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ORAL ABSTRACTS

114.SICKLE CELL DISEASE, SICKLE CELL TRAIT AND OTHER HEMOGLOBINOPATHIES, EXCLUDING THALASSEMIAS: CLINICAL AND EPIDEMIOLOGICAL

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

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BACKGROUND In a Phase I study (NCT04000165, Xu et al, 2022), we showed that mitapivat, an investigational oral allosteric activator of pyruvate kinase (PK), demonstrated an acceptable safety and tolerability profile at multiple ascending dose levels in patients (pts) with sickle cell disease (SCD). We also established proof-of-concept for activating PK as a viable therapeutic approach; mitapivat decreased 2,3- diphosphoglycerate (2,3-DPG) and increased adenosine triphosphate (ATP) levels, improved hematologic parameters, and reduced sickling in pts with SCD (HbSS). In this extension study (NCT04610866), we evaluated the safety, tolerability and efficacy of mitapivat as a long-term maintenance therapy for pts with SCD.

METHODS

We enrolled 15 adult pts (age >18 years) with confirmed SCD (HbSS) and baseline hemoglobin (Hb) 7.1 - 10.5 g/dL, with no recent blood transfusions, erythropoietin therapy, or changes in SCD-specific therapies including hydroxyurea (HU) and L-glutamine. Thirteen pts had participated in the Phase 1 study and 2 pts were mitapivat naïve. All pts started mitapivat at 50 mg twice daily (BID), escalating after 4 weeks (wks) to 100 mg BID, unless a rapid Hb rise was observed (increase of ≥2 g/dL), the maximum Hb level of 12.5 g/dL had been reached, or per PI discretion. Patients continued on this maintenance dose of mitapivat through the end of the study. Dose reductions were performed at any time during the extension phase for safety and tolerability. After completion of the 24-wk core period, pts had an option to continue on mitapivat treatment in the extension period for up to 6 years. Study visits were conducted every 2 wks (x2), 4 wks (x2), and then every 12 wks for first 2 years (yrs) and will continue every 6 months for the remaining 4 yrs. The extension period of the study is ongoing; here we report data for up to 2 years (data cutoff March 23, 2023). Any and all vaso-occlusive crises (VOCs) that occurred while on study, regardless of attribution, were considered adverse events.

RESULTS

Of the 15 pts who completed the core period, 14 entered the extension study with 1 pt on 5 mg BID, 1 pt on 50 mg BID, 3 alternating between 50 and 100 mg BID, and the rest on 100 mg BID. Mean age of the 15 pts was 39 yrs (range: 25-57 yrs); 10 were male, and 11 were on HU. As of the cut-off date, median duration of mitapivat treatment for pts who entered the extension period was 84 wks (range: 48-108 wks), 1 pt discontinued after 2 yrs (pt decision) and 10 pts received 72 wks or more of treatment (Table 1) with a total of 1080 pt-wks of drug exposure thus far.

Mitapivat was generally well tolerated; no treatment emergent adverse events (TEAEs) resulted in discontinuation of study drug or death during the extension period. The most common TEAEs (reported in 5 or more pts) were VOCs (n=8), estrone decrease (n=7), testosterone increase (n=6) and cough (n = 5); changes in laboratory values were not clinically significant. The most common serious TEAEs (reported in 2 or more pts) were VOCs (n=8) and lung infection (n = 2). Two pts experienced VOCs that were assessed as possibly drug-related (1 during drug escalation, and 1 during drug taper). All VOCs occurred in

the setting of known VOC triggers. Three pts required dose reduction, 1 each secondary to pruritis, bloating and insomnia, respectively. In the latter 2 cases, the doses were subsequently increased to 100 mg BID, as TEAEs resolved. Other serious TEAEs were not considered related to study drug.

The mean Hb at 24 wks increased significantly from baseline (mean: 1.38 g/dL, SD: 0.88 g/dL; $p<0.0001$), a result generally upheld at other follow-up periods (Fig. 1). 14/15 (93%) of the pts achieved a Hb response, defined as a $\geq$ 1 g/dL increase in Hb at any timepoint within the core period, compared to baseline. Improvements in Hb achieved in the core period were accompanied by improvements in markers of hemolysis, oxygen affinity (p50), sickling kinetics (t50), decreases in 2,3-DPG and increases in ATP levels, and were sustained in the extension study (Fig. 1 and 2). Concurrently, there were also improvements in red cell deformability (LORRCA) (Lundt et al, 2022) and trends in improvements in cardiopulmonary status (not shown).

CONCLUSION

Long-term use of mitapivat is safe and well tolerated in pts with SCD with evidence of sustained long-term improvements in Hb, hemolytic and sickling kinetics. Mitapivat offers a novel disease-modifying approach.

Disclosures Xu: *GlaxoSmithKline:* Membership on an entity's Board of Directors or advisory committees, Research Funding; *Agios Pharmaceuticals, Inc.:* Other: US national principal investigator for the Phase 1 clinical trial pf AG-946 in patients with sickle cell disease.. **Yates:** *Agios Pharmaceuticals Inc.:* Current Employment, Current equity holder in publicly-traded company. **Wind-Rotolo:** *Agios Pharmaceuticals, Inc.:* Current Employment, Current equity holder in publicly-traded company.

OffLabel Disclosure: Mitapivat as an anti-sicking therapy in patients with sickle cell disease

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	Baseline		Week 4 change from Baseline			Week 12 change from Baseline			Week 24 change from Baseline			Week 48 change from Baseline			Week 72 change from Baseline		
	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*
Hb (g/dL)	15	8.63 (1.11)	15	1.16 (0.73)	< 0.0001	14	1.26 (0.85)	< 0.0001	15	1.38 (0.88)	< 0.0001	13	1.13 (1.2)	0.0004	10	0.9 (1.03)	0.004
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
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
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
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
P50 (torr)	13	32.36 (3.23)	11	-9.31% (9.15%)	0.0004	10	-15.63% (11.02%)	< 0.0001	10	-11.67% (8.3%)	< 0.0001	10	-9.85% (8.43%)	< 0.0001	8	-11.37% (11.82%)	0.004
T50 (min)	13	159.58 (89.47)	13	26.93% (36.17%)	0.005	12	48.56% (59.16%)	0.003	13	38.89% (77.21%)	0.06	11	25.36% (71.52%)	0.22	8	78.38% (211.59%)	0.26
2,3-DPG (ug/mL)	15	16.97 (1.82)	15	-25.02% (10.18%)	< 0.0001	14	-21.46% (11.71%)	< 0.0001	14	-22.39% (12.39%)	< 0.0001	13	-17.48% (13.68%)	< 0.0001	10	-11.14% (21.29%)	0.08
ATP (ug/mL)	15	7.93 (1.03)	15	26.17% (11.27%)	< 0.0001	14	25.48% (19.36%)	< 0.0001	14	14.35% (22.78%)	0.01	13	26.15% (25.22%)	< 0.0001	10	41.26% (19.46%)	< 0.0001
ATP/2,3-DPG ratio	15	0.47 (0.06)	15	70.94% (25.46%)	< 0.0001	14	60.22% (15.95%)	< 0.0001	14	49.61% (32.69%)	< 0.0001	13	55.57% (36.96%)	< 0.0001	10	66.43% (44.16%)	< 0.0001

Note:

- SD, Standard Deviation; Hb, Hemoglobin; ARC, Absolute reticulocyte count; LDH, Lactate Dehydrogenase; AST, Aspartate Aminotransferase; T. Bili, Total Bilirubin; 2,3-DPG: 2,3-Diphosphoglyceric Acid; ATP, Adenosine Triphosphate
- n should be 14 and 10 for complete dataset at timepoints Week 48 and 72, respectively. Missing data reflected in the sample sizes shown were largely the result of disruptions related to the COVID-19 pandemic.
- Mean change was calculated from baseline (prior to drug initiation) and was reported as absolute change for clinical laboratory measures (first 5 rows) and as percent change for p50 and t50, 2,3-DPG, ATP and ATP/2,3-DPG (last 5 rows). p50 is defined as the partial pressure of oxygen (torr) at which Hb is 50% saturated with oxygen; t50 is defined as the time at which 50% of erythrocytes are sickled in response to gradual deoxygenation with nitrogen to 5% oxygen; 2,3-DPG and ATP levels used in analyses were corrected for hematocrit.

Figure 1.
Change in Hemoglobin from baseline in response to mitapivat therapy at various longitudinal timepoints.