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Agios at ASH 2022

December 12, 2022

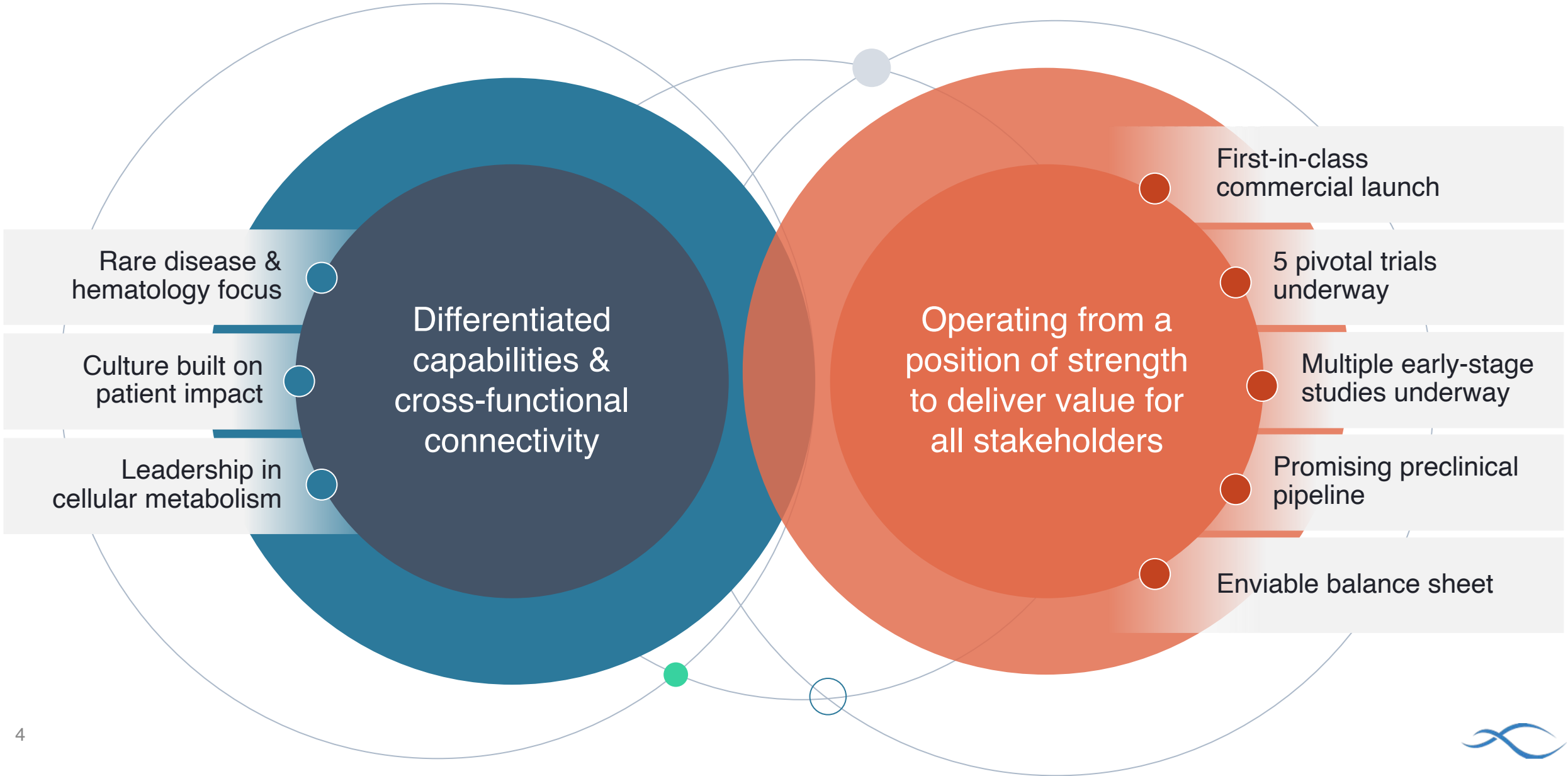
Forward-looking statements

This communication contains forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding Agios' plans, strategies and expectations for the preclinical, clinical and commercial advancement of its drug development programs, including PYRUKYND® (mitapivat) and AG-946; the potential benefits of Agios' products and product candidates; Agios' key milestones and guidance for 2022; its financial guidance regarding the period in which it will have capital available to fund its operations; 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. Management's expectations and, therefore, any forward-looking statements in this communication 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 on 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 future approved products, and launching, marketing and selling 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 and 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 establish and maintain collaborations; the failure of Agios to receive milestone or royalty payments related to the sale of its oncology business, the uncertainty of the timing of any receipt of any such payments, and the uncertainty of the results and effectiveness of the use of proceeds from the transaction with Servier; 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, or SEC, including the risks and uncertainties set forth under the heading Risk Factors in our filings with the SEC. While the list of factors presented here is considered representative, this list should not be considered to be a complete statement of all potential risks and uncertainties. Any forward-looking statements contained in this communication are made only as of the date hereof, and we undertake no obligation to update forward-looking statements to reflect developments or information obtained after the date hereof and disclaim any obligation to do so other than as may be required by law.

IR Event Draft Agenda

	TOPIC	SPEAKER
5 mins	Opening Remarks	Brian Goff, CEO
15 mins	PK activation mechanism and therapeutic benefit across hemolytic and acquired anemias	Sarah Gheuens, M.D., Ph.D., CMO and Head of R&D
20 mins	Impact of long-term treatment with PYRUKYND® in thalassemia and unmet need	Kevin Kuo, M.D., M.Sc., FRCPC University Health Network, University of Toronto
10 mins	Review of SAD/MAD data in healthy volunteers treated with novel PK activator AG-946	Mike Callaghan, M.D., Medical Director
10 mins	AG-946 development in lower-risk MDS	Melissa DiBacco, M.D., Medical Director
30 mins	Closing Remarks and Q&A	Presenters + Cecilia Jones, CFO

Our strategy is anchored to differentiated capabilities, building a sustainable business from a position of strength



With more than 7 years of clinical experience and the largest dataset for any PK activator, PYRUKYND® data are consistent and compelling

Pursuing broad pivotal programs across disease areas	Continued focus on publishing data to support PK activation mechanism & elucidate burden of under-appreciated diseases	Only company with POC across three disease areas
ENERGIZE ENERGIZE-T ACTIVATE-Kids™ ACTIVATE-KidsT™ RISE UP	The New England Journal of Medicine blood® The Lancet Haematology THE LANCET	PK Deficiency Thalassemia Sickle Cell Disease

+ PIONEERING FIRSTS:

- 1st GLOBAL PK DEFICIENCY REGISTRY
- 1st PEDIATRIC STUDY OF A PK ACTIVATOR
- 1st COMPANY TO PURSUE MDS WITH A PK ACTIVATOR
- 1st APPROVAL OF A PK ACTIVATOR FOR PK DEFICIENCY
- 1st CLINICAL TRIAL EVALUATING TREATMENT IN α-THALASSEMIA

*PK = pyruvate kinase

Development strategy positions Agios for meaningful expansion opportunities for the PK activation franchise, with near-term opportunity in thalassemia

Potential for two additional PYRUKYND® indications by 2026

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

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

Thalassemia
Potential U.S. approval in 2025

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

Sickle cell disease
Potential U.S. approval in 2026

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

ADDITIONAL OPPORTUNITIES FOR THE FRANCHISE WITH NOVEL PK ACTIVATOR AG-946

Myelodysplastic syndrome

~50K patients
in the U.S./EU5

- Orphan patient populations
- High unmet need
- Focused prescriber pool
- Differentiated product profile

Source: Agios internal estimates

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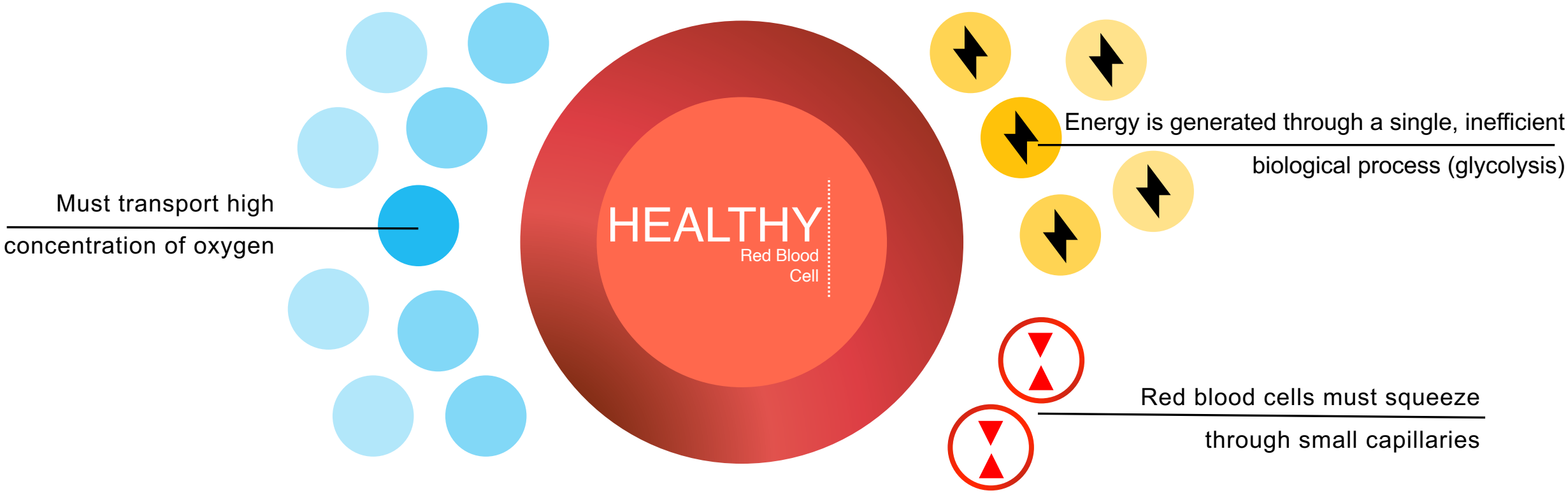
Pyruvate Kinase (PK) Activation: Understanding the Mechanism & Potential Therapeutic Benefit Across Hemolytic and Acquired Anemias

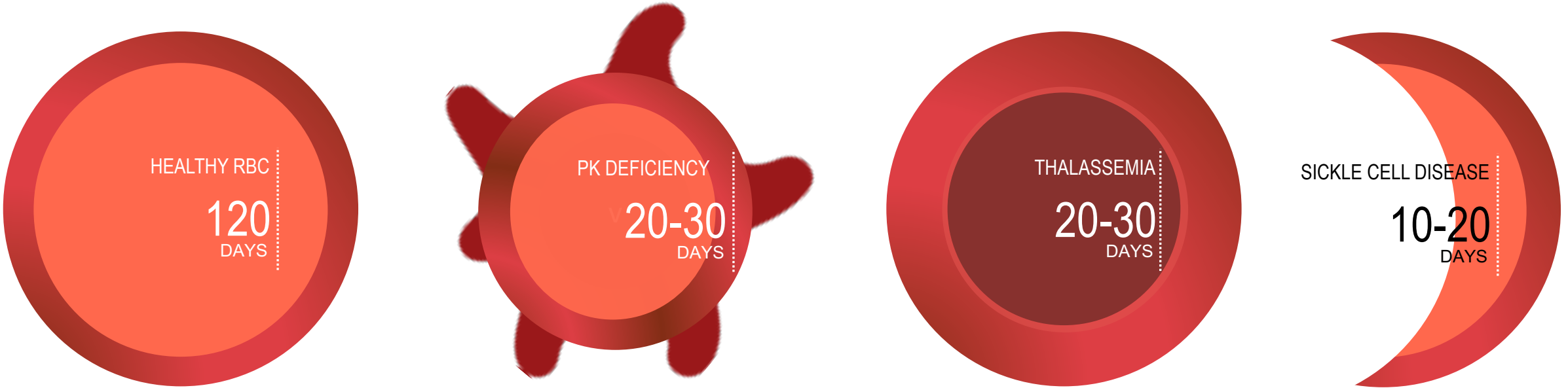
Sarah Gheuens, M.D., Ph.D.,
CMO and Head of Research & Development at Agios

Red blood cells deliver oxygen to tissues, which is necessary for energy and organ health



Red blood cell metabolic stress can lead to severe hematological disease

Insufficient energy supply (ATP) in red blood cells can cause cell damage and shortened red blood cell lifespan

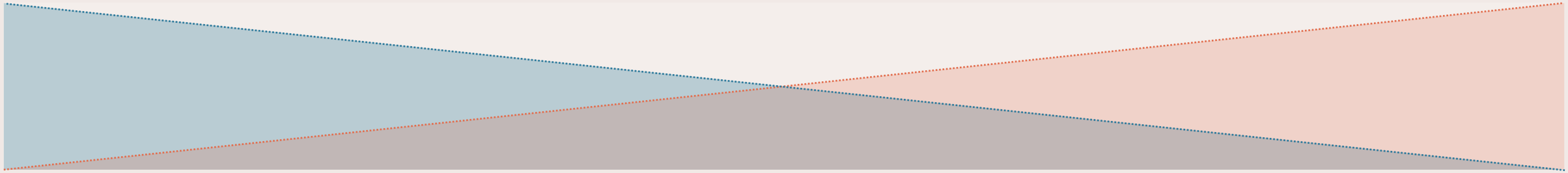


N Engl J Med 1968; 278:73-81; Blood (2004) 104 (11): 3616; J Kanter Blood Reviews 27:6 November 2013 279-287

Excessive hemolysis or ineffective erythropoiesis can cause anemia and long-term organ damage

Red Blood Cell Metabolic Stress

PK Deficiency | Sickle Cell Disease | Thalassemia | MDS Associated Anemia



Chronic Hemolysis

Chronic hemolysis is the destruction of red blood cells.

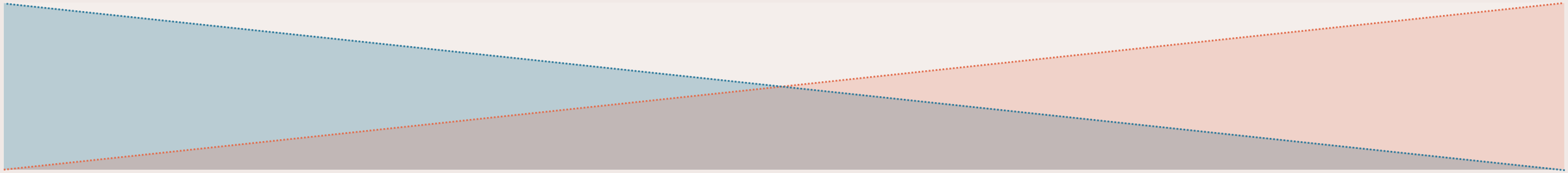
Ineffective Erythropoiesis

Ineffective erythropoiesis is characterized by a decreased output of red blood cells from the bone marrow

Hemolytic and acquired anemias share a common clinical presentation of serious complications and comorbidities driven by chronic hemolysis and ineffective erythropoiesis

Red Blood Cell Metabolic Stress

PK Deficiency | Sickle Cell Disease | Thalassemia | MDS Associated Anemia



Chronic Hemolysis (RBC Health & Longevity)

Ineffective Erythropoiesis (RBC Development)

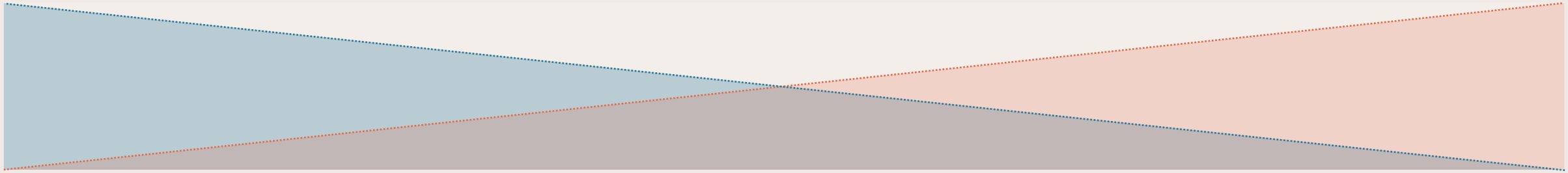
Significant near and long-term clinical consequences of chronic hemolysis and ineffective erythropoiesis…

ANEMIA	TRANSFUSION BURDEN	IRON OVERLOAD	REDUCED BONE MINERAL DENSITY	LONG-TERM ORGAN DAMAGE

These anemia-driven complications and comorbidities severely impact quality of life

Red Blood Cell Metabolic Stress

PK Deficiency | Sickle Cell Disease | Thalassemia | MDS Associated Anemia



Chronic Hemolysis (RBC Health & Longevity)

Ineffective Erythropoiesis (RBC Development)

Significant near and long-term clinical consequences of chronic hemolysis and ineffective erythropoiesis…

ANEMIA	TRANSFUSION BURDEN	IRON OVERLOAD	REDUCED BONE MINERAL DENSITY	LONG-TERM ORGAN DAMAGE

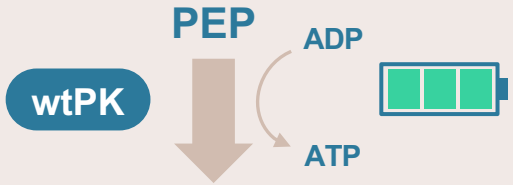
..that lead to major implications for patient quality of life and how they feel and function.

CHRONIC FATIGUE, SUSCEPTIBILITY TO ILLNESS	CHALLENGES WITH BASIC SOCIAL, SCHOOL / WORK ACTIVITIES	IMPACT ON EMOTIONAL AND MENTAL HEALTH	PAIN AND FRACTURES	ECONOMIC BURDEN

PK activation has the potential to correct red blood cell metabolism and address the underlying pathophysiology of a range of hemolytic and acquired anemias

Normal RBC

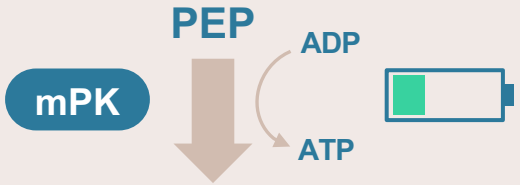
Red Blood Cell



ATP production meets demand

Mutant PK

Pyruvate Kinase Deficiency

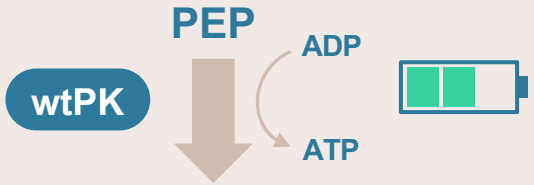


Inadequate production of ATP

PK mutations decrease PK stability, ATP generation, and RBC membrane integrity and increase RBC destruction, leading to chronic hemolytic anemia

Wild-Type PK

Other Anemias



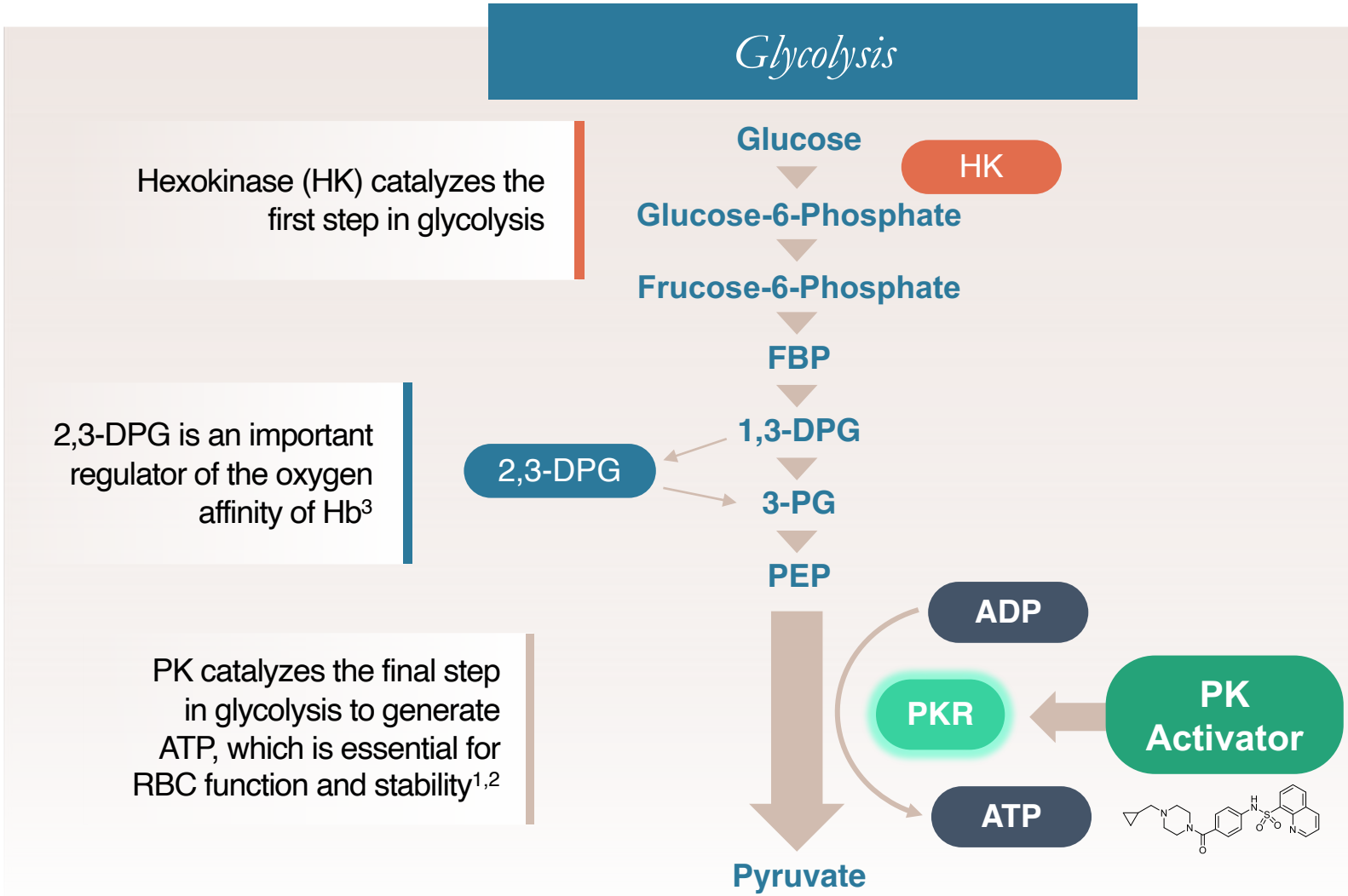
Increased demand of ATP

In many other anemias, there is an increase in ATP demand and impaired ATP production, leading to damage and premature death of RBCs, hemolysis, and anemia

ADP = adenosine diphosphate; ATP = adenosine triphosphate; DPG = diphosphoglycerate; FBP = fructose bisphosphate; m = mutant; PEP = phosphoenolpyruvate; PG = phosphoglycerate; PK = pyruvate kinase; PKR = RBC-specific PK; RBC = red blood cell

1. Kung C et al. Blood 2017;130:1347; 2. Valentini G et al. J Biol Chem 2002;277:23807; 3. Rab MAE et al. Blood 2021;137:2997–3001

PYRUKYND® (mitapivat) and AG-946 are oral, small-molecule allosteric activators of pyruvate kinase with the potential to correct RBC metabolism



PK activation is expected to correct RBC metabolism by:

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

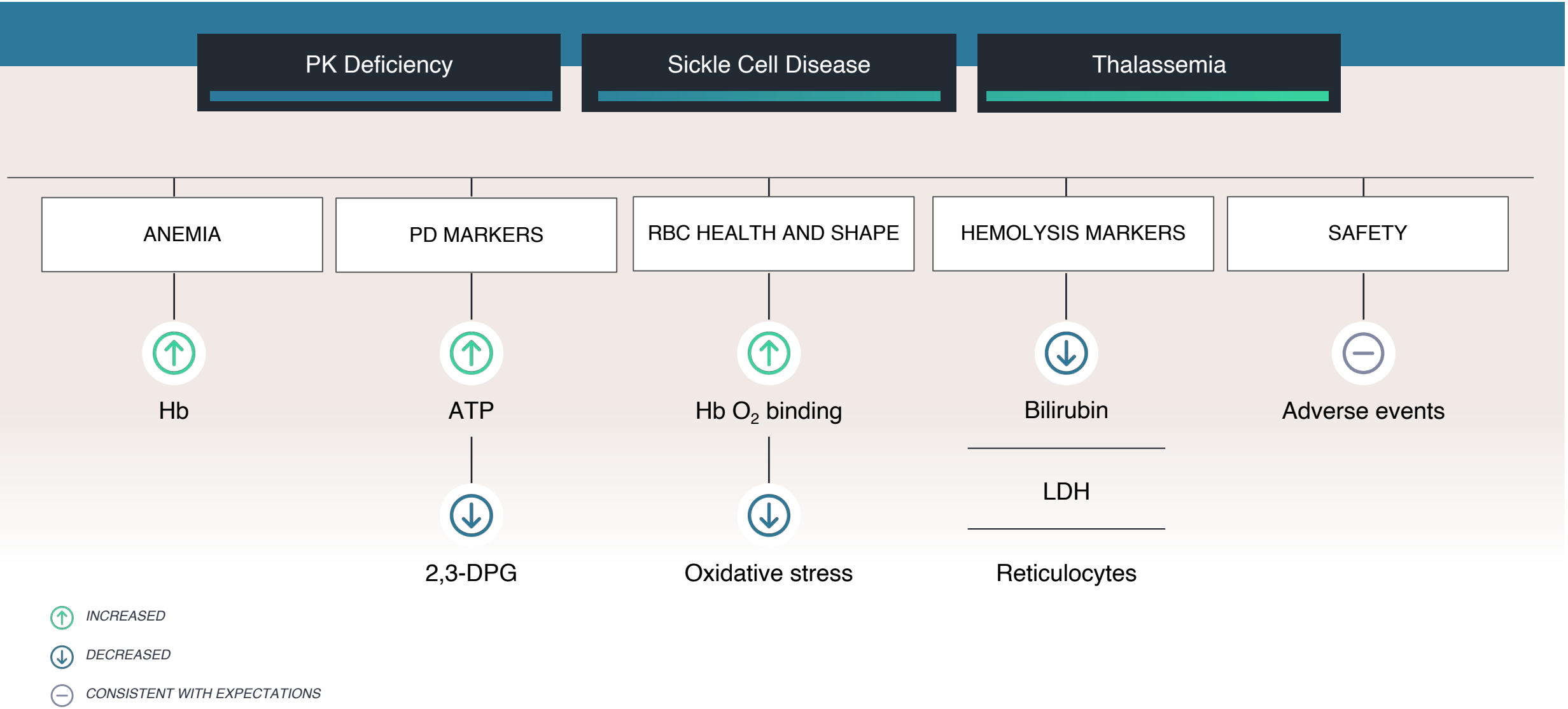
Reducing 2,3-DPG levels - Elevated 2,3-DPG levels are associated with RBC sickling in SCD

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

ADP = adenosine diphosphate; ATP = adenosine triphosphate; DPG = diphosphoglycerate; FBP = fructose bisphosphate; m = mutant; PEP = phosphoenolpyruvate; PG = phosphoglycerate; PK = pyruvate kinase; PKR = RBC-specific PK; RBC = red blood cell

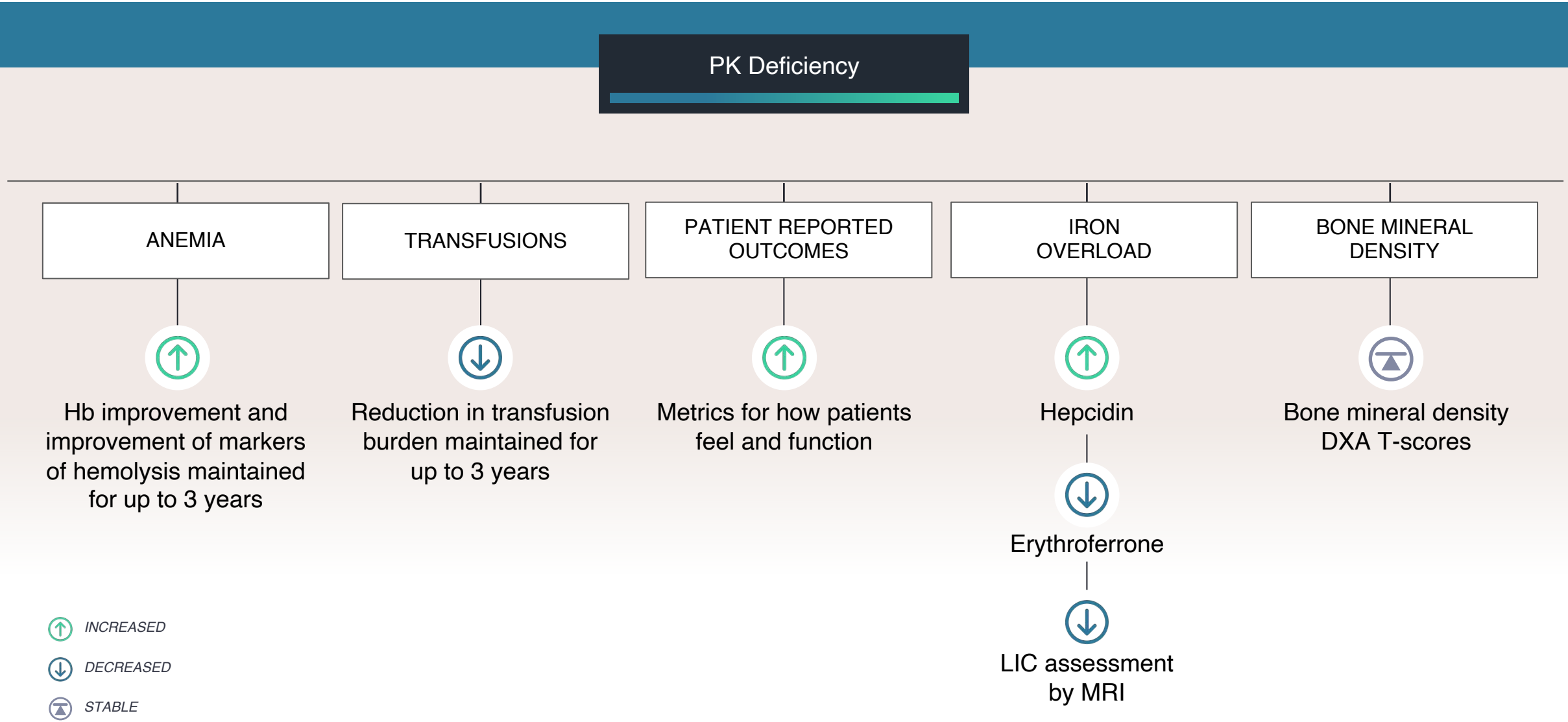
1. Kung C et al. Blood 2017;130:1347; 2. Valentini G et al. J Biol Chem 2002;277:23807; 3. Rab MAE et al. Blood 2021;137:2997–3001

With more than 7 years of clinical experience and the largest dataset for any PK activator, PYRUKYND® demonstrated consistent results across 3 distinct diseases



Sources: PYRUKYND® U.S. prescribing information; Kuo KHM et al. Lancet 2022; 400: 493–501; NIH data ASH 2021; Utrecht data EHA 2022

Long-term clinical data for treatment with PYRUKYND® in PK deficiency support maintenance of effect and impact on downstream consequences of anemia



Source: ASH 2022

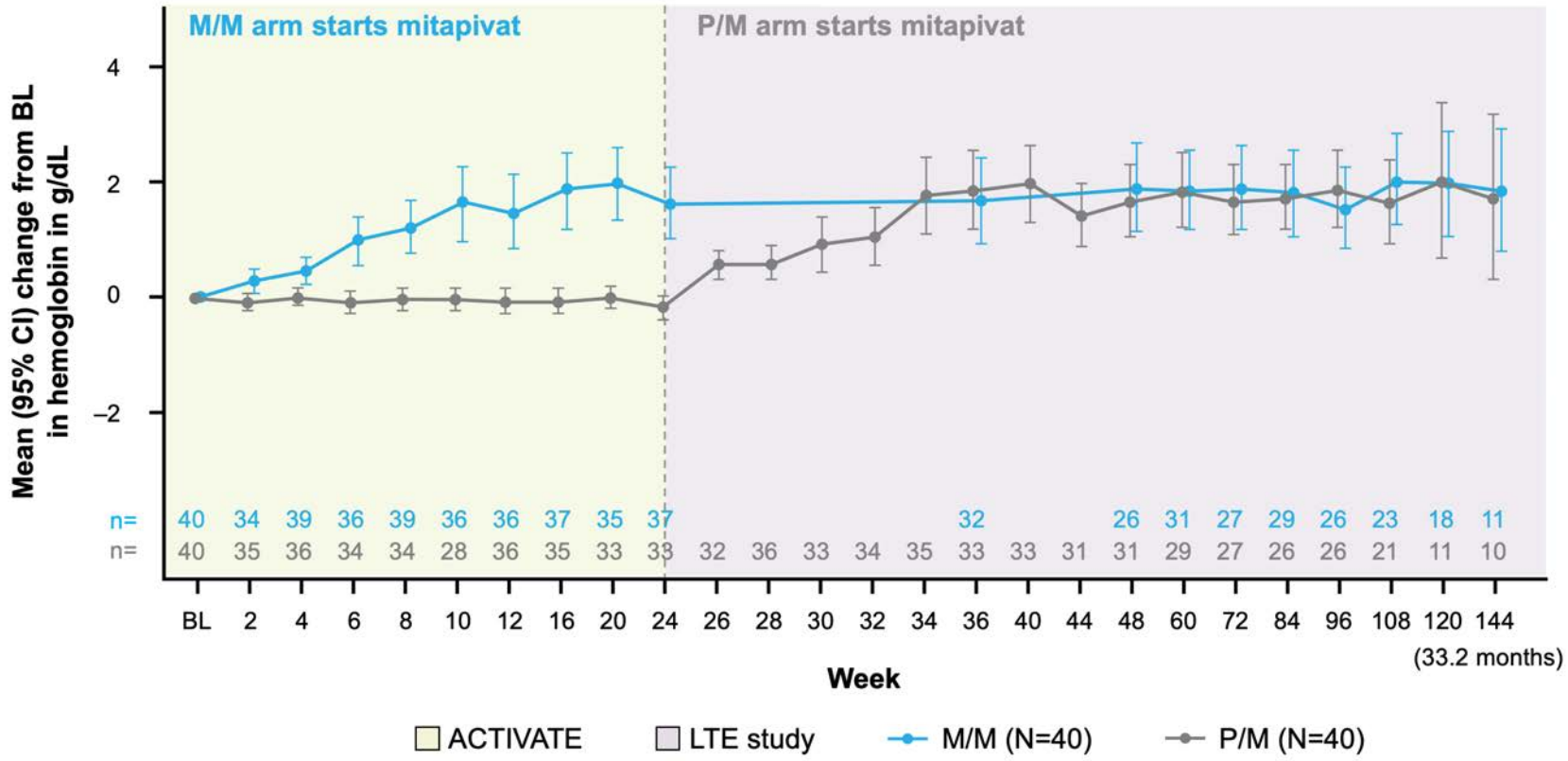
ANEMIA

Hb improvement and improvement of markers of hemolysis maintained for up to 3 years

Hemoglobin response was sustained with long-term PYRUKYND® treatment in PK deficiency

Median duration of Hb response among the 31 Hb responders from ACTIVATE and the LTE study was 18.3 months, with responses ongoing up to 32.9 months*

Change from baseline in Hb over time in patients randomized to mitapivat or placebo in ACTIVATE and continued in the LTE on mitapivat



Source: ASH 2022

Reduction in transfusion burden was sustained with long-term PYRUKYND® treatment in PK deficiency

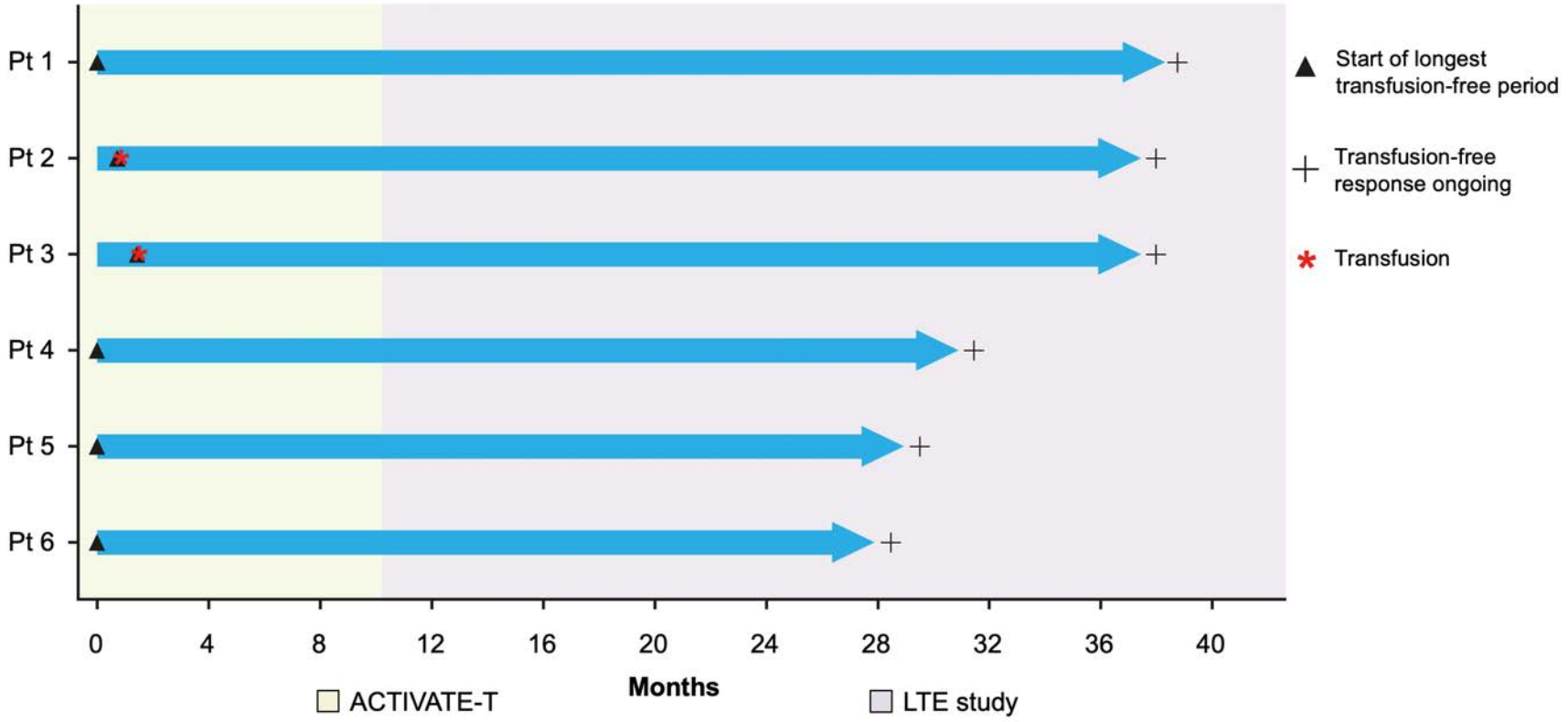
In ACTIVATE-T, 37% (10/27) of patients achieved a transfusion reduction response and 22% (6 patients) achieved transfusion-free status[12]

- Transfusion reduction responses were maintained in the LTE up to 37.1 months
- Transfusion-free status was maintained in the LTE up to 38.3 months

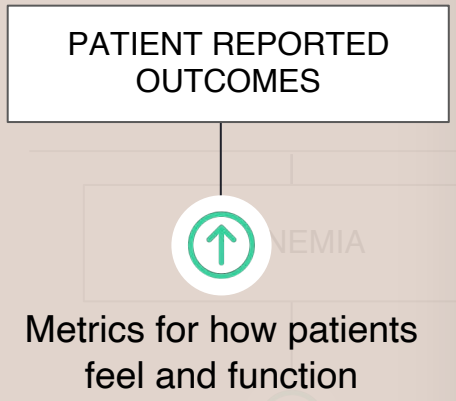
TRANSFUSIONS

Reduction in transfusion burden maintained for up to 3 years

Duration of transfusion-free response among transfusion-free patients from ACTIVATE-T through to the LTE study



Source: ASH 2022

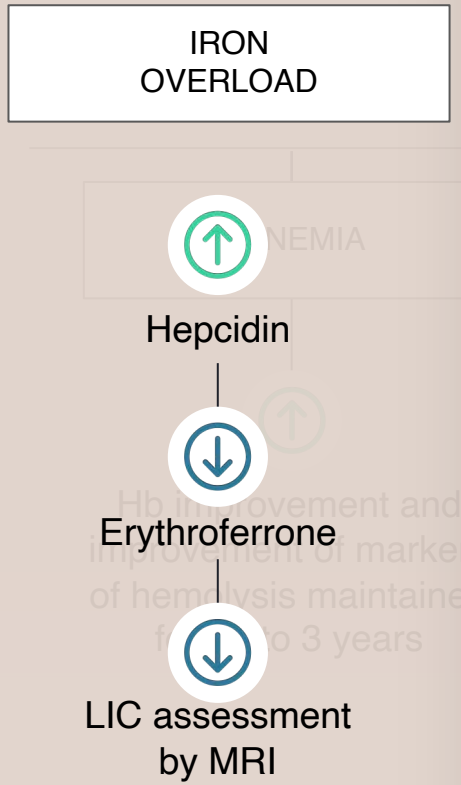


Improvements in patient-reported outcomes (PROs) were sustained with long-term PYRUKYND® treatment in PK deficiency

- As assessed by two PK deficiency-specific PRO instruments, treatment with PYRUKYND® was associated with long-term, durable, and clinically meaningful improvements in PK deficiency signs, symptoms and functional impact, irrespective of transfusion status
- At Week 84 of the LTE study, clinically meaningful improvements on PKDD and PKDIA were achieved in over 50% of patients treated with PYRUKYND

These long-term data suggest that treatment with PYRUKYND® may improve how responding patients feel and function by addressing the underlying pathophysiology of red blood cell metabolic stress

Source: ASH 2022



Meaningful and continued improvements in mean hepcidin, erythroferrone, and sTfR, and median LIC by MRI results were observed with mitapivat up to Week 96

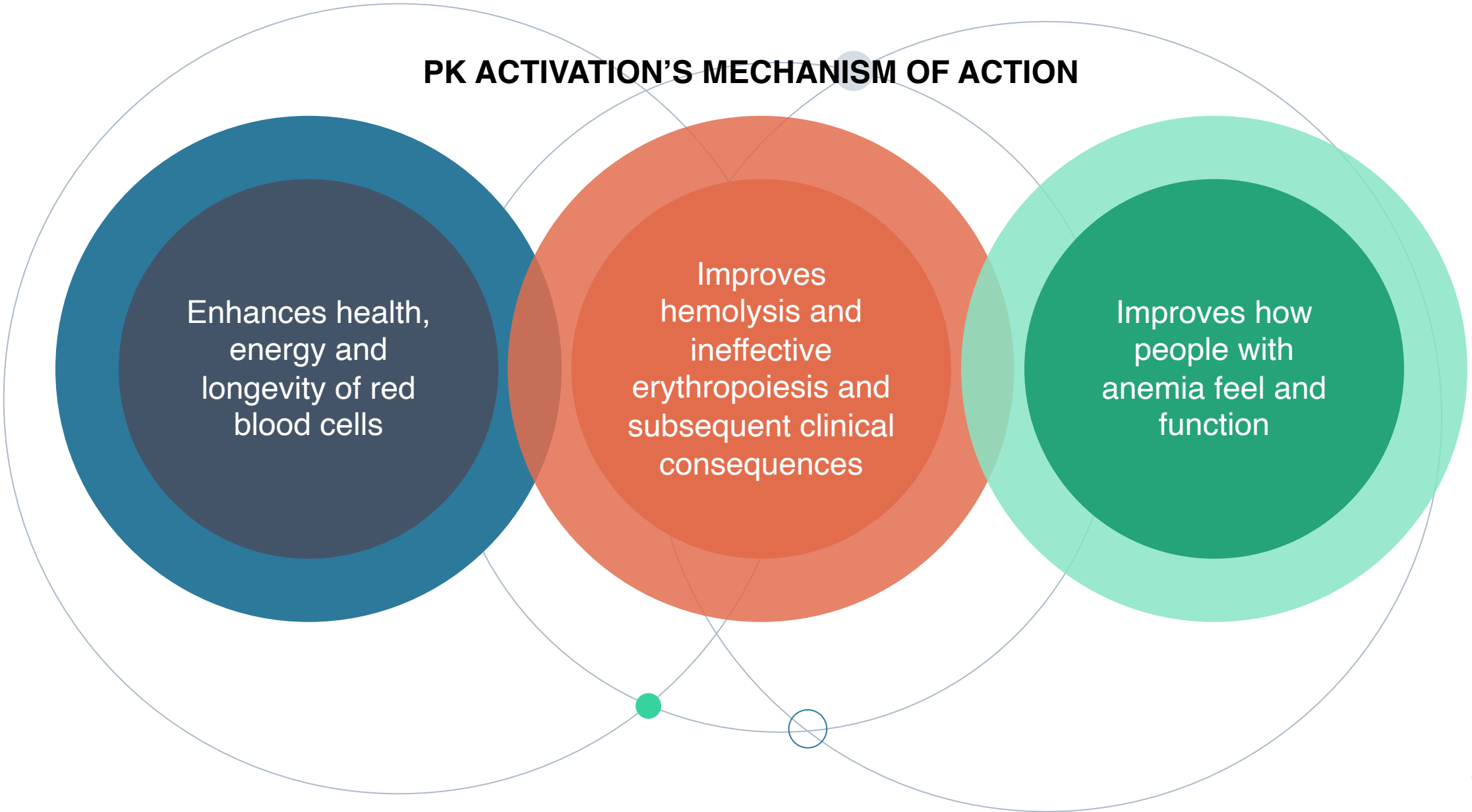
- M/M arm: Improvements in all these markers from BL to Week 24 were observed with mitapivat treatment, and were sustained from Week 24 up to Week 96 in the LTE
- P/M arm: These markers remained relatively unchanged from BL to Week 24 while receiving placebo, but upon transitioning to mitapivat LTE, improvements similar to the M/M arm were observed from Week 24 up to Week 96

LIC changes over time (up to 96 weeks) in patients with evidence of iron overload at BL

- Among patients treated with mitapivat (N=78), 55.1% (n=43) met the criteria for iron overload at BL
- These patients showed clinically meaningful and continued improvements in iron overload over time as measured by LIC (median [Q1, Q3] decrease from BL to Week 96 of mitapivat treatment of –1.95 [–4.85, –0.70] mg Fe/g dw)

Source: ASH 2022

PK activation represents a differentiated mechanism of action that directly addresses the underlying cause of hemolytic and acquired anemias



Mitapivat improves markers of erythropoietic activity in long-term study of adults with alpha- or beta-non–transfusion-dependent thalassemia

Kevin Kuo, M.D., M.Sc., FRCPC
University Health Network, University of Toronto

Kevin HM Kuo, MD,[1] D Mark Layton, MB BS,[2] Ashutosh Lal, MD,[3] Hanny Al-Samkari, MD,[4] Penelope A Kosinski, MS[5], Bo Tong, PhD,[5] Jeremie H Estepp, MD,[5] Katrin Uhlig, MD,[5] Elliott P Vichinsky, MD[3]

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

PYRYKYND® is currently under investigation for thalassemia and not approved in any country for use in thalassemia.

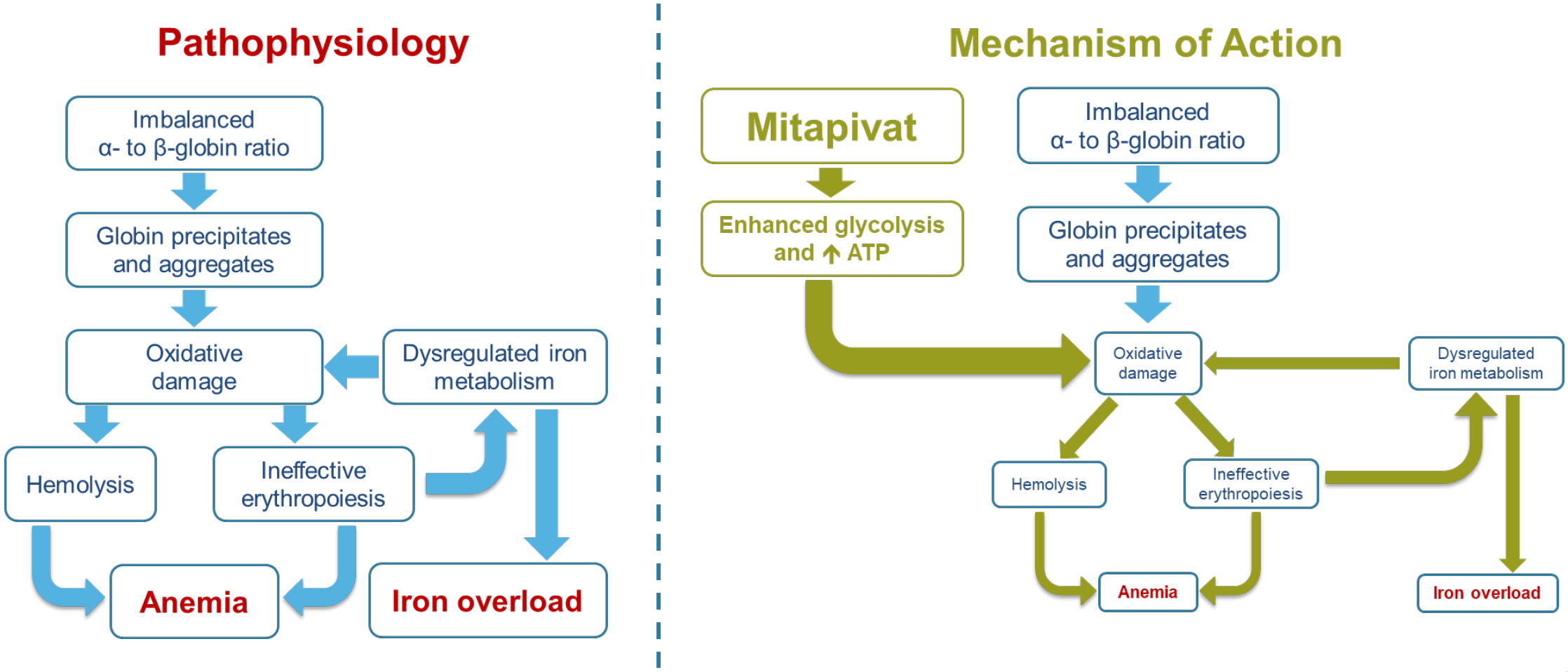
Background

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

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

Background

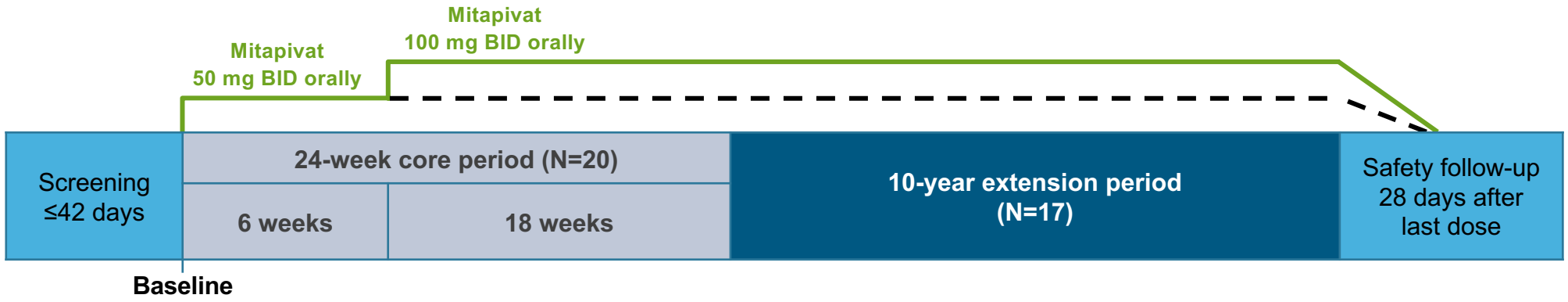
Figure 2. Pathophysiology and proposed mitapivat mechanism of action in thalassemia



ATP, adenosine triphosphate

Overview of Phase 2 core period

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



Core period[11]

Primary endpoint

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

Additional efficacy and safety results

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

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

Objective of data cut presented at ASH

To report erythropoietic activity, hemolysis, and iron homeostasis from the LTE period through Week 72 (data cutoff 27March2022)

Results

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

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

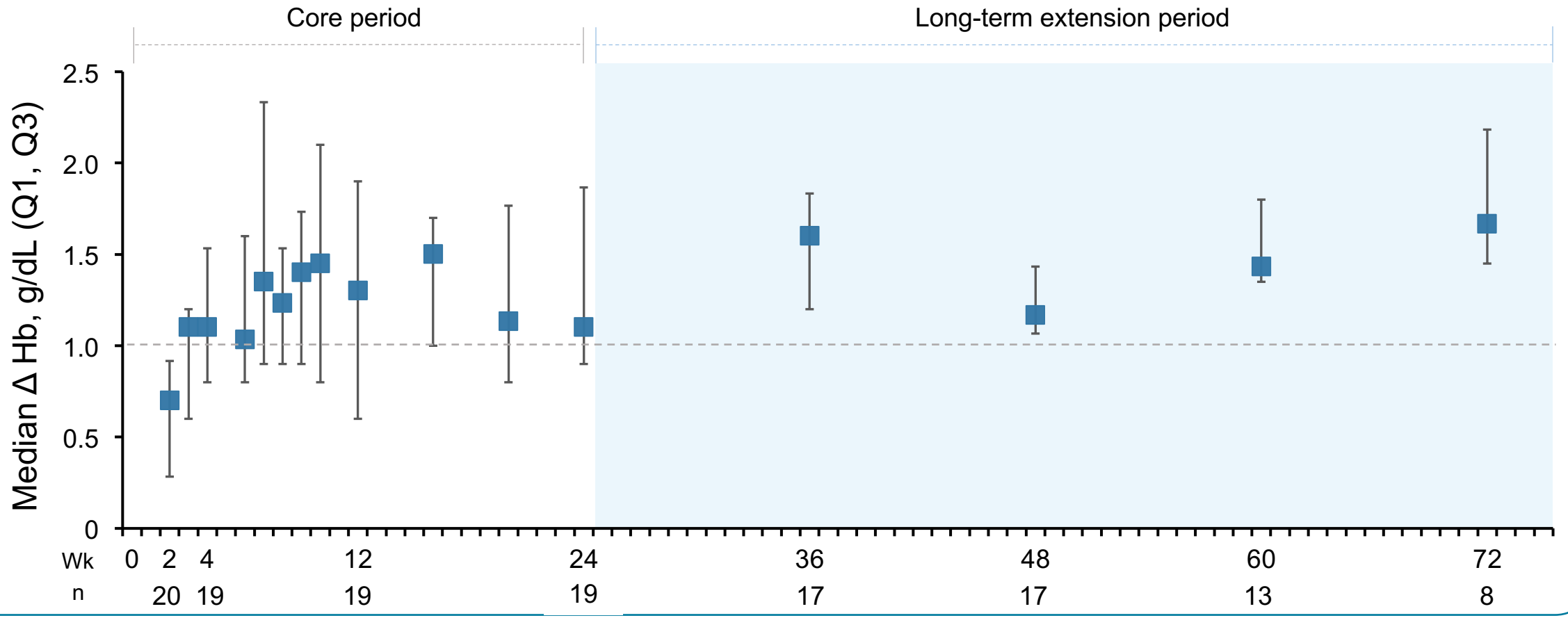
Baseline biomarkers from the core period[11]	All patients (N=20)
Hb baseline, median (Q1, Q3), g/dL	8.4 (6.78, 8.98)
Erythropoietin, median (Q1, Q3), IU/L	79.0 (29.0, 137.0)
Erythroferrone, median (Q1, Q3), ng/L	10,760.0 (3627.5, 17,712.5)
Indirect bilirubin, median (Q1, Q3), µmol/L	21.0 (15.5, 36.1)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

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

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

Results: Sustained improvements in hemoglobin were observed throughout the extension period

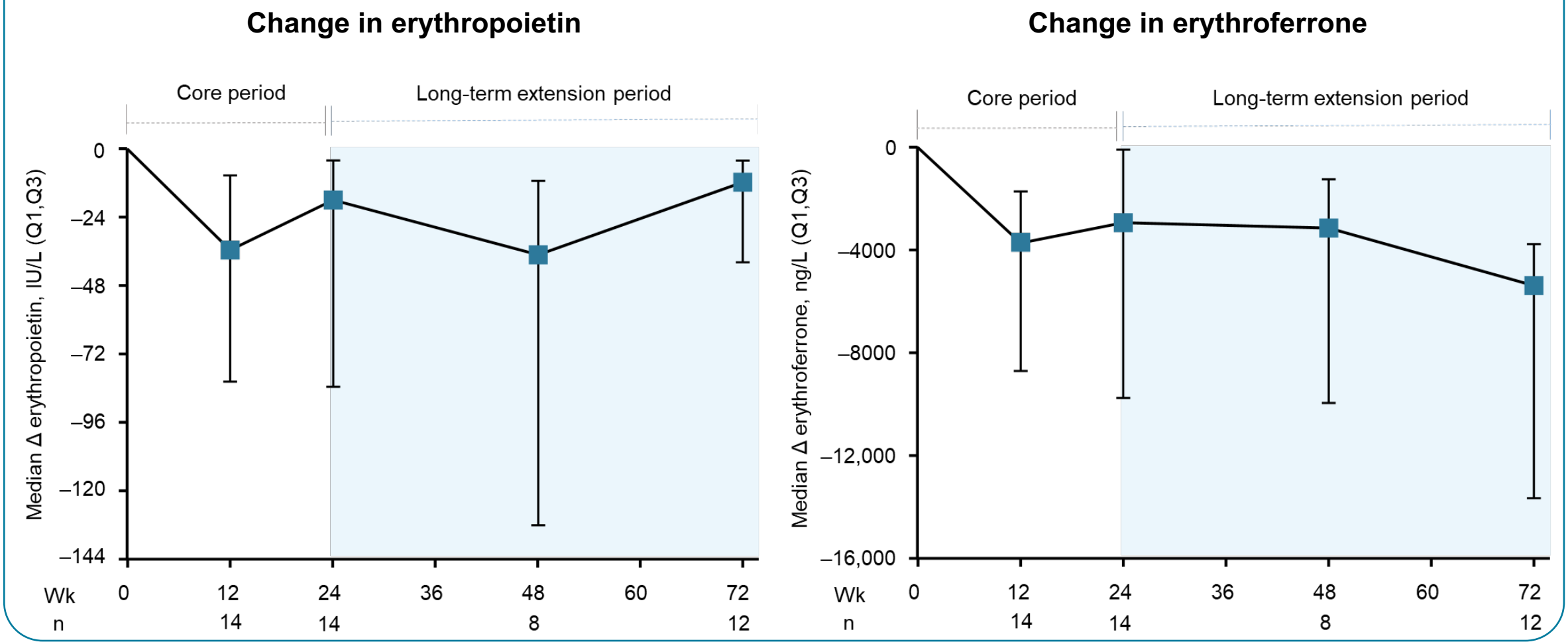
Figure 4. Median Hb change from baseline over time



Hb, hemoglobin; Q, quartile; Wk, week

Results: Markers of erythropoietic activity remained stable or improved through Week 72

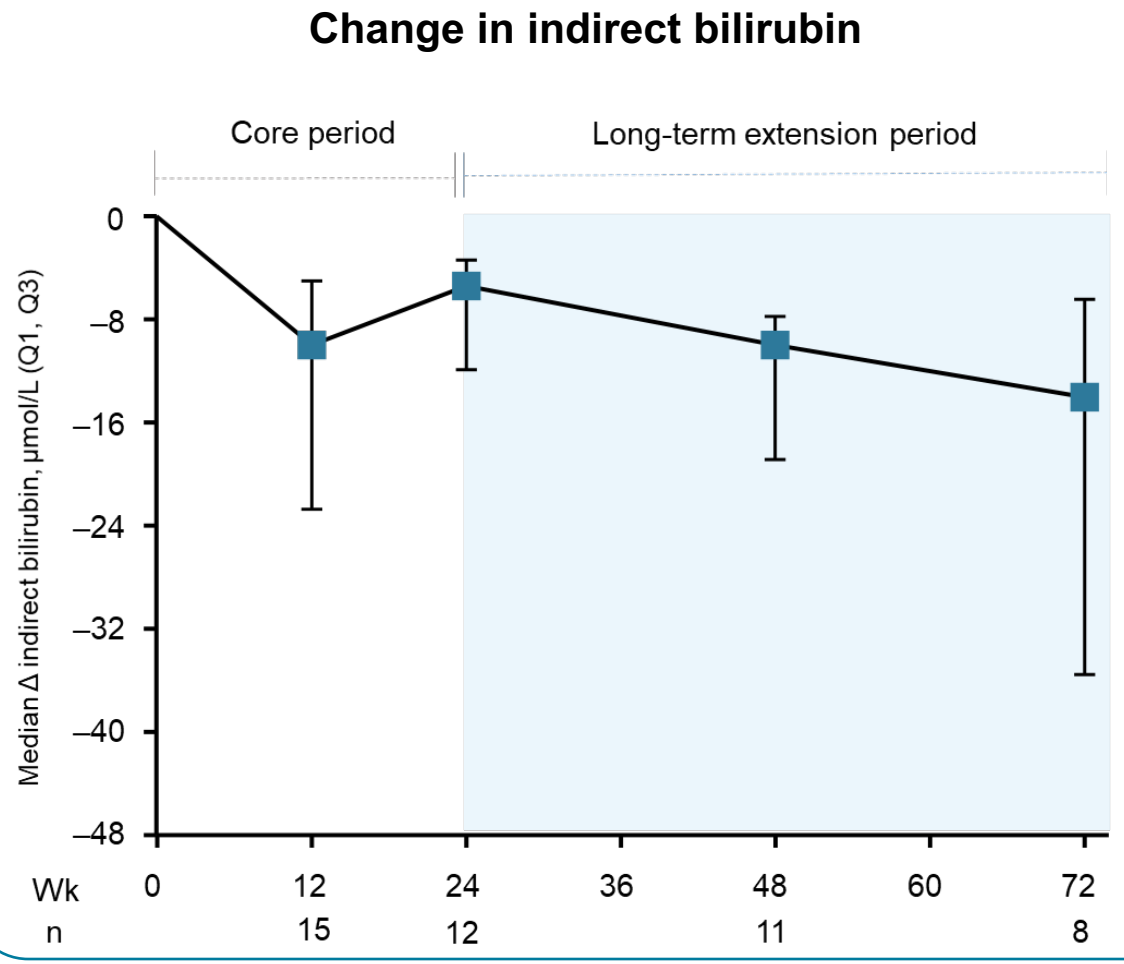
Figure 5. Markers of erythropoietic activity

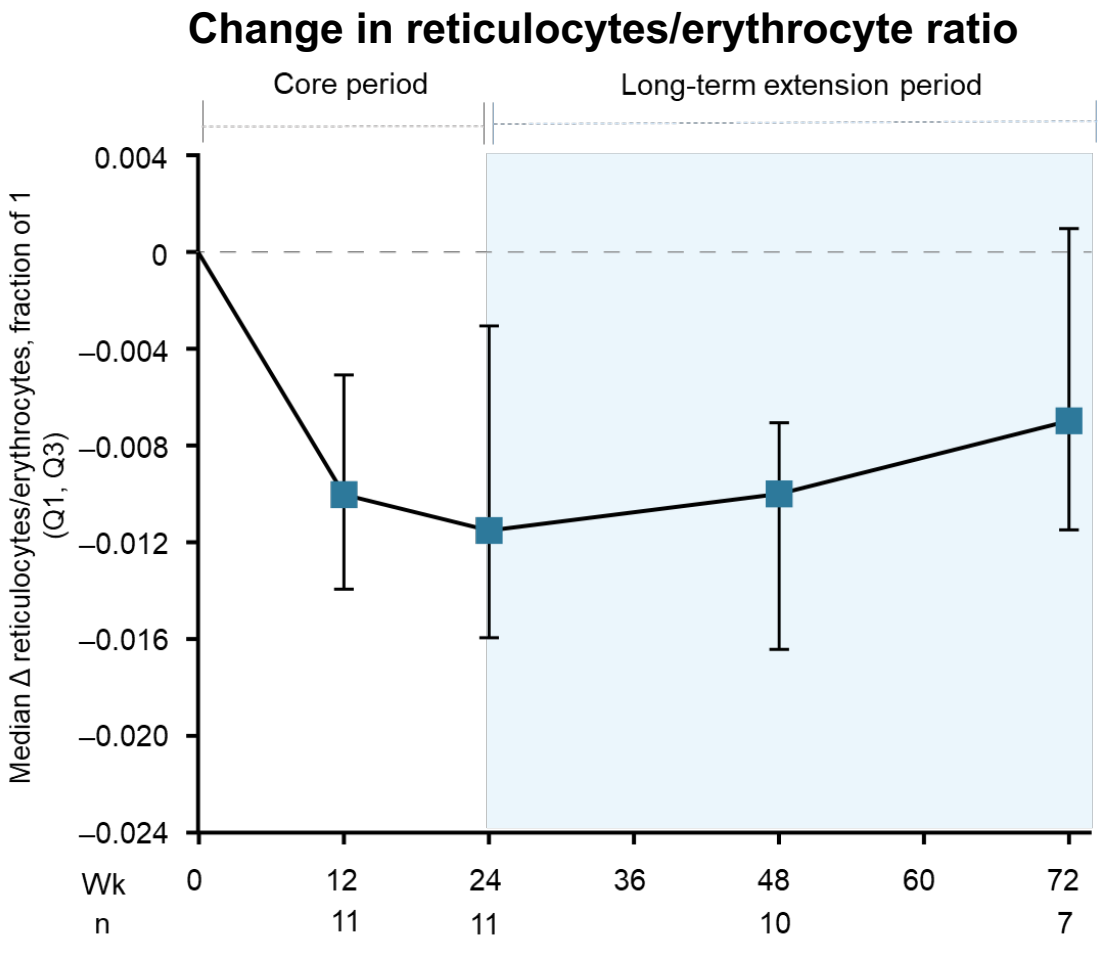


Q, quartile; Wk, week

Results: Improvements in markers of hemolysis were observed through Week 72

Figure 6. Markers of hemolysis



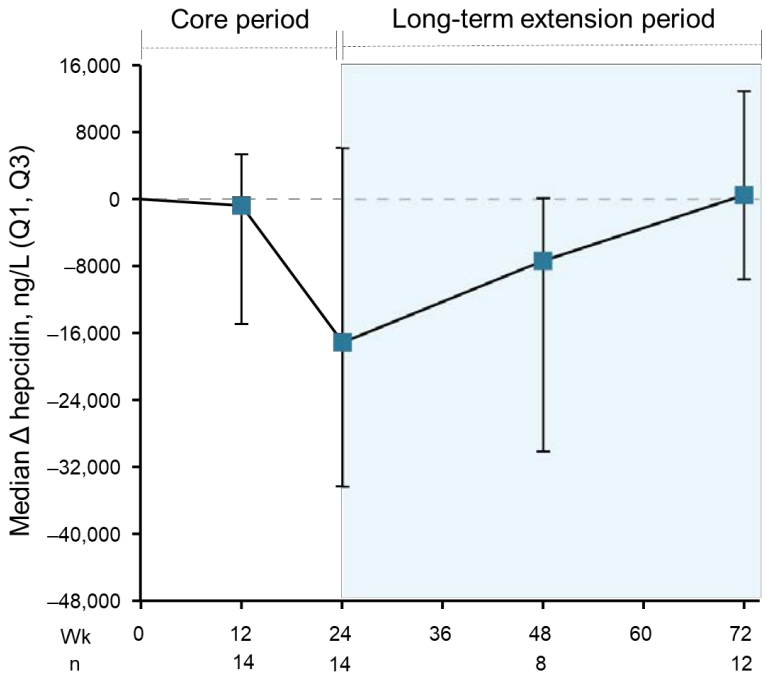


Q, quartile; Wk, week

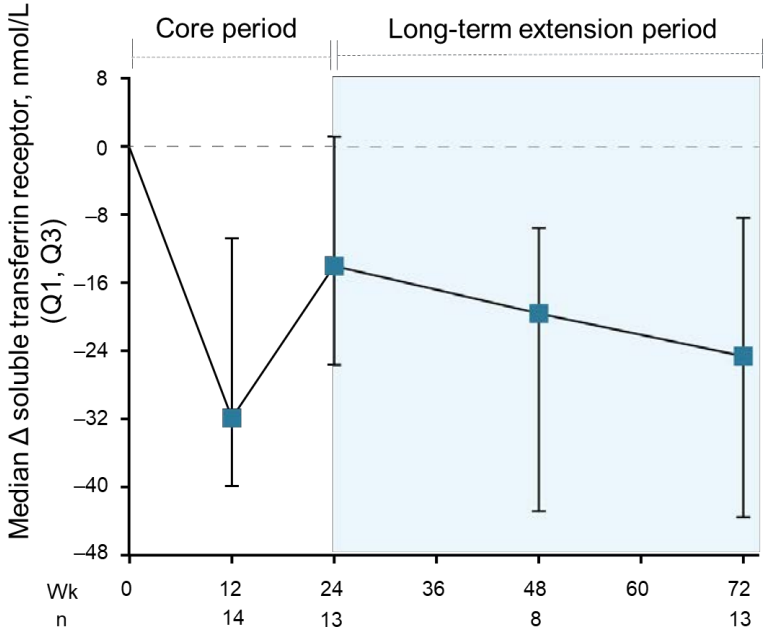
Results: Markers of iron homeostasis remained stable or improved through Week 72

Figure 7. Markers of iron homeostasis

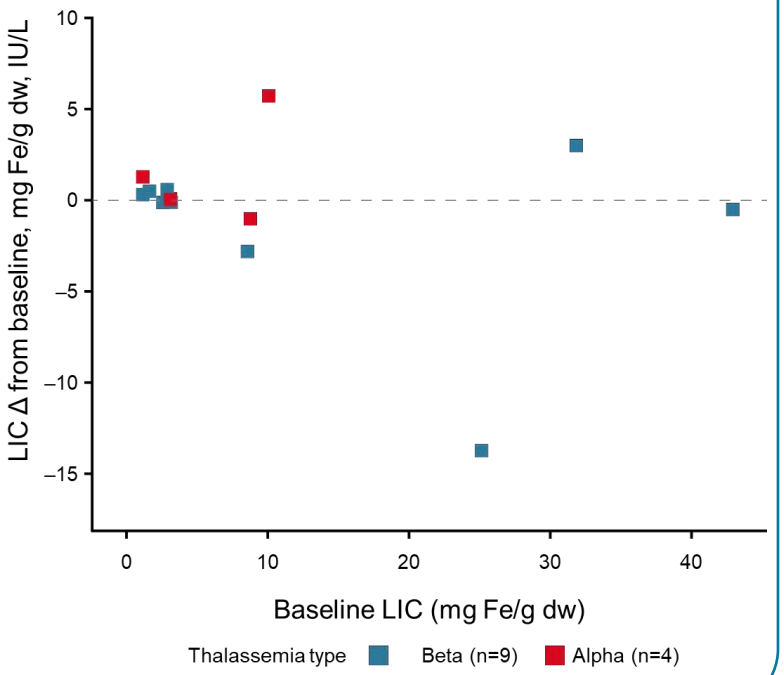
Change in hepcidin



Change in soluble transferrin receptor



Change in liver iron concentration



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

Conclusion

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

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

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

Acknowledgments, disclosures and references

Acknowledgments

- We would like to thank the patients who took part in this study. Editorial assistance was provided by Kate Collins, MPharm, Adelphi Communications, Macclesfield, UK, and supported by Agios Pharmaceuticals, Inc.

Disclosures

- This study was funded by Agios Pharmaceuticals, Inc.
- Author conflict of interest disclosures as follows:
  - **KHM Kuo**: Agios, Alexion, Apellis, bluebird bio, Celgene, Novartis, Pfizer – consultancy; Alexion, Novartis – honoraria; Agios, Bioverativ – membership on an entity's Board of Directors or advisory committees; Pfizer – research funding
  - **DM Layton**: Agios, Novartis – consultancy; Agios, Cerus, Novartis – membership on an entity's Board of Directors or advisory committees
  - **A Lal**: bluebird bio, Celgene, Forma Therapeutics, Insight Magnetics, La Jolla Pharmaceutical Company, Novartis, Protagonist Therapeutics, Terumo Corporations – research funding; Agios, Chiesi USA – consultancy; Celgene, Protagonist Therapeutics – membership on an entity's Board of Directors or advisory committees
  - **H Al-Samkari**: Agios Pharmaceuticals, argenx, Dova/Sobi, Forma, Moderna, Novartis, Rigel – consultancy; Agios Pharmaceuticals, Amgen, Dova – research funding
  - **PA Kosinski**: Agios – consultancy and shareholder
  - **B Tong**: Agios – shareholder
  - **JH Estepp:** Agios – employee and shareholder
  - **K Uhlig**: Agios – employee and shareholder
  - **EP Vichinsky**: Agios, bluebird bio, Global Blood Therapeutics, Novartis, Pfizer – consultancy and research funding

References

1. Taher AT et al. *Lancet* 2018;391:155–67.
2. Galanello R et al. *Orphanet J Rare Dis* 2010;5:11.
3. Khandros E et al. *Blood* 2012;119:5265–75.
4. Shaeffer JR. *J Biol Chem* 1988;263:13663–9.
5. Musallam KM et al. *Haematologica* 2021;106:2489–92.
6. Kung C et al. *Blood* 2017;130:1347–56.
7. Yang H et al. *Clin Pharmacol Drug Dev* 2019;8:246–59.
8. Valentini G et al. *J Biol Chem* 2002;277:23807–14.
9. Rab MAE et al. *Blood* 2019; 134(S1): 3506.
10. Matte A et al. *J Clin Invest* 2021;131:e144206.
11. Kuo KHM et al. *Lancet* 2022;400:493–501.
12. Kuo KHM et al. *Blood* 2021;138(S1):576.

Results from the single and multiple ascending dose study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of AG-946 in healthy volunteers

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Medical Director at Agios

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[1]Agios Pharmaceuticals, Inc., Cambridge, MA, USA; [2]Merica Clinical Consulting LLC, Boston, MA

Background

- Pyruvate kinase (PK) red cell isoform catalyzes the final step of adenosine triphosphate (ATP) production via glycolysis in red blood cells (RBCs), which is critical for maintaining RBC function and stability[1–4]
- PK activation leading to reduced levels of the glycolytic metabolite 2,3-diphosphoglycerate (2,3-DPG) and enhanced ATP production is under investigation as a potential therapeutic approach in various hemolytic anemias
- AG-946 is an investigational, potent, small-molecule, allosteric activator of PK that has the potential to enhance RBC functionality and survival by increasing glycolysis and ATP production (**Figure 1**)

1. Kung C et al. *Blood* 2017;130:1347–56. 2. Rab MAE et al. *Blood* 2021;137:2997–3001. 3. Yang H et al. *Clin Pharmacol Drug Dev* 2019;8:246–59. 4. Valentini G et al. *J Biol Chem* 2002;277:23807–14.

Objective

To assess safety, pharmacokinetic, and pharmacodynamic results from the Phase 1 study of AG-946 in healthy volunteers (NCT04536792)

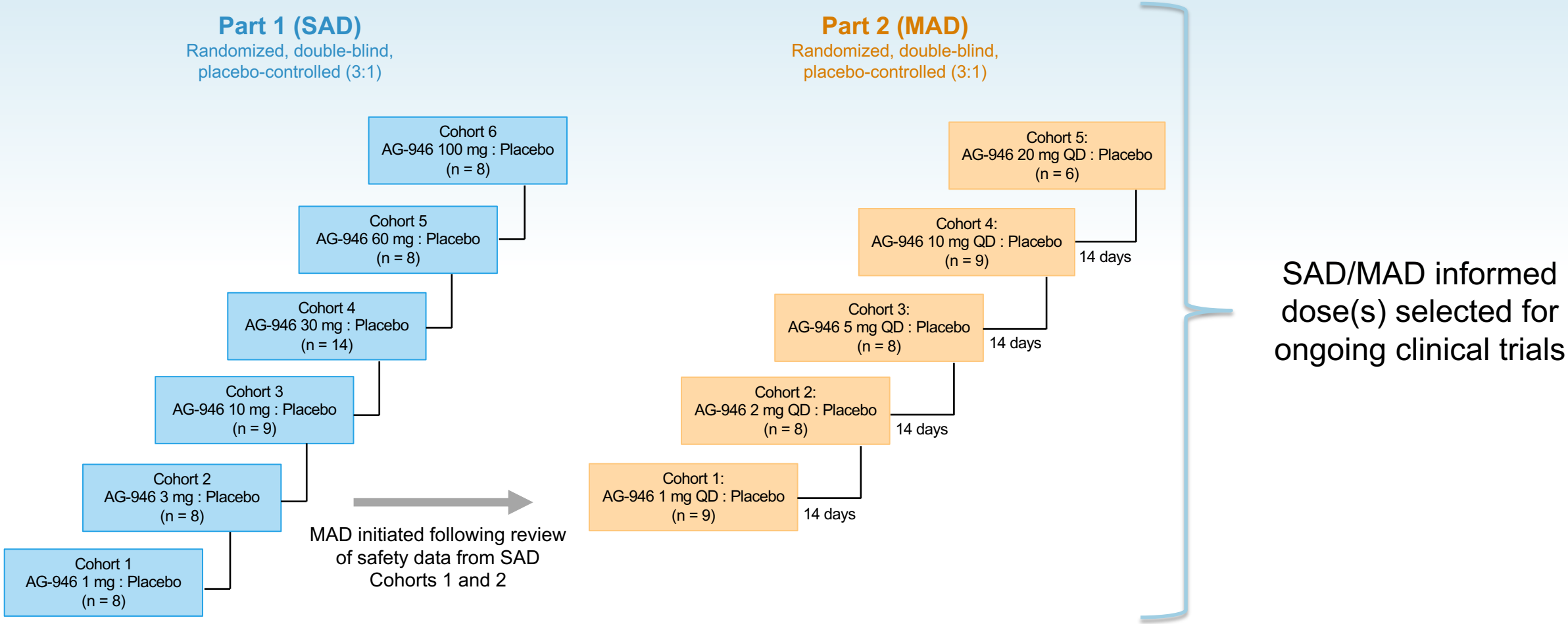
Methods

- In this Phase 1, randomized, double-blind, placebo-controlled study, single ascending doses (SAD) or multiple ascending doses (MAD) of AG-946 or placebo were administered to healthy men and women (18–55 years of age) in sequential cohorts (**Figure 2**)
  - In SAD:
    - 6 cohorts of 8 subjects each were randomized to receive a single dose of AG-946 (n=6) or placebo (n=2) under fasted conditions, with 2 subjects initially randomized (1:1) and then 6 subjects randomized (5:1) to receive AG-946 or placebo
    - Dose levels studied in SAD were 1, 3, 10, 30, 60, and 100 mg
  - In MAD:
    - 5 cohorts of 8 subjects each were randomized (3:1) to receive AG-946 or placebo QD under fasted conditions for 14 days
    - Dose levels studied in MAD were 1, 2, 5, 10, and 20 mg QD

QD, once daily

Methods

Figure 2. Study Design for SAD and MAD[a]



[a]Cohorts and subject numbers included in this presentation represent the study as conducted. MAD, multiple ascending doses; QD, once daily; SAD, single ascending doses.

Methods

- Safety assessments included vital signs, physical exams, electrocardiograms, clinical laboratory parameters and adverse events

- Serial blood samples were drawn for pharmacokinetic and pharmacodynamic (2,3-DPG, ATP) assessments at regular intervals throughout the study period

- Safety, pharmacokinetic, and pharmacodynamic evaluations were performed through:
  - At least 168 h (Day 8) for SAD with follow-up visits occurring at 264 h (Day 10)
  - At least 504 h (Day 21) for MAD with follow-up visits occurring at 816 h (Day 35)

ATP, adenosine triphosphate; DPG, diphosphoglycerate; h, hour; MAD, multiple ascending doses; SAD, single ascending doses

Demographic and baseline characteristics were balanced

Table 1. Demographic and baseline characteristics - SAD cohorts

Baseline characteristics	Placebo (N = 14)	AG-946 (N = 41)
Age, median (range), years	29.0 (21, 55)	35.0 (22, 54)
Male, n (%)	14 (100.0)	32 (78.0)
Race, n (%)		
Black/African American	5 (35.7)	13 (31.7)
White	9 (64.3)	28 (68.3)
BMI, median (range), kg/m^2	27.2 (21.7, 31.7)	27.8 (20.5, 31.9)

Table 2. Demographic and baseline characteristics - MAD cohorts

Baseline characteristics	Placebo (N = 9)	AG-946 (N = 31)
Age, median (range), years	39.0 (22, 51)	36.0 (21, 56)
Male, n (%)	9 (100.0)	31 (100)
Race, n (%)		
Asian	0	1 (3.2)
Black/African American	5 (55.6)	13 (41.9)
Native Hawaiian/Other Pacific Islander	0	1 (3.2)
White	4 (44.4)	15 (48.4)
Multiple	0	1 (3.2)
BMI, median (range), kg/m^2	26.1 (19.6, 29.7)	28.1 (19.2, 31.7)

BMI, body mass index; MAD, multiple ascending doses; SAD, single ascending doses

SAD safety results:
AG-946 was well tolerated in healthy adult subjects

- Overall, 6 (14.6%) of the 41 subjects treated with AG-946 in SAD experienced treatment-emergent adverse events (TEAEs)
  - No serious TEAEs, no grade ≥3 TEAEs, and no treatment-related TEAEs were reported

- The frequency of subjects with TEAEs was similar for the placebo (14.3%) and AG-946 (14.6%) treatment arms

SAD, single ascending doses

MAD safety results

Frequency of Subjects with Events	Placebo (N = 9)	AG-946 1 mg QD (N = 7)	AG-946 2 mg QD (N = 6)	AG-946 5 mg QD (N = 6)	AG-946 10 mg QD (N = 7)	AG-946 20 mg QD (N = 5)	Pooled AG-946 (N = 31)
Any TEAE, n (%)	4 (44.4)	2 (28.6)	0	1 (16.7)	4 (57.1)	5 (100)	12 (38.7)
Any TEAE Grade ≥3, n (%)	0	0	0	0	0	1 (20.0)	1 (3.2)
Any Treatment-Related TEAE, n (%)	0	0	0	0	1 (14.3)	5 (100)	6 (19.4)
Any TEAE Leading to Treatment Discontinuation, n (%)	0	0	0	0	1 (14.3)	5 (100)	6 (19.4)
Any Serious TEAE, n (%)	1 (11.1)	0	0	0	0	0	0

MAD, multiple ascending doses; QD, Once daily; SAE, serious adverse event; TEAE, Treatment emergent adverse event

MAD safety results

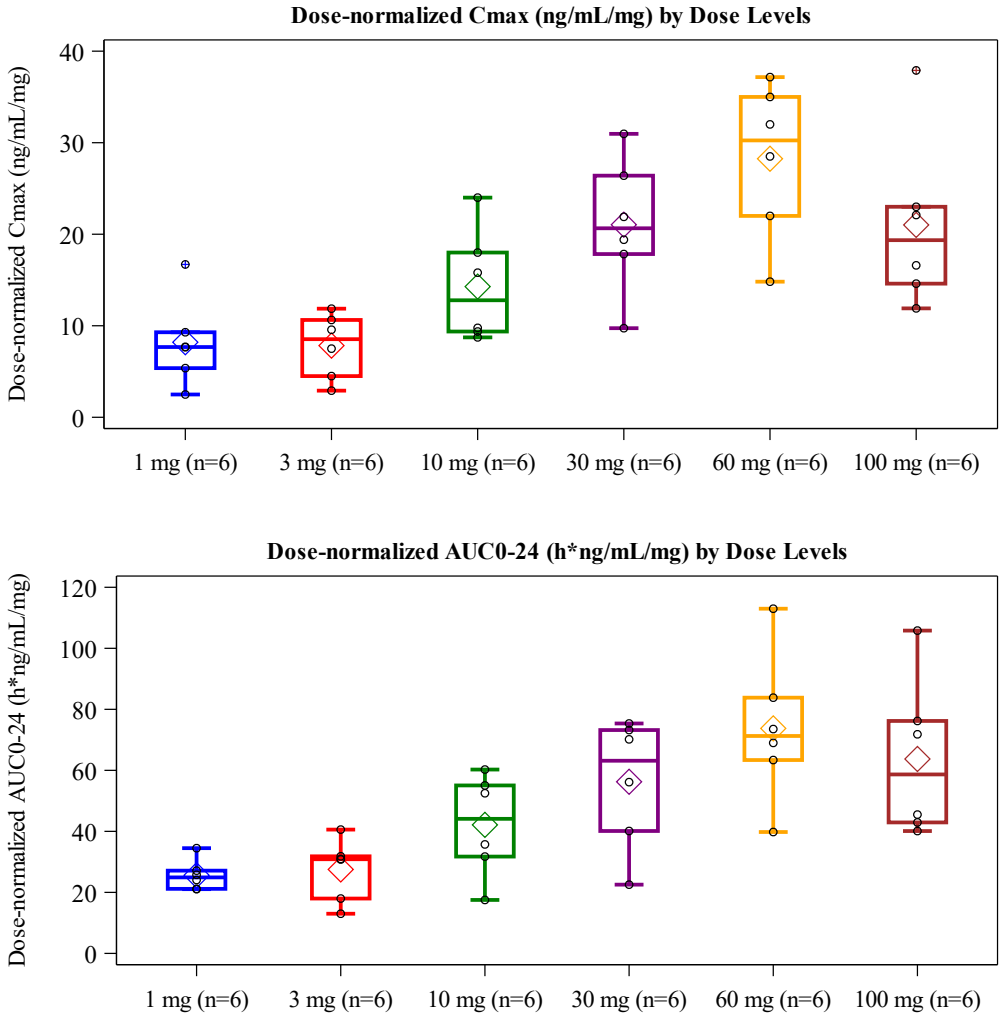
- Overall, 12 (38.7%) of the 31 subjects treated with AG-946 in MAD experienced TEAEs
- The frequency of subjects with TEAEs was similar for the placebo (44.4%) and AG-946 (38.7%) treatment arms
- No serious TEAEs were reported in subjects receiving AG-946; one serious TEAE (Grade 2) of rhabdomyolysis was reported in one subject receiving placebo
- Treatment-related TEAEs of decreased platelets occurred in 6 subjects treated with AG-946
  - None at doses <10 mg QD, 1 at 10 mg QD (Grade 1), and 5 at 20 mg QD (4 Grade 1, 1 Grade 3)
  - Decreased platelet events were asymptomatic and reversible with treatment discontinuation
- All other TEAEs in subjects receiving AG-946 occurred in 1 subject each, were Grade 1-2 in severity, and were not related to treatment

MAD, multiple ascending doses; QD, Once daily; SAE, serious adverse event; TEAE, treatment-emergent adverse events

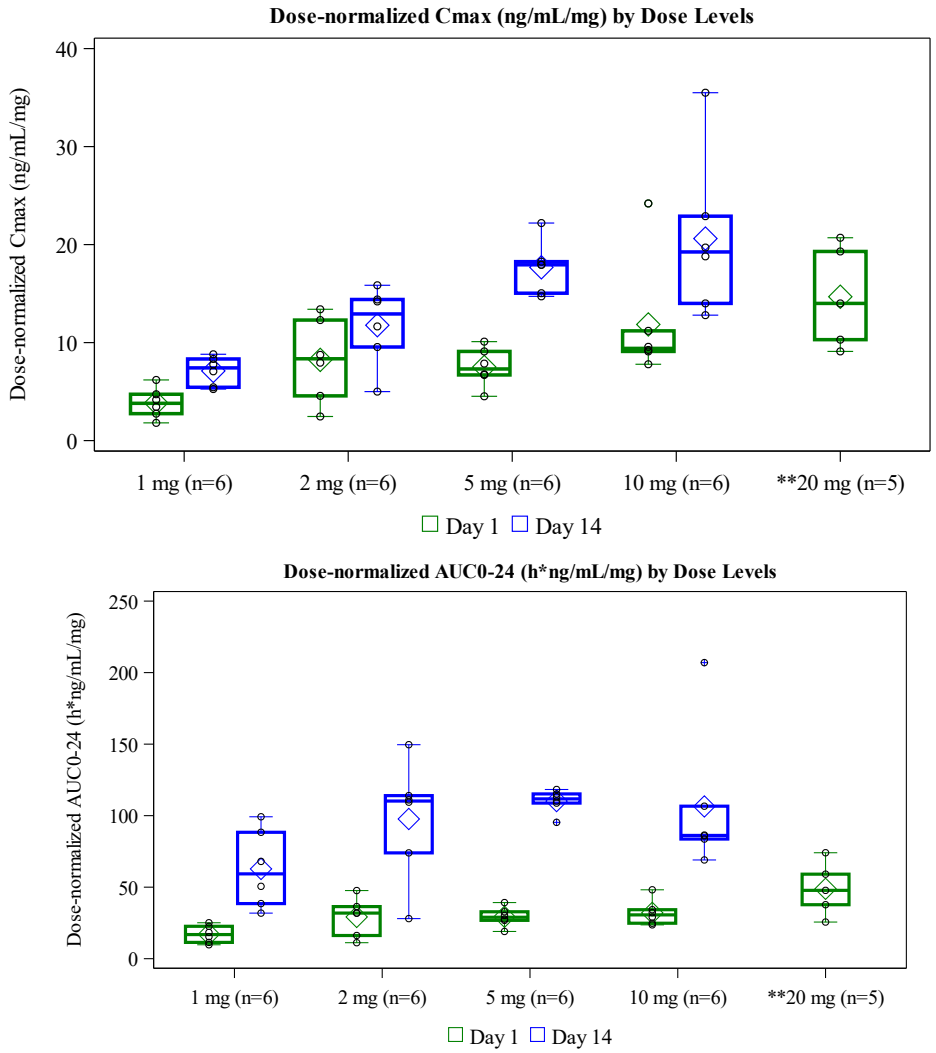
Over proportional increases in AG-946 exposure were observed in SAD, with ~3- to 4-fold accumulation observed following 14 days of dosing in MAD

Figure 3. Dose-normalized AG-946 exposures in (A) SAD and (B) MAD cohorts

A



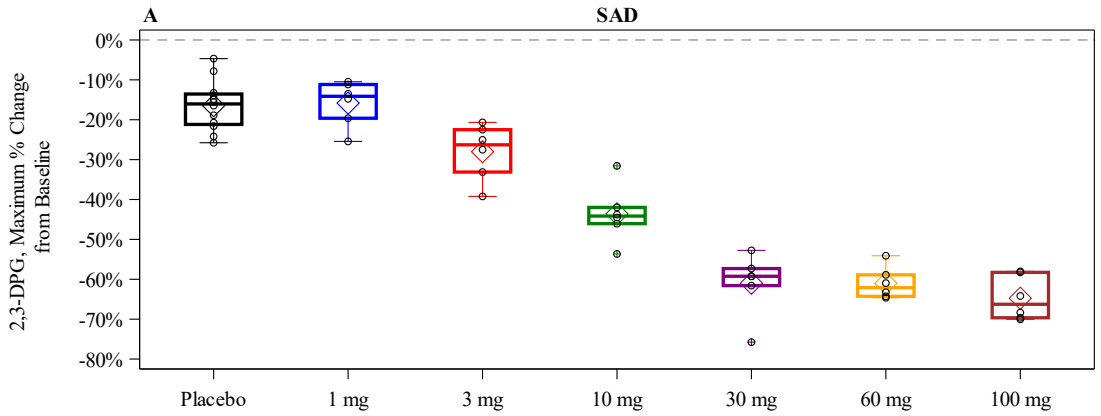
B

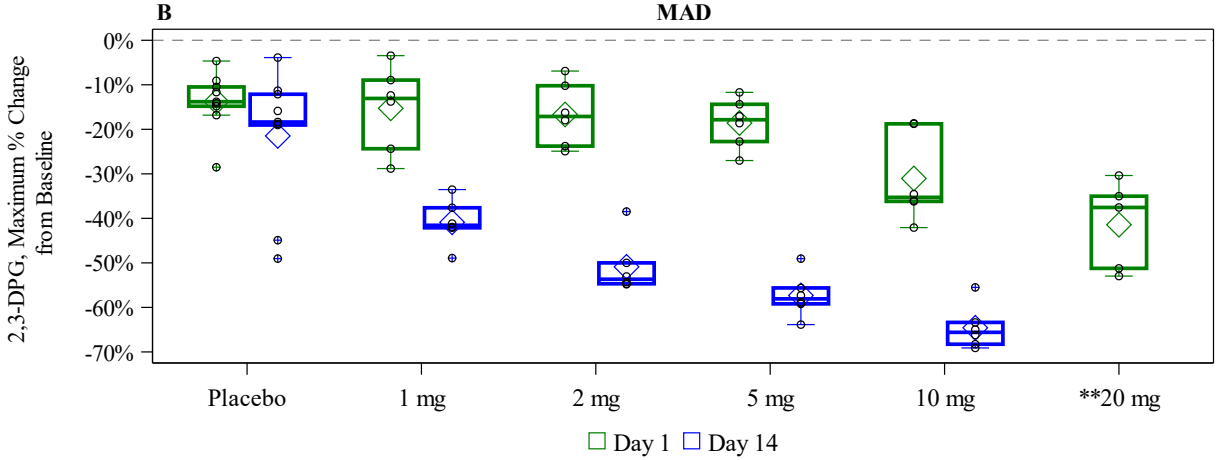


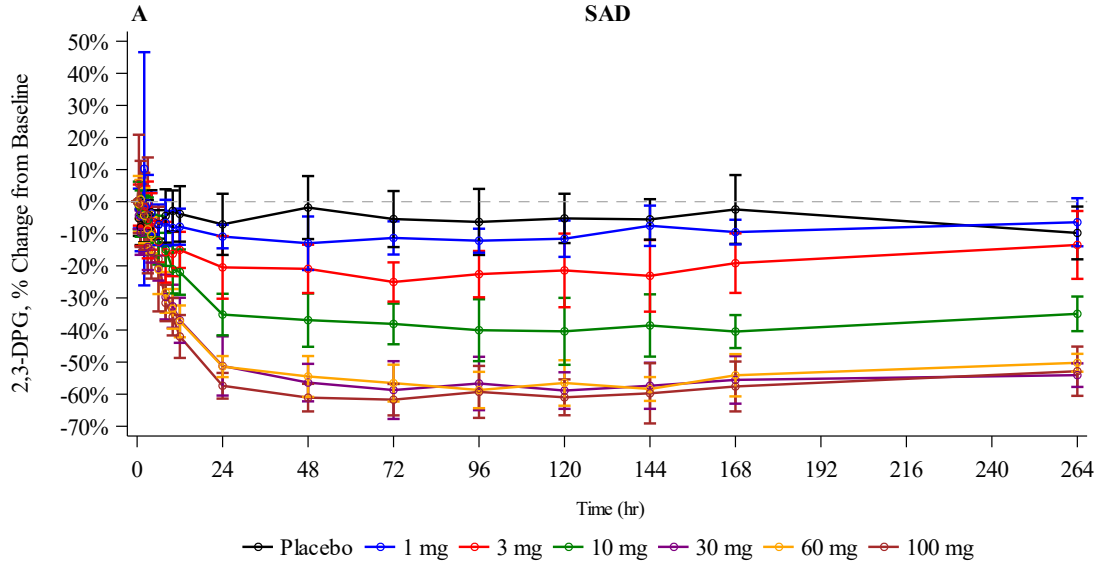
**In the 20 mg QD cohort, subjects started discontinuing from the study on Day 9, with all subjects discontinued by Day 13.
AUC_{0-24}, area under the plasma concentration versus time curve from 0 to 24 hours; C_{max}, maximum observed plasma concentration; MAD, multiple ascending doses; QD, once daily; SAD, single ascending doses

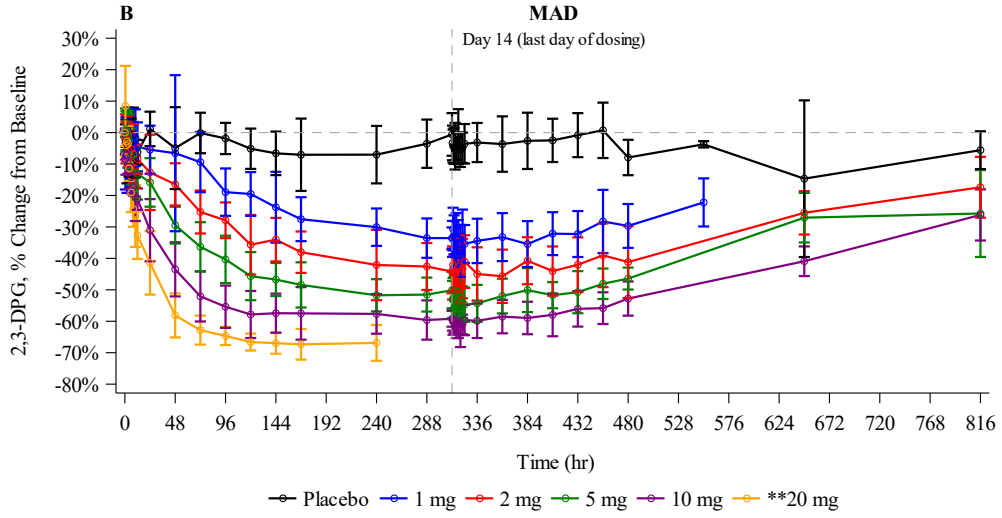
In both SAD and MAD cohorts, an increase in AG-946 dose was associated with a decrease in 2,3-DPG concentrations

Figure 4. Maximum percent change from baseline (top) and percent change from baseline over time (bottom), in 2,3-DPG concentration for (A) SAD and (B) MAD cohorts





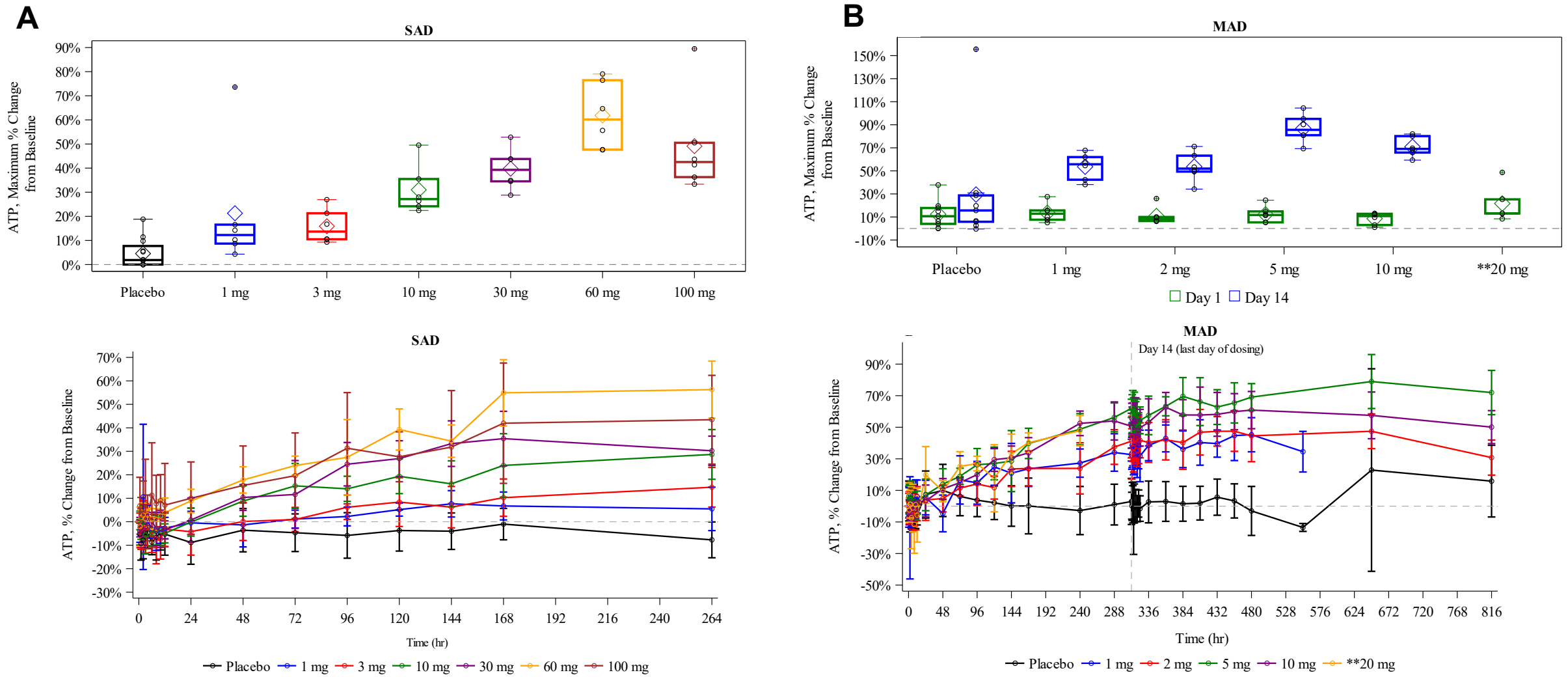




*Per protocol, the last planned pharmacodynamic sample was collected at the follow-up visit (Day 24, 25, or 26) for the 1 mg QD cohort and on Day 35 for the 2, 5, 10, and 20 mg QD cohorts. **In the 20 mg QD cohort, subjects started discontinuing from the study on Day 9, with all subjects discontinued by Day 13. DPG, diphosphoglycerate; MAD, multiple ascending doses; QD, once daily; SAD, single ascending doses

In both SAD and MAD cohorts, an increase in AG-946 dose was associated with an increase in ATP concentrations

Figure 5. Maximum percent change from baseline (top) and percent change from baseline over time (bottom), in ATP concentration for (A) SAD and (B) MAD cohorts



*Per protocol, the last planned pharmacodynamic sample was collected at the follow-up visit (Day 24, 25, or 26) for the 1 mg QD cohort and on Day 35 for the 2, 5, 10, and 20 mg QD cohorts. **In the 20 mg QD cohort, subjects started discontinuing from the study on Day 9, with all subjects discontinued by Day 13. ATP, adenosine triphosphate; MAD, multiple ascending doses; QD, once daily; SAD, single ascending doses

Conclusions

- AG-946, an oral, potent PK activator, showed a favorable safety profile at pharmacologically active doses
- The pharmacokinetic profile of AG-946 supports QD dosing, and is accompanied by sustained dose-dependent decreases in 2,3-DPG and increases in ATP consistent with activation of the glycolytic pathway
- Doses of AG-946 up to 5 mg QD are currently being evaluated in clinical trials

AG-946 supported a QD regimen and showed potent, sustained activation of the glycolytic pathway in RBCs with prolonged effects on pharmacodynamics (2,3-DPG, ATP), supporting further clinical advancement.

ATP, adenosine triphosphate; DPG, diphosphoglycerate; PK, pyruvate kinase; QD, once a day; RBC, red blood cell

Acknowledgments, disclosures and references

Acknowledgements

- We would like to thank the volunteers who took part in this study. Editorial assistance was provided Joseph Hodgson, PhD, of Adelphi Communication, Macclesfield, UK, and supported by Agios Pharmaceuticals, Inc.

Disclosures

- This study was funded by Agios Pharmaceuticals, Inc.
- **X Dai, V Iyer, A Claeys, S Patil, R Urbstonaitis, J Xiao, MU Callaghan**: Agios – employees and shareholders
- **E Merica**: Nothing to disclose

References

1. Kung C et al. Blood 2017;130:1347–56.
2. Rab MAE et al. Blood 2021;137:2997–3001.
3. Yang H et al. Clin Pharmacol Drug Dev 2019;8:246–59.
4. Valentini G et al. J Biol Chem 2002;277:23807–14.
5. Kornberg A, Goldfarb A. Arch Intern Med 1986;146:785–6.
6. Kahn A et al. Clinica Chimica Acta 1976;71:379–87.
7. Data on file.
8. Iyer V et al. 63rd ASH Annual Meeting and Exposition 2021: Abstract #2043.
9. Yang H et al. Clin Pharmacol Drug Dev 2021;8:246–59.
10. Brown KA. Lab Med 1996;27:329–33.
11. Ploszczyca K et al. Front Physiol 2021;12:670977.

Novel PK Activator AG-946: Clinical Development in MDS

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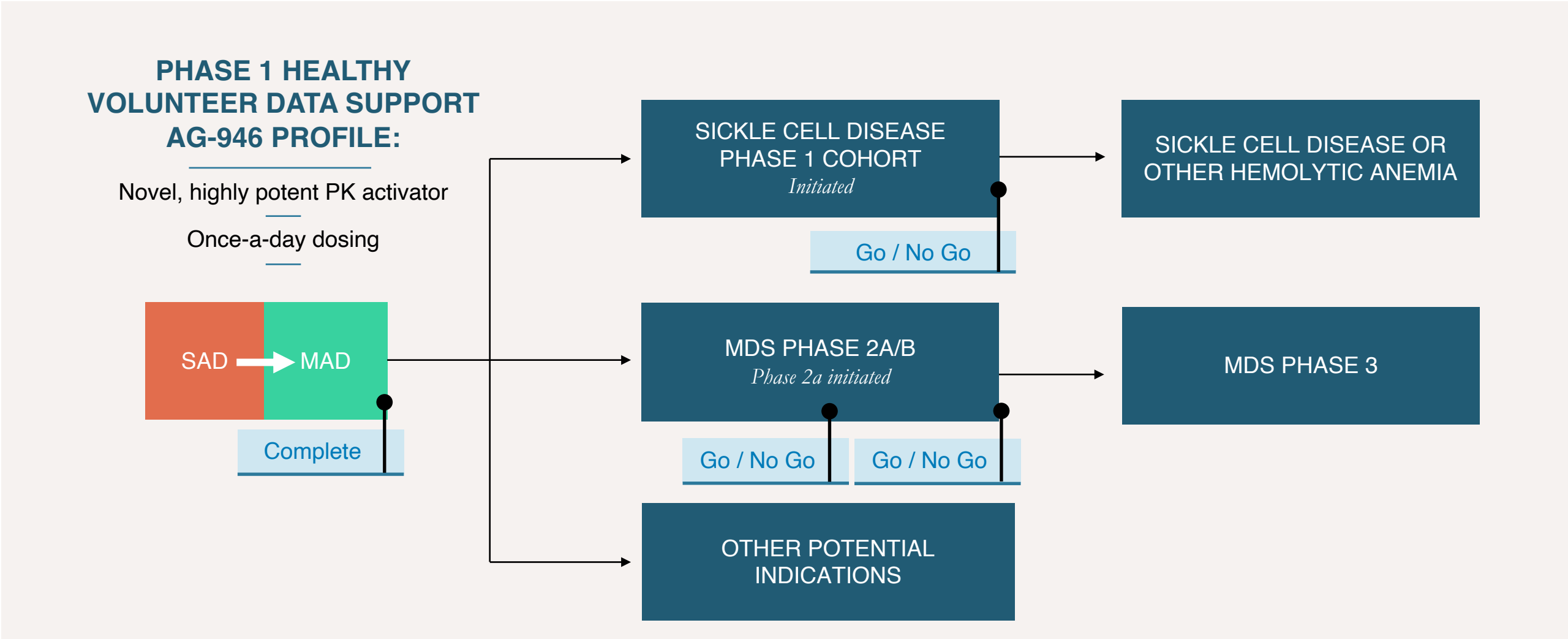
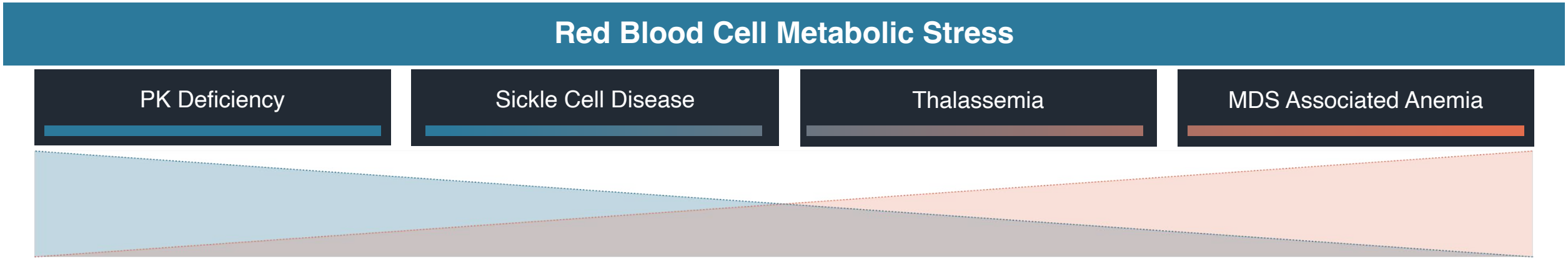
Novel PK activator AG-946 provides opportunity to build on PYRUKYND® franchise and pursue multiple paths in parallel if data support advancement



Source: ASH 2021

Ineffective Erythropoiesis is a Hallmark of MDS-Associated Anemia



Myelodysplastic Syndromes (MDS)

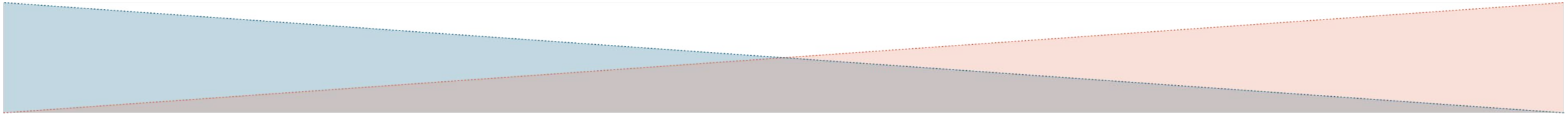
- Heterogeneous group of rare hematological malignancies
- Characterized by ineffective erythropoiesis leading to progressive cytopenia (most commonly, anemia) and abnormal cellular maturation

- **Lower-risk MDS (LR-MDS)** accounts for approximately 70% of MDS cases
- Symptomatic anemia is the primary concern for the majority of LR-MDS patients
- The goal of LR-MDS treatment is to improve quality of life by managing the underlying cytopenias and their side effects
- Limited therapeutic options to address LR-MDS

PK activation has the potential to correct red blood cell metabolism and address ineffective erythropoiesis in LR-MDS

Red Blood Cell Metabolic Stress

PK Deficiency | Sickle Cell Disease | Thalassemia | MDS Associated Anemia



Chronic Hemolysis

Chronic hemolysis is the destruction of red blood cells.

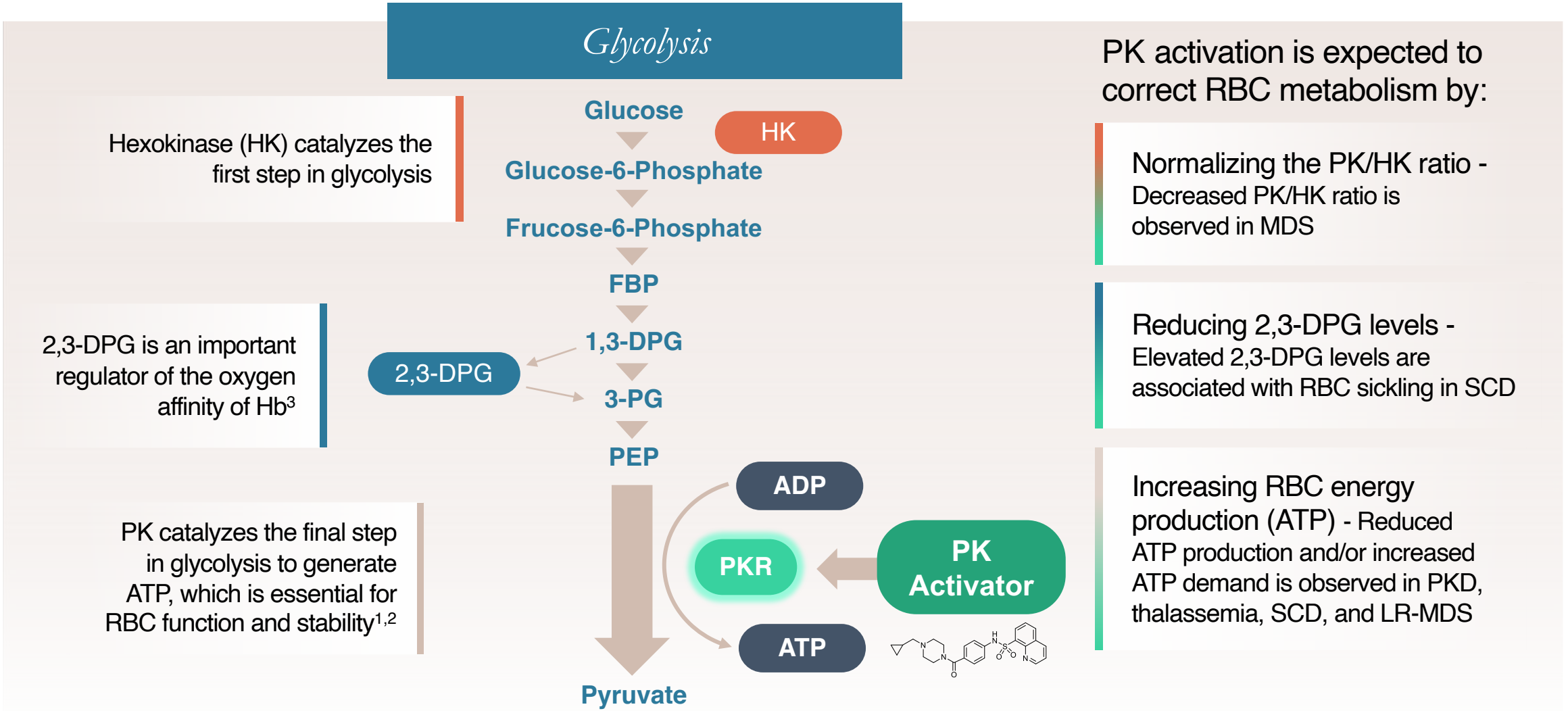
Ineffective Erythropoiesis

Ineffective erythropoiesis is characterized by a decreased output of red blood cells from the bone marrow

- **Ineffective erythropoiesis is a hallmark of both LR-MDS and thalassemia**
- **Data suggest dysfunction of glycolysis and acquired PK deficiency in LR-MDS**
- **Consistency in clinical data across a range of hemolytic and acquired anemias support that PK activation may improve red blood cell energy and address ineffective erythropoiesis**

Hypothesis: PK activation will reduce symptomatic anemia and transform the course of LR-MDS by addressing ineffective erythropoiesis

PK activation is a promising therapeutic approach for anemia associated with LR-MDS



PK activation is expected to correct RBC metabolism by:

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

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

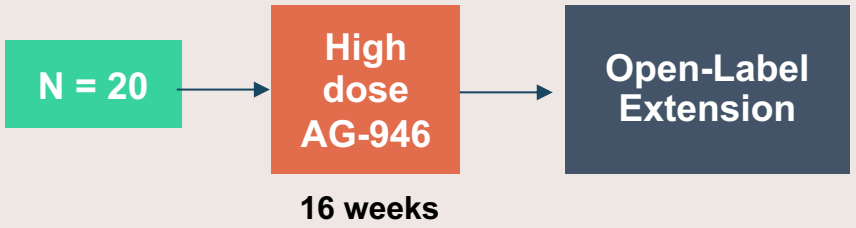
Increasing RBC energy production (ATP) - Reduced ATP production and/or increased ATP demand is observed in PKD, thalassemia, SCD, and LR-MDS

ADP = adenosine diphosphate; ATP = adenosine triphosphate; DPG = diphosphoglycerate; FBP = fructose bisphosphate; m = mutant; PEP = phosphoenolpyruvate; PG = phosphoglycerate; PK = pyruvate kinase; PKR = RBC-specific PK; RBC = red blood cell

1. Kung C et al. Blood 2017;130:1347; 2. Valentini G et al. J Biol Chem 2002;277:23807; 3. Rab MAE et al. Blood 2021;137:2997–3001

Seamless Phase 2a proof-of-concept + Phase 2b trials of AG-946 focused on establishing proof-of-concept and dose selection in LR-MDS

Phase 2a — Open Label

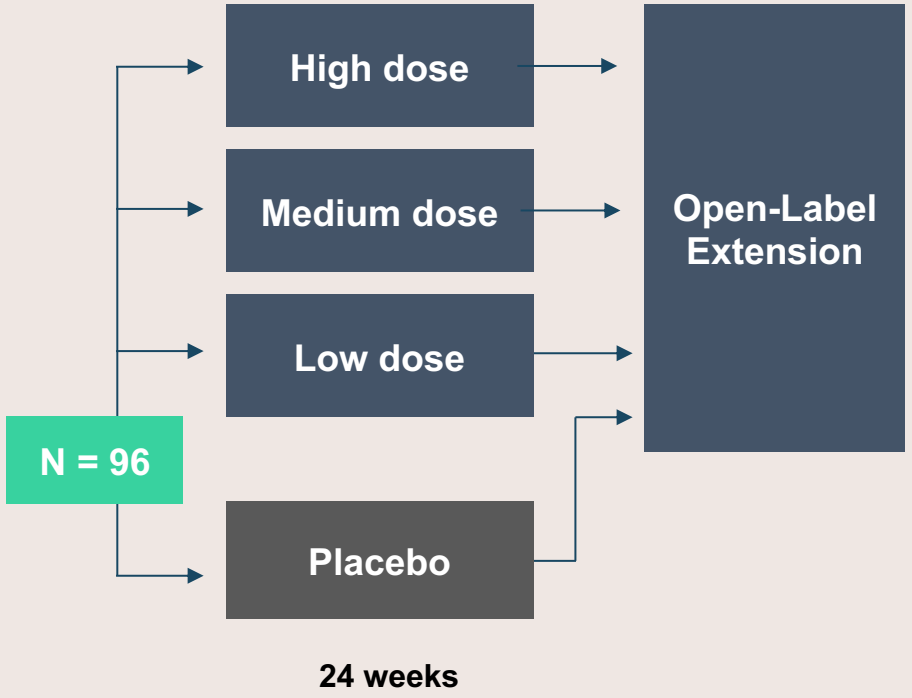


Primary endpoints:

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

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

Phase 2b — Double Blind, 1:1:1:1 Randomization



PK activation is a promising therapeutic approach for anemia associated with LR-MDS

Myelodysplastic Syndromes (MDS) are a heterogeneous group of rare hematological malignancies characterized by ineffective erythropoiesis and acquired PK deficiency leading to anemia

Lower-risk MDS (LR-MDS) accounts for approximately **70% of MDS cases**

Symptomatic anemia is the primary concern for the majority of LR-MDS patients

Agios' **consistent and compelling clinical data** across a range of anemias support development in LR-MDS and suggest that PK activation may improve red blood cell energy and address ineffective erythropoiesis

Currently enrolling a **Phase 2a/b study** of novel PK activator AG-946 to establish proof-of-concept and dose-selection in LR-MDS

Conclusions

With more than 7 years of clinical experience and the largest dataset for any PK activator, **PYRUKYND® data are consistent and compelling** across indications and support continued development

PYRUKYND® is first and only PK activator approved in U.S. and EU (adult PK deficiency)

Hemolytic and acquired anemias share a common clinical presentation with serious complications and comorbidities driven by chronic hemolysis and ineffective erythropoiesis

PK activation has the potential to **correct red blood cell metabolism and address the underlying pathophysiology** of a range of hemolytic and acquired anemias by addressing both chronic hemolysis and ineffective erythropoiesis

Development strategy positions Agios for **meaningful expansion opportunities** for the PK activation franchise, with the potential to unlock significant value for patients and shareholders

agios

Q&A