ACCADEMIA NAZIONALE DI MEDICINA

AIEOP

AIEOP YOUNG PRECEPTORSHIP 2026
Nuovi approcci terapeutici in Ematologia pediatrica non oncologica

Nuovi farmaci nel trattamento della drepanocitosi

Raffaella Colombatti

Dipartimento Salute Donna e Bambino
Università degli Studi di Padova

Disclosure

Il/La sottoscritto/a

in qualità di docente/moderatore/relatore/ tutor, ai sensi dell'art. 76, comma 4 dell'Accordo Stato-Regioni del 2 febbraio 2017 e del paragrafo 4.5. del Manuale nazionale di accreditamento per l'erogazione di eventi ECM

Dichiara

che negli ultimi due anni ha avuto i seguenti rapporti con soggetti portatori di interessi commerciali in ambito sanitario:

- NovoNordisk
- Agios
- Theravia
- Pfizer
- Vertex

Overview

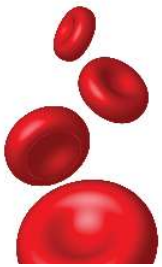
- Recall Sickle Cell Disease (SCD) characteristics that should be considered while thinking about the use of new drugs
- What are the main categories of disease modifying therapies (DMT) that are available for SCD?
- What new drugs as DMT can we offer (to children, adolescents and adults) beyond the standard of care in Italy?
- (How to choose? Single agent, combination therapies, new drugs, sequential combination strategies?)

40TH ANNIVERSARY ISSUE

AJH

Evolution of sickle cell disease from a life-threatening disease of children to a chronic disease of adults: The last 40 years

Shruti Chaturvedi[1] and Michael R. DeBaun[2]*



Chaturvedi S, DeBaun MR. Am J Hematol. 2016 Jan;91(1):5-14.

SCD - Genetic Disorder with Complex Pathophysiology

Autosomic recessive disorder:
abnormal β-globin alleles carrying the sickle mutation in the HBB gene (Glu6Val; βS)

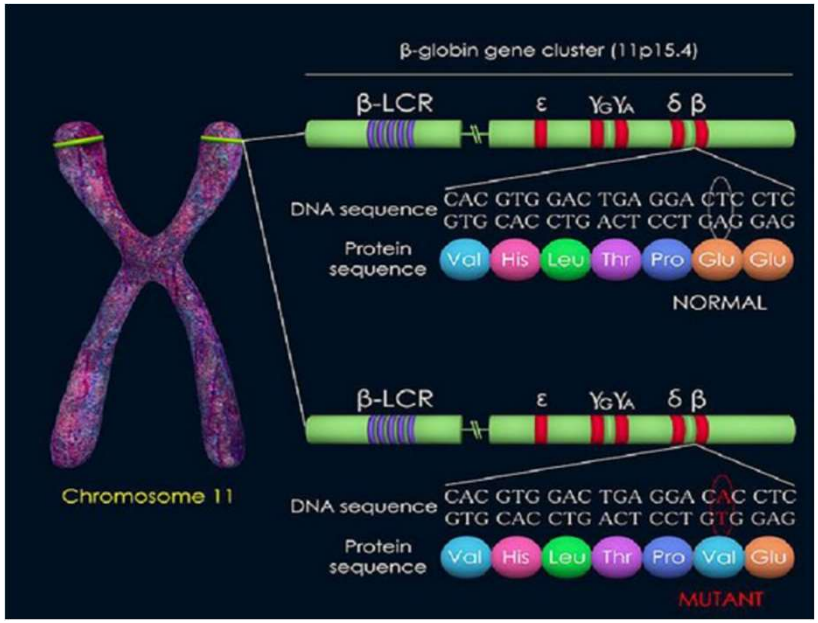
SS
Sβ°

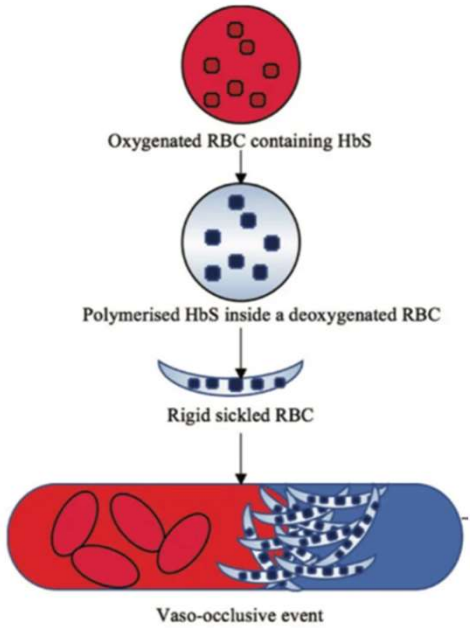
Severe

SC
Sβ+

«Mild» ?

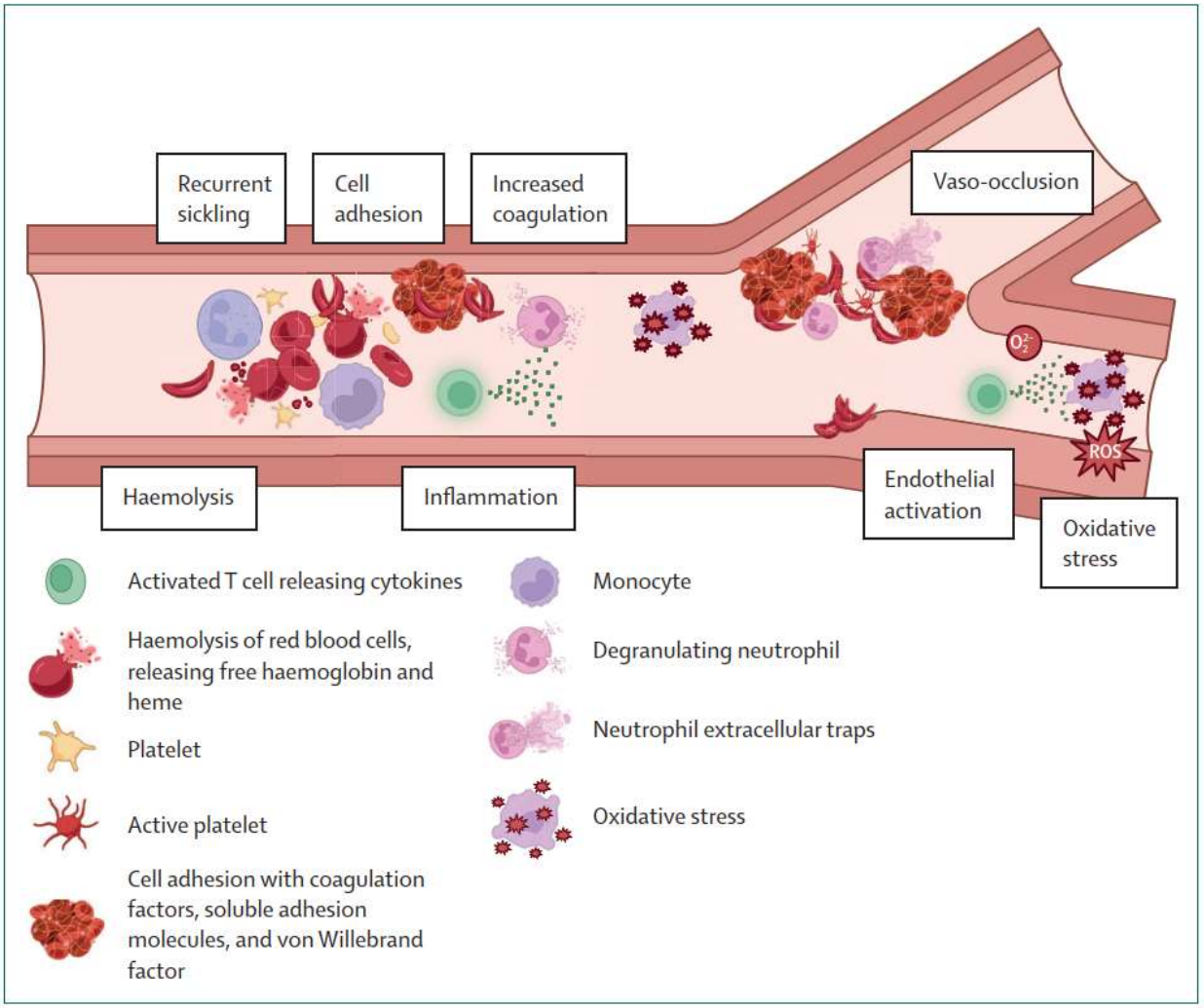
SOArab
SDPunjab





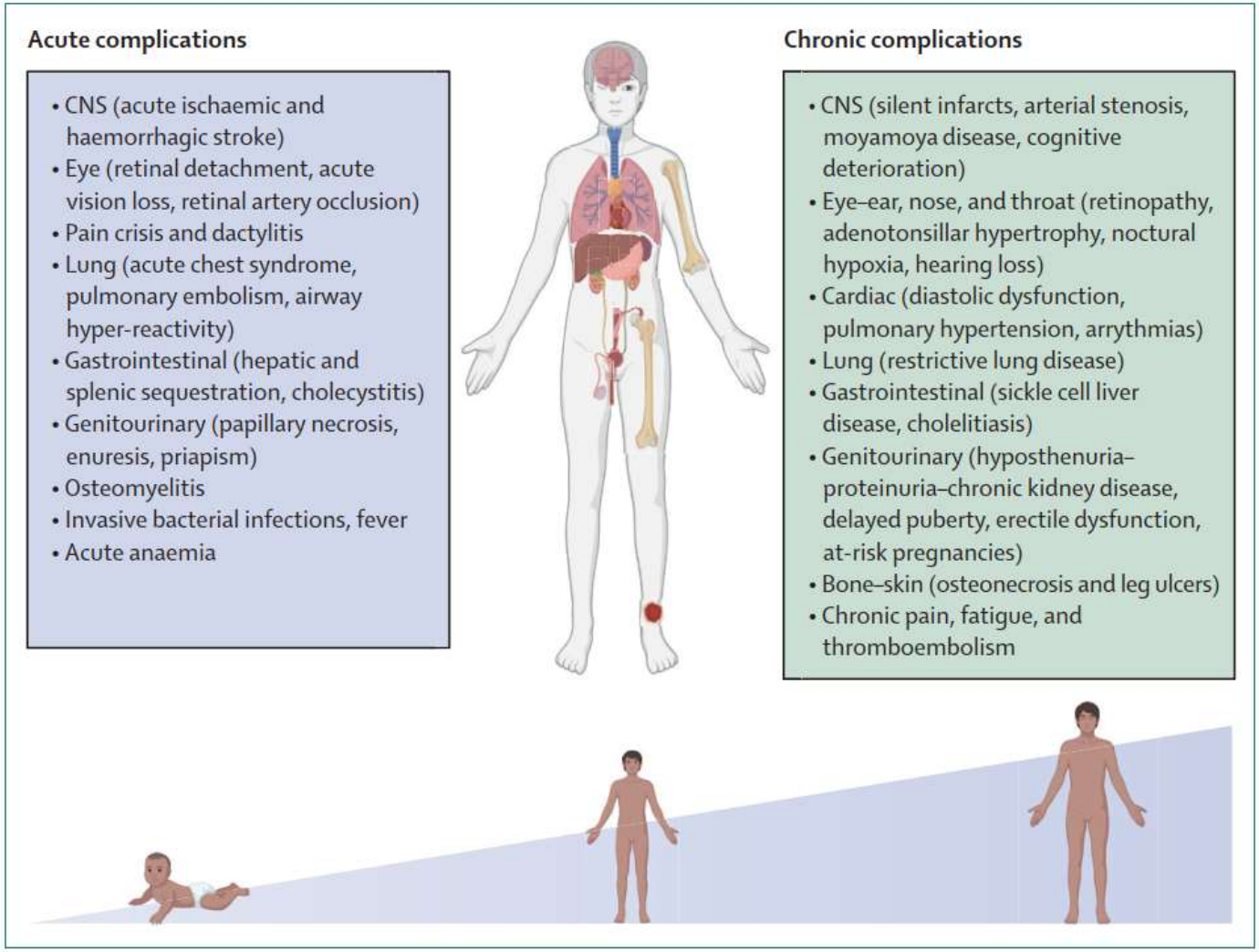
Peredes MB et al. https://revistabionatura.com/cs-2019.02.01.19.html ; https://www.sciencerepository.org/turning-back-the-sickle-cell-disease-a-new-drug-into-play

SCD - Genetic Disorder with Complex Pathophysiology



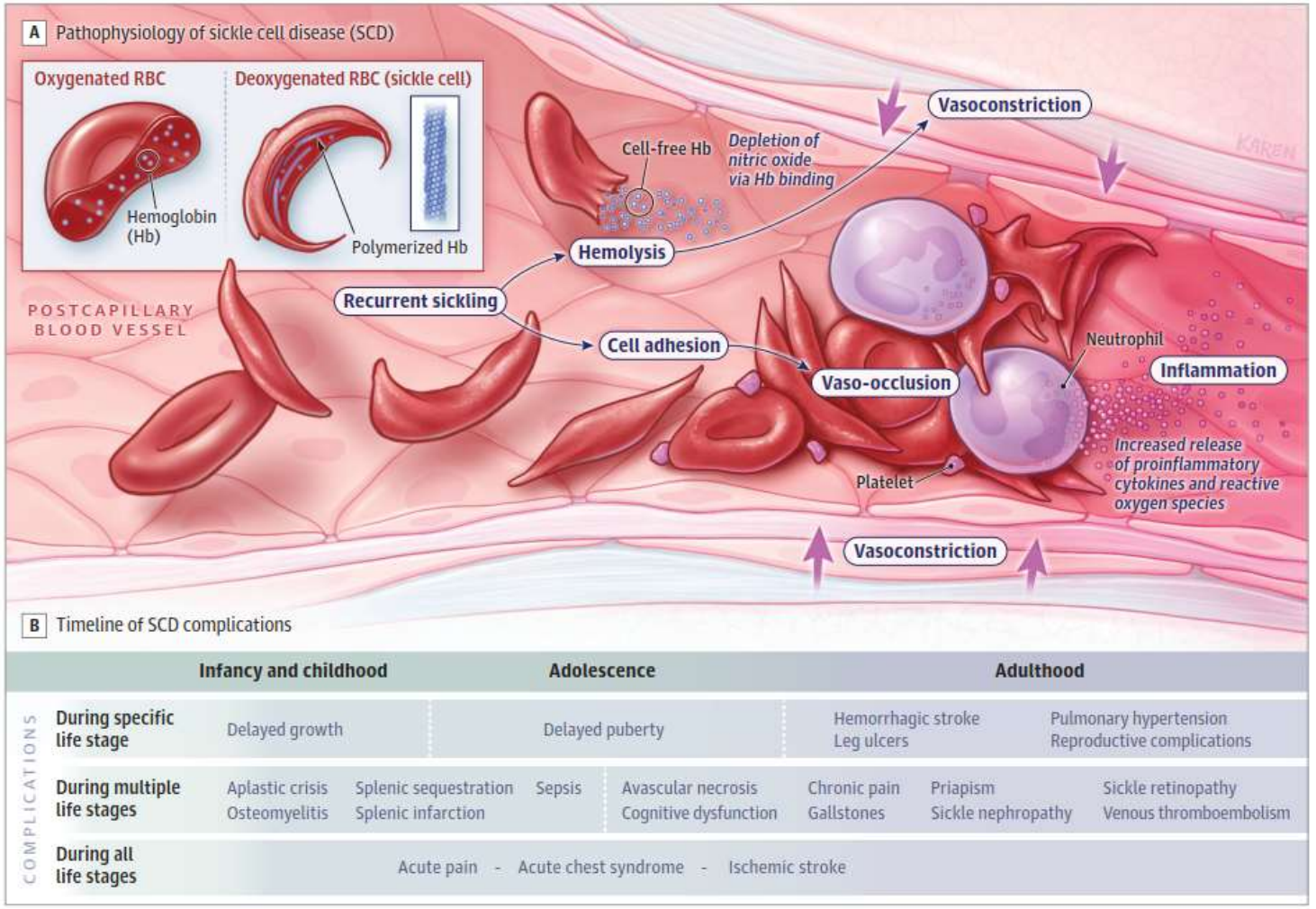
Colombatti R, et al. Lancet. 2026 Mar 14;407(10533):1095-1111

SCD – A chronic progressive disorder with acute manifestations



Colombatti R, et al. Lancet. 2026 Mar 14;407(10533):1095-1111.

SCD – A congenital disorder with a phenotype that evolves over time



PHENOTYPIC VARIABILITY?

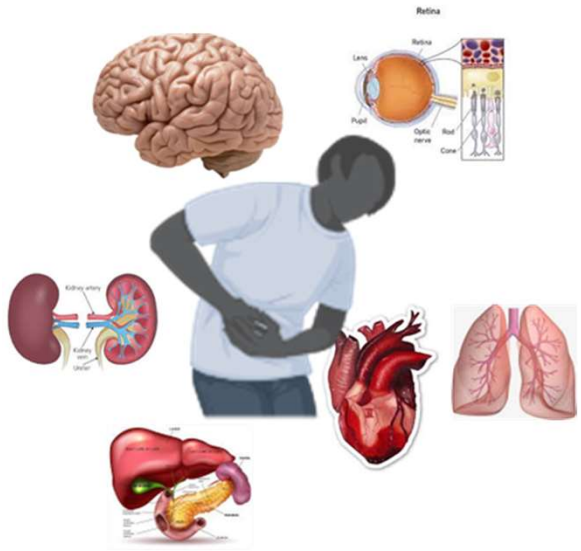
SEVERITY?

Kavanagh PL et al. JAMA. 2022;328(1):57-68

SCD – an evolving clinical, emotional and psychological burden

Mental Health

Coping with disease



Adherence to treatment

Therapeutic choices

Complex clinical and emotional history

REGULAR ARTICLE

blood advances

Check for updates

Successes and pitfalls in orphan drug development for sickle cell disease

Enrico Costa,[1] Antonella Isgrò,[2] Mariane de Montalembert,[3] Hubert G. M. Leufkens,[4] Russell E. Ware,[5] and Lucia De Franceschi[6]

[1]Division of Pharmacoepidemiology and Clinical Pharmacology, World Health Organization Collaborating Centre for Pharmaceutical Policy and Regulation, Utrecht University, Utrecht, The Netherlands; [2]Centralized Procedures Office, Innovation and Pharmaceutical Strategy Division, Italian Medicines Agency, Rome, Italy; [3]Department of Pediatrics, Necker-Enfants Malades Hospital, Assistance Publique-Hopitaux de Paris Centre, Paris, France; [4]Emeritus Professor Regulatory Science and Pharmaceutical Policy, Division of Pharmacoepidemiology and Clinical Pharmacoepidemiology, Utrecht University, Utrecht, The Netherlands; [5]Division of Hematology and Global Health Center, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; and [6]Department of Medicine, University of Verona & AOUI Verona, Verona, Italy

DOI: 10.1002/hem3.70082

EDITORIAL

HemaSphere eha

What's wrong with drug development for sickle cell disease?

Valentine Brousse[1,2] | **David Rees**[3,4] | **Raffaella Colombatti**[5,6]

Correspondence: Valentine Brousse (valentine.brousse@gmail.com)

Brousse V, et al. Hemasphere. 2025 Feb 6;9(2):e70082; Costa Ee t al Blood Adv. 2024 May 28;8(10):2455-2465. .

Hematopoietic Stem Cell Transplantation / ***gene therapy***

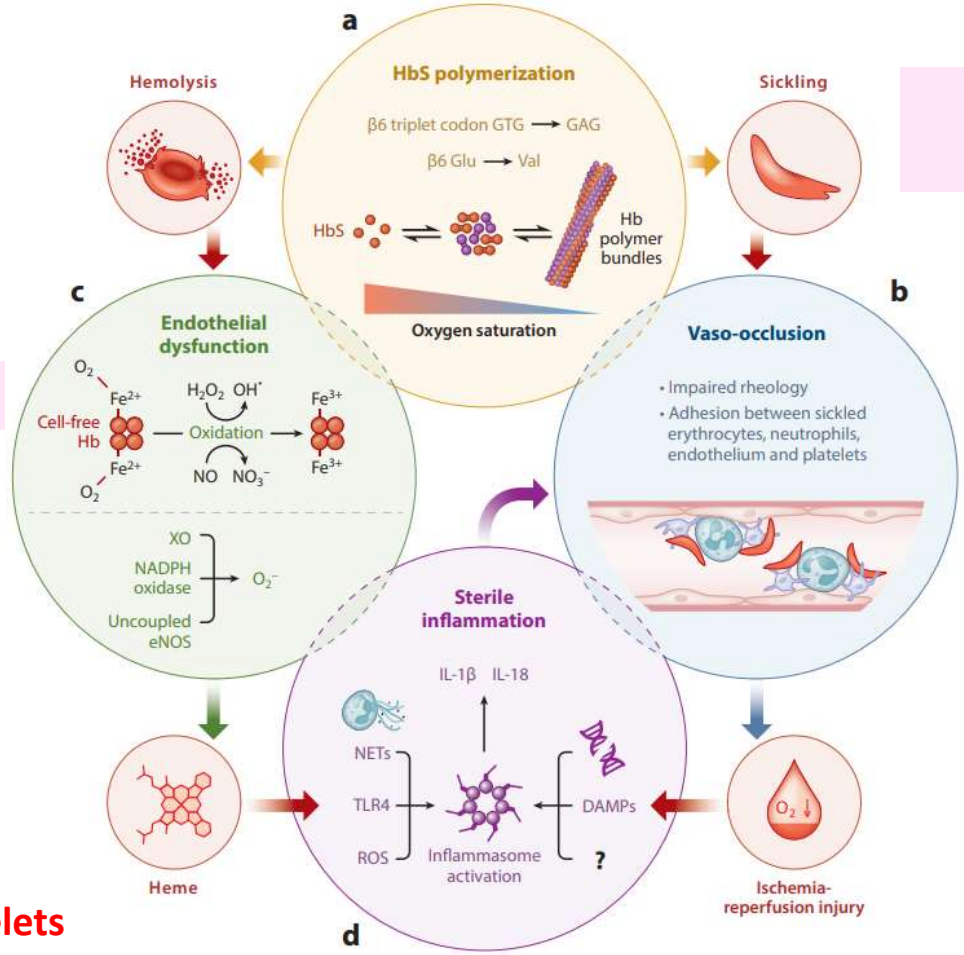
osivelotor / mitapivat / etavopivat

Hydroxyurea ***/ mitapivat / etavopivat/Tebapivat***

chronic transfusion regimen

L-glutamine

Hydroxyurea / ***decitabine-tetrahydrouridine/ Inclacumab***



- **Prasugrel, Tecagrelor, antiplatelets**
- **Crizanlizumab, Anti P selectin Ab**
- **Voxelotor, HbS polim inhibitor**

canakinumab/haemopexin

Sundd P et al. *Annu Rev Pathol*. 2019;14:263-292. Kato GJ. *Nat Rev Dis Primers*. 2018;4:18010.

INNOVATIVE THERAPEUTIC APPROACHES:

new drugs

Crizanlizumab

Ab Anti P Selectin; TRIAL Phase 2 in Adults; endpoint: ↓VOC

FDA Approval in the USA

EMA conditional approval in Europe → request of a Phase 3 trial → different results from Phase 2

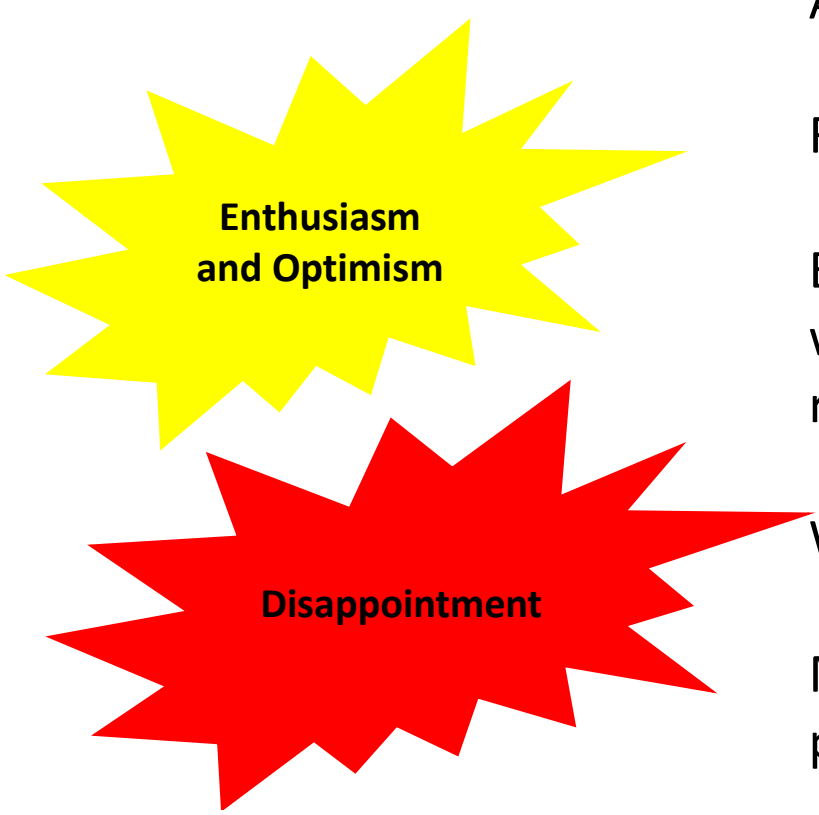
Withdrawal of approval by EMA

Many patients benefit from the drug and many physicians without alternatives

INNOVATIVE THERAPEUTIC APPROACHES:

new drugs

Voxelotor



Inhibitor of Hb polimerization; TRIAL Phase 3 in Adolescents and Adults → endpoint: ↑ 1 gr Hb

FDA Approval in the USA

EMA conditional approval in Europe → request of Trials with clinical endpoints and postmarketing → different results from Phase 3: deaths and severe events

Withdrawal of drug from market

Many patients benefit from the drug and many physicians without alternatives

	Phase	Primary endpoint	Clinical trial number
Fetal haemoglobin inducers			
Oral decitabine–tetrahydrouridine	2	Change in total haemoglobin at 24 weeks	NCT05405114
Oral decitabine–tetrahydrouridine plus nicotinamide	1	Change in total haemoglobin	NCT04055818
FTX-6058	1	Safety, tolerability, pharmacokinetics, and pharmacodynamics	NCT05169580
BMS-986470	1/2	Safety, tolerability, pharmacokinetics, and pharmacodynamics	NCT06481306
Panobinostat	1	Safety, dose-limiting toxic effects	NCT01245179
GSK4172239D	1	Safety, tolerability, pharmacokinetics, and pharmacodynamics	NCT05660265
ITU512	1/2	Safety and tolerability	NCT06546670
Anti-haemolytic agents			
Vamifeport	2a	Mean change from baseline in haemolysis markers	NCT04817670
GBT021601	2/3	Co-primary endpoints: haemoglobin response (increase from baseline of >1 g/dL); annualised rate of vaso-occlusive crises at week 48	NCT05431088
Pyruvate-kinase activators			
Mitapivat	3	Percentage of participants with haemoglobin response at week 52; annualised rate of pain crises	NCT05031780
Etavopivat	2, open label	Change in cerebral haemodynamics at week 24	NCT05725902
Etavopivat	2, open label	Change in transcranial Doppler velocity	NCT05953584
Etavopivat	2/3	Haemoglobin response rate at week 24 (increase of >1 g/dL [>10 g/L] from baseline); annualised vaso-occlusive crisis rate	NCT04624659
Etavopivat	1/2; children	Pharmacokinetics and safety	NCT06198712
Tebapivat	1	Safety, tolerability, pharmacokinetics, and pharmacodynamics	NCT06924970
Anti-adhesion agents			
Inclacumab	3	Rate of vaso-occlusive crises during the 48-week treatment period	NCT04935879

HbF

Hemolysis

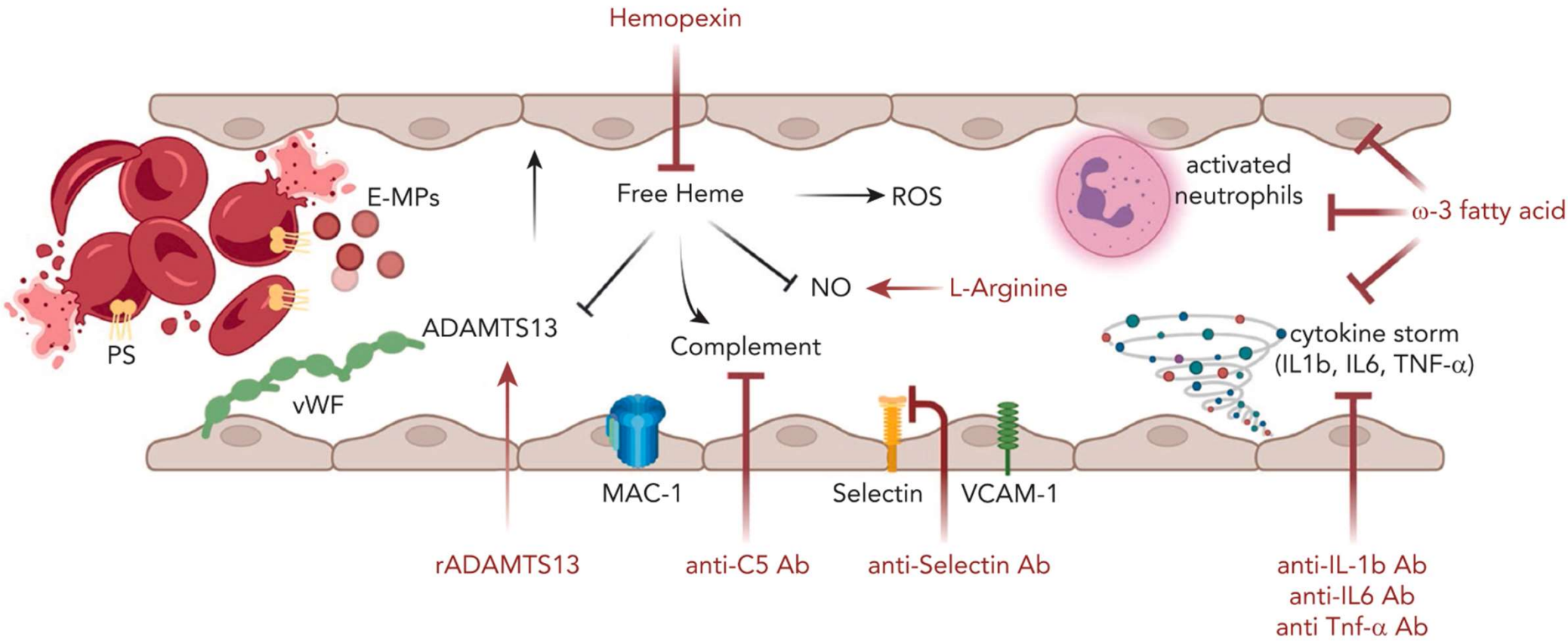
PK

STOP

Colombatti R, et al. Lancet. 2026 Mar 14;407(10533):1095-1111.

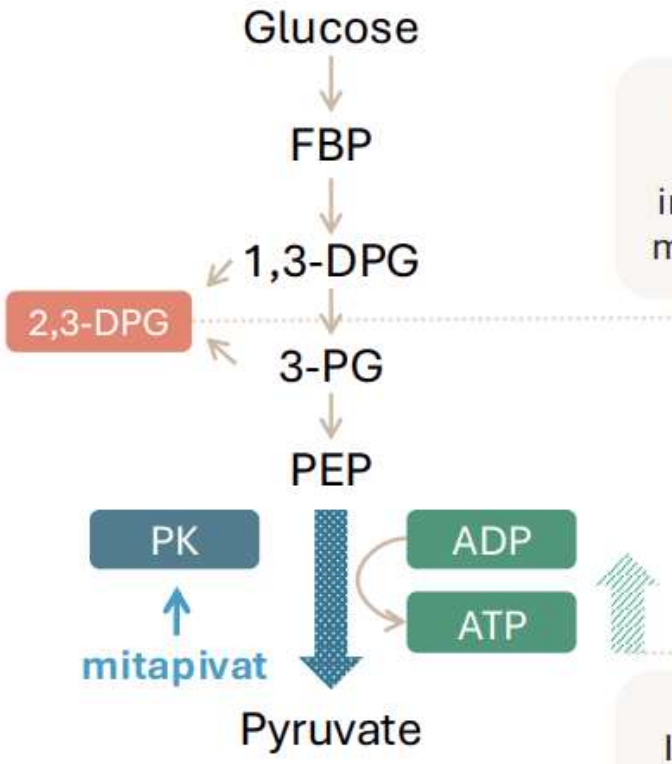
Individual agents			
Epeleuton (synthetic ω-3 fatty acid)	2	Pharmacokinetics, pharmacodynamics, and safety	NCT05861453
Tadalafil (PDE-5 inhibitor)	2	Change in the recurrence rate of priapism	NCT05142254
HBI-002 (oral carbon monoxide)	2a	Safety	NCT06144749
Tocilizumab (IL-6 inhibitor)	2	Time-weighted pulse oximetry oxygen saturation to fraction of inspired oxygen ratio in patients with acute chest syndrome	NCT05640271
L-citrulline (increase nitric oxide production)	2	Time to crisis resolution	NCT06635902
TAK-755 (recombinant ADAMTS13 enzyme)	1	Safety and development of anti-ADAMTS13 antibodies	NCT03997760
CSL889 (human-derived haemopexin)	2/3	Time to resolution of vaso-occlusive crises	NCT06699849
Oral ketamine	3	Change in pain intensity during vaso-occlusive crises	NCT05378555
Crovalimab (anti-C5 inhibitor)	1b	Safety	NCT04912869
Crovalimab (anti-C5 inhibitor)	2a	Annualised rate of medical facility vaso-occlusive episodes	NCT04912869
Rilzabrutinib (Bruton tyrosine kinase inhibitor)	3	Annualised rate of clinical vaso-occlusive crises	NCT06975865

Colombatti R, et al. Lancet. 2026 Mar 14;407(10533):1095-1111.



Pinto VM et al. Blood. 2024 Aug 22;144(8):853-866.

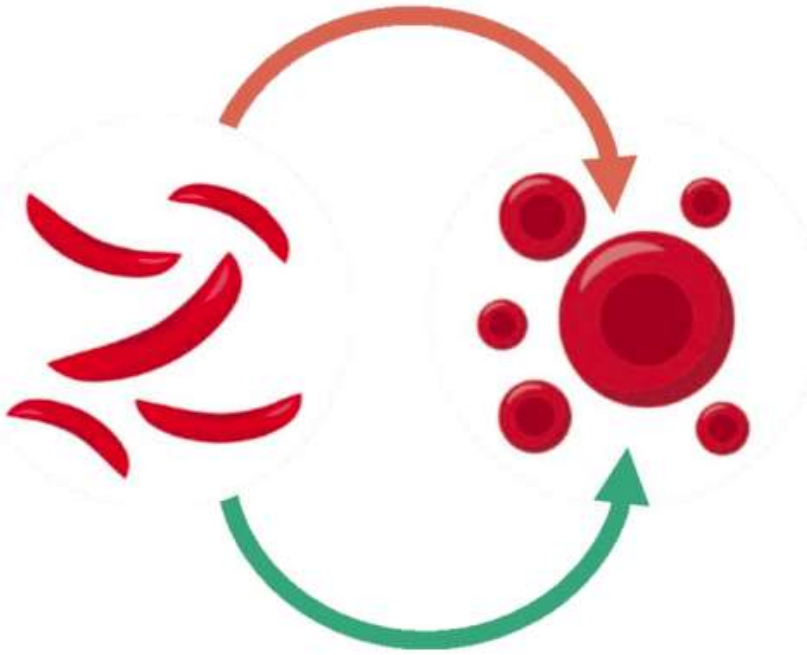
Mitapivat MoA – increases ATP, decreases 2,3-DPG



Decreasing 2,3-DPG reduces HbS polymerization by increasing Hb oxygenation and may inhibit the sickling process

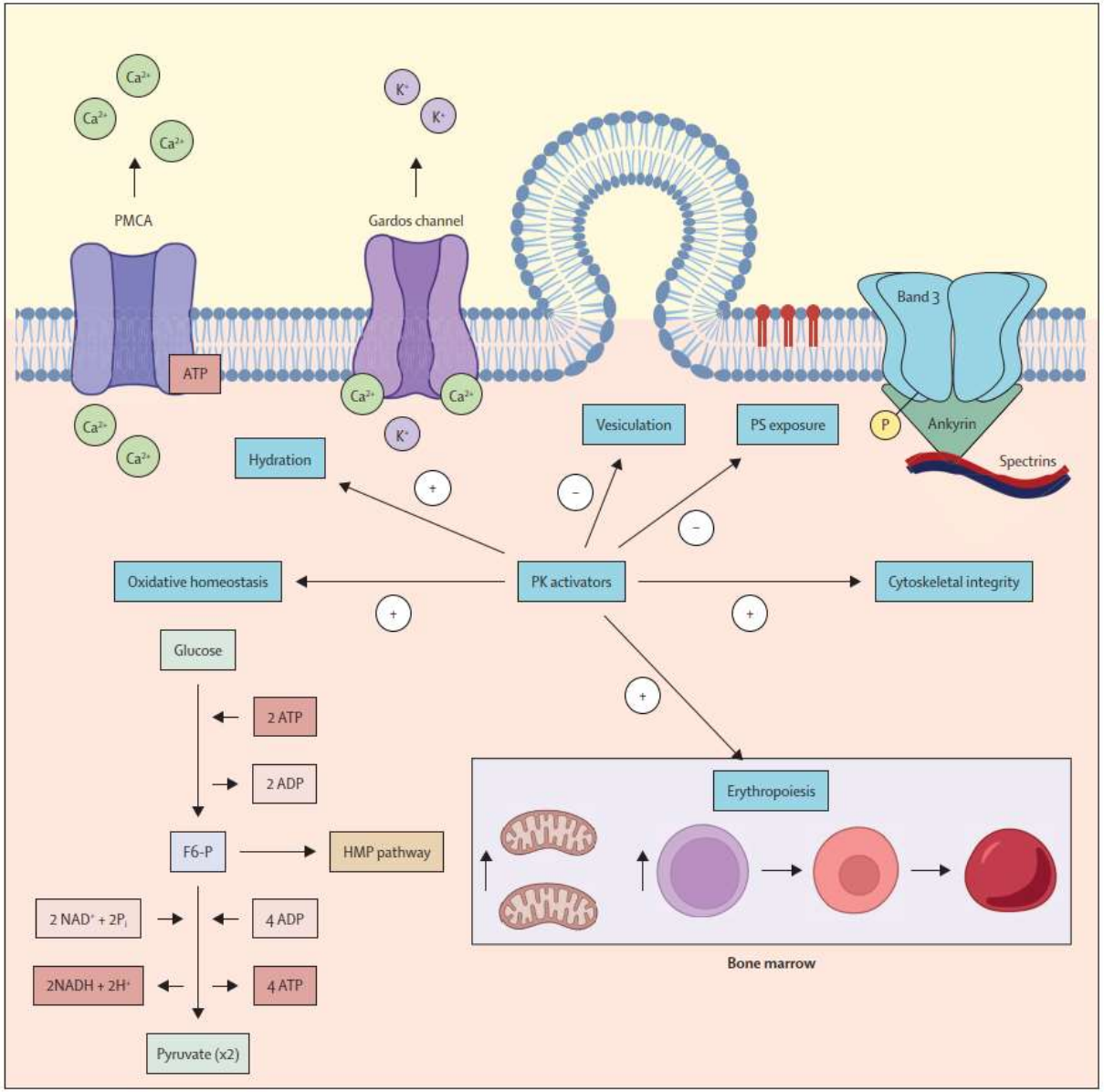
Increasing ATP enhances RBC energy metabolism and may improve membrane integrity

REDUCTION OF VOCs



INCREASE OF HEMOGLOBIN

Mitapivat influences red cell survival

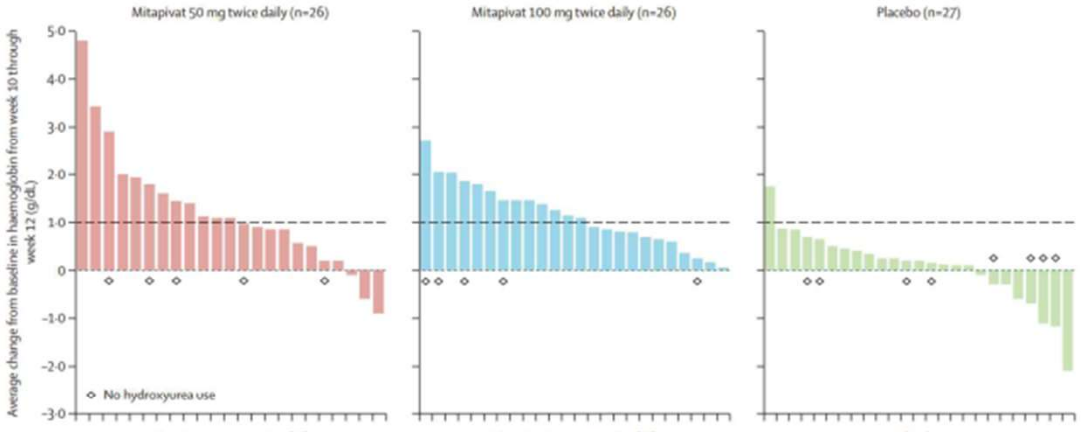


Doeven T, et al. Lancet. 2026 Mar 12:S0140-6736(26)00150-9

Safety and efficacy of mitapivat in sickle cell disease (RISE UP): results from the phase 2 portion of a global, double-blind, randomised, placebo-controlled trial

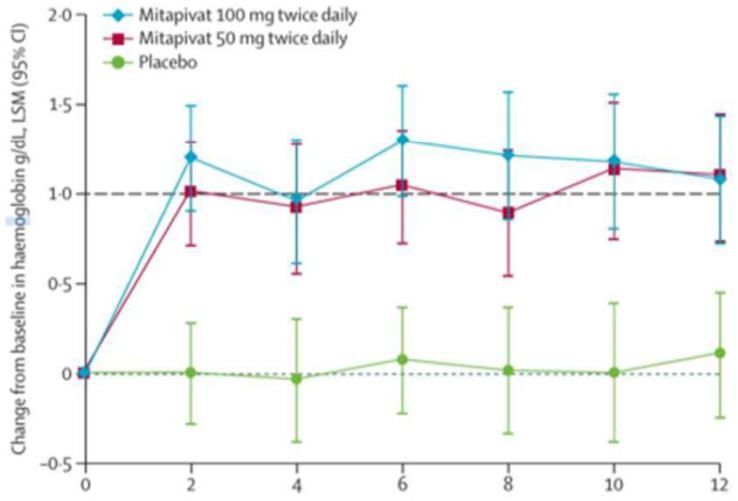
Modupe Idowu, Lucas Otieno, Bogdan Dumitriu, Clarisse L C Lobo, Swee Lay Thein, Biree Andemariam, Obiageli E Nnodu, Adlette Inati, Alexander K Glaros, Pablo Bartolucci, Raffaella Colombatti, Ali T Taher, Miguel R Abboud, Deepika Darbari, Kenneth I Ataga, Ali Bülent Antmen, Kevin H M Kuo, Samuel de Souza Medina, Abdulafeez Oluyadi, Varsha Iyer, Susan Morris, Amber M Yates, Hui Shao, Spurthi Patil, Rolandas Urbstonaitis, Ahmar U Zaidi, Sarah Gheuens, Wally R Smith

Primary endpoint: Hb response (increase >1 g/dL) through week 12 compared with baseline



	Mitapivat 50 mg twice daily	Mitapivat 100 mg twice daily	Placebo
Haemoglobin response, n (%)	12 (46·2%)	13 (50·0%)	1 (3·7%)
Difference in response rate (mitapivat–placebo), percentage points (95% CI)	42·5 (18·8–63·4)	46·3 (22·0–66·8)	NA
p value	p=0·0003	p=0·0001	NA

Secondary endpoint: change from baseline in Hb concentrations through week 12



Number of patients							
Mitapivat 100 mg twice daily	26	23	23	24	23	23	23
Mitapivat 50 mg twice daily	26	23	29	22	24	22	22
Placebo	27	24	22	25	24	21	22

Idowu M, et al. Lancet Haematol. 2025 Jan;12(1):e35-e44. Epub 2024 Dec 4. Erratum in: Lancet Haematol. 2025 Jan;12(1):e9

Safety and efficacy of mitapivat in sickle cell disease (RISE UP): results from the phase 2 portion of a global, double-blind, randomised, placebo-controlled trial

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- Increase in Hb
- No serious adverse event
- Trend towards reduction of VOCs compared to before treatment
- Contrasting results for Fatigue (PROMs)

Idowu M, et al. Lancet Haematol. 2025 Jan;12(1):e35-e44. Epub 2024 Dec 4. Erratum in: Lancet Haematol. 2025 Jan;12(1):e9

PRESS RELEASE

Agios Announces Topline Results from RISE UP Phase 3 Trial of Mitapivat in Sickle Cell Disease

- Trial met primary endpoint of hemoglobin response and key secondary endpoints of change from baseline in hemoglobin concentration and indirect bilirubin
- Trial showed trend favoring mitapivat but did not meet statistical significance in primary endpoint of annualized rate of SCPCs (pain crises), and the key secondary endpoint of change from baseline in PROMIS Fatigue was not met
- Patients in the mitapivat arm who achieved hemoglobin response had clinically meaningful benefits in SCPC-related endpoints and PROMIS Fatigue
- Favorable safety profile observed in RISE UP Phase 3 trial was consistent with that observed in prior mitapivat sickle cell disease trials

> 16 years of age

November 2025

Hemoglobin Responders Post Hoc Analysis Results

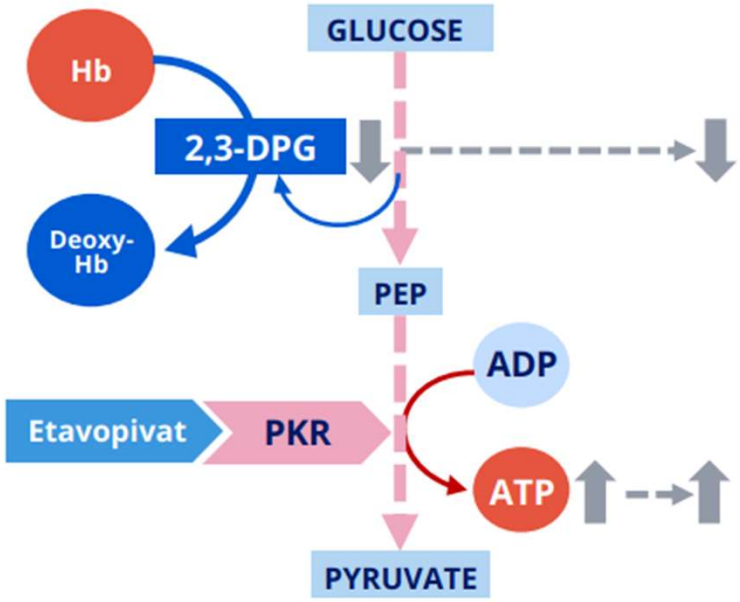
In the subset of patients in the mitapivat arm achieving the primary endpoint of hemoglobin response the following was observed:

- **Annualized Rate of SCPCs:** The annualized rate of SCPCs was 2.20 for hemoglobin responders and 2.98 for non-hemoglobin responders (rate ratio [RR]=0.74, 95% confidence interval [CI]=0.58 to 0.94).

- **Annualized Rate of Hospitalizations for SCPCs:** The annualized frequency of hospitalizations for SCPCs was 1.16 for hemoglobin responders and 1.76 for non-hemoglobin responders (RR=0.66, 95% CI=0.48 to 0.91).

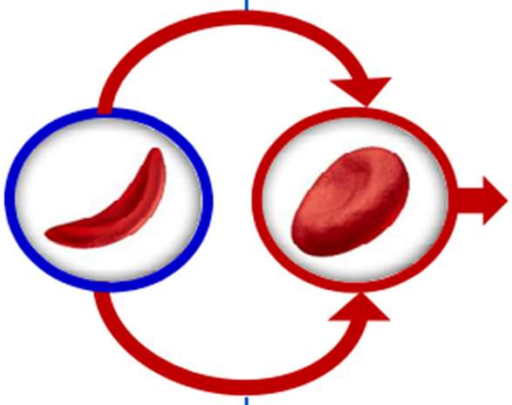
- **Change from Baseline in PROMIS Fatigue Score:** The average change in PROMIS Fatigue score between Week 24 and Week 52 was -5.19 for hemoglobin responders and -2.55 for non-hemoglobin responders (95% CI=-5.59 to 0.32). The results for hemoglobin responders in the mitapivat arm exceeded -4.1, the threshold for a clinically meaningful change from baseline for PROMIS Fatigue score.

Etavopivat



Hypothesis #1:
PKR activation decreases 2,3-DPG, reducing HbS polymerization and sickling

HbS polymerization



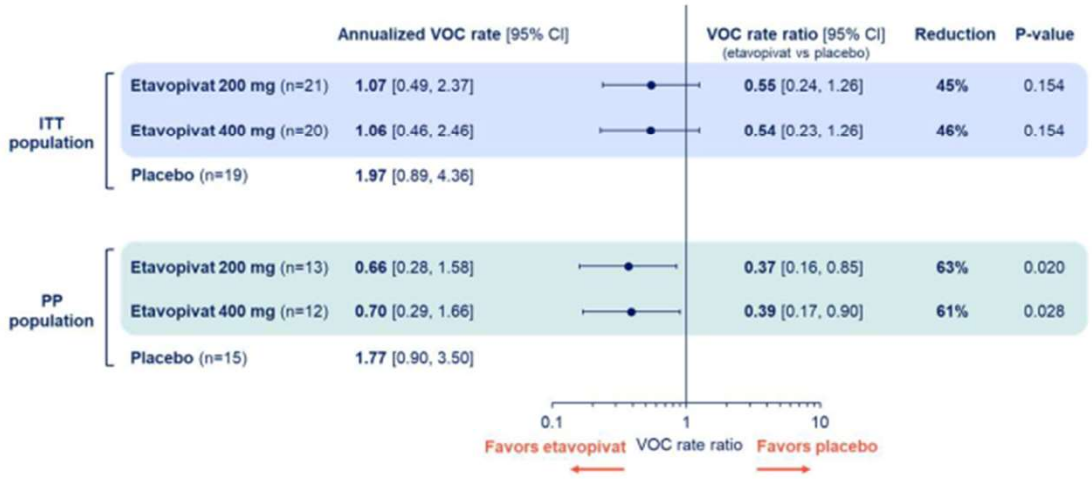
RBC membrane integrity

Expected Clinical Outcome:
Increased Hb levels
Decreased vaso-occlusion

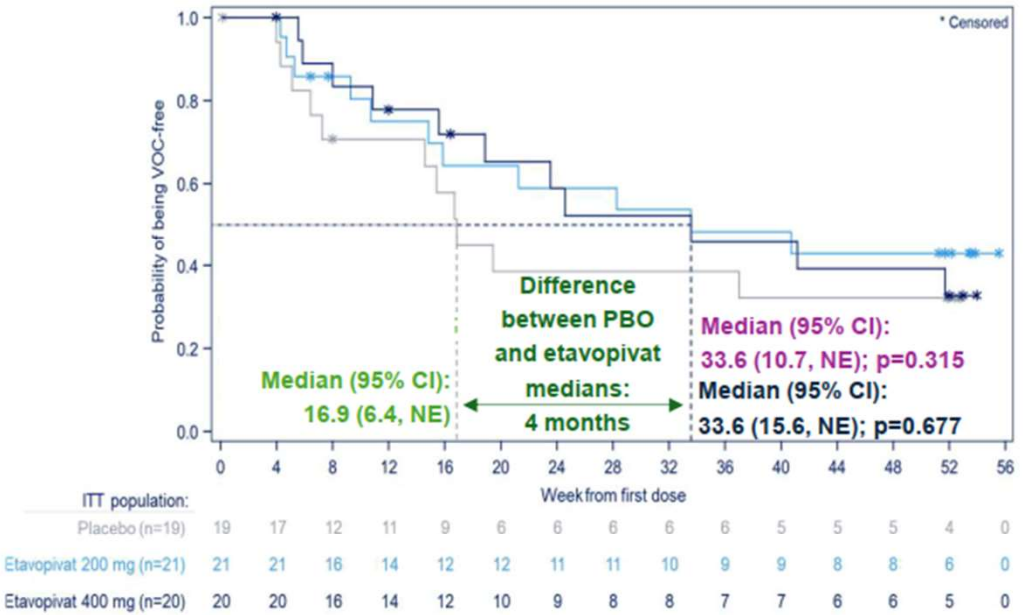
Hypothesis #2:
PKR activation increases ATP, promoting RBC repair/health and reducing hemolysis

HIBISCUS: Etavopivat reduced the annualized VOC rate and time to first adjudicated VOC compared with placebo

Phase 3 primary endpoint: Annualized VOC rate over 52 weeks



Secondary endpoint: Time to first adjudicated VOC



ITT population = all participants randomized. PP population = ≥80% protocol compliance, completion of the double-blind period, and no major protocol deviations impacting efficacy assessments.
Adjudicated in a blinded manner by a VOC Review Committee, comprising physicians experienced in the treatment of SCD. Negative binomial model for VOC events, based on a generalized linear model with treatment group as fixed effect and the natural log of the duration (years) of study treatment exposure.
CI, confidence interval; ITT, intent to treat; NE, not estimable; PBO, placebo; PP, pre-protocol cohort; SCD, sickle cell disease; VOC, vaso-occlusive crises.
Delicou S, et al. Blood 2024;144 (Supplement 1):179.

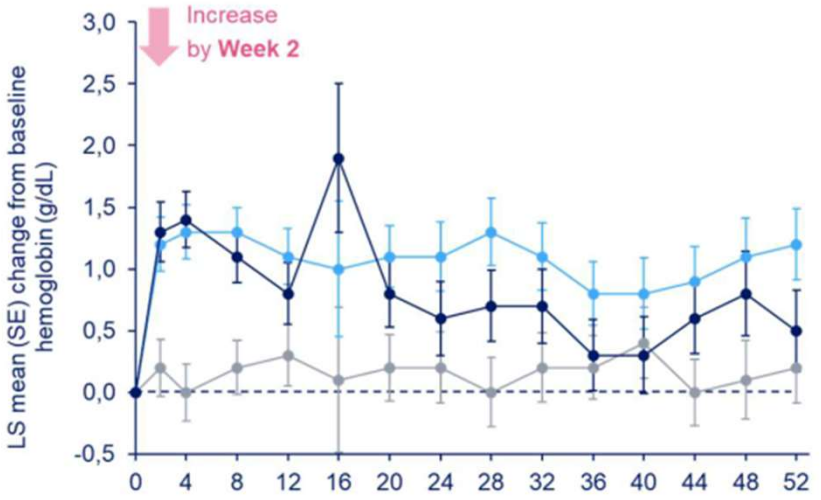
HIBISCUS: Increased Hb response rates at week 24 and an early increase in Hb concentration was observed in patients treated with etavopivat

Novo Nordisk®

Primary endpoint: Hb response (increase >1 g/dL) at week 24

	Etavopivat 200 mg/day	Etavopivat 400 mg/day	Placebo
ITT population	n=21	n=20	n=19
Hb responders at Week 24, %	**38.1**	**25.0**	**10.5**
Rate difference vs placebo	27.6	14.5	
p-value	p=0.187	p=0.660	
PP population	n=13	n=12	n=15
Hb responders at Week 24, %	**46.2**	**33.3**	**13.3**
Rate difference vs placebo	32.8	20.0	
p-value	p=0.248	p=0.680	

Secondary endpoint: Change from baseline in Hb at Week 52 during the blinded treatment period



ITT population:													
Placebo (n=19)	16	13	15	15	13	15	14	15	16	15	16	13	13
Etavopivat 200 mg (n=21)	20	17	18	17	17	14	15	15	14	14	12	14	13
Etavopivat 400 mg (n=19)	14	14	15	14	12	13	12	10	11	11	12	10	9

Hb response: >1 g/dL increase from baseline (using the mean of Hb measurements at Weeks 16, 20, and 24); one-sided p-value was obtained from an exact Cochran-Mantel-Haenszel general association test between the indicated etavopivat group versus placebo and stratified by the randomization stratification factors; the test was considered statistically significant if one-sided p-value <0.025. LS mean change from baseline hemoglobin:
the mixed model for repeated measures was based on change from baseline and includes a random effect for patient and fixed effects for treatment group, baseline, randomization stratification factors (age, prior/concomitant treatment, vaso-occlusive crisis), nominal study visit, and treatment group by visit interaction.
Hb, hemoglobin; ITT, intent-to-treat; PP, per-protocol; LS, least square; SE, standard error.
Delicou S, et al. Blood 2024;144 (Supplement 1):179.

Etavopivat in Adolescents with Sickle Cell Disease: Emerging Safety and Efficacy Findings from the First Cohort of the Ongoing Phase 1/2 HIBISCUS Kids Study

Adlette Inati,[1] Bernhards Ogutu,[2,3] E. Leila Jerome Clay,[4] Pavithra Dhayakar[5], Kaming Lo,[6] and Miguel R. Abboud[7]

[1]Lebanese American University Gilbert and Rose-Marie Chagoury School of Medicine, Byblos and NINI Hospital, Tripoli, Lebanon; [2]KEMRI Kondele Children's Hospital, Kisumu, Kenya; [3]CREATES, Strathmore University, Nairobi, Kenya; [4]Novo Nordisk Inc., Princeton, NJ, USA; [5]Novo Nordisk, Bangalore, India; [6]Novo Nordisk Inc., Lexington, MA, USA; [7]American University of Beirut, Beirut, Lebanon

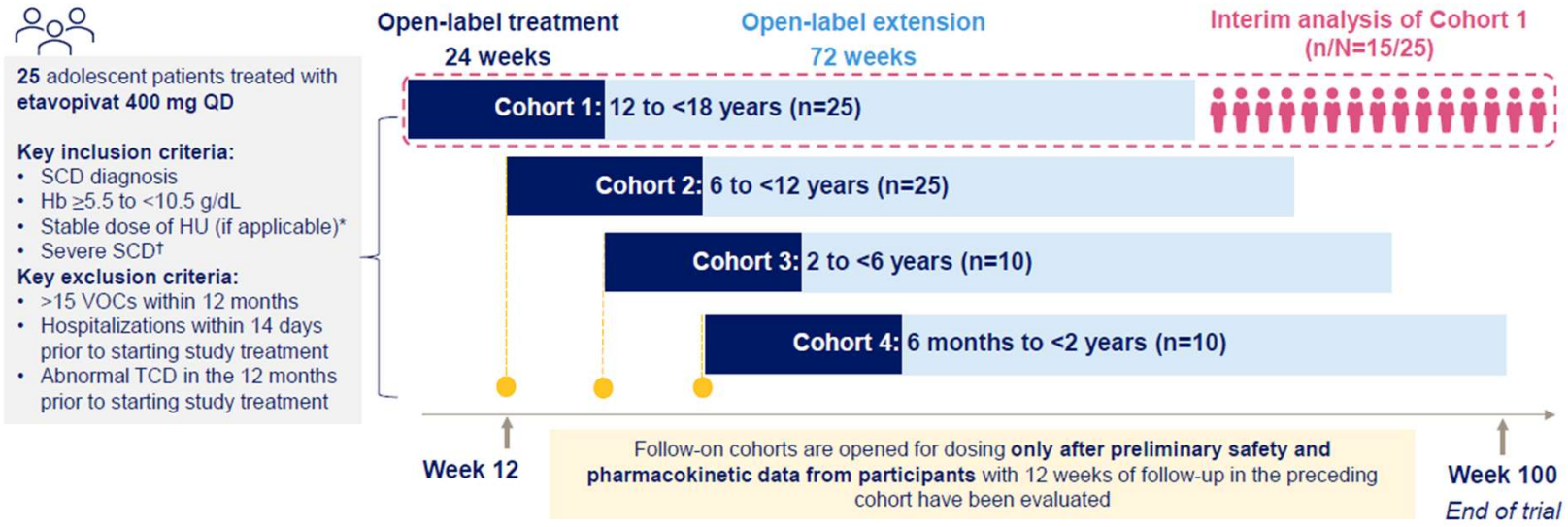
Presented at the American Society of Hematology (ASH) Congress, Orlando, Florida, USA, December 6–9, 2025.
This material is intended to be used at the ASH 2025 congress only.

The study was sponsored and funded by Novo Nordisk A/S.
Medical writing support was provided by AXON Communications, London, UK, and funded by Novo Nordisk.

https://sciencehub.novonordisk.com/congresses/ash2025/etavopivat.html

HIBISCUS Kids: Study design[1]

Single-arm, four-cohort, open-label, ongoing phase 1/2 study investigating the pharmacokinetics and safety of etavopivat in children and adolescents with SCD (aged 6 months to <18 years)



*Stable dose concurrent therapy with hydroxyurea, crizanlizumab, and L-glutamine was permitted. †**Pediatric patients with severe SCD defined by ≥1 of the following within 12 months of screening: 2–15 documented VOCs; hospitalization for SCD complication; proteinuria as defined by urinary albumin:creatinine ratio (ACR) >100 mg/g on two measures; or conditional TCD ultrasonography.**

Hb, hemoglobin; HU, hydroxyurea; QD, once daily; SCD, sickle cell disease; TCD, Transcranial Doppler; VOC, vaso-occlusive crisis.

1. Novo Nordisk A/S. NCT06198712. Last updated September 18, 2025. Accessed December 2025. Available from: https://clinicaltrials.gov/study/NCT06198712.

https://sciencehub.novonordisk.com/congresses/ash2025/etavopivat.html

Study objectives and endpoints

Objective To assess pharmacokinetics, safety, and tolerability of etavopivat in adolescent and pediatric patients during the 24-week primary treatment period and the 72-week treatment extension period

Study objectives	Study endpoints
Primary:	**Primary:**
1. Pharmacokinetics of etavopivat	1. Single-dose and steady-state etavopivat exposure profile
2. Safety and tolerability of etavopivat at week 24	2. Incidence of AEs, serious AEs, etavopivat discontinuations, dosing interruptions, and dose reductions at week 24
Secondary:	**Secondary:**
1. Effect of etavopivat on Hb response	1. Hb response >1.0 g/dL increase from baseline at weeks 12 and 24
2. Occurrence of VOCs	2. Number of VOCs during the 24-week treatment period
3. Changes in fatigue	3. Change from baseline in PROMIS Fatigue T-score at week 24
4. Changes in cerebral blood flow	4. Change from baseline in TAMMV by TCD at week 24
Not presented here	
5. Safety and tolerability of etavopivat during the 72-week treatment extension period	5. AEs, serious AEs, etavopivat discontinuations, dosing interruptions, and dose reductions

AE, adverse event; Hb, hemoglobin; PROMIS, Patient-Reported Outcome Measurement Information System; SCD, sickle cell disease; TAMMV, time-averaged mean of the maximum velocity; TCD, Transcranial Doppler; VOC, vaso-occlusive crisis.

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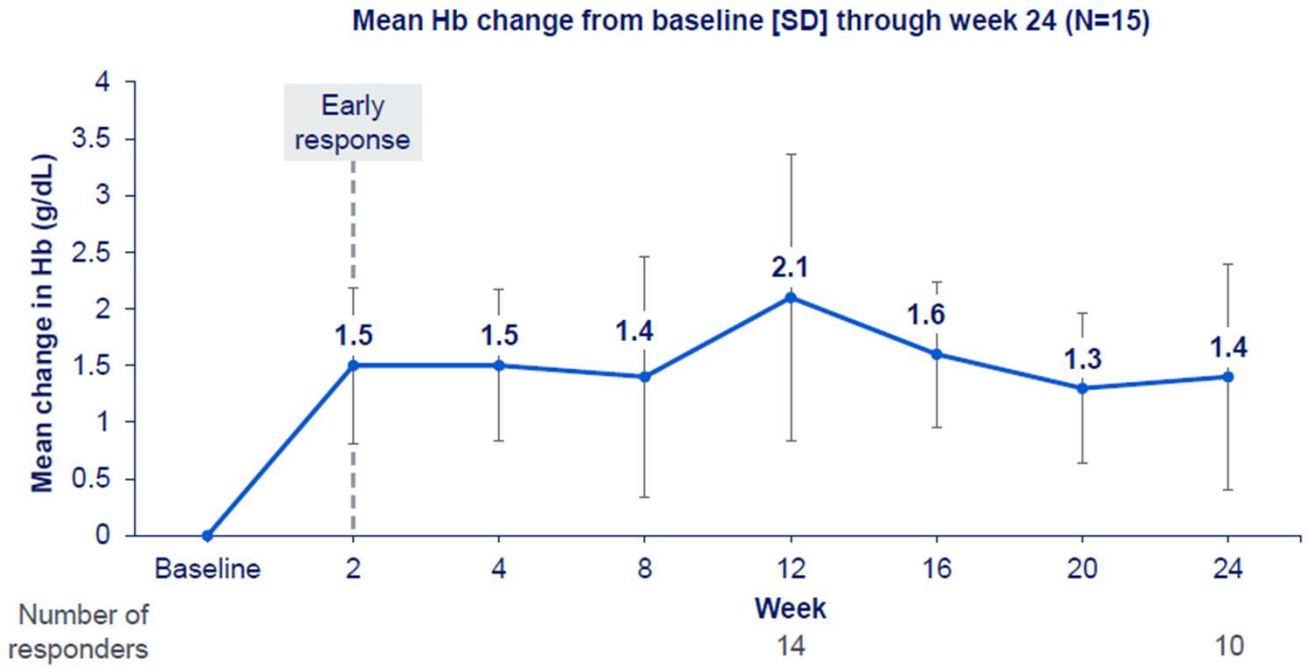
Hemoglobin responses were achieved as early as week 2 and maintained through weeks 12 and 24



At week 24, **10 out of 15** participants demonstrated an Hb response*

Over 24 weeks, the **mean (SD) VOC** was **1.8 (1.9)** (total number of VOC was **27**)

*Hb response was defined as greater than 1.0 g/dL increase from baseline. Baseline was defined as the average of screening and day 1 measurement prior to first dose of etavopivat.
Hb, hemoglobin; N, number; SD, standard deviation; VOC, vaso-occlusive crisis.

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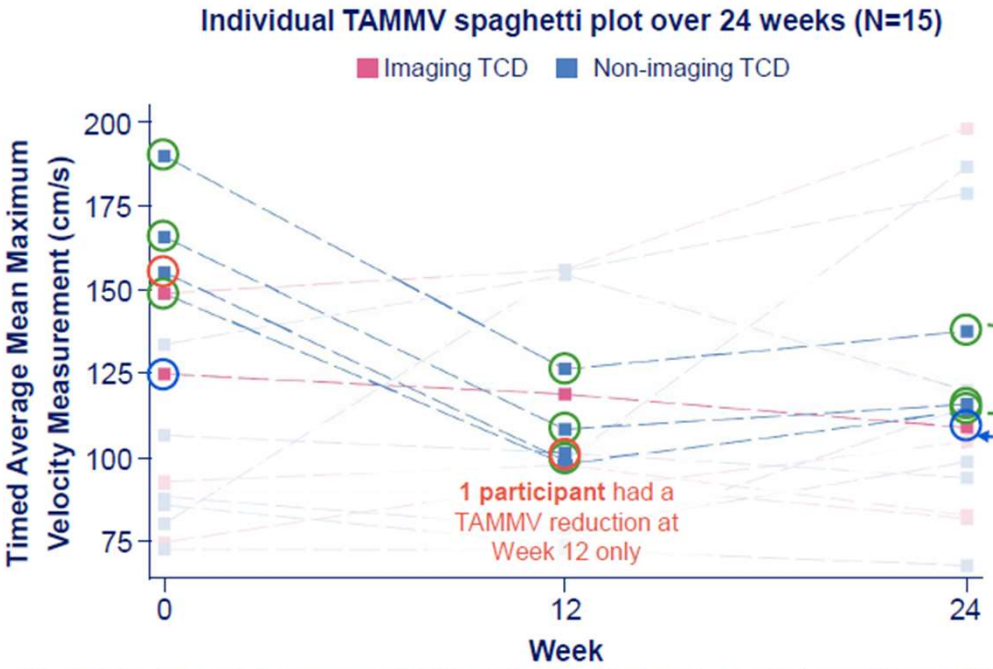
Cerebral blood flow velocity improvement was observed at Weeks 12 and 24 in four participants*



3 participants had a TAMMV reduction at Weeks 12 + 24

1 participant had a TAMMV reduction at Week 24 only

The **one participant who had a conditional TCD** (non-imaging TCD >170 cm/s) at baseline also demonstrated a **TAMMV reduction**

An improvement in TAMMV was defined as a **TAMMV reduction** of **>15 cm/s** from baseline

*Cerebral blood flow velocity improvement (>15 cm/s from baseline) was observed in four participants at Week 12 and four participants at Week 24. Three participants achieved improvement at both Weeks 12 and 24; one patient only achieved improvement at Week 12 and one only at Week 24.
TAMMV, time-averaged mean of the maximum velocity; TCD, transcranial doppler.

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«INNOVATIVE THERAPEUTIC APPROACHES»:

rethink and optimize «old drugs» and «old therapeutic approaches»

- HYDROXYUREA → Dose optimization, check adherence, personalized medicine
- RED CELL TRANSFUSION → Reduce risk of alloimmunization; use when necessary, improve safety
- BONE MARROW TRANSPLANTATION → Increase donor pool and safety; reducing long term effects
- PAIN MANAGEMENT → Personalize and optimize schedules, reduce oppiod dependance…

Conclusions

- Other therapeutic options are becoming available – link with reference centers with open trials
- Ensure that Standard of care is delivered
- Optimization of HU, RBC Transfusion and HSCT
- Focus on improving health care organization and networking
- Enrollment in Clinical Trials and Research Protocols (including data collection for outcome evaluation)

città della speranza

Azienda Ospedale Università Padova

Università degli Studi di Padova

European Reference Network
for rare or low prevalence complex diseases
Network Hematological Diseases (ERN EuroBloodNet)

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