Follow-up results of a phase 2 study assessing the safety and efficacy of mitapivat treatment, an oral pyruvate kinase activator, for up to 60 weeks in subjects with sickle cell disease

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BACKGROUND

- In sickle cell disease (SCD), polymerization of hemoglobin S (HbS) upon deoxygenation results in poorly deformable sickled red blood cells (RBCs) with a shortened lifespan.
- 2,3-Diphosphyglycerate (2,3-DPG), a glycolytic intermediate in RBCs, promotes deoxygenation by lowering hemoglobin (Hb)-oxygen affinity.
- Mitapivat (AG-348) is an oral allosteric activator of pyruvate kinase (PK), a key enzyme in RBC glycolysis generating adenosine triphosphate (ATP) and reducing 2,3-DPG levels (**Figure 1**).

OBJECTIVE

To report follow-up data of the safety and efficacy of mitapivat treatment in subjects with SCD enrolled in the currently ongoing phase 2, investigator initiated, open-label study: the ESTIMATE study (www.trialregister.nl NL8517; EudraCT 2019-003438-18). *Cut-off date: January 1, 2022.*

METHODS

Time periods over which study data were considered are depicted in the study schema (**Figure 2**). The 8-week mitapivat dose finding period is followed by a 52-week fixed dose extension period (FDEP).

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 >6.1 g/dL and ≤11.1 g/dL;
- Stable dose of hydroxyurea, if applicable (≥3 months prior to the first day of study drug);
- Adequate organ function;
- No chronic transfusion (not >4 RBC units during the 12-month period and/or within the 3 months prior to the first day of study drug).

RESULTS

Baseline characteristics: n=9 received mitapivat treatment:

- Median age 22 years (range 16-59);
- 6/9 (67%) female;
- 6/9 (67%) used hydroxyurea;
- 7/9 (78%) HbSS, 1/9 (11%) HbS/β^0, 1/9 (11%) HbS/β^+.

Safety results:

- The most common treatment-emergent AEs (TEAEs; n>2 subjects): ALT or AST increase (both 5/9, 56%; all grade 1), headache (4/9, 44%; grade 1-2);
- n=1 non-treatment related SAE of a urinary tract infection (grade 4), lost to follow-up shortly after first dosing;
- Median treatment duration of remaining n=8 of 38 weeks (range 11-60 weeks);
- No other SAEs or treatment-emergent AEs (TEAEs) grade ≥3.

Efficacy results:

- **Table 1** summarizes mean changes in primary and secondary endpoint parameters in the FDEP versus baseline;
- Hb level significantly increased, accompanied by a decrease in markers of hemolysis (absolute reticulocyte count (ARC), total bilirubin, lactate dehydrogenase (LDH)) **(Figure 3A-D)**;
- RBC sickling (point of sickling (PoS), oxygen gradient ektacytometry) and 2,3-DPG level decreased, and Hb-oxygen affinity (p50, Hemox Analyzer) as well as ATP/2,3-DPG ratio significantly improved **(Figure 3E-H)**;
- Mean annual VOC rate and SCD-related hospital admission days in the 2 years prior to starting study treatment were, respectively, 1.5±1.3 and 5.9±7.1 days, and reduced to 0.5±0.7 and 1.6±3.1 days when weighting cases by follow-up duration (p=0.021 and p=0.134, respectively).

CONCLUSIONS

- Treatment with mitapivat for up to 60 weeks in subjects with SCD showed no treatment related TEAEs grade ≥3.
- Improvements in anemia, markers of hemolysis, Hb-oxygen affinity, 2,3-DPG level and ATP/2,3-DPG ratio were seen.
- Preliminary data on VOC rate and SCD-related hospital admission days showed beneficial effects.

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

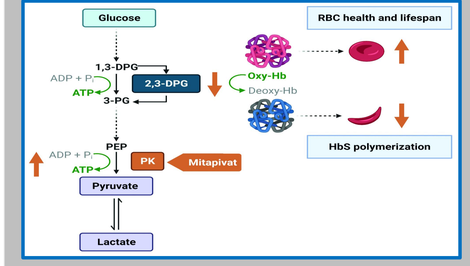


Figure 2. Study schema of the ESTIMATE study

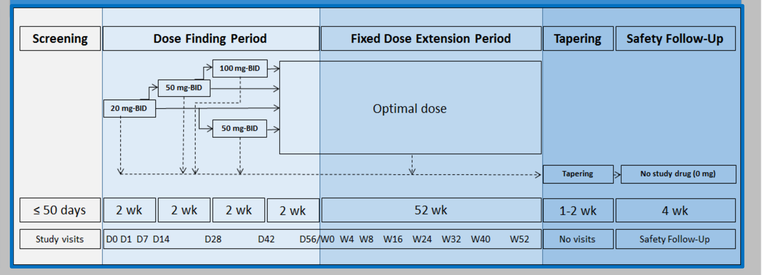
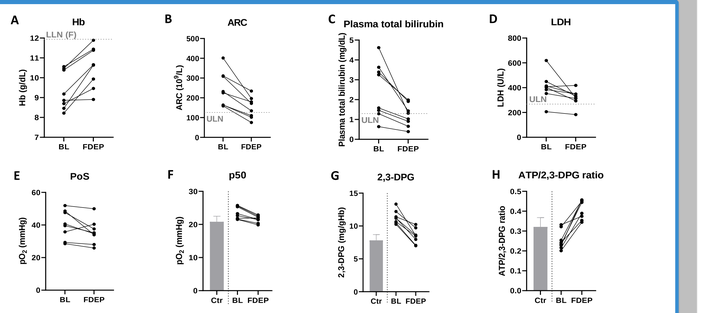


Table 1. Mean changes in Hb, parameters of hemolysis, sickling tendency, and biochemical parameters in the FDEP compared to baseline of patients with SCD treated with mitapivat (n=8)

Parameter (unit)	Baseline	FDEP	p-value*
Hb (g/dL)	9.4 ± 1.0	10.5 ± 1.0	0.001
ARC (10^9/L)	246 ± 88	150 ± 54	0.001
Total bilirubin (mg/dL)	2.5 ± 1.4	1.2 ± 0.6	0.010
LDH (U/L)	404 ± 114	320 ± 67	0.017
PoS (mmHg)	40.2 ± 8.8	35.7 ± 7.5	0.065
p50 (mmHg)	23.4 ± 1.8	21.6 ± 1.0	0.002
2,3-DPG (mg/gHb)	11.3 ± 1.0	8.6 ± 1.3	<0.001
ATP (mg/gHb)	2.9 ± 0.7	3.4 ± 0.3	0.161
ATP/2,3-DPG ratio	0.25 ± 0.05	0.41 ± 0.05	0.002

Data are presented as mean ± standard deviation. *Paired t-tests or Wilcoxon signed-rank tests were used when appropriate. FDEP, fixed dose extension period; SCD, sickle cell disease; Hb, hemoglobin; 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-diphosphyglycerate; ATP, adenosine triphosphate

Figure 3. Improvements of efficacy parameters in the FDEP of mitapivat treatment in patients with SCD (n=8)



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