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POSTER ABSTRACTS

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

One-Year Safety and Efficacy of Mitapivat in Sickle Cell Disease: Follow-up Results of a Phase 2, Open-Label Study

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Background

Targeting the primary pathogenic event of sickle cell disease (SCD), polymerization of deoxygenated sickle hemoglobin (HbS), may prevent downstream clinical events. Mitapivat, an oral allosteric activator of pyruvate kinase (PK), has shown therapeutic potential by increasing adenosine triphosphate (ATP) and decreasing 2,3-diphosphoglycerate (2,3-DPG), a glycolytic red blood cell (RBC) intermediate. In addition to improving anemia and hemolysis, mitapivat may reduce HbS polymerization and inhibit sickling by decreasing 2,3-DPG levels in patients with SCD. In the previously reported 8-week dose-finding period (DFP) of this phase 2 study, mitapivat was well tolerated and showed efficacy in SCD (*Van Dijk et al. Am J Hematol. 2022*). Here, the safety and efficacy of treatment with mitapivat in patients with SCD from the 1-year fixed-dose extension period (FDEP) are reported (EudraCT 2019-003438-18, ESTIMATE study).

Methods

The ESTIMATE study is a phase 2, investigator initiated, open-label study in which subjects ≥16 years with SCD (HbSS, HbS/β^0, HbS/β^+) with a baseline hemoglobin (Hb) >4.0 g/dL and ≤11.1 g/dL, no chronic transfusion and adequate organ function were eligible. After the 8-week DFP in which patients were dosed mitapivat 20 mg, 50 mg or 100 mg twice daily depending on safety, patients could continue in the 1-year FDEP. The primary endpoints were safety, evaluated by frequency and severity of adverse events (AEs), and efficacy of mitapivat including the evaluation of a hematological response (improvement in mean Hb level of ≥1 g/dL compared to baseline during the FDEP). RBC sickling was evaluated by oxygen gradient ektacytometry (point of sickling, Lorrca). Secondary endpoints included changes in hematological parameters including Hb, absolute reticulocyte count (ARC), total bilirubin, lactate dehydrogenase (LDH), levels of ATP and 2,3-DPG and Hb-oxygen affinity, as reflected by the oxygen tension at which Hb is 50% saturated (p50, Hemox Analyzer). Exploratory endpoints included changes in annualized rates of vaso-occlusive events (VOEs) and annualized SCD-related hospital admission days. Intention-to-treat analysis was performed using IBM SPSS Statistics (version 27.0.0.0) and Graphpad Prism (version 9.3.0) with the paired sample t-test or Wilcoxon signed-rank test used when appropriate.

Results

In total, ten patients were included in this study. Safety analysis showed mostly mild treatment-emergent adverse events (most commonly [n>2 patients]: transaminase increase [all grade 1] and headache [grade 1-2]). Apart from the non-treatment-related serious adverse event (SAE) of a urinary tract infection in the DFP in a patient who was lost to follow-up afterwards, one non-treatment-related SAE occurred in the FDEP in a patient who died of massive pulmonary embolism due to COVID-19. Importantly, sustained improvements in Hb level (mean increase: 1.1 ± 0.7 g/dL; p=0.0014) were seen in the nine patients who continued treatment with mitapivat 50 mg twice daily (n=2) or 100 mg twice daily (n=7) in the FDEP (Table 1). These improvements were accompanied by decreases in markers of hemolysis (ARC, total bilirubin and LDH) (Table 1). On a cellular level, the ATP/2,3-DPG ratio and Hb-oxygen affinity increased significantly, and RBC sickling was reduced, though non-significantly (Table 1). In addition, the annualized rate of vaso-occlusive events reduced significantly from 1.33 ± 1.32 to 0.64 ± 0.87 (p=0.0489) when combining the DFP and FDEP (Table 1 and Figure 1).

Conclusion

Overall, this study demonstrated long-term safety and efficacy of treatment with mitapivat in SCD, warranting further evaluation in the ongoing phase 2/3 RISE UP study (ClinicalTrials.gov NCT05031780).

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Table 1

	Baseline (n=9)	*End of DFP (n=9)*	Mean of FDEP (n=9)	p-value (baseline vs mean of FDEP)
Hb, g/dL	8.8 (1.8)	*10.3 (1.3)*	9.9 (1.8)	0.0014
Reticulocytes:				
ARC, 10^9/L	235 (88)	*141 (50)*	156 (50)	0.0038
% of RBCs	8.2 (2.3)	*4.2 (1.4)*	5.0 (1.4)	0.0003
Total bilirubin, mg/dL	2.6 (1.3)	*1.2 (0.5)*	1.4 (0.7)	0.0025
LDH, U/L	500 (307)	*328 (113)*	401 (224)	0.0217
ATP, mg/gHb	2.9 (0.7)	*3.6 (0.5)*	3.6 (0.5)	0.1386
2,3-DPG, mg/gHb	11.4 (1.0)	*7.9 (1.1)*	9.0 (1.1)	0.0004
ATP/2,3-DPG ratio	0.25 (0.05)	*0.46 (0.09)*	0.40 (0.06)	0.0009
p50, mmHg	24.0 (2.4)	*21.5 (1.4)*	22.5 (1.8)	0.0032
PoS, mmHg	40.2 (8.8)*	*33.1 (9.7)**	36.2 (6.3)*	0.0802
Annualized VOE rate:				
- DFP + FDEP	1.33 (1.32)	0.64 (0.87)		0.0489†
- FDEP	1.33 (1.32)	*0.72 (2.17)*	0.60 (0.78)	0.0625
Annualized SCD-related hospital admission days	5.3 (7.0)	*0.0 (0.0)*	4.1 (5.6)	0.4452

*Due to technical issues of the oxygen gradient ektacytometer, data is missing of n=1 patient, a week 52 visit (n=1 patient) and four visits from week 24 to week 52 in the FDEP (n=2 patients).

†ITT analysis of baseline versus the total period on study drug treatment (DFP and FDEP combined) instead of only the FDEP.

Figure 1

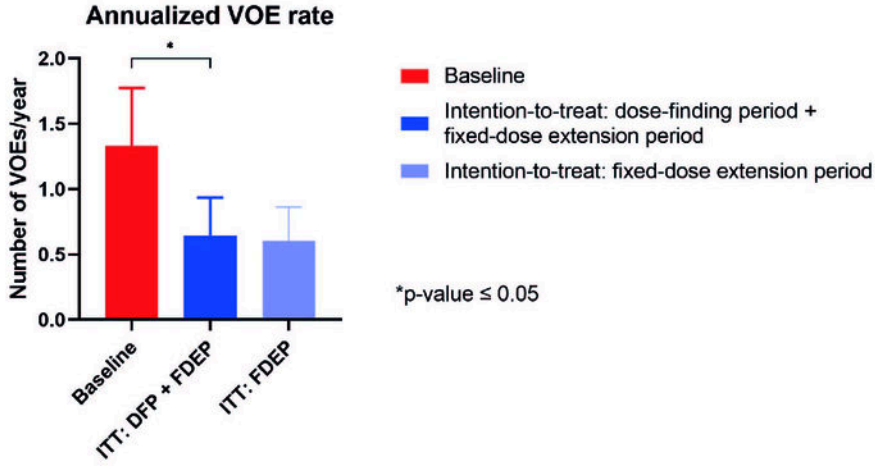

Figure 1

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