Topline Results: Phase 3 ENERGIZE Study of PYRUKYND® (mitapivat) in Thalassemia

January 3, 2024

Agios conference call participants

TOPIC	PARTICIPANT
Opening Remarks	Brian Goff, Chief Executive Officer
Data Highlights from Phase 3 ENERGIZE Study	Jeremie Estepp, M.D., Medical Director
Framing Phase 3 ENERGIZE-T Study Readout	Sarah Gheuens, M.D., Ph.D., Chief Medical Officer, Head of Research and Development
Closing Remarks	Brian Goff, Chief Executive Officer
Q&A	Mr. Goff, Dr. Estepp, Dr. Gheuens, Cecilia Jones (CFO), and Tsveta Milanova (CCO)

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 mitapivat; Agios' plans for the future clinical development of mitapivat in alpha-and-beta thalassemia; and Agios' strategic plans and prospects. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "plan," "predict," "project," "would," "could," "potential," "possible," "hope" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. Such statements are subject to numerous important factors, risks and uncertainties that may cause actual events or results to differ materially from Agios' current expectations and beliefs. For example, there can be no guarantee that any product candidate Agios or its collaborators is developing will successfully commence or complete necessary preclinical and clinical development phases, or that development of any of Agios' product candidates will successfully continue. Moreover, there can be no guarantee that any medicines ultimately commercialized by Agios will receive commercial acceptance. There can be no guarantee that any positive developments in Agios' business will result in stock price appreciation. Management's expectations and, therefore, any forward-looking statements in this 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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Opening Remarks

Brian Goff
Chief Executive Officer

Data Highlights from Phase 3 ENERGIZE Study

Jeremie Estepp, M.D.
Medical Director at Agios

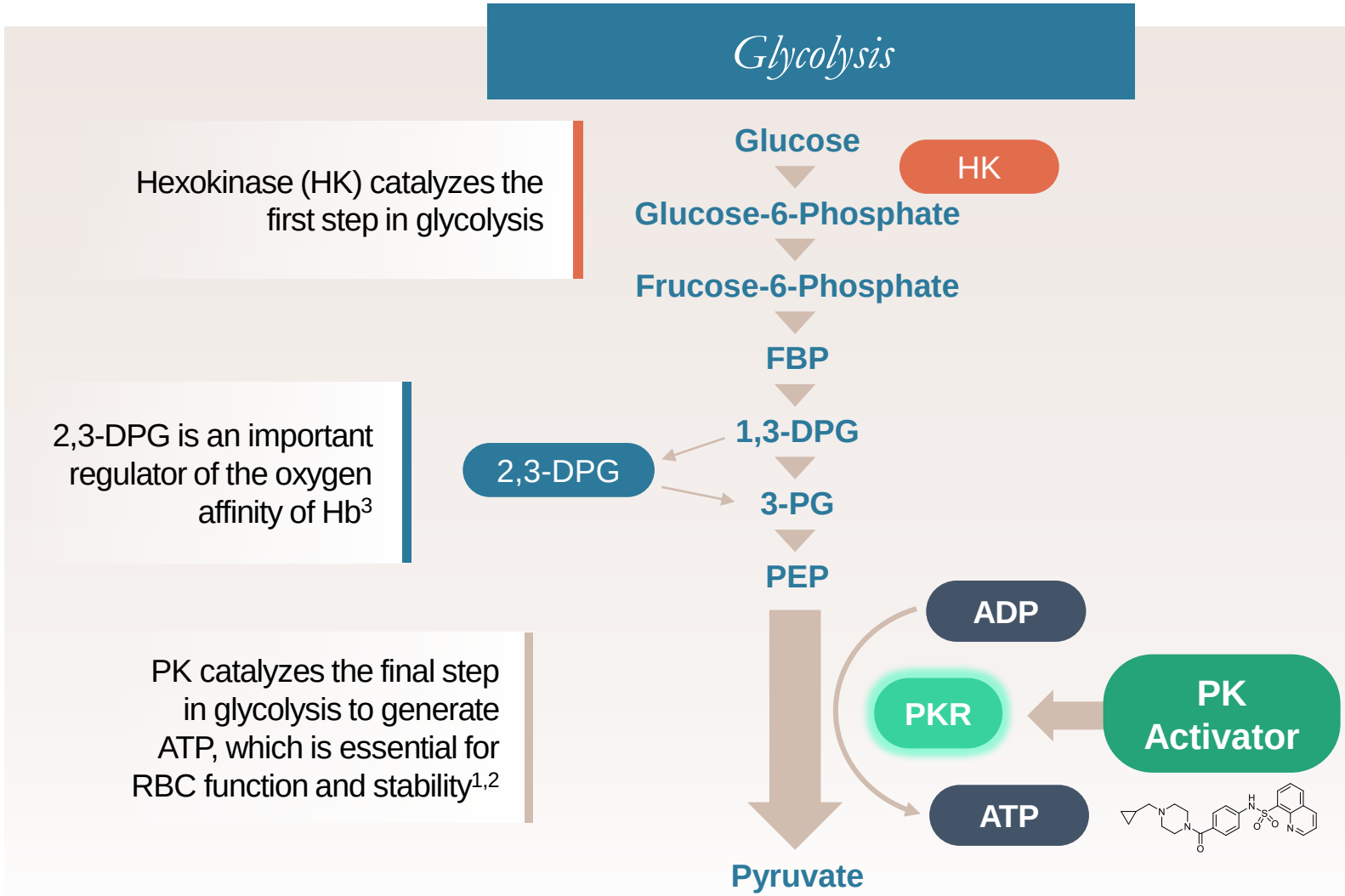
There are no approved oral treatments for non-transfusion-dependent thalassemia (NTDT)

- Thalassemia is a group of genetic disorders impacting α- and/or β-globin genes, resulting in an imbalance of globin production[1,2]
  - Excess globin chains precipitate and are toxic to red blood cells (RBCs), directly leading to ineffective erythropoiesis and hemolysis[2]
- Thalassemic RBCs lack sufficient levels of ATP to meet the increased energy demands associated with degradation of globin chain precipitates and cellular oxidative stress responses[3,4]
- Although patients with non–transfusion-dependent thalassemia (NTDT) do not require regular blood transfusions for survival, they can experience chronic anemia and serious complications[1,2]
  - Treatment options for NTDT are supportive only, highlighting an unmet need for disease-modifying therapies[5]
- Mitapivat is an investigational, first-in-class, oral, small-molecule allosteric activator of pyruvate kinase (PK) in RBCs, a key enzyme that regulates ATP production[6]

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

ATP, adenosine triphosphate; NTDT, non–transfusion-dependent thalassemia; PK, pyruvate kinase; RBC, red blood cell; 1. Taher AT et al. Lancet 2018;391:155–67; 2. Galanello R et al. Orphanet J Rare Dis 2010;5:11; 3. Khandros E et al. Blood 2012;119:5265–75; 4. Shaeffer JR. J Biol Chem 1988;263:13663–9; 5. Musallam KM et al. Haematologica 2021;106:2489–92; 6. Kung C et al. Blood 2017;130:1347–56

PYRUKYUND® (mitapivat) is an oral, small molecule allosteric activator of pyruvate kinase with the potential to correct RBC metabolism



PK activation is expected to correct RBC metabolism by:

Normalizing the PK/HK ratio - Decreased PK/HK ratio is observed in MDS

Reducing 2,3-DPG levels - Elevated 2,3-DPG levels are associated with RBC sickling in SCD

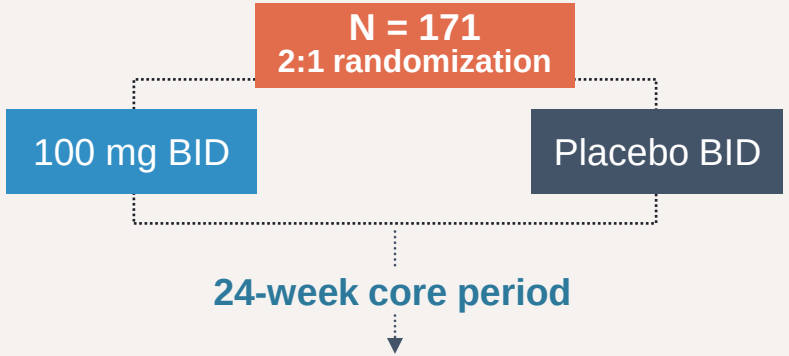
Increasing RBC energy production (ATP) - Reduced ATP production and/or increased ATP demand is observed in PKD, thalassemia, SCD, and LR-MDS

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® in thalassemia encompass broad range of thalassemia patients

ENERGIZE



Primary endpoint

- Mean Hb ↑ ≥ 1 g/dL from baseline

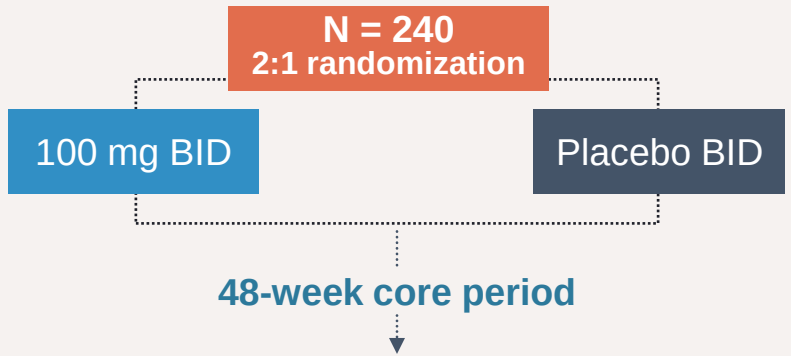
Secondary endpoints

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

Key inclusion criteria

- ≥ 18 years
- β-thalassemia ± α-globin mutations, HbE β-thalassemia, or α-thalassemia (HbH disease)
- Non-transfusion-dependent defined as ≤5 RBC units during the 24-week period before randomization and no RBC transfusions ≤8 weeks prior
- Hb ≤ 10.0 g/dL

ENERGIZE-T



Primary endpoint

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

Secondary endpoints

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

Key inclusion criteria

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

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

Phase 3 ENERGIZE study: primary endpoint achieved

- 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

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

- 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**

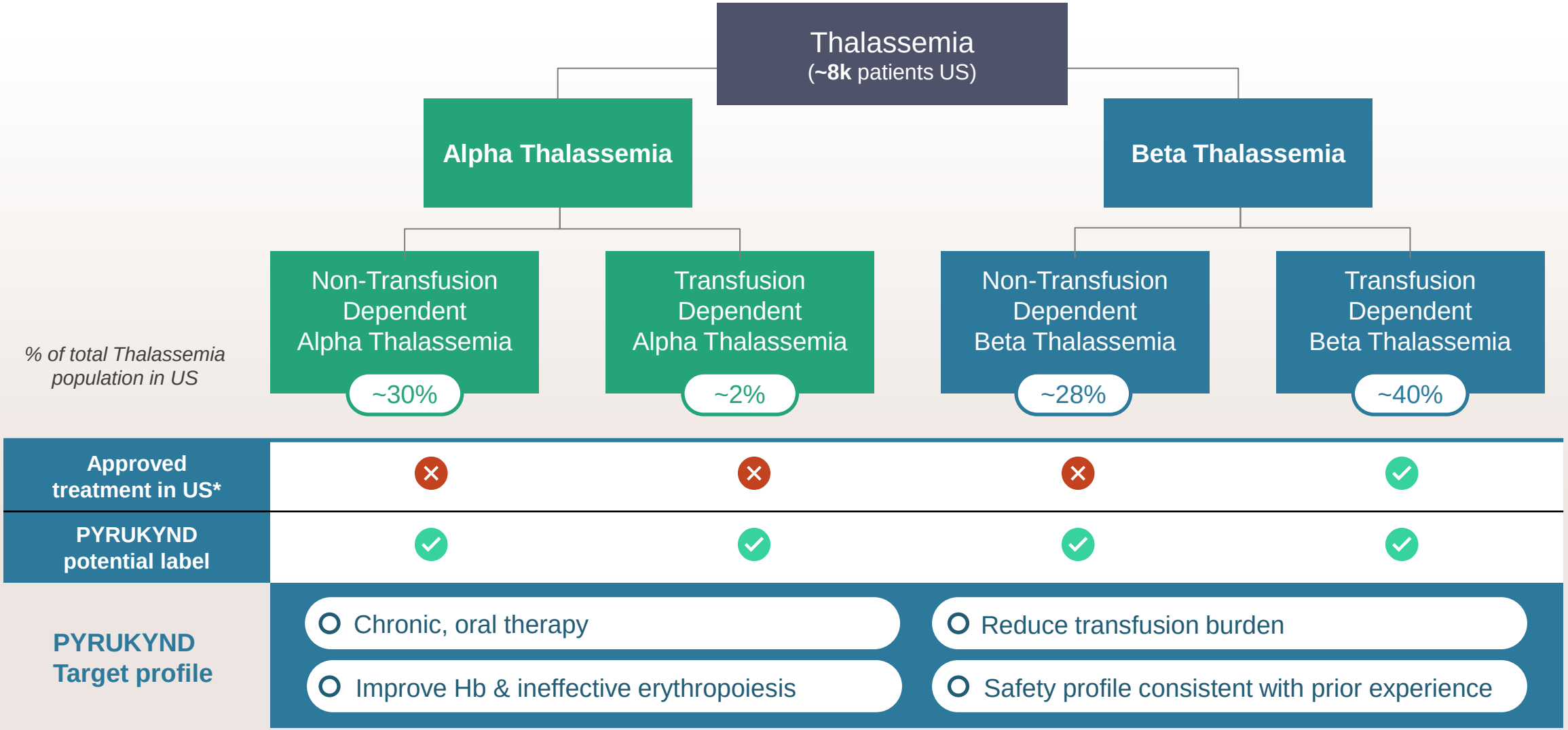
Safety

- Overall, during the 24-week double-blind period, incidence of adverse events was similar across mitapivat and placebo arms
- Four (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

Framing the Upcoming Phase 3 ENERGIZE-T Readout

Sarah Gheuens, M.D., Ph.D.,
Chief Medical Officer, Head of Research and Development

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



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

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

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

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

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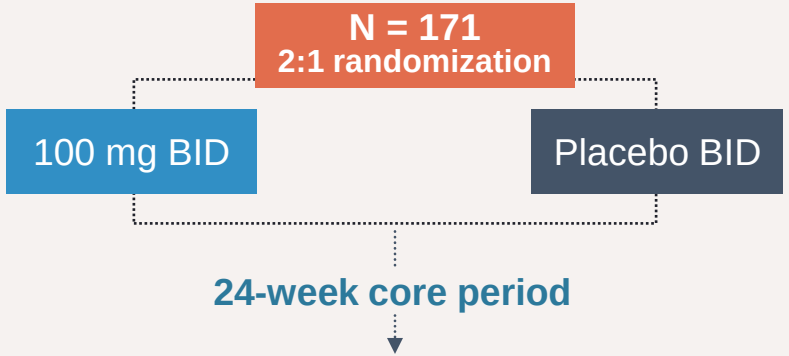

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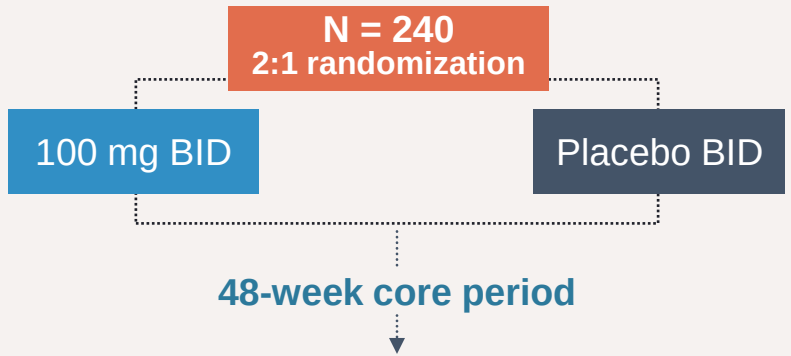
ENERGIZE-T



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Planning single regulatory filing incorporating data from ENERGIZE and ENERGIZE-T

ENERGIZE-T data readout expected mid-2024

Anticipated filing encompassing data from ENERGIZE and ENERGIZE-T by year-end 2024

Seeking broad indication for all thalassemia patients

Potential FDA approval in 2025

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Closing Remarks

Brian Goff
Chief Executive Officer

Leaders in PK activation positioned for meaningful near-term growth

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

Four late-stage data readouts expected by end of 2025

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

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

Thalassemia
Potential U.S. approval in 2025

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

Sickle cell disease
Potential U.S. approval in 2026

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

Lower-risk myelodysplastic syndrome

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

AG-946
Novel PK Activator
provides additional opportunities for the franchise

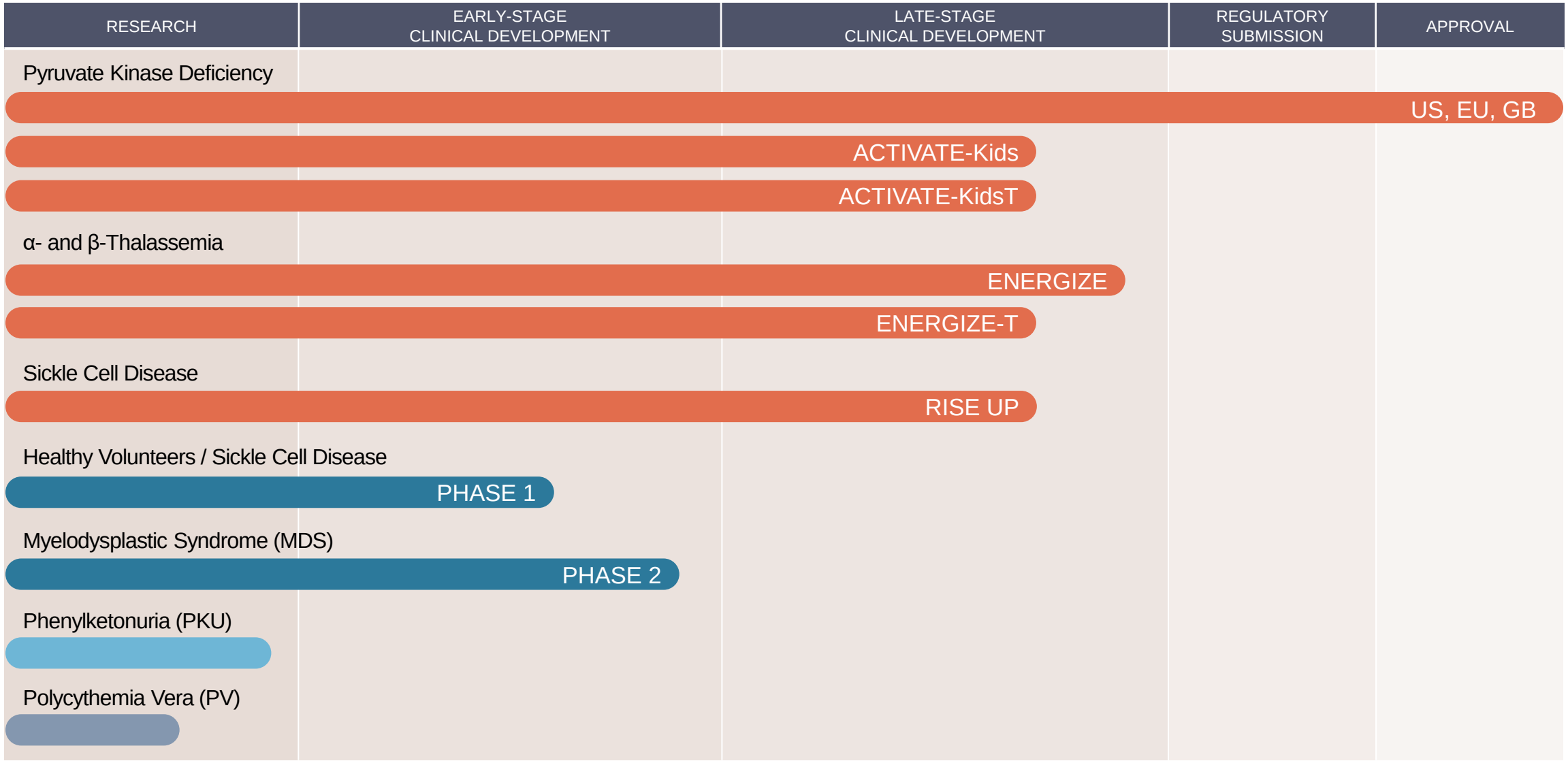
Building **PYRUKYND**

Larger patient populations →
Higher diagnostic rates →
Higher burden of disease →

AG-946
Second PK Activator

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

Building a diverse pipeline in rare disease



PYRUKYND®
First-in-class PK activator

AG-946
Novel PK activator

Phenylalanine hydroxylase (PAH) stabilizer

siRNA Targeting TMPRSS6

Four late-stage data readouts expected by the end of 2025

	2024	2025	2026
Thalassemia PYRUKYND®	**Phase 3 ENERGIZE (announced today)** **Phase 3 ENERGIZE-T (mid-year)**	**Potential approval**	
Pediatric PK Deficiency PYRUKYND®		**Phase 3 ACTIVATE-kids** **Phase 3 ACTIVATE-kidsT**	**Potential approval**
Sickle Cell Disease PYRUKYND®		**Phase 3 RISE UP**	**Potential approval**
Lower-Risk MDS AG-946 (Novel PK Activator)	**Initiate Phase 2b study (mid-year)**		

Leader in pyruvate kinase (PK) activation poised for significant growth

Compelling and consistent data across connected diseases

Robust clinical data set supports potential of PK activation to transform patient function, quality of life, and long-term outcomes

Meaningful commercial opportunities on the horizon

First rare disease launch building capabilities to maximize anticipated franchise expansion

Potential for two additional PYRUKYND® indications by 2026

Well capitalized to advance and expand

Strong cash position expected to support completion of ongoing programs and disciplined portfolio expansion at least into 2026

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Q&A