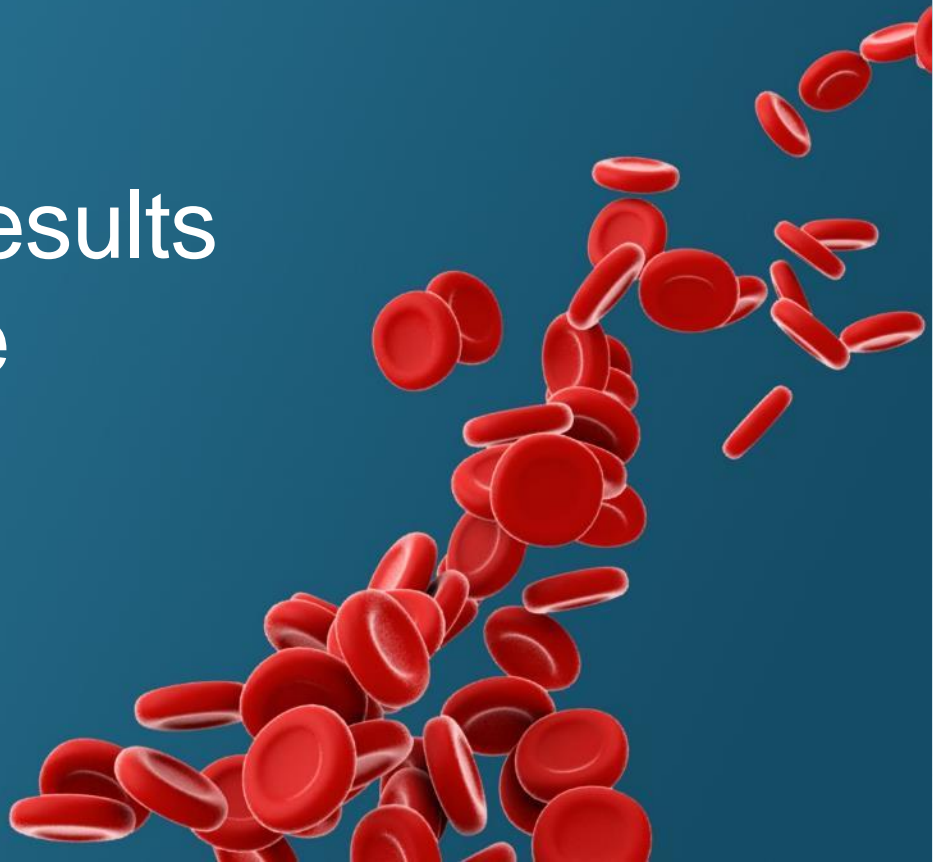




Q3 2024 Financial Results and Business Update

October 31, 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
Third Quarter 2024 Financial Results	Cecilia Jones, Chief Financial Officer
Q&A	Mr. Goff, Dr. Gheuens, Ms. Milanova, Ms. Jones



Forward-looking statements

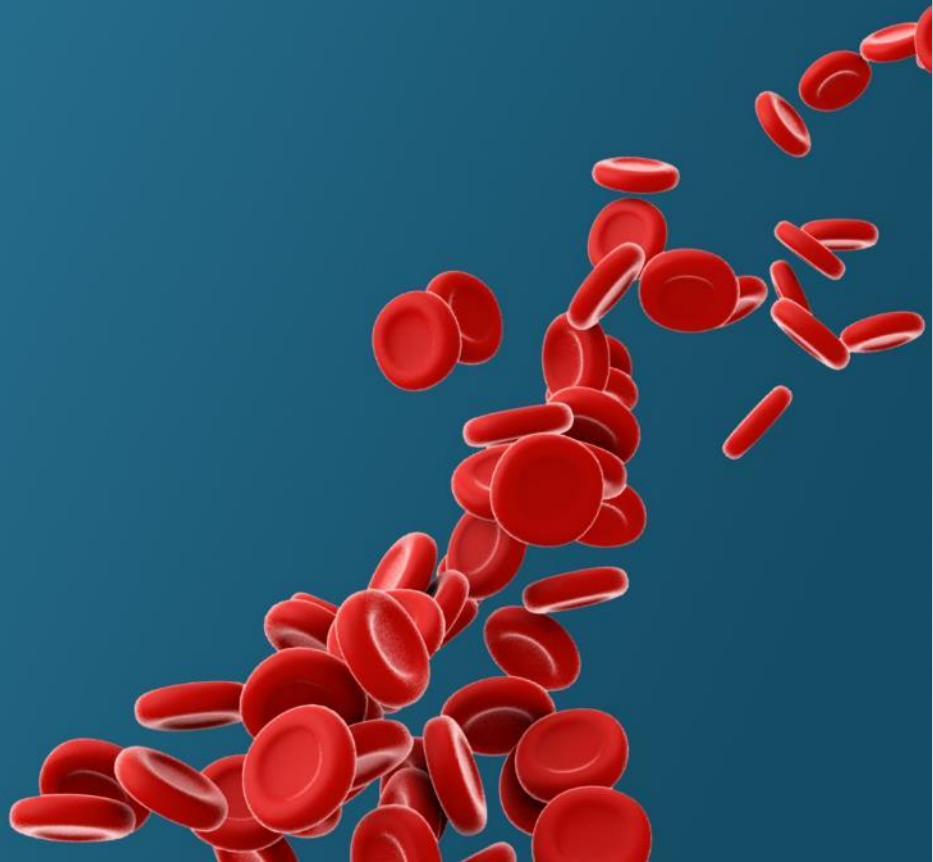
This presentation and various remarks we make during this presentation contain forward-looking statements within the meaning of The Private Securities Litigation Reform Act of 1995. Such forward-looking statements include those regarding the potential benefits of PYRUKYND® (mitapivat), tebapivat (AG-946), TMPRSS6 siRNA and AG-181, Agios' PAH stabilizer; Agios' plans, strategies and expectations for its preclinical, clinical and commercial advancement of its drug development, including PYRUKYND®, tebapivat and AG-181; Agios' use of proceeds from the transaction with Royalty Pharma; potential U.S. net sales of vorasidenib and potential future royalty payments; 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; competitive factors; Agios' ability to obtain, maintain and enforce patent and other intellectual property protection for any product candidates it is developing; Agios' ability to establish and maintain key collaborations; uncertainty regarding any royalty payments related to the sale of its oncology business or any milestone or royalty payments related to 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 Agios' cash and cash equivalents; 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.





Business Overview

Brian Goff
Chief Executive Officer



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

PKa franchise with multi-billion-dollar potential

Large opportunities with substantial value - potential for two additional **first and best-in-class** indications for PYRUKYND® 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**



\$1.7 billion in cash and equivalents as of September 30, 2024

Including \$1.1 billion in payments related to the FDA approval of vorasidenib (announced August 6, 2024)



Key milestones in Q3 2024 and continued positive momentum

Completed enrollment in Phase 3 RISE UP study of mitapivat in sickle cell disease (10/24)

For tebapivat, commenced enrollment of the Phase 2b study in Lower-Risk Myelodysplastic Syndromes (LR-MDS); Granted FDA Orphan Drug Designation for treatment of MDS

Received a total of \$1.1 billion in payments in Q3 following the FDA approval of vorasidenib; \$905 million from purchase agreement for vorasidenib royalty; \$200 million milestone from Servier

Reported topline data from the Phase 3 ACTIVATE-KidsT study of mitapivat in children with PK deficiency who are regularly transfused

Announced PYRUKYND commercial partnership for Gulf Cooperation Council (GCC) region



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



Thalassemia PYRUKYND®

Phase 3 data readout
for ENERGIZE-T study



Pediatric PK Deficiency PYRUKYND®

Complete enrollment Phase 3
ACTIVATE-Kids study



Lower-Risk MDS Tebapivat (AG-946)

Begin patient enrollment of
Phase 2b study



Pediatric PK Deficiency PYRUKYND®

Phase 3 data readout
ACTIVATE-KidsT study

YEAR-END 2024

Thalassemia PYRUKYND®

Filing for
FDA Approval



Sickle Cell Disease PYRUKYND®

Complete Phase 3
enrollment



Capturing larger patient populations positions PYRUKYND® for significant near-term growth as a first- and best-in-class therapy



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

PK deficiency **2022**

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

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18-23K patients
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>1M patients worldwide

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Potential U.S. approval

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~150K patients
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>3M patients
worldwide

Sickle cell disease **2026**

Potential U.S. approval

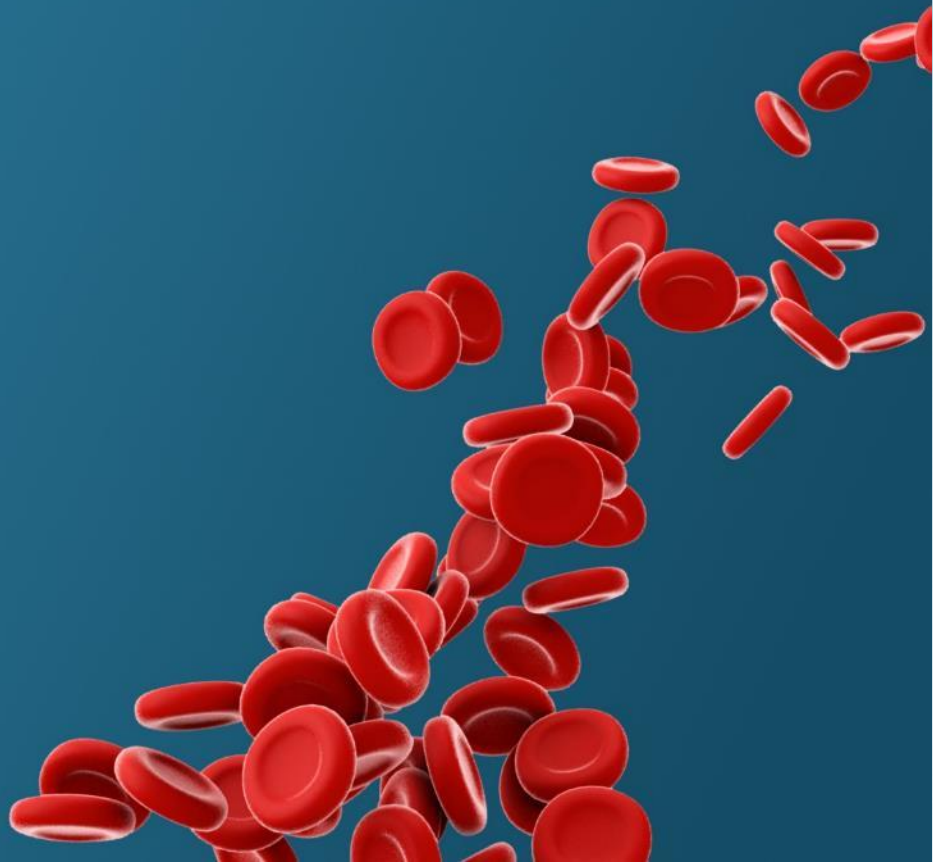
OUR GOAL
Deliver a novel oral therapy
that improves anemia and
reduces VOCs





Clinical Overview

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



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 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**
- **Enrollment completed** (10/24)
- Expected data readout late 2025
- Potential US **launch in 2026**

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



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



Phase 3 primary endpoints⁽¹⁾:

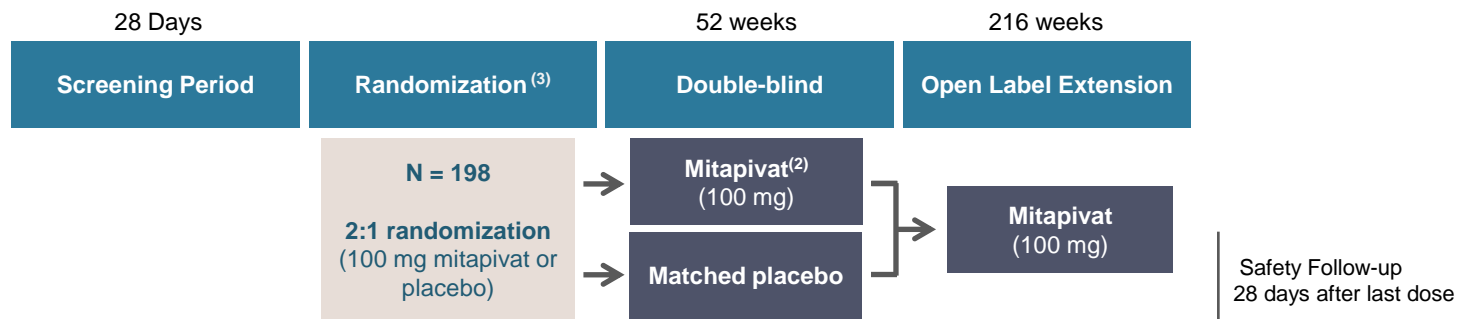
Hb response, defined as a ≥ 1.0 g/dL increase in average Hb concentration over Weeks 24–52 compared with baseline, and annualized rate of SCPCs

Key inclusion criteria

- ≥ 16 years of age
- Documented SCD (HbSS, HbSC, HbS β 0/HbS β + 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).



Agios aims to deliver the first therapy for all thalassemia subtypes

Mitapivat Thalassaemia Phase 3 program

ENERGIZE

- Alpha- and Beta-thalassaemia Non-transfusion dependent patients
- Primary endpoint achieved: Hemoglobin (Hb) response

✓ **Topline data announced January 3, 2024**

✓ **Data set presented during plenary session at EHA June 15, 2024**

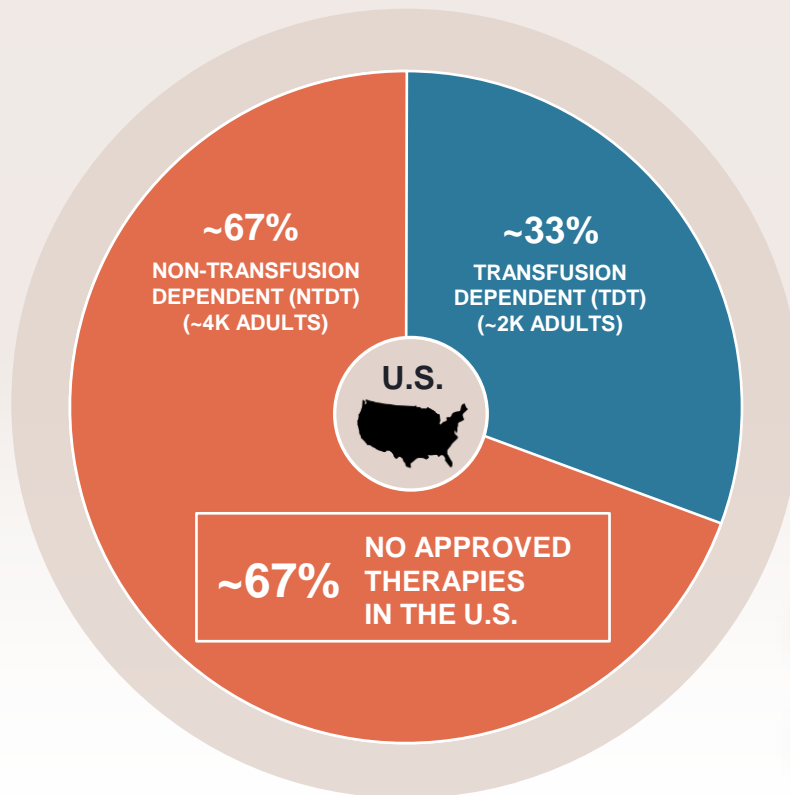
Mitapivat Thalassaemia Phase 3 program

ENERGIZE-T

- Alpha- and Beta-thalassaemia Transfusion dependent patients
- Primary endpoint achieved: Transfusion Reduction Response

✓ **Topline data announced June 3, 2024**

○ **Data set to be presented at upcoming medical meeting**



PYRUKYND significantly increases Hb and improves quality-of-life measures, highlighting potential to address unmet need in underserved community



Phase 3 Data

- **Statistically significant improvements in hemoglobin and fatigue** observed across the full range of NTDT for both subtypes compared to placebo
- **Improvements in markers of hemolysis and erythropoiesis** observed compared to placebo - consistent with mechanism ¹⁻³
- **Significantly improved fatigue, walking capacity, and disease symptoms** with mitapivat compared with placebo
- Overall, during the 24-week double-blind period, incidence of adverse events (AEs) was similar across mitapivat and placebo arms; In mitapivat arm, 3.1% of the patients experienced an AE leading to discontinuation, compared to zero in the placebo arm ³⁻⁶

NTDT = non-transfusion-dependent thalassemia

1. Kung C et al. Blood 2017;130:1347-56; 2. Matte A et al. J Clin Invest 2021;131:e144206; 3. Kuo KHM et al. Lancet 2022;400:493-501; 4. Al-Samkari H et al. NEJM 2022;386:1432-42; 5. Glenthøj A et al. Lancet Haematol 2022;9:e724-32; 6. Idowu M et al. Blood 2023;142:271.



PYRUKYND has the potential to reduce transfusion burden and improve lives with unprecedented durability of effect

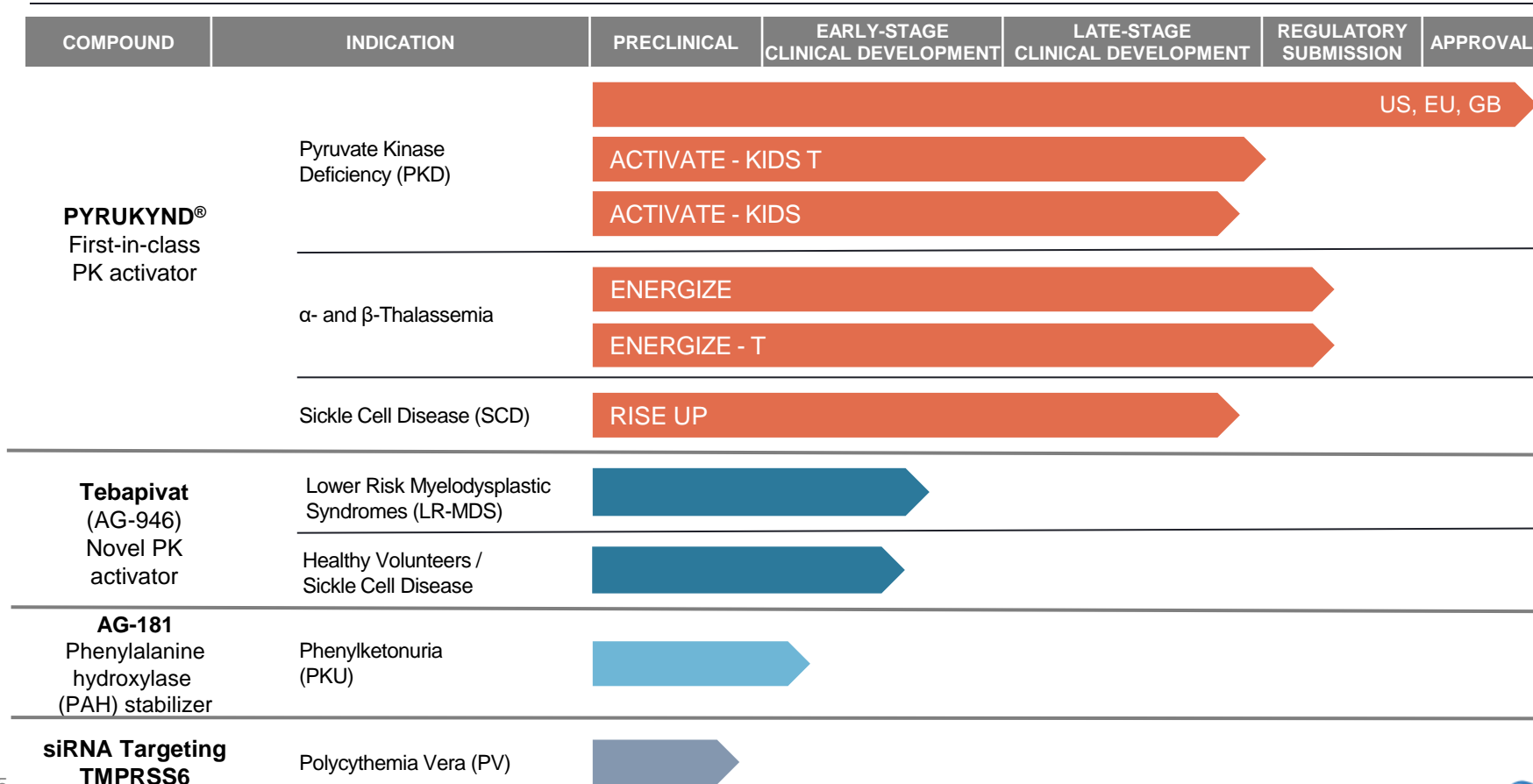


Phase 3 Data

- **Statistically significant transfusion reduction response** observed in the mitapivat arm (30.4%) compared to placebo (12.6%)
- **Transfusion independence achieved** in a higher proportion of patients in the mitapivat arm (9.9%) compared to placebo (1.1%)
- Statistical significance observed on **all key secondary endpoints evaluating additional measures of reducing transfusion burden** compared to placebo
- Safety profile consistent across both arms with 5.8% discontinuing in the mitapivat arm and 1.2% discontinuing in the placebo arm due to AEs



Significant advancement building depth and breadth in our rare disease pipeline



Phase 2b open-label study of Tebapivat (AG-946) in lower-risk MDS

Phase
2b

Primary endpoint:

Transfusion independence, defined as transfusion-free for ≥ 8 consecutive weeks during the Core Period

Secondary endpoints: safety, change in hemoglobin, TI for 12 weeks, additional measures of anemia, PK and PD biomarkers

Tebapivat (AG-946) Treatment Period

Dose Level 1
10mg QD
Core Period

Dose Level 1
10mg QD
Extension Period

Tebapivat (AG-946) Treatment Period

Dose Level 2
15mg QD
Core Period

Dose Level 2
15mg QD
Extension Period

Tebapivat (AG-946) Treatment Period

Dose Level 3
20mg QD
Core Period

Dose Level 3
20mg QD
Extension Period

Core Period: **24 Weeks**

Extension Period: **156 Weeks**

Key inclusion criteria

- ≥ 18 years of age
- Lower-risk MDS (risk score: ≤ 3.5) according to IPSS-R classification (WHO classification; Arber et al, 2016)
- Transfusion dependent, with LTB or HTB according to revised IWG 2018 criteria
- An Hb concentration < 10.0 g/dL
- Up to 2 prior therapies, including ESAs and/or luspatercept

Key exclusion criteria

- Known history or AML or secondary MDS
- Prior exposure to a PK activator, IDH inhibitors, IST, stem cell transplant
- Currently receiving imetelstat, lenalidomide, HMAs allowed after sufficient washout period

N=60

*Completion of enrollment in one cohort triggers the opening of enrollment in the next cohort



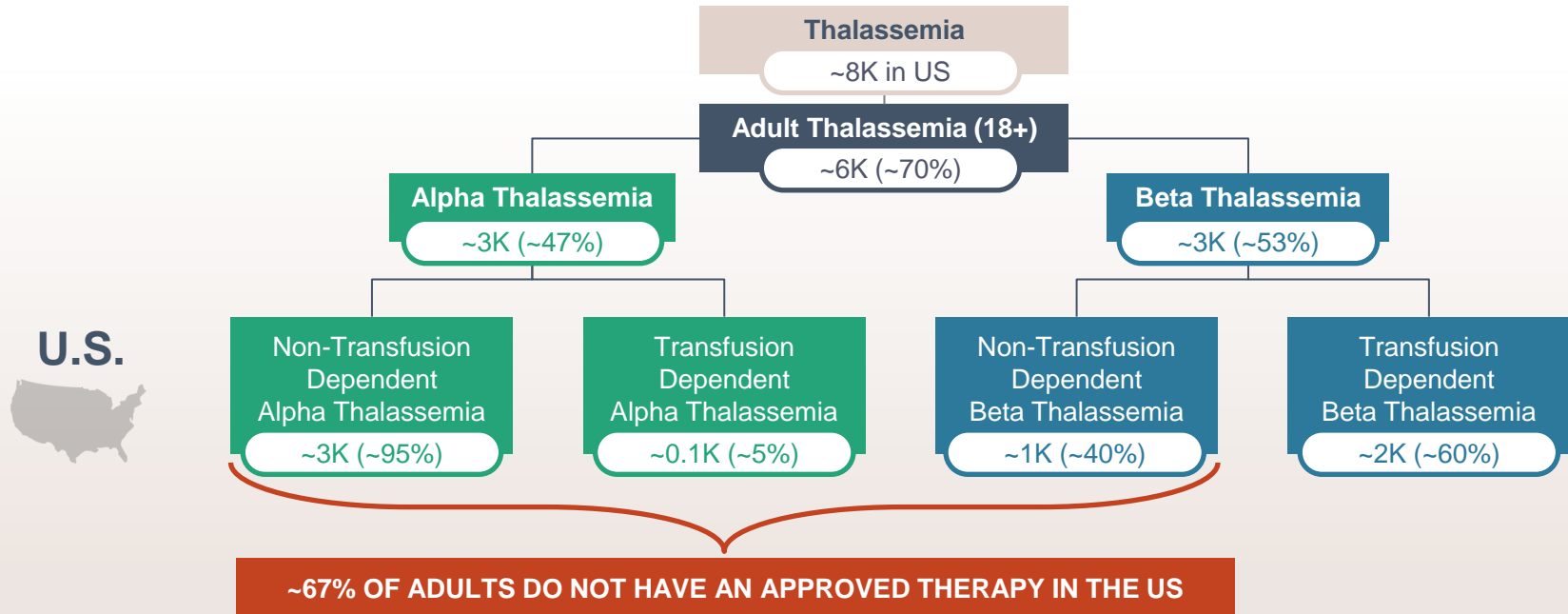


Commercial Overview

Tsveta Milanova
Chief Commercial Officer



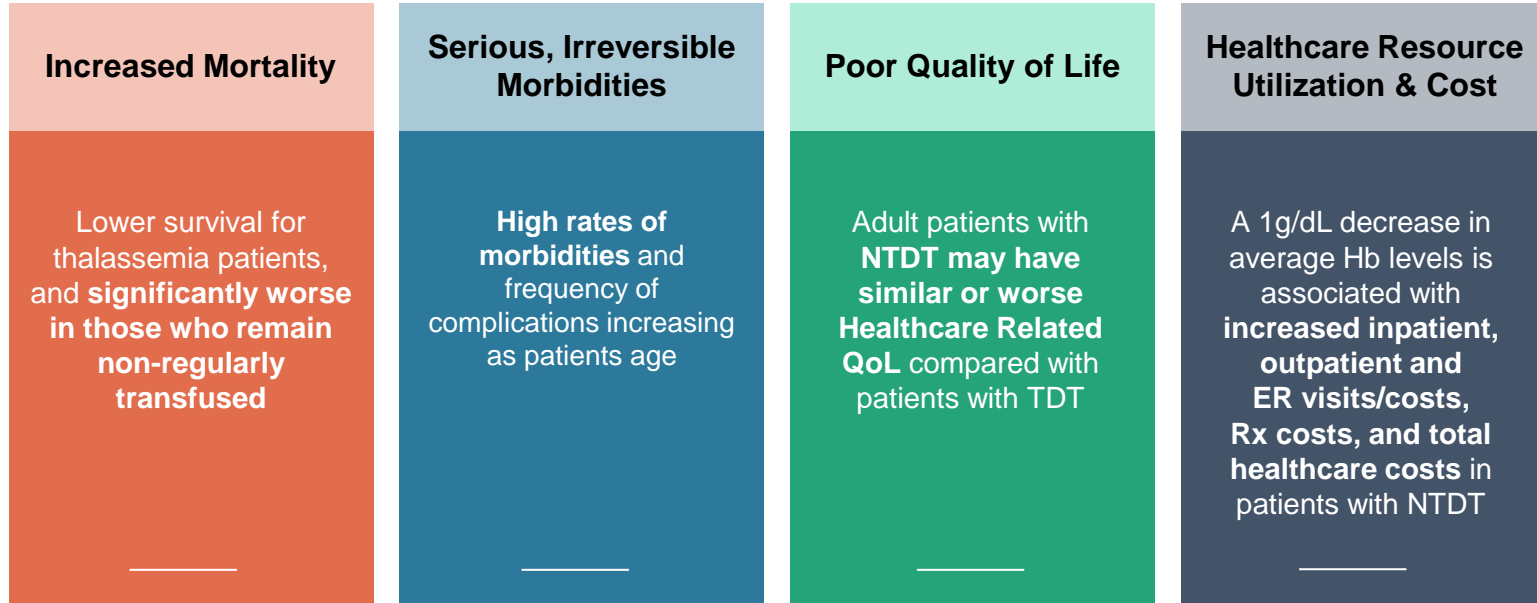
PYRUKYND® has the potential to become the first therapy approved for all thalassemia subtypes



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



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

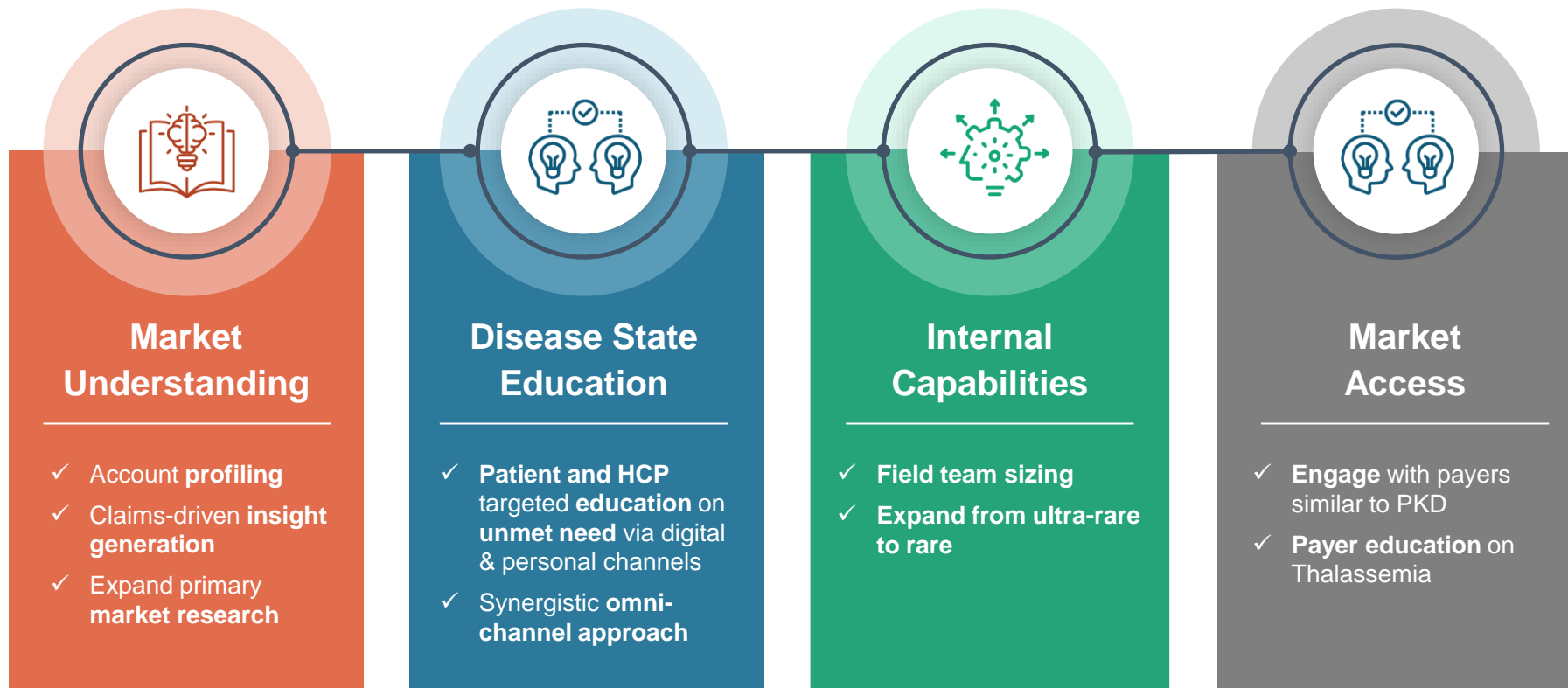


TDT = transfusion dependent thalassemia

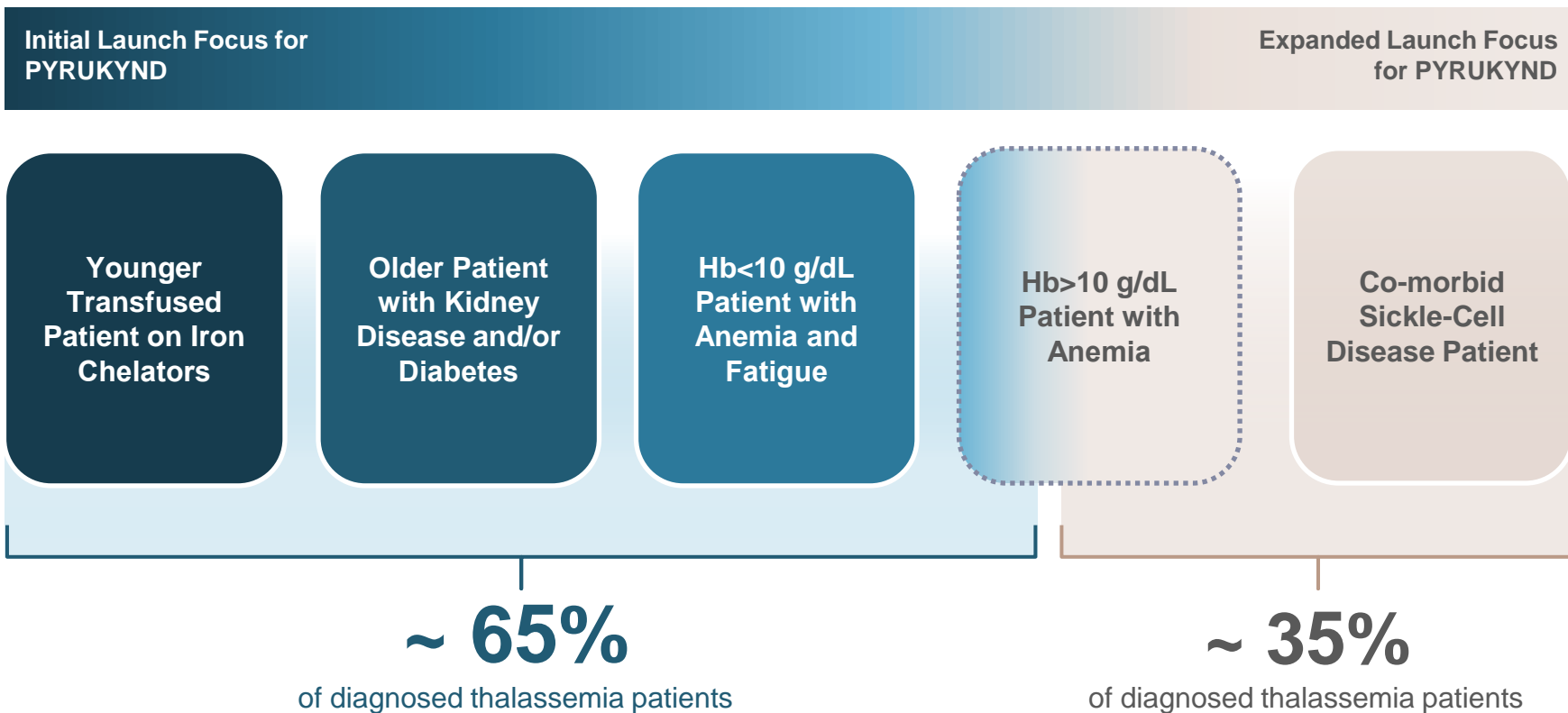
Source: Musallam, K, et al.. 2022. Hemasphere 6(12) e806;Thalassemia International Federation, 2023; Musallam, K, et al., 2021. Am J Hematol 97(2) E78-E80; Association of Hemoglobin Levels with Healthcare Resource Utilization and Costs in Non-Transfusion Dependent Alpha and Beta Thalassemia: A Retrospective 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



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



PYRUKYND's initial launch focus will address approximately 65% of the thalassemia patient population



Disease state education (DSE) campaigns have been launched for both patients and health care providers

DSE Objectives



Educate on the pathophysiology of the disease



Highlight Disease Burden



Encourage Disease Monitoring and Management

DSE campaign was well received following Q2 launch

HCP: "I haven't seen this pathophysiology detail in a long time, it's helpful to be reminded that it's not just ineffective erythropoiesis, but hemolysis too"

HCP: "I didn't realize there was so much going on for my patients with thalassemia"


Patient: "I didn't know thalassemia had so many complications. I appreciate talking to someone who understands. I've never had anyone"

HCP: "I need to take a closer look at what's going on with my patients who have thalassemia"

HCP: "This monitoring guide is exactly what we need"

Patient: "The Monitoring Guide is great. I feel more confident talking to my doctor about getting monitored."



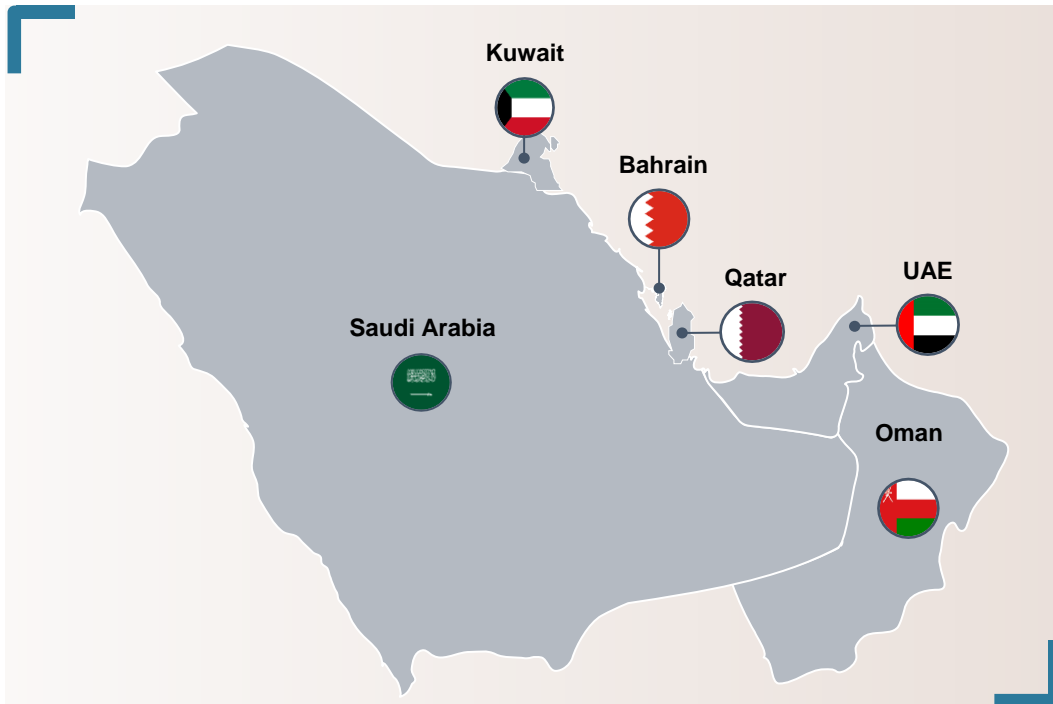
A woman with short brown hair, wearing a light blue sweater, stands in a living room. The room is decorated with several framed posters on the wall, including 'Organ Damage', 'Blood Clots', 'PULMONARY HYPERTENSION', 'Iron Overload', 'STROKE', 'Heart Damage', and 'LIVER DISEASE'. There is a fireplace, a bookshelf, and a couch with pillows labeled 'Fatigue', 'Anemia', and 'Heart'. The text 'LOOK CLOSER TO SEE WHAT THALASSEMIA IS HIDING' is overlaid on the image.

LOOK CLOSER TO SEE WHAT THALASSEMIA IS HIDING

Even if you don't receive regular transfusions, thalassemia may come with serious risks. Learn more about these risks and what you can do about them.

The GCC region represents a significant opportunity for PYRUKYND in thalassemia; distribution partner signed to unlock value

Approximately 70k Thalassemia Patients in Gulf Cooperation Council (GCC) Countries



High unmet need given disproportionately high prevalence



Entered **distribution agreement** with **NewBridge**; a leading specialty company with **regulatory and commercial expertise in the GCC**



Saudi Arabia accounts for the majority of patients in GCC region



Mitapivat received **Breakthrough Medicine Designation** by the SFDA (Saudi FDA); one of the first products to receive BMD



The **access path** in the GCC region begins with a price set at the regulatory level, followed by access with health authorities, local institutions, and the private sector, and national tenders



PYRUKYND® Q3 2024 performance metrics highlight continued progress

\$9.0M net sales of PYRUKYND®

4% growth over Q2 2024

127 patients on PYRUKYND®,

which includes new prescriptions and those continuing treatment

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

211 unique patients completed PYRUKYND® prescription enrollment forms,

including 10 in Q3, a 5% increase over Q2 2024

Unique prescriber base of 181 physicians, diversified across the country



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

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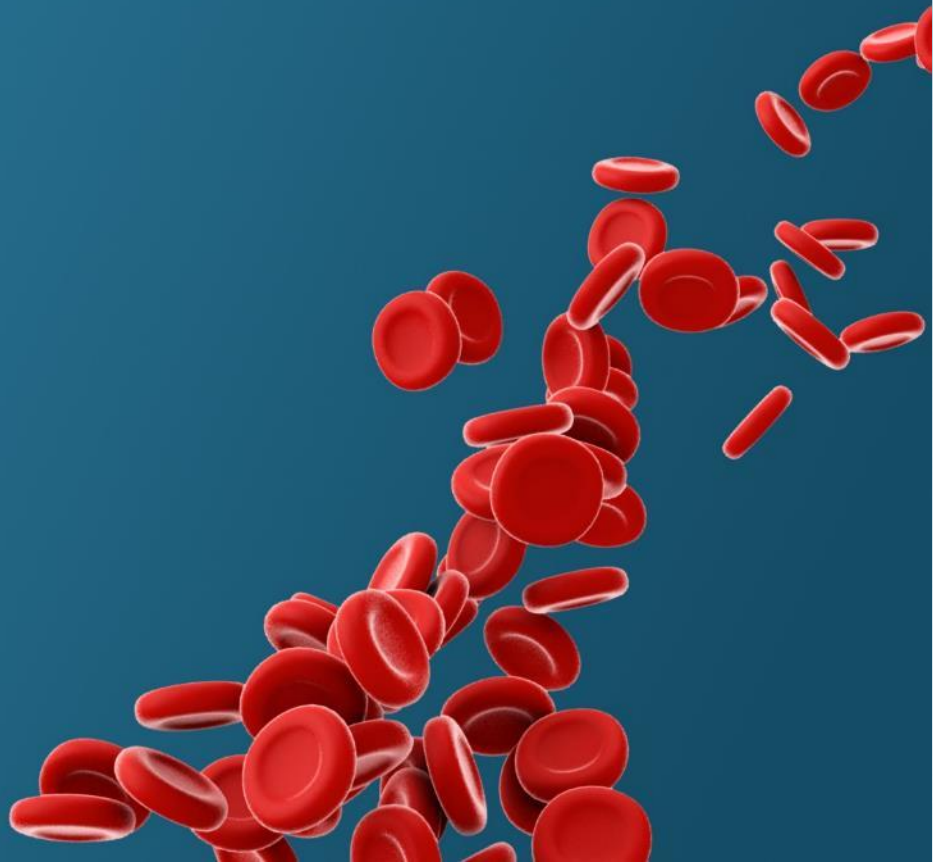
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Deliver a novel oral therapy
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Financial Overview

Cecilia Jones
Chief Financial Officer



Third quarter 2024 financial results

Statement of Operations	Three Months Ended 9/30/24	Three Months Ended 9/30/23
PYRUKYND® Net Revenue	\$9.0M	\$7.4M
Cost of Sales	\$0.8M	\$0.6M
Research & Development Expense	\$72.5M	\$81.8M
Selling, General & Administrative Expense	\$38.5M	\$25.8M
Net Income (Loss)	\$947.9M	(\$91.3M)

Balance Sheet	9/30/24	12/31/23
Cash, Cash Equivalents and Marketable Securities*	\$1.7B	\$806.4M

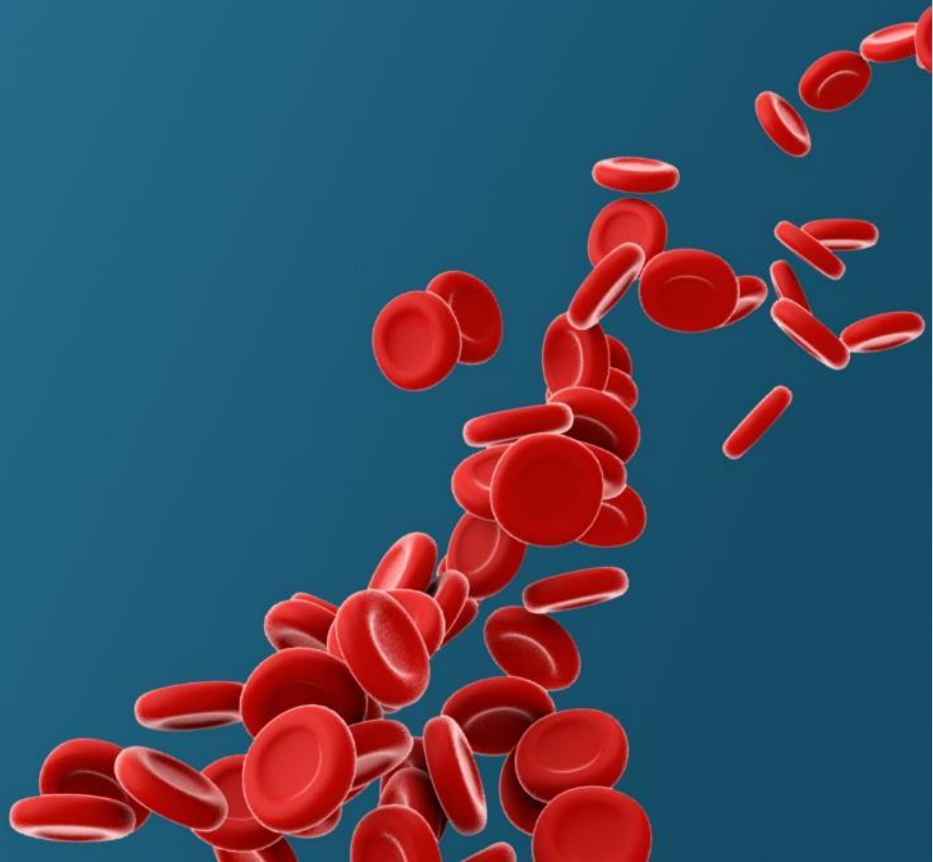
*Agius received a total of \$1.1 billion in payments upon the FDA approval of vorasidenib (August 6, 2024). Agius retains a 3% royalty on annual U.S. net sales greater than \$1 billion.





Closing Remarks

Brian Goff
Chief Executive Officer



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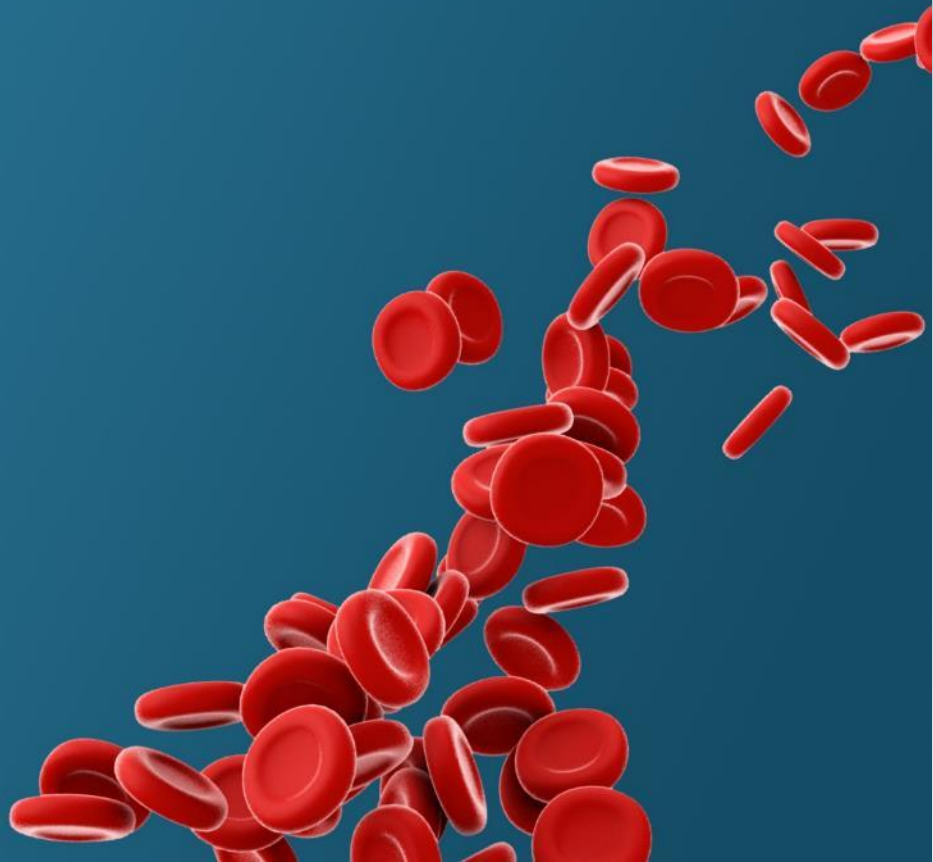
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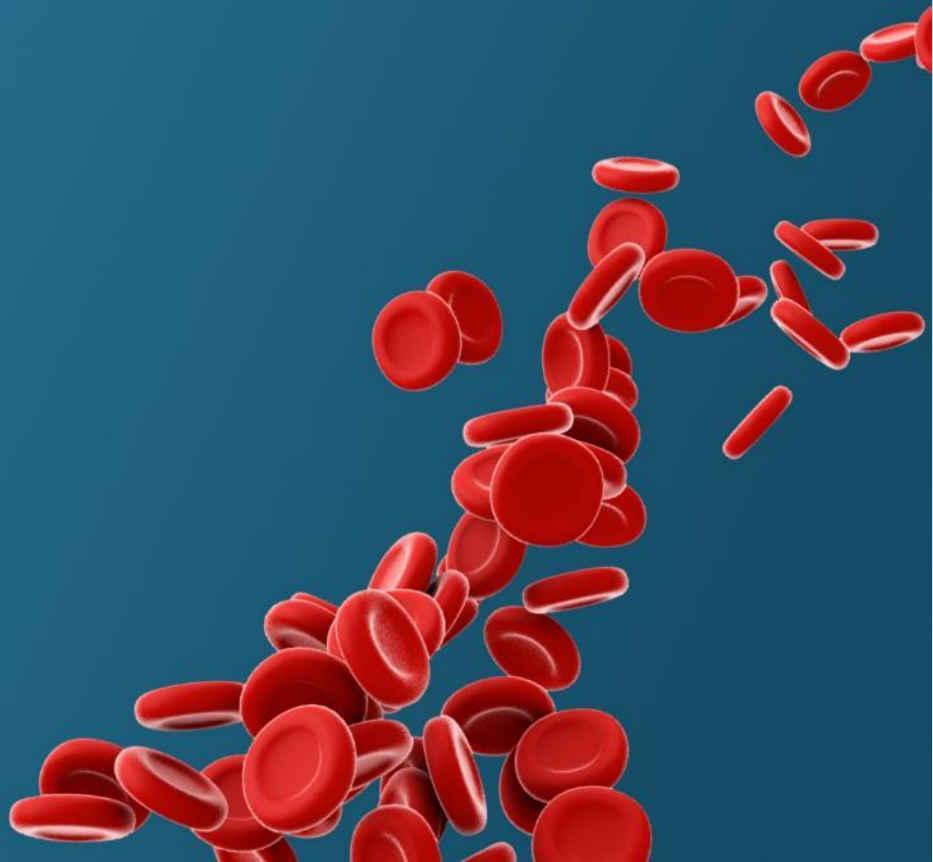


Thank You

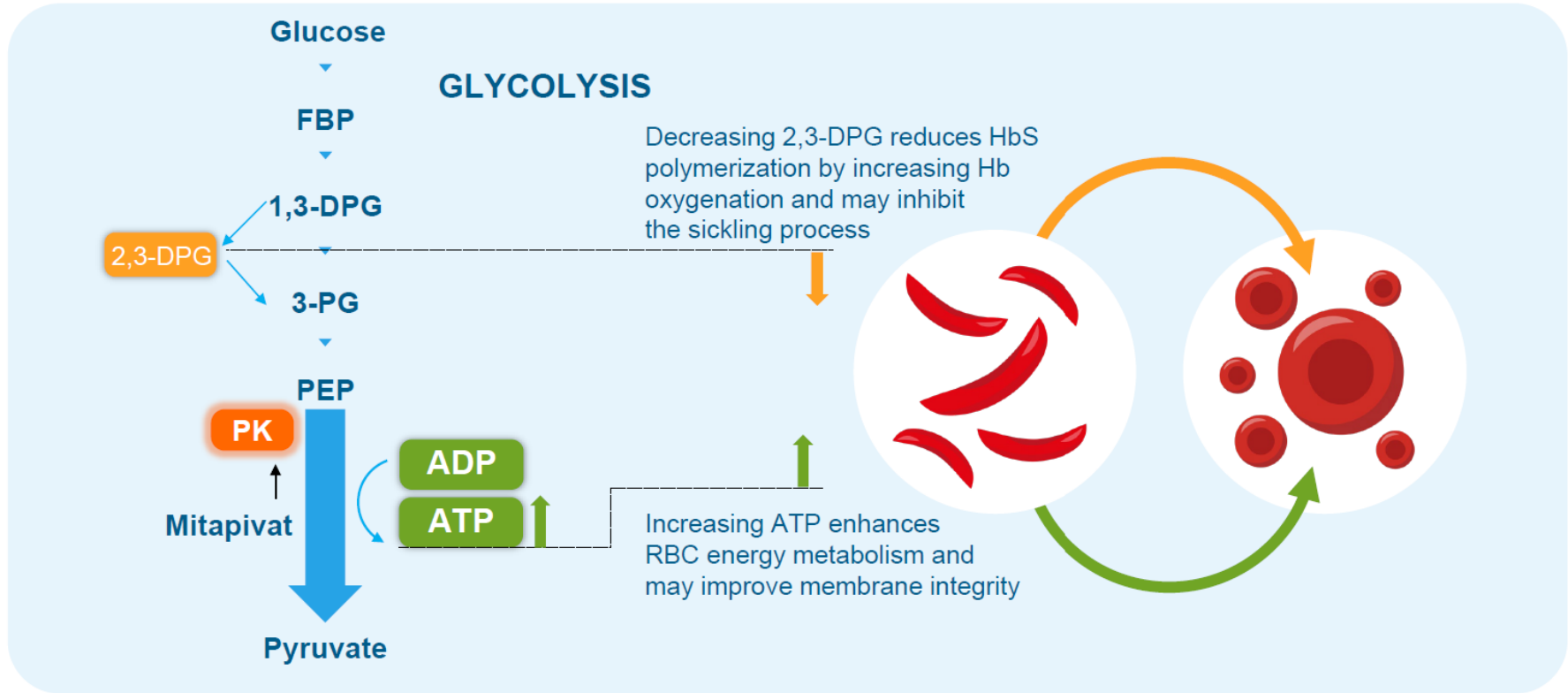




Appendix



PK Activation in Sickle Cell Disease modulates 2,3-DPG and ATP, which may improve anemia and reduce sickling



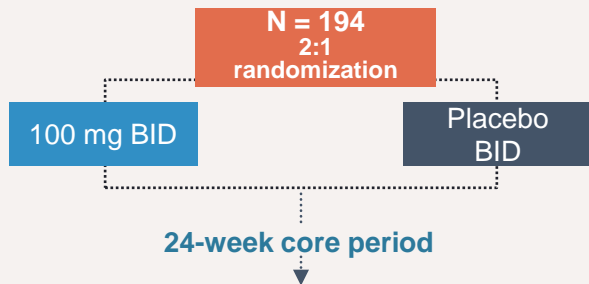
ADP = adenosine diphosphate; ATP = adenosine triphosphate; DPG = diphosphoglycerate; FBP = fructose bisphosphate; m = mutant; PEP = phosphoenolpyruvate; PG = phosphoglycerate; PK = pyruvate kinase; PKR = RBC-specific PK; RBC = red blood cell

1. Kung C et al. Blood 2017;130:1347; 2. Valentini G et al. J Biol Chem 2002;277:23807; 3. Rab MAE et al. Blood 2021;137:2997-3001



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

 **ENERGIZE**



Open-label extension (up to 5 years)

Primary endpoint

- Mean Hb ↑
≥ 1 g/dL from baseline

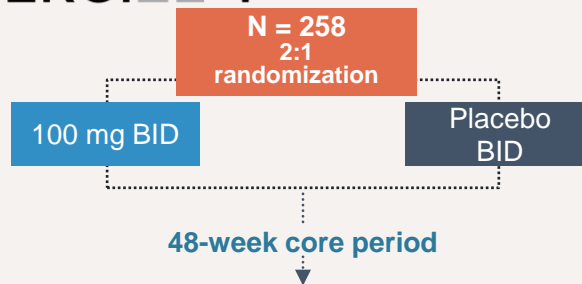
Secondary endpoints

- 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**



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

HbE = hemoglobin E; HbH = hemoglobin H



Phase 3 ENERGIZE study attained primary and key secondary endpoints; statistically significant improvements in Hb and fatigue



- This global study was the first to enroll patients with α -thalassemia in addition to β -thalassemia
- The primary and key secondary endpoints were met, with statistically significant improvements in Hb and fatigue with mitapivat vs placebo
- Improvements in markers of hemolysis and erythropoietic activity were observed, consistent with the mechanism of mitapivat¹⁻³
- Overall, during the 48-week double-blind period, incidence of adverse events (AEs) was similar across mitapivat and placebo arms; In the mitapivat arm, four (3.1%) of patients experienced an AE leading to discontinuation, compared to zero in the placebo arm

ENERGIZE demonstrated efficacy of mitapivat, a disease-modifying therapy, with significant improvements in both Hb and fatigue across the full range of NTD, including both α - and β -thalassemia

NTD = non-transfusion-dependent thalassemia

1. Kung C et al. Blood 2017;130:1347-56; 2. Matte A et al. J Clin Invest 2021;131:e144206; 3. Kuo KHM et al. Lancet 2022;400:493-501; 4. Al-Samkari H et al. NEJM 2022;386:1432-42; 5. Glenthøj A et al. Lancet Haematol 2022;9:e724-32; 6. Idowu M et al. Blood 2023;142:271.



Significant improvements in quality-of-life-related outcomes data from the Phase 3 ENERGIZE study



- In the 24-week double-blind period of ENERGIZE, significant improvements in fatigue, measured by FACIT-Fatigue, were demonstrated in the mitapivat arm compared with the placebo arm
 - A higher proportion of patients reported clinically meaningful improvements with mitapivat vs placebo
- Functional improvement in patients with mitapivat, measured by the 6MWT, exceeded a previously reported meaningful change threshold from the literature¹⁸
- A higher proportion of patients with mitapivat reported improved fatigue, disease symptoms, and walking capacity via PGIC with mitapivat vs placebo

Mitapivat is the first oral, disease-modifying, investigational therapy to improve fatigue and walking capacity in patients with α - or β -NTDT



Phase 3 ENERGIZE-T Study: Primary endpoint achieved



- Total of 258 patients were randomized 2:1 to 100 mg mitapivat (n=171) or placebo (n=87)
- 155 patients (90.6%) in the mitapivat arm and 83 patients (95.4%) in the placebo arm completed the 48-week double-blind period of the study
- Transfusion reduction response (TRR) is defined as $\geq 50\%$ reduction in transfused RBC units of ≥ 2 units of transfused RBCs in any consecutive 12-week period compared to baseline
- **Treatment with mitapivat demonstrated a statistically significant transfusion reduction response compared to placebo**

Primary Endpoint	Placebo N=87	Mitapivat 100 mg BID N=171
TRR responders, n (%)	11 (12.6)	52 (30.4)
Adjusted difference TRR rate (Mitapivat-Placebo), %		17.6
95% CI		(8.0, 27.2)
2-sided p-value		0.0003

TRR = transfusion reduction response.

Subjects withdrawn from the study before Week 12 (Day 85) are considered non-responders.

Baseline transfusion burden standardized to 12 weeks=total number of RBC units transfused during the 24-week period (168 days) before 'reference date' x12/24, where 'reference date' is the randomization date for subjects randomized and not dosed or the start of study treatment for subjects randomized and dosed.

The 95% CI and p-value are based on the Mantel-Haenszel stratum weighted method adjusting for randomization stratification factors.



Efficacy

Treatment with mitapivat demonstrated statistically significant improvements on all key secondary endpoints evaluating additional measures of reduction in transfusion burden:

- ≥50% reduction in transfused RBC units in any consecutive 24-week period through week 48 compared to baseline
- ≥33% reduction in transfused RBC units from week 13 through week 48 compared to baseline
- ≥50% reduction in transfused RBC units from week 13 through week 48 compared to baseline

Transfusion independence

- A higher proportion of patients in the mitapivat arm (9.9%) compared to the placebo arm (1.1%) achieved the secondary endpoint of transfusion independence (transfusion-free for ≥8 consecutive weeks through week 48)

Safety

- Overall, during the 48-week double-blind period, incidence of adverse events (AEs) was similar across mitapivat and placebo arms
- In the mitapivat arm, 5.8% of the patients experienced an AE leading to discontinuation, compared to 1.2% of patients in the placebo arm

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



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

Abbreviation: RBC = red blood cell

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

Assessments collected within 8 weeks after an RBC transfusion are excluded from the analysis.

Subjects who do not have any Hb concentration assessments from Week 10 through Week 12 are considered nonresponders.

(1) Exact 95% CI

(2) The p-value is based on the Fisher's exact test



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



CRC Adjudicated Data

Negative Binomial Regression Model

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

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

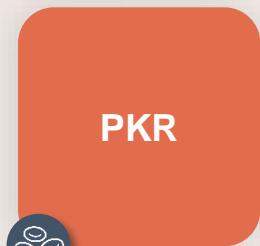
The estimates and 95% CIs are based on a negative binomial regression model with natural log link. The model included the number of SCPC events during the Double-blind Period of the study as the response variable and treatment arm as the independent variable. The natural log of time on study was used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

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



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