Long-term Safety and Efficacy of Mitapivat, an Oral Pyruvate Kinase Activator, in Adults with Sickle Cell Disease: Extension of a Phase 1 Dose Escalation Study

NCT04610866 Investigator-initiated trial; Principal Investigator: Swee Lay Thein

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Pyruvate Kinase (PK) Activation in Sickle Cell Disease (SCD)

Key factors that promote sickling

2,3-DPG (increased in patients with SCD)

- Preferentially binds to polymerizing HbS (T) conformation
- Stabilizes HbS fiber
- Decreases the intra-erythrocyte pH

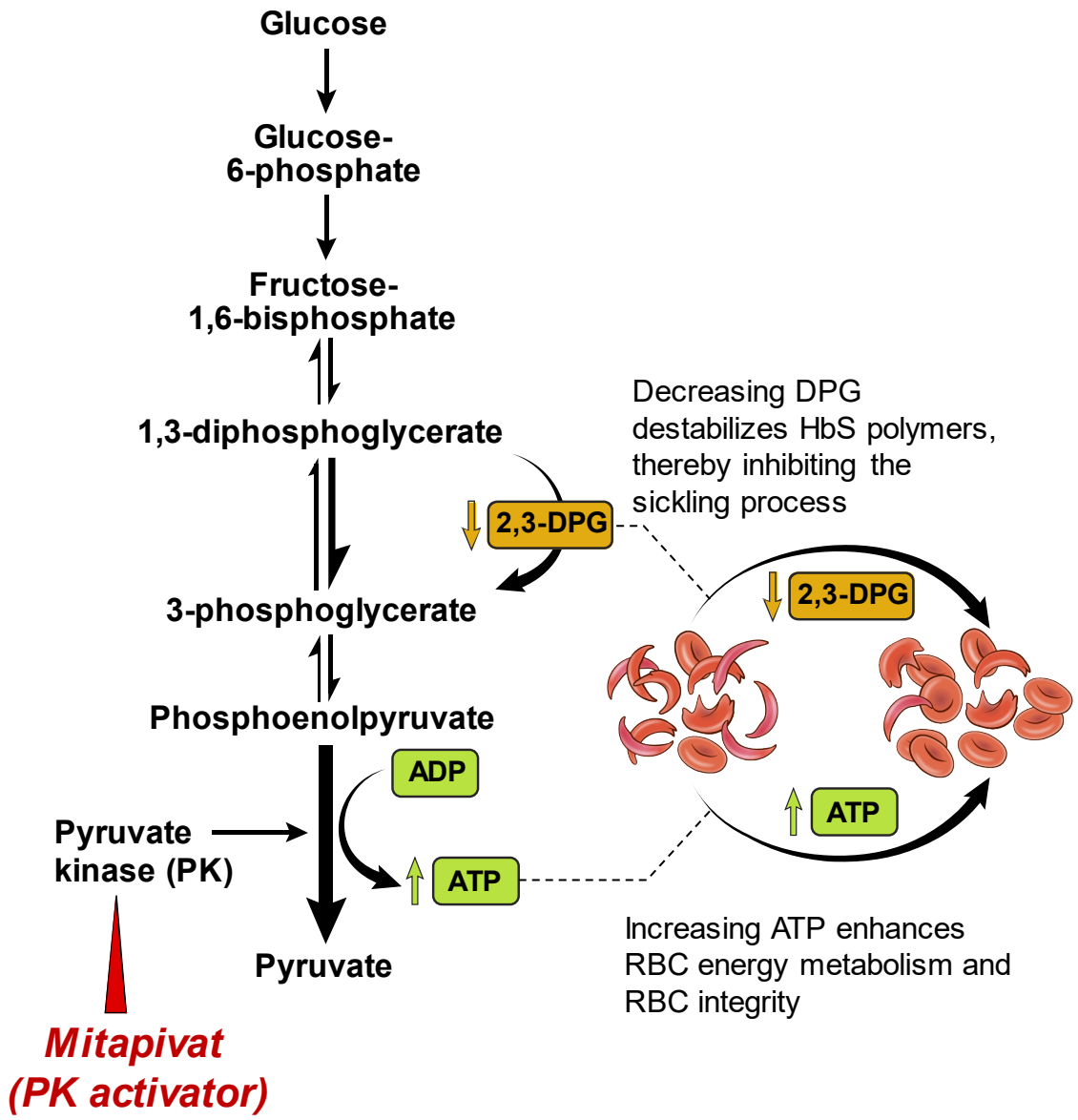
ATP is decreased in SCD

- Essential for water and ion homeostasis
- Reduced ATP leads to water and ion loss
- RBC dehydration promotes sickling

Mitapivat :

- ❖ Approved by FDA for treating PK deficiency
- ❖ Also activates wild type PK in SCD

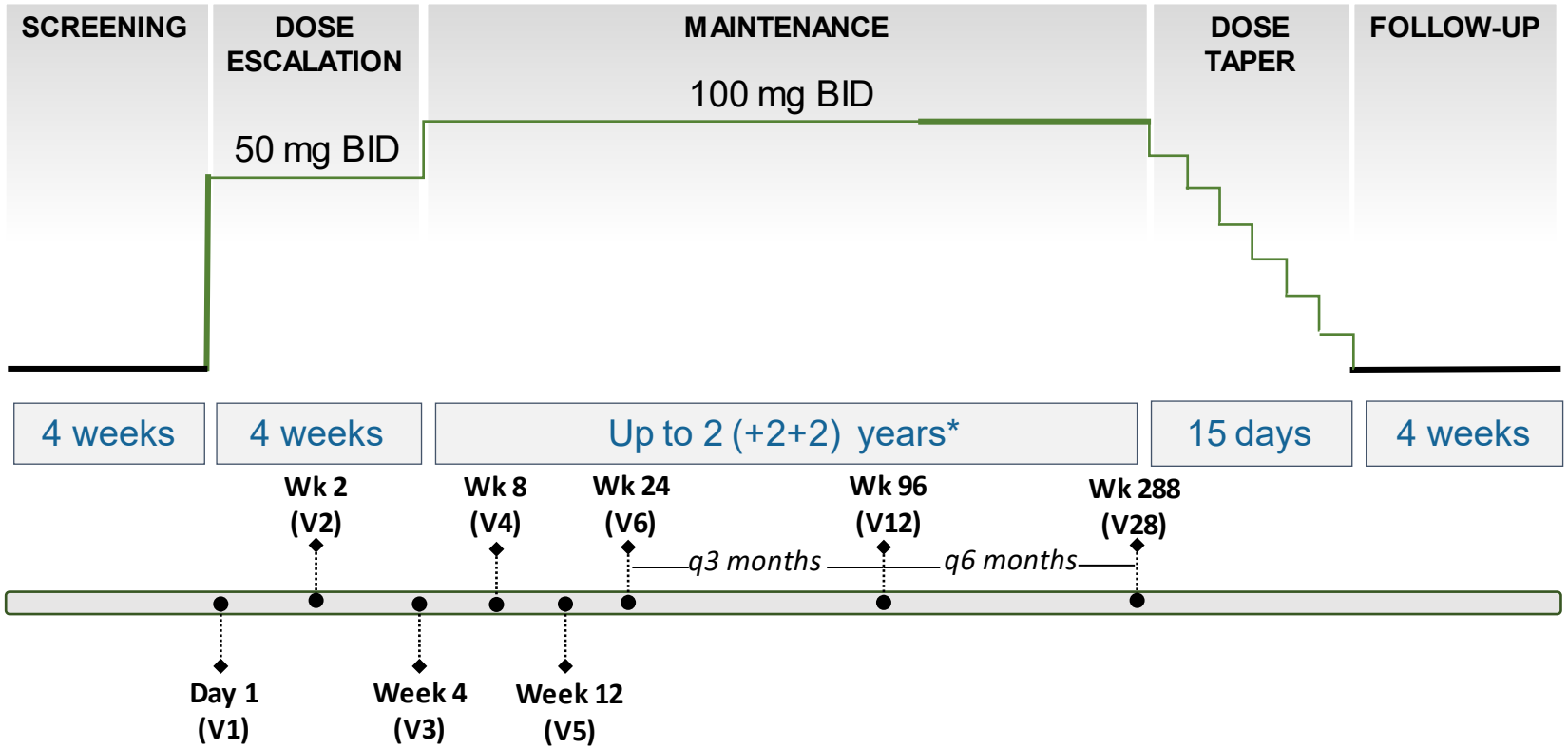
- Generally safe and tolerable
- Increased ATP and decreased 2,3-DPG levels in a dose-dependent manner
- Improved Hb levels and reduced hemolytic markers



Xu et al. Blood 2022; 140: 2052.

Study Design: Extended Treatment with Mitapivat in patients with SCD (NCT04610866)

- Subjects who have completed previous dose escalation study +/- mitapivat naïve subjects (N=15 completing 24-week endpoints)
- Escalate to 100 mg BID dose level as tolerated



[1]Evaluation of primary endpoint at 48 weeks;
[2]Evaluation of secondary endpoints at 24 and 48 weeks
*Option of 2 +2+2 years with amendment 08-27-2022

Primary endpoints[1]:

- Long-term safety and tolerability

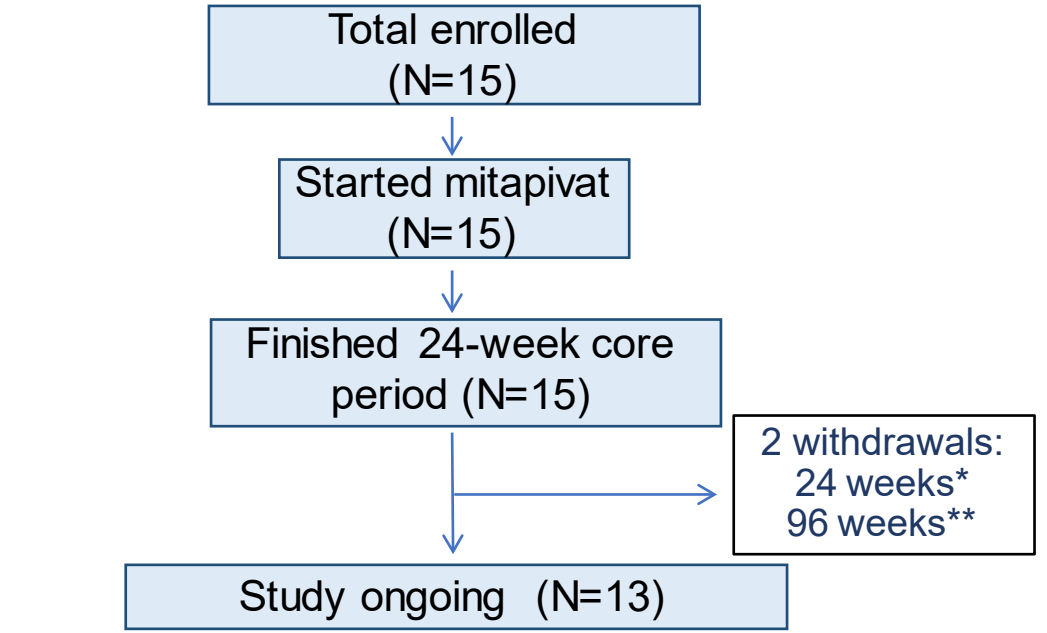
Secondary endpoints[2]:

- Hb response (Hb increase ≥ 1 g/dL above baseline) and changes in hemolytic markers (reticulocyte, LDH, bilirubin)
- Sustained Hb response (increase in Hb at ≥ 2 timepoints within the core 24 week period.)
- Pharmacokinetics
- Pharmacodynamics (2,3-DPG and ATP levels)
- p50 (O2 affinity) and t50 (HbS polymerization kinetics)

Demographics, Baseline Characteristics, and Disposition

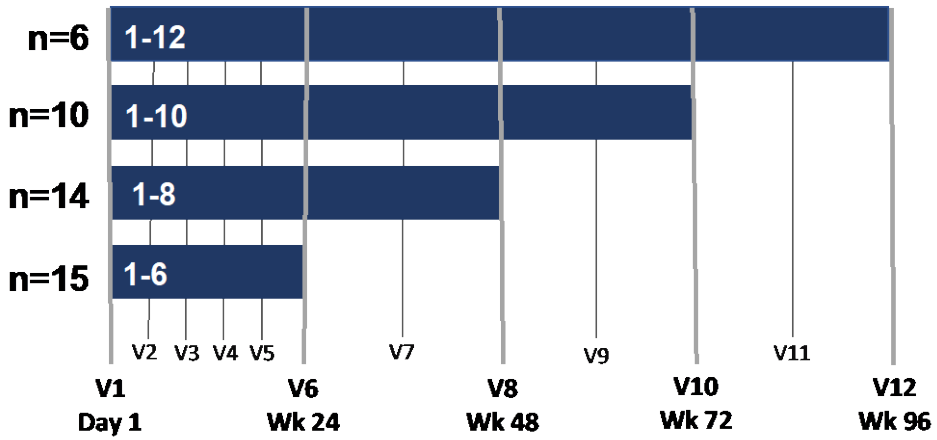
Baseline Characteristics at Enrollment	N=15
Age, mean (range), years	39 (25-57)
Sex, no. (%) Female Male	 5 (33.3) 10 (66.7)
African or African-American, N (%)	15 (100)
Hydroxyurea use, N (%)	11 (73.3)
Baseline Laboratory Measures	**N=15**
Hemoglobin, mean (SD), g/dL	8.63 (1.11)
Abs reticulocyte count, mean (SD), K/μL	217.21 (88.27)
Total bilirubin, mean (SD), mg/dL	2.73 (1.43)
Lactate dehydrogenase, mean (SD), U/L	536.71 (222.16)
Hemoglobin F, mean (SD), %	15.93 (10.53)

* #3 - withdrawn due to moving out of the country
** #2 - pt decision to withdraw to try to conceive
*** #5 - Hb level exceeded protocol cut-off of 12.5 mg/kg at 50mg and 20mg BID. Hb stable 11.5-12.3 g/dL on 5mg BID



(8 @ 100mg, 1 @ 50mg, 3 @ 50-100mg, *** 1 @ 5mg)

(Data cut : March 23, 2023)



Mitapivat Was Generally Safe and Well Tolerated

Treatment Emergent Adverse Events (TEAEs)	N=15 (%)	
	All Grades (≥ 10%)	Grade ≥ 3
All	**15 (100%)**	**11 (73.3%)**
Vaso-occlusive crisis (VOC)	8 (53.3%)	8 (53.3%)
Estrone decreased	7 (46.7%)	0 (0%)
Testosterone increased, total	6 (40%)	0 (0%)
Cough	5 (33.3%)	0 (0%)
ALT increased	4 (26.7%)	0 (0%)
Arthralgia	4 (26.7%)	0 (0%)
Bloating	4 (26.7%)	0 (0%)
Estradiol decreased	4 (26.7%)	0 (0%)

Serious Adverse Events (SAEs)	N=15 (%)
All	**9 (60%)**
VOC	8 (53.3%)
Lung infection	2 (13.3%)
Pain	1 (6.7%)
COVID-19 infection	1 (6.7%)
Vomiting	1 (6.7%)

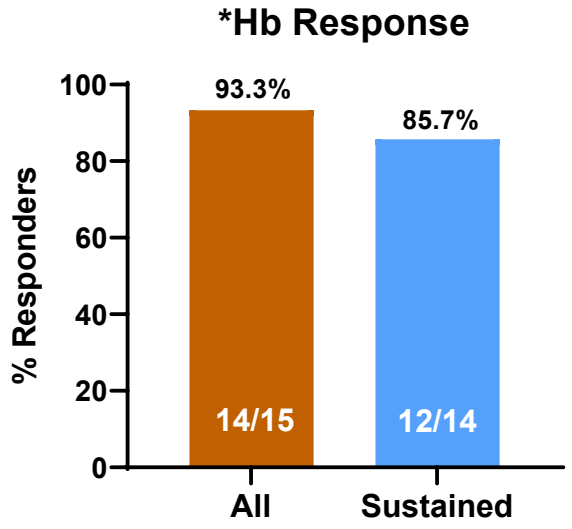
Summary of VOCs, SAEs or Grade 3 AEs:

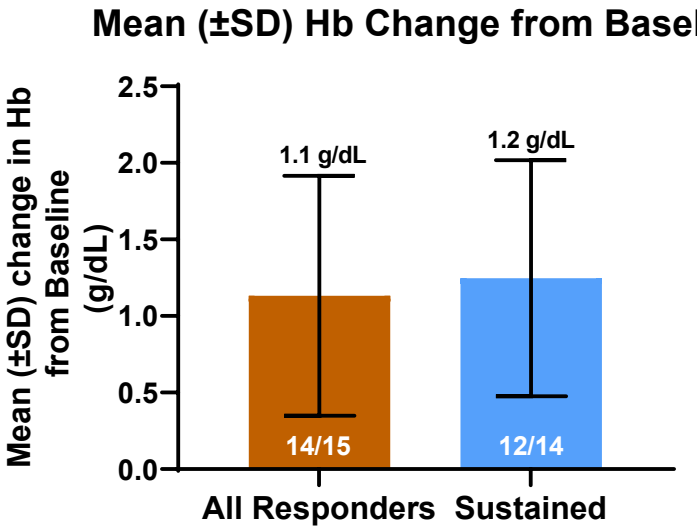
- All VOCs occurred in setting of known VOC triggers.
- 2 VOCs → possibly drug related (1 during drug escalation and 1 during drug taper).
- All other SAEs were not considered related to study drug.
- No TEAEs requiring drug discontinuation.
- Changes in laboratory values were not clinically significant.
- 3 patients required dose reduction to 50 mg (pruritis, bloating, insomnia), dose subsequently increased to 100 mg in 2 patients as TEAEs resolved.
- Total of 1080 patient-weeks of drug exposure thus far.

(Data cut : March 23, 2023)

(VOCs: vaso-occlusive crises)

Mitapivat met the Secondary endpoint of Hb Response





Hemoglobin (g/dL)

Timepoint	n	**Mean (SD)	P-value
Baseline	15	8.63 (1.11)	-
Week 4	15	1.16 (0.73)	<0.0001
Week 12	14	1.26 (0.85)	<0.0001
Week 24	15	1.38 (0.88)	<0.0001
Week 48	13	1.13 (1.2)	0.0004
Week 72	10	0.9 (1.03)	0.004

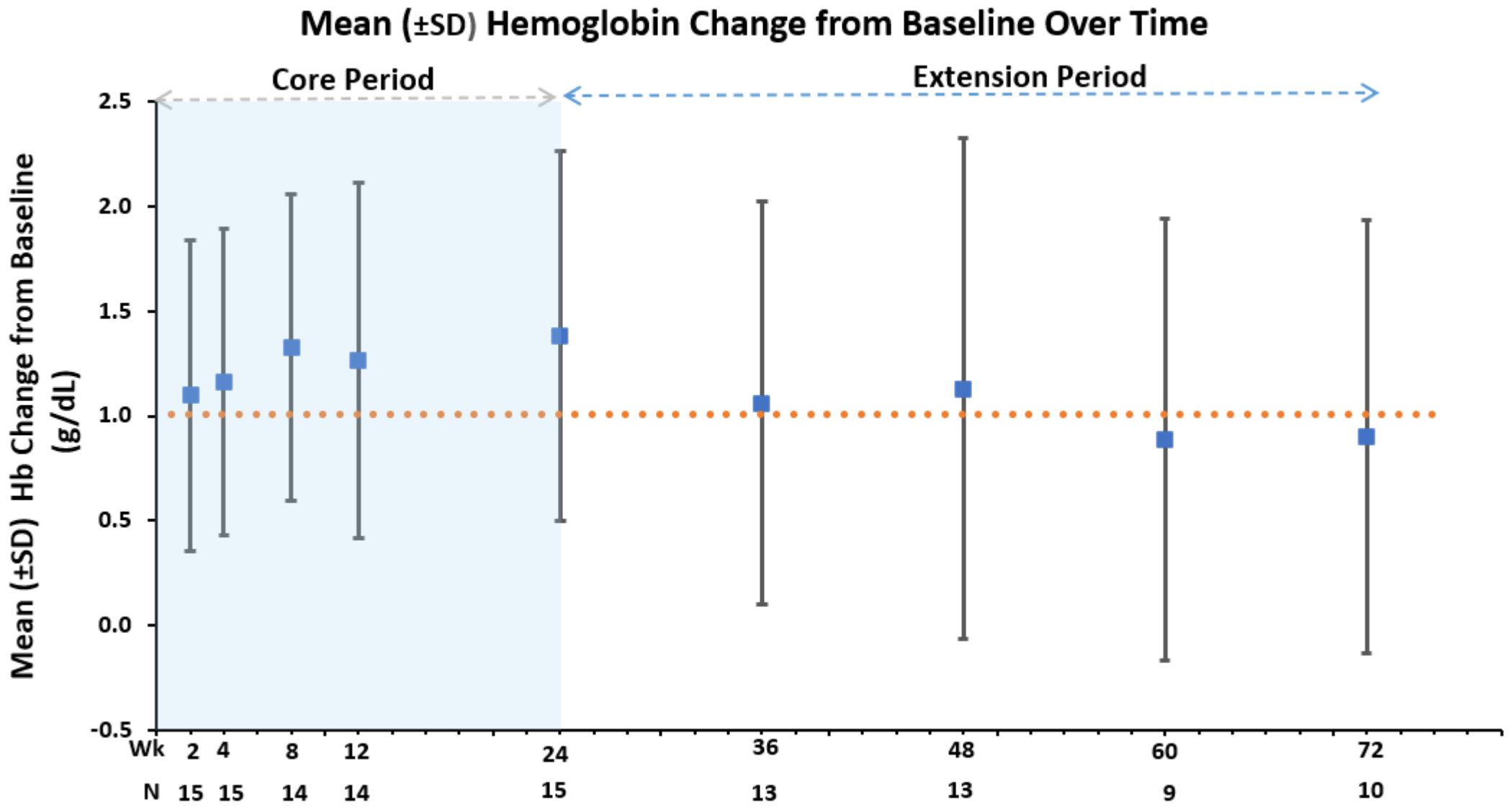
*** Mean (SD) change from baseline*

- 14/15 (93%) of the patients met secondary endpoint at 24 wks
- Response sustained in 12/14 patients
- Mean Hb change from baseline:
  - 1.1 g/dL in all 14 responders
  - 1.2 g/dL in 12 in which response is sustained.

- *Hb response, defined as a ≥ 1 g/dL increase in Hb at any timepoint within the core period 24 weeks compared to baseline.
- Sustained Hb response, defined as a ≥ 1 g/dL increase in Hb at 2 or more timepoints within the core 24-week period.

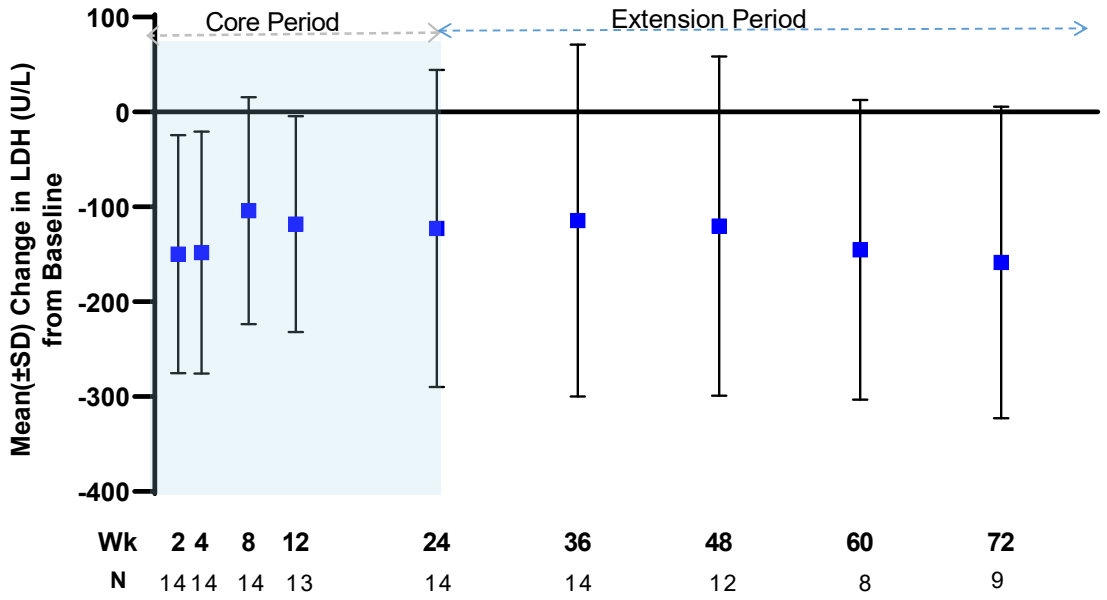
Hb: hemoglobin

Improvements in Hemoglobin Were Rapid and Maintained Through the Extension Period

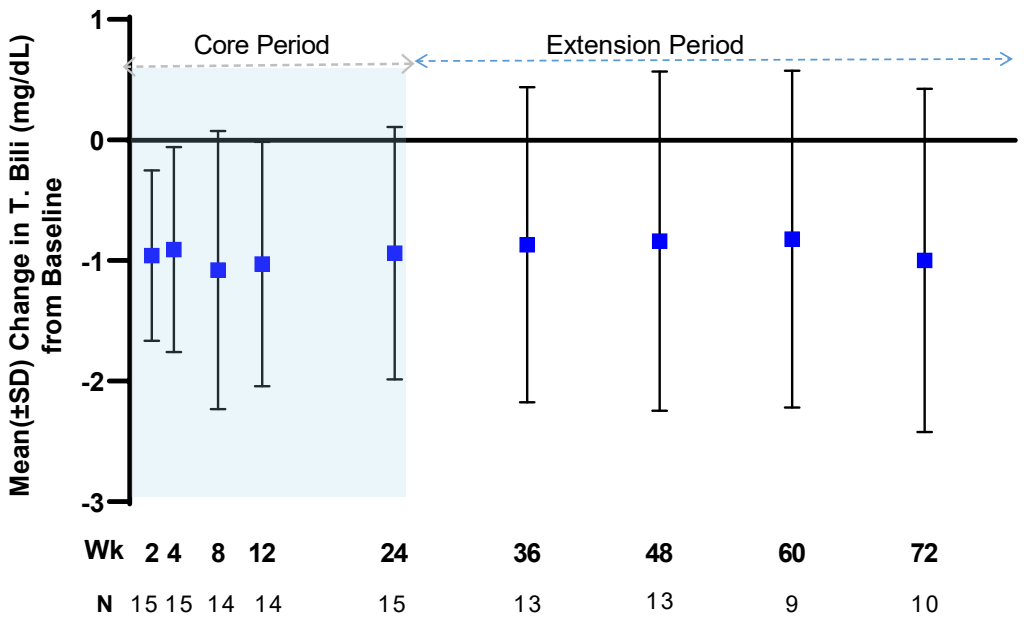


Improvements Were Observed in Markers of Hemolysis and Were Sustained

Mean (±SD) Change in LDH from Baseline



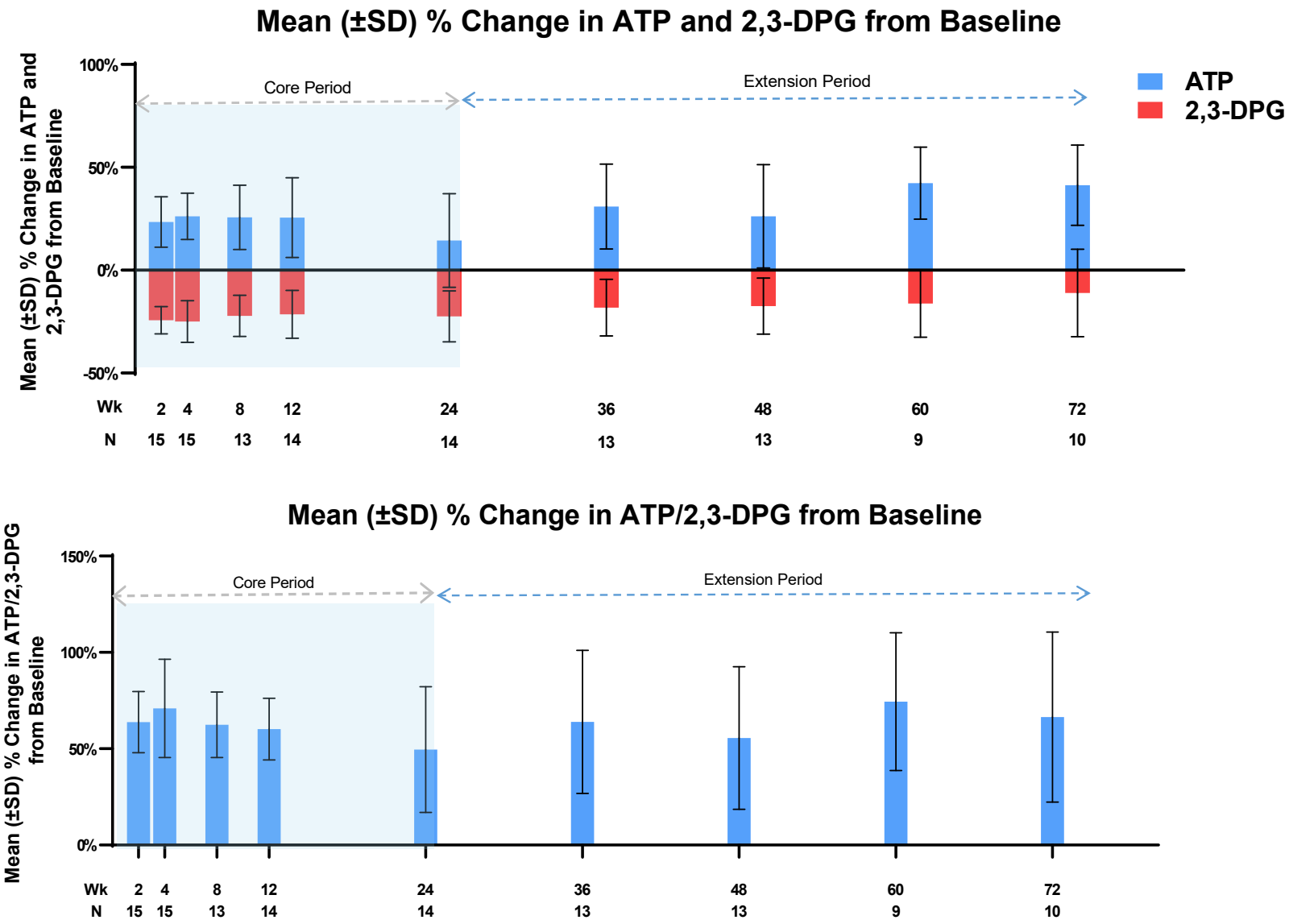
Mean (±SD) Change in T. Bili from Baseline



			Change from Baseline											
	Baseline		Week 4			Week 12			Week 24			Week 48			Week 72		
	n	Mean (SD)	n	Mean (SD)	p-value	n	Mean(SD)	p-value	n	Mean (SD)	p-value	n	Mean (SD)	p-value	n	Mean (SD)	p-value
LDH (U/L)	14	536.71 (222.16)	14	-147.93 (127.85)	< 0.0001	13	-118.23 (113.8)	< 0.0001	14	-122.86 (167.28)	0.004	12	-120.25 (178.83)	0.01	9	-158.67 (164.48)	0.002
T. Bili (mg/dL)	15	2.73 (1.43)	15	-0.91 (0.85)	< 0.0001	14	-1.03 (1.01)	< 0.0001	15	-0.94 (1.05)	0.0003	13	-0.84 (1.41)	0.03	10	-1 (1.42)	0.02
ARC (K/mcL)	15	217.21 (88.27)	15	-17.23 (68.03)	0.31	14	-23.68 (78.25)	0.24	15	-10.51 (73.37)	0.57	13	8.98 (82.26)	0.68	10	-19.72 (76.5)	0.39
AST (U/L)	15	39.67 (15.01)	15	0.13 (17.15)	0.98	14	-3.71 (8.29)	0.08	15	-2.93 (9.84)	0.23	13	-0.38 (13.1)	0.91	10	3.6 (11.7)	0.31

Abs. Retics: absolute reticulocyte count; LDH: lactate dehydrogenase; AST: Aspartate transaminase; T. Bili: Total bilirubin

Changes in Pharmacodynamics Were Consistent and Sustained



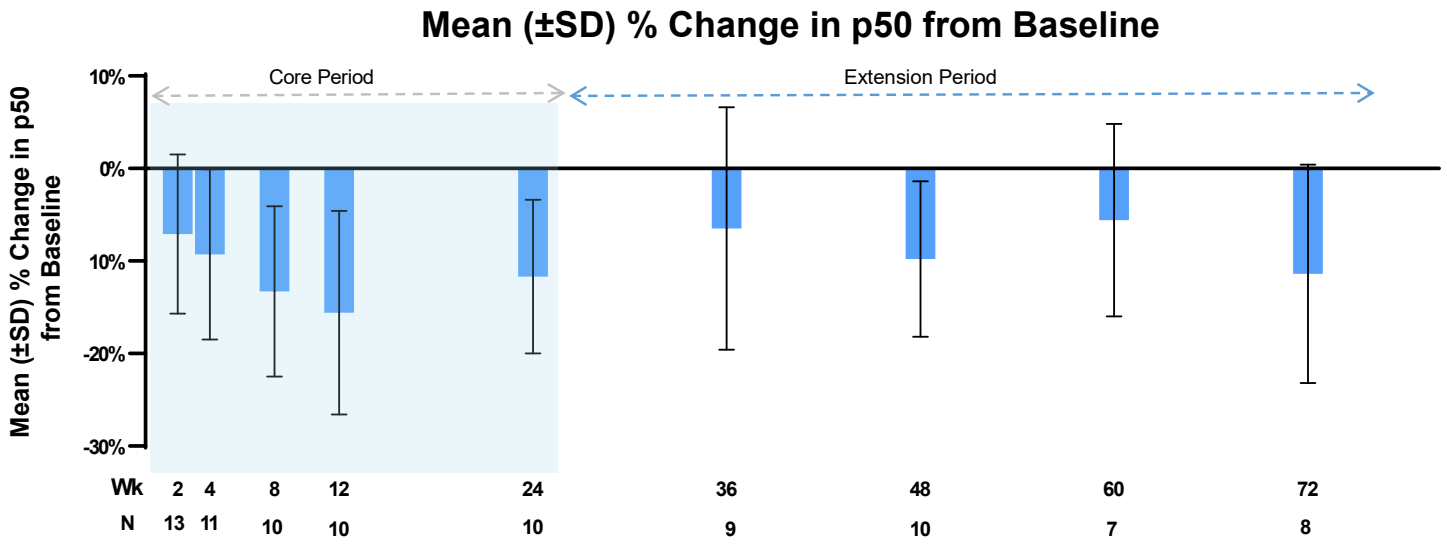
At weeks 4, 12, 24, 48 and 72 (except 2,3-DPG)

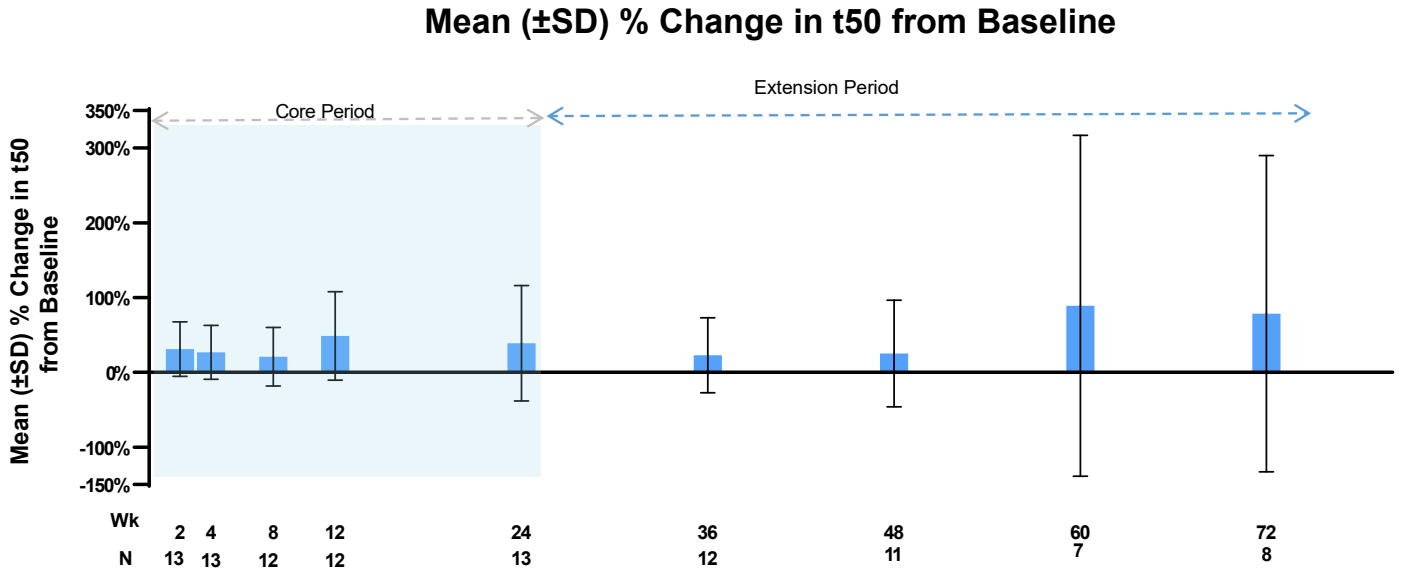
- Increases in ATP, decreases in 2,3-DPG significant and sustained
- Increases in ATP/2,3-DPG significant and sustained

Note: % Changes in 2,3-DPG and ATP refer to intracellular concentrations, determined from whole blood concentrations divided by the hematocrit.

ATP: adenosine triphosphate; 2,3DPG: 2,3- diphosphoglycerate

Improvements in Oxygen Affinity (p50) and Sickling Kinetics (t50) Were Sustained





- Decrease in **p50** (indicates less HbS polymer) at Weeks 4, 12, 24, 48 and 72, from baseline, significant and sustained
- Increase in **t50** (slower HbS polymerization kinetics) at weeks 4, 12 and 24, significant

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.

Note: Missing data are the result of disruptions in equipment availability

Summary

- Mitapivat, an oral Pyruvate Kinase activator, is safe and well tolerated as a long-term maintenance therapy in subjects with SCD.
  - No TEAEs led to discontinuation of drug
- Treatment with mitapivat demonstrated statistically significant and clinically meaningful improvements in hemoglobin response that were sustained throughout duration.
- Improvements in hemoglobin were accompanied by improvements in markers of hemolysis.
- Mitapivat reduced 2,3-DPG and increased ATP, consistent with its mechanism of action, with expected increase in oxygen affinity and improvements in sickling kinetics. Changes were sustained.
- This study supports mitapivat as a long-term disease modifying medication for patients with SCD, and continues to be evaluated in extension study (ClinicalTrials.gov NCT04610866).
- Agios Pharmaceuticals is actively recruiting patients for their phase 3 portion of RISE UP study (NCT05031780), evaluating a 100 mg BID dose of mitapivat.

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