# PYRUKIND® (mitapivat)
# RISE UP Phase 2 Topline Results

*June 26, 2023*

# Agenda

| TOPIC | PARTICIPANT |
| --- | --- |
| Introduction | **Brian Goff**<br>Chief Executive Officer |
| RISE UP Phase 2 Data Highlights | **Ahmar Zaidi, M.D.**<br>Agios Medical Director, Clinical Development |
| RISE UP Phase 3 Trial Design | **Sarah Gheuens, M.D., Ph.D.**<br>Chief Medical Officer, Head of Research and Development |
| Summary and Anticipated Milestones | **Brian Goff**<br>Chief Executive Officer |
| Q&A | **Mr. Goff, Dr. Gheuens, Dr. Zaidi, Cecilia Jones** (Chief Financial Officer), **Tsveta Milanova** (Chief Commercial Officer) |

# 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 and its other product candidates; 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. 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 could also be affected by risks and uncertainties relating to a number of other important factors, including, without limitation: 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 and 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 collaborations; the failure of Agios to receive milestone or royalty payments related to the sale of its oncology business, the uncertainty of the timing of any receipt of any such payments, and the uncertainty of the results and effectiveness of the use of proceeds from the transaction with Servier; 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; 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 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

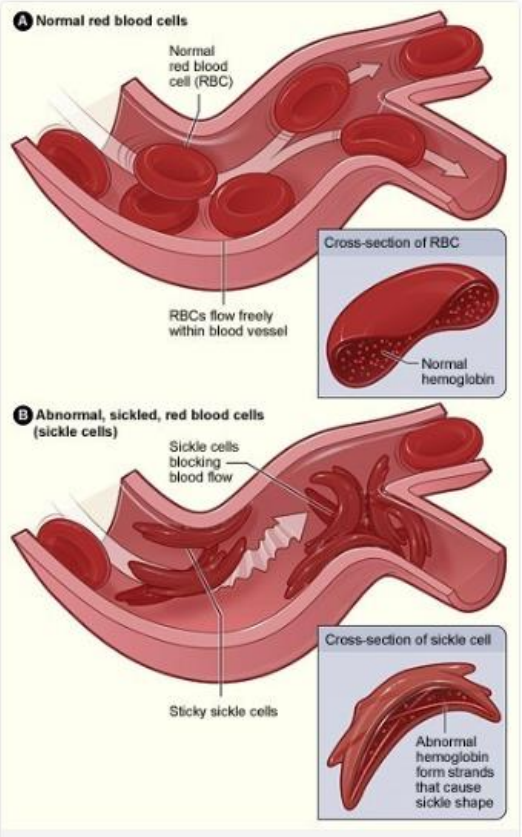
Brian Goff, Chief Executive Officer

# RISE UP Phase 2 Data Highlights

Ahmar Zaidi, M.D., Agios Medical Director, Clinical Development

# Sickle Cell Disease: an underserved indication with significant unmet need

- Estimated 100,000 individuals living with SCD in the U.S and more than 3 million worldwide[1]
- Characterized by inheritance of sickle hemoglobin (HbS) in combination with either another HbS allele or other hemoglobin mutations resulting in a sickling disorder[2]
- Upon deoxygenation HbS polymerizes resulting in rigidity in the red blood cell and creating its characteristic sickled shape[2]
- Clinical complications of SCD include:
  - Vaso-occlusive crisis
  - Anemia
  - Acute chest syndrome
  - Hepatopathy
  - Pulmonary hypertension
  - Renal disease
  - Retinopathy
  - Stroke

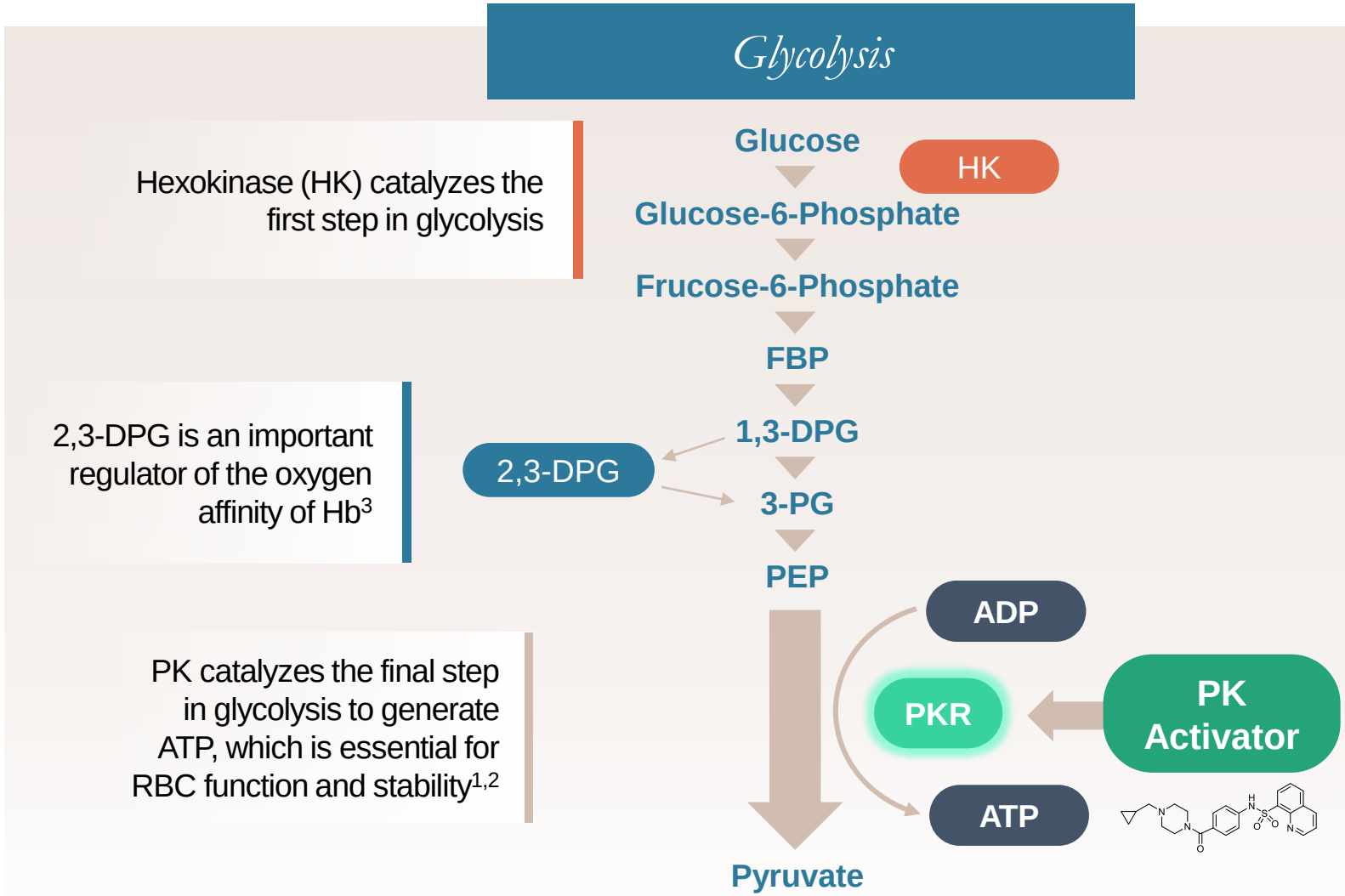



Normal red blood cells and sickle red cells.[4]



1. Brandow et al. J Hematol Oncol 15, 20 (2022). 2. Ware RE et al. Lancet. 2017;390(10091):311-323. 3. Piel FB et al. NEJM. 2017;376:1561-1573. 4. National Heart, Lung, Blood Institute. Public Domain.

# PYRUKYND® (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

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

*Evaluate totality of available data & external environment to trigger Phase 3 including:*

## Phase 2

- 1:1:1 randomization to mitapivat 50 mg BID, 100 mg BID or matched placebo
- N=69
- 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 Phase 2 dose 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



PYRUKYND® is under investigation for sickle cell disease and is not approved anywhere for that use.

# Data highlights: primary efficacy endpoint achieved for both doses

**The Phase 2 portion of the global RISE UP study of mitapivat in sickle cell disease met its primary endpoint of hemoglobin response for both 50 mg BID and 100 mg BID**

- RISE UP Phase 2 study enrolled 79 patients, with 27 patients on placebo, 26 on 50 mg BID and 26 on 100 mg BID
- Treatment with mitapivat (50 mg BID and 100 mg BID) demonstrated a **statistically significant increase in hemoglobin response rate** compared to placebo
- The results for the secondary endpoints in both treatment arms were generally supportive of the results observed for the primary endpoint
  - **Improvements in markers of hemolysis and erythropoiesis** were observed at both doses compared to placebo
  - A **trend in sickle cell pain crises reduction** was observed at both doses compared to placebo
- The safety profile for mitapivat observed in the study was generally consistent with previously reported data in other studies of sickle cell disease and other hemolytic anemias
- There were no adverse events (AEs) leading to discontinuation in either the mitapivat or the placebo arms
- Of the 79 patients enrolled in the study, 73 continued into the Phase 2 open-label extension period

# 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

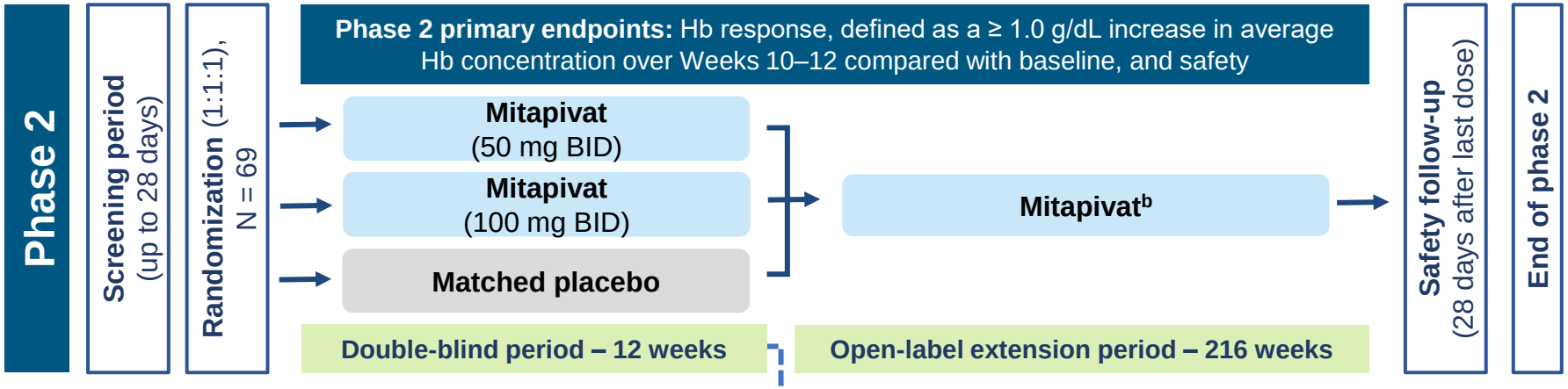
The estimates and 95% CIs are based on a negative binomial regression model with natural log link. The model included the number of SCPC events during the Double-blind Period of the study as the response variable and treatment arm as the independent variable. The natural log of time on study was used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

# RISE UP Phase 3 Trial Design

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

# RISE UP Study Design

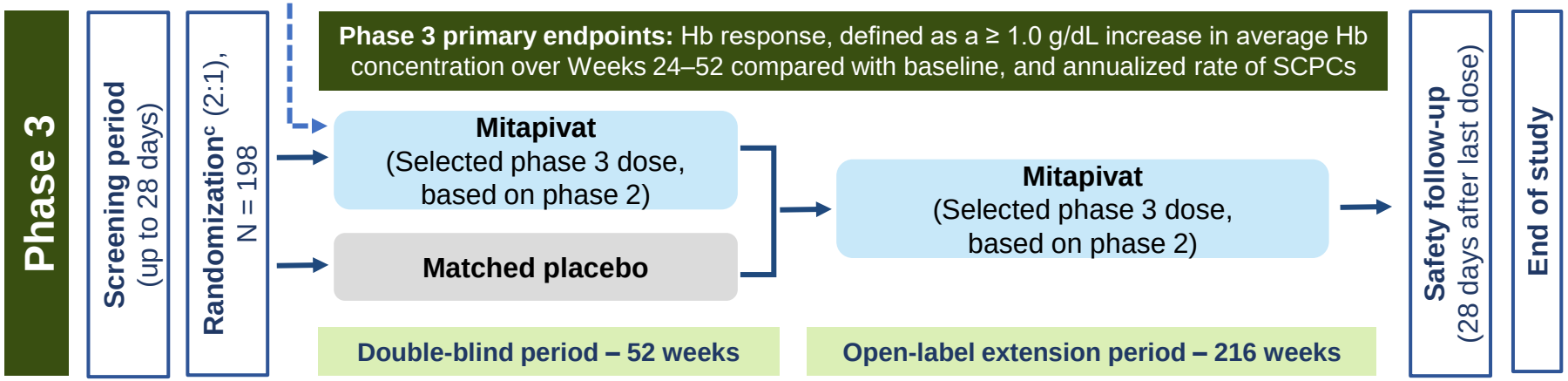



**Key inclusion criteria**

- ≥ 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




[a]Phase 2 and phase 3 components are part of a single study/protocol; [b]Patients who receive mitapivat in the double-blind period will continue to receive the same dose of mitapivat in the open-label extension period, patients who receive placebo will be randomized 1:1 to mitapivat 50 mg BID or 100 mg BID; [c]Randomization stratification factors: Number of SCPCs in the prior year (< 5, ≥ 5), hydroxyurea use (yes, no). BID = twice daily; Hb = hemoglobin; SCPC = sickle cell pain crises.

# RISE UP Phase 3 Study: first patient enrolled expected in Q4 2023

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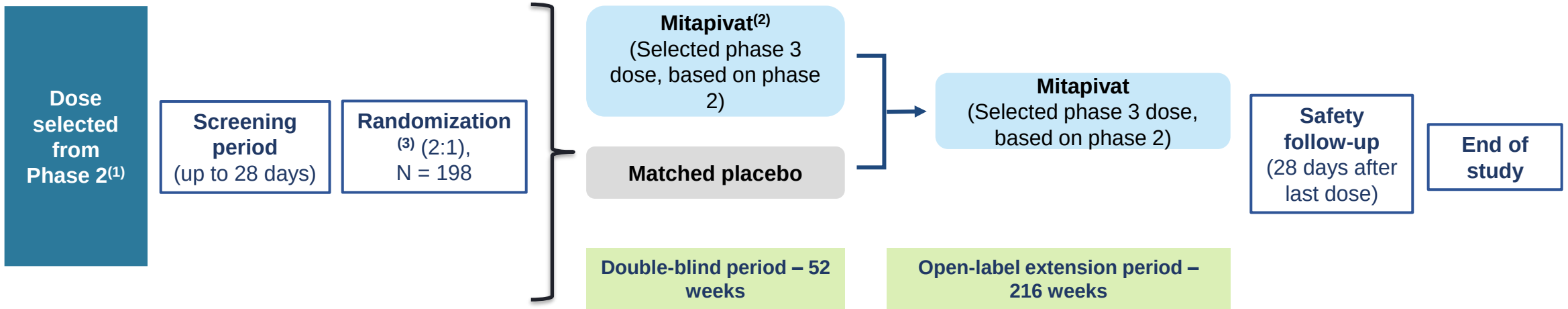
**Key exclusion criteria**
- Receiving regularly scheduled blood transfusions
- Severe kidney disease or hepatobiliary disorders
- Currently receiving treatment with SCD therapies (excluding HU)
- Prior exposure to gene therapy, or prior bone marrow or stem cell transplantation

**Phase 3 primary endpoints:** 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




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).

# Sickle Cell Disease: no novel oral therapy improves anemia and reduces sickle cell pain crises

- Estimated 120-135K patients across the U.S. & EU5
- Significant opportunity outside of U.S./EU

**Global Reach**

- Deliver a novel oral therapy that improves anemia, reduces VOCs and is supported by the largest body of clinical evidence

**PYRUKYND® Opportunity**

- Innovative seamless Phase 2/3 trial RISE UP developed with community input
- Global approach to clinical development
- Connections with SCD patient and physician communities

**Critical Success Factors**

TARGET PROFILE

*PYRUKYND®*

- Chronic Therapy
- Oral
- Improved hemolytic anemia
- Improvement in sickle cell pain crises (vaso-occlusive crises; VOCs) QoL data
- Safety profile consistent with prior clinical experience

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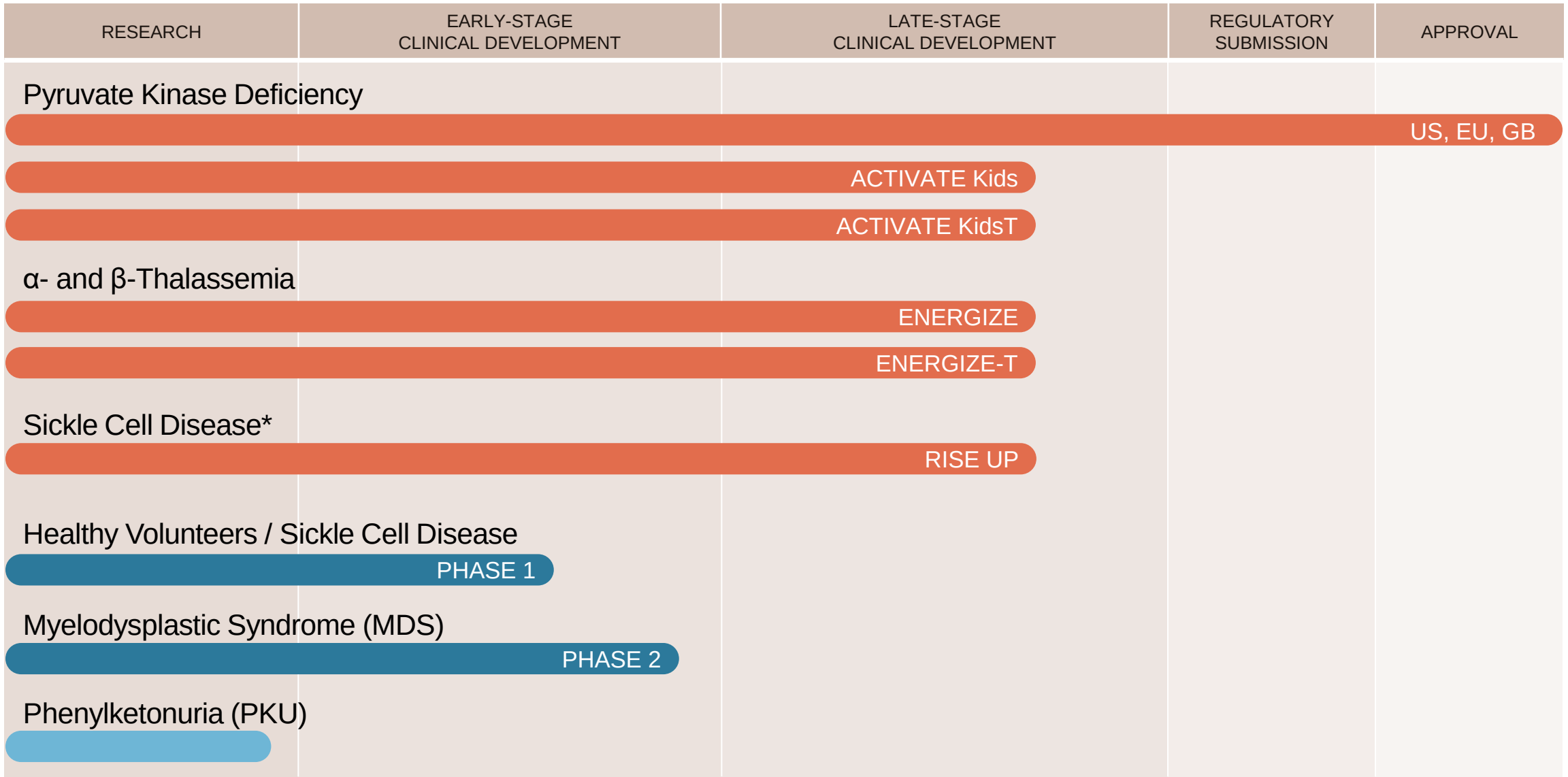
# Closing Remarks

Brian Goff, Chief Executive Officer

# Building a diverse pipeline leveraging our expertise in cellular metabolism




*In addition to RISE UP, two investigator-sponsored trials are ongoing with the NIH and University of Utrecht.

**PYRUKYND®**
First-in-class PK activator

**AG-946**
Novel PK activator

Phenylalanine hydroxylase (PAH) stabilizer

# Clinical and regulatory milestones targeted in 2023 lay the foundation for transformational data readouts

2023

**Thalassemia**
PYRUKYND®
Complete enrollment of Phase 3 ENERGIZE and ENERGIZE-T studies
(MID-YEAR)

**Sickle Cell Disease**
PYRUKYND®
Phase 2 RISE UP data readout & go/no-go to Phase 3 decision
(MID-YEAR)

**Pediatric PK Deficiency**
PYRUKYND®
Enroll at least half of patients in the Phase 3 ACTIVATE-kids and ACTIVATE-kidsT studies
(YEAR-END)

**Pipeline**
File IND for PAH stabilizer for the treatment of PKU
(YEAR-END)

**Lower-Risk MDS**
AG-946 (Novel PK Activator)
Complete enrollment of Phase 2a study
(YEAR-END)

**Sickle Cell Disease**
PYRUKYND®
Begin patient enrollment in Phase 3 RISE UP study
(YEAR-END)

**NEW 2023 MILESTONE**

**Lower-Risk MDS**
AG-946
Phase 2a data readout
(YEAR-END)

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

# Potential for two additional PYRUKYND® indications by 2026

| | 2024 | 2025 | 2026 |
|---|---|---|---|
| **Thalassemia**<br>PYRUKYND® | **Phase 3 ENERGIZE (1H) and ENERGIZE-T (2H) readouts** | **Potential approval** | |
| **Pediatric PK Deficiency**<br>PYRUKYND® | | **Phase 3 ACTIVATE-kids and ACTIVATE-kidsT readouts** | **Potential approval** |
| **Sickle Cell Disease**<br>PYRUKYND® | | **Potential Phase 3 RISE UP readout** | **Potential approval** |
| **Lower-Risk MDS**<br>AG-946 (Novel PK Activator) | **Phase 2a readout**<br>(accelerated to YE 2023) | | |


# Q&A