UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): January 8, 2024

Agios Pharmaceuticals, Inc.
(Exact Name of Registrant as Specified in Charter)

Delaware	**001-36014**	**26-0662915**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

88 Sidney Street, Cambridge, MA	**02139**
(Address of Principal Executive Offices)	**(Zip Code)**

Registrant's telephone number, including area code: (617) 649-8600

(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (*see* General Instruction A.2. below):

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading symbol(s)**	**Name of each exchange on which registered**
Common Stock, Par Value $0.001 per share	AGIO	Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company ☐

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 7.01 Regulation FD Disclosure.

On January 8, 2024, Agios Pharmaceuticals, Inc. (the "Company") issued a press release outlining its anticipated 2024 milestones and value-driving catalysts through 2026, which will be discussed at the Company's presentation at the 42nd Annual J.P. Morgan Healthcare Conference on January 10, 2024. The full text of the press release is furnished as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated herein by reference. The slides to be presented by the Company at the 42nd Annual J.P. Morgan Healthcare Conference are furnished as Exhibit 99.2 to this Current Report on Form 8-K and are incorporated herein by reference.

The information in this Item 7.01 (including Exhibit 99.1 and Exhibit 99.2) shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits.

Exhibit No.	Description
99.1	Press release issued January 8, 2024.
99.2	Presentation at the 42nd Annual J.P. Morgan Healthcare Conference
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

AGIOS PHARMACEUTICALS, INC.

Date: January 8, 2024

By: /s/ Brian Goff
Brian Goff
Chief Executive Officer

Agios Announces Key Anticipated 2024 Milestones Across Rare Disease Portfolio

– Industry-leading PK Activator Franchise Has Demonstrated Clinical Efficacy in Four Hematological Diseases, Including New Positive Phase 3 Data in Non-Transfusion-Dependent Thalassemia –

– Company Expects Four Additional Phase 3 Readouts by the End of 2025, with Potential FDA Approvals in Thalassemia in 2025 and Sickle Cell Disease in 2026 –

– Strong Cash Position Expected to Support Completion of Ongoing Programs and Disciplined Pipeline Expansion at least into 2026 –

CAMBRIDGE, Mass., Jan. 8, 2024 — Agios Pharmaceuticals, Inc. (Nasdaq: AGIO), a leader in the field of cellular metabolism pioneering therapies for rare diseases, today announced its anticipated 2024 milestones and value-driving catalysts through 2026 that support the company's mission to transform patient outcomes in rare diseases. Agios will present at the 42nd Annual J.P. Morgan Healthcare Conference on Wednesday, January 10, 2024, at 7:30 a.m. PT, and a live webcast will be available at investor.agios.com.

"We were pleased to announce positive topline data from the Phase 3 study of our lead PK activator, mitapivat, in non-transfusion-dependent alpha- or beta-thalassemia last week, a segment of the population with no currently approved therapeutic options in the U.S. We look forward to data readouts from four additional Phase 3 studies across our industry-leading PK activator franchise by the end of 2025," said Brian Goff, chief executive officer at Agios. "This robust series of near-term catalysts positions Agios for potential launches of a first- and best-in-class therapy in thalassemia in 2025 and in sickle cell disease in 2026, and we look forward to maximizing the commercial opportunities ahead of us. Supported by our strong cash position, Agios is poised for significant progress in the next 12-24 months, and we look forward to the opportunity to deliver a novel oral treatment option for two additional hematologic diseases with high unmet need."

2023 Highlights

- *Thalassemia:* Completed enrollment in the Phase 3 ENERGIZE and ENERGIZE-T studies of mitapivat in non-transfusion-dependent and transfusion-dependent thalassemia, respectively
- *Sickle Cell Disease:* Announced positive data from the Phase 2 portion of the RISE UP study of mitapivat and dosed the first patients in the Phase 3 portion
- *Pediatric PK Deficiency:* Completed enrollment in the Phase 3 ACTIVATE kids-T study of mitapivat in children with PK deficiency who are regularly transfused. Enrolled more than half of patients in the Phase 3 ACTIVATE-kids study of mitapivat in children with pediatric PK deficiency who are not regularly transfused
- *Lower-risk Myelodysplastic Syndromes (LR-MDS):* Announced clinical proof-of-concept in Phase 2a study of AG-946, supporting continued development in Phase 2b
- *Earlier-stage Pipeline:* Filed an Investigational New Drug Application (IND) for PAH stabilizer for the treatment of phenylketonuria (PKU)
- *Business Development:* Announced exclusive worldwide license agreement with Alnylam for novel siRNA targeting TMPRSS6 for the potential treatment of polycythemia vera (PV)

- *Data Presentations:* Presented broad set of clinical and translational data at the 65th American Society of Hematology (ASH) Annual Meeting & Exposition, including positive data from the Phase 2 portion of the RISE UP study of mitapivat in sickle cell disease

Anticipated 2024 Milestones

- *Thalassemia:* Following the announcement of topline data from the Phase 3 ENERGIZE study last week, Agios plans to report topline data from the Phase 3 ENERGIZE-T study of mitapivat in transfusion-dependent thalassemia (mid-year) and submit a New Drug Application (NDA) for mitapivat in thalassemia (year-end)
- *Sickle Cell Disease:* Complete enrollment in the Phase 3 portion of the RISE UP study of mitapivat (year-end)
- *Pediatric PK Deficiency:* Complete enrollment in the Phase 3 ACTIVATE-kids study of mitapivat (mid-2024). Report topline data from Phase 3 ACTIVATE kids-T study (year-end)
- *Lower-risk Myelodysplastic Syndromes (LR-MDS):* Dose first patient in Phase 2b study of AG-946 (mid-year)
- *Earlier-stage Pipeline:* Dose the first patient in the Phase 1 study of PAH stabilizer for the treatment of PKU (H1 2024)

Four Additional Phase 3 Readouts and Two Potential New Indication Approvals Expected by End of 2026

2024

- Data readout from Phase 3 ENERGIZE study of mitapivat in non-transfusion-dependent thalassemia (announced January 3, 2024)
- Data readout from Phase 3 ENERGIZE-T study of mitapivat in transfusion-dependent thalassemia (mid-year)
- Data readout from Phase 3 ACTIVATE kids-T study of mitapivat in pediatric PK deficiency (year-end)

2025

- Data readout from Phase 3 portion of the RISE UP study of mitapivat in sickle cell disease
- Data readout from Phase 3 ACTIVATE kids study of mitapivat in pediatric PK deficiency
- Potential FDA approval for mitapivat in thalassemia

2026

- Potential FDA approval for mitapivat in sickle cell disease
- Potential FDA approval for mitapivat in pediatric PK deficiency

Presentation at 42nd Annual J.P. Morgan Healthcare Conference

Agios will webcast its corporate presentation from the 42nd Annual J.P. Morgan Healthcare Conference on Wednesday, January 10 at 7:30 a.m. PT. A live webcast of the presentation can be accessed under “Events & Presentations” in the Investors section of the company’s website at agios.com. A replay of the webcast will be archived on the Agios website for at least two weeks following the presentation.

About Agios

Agios is the pioneering leader in PK activation and is dedicated to developing and delivering transformative therapies for patients living with rare diseases. In the U.S., Agios markets a first-in-class pyruvate kinase (PK) activator for adults with PK deficiency, the first disease-modifying therapy for this rare, lifelong, debilitating hemolytic anemia. Building on the company's deep scientific expertise in classical hematology and leadership in the field of cellular metabolism and rare hematologic diseases, Agios is advancing a robust clinical pipeline of investigational medicines with programs in alpha- and beta-thalassemia, sickle cell disease, pediatric PK deficiency and MDS-associated anemia. In addition to its clinical pipeline, Agios is advancing a preclinical TMPRSS6 siRNA as a potential treatment for polycythemia vera (PV), and a preclinical PAH stabilizer as a potential treatment for phenylketonuria (PKU). For more information, please visit the company's website at www.agios.com.

Cautionary Note Regarding Forward-Looking Statements

This press release contains 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, Agios's PAH stabilizer and its novel siRNA Targeting TMPRSS6; Agios' plans, strategies and expectations for its preclinical, clinical and commercial advancement of its drug development, including PYRUKYND®, AG-946, its PAH stabilizer and its novel siRNA Targeting TMPRSS6; Agios' strategic vision and goals, including its key milestones for 2024 and potential catalysts through 2026; and the potential benefits of Agios's strategic plans and focus. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "would," "could," "potential," "possible," "hope," "strategy" and "vision" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Such statements are subject to numerous important factors, risks and uncertainties that may cause actual events or results to differ materially from Agios' current expectations and beliefs. For example, there can be no guarantee that any product candidate Agios or its collaborators is developing will successfully commence or complete necessary preclinical and clinical development phases, or that development of any of Agios' product candidates will successfully continue. Moreover, there can be no guarantee that any medicines ultimately commercialized by Agios will receive commercial acceptance. 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 press release 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 pandemics 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; Agios' ability to obtain, maintain and enforce patent and other intellectual property protection for any product candidates it is developing; Agios' ability to establish and maintain 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; competitive factors; 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 press release 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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Exhibit 99.2

agios

J.P. Morgan Healthcare Conference

Agios Pharmaceuticals

Brian Goff, Chief Executive Officer
January 10, 2024

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 2024 and potential catalysts through 2026; and the potential benefits of Agios' strategic plans and focus. The words "anticipate," "expect," "goal," "hope," "milestone," "opportunity," "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 pandemics 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; Agios' ability to obtain, maintain and enforce patent and other intellectual property protection for any product candidates it is developing; Agios' ability to establish and maintain 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; competitive factors; 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.

Our Mission

Ryan
Thalassemia

Develop and deliver transformative medicines that elevate and extend the lives of patients

Our Vision

Tamara
Pyruvate Kinase Deficiency

To become a leading rare disease company providing first-in-class and/or best-in-class new therapies for diseases with high unmet need

Our Values

Sharonda
Sickle Cell Disease

Aim High

Come Together

Embrace Differences

Bring Your Whole Self

Blaze New Trails

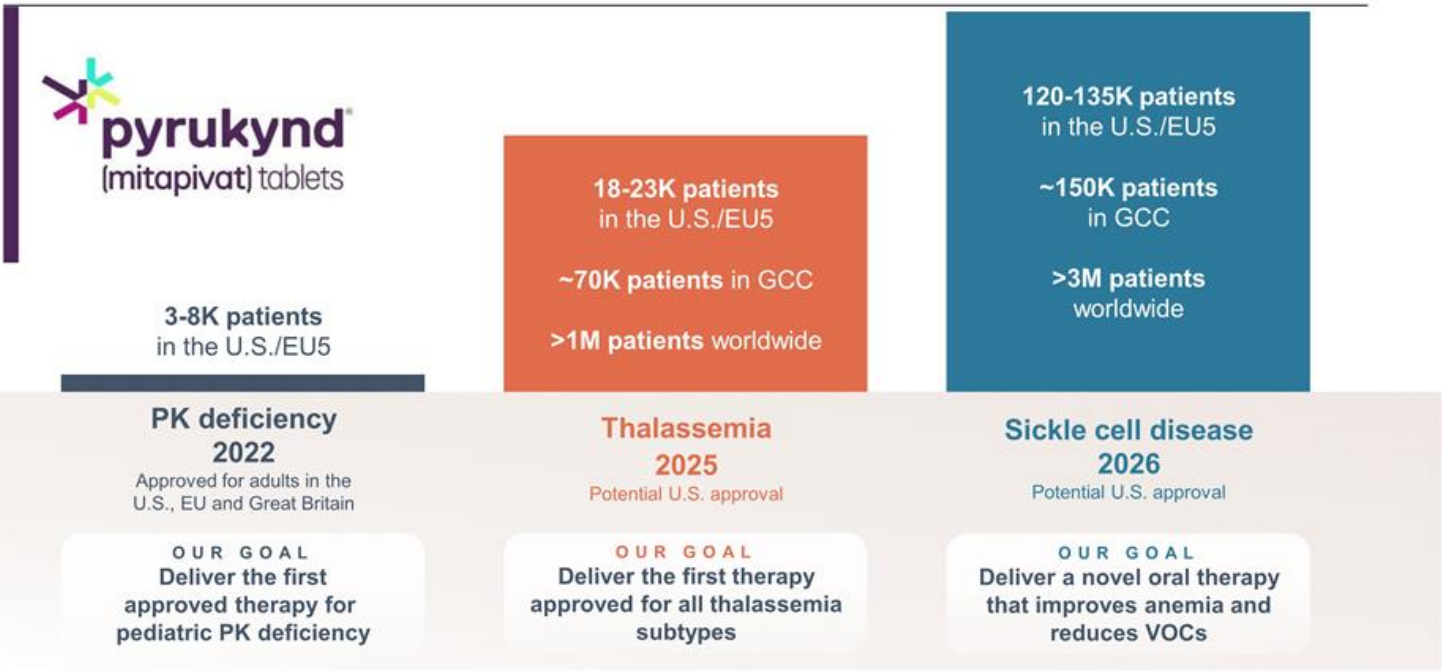
Fueled by Connections to Transform Rare Diseases

Well-positioned with multiple near-term catalysts to enter multi-billion dollar markets and deliver significant value

PKa franchise with multi-billion dollar potential	Differentiated mechanism of action	Increasing probability of success	Growing pipeline
Large opportunities with substantial value - potential for two additional **first and best-in-class** indications for PYRUKYND® by 2026	**Clearly differentiated** PK activation franchise targeting red blood cell health **beyond hemoglobin** increase	Proven track record supported by **compelling and consistent data** to date	Diversified pipeline addressing the underlying pathophysiology of **rare diseases with high unmet need**

PK = pyruvate kinase
Pka = pyruvate kinase activation

PYRUKYND® expansion into diseases with larger patient populations provides significant near-term growth potential for first- and best-in-class therapies



PK deficiency
2022
Approved for adults in the U.S., EU and Great Britain

OUR GOAL
Deliver the first approved therapy for pediatric PK deficiency

Thalassemia
2025
Potential U.S. approval

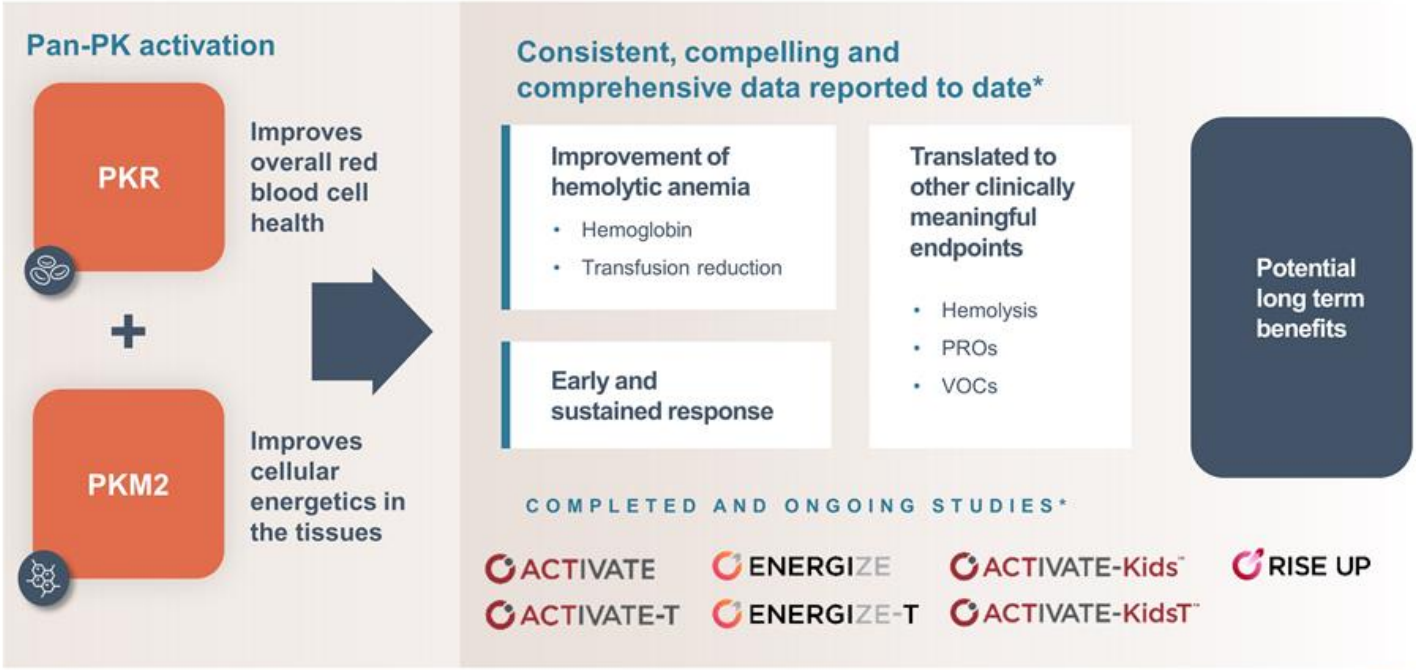
OUR GOAL
Deliver the first therapy approved for all thalassemia subtypes

Sickle cell disease
2026
Potential U.S. approval

OUR GOAL
Deliver a novel oral therapy that improves anemia and reduces VOCs

PYRUKYND® is approved in the U.S., EU, and Great Britain for adult PK deficiency and is under investigation for pediatric PK deficiency, thalassemia, and sickle cell disease.
Source: Agios internal estimates

Unique PK activation mechanism has demonstrated comprehensive benefits beyond hemoglobin improvement

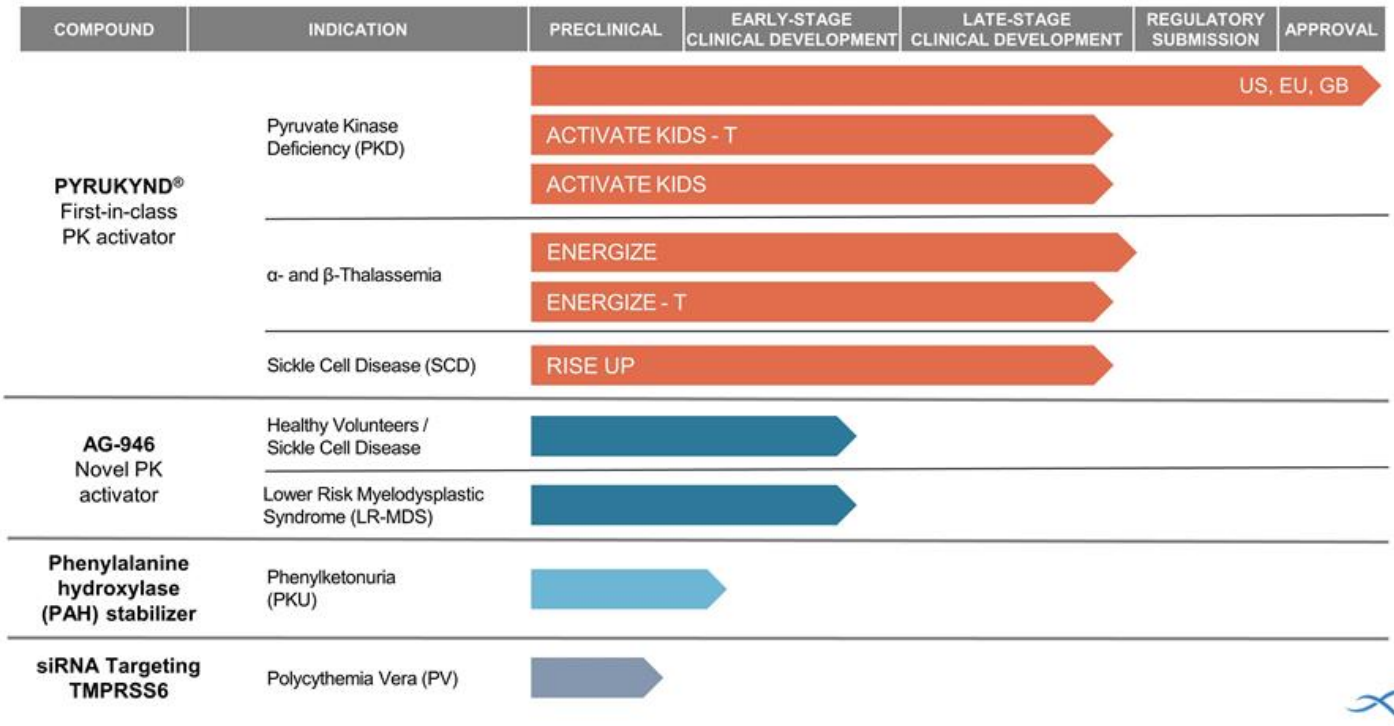


*Completed studies/reported/published data include: ACTIVATE and ACTIVATE-T (PKD), ENERGIZE (Thalassemia), RISE UP Phase 2 portion (SCD). Additional data expected from four ongoing phase 3 studies

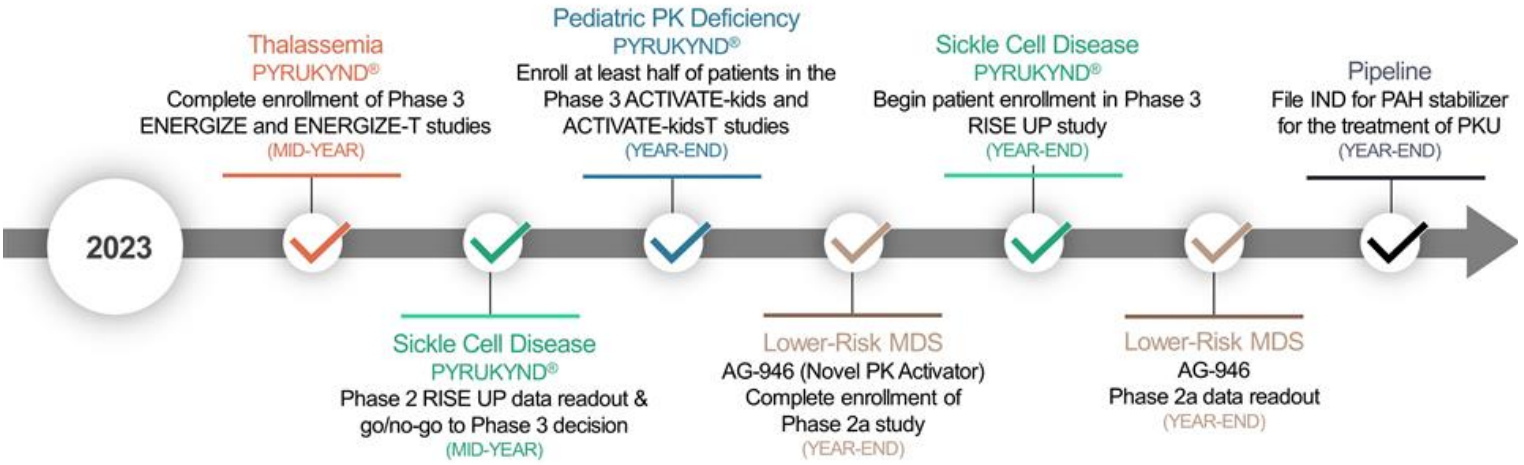
2020 Pipeline: the beginning of a rare disease portfolio leveraging our expertise in cellular metabolism

COMPOUND	INDICATION	PRECLINICAL	EARLY-STAGE CLINICAL DEVELOPMENT	LATE-STAGE CLINICAL DEVELOPMENT	REGULATORY SUBMISSION	APPROVAL
PYRUKYND® First-in-class PK activator	Pyruvate Kinase Deficiency (PKD)	ACTIVATE AND ACTIVATE- T				
	α- and β-Thalassemia	PHASE 2				
AG-946 Novel PK activator	Healthy Volunteers / Sickle Cell Disease (SCD)	PHASE 1				

2024 Pipeline: significant advancement building depth and breadth in our rare disease pipeline



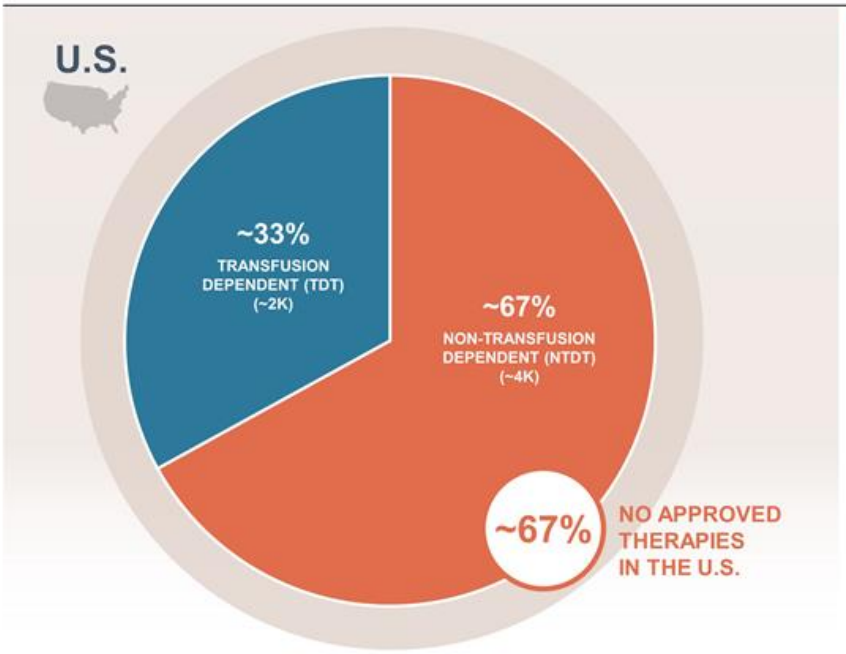
Momentum building as we delivered on all 2023 goals to expand and advance our pipeline and strengthened clinical evidence across our PKa franchise



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

Pipeline
License Agreement with Alnylam for novel siRNA for potential treatment of PV
(Q3 2023)

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



Mitapivat Thalassemia Phase 3 program

ENERGIZE

- **Alpha- and Beta-thalassemia Non-transfusion dependent** patients
- Primary endpoint: Hemoglobin (Hb) response
- **Data announced January 2024**

ENERGIZE-T

- **Alpha- and Beta-thalassemia Transfusion dependent** patients
- Primary endpoint: Transfusion Reduction Response
- **Data readout mid-2024**

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.

Thalassemia in all forms remains an area of high unmet need, high morbidity and significant impact on quality of life

Disease Impact

Increased Mortality

Survival is lower than the general population and **is significantly worse in those who remain non-regularly transfused than those who are regularly transfused**

Serious, Irreversible Morbidities

High rates of morbidities (even compared to TDT – e.g., thrombosis); frequency of complications increasing as patients age

Poor Quality of Life

Adult patients with **NTDT may have similar or worse Healthcare Related QoL** compared with patients with TDT

Healthcare Resource Utilization & Cost

A 1g/dL decrease in average Hb levels is associated with **increased inpatient, outpatient and ER visits/costs, Rx costs, and total healthcare costs** in patients with NTDT

NTDT = non-transfusion dependent thalassemia; TDT = transfusion dependent thalassemia; GCC = Gulf Council Countries

Source: Musallam, K, et al., 2022. Hemasphere 6(12) e806; Thalassemia International Federation, 2023; Musallam, K, et al., 2021. Am J Hematol 97(2) E78-E80; Association of Hemoglobin Levels with Healthcare Resource Utilization and Costs in Non-Transfusion Dependent Alpha and Beta Thalassemia: A Retrospective Observational Study Using Real-World Data (August 1, 2023); Musallam KM et al. Ann Hematol 2021. doi: 10.1007/s00277-020-04370-2; Musallam K., et al. Haematologica. 2021 Sep 1; 106(9): 2489–2492.

ENERGIZE: achieved significance across both primary and all key secondary endpoints

ENERGIZE

Key findings in ENERGIZE trial

- Total of **194 patients** were randomized 2:1 to 100 mg mitapivat (n=130) or placebo (n=64)
- **Statistically significant increase in hemoglobin response rate (42.3%)** compared to patients on placebo (1.6%)
- Statistically significant change from baseline in **average FACIT-Fatigue score and average hemoglobin concentration**
- During the 24-week double-blind period, 4 subjects in the mitapivat arm experienced adverse events (AEs) leading to discontinuation; no AEs in the placebo arm leading to discontinuation
- All pre-specified subgroup analyses favored the mitapivat treatment arm compared to placebo

Next Steps

- Full data set to be presented at an upcoming medical meeting
- ENERGIZE T readout expected by **mid-year**
- Data to be submitted together to FDA **by year end**
- Potential US **launch in 2025**

Hemoglobin response is defined as ≥1.0 g/dL (10 g/L) increase in average Hb concentrations from Week 12 through Week 24 compared with baseline.

Thalassemia: an attractive global rare disease opportunity with limited or no treatment options and geographic concentration

US Thalassemia Market Opportunity

- **6,000** diagnosed adult patients in US
- Most patients diagnosed before adulthood
- Nearly **70% of patients** have no treatment options
- **Concentrated** providers: ~50% of active adult patients in <150 hem/onc practices
- **Recognized** high unmet need
- Well-established **ICD-10 codes**
- Established patient advocacy organizations

+ GCC prevalence ~8-9x the US

PYRUKYND

- **All-inclusive** global trial design
- ENERGIZE demonstrated **statistically significant results** on primary and all key secondary endpoints
- ENERGIZE-T readout in mid-2024
- Opportunity to deliver **best-in-class** therapy and transform treatment for the **full range** of thalassemia patients
- Potential US **launch in 2025**

Source: Compile Claims Analysis August 2023; Note: active patients defined as those with transfusion or thalassemia ICD-10 diagnosis code in 2022; heme/oncs include PCPs and NP/PAs affiliated with heme/oncs; COEs CDC Funded Thalassemia Treatment Centers, Thalassemia Western Consortium, BMS / Agios Clinical Trial Sites; top affiliated practices include community and academic heme/onc practices in top 5 deciles; 3+ heme/onc visits within 1 year
NTD: non-transfusion dependent; TD: transfusion dependent; GCC = Gulf Council Countries

Sickle Cell Disease remains an area of significant need for innovative therapies that can demonstrate meaningful benefits beyond hemoglobin increase

Disease Overview

Genetic blood disorder that causes **sickling of red blood cells**

Caused by mutations in HBB gene leading to **anemia, hemolysis and sickle cell pain crises**

Market Opportunity

No novel oral therapy **improves anemia and reduces sickle cell pain crises (SCPC)**

Significant global opportunity
~100,000 patients in the U.S.
>3 million worldwide

Lifelong impact on SCD patients

~45 years
Average life expectancy

~10%
Deaths from renal impairment

~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; Platt et al, 1994; Brandow et al. J Hematol Oncol 15, 20 (2022). Agios market research

PYRUKYND: a novel oral therapy with potential to be best-in-class improving anemia, reducing SCPCs and improving how patients feel and function

RISE UP

Phase 2 Data

- **Statistically significant increase in hemoglobin response** rate observed in both doses compared to placebo
- **Improvements in markers of hemolysis and erythropoiesis** observed at both doses compared to placebo
- A **trend in sickle cell pain crises reduction** was observed at both doses compared to placebo
- No adverse events (AEs) leading to discontinuation

Phase 3 Design[2]

- **Phase 3 primary endpoints:** Hb response[3] and annualized rate of SCPCs
- **N = 198** with a 2:1 randomization (100 mg mitapivat and placebo)
- **52-week** double blinded period followed by 216-week open label extension

PYRUKYND

- Seamless Phase 2/3 global study **designed with community input**
- Potential for mitapivat to:
  - **improve anemia**
  - **reduce sickle cell pain crises**
  - **improve how patients feel and function**
- Expected data readout in 2025
- Potential US **launch in 2026**

Abbreviations: BID = twice daily; Hb = hemoglobin; SCPC = sickle cell pain crises
(1) 100mg was selected for Phase 3 portion of the study
(2) Phase 2 and phase 3 components are part of a single study/protocol
(3) Hb response is defined as a ≥ 1.0 g/dL increase in average Hb concentration over Weeks 24–52 compared with baseline

Fueling growth beyond 2026, an early-stage pipeline addressing the underlying pathophysiology of rare diseases with high unmet need

Lower-Risk MDS

~75-80k patients in the U.S. and EU5

No oral therapy addresses ineffective erythropoiesis

40% Achieved Transfusion Independence endpoint in open-label Phase 2a study

Expect to initiate Phase 2b study of AG-946 in mid-2024

Phenylketonuria (PKU)

~35-40k patients in the U.S. and EU5

Limited treatment options; patients consume high restricted diet

IND filed December 2023

Expect to initiate Phase 1 study of oral PAH stabilizer in 2024

Polycythemia Vera (PV)

~100k patients in the U.S.

Phlebotomy is the standard of care

In-licensed siRNA from Alnylam in 2023

Advancing to pre-IND studies

Continuing clinical and regulatory milestone momentum into 2024

2024

EARLY

Thalassemia PYRUKYND®

Phase 3 data readout for ENERGIZE study (COMPLETED)

Pipeline

Begin Phase 1 dosing for PAH stabilizer for the treatment of PKU

MID-YEAR

Thalassemia PYRUKYND®

Phase 3 data readout for ENERGIZE-T study

Pediatric PK Deficiency PYRUKYND®

Complete enrollment Phase 3 ACTIVATE kids study

Lower-Risk MDS

AG-946 (Novel PK Activator)

Begin patient enrollment of Phase 2b study

YEAR-END

Thalassemia PYRUKYND®

Filing for FDA Approval

Sickle Cell Disease PYRUKYND®

Complete Phase 3 enrollment

Pediatric PK Deficiency PYRUKYND®

Phase 3 data readout ACTIVATE kids-T study

Strong beginning of 2024 with positive Thalassemia Phase 3 ENERGIZE readout and four additional Phase 3 readouts expected by the end of 2025

2024	2025	2026
✓ Thalassemia PYRUKYND® Phase 3 ENERGIZE readout (completed)	Sickle Cell Disease PYRUKYND® Phase 3 RISE UP readout	Sickle Cell Disease PYRUKYND® Potential approval
Thalassemia PYRUKYND® Phase 3 ENERGIZE-T readout	Thalassemia PYRUKYND® Potential approval	Pediatric PK Deficiency PYRUKYND® Potential approval
Pediatric PK Deficiency PYRUKYND® Phase 3 ACTIVATE kids-T readout	Pediatric PK Deficiency PYRUKYND® Phase 3 ACTIVATE kids readout	

Well-positioned with multiple near-term catalysts to enter multi-billion dollar markets and deliver significant value

PKa franchise with multi-billion dollar potential	Differentiated mechanism of action	Increasing probability of success	Growing pipeline
Large opportunities with substantial value - potential for two additional **first and best-in-class** indications for PYRUKYND® by 2026	**Clearly differentiated** PK activation franchise targeting red blood cell health **beyond hemoglobin** increase	Proven track record supported by **compelling and consistent data** to date	Diversified pipeline addressing the underlying pathophysiology of **rare diseases with high unmet need**

PK = pyruvate kinase
Pka = pyruvate kinase activation


agios
Thank you


agios
Appendix

PYRUKYND®: first Phase 3 program to encompass full range of thalassemia patients

ENERGIZE

24-week core period

Open-label extension (up to 5 years)

Primary endpoint

- Mean Hb ↑
  ≥ 1 g/dL from baseline

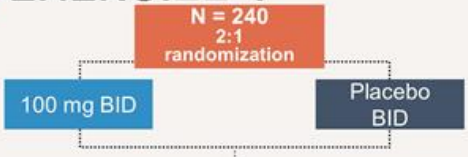
Secondary endpoints

- 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



48-week core period

Open-label extension (up to 5 years)

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.

Phase 3 ENERGIZE study: primary endpoint achieved

ENERGIZE

- Total of 194 patients were randomized 2:1 to 100 mg mitapivat (n=130) or placebo (n=64)
- Hemoglobin response is defined as ≥1.0 g/dL (10 g/L) increase in average Hb concentrations from Week 12 through Week 24 compared with baseline.
- **Treatment with mitapivat demonstrated a statistically significant increase in hemoglobin response rate compared to placebo**

Primary Endpoint	Placebo N=64	Mitapivat 100 mg BID N=130
Hemoglobin responders, n (%)	1 (1.6)	55 (42.3)
Adjusted difference of response rate (Mitapivat-Placebo), %		40.9
95% CI		(32.0, 49.8)
2-sided p-value		<0.0001

Abbreviations: RBC = red blood cell; Hb = hemoglobin. Subjects who do not have at least 2 on-treatment Hb concentration assessments between Week 12 and Week 24 are considered non-responders.

Baseline is defined as the average of all assessments within 42 days before randomization for subjects randomized and not dosed or within 42 days before the start of study treatment for subjects randomized and dosed.

Hb concentrations assessed within 8 weeks after an RBC transfusion are excluded from the baseline derivation and from the analysis.

The estimated adjusted difference in response rate, 95% CI and p-value are based on Mantel-Haenszel stratum weighted method adjusting for the randomization stratification factors.

Statistical significance also achieved for both key secondary endpoints

ENERGIZE

Key secondary endpoints: change from baseline in both hemoglobin concentration and FACIT-Fatigue Score

- Change from baseline in average hemoglobin concentration from Week 12 to Week 24
- Change from baseline in average FACIT-Fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue) subscale score from Week 12 to Week 24
- **Treatment with 100 mg mitapivat demonstrated statistically significant improvements on both key secondary endpoints compared to placebo**

Safety

- Overall, incidence of adverse events was similar across mitapivat and placebo arms.
- During the 24-week double-blind period, 4 (3.1%) subjects in the mitapivat arm experienced adverse events (AEs) leading to discontinuation; there were no AEs in the placebo arm leading to discontinuation

Advancing RISE UP Phase 3 Study of PYRUKYND® in sickle cell disease with expected readout in 2025

RISE UP

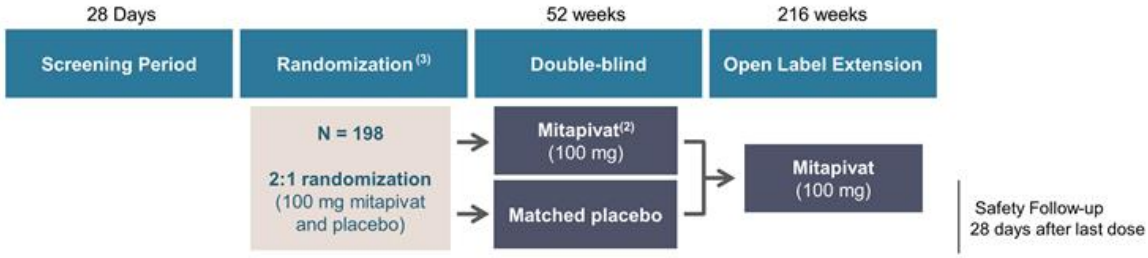
Phase 3 primary endpoints [1]:
Hb response, defined as a ≥ 1.0 g/dL increase in average Hb concentration over Weeks 24–52 compared with baseline, and annualized rate of SCPCs

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).

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

RISE UP

	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

RISE UP

CRC Adjudicated Data

Negative Binomial Regression Model

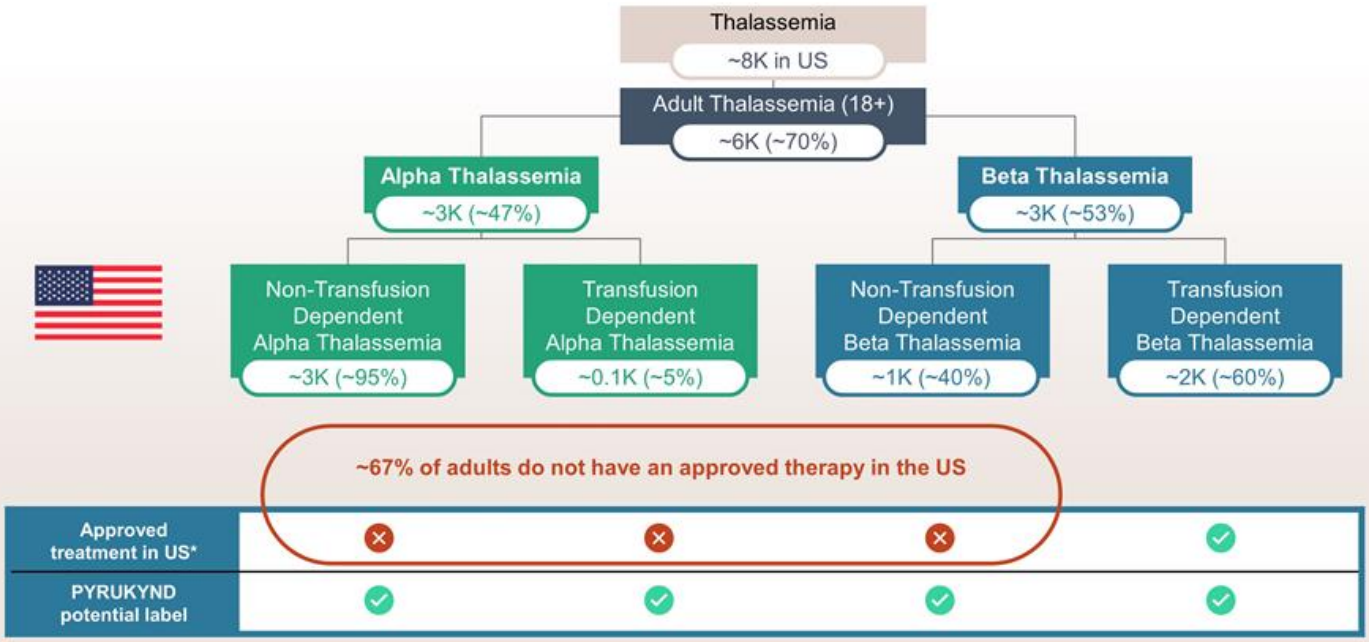
	Placebo N=27	Mitapivat 50 mg BID N=26	Mitapivat 100 mg BID N=26
Annualized Rate of SCPC	1.71	0.83	0.51
95% CI	(0.95, 3.08)	(0.34, 1.99)	(0.16, 1.59)
Rate ratio (Mitapivat/Placebo)		0.48	0.30
95% CI		(0.17, 1.39)	(0.08, 1.07)

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.

PYRUKYND® has the potential to become the first therapy approved for all thalassemia subtypes



Beta-THAL prevalence: HEOR Global THAL Epidemiology SLE (XCENDA, 2021); US: Paramore, et.al; 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