Targeted Drug Discovery in Sickle Cell Disease: From Concept to Clinic

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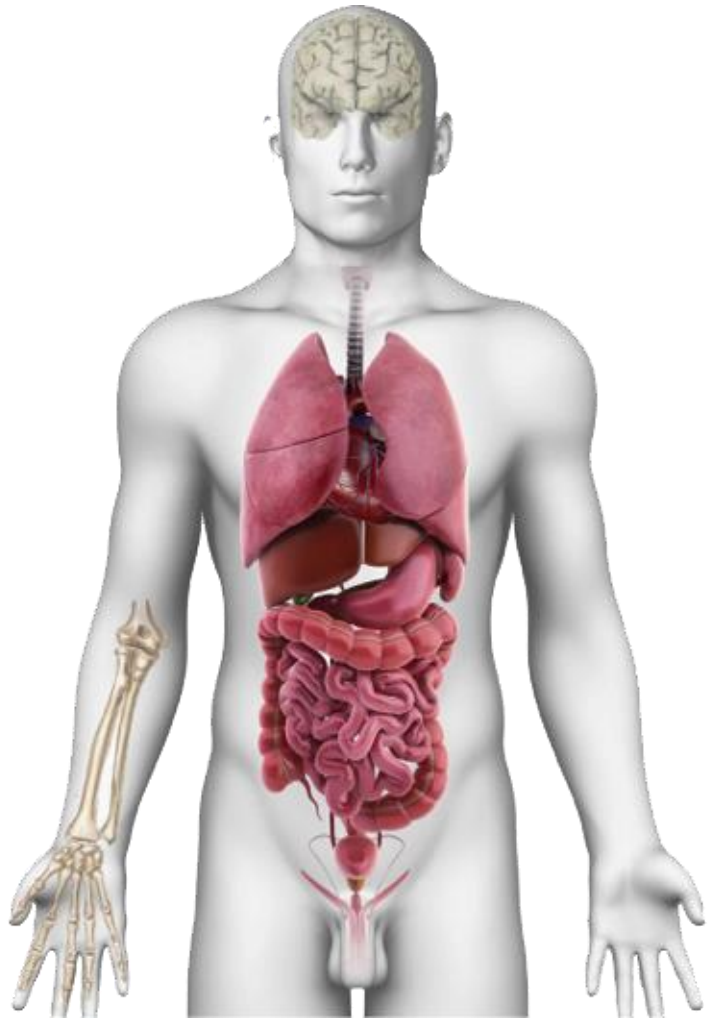
(NASDAQ:GBT)

GBT

Hope + Science + Community

SCD: DISABLING INHERITED BLOOD DISORDER

- **SCD impacts hemoglobin, a protein found in red blood cells (RBCs) that carries oxygen throughout the body**
- **Caused by a genetic mutation in the beta-chain of hemoglobin**
  - Results in the formation of abnormal hemoglobin
  - Sickled RBCs stick together and block the flow of blood and oxygen
- **Devastating morbidity and mortality**
  - Hemolytic anemia, vaso-occlusion, inflammation/vascular injury
  - Results in multi-organ damage
  - 2 to 3 decade reduction in life expectancy
  - Current treatments are limited
- **Who SCD affects:**
  - ~100,000 patients in U.S.; ~60,000 in EU
    - ~90% are African-American
  - Disease is concentrated in populations of African, Middle Eastern and South Asian descent
- **SCD represents a global health problem and new treatment options are desperately needed**



No Organ Spared Common Morbidities

Brain
Cerebral infarcts, strokes
Thrombosis or hemorrhage causing paralysis, sensory deficits or death

Lung
Acute chest syndrome
Pulmonary hypertension
Pneumonia

Kidney
Hematuria
Renal insufficiency
Renal failure

Bones and joints
Bone marrow hyperplasia
Osteomyelitis
Avascular necrosis/osteonecrosis

Eye
Hemorrhage
Retinal detachment
Blindness
Retinopathy

Heart
Cardiomegaly
Heart failure

Spleen
Splenic atrophy(autosplenectomy)

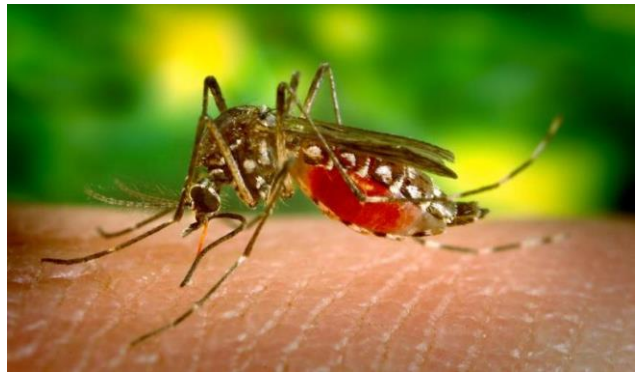
Liver-gallbladder
Hepatomegaly
Gallstones

Skin
Stasis ulcers of hands, ankles and feet

Men/Women
Priapism
Adverse pregnancy outcomes

MALARIA IS THE CULPRIT

Malaria drove gene selection for common red cell disorders including SCD



Plasmodium falciparum evolves from a common precursor in Africa by zoonotic introduction of animal malaria into humans.

~60,000 to 25,000 BP

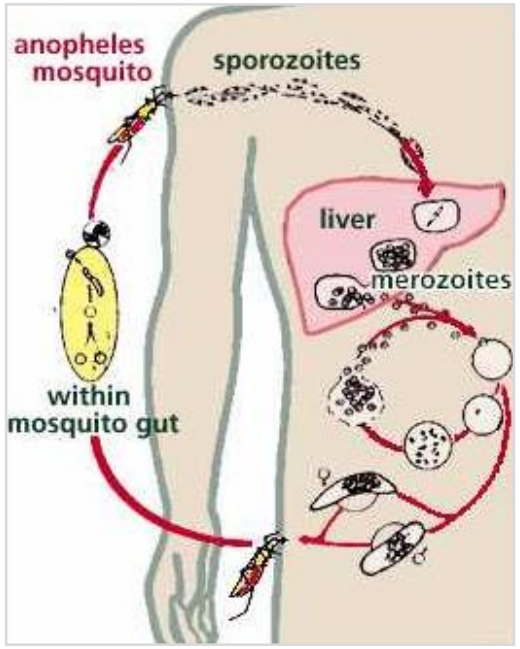
Advent of horticulture and stable, stationary human populations in areas where water was abundant and mosquitos could breed. P. falciparum becomes a major human pathogen.

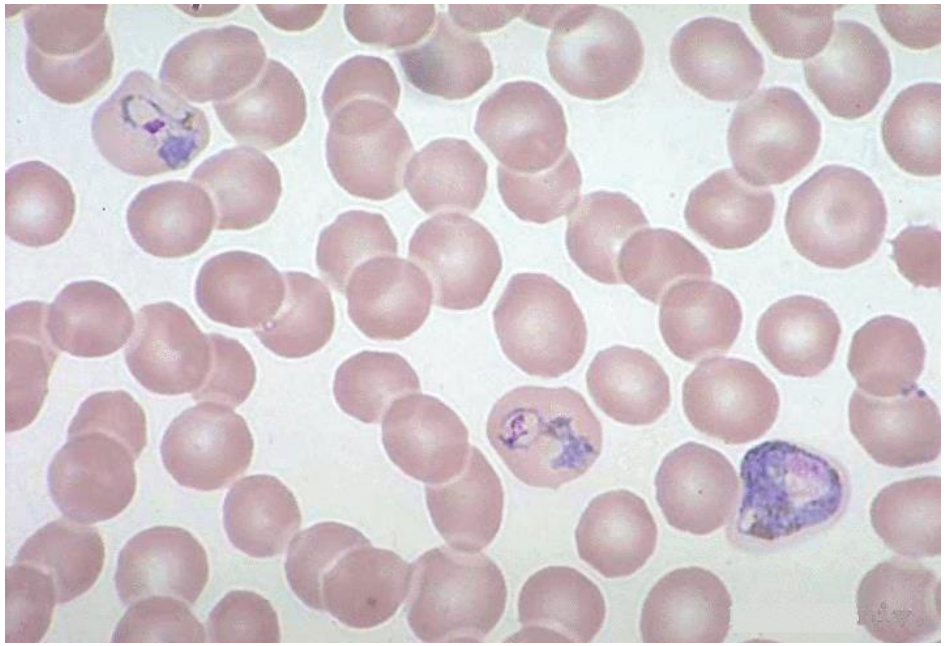
~10,000 BP

P. falciparum spreads from Africa to other sub-tropical regions of the Old World.

~6,000 BP

RBC AS A POINT OF MALARIA DEFENSE





P. falciparum has an obligate red cell stage

Red cells are expendable and renewable

Mechanisms that selectively destroy parasitized red cells reduce the parasite burden

Reduced parasite burden correlates with improved survival

HBS ROSE TO HIGH PREVALENCE INDEPENDENTLY IN AFRICA AND INDIA

Africa- HbS rose to high prevalence independently at least 4 times

+ Senegal, Benin, Central African Republic and Cameroon haplotypes

India- A high prevalence HbS haplotype in India spread to the Middle East

Mapping HbS haplotypes in different geographies is used in molecular anthropology

RED CELL DEFENSES AGAINST MALARIA

Cell Component	Alteration	Global Distribution
Membrane	Duffy antigen null	West Africa
	Melanesian elliptocytosis	Melanesia
Hemoglobin	Hemoglobin S	Africa, Middle East, India
	Hemoglobin C	West Africa
	Hemoglobin E	S.E. Asia
	β-thalassemia	Africa, Mediterranean, India, S.E. Asia, Melanesia
	α-thalassemia	Africa, India, S.E. Asia, Melanesia
Enzymes	G6PD Deficiency	Africa, Mediterranean, India, S.E. Asia

SCD SPURRED ADVANCES IN MOLECULAR BIOLOGY AND GENETICS FOR A CENTURY

1910

James Herrick and Ernest E. Irons at Cook County Hospital in Chicago first described sickle cell disease in a student from Grenada, Walter Clement Noel. He had an anemia marked by red cells that looked like “crescents or sickles.” Noel returned to Grenada after training in dentistry.

1949

Harvey Itano and Linus Pauling used the newly invented technique of protein electrophoresis to demonstrate that sickle hemoglobin (HbS) differed from normal hemoglobin (HbA).

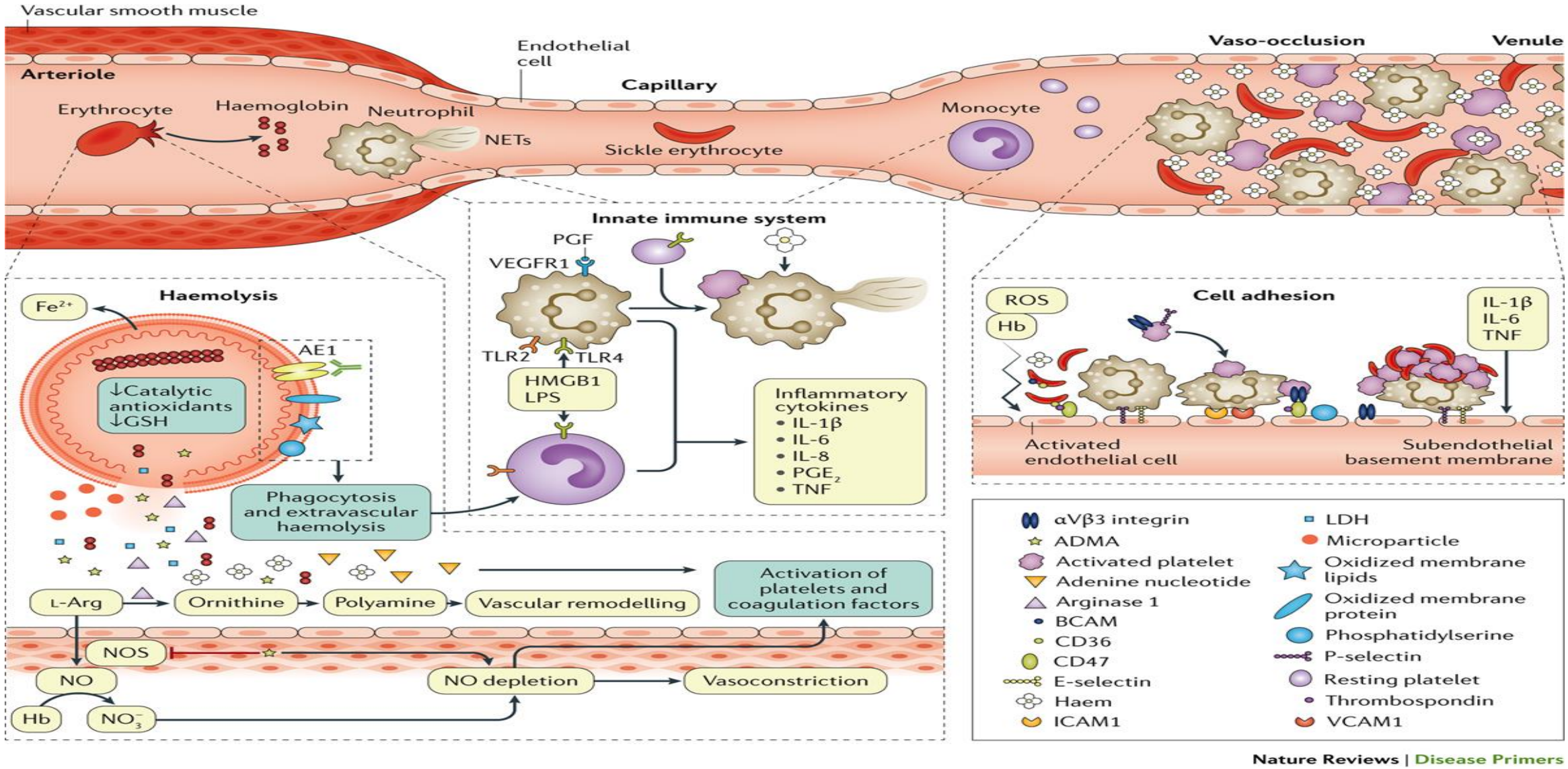
***First demonstration of disease due to an abnormal protein**

1956

Vernon Ingram at MRC in London used protein sequencing to demonstrate that HbS derived from a glutamic acid to valine amino acid change at position β-6. The recently elucidated genetic code allowed deduction of the nucleotide change (GAG → GTG).

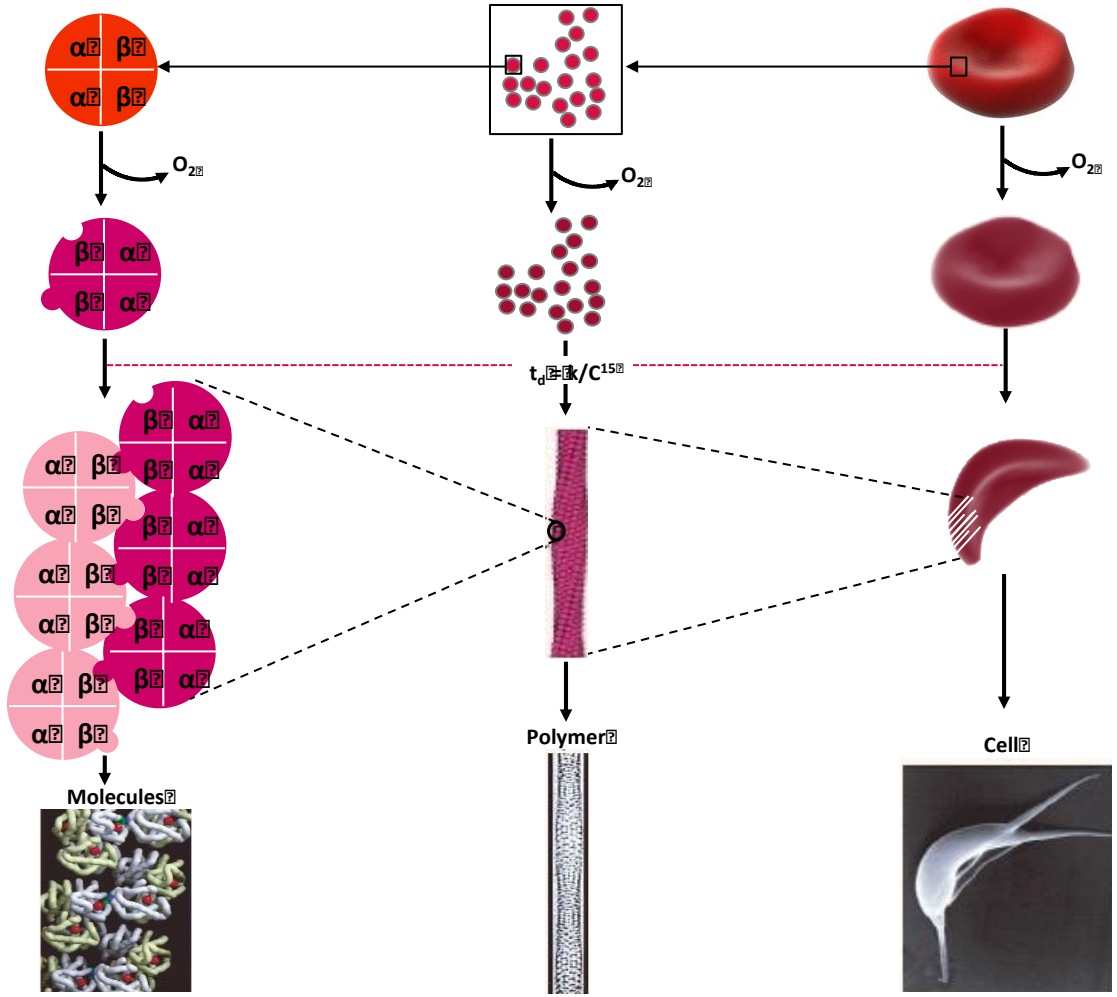
***First demonstration of disease due to a specific DNA mutation**

MOLECULAR PATHOLOGY OF SCD



Kato, G. J. et al. (2018) Sickle cell disease, *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2018.10

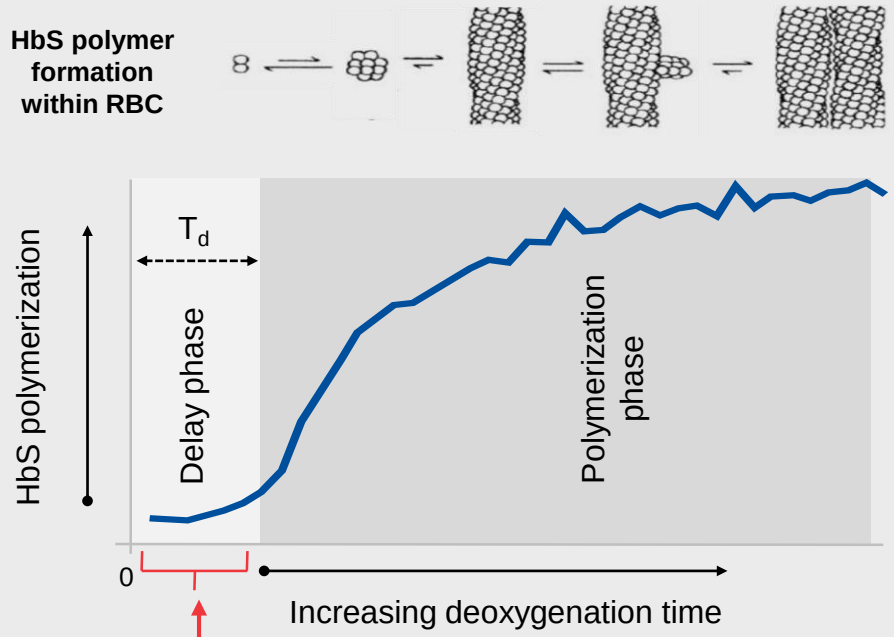
HEMOGLOBIN S POLYMERIZATION IS THE TRIGGER IN SICKLE CELL DISEASE



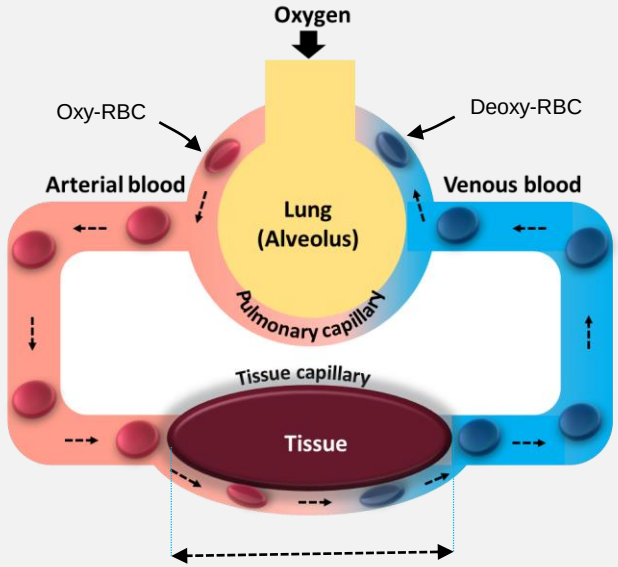
Bunn HF. *N Engl J Med.* 1997.

HBS POLYMERIZATION OCCURS DURING TRANSIT TIME THROUGH DEOXYGENATED MICROCIRCULATION

HbS Polymerization Delay Time (T_d)



Transit Time through Microcirculation



If Delay Time (Td) > Transit Time, then RBC remains deformable and does not sickle

Ferrone F. *Am Journal of Hematology*, 2015. Bunn HF. *N Engl J Med.* 1997.

HEMOGLOBIN F (HBF) DOES NOT PARTICIPATE IN HBS POLYMERIZATION AND PRODUCES AN ASYMPTOMATIC CONDITION AT CONCENTRATIONS OF ~10-30%

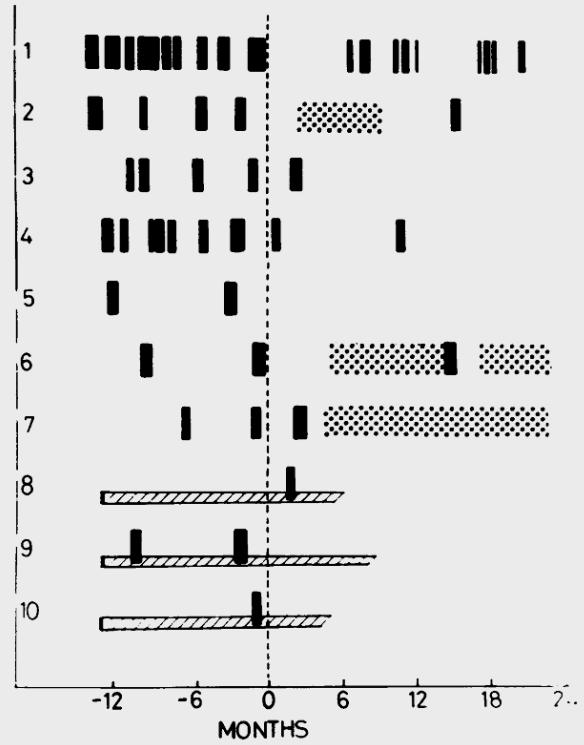
Cases of individuals with Co-Inherited HbSS and Hereditary Persistence of Fetal Hemoglobin (HPFH)

Cases	HbF (%)	Hb (g/dL)	Reticulocytes (%)	Irreversibly Sickled Cells (%)	Clinical Symptoms
Male, 52 yo [1]	**24%**	12.5	N/A	N/A	**Asymptomatic**
Female, 47 yo [1]	**22%**	N/A	N/A	N/A	**Asymptomatic**
Female, 16 yo [2]	**35%**	14.0	1%	0%	**Asymptomatic**
Female, 22 yo [2]	**26%**	11.6	3%	0%	**Asymptomatic**
Female, 24 yo [2]	**28%**	12.8	2%	0%	**Mild retinopathy**
Male, 46 yo [2]	**30%**	16.2	1%	0%	**Mild retinopathy**
Male, 39 yo [3]	**25%**	16.4	N/A	N/A	**No SCD manifestations except possibly aseptic necrosis of right hip**
Female, 10 yo [4]	**20%**	10.3	1%	N/A	**Asymptomatic**
28 cases [5]	**31% (mean)**	13.0 (mean)	N/A	N/A	**Asymptomatic**
Several cases (Hb Kenya-HbS) [5]	**10% (mean)**	N/A	N/A	N/A	**Mild microcytic anemia**

[1] Natta CL, *Journal of Clin Invest.* 1974
[2] Talbot J.F., *British Journal of Ophthalmology* 1983
[3] Bethlenfalvay N, *Am J Hum Genet* 1975
[4] Stamatoyannopoulos G, *Blood* 1975
[5] Akinsheye I, *Blood* 2011

FREQUENCY OF PAINFUL CRISES DECREASED BY 80% WITH EXTRACORPOREAL CARBAMYLATION

Frequency and Duration of Painful Crises (n=10)



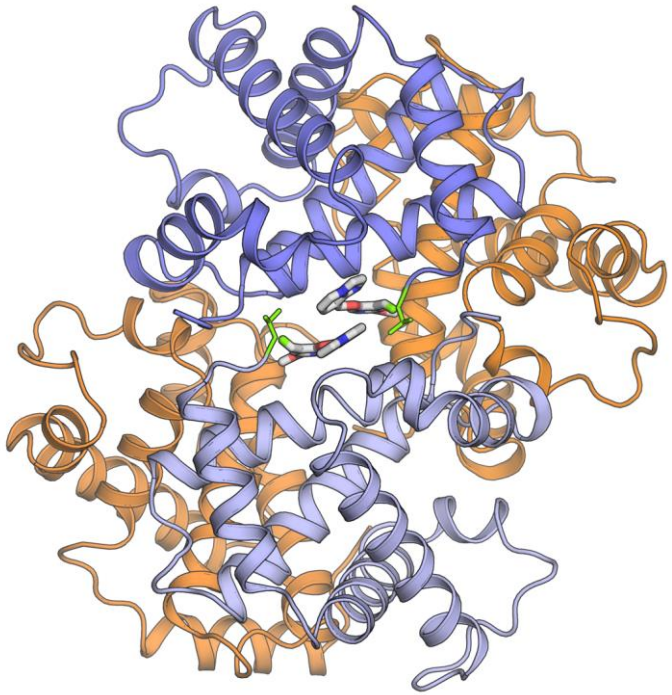
Frequency of painful crises reduced by 80%
comparing 24 months prior vs. 24 months with carbamylation

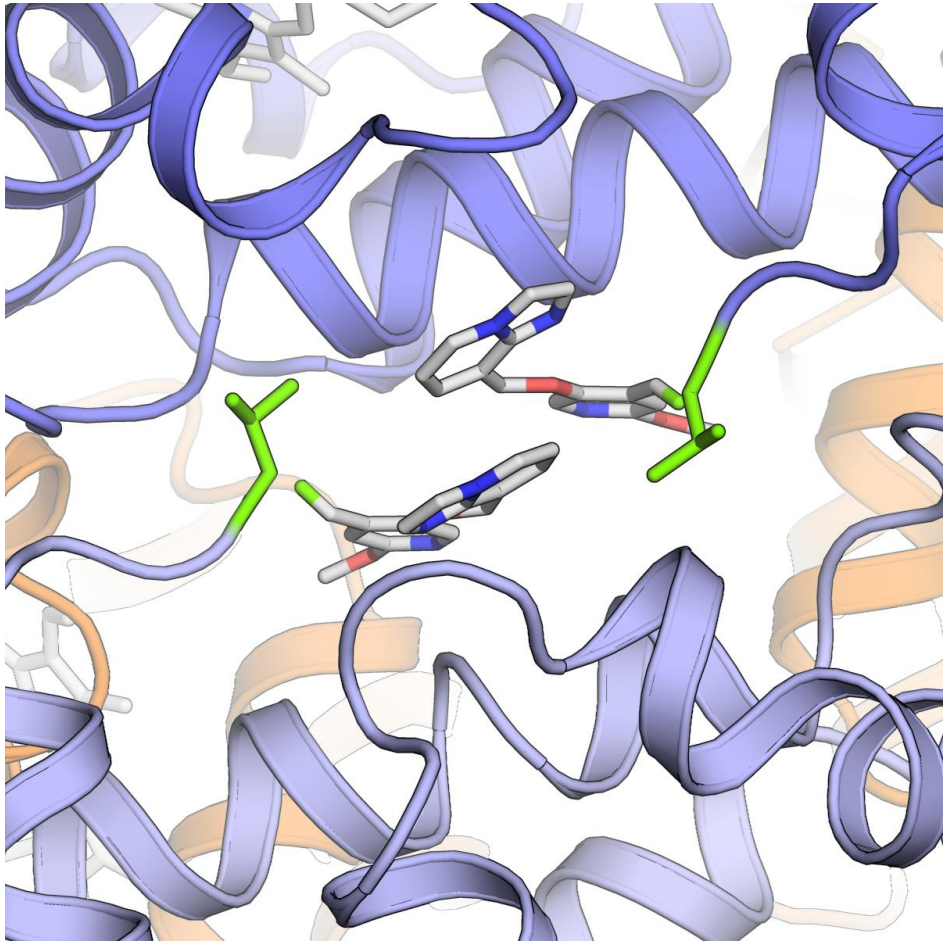
+ Total hospital crisis days decreased by 85% from 461 to 71 days
+ # of spontaneous crises decreased from 35 to 1

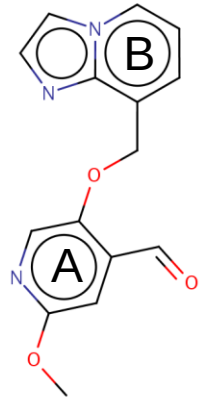
Complete healing of chronic ulcerations in 3/3 patients

D Diederich, Journal of Clin Inv 1976. Frequency and duration of crises before and during extracorporeal carbamylation. Each crisis depicted by black bar with width of each bar proportionate to the duration of crises. Weekly carbamylation begun at week 0; subsequent carbamylation interruptions shown by the dotted areas in patients 2, 6, 7. Open active malleolar ulcerations in patients 8-10 is depicted by horizontal lines.

GBT104 DESIGNED TO HAVE TIGHTER INTERACTION. FOUND TO BIND MUCH FASTER THAN INN-312. INACTIVE IN WHOLE BLOOD

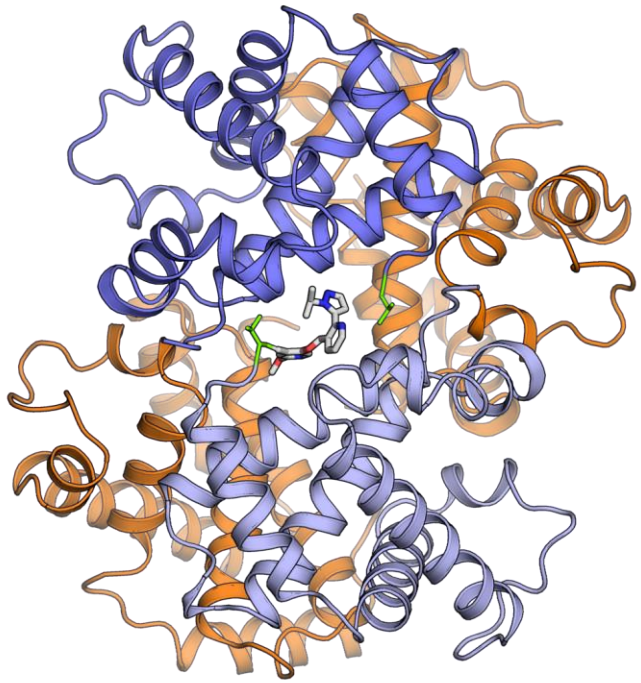


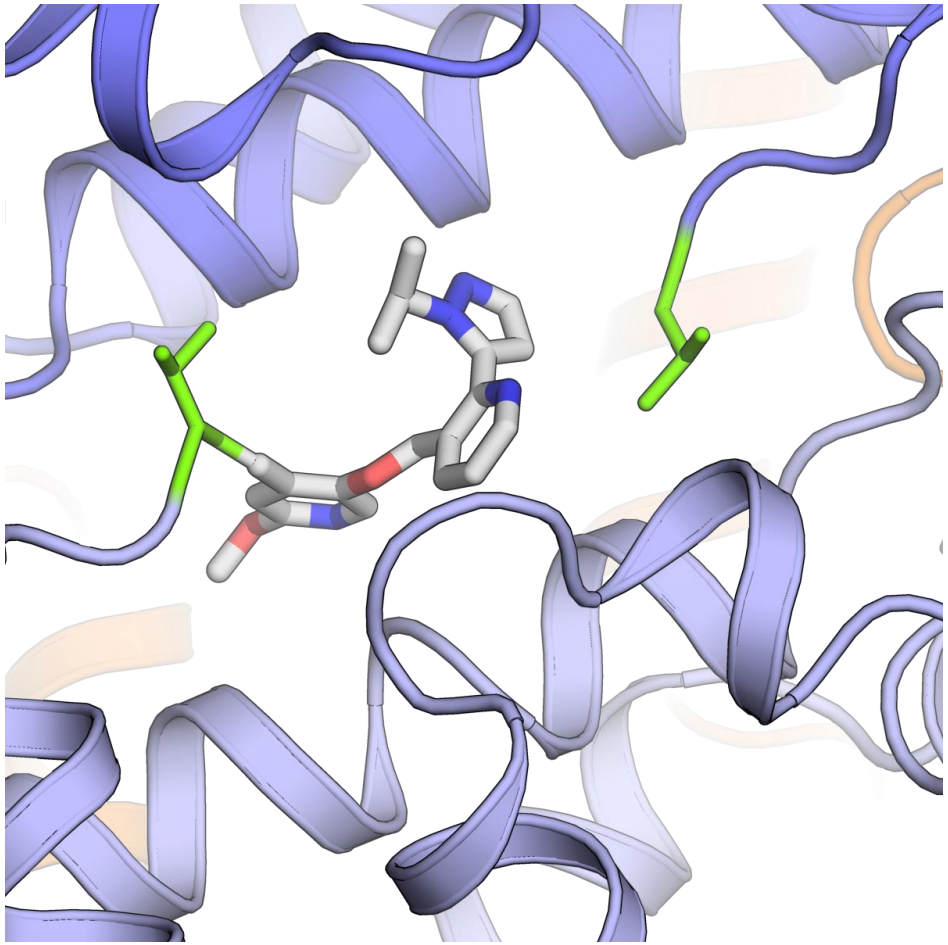


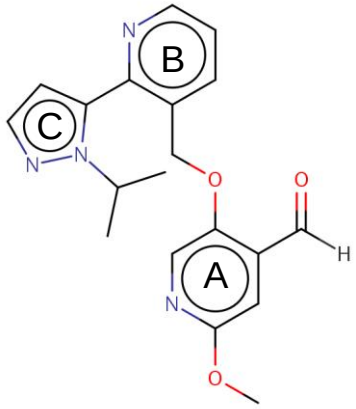


GBT104

GBT324 IS ACTIVE IN WHOLE BLOOD, BUT NOT ORALLY AVAILABLE. HBS CO-CRYSTALLIZED WITH GBT324. 1:1 STOICHIOMETRY

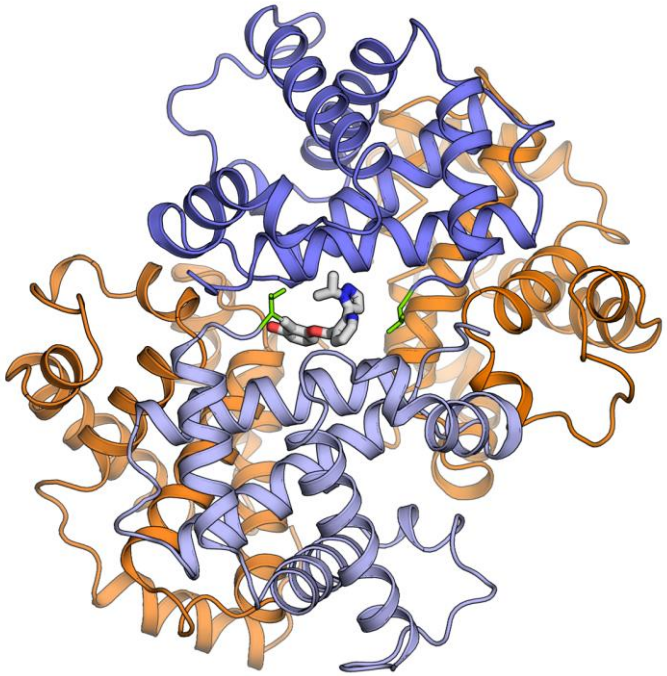


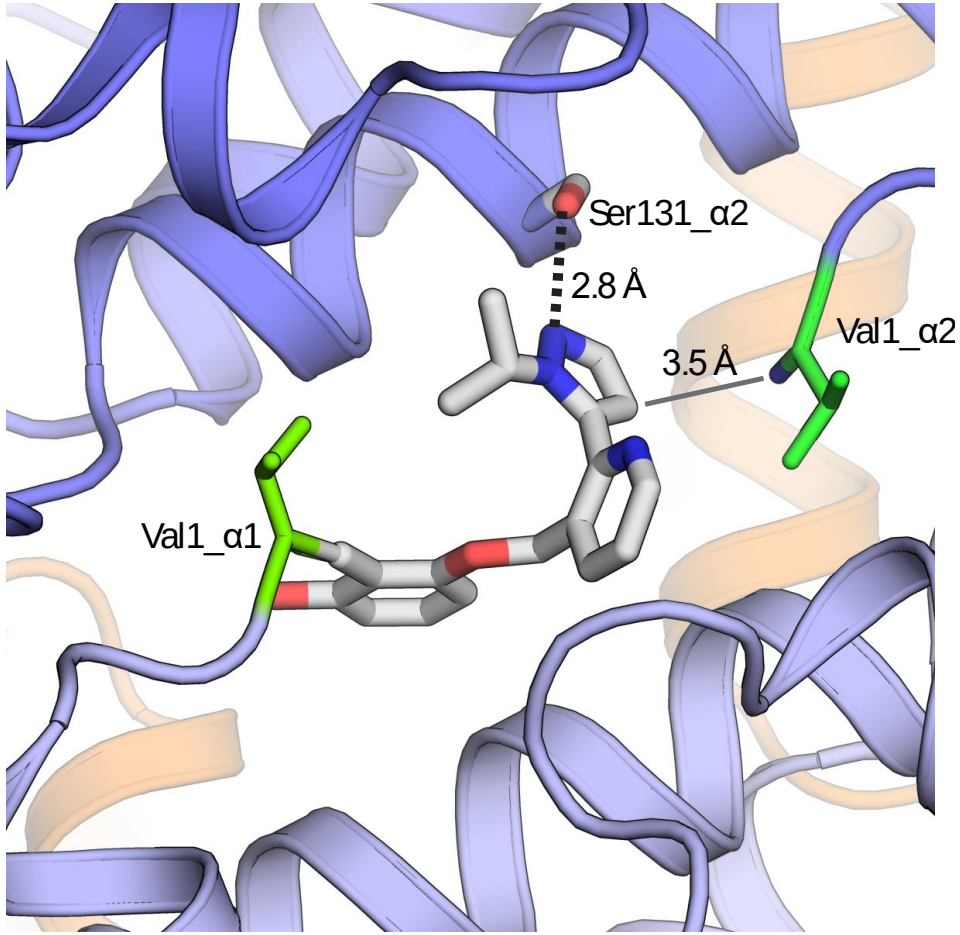


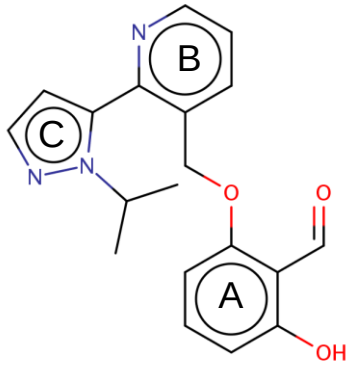


GBT324

VOXELOTOR (GBT440) FIRST ORALLY AVAILABLE COMPOUND. DRAMATIC PARTITIONING INTO BLOOD VS PLASMA



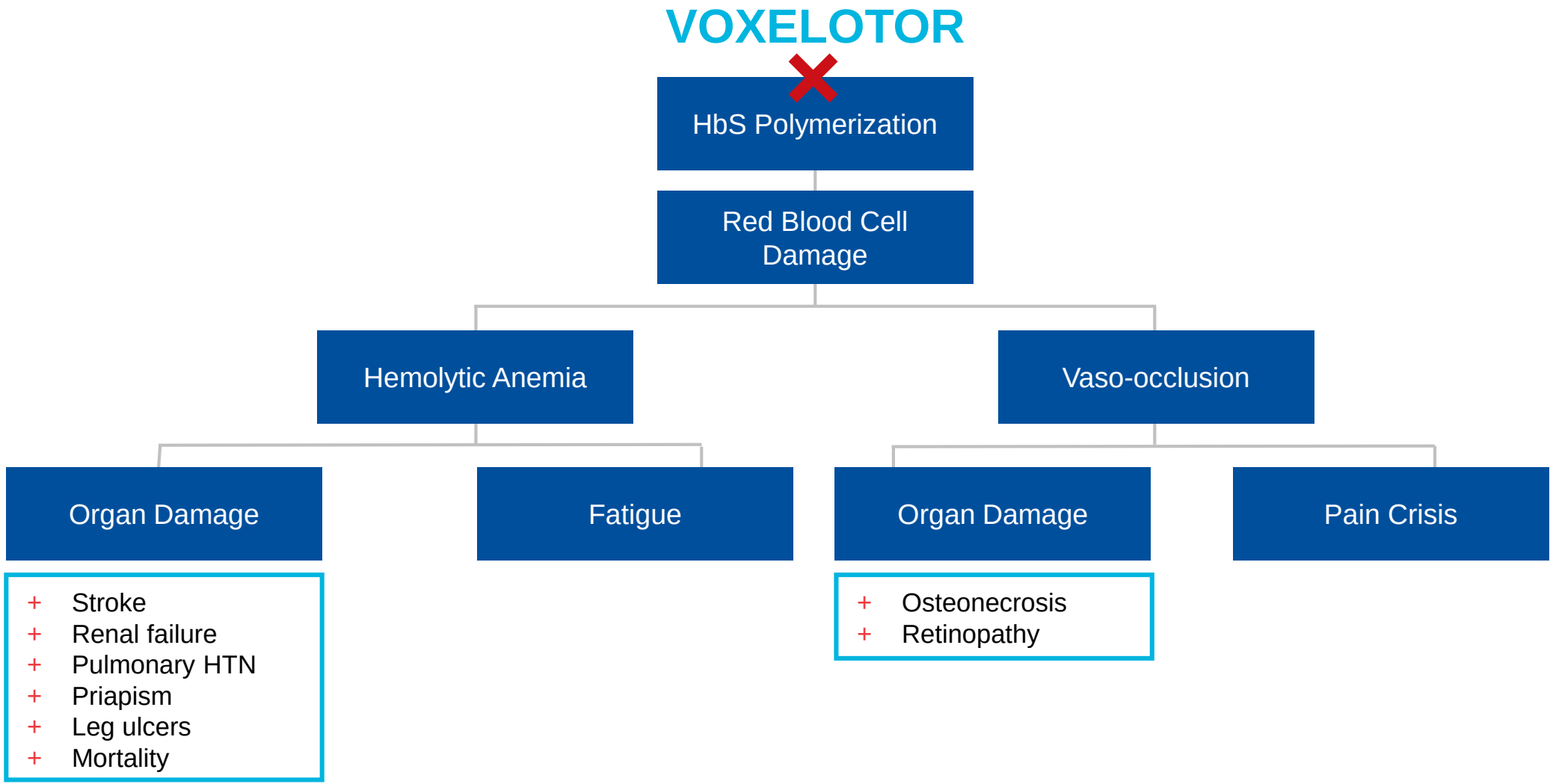




Voxelotor (GBT440)

High partitioning believed to reduce risk of systemic toxicity via low plasma concentrations.

VOXELOTOR INHIBITS ABNORMAL HBS POLYMERIZATION, THE FUNDAMENTAL CAUSE OF SCD PATHOPHYSIOLOGY



Eaton W, Bunn F. Targeting HbS Polymerization, Blood 2017.

001: STUDY DESIGN -- CHRONIC DOSING FOR 90 DAYS AND BEYOND

001: Phase 1/2, Randomized, Double-blind, Placebo-controlled Study in Adult HbSS, HbS/β0thalassemia, HbS/β+thalassemia, or HbSC Patients

Part A – Single Dose

+ Healthy volunteers: 5 cohorts (100, 400, 1000, 2000, 2800 mg)
+ SCD patients: 1 cohort (1000 mg)

Part B – Multiple Doses (15 and 28 days)

+ Healthy volunteers: 3 cohorts (300, 600, 900 mg per day x 15 days)
+ SCD patients: 3 cohorts (500 mg, 700 mg, 1000 mg per day x 28 days)
+ Variant genotype (HbSC): 1 cohort (600 mg per day x 28 days)

Part C – Multiple Doses (90 days)

+ SCD patients: 2 cohorts (700 mg, 900 mg per day x 90 days)

Cohorts = 8 people (6 active, 2 placebo)*

Objectives

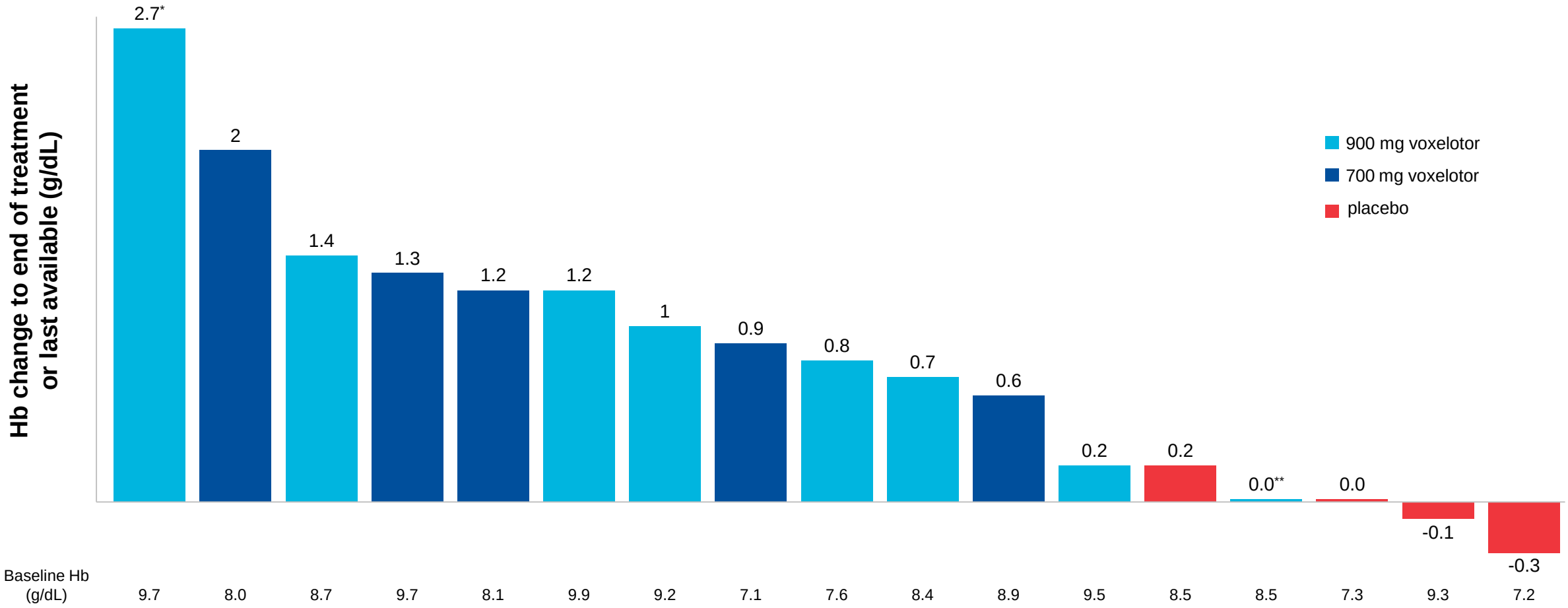
+ Pharmacokinetics
+ Pharmacodynamics
+ SCD patients: hematologic parameters
+ Safety

024 (open-label extension study)

Extended dosing of voxelotor (Cohort 17, 900 mg) for a total of 6 months

*Except SCD patients in Part B: 500 mg cohort (10:4); 700 mg cohort (12:4)

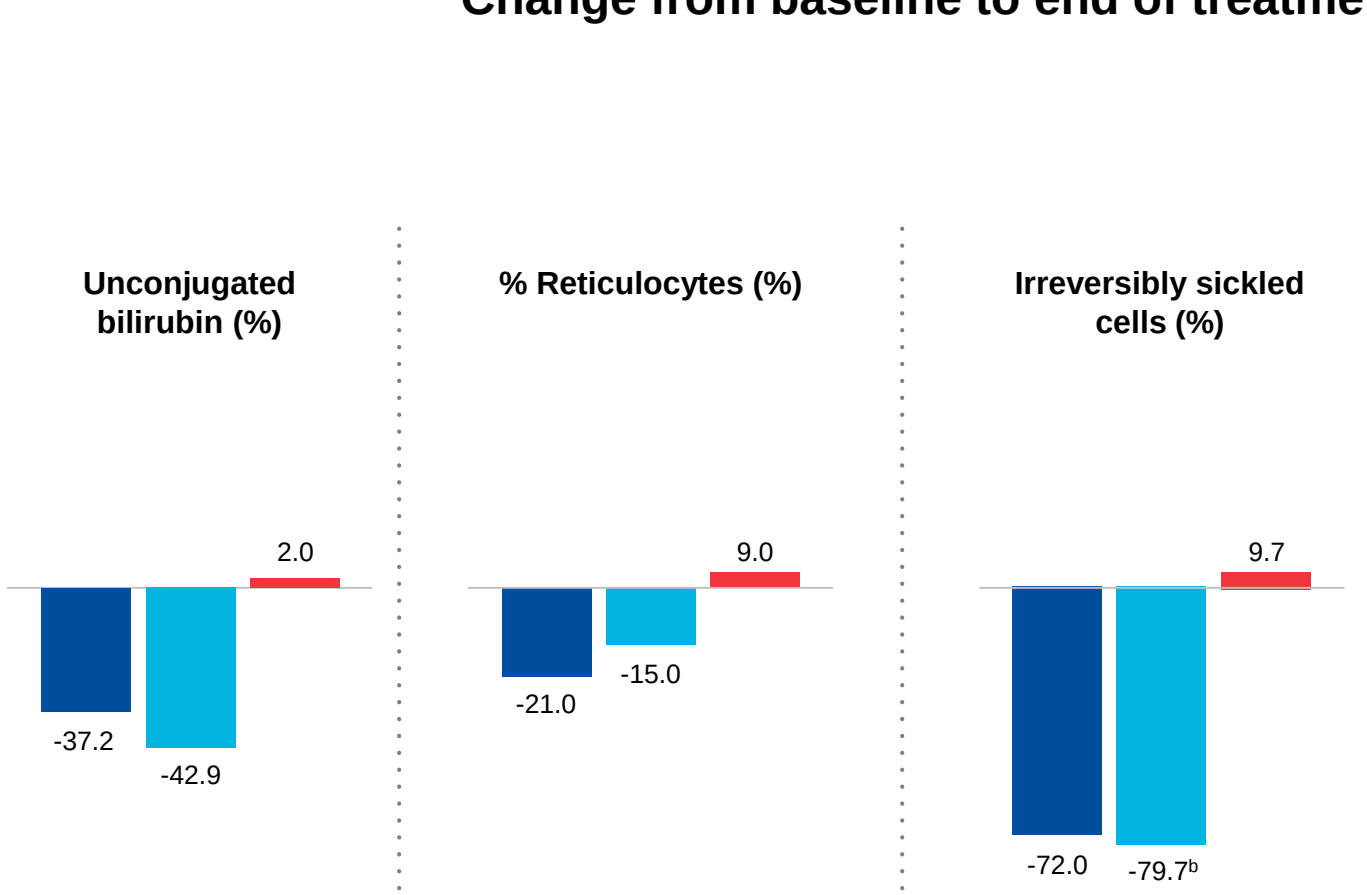
001: 46% OF PATIENTS ACHIEVE HEMOGLOBIN RESPONSE >1 G/DL

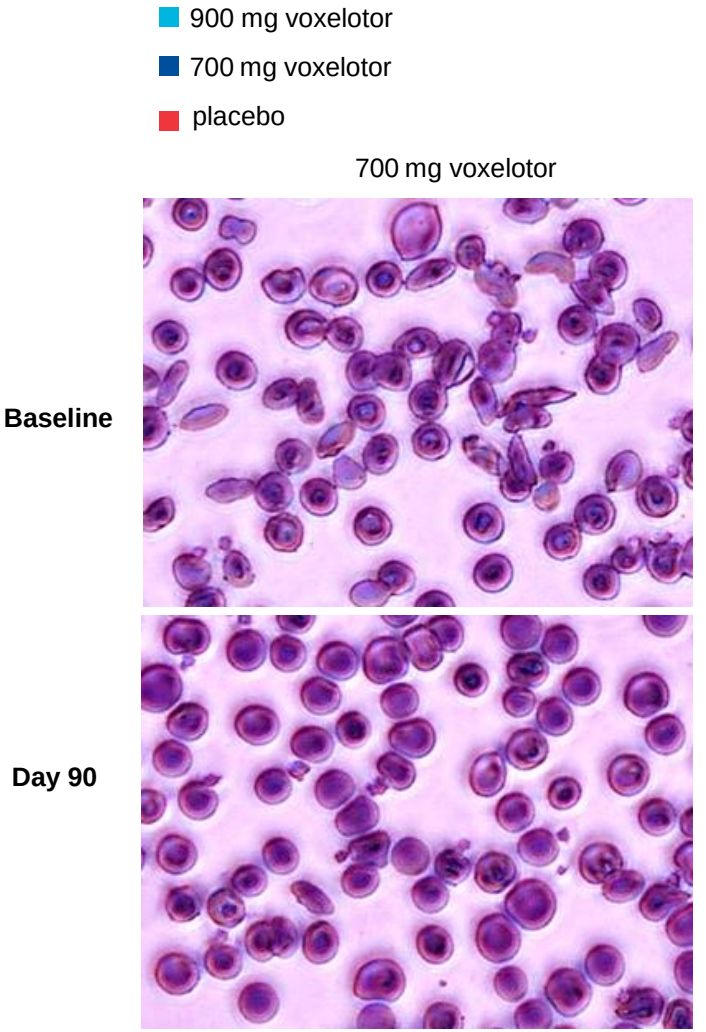


*Day 15 data presented due to a protocol-specified dose reduction on Day 17 because of a large increase in Hb
**Patient documented non-adherence with study drug regimen

001: ALL PATIENTS DOSED WITH VOXELOTOR SHOWED A REDUCTION IN HEMOLYSIS, RETICULOCYTES AND/OR SICKLE CELLS

Change from baseline to end of treatment





[a]Data available for n=4
[b]Data available for n=5

001: SAFETY AND TOLERABILITY PROFILE

- Voxelotor was well tolerated
- No drug-related serious or severe adverse events
- No evidence of tissue hypoxia
  - No increase in erythropoietin
  - No decrease in O_2 consumption with exercise

007: STUDY DESIGN

HOPE-KIDS 1 (007): Phase 2a Open-label, Single- and Multiple-dose Clinical Trial in Pediatric Population

Part A – Single Dose

+ Cohort 1: SCD patients age 12-17: 600 mg
+ Cohort 2: SCD patients age 6 -11: 600 mg

Part B – Multiple Doses

+ Cohort 1: SCD patients age 12-17: 900 mg per day x 24 weeks
    - ***EHA poster presentation provided results (24 weeks)***
+ Cohort 2: SCD patients age 12-17: 1500 mg per day x 24 weeks

Objectives

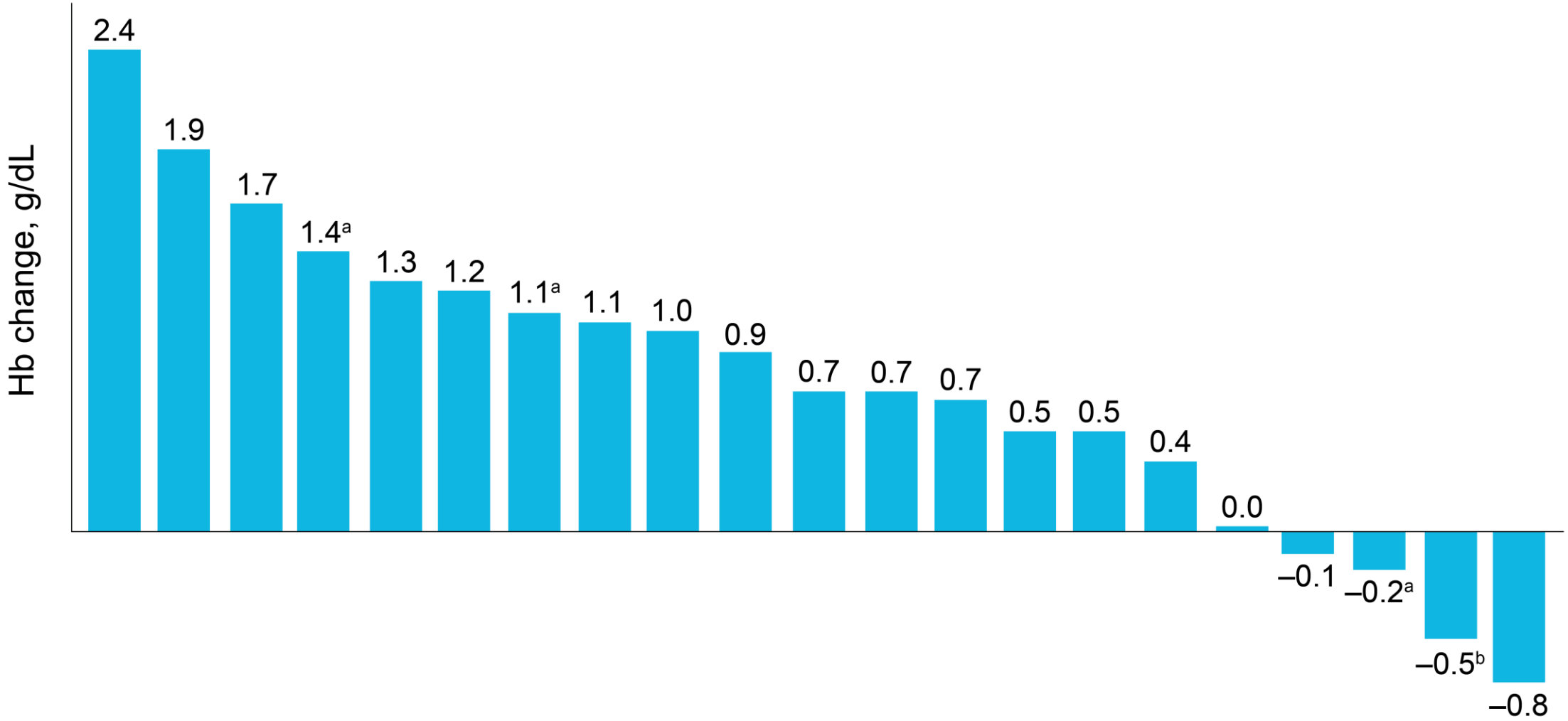
+ Assess efficacy as measured by improvement in anemia
+ Effect on clinical measures of hemolysis
+ Effects on total symptom score (TSS) from PRO
+ Pharmacokinetics
+ Safety/tolerability

007: BASELINE CHARACTERISTICS (Data as of April 16, 2018)

Baseline Characteristics	900 mg/d N=25 All Treated Patients to Date (Safety Population)
Male, n (%)	14 (56)
Age, median (range), y	14 (12-17)
HbSS genotype,[a] n (%)	24 (96)
Number of VOCs in prior year, n (%)	
0	11 (44)
1-4	12 (48)
>4	2 (8)
Current HU use, n (%)	22 (88)
Baseline[b] Hb, median (range), g/dL	8.9 (6.3-11.0[c])
Baseline[b] HbF, median (range), %	10.8 (3.7-29.0)
Baseline[b] TAMM for TCD, median (range), cm/s	110 (74-149)

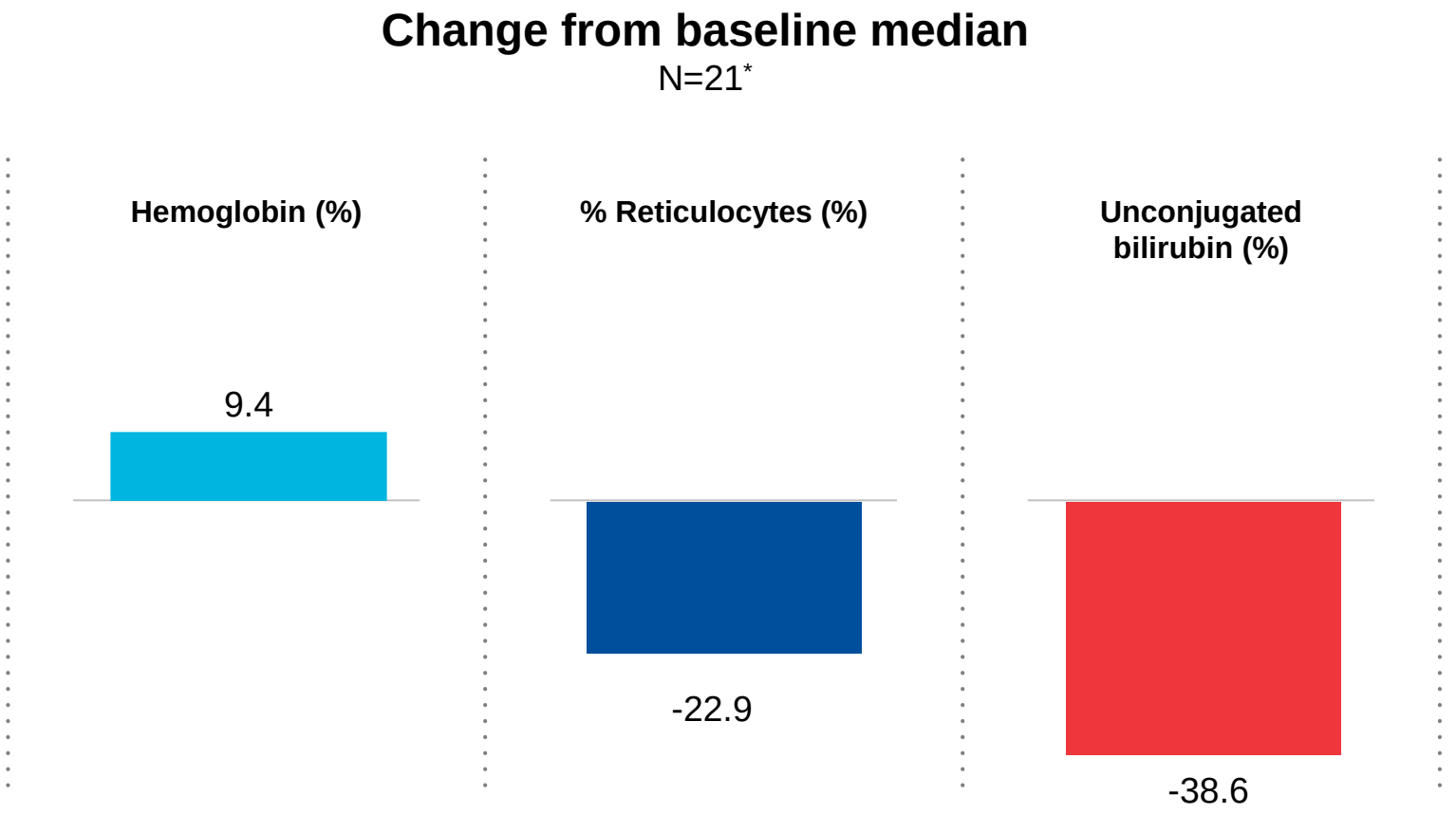
HbF, fetal hemoglobin; HU, hydroxyurea; TAMM, time-averaged mean of maximum velocity; TCD, transcranial Doppler ultrasound.
[a]1 patient with HbSβ^0 thal.
[b]Baseline is the average of the values obtained prior to the first dose.
[c]One patient had a baseline Hb level >10.5 g/dL.

007: 43% OF PATIENTS ACHIEVED HEMOGLOBIN RESPONSE ≥1 g/dL AT 24 WEEKS



[a]Not receiving concurrent hydroxyurea.
[b]Documented noncompliance.

007: HEMOLYSIS MEASURES AT 24 WEEKS



*3 subjects discontinued dosing prior to 24 weeks (withdrew consent, lost to follow-up, noncompliance)
1 subject excluded due to a concurrent acute chest syndrome at week 24.

STOP-1 STUDY: REDUCED HBS CONCENTRATION DRAMATICALLY REDUCES STROKE RISK

The STOP-1 study investigated RBC transfusions to reduce HbS concentration to <30 percent total hemoglobin in children with abnormal TCD

Key Findings:

- In the standard-of-care group, the rate of stroke was 10 percent per year
- Risk of stroke in the transfusion group was 92 percent lower (p=0.002) than the standard-of-care group over 30 months.
- Within the transfusion group, 78 percent of patients had at least one hemoglobin S measurement that exceeded the target threshold.
- Two years after publication of the STOP-1 study results, SCD stroke rates in the state of California dropped by a factor of 5.

Adams RJ, McKie VC. Prevention of a first stroke by transfusions in children with sickle cell anemia and abnormal results on transcranial Doppler ultrasonography. NEJM 1998.

STOP-2 STUDY: INCREASING HEMOGLOBIN REDUCES STROKE RISK

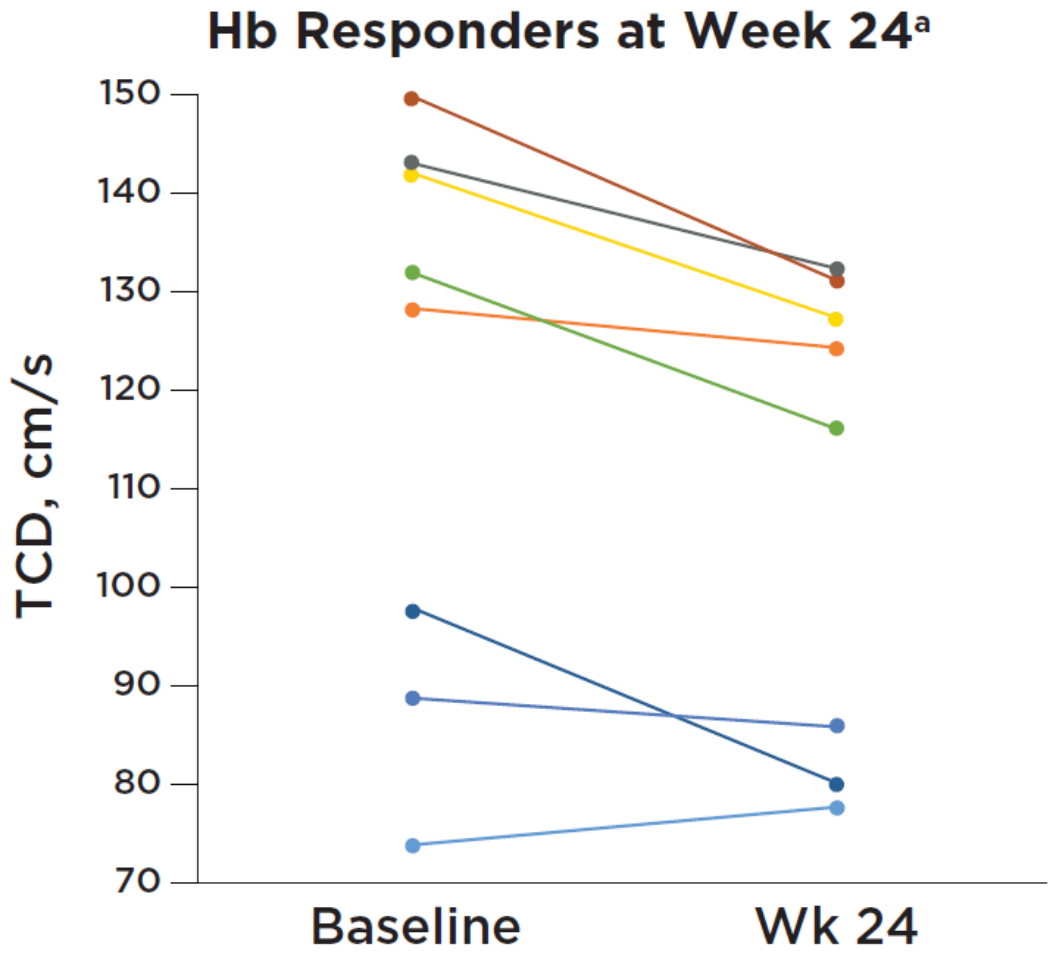
The STOP-2 study assessed the discontinuation of transfusions vs. continued transfusions among children with receiving transfusions for abnormal TCD

Key Findings:

+ Increase in stroke risk after discontinuation of transfusions
+ Probability of converting to normal TCD increased by 26.6% per 1g/dL increase in Hb
+ Transfusion group overall associated with +1.7 g/dL Hb and complete protection from stroke/abnormal TCD versus 39% risk

Adams, RJ, Brambilla, D. Discontinuing prophylactic transfusions used to prevent stroke in sickle cell disease, NEJM 2005.

007: TRANSCRANIAL DOPPLER (TCD)-Hb RESPONDERS: TCD CHANGE AT WEEK 24 (N=8)



[a]One Hb responder did not have a TCD assessment performed at 24 weeks.

007: SAFETY AND TOLERABILITY

- Voxelotor 900 mg was well tolerated
- Drug-related AEs were Grade 1 or 2 (except one Grade 3 rash*)
- No drug-related SAEs
- No study drug discontinuations due to AEs

*Did not recur with continued dosing

HOPE STUDY

Hemoglobin **O**xygen Affinity Modulation to Inhibit HBS **P**olym**E**rization

A randomized, double-blind, placebo-controlled, multi-national, Phase 3 study

031: ORIGINAL PHASE 3 HOPE STUDY DESIGN AND STATUS

HOPE
Sickle Cell Disease Clinical Study

In discussions with the FDA on registrational pathway for voxelotor, including potential accelerated approval

SCD Patient Population:

+ 1-10 VOCs in prior year
+ Baseline Hb ≤10.5 g/dL
+ ≥12 years old
+ Concomitant hydroxyurea allowed

Part A

Randomize Up to 150 Patients

- Voxelotor 1500 mg
- Voxelotor 900 mg ★
- Placebo

3 months treatment

+ **Select dose**
+ **Finalize secondary endpoints**
+ **Announce top-line data (1H'18)**

Endpoints:

+ Primary: Proportion of patients who achieve a >1 g/dL Hb improvement at week 24
+ Key Secondaries: PRO exacerbation days and/or Total Symptom Score, VOC requiring a HCP interaction, hospitalizations

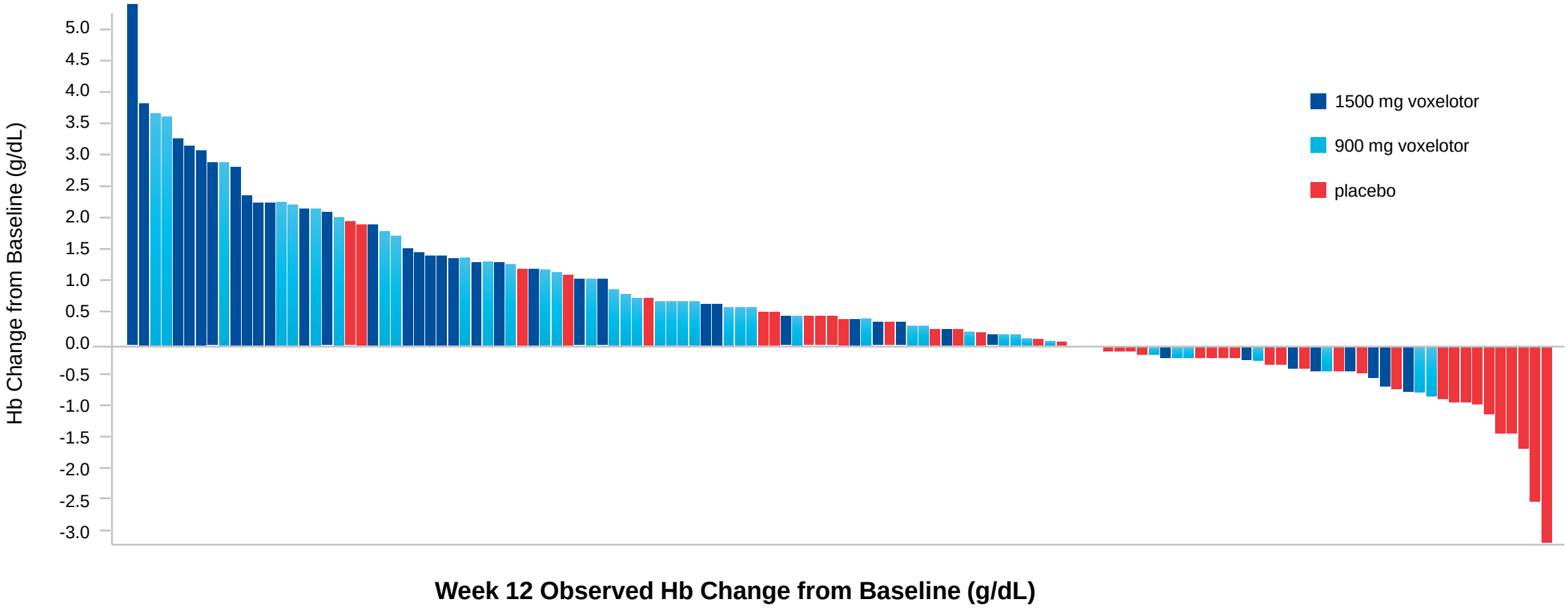
Part B

Randomize 250 SCD Patients

- Voxelotor selected dose ★
- Placebo

6 months treatment

031: 58% OF PATIENTS ON 1500 MG ACHIEVED PRIMARY ENDPOINT OF HB RESPONSE ≥1 g/dL AT 12 WEEKS (p<0.0001)



031: EFFICACY AND SAFETY SUMMARY FOR PART A

- **Improvement in hemolytic anemia:** statistically significant and dose-dependent improvements in hemoglobin, reticulocytes and bilirubin occurred with both voxelotor doses
  - Improvements were similar in patients with or without background use of hydroxyurea. Approximately 64% of patients enrolled in Part A are on background use of hydroxyurea.
- **Numerically fewer VOC episodes** in both voxelotor groups than in the placebo group.
- **Voxelotor was generally safe and well tolerated** with similar safety profiles between the two doses. There was no evidence of tissue hypoxia at either dose.

031: POTENTIAL ACCELERATED APPROVAL BASED ON HEMOLYTIC ANEMIA EFFICACY

*The FDA instituted its Accelerated Approval Program to allow for earlier approval of drugs that **treat serious conditions**, and that fill an **unmet medical need** based on a surrogate endpoint. A surrogate endpoint is a marker, such as a laboratory measurement, radiographic image, physical sign or other measure that is thought to **predict clinical benefit**, but is not itself a measure of clinical benefit. The use of a surrogate endpoint can considerably shorten the time required prior to receiving FDA approval.*

- We believe voxelotor meets criteria for accelerated approval under subpart H:
  - SCD is a **serious and life-threatening illness**
  - **Well-established association between chronic hemolytic anemia and SCD-related morbidity and mortality**
  - **Clinically meaningful increase in hemoglobin** and **improvement in hemolysis** demonstrated in Part A results of the HOPE Study
- In discussions with FDA regarding potential accelerated approval
  - Requires post-marketing clinical studies to confirm clinical benefit and maintain approval

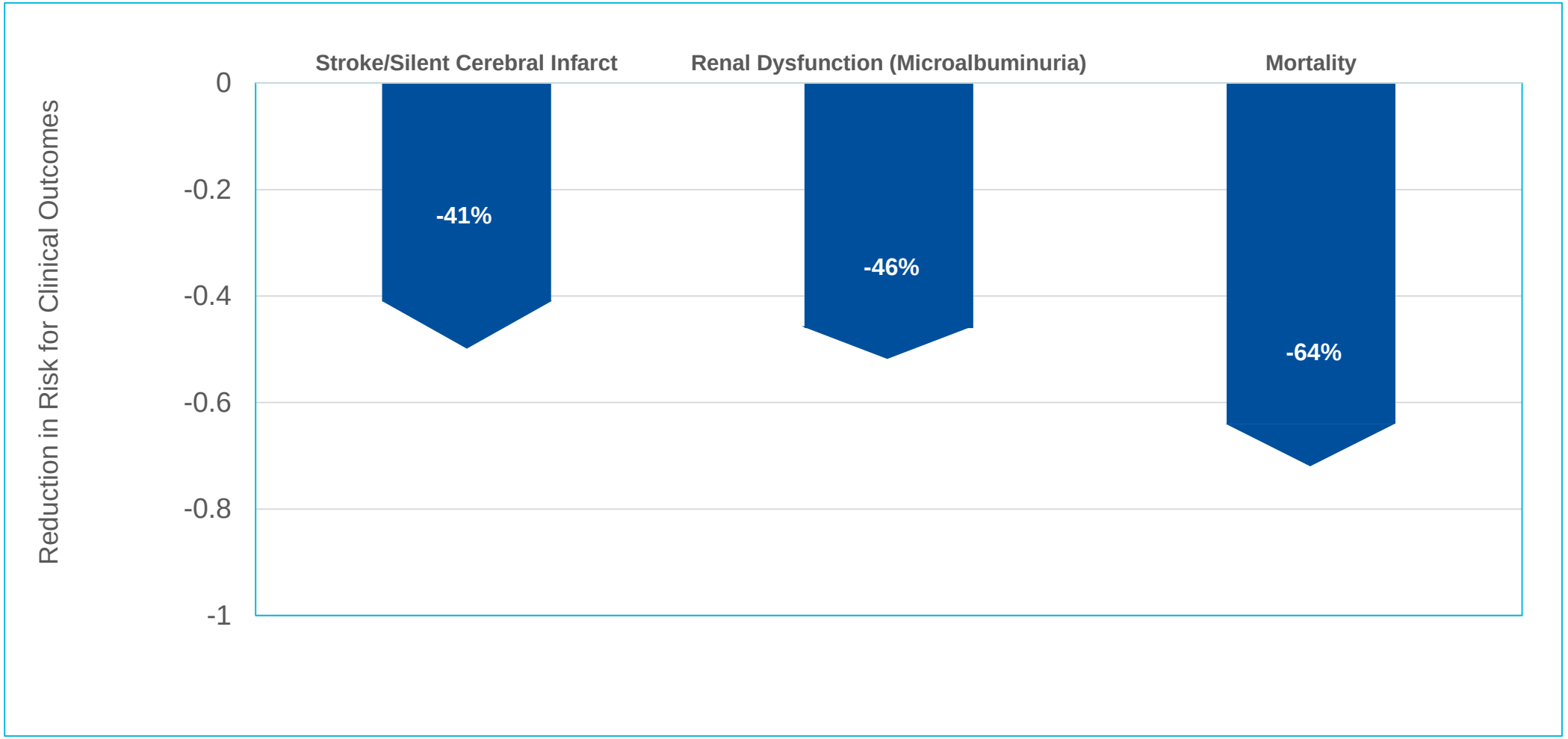
LOWER HEMOGLOBIN LEVELS ARE ASSOCIATED WITH NEGATIVE CLINICAL OUTCOMES IN SCD

Clinical Outcome/Event	Δ Hb compared to those without clinical outcome/event* Mean (95% Confidence Interval), g/dL	P-value
Stroke/SCI History	-0.37 (-0.47, -0.28)	<0.001
Abnormal TCD Velocity	-0.47 (-0.57, -0.37)	<0.001
Microalbuminuria	-0.65 (-0.84, -0.46)	<0.001
Elevated PASP	-0.94 (-1.20, -0.67)	<0.001
Death	-0.55 (-0.72, -0.39)	<0.001

SCI – Silent Cerebral Infarct; TCD – Transcranial Doppler Ultrasound; PASP – Pulmonary Artery Systolic Pressure

*Meta-analysis conducted based on data from studies identified from a comprehensive systematic literature review evaluating 139 sickle cell disease peer reviewed publications published over the last 20 years; GBT data on file.

PREDICTED RISK REDUCTION OF STROKE, RENAL DISEASE, AND MORTALITY ASSOCIATED WITH INCREASING HB BY ≥ 1 G/DL*



***Based on meta-analysis conducted based on comprehensive systematic literature review evaluating 139 sickle cell disease peer-reviewed publications published over the last 20 years, GBT data on file.**

CONCLUSIONS

Despite advances in clinical care, SCD shortens median lifespan by at least three decades.

People with SCD survive through adolescence roughly on par with those in the general population.

Lower hemoglobin levels lead to greater complications and mortality.

New therapies are needed to address the fundamental pathogenesis of SCD.

Voxelotor is uniquely suited to address unmet medical need.