Progress in Management of Sickle Cell Disease – since 3rd Global Congress in 2017

Global Sickle Cell Disease Network Congress 2022

Disclosures

Research	Biomarin, bluebird bio, BMS/Celgene, Editas, Novartis
Consultant	Agios, Beam, bluebird bio, Celgene
Speaker's Bureau	None
Board/Advisory	Global Blood Therapeutics
Royalties	None

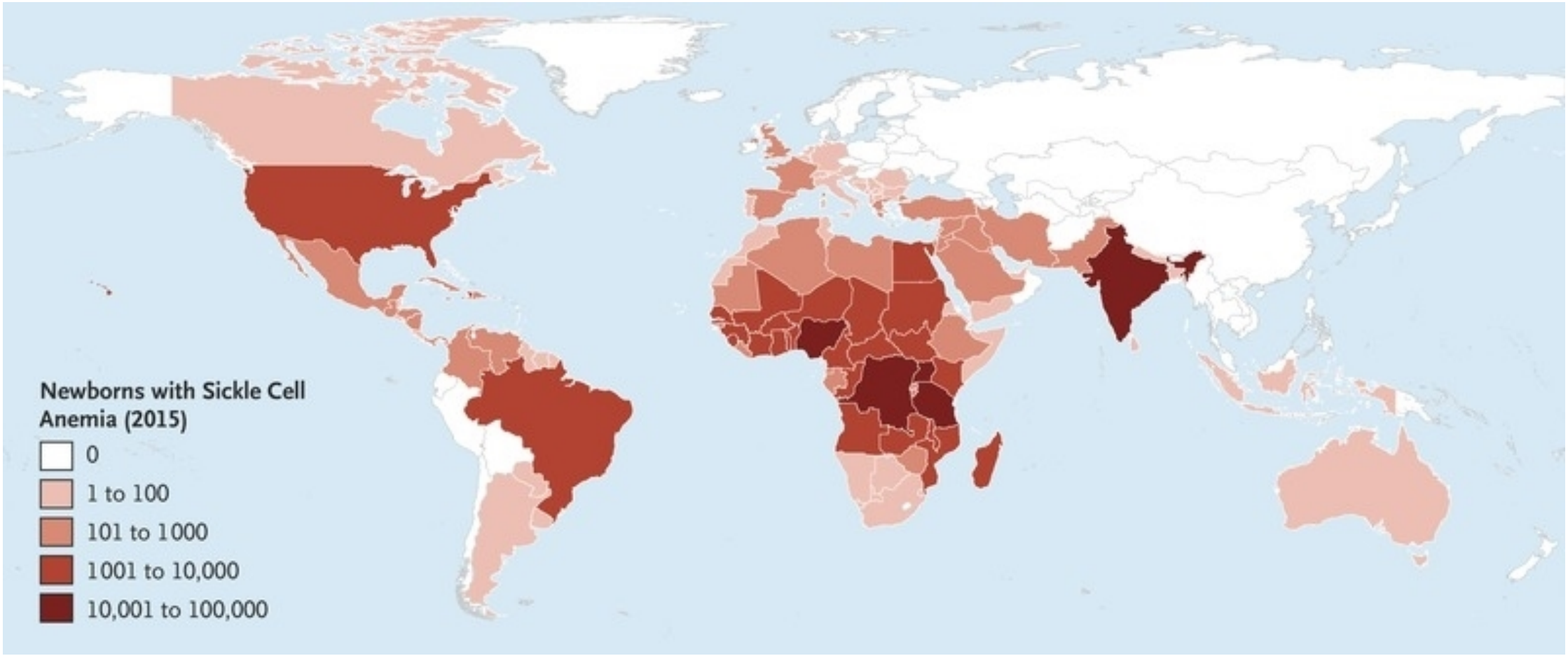
Where we were then, where we're going now

- Progress to date with disease modifying therapies
- Curative landscape
- Challenges
- Just over the horizon

Sickle Cell Disease: Where were we in 2017?

- Only one approved agent for SCD – hydroxyurea/hydroxycarbamide
- Curative therapy primarily allogeneic stem cell transplant using HLA matched sibling donors
- Newborn screening universal in U.S. and U.K., but few other high resourced countries, and very limited in high burden regions

Global burden of SCD (2017)



Estimated >300,000 newborns/yr with HbSS, highest burden on Nigeria, DRC and India

Piel FB, Hay SI, Gupta S, Weatherall DJ, et al. (2013) Global Burden of Sickle Cell Anaemia in Children under Five, 2010–2050: Modelling Based on Demographics, Excess Mortality, and Interventions. PLoS Med 10(7): e1001484.; Piel FB et al N Engl J Med 2017; 376:1561-1573

Updated Estimates of Child Mortality

- Retrospective, multicenter case-control study
- Recruitment Sept 2017-Nov 2020 in sub-Saharan African countries

	Control families		Families with cases of sickle cell anaemia		Children with sickle cell anaemia (estimated)*		Estimated relative risk of death (95% CI)
	n	Mortality rate (95% CI)	n	Mortality rate (95% CI)	n	Mortality rate (95% CI)	
Younger than 1 year	5321	4·1% (3·5–4·6)	4803	6·9% (6·2–7·6)	1201	15·3% (13·3–17·3)	3·73 (3·10–4·50)
Younger than 5 years	4727	6·8% (6·2–7·4)	4017	14·2% (13·3–15·2)	1004	36·4% (33·4–39·4)	5·35 (4·68–6·12)
Younger than 10 years	2699	7·2% (6·5–7·8)	2286	15·8% (14·8–16·8)	572	43·3% (39·3–47·3)	6·01 (5·11–7·11)

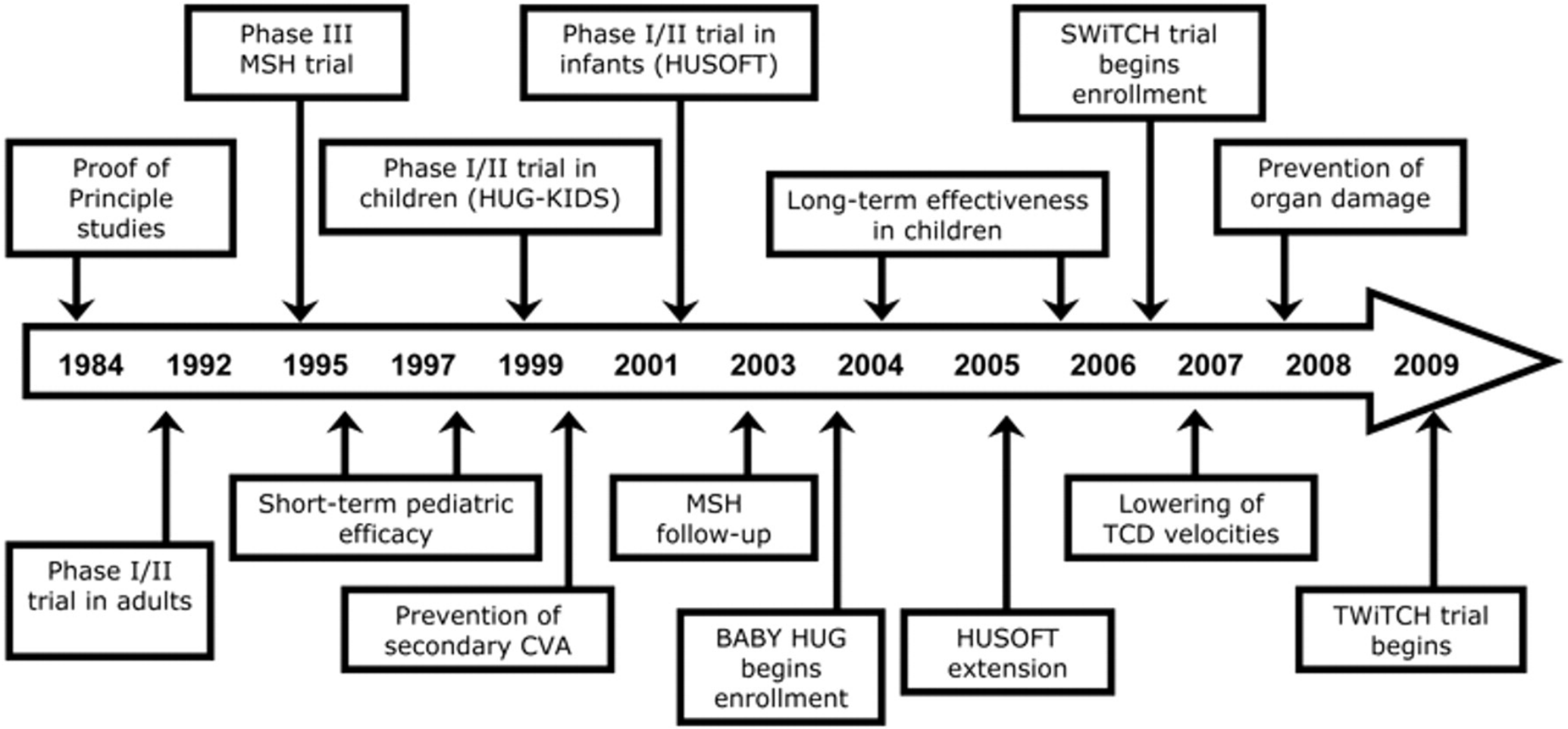
n indicates the number of children (alive) at risk after exclusion of the index cases in families with cases of sickle cell anaemia. *The mortality of children with sickle cell anaemia was estimated from the mortality rates of control and families with cases of sickle cell anaemia assuming that 25% of children born in families with cases of sickle cell anaemia have sickle cell anaemia.

***Table 2:* Mortality rates by age category**

- Estimated relative risk of death in children with HbSS high
- Lower mortality rates than previous reports, suggesting improvements in care

Ranque B et al, Lancet Haematol. 2022 Mar;9(3):e208-e216.

Pre-2017: Evolution of Hydroxyurea in SCD



Ware, and Aygun, Advances in the use of hydroxyurea, Hematology Am Soc Hematol Educ Program, 2009

A Prospective Multi-National Trial of Hydroxyurea for Sickle Cell Anemia in Sub-Saharan Africa (REACH)

Study Design

Phase I/II open-label hydroxyurea trial
- 4 sites in sub-Saharan Africa (Angola, DRC, Kenya, Uganda)
- 600 children, age 1-10 years
- Coordinated by Cincinnati Children's

Innovative study design for safety
- Simon's two-stage design
- Online dosing calculators

Hydroxyurea study treatment
- Drug capsules donated by Bristol Myers-Squibb
- Fixed dose (15-20 mg/kg/day) then escalation to MTD

Summary and Conclusions

Hydroxyurea is feasible, safe, and effective treatment for African children with sickle cell anemia.

Hydroxyurea is associated with reduced rates of malaria and other infections, leading to improved survival.

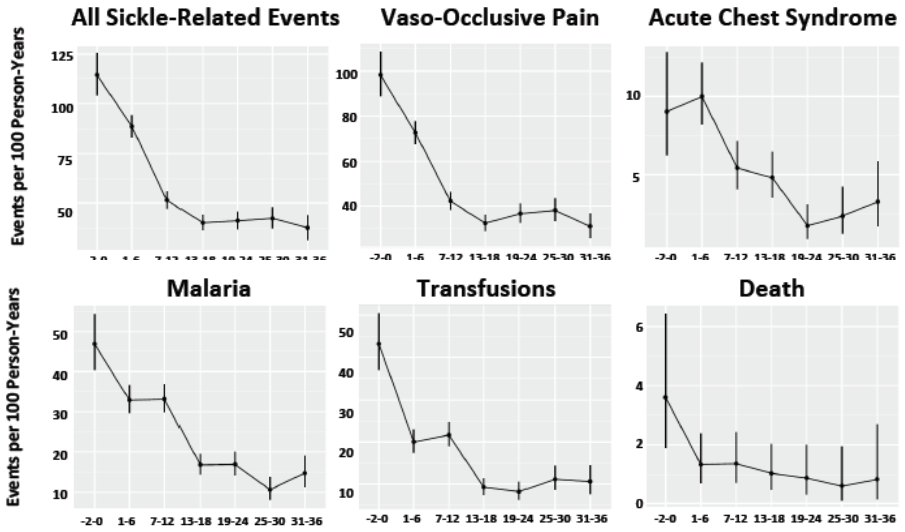
Wider access to hydroxyurea for sickle cell anemia has the potential to save millions of lives in Africa.

Laboratory Benefits

	Month 0	Month 3	Month 12	
Hemoglobin (g/dL)	7.3	8.0	8.3	+1.0 g/dL
Fetal hemoglobin (%)	10.9	17.3	23.4	+12.5 %
MCV (fL)	77	84	89	
Neutrophils (x10^3/µL)	6800	5200	4200	~4000
Reticulocytes (x10^3/µL)	344	233	187	~150-200
Platelets (x10^3/µL)	411	372	343	

- Dose-limiting toxicity – similar rates during screening and on treatment

Clinical Benefits

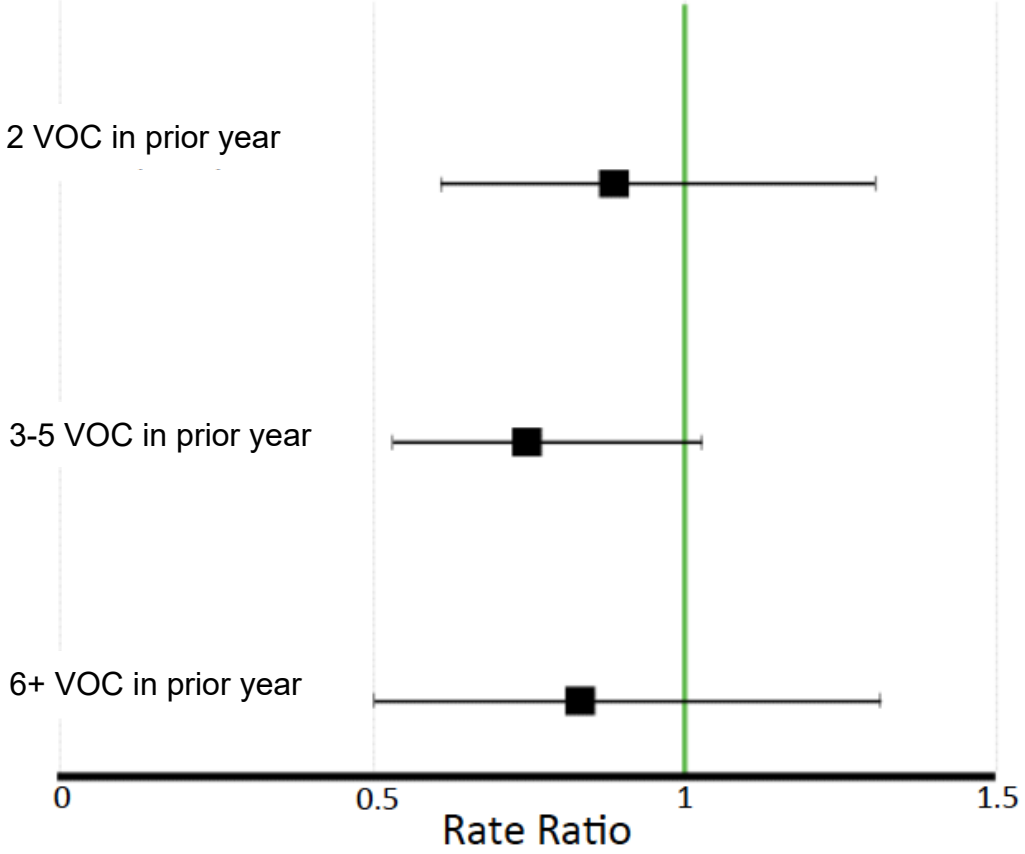


– Tshilolo et al., NEJM. 2019 Jan 10;380(2):121-131

New Therapies in SCD

- L-Glutamine (Endari)
  - Reduces RBC oxidative stress, hemolysis and adhesion
  - FDA approved July 2017, > age 5 years
- GBT-440 (Voxelotor; Oxbryta)
  - Rationally designed anti-sickling agent, binds alpha globin, inhibits HbS polymerization
  - FDA Approved November 2019, > age 4 years (2021)
- SelG1 (Crizanlizumab; Adakveo)
  - P-selectin inhibitor, inhibits RBC-endothelial interaction
  - FDA-approved November 2019, > age 16 years

Consistent Benefit of L-glutamine

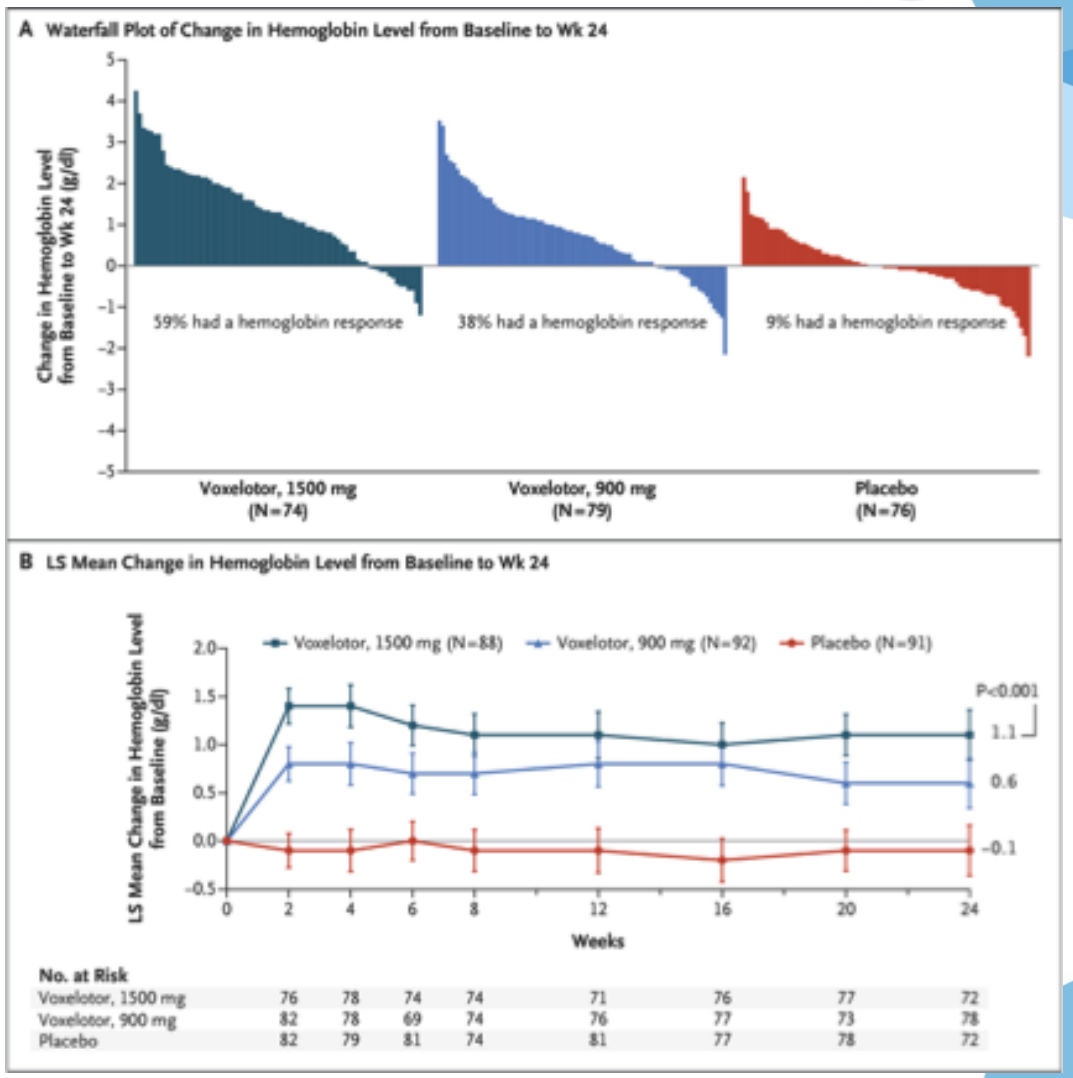


Forest plot of the ratio of crises on L-glutamine divided by crises on placebo where less than 1.0 favors L-glutamine (Rate ratios with 95% confidence intervals)

Categories	Statistics	Placebo (N=78)	Rate Ratios	L-glutamine (N=152)
2 VOC in prior year	Number of Subjects	26		53
	Rate Ratio (95% CI)	2.95 (2.10, 4.13)	**0.87** (0.58, 1.33)	2.57 (1.99, 3.33)
3-5 VOC in prior year	Number of Subjects	36		76
	Rate Ratio (95% CI)	4.28 (3.27, 5.61)	**0.74** (0.53, 1.04)	3.19 (2.56, 3.99)
≥ 6 VOC in prior year	Number of Subjects	16		22
	Rate Ratio (95% CI)	5.85 (4.01, 8.53)	**0.82** (0.50, 1.34)	4.77 (3.44, 6.63)

Voxelotor (GBT440, Oxbryta)

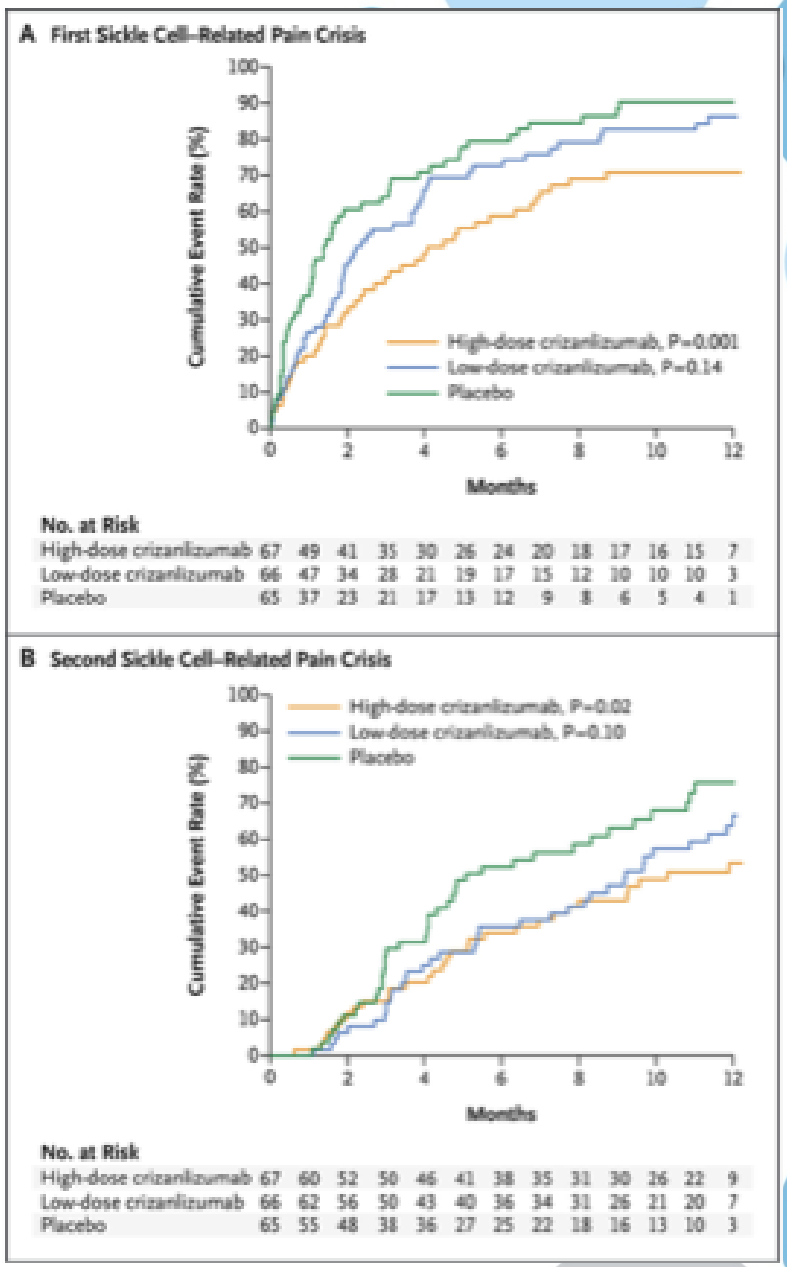
- HbS polymerization inhibitor
- Phase 3 RCT voxelotor significantly increased hemoglobin levels and reduced markers of hemolysis compared to placebo
- Administered oral daily
- FDA approved November 2019 for SCD patients age >12 years, lowered to >age 4 years in 2021



E Vichinsky et al. N Engl J Med 2019;381:509-519.

Crizanlizumab

- P-Selectin inhibitor
- Significantly reduced median rate of crises per year (p=0.01), median time to first pain VOE (p=0.001) and time to second VOE (p=0.02) compared to placebo in double blind phase 2 RCT
- Administered IV monthly
- FDA approved November 2019 for SCD patients age 16 years and older

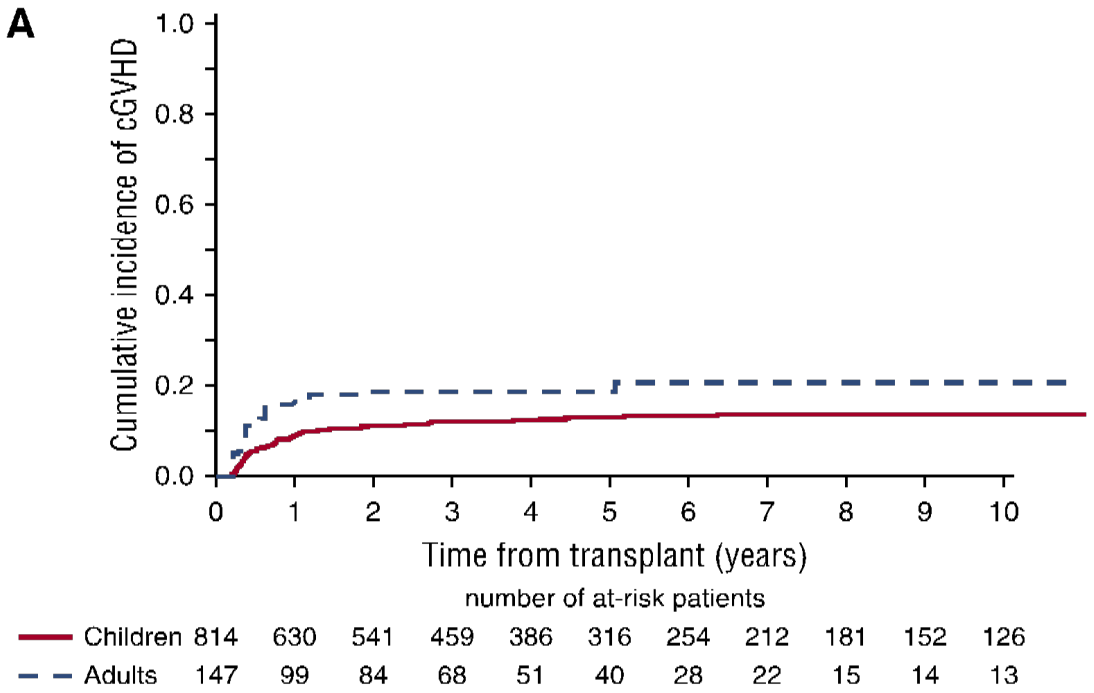


Ataga KI et al. N Engl J Med 2017;376:429-439.

30+

Approximate number of active SCD-related therapeutics in the clinical development pipeline

HLA-matched Sibling Donor Transplants: Standard of Care Curative Option for SCD



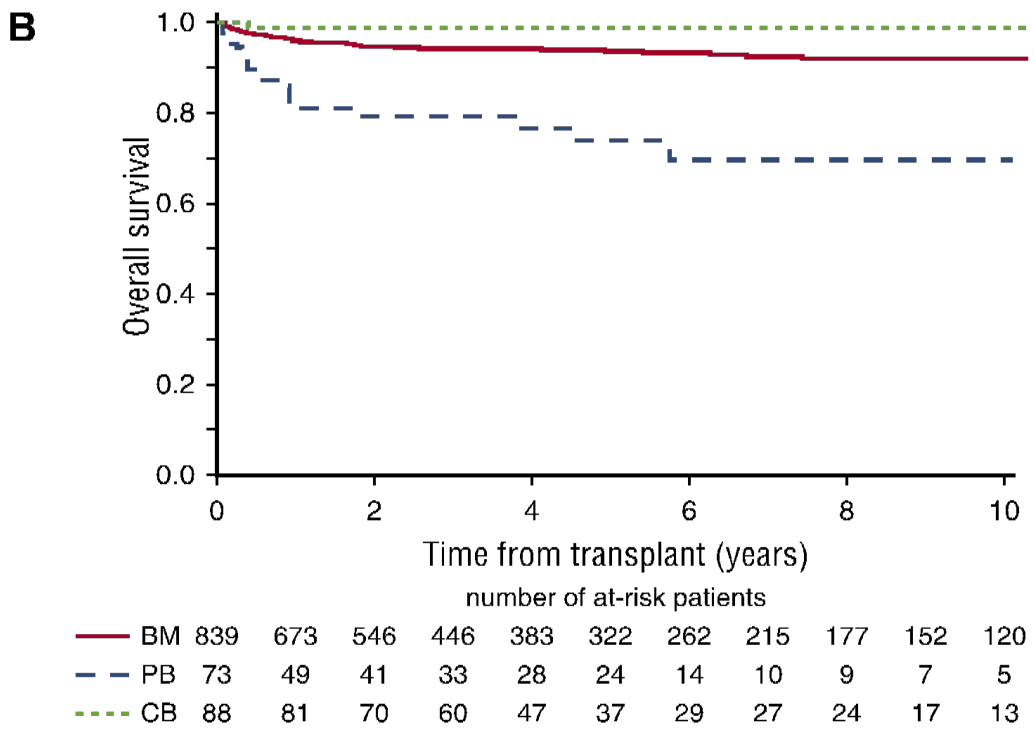


Table 3. Multivariate analysis for EFS and OS

	EFS		OS	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
PB vs BM	1.93 (0.87-4.26)	.104	2.62 (1.17-5.89)	.019
CB vs BM	0.55 (0.13-2.31)	.412	Not applicable*	
Age	1.09 (1.05-1.12)	<.001	1.10 (1.06-1.14)	<.0001
Transplant year, ≥2007 vs ≤2006	0.95 (0.90-0.99)	.013	0.96 (0.91-1.00)	.101
Conditioning regimen, RIC vs MAC	1.13 (0.46-2.81)	.793	0.83 (0.29-2.39)	.735
In vivo T-cell depletion, yes vs no	1.34 (0.63-2.82)	.445	1.10 (0.49-2.48)	.806

The adjusted Cox regression analysis was stratified by registry (EBMT and CIBMTR); age was considered as a continuous variable, and when considering the graft source, PB and CB were compared, separately, with BM (baseline) for the EFS.

*Not evaluable, as there was only 1 event in the CB group; therefore, for OS, the CB transplants were included with BM transplants.

Gluckman E, et al. Blood. 2017;129:1548-1556.

EBMT Hemoglobinopathy Registry
3856 Patients: Outcome

	OS	EFS	Rejection	NRM
24 mo	91% (90-92)	86% (85-87)	8% (7-9)	6% (6-7)

Age and outcome

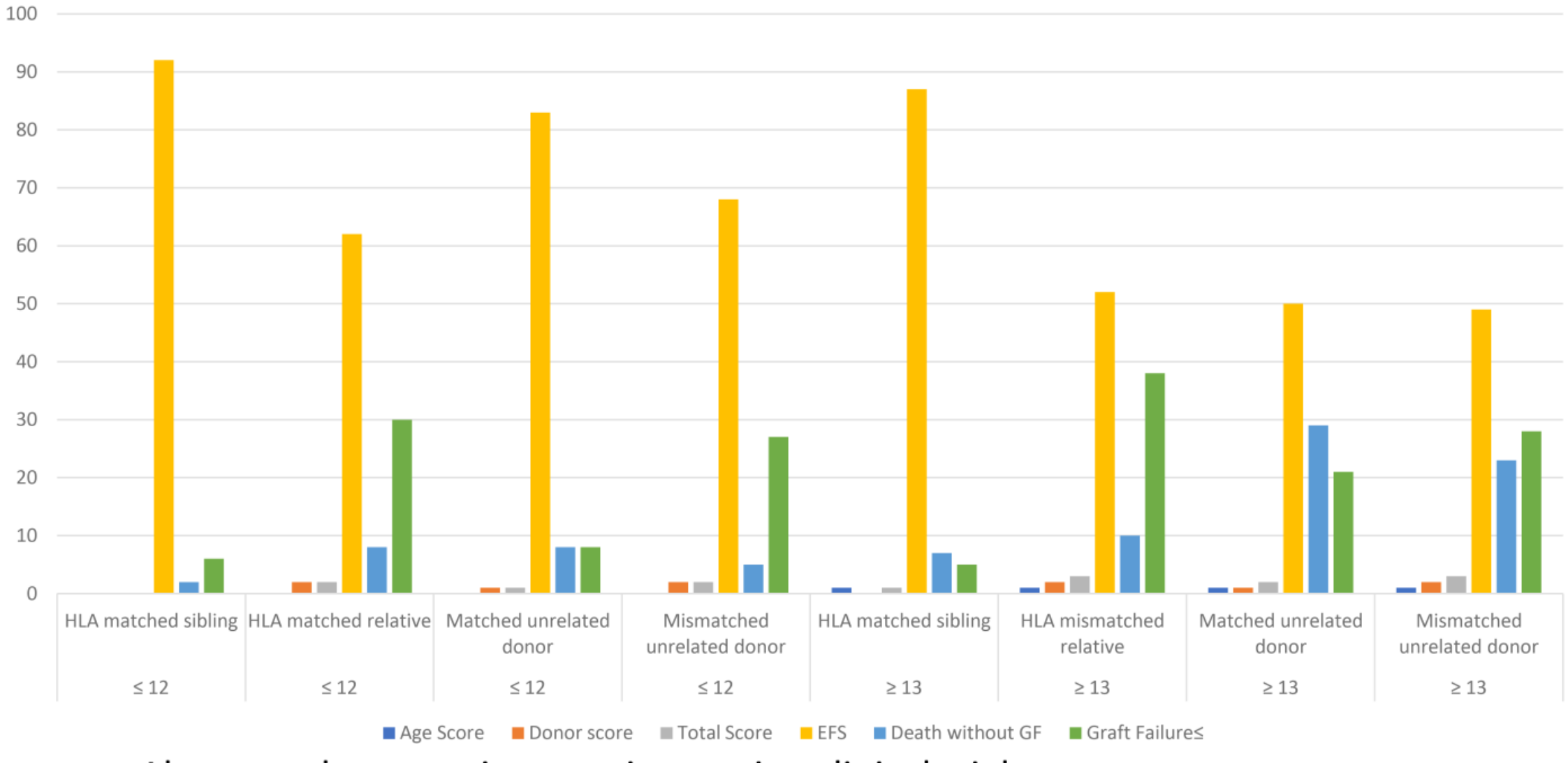
		Age <14yo	Age ≥14 years	
SCD	OS	95% (93-97)	90% (85-95)	p=0.001
	EFS	93% (90-95)	90% (84-96)	P=0.064

Source of Stem Cells and Outcome

	BM	CB	PB	
SCD OS	95% (93-96)	98% (94-100)	84% (74-94)	P=0.004
SCD EFS	92% (90-95)	97% (93-100)	83% (73-94)	P=0.004

ASH Abstract #168, 2019

Recipient Age and Donor HLA Match Important Factors in Transplant Outcomes



Krishnamurti, *Hematology,* Am Soc Hematol Educ Program, 2021,

Other Considerations

- Most patients with SCD lack a suitable matched related or unrelated stem cell donor
- Open research studies for unrelated with reduced intensity and also haploidentical donors
- Potential complications
    - Nonengraftment/Graft Failure
    - Infections
    - Graft versus Host Disease
    - Infertility
    - Transplant-related Mortality

Possible genomic therapy strategies

- Gene correction: Replacement of sequences at site of native gene
- Gene Addition: Introduce copies of a normal gene, leaving defective native gene intact
- Modify expression of other genes that play a role in disease phenotype or pathogenesis
- Genome editing: Directly repair specific sequences

Genome editing and gene therapy clinical trials in SCD

Goal	Viral vector	Sponsor, collaborator	Clinical trial ID	Estimated participants
Repair HbS mutation	Lenti/G-βAS3-FB lentiviral Vector	California Institute for Regenerative Medicine	NCT02247843	6
Elevate HbF	ARU-1801	Aruvant Sciences GmbH	NCT02186418	10
Repair HbS mutation	GLOBE1 lentiviral vector expressing the βAS3 globin gene	Assistance Publique–Hôpitaux de Paris	NCT03964792	10
Repair HbS mutation	LentiGlobin BB305 lentiviral vector	bluebird bio	NCT04293185	35
Repair HbS mutation	Lentiviral vector encoding the normal β-globin gene	Memorial Sloan Kettering Cancer Center, Sanofi	NCT02193191	39
Repair HbS mutation	LentiGlobin BB305 lentiviral vector	bluebird bio	NCT02140554	50
Elevate HbF	Lentiviral vector containing a short hairpin RNA targeting BCL11A	Boston Children's Hospital	NCT03282656	15

as of March 2021

Jones RL and Debaun MR Blood 138:11 (2021)

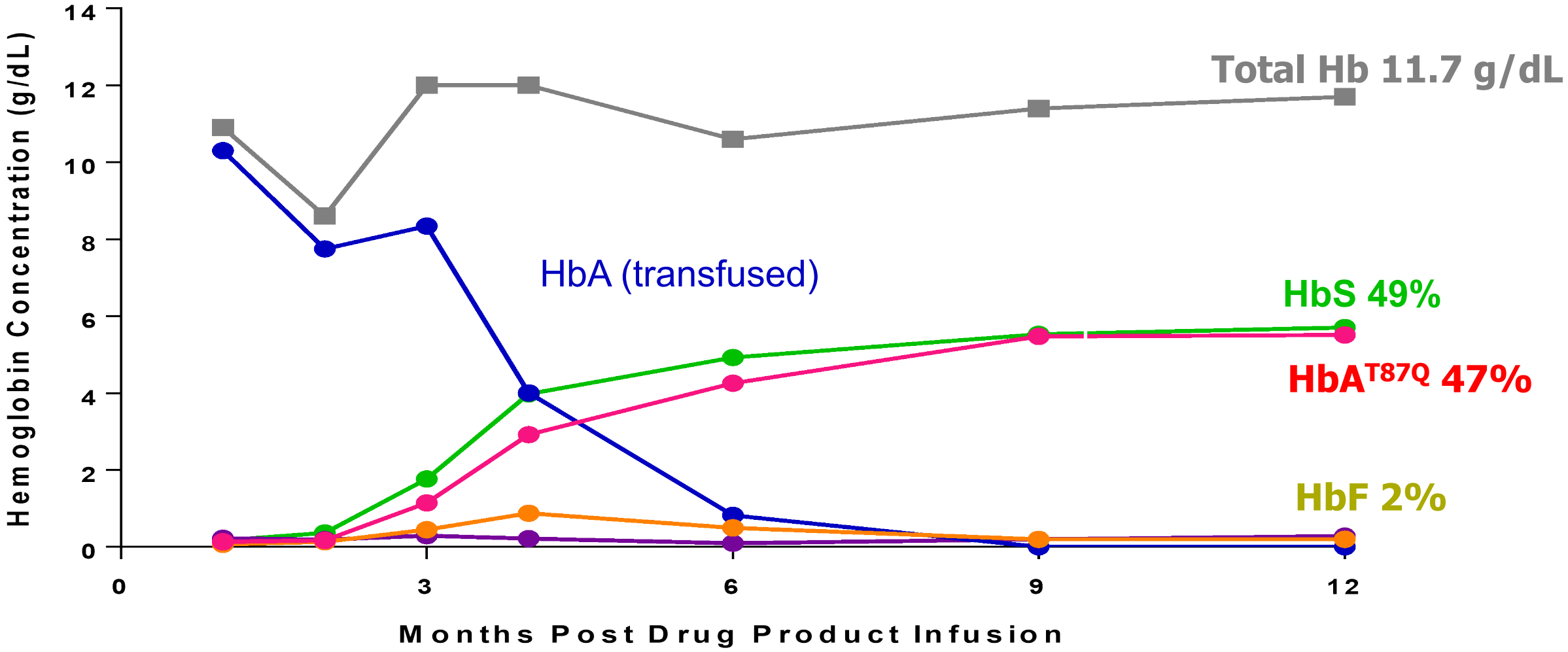
Genome editing and gene therapy clinical trials in SCD

Goal	Nuclease/target	Sponsor, collaborator	Clinical trial ID	Estimated participants
Elevate HbF	CTX001/BCL11A	Vertex Pharmaceuticals Incorporated, CRISPR Therapeutics	NCT03745287	45
Elevate HbF	Plerixafor/BCL11A	Bioverativ, a Sanofi company	NCT03653247	8
Elevate HbF	OTQ923 or HIX763/BCL11A	Novartis Pharmaceuticals	NCT04443907	30

as of March 2021

Jones RL and Debaun MR Blood 138:11 (2021)

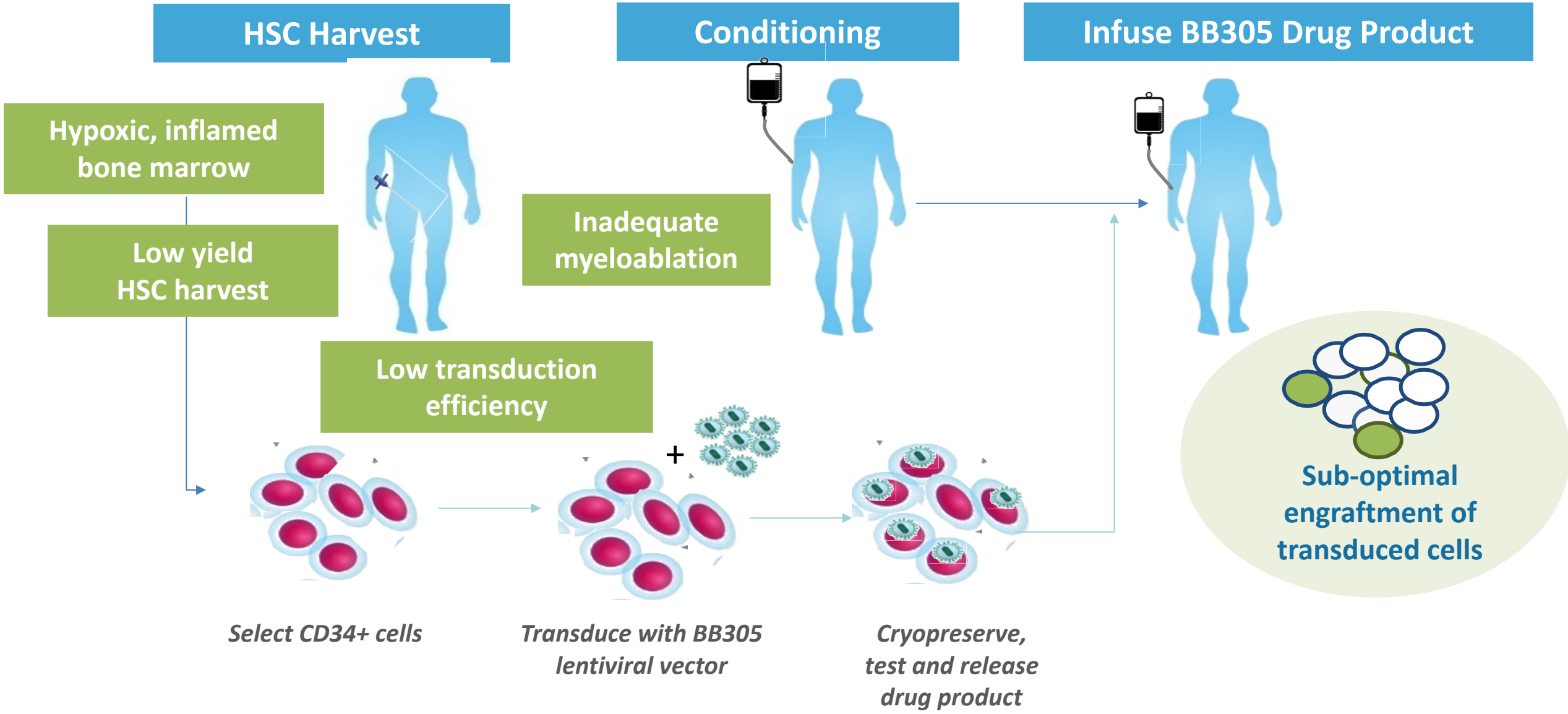
Gene Therapy for Severe SCD (2017)



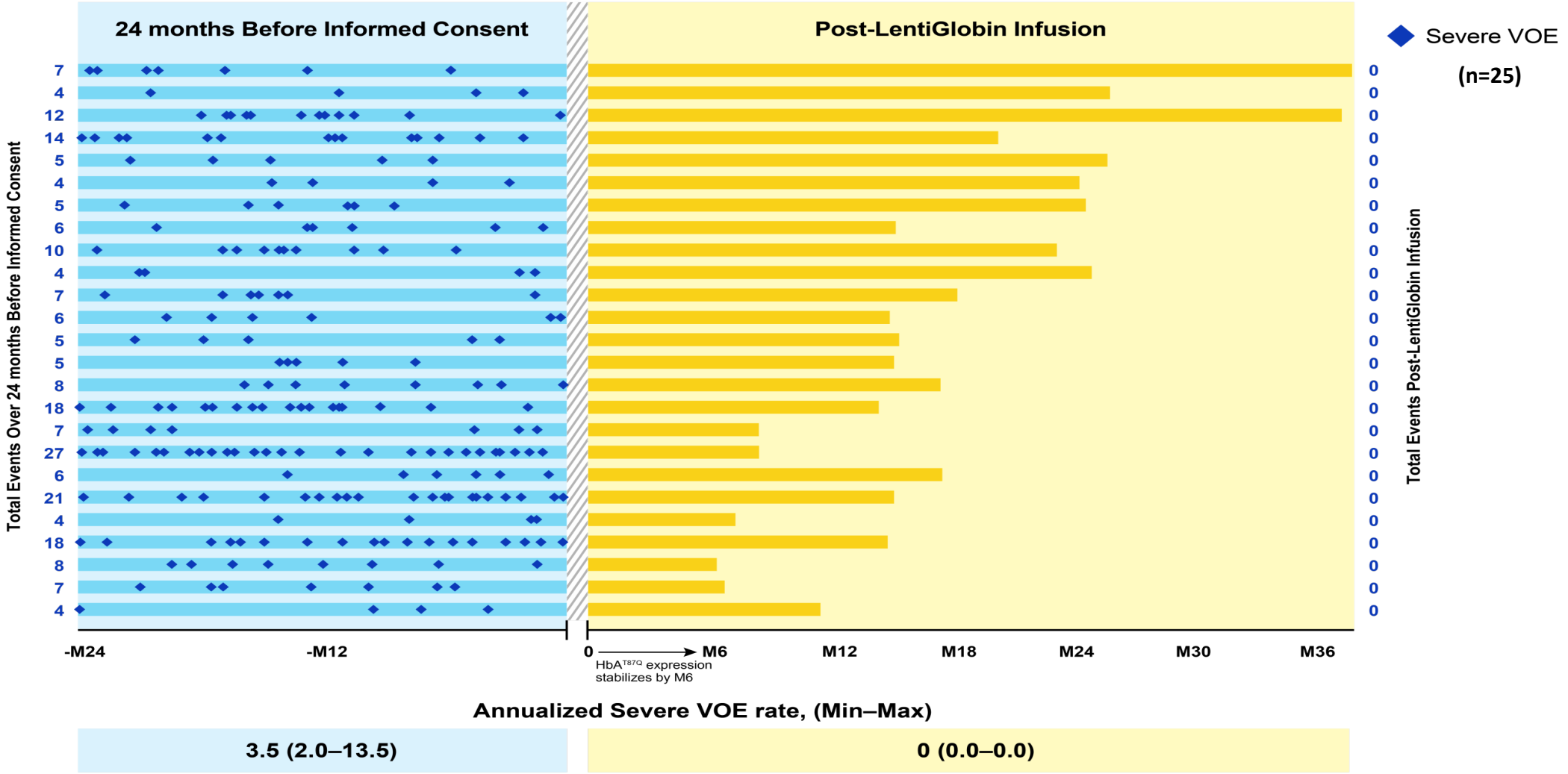
Level of therapeutic antisickling β-globin remained high after 15 months without recurrence of sickle pain and with correction of the biologic hallmarks of SCD

N Engl J Med 2017; 376:848-855

What we've learned – challenges in SCD gene therapy

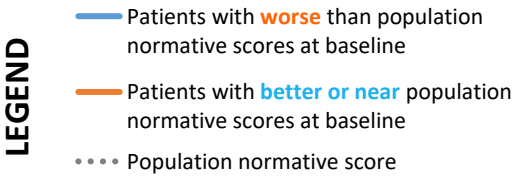


HGB-206 Group C: Complete resolution of severe VOEs ≥ 6 months post-LentiGlobin infusion

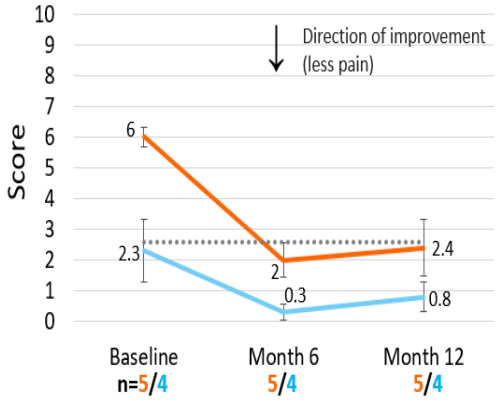


No VOEs occurred after stabilization of HbA^{T87Q} expression

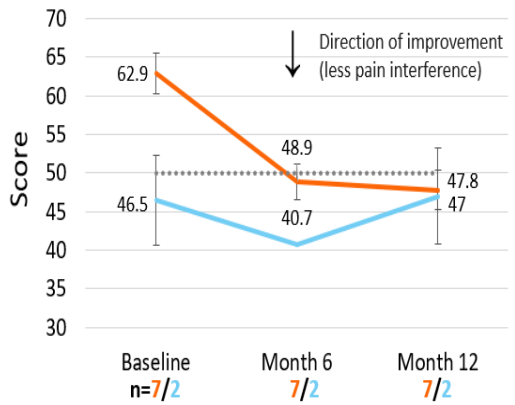
Improved QOL: PROMIS-57 results



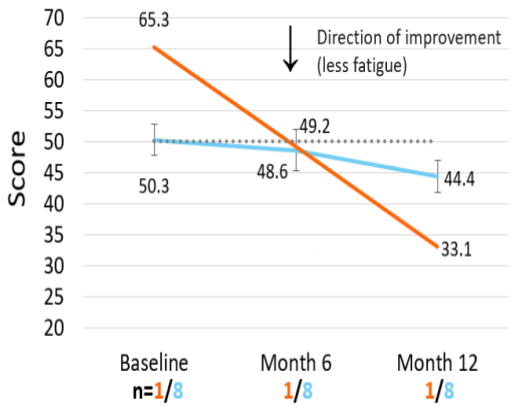
Pain Intensity NRS



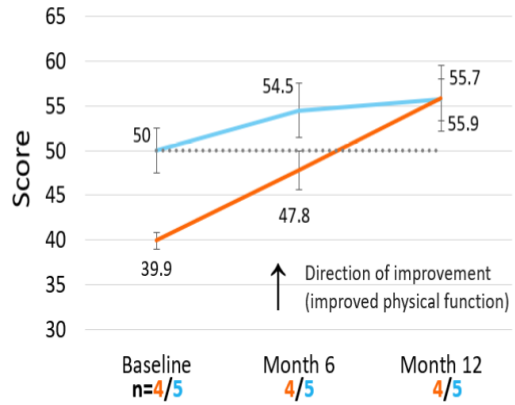
Pain Interference



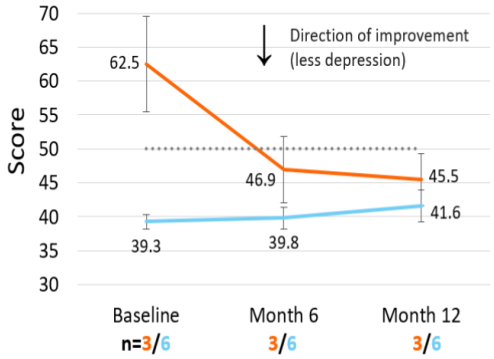
Fatigue



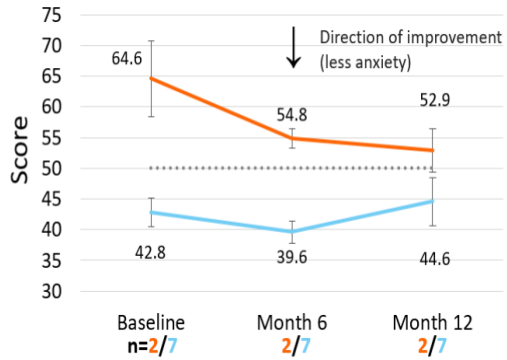
Physical Function



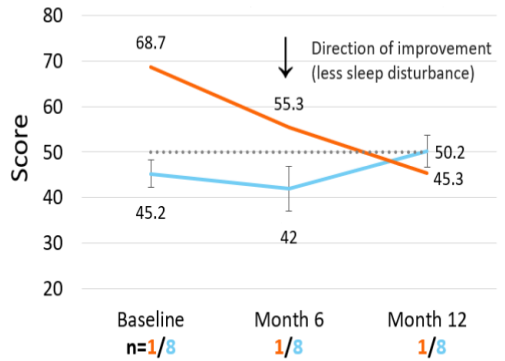
Depression



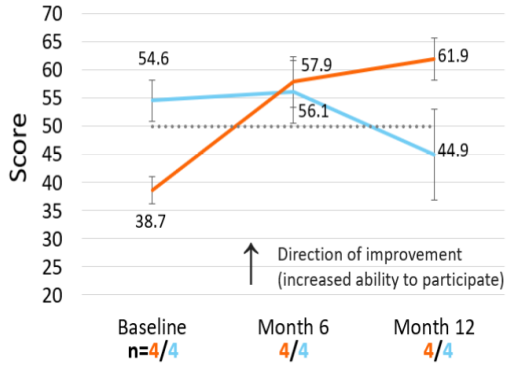
Anxiety



Sleep Disturbance

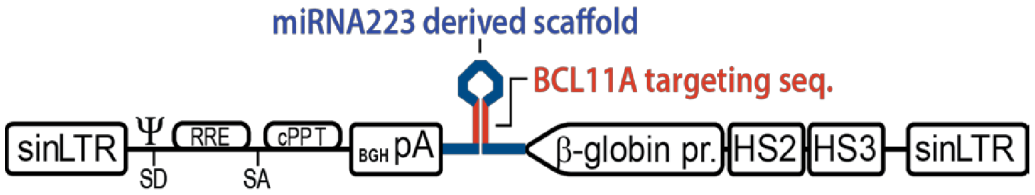


Ability to Participate in Social Roles/Activities

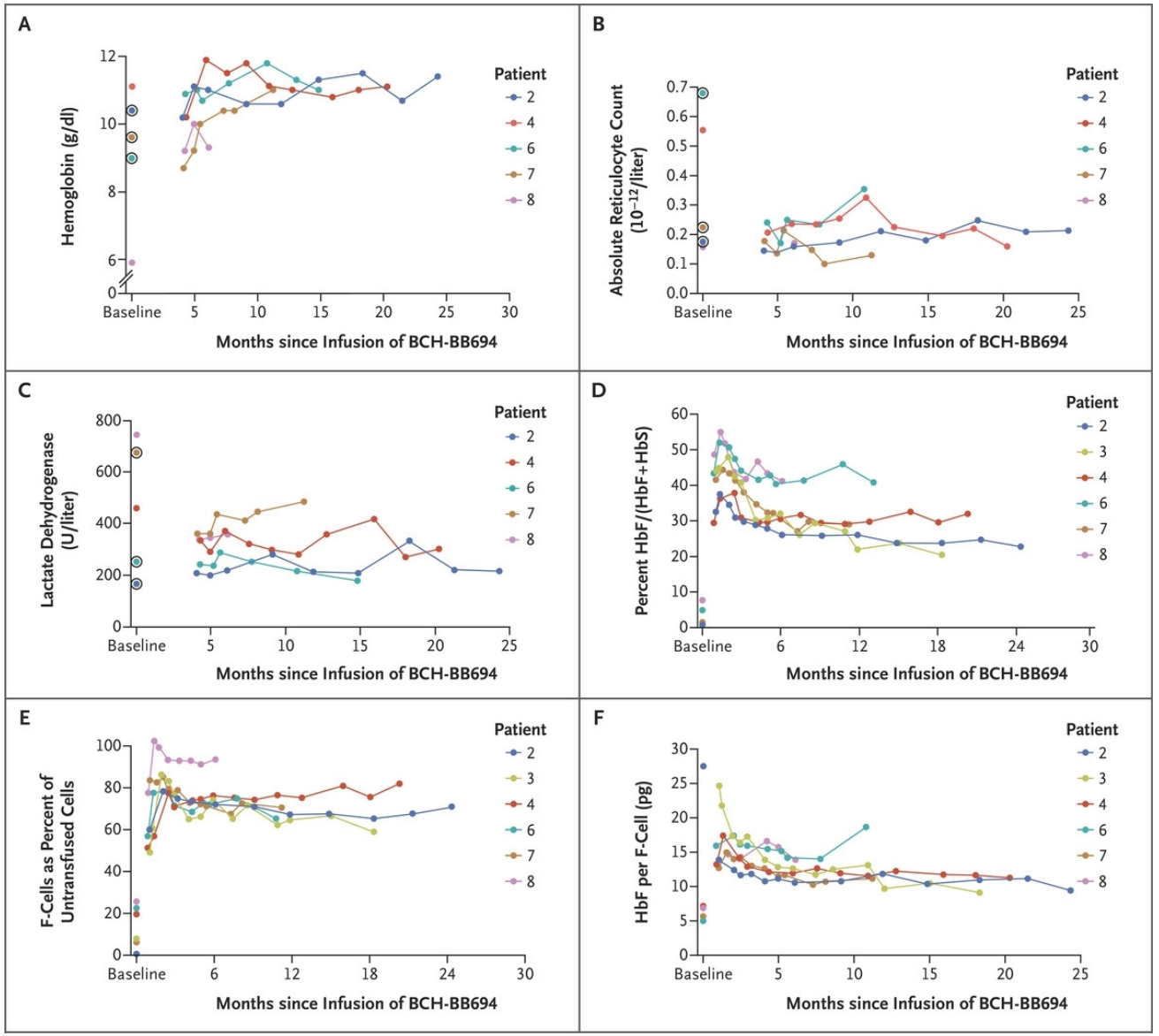


Data as of 20 August 2020

LVV shmiR targeting BCL11A: Fetal Hemoglobin Induction and Gene Marking after Gene Therapy

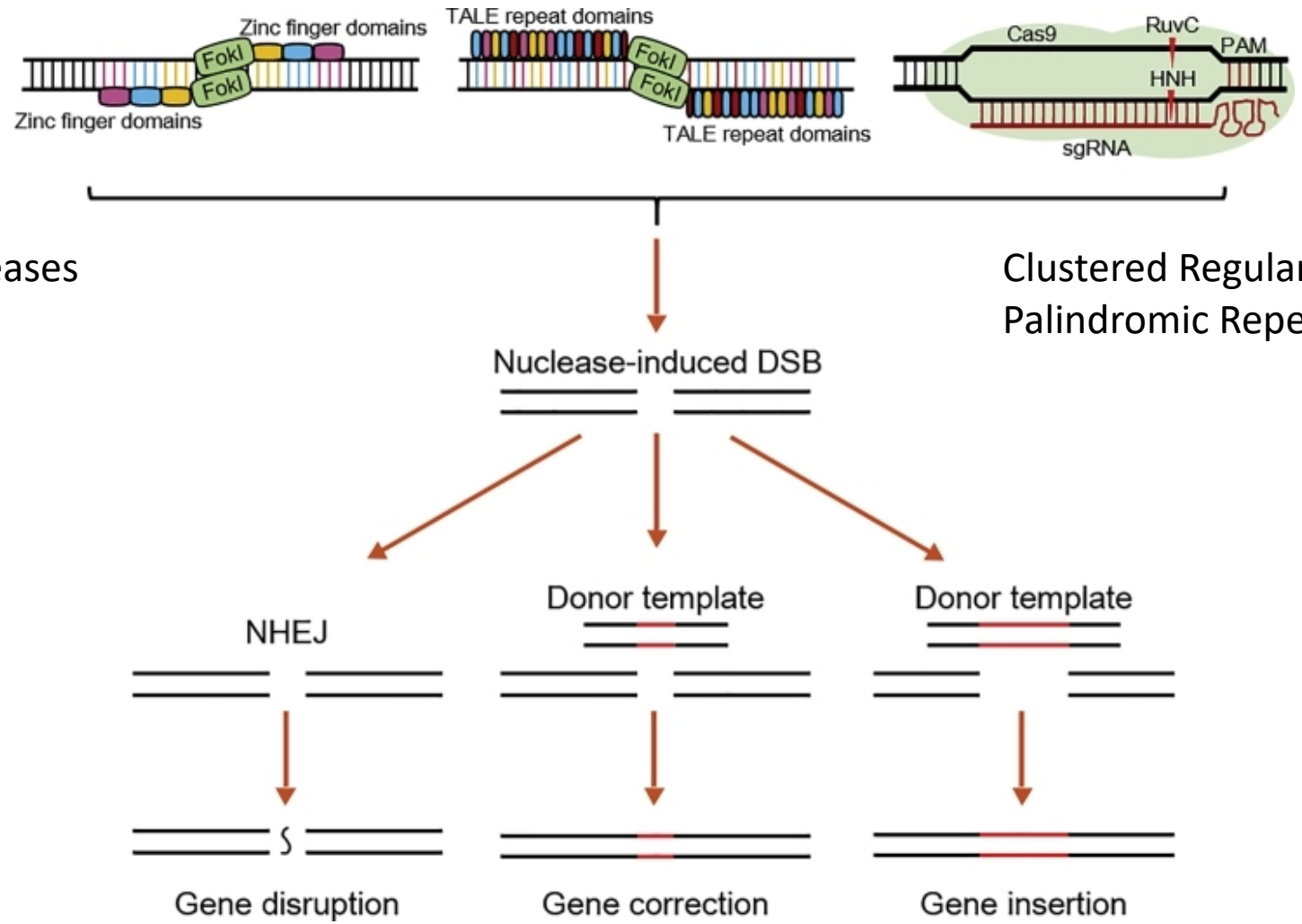


- 6 SCD patients
- Median follow-up 18 months
- All engrafted
- AE consistent with busulfan myeloablation
- Robust and stable HbF induction



EB Esrick et al. N Engl J Med 2020. DOI: 10.1056/NEJMoa2029392

Gene-Editing Approaches

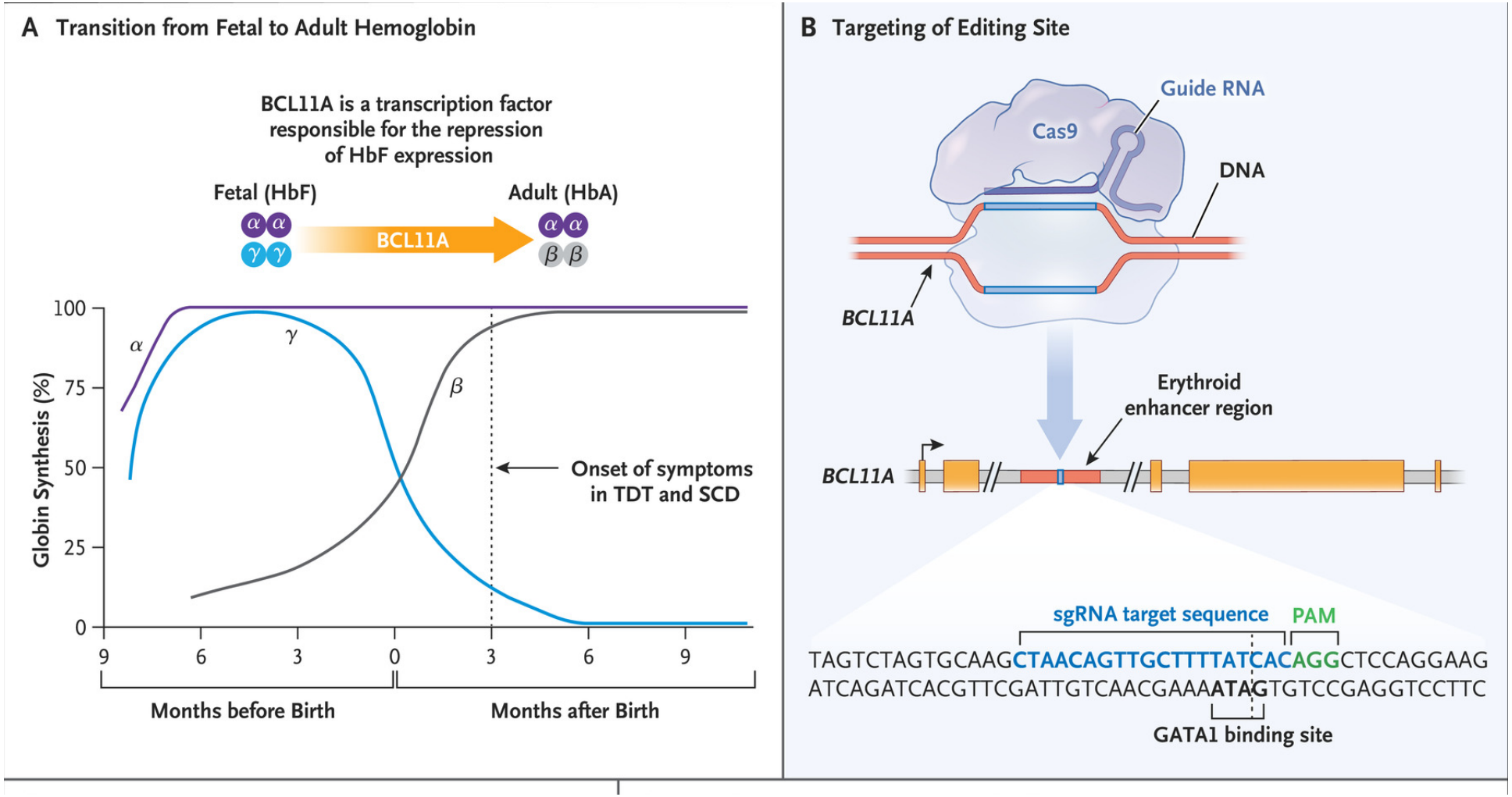


Zinc Finger Nucleases

Clustered Regularly Interspersed Palindromic Repeats (CRISPR)

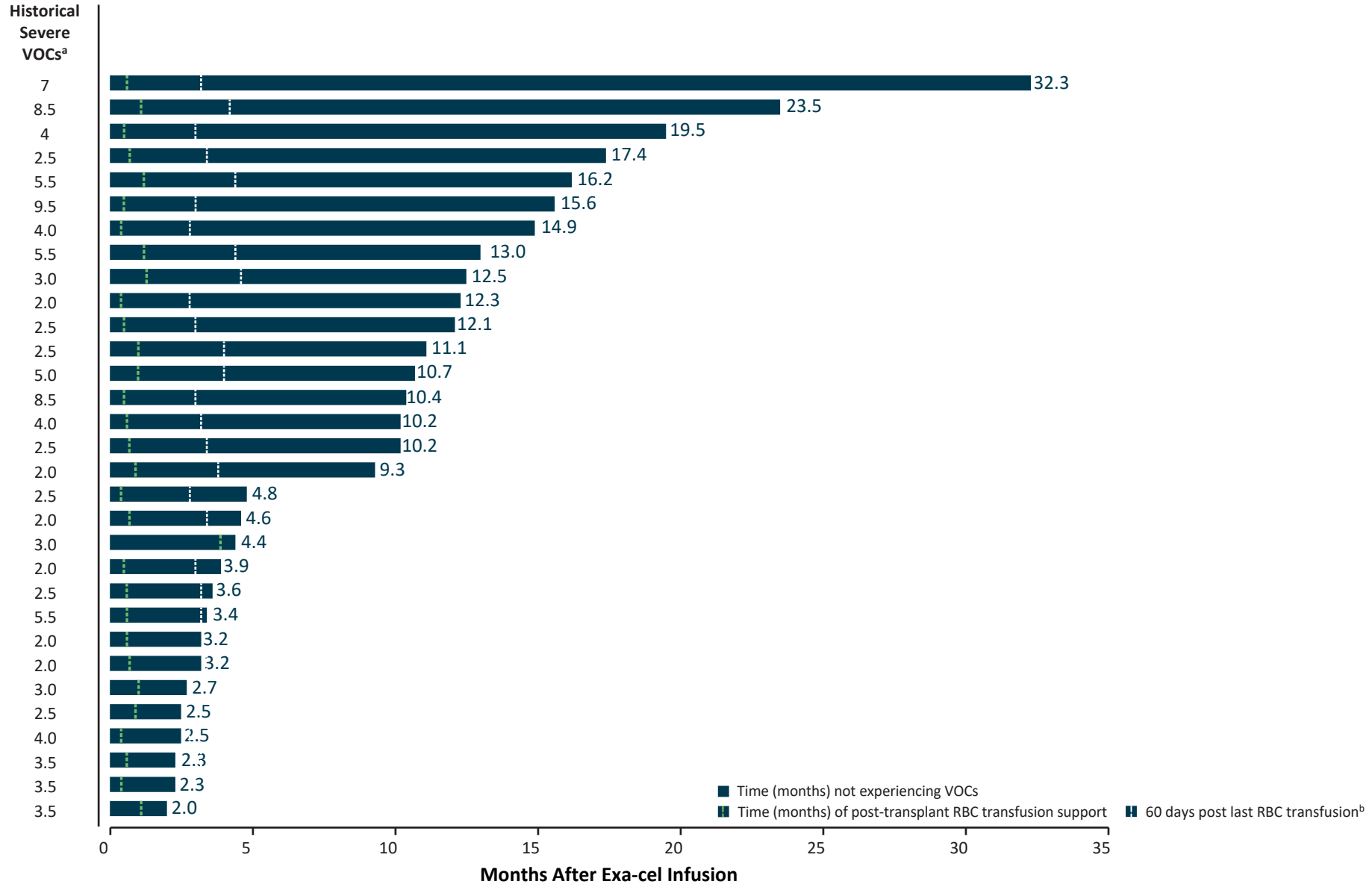
- Joung JK, et al. Nat Rev Mol Cell Biol. 2013;14:49-55; Ferrari G, et al. Nat Rev Genet. 2021;22:216-234.

CTX-001: CRISPR Cas9 targeting BCL11A gene



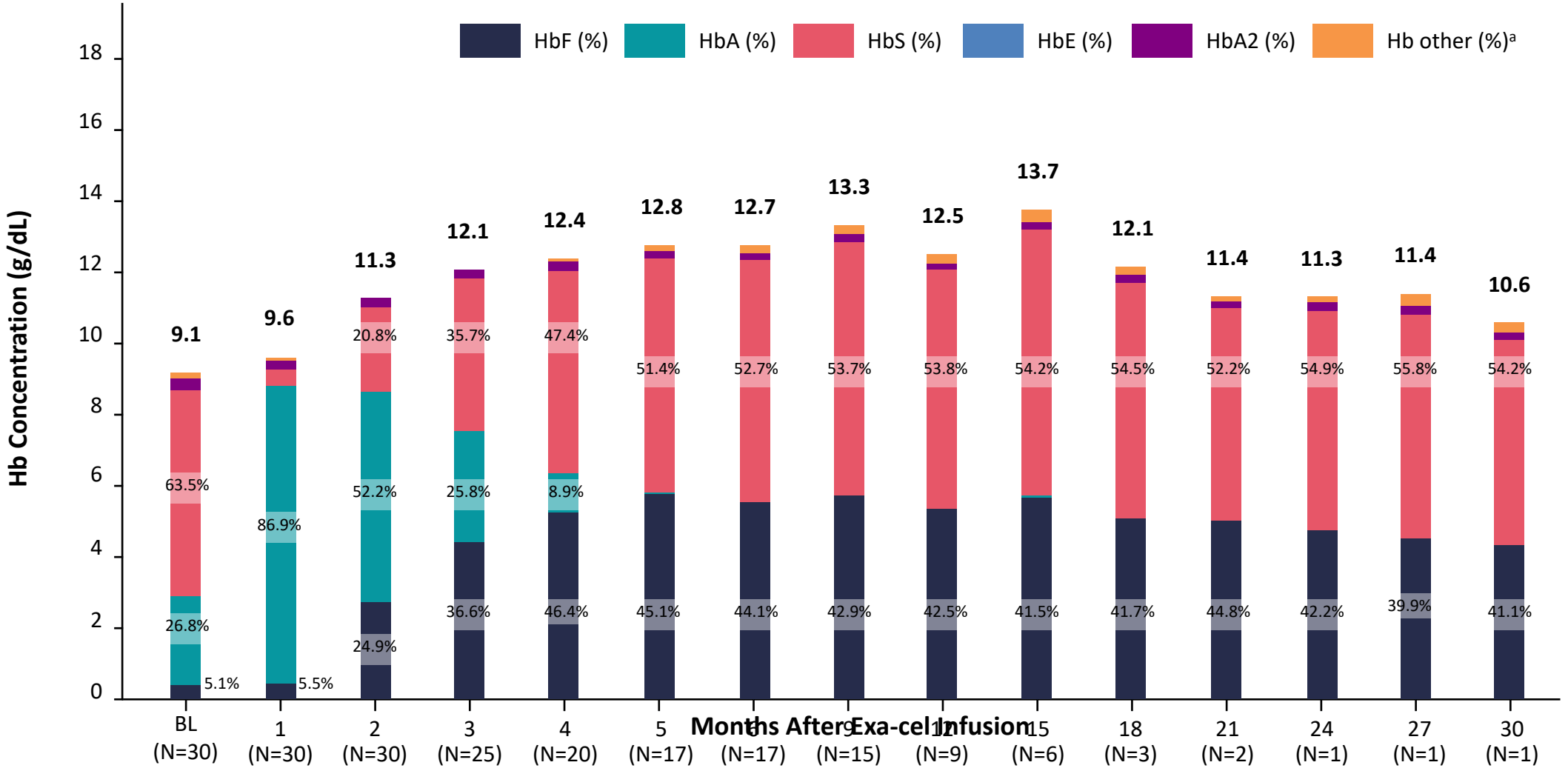
H Frangoul et al. N Engl J Med 2020. DOI: 10.1056/NEJMoa2031054

All Patients With SCD Treated With CTX-001 (Exa-cel) are VOC-Free



31 of 31 patients were VOC-free after exa-cel infusion (duration from 2.0 to 32.3 months)

Patients With SCD Had Clinically Meaningful Increases in HbF (>20%) That Occurred Early and Were Sustained Over Time

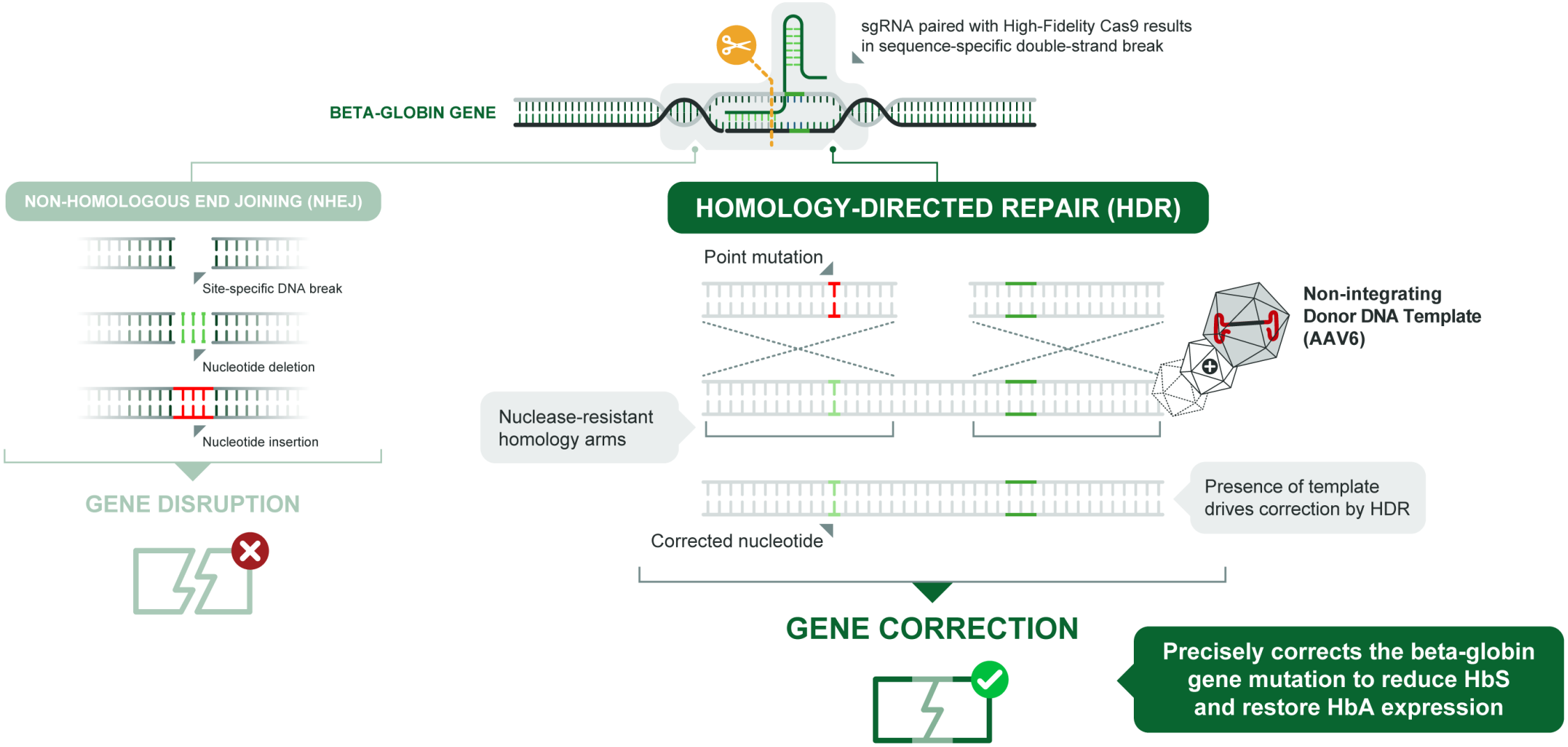


BL, baseline; Hb, hemoglobin; HbA, adult hemoglobin; HbA2, hemoglobin, alpha 2; HbE, hemoglobin E; HbF, fetal hemoglobin; HbS, sickle hemoglobin; SCD, sickle cell disease.

Bars show mean Hb (g/dL). Labels indicate mean proportion of HbS and HbF as a percentage of total Hb. Mean total Hb concentrations are shown directly above bars.

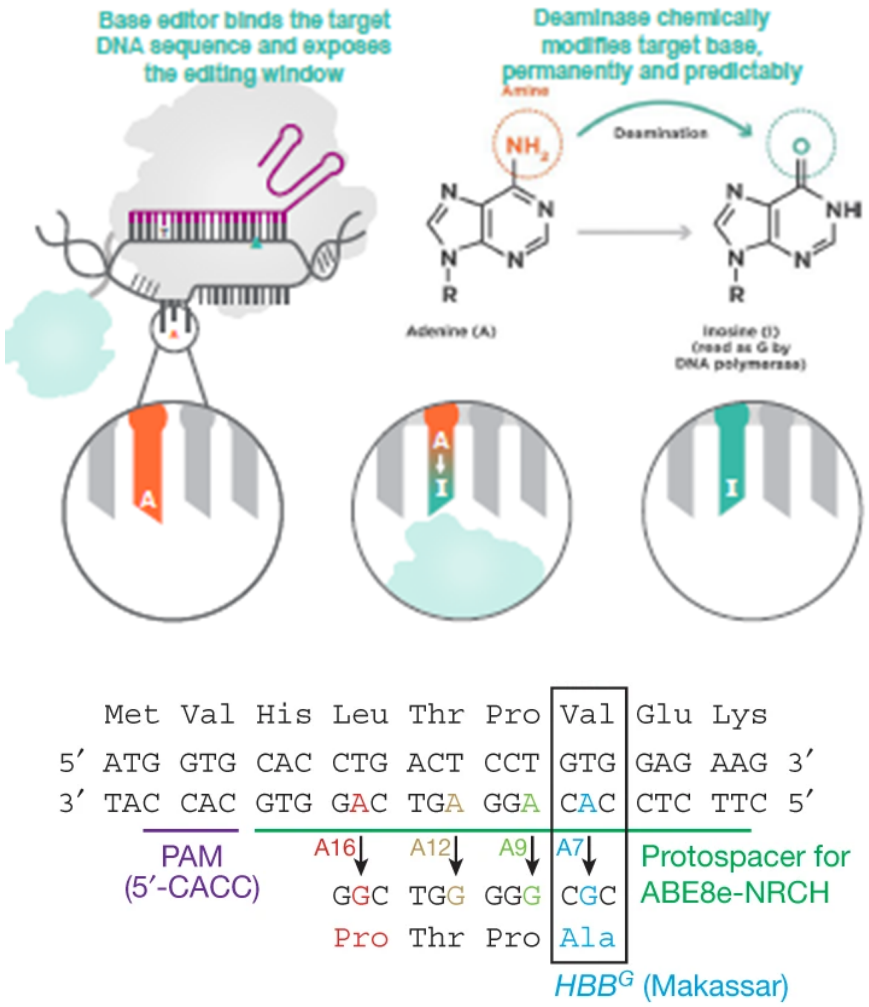
[a]Hb adducts and other variants.

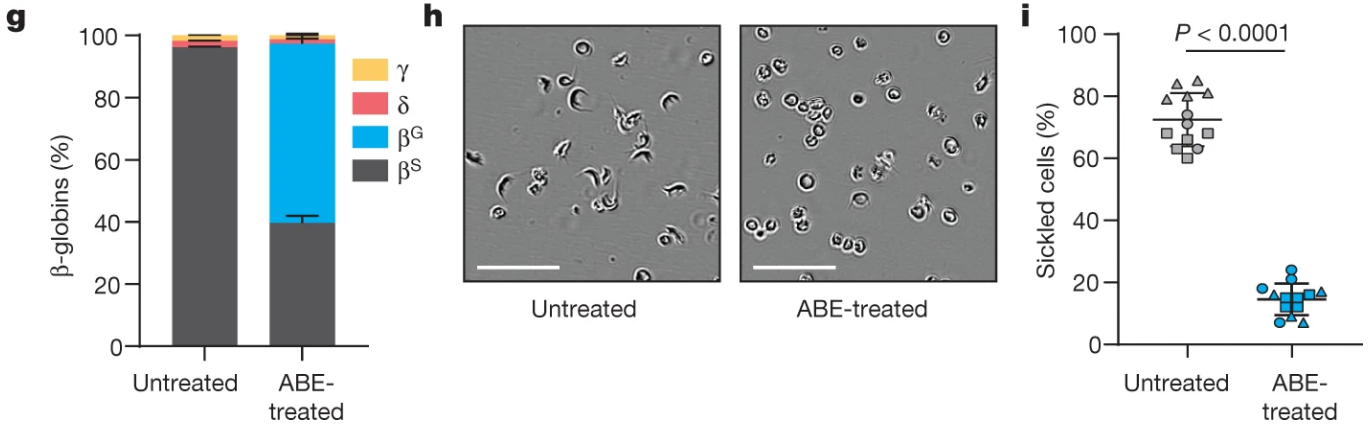
High efficiency HDR via CRISPR/HiFi Cas9 corrects the SCD mutation



AAV6, adeno-associated virus type 6; Cas9, CRISPR-associated protein 9; CRISPR, clustered regularly interspaced short palindromic repeats; DNA, deoxyribonucleic acid; HbA, adult hemoglobin; HbS, hemoglobin sickle cell; HDR, homology-directed repair; INDEL, insertion and/or deletion; RBC, red blood cell; SCD, sickle cell disease.

Adenine Base Editor: Hb S to Hb Makassar (V6A)





Direct conversion of one base pair to another at a target location, without double-stranded breaks

- Newby GA, et al. Nature. 2021;595:295-302.

AML Cases on bluebird bio studies of LentiGlobin for Sickle Cell Disease (bb1111)

Case 1: Patient in Group A diagnosed with AML in 2018

- At ~36 months post LentiGlobin GT, a patient was diagnosed with MDS and passed away due to relapsed AML in 2020
- BM biopsy showed 15% myeloblasts and dysplasia
- Cytogenetics showed monosomy 7, abnormal chromosome 19p in 8 of 20 metaphases, mutations in RUNX1 and PTPN11 detected
- No vector insertion detected in AML blasts
- Based on available results, it is unlikely AML was related to the BB305 lentiviral vector

Case 2: Patient in Group A diagnosed with AML (treated >5 years ago)

- Based on available results, it is unlikely AML was related to the BB305 lentiviral vector
- Lab analyses showed significant chromosomal abnormalities and mutations in genes typically associated with the development of AML, specifically, Monosomy 7 and mutations in RUNX1 and PTPN11
- Vector insertion in the AML cells took place in the VAMP4 gene, which has no known role in the development of AML or with any cellular process related to cancer
- Insertion into the VAMP4 gene had no impact on gene expression or gene regulation

Working hypotheses:

- Use of alkylating agents such as busulfan carry some risk of therapy related myeloid neoplasm
- SCD is associated with an increased relative risk but very low absolute risk of therapy related myeloid neoplasms
- Switch from homeostatic to regenerative hematopoiesis drives clonal expansion and leukemic transformation of pre-existing clonal hematopoiesis of indeterminate potential (CHIP) in SCD

Hsieh MM et al Blood Adv 4:9 (20200; Goyal S et al, NEJM 386:2 (2022); Jones RL and Debaun MR Blood 138:11 (2021)

SCD and Risk of Cancer?

- In 2017, increased risk of leukemia in SCD reported from the California Cancer Registry *(Brunson et al Blood 130(13): 1597-99)*
  - –72% increased risk of hematologic malignancies in SCD compared to CA state population
  - –Female and AYA SCD patients had 3 fold increased risk for leukemia
  - –Patients with severe SCD (>3 visits per year) had a 4 fold increased risk

	Matched 0170 TBI/Campath	Matched 0077 TBI/Campath Pentostatin/Cy	Matched (Chicago,Riyadh) TBI/Campath	Haplo 0225 TBI/Campath -/+ Cy	Haplo 0069 TBI/Campath/Cy Pentostatin/Cy	Eapen CIBMTR Many types	Gene Therapy with BB305 LVV Busulfan	
							LentiGlobin for SCD‡	Beti-cel§ for TDT
N in study	58	26	64	21	19	910	**49** Median follow up (min –max) months **23.1 (0.8–74.9)**	**63** Median follow up (min –max) months **29.54 (0.9–76.4)**
MDS, AML	2 (3.5%)	1 (3.8%)	1 (1.6%)	3 (14%)*	0	6† (1.0%)	2 (4.3%)	0
	1 graft failure (MDS)	1 low engraft (AML)	1 graft failure (MDS)	2 graft failure MDS, AML		Details not available	2 in Group A[1,2]	

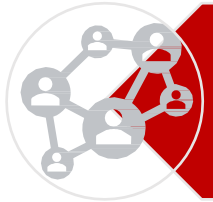
1. Hsieh MM et al. *Blood Adv*. 2020; 4: 2058–2063; 2. Kwiatkowski J et al. ASPHO., 2021. Virtual. 3. Eapen M et al. *Lancet Hematol*. 2019: 6:e585-e596; 4, Ghannam JY et al *Blood*. 2020:135:1185-1188

Sickle Cell Disease Coalition (SCDC)

- Established in 2016 to unite diverse stakeholders dedicated to conquering SCD

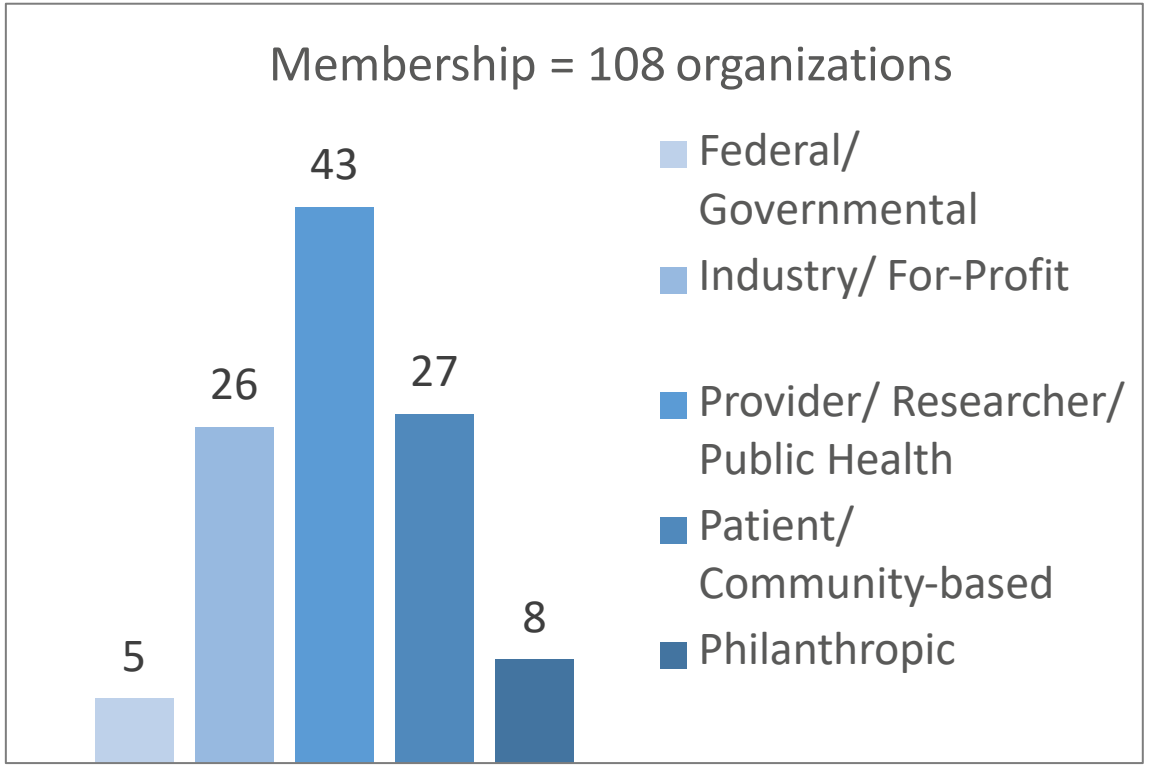
Coalition Goals

Amplify voice of global SCD stakeholder community

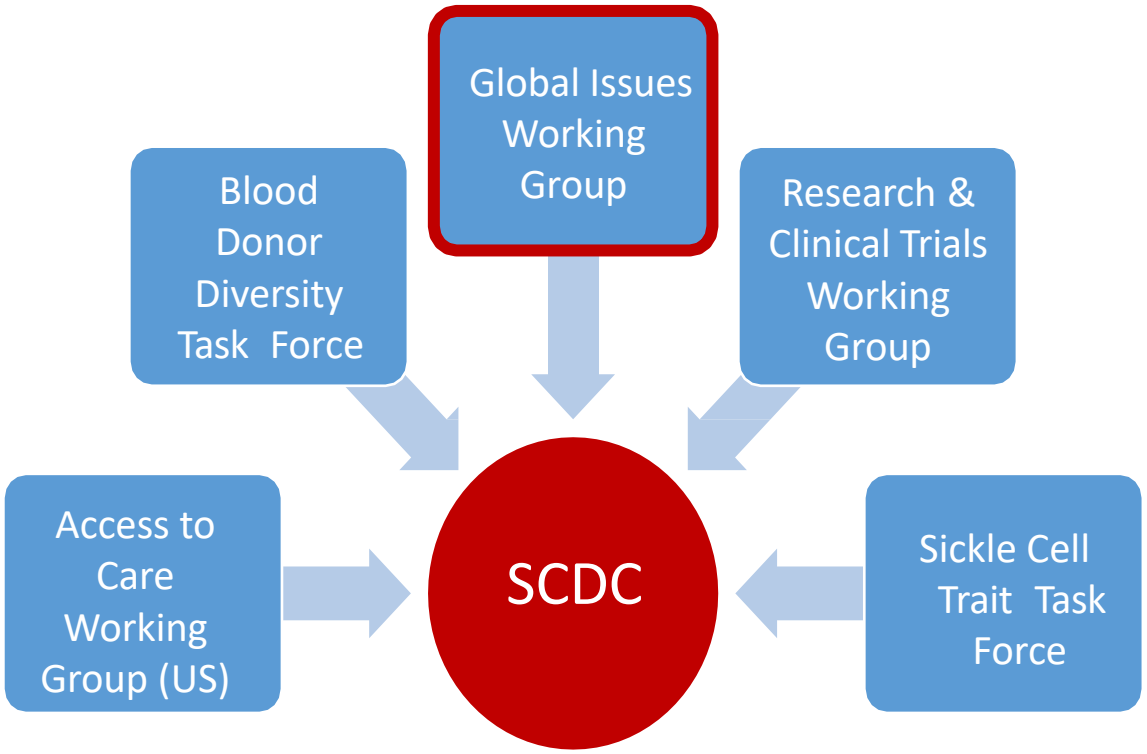


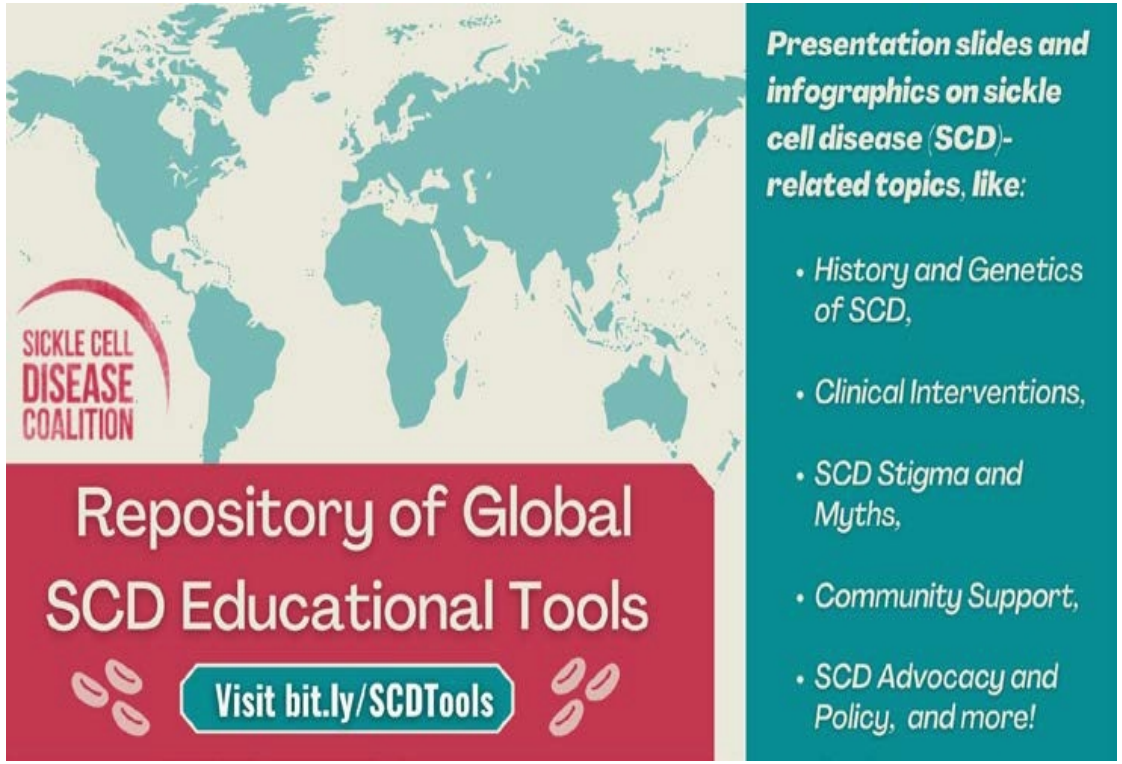
Coordinate efforts and foster multi-stakeholder partnerships

Improve quality of life and outcomes for individuals with SCD

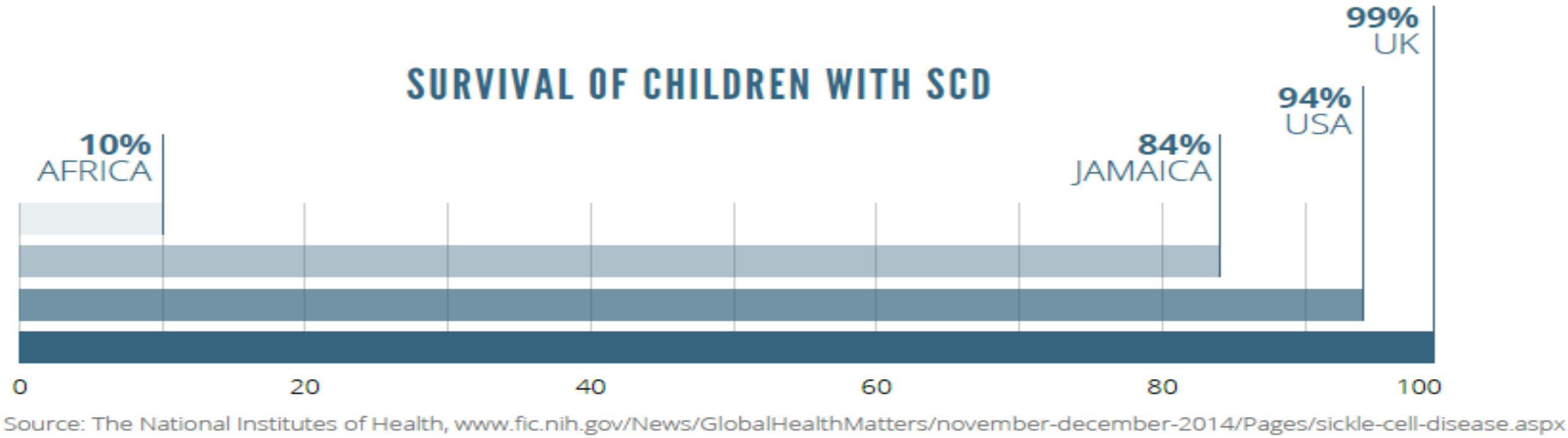


SCDC Global Activities





The promise of newborn screening programs in management of SCD complications



Source: The National Institutes of Health, www.fic.nih.gov/News/GlobalHealthMatters/november-december-2014/Pages/sickle-cell-disease.aspx

Some middle-income countries are making advancements in both early diagnosis and management of SCD.

American Society *of* Hematology
Helping hematologists conquer blood diseases worldwide

consa
Consortium on Newborn Screening in Africa for SCD

Consortium on Newborn Screening in Africa (CONSA)

Goal:

- Demonstrate the effectiveness of **laboratory-based** newborn screening and early intervention services in seven African countries.

Activities:

- Screen 10,000-16,000 babies per year in each country.
- Enroll SCD positive babies in clinical protocol (up to five years of age).
- Capture screening and clinical data in consortium registry for further research.
- Work with national and international partners for the sustainability of programs.

Current CONSA Programming

- Screenings are underway at all seven networks.
- Current Data:
  - Over 40,000 babies have been screened
  - Roughly 20.3% with SCT*
  - Roughly 1.8% with SCD*
- Ongoing data collection and research planning.
- Working with stakeholders to ensure sustainability of programs.
  - Improving drug access.
  - Providing family education and counseling.
  - Working with governments to institutionalize SCD screening and care.
  - Advocating at local, national and global levels for SCD screening and care.

**Preliminary Data – Subject to Change*

Opportunities and Gaps: *What is still needed?*

- New therapeutics that are effective and accessible
- Better understanding of the science
- Continued population-based longitudinal data collection
- Advocate for interoperability of SCD data resources
- Education and awareness for the general population, patients, families, and medical professionals
- Better access to high-quality health care from knowledgeable providers, i.e. health equity

Summary

- We have unprecedented opportunities to advance research and provide high quality medical care for patients with SCD
- Hydroxyurea is an effective agent to control many complications but it is currently underutilized
- Approval of new disease-modifying therapies expands options for patients
- Newborn screening in highly prevalent regions will identify many more individuals and insure proper treatment to save lives
- Early results with gene therapy and gene-editing are promising
- Knowledge gaps in SCD have created opportunities for research and potential improvements in care

Forever Grateful, KOF