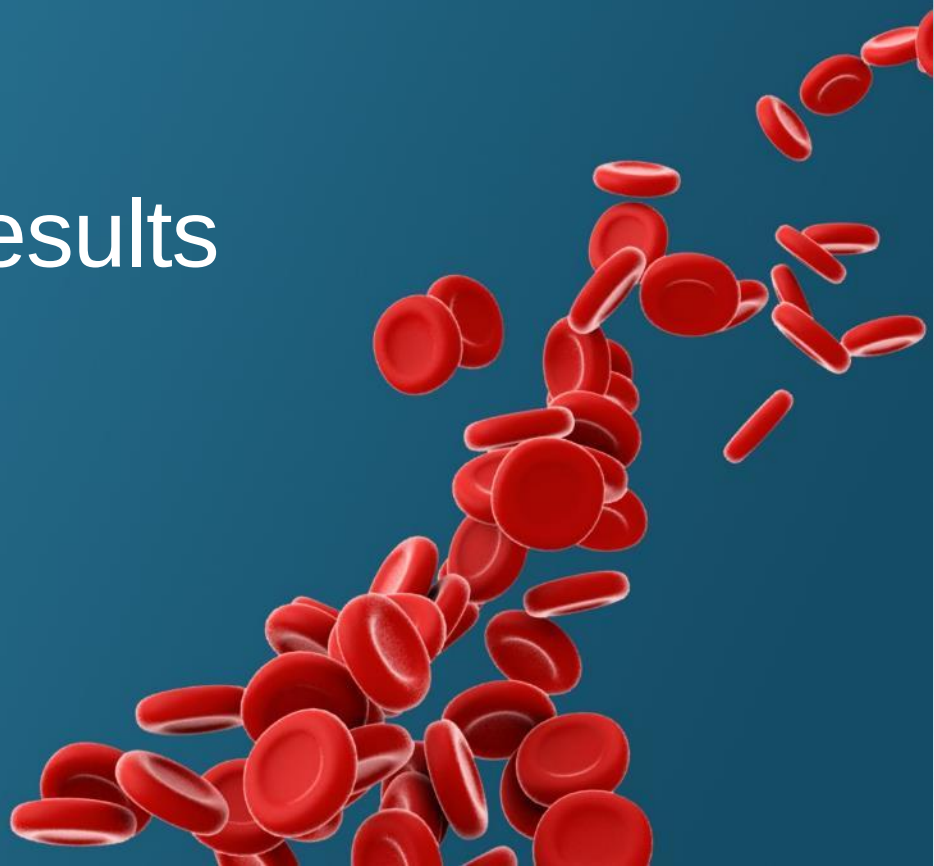
Q1 2024 Financial Results

May 2, 2024



Agios conference call participants

TOPIC	PARTICIPANT
Introduction	Chris Taylor, VP Investor Relations and Corporate Communications
Business Update	Brian Goff, Chief Executive Officer
R & D Update	Sarah Gheuens, M.D., Ph.D., Chief Medical Officer, Head of R&D
Commercial Update	Tsveta Milanova, Chief Commercial Officer
First Quarter 2024 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, AG-181, and TMPRSS6 siRNA; 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.

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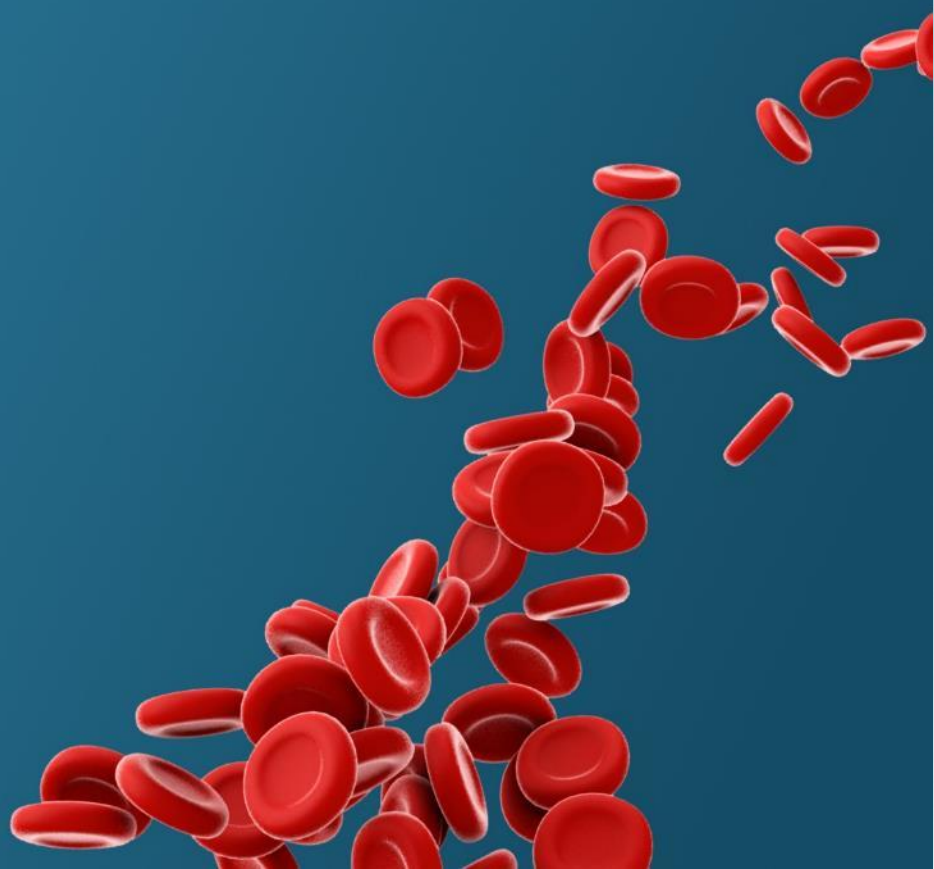
Business Overview

Brian Goff
Chief Executive Officer



Continuing clinical and regulatory milestone momentum, with three Phase 3 data readouts in 2024

EARLY 2024

Thalassemia
PYRUKYND®
Phase 3 data readout for ENERGIZE study

PKU
AG-181
Begin Phase 1 dosing for AG-181 (PAH stabilizer) for the treatment of PKU

MID-YEAR 2024

Q2

Thalassemia
PYRUKYND®
Phase 3 data readout for ENERGIZE-T study

Lower-Risk MDS
AG-946 (Novel PK Activator)
Begin patient enrollment of Phase 2b study

Pediatric PK Deficiency
PYRUKYND®
Complete enrollment Phase 3 ACTIVATE kids study

Pediatric PK Deficiency
PYRUKYND®
Phase 3 data readout ACTIVATE kids-T study

YEAR-END 2024

Thalassemia
PYRUKYND®
Filing for FDA Approval

Sickle Cell Disease
PYRUKYND®
Complete Phase 3 enrollment

Abbreviations: PKU = Phenylketonuria; PAH = Phenylalanine hydroxylase

Updated timeline

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

2024

Thalassemia
PYRUKYND®
Phase 3 ENERGIZE readout

Thalassemia
PYRUKYND®
Phase 3 ENERGIZE-T readout

Pediatric PK Deficiency
PYRUKYND®
Phase 3 ACTIVATE kids-T readout

2025

Sickle Cell Disease
PYRUKYND®
Phase 3 RISE UP readout

Thalassemia
PYRUKYND®
Potential approval

Pediatric PK Deficiency
PYRUKYND®
Phase 3 ACTIVATE kids readout

2026

Sickle Cell Disease
PYRUKYND®
Potential approval

Pediatric PK Deficiency
PYRUKYND®
Potential approval

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

pyrukynd (mitapivat) tablets

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

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Deliver a novel oral therapy that improves anemia and reduces VOCs

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

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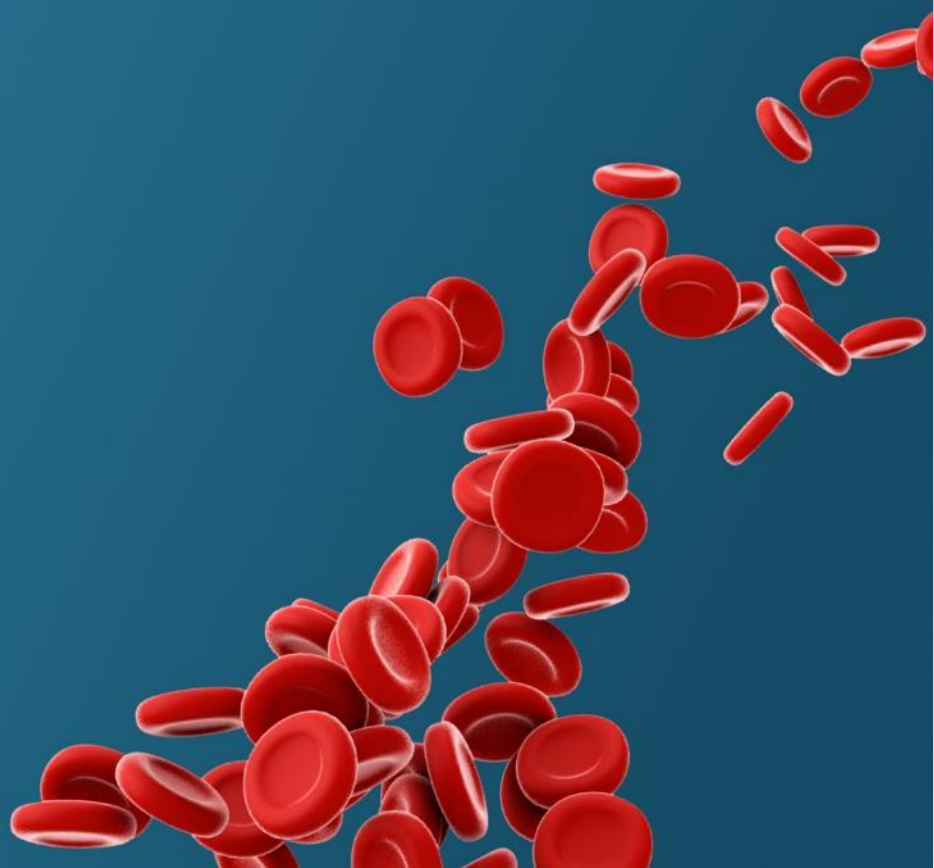
Clinical Overview

Sarah Gheuens, M.D., Ph.D.
Chief Medical Officer, Head of R&D

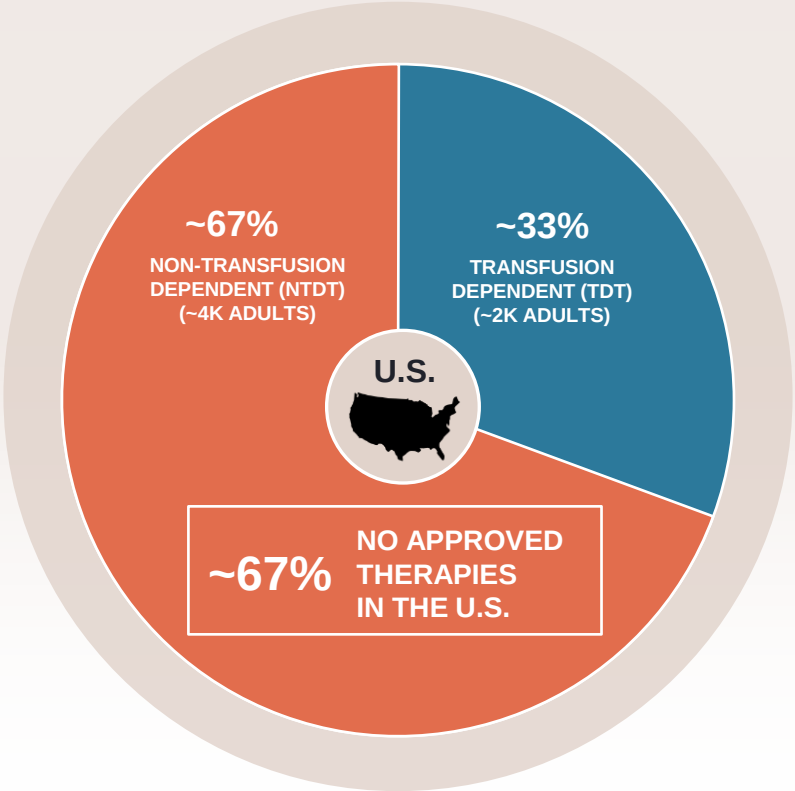


Agios aims to deliver the first therapy approved for all thalassemia subtypes

Mitapivat Thalassemia Phase 3 program

ENERGIZE

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



Mitapivat Thalassemia Phase 3 program

ENERGIZE-T

- **Alpha- and Beta-thalassemia Transfusion dependent** patients
- Primary endpoint: Transfusion Reduction Response
- **Data readout Q2 2024**

Beta-THAL prevalence: HEOR Global THAL Epidemiology SLE (XCENDA, 2021); US: Paramore, et.al; DE: Borchert, et.al; Alpha-THAL prevalence: Agios internal estimates; LEK Analysis | Beta-THAL TD/NTD split: Thuret, et.al., Haematologica 2010; Magnolia TPP MR, April 2020 | Alpha-THAL TD/NTD split; 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.

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 in **Q2 2024**
- 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.

ENERGIZE topline data received positive feedback from thalassemia patients and clinicians

ENERGIZE

Thalassemia ENERGIZE results

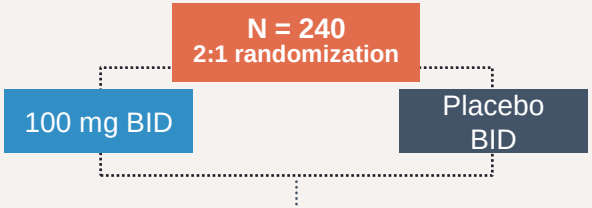
- Statistically significant increases in hemoglobin response rate and change from baseline in average hemoglobin concentration
- Statistically significant change from baseline in average FACIT-Fatigue score (Patient Reported Outcome, PRO)
- Rapid enrollment, high completion and rollover rates

Implications for Mitapivat

- **Mitapivat has the potential to be the first therapy to improve hemoglobin and make patients with thalassemia feel less fatigued**
- **Clinicians** appreciate the potential longer-term benefits of reducing markers of hemolysis
- Potential to reduce high rate of serious morbidities, including thrombosis and premature death, in the real world
- Potential for significant commercial adoption

ENERGIZE-T: trial design reflects real-world clinical treatment dynamics

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

Key Considerations

- Individualized Hb threshold determines the Hb value by which a given patient will receive a transfusion
  - Individualized Hb thresholds based on transfusion history (24 wks) prior to enrollment
- Two ways to demonstrate a reduction in transfusion burden
  - Reduced number of units transfused and/or
  - Extended interval between transfusions
- Primary endpoint is a dynamic assessment of transfusion reduction, better aligned to real-world circumstances

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

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 at 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(1)

- **Phase 3 primary endpoints:** Hb response(2) and annualized rate of SCPCs
- **N = 198** with a 2:1 randomization (100 mg mitapivat and placebo)
- **52-week** double blind 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) Phase 2 and phase 3 components are part of a single study/protocol; 100mg was selected for Phase 3 portion of the study
(2) 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

Initiated dosing in Phase 1 study of AG-181 in March 2024

Polycythemia Vera (PV)

~100k patients in the U.S.

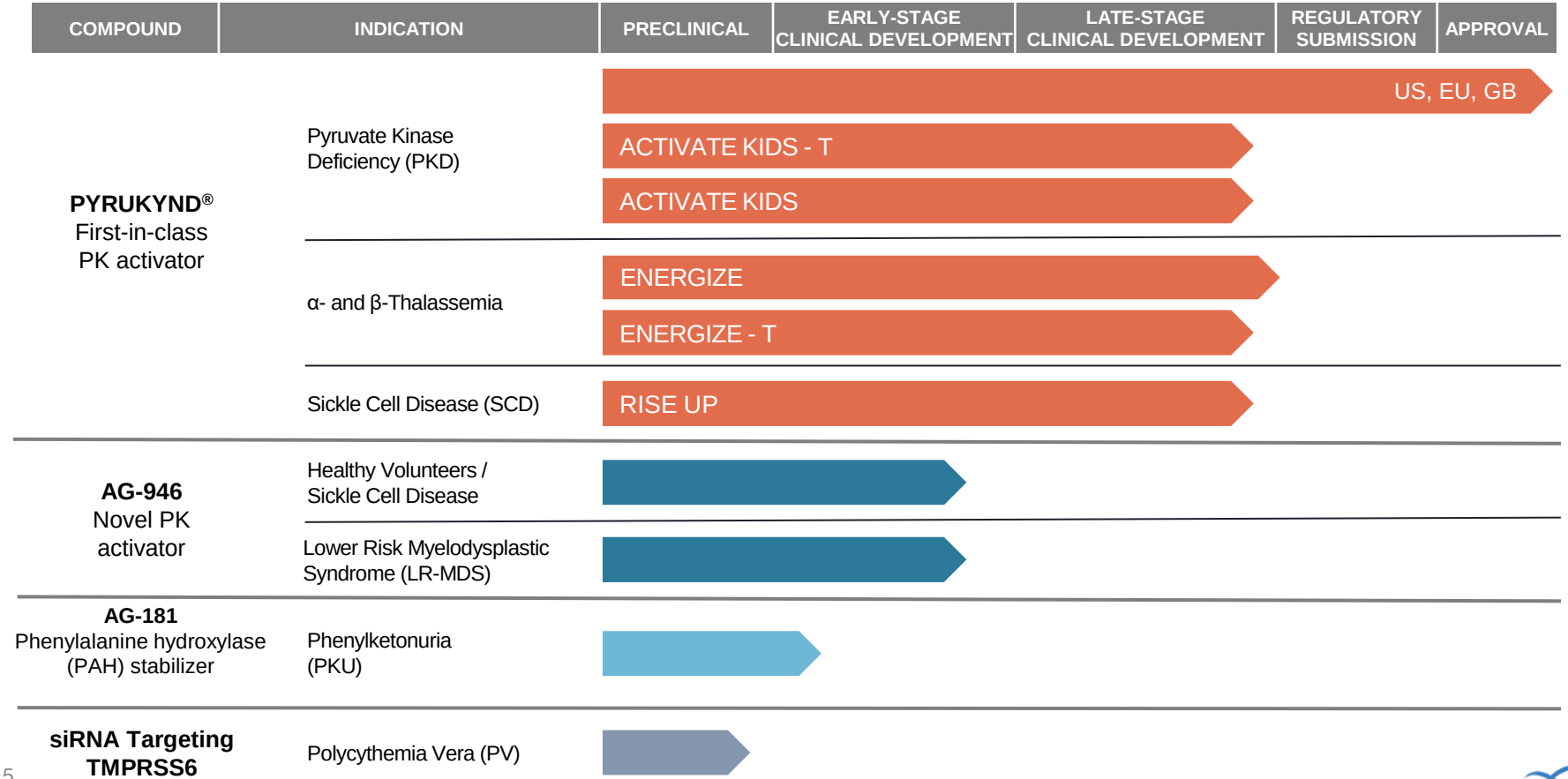
Phlebotomy is the standard of care

In-licensed TMPRSS6 siRNA from Alnylam in 2023

Advancing to pre-IND studies

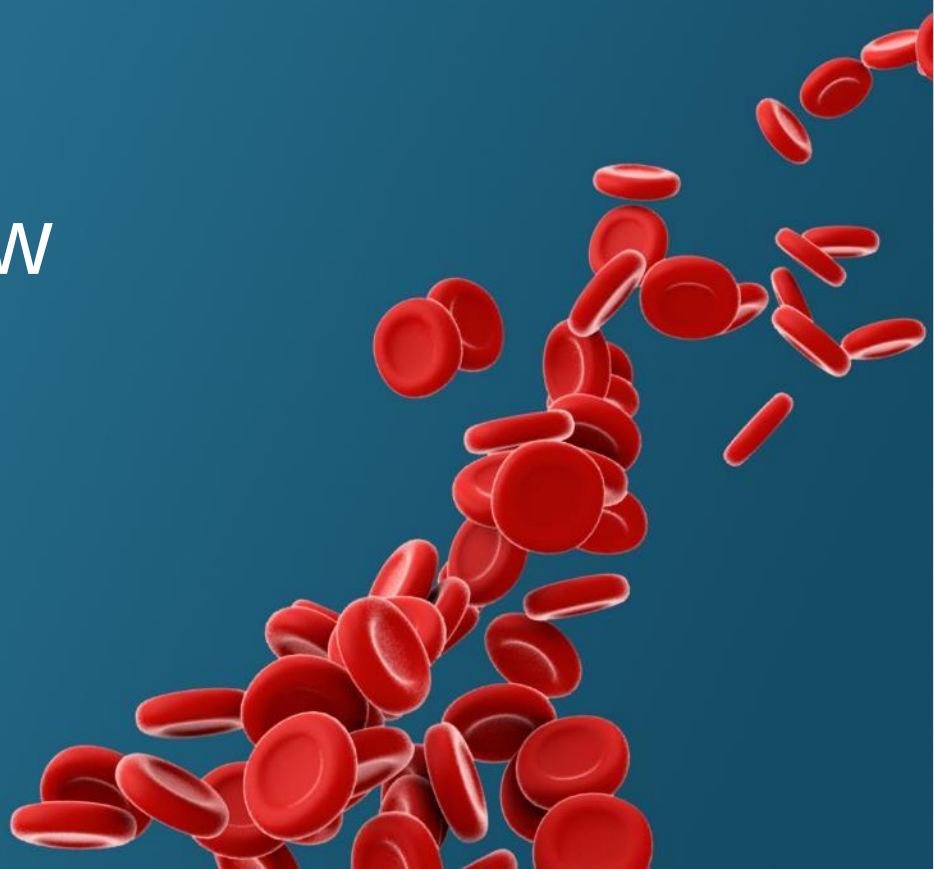
Abbreviations: PKU = Phenylketonuria; PAH = Phenylalanine hydroxylase

Significant advancement building depth and breadth in our rare disease pipeline



Commercial Overview

Tsveta Milanova
Chief Commercial Officer



Thalassemia remains an area of high unmet need with few treatment options and significant burden of disease regardless of transfusion needs

Increased Mortality	Serious, Irreversible Morbidities	Poor Quality of Life	Healthcare Resource Utilization & Cost
Lower survival for thalassemia patients, and **significantly worse in those who remain non-regularly transfused**	**High rates of morbidities** and frequency of complications increasing as patients age	Adult patients with **NTDT may have similar or worse Healthcare Related QoL** compared with patients with TDT	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

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

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

Thalassemia
~8K in US

Adult Thalassemia (18+)
~6K (~70%)

Alpha Thalassemia
~3K (~47%)

Beta Thalassemia
~3K (~53%)

Non-Transfusion Dependent Alpha Thalassemia	Transfusion Dependent Alpha Thalassemia	Non-Transfusion Dependent Beta Thalassemia	Transfusion Dependent Beta Thalassemia
~3K (~95%)	~0.1K (~5%)	~1K (~40%)	~2K (~60%)

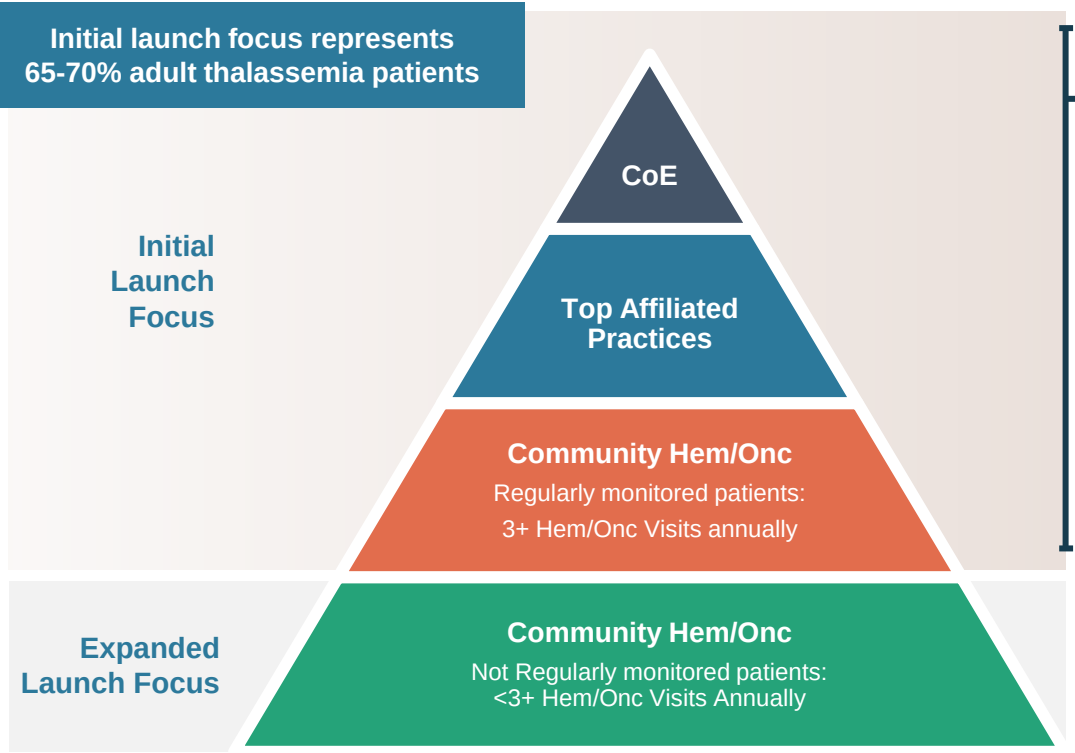
~67% OF ADULTS DO NOT HAVE AN APPROVED THERAPY IN THE US

Approved treatment in US*	✗	✗	✗	✓
PYRUKYND potential label	✓	✓	✓	✓

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: 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

Concentration of treating physicians facilitates initial PYRUKYND® launch plan

Initial launch focus represents 65-70% adult thalassemia patients



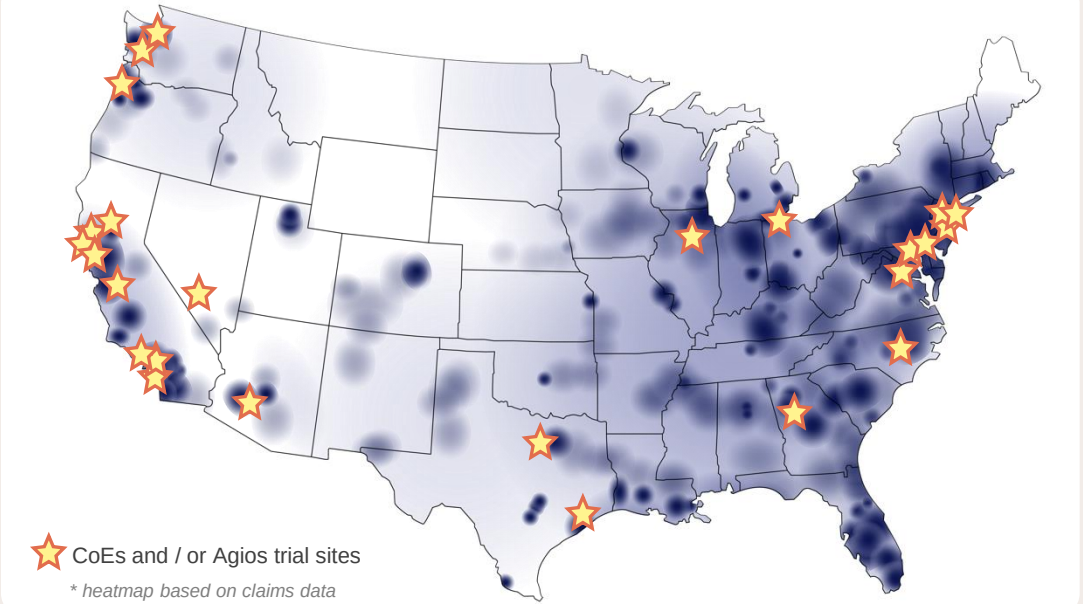
Target Treating Physician Segments

- **Centers of Excellence and Top Affiliated Practices** | ~50% of active adult patients concentrated <150 affiliated hematology & oncology academic or community practices
- **Community Hem/Onc** | Involved in lifelong thalassemia patient treatment management and monitoring

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

Strong alignment with trial sites, key centers for thalassemia patients across US

Patient prevalence heatmap alongside Agios trial sites and /or Centers of Excellence (COE)

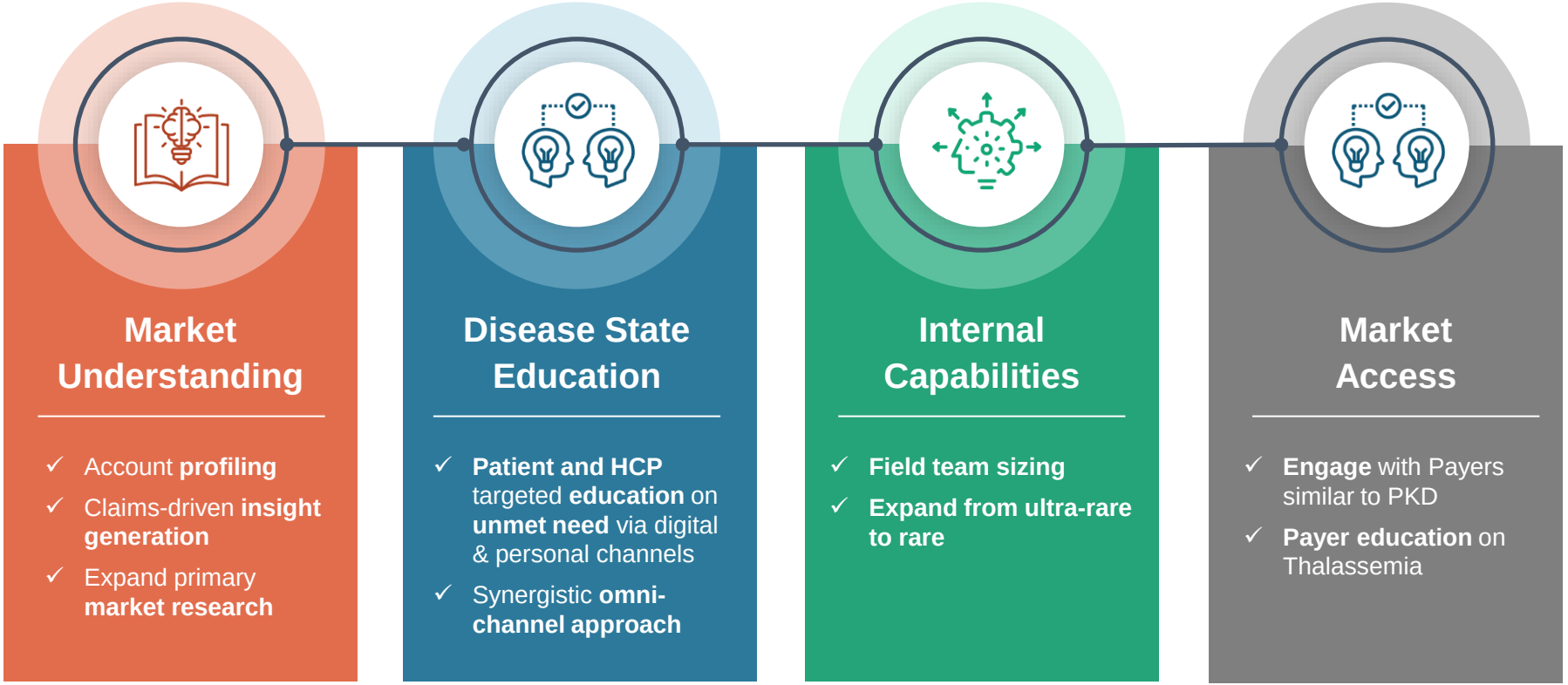


- Availability of **newborn** Thalassemia **screening**
- Well established **ICD-10 codes in Thalassemia**
- **Agios trial sites** aligned to key Health Care Providers and Centers of Excellence

Centers of Excellence: CDC Funded Thalassemia Treatment Centers and Thalassemia Western Consortium

Source: Compile Claims Analysis August 2023; BELIEVE NEJM Appendix 2020, BEYOND Lancet Hematology Appendix 2022, ENERGIZE ct.gov (accessed August 2023), ENERGIZE-T ct.gov (accessed August 2023); Agios Medical Affairs

Strengthening our commercial capabilities to support Thalassemia launch in a meaningfully larger patient population



PYRUKYND® Q1 2024 performance metrics highlight continued progress

$8.2M net sales of PYRUKYND®
15% growth over Q4 2023

120 patients on PYRUKYND®,
which includes new prescriptions and those continuing treatment, a 10% increase from Q4

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

188 unique patients completed PYRUKYND® prescription enrollment forms, including 10 in Q1, a 6% increase over Q4 2023

Unique prescriber base of 162 physicians, diversified across the country, a 5% increase over Q4 2023

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

pyrukynd® (mitapivat) tablets

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

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

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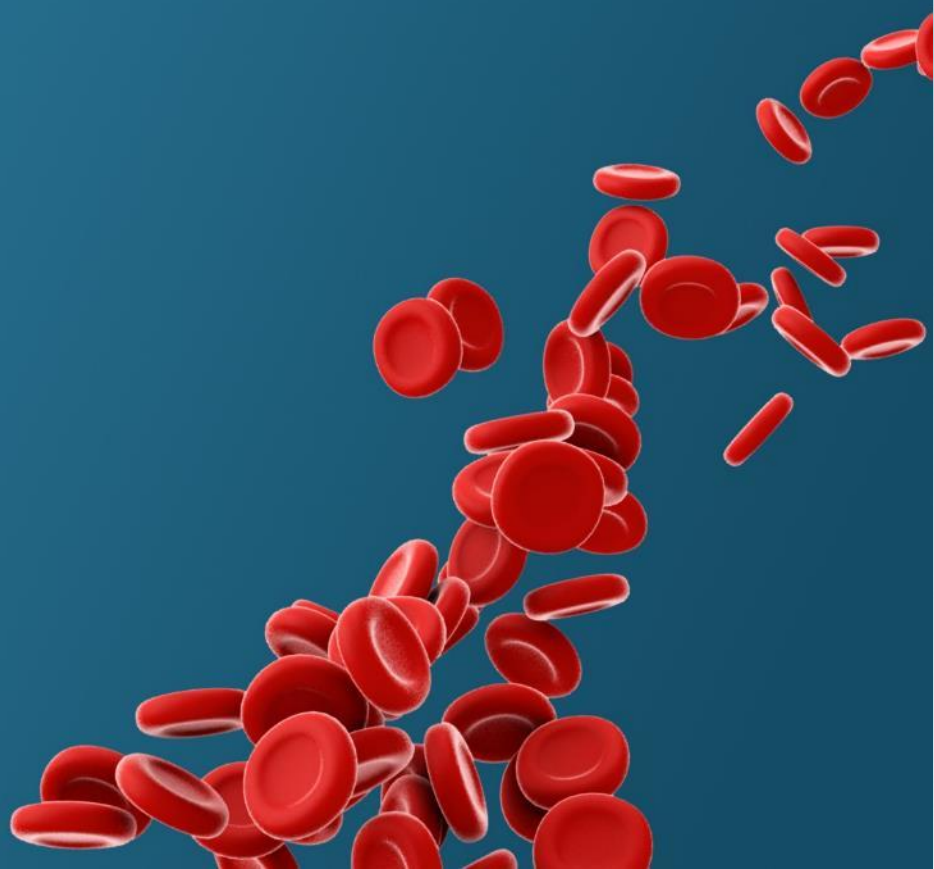
Source: Agios internal estimates

Financial Overview

Cecilia Jones
Chief Financial Officer



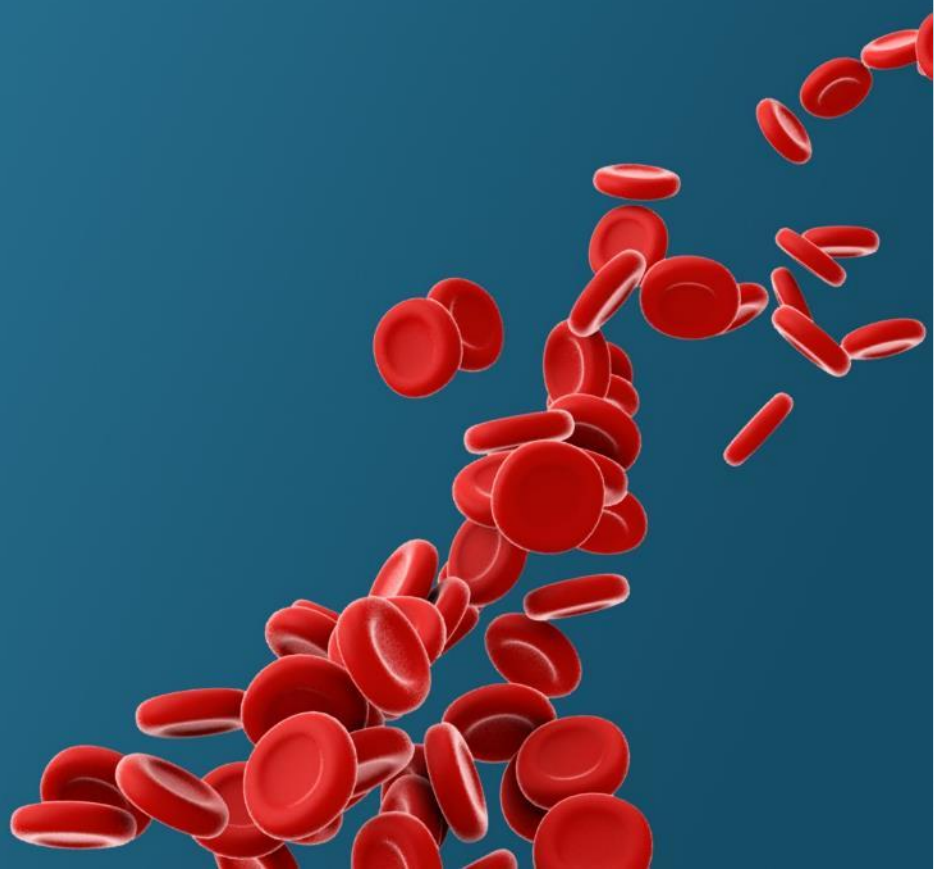
First quarter 2024 financial results

Statement of Operations	Three Months Ended 3/31/24	Three Months Ended 3/31/23
PYRUKYND® Net Revenue	$8.2M	$5.6M
Cost of Sales	$0.6M	$0.6M
Research & Development Expense	$68.6M	$67.3M
Selling, General & Administrative Expense	$31.0M	$28.4M
Net Loss	($81.5M)	($81.0M)

Balance Sheet	3/31/24	12/31/23
Cash, Cash Equivalents and Marketable Securities	$714.3M	$806.4M

Closing Remarks

Brian Goff
Chief Executive Officer



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**

$714.3M in cash and equivalents as of March 31, 2024

Retained economics related to vorasidenib include $200M milestone upon FDA approval and 15% royalty on net US sales

PK = pyruvate kinase
Pka = pyruvate kinase activation

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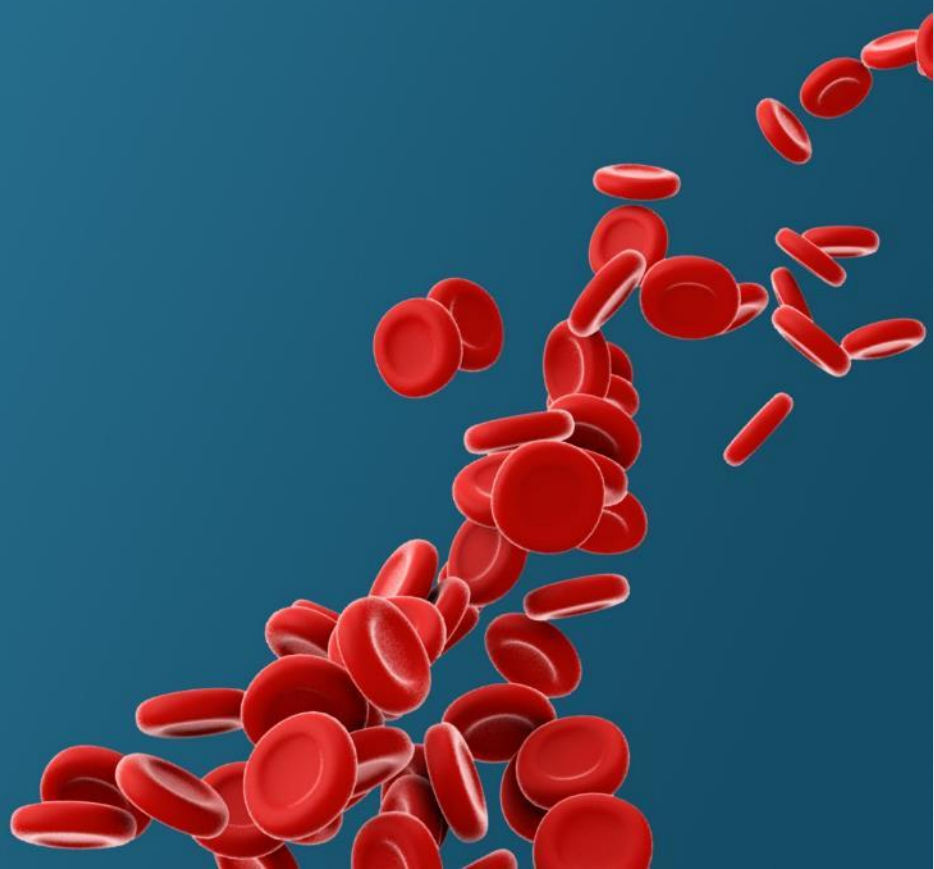
Thank You



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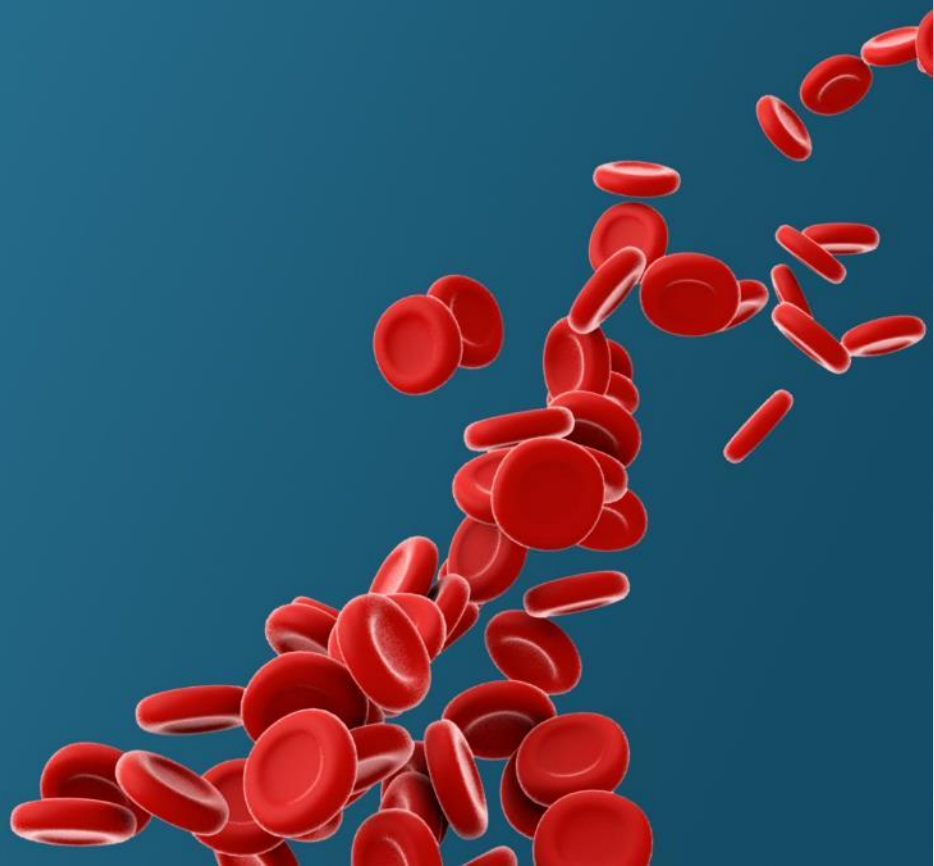
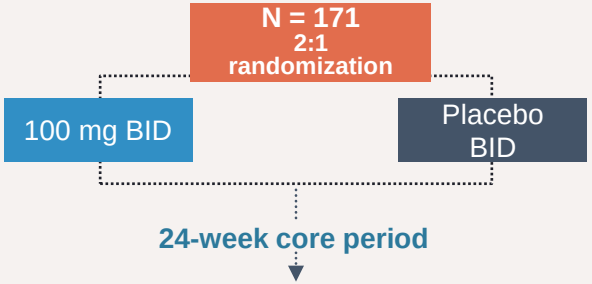
Appendix



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

ENERGIZE



Primary endpoint

- Mean Hb ↑ ≥ 1 g/dL from baseline

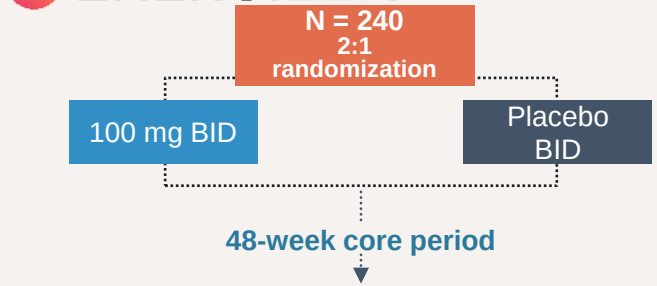
Secondary endpoints

- 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.

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 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

RISE UP Phase 2/3 operationally seamless trial of PYRUKYND® in sickle cell disease allows for speed and flexibility of clinical program

Phase 2

- 1:1:1 randomization to mitapivat 50 mg BID, 100 mg BID or matched placebo
- N=79
- 12-week core period
- Primary endpoint:
- Safety and ≥1 g/dL ↑ in average Hb concentration from week 10 to 12 compared to baseline

PHASE 2 PRIMARY ENDPOINTS

Hemoglobin response	Safety profile

OTHER PHASE 2 DATA

Change in markers of hemolysis	Change in patient-reported fatigue
Annualized rate of sickle cell pain crises	PK/PD

COLLABORATOR-LED STUDIES

NIH Phase 1 extension	Utrecht Phase 2 ESTIMATE extension

OTHER AVAILABLE DATA

Phase 3

- 2:1 randomization to mitapivat 100 mg BID or matched placebo
- N=198
- 52-week core period
- Primary endpoints:
- Mean Hb ↑ ≥ 1 g/dL from baseline & annualized rate of sickle cell pain crises

BID = twice daily; Hb = hemoglobin

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.

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

RISE UP

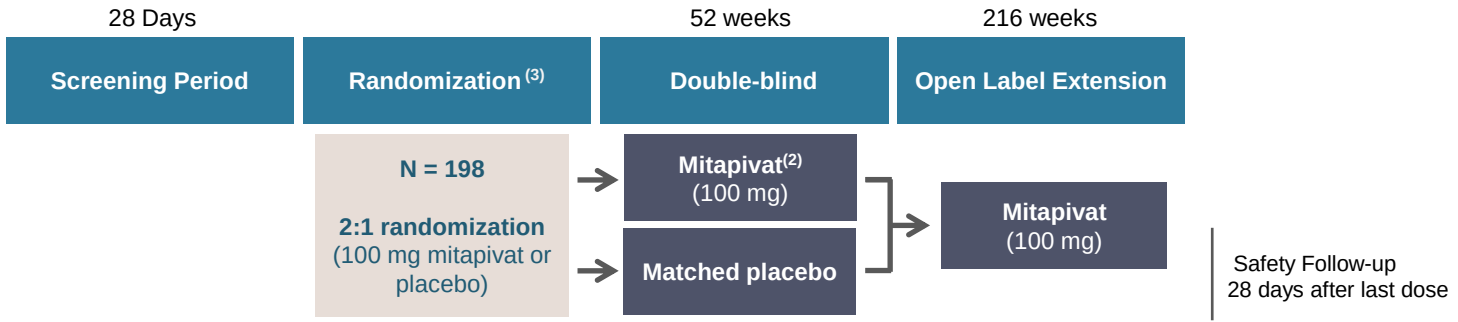
Phase 3 primary endpoints [1]:
Hb response, defined as a ≥ 1.0 g/dL increase in average Hb concentration over Weeks 24–52 compared with baseline, and annualized rate of SCPCs

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

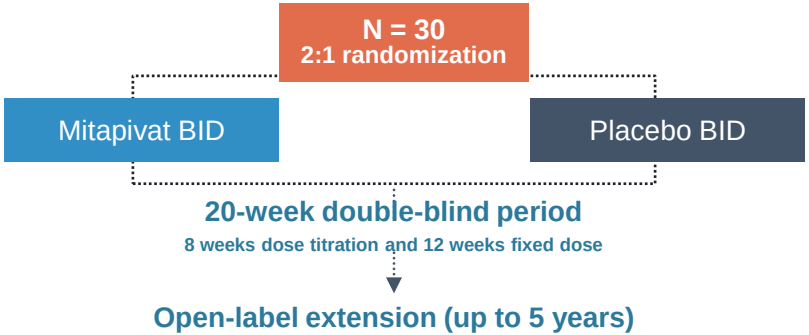
- Receiving regularly scheduled blood transfusions
- Severe kidney disease or hepatobiliary disorders
- Currently receiving treatment with SCD therapies (excluding HU)
- Prior exposure to gene therapy, or prior bone marrow or stem cell transplantation



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).

Pediatric PK Deficiency Program: Two Phase 3 studies evaluating regularly transfused and not regularly transfused pediatric patients with PKD

ACTIVATE-Kids



Primary endpoint

- > 1.5 g/dL (0.93 mmol/L) increase in Hb concentration from baseline that is sustained at 2 or more scheduled assessments at weeks 12, 16 and 20 during the double-blind period

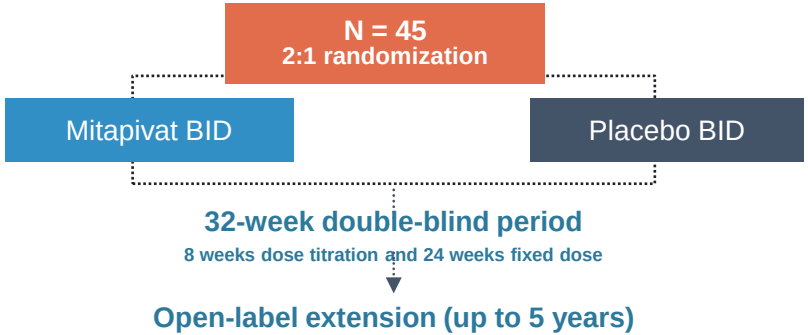
Secondary endpoints

- Additional measures of Hb ↑, hemolysis, HRQOL, iron metabolism, safety, PK/PD

Key inclusion criteria

- Aged 1 to <18 years
- Clinical laboratory confirmation of PK deficiency
- Not regularly transfused defined as ≤5 RBC transfusion episodes during the 52-week period before informed consent/assent and no RBC transfusions ≤12 weeks prior to randomization
- Hb ≤10 g/dL for subjects 12 to <18 years of age or ≤9 g/dL for subjects 1 to <12 years of age`

ACTIVATE-KidsT



Primary endpoint

- ≥33% reduction in the total RBC transfusion volume from Week 9 through Week 32 of the double-blind period normalized by weight and actual study drug duration compared with the historical transfusion volume standardized by weight and to 24 weeks

Secondary endpoints

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

Key inclusion criteria

- Aged 1 to <18 years
- Clinical laboratory confirmation of PK deficiency
- Regularly transfused defined as 6 to 26 RBC transfusion episodes during the 52-week period before informed consent/assent

BID = twice daily; Hb = hemoglobin; PK = pharmacokinetics; PD = pharmacodynamics, RBC = red blood cell.