Results from Phase 1 Multiple Ascending Dose Study 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], Eveline Gwaabe[1], Laurel A. Menapace[1], Laxminath Tumburu[1], Maureen Lundt[1], Quan Li[2], Kristen Glass[2], Varsha Iyer[3], Heidi Mangus[3], Charles Kung[3], Lenny Dang[3], Penelope A. 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 #10 63rd American Society of Hematology Annual Meeting

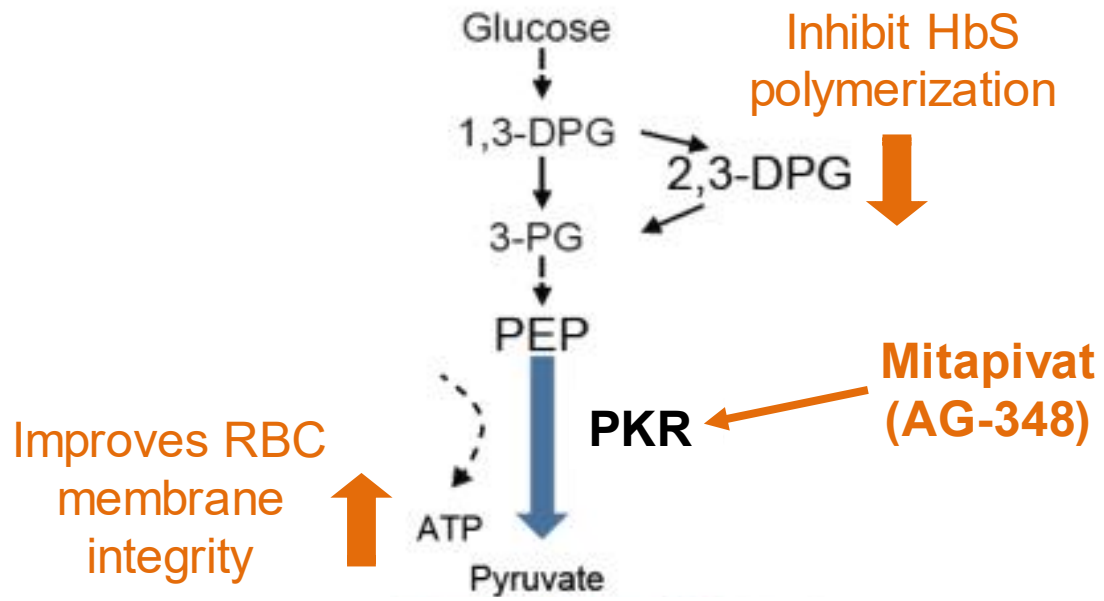
December 11, 2021

NIH National Heart, Lung, and Blood Institute

Pyruvate Kinase R (PKR) Activation in Sickle Cell Disease (SCD)

Key Factors in RBC Sickling		
2,3-DPG	Increased in SCD	• Stabilizes HbS in polymerizing T form • Decreases hemoglobin (Hb) oxygen affinity • Promotes sickling
ATP	Decreased in SCD	• Essential for water and ion homeostasis • Reduced ATP leads to water and ion loss • RBC dehydration promotes sickling

Mitapivat (AG-348) activates PKR → decreases 2,3-DPG and increases ATP in SCD[1,2]

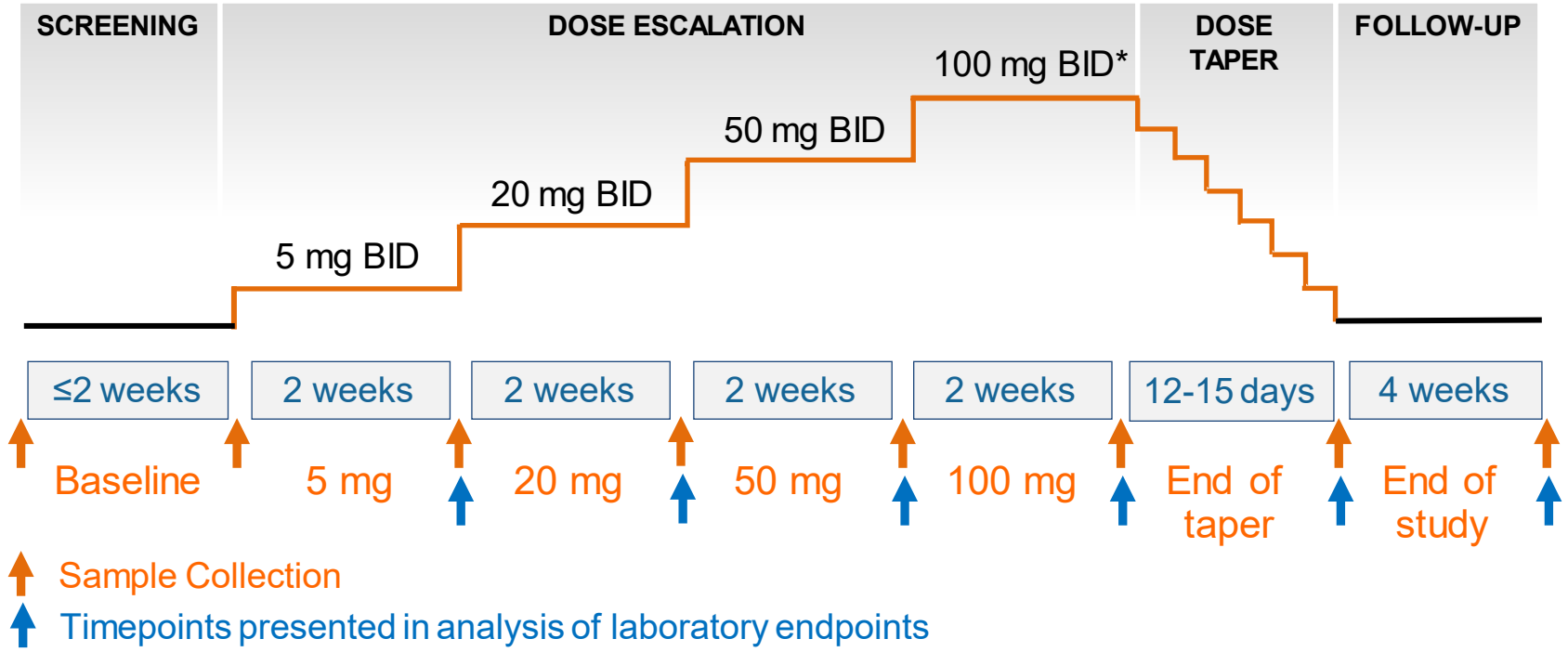


ATP, adenosine triphosphate; DPG, diphosphoglycerate; Hb, hemoglobin; PKR, red-cell pyruvate kinase; RBC, red blood cell; SCD, sickle cell disease.

[1] Rab et al. Blood. 2021 May 27; 137(21): 2997–3001; [2] Xu et al. Abstract, ASH 2020.

Study Design of Mitapivat Dose Escalation Study in SCD

- Nonrandomized, open-label, Phase 1 study; N =17
- Adults (age ≥ 18 years) with stable Hb SS disease eligible
- No transfusions or changes in hydroxyurea/L-glutamine within 90 days



Primary endpoints:

- Safety and tolerability
- Changes in Hb and hemolytic markers

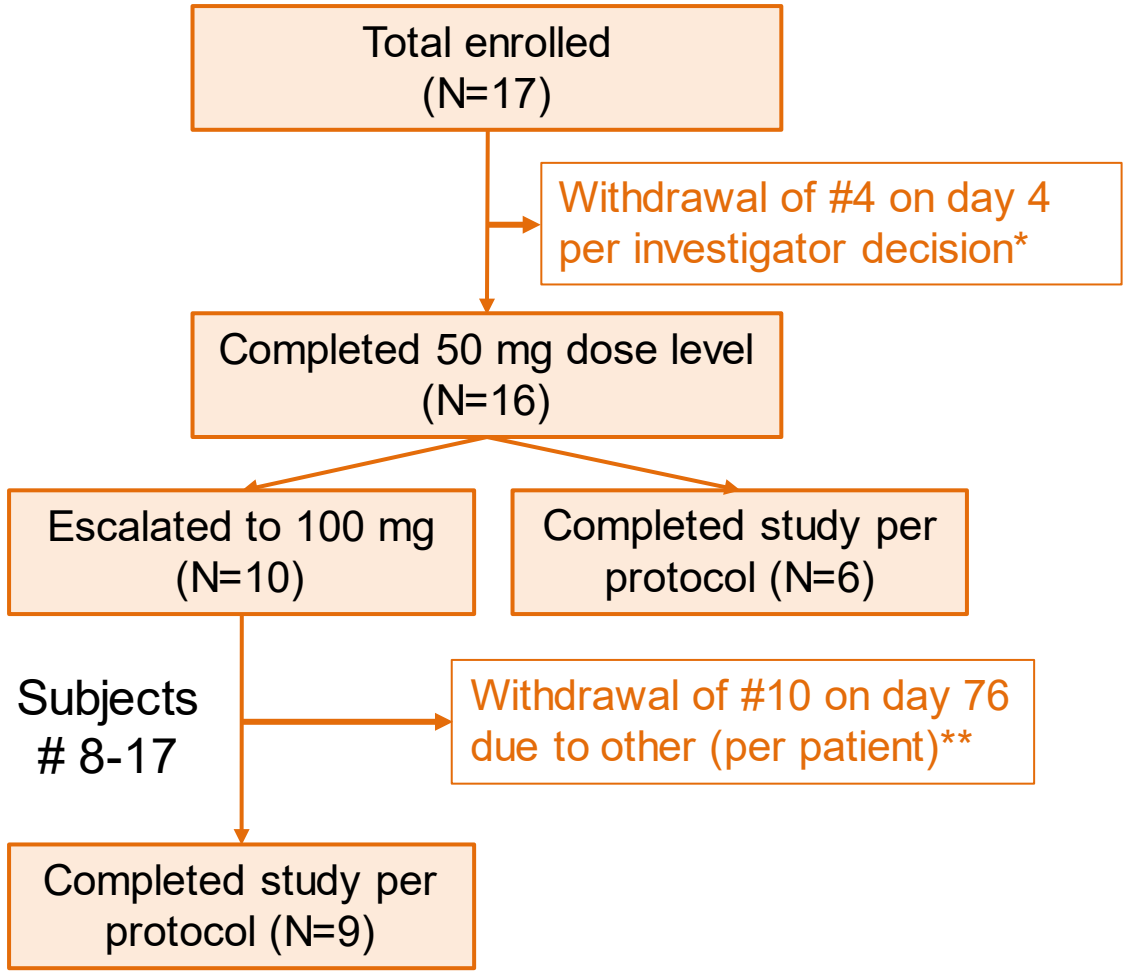
Secondary endpoints:

- Pharmacokinetics
- 2,3-DPG and ATP levels
- p50 (O_2 affinity) and t50 (HbS polymerization)

*100 mg dose level added to protocol with amendment #6.
ATP, adenosine triphosphate; BID, twice daily; DPG, diphosphoglycerate; Hb, hemoglobin.

Demographics, Disease Characteristics, and Disposition

Baseline Characteristics at Enrollment	N=17
Age, mean (range), years	39 (23-55)
Male, N (%)	11 (64.7)
African or African-American, N (%)	17 (100)
Hydroxyurea use, N (%)	12 (70.6)
L-glutamine use, N (%)	1 (5.9)
Baseline Laboratory Measures	**N=16***
Hemoglobin, mean (SD), g/dL	9.2 (1.1)
Abs reticulocyte count, mean (SD), K/μL	188.2 (99.2)
Total bilirubin, mean (SD), mg/dL	2.0 (0.9)
Lactate dehydrogenase, mean (SD), U/L	375.2 (120.6)
Hemoglobin F % by HPLC, mean (SD), %	19.0 (9.8)



* #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 prior to completing 100 mg dose level due to an AE unrelated to drug; analyzed with 50 mg dose cohort.
AE, adverse event; Abs, absolute; HPLC, high-performance liquid chromatography; SD, standard deviation.

Mitapivat is Safe and Tolerable for SCD Patients

Treatment Related Adverse Events (AEs)*	N=17 (%)	
	All Grades (≥ 10%)	Grade ≥ 3
All	**8 (47.1%)**	**3 (17.6%)**
Insomnia	6 (35.3%)	0 (0%)
Arthralgia	3 (17.6%)	0 (0%)
Hypertension	3 (17.6%)	1 (5.9%)
Vaso-occlusive crisis (VOC)	2 (11.8%)	2 (11.8%)
Headache	2 (11.8%)	0 (0%)
Heart rate increased	2 (11.8%)	0 (0%)
Anemia	-	1 (5.9%)
Fatigue	-	1 (5.9%)

Serious Adverse Events (SAEs)	N=17 (%)
All	**6 (35.3%)**
VOC	4 (23.5%)
Pain (shoulder)	1 (5.9%)
Pulmonary embolism (PE)**	1 (5.9%)

Summary of VOCs:

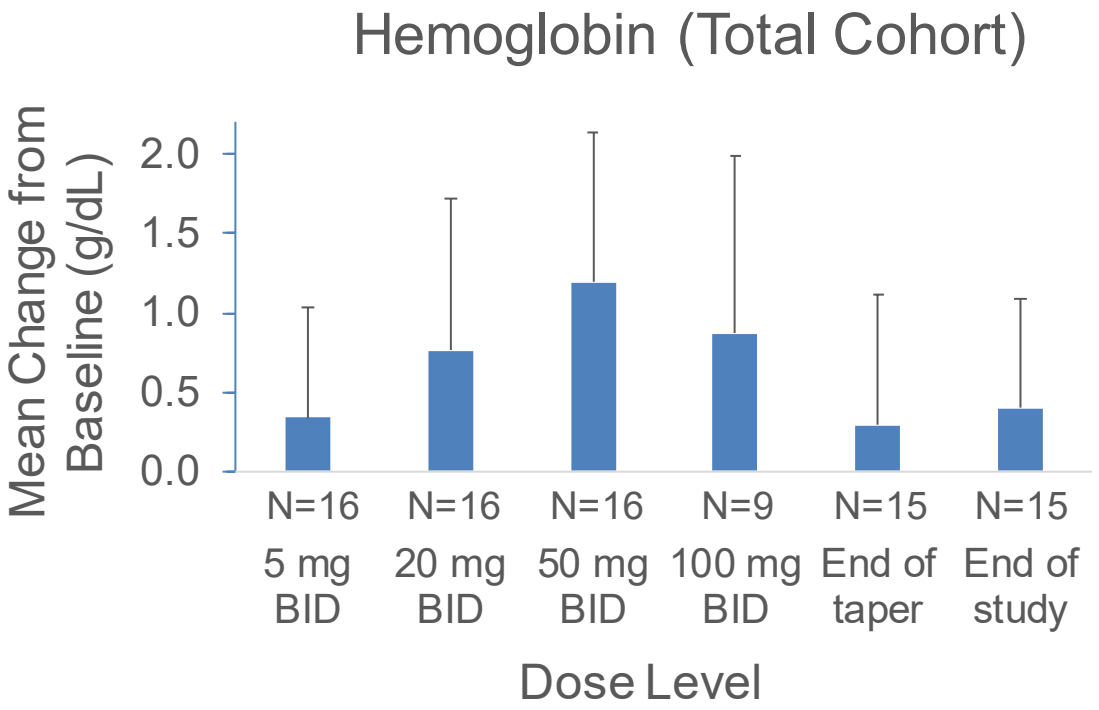
- No VOC during dose escalation
- 2 VOCs during drug taper† → possibly drug related
- 2 VOCs during 28-day safety follow-up in setting of known VOC triggers → unlikely drug related

Summary of other SAEs or Grade 3 AEs:

- No AEs requiring drug discontinuation
- Grade 3 hypertension in subject with baseline Grade 2 hypertension
- Anemia and fatigue in same patient following drug taper

* Defined as possibly, probably, or definitely related to study drug.
** Pre-existing PE discovered 4 days after study drug initiation; patient withdrawn (subject #4).
† First VOC on study triggered protocol amendment to extend length of taper.

Mitapivat Improves Anemia in SCD



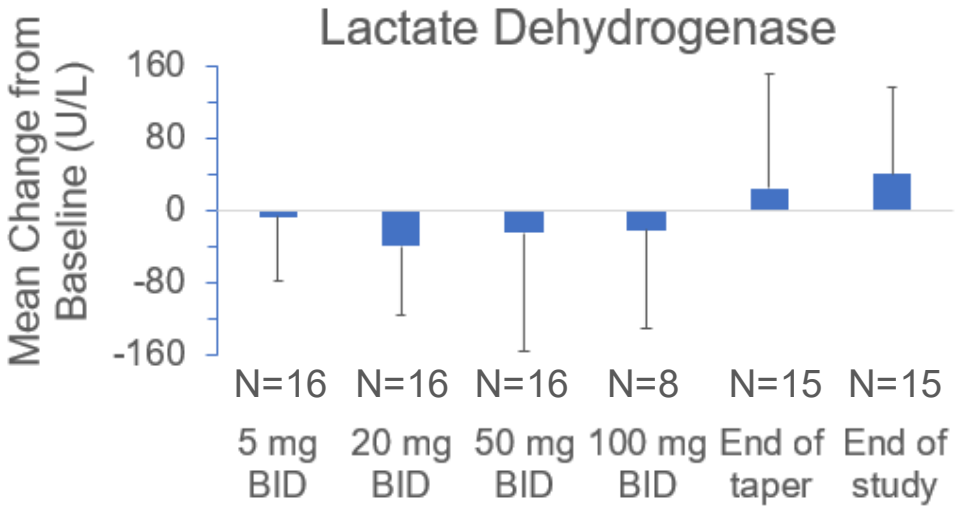
Linear mixed effects model with age and gender as covariates:

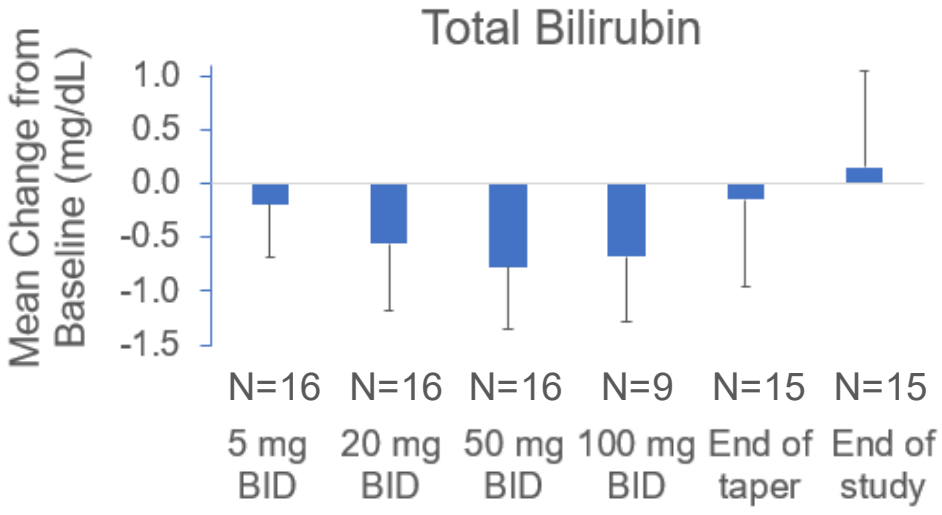
Variable	Value	SE	DF	t-value	p-value
Baseline	8.73	0.51	81	16.95	< 0.0001
5 mg BID	0.34	0.22	81	1.56	0.12
20 mg BID	0.76	0.22	81	3.53	0.0007
50 mg BID	1.19	0.22	81	5.5	< 0.0001
100 mg BID	0.92	0.26	81	3.52	0.0007
End of taper	0.34	0.22	81	1.52	0.13
End of study	0.37	0.22	81	1.7	0.09
Age	-0.02	0.03	13	-0.49	0.63
Male gender	0.68	0.6	13	1.13	0.28

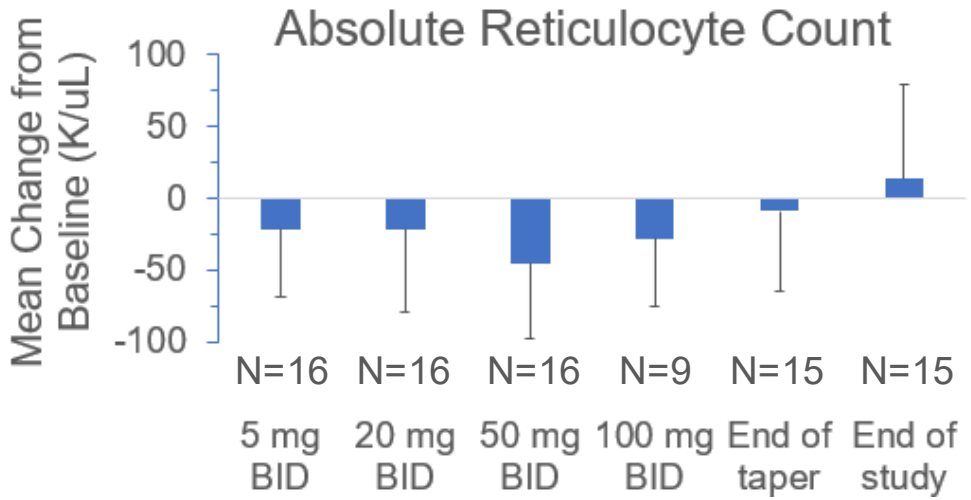
9/16 (56.3%) achieved a Hb response (≥ 1g/dL increase from baseline)

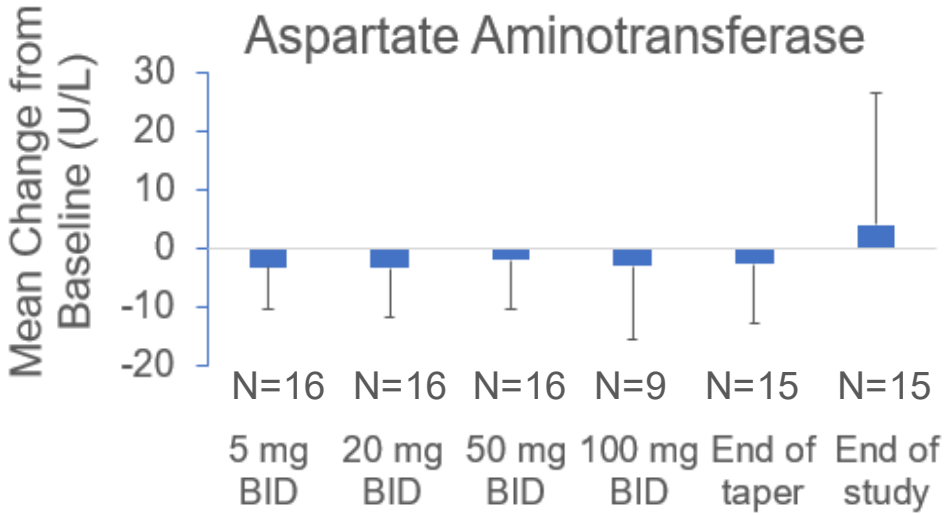
BID, twice daily; DF, degrees of freedom; Hb, hemoglobin; SE, standard error.

Mitapivat Decreases Markers of Hemolysis in SCD







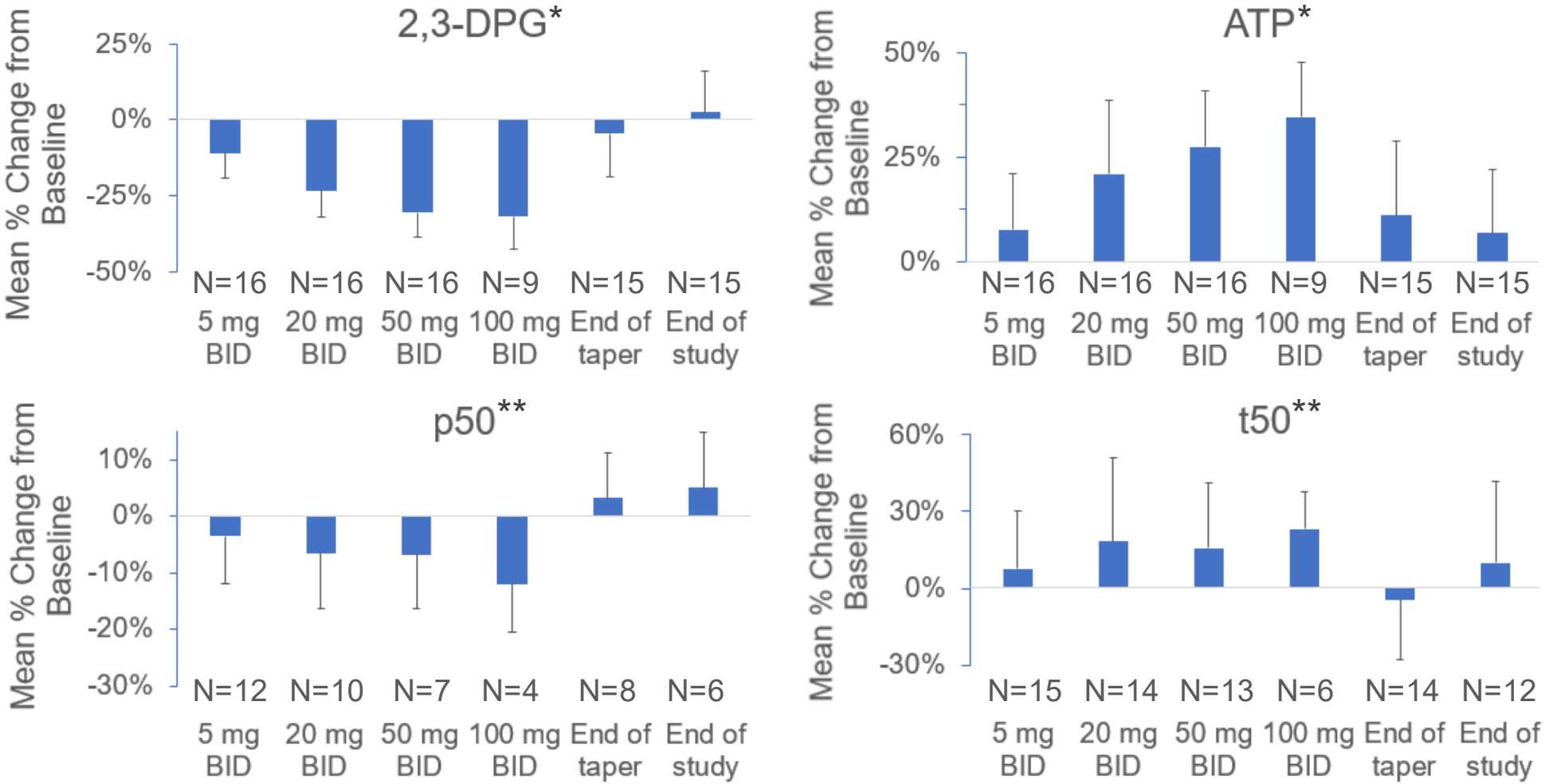


<u>Pharmacokinetics:</u>

- Mitapivat exposure increased in a dose-proportional manner up to 50 mg
- ~20% reduction in exposure was observed following 14 days of multiple dosing with 100 mg BID compared to the first 100 mg dose administration

BID, twice daily.

PD Results Suggest Increased O_2 Affinity and Slower Sickling



p50: partial pressure of O_2 at which 50% of hemes in Hb molecule have O_2 bound.

t50: time in minutes at which 50% of RBCs are sickled in response to gradual deoxygenation with nitrogen to final O_2 partial pressure of 38 torr.

* Percent changes in 2,3-DPG and ATP refer to intracellular concentrations, determined from whole blood concentrations divided by the hematocrit.

** Missing data are the result of disruptions related to the COVID-19 pandemic.

ATP, adenosine triphosphate; BID, twice daily; DPG, diphosphoglycerate; Hb, hemoglobin; O_2, oxygen; PD, pharmacodynamic.

Summary

- Mitapivat, an oral PKR activator, was safe and well tolerated at multiple ascending dose levels in subjects with SCD.
- Mitapivat reduced 2,3-DPG and increased ATP, with an expected increase in oxygen affinity and decrease in sickling rate, signaling its potential to improve clinically meaningful outcomes in SCD.
- This study provides proof of concept that mitapivat improves anemia and decreases hemolysis in SCD.
- Long-term disease modifying effects of mitapivat treatment in SCD are being evaluated in an ongoing extension study (ClinicalTrials.gov NCT04610866).
- Agios Pharmaceuticals is actively recruiting patients for their phase 2/3 clinical trial RISE UP (NCT05031780), evaluating safety and efficacy of mitapivat in SCD, including both hemoglobin response and frequency of sickle cell pain crises (ASH Abstract 3109).

Acknowledgments

NHLBI

- **Swee Lay Thein, MD, DSc**
- Anna Conrey, NP
- Eveline Gwaabe, NP
- Ingrid Frey, RN
- Jim Nichols, RN
- Laurel Menapace, MD
- Neal Jeffries, PhD
- Lax Tumburu, PhD
- Maureen Lundt, MS
- Tim Lequang, MS

Agios Pharmaceuticals, Inc.

- Varsha Iyer, PhD
- Heidi Mangus, BS
- Charles Kung, PhD
- Lenny Dang, BA
- Penelope Kosinski, MS
- Peter Hawkins, PhD
- Maggie Grasso, MD
- Thomas Winkler, MD
- Keely Gilroy, PhD
- Sarah Gheuens, MD, PhD, MMSc

NIDDK

- **William Eaton, MD, PhD**
- Quan Li, PhD
- Kristen Glass, BA
- Emily Dunkelberger, PhD
- Eric Henry, PhD
- Troy Cellmer, PhD