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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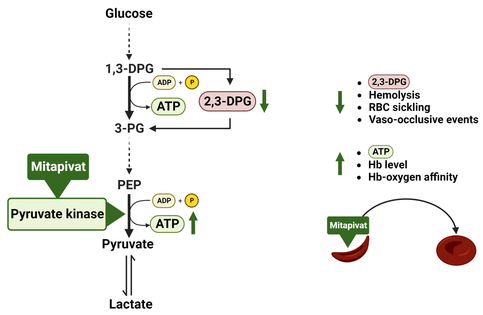
Aim

To report on safety and efficacy results of the 1-year fixed-dose extension period (FDEP) of treatment with mitapivat in subjects with sickle cell disease (SCD) enrolled in the ESTIMATE study *(www.clinicaltrialsregister.eu NL8517; EudraCT 2019-003438-18)*

Introduction

- Targeting the primary pathogenic event of SCD, namely the polymerization of deoxygenated sickle hemoglobin (HbS) molecules, may prevent downstream clinical events.
- Mitapivat, an oral allosteric activator of pyruvate kinase (PK), has therapeutic potential by increasing adenosine triphosphate (ATP) and decreasing 2,3-diphosphoglycerate (2,3-DPG), a glycolytic red blood cell (RBC) intermediate which promotes deoxygenation by lowering the oxygen affinity of hemoglobin (Hb) (**Figure 1**).
- In the previously reported 8-week dose-finding period (DFP) of this study, mitapivat was well tolerated and showed efficacy in SCD.[1]

Figure 1



References:
1. van Dijk MJ, Rab MAE, van Oirschot BA, et al. Safety and efficacy of mitapivat, an oral pyruvate kinase activator, in sickle cell disease: A phase 2, open-label study. Am J Hematol. 2022;97(7):E226–E229.

Methods

The ESTIMATE study is a phase 2, investigator initiated, open-label study with the following major eligibility criteria:

- Subjects ≥16 years with SCD (HbSS, HbS/β^0, HbS/β^+)
- 1-10 vaso-occlusive episodes (VOEs) in the prior year and/or prior SCD-related complications;
- Hb level >4.0 g/dL and ≤11.1 g/dL;
- Stable dose of hydroxyurea (≥3 months), if applicable;
- No chronic transfusion (not >4 RBC units within the 12 months and/or ≥1 within the 3 months prior to the first day of study drug).

After the 8-week DFP in which subjects were dosed mitapivat 20 mg, 50 mg or 100 mg twice daily depending on safety,[1] subjects continued in the 1-year FDEP

- Safety analysis included all subjects who received ≥1 dose of mitapivat;
- Efficacy analysis of the FDEP was based on the intention-to-treat principle.

Results

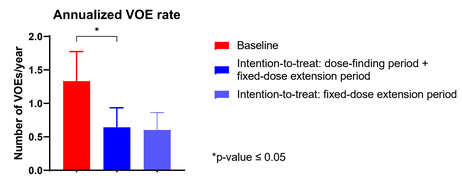
- Baseline characteristics (n=10): median (range) age was 26 years (16-59); 6/10 (60%) were female; 6/10 (60%) used hydroxyurea; 8/10 (80%) HbSS, 1/10 (10%) HbS/β^0, and 1/10 (10%) HbS/β^+
- Safety analysis showed mostly mild treatment-emergent adverse events, most commonly (n>2 subjects): transaminase 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 (lost to follow-up),[1] one non-treatment-related SAE occurred in the FDEP in a subject who died of massive pulmonary embolism due to COVID-19.
- Importantly, sustained improvement in Hb level was seen (mean increase: 1.1 ± 0.7 g/dL; p=0.0014), which was accompanied by decreases in markers of hemolysis in the nine subjects who continued treatment with mitapivat 50 mg twice daily (n=2) or 100 mg twice daily (n=7) in the FDEP (**Table 1**).
- The ATP/2,3-DPG ratio and Hb-oxygen affinity significantly increased, and RBC sickling (Point of Sickling) non-significantly reduced (**Table 1**).
- In addition, the annualized rate of VOEs reduced significantly from a historic baseline of 1.33 ± 1.32 to 0.64 ± 0.87 (p=0.0489) when combining the DFP and FDEP (**Table 1** and **Figure 2**).

Table 1

	Baseline (n=9)	End of the DFP (n=9)	Mean of the FDEP (n=9)	p-value (baseline vs mean of the 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
Point of Sickling, mmHg	40.2 (8.8)*	33.1 (9.7)*	36.2 (6.3)*	0.0802
Elmax, EI	0.450 (0.074)*	0.477 (0.059)*	0.478 (0.061)*	0.0017
Elmin, EI	0.067 (0.048)*	0.116 (0.049)*	0.101 (0.066)*	0.0054
p50, mmHg	24.0 (2.4)	21.5 (1.4)	22.5 (1.8)	0.0032
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

Data are presented as mean (standard deviation). P-values derived from paired sample t-test or Wilcoxon signed-rank test when appropriate. *Due to technical issues of the oxygen gradient ektacytometer, data is missing for n=1 subject, a week 52 visit (n=1 subject) and four visits from week 24 to week 52 in the FDEP (n=2 subjects).

Figure 2



Conclusion

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

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