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

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Conflict of Interest Disclosure

No disclosures

Background on sickle cell disease

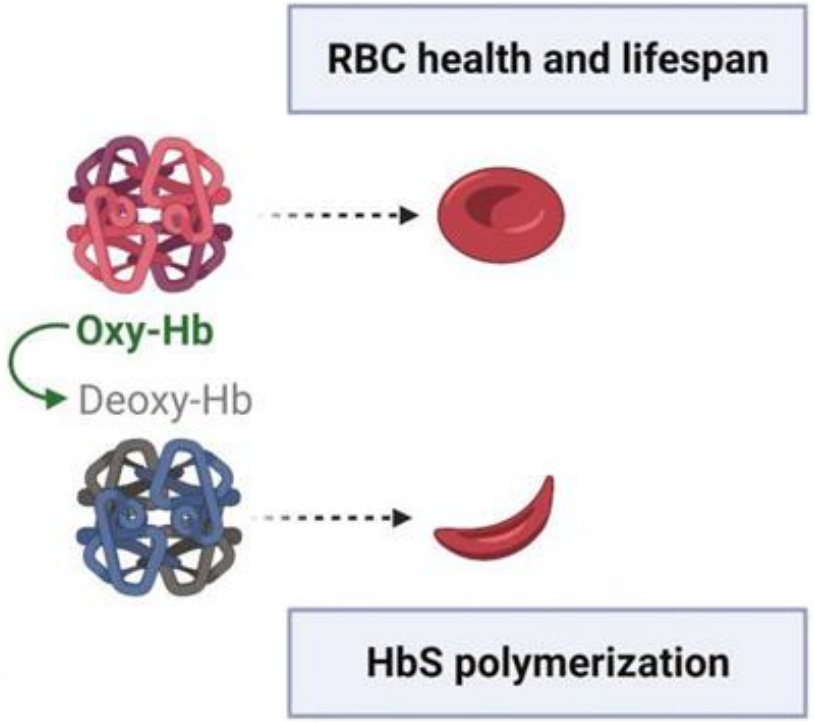


Figure:Van Dijk et al. Am J Hematol. 2022

Background on mitapivat

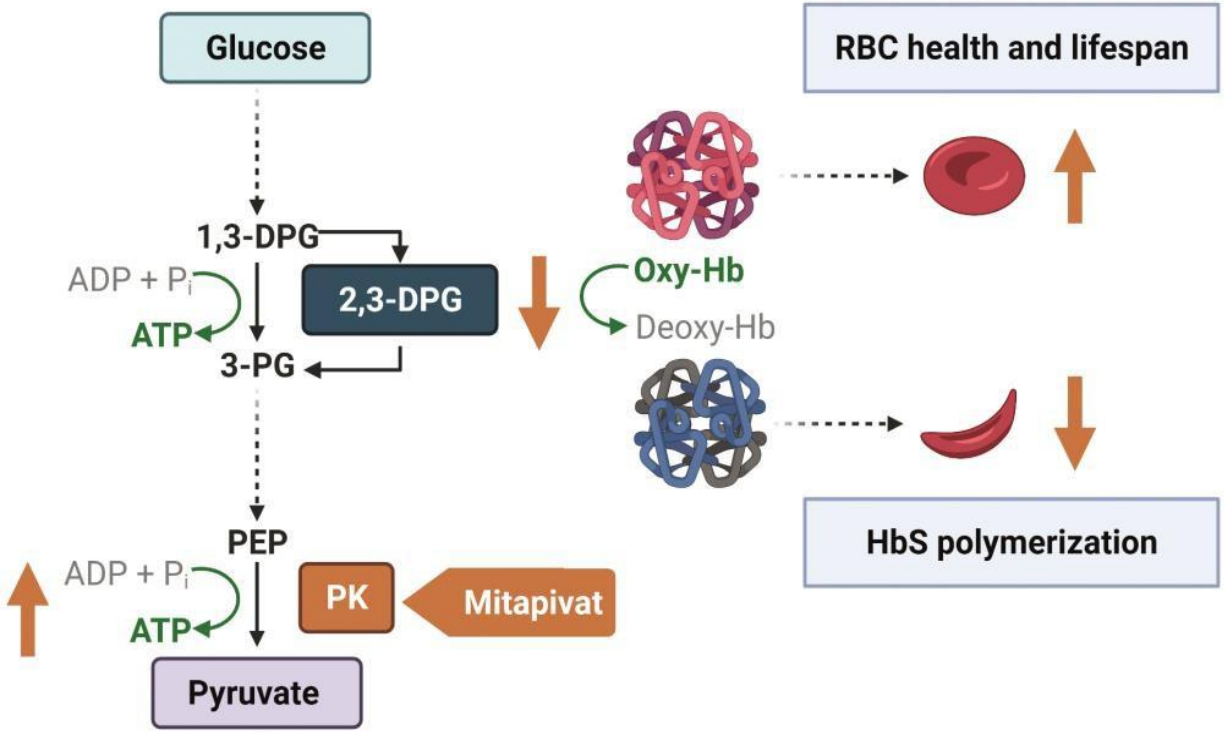


Figure:Van Dijk et al. Am J Hematol. 2022

Study design

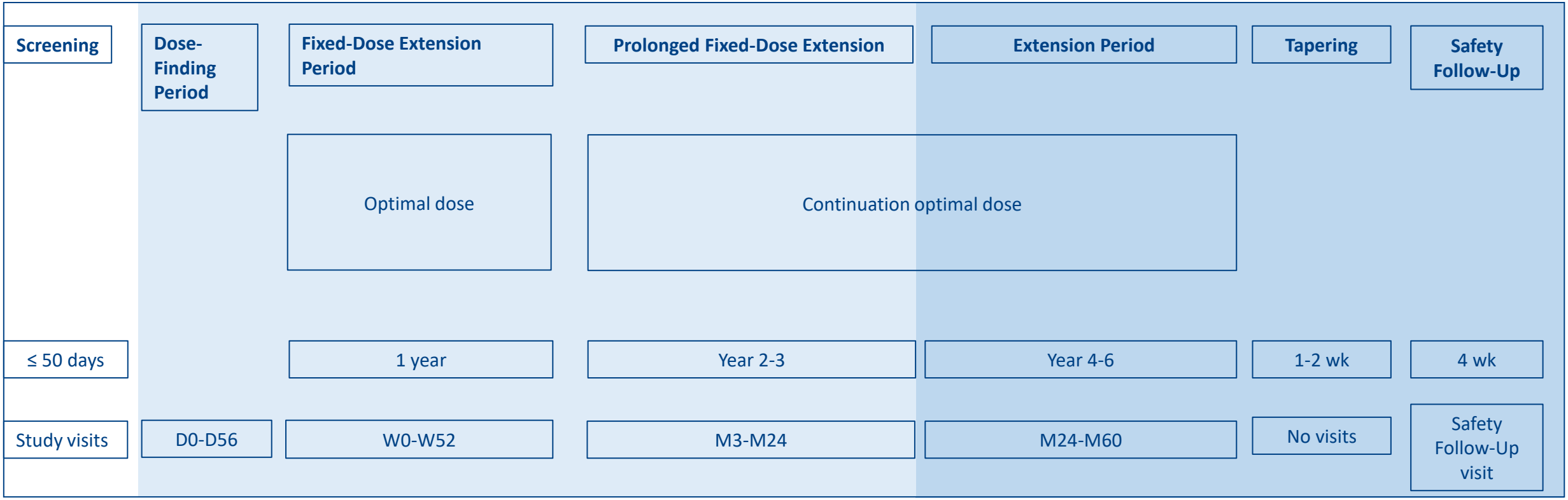
Major Inclusion criteria:
- Patients ≥16 years of age with SCD (HbSS, HbS/β0 or HbS/β+ thalassemia);
- 1-10 vaso-occlusive events (VOEs) in the previous year and/or previous SCD-related complications;
- Hb >6.1 g/dL and ≤11.1 g/dL;
- For patients taking hydroxyurea: stable dose ≥3 months;
- No chronic transfusions.

Primary endpoints:
- Safety: Serious adverse events
- Efficacy on RBC sickling

Secondary endpoints:
- Changes in hematological parameters

Exploratory endpoint:
- Urinary parameters related to renal outcome
- Sex hormones, surrogate lab markers of organ damage and DEXA scans

Study timeline



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Baseline characteristics

	At start Dose-finding (N = 10)	At start Prolonged fixed-dose extension (N=7)
Age in y, median (range)	26 (16-59)	24 (18-61)
Female, N (%)	6 (60)	4 (57)
SCD-genotype, N (%)		
HbSS	8 (80)	5 (71)
HbS/β^0-thalassemia	1 (10)	1 (14)
HbS/β^+-thalassemia	1 (10)	1 (14)
Hydroxyurea, N (%)	6 (60)	4 (57)

Results – Safety: Until year 1

	Grade 1	Grade 2	Grade 4	Grade 5
Frequency of adverse events (by grade)				
ALT increase	7			
AST increase	6			
Headache	3	1		
Dyspepsia	2			
Abdominal pain	2			
Insomnia	2			
Diarrhea	2			
Lymphocyte count increased		2		
Urinary tract infection			1	
Pulmonary embolism due to COVID-19				1
Total number of events per grade	34	8	1	1
(% of total events)	(77%)	(18%)	(2%)	(2%)

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Results – Safety (Year 2-3)

	Grade 1	Grade 2	Grade 3
Frequency of adverse events (by grade)			
ALT increase	5		
AST increase	4		
Headache	2		
Lumbosacral radiculitis			1
Pneumonia with subsegmental pulmonary emboli			1
Total number of events per grade	19	1	2
(% of total events)	(86.4%)	(4.5%)	(9.1%)

Results – Safety & Efficacy

Parameter, unit	Baseline (N=9)	Fixed-dose extension (N=9)	Prolonged Fixed-dose extension (N=7)	P value (baseline vs PFDEP) (N=7)
Hb, g/dL	8.8 (1.8)	9.9 (1.8)	9.6 (1.7)	**0.008**
Absolute reticulocyte count, 10^9 per L	235 (88)	156 (50)	177(78)	**0.005**
Reticulocytes (%)	8.2 (2.3)	5.0 (1.4)	5.7(2.2)	**0.001**
Total bilirubin, mg/dL	2.6 (1.3)	1.4 (0.7)	1.4(0.66)	**0.017**
LDH, U/L	500(307)	401 (224)	421(204)	0.08
AST, U/L	44(33)	47(30)	36(27)	0.16
ALT, U/L	25(13)	36(21)	26(13)	0.09

This table shows mean values of the intention to treat analysis. Data are presented as mean (standard deviation). P-values are derived from paired sample t-test or Wilcoxon rank test, when appropriate, to compare baseline values with the mean values during the prolonged fixed-dose extension period. ARC: absolute reticulocyte count. AST: Aspartate aminotransferase ALT: Alanine aminotransferase

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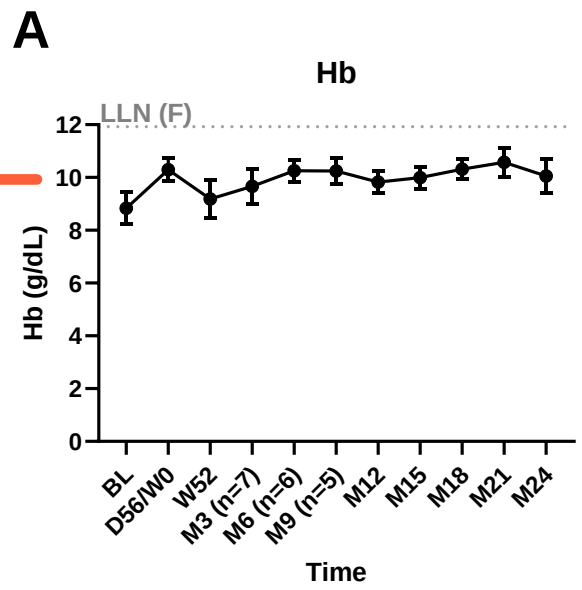
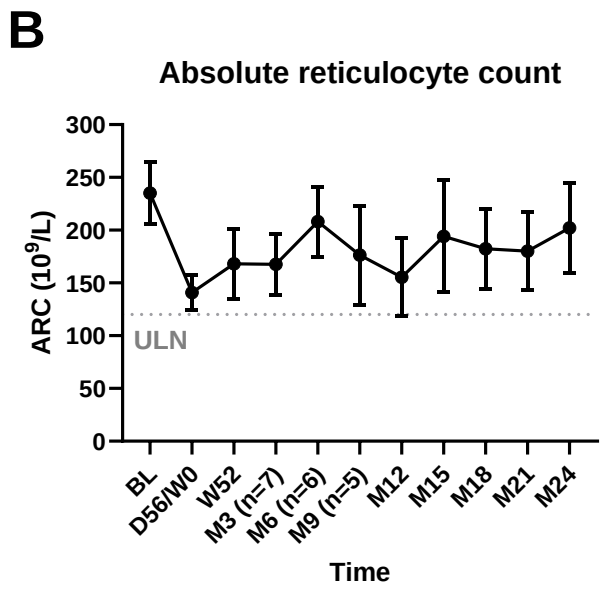
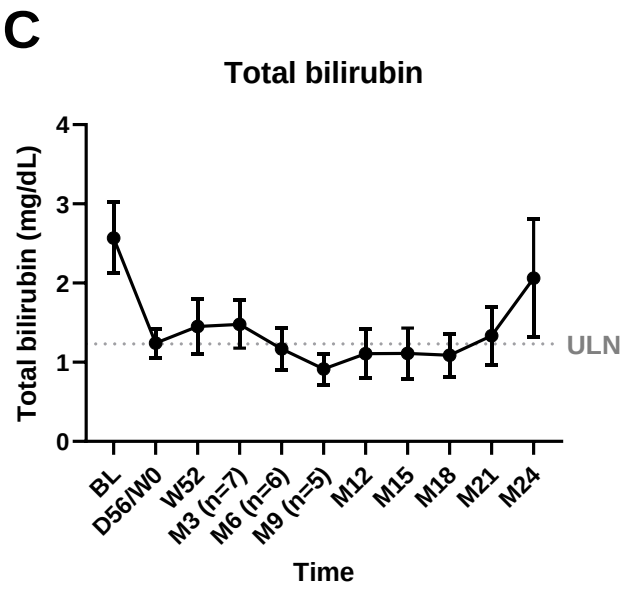
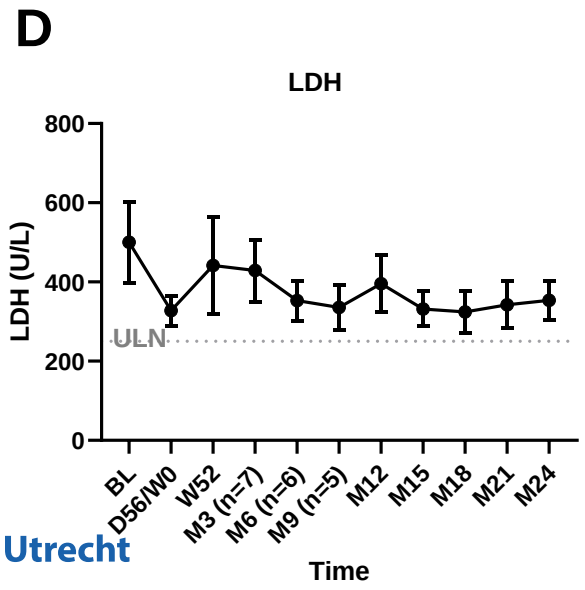
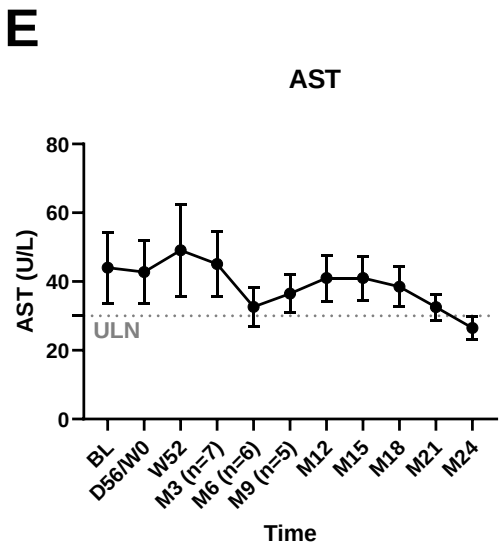


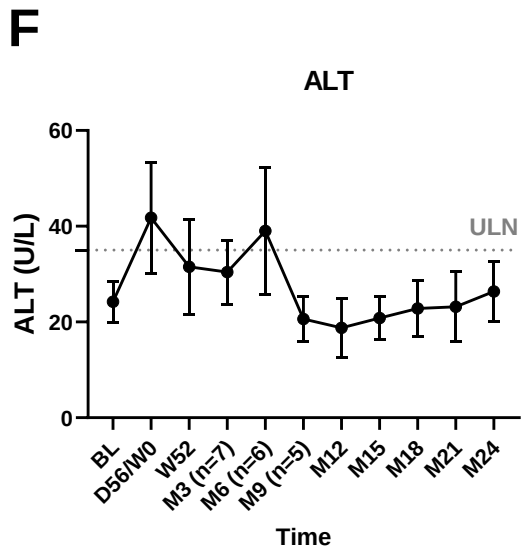




LLN: Lower limit of normal
ULN: Upper limit of normal







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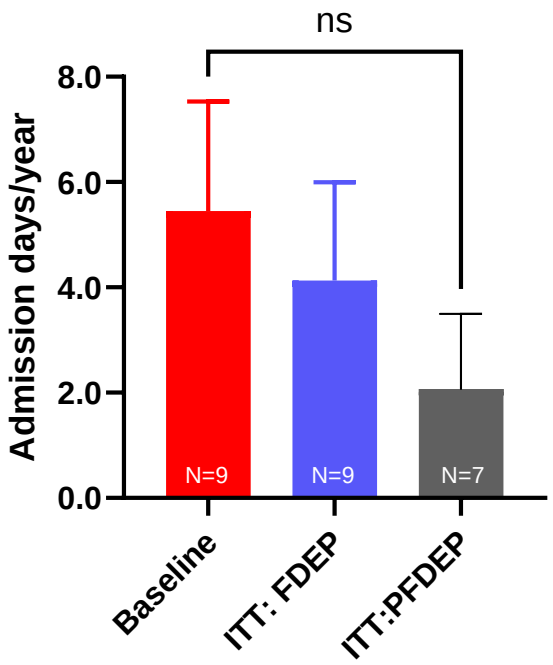
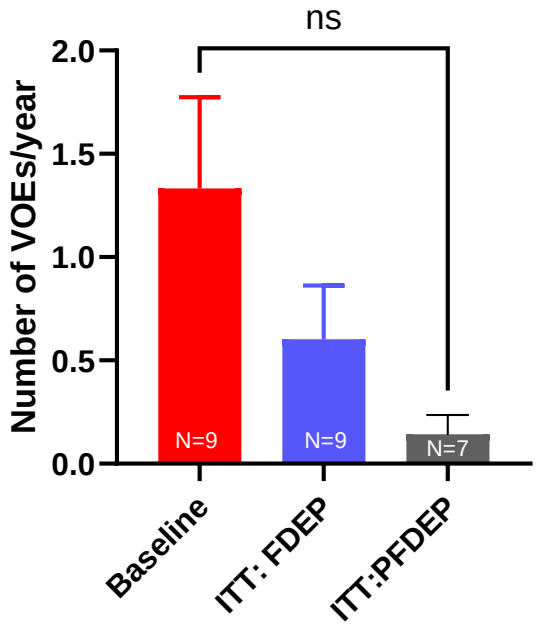
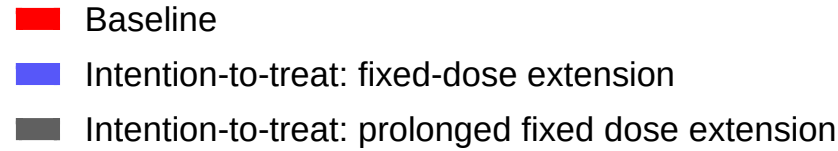
Results - Efficacy

Annualized SCD-related admission days



Annualized VOE rate





Results – Renal outcomes - Background

Sickle cell nephropathy:

- Prevalence ± 30% [1,2]

Glomerular markers:

- Nephrin and hemoglobin[3,4]

Tubular markers:

- beta-N-acetylglucosaminidase (NAG) and kidney injury molecule-1 (KIM-1)[5,6]

Urinary markers:

- Baseline and Year 1 or Year 2

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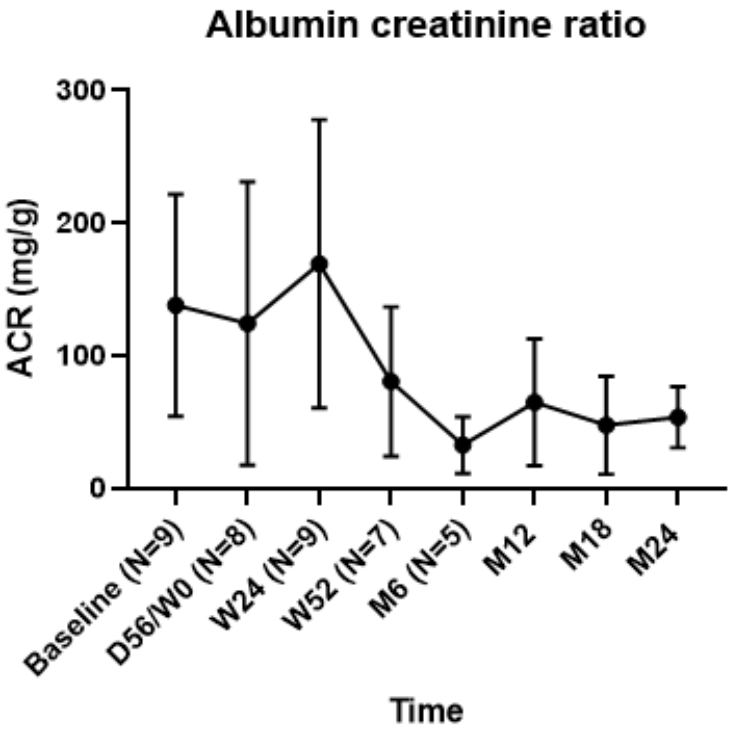
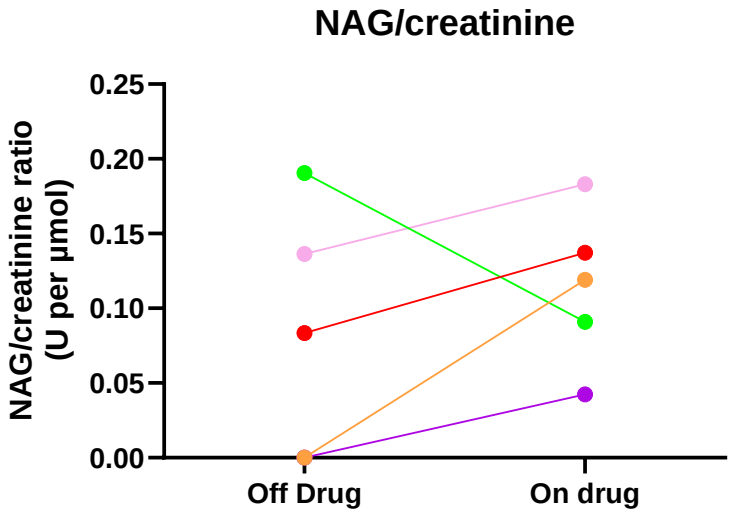
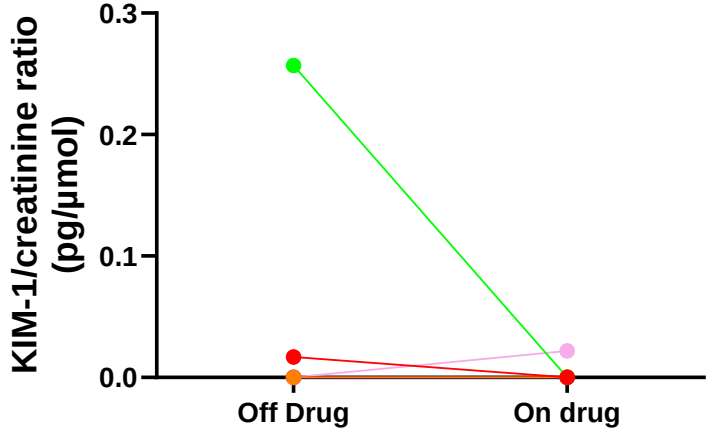
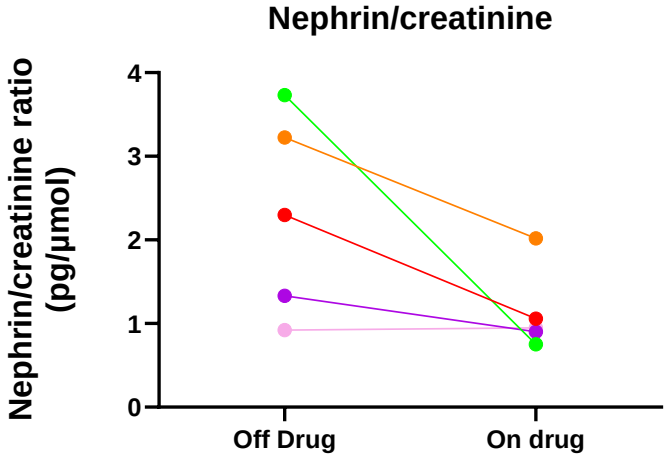
1:Olaniran KO, et al. Sickle Cell Nephropathy in the Pediatric Population. Blood Purification. 2019;47(1-3):205-
2:Gosmanova, E. O., et al. (2014). "Prevalence and progression of chronic kidney disease in adult patients with sickle cell disease." J Investig Med 62(5): 804-807.
3: Heimlich, J.B., et al., Nephrin as a biomarker of sickle cell glomerulopathy in Malawi. Pediatr Blood Cancer, 2018. 65(6): p. e26993.
4: Saraf, S.L., et al., Haemoglobinuria is associated with chronic kidney disease and its progression in patients with sickle cell anaemia. Br J Haematol, 2014. 164(5): p. 729-39.
5: Hamideh, D., et al., *Albuminuria correlates with hemolysis and NAG and KIM-1 in patients with sickle cell anemia.* Pediatr Nephrol, 2014. 29(10): p. 1997-2003.
6: Laurentino, M.R., et al., *Non-invasive urinary biomarkers of renal function in sickle cell disease: an overview.* Ann Hematol, 2019. 98(12): p. 2653-2660.

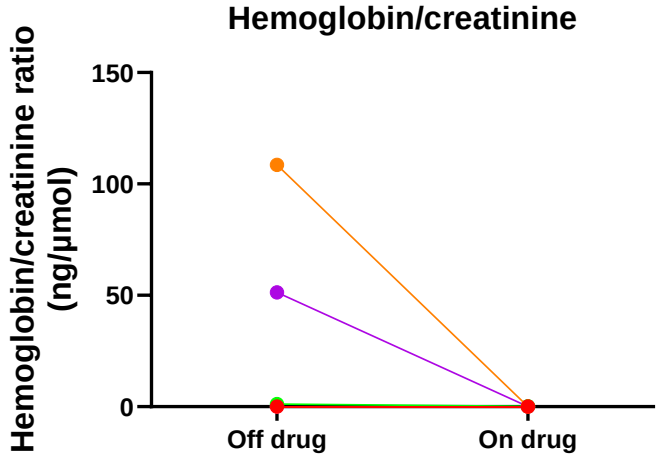
Results – Renal outcomes











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Conclusions

- **Long-term treatment with mitapivat in SCD patients is associated with sustained improvements in laboratory markers and a downward trend in VOEs and hospitalizations.**
- **Mitapivat is well tolerated, with mostly mild events and no serious concerns about safety.**
- **The explorative urine markers need to be confirmed in larger trials.**

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Discussion