

Efficacy and Safety of a Single Dose of Exagamglogene Autotemcel for Transfusion-Dependent β -Thalassemia and Severe Sickle Cell Disease

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Disclosures

Name of Company	Research Support	Employee	Consultant	Stockholder	Speaker's Bureau	Advisory Board	Other
Miltenyi					X		
Bellicum	X				X	X	
Amgen					X	X	
Jazz Pharm.					X		
Medac					X		
Neovii					X	X	
Novartis					X	X	
Sanofi						X	
SOBI					X		
Gilead					X		
BluebirdBio					X		
Vertex						X	

Exa-cel Is a Cell Therapy That Uses Non-Viral, *Ex Vivo* CRISPR/Cas9-Mediated Editing of *BCL11A* to Increase HbF Levels¹

- Naturally occurring genetic polymorphisms in *BCL11A* are associated with elevated HbF and decreased severity of TDT and SCD²⁻⁴
- *BCL11A* suppresses expression of γ -globin and thus HbF
- Editing of *Bcl11a* reactivates γ -globin expression and formation of HbF ($\alpha_2\gamma_2$) in mouse models⁴
- Exa-cel is produced using non-viral, *ex vivo* editing of the erythroid-specific enhancer region of *BCL11A* in CD34⁺ HSPCs and reduces erythroid-specific expression of *BCL11A*
- Infusion of exa-cel leads to an increase in HbF levels in erythroid cells *in vivo*

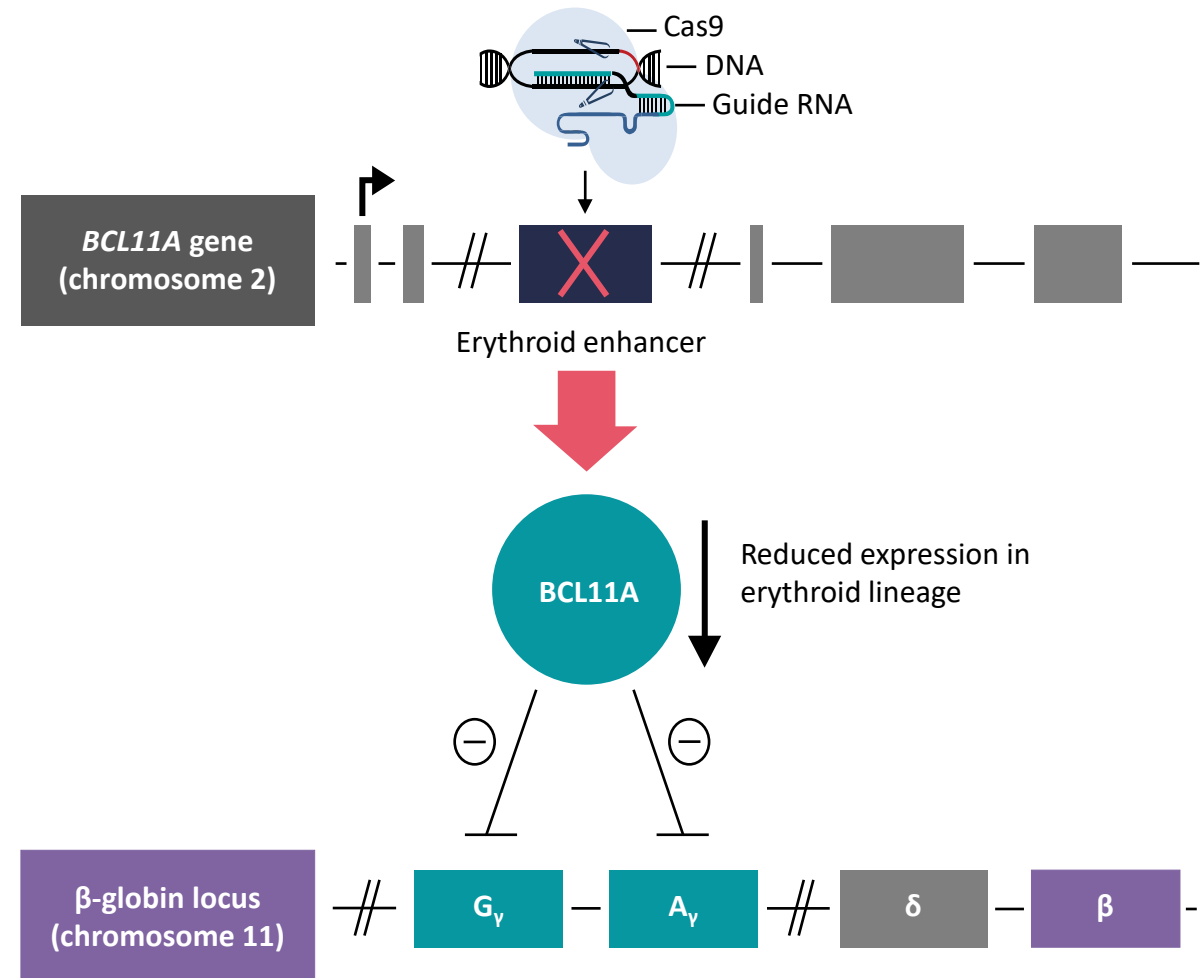


Figure modified from Canver, et al.¹

BCL11A, B-cell lymphoma/leukemia 11A; CRISPR, clustered regularly interspaced short palindromic repeats; DNA, deoxyribonucleic acid; HbF, fetal hemoglobin; HSPC, hematopoietic stem and progenitor cell; RNA, ribonucleic acid; SCD, sickle cell disease; TDT, transfusion dependent β -thalassemia.

1. Canver MC, et al. *Blood*. 2016;127:2536-2545; 2. Murray N, et al. *Br J Haematol*. 1988;69:89-92; 3. Bank A. *Blood*. 2006;107:435-443; 4. Bauer DE, et al. *Science*. 2013;342:253-257.

CLIMB THAL-111 and CLIMB SCD-121 Pivotal Trials of Exa-cel in Patients With TDT and Severe SCD Are Ongoing



Design	International, multicenter, open-label, single-arm pivotal study of exa-cel (NCT03655678)	International, multicenter, open-label, single-arm pivotal study of exa-cel (NCT03745287)
Key Inclusion Criteria	Twelve to 35 years of age with TDT, including β^0/β^0 genotypes, defined as a history of ≥ 100 mL/kg/year or ≥ 10 units/year of pRBC transfusions in the previous 2 years	Twelve to 35 years of age with severe SCD and a history of ≥ 2 VOCs per year in the previous 2 years
Primary Endpoint	<i>Primary efficacy endpoint:</i> Proportion of patients achieving a maintained weighted average Hb ≥ 9 g/dL without RBC transfusions for at least 12 consecutive months after exa-cel infusion	<i>Primary efficacy endpoint:</i> Proportion of patients who have not experienced any severe VOC for at least 12 consecutive months after exa-cel infusion
Clinical Assessments	Engraftment, total Hb, HbF, <i>BCL11A</i> edited alleles, transfusions, and AEs	Engraftment, total Hb, HbF, <i>BCL11A</i> edited alleles, transfusions, VOCs, and AEs

Data presented on all patients infused with exa-cel who have TDT (n = 44) or severe SCD (n = 31) as of February 2022 (N = 75)

Baseline Demographics and Clinical Characteristics of the 44 Patients With TDT Infused With Exa-cel



Exa-cel (TDT) n = 44	
Sex, n (%)	
Male	21 (47.7)
Female	23 (52.3)
Genotype, n (%)	
β^0/β^0	14 (31.8)
β^0/β^0 -like (β^0 /IVS-I-110; IVS-I-110/IVS-I-110)	12 (27.3)
Non- β^0/β^0 -like	18 (40.9)
Age at baseline, years, mean (min, max)	21.3 (12, 35)
Historical RBC transfusions per year,^a units, mean (min, max)	36.0 (15, 71)

RBC, red blood cell; TDT, transfusion dependent β -thalassemia.

^aAnnualized over 2 years before signing of the informed consent form or the latest rescreening.

Baseline Demographics and Clinical Characteristics of the 31 Patients With SCD Infused With Exa-cel



Exa-cel (SCD) n = 31	
Sex, n (%)	
Male	16 (51.6)
Female	15 (48.4)
Genotype, n (%)	
β^S/β^S	29 (93.5)
β^S/β^0	2 (6.5)
Age at baseline, years, mean (min, max)	22.5 (12, 34)
Historical VOC episodes per year,^a mean (min, max)	3.9 (2.0, 9.5)

SCD, sickle cell disease; VOC, vaso-occlusive crisis.

^aAnnualized rate during the 2 years before signing of the informed consent form or the latest rescreening.

All Patients Engrafted Neutrophils and Platelets After Exa-cel Infusion



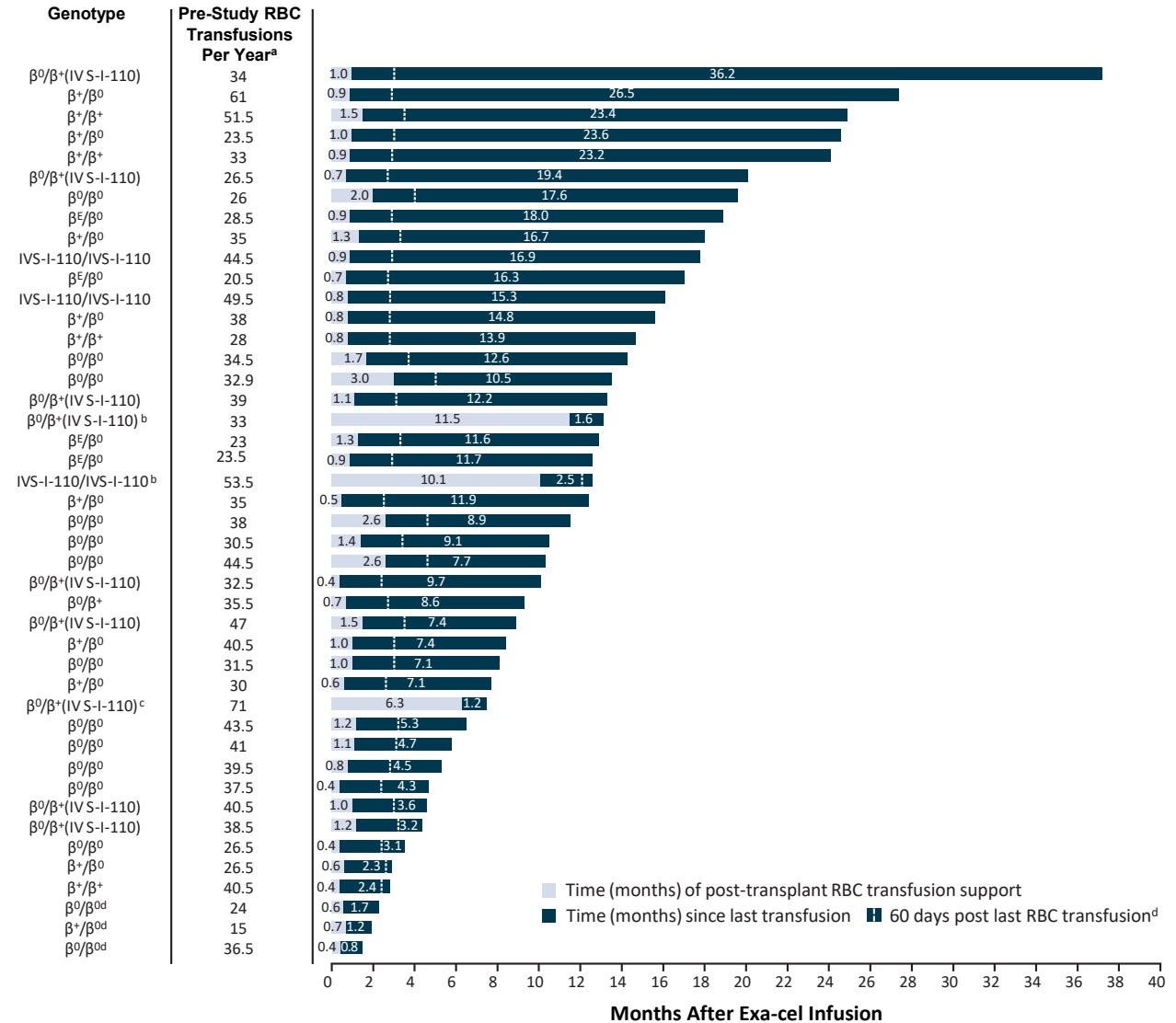
	Exa-cel (TDT) n = 44	Exa-cel (SCD) n = 31
Drug product cell dose,^a median (range) CD34 ⁺ cells × 10 ⁶ /kg	7.5 (3.0, 19.7)	4.0 (2.9, 14.4)
Neutrophil engraftment,^b median (range) Study Day ^c	29.0 (12, 56)	27.0 (15, 38)
Platelet engraftment,^d median (range) Study Day ^c	43.5 (20, 213)	32.0 (23, 74)
Duration of follow-up, median (range) Months ^c	11.9 (1.2, 37.2)	10.2 (2.0, 32.3)

SCD, sickle cell disease; TDT, transfusion dependent β-thalassemia.

^aAcross multiple drug product lots per patient; ^bDefined as the first day of 3 consecutive measurements of absolute neutrophil count ≥500 cells/μL on 3 different days; ^cDefined as day after exa-cel infusion; ^dDefined as the first day of 3 consecutive measurements of unsupported (no platelet transfusion in last 7 days) platelet count ≥20,000/μL on 3 different days after exa-cel infusion (TDT) and as the first day of 3 consecutive measurements of unsupported (no platelet transfusions for last 7 days) platelet count ≥50,000/μL on 3 different days after exa-cel infusion (SCD).

Forty-Two of 44 Patients With TDT Treated With Exa-cel Are Transfusion-Free

- Time (months) of post-transplant RBC transfusion support is indicated by the light blue bar and time (months) since last transfusion is indicated by the dark blue bar
- 42 of 44 patients stopped RBC transfusions (duration from 0.8 to 36.2 months)
- Two patients had not yet stopped transfusions but have 75% and 89% reductions in transfusion volume



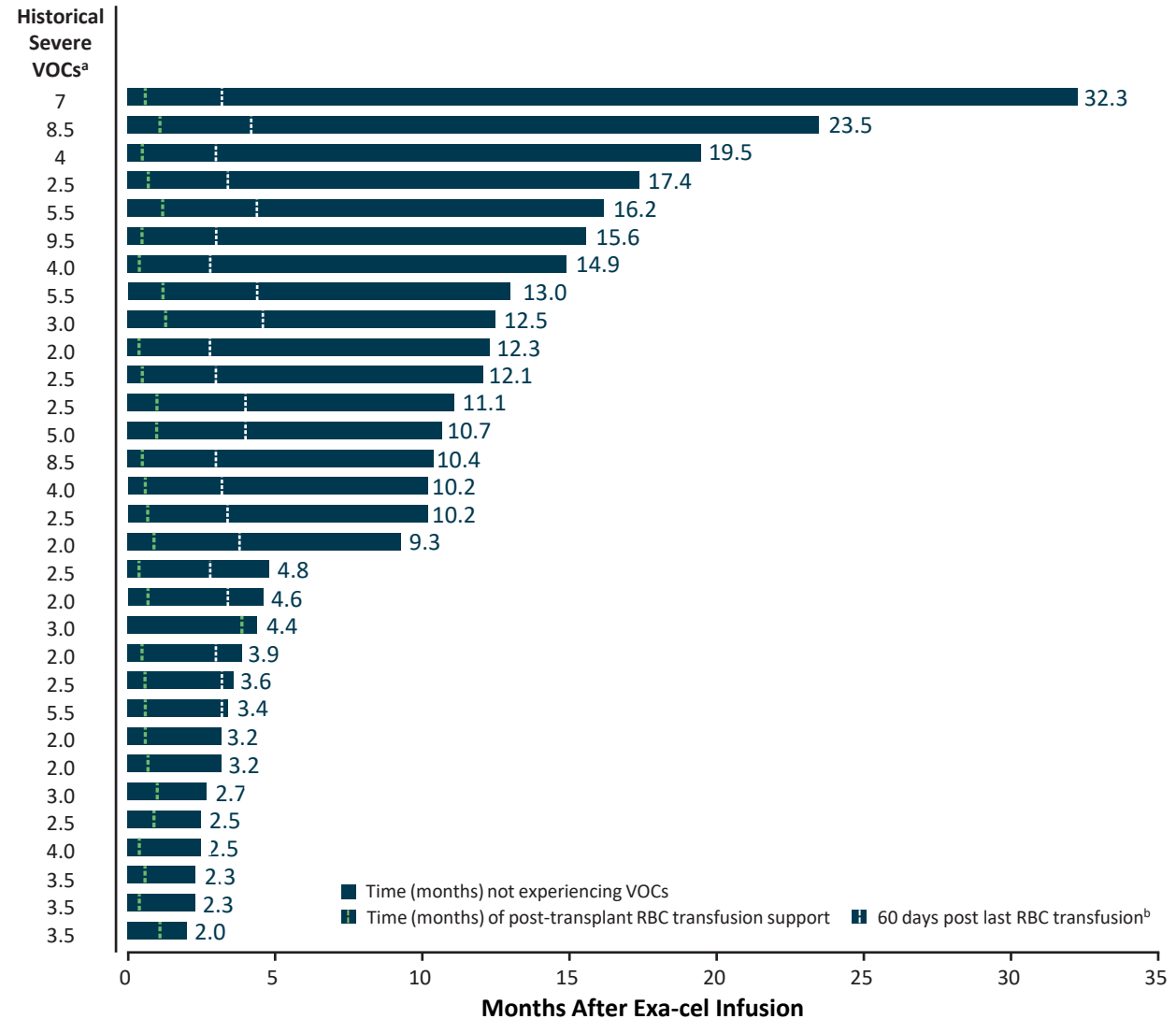
Hb, hemoglobin; RBC, red blood cell; TDT, transfusion-dependent β -thalassaemia.

Each row in the figure on the right represents an individual patient.

^aNumber of transfusion units annualized over 2 years; ^bReceived RBC transfusions at or after data cut; ^cPatient stopped transfusions after data cut; ^dPatients are evaluable for elimination of transfusions starting 60 days after their last transfusion.

All Patients With SCD Treated With Exa-cel are VOC-Free

- Time (months) since exa-cel infusion is indicated by the dark bar
- 31 of 31 patients were VOC-free after exa-cel infusion (duration from 2.0 to 32.3 months)

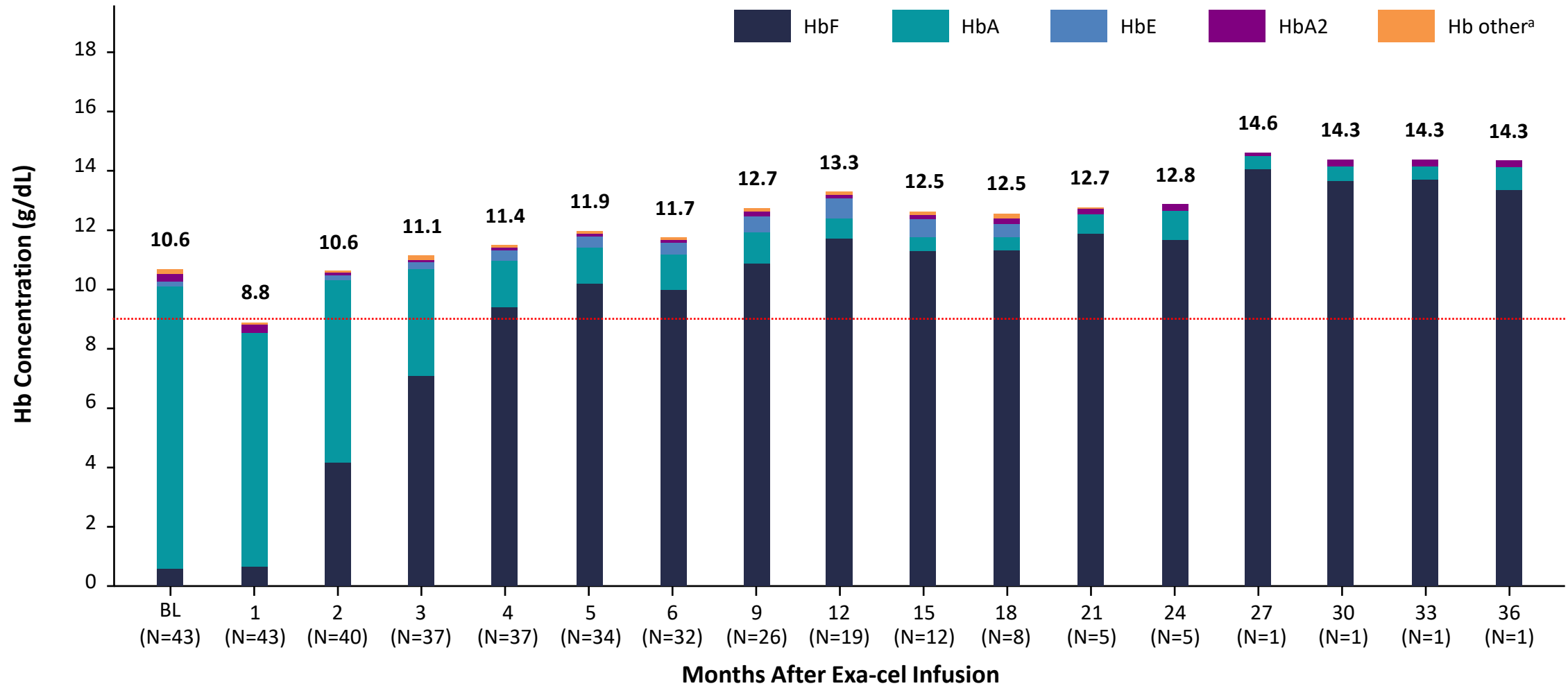


RBC, red blood cell; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

Each row in the figure on the right represents an individual patient.

^aPre-study severe VOCs annualized over 2 years; ^bPatients are evaluated for elimination of VOCs starting 60 days after their last transfusion.

Patients With TDT Had Early Increases in HbF That Drive Increases in Total Hb Above the Transfusion Threshold

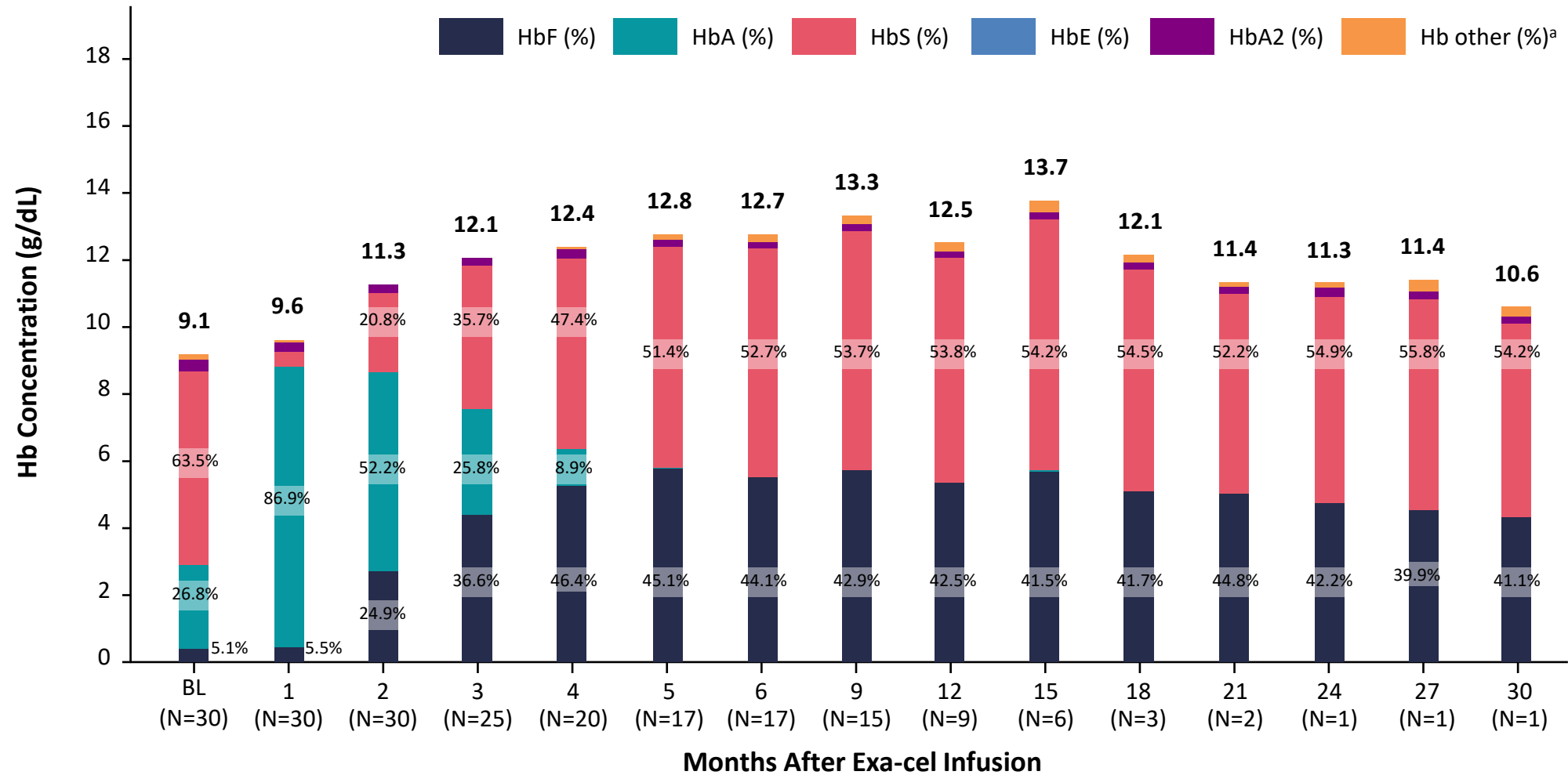


BL, baseline; Hb, hemoglobin; HbA, adult hemoglobin; HbA2, hemoglobin, alpha 2; HbE, hemoglobin E; HbF, fetal hemoglobin; TDT, transfusion-dependent β -thalassemia.

Mean total Hb concentrations are shown directly above bars.

^aHb adducts and other variants.

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

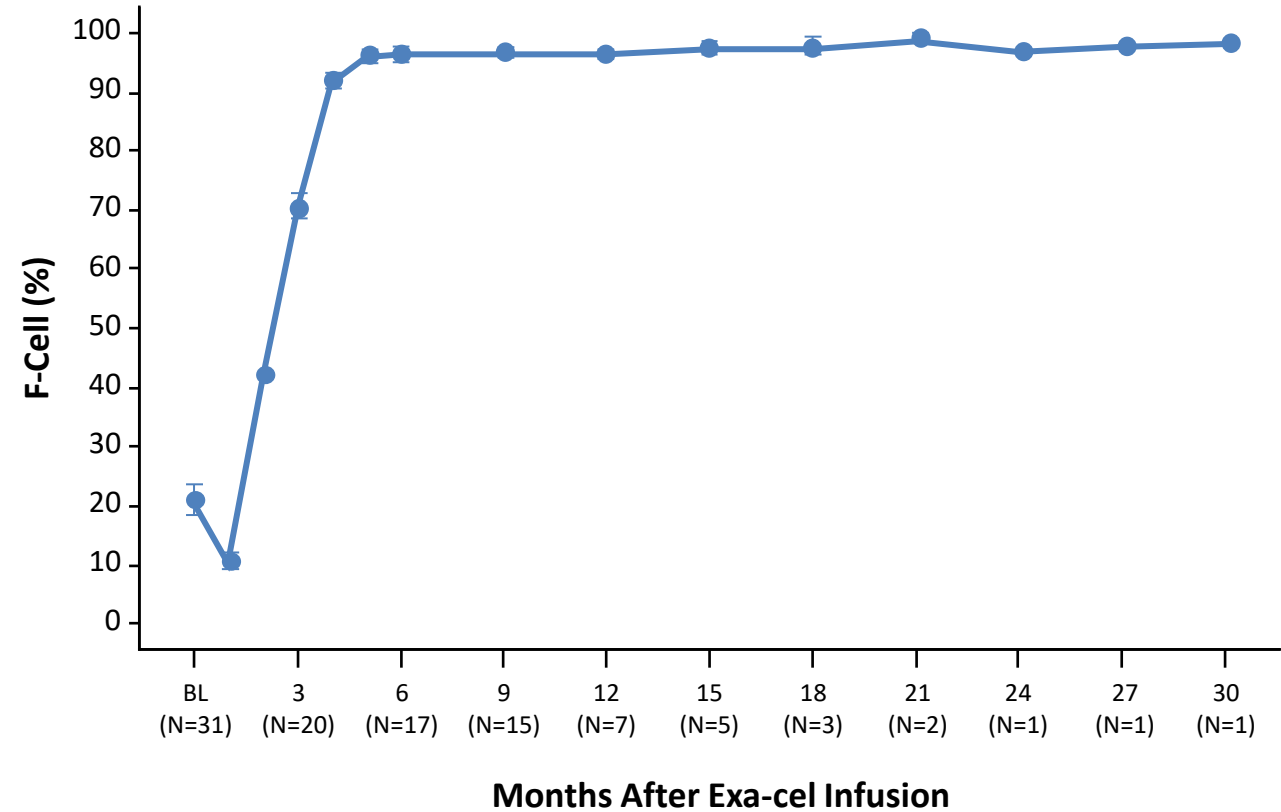
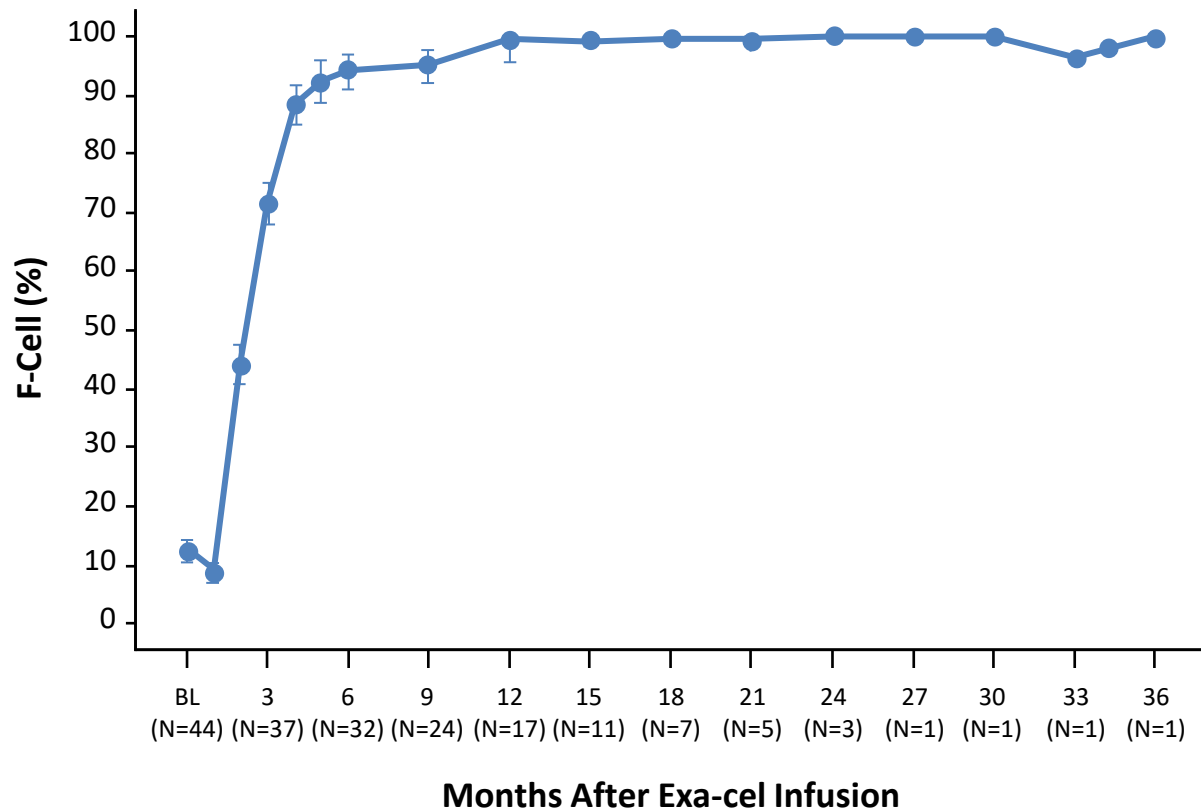


BL, baseline; Hb, hemoglobin; HbA, adult hemoglobin; HbA2, hemoglobin, alpha 2; HbE, hemoglobin E; HbF, fetal hemoglobin; HbS, sickle hemoglobin; SCD, sickle cell disease.

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

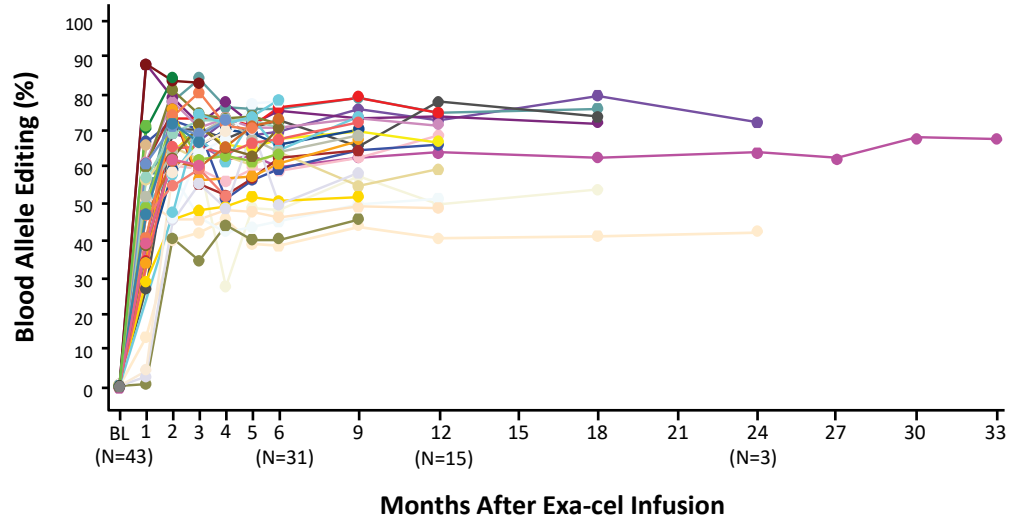
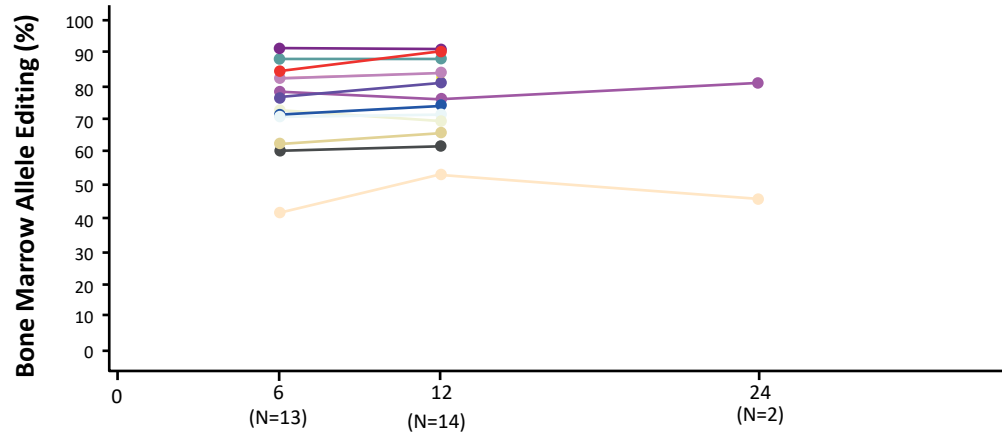
^aHb adducts and other variants.

Pancellular Distribution of HbF Is Maintained Over Time

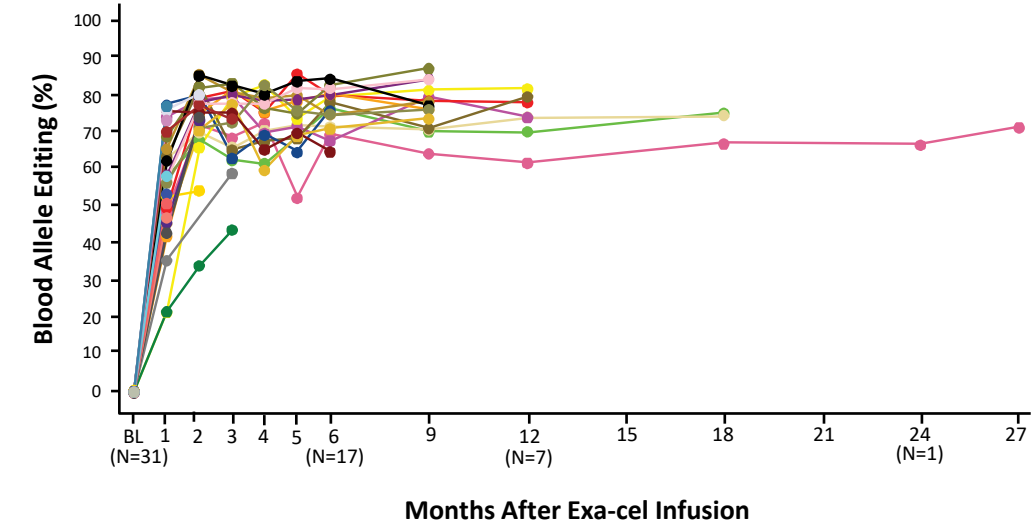
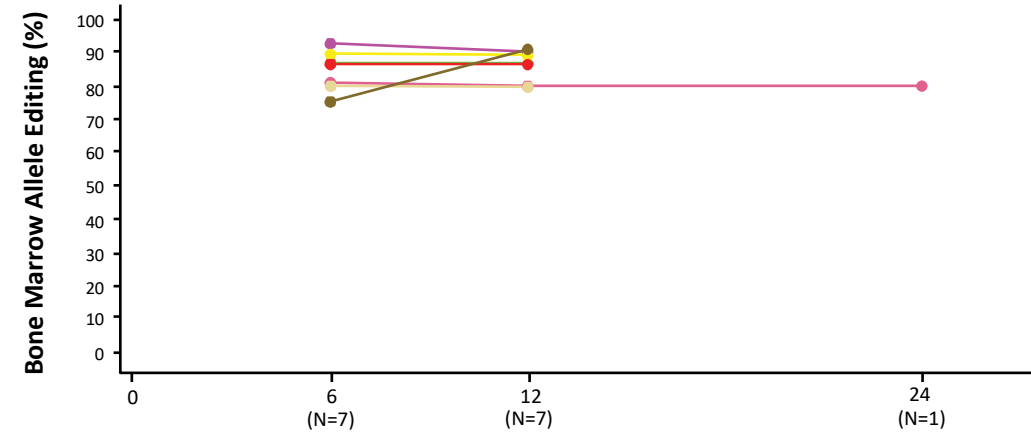


Durable *BCL11A* Editing Achieved in Bone Marrow (CD34⁺ Cells) and Peripheral Blood (Nucleated Cells)

CLIMB
THAL-111



CLIMB
SCD-121



Exa-cel Safety Profile Is Consistent With That of Busulfan Myeloablation and Autologous HSCT



Post-Exa-cel AE Overview	TDT (n = 44)	SCD (n = 31)
Patient-time exposure, Patient-months	520.2	288.6
Patients with any AEs, n (%)	44 (100.0)	31 (100.0)
Patients with AEs related to exa-cel, n (%) ^a	12 (27.3)	9 (29.0)
Patients with AEs related to busulfan, n (%) ^a	43 (97.7)	31 (100.0)
Patients with AEs Grade 3/4, n (%)	38 (86.4)	31 (100.0)
Patients with SAEs, n (%)	15 (34.1)	10 (32.3)
Patients with SAEs related to exa-cel, n (%) ^a	2 (4.5)	0
Patients with AEs leading to death, n (%)	0	0

AE, adverse event; HSCT, hematopoietic stem cell transplantation; SAE, serious adverse event; SCD, sickle cell disease; TDT, transfusion-dependent β -thalassemia.

^aIncludes related and possibly related AEs.

Two Patients With TDT and No Patients With SCD Had Exa-cel Related SAEs

- One patient with TDT had 3 SAEs related to exa-cel of hemophagocytic lymphohistiocytosis (HLH; macrophage activation syndrome), acute respiratory distress syndrome, and headache, and 1 SAE of idiopathic pneumonia syndrome related to both exa-cel and busulfan
 - All began peri-engraftment and occurred in the context of HLH. Events fully resolved with steroid and immunosuppressant treatment
 - HLH is a systemic hyperinflammatory non-infectious syndrome that has been reported after autologous HSCT
- One patient with TDT had SAEs related to both exa-cel and busulfan of delayed neutrophil engraftment and thrombocytopenia
 - Both SAEs resolved. Neutrophil engraftment was achieved on Day 56 without use of backup cells
 - All other patients in both exa-cel trials achieved neutrophil engraftment within 43 days of exa-cel infusion
- No patients with SCD had an SAE considered related or possibly related to exa-cel

Conclusions

- Data from 75 patients with TDT and severe SCD shows a **single dose of exa-cel leads to early increases in HbF and total Hb** that are durable up to 3 years
- 42 of 44 patients with TDT **stopped RBC transfusions** and all 31 patients with severe SCD are **free of VOCs**
- Patients with ≥ 1 year of follow up have stable proportions of *BCL11A* edited alleles in bone marrow and peripheral blood, **indicating successful and durable editing** of long-term HSCs
- **Safety profile of exa-cel is consistent** with that of busulfan myeloablative conditioning and autologous hematopoietic stem cell transplantation
- Exa-cel has the potential to be the first CRISPR/Cas9-based therapy to provide a **functional cure for patients with TDT and severe SCD**

Treatment with exa-cel is associated with early, consistent, and durable increases in HbF levels leading to elimination of transfusions in almost all patients with TDT and elimination of VOCs in all patients with SCD

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