agios

Agios at ASH 2021

December 14, 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 and AG-946; Agios' plans, strategies and expectations for its preclinical, clinical and commercial advancement of its drug development, including mitapivat and AG-946; Agios' key milestones for 2021 and 2022; Agios' plans regarding future data presentations; 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 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 – 7:40 AM	Our Differentiated Approach to Clinical Development	Sarah Gheuens, M.D., Ph.D.
7:40 – 7:55 AM	Long-term Safety and Efficacy of Mitapivat in Thalassemia	Kevin Kuo, M.D., M.Sc., FRCPC University Health Network, University of Toronto
7:55 – 8:15 AM	Review of Clinical Data for Mitapivat in Sickle Cell Disease from Two Investigator-sponsored Studies	Mike Callaghan, M.D. Ahmar Zaidi, M.D.
8:15 – 8:30 AM	Elucidating the Burden of Pyruvate Kinase (PK) Deficiency and Long-term Clinical Data of Mitapivat in PK Deficiency	Sarah Gheuens, M.D., Ph.D.
8:30 – 9:00 AM	Closing Remarks and Q&A	Presenters + Dr. Bruce Car, Richa Poddar

Cellular metabolism drove our start 14 years ago.

Our IDH work resulted in two precision oncology therapies within 10 years.

WE ARE FUELED BY CONNECTIONS

We increase our impact through strong bonds with patient communities, healthcare professionals, partners and colleagues.

We use collaboration, creativity and productivity to bring life-changing treatments for **genetically defined diseases.**

We are poised to expand our impact.

Our work in PK activation has yielded three proofs of concept with the potential to revolutionize treatment options for certain genetically defined diseases.

agios at-a-glance

FOUNDED	IPO	1ST APPROVED THERAPIES	HEADQUARTERS	PK ACTIVATION PROGRAMS
2008	July 2013	2017 & 2018	Cambridge, Mass.	Pyruvate Kinase Deficiency Thalassemia Sickle Cell Disease

We LISTEN to our PATIENTS and work WITH them to create solutions

TAMARA
Pyruvate Kinase Deficiency

SHARONDA
Sickle Cell Disease

RYAN
Thalassemia

We are the pioneering leaders in PK activation

STUDYING PK ACTIVATION IN THE CLINIC SINCE 2014

PIVOTAL CLINICAL PROGRAMS

- ENERGIZE
- ENERGIZE-T
- ACTIVATE
- ACTIVATE-T
- RISE UP

PUBLICATIONS

DISEASES WITH POC ACHIEVED

- PK Deficiency
- Thalassemia
- Sickle Cell Disease

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
- 1st CLINICAL TRIAL EVALUATING TREATMENT IN α-THALASSEMIA

Our Differentiated Approach to Clinical Development

Dr. Sarah Gheuens, Chief Medical Officer

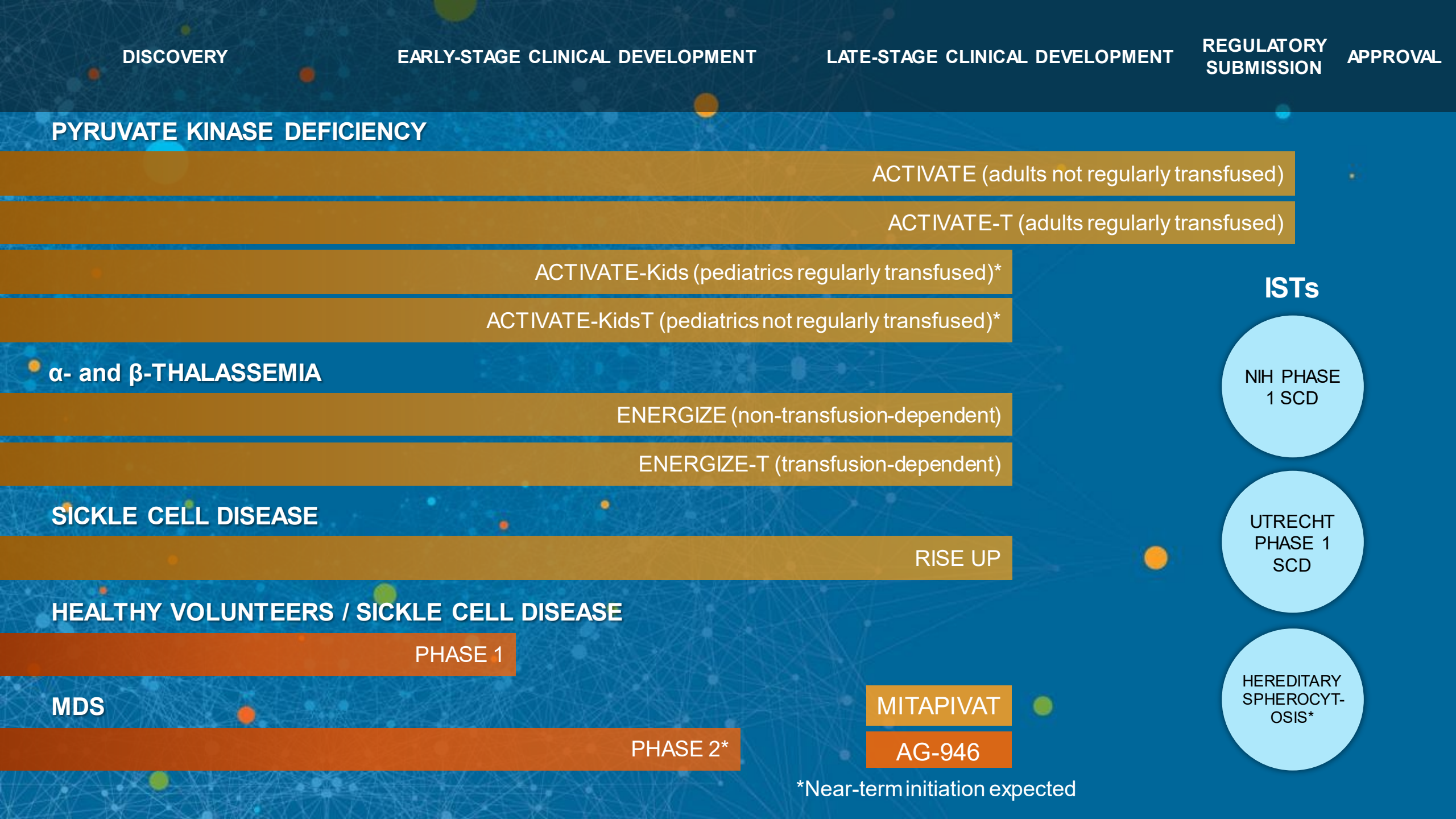
What you'll hear today

01 We pioneered PK activation clinical development with a differentiated approach to global development and community partnerships

02 Extension data for mitapivat highlight long-term safety profile and durable improvement in hemoglobin and markers of hemolysis in thalassemia patients for up to 72 weeks

03 Data from investigator-led studies of mitapivat in adults with sickle cell disease underscore potential of mitapivat to improve clinically meaningful outcomes for patients, including anemia, hemolysis and sickling parameters

04 Long-term extension data demonstrate durability of hemoglobin response, transfusion burden reduction, and improvement in ineffective erythropoiesis and iron overload in adults with pyruvate kinase (PK) deficiency


DISCOVERY
EARLY-STAGE CLINICAL DEVELOPMENT
LATE-STAGE CLINICAL DEVELOPMENT
REGULATORY SUBMISSION
APPROVAL
PYRUVATE KINASE DEFICIENCY
ACTIVATE (adults not regularly transfused)
ACTIVATE-T (adults regularly transfused)
ACTIVATE-Kids (pediatrics regularly transfused)*
ACTIVATE-KidsT (pediatrics not regularly transfused)*
α- and β-THALASSEMIA
ENERGIZE (non-transfusion-dependent)
ENERGIZE-T (transfusion-dependent)
SICKLE CELL DISEASE
RISE UP
HEALTHY VOLUNTEERS / SICKLE CELL DISEASE
PHASE 1
MDS
PHASE 2*
MITAPIVAT
AG-946
ISTs
NIH PHASE 1 SCD
UTRECHT PHASE 1 SCD
HEREDITARY SPHEROCYT-OSIS*
*Near-term initiation expected

Our differentiated approach to clinical development

Global Reach

Solicit regulatory feedback on trial designs from the U.S. and the EU at the same time

Site selection focused on going where the patients are

Remove barriers for clinical trial participation by listening to patients all over the world

Top-notch Team

Broad industry experience throughout all levels of the clinical organization

Medical team includes academic physicians with detailed knowledge of the disease states

Where science meets heart

Extensive Network

Focus on fostering meaningful connections with the patient community

Strong ties to top KOLs across all disease states

Name recognition across industry and academia with Agios' 10+ years in hematology

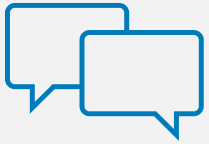
Input from sickle cell and thalassemia communities helped to shape and validate our study designs for these indications

Enrollment criteria

- Inclusion of α- and β-thalassemia patients
- Inclusion of non-regularly and regularly transfused patients in ENERGIZE/ENERGIZE-T
- Allowing concomitant use of hydroxyurea and occasional transfusions in RISE UP
- Broad definitions of pain events and episodic transfusions in RISE UP

Study endpoints

- Relevant to show benefit across the entire thalassemia patient population
- Broad consensus from the SCD warriors who inputted, that pain and Hb are the two most important endpoints for them
- Inclusion of patient-reported outcome measures in the study was highlighted as important by both communities

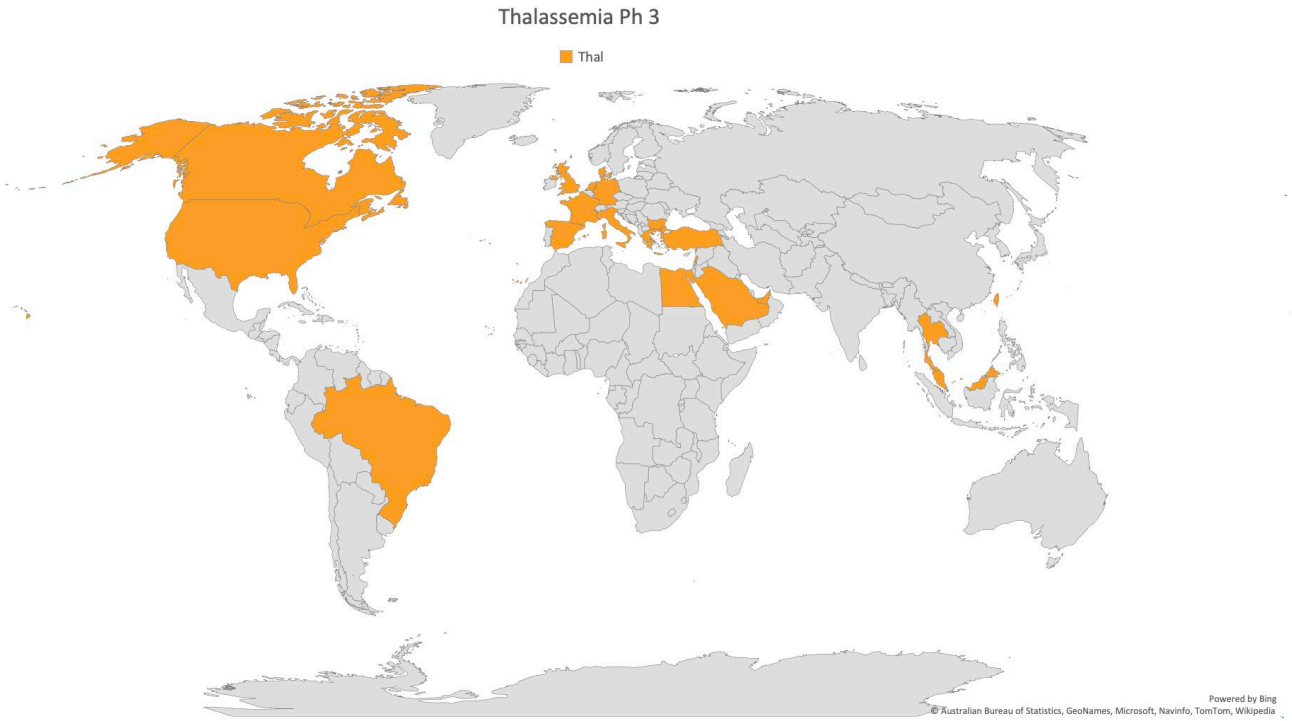


Visits and assessments

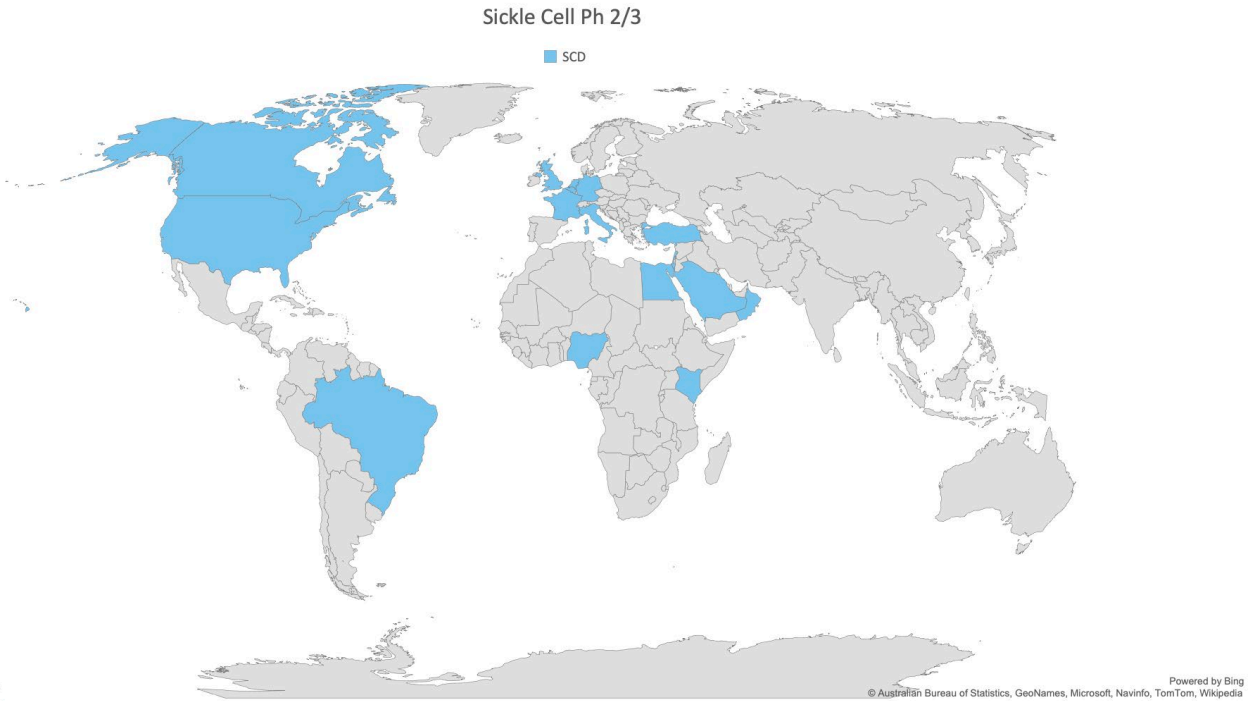
- We aim to provide flexibility and support – giving participants the option of home visits, in-person center appointments, and tele-medicine appointments wherever possible

We are leading the way in global site engagement

ENERGIZE ENERGIZE-T



RISE UP



Our clinical focus is to transform the course of hemolytic anemia by increasing red blood cell **ENERGY, HEALTH** and **LONGEVITY**

In PK deficiency, thalassemia and sickle cell disease, RBCs have:

- Insufficient energy
- Increased oxygen radical injury
- Abnormal RBC shape changes

- Chronic fatigue, iron overload
- Challenges with social, emotional health
- Challenges with school and work activities
- Potentially serious complications

All of these hemolytic anemias cause major complications and impact patient quality of life

Long-Term Efficacy and Safety of the Oral Pyruvate Kinase Activator Mitapivat in Adults with Non–Transfusion-Dependent Alpha- or Beta-Thalassemia

Dr. Kevin Kuo, University Health Network, University of Toronto

Background – thalassemia

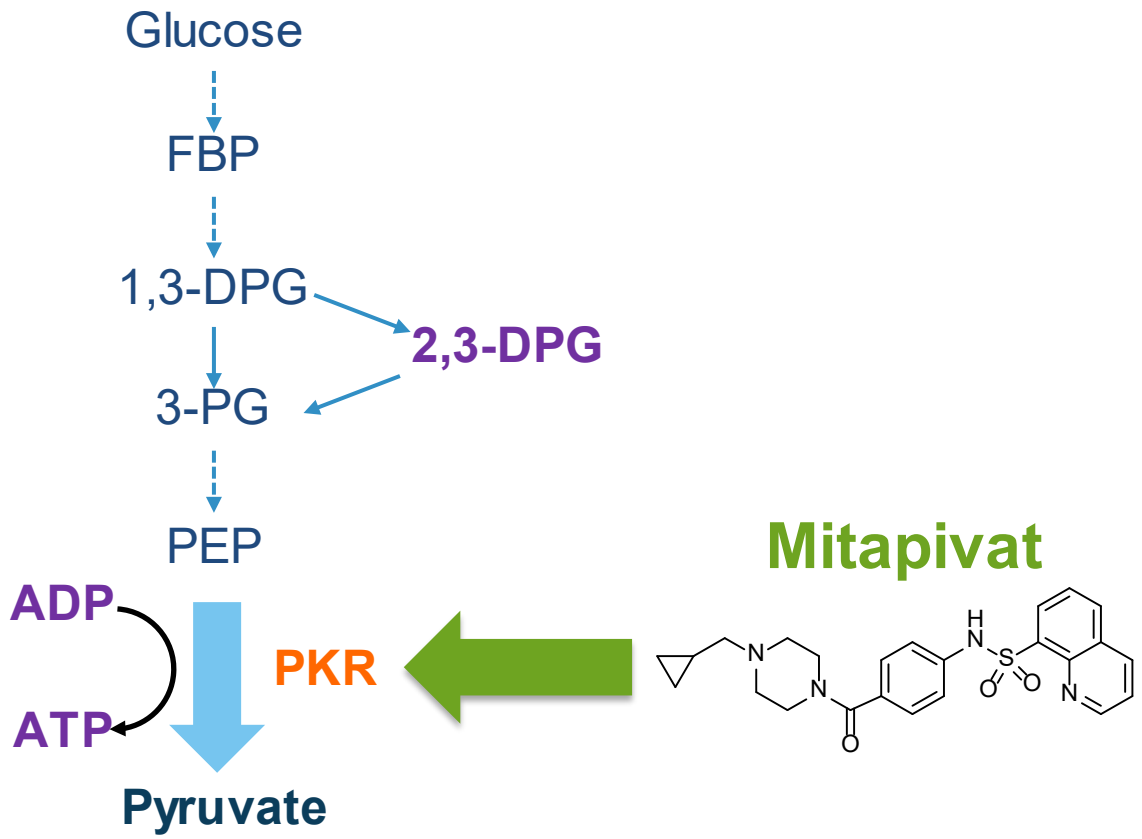
- Thalassemia is a red blood cell (RBC) disorder in which ineffective erythropoiesis and hemolysis occur due to imbalanced globin production and precipitation of excess globin chains[1,2]
- Thalassemic RBCs have insufficient levels of ATP to meet increased energy demands associated with globin chain precipitation, protein degradation, and cellular oxidative stress responses[3,4]
- Thalassemia can result in complications including[1,2]
  - Anemia, bone marrow expansion, extramedullary hematopoiesis, osteoporosis and bone deformities, iron overload, gallstones, and splenomegaly
- Treatment options for non-transfusion-dependent thalassemia (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 RBC pyruvate kinase (PKR), a key glycolytic enzyme that regulates ATP production[6]

ATP = adenosine triphosphate; NTDT = non–transfusion-dependent thalassemia; PKR = RBC-specific form of pyruvate kinase; RBC = red blood cell.

1. Taher AT et al. *Lancet* 2018;391:155–67. **2.** Galanello et al. *Ophanet 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 – proposed mitapivat mechanism of action in thalassemia

Mitapivat activates wild-type and mutant PKR[1] and increases RBC ATP levels[2]

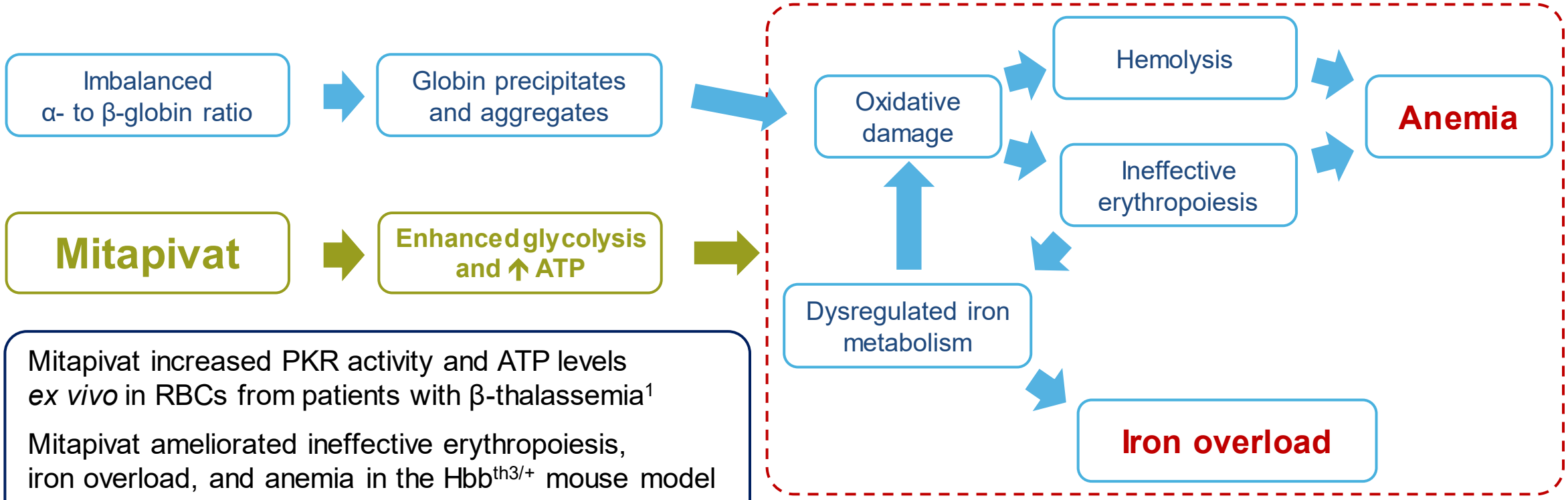


- Mitapivat activates PKR, which catalyzes the final step of glycolysis in RBCs[1]
- ATP generation is essential for RBC function and stability[2,3]

ADP = adenosine diphosphate; ATP = adenosine triphosphate; DPG = diphosphoglyceric acid; FBP = fructose 1,6–bisphosphate; PEP = phosphoenolpyruvic acid; PG = phosphoglyceric acid; PKR = RBC-specific form of pyruvate kinase; RBC = red blood cell.

1. Yang H et al. *Clin Pharmacol Drug Dev* 2019;8:246–59. **2.** Kung C et al. *Blood* 2017;130:1347–56. **3.** Valentini G et al. *J Biol Chem* 2002;277:23807–14.

Background – proposed mitapivat mechanism of action in thalassemia



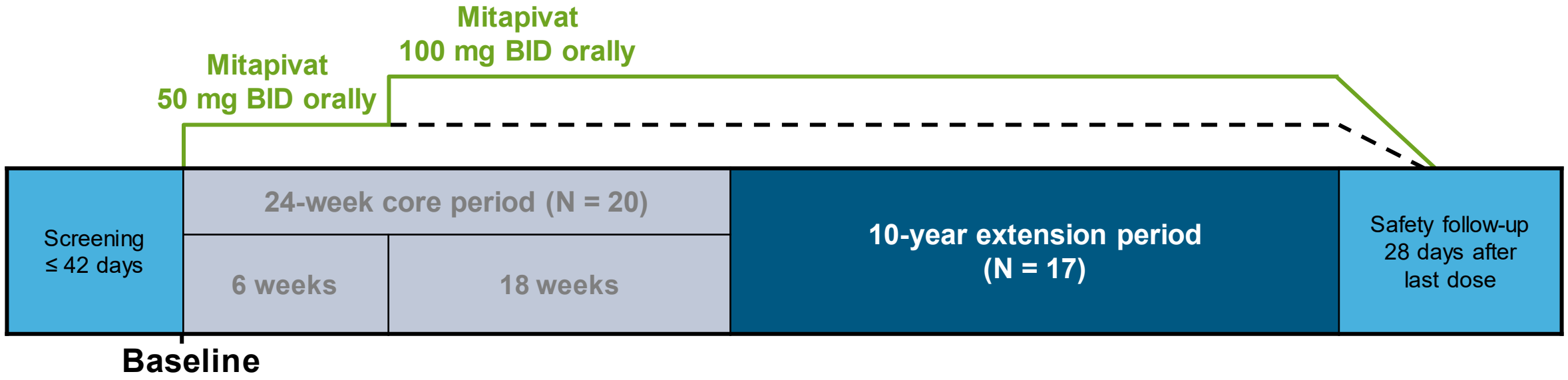
Mitapivat increased PKR activity and ATP levels *ex vivo* in RBCs from patients with β-thalassemia[1]

Mitapivat ameliorated ineffective erythropoiesis, iron overload, and anemia in the $Hbb^{th3/+}$ mouse model of β-thalassemia[2]

ATP = adenosine triphosphate; PKR = RBC-specific form of pyruvate kinase; RBC = red blood cell.

1. Rab MAE et al. *ASH Annual Congress* 2019; Abstract 3506. **2.** Matte A et al. *J Clin Invest* 2021;131:e144206.

Design of phase 2 study of mitapivat in adults with α- or β-NTDT[a]



Core period[1] – key inclusion criteria

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

Long-term extension – key inclusion criteria

- Completed 24-week core period
- Achieved a primary Hb response, or achieved a delayed Hb response (Hb increase of ≥ 1.0 g/dL at ≥ 1 assessment after Week 12)
- No ongoing grade ≥ 3 treatment-emergent adverse events (TEAEs) related to study drug

[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; RBC = red blood cell; TEAE = treatment-emergent adverse event. **1.** Kuo KHM et al. *EHA Annual Congress* 2021; Oral presentation S26.

Phase 2, open-label trial of mitapivat in adults with α- or β-NTDT[a]

Results from core period (previously presented)[1]

- The primary endpoint of Hb response was met in 80.0% (16/20) of patients
  - Hb response defined as: ≥ 1.0 g/dL increase in Hb concentration from baseline at 1 or more assessments between Weeks 4–12, inclusive
- Improvements in markers of hemolysis and ineffective erythropoiesis were also observed
- Mean ATP percent increase from baseline was similar to that previously observed with mitapivat in healthy volunteers
- Mitapivat was generally well tolerated, and the safety profile was consistent with that of previously published mitapivat studies

Long-term extension period

Here, we report on long-term efficacy and safety of mitapivat in patients who continue treatment in the ongoing extension period (up to Week 72; data cutoff 27Mar2021)

Change in Hb from baseline

Markers of hemolysis

Markers of ineffective erythropoiesis

Safety

[a]EudraCT 2018-002217-35, ClinicalTrials.gov: NCT03692052.
ATP = adenosine triphosphate; Hb = hemoglobin; NTDT = non–transfusion-dependent thalassemia; PKR = RBC-specific form of pyruvate kinase.
1. Kuo KHM et al. *EHA Annual Congress 2021*; Oral presentation S267.

Patient demographics and baseline[a] characteristics for patients who entered the long-term extension period

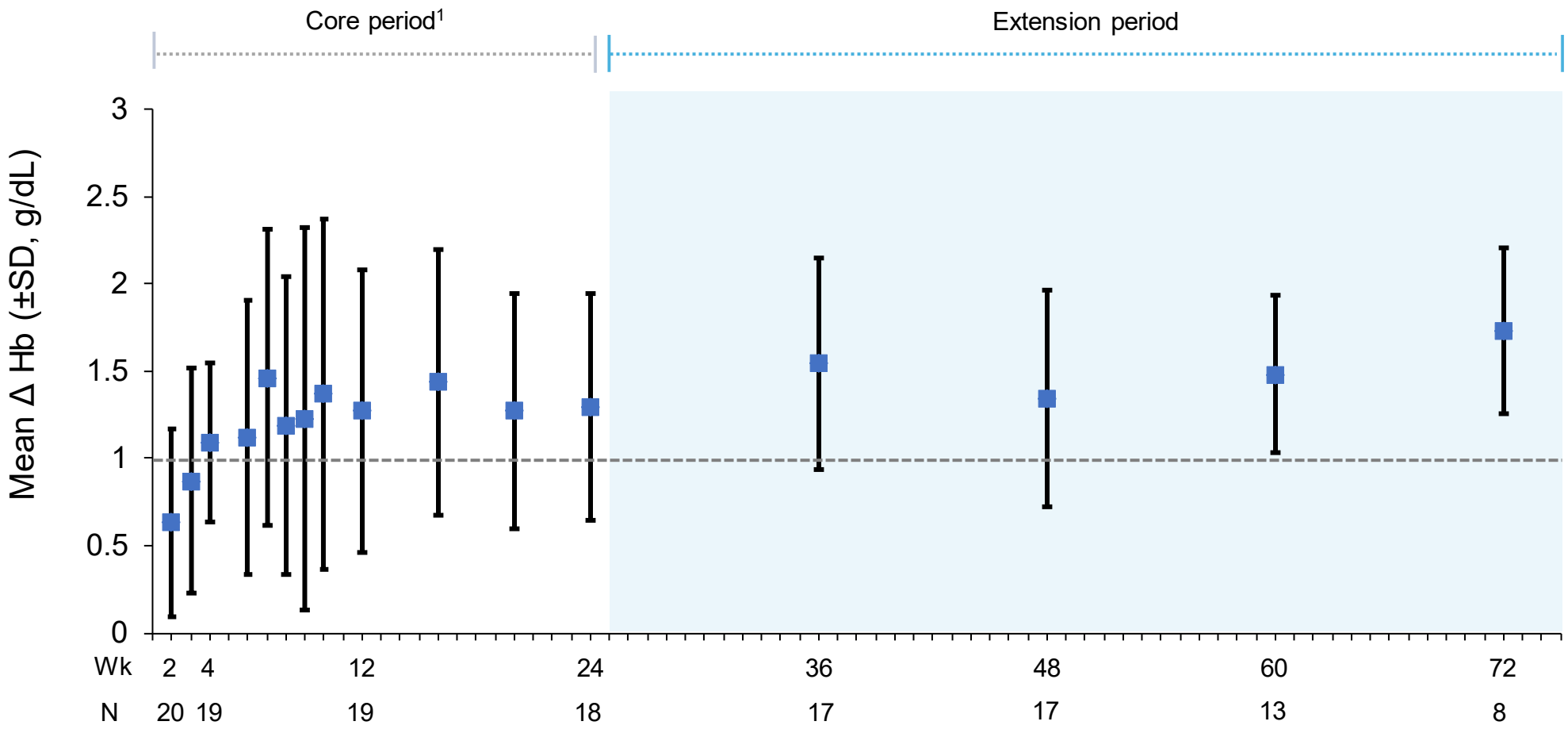
Patient demographics and baseline[a] characteristics	All patients (N = 17)	
Median (range) duration of treatment, weeks	70.9	(54.7, 105.6)
Sex, n (%)		
Male	5	(29.4)
Female	12	(70.6)
Age, median (range), years	44	(29, 67)
Race, n (%)		
Asian	8	(47.1)
White	4	(23.5)
Native Hawaiian or other Pacific Islander	1	(5.9)
Other	3	(17.6)
Not reported	1	(5.9)
Thalassemia type, n (%)		
α-thalassemia	4	(23.5)
β-thalassemia	13	(76.5)
Hb baseline, median (range), g/dL	8.5	(5.6, 9.8)
Total bilirubin, median (range), µmol/L	32.0	(8.6, 90.0)
LDH, median (range), U/L	245.0	(126.0, 513.0)
Erythropoietin, median (range), IU/L	70.5	(15.0, 11191.0)

Genotype	Patients (N = 16)[b]	
β-thalassemia, n (%)		
Intermedia	5	(26.7)
Intermedia + α duplication	3	(20.0)
Heterozygote/phenotypic β-thalassemia intermedia	2	(13.3)
HbE/β-thalassemia, n (%)		
HbE/β^0	2	(13.3)
α-thalassemia, n (%)		
Deletional	1	(6.7)
Non-deletional	3	(20.0)

[a]Baseline is defined as the last assessment on or before the start of study treatment in core period; [b]17 patients entered the extension, genotype data are unknown for 1 patient.
BID = twice daily; Hb = hemoglobin; HbE = hemoglobin E; IU = international units; LDH = lactate dehydrogenase; SD = standard deviation; U = units.

Durable improvements in Hb concentration were observed in the extension period

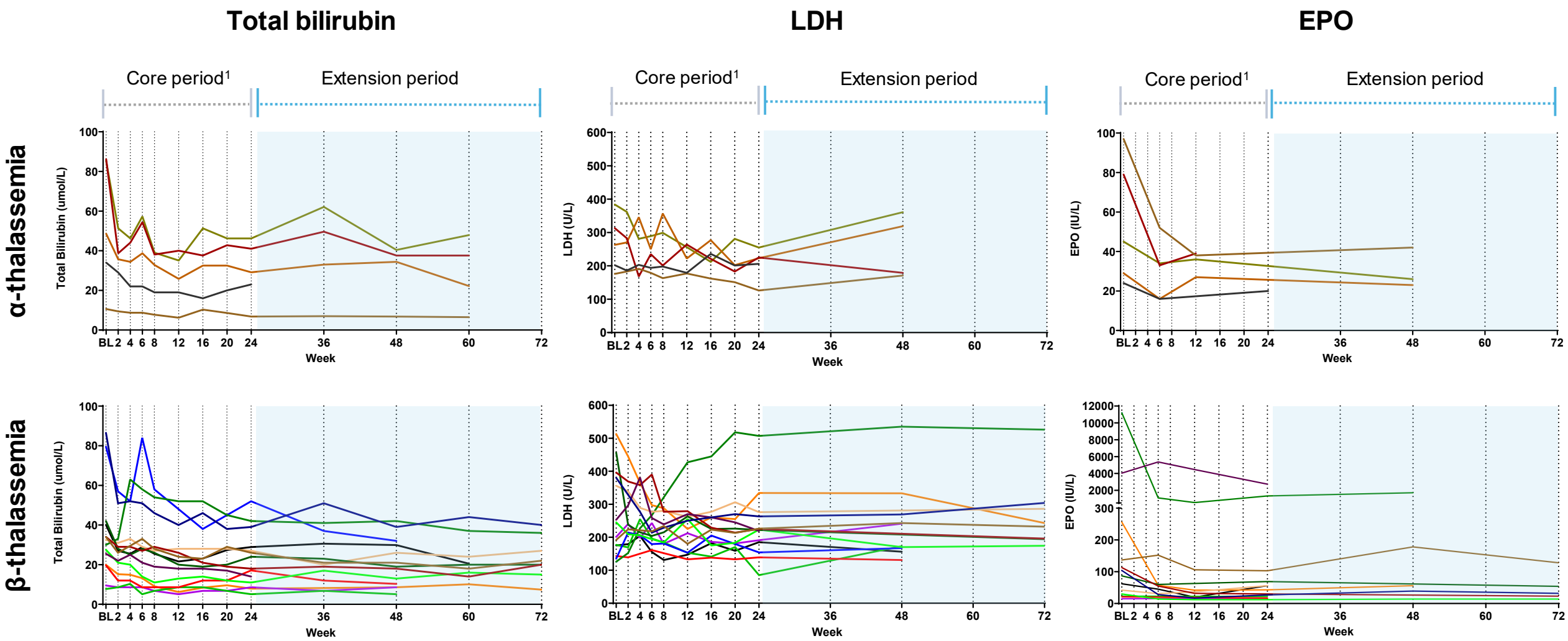
Mean Hb change from baseline over time



Hb = hemoglobin; SD = standard deviation; Wk = week; Δ = change.

1. Kuo KHM et al. *EHA Annual Congress 2021;* Oral presentation S267.

Improvements in markers of hemolysis and ineffective erythropoiesis observed in the core period were maintained in the extension period up to Week 72



EPO = erythropoietin; IU = international units; LDH = lactate dehydrogenase; SD = standard deviation; U = units.

1. Kuo KHM et al. *EHA Annual Congress 2021;* Oral presentation S267.

Safety summary for the core and extension periods

Category	Core period, n (%)[1] (N = 20) Weeks 0–24	Extension period, n (%)[a] (N = 17)[b] Weeks 25–72
Treatment-related TEAEs	13 (65.0)	2 (11.8)
Grade ≥ 3 TEAEs	5 (25.0)	2 (11.8)
Grade ≥ 3 treatment-related TEAEs	1 (5.0)	0
Serious TEAEs	1 (5.0)	2 (11.8)
TEAEs leading to study drug:		
Dose reduction	3 (15.0)	1 (5.9)
Interruption	1 (5.0)	0
Discontinuation	1 (5.0)[c]	1 (5.9)[c]

- The majority of events occurred earlier in the study and were transient in nature
- There were no treatment-related serious AEs during the extension period

[a]TEAEs listed in the extension period are new AEs that occurred after entering the extension period; [b]16 patients received 100 mg BID mitapivat and 1 received 50 mg BID; [c]1 patient discontinued during the core period as a result of an AE. One further patient discontinued during the extension period (patient decision) as of the cutoff date (27Mar2021).
AE = adverse event; TEAE = treatment-emergent adverse event. **1.** Kuo KHM et al. *EHA Annual Congress 2021;* Oral presentation S267.

The safety profile was consistent with that observed during the core period

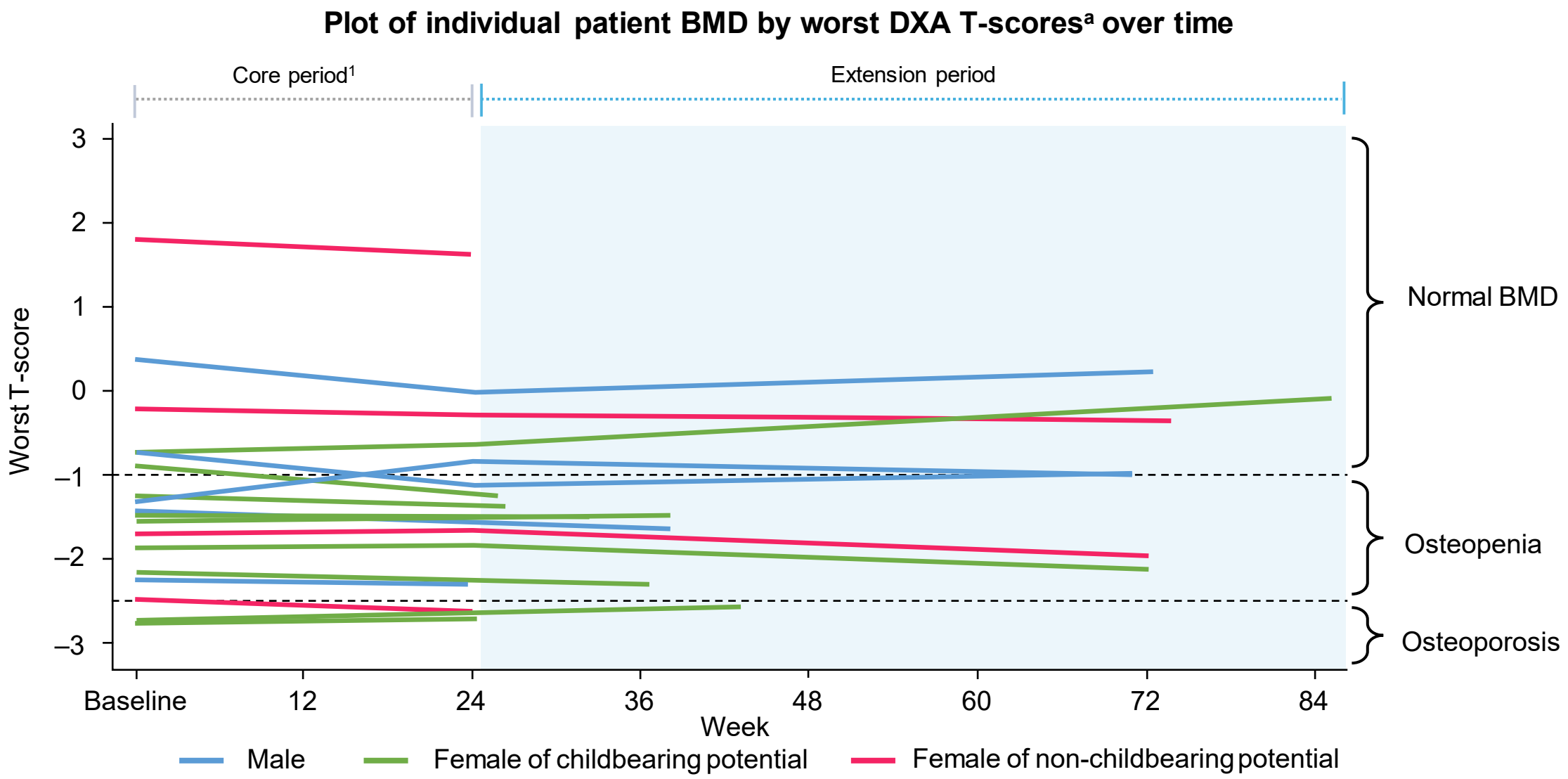
Most common TEAEs (any grade in ≥ 15% of patients)	Core period (N = 20)[1] Weeks 0–24	Extension period (N = 17)[a] Weeks 25–72
	Any grade, n (%)	Any grade, n (%)
Patients with events	17 (85.0)	13 (76.5)
Initial insomnia	10 (50.0)	0
Dizziness	6 (30.0)	1 (5.9)
Headache	5 (25.0)	5 (29.4)
Cough	4 (20.0)	0
Dyspepsia	4 (20.0)	1 (5.9)
Fatigue	4 (20.0)	0
Nasal congestion	4 (20.0)	0
Upper respiratory tract infection	4 (20.0)	0
Abdominal pain	3 (15.0)	1 (5.9)
Diarrhea	3 (15.0)	2 (11.8)
Ocular icterus	3 (15.0)	0
Pain	3 (15.0)	0
Pain in extremity	3 (15.0)	2 (11.8)
Abdominal distension	3 (15.0)	0
Nausea	3 (15.0)	1 (5.9)
Oropharyngeal pain	3 (15.0)	0
Back pain	2 (10.0)	3 (17.6)

- AEs occurring in ≥ 15% of patients during the extension period were headache (5/17) and back pain (3/17), none of which were grade ≥ 3
- No new safety findings were reported in the extension period

[a]TEAEs listed in the extension period are new AEs that occurred after entering the extension period.
AE = adverse event; TEAE = treatment-emergent adverse event.

1. Kuo KHM et al. *EHA Annual Congress 2021;* Oral presentation S267.

No trends for decreases in bone mineral density (BMD) were observed



[a]Adjusted spine and femoral total were used to determine worst DXA T-scores; assessed at baseline, Week 24, and Week 72.
BMD = bone mineral density; DXA = Dual-energy X-ray absorptiometry.

Conclusion

- A favorable efficacy-safety profile was observed with long-term treatment with mitapivat in patients with either α- or β-thalassemia
- Consistent and durable improvements in Hb concentration, and markers of hemolysis and ineffective erythropoiesis, were observed with up to 72 weeks of treatment in a cohort with heterogeneity of globin genotypes
- There were no new safety findings
  - BMD remained stable over time
- Mitapivat, through its unique mechanism of action, may represent a novel therapeutic approach for this condition
- Two phase 3 trials of mitapivat in α- and β-thalassemia, one in patients who are non-transfusion-dependent (ENERGIZE; NCT04770753) and one in patients who are transfusion-dependent (ENERGIZE-T; NCT04770779), are enrolling

BMD = bone mineral density; Hb = hemoglobin.

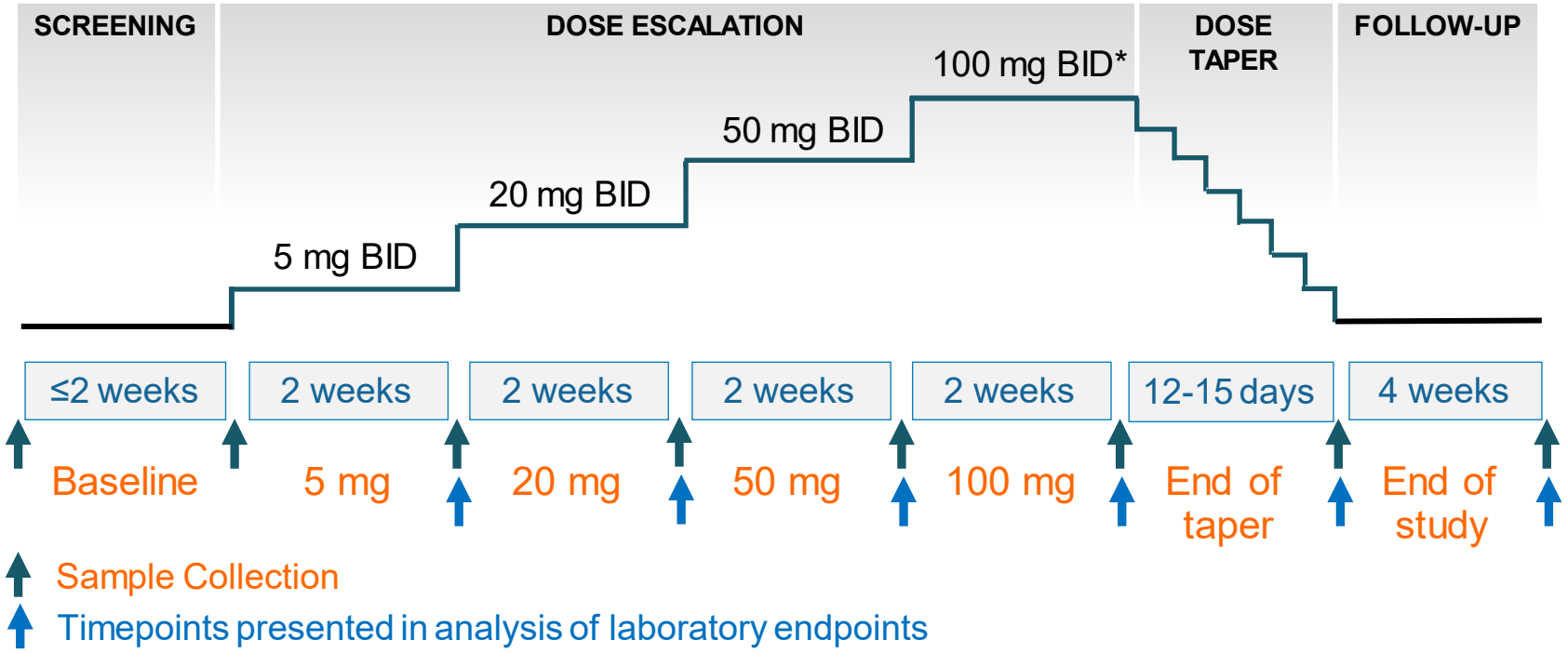
Q&A

NIH Phase 1 Mitapivat SCD Study

Dr. Ahmar Zaidi, Medical Director

Study Design of Mitapivat Dose Escalation Study in SCD

- Nonrandomized, open-label, Phase 1 study; N =17
- Adults (age ≥ 18 years) with stable Hb SS disease eligible
- No transfusions or changes in hydroxyurea/L-glutamine within 90 days



Primary endpoints:

- Safety and tolerability
- Changes in Hb and hemolytic markers

Secondary endpoints:

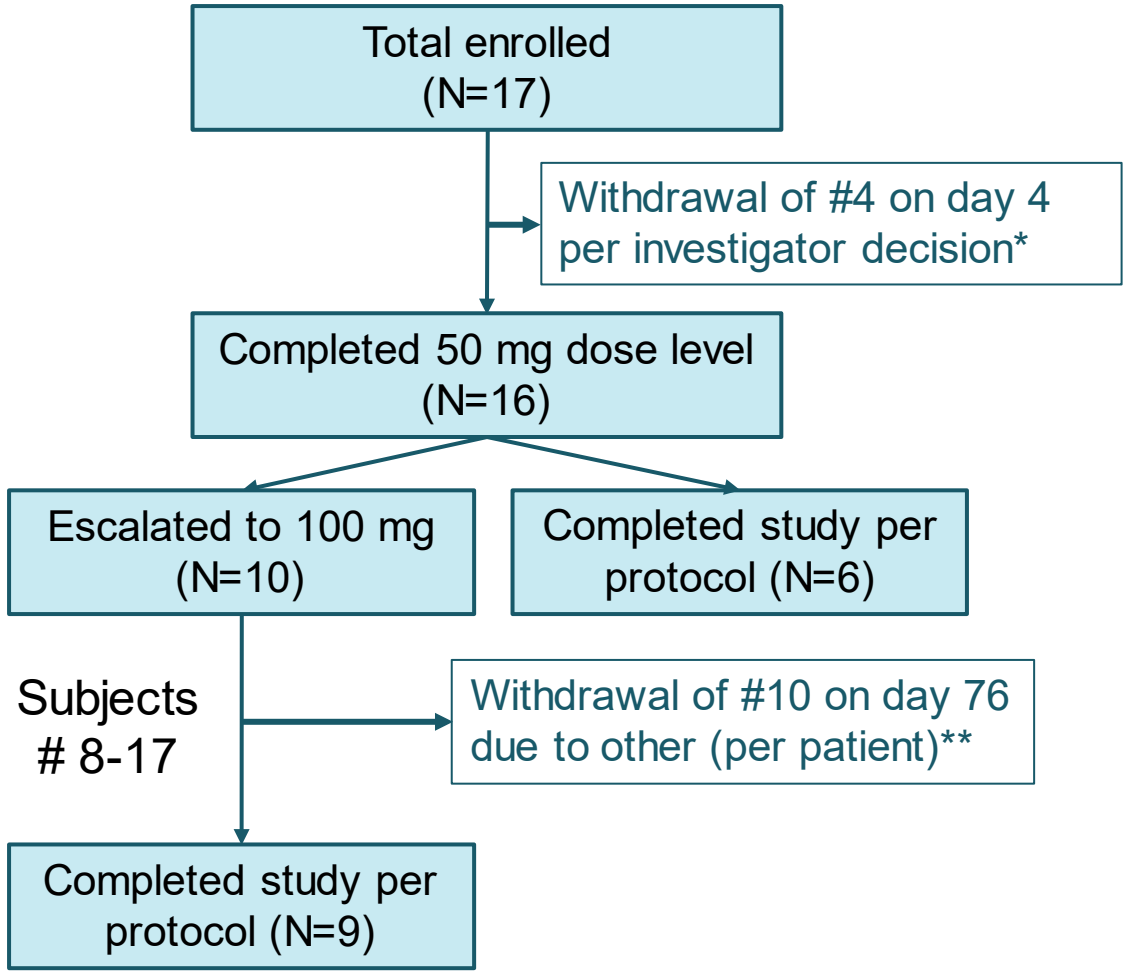
- Pharmacokinetics
- 2,3-DPG and ATP levels
- p50 (O_2 affinity) and t50 (HbS polymerization)

*100 mg dose level added to protocol with amendment #6.

ATP, adenosine triphosphate; BID, twice daily; DPG, diphosphoglycerate; Hb, hemoglobin.

Demographics, Disease Characteristics, and Disposition

Baseline Characteristics at Enrollment	N=17
Age, mean (range), years	39 (23-55)
Male, N (%)	11 (64.7)
African or African-American, N (%)	17 (100)
Hydroxyurea use, N (%)	12 (70.6)
L-glutamine use, N (%)	1 (5.9)
Baseline Laboratory Measures	**N=16***
Hemoglobin, mean (SD), g/dL	9.2 (1.1)
Abs reticulocyte count, mean (SD), K/μL	188.2 (99.2)
Total bilirubin, mean (SD), mg/dL	2.0 (0.9)
Lactate dehydrogenase, mean (SD), U/L	375.2 (120.6)
Hemoglobin F % by HPLC, mean (SD), %	19.0 (9.8)



* #4 withdrawn due to need for medical interventions for an AE unrelated to drug and lost to follow-up; not evaluable for laboratory response.
** #10 self-discontinued therapy prior to completing 100 mg dose level due to an AE unrelated to drug; analyzed with 50 mg dose cohort.
AE, adverse event; Abs, absolute; HPLC, high-performance liquid chromatography; SD, standard deviation.

Mitapivat is Safe and Tolerable for SCD Patients

Treatment Related Adverse Events (AEs)*	N=17 (%)	
	All Grades (≥ 10%)	Grade ≥ 3
All	**8 (47.1%)**	**3 (17.6%)**
Insomnia	6 (35.3%)	0 (0%)
Arthralgia	3 (17.6%)	0 (0%)
Hypertension	3 (17.6%)	1 (5.9%)
Vaso-occlusive crisis (VOC)	2 (11.8%)	2 (11.8%)
Headache	2 (11.8%)	0 (0%)
Heart rate increased	2 (11.8%)	0 (0%)
Anemia	-	1 (5.9%)
Fatigue	-	1 (5.9%)

Serious Adverse Events (SAEs)	N=17 (%)
All	**6 (35.3%)**
VOC	4 (23.5%)
Pain (shoulder)	1 (5.9%)
Pulmonary embolism (PE)**	1 (5.9%)

Summary of VOCs:

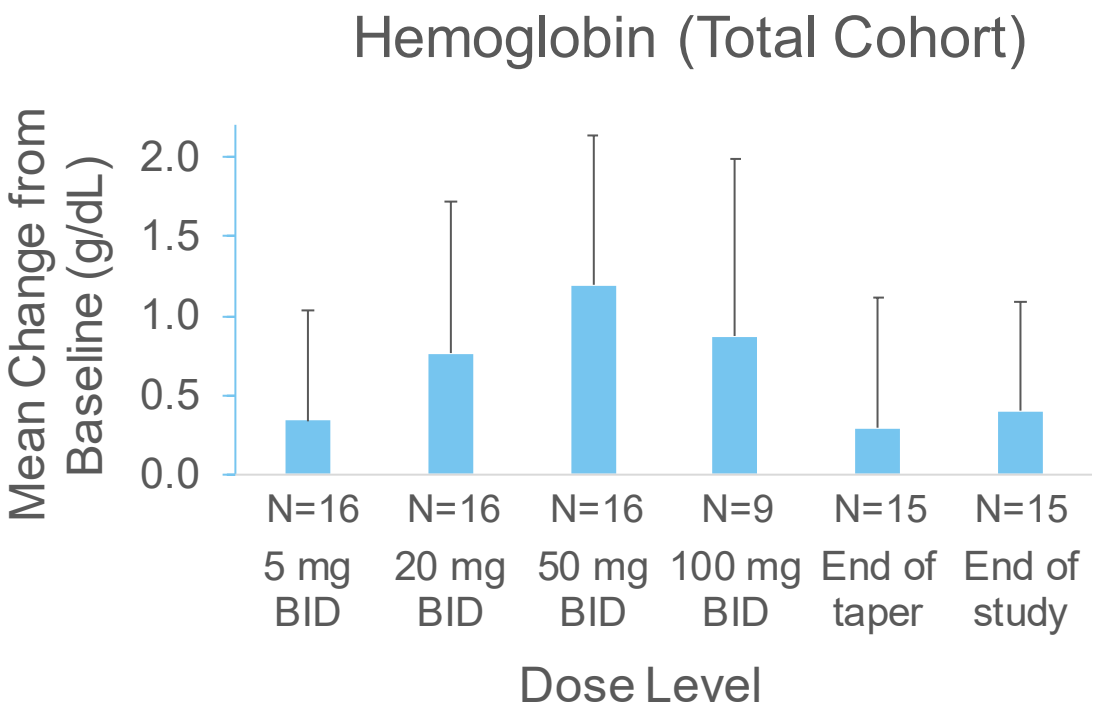
- No VOC during dose escalation
- 2 VOCs during drug taper† → possibly drug related
- 2 VOCs during 28-day safety follow-up in setting of known VOC triggers → unlikely drug related

Summary of other SAEs or Grade 3 AEs:

- No AEs requiring drug discontinuation
- Grade 3 hypertension in subject with baseline Grade 2 hypertension
- Anemia and fatigue in same patient following drug taper

* Defined as possibly, probably, or definitely related to study drug.
** Pre-existing PE discovered 4 days after study drug initiation; patient withdrawn (subject #4).
† First VOC on study triggered protocol amendment to extend length of taper.

Mitapivat Improves Anemia in SCD



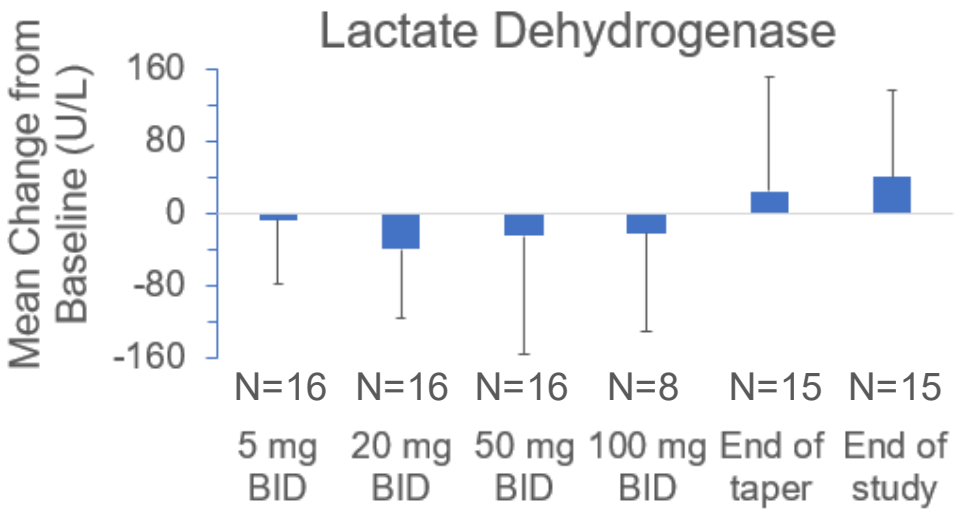
Linear mixed effects model with age and gender as covariates:

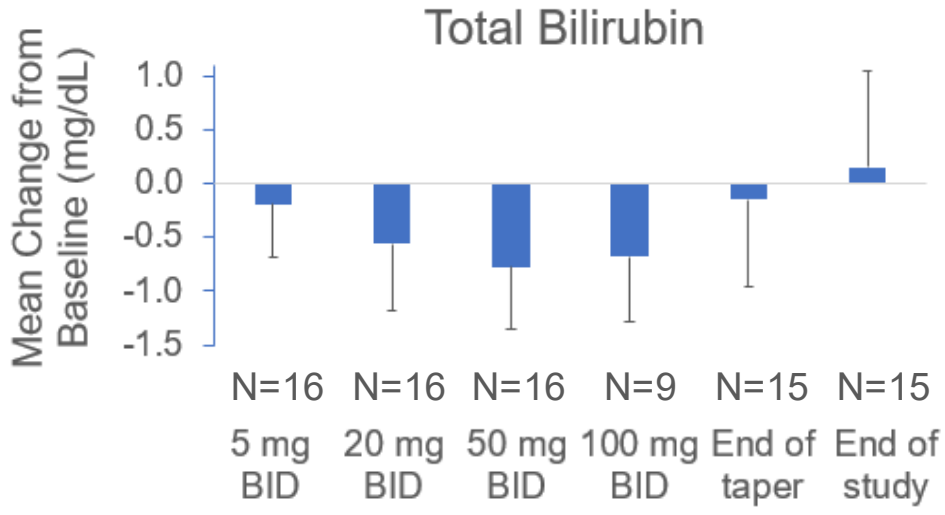
Variable	Value	SE	DF	t-value	p-value
Baseline	8.73	0.51	81	16.95	< 0.0001
5 mg BID	0.34	0.22	81	1.56	0.12
20 mg BID	0.76	0.22	81	3.53	0.0007
50 mg BID	1.19	0.22	81	5.5	< 0.0001
100 mg BID	0.92	0.26	81	3.52	0.0007
End of taper	0.34	0.22	81	1.52	0.13
End of study	0.37	0.22	81	1.7	0.09
Age	-0.02	0.03	13	-0.49	0.63
Male gender	0.68	0.6	13	1.13	0.28

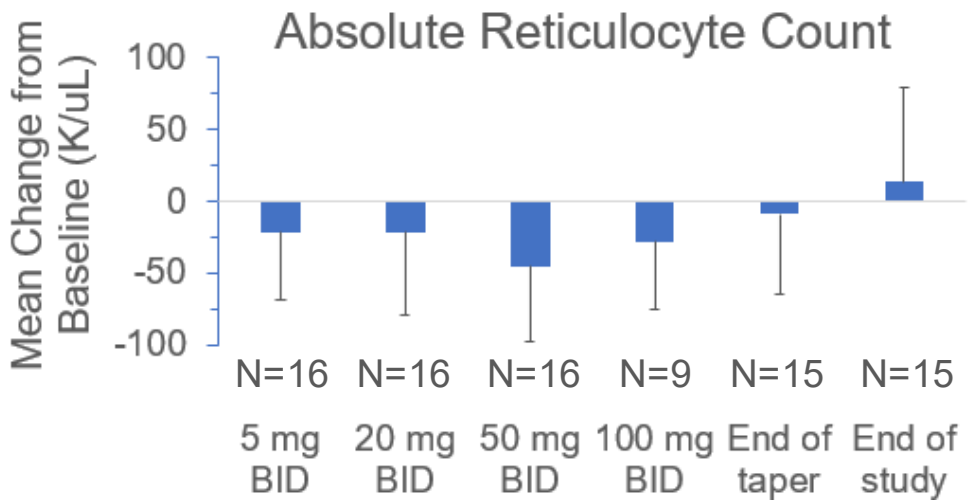
9/16 (56.3%) achieved a Hb response (≥ 1g/dL increase from baseline)

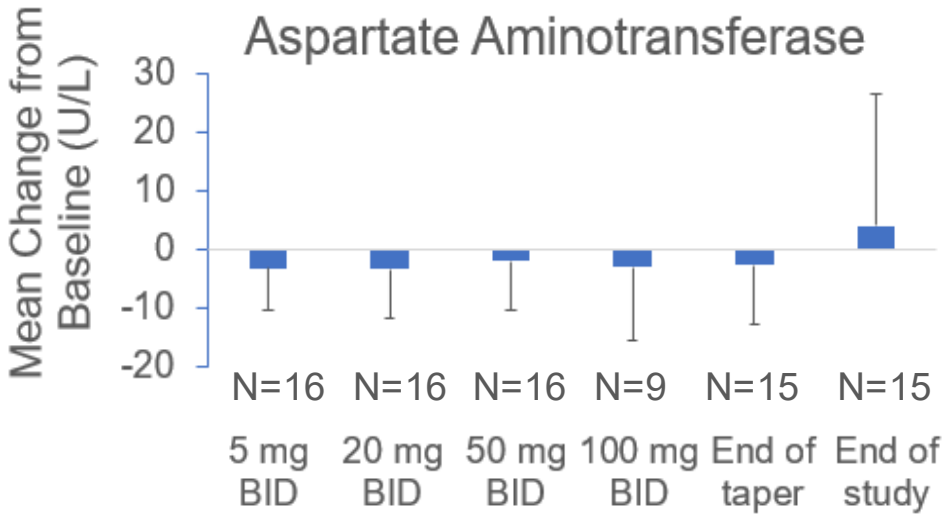
BID, twice daily; DF, degrees of freedom; Hb, hemoglobin; SE, standard error.

Mitapivat Decreases Markers of Hemolysis in SCD







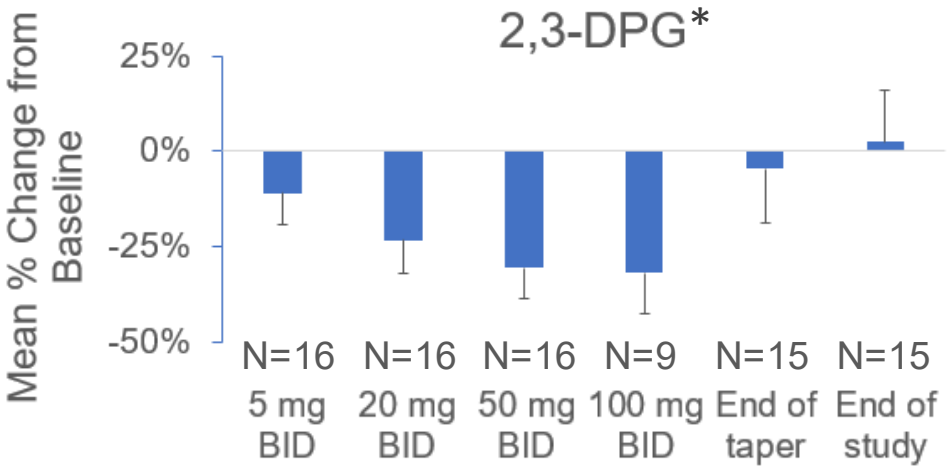


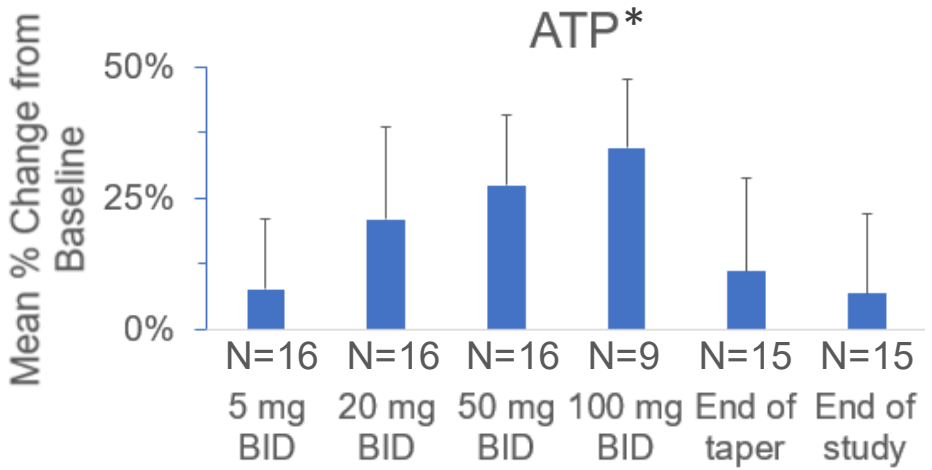
<u>Pharmacokinetics:</u>

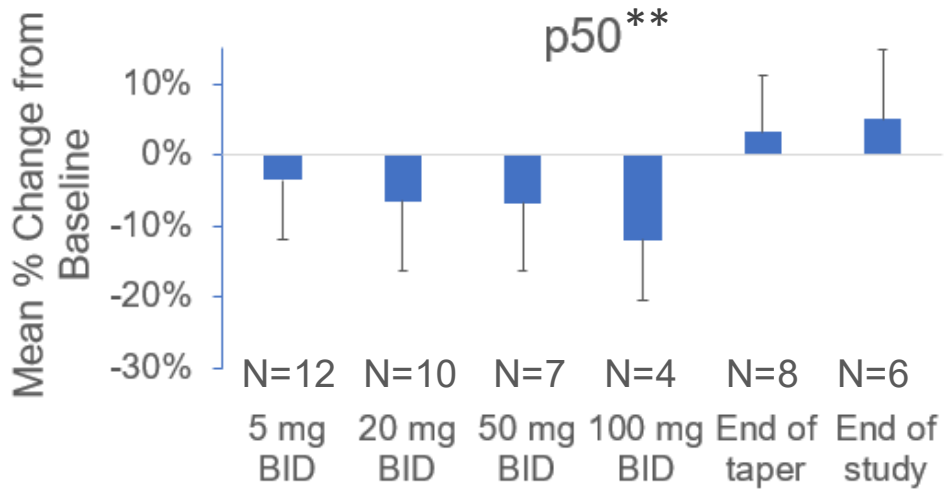
- Mitapivat exposure increased in a dose-proportional manner up to 50 mg
- ~20% reduction in exposure was observed following 14 days of multiple dosing with 100 mg BID compared to the first 100 mg dose administration

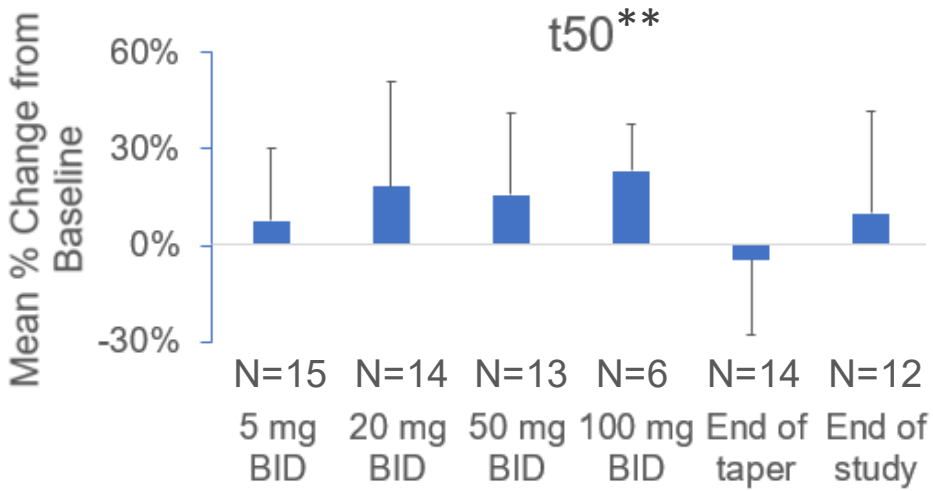
BID, twice daily.

PD Results Suggest Increased O2 Affinity and Slower Sickling









p50: partial pressure of O_2 at which 50% of hemes in Hb molecule have O_2 bound.

t50: time in minutes at which 50% of RBCs are sickled in response to gradual deoxygenation with nitrogen to final O_2 partial pressure of 38 torr.

* Percent changes in 2,3-DPG and ATP refer to intracellular concentrations, determined from whole blood concentrations divided by the hematocrit.
** Missing data are the result of disruptions related to the COVID-19 pandemic.
ATP, adenosine triphosphate; BID, twice daily; DPG, diphosphoglycerate; Hb, hemoglobin; O_2, oxygen; PD, pharmacodynamic.

Summary

- Mitapivat, an oral PKR activator, was safe and well tolerated at multiple ascending dose levels in subjects with SCD.
- Mitapivat reduced 2,3-DPG and increased ATP, with an expected increase in oxygen affinity and decrease in sickling rate, signaling its potential to improve clinically meaningful outcomes in SCD.
- This study provides proof of concept that mitapivat improves anemia and decreases hemolysis in SCD.
- Long-term disease modifying effects of mitapivat treatment in SCD are being evaluated in an ongoing extension study (ClinicalTrials.gov NCT04610866).
- Agios Pharmaceuticals is actively recruiting patients for their phase 2/3 clinical trial RISE UP (NCT05031780), evaluating safety and efficacy of mitapivat in SCD, including both hemoglobin response and frequency of sickle cell pain crises (ASH Abstract 3109).

Utrecht Phase 1 Mitapivat SCD Study - ESTIMATE

Dr. Mike Callaghan, Medical Director

Study Design

OBJECTIVE

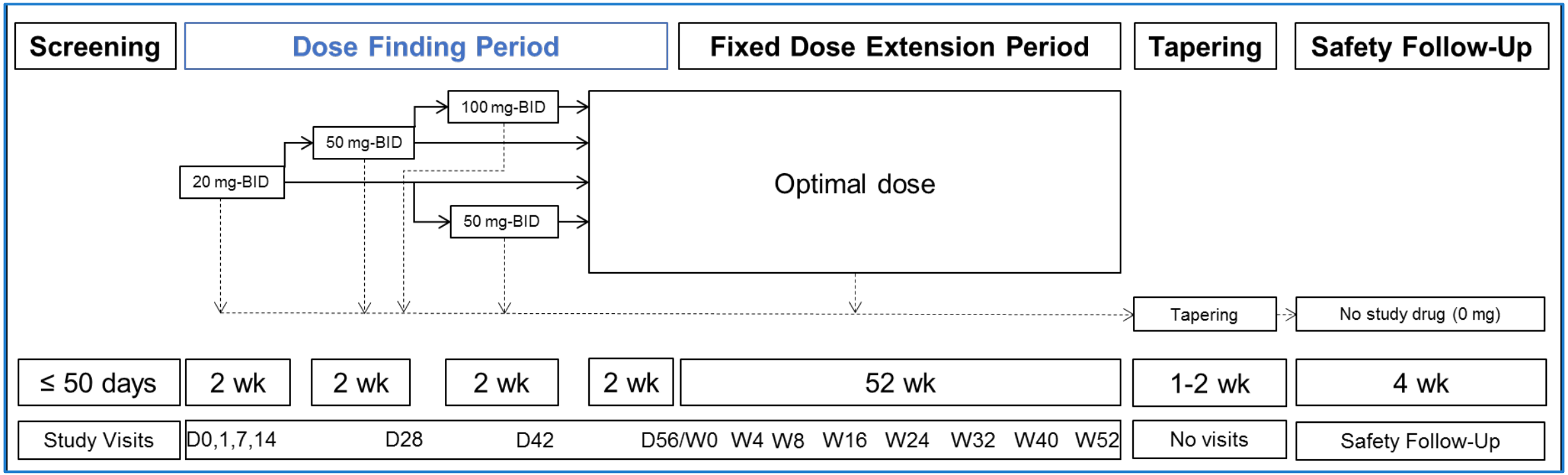
- To assess safety and provide proof of concept of the efficacy of mitapivat in subjects with SCD (ESTIMATE study, NTR NL8517)
- **Primary endpoints**: point of sickling (PoS), (serious) adverse events
- **Key secondary endpoints**: changes in Hb, 2,3-DPG and ATP levels, hemolysis parameters and surrogate markers of mortality and organ damage in SCD

MAJOR ELGIBILITY CRITERIA

- Subjects ≥16 years with SCD (HbSS, HbS/β0, HbS/β+) and prior SCD-related complications;
- Hb >6.1 g/dL and ≤11.1 g/dL;
- Stable dose of hydroxyurea;
- No chronic transfusion.

Study Design

Figure 2. Schema of the ESTIMATE study



STUDY STATUS

- We report results of the 8-week dose finding period of this Dutch, phase 2, open label, monocenter pilot study

Baseline

ENROLLMENT

- Six subjects have been enrolled as of September 2020 and completed the dose finding period on mitapivat, all reaching 100 mg BID dosing

BASELINE CHARACTERISTICS

- 5/6 (83.3%) HbSS and 1/6 (16.7%) HbS/β0;
- Median age of 36 years (range 20-59);
- 4/6 (66.7%) were female;
- 5/6 (83.3%) concomitant use of hydroxyurea.

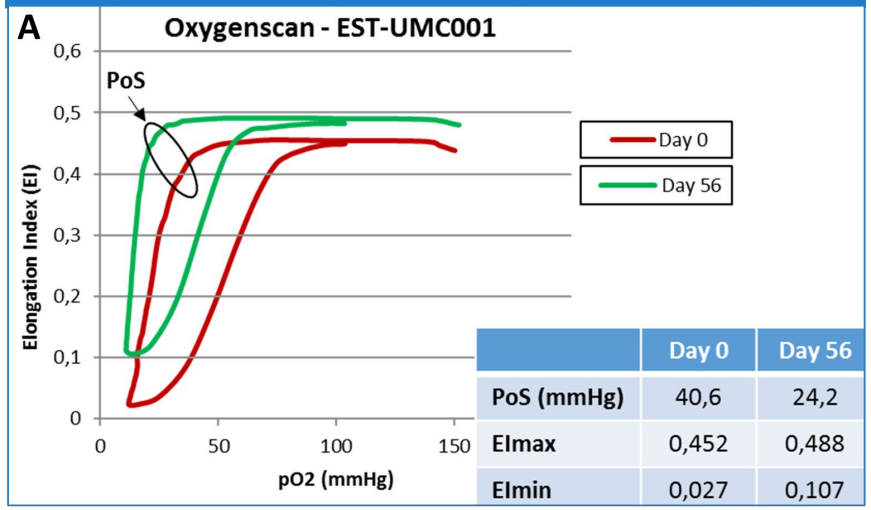
Safety Results

- No serious adverse events occurred
- Adverse events were mild (all Grade 1) and mostly transient with the most common (>n=1):
  - transaminase increase (n=3 [50.0%]);
  - gastrointestinal disorders (n=3 [50.0%]);
  - headache (n=3 [50.0%]).
- One vaso-occlusive crisis occurred without hospital admission and did not require dose reduction or discontinuation

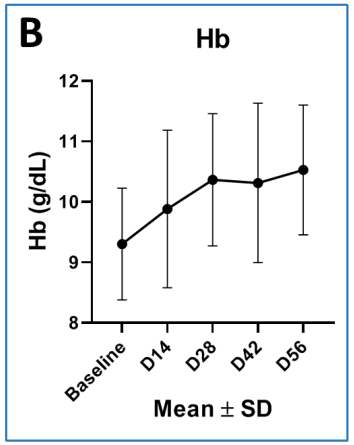
Efficacy Results

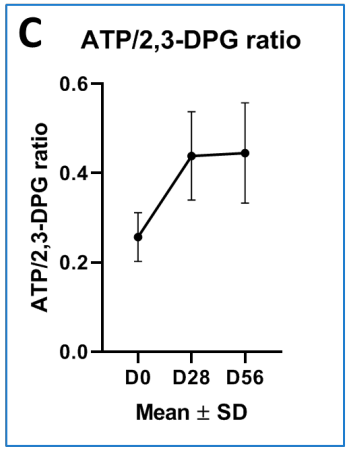
- All 6 subjects had improvements in point-of-sickling (PoS)
- 5/6 subjects (83.3%) achieved a Hb increase of ≥1 g/dL

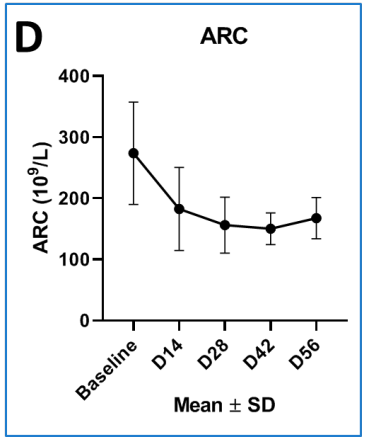
Figure 3A-F. Effects of mitapivat on sickling, hemoglobin, hemolysis and ATP/2,3-DPG assays

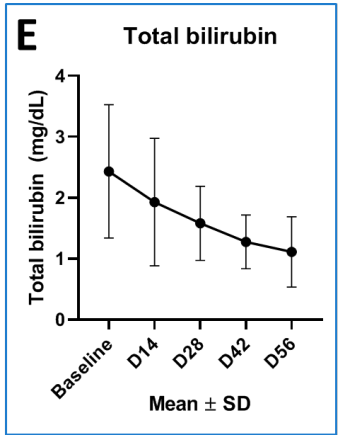


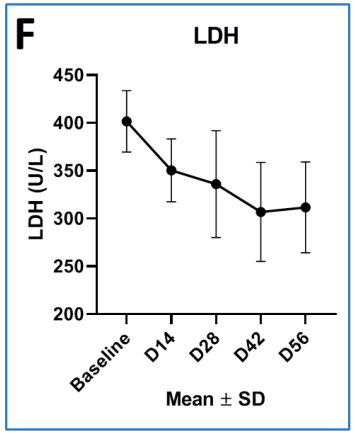
	Day 0	Day 56
PoS (mmHg)	40,6	24,2
EImax	0,452	0,488
EImin	0,027	0,107











Efficacy Results

Table 1. Mean response in sickling, hemoglobin, hemolysis, biochemical parameters and biomarkers at treatment day 56 compared to baseline in the dose finding period (n=6)

	Baseline	Day 56	
Sickling parameters			p-value*
PoS (mmHg)	40.3 (7.3)	31.3 (6.0)	**0.009**
p50 (mmHg)	22.7 (1.5)	20.9 (1.3)	**0.009**
Hemolysis parameters			
Hb (g/dL)	9.3 (0.9)	10.5 (1.1)	**0.004**
ARC (10^9/L)	274 (84)	168 (34)	**0.005**
RETC (%)	9.2 (1.5)	4.9 (0.8)	**0.001**
Bilirubin, total (mg/dL)	2.43 (1.09)	1.11 (0.58)	**0.004**
LDH (U/L)	402 (32)	312 (47)	**0.007**
Biochemical parameters			
2,3-DPG (10^3 µg/gHb)	11.5 (1.1)	8.1 (1.3)	**0.001**
ATP (10^3 µg/gHb)	3.0 (0.9)	3.5 (0.6)	0.173
ATP/2,3-DPG ratio	0.26 (0.05)	0.45 (0.11)	**0.003**
Biomarkers			
Albumin-to-creatinine ratio (mg/g)†	35.0 (23.7)	18.2 (17.9)	**0.010**
CRP (mg/L)	6.5 (5.1)	8.3 (3.4)	0.359
NT-proBNP (pg/mL)	83 (44)	68 (44)	0.299
VWF-antigen (%)	215 (70)	179 (82)	0.160
D-dimer (ng/mL)	2062 (1774)	1603 (1010)	0.549
LDH/HbCO ratio†	2531 (1247)	2663 (874)	0.812

Data are presented as mean (standard deviation) for baseline and treatment day 56 results (n=6). *Paired t-tests or Wilcoxon signed-rank tests are used when appropriate. †Results based on n=5. In one subject, albumin-to-creatinine ratio could not be calculated because of too high total protein, with a protein-to-creatinine ratio of 865 mg/g at baseline and 824 mg/g at day 56 (reduction of 41 mg/g). PoS point of sickling; p50 oxygen pressure at an oxygen saturation of 50%; Hb hemoglobin; ARC absolute reticulocyte count; RETC reticulocytes; LDH lactate dehydrogenase; 2,3-DPG 2,3-diphosphyglycerate; ATP adenosine triphosphate; CRP C-reactive protein; NT-proBNP N-terminal pro-brain natriuretic peptide; VWF Von Willebrand Factor; HbCO carboxyhemoglobin; ACR, albumin-to-creatinine ratio.

- Sickling, hemoglobin, hemolysis, biochemical and renal parameters all improved (**Table 1**)

Conclusion

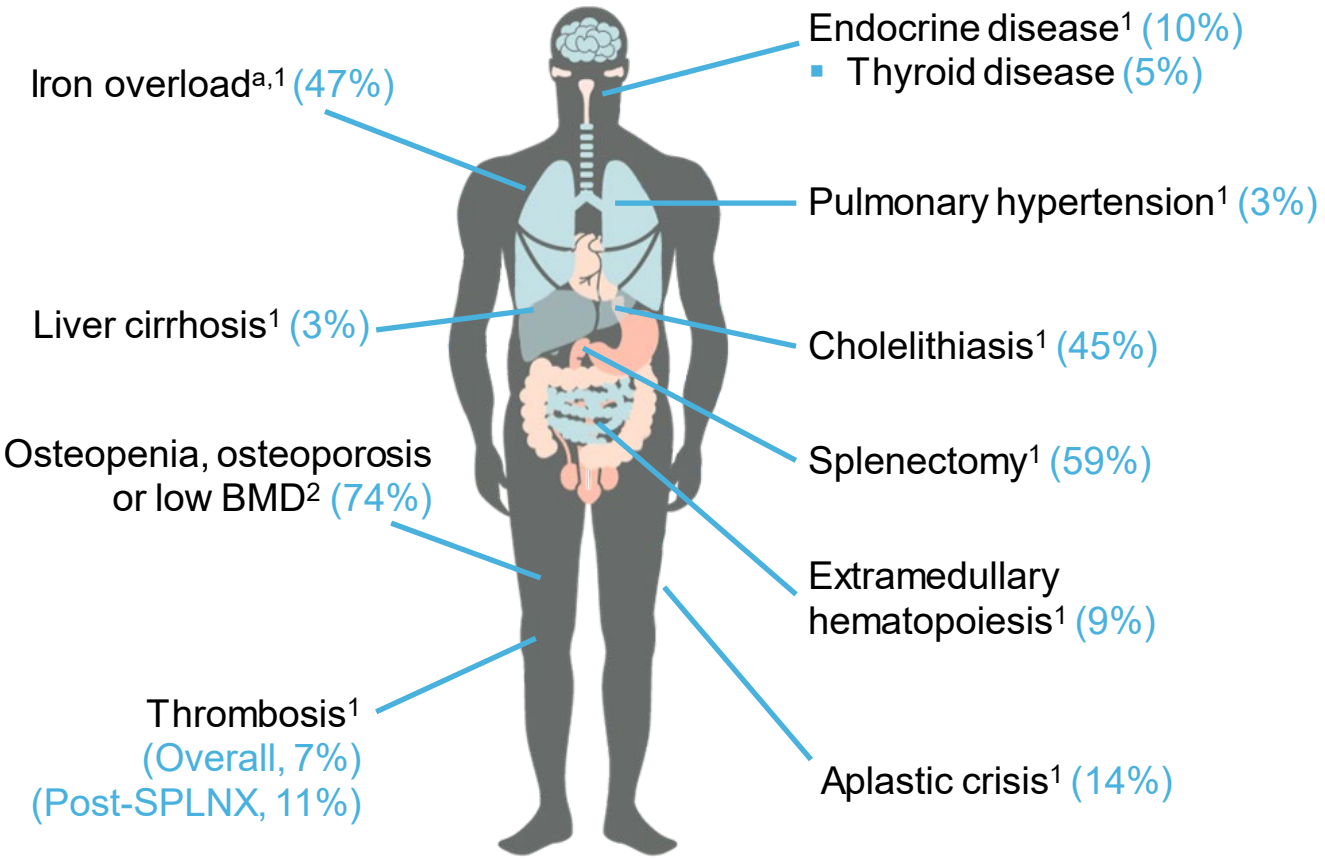
- Mitapivat, an oral PK-R activator, demonstrated an adequate safety profile during the 8-week dose finding period in subjects with SCD
- Mitapivat increased Hb level and decreased hemolysis and sickling parameters
- The observed changes in 2,3-DPG and ATP levels are consistent with the proposed mechanism of the drug
- Early improvements in albumin-to-creatinine ratio were observed
- Follow-up data of this ongoing study will be reported at a later stage

Elucidating the Burden of Pyruvate Kinase (PK) Deficiency and Long-term Clinical Data of Mitapivat in PK Deficiency

Dr. Sarah Gheuens, Chief Medical Officer, Agios

Pyruvate kinase (PK) deficiency is a rare, lifelong, hereditary anemia

Comorbidities and long-term complications are common and affect multiple organ systems[1,2]



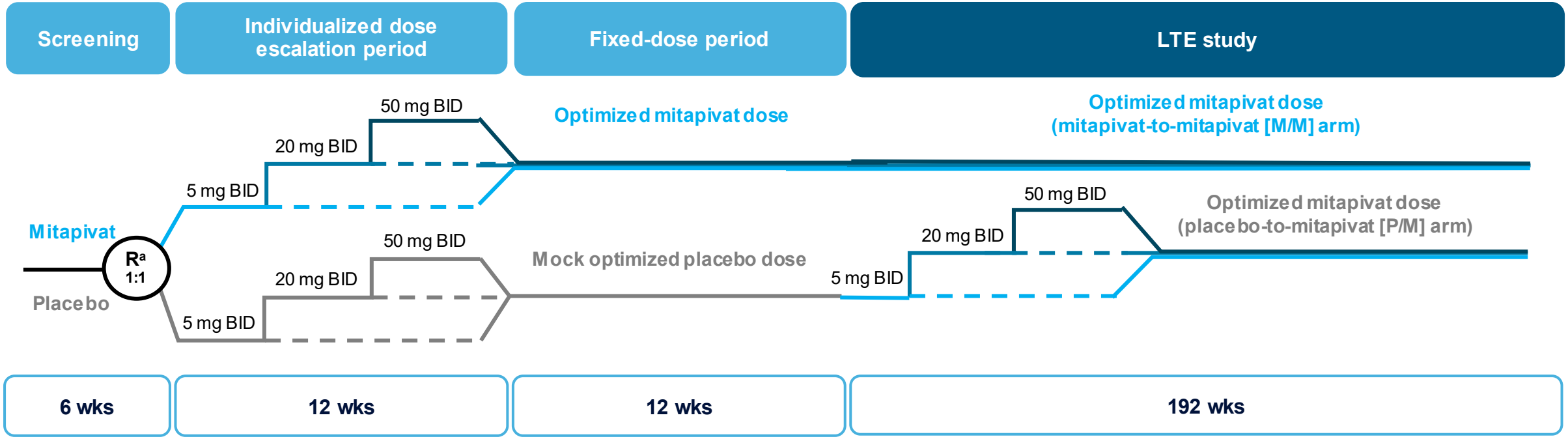
- Caused by mutations in the *PKLR* gene, encoding the red blood cell PK (PKR) enzyme[3,4]
- Defects in PKR lead to chronic hemolytic anemia and serious complications – independent of transfusion needs[1,2,5–7]
- There are no approved disease-modifying pharmacotherapies
- Available supportive therapies are associated with short- and long-term complications[8]

[a]Iron overload is 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 enrolment or had received chelation therapy in the 12 months before enrolment. BMD = bone mineral density; MRI = magnetic resonance imaging; PK = pyruvate kinase; PKR = red blood cell-specific form of PK; post-SPLNX = post-splenectomy.

1. Grace RF et al. *Blood* 2018;131:2183–92. **2.** Al-Samkari H et al. *06/09/21;325452;EP692 EHA Library*. **3.** Grace RF et al. *Am J Hematol* 2015;90:825–30. **4.** Zanella A et al. *Br J Haematol* 2005;130:11–25. **5.** van Beers EJ et al. *Haematologica* 2019;104:e51–3. **6.** Grace RF et al. *Eur J Haematol* 2018;101:758–65. **7.** Boscoe AN et al. *Eur J Haematol* 2021;106:484–92. **8.** Grace RF et al. *Br J Haematol* 2019;184:721–34.

ACTIVATE and the LTE study design

ACTIVATE



Key eligibility criteria

- ≥ 18 years of age
- Documented ≥ 2 mutant alleles in *PKLR* with ≥ 1 missense mutation (excluding patients homozygous for R479H mutation or have who have 2 non-missense mutations, without another missense mutation)
- Not regularly transfused (≤ 4 transfusion episodes in previous year)
- Baseline (BL) Hb ≤ 10 g/dL
- LTE study: patients must have completed the fixed-dose period and demonstrated clinical benefit from mitapivat or were assigned to placebo and continued to the LTE

[a]Stratified by average of screening Hb values (< 8.5 g/dL vs ≥ 8.5 g/dL) and *PKLR* gene mutation category (missense/missense vs missense/non-missense. *ClinicalTrials.gov:* ACTIVATE (NCT03548220); LTE study (NCT03853798); BID = twice daily; BL = baseline; Hb = hemoglobin; LTE = long-term extension; M/M = mitapivat-to-mitapivat; P/M = placebo-to-mitapivat; R = randomized; Wks = weeks.

ACTIVATE-T and the LTE study design

ACTIVATE-T

Screening	Individualized dose-escalation period	Fixed-dose period	LTE study
< 8 wks[a]	16 wks	24 wks	192 wks

Key eligibility criteria

- ≥ 18 years of age
- Documented ≥ 2 mutant alleles in *PKLR* with ≥ 1 missense mutation (excluding patients homozygous for R479H mutation or have who have 2 non-missense mutations, without another missense mutation)
- Regularly transfused (≥ 6 transfusion episodes in previous year)
- LTE study: patients must have completed the fixed-dose period of ACTIVATE-T and demonstrated clinical benefit from mitapivat treatment

[a]Screening may have been extended beyond 8 wks if there was a delay in obtaining a patient's complete transfusion history or to ensure that the first dose of study drug could be administered 2–7 days after the most recent transfusion. *ClinicalTrials.gov:* ACTIVATE-T (NCT03559699); LTE study (NCT03853798); BID = twice daily; LTE = long-term extension; Wks = weeks.

Phase 3 studies, ACTIVATE and ACTIVATE-T, met primary endpoints

ACTIVATE

- **Primary efficacy endpoint achieved**: 40% of patients treated with mitapivat achieved a sustained Hb increase of ≥ 1.5 g/dL compared to 0 placebo patients (2-sided $p < 0.0001$)[1]
- Treatment with mitapivat also demonstrated statistically significant improvements over placebo across pre-specified key secondary endpoints, including patient-reported outcomes based on changes from baseline in the *PK deficiency diary* and *PK deficiency impact assessment* scores
- Safety profile was generally consistent with previously reported data

ACTIVATE-T

- **Primary efficacy endpoint achieved**: 37% of patients treated with mitapivat achieved a ≥ 33% reduction in transfusion burden compared to individual historical transfusion burden standardized to 24 weeks (1-sided $p = 0.0002$)[2]
- 22% of patients treated with mitapivat were transfusion-free during the 24-week fixed-dose period
- Safety profile was generally consistent with previously reported data

Hb = hemoglobin; PK = pyruvate kinase.

1. Al-Samkari H. 06/09/21;324678;S270 *EHA Library*. **2.** Glenthøj A. 06/09/21;324679;S271 *EHA Library*.

Mitapivat Improves Ineffective Erythropoiesis and Reduces Iron Overload in Patients with Pyruvate Kinase Deficiency

Eduard J. van Beers, MD[1], Hanny Al-Samkari, MD[2], Rachael F. Grace, MD[3], Wilma Barcellini, MD[4], Andreas Glenthøj, MD[5], Malia P. Judge, BS[6], Penelope A. Kosinski, MS[6], Rengyi Xu, PhD[6], Vanessa Beynon, MD[6], Bryan McGee, PharmD[6], John B. Porter, MD[7], Kevin H.M. Kuo, MD[8]

[1]Van Creveldkliniek, Department of Internal Medicine, University Medical Center Utrecht, Utrecht, Netherlands; [2]Division of Hematology, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; [3]Dana-Farber/Boston Children's Cancer and Blood Disorders Center, Boston, MA, USA; [4]Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy; [5]Department of Haematology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [6]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [7]Haematology Department, University College London Hospitals, London, UK; [8]Division of Hematology, University of Toronto, Toronto, ON, Canada

This study was funded by Agios Pharmaceuticals, Inc.

Objective

To assess the effect of mitapivat on markers of erythropoietic activity and iron overload in adult patients with PK deficiency enrolled in ACTIVATE, ACTIVATE-T, and their long-term extension (LTE) study (NCT03853798)

LTE = long-term extension; PK = pyruvate kinase.

Methods

Endpoints and analyses:

- ***Markers of erythropoietic activity*** – erythropoietin (EPO), erythroferrone, reticulocytes, and soluble transferrin receptor (sTfR)
- ***Markers of iron metabolism and indicators of iron overload*** – hepcidin, iron, transferrin saturation (TSAT), ferritin, total iron binding capacity, and liver iron concentration (LIC) by magnetic resonance imaging (MRI)
- In the ACTIVATE/LTE study, patients assigned mitapivat in ACTIVATE were categorized into the mitapivat-to-mitapivat (M/M) arm and patients assigned placebo in ACTIVATE were categorized into the placebo-to-mitapivat (P/M) arm; the analysis assessed change in markers from BL over time in both study arms
- The ACTIVATE-T/LTE study analysis was descriptive and limited to patients who achieved transfusion-free status in the fixed-dose period of ACTIVATE-T to mitigate the confounding effect of transfusions on markers of erythropoietic activity, iron metabolism, and iron overload

BL = baseline; EPO = erythropoietin; LIC = liver iron concentration; LTE = long-term extension; M/M = mitapivat-to-mitapivat; MRI = magnetic resonance imaging; P/M = placebo-to-mitapivat; TSAT = transferrin saturation; sTfR = soluble transferrin receptor.

Decreases in markers of erythropoietic activity in M/M and P/M arms with mitapivat treatment in ACTIVATE and the LTE study

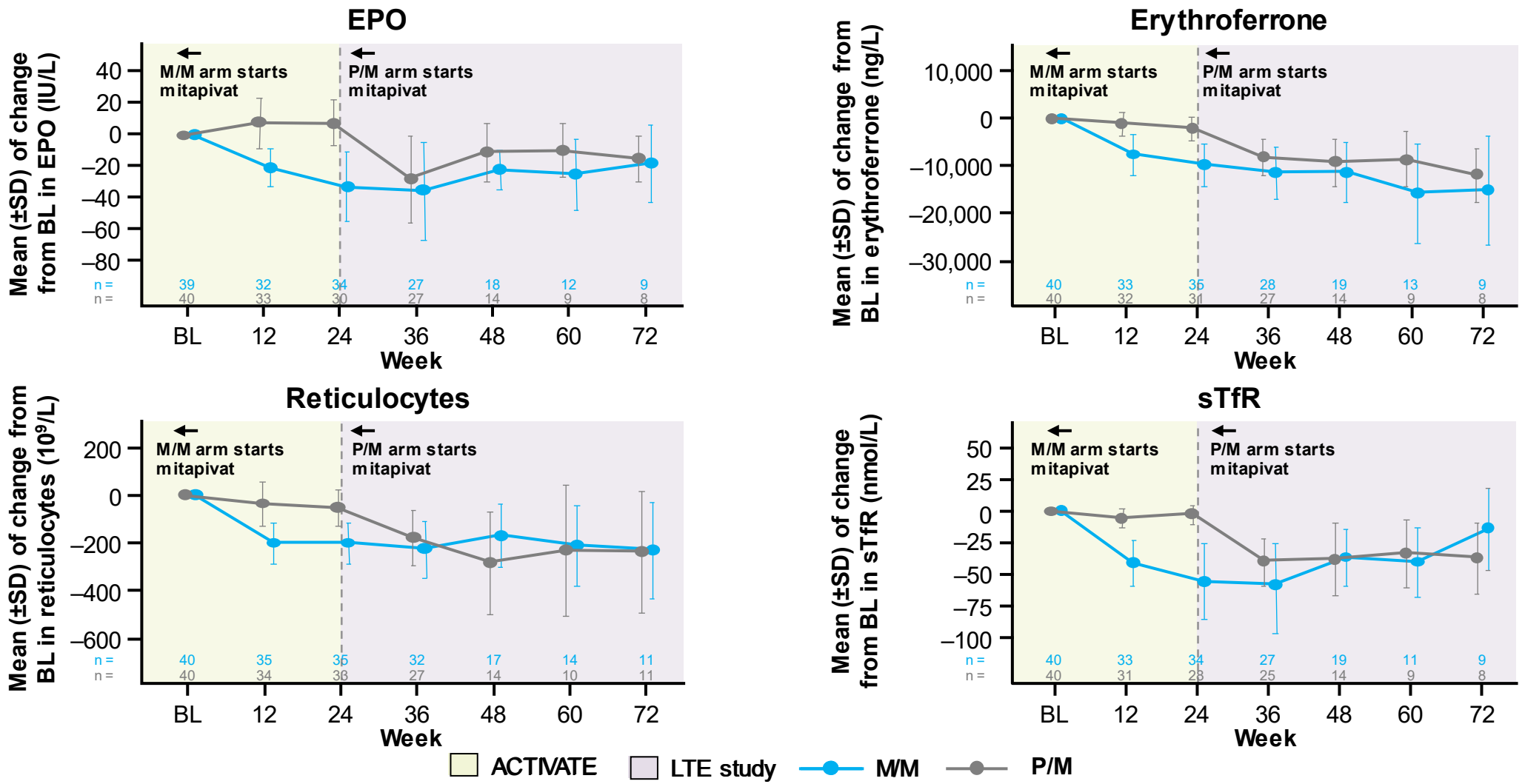
Marker	M/M	P/M
EPO, IU/L		
BL[a]	n = 39	n = 40
Mean (SD)	73.9 (59.85)	74.1 (57.01)
Wk 24 (change from BL)	n = 34	n = 30
Mean (SD)	–32.9 (62.47)	7.0 (38.18)
Wk 48 (change from BL)	n = 18	n = 14
Mean (SD)	–22.0 (24.43)	–11.6 (30.74)
Reticulocytes, 10^9/L		
BL[a]	n = 40	n = 40
Mean (SD)	817.8 (454.18)	901.7 (465.69)
Wk 24 (change from BL)	n = 35	n = 33
Mean (SD)	–202.0 (246.97)	–52.1 (210.68)
Wk 48 (change from BL)	n = 17	n = 14
Mean (SD)	–168.6 (257.34)	–283.7 (374.27)

Marker	M/M	P/M
Erythroferrone, ng/L		
BL[a]	n = 40	n = 40
Mean (SD)	21079.8 (16029.26)	20379.8 (13095.47)
Wk 24 (change from BL)	n = 35	n = 31
Mean (SD)	–9834.9 (13081.15)	–2132.9 (6278.41)
Wk 48 (change from BL)	n = 19	n = 14
Mean (SD)	–11341.8 (12556.80)	–9246.1 (8314.17)
sTfR, nmol/L		
BL[a]	n = 40	n = 40
Mean (SD)	187.0 (75.85)	174.3 (68.90)
Wk 24 (change from BL)	n = 34	n=28
Mean (SD)	–56.0 (82.57)	–2.1 (17.23)
Wk 48 (change from BL)	n = 19	n = 14
Mean (SD)	–36.9 (45.17)	–38.7 (48.37)

BL Patients on mitapivat Patients on placebo

[a]BL is defined as the average of all screening assessments within 45 (42 + 3) days before randomization for patients randomized and not dosed or before start of study treatment for patients randomized and dosed. Assessments collected within 61 days after a transfusion are excluded from the BL derivation. n is the number of pts in the full analysis set within each treatment group with an assessment at the visit or (for change from BL summaries) with BL and at least 1 post-BL assessment at the visit. BL = baseline; EPO = erythropoietin; LTE = long-term extension study; M/M = mitapivat-to mitapivat; P/M = placebo-to-mitapivat; SD = standard deviation; sTfR = soluble transferrin receptor; Wk = week.

Decreases in markers of erythropoietic activity in M/M and P/M arms with mitapivat treatment in ACTIVATE and the LTE study



BL is defined as the average of all screening assessments within 45 (42 + 3) days before randomization for patients randomized and not dosed, or before start of study treatment for patients randomized and dosed. Assessments collected within 61 days after a transfusion are excluded from the BL derivation. n is the number of patients in the full analysis set within each treatment group with an assessment at the visit or (for change from BL summaries) with BL and ≥ 1 post-BL assessment at the visit. BL = baseline; EPO = erythropoietin; LTE = long-term extension study; M/M = mitapivat-to-mitapivat; P/M = placebo-to-mitapivat; SD = standard deviation; sTfR = soluble transferrin receptor.

Improvements in markers of iron metabolism and overload in M/M and P/M arms with mitapivat treatment in ACTIVATE and the LTE study

Marker	M/M (N = 40)	P/M (N = 40)
Hepcidin, ng/L		
BL[a] Mean (SD)	n = 40 25,920.0 (27899.90)	n = 40 29,988.8 (18,044.22)
Wk 24 (change from BL) Mean (SD)	n = 35 4770.0 (18,346.74)	n = 31 –3282.3 (14,735.06)
Wk 48 (change from BL) Mean (SD)	n = 19 2642.1 (27,623.45)	n = 14 15,875.0 (22,232.27)
Iron, µmol/L		
BL[a] Mean (SD)	n = 40 24.1 (9.78)	n = 40 26.6 (9.32)
Wk 24 (change from BL) Mean (SD)	n = 37 –0.8 (9.93)	n = 32 1.3 (8.94)
Wk 48 (change from BL) Mean (SD)	n = 20 –1.4 (10.98)	n = 14 –2.4 (13.38)
TSAT, fraction of 1[c]		
BL[a] Mean (SD)	n = 40 0.5 (0.22)	n = 40 0.5 (0.19)
Wk 24 (change from BL) Mean (SD)	n = 37 –0.01 (0.185)	n = 31 0.03 (0.205)
Wk 48 (change from BL) Mean (SD)	n = 19 –0.01 (0.196)	n = 14 –0.06 (0.257)

Marker	M/M (N = 40)	P/M (N = 40)
Ferritin, µg/L		
BL[a] Mean (SD)	n = 39 747.9 (1116.18)	n = 38 688.0 (605.25)
Wk 24 (change from BL) Mean (SD)	n = 36 39.3 (285.39)	n = 31 –50.2 (216.53)
Wk 48 (change from BL) Mean (SD)	n = 18 3.2 (374.93)	n = 14 –17.8 (206.08)
LIC assessment by MRI, mg Fe/g dw		
BL[b] Mean (SD) Median (Q1, Q3)	n = 38 7.6 (10.78) 3.05 (1.70, 6.50)	n = 39 6.1 (8.01) 3.40 (2.00, 6.30)
Wk 24 (change from BL) Mean (SD) Median (Q1, Q3)	n = 31 1.7 (15.75) –0.40 (–1.10, 0.70)	n = 31 1.4 (12.38) 0.30 (–0.30, 1.20)
Wk 48 (change from BL) Mean (SD) Median (Q1, Q3)	n = 15 –1.6 (5.79) –1.80 (–2.80, –0.20)	n = 16 –2.7 (6.08) –0.10 (–2.40, 0.45)

BL Patients on mitapivat Patients on placebo

[a]BL is defined as the average of all screening assessments within 45 (42 + 3) days before randomization for patients randomized and not dosed, or before start of study treatment for patients randomized and dosed. Assessments collected within 61 days after a transfusion are excluded from the BL derivation. [b]BL LIC by MRI is defined as the last assessment before randomization for patients randomized and not dosed or the last assessment before start of study treatment for patients randomized and dosed. [c]Mean (SD) TSAT may also be reported as a percentage: M/M (Wk 24) = – 1% (18.5%); M/M (Wk 48) = – 1% (19.6%); P/M (Wk 24) = 3% (20.5%); P/M (Wk 48) = – 6% (25.7%). n is the number of patients in the full analysis set within each treatment group with an assessment at the visit or (for change from BL summaries) with BL and ≥ 1 post-BL assessment at the visit. BL = baseline; dw = dry weight; LIC = liver iron concentration; LTE = long-term extension study; M/M = mitapivat-to-mitapivat; MRI = magnetic resonance imaging; P/M = placebo-to-mitapivat; SD = standard deviation; TSAT = transferrin saturation; Wk = week.

ACTIVATE-T Results

- Transfusion-free responders from ACTIVATE-T (n = 6) experienced improvements in markers of erythropoietic activity and iron overload in the LTE study
- None of the transfusion-free responders had a dose increase in iron chelation, 1 patient had an iron chelation dose reduction, and 2 patients discontinued iron chelation completely
- One additional patient, who was a transfusion burden reduction responder in ACTIVATE-T, did not receive any transfusions after the start of the LTE and had an iron chelation dose reduction

LTE = long-term extension study.

Conclusion

- Data from ACTIVATE, ACTIVATE-T, and the LTE study show that activation of PKR with mitapivat improves markers of ineffective erythropoiesis and iron metabolism in patients with PK deficiency, regardless of transfusion status

- Through this mechanism, mitapivat improves ineffective erythropoiesis and may have the potential to improve iron homeostasis, thereby reducing iron overload

Mitapivat has the potential to become the first approved therapy in patients with PK deficiency, with a beneficial effect on ineffective erythropoiesis and iron overload, independent of transfusion needs

LTE = long-term extension; PK = pyruvate kinase; PKR = red blood cell-specific form of PK.

Durability of Hemoglobin Response and Reduction in Transfusion Burden is Maintained Over Time in Patients With Pyruvate Kinase Deficiency Treated with Mitapivat in a Long-Term Extension Study

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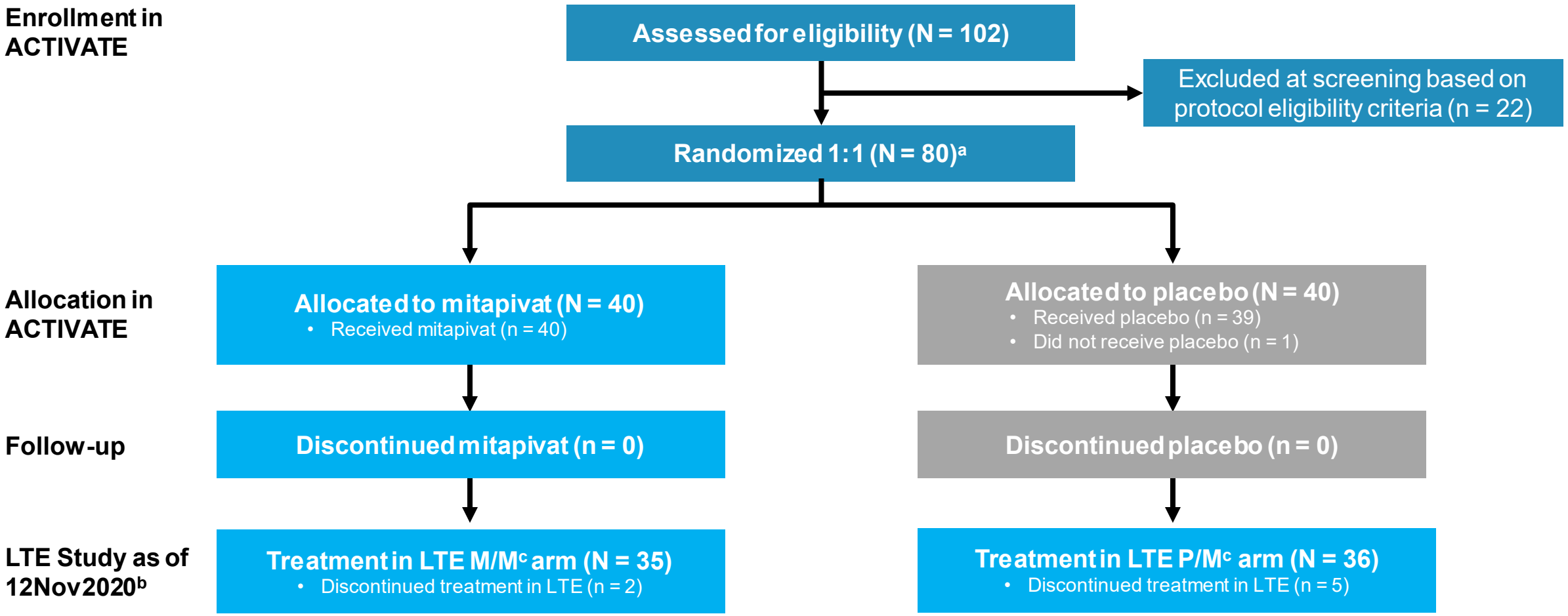
Objective

To assess the duration of effects of mitapivat on Hb response and transfusion burden reduction in patients with PK deficiency in ACTIVATE, ACTIVATE-T, and their long-term extension (LTE) study

Hb = hemoglobin; LTE = long-term extension; PK = pyruvate kinase.

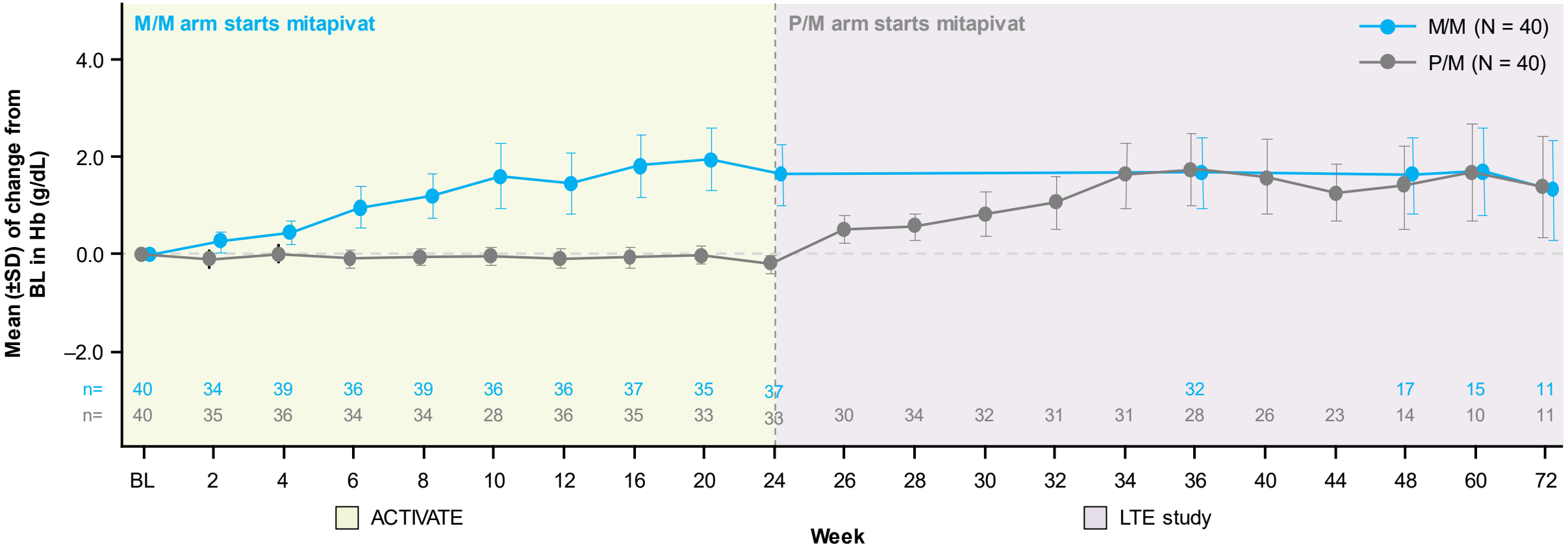
Patient disposition in ACTIVATE and the LTE study



[a]Disposition for end of randomization reflects the disposition after randomization, but before the start of study treatment. [b]As of data cut-off date 12Nov2020 not all the patients from ACTIVATE had been dosed for the LTE study. [c]LTE study is ongoing; 0 patients have completed treatment. LTE = long-term extension; M/M = mitapivat-to-mitapivat; P/M = placebo-to-mitapivat.

Mean improvement in Hb concentrations was maintained with long-term mitapivat treatment in ACTIVATE and the LTE study

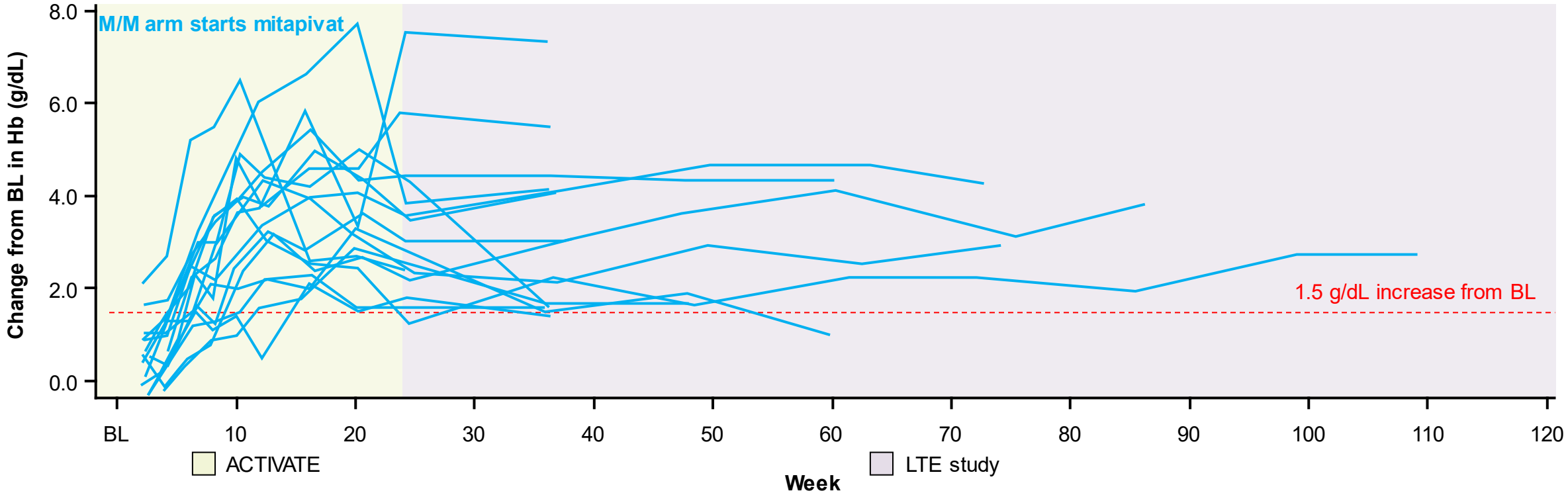
Mean change from baseline[a] in Hb over time in patients randomized to mitapivat or placebo in ACTIVATE who then continued in the LTE study on mitapivat[b,c]



[a]Baseline is defined as the average of all screening assessments within 45 (42 + 3) days before randomization for patients randomized and not dosed or before start of study treatment for patients randomized and dosed. Assessments collected within 61 days after a transfusion are excluded from the baseline derivation. [b]Patients in the M/M arm were assessed every 12 weeks after the completion of the fixed-dose period in ACTIVATE (Week 24) and up to Week 48 of the LTE. [c]Data are shown up to 72 weeks, which is the timepoint where each arm has > 5 patients. BL = baseline; Hb = hemoglobin; LTE = long-term extension; M/M = mitapivat-to-mitapivat; P/M = placebo-to-mitapivat; SD = standard deviation.

Hb response was sustained in mitapivat-to-mitapivat patients in the ACTIVATE and the LTE studies

Change from baseline[a] in Hb over time among patients treated with mitapivat in ACTIVATE who achieved an Hb response in the fixed-dose period and received ongoing treatment in the LTE study

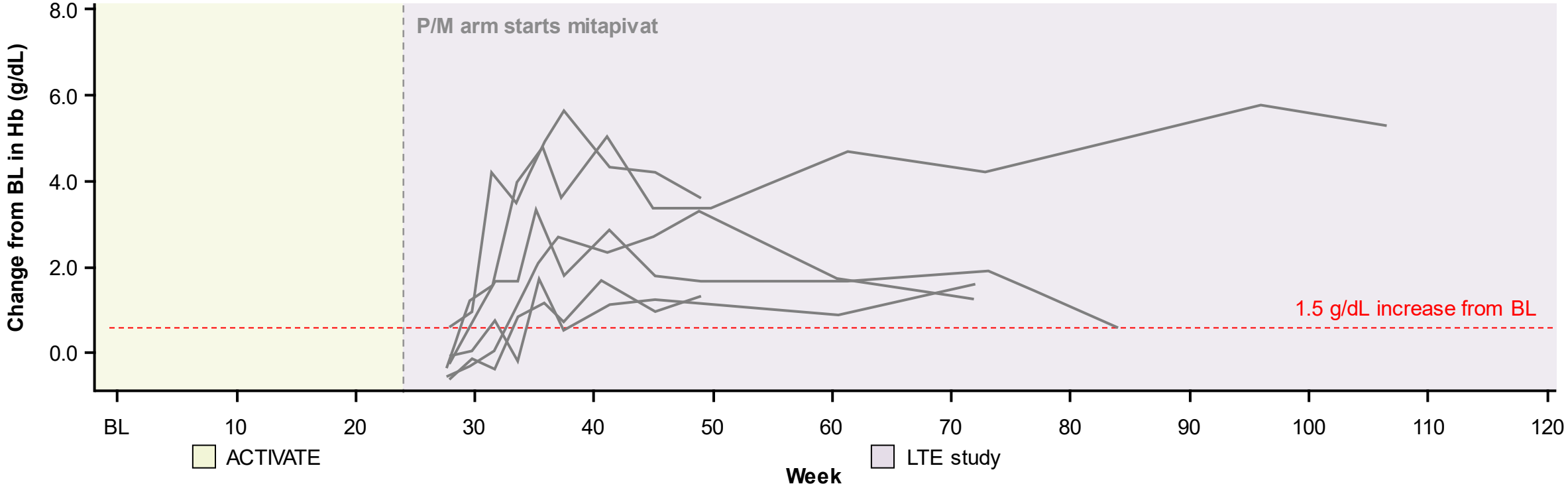


At all Hb assessments, 86.7% (13/15) of M/M patients with a Hb response in ACTIVATE and evaluable timepoints in the LTE maintained increases in Hb concentration from baseline above the response threshold of ≥ 1.5 g/dL up to 19.5 months

[a]Baseline is defined as the average of all screening assessments within 45 (42 + 3) days before randomization for patients randomized and not dosed or before the start of study treatment for patients randomized and dosed. Assessments collected within 61 days after a transfusion are excluded from the baseline derivation. BL = baseline; Hb = hemoglobin; LTE = long-term extension; M/M = mitapivat-to-mitapivat.

Hb response was achieved and sustained in placebo-to-mitapivat patients in the LTE study

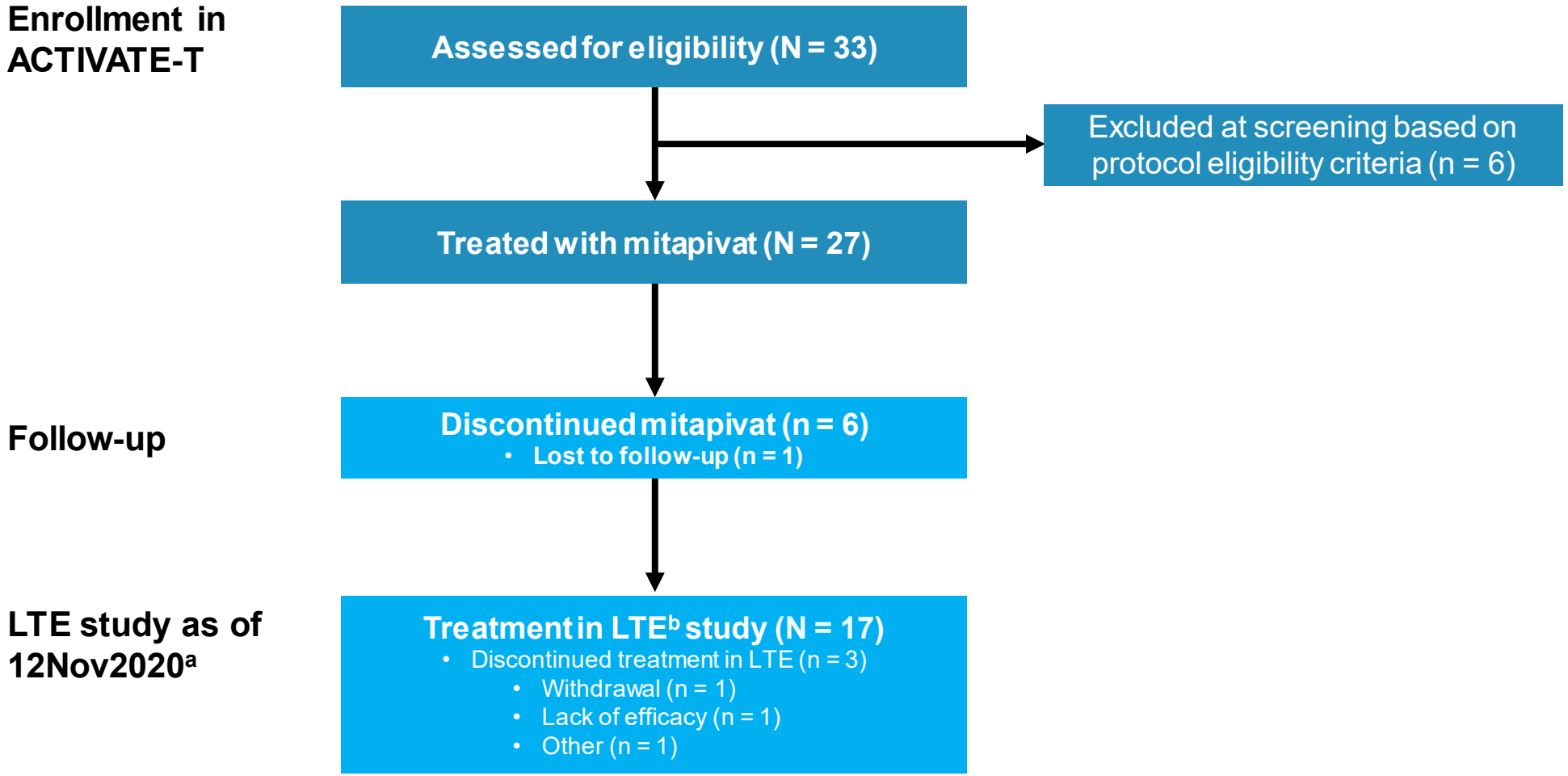
Change from baseline[a] in Hb over time among patients randomized to placebo in ACTIVATE and who started mitapivat treatment in the LTE study and achieved a Hb response



35% (6/17) of P/M patients achieved Hb responses in the LTE, and all maintained Hb responses for the duration of follow-up

[a]Baseline is the average of all available measurements from the central laboratory within 45 (42 + 3) days before start of study treatment in the LTE study, excluding values within 61 days after a transfusion, or the baseline value from the ACTIVATE study if no assessment was available. BL = baseline; Hb = hemoglobin; LTE = long-term extension study; P/M = placebo-to-mitapivat.

Patient disposition in ACTIVATE-T and the LTE study

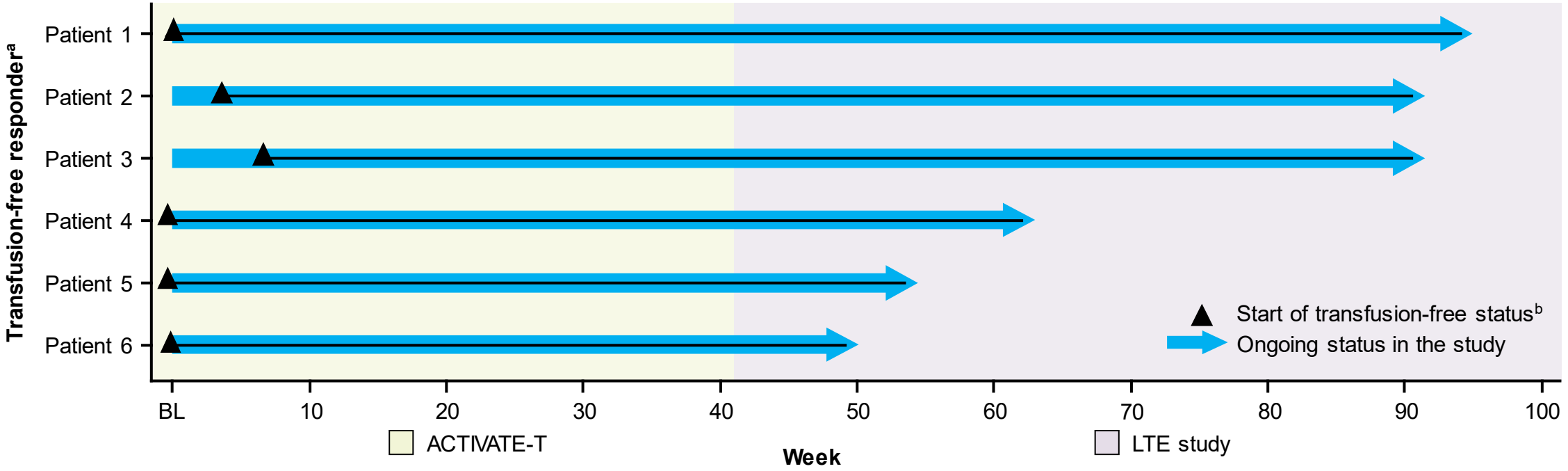


[a]As of data cut-off 12Nov2020, not all the patients from ACTIVATE-T had been dosed for the LTE study. [b]LTE study is ongoing; 0 patients have completed treatment.
LTE = long-term extension.

Transfusion reduction response and duration of transfusion-free status of patients in the ACTIVATE-T and LTE studies

- As of 12Nov2020, 9 patients (33.3%) in the LTE study met the criteria for a transfusion reduction response

Transfusion-free duration among transfusion-free responders from ACTIVATE-T through the LTE study



All 6 patients who achieved transfusion-free status in ACTIVATE-T maintained the status in the LTE study for up to 21.9 months

[a]Patient received no transfusions in the fixed-dose period of ACTIVATE-T. [b]The start of transfusion-free responder status was from 1 day after the last transfusion date.
BL = baseline; LTE = long-term extension.

Conclusion

- PK deficiency is a lifelong serious hemolytic anemia with no approved pharmacotherapies
- Non-regularly transfused patients randomized to mitapivat in ACTIVATE showed maintenance of Hb response through the LTE study for up to 19.5 months
  - Similarly, 35% of ACTIVATE patients who switched from placebo to mitapivat in the LTE study achieved a Hb response, which was maintained for the duration of follow-up
- All regularly transfused patients who achieved transfusion-free status in ACTIVATE-T with mitapivat treatment maintained the status through the LTE study for up to 21.9 months

These data show the consistency and long-term durability of response in patients with PK deficiency, independent of transfusion needs, and continue to support the potential of mitapivat to become the first approved disease-modifying pharmacotherapy for PK deficiency

Hb = hemoglobin; LTE = long-term extension; PK = pyruvate kinase.

Q&A