# 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

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**Abstract #681**

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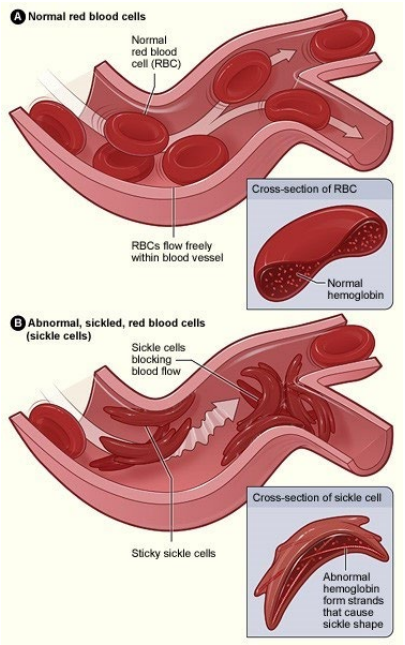
NIH National Heart, Lung, and Blood Institute

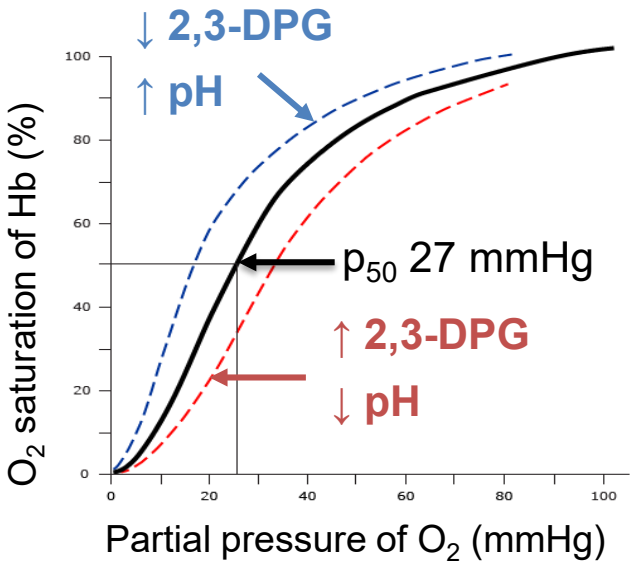
# Pyruvate Kinase R (PKR): A new disease modifying target in SCD?

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

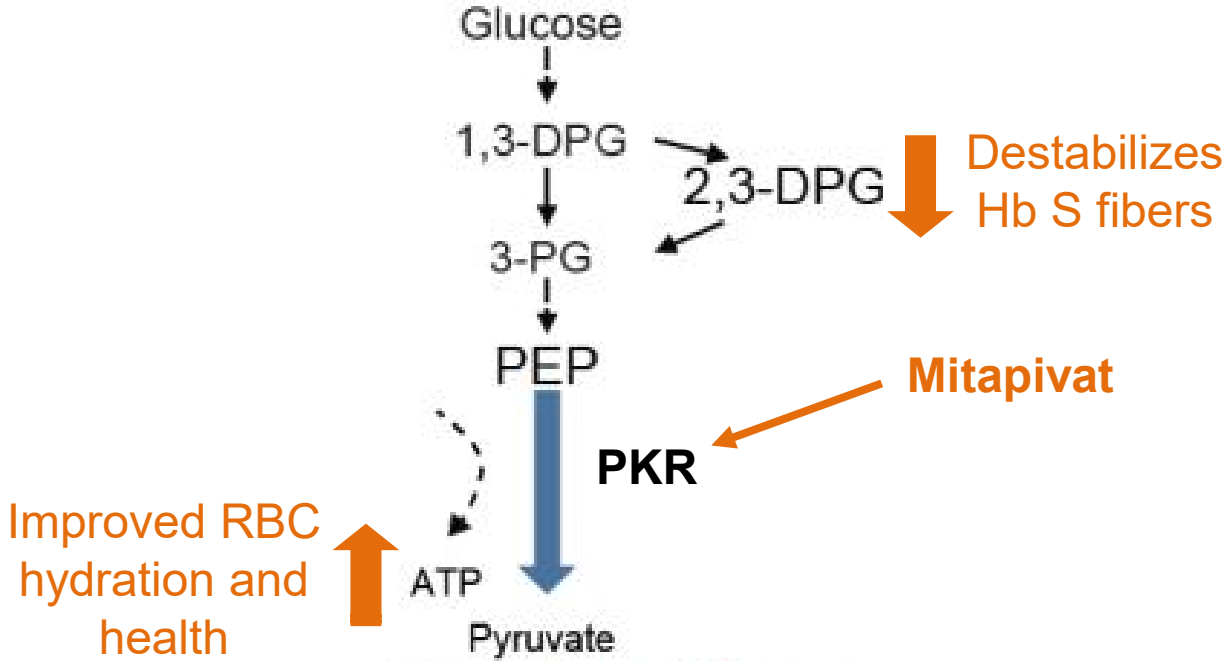



https://www.nhlbi.nih.gov/health-topics/sickle-cell-disease

- 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]

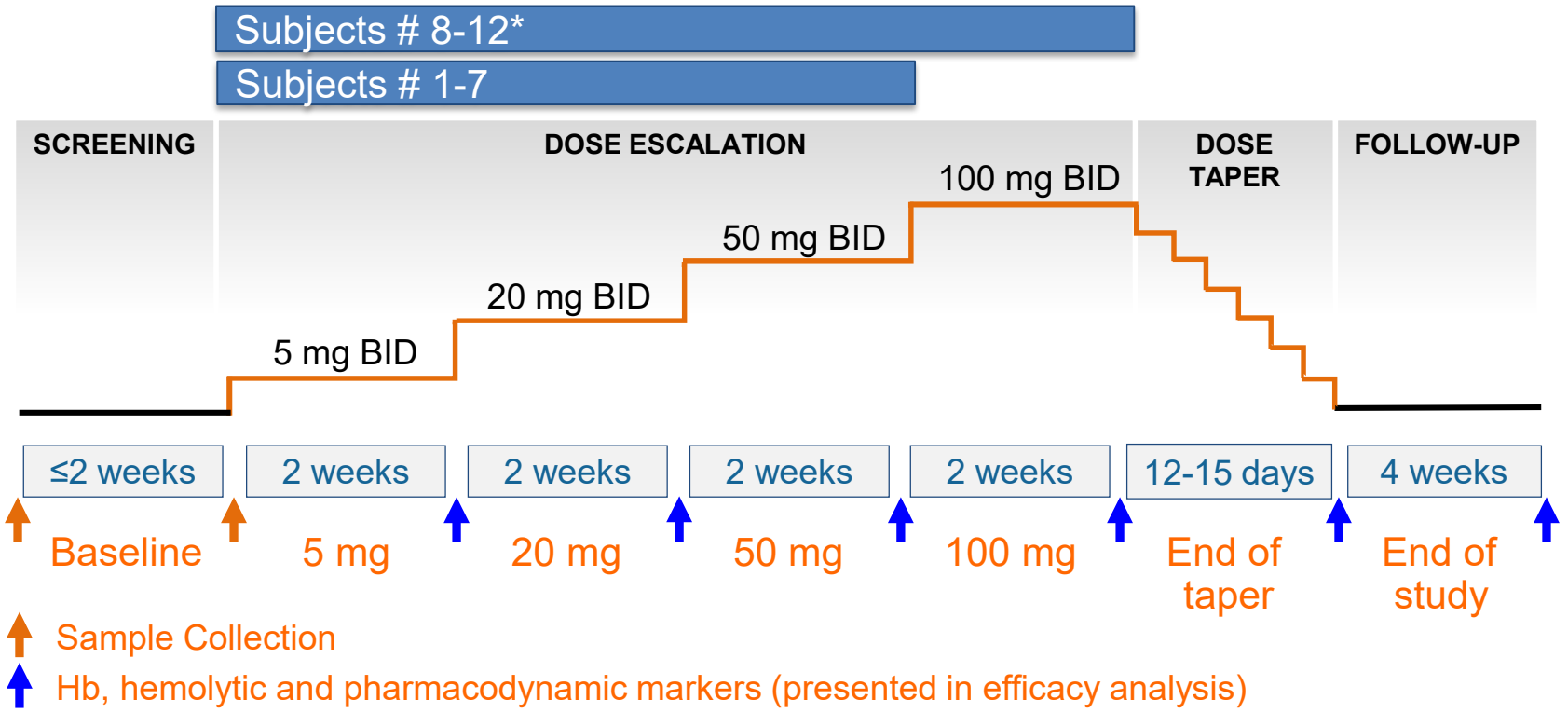



ATP, adenosine triphosphate; DPG, diphosphoglycerate; Hb, hemoglobin; $O_2$, oxygen; PKR, red-cell pyruvate kinase; RBC, red blood cell.

[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:

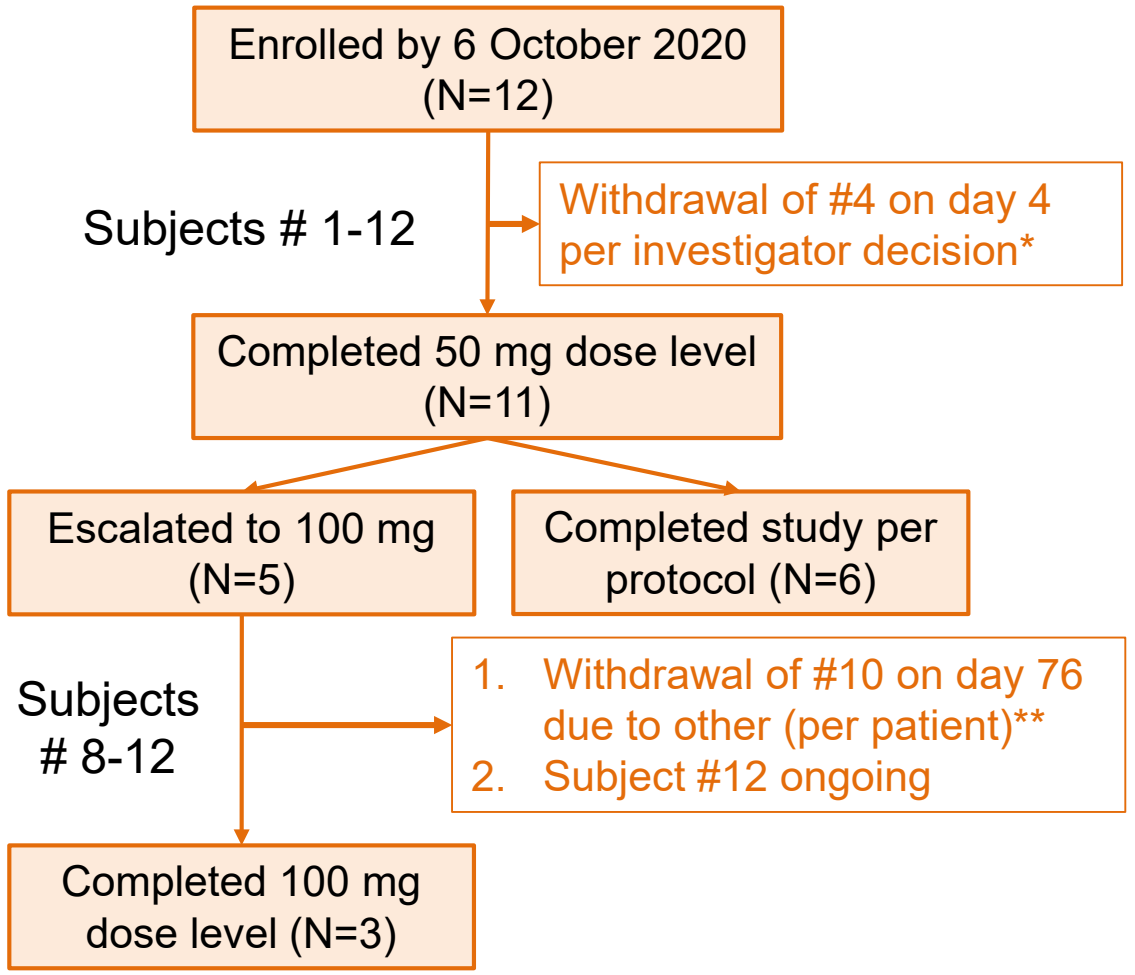
- Safety and tolerability
  - Changes in Hb and hemolytic markers

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%) |

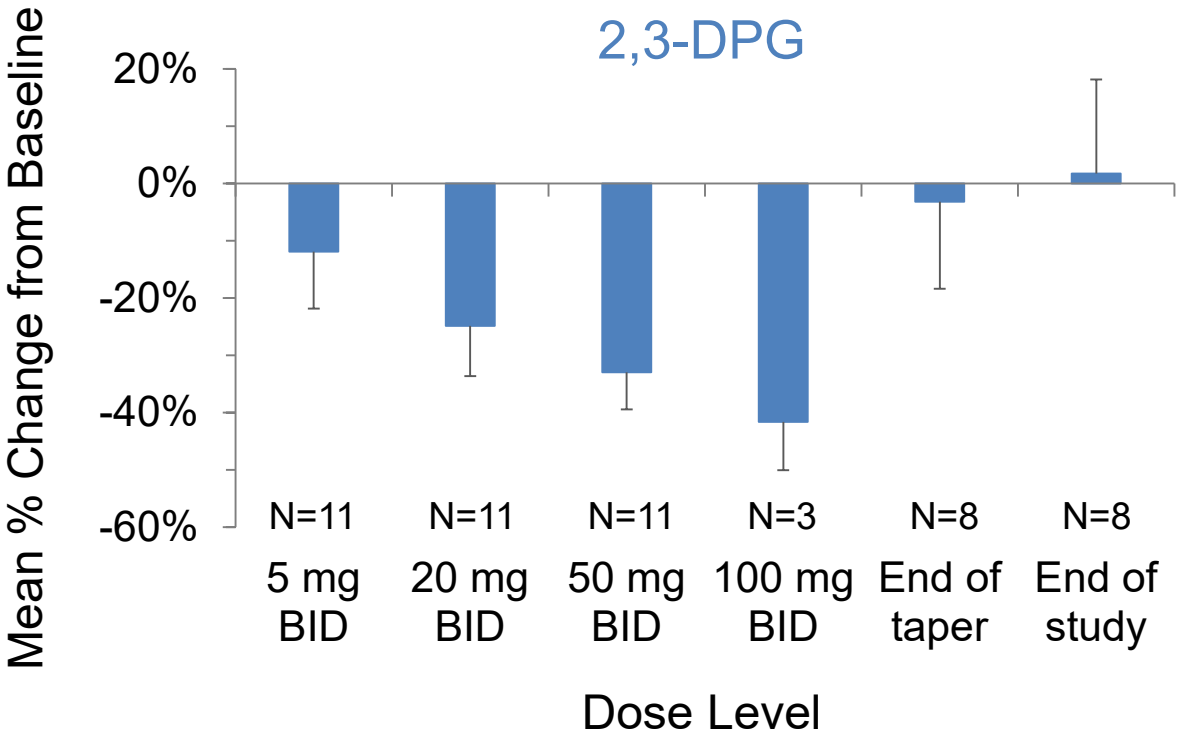
| Serious Adverse Events (SAEs) | N=12 (%) |
|---|---|
| **All** | **5 (41.7)** |
| VOC* | 3 (25) |
| Pain (shoulder) | 1 (8.3) |
| Pulmonary embolism (PE)** | 1 (8.3) |

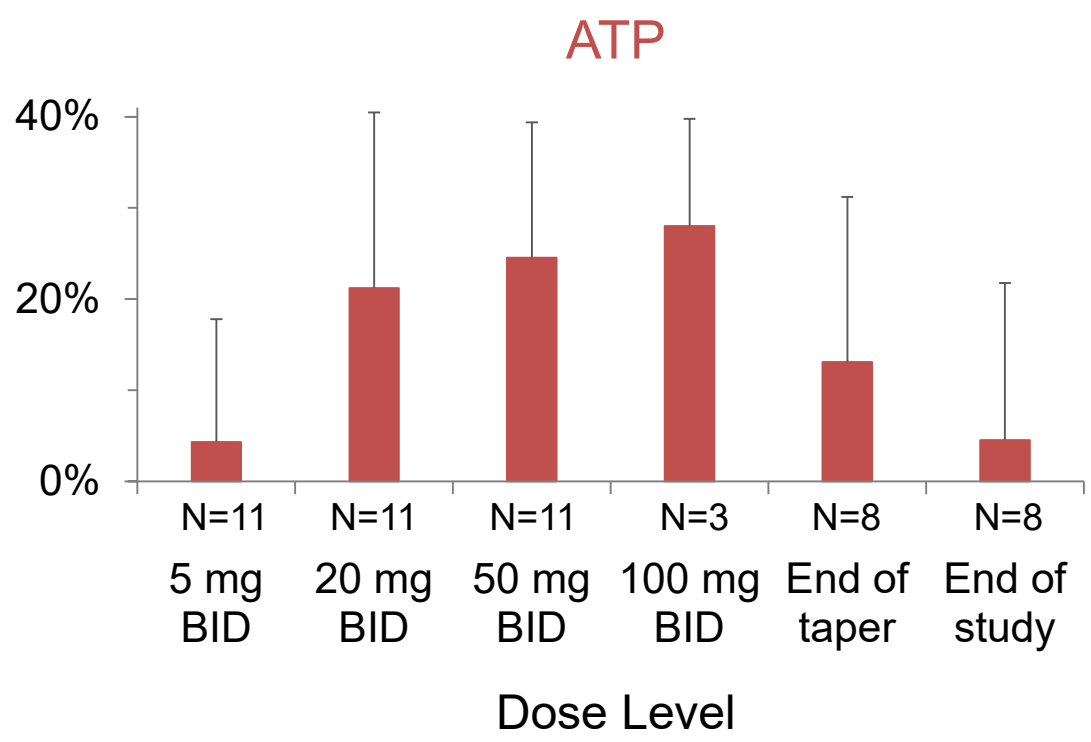
Summary of VOCs:

- 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

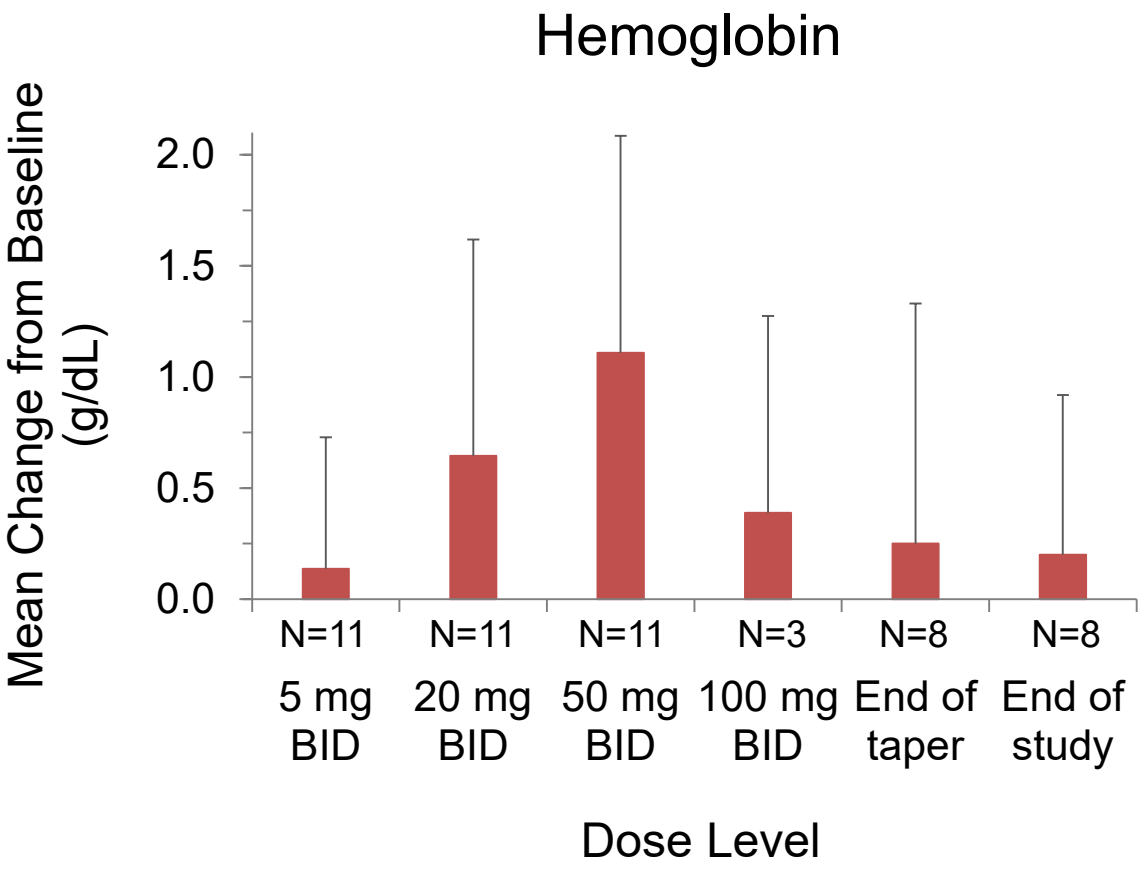



- Linear PK was observed up to 50 mg BID.
- After 100 mg BID, CYP3A auto-induction effect resulted in ~20% reduction in exposure.

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

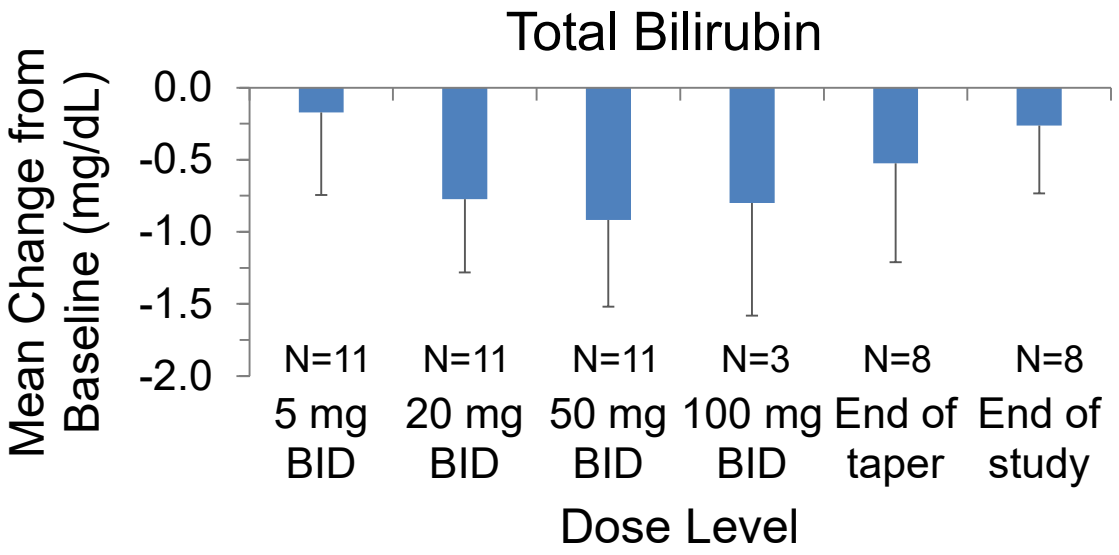
# Mitapivat Increases Hemoglobin Level

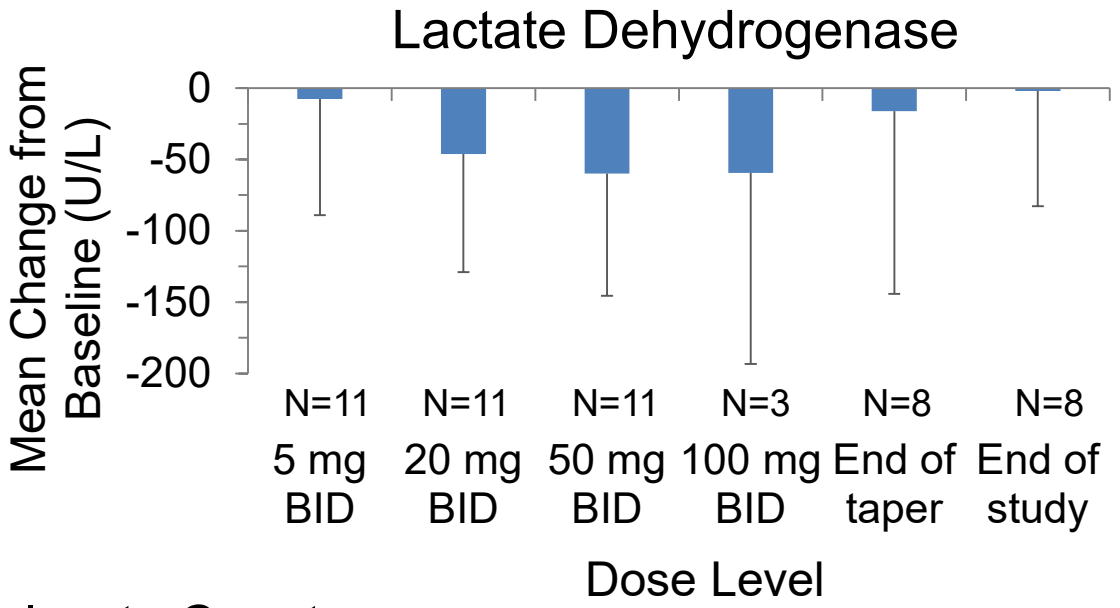


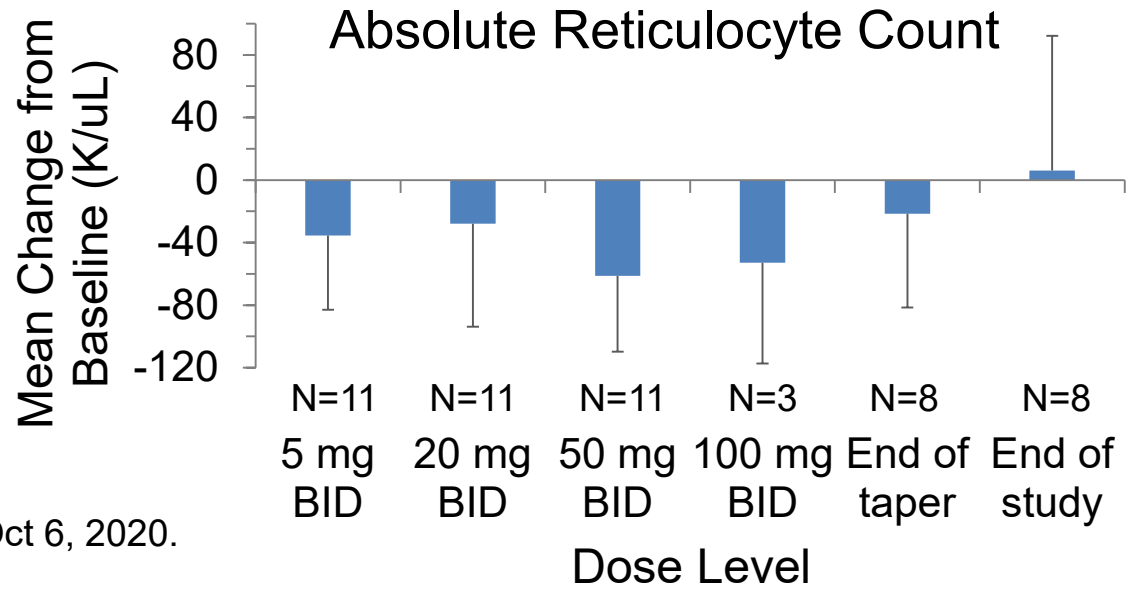

| Response parameter | N=11 |
|---|---|
| Maximal Hb increase, mean (SD), g/dL | 1.3 (0.8) |
| Hb increase ≥ 1g/dL, N (%) | 6 (54.5) |
| Maximal Hb increase in subjects with ≥ 1g/dL response*, mean (SD), g/dL | 1.9 (0.7) |

* 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.

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