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Agios at EHA 2022

June 13, 2022

Forward-looking statements

This presentation and various remarks we make during this presentation contain forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding the potential benefits of PYRUKYND® (mitapivat) and AG-946; Agios' plans, strategies and expectations for its preclinical, clinical and commercial advancement of its drug development, including PYRUKYND® (mitapivat) and AG-946; Agios' key milestones; 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*
8:00 – 8:05 AM	Opening Remarks	Jackie Fouse, Ph.D.
8:05 – 8:20 AM	New Data from Pivotal Studies of Mitapivat in Pyruvate Kinase (PK) Deficiency & PEAK Registry	Sarah Gheuens, M.D, Ph.D.
8:20 – 8:30 AM	Thalassemia Burden of Disease and Mitapivat Clinical Program	Sarah Gheuens, M.D, Ph.D.
8:30 – 8:45 AM	Review of Data from the ESTIMATE Study of Mitapivat in Sickle Cell Disease	Eduard J. van Beers, M.D., Ph.D., *Hematologist and associate professor at University Medical Center Utrecht*
8:45 – 9:15 AM	Closing Remarks and Q&A	Dr. Fouse, Dr. Gheuens, Dr. van Beers, Richa Poddar, Jonathan Biller

Strong connections to patients mean we *listen* to and work *with* them to create solutions

Tamara
Pyruvate Kinase Deficiency

Sharonda
Sickle Cell Disease

Ryan
Thalassemia

We have been the pioneering leaders in PK activation for 8+ years

Pursuing broad pivotal programs across disease areas

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

Continued focus on publishing data to support PK activation mechanism & elucidate burden of under-appreciated diseases

Only company with POC across three disease areas

- 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 APPROVAL OF PK ACTIVATOR FOR PK DEFICIENCY
- 1st CLINICAL TRIAL EVALUATING TREATMENT IN α-THALASSEMIA

The future of Agios is driven by *innovation* & *impact*

01 We intentionally cultivate internal and external connections

02 We have a strong balance sheet and are well capitalized to execute on our near- and long-term business strategy

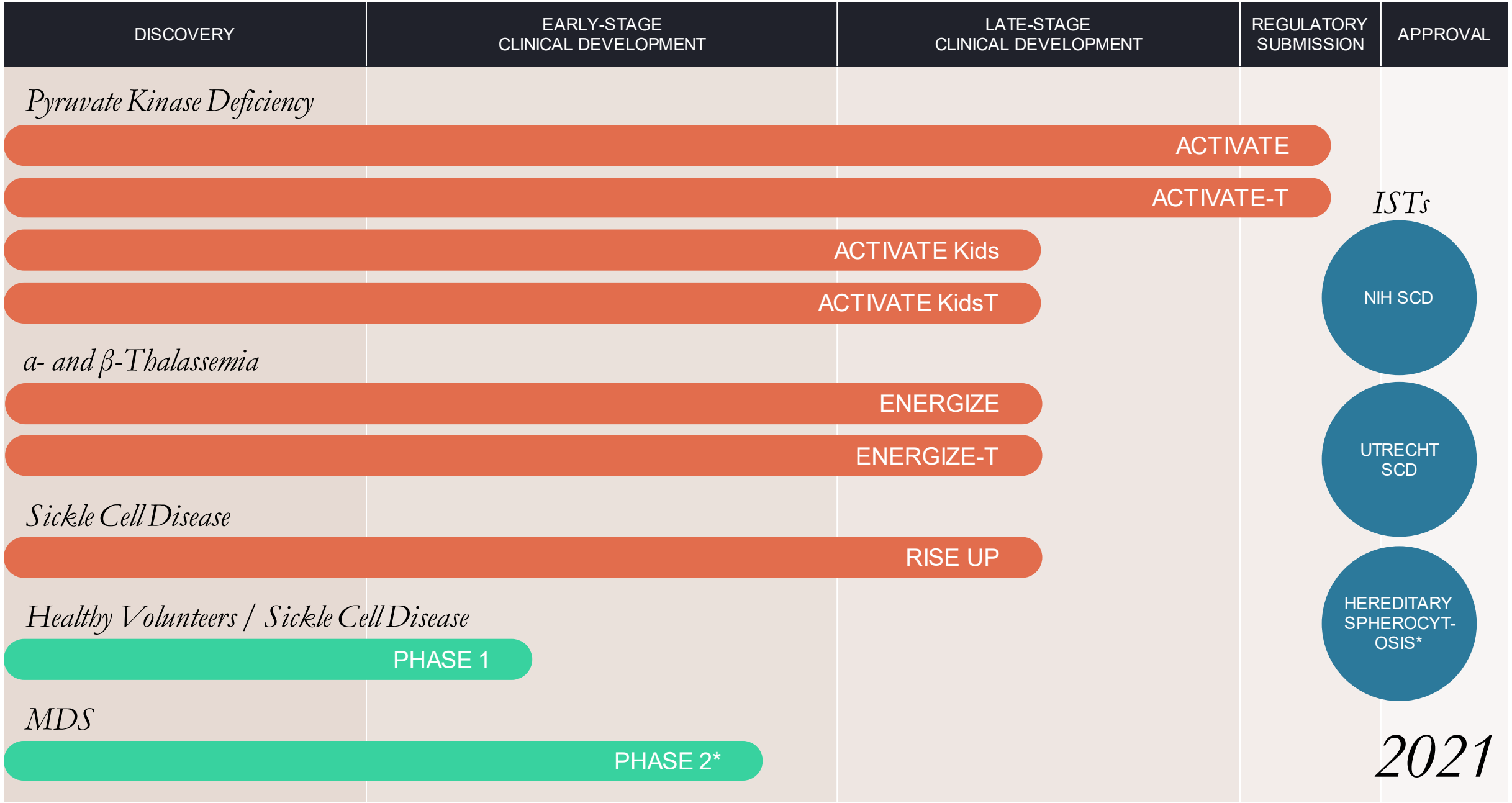
03 Our unmatched expertise in cellular metabolism has yielded a pipeline with the depth, breadth and optionality to deliver sustained productivity

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

05 We are ready to maximize the success of our first genetically defined disease product launch in a serious disease with no approved therapies

PK (Pyruvate Kinase) Activator Clinical Development

Sarah Gheuens, M.D., Ph.D.
Chief Medical Officer, Agios



MITAPIVAT AG-946

*Near-term initiation expected

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

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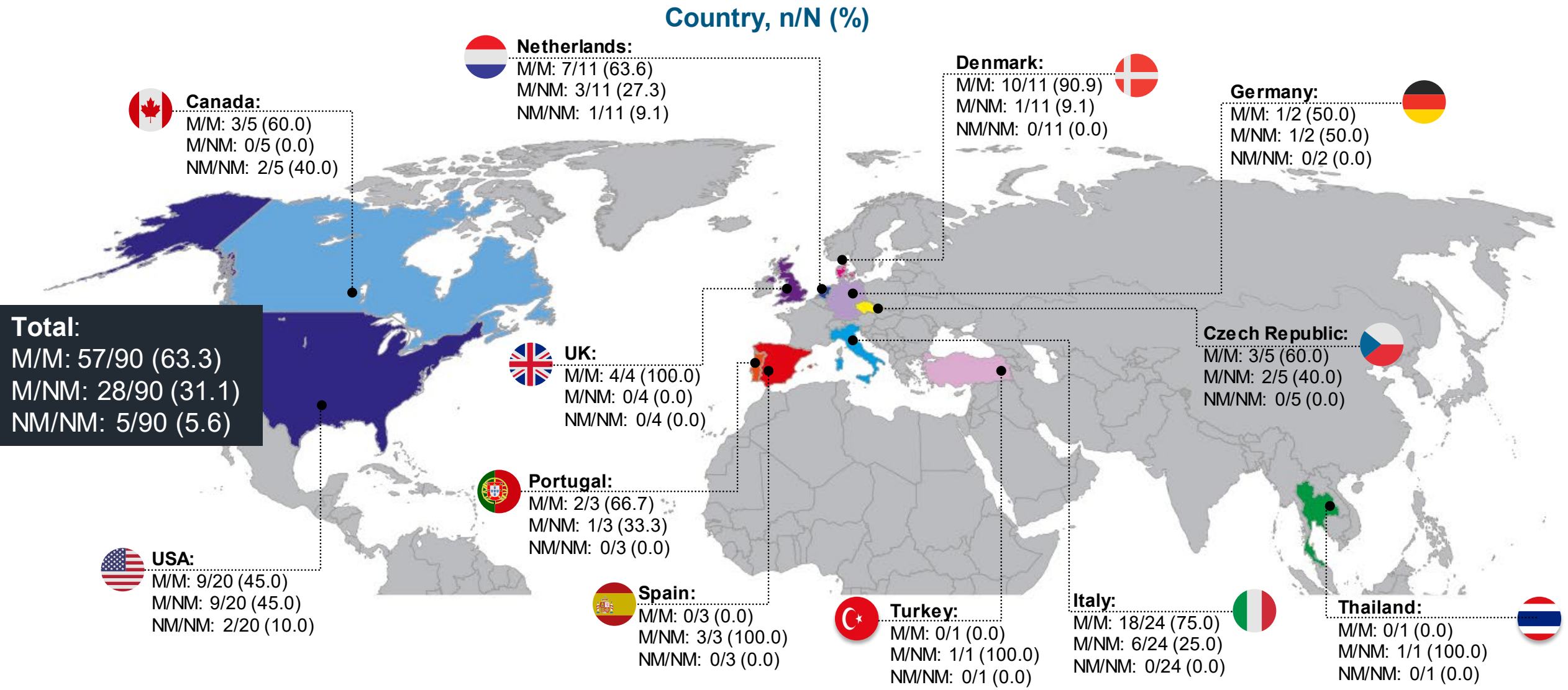
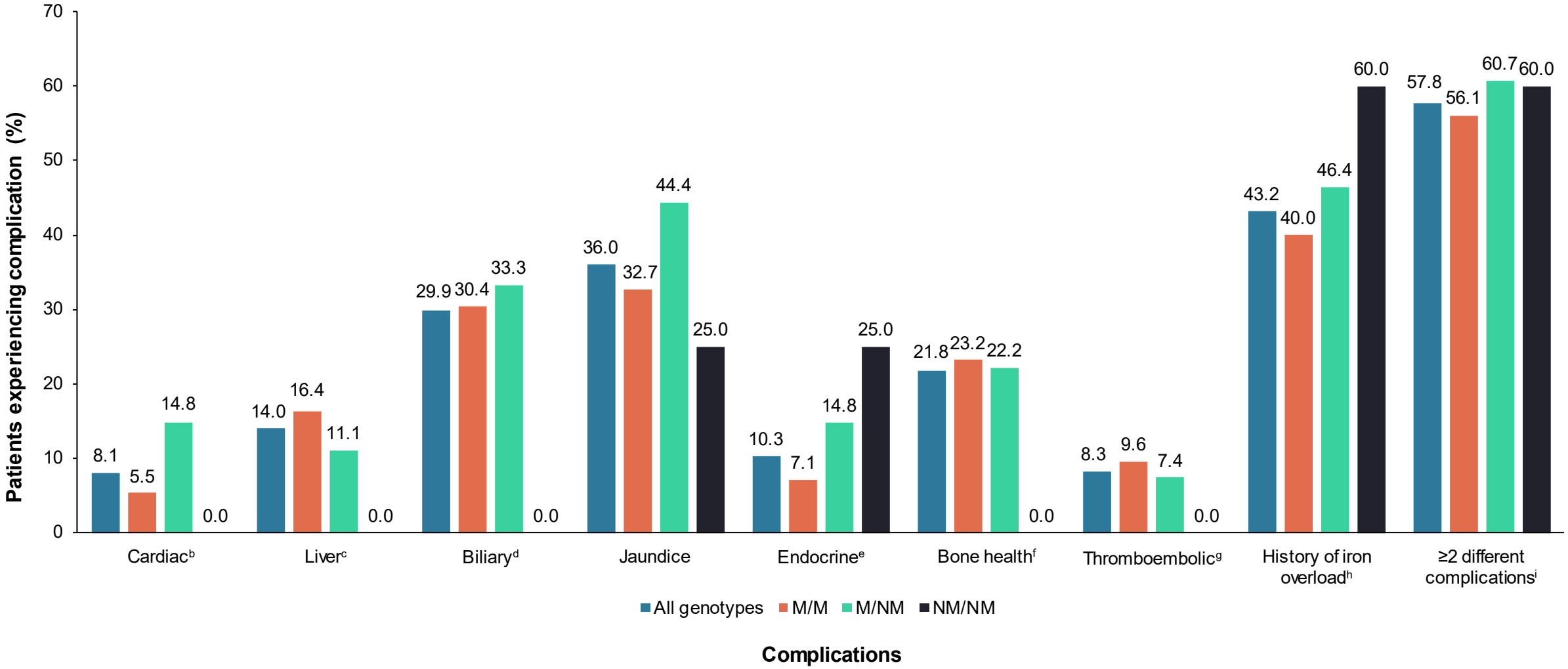
PK Deficiency

P1542: "Comorbidities and complications across genotypes in adult patients with pyruvate kinase deficiency: Analysis from the Peak Registry"



N represents the total number of adult patients from each country with available age at enrollment and complete *PKLR* genotype data in the Peak Registry as of June 2021; n represents the number of adult patients with each PK deficiency genotype enrolled in each country; M/M, missense/missense; M/NM, missense/non-missense; NM/NM, non-missense/non-missense; PK, pyruvate kinase

Regardless of genotype, adult PK deficiency patients experience a wide range of serious comorbidities/complications and require disease management



[a]Low NM/NM patient numbers make the true prevalence of complications difficult to assess; [b]Pulmonary hypertension, arrythmia, left ventricular hypertrophy, cardiac failure congestive; [c]Non-alcoholic steatohepatitis, non-alcoholic fatty liver, hepatic cirrhosis, hepatomegaly; [d]Cholecystisis, cholangitis, asymptomatic gallstones, bile duct stone; [e]Hypothyroidism, growth hormone deficiency, hypoparathyroidism, secondary hypogonadism, diabetes mellitus, nocturia, microalbuminuria, hyperthyroidism, Hashimoto's disease, Basedow's disease, thyroid mass; [f]Fracture, osteoporosis, osteopenia, bone pain; [g]Deep vein thrombosis, pulmonary embolism, 2 events classified as "other"; [h]History of iron overload defined as ever having received: 1) chelation therapy or 2)phlebotomy for removal of iron; or within 3 months of enrollment had any of: 3) ferritin >1000 ng/mL, 4) liver MRI (including FerriScan®) >3 mg Fe/g dry weight, or 5) cardiac T2* MRI ≤20 ms; [i]Complications included in the calculation of "≥2 different complications" were cardiac, biliary, liver, jaundice, endocrine, bone health, thromboembolic events, and history of iron overload; M/M, missense/missense; M/NM, missense/non-missense; MRI, magnetic resonance imaging; NM/NM, non-missense/non-missense

P1547: "Long-term treatment with oral mitapivat is associated with normalization of hemoglobin levels in patients with pyruvate kinase deficiency"

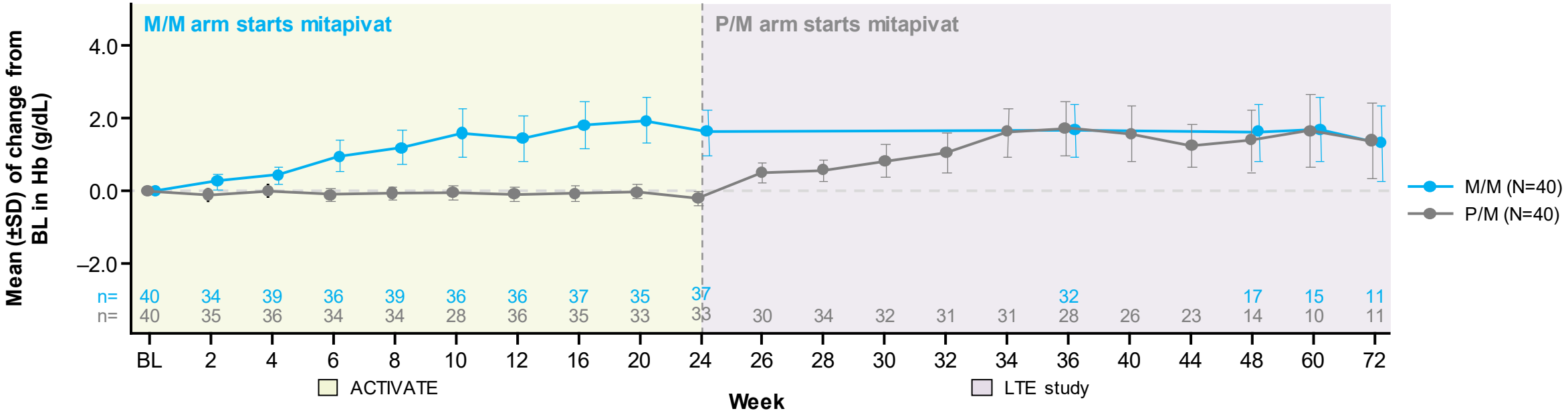


Figure 6. Mean change from baseline[a] in Hb over time in patients randomized to mitapivat or placebo in ACTIVATE who then continued in its LTE study on mitapivat[b,c]

[a]BL is defined as the average of all screening assessments within 45 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; RBC, red blood cell; SD, standard deviation

36% of all study patients and 83.9% of hemoglobin endpoint responders achieved a normal hemoglobin level at least once while receiving PYRUKYND®

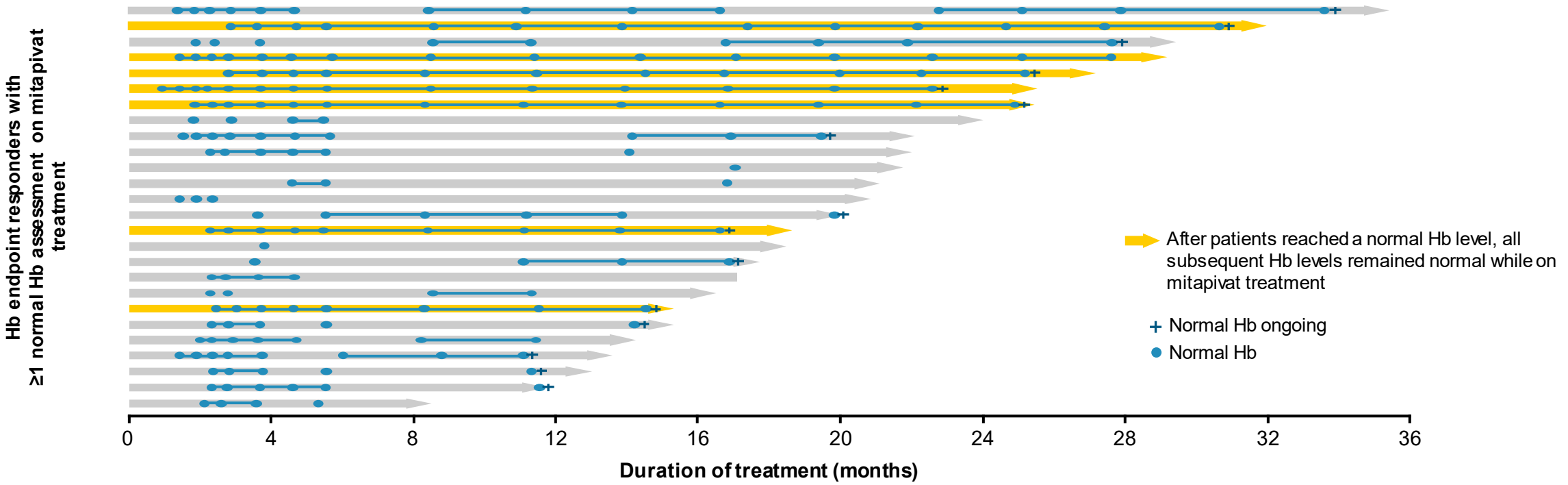
	M/M arm	P/M arm	Total
All patients in ACTIVATE and its LTE, n	40	38	78
Hb at baseline, mean (SD) g/dL	8.6 (9.90)	8.4 (9.33)	8.5 (9.58)
Patients who achieved a normal Hb level at least once during mitapivat treatment[a], n (%)	15 (37.5)	13 (34.2)	28 (35.9)
Patients in ACTIVATE and its LTE who achieved a Hb response, n (%)	16 (40.0)	15 (39.5)	31 (39.7)
Hb endpoint responders who achieved a normal Hb level at least once during mitapivat treatment[a], n (%)	14 (87.5)	12 (80.0)	26 (83.9)

Table 1. Patients who achieved a normal Hb level at least once during mitapivat treatment in ACTIVATE and its LTE

Treatment with PYRUKYND® was associated with early and robust hemoglobin responses

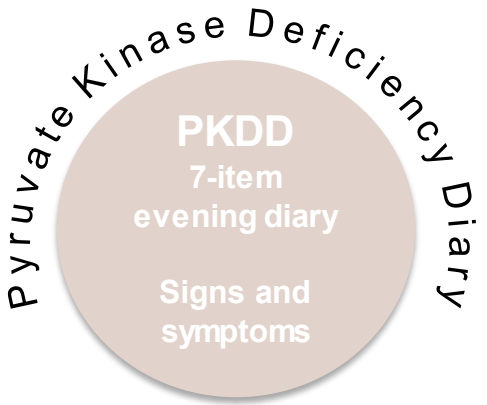
- The majority of patients in the M/M arm and all patients in the P/M arm who achieved a normal Hb level at least once in the ACTIVATE and LTE studies achieved their first normal Hb level within 4 months of treatment with mitapivat
- After reaching a normal Hb level, all subsequent Hb levels remained normal in 7 patients while on mitapivat treatment (**Figure 7**)

Figure 7. Hb endpoint responders who achieved normal Hb level at least once while receiving mitapivat



P1735: "Improvements in patient-reported outcomes in mitapivat-treated patients with pyruvate kinase deficiency: A descriptive analysis from the Phase 3 ACTIVATE trial"

- The PKDD and PKDIA were developed as self-administered tools to assess and capture changes in symptom burden and HRQoL impact in patients with PK deficiency



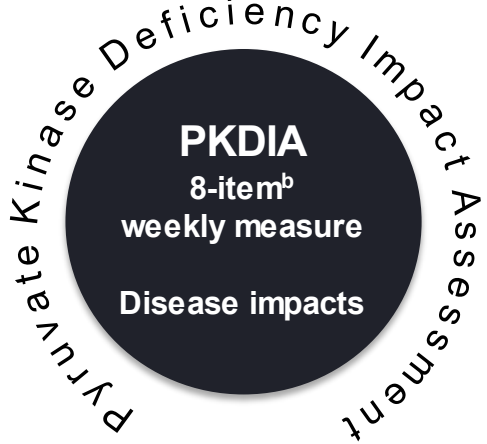
1. Tiredness at its worst
2. Tired after finishing daily activities
3. Jaundice
4. Bone pain
5. Shortness of breath
6. Energy level at beginning of day
7. Energy level at end of day

Daily sum score

Scoring algorithm

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

MCIC[a] is a reduction of 4.2



1. Finishing 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

MCIC[a] is a reduction of 5.5

In-trial validation

High internal consistency ☑

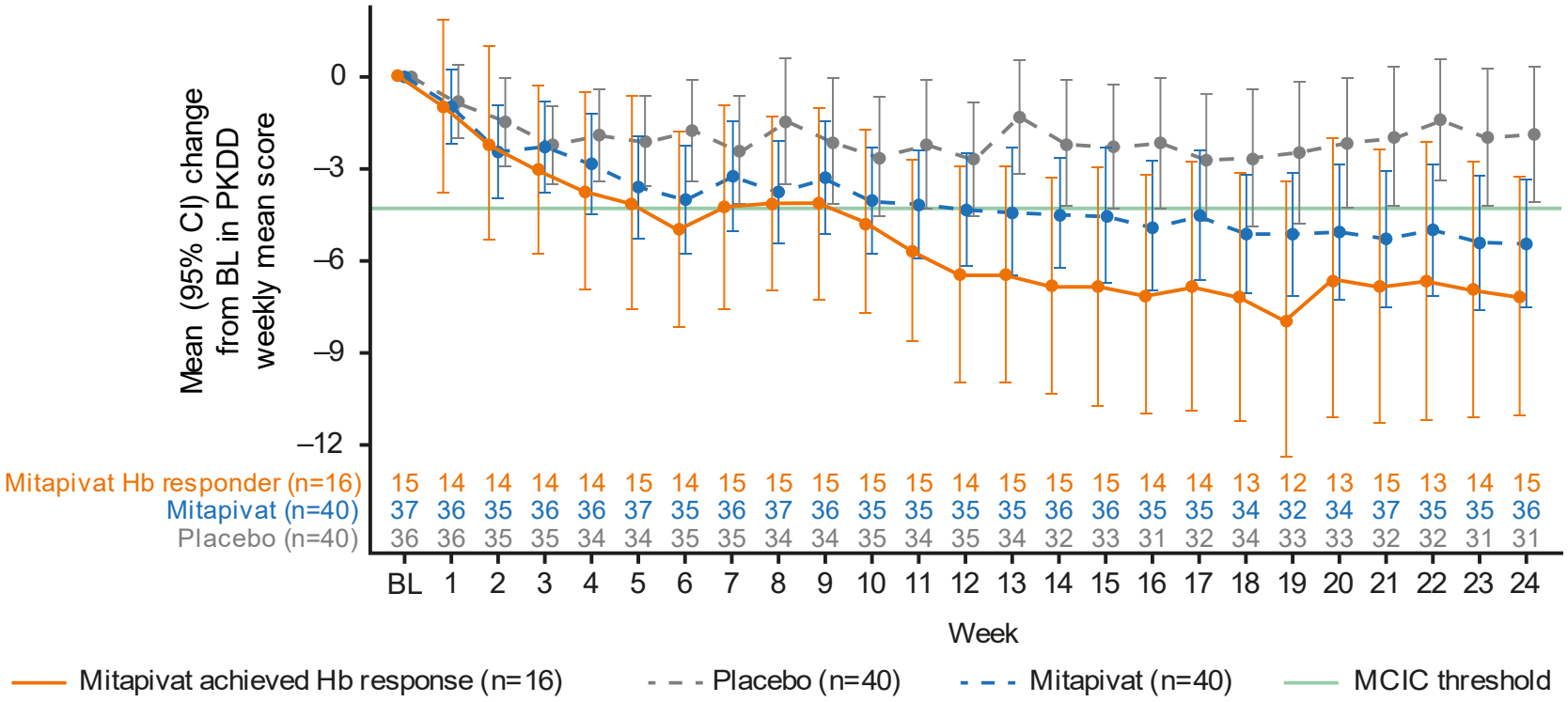
Excellent retest reliability ☑

Lower score = lower disease burden

Across both PRO instruments, improvements in quality of life were greater and clinically meaningful in hemoglobin endpoint responders

- Mitapivat led to early and sustained improvements in PKDD weekly mean score; improvements were even more pronounced in the 16 mitapivat-treated patients who achieved the primary endpoint of Hb response

Figure 5. Mean (95% CI) change from baseline in PKDD weekly mean score for patients who achieved Hb response and overall

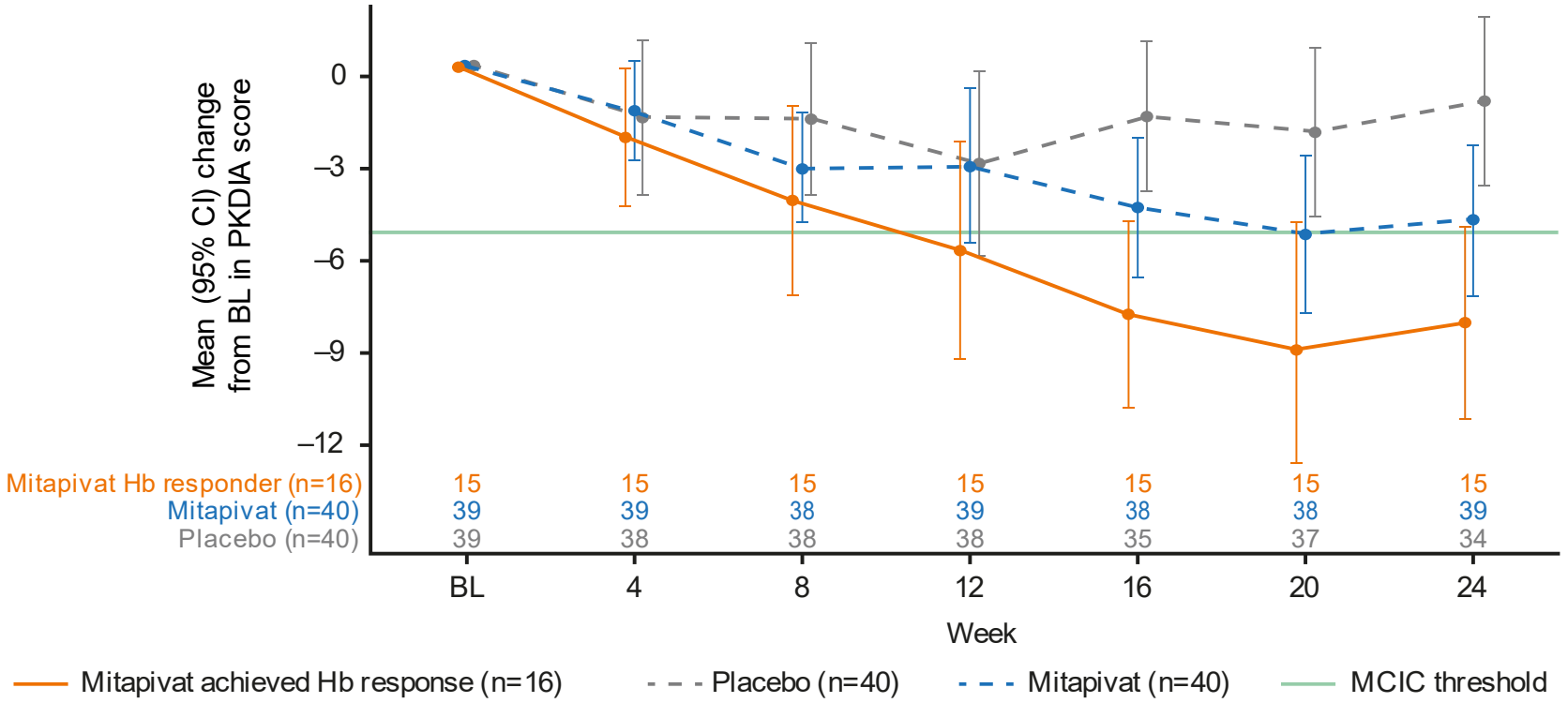


Analyses performed on the Full Analysis Set, defined as all patients who were randomized. Achieved Hb response defined as ≥1.5 g/dL increase in Hb from BL, sustained at ≥2 scheduled assessments at Wks 16, 20, and 24; BL, baseline; CI, confidence interval; Hb, hemoglobin; MCIC, minimal clinically important change; PKDD, pyruvate kinase deficiency diary; Wk, Week

Across both PRO instruments, improvements in quality of life were greater and clinically meaningful in hemoglobin endpoint responders

- Mitapivat led to early and sustained improvements in PKDIA score; improvements were even more pronounced in the 16 mitapivat-treated patients who achieved the primary endpoint of Hb response

Figure 6. Mean (95% CI) change from baseline in PKDIA score for patients who achieved Hb response and overall



Analyses performed on the Full Analysis Set, defined as all patients who were randomized. Achieved Hb response defined as ≥1.5 g/dL increase in Hb from BL, sustained at ≥2 scheduled assessments at Wks 16, 20, and 24; BL, baseline; CI, confidence interval; Hb, hemoglobin; MCIC, minimal clinically important change; PKDIA, pyruvate kinase deficiency impact assessment; Wk, Week

Key takeaways

- Findings from the PEAK registry show that adult patients across PKLR genotypes experienced a wide range of serious comorbidities/complications across multiple systems
- Treatment with mitapivat was associated with early and robust Hb responses, with 36% of all study patients and 83.9% of Hb endpoint responders achieving a normal Hb level at least once while receiving mitapivat
- The post hoc analysis from ACTIVATE further suggests that across both PRO instruments, improvements in HRQoL were even greater and were clinically meaningful in the subset of mitapivat-treated patients who achieved the primary endpoint of Hb response
- These new findings add to previously reported data from ACTIVATE, ACTIVATE-T, and their LTE and provide additional evidence that mitapivat is an effective and disease-modifying therapy for patients with PK deficiency, irrespective of transfusion needs

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Thalassemia

Thalassemia represents a significant opportunity to make a global impact

Global Reach

- Estimated 18–23K α- and β-thalassemia patients across the U.S. & 5EU
  - Approx. 50/50 split between U.S. and EU
  - Approx. 1/3 are α-thalassemia patients
- Significant opportunity outside of U.S./EU

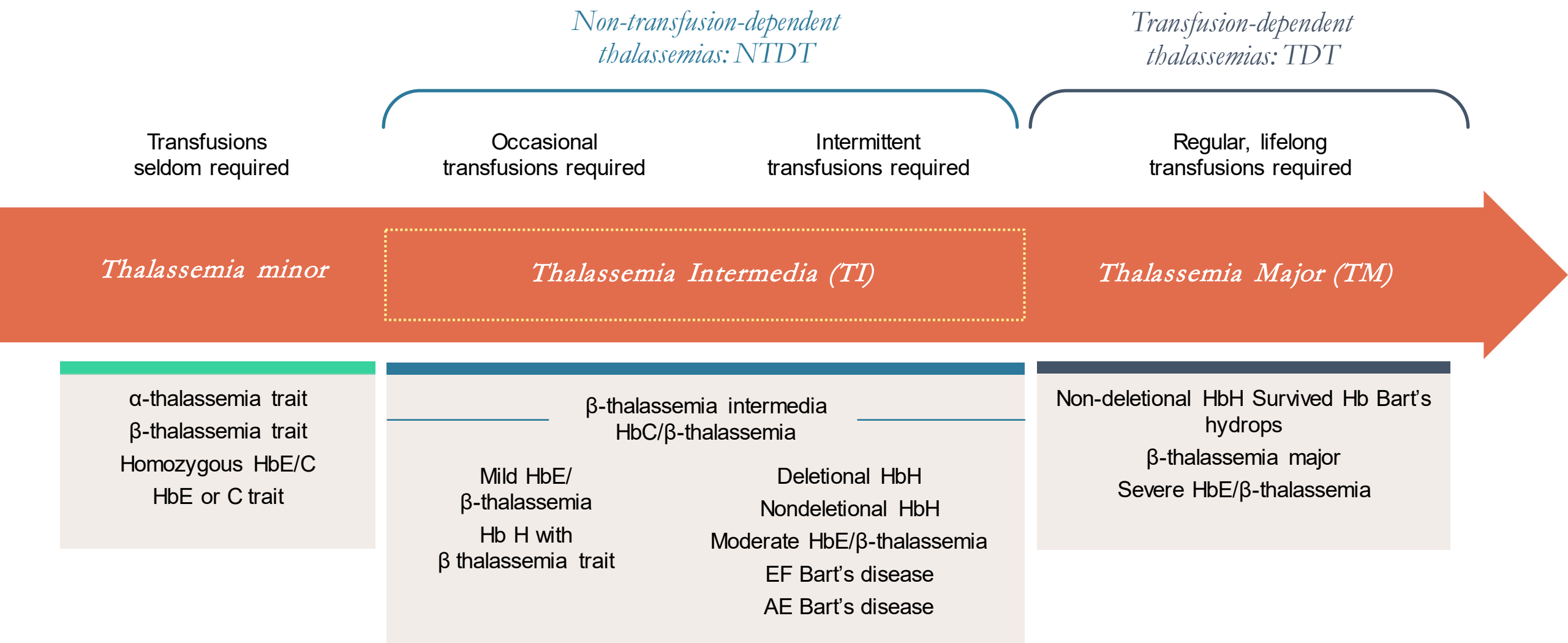
Unmet Medical Need

- No approved therapies for α-thalassemia
- Limited options in β-thalassemia and NTD
- NTD and α-thalassemia not well understood

Critical Success Factors

- Evaluating mitapivat across full spectrum of disease
- Global approach to clinical development
- Building connections with thalassemia patient and physician communities

Current classification of thalassemia syndromes



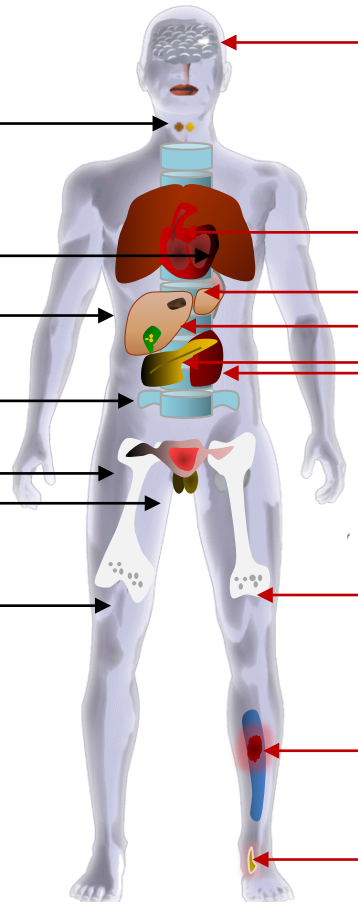
Hb = hemoglobin; NTDT = non-transfusion-dependent thalassemia; TDT = transfusion-dependent thalassemia.

Viprakasit V, Ekwattanakit S. Hematol Oncol Clin North Am 2018;32:193–211.

Common clinical complications in TDT vs. NTDT

TDT

- Hypothyroidism
- Hypoparathyroidism
- Cardiac siderosis
- Left-sided heart failure
- Hepatic failure
- Viral hepatitis
- Diabetes mellitus
- Hypogonadism
- Osteoporosis



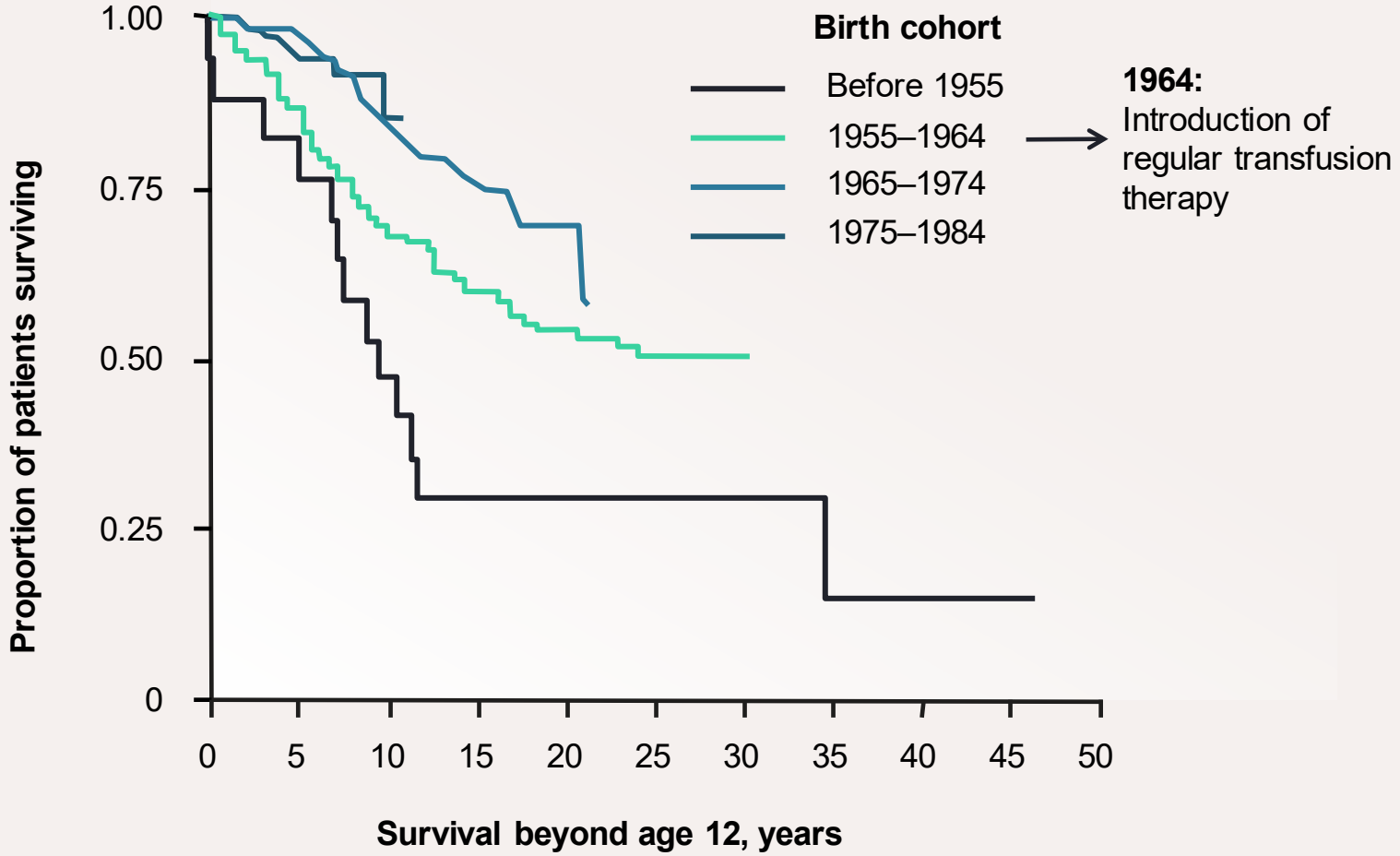
NTDT

- Silent cerebral ischemia
- PHT
- Right-sided heart failure
- Extramedullary hematopoietic pseudotumors
- Hepatic fibrosis, cirrhosis, and cancer
- Gallstones
- Splenomegaly
- Osteoporosis
- Venous thrombosis
- Leg ulcers

NTDT, non-transfusion-dependent thalassemia; PHT, pulmonary hypertension; TDT, transfusion-dependent β-thalassemia.
Adapted from Musallam KM et al. Haematologica 2013;98:833–44.

The introduction of transfusions improved survival with TDT[1,2]

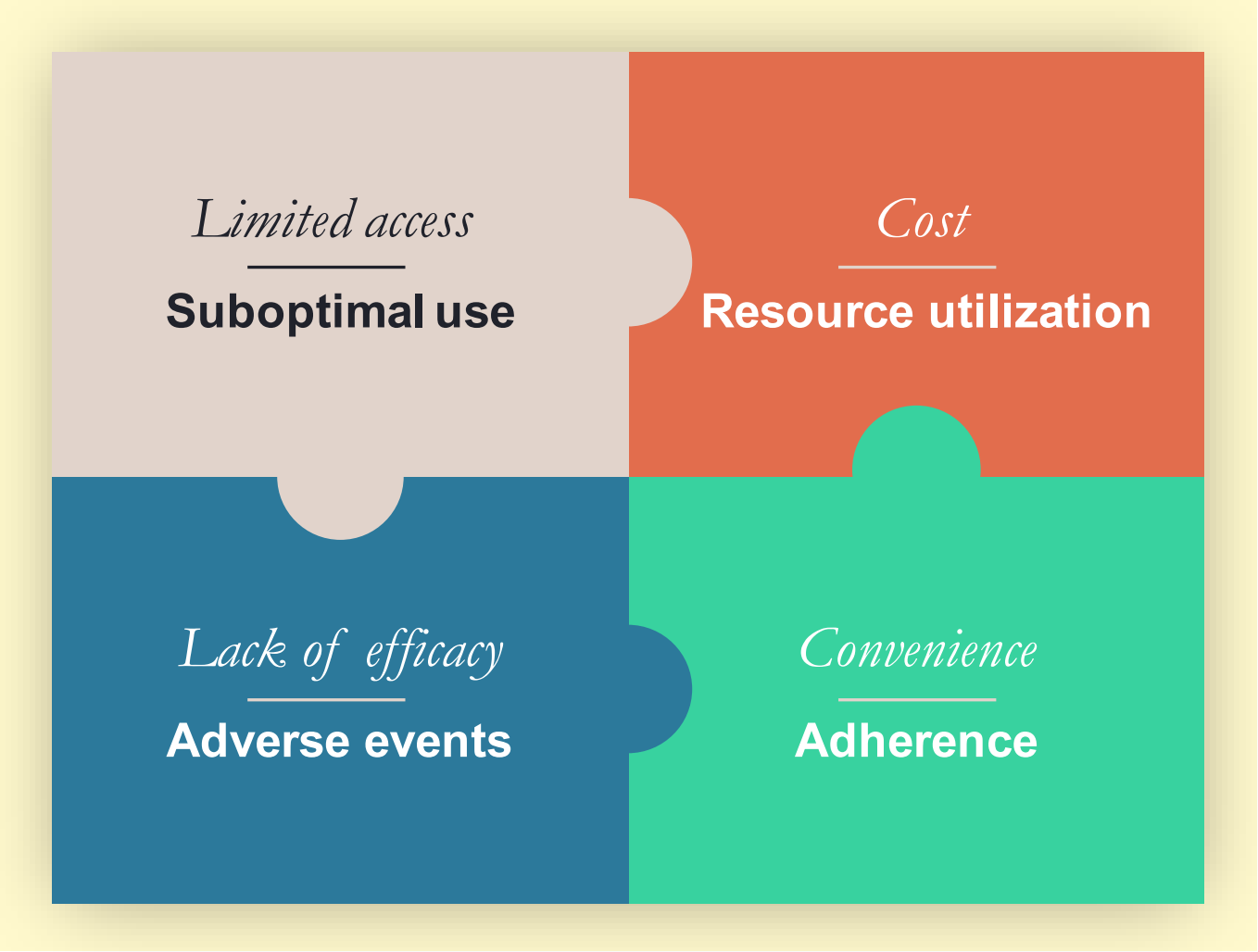
Left untreated, patients would die within a few years of birth[1]



TDT, transfusion-dependent β-thalassemia

1. Cao A. Haematologica 2004;89:1157–59; 2. Modell B et al. Lancet 2000;355:2051–2.

Despite significant advances, continued challenges remain in the management of TDT



Clinical Therapeutics/Volume 42, Number 2, 2020

Reviews

Systematic Literature Review of the Burden of Disease and Treatment for Transfusion-dependent β-Thalassemia

Marissa Betts, MS[1]; Patrick A. Flight, PhD[2]; L. Clark Paramore, MSPH[2]; Li Tian, PhD[1]; Dušan Milenković, MSc[3]; and Sujit Sheth, MD[4]

[1]*Evidera, Waltham, MA, USA;* [2]*bluebird bio, Cambridge, MA, USA;* [3]*Evidera, London, United Kingdom; and* [4]*Department of Pediatrics, Weill Cornell Medicine, New York, NY, USA*

Received: 1 February 2019 | Accepted: 5 February 2019

DOI: 10.1002/ajh.25429

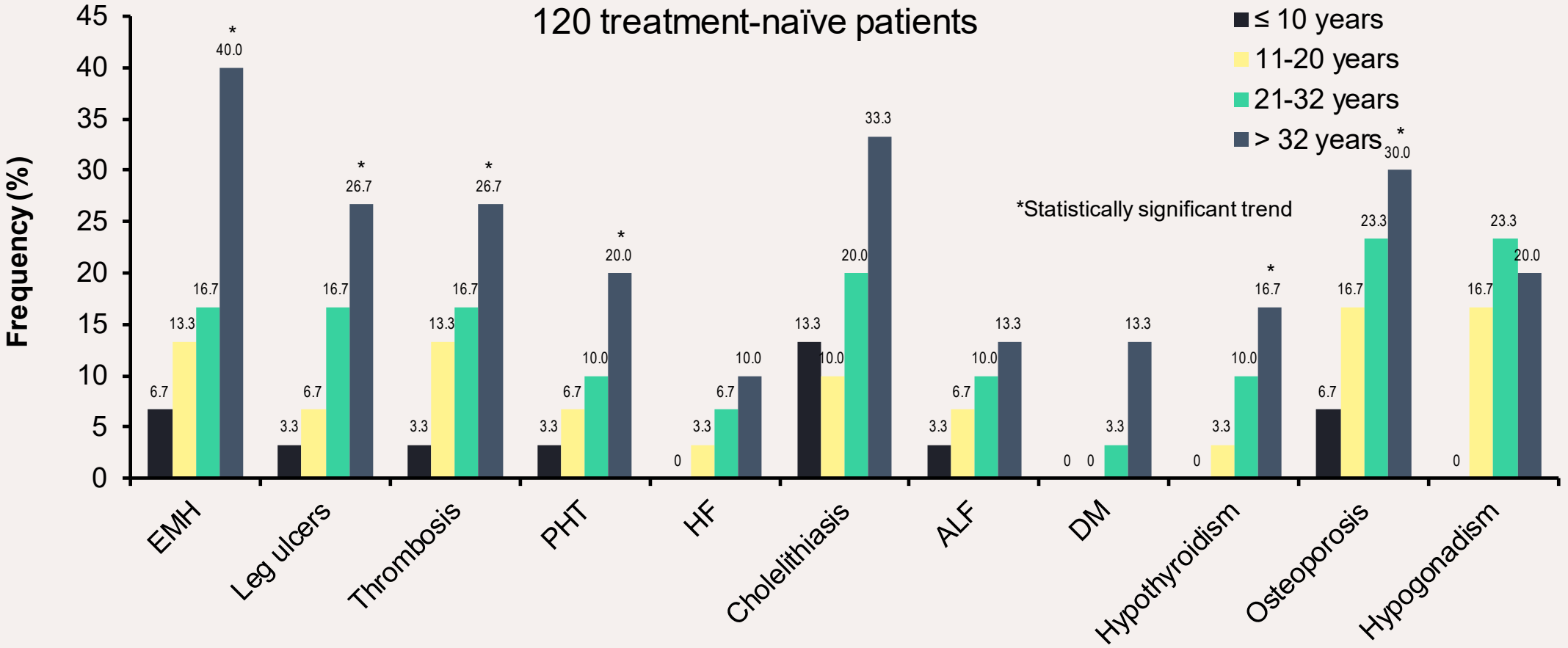
Clinical and economic burden of regularly transfused adult patients with β-thalassemia in the United States: A retrospective cohort study using payer claims

Mia Weiss[1,2]; Monica Parisi Jun[2]; Sujit Sheth[3]
[1]Columbia University Mailman School of Public Health, New York, New York
[2]Celgene Corporation Summit, New Jersey
[3]Weill Cornell Medicine, New York, New York

1. Weiss M et al. Am J Hematol 2019;94:E129–E132; 2. Betts M et al. Clin Ther 2020;42:322–37.

Patients with NTDT experience significant disease burden that increases with advancing age

Frequency of complications across the different age quartiles

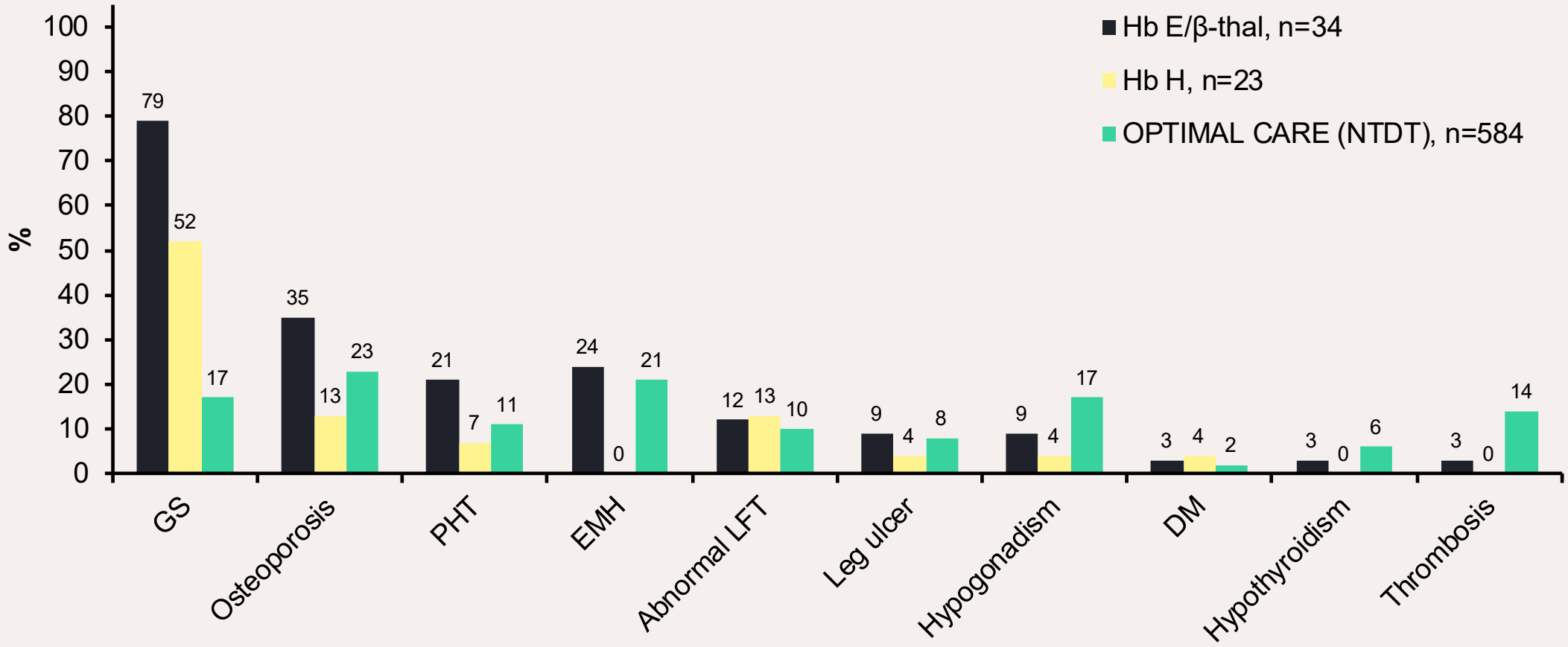


ALF, abnormal liver function; DM, diabetes mellitus; EMH, extramedullary hematopoiesis; HF, heart failure; NTDT, non-transfusion-dependent β-thalassemia; PHT, pulmonary hypertension.

Taher AT et al. Br J Haematol 2010;150:486–9.

Significant disease burden for patients with α-Thalassemia (HbH)

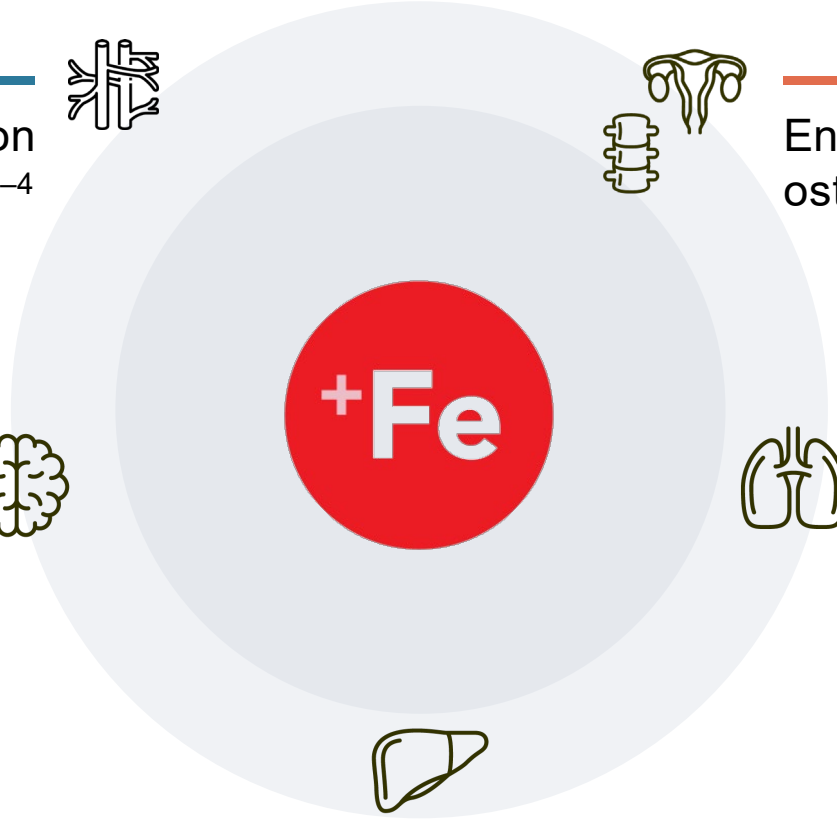
Comparison of thalassemia-related complications (%)



GS; gall stones; DM, diabetes mellitus; EMH, extramedullary hematopoiesis; PHT, pulmonary hypertension.

1. Ekwattanakit S et al. Am J Hematol 2018;93:623–629; 2. Taher AT et al. Blood 2010;155:1886-92.

Iron overload is a major contributor to multiple morbidities in NTDT



Pulmonary hypertension and venous thrombosis[1–4]

Endocrinopathy and osteoporosis[1–4]

Silent cerebral infarcts (MRI), large vessel stenosis (MRA), decreased neuronal function (PET-CT)[5–7]

Proteinuria and end-stage renal disease[8,9]

Hepatic fibrosis, cirrhosis, and HCC[10,11]

OPTIMAL CARE (n = 584)

ORIENT (n = 52)

Other local and regional collaborations

Notable absence of cardiac siderosis despite elevated liver iron content

HCC, hepatocellular carcinoma; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NTDT, non-transfusion-dependent β-thalassemia; PET-CT, positron emission tomography-computed tomography.

1. Musallam KM et al. Haematologica 2011;96:1605–12; 2. Musallam KM et al. Blood Cells Mol Dis 2013;51:35–8; 3. Musallam KM et al. Haematologica 2014;99:e218–e221; 4. Taher AT et al. Blood 2010;115:1886–92; 5. Taher AT et al. J Thrombosis Haemost 2010;8:54–9; 6. Musallam KM et al. Eur J Haematol 2011;87:539–46; 7. Musallam KM et al. Ann Hematol 2012;91:235–41; 8. Ziyadeh FN et al. Nephron Clin Pract 2012;121:c136–143; 9. Mallat NS et al. Blood Cells Mol Dis 2013;51:146–8; 10. Musallam KM et al. Blood Cells Mol Dis 2012;49:136–9; 11. Moukhadder HM et al. Cancer 2017;123:751–8.

Phase 2, open-label trial of mitapivat in adults with α- or β-NTDT supports advancement of pivotal program

Results from core period[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

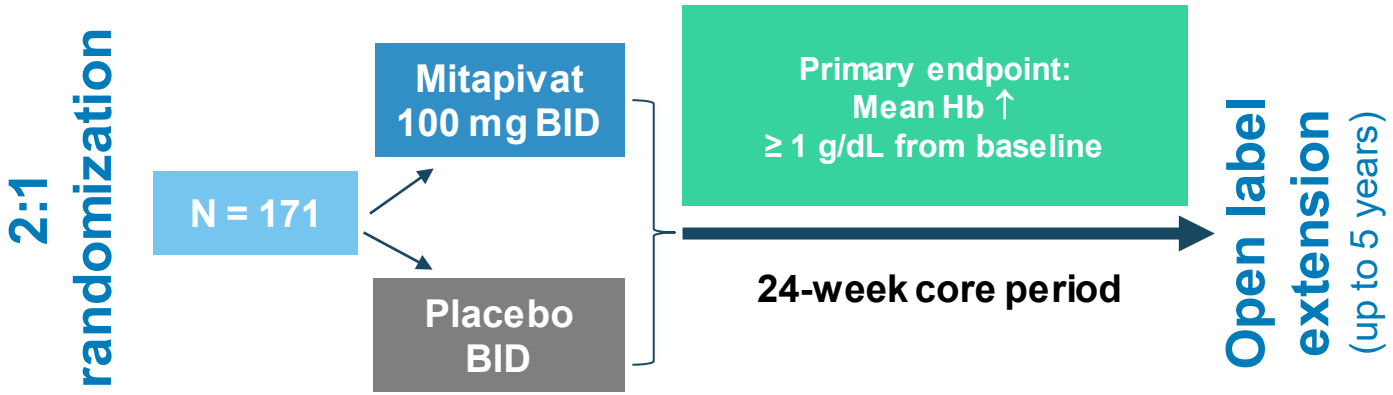
Extension period[2]

- 17 patients entered the extension period and 16 remain on treatment as of the data cutoff
- 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
- The safety profile was consistent with that observed during the core period
  - BMD remained stable over time

[1]Data presented at EHA 2021
[2]Data presented at ASH 2022

Two global, Phase 3, randomized controlled trials of mitapivat in thalassemia recently initiated

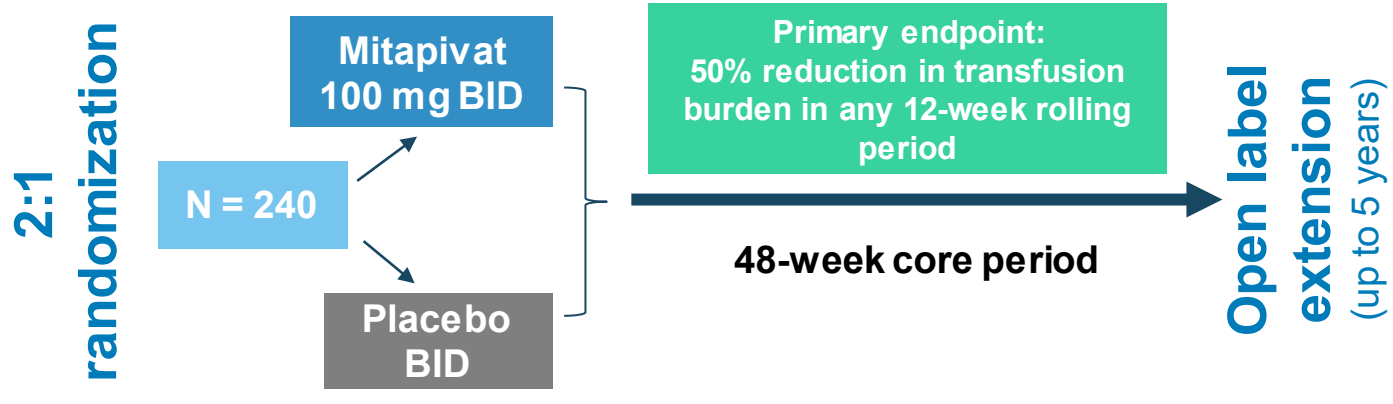
ENERGIZE



Key inclusion criteria

- ≥ 18 years
- β-thalassemia ± α-globin mutations, HbE β-thalassemia, or α-thalassemia (HbH disease)
- Non-transfusion-dependent defined as ≤5 RBC units during the 24-week period before randomization and no RBC transfusions ≤8 weeks prior
- Hb ≤ 10.0 g/dL

ENERGIZE-T



Key inclusion criteria

- ≥ 18 years
- β-thalassemia ± α-globin mutations, HbE β-thalassemia, or α-thalassemia (HbH disease)
- Transfusion-dependent defined as 6 to 20 RBC units transfused and ≤6-week transfusion-free period during the 24-week period before randomization

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

Key takeaways

1. Thalassemia represents a significant opportunity to make a global impact, and mitapivat has the potential to address a range of thalassemia types and severity

2. Despite significant advances, continued challenges remain in the management of thalassemia

3. Patients with non-transfusions dependent thalassemia experience significant disease burden that increases with age

4. There is a lack of literature in non-transfusion dependent thalassemia and alpha-thalassemia in particular

5. Agios is actively working on a number of activities to fill these data gaps and improve the understanding of the burden in alpha-thalassemia

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Sickle Cell Disease

Our approach in sickle cell disease sets us apart

Global Reach

- Estimated 120-135K patients across the U.S. & 5EU
- Significant opportunity outside of U.S./EU

Unmet Medical Need

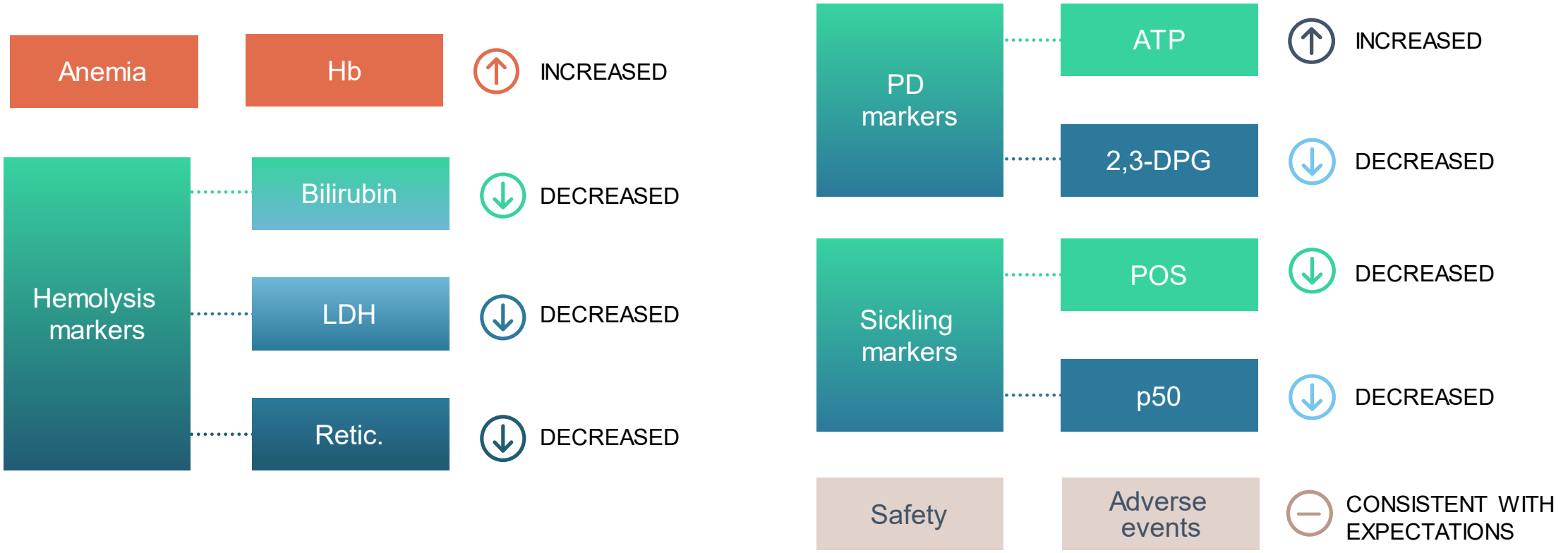
- No approved therapy addresses both pain episodes and anemia
- Need for innovative therapies with convenient, oral administration

Critical Success Factors

- Innovative seamless Phase 2/3 trial developed with community input reduces enrollment barriers & addresses key aspects of disease
- Global approach to clinical development
- Building connections with SCD patient and physician communities

Two collaborator-led studies of mitapivat in sickle cell disease support advancement of program to pivotal studies

Data from collaborator-led studies from NIH and University of Utrecht confirm safety profile and demonstrate early efficacy in 20+ patients with sickle cell disease

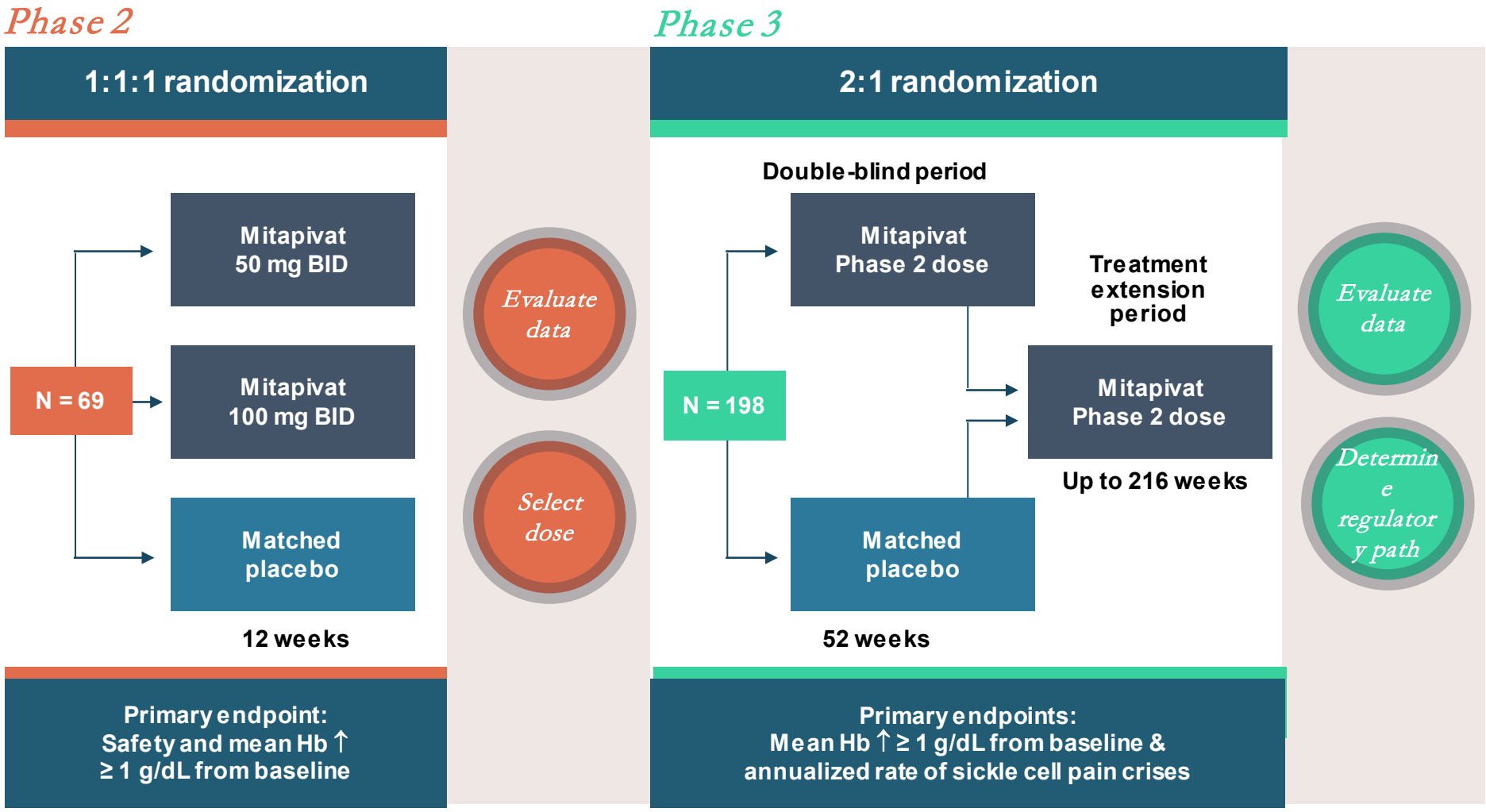


Xu JS et al. *42nd ASH Annual Congress 2020*: Abstract #681; Data on File; Agios Pharmaceuticals Press Release; Dec 07, 2020.
ATP = adenosine triphosphate; BID = twice daily; DPG = diphosphoglycerate; Hb = hemoglobin; Hb SS = sickle cell anemia.

RISE UP Phase 2/3 operationally seamless trial in sickle cell disease to initiate by YE 2021

ENROLLMENT CRITERIA

- ≥ 16 years
- Had 2-10 sickle cell crises in the past 12 months
- Hb ≥ 5.5 and ≤ 10.5 g/dL
- Patients currently receiving treatment with voxelotor, crizanlizumab, or any other agent intended to increase Hb-oxygen affinity are excluded
- Treatment with hydroxyurea is allowed



BID = twice daily; Hb = hemoglobin

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Dr. Eduard van Beers is Attending Physician at the Van Creveld Clinic and an Internist/Hematologist in Internal Medicine/Hematology at the University Medical Center Utrecht in Utrecht, Netherlands. He is also Associate Professor in the Department of Clinical Chemistry and Hematology and Associate Investigator at the Van Creveldkliniek, Center for Benign Hematology, UMCU, Utrecht University, the Netherlands.

After receiving his medical degree, Dr. van Beers completed his doctorate in Medicine at the University of Amsterdam in Amsterdam, Netherlands on sickle cell disease, pathophysiology, and clinical complications. Following receipt of his degrees, he then completed fellowships in Hematology at the Academic Center in Amsterdam, Netherlands, and served as a visiting fellow at the Gregory Kato lab, Hematology branch NIH, NHLBI, Bethesda, Maryland. He is currently the coordinator of research and trials for the European Reference Network Eurobloodnet.

Dr. Van Beers' areas of interest include classical hematological conditions, coagulation disorders, and patients with congenital or acquired defects of the red blood cells and platelets, and increased bleeding or increased clotting tendency. He specializes in rare hereditary hemolytic diseases, such as pyruvate kinase deficiency. His current research focuses on the effects of anemia caused by the abnormal and accelerated destruction of red blood cells. Dr. van Beers has authored several peer-reviewed manuscripts and is a member of multiple professional societies.

Dr. Eduard Van Beers has been involved in the following studies with Agios for PK Deficiency: DRIVE PK, NHS, PEAK, ACTIVATE and ACTIVATE-T, Maintenance of effect and Pooled 003/006/007 BMD on-treatment., Iron Overload and Ineffective Erythropoiesis on-treatment, ESTIMATE (IST).

Follow-up results of a phase 2 study assessing the safety and efficacy of mitapivat treatment, an oral pyruvate kinase activator, for up to 60 weeks in subjects with sickle cell disease

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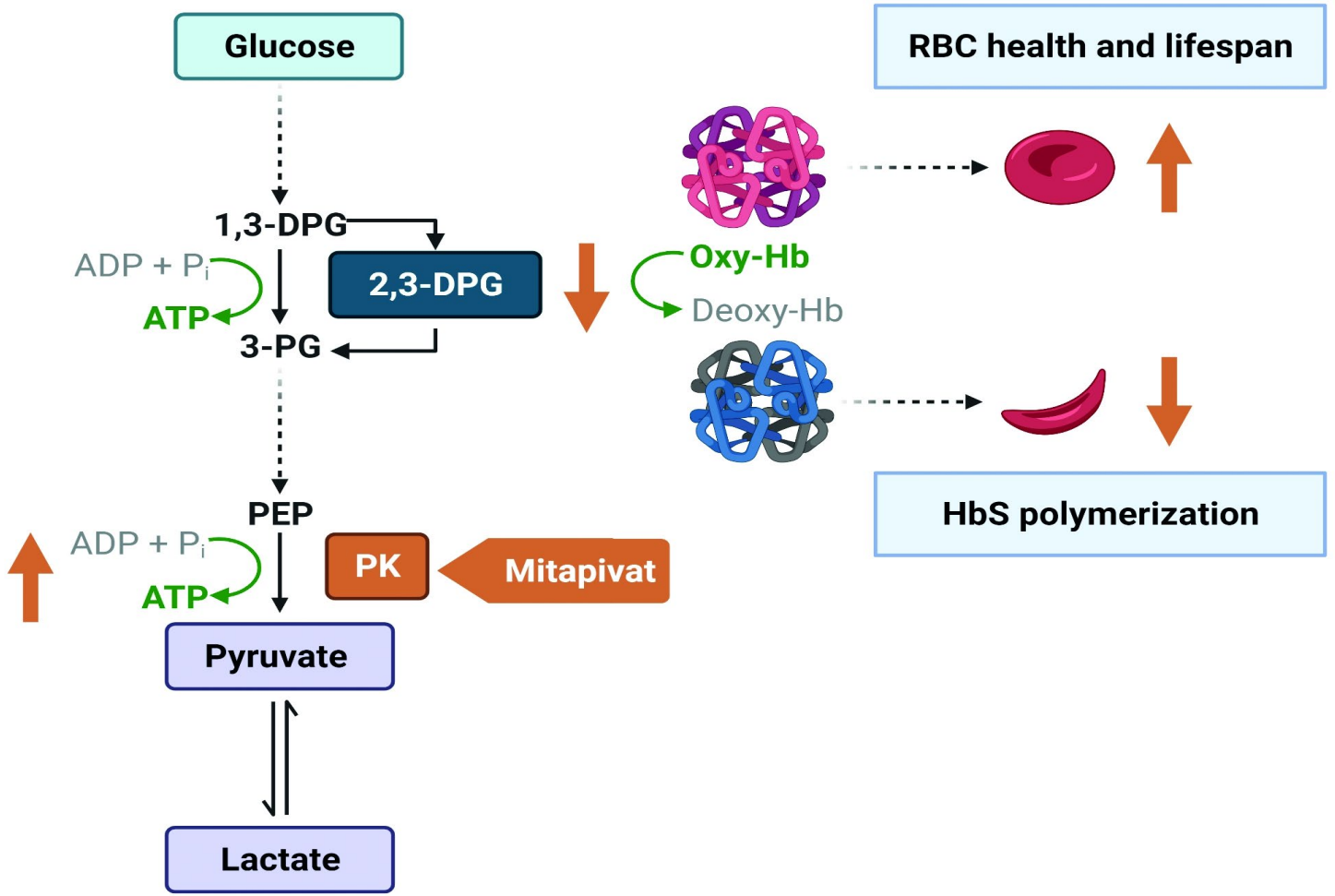
Background

- In SCD, polymerization of HbS upon deoxygenation results in poorly deformable sickled RBCs with a shortened lifespan
- 2,3-DPG, a glycolytic intermediate in RBCs, promotes deoxygenation by lowering Hb-oxygen affinity
- Mitapivat (AG-348) is an oral allosteric activator of PK, a key enzyme in RBC glycolysis generating ATP and reducing 2,3-DPG levels (**Figure 1**)

Figure 1. Effects of mitapivat-mediated PK activation in SCD



2,3-DPG, 2,3-diphosphyglycerate; ATP, adenosine triphosphate; Hb, hemoglobin; HbS, hemoglobin S; PK, pyruvate kinase; RBC, red blood cell; SCD, sickle cell disease

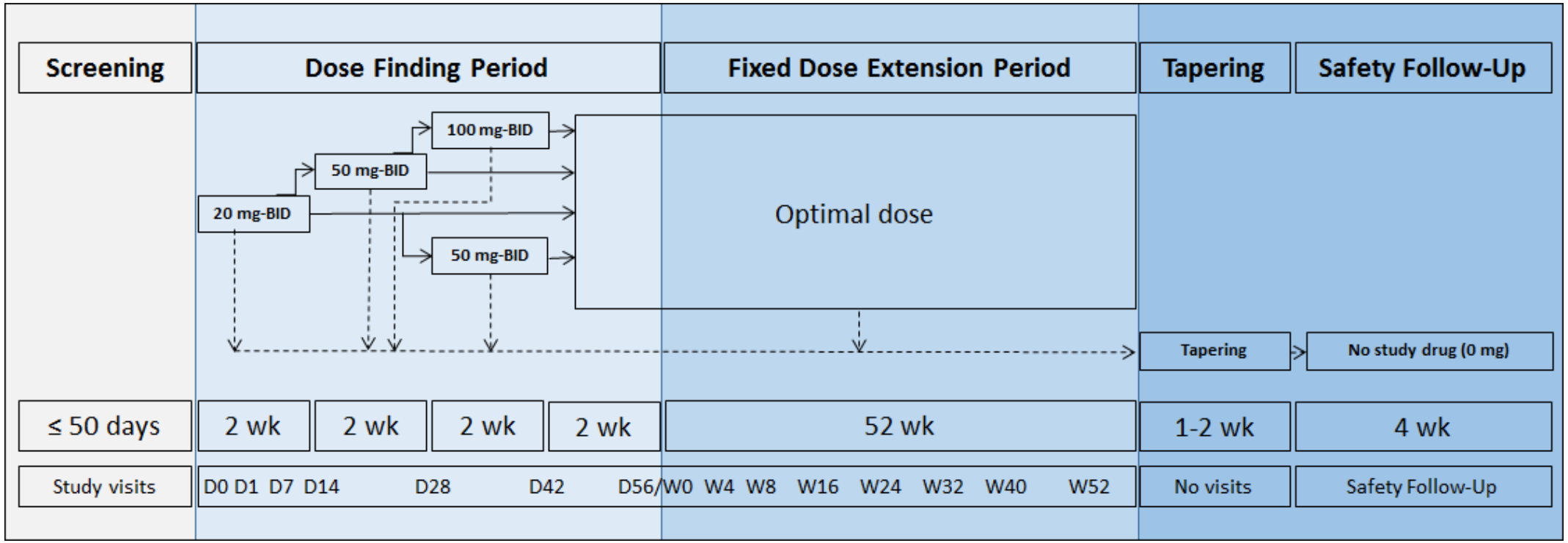
Objective

- To report follow-up data of the safety and efficacy of mitapivat treatment in subjects with SCD enrolled in the currently ongoing phase 2, investigator initiated, open-label study: the ESTIMATE study (www.trialregister.nl NL8517; EudraCT 2019-003438-18). *Cut-off date: January 1, 2022*

Methods

- Time periods over which study data were considered are depicted in the study schema (**Figure 2**)
- The 8-week mitapivat dose finding period is followed by a 52-week FDEP

Figure 2. Study schema of the ESTIMATE study



FDEP, fixed-dose extension period

Major eligibility criteria

- Subjects ≥16 years with SCD (HbSS, HbS/β0, HbS/β+)
- 1-10 VOCs in the prior year and/or prior SCD-related complications
- Hb level >6.1 g/dL and ≤11.1 g/dL
- Stable dose of hydroxyurea, if applicable (≥3 months prior to the first day of study drug)
- Adequate organ function
- No chronic transfusion (not >4 RBC units during the 12-month period and/or within the 3 months prior to the first day of study drug)

Hb, hemoglobin; RBC, red blood cell; SCD, sickle cell disease; VOC, vaso-occlusive crisis

Results: Baseline characteristics

- n=9 received mitapivat treatment
- Median age 22 years (range 16-59);
- 6/9 (67%) female
- 6/9 (67%) used hydroxyurea;
- 7/9 (78%) HbSS, 1/9 (11%) HbS/β^0, 1/9 (11%) HbS/β^+

Results: Safety

- The most common TEAEs; n>2 subjects): ALT or AST increase (both 5/9, 56%; all grade 1), headache (4/9, 44%; grade 1–2)
- n=1 non-treatment related SAE of a urinary tract infection (grade 4), lost to follow-up shortly after first dosing
- Median treatment duration of remaining n=8 of 38 weeks (range 11–60 weeks)
- No other SAEs or TEAEs grade ≥3

ALT, alanine transaminase; AST, aspartate aminotransferase; SAE, serious adverse event; TEAE, treatment-emergent adverse event

Results: Efficacy

- **Table 1** summarizes mean changes in primary and secondary endpoint parameters in the FDEP versus baseline
- Hb level significantly increased, accompanied by a decrease in markers of hemolysis (ARC, total bilirubin, LDH) (**Figure 3A-D**)
- RBC sickling (PoS, oxygen gradient ektacytometry) and 2,3-DPG level decreased, and Hb oxygen affinity (p50, Hemox Analyzer) as well as ATP/2,3-DPG ratio significantly improved (**Figure 3E-H**)
- Mean annual VOC rate and SCD-related hospital admission days in the 2 years prior to starting study treatment were, respectively, 1.5±1.3 and 5.9±7.1 days, and reduced to 0.5±0.7 and 1.6±3.1 days when weighting cases by follow-up duration (p=0.021 and p=0.134, respectively)

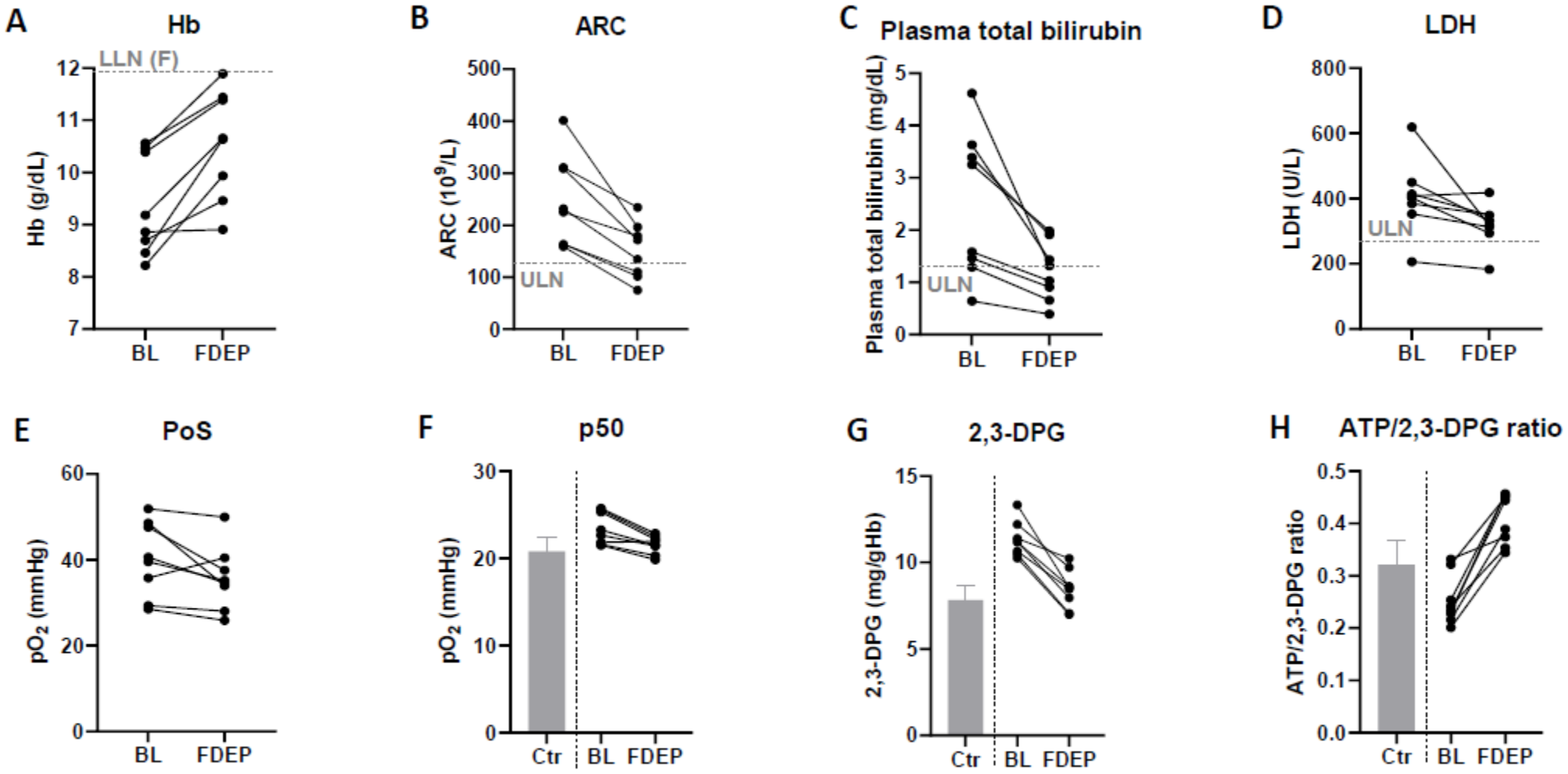
2,3-DPG, 2,3-diphosphyglycerate; ARC, absolute reticulocyte count; ATP, adenosine triphosphate; FDEP, fixed-dose extension period; Hb, hemoglobin; LDH, lactate dehydrogenase; p50, oxygen pressure at which Hb is 50% saturated with oxygen; PoS, point of sickling; RBC, red blood cell; SCD, sickle cell disease; VOC, vaso-occlusive crisis

Table 1. Mean changes in Hb, parameters of hemolysis, sickling tendency, and biochemical parameters in the FDEP compared to baseline of patients with SCD treated with mitapivat (n=8)

Parameter (unit)	Baseline	FDEP	p-value[a]
Hb (g/dL)	9.4±1.0	10.5±1.0	0.001
ARC (10^9/L)	246±88	150±54	0.001
Total bilirubin (mg/dL)	2.5±1.4	1.2±0.6	0.010
LDH (U/L)	404±114	320±67	0.017
PoS (mmHg)	40.2±8.8	35.7±7.5	0.065
p50 (mmHg)	23.4±1.8	21.6±1.0	0.002
2,3-DPG (mg/gHb)	11.3±1.0	8.6±1.3	<0.001
ATP (mg/gHb)	2.9±0.7	3.4±0.3	0.161
ATP/2,3-DPG ratio	0.25±0.05	0.41±0.05	0.002

Data are presented as mean ± standard deviation. [a]Paired t-tests or Wilcoxon signed-rank tests were used when appropriate; 2,3-DPG, 2,3-diphosphyglycerate; ARC, absolute reticulocyte count; ATP, adenosine triphosphate; Hb, hemoglobin; FDEP, fixed dose extension period; LDH, lactate dehydrogenase; p50, oxygen pressure at which Hb is 50% saturated with oxygen; PoS, point of sickling; SCD, sickle cell disease

Figure 3. Improvements of efficacy parameters in the FDEP of mitapivat treatment in patients with SCD (n=8)



2,3-DPG, 2,3-diphosphyglycerate; ARC, absolute reticulocyte count; ATP, adenosine triphosphate; BL, baseline; Ctr, control; Hb, hemoglobin; FDEP, fixed dose extension period; LDH, lactate dehydrogenase; LLN, lower limit of normal; p50, oxygen pressure at which Hb is 50% saturated with oxygen; pO_2, partial pressure of oxygen; SCD, sickle cell disease; ULN, upper limit of normal

Conclusions

- Treatment with mitapivat for up to 60 weeks in subjects with SCD showed no treatment related TEAEs grade ≥3
- Improvements in anemia, markers of hemolysis, Hb-oxygen affinity, 2,3-DPG level and ATP/2,3-DPG ratio were seen
- Preliminary data on VOC rate and SCD-related hospital admission days showed beneficial effects

2,3-DPG, 2,3-diphosphyglycerate; ATP, adenosine triphosphate; Hb, hemoglobin; SCD, sickle cell disease; TEAE, treatment-emergent adverse event; VOC, vaso-occlusive crisis

Q&A