agios

2021 Investor Day

November 17, 2021

Forward-looking statements

This presentation and various remarks we make during this presentation contain forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding the potential benefits of mitapivat and AG-946; Agios' plans, strategies and expectations for its preclinical, clinical and commercial advancement of its drug development, including mitapivat and AG-946; Agios' key milestones for 2021 and 2022; Agios' plans regarding future data presentations; and the potential benefits of Agios' strategic plans and focus. The words "anticipate," "expect," "goal," "hope," "milestone," "plan," "potential," "possible," "strategy," "will," "vision," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Such statements are subject to numerous important factors, risks and uncertainties that may cause actual events or results to differ materially from Agios' current expectations and beliefs. For example, there can be no guarantee that any product candidate Agios is developing will successfully commence or complete necessary preclinical and clinical development phases, or that development of any of Agios' product candidates will successfully continue. There can be no guarantee that any positive developments in Agios' business will result in stock price appreciation. Management's expectations and, therefore, any forward-looking statements in this presentation and various remarks we make during this presentation could also be affected by risks and uncertainties relating to a number of other important factors, including, without limitation: risks and uncertainties related to the impact of the COVID-19 pandemic to Agios' business, operations, strategy, goals and anticipated milestones, including its ongoing and planned research activities, ability to conduct ongoing and planned clinical trials, clinical supply of current or future drug candidates, commercial supply of current or future approved products, and launching, marketing and selling current or future approved products; Agios' results of clinical trials and preclinical studies, including subsequent analysis of existing data and new data received from ongoing and future studies; the content and timing of decisions made by the U.S. FDA, the EMA or other regulatory authorities, investigational review boards at clinical trial sites and publication review bodies; Agios' ability to obtain and maintain requisite regulatory approvals and to enroll patients in its planned clinical trials; unplanned cash requirements and expenditures; competitive factors; Agios' ability to obtain, maintain and enforce patent and other intellectual property protection for any product candidates it is developing; Agios' ability to maintain key collaborations; and general economic and market conditions. These and other risks are described in greater detail under the caption "Risk Factors" included in Agios' public filings with the Securities and Exchange Commission. Any forward-looking statements contained in this presentation and various remarks we make during this presentation speak only as of the date hereof, and Agios expressly disclaims any obligation to update any forward-looking statements, whether as a result of new information, future events or otherwise, except as required by law.

Today's agenda

	TOPIC	SPEAKER
2:00 – 2:05 PM	Opening Remarks	 Jackie Fouse, Ph.D.
2:05 – 2:10 PM	Discover, Develop, Deliver: A Seamless Connection Between Research, Clinical and Commercial	 Charlie Newman
2:10 – 2:45 PM	Research Approach, Strategy and Pipeline: The Next Wave of Agios Innovation	 Bruce Car, DVM, Ph.D.
2:45 – 2:50 PM	KOL Perspective: Unmet Need in MDS	 Hanny Al-Samkari, M.D. MGH / Harvard Medical School
2:50 – 3:25 PM	PK Activator Clinical Programs: Expansion and Momentum	 Sarah Gheuens, M.D., Ph.D.
3:25 – 3:45 PM	KOL Perspective: Transforming Care in PK Deficiency	 Hanny Al-Samkari, M.D. MGH / Harvard Medical School
3:45 – 4:15 PM	Critical Success Factors for Commercial Launch of Mitapivat in PK Deficiency and Other Hemolytic Anemias	 Darrin Miles
4:15 – 5:00 PM	Q&A	

Welcome to 2021 Investor Day

Dr. Jackie Fouse, Chief Executive Officer

We were founded to unlock a new field of discovery in cellular metabolism.

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

WE ARE FUELED BY CONNECTIONS

The strong bonds we build with patient communities, healthcare professionals, partners and colleagues enrich the impact we have as experts in **cellular metabolism** and enhance our collaboration, creativity and productivity – driving our ability to develop life-changing treatments for patients with **genetically defined diseases.**

Today, we are poised to expand our impact.

Our pioneering research in PK activation has yielded three promising proofs of concept that have the potential to revolutionize treatment options for people living with genetically defined diseases.

agios at-a-glance

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

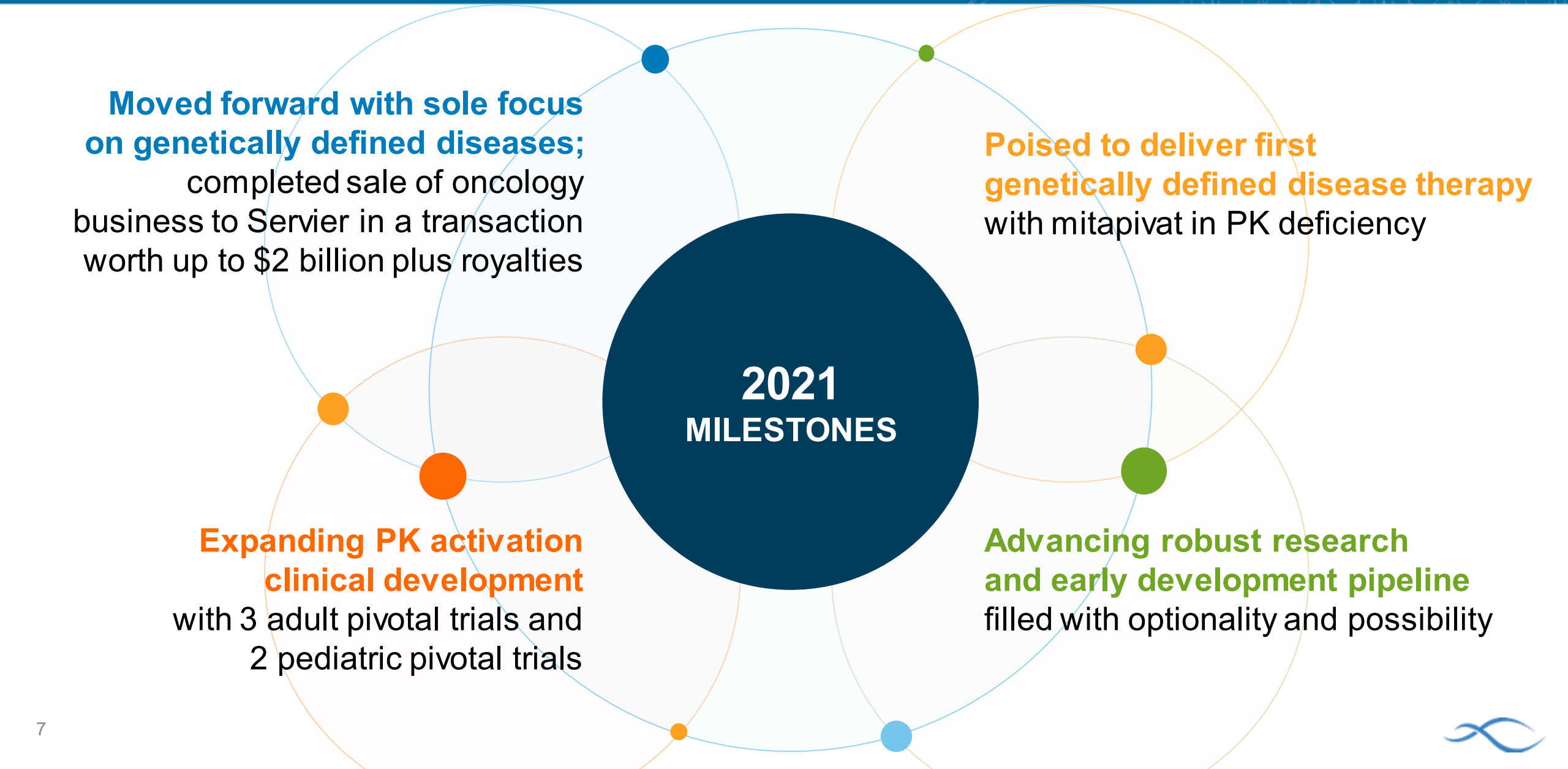
Patient voices inform our work and drive our sense of urgency

TAMARA
Pyruvate Kinase Deficiency

SHARONDA
Sickle Cell Disease

RYAN
Thalassemia

2021: A year of transformation, execution and value creation



Moved forward with sole focus on genetically defined diseases; completed sale of oncology business to Servier in a transaction worth up to $2 billion plus royalties

Poised to deliver first genetically defined disease therapy with mitapivat in PK deficiency

Expanding PK activation clinical development with 3 adult pivotal trials and 2 pediatric pivotal trials

Advancing robust research and early development pipeline filled with optionality and possibility

agios

AGIOS VISION:

Focused Innovation. Ambitious Development.
Transformative Treatments for Patients with Genetically Defined Diseases.

MITAPIVAT APPROVALS IN 3 INITIAL INDICATIONS

5+ MOLECULES EXPLORING 10+ INDICATIONS

PIPELINE POISED TO DELIVER NEW IND EVERY 12-24 MONTHS

CASH FLOW POSITIVE

What you'll hear today

01 Portfolio management approach: Agios intentionally cultivates internal and external connections that drive innovation and impact

02 Research: Our unmatched expertise in cellular metabolism has yielded a pipeline with the depth, breadth and optionality to yield sustained productivity

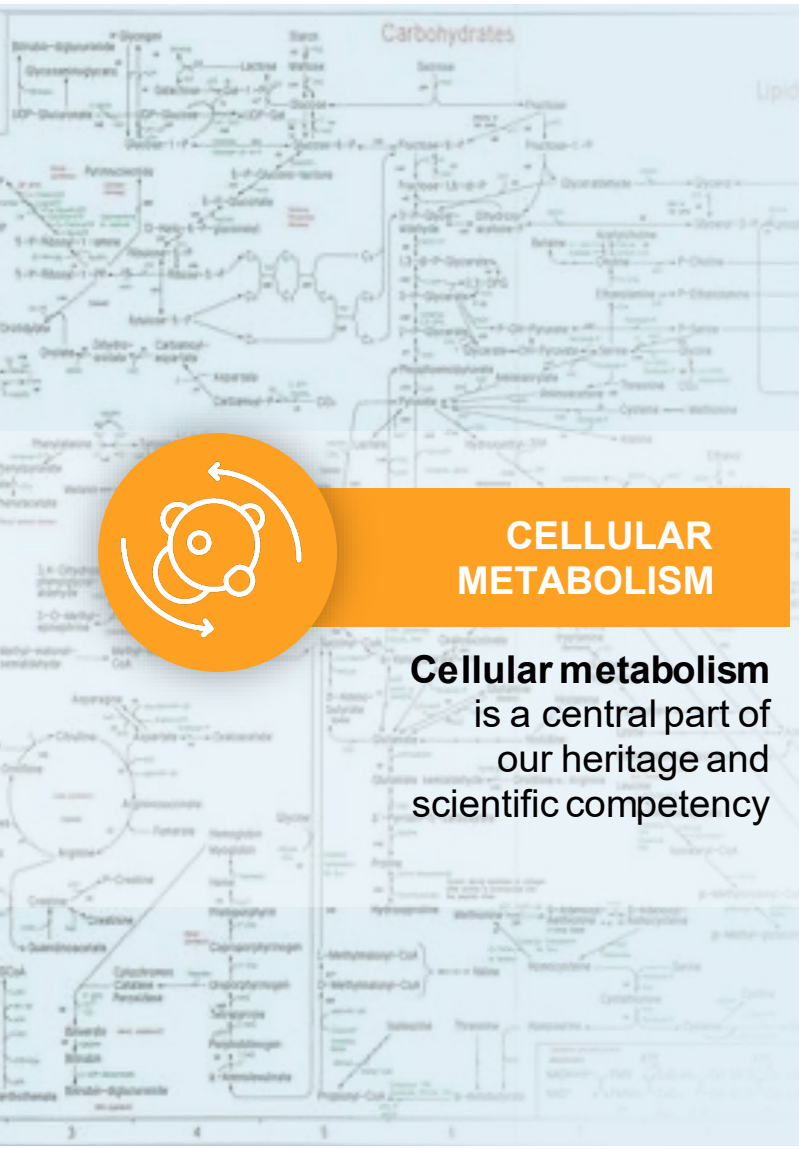
03 Clinical: Agios is the pioneering leader in PK activation clinical development with a differentiated approach to global development and community partnerships

04 Commercial: Agios is poised to maximize the success of our first genetically defined disease product launch in a serious disease with no approved therapies

Discover, Develop, Deliver: A Seamless Connection Between Research, Clinical and Commercial

Charlie Newman, Senior Vice President, Genetically Defined Disease Portfolio Leader

Our strategic focus is defined by a combination of our most differentiated foundational expertise across research, clinical and commercial domains



CELLULAR METABOLISM

Cellular metabolism is a central part of our heritage and scientific competency

GENETICALLY DEFINED DISEASES + CELLULAR METABOLISM

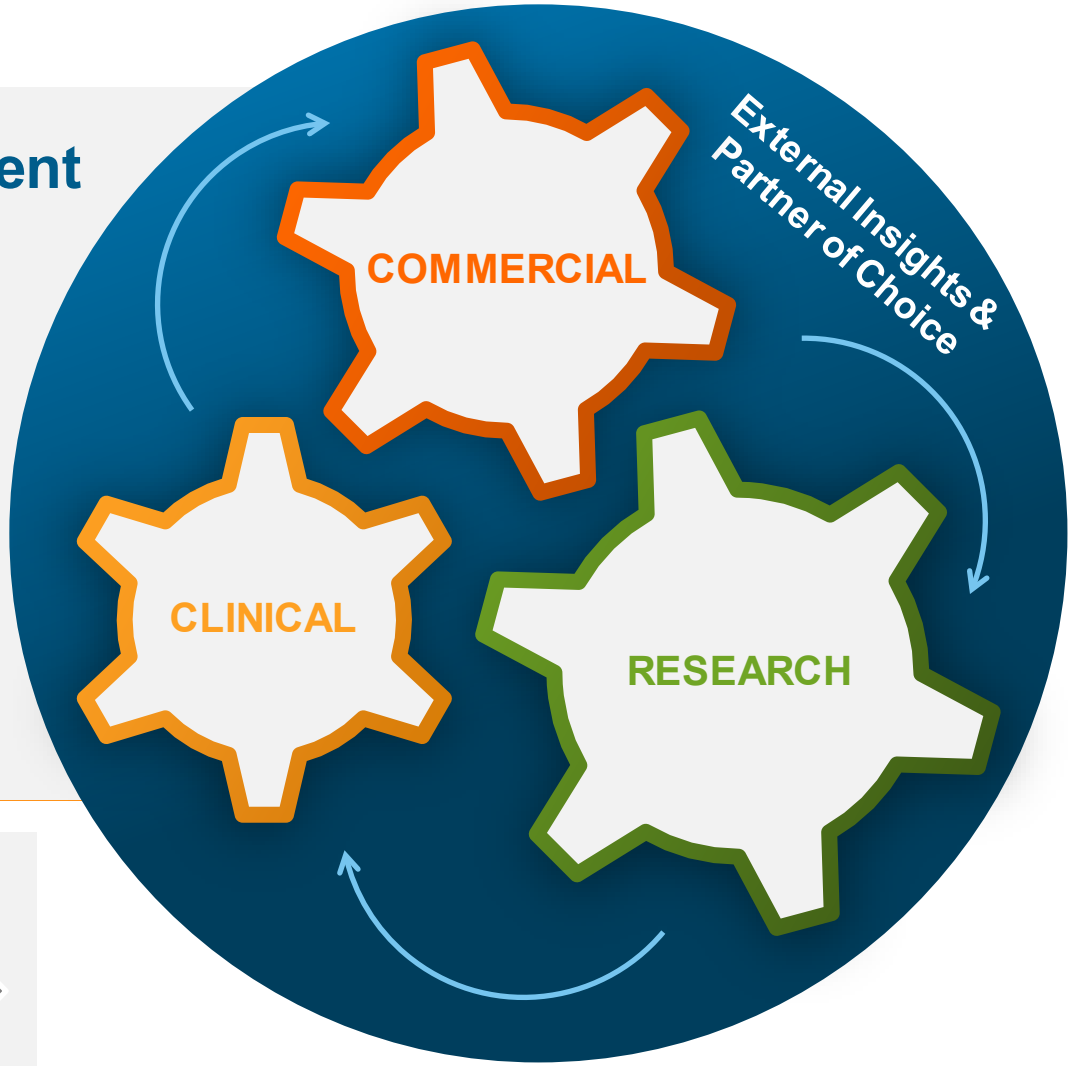
GENETICALLY DEFINED DISEASE

Genetically defined disease is a broad umbrella that encompasses both rare and more common diseases

Agios intentionally cultivates a hyper-connected organization that fuels innovation and impact

Interconnected Approach to Drug Development

- Our research, clinical and commercial teams are deeply integrated; insights from each drive new innovation
- Synergy among programs enables them to inform and potentially de-risk others
- Agios is highly connected with external stakeholders and a partner of choice



Conventional View of Drug Development

RESEARCH → CLINICAL → COMMERCIAL

Our business development strategy is designed to leverage Agios' core capabilities to maximize value for patients and shareholders

IDEAL IN-LICENSING CANDIDATES

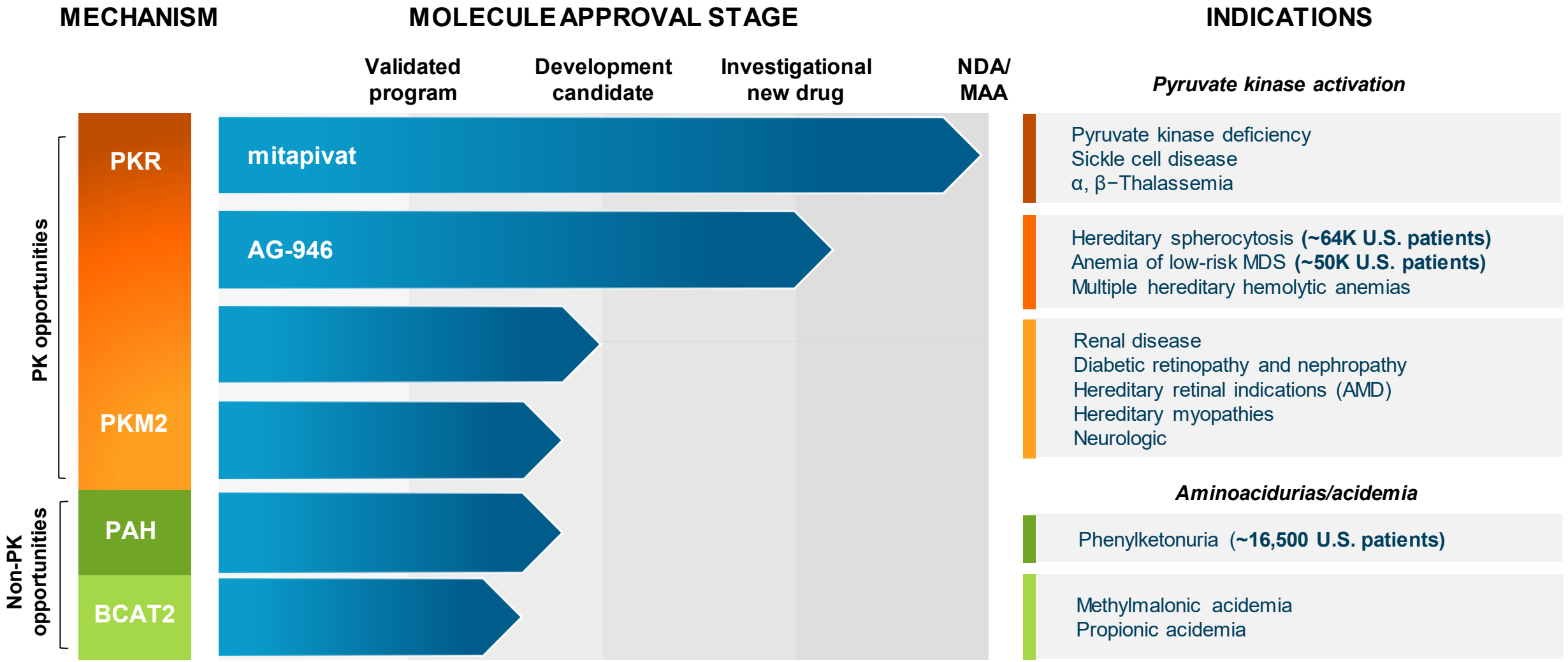
- ✓ Around IND stage
- ✓ Aligned with our therapeutic focus areas
- ✓ Ability to leverage commercial infrastructure and capabilities

Continually Evaluating
OPPORTUNITIES TO IDENTIFY STRATEGIC FIT

OUT-LICENSING CRITERIA

- ✓ Significant potential for patient impact
- ✓ Outside our core therapeutic focus areas
- ✓ Larger patient populations managed by HCP network outside current targets

Our interconnected research, clinical and commercial functions enable us to maximize the opportunities in our pipeline



Source: Agios market research

Pipeline products are under clinical investigation, and effectiveness and safety has not been established. There is no guarantee that any pipeline product will receive health authority approval or become commercially available in any country for the use being investigated.

Research Approach, Strategy and Pipeline: The Next Wave of Agios Innovation

Dr. Bruce Car, Chief Scientific Officer

What you'll hear today

01 Discovery at Agios: Cellular metabolism and in-born errors of metabolism

02 Overview of BCAT2 program

03 Overview of PAH program

04 PKM2 disease indication strategy

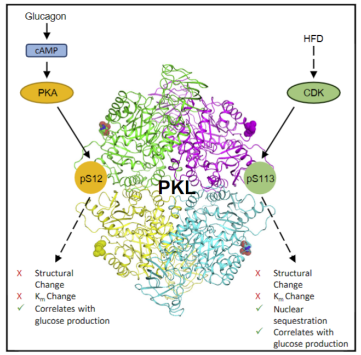
05 PKR/PKM2: Low to intermediate risk myelodysplastic syndrome (L-IR MDS)

Our expertise in cellular metabolism is unmatched

Cell Reports

Distinct Hepatic PKA and CDK Signaling Pathways Control Activity-Independent Pyruvate Kinase Phosphorylation and Hepatic Glucose Production

Graphical Abstract



Authors

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In Brief

Gassaway et al. identify a diet-induced, cyclin-dependent kinase-regulated phosphorylation site at S113 on pyruvate kinase. Although they determine that neither phosphorylation of this site nor the canonical PKA-regulated S12 site directly impacts enzyme kinetics, they demonstrate that S113 phosphorylation alters pyruvate kinase subcellular localization and influences glucose production.

ELSEVIER

Journal of Chromatography B

Volumes 1061–1062, 1 September 2017, Pages 89-96

A fit-for-purpose LC–MS/MS method for the simultaneous quantitation of ATP and 2,3-DPG in human K_2EDTA whole blood

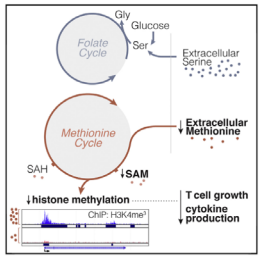
Hyeryun Kim [a], Penelope Kosinski [a], Charles Kung [a], Lenny Dang [a], Yue Chen [a], Hua Yang [a], Yuan-Shek Chen [b], Jordyn Kramer [b], Guowen Liu [a]

Show more

Cell Metabolism

Methionine Metabolism Shapes T Helper Cell Responses through Regulation of Epigenetic Reprogramming

Graphical Abstract



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In Brief

CD4+ T helper (Th) cells are central drivers of autoimmune pathology in diseases such as multiple sclerosis. Roy and Chen et al. identify methionine as an essential nutrient for Th cell epigenetic programming and demonstrate that dietary methionine restriction impacts T cell-mediated autoimmunity through effects on Th17 cell proliferation and cytokine production.

blood

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Blood. 2017 Sep 14; 130(11): 1347–1356. PMCID: PMC5609468

Prepublished online 2017 Jul 31. doi: 10.1182/blood-2016-11-753525 PMID: 28760888

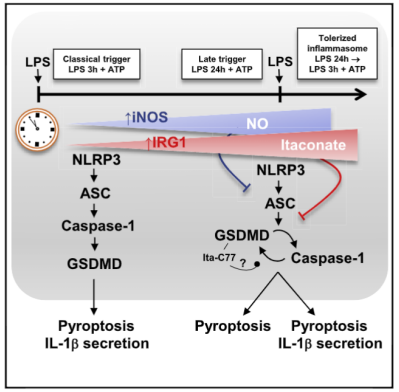
AG-348 enhances pyruvate kinase activity in red blood cells from patients with pyruvate kinase deficiency

Charles Kung,[✉1] Jeff Hixon,[1] Penelope A. Kosinski,[1] Giovanni Cianchetta,[1] Gavin Histen,[1] Yue Chen,[1] Collin Hill,[1] Stefan Gross,[1] Yaguang Si,[1] Kendall Johnson,[1] Byron DeLaBarre,[1] Zhiyong Luo,[2] Zhiwei Gu,[2] Gui Yao,[2] Huachun Tang,[2] Cheng Fang,[2] Yingxia Xu,[2] Xiaobing Lv,[2] Scott Biller,[1] Shin-San Michael Su,[1] Hua Yang,[1] Janeta Popovici-Muller,[1] Francesco Salituro,[1] Lee Silverman,[1] and Lenny Dang[1]

Cell Reports

Itaconate confers tolerance to late NLRP3 inflammasome activation

Graphical Abstract



Authors

Monika Bambouskova, Lucie Potuckova, Tomas Paulenda, ..., Russell G. Jones, Donald M. Simons, Maxim N. Artyomov

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In brief

Bambouskova et al. determine the *in vitro* phenotype of *Irg1*$^{-/-}$ macrophages and define itaconate as a key regulator of tolerance to late NLRP3 inflammasome activation.

nature COMMUNICATIONS

ARTICLE

https://doi.org/10.1038/s41467-018-07928-x OPEN

Structure and inhibition mechanism of the catalytic domain of human squalene epoxidase

Anil K. Padyana[1], Stefan Gross[1], Lei Jin[2], Giovanni Cianchetta[1,5], Rohini Narayanaswamy[1], Feng Wang[3], Rui Wang[3,6], Cheng Fang[4], Xiaobing Lv[4,7], Scott A. Biller[1], Lenny Dang[1], Christopher E. Mahoney[1], Nelamangala Nagaraja[1], David Pirman[1], Zhihua Sui[1], Janeta Popovici-Muller[1,8] & Gromoslaw A. Smolen[1,9]

MOLECULAR CANCER THERAPEUTICS | SMALL MOLECULE THERAPEUTICS

Selective Vulnerability to Pyrimidine Starvation in Hematologic Malignancies Revealed by AG-636, a Novel Clinical-Stage Inhibitor of Dihydroorotate Dehydrogenase

Gabrielle McDonald[1], Victor Chubukov[1], John Coco[1], Kevin Truskowski[1], Rohini Narayanaswamy[1], Sung Choe[1], Mya Steadman[1], Erin Artin[1], Anil K. Padyana[1], Lei Jin[1], Sebastien Ronseaux[1], Charles Locuson[1], Zi-Peng Fan[1], Tabea Erdmann[2], Alan Mann[1], Sebastian Hayes[1], Mark Fletcher[1], Kavitha Nellore[3], Siva Sanjeeva Rao[4], Hosahalli Subramanya[3], K. Satish Reddy[3], Sunil K. Panigrahi[3], Thomas Antony[3], Sreevalsam Gopinath[3], Zhihua Sui[1], Nelamangala Nagaraja[1], Lenny Dang[1], Georg Lenz[2], Jonathan Hurov[1], Scott A. Biller[1], Josh Murtie[1], Kevin M. Marks[1], and Danielle B. Ulanet[1]

The Agios research engine offers a unique value proposition

Deep expertise in cellular metabolism and genetics

- Publication history reflects 13 years leadership in the field of PK activation
- Laboratory capabilities are specialized to enable complex, genetically defined disease studies
- Research team with significant expertise in the field of cellular metabolism, biochemistry and drug discovery

Focus on genetically defined diseases has enabled expansion of our research and new promising biological insights

- Highly translatable work from murine and cell-based models recapitulating human disease yields deep insights into treating genetically defined diseases and disease adjacencies

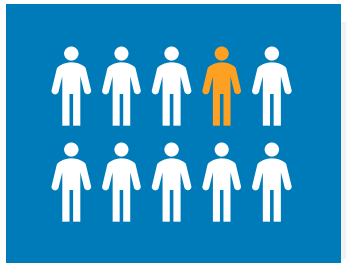
Favor targets that may impact an array of diseases or mutations, yielding a "pipeline within a mechanism"

- Our focus on modulating pyruvate kinase activation, cellular bioenergetics and amino acid metabolism allows preclinical exploration of both clinical and novel assets in multiple indications

What is a genetically defined disease at Agios?

Is defined by flexible, opportunistic and scientifically rigorous approaches

Includes both monogenic and polygenic diseases



Includes rare (sentinel), but not ultra-rare conditions

Includes non-genetic disease adjacencies to the genetically defined conditions

Extensive industry and academic networks

Excellence in drug discovery execution

- Tenured R&D leadership team (average >20 years)
- Deep experience
- Integration of knowledge across all disciplines
- Balanced internal and external capabilities

In-depth experience in cellular metabolism

- Academia and industry

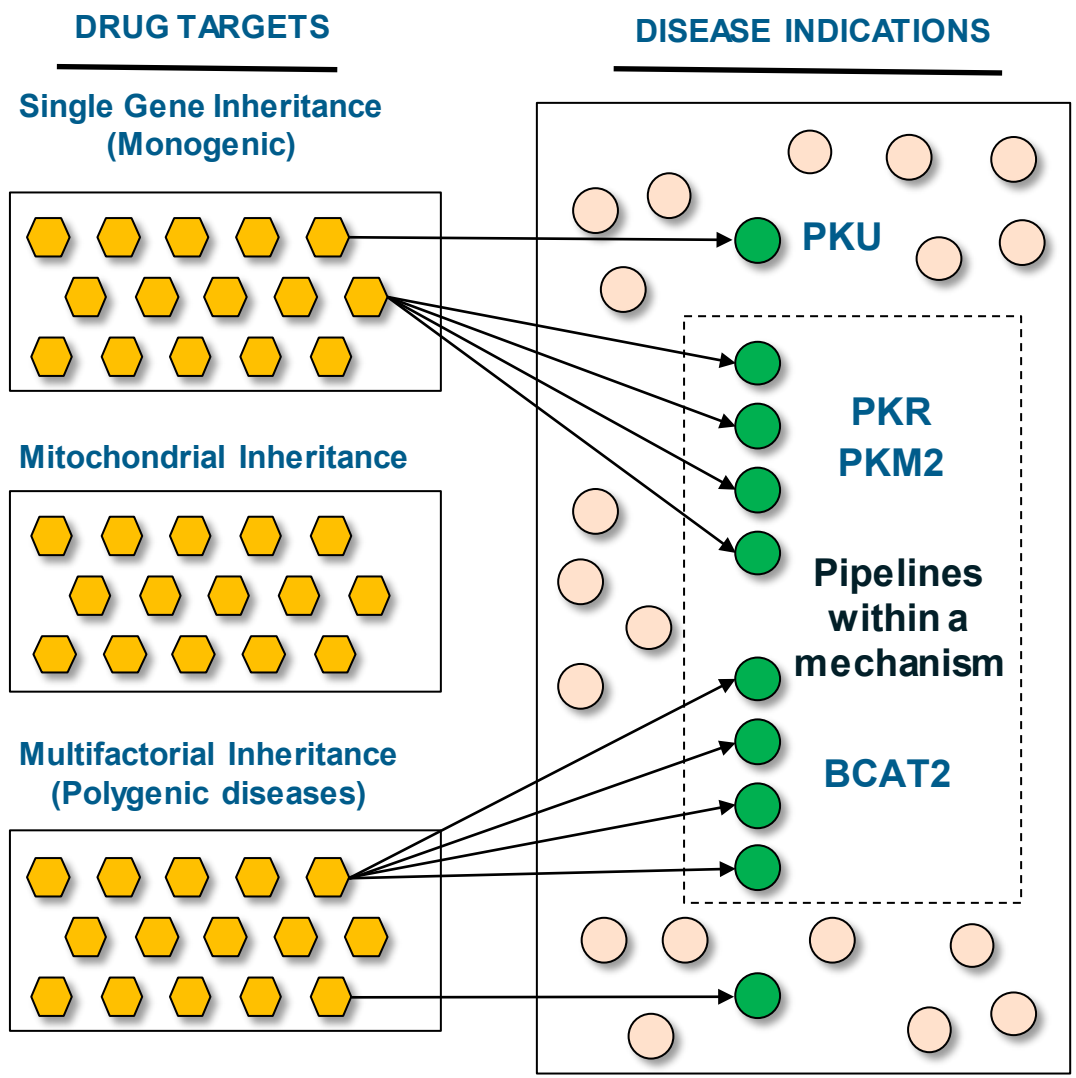
Building teams to augment future vision

- Genetically defined diseases

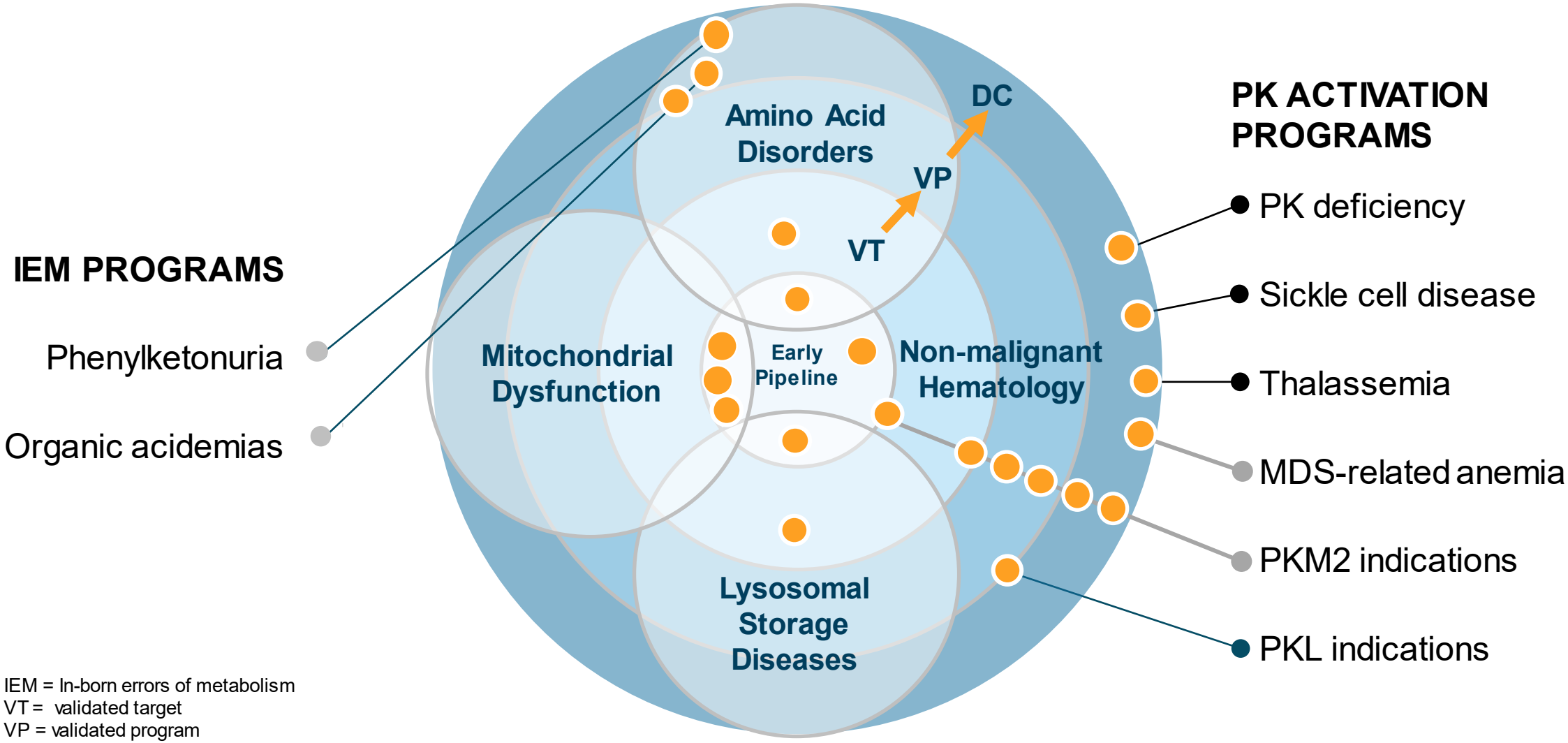
Framework for the selection of new drug discovery programs at Agios

Selection Considerations

- Cellular metabolism and following the science
- Small molecule platform
- Potential for pipeline within a mechanism
- Alignment to hematology and in-born errors of metabolism
- Competition

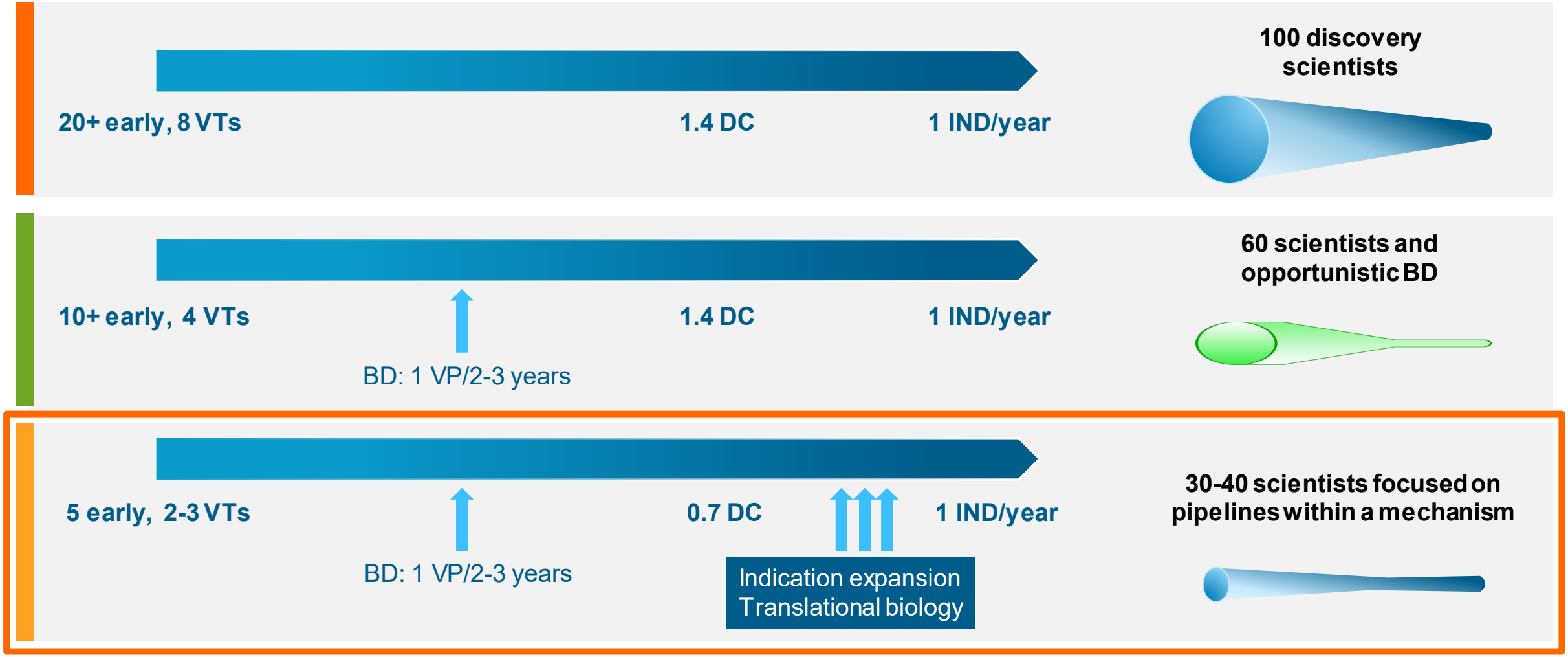


Leveraging expertise in cellular metabolism to discover new targets across a range of therapeutic areas



IEM = In-born errors of metabolism
VT = validated target
VP = validated program
DC = development candidates

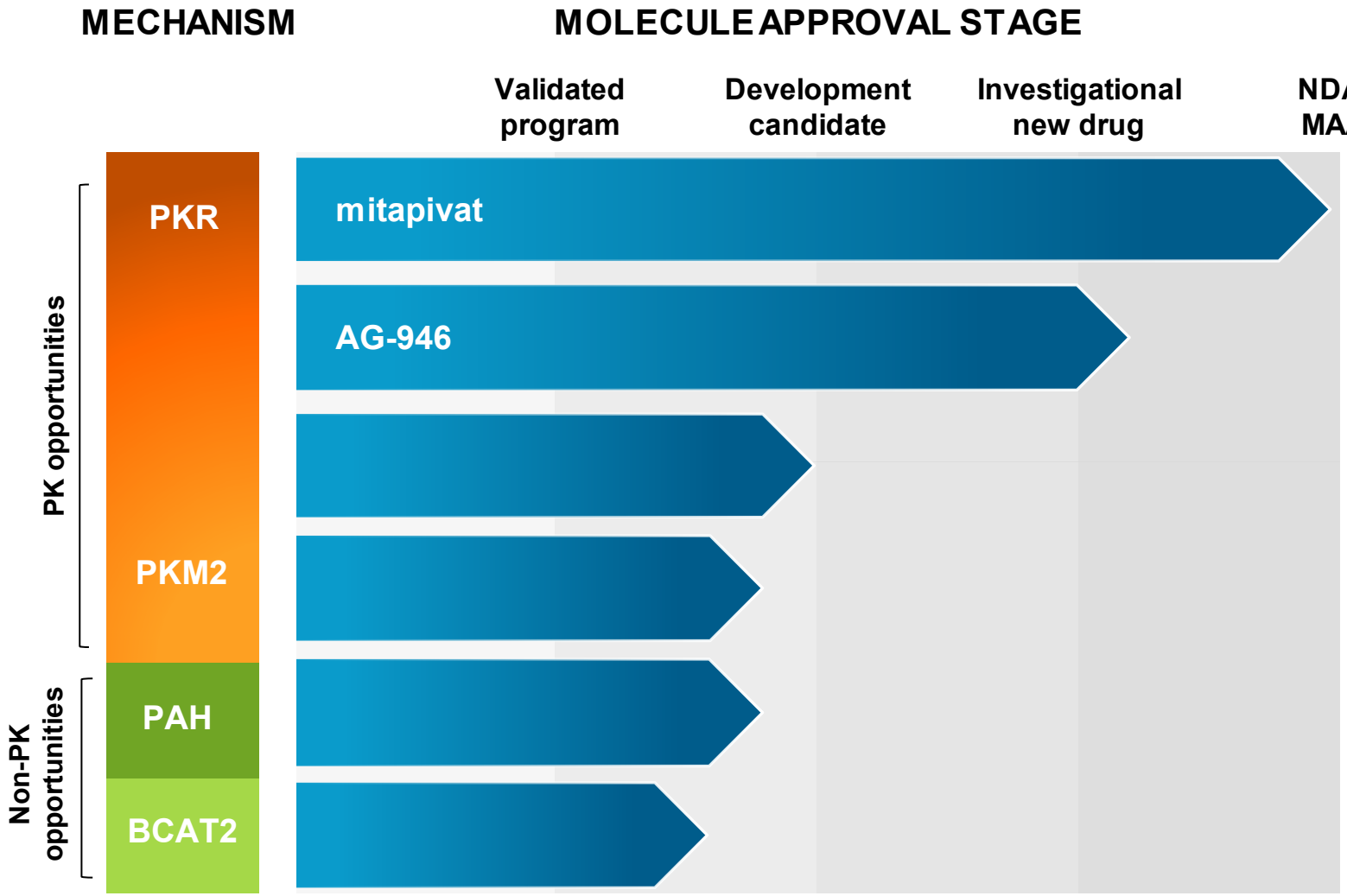
How do we improve our chances of success and resource optimally in discovery?



Scaled to 1 IND for illustrative purposes only

BD = business development, VT = validated target, VP = validated program, DC = development candidate

Our rich pipeline fuels ongoing, sustainable innovation



INDICATIONS

Pyruvate kinase activation

- Pyruvate kinase deficiency
- Sickle cell disease
- α, β−Thalassemia

- Hereditary spherocytosis **(~64K U.S. patients)**
- Anemia of low-risk MDS **(~50K U.S. patients)**
- Multiple hereditary hemolytic anemias

- Renal disease
- Diabetic retinopathy and nephropathy
- Hereditary retinal indications (AMD)
- Hereditary myopathies
- Neurologic

Aminoacidurias/acidemia

- Phenylketonuria **(~16,500 U.S. patients)**

- Methylmalonic acidemia
- Propionic acidemia

Source: Agios market research

Pipeline products are under clinical investigation, and effectiveness and safety has not been established. There is no guarantee that any pipeline product will receive health authority approval or become commercially available in any country for the use being investigated.

Branched chain amino acid aminotransferase-2 (BCAT2) inhibitors for the treatment of propionic and methylmalonic acidemia

DISEASE OVERVIEW

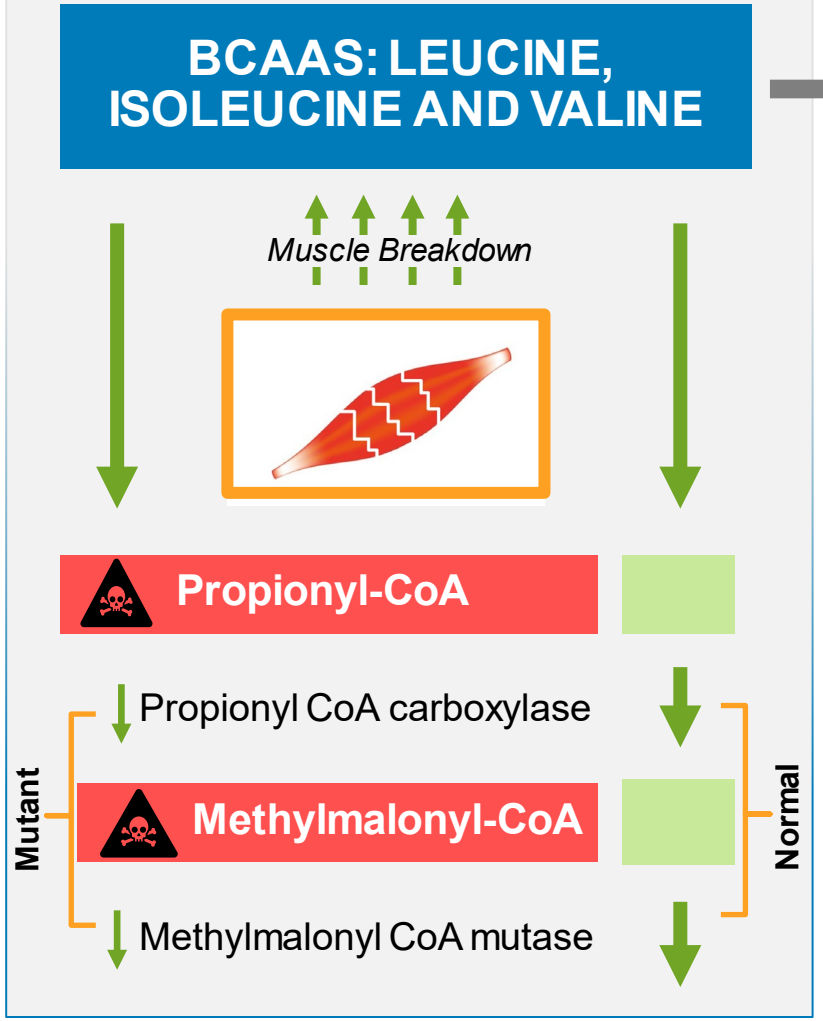
- Propionic and methylmalonic acidemia are a group of inherited in-born errors of metabolism, in which the body cannot break down branched chain amino acids, leading to an accumulation of toxic substances

SCIENTIFIC STRATEGY

- Agios' BCAT2 inhibitors are designed for convenient oral administration
- Substrate reduction therapy: BCAT2 inhibition reduces the formation of the toxic metabolites, methylmalonic acid (MMA) and propionic acid (PA)
- BCAT2 can be employed in toxic substrate reduction for several additional genetically defined diseases
- Prevention of MMA and PA accumulation and metabolic crises will enable patients to have fewer dietary/other restrictions, providing them an arc of life with significantly improved or normal milestones

BCAT2 inhibition: Treatment of methylmalonic and propionic acidemia

BCAAS: LEUCINE, ISOLEUCINE AND VALINE



ACUTE METABOLIC DECOMPENSATION

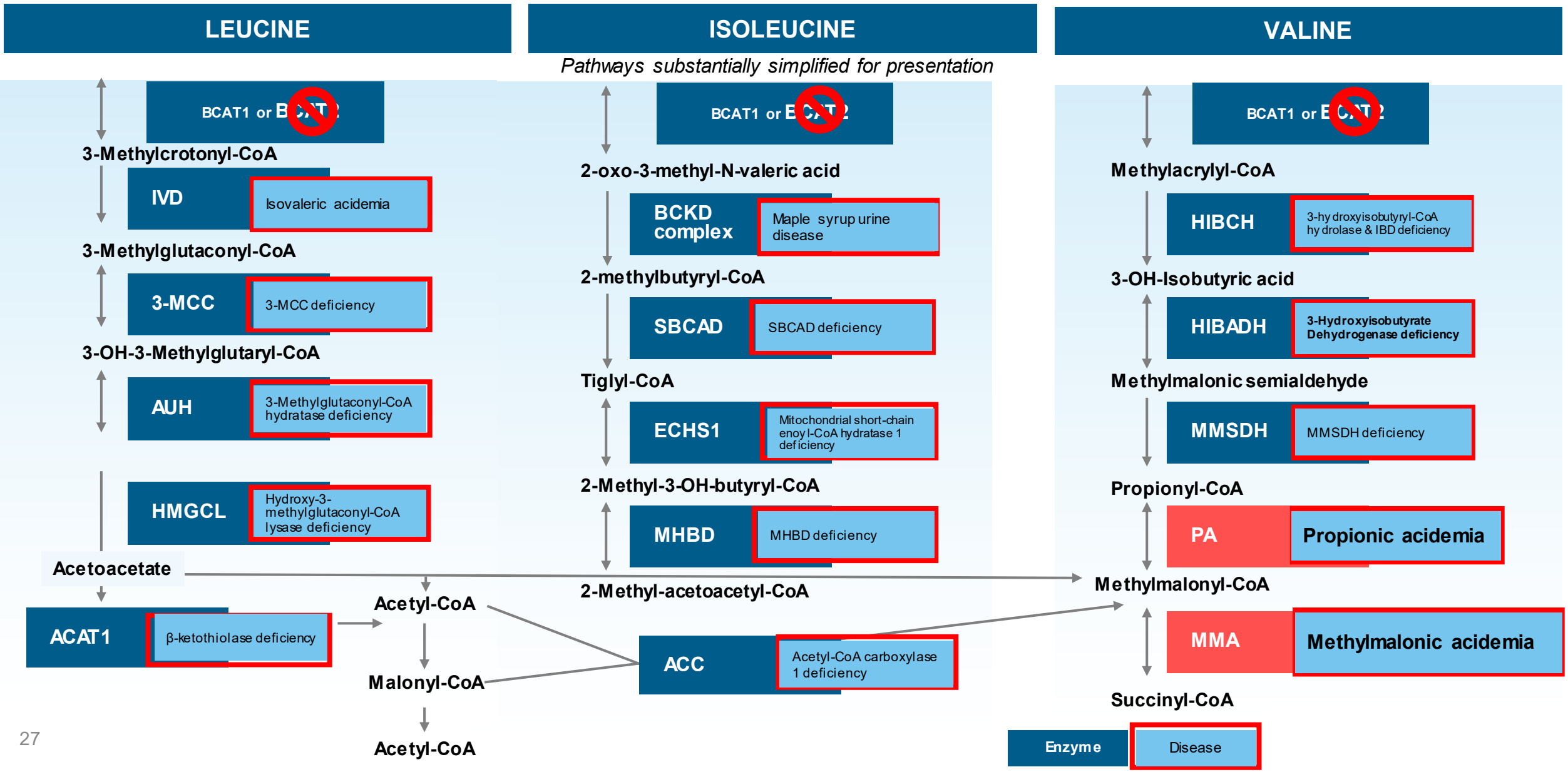
- Occurs shortly after birth if untreated
- Triggered by external factors later in life
- Can be fatal and produce long-lasting damages

CHRONIC MANIFESTATIONS

- Delayed/reduced cognitive development
- Renal insufficiency (MMA)/cardiac issues (PA)

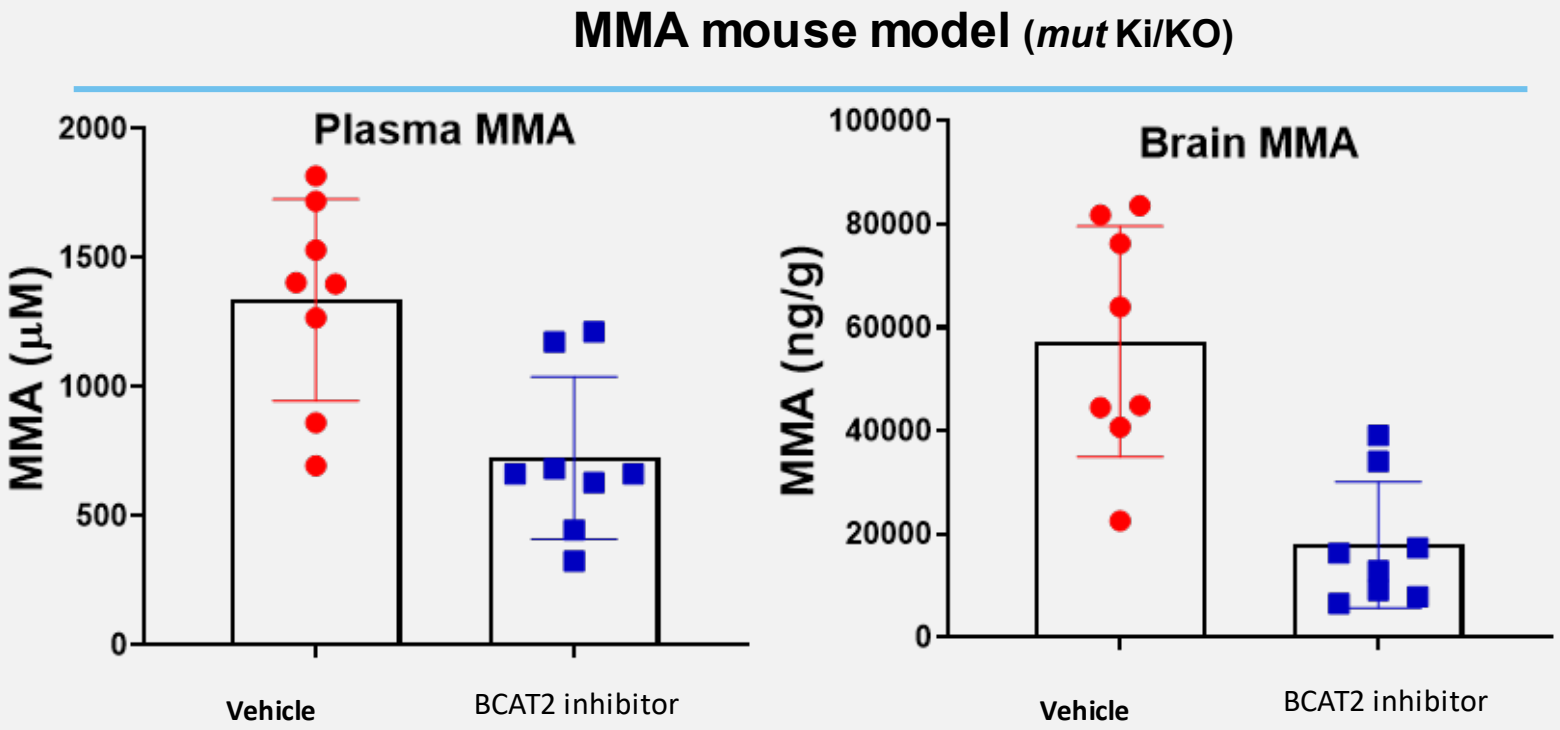
MMA and PA are associated with increased mortality (few patients over 35)

Selective BCAT2 inhibition has the potential to be a pipeline in a mechanism



Reduction of MMA by BCAT2 inhibition

Exogenously added BCAAs to mimic acute metabolic decompensation (AMD)



- Potent, selective, orally bioavailable molecules demonstrate BCAT2 inhibition *in vivo*
- Induced "metabolic crisis" markedly diminished both in periphery and brain

Source: Agios-directed research

BCAT2 inhibitors: Progress

PROGRESS

- Acute studies demonstrate *in vivo BCAT2* inhibition and correction of metabolic crises
- Late lead optimization project evaluating effects in chronic efficacy studies
- Orally bioavailable, single digit nM, selective (BCAT2 over BCAT1) molecules with extensive drug property optimization in hand

Phenylalanine hydroxylate (PAH) stabilizers for the treatment of phenylketonuria (PKU)

DISEASE OVERVIEW

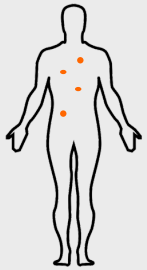
- PKU is a rare, inherited disease that causes phenylalanine to accumulate
- Disease management consists of a diet low in phenylalanine combined with approved therapies. Significant unmet need exists in PKU, despite approved drugs
- PKU affects people from infancy to adulthood

SCIENTIFIC STRATEGY

- Agios' PAH stabilizer is an investigational medicine designed for convenient oral administration
- Normalizing plasma phenylalanine concentrations may allow patients to increase natural protein intake and provide them with normal milestones and increased quality of life from childhood to old age

PKU: Mutations in PAH

1



Normal Protein Diet

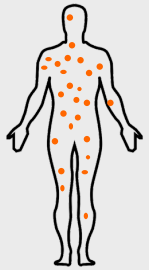
A mixed diet provides your body Phe

2

Defective PAH enzyme

PAH fails to process the Phe to Tyr

3



Increase in Phenylalanine

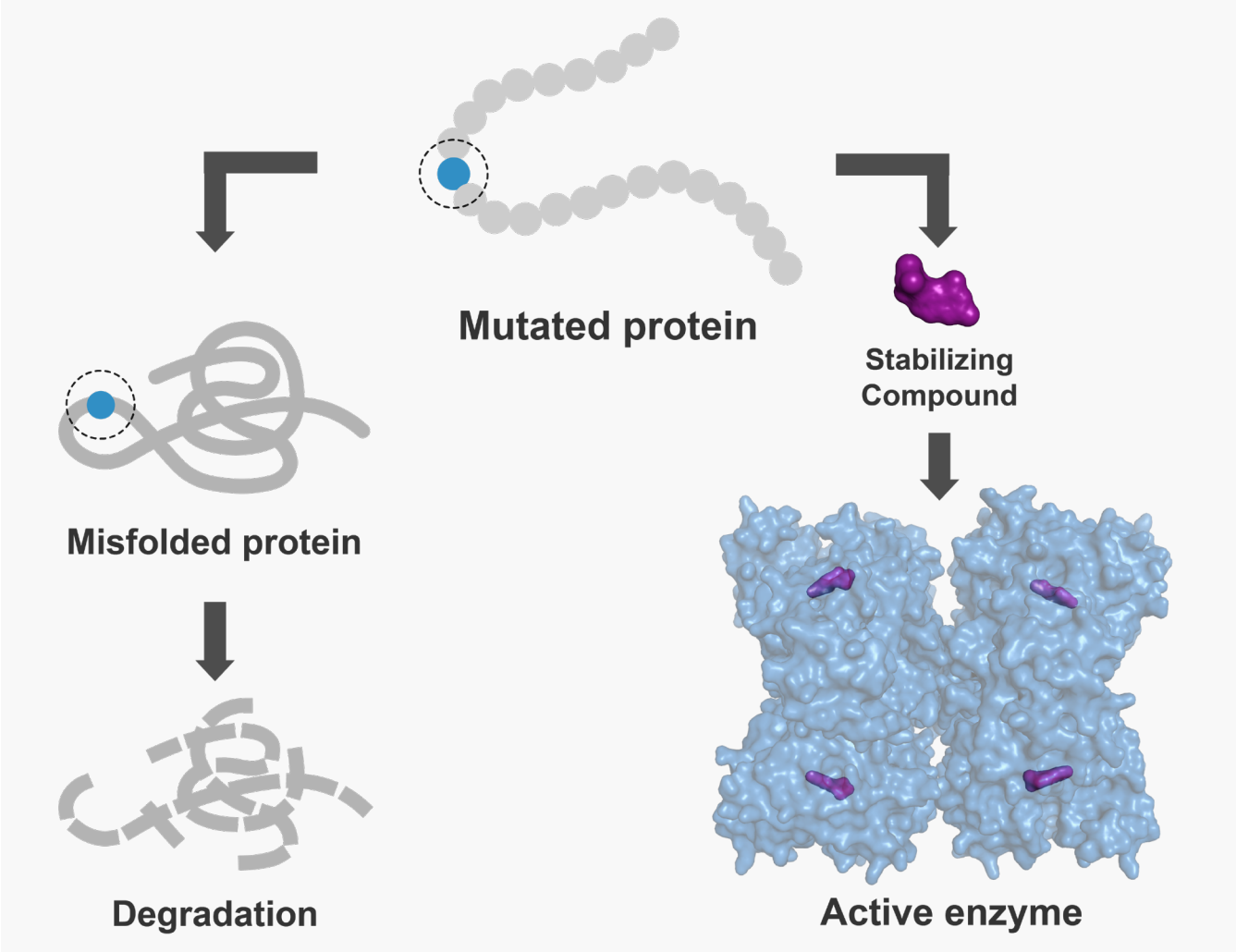
This leads to high Phe levels in the blood, which results in neurocognitive defects

- **~16,000 PKU patients in U.S.**

  ~60% of patients have severe disease
- **Severity of disease correlates with extent of phenylalanine elevation**
- **Phenylalanine elevation causes neurocognitive defects and intellectual disability**
- **High unmet medical need remains:**
  - Highly restricted diet is key part of the standard of care

Sources: National PKU Alliance, www.npkua.org and Weisbren et al 'Phenylalanine blood levels and clinical outcomes in phenylketonuria'

Therapeutic strategy: Stabilize mutant PAH to rescue enzyme activity



> 1000 different mutations found in PAH

Most mutations result in misfolded proteins, leading to degradation

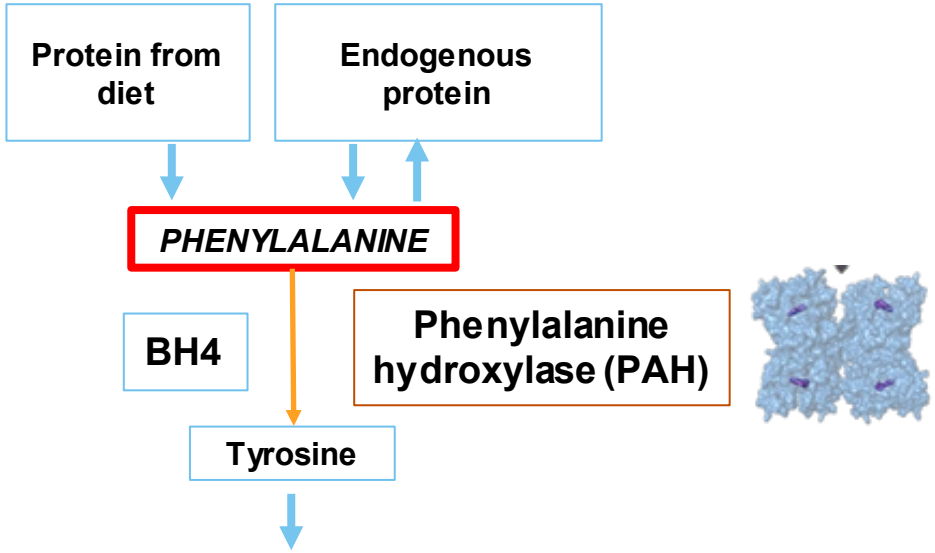
Agios' approach is to stabilize the mutant PAH molecule into the active tetrameric form

Stabilization leads to increase in active PAH protein and lowering of blood phenylalanine

Source: PAHvdb (http://www.biopku.org/pah/); www.BIOPKU.org; https://www.ncbi.nlm.nih.gov/books/NBK1504/

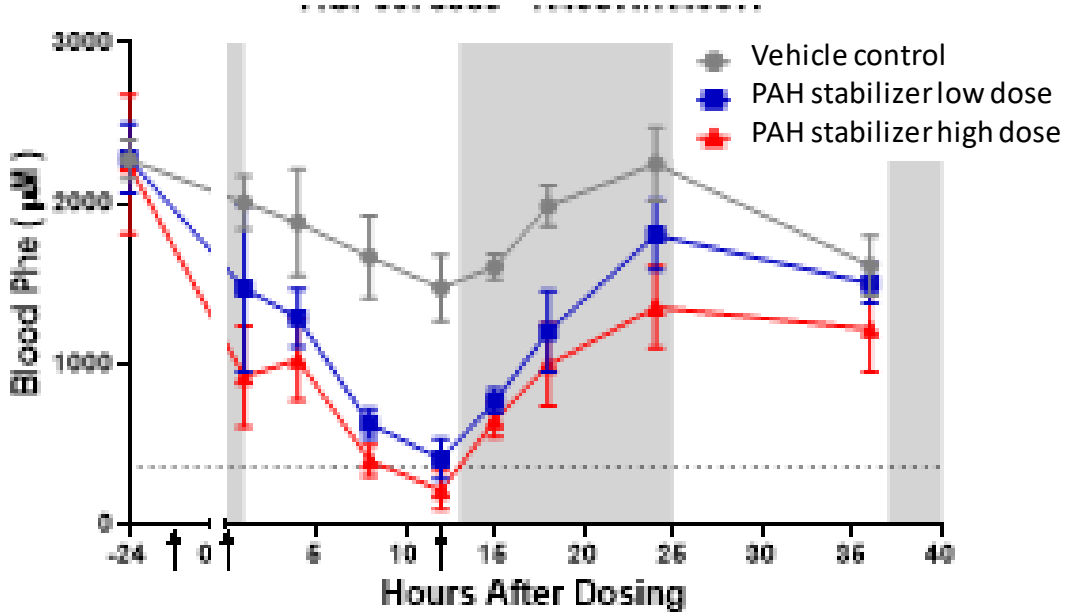
PAH stabilizers: Efficacy in disease model

METABOLIC PATHWAY



Pathway substantially simplified for presentation

BLOOD PHENYLALANINE
(PAH-mutant mice fed standard diet *ad lib*)



- First-in-class molecule that stabilizes protein folding to generate active PAH enzyme
- Dose-dependent Phe reduction on animals with normal diet in severe PKU genetic background

Source: Agios-directed research

PAH stabilizer program: Progress to IND

PROGRESS

- Late lead optimization approaching development candidate milestone
- Novel DC candidate chemistry offers substantial advantages
  - Properties contributing to lower human dosage projection
  - Optimized CMC and significantly enhanced pharmacologic properties
  - Development timelines will be significantly shorter than for original DC

Pyruvate kinase activation

01 Leadership position in understanding the biology and biochemistry of PK activation built over 13 years of laboratory research

02 Agios has expertise in creating well tolerated, orally bioavailable activators with a dialable range of potencies, activities and tissue disposition

03 Clinical research focusing on benefit of PKR activation in hereditary hemolytic anemias

04 Nonclinical research focusing on benefit of PKM2 activation and its synergy with PKR activation

We are expanding the impact of our PK activation portfolio by exploring the therapeutic potential of PKM2 activation

MULTIPLE PK ACTIVATOR ASSETS

- Mitapivat, AG-946 and others, including brain-penetrant molecules
- Drug candidates tailored to indications, price points, and compelling science
- PKM2 indications are covered in our patent space and applications
- PKM2 activation has the potential to have broad and transformational impact across multiple disease indications

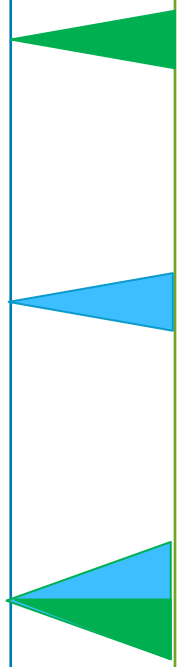
SCIENTIFIC STRATEGY

- Restoring energetics in acquired and hereditary PKR deficiency
- Normalizing energetics and correcting one-carbon metabolism in acquired PKM2 deficiency states and other conditions
- Improving mitochondrial function
- Exploiting the diversion of one-carbon metabolism in multiple genetically defined diseases

How does PK multi-isoform activation impact disease?

There is potential to have an accelerated, positive impact on disease by improving the delivery of oxygen to tissues with PKM2 activation-correctible pathologies

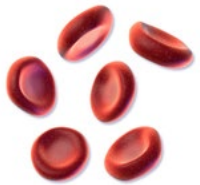
- **PKR activation**
  - Improves red cell health
- **PKM2 activation**
  - Diverts one carbon metabolism and improves cellular energetics
- **Combined effects of both PKR/PKM2**
  - Broad disease indications, including many genetically defined diseases



- ↑ATP, ↓2,3 DPG (↑ O_2 affinity)
- ↑ antioxidant effects in RBCs
- ↑ hemoglobin
- ↑ ATP
- ↓1,3 BPG → ↓ serine, glycine → …
- ↑ pyruvate/lactate → …

➢ Improved O_2 delivery to tissues receiving PKM2 pharmacologic benefit

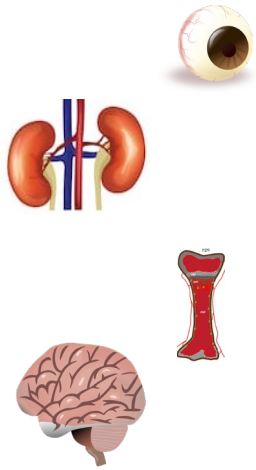
PKM2 activation: Multiple opportunities for reversing disease pathology



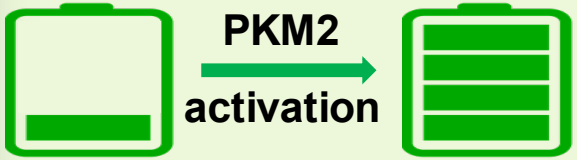
TESTED therapeutic hypothesis

- Strong rationale for treatment of hereditary anemias, and anemias with acquired PK deficiency

Red blood cells (PKR), bone marrow (PKM2) – pyruvate kinase deficiency, thalassemia, sickle cell disease, others



UNTESTED therapeutic hypothesis

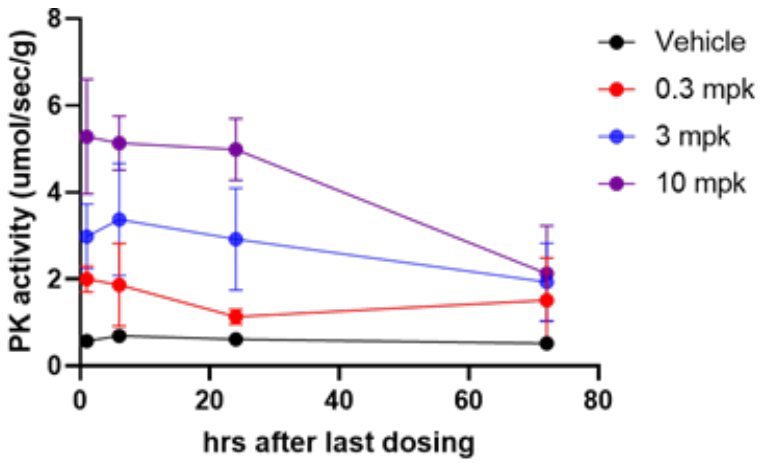


- Strong rationale for the treatment of renal disease, hereditary and acquired neurologic conditions, retinal disease, dys-erythropoiesis (hematopoiesis), and others
- PKR and PKM2 are anticipated to have synergistic benefit

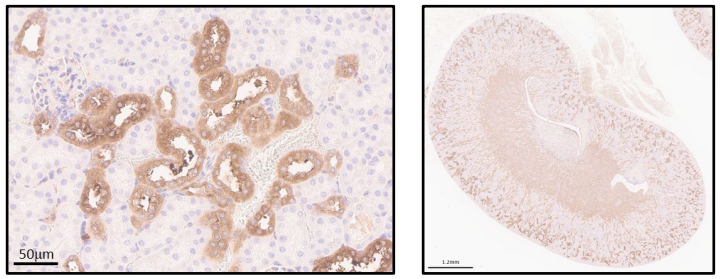
Retina, kidney, bone marrow, liver, CNS/PNS astrocytes and Schwann cells express abundant PKM2.

PKM2 renal activation translates to pharmacologic and disease activity

Renal pyruvate kinase activation

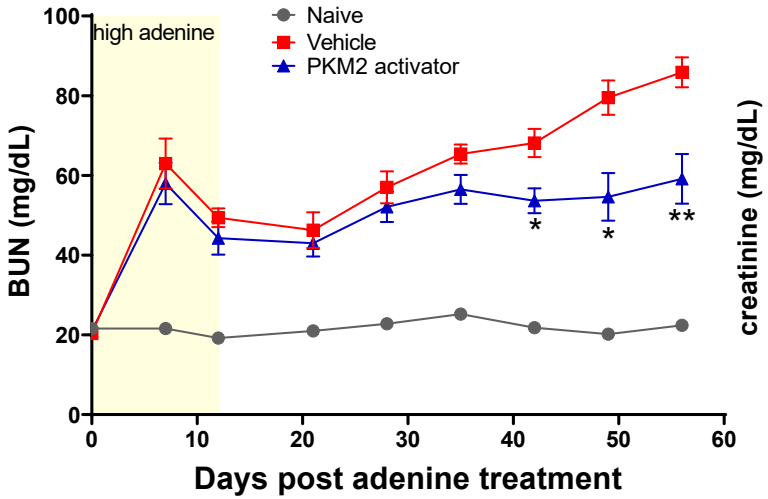


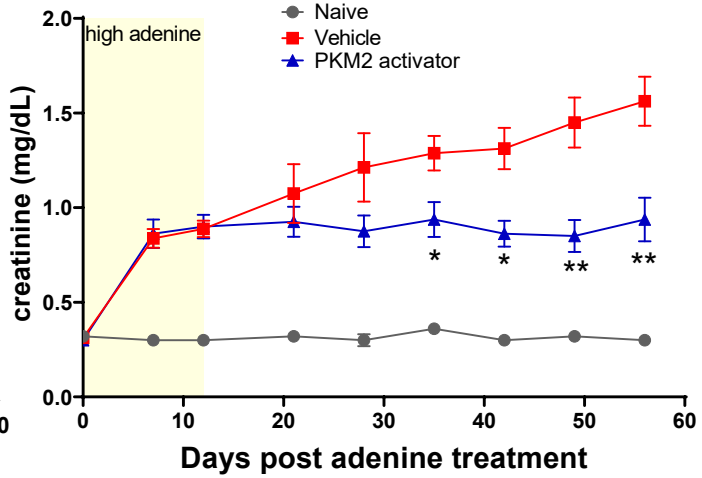
Renal Immunohistochemistry: PKM2



PKM2 expression at desired sites of action

Toxic nephropathy: Adenine-induced chronic kidney disease (CKD) in rats

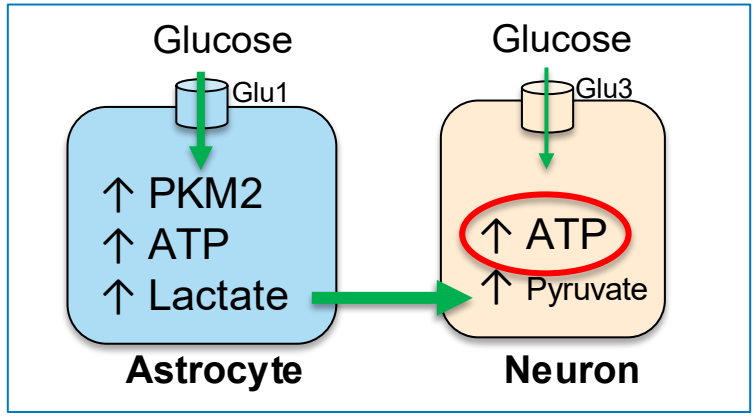




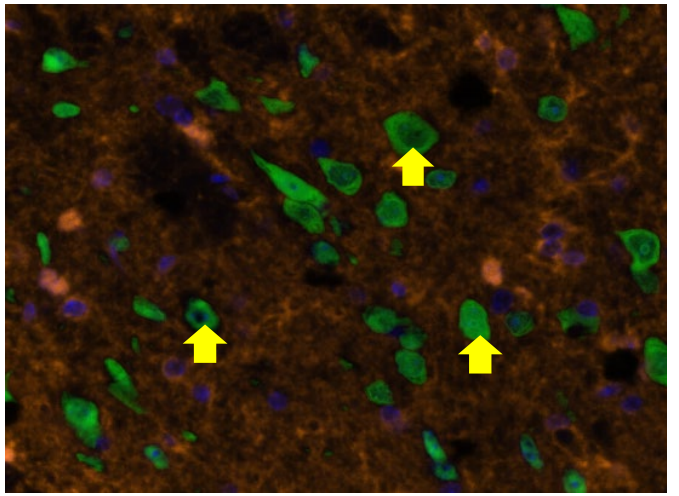
- PKM2 expression and activation observed in renal tissue
- Renal PKM2 activation stabilizes renal function in CKD model
- In this model of anemia of CKD, PK activation modestly increased hemoglobin and reduced reticulocyte counts

Source: Agios-directed research

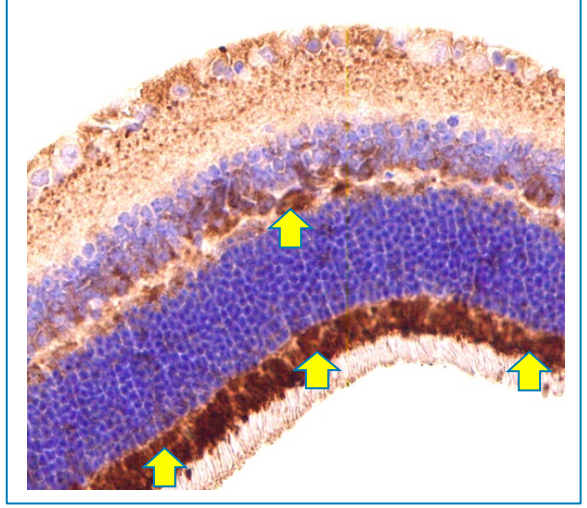
Central PKM2 activation translates to pharmacologic and disease activity



Hypothesis: PKM2-facilitated lactate shunt overcomes Glu3 dysfunction*



Astrocytic PKM2 expression

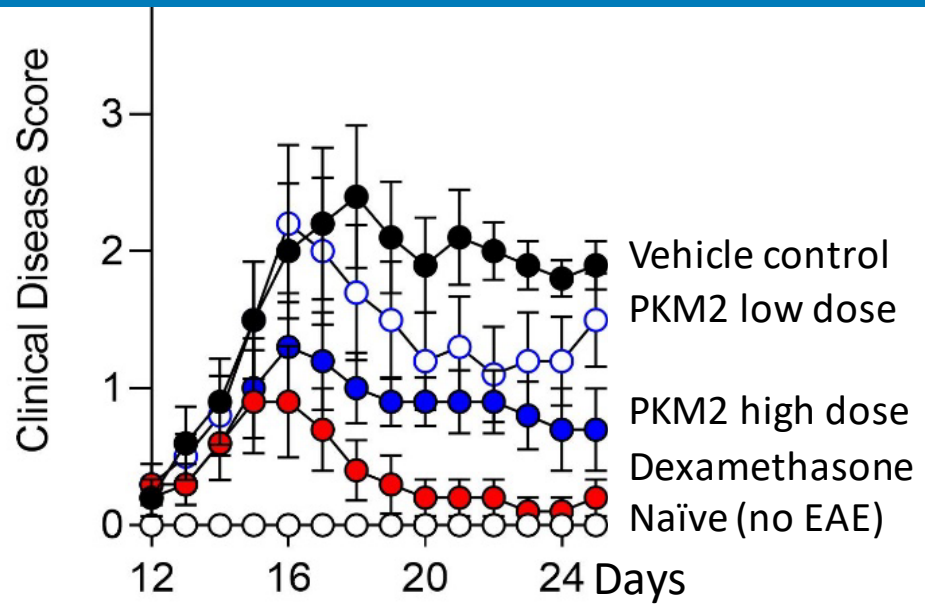


Retinal PKM2 expression

J Cerebral Blood Flow & Metabolism 2017: 37(6) 1927

Source: Agios-directed research

Th17 and centrally driven effects



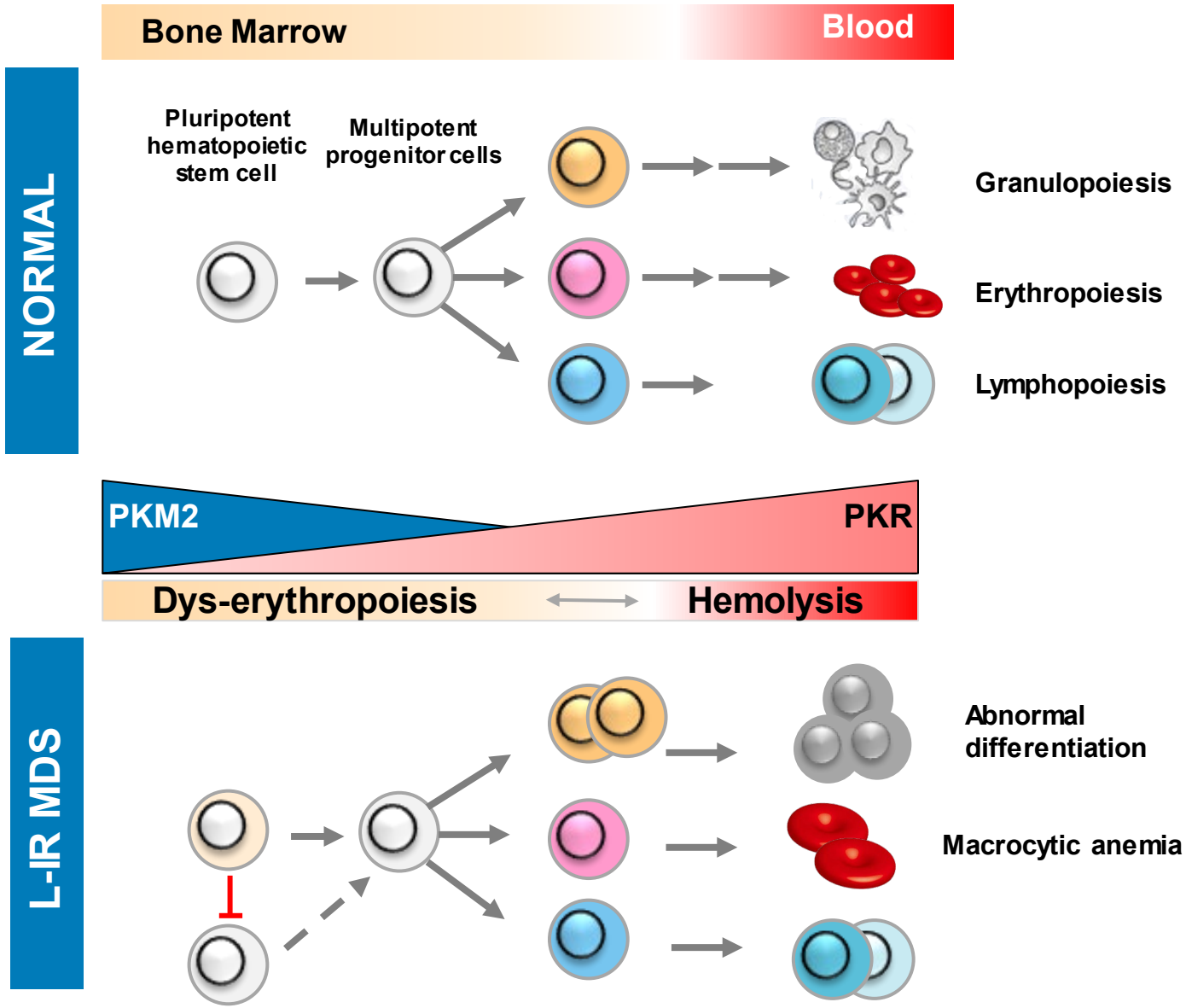
- PKM2 expression and activation observed in brain
- PKM2 substantially reduces disease score in preventative and therapeutic EAE models

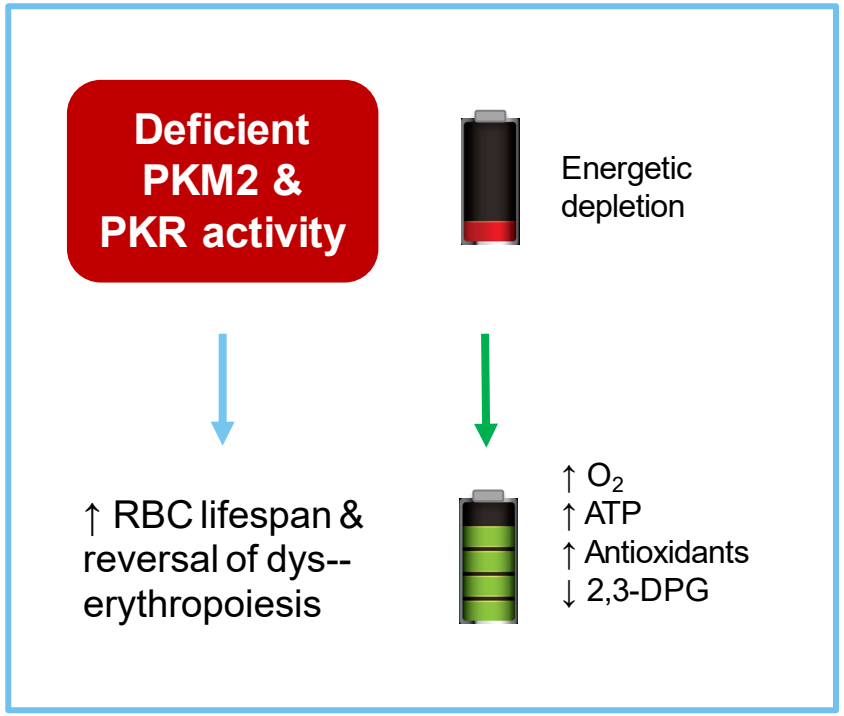
PKM2 activation programs: Progress to IND

PROGRESS

- Immunohistochemistry and PKM2 activity assays, together with *in vitro* and *in vivo* disease models have identified several compelling indications. Of those indications, renal and CNS indications are the most mature.
- One DC selected and additional potential DCs with brain penetrance in late lead optimization.

PK activation: Opportunity in low to intermediate risk (L-IR) myelodysplastic syndrome (MDS)

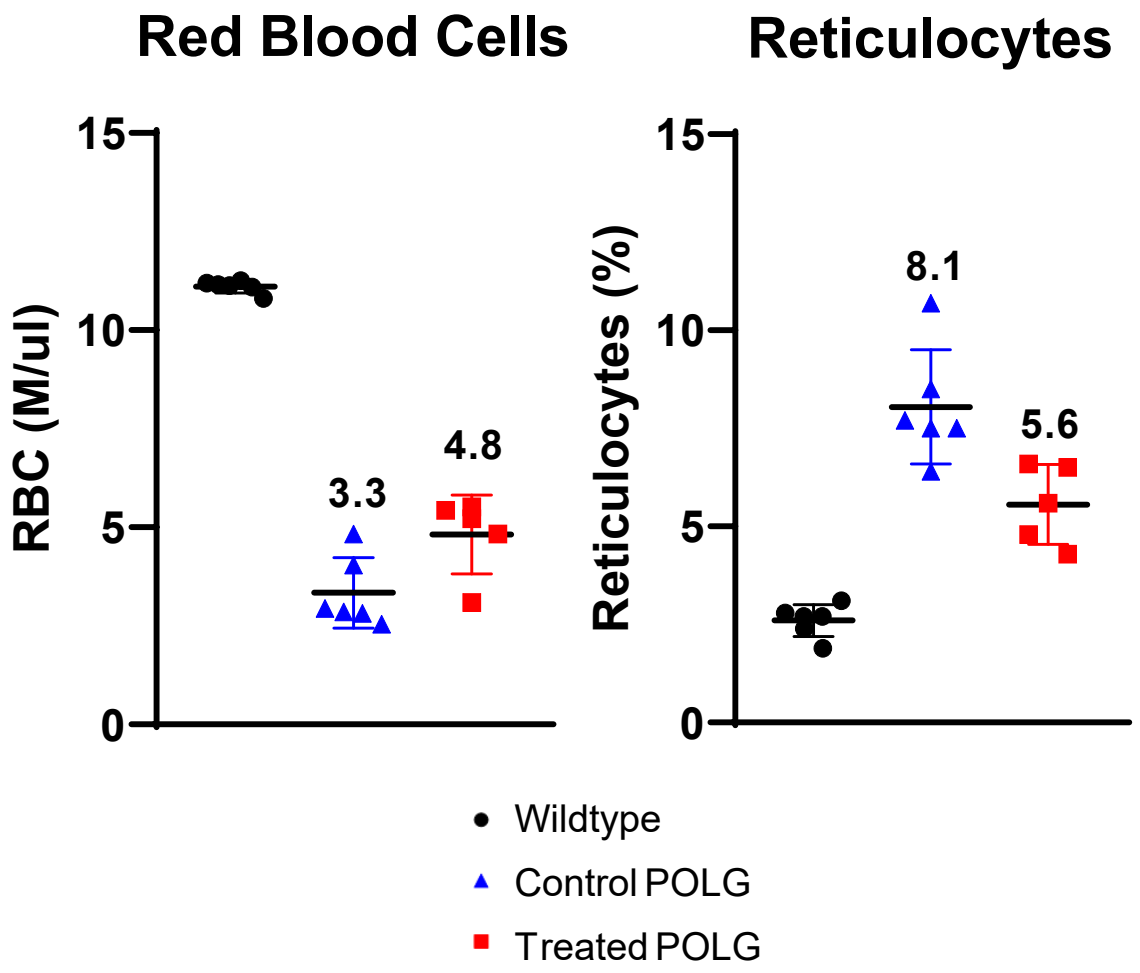




In a pilot mouse model of severe MDS anemia, PK activator partially reverses the disease phenotype

Preliminary animal modeling data with MDS mice

- Underpinning the PK treatment hypothesis in MDS is abundant literature documenting deficient PK activity in MDS erythrocytes*
- Untreated $Polg^{D257A}$ mice have severely decreased hemoglobin at 6.5 months of age
- After 18 weeks of treatment, mice show a ~2g/dL increase in hemoglobin
- Commensurate with increased hemoglobin is a marked decrease in reticulocyte count



Source: Agios-directed research

Sources: Biovin P et al. Pathol Biol 1970; 18(3): 175; Valentine WN et al. Blood 1973; 41(6): 857; Boivin P et al. British J Haematol 1975; 31(4): 531; Arnold H et al. Clinica Chimica Acta 1974; 57: 187, Lin G et al. Chin J Hematol 1997; 18(7): 350

MDS: Progress to clinical development

PROGRESS

- Nonclinical *in vitro* biochemical and *in vivo* disease modeling supports indication expansion with AG-946
- AG-946 advancing to Phase 2 clinical development in L-IR MDS in 2022

Key takeaways

01 Our expertise in cellular metabolism is unmatched

02 BCAT2 inhibitors and PK activators have the potential to create pipelines-within-a-mechanism

03 PAH stabilization provides a potentially unique and effective mechanism for the treatment of phenylketonuric patients

04 Our approach to treating genetically defined diseases enables us to address monogenic and polygenic conditions, and disease adjacencies

05 Based on the breadth and depth of our pipeline, we are confident we can deliver a sustained level of productivity

KOL Perspective:
Unmet Need in MDS

Dr. Hanny Al-Samkari
Mass General Hospital
Harvard Medical School

MDS background

Myelodysplastic syndromes (MDS) are a heterogeneous group of rare hematological malignancies characterized by dysfunctional hematopoiesis, progressive cytopenia and an increased risk of progression to acute myeloid leukemia (AML):

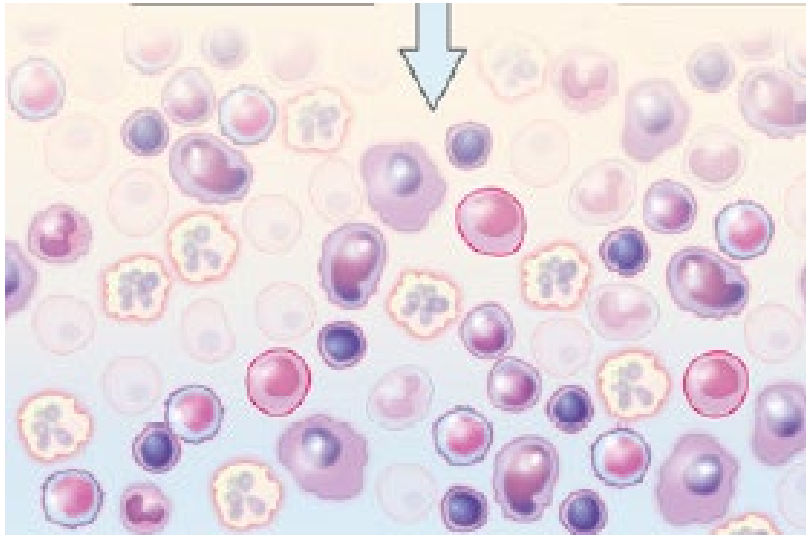
- Isolated or multiple cytopenias of red blood cells (anemia), leukocytes (neutropenia), and/or platelets (thrombocytopenia) in the periphery,
- Clonal hematopoiesis leading to abnormal cellular maturation in the bone marrow, and
- Heterogeneous genetic abnormalities.

Diagnosis typically established via routine exam based on unexplained persistent cytopenia(s) requiring bone marrow biopsy and may be delayed by years from 1st abnormal heme laboratory exam

- Cytogenetic testing is needed for diagnosis
- Awareness for molecular testing is increasing

Heterogeneous clinical presentation, patients are at risk for symptomatic anemia, infection, and bleeding, with variable rates of transformation to AML

- Fatigue is a predominant symptom
- Disease can be more or less aggressive depending on IPSS classification
- Low risk MDS rarely progresses to AML
- Other complications depend on comorbidities
- Inability to tolerate intensive treatments



MDS or CCUS

Clonal hematopoiesis progressively expands and becomes dominant in the bone marrow.

A small **subclone** carries a co-mutation favoring proliferation and abrogating differentiation.

Lewis et al. Cancer Management and Research 2021:13 645–657

Epidemiology[1]

MDS occurs most commonly in older adults

- Median age ~70 years
- Additional co-morbidities and frailty in older population
- U.S.: Medicare/Medicaid population

Incidence is increasing with age[2]

- Age 50 - 59 = 5 cases/100K/yr;
- Age 60 - 69 = 9.3/100K/yr;
- Age 70 - 79 = 30.2/100K/yr;
- > 80 years = 59.8/100K/yr.

Male patients have higher incidence rate and significant survival disadvantage vs female patients across subtypes

- Exception: MDS with isolated del(5q) is more common in women

[1] Surveillance, Epidemiology and End Results (SEER) Program
[2] Noone et al. 2018.

Diagnosis and risk stratification

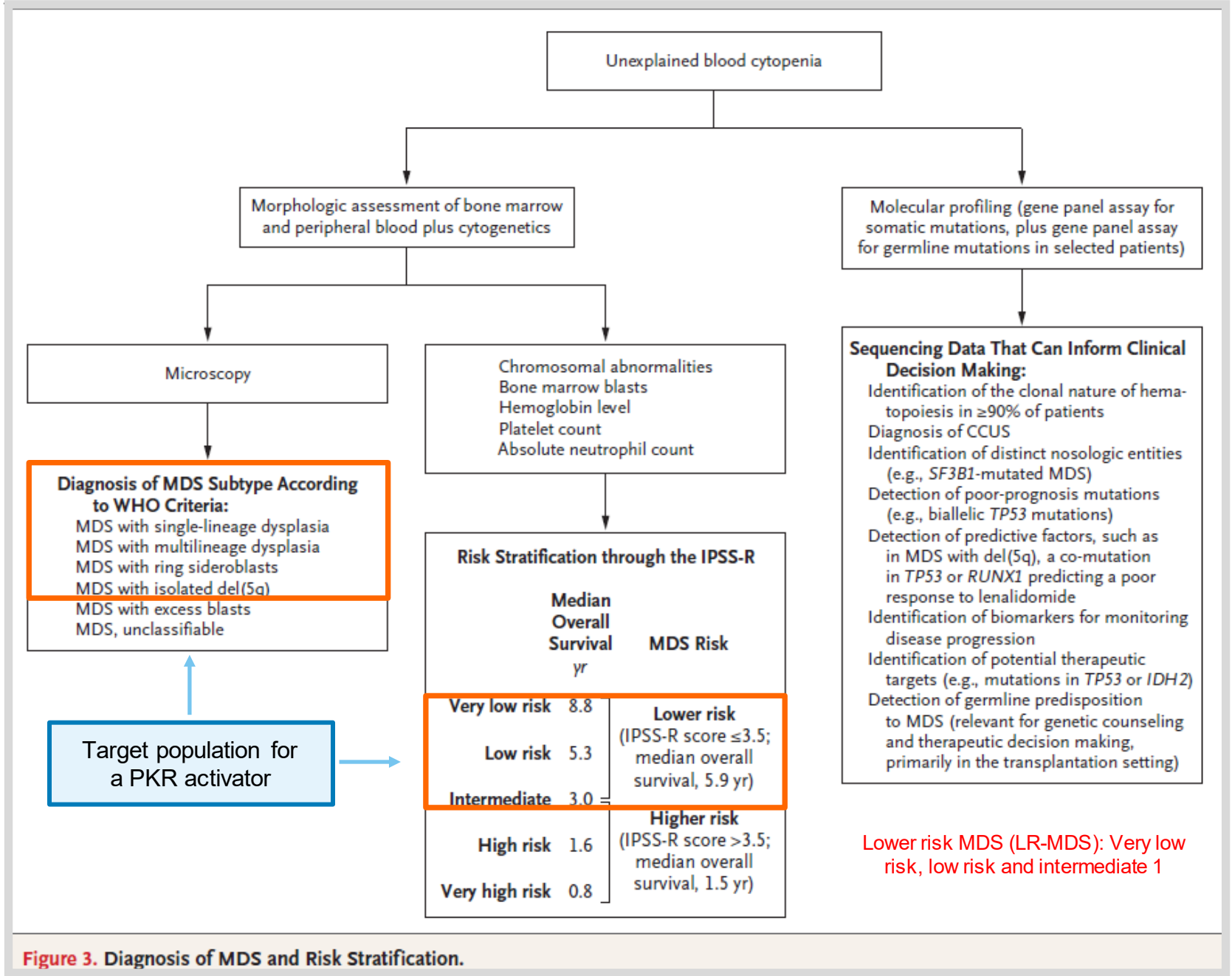
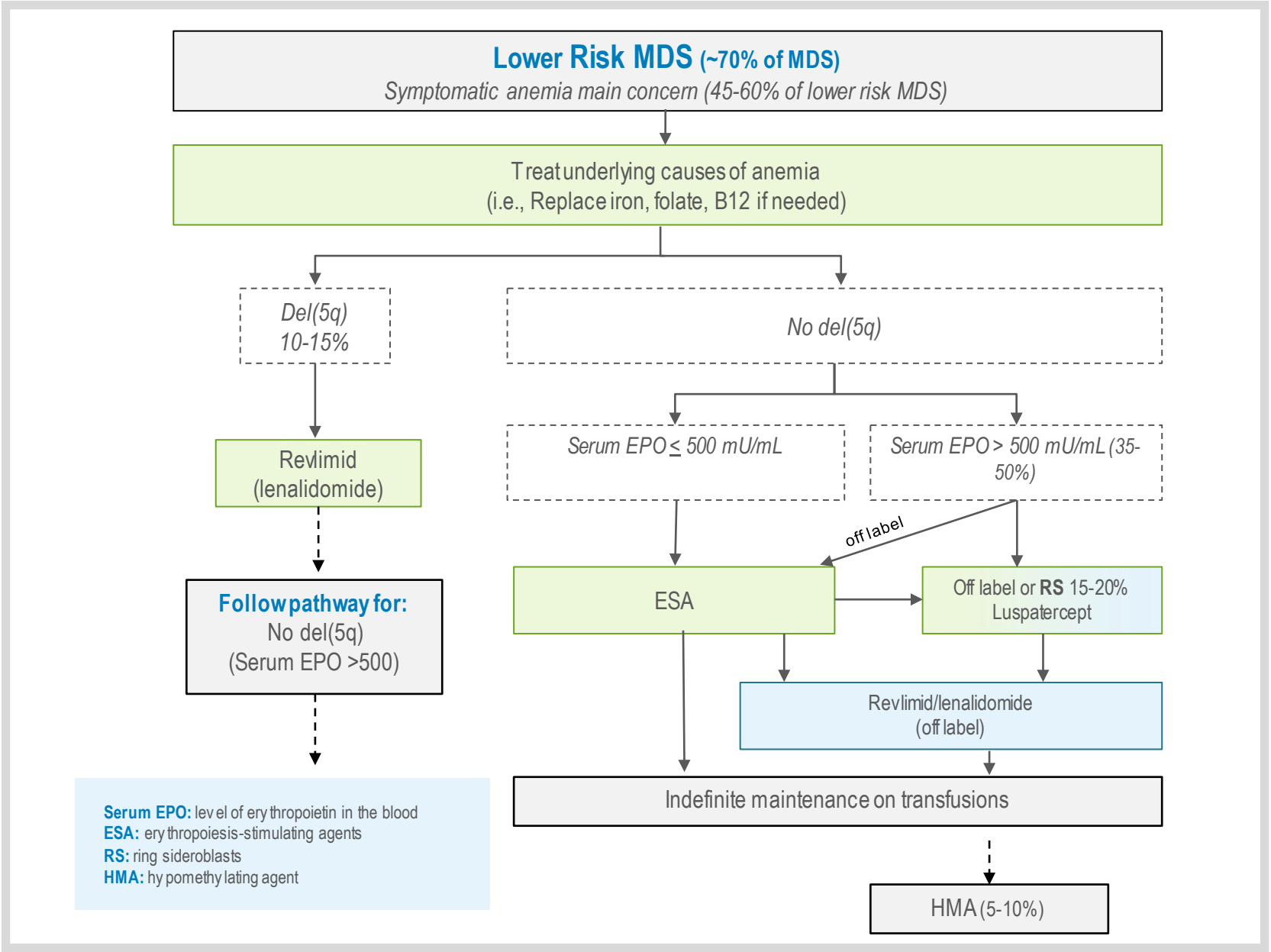


Figure 3. Diagnosis of MDS and Risk Stratification.

Lower risk MDS (LR-MDS): Very low risk, low risk and intermediate 1

Cazzola M, Myelodysplastic Syndromes, NEJM, 1 Oct 2020

Lower risk MDS: Treatment flow



Key takeaways

- The most common type of MDS is low to intermediate risk (L-IR), but many existing therapies or therapies under development focus on high risk MDS
- Current treatment options for L-IR MDS often require in-office visits and transfusions and/or are only approved in a subset of patients
- There is significant unmet need for convenient, effective therapies for L-IR MDS

PK Activator Clinical Programs: Expansion and Momentum

Dr. Sarah Gheuens, Chief Medical Officer

What you'll hear today

01 We are the pioneering leaders in PK activation

02 We are expanding our clinical PK activation pipeline with plans to initiate a POC study of novel PK activator AG-946 in low to intermediate risk MDS-associated anemia

03 We are differentiated in our approach to thalassemia and SCD through global clinical development and patient/physician partnerships

04 We are poised to impact the full spectrum of patients with PK deficiency, thalassemia, and sickle cell disease – regardless of transfusion status or disease subtype – including pediatrics

We are the pioneering leaders in PK activation

STUDYING PK ACTIVATION IN THE CLINIC SINCE 2014

PIVOTAL CLINICAL PROGRAMS

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

PUBLICATIONS

DISEASES WITH POC ACHIEVED

- PK Deficiency
- Thalassemia
- Sickle Cell Disease

+ A LOT OF FIRSTS:

- 1st GLOBAL PK DEFICIENCY REGISTRY
- 1st INTERNATIONAL PK DEFICIENCY ADVOCACY COUNCIL
- 1st HEMOLYTIC ANEMIA ADVOCACY COALITION BUILDING
- 1st POSITIVE PHASE 3 READOUT IN PK DEFICIENCY
- 1st CLINICAL TRIAL EVALUATING TREATMENT IN α-THALASSEMIA

Our approach to clinical development is highly differentiated

Global Reach

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

Site selection focused on going where the patients are

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

Top-notch Team

Broad industry experience throughout all levels of the clinical organization

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

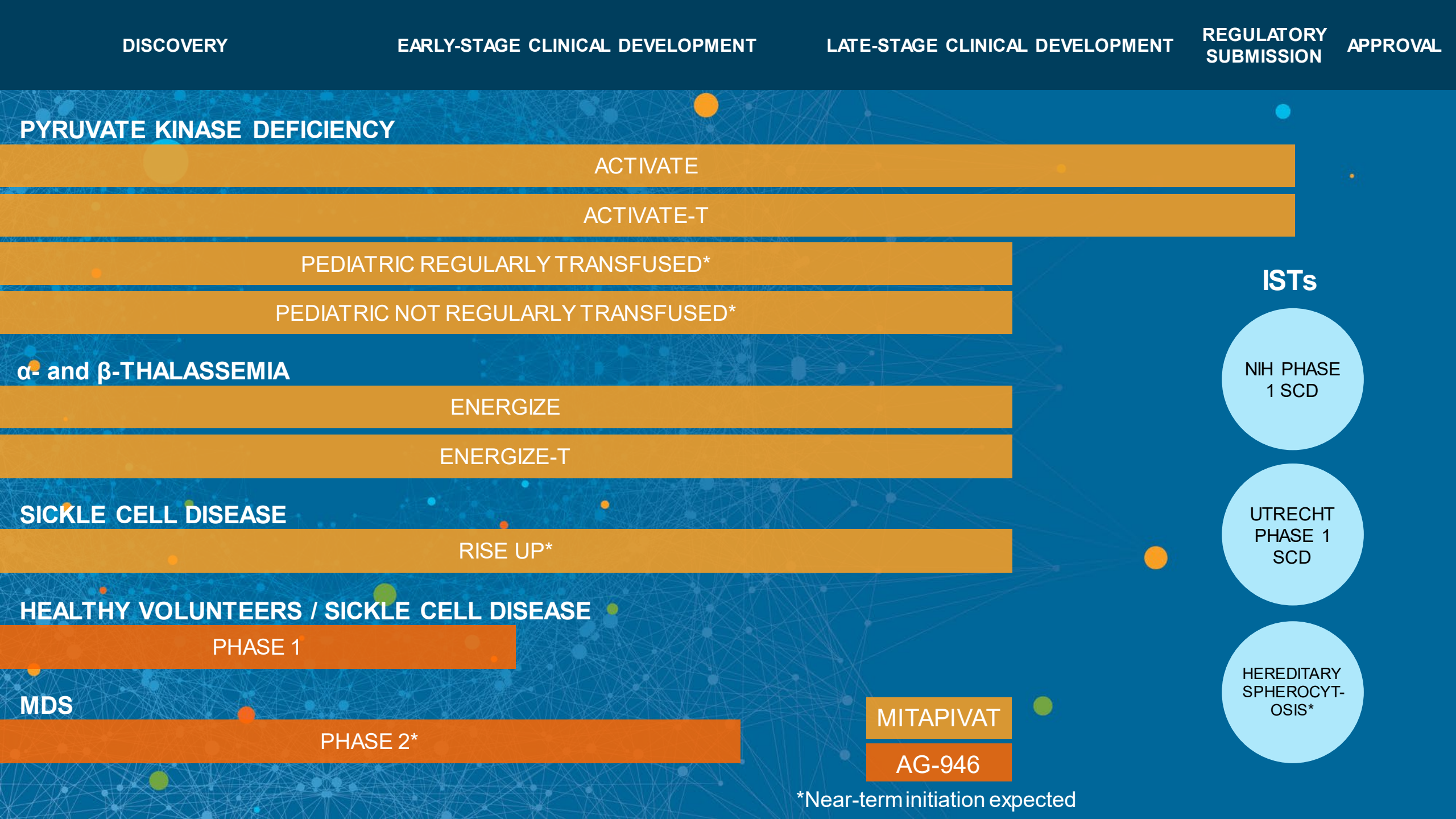
Where science meets heart

Extensive Network

Focus on fostering meaningful connections with the patient community

Strong ties to top KOLs across all disease states

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

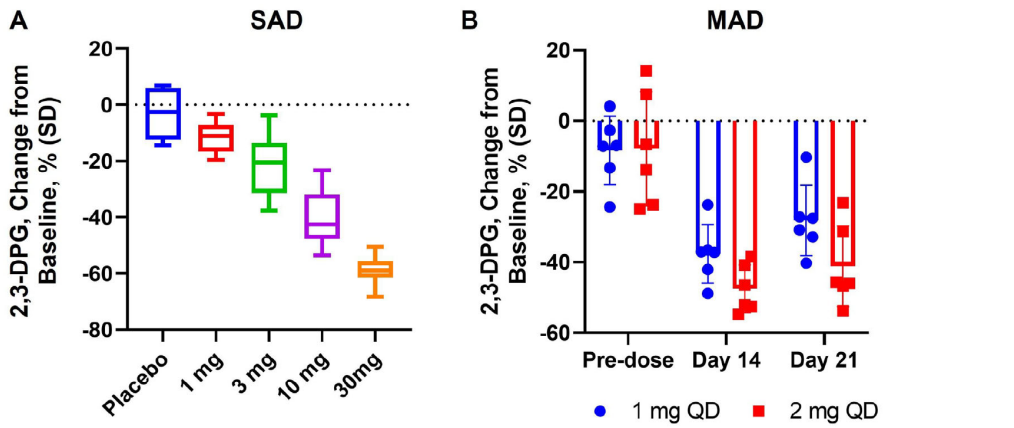

DISCOVERY
EARLY-STAGE CLINICAL DEVELOPMENT
LATE-STAGE CLINICAL DEVELOPMENT
REGULATORY SUBMISSION
APPROVAL
PYRUVATE KINASE DEFICIENCY
ACTIVATE
ACTIVATE-T
PEDIATRIC REGULARLY TRANSFUSED*
PEDIATRIC NOT REGULARLY TRANSFUSED*
α- and β-THALASSEMIA
ENERGIZE
ENERGIZE-T
SICKLE CELL DISEASE
RISE UP*
HEALTHY VOLUNTEERS / SICKLE CELL DISEASE
PHASE 1
MDS
PHASE 2*
MITAPIVAT
AG-946
ISTs
NIH PHASE 1 SCD
UTRECHT PHASE 1 SCD
HEREDITARY SPHEROCYT-OSIS*
*Near-term initiation expected

AG-946 – a novel PK activator – creates optionality for clinical expansion of PK activation

- First clinical data from SAD and MAD cohorts of the Phase 1 study of healthy volunteers to be presented at ASH
  - Well tolerated following single dose administrations up to 30 mg and multiple 14-day dosing with 1 mg QD and 2 mg QD
  - PK profile supports once-daily dosing
  - Sustained dose-dependent increases in ATP and decreases in 2,3-DPG

2,3-DPG

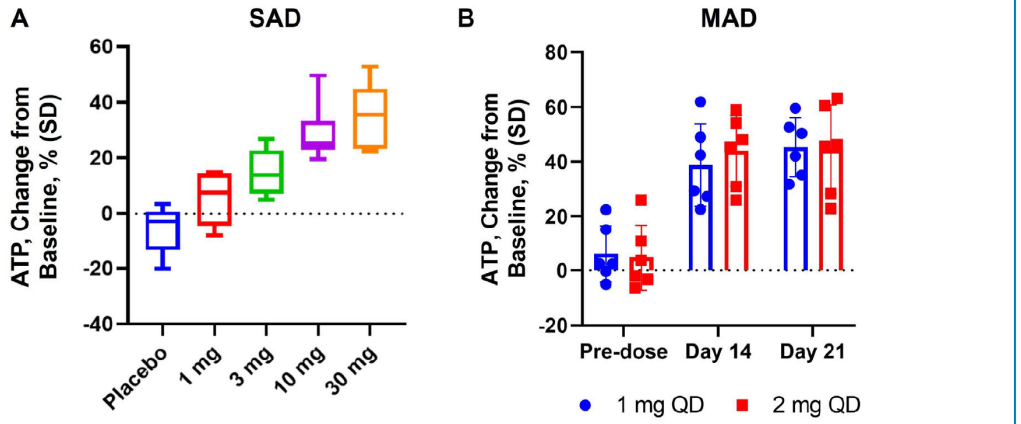
Figure 1. Change from baseline in 2,3-DPG concentration following (A) single dosing and (B) multiple dosing of AG-946



2,3-DPG = 2,3-diphosphoglycerate; MAD = multiple ascending oral doses; QD = once daily; SAD = single ascending oral doses.

ATP

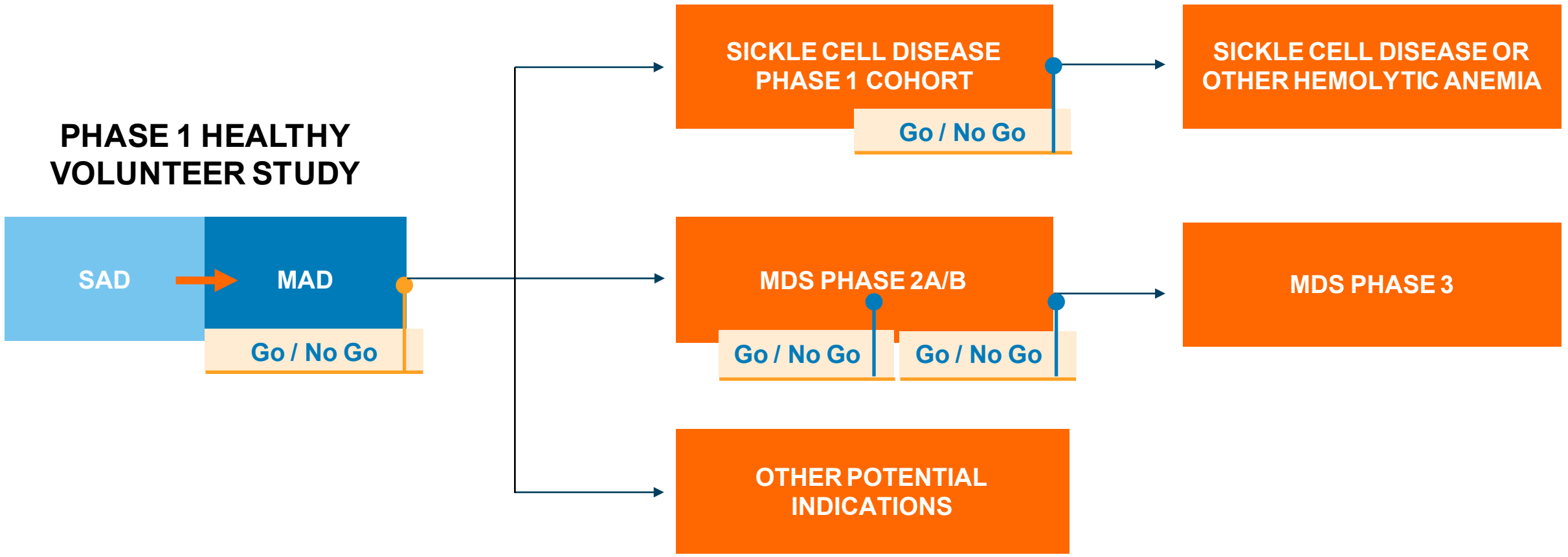
Figure 2. Change from baseline in ATP concentration following (A) single dosing and (B) multiple dosing of AG-946



ATP = adenosine triphosphate; MAD = multiple ascending oral doses; QD = once daily; SAD = single ascending oral doses.

Source: ASH 2021 abstracts

Ability to pursue multiple clinical paths in parallel if data support advancement



Therapeutic rationale for a PK activator in L-IR MDS

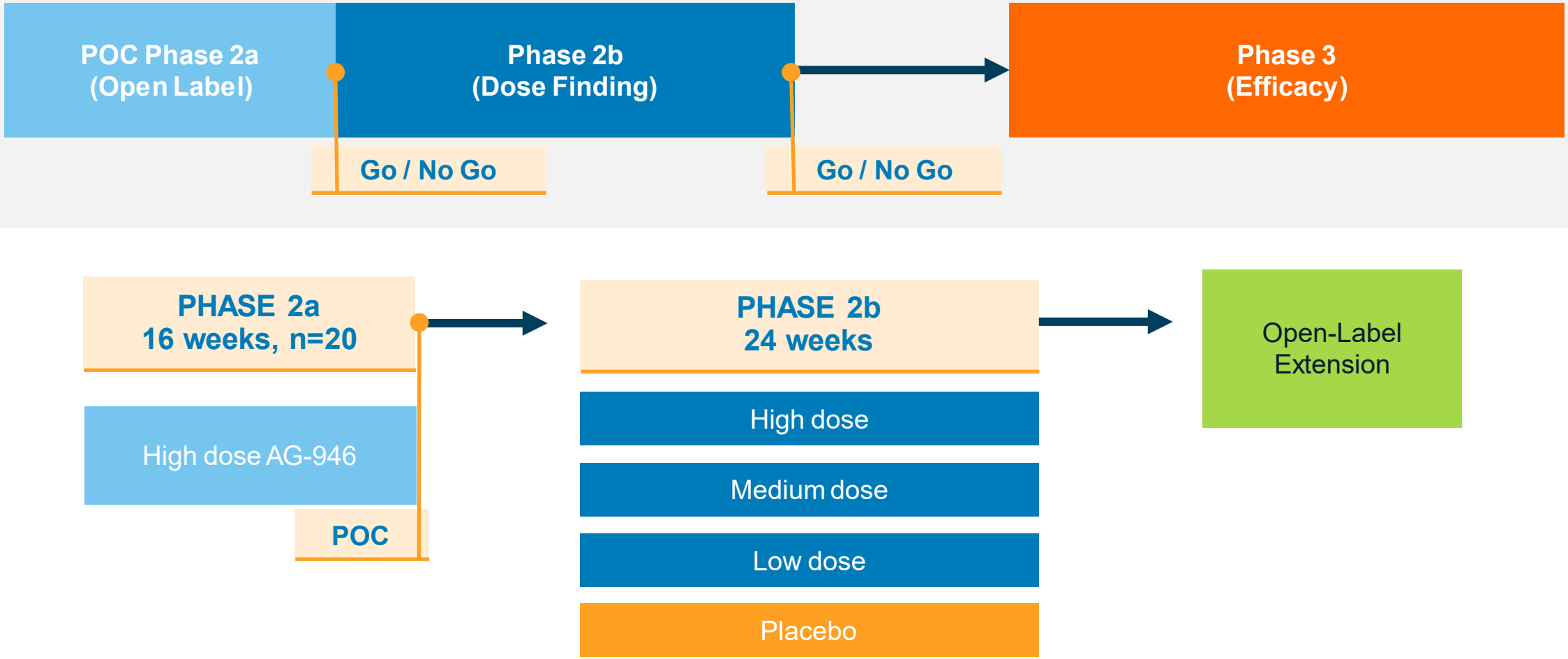
Evidence of the multivariate effects of PKR activator on ineffective erythropoiesis that can be expected to translate to L-IR MDS

- Features of ineffective erythropoiesis are similar between thalassemia and MDS
- PKR activator can improve survival and differentiation of erythroid cells in the bone marrow
- PKR activator improves RBC functionality via increasing energy ATP, nucleotide biosynthesis, and antioxidative-stress responses via activating glycolysis

Acquired PK deficiency has been observed in MDS, suggesting that PKR may play a key role in MDS-associated anemia

- Strong clinical validation that activating PKR is beneficial when PKR is insufficient
- Therefore, PKR (re)activation could be a validated therapeutic approach in certain sub-populations

AG-946 MDS clinical development plan: Seamless Phase 2a proof-of-concept + Phase 2b



POC Phase 2a to be initiated in 2H 2022

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

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

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

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

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

Thalassemia poses significant impacts on patients' lives

Both α- and β-thalassemia patients experience debilitating chronic symptoms and serious complications regardless of transfusion status

Anemia and fatigue

Transfusion burden

Risk of organ damage and infection

Pain and fractures

Economic burden and inconvenience

Thalassemia represents a significant opportunity to make a global impact

GLOBAL REACH

Estimated 18–23K α- and β-thalassemia patients across the U.S. & 5EU

Significant opportunity outside of U.S./EU

UNMET MEDICAL NEED

No approved therapies for α-thalassemia

Limited options in β-thalassemia

NTD and α-thalassemia not well understood

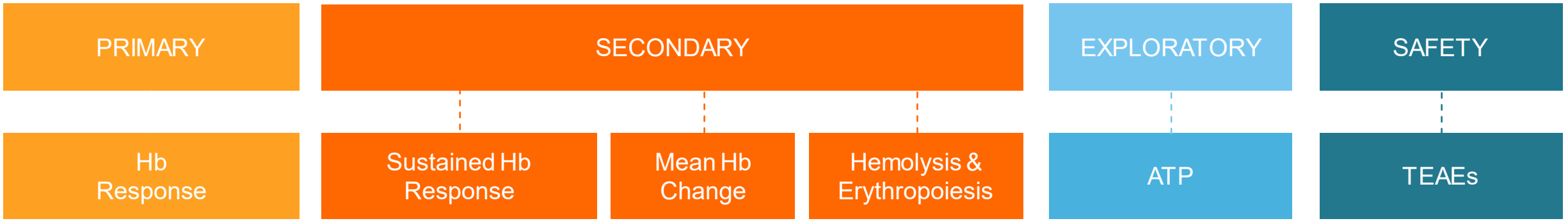
CRITICAL SUCCESS FACTORS

Evaluating mitapivat across full spectrum of disease

Global approach to clinical development

Building connections with thalassemia patient and physician communities

Mitapivat in non–transfusion-dependent α- and β-thalassemia: *Summary of Phase 2 study results*



EXTENSION DATA AT ASH

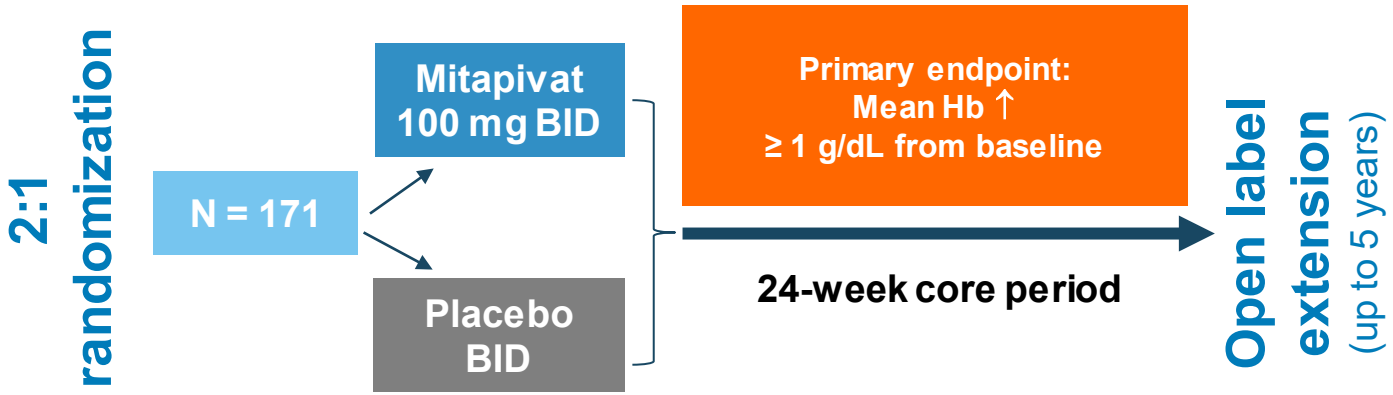
Long-term extension data (median 70.9 weeks of treatment) showed sustained improvements in Hb, hemolysis and ineffective erythropoiesis and no new safety findings.

ATP = adenosine triphosphate; Hb = hemoglobin; LDH = lactate dehydrogenase; MoA = mechanism of action; PK = pyruvate kinase; PKR = PK in RBCs; TEAE = treatment-emergent adverse event.

Kuo KHM et al. *EHA 2021*: Abstract #S267.

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

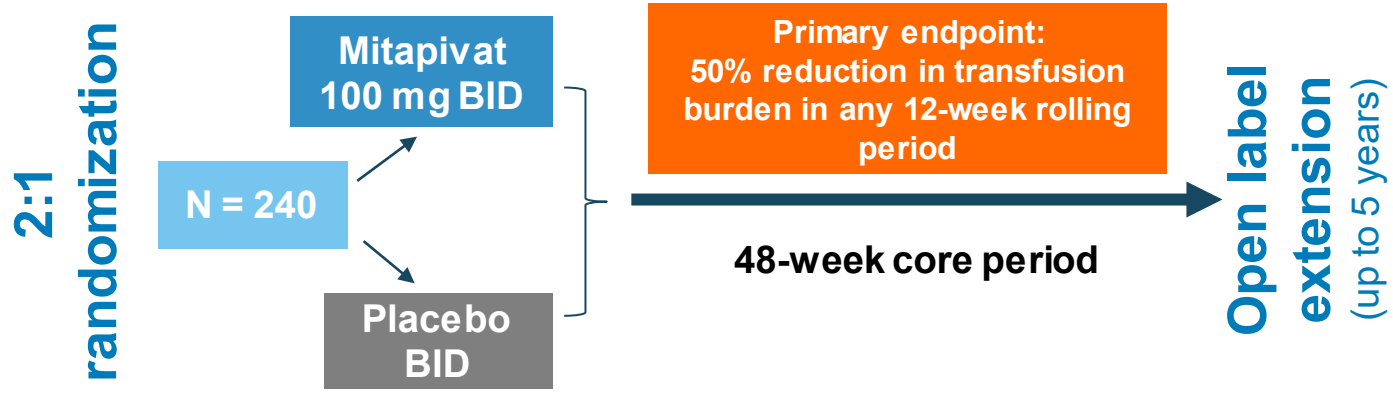
ENERGIZE



Key inclusion criteria

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

ENERGIZE-T



Key inclusion criteria

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

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

Key features of the ENERGIZE and ENERGIZE-T studies

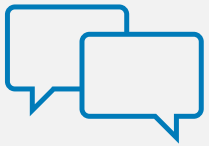
ENERGIZE ENERGIZE-T

Enrollment criteria

- Inclusion of α- and β-thalassemia patients
- Inclusion of non-regularly and regularly transfused patients

Study endpoints

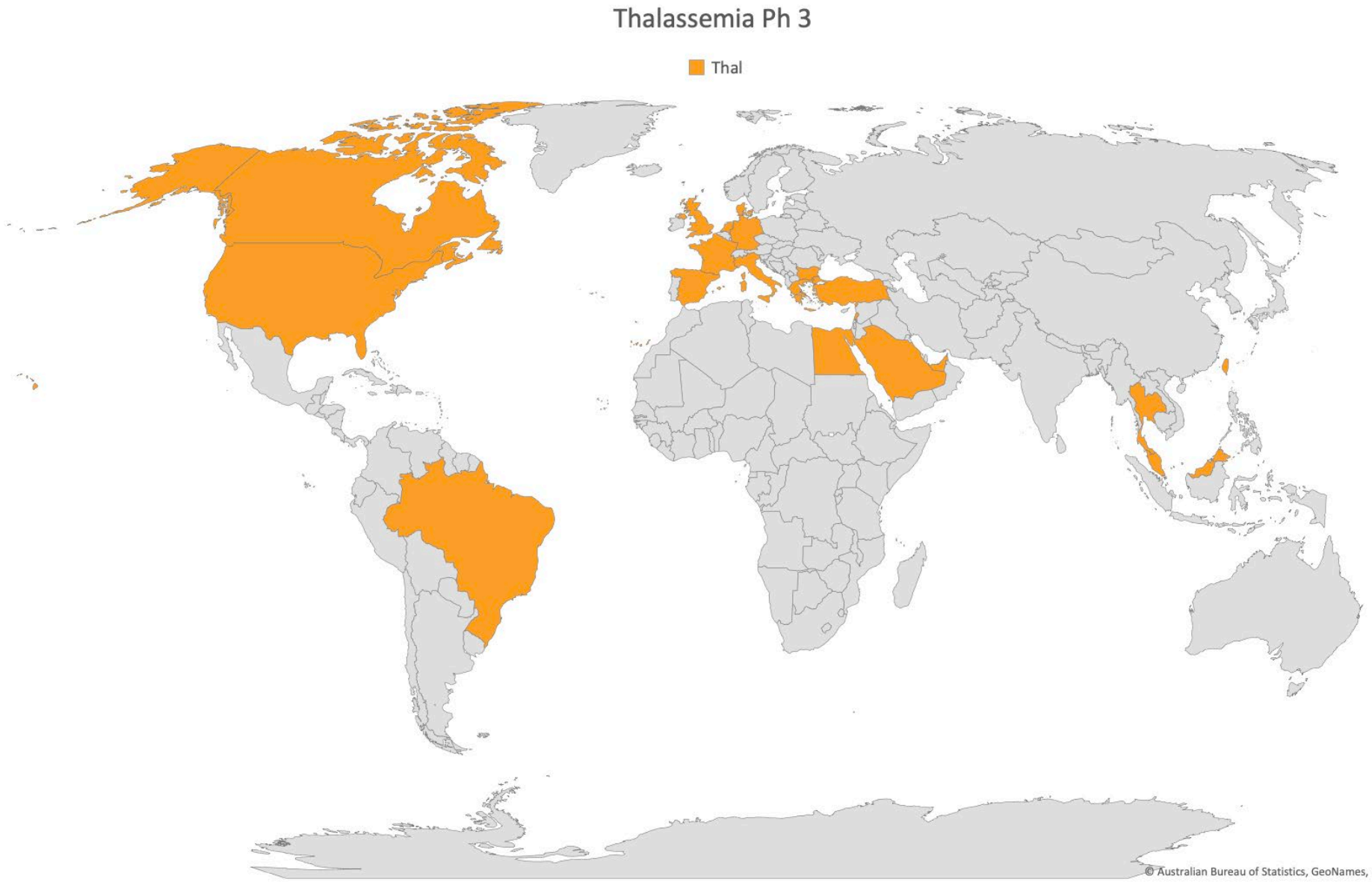
- Relevant to show benefit across the entire patient population
- Inclusion of patient-reported outcome measures in the study



Visits and assessments

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

We are leading the way in global site engagement



Significant lifelong impact of sickle cell disease on patients

50%

Patients have at least 1 VOC per year

<10 g/dL

Hb level of almost all patients

~30%

Patients are regularly transfused

~30 years

Shortened life expectancy

53%

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

Our approach in sickle cell disease sets us apart

GLOBAL REACH

Estimated 120-135K patients across the U.S. & 5EU

Significant opportunity outside of U.S./EU

UNMET MEDICAL NEED

No approved therapy addresses both pain episodes and anemia

Need for innovative therapies with convenient, oral administration

CRITICAL SUCCESS FACTORS

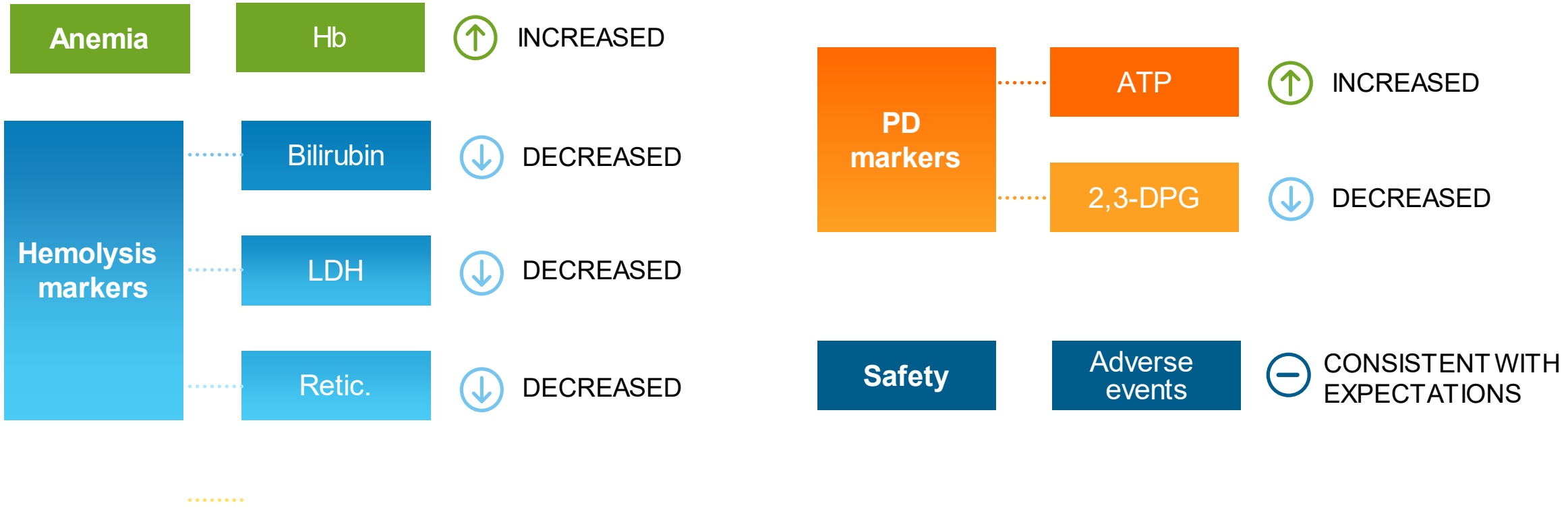
Innovative seamless Phase 2/3 trial developed with community input reduces enrollment barriers & addresses key aspects of disease

Global approach to clinical development

Building connections with SCD patient and physician communities

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

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



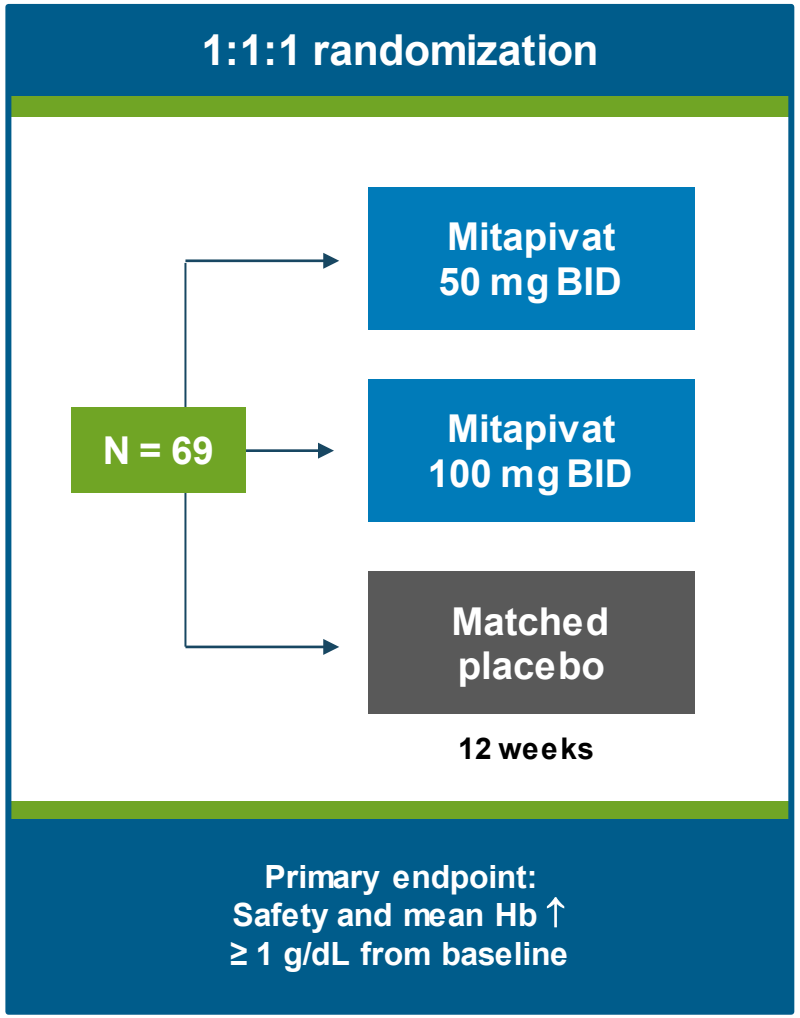
Xu JS et al. *42nd ASH Annual Congress 2020*: Abstract #681; Data on File; Agios Pharmaceuticals Press Release; Dec 07, 2020.
ATP = adenosine triphosphate; BID = twice daily; DPG = diphosphoglycerate; Hb = hemoglobin; Hb SS = sickle cell anemia.

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

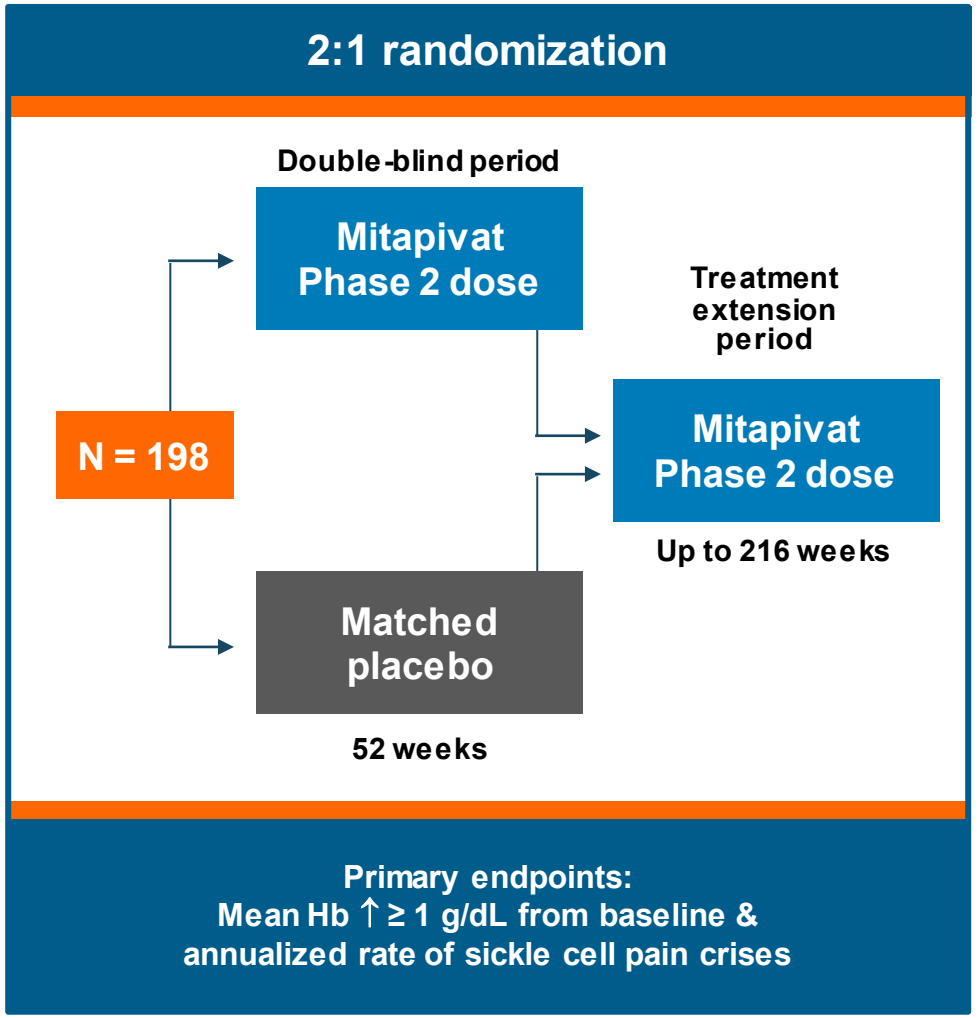
ENROLLMENT CRITERIA

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

PHASE 2



PHASE 3



BID = twice daily; Hb = hemoglobin

Input from sickle cell community helped to shape and validate this study design

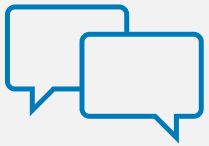
RISE UP

Enrollment criteria

- The **lower Hb limit of 5.5 g/dL** will broaden access to the study
- Allowing **concomitant use of hydroxyurea** and occasional transfusions will reduce barriers to study eligibility
- **Broad definitions** of pain events and episodic transfusions will also help reduce barriers to entry

Study endpoints

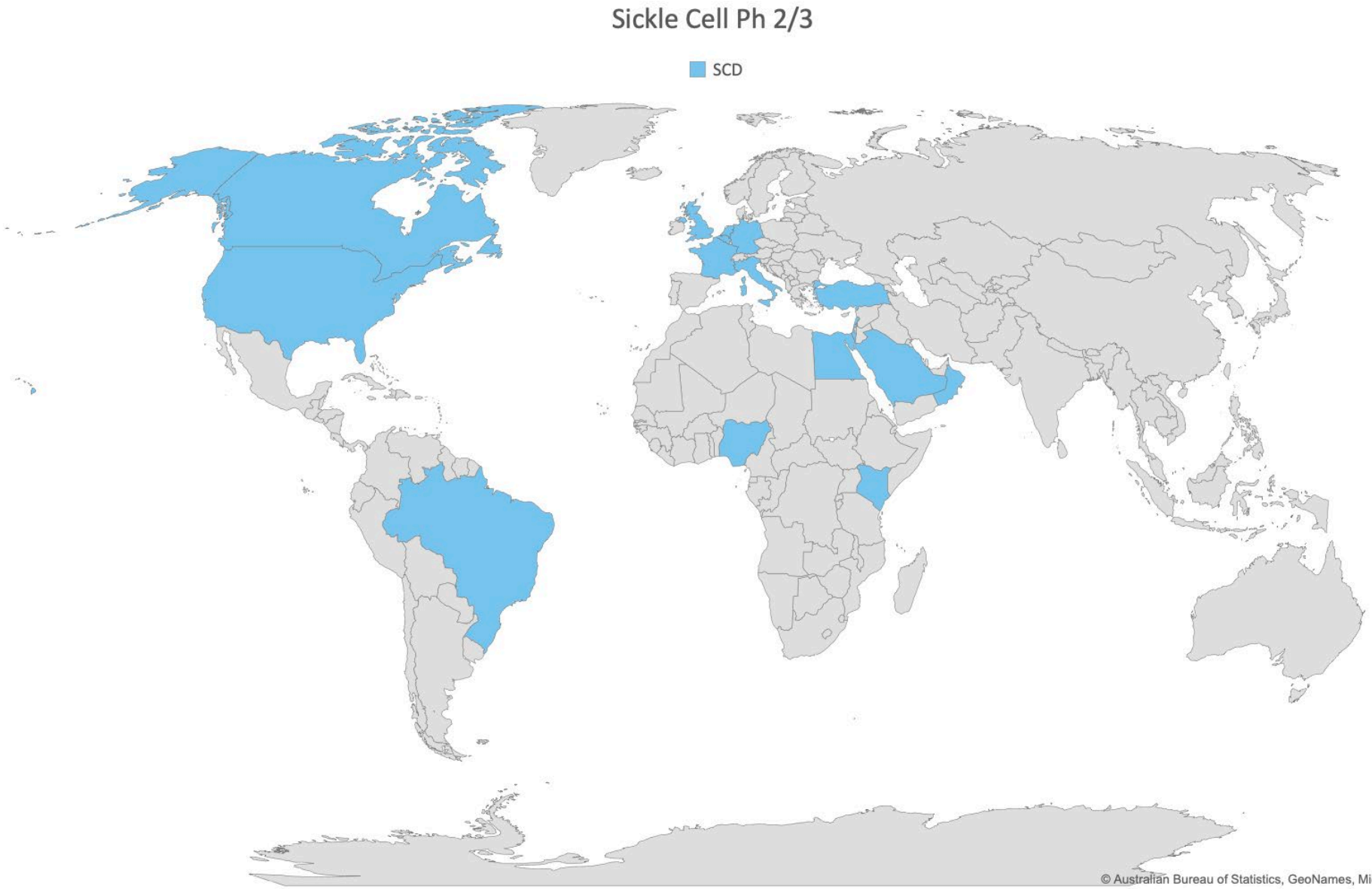
- Broad consensus from the SCD warriors who inputted, that **pain and Hb** are the two most important endpoints for them
- Inclusion of **patient-reported outcome** measures in the study was highlighted as important by the community



Visits and assessments

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

We are differentiated by our global approach to clinical development



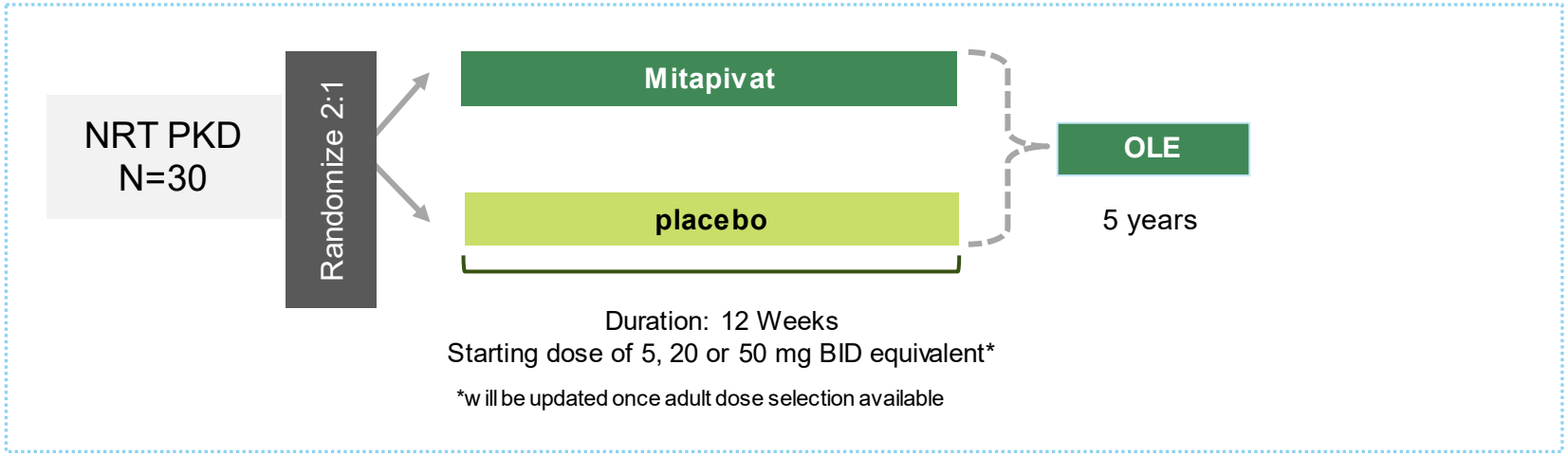
Data from pivotal program support mitapivat's potential to treat the full range of PK deficiency patients

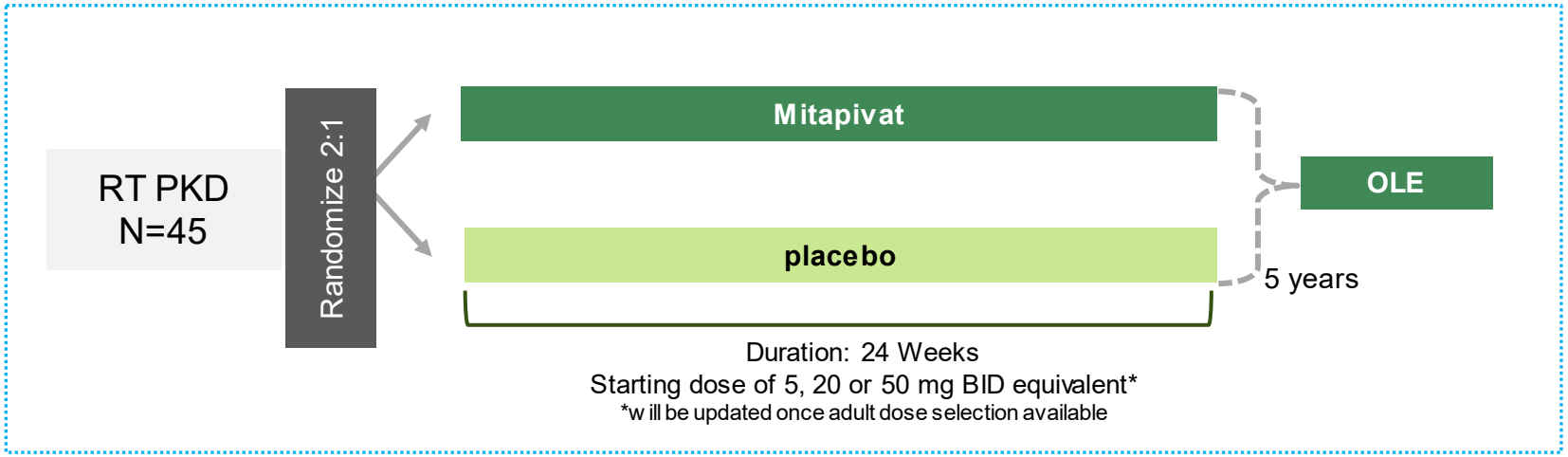
ACTIVATE ACTIVATE-T

- **Broad spectrum of PK deficiency patients participated in both studies**
- **Primary and secondary efficacy endpoints achieved across both studies**
- **Safety profile** was generally **consistent** with previously reported data across both studies
- **LTE data reinforce patient impact**:
  - Patients who were randomized to placebo in ACTIVATE showed similar improvements in hemoglobin levels after switching to mitapivat, and both cohorts demonstrated sustained hemoglobin response
  - A similar percentage of patients achieved a transfusion response in ACTIVATE-T and LTE, and reduction in transfusion burden was maintained over time

FDA and EMA regulatory filings accepted
Mitapivat received U.S. Priority Review; PDUFA date February 17, 2022

Pediatric PK deficiency clinical program expected to begin in 2022





Eligibility:

- Mean Hb concentration of ≤10 g/dL for patients 12 to <18 years or ≤9 g/dL for patients 1 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

Don’t miss out on our significant updates across all clinical programs at ASH 2021!

Oral Presentations

- PK deficiency long-term extension study: Hemoglobin response and reduction in transfusion burden are maintained over time
- Thalassemia long-term extension study: Sustained improvements in hemoglobin, hemolysis, and ineffective erythropoiesis; favorable long-term safety profile
- Complete NIH Phase 1 SCD data: Strong safety profile; improvements in anemia, hemolysis, oxygen affinity, and hemoglobin S polymerization kinetics
- Mitapivat improves ineffective erythropoiesis and reduces iron overload in patients with pyruvate kinase deficiency

Select Poster Presentations

- AG-946 Phase 1 healthy volunteer study: First data show dose-dependent changes in ATP and 2,3-DPG
- University of Utrecht Phase 2 SCD study (ESTIMATE): First data show promising efficacy with improved point of sickling, increased hemoglobin, decrease in markers of hemolysis
- Bone mineral density remains stable in pyruvate kinase deficiency patients receiving long-term treatment with mitapivat

Key takeaways

01 We are the pioneering leaders in PK activation

02 We are expanding our clinical PK activation pipeline with plans to initiate a POC study of novel PK activator AG-946 in L-IR MDS-associated anemia

03 We are differentiated in our approach to thalassemia and sickle cell disease through global clinical development and patient/physician partnerships

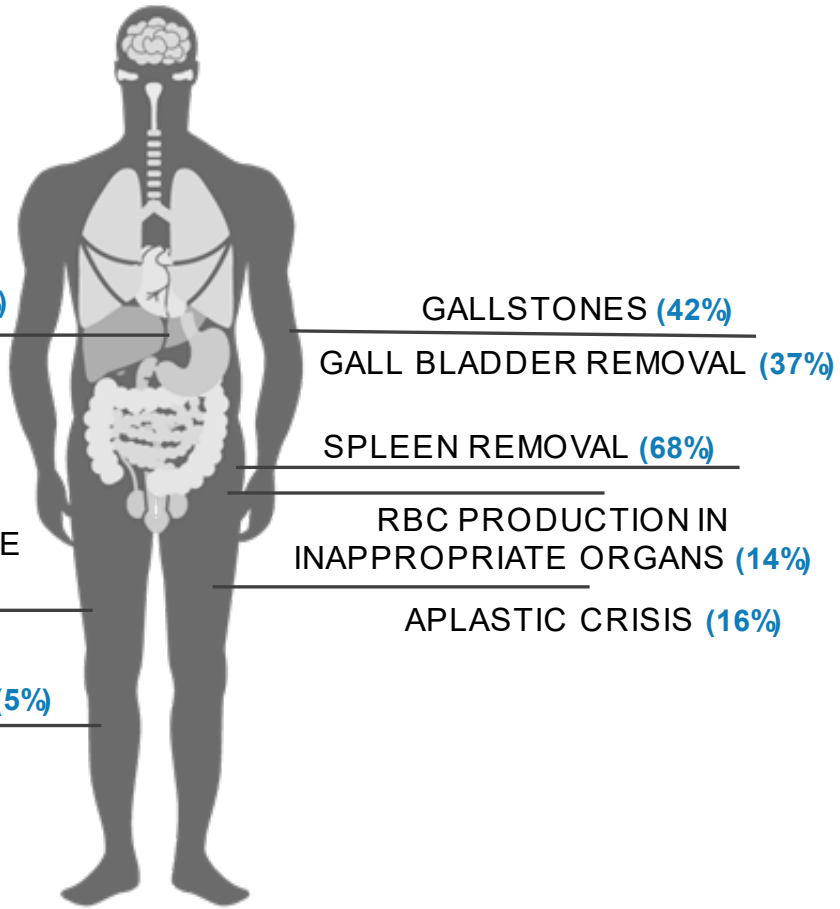
04 We are poised to impact the full spectrum of patients with PK deficiency, thalassemia, and sickle cell disease – regardless of transfusion status or disease subtype – including pediatrics

KOL Perspective:
Transforming Care in PK Deficiency

Dr. Hanny Al-Samkari
Mass General Hospital
Harvard Medical School

PK deficiency has long-term impact with risk of serious complications regardless of transfusion status

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 meeting 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

PK deficiency reduces life expectancy

- 18 patients with a physician-documented diagnosis of PK deficiency between January 1995 and July 2019 were selected from the U.S. Veterans Health Administration (VHA) database and were matched to 90 individuals from the general VHA population with no diagnosis of PK deficiency*
- The median follow-up period was 6 years for the PK deficiency population and 8 years for the non-PK deficiency cohort

Mortality Risk Among Patients in the VHA With PK Deficiency*

	PK Deficiency Cohort (n=18)	Non-PK Deficiency Cohort (n=90)
Median time until death	10.9 years	17.1 years
Observed deaths during follow-up period	50% (9/18)	31% (28/90)

Patients with PK deficiency from the VA study showed more deaths compared with matched controls

Patients in the non-PK deficiency cohort had a significantly longer time to death than the PK deficiency cohort (HR: 2.3; P=.0306)*

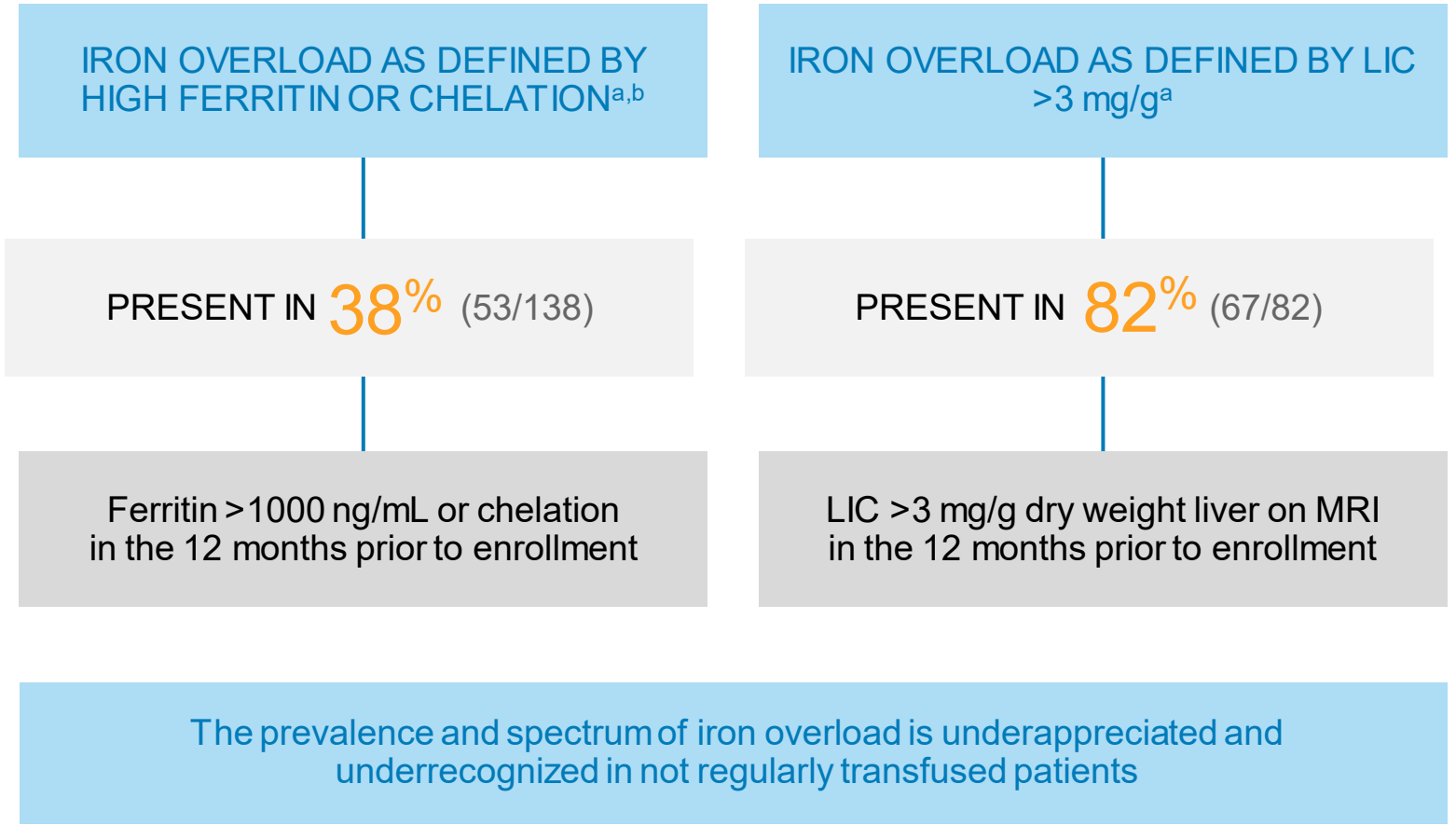
*Each patient in the PK deficiency cohort (n=18) was matched 1:5 by age at index, sex, and index year (+/–1 year) to patients from the general VHA population with no diagnosis codes related to PK deficiency (non-PK deficiency cohort, n=90).

The median age for both cohorts at index was 57 years and 94% of patients were male, 83%-85% were white.

Reference: Zagadailov E et al. Mortality among veterans with a diagnosis of pyruvate kinase (PK) deficiency: a real-world study using US Veterans Health Administration data. Abstract of paper to be presented at: 62nd ASH Annual Meeting and Exposition; December 5-8, 2020. Accessed November 5, 2020. https://ash.confex.com/ash/2020/webprogram/Paper136693.html

Not regularly transfused PK deficiency patients have a significant need for treatment to address disease symptoms and complications

- In the Pyruvate Kinase Deficiency Natural History Study, patients were defined as regularly transfused (≥6 transfusions) or not regularly transfused (<6 transfusions) in the 12 months prior to enrollment
- At enrollment, 82% (198/242) of patients were not receiving regular transfusions



LIC = liver iron concentration.

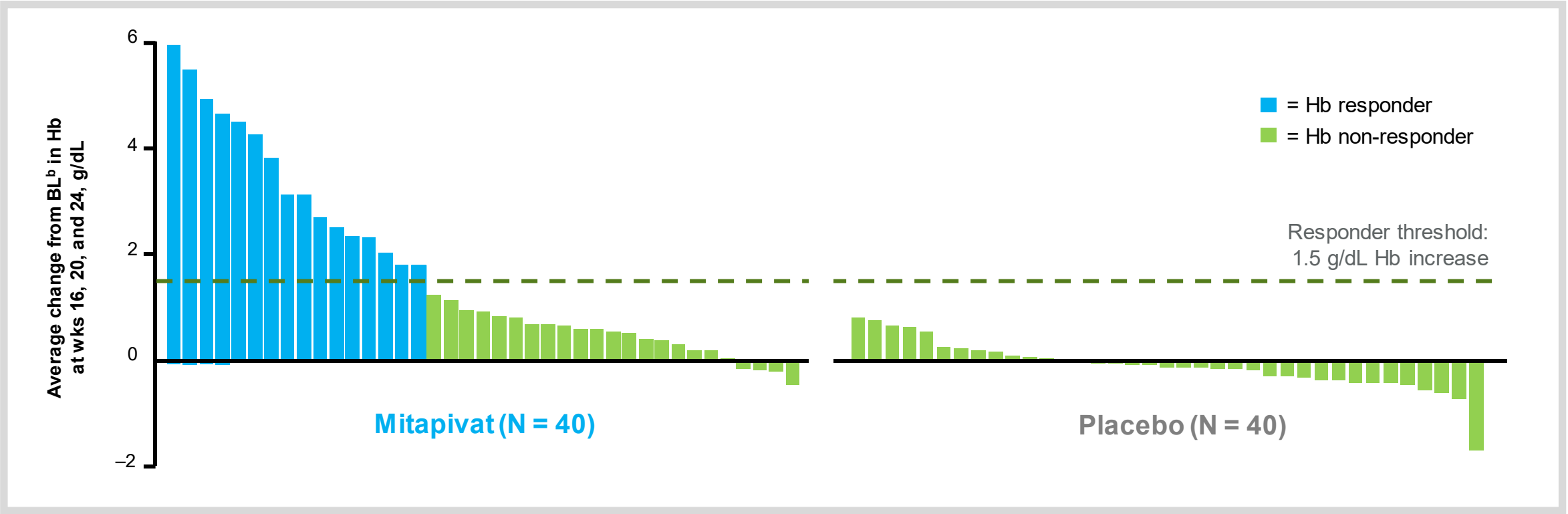
In the Pyruvate Kinase Deficiency Natural History Study, iron overload was conservatively defined as a maximum ferritin >1000 ng/mL or treatment with chelation therapy in the past 12 months.

[a]Chelation therapy may be indicated with ferritin >1000 ng/mL, liver iron concentration (LIC) >3 mg/g dry weight liver, and/or cardiac iron ≤20 ms. [b]Ferritin blood values may underestimate LIC.

van Beers et al. *Haematologica*. 2019;104(2):e51-e53.

Mitapivat has the potential to provide clinically meaningful impact across spectrum of PK deficiency patients as first disease-modifying therapy

	Mitapivat N = 40	Placebo N = 40	Difference[a] (95% CI)	2-sided p-value
Hemoglobin response n (%)	16 (40.0)	0 (0)	39.3 (24.1, 54.6)	< 0.0001



NB: Each bar represents an individual patient randomized to either mitapivat or placebo; summarized based on full analysis set (all patients who were randomized to treatment).

[a]Adjusted difference in response rate for primary endpoint; [b]BL is defined as the average of all screening assessments within 45 (42 + 3) days before randomization for subjects randomized and not dosed or before start of study treatment for subjects randomized and dosed.

BL = baseline; CI = confidence intervals; Hb = hemoglobin; wks = weeks.

Mitapivat is under clinical investigation and there is no guarantee it will receive health authority approval or become commercially available in any country for the uses being investigated

Source: EHA 2021

Mitapivat was well tolerated and adverse events were consistent with previously reported data

ACTIVATE

Patients, n (%)	Mitapivat N = 40	Placebo N = 39
Any TEAEs	35 (87.5)	35 (89.7)
Treatment-related TEAEs	23 (57.5)	14 (35.9)
Grade ≥ 3 TEAEs	10 (25.0)	5 (12.8)
Grade ≥ 3 treatment-related TEAEs	3 (7.5)	0
Serious TEAEs	4 (10.0)	2 (5.1)
TEAEs leading to dose reduction of study drug	0	0
TEAEs leading to interruption of study drug	0	2 (5.1)
TEAEs leading to discontinuation of study drug	0	0
TEAEs leading to death	0	0

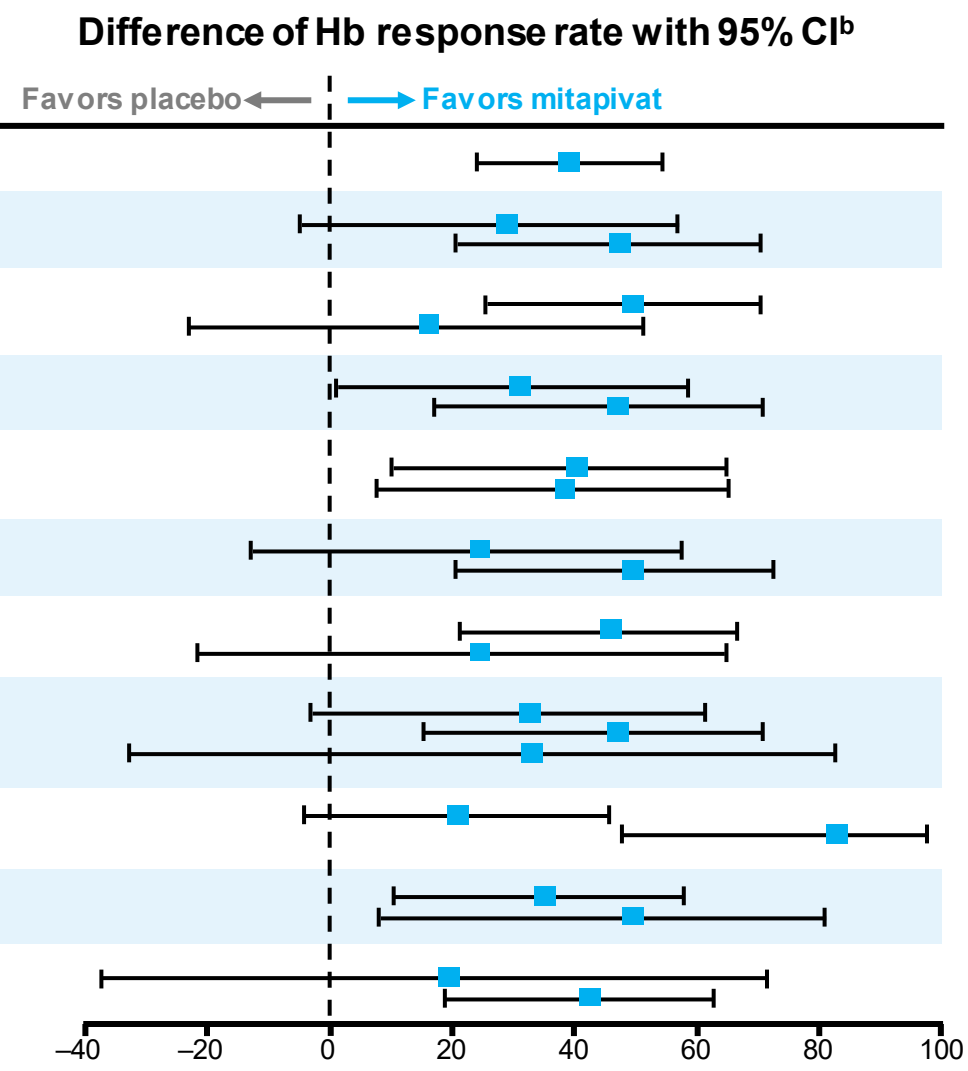
ACTIVATE-T

Patients, n (%)	Total (N = 27)
Any TEAE	27 (100)
Grade ≥ 3 TEAE	8 (29.6)[a]
Treatment-related TEAEs	18 (66.7)
Grade ≥ 3 treatment-related TEAEs	2 (7.4)
Serious TEAEs	3 (11.1)
Serious treatment-related TEAEs	0
TEAEs leading to discontinuation of study drug	0
TEAEs leading to dose reduction of study drug	1 (3.7)
TEAEs leading to interruption of study drug	0
TEAEs leading to death	0

Source: EHA 2021

In ACTIVATE, hemoglobin response was seen across all pre-defined patient subgroups

Characteristic	Subgroup	Hb response rate, % (n/N) Mitapivat	Hb response rate, % (n/N) Placebo
Overall study population[a]:		**40.0 (16/40)**	**0 (0/40)**
Average of screening Hb:	< 8.5 g/dL	29.4 (5/17)	0 (0/18)
	≥ 8.5 g/dL	47.8 (11/23)	0 (0/22)
***PKLR* mutation category:**	Missense/Missense	50.0 (14/28)	0 (0/27)
	Missense/Non-missense	16.7 (2/12)	0 (0/13)
Baseline Hb:	< 8.5 g/dL	31.6 (6/19)	0 (0/21)
	≥ 8.5 g/dL	47.6 (10/21)	0 (0/19)
Age at screening:	< 35 years	40.9 (9/22)	0 (0/20)
	≥ 35 years	38.9 (7/18)	0 (0/20)
Sex:	Male	25.0 (4/16)	0 (0/16)
	Female	50.0 (12/24)	0 (0/24)
Race:	White	46.4 (13/28)	0 (0/32)
	Other[c]	25.0 (3/12)	0 (0/8)
Geographic region:	North America	33.3 (5/15)	0 (0/16)
	Western Europe	47.4 (9/19)	0 (0/20)
	Rest of the World[c]	33.3 (2/6)	0 (0/4)
Prior splenectomy:	Yes	21.4 (6/28)	0 (0/30)
	No	83.3 (10/12)	0 (0/10)
Prior cholecystectomy:	Yes	35.7 (10/28)	0 (0/30)
	No	50.0 (6/12)	0 (0/10)
Prior chelation therapy:	Yes	20.0 (1/5)	0 (0/10)
	No	42.9 (15/35)	0 (0/30)



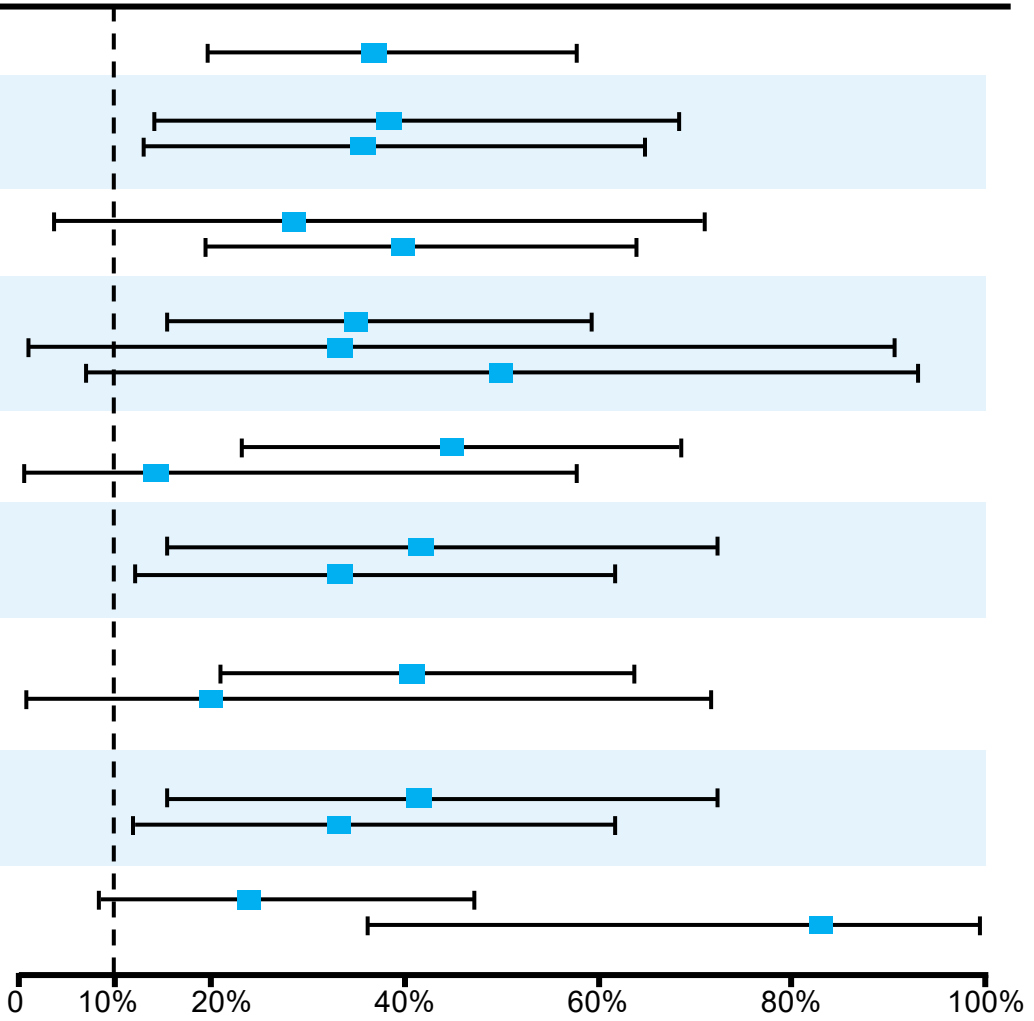
NB: Summarized based on full analysis set (all patients who were randomized to treatment).

[a]Stratified by the Average of Screening Hb concentrations and PKLR gene mutation category; [b]For overall study population difference is based on Mantel-Haenszel stratum weighted method adjusting for randomization stratification factors; for subgroups difference is based on unstratified analyses; [c]Pre-specified subgroups with ≤10% of the subjects in the full analysis set were pooled (race, Asian and Other were pooled). CI = confidence interval; Hb = hemoglobin; N = number of patients randomized; *PKLR* = gene encoding the pyruvate kinase liver and red blood cell isozymes.

Source: EHA 2021

In ACTIVATE-T, the effect of mitapivat on reducing transfusion burden was seen across all pre-defined patient subgroups

Characteristic	Subgroup	Response rate, % (n/N)[a]
Overall study population[a]:		37.0 (10/27)
Age at screening:	< 35 years	38.5 (5/13)
	≥ 35 years	35.7 (5/14)
Sex:	Male	28.6 (2/7)
	Female	40.0 (8/20)
Race:	White	35.0 (7/20)
	Asian	33.3 (1/3)
	Other	50.0 (2/4)
***PKLR* mutation category:**	Missense/Missense	45.0 (9/20)
	Missense/Non-missense	14.3 (1/7)
Baseline individual transfusion trigger:	< 8.5 g/dL	41.7 (5/12)
	≥ 8.5 g/dL	33.3 (5/15)
Individual historical transfusion burden, number of episodes[c]:	≤ 6 episodes	40.9 (9/22)
	> 6 episodes	20.0 (1/5)
Individual historical transfusion burden, number of RBC units[c]:	≤ 6 units	41.7 (5/12)
	> 6 units	33.3 (5/15)
Prior splenectomy:	Yes	23.8 (5/21)
	No	83.3 (5/6)



[a]Transfusion reduction responders defined as patients who had ≥ 33% reduction in the number of RBC units transfused during the fixed-dose period standardized to 24 wks compared with the historical number of RBC units transfused standardized to 24 wks; [b]The estimated 95% CI is based on the exact binomial distribution; [c]During the 52 wks before Informed Consent, standardized to 24 wks'.
CI = confidence interval; PKLR = gene encoding the pyruvate kinase liver and red blood cell isozymes; RBC = red blood cell; wks = weeks.

Source: EHA 2021

Patient case story

U.S. Commercial Launch Readiness

Darrin Miles, Chief Commercial Officer

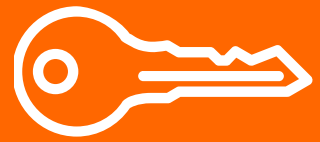
Agios is prepared to win in PK deficiency on behalf of patients and the business

PILLARS OF LAUNCH SUCCESS

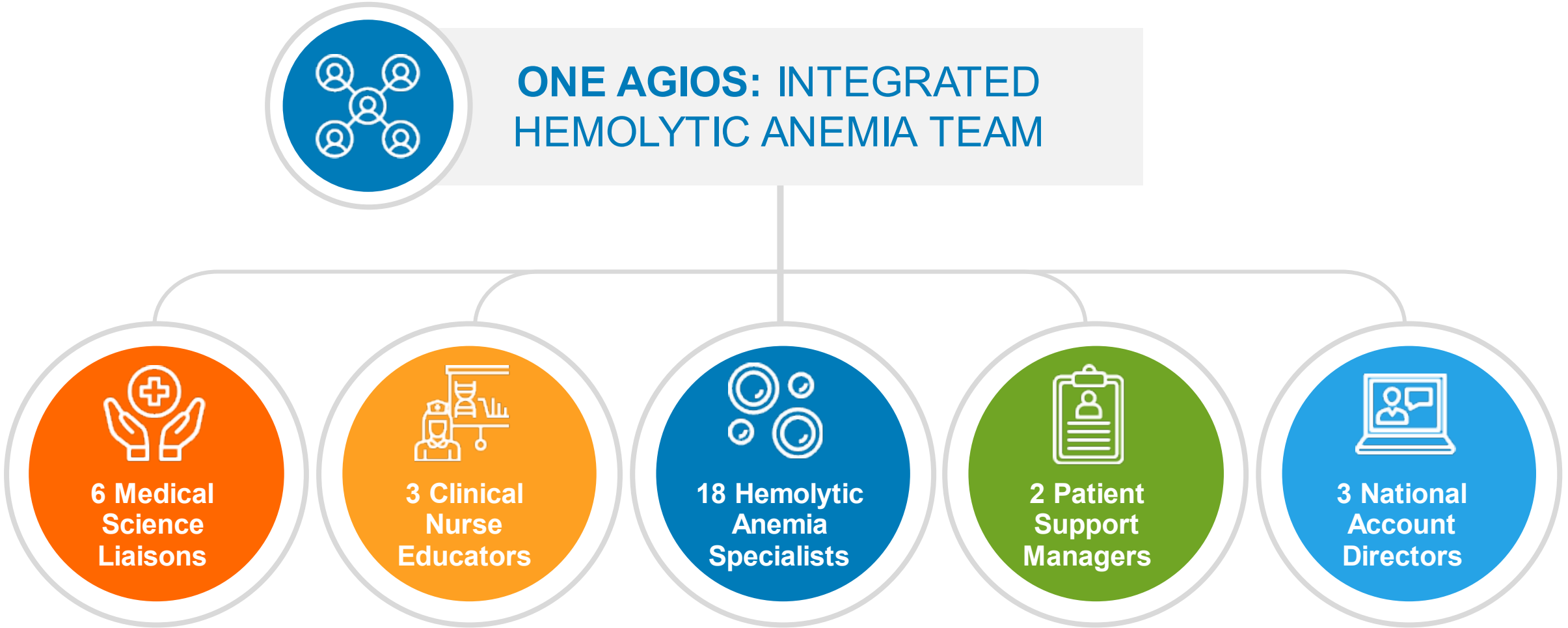
Build the Right Team

Optimize Patient & Provider Journey

Broad Access



We've assembled an exceptionally talented and experienced rare disease organization



Commercial model evolved from prior oncology business to meet needs of a rare disease

Experience and talent complemented by advanced digital and analytics capabilities to ensure focused execution

>150

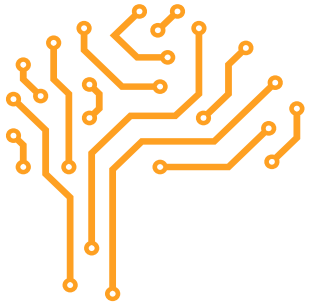
years of rare disease experience

>60

rare disease product launches

Enhanced digital / omnichannel communication network

ADVANCED ANALYTICS



(Machine Learning)

Hired from ~15 rare disease biopharmas

EXPECTED COVERAGE

~2,600

Hematologists/Oncologists
(50/50 Hospital vs. Community)

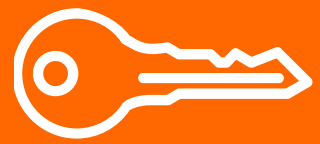
Agios is prepared to win in PK deficiency on behalf of patients and the business

PILLARS OF LAUNCH SUCCESS

Build the Right Team

Optimize Patient & Provider Journey

Broad Access



Commercial strategy & execution rooted in understanding the patient & provider experience

Optimizing Patient & Provider Journey

JOURNEY STAGE

DIAGNOSIS	UNDERSTANDING DISEASE BURDEN	PRESCRIBING	ADHERENCE
			

BARRIERS

DIAGNOSIS	UNDERSTANDING DISEASE BURDEN	PRESCRIBING	ADHERENCE
Little historical motivation to definitively diagnose	Disease burden and progression historically poorly characterized and underestimated	No treatment options exist beyond transfusion	Patients on chronic treatment need support with compliance & persistency

Patients with PK deficiency have historically faced obstacles in obtaining appropriate diagnosis and treatment for their disease

MEET NATHAN

Nathan's Story

- 40 years old
- From Idaho
- Diagnosed with PK deficiency at birth
- Has an older brother with PK deficiency

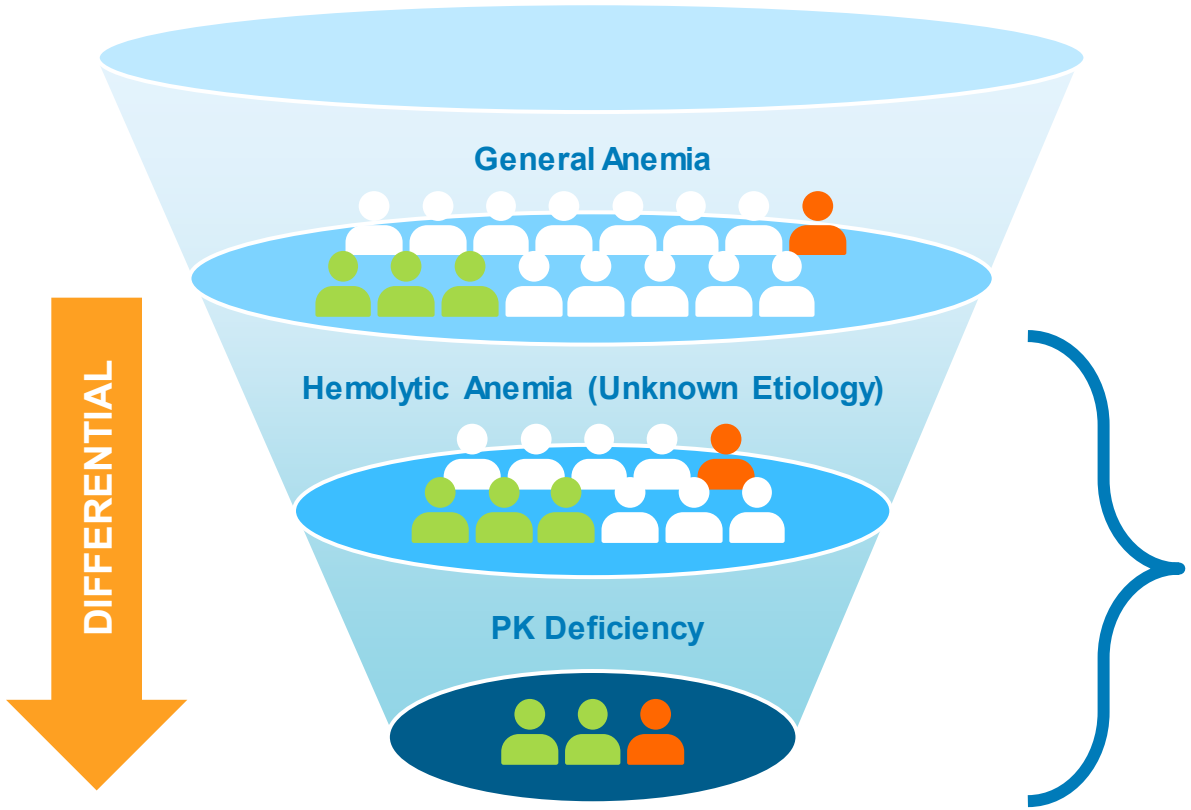
Treatment History

- Hemoglobin <10
- Gets transfusions as needed for complications
- Has osteoporosis
- Struggled to find a physician that understood his PK deficiency
- Currently travels from his home in Idaho to Utah to see a specialist

Nathan's YouTube Channel

Poor understanding of natural history, no approved treatments resulted in inadequate diagnosis; greatest opportunity among patients of unknown etiology

Diagnosis for PK Deficiency Patients Historically



Growing But Inadequate Awareness and Diagnosis of PK Deficiency

- >50% providers agree PK deficiency is under diagnosed *(vs. 40% in '20)*
- 85% of providers are somewhat or very familiar
- But only 20% of providers suspect PK deficiency when exposed to a blinded case

Agios' focus:
Drive differential to diagnosis especially amongst providers w/ hemolytic anemia of unknown etiology patients

Source: 2021 PK Deficiency Mitapivat Demand Study, 2020 PKD ATU Study

Agios' diagnosis strategy: Exhaustive multi-channel approach to improve diagnosis

Strategies for Improving Diagnosis of PK Deficiency

Identify potential patients

- Claims-based Targeting
- Partnership with 23andMe
- Exploring Electronic Medical Records + ICD-10 codes
- Provider Customer Engagement

To date, 2-3K HCP targets profiled, each with average 3-5 hemolytic anemia patients

Activate providers and patient to obtain or confirm diagnosis

- AnemiaID offers **free genetic testing** on behalf of patients
- InformedDNA Genetics, Decoded. — Genetic Counseling Support to allow for patient-initiated testing
- myagios™ — Empowers patients to proactively manage their disease

HCPs indicate they intend to order AnemiaID for ~85% of appropriate patients

Sources: Mitapivat PK Deficiency US Demand Study, Agios Commercial Analytics, Charles River Associates, June 2021, Agios Commercial Analytics, Oct 2021

Until recently, the PK deficiency disease burden has been poorly characterized and underestimated

"I was just recently diagnosed with osteoporosis…I've got, like, bone on bone in my hip…if I was trying to do that and have a job at the same time, it would never work. It would never work. But I do miss the regimen of having a job. I do miss contributing stuff."

-Nathan, Not Regularly Transfused PK Deficiency patient

MYTH	vs.	NATHAN'S REALITY
• Not regularly transfused = mild disease • Sequelae of disease are generally a result of transfusions • Minimal impact on his quality of life, social and emotional well-being		• Symptoms **are wide-ranging, lifelong**, and accompanied by **profound fatigue**[1] • Comorbidities and complications like iron overload and osteopenia can **occur irrespective of age, hemoglobin level, or transfusion history**[2] • Feelings of social and professional **isolation**[3]

References: 1. Grace RF, Bianchi P, van Beers EJ, et al. *Blood*. 2018;131(20):2183-2192. doi:10.1182/blood-2017-10-810796 **2.** Boscoe AN, Yan Y, Hedgeman E, et al. *Eur J Haematol*. 2021;106(4):484-492. doi:10.1111/ejh.13572 **3.** Grace RF, Cohen J, Egan S, et al. *Eur J Haematol*. 2018;101(6):758-765. doi:10.1111/ejh.13128

Agios has built a comprehensive assortment of tools and engagements focused on education and raising awareness

Strategies to Improve the Understanding of the Burden of Disease for PK Deficiency Patients

Broaden and educate community of PK Deficiency Experts

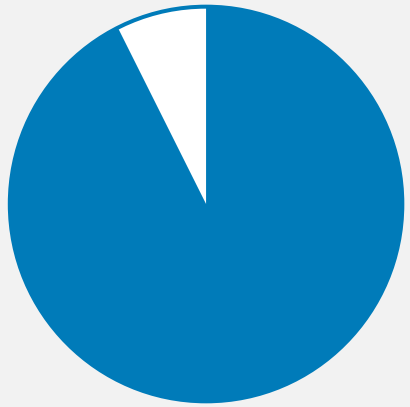
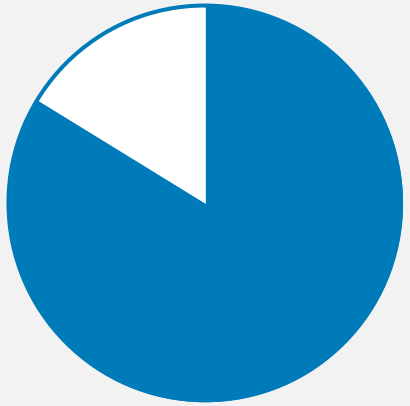
Amplify medical education re: disease and diagnosis amongst community of providers, patients and others

Execution

1. Medical Communications & Publications
2. Digital Media & Live Programming
3. Patient Support & Advocacy

Physician prescribing expected to be consistent across patient types regardless of transfusion history

Patient Segments and Indicated Prescribing by Patient Profile

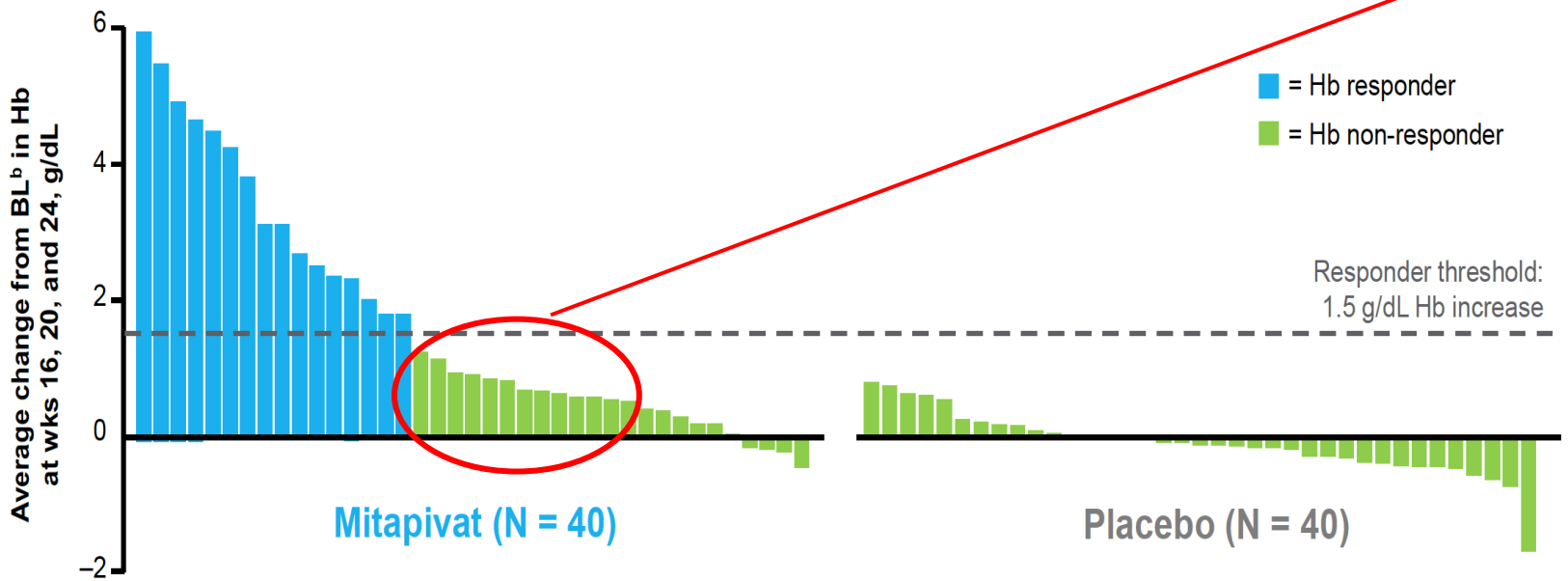
	Transfusion Dependent	Less Frequently Transfused (or not at all)
Size of PK Deficiency Patient Segments	**~10-20%**	**~80-90%**
Likely Proportion of Patients to be Rx'd Mitapivat According to Quantitative Market Research		

Source: 2021 PK Deficiency Mitapivat Demand Study

Physicians may see clinical value beyond 1.5 g/dL improvement in Hb and will evaluate totality of response

Mitapivat met the primary endpoint, demonstrating a higher hemoglobin response rate as compared with placebo

	Mitapivat N = 40	Placebo N = 40	Difference[a] (95% CI)	2-sided p-value
Hemoglobin response n (%)	16 (40.0)	0 (0)	39.3 (24.1, 54.6)	< 0.0001



An additional 33% of patients showed ≥0.5 g/dL ↑ in Hb

- 5% achieve improvement between 1.0 to <1.5 g/dL

Deciding on continuation of treatment

- Providers will individualize assessment of clinical response
- They will consider changes in markers of hemolysis and QoL in addition to change in Hb

Source: EHA 2021

myAgios will offer streamlined, patient-oriented education and support to remove barriers to access and adherence

Challenge: Complexity, out-of-pocket costs and treatment fatigue can impact adherence

myAgios is built to make treatment start and maintenance simple for patients and providers

Provider completes enrollment form & sends to myAgios Patient Support Services

A single point of engagement for providers and patients

myagios™

Single Specialty Pharmacy

Patient Support Manager

agios

myAgios has the potential to minimize abandonment and encourage adherence through education and extensive support

Patients like Nathan can expect dedicated, tailored support while on treatment

myagios™

- Dedicated patient support managers
- Clinically trained staff
- Deep experience in rare disease

- Customized adherence support and mobile app
- Disease education
- Connections to PK deficiency patient community

- Copay assistance
- Free product support
- Treatment interference support
- Ongoing reimbursement services

Continued engagement

- Regular calls and emails
- Monthly live and virtual education
- Social support

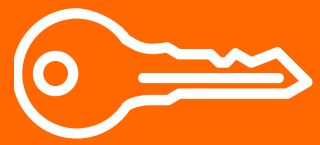
Agios is prepared to win in PK deficiency on behalf of patients and the business

PILLARS OF LAUNCH SUCCESS

Build the Right Team

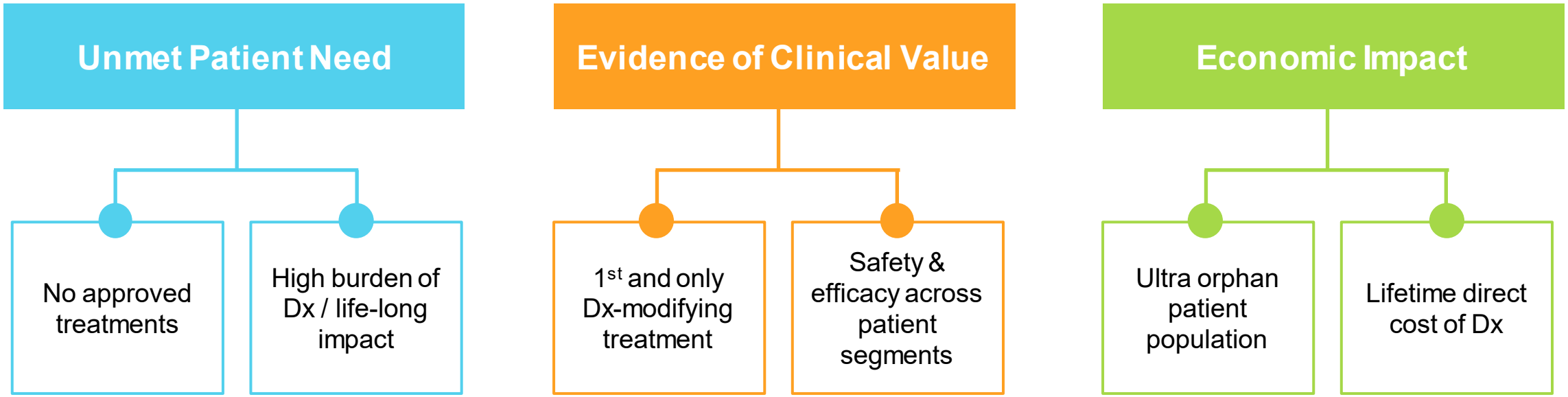
Optimize Patient & Provider Journey

Broad Access



Unmet need, safety/efficacy and economic impact of greatest interest to payors

Components of Effective Payor Dialogue

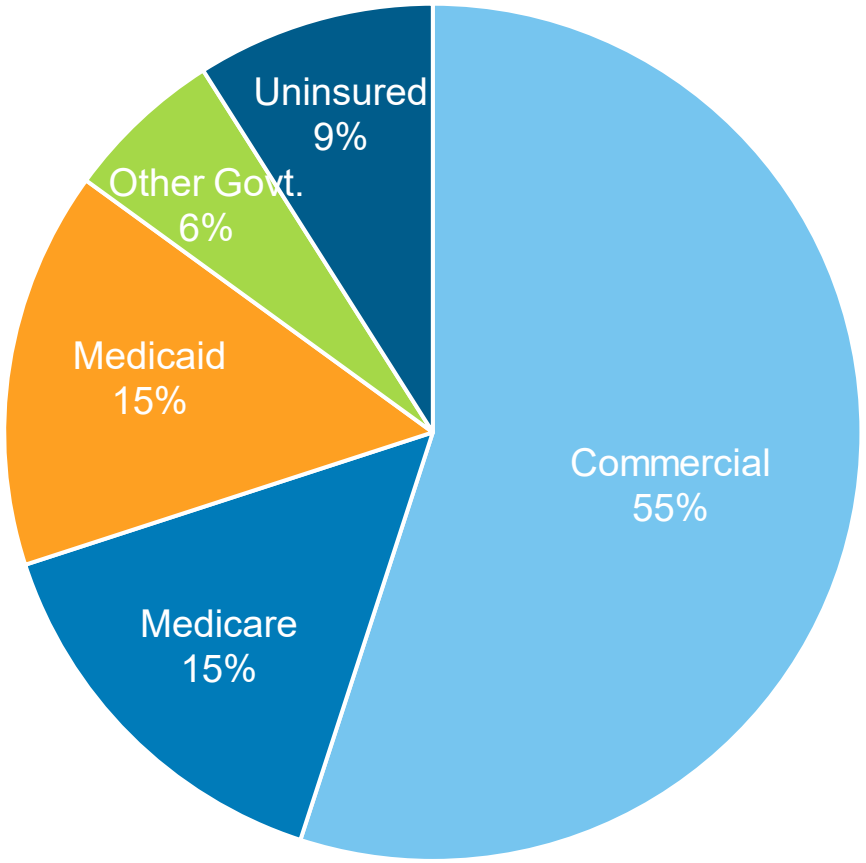


Based on research, when payors are fully informed on burden of disease and mitapivat profile, they see the clinical value and utility of mitapivat across the spectrum of PK deficiency patients

References: 1. Al-Samkari H et al. Early-onset osteopenia and osteoporosis in patients with pyruvate kinase deficiency. Abstract presented at: ASH 2020 Accessed November 5, 2020. https://ash.confex.com/ash/2020/webprogram/Paper136598.html **2.** Boscoe AN et al. *Blood*. 2019;134(suppl 1):2175.

Anticipate steady expansion in formulary coverage over first year post-approval

Anticipated Payor Mix
(% Covered Lives)



Expected Time to Formulary Coverage Across Payor Types

- Expect commercial payors to reach full formulary coverage by one year post-approval
  - P&T committees meet on fixed schedules
  - Medical exception process in early months
- Medicare and Medicaid will lag
- No impact to prescribing or peak sales, but may result in longer time from prescribing to fulfillment over first year
- Newly approved ICD-10 code will help with accelerating coverage decisions and patient profiling

ICD-10-CM Code	Description
D55.21	Anemia due to pyruvate kinase deficiency

Expect routine payor requirements for initial and continued coverage

Based on market research and payor interactions, we expect prior authorization criteria to align with FDA-approved label or clinical trial eligibility criteria

New Prescription

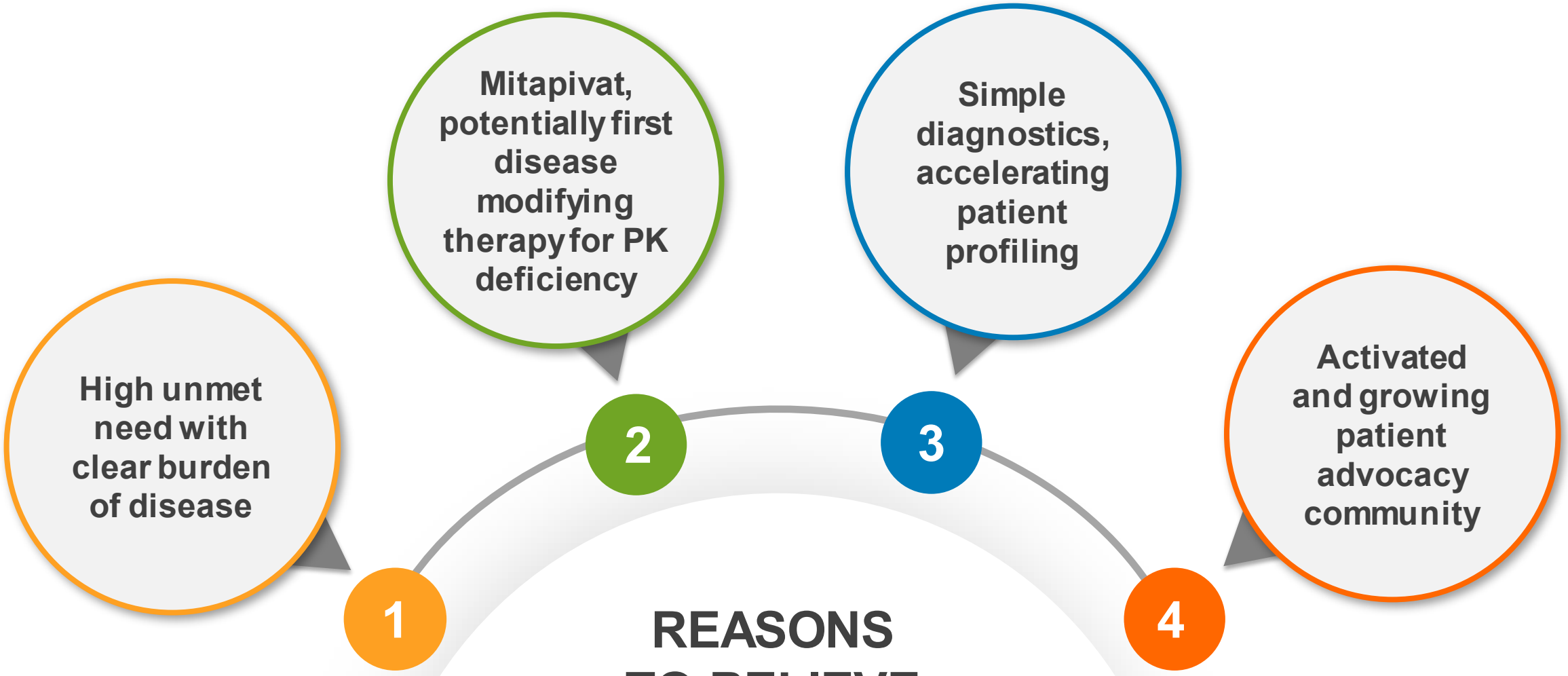
Potential Prior Authorization Criteria	• Anchored to label or clinical trial eligibility criteria • Age 18+ • Dx confirmation • Baseline Hb • Specialty prescriber • Dosing schedule
Time to Fulfillment	~4-6 weeks on average depending on payor requirements

At time of approval, expect "new to market" designation at time of approval which will require medical exception

Reauthorization

Potential Reauthorization Criteria	• Stable or improving Hb • Transfusion history • Supportive secondary endpoints/labs
Reauthorization Timing	Every 3-12 months depending on payor and formulary tier

The fundamentals essential for successful commercialization are in place



Understanding U.S. commercial opportunity: State of play at time of launch

Estimated U.S. Prevalent Pyruvate Kinase Deficiency
~3,000 (midpoint)
(Range: 1,500 – 4,000)

- Estimate ~30%+ diagnosed at time of launch

Adult
~80%

Pediatric
~20%

- 30% patients have Hb ≥10 g/dL (Natural History Study)
- 9-15% double non-missense (Peak Registry)

% Likely Prescribed

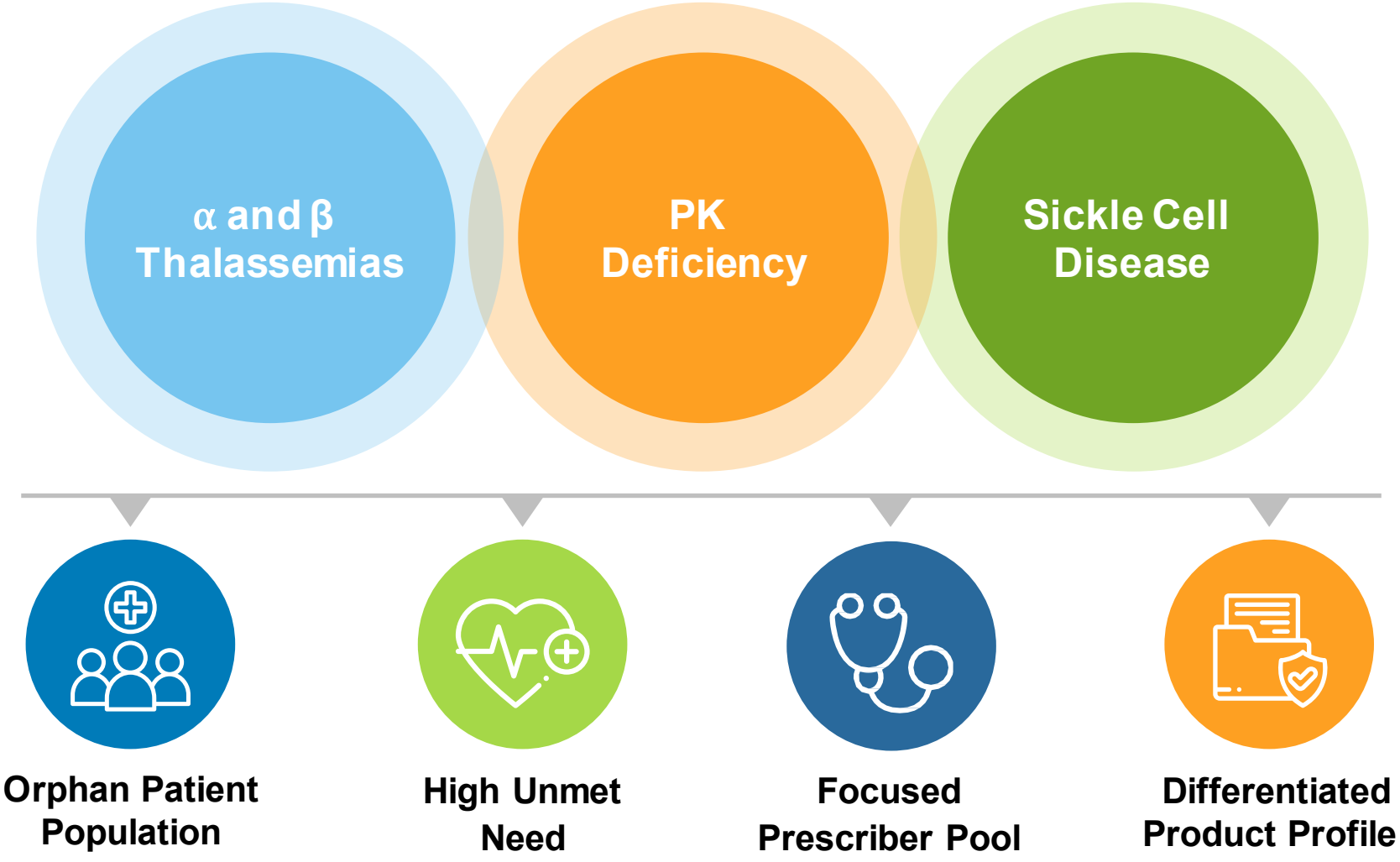
- Expect eligible patients who initiate treatment to trial for ~3-6 months before clinical assessment of response
- Many payors will want to recertify patients at 3-6 months

% ↑Hb ≥1.5 g/dL
~40-45%

- An additional 5% of patients will achieve improvement between 1.0 to <1.5 g/dL
- Consider likely adherence to chronic treatment

Key Details and Considerations

Success in PK deficiency positions Agios well for thalassemias and sickle cell disease, if approved



Key takeaways

01 Built the right team with advanced analytical capabilities

02 Growing understanding of disease burden and urgency to diagnose

03 Strong provider interest to prescribe across spectrum of PK deficiency patients; clear and convincing payor value proposition

04 Tailored patient support to address barriers to access and adherence

05 Compelling commercial opportunity

Meet Richa Poddar

AGIOS

Focused Innovation. Ambitious Development. Patient Impact.

BY LEVERAGING

- Culture of continuous development and patient-first orientation
- Deep understanding of disease biology and expertise in cellular metabolism
- Emphasis on translational research, starting in early-stage discovery
- Proven success in drug discovery, development and commercialization

Focus on Genetically Defined Diseases

WE CAN

- **Deliver groundbreaking science with an energized focus and mission**
- **Fully develop potential for PK franchise and grow our clinical pipeline**
- **Strengthen the business**

Q&A