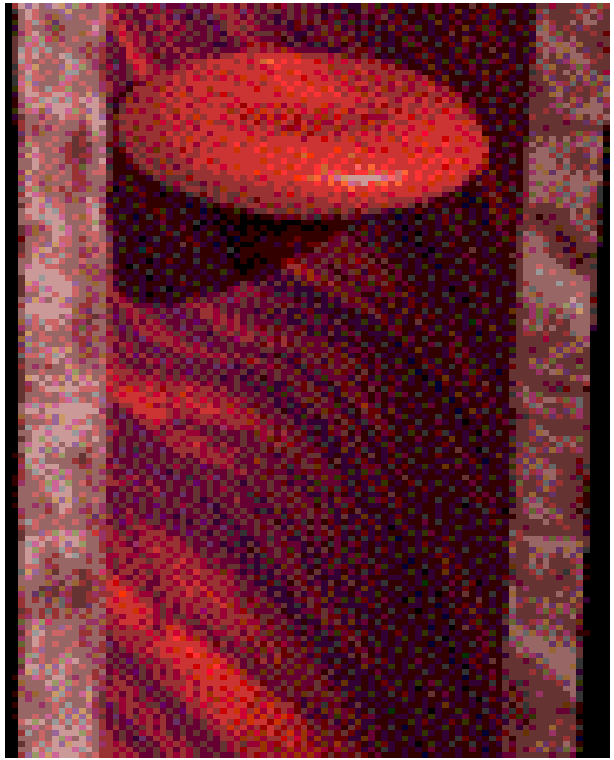
EuroBloodNet

Webinar October 6 2021

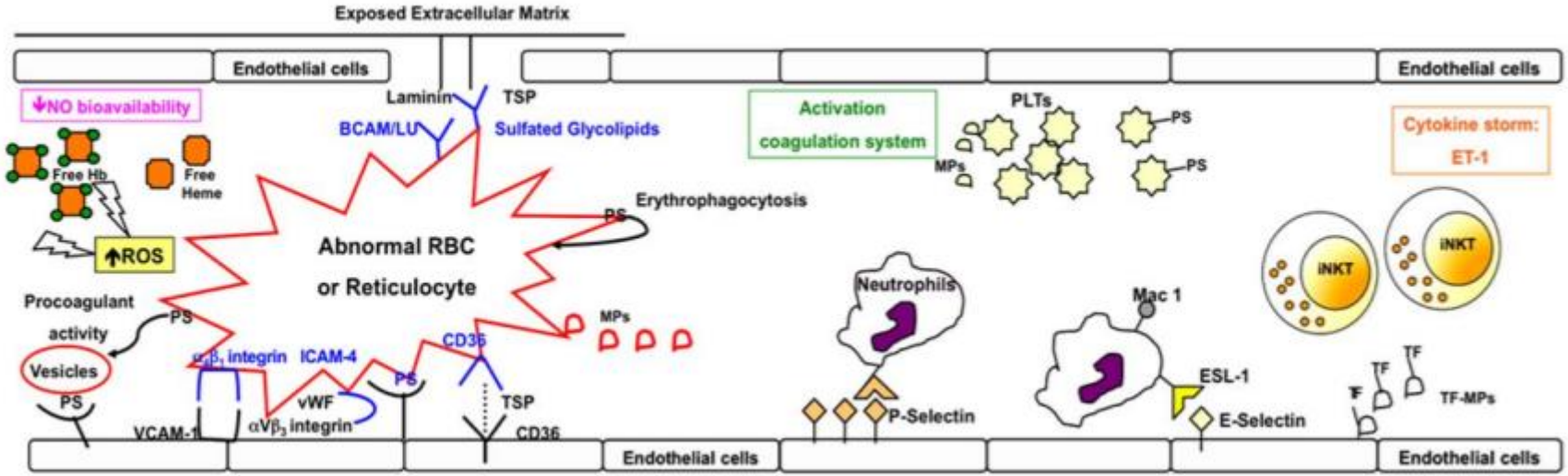
New Drugs in Sickle Cell Disease

Mariane de Montalembert

Sickling

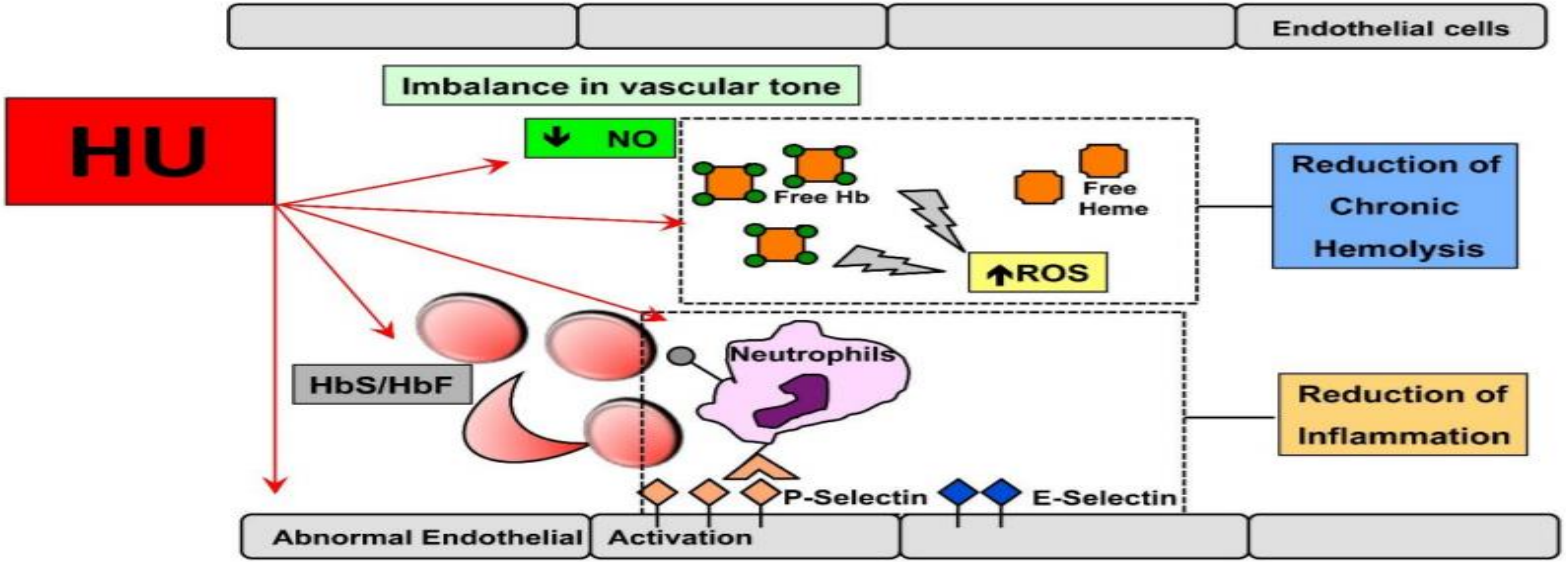


Pathophysiology of Sickle cell disease

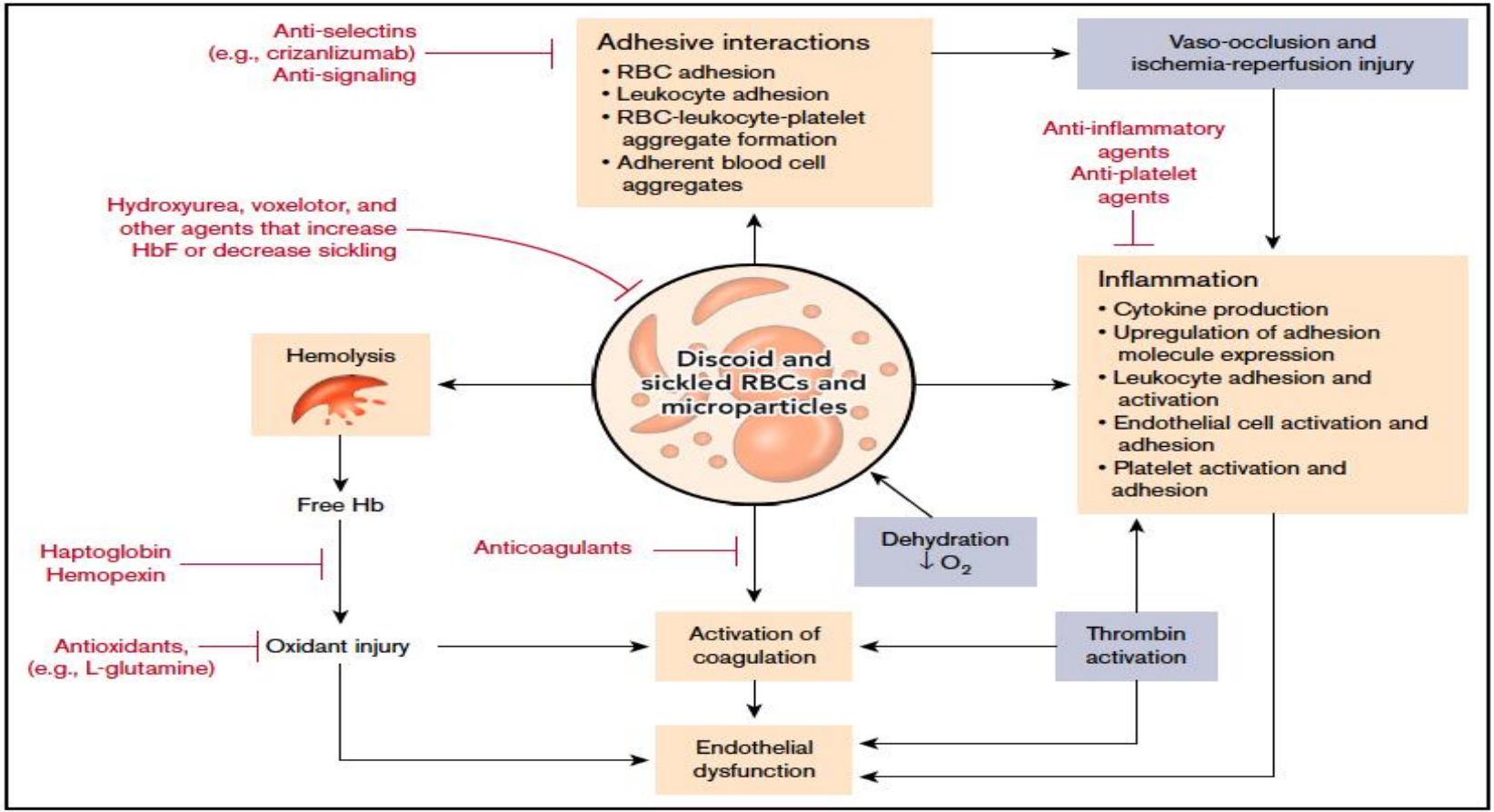


Matte A, Mediterr J Hematol Infect Dis 2019

Mechanisms of action of HU in SCD



Matte A, Mediterr J Hematol Infect Dis 2019



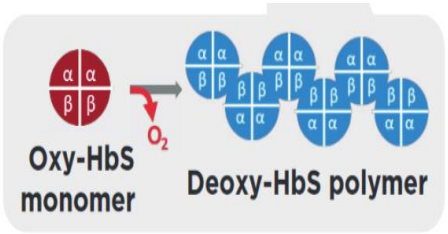
Telen MJ, Blood 2020

Voxelotor
Oral antisickling agent

The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 8, 2019 VOL. 381 NO. 6

A Phase 3 Randomized Trial of Voxelotor in Sickle Cell Disease

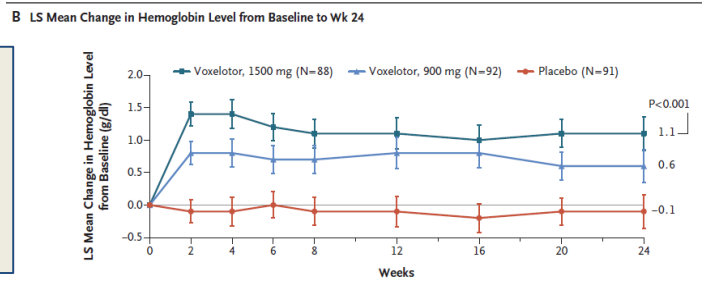
Elliott Vichinsky, M.D., Carolyn C. Hoppe, M.D., Kenneth I. Ataga, M.D., Russell E. Ware, M.D., Ph.D.,



Stabilizes Hb in high O2 affinity state, delaying HbS polymerization and sickling

- 274 SCD patients > 12 years of age (median age: 24 yrs)
- 3 groups: placebo, 900 mg, 1500 mg/d
- Primary endpoint: % of patient with increase of Hb level >1 g/dl at week 24

Primary end point met
in 51% of patients
in the group receiving 1500 mg
vs 7% in placebo group



In the group receiving 1500 mg

- Significant decrease in retics and indirect bilirubin
- No influence of concomitant HU treatment on Hb increase (64% on HU)

Trend for a reduced incidence of VOC overtime with voxelotor

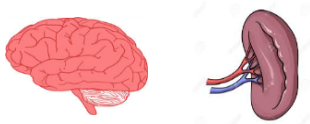
Oxbryta® (voxelotor) Tablets Indications and Usage

- OXBRYTA is indicated in the United States for the treatment of sickle cell disease (SCD) in adults and pediatric patients 12 years of age and older.
- This indication is approved under accelerated approval based on increase in hemoglobin (Hb). Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trial(s).

Indication: low Hb level in SCD patients

Unanswered questions:

- impact on VOC
- impact on organ failure, especially vasculopathy



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Real-World Experience of Voxelotor for the Treatment of Patients With Sickle Cell Disease: A Single-Center Study

77 patients included: mean (SD) age of 30.4 years (14.2 years), 63% female, and 86% with the HbSS (sickle cell anemia) genotype

Mean (range) duration of voxelotor treatment: 9.7 months (1.9-17 months)

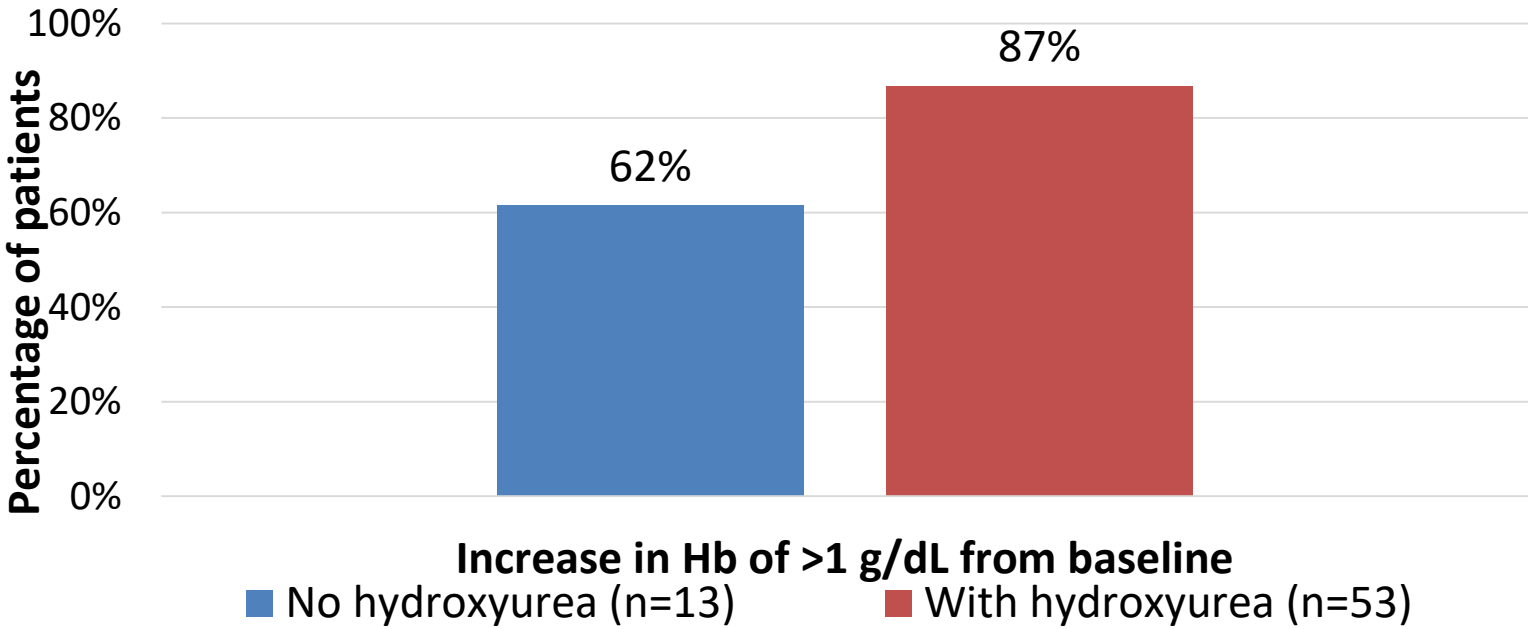
Muschik K, et al. EHA 2021; Poster EP1209

Response to Voxelotor Treatment

	Pre-voxelotor	Post-voxelotor	Absolute change from baseline	Relative change from baseline
Hb, g/dL				
N	74	66	66	66
Mean (SD/confidence interval)	8.3 (1.4)	10.3 (1.5)	2.0 (1.0)	25.6 (22.1, 29.0)
Reticulocytes, %				
N	73	66	66	66
Mean (SD/confidence interval)	11.5 (5.9)	6.5 (4.1)	–4.6 (3.9)	–37.6 (–44.2, –31.0)
Total bilirubin, mg/dL				
N	72	65	65	65
Mean (SD/confidence interval)	3.5 (2.7)	2.0 (1.4)	–1.4 (2.1)	–31.9 (–41.6, –22.1)

Muschik K, et al. EHA 2021; Poster EP1209

Response to Voxelotor Treatment by Hydroxyurea Use



Muschik K, et al. EHA 2021; Poster EP1209

Adverse Events Leading to Temporary Dose Modification

- Adverse effects of voxelotor therapy were mostly mild and self-limited. Four patients had adverse events (2 diarrhea, 1 rash, 1 fever) that led to temporary dose modification.

Reported adverse event	Action taken	Event resolved
Diarrhea	Reduced dose to 1000 mg for 1 month; resumption to 1500 mg	Yes
Diarrhea	Reduced dose to 1000 mg; resumption to 1500 mg	Yes
Rash	Reduced dose to 1000 mg; resumption to 1500 mg with loratadine	Yes
Fever	Reduced dose to 500 mg; resumption to 1500 mg	Yes

Muschik K, et al. EHA 2021; Poster EP1209

HOPE-KIDS 1: Evaluation of Voxelotor in Pediatric Patients

Part C: Voxelotor 1500 mg*
n=56[a]
45 pediatric patients (aged 4 to 11 years)
11 adolescent patients (aged 12 to 17 years)

48-week treatment period

Age group	Dosing
12-17 years	1500 mg
4-11 years	
10 to <20 kg	600 mg
20 to <40 kg	900 mg
≥40 kg	1500 mg

47.1% of patients achieved a Hb response (defined as >1 g/dL Hb increase) at 24 weeks (95% CI, 29.8%-64.9%)

The mean percent change from baseline to Week 24 for patients aged 4-11 was a decrease of 38% for indirect bilirubin and decreases of about 3% for both LDH and percent reticulocytes.

Estepp JH, et al; EHA 2021

Safety and Tolerability of Voxelotor in Children

- **Weight-based dose of voxelotor was well tolerated in children**
- **Majority of drug-related AEs related to voxelotor were Grade 1 or 2**
  - 2 of 45 patients discontinued the drug due to AEs considered related to voxelotor

Most Common Drug-related AEs Reported

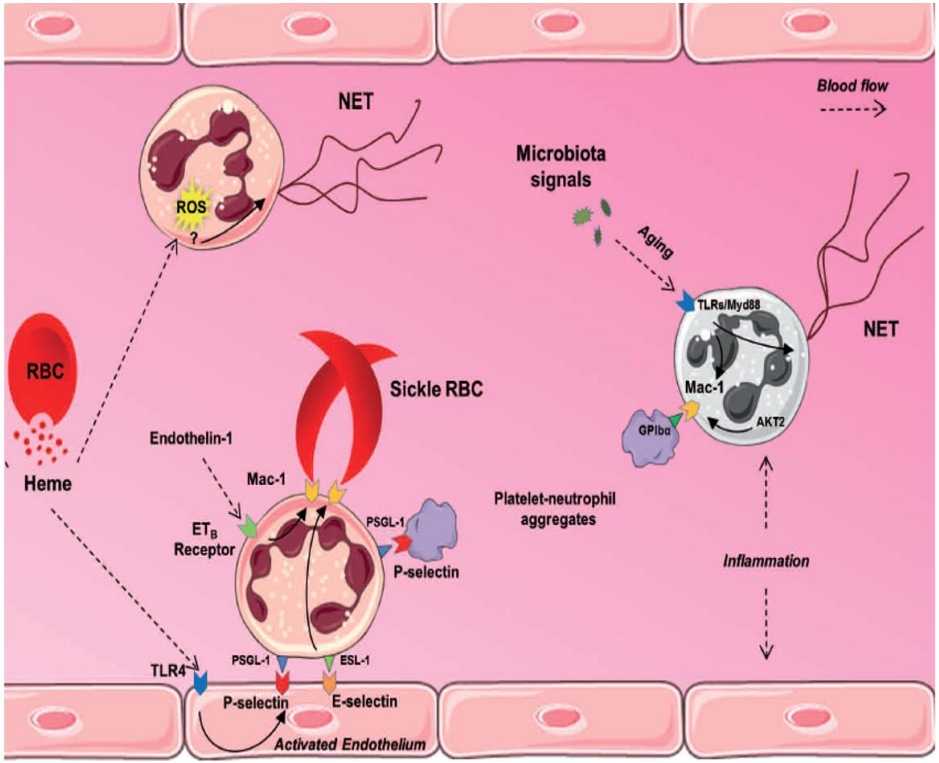
Adverse events n (%)	4-11 years n=45
Any TEAE	22 (48.9)
Diarrhea	5 (11.1)
Rash	5 (11.1)
Vomiting	5 (11.1)
Abdominal pain	4 (8.9)

Estepp JH et al; EHA 2021

HOPE-KIDS 2 (NCT04218084) post-approval confirmatory study using TCD flow velocity to evaluate reduction in stroke risk in children 2 to 15 years of age

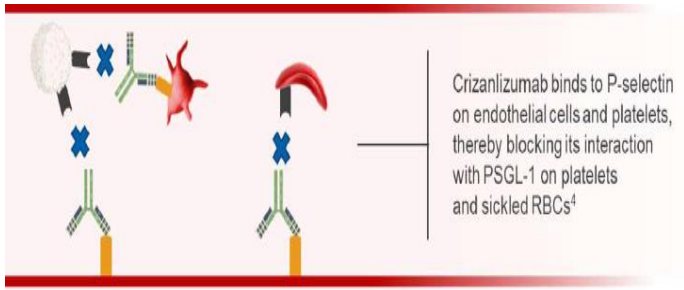
Cell adhesion role of P-selectin in SCD

- P-selectin is expressed on platelets and endothelial cells
- P-selectin participates in the adhesion, rolling, and capture of blood cells and contributes to a chronic inflammatory state
- Secondary capture of platelets to adherent neutrophils occurs when P-selectin on the platelet surface binds PSGL-1 on the neutrophil surface
- Targeting multicellular adhesion via P-selectin may result in decreased VOC incidence



Allali S, Haematologica 2020

Crizanluzimab
I.V. anti-adhesion agent



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

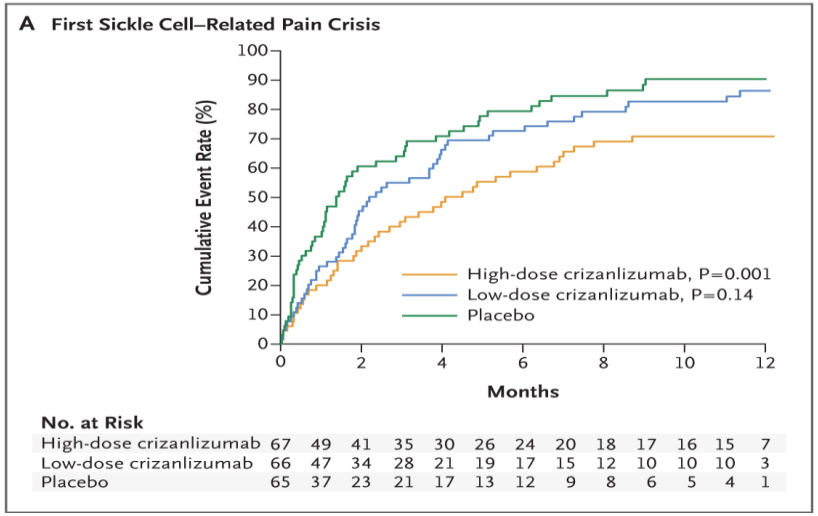
Crizanlizumab for the Prevention of Pain Crises in Sickle Cell Disease

K.I. Ataga, A. Kutlar, J. Kanter, D. Liles, R. Cancado, J. Friedrisch, T.H. Guthrie,

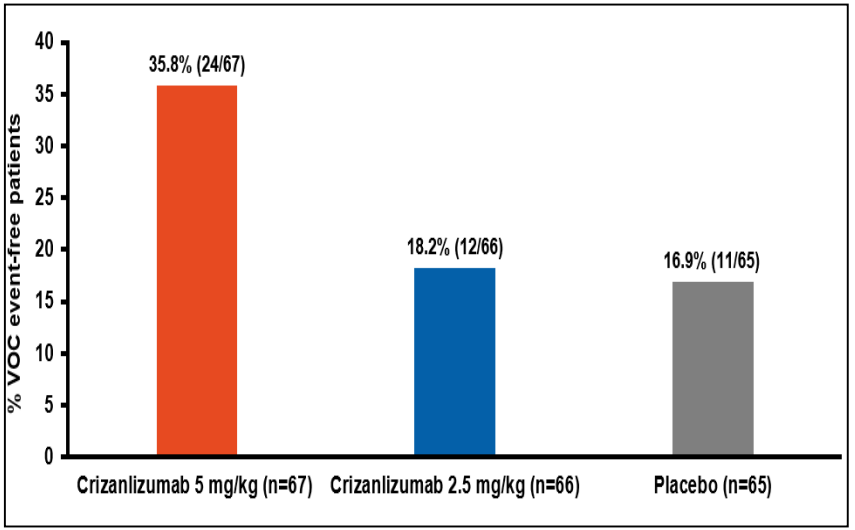
- Double-blind, randomized, placebo-controlled, phase 2 trial, 52 weeks
- IV, Low-dose crizanlizumab (2.5 mg/kg), high-dose crizanlizumab (5.0 mg/kg), or placebo
- Primary endpoint: annual rate of VOC
- 129 patients, 16-65 yrs , 2-10 VOC/yr , 63% under HU

VOC frequency decrease by 45%

Ataga KI, NEJM 2019



VOC frequency decrease by 45%

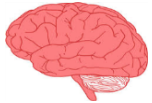


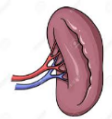
“On November 15, 2019, Food and Drug Administration approved crizanlizumab-tmca (ADAKVEO, Novartis) to reduce the frequency of vaso-occlusive crises (VOCs) in adults and pediatric patients aged 16 years and older with sickle cell disease”

Indication: pain in SCD patients

Unanswered question:

Impact on organ failure (especially cerebral vasculopathy)





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EMA 28/10/2020

Crizanluzimab is indicated for the prevention of recurrent VOCs in sickle cell disease patients aged 16 years and older. It can be given as an add on therapy to hydroxyurea or as monotherapy in patients for whom HU is inappropriate or inadequate.

Specific obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14-a of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
In order to further confirm the efficacy and safety of crizanlizumab, the MAH should submit the results of the primary analysis of a phase III CSEG101A2301 study of crizanlizumab with or without hydroxyurea/hydroxycarbamide in adolescent and adult sickle cell disease patients with vaso-occlusive crises	Clinical study report primary analysis: December 2025
In order to further confirm the efficacy and safety of crizanlizumab, the MAH should submit the final results of the phase II CSEG101A2202 study of crizanlizumab with or without hydroxyurea/hydroxycarbamide in sickle cell disease patients with vaso-occlusive crisis	Clinical study report: December 2025

The SENTRY study umbrella explores the benefits of crizanlizumab in patients with SCD

Key SENTRY studies

SOLACE-adults
CSEG101
A2202
Ongoing
(Enrollment completed)

SOLACE-kids
CSEG101
B2201
Ongoing
(Temporary enrollment halt*)

STAND
CSEG101
A2301
Ongoing
(FPFV Jul 2019,
208/245 patients randomized)

SPARTAN
CSEG101
AUS05
Ongoing
(FPFV Oct 2019,
16/56 patients randomized)

STEADFAST
CSEG101
A2203
Ongoing
(FPFV Dec 2019,
28/148 patients randomized)

VOC prevention

Organ protection

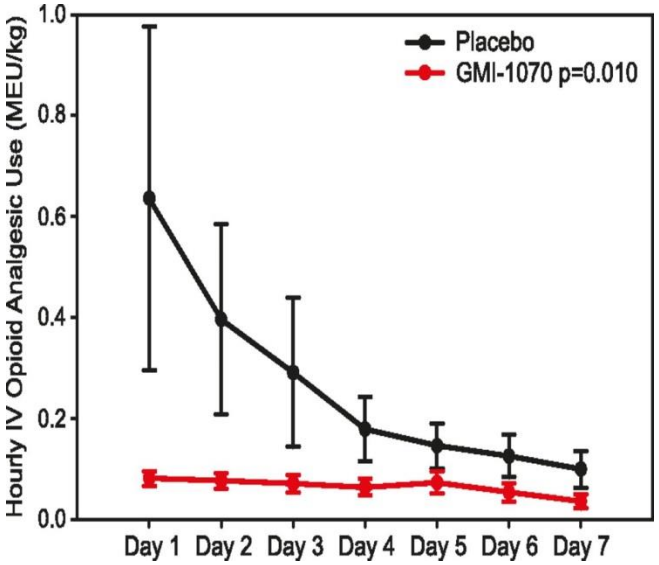
*Novartis has temporarily halted the recruitment of new patients until the dose in Group 2 is confirmed. The safety and benefit/risk remain unchanged and enrolled patients continue to be treated as per protocol.
FPFV, first-patient first-visit; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

Pan-selectin inhibitor: rivipansel

- GMI 1070 (Glycomimetics)
Pan-selectin inhibitor,
with maximal activity against E-selectin

- Phase III study: RESET (NCT02187003), stopped in August 2019 for lack of efficacy

Mean hourly opioid use by day.



Telen MJ, Blood 2015

Early initiation of Rivipansel for VOC achieves earlier discontinuation of IV opioids and shorter hospital stay

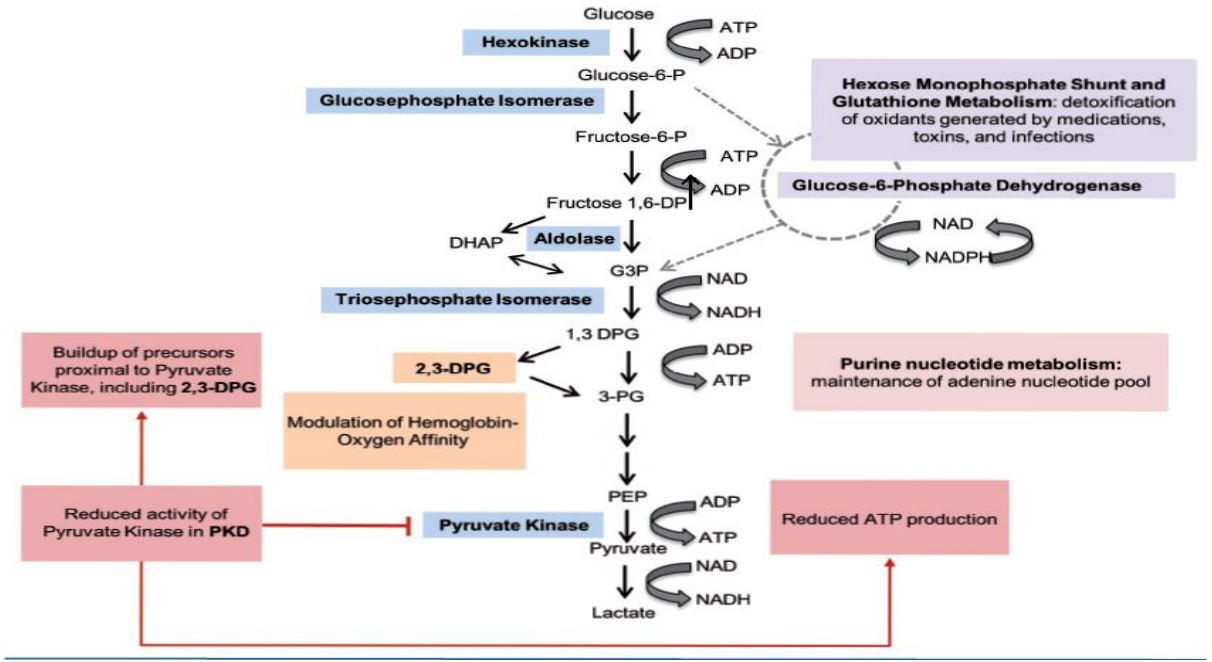
Table 2. RESET Study Hazard Ratios and 95% CIs for Key Efficacy Endpoints

	TTRFD	TTD	TTDIVO
Early Treatment (≤26.4 H from VOC Onset), Overall Population	0.58 (0.35, 0.96) *P = 0.0347*	0.54 (0.33, 0.89) *P = 0.0154*	0.58 (0.35, 0.94) *P = 0.0274*
Early Treatment (≤30 H from VOC Onset), Ages 6-17 yrs	0.42 (0.20, 0.87) *P = 0.0193*	0.42 (0.21, 0.86) *P = 0.0169*	0.49 (0.24, 0.98) *P = 0.045*

A Cox proportional hazards regression model with age group and genotype group as stratification covariates is used to estimate the hazard ratio (Placebo/Rivipansel), the corresponding 95% CI, and P-value.
TTRFD = Time to Ready for Discharge
TTD = Time to Discharge
TTDIVO = Time to Discontinuation of IV Opioids

Dampier CD, et al. ASH 2020, Abstract 678

Allosteric Activator
RBC Pyruvate-Kinase R



The glycolytic pathway

Al-Samkari H, Haematologica 2020

HbS RBC

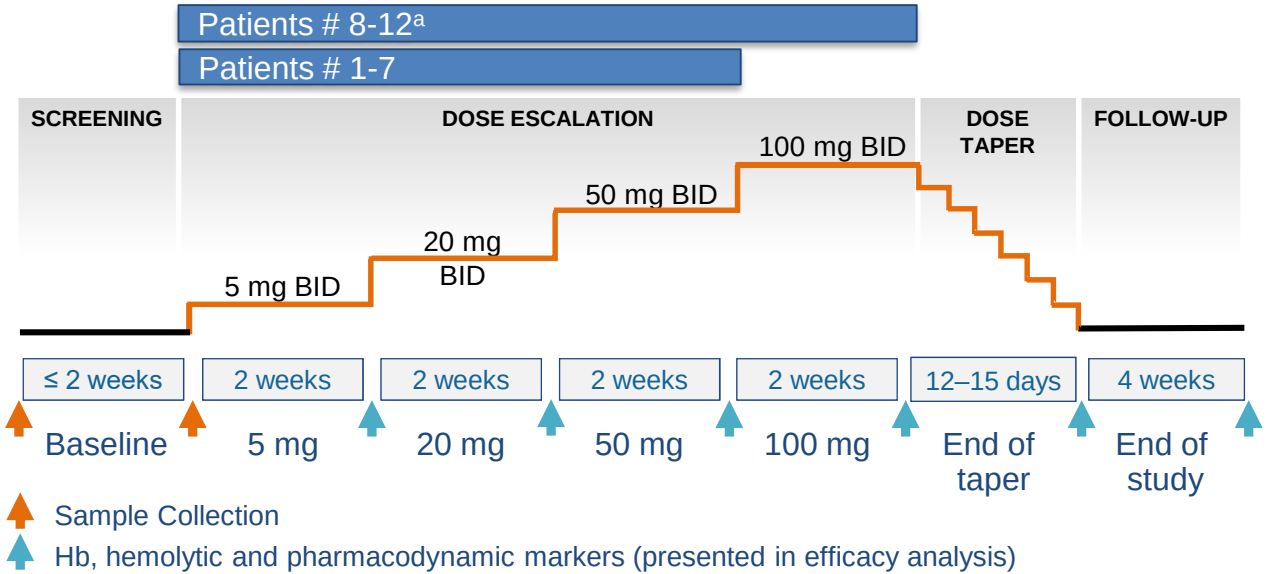
↑ 2,3 – DPG

↓ 0_2 affinity

↓ RBC ATP

NIH Study design: Phase 1 multiple ascending dose study of mitapivat in SCD

- Nonrandomized, open-label, phase 1 study; N ≈ 15–25
- Adults (age ≥ 18 years) with stable Hb SS disease eligible
- No transfusions or changes in hydroxyurea/L-glutamine within 90 days



Primary endpoints:

- Safety and tolerability
- Changes in Hb and hemolytic markers

Secondary endpoints:

- Pharmacokinetics
- 2,3-DPG and ATP levels
- O_2 dissociation and sickling tendency[b]

[a]100 mg dose level added to protocol with amendment #6. [b]Data is incomplete due to disruptions related to COVID-19 pandemic.
NIH=National Institute of Health; ATP = adenosine triphosphate; BID = twice daily; DPG = diphosphoglycerate; Hb = hemoglobin; Hb SS = sickle cell anemia; O_2 = oxygen; SCD = sickle cell disease.
Xu J et al. 2020 ASH Annual Meeting, Abstract 681.

Date of preparation: May 2021 [MIT-ALL-0047]

Mitapivat increased Hb levels in SCD

Response parameter	N = 11
Maximal Hb increase, mean (SD), g/dL	1.3 (0.8)
Hb increase ≥ 1g/dL, n (%)	6 (54.5)
Maximal Hb increase in patients with ≥ 1g/dL response, mean (SD), g/dL	1.9 (0.7)[a]

Decrease in total Bilirubin, LDH and retic count

Data cut: 6Oct2020.
[a]n=6. BID, twice daily; Hb = hemoglobin; SD = standard deviation.
Xu J et al. 2020 ASH Annual Meeting, Abstract 681.

Date of preparation: May 2021 [MIT-ALL-0047]

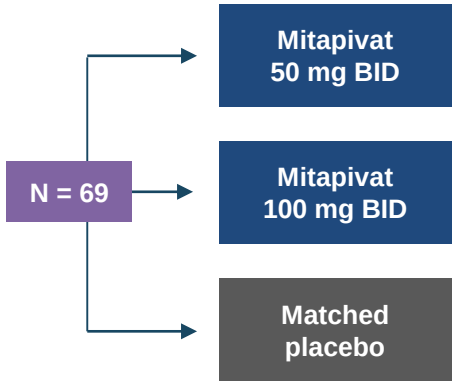
Phase 2/3 SCD trial design

ENROLLMENT CRITERIA

- ≥ 16 years
- 2-10 sickle cell crises in the past 12 months
- Hb ≥ 5.5 and ≤ 10.5 g/dL
- Currently receiving treatment with voxelotor, crizanlizumab, or any other agent intended to increase Hb-oxygen affinity are excluded
- Treatment with hydroxyurea is allowed

PHASE 2

1:1:1 randomization

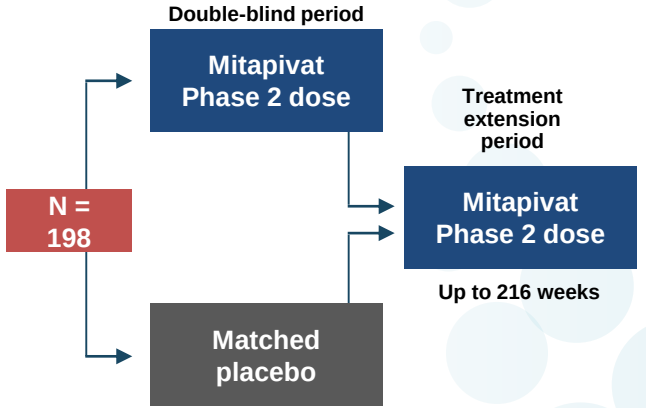


12 weeks

Primary endpoint:
Safety and % of patients with mean Hb ↑ ≥ 1 g/dL from baseline

PHASE 3

2:1 randomization



52 weeks

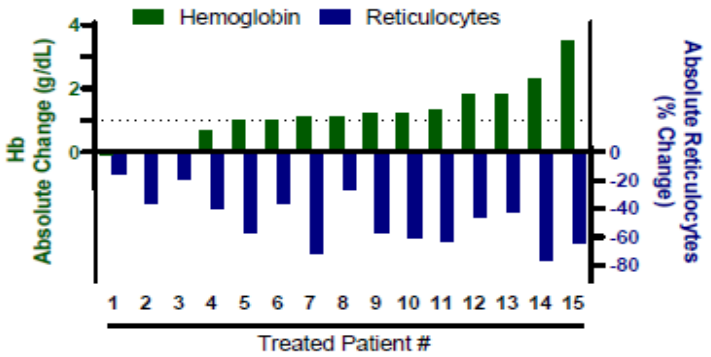
Primary endpoints:
% of patients with mean Hb ↑ ≥ 1 g/dL from baseline & annualized rate of sickle cell pain crises

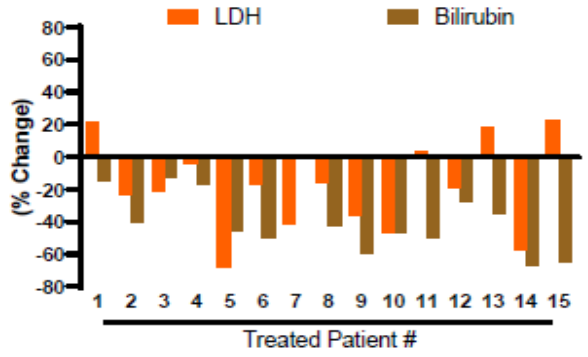
Date of preparation: May 2021 [MIT-ALL-0047]

BID = twice daily; Hb = hemoglobin

Etavopivat in adult patients with SCD

Etavopivat 300 mg or 600 mg Once Daily for 2 Weeks Significantly Improves Hematologic and Hemolytic Parameters





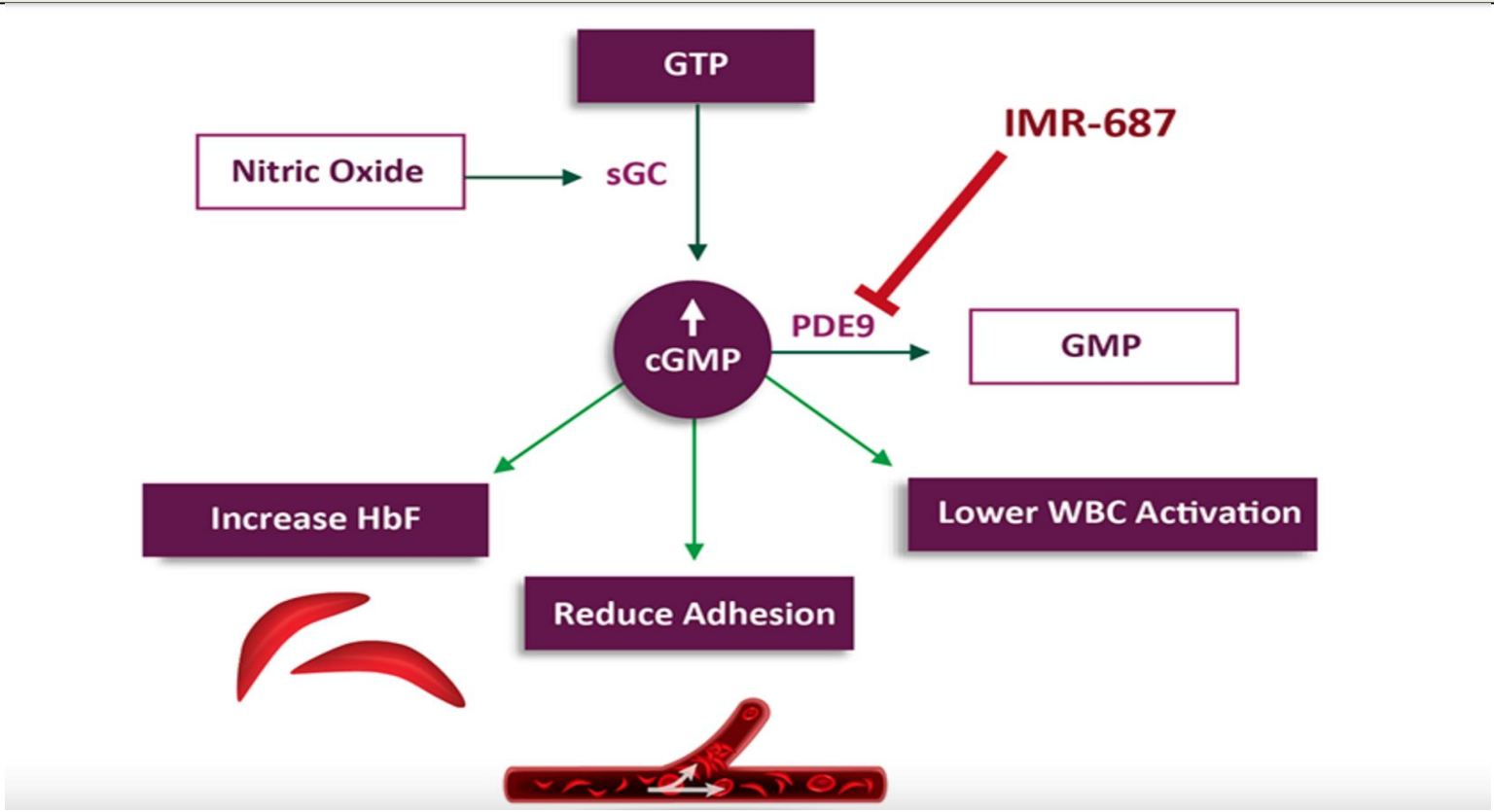
- In patients treated with etavopivat and evaluable for response (n=15):
  - 73% (11/15) achieved Hb ≥ 1 g/dL over baseline at EOT (mean ↑ 1.2 g/dL; $p<0.002$)
  - 100% (15/15) had ↓ absolute reticulocytes relative to baseline at EOT (mean ↓ 47%; $p<0.001$)
  - 73% (11/15) had ↓ LDH levels over baseline at EOT (mean ↓ 19%; $p<0.07$)
  - 93% (14/15) had ↓ indirect bilirubin levels over baseline at EOT (mean ↓ 38%; $p<0.002$)

EOT=end of treatment; Hb=hemoglobin; LDH=lactate dehydrogenase
Brown RC, et al. Presented at EHA 2021 Virtual Meeting; Jun 9-17, 2021 [E-Poster EP1202].

Data as of May 10, 2021

forma THERAPEUTICS

IMR-687
phosphodiesterase-9 inhibitor



HYDROXYUREA	
Anemia/Hemolysis	↓
Vaso-occlusion	↓
Acute Chest Syndrome	↓
Stroke	?
Nephropathy	?
Pulmonary Hypertension	?
Fatigue and QoL	↓ for some patients
Mortality	↓

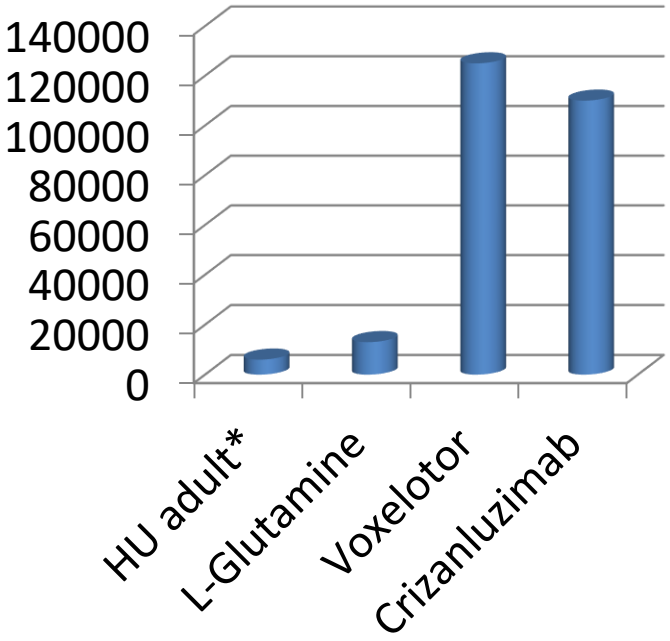
L-GLUTAMINE	
Anemia/Hemolysis	→
Vaso-occlusion	↓
Acute Chest Syndrome	↓
Stroke	No evidence
Nephropathy	No evidence
Pulmonary Hypertension	No evidence
Fatigue and QoL	→
Mortality	No evidence

VOXELOTOR	
Anemia/Hemolysis	↓
Vaso-occlusion	→
Acute Chest Syndrome	→
Stroke	No evidence
Nephropathy	No evidence
Pulmonary Hypertension	No evidence
Fatigue and QoL	→
Mortality	No evidence

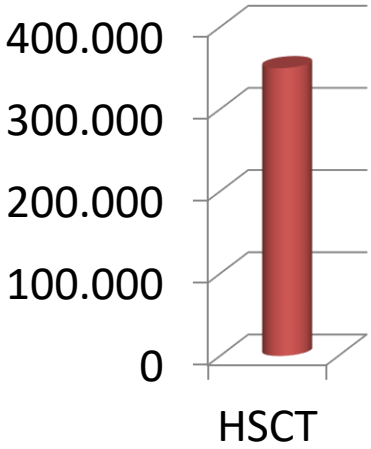
CRIZANLIZUMAB	
Anemia/Hemolysis	→
Vaso-occlusion	↓
Acute Chest Syndrome	→
Stroke	No evidence
Nephropathy	No evidence
Pulmonary Hypertension	No evidence
Fatigue and QoL	→
Mortality	No evidence

Telen MJ, Blood 2020

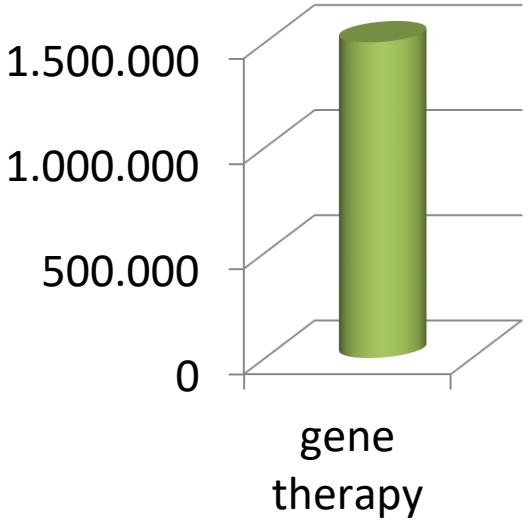
Approximated costs of drugs/yr ($)



Approximated cost of HSCT ($) (1st yr)



Approximated cost of Gene therapy ($)



- 65 kg, 25 mg/kg/d
- Licensed drug SIKLOS