agios

ASH Investor Event

December 8, 2020

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, strategies and expectations for its and its collaborator's preclinical, clinical and commercial advancement of its drug development, including mitapivat; Agios' key milestones for 2020 and 2021; Agios' plans regarding future data presentations; and the potential benefits of Agios' strategic plans and focus. The words "anticipate," "expect," "goal," "hope," "milestone," "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 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 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 the COVID-19 pandemic 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 maintain key collaborations; 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.

Today's Agenda

	TOPIC	SPEAKER
8:00 – 8:10 AM	Opening Remarks	Jackie Fouse, Ph.D.
8:10 – 8:30 AM	Mitapivat Mechanism of Action & Clinical Updates: Thalassemia Pivotal Plan and Topline ACTIVATE Data	Chris Bowden, M.D.
8:30 – 8:50 AM	Review Updated Data from the Phase 1 NIH Study of Mitapivat in Sickle Cell Disease	Swee Lay Thein, M.D.
8:50 – 9:30 AM	Q&A	Dr. Fouse, Dr. Bowden, Dr. Thein and Darrin Miles

We are driven by our sense of urgency to help patients.

"The disease has affected my career. I spent 11 years to get a PhD in nutrition...My heart wants more but my body can't handle it."

—Tamara S., Minnesota

Currently 50 years old. Diagnosed with PK deficiency at the age of 6.

"On a bad day, it's like watching some electronic toy slowly lose the battery."

—Tamara S., Minnesota

Agios is a commercial-stage biopharmaceutical company passionately committed to applying our scientific leadership in the field of cellular metabolism to transform the lives of patients with cancer and rare genetic diseases.

Agios pioneered a novel path to treating hematological diseases by following the science of cellular metabolism…

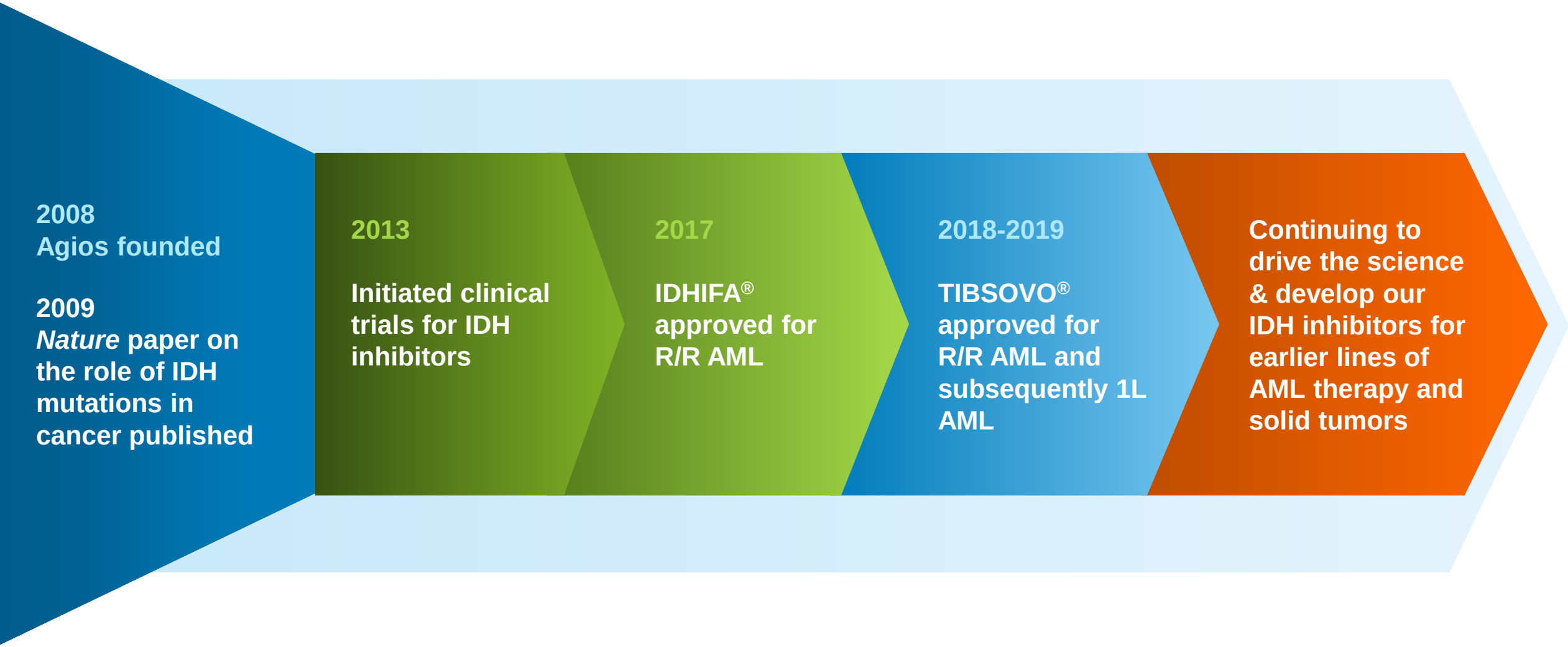
Hematology Is At Our Core

Activating PKR in rare hemolytic anemias

Unlocking the promise of IDH in hematologic malignancies

…and we are leading the way in PKR activation for treating hemolytic anemias.

Leading the Science for IDH Mutations in Cancer



Four IDH-focused Presentations at ASH Highlight Our Scientific and Clinical Leadership in This Space

ORAL PRESENTATION

Ivosidenib Improves Overall Survival Relative to Standard Therapies in Relapsed or Refractory Mutant IDH1 AML: Results from Matched Comparisons to Historical Controls	Presented: Monday, Dec. 7 at 10:15a.m. PT

POSTER PRESENTATIONS

Molecular Characterization of Clinical Response and Relapse in Patients with IDH1-Mutant Newly Diagnosed Acute Myeloid Leukemia Treated with Ivosidenib and Azacitidine	Presented: Sunday, Dec. 6 at 7a.m. PT
AGILE: Phase 3, Double-Blind, Randomized, Placebo-Controlled Study of Ivosidenib in Combination with Azacitidine in Adults with Newly Diagnosed Acute Myeloid Leukemia and an IDH Mutation	Presented: Monday, Dec. 7 at 7a.m. PT
Longitudinal Molecular Profiling in Patients with IDH1-Mutant Newly Diagnosed Acute Myeloid Leukemia Treated with Ivosidenib	Presented: Monday, Dec. 7 at 7a.m. PT

Our Leadership in PKR Activation

6 YEARS

STUDYING PKR ACTIVATION IN THE CLINIC

~190	17	15	17	3
PATIENTS TREATED	CLINICAL TRIALS	JOURNAL ARTICLES PUBLISHED	MEDICAL/SCIENTIFIC COLLABORATIONS	DISEASES WITH POC ACHIEVED

+ A LOT OF FIRSTS:

- BUILT 1st GLOBAL PK DEFICIENCY REGISTRY
- ESTABLISHED 1st INTERNATIONAL PK DEFICIENCY ADVOCACY ADVISORY COUNCIL
- SUPPORTED 1st HEMOLYTIC ANEMIA ADVOCACY COALITION BUILDING MEETING

Presentations at ASH Underscore Severity of PK Deficiency and Broad Utility of the PK Activation Mechanism Across Hemolytic Anemias

ORAL PRESENTATIONS

Phase 1 Multiple Ascending Dose Study of Safety, Tolerability, and Pharmacokinetics/Pharmacodynamics of Mitapivat (AG-348) in Subjects with Sickle Cell Disease	Presented: Monday, Dec. 7 at 2:30p.m. PT
The Pyruvate Kinase Activator AG-348 ameliorates anemia and prevents iron overload in a mouse model of hereditary spherocytosis	Presented: Saturday, Dec. 5 at 10:15a.m. PT

POSTER PRESENTATIONS

Mortality Among Veterans with a Diagnosis of Pyruvate Kinase (PK) Deficiency: A Real-World Study Using US Veterans Health Administration Data	Presented: Saturday, Dec. 5 at 7a.m. PT
Early-Onset Osteopenia and Osteoporosis in Patients with Pyruvate Kinase Deficiency	Presented: Sunday, Dec. 6 at 7a.m. PT
Baseline Characteristics of Patients in Peak: A Global, Longitudinal Registry of Patients with Pyruvate Kinase Deficiency	Presented: Monday, Dec. 7 at 7a.m. PT
Proof of Concept for the Oral Pyruvate Kinase Activator Mitapivat in Adults with Non-Transfusion-Dependent Thalassemia: Interim Results from an Ongoing, Phase 2, Open-Label, Multicenter Study	Presented: Monday, Dec. 7 at 7a.m. PT

Key Takeaways

1. ACTIVATE met its primary endpoint, and mitapivat is on track to be the first potential disease-modifying therapy for patients with PK deficiency with U.S. and EU submission planned in 2021
2. Agios has developed a broad clinical development plan for β- and α-thalassemia and will initiate two studies in 2021
3. Updated data for mitapivat in sickle cell disease (SCD) are impressive and support advancement to pivotal development in 2021
4. Agios continues to lead the science behind IDH mutations in AML

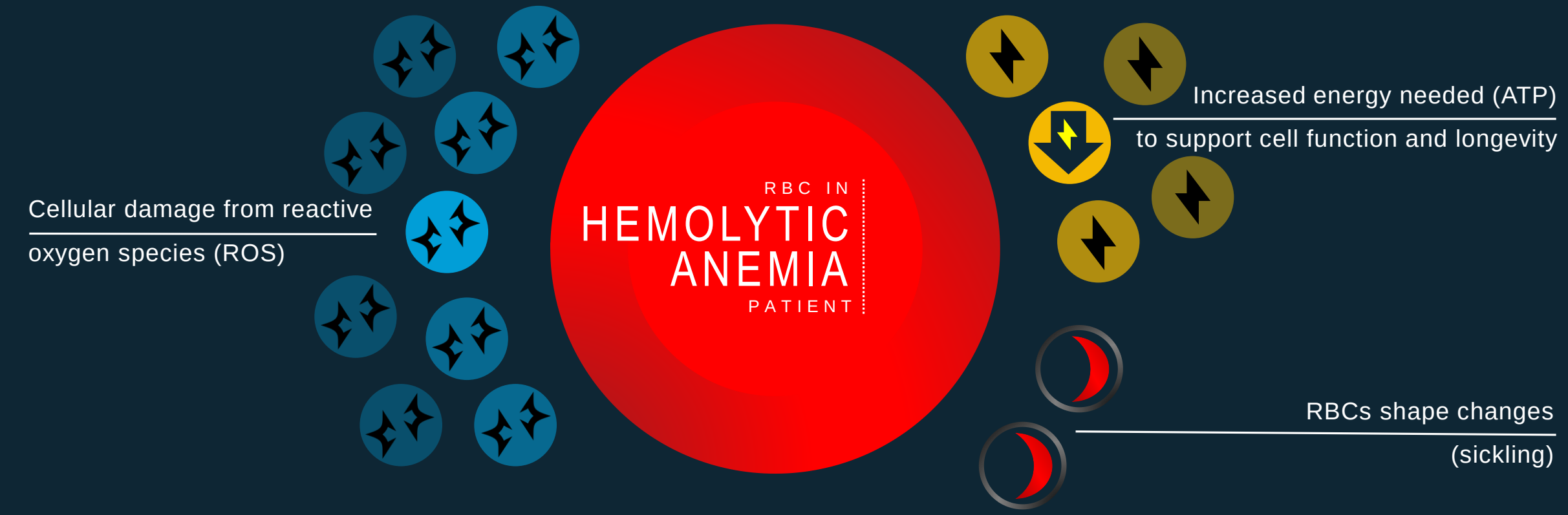
 Mitapivat is an investigational product and is not approved for use by any regulatory authority for any use.

PKR Activation as a Potential Treatment for Serious Hemolytic Anemias

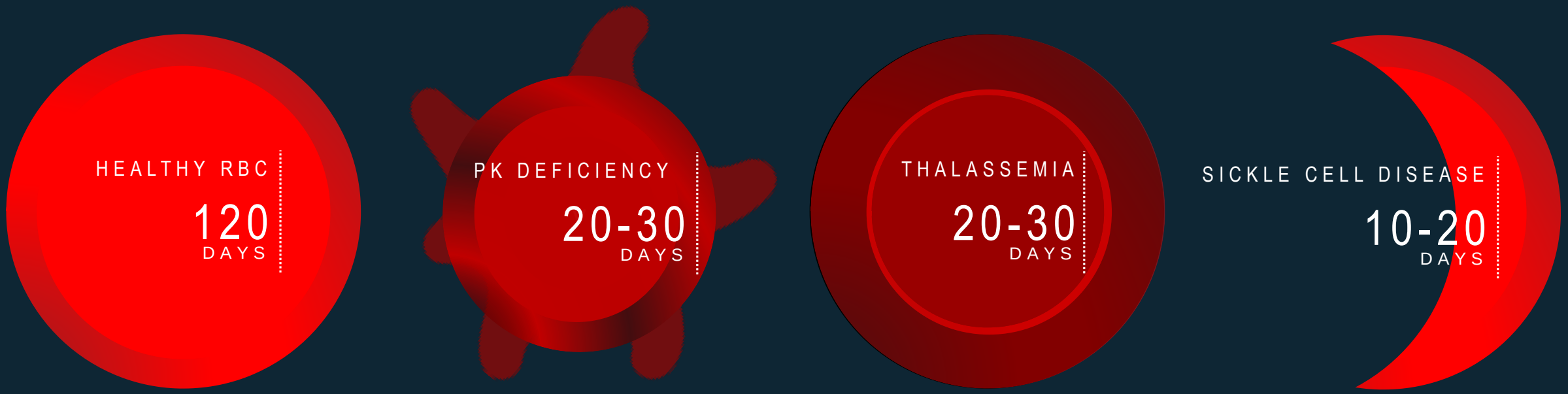
Dr. Chris Bowden

RBCs Deliver Oxygen to Tissues, Which Is Necessary for Energy and Organ Health

RBCs in Patients With Hemolytic Anemia Have Insufficient ATP, Increased ROS Damage or Sickling



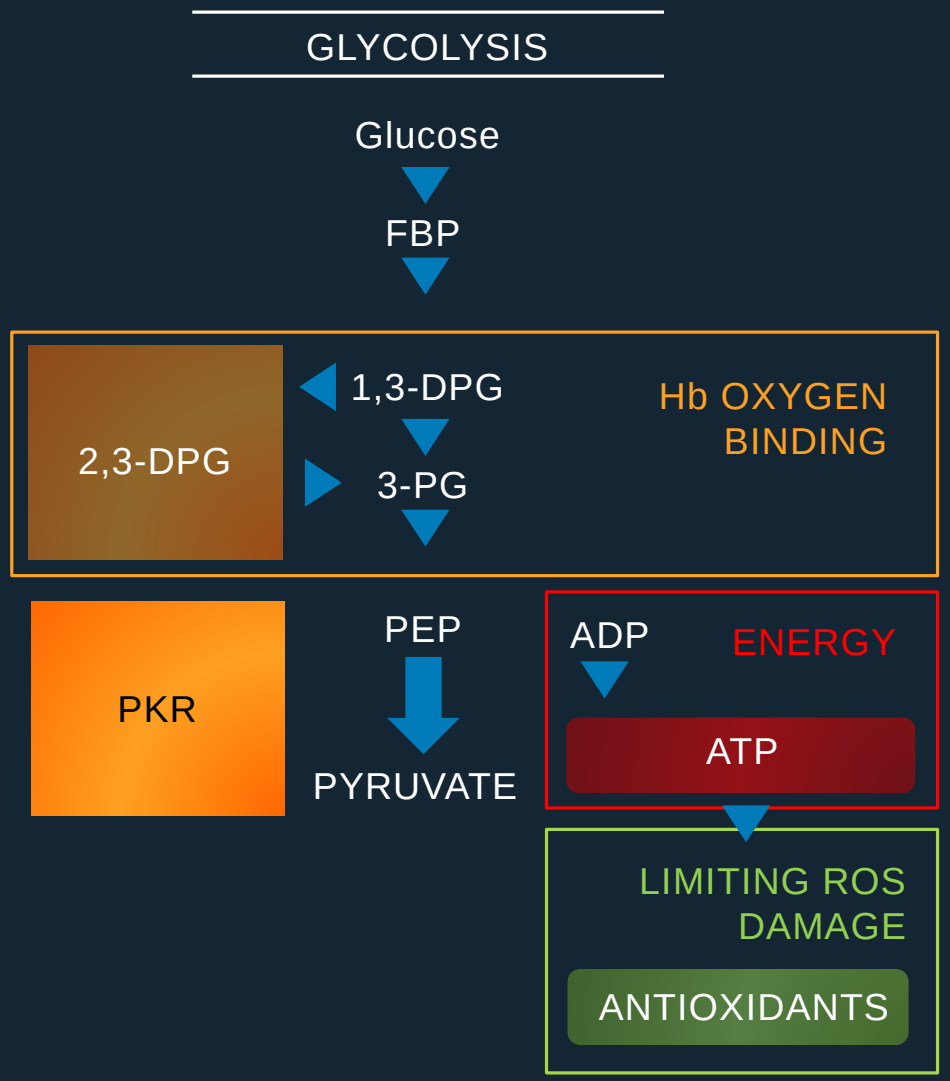
Shortened RBC Lifespan Can Lead to Chronic Fatigue, Iron Overload and Potentially Serious Complications



	HEMOGLOBIN (Hb) FUNCTIONAL	HEMOGLOBIN (Hb) INSUFFICIENT	HEMOGLOBIN (Hb) HBS POLYMERS
	PYRUVATE KINASE MUTATED	PYRUVATE KINASE FUNCTIONAL	PYRUVATE KINASE FUNCTIONAL

N Engl J Med 1968; 278:73-81; Blood (2004) 104 (11): 3616; J Kanter Blood Reviews 27:6 November 2013 279-287

PKR Is the Rate-Limiting Step for RBC Energy Production



Pyruvate kinase-R (PKR) is required for:

- Maintaining RBC energy levels
- Maintaining antioxidants, which limit cellular damage
- Regulating 2,3-DPG levels, which governs oxygen binding to hemoglobin

Mitapivat Has the Potential to Be the First Agent to Transform the Course of Hemolytic Anemia by Increasing RBC Energy, Health and Longevity

ATP

Increases ATP production, helps to match RBC energy needs

ANTIOXIDANTS (ROS)

Mitapivat has been shown in preclinical models to reduce ROS levels, reducing cellular damage

2,3 DPG

Mitapivat decreases 2,3-DPG, which reversibly increases oxygen affinity for Hb, potentially reducing sickling in SCD

Agios PKR Clinical Pipeline

Preclinical	Early Stage Clinical	Late Stage Clinical	Regulatory Submission	Near-Term Milestones	Worldwide Commercial Rights
Mitapivat Not Regularly Transfused (NRT) Adult PK Deficiency (ACTIVATE)				Topline data announced 12/1; NDA filing in 2021	agios
Mitapivat Regularly Transfused (RT) Adult PK Deficiency (ACTIVATE-T)				Topline data in Q1 ’21	agios
Mitapivat Thalassemia				Finalize pivotal dev plan by YE; Initiate pivotal program in 2021	agios
Mitapivat Sickle Cell Disease				Finalize pivotal dev plan in 1H ’21; Initiate pivotal program in 2021	agios
Mitapivat Pediatric PK Deficiency		*Mitapivat is also being evaluated for pediatric populations for thalassemia & sickle cell disease*		Finalized pivotal dev plan	agios
AG-946				Initiated Phase 1 HV study in Aug. 2020	agios
Other PK Activators				Development candidate selection	agios

Thalassemia Pivotal Plan

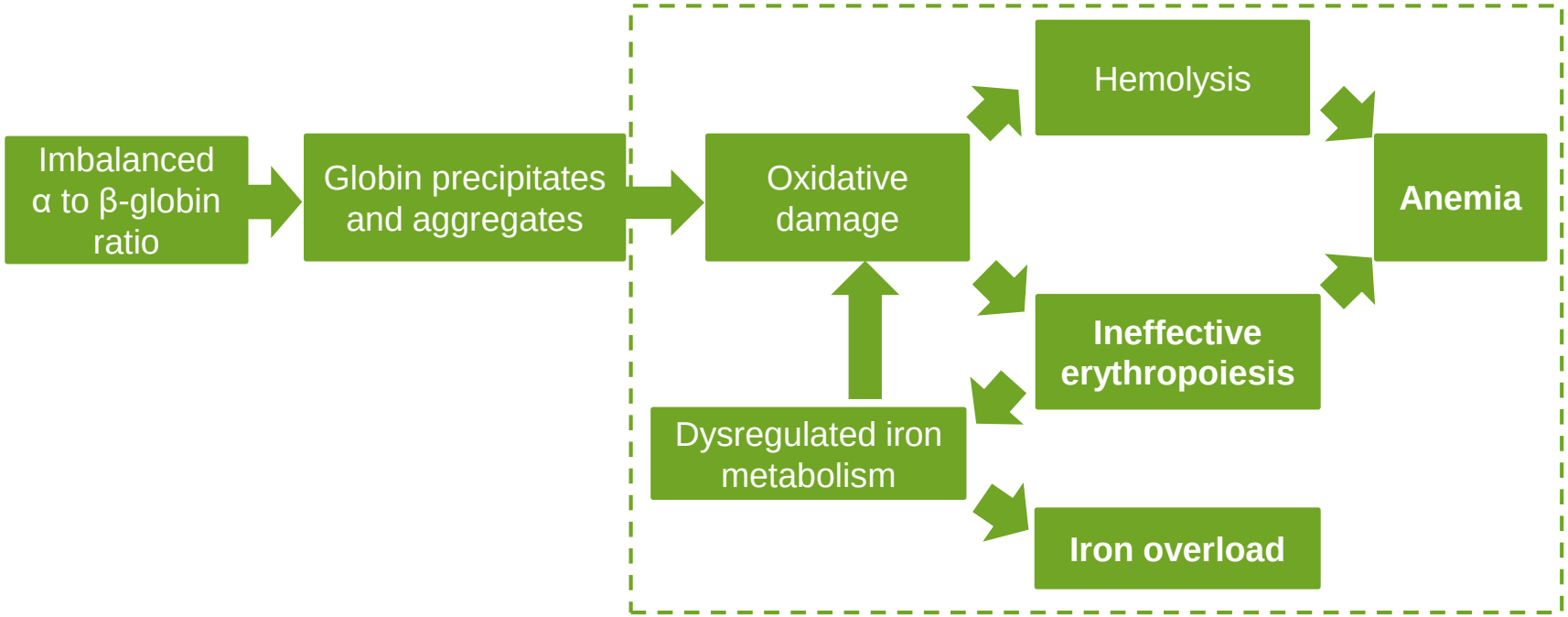
What Is Thalassemia?

- An inherited blood disorder that reduces the production of functional hemoglobin, the protein in RBCs that carries oxygen
- This causes a shortage of RBCs and low levels of oxygen in the bloodstream, leading to a variety of health problems
- Estimated 18-23K patients in the U.S. and EU5

TWO MAIN TYPES

Alpha thalassemia, caused by mutations in alpha globin

Beta thalassemia, caused by mutations in beta globin



Globin precipitates in thalassemia cause oxidative damage, leading to hemolytic anemia, ineffective erythropoiesis and iron overload

Agios market research; EHA 2020

Phase 2 Data Supportive of Advancing Mitapivat to Pivotal Development in Thalassemia

- The first clinical study evaluating PKR activation as a therapeutic option in α- and β-thalassemia, and the first drug trial aimed at treating α-thalassemia

Proof of concept demonstrated

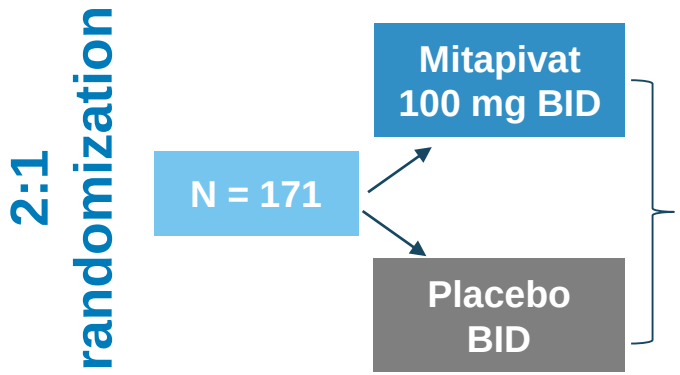
- >90% of patients met primary endpoint: clinically significant Hb increase
- All four α-thalassemia patients and 8 of 9 β-thalassemia patients were responders
- Sustained Hb response observed over time in patients with longer follow-up
- Improvements in markers of hemolysis and erythropoiesis were consistent with mitapivat's mechanism of action

- Mitapivat was generally well-tolerated. Safety profile was consistent with previous studies in PK deficiency

- 17 of 20 patients remain in the extension portion of the Phase 2; data on all 20 patients to be submitted for presentation at EHA 2021
- Data support broad pivotal development plan spanning regularly transfused and not regularly transfused thalassemia as well as β- and α-thalassemia
  - Pivotal study to be initiated in 2021

Two Global, Phase 3, Randomized Controlled Trials of Mitapivat in Thalassemia Are Planned for 2021

ENERGIZE



Primary endpoint:
% of patients with mean Hb ↑ ≥ 1 g/dL from baseline

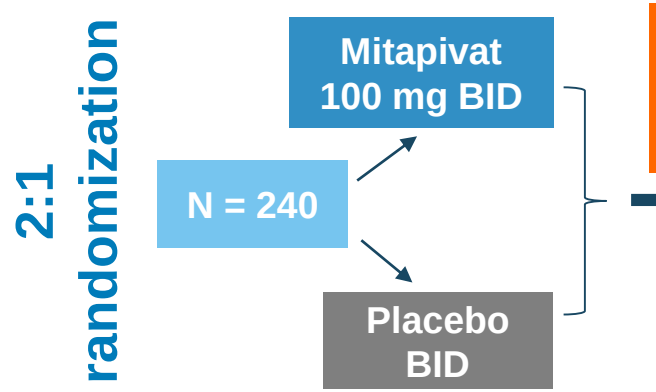
24-week core period

Open label extension (up to 5 years)

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

48-week core period

Open label extension (up to 5 years)

Key inclusion criteria

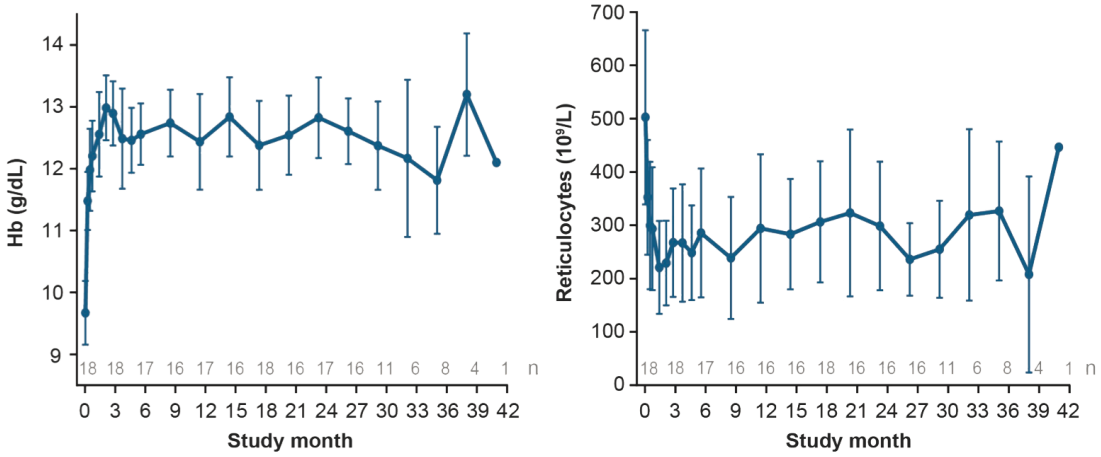
- ≥ 18 years
- β-thalassemia ± α-globin mutations, HbE β-thalassemia, or α-thalassemia (HbH disease)
- Transfusion-dependent defined as 6 to 20 RBC units transfused and ≤6-week transfusion-free period during the 24-week period before randomization

BID = twice daily; Hb = hemoglobin; HbE = hemoglobin E; HbH = hemoglobin H.

ACTIVATE Topline Results

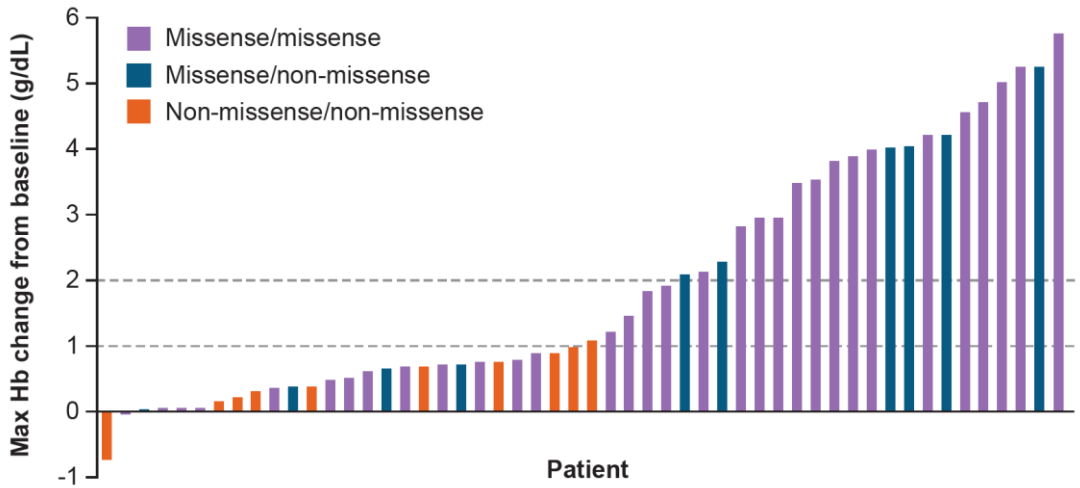
Mitapivat Has Demonstrated Long-term Durable Responses in the DRIVE PK Study

Improvements in hemoglobin and other hemolysis markers maintained for more than 3 years in responding patients from DRIVE PK extension (n=18)



Chronic daily dosing with mitapivat for a median of 3 years and up to 42 months was well tolerated

25 of 42 (59.5%) patients who had ≥1 missense mutation had an Hb increase >1.0 g/dL



Maximum Hb increases observed by genotype

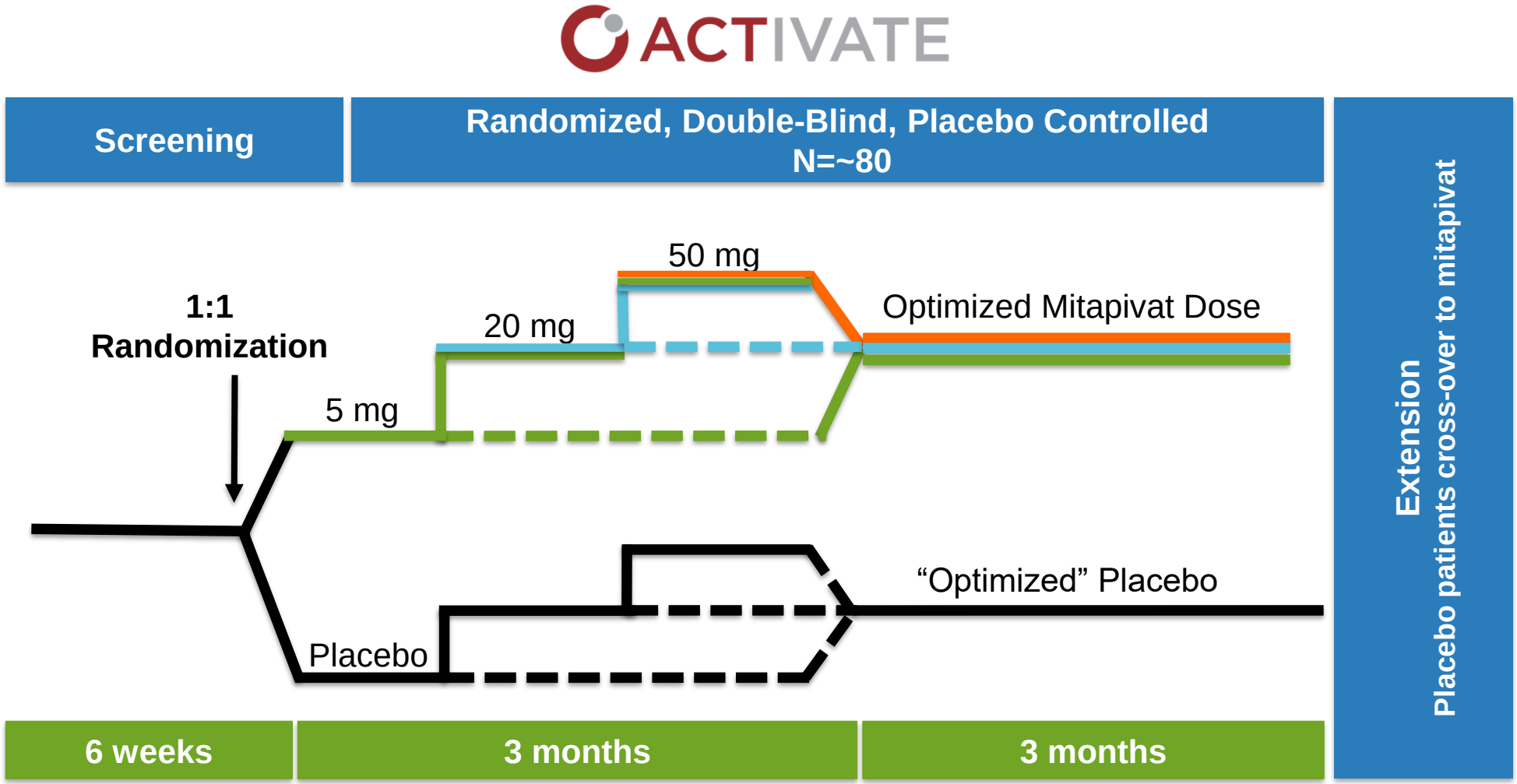
The NEW ENGLAND JOURNAL of MEDICINE

Improvements in hemoglobin and other hemolysis markers were also sustained at optimized individual doses during the extension period

Most AEs were low-grade and resolved within 7 days of initiation of treatment

Source: Data presented at ASH 2019; van Beers EJ, et al. *Haematologica*. 2019;104(2):e51-e53.

ACTIVATE Trial for Adults PK Deficiency Patients Who Are Not Regularly Transfused



Primary Efficacy Endpoint: Proportion of patients who achieve at least a 1.5 g/dL increase in hemoglobin sustained over multiple visits

ACTIVATE Achieved Primary and Secondary Endpoints

40% of patients randomized to mitapivat achieved a hemoglobin response, defined as a sustained ≥1.5 g/dL increase in hemoglobin concentration from baseline, compared to 0 patients randomized to placebo

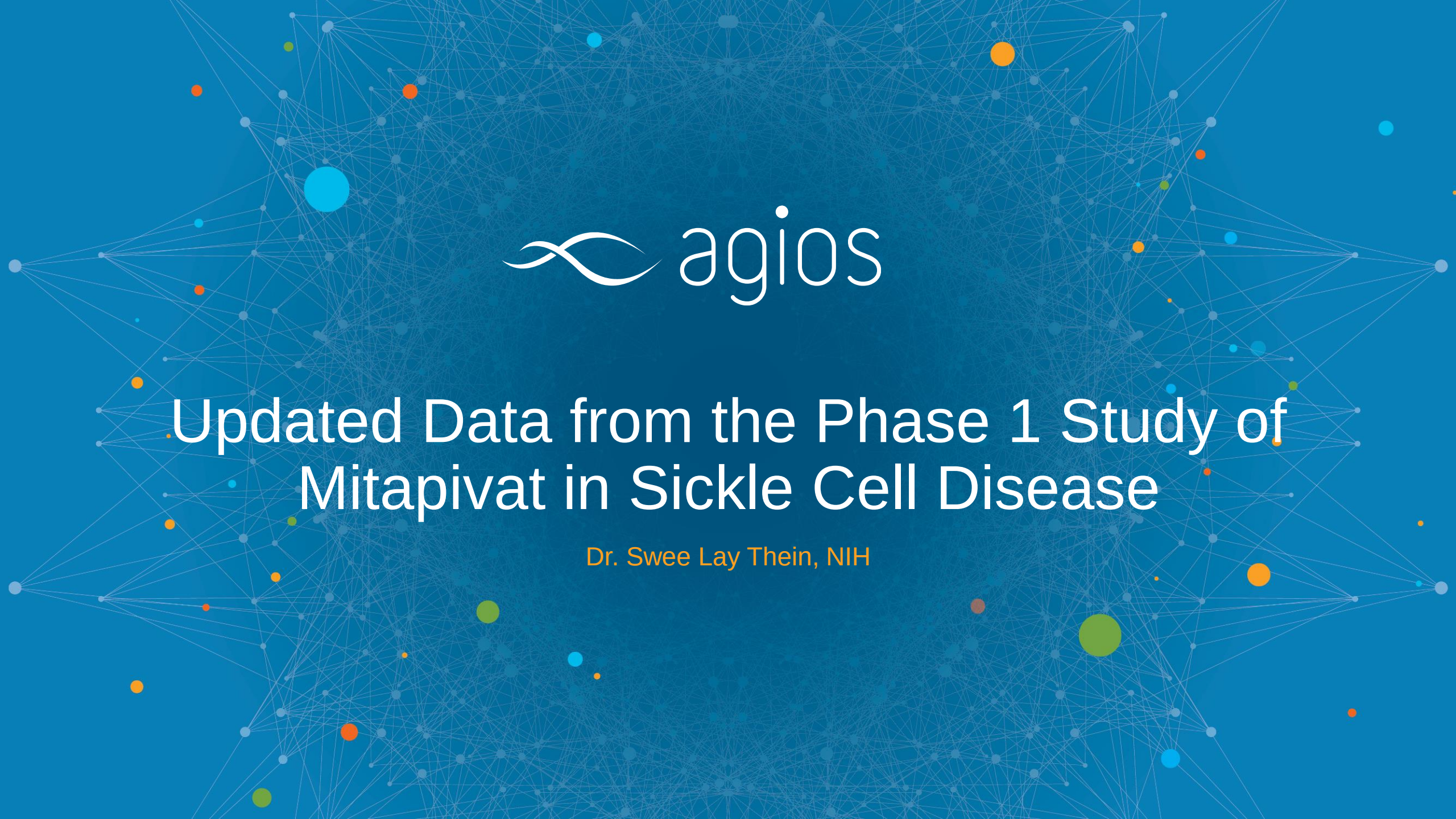
Treatment with mitapivat demonstrated statistically significant improvements over placebo across pre-specified key secondary endpoints, including:

- Average change from baseline in hemoglobin concentration at Weeks 16, 20, and 24
- Markers of hemolysis (indirect bilirubin, haptoglobin, LDH activity)
- Markers of hematopoietic activity (reticulocyte percentages)

Safety profile observed in the study was generally consistent with previously reported data. There were no AEs leading to discontinuation in either the mitapivat or the placebo arm.

Full analysis of the ACTIVATE data in process, including patient-reported outcomes. Complete results to be submitted for presentation at EHA in June 2021.

U.S. and EU regulatory approval filings planned for 2021 with a potential 2022 commercial launch



Updated Data from the Phase 1 Study of Mitapivat in Sickle Cell Disease

Dr. Swee Lay Thein, NIH

Phase 1 Multiple Ascending Dose Study of Safety, Tolerability, and Pharmacokinetics/Pharmacodynamics of Mitapivat (AG-348) in Subjects with Sickle Cell Disease

NCT04000165; Investigator-initiated trial; Principal Investigator: Swee Lay Thein

Julia Z. Xu[1], Anna Conrey[1], Ingrid Frey[1], Jim Nichols[1], Laurel A. Menapace[1], Laxminath Tumburu[1], Timothy Lequang[1], Quan Li[2], Emily B. Dunkelberger[2], Eric R. Henry[2], Troy Cellmer[2], Varsha Iyer[3], Heidi Mangus[3], Charles Kung[3], Lenny Dang[3], Penelope Kosinski[3], Peter Hawkins[3], Neal Jeffries[4], William A. Eaton[2], and Swee Lay Thein[1]

[1]Sickle Cell Branch, National Heart, Lung, and Blood Institute, [2]Laboratory of Chemical Physics, National Institute of Diabetes and Digestive and Kidney Diseases, NIH, Bethesda, United States; [3]Agios Pharmaceuticals, Inc., Cambridge, MA, United States, [4]Office of Biostatistics Research, National Heart, Lung, and Blood Institute, NIH, Bethesda, United States

Abstract #681

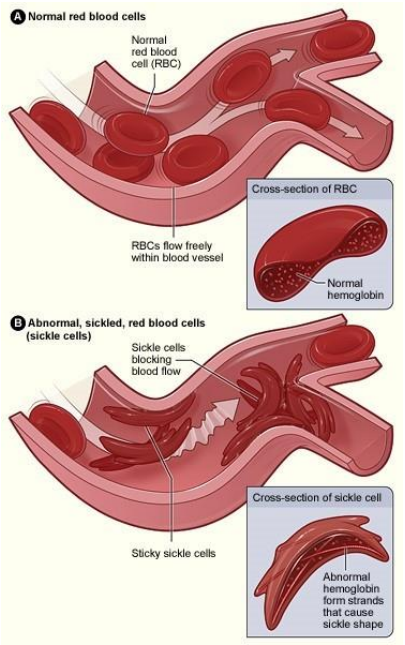
62nd American Society of Hematology Annual Meeting

December 7, 2020

NIH National Heart, Lung, and Blood Institute

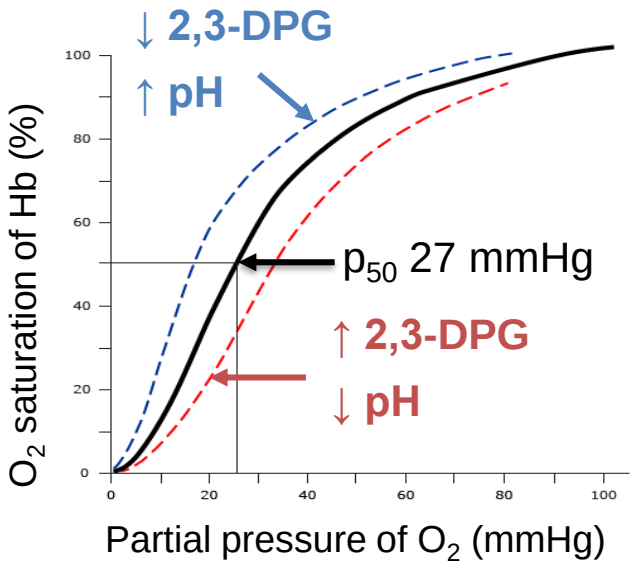
Pyruvate Kinase R (PKR): A new disease modifying target in SCD?

Polymerization of deoxy-Hb S results in vaso-occlusion and hemolytic anemia and is the root cause of sickle cell disease (SCD) complications.

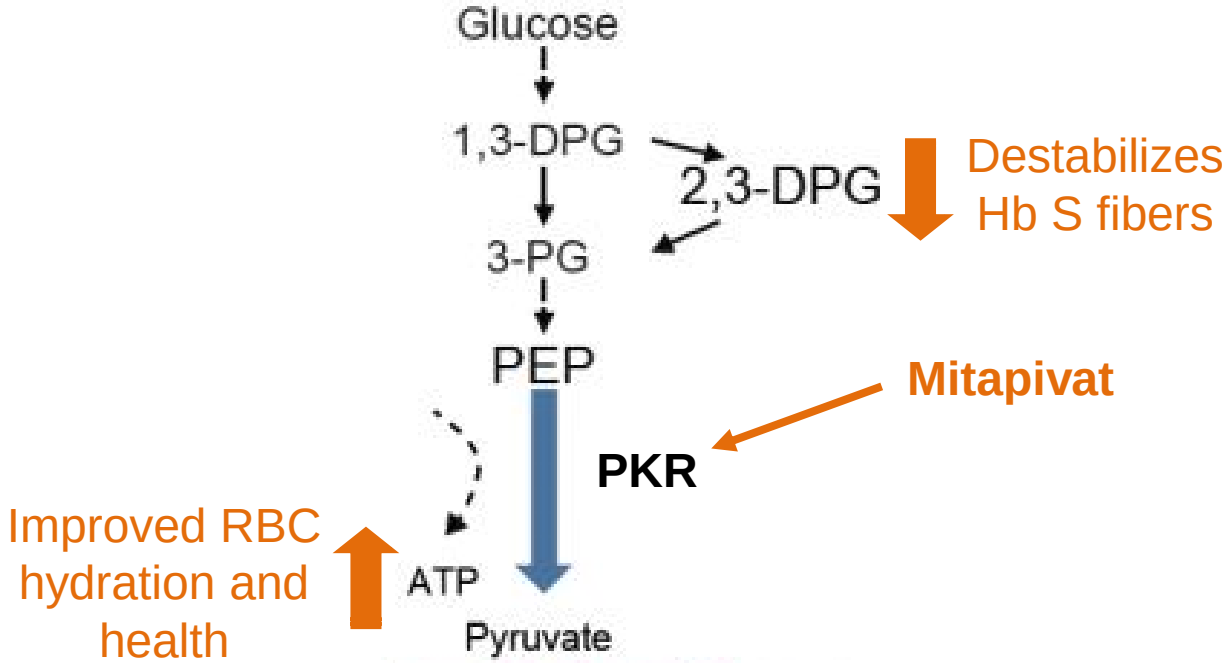


https://www.nhlbi.nih.gov/health-topics/sickle-cell-disease

- Elevated 2,3-DPG levels promote polymerization.



Mitapivat (AG-348) is an oral PKR activator that decreases 2,3-DPG and increases ATP levels[1] and improves anemia in PK deficiency and thalassemia.[2,3]

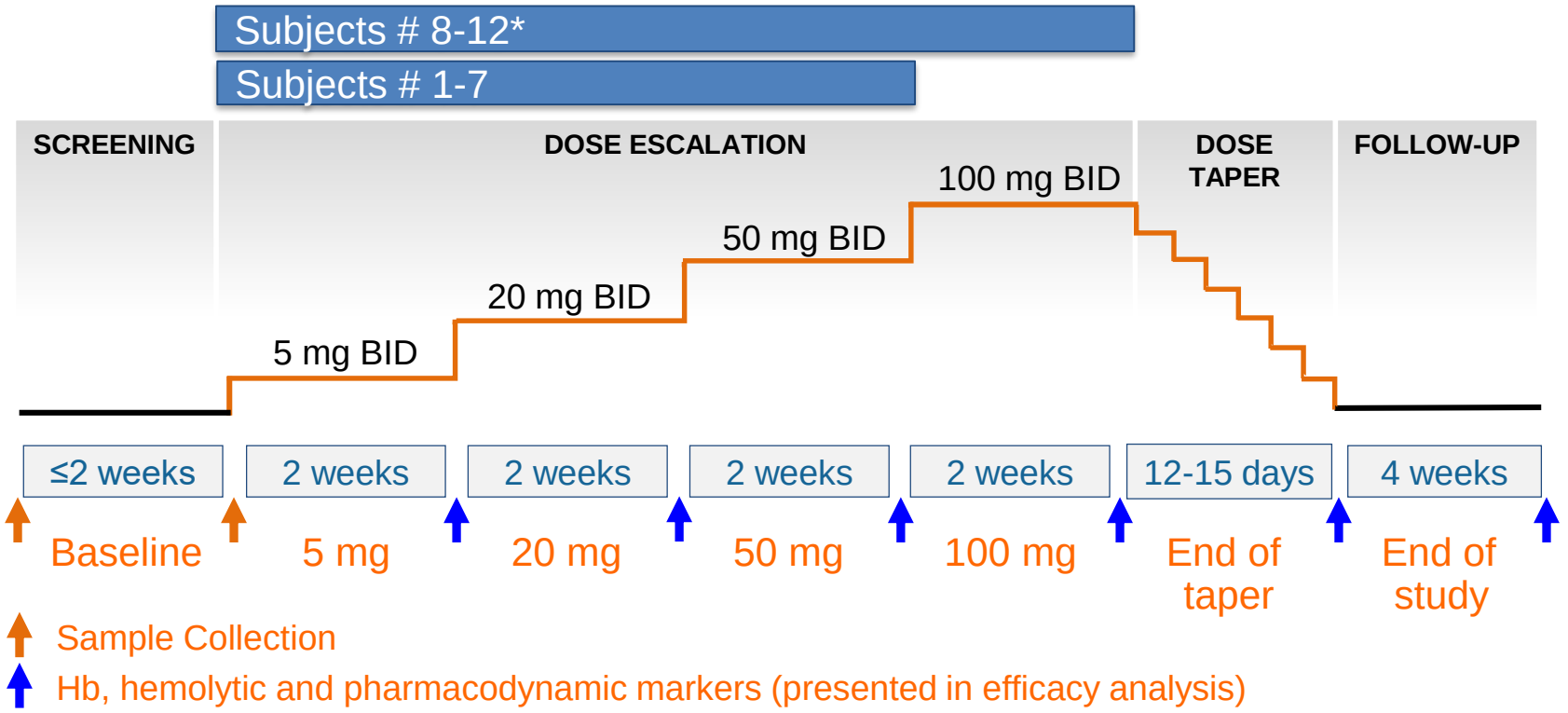


ATP, adenosine triphosphate; DPG, diphosphoglycerate; Hb, hemoglobin; O_2, oxygen; PKR, red-cell pyruvate kinase; RBC, red blood cell.

[1] Yang et al. Clin Pharmacol Drug Dev. 2018,00(0)1–14; [2] Grace et al. NEJM. 2019;5;381(10):933-944; [3] Kuo et al. Abstract, EHA 2020.

Study Design: Dose Escalation of Mitapivat in SCD

- Nonrandomized, open-label, Phase 1 study; N ≈ 15–25
- Adults (age ≥ 18 years) with stable Hb SS disease eligible
- No transfusions or changes in hydroxyurea/L-glutamine within 90 days



*100 mg dose level added to protocol with amendment #6. BID, twice daily.
** Data is incomplete due to disruptions related to COVID-19 pandemic.

Primary endpoints:

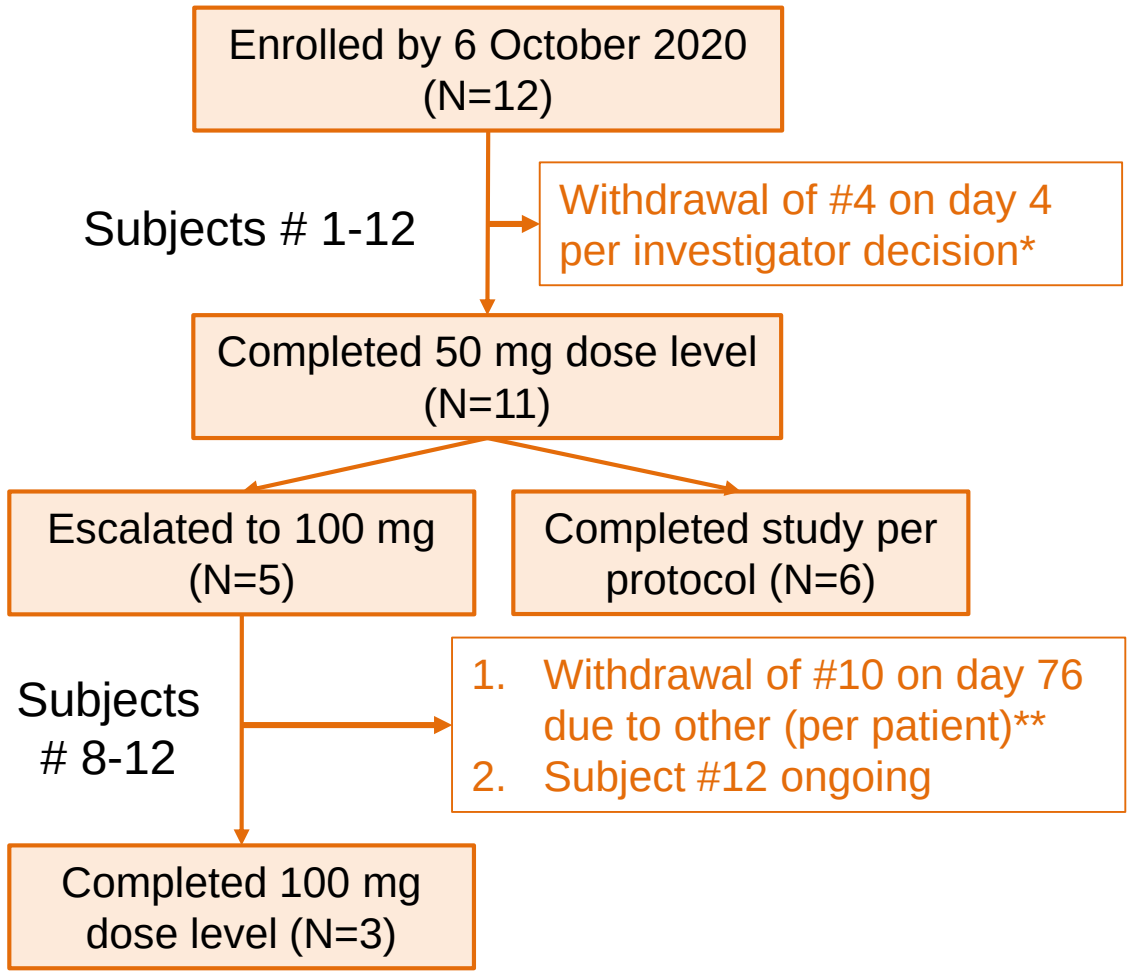
- Safety and tolerability
  - Changes in Hb and hemolytic markers

Secondary endpoints:

- Pharmacokinetics
- 2,3-DPG and ATP levels
- O_2 dissociation and sickling tendency**

Demographics, Disease Characteristics, and Disposition

Baseline Characteristics at Enrollment	N=12
Age, mean (range), years	40.2 (27-55)
Male, N (%)	8 (66.7)
African or African-American, N (%)	12 (100)
Hydroxyurea use, N (%)	8 (66.7)
L-glutamine use, N (%)	1 (8.3)
Baseline Laboratory Measures	**N=11***
Hemoglobin, mean (SD), g/dL	9.5 (1.0)
Abs reticulocyte count, mean (SD), K/µL	191.0 (109.3)
Total bilirubin, mean (SD), mg/dL	2.2 (0.9)
Lactate dehydrogenase, mean (SD), U/L	374.6 (140.9)
Hemoglobin F % by HPLC, mean (SD), %	18.3 (10.7)



* #4 withdrawn due to need for medical interventions for an AE unrelated to drug and lost to follow-up; not evaluable for laboratory response.
** #10 self-discontinued therapy due to an AE unrelated to drug; in safety follow-up.
AE, adverse event; Abs, absolute; HPLC, high-performance liquid chromatography; SD, standard deviation; Data cut date: Oct 6, 2020.

Consistent Safety Profile

Adverse Events	N=12 (%)	
	All Grades (≥10%)	Grade ≥ 3
Pain	4 (30.8%)	2 (15.4%)
Hyperglycemia	4 (30.8%)	0 (0%)
Vaso-occlusive crisis (VOC)	3 (23.1%)	3 (23.1%)
Anemia	3 (23.1%)	2 (15.4%)
Hypertension	3 (23.1%)	1 (7.7%)
Insomnia	3 (23.1%)	0 (0%)
Heart rate increased	3 (23.1%)	0 (0%)
AST increased	2 (15.4%)	0 (0%)
Blood bicarbonate decreased	2 (15.4%)	0 (0%)
Hyponatremia	2 (15.4%)	0 (0%)
Sore throat	2 (15.4%)	0 (0%)
Upper respiratory infection	2 (15.4%)	0 (0%)
Fatigue	1 (7.7%)	1 (7.7%)
Pulmonary embolism	1 (7.7%)	1 (7.7%)

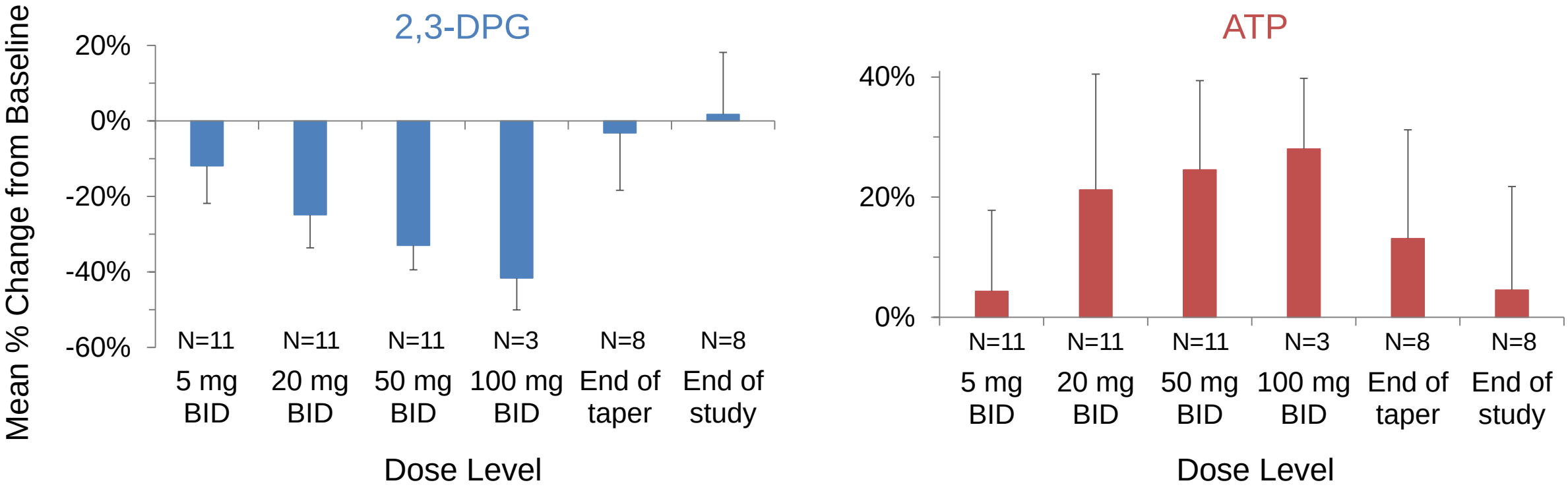
Serious Adverse Events (SAEs)	N=12 (%)
All	**5 (41.7)**
VOC*	3 (25)
Pain (shoulder)	1 (8.3)
Pulmonary embolism (PE)**	1 (8.3)

Summary of VOCs:

- No VOC during dose escalation
- 2 VOCs during 28-day safety follow-up post drug exposure due to known VOC triggers
- 1 VOC during drug taper, improved with extended dosing†

* Regardless of relationship to study treatment.
** Pre-existing PE discovered 4 days after study drug initiation; patient withdrawn (subject #4).
† Triggered protocol amendment to extend length of taper.
AST, aspartate aminotransferase.
Data cut date: Oct 6, 2020.

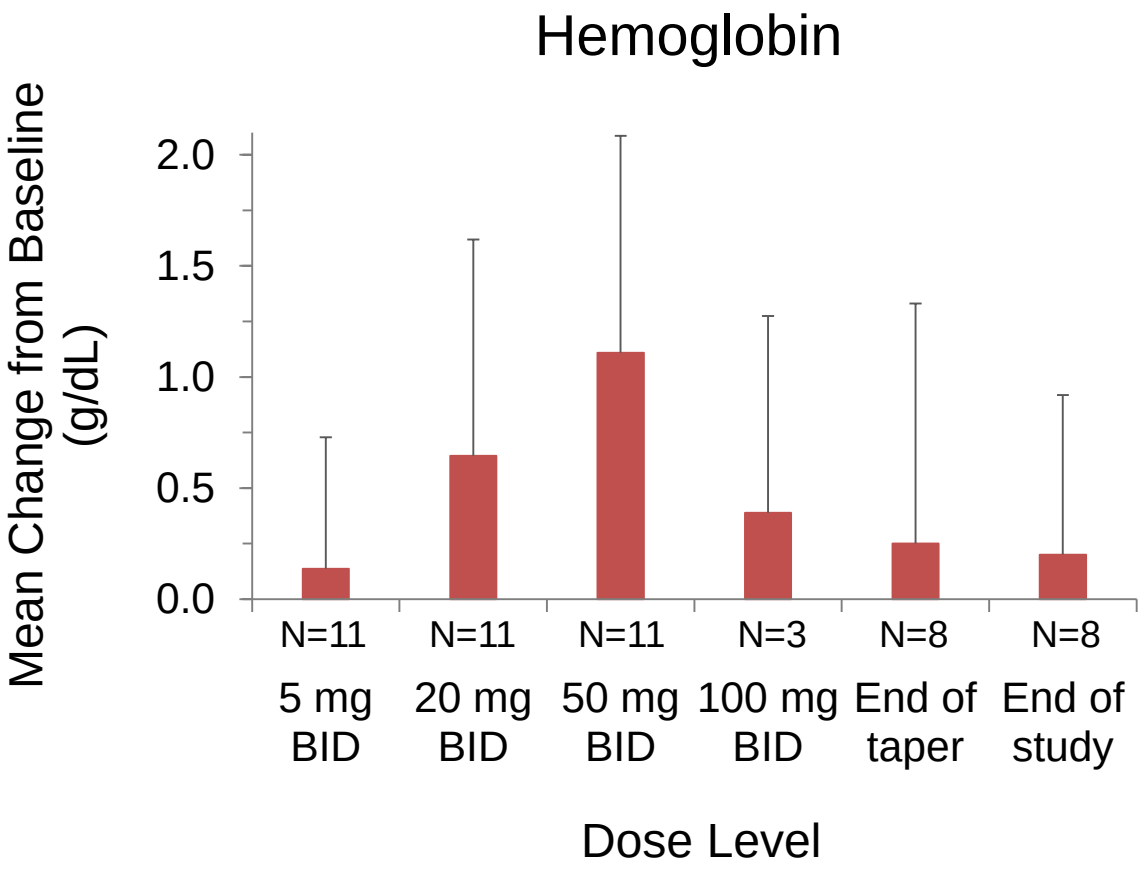
Mitapivat Decreases 2,3-DPG and Increases ATP in SCD



- Linear PK was observed up to 50 mg BID.
- After 100 mg BID, CYP3A auto-induction effect resulted in ~20% reduction in exposure.

BID, twice daily; PK, pharmacokinetic. Data cut date: Oct 6, 2020.

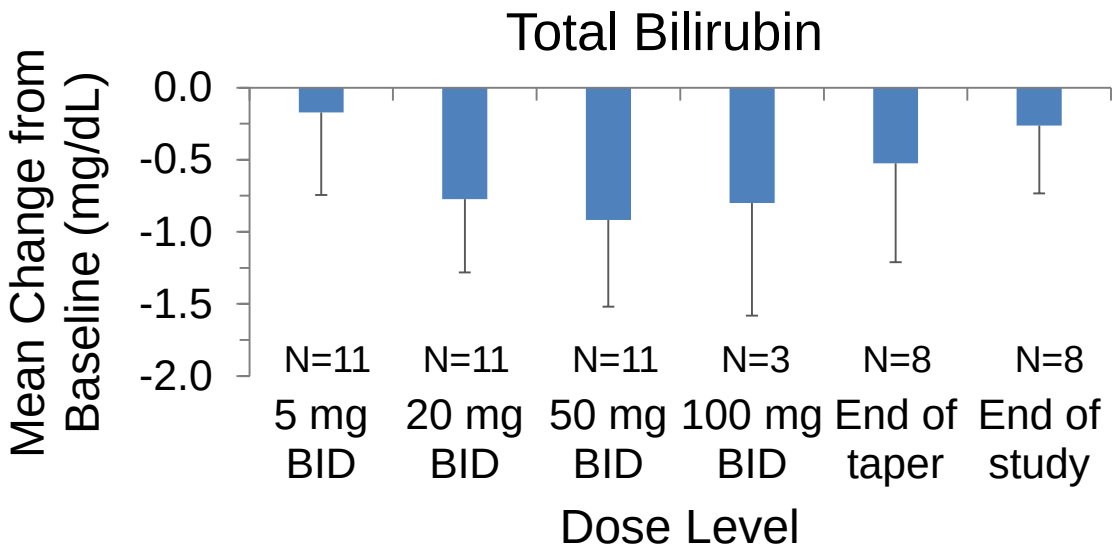
Mitapivat Increases Hemoglobin Level

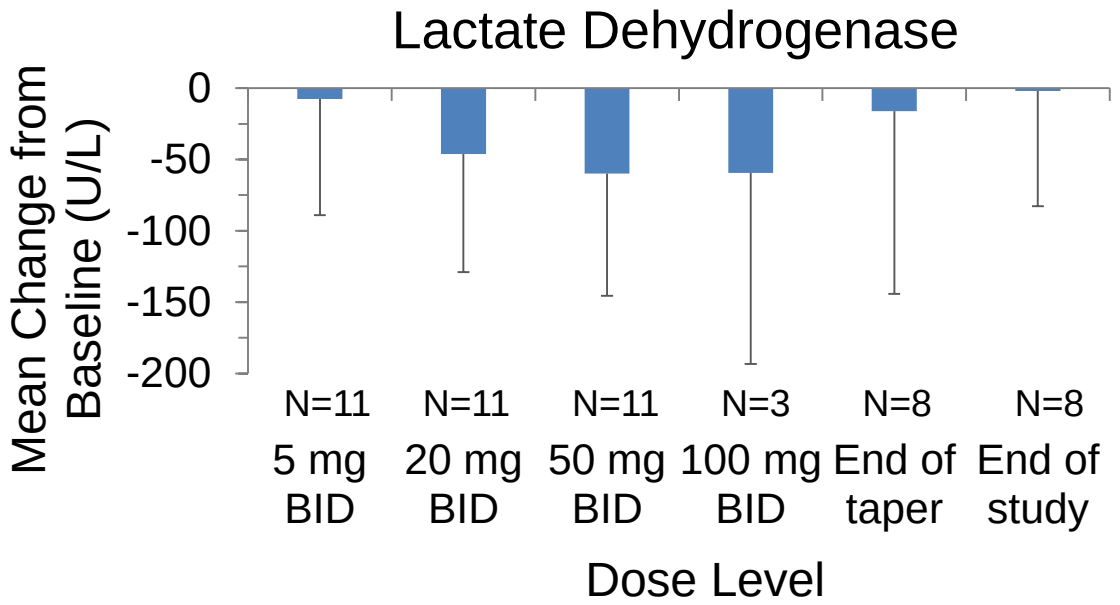


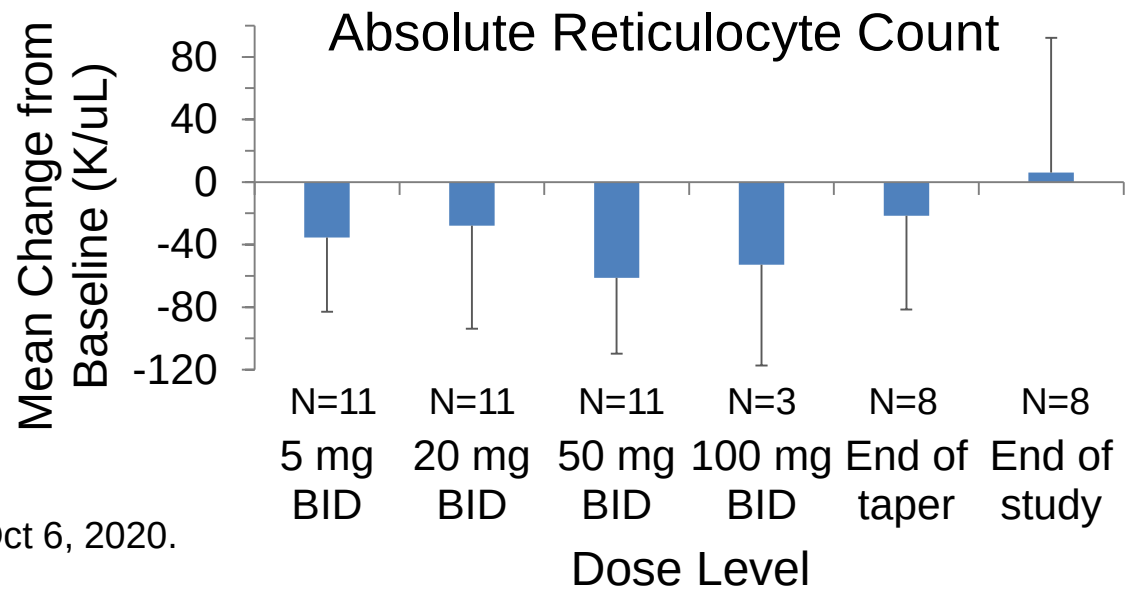
Response parameter	N=11
Maximal Hb increase, mean (SD), g/dL	1.3 (0.8)
Hb increase ≥ 1g/dL, N (%)	6 (54.5)
Maximal Hb increase in subjects with ≥ 1g/dL response*, mean (SD), g/dL	1.9 (0.7)

* N=6.
BID, twice daily. Data cut date: Oct 6, 2020.

Mitapivat Decreases Markers of Hemolysis







BID, twice daily. Data cut date: Oct 6, 2020.

Summary

- Mitapivat, an oral, twice daily PKR activator was well tolerated in subjects with SCD.
- Pharmacokinetic and safety profile in SCD resembles results from previous studies in PK deficiency and thalassemia.
- This study provides proof of concept:
  - Mitapivat reduces 2,3-DPG and increases in ATP in patients with SCD.
  - During a short period (6-8 weeks) of dose escalation, mitapivat increased Hb by ≥ 1g/dl in 6/11 evaluable subjects and decreased hemolytic markers, signaling its potential to improve clinical outcomes in SCD.
- An extension study (ClinicalTrials.gov NCT04610866) will evaluate safety, tolerability, pharmacokinetics, and pharmacodynamics of long-term mitapivat dosing in SCD subjects enrolled on NCT04000165.


agios
Q&A