mg QD: 58 h·ng/mL; 5 mg QD: 197 h·ng/mL) and Day 15 (2 mg QD: 157 h·ng/mL; 5 mg QD: 447 h·ng/mL) were comparable to exposures in HVs[15]

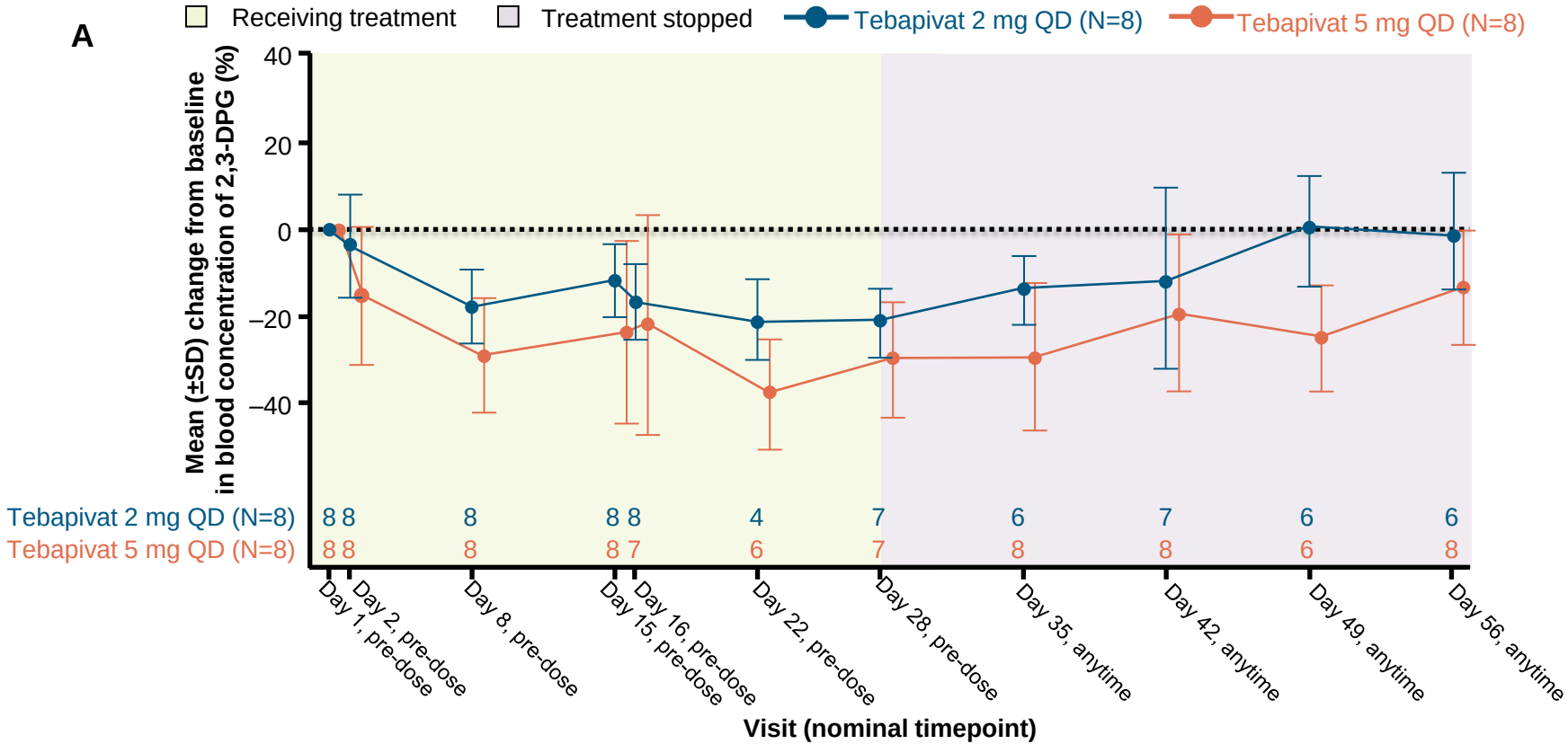
Pharmacodynamics

- Dose-dependent pharmacodynamic effects on 2,3-DPG and ATP levels were demonstrated with tebapivat, with higher doses resulting in greater changes from baseline
- 2,3-DPG and ATP concentrations reached steady state after 2 weeks of QD dosing
- At Day 28 (pre-dose [sample collected ≤60 minutes before the administration of tebapivat]), mean (SD) percent reduction in 2,3-DPG from baseline was 20.9% (7.1) and 29.4% (12.7) for the 2 mg and 5 mg cohorts, respectively (**Figure 5A**)
- At Day 28 (pre-dose), mean (SD) percent increase in ATP from baseline was 46.3% (29.1) and 67.8% (30.9) for the 2 mg and 5 mg cohorts, respectively (**Figure 5B**)
- A sustained pharmacodynamic effect was observed up to 4 weeks after 28 days of QD dosing

ATP, adenosine triphosphate; DPG, diphosphoglycerate; HV, healthy volunteer; QD, once daily; SCD, sickle cell disease; SD, standard deviation

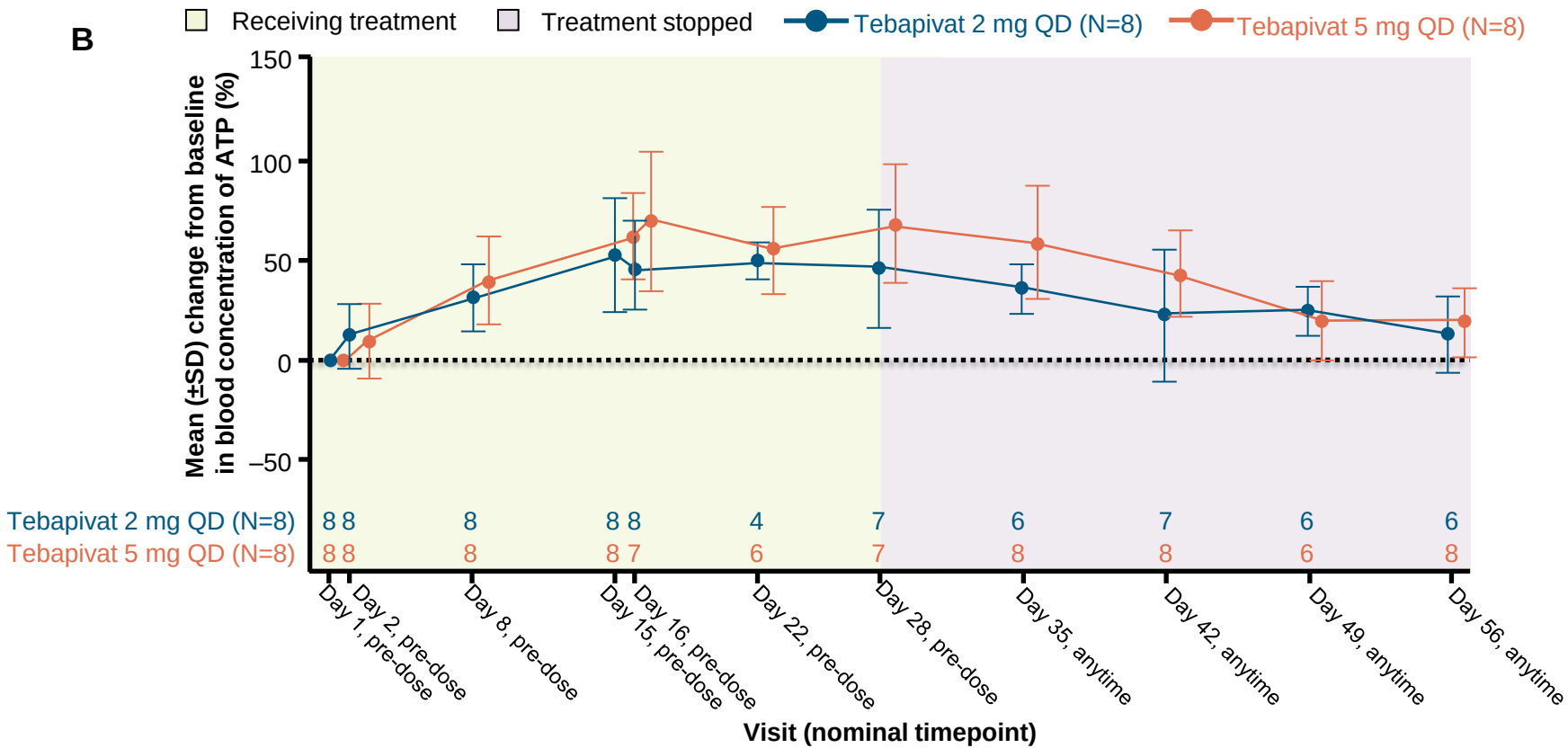
15. Dai Gurov X et al. *64th ASH Annual Meeting and Exposition* 2022: Poster 2043

Figure 5A. Mean (±SD) percent change from baseline in 2,3-DPG



Baseline was defined as the pre-dose concentration on study Day 1. “Pre-dose” refers to samples collected ≤60 minutes before the administration of tebapivat. “Anytime” refers to samples collected at any point during that day. DPG, diphosphoglycerate; QD, once daily; SD, standard deviation

Figure 5B. Mean (±SD) percent change from baseline in ATP



Baseline was defined as the pre-dose concentration on study Day 1. “Pre-dose” refers to samples collected ≤60 minutes before the administration of tebapivat. “Anytime” refers to samples collected at any point during that day. ATP, adenosine triphosphate; QD, once daily; SD, standard deviation

Conclusions

- Tebapivat was well tolerated in patients with SCD receiving either 2 mg or 5 mg QD for 28 days
- Increases in Hb and trends towards improvement in hemolytic and erythropoietic markers were observed, and there was a sustained effect after tebapivat was stopped
- ATP levels were increased and 2,3-DPG levels decreased during the study, consistent with the proposed mechanism of action of tebapivat
  - A sustained pharmacodynamic effect was observed up to 4 weeks after the last dose
- Tebapivat will be further evaluated in additional clinical studies

Tebapivat is a potent pyruvate kinase activator with the potential to provide benefit in SCD

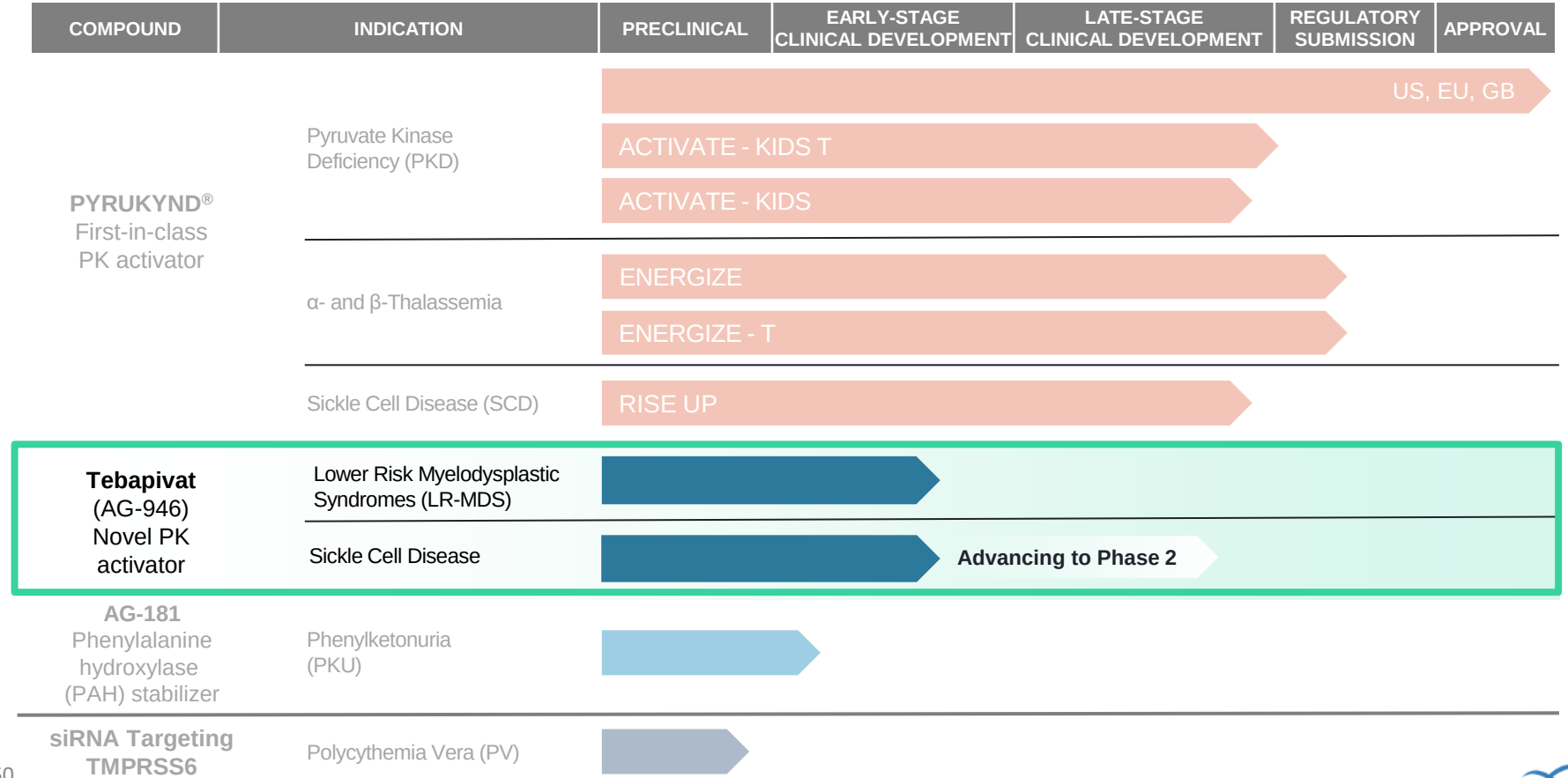
ATP, adenosine triphosphate; DPG, diphosphoglycerate; Hb, hemoglobin; QD, once daily; SCD, sickle cell disease

Tebapivat Clinical Development

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

Chief Medical Officer, Head of Research and Development

Tebapivat development now advancing in two indications in Phase 2 including Lower-Risk MDS and Sickle Cell Disease



Phase 2b open-label study of Tebapivat (AG-946) in lower-risk MDS (enrolling)

Phase 2b

Primary endpoint:
Transfusion independence, defined as transfusion-free for ≥8 consecutive weeks during the Core Period

Secondary endpoints: safety, change in hemoglobin, TI for 12 weeks, additional measures of anemia, PK and PD biomarkers

N=60

*Completion of enrollment in one cohort triggers the opening of enrollment in the next cohort

Tebapivat (AG-946) **Treatment Period**

Core Period	Extension Period
Dose Level 1 **10mg QD**	Dose Level 1 **10mg QD**

Tebapivat (AG-946) **Treatment Period**

Core Period	Extension Period
Dose Level 2 **15mg QD**	Dose Level 2 **15mg QD**

Tebapivat (AG-946) **Treatment Period**

Core Period	Extension Period
Dose Level 3 **20mg QD**	Dose Level 3 **20mg QD**

Core Period: **24 Weeks** | Extension Period: **156 Weeks**

Key inclusion criteria

- ≥ 18 years of age
- Lower-risk MDS (risk score: ≤3.5) according to IPSS-R classification (WHO classification; Arber et al, 2016)
- Transfusion dependent, with LTB or HTB according to revised IWG 2018 criteria
- An Hb concentration <10.0 g/dL
- Up to 2 prior therapies, including ESAs and/or luspatercept

Key exclusion criteria

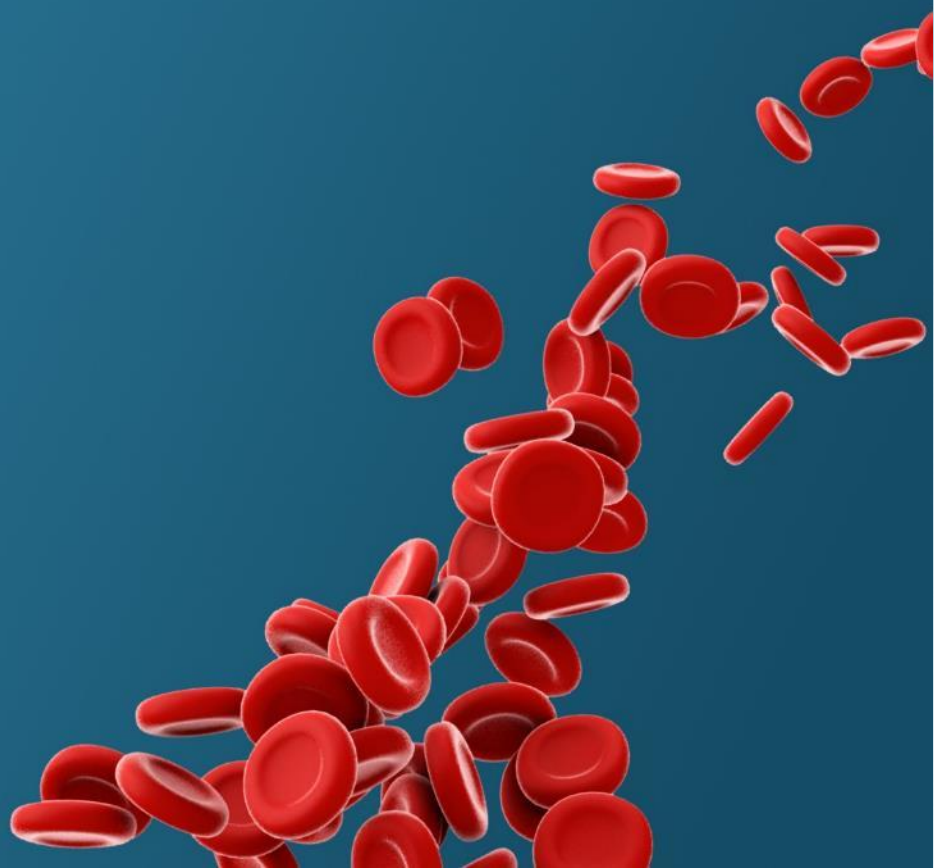
- Known history or AML or secondary MDS
- Prior exposure to a PK activator, IDH inhibitors, IST, stem cell transplant
- Currently receiving imetelstat, lenalidomide, HMAs allowed after sufficient washout period

QD = once daily; TI = transfusion independence
HTB = high transfusion burden; LTB = low transfusion burden; IWG = International Working Group; AML = Acute myeloid leukemia

Closing Remarks

Brian Goff

Chief Executive Officer



Achieved all clinical and regulatory milestones for 2024, reinforcing momentum in corporate mission

EARLY 2024

Thalassemia
PYRUKYND®
Phase 3 data readout for ENERGIZE study

PKU
AG-181
Begin Phase 1 dosing for AG-181 (PAH stabilizer) for the treatment of PKU

MID-YEAR 2024

Thalassemia
PYRUKYND®
Phase 3 data readout for ENERGIZE-T study

Lower-Risk MDS
Tebapivat (AG-946)
Begin patient enrollment of Phase 2b study

Pediatric PK Deficiency
PYRUKYND®
Complete enrollment Phase 3 ACTIVATE-Kids study

Pediatric PK Deficiency
PYRUKYND®
Phase 3 data readout ACTIVATE-KidsT study

YEAR-END 2024

Thalassemia
PYRUKYND®
Filing for FDA Approval

Sickle Cell Disease
PYRUKYND®
Complete Phase 3 enrollment

PKU = Phenylketonuria; PAH = Phenylalanine hydroxylase

Well-positioned with multiple clinical and regulatory 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**

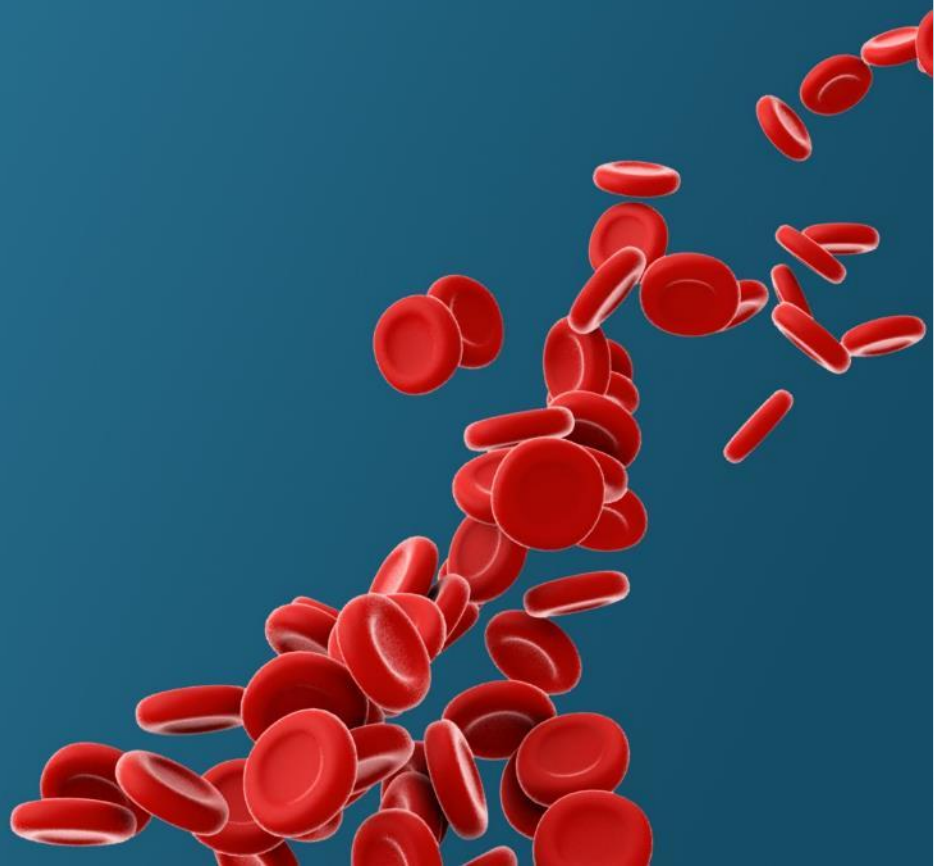
$1.7 billion in cash and equivalents as of September 30, 2024

Including $1.1 billion in payments related to the FDA approval of vorasidenib (announced August 6, 2024)

PKa = pyruvate kinase activation

agios

Q&A



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

Supplemental materials

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

Maria Domenica Cappellini, MD, Sujit Sheth, MD, Ali T Taher, MD, PhD, FRCP, Hanny Al-Samkari, MD, Ali Bülent Antmen, MD, PhD, David Beneitez, MD, Giovanna Cannas, MD, Thomas Coates, MD, Lauren Czapla, ANP, Jayme L Dahlin, MD, PhD, Jeremie H Estepp, MD, Elizabeth Feenstra, MD, Pencho Georgiev, MD, PhD, Sarah Gheuens, MD, PhD, Keely S Gilroy, PhD, Andreas Glenthøj, MD, PhD, Khaled M Musallam, MD, PhD, Kareem Osman, MD, John B Porter, MD, Hui Shao, PhD, Katrin Uhlig, MD, MS, Eduard J van Beers, MD, PhD, Vip Viprakasit, MD, Dphil (Oxon), Kevin HM Kuo, MD, MSc, FRCPC, Antonis Kattamis, MD

Session Name: 112. Thalassemia and Globin Gene Regulation: We're Going to Catch a Big One: Towards Targeted Therapies in Thalassemia
Session Date: Sunday, December 8, 2024
Session Time: 9:30–11:00 AM
Presentation Time: 9:30 AM
Room: San Diego Convention Center, Room 31

This study was funded by Agios Pharmaceuticals, Inc.
Presented at the 66th American Society of Hematology (ASH) Annual Meeting and Exposition, December 7–10, 2024, San Diego, CA, and online

Statistical methods

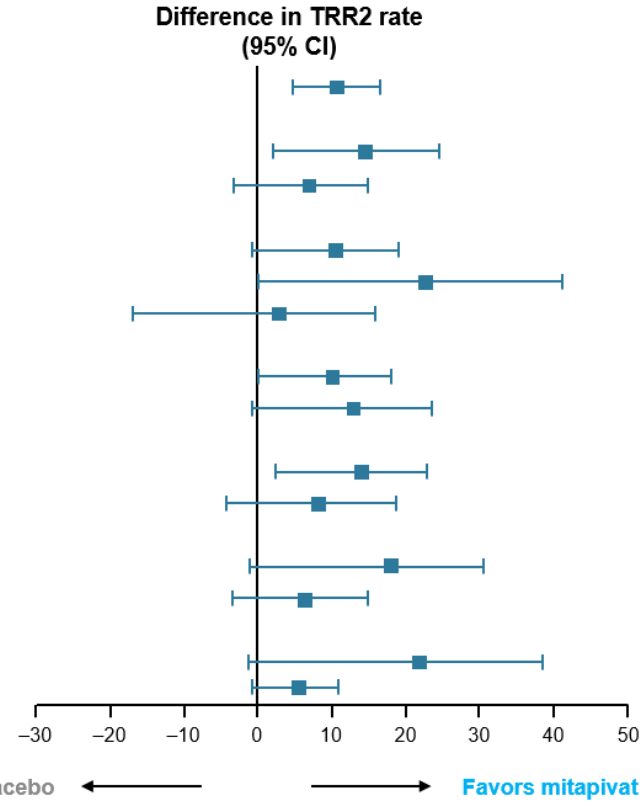
- The primary endpoint of TRR and key secondary endpoints of TRR2–4 were tested using the Mantel–Haenszel stratum weighted method, after adjusting for randomization stratification factors
  - The response rate based on different definitions of response were summarized for each treatment group, and the adjusted difference in TRR rate between the mitapivat and placebo groups, along with the 95% CI and the 2-sided p-value, were provided
- The primary and key secondary endpoints were summarized for prespecified subgroups
  - Within each subgroup, response rate was summarized for each treatment arm, and the difference in response rate between the mitapivat arm and the placebo arm was estimated (difference in Hb response rate and 95% CI) using an unstratified method
- The frequency of patients achieving transfusion independence was summarized for each treatment group
  - The adjusted difference in the proportion of patients who achieved transfusion independence between the mitapivat and placebo groups was calculated using a Mantel–Haenszel stratum weighted method adjusting for randomization stratification factors, along with the 95% CI
- Descriptive statistics were reported for the safety endpoints based on the Safety Analysis Set

CI, confidence interval; Hb, hemoglobin; TRR, transfusion reduction response.

Subgroup analysis of TRR2: Reduction in transfusion burden was not driven by any prespecified subgroups

Subgroup analysis of key secondary endpoint

Subgroup	TRR2 rate, % (n/N) Placebo	Mitapivat	Difference (95% CI)[b]
All patients (stratified)[a]	2.3 (2/87)	13.5 (23/171)	11.1 (5.1, 17.0)
Thalassemia genotype			
Non-β^0/β^0	4.2 (2/48)	18.8 (18/96)	14.6 (2.1, 24.8)
β^0/β^0	0.0 (0/39)	6.7 (5/75)	6.7 (–3.1, 14.9)
Geographic region, n (%)			
North America and Europe	3.7 (2/54)	14.2 (15/106)	10.4 (–0.5, 19.4)
Asia-Pacific	0.0 (0/16)	22.6 (7/31)	22.6 (–0.2, 41.2)
Rest of world	0.0 (0/17)	2.9 (1/34)	2.9 (–17.0, 15.9)
Age at screening (year)			
<35	0.0 (0/44)	9.9 (9/91)	9.9 (0.1, 18.0)
≥35	4.7 (2/43)	17.5 (14/80)	12.8 (–0.5, 23.9)
Sex			
Female	0.0 (0/43)	14.0 (13/93)	14.0 (2.4, 22.7)
Male	4.5 (2/44)	12.8 (10/78)	8.3 (–4.3, 18.7)
Race			
Asian	0.0 (0/22)	17.9 (10/56)	17.9 (–1.0, 30.4)
White	3.6 (2/56)	10.1 (10/99)	6.5 (–3.5, 14.9)
24-week baseline transfusion burden			
≤12 RBC units	9.5 (2/21)	31.5 (17/54)	22.0 (–1.3, 38.6)
>12 RBC units	0.0 (0/66)	5.1 (6/117)	5.1 (–0.7, 10.9)

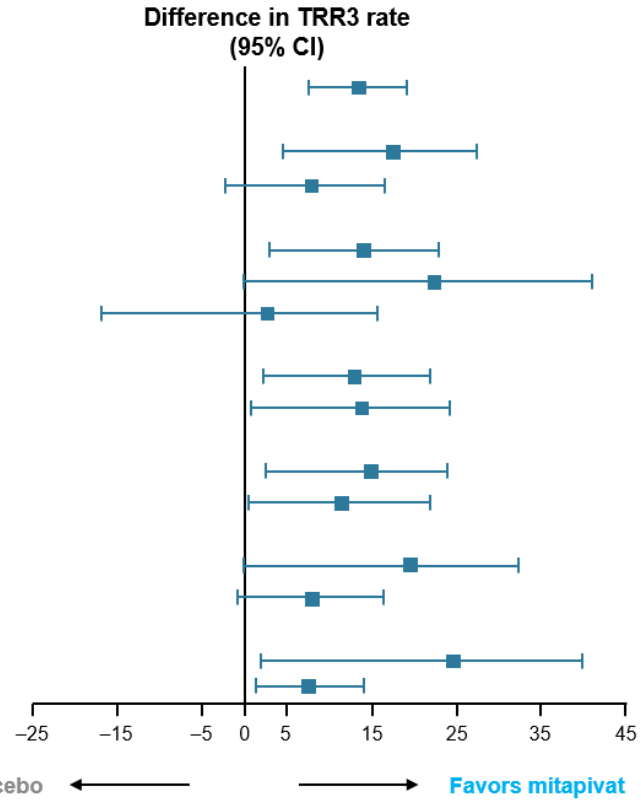


Analysis conducted on Full Analysis Set. TRR2 was defined as a ≥50% reduction from baseline in transfused RBC units in any consecutive 24-week period through Week 48. [a]Stratified by thalassemia genotype and geographic region. [b]For "All patients," the estimates for the difference and the 95% CI are 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. CI, confidence interval; RBC, red blood cell; TRR, transfusion reduction response.

Subgroup analysis of TRR3: Reduction in transfusion burden was not driven by any prespecified subgroups

Subgroup analysis of key secondary endpoint

Subgroup	TRR3 rate, % (n/N) Placebo	Mitapivat	Difference (95% CI)[b]
All patients (stratified)[a]	1.1 (1/87)	14.6 (25/171)	13.4 (7.7, 19.1)
Thalassemia genotype			
Non-β^0/β^0	2.1 (1/48)	19.8 (19/96)	17.7 (4.7, 27.5)
β^0/β^0	0.0 (0/39)	8.0 (6/75)	8.0 (–2.2, 16.7)
Geographic region, n (%)			
North America and Europe	1.9 (1/54)	16.0 (17/106)	14.2 (3.0, 23.0)
Asia-Pacific	0.0 (0/16)	22.6 (7/31)	22.6 (–0.2, 41.2)
Rest of world	0.0 (0/17)	2.9 (1/34)	2.9 (–17.0, 15.9)
Age at screening (year)			
<35	0.0 (0/44)	13.2 (12/91)	13.2 (2.3, 22.0)
≥35	2.3 (1/44)	16.3 (13/80)	13.9 (0.7, 24.4)
Sex			
Female	0.0 (0/43)	15.1 (14/93)	15.1 (2.4, 24.0)
Male	4.5 (2/44)	14.1 (11/78)	11.8 (0.6, 22.1)
Race			
Asian	0.0 (0/22)	19.6 (11/56)	19.6 (–0.1, 32.4)
White	1.8 (1/56)	10.1 (10/99)	8.3 (–0.8, 16.4)
24-week baseline transfusion burden			
≤12 RBC units	4.8 (1/21)	29.6 (16/54)	24.9 (2.0, 40.0)
>12 RBC units	0.0 (0/66)	7.7 (9/117)	7.7 (1.4, 14.2)

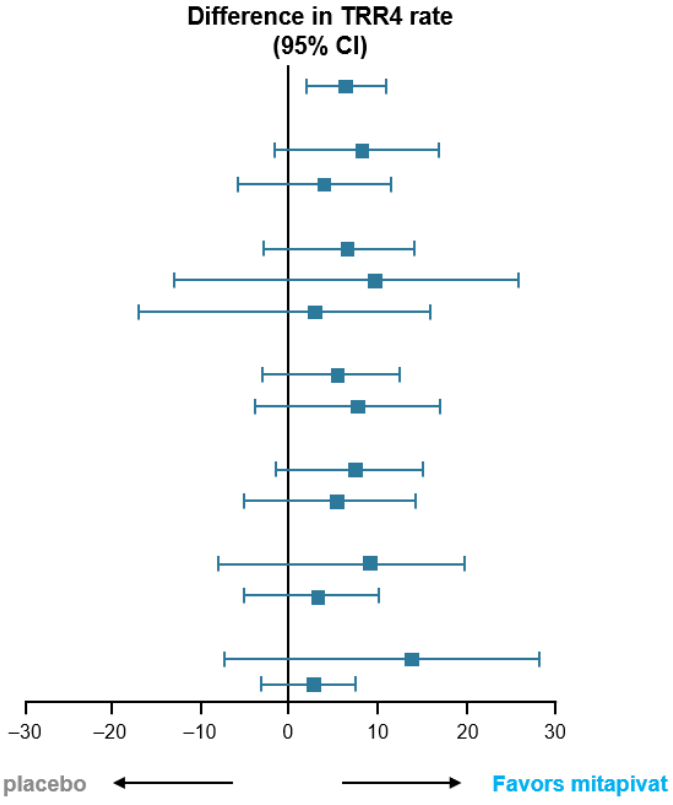


Analysis conducted on Full Analysis Set. TRR3 was defined as a ≥33% reduction from baseline in transfused RBC units in Weeks 13–48. [a]Stratified by thalassemia genotype and geographic region. [b]For "All patients," the estimates for the difference and the 95% CI are based on the Mantel–Haenszel stratum weighted method adjusting for the randomization stratification factors. For subgroups, the estimates for the difference and the 95% CIs are based on unstratified analyses. CI, confidence interval; RBC, red blood cell; TRR, transfusion reduction response.

Subgroup analysis of TRR4: Reduction in transfusion burden was not driven by any prespecified subgroups

Subgroup analysis of key secondary endpoint

Subgroup	TRR4 rate, % (n/N) Placebo	Mitapivat	Difference (95% CI)[b]
All patients (stratified)[a]	1.1 (1/87)	7.6 (13/171)	6.4 (1.9, 10.9)
Thalassemia genotype			
Non-β^0/β^0	2.1 (1/48)	10.4 (10/96)	8.3 (–1.6, 16.7)
β^0/β^0	0.0 (0/39)	4.0 (3/75)	4.0 (–5.9, 11.4)
Geographic region, n (%)			
North America and Europe	1.9 (1/54)	8.5 (9/106)	6.6 (–2.8, 14.1)
Asia-Pacific	0.0 (0/16)	9.7 (3/31)	9.7 (–13.1, 25.9)
Rest of world	0.0 (0/17)	2.9 (1/34)	2.9 (–17.0, 15.9)
Age at screening (year)			
<35	0.0 (0/44)	5.5 (5/91)	5.5 (–3.1, 12.5)
≥35	2.3 (1/44)	10.0 (8/80)	7.7 (–4.0, 17.0)
Sex			
Female	0.0 (0/43)	7.5 (7/93)	7.5 (–1.5, 15.1)
Male	2.3 (1/44)	7.7 (6/78)	5.4 (–5.1, 14.2)
Race			
Asian	0.0 (0/22)	8.9 (5/56)	8.9 (–7.9, 19.8)
White	1.8 (1/56)	5.1 (5/99)	3.3 (–5.1, 10.0)
24-week baseline transfusion burden			
≤12 RBC units	4.8 (1/21)	18.5 (10/54)	13.8 (–7.4, 28.2)
>12 RBC units	0.0 (0/66)	2.6 (3/117)	2.6 (–3.2, 7.5)



Analysis conducted on Full Analysis Set. TRR4 was defined as a ≥50% reduction from baseline in transfused RBC units in Weeks 13–48. [a]Stratified by thalassemia genotype and geographic region. [b]For "All patients," the estimates for the difference and the 95% CI 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. CI, confidence interval; RBC, red blood cell; TRR, transfusion reduction response.