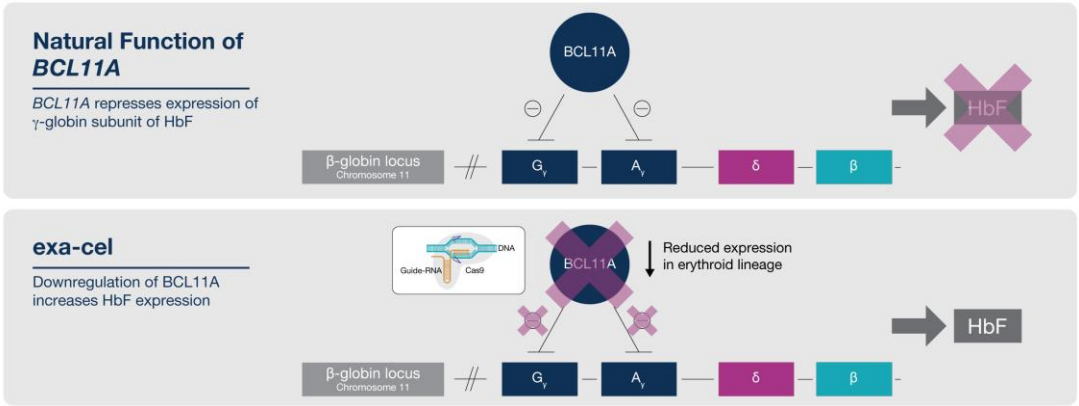
Durable Clinical Benefits With Exagamglogene Autotemcel for Greater Than 6 Years of Follow-up in Trans-fusion Dependent β-Thalassemia and Sickle Cell Disease With Recurrent Vaso-occlusive Crises

Franco Locatelli, Haydar Frangoul, Peter Lang, Akshay Sharma, Roland Meisel, Selim Corbacioglu, Josu de la Fuente, Monica Bhatia, Markus Mapara, Lyndsay Molinari, Robert I. Liem, Laurence Dedeken, Amanda M. Li, Ami J. Shah, Mattia Algeri, Ben Carpenter, Janet L. Kwiatkowski, Joachim Rupprecht, Hayley Merkeley, Kevin H. M. Kuo, Kevin Boerner, Tina Liu, Sakellarios Zairis, William Hobbs, Stephan A. Grupp

Disclosure statement

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		
MEDAC					X		
Sanofi						X	
SOBI					X		
Vertex						X	

Exa-cel: The First Approved CRISPR/Cas9 Gene Editing Therapy
Durable Clinical Benefit for Over 6 Years in SCD and TDT



- **Exa-cel is approved** for treatment of patients aged 12 years and older with sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOC) and with transfusion-dependent β-thalassemia (TDT)[1]
- **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***
- Exa-cel results in **reactivation of HbF** synthesis to levels known to result in **reduced morbidity and mortality** in patients with hemoglobinopathy and hereditary persistence of HbF[2,3]
- Exa-cel Phase 1/2/3 clinical trial data has demonstrated **reactivation of HbF** to levels that lead to **elimination of VOC in SCD**[4] and **transfusion dependence in TDT**[5]
- We report data demonstrating **durable clinical benefit** with a **median follow-up of 3.7 years** and **longest follow-up of 6.1 years for SCD** and **median follow-up of 4.1 years** and **longest follow-up of 6.6 years for TDT**

Data shown are as of Jul 2025.

***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; **HbF:** fetal hemoglobin; **HSPC:** hematopoietic stem and progenitor cell; **RNA:** ribonucleic acid; **SCD:** sickle cell disease; **TDT:** transfusion-dependent β-thalassemia; **VOC:** vaso-occlusive crisis.

1. Refer to regional label for specific indication. 2. Musallam, KM, et al. *Blood*. 2013; 121:2199-2212. 3. Bauer DE, et al. *Curr Opin Gene Dev*. 2015;33:62-70. 4. Frangoul H, et al. *N Engl J Med*. 2024; 390(18):1649-1662 5. Locatelli F, et al. *N Engl J Med*. 2024;390(18):1663-1676.

Exa-cel Pivotal Phase 3 Trial Designs

	SCD: CLIMB SCD-121 (NCT03745287): Study Complete	TDT: CLIMB THAL-111 (NCT03655678)
Study Design	Global, multicenter, open-label, single-arm, 2-year Phase 1/2/3 trial of a single infusion of exa-cel	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	12 to 35 years of age with TDT defined as a history of ≥100 mL/kg/year or ≥10 units/year of RBC transfusions 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)**	**Primary**: Proportion of participants **transfusion independent for ≥12 consecutive months** while maintaining a weighted average hemoglobin ≥9 g/dL **(TI12)**
Secondary Efficacy Endpoints	• **Duration of VOC freedom for participants who achieved VF12** • **Measures of hemolysis (lactate dehydrogenase, haptoglobin, reticulocytes, and indirect bilirubin)**	• **Duration of transfusion independence for participants who achieved TI12** • **Measures of iron overload (Serum Ferritin, Liver Iron Concentration[a], and Cardiac Iron Content[b])** • **Proportion of participants receiving iron chelation therapy over time[c]**
	• **Total Hb and HbF levels** • **Allelic editing at the intended locus in bone marrow CD34$^+$ HSCs and peripheral blood cells** • **Patient-reported outcomes**	

CLIMB-131 (NCT04208529)

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

exa-cel: exagamglogene autotemcel; **Hb**: hemoglobin; **HbF**: fetal hemoglobin; **HSCs**: hematopoietic stem cells; **MRI**: magnetic resonance imaging; **RBC**: red blood cell; **SCD**: sickle cell disease; **TDT**: transfusion dependent β-thalassemia; **VOC**: vaso-occlusive crisis

[a] Liver iron concentration measured by R2 MRI
[b] Cardiac iron content measured by T2* MRI
[c] Analysis included all types of iron removal therapy, including chelation and/or phlebotomy

SCD: Key Demographics, Baseline Characteristics, and Treatment Features

	Full Analysis Set[a] N = 46	
Demographics and Baseline Characteristics		
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)	
Treatment and Mobilization/Apheresis Characteristics		
Duration (months) of follow-up after exa-cel infusion, median (range)	**44.7 (8.9, 73.7)**	
Time (days) to neutrophil engraftment, median (range)	27 (15, 40)	
Duration (days) of neutropenia, median (range)	17 (6, 30)	
Time (days) to platelet engraftment, median (range)	34.5 (23, 126)	
Time (days) to hospital discharge[c], median (range)	31.5 (21, 54)	
No. of mobilization/apheresis cycles needed for Drug Product, mean (range)	**2.4 (1, 6)**	
	Adolescents N = 12	**Adults N = 34**
No. of participants requiring 1-2 mobilization/apheresis cycles for drug product, n (%)	11 (91.7)	19 (55.9)
No. of participants requiring >2 mobilization/apheresis cycles for drug product n (%)	1 (8.3)	15 (44.1)
Baseline (pre-plerixafor) $CD34^+$ cells/µL, Cycle 1 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, Cycle 1 Day 1; mean (range)	88.2 (11.0, 178.7)	50.1 (11.4, 189.0)

Adolescents: ≥12 and <18 years; **Adults**: ≥18 and ≤35 years, **exa-cel**: exagamglogene autotemcel; **hrs**: hours; **No.**: number; **SD**: standard deviation; **VOC**: vaso-occlusive crisis

[a] Includes participants who received exa-cel infusion.

[b] Annualized over 2 years before screening

[c] Defined as the number of days from exa-cel infusion to hospital discharge following neutrophil engraftment

TDT: Key Demographics, Baseline Characteristics, and Treatment Features

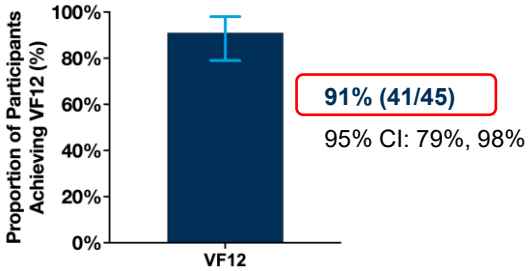
	Full Analysis Set[a] N = 56
Demographics and Baseline Characteristics	
Age (years) at screening, mean (SD)	21.2 (6.5)
≥12 and <18 years, n (%)	20 (35.7)
≥18 and ≤35 years, n (%)	36 (64.3)
Genotype, n (%)	
β^0/β^0	22 (39.3)
β^0/β^0-like (β^0/IVS-I-110; IVS-I-110/IVS-I-110)	13 (23.2)
Non-β^0/β^0-like	21 (37.5)
Annualized volume of RBC transfusions (mL/kg), median (range)[b]	206.7 (48.3, 330.9)
Annualized units of RBC transfusions, median (range)[b]	36.0 (11.0, 71.0)
Treatment and Mobilization/Apheresis Characteristics	
Duration (months) of follow-up after exa-cel, median (range)	**49.6 (19.4, 78.6)**
Time (days) to neutrophil engraftment, median (range)	29 (12, 56)
Duration (days) of neutropenia, median (range)	20.5 (4, 48)
Time (days) to platelet engraftment, median (range)	43.5 (20, 200)
Time (days) to hospital discharge[c], median (range)	39.0 (23, 110)
No. of mobilization/apheresis cycles needed for Drug Product, mean (range)	**1.3 (1, 4)**

exa-cel: exagamglogene autotemcel; **IQR:** interquartile range; **RBC:** red blood cell; **SD:** standard deviation.
[a] Includes participants who received exa-cel infusion
[b] in the 2 years prior to enrollment
[c] Defined as the number of days from exa-cel infusion to hospital discharge following neutrophil engraftment
Data shown are as of July 2025

Final CLIMB SCD-121 Results: Primary and Key Secondary Endpoint

Over 90% of Participants Achieved VF12 and HF12 in CLIMB SCD-121

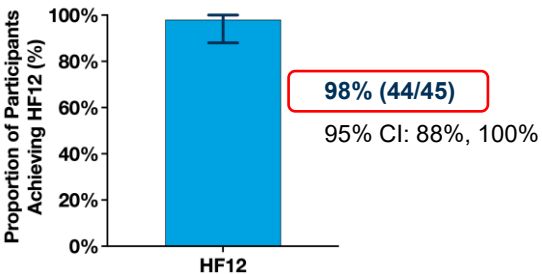
Primary Endpoint: VF12



91% (41/45)

95% CI: 79%, 98%

Key Secondary Endpoint: HF12



98% (44/45)

95% CI: 88%, 100%

Secondary Endpoint

VOC-free Duration

- Mean: 3.4 years
- Range: 1.6 to 5.9 years

Hospitalization-free Duration

- Mean: 3.4 years
- Range: 1.6 to 5.9 years

- Similar proportion of participants achieved VF12 across age and genotype subgroups
  - Age: 90% (31/34) of adults and 92% (11/12) of adolescents
  - Genotype: 90% (37/41) of β^s/β^s and 100% (5/5) of non- β^s/β^s (includes β^s/β^0 and β^s/β^+ genotypes)

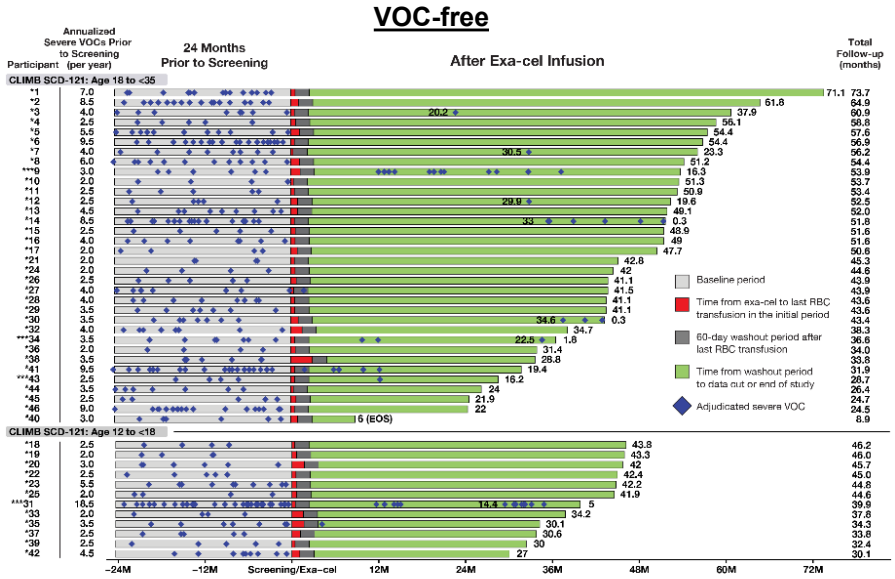
CI: confidence interval; **exa-cel:** exagamglogene autotemcel; **HF12:** free from in-patient hospitalization for severe VOCs for ≥12 consecutive months; **VF12:** no severe VOCs for ≥12 consecutive months; **VOC**, vaso-occlusive crises.

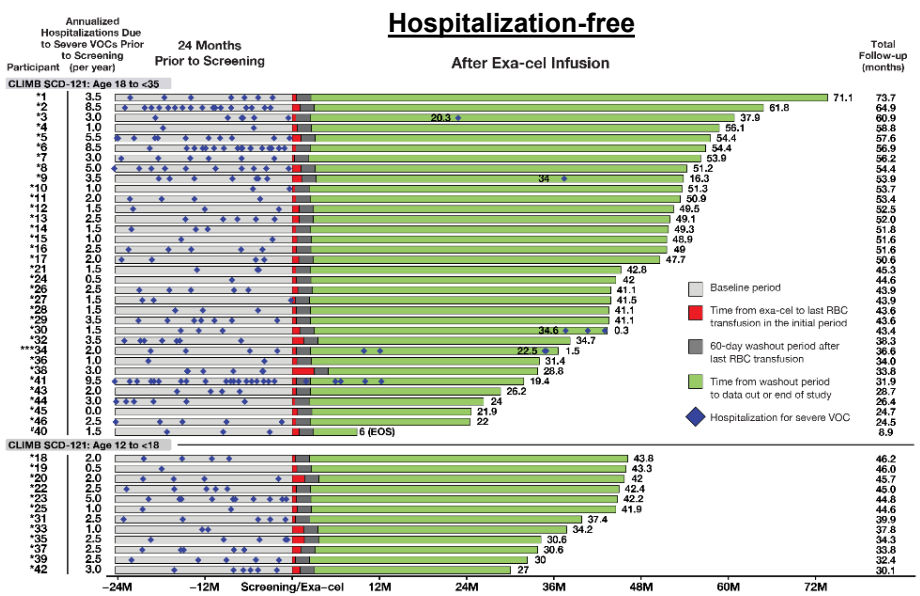
The proportion of participants who achieved VF12 or HF12 in Study CLIMB SCD-121 was calculated relative to the number of participants who received exa-cel, excluding the participant who died respiratory failure due to COVID-19 infection; not related to exa-cel.

Data shown are as of Jul 2025.

SCD: Durable VOC-Free and Hospitalization-Free After Exa-cel

All Participants (100%) Achieved VF12 and HF12 with Longer Follow-up in CLIMB-131





- 100% (45/45) of evaluable participants achieved VF12 and HF12 in CLIMB SCD-121 and CLIMB-131 combined
- Mean duration of VOC-free was 3.2 years and hospitalization-free was 3.4 years in CLIMB SCD-121 and CLIMB-131 combined
- VOCs after exa-cel were all acute pain events, and most did not require in-patient hospitalization. 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)

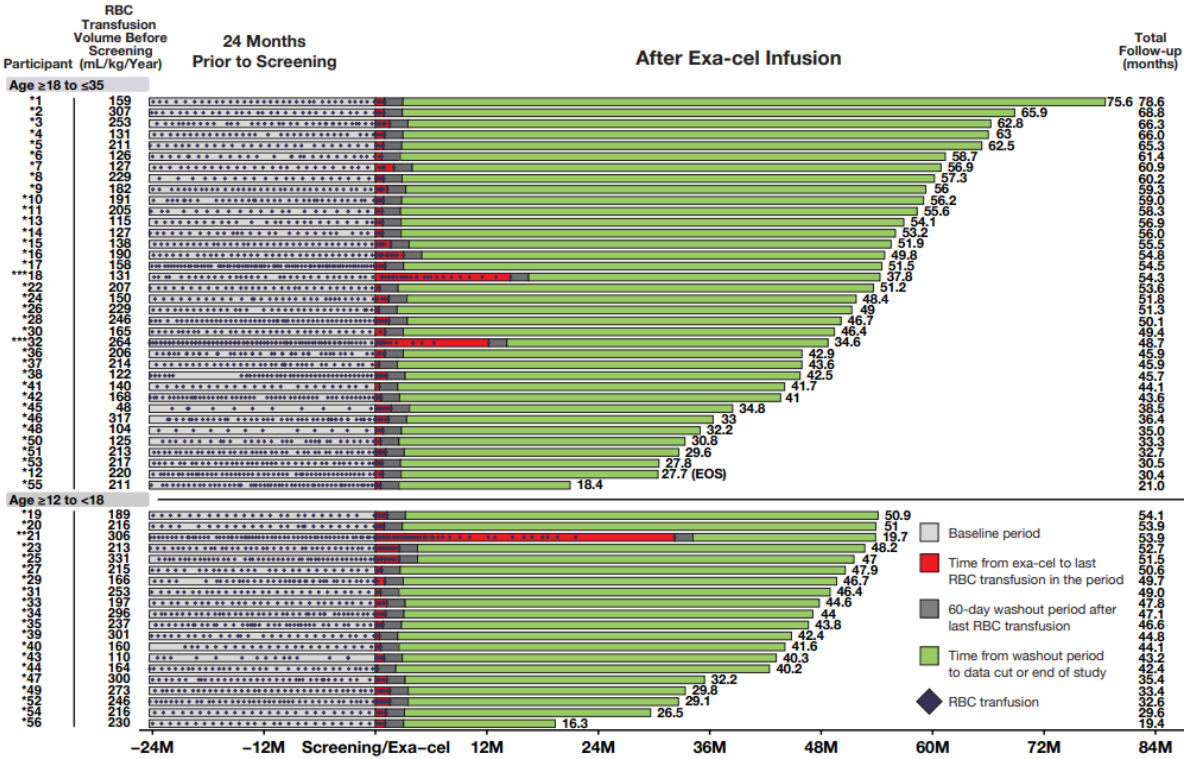
HF12: free from in-patient hospitalization for severe VOCs for ≥12 consecutive months; **VF12:** free of severe VOCs for ≥12 consecutive months; **VOC:** vaso-occlusive crisis

* Achieved VF12/HF12 in CLIMB SCD-121; **Did not achieve VF12/HF12 in CLIMB SCD-121; *** Achieved VF12/HF12 in CLIMB SCD-131; # participant died from respiratory failure due to COVID-19 infection; not related to exa-cel.

Data shown are as of Jul 2025.

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

Transfusion Independence Achieved in 98% and Maintained for up to 6.3 Years



- 98% (55/56) of evaluable participants achieved TI12 in CLIMB THAL-111 and CLIMB-131 combined
  - 95% (53/56) of evaluable participants achieved TI12 in CLIMB THAL-111
- Median duration of transfusion independence 3.9 years (range: 1.4 to 6.3)
- 1 participant who has not yet achieved TI12 has been transfusion free for the last 1.6 years

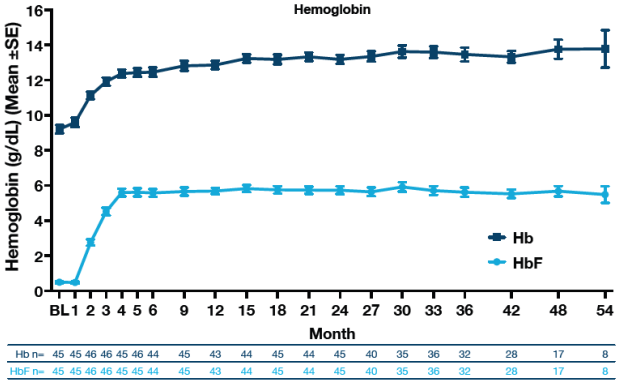
EOS: end of study; **exa-cel:** exagamglogene autotemcel; **Hb**: hemoglobin; **RBC:** red blood cell; **TI12:** transfusion independent for ≥12 consecutive months while maintaining a weighted average hemoglobin ≥9 g/dL.

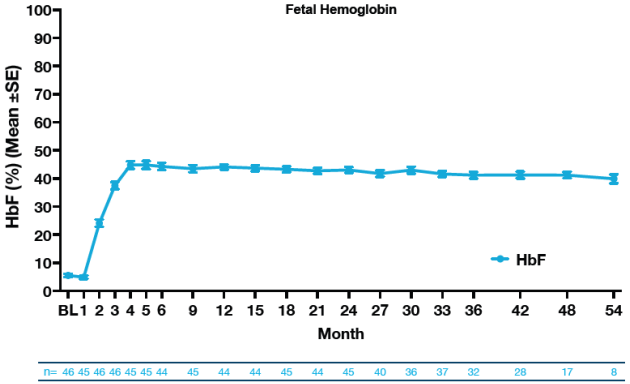
* Achieved TI12 in CLIMB-111; **Did not achieve TI12 (due to not having weighted average Hb ≥9 g/dL); ***Achieved TI12 in CLIMB-131 only

Data shown are as of Jul 2025.

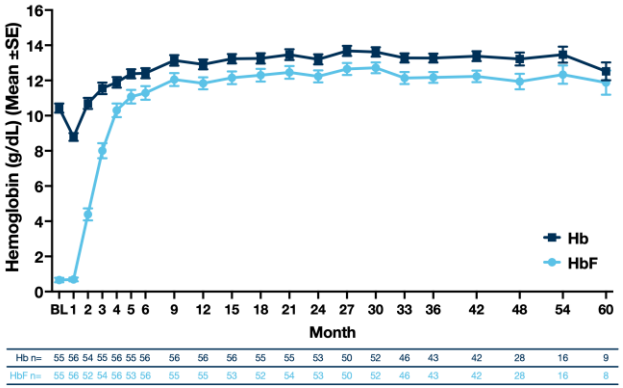
Durable Increases in Total Hb and Fetal Hemoglobin in SCD and TDT

SCD





TDT



SCD: Mean HbF increases to ~40%

SCD and TDT:

- Normal or near normal levels of Total Hb
- Pancellular HbF distribution (durable >95% proportion of red blood cells containing HbF [F-cells])[1,2]

SCD and TDT: Durable bone marrow and peripheral blood allelic editing[1,2]

BL: baseline; **Hb:** hemoglobin; **HbF:** fetal hemoglobin; **SCD**: sickle cell disease; **SE:** standard error; **TDT:** transfusion-dependent β-thalassemia.

1. Frangoul, H. et al. *N Engl J Med*. 2024;390(18):1649-1662. 2. Locatelli, F, et al. *N Engl J Med* 2024;390(18):1663-1676.

Figures depict data for all timepoints where at least 5 participants have completed the specified visit.

Data shown are as of Jul 2025

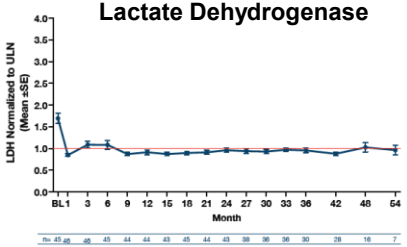
Exa-cel Demonstrated Additional Clinical Benefits:

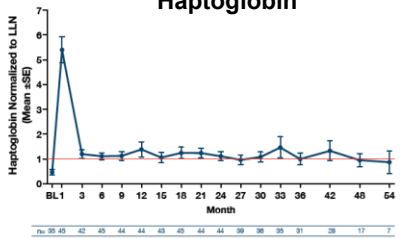
Improved in Patient-Reported Outcomes (SCD/TDT), Hemolysis (SCD), and Iron Overload (TDT)

SCD and TDT: exa-cel demonstrated clinically meaningful improvements in **patient-reported outcome measures**[1,2] EQ-5D-5L/EQ-5D-Y, FACT-BMT, PedsQL, and ASCQ-Me (SCD only) and pain NRS (SCD only)

SCD: Improved Hemolysis Measures

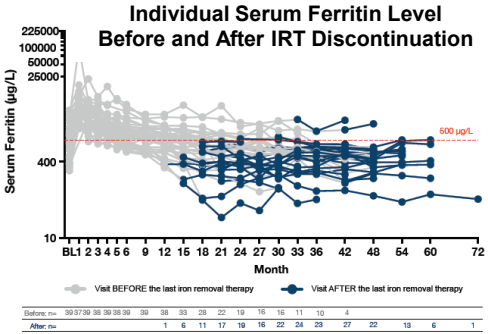
Improvements in **hemolysis markers** (lactate dehydrogenase, haptoglobin, reticulocyte count, indirect bilirubin) were maintained[3]

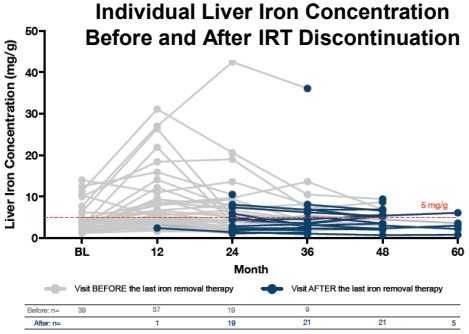




TDT: Improvement in Iron Overload Measures

Measures of iron overload and biomarkers of erythropoiesis improved after exa-cel[4], with no progressive increases in serum ferritin after iron removal therapy (IRT) discontinuation





1. Sharma A, et al. Blood Adv. 2025; 9(24):6481-6490; 2. de la Fuente J, et al. Blood Adv. 2025; 9(24):6502-6510; 3. Frangoul H, et al. N Engl J Med. 2024; 390(18): 1649-1662; 4. Locatelli F, et al. N Engl J Med. 2024;390(18):1663-1676

Data for measures of hemolysis and iron overload measures shown are as of Jul 2025

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

AE Overview	CLIMB SCD-121	CLIMB THAL-111
Participants with	**N = 46**	**N = 56**
Any AEs, n (%)	46 (100.0)	56 (100.0)
AEs related to exa-cel, n (%)[a]	13 (28.3)	16 (28.6)
AEs related to busulfan, n (%)[a]	46 (100.0)	55 (98.2)
AEs Grade 3/4, n (%)	46 (100.0)	50 (89.3)
SAEs, n (%)	22 (47.8)	19 (33.9)
SAEs related to exa-cel, n (%)[a,b]	0	2 (3.6)
AEs leading to death, n (%)[c]	1 (2.2)	0
Any malignancies, n (%)	0	0

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

[a] Includes related and possibly related AEs or SAEs.

[b] SAEs previously reported in 2 participants in CLIMB THAL-111 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).

[c] One death in CLIMB SCD-121, from respiratory failure due to COVID-19 infection, was not related to exa-cel.

- Most AEs occurred in the first 6 months with rates decreasing over time
- Safety is consistent in adolescents and adults
- TDT: 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
- Long-term follow-up study CLIMB-131:
  - There were no malignancies or deaths
  - TDT: Of 54 participants enrolled, there were no participants with AEs related to exa-cel; 7 (13.0%) had SAEs (none related to exa-cel)
  - SCD: Of 45 participants enrolled, there were no participants with AEs related to exa-cel; 11 (24.4%) had SAEs (none related to exa-cel)

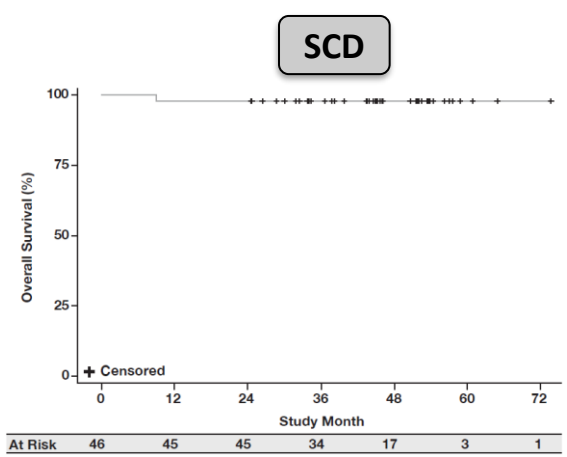
AEs: adverse events; **exa-cel**: exagamglogene autotemcel; **HLH**: hemophagocytic lymphohistiocytosis; **HSCT**: hematopoietic stem cell transplantation; **SAEs**: serious adverse events; **SCD:** sickle cell disease; **TDT**: transfusion-dependent β-thalassemia; **VOD**, veno-occlusive disease

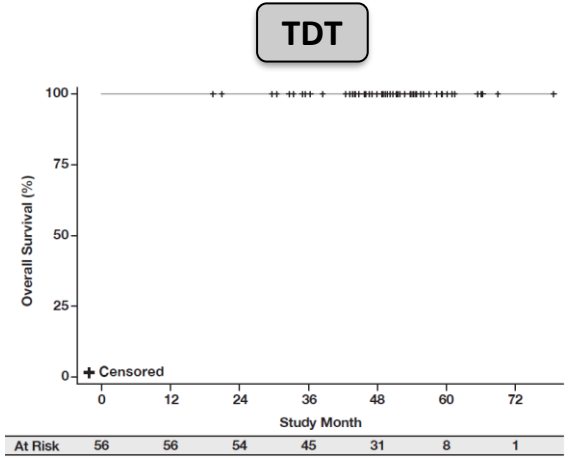
Data shown are as of Jul 2025.

Overall and Event-Free Survival

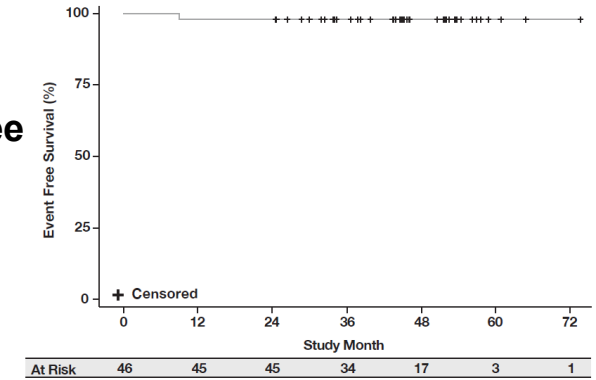
OS and EFS as typically defined for allogeneic HSCT

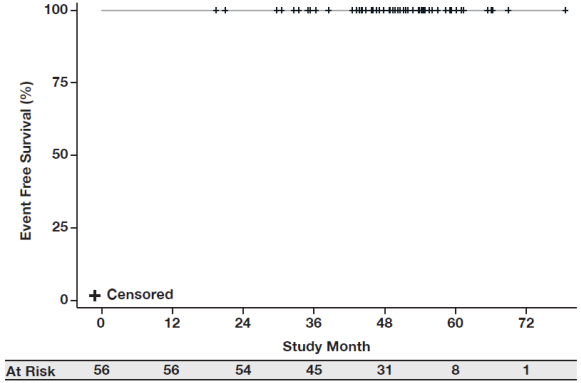
Overall Survival





Event-free Survival





- OS was defined as incidence of death from any case
- EFS was defined as incidence of graft failure or death from any cause. No events of graft-versus-host disease were reported, consistent with exa-cel being an autologous cellular therapy.
- OS and EFS rates: **97.8%* for SCD, 100% for TDT**

EFS: event-free survival; **HSCT:** hematopoietic stem cell transplantation; **OS:** overall survival; **SCD:** sickle cell disease; **TDT:** transfusion-dependent β-thalassemia
*One death in CLIMB SCD-121, from respiratory failure due to COVID-19 infection, was not related to exa-cel.

Conclusions

- Exa-cel is the first and only approved CRISPR/Cas9 gene editing therapy
- Long-term follow-up for >6 years demonstrates that all SCD and TDT participants achieved durable clinical benefit:

  SCD: 100% (45/45) achieved freedom from VOC for ≥12 months; mean duration VOC-free over 3 years
  - VOCs after exa-cel were all acute pain events, and most did not require in-patient hospitalization

  TDT: 98% (55/56) achieved TI12, with mean duration of transfusion independence of over 3 years

  TDT and SCD: Durable increases in pancellular HbF and stable allelic editing in bone marrow and peripheral blood
- Additional durable clinical benefits:

  TDT and SCD: Improvements in patient-reported outcomes across all assessed instruments and domains

  SCD: clinically meaningful improvement in measures of hemolysis

  TDT: clinically meaningful improvement in measures of iron overload

Safety profile consistent with myeloablative busulfan conditioning and autologous HSCT; no malignancies reported to date

Long-term follow-up continues to demonstrate that exa-cel has the potential to provide a one-time functional cure to patients with SCD and TDT

CRISPR/Cas9: clustered regularly interspaced short palindromic repeats and CRISPR-associated 9 nuclease**; exa-cel:** exagamglogene autotemcel; **HbF**: fetal hemoglobin; **HSC**: hematopoietic stem cell; **HSCT:** hematopoietic stem cell transplantation; **HSPCs**: hematopoietic stem and progenitor cells; **LIC**: liver iron concentration; **TDT:** transfusion-dependent β-thalassemia; **TI12**: transfusion independent for ≥12 consecutive months while maintaining a weighted average hemoglobin ≥9 g/dL; **SCD**: sickle cell disease; **VOC**: vaso-occlusive crisis

Data shown are as of Jul 2025.

Acknowledgements

Many thanks to trial participants & their families, as well as sites, investigators, nurses, & the entire exa-cel team

The authors acknowledge the site investigators

Mattia Algeri[1]	IRCCS, Ospedale Pediatrico Bambino Gesù Rome
Monica Bhatia[1,2]	Columbia University Medical Center
Ben Carpenter[1]	University College London Hospitals NHS Foundation Trust
Marina Cavazzana[2]	Hospital Necker Enfants Malades
Selim Corbacioglu[1,2]	Regensburg University Hospital
Josu de la Fuente[1,2]	Imperial College Healthcare/Hammersmith Hospital
Laurence Dedeken[2]	Hospital Universitaire des Enfants Reine Fabiola
Michael Eckrich[2]	Levine Children's Cancer & Blood Disorders
Haydar Frangoul[1,2]	Sarah Cannon Research Institute at The Children's Hospital at TriStar Centennial
Stephan Grupp[2]	Children's Hospital of Philadelphia
Rupert Handgreitinger[1]	Children's Hospital University, Tubingen
Janet L. Kwiatkowski[1]	The Children's Hospital of Philadelphia
Peter Lang[1]	University Hospital Tuebingen
Amanda M. Li[1]	The University of British Columbia
Robert Liem[1,2]	Ann and Robert Lurie Children's Hospital of Chicago
Franco Locatelli[1,2]	IRCCS, Ospedale Pediatrico Bambino Gesù Rome, Catholic University of the Sacred Heart
Markus Mapara[1,2]	Columbia University Medical Center
Roland Meisel[2]	University Hospital Duesseldorf
Lyndsay Molinari[2]	Methodist Healthcare System of San Antonio Children's Hospital
Damiano Rondelli[2]	University of Illinois at Chicago Hospitals and Health Systems
Ami J. Shah[1,2]	Lucile Packard Children's Hospital Stanford
Akshay Sharma[2]	St. Jude Children's Research Hospital
Paul Telfer[2]	Royal London and St. Bartholomew's Hospital
Donna Wall[1,2]	The Hospital for Sick Children (SickKids)

Medical writing and editorial coordination was provided by Crystal Kellas, PhD, who is an employee of Vertex Pharmaceuticals Incorporated and holds stock and/or stock options at the company

Graphic support was provided by Jonathan Kirk, M.S. who is an employee of Vertex Pharmaceuticals Incorporated and holds stock and/or stock options at the company

CLIMB THAL-111, **CLIMB SCD-121**, and **CLIMB-131** trials are sponsored by Vertex Pharmaceuticals Incorporated and CRISPR Therapeutics

1. CLIMB THAL-111; 2. CLIMB SCD-121

EBMT

52nd Annual Meeting

Madrid, Spain

22-25 March 2026

Advancing the Art of Patient Care

#EBMT26

Thanks!