agios

EHA Investor Event

June 11, 2021

Forward-Looking Statements

This presentation and various remarks we make during this presentation contain forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding the potential benefits of mitapivat; Agios' plans, strategies and expectations for its and its collaborator's preclinical, clinical and commercial advancement of its drug development programs, including mitapivat; Agios' key milestones for 2021; and the potential benefits of Agios' strategic plans and focus. 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. 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 the COVID-19 pandemic 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 maintain key collaborations; 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.

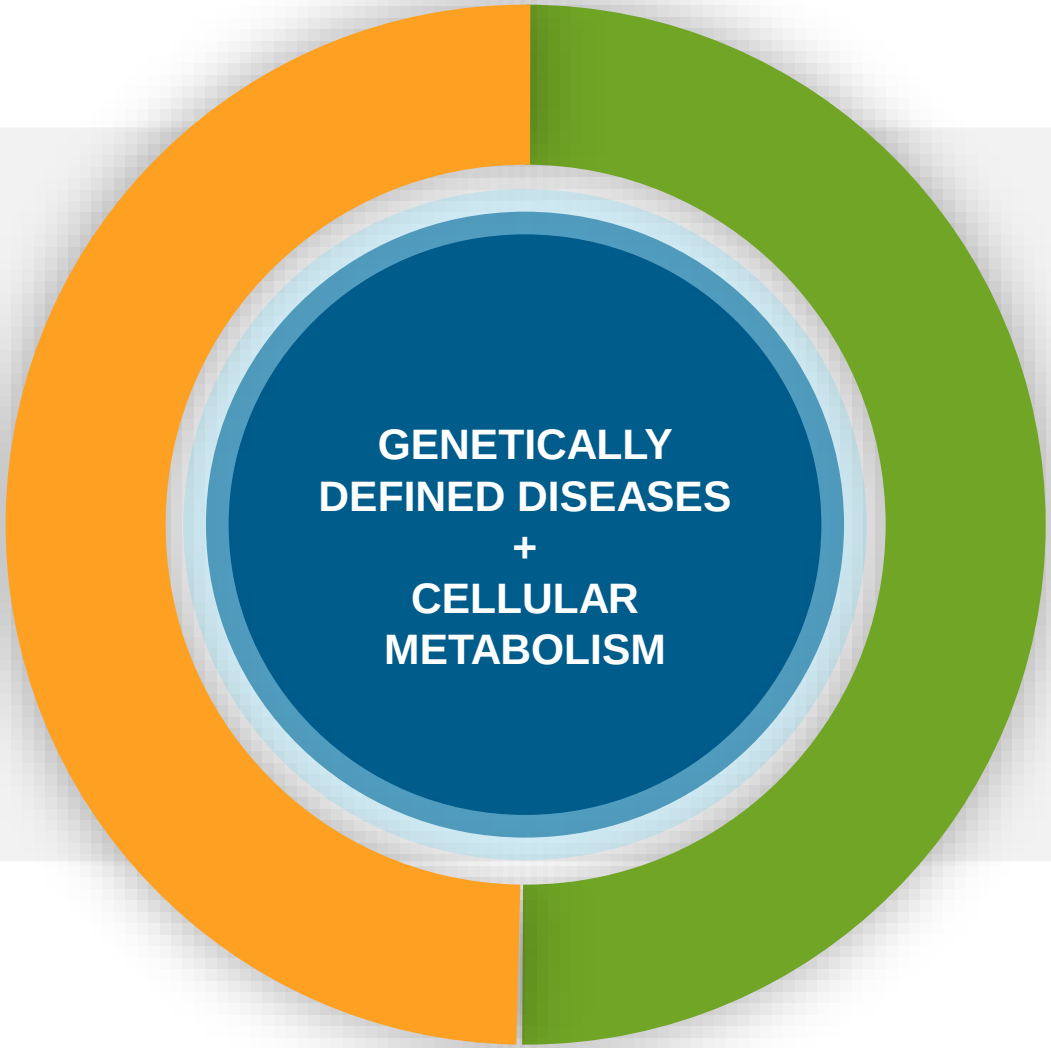
Today's Agenda

	TOPIC	SPEAKER
7:30 – 7:35 AM	Opening Remarks	Jackie Fouse, Ph.D.
7:35 – 7:45 AM	Mitapivat Mechanism of Action	Chris Bowden, M.D.
7:45 – 7:55 AM	Elucidating the Burden of Pyruvate Kinase (PK) Deficiency	Chris Bowden, M.D.
7:55 – 8:15 AM	Review of Data from ACTIVATE and ACTIVATE-T, the Phase 3 Studies of Mitapivat in PK Deficiency	Andreas Glenthøj, M.D., Ph.D. *Associate Prof, Department of Hematology, Rigshospitalet; Copenhagen, Denmark*
8:15 – 8:30 AM	Disease Burden of Thalassemia and Review of Data from the Phase 2 Study	Kevin H.M. Kuo, M.D., MSc, FRCPC *Division of Medical Oncology and Hematology, Department of Medicine, University Health Network*
8:30 – 9:00 AM	Closing Remarks and Q&A	Dr. Fouse, Dr. Bowden, Dr. Bruce Car, Darrin Miles, Dr. Glenthøj, Dr. Kuo

Our refocused therapeutic area is defined by a combination of our most differentiated foundational elements

CELLULAR METABOLISM

Cellular metabolism is a central part of our heritage and scientific competency



GENETICALLY DEFINED DISEASE

Genetically defined disease is a broad umbrella that encompasses both rare and more common diseases

We are the pioneering leaders in PK activation

6 YEARS

STUDYING PK ACTIVATION IN THE CLINIC

~190	17	15	17	3
PATIENTS TREATED	CLINICAL TRIALS	JOURNAL ARTICLES PUBLISHED	MEDICAL/SCIENTIFIC COLLABORATIONS	DISEASES WITH POC ACHIEVED

+ A LOT OF FIRSTS:

- 1st GLOBAL PK DEFICIENCY REGISTRY
- 1st INTERNATIONAL PK DEFICIENCY ADVOCACY COUNCIL
- 1st HEMOLYTIC ANEMIA ADVOCACY COALITION BUILDING
- 1st POSITIVE PHASE 3 READOUT IN PK DEFICIENCY

We are driven by our sense of urgency to help patients.

"The disease has affected my career. I spent 11 years to get a PhD in nutrition...My heart wants more but my body can't handle it."

—Tamara S., Minnesota

Currently 50 years old. Diagnosed with PK deficiency at the age of 6.

"On a bad day, it's like watching some electronic toy slowly lose the battery."
—Tamara S., Minnesota

In mitapivat, we are building a robust pipeline with the ability to rapidly expand to three indications

Mitapivat Pipeline Overview

Early Stage Clinical	Late Stage Clinical	Regulatory Submission	Near-Term Milestones	Anticipated Approval
Non-transfusion Dependent Adult PK Deficiency (ACTIVATE)			NDA filing in Q2; MAA filing in mid-2021	2022
Transfusion Dependent Adult PK Deficiency (ACTIVATE-T)				2022
Non-transfusion Dependent Adult Thalassemia (ENERGIZE)			Initiate pivotal study in 2H 2021	2025
Transfusion Dependent Adult Thalassemia (ENERGIZE-T)			Initiate pivotal study in 2H 2021	2025
Sickle Cell Disease			Initiate Phase 2/3 study by YE 2021	2026
Pediatric PK Deficiency			Initiate pivotal studies in 2022	
Pediatric Thalassemia			Planning in process	
Pediatric Sickle Cell Disease			Planning in process	

~3-8K PATIENTS IN U.S. & EU5

Pyruvate Kinase Deficiency

~18-23K PATIENTS IN U.S. & EU5

β- and α-Thalassemia

~120-135K PATIENTS IN U.S. & EU5

Sickle Cell Disease

Today's key takeaways

1. For nearly a decade, Agios has been leading the science behind PK activation and is focused on rapidly advancing our lead program, mitapivat, to its first regulatory submission in PK deficiency and initiating late-stage development in thalassemia and sickle cell disease

2. ACTIVATE and ACTIVATE-T demonstrated that mitapivat improved hemoglobin, reduced hemolysis, improved measures of health-related quality of life, and reduced transfusion burden in patients with pyruvate kinase deficiency

3. Mitapivat provides a potential treatment for previously underserved thalassemia patients, regardless of subtype (α or β), and the Phase 2 data supports the evaluation of mitapivat in two pivotal Phase 3 trials

Mitapivat is an investigational product and is not approved for use by any regulatory authority for any use.

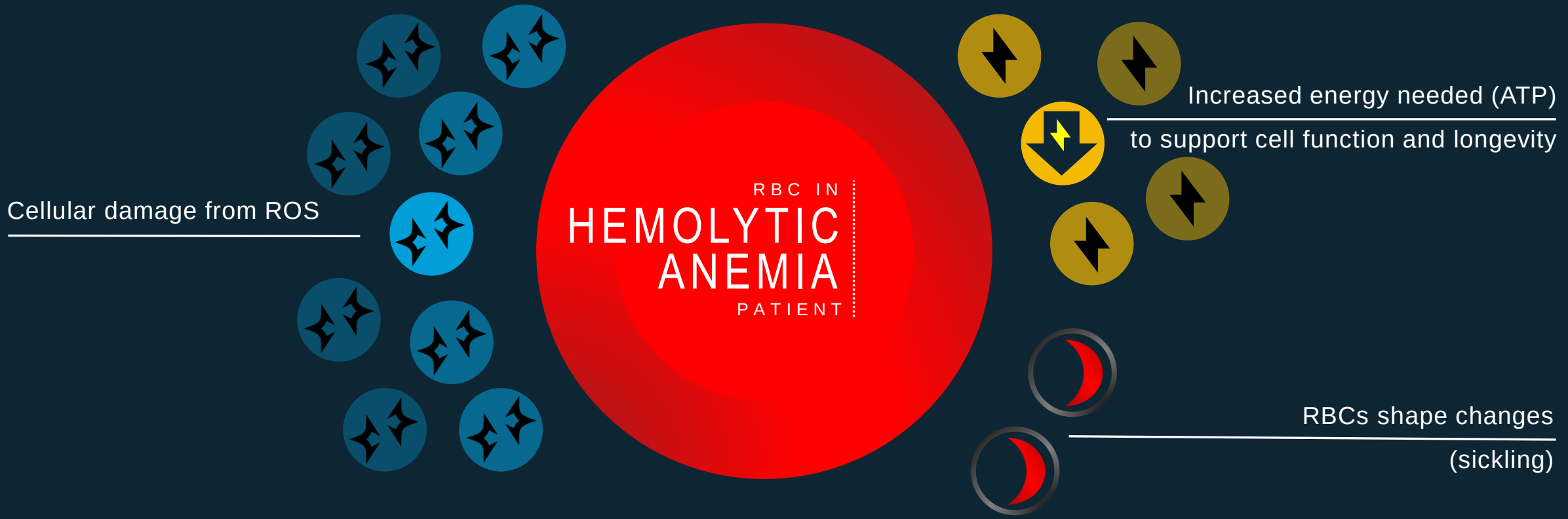
PK Activation as a Potential Treatment for Serious Hemolytic Anemias

Dr. Chris Bowden

RBCs deliver oxygen to tissues, which is necessary for energy and organ health

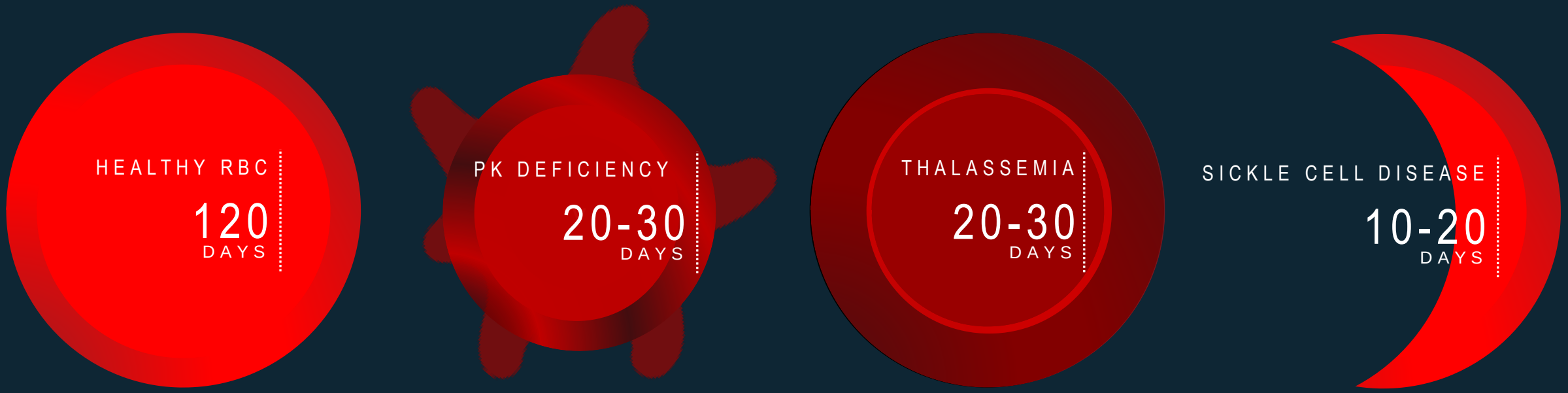
RBCs = red blood cells

RBCs in patients with hemolytic anemia have insufficient ATP, increased ROS damage or sickling



ROS = reactive oxygen species; ATP= adenosine triphosphate

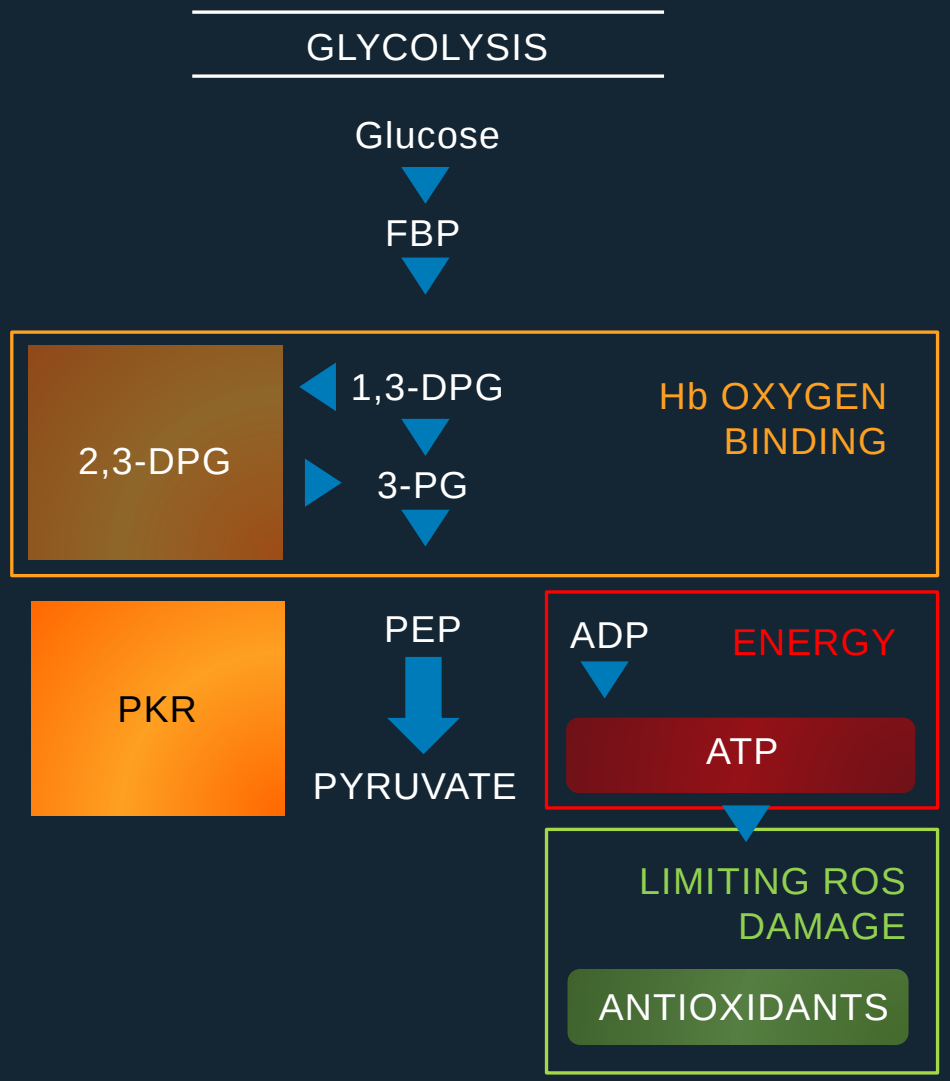
Shortened RBC lifespan can lead to chronic fatigue, iron overload and potentially serious complications



	HEMOGLOBIN (Hb) FUNCTIONAL	HEMOGLOBIN (Hb) INSUFFICIENT	HEMOGLOBIN (Hb) HBS POLYMERS
	PYRUVATE KINASE MUTATED	PYRUVATE KINASE FUNCTIONAL	PYRUVATE KINASE FUNCTIONAL

N Engl J Med 1968; 278:73-81; Blood (2004) 104 (11): 3616; J Kanter Blood Reviews 27:6 November 2013 279-287

Pyruvate kinase-R (PKR) is the rate-limiting step for RBC energy production



Pyruvate kinase-R (PKR) is required for:

- Maintaining RBC energy levels
- Maintaining antioxidants, which limit cellular damage
- Regulating 2,3-DPG levels, which governs oxygen binding to hemoglobin

Mitapivat has the potential to be the first agent to transform the course of hemolytic anemia by increasing RBC energy, health and longevity

ATP

Increases ATP production, helps to match RBC energy needs

ANTIOXIDANTS (ROS)

Mitapivat has been shown in preclinical models to reduce ROS levels, reducing cellular damage

2,3 DPG

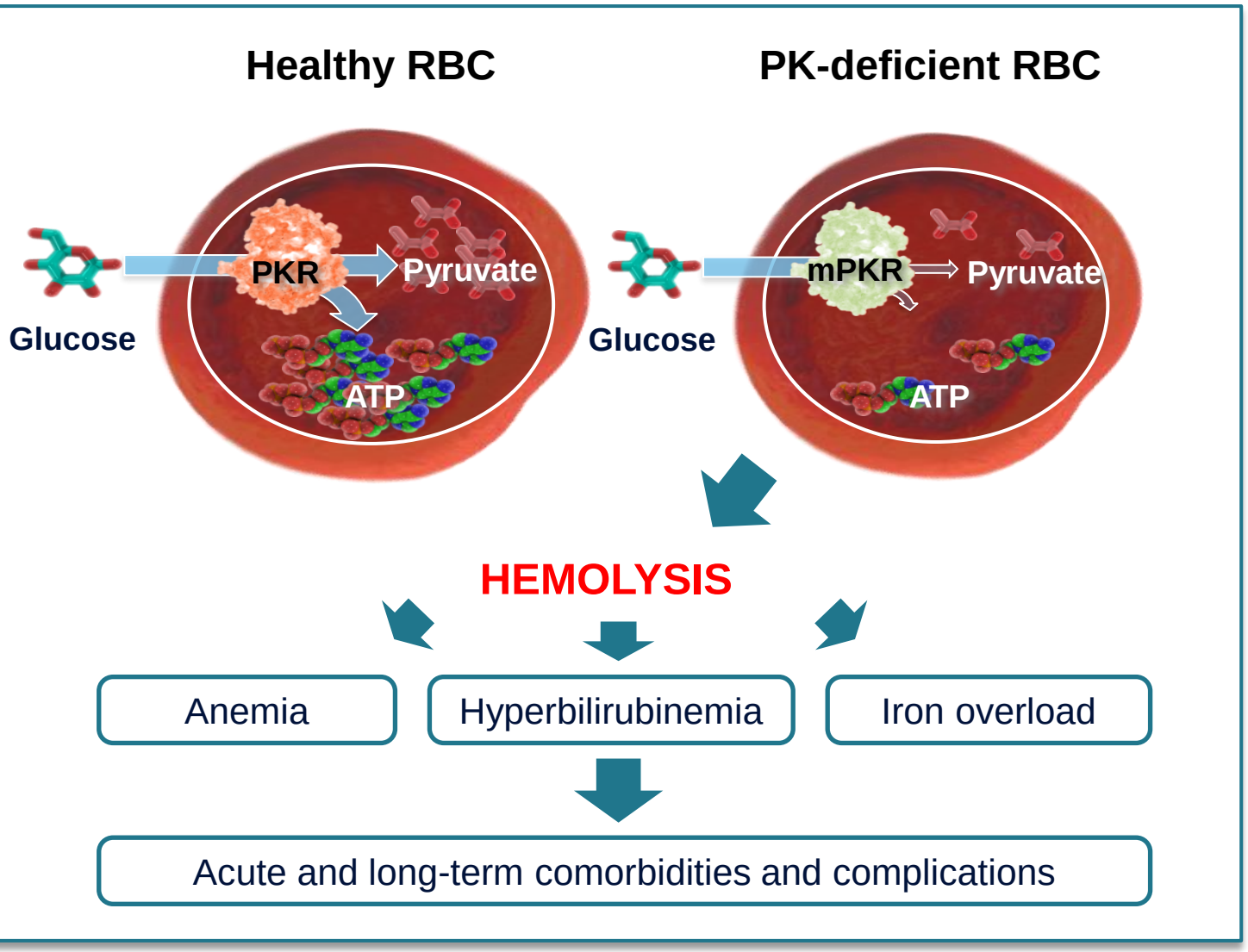
Mitapivat decreases 2,3-DPG, which reversibly increases oxygen affinity for Hb, potentially reducing sickling in SCD

SCD = sickle cell anemia

Elucidating the Burden of PK Deficiency

Dr. Chris Bowden

PK deficiency: pathophysiology overview



Mutation in *PKLR* gene

↓ PK activity
↓ PK stability

Inefficient glycolysis
↓ ATP generation

↓ RBC membrane integrity
↑ RBC destruction[a]

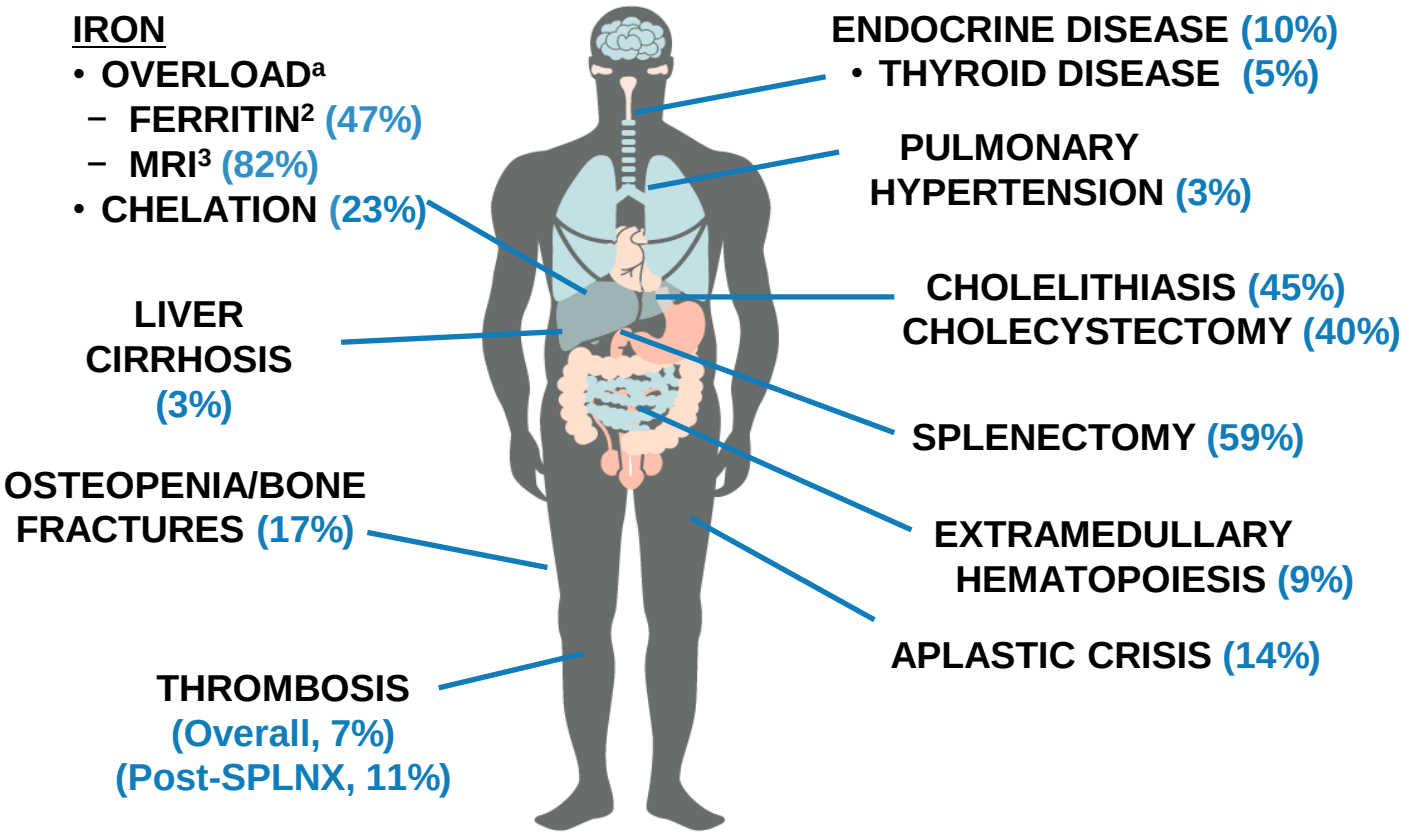
Chronic hemolysis

[a]RBCs with diminished PKR activity and reduced energy levels are damaged in the capillaries of the spleen and are primarily cleared by the spleen and liver.
ATP = adenosine triphosphate; m = mutant; PK = pyruvate kinase; *PKLR* = pyruvate kinase liver and RBC; PKR = RBC-specific PK; RBC = red blood cell.

PK deficiency is a heterogeneous disease that can be associated with both acute and long-term comorbidities and complications

- Serious complications can present early-on in infancy or manifest later in life[1]
- Patients often suffer from chronic fatigue and a reduced quality of life[1]
- Chronic hemolysis results in systemic complications impacting most organ systems that worsen over the lifespan, including iron overload, bone disease, thrombosis, endocrinopathy, and others[1]

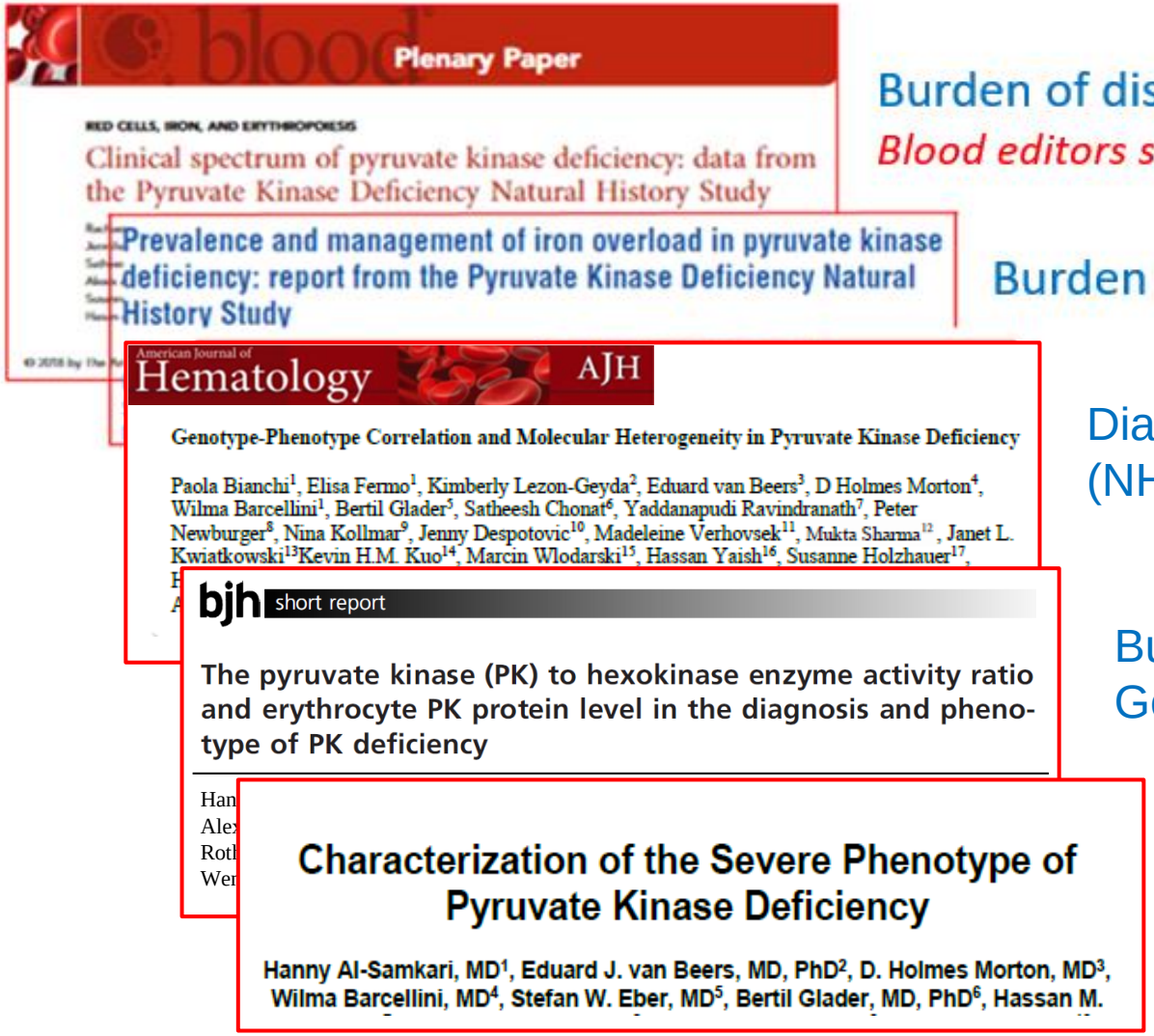
Baseline and retrospective data from patients with PK deficiency in Natural History Study (N = 254)



[a]Iron overload defined as a ferritin level of > 1000 ng/mL or a liver iron concentration > 3 mg Fe/g dry weight liver on T2* MRI in the 12 months prior to enrollment or had received chelation therapy in the 12 months before enrollment. MRI = magnetic resonance imaging; PK = pyruvate kinase; SPLNX = splenectomized.

1. Al-Samkari H et al. *Haematologica* 2020;105:2229–39. **2.** Grace RF et al. *Blood* 2018;131:2183–92. **3.** van Beers EJ et al. *Haematologica* 2019;104:e51–3.

Disease burden in PK deficiency is high and new treatment options are needed



Burden of disease: NHS Clinical Characteristics*

Blood editors selection for top 10 manuscript of 2018

Burden of disease: NHS Iron Overload*

Diagnosis and Burden of Disease (NHS)

Burden of Disease Genotype-Phenotype (NHS)

Severe Phenotype (NHS)

Iron overload is common in PK deficiency regardless of transfusion status

In the NHS, in patients with PK deficiency <u>not receiving regular transfusions</u>, iron overload was demonstrated

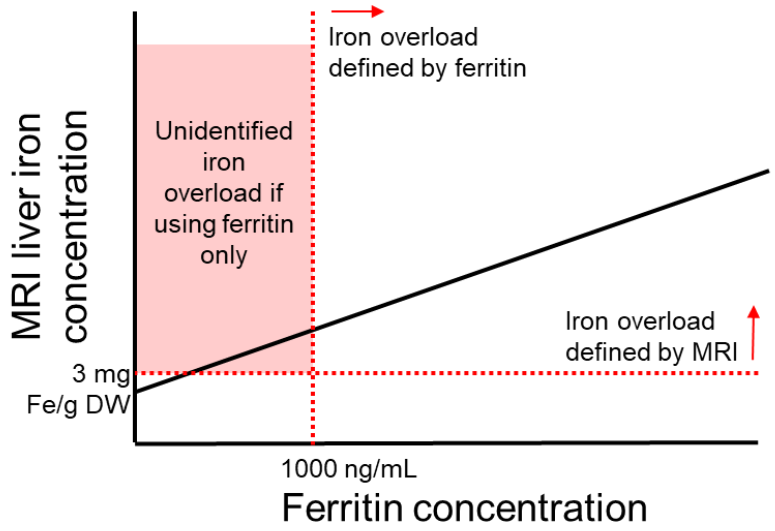
Elevated Ferritin

- Present in 38% (53/138)
- Maximum ferritin > 1000 ng/ml[a]

LIC by MRI

- Present in 82% (67/82)[a]
- LIC > 3 mg Fe/g dry weight liver on T2* MRI in the 12 months prior to enrollment

Some patients have iron overload by MRI even with ferritin < 1000 ng/mL[b]



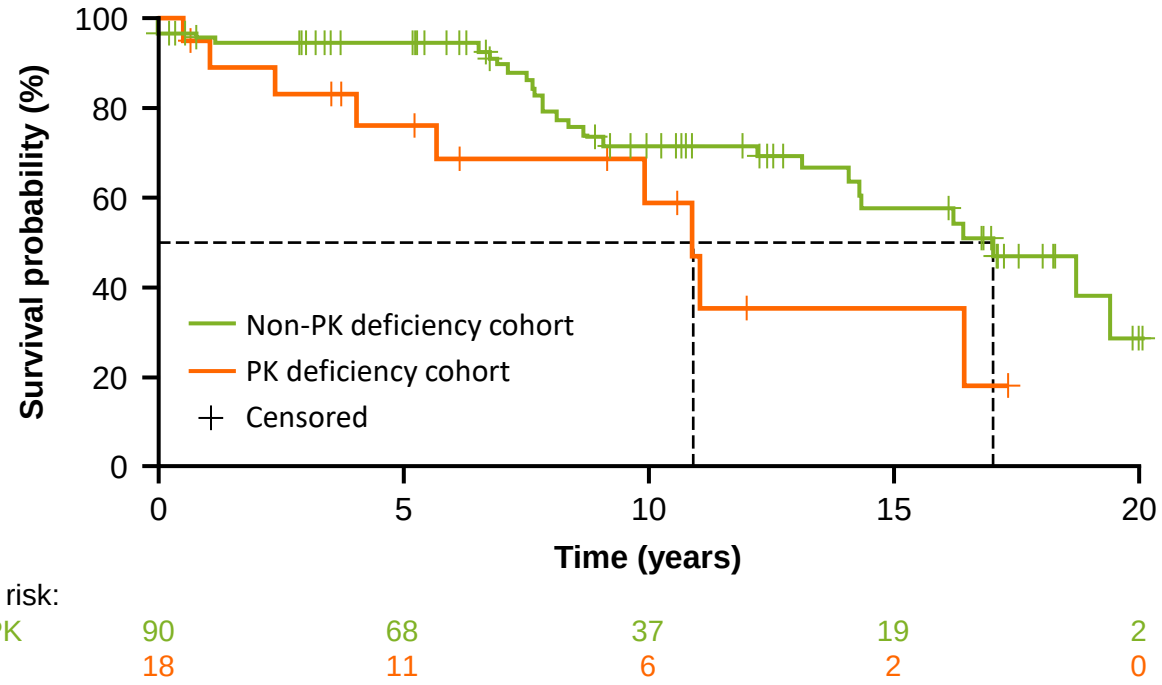
- The sensitivity to predict LIC > 3 mg/g DW using a ferritin level of > 1000 ng/mL was only 53%
- At a ferritin cut-off of 500 ng/mL, the sensitivity for LIC > 3 mg/g DW was 90%

.
[a]Results based on 82 patients with MRI data available.
[b]Paired ferritin and LIC measurements were available for 45 patients; ferritin levels correlated with LIC (r = 0.45, p < 0.001).
DW = dry weight; LIC = liver iron concentration; MRI = magnetic resonance imaging; NHS = Natural History Study; PK = pyruvate kinase.
van Beers EJ et al. *Haematologica* 2019;104:e51–3.

Mortality among veterans with a diagnosis of PK deficiency: A real-world study using US Veterans Health Administration data

EHA 2021
Abstr EP710

Survival analysis



	PK deficiency cohort (N = 18)	Non-PK deficiency cohort (N = 90)
Years of follow-up, mean ± SD [median]	7.3 ± 5.2 [6.0]	9.2 ± 5.8 [8.0]
Observed deaths over follow-up period, n (%)	9 (50%)	28 (31%)
Years until death, median	10.9	17.1

- Patients in the non-PK deficiency cohort had a significantly longer time to death than the PK deficiency cohort (hazard ratio: 2.3; p = 0.0306)
- 10 years after index, 42% of patients in the PK deficiency cohort had died compared with 28% of those in the non-PK deficiency cohort

PK = pyruvate kinase; SD = standard deviation.
Zagadailov E et al. 2020 ASH Annual Meeting: Abstract 1627.

Data presented at EHA elucidate lifetime physical and financial burden of PK deficiency

Osteopenia and osteoporosis are serious complications that present early in life for patients with PK deficiency

Patients treated with mitapivat for up to 4 years do not appear to experience progression of bone mineral density abnormalities despite its mild aromatase inhibition effect

Patients with PK deficiency have an increased risk of mortality and they have a lifetime economic burden of >$3M in direct costs

First pediatric analysis of PEAK registry demonstrated a high disease burden early in life in PK deficiency

While PK deficiency has been historically underdiagnosed, efforts are underway to standardize diagnosis and reduce logistical burdens, allowing proper identification of patients with PK deficiency

ACTIVATE

Andreas Glenthøj, M.D., Ph.D.

ACTIVATE: A Phase 3, Randomized, Multicenter, Double-blind, Placebo-Controlled Study Of Mitapivat In Adults With Pyruvate Kinase Deficiency Who Are Not Regularly Transfused

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This study was funded by Agios Pharmaceuticals, Inc.

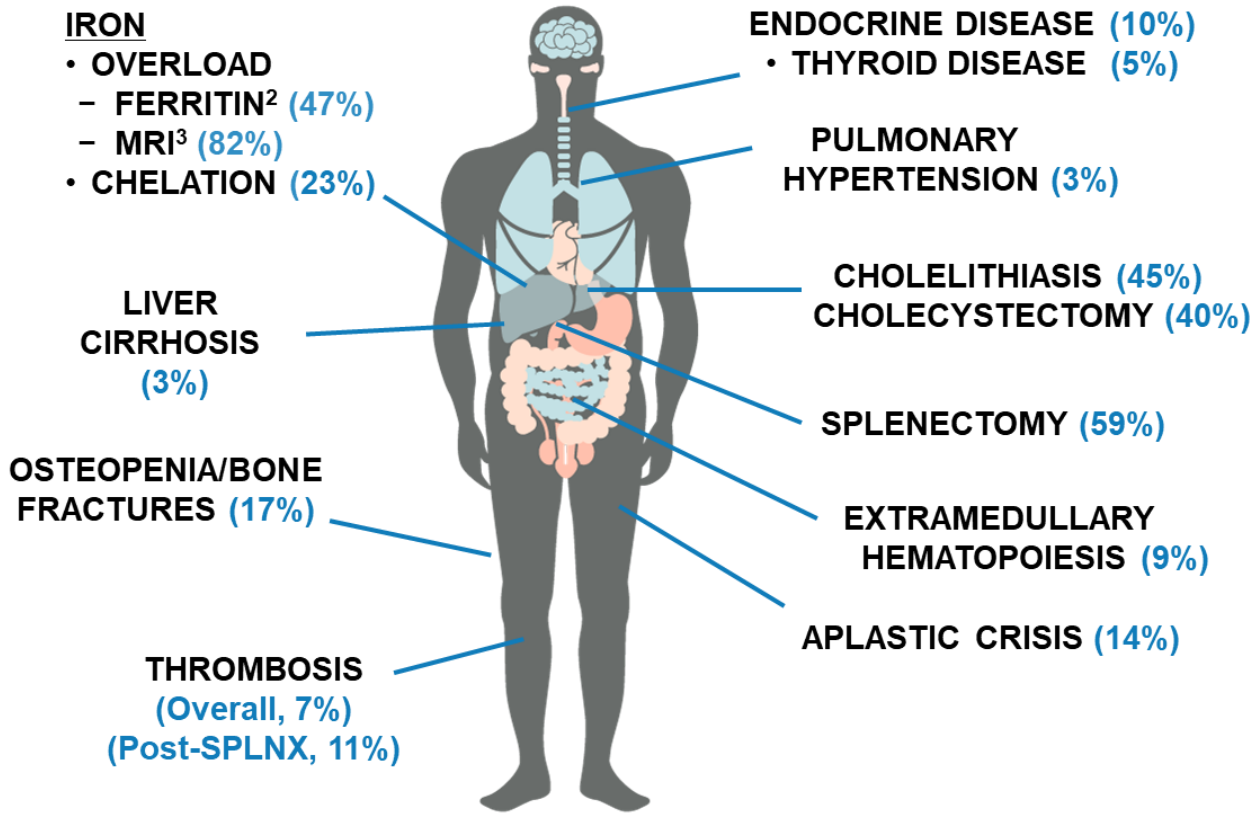
Disclosures

- This study was funded by Agios Pharmaceuticals, Inc.
- Author conflict of interest disclosures as follows:
  - **Hanny Al-Samkari**: Agios, argenx, Dova, Novartis, Rigel, Sobi – consultancy; Agios, Dova, Amgen – research funding
  - **Frédéric Galactéros**: Addmedica – board membership or advisory committee
  - **Andreas Glenthøj**: Agios, bluebird bio, Celgene, Novartis – consultancy and advisory board member; Alexion – research grant; Novo Nordisk – honoraria
  - **Jennifer A. Rothman**: Pfizer – consultancy; Agios, Novartis, Pfizer – honoraria; Agios, bluebird bio, Novartis, Pfizer – research funding
  - **Oliver Andres**: Agios – Advisory board member
  - **Rachael F. Grace**: Agios, Novartis, Pfizer – research funding; Dova – membership of an entity's Board of Directors or advisory committees
  - **Marta Morado Arias**: Sanofi Genzyme – honoraria and other grants
  - **D. Mark Layton**: Agios, Novartis – consultancy; Agios, Cerus, Novartis – membership of an entity's Board of Directors or advisory committees
  - **Koichi Onodera**: No affiliations
  - **Madeleine Verhovsek**: Vertex – consultancy
  - **Wilma Barcellini**: Agios, Alexion, Novartis – honoraria; Agios – research funding; Bioverativ, Incyte – board membership or advisory committee
  - **Malia P. Judge, Vanessa Beynon, Emily Xu, Peter Hawkins, Erin Zagadailov, Sarah Gheuens**: Agios – employees and shareholders
  - **Eduard J. van Beers**: Agios – advisory board member; Agios, Novartis, Pfizer, RR Mechatronics – research funding

Pyruvate kinase deficiency - disease overview

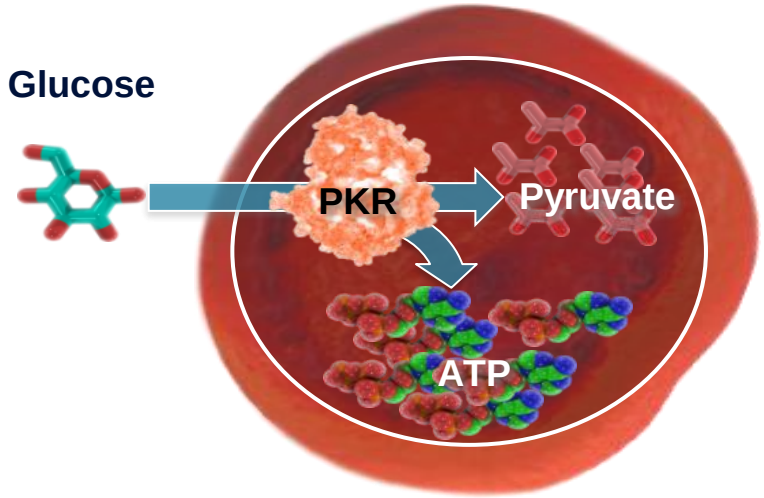
- Underrecognized, rare, hereditary chronic hemolytic anemia[1,2]
- Due to mutations in *PKLR,* resulting in chronic hemolysis[1–4]
- Numerous comorbidities and complications[3–6]
- Current management limited to supportive care and splenectomy[3,7]
- No approved disease-modifying agents

Comorbidities and long-term complications are common and affect multiple organ systems[6]

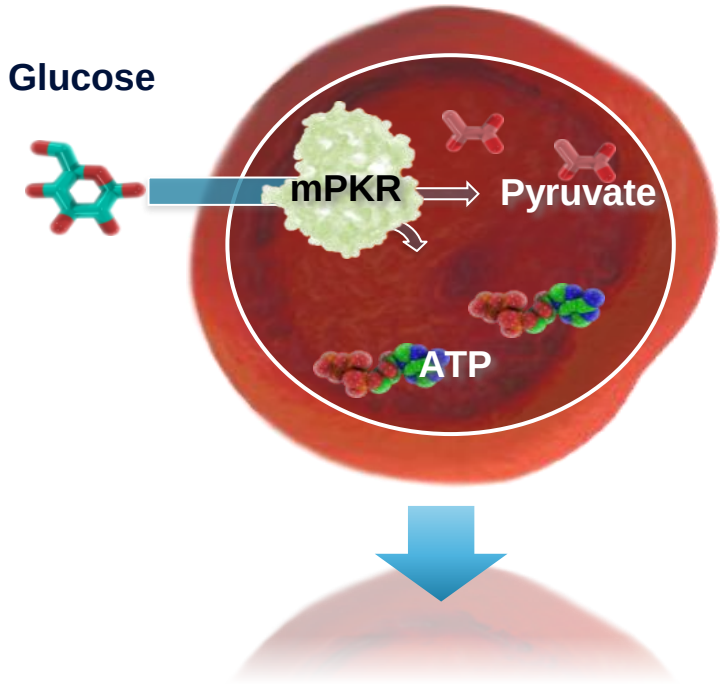


Mitapivat, an oral pyruvate kinase activator

Healthy RBC, wild-type PKR

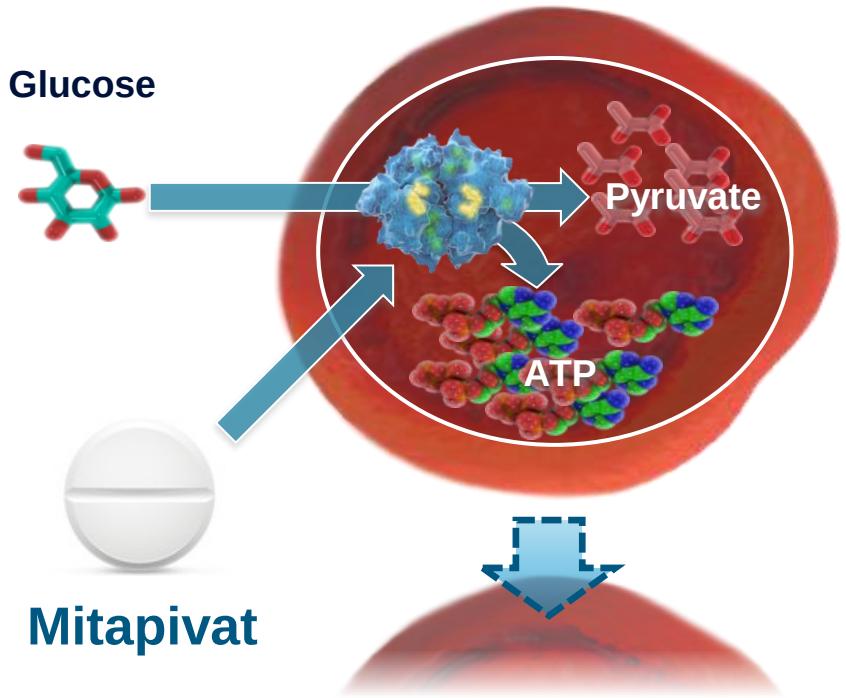


PK-deficient RBC, mPKR



HEMOLYSIS

RBC Post Mitapivat Treatment



HEMOLYSIS IMPROVEMENT

ACTIVATE was a Phase 3, randomized, double-blind, placebo-controlled study that evaluated the efficacy and safety of mitapivat in adult patients with PK deficiency who were not regularly transfused

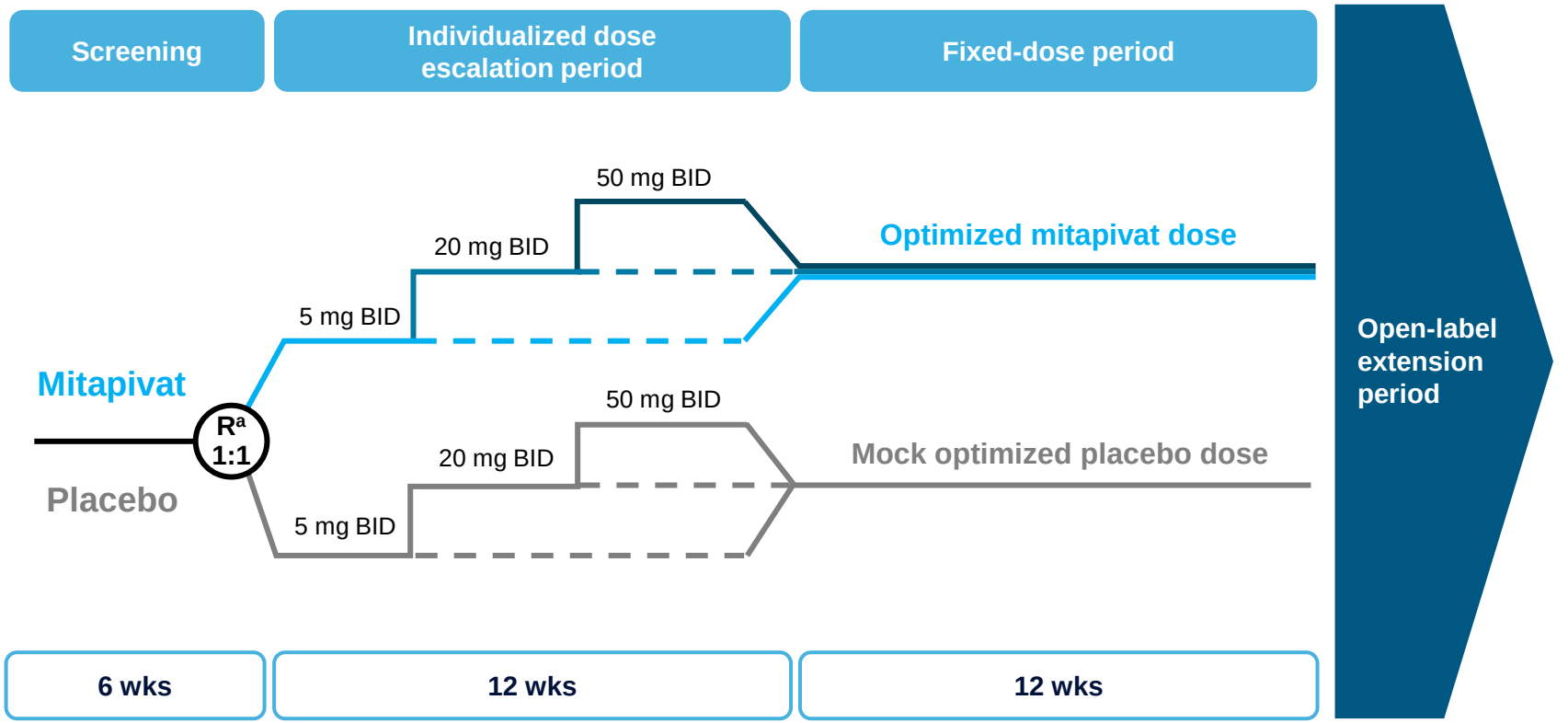
ACTIVATE

Key eligibility criteria:

- ≥ 18 yrs of age
- Documented ≥ 2 mutant alleles in *PKLR* (≥ 1 missense mutation)
- Not regularly transfused (≤ 4 transfusion episodes in previous year)
- Baseline Hb ≤ 10 g/dL
- Adequate organ function

Key exclusion criteria:

- Homozygous for R479H mutation or have 2 non-missense mutations, without another missense mutation, in *PKLR*
- Splenectomy during study, or within 12 months of enrollment
- Prior bone marrow or stem cell transplant



Primary and secondary efficacy endpoints

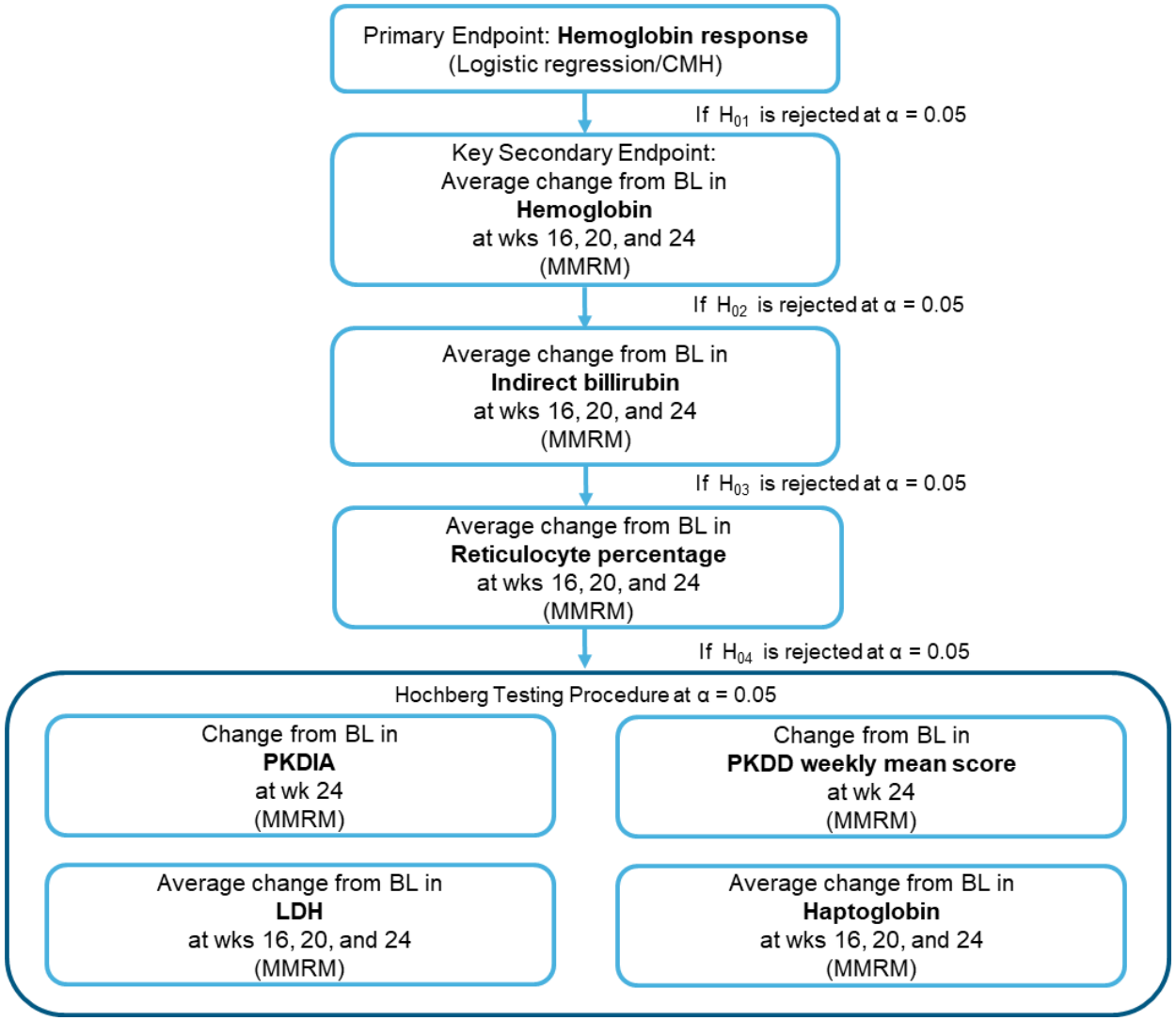
Primary endpoint: Hb response, defined as ≥ 1.5 g/dL increase in Hb concentration from BL sustained at ≥ 2 scheduled assessments at wks 16, 20, or 24 during fixed-dose period

Key secondary endpoint: Average change from BL in Hb concentration at wks 16, 20, and 24

Other secondary endpoints:

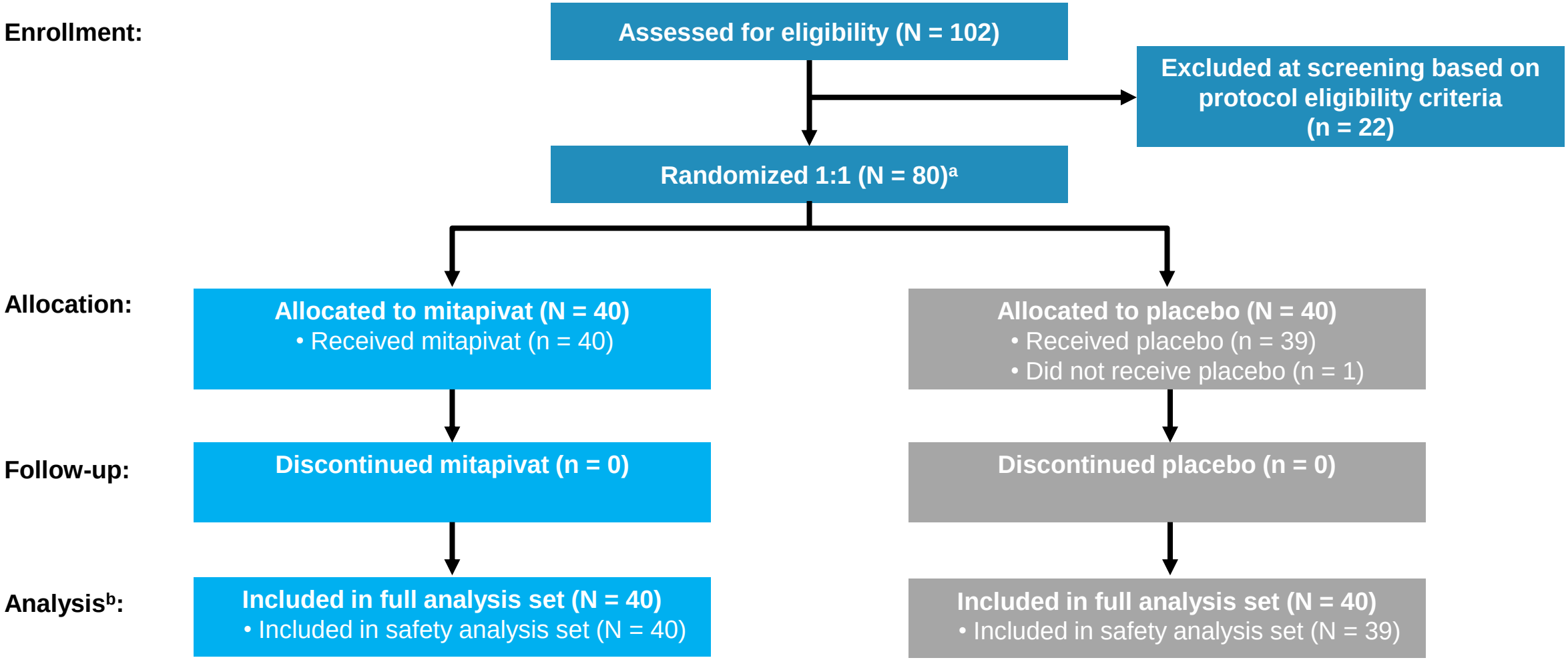
- Average change from BL at wks 16, 20, and 24 in markers of hemolysis: bilirubin, LDH, and haptoglobin levels
- Average change from BL at wks 16, 20, and 24 in markers of hematopoietic activity: reticulocyte percentages (fraction of 1)
- Change from BL at wk 24 in HRQoL PRO scores: PKDIA and PKDD

Statistical testing strategy



H01: Hb Odds Ratio = 1; H0j: Difference in average of mean change from baseline = 0, for j≥ 2.
BL = baseline; CMH = Cochran-Mantel-Haenszel test; Hb = hemoglobin; HRQoL = health-related quality of life; LDH = lactate dehydrogenase; MMRM = Mixed-Effect Model Repeated Measure; PRO = patient-reported outcomes; PKDD = Pyruvate Kinase Deficiency Diary; PKDIA = Pyruvate Kinase Deficiency Impact Assessment; wks = weeks.

Patient disposition



Demographics

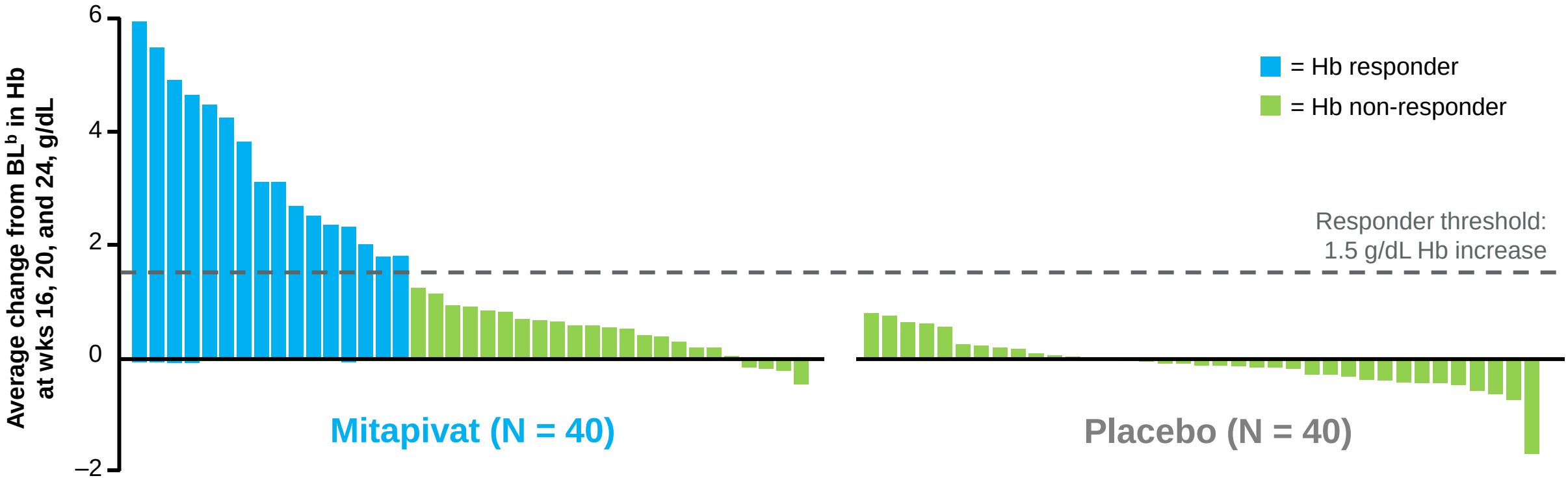
Patient demographics	Mitapivat N = 40	Placebo N = 40
Age (years)		
Mean (SD)	36.0 (15.2)	37.2 (15.9)
Range	18–70	19–78
Sex, n (%)		
Male	16 (40.0)	16 (40.0)
Female	24 (60.0)	24 (60.0)
Race, n (%)		
White	28 (70.0)	32 (80.0)
Asian	5 (12.5)	3 (7.5)
Native Hawaiian or Other Pacific Islander	1 (2.5)	0
American Indian or Alaska Native	0	0
Black or African American	0	0
Other	0	1 (2.5)
Not reported	6 (15.0)	4 (10.0)
Geographic Region, n (%)		
Western Europe	19 (47.5)	20 (50.0)
North America	15 (37.5)	16 (40.0)
Asia	5 (12.5)	3 (7.5)
Middle East	0	1 (2.5)
Latin America	1 (2.5)	0

Baseline characteristics

Baseline characteristics	Mitapivat N = 40	Placebo N = 40
Hb (g/dL), mean (SD)	8.6 (0.99)	8.5 (0.85)
Ferritin (µg/L), mean (SD)	748 (1116.2)	688 (605.2)
Hemolysis markers, mean (SD)		
Indirect bilirubin (µmol/L)	81.8 (61.32)	89.1 (61.79)
LDH (U/L)	348 (276.0)	260 (140.2)
Haptoglobin (g/L)	0.08 (0.107)	0.08 (0.138)
Reticulocyte (fraction of 1)	0.37 (0.241)	0.40 (0.222)
Prior transfusions, n (%)		
0	29 (72.5)	30 (75.0)
1	8 (20.0)	7 (17.5)
2	0	1 (2.5)
3	3 (7.5)	1 (2.5)
≥4	0	1 (2.5)
Prior splenectomy, n (%)	28 (70.0)	30 (75.0)
Prior cholecystectomy, n (%)	28 (70.0)	30 (75.0)
Prior chelation therapy, n (%)[a]	5 (12.5)	10 (25.0)
DXA T-Score, mean (SD)		
Femoral total[b]	–1.12 (1.081)	–0.79 (1.098)
Adjusted spine	–1.78 (1.104)	–1.14 (1.153)
***PKLR* mutation category**		
Missense/Missense	28 (70.0)	27 (67.5)
Missense/Non-missense	12 (30.0)	13 (32.5)

Mitapivat met the primary endpoint, demonstrating a higher hemoglobin response rate as compared with placebo

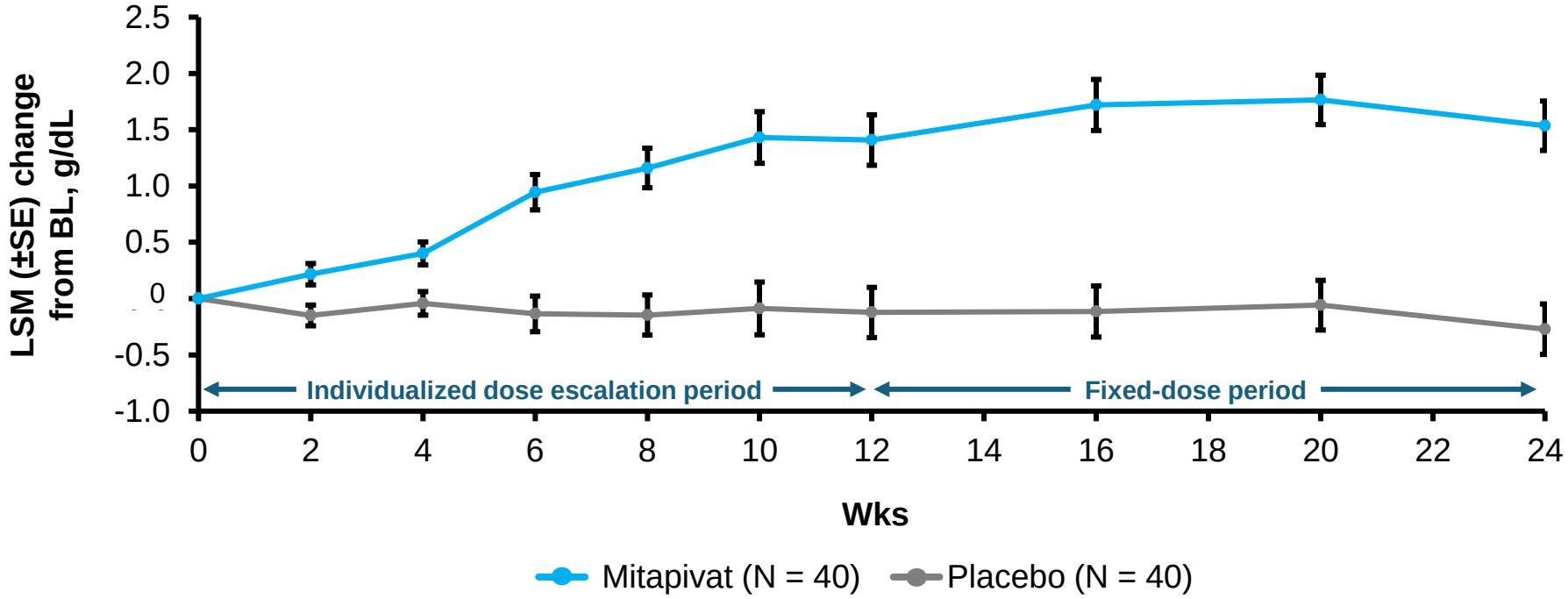
	Mitapivat N = 40	Placebo N = 40	Difference[a] (95% CI)	2-sided p-value
Hemoglobin response n (%)	16 (40.0)	0 (0)	39.3 (24.1, 54.6)	< 0.0001



Mitapivat led to early and sustained improvement in Hb

Average change from BL at wks 16, 20, and 24 in Hb

	Mitapivat N = 40	Placebo N = 40	Difference in LSM (95% CI)	2-sided p-value
Hb (g/dL), LSM (95% CI)	1.67 (1.26, 2.09)	–0.15 (–0.56, 0.27)	1.82 (1.24, 2.40)	< 0.0001



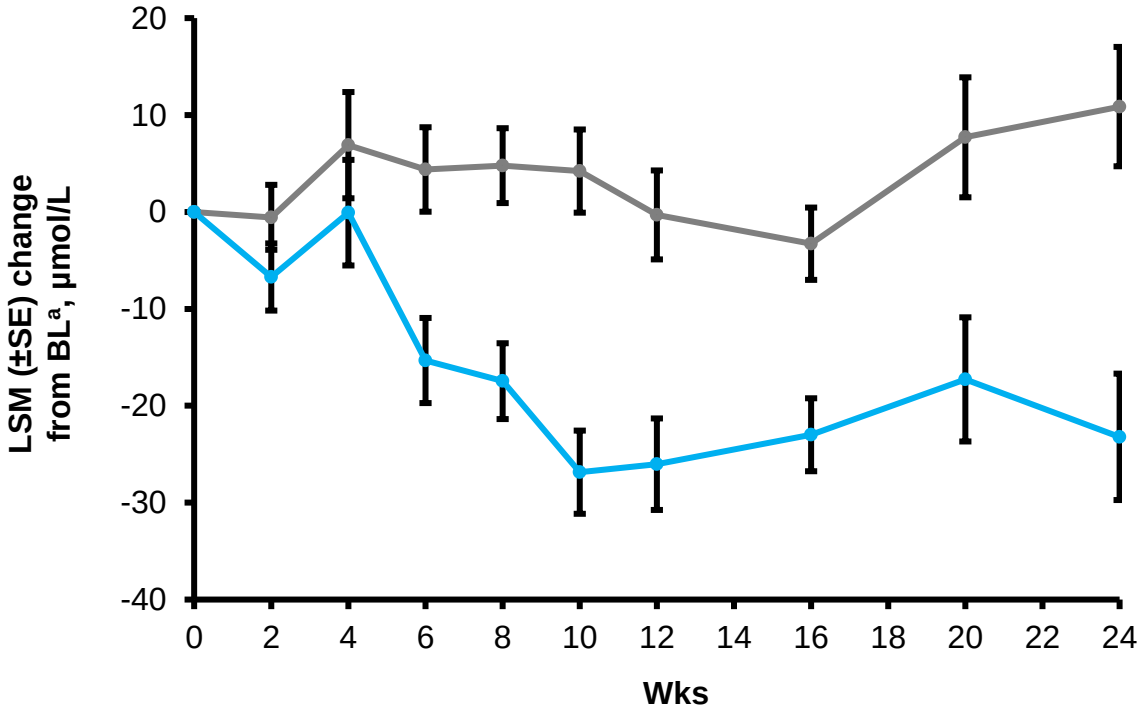
Mitapivat led to improvements in markers of hemolysis

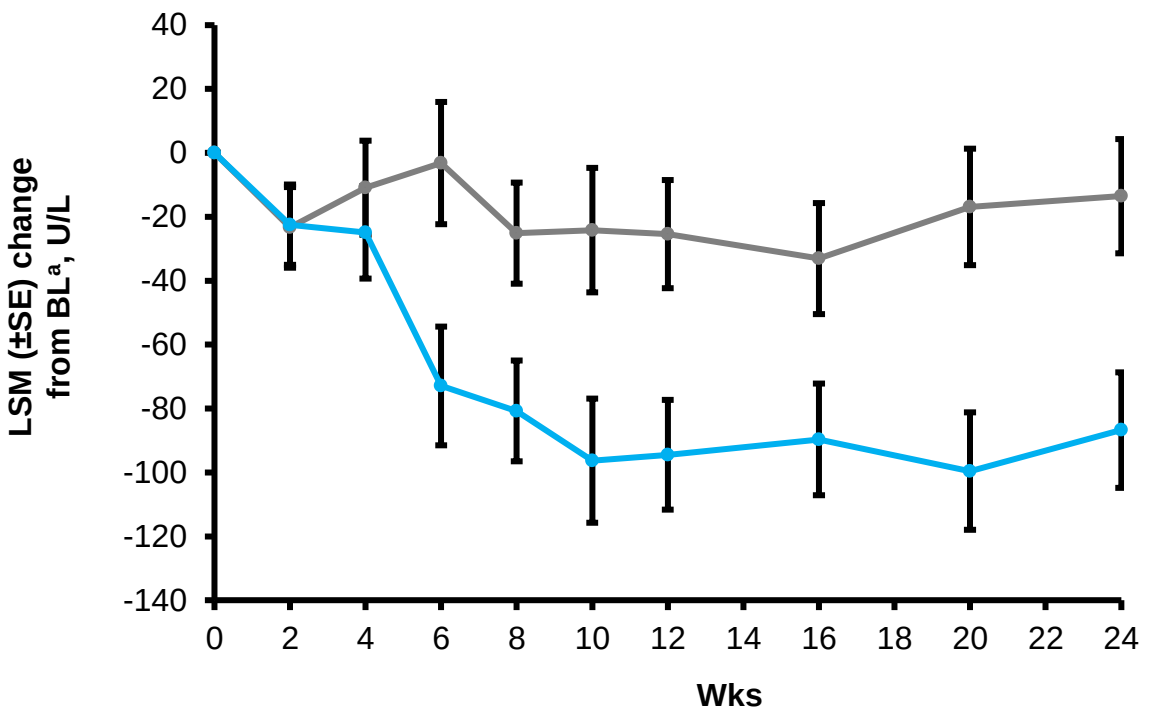
Average change from BL at wks 16, 20, and 24 in indirect bilirubin

	Mitapivat N = 40	Placebo N = 40	Difference in LSM (95% CI)	2-sided p-value
Indirect bilirubin (µmol/L) LSM (95% CI)	–21.16 (–29.59, –12.72)	5.10 (–3.00, 13.21)	–26.26 (–37.82, –14.70)	< 0.0001

Average change from BL at wks 16, 20, and 24 in LDH

	Mitapivat N = 40	Placebo N = 40	Difference in LSM (95% CI)	2-sided p-value
LDH (U/L) LSM (95% CI)	–91.99 (–124.47, –59.50)	–21.18 (–53.30, 10.94)	–70.81 (–115.88, –25.74)	0.0027





Mitapivat (N = 40) Placebo (N = 40)

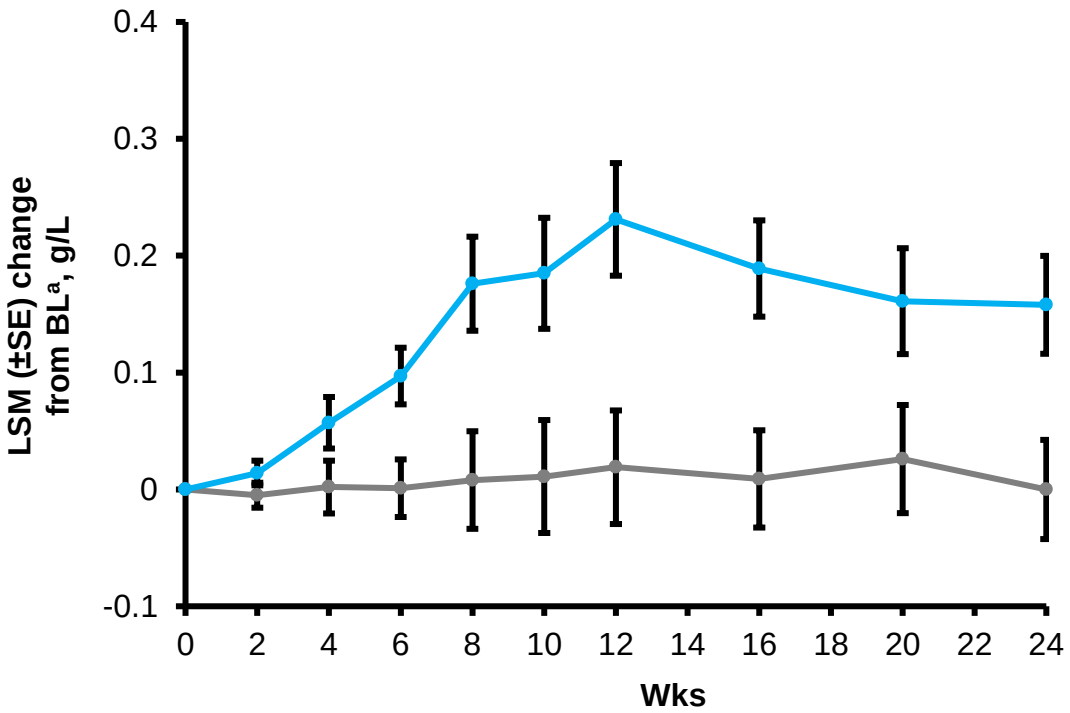
Mitapivat led to improvements in markers of hemolysis and hematopoiesis

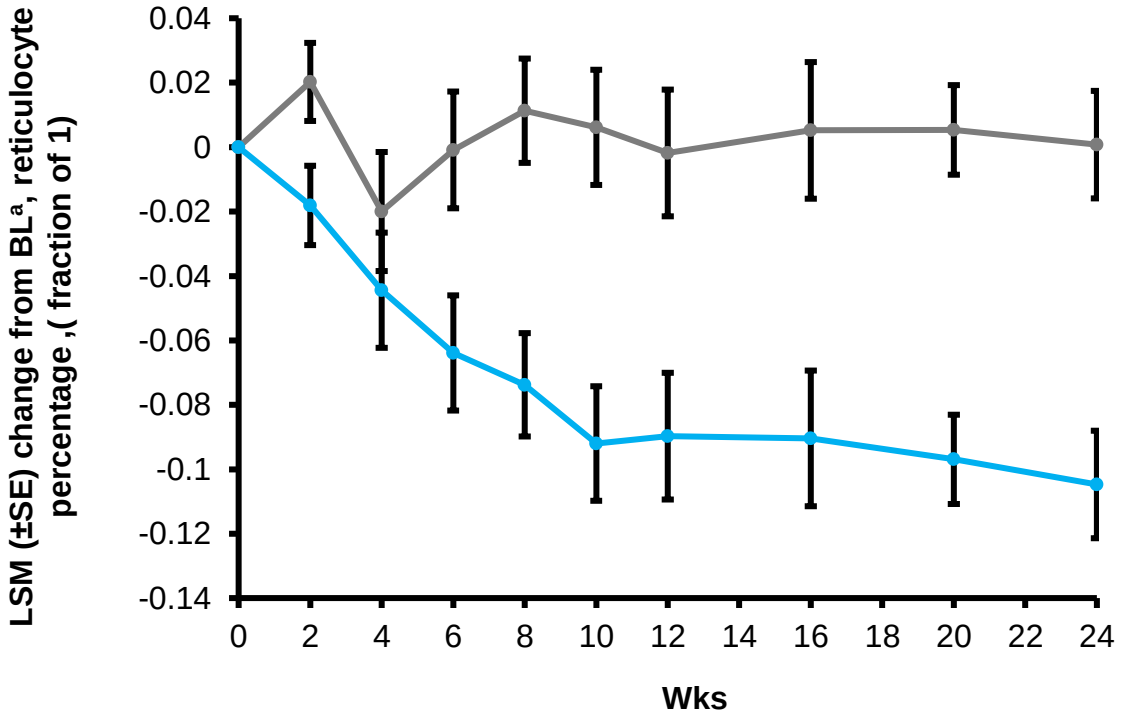
Average change from BL at wks 16, 20, and 24 in haptoglobin

	Mitapivat N = 40	Placebo N = 40	Difference in LSM (95% CI)	2-sided p-value
Haptoglobin (g/L) LSM (95% CI)	0.169 (0.088, 0.251)	0.012 (–0.070, 0.094)	0.158 (0.043, 0.273)	0.0079

Average change from BL at wks 16, 20, and 24 in reticulocyte percentage (fraction of 1)

	Mitapivat N = 40	Placebo N = 40	Difference in LSM (95% CI)	2-sided p-value
Reticulocyte percentage (fraction of 1) LSM (95% CI)	–0.0973 (–0.1252, –0.0694)	0.0038 (–0.0239, 0.0315)	–0.1011 (–0.1391, –0.0632)	< 0.0001

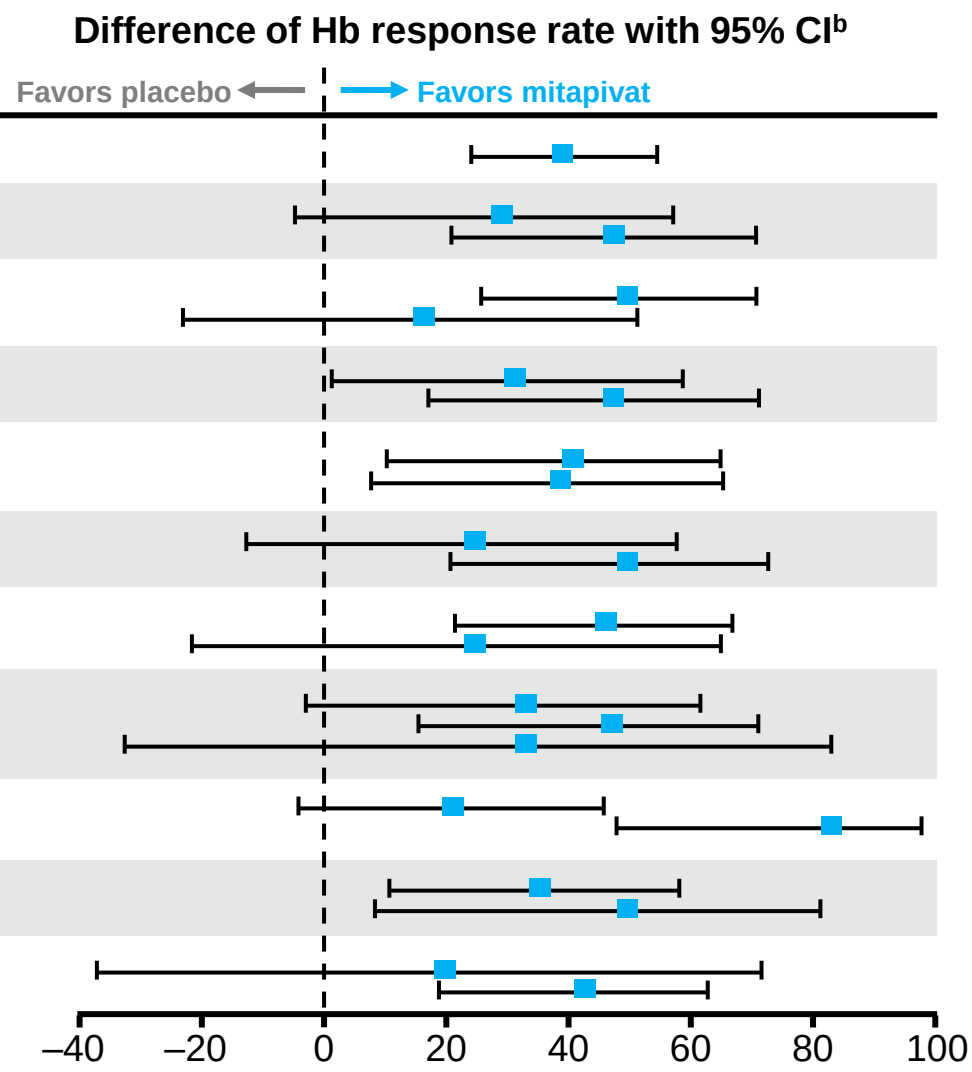




Mitapivat (N = 40) Placebo (N = 40)

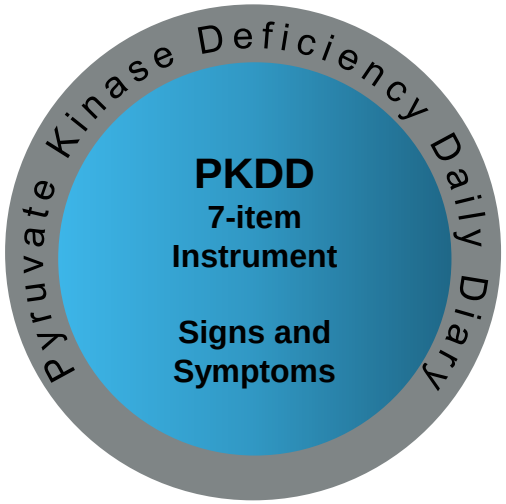
Hemoglobin response was seen across all pre-defined patient subgroups

Characteristic	Subgroup	Hb response rate, % (n/N) Mitapivat	Hb response rate, % (n/N) Placebo
Overall study population[a]:		**40.0 (16/40)**	**0 (0/40)**
Average of screening Hb:	< 8.5 g/dL	29.4 (5/17)	0 (0/18)
	≥ 8.5 g/dL	47.8 (11/23)	0 (0/22)
***PKLR* mutation category:**	Missense/Missense	50.0 (14/28)	0 (0/27)
	Missense/Non-missense	16.7 (2/12)	0 (0/13)
Baseline Hb:	< 8.5 g/dL	31.6 (6/19)	0 (0/21)
	≥ 8.5 g/dL	47.6 (10/21)	0 (0/19)
Age at screening:	< 35 years	40.9 (9/22)	0 (0/20)
	≥ 35 years	38.9 (7/18)	0 (0/20)
Sex:	Male	25.0 (4/16)	0 (0/16)
	Female	50.0 (12/24)	0 (0/24)
Race:	White	46.4 (13/28)	0 (0/32)
	Other[c]	25.0 (3/12)	0 (0/8)
Geographic region:	North America	33.3 (5/15)	0 (0/16)
	Western Europe	47.4 (9/19)	0 (0/20)
	Rest of the World[c]	33.3 (2/6)	0 (0/4)
Prior splenectomy:	Yes	21.4 (6/28)	0 (0/30)
	No	83.3 (10/12)	0 (0/10)
Prior cholecystectomy:	Yes	35.7 (10/28)	0 (0/30)
	No	50.0 (6/12)	0 (0/10)
Prior chelation therapy:	Yes	20.0 (1/5)	0 (0/10)
	No	42.9 (15/35)	0 (0/30)



PKDD and PKDIA were developed to assess and capture changes in symptom burden and HRQoL impact in patients with PK deficiency

In-trial Validation

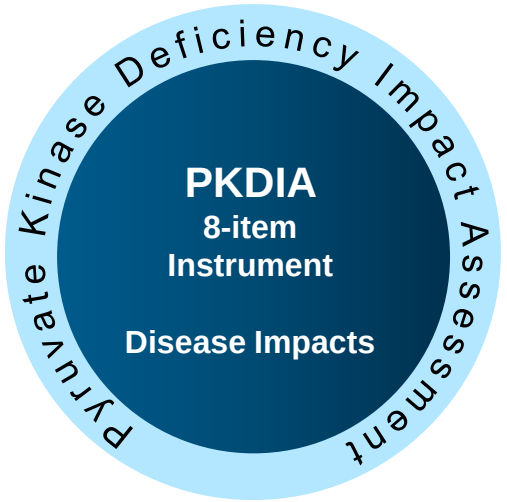


1. Tiredness at its worst
2. Tired after finishing daily activities
3. Jaundice
4. Bone pain
5. Shortness of breath
6. Energy level at beginning of day
7. Energy level at end of day

Daily Sum Score

Scoring Algorithm

T-score
Mean 50, SD 10
Min 25, Max 76



1. Starting things you wanted to get done
2. Household activities
3. Negative impact on social activities
4. Negative impact on leisure activities
5. Relationships with friends or family negatively affected
6. Difficulty concentrating
7. Difficulty performing moderate physical activity
8. Needing additional rest or sleep

Sum Score

Scoring Algorithm

T-score
Mean 50, SD 10
Min 30, Max 76

High internal consistency ☑

Excellent retest reliability ☑

Higher score = Higher disease burden

HRQoL = health related quality of life; PK = pyruvate kinase; PKDD = PK deficiency diary; PKDIA = PK deficiency impact assessment; SD = standard deviation.

Statistically significant improvement in change from baseline at Week 24 was demonstrated on PKDD and PKDIA mean weekly score

PRO	Mitapivat		Placebo		LSM[a] Difference	2-sided p-value
	BL Mean (SD)	LSM Change from BL at W24	BL Mean (SD)	LSM Change from BL at W24		
PKDD	50.45 (7.315)	–5.16	47.04 (8.103)	–2.05	–3.11 (95% CI:–5.80, –0.41)	0.0247
PKDIA	49.2 (9.00)	–4.65	48.5 (9.15)	–1.39	–3.25 (95% CI: –6.39, –0.12)	0.0421

Safety

Patients, n (%)	Mitapivat N = 40	Placebo N = 39
Any TEAEs	35 (87.5)	35 (89.7)
Treatment-related TEAEs	23 (57.5)	14 (35.9)
Grade ≥ 3 TEAEs	10 (25.0)	5 (12.8)
Grade ≥ 3 treatment-related TEAEs	3 (7.5)	0
Serious TEAEs	4 (10.0)	2 (5.1)
TEAEs leading to dose reduction of study drug	0	0
TEAEs leading to interruption of study drug	0	2 (5.1)
TEAEs leading to discontinuation of study drug	0	0
TEAEs leading to death	0	0

Most frequently reported (≥ 10%) Adverse Events in ACTIVATE

Preferred Term	Mitapivat N = 40	Placebo N = 39
Patients with events, n (%)	35 (87.5)	35 (89.7)
Nausea	7 (17.5)	9 (23.1)
Headache	6 (15.0)	13 (33.3)
Nasopharyngitis	5 (12.5)	6 (15.4)
Fatigue	5 (12.5)	4 (10.3)
Back pain	5 (12.5)	3 (7.7)
Diarrhea	4 (10.0)	7 (17.9)
Dizziness	4 (10.0)	3 (7.7)
Abdominal pain	4 (10.0)	2 (5.1)
Arthralgia	4 (10.0)	2 (5.1)
Dyspnea	3 (7.5)	4 (10.3)
Alanine aminotransferase increased	1 (2.5)	6 (15.4)
Initial insomnia	1 (2.5)	4 (10.3)
Upper respiratory tract infection	0	4 (10.3)

Mitapivat has the potential to be the first disease-modifying drug therapy for patients with pyruvate kinase deficiency

- Mitapivat demonstrated sustained improvement in hemolytic anemia in non-regularly transfused patients with PK deficiency
  - 40% in mitapivat group achieved a Hb response compared to 0% in placebo group (2-sided $p < 0.0001$)
  - Increase in Hb occurred early and was sustained
  - The effect of mitapivat on Hb response compared to placebo was observed consistently across all predefined subgroups
- Statistically significant improvements were also demonstrated for the secondary endpoints, including:
  - Average change from baseline in Hb concentration
  - Average change from baseline in markers of hemolysis and hematopoietic activity
  - Change from baseline in novel, PK deficiency-specific PROs
- Mitapivat was well-tolerated with safety profile consistent with prior studies; no TEAEs leading to discontinuation

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ACTIVATE-T

Andreas Glenthøj, M.D., Ph.D.

ACTIVATE-T: A Phase 3, Open-label, Multicenter Study Of Mitapivat In Adults With Pyruvate Kinase Deficiency Who Are Regularly Transfused

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Disclosures

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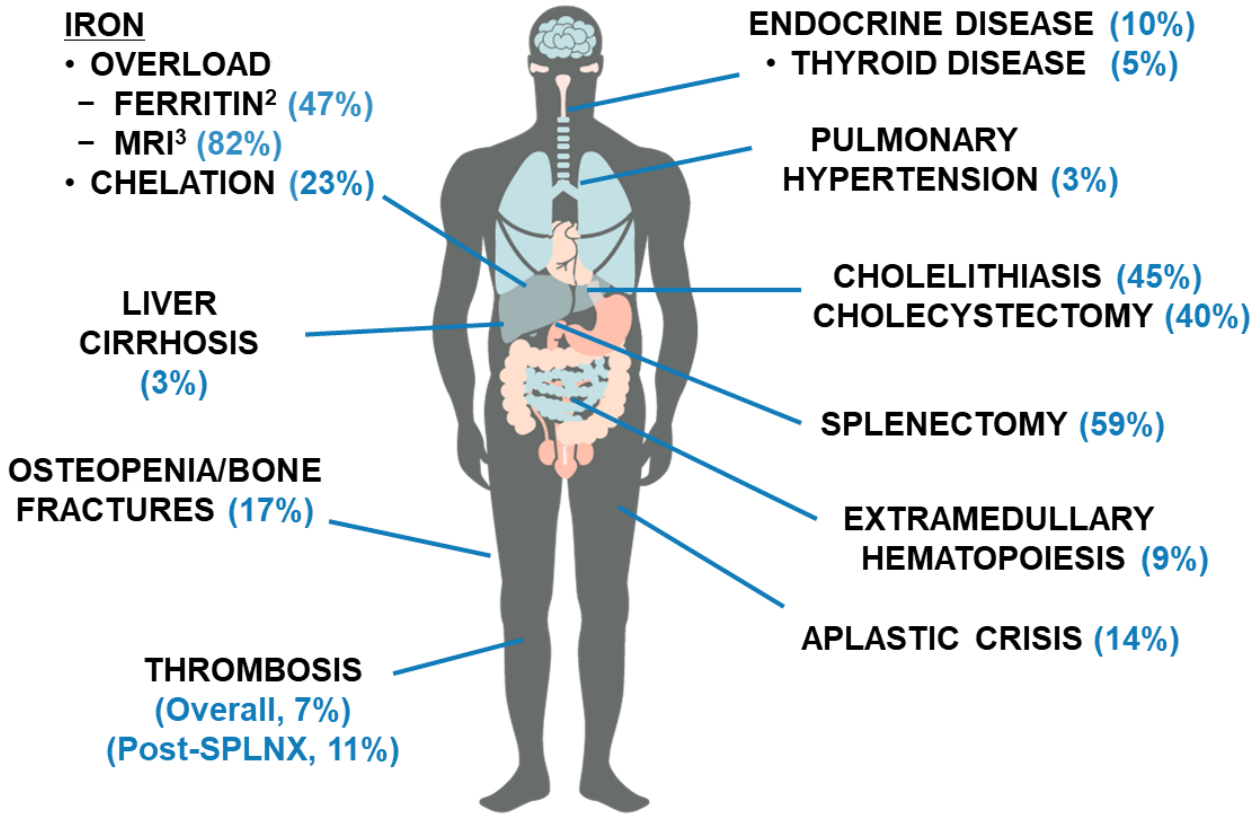
  - **Andreas Glenthøj**: Agios, bluebird bio, Celgene, Novartis – consultancy and advisory board member; Alexion – research grant; Novo Nordisk – honoraria
  - **Eduard J. van Beers**: Agios – advisory board member; Agios, Novartis, Pfizer, RR Mechatronics – research funding
  - **Hanny Al-Samkari**: Agios, argenx, Dova, Novartis, Rigel, Sobi – consultancy; Agios, Dova, Amgen – research funding
  - **Vip Viprakasit**: Bristol-Myers Squibb, Novartis – consultancy, honoraria, research funding, speakers bureau; Agios, Ionis, La Jolla Pharmaceuticals, Protagonist Therapeutics, Vifor Pharma – consultancy, research funding
  - **Kevin H. M. Kuo**: Agios, Alexion, Apellis, bluebird bio, Celgene, Pfizer, Novartis – consultancy; Alexion, Novartis – honoraria; Bioverativ – membership on an entity's Board of Directors or advisory committees; Pfizer – research funding
  - **Frédéric Galactéros**: Addmedica – board membership or advisory committee
  - **Satheesh Chonat**: Agios, Alexion, Novartis, Global Blood Therapeutics, and Novartis – consultancy/research funding
  - **John Porter**: No affiliations
  - **Sarah Gheuens, Vanessa Beynon, Emily Xu, Peter Hawkins, Erin Zagadailov**, and **Abdulafeez Oluyadi**: Agios – employees and shareholders
  - **W. Barcellini**: Agios, Alexion, Novartis – honoraria; Agios – research funding; Bioverativ, Incyte – board membership or advisory committee

Pyruvate kinase deficiency – disease overview

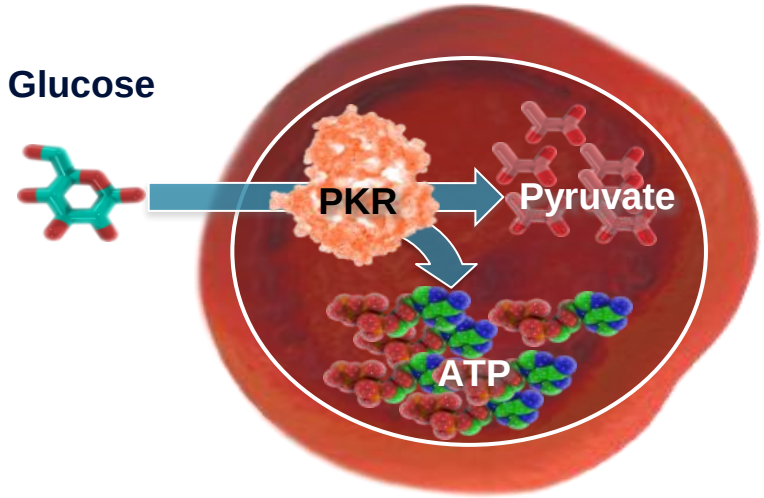
- Underrecognized, rare, hereditary chronic hemolytic anemia[1,2]
  - Characterized by mutations in the *PKLR* gene encoding PKR, which is critical for maintaining RBC energy levels and morphology, with defects in PKR causing chronic hemolysis[1–4]
- Associated with serious complications and a poor quality of life[3–6]
  - Current management strategies including RBC transfusions and splenectomy, are associated with both short- and long-term risks[3,7]
  - Regular transfusions are associated with iron overload and end organ damage[3,7]
- There are no approved disease-modifying drug therapies for PK deficiency

Comorbidities and long-term complications are common and affect multiple organ systems[6]

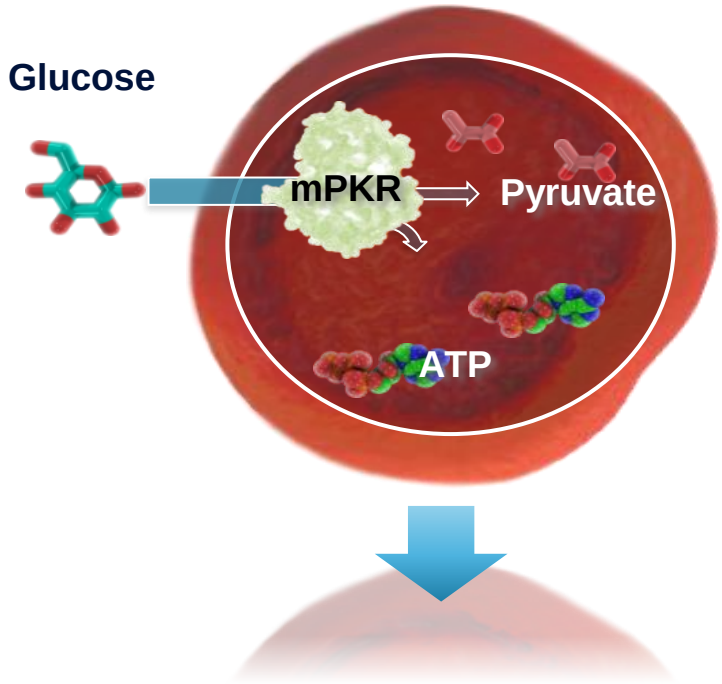


Mitapivat, an oral pyruvate kinase activator

Healthy RBC, wild-type PKR

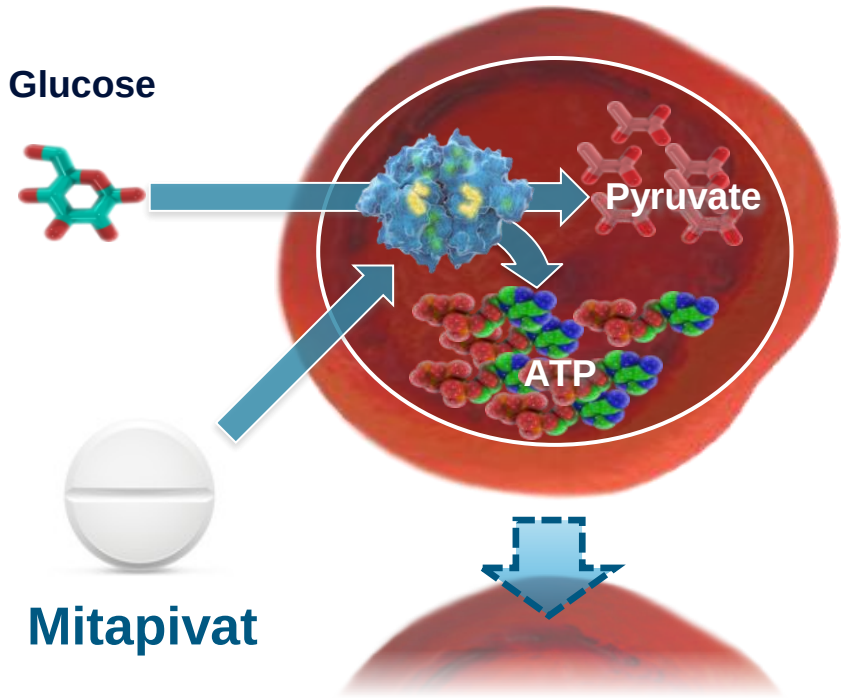


PK-deficient RBC, mPKR



HEMOLYSIS

RBC Post Mitapivat Treatment



HEMOLYSIS IMPROVEMENT

ACTIVATE-T was a Phase 3, open-label study that evaluated the efficacy and safety of mitapivat in adult patients with PK deficiency who were regularly transfused

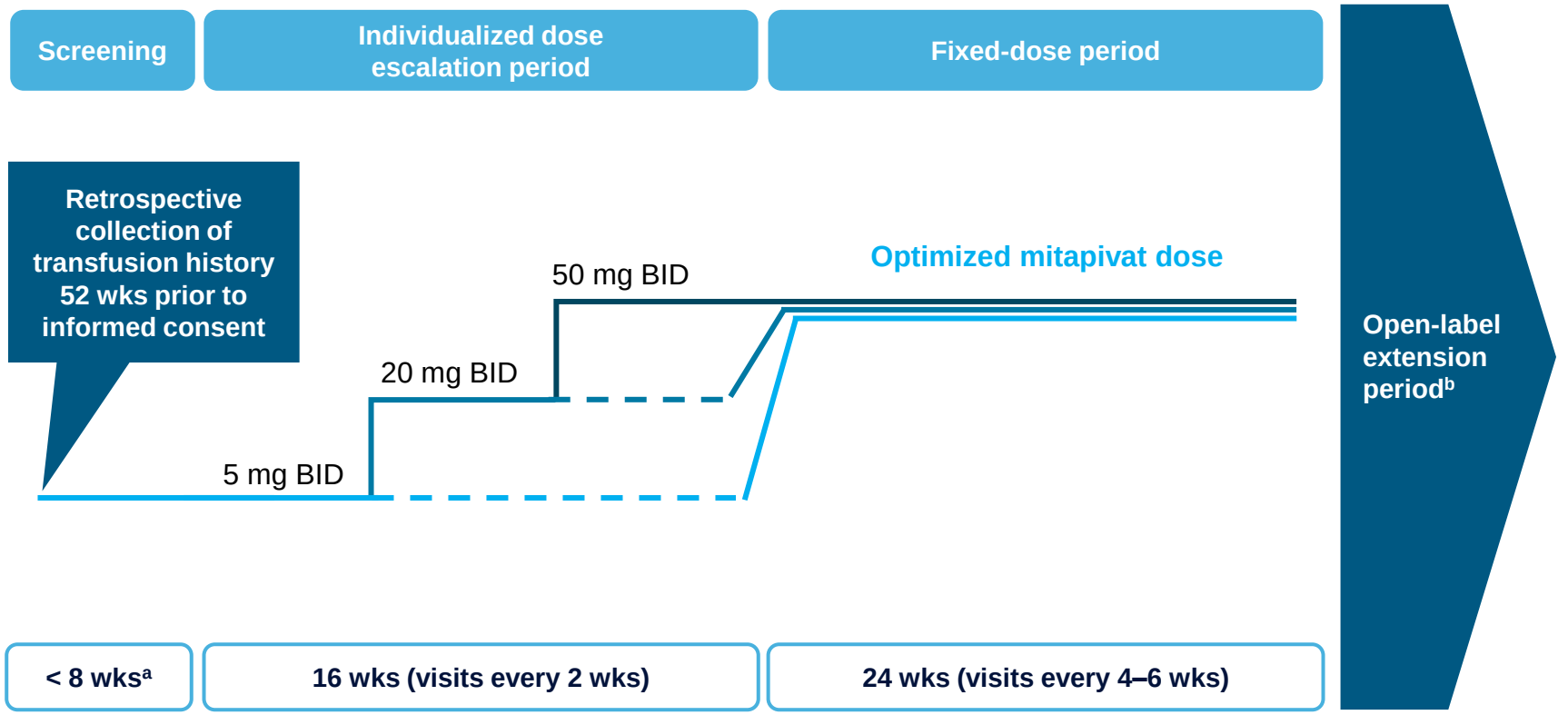
ACTIVATE-T

Key eligibility criteria:

- ≥ 18 yrs of age
- Documented ≥ 2 mutant alleles in *PKLR* (≥ 1 missense mutation)
- ≥ 6 transfusion episodes in the past 1 yr
- Complete records of transfusion history for the 52 wks prior to informed consent form
- Adequate organ function

Key exclusion criteria:

- Homozygous for R479H mutation or have 2 non-missense mutations, without another missense mutation, in *PKLR*
- > 1 transfusion episode every 3 wks in the past 1 yr
- Splenectomy during study, or within 12 months of enrollment



Primary and secondary efficacy endpoints

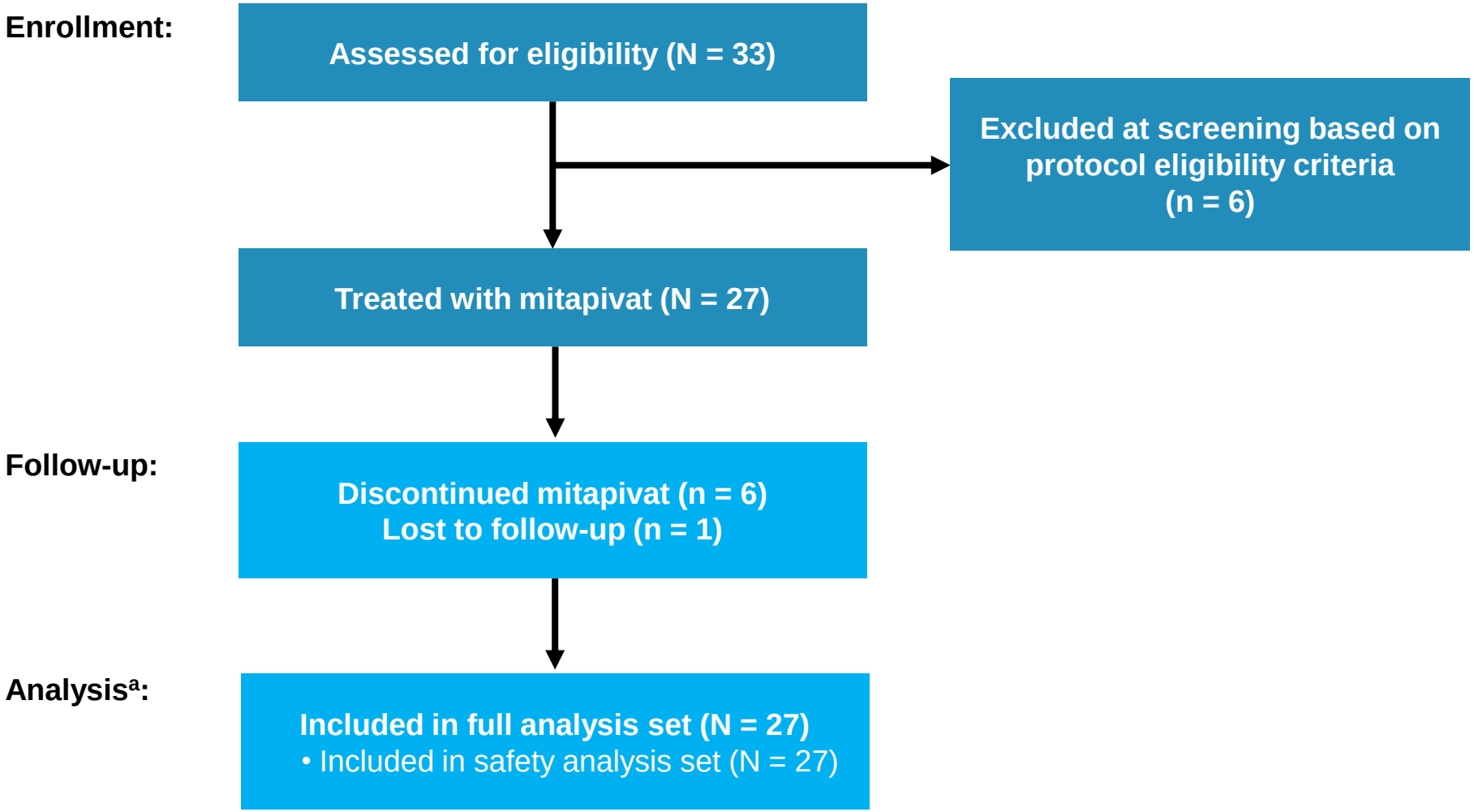
Primary Efficacy Endpoint: Achievement of transfusion burden reduction

- Defined as a ≥ 33% reduction in the number of RBC units transfused during the fixed-dose period, compared with the patient's individual historical transfusion burden standardized to 24 wks

- **Secondary Efficacy Endpoints:**
  - Annualized total number of RBC units transfused during the study compared with the historical transfusion burden
  - Number of transfusion episodes during the fixed-dose period compared with the historical transfusion burden standardized to 24 wks
  - Becoming transfusion-free, defined as no transfusions during the fixed-dose period
  - Achieving Hb concentrations in the normal range at least once, 8 wks or more after a transfusion in the fixed-dose period

- **Exploratory Efficacy Endpoints:**
  - Change in markers of hemolysis including reticulocyte fraction, haptoglobin, LDH and indirect bilirubin
  - Change from baseline in PKDIA and PKDD, which are novel PK deficiency-specific patient-reported outcomes (PROs), developed to assess and capture changes in symptom burden and HRQoL impact in PK deficiency
    - For both PROs a higher score indicates more severe disease impact

Patient disposition



Patient demographics

Patient demographics	Total (N = 27)
Age (years)	
Median (range)	36.0 (18–68)
< 35, n (%)	13 (48.1)
≥ 35, n (%)	14 (51.9)
Sex, n (%)	
Male	7 (25.9)
Female	20 (74.1)
Race, n (%)	
White	20 (74.1)
Asian	3 (11.1)
America Indian or Alaska Native	0
Black or African American	0
Native Hawaiian or Other Pacific Islander	0
Not reported	4 (14.8)
Region, n (%)	
Western Europe	21 (77.8)
North America	4 (14.8)
Asia	2 (7.4)

Baseline characteristics

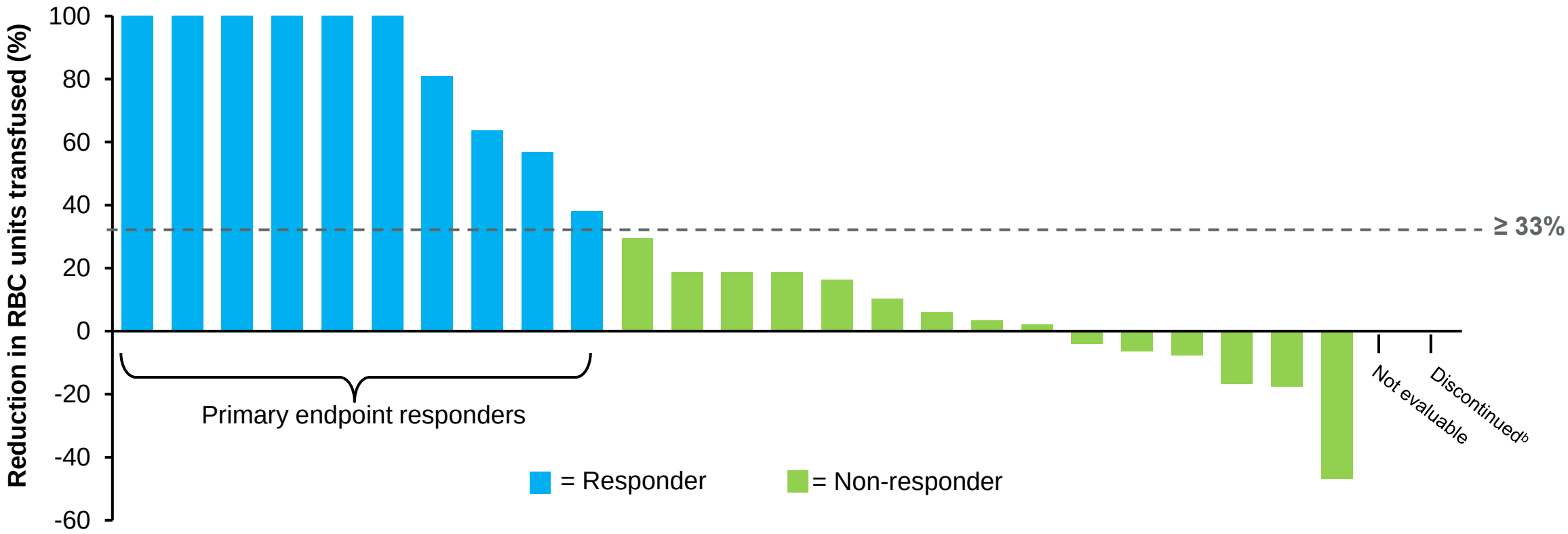
Baseline characteristics	Total (N = 27)
Hb (g/dL), mean (SD)	9.2 (0.98)
Ferritin (µg/L), mean (SD)[a]	1153.7 (1221.41)
Prior splenectomy, n (%)	21 (77.8)
Prior cholecystectomy, n (%)	23 (85.2)
Prior chelation therapy, n (%)[b]	24 (88.9)
DXA T-Score, mean (SD)[c]	
Femoral total[d]	–1.1 (0.83)
Adjusted spine	–1.4 (1.17)
***PKLR* mutation category, n (%)**	
Missense/Missense	20 (74.1)
Missense/Non-missense	7 (25.9)

Transfusion history during 52 wks before Informed Consent	Total (N = 27)
No. RBC transfusion episodes[e], mean (SD)	9.7 (3.62)
No. RBC transfusion episodes[e], standardized to 24 wks, mean (SD)	4.5 (1.67)
No. RBC transfusion episodes[e], standardized to 24 wks, category	
≤ 6, n (%)	22 (81.5)
> 6, n (%)	5 (18.5)
No. RBC units transfused, mean (SD)	16.6 (8.63)
No. RBC units transfused, standardized to 24 wks, mean (SD)	7.7 (3.98)
No. RBC units transfused, standardized to 24 wks, category	
≤ 6, n (%)	12 (44.4)
> 6, n (%)	15 (55.6)

Mitapivat met the primary endpoint, demonstrating a significant reduction in transfusion burden

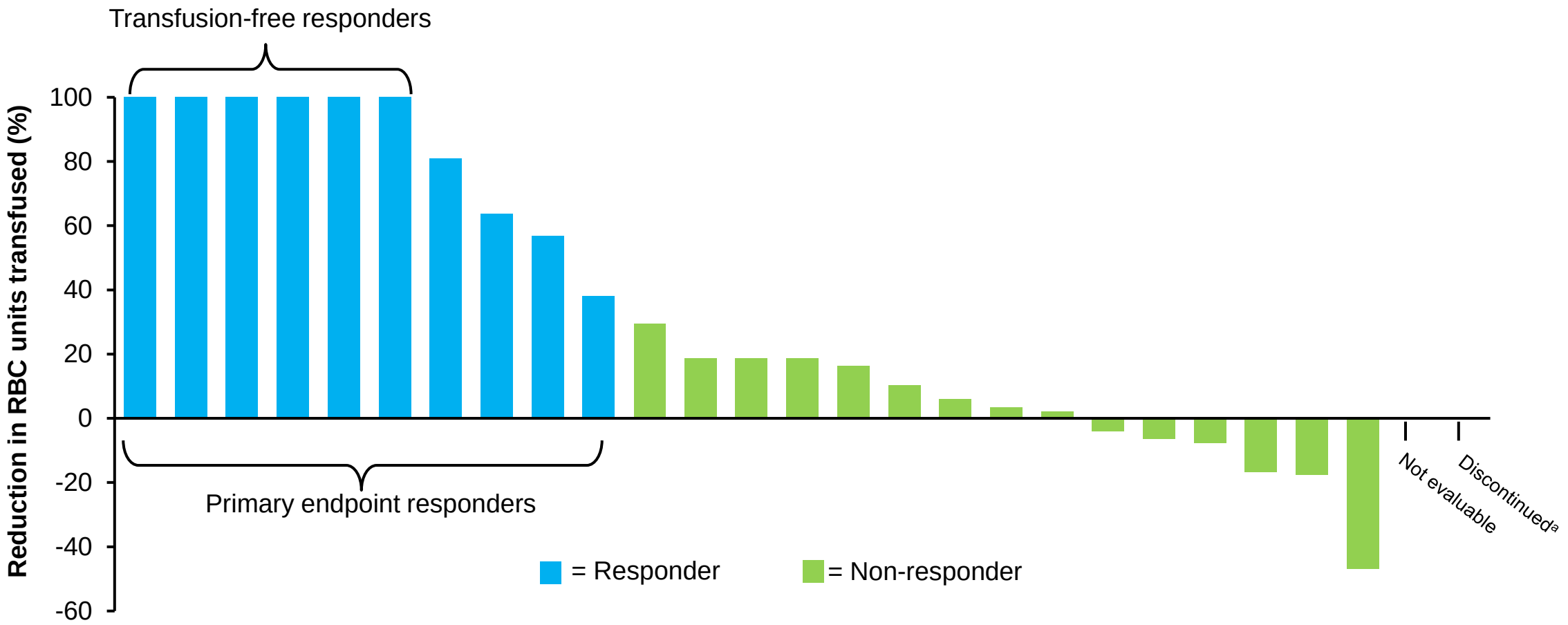
10 patients (37%; 95% CI: 19–58) achieved a reduction in transfusion burden (1-sided p = 0.0002[a])

9 patients (33%) achieved ≥ 50% reduction in total number of RBC units transfused



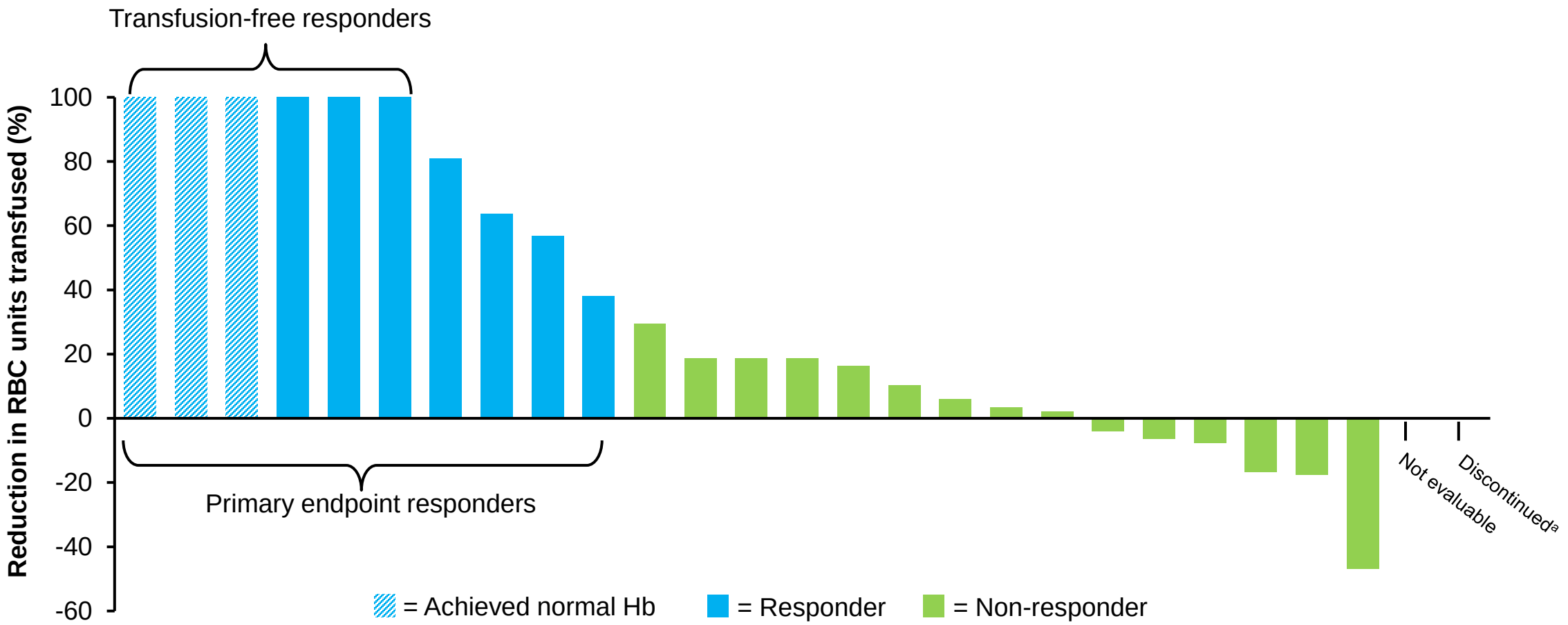
Transfusion-free responders

6 patients (22%; 95% CI: 9–42) achieved transfusion-free status during the 24 wk fixed-dose period



Hb concentrations in normal range

3 patients (11%; 95% CI: 2–29) achieved Hb concentrations in the normal range at least once 8 weeks or more after transfusion in 24 wk fixed-dose period



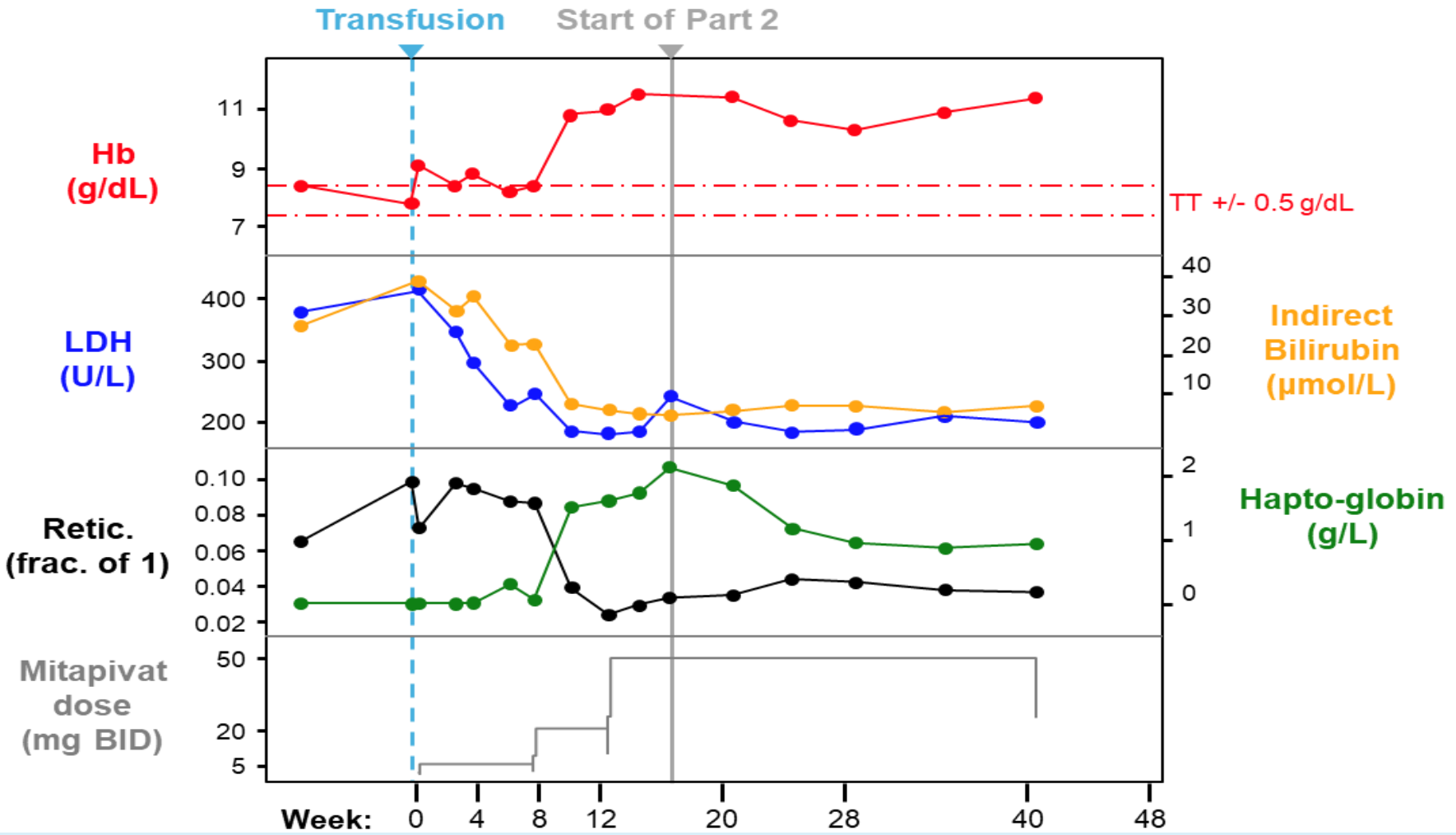
On-treatment transfusions compared to historical transfusions

	Historical (standardized to 24 wks) (n = 27)	On-treatment[a] (24 wks) (n = 26)	% Reduction[b]
Number of transfusion episodes, Mean (SD)	4.46 (1.669)	2.88 (2.694)	39.57 (44.424)
RBC units transfused, Mean (SD)	7.68 (3.981)	5.40 (5.739)	37.09 (46.804)

Similar improvements were seen when comparing annualized RBC units transfused

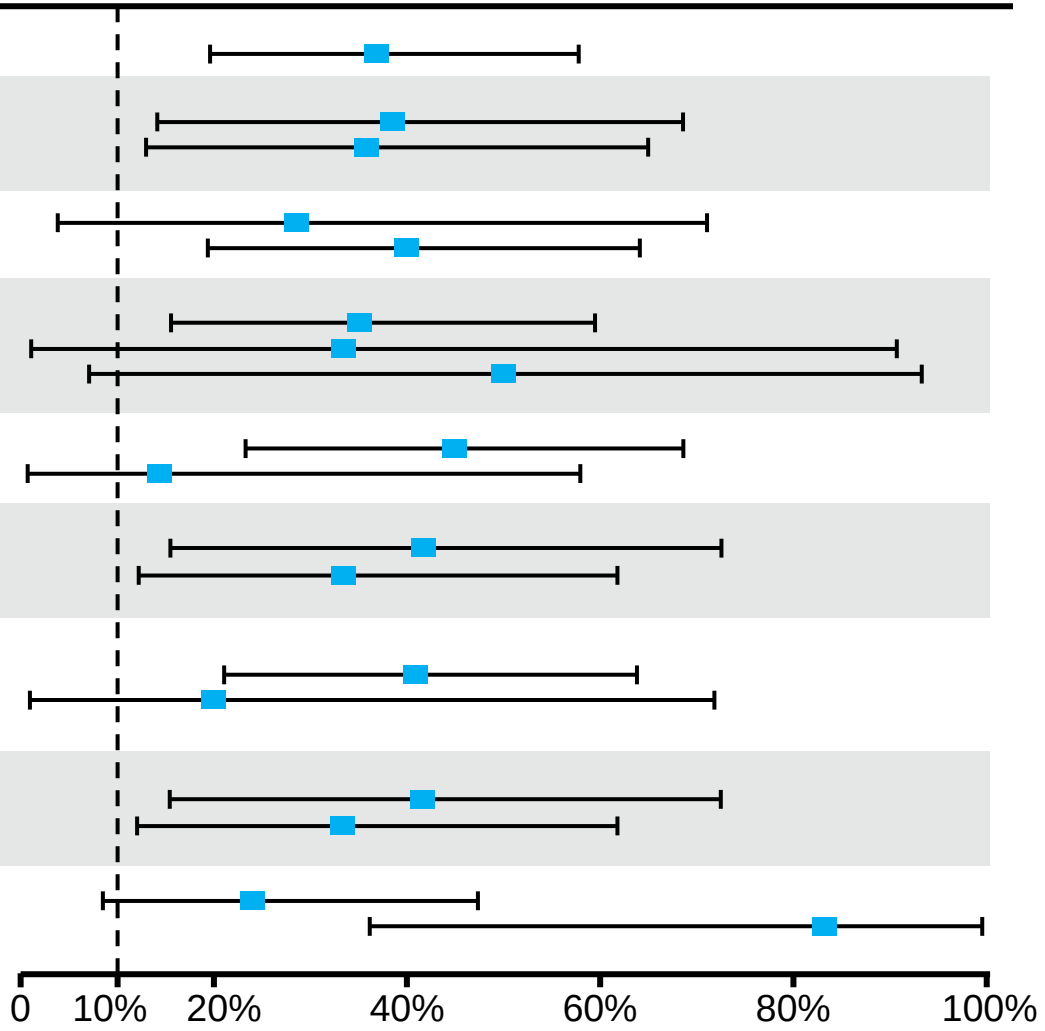
Mitapivat has the potential to normalize Hb levels and improve markers of hemolysis in transfusion-free responders

Hb and hemolysis markers over time in a transfusion-free[a] responder:

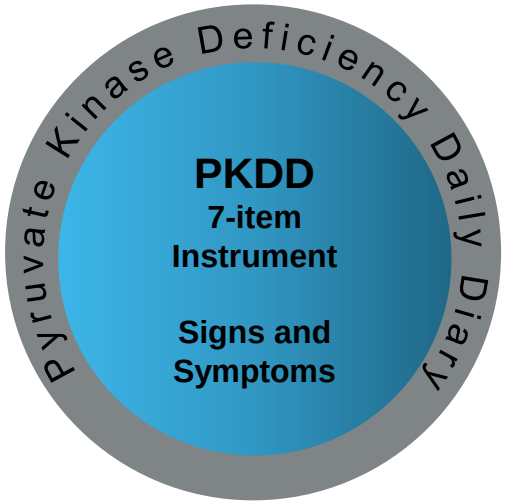


The benefit of mitapivat on the primary endpoint of reducing transfusion burden was seen across patient subgroups

Characteristic	Subgroup	Response rate, % (n/N)[a]
Overall study population[a]:		37.0 (10/27)
Age at screening:	< 35 years ≥ 35 years	38.5 (5/13) 35.7 (5/14)
Sex:	Male Female	28.6 (2/7) 40.0 (8/20)
Race:	White Asian Other	35.0 (7/20) 33.3 (1/3) 50.0 (2/4)
***PKLR* mutation category:**	Missense/Missense Missense/Non-missense	45.0 (9/20) 14.3 (1/7)
Baseline individual transfusion trigger:	< 8.5 g/dL ≥ 8.5 g/dL	41.7 (5/12) 33.3 (5/15)
Individual historical transfusion burden, number of episodes[c]:	≤ 6 episodes > 6 episodes	40.9 (9/22) 20.0 (1/5)
Individual historical transfusion burden, number of RBC units[c]:	≤ 6 units > 6 units	41.7 (5/12) 33.3 (5/15)
Prior splenectomy:	Yes No	23.8 (5/21) 83.3 (5/6)



PKDD and PKDIA were developed to assess and capture changes in symptom burden and HRQoL impact in patients with PK deficiency



In-trial Validation

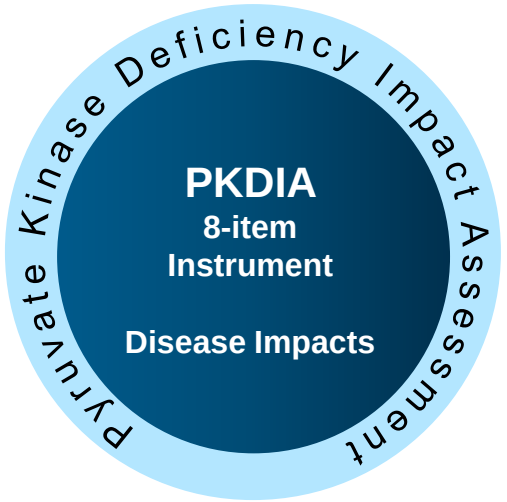
1. Tiredness at its worst
2. Tired after finishing daily activities
3. Jaundice
4. Bone pain
5. Shortness of breath
6. Energy level at beginning of day
7. Energy level at end of day

Daily Sum Score

Scoring Algorithm

T-score

Mean 50, SD 10
Min 25, Max 76



1. Starting things you wanted to get done
2. Household activities
3. Negative impact on social activities
4. Negative impact on leisure activities
5. Relationships with friends or family negatively affected
6. Difficulty concentrating
7. Difficulty performing moderate physical activity
8. Needing additional rest or sleep

Sum Score

Scoring Algorithm

T-score

Mean 50, SD 10
Min 30, Max 76

High internal consistency ☑

Excellent retest reliability ☑

Higher score = Higher disease burden

Improvement in signs, symptoms, and disease impacts was observed throughout the study based on the PKDD and PKDIA

PRO Score by study visit	Total (N = 27)	
	PKDD	PKDIA
Baseline		
n	24	24
Mean (SD)	51.9 (8.51)	52.6 (7.88)
Change from baseline, dose escalation period Week 12		
n	23	23
Mean (SD)	–5.3 (11.63)	–4.9 (9.97)
Change from baseline, fixed-dose period Week 12		
n	17	17
Mean (SD)	–3.6 (12.22)	–6.0 (12.30)
Change from baseline, fixed-dose period Week 24		
n	14	14
Mean (SD)	–2.4 (11.30)	–9.1 (11.50)

N is the number of subjects who received at least one dose of mitapivat; n shows how many subjects are included at each visit.
PK = pyruvate kinase; PKDD = PK deficiency diary; PKDIA = PK deficiency impact assessment; SD = standard deviation.

Mitapivat was well tolerated and adverse events were consistent with previously reported data

Patients, n (%)	Total (N = 27)	
Any TEAE	27 (100)	
Grade ≥ 3 TEAE	8 (29.6)[a]	
Treatment-related TEAEs	18 (66.7)	
Grade ≥ 3 treatment-related TEAEs	2 (7.4)	
Serious TEAEs	3 (11.1)	
Serious treatment-related TEAEs	0	
TEAEs leading to discontinuation of study drug	0	
TEAEs leading to dose reduction of study drug	1 (3.7)	
TEAEs leading to interruption of study drug	0	
TEAEs leading to death	0	
Most common TEAEs (occurring in ≥ 15%)	**Any grade**	**Grade ≥ 3**
ALT increased	10 (37.0)	0
Headache	10 (37.0)	0
AST increased	5 (18.5)	1 (3.7)
Fatigue	5 (18.5)	0
Nausea	5 (18.5)	0

- The majority of TEAEs were Grade 1 or 2
- Two patients experienced Grade 3 treatment-related TEAEs[a]
  - AST increase; joint swelling
- There were no TEAEs leading to death and no patients discontinued or interrupted treatment due to an AE

Mitapivat has the potential to be the first disease-modifying drug therapy for regularly-transfused patients with PK deficiency

- ACTIVATE-T was the first clinical study in patients with PK deficiency who are regularly transfused and demonstrated that mitapivat is an effective therapy for reducing transfusion burden in this population
  - 37% of patients achieved a transfusion reduction response in fixed-dose period
  - 22% of patients were transfusion-free during the fixed-dose period
  - 11% of patients achieved normal Hb concentrations during the fixed-dose period
  - PK deficiency-specific quality of life measures demonstrated improvements
- Mitapivat was well tolerated, and safety profile was consistent with previously reported data

Acknowledgements

- We would like to thank the patients taking part in this study
- This study was funded by Agios Pharmaceuticals, Inc.
- Editorial assistance was provided by Onyx Medica, London, UK, and supported by Agios Pharmaceuticals, Inc.

Phase 2 Thalassemia Study

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

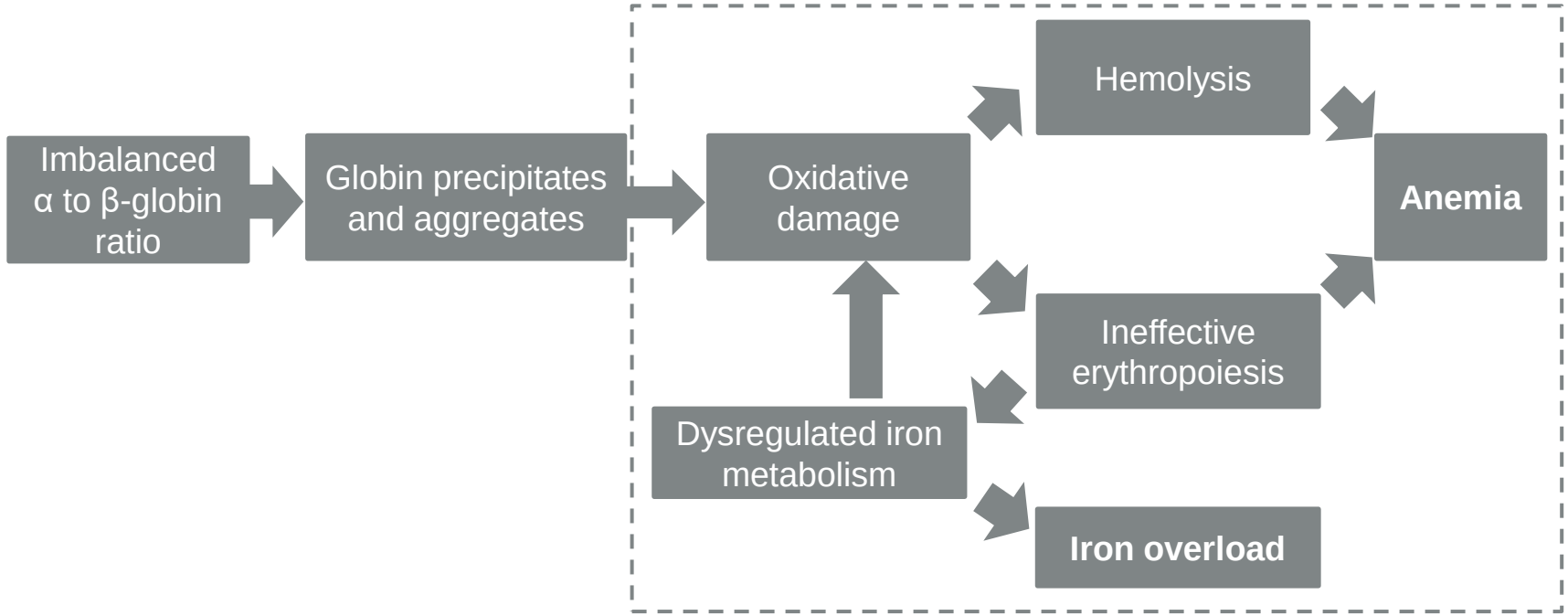
What is thalassemia?

- An inherited blood disorder that reduces the production of functional hemoglobin, the protein in RBCs that carries oxygen
- This causes a shortage of RBCs and low levels of oxygen in the bloodstream, leading to a variety of health problems
- Estimated 18-23K patients in the U.S. and EU

TWO MAIN TYPES

Alpha thalassemia, caused by mutations in alpha globin

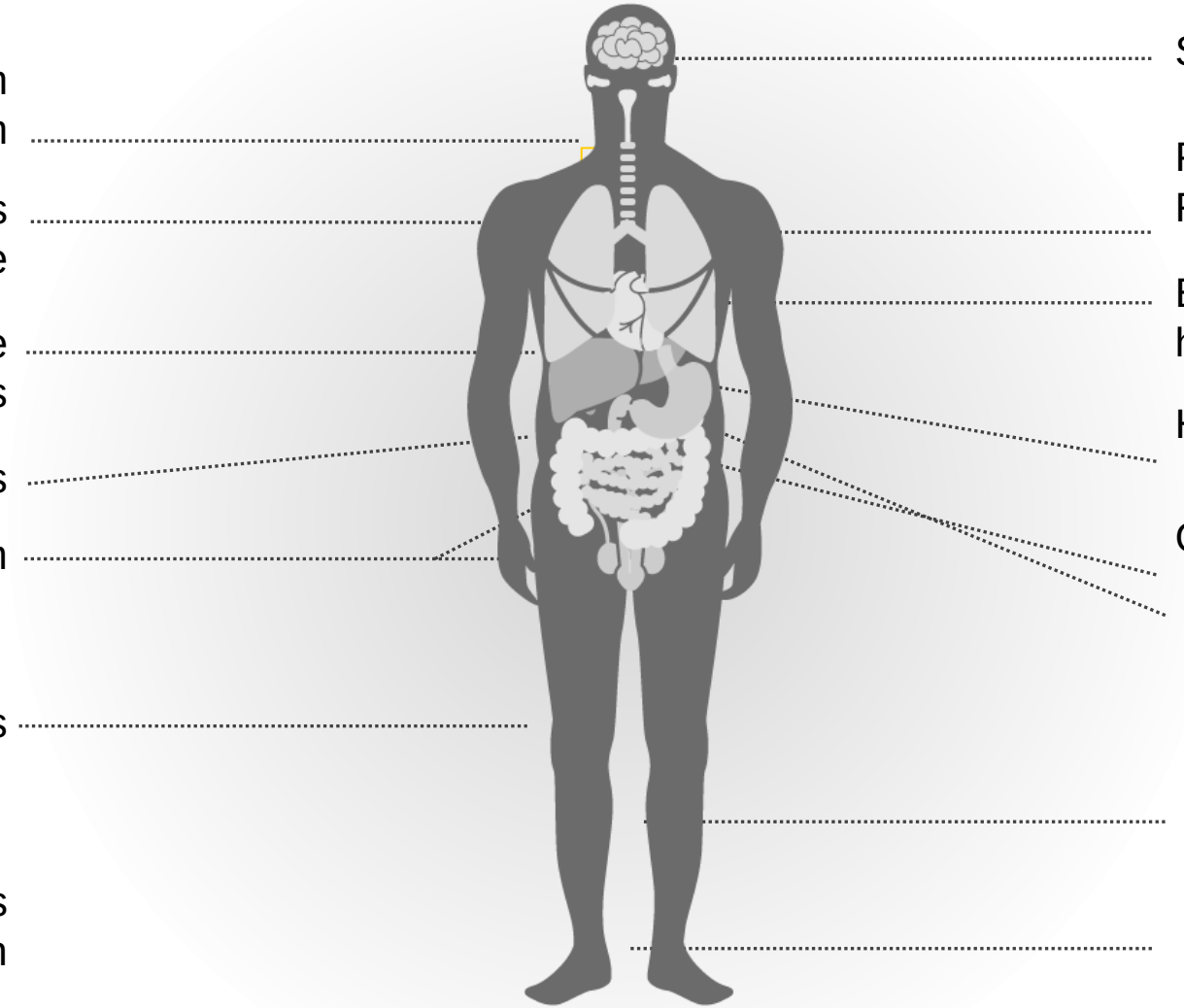
Beta thalassemia, caused by mutations in beta globin



Globin precipitates in thalassemia cause oxidative damage, leading to hemolytic anemia, ineffective erythropoiesis and iron overload

Agios market research; EHA 2020

Complications from thalassemia occur regardless of transfusion status



Hypothyroidism
Hypoparathyroidism

Cardiac siderosis
Left-sided heart failure

Hepatic failure
Viral hepatitis

Diabetes mellitus

Hypogonadism

Osteoporosis

Transfusion reactions
Alloimmunization

Silent cerebral ischemia

Pulmonary hypertension
Right-sided heart failure

Extramedullary hematopoiesis

Hepatic fibrosis, cirrhosis, and cancer

Gallstones

Splenomegaly

Venous thrombosis

Leg ulcers

NTDT, non-transfusion-dependent β-thalassemia; PHT, pulmonary hypertension; TDT, transfusion-dependent β-thalassemia.
Musallam. *Acta Haematol*. 2013;130:64. Musallam. *Haematologica*. 2013;98:833.

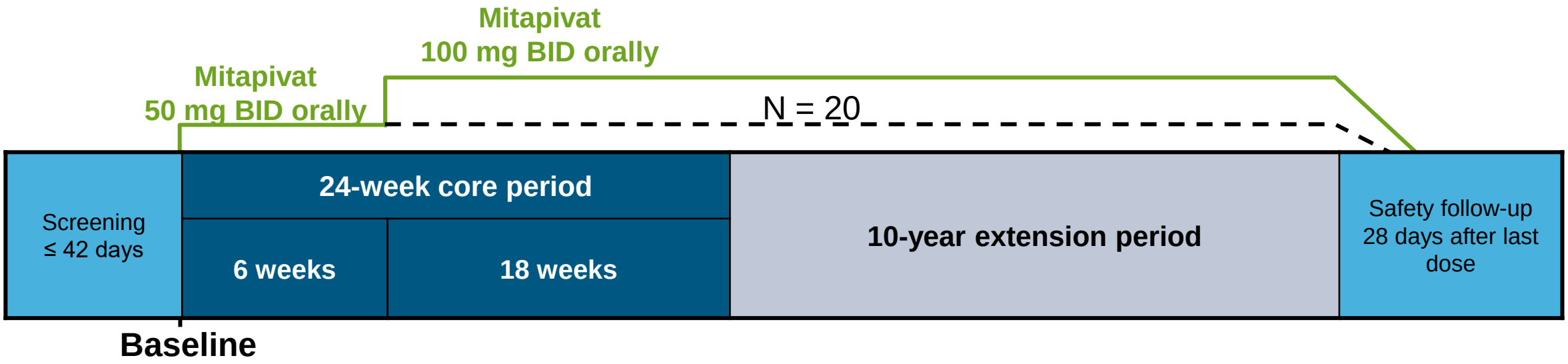
Results from a phase 2, open-label, multicenter study of the oral pyruvate kinase activator mitapivat in adults with non–transfusion-dependent alpha- or beta-thalassemia

Kevin H.M. Kuo, MD,[1] D. Mark Layton, MB BS,[2] Ashutosh Lal, MD,[3] Hanny Al-Samkari, MD,[4] Joy Bhatia, MD,[5] Bo Tong, PhD,[5] Megan Lynch, MSN,[5] Katrin Uhlig, MD,[5] Elliott P. Vichinsky, MD[3]

[1]Division of Hematology, University of Toronto, Toronto, Canada; [2]Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK; [3]UCSF Benioff Children's Hospital Oakland, Oakland, CA, USA; [4]Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [5]Agios Pharmaceuticals, Inc., Cambridge, MA, USA

Presented at European Hematology Association (EHA) Virtual Congress; 9–17 June 2021
This study was funded by Agios Pharmaceuticals, Inc.,

This phase 2, open-label, multicenter study investigated the efficacy and safety of mitapivat in non–transfusion-dependent α- and β-thalassemia[a]



Key inclusion criteria:

- β-thalassemia ± α-globin gene mutations, HbE β-thalassemia, or α-thalassemia (HbH disease)
- Hb ≤ 10.0 g/dL
- Non–transfusion-dependent[b]

Primary endpoint[c]

- Hb response, defined as increase of ≥ 1.0 g/dL from baseline at any time between Weeks 4–12, inclusive

Secondary and exploratory endpoints

- Sustained Hb response; delayed Hb response; markers of hemolysis and erythropoiesis; safety

[a]EudraCT 2018-002217-35, ClinicalTrials.gov: NCT03692052; [b]≤ 5 RBC units transfused in the preceding 24 weeks and none in the 8 weeks prior to study drug; [c]With the originally planned sample size of 17 patients, the study would have 80% power to reject a ≤ 30% response rate at a 1-sided 0.05 type 1 error rate.
BID = twice daily; dL = deciliter; Hb = hemoglobin; HbE = hemoglobin E; HbH = hemoglobin H; RBC = red blood cell.

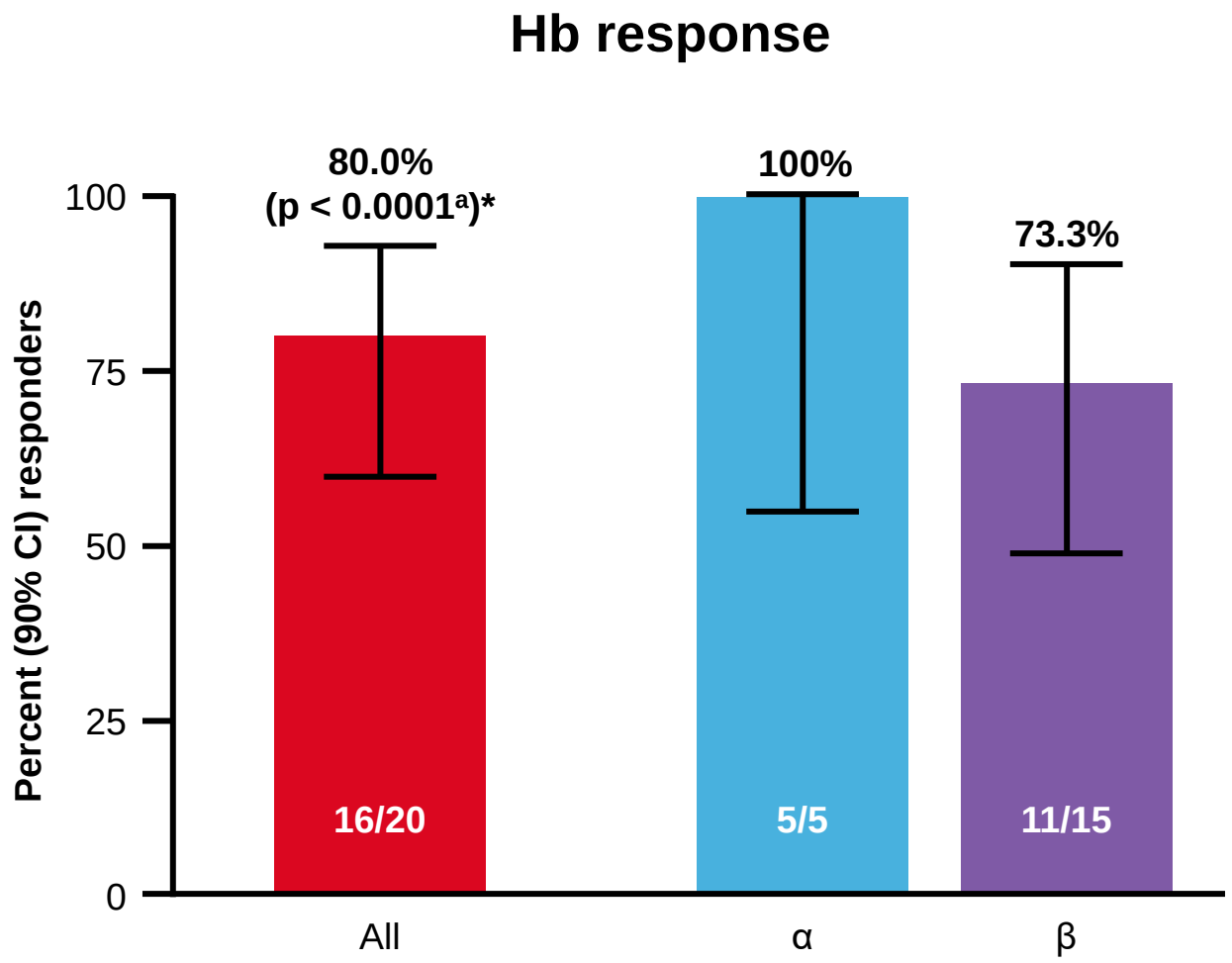
Patient demographics and baseline characteristics

Patient demographics and BL characteristics	All patients (N = 20)
Completed 24-week core treatment period, n (%)	19 (95)
Sex, n (%)	
Male	5 (25.0)
Female	15 (75.0)
Age, median (range), years	44.0 (29–67)
Race, n (%)	
Asian	10 (50.0)
White	4 (20.0)
Black or African American	1 (5.0)
Native Hawaiian or other Pacific Islander	1 (5.0)
American Indian or Alaska Native	0
Other	3 (15.0)
Not reported	1 (5.0)
Thalassemia type, n (%)	
α-thalassemia	5 (25%)
β-thalassemia	15 (75%)
Hb baseline, median (range), g/dL	8.43 (5.13–9.80)
Total bilirubin, median (range), µmol/L	31.00 (8.6–90.0)
LDH, median (range), U/L	249.00 (126.0–513.0)
Erythropoietin, median (range), IU/L	79.00 (15.0–11191.0)

Genotype	Patients (N = 18)[a]
β-thalassemia, n (%)	
Intermedia	6 (33.3)
Intermedia + α duplication	3 (16.7)
Trait/phenotypic β-thalassemia intermedia	2 (11.1)
HbE/β-thalassemia, n (%)	
HbE/β^0	2 (11.1)
α-thalassemia, n (%)	
Deletional	2 (11.1)
Non-deletional	3 (16.7)

[a]Genotype data is unknown for 2 patients.
AE = adverse event; BL = baseline; Hb = hemoglobin; HbE = hemoglobin E; IU = international units; LDH = lactate dehydrogenase; U = units.

Mitapivat met the primary endpoint of a Hb response in 80% of patients



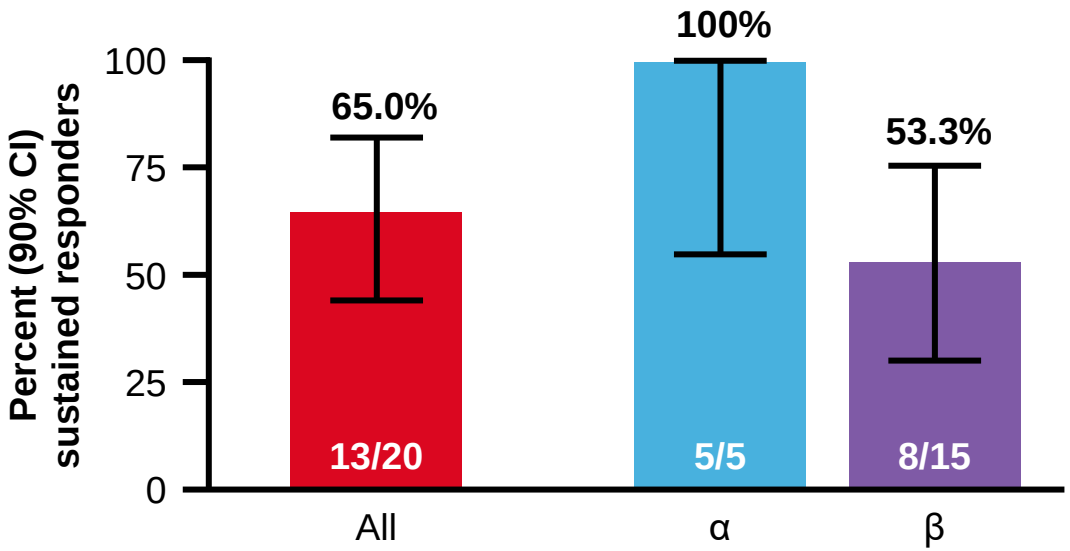
Primary endpoint

Hb response:
≥ 1.0 g/dL increase in Hb concentration from BL at ≥ 1 assessments between Weeks 4–12 (inclusive)

NB: Primary endpoint; Hb response, defined as a ≥1.0 g/dL increase in Hb concentration from baseline at 1 or more assessments between Week 4 and Week 12 (inclusive).
[a]1-sided p-value based on Clopper-Pearson method.
BL = baseline; CI = confidence interval; Hb = hemoglobin.

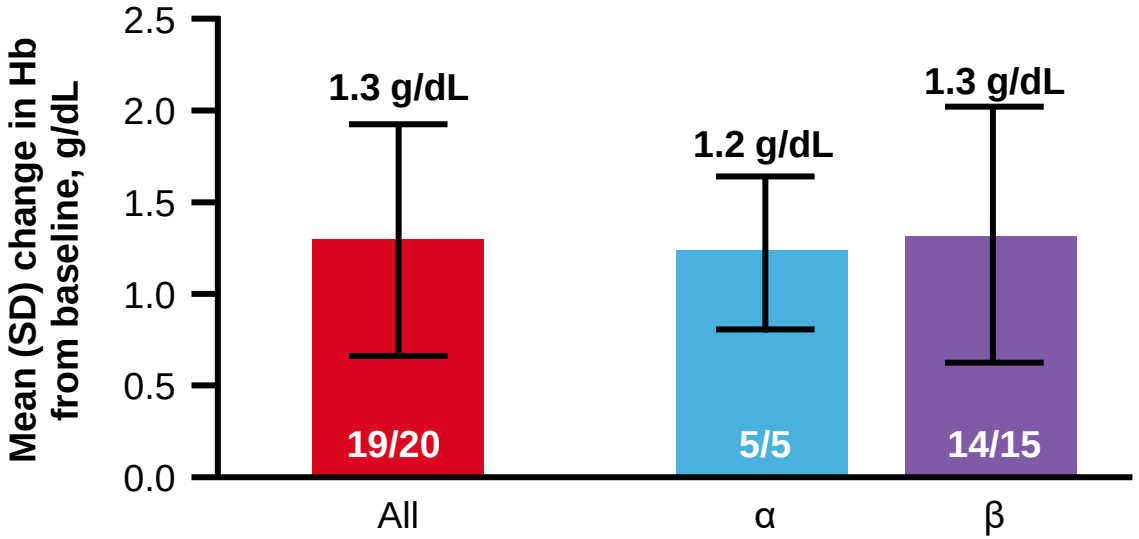
Secondary endpoints: sustained Hb response and consistent increases in mean Hb

Sustained Hb response



Sustained Hb response:
A primary endpoint response during Weeks 4–12 and a ≥ 1.0 g/dL increase in Hb concentration at ≥ 2 assessments between Weeks 12 and 24

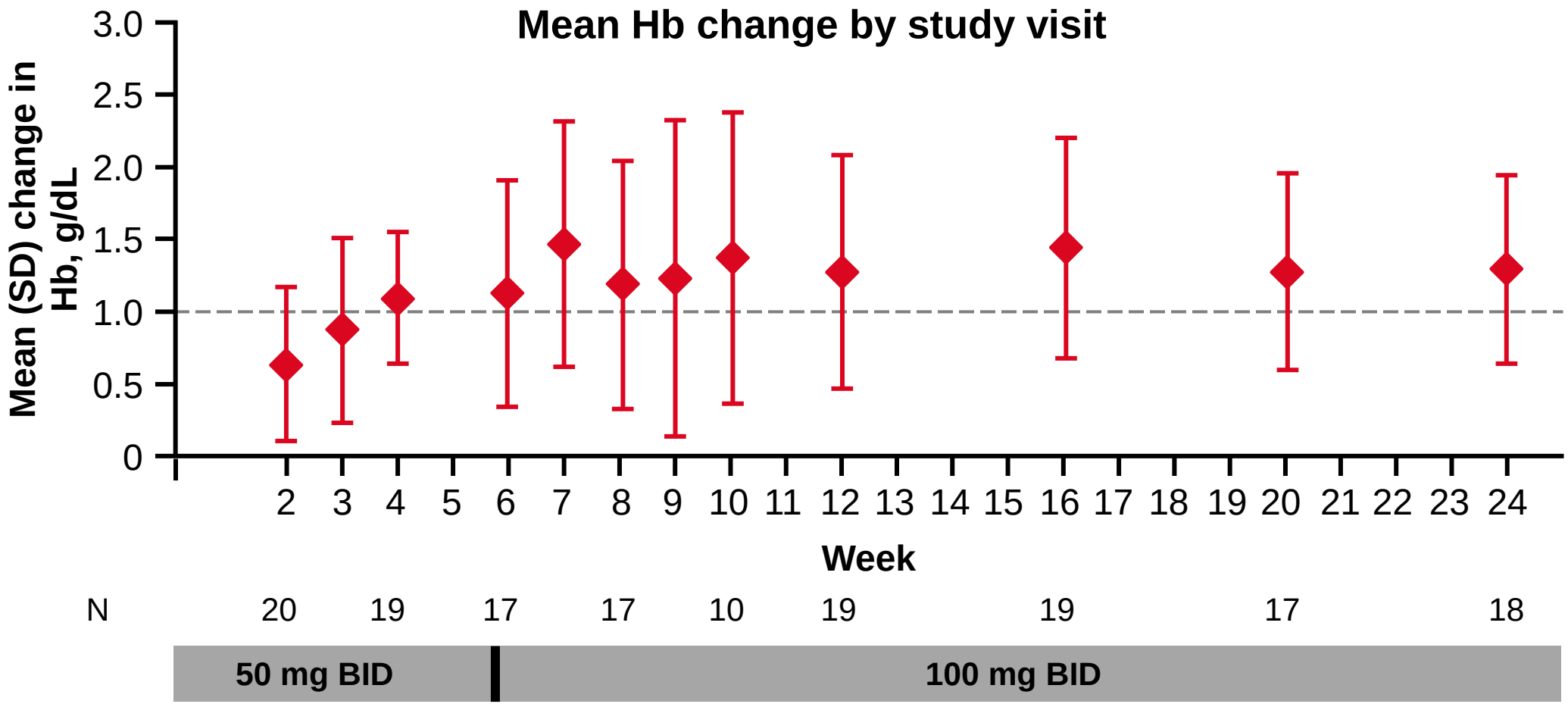
Mean Hb change



Mean Hb change:
Mean change from BL in Hb concentrations over a 12-week interval from Weeks 12 and 24

BL = baseline; CI = confidence interval; Hb = hemoglobin; SD = standard deviation.

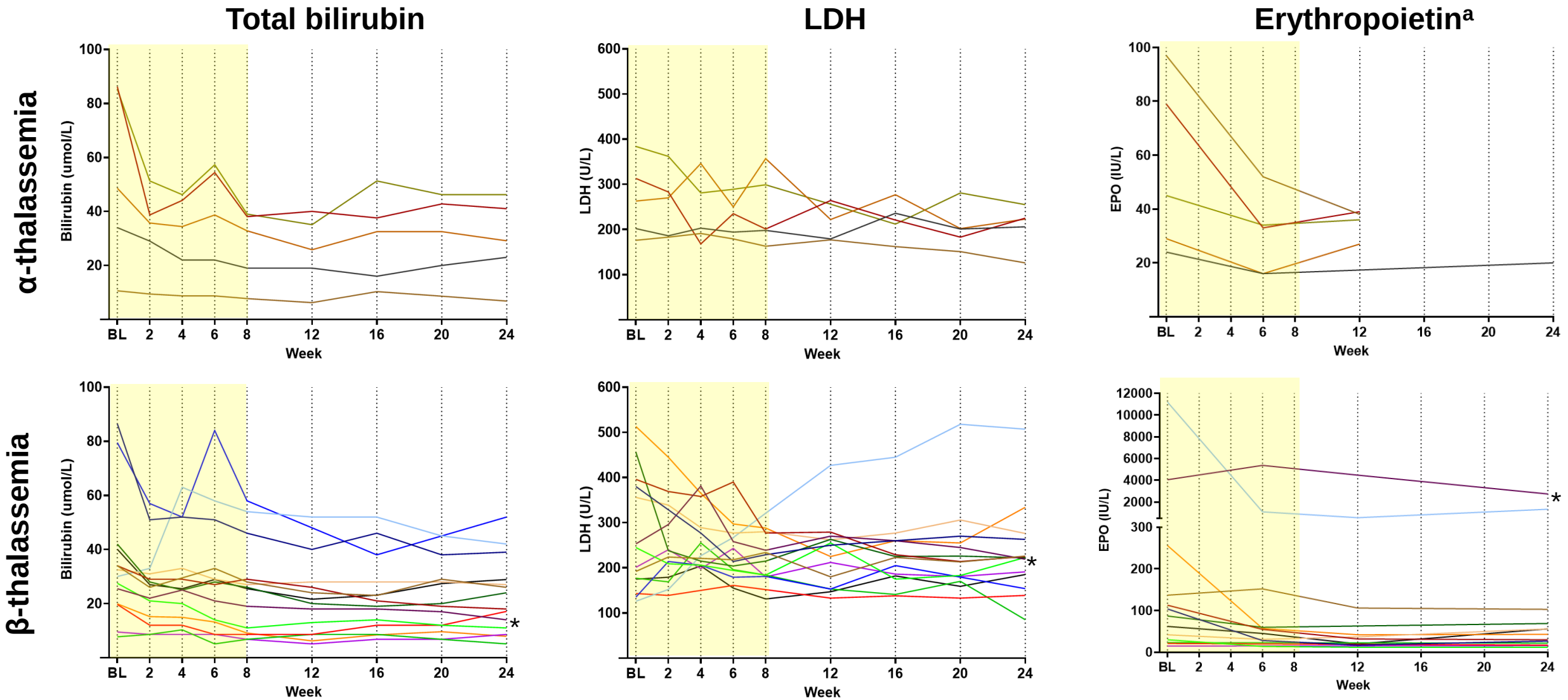
Improvements in Hb were rapid and maintained over the duration of the core treatment period



- Mean (SD) time to first Hb increase of ≥ 1 g/dL among responders was 4.5 (3.2) weeks

NB: Mean change from baseline in Hb concentrations over a continuous 12-week interval from Week 12 to Week 24
BID = twice daily; Hb = hemoglobin; SD = standard deviation.

Treatment with mitapivat improved markers of hemolysis and erythropoiesis in both α- and β-thalassemia



*Non-responder (purple line). [a]Week 24 data are missing for four of the five α-thalassemia patients, due to COVID-19.
NB: Predefined secondary endpoints, mean (SD) values of markers of hemolysis: bilirubin, LDH, and mean (SD) values of markers of erythropoietic activity: erythropoietin.
BL = baseline; EPO = erythropoietin; Hb = hemoglobin; IU = international units; LDH = lactate dehydrogenase; SD = standard deviation; U = units; µmol = micromole.

Improvements in ATP support mitapivat's proposed mechanism of action in thalassemia

Treatment dose	Visit	Mean (CV%) ATP change from baseline in blood, %
50 mg BID	Week 6 (n = 11)	78.2 (82.7)
100 mg BID	Week 8 (n = 12)	72.7 (67.9)
100 mg BID	Week 12 (n = 12)	86.7 (68.7)
100 mg BID	Week 24 (n = 8)	61.6 (62.7)

- Mean ATP percent increase from baseline was similar to that previously observed with mitapivat in healthy volunteers[1]

NB: Exploratory endpoint, change from baseline in ATP
ATP = adenosine triphosphate; BID = twice daily; CV = coefficient of variation.
1. Yang H et al. *Clin Pharmacol Drug Dev* 2019;8:246–59.

Common treatment-emergent adverse events reported

Most common TEAEs (any grade in ≥ 15% of patients)	All patients (N = 20)
	Any grade, n (%)
Patients with events	17 (85.0)
Initial insomnia	10 (50.0)
Dizziness	6 (30.0)
Headache	5 (25.0)
Cough	4 (20.0)
Dyspepsia	4 (20.0)
Fatigue	4 (20.0)
Nasal congestion	4 (20.0)
Upper respiratory tract infection	4 (20.0)
Abdominal pain	3 (15.0)
Diarrhea	3 (15.0)
Ocular icterus	3 (15.0)
Pain	3 (15.0)
Pain in extremity	3 (15.0)
Abdominal distension	3 (15.0)
Nausea	3 (15.0)
Oropharyngeal pain	3 (15.0)

MedDRA version 23.0 and CTCAE version 4.03 were used.
CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Medical Regulatory Activities; TEAE = treatment-emergent adverse event.

Safety summary

All patients (n = 20)	Patients, n (%)	TEAEs[a]
Treatment-related TEAEs	13 (65.0)	Initial insomnia (n = 10), diarrhea (n = 3), dyspepsia (n = 3), abdominal distension (n = 3), nausea (n = 3)
Grade ≥ 3 TEAEs	5 (25.0)	Initial insomnia (n = 1), arthralgia (n = 1), renal impairment (n = 1), anemia (n = 1), vertigo positional (n = 1)
Grade ≥ 3 treatment-related TEAEs	1 (5.0)	Initial insomnia (grade 3)
Serious TEAEs	1 (5.0)	Renal impairment (grade 3)
TEAEs leading to study drug:		
Dose reduction	3 (15.0)	Abdominal distension and dyspepsia (both grade 2), initial insomnia (grade 3), renal impairment (grade 3)
Interruption	1 (5.0)	Vertigo positional (grade 3)
Discontinuation	1 (5.0)	Renal impairment (grade 3) Patient discontinued after the Week 4 visit

- The adverse event leading to study drug discontinuation was not treatment related
- There were no deaths during the study

Patients with multiple adverse events within a PT are counted only once in that PT; for patients with multiple occurrences of an adverse event, the adverse event with the worst CTCAE grade is included in the summary; MedDRA version 23.0 and CTCAE version 4.03 were used.

[a]TEAEs ≥ 20% listed for 'any TEAEs'; ≥ 20% listed for 'treatment-related TEAEs'; all TEAEs listed for other sections. CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Medical Regulatory Activities; PT = preferred term; TEAE = treatment-emergent adverse event.

Conclusions

- This is the first clinical study evaluating PKR activation as a therapeutic option in α- and β-thalassemia, and is the first drug trial aimed at evaluating treatment in α-thalassemia
- The study met its primary endpoint, and demonstrated a sustained Hb response and improvements in hemolysis and ineffective erythropoiesis in patients with α- and β-thalassemia
- Mitapivat was well tolerated; the safety profile was consistent with previous studies
  - 17 patients continued to the extension period of the study and, as of 29 April 2021, 16 patients remain on study drug
- Mitapivat, through activation of wild-type PKR, may represent a novel therapeutic option for patients with α- or β-thalassemia
  - Two pivotal phase 3 trials, ENERGIZE (NTDT) and ENERGIZE-T (TDT), for patients with α- or β-thalassemia will be initiated in 2021

Hb = hemoglobin; NTDT = non-transfusion-dependent thalassemia; PK = pyruvate kinase; PKR = PK in RBCs; RBC = red blood cell; TDT = transfusion-dependent thalassemia..

Summary

Dr. Chris Bowden

Summary & Key Upcoming Milestones

- EHA presentations underscore the potential of mitapivat to become an important treatment option for PK deficiency and thalassemia
- Global regulatory filings for mitapivat in adults with PK deficiency remain on track; Commercial preparations underway for potential launch
- Late-stage studies of mitapivat in thalassemia and sickle cell disease on track to initiate this year
- Mitapivat development expanding in pediatric patients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Q&A