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Q2 2023 Financial Results

August 3, 2023

Agios conference call participants

TOPIC	PARTICIPANT
Introduction	Chris Taylor, Investor Relations and CorpComm
Business Update	Brian Goff, Chief Executive Officer
Research & Development Update	Sarah Gheuens, M.D., Ph.D., Chief Medical Officer, Head of Research and Development
Commercial Update	Tsveta Milanova, Chief Commercial Officer
Second Quarter 2023 Financial Results	Cecilia Jones, Chief Financial Officer
Q&A	Mr. Goff, Dr. Gheuens, Ms. Milanova, Ms. Jones

Forward-looking statements

This presentation and various remarks we make during this presentation contain forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding the potential benefits of PYRUKYND® (mitapivat), AG-946, TMPRSS6 siRNA and its PAH stabilizer; Agios' plans, strategies and expectations for its preclinical, clinical and commercial advancement of its drug development, including PYRUKYND®, AG-946 and its PAH stabilizer; Agios' strategic vision and goals, including its key milestones for 2023 and potential catalysts through 2026; 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 or other public health emergencies 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; uncertainty regarding any milestone or royalty payments related to the sale of Agios' oncology business or its in-licensing of TMPRSS6 siRNA , and the uncertainty of the timing of any such payments; uncertainty of the results and effectiveness of the use of proceeds from the transaction with Servier; and general economic and market conditions. These and other risks are described in greater detail under the caption "Risk Factors" included in Agios' public filings with the Securities and Exchange Commission. 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.

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Opening Remarks

Q2 2023 highlights

Pipeline updates

- Completed enrollment of Phase 3 ENERGIZE and ENERGIZE-T clinical trials of mitapivat in thalassemia; on track for data readouts in 2024
- Announced positive topline data of Phase 2 RISE UP study of mitapivat in sickle cell disease; on track to enroll first patient in Phase 3 portion in Q4 this year
- Completed enrollment of Phase 2a study of AG-946 in lower-risk myelodysplastic syndrome; on track for data readout by year-end 2023
- PYRUKYND® net revenue $6.7M in Q2 2023; launch providing platform to support potential expansion in larger patient populations

Corporate updates

- Expanded pipeline through license agreement with Alnylam for novel siRNA for potential treatment of polycythemia vera (PV)
- Appointed Catherine Owen to the Agios board of directors
- $947M in cash, cash equivalents, and marketable securities as of June 30, 2023

Preclinical siRNA targeting TMPRSS6 is a potential disease-modifying treatment for Polycythemia Vera (PV)

Agreement combines Agios' scientific expertise and capabilities in rare hematological diseases with Alnylam's industry-leading siRNA platform

PV is a rare hematological disease with no disease-modifying treatments that affects approximately 100,000 patients in the U.S.

PV is characterized by excessive production of red blood cells, which leads to increased blood volume and viscosity, and can result in thrombosis, cardiovascular events, and death

Development candidate has demonstrated 90% knockdown of TMPRSS6, a key driver of red blood cell production, and a favorable safety profile

Aim to initiate IND-enabling studies in 2023 and deliver a convenient, disease-modifying treatment option that reduces or eliminates the need for phlebotomy

Clinical and regulatory milestones targeted in 2023 lay the foundation for transformational data readouts

2023

Thalassemia
PYRUKYND®
Complete enrollment of Phase 3 ENERGIZE and ENERGIZE-T studies
(MID-YEAR)

Sickle Cell Disease
PYRUKYND®
Phase 2 RISE UP data readout & go/no-go to Phase 3 decision
(MID-YEAR)

Pediatric PK Deficiency
PYRUKYND®
Enroll at least half of patients in the Phase 3 ACTIVATE-kids and ACTIVATE-kidsT studies
(YEAR-END)

Pipeline
File IND for PAH stabilizer for the treatment of PKU
(YEAR-END)

Lower-Risk MDS
AG-946 (Novel PK Activator)
Complete enrollment of Phase 2a study
(YEAR-END)

Sickle Cell Disease
PYRUKYND®
Begin patient enrollment in Phase 3 RISE UP study
(YEAR-END)

NEW 2023 MILESTONE

Lower-Risk MDS
AG-946
Phase 2a data readout
(YEAR-END)

Evaluate business development opportunities to expand pipeline and build commercial capabilities to efficiently launch additional indications

1 *Clinical*

2 *Commercial*

3 *Financial*

RISE UP Phase 2: primary efficacy endpoint achieved for both doses

The Phase 2 portion of the global RISE UP study of mitapivat in sickle cell disease met its primary endpoint of hemoglobin response for both 50 mg BID and 100 mg BID

- RISE UP Phase 2 study enrolled 79 patients, with 27 patients on placebo, 26 on 50 mg BID and 26 on 100 mg BID
- Treatment with mitapivat (50 mg BID and 100 mg BID) demonstrated a **statistically significant increase in hemoglobin response rate** compared to placebo
  - 46.2 percent of patients in the 50 mg BID mitapivat arm and 50.0 percent of patients in the 100 mg BID mitapivat arm achieved a hemoglobin response, compared to 3.7 percent of patients in the placebo arm (2-sided p=0.0003 and 0.0001, respectively).
- The results for the secondary endpoints in both treatment arms were generally supportive of the results observed for the primary endpoint
  - **Improvements in markers of hemolysis and erythropoiesis** were observed at both doses compared to placebo
  - A **trend in sickle cell pain crises reduction** was observed at both doses compared to placebo
- The safety profile for mitapivat observed in the study was generally consistent with previously reported data in other studies of sickle cell disease and other hemolytic anemias
- There were no adverse events (AEs) leading to discontinuation in either the mitapivat or the placebo arms
- Of the 79 patients enrolled in the study, 73 continued into the Phase 2 open-label extension period

RISE UP Phase 3 Study: first patient enrolled expected in Q4 2023

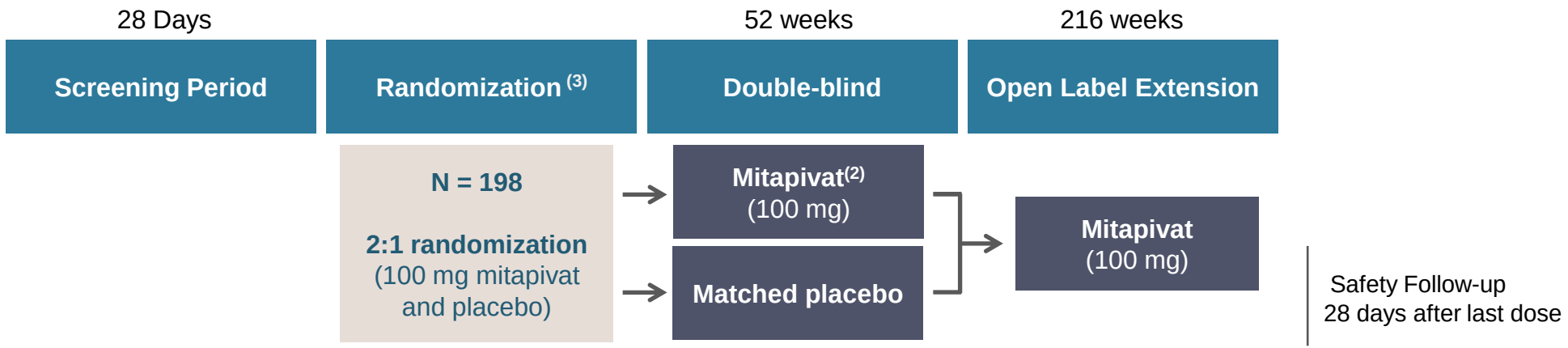
Phase 3 primary endpoints [(1)]:
Hb response, defined as a ≥ 1.0 g/dL increase in average Hb concentration over Weeks 24–52 compared with baseline, and annualized rate of SCPCs

Key inclusion criteria

- ≥ 16 years of age
- Documented SCD (HbSS, HbSC, HbSβ0/HbSβ+ thalassemia, other SCD variants)
- Recurrent VOCs (vaso-occlusive crises) – defined as the occurrence of 2–10 SCPCs (acute pain needing medical contact, acute chest syndrome, priapism, hepatic or splenic sequestration) in the prior 12 months
- Anemia – defined as a Hb level of 5.5–10.5 g/dL
- If taking HU, the dose must be stable for ≥ 90 days before starting study drug

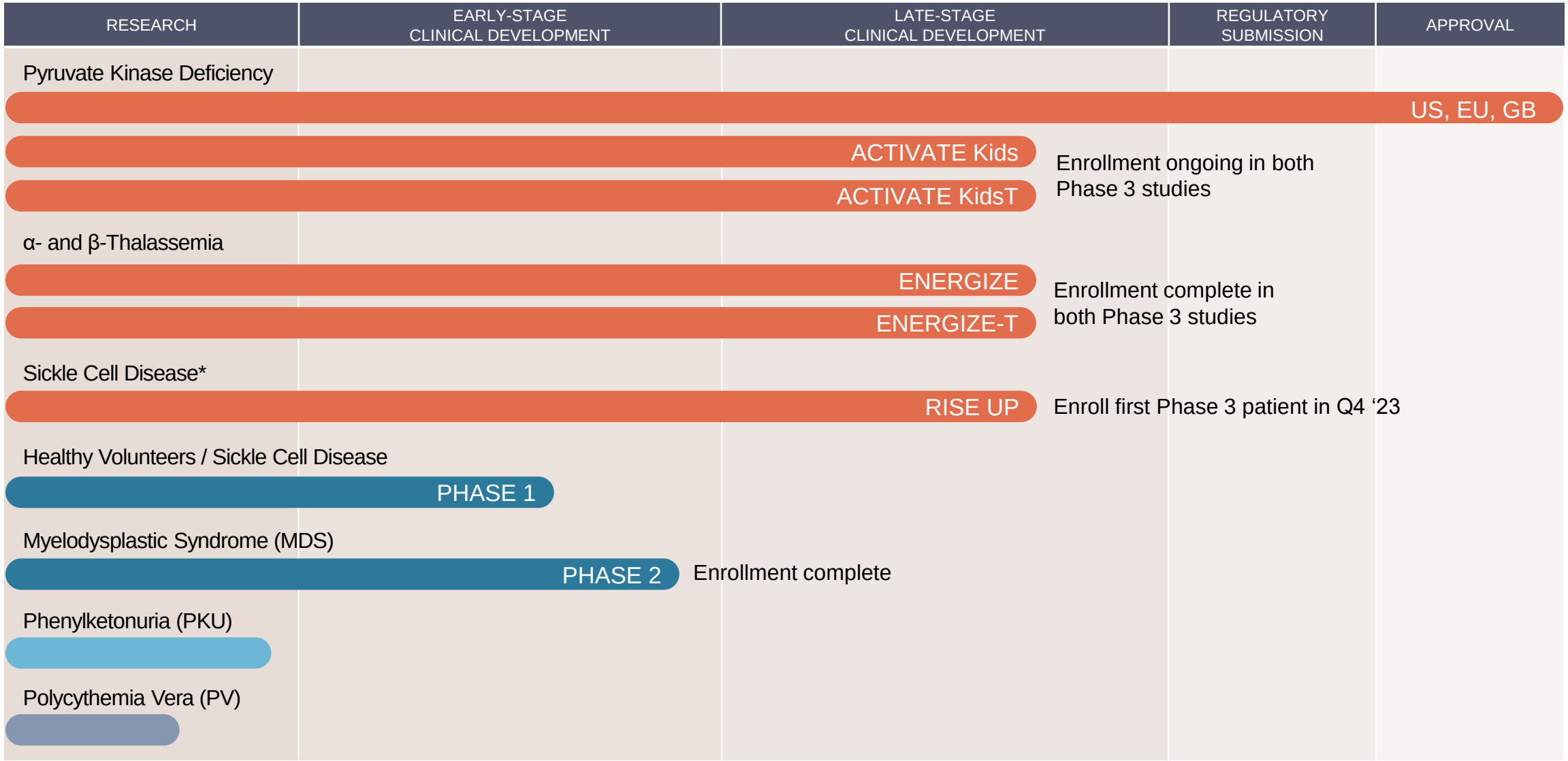
Key exclusion criteria

- Receiving regularly scheduled blood transfusions
- Severe kidney disease or hepatobiliary disorders
- Currently receiving treatment with SCD therapies (excluding HU)
- Prior exposure to gene therapy, or prior bone marrow or stem cell transplantation



Abbreviations: BID = twice daily; Hb = hemoglobin; SCPC = sickle cell pain crises; HU = hydroxyurea
(1) Phase 2 and phase 3 components are part of a single study/protocol; (2) Patients who receive mitapivat in the double-blind period will continue to receive the same dose of mitapivat in the open-label extension period;
(3)Randomization stratification factors: Number of SCPCs in the prior year (< 5, ≥ 5), hydroxyurea use (yes, no).

Building a diverse pipeline leveraging our expertise in cellular metabolism



*In addition to RISE UP, two investigator-sponsored trials are ongoing with the NIH and University of Utrecht.

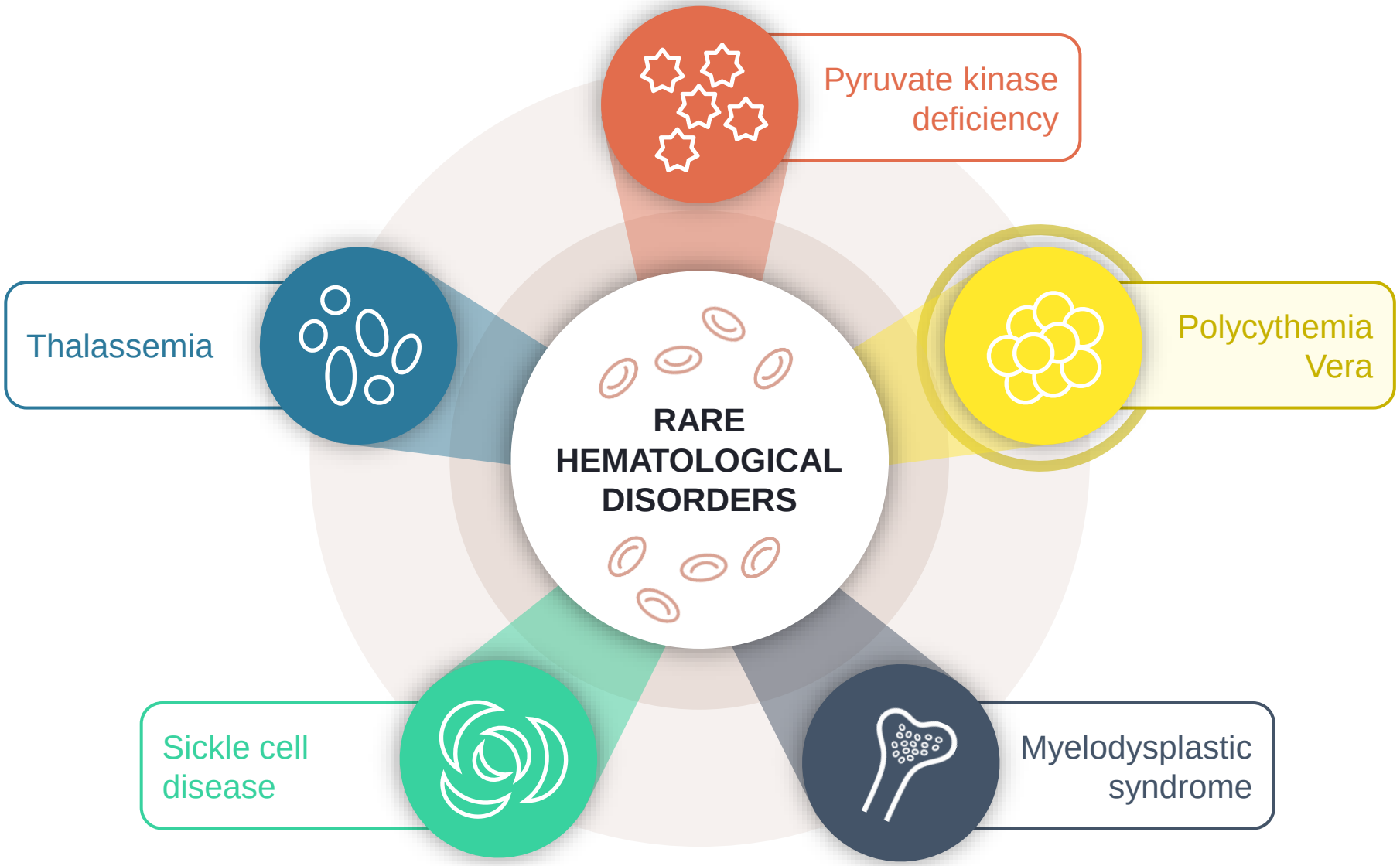
PYRUKYND® First-in-class PK activator

AG-946 Novel PK activator

Phenylalanine hydroxylase (PAH) stabilizer

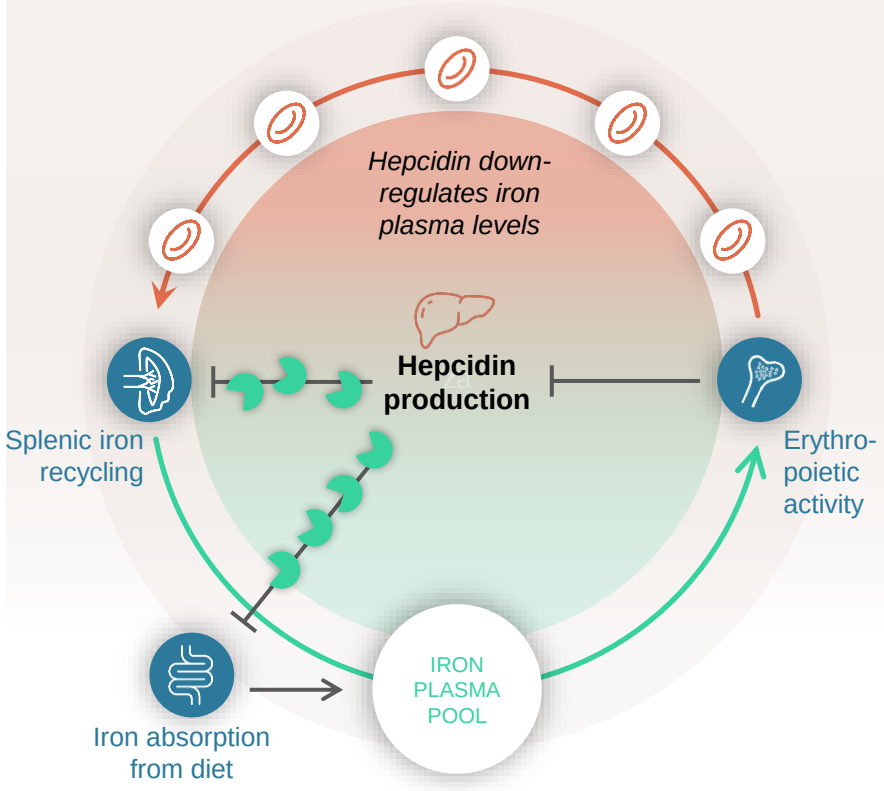
siRNA Targeting TMPRSS6

Strengthening therapeutic breadth in rare disease



Polycythemia Vera and TMPRSS6 siRNA mechanism of action

1
Hepcidin is a master regulator of iron metabolism.

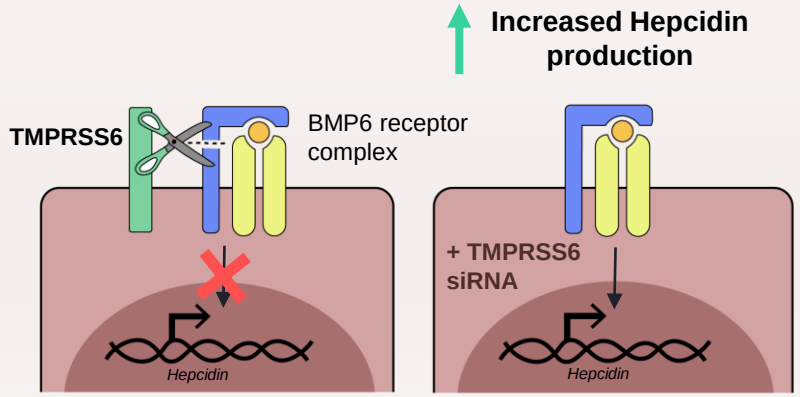


2
PV causes iron deficiency in the absence of anemia

- ↑ Erythropoietic activity
- ↑ Hemoglobin
- ↑ Hematocrit
- ↓ Iron availability
- ↓ Hepcidin

Phlebotomy reduces iron availability to the erythroid cells resulting in reduced erythropoiesis. Intensive phlebotomy treatment can worsen the iron deficit.

3
Hepcidin is negatively regulated in hepatocytes by the membrane protease TMPRSS6



TMPRSS6 siRNA therapy could be used as a "phlebotomy mimetic" to control erythropoiesis, while possibly avoiding the adverse consequences of chronic phlebotomy.

1 *Clinical*

2 *Commercial*

3 *Financial*

PYRUKYND® Q2 2023 performance metrics highlight continued progress

$6.7M net U.S. sales of PYRUKYND®
a 20% increase over Q1 2023

99 patients on PYRUKYND®,
which includes new prescriptions and those continuing treatment, an 11% increase over Q1 2023

Patients on therapy represent broad demographic range;
consistent with the adult PK deficiency population

147 unique patients completed PYRUKYND® prescription enrollment forms,
a 16% increase over Q1 2023

Unique prescriber base of 130 physicians, diversified across the country, a 15% increase over Q1 2023

Implementing a comprehensive commercial strategy that addresses each stage of the patient journey

Awareness and Education

Increase disease awareness and educate on available treatment options

Access and Initiation

Accelerate access by reducing the time between diagnosis and treatment initiation

Adherence and Persistency

Support adherence and maintain reimbursement over the long term

Drive operational excellence in current launch and build capabilities for anticipated launches

PK activation franchise positioned for meaningful expansion, with near-term opportunity in thalassemia

PYRUKYND® is the first and only disease-modifying treatment approved for adults with PK deficiency

Potential for two additional PYRUKYND® indications by 2026

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

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

Thalassemia
Potential U.S. approval in 2025

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

Sickle cell disease
Potential U.S. approval in 2026

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

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

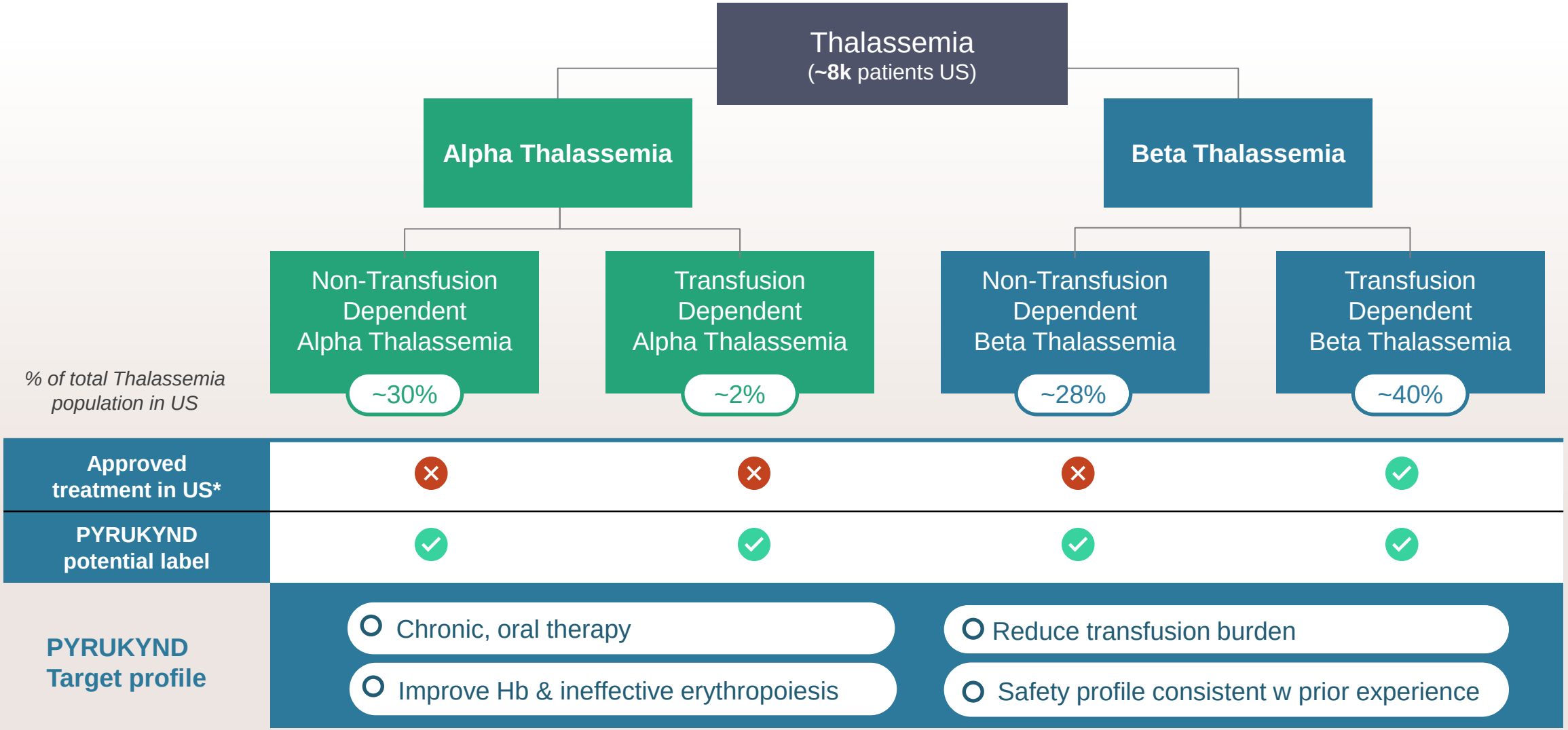
Lower-risk myelodysplastic syndrome

75-80K patients
in the U.S./EU5

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

Source: Agios internal estimates

Agios aims to deliver the first therapy approved for all thalassemia subtypes

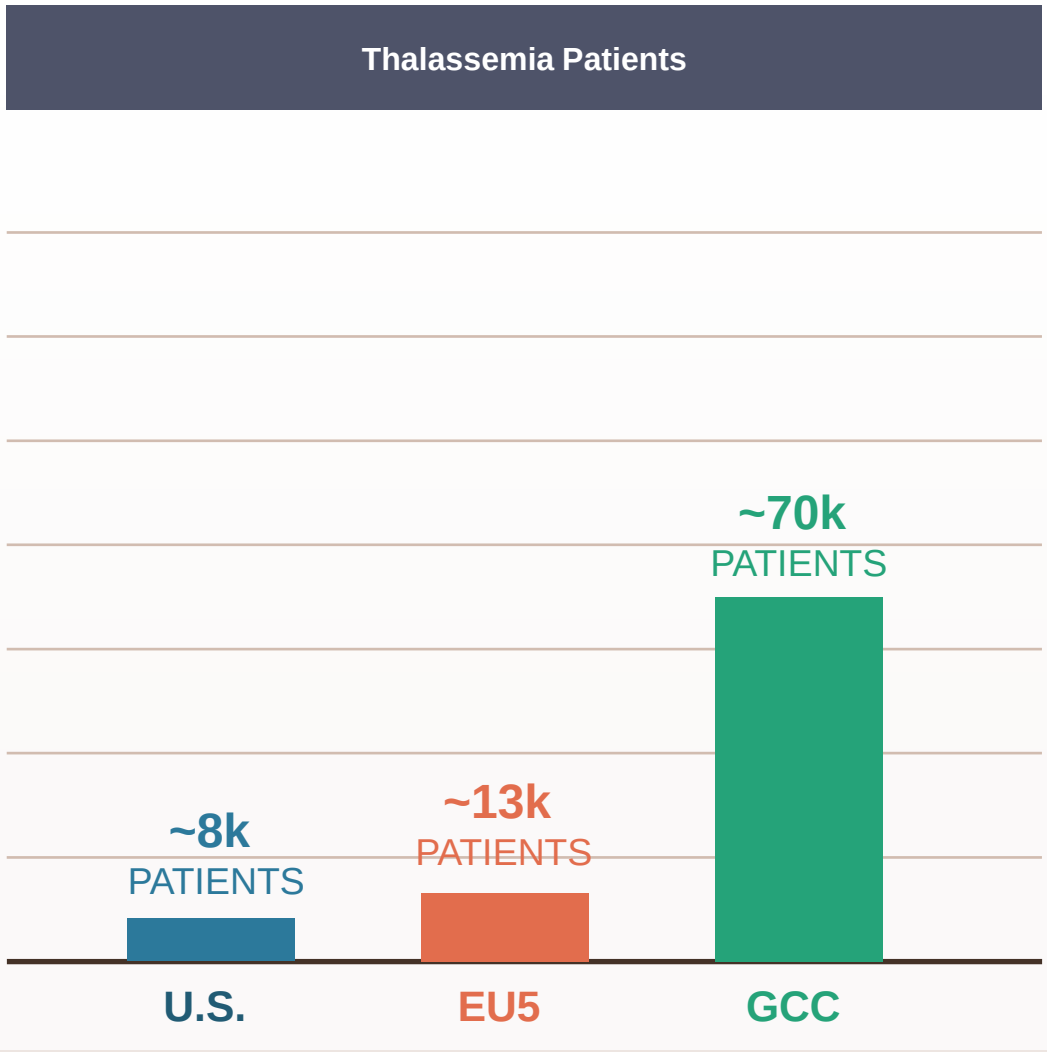


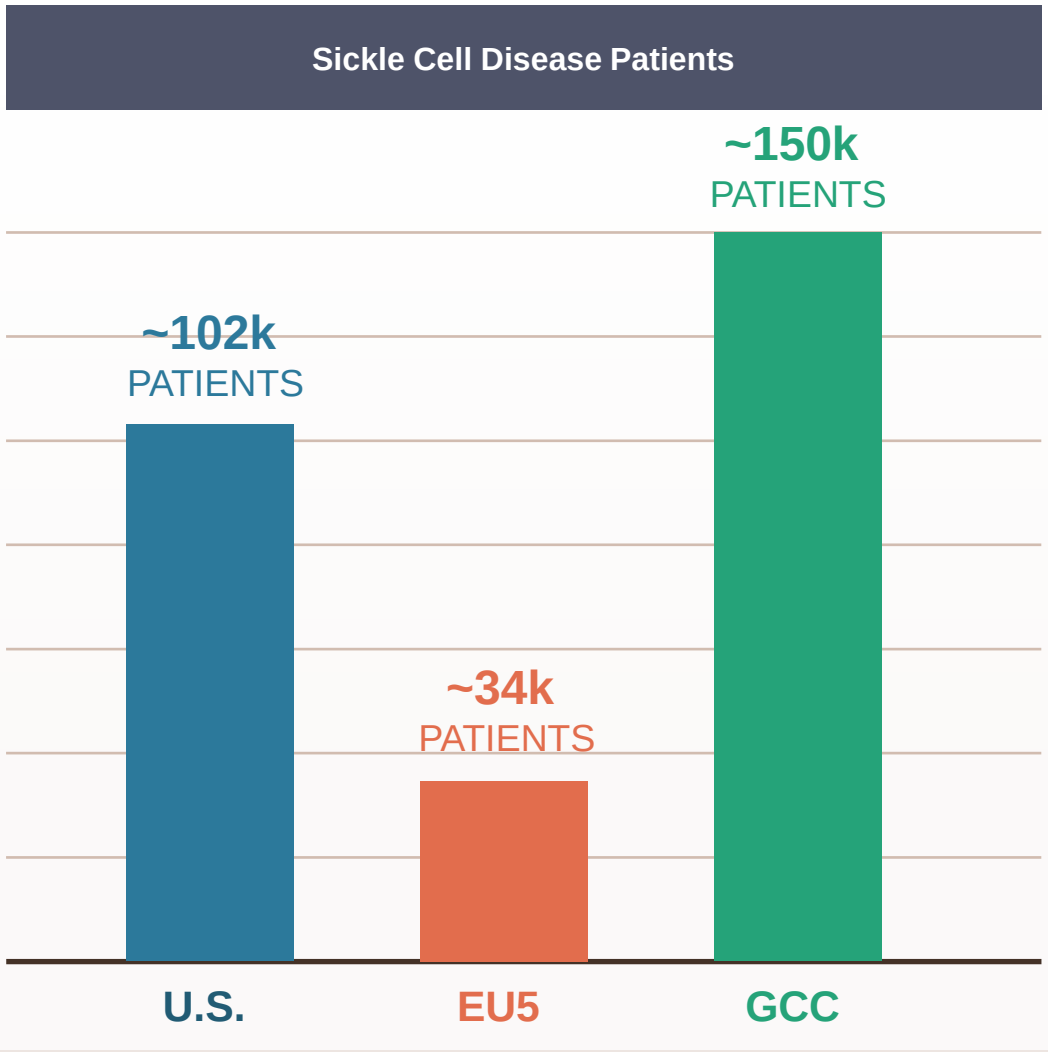
Beta-THAL prevalence: HEOR Global THAL Epidemiology SLE (XCENDA, 2021); US: Paramore, et.al; DE: Borchert, et.al; IT: Italian Society of Thal & Hemoglobinopathies Patient Registry, Jan 2021, Angelucci, et.al, 2017; FR: French registry for thal (Thuret, et.al.); ES: Cela, et.al.; UK Registry for Hemoglobinopathies, 2020; Alpha-THAL prevalence: Agios internal estimates; LEK Analysis | Beta-THAL TD/NTD split (60% / 40%): Thuret, et.al., Haematologica 2010; Magnolia TPP MR, April 2020 | Alpha-THAL TD/NTD split (5% / 95%): Taher, et.al., Vox Sanguinis, 2015; Magnolia TPP MR, April 2020.

PYRUKYND® is under investigation for thalassemia and is not approved anywhere for that use.

*Note: Reblozyl also approved in non-transfusion dependent beta-thalassemia EU

Thalassemia and SCD markets concentrated in select geographies





GCC: Kingdom of Saudi Arabia, Oman, United Arab Emirates, Qatar, Bahrain, Kuwait
EU5: United Kingdom, Germany, France, Spain, Italy
Sources: Borchert (2018); Agouti (2019); UK Thalassemia Society (2021); Angelucci (2017); Bardón Cancho (2020); BLUE (2019); Makkawi (2021); Oktay (2016); Paramore (2017); Thuret (2010); ZS Global Thal (2022)

1 *Clinical*

2 *Commercial*

3 *Financial*

Second quarter 2023 financial results

Statement of Operations	Three Months Ended 6/30/23	Three Months Ended 6/30/22
PYRUKYND® Net Revenue	$6.7M	$3.1M
Cost of Sales	$1.1M	$0.4M
Research & Development Expense	$68.9M	$74.5M
Selling, General & Administrative Expense	$30.4M	$28.3M
Gain on Sale of Oncology Business (TIBSOVO® Royalties)	--	$2.7M

Balance Sheet	6/30/23	12/31/22
Cash, Cash Equivalents and Marketable Securities	$947M	$1.1B

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Closing Remarks

Potential for two additional PYRUKYND® indications by 2026

	2024	2025	2026
Thalassemia PYRUKYND®	**Phase 3 ENERGIZE (1H) and ENERGIZE-T (2H) readouts**	**Potential approval**	
Pediatric PK Deficiency PYRUKYND®		**Phase 3 ACTIVATE-kids and ACTIVATE-kidsT readouts**	**Potential approval**
Sickle Cell Disease PYRUKYND®		**Potential Phase 3 RISE UP readout**	**Potential approval**
Lower-Risk MDS AG-946 (Novel PK Activator)	**Phase 2a readout** (accelerated to YE 2023)		

Q&A

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Appendix

Treatment with mitapivat demonstrated a statistically significant increase in hemoglobin response rate compared to placebo

	Placebo N=27	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26
Hemoglobin responders, n (%)	1 (3.7)	12 (46.2)	13 (50.0)
Difference of response rate (Mitapivat-Placebo), %		42.5	46.3
95% CI(1)		(18.8, 63.4)	(22.0, 66.8)
2-sided p-value(2)		0.0003	0.0001

Abbreviation: RBC = red blood cell
Hemoglobin response is defined as ≥1.0 g/dL (10 g/L) increase in average Hb concentrations from Week 10 through Week 12 compared to baseline.
Assessments collected within 8 weeks after an RBC transfusion are excluded from the analysis.
Subjects who do not have any Hb concentration assessments from Week 10 through Week 12 are considered nonresponders.
(1) Exact 95% CI
(2) The p-value is based on the Fisher's exact test

Annualized rates of sickle cell pain crises for patients in the mitapivat arms were lower compared to patients in the placebo arm

CRC Adjudicated Data

Negative Binomial Regression Model

	Placebo N=27	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26
Annualized Rate of SCPC	1.71	0.83	0.51
95% CI	(0.95, 3.08)	(0.34, 1.99)	(0.16, 1.59)
Rate ratio (Mitapivat/Placebo)		0.48	0.30
95% CI		(0.17, 1.39)	(0.08, 1.07)

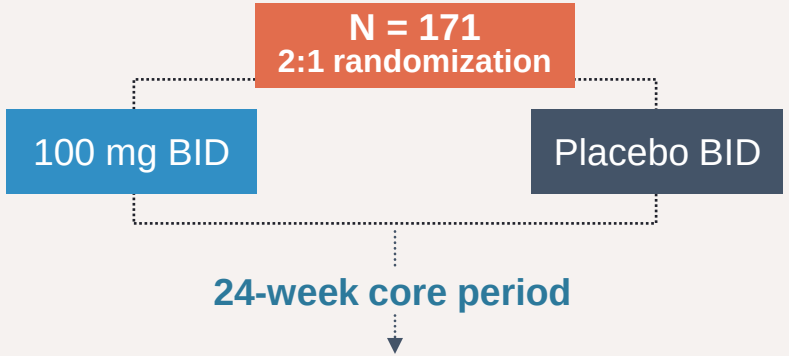
Abbreviations: CRC = crisis review committee; SCPC = sickle cell pain crisis

The estimates and 95% CIs are based on a negative binomial regression model with natural log link. The model included the number of SCPC events during the Double-blind Period of the study as the response variable and treatment arm as the independent variable. The natural log of time on study was used as the offset to account for the varying lengths of subjects' time in the Double-blind Period of the study.

SCPC events that occur within 7 days of a prior SCPC onset are not counted as a separate event. Each subject time in the Double-blind Period is defined as (end date – date of randomization + 1), where end date is last dose of study drug during the Double-blind Period for subjects randomized and dosed, or the randomization date for subjects randomized and not dosed.

Two global, Phase 3, randomized controlled trials of PYRUKYND® in thalassemia encompass broad range of thalassemia patients

ENERGIZE



Primary endpoint

- Mean Hb ↑ ≥ 1 g/dL from baseline

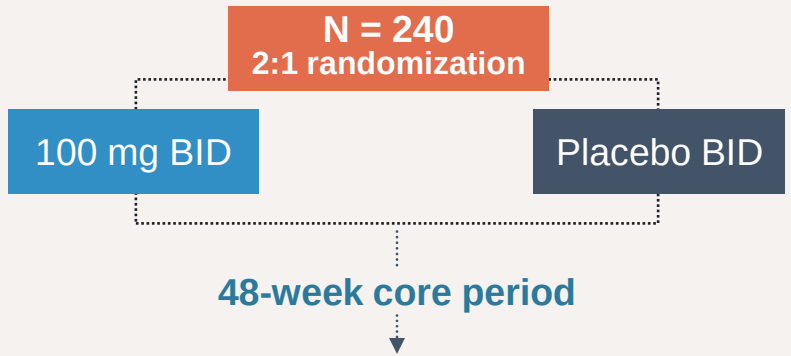
Secondary endpoints

- Fatigue, additional measures of Hb ↑, hemolysis, patient-reported outcomes, physical activity, iron metabolism, safety, PK/PD

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



Primary endpoint

- 50% reduction in transfusion burden in any 12-week rolling period

Secondary endpoints

- Additional measures of transfusion reduction, safety, PK/PD

Key inclusion criteria

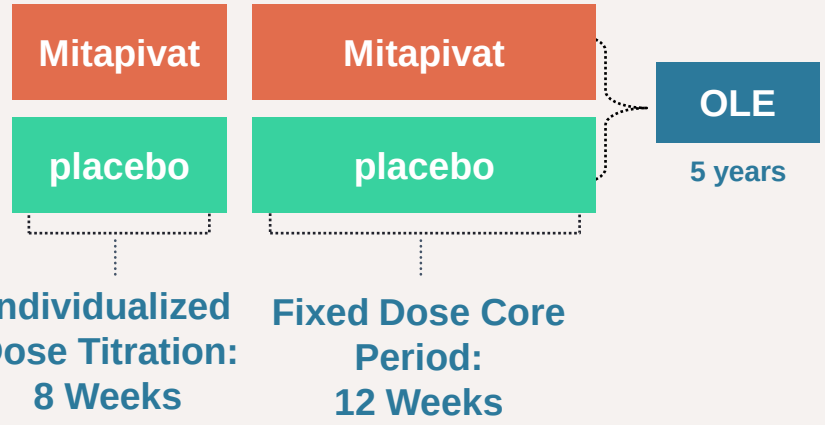
- ≥ 18 years
- β-thalassemia ± α-globin mutations, HbE β-thalassemia, or α-thalassemia (HbH disease)
- Transfusion-dependent defined as 6 to 20 RBC units transfused and ≤6-week transfusion-free period during the 24-week period before randomization

BID = twice daily; Hb = hemoglobin; HbE = hemoglobin E; HbH = hemoglobin H; PK = pharmacokinetics; PD = pharmacodynamics.

Mitapivat development program in pediatric PK deficiency to support potential label expansion to those under 18

ACTIVATE-Kids™

Not Regularly Transfused PK Deficiency N=30
Randomize 2:1

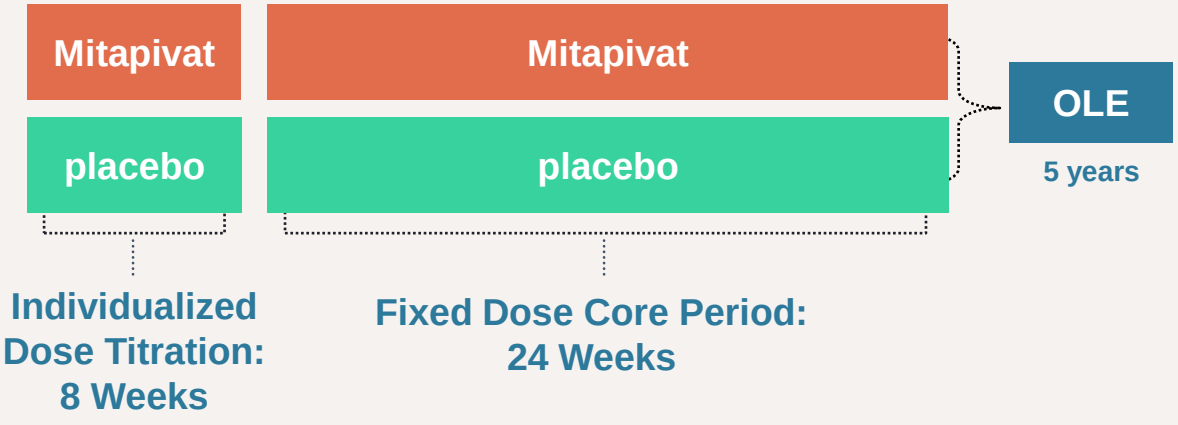


Eligibility

- 1 to <18 years of age
- 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 five transfusions in the 12 months prior and no transfusions in the 12 weeks prior to the first day of study treatment

ACTIVATE-KidsT™

Regularly Transfused PK Deficiency N=45
Randomize 2:1



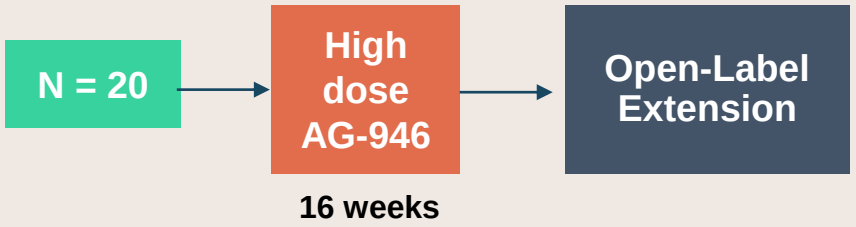
Eligibility

- 1 to <18 years of age
- Six to 26 transfusion episodes in the 52-week period before providing informed consent

OLE = open label extension.

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

Phase 2a — Open Label

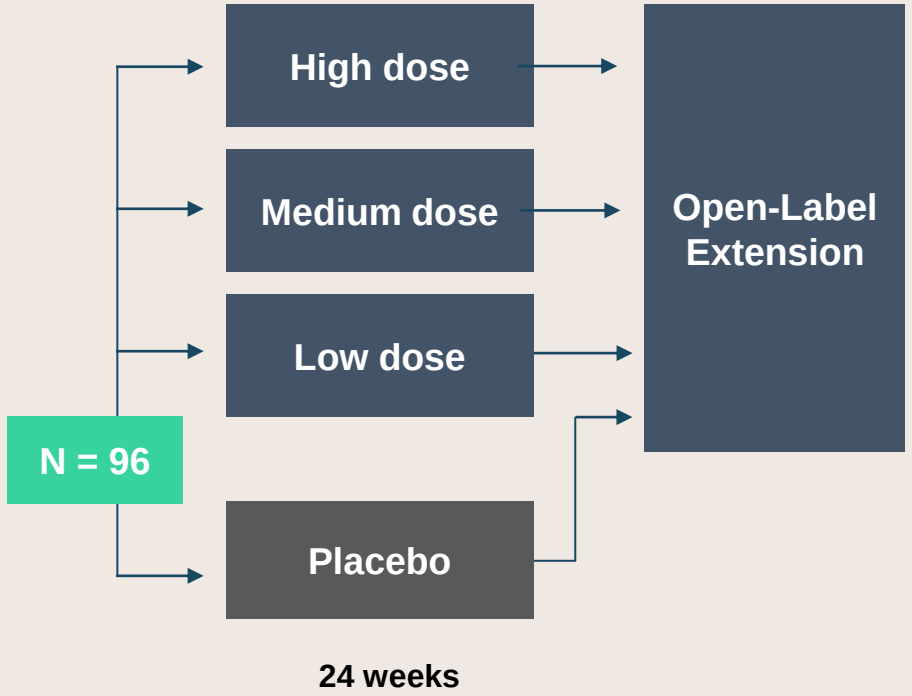


Primary endpoints:

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

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

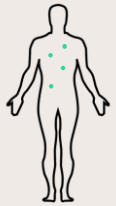
Phase 2b — Double Blind, 1:1:1:1 Randomization



LR-MDS = Lower-risk Myelodysplastic Syndrome; PK = pharmacokinetics; PD = pharmacodynamics.

Lead research program aimed to address phenylketonuria (PKU)

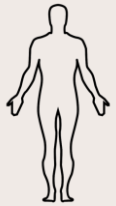
1



Normal Protein Diet

A mixed diet provides your body Phe

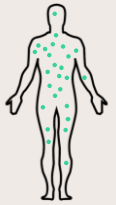
2



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 PKU

PHENYLKETONURIA (PKU)

- Rare, genetic disease with limited treatment options
- Prevalence: total of ~35-40K patients in the U.S. and EU5
- Driven by deficiency of phenylalanine hydroxylase (PAH) enzyme
- Lack of PAH activity leads to accumulation of phenylalanine and downstream sequelae
- PKU patients are often advised to consume a highly restricted diet, further reducing quality of life

AGIOS PROGRAM

- Oral PAH stabilizer designed to reduce phenylalanine levels
- Targeting IND filing by year-end 2023

Sources: National PKU Alliance, www.npkua.org and Weisbren et al ‘Phenylalanine blood levels and clinical outcomes in phenylketonuria’; The American Journal of Human Genetics 107, 234–250, August 6, 2020; Agios internal estimates