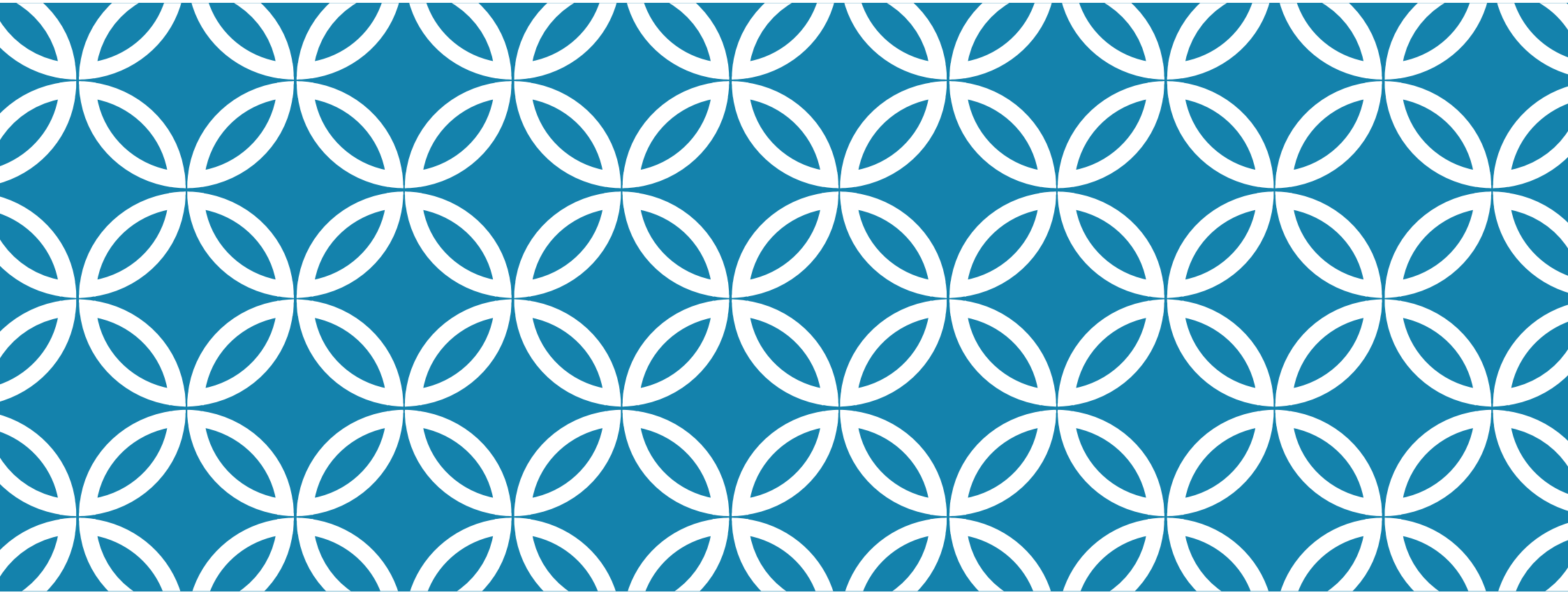


GENE THERAPY IN SICKLE CELL DISEASE (SCD) & TRANSFUSION-DEPENDENT THALASSAEMIA (TDT)

Tom Mayo
Haematology SpR

THE CURRENT CONTEXT

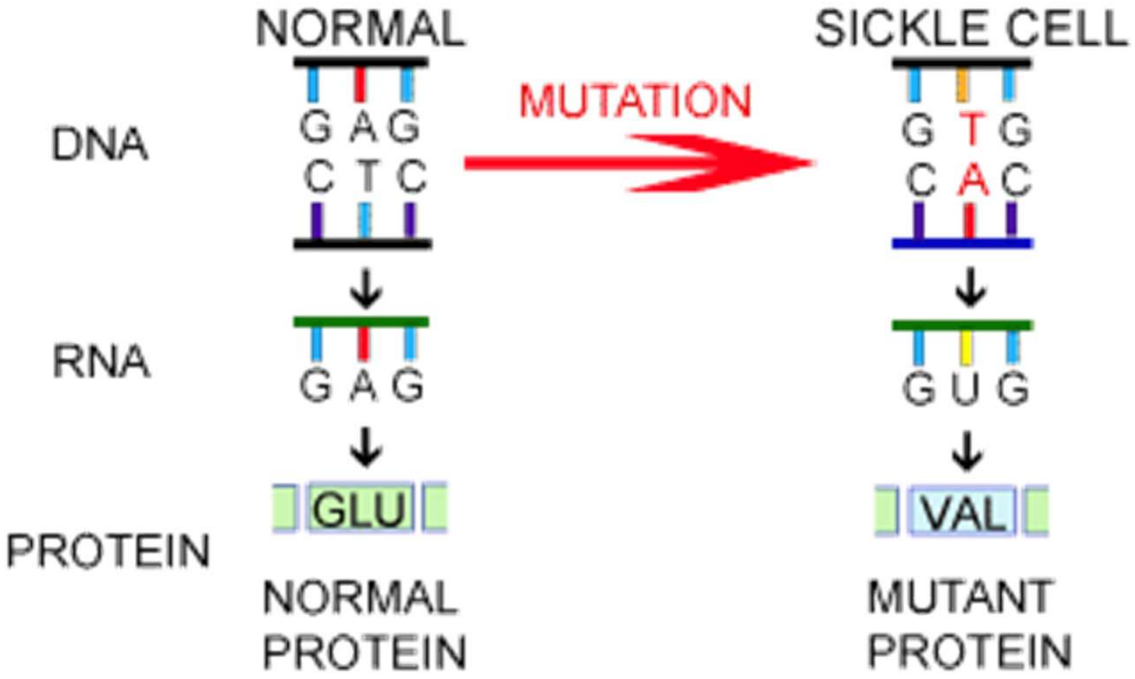
SCD & TDT are lifelong conditions, with significant associated morbidity and mortality.

Current treatment options are few, with limited disease-modifying options

- SCD: hydroxycarbamide, transfusion, organ screening, haemopoietic stem cell transplantion (HSCT)
- TDT: transfusion, organ screening, HSCT

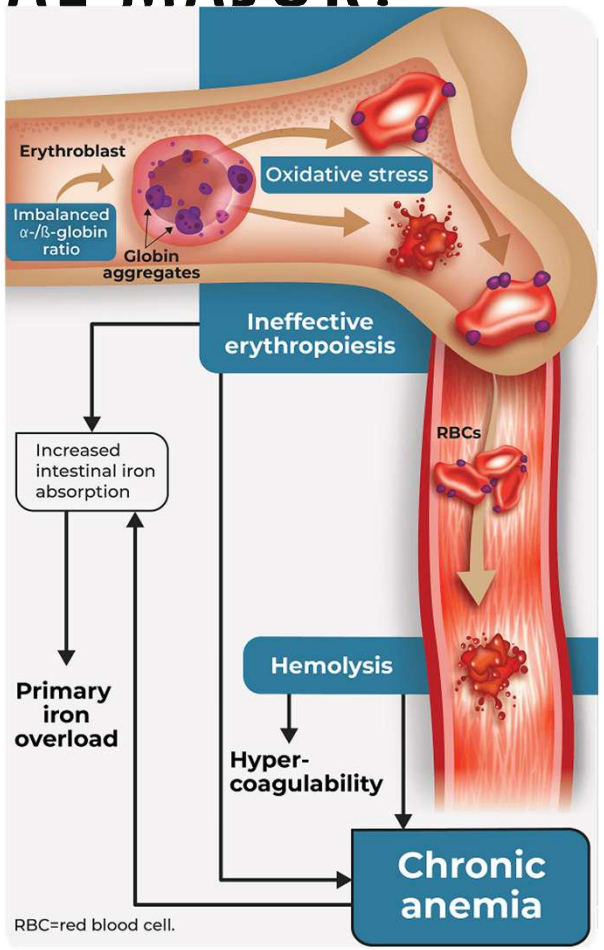
WHAT IS THE CAUSES OF SCD?

- Point mutation, B-globin gene (haemoglobin)
- Chromosome 11
- Qualitative and quantitative problem – sickling + haemolysis



WHAT IS THE CAUSES OF TDT/B-THAL MAJOR?

- >350 different mutations, all in the B-globin gene (haemoglobin)
- Chromosome 11
- Quantitative problem – transfusion-dependent anaemia



HOW MIGHT GENE THERAPY HELP?

Both conditions – lack of ‘normal’ haemoglobin (HbA) which can deliver oxygen

Potential solution – HbF (foetal)

BCL11a – the prison guard analogy.

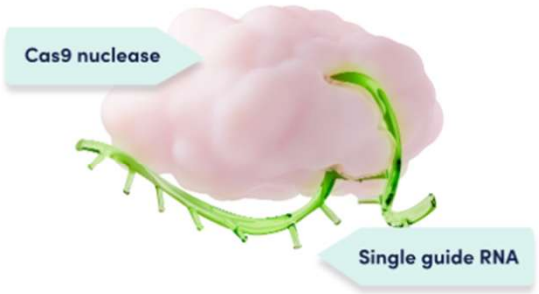
BCL11a regulates/reduces HbF expression

Put the guard (BCL11a) to sleep to enable the prisoners (HbF) to rise up…

1

Precise targeting; nonviral delivery[1,3]

CRISPR/Cas9 precisely targets the erythroid-specific enhancer region of the *BCL11A* gene using a nonviral delivery method

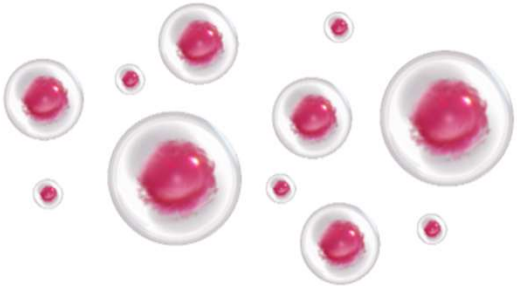


CRISPR/Cas9 complex

2

Decreased *BCL11A* expression[1]

Gene-edited CD34$^+$ HSCs engraft and have reduced expression of *BCL11A* specifically in erythroid lineage cells



Gene-edited CD34$^+$ HSCs

3

Increased HbF expression[1]

Reduced *BCL11A* expression leads to an increase in γ-globin expression and HbF levels

HbF

EXAGAMGLOGENE / CASGEVY / EXA-CEL – HOW DOES IT WORK?

Concept

- 'Enhancing' patients' bone marrow cells to produce more haemoglobin (HbF).
- One-off procedure

Steps:

- Stem cell apheresis/collection, CRISPR/Cas9 gene editing of BCL11a, myeloablative chemo (i.e. busulfan), modified stem cell re-infusion, await count-recovery and see…

What does this do?

- SCD – Increased HbF% → less HbS% → less sickling/VOC
- TDT – Increased HbF → more a-globin used productively → fewer a-globin tetramers → less inefficient haemopoiesis → less iron overload (from gut absorption and RBC)

Treatment Process at a Glance

1
Mobilise & collect
G-CSF + plerixafor (TDT)
Plerixafor only (SCD)

2
Ex vivo CRISPR editing
BCL11A enhancer targeted
in CD34+ HSCs

3
Manufacturing
Up to 6 months
Quality tested

4
Myeloablation
Busulfan conditioning
~1 month inpatient

5
Infusion & engraftment
Single IV infusion
Monitor engraftment

ELIGIBILITY & INDICATIONS FOR GENE THERAPY

Eligibility:

- Age ≥12 (no strict max age, trials included ≤35yrs)
- Appropriate for HSCT (organ function etc) but no matched sibling donor present
- Ideally: patient motivation + potential for fertility preservation

SCD indications:

- HbSS/SB^{+}/SB^{0}
- ≥2 severe VOCs/year for last 2 years (despite optimal therapy)

TDT indications:

- Transfusion requirement: ≥100ml/kg/year or ≥10 RBC/year.
- No: liver (<7mg/g) & heart (>20ms) iron loading, HSM, gallstones.

Gene Therapy Referral Pathway

Gene therapy eligible patient identified

A patient may be identified as transplant eligible as part of their annual review. Alternatively, a patient may approach their clinical team as being interested in transplant and their eligibility can be assessed following this.

For more information on gene therapy eligibility criteria, please access the Sickle Cell Disease in Adults clinical guideline.

Perform HLA typing for patient

HLA typing can be performed for the patient through the haemoglobinopathy clinic during their annual review. Typing of both patient and siblings must be performed as only patients without a matched sibling donor can be considered for gene therapy.

The request form for HLA typing (patient and donors) can be found here: 3c-haematopoietic-stem-cell-transplantation-recipients-donors.pdf

Obtain sibling contact details

The patient should contact their siblings to find out whether they would be happy for HLA typing to be performed. If the relative is happy for this to go ahead, the patient should supply the haemoglobinopathy team with the following information:

- Full name
- Date of birth
- Address
- Telephone number
- Email address
- NHS number (if known)

Refer to Bone Marrow Transplant/Cellular Therapies (BMT) team

A completed referral form should be sent by the haemoglobinopathy team to the BMT team with the details of the patient and the siblings. The siblings will be contacted to arrange sample collection.

Once results are compiled by the NHSBT H&I Team, the results will be returned to both the BMT and haemoglobinopathy teams. The BMT team will contact the relatives to inform them of their status.

The haemoglobinopathy team should not inform the patient of the relative's results until the relative has given consent for this information to be shared.

Discuss case in South West Haemoglobinopathy Coordinating Centre (HCC) MDT

The case should be discussed in the HCC MDT to approve the indication and appropriateness for gene therapy. This can happen before or after the clinic appointment with the BMT team.

Please complete the following referral form: https://southwesthcc.nhs.uk/wp-content/uploads/2025/04/SW-HCC-MDT-proforma.docx

Discuss case in National Haemoglobinopathy Panel (NHP) MDT

The case should be discussed in the NHP MDT for national approval before proceeding to transplant. Cases are usually presented by haemoglobinopathy consultants within the UHBW Specialist Haemoglobinopathy Team (SHT) or a nominated deputy.

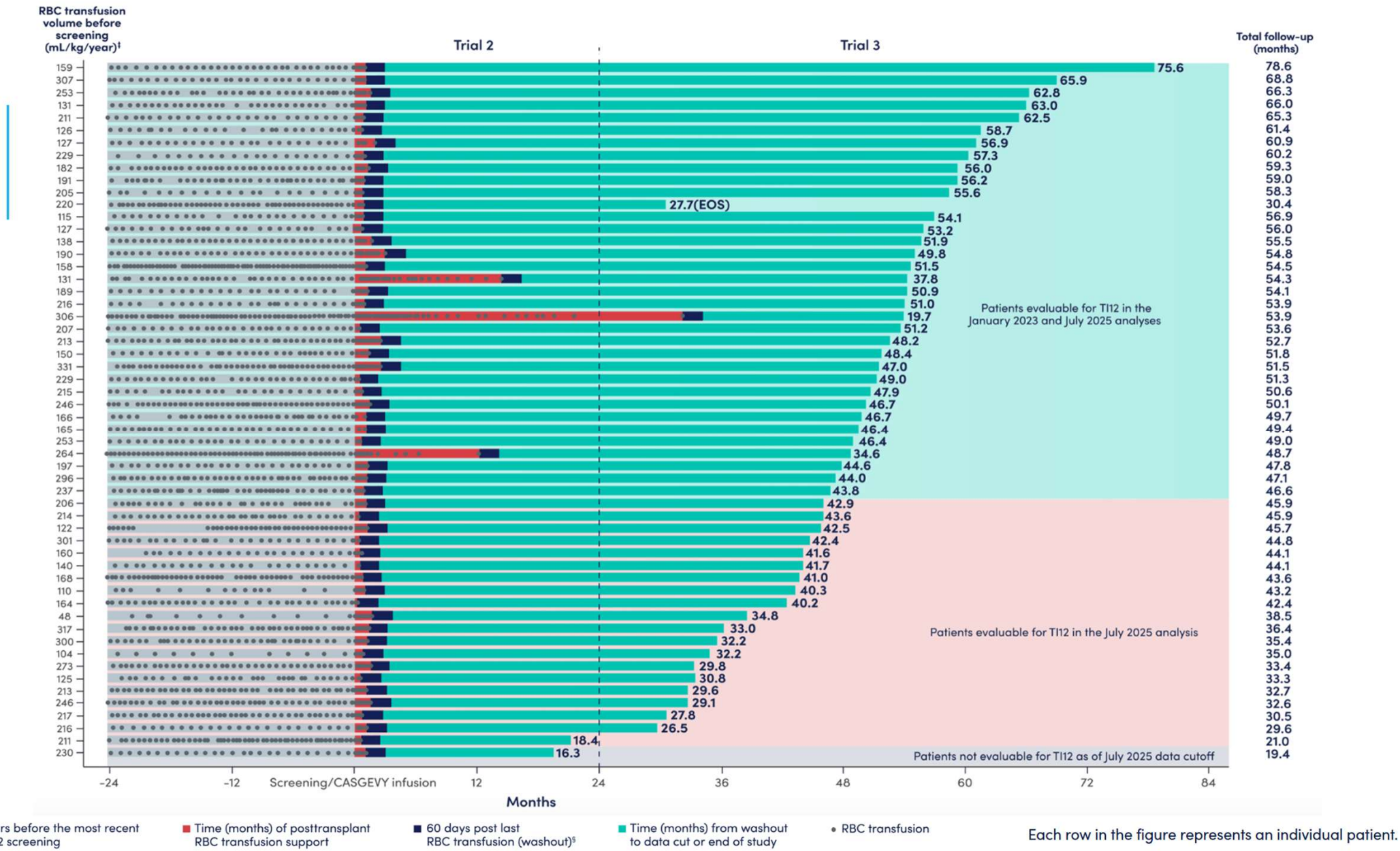
Please complete the following referral form: https://s3.eu-west-1.amazonaws.com/cdn.webfactore.co.uk/14668-_referral%20form_general_nhp%20mdt.%20v4%202024-12.docx

Refer to UCLH Cellular Therapies Service

Patients for consideration of gene therapy should be referred to the Cellular Therapies team in University College London Hospitals (UCLH) where they will be booked into clinic for an initial consultation to discuss the gene therapy process. If they choose to go ahead with the procedure, their follow up will continue with the London team in this clinic.

NHS
University Hospitals Bristol and Weston
NHS Foundation Trust

TDT EFFICACY - CLIMB THAL-111



Each row in the figure represents an individual patient.

TOXICITIES - TDT

Table 3. Grade 3 or 4 Adverse Events after Exa-Cel Infusion.

Adverse Event	Full Analysis Population (N=52)
	no. of patients (%)
Any grade 3 or 4 event	46 (88)
Grade 3 or 4 events occurring in ≥5% of patients*	
Febrile neutropenia	28 (54)
Stomatitis	21 (40)
Anemia	20 (38)
Platelet count decrease	18 (35)
Thrombocytopenia	18 (35)
Mucosal inflammation	17 (33)
Neutrophil count decrease	14 (27)
Decrease in appetite	12 (23)
Epistaxis	7 (13)
Neutropenia	7 (13)
White-cell count decrease	7 (13)
Veno-occlusive liver disease	5 (10)
Blood bilirubin increase	4 (8)
Hypokalemia	4 (8)
Hypophosphatemia	4 (8)
Iron overload	4 (8)
Nausea	4 (8)
Vomiting	4 (8)
CD4 lymphocyte count decrease	3 (6)
Hematuria	3 (6)
Headache	3 (6)
Hypoxia	3 (6)

* Terms for adverse events are adapted from the *Medical Dictionary for Regulatory Activities*, version 25.1, preferred terms.

SCD EFFICACY - CLIMB SCD-121

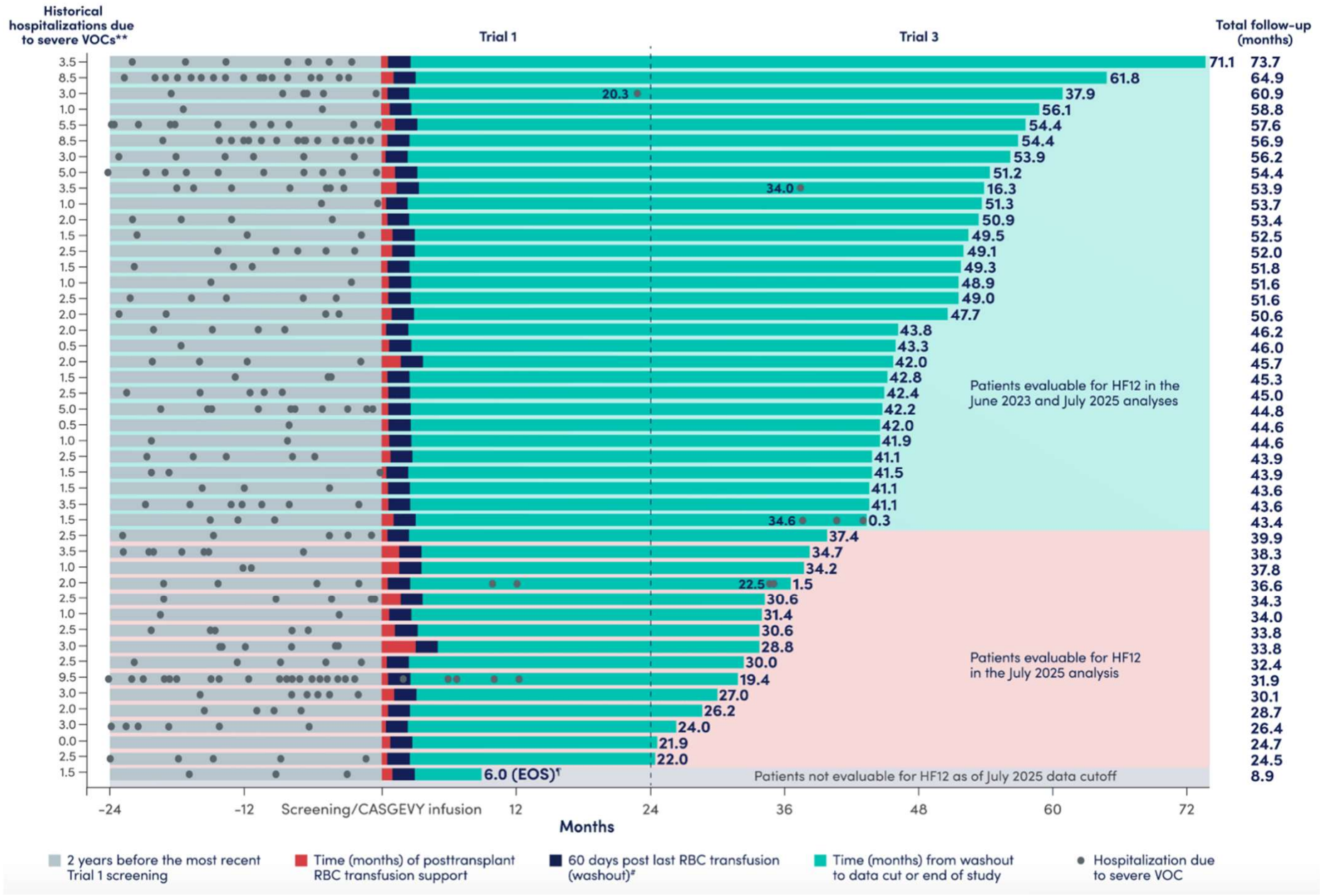
- VF12 defined as the proportion of patients **free from protocol-defined severe VOCs** for ≥12 consecutive months[1]

- HF12 defined as the proportion of patients **free from inpatient hospitalizations** for severe VOCs for ≥12 consecutive months[1]

Secondary endpoint: Median duration of protocol-defined severe-VOC-free period of patients who achieved VF12

(range: 14.8-45.5)§
(n=29, PES)

22.2 months†


Historical hospitalizations due to severe VOCs**
Trial 1
Trial 3
Total follow-up (months)
3.5 71.1 73.7
8.5 61.8 64.9
3.0 20.3 37.9 60.9
1.0 56.1 58.8
5.5 54.4 57.6
8.5 54.4 56.9
3.0 53.9 56.2
5.0 51.2 54.4
3.5 34.0 16.3 53.9
1.0 51.3 53.7
2.0 50.9 53.4
1.5 49.5 52.5
2.5 49.1 52.0
1.5 49.3 51.8
1.0 48.9 51.6
2.5 49.0 51.6
2.0 47.7 50.6
2.0 43.8 46.2
0.5 43.3 46.0
2.0 42.0 45.7
1.5 42.8 45.3
2.5 42.4 45.0
5.0 42.2 44.8
0.5 42.0 44.6
1.0 41.9 44.6
2.5 41.1 43.9
1.5 41.5 43.9
1.5 41.1 43.6
3.5 41.1 43.6
1.5 34.6 0.3 43.4
2.5 37.4 39.9
3.5 34.7 38.3
1.0 34.2 37.8
2.0 22.5 1.5 36.6
2.5 30.6 34.3
1.0 31.4 34.0
2.5 30.6 33.8
3.0 28.8 33.8
2.5 30.0 32.4
9.5 19.4 31.9
3.0 27.0 30.1
2.0 26.2 28.7
3.0 24.0 26.4
0.0 21.9 24.7
2.5 22.0 24.5
1.5 6.0 (EOS)¶ 8.9
Patients evaluable for HF12 in the June 2023 and July 2025 analyses
Patients evaluable for HF12 in the July 2025 analysis
Patients not evaluable for HF12 as of July 2025 data cutoff
-24
-12
Screening/CASGEVY infusion
12
24
36
48
60
72
Months
2 years before the most recent Trial 1 screening
Time (months) of posttransplant RBC transfusion support
60 days post last RBC transfusion (washout)#
Time (months) from washout to data cut or end of study
Hospitalization due to severe VOC

TOXICITIES - SCD

Table 3. Grade 3 or 4 Adverse Events after Exa-Cel Infusion.

Event	Full Analysis Population (N = 44)
	no. of patients (%)
Grade 3 or 4 adverse event	42 (95)
Grade 3 or 4 adverse event occurring in ≥5% of patients*	
Stomatitis	24 (55)
Febrile neutropenia	21 (48)
Platelet count decrease	21 (48)
Appetite decrease	18 (41)
Neutrophil count decrease	17 (39)
Mucosal inflammation	14 (32)
Anemia	11 (25)
Thrombocytopenia	11 (25)
Neutropenia	10 (23)
White-cell count decrease	6 (14)
Abdominal pain	5 (11)
CD4 lymphocyte count decrease	5 (11)
Cholelithiasis	5 (11)
Pruritus	5 (11)
Constipation	4 (9)
Headache	4 (9)
Nausea	4 (9)
Noncardiac chest pain	4 (9)
Pneumonia	4 (9)
Upper abdominal pain	3 (7)
Arthralgia	3 (7)
Back pain	3 (7)
Deep-vein thrombosis	3 (7)
Oropharyngeal pain	3 (7)
Pain	3 (7)
Weight decreased	3 (7)

* Adverse events are adapted from the *Medical Dictionary of Regulatory Activities*, version 26.0, preferred terms.

GRAFT SUCCESS

No GvHD or graft failures

Neutrophil engraftment: 27 (SCD) - 29 (TDT)

Platelet engraftment: 35 (SCD) - 44 (TDT)

Infertility

REMAINING QUESTIONS

Long-term HbF durability

2ndry malignancies / off-target CRISPR effects

Pre-existing chronic pain

How to prioritise/ensure equity of access within ~50/year ‘limit’


That's all Folks!

REFERENCES

Locatelli, F., Lang, P., Wall, D., Meisel, R., Corbacioglu, S., Li, A.M., De La Fuente, J., Shah, A.J., Carpenter, B., Kwiatkowski, J.L. and Mapara, M., 2024. Exagamglogene autotemcel for transfusion-dependent β-thalassemia. *New England Journal of Medicine*, *390*(18), pp.1663-1676.

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