One-year follow-up of a phase 2 study of mitapivat, an oral pyruvate kinase activator, for the treatment of sickle cell disease

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Purpose

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

Introduction

- Sickle cell disease (SCD) is a hereditary red blood cell (RBC) disorder characterized by sickle hemoglobin (HbS) polymerization upon deoxygenation
- In SCD, 2,3-diphosphoglycerate (2,3-DPG), a glycolytic RBC intermediate, promotes deoxygenation by lowering oxygen affinity of hemoglobin (Hb)
- Mitapivat, an oral allosteric activator of pyruvate kinase (PK), which is a key enzyme in RBC glycolysis generating adenosine triphosphate (ATP) and reducing 2,3-DPG levels, provides a treatment rationale (**Figure 1**)

Methods

The ESTIMATE study is a phase 2, investigator initiated, open-label study.

Major eligibility criteria:

- Subjects ≥16 years with SCD (HbSS, HbS/β^0, HbS/β^+)
- 1-10 vaso-occlusive crises (VOCs) 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).

If eligible, subjects enter the 1-year FDEP after the previously reported 8-week dose-finding period with similar endpoints (**Figure 2**)[1]

- Safety Analysis Set (SAS): all subjects who received ≥1 dose in the FDEP
- Per Protocol Set (PPS): all dosed subjects with Point of Sickling (PoS; oxygen gradient ektacytometry) and Hb assessments at D0 and W52
- Post-hoc analysis: the PPS without visits at which the subject was found to be study drug non-compliant 7 days before (<80% of pills taken).

Figure 1. Effects of mitapivat-mediated PK activation in SCD[1]

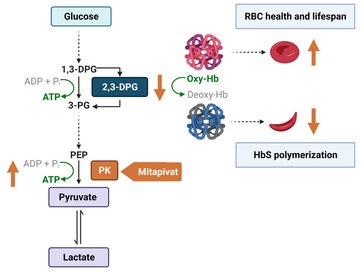

Figure 2. Study schema of the ESTIMATE study

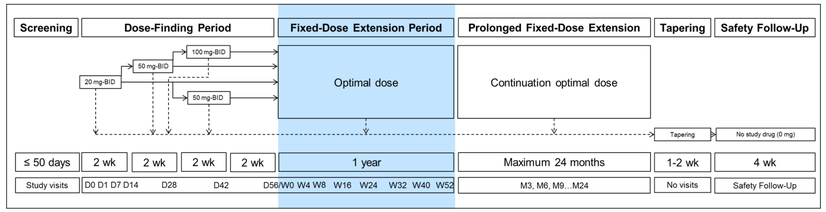

Table 1. Mean changes in Hb level, parameters of hemolysis, sickling tendency, biochemical parameters and markers of clinical complication rate from baseline to the mean of scheduled visits in the FDEP of subjects with SCD treated with mitapivat (n=6)

Parameter (unit)	Baseline	FDEP	p-value*
Hb (g/dL)	9.4 ± 0.9	10.5 ± 1.1	0.035
ARC (10^9/L)	251 ± 103	159 ± 61	0.018
Total bilirubin (mg/dL)	2.5 ± 1.6	1.3 ± 0.7	0.027
LDH (U/L)	400 ± 133	325 ± 89	0.091
PoS (mmHg)†	39.6 ± 9.4	35.3 ± 6.9	0.018
p50 (mmHg)	23.3 ± 2.0	22.0 ± 1.2	0.040
2,3-DPG (mg/gHb)	11.1 ± 0.7	9.1 ± 1.4	0.005
ATP (mg/gHb)	2.8 ± 0.4	3.6 ± 0.4	0.046
ATP/2,3-DPG ratio	0.20 ± 0.10	0.40 ± 0.06	0.002
Annualized VOC rate	1.33 ± 1.17		
PPS		0.67 ± 0.83	0.194
Post-hoc analysis		0.17 ± 0.42	0.052
Annualized SCD-related hospital admission days	6.67 ± 7.94		
PPS		3.87 ± 4.91	0.129
Post-hoc analysis		0.85 ± 2.08	0.069

Data are presented as mean ± standard deviation. *Paired t-tests or Wilcoxon signed-rank tests were used when appropriate. †Missing data from April, 2022 because of a defective device.
Hb, hemoglobin; FDEP, fixed-dose extension period; SCD, sickle cell disease; PPS, Per Protocol Set; ARC, absolute reticulocyte count; LDH, lactate dehydrogenase; PoS, Point of Sickling; p50, oxygen pressure at which Hb is 50% saturated with oxygen; 2,3-DPG, 2,3-diphosphoglycerate; ATP, adenosine triphosphate; VOC, vaso-occlusive crisis.

Results

n=9 subjects were treated with mitapivat in the FDEP (SAS), of which n=6 subjects completed the FDEP (PPS)
(n=1 ongoing, n=1 death due to massive pulmonary embolism (COVID-19), n=1 withdrew consent because of a pregnancy wish)

Baseline characteristics:

- Median (range) age was 30 years (16-59);
- 5/9 (56%) were female;
- 6/9 (67%) used hydroxyurea;
- 7/9 (78%) HbSS, 1/9 (11%) HbS/β^0, and 1/9 (11%) HbS/β^+.

Safety results (SAS):

- One non-treatment related SAE of massive pulmonary embolism due to COVID-19 resulted in death of a subject
- No other SAEs or treatment-emergent AEs (TEAEs) grade ≥3 in the FDEP
- Most common (ongoing or firstly) reported TEAEs were (n>2 subjects): ALT or AST increase (resp. 6/9 (67%) or 5/9 (56%); all grade 1), headache (3/9 (33%); grade 1-2), and lymphocytosis (3/9 (33%); grade 2)

Efficacy results (PPS and post-hoc analysis)

- **Table 1** summarizes mean changes in endpoints from baseline to the mean of scheduled visits in the FDEP
- Mean Hb level significantly increased, accompanied by a significant decrease in markers of hemolysis (reticulocyte count and total bilirubin)
- Mean PoS, p50, 2,3-DPG and ATP levels, and ATP/2,3-DPG ratio all significantly improved
- In total, 4 VOCs occurred in 3 subjects. 3/4 (75%) VOCs occurred following 7 days of documented non-compliance. There was a trend towards decreased annualized VOC rate and SCD-related hospital admission days compared to baseline (2-year historical data)

Conclusion

One-year fixed-dose treatment with mitapivat in subjects with SCD was well tolerated and associated with a general improvement of anemia, reduced hemolysis, and sickling. Hence, these data further strengthen the potential benefit of mitapivat in SCD.

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References: 1. van Dijk MJ, Rab MAE, van Oirschot BA, et al. *Am. J. Hematol*. 2022;97(7):E226–E229.

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