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

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Disclosures

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  - **K. 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
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Background – thalassemia

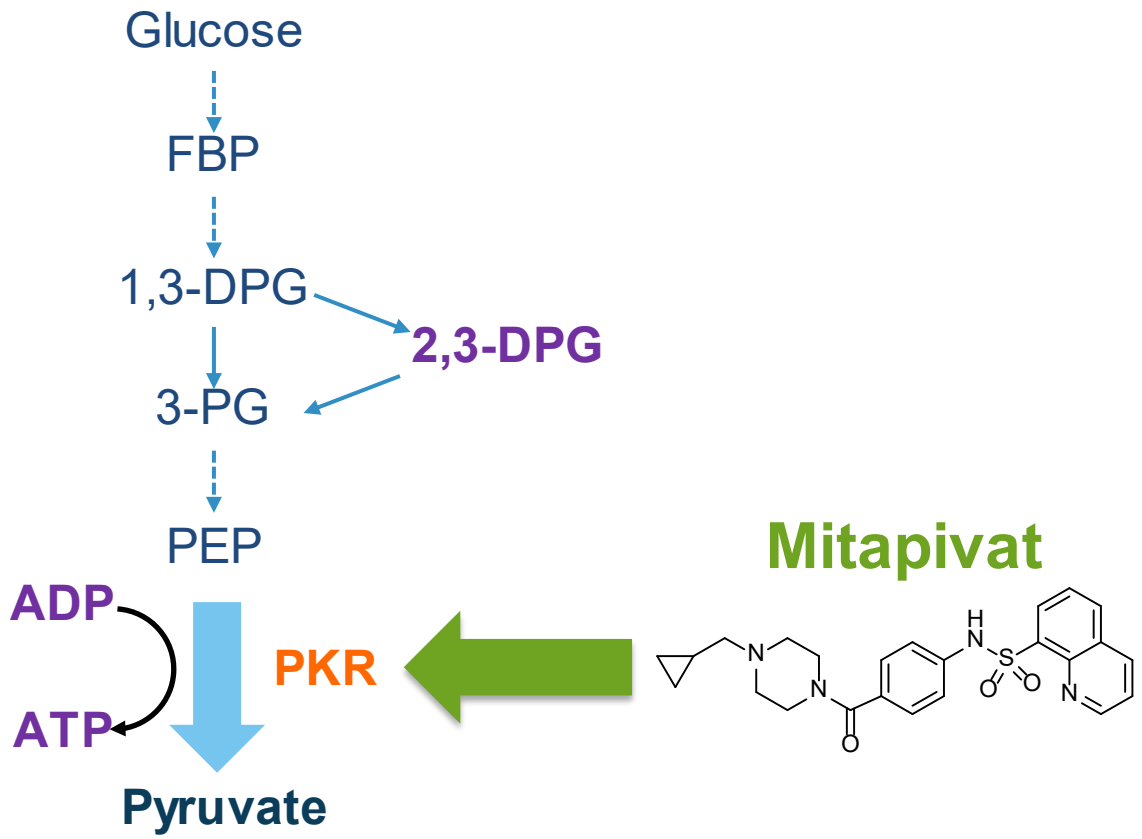
- Thalassemia is a red blood cell (RBC) disorder in which ineffective erythropoiesis and hemolysis occur due to imbalanced globin production and precipitation of excess globin chains[1,2]
- Thalassemic RBCs have insufficient levels of ATP to meet increased energy demands associated with globin chain 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]

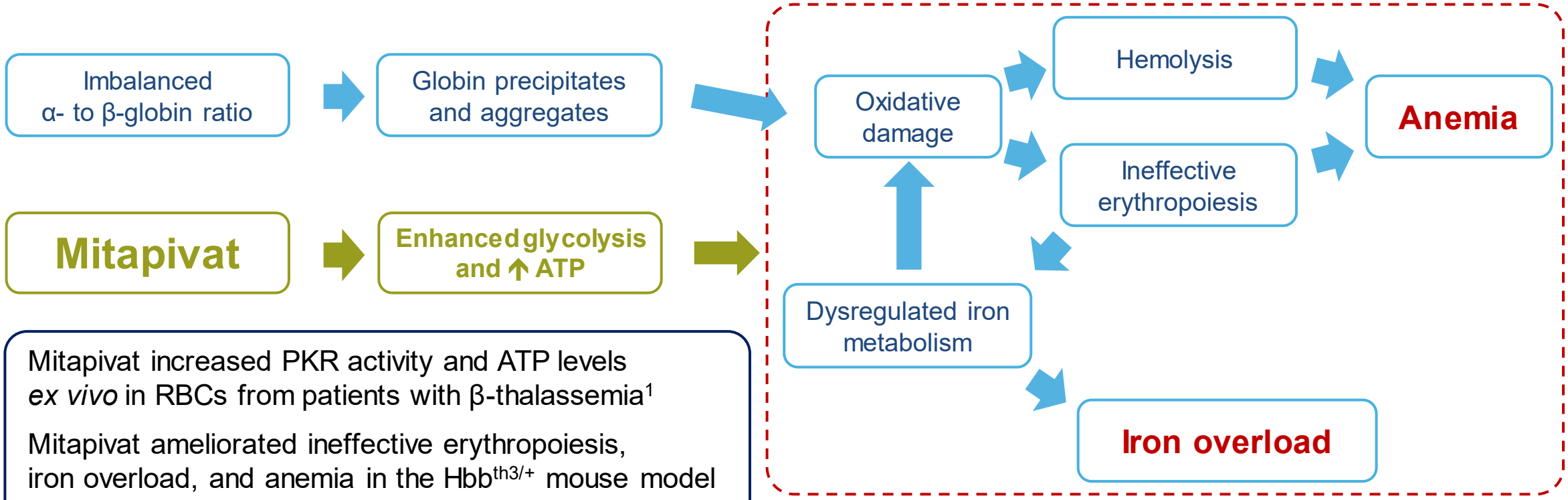


- Mitapivat activates PKR, which catalyzes the final step of glycolysis in RBCs[1]
- ATP generation is essential for RBC function and stability[2,3]

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



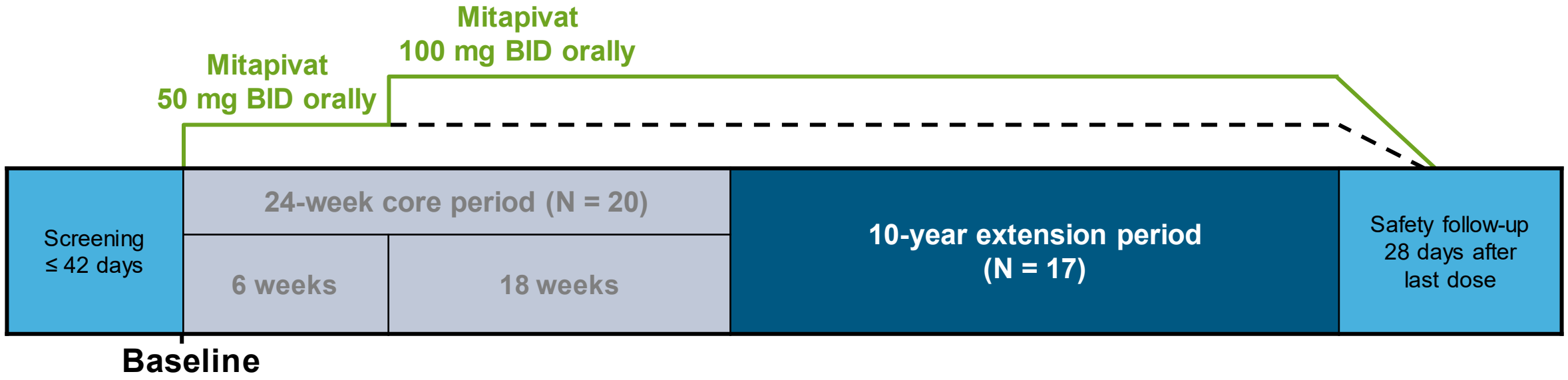
Mitapivat increased PKR activity and ATP levels *ex vivo* in RBCs from patients with β-thalassemia[1]

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 (defined on slide 8), 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

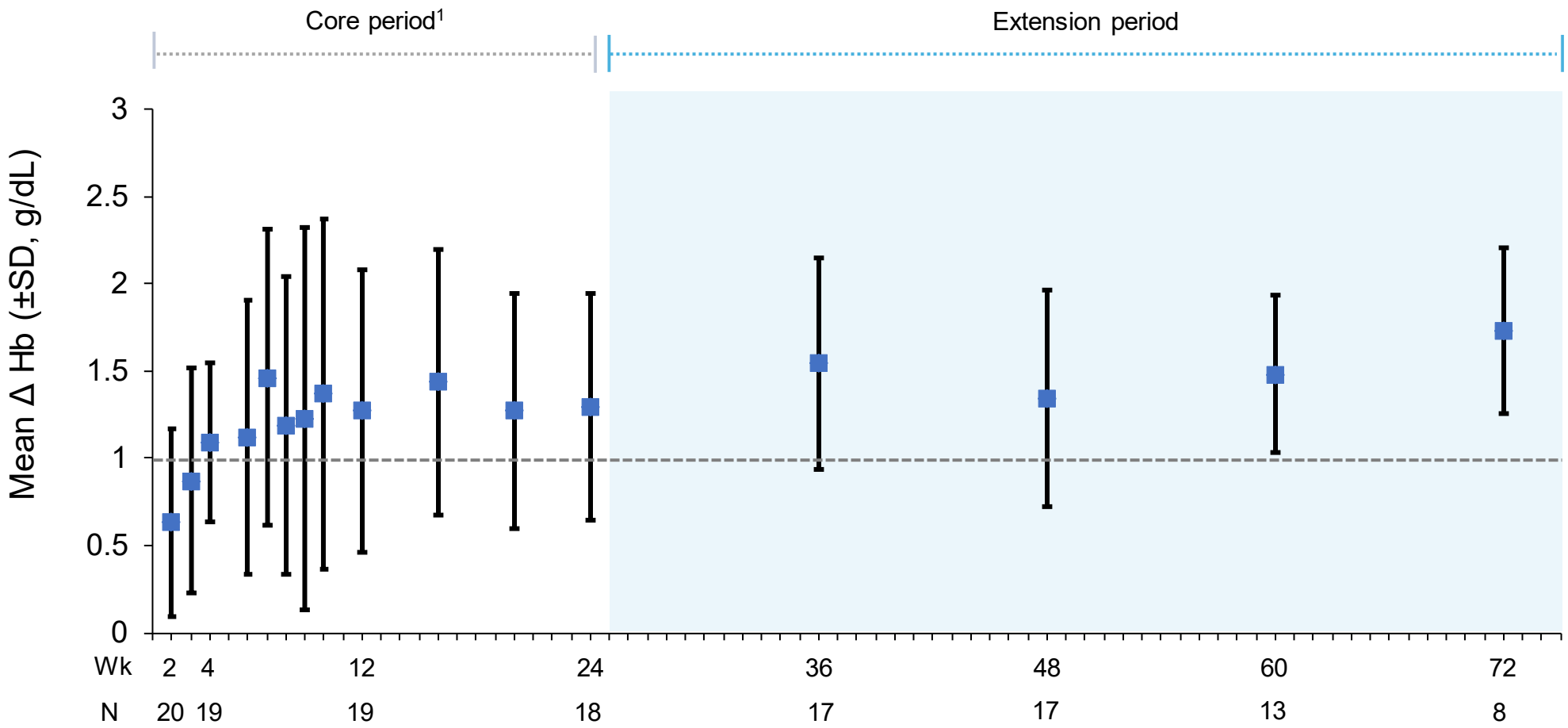
Patient demographics and baseline[a] characteristics	All patients (N = 17)	
Median (range) duration of treatment, weeks	70.9	(54.7, 105.6)
Sex, n (%)		
Male	5	(29.4)
Female	12	(70.6)
Age, median (range), years	44	(29, 67)
Race, n (%)		
Asian	8	(47.1)
White	4	(23.5)
Native Hawaiian or other Pacific Islander	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

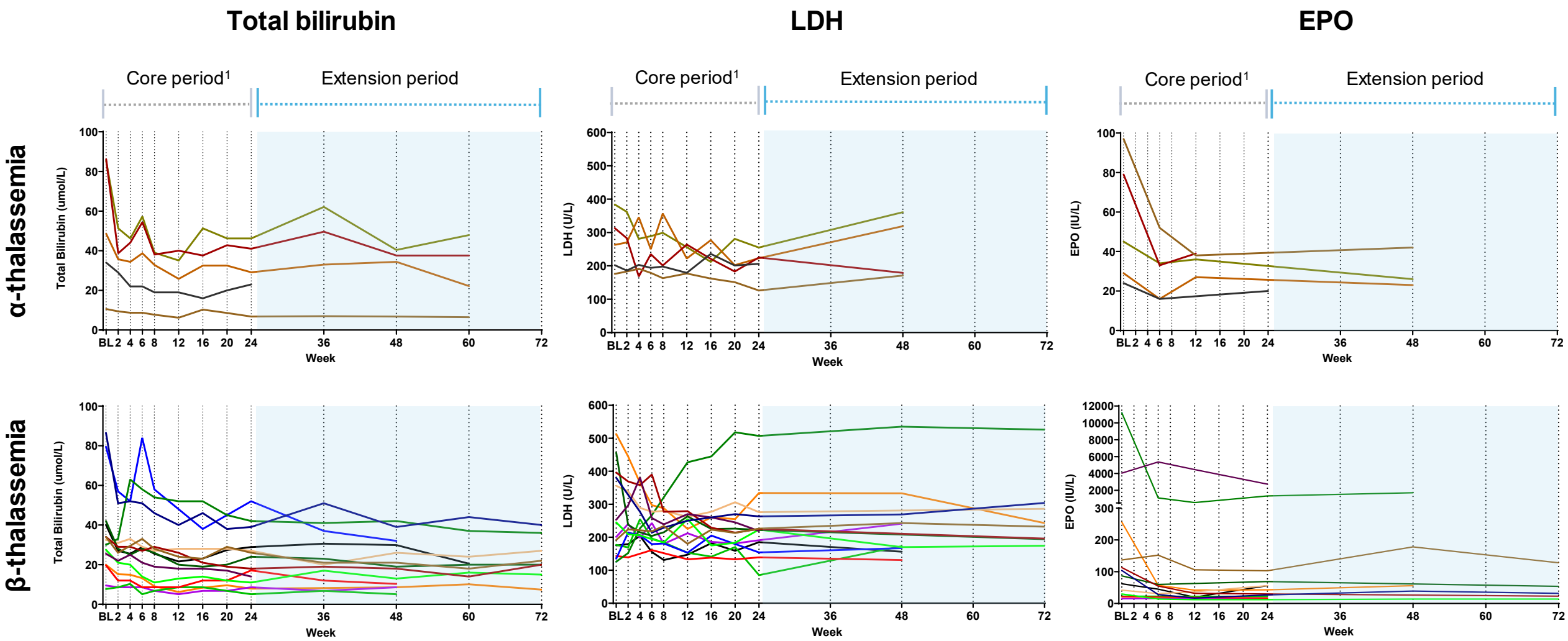
Mean Hb change from baseline over time



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

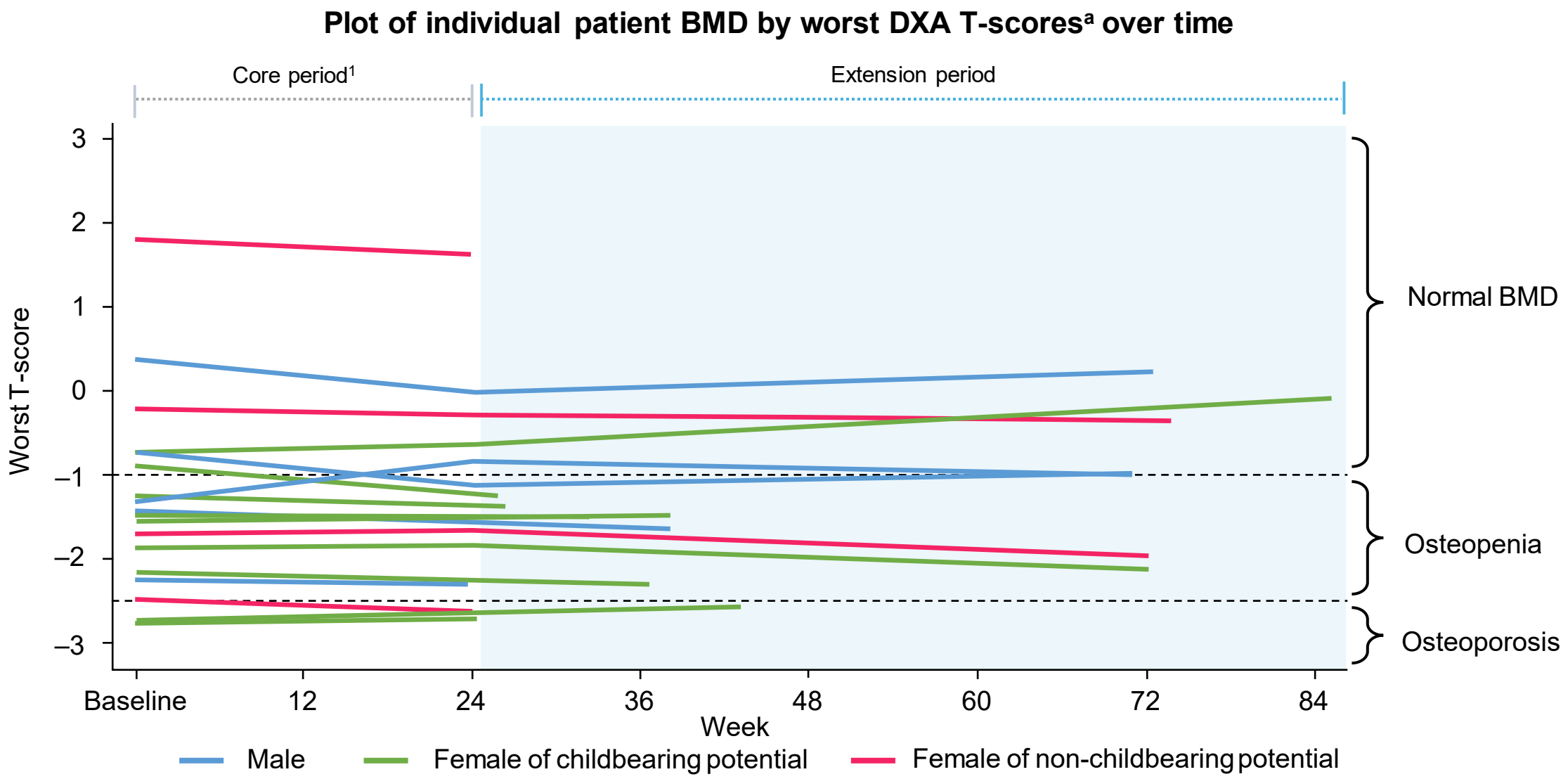
Most common TEAEs (any grade in ≥ 15% of patients)	Core period (N = 20)[1] Weeks 0–24	Extension period (N = 17)[a] Weeks 25–72
	Any grade, n (%)	Any grade, n (%)
Patients with events	17 (85.0)	13 (76.5)
Initial insomnia	10 (50.0)	0
Dizziness	6 (30.0)	1 (5.9)
Headache	5 (25.0)	5 (29.4)
Cough	4 (20.0)	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.