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# Three-year safety, efficacy, and renal outcomes of mitapivat treatment in sickle cell disease: results from the phase 2 open-label study

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**Three-year safety, efficacy, and renal outcomes of mitapivat treatment in sickle cell disease: results from the phase 2 open-label study**

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Geoffrey Z.L. Kuppens, Myrthe J. van Dijk, Cleo Derichs, Joline Saes, and Eduard J. van Beers performed the research and acquired data.
Maria Armila D Ruiz and Santosh L. Saraf advised on and analyzed the renal samples.
Geoffrey Z.L. Kuppens and Eduard J. van Beers analyzed and interpreted data.
Geoffrey Z.L. Kuppens wrote the manuscript; Marije Bartels, Santosh L. Saraf and Eduard J. van Beers reviewed and revised the manuscript.
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**Letter to editor**

Over the past decade, the number of people living with sickle cell disease (SCD) worldwide has increased and reached an estimated 7.74 million in 2021. This increase has been accompanied by a rise in the disease burden related to SCD.[1] HbS polymerizes upon deoxygenation, initially reversible but becoming irreversible with repeated sickling, ultimately leading to rigidity, hemolysis and vaso-occlusion. This can lead to chronic hemolysis, vaso-occlusive events (VOEs), and progressive multiorgan damage, and resulting in reduced life expectancy. [2-5]

Mitapivat, an oral allosteric activator of pyruvate kinase (PK), a key enzyme in RBC glycolysis, that generates adenosine triphosphate (ATP) and reduces 2,3-diphosphoglycerate (2,3-DPG) levels, has recently emerged as a potential treatment. SCD is characterized by metabolic dysregulation, particularly within red blood cells. A hallmark of this disturbance is a reduced ATP/2,3-DPG ratio which contributes to impaired energy homeostasis and promotes Hb deoxygenation and sickling of red cells.[6-8] Early clinical trials have demonstrated that mitapivat increases the ATP/2,3-DPG ratio, raises hemoglobin (Hb), and decreases hemolysis in patients with SCD.[9-11]

Of the organs affected by SCD, the kidneys are particularly susceptible to damage, often resulting in the early onset of progressive sickle cell nephropathy affecting up to 28-42% of the patients and considered to be the cause of death in 16.4% of patients with SCD. Sickle cell nephropathy can be assessed by evaluating renal markers such as Hb and nephrin, which indicate glomerular injury [12, 13]; β-N-acetylglucosaminidase (NAG) and kidney injury molecule-1 (KIM-1), which reflect proximal tubular dysfunction.[14] These markers are elevated in patients with SCD before overt clinical sickle cell nephropathy becomes apparent.

We previously reported one-year follow-up data from the investigator-initiated phase 2 ESTIMATE trial showing sustained hematologic improvement and reduced VOE frequency in nine patients with SCD treated with mitapivat. Here, we provide the first three-year results, extending observations into the prolonged fixed-dose extension period (PFDEP) and including exploratory renal outcomes.

The ESTIMATE study (EUCT 2024-515569-32-00) is an open-label, single-center phase 2 trial conducted at the University Medical Center Utrecht. Approval was obtained from the Medical Research Ethics Committee Utrecht), and all participants provided written informed consent. The study was conducted according to the Declaration of Helsinki, Good Clinical Practice, and GDPR regulations.

Eligible participants were aged ≥ 16 years with genotypes HbSS, HbS/$\beta^0$, or HbS/$\beta^+$; Hb levels 4.0–11.1 g/dL; and one to ten VOEs per year or another recent SCD-related complication. Patients were not receiving chronic transfusions. After an eight-week dose-finding phase (20–100 mg twice daily), responders entered a one-year fixed-dose extension period (FDEP) followed by a two-year PFDEP. Participants received dose adjustments as clinically indicated, with monitoring according to Good Clinical Practice and the Declaration of Helsinki. Normality was assessed visually (QQ-plots) for each variable and using the Shapiro–Wilk test, data are presented as mean ± SD or median [IQR] according to distribution. Non-parametric tests were applied when appropriate.

Ten patients received at least one dose of mitapivat; nine completed the initial phase, and seven entered the PFDEP. Two discontinued during the PFDEP (one self-discontinued after three months and one withdrawn for non-compliance), leaving five patients who completed three years of therapy. Another two patients discontinued earlier, one because of pregnancy planning and one due to COVID-19–related pulmonary embolism during the first-year extension. At the time of this report, five participants continue long-term treatment in the ongoing extension phase. See Table 1 for baseline characteristics.

Over the full study duration, mitapivat demonstrated a favorable safety profile. All participants experienced at least one treatment-emergent adverse event (TEAE), the vast majority being mild (grade 1) and transient. During the two-year PFDEP, 22 TEAEs occurred across seven participants; 86% were grade 1, 4.5% grade 2, and 9.1% grade 3. The most frequent findings were asymptomatic alanine aminotransferase (ALT) and aspartate aminotransferase (AST) elevations, each observed in three participants. The mean transaminase values remained within normal limits, without any trend toward cumulative hepatotoxicity. No dose reductions or permanent discontinuations were required because of liver enzyme changes, and all elevations resolved spontaneously.

Two grade 3 events were reported, infectious lumbosacral radiculitis and pneumonia with small subsegmental pulmonary emboli, both in participants with recent non-compliance. No grade 4 or 5 events occurred during the PFDEP, and no patient discontinued treatment for safety reasons. Details are shown in Table 2. The single fatal event in the entire study, a massive COVID-19–related pulmonary embolism, occurred during the first-year extension while the participant was on mitapivat and was deemed unrelated by the investigator.

Efficacy outcomes remained consistent with earlier findings. Across all treated participants, mean Hb increased from 8.8 ± 1.8 to 9.6 ± 1.7 g/dL after three years ($p = 0.01$), while absolute reticulocyte count decreased from 235 ± 88 to 170 ± 81 × $10^9$/L ($p < 0.01$). Total bilirubin declined from 2.6 ± 1.3 to 1.4 ± 0.7 mg/dL ($p = 0.02$). Lactate dehydrogenase (LDH) decreased numerically but not significantly (500 to 421 U/L; $p = 0.08$). These sustained hematologic effects mirror the one-year data and support a long-term disease-modifying impact of PK activation. (See Supplementary Figure 1 for mean laboratory results over time)

The annualized VOE rate fell from 1.33 ± 1.32 events per year before enrollment to 0.60 ± 0.78 during the one-year FDEP and 0.14 ± 0.24 during the PFDEP ($p = 0.07$). The two VOEs recorded in the PFDEP both occurred in non-compliant participants, suggesting that treatment adherence critically influences efficacy. Likewise, SCD-related hospitalization days declined from 5.5 ± 6.6 to 2.1 ± 2.3 days per year ($p=0.25$). Intention to treat laboratory and clinical endpoints are shown in Table 3. Although not statistically significant owing to the small sample size, these reductions are clinically relevant and aligned with the improvements in hemolysis and Hb. The reduction in VOE frequency may in part reflect closer clinical monitoring during the study; however, events were prospectively captured and independently adjudicated.

Exploratory renal analyses were performed on five patients with paired urine samples collected at baseline and after one or two years of therapy. Urinary albumin-to-creatinine ratio (UACR) was assessed in a single spot urine sample at baseline and follow-up. Renal markers were normalized to urinary creatinine. Glomerular injury markers showed marked proportional declines: nephrin/creatinine decreased by 50.7%, and urinary hemoglobin-to-creatinine ratio by 99.8%. In contrast, the tubular marker KIM-1/creatinine declined by 92.0%, while β-N-acetylglucosaminidase (NAG)/creatinine increased by 40.2%. These opposite trends in glomerular and tubular indicators may reflect distinct pathophysiological responses to improved erythrocyte energetics. UACR categories remained stable in all five subjects, with Subjects 1 and 3 remaining in the moderately elevated range and Subjects 2, 9, and 10 remaining within the normoalbuminuria range. For eGFR, all patients remained > 90 mL/min/1.73 $m^2$ and none showed a decline below this threshold at last follow-up, suggesting absence of progressive renal impairment during treatment. The observed nephrin and hemoglobinuria declines, though underpowered for statistical testing, are consistent with reduced glomerular stress and deserve confirmation in larger cohorts. (See Supplementary Figure 2 for renal outcomes)

Other exploratory safety endpoints included bone mineral density (BMD) and sex hormones, measured annually by DEXA and immunoassay. No significant changes were seen in testosterone, estrone, or estradiol levels over three years, and BMD scores remained stable, with a slight upward trend in hip Z-scores. These findings suggest that long-term PK activation does not adversely affect bone or endocrine homeostasis.

The per-protocol analysis, limited to patients with ≥ 80% adherence, confirmed sustained hematologic benefit, particularly in Hb. In the strict per-protocol subset excluding non-compliant participants, both the annualized VOE rate and hospitalization days were zero during the PFDEP. The concordance between biochemical and clinical improvements further underscores the importance of continuous dosing for optimal response.

Overall, these data show that mitapivat is well tolerated and produces durable improvement in hemolysis and anemia in SCD over three years of treatment. The safety profile remained stable without new or cumulative toxicity, and the only severe events were unrelated or occurred in non-adherent participants. The consistent hematologic gains, combined with a striking reduction in VOEs and hospitalization days, highlight mitapivat's potential as a long-term disease-modifying therapy targeting RBC metabolism.

This study also contributes novel exploratory insights into renal outcomes in SCD. While limited by small sample size, the reduction in glomerular injury markers such as nephrin/creatinine and hemoglobinuria may indicate early renal protection through PK activation. Preclinical studies have shown that PKM2 activation can reduce fibrosis and iron deposition in murine SCD nephropathy, supporting the plausibility of this mechanism. Although tubular markers showed mixed trends, the overall pattern does not suggest worsening renal injury.

We acknowledge the primary limitation of this study, the small cohort inherent to a first-in-class, investigator-initiated trial in a rare disease setting. The resulting lack of statistical power restricts inferential conclusions. Nevertheless, the longitudinal follow-up of nearly 1000 patient-weeks provides valuable real-world insight into chronic PK activation. Given the consistency of effects across all treated participants and the alignment with earlier phase 1–2 findings, these results are meaningful for clinical translation.

In conclusion, three years of mitapivat therapy in patients with SCD demonstrated sustained hematologic and clinical benefits, a reassuring long-term safety profile, and preliminary evidence suggesting renal benefit. These findings strengthen the rationale for larger, controlled trials assessing PK activation as a metabolic disease-modifying strategy in sickle cell disease.

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**Tables:**

**Table 1**
**Baseline characteristics of patients with sickle cell disease treated with mitapivat.**

| | **Dose-finding period (N = 10)** | **Fixed-dose extension period (N=9)** | **Prolonged fixed-dose extension period (N=7)** |
|---|---|---|---|
| Age in y, median (range) | 26 (16-59) | 30 (16-59) | 24 (18-61) |
| Female, n (%) | 6 (60) | 5 (56) | 4 (57) |
| SCD-genotype, n (%) | | | |
| HbSS | 8 (80) | 7 (78) | 3 (60) |
| HbS/$\beta^0$-thalassemia | 1 (10) | 1 (11) | 1 (14) |
| HbS/$\beta^+$-thalassemia | 1 (10) | 1 (11) | 1 (14) |
| Concomitant hydroxyurea therapy, n (%) | 6 (60) | 6 (67) | 4 (57) |

SCD=sickle cell disease

**Table 2: TEAEs of patients with sickle cell disease treated with mitapivat (N=7): safety analysis set of prolonged fixed-dose extension period**

| Adverse event | **Grade 1** | **Grade 2** | **Grade 3** | **Grade 4** | **Grade 5** |
|---|---|---|---|---|---|
| Total | 19(86.4%) | 1(4.5%) | 2(9.1%) | 0 | 0 |
| Seborrheic keratosis | 1 (4.5%) | | | | |
| Aspartate aminotransferase increased | 4(18.2%) | | | | |
| Alanine aminotransferase increased | 5(22.7%) | | | | |
| Thrombocytosis | 1(4.5%) | | | | |
| Conjunctivitis | 1(4.5%) | | | | |
| Headache | 2(9.1%) | | | | |
| Pain in hip joint | 1(4.5%) | | | | |
| Gastro-intestinal discomfort | 1(4.5%) | | | | |
| Palpitations | 1(4.5%) | | | | |
| Insomnia | 1(4.5%) | | | | |
| Nausea and vomitus | 1(4.5%) | | | | |
| Dyspnea | | 1(4.5%) | | | |
| Lumbosacral radiculitis | | | 1(4.5%) | | |
| Pneumonia with pulmonary emboli | | | 1(4.5%) | | |

Data are n (%). Patients with multiple AEs within a preferred term were counted only once in that preferred term. For participants with multiple occurrences of an AE, the AE with the worst Common Terminology Criteria for Adverse Events grade is included in the summary. TEAE= treatment emergent adverse event

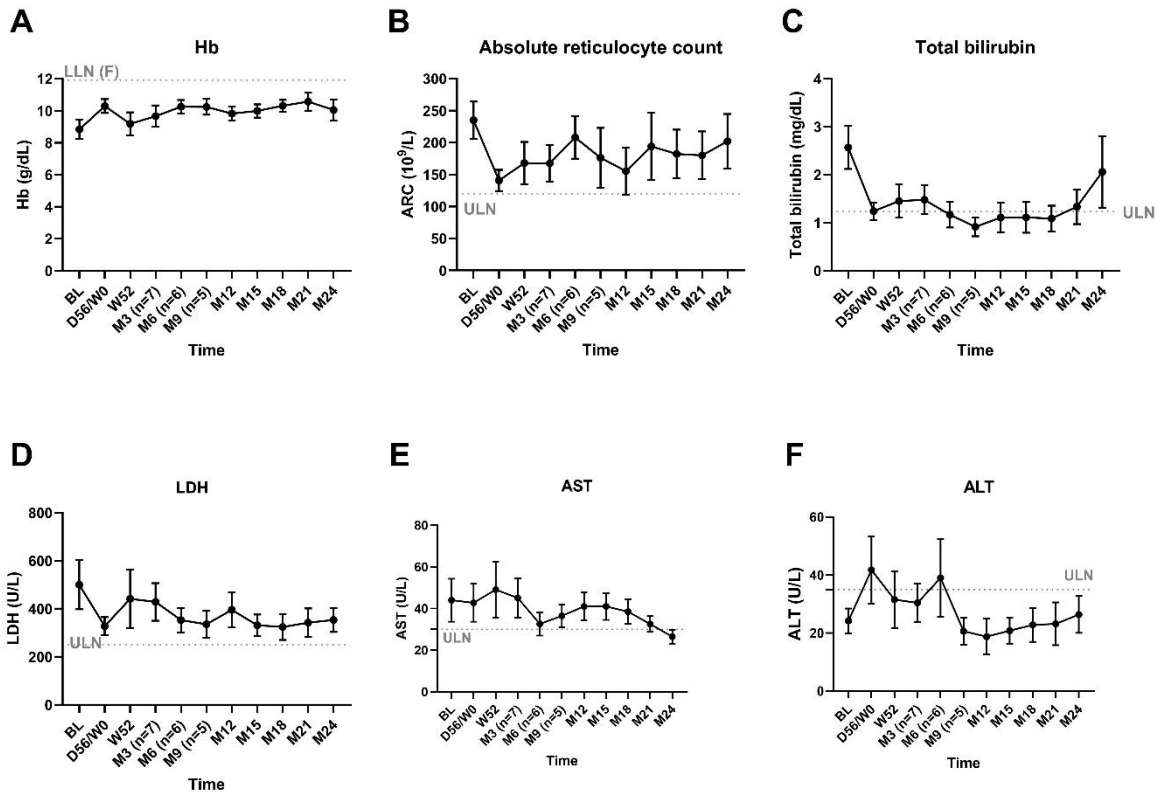
**Table 3: Intention to treat analysis**

| | Baseline (N=9) | Mean of the FDEP (N=9) | Mean of the PFDEP (N=7) | *P* (baseline vs PFDEP) (N=7) |
|---|---|---|---|---|
| **Hb level and markers of hemolysis** | | | | |
| Hb, g/dL | 8.8 (1.8) | 9.9 (1.8) | 9.6 (1.7) | 0.01 |
| ARC, $10^9$ per L | 235 (88) | 156 (50) | 170 (81) | <0.01 |
| Total bilirubin, mg/dL | 2.6 (1.3) | 1.4 (0.7) | 1.4 (0.7) | 0.02 |
| LDH, U/L | 500 (307) | 398 (216) | 421 (204) | 0.08 |
| **Biochemical parameters** | | | | |
| AST, U/L | 44 (31) | 47 (30) | 36 (27) | 0.16 |
| ALT, U/L | 25 (13) | 36 (21) | 26 (13) | 0.11 |
| **Surrogate markers** | | | | |
| Erythropoietin IU/L * | 181 (240) | 156 (226) | 164 (166) | 0.81 |
| NT-proBNP, pg/ml * | 342 (792) | 267 (524) | 79 (72) | 1.00 |
| CRP, mg/L | 5.6 (5.1) | 6.9 (6.7) | 8.7 (3.3) | 0.22 |
| LDH/HbCO ratio | 3838 (3554) | 4640 (2420) | 3907 (2689) | 0.84 |
| D-dimer mg/L | 2.8 (3.1) | 4.1 (7.0) | 1.6 (1.5) | 1.00 |
| VWF Antigen, % | 188 (73) | 160 (49) | 189 (71) | 0.85 |
| ACR mg/mmol * | 133 (214) | 170 (327) | 49 (67) | 0.84 |
| **Markers of SCD-related complications** | | | | |
| Annualized VOE Rate | 1.33 (1.32) | 0.60 (0.78) | 0.14 (0.24) | 0.07 |
| Annualized SCD-related hospital admission days* | 5.5 (6.6) | 4.1 (5.6) | 2.1 (3.8) | 0.25 |

Data are presented as mean (standard deviation). P-values are derived from paired sample t-tests or Wilcoxon signed-rank tests, based on participants with complete paired measurements (N=7), comparing baseline values with PFDEP values. Variables marked with * were non-normally distributed and therefore analyzed with the Wilcoxon signed-rank test. FDEP: Fixed Dose Extension Period; PFDEP: Prolonged Fixed Dose Extension Period; Hb: hemoglobin; ARC: absolute reticulocyte count; LDH: lactate dehydrogenase; AST: aspartate aminotransferase; ALT: alanine transaminase; CRP: C-reactive protein; LDH/HbCO: lactate dehydrogenase to carboxyhemoglobin ratio; VWF: von Willebrand factor; ACR: albumin-to-creatinine ratio; VOE: vaso-occlusive event; SCD: sickle cell disease.

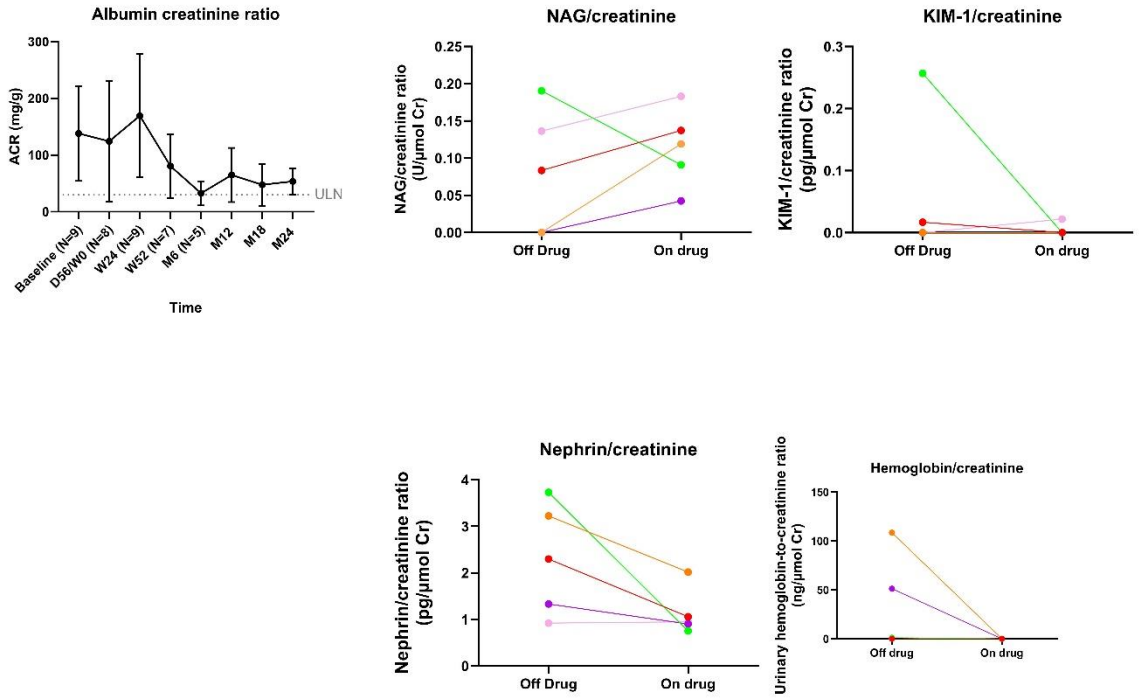
Supplementary Figures:

Supplementary Figure 1




*Supplementary Figure 1: Improvements in laboratory parameters during the three-year study duration. (A) Hemoglobin (Hb) levels over time. B Absolute reticulocyte count (ARC) over time. (C) total bilirubin over time. (D) Lactate dehydrogenase (LDH) over time. (E) Aspartate aminotransferase (AST) over time. (F) Alanine aminotransferase (ALT) over time.*
*BL: Baseline, D: Day, W: Week, M: Month, LLN(F): Lower limit of normal, F: female, ULN: upper limit of normal*

Supplementary Figure 2




*Supplementary Figure 2. Top left figure mean albumin creatinine ratio (ACR) over time. ULN: Upper limit of normal. Ratio of absolute changes in renal biomarkers, corrected for urinary creatinine, comparing baseline values with samples collected either at the end of the FDEP period (year 1) or mid-PFDEP (year 2). NAG =b-N-acetylglucosaminidase, KIM-1=Kidney injury molecule-1, FDEP= Fixed Dose Extension Period until year 1. PFDEP= Prolonged Fixed Dose Extension Period*