EDITING GENOMICO

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SITE
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Disclosures of Franco Locatelli

Name of Company	Research Support	Employee	Consultant	Stockholder	Speaker's Bureau	Advisory Board	Other
Miltenyi					X		
Amgen					X	X	
Novartis					X	X	
BMS					X		
GILEAD					X		
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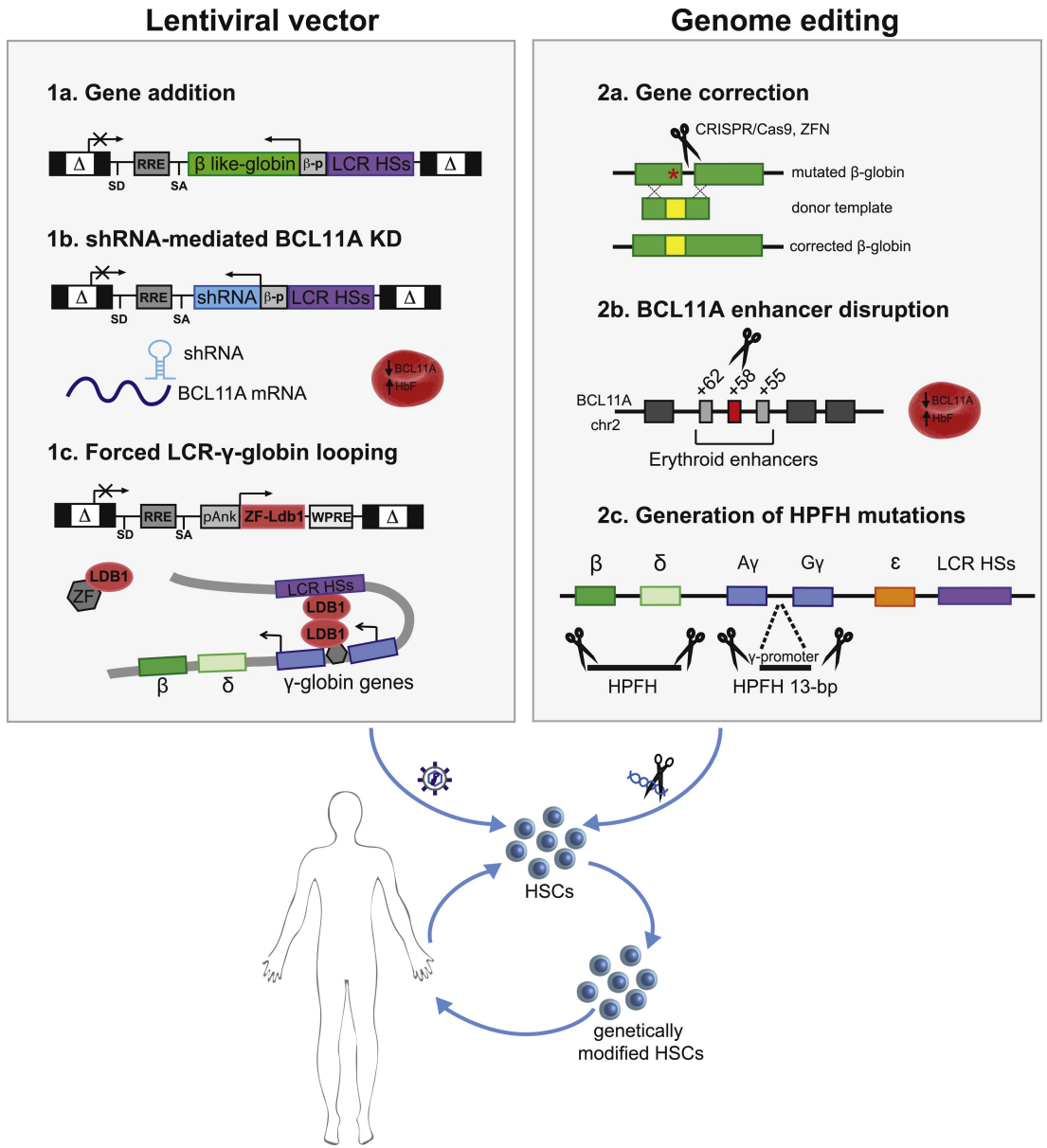
SOBI					X		
Vertex						X	

The paradigmatic model of gene therapy for Hemoglobinopathies

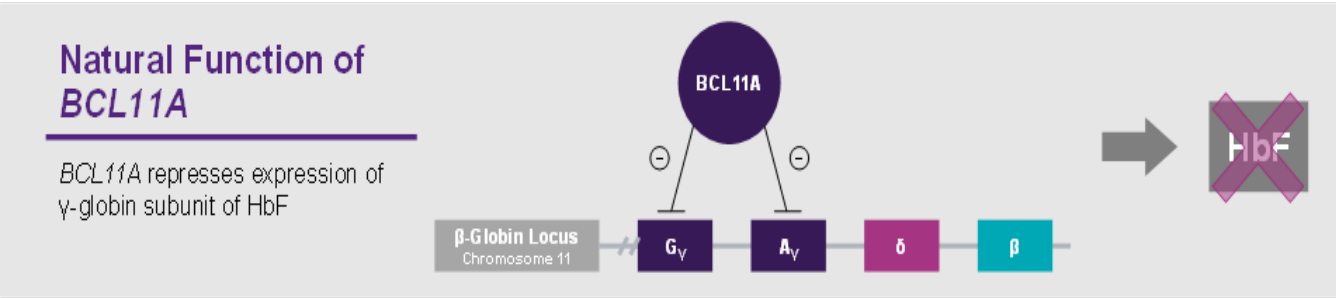
More Than One Option

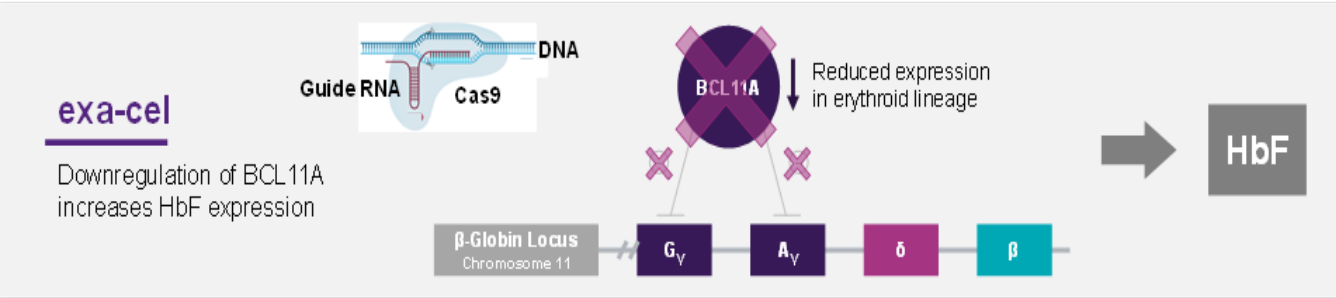
- Gene Therapy
- Genome Editing



Cavazzana et al. – Mol Therapy 2017

Exa-cel Mechanism of Action





- **Exa-cel** has been demonstrated to result in **durable transfusion independence** in patients with **TDT**[1]
- **Exa-cel** mechanism of action, grounded in human genetics, is the **reactivation of high levels of HbF**, which is known to result in **reduced morbidity and mortality** in patients with hemoglobinopathy and hereditary persistence of HbF[2,3]
- **Exa-cel** is produced using non-viral, *ex vivo* editing of the erythroid-specific enhancer region of BCL11A in $CD34^+$ HSPCs to **reduce erythroid-specific expression of *BCL11A*, resulting in reactivation of HbF**
- Infusion of **exa-cel increases HbF** to levels resulting in normal/near normal total Hb levels, **eliminating the need for RBC transfusions**[1]

***BCL11A*:** B-cell lymphoma/leukemia 11A; **Cas9:** CRISPR-associated 9 nuclease; **CRISPR:** clustered regularly interspaced short palindromic repeats; **DNA:** deoxyribonucleic acid; **exa-cel:** exagamglogene autotemcel; **Hb:** hemoglobin; **HbF:** fetal hemoglobin; **HSPC:** hematopoietic stem and progenitor cell; **RBC:** red blood cell; **RNA:** ribonucleic acid; **TDT:** transfusion dependent β-thalassemia.

1. Locatelli F, et al. *N Engl J Med*. 2024;390(18):1663-1676. 2. Musallam, KM, et al. *Blood*. 2013;121:2199-2212. **3**. Bauer DE, et al. *Curr Opin Gene Dev*. 2015;33:62-70.

Durable Clinical Benefits and Improvement of Tissue Iron Overload with Exagamglogene Autotemcel for Transfusion-Dependent β-Thalassemia

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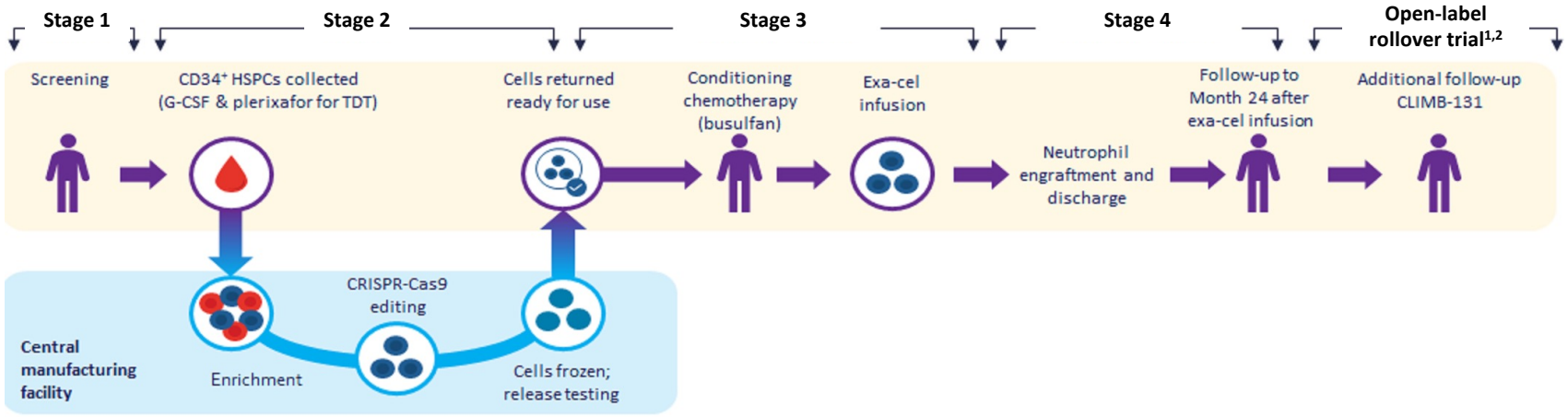
CLIMB THAL-111 Trial Design and Rollover into Long-Term Study CLIMB-131 for Exa-cel in TDT



CLIMB THAL-111[1,2]	
Study Design	• Global, multicentre, open-label, single-arm, 2-year Phase 1/2/3 trial of a single infusion of exa-cel (NCT03655678)
Participants	• 12 to 35 years of age with TDT defined as a history of ≥100 mL/kg/year or ≥10 units/year of RBC transfusions per year in the previous 2 years
Primary Efficacy Endpoint	• Proportion of participants transfusion independent for ≥12 consecutive months while maintaining a weighted average haemoglobin ≥9 g/dL (TI12) from 60 days after last RBC transfusion up to 24 months post-infusion
Secondary And Additional Efficacy Endpoints	• Duration of transfusion independence for participants who achieved T112 • Total Hb and HbF levels • Allelic editing at the intended locus in bone marrow CD34+ HSCs and peripheral blood cells • Measures of iron overload (Serum Ferritin, Liver Iron Concentration[a], and Cardiac Iron Content[b]) • Proportion of subjects receiving iron chelation therapy over time (Note: Analysis included all types of iron removal therapy, including phlebotomy)
CLIMB-131[3]	
Study Design	• Global, multicentre, open-label, rollover Phase 3 study to provide up to 15 years of long-term efficacy and safety follow-up (NCT04208529)
Primary Endpoints	• New malignancies, new or worsening hematologic disorders, all-cause mortality, serious adverse events, exa-cel related adverse events
Select Secondary Endpoints	• Proportion of participants achieving transfusion independence for ≥12 consecutive months (TI12) from 60 days after last RBC infusion up to 15 years post-infusion • Proportion of participants achieving transfusion independence for ≥6 consecutive months (TI6) from 60 days after last RBC infusion up to 15 years post-infusion

[a]Liver iron concentration measured by R2 MRI [b]Cardiac iron content measured by T2* MRI

CRISPR/Cas9, clustered regularly interspaced short palindromic repeats-associated 9 nuclease; **exa-cel,** exagamglogene autotemcel; **G-CSF,** granulocyte colony-stimulating factor; **HSPC,** hematopoietic stem and progenitor cell; **RBC,** red blood cell; **TDT,** transfusion dependent β-thalassemia.

1. Locatelli F et al. *N Engl J Med*. 2024;390(18):1663-1676. **2.** Locatelli F, et al. Poster Presented at 30th Annual European Hematology Association; 13 Jun 2025. Milan, Italy. **3.** Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT04208529. Accessed Jun 2025.

Baseline Characteristics, Demographics, and Treatment Features

CLIMB THAL-111

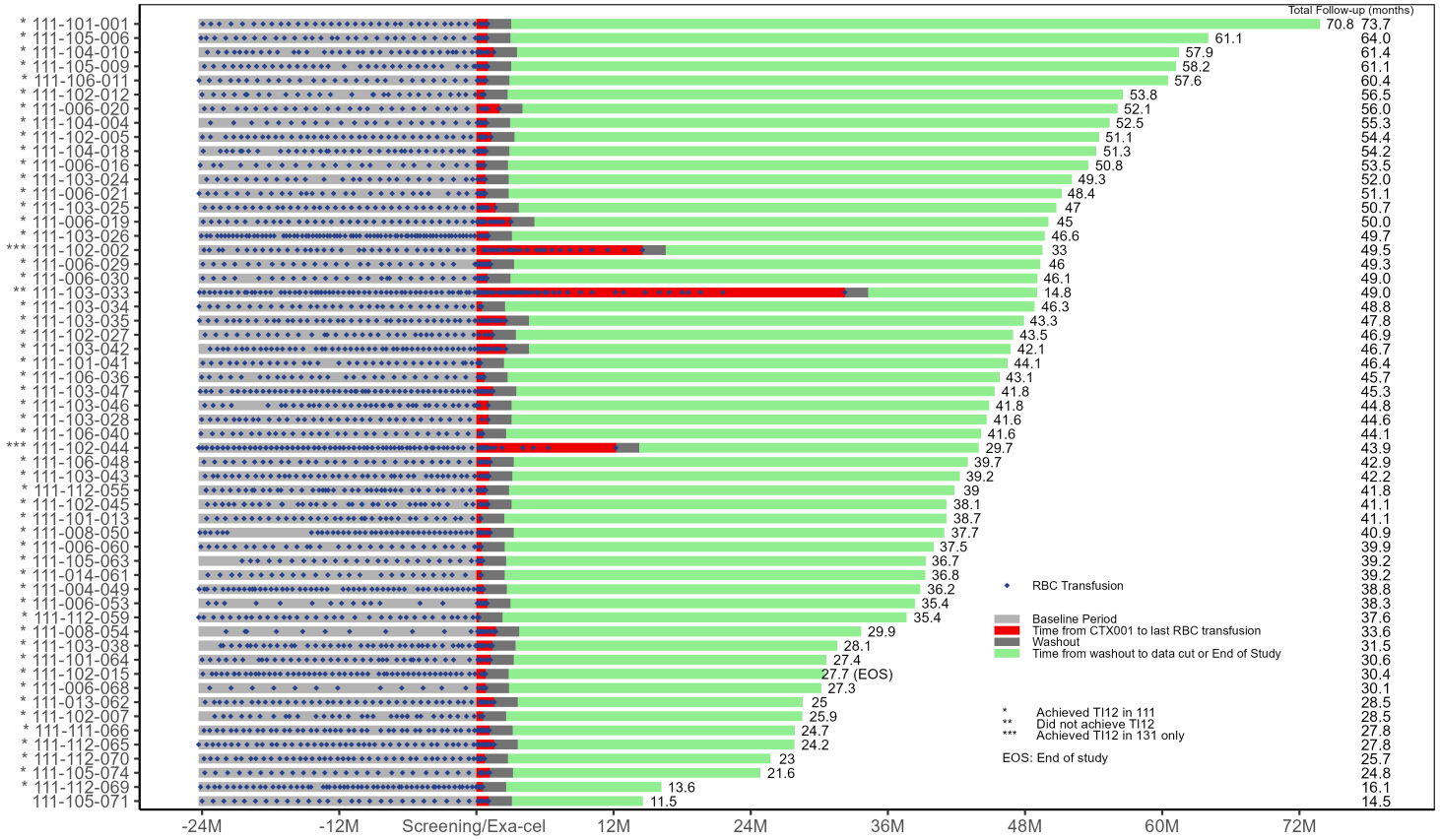
	Full Analysis Set[a] N = 56
Age (years) at screening, mean (SD)	21.2 (6.5)
≥12 and <18 years, n (%)	20 (35.7)
≥18 and ≤35 years, n (%)	36 (64.3)
Genotype, n (%)	
β^0/β^0	22 (39.3)
β^0/β^0-like (β^0/IVS-I-110; IVS-I-110/IVS-I-110)	13 (23.2)
Non-β^0/β^0-like	21 (37.5)
Serum Ferritin[b] (µg/L)	
median (IQR)	1280.5 (678.00, 1997.00)
range	260.0, 4823.0
Liver Iron Concentration[b] (mg/g)	
median (IQR)	3.6 (2.40, 6.25)
range	1.2, 14.8
Cardiac T2*[b] (msec)	
median (IQR)	34.0 (29.30, 39.45)
range	12.4, 61.1
Annualized volume of RBC transfusions (mL/kg), median (range)[c]	206.7 (48.3, 330.9)
Annualized units of RBC transfusions, median (range)[c]	36.0 (11.0, 71.0)
Duration (months) of follow-up after exa-cel, median (range)	44.7 (14.5, 73.7)

[a]Includes participants who received exa-cel infusion as of Feb 2025. 54 participants have completed CLIMB THAL-111 and 53 are currently enrolled in CLIMB-131 (1 withdrew consent in 131- not due to an adverse event).
[b]At baseline
[c]In the 2 years prior to enrollment

exa-cel, exagamglogene autotemcel; IQR, interquartile range; RBC, red blood cell; SD, standard deviation; TDT, transfusion-dependent β-thalassemia.

Locatelli F, et al. Poster Presented at 30th Annual European Hematology Association; 13 Jun 2025. Milan, Italy

Durable Transfusion Independence Achieved After Exa-cel (CLIMB THAL-111 and 131)



Durable transfusion independence achieved

- 98.2% (54/55) of evaluable participants achieved TI12 in CLIMB THAL-111 and CLIMB-131 combined (95% CI: 90.3%, 100%)
    - 94.5% (52/55) of evaluable participants achieved TI12 in CLIMB THAL-111 (95% CI: 84.9%, 98.9%)
- Mean duration of transfusion independence *40.5 months (range 13.6 to 70.8)*
- 1 participant who has not yet achieved TI12 has been transfusion free for the last 14.8 months

****** participant who has not yet achieved TI12 (due to not having weighted Hb ≥9g/dL)

EOS: end of study; **exa-cel:** exagamglogene autotemcel; **RBC:** red blood cell; **TI12:** transfusion independent for ≥12 consecutive months while maintaining a weighted average hemoglobin ≥9 g/dL.

Data are shown as of Feb 2025.

Participants Achieving TI12 After Exa-cel Infusion Across Subgroups[1]

Age Subgroup

	Adults n/N (%)	Adolescents n/N (%)
TDT: TI12	35/35 (100%)	18/19 (95%)

Genotype Subgroup

	β^0/β^0 and β^0/β^0 -like n/N (%)	Non-β^0/β^0 n/N (%)
TDT: TI12	32/33 (97%)	21/21 (100%)

- Consistent clinical benefits observed in participants across age and genotype subgroups in either CLIMB THAL-111 or CLIMB-131 combined

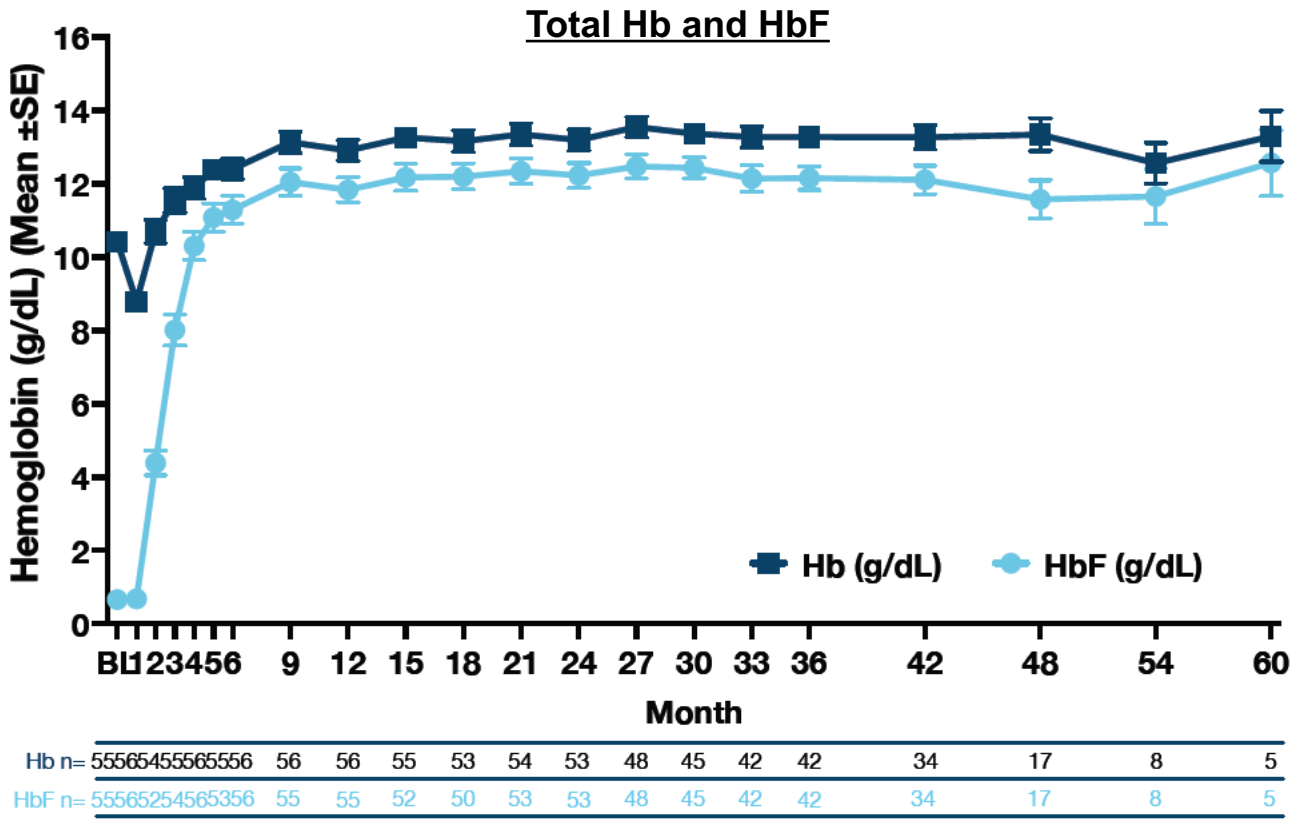
Data shown are based on Primary Efficacy Set, defined as participants evaluable for the primary endpoint as of Aug 2024.
TI12 is a primary endpoint in CLIMB THAL-111 and a secondary endpoint in CLIMB-131[2]

TI12, transfusion independent for ≥12 consecutive months while maintaining a weighted average hemoglobin ≥9 g/dL**; TDT,** transfusion-dependent β-thalassemia.

1. Locatelli F, et al. Presented at 66th Annual American Society of Hematology; 8 Dec 2024. San Diego, USA. **2.** Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT04208529. Accessed November 2024.

Total Haemoglobin and Foetal Hemoglobin[1]

CLIMB THAL-111 and CLIMB-131



- Normal or near normal levels of total Hb
- Durable high (>95%) proportion of red blood cells containing HbF (F-cells) observed after exa-cel in TDT[2]

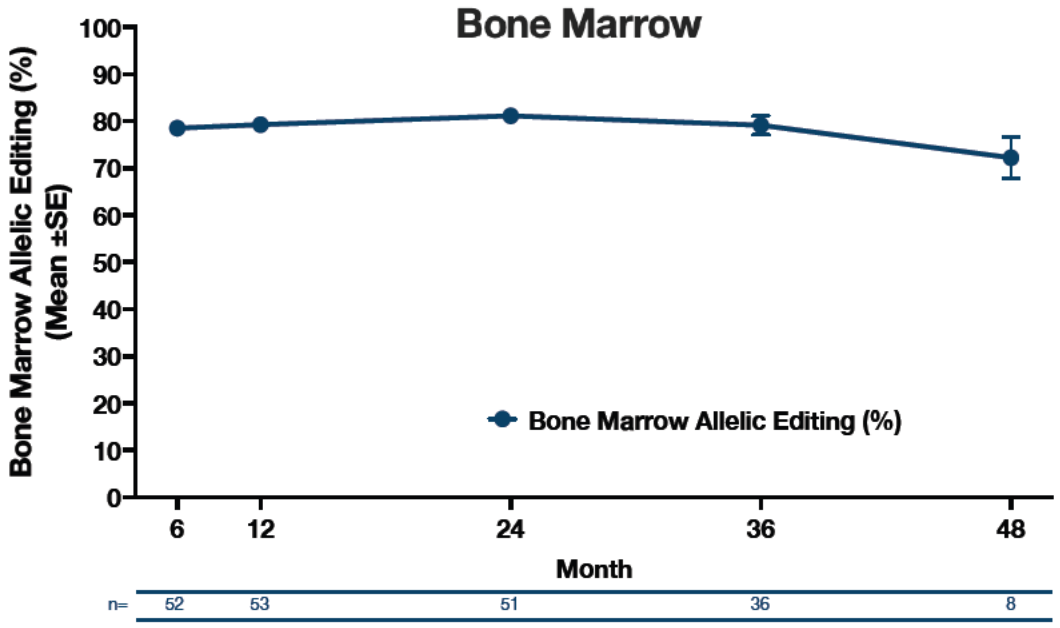
Data shown are as of Feb 2025. Figures depict data for all timepoints where at least 5 participants have completed the specified visit.

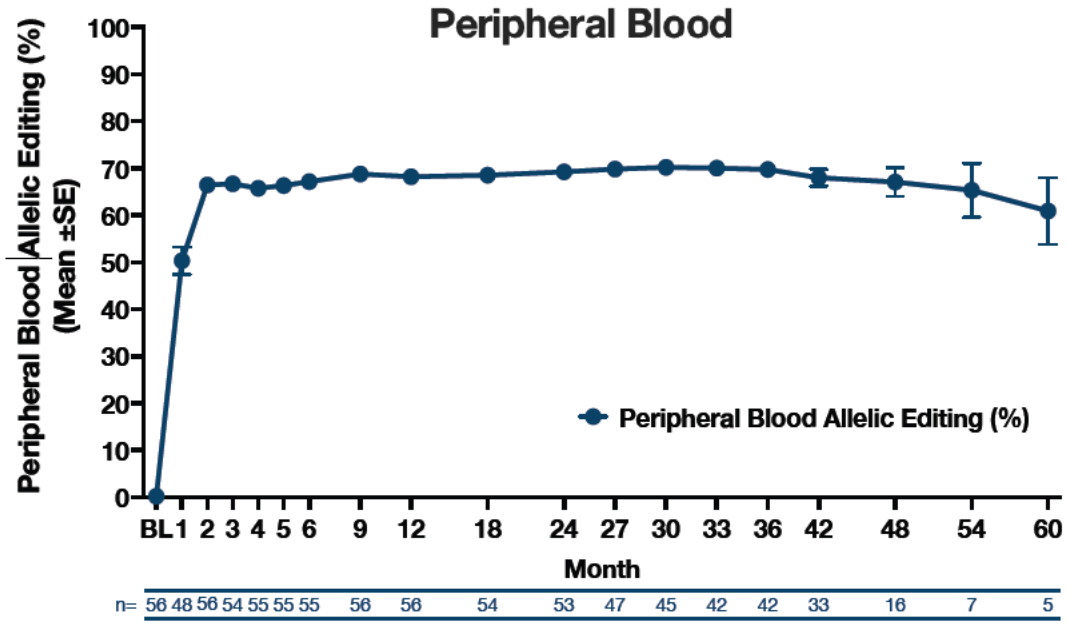
BL, baseline; Hb, haemoglobin; HbF, foetal haemoglobin; SE, standard error; TDT, transfusion-dependent β-thalassemia.

1. Locatelli F, et al. Poster Presented at 30th Annual European Hematology Association; 13 Jun 2025. Milan, Italy. 2. Locatelli F, et al. *N Engl J Med*. 2024;390(18):1663-1676.

BCL11A Editing in Bone Marrow and Peripheral Blood

CLIMB THAL-111 and CLIMB-131





- Successful editing of long-term HSCs consistent with durable clinical benefit
- Allelic editing in bone marrow and peripheral blood in individual participants was maintained over time

Data shown are as of Feb 2025. Figures depict data for all timepoints where at least 5 participants have completed the specified visit.

BL, baseline. HSCs, hematopoietic stem cells, SE, standard error.

Locatelli F, et al. Poster Presented at 30th Annual European Hematology Association; 13 Jun 2025. Milan, Italy.

Exa-cel Safety Profile Is Consistent With Myeloablative Busulfan Conditioning and Autologous HSCT

Table 2: AE Overview in CLIMB THAL-111	Exa-cel N = 56
Participants with	
Any AEs, n (%)	56 (100.0)
AEs related to exa-cel, n (%)[a]	16 (28.6)
AEs related to busulfan, n (%)[a]	55 (98.2)
AEs Grade 3/4, n (%)	50 (89.3)
SAEs, n (%)	19 (33.9)
SAEs related to exa-cel, n (%)[a,b]	2 (3.6)
AEs leading to death, n (%)	0
Any malignancies, n (%)	0

All participants engrafted neutrophils and platelets. Data are presented from exa-cel infusion to Month 24.
[a] Includes related and possibly related AEs (or SAEs).[b] SAEs previously reported in 2 participants and fully resolved. One participant had SAEs starting peri-engraftment and in context of HLH (HLH, acute respiratory distress syndrome, and headache were related to exa-cel; idiopathic pneumonia syndrome was related to exa-cel and busulfan). One participant had SAEs of delayed neutrophil engraftment and thrombocytopenia both related to exa-cel and busulfan (neutrophil engraftment achieved on Day 56 without use of backups cells).

Table 3: Common AE in CLIMB THAL-111	
Preferred Term, n (%)	**Exa-cel N = 46**
Febrile neutropenia	34 (60.7)
Headache	31 (55.4)
Stomatitis	30 (53.6)
Thrombocytopenia	25 (44.6)
Anemia	25 (44.6)
Nausea	24 (42.9)
Mucosal inflammation	23 (41.1)
Vomiting	23 (41.1)
Abdominal pain	23 (41.1)

Table includes common AEs occurring in ≥40% of participants from exa-cel infusion through Month 24.

- In long-term follow up study CLIMB-131, of 54 participants enrolled, there were no subjects with AEs related to exa-cel with onset after Month 24; 6 (11.1%) had SAEs (none related to exa-cel). There were no malignancies or deaths.

7 (12.5%) participants had VOD events
- all events were related to busulfan conditioning
- all events resolved after defibrotide treatment without any participant receiving ventilatory support or dialysis

- Most AEs occurred in the first 6 months with rates decreasing over time; safety is consistent in adolescents and adults.

Data shown are as of Feb 2025.
AE: adverse event; **exa-cel:** exagamglogene autotemcel; **HLH:** hemophagocytic lymphohistiocytosis; **HSCT:** hematopoietic stem cell transplantation; **SAE:** serious adverse event; **VOD:** venoocclusive liver disease.

Summary of Reported Adverse Events

CLIMB THAL-111 and CLIMB-131

AE Overview in CLIMB THAL-111	Exa-cel N = 56
Any AEs, n (%)	56 (100.0)
AEs related to exa-cel, n (%)[a]	16 (28.6)
AEs related to busulfan, n (%)[a]	55 (98.2)
AEs Grade 3/4, n (%)	50 (89.3)
SAEs, n (%)	19 (33.9)
SAEs related to exa-cel, n (%)[b]	2 (3.6)
AEs leading to death, n (%)	0
Any malignancies, n (%)	0

All participants engrafted neutrophils and platelets. Data are presented from exa-cel infusion to Month 24.
[a]Includes related and possibly related AEs (or SAEs).[b] SAEs previously reported in 2 participants and fully resolved. One participant had SAEs starting peri-engraftment and in context of HLH (HLH, acute respiratory distress syndrome, and headache were related to exa-cel; idiopathic pneumonia syndrome was related to exa-cel and busulfan). One participant had SAEs of delayed neutrophil engraftment and thrombocytopenia both related to exa-cel and busulfan (neutrophil engraftment achieved on Day 56 without use of backups cells).

Common AEs in CLIMB THAL-111, n (%)	Exa-cel N = 56
Febrile neutropenia	34 (60.7)
Headache	32 (57.1)
Stomatitis	30 (53.6)
Thrombocytopenia	25 (44.6)
Anemia	25 (44.6)
Nausea	25 (44.6)
Abdominal pain	24 (42.9)
Mucosal inflammation	23 (41.1)
Vomiting	23 (41.1)

Table includes common AEs occurring in ≥40% of participants from exa-cel infusion through Month 24.

- Most AEs occurred in the first 6 months with rates decreasing over time; safety is consistent in adolescents and adults.
- In CLIMB-131, of 54 participants enrolled, there were no subjects with AEs considered related to exa-cel; 6 (11.1%) had SAEs (none related to exa-cel
- No malignancies or deaths

7 (12.5%) participants had VOD events
- all events were related to busulfan conditioning
- all events resolved after defibrotide treatment without any participant receiving ventilatory support or dialysis

Exa-cel safety profile is consistent with myeloablative busulfan conditioning and autologous HSCT

Data shown are as of Feb 2025.
AE, adverse event; exa-cel, exagamglogene autotemcel; HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplantation; SAE, serious adverse event; VOD, venoocclusive liver disease.
Locatelli F, et al. Poster Presented at 30th Annual European Hematology Association; 13 Jun 2025. Milan, Italy.

Iron Removal Therapy After Exa-cel

CLIMB THAL-111 and CLIMB-131

Iron Removal Therapy after Exa-cel	
	Full Analysis Set[a] N = 56
Participants who restarted iron chelation and/or phlebotomy after exa-cel, n (%)	56 (100%)
Participants who received chelation alone, n (%)	17 (30.4%)
Participants who received phlebotomy alone, n (%)	19 (33.9%)
Participants who received both chelation and phlebotomy, n (%)	20 (35.7%)
Median (range) time to restarting iron removal therapy (months), n = 56	6.6 (2.0, 27.4)
Median (range) time to restarting chelation (months), n = 37	6.6 (2.0, 30.1)
Median (range) time to restarting phlebotomy (months), n = 39	9.4 (2.9, 37.0)
Median (range) duration of iron removal therapy (months), n = 56	18.2 (1.0, 50.1)
Participants who stopped and were off chelation and/or phlebotomy for at least 6 months, n (%)	**39 (69.6%)**

- All participants (56/56, 100%) resumed iron removal therapy (chelation and/or phlebotomy) after exa-cel
- Due to improvements in measures of tissue iron overload, 39/56 (69.6%) were able to stop iron removal therapy[b]

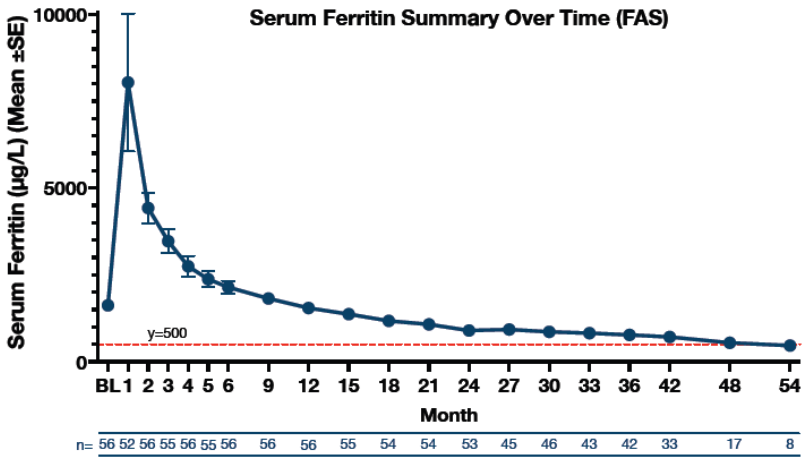
[a]Includes participants who received exa-cel infusion as of Feb 2025.
[b]Includes participants who were off iron removal therapy for at least 6 months .

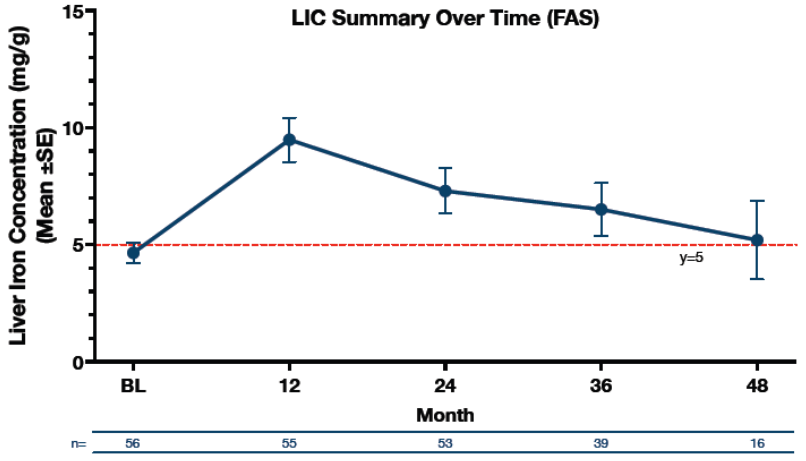
exa-cel, exagamglogene autotemcel.

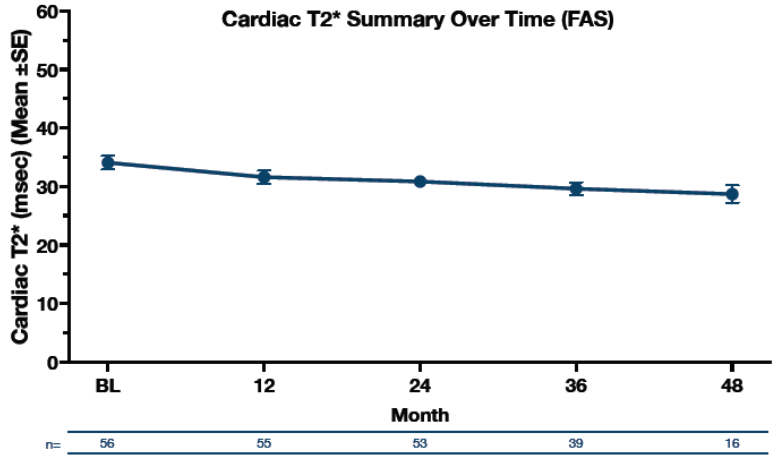
Locatelli F, et al. Poster Presented at 30th Annual European Hematology Association; 13 Jun 2025. Milan, Italy.

Improvement in Iron Overload Measures After Exa-cel[1]

CLIMB THAL-111 and CLIMB-131







- Iron overload measures progressively improve after exa-cel, consistent with the known slow kinetics of the removal of storage iron post-HSCT[2,3]
  - Mean serum ferritin levels decrease to below baseline by Month 12, and to below 500 mcg/L by Month 54[4]
  - Liver iron concentration (LIC) decreases to mean ~5 mg/g[4] by Month 48
  - Cardiac T2* mean levels were normal at baseline, and remained >20 msec throughout the study
  - Initial increases in serum ferritin and LIC are expected due to pre-exa-cel hyper-transfusion, myeloablative conditioning, and post-infusion RBC support while chelation therapy was withheld per protocol.

Data shown are as of Feb 2025. Figures depict data for all timepoints where at least 5 participants have completed the specified visit. LIC was measured using R2 MRI. Red dashed line indicates protocol recommended level to stop iron removal therapy.

BL: baseline, exa-cel: exagamglogene autotemcel, FAS: Full Analysis Set; LIC: liver iron concentration, MRI: magnetic resonance imaging, SE: standard error

1. Locatelli F, et al. Poster Presented at 30th Annual European Hematology Association; 13 Jun 2025. Milan, Italy. 2. Chaudhury S, et al. Biol Blood Marrow Transplant. 2017;23(10):1695-700. 3. Angelucci et al. Blood. 1997;90(3):994-8. 4. Locatelli F, et al. *N Engl J Med*. 2024;390(18):1663-1676. .

Health-Related Quality of Life in Patients with Transfusion-Dependent β-Thalassemia Following Exa-cel Infusion

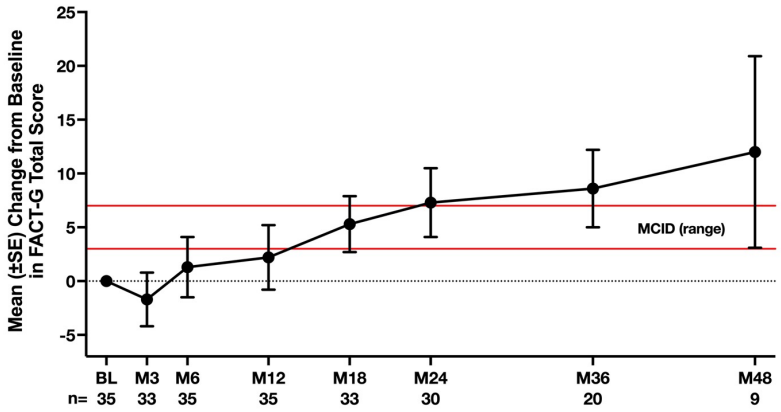
Context of Research

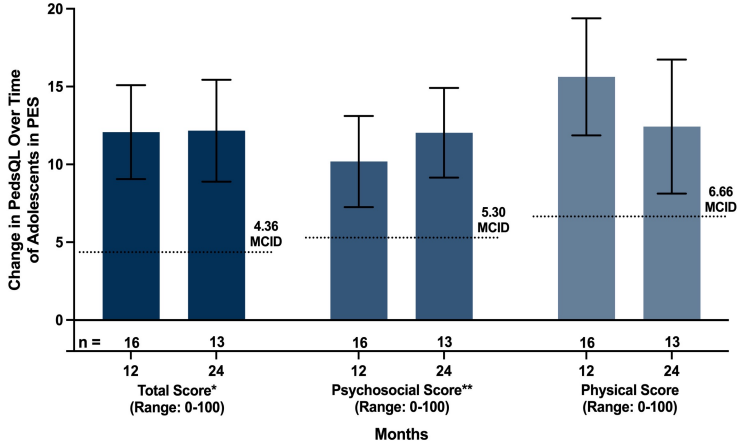
Exagamglogene autotemcel (exa-cel) is a one-time, ex vivo CRISPR-Cas9 gene-edited cell therapy for transfusion-dependent β-thalassemia (TDT) shown in a Phase 3 clinical trial to result in transfusion independence in most participants

Aim of This Study

To understand changes in patient-reported quality of life in adults (18 to 35 years) and adolescents (12 to <18 years) with TDT following exa-cel infusion

Findings





Results: Adults (n=35) had increases in all measures of overall well-being and quality of life that exceeded established minimal clinically important differences (MCIDs) and were maintained through the 4-year follow up period.

Results: Adolescents (n=19) had increases in all measures of overall well-being and physical and psychosocial health that exceeded established MCIDs and were maintained through the 2-year follow up period.

Conclusions: Exa-cel infusion led to broad and clinically-meaningful improvements in patient-reported quality-of-life in both adults and adolescents with TDT.

De la Fuente et al. Blood Advances 2025, in press.

Conclusions

- **Long-term follow-up to over 6 years demonstrates that all TDT participants achieved durable clinical benefits**
  - **98.2% achieved transfusion independence**
  - **Mean duration of transfusion independence 40.5 months (range 13.6 to 70.8)**
  - **Durable increases in HbF resulting in total hemoglobin at normal or near normal levels**
  - **Stable allelic editing in bone marrow and peripheral blood, demonstrates durable editing of long-term HSCs**
- **Safety profile consistent with myeloablative busulfan conditioning and autologous HSCT; no malignancies**
- **Storage iron can be successfully removed by iron removal therapy (chelation and/or phlebotomy) after exa-cel**
- **70% of participants were able to discontinue iron removal therapy after exa-cel**
- **Ferritin and LIC remain generally stable for up to 57.2 months of follow-up after iron removal therapy discontinuation suggesting that exa-cel has the potential to correct ineffective erythropoiesis**
- **Long term follow-up continues to demonstrate that exa-cel has the potential to provide a one-time functional cure to patients with TDT**

exa-cel: exagamglogene autotemcel; **HbF**: fetal hemoglobin; **HSCT,** hematopoietic stem cell transplantation; **LIC**: liver iron concentration; **TDT:** transfusion-dependent β-thalassemia

Durable Clinical Benefits with Exagamglogene Autotemcel for Sickle Cell Disease with Recurrent Vaso-occlusive Crisis and Factors Impacting CD34+ Hematopoietic Stem Cell Collection

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Exa-cel Pivotal Phase 3 Trial Design

SCD: CLIMB SCD-121 (NCT03745287)	
Study Design	Global, multicenter, open-label, single-arm, 2-year Phase 1/2/3 trial of a single infusion of exa-cel
Participants	12 to 35 years of age with severe SCD and a history of ≥2 severe VOCs per year in the previous 2 years
Primary and Key Secondary Efficacy Endpoint	**Primary:** Proportion of participants **free of severe VOCs for ≥12 consecutive months (VF12)** **Key Secondary:** Proportion of participants **free from in-patient hospitalization for severe VOCs for ≥12 consecutive months (HF12)**
Secondary And Additional Efficacy Endpoints	• **Duration of VOC freedom for participants who achieved VF12** • **Total Hb and HbF levels** • **Allelic editing at the intended locus in bone marrow CD34⁺ HSCs and peripheral blood cell**
Method for Assessing Factors Impacting CD34⁺ HSPC collection	• **Clinical factors assessed were measures of disease severity (annualized rates of severe VOCs, inpatient hospitalizations for severe VOCs, annualized duration of inpatient hospitalizations for severe VOCs, annualized RBC units transfused for SCD-related indication), hemolysis markers (lactate dehydrogenase, haptoglobin, indirect bilirubin, reticulocyte count), additional laboratory measures (Total Hb, WBC, platelet count, alkaline phosphatase, pre-transfusion HbS % before Cycle 1, Post-Transfusion HbS % before Cycle 1, HbS % (Cycle 1 Day 1), HbF %, C-reactive protein), and other factors (sex).** • **Average number of CD34+ cells collected (cells/kg/cycle) was calculated for each participant and was correlated with each factor** • **Univariate analysis was done using Pearson's correlation for continuous variable except that p-value for sex is based on Wilcoxon rank sum test** • **A Mixed Model for Repeated Measures (MMRM) analysis was done to show that cell collection from each cycle do not vary over cycles**

CLIMB 131 (NCT04208529)

Global, multicenter, open-label, rollover Phase 3 study to provide up to 15 years of long-term efficacy and safety follow-up

exa-cel: exagamglogene autotemcel; **Hb**: hemoglobin; **HbF**: fetal hemoglobin**; HbS**; sickle hemoglobin; **HSCs**: hematopoietic stem cells; **HSPC**: hematopoietic stem and progenitor cells; **RBC**: red blood cell; **SCD**: sickle cell disease; **VOC**: vaso-occlusive crisis; **WBC**: white blood cell

Baseline Characteristics, Demographics & Treatment Features

CLIMB SCD-121

	Full Analysis Set[a] N = 46
Age (years) at screening, mean (SD)	21.4 (6.0)
≥12 and <18 years, n (%)	12 (26.1)
≥18 and ≤35 years, n (%)	34 (73.9)
Genotype, n (%)	
β^s/β^s	41 (89.1)
β^s/β^0	3 (6.5)
β^s/β^+	2 (4.3)
Historical VOC episodes per year[b], mean (range)	4.2 (2.0, 18.5)
Historical inpatient hospitalizations for severe VOCs per year[b], mean (range)	2.7 (0.0, 9.5)
Duration (months) of follow-up after exa-cel infusion, median (range)	39.8 (8.9, 68.8)

[a] Full Analysis Set includes participants who received exa-cel infusion as of Feb 2025.
[b] Annualized over 2 years before screening

exa-cel, exagamglogene autotemcel; SD, standard deviation; VOC, vaso-occlusive crisis.

Frangoul H, et al. Poster presented at 30th Annual European Hematology Association; 13 Jun 2025. Milan, Italy.

Mobilisation and Apheresis Characteristics

CLIMB SCD-121

	Full Analysis Set[a] N = 46	
No. of mobilisation/apheresis cycles needed for Drug Product, mean (range)	2.4 (1, 6)	
	Adolescents N = 12	**Adults** N = 34
No. of participants requiring 1-2 mobilisation/apheresis cycles for drug product	11 (91.7%)	19 (55.9%)
No. of participants requiring >2 mobilisation/apheresis cycles for drug product	1 (8.3%)	15 (44.1%)
Baseline (pre-plerixafor) CD34$^+$ cells/µL, Cycle1 Day 1; mean (range)	14.9 (2.8, 38.0)	7.7 (1.1, 20.0)
Pre-apheresis (2 hrs post-plerixafor) CD34+ cells/µL, Cycle1 Day1 mean (range)	88.2 (11.0, 178.7)	50.1 (11.4, 189.0)

[a] Includes participants who received exa-cel infusion as of Feb 2025.

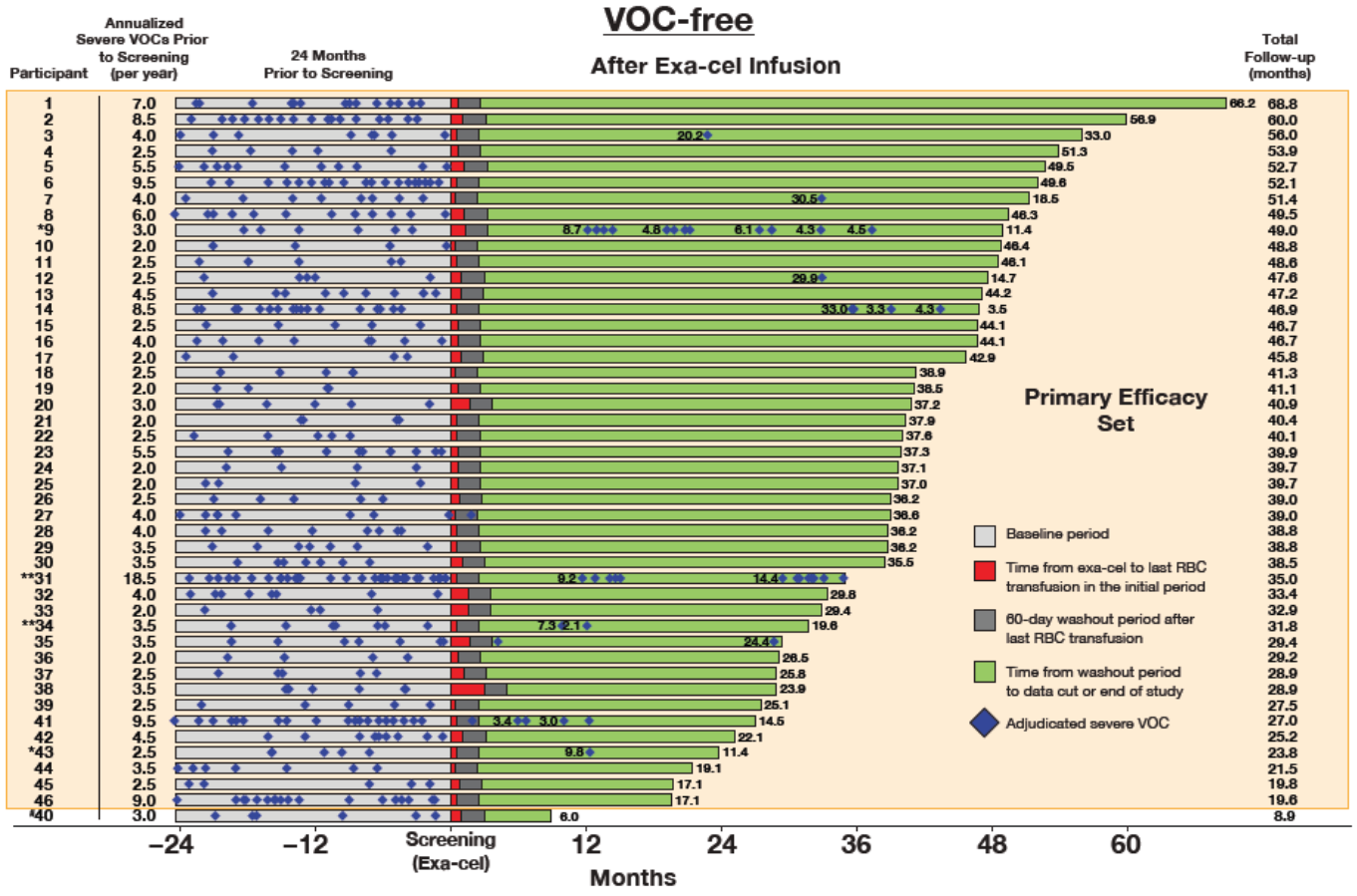
- Adolescents underwent fewer cycles to achieve a Drug Product than adults (92% of adolescents achieved a Drug Product in 1-2 cycles) and had higher pre-plerixafor and pre-apheresis (2 hours post-plerixafor) peripheral blood CD34$^+$ cell counts than adults

Adolescents: ≥12 and <18 years; Adults: ≥18 and ≤35 years.

Frangoul H, et al. Poster presented at 30th Annual European Hematology Association; 13 Jun 2025. Milan, Italy.

VOC-Free Status After Exa-cel Infusion[1]

CLIMB SCD-121 and CLIMB-131



- 91.1% (41/45) of evaluable participants achieved VF12 in CLIMB SCD-121 (95% CI: 78.8%, 97.5%)
- 95.6% (43/45) of evaluable participants achieved VF12 in CLIMB SCD-121 and CLIMB-131 combined (95% CI: 84.9%, 99.5%)
  - Mean duration of VOC-free period is 35.0 months (range 14.4 to 66.2)
  - VOCs after exa-cel were all acute pain events. These pain events generally occurred in adult participants with a history of chronic pain and/or following an identifiable pain trigger (e.g., infections, procedures and psychosocial stressors)

*participants who have not achieved VF12; **participants who achieved VF12 in CLIMB-131 only; **#**participant died from respiratory failure due to COVID-19 infection; not related to exa-cel. Numerical values before the VOC indicate the number of months a participant was VOC-free since the washout period/previous VOC. VOCs were adjudicated by an independent data monitoring committee. Data shown are as of Feb 2025.

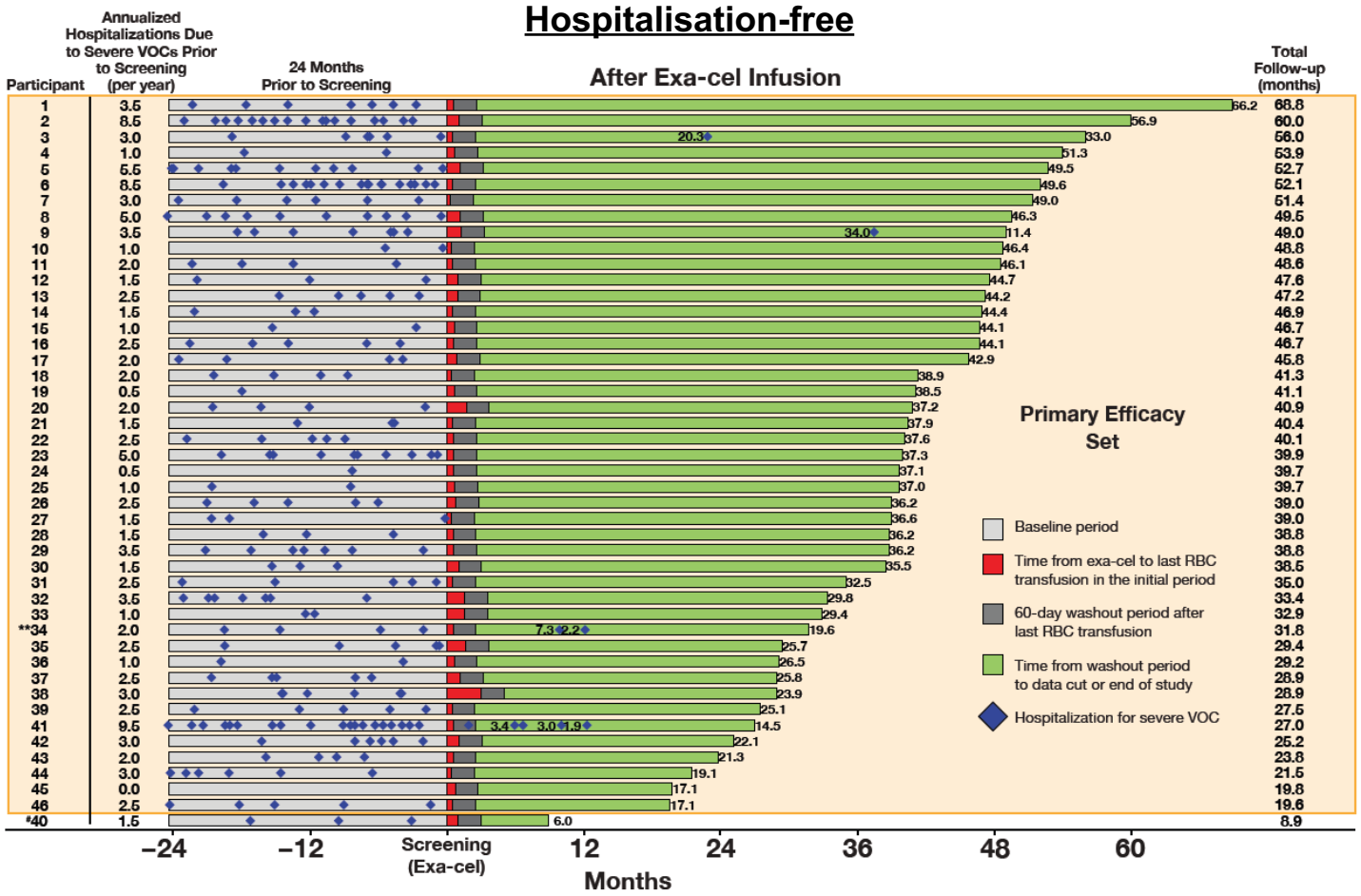
[a]VF12 is a primary endpoint in CLIMB SCD-121 and a secondary endpoint in CLIMB-131[2]

exa-cel, exagamglogene autotemcel; RBC, red blood cell; VF12, free of severe VOCs for ≥12 consecutive months; VOC, vaso-occlusive crisis

1. Frangoul H, et al. Poster presented at 30th Annual European Hematology Association; 13 Jun 2025. Milan, Italy. **2.** Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT04208529. Accessed Jun 2025.

Hospitalisation-Free Status After Exa-cel Infusion[1]

CLIMB SCD-121 and CLIMB-131



- 97.8% (44/45) of evaluable participants achieved HF12 in CLIMB SCD-121 (95% CI: 88.2%, 99.9%)
- 100% (45/45) of participants achieved HF12 in CLIMB SCD-121 and 131 combined (95% CI: 92.1%, 100%)
  - Mean duration of hospitalisation-free period is 36.1 months (range 14.5 to 66.2)

**participants who achieved HF12 in CLIMB-131 only; #participant died from respiratory failure due to COVID-19 infection; not related to exa-cel.
Numerical values before the hospitalisation indicate the number of months a participant was hospitalisation-free since the washout period/previous hospitalization.

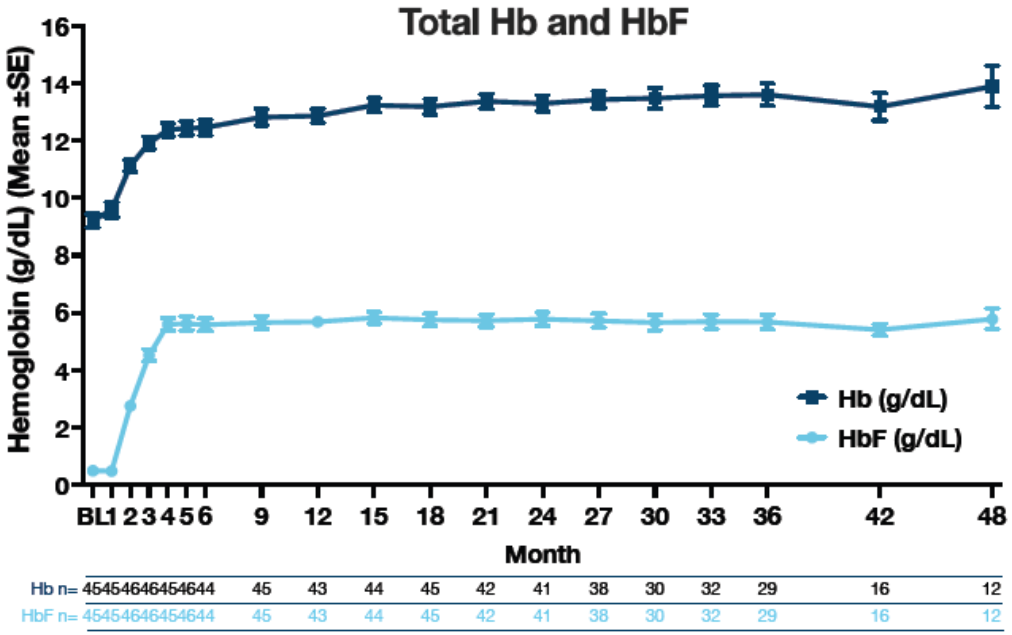
[a]HF12 is a secondary endpoint in CLIMB SCD-121 and CLIMB-131[2]

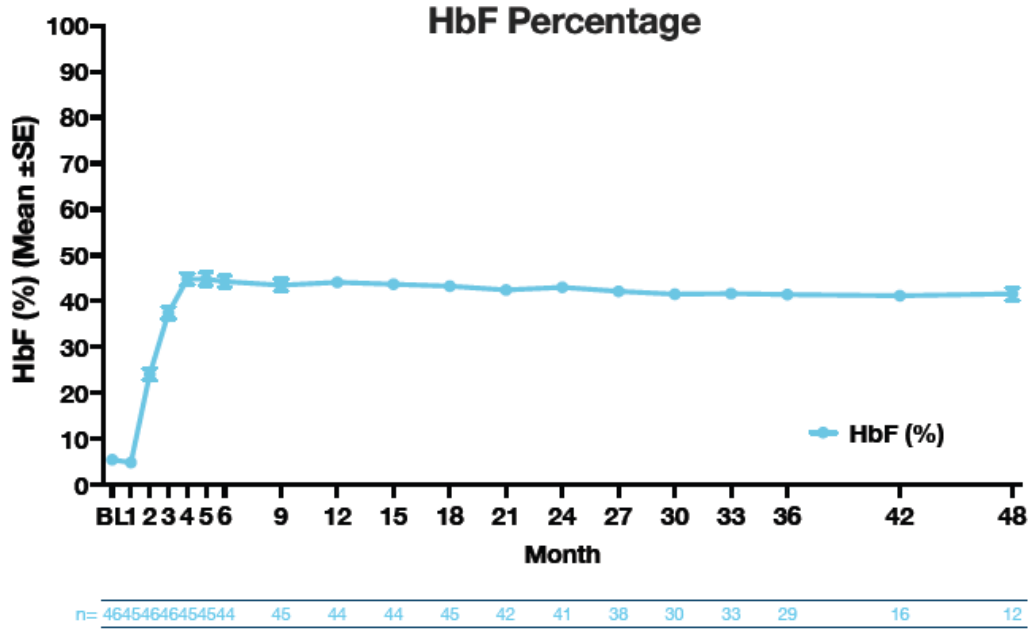
exa-cel, exagamglogene autotemcel; RBC, red blood cell; HF12, free from hospitalisation for severe VOCs for ≥12 consecutive months; VOC, vaso-occlusive crisis.

1. Frangoul H, et al. Poster presented at 30th Annual European Hematology Association; 13 Jun 2025. Milan, Italy. USA. **2.** Clinicaltrials.gov. https://clinicaltrials.gov/ct2/show/NCT04208529. Accessed Jun 2025.

Total Haemoglobin and Foetal Hemoglobin[1]

CLIMB SCD-121 and CLIMB-131





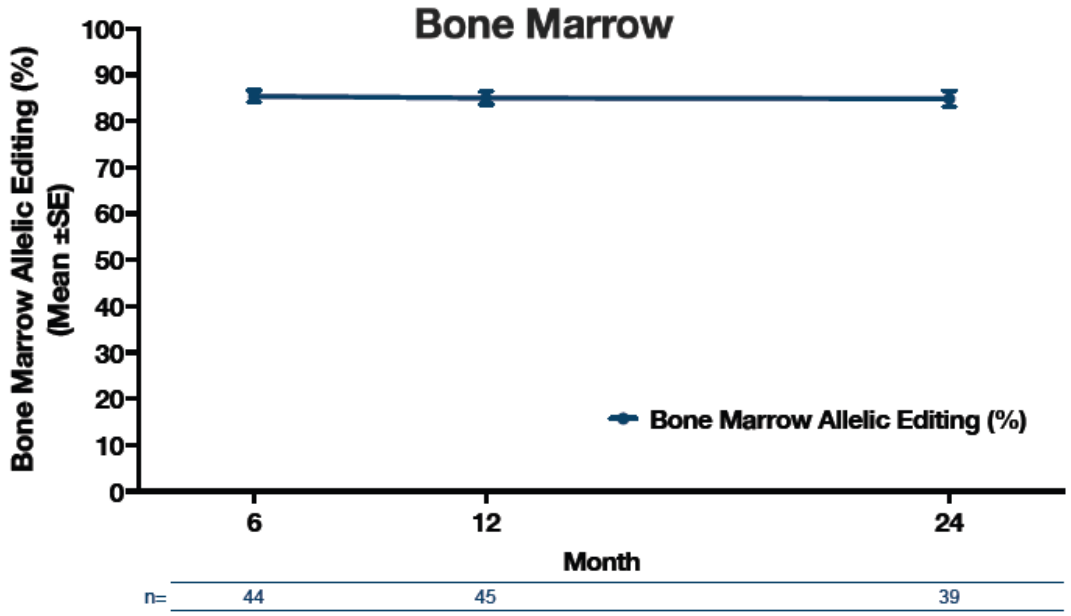
- Foetal hemoglobin increases to ~40%
- Pancellular HbF distribution (durable > 95% proportion of red blood cells containing HbF [F-cells]) and clinically meaningful improvements in measures of haemolysis are observed after exa-cel[2]

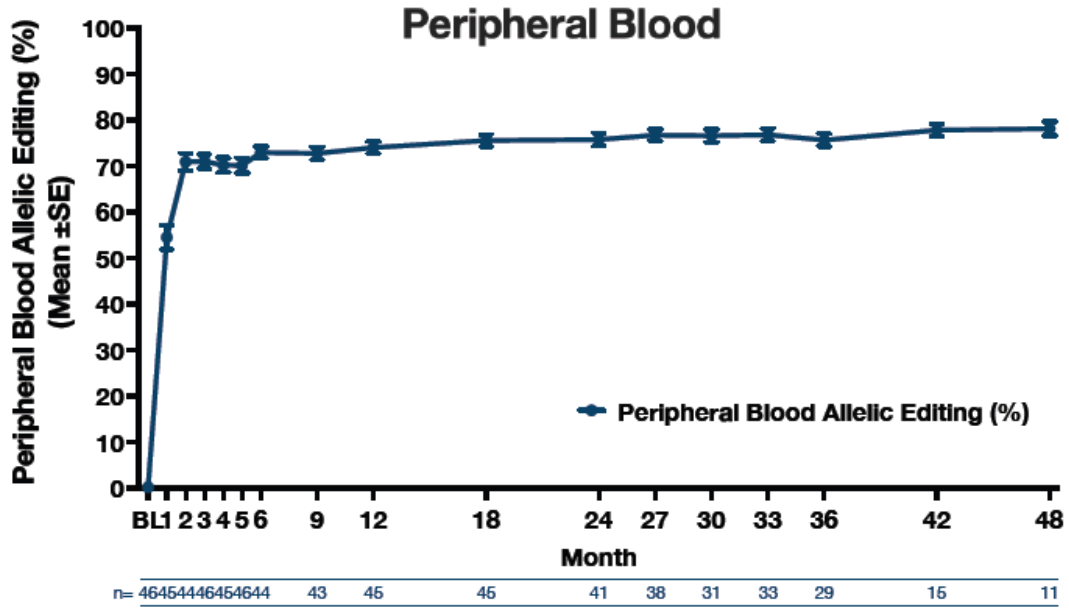
Data shown are as of Feb 2025. Figures depict data for all timepoints where at least 5 participants have completed the specified visit.
BL, baseline; Hb, haemoglobin; HbF, foetal hemoglobin; SE, standard error.

1. Frangoul H, et al. Poster presented at 30th Annual European Hematology Association; 13 Jun 2025. Milan, Italy. 2. Frangoul H, et al. *N Engl J Med*. 2024;390(18):1649-1662.

BCL11A Editing in Bone Marrow and Peripheral Blood

CLIMB SCD-121 and CLIMB-131





- Successful editing of long-term HSCs consistent with durable clinical benefit

Data are shown are as of Feb 2025. Figures depict data for all timepoints where at least 5 participants have completed the specified visit.
BL, baseline; HSCs, haematopoietic stem cells; SE, standard error.

1. Frangoul H, et al. Poster presented at 30th Annual European Hematology Association; 13 Jun 2025. Milan, Italy.

Summary of Adverse Events

CLIMB SCD-121 and CLIMB-131

AE Overview in CLIMB SCD-121	Exa-cel N = 46
Any AEs, n (%)	46 (100.0)
AEs related to exa-cel, n (%)[a]	13 (28.3)
AEs related to busulfan, n (%)[a]	46 (100.0)
AEs Grade 3/4, n (%)	46 (100.0)
SAEs, n (%)	22 (47.8)
SAEs related to exa-cel, n (%)[a]	0
AEs leading to death, n (%)[b]	1 (2.2)
Any malignancies, n (%)	0

All participants engrafted neutrophils and platelets. Data presented from infusion to Month 24.

[a] Includes related and possibly related AEs.

[b] **One death, from respiratory failure due to COVID-19 infection, was not related to exa-cel.**

Common AEs in CLIMB SCD-121	Exa-cel N = 46
Nausea	32 (69.6)
Stomatitis	29 (63.0)
Vomiting	27 (58.7)
Febrile neutropenia	25 (54.3)
Headache	25 (54.3)
Abdominal pain	24 (52.2)
Pruritus	23 (50.0)

Table includes common adverse events occurring in ≥50% of participants from exa-cel infusion to Month 24.

- Exa-cel safety profile is consistent with myeloablative busulfan conditioning and autologous HSCT
- Most AEs occurred in the first 6 months with rates decreasing over time
- Safety is consistent in adolescents and adults
- In CLIMB-131, of 41 participants enrolled, there were no subjects with AEs related to exa-cel; 6 (14.6%) had SAEs (none considered related to exa-cel). There were no malignancies or deaths

Data shown are as of Feb 2025.

AE, adverse event; exa-cel, exagamglogene autotemcel; HSCT, haematopoietic stem cell transplantation; SAE, serious adverse event.

Frangoul H, et al. Poster presented at 30th Annual European Hematology Association; 13 Jun 2025. Milan, Italy.

Factors that Correlate with CD34$^+$ HSPC Collection

CLIMB SCD-121

Factors that Correlate with CD34$^+$ HSPC Collection			
Correlation to CD34$^+$ HSPC Collection	**Factor Assessed**	**Pearson Correlation Coefficient**	**P Value[a]**
Positive Correlation	Pre-apheresis (2hrs post-plerixafor) CD34$^+$ Cell Count (10^6/L; Cycle 1)	0.67	<.001
	Baseline (pre-plerixafor) CD34$^+$ Cell Count (10^6/L; Cycle 1)	0.65	<.001
Negative Correlation	Age at Screening (years)	-0.48	<.001

- Based on univariate analysis, age and baseline and pre-apheresis blood CD34$^+$ count are among the factors correlated with CD34$^+$ HSPC collection
- Multivariate analysis confirmed that younger age and higher blood CD34$^+$ count (baseline and pre-apheresis) are the factors correlated with higher CD34$^+$ HSPC collection[b]
- The number of CD34$^+$ cells collected is generally similar across cycles for each participant (P value = 0.4)[c]
- Alkaline phosphatase and platelet count were identified in univariate analysis but not confirmed in multivariate analysis[c]

[a]P values for Pearson correlation coefficient

[b]All factors of interest were included in a multivariate stepwise model selection with selection criterion P value <0.05

[c]Based on results from a Mixed Model for Repeated Measures (MMRM) analysis. P value >0.05 for the effect of cycles indicating cell collection from each cycle do not vary over cycles

Data are shown for participants who started mobilization as of Feb 2025. All laboratory assessments are from baseline unless indicated. Baseline is defined as most recent non-missing measurement before the start of mobilization.

HSPC, hematopoietic stem and progenitor cell.

Frangoul H, et al. Poster presented at 30th Annual European Hematology Association; 13 Jun 2025. Milan, Italy.

Factors that Do Not Correlate with CD34+ HSPC Collection

CLIMB SCD-121

Factors that Do Not Correlate with CD34+ HSPC Collection		
Correlation to CD34+ HSPC Collection[a]	**Factor Assessed**	**P Value**
No Evidence of Correlation	**Markers of disease severity**	
	Annualised Rate of Severe VOCs	0.70
	Annualized Rate of Inpatient Hospitalisations for Severe VOCs	0.77
	Annualised Duration of Inpatient Hospitalisations for Severe VOCs (days)	0.94
	Annualised units of RBCs transfused for SCD-related indication	0.68
	Markers of Haemolysis	
	Lactate Dehydrogenase (U/L)	0.52
	Haptoglobin (g/L)	0.77
	Indirect Bilirubin (μmol/L)	0.84
	Reticulocyte Count (10^9/L)	0.91
	Other assessments	
	Total Hb (g/dL)	0.18
	WBC (10^9/L)	0.21
	Pre-Transfusion HbS (%) before Cycle 1[b]	0.16
	Post-Transfusion HbS (%) before Cycle 1[c]	0.85
	HbS (%; Cycle 1 Day 1)	0.31
	HbF (%)	0.36
	C-reactive Protein (μg/mL)	0.75
	Sex	0.24

[a]Average number of CD34+ cells collected (cells/kg) was calculated for each participant and was correlated with each factor

P values for Pearson correlation coefficient, except that P value for sex is based on Wilcoxon rank sum test

[b]8-week weighted average of pre-RBC transfusion HbS(%) before mobilization cycle 1

[c]8-week weighted average of post-RBC transfusion HbS(%) before mobilization cycle 1

Hb, hemoglobin; HbF, fetal hemoglobin; HbS, sickle hemoglobin; HSPC, hematopoietic stem and progenitor cell; RBC, red blood cell; VOCs, vaso-occlusive crises; WBC, white blood cell.

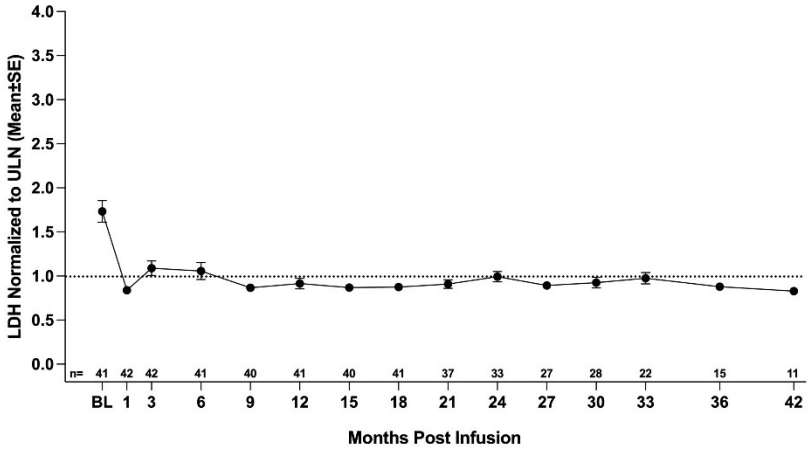
Frangoul H, et al. Poster presented at 30th Annual European Hematology Association; 13 Jun 2025. Milan, Italy.

Markers of Haemolysis

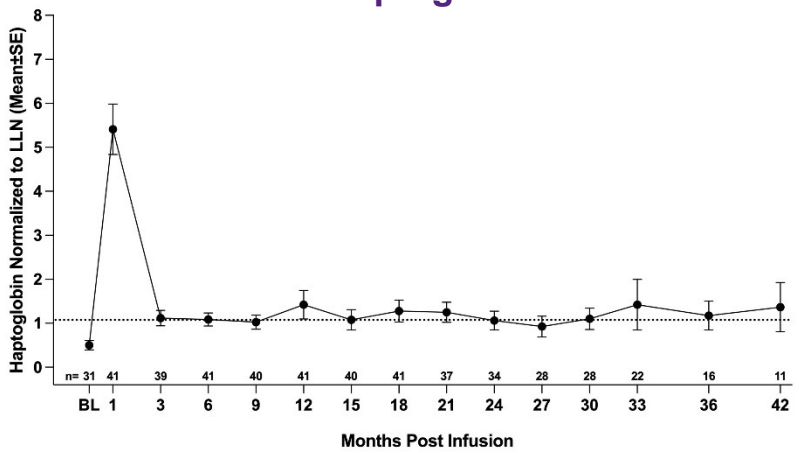
CLIMB SCD-121 and CLIMB-131 (ASH 2024: August 2024 data cut)

- Clinically meaningful improvements in haemolysis markers were observed and maintained over time.

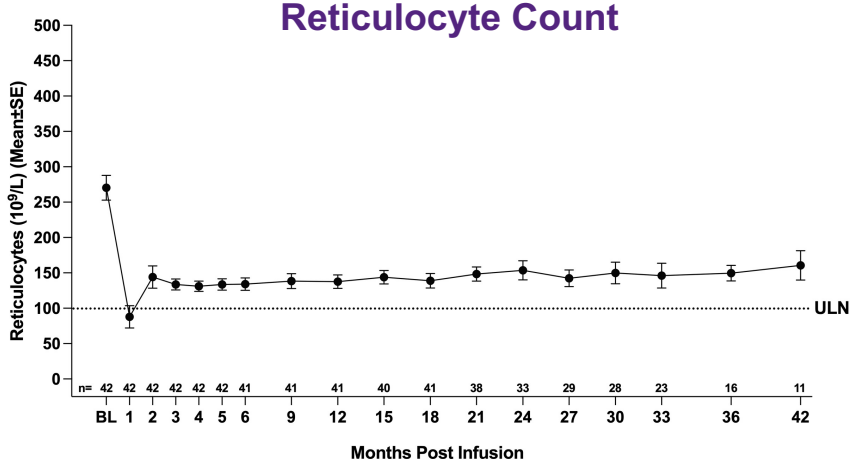
Lactate Dehydrogenase



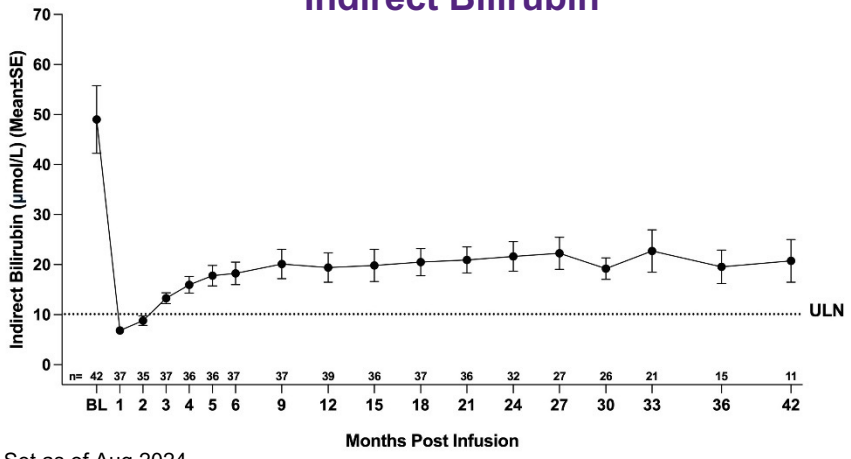
Haptoglobin



Reticulocyte Count



Indirect Bilirubin



Figures depict data for all timepoints where at least 5 participants have completed the specified visit. Data are displayed for the Primary Efficacy Set as of Aug 2024.
ULN for absolute reticulocyte count and indirect bilirubin, based on American Board of Internal Medicine (ABIM) Laboratory Test Reference Ranges – Jan 2024. ULN for LDH and LLN for haptoglobin were based on the lab normal range as collected.

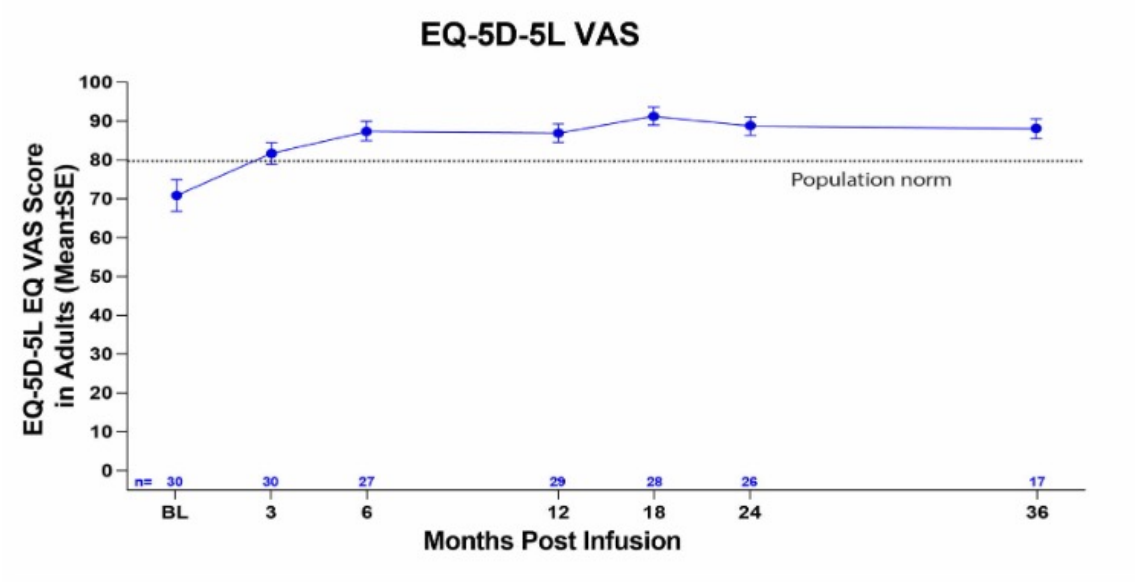
BL: baseline; **exa-cel:** exagamglogene autotemcel; **LDH:** lactate dehydrogenase; **LLN:** lower limit of normal; **ULN:** upper limit of normal.

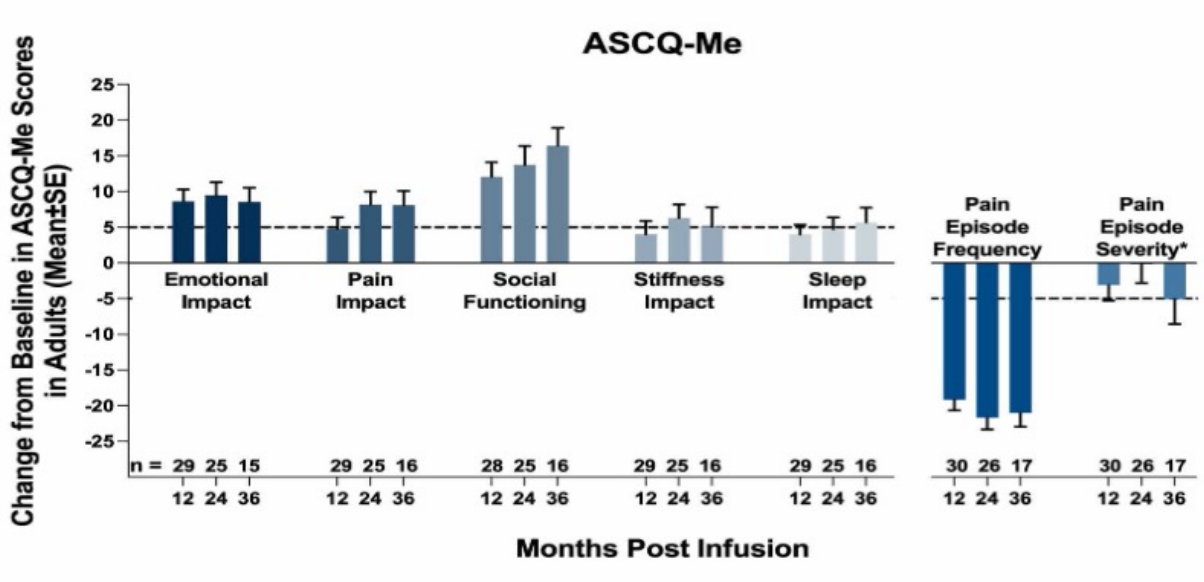
Frangoul H, et al. Poster presented at 66th Annual American Society of Hematology; 9 Dec 2024. San Diego, USA.

Patient-Reported Outcomes in Adults

CLIMB SCD-121 and CLIMB-131

Adults





Data are shown for the Primary Efficacy Set as of Aug 2024. The dashed lines in the ASCQ-Me graphs represent the MCID.
*Pain episode severity measures the severity of the last pain crisis, which could be before participants received exa-cel.

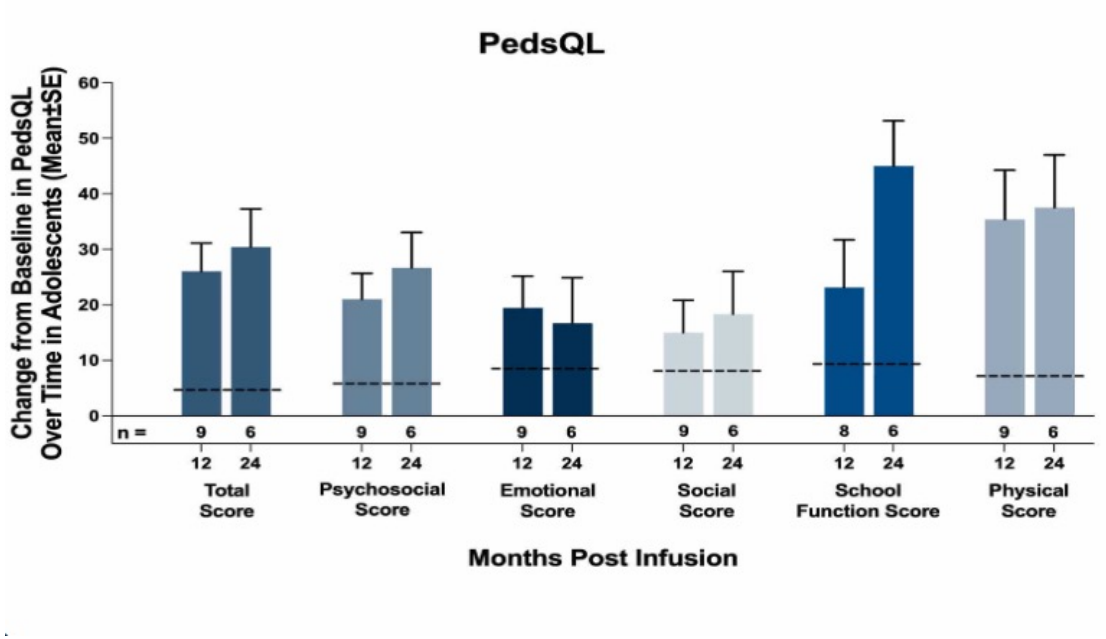
MCID, minimum clinically important difference**; SCD,** sickle cell disease

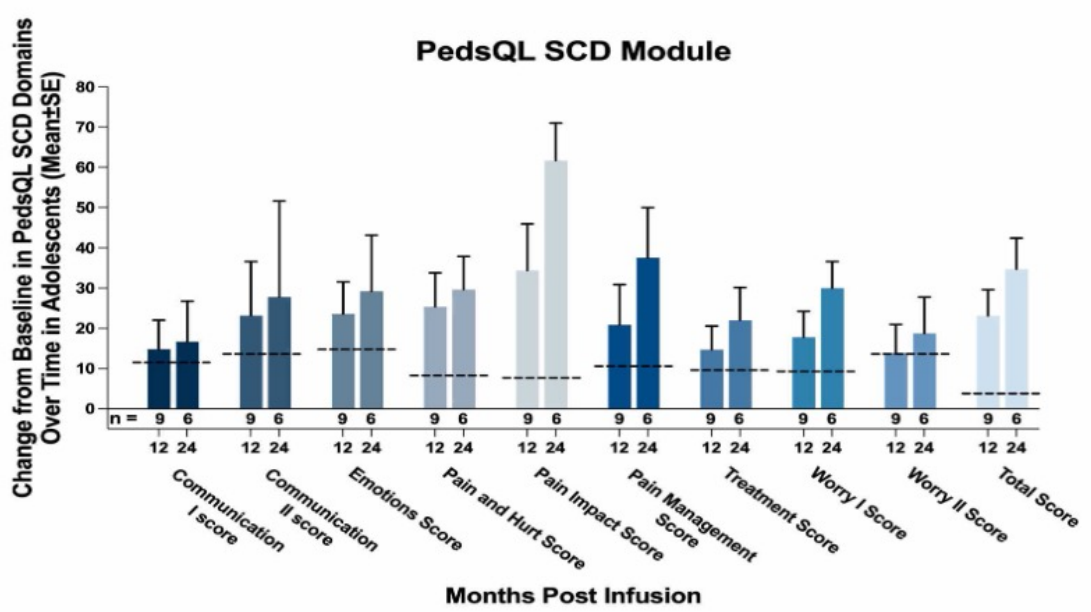
Frangoul H, et al. Poster presented at 66th Annual American Society of Hematology; 9 Dec 2024. San Diego, USA.

Patient-Reported Outcomes in Adolescents

CLIMB SCD-121 and CLIMB-131

Adolescents





Data are shown for the Primary Efficacy Set as of Aug 2024. The dashed lines in the PedsQL, and PedsQL SCD Module graphs represent the MCID.

MCID, minimum clinically important difference**; SCD,** sickle cell disease

Frangoul H, et al. Blood Advances 2025, *in press*.

Conclusions

- **Long-term follow-up for up to over 5 years demonstrates that all SCD participants achieved durable clinical benefit**
  - **96% achieved freedom from VOC for at least 12 months and remained VOC free, with a mean duration of 35 months (range 14.4 to 66.2)**
  - **100% achieved freedom from hospitalization for VOC for at least 12 months, with a mean duration of 36.1 months (range 14.5 to 66.2)**
  - **Durable increases in HbF to ~40% with pancellular distribution resulted in total hemoglobin at normal or near normal levels**
  - **Stable allelic editing in bone marrow and peripheral blood demonstrating durable editing of long-term HSCs**
- **Safety profile consistent with myeloablative busulfan conditioning and autologous HSCT; no malignancies**
- **Adolescents underwent fewer cycles to achieve a Drug Product than adults (92% of adolescents achieved a Drug Product in 1-2 cycles) and had higher pre-plerixafor and pre-apheresis (2 hours post-plerixafor) peripheral blood $CD34^+$ cell counts than adults**
  - **Consistent with this observation, the number of CD34+ HSPCs collected correlated with age and pre-plerixafor and pre-apheresis (2 hours post-plerixafor) peripheral blood $CD34^+$ cell count**
  - **The number of $CD34^+$ HSPCs collected also correlated with baseline platelet count and alkaline phosphatase levels, with no correlation observed with markers of disease severity, laboratory measures of hemolysis, other laboratory measures, or sex**
- **This is the largest data set analyzed to date describing single agent plerixafor mobilization and apheresis collection characteristics of patients with SCD; the data may inform the approach to mobilization and apheresis of patients with SCD prior to autologous genetic therapy**
- **Long term follow-up continues to demonstrate that exa-cel has the potential to provide a one-time functional cure to patients with SCD**

HbF: fetal hemoglobin; **HbS**: sickle hemoglobin; **HSPCs**: hematopoietic stem and progenitor cells; **SCD**: sickle cell disease; **VOC**: vaso-occlusive crisis

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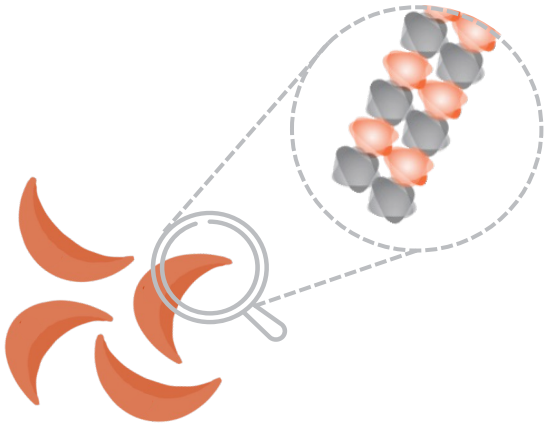
CLIMB THAL-111 and **CLIMB-131** trials are sponsored by Vertex Pharmaceuticals Incorporated and CRISPR Therapeutics

BEAM-101 uses precise base editing to increase levels of HbF

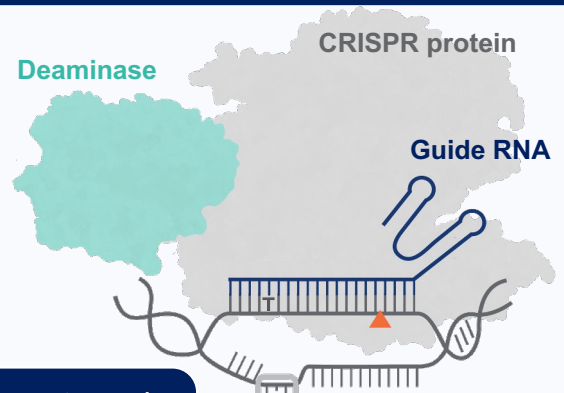
Sickle cell disease[1,2]

HbS ↓ ↑ HbF

Increased HbS leading to sickled cells

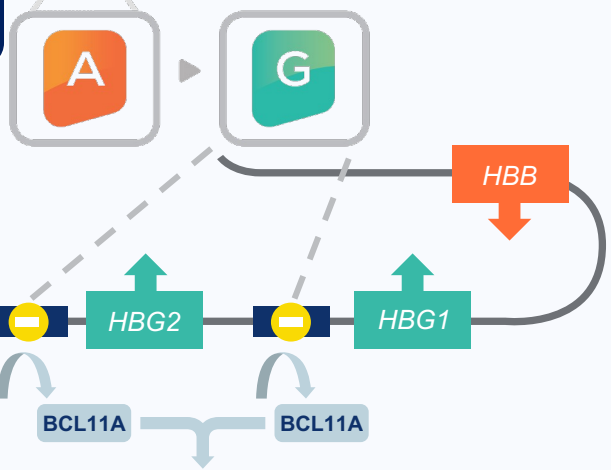


Base editing with BEAM-101[3,4]



Editing of *HBG1/2* promoters is designed to eliminate BCL11A binding sites without disrupting other BCL11A-regulated pathways

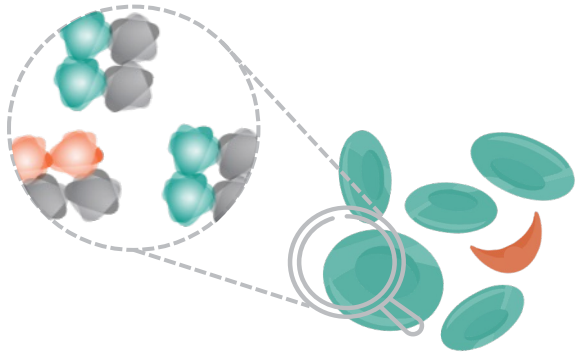
Does not require double-stranded breaks



Following treatment with BEAM-101[2,5]

Increased HbF leading to fewer sickled cells

HbF ↑ ↓ HbS



1. Eaton WA, Bunn HF. Blood 2017;129:2719–2726; 2. Akinsheye I, et al. Blood 2011;118:19–27; 3. Beam Therapeutics Inc. Protocol BTX-AUT-001; 4. Beam Therapeutics Inc. Investigator's brochure; 5. Steinberg MH, et al. Blood 2014;123:481–485. A, adenine; BCL11A, transcription factor B-cell lymphoma/leukemia 11A; CRISPR, clustered regularly interspaced short palindromic repeats; G, guanine; HBB, hemoglobin subunit beta; HBG, hemoglobin subunit gamma; HbF, fetal hemoglobin; HbS, sickle hemoglobin; RNA, ribonucleic acid

BEAM-101 treatment characteristics

Dosing	N=7
Number of mobilization and apheresis cycles, mean (range)	1.4 (1–2)
Busulfan cumulative AUC (µg*h/mL), mean (range)	73.9 (61.8–83.2)
BEAM-101 dose infused (×10^6 CD34+ cells/kg) mean (range)	10.7 (3.2–23.4)
Duration (months) of follow up after BEAM-101 dosing, mean (range)	5.6 (1.4–11.0)
Day of last RBC transfusion, median (range)	15 (7–122*)

BEAM-101's efficient manufacturing process resulted in patients requiring few collection cycles

Data cutoff Oct 28, 2024

Therapeutic drug monitoring for busulfan was performed and dosing was adjusted based upon plasma busulfan concentrations to maintain a daily target busulfan AUC of 20 µg*h/mL with a cumulative AUC target of 80 µg*h/mL

*One patient required blood transfusions up to Day 122 as part of ongoing management of critical illness; excluding this patient, the mean (range) last day of RBC transfusion is 11.8 (7–17)

AUC, area under the curve; RBC, red blood cell

BEAM-101 treatment and engraftment characteristics

Dosing	N=7
Number of mobilization and apheresis cycles, mean (range)	1.4 (1–2)
Busulfan cumulative AUC (μg*h/mL), mean (range)	73.9 (61.8–83.2)
BEAM-101 dose infused ($\times 10^6$ CD34+ cells/kg) mean (range)	10.7 (3.2–23.4)
Duration (months) of follow up after BEAM-101 dosing, mean (range)	5.6 (1.4–11.0)
Day of last RBC transfusion, median (range)	15 (7–122*)
Time to neutrophil engraftment (days), mean (range)	17.1 (15–21)
Duration of neutropenia (ANC <500 cells/μL), (days), mean (range)	6.3 (4–9)
Time to platelet engraftment (days), mean (range)	19.1 (11–34)

Patients had rapid neutrophil and platelet engraftment with a low number of neutropenic days

Data cutoff Oct 28, 2024

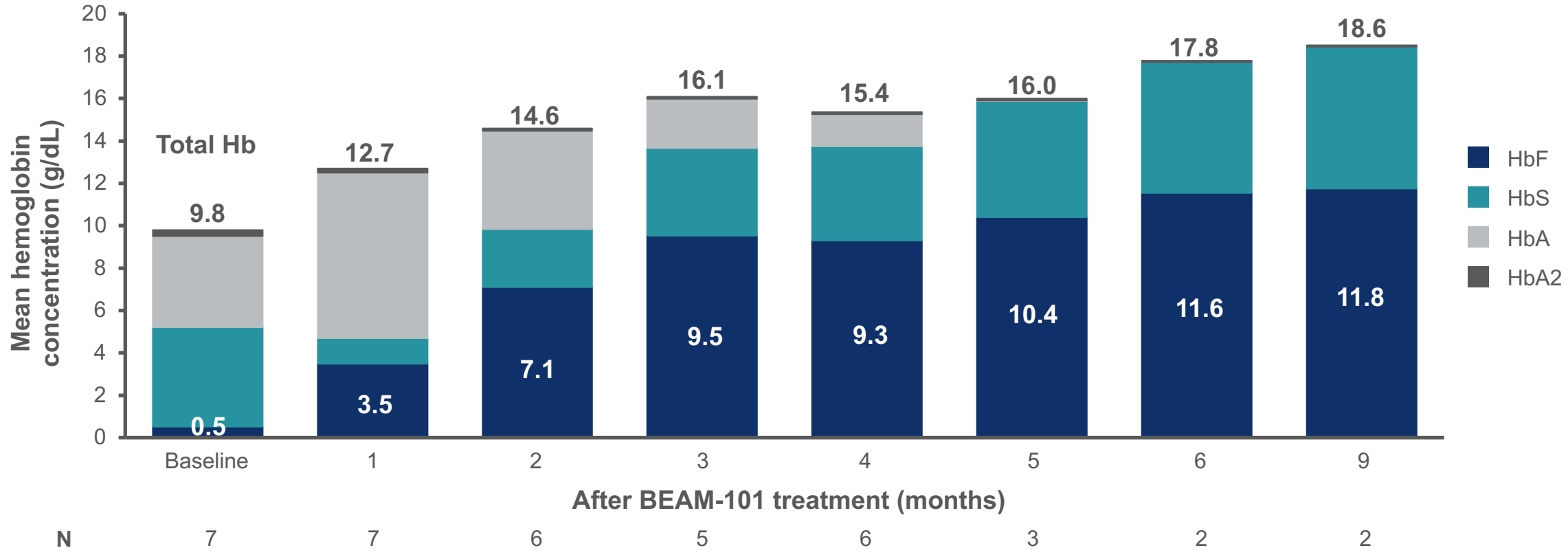
Neutrophil engraftment defined as ANC ≥500 cells/μL for 3 consecutive days independent of growth factor support. Platelet engraftment defined as post-nadir platelet count ≥50,000 per μL on 3 separate days without receiving a platelet transfusion for at least 7 days prior to the first of the 3 measurements through to the last measurement

*One patient required blood transfusions up to Day 122 as part of ongoing management of critical illness; excluding this patient, the mean (range) last day of RBC transfusion is 11.8 (7–17)

ANC, absolute neutrophil count; AUC, area under the curve; RBC, red blood cell

Patients achieved rapid and robust HbF induction with corresponding HbS reduction

All patients achieved endogenous HbF >60% and HbS <40% by 1 month after BEAM-101 treatment



N	7	7	6	5	6	3	2	2
%HbF (HbF/HbF+HbS)	10%	74%	72%	70%	67%	65%	65%	64%

Data cutoff Oct 28, 2024

Female total Hb LLN-ULN: 11.5-15 g/dL; Male LLN-ULN: 13-17 g/dL. Hb, hemoglobin; HbA, adult hemoglobin; HbF, fetal hemoglobin; HbS, sickle hemoglobin; LLN, lower limit of normal; ULN, upper limit of normal