Emerging pharmacological treatments for haemoglobinopathies

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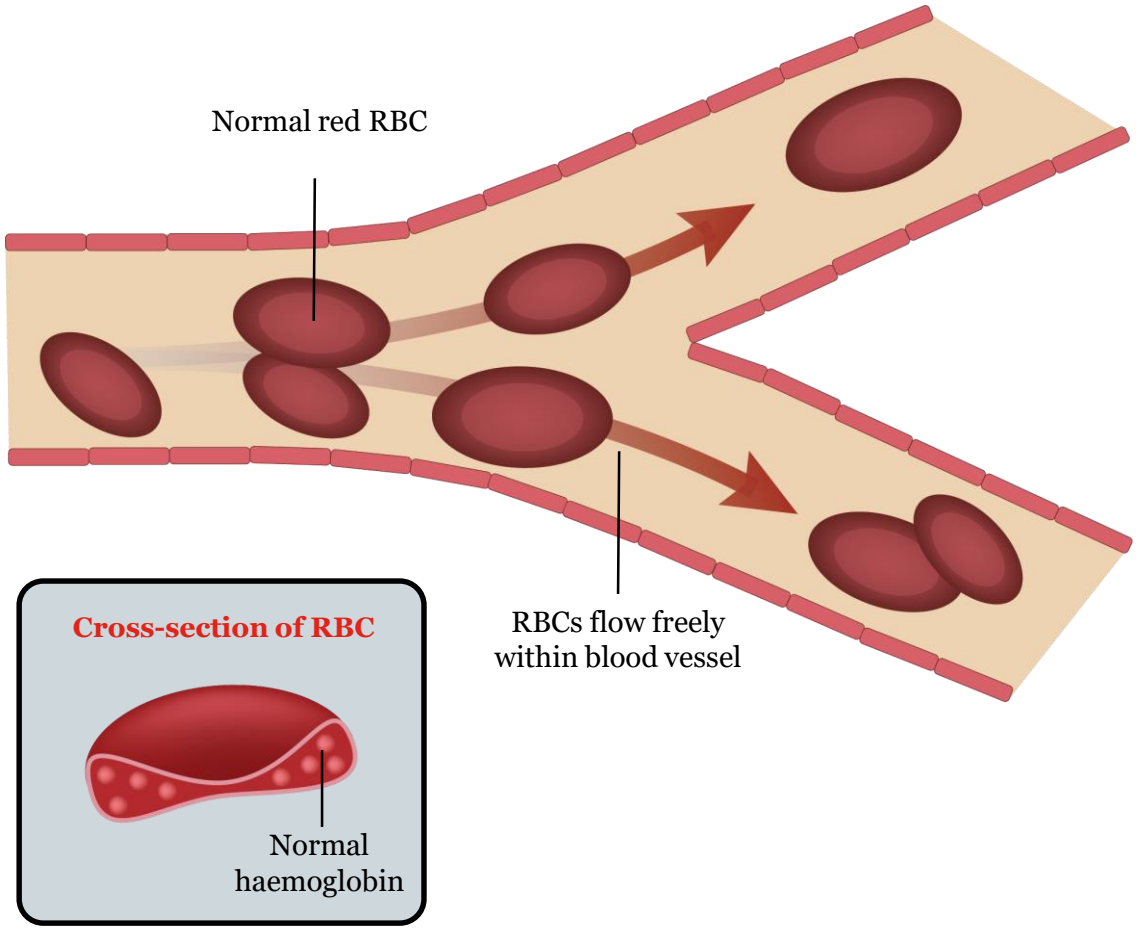
Guy's and St Thomas' NHS Foundation Trust

Successful Transition from Pediatric to Adult Care in Sickle Cell Disease: Challenges and Strategies

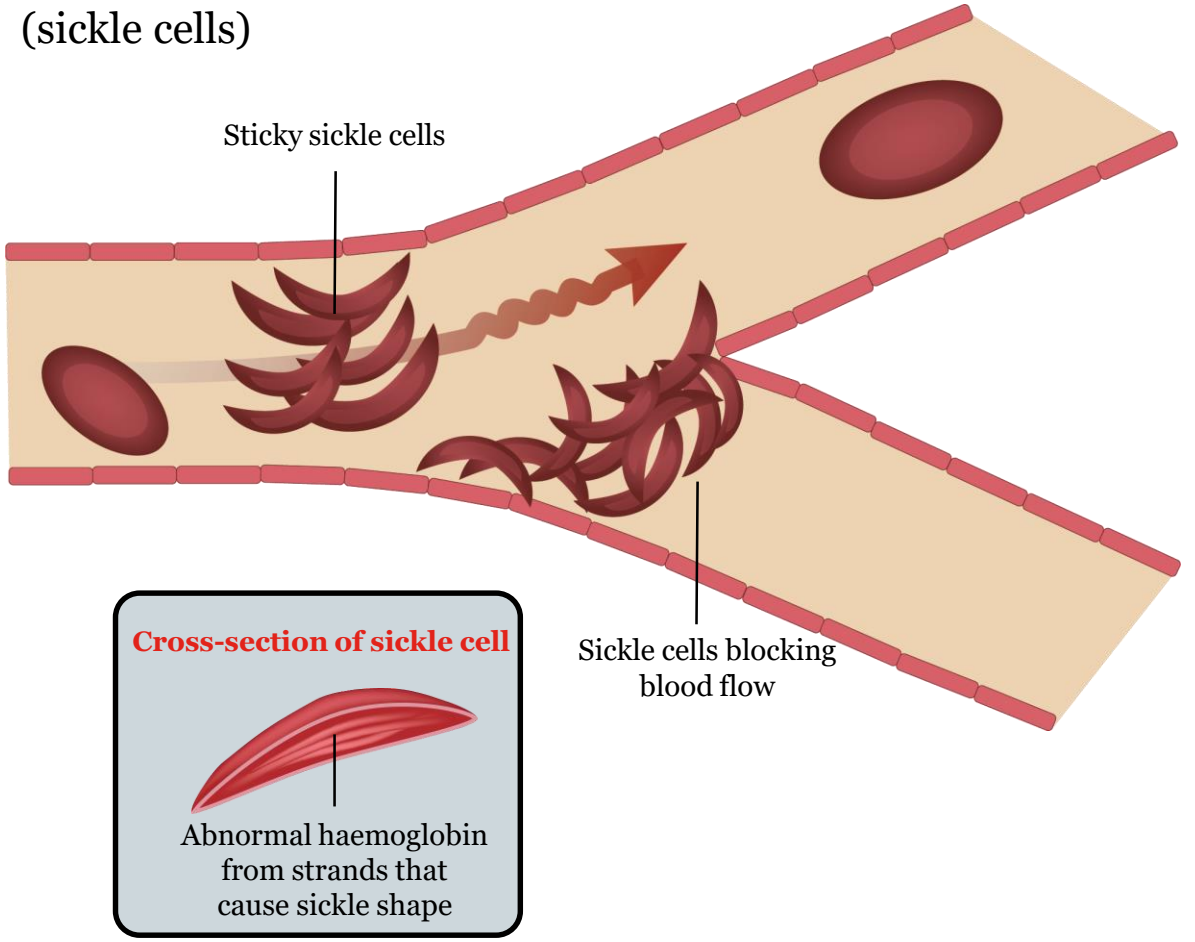
- **Pathophysiology**
- **Therapeutic targets**
- FDA approved Drugs
- Agents under development
- **Summary**

Traditionally, SCD Pathology Was Thought to Be Due to Vascular Blockages Caused By Sickle RBCs

A. Normal red blood cells



B. Abnormal, sickled, red blood cells (sickle cells)

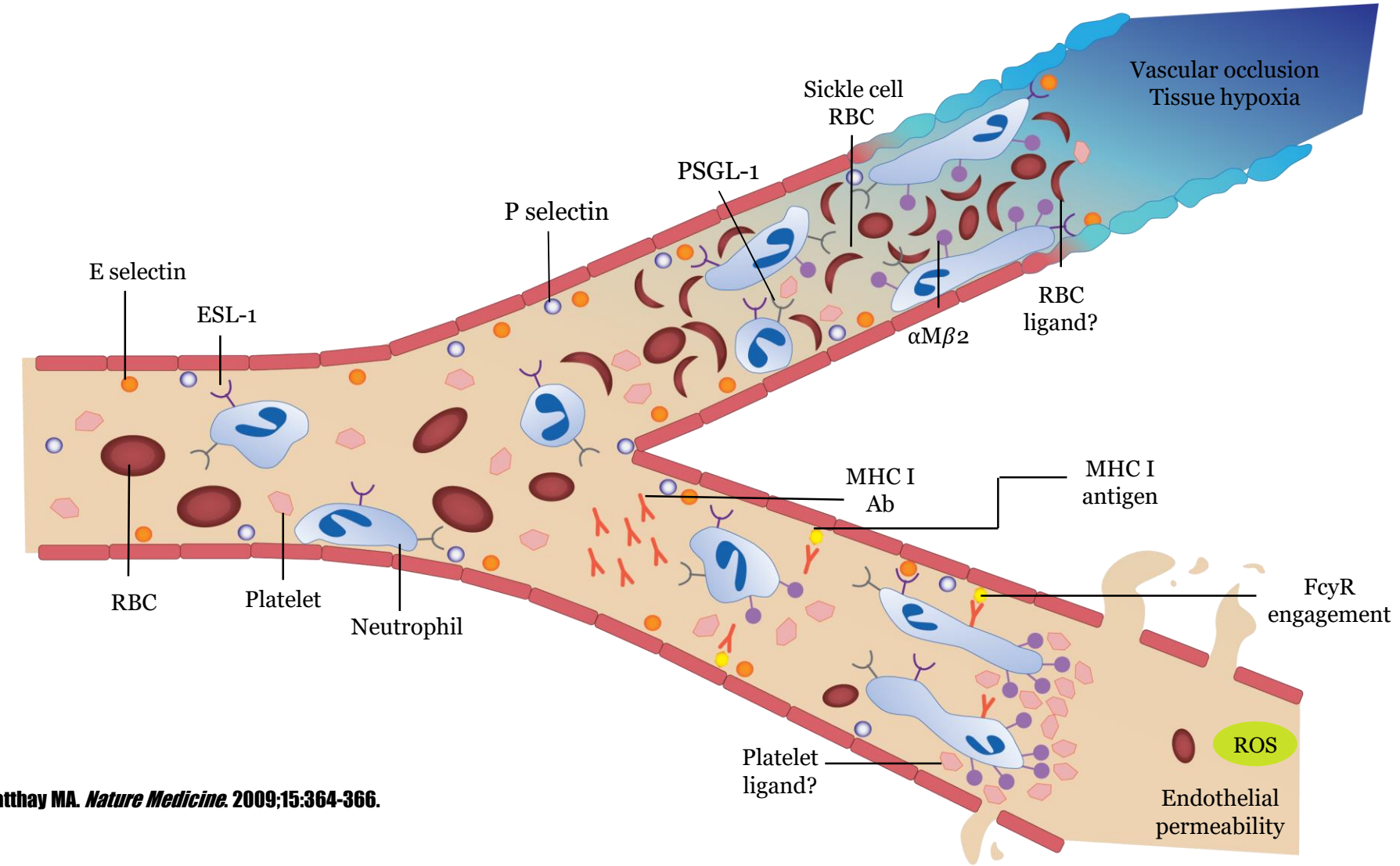


Adapted from Sickle Cell Disease. *National Heart Lung and Blood Institute*. https://www.nhlbi.nih.gov/health-topics/sickle-cell-disease

RBC, red blood cell.

Sickle Cell Disease. *National Heart Lung and Blood Institute*. https://www.nhlbi.nih.gov/health-topics/sickle-cell-disease. Accessed May 31, 2019.

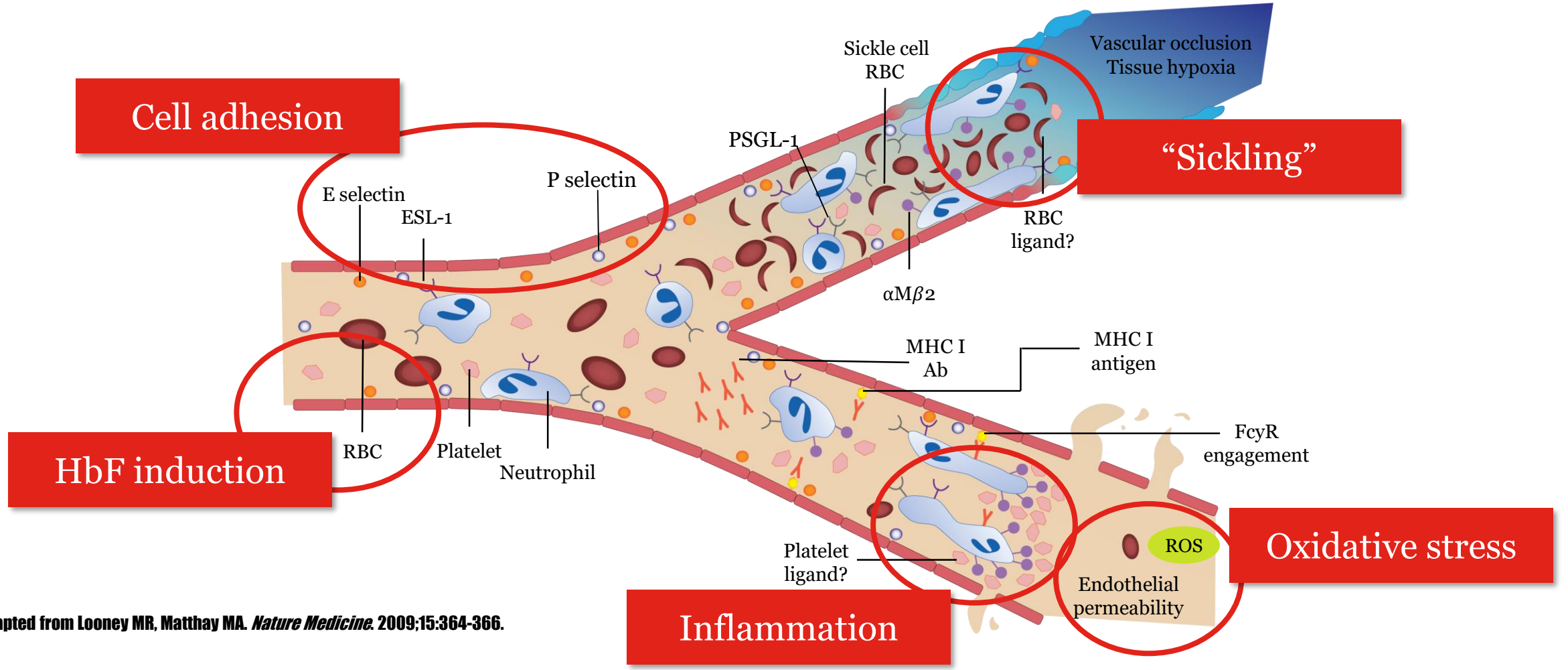
Sickle Cell Vasculopathy



Adapted from Looney MR, Matthay MA. *Nature Medicine*. 2009;15:364-366.

Ab, antibody; ESL-1, E-selectin ligand-1; FcyR, Fc receptor for immunoglobulin G; PSGL-1, P-selectin glycoprotein ligand-1; RBC, red blood cell; MHC 1, major histocompatibility complex class I; ROS, reactive oxygen species.
Looney MR, Matthay MA. *Nature Medicine*. 2009;15:364-366.

Factors that Lead to Sickle Cell Vasculopathy Can Be Potential Targets of Therapy



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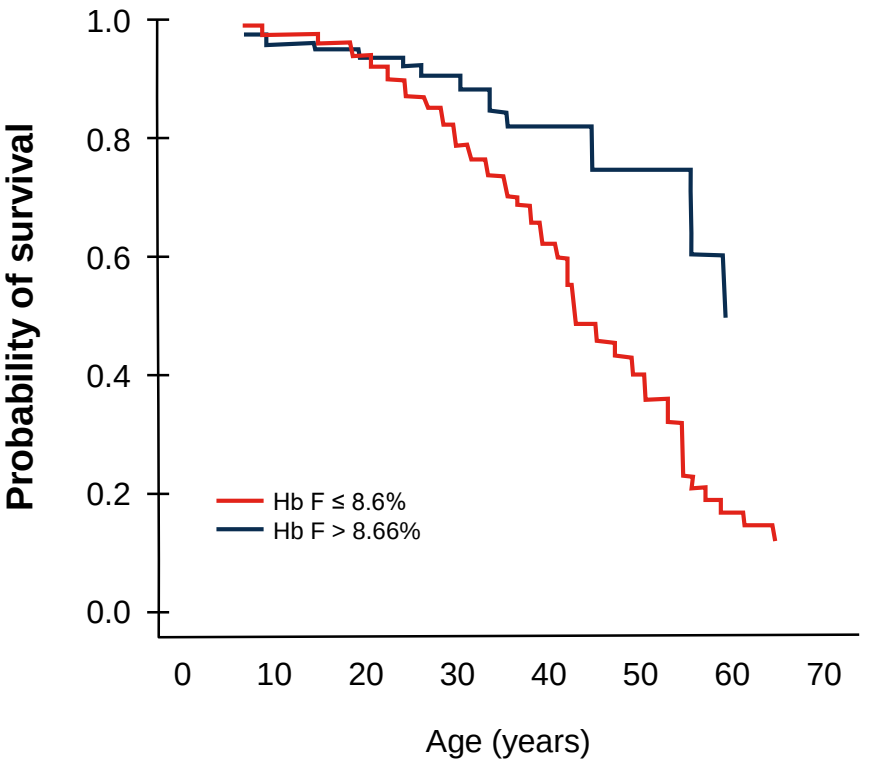
Looney MR, Matthay MA. *Nature Medicine*. 2009;15:364-366.

Fetal Haemoglobin (HbF) Induction Can Have Protective Effects in SCD Patients

Effects[1,2]:

- Reduces sickle haemoglobin (HbS) concentration
- Increases haemoglobin levels
- Reduces haemolysis
- Inhibits cellular adhesion
- Vasodilation

Hydroxyurea (*NEJM* 1995)[3]
Gene editing (*NEJM* 2017)[4]



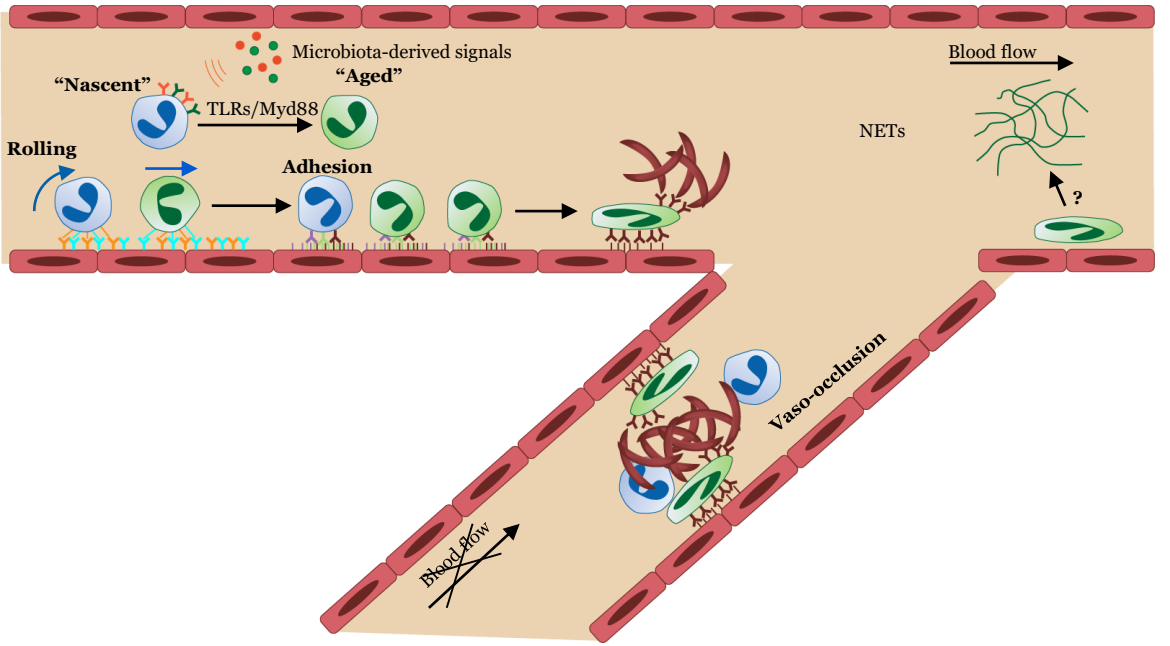
Adapted from Platt OS, Brambilla DJ, et al. *N Eng J Med.* 1994;330(23):1639-1644.

NEJM, The New England Journal of Medicine.

1. Wang WC. *Exp Biol Med.* 2016;241(7):730-736. 2. Fathallah H, Atweh GF. *Hematol.* 2006;2006(1):58-62. 3. Ho PTC, Murgo AJ. *N Eng J Med.* 1995;333(15):1008-1009. 4. Ribeil J-A, Hacein-Bey-Abina S, et al. *N Eng J Med.* 2017;376(9):848-855. 5. Platt OS, Brambilla DJ, et al. *N Eng J Med.* 1994;330(23):1639-1644.

Role of Selectins in Multicellular Adhesion

- P-selectin is expressed on platelets and endothelial cells[1,2]
- E-selectin is rapidly induced by inflammatory cytokines[2]
- L-selectin is expressed on all granulocytes and monocytes and on most lymphocytes[2]
- Selectins participate in the adhesion, rolling, and capture of blood cells[2]



Adapted from Zhang D, Chen G, et al. *Blood*. 2016;127(7):801-809.

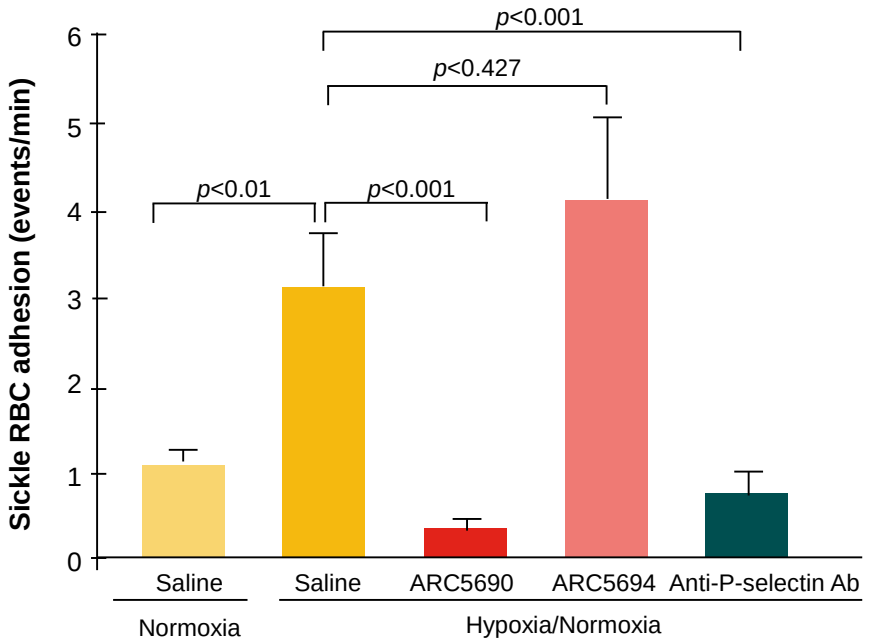
NETs, neutrophil extracellular traps; TLR, toll-like receptors.

1. Mcever RP. *Cardiovasc Res*. 2015;107(3):331-339. 2. Ley K. *Trends Mol Med*. 2003;9(6):263-268. 2.. 3. Zhang D, Chen G, et al. *Blood*. 2016;127(7):801-809.

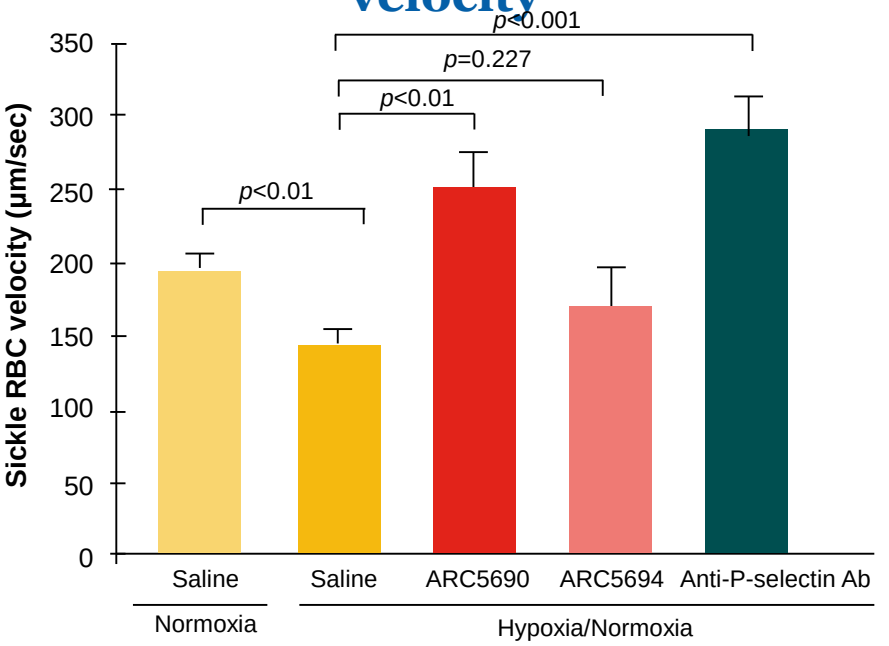
P-Selectin Is Involved in RBC Adhesion and Flow Velocity

P-selectin inhibition in mouse models shows decreased RBC adhesion and increased RBC flow velocity[1]

Inhibition of RBC adhesion



Promotion of RBC flow velocity



Adapted from Gutsaeva DR, Parkerson JB, et al. *Blood*. 2010;117(2):727-735.

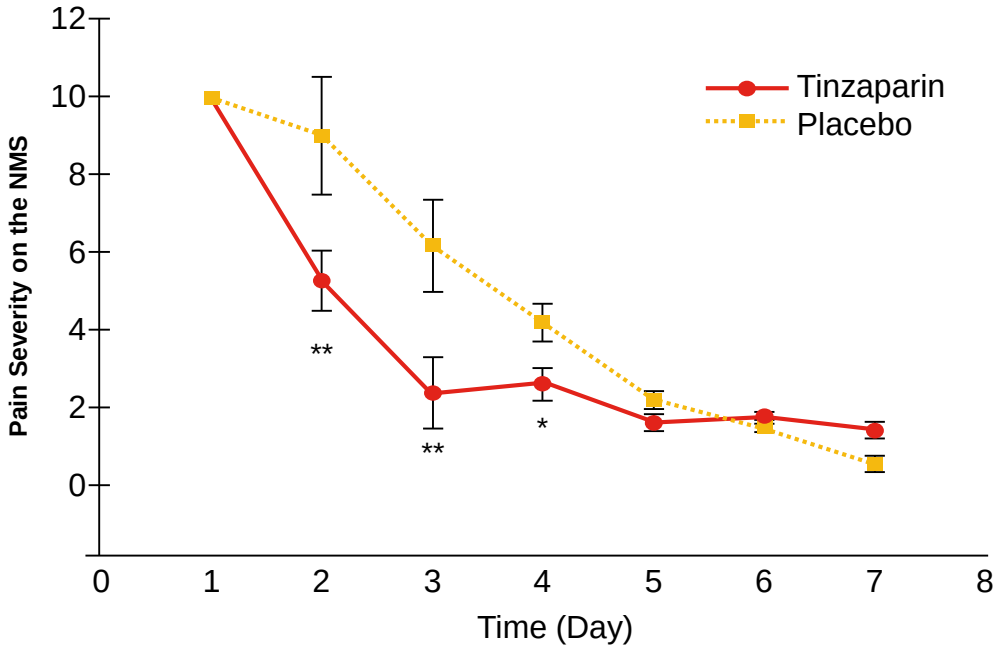
Crizanlizumab (*NEJM* 2017)[2]

Ab, antibody; ARC5690, anti–mouse P-selectin aptamer; ARC5694, negative control; RBC, red blood cell.

1. Gutsaeva DR, Parkerson JB, et al. *Blood*. 2010;117(2):727-735. 2. Ataga KI, Kutlar A, et al. *N Engl J Med*. 2017;376(5):429-439.

Tinzaparin Improved VOC Resolution

- Improved time to resolution VOC
- Reduced duration of hospital stay
- P selectin mediated…?



Characteristics and effect of tinzaparin on painful crisis and duration of hospitalization in sickle cell patients.

	Study Group (n=127)	Control Group (n=126)
Mean age (years)	22.8 ± 4.5	21.6 ± 3.8
Sex		
Male	58 (46%)	63 (50%)
Female	69 (54%)	63 (50%)
No. of days with severest pain score on NMS	1.28 ± 0.20*	1.74 ± 0.15
Duration of painful crisis (days)	2.57 ± 0.45*	4.35 ± 0.78
Total duration of hospitalization (days)	7.08 ± 1.8*	12.06 ± 2.2

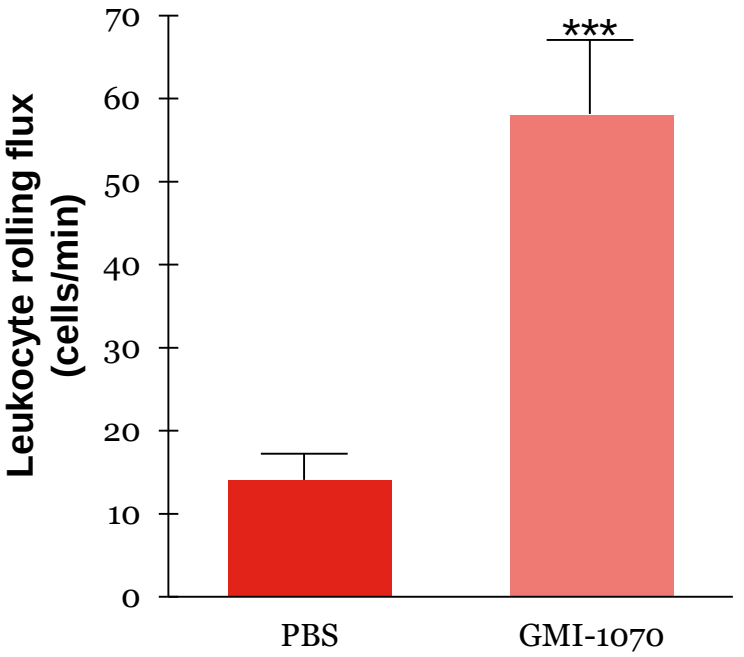
Tinzaparin was administered at 175 IU/kg, s.c. once a day for 7 days. Data represent mean ± SD, *P <0.05. NMS = numerical pain scale.

Qari MH, Aljaouni SK, Alardawi MS, et al. *Thromb Haemost*. 2007;98(08):392-396.

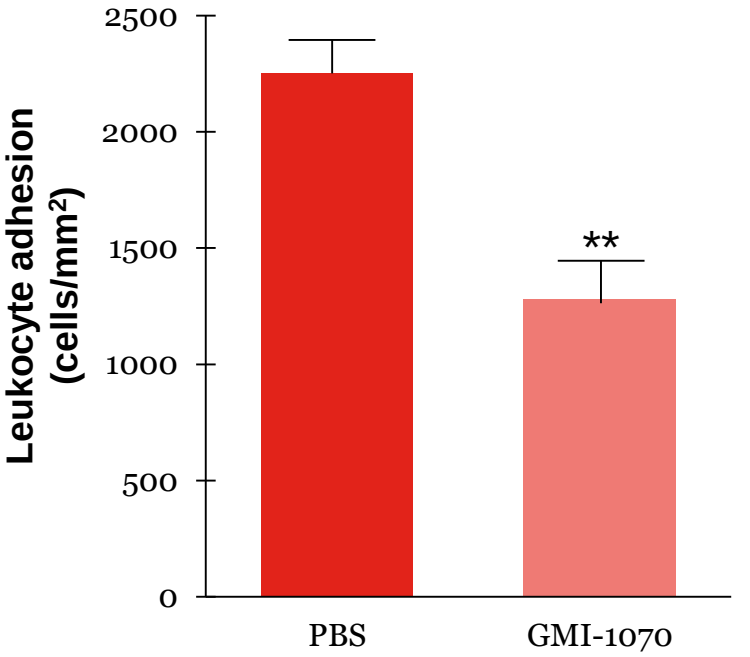
E-Selectin Is Involved in Leukocyte Rolling and Adherence

E-selectin inhibition in mouse models shows increased leukocyte rolling and decreased adherence[1]

Increase in leukocyte rolling



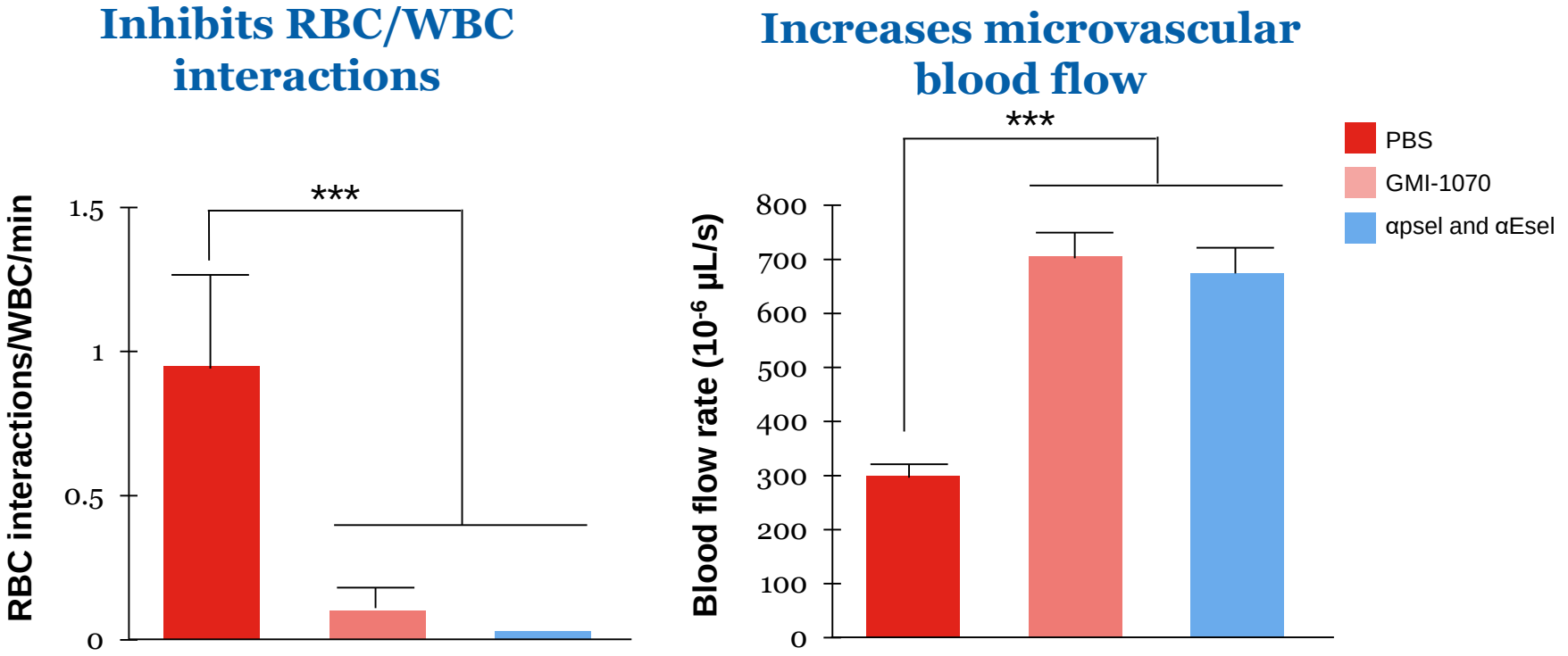
Inhibition of WBC adherence



Adapted from Chang J, Patton JT, et al. *Blood*. 2010;116:1779-1186.

***$p<0.001$, **$p<0.01$.
αEsel, anti-E selectin; αpsel, anti-P selectin; GMI-1070, pan-selectin antagonist; PBS, phosphate-buffered saline; RBC, red blood cell; WBC, white blood cell.
Chang J, Patton JT, et al. *Blood*. 2010;116:1779-1186.

E-Selectin Is Involved in RBC/WBC Interactions and Microvascular Blood Flow



Rivipansel (*Blood* 2015)[2]

Adapted from Chang J, Patton JT, et al. *Blood.* 2010;116:1779-1186.

***$p<0.001$.

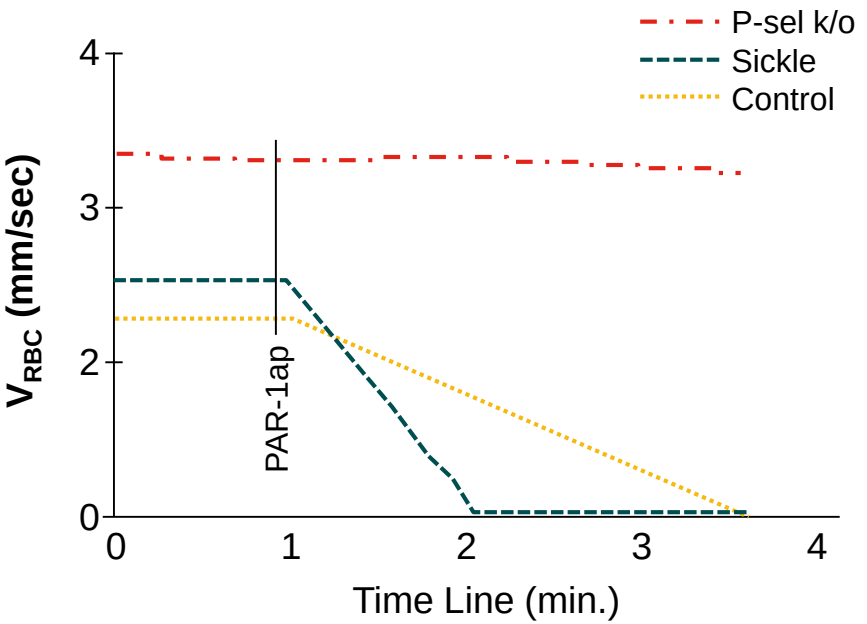
αEsel, anti-E selectin; αpsel, anti-P selectin; GMI-1070, pan-selectin antagonist; PBS, phosphate-buffered saline; RBC, red blood cell; WBC, white blood cell.

1. Chang J, Patton JT, et al. *Blood.* 2010;116:1779-1186. . 2. Telen MJ, Wun T, et al. *Blood.* 2015;125(17):2656-2664.

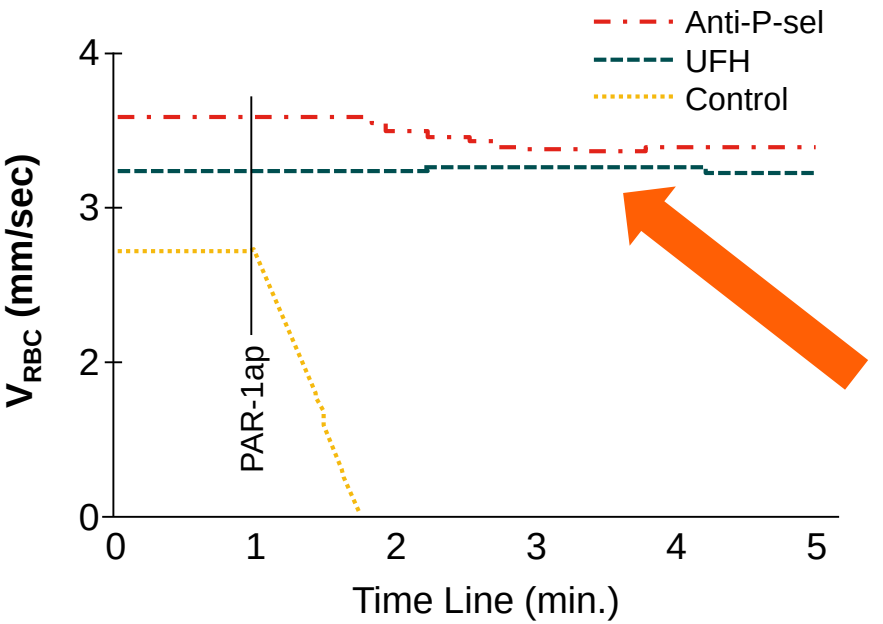
Heparin Inhibits P-Selectin and Prevents Vaso-Occlusion

Mouse Models of SCD[1]

Heparin inhibits P-selectin



Heparin prevents vaso-occlusion



Adapted from Embury SH. *Blood*. 2004;104(10):3378-3385.

k/o, knock-out; PAR-1ap, protease-activated receptor-1 agonist peptide; P-sel, P-selectin; RBC, red blood cell; UFH, unfractionated heparin; V_{RBC}, red blood cell velocity.

1. Embury SH. *Blood*. 2004;104(10):3378-3385.

Hydroxyurea
Mainstay of SCD therapy

FDA-approved medication for SCD[1]

Hydroxyurea (HU) therapy can improve the clinical course of SCD in some adults with 3+ crises per year[2]

- **Lower annual rates of crises** vs placebo (median 2.5 for hydroxyurea vs 4.5 for placebo, per year, $p < 0.001$)

- **Longer median time to first crisis** (3 mo for hydroxyruea vs 1.5 mo for placebo, $p = 0.01$) **and second crisis** vs placebo (8.8 mo vs 4.6 mo, $p < 0.01$)

Maximal tolerated doses of hydroxyurea **may not be necessary** to achieve a therapeutic effect[2]

Pediatric studies in hydroxyurea have proven **similar safety**[3]

FDA, Food and Drug Administration.

1. Office of the Commissioner. *FDA*. https://www.fda.gov/consumers/consumer-updates/fda-encourages-new-treatments-sickle-cell-disease. Accessed May 21, 2019. 2. Charache S, Terrin ML. *N Engl J Med*. 1995;332:1317-1322.
3. Heeney MM. *Hematol Oncol Clin North Am*. 2010;24:199-214.

L-Glutamine (Endari)

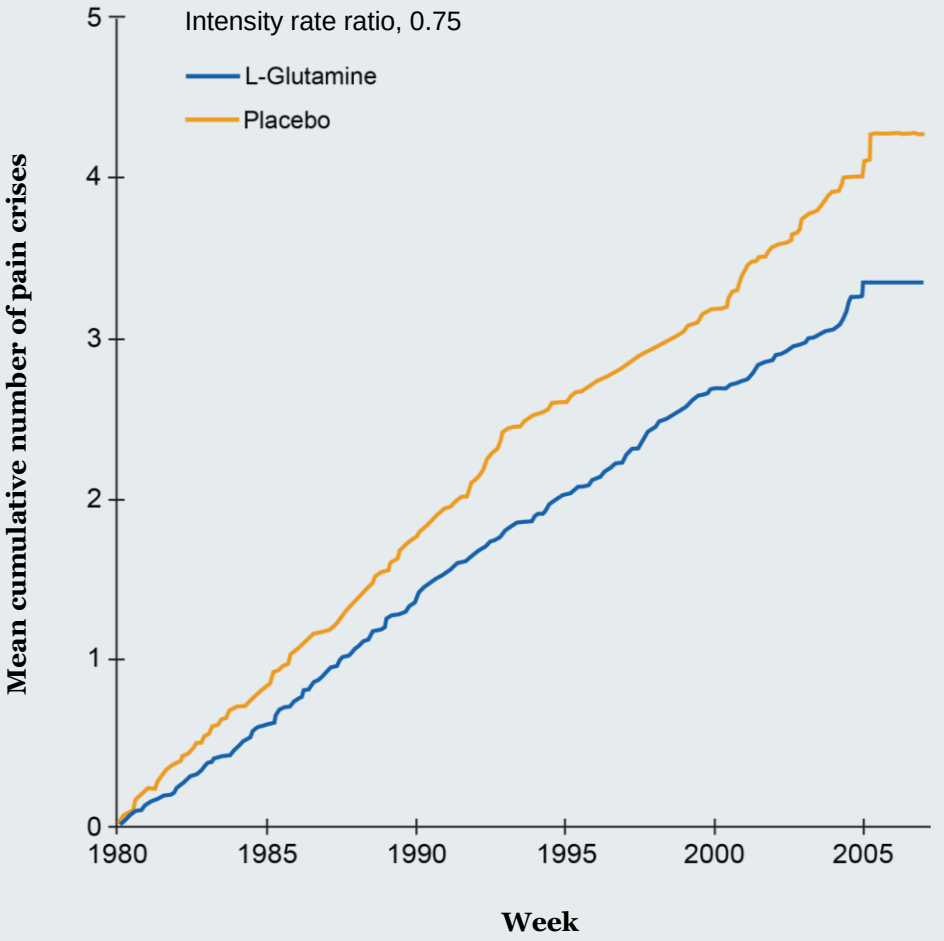
Phase 3 trial of L-glutamine in SCD

25% reduction in number of pain crises (3.0 vs 4.0; $p < 0.005$)

30% lower hospitalization rates (2.0 vs 3.0; $p < 0.005$)

Reduced number of episodes of acute chest syndrome (≈8% vs 23%; $p = 0.003$)

Recurrent events of sickle cell–related pain crisis over time



Niihara Y, Miller ST, et al. *N Engl J Med*. 2018;379(3):226-235.

Adapted from Niihara Y, Miller ST, et al. *N Engl J Med*. 2018;379(3):226-235.

L-Glutamine (Endari)

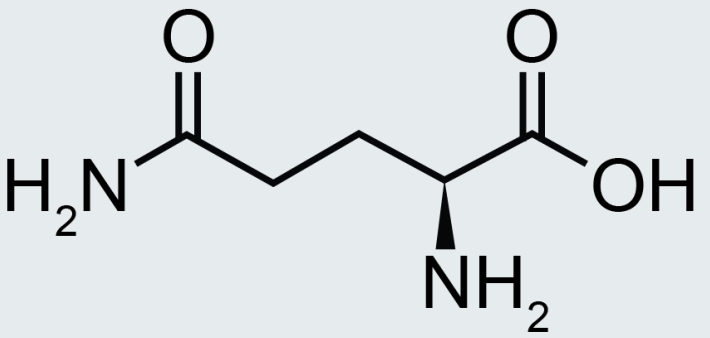
L-glutamine is an amino acid indicated to reduce the acute complications of SCD in adult and pediatric patients 5 years of age and older[1,2]

The safety and efficacy of L-glutamine were studied in a randomized trial of patients ages 5–58 years with SCD who had two or more painful crises within the 12 months prior to enrollment in the trial[2]

Long-term benefits and medication adherence unclear[3]

Patients who were treated with L-glutamine experienced the following[2]:

- Fewer hospital visits for pain on average, compared with patients who received a placebo (median 3 vs 4)
- Fewer hospitalizations for sickle cell pain (median 2 vs 3)
- Fewer days in the hospital (median 6.5 days vs 11 days)

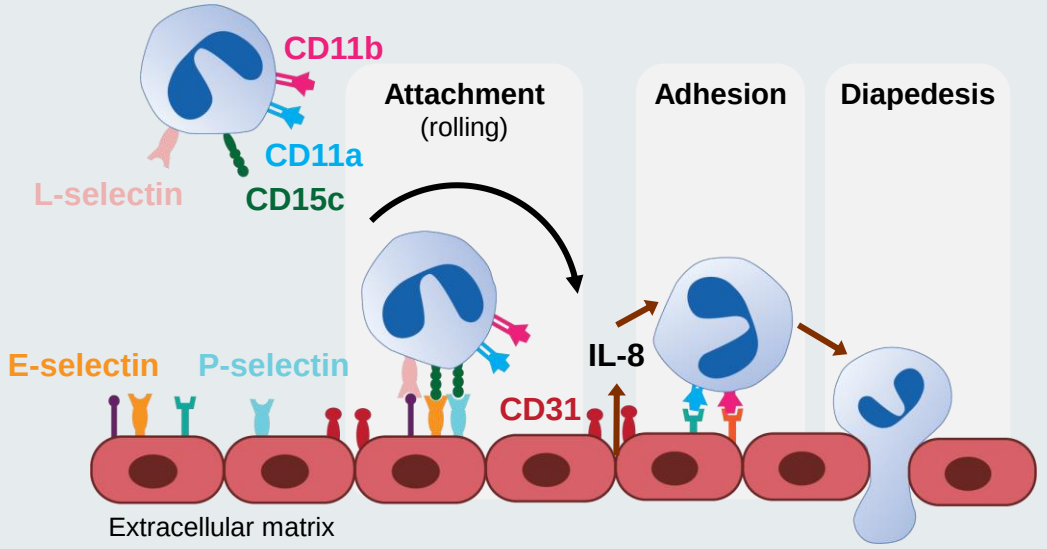


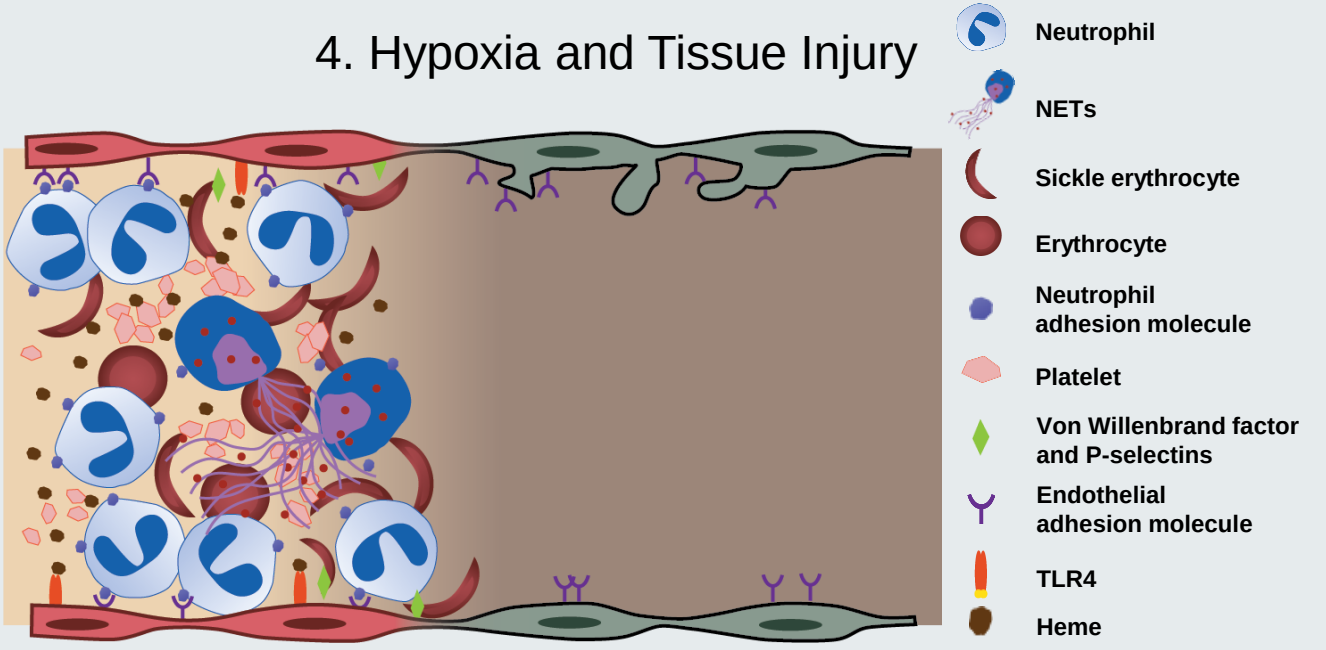
Adapted from L-Glutamine G3126. Sigma. https://www.sigmaaldrich.com/catalog/product/sigma/g3126?lang=en®ion=CA. Accessed May 21, 2019.

1. L-Glutamine G3126. Sigma. https://www.sigmaaldrich.com/catalog/product/sigma/g3126?lang=en®ion=CA. Accessed May 21, 2019. 2. Niihara Y, Miller ST, et al. *N Engl J Med*. 2018;379(3):226-235.
3. Heeney MM, *Hematol Oncol Clin North Am*. 2010;24:199-214.

Selectins Are Important Vascular Adhesion Molecules

1. Neutrophil entry into tissues
2. Endothelial Neutrophil Activation
3. Vaso-occlusion
4. Hypoxia and Tissue Injury





Adapted from Tedder TF, Steeber DA, et al. *FASEB J.* 1995;9:866-73 and Dutra FF, Bozza MT. *Front Pharmacol.* 2014;5.

Selectins are expressed on endothelial cells, platelets, and leukocytes, as well as other cell types[1]

- P-selectin and E-selectin mediate rolling and tethering of blood cells to the endothelium[2]
- May initiate vaso-occlusion in the post-capillary venules[3]

CD, cluster of differentiation; IL-8, interleukin 8; NETs, neutrophil extracellular trap; TLR4, toll-like receptor 4.

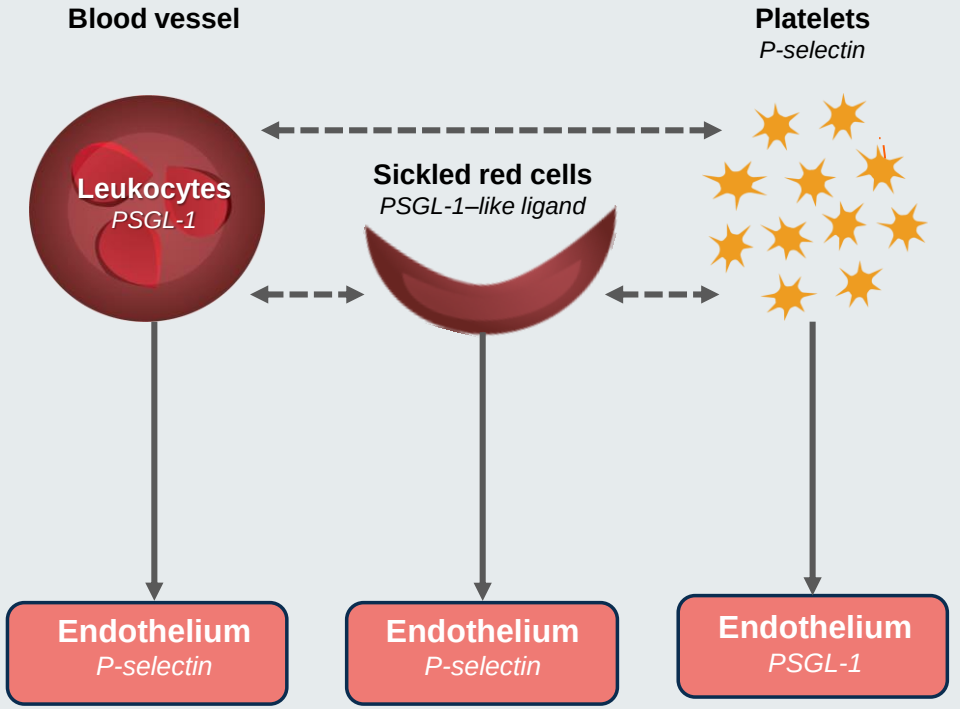
1. Tedder TF, Steeber DA, et al. *FASEB J.* 1995;9:866-873. 2. Ley K, Laudanna C, et al. *Nat Rev Immunol.* 2007;7:678-689. 3. Manwani D & Frenette PS. *Blood.* 2013;122:3892-3898. 4. Dutra FF, Bozza MT. *Front Pharmacol.* 2014;5.

Crizanlizumab: A New Molecule Targeting P-selectin

Sickle cell-related pain crises (SCPCs), also known as vaso-occlusive crises (VOCs), are a substantial cause of morbidity in patients with SCD[1]

P-selectin plays a role in the pathogenesis of vaso-occlusion in SCD, which leads to SCPCs[2]

Crizanlizumab is a humanized immunoglobulin G2 (IgG2) antibody that inhibits P-selectin[3,4]



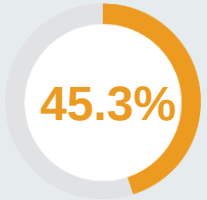
Crizanlizumab is an investigational agent that has not been approved by the US FDA or any other regulatory agency worldwide for the uses under investigation

FDA, Food and Drug Administration; PSGL-1, P-selectin glycoprotein ligand-1.

1. Ballas SK, Lusardi M. *Am J Hematol.* 2005;79(1):17-25. 2. Matsui NM, Borsig L, et al. *Blood.* 2001;98(6):1955-1962. 3. Ataga KI, Kutlar A, et al. *N Engl J Med.* 2017;376(5):429-439. 4. Kaplon H, Reichert JM. *MAbs*. 2018;10(2):183-203.

SUSTAIN Phase II Study – Results

Compared to placebo, crizanlizumab (5.0 mg/kg) treatment resulted in[1]:



(median 1.6 vs 3.0; $p = 0.010$)

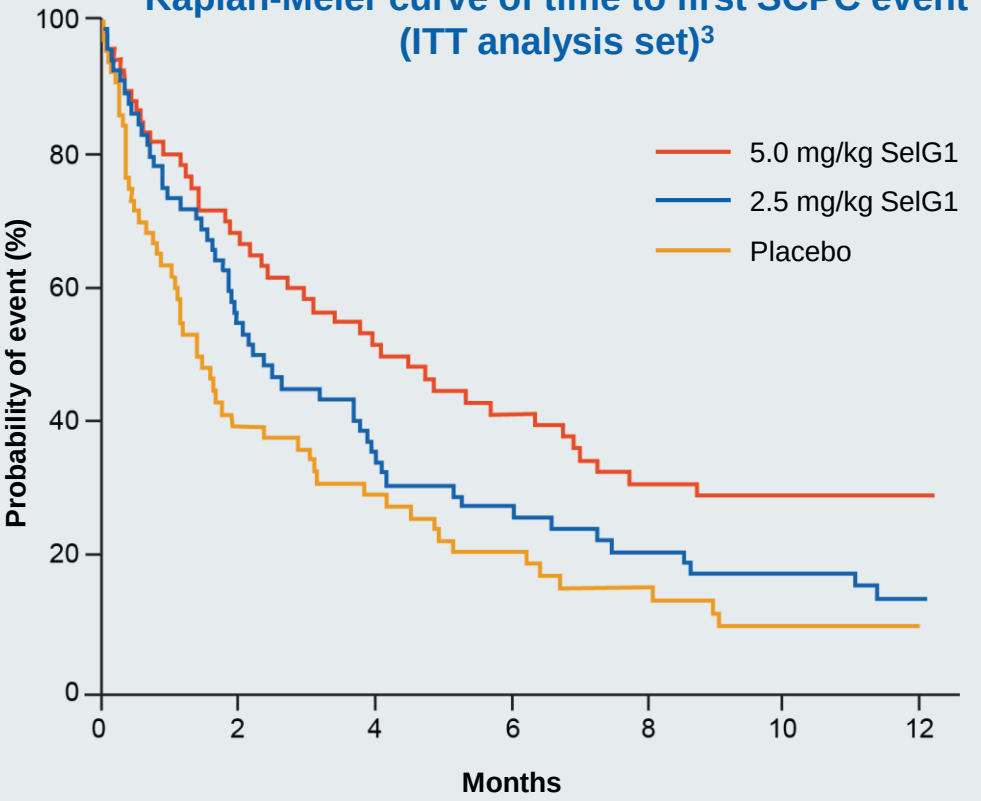
Annual rate of VOCs

Adverse events occurring in ≥5% of patients in an active dose group and were ≥2-fold higher over placebo were[1]:

Arthralgia | Diarrhea | Vomiting | Chest pain | Pruritus

Time to first SCPC in the crizanlizumab 5.0 mg/kg group was significantly increased vs placebo (median 4.1 vs 1.4 months; $p = 0.001$)[2]

Kaplan-Meier curve of time to first SCPC event (ITT analysis set)[3]



Adapted from Ataga KI, Kutlar A, et al. *Blood*. http://www.bloodjournal.org/content/128/22/1. Published December 2, 2016. Accessed May 22, 2019.

ITT, Intent-To-Treat; SCPC, sickle cell pain crisis.

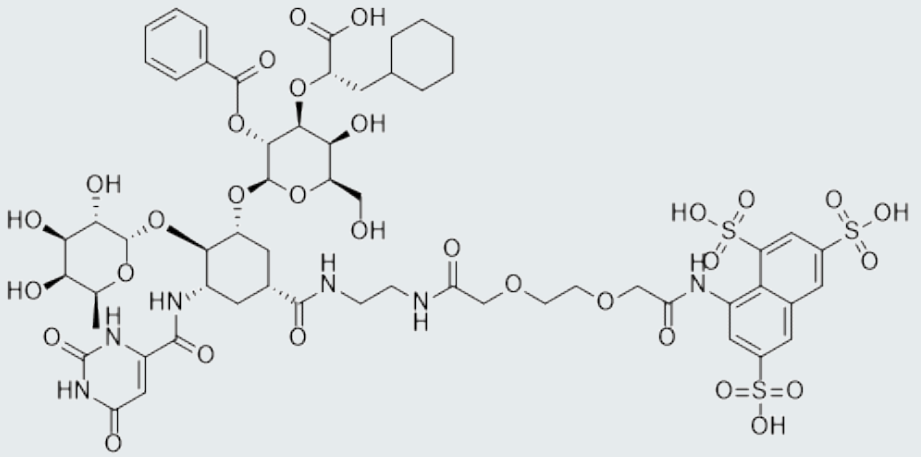
1. Ataga KI, Kutlar A, *et al. N Engl J Med.* 2017;376:429-439. 2. Ataga KI, Kutlar A, et al. *Blood*. 2016;128(22):1. 3. Ataga KI, Kutlar A, et al. *Blood*. http://www.bloodjournal.org/content/128/22/1. Published December 2, 2016. Accessed May 22, 2019

Crizanlizumab Clinical Trials in Various Patient Populations

Study Name (NCT Number)[1]	Phase	Patient Population
Completed **SUSTAIN: Study to Assess Safety and Impact of SelG1 With or Without Hydroxyurea Therapy in Sickle Cell Disease Patients With Pain Crises (NCT01895361)[1]**	Phase 2	Patients with SCD (16 years to 65 years old)
SOLACE-adults: Pharmacokinetics and Pharmacodynamics Study of SEG101 (Crizanlizumab) in Sickle Cell Disease (SCD) Patients With Vaso- Occlusive Crisis (VOC) (NCT03264989)[2]	Phase 2	Patients with SCD (16 years to 70 years old)
SOLACE-kids: Study of Dose Confirmation and Safety of Crizanlizumab in Pediatric Sickle Cell Disease Patients (NCT03474965)[3]	Phase 2	Pediatric patients with SCD (6 months to <18 years)
STAND: Study of Two Doses of Crizanlizumab Versus Placebo in Adolescent and Adult Sickle Cell Disease Patients (NCT03814746)[4]	Phase 3	Patients with SCD (12 years and older)
SPARTAN: A Study to Evaluate the Safety and Efficacy of Crizanlizumab in Sickle Cell Disease Related Priapism (NCT03938454)[5]	Phase 2	Male patients with SCD (16 years and older)

1. Ataga KI et al. *N Engl J Med*. 2017;376:429-439. 2. Novartis announces new crizanlizumab (SEG101) data analysis in sickle cell disease, and investment in SENTRY clinical program. Novartis. https://www.novartis.com/news/media-releases/novartis-announces-new-crizanlizumab-seg101-data-analysis-sickle-cell-disease-and-investment-sentry-clinical-program. Accessed April 11, 2019. 3. Pharmacokinetics and Pharmacodynamics Study of SEG101 (Crizanlizumab) in Sickle Cell Disease (SCD) Patients With Vaso- Occlusive Crisis (VOC). https://clinicaltrials.gov/ct2/show/NCT03264989. Accessed April 11, 2019. 4. Study of Dose Confirmation and Safety of Crizanlizumab in Pediatric Sickle Cell Disease Patients. https://clinicaltrials.gov/ct2/show/NCT03474965. Accessed April 11, 2019. 5. Study of Two Doses of Crizanlizumab Versus Placebo in Adolescent and Adult Sickle Cell Disease Patients (STAND). https://clinicaltrials.gov/ct2/show/NCT03814746. Accessed April 11, 2019. 6. A Study to Evaluate the Safety and Efficacy of Crizanlizumab in Sickle Cell Disease Related Priapism. https://clinicaltrials.gov/ct2/show/NCT03938454. Accessed May 17, 2019.

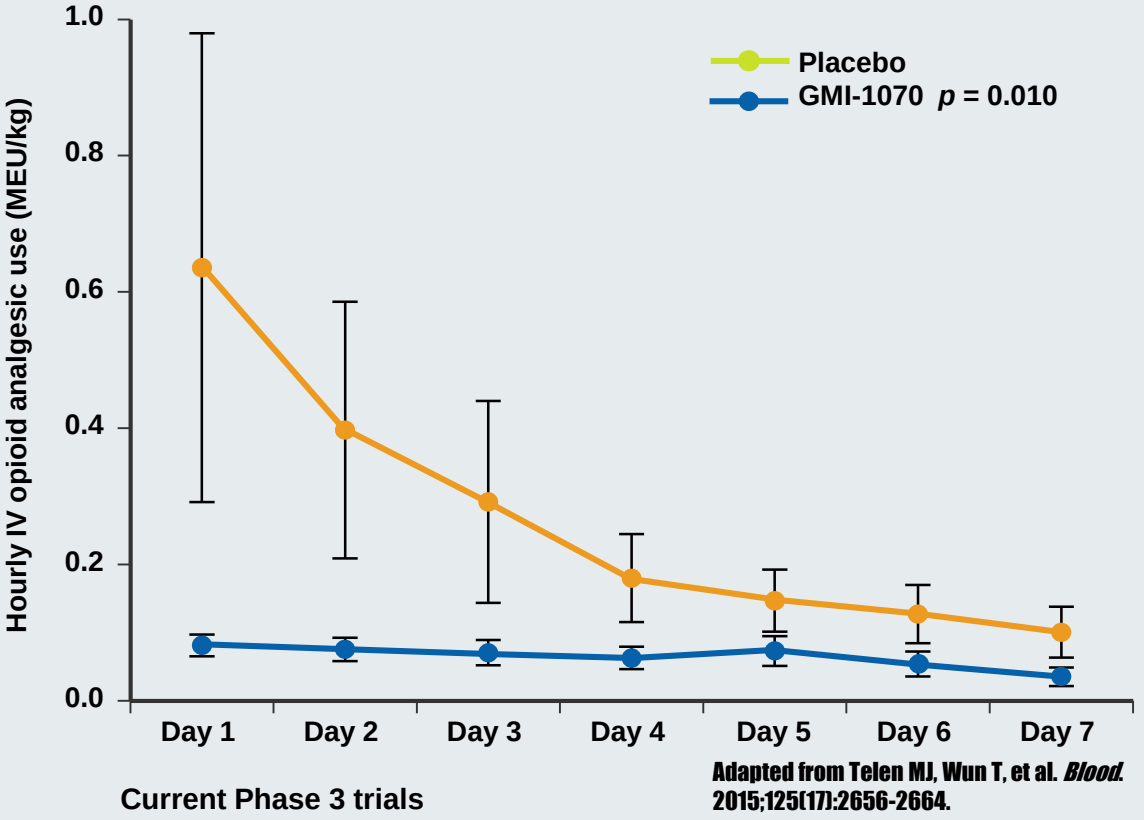
Rivipansel: A Pan-selectin Antagonist



Mechanism of action[1]

- Glycomimetic pan-selectin antagonist that reduces cell adhesion[1]
- Binds to all three members of the selectin family: E-, P-, and L-selectin, although primarily to E-selectin

Rivipansel is an investigational agent that has not been approved by the US FDA or any other regulatory agency worldwide for the uses under investigation



- Safety Of Rivipansel (GMI-1070) In The Treatment Of One or More Vaso-occlusive Crises In Hospitalized Subjects With Sickle Cell Disease[2] https://clinicaltrials.gov/ct2/show/NCT02433158
- Efficacy and Safety of Rivipansel (GMI-1070) in the Treatment of Vaso-Occlusive Crisis in Hospitalized Subjects With Sickle Cell Disease[3,4] https://clinicaltrials.gov/ct2/show/NCT02187003

IV, intravenous; MEU, morphine equivalent units.

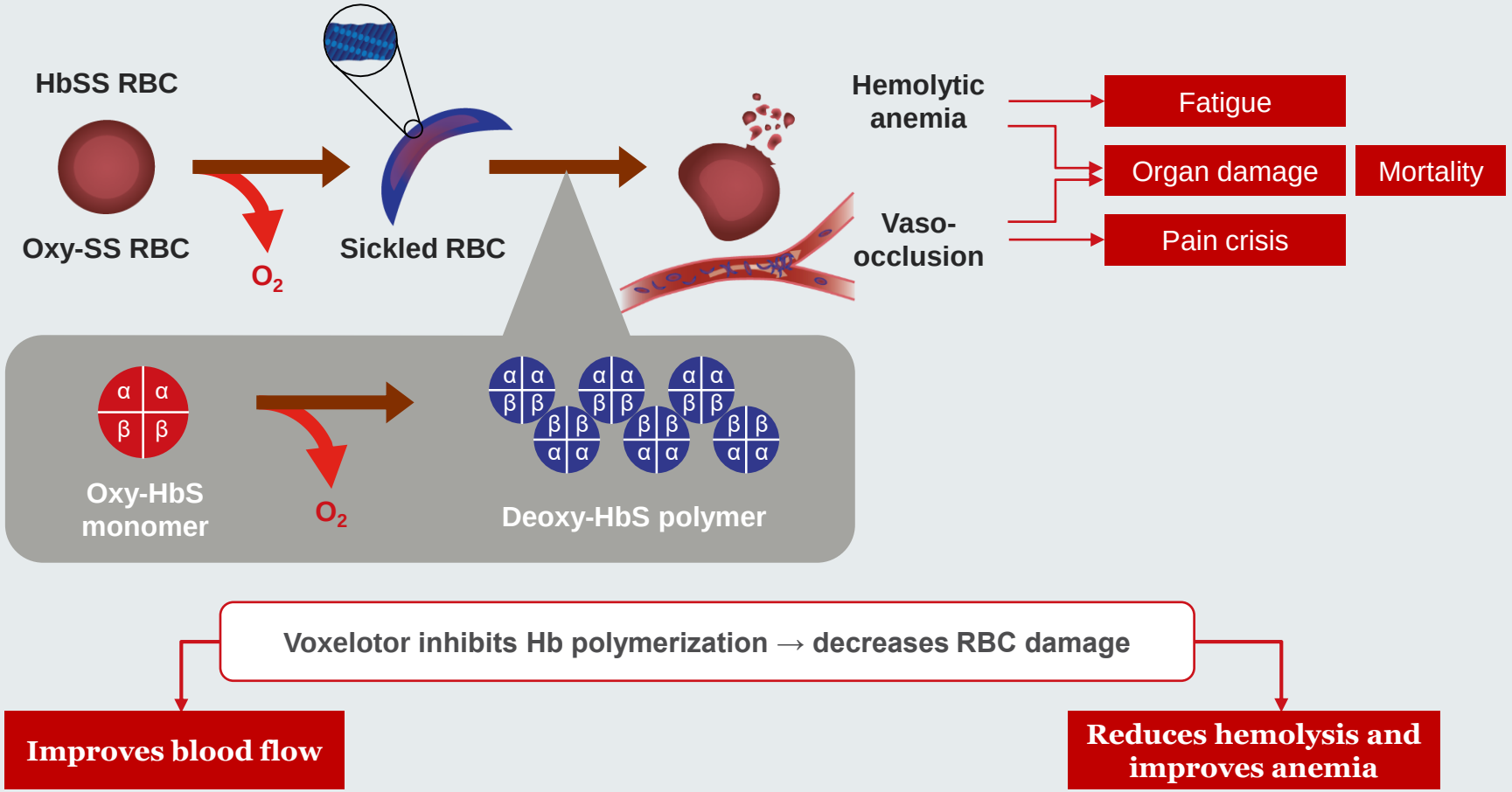
1. Chang J, Patton JT, et al. *Blood*. 2010;116(10):1779-1786. 2. ClinicalTrials.gov. Identifier: NCT02433158. https://clinicaltrials.gov/ct2/show/NCT02433158. Accessed April 2, 2019.
3. ClinicalTrials.gov. Identifier: NCT02187003. https://clinicaltrials.gov/ct2/show/NCT02187003. Accessed April 2, 2019. 4. Telen MJ, Wun T, et al. *Blood*. 2015;125(17):2656-2664.

Voxelotor Ongoing Trials

Current Phase 3 trials[1,2]

- A Phase 3, Double-Blind, Randomized, Placebo-controlled, Multicenter Study of Voxelotor Administered Orally to Patients with Sickle Cell Disease[1] https://clinicaltrials.gov/ct2/show/NCT03036813
- An Open Label Extension Study of GBT440 Administered Orally to Patients With Sickle Cell Disease Who Have Participated in GBT440 Clinical Trials[2] https://clinicaltrials.gov/ct2/show/NCT03573882

Voxelotor is an investigational agent that has not been approved by the US FDA or any other regulatory agency worldwide for the uses under investigation.



Adapted from Lehrer-Graiwer J, Hemmaway C, et al. GBT440, a Novel HbS Polymerization Inhibitor, Increases Hb Oxygen Affinity and Results in a Rapid Improvement in Hemolysis and Anemia. 2016. https://www.gbt.com/file.cfm/83/docs/EHA_2016_GBT440_a_Novel_HbS_Polymerization_Inhibitor.pdf. Accessed March 3, 2019

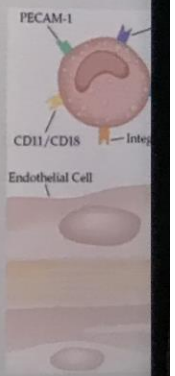
Deoxy, deoxygenated; Hb, hemoglobin; HbS, sickle hemoglobin; HbSS, sickle cell anemia; O_2, oxygen; oxy, oxygenated; RBC, red blood cell.

1. ClinicalTrials.gov. Identifier: NCT03036813. https://clinicaltrials.gov/ct2/show/NCT03036813. Accessed March 3, 2019. 2. ClinicalTrials.gov. Identifier: NCT03573882. https://clinicaltrials.gov/ct2/show/NCT03573882. Accessed June 4, 2019. 3. Lehrer-Graiwer J, Hemmaway C, et al. GBT440, a Novel HbS Polymerization Inhibitor, Increases Hb Oxygen Affinity and Results in a Rapid Improvement in Hemolysis and Anemia. 2016. https://www.gbt.com/file.cfm/83/docs/EHA_2016_GBT440_a_Novel_HbS_Polymerization_Inhibitor.pdf. Accessed March 3, 2019.

SLIDE REVIEW (SLIDE 96 OF 232)

Downstream Clinical Implications

	Hydroxyurea	L-glutamine	Crizanlizumab	Voxelotor
	↓ VOC ↓ Transfusions ↓ ACS	↓ VOC	↓ VOC	↓ Anemia
	↓ Stroke	???	Priapism???	Organ Dysfunction?
	↓ Mortality	???	???	???



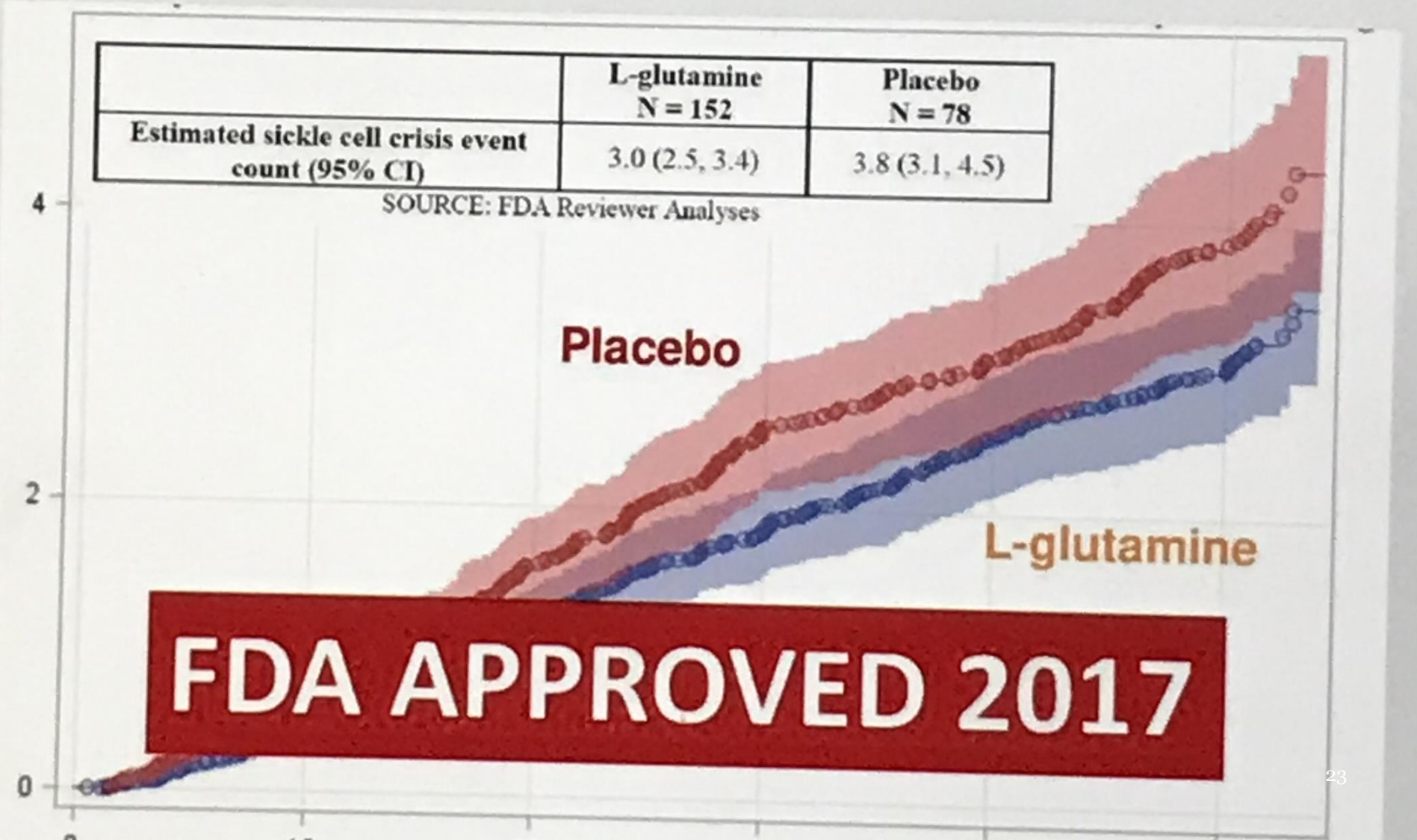
Nonmalignant Disorders of Leukocytes. http://what-when-how.com/acp-medicine/nonmalignant-disorders-of-leukocytes-part-2/. Accessed December 3, 2019.

RETURN TO LIVE SLIDE

L-glutamine Efficacy

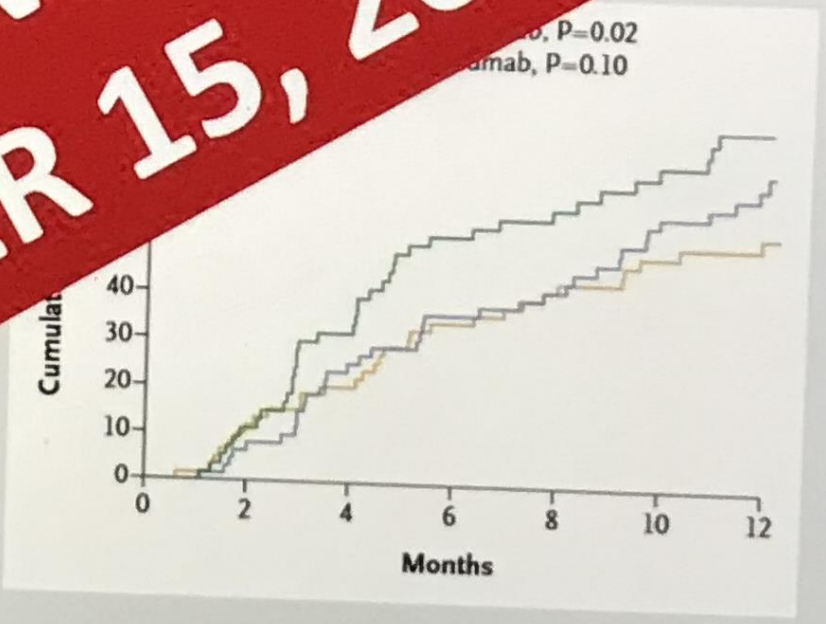
	L-glutamine N = 152	Placebo N = 78
Estimated sickle cell crisis event count (95% CI)	3.0 (2.5, 3.4)	3.8 (3.1, 4.5)

SOURCE: FDA Reviewer Analyses



Crizanlizumab Phase 2

Time to First VOC



FDA APPROVED
NOVEMBER 15, 2019

Ataga KI, et al. *N Engl J Med.* 2017;376(5):429-39.

Red Cell Function

Antipolymerization agents

5HMF

Voxelotor

FDA APPROVED NOVEMBER 25, 2019

National Institute for Health and Care Excellence Single Technology Appraisal

1. **Voxelotor for treating sickle cell disease ID1403;** Expected publication date-TBC

1. **Crizanlizumab for preventing sickle cell crises in sickle cell disease [ID1406]-**Expected publication date: 24 March 2021

2. **Luspatercept for treating beta-thalassaemia ID1554;** Expected publication date: 16 September 2020

3. **Canakinumab** for treating systemic juvenile idiopathic arthritis (terminated appraisal) 2013

4. **Zynteglo for treating transfusion-dependent beta-thalassaemia ID968- Gene therapy** Expected publication date: 15 July 2020

Olinciguat (IW-1701)-Cyclerion

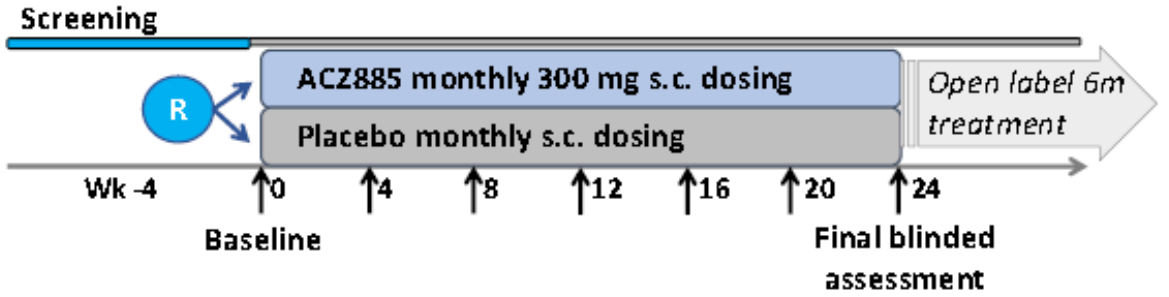
1. Olinciguat (IW-1701) is a selective stimulator of soluble guanylate cyclase (sGC). Olinciguat directly stimulates sGC and synergizes with endogenous nitric oxide (NO) to produce cyclic guanosine 3',5'-monophosphate (cGMP). The synergy has been demonstrated both in whole cells and with purified sGC enzyme.
2. Olinciguat, an orally administered sGC stimulator, is being developed for the treatment of disorders associated with deficient NO-sGC-cGMP signaling. Olinciguat has been evaluated in nonclinical studies as well as in a healthy subject Phase 1a single-ascending-dose (SAD) study and Phase 1b multiple ascending-dose (MAD)/food-effect study.

Double-blind, randomized study of canakinumab treatment in pediatric and young adult patients with sickle cell anemia

D Rees, Y Kilinc, Selma Unal, C Dampier, BS Pace, B Kaya, S Trompeter, I Odame, J ahlangu, Sule Unal, J Brent, R Grosse, BR Fuh, BPD Inusa, A Koren, C Levin, S Mortier, E McNamara, K Meiser, S J Oliver

Anti-IL-1β mAb (ACZ885; canakinumab) in SCA

Multi-center, ambulatory, randomized, double-blinded



Outpatient visit
Treatment & outcomes
- Clinical
- Safety

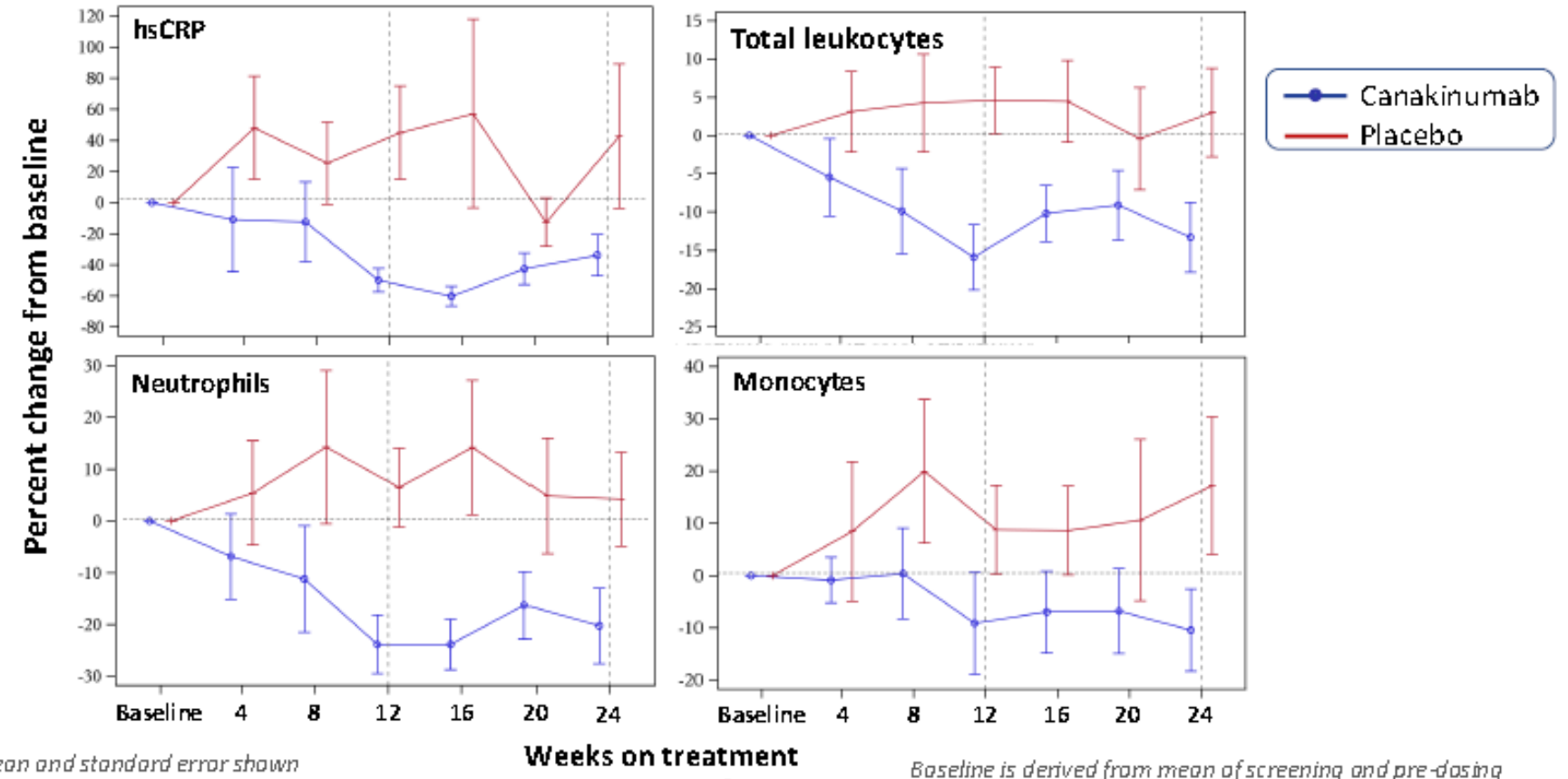
- Patients (HbSS *or* HbSβThal^0)
  - Age 8-20y
  - History of ≥2 major sickle cell pain flares/year
  - Detectable pain over screening period:
    - baseline average daily pain ≥1 cm without analgesic use or,
    - ≥1 pain episode requiring analgesia
  - C-reactive protein >1 mg/L

- Study outcomes
  - Primary: average daily pain VAS*
  - Secondary:
    - Average daily fatigue VAS*
    - School or work absences*
    - Wrist actigraphy
    - Transcranial Doppler velocities (*baseline, Week 12*)
    - Vaso-occlusive pain events, crises, SCA-related AEs
    - Inflammatory markers CRP, WBC, absolute counts of neutrophils, monocytes

**ePRO diary*

Laboratory markers of inflammation

Canakinumab treatment reduces markers inflammation vs. placebo group

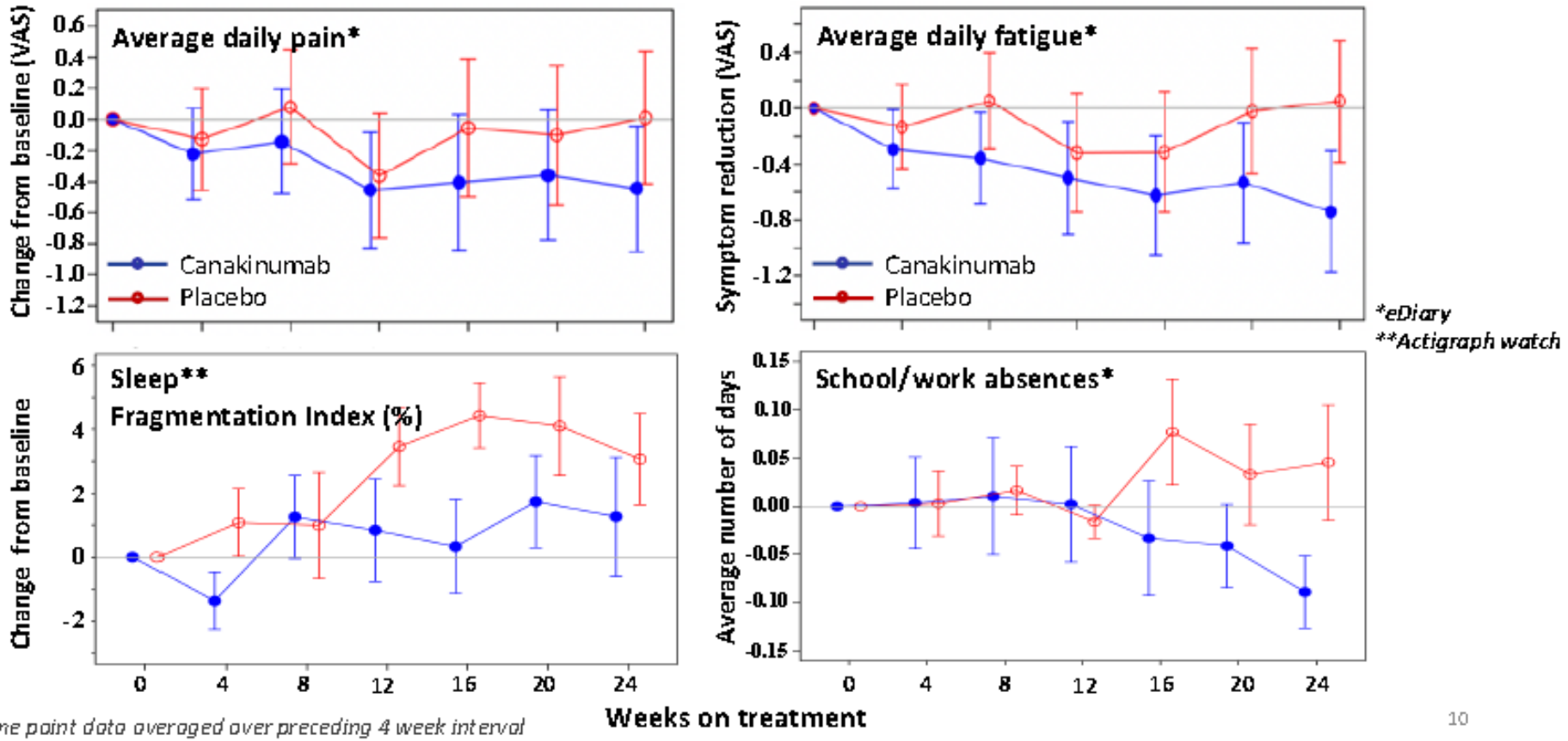


Mean and standard error shown

Baseline is derived from mean of screening and pre-dosing

Daily recorded patient activity

Canakinumab with less pain & fatigue, sleep better, less school/work absences vs placebo group



**eDiary*
***Actigraph watch*

Time point data averaged over preceding 4 week interval

Conclusions

- Canakinumab is tolerated in combination with hydroxurea in children and young adults with sickle cell anemia
- Canakinumab reduced systemic markers of inflammation
- IL-1β-mediated inflammation contributes to SCA clinical disease manifestations, demonstrated by response to canakinumab for:
  - Daily pain, fatigue, sleep quality and school attendance
  - Transcranial Doppler flow velocities
  - Adverse events and annualized rate of hospitalization
- Additional studies needed to confirm and expand upon these findings

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Olinciguat, an orally administered sGC stimulator, is being developed for the treatment of disorders associated with deficient NO-sGC-cGMP signaling. Olinciguat has been evaluated in nonclinical studies as well as in a healthy subject Phase 1a single-ascending-dose (SAD) study and Phase 1b multiple ascending-dose (MAD)/food-effect study.

Benefit

Pre-treatment with olinciguat and hydroxyurea (HU) also attenuated TNFα-induced activation of endothelial cells as measured by leukocyte rolling in postcapillary venules of the mouse cremaster muscle. These data suggest that olinciguat alone or as adjunct to HU may reduce vascular inflammation in SCD, which in turn may impact occurrence of symptoms of SCD, including vaso-occlusive pain.

10 µM olinciguat partially inhibited aggregation stimulated with adenosine diphosphate (ADP) or thrombin receptor activating peptide (TRAP

Side effects

1. In male normotensive and spontaneously hypertensive rats (SHR), olinciguat elicited dose dependent decreases in mean arterial pressure (MAP), and systolic and diastolic blood pressure (BP). At the 3-mg/kg dose level, MAP changes from baseline of -10.3 (±2.0) and -18.2 (±3.1) mmHg were observed in normotensive rats and SHRs, respectively, corresponding to between 10% and 13% reductions from baseline.
2. 10 µM olinciguat partially inhibited aggregation stimulated with adenosine diphosphate (ADP) or thrombin receptor activating peptide (TRAP

Update on approvals –NICE

Paediatric Sickle Cell and Thalassaemia Team

Acknowledgments

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Fiona French

Kemi Ajamufua

Michelle Anderson

Stephanie Quirk

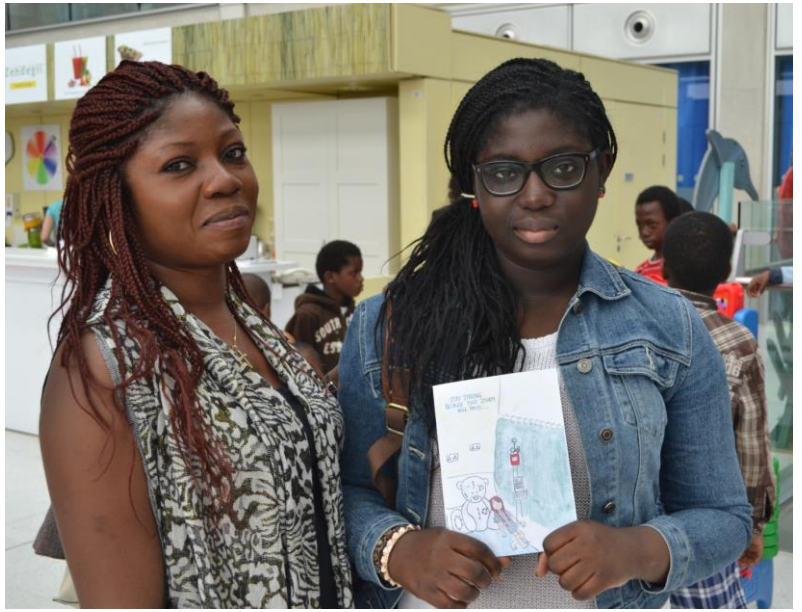
Dr Anna Hurley

Dr Hatel Bhatt

Luhanga Musumadi

Heroes

Mum's lifeline to sickle cell son



Thanks and Q&A

- Acknowledgement