Safety and Efficacy of Mitapivat (AG-348), an Oral Activator of Pyruvate Kinase R, in Subjects with Sickle Cell Disease: A Phase 2, Open-Label Study (ESTIMATE)

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BACKGROUND

- In sickle cell disease (SCD), hemoglobin S (HbS) polymerizes upon deoxygenation, causing red blood cell (RBC) sickling, hemolysis and vaso-occlusion.
- RBC sickling is associated with increased levels of 2,3-diphosphoglycerate (2,3-DPG) which lowers the oxygen affinity of hemoglobin (Hb), thereby promoting deoxygenation and polymerization of HbS.[2]
- Pyruvate kinase (PK)-R is a key enzyme in RBC metabolism catalyzing the last step of glycolysis (**Figure 1**).[1]
- Mitapivat (AG-348) is an oral, small molecule allosteric activator of PK-R.[3]
- Ex vivo treatment of SCD RBCs with mitapivat improved PK activity and thermostability, ATP/2,3-DPG ratio and markers of oxygen affinity (p50) and RBC sickling (e.g. point of sickling (PoS) as determined by oxygen gradient ektacytometry).[4]

OBJECTIVE

- To assess safety and provide proof of concept of the efficacy of mitapivat in subjects with SCD (ESTIMATE study, NTR NL8517).

METHODS

The 8-week dose finding period of this Dutch phase 2, open label, monocenter pilot study is depicted in the study schema (**Figure 2**).

Major inclusion criteria:

- Subjects ≥16 years with SCD (HbSS, HbS/β0, HbS/β+) and prior SCD-related complications;
- Hb >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.

Major exclusion criteria:

- Chronic transfusion (>4 RBC units during the 12-month period and/or within the 3 months prior to the first day of study drug).

Figure 1. Glycolysis

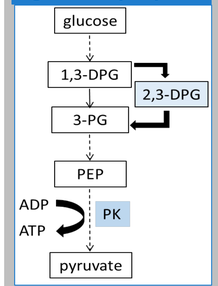


Figure 2. Schema of the ESTIMATE study

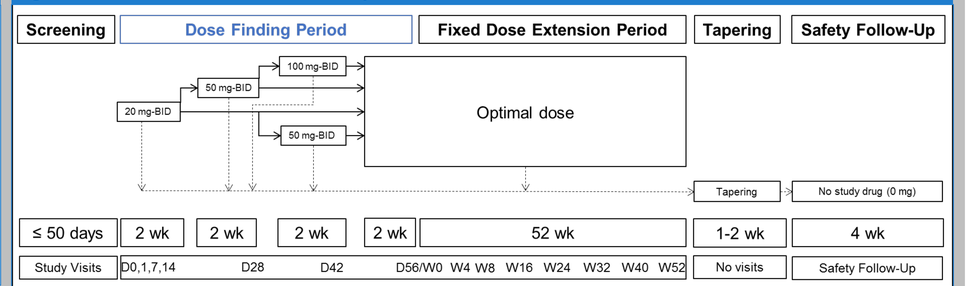
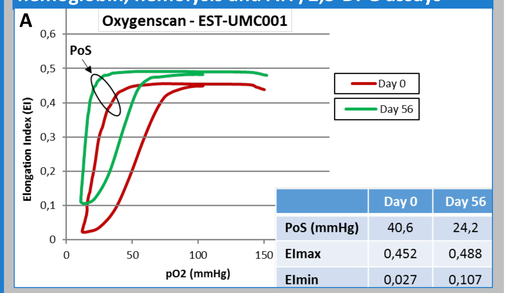


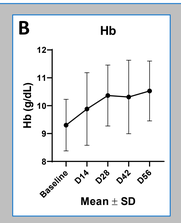
Table 1. Mean response in sickling, hemoglobin, hemolysis, biochemical and renal parameters at treatment day 56 compared to baseline in the dose finding period (n=6)

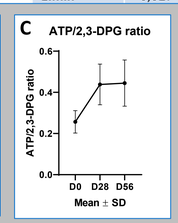
	Baseline	Day 56	
Sickling parameters			p-value*
PoS (mmHg)	40.3 (7.3)	31.3 (6.0)	0.009
p50 (mmHg)	22.7 (1.5)	20.9 (1.3)	0.009
Hemolysis parameters			
Hb (g/dL)	9.3 (0.9)	10.5 (1.1)	0.004
ARC (10^9/L)	274 (84)	168 (34)	0.005
RETC (%)	9.2 (1.5)	4.9 (0.8)	0.001
Bilirubin, total (mg/dL)	2.43 (1.09)	1.11 (0.58)	0.004
LDH (U/L)	402 (32)	312 (47)	0.007
Biochemical parameters			
2,3-DPG (10^3 µg/gHb)	11.5 (1.1)	8.1 (1.3)	0.001
ATP (10^3 µg/gHb)	3.0 (0.9)	3.5 (0.6)	0.173
ATP/2,3-DPG ratio	0.26 (0.05)	0.45 (0.11)	0.003
Renal parameter†			
ACR (mg/g)‡	35.0 (23.7)	18.2 (17.9)	0.010

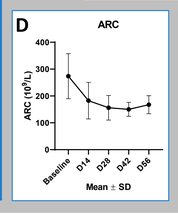
Data are presented as mean (standard deviation) for baseline and treatment day 56 results (n=6).
*Paired t-tests or Wilcoxon signed-rank tests are used when appropriate.
†Additional biomarkers were measured but did not reach statistical significance and will be followed longer-term.
‡Results based on n=5. In one subject, albumin-to-creatinine ratio could not be calculated because of too high total protein, with a protein-to-creatinine ratio of 865 mg/g at baseline and 824 mg/g at day 56 (reduction of 41 mg/g).
PoS point of sickling; p50 oxygen pressure at an oxygen saturation of 50%; Hb hemoglobin; ARC absolute reticulocyte count; RETC reticulocytes; LDH lactate dehydrogenase; 2,3-DPG 2,3-diphosphyglycerate; ATP adenosine triphosphate; CRP C-reactive protein; NT-proBNP N-terminal pro-brain natriuretic peptide; VWF Von Willebrand Factor; HbCO carboxyhemoglobin; ACR, albumin-to-creatinine ratio.

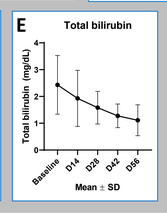
Figure 3A-F. Effects of mitapivat on sickling, hemoglobin, hemolysis and ATP/2,3-DPG assays

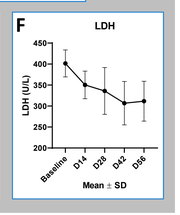












RESULTS

- 6 subjects have been enrolled as of September 2020 and completed the 8-week dose finding period on mitapivat, all reaching 100 mg BID dosing.
- Baseline characteristics were: 5/6 (83.3%) HbSS and 1/6 (16.7%) HbS/β0; median age of 36 years (range 20-59); 4/6 (66.7%) were female and 5/6 (83.3%) were on stable-dose hydroxyurea.
- Sickling, hemoglobin, hemolysis, biochemical and renal parameters all improved (**Table 1; Figure 3 A-F**).
- All 6 subjects had improvements in PoS and 5/6 subjects (83.3%) achieved a Hb increase of ≥1 g/dL.
- No serious adverse events occurred.
- Adverse events were mild (all Grade 1) and mostly transient with the most common (occurring in more than 1 subject): transaminase increase, gastrointestinal disorders and headache (all in 3 subjects [50.0%]).
- One VOC occurred without hospital admission and did not require dose reduction or discontinuation.

CONCLUSION

- Mitapivat, an oral PK-R activator, demonstrated an adequate safety profile during the 8-week dose finding period in subjects with SCD.
- Mitapivat increased Hb and decreased hemolysis and sickling parameters.
- The observed changes in 2,3-DPG and ATP levels are consistent with the proposed mechanism of the drug.
- Early improvements in albumin-to-creatinine ratio were observed.
- Follow-up data of this ongoing study will be reported at a later stage.

Acknowledgements
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Disclosures
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