Agios at ASH 2023

December 11, 2023

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), AG-946, TMPRSS6 siRNA and Agios' PAH stabilizer; Agios' plans, strategies and expectations for its preclinical, clinical and commercial advancement of its drug development; Agios' strategic vision and goals, including its key milestones for 2023 and potential catalysts through 2026; and the potential benefits of Agios' strategic plans and prospects. The words "anticipate," "expect," "goal," "hope," "milestone," "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 or its collaborators 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. Moreover, there can be no guarantee that any medicines ultimately commercialized by Agios will receive commercial acceptance. 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 proceeds from the transaction with Servier; 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.

Agenda

TOPIC	PARTICIPANT
Company Overview	Brian Goff, Chief Executive Officer
Agios Highlights at ASH 2023	Sarah Gheuens, M.D., Ph.D., Chief Medical Officer, Head of Research and Development
Sickle Cell Disease: Phase 2 RISE UP Data Update	Ahmar Zaidi, M.D., Senior Medical Director
Thalassemia: Phase 2 Data Review	Jeremie Estepp, M.D., Medical Director
Thalassemia: Framing Upcoming Phase 3 ENERGIZE Study Readouts	Sarah Gheuens, M.D., Ph.D., Chief Medical Officer, Head of Research and Development
Closing Remarks and Q&A	Presenters + Cecilia Jones, Chief Financial Officer and Tsveta Milanova, Chief Commercial Officer

Building a Leading Hematology Franchise

Brian Goff
Chief Executive Officer at Agios

Leader in pyruvate kinase (PK) activation poised for significant growth

Compelling and consistent data across connected diseases

Robust clinical data set supports potential of PK activation to transform patient function, quality of life, and long-term outcomes

Meaningful commercial opportunities on the horizon

First rare disease launch building capabilities to maximize anticipated franchise expansion

Potential for two additional PYRUKYND® indications by 2026

Well capitalized to advance and expand

Strong cash position expected to support completion of ongoing programs and disciplined portfolio expansion into 2026

Leaders in PK activation positioned for meaningful near-term growth

PYRUKYND® is the first and only disease-modifying treatment approved for adults with PK deficiency

Five late-stage data readouts expected by end of 2025

PK deficiency
Approved for adults in the U.S. and EU

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

Thalassemia
Potential U.S. approval in 2025

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

Sickle cell disease
Potential U.S. approval in 2026

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

Lower-risk myelodysplastic syndrome

75-80K patients
in the U.S./EU5

AG-946
Novel PK Activator
provides additional opportunities for the franchise

Building **PYRUKYND**

Larger patient populations →
Higher diagnostic rates →
Higher burden of disease →

AG-946
Second PK Activator

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

Momentum building: on track to deliver on all 2023 goals

2023

Thalassemia
PYRUKYND®
Complete enrollment of Phase 3 ENERGIZE and ENERGIZE-T studies
(MID-YEAR)

Sickle Cell Disease
PYRUKYND®
Phase 2 RISE UP data readout & go/no-go to Phase 3 decision
(MID-YEAR)

Pediatric PK Deficiency
PYRUKYND®
Enroll at least half of patients in the Phase 3 ACTIVATE-kids and ACTIVATE-kidsT studies
(YEAR-END)

Lower-Risk MDS
AG-946 (Novel PK Activator)
Complete enrollment of Phase 2a study
(YEAR-END)

Sickle Cell Disease
PYRUKYND®
Begin patient enrollment in Phase 3 RISE UP study
(YEAR-END)

Lower-Risk MDS
AG-946
Phase 2a data readout
(YEAR-END)

Pipeline
File IND for PAH stabilizer for the treatment of PKU
(YEAR-END)

Evaluate business development opportunities to expand pipeline and build commercial capabilities to efficiently launch additional indications

Pipeline
License Agreement with Alnylam for novel siRNA for potential treatment of PV
(Q3 2023)

Five late-stage data readouts by the end of 2025

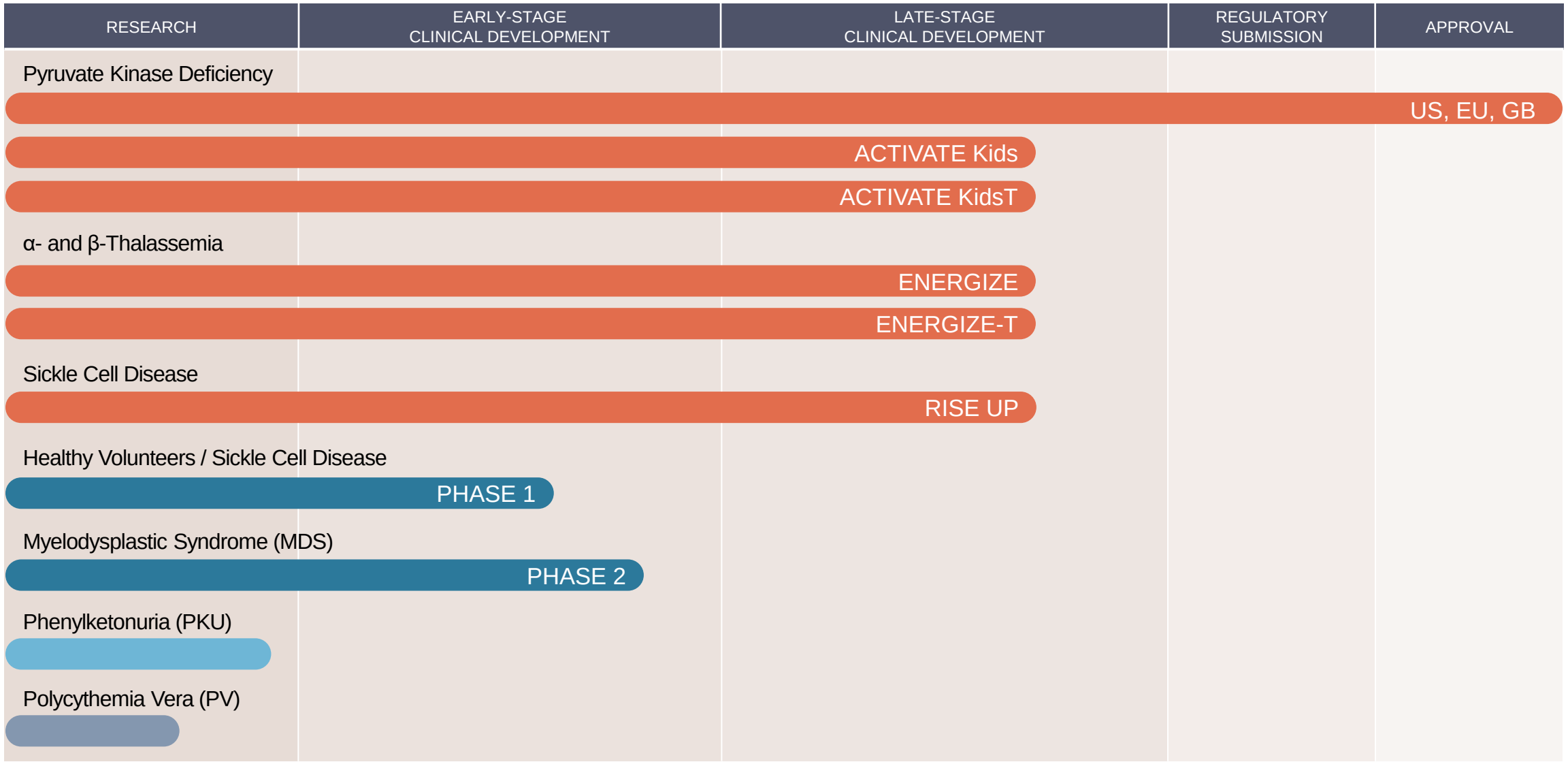
	2024	2025	2026
Thalassemia PYRUKYND®	Phase 3 ENERGIZE (1H) Phase 3 ENERGIZE-T (2H)	Potential approval	
Pediatric PK Deficiency PYRUKYND®		Phase 3 ACTIVATE-kids Phase 3 ACTIVATE-kidsT	Potential approval
Sickle Cell Disease PYRUKYND®		Phase 3 RISE UP	Potential approval
Lower-Risk MDS AG-946 (Novel PK Activator)	Initiate Phase 2b study (mid-year)		

T = Transfusion Dependent patient population

Agios Highlights at ASH 2023

Sarah Gheuens, M.D., Ph.D.,
CMO and Head of Research & Development at Agios

Building a diverse pipeline anchored in our core areas of expertise



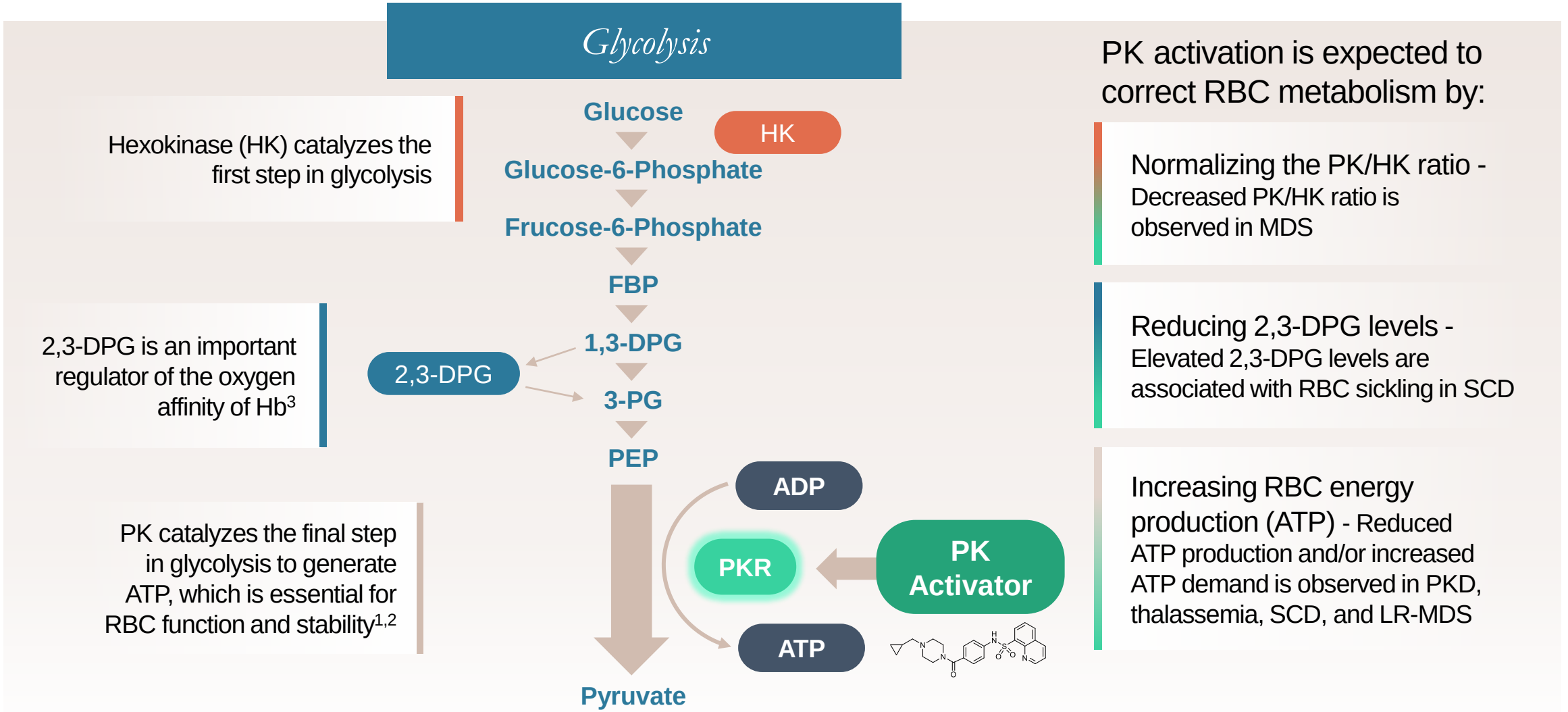
PYRUKYND®
First-in-class PK activator

AG-946
Novel PK activator

Phenylalanine hydroxylase (PAH) stabilizer

siRNA Targeting TMPRSS6

PK activation has the potential to correct red blood cell metabolism across multiple diseases



PK activation is expected to correct RBC metabolism by:

Normalizing the PK/HK ratio - Decreased PK/HK ratio is observed in MDS

Reducing 2,3-DPG levels - Elevated 2,3-DPG levels are associated with RBC sickling in SCD

Increasing RBC energy production (ATP) - Reduced ATP production and/or increased ATP demand is observed in PKD, thalassemia, SCD, and LR-MDS

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

Highlighting key pipeline progress at ASH 2023

American Society of Hematology Annual Meeting

December 9-12, 2023 | San Diego

PK Deficiency

Thalassemia

Sickle Cell Disease

Patient Advocacy

Educational Session on PK Activation Independently Organized by ASH

Energizing the Red Cell: Pyruvate Kinase Activators for Treatment of Hereditary Hemolytic Anemias

(today at 10:30 am; Room 28 A-D)

Agios data at ASH 2023 reinforce efficacy of PK activation and burden of disease across targeted indications

Sickle Cell Disease

- *A Phase 2/3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study of Mitapivat in Patients With Sickle Cell Disease: RISE UP Phase 2 Results*
- *Long-term safety and Efficacy of Mitapivat, an Oral Pyruvate Kinase Activator, in Adults with Sickle Cell Disease: Extension of a Phase 1 Dose Escalation Study*

Thalassemia

- *Mitapivat Treatment Increases β-thalassemic Erythroblasts Energy Production and Responsiveness to Oxidative Stress*
- *Association of Hemoglobin Levels With Healthcare Resource Utilization and Costs in Non–Transfusion-Dependent α- and β-Thalassemia: A Retrospective Observational Study Using Real-World Data*
- *Burden of Illness of Alpha- and Beta-Thalassemia: A Qualitative Study*

Lower-risk MDS

- *AG-946, An Activator of Pyruvate Kinase, Improves Ineffective Erythropoiesis in the Bone Marrow of Mouse Models of Myelodysplastic Syndromes*
- *The Pyruvate Kinase (PK) Activator AG-946 Improves PK Properties and Red Blood Cell (RBC) Characteristics upon Ex Vivo Treatment of RBCs from Patients with Myelodysplastic Syndromes*

Patient Advocacy

- *Cross-community Collaboration and Data Collection to Optimize Patient Care in Hemolytic Anemias*
- *Setting Industry Standards for Patient Engagement, Partnership, Allyship and Care: The Patient Vision Project*

Data Update from the Phase 2 Portion of the RISE UP Study of Mitapivat in Sickle Cell Disease*

Ahmar U. Zaidi, M.D.
Senior Medical Director at Agios

** Selected excerpts from data presentation at ASH 2023*

A Phase 2/3, Double-Blind, Randomized, Placebo-Controlled, Multicenter Study of Mitapivat in Patients With Sickle Cell Disease: RISE UP Phase 2 Results

Modupe Idowu, MD,[1] Lucas Otieno, MD, MPH,[2] Bogdan Dumitriu, MD,[3] Clarisse LC Lobo, MD, PhD,[4] Swee Lay Thein, MD, DSc,[5] Biree Andemariam, MD,[6] Obiageli E Nnodu, MD,[7] Adlette Inati, MD,[8] Alexander K Glaros, MD,[9] Sara T Olalla Saad, MD, PhD,[10] Pablo Bartolucci, MD, PhD,[11] Raffaella Colombatti, MD, PhD,[12] Ali T Taher, MD, PhD,[13] Miguel R Abboud, MD,[13] Abdulafeez Oluyadi, PharmD,[14] Varsha Iyer, PhD,[15,*] Ophelia Yin, PhD,[16,*] Susan Morris, PhD,[14] Amber M Yates, MD,[14] Hui Shao, PhD,[14] Spurthi Patil, MS,[14] Rolandas Urbstonaitis, PharmD, MBS,[14] Ahmar U Zaidi, MD,[14] and Wally R Smith, MD,[17] on behalf of the RISE UP Investigators

[1]McGovern Medical School, UTHealth, Houston, Texas; [2]Victoria Biomedical Research Institute, Kisumu, Kenya; [3]Mid-Atlantic Permanente Medical Group, Largo, Maryland; [4]Research Division, HEMORIO, Rio de Janeiro, RJ, Brazil; [5]Sickle Cell Branch, The National Heart, Lung, and Blood Institute, Bethesda, Maryland; [6]New England Sickle Cell Institute, UConn Health, Farmington, Connecticut; [7]Centre of Excellence for Sickle Cell Disease Research and Training, Department of Haematology and Blood Transfusion, College of Health Sciences, University of Abuja, Abuja, Nigeria; [8]Lebanese American University Gilbert and Rose-Marie Chagoury School of Medicine, Byblos and NINI Hospital, Tripoli, Lebanon; [9]Central Michigan University, Children's Hospital of Michigan, Detroit, Michigan; [10]Hematology And Transfusion Medicine Center, University of Campinas, Campinas, Brazil; [11]Reference Center of Sickle Cell Disease, Mondor University Hospital, Créteil, France; [12]Pediatric Hematology Oncology Unit, University of Padova, Padova, Italy; [13]American University of Beirut Medical Center, Beirut, Lebanon; [14]Agios Pharmaceuticals, Inc., Cambridge, Massachusetts; [15]Fog Pharmaceuticals, Inc., Cambridge, Massachusetts; [16]iTeos Therapeutics, Watertown, Massachusetts; [17]Virginia Commonwealth University, Richmond, Virginia

**Employee of Agios Pharmaceuticals, Inc. at time of research.*

PYRUKYND® is approved in the U.S., EU, and Great Britain for adult PK deficiency and is under investigation for pediatric PK deficiency, thalassemia, and sickle cell disease.

This study was funded by Agios Pharmaceuticals, Inc.
Presented at the 65th American Society of Hematology Annual Meeting and Exposition; December 9–12, 2023; San Diego, CA, and Online

Sickle Cell Disease

- Sickle cell disease (SCD) is characterized by the presence of hemoglobin S (HbS), a structural variant caused by a mutation in the β-globin gene (*HBB)*[1]
- Deoxygenated HbS molecules rapidly polymerize into “fibers,” causing red blood cells (RBCs) to sickle and hemolyze[1,2]
  - Sickled RBCs have a shortened life span and impede blood flow to tissues, causing painful vaso-occlusive crises (VOCs)[1]
  - Recurrent microvascular damage and chronic hemolytic anemia result in progressive multi-organ damage (including the kidneys, heart, lung, and liver)[1]

HBB, β-globin gene; HbS, hemoglobin S; RBC, red blood cell; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

1. Piel FB, et al. *N Eng J Med*. 2017;376(16):1561-1573. 2. Kaperonis AA, et al. *Am J Hematol*. 1986;21(3):269-275.

Sickle Cell Disease

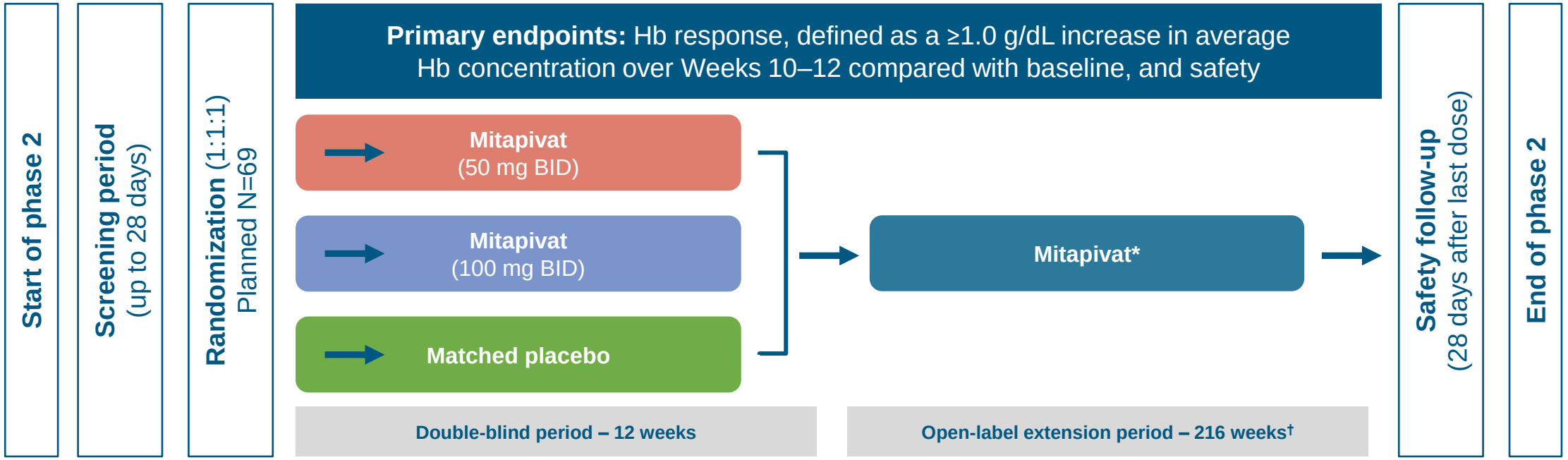
- Approximately 8 million people are affected by SCD worldwide[1]; the life expectancy for patients with SCD is reduced by about 30 years and the quality of life is often poor[2]
- Common self-reported symptoms occurring in patients with SCD include fatigue (50% to 79%) and bone aches (43% to 66%)[3]
- A meta-analysis of 41 phase 2, 3, and 4 clinical trials in patients with SCD reported that an increase in Hb of ≥1.0 g/dL was associated with a 41% to 57% reduction in the risk for negative clinical outcomes and a 64% reduction in the risk of mortality[4]

Hb, hemoglobin; SCD, sickle cell disease.

1. GBD 2021 Sickle Cell Disease Collaborators. *Lancet Haematol*. 2023;10(8):e585-e589. 2. Piel FB, et al. *N Eng J Med*. 2017;376(16):1561-1573. 3. Osunkwo I, et al. *Am J Hematol*. 2022;97(8):1055-1064.
4. Ataga KI, et al. *PLoS One.* 2020;15(4):e0229959.

RISE UP Study Design (Phase 2 Portion)

- RISE UP is a global, phase 2/3, double-blind, randomized, placebo-controlled trial evaluating the efficacy and safety of mitapivat in patients with SCD (NCT05031780)
- The phase 2 portion of RISE UP was a dose-finding study evaluating 2 doses of mitapivat (50 mg BID and 100 mg BID) vs placebo to select the dose of mitapivat for assessment in the phase 3 portion



*Patients who receive mitapivat in double-blind period will continue to receive the same dose of mitapivat in the open-label extension period; patients who receive placebo will be randomized 1:1 to mitapivat 50 mg BID or 100 mg BID.
†Patients who have completed the 12-week phase 2 double-blind period and do not have ongoing grade ≥3 TEAEs can receive mitapivat in the 216-week open-label extension period.

BID, twice daily; Hb, hemoglobin; SCD, sickle cell disease; TEAE, treatment-emergent adverse event.

Eligibility Criteria

Key Inclusion Criteria

- ≥16 years of age
- Confirmed diagnosis of SCD (any genotype)
- 2-10 sickle cell pain crises (SCPCs) in the prior 12 months, including:
  - Acute pain
  - Acute chest syndrome
  - Priapism
  - Hepatic or splenic sequestration
- Anemia (≥5.5 and ≤10.5 g/dL)
- If taking hydroxyurea (HU), the dose must be stable for ≥90 days before starting study drug

Key Exclusion Criteria

- Pregnant or breastfeeding
- Receiving regular RBC transfusion therapy
- Hospitalized for SCPC or other vaso-occlusive event ≤14 days prior to informed consent (IC) or during Screening
- Received disease-modifying treatment for SCD except HU or hematopoiesis-stimulating agents ≤90 days before randomization
- Cardiovascular or pulmonary disease

HU, hydroxyurea; IC, informed consent; RBC, red blood cell; SCD, sickle cell disease; SCPC, sickle cell pain crisis.

Primary and Secondary Endpoints

- Primary endpoints:
  - Hb response, defined as ≥1.0 g/dL increase in average Hb concentration from Week 10 through Week 12 compared with baseline
  - Adverse events (AEs) and serious adverse events (SAEs), including type, severity, and relationship to study drug
- Prespecified secondary endpoints:
  - Average change from baseline from Week 10 through Week 12 in:
    - Hb levels
    - Indirect bilirubin
    - Lactate dehydrogenase (LDH)
    - Absolute reticulocyte count and percent reticulocytes
    - Erythropoietin
    - Patient-Reported Outcomes Measurement Information System® (PROMIS) Fatigue 13a Short Form (SF) score
  - Annualized rate of SCPCs

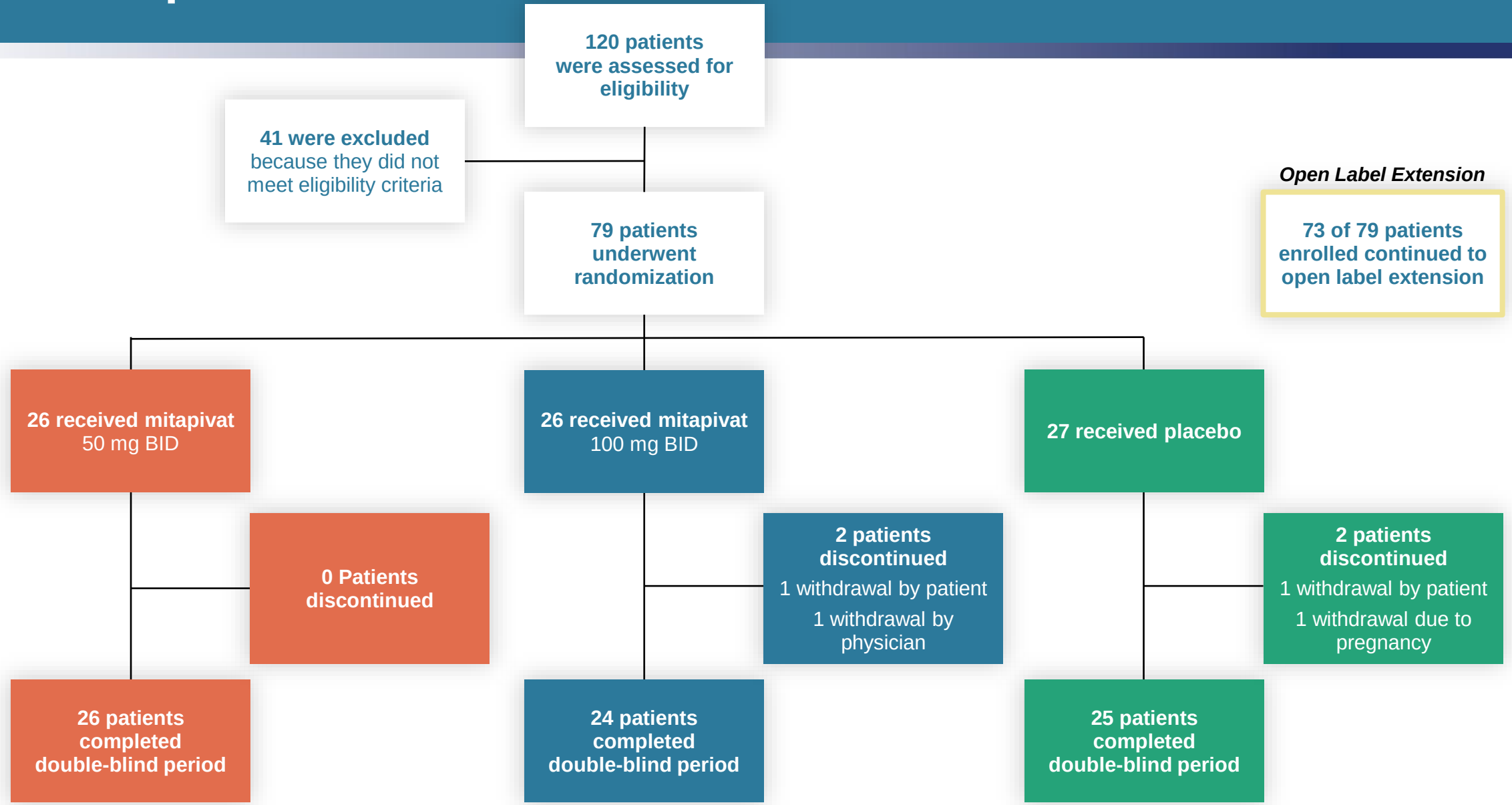
AE, adverse event; Hb, hemoglobin; LDH, lactate dehydrogenase; PROMIS, Patient-Reported Outcomes Measurement Information System; SAE, serious adverse event; SCPC, sickle cell pain crisis; SF, Short Form.

Primary and Secondary Endpoints – Statistical Methods

- The difference in Hb response rates (proportion of patients with Hb response) between each of the mitapivat arms and the placebo arm was estimated and the exact 95% CIs and 2-sided p-values based on Fisher's exact test (significance level of 0.05) were calculated
- Secondary endpoints associated with change from baseline were analyzed based on a mixed model for repeated measures. The model included change from baseline as the dependent variable, baseline value as a covariate, treatment arm, study visit, and treatment-by-visit interaction as fixed factors, and subject as the random effect. The estimated treatment difference between each of the mitapivat arms and the placebo arm was estimated based on the LS mean and associated 95% CIs for each endpoint
- The annualized rates of SCPCs between each of the mitapivat arms and the placebo arm were compared based on a negative binomial regression model with natural log link. The model included the number of SCPCs as the response variable and the treatment arm as an independent variable

Hb, hemoglobin; LS, least squares; SCPC, sickle cell pain crisis.

Patient Disposition



BID, twice a day.

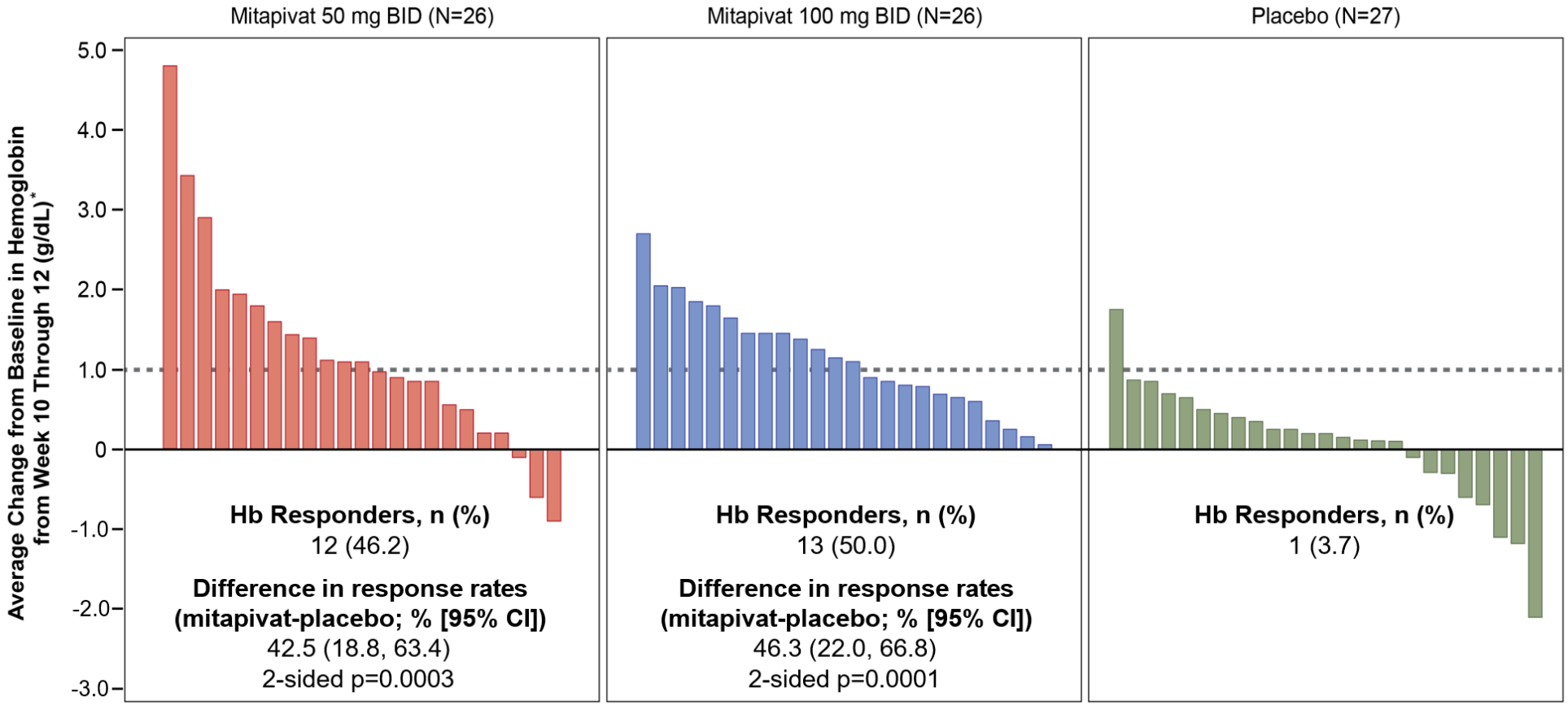
Demographics and Baseline Characteristics

	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
Age, mean (SD), years	29.9 (7.79)	30.2 (10.52)	28.5 (10.3)
Sex, n (%)			
Male	11 (42.3)	10 (38.5)	7 (25.9)
Female	15 (57.7)	16 (61.5)	20 (74.1)
Race, n (%)			
Black or African American	16 (61.5)	14 (53.8)	16 (59.3)
White	9 (34.6)	9 (34.6)	8 (29.6)
Asian	0	1 (3.8)	1 (3.7)
Multiracial	1 (3.8)	2 (7.7)	2 (7.4)
Hb, mean (SD), g/dL	8.76 (1.29)	8.82 (0.90)	8.49 (1.14)
Indirect bilirubin, mean (SD), µmol/L	31.51 (21.87)	31.27 (23.13)	30.42 (22.41)
LDH, mean (SD), U/L	403.15 (147.19)	422.10 (148.97)	381.25 (128.91)
Erythropoietin, mean (SD), IU/L	115.01 (125.88)	110.26 (128.36)	149.64 (285.09)
No. of SCPCs,* mean (SD)	3.1 (1.83)	3.2 (1.65)	3.4 (1.91)
Hydroxyurea use, n (%)	20 (76.9)	21 (80.8)	19 (70.4)

*Includes SCPCs within 12 months before IC and during screening.

BID, twice a day; Hb, hemoglobin; IC, informed consent; LDH, lactate dehydrogenase; No, number; SCPC, sickle cell pain crisis.

Mitapivat Met the Phase 2 Primary Endpoint, Demonstrating Higher Hb Response Rates Compared With Placebo



*Baseline was defined as the average of all assessments during the screening period up to the randomization date. Assessments collected within 8 weeks after an RBC transfusion were excluded from the baseline derivation and from the analysis. Subjects who do not have any Hb concentration assessments from Week 10 through Week 12 are considered as nonresponders.

BID, twice a day; Hb, hemoglobin; RBC, red blood cell.

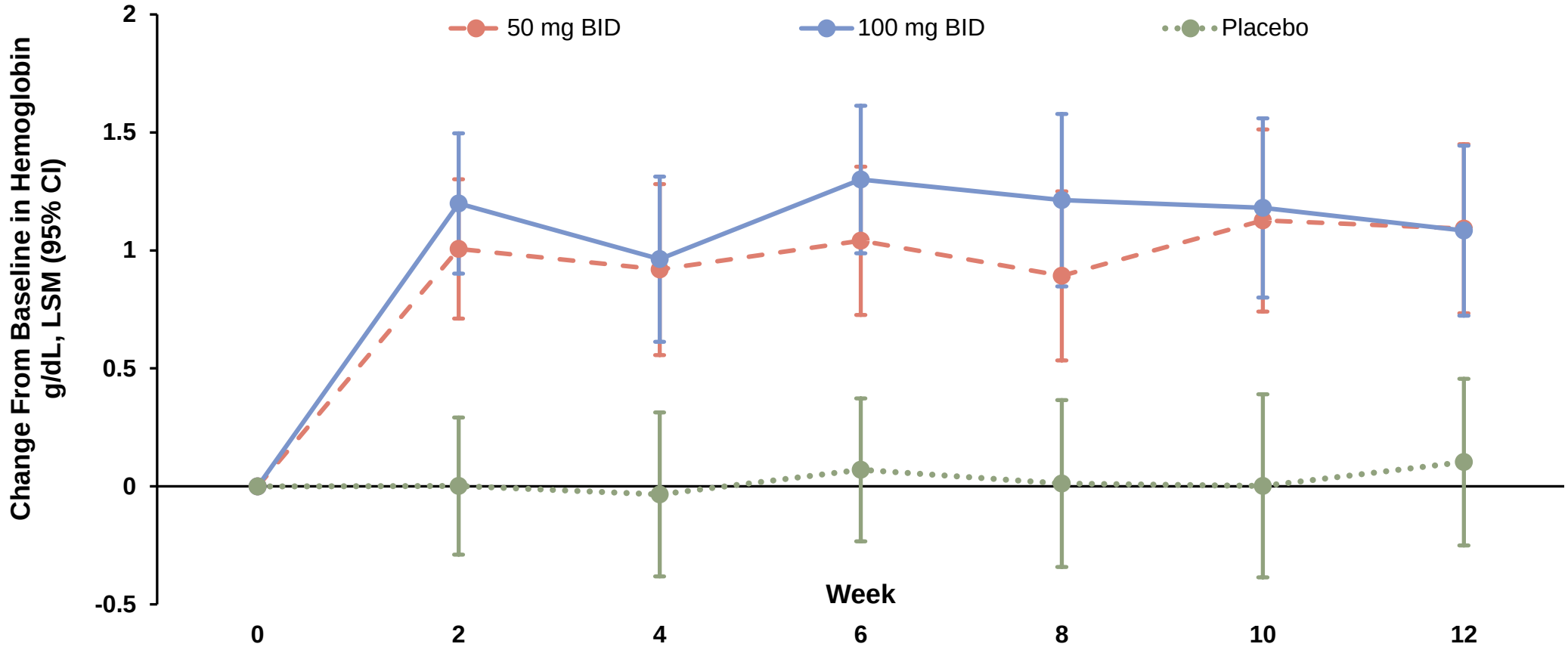
Improvements in Hb Levels Were Observed With Both Doses of Mitapivat Compared With Placebo

	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
Baseline Hb level (g/dL)			
Mean (SD)	8.76 (1.29)	8.82 (0.90)	8.49 (1.14)
Average change from baseline in Hb level from Week 10 through Week 12 (g/dL)			
LSM (95% CI)	1.11 (0.77, 1.45)	1.13 (0.79, 1.47)	0.05 (−0.28, 0.39)
Difference (LSM [95% CI]; mitapivat−placebo)	1.06 (0.58, 1.53)	1.08 (0.60, 1.56)	

NOTE: The estimates and 95% CIs are based on the mixed-effect model repeated measure (MMRM) method, which includes change from baseline as the dependent variable, baseline as a covariate, and treatment group, visit, treatment-by-visit interaction, and subject as the random effect.

BID, twice a day; Hb, hemoglobin; LSM, least squares mean.

Hemoglobin Levels Improved Early With Both Mitapivat Doses and Were Sustained Through Week 12



Mitapivat 100 mg BID, n=	26	23	23	24	23	23	23
Mitapivat 50 mg BID, n=	26	23	19	22	24	22	22
Placebo, n=	27	24	22	25	24	21	22

NOTE: The estimates and 95% CIs are based on the mixed-effect model repeated measure (MMRM) method, which includes change from baseline as the dependent variable, baseline as a covariate, and treatment group, visit, treatment-by-visit interaction, and subject as the random effect.

BID, twice a day; LSM, least squares mean.

Reductions in SCPCs Were Observed at Both Doses Compared With Placebo

	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
Sickle cell pain crises			
Annualized rate (95% CI)	0.83 (0.34, 1.99)	0.51 (0.16, 1.59)	1.71 (0.95, 3.08)
Mitapivat/placebo rate ratio (95% CI)	0.48 (0.17, 1.39)	0.30 (0.08, 1.07)	
Rate reduction (mitapivat vs placebo), % (95% CI)*	51.6 (−39.4, 83.2)	70.0 (−7.4, 91.6)	

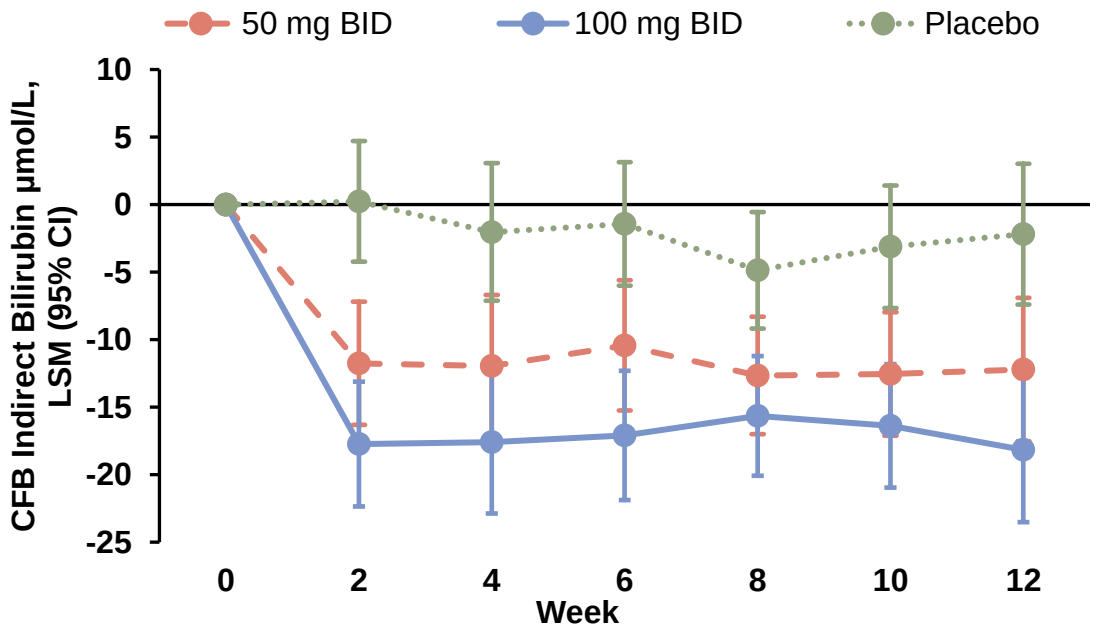
*Rate reduction is defined as 100% x 1−rate ratio).

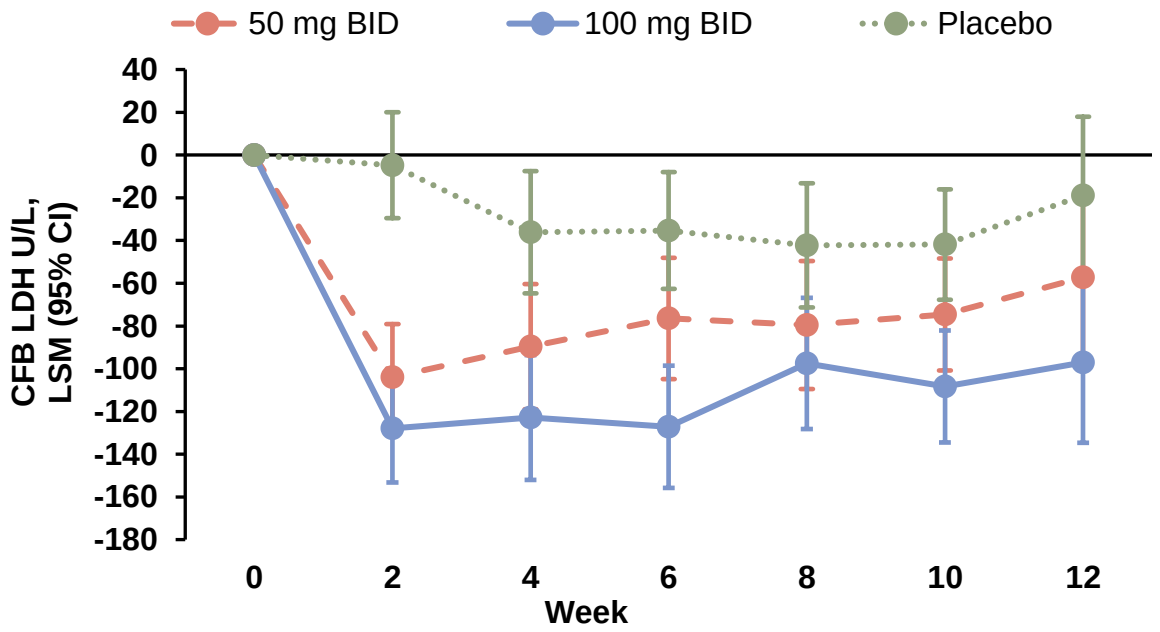
BID, twice a day; SCPCs, sickle cell pain crises.

Improvements in Markers of Hemolysis Were Observed With Both Doses of Mitapivat Compared With Placebo

Average CFB in indirect bilirubin from Week 10 through Week 12 (µmol/L)	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
LSM (95% CI)	−12.36 (−17.04, −7.69)	−17.26 (−21.98, −12.55)	−2.65 (−7.23, 1.93)
Difference (LSM [95% CI]; mitapivat−placebo)	−9.72 (−16.26, −3.17)	−14.62 (−21.19, −8.05)	

Average CFB in LDH from Week 10 through Week 12 (U/L)	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
LSM (95% CI)	−65.90 (−95.08, −36.72)	−102.71 (−132.17, −73.26)	−30.36 (−58.99, −1.73)
Difference (LSM [95% CI]; mitapivat−placebo)	−35.54 (−76.44, 5.36)	−72.35 (−113.54, −31.17)	





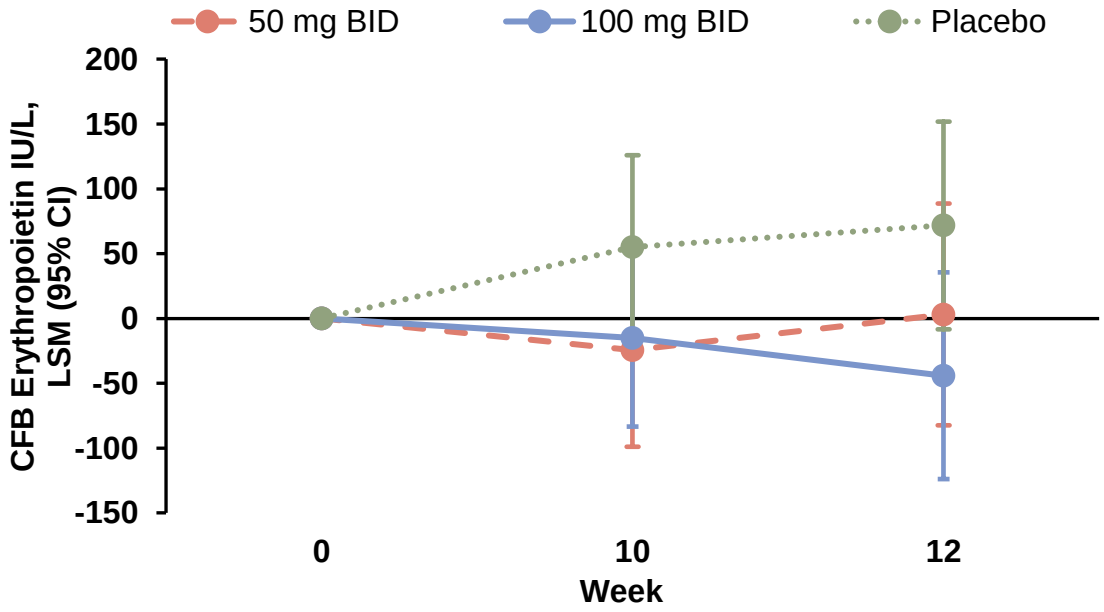
NOTE: The estimates and 95% CIs are based on the mixed-effect model repeated measure (MMRM) method, which includes CFB as the dependent variable, baseline as a covariate, and treatment group, visit, treatment-by-visit interaction, and subject as the random effect.

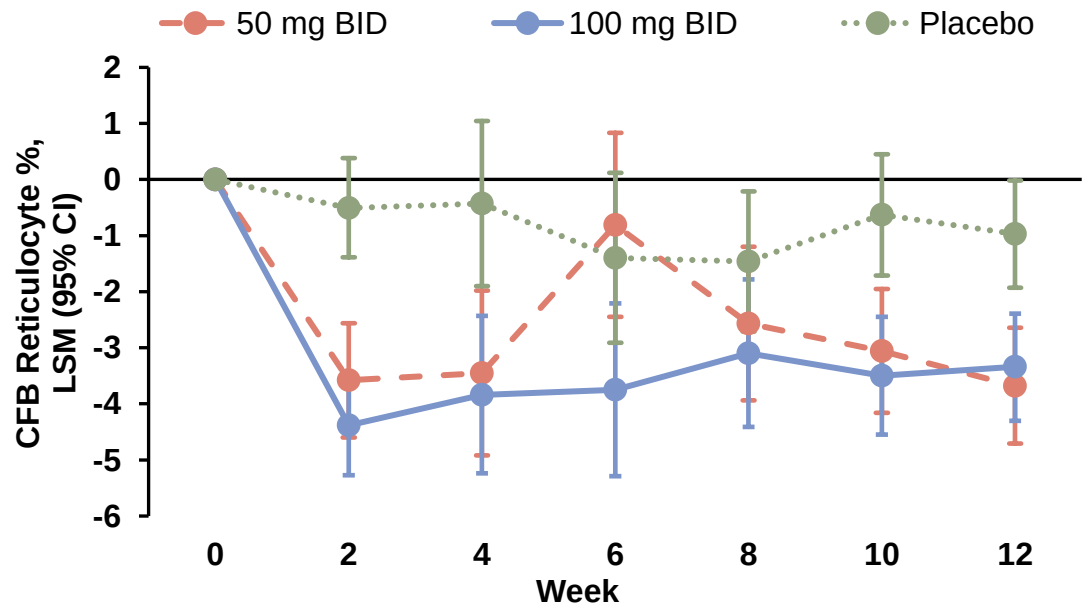
BID, twice a day; CFB, change from baseline; LDH, lactate dehydrogenase; LSM, least squares mean.

Improvements in Markers of Erythropoiesis Were Observed With Both Doses of Mitapivat Compared With Placebo

Average CFB in erythropoietin from Week 10 through Week 12 (IU/L)	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
LSM (95% CI)	−10.66 (−87.23, −65.91)	−29.66 (−100.16, 40.85)	63.47 (−7.72, 134.67)
Difference (LSM [95% CI]; mitapivat−placebo)	−74.13 (−178.92, 30.65)	−93.13 (−193.39, 7.13)	

Average CFB in percent reticulocytes from Week 10 through Week 12 (%)	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
LSM (95% CI)	−3.37 (−4.28, −2.47)	−3.42 (−4.27, −2.57)	−0.8 (−1.66, 0.06)
Difference (LSM [95% CI]; mitapivat−placebo)	−2.57 (−3.82, −1.32)	−2.62 (−3.83, −1.40)	





NOTE: The estimates and 95% CIs are based on the mixed-effect model repeated measure (MMRM) method, which includes CFB as the dependent variable, baseline as a covariate, and treatment group, visit, treatment-by-visit interaction, and subject as the random effect.

BID, twice a day; CFB, change from baseline; LSM, least squares mean.

Improvement in PROMIS Fatigue Scores Was Observed With Mitapivat 50 mg BID Compared With Placebo

Average CFB in PROMIS Fatigue 13a Short Form T score from Week 10 through Week 12	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
LSM (95% CI)	−3.80 (−7.16, −0.45)	−0.10 (−3.27, 3.08)	−0.17 (-3.40, 3.07)
Difference (LSM [95% CI]; mitapivat−placebo)	−3.64 (−8.30, 1.03)	0.07 (−4.46, 4.60)	

BID, twice a day; CFB, change from baseline; LSM, least squares mean; PROMIS, Patient-Reported Outcomes Measurement Information System.

Summary of Treatment-Emergent Adverse Events

	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
Any TEAEs, n (%)	19 (73.1)	23 (88.5)	22 (81.5)
Grade ≥3 TEAEs, n (%)	3 (11.5)	5 (19.2)	2 (7.4)
Treatment-related TEAEs, n (%)	10 (38.5)	8 (30.8)	7 (25.9)
Grade ≥3 treatment-related TEAEs, n (%)	0	0	0
Serious TEAEs, n (%)*	2 (7.7)	4 (15.4)	3 (11.1)
Serious treatment-related TEAEs, n (%)	0	0	0
TEAEs leading to discontinuation of study drug, n (%)	0	0	0
TEAEs leading to dose reduction	0	0	0
TEAEs leading to interruption of study drug	0	0	0
TEAEs leading to death	0	0	0
Treatment-related TEAEs leading to death	0	0	0

*Serious TEAEs included infections, bone fracture, pulmonary embolism, and anemia.

BID, twice a day; TEAE, treatment-emergent adverse event.

Mitapivat Was Generally Safe and Well Tolerated

Patients with most common TEAEs, n (%)*	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26	Placebo N=27
Headache	6 (23.1)	6 (23.1)	7 (25.9)
Arthralgia	3 (11.5)	5 (19.2)	9 (33.3)
Dysmenorrhea	0	3 (11.5)	0
Pain	3 (11.5)	3 (11.5)	2 (7.4)
Pain in extremity	1 (3.8)	3 (11.5)	6 (22.2)
Back pain	4 (15.4)	2 (7.7)	3 (11.1)
Nausea	1 (3.8)	2 (7.7)	4 (14.8)
Fatigue	4 (15.4)	1 (3.8)	5 (18.5)
Influenza-like illness	1 (3.8)	1 (3.8)	3 (11.1)

*Most common TEAEs are those of any grade in ≥10% of patients in any treatment group.
NOTE: Patients with multiple occurrences of one AE type are counted once for that AE type.

AE, adverse event; BID, twice a day; TEAE, treatment-emergent adverse event.

Conclusions

- In the phase 2, 12-week, randomized, placebo-controlled, double-blind period of RISE UP, treatment with mitapivat demonstrated statistically significant and clinically meaningful improvements in Hb response at both dose levels (50 mg BID and 100 mg BID) compared with placebo
- A reduction in the annualized rate of SCPCs was observed in both mitapivat treatment arms compared with placebo
- Improvements in markers of hemolysis/erythropoiesis were observed in both mitapivat treatment arms compared with placebo
  - The magnitude of improvements were generally larger in the mitapivat 100-mg BID arm
- Mitapivat had an observed safety profile consistent with previously reported data of mitapivat in SCD and other hemolytic anemias
  - No AEs led to study drug reduction, discontinuation, interruption, or death

AE, adverse event; BID, twice a day; Hb, hemoglobin; SCD, sickle cell disease; SCPC, sickle cell pain crisis.

Conclusions

Mitapivat, through its dual mechanism of action*, may provide clinical benefit to patients with SCD. Current phase 2 data support continued development in the phase 3 portion of the RISE UP trial evaluating a 100-mg BID dose**

*Reducing 2,3 DPG and increasing ATP as referred to on slide 12
**The phase 3 portion of RISE UP is currently recruiting patients (NCT05031780)

BID, twice a day; SCD, sickle cell disease.

RISE UP Phase 3 Study: patient enrollment and dosing underway

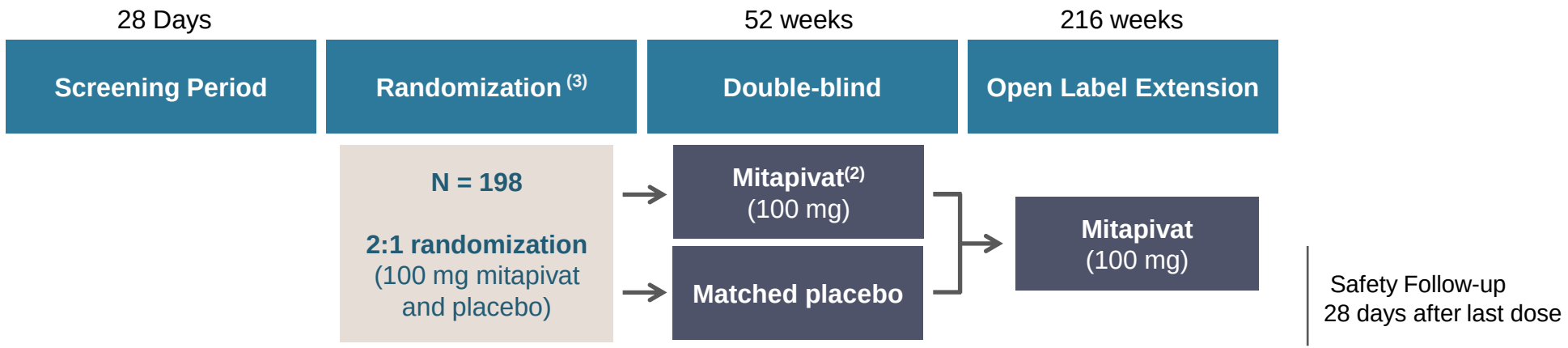
Phase 3 primary endpoints [(1)]:
Hb response, defined as a ≥ 1.0 g/dL increase in average Hb concentration over Weeks 24–52 compared with baseline, and annualized rate of SCPCs

Key inclusion criteria

- ≥ 16 years of age
- Documented SCD (HbSS, HbSC, HbSβ0/HbSβ+ thalassemia, other SCD variants)
- Recurrent VOCs (vaso-occlusive crises) – defined as the occurrence of 2–10 SCPCs (acute pain needing medical contact, acute chest syndrome, priapism, hepatic or splenic sequestration) in the prior 12 months
- Anemia – defined as a Hb level of 5.5–10.5 g/dL
- If taking HU, the dose must be stable for ≥ 90 days before starting study drug

Key exclusion criteria

- Receiving regularly scheduled blood transfusions
- Severe kidney disease or hepatobiliary disorders
- Currently receiving treatment with SCD therapies (excluding HU)
- Prior exposure to gene therapy, or prior bone marrow or stem cell transplantation



Abbreviations: BID = twice daily; Hb = hemoglobin; SCPC = sickle cell pain crises; HU = hydroxyurea
(1) Phase 2 and phase 3 components are part of a single study/protocol; (2) Patients who receive mitapivat in the double-blind period will continue to receive the same dose of mitapivat in the open-label extension period;
(3)Randomization stratification factors: Number of SCPCs in the prior year (< 5, ≥ 5), hydroxyurea use (yes, no).

Review of Phase 2 Data of Mitapivat in Thalassemia*

Jeremie Estepp, M.D.
Medical Director at Agios

** Selected excerpts from data presentation at ASH 2022*

Background

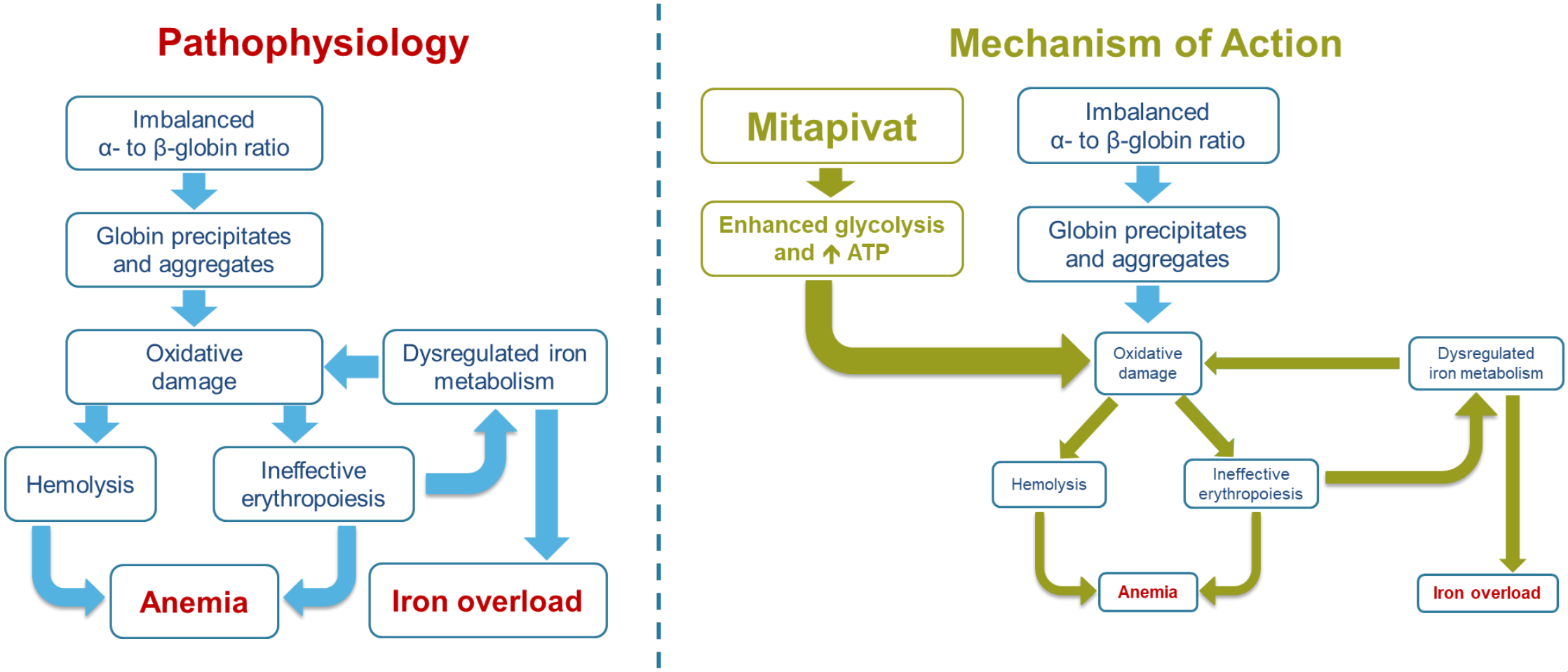
- Thalassemia is a group of genetic disorders impacting α- and/or β-globin genes, resulting in an imbalance of globin production[1,2]
  - Excess globin chains precipitate and are toxic to red blood cells (RBCs), directly leading to ineffective erythropoiesis and hemolysis[2]
- Thalassemic RBCs lack sufficient levels of ATP to meet the increased energy demands associated with degradation of globin chain precipitates and cellular oxidative stress responses[3,4]
- Although patients with non–transfusion-dependent thalassemia (NTDT) do not require regular blood transfusions for survival, it can result in chronic anemia and serious complications[1,2]
  - Treatment options for NTDT are supportive only, highlighting an unmet need for disease-modifying therapies[5]
- Mitapivat is an investigational, first-in-class, oral, small-molecule allosteric activator of pyruvate kinase (PK) in RBCs, a key enzyme that regulates ATP production[6]

PYRUKYND® is approved in the U.S., EU, and Great Britain for adult PK deficiency and is under investigation for pediatric PK deficiency, thalassemia, and sickle cell disease.

ATP, adenosine triphosphate; NTDT, non–transfusion-dependent thalassemia; PK, pyruvate kinase; RBC, red blood cell; 1. Taher AT et al. *Lancet* 2018;391:155–67; 2. Galanello R et al. *Orphanet J Rare Dis* 2010;5:11; 3. Khandros E et al. *Blood* 2012;119:5265–75; 4. Shaeffer JR. *J Biol Chem* 1988;263:13663–9; 5. Musallam KM et al. *Haematologica* 2021;106:2489–92; 6. Kung C et al. *Blood* 2017;130:1347–56

Background

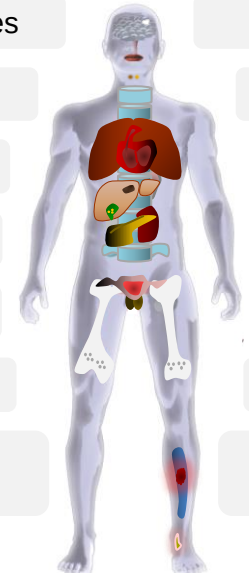
Figure 2. Pathophysiology and proposed mitapivat mechanism of action in thalassemia



ATP, adenosine triphosphate

α- & β-thalassemia: increased morbidity, limited & evolving therapeutic landscape

Multiple Organ System Damage



- Bone deformities
- Endocrinopathy
- Thrombosis
- Growth & pubertal delay
- PHT & Heart failure
- Arrhythmia
- Hepatosplenomegaly
- Liver fibrosis & cirrhosis
- Gallstones
- Renal disease
- Leg ulcers
- Osteoporosis
- Extramedullary hematopoiesis
- Cancers

Reduced Quality of Life

Early Death[1]

Therapeutic Landscape

Transfusions (*cornerstone*):

1. *Chronic*—severe anemia (<7 g/dL) or stigmata of disease
2. *Intermittent*—rapid hemoglobin rise needed for exacerbation of anemia
3. *Paradigm changing*—hemoglobin ≤10 g/dL now identified as risk factor for morbidity and mortality[1]

Splenectomy:

1. Increases hemoglobin by 1.0-2.0 g/dL
2. Increased risks: thrombosis, PHT and infection
3. Recommendation to reserve for patients who cannot receive chronic transfusions

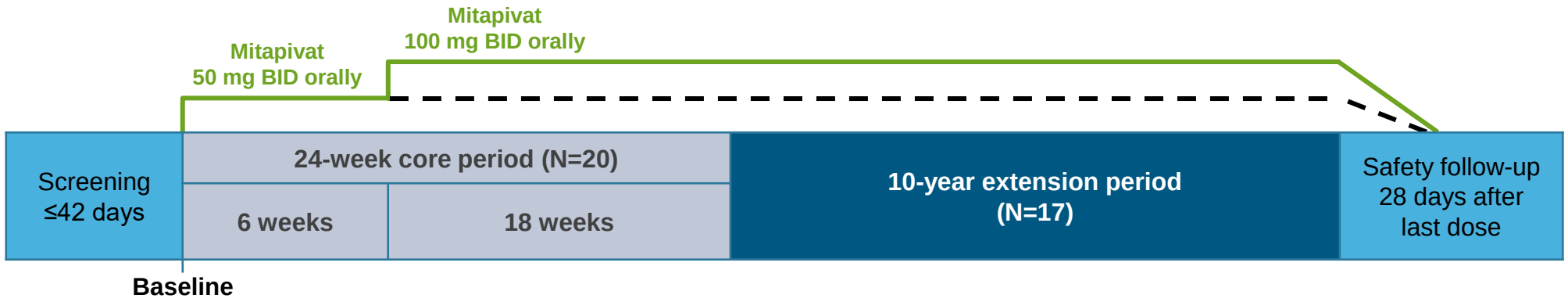
Luspatercept (approval for treatment of anemia in adults)**:**

1. FDA & EMA: Transfusion Dependent β-thalassemia
2. EMA: Non-transfusion Dependent β-thalassemia
3. No approval for α-thalassemia

EHP = extramedullary hematopoietic pseudotumors; HCC = hepatocellular carcinoma; PHT = pulmonary hypertension. Modified from Taher AT et al. N Engl J Med 2021;384:727–43. 1. Guidelines for the management of non-transfusion dependent thalassemia (NTDT). 3rd Ed. Nicosia, Cyprus. thalassemia International Federation, 2023

Overview of Phase 2 core period

Figure 3. Design of open-label, phase 2 study of mitapivat in adults with α- or β-NTDT[a]



Core period[11]

Primary endpoint

- Hb response, defined as: ≥1.0 g/dL increase in Hb concentration from baseline at 1 or more assessments between Weeks 4 and 12, inclusive
- The primary endpoint of hemoglobin (Hb) response was met in 80.0% (16/20) of patients

Additional efficacy and safety results

- Improvements in markers of hemolysis and erythropoietic activity were also observed
- Mitapivat was generally well tolerated at both the initial 50 mg twice-daily dose and the increased 100 mg twice-daily dose
- The most common AEs were initial insomnia (50%), dizziness (30%), and headache (25%)

[a]EudraCT 2018-002217-35, ClinicalTrials.gov: NCT03692052; BID, twice daily; dL, deciliter; Hb, hemoglobin; HbE, hemoglobin E; HbH, hemoglobin H; NTDT, non–transfusion-dependent thalassemia
TEAE, treatment-emergent adverse event; 11. Kuo KHM et al. *Lancet* 2022;400:493–501; 12. Kuo KHM et al. *Blood* 2021;138(S1):576

Results summary from core period and long-term extension

Results from core period (previously presented)[11]

- The primary endpoint of hemoglobin (Hb) response was met in 80.0% (16/20) of patients
- Improvements in markers of hemolysis and erythropoietic activity were also observed
- Mitapivat was generally well tolerated at both the initial 50 mg twice-daily dose and the increased 100 mg twice-daily dose
  - The most common AEs were initial insomnia (50%), dizziness (30%), and headache (25%)

Results from long-term extension (LTE) period (previously presented)[12]

- In the LTE period, the increase in Hb was sustained with a mean Hb (SD) increase of 1.7 g/dL (0.5) at Week 72
- Improvements in erythropoietin, total bilirubin, and LDH were maintained up to data cutoff at Week 72
- Mitapivat was generally well tolerated, and the safety profile was consistent with that of previously published mitapivat studies

AE, adverse event; Hb, hemoglobin; LTE, long-term extension; SD, standard deviation; 11. Kuo KHM et al. *Lancet* 2022;400:493–501; 12. Kuo KHM et al. *Blood* 2021;138(S1):576

Patient demographics and baseline characteristics

Table 1. Patient demographics and baseline[a] characteristics for patients in the core study period

Patient demographics and baseline characteristics from the core period[11]	All patients (N=20)
Sex, n (%)	
Male	5 (25)
Female	15 (75)
Age, median (Q1, Q3), years	44 (35, 56)
Race, n (%)	
Asian	10 (50)
White	4 (20)
Black or African	1 (5)
Native Hawaiian or other Pacific Islander	1 (5)
Other	3 (15)
Not reported	1 (5)
Thalassemia type, n (%)	
α-thalassemia	5 (25)
β-thalassemia	15 (75)

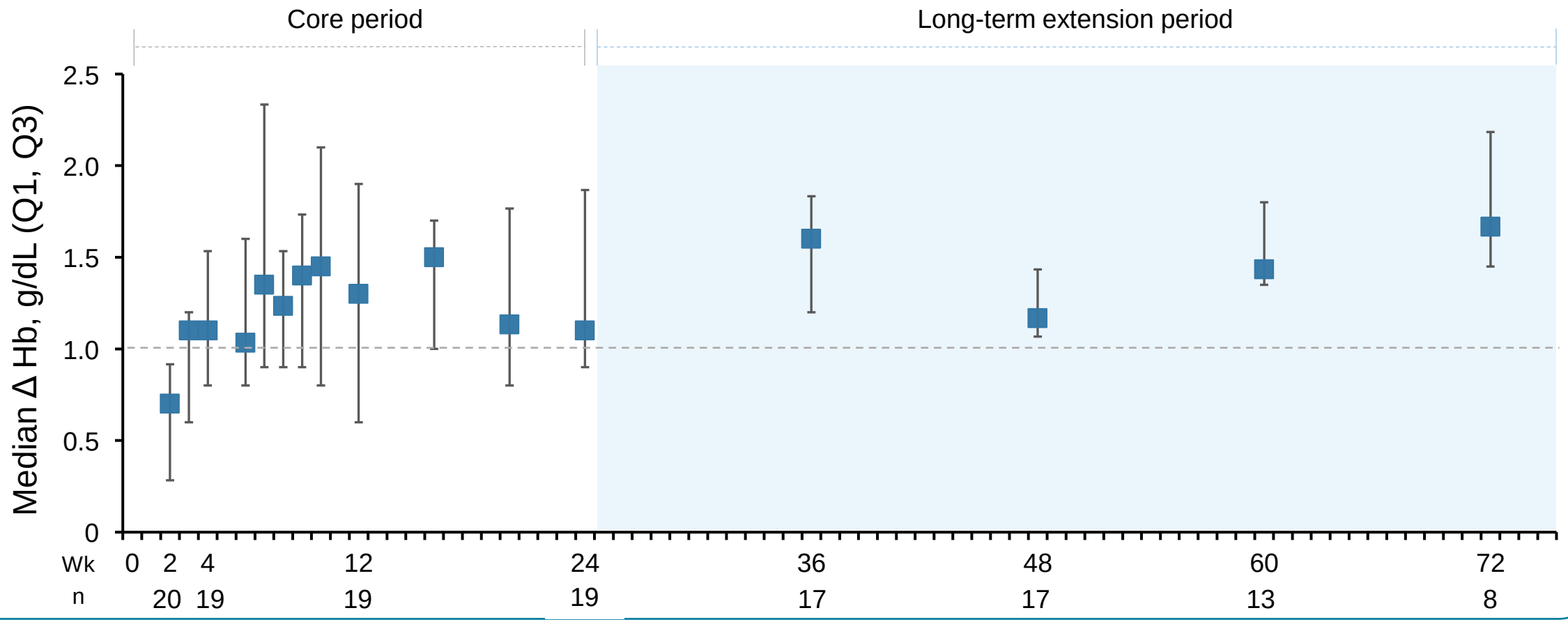
Baseline biomarkers from the core period[11]	All patients (N=20)
Hb baseline, median (Q1, Q3), g/dL	8.4 (6.78, 8.98)
Erythropoietin, median (Q1, Q3), IU/L	79.0 (29.0, 137.0)
Erythroferrone, median (Q1, Q3), ng/L	10,760.0 (3627.5, 17,712.5)
Indirect bilirubin, median (Q1, Q3), µmol/L	21.0 (15.5, 36.1)
Reticulocytes/erythrocytes, median (Q1, Q3), fraction of 1	0.04 (0.030, 0.044)
Hepcidin, median (Q1, Q3), ng/L	40,750.0 (27,250.0, 53,750.0)
Soluble transferrin receptor, median (Q1, Q3), nmol/L	174.1 (90.59, 268.24)

- The baseline characteristics of the subset of patients who entered the LTE (N=17) were similar to those of the core period full analysis set (N=20)
- At baseline, biomarkers were consistent with ineffective erythropoiesis and hemolysis (**Table 1**)

[a]Baseline is defined as the last assessment on or before the start of study treatment in core period
Hb, hemoglobin; 11. Kuo KHM et al. *Lancet* 2022;400:493–501

Sustained improvements in hemoglobin were observed throughout the extension period

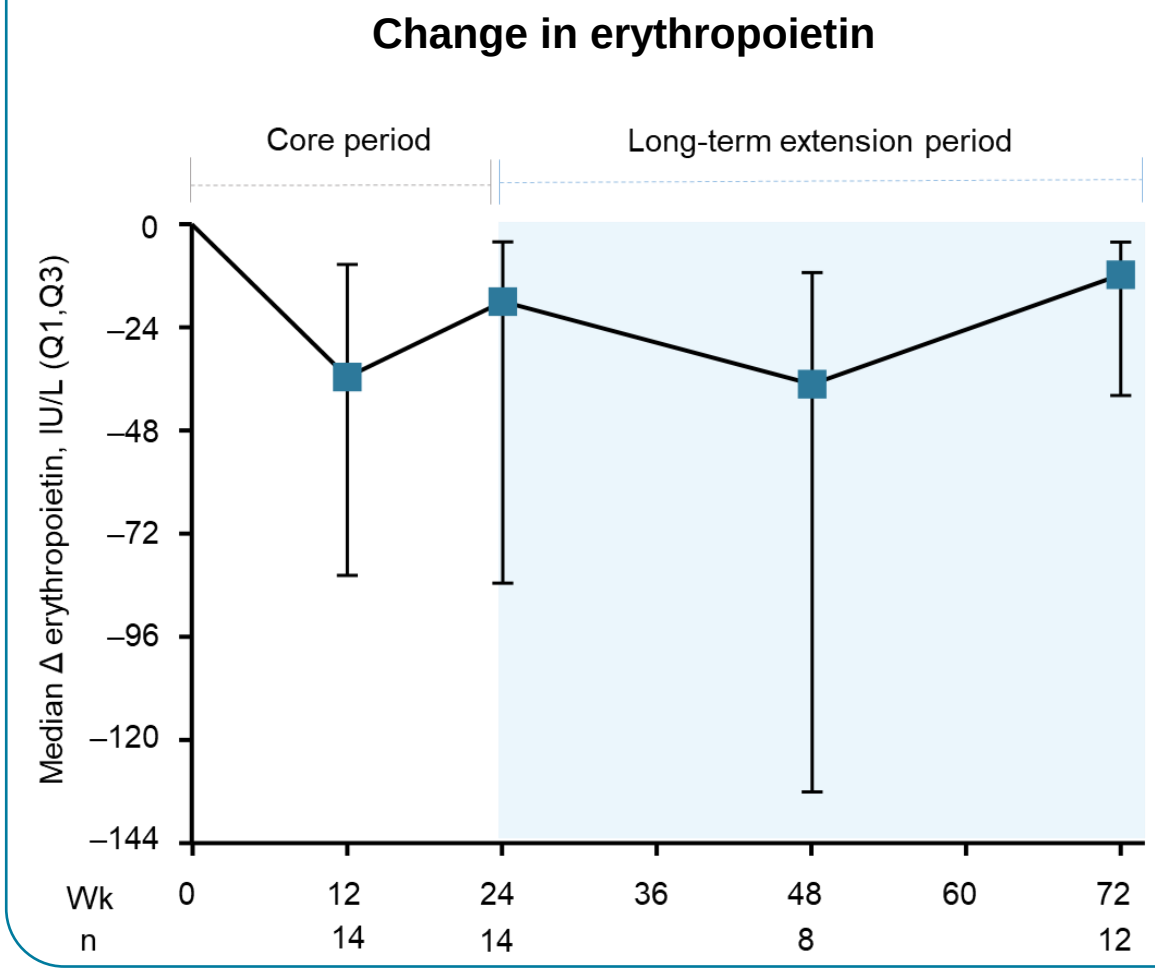
Figure 4. Median Hb change from baseline over time

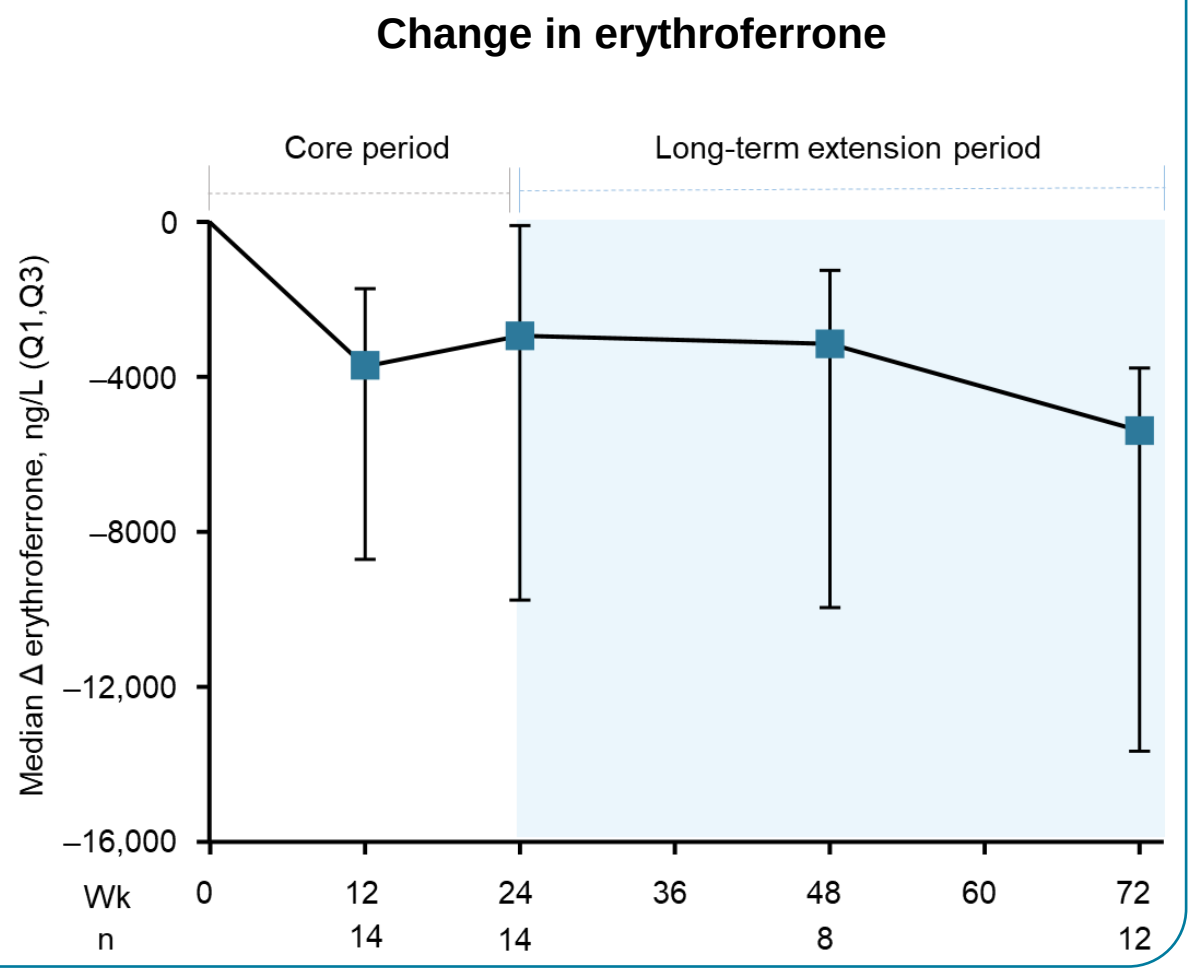


Hb, hemoglobin; Q, quartile; Wk, week

Markers of erythropoietic activity remained stable or improved through Week 72

Figure 5. Markers of erythropoietic activity

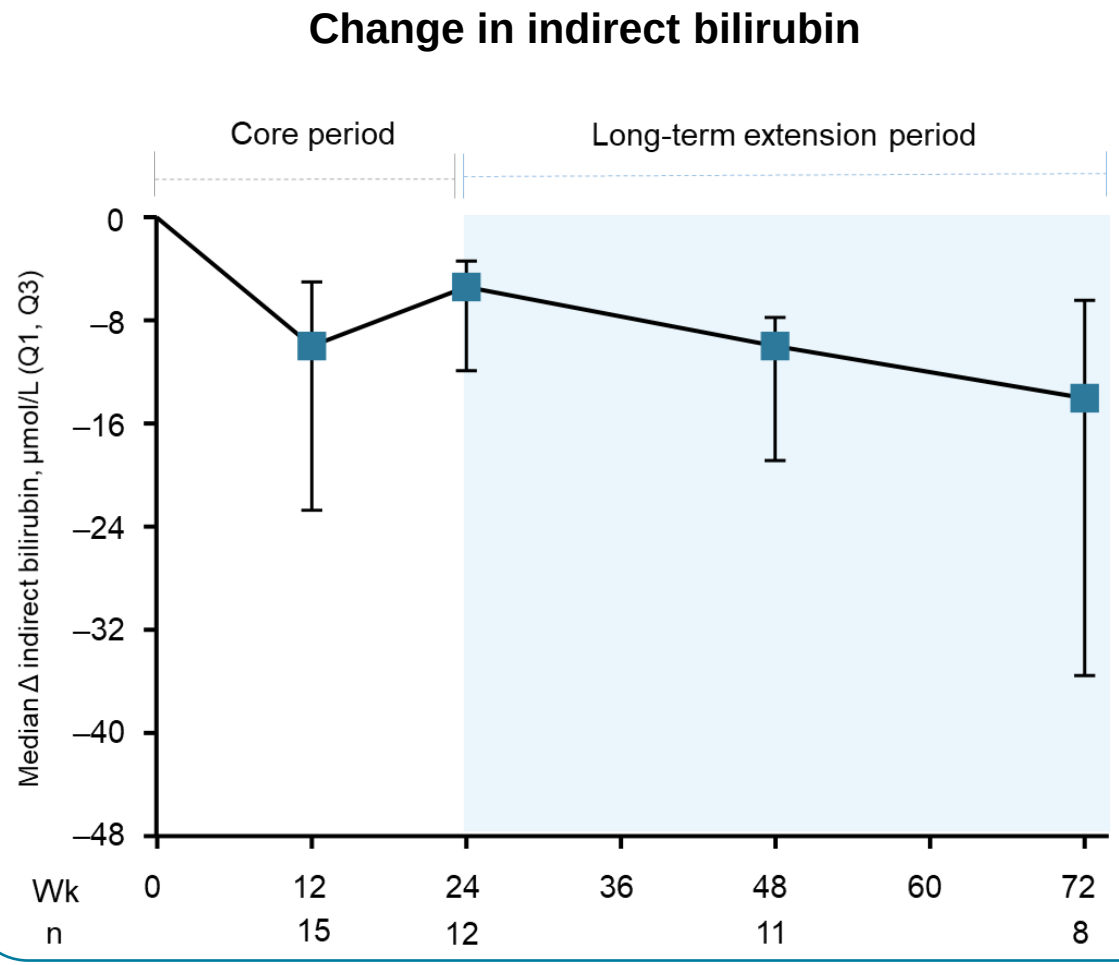


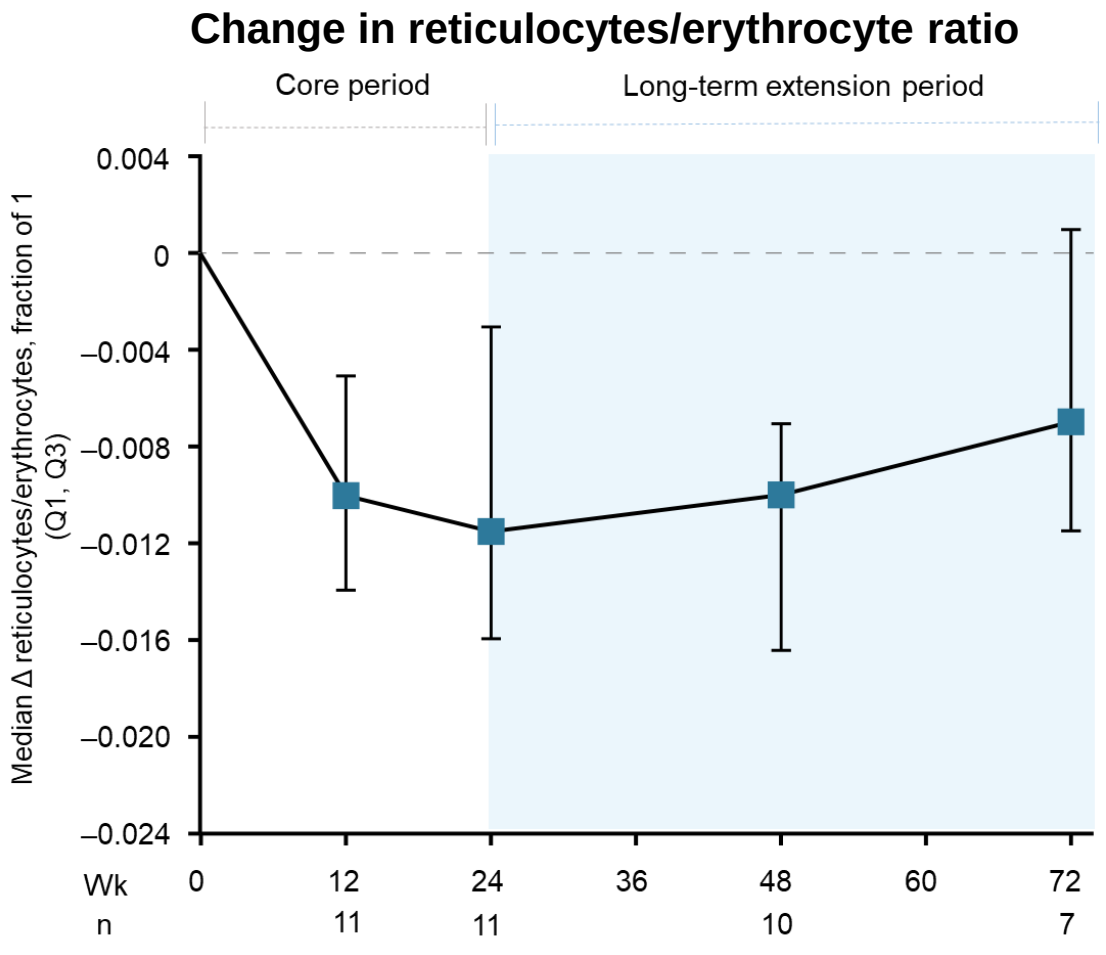


Q, quartile; Wk, week

Improvements in markers of hemolysis were observed through Week 72

Figure 6. Markers of hemolysis



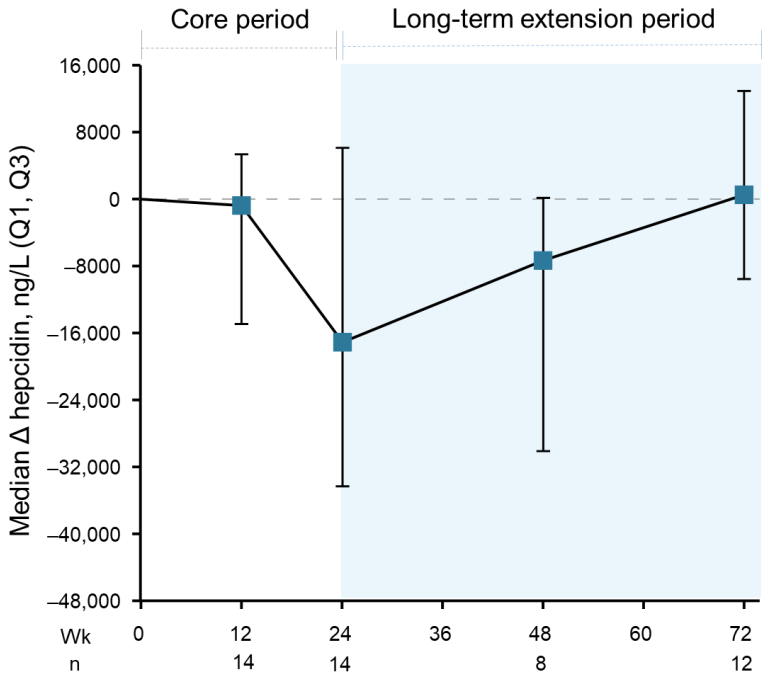


Q, quartile; Wk, week

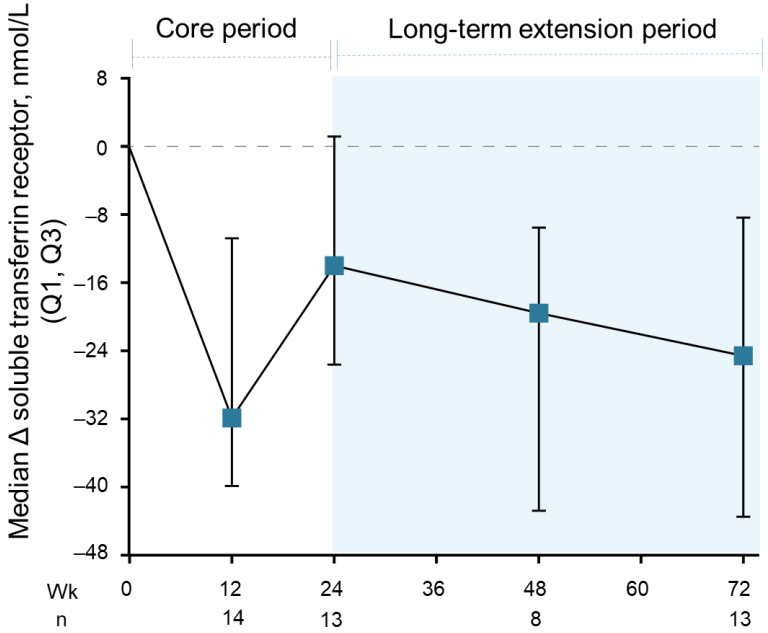
Markers of iron homeostasis remained stable or improved through Week 72

Figure 7. Markers of iron homeostasis

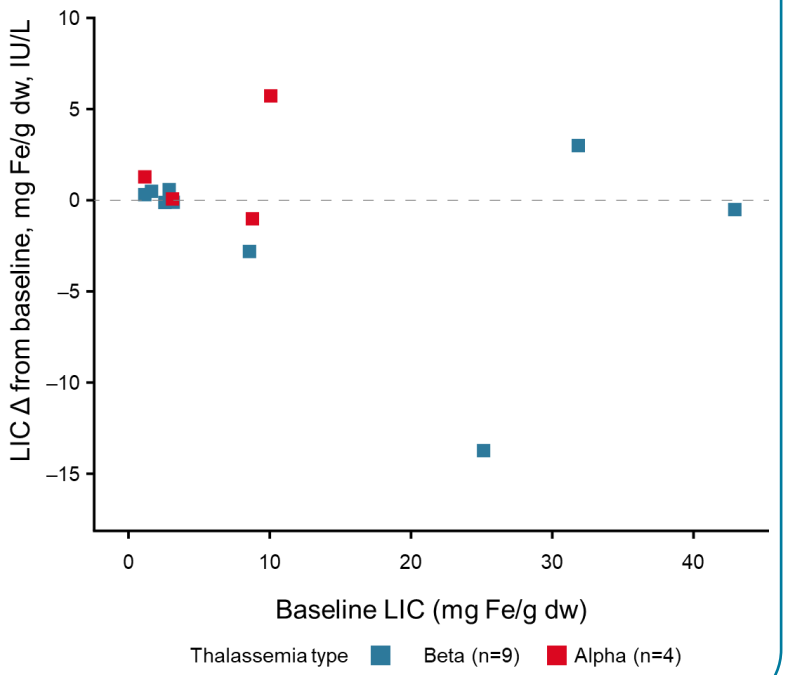
Change in hepcidin



Change in soluble transferrin receptor



Change in liver iron concentration



dw, dry weight; LIC, liver iron concentration; Q, quartile; Wk, week

Conclusion

- Along with long-term improvements in Hb concentration, improvements in markers of erythropoietic activity and hemolysis were observed through Week 72 in patients with α- or β-NTDT treated with mitapivat
- Markers of iron homeostasis remained stable or improved through Week 72
- These new data suggest that mitapivat's mechanism of action may ameliorate multiple aspects of the complex pathophysiology underlying α- or β-NTDT
- Phase 3 studies[a,b] in patients with α- and β-NTDT and transfusion-dependent thalassemia are ongoing

Mitapivat may offer a novel disease-modifying approach with potential long-term benefits in hemolysis, erythropoiesis, and iron homeostasis for patients with α- or β-NTDT

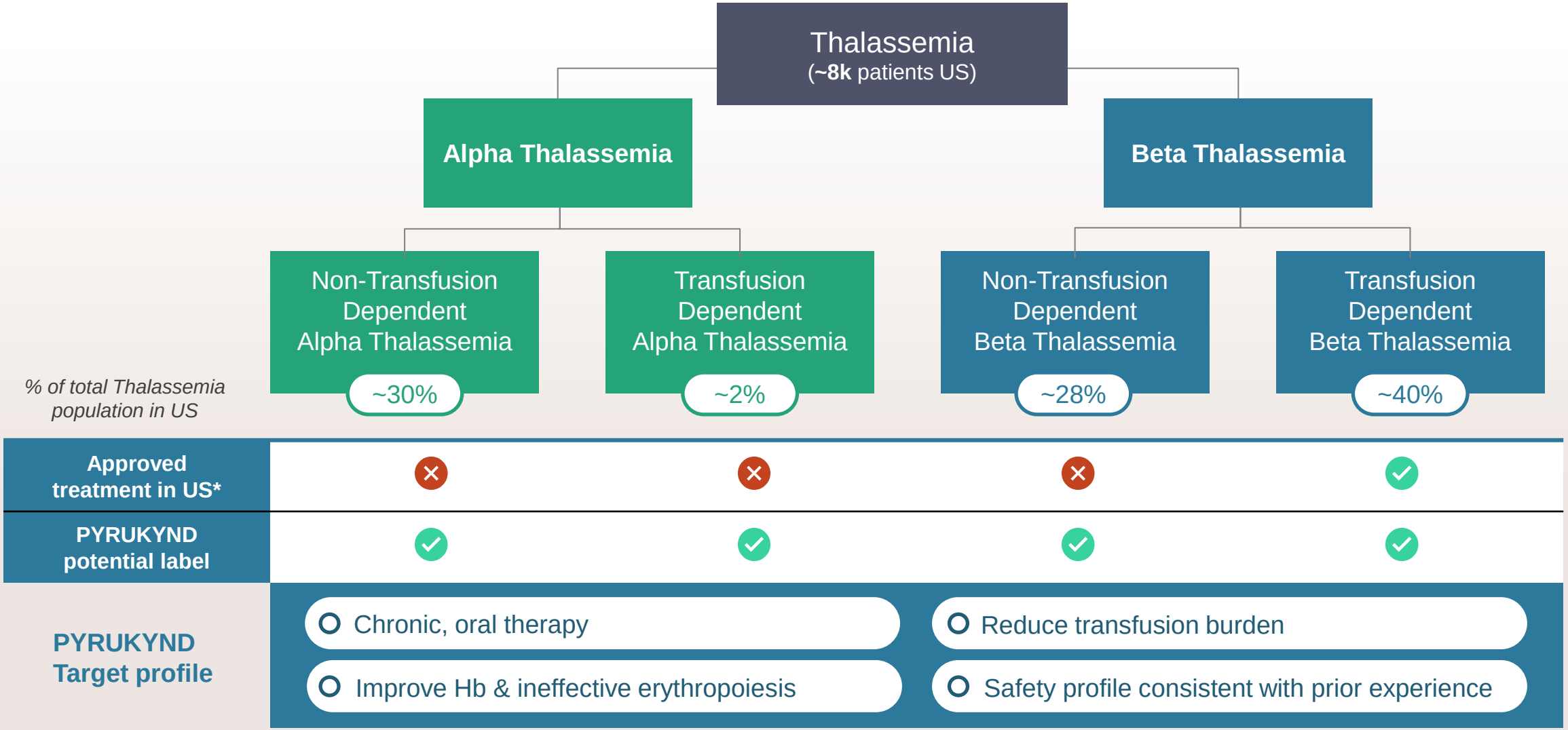
[a]EudraCT 2021-000211-23, ClinicalTrials.gov: NCT04770753; [b]EudraCT 2021-000212-34, ClinicalTrials.gov: NCT04770779
Hb, hemoglobin; NTDT, non–transfusion-dependent thalassemia

Framing Agios' Next Data Readout:

Phase 3 ENERGIZE Study of Mitapivat in Thalassemia

Sarah Gheuens, M.D., Ph.D.,
CMO and Head of Research & Development at Agios

Agios aims to deliver the first therapy approved for all thalassemia subtypes

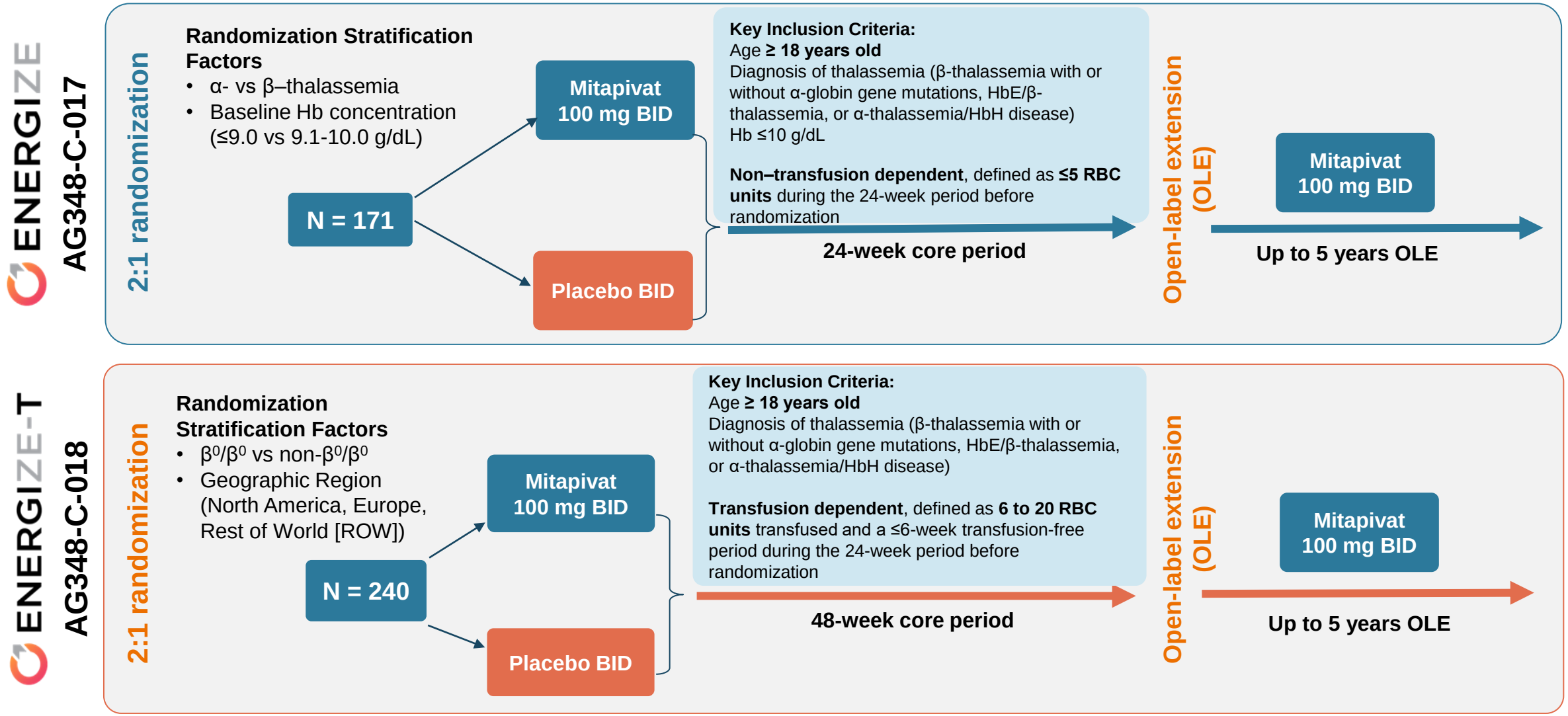


Beta-THAL prevalence: HEOR Global THAL Epidemiology SLE (XCENDA, 2021); US: Paramore, et.al; DE: Borchert, et.al; IT: Italian Society of Thal & Hemoglobinopathies Patient Registry, Jan 2021, Angelucci, et.al, 2017; FR: French registry for thal (Thuret, et.al.); ES: Cela, et.al.; UK Registry for Hemoglobinopathies, 2020; Alpha-THAL prevalence: Agios internal estimates; LEK Analysis | Beta-THAL TD/NTD split (60% / 40%): Thuret, et.al., Haematologica 2010; Magnolia TPP MR, April 2020 | Alpha-THAL TD/NTD split (5% / 95%): 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.

*Note: Reblozyl also approved in non-transfusion dependent beta-thalassemia EU

ENERGIZE Program: The FIRST Phase 3 pivotal program to include both α- and β- and NTD/TD thalassemia patients



BID = twice daily; Hb = hemoglobin; HbE = hemoglobin E; HbH = hemoglobin H.

ENERGIZE Program: key endpoints over the broad diversity of thalassemia

ENERGIZE		ENERGIZE-T
• ***Hemoglobin (Hb) response, defined as a ≥1.0 g/dL increase in average Hb concentration from Wk 12—Wk 24*** *(vs baseline)* • **Change from baseline in average Hb concentration** • Hb 1.5+ response, defined as a ≥1.5 g/dL increase in average Hb concentration from Wk 12 – Wk 24 compared with baseline	**Anemia**	• ***Transfusion Reduction Response (≥50% reduction in transfused RBC units with a reduction of ≥2 units in any consecutive 12-wk period through Wk 48*** *(vs baseline)* • Change from baseline in transfused RBC units from Wk 13–Wk 48 • Transfusion independence, defined as transfusion-free for ≥8 consecutive wks
• **Change from baseline in average FACIT-Fatigue subscale score** • Additional Patient Reported Outcome measurements • Exit interviews	**PROs** (measures of fatigue, physical activity)	• Change from baseline in Transfusion-Dependent Quality of Life Questionnaire score • Additional Patient Reported Outcome measurements
• Change from baseline in indirect bilirubin, LDH, and haptoglobin • Change from baseline in reticulocytes and erythropoietin	**Hemolysis & Ineffective erythropoiesis**	• Change from baseline in indirect bilirubin, lactate dehydrogenase and haptoglobin • Change from baseline in reticulocytes and erythropoietin
• Change from baseline in markers of iron metabolism, including serum ferritin and transferrin saturation	**Iron metabolism**	• Change from baseline in iron, serum ferritin, total iron binding capacity, and transferrin saturation • Change from baseline in hepatic iron concentration and daily dose of iron chelation therapy
• Type, severity, and relationship of AEs and SAEs	**Safety**	• Type, severity, and relationship of AEs and SAEs

Primary endpoints in bold italic font. Key secondary endpoints in bold font.

Closing Remarks

Brian Goff
Chief Executive Officer at Agios

Five late-stage data readouts by the end of 2025

	2024	2025	2026
Thalassemia PYRUKYND®	Phase 3 ENERGIZE (1H) Phase 3 ENERGIZE-T (2H)	Potential approval	
Pediatric PK Deficiency PYRUKYND®		Phase 3 ACTIVATE-kids Phase 3 ACTIVATE-kidsT	Potential approval
Sickle Cell Disease PYRUKYND®		Phase 3 RISE UP	Potential approval
Lower-Risk MDS AG-946 (Novel PK Activator)	Initiate Phase 2b study (mid-year)		

T = Transfusion Dependent patient population

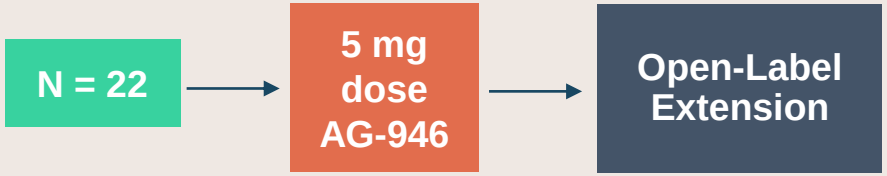
Q&A

agios

Appendix

Clinical proof-of-concept achieved in Phase 2a study of AG-946 in lower-risk MDS; Phase 2b to commence mid-2024

Phase 2a — **Open Label**



16 weeks

Patient classification:
Non-transfused (N=12)
Low transfusion burden (N=10)

Primary endpoints:

- Hemoglobin (Hb) response, defined as a ≥1.5-g/dL increase from baseline in the average Hb concentration from Week 8 through Week 16
- Transfusion independence, defined as transfusion-free for ≥8 consecutive weeks during the Core Period (participants with low transfusion burden only)

Secondary endpoints: safety, additional measures of anemia, PK and PD biomarkers

4 of 10 patients with low transfusion burden achieved the transfusion independence endpoint

1 of 22 patients achieved the hemoglobin response endpoint

The observed safety profile was consistent with data reported in the healthy volunteer study

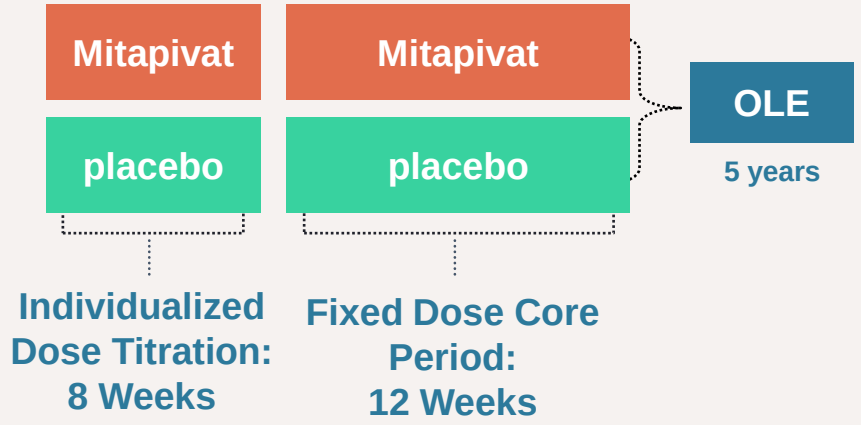
Of the 22 patients enrolled in the Phase 2a portion, 19 continued into the extension period

Expect to initiate Phase 2b study in mid-2024

Enrollment complete in Phase 3 ACTIVATE-KidsT study aimed to support potential label expansion to PK deficiency patients under 18

ACTIVATE-Kids™

Not Regularly Transfused PK Deficiency N=30
Randomize 2:1



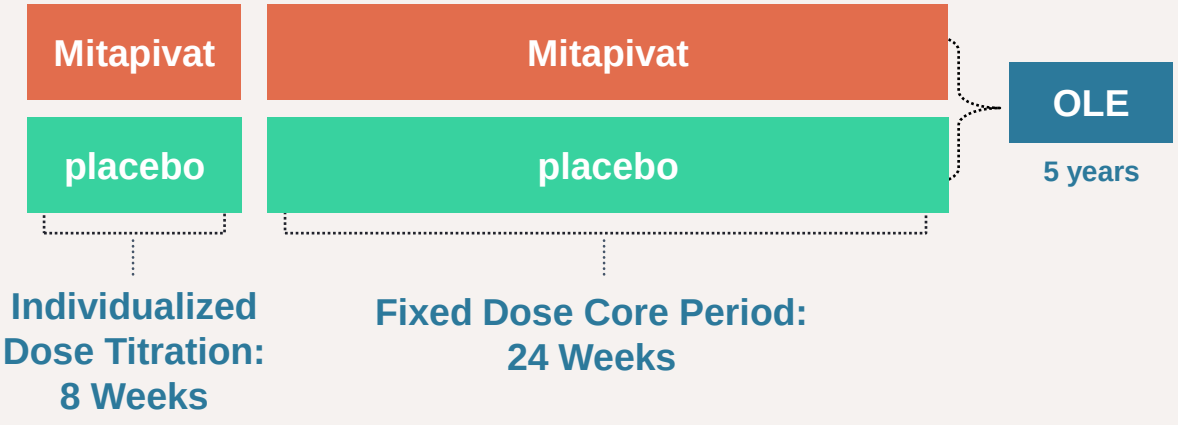
Eligibility

- 1 to <18 years of age
- Mean Hb concentration of ≤10 g/dL for patients 12 to <18 years or ≤9 g/dL for patients 1 to <12 years
- Not regularly transfused, with no more than five transfusions in the 12 months prior and no transfusions in the 12 weeks prior to the first day of study treatment

>50% enrolled

ACTIVATE-KidsT™

Regularly Transfused PK Deficiency N=45
Randomize 2:1



Eligibility

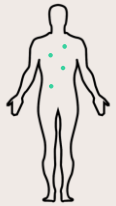
- 1 to <18 years of age
- Six to 26 transfusion episodes in the 52-week period before providing informed consent

Enrollment complete

OLE = open label extension.

PAH program aimed to address the underlying cause of phenylketonuria (PKU)

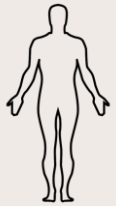
1



Normal Protein Diet

A mixed diet provides your body Phe

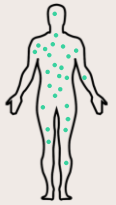
2



Defective PAH enzyme

PAH fails to process the Phe to Tyr

3



Increase in Phenylalanine

This leads to high Phe levels in the blood, which results in PKU

PHENYLKETONURIA (PKU)

- Rare, genetic disease with limited treatment options
- Prevalence: total of ~35-40K patients in the U.S. and EU5
- Driven by deficiency of phenylalanine hydroxylase (PAH) enzyme
- Lack of PAH activity leads to accumulation of phenylalanine and downstream sequelae
- PKU patients are often advised to consume a highly restricted diet, further reducing quality of life

AGIOS PROGRAM

- Oral PAH stabilizer designed to reduce phenylalanine levels

Targeting IND filing by year-end 2023

PHE = phenylalanine, TYR = tyrosine

Sources: National PKU Alliance, www.npkua.org and Weisbren et al ‘Phenylalanine blood levels and clinical outcomes in phenylketonuria’; The American Journal of Human Genetics 107, 234–250, August 6, 2020; Agios internal estimates