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Pyruvate Kinase-R Activation Webinar

November 19, 2020

Forward-Looking Statements

This presentation and various remarks we make during this presentation contain forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding the potential benefits of mitapivat; Agios' plans, strategies and expectations for its and its collaborator's preclinical, clinical and commercial advancement of its drug development, including mitapivat; Agios' key milestones for 2020 and 2021; Agios' plans regarding future data presentations; and the potential benefits of Agios' strategic plans and focus. The words "anticipate," "expect," "goal," "hope," "milestone," "plan," "potential," "possible," "strategy," "will," "vision," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Such statements are subject to numerous important factors, risks and uncertainties that may cause actual events or results to differ materially from Agios' current expectations and beliefs. For example, there can be no guarantee that any product candidate Agios or its collaborators is developing will successfully commence or complete necessary preclinical and clinical development phases, or that development of any of Agios' product candidates will successfully continue. There can be no guarantee that any positive developments in Agios' business will result in stock price appreciation. Management's expectations and, therefore, any forward-looking statements in this presentation and various remarks we make during this presentation could also be affected by risks and uncertainties relating to a number of other important factors, including, without limitation: risks and uncertainties related to the impact of the COVID-19 pandemic to Agios' business, operations, strategy, goals and anticipated milestones, including its ongoing and planned research activities, ability to conduct ongoing and planned clinical trials, clinical supply of current or future drug candidates, commercial supply of current or future approved products, and launching, marketing and selling current or future approved products; Agios' results of clinical trials and preclinical studies, including subsequent analysis of existing data and new data received from ongoing and future studies; the content and timing of decisions made by the U.S. FDA, the EMA or other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies; Agios' ability to obtain and maintain requisite regulatory approvals and to enroll patients in its planned clinical trials; unplanned cash requirements and expenditures; competitive factors; Agios' ability to obtain, maintain and enforce patent and other intellectual property protection for any product candidates it is developing; Agios' ability to maintain key collaborations; and general economic and market conditions. These and other risks are described in greater detail under the caption "Risk Factors" included in Agios' public filings with the Securities and Exchange Commission. Any forward-looking statements contained in this presentation and various remarks we make during this presentation speak only as of the date hereof, and Agios expressly disclaims any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

Today's Agenda

	TOPIC	SPEAKER	
8:00 – 8:10 AM	Opening Remarks		Jackie Fouse, Ph.D.
8:10 – 8:30 AM	An Overview of Serious Hemolytic Anemias: Pyruvate Kinase (PK) Deficiency, Sickle Cell Disease and Thalassemia		Eduard van Beers, M.D., Ph.D.
8:30 – 8:45 AM	Biology of Pyruvate Kinase-R (PKR) Activation		Bruce Car, Ph.D.
8:45 – 9:05 AM	Clinical Development & Data in PK Deficiency, Sickle Cell Disease and Thalassemia		Chris Bowden, M.D.
9:05 – 9:25 AM	PK Deficiency Patient Story and Fireside Chat		Christa Kerkorian Tamara Schryver
9:25 – 10:00 AM	Partnering With the Hemolytic Anemia Community to Transform Care		Darrin Miles
10:00 – 10:30 AM	Q&A		

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

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

—Tamara S., Minnesota

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

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

—Tamara S., Minnesota

Agios is a commercial-stage biopharmaceutical company passionately committed to applying our scientific leadership in the field of cellular metabolism to transform the lives of patients with cancer and rare genetic diseases.

Agios pioneered a novel path to treating hematological diseases by following the science of cellular metabolism…

Hematology Is At Our Core

Activating PKR in rare hemolytic anemias

Unlocking the promise of IDH in hematologic malignancies

…and we are leading the way in PKR activation for treating hemolytic anemias.

Our Leadership in PKR Activation

6 YEARS

STUDYING PKR ACTIVATION IN THE CLINIC

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

+ A LOT OF FIRSTS:

- BUILT 1st GLOBAL PK DEFICIENCY REGISTRY
- ESTABLISHED 1st INTERNATIONAL PK DEFICIENCY ADVOCACY ADVISORY COUNCIL
- SUPPORTED 1st HEMOLYTIC ANEMIA ADVOCACY COALITION BUILDING MEETING

Agios PKR Clinical Pipeline

Preclinical	Early Stage Clinical	Late Stage Clinical	Regulatory Submission	Near-Term Milestones	Worldwide Commercial Rights
Mitapivat Not Regularly Transfused (NRT) Adult PK Deficiency (ACTIVATE)				Topline data by YE	agios
Mitapivat Regularly Transfused (RT) Adult PK Deficiency (ACTIVATE-T)				Topline data in Q1 ’21	agios
Mitapivat Thalassemia				Finalize pivotal dev plan by YE; Initiate pivotal program in 2021	agios
Mitapivat Sickle Cell Disease				Finalize pivotal dev plan in 1H ’21; Initiate pivotal program in 2021	agios
Mitapivat Pediatric PK Deficiency		*Mitapivat is also being evaluated for pediatric populations for thalassemia & sickle cell disease*		Finalized pivotal dev plan	agios
AG-946				Initiated Phase 1 HV study in Aug. 2020	agios
Other PK Activators				Development candidate selection	agios

The PKR Platform: A Significant Global Opportunity in Hemolytic Anemias and Other Indications with High Unmet Need

1. Our PKR activation portfolio has potential broad utility across hemolytic anemias and several near-term milestones
2. Mitapivat is on track to be the first potential disease-modifying therapy for patients with PK deficiency with U.S. and EU submission planned in 2021
3. Mitapivat has potential to be first-in-class therapy for β- and α-thalassemia and sickle cell disease, progressing into pivotal development in 2021
4. Our initial disease areas of focus are highly synergistic, and we can leverage our experience and relationships in PK deficiency to engage with the thalassemia and sickle cell disease communities

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

Meet Dr. Eduard J. van Beers, M.D., Ph.D.

University Medical Center Utrecht

- Dr. Eduard J. van Beers, M.D., Ph.D., is a leading expert in hematology at the Van Creveldkliniek, center for benign hematology, University Medical Center Utrecht, Utrecht University, the Netherlands
- Served as an investigator in the DRIVE PK and ACTIVATE studies of mitapivat in PK deficiency and is also running an investigator-sponsored trial of mitapivat in sickle cell disease
- Coordinator of the transversal field of action on Clinical Trials and Research of Eurobloodnet (European Reference Network for rare hematological disease in EU)

Overview of Serious Hemolytic Anemias: PK Deficiency, Thalassemia and Sickle Cell Disease

Dr. Eduard J. van Beers, Utrecht University

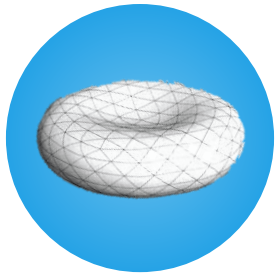
Causes of Hereditary Hemolytic Anemia

Disturbance in hemoglobin production:

- Sickle cell
- Thalassemia

Disturbance in (energy) metabolism:

- PK deficiency (most prevalent glycolytic enzyme defect)



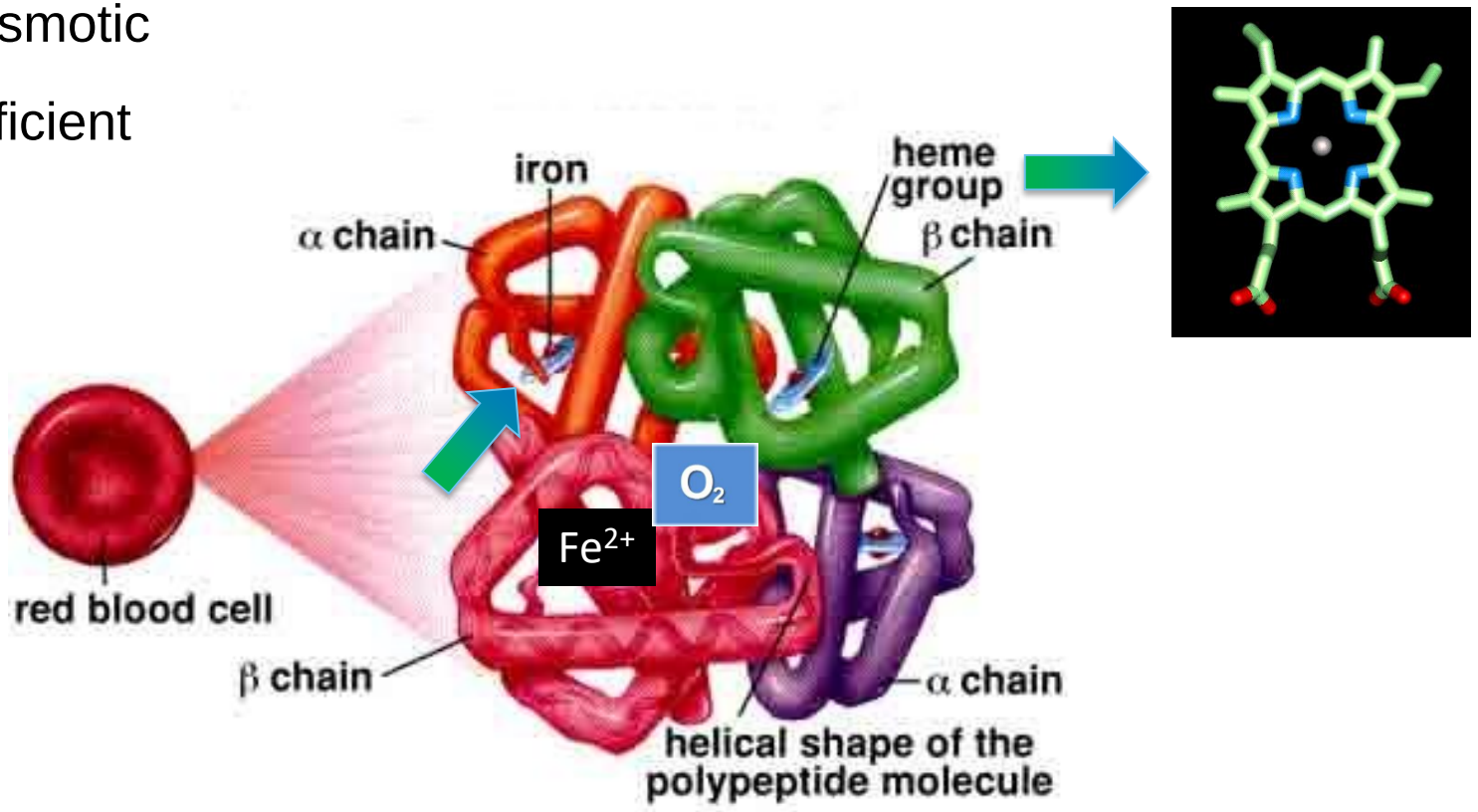
Disturbance in red cell membrane:

- Spherocytosis
- Stomatocytosis

Red Blood Cell Function

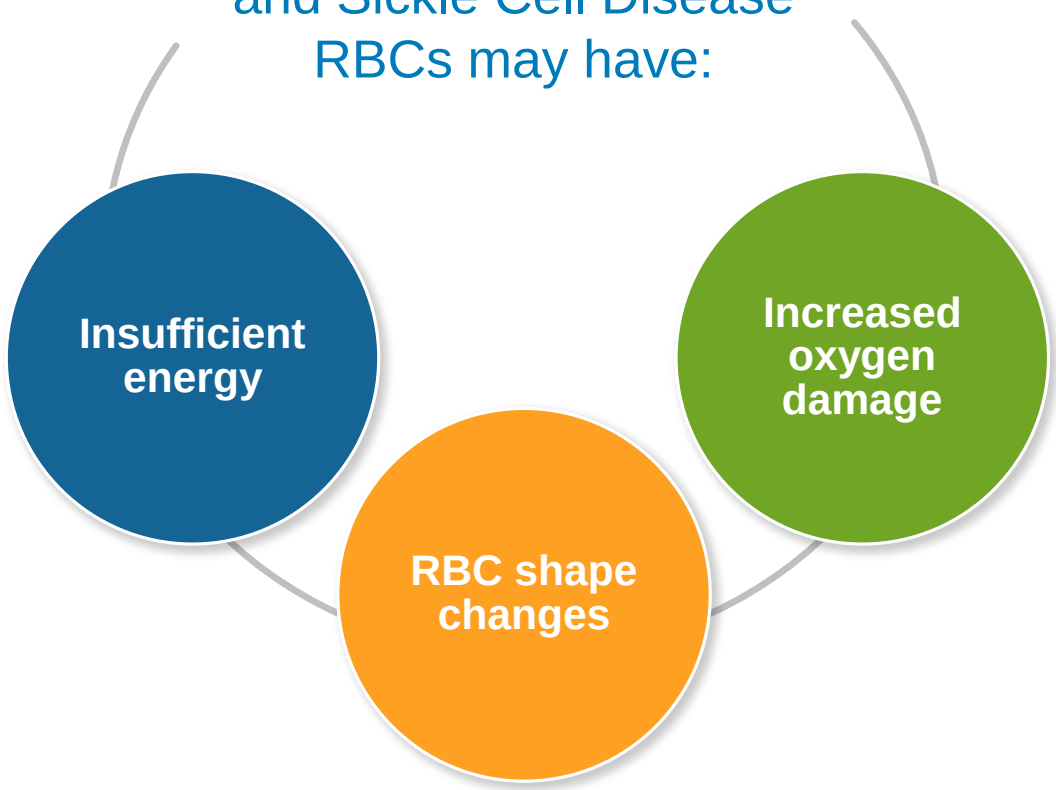
Oxygen transport via hemoglobin

- Free plasma Hb toxic in osmotic
- Packed Hb much more efficient

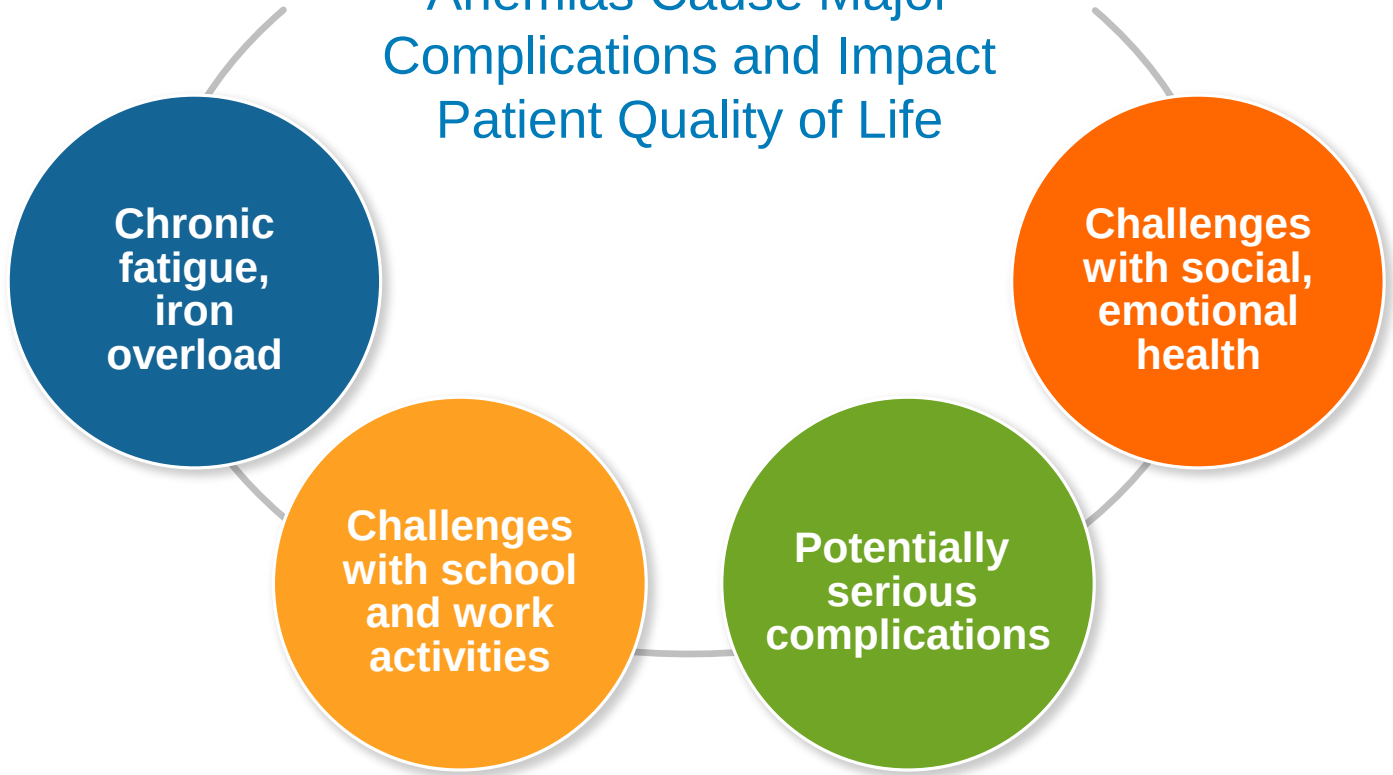


PK Deficiency, Thalassemia and Sickle Cell Disease All Damage the Red Blood Cell (RBC) and Have Major Physical and Psychosocial Impacts

In PK Deficiency, Thalassemia and Sickle Cell Disease RBCs may have:



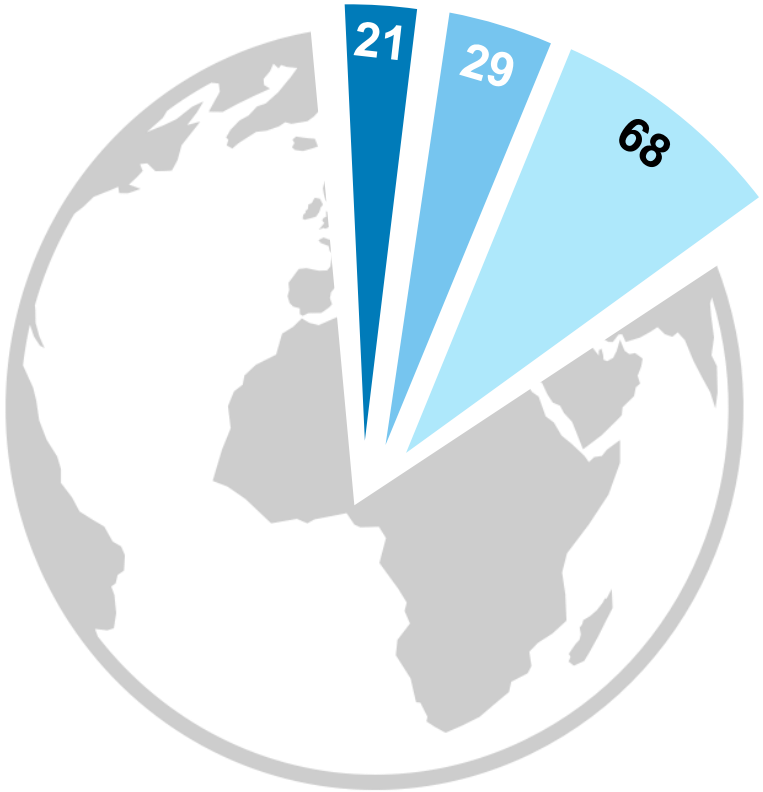
All of These Hemolytic Anemias Cause Major Complications and Impact Patient Quality of Life



PKR activation has the potential to transform the course of hemolytic anemia by increasing RBC energy, health and longevity

Years Lived with Disability (YLD)

2010



6,916,000,000

772,000,000

DM	21,000,000
COPD	29,000,000
Anemia	68,000,000

Lancet Dec 13, 2012 Icons: C Shannon, J Cabesaz, A Coscovelnita, M Vanco.

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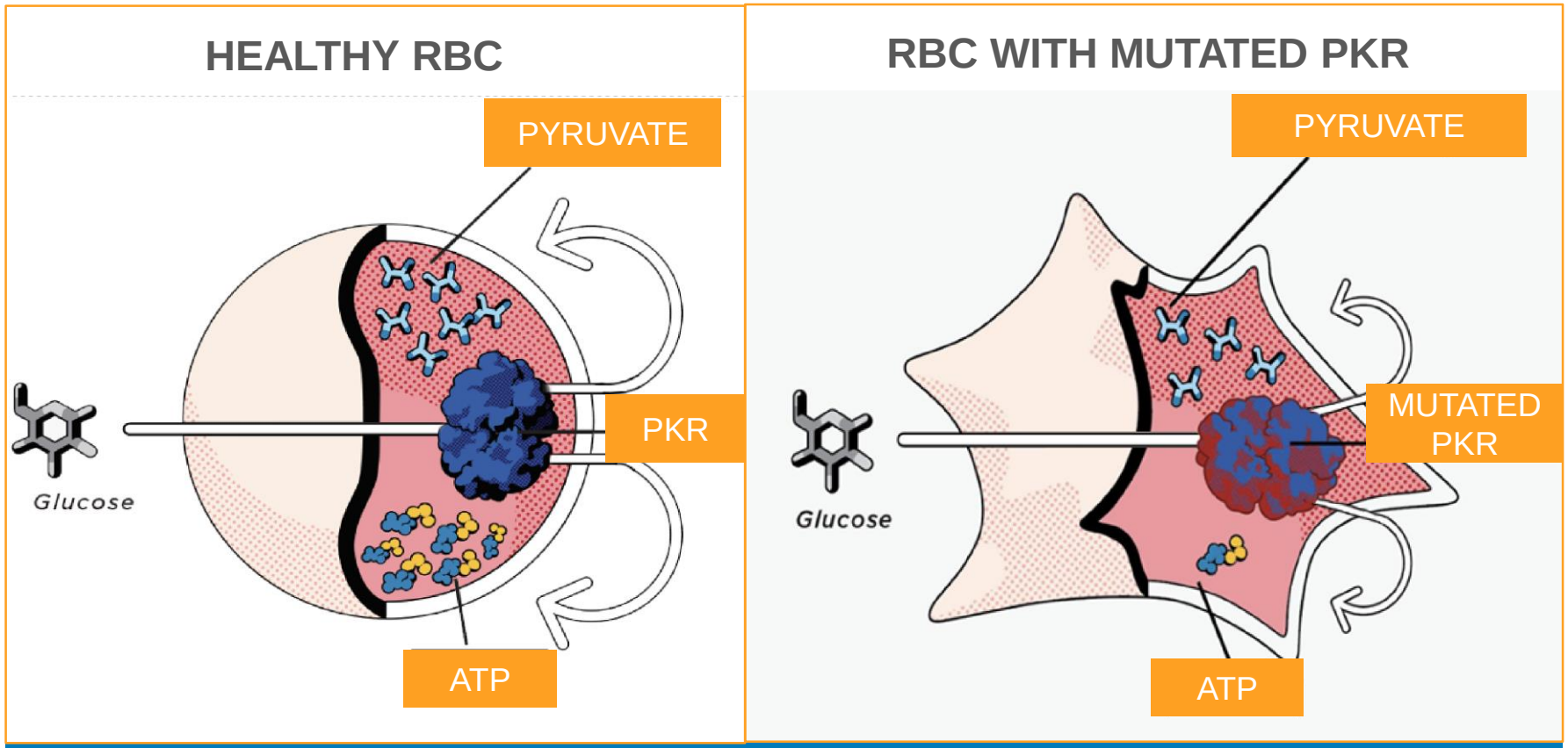
Pyruvate Kinase Deficiency

What Is Pyruvate Kinase Deficiency?

- A rare, inherited enzyme deficiency that affects RBCs
- Hemolytic anemia results when RBCs are broken down faster than they are made
- Often presents at birth with jaundice and can cause lifelong hemolytic anemia and associated morbidities
- Estimated 3-8K patients in the U.S. and EU
- No currently approved therapies

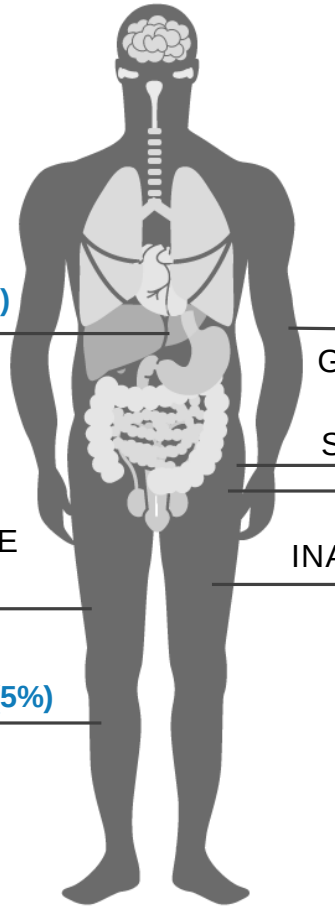


- The PKR enzyme performs the last step of glycolysis
- RBCs convert glucose into pyruvate to make ATP (adenosine triphosphate)
- Deficient PKR leads to less ATP, so RBCs have less energy

Grace R et al. *Am J Hematol* 2015;90(9):825-30; [1]Mohrenweiser HW *PNAS* 1981;78(8):5046-50; [2]Carey PJ et al. *Blood* 2000;96(12):4005-6; [3]Beutler E & Gelbart T *Blood* 2000;95(11):3585-8; [4]deMedicis et al. *Hum Hered* 1992;42(3):179-83.

PK Deficiency Is a Lifelong Disease With Risk of Serious Complications

Burden of Disease



Therapies are Only Supportive and Have Complications

	Supportive Treatments	Complications
INFANT	• Phototherapy • Blood transfusions	• Iron overload → iron chelation therapy
CHILD	• Removal of spleen • Removal of gall bladder • Blood transfusions	• Infection risk → lifelong prophylactic antibiotics • Thrombosis risk • Iron overload → iron chelation therapy
ADULT	• Blood transfusions	• Iron overload → iron chelation therapy

Baseline and retrospective data from 144 NHS patients | Source: R. Grace, poster ASH 2015.

PK Deficiency Has a Lifelong Impact on Patients

PHYSICAL LIMITATIONS

- Need for additional rest
- Difficulty with exercise/sports
- Difficulty climbing stairs/walking uphill
- Susceptibility to illness

ACTIVITIES OF DAILY LIVING

- Difficulty with household activities
- Decreased productivity
- Difficulty meetings demands of work and/or school

PHYSICAL IMPACT

- Pain and fracture
- Risk of organ damage
- Impact of repeated transfusions

SOCIAL & ECONOMIC IMPACT

- Social isolation and negative impact on relationships
- Unwanted attention
- Economic burden and inconvenience

FDA PK Deficiency Voice of the Patient Report; Agios market research

Thalassemia

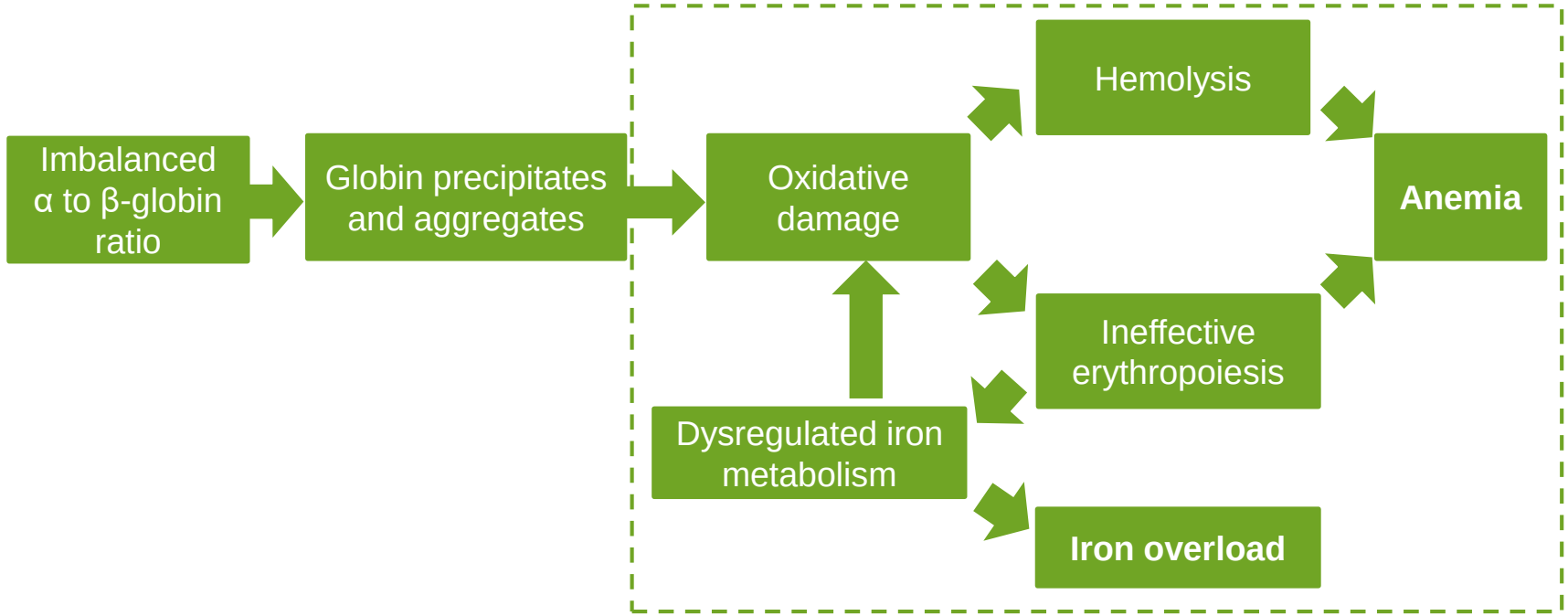
What Is Thalassemia?

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

TWO MAIN TYPES

Alpha thalassemia, caused by mutations in alpha globin

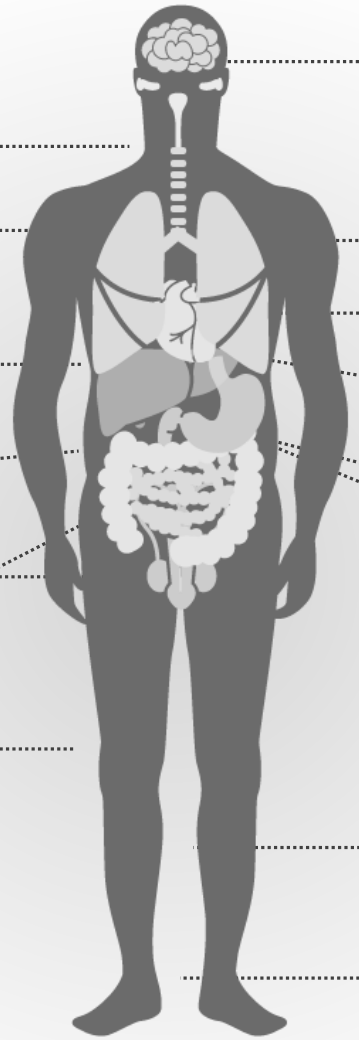
Beta thalassemia, caused by mutations in beta globin



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

Agios market research; EHA 2020

Complications From Thalassemia Occur Regardless of Transfusion Status



Hypothyroidism
Hypoparathyroidism

Cardiac siderosis
Left-sided heart failure

Hepatic failure
Viral hepatitis

Diabetes mellitus

Hypogonadism

Osteoporosis

Transfusion reactions
Alloimmunization

Silent cerebral ischemia

Pulmonary hypertension
Right-sided heart failure

Extramedullary
hematopoietic pseudotumors

Hepatic fibrosis, cirrhosis, and cancer

Gallstones

Splenomegaly

Venous thrombosis

Leg ulcers

Musallam. *Acta Haematol*. 2013;130:64. Musallam. *Haematologica*. 2013;98:833.

Thalassemia Poses Significant Impacts on Patients' Lives

Anemia and fatigue

Transfusion burden

Risk of organ damage and infection

Pain and fractures

Economic burden and inconvenience

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Sickle Cell Disease

What Is Sickle Cell Disease (SCD)?

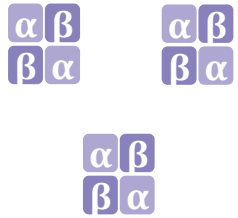
A rare blood disorder characterized by:

- Recurrent acute clinical events (eg, acute pain)
- Chronic anemia
- Both are a direct result of sickled RBCs, which are rigid, adhesive, and fragile
- Sticky sickled RBCs, together with other blood components cause microvascular occlusion, ischemia and depletion of the oxygen supply to tissues
- Fragile sickled cells cause chronic anemia
- Estimated 120-135K patients in the U.S. and EU

HEALTHY

β-globin subunit from wild-type gene

HbA
HbA molecules do not polymerize

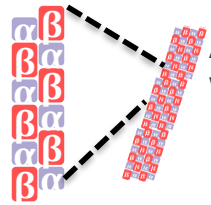


Healthy RBC
Retain flexible, biconcave shape

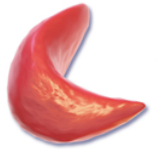
Full of individual HbA molecules

SICKLE CELL ANEMIA

β globin subunit from mutant gene

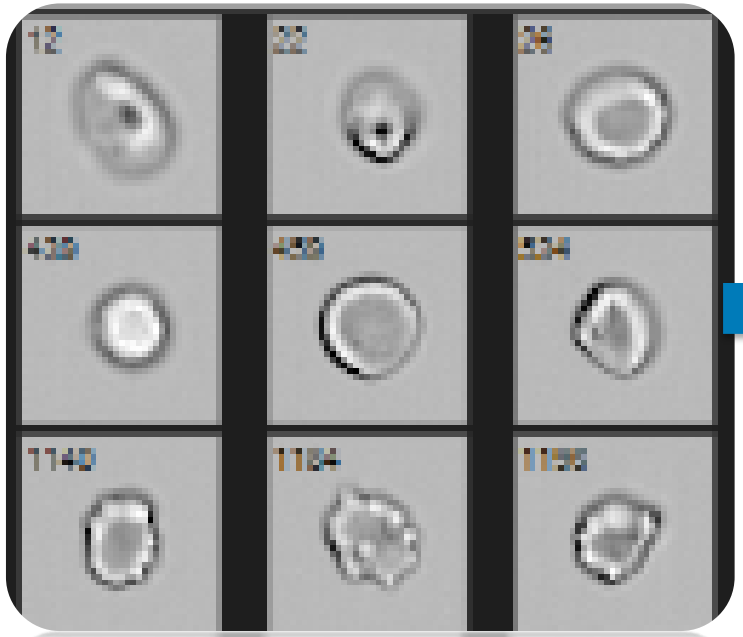


Abnormal "sickle" HbS
When deoxygenated, molecules polymerize into a fiber

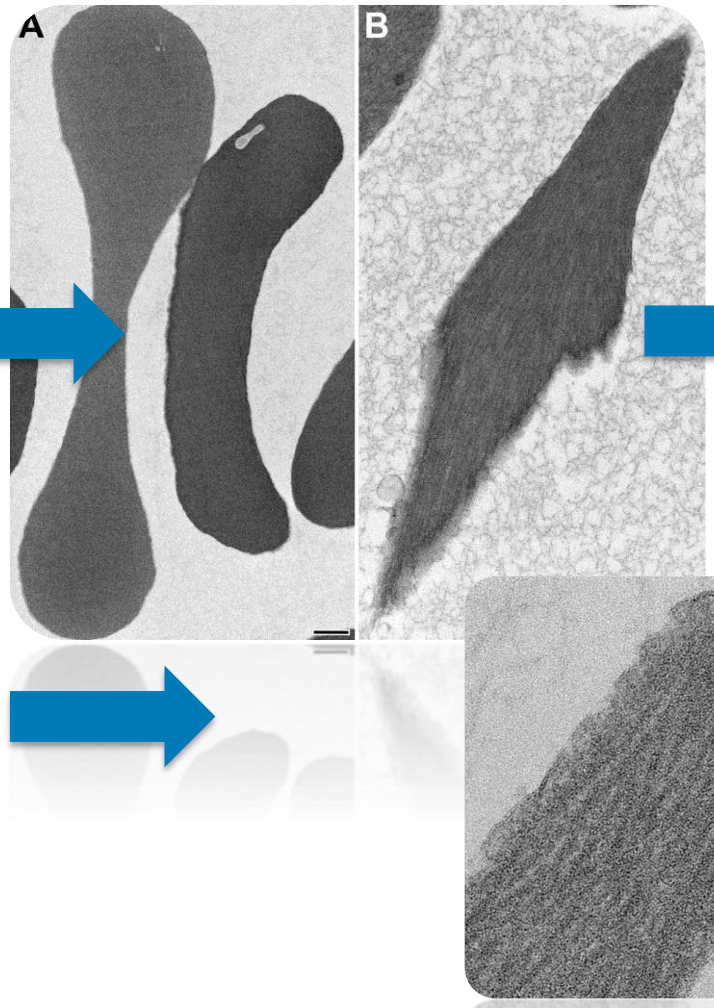


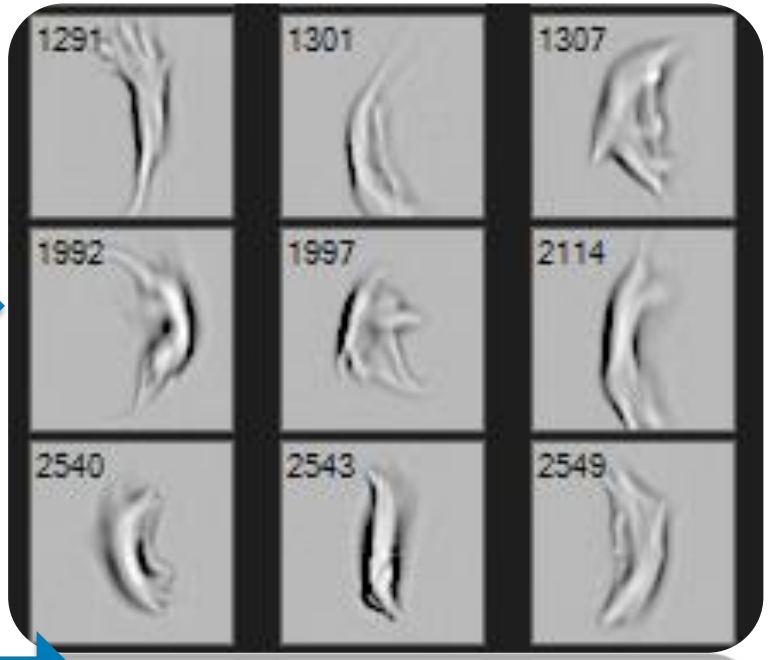
Sickled RBC
When deoxygenated, have elongated, rigid shape due to abnormal Hb fibers

Pathophysiology of Sickle Cell Anemia



High oxygen
High Ph





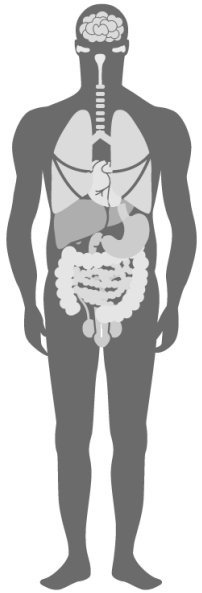
Low oxygen
Low Ph

v Beers et al.

SCD Results in Morbidity and Mortality via Distinct Pathways; Opportunity for Therapy That Addresses Hemolytic Anemia and Vaso-occlusion

HbS polymerization, which causes RBC damage, is the root cause of SCD

Hemolytic anemia and vaso-occlusive crises



Organ Damage

- Stroke
- Renal Failure
- Pulmonary Hypertension
- Priapism
- Leg Ulcers
- Osteonecrosis
- Retinopathy

Profound Quality of Life Impact

Fatigue | Hospitalization | Pain | School and Work Challenges

Significant Impact of SCD on Patients

50%

Of patients have at least 1 VOC per year

<10 g/dL

Hb level of almost all patients

~30%

Of patients are regularly transfused

~30 years

Shortened life expectancy

53%

Of adults have had a cerebral silent infarction

10-20 days

Sickle RBC life vs. 90-120 days for normal RBCs

24%

Patients have a stroke by 45 years of age

N Shah, et al, *PLoS One*. 2019; 14(7): e0214355; Lanzkron, S. et al. *Public Health Rep*. Mar-Apr 2013; 128(2):110-6;Kanter J, Kruse-Jarres R. *Blood Rev*. 2013;27(6):279-287; Vichinsky, E. *Hematology*. 2017(1):435-439.; The American Journal Med 1978 Vol 64,2: 53-258; Agios market research

PK Deficiency, Thalassemia and Sickle Cell Disease All Damage the RBC and Have Major Physical and Psychosocial Impacts

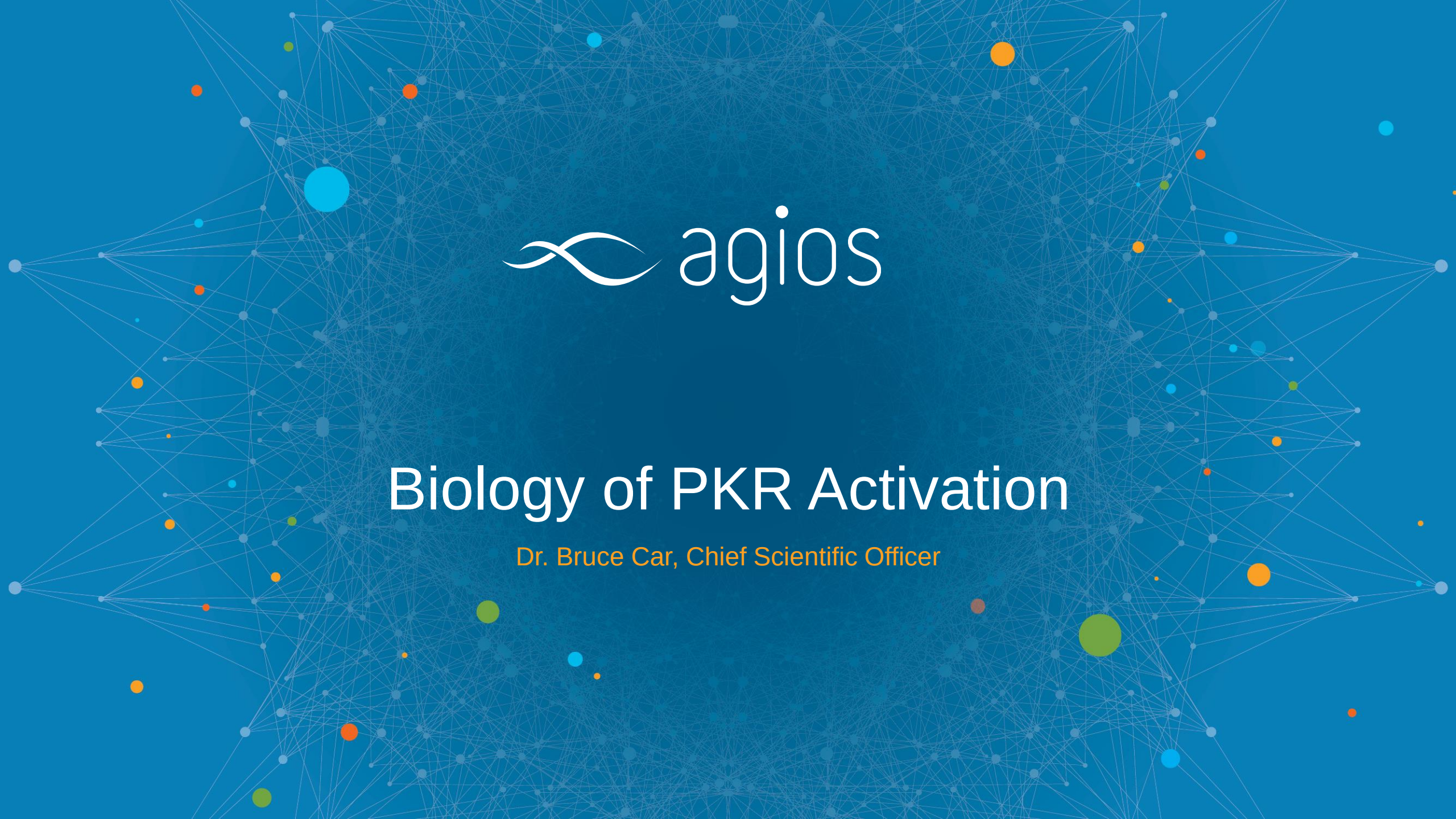
In PK Deficiency, Thalassemia and Sickle Cell Disease RBCs may have:

- Insufficient energy
- Increased oxygen damage
- RBC shape changes

All of These Hemolytic Anemias Cause Major Complications and Impact Patient Quality of Life

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

PKR activation has the potential to transform the course of hemolytic anemia by increasing RBC energy, health and longevity

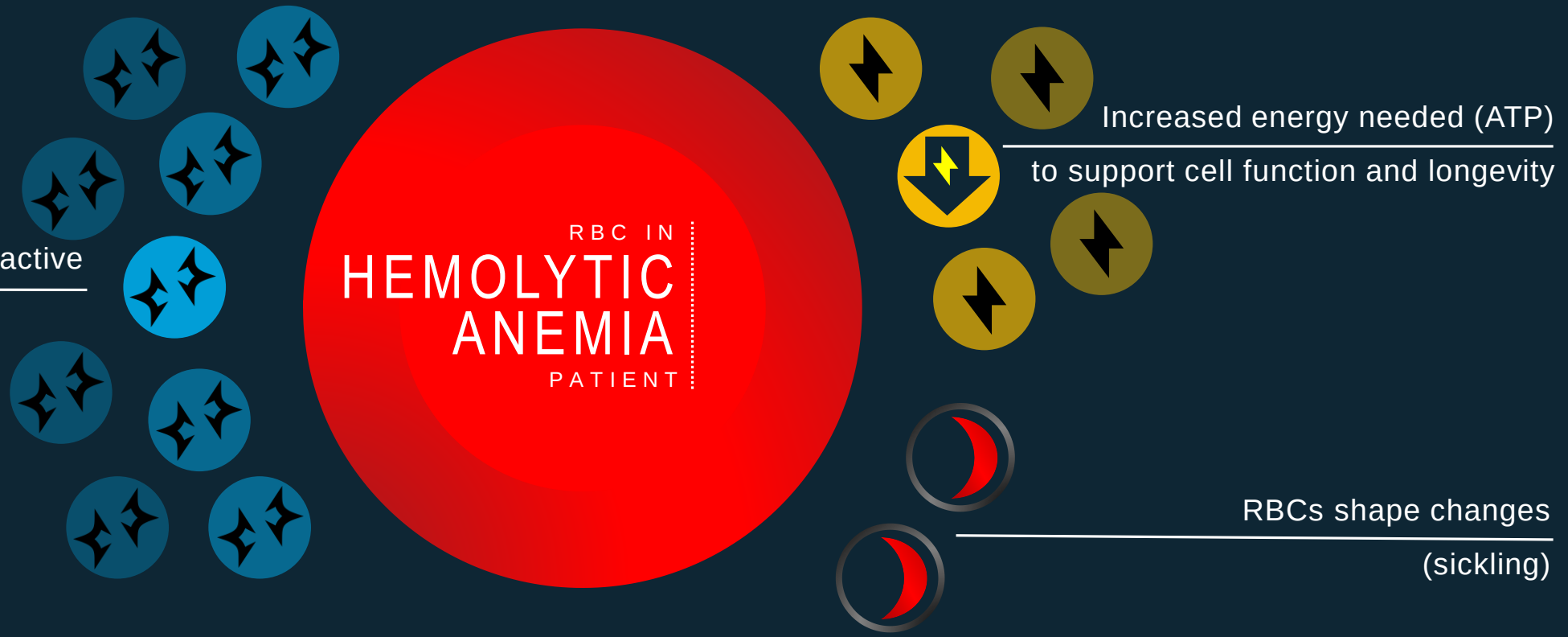


Biology of PKR Activation

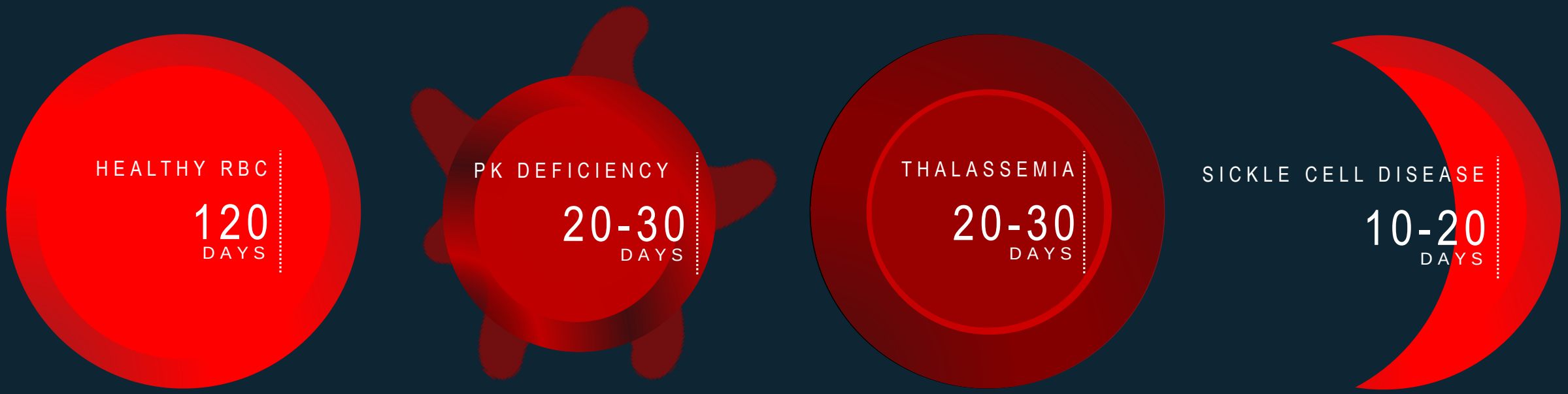
Dr. Bruce Car, Chief Scientific Officer

RBCs Deliver Oxygen to Tissues, Which Is Necessary for Energy and Organ Health

RBCs in Patients With Hemolytic Anemia Have Insufficient ATP, Increased ROS Damage or Sickling



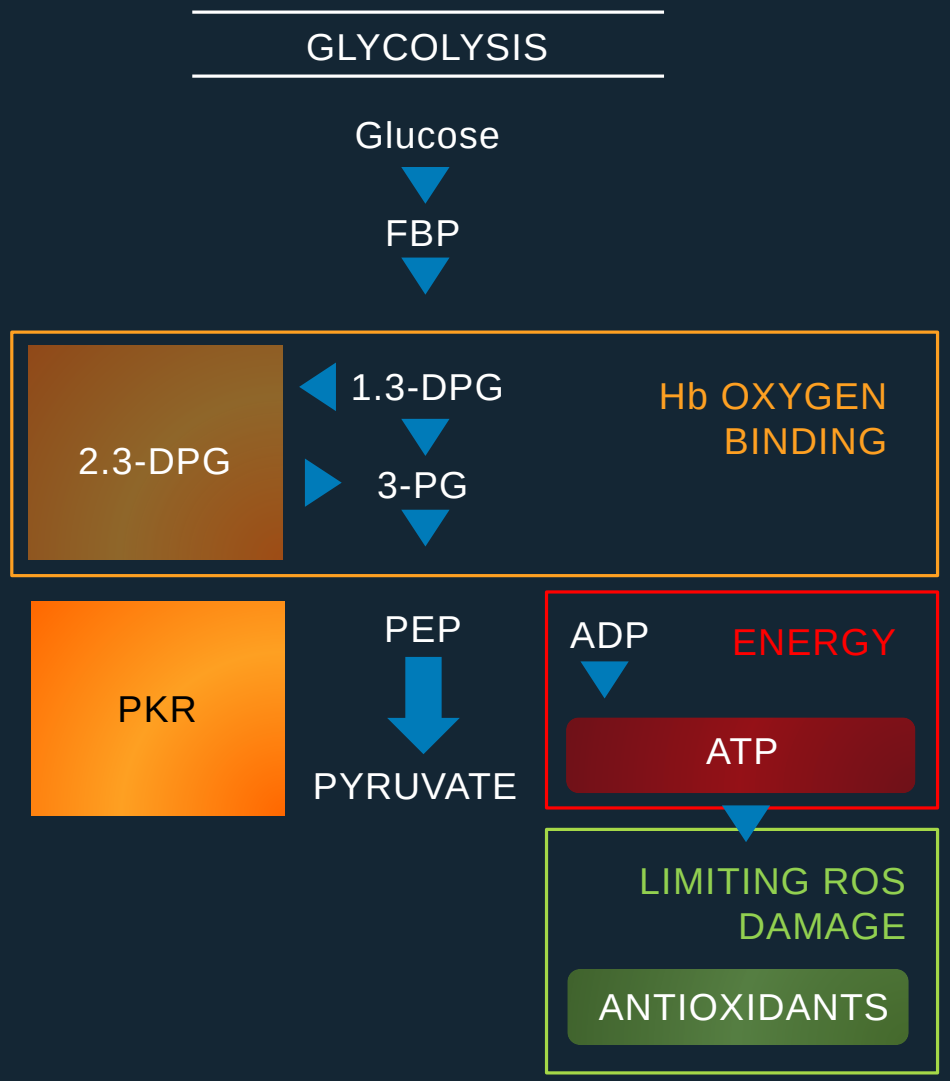
Shortened RBC Lifespan Can Lead to Chronic Fatigue, Iron Overload and Potentially Serious Complications



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

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

PKR Is the Rate-Limiting Step for RBC Energy Production



Pyruvate kinase-R (PKR) is required for:

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

Mitapivat Has the Potential to Be the First Agent to Transform the Course of Hemolytic Anemia by Increasing RBC Energy, Health and Longevity

ATP

Increases ATP production, helps to match RBC energy needs

ANTIOXIDANTS (ROS)

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

2,3 DPG

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

Broad Potential for PK Activator Development

PK Agonist Development*

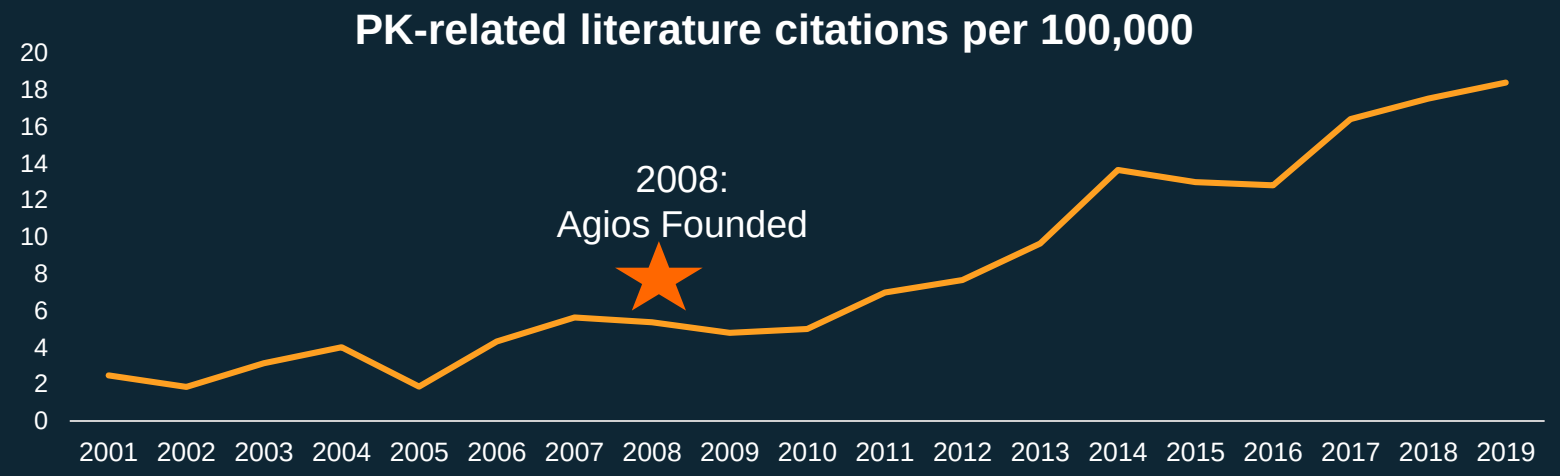
- **Hemolytic Anemia**
- **CKD Anemia**
- **Rare musculoskeletal cardiac diseases**
- **Metabolic**
- **Neurologic**
- **Retinal**
- **Cancer-related**

Pyruvate Kinase Deficiency
α and β-Thalassemia
Sickle Cell Disease

Clinical POC Established

Hereditary Spherocytosis
(Elliptocytosis, rare Pyropoikilocytosis)
Low-risk MDS-associated Anemia
Diamond Blackfan Anemia
Enzyme/membranopathy (Xerocytosis, G6PDH, etc.)
Other hereditary hemolytic anemias

Potential Near-term Expansion Indications



*Indications supported by literature.

PKR Clinical Development

Dr. Chris Bowden, Chief Medical Officer

Mitapivat Has the Potential to Transform the Course of Hemolytic Anemia By Increasing RBC Energy, Health and Longevity

PK Deficiency

- First potential agent to improve hemolytic anemia associated with PK deficiency
- May reduce transfusion burden and the need for other supportive therapy. May improve QoL by reducing the severe chronic fatigue associated with PK deficiency

Thalassemia

- First potential agent to improve hemolytic anemia and ineffective erythropoiesis
- May reduce transfusion burden and the need for other supportive therapy. May improve QoL by reducing transfusions and severe chronic fatigue associated with thalassemia

Sickle Cell Disease

- First potential agent to improve hemolytic anemia and reduce VOCs
- May improve QoL by increasing “native” Hb (allows for the release of oxygen on demand) resulting in reduced pain and fatigue associated with SCD

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

Adverse events reported for mitapivat were consistent across clinical trials with the convenience of oral delivery

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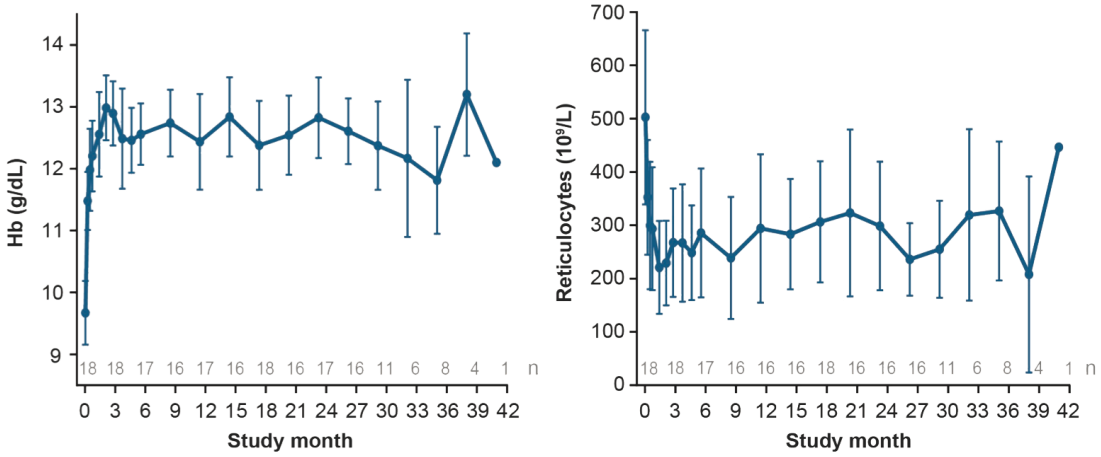
Pyruvate Kinase Deficiency

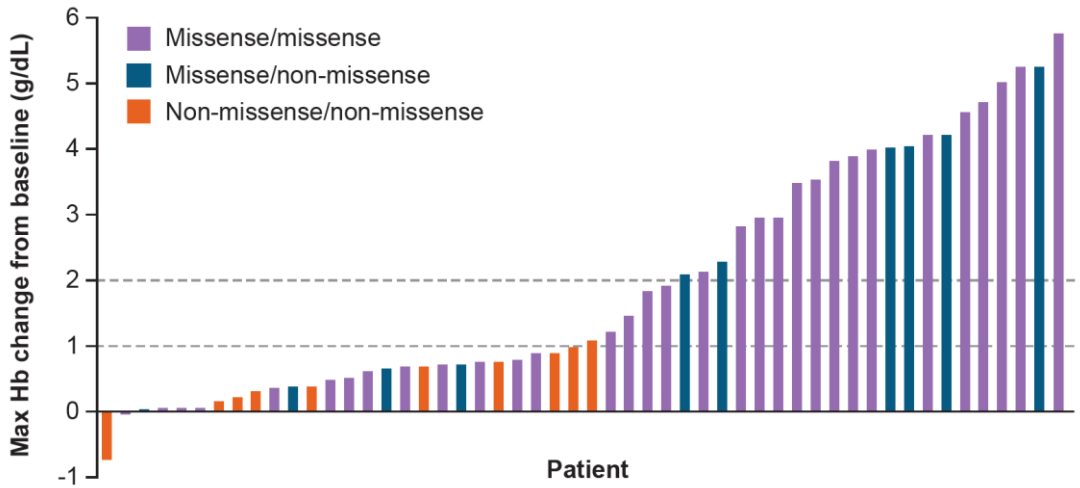
Mitapivat Has Demonstrated Long-term Durable Responses in the DRIVE PK Study

Improvements in hemoglobin and other hemolysis markers maintained for more than 3 years in responding patients from DRIVE PK extension (n=18)



Chronic daily dosing with mitapivat for a median of 3 years and up to 42 months was well tolerated

25 of 42 (59.5%) patients who had ≥1 missense mutation had an Hb increase >1.0 g/dL



Maximum Hb increases observed by genotype

The NEW ENGLAND JOURNAL of MEDICINE

Improvements in hemoglobin and other hemolysis markers were also sustained at optimized individual doses during the extension period

Most AEs were low-grade and resolved within 7 days of initiation of treatment

Source: Data presented at ASH 2019; van Beers EJ, et al. *Haematologica*. 2019;104(2):e51-e53.

Pivotal Program in PK Deficiency Designed to Support a Broad Label

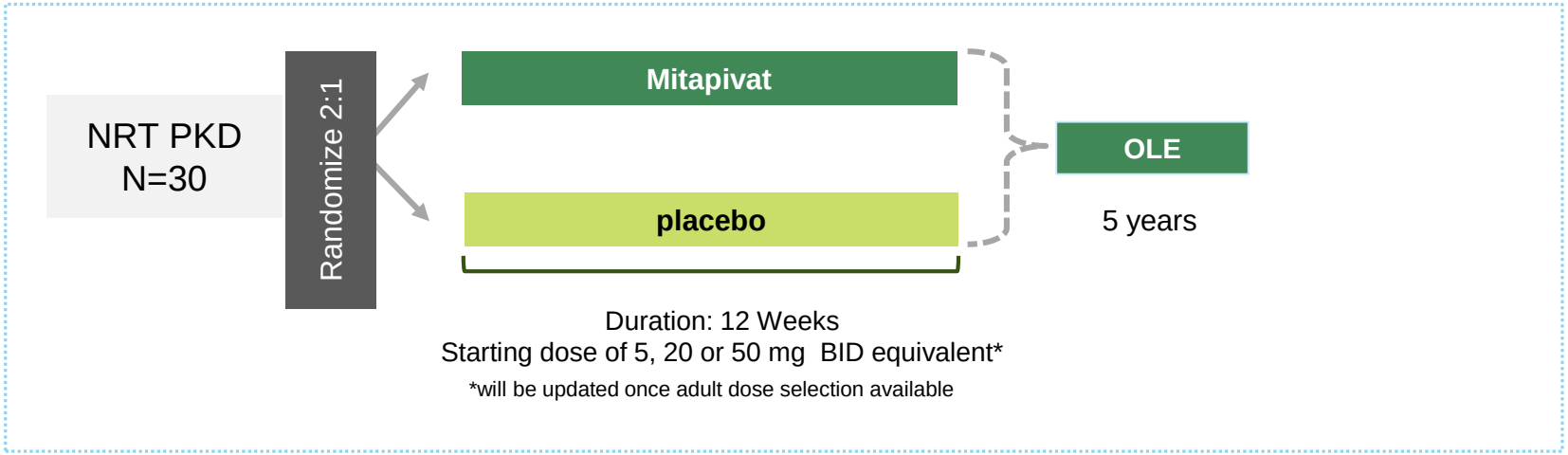
ACTIVATE

- A 1:1 randomized, placebo-controlled trial of 80 patients who do not receive regular transfusions
- **Primary Efficacy Endpoint**: Proportion of patients who achieve at least a 1.5 g/dL increase in hemoglobin sustained over multiple visits
- Topline data expected by YE 2020

ACTIVATE-T

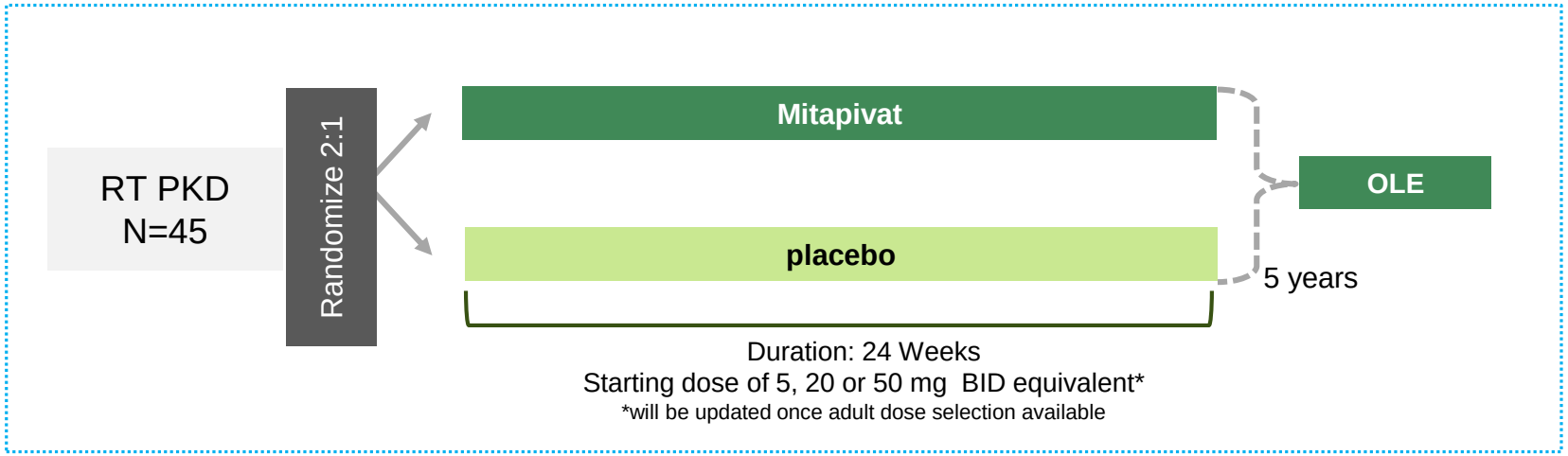
- A single-arm open-label trial of 27 regularly transfused patients who received a minimum of 6 transfusions over the year preceding enrollment
- **Primary Efficacy Endpoint**: Reduction in transfusion burden of ≥33% over a 6-month period compared to the patient's transfusion history
- Topline data expected in Q1 2021

Pediatric PK Deficiency Study Planning Underway



Eligibility:

- Mean Hb concentration of ≤10 g/dL for patients 12 to <18 years or ≤9 g/dL for patients 6 months to <12 years
- Not regularly transfused, with no more than 5 transfusions in the 12-months prior and no transfusions in the 12 weeks prior to the first day of study treatment



Eligibility:

- Children >1 year old
- A minimum of 6 transfusion episodes in the 12-month period prior to date of informed consent

Thalassemia

Study Design: Open-label, Phase 2, Multicenter Trial of Mitapivat in Thalassemia

KEY INCLUSION CRITERIA

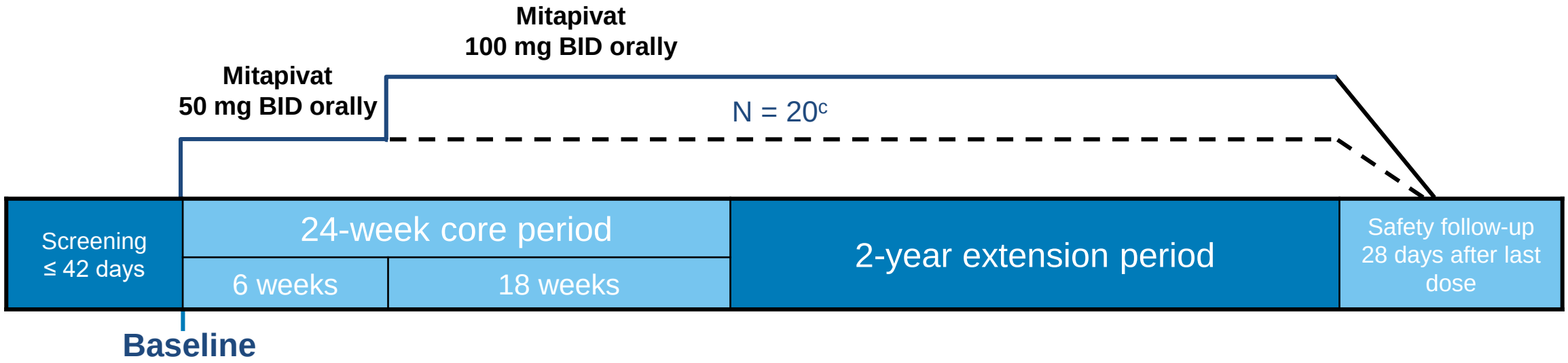
- β-thalassemia ± α-globin gene mutations, HbE β-thalassemia, or α-thalassemia (HbH disease)
- Hb ≤10.0 g/dL
- Non–transfusion-dependent[a]

PRIMARY ENDPOINT

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

SECONDARY/EXPLORATORY ENDPOINTS

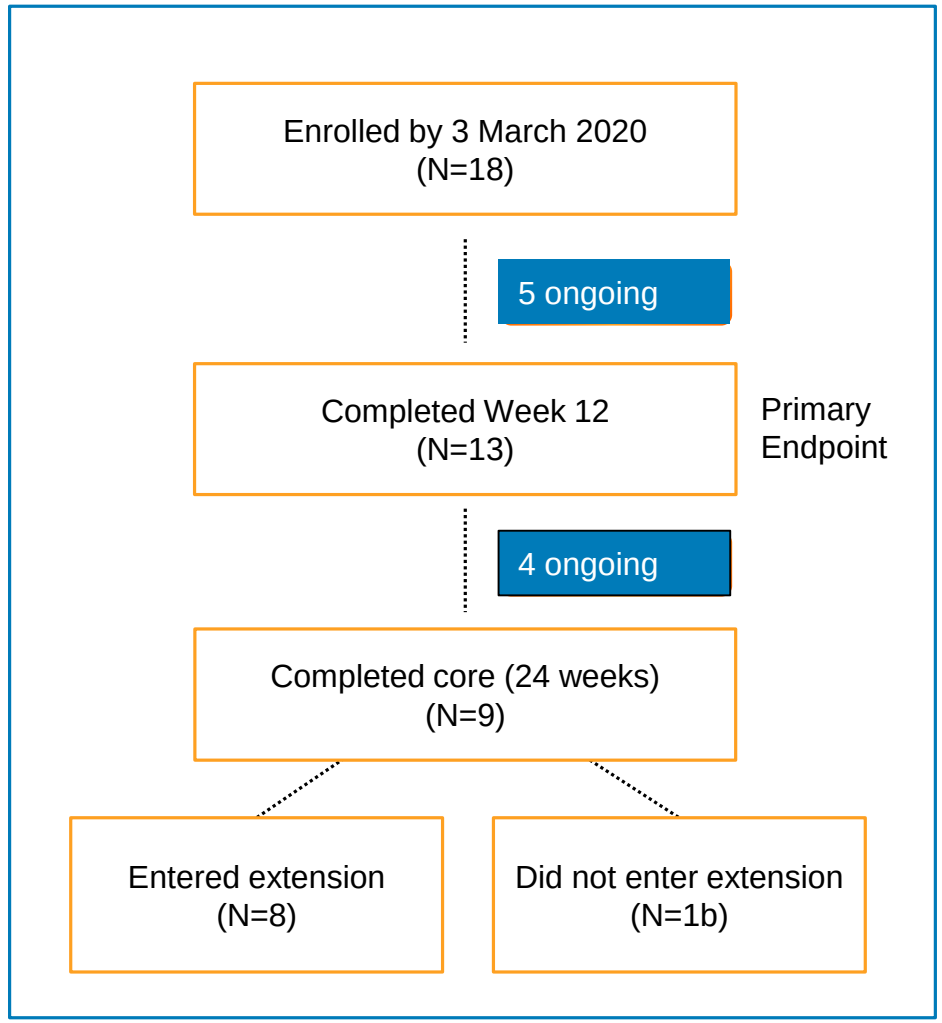
- Sustained Hb response; delayed Hb response; markers of hemolysis; hematopoietic activity; safety



[a]≤ 5 RBC units transfused in the preceding 24 weeks and none in the 8 weeks prior to study drug. [b]With the originally planned sample size of 17 patients enrolled, the study would have 80% power to reject a ≤ 30% response rate at a one-sided 0.05 type 1 error rate. [c]Fully enrolled. BID = twice daily.

Demographics and Disposition

Baseline characteristics	Total (N=18)
Median (range) duration of treatment, weeks	20.6 (1.1–50.0)
Male/female, n	5/13
Age at informed consent, median (range), years	43.5 (29–67)
Race, n (%) Asian White Native Hawaiian or other Pacific Islander Other[a]	9 (50.0) 4 (22.2) 1 (5.6) 4 (22.2)
Thalassemia type, n (%) α β	5 (27.8) 13 (72.2)
Hb baseline, median (range), g/dL	8.43 (5.6–9.8)
Indirect bilirubin, median (range), mg/dL	1.17 (0.31–5.52)
Lactate dehydrogenase, median (range), U/L	249 (126–513)
Erythropoietin, median (range), mU/mL	70.5 (15–11,191)



Hydroxyurea, splenectomy, and prior transfusions were reported in two patients each at baseline.
[a]Includes patients who reported more than one category, and one not reported. [b]Investigator decision.
Data from Kuo et al EHA 2020

Interim Phase 2 Results: Primary Endpoint Met in 92.3% of Patients

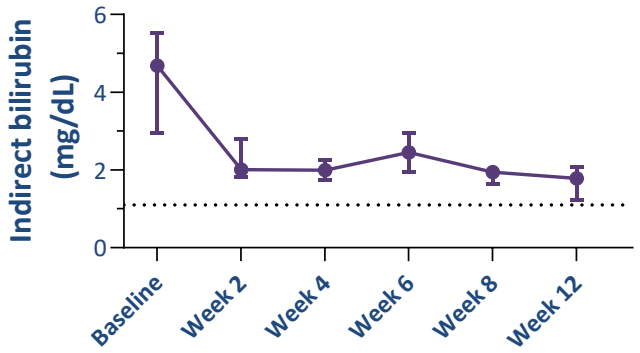
Endpoint	Genotype	N/N	%	90% CI
Hb responders during Weeks 4–12 among those who completed 12 weeks	All	12/13	92.3	68.4, 99.6
	α	4/4	100	47.3, 100
	β	8/9	88.9	57.1, 99.4
Hb responders during Weeks 12–24 among those who completed 24 weeks	β[a]	8/9	88.9	57.1, 99.4
Sustained responders: primary response and ≥2 Hb responses during Weeks 12–24	β[a]	7/8	87.5	52.9, 99.4

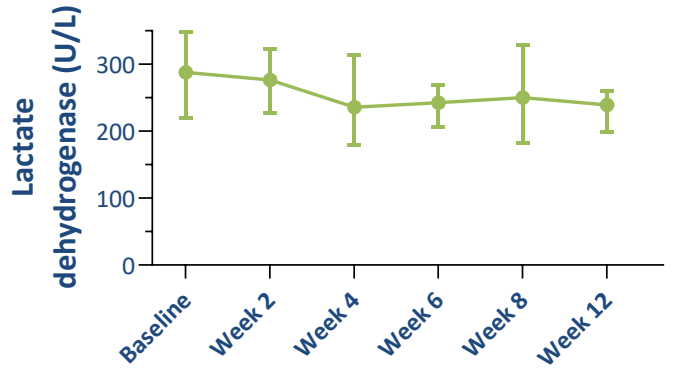
Patient population	N	Weeks	Mean (SD) change from baseline Hb, g/dL
All patients	13	4–12	1.34 (0.7)
α-thalassemia	4	4–12	1.17 (0.4)
β-thalassemia	9	4–24	1.43 (0.8)
β-thalassemia responders	8	4-24	1.63 (0.5)
All responders	12	4-12	1.47 (0.5)

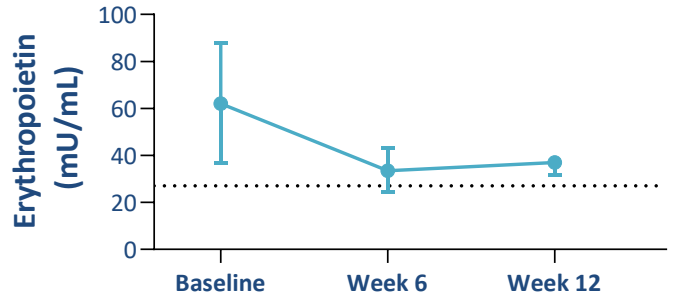
Hb responder is defined as a ≥ 1.0 g/dL Hb increase from baseline at least once; Only patients with β-thalassemia had completed 24 weeks of treatment at the time of datacut
Data from Kuo et al EHA 2020

Interim Phase 2 Results: Improvement Shown in All Key Markers Consistent With Changes Seen With Hb

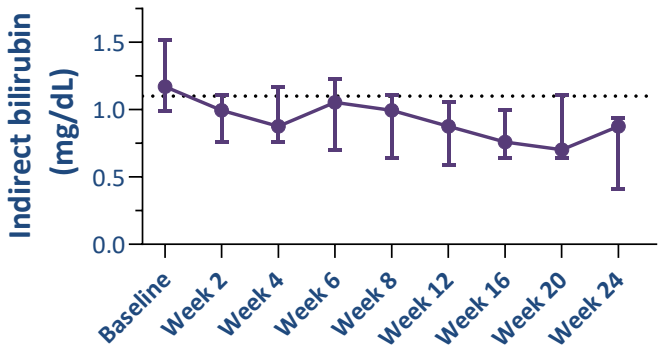
α-thalassemia (N = 4)

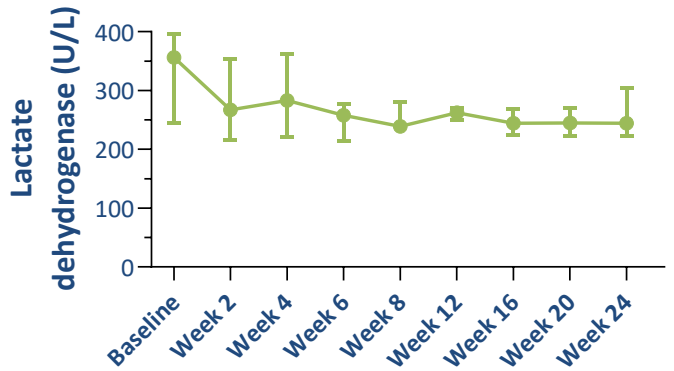


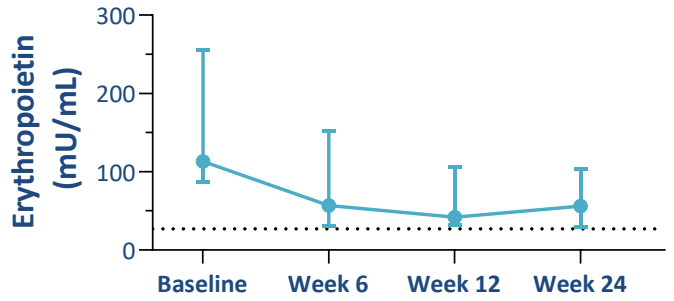




β-thalassemia (N = 9)







All graphs show median (IQR)

Dashed lines indicate upper limit of normal range. For α-thalassemia: N = 4 for lactate dehydrogenase and erythropoietin, for indirect bilirubin N = 3 at baseline, weeks 2, 8 and 12, and N = 2 at weeks 4 and 6; for β-thalassemia: N = 9 for erythropoietin, for lactate dehydrogenase N = 9 at baseline, Weeks 6, 8, 12, and 20 and N = 8 at Weeks 2, 4, 16, and 24, for indirect bilirubin N = 9 at baseline and N = 7 at the remaining times. IQR = interquartile range (25^{th}–75^{th} centiles).
Data from Kuo et al EHA 2020

Interim Phase 2 Safety Summary[a]: No SAEs or AEs Leading to Treatment Discontinuation; Dose Escalation to 100 mg BID Well-tolerated

	Total (N = 18)
Patients with any AE, n (%)	13 (72.2)
Patients with any related AE, n (%)	11 (61.1)
Patients with AEs by maximum severity, n (%)	
Grade 1	4 (22.2)
Grade 2	7 (38.9)
Grade 3[b]	2 (11.1)

- No serious adverse events (AEs) or AEs leading to treatment discontinuation as of the data cut
- Dose escalation to 100 mg BID was well-tolerated and not associated with an increase in AEs
- Reported in one patient each:
  - AE leading to treatment interruption (grade 3, postural vertigo, not related)
  - AE leading to treatment modification (grade 2, bloating and heartburn, related)
- Post data cut, 1 serious AE of renal dysfunction was reported, which resolved upon treatment discontinuation

AEs coded using MedDRA, version 22.0.
[a]As of datacut of 3 March 2020.
[b]Neither were judged related.
Data from Kuo et al EHA 2020

Phase 2 Data Supportive of Advancing Mitapivat to Pivotal Development in Thalassemia

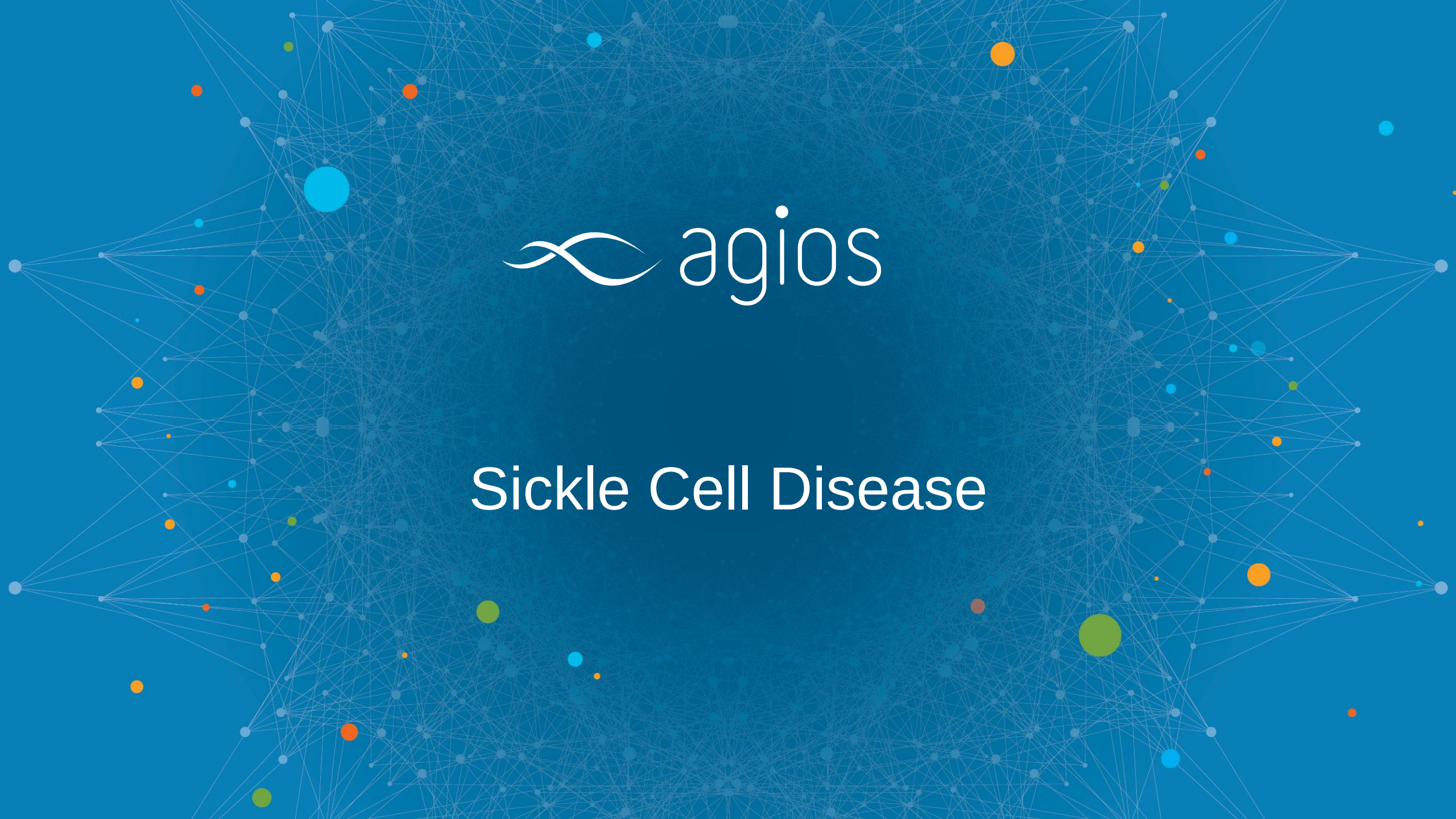
- The first clinical study evaluating PKR activation as a therapeutic option in α- and β-thalassemia, and the first drug trial aimed at treating α-thalassemia

Proof of concept demonstrated

- >90% of patients met primary endpoint: clinically significant Hb increase
- All four α-thalassemia patients and 8 of 9 β-thalassemia patients were responders
- Sustained Hb response observed over time in patients with longer follow-up
- Improvements in markers of hemolysis and erythropoiesis were consistent with mitapivat's mechanism of action

- Mitapivat was generally well-tolerated. Safety profile was consistent with previous studies in PK deficiency

- Data support broad pivotal development plan spanning TD and NTD thalassemia as well as β- and α-thalassemia
  - Pivotal plan to be finalized by YE and initiated in 2021



Sickle Cell Disease

NHLBI & Agios CRADA Study of Mitapivat in SCD: Study Design

Primary

Safety and tolerability

- Frequency and severity of adverse events
- Changes in laboratory parameters (including reticulocyte counts and levels of hemoglobin, bilirubin, and lactate dehydrogenase)

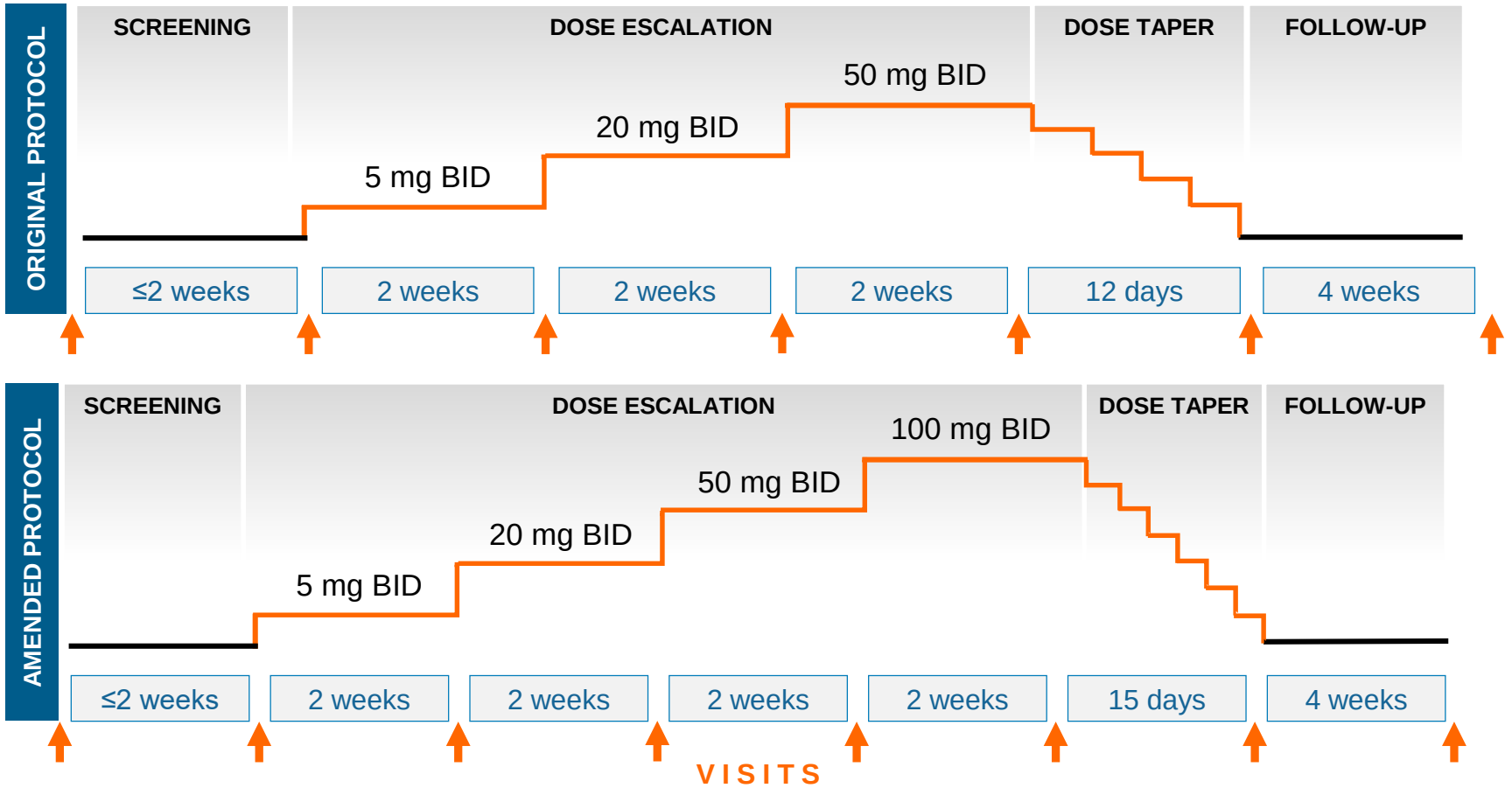
Secondary

Pharmacokinetics/pharmacodynamics

- Pharmacokinetics of mitapivat
- Levels of 2,3-DPG, PK-R, and ATP, and oxygen dissociation sickling in RBCs
- Relationship between mitapivat pharmacokinetics and safety

Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of Escalating Multiple Oral Doses of Mitapivat in Subjects With Stable SCD

ClinicalTrials.gov NCT04000165: Nonrandomized, open-label, Phase 1 study; N ≈ 15–25



CRADA, Cooperative Research and Development Agreement; NHLBI; National Heart, Lung, and Blood Institute; SCD, sickle cell disease; BID, twice daily.

Clinical Proof of Concept for Mitapivat Established in Sickle Cell Disease

7 of 8 (88%) efficacy evaluable patients experienced a Hb increase, and 5 of 8 (63%) patients achieved a Hb increase of ≥1.0 g/dL from baseline (range 1.0-2.7 g/dL) at doses of 50 mg BID or lower.

Treatment with mitapivat was associated with decreases in hemolytic markers, such as bilirubin, LDH, and reticulocytes.

2,3-DPG decreases and increases in ATP levels were observed. Sickling curves (t50) and oxygen dissociation curves (p50) consistent with decreases in both sickling and HbS polymerization.

AEs generally consistent with previously reported data with mitapivat treatment or are to be expected in the context of SCD. One SAE, a VOC, occurred during drug taper and was possibly attributed to mitapivat.

ASH Abstract Provides Additional Insight Into Proof-of-Concept Data

	Pharmacodynamic and Sickling Measures				Clinical Laboratory Measures				
	2,3-DPG (µM/mL packed RBCs)	**ATP** (µM/mL packed RBCs)	**p50** (torr)	**t50** (minutes)	**Hb** (g/dL)	**ARC** (K/µL)	**Bilirubin** (mg/dL)	**LDH** (U/L)	**MCV** (fL)
Mean **baseline** value (SD)	6515.3 (621.8)	1490.1 (168.8)	31.8 (3.0)	250.4 (91.8)	9.2 (1.0)	175.6 (92.8)	2.2 (0.8)	374.9 (141.6)	102.5 (11.7)
Mean change on **5 mg BID** (SD)	-10% (8%)	6% (11%)	-1% (7%)	8% (24%)	0.1 (0.6)	-40.5 (41.8)	-0.1 (0.5)	-24.5 (67.0)	-0.7 (2.4)
Mean change on **20 mg BID** (SD)	-22% (9%)	24% (16%)	-7% (9%)	29% (51%)	0.6 (0.9)	-25.1 (65.9)	-0.8 (0.5)	-60.6 (84.9)	0.7 (4.4)
Mean change on **50 mg BID** (SD)	-32% (9%)	27% (11%)	-7% (12%)	17% (30%)	1.2 (1.0)	-57.5 (31.0)	-1.0 (0.6)	-77.5 (88.1)	1.6 (5.2)
Mean change on **100 mg BID** (SD)*	-40% (11%)	29% (16%)	- (-)	-3% (0%)	0.9 (0)	-70.1 (80.8)	-1.1 (0.9)	-96.0 (166.9)	3.8 (0.8)
Mean change after **taper** (SD)	-3% (13%)	12% (18%)	7% (5%)	-1% (28%)	0.3 (1.1)	-21.6 (60.0)	-0.5 (0.7)	-16.0 (128.3)	0.9 (5.7)
Mean change after **4 weeks** (SD)†	2% (15%)	7% (15%)	10% (9%)	2% (40%)	0.2 (0.7)	6.0 (86.2)	-0.3 (0.5)	-2.0 (80.8)	1.2 (4.4)

Table 1. Biochemical, sickling, and clinical laboratory measures at baseline (prior to start of study drug), at steady state (after 14 days of treatment) on each dose level, after taper (1+3 days after the last dose of mitapivat), and 4 weeks (+3 days) after discontinuation of mitapivat for the 8 subjects who completed the study. The change in each measure was calculated from the baseline measurement immediately prior to start of study drug. The mean change was reported as percent change for PD and sickling measures and as absolute change for the clinical laboratory measures. SD = standard deviation; BID = twice daily; 2,3-DPG = 2,3-diphosphoglycerate; ATP = adenosine triphosphate; p50 = partial pressure of oxygen at which 50% of the hemes in the hemoglobin (Hb) molecule have oxygen bound; t50 = time at which 50% of erythrocytes are sickled in response to gradual deoxygenation of erythrocytes with nitrogen to a final oxygen partial pressure of 38 torr; Hb = hemoglobin; ARC = absolute reticulocyte count; Bilirubin = total serum bilirubin; LDH = lactate dehydrogenase; MCV = mean corpuscular volume.
* As only the last 2 subjects completed the 100 mg BID dose level, all reported mean changes at the 100 mg BID time point reflect a sample size of 2, except for p50 (no data) and t50 (n=1) due to disruptions related to the COVID-19 pandemic. The mean changes reported for the 5, 20, and 50 mg BID dose levels include all 8 subjects, with occasional missing data (overall mean sample size was 7.5, with a SD of 1.1 and a range of 4-8 measurements).
† One subject received a blood transfusion for fatigue after the end of drug taper, which may have affected measures reported for mean change after 4 weeks. No other subjects received transfusions during the study period.

Data source: ASH 2020 abstract

Preliminary Phase 1 Data Supportive of Advancing Mitapivat to Pivotal Development in Sickle Cell Disease

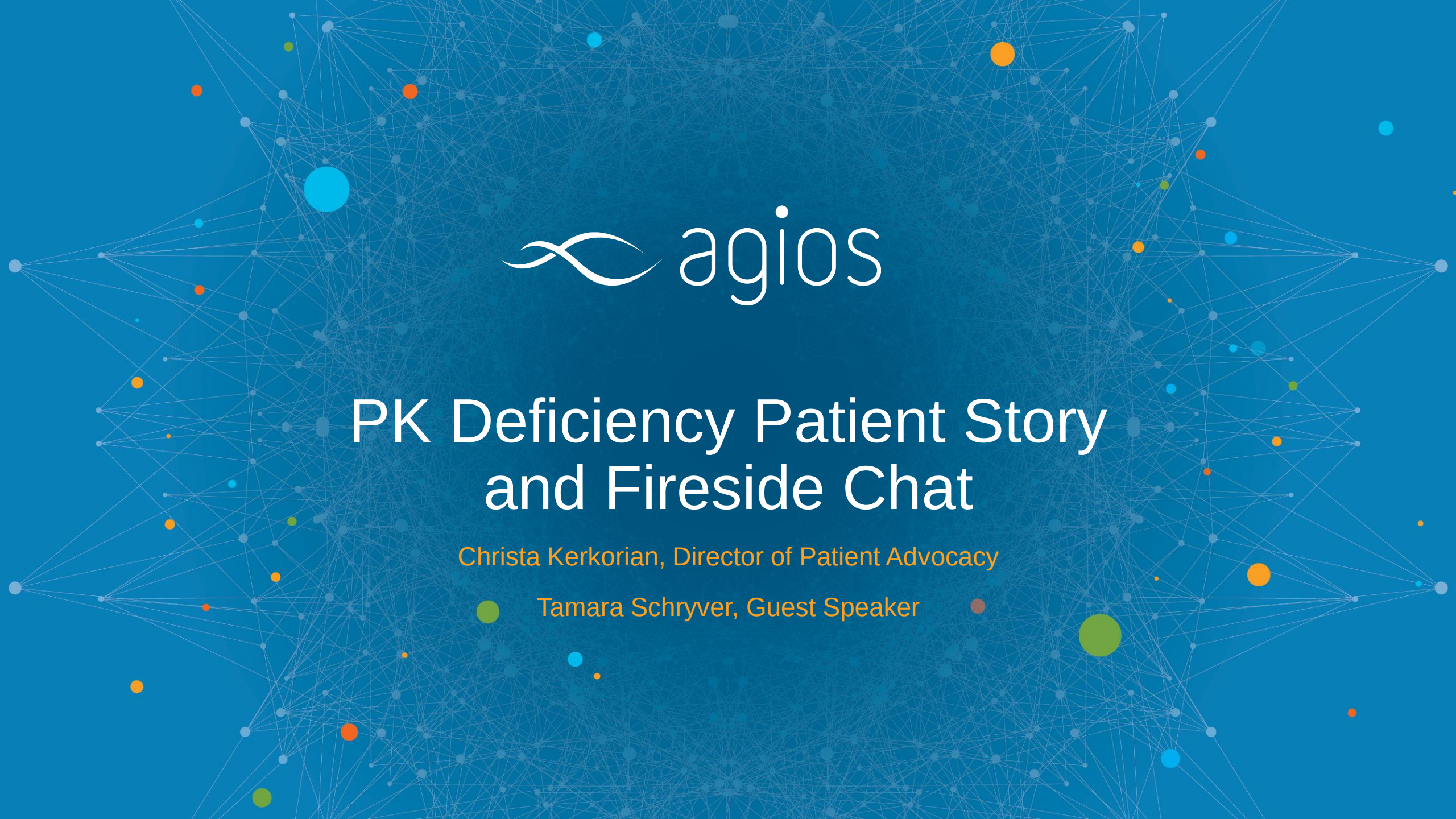
- Mitapivat demonstrated an acceptable safety profile across the tested dose levels in 8 subjects with SCD; updated data on 11 patients to be presented in oral presentation at ASH

Proof of concept demonstrated

- Analyses of data show promising evidence of efficacy in terms of Hb increase from baseline with concomitant decreases in hemolytic markers
- The accompanying changes in metabolites and sickling studies are consistent with the proposed mechanism of mitapivat

- The study is ongoing with a planned sample size of 15-25 subjects completing 6-8 weeks of treatment

- Data support pivotal development plan, which will be finalized in the first half of 2021 and initiated that year



PK Deficiency Patient Story and Fireside Chat

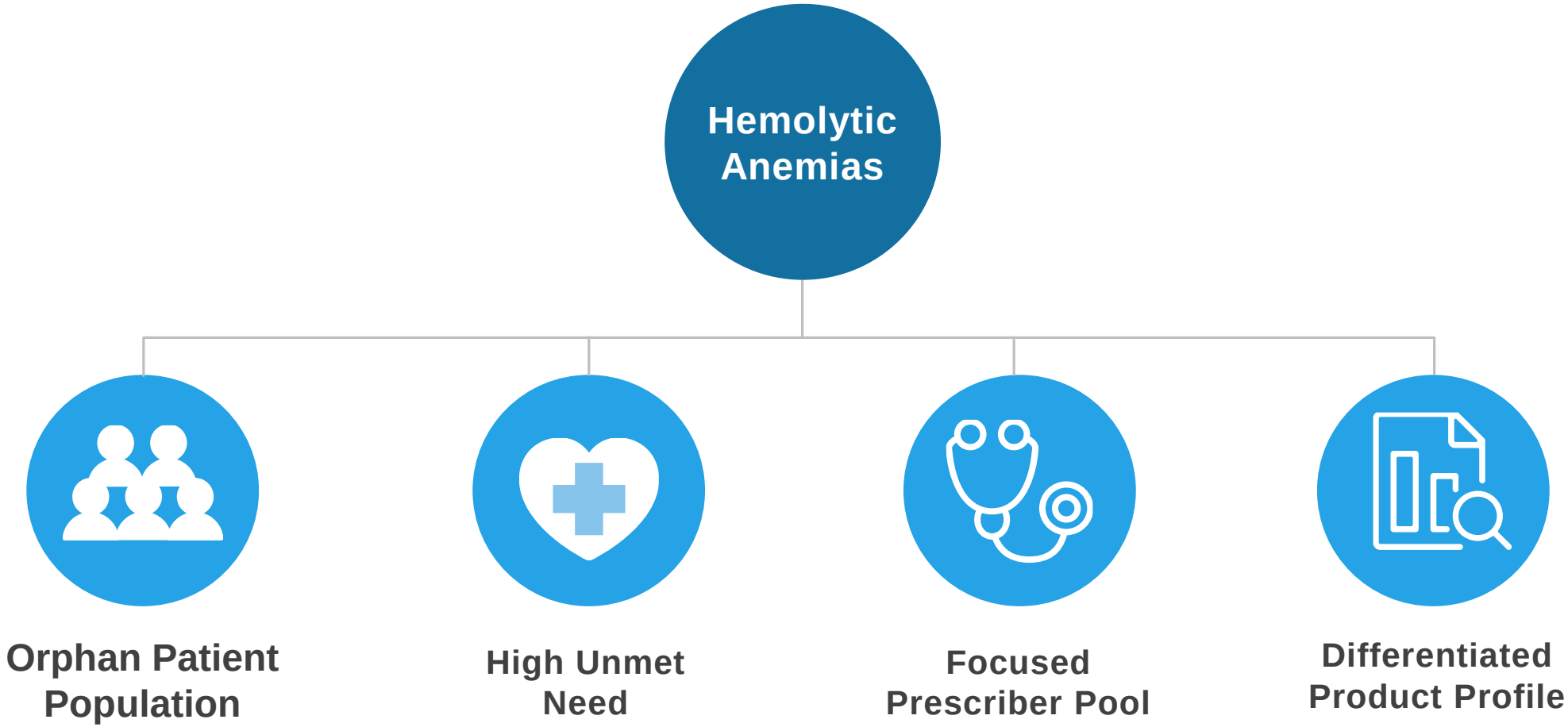
Christa Kerkorian, Director of Patient Advocacy

Tamara Schryver, Guest Speaker

Partnering With the Hemolytic Anemia Community to Transform Care

Darrin Miles, SVP, U.S. Commercial and Global Marketing

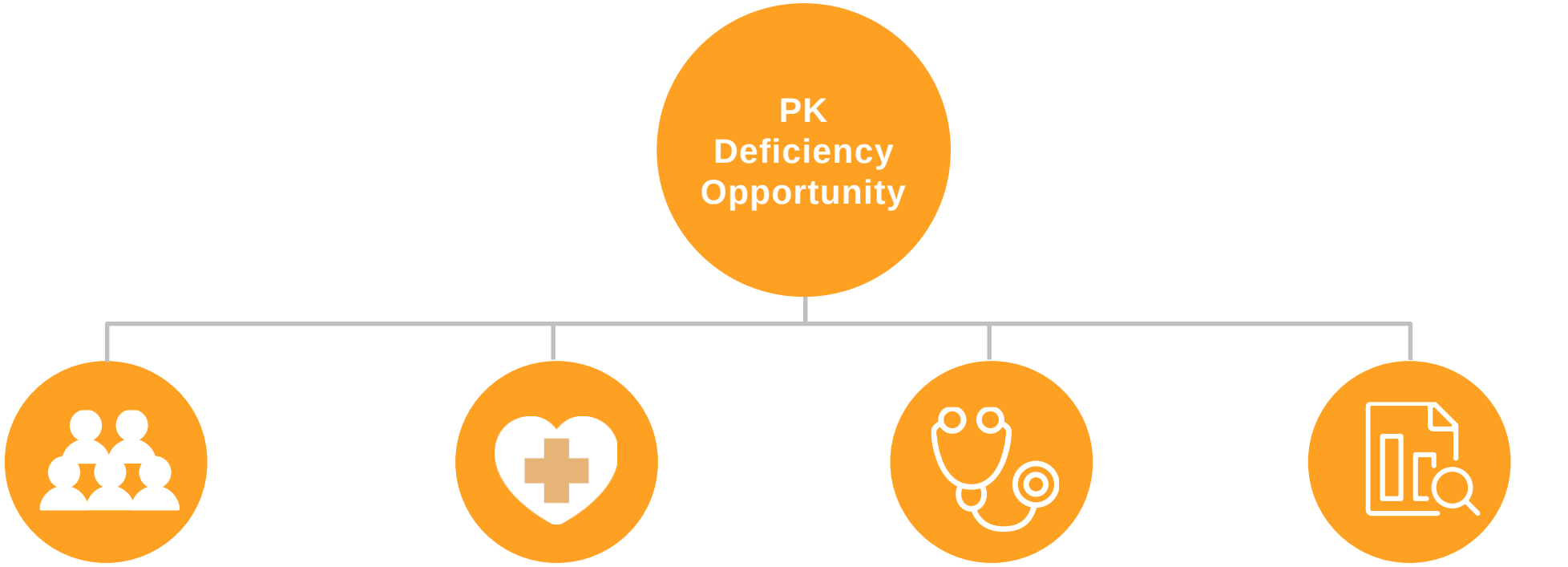
Mitapivat Has the Potential to Transform Care Across PK Deficiency, Thalassemia and Sickle Cell Disease



agios

PK Deficiency:
The Foundation of Our Commitment

In PK Deficiency, Mitapivat Has the Potential to Transform the Course of Disease by Improving RBC Energy, Health and Longevity



Orphan Patient Population

Estimated 3-8K patients across the U.S. & 5EU

High Unmet Need

Poorly diagnosed and misunderstood, with suboptimal treatments

Focused Prescriber Pool

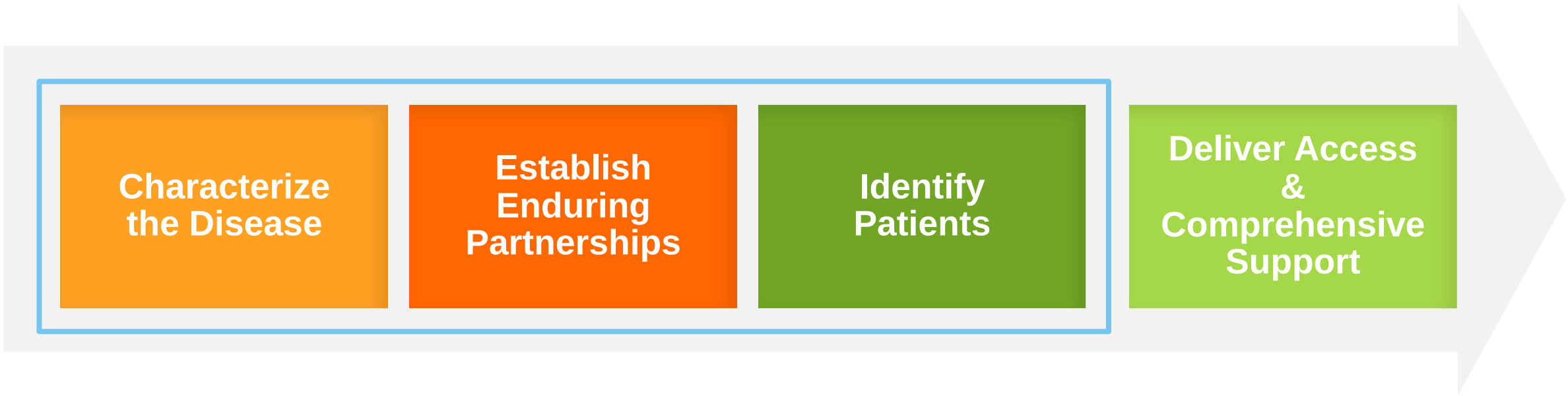
Hematologists

Differentiated Product Profile

Potentially addresses chronic hemolysis

Agios market research

Building the Foundation for Mitapivat in PK Deficiency



Agios Supports the Characterization of This Historically Misunderstood and Mismanaged Disease

PK Deficiency Natural History Study

Boston Children's Hospital
Until every child is well™

agios

Observational patient registry assessing the range and incidence of symptoms, treatments, and complications related to PK deficiency.

255 Participants

2013-2019

The Peak Registry

A Global Longitudinal Study of PK Deficiency

Integrates and extends the Natural History Study with additional patients and longer follow-up from an expanded geographical distribution to further understand:

- Natural history
- Disease burden
- Patient/caregiver-reported outcomes
- Current treatment and outcomes

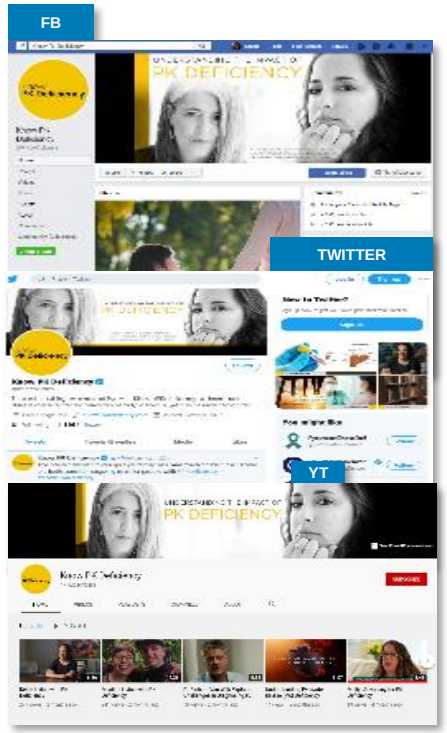
Up to 500 Participants

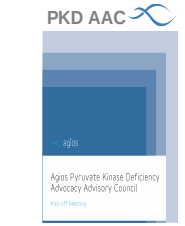
2018-2027

Agios is a Trusted Partner in Hemolytic Anemia

Partnering with physicians and advancing science

Connecting with patients and advancing advocacy



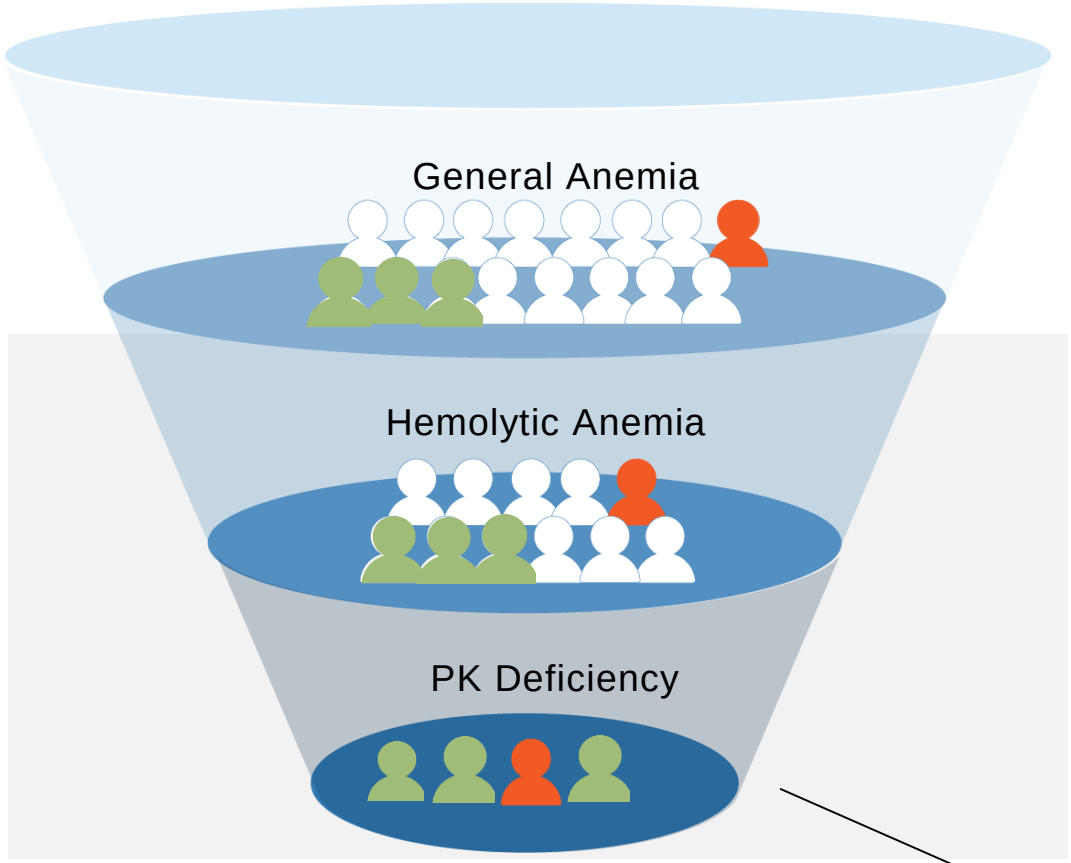


Patient-Focused Drug Development meeting with FDA

"On education and diagnosis, Agios owns PK deficiency." - US KOL

Agios is Building on Relationships to Educate the Community on Improving PK Deficiency Patient Diagnosis

Diagnosis for PK Deficiency Patients



Incompletely Diagnosed Patients

Patients Diagnosed With PK Deficiency

Patients Undiagnosed With PK Deficiency

ID physicians with patients previously diagnosed with PK deficiency

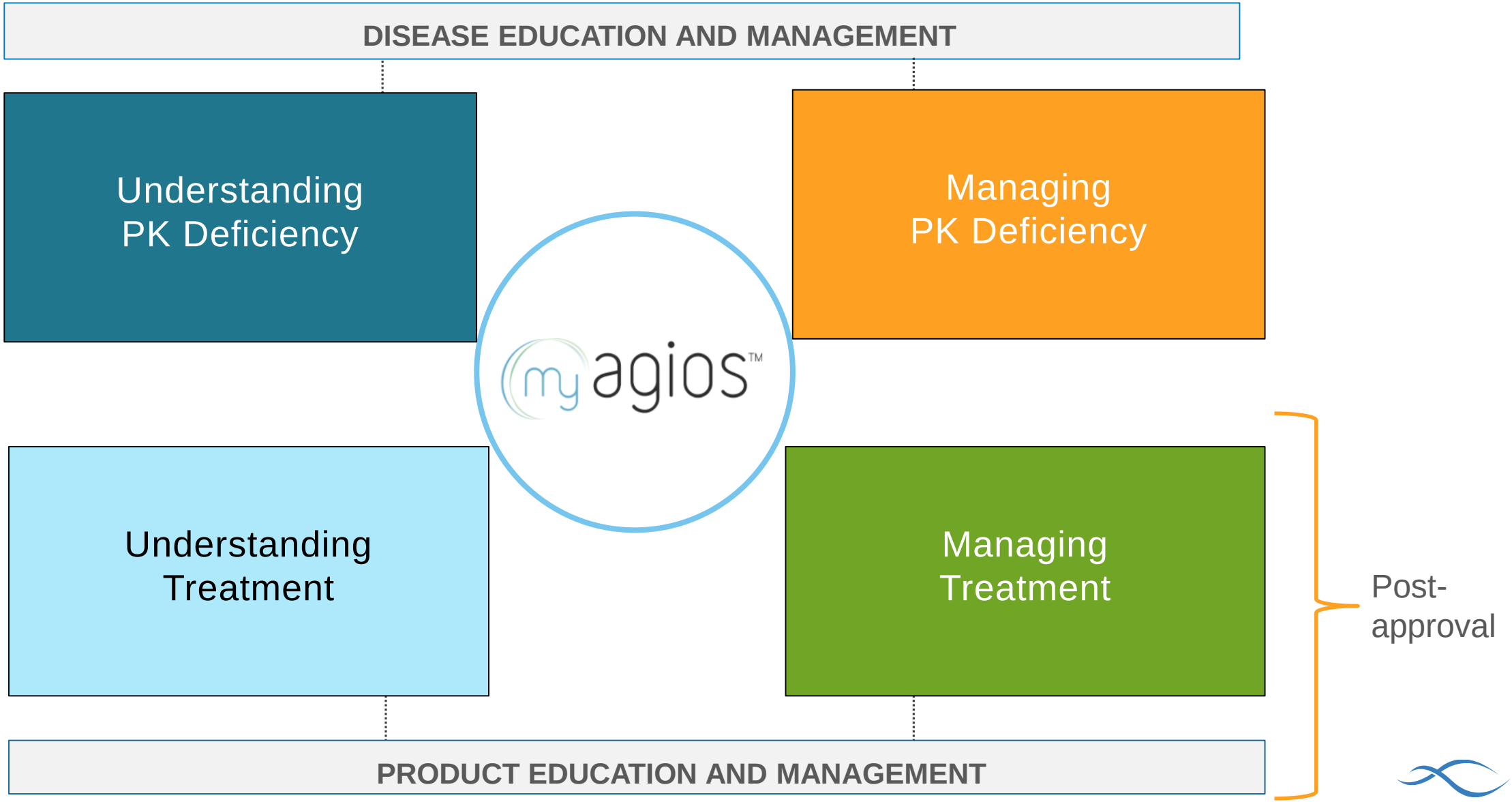
Convey importance of diagnosing and managing the disease → and support testing

ID new patients with PK deficiency

Spanish NGS Screening Initiative: ***Early results 25% of patients with inherited HAs had PK Deficiency***

Haematologica Vol. 105 Oct. 2020

Going Beyond the Drug: Comprehensive Support Will Improve Patient Management



Mitapivat May be Well Positioned and a Highly Differentiated Treatment Option for PK Deficiency

TARGET PROFILE

MITAPIVAT

Chronic Therapy

Oral

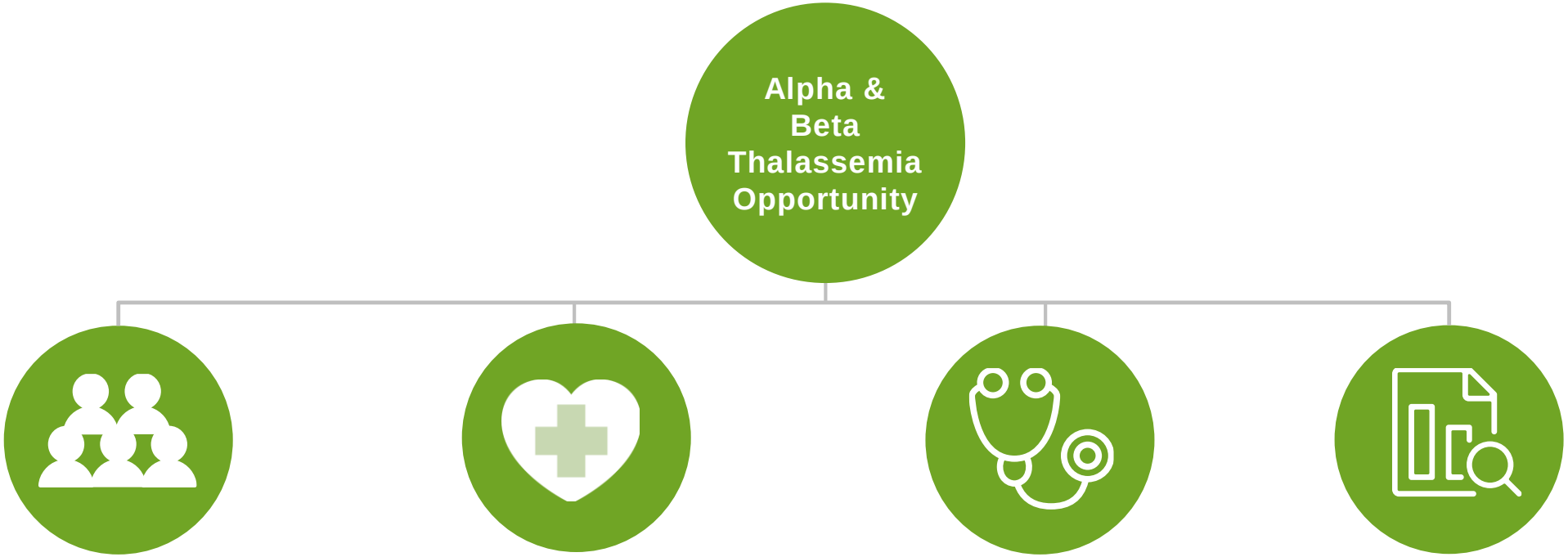
Broad eligible patient population

Insomnia, Headache

"If a patient is eligible to trial a PK activator, strong consideration should be made for trialing this first and considering gene therapy in those who fail to respond or tolerate this treatment." –Grace et al *Blood.* 2020.

Thalassemia & Sickle Cell Disease: Building on Our Foundation

In Thalassemia, Mitapivat Has the Potential to be the Only Treatment to Improve Hemolytic Anemia and Ineffective Erythropoiesis



Orphan Patient Population

Estimated 18–23K patients across the U.S. & 5EU

High Unmet Need

High degree of comorbidities with burdensome treatments

Focused Prescriber Pool

Hematologists

Differentiated Product Profile

Potentially addresses chronic hemolysis and ineffective erythropoiesis

Agios market research

We Have the Potential to Offer a Differentiated, Less Burdensome Solution for Patients with Thalassemias

TARGET PROFILE

MITAPIVAT

Chronic therapy

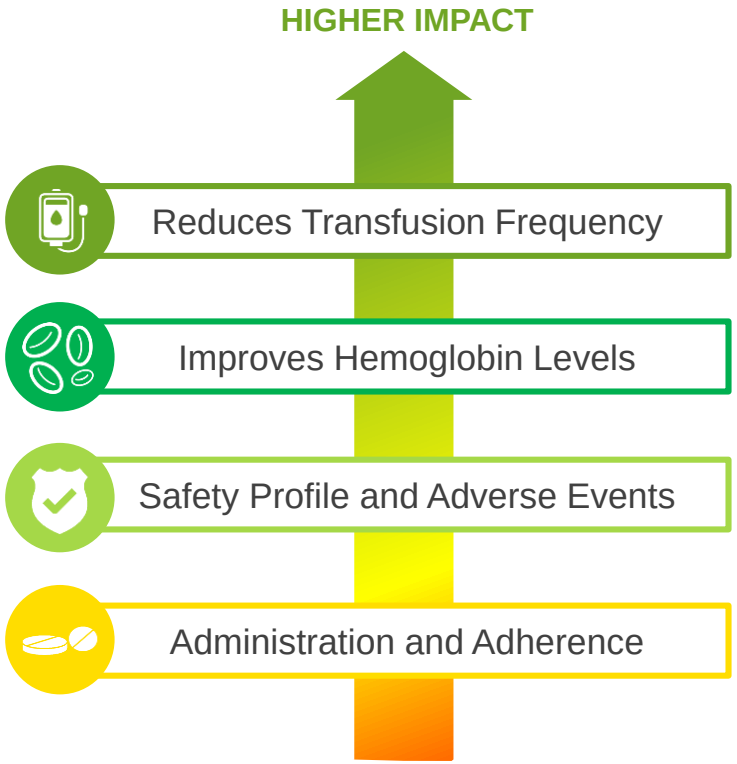
Oral

Improved Hb and reduced transfusion

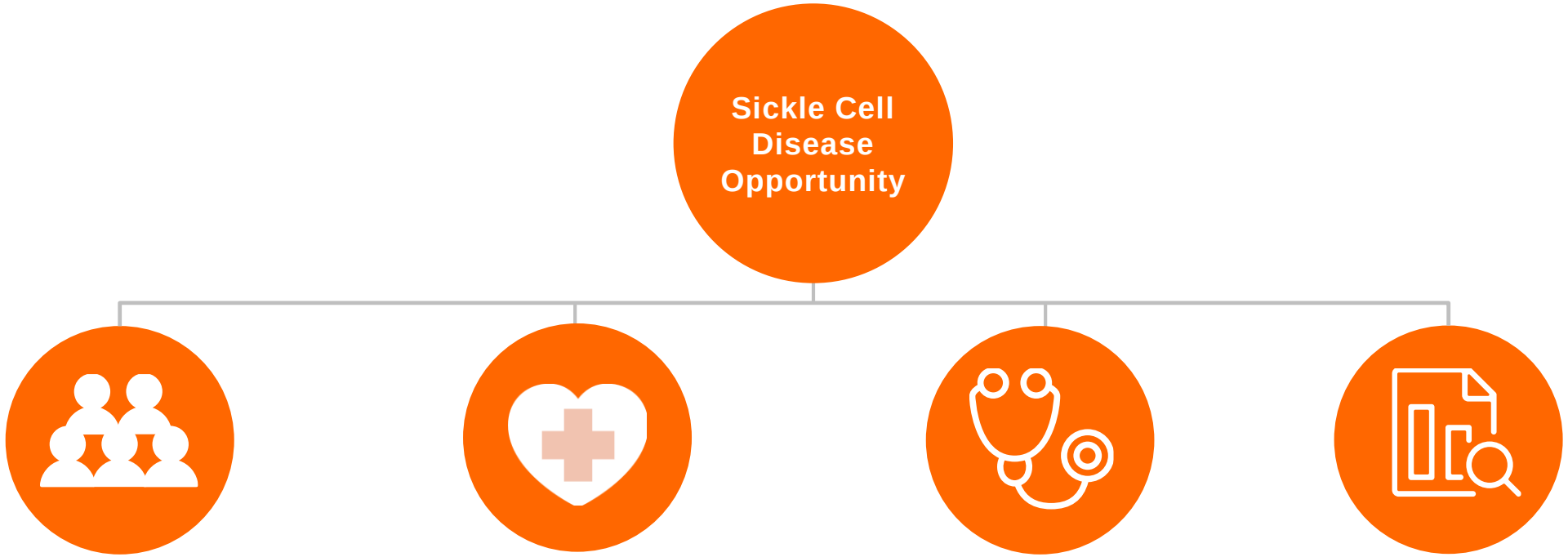
Improved hemolytic anemia and ineffective erythropoiesis

Insomnia, headache

HCP Rating of Product Attributes



In Sickle Cell Disease, Mitapivat has the Potential to be the First Treatment to Improve Hemolytic Anemia and Vaso-Occlusive Crisis



Mitapivat Is Well Positioned to Potentially Offer a Holistic Solution for the Treatment of SCD with the Convenience of an Oral Therapy

TARGET PROFILE

MITAPIVAT

Chronic Therapy

Oral

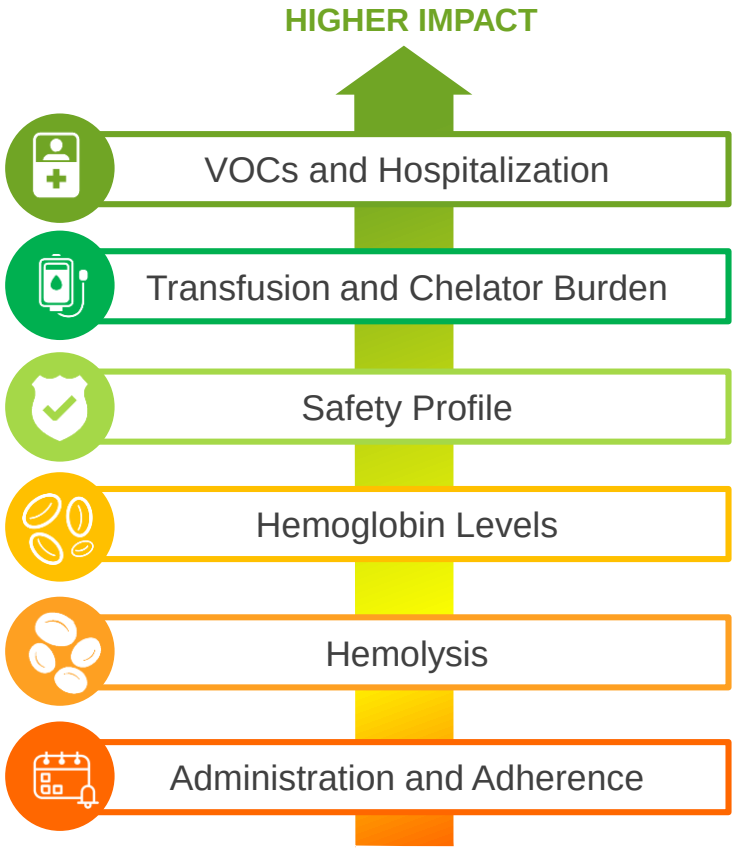
Improved hemolytic anemia

VOC improvement

QoL data

Insomnia, headache

HCP Rating of Product Attributes



Our PK Deficiency Partnerships Will Be Synergistic with Thalassemia and SCD …and We Are Investing in New Relationships with SCD-Specific Groups

Continued partnerships

Expanded engagement

Investing in new relationships

Our Initial Focus is U.S. & EU…But Rest of World Could Double the Market Opportunity

~18-23K PATIENTS IN U.S. & 5EU

α-and β-Thalassemia

~3-8K PATIENTS IN U.S. & 5EU

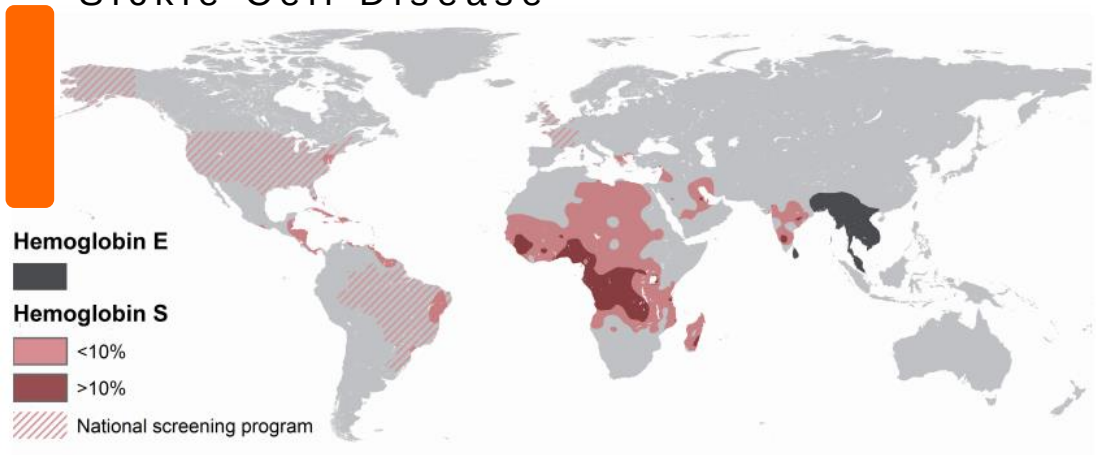
Pyruvate Kinase Deficiency

~120-135K PATIENTS IN U.S. & 5EU

Sickle Cell Disease

Thalassemia

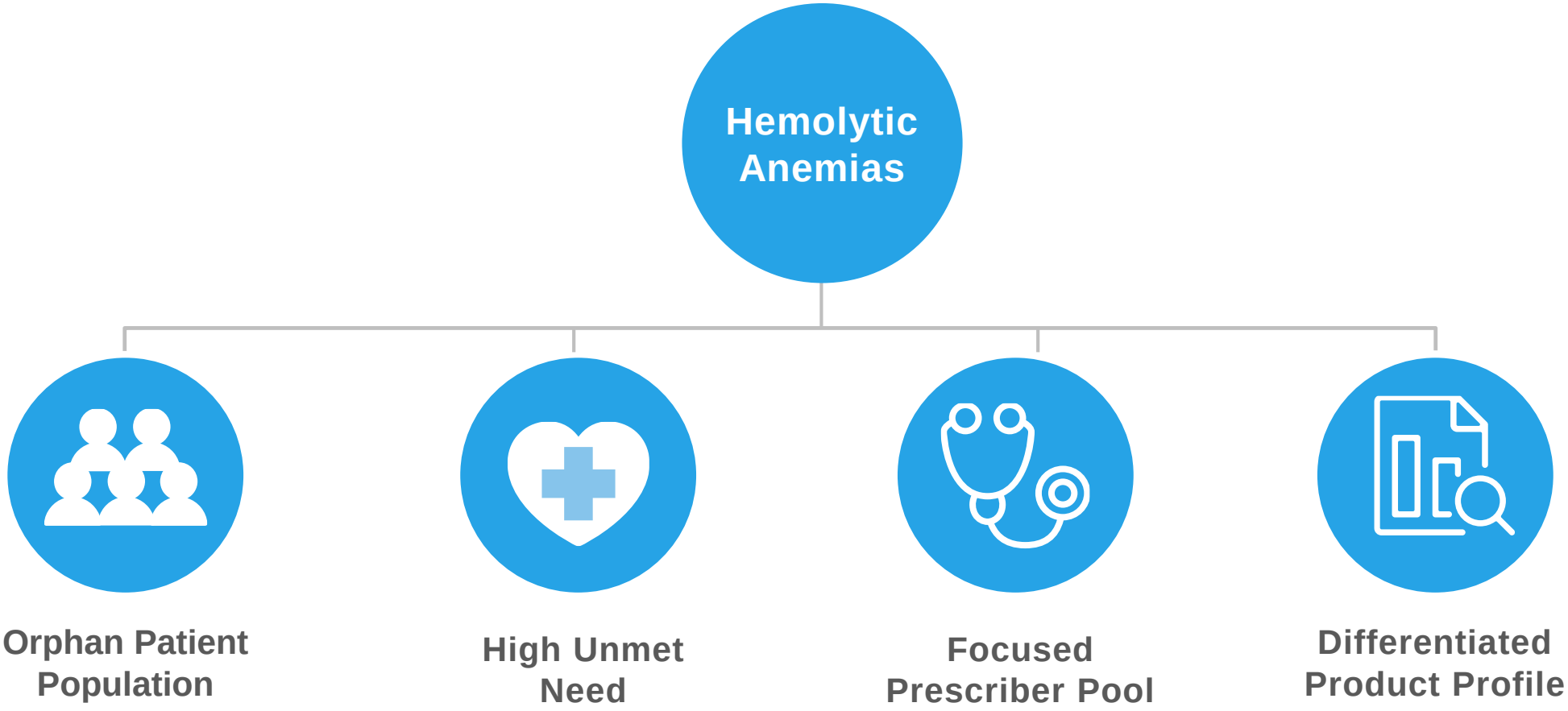
Sickle Cell Disease



*Estimates include estimated beta-thalassemia diagnosed prevalence, do not include alpha thalassemia, Agios market research.

Sources: Piel F, *NEJM,* 2017; Piel F, Hematology Education: the education program for the annual congress of the European Hematology Association | 2015; 9(1); Origa R, Genetics in Medicine, Vol 19, No 6, 2017; ASH State of Sickle Cell Disease 2016 Report; https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3182125

Mitapivat Has the Potential to Transform Care Across PK Deficiency, Thalassemia and Sickle Cell Disease



Closing Remarks

The PKR Platform: A Significant Global Opportunity in Hemolytic Anemias and Other Indications with High Unmet Need

1. Our PKR activation portfolio has potential broad utility across hemolytic anemias and several near-term milestones
2. Mitapivat is on track to be the first potential disease-modifying therapy for patients with PK deficiency with U.S. and EU submission planned in 2021
3. Mitapivat has potential to be first-in-class therapy for β- and α-thalassemia and sickle cell disease, progressing into pivotal development in 2021
4. Our initial disease areas of focus are highly synergistic, and we can leverage our experience and relationships in PK deficiency to engage with the thalassemia and sickle cell disease communities

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


agios
Q&A