Sickle cell and adult stem cell transplant. Finally, a cure…

Dr Steven Okoli
Imperial College NHS Trust, London

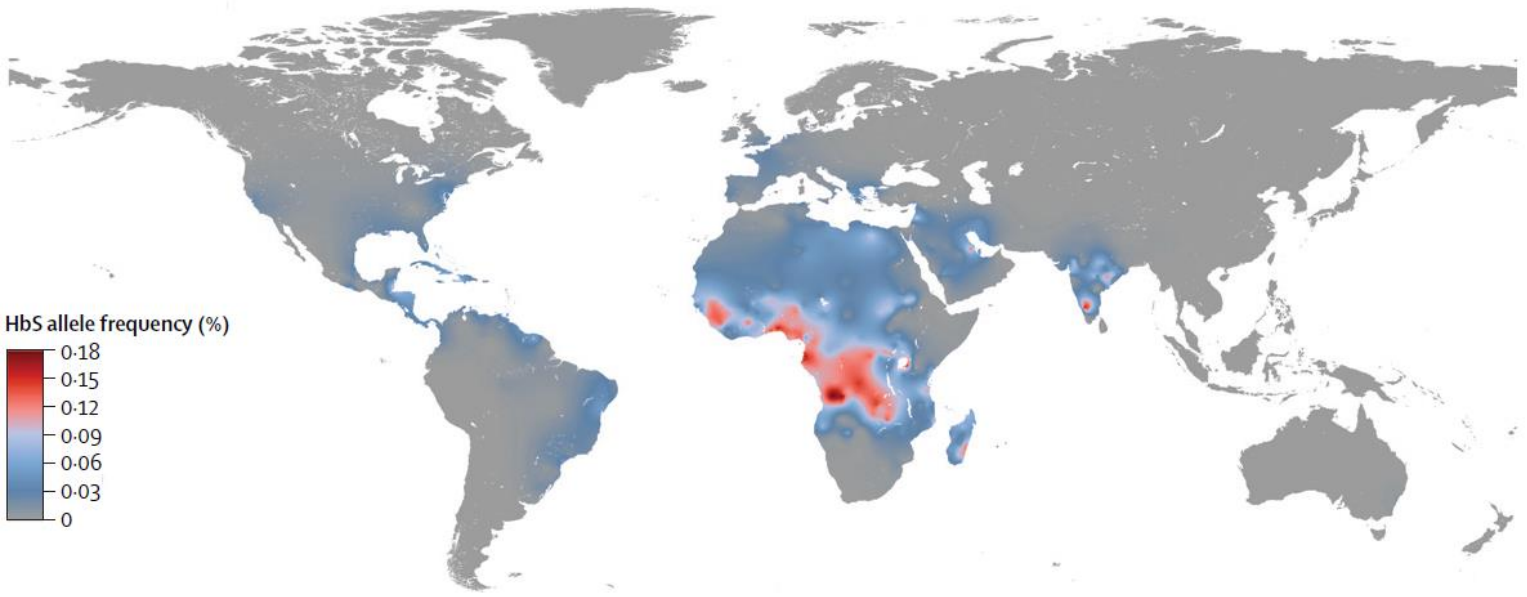
24th September 2024

Objectives

- Pathology of sickle cell disease
- Current treatment landscape
- Cellular therapies
- Stem cell transplant and challenges
- Stem cell transplant options
- Clinical trial data in cellular therapies

Epidemiology

- Most common and most rapidly growing monogenetic disorder worldwide[1]
- More than 17,000 cases in UK[2]
  - 70% in London
- UK children surviving to adulthood (~99%)[3]

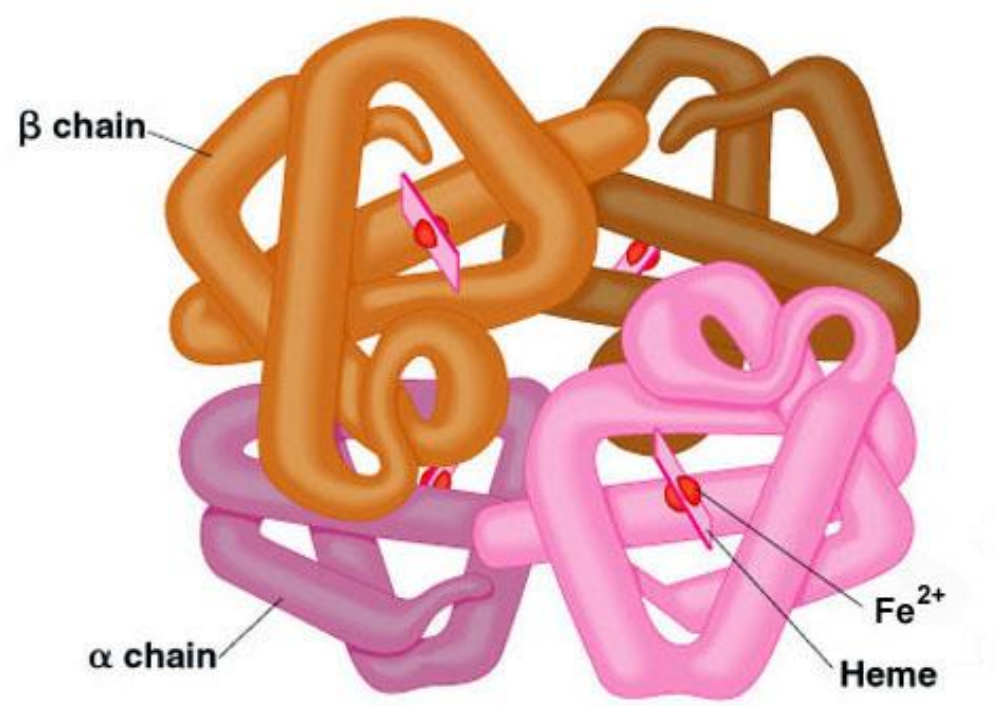


HbS, sickle haemoglobin.

1. Piel FB, et al. *Lance*t 2013;381:142–151; 2. NHS England data, June 2023; 3. Telfer P, et al. *Haematologica* 2007; 92:905–912.

Pathology

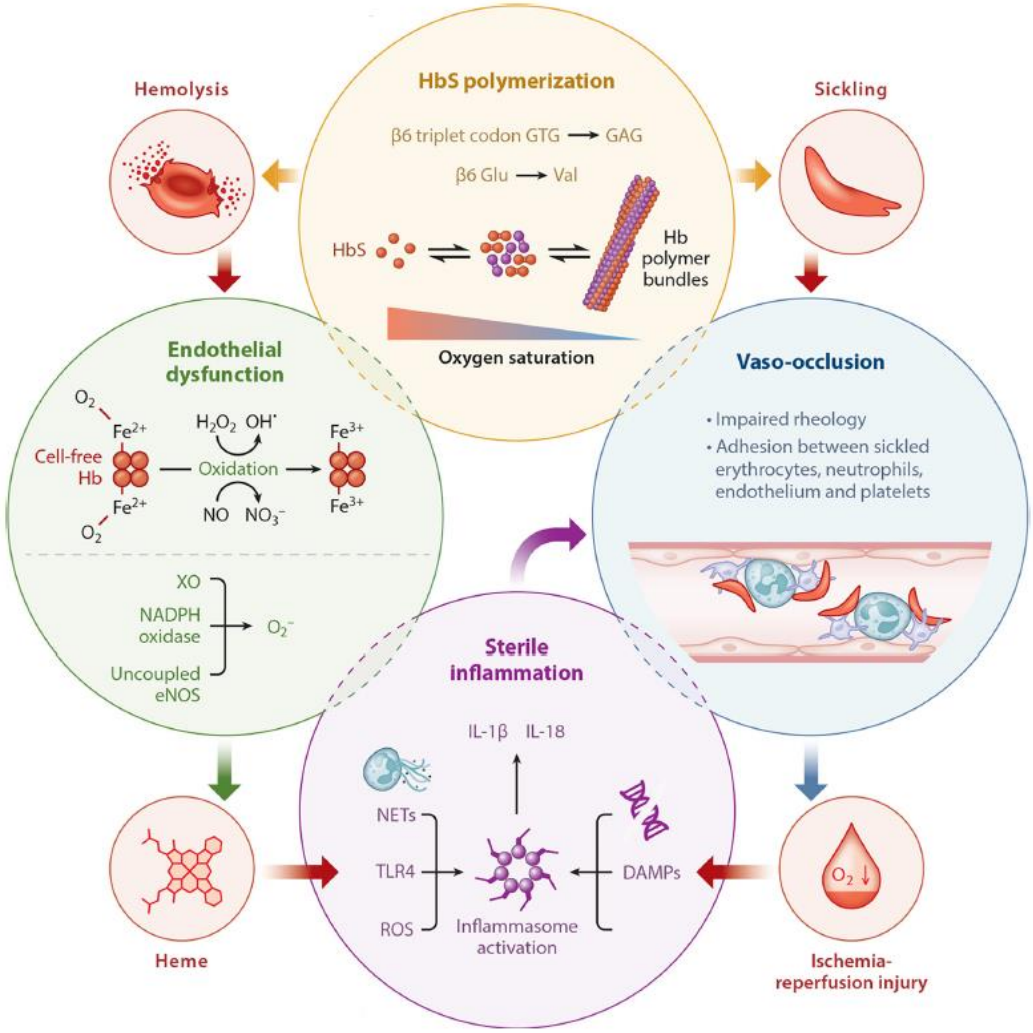
Adult Haemoglobin



2 α and 2 β globin chains each with a central haem

- SNP at **Chr 11p** with A→T in the β-globin chain of haemoglobin
- Replace hydrophilic glutamic acid with hydrophobic valine at sixth position

SCD pathology[1]



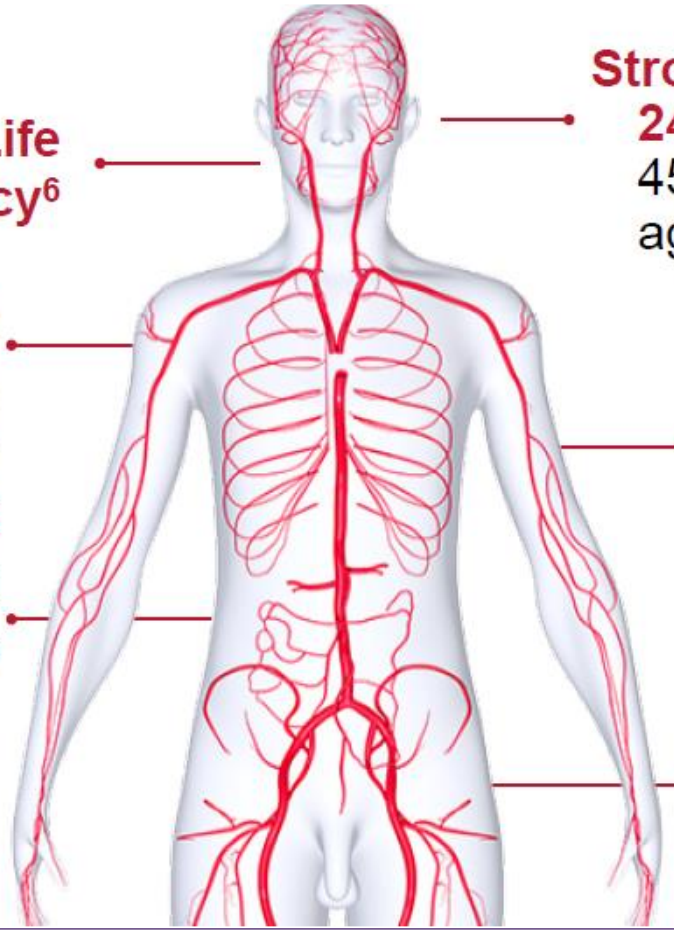
DAMP, damage-associated molecular pattern; eNOS, endothelial nitric oxide synthase; Glu, glutamic acid; Hb, haemoglobin; HbS, sickle haemoglobin; IL, interleukin; NADPH, nicotinamide adenine dinucleotide phosphate; NET, neutrophil extracellular traps; ROS, reactive oxygen species; SCD, sickle cell disease; TLR, Toll-like receptor; Val, valine.

1. Sundd P, et al. *Annu Rev Pathol* 2019;14:263–292.

Complications

Pain

Impact of sickle cell disease



Shortened Life Expectancy[6]

Stroke[1]
24% of patients experience a stroke by age 45; **11%** of patients experience a stroke by age 20

Acute Chest Syndrome[4]
occurs in **42%** of SCD adults (a leading cause of death)

Pain[5]
SCD patients experience pain **54%** of days

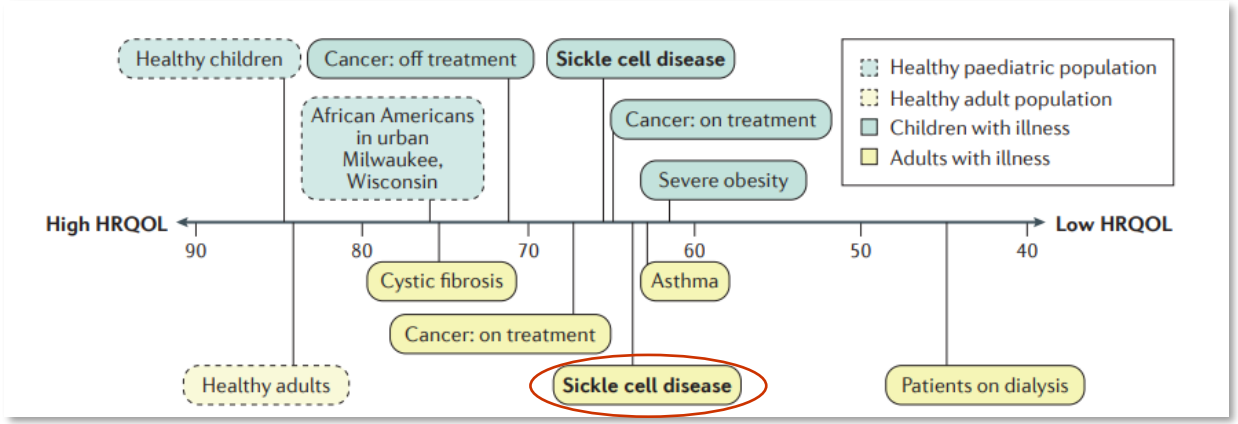
Kidney Failure[3]
Life expectancy of 1 year with dialysis

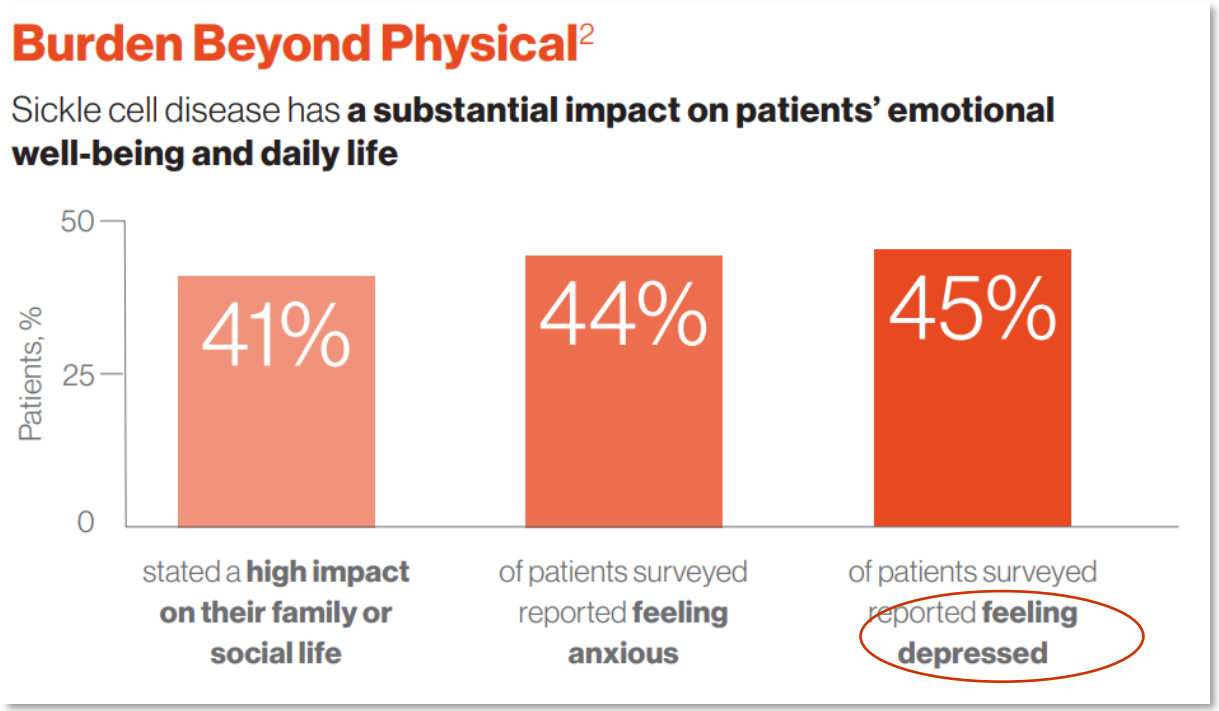
Priapism[2]
Occurs in **35%** of male patients and can result in erectile dysfunction or penile necrosis

Figure provided by speaker. SCD, sickle cell disease.

1. Verduzco LA, et al. *Blood.* 2009;114:5117–5125; 2. Adeyoju AB, et al. *BJU Int.* 2002;90:898–902; 3. McClellan AC, et al. *Br J Haematol*. 2012;159:360–367; 4. Vichinsky EP, et al. *N Engl J Med.* 2000;342:1855–1865; 5. Ballas SK, et al. *Blood.* 2012;120:3647–3656; 6. Elmariah H, et al. *Am J Hematol.* 2014;89:530–535.

Impact of SCD on QoL[1,2]





HRQOL, health-related quality of life; QoL, quality of life; SCD, sickle cell disease.

1. Kato GJ, et al. *Nature* 2018;4:1–22; 2. Osunkwo I, et al. Poster presented at: The American Society of Hematology Annual Meeting; December 7–10, 2019.

Patient case study

34-year-old male

- Sickle cell disease (HbSS)
- Frequent painful crises in childhood
- Recurrent acute chest syndromes

Commenced on hydroxycarbamide (2009)

- Further ACS requiring ITU admission
- Discontinued (2011)

Red cell exchange programme commenced

Hepatic iron overload

- Good compliance with oral chelation therapy

Patient case study continued

- 6-weekly red cell exchange programme (2016)
  - Pneumonia and acute chest syndrome (2018)
  - Urgent red cell exchange and ITU admission for NIV
- Bilateral femoral head AVN (2017)
  - Core decompression
- New AVN left humoral head (2022)
- Echocardiogram (2024)
  - dilated cardiac chambers
  - Mild RWMA with EF 50%
  - chronic pulmonary hypertension

NIV, non-invasive ventilation; AVN, avascular necrosis; RWMA, regional wall motion abnormalities; EF, ejection fraction.

SCD survival over time[1]

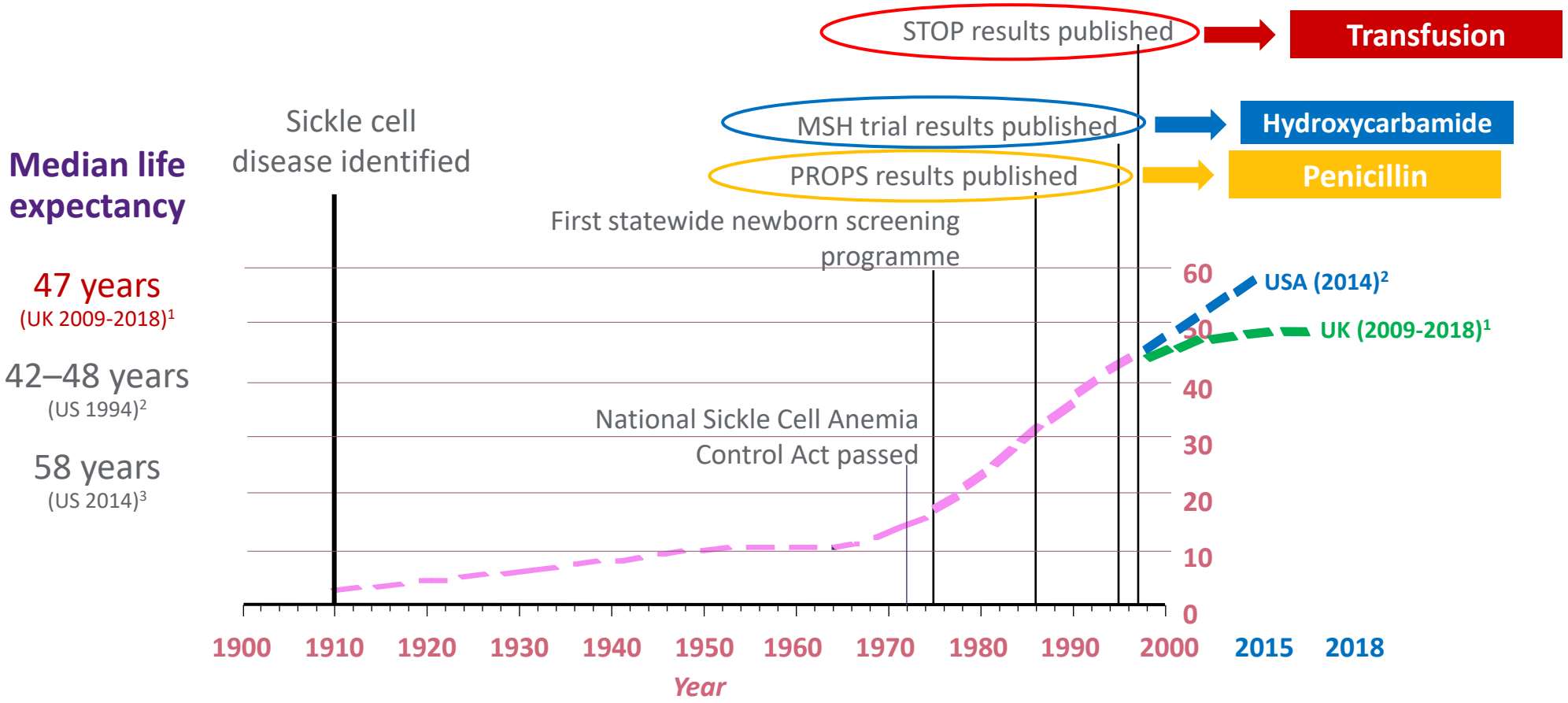
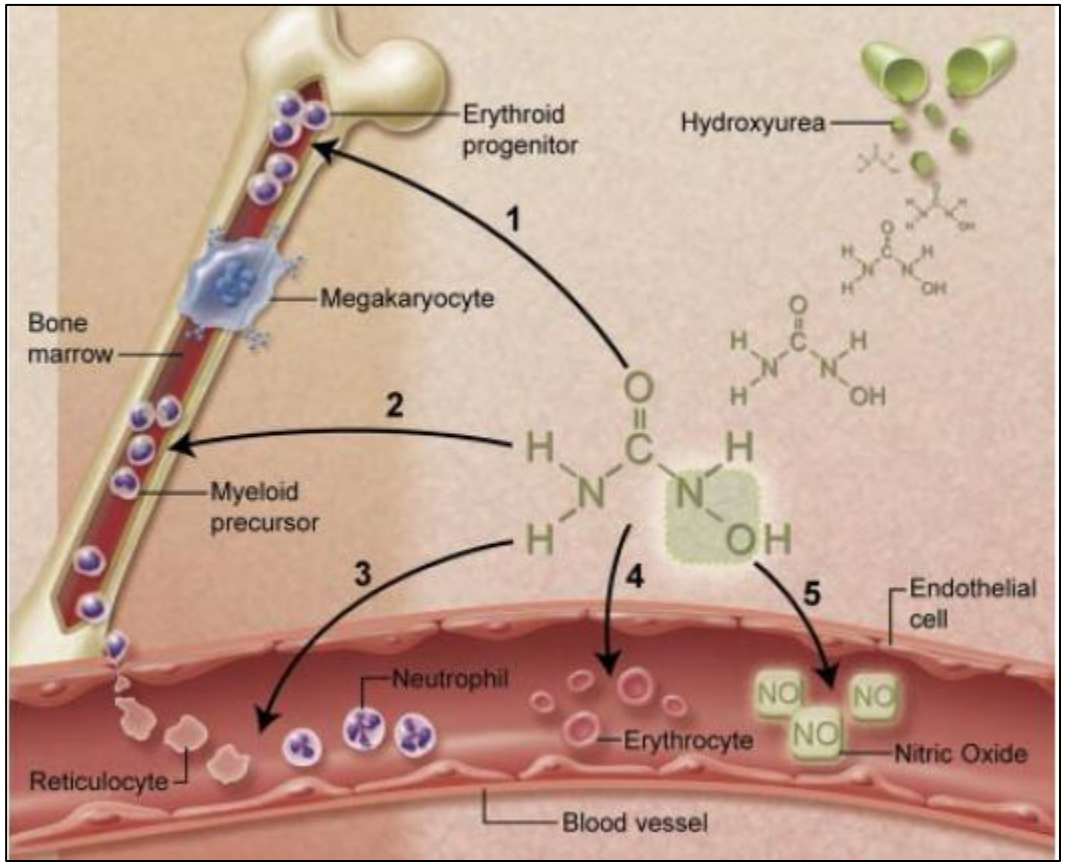


Figure provided by speaker. HES, hospital episode statistics;MSH, Multicenter Study of Hydroxyurea; PROPS, Penicillin Prophylaxis in Sickle Cell Disease; STOP, Stroke Prevention Study; SCD, sickle cell disease. 1. Piel FB, et al. *Blood Cells Mol Dis.* 2021;89:2–7; 2. Platt OS, et al. N Engl J Med 1994;330:1639-1644; 3. Elmariah H, et al. *Am J Hematol* 2014;89:530–535.

Current treatments

Hydroxycarbamide in SCD: Multiple modes of action[1–3]

- Increases HbF production
- Improved red cell hydration
- Reduced neutrophil count
- Modifies endothelial cell interactions
- Acts as a nitric oxide donor



HbF, foetal haemoglobin; SCD, sickle cell disease.

1. Ware Re. *Blood* 2010;115:5300–5311; 2. Xromi SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/xromi-epar-product-information_en.pdf. Accessed November 2023; 3. Siklos SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/siklos-epar-product-information_en.pdf. Accessed November 2023.

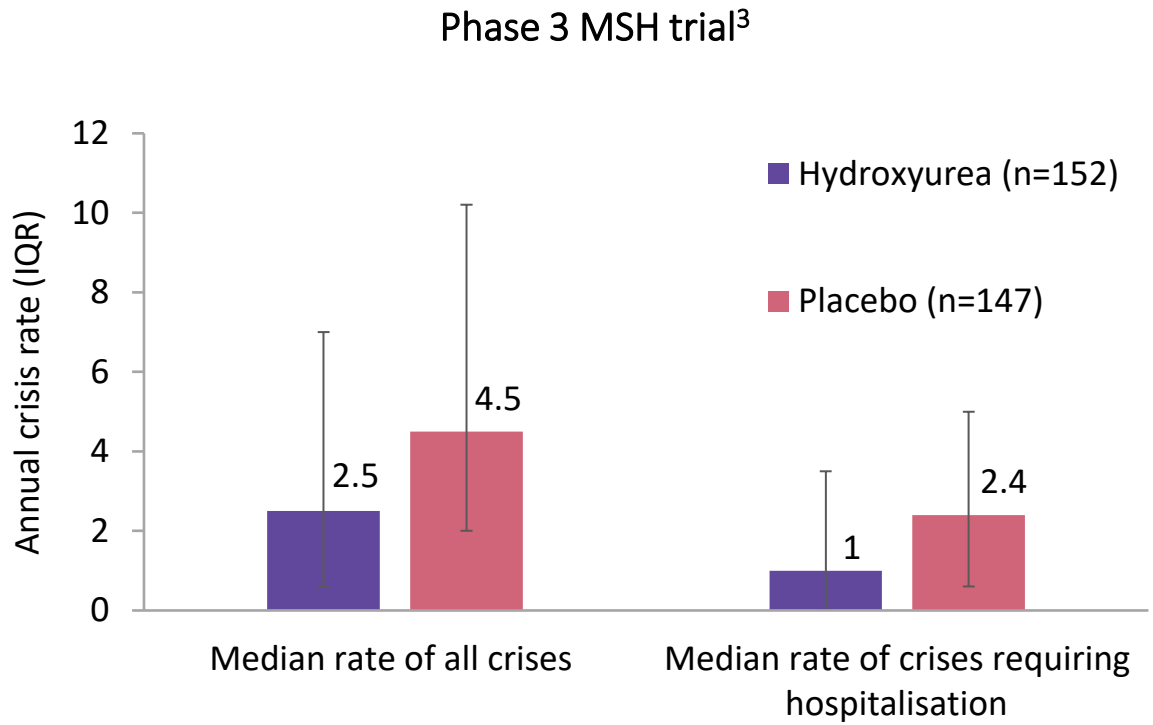
Hydroxycarbamide

Hydroxycarbamide[1,2] vs placebo[3]

- Reduced painful crises (33%)[2,3]
- Reduced acute chest syndrome (50%)[3,4]
- Ongoing organ damage[3]
- Improved mortality and morbidity[4]

Limitations

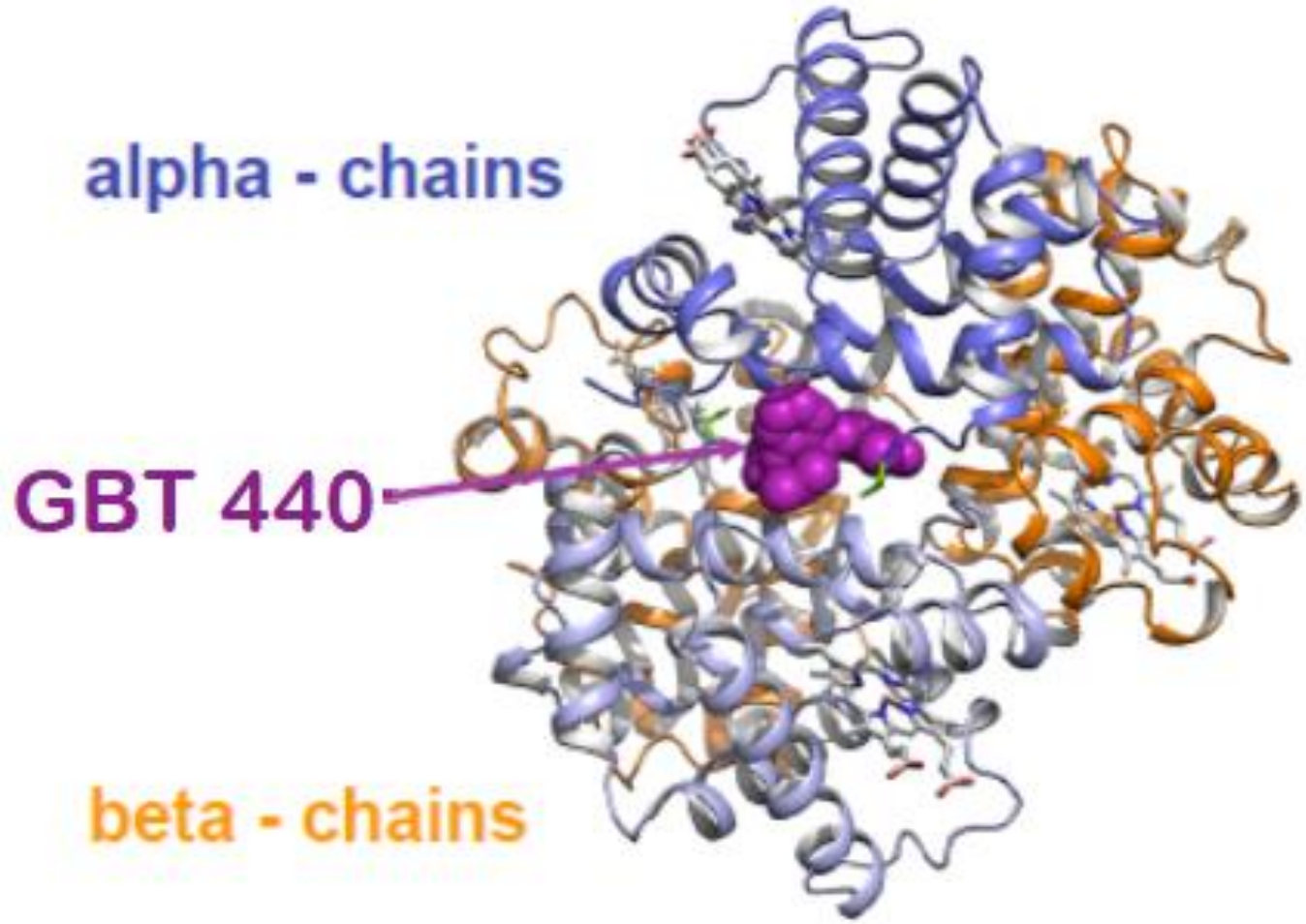
- Side effects[1,2]
- Tolerance[5]
- Non-adherence[5]
- Misconceptions[5]



MSH, Multicentre Study of Hydroxyurea.

1. Xromi SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/xromi-epar-product-information_en.pdf. Accessed November 2023; 2. Siklos SmPC. Available at: https://www.ema.europa.eu/en/documents/product-information/siklos-epar-product-information_en.pdf. Accessed November 2023; 3. Charache S, et al. *N Engl J Med* 1995;332:1317–1322; 4. Steinberg MH, et al. *JAMA* 2003;289:1645–1651; 5. Jose J, et al. *Oman Med J* 2019;34(4):327–335.

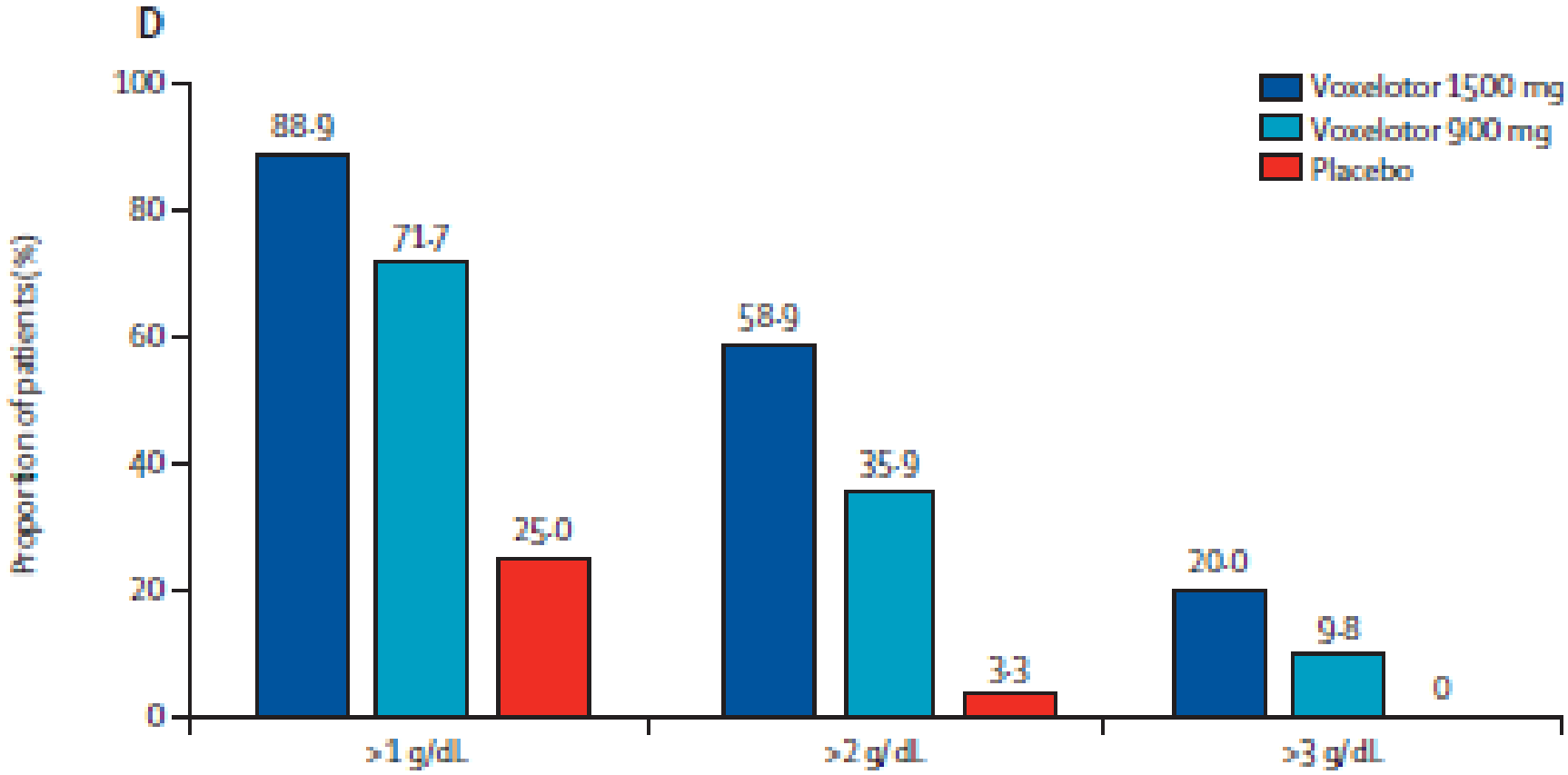
Voxelotor



HOPE study

Phase 3, multicentre, placebo controlled study	274 patients (low dose: high dose: placebo) 12-65 years 1-10 VOC in last 12 months Severe sickle phenotypes
Primary end point	Proportion to achieve Hb response (>10g/l) by week 24
Secondary end points	Reduction in haemolytic markers Reduction in annualised incidence rate of vaso-occlusive crises
Followed up - 72 weeks	

Hb rise at 24 weeks

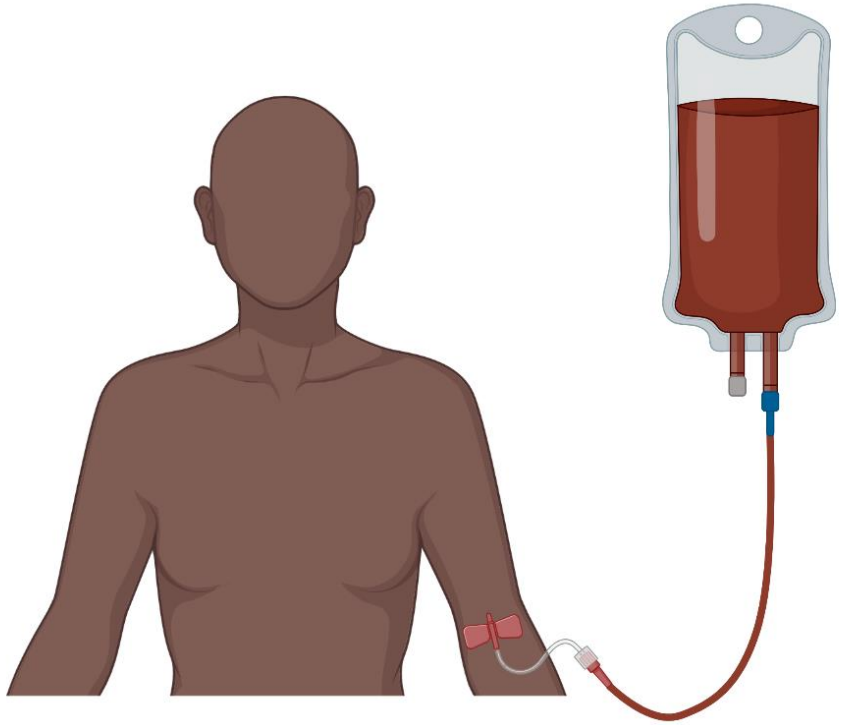


SCD, sickle cell disease.

1. Howard J. *ISBT Science Series* 2013;8:225–228.

Transfusion in SCD[1]

- Top up/exchange
- Problems:
  - Red cell antibodies
    - Delayed transfusion reactions
  - Iron overload
  - Infections



SCD, sickle cell disease.

1. Howard J. *ISBT Science Series* 2013;8:225–228.

Comorbidities in subgroups[1]

Patient cohort	Crises sub-cohort*	Transfusions sub-cohort*	Crises + transfusions sub-cohorts*	Other SCD sub-cohort	Entire cohort
Patients (n)	1171	201	1372	8131	9503
Males (n)	562	101	663	3761	4424
Occurrence of co-morbidity*					
Acute chest syndrome	53.9%	30.8%	50.5%	24.3%	28.1%
Osteonecrosis	31.3%	10.4%[ns]	28.2%	9.9%	12.6%
Cardiomegaly	24.9%	10.0%[ns]	22.7%	9.9%	11.7%
Sepsis	26.1%	16.9%	24.8%	8.8%	11.1%
Acute renal failure	18.4%	14.9%	17.9%	7.4%	8.9%
Retinal disorders	13.3%	10.0%[ns]	12.8%	8.0%	8.7%
Cerebrovascular symptoms	11.6%	51.2%	17.4%	6.5%	8.1%
Priapism[a]	17.3%	11.9%	16.4%	5.6%	7.3%
Depression & anxiety	18.5%	9.0%	17.1%	5.6%	7.3%
Hyposplenism	16.1%	11.4%	15.4%	5.5%	7.0%
Pulmonary hypertension	12.3%	10.0%	12.0%	5.2%	6.1%
Chronic kidney disease	7.0%	11.9%	7.7%	4.8%	5.2%
Stroke	5.5%	19.4%	7.5%	3.2%	3.8%
Number of co-morbidities					
Any co-morbidity	85.2%	86.6%	85.4%	51.5%	56.4%
1 co-morbidity	22.0%	30.3%	23.3%	26.2%	25.8%
2 co-morbidities	21.9%	25.4%	22.4%	12.7%	14.1%
3 co-morbidities	14.2%	13.9%	14.1%	6.2%	7.4%
4+ co-morbidities	27.2%	16.9%	25.7%	6.4%	9.2%
No co-morbidities	14.8%	13.4%	14.6%	48.5%	43.6%
Mean no. of co-morbidities	2.5	2.1	2.4	1.0	1.2
Median no. of co-morbidities (IQR)	2 (1–4)	2 (1–3)	2 (1–4)	1 (0–2)	1 (0–2)

*All results statistically significantly different ($p<0.05$) vs. other SCD sub-cohort unless noted. [a] % of males.
IQR, interquartile range; ns, not significant; SCD, sickle cell disease.
1. Piel FB, et al. *Blood Cells Mol Dis* 2021;89:2–7.

10-year mortality subgroups[1]

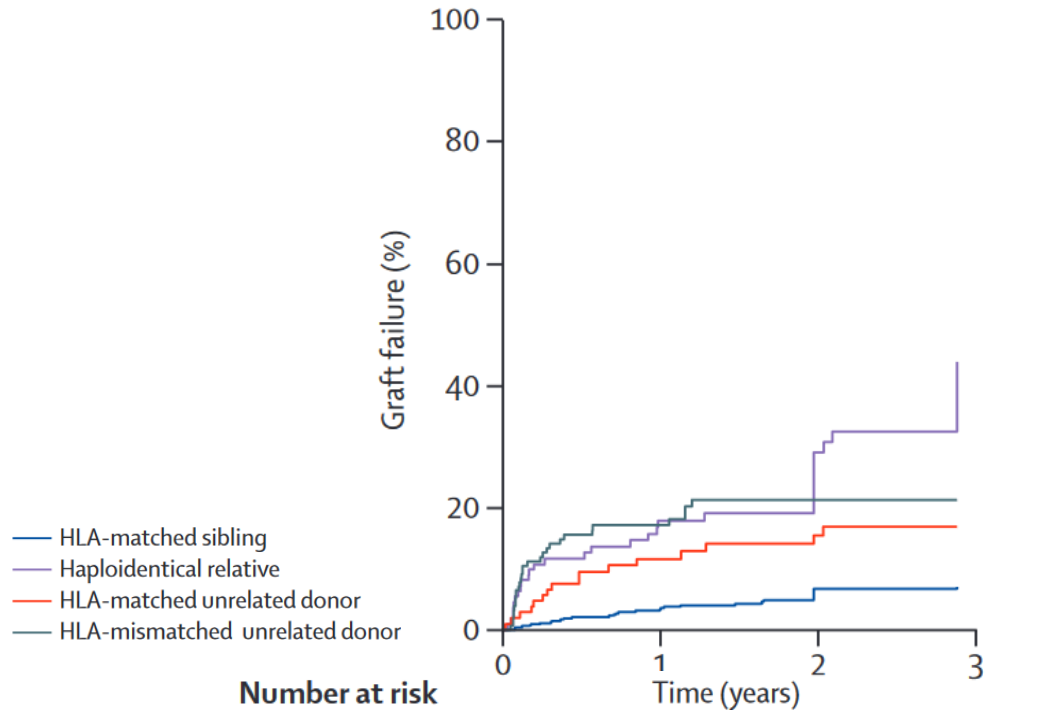
Age in 2009	Crises sub-cohort				Transfusions sub-cohort				Crises + transfusions sub-cohorts				Other SCD sub-cohort				Entire cohort			
	n.	Died	%*	E&W%[a]	n.	Died	%*	E&W%[a]	n.	Died	%*	E&W%[a]	n.	Died	%*	E&W%[a]	n.	Died	%*	E&W%[a]
0–9	172	2	1.2%[ns]	0.2%	49	1	2.0%	0.1%	221	3	1.4%	0.2%	2163	21	1.0%	0.2%	2384	24	1.0%	0.2%
10–19	320	15	4.7%	0.3%	70	1	1.4% [ns]	0.3%	390	16	4.1%	0.3%	1748	40	2.3%	0.3%	2138	56	2.6%	0.3%
20–29	324	14	4.3%	0.5%	25	5	20.0%	0.5%	349	19	5.4%	0.5%	1560	45	2.9%	0.5%	1909	64	3.4%	0.5%
30–39	212	31	14.6%	1.1%	22	2	9.1%	1.2%	234	33	14.1%	1.1%	1136	53	4.7%	1.1%	1370	86	6.3%	1.1%
40–49	114	25	21.9%	2.2%	22	7	31.8%	2.5%	136	32	23.5%	2.3%	989	99	10.0%	2.4%	1125	131	11.6%	2.3%
50+	29	7	24.1%	9.0%	13	7	53.8%	10.6%	42	14	33.3%	9.5%	535	132	24.7%	13.7%	577	146	25.3%	13.4%
Total	1171	94	8.0%	0.9%	201	23	11.4%	1.3%	1372	117	8.5%	0.9%	8131	390	4.8%	1.5%	9503	507	5.3%	1.5%

E&W, England and Wales; SCD, sickle cell disease.

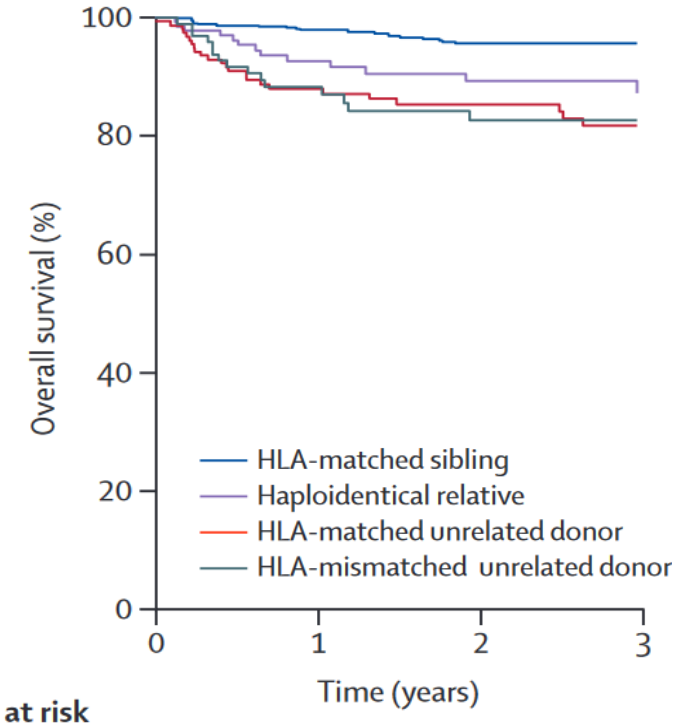
1. Piel FB, et al. *Blood Cells Mol Dis* 2021;89:2–7.

Stem cell transplantation

Effect of donor type and conditioning regimen intensity on allogeneic transplantation outcomes in SCD patients



Number at risk				
HLA-matched sibling	557 (0)	444 (97)	349 (185)	261 (265)
Haploidentical relative	137 (0)	85 (34)	61 (56)	33 (69)
HLA-matched unrelated donor	111 (0)	72 (27)	57 (40)	40 (55)
HLA-mismatched unrelated donor	104 (0)	61 (18)	42 (33)	36 (39)



Number at risk				
HLA-matched sibling	557 (0)	460 (86)	362 (175)	276 (261)
Haploidentical relative	137 (0)	97 (31)	71 (54)	50 (74)
HLA-matched unrelated donor	111 (0)	79 (14)	63 (27)	45 (42)
HLA-mismatched unrelated donor	104 (0)	82 (11)	64 (25)	52 (37)

Eapen M, et al. *Lancet* 2019; 6:e585–96.

Sickle cell cellular therapies - current status

	12-18 years	≥19 years
Sibling HSCT	✓	✓
Haploidentical HSCT	✓	Trial
Unrelated HSCT	✓	✗
CRISPR gene editing	?*	?*

HSCT – haematopoietic stem cell transplant
*Approved by MHRA and under consideration with NICE

Sibling transplant

Non-myeloablative sibling donor transplant in sickle cell disease

Research

Original Investigation

Nonmyeloablative HLA-Matched Sibling Allogeneic Hematopoietic Stem Cell Transplantation for Severe Sickle Cell Phenotype

Matthew M. Hsieh, MD; Courtney D. Fitzhugh, MD; R. Patrick Weitzel, PhD; Mary E. Link, BSN; Wynona A. Coles, MPH; Xiongce Zhao, PhD; Griffin P. Rodgers, MD; Jonathan D. Powell, MD; John F. Tisdale, MD

Biol Blood Marrow Transplant 25 (2019) 1179–1186

ELSEVIER

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

ASTCT American Society for Transplantation and Cellular Therapy

Nonmyeloablative Matched Sibling Donor Hematopoietic Cell Transplantation in Children and Adolescents with Sickle Cell Disease

Gregory M.T. Guilcher[1,*], Dania A. Monagel[2], Alberto Nettel-Aguirre[2], Tony H. Truong[1],

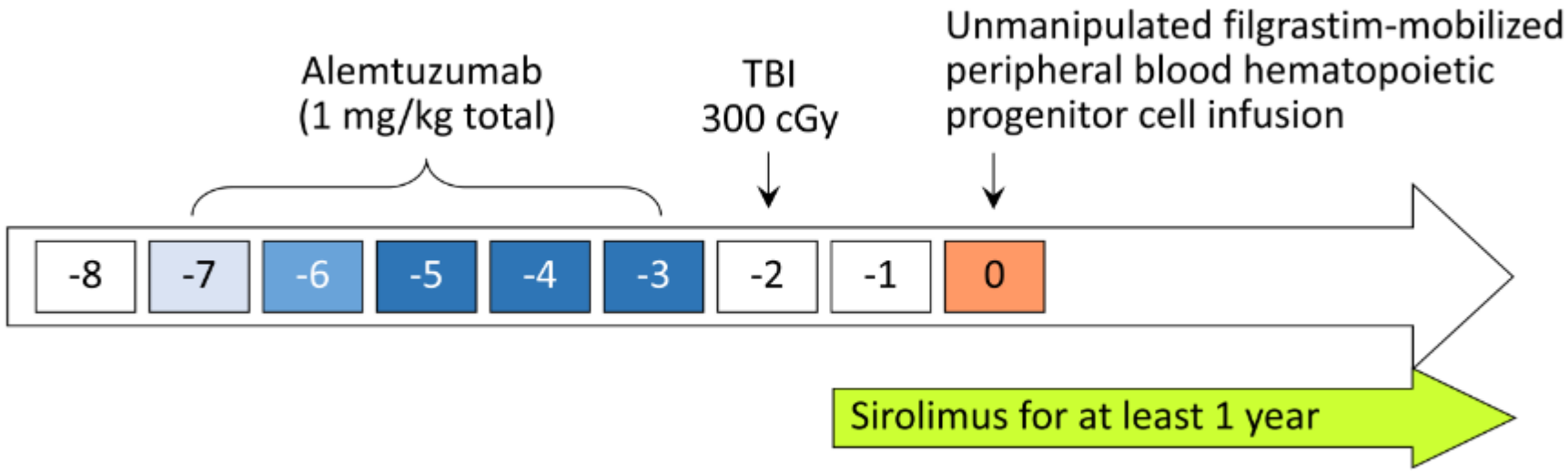
HLA, human leukocyte antigens.

Heish MM, et al. *JAMA* 2014;312:48–56; Guilcher GMT, et al. *Biol Blood Marrow Transplant* 2019;25:1179–1186.

Sibling allograft – Campath/TBI schedule

bjh research paper

Non-myeloablative human leukocyte antigen-matched related donor transplantation in sickle cell disease: outcomes from three independent centres



cGy, centigray; TBI, total body irradiation.
Alzahrani M, et al. *Br J Haematol* 2021;192:761–768.

Patient characteristics

- 2 US centres and 1 Saudi centre
- 122 patients
  - 101 HbSS (83%)
  - 72 (59%) male, 50 (41%) female
  - Median age in years (range): 29 (10–65)

Indications:

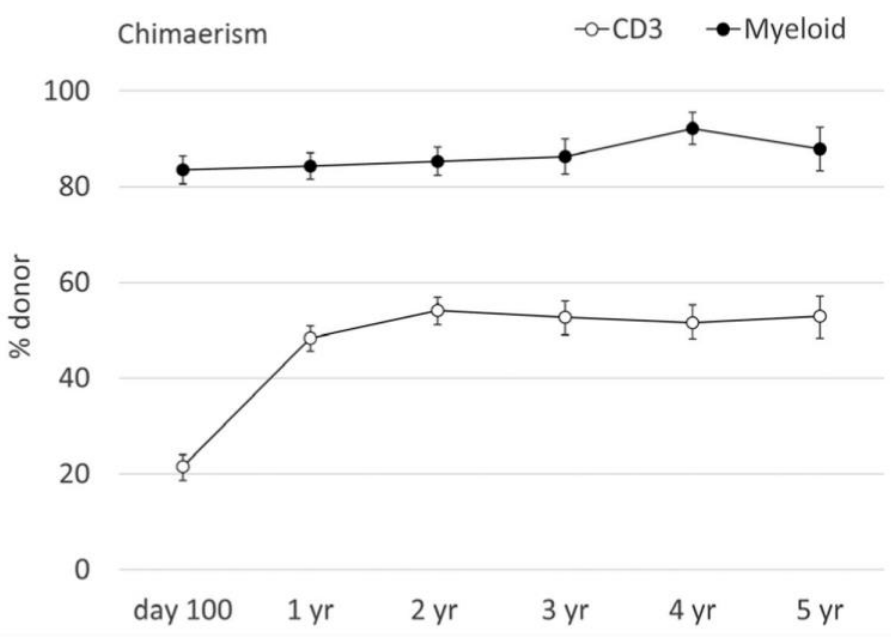
- >2 pain episodes per year: 107 (88%)
- Chest syndrome: 43 (35%)
- Stroke: 26 (21%)
- Cerebral vasculopathy: 18 (15%)

- Additional liver, renal and AVN complications also seen in study population

cGy, centigray; TBI, total body irradiation.
Alzahrani M, et al. *Br J Haematol* 2021;192:761–768.

Results

Donor white cell chimerism



- Engraftment between day 8–39
- 16 patients (13%) experienced graft failure, 3 patients near to or beyond 1 year
- 2 patients had low grade GvHD - resolving with topical therapy
- Infectious complications were limited and manageable

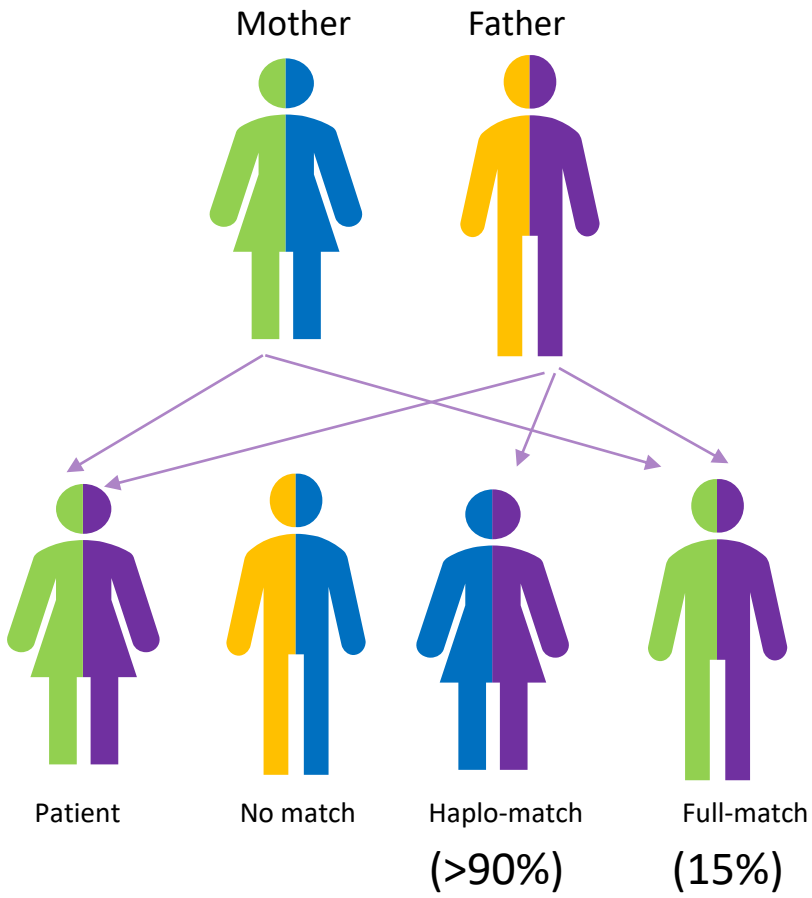
- **Late effects:**
- 2 MDS (1 previous allogeneic HSCT) - both had graft failure
- 1 CML (recipient origin)
- Fertility - 21 pregnancies (7 male and 7 females)

- 7 deaths, 5 after graft failure. 2 sickle-related, 1 aplasia, 2 MDS and haemorrhage, 2 sudden deaths

CML, chronic myelogenous leukaemia; GvHD, graft-versus-host disease; HSCT, haematopoietic stem cell transplantation; MDS, myelodysplastic syndromes.

Alzahrani M, et al. *Br J Haematol* 2021;192:761–768.

Donor identification challenges - HLA system



Patient case study continued

- Number of family members tissue typed – six
  - Two parents and four siblings

- Four haploidentical matches
  - both parents
  - sister and brother

- Brother selected
  - shared phenotypic haplotype (HLA-A*23; B*15; C*16; DRB1*11; DQB1*03)
  - No DSA
  - 27 years old
  - Sex matched
  - O^+
  - CMV matched

Haploidentical transplant

REDRESS (NCT05392894): Assessing the effects of related haplo-donor haematopoietic stem cell transplantation vs. SOC on treatment failure in SCD

Ongoing Trial

REDRESS
Confidential

King's College Hospital NHS
NHS Foundation Trust

KING'S College LONDON

UKCRC Registered Clinical Trials Units

PROTOCOL FULL TITLE

A multi-centre open randomised controlled trial to assess the effect of related haplo-donor haematopoietic stem cell transplantation versus standard of care (no transplant) on treatment failure at 24 month in adults with severe sickle cell disease

Protocol Short Title

RElated haplo-DonoR haematopoietic stEm cell transplantation for adults with Severe Sickle cell disease (REDRESS).

REDRESS

120 patients randomised 1:1 to HSCT or best supportive care[1]

HSCT, haematopoietic stem cell transplantation; SOC, standard of care.

REDRESS. Available at: https://classic.clinicaltrials.gov/ct2/show/NCT05392894. Accessed June 2023.

REDRESS study

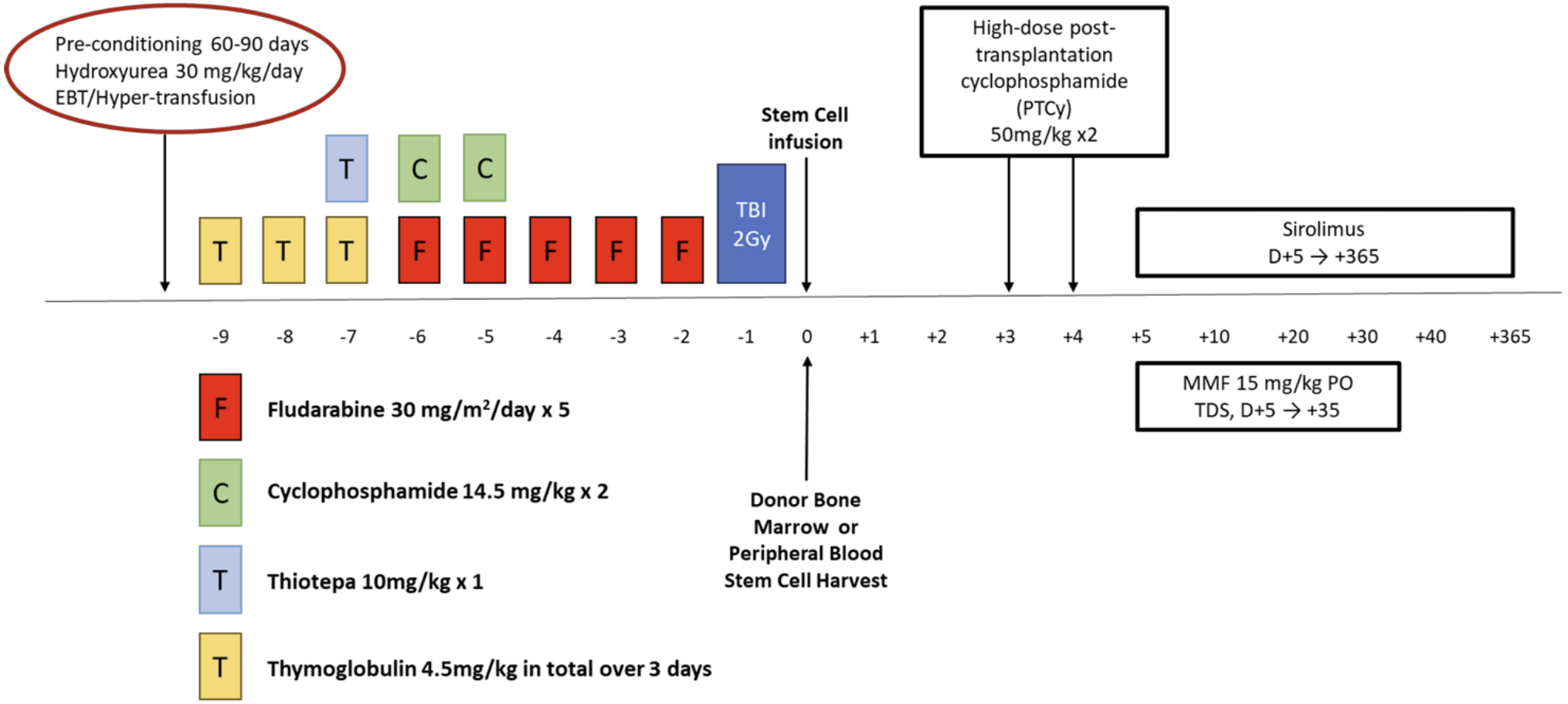
Main Inclusion Criteria:

- **>18 years old.**
- **Confirmed haploidentical donor.**
- **Severe SCD phenotype who are at high risk for morbidity and mortality. Severe SCD is defined by at least one of the following:**
  - Clinically significant neurologic event (stroke) or deficit lasting > 24 hours.
  - History of ≥2 acute chest syndromes in a 2-year period preceding enrolment despite optimum treatment, e.g. with HU
  - History of ≥3 severe pain crises per year in a 2-year period preceding enrolment despite the institution of supportive care measures (e.g. optimum treatment with HC).
  - Administration of regular transfusion therapy (=8 packed red blood transfusions per year for 1 year to prevent VOCs).
  - Patients assessed as requiring transfusion but with red cell allo-antibodies/very rare blood type, rendering it difficult to continue/commence chronic transfusion.
  - Patients requiring HC/transfusion for treatment of SCD complications who cannot tolerate either therapy due to significant adverse reactions.
  - Established end organ damage relating to SCD, including but not limited to progressive sickle vasculopathy and hepatopathy.

Primary exclusion criteria:

- Fully matched sibling donor.
- Previous bone marrow transplant.
- Clinically significant donor specific HLA antibodies.
- Active blood borne viruses.
- Uncontrolled bacterial, fungal or viral infection.
- Pre-existing condition deemed to significantly increase the risk of haploidentical SCT by the local PI.

Haploidentical allograft – Vanderbilt schedule



PTCy (post-transplant cyclophosphamide), MMF (mycophenolate mofetil),
PO (by mouth), TID (three times a day),
TBI (total body irradiation)

Patient case study continued

Therapy	Days	Dates	Dosage (dose)
ATG	-9 only	05-May-24	0.5 mg/kg (40 mg)
ATG	-8 to -7	06-May-24 to 07-May-24	2 mg/kg (160 mg)
Thiotepa	-7 only	7-May-24	10 mg/kg (790 mg) od iv
Fludarabine	-6 to -2	8-May-24 to 12-May-24	30 mg/m^2 (60 mg) od iv
Cyclophosphamide	-6 to -5	8-May-24 to 09-May-24	14.5 mg/kg (1120 mg) od iv
TBI	-1 only	13-May-24	Total 2 Gy
MESNA	3 to +4	17-May-24 to 18-May-24	50 mg/kg (4200 mg) bd iv
Cyclophosphamide	3 to +4	17-May-24 to 18-May-24	50 mg/kg (4180 mg) od iv
Sirolimus	5 to +365	19-May-24 to 18-May-25	5 mg po daily
Mycophenolate (MMF)	+5 to +35	19-May-24 to 18-Jun-24	15 mg/kg (1000 mg) tds iv or po

Reduced Intensity Haploidentical HSCT in Adults with Severe Sickle Cell Disease: CTN 1507

Table: Demographic and clinical characteristics of participants. (n=42)

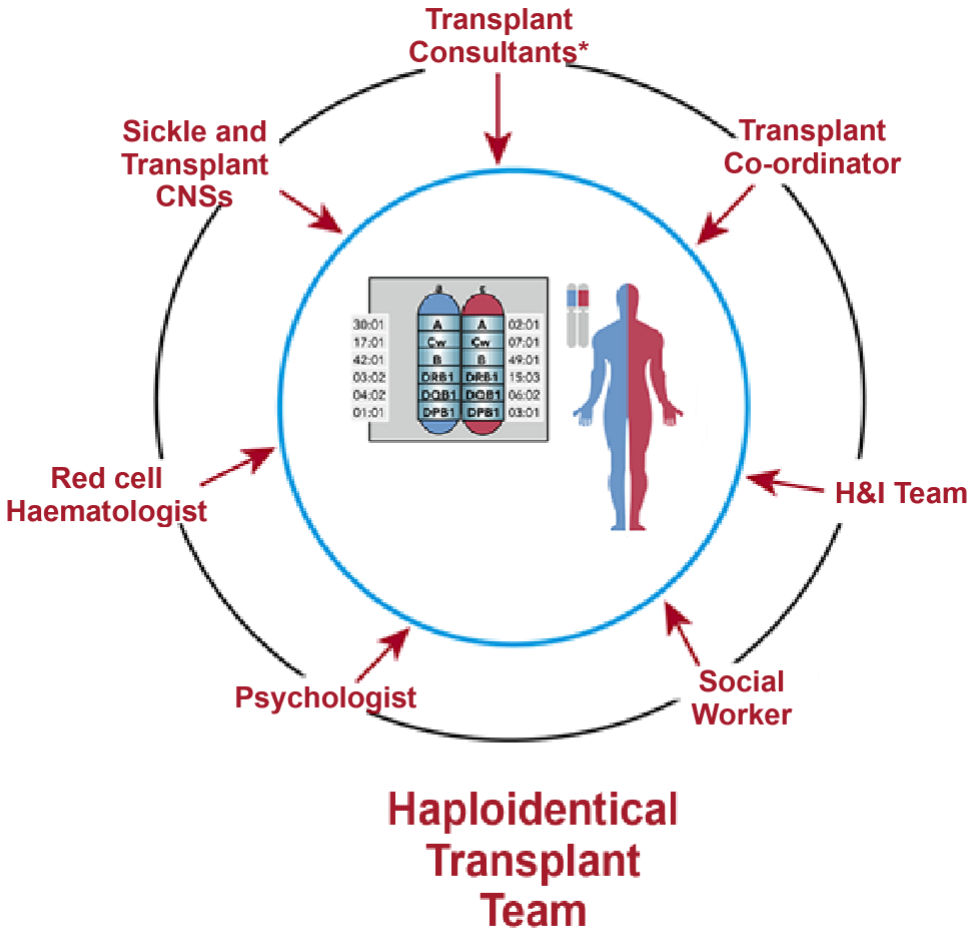
Variable	Adult (n=42)	Percentage (%)
Median age (years)	22.8 (15.5-43.2)	N/A
Transplanted	42	78%
Follow-up time (days), median (IQR) (n=42)	743.5 (214.0-1393)	N/A
SCD genotype (SS and Sβ^0-thalassemia), n (%)	47	87%
TNC dose (10^8/kg), median IQR (n=37)	3.5 (2.0-5.4)	N/A
CD34$^+$ cell dose (10^6/kg), median IQR (n=41)	3.6 (0.9-7.9)	N/A
Days post-transplant to neutrophil >500/mcL, median (IQR) (n=42)	25.5 (1.0-197.0)	N/A
Days post-transplant platelets >50 x 10^9/L, median (IQR) (n=42)	34.5 (19.0 – 735.0)	N/A
Primary graft failure, n (%) (n=42)	2	4.8%
Secondary graft failure, n (%) (n= 42)	1	2.4%
Death, n (%)	2	4.7%
Acute graft-versus-host-disease (grades III) (%)	2	4.8%
Chronic graft-versus-host disease, severe (%)	3	7.1%

Deaths (n=3)

Study ID	Age at Transplant (years)	Days post-transplant	Cause of Death
#1	28	Day – 63 (23 days after the start of hydroxyurea therapy, prior to transplant)	Intracranial hemorrhage from a left posterior inferior cerebellar artery aneurysm with evidence of subarachnoid hemorrhage. Progression of ischemic changes involving the left temporoparietal lobes with multifocal bilateral cerebral infarctions and vasospasm
#2	29	261	Sudden death of unclear etiology (after a febrile episode, likely cardio-respiratory failure).
#3	18	291	Acute respiratory distress syndrome

Imperial experience (2023-2024)

- Adult stem cell transplants (207)
  - 32% increase on 2022-2023
  - Haploidentical transplants (22)
- 547 sickle cell patients
- >2000 patients within network
- Paediatric programme in sickle cell
  - >20 years
  - 34-37 transplants/year



*Adult transplant team supported by the Prof dela Fuente – paediatric haemoglobinopathy transplant consultant

Patient case study continued

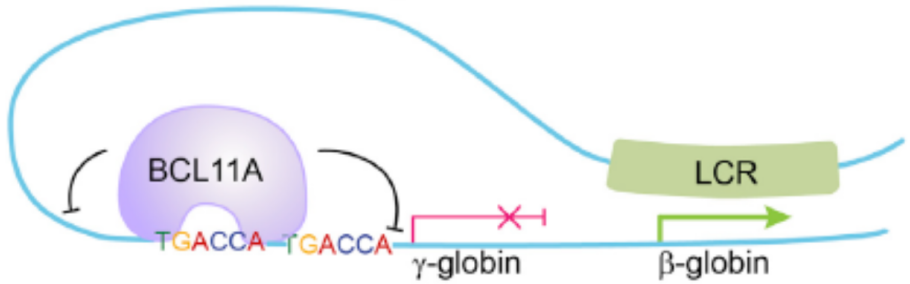
- Fully engrafted by D+26
- Last sickle pain prior
- D+130
  - Biliary complications
  - HbS <20%
- Ongoing psychological support

Gene editing

Bcl11a – ‘genetic switch’

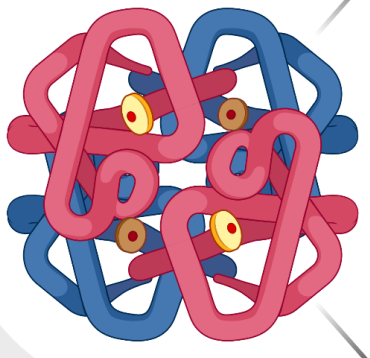
Erythoid stem cells

Sickle stem cell



Defective Beta chain expression

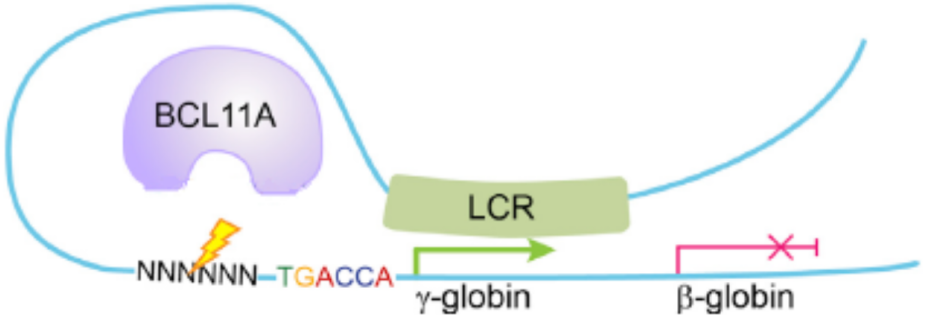
HbS



Sickle β chain

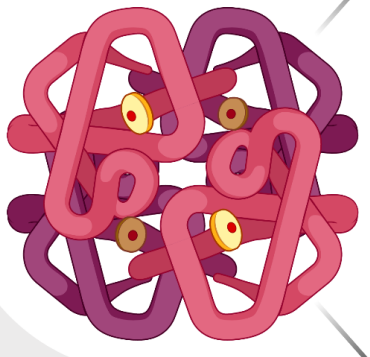
α chain

Manipulated stem cell



Gamma chain expression

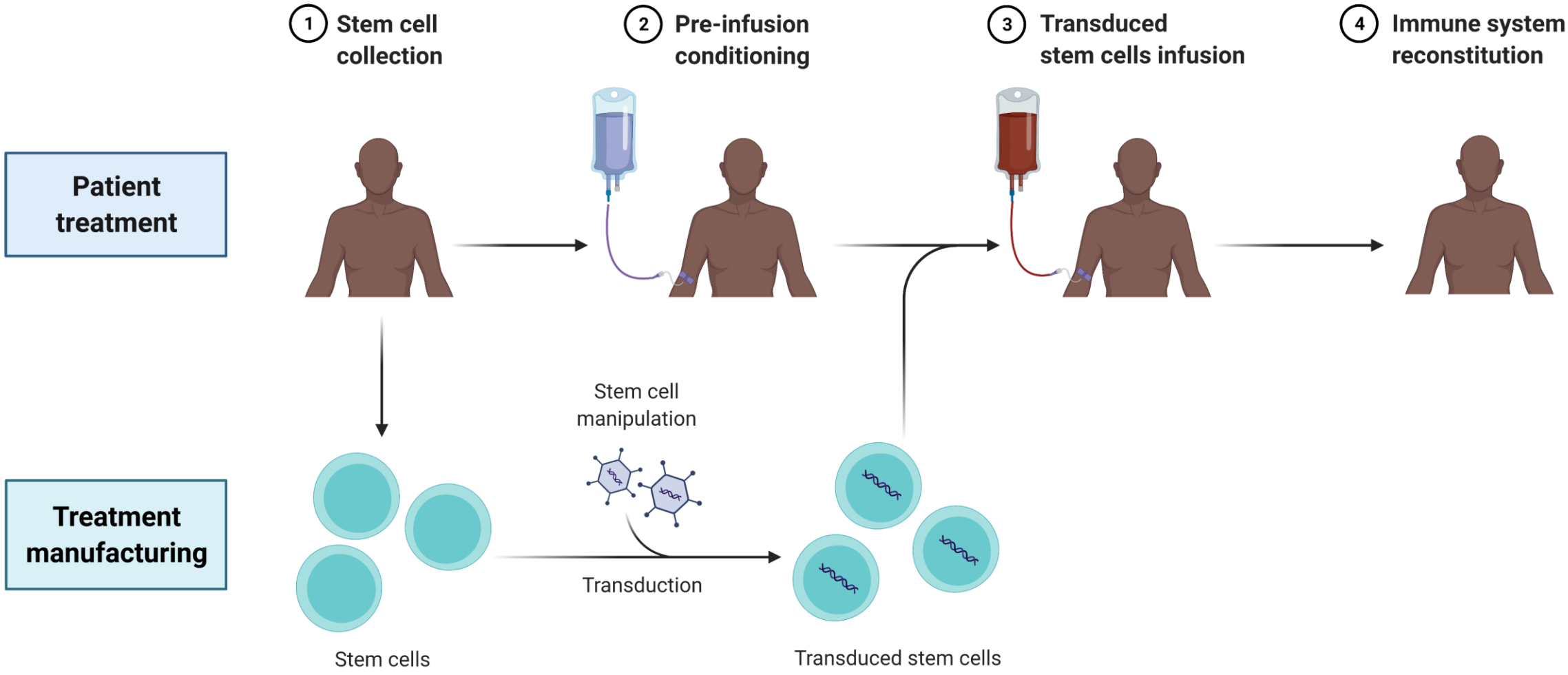
HbF



γ chain

α chain

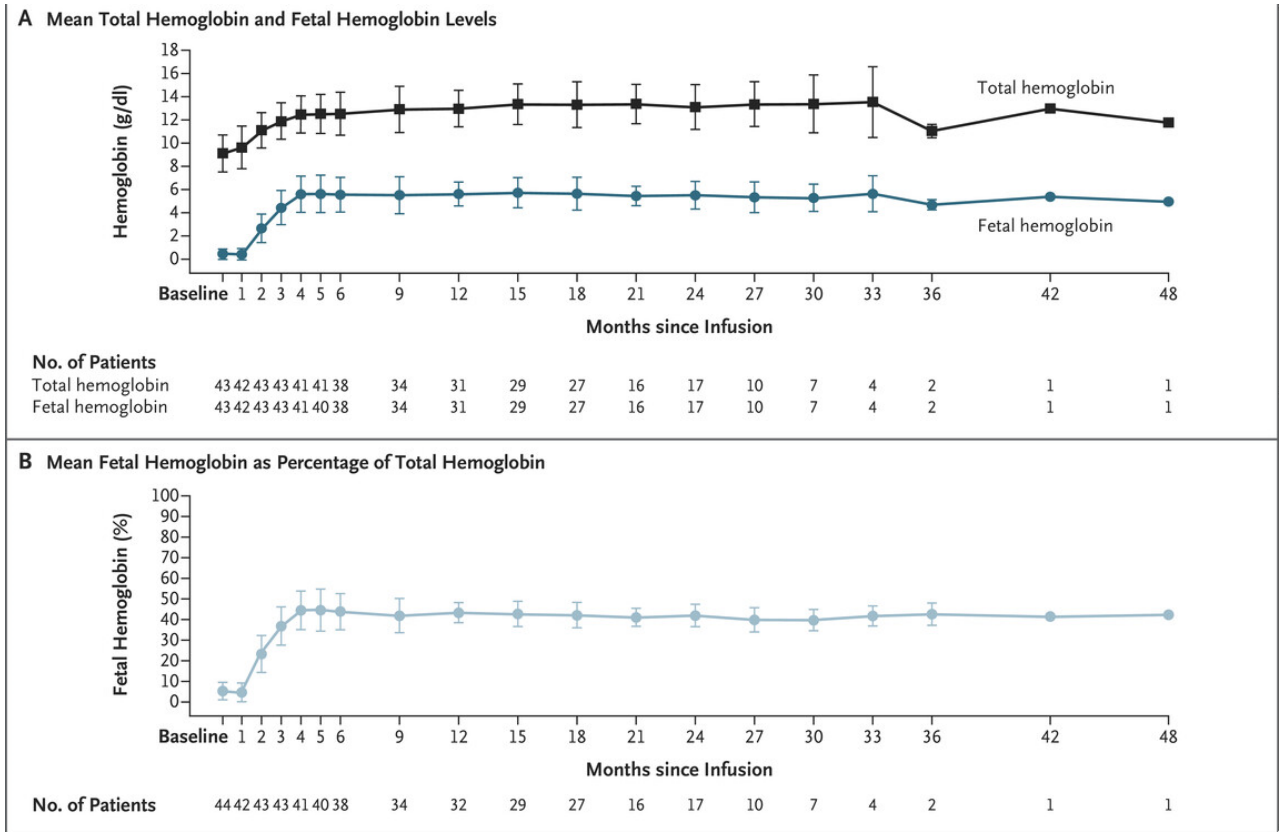
Gene therapy - editing

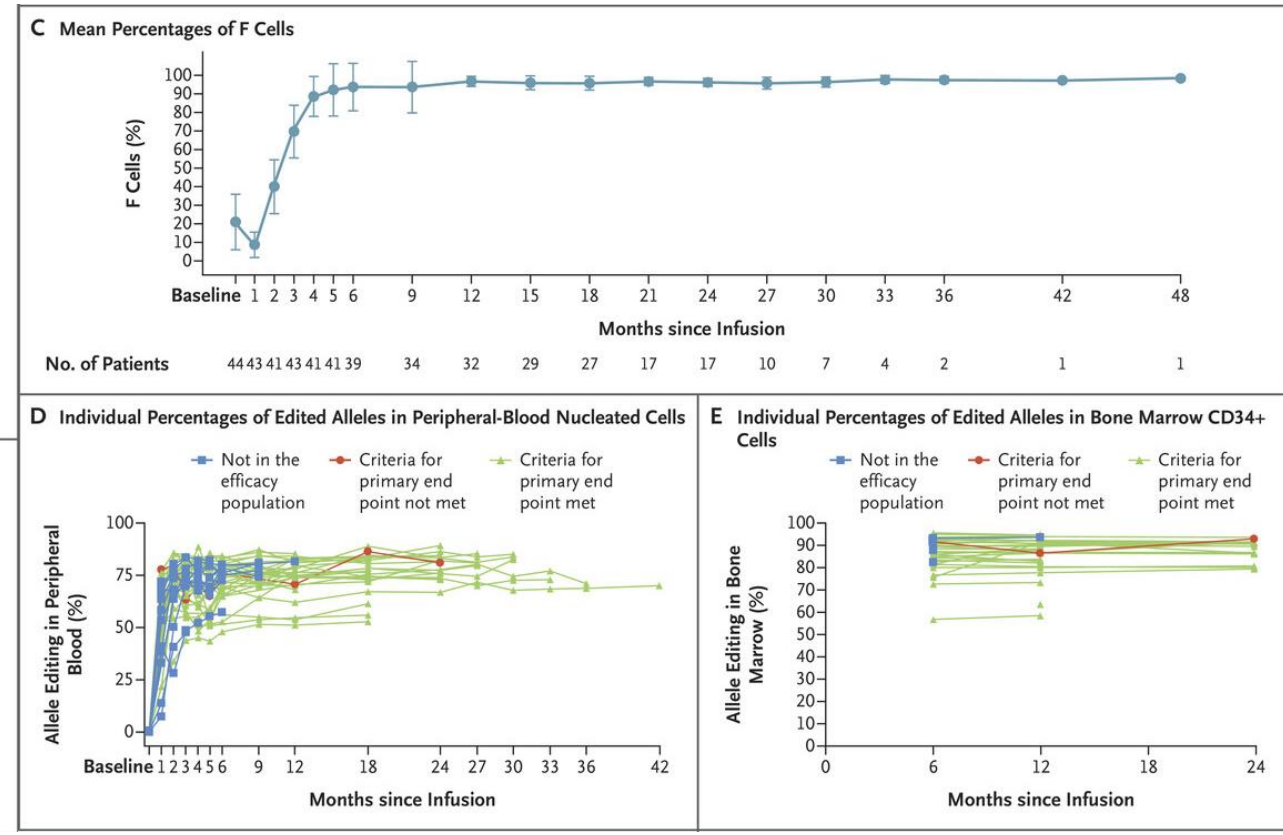


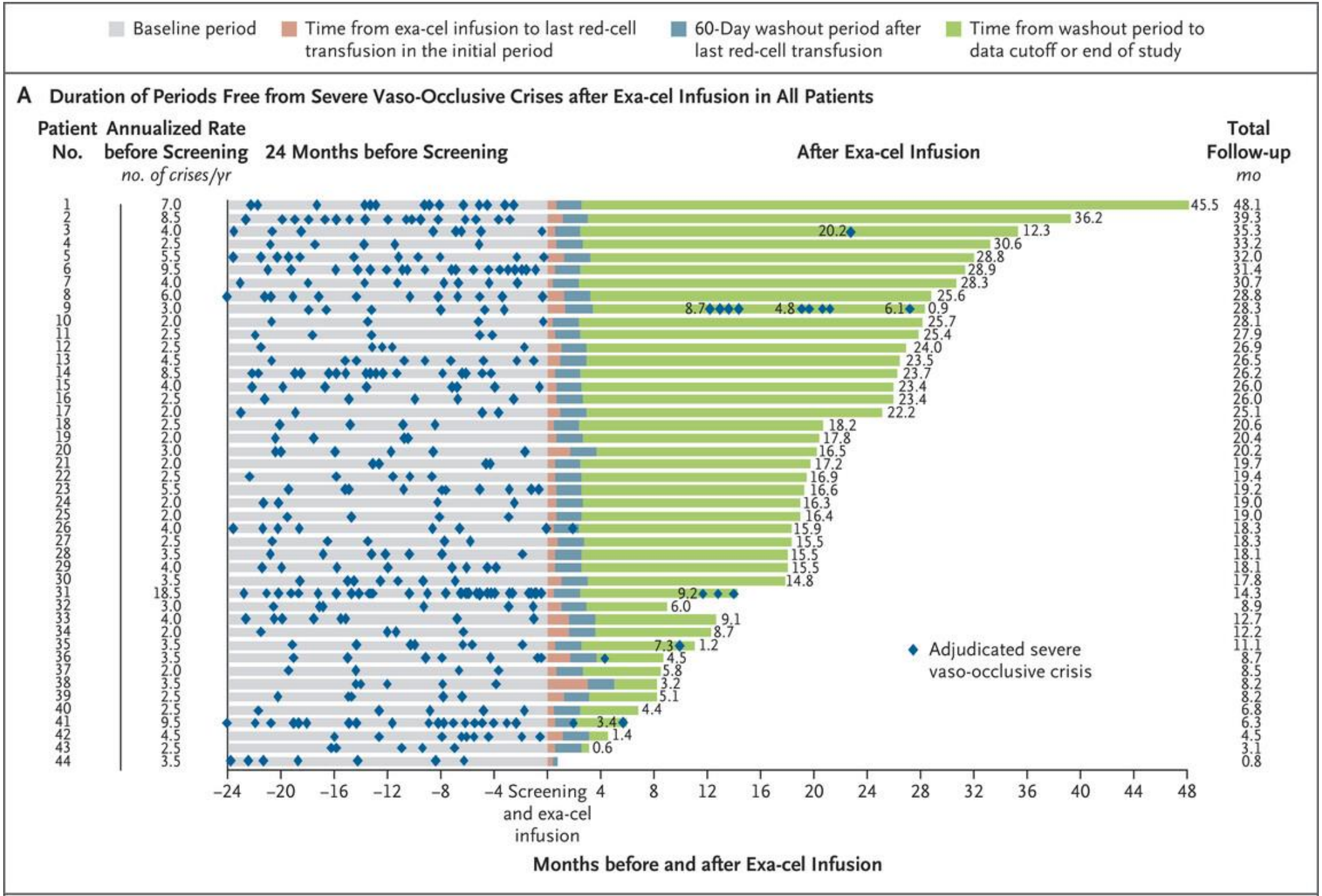
Gene editing for severe SCD

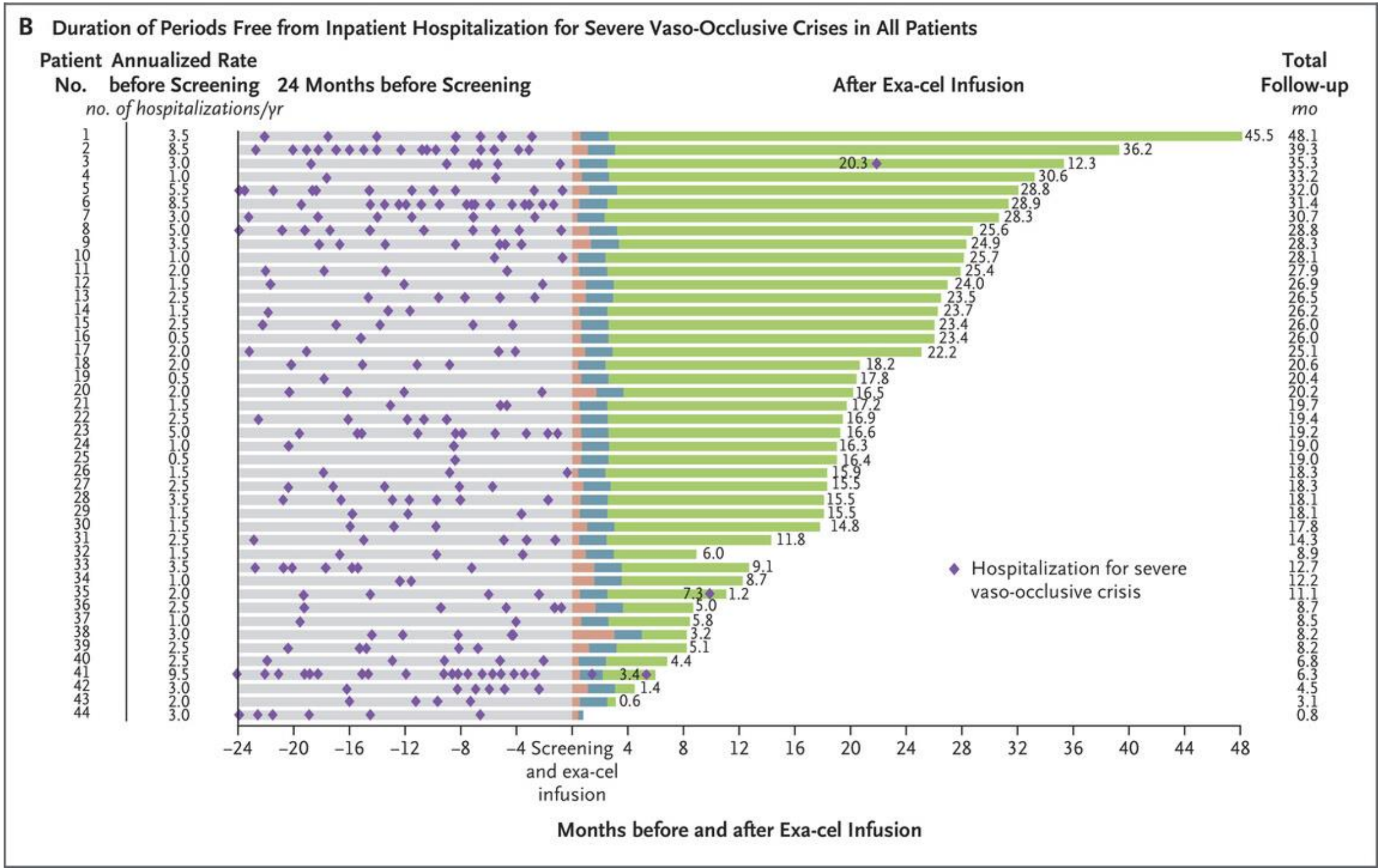
- Both disease due to defective β globin subunit gene
- Exa-cel (Casgevy) – CRISPR Cas9 product
- Disrupts Bcl11a enhancer binding site

- Phase 1/2 CLIMB Thal-111 trial
  - Transfusion dependant β-thalassaemia
- Phase 1/2 CLIMB Sickle-121 trial
  - Severe sickle cell disease


A Mean Total Hemoglobin and Fetal Hemoglobin Levels
Hemoglobin (g/dl)
Total hemoglobin
Fetal hemoglobin
Baseline 1 2 3 4 5 6 9 12 15 18 21 24 27 30 33 36 42 48
Months since Infusion
No. of Patients
Total hemoglobin 43 42 43 43 41 41 38 34 31 29 27 16 17 10 7 4 2 1 1
Fetal hemoglobin 43 42 43 43 41 40 38 34 31 29 27 16 17 10 7 4 2 1 1
B Mean Fetal Hemoglobin as Percentage of Total Hemoglobin
Fetal Hemoglobin (%)
Baseline 1 2 3 4 5 6 9 12 15 18 21 24 27 30 33 36 42 48
Months since Infusion
No. of Patients 44 42 43 43 41 40 38 34 32 29 27 16 17 10 7 4 2 1 1


C Mean Percentages of F Cells
F Cells (%)
Baseline 1 2 3 4 5 6 9 12 15 18 21 24 27 30 33 36 42 48
Months since Infusion
No. of Patients 44 43 41 43 41 41 39 34 32 29 27 17 17 10 7 4 2 1 1
D Individual Percentages of Edited Alleles in Peripheral-Blood Nucleated Cells
Not in the efficacy population
Criteria for primary end point not met
Criteria for primary end point met
Allele Editing in Peripheral Blood (%)
Baseline 1 2 3 4 5 6 9 12 18 24 27 30 33 36 42
Months since Infusion
E Individual Percentages of Edited Alleles in Bone Marrow CD34+ Cells
Not in the efficacy population
Criteria for primary end point not met
Criteria for primary end point met
Allele Editing in Bone Marrow (%)
0 6 12 18 24
Months since Infusion


Baseline period
Time from exa-cel infusion to last red-cell transfusion in the initial period
60-Day washout period after last red-cell transfusion
Time from washout period to data cutoff or end of study
A Duration of Periods Free from Severe Vaso-Occlusive Crises after Exa-cel Infusion in All Patients
Patient No.
Annualized Rate before Screening
no. of crises/yr
24 Months before Screening
After Exa-cel Infusion
Total Follow-up
mo
Adjudicated severe vaso-occlusive crisis
−24 −20 −16 −12 −8 −4 Screening and exa-cel infusion 4 8 12 16 20 24 28 32 36 40 44 48
Months before and after Exa-cel Infusion


B Duration of Periods Free from Inpatient Hospitalization for Severe Vaso-Occlusive Crises in All Patients
Patient No.
Annualized Rate before Screening
no. of hospitalizations/yr
24 Months before Screening
After Exa-cel Infusion
Total Follow-up
mo
Hospitalization for severe vaso-occlusive crisis
Screening and exa-cel infusion
Months before and after Exa-cel Infusion

Patient reported outcome measures in SCD

Visit	EQ VAS (Range: 0-100)	FACT-G Total Score (Range: 0-108)	BMT Score (Range: 0-40)
Baseline mean (SD), points	63.5 (22.5) N=17	67.5 (18.3) N=17	26.1 (3.5) N=17
Change at Month 6, mean (SD), points	+24.3 (27.1) N=16	+16.5 (17.4) N=16	+3.6 (6.2) N=16
Change at Month 12, mean (SD), points	+25.3 (23.2) N=17	+20.5 (18.0) N=17	+5.3 (4.5) N=17
Change at Month 18, mean (SD), points	+33.1 (17.2) N=11	+27.2 (20.3) N=11	+6.7 (4.2) N=11
MCID	7 to 10 points	3 to 7 points	2 to 3 points

BMT, bone marrow transplantation subscale; **EQ VAS**, EuroQol visual analog scale; **FACT-G,** Functional Assessment of Cancer Therapy-General; **MCID,** minimum clinically important difference; **SD,** standard deviation.

Key message

- Sickle cell disease – severe/life limiting disorder
- Currently limited treatment landscape
- Fully matched sibling transplant – option for the few
- Haploidentical transplant is safe and effective options for most
- Likely to be competing curative options in future