



# J.P. Morgan Healthcare Conference

## AgiOS Pharmaceuticals

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Brian Goff, Chief Executive Officer  
January 10, 2024



# Forward-looking statements

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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

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## PKa franchise with multi-billion dollar potential

**Large opportunities** with substantial value - potential for two additional **first and best-in-class** indications for PYRUKYND<sup>®</sup> by 2026

## Differentiated mechanism of action

**Clearly differentiated** PK activation franchise targeting red blood cell health **beyond hemoglobin** increase

## Increasing probability of success

Proven track record supported by **compelling and consistent data** to date

## Growing pipeline

Diversified pipeline addressing the underlying pathophysiology of **rare diseases with high unmet need**



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



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

## **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**

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

**~70K patients** in GCC

**>1M patients** worldwide

## **Thalassemia** **2025**

Potential U.S. approval

**OUR GOAL**  
**Deliver the first therapy**  
**approved for all thalassemia**  
**subtypes**

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

**~150K patients**  
in GCC

**>3M patients**  
worldwide

## **Sickle cell disease** **2026**

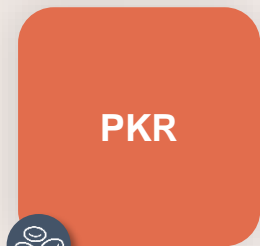
Potential U.S. approval

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



# Unique PK activation mechanism has demonstrated comprehensive benefits beyond hemoglobin improvement

## Pan-PK activation

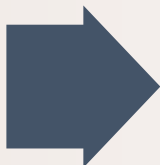


Improves overall red blood cell health

+



Improves cellular energetics in the tissues



## Consistent, compelling and comprehensive data reported to date\*

### Improvement of hemolytic anemia

- Hemoglobin
- Transfusion reduction

### Translated to other clinically meaningful endpoints

- Hemolysis
- PROs
- VOCs

### Early and sustained response

Potential long term benefits

## COMPLETED AND ONGOING STUDIES\*

 **ACTIVATE**

 **ENERGIZE**

 **ACTIVATE-Kids™**

 **RISE UP**

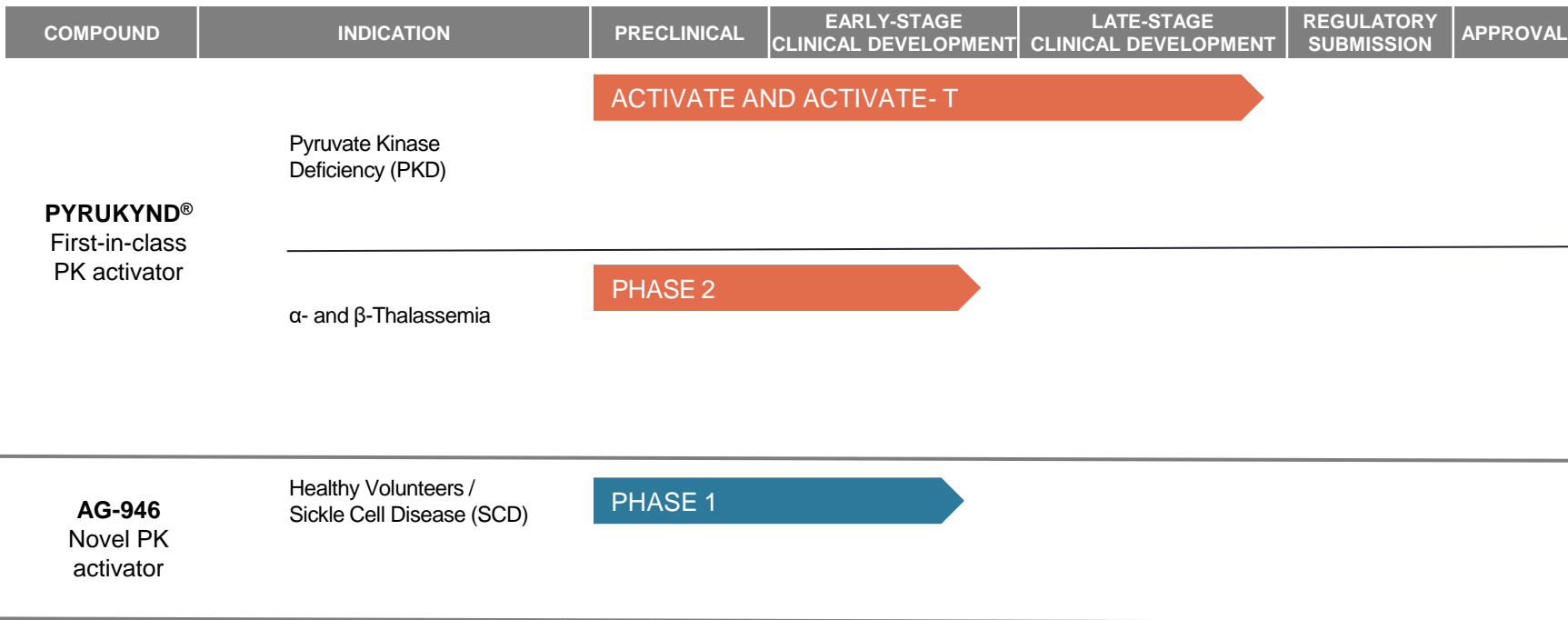
 **ACTIVATE-T**

 **ENERGIZE-T**

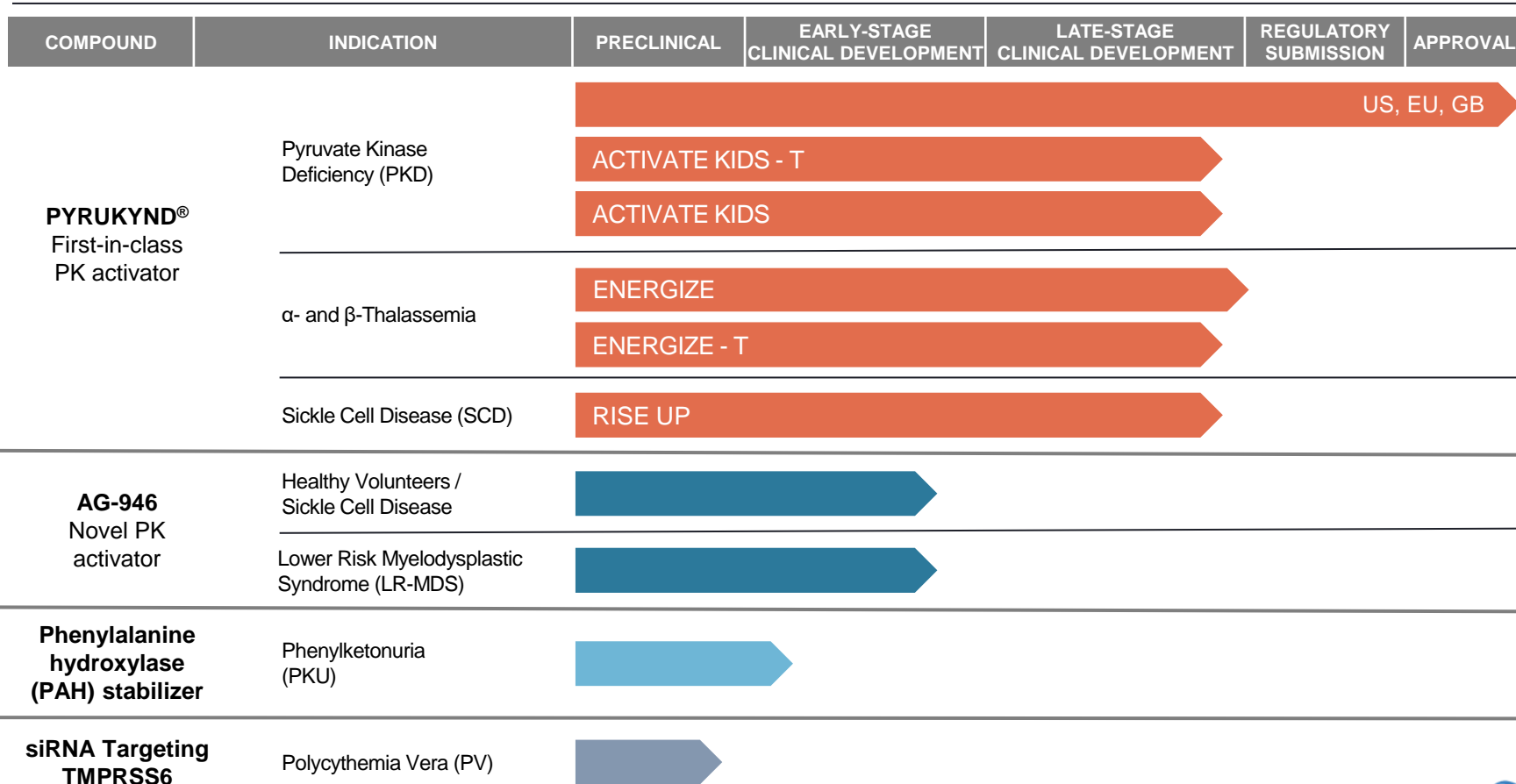
 **ACTIVATE-KidsT™**



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

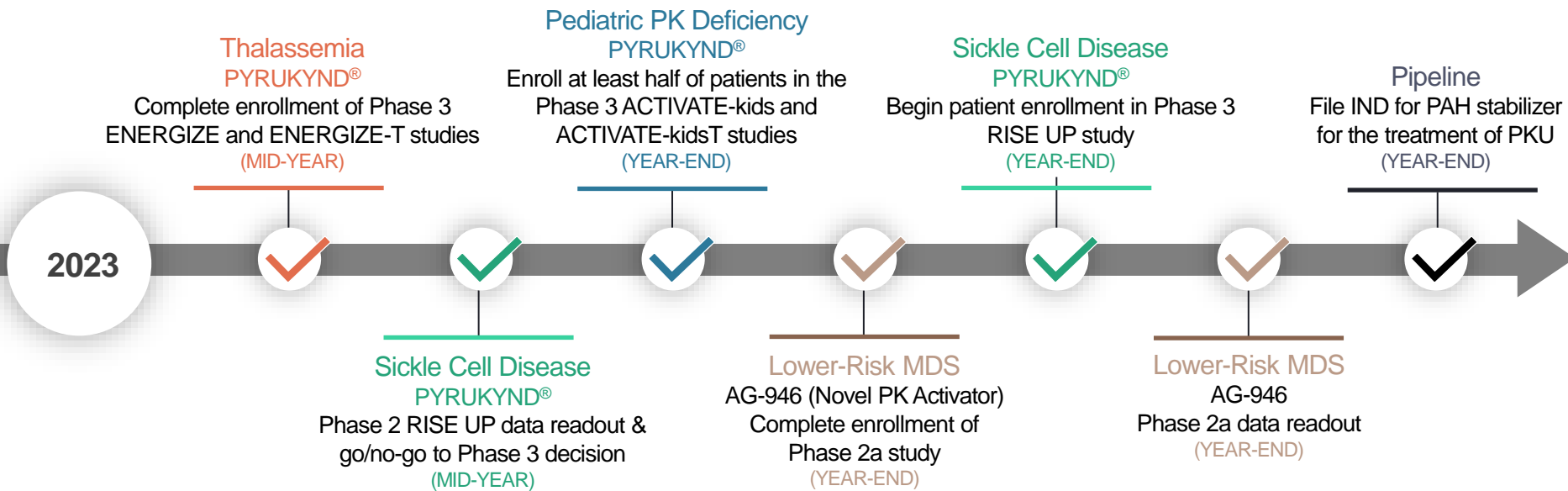


# 2024 Pipeline: significant advancement building depth and breadth in our rare disease pipeline





# 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

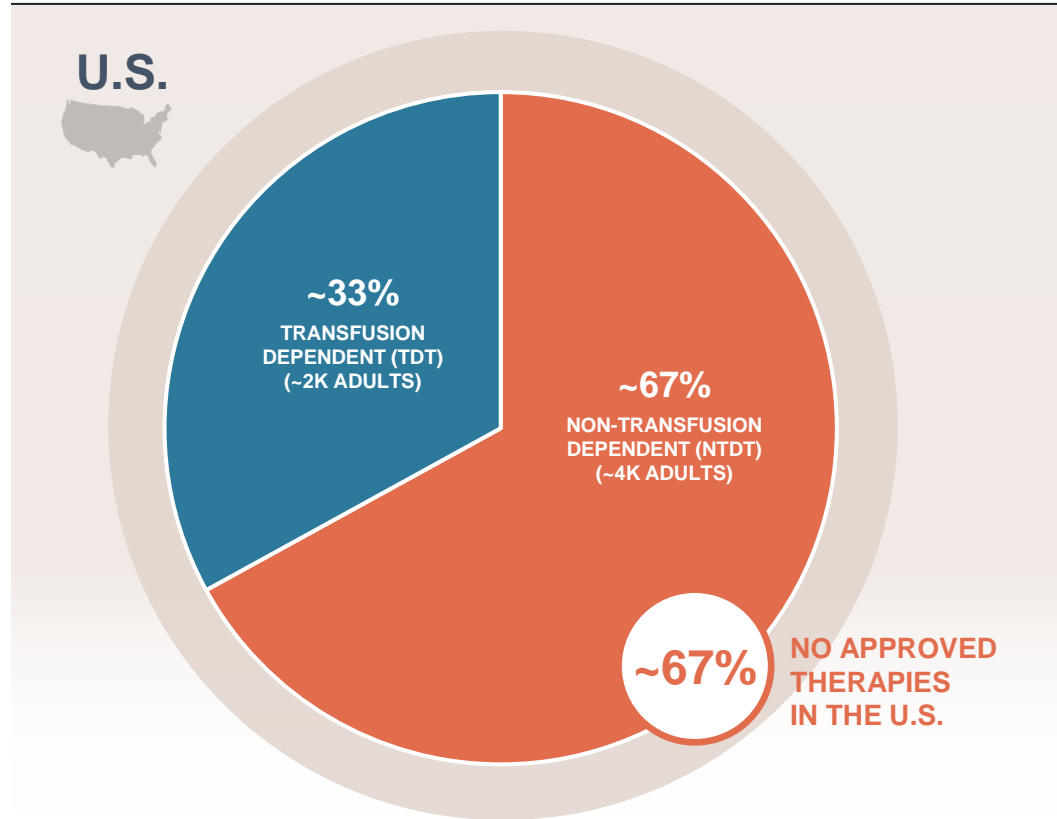


## Pipeline

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**



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

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

**~70K patients**  
in GCC

**>1M patients**  
worldwide

## 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



## 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**



# 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**



# 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



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



## 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<sup>(2)</sup>

- **Phase 3 primary endpoints:** Hb response<sup>(3)</sup> 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  $\geq 1.0$  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®**

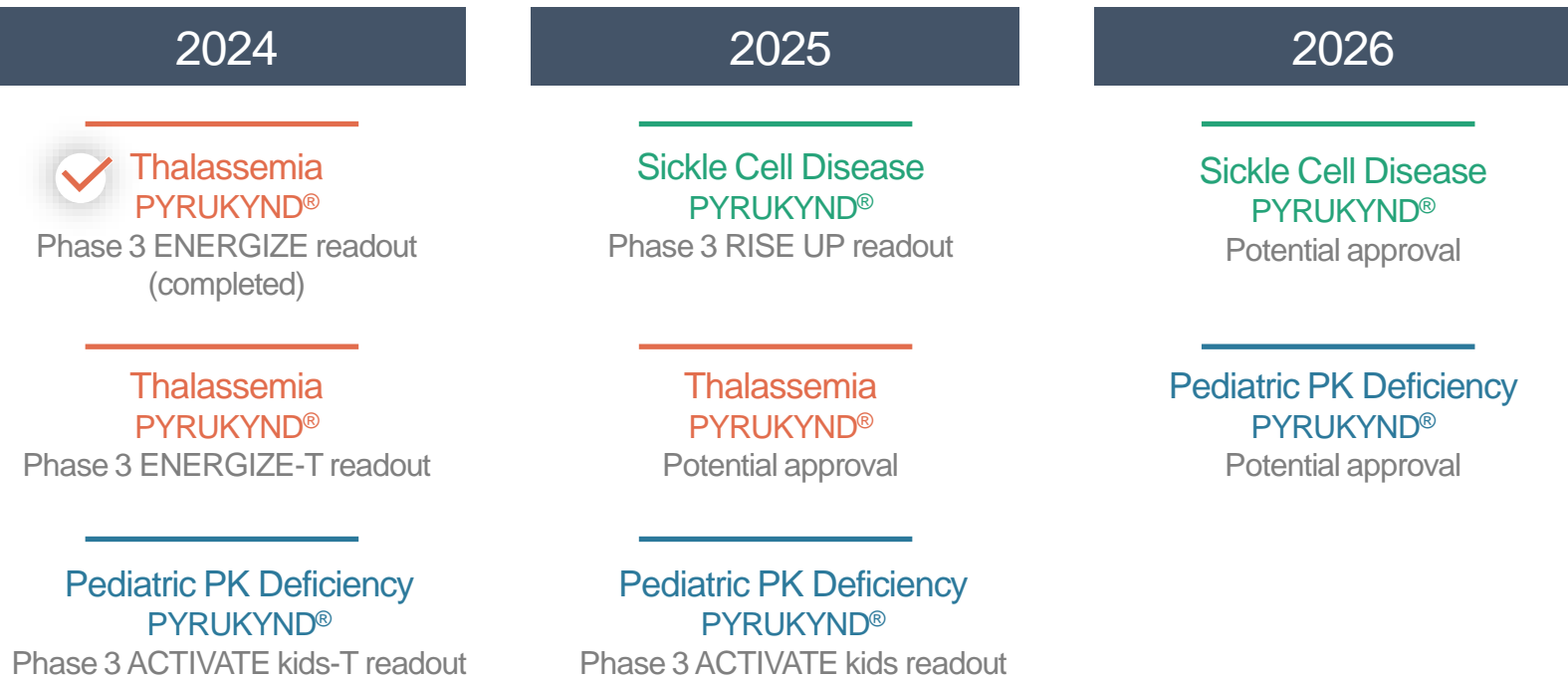
Complete Phase 3 enrollment

**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



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

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## PKa franchise with multi-billion dollar potential

**Large opportunities** with substantial value - potential for two additional **first and best-in-class** indications for PYRUKYND<sup>®</sup> by 2026

## Differentiated mechanism of action

**Clearly differentiated** PK activation franchise targeting red blood cell health **beyond hemoglobin** increase

## Increasing probability of success

Proven track record supported by **compelling and consistent data** to date

## Growing pipeline

Diversified pipeline addressing the underlying pathophysiology of **rare diseases with high unmet need**





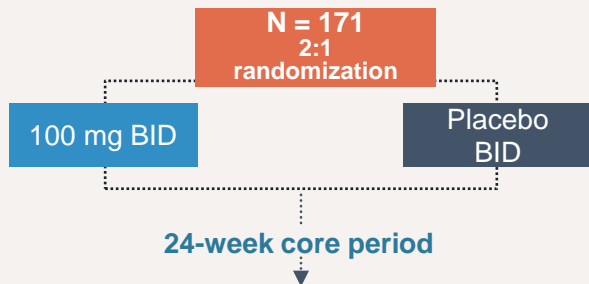
Thank you



# Appendix

# PYRUKYND<sup>®</sup>: first Phase 3 program to encompass full range of thalassemia patients

## ENERGIZE



Open-label extension (up to 5 years)

### Primary endpoint

- Mean Hb  $\uparrow$   
 $\geq 1$  g/dL from baseline

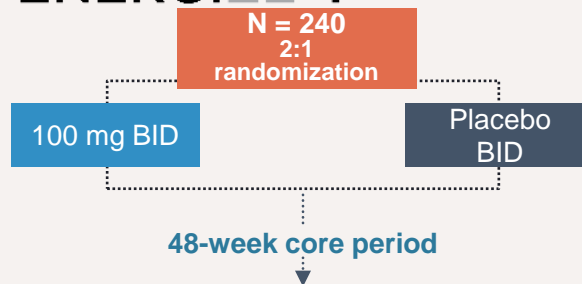
### Secondary endpoints

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

### Key inclusion criteria

- $\geq 18$  years
- $\beta$ -thalassemia  $\pm$   $\alpha$ -globin mutations, HbE  $\beta$ -thalassemia, or  $\alpha$ -thalassemia (HbH disease)
- Non-transfusion-dependent defined as  $\leq 5$  RBC units during the 24-week period before randomization and no RBC transfusions  $\leq 8$  weeks prior
- Hb  $\leq 10.0$  g/dL

## ENERGIZE-T



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

- $\geq 18$  years
- $\beta$ -thalassemia  $\pm$   $\alpha$ -globin mutations, HbE  $\beta$ -thalassemia, or  $\alpha$ -thalassemia (HbH disease)
- Transfusion-dependent defined as 6 to 20 RBC units transfused and  $\leq 6$ -week transfusion-free period during the 24-week period before randomization



- Total of 194 patients were randomized 2:1 to 100 mg mitapivat (n=130) or placebo (n=64)
- Hemoglobin response is defined as  $\geq 1.0$  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)
<b>Adjusted difference of response rate (Mitapivat-Placebo), %</b>		40.9
<b>95% CI</b>		(32.0, 49.8)
<b>2-sided p-value</b>		<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.



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

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

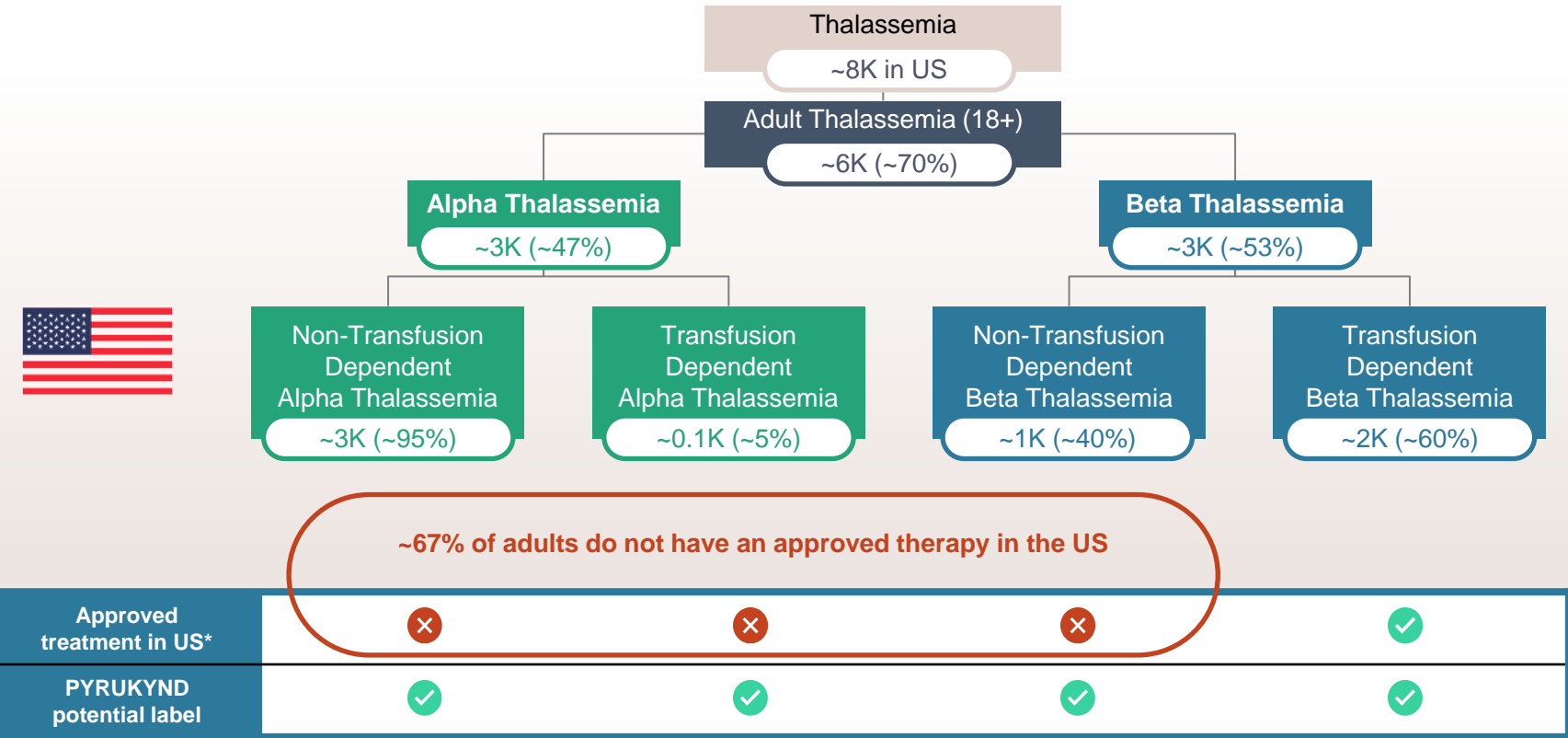
## Safety

- 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





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



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



## Phase 3 primary endpoints<sup>(1)</sup>:

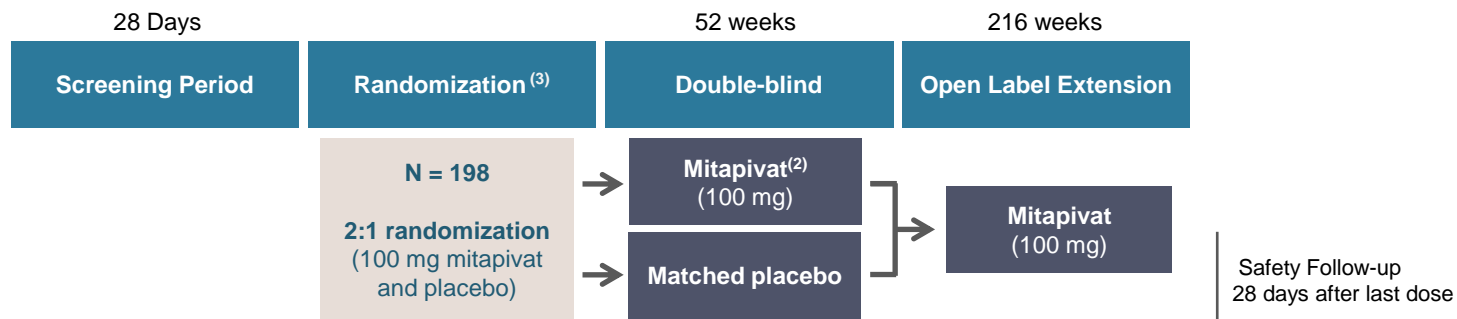
Hb response, defined as a  $\geq 1.0$  g/dL increase in average Hb concentration over Weeks 24–52 compared with baseline, and annualized rate of SCPCs

### Key inclusion criteria

- $\geq 16$  years of age
- Documented SCD (HbSS, HbSC, HbS $\beta$ 0/HbS $\beta$ + 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  $\geq 90$  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

<sup>(1)</sup> Phase 2 and phase 3 components are part of a single study/protocol; <sup>(2)</sup> Patients who receive mitapivat in the double-blind period will continue to receive the same dose of mitapivat in the open-label extension period;

<sup>(3)</sup> Randomization stratification factors: Number of SCPCs in the prior year ( $< 5$ ,  $\geq 5$ ), hydroxyurea use (yes, no).



# 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
<b>Hemoglobin responders, n (%)</b>	1 (3.7)	12 (46.2)	13 (50.0)
<b>Difference of response rate (Mitapivat-Placebo), %</b>		42.5	46.3
<b>95% CI<sup>(1)</sup></b>		(18.8, 63.4)	(22.0, 66.8)
<b>2-sided p-value<sup>(2)</sup></b>		0.0003	0.0001

Abbreviation: RBC = red blood cell

Hemoglobin response is defined as  $\geq 1.0$  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
<b>Annualized Rate of SCPC</b>	1.71	0.83	0.51
<b>95% CI</b>	(0.95, 3.08)	(0.34, 1.99)	(0.16, 1.59)
<b>Rate ratio (Mitapivat/Placebo)</b>		0.48	0.30
<b>95% CI</b>		(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.

