Safety and Efficacy of CTX001™ in Patients With Transfusion-Dependent β-Thalassemia or Sickle Cell Disease: Early Results From the CLIMB THAL-111 and CLIMB SCD-121 Studies of Autologous CRISPR-CAS9-Modified CD34^{+} Hematopoietic Stem and Progenitor Cells

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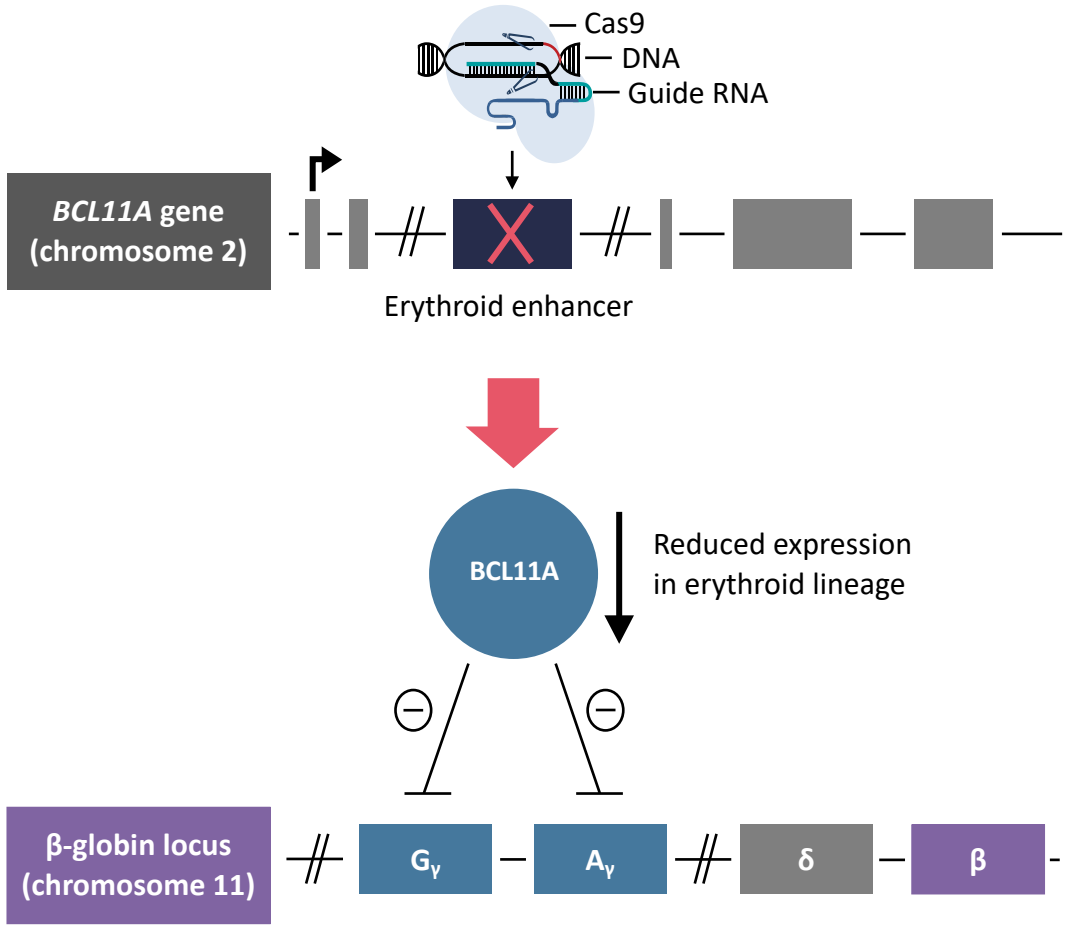
Studies in Patients With Transfusion-dependent β-Thalassemia (TDT) and Sickle Cell Disease (SCD) Are Ongoing

	CLIMB THAL-111	CLIMB SCD-121
Design	Phase 1 / 2, international, multicenter, open-label, single-arm study (NCT03655678)	Phase 1 / 2, international, multicenter, open-label, single-arm study (NCT03745287)
Target enrollment	45 patients aged 12 to 35 years with TDT, including β^0 / β^0 genotypes, defined as a history of at least 100 mL/kg/year or 10 units/year of pRBC transfusions in the previous 2 years	45 patients aged 12 to 35 years with severe SCD and a history of ≥2 vaso-occlusive crises per year over the previous 2 years
Primary endpoints	Proportion of patients achieving sustained transfusion reduction of 50% for at least 6 months starting 3 months after CTX001 infusion	Proportion of patients with HbF ≥20% sustained for at least 3 months starting 6 months after CTX001 infusion

Here, we present safety and efficacy results from the first 10 patients infused with CTX001

HbF: fetal hemoglobin; pRBC: packed red blood cell; SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia.

CRISPR-Cas9-Mediated Editing of *BCL11A* Increases HbF Levels[1]

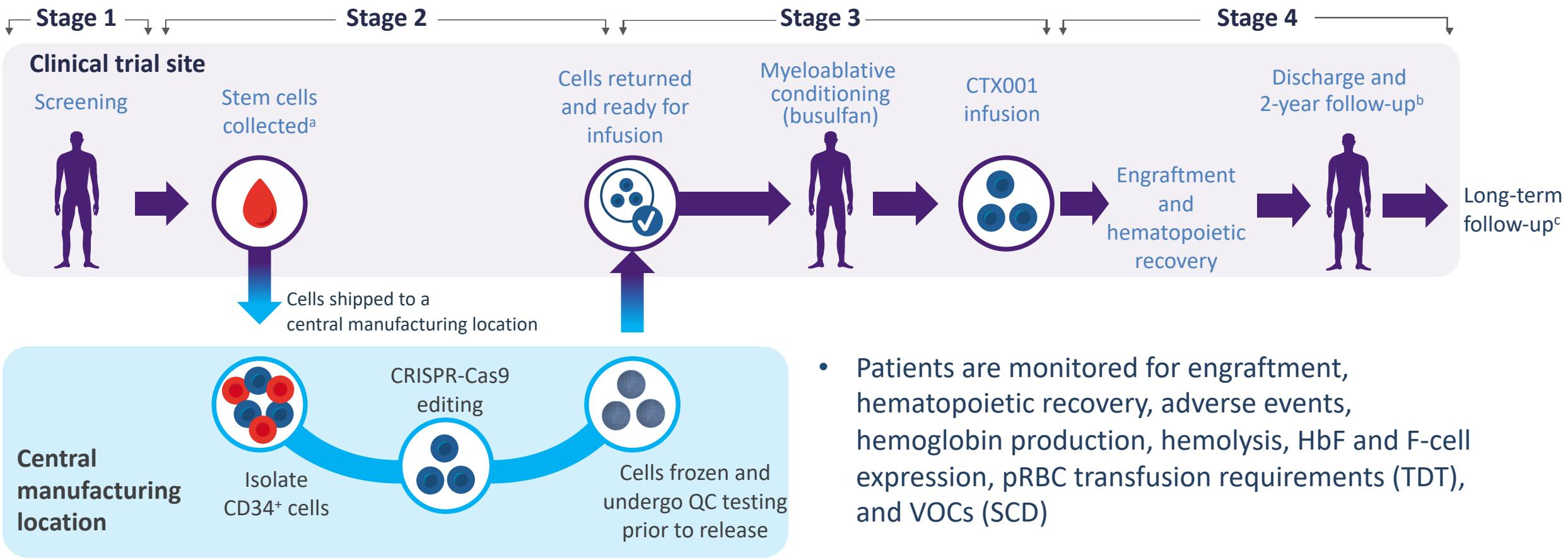


- Naturally occurring genetic polymorphisms in *BCL11A* are associated with elevated HbF and decreased severity of TDT and SCD[2-4]
- BCL11A suppresses expression of HbF
- Editing of *BCL11A* results in reactivation of γ-globin expression and formation of HbF ($\alpha 2\gamma 2$) in mouse models
- CTX001 is produced using ex vivo editing of the erythroid enhancer region of *BCL11A* in $CD34^+$ HSPCs and reduces erythroid-specific expression of BCL11A
- Infusion of CTX001 leads to an increase in HbF levels in erythroid cells in vivo

HbF: fetal hemoglobin; HSPCs: hematopoietic stem progenitor cells; SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia.

1. Figure modified from Canver MC, Orkin SH. *Blood*. 2016;127:2536-2545; 2. Murray N, et al. *Br J Haematol*. 1988;69:89-92; 3. Conley CL, et al. *Blood*. 1963;21:261-281; 4. Bank A. *Blood*. 2006;107:435-443.

CTX001 Infusion Process



- Patients are monitored for engraftment, hematopoietic recovery, adverse events, hemoglobin production, hemolysis, HbF and F-cell expression, pRBC transfusion requirements (TDT), and VOCs (SCD)

F-cell: HbF-containing cell; HbF: fetal hemoglobin; pRBC: packed red blood cell; SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia; QC: quality control; VOCs: vaso-occlusive crises.
[a]Patients enrolled in CLIMB THAL-111 received a combination of plerixafor and filgrastim for mobilization, while patients enrolled in CLIMB SCD-121 received plerixafor only. Back-up cells kept at site as a safety measure; [b]Patients will be followed for 24 months after CTX001 infusion with physical exams, laboratory and imaging assessments, and adverse-event evaluations; [c]All patients who receive CTX001 will be followed for 15 years in a long-term follow-up study (NCT04208529) after completion or withdrawal from CLIMB THAL-111 or CLIMB SCD-121.

TDT: Patient Baseline and Treatment Characteristics

Patients with ≥3-month follow-up (n=7)

Patient characteristics		
Genotype, n	**β^+ / β^+**	**2**
	β^0 / β^+ (not IVS-I-110)	**2**
	β^0 / β^+ (IVS-I-110)[a]	**2**
	β^0 / β^0	**1**
Gender, Female/Male, n		**5/2**
Age at consent, years Median (range)		**23** (19 – 26)
Pre-study pRBC transfusions[b]		
Units/year, median (range)		**33.0** (23.5–61.0)
Transfusions episodes/year, median (range)		**15.0** (12.5–16.5)

Treatment characteristics	Median (range)
Drug product cell dose, $CD34^+$ cells × 10^6/kg	**11.6** (4.5 – 16.6)
Neutrophil engraftment,[c] Study Day[d]	**32** (20 – 39)
Platelet engraftment,[e] Study Day[d]	**37** (29 – 52)
Duration of follow-up, Months	**8.9** (3.8 – 21.5)

pRBC: packed red blood cell; TDT: transfusion-dependent β-thalassemia.

[a]IVS-I-110 phenotype is severe and similar to β^0 / β^0; [b]Annualized number during the 2 years before consenting to study participation; [c]Defined as the first day of 3 measurements of absolute neutrophil count ≥500 cells/µL on 3 consecutive days; [d]Study day defined as day after CTX001 infusion; [e]Defined as the first day of 3 consecutive measurements of platelet count ≥20,000/µL on 3 different days after CTX001 infusion, without a platelet transfusion in the past 7 days.

TDT: Summary of Adverse Events

Patients with ≥3-month follow-up (n=7)

AEs were generally consistent with myeloablation and autologous stem cell transplant

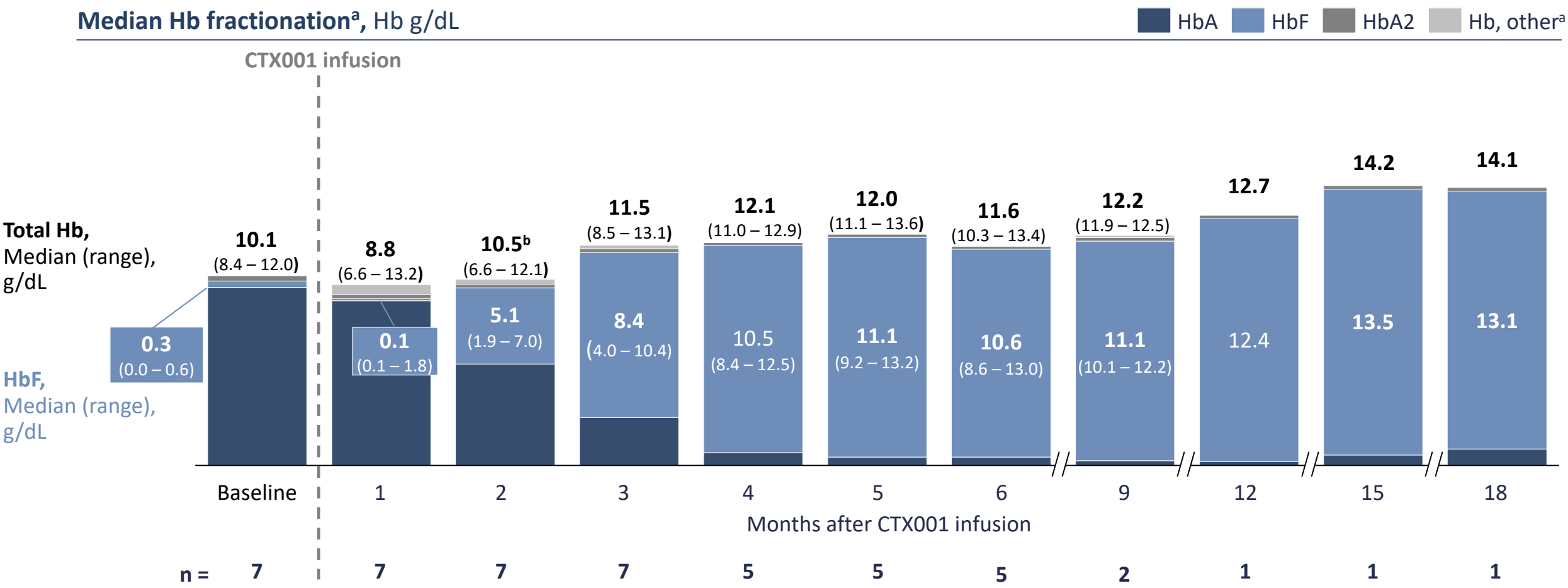
Months of follow-up, median (range)	8.9 (3.8–21.5)	
	Patients with non-serious AEs, n	**Patients with SAEs,** n
Relationship[a]		
Related to plerixafor and/or G-CSF	6	0
Related to busulfan only	7	2
Related to CTX001 only	1[b]	1
Related to busulfan and CTX001	3[c]	1
Not related to any study drug	7	4

- Majority of AEs occurred within first 60 days after CTX001 infusion
- 2 patients experienced a combined total of 5 SAEs related or possibly related to busulfan only: venoocclusive liver disease (in both patients), febrile neutropenia (2 events in 1 patient), and colitis; all resolved
- One patient experienced 4 SAEs related or possibly related to CTX001: headache, haemophagocytic lymphohistiocytosis (HLH), acute respiratory distress syndrome, and idiopathic pneumonia syndrome (latter also related to busulfan). All SAEs occurred in the context of HLH and have resolved.
- No CTX001-related SAEs were reported in the other patients

AEs: adverse events; G-CSF: granulocyte colony-stimulating factor; SAEs: serious adverse events.

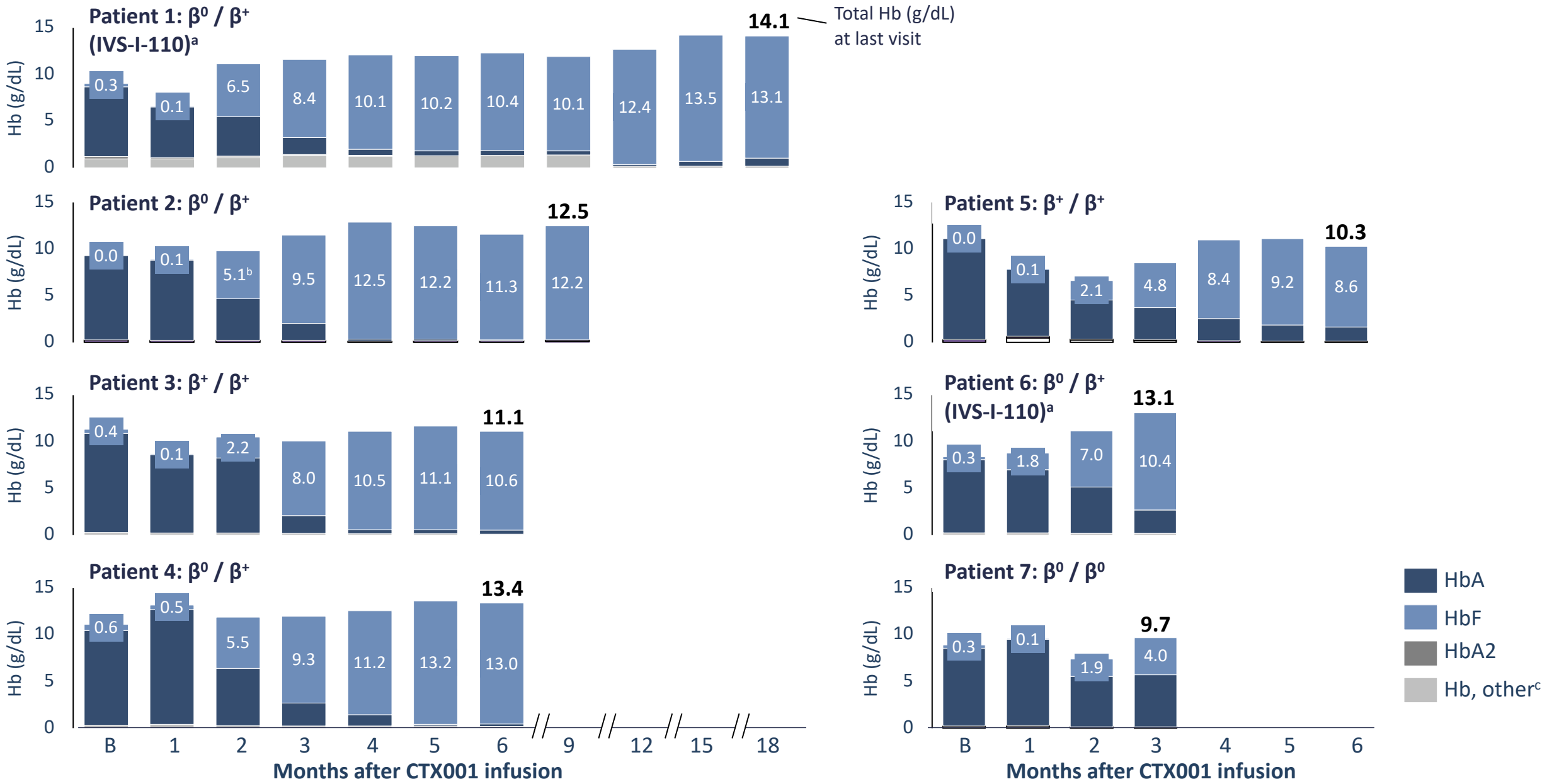
[a]Includes related and possibly related AEs. [b]1 patient experienced a non-serious AE of anaemia possibly related to CTX001 (resolved). [c]3 patients experienced non-serious AEs related or possibly related to busulfan and CTX001: petechiae, pyrexia, epistaxis, lymphocyte count decreased, neutrophil count decreased, WBC count decreased, and platelet count decreased.

TDT: Clinically Meaningful HbF and Total Hb Are Achieved Early and Maintained



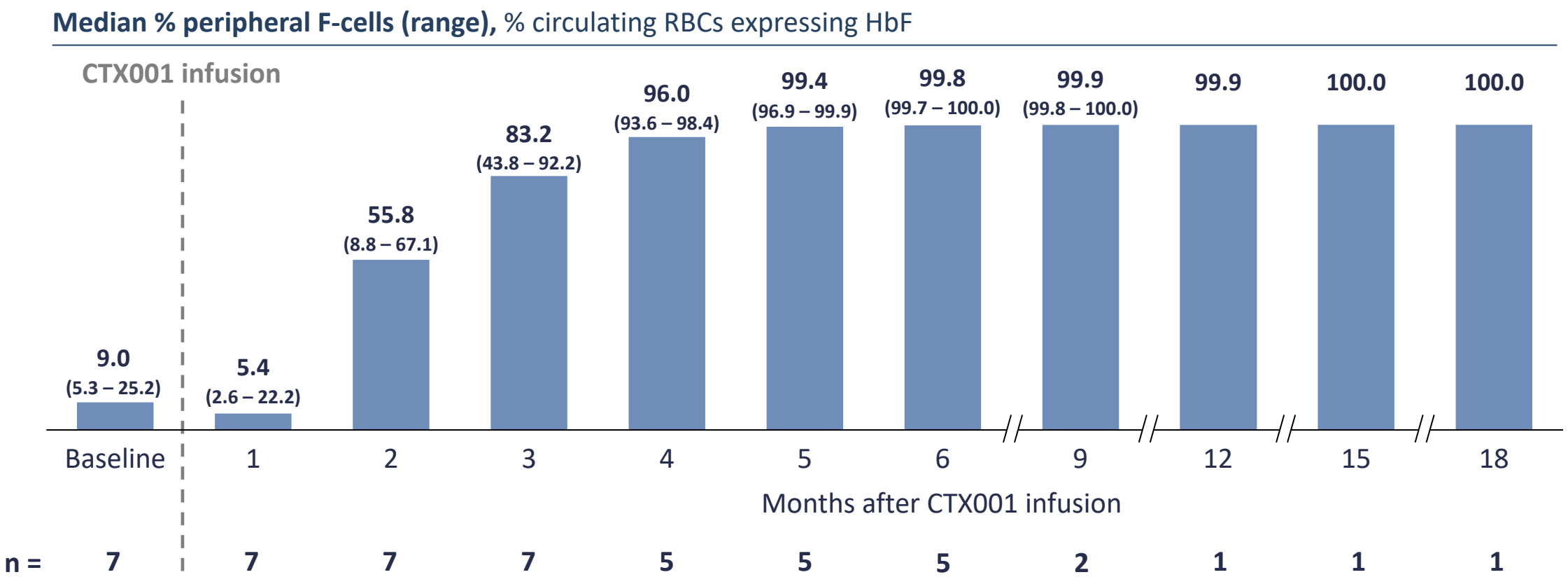
Hb: hemoglobin; HbA: adult hemoglobin; HbF: fetal hemoglobin; TDT: transfusion-dependent β-thalassemia.
[a]Hb adducts and other variants. [b]With respect to Patient 2, Total Hb from local laboratory and Hb fraction from central laboratory.

TDT: Early, Sustained Increases in Total Hb & HbF Across Genotypes



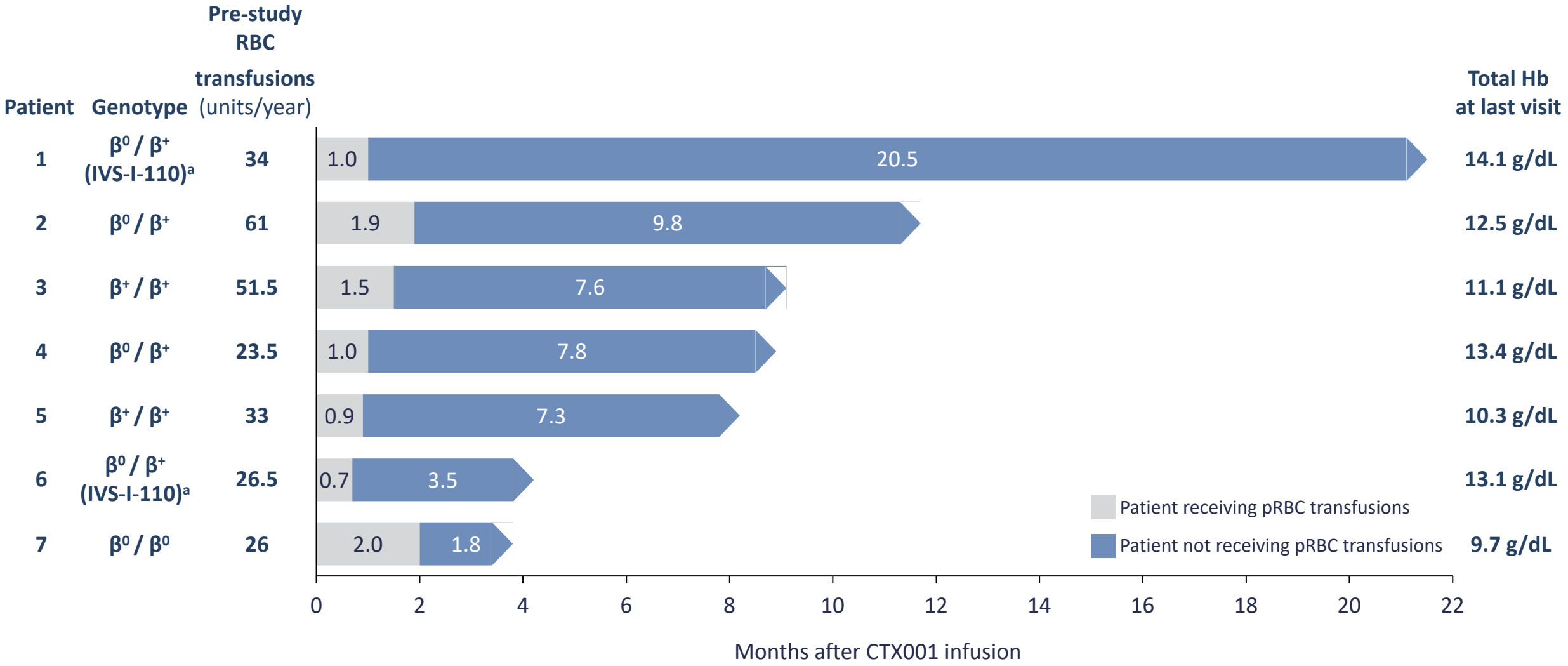
B: Baseline, Hb: hemoglobin; HbA: adult hemoglobin; HbF: fetal hemoglobin; TDT: transfusion-dependent β-thalassemia. [a]Total Hb from local laboratory and Hb fraction from central laboratory.
[a]IVS-I-110 phenotype is severe and similar to β⁰ / β⁰ [c]Hb adducts and other variants

TDT: Pancellular Expression of HbF Is Maintained



F-cells: HbF-containing cells; HbF: fetal hemoglobin; RBCs: red blood cells; TDT: transfusion-dependent β-thalassemia.

TDT: Duration of Transfusion Independence After CTX001



[a]IVS-I-110 phenotype is severe and similar to β^0 / β^0.

Hb: hemoglobin; pRBC: packed red blood cell; RBC: red blood cell; TDT: transfusion-dependent β-thalassemia.

SCD: Patient Baseline and Treatment Characteristics

Patients with ≥3-month follow-up (n=3)

Patient characteristics		
Genotypes, n	**β^S / β^S**	**3**
Gender, Female/Male, n		**2/1**
Age at consent, years Median (range)		**22** (22 – 33)
Pre-study VOCs VOCs/year[a], Median (range)		**7** (4.0 – 7.5)

Treatment characteristics	**Median** (range)
Drug product cell dose,[b] $CD34^+$ cells × 10^6/kg	**3.8** (3.1 – 3.9)
Neutrophil engraftment,[c] Study Day[d]	**22** (17 – 30)
Platelet engraftment,[e] Study Day[d]	**30** (30 – 33)
Duration of follow-up, Months	**7.8** (3.8 – 16.6)

SCD: sickle cell disease; VOCs: vaso-occlusive crises.

[a]Annualized rate during the 2 years before consenting to study participation; [b]Across multiple drug product lots per patient; [c]Defined as the first day of 3 measurements of absolute neutrophil count ≥500 cells/µL on 3 consecutive days; [d]Study day defined as day after CTX001 infusion [e]Defined as the first day of 3 consecutive measurements of platelet count ≥50,000/µL on 3 different days after CTX001 infusion, without a platelet transfusion in the past 7 days.

SCD: Summary of Adverse Events

Patients with ≥3-month follow-up (n=3)

AEs were generally consistent with myeloablation and autologous stem cell transplant

Months of follow-up, *median (range)*	7.8 (3.8 – 16.6)	
	Patients with non-serious AEs, n	**Patients with SAEs,** n
Relationship[a]		
Related to plerixafor only	3	1
Related to busulfan only	3	1
Related to CTX001 only	0	0
Related to busulfan and CTX001	2[b]	0
Not related to any study drug	3	2

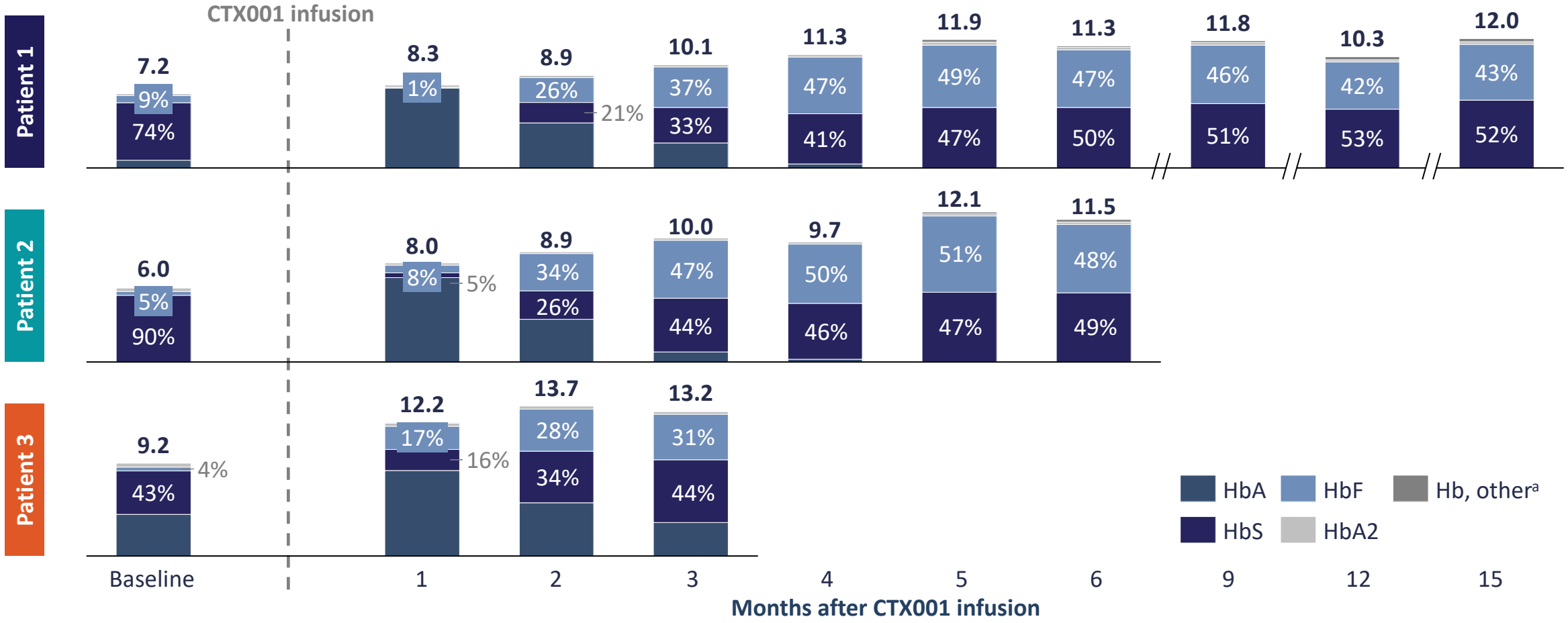
- Majority of AEs occurred within first 60 days after CTX001 infusion
- 1 patient experienced SAEs related to plerixafor: chest pain, neck pain, headache, and abdominal pain; all resolved
- Post-CTX001, only 1 patient experienced SAEs: sepsis (related to busulfan), cholelithiasis, and abdominal pain (both unrelated to any study drug); all resolved
- There were no SAEs related to CTX001

AEs: adverse events; SAEs: serious adverse events.

[a]Includes related and possibly related AEs. [b]2 patients experienced non-serious AEs related or possibly related to busulfan and CTX001: lymphopenia and dermatitis.

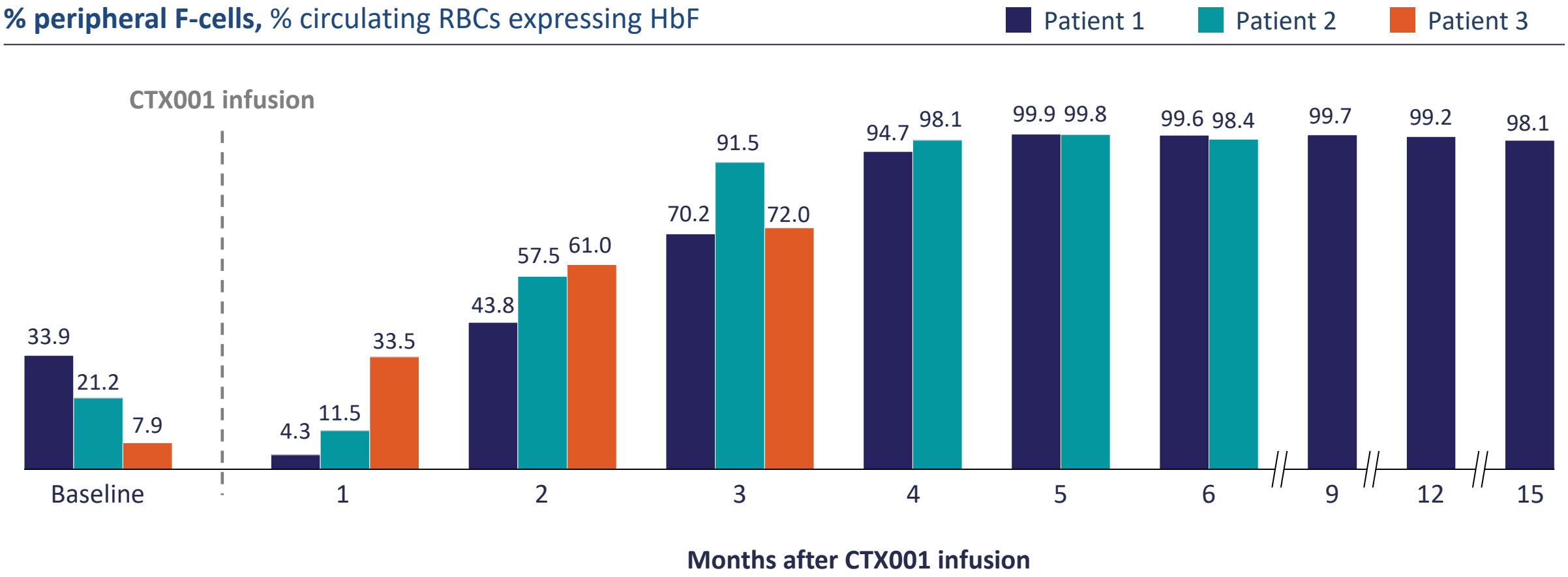
SCD: Clinically Meaningful HbF and Total Hb Are Achieved Early and Maintained

Hb fractionation[a], Hb g/dL



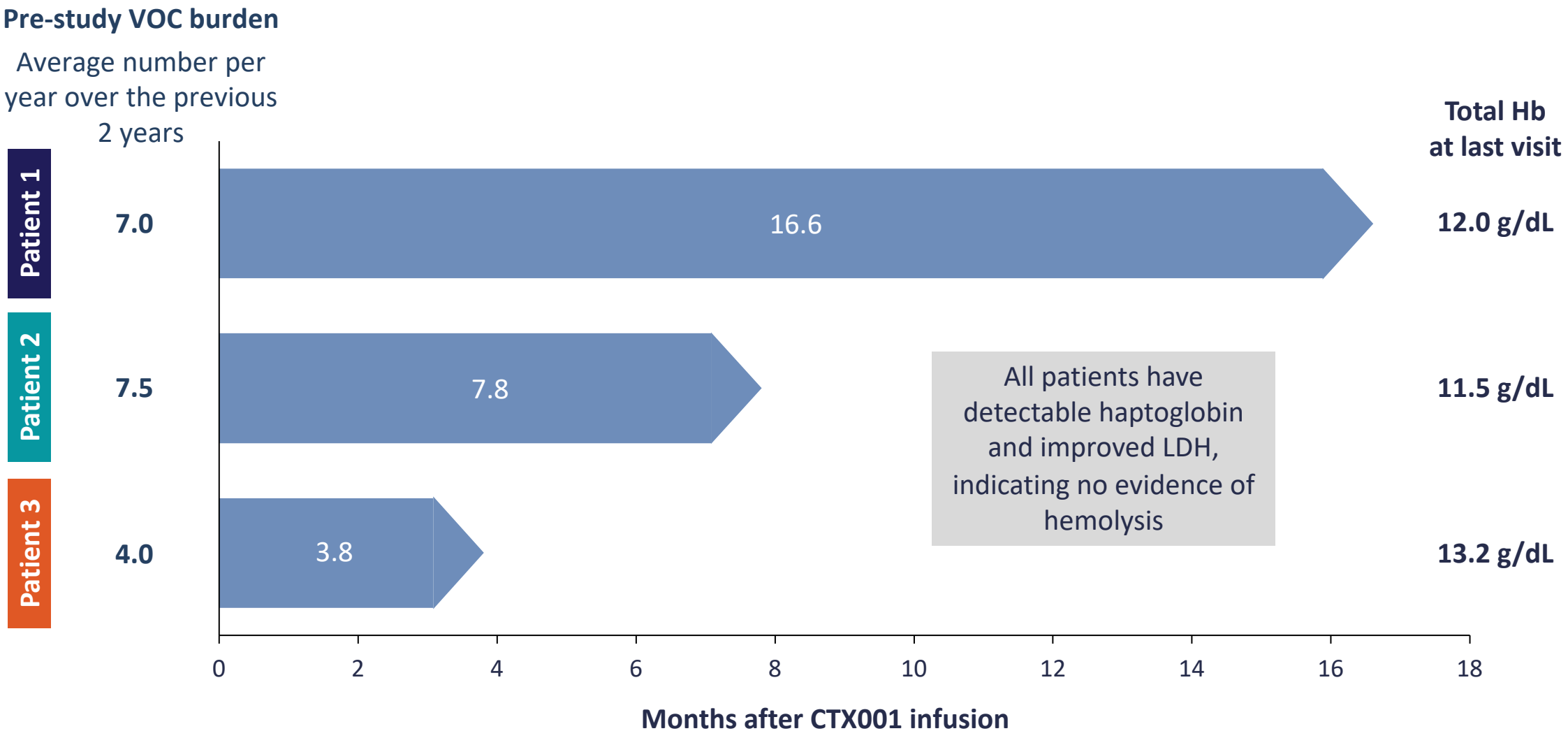
Hb: hemoglobin; HbA: adult hemoglobin; HbF: fetal hemoglobin; HbS: sickle hemoglobin; SCD: sickle cell disease.
[a]Hb adducts and other variants.

SCD: Pancellular HbF Expression is Maintained



F-cells: HbF-containing cells; HbF: fetal hemoglobin; RBCs: red blood cells; SCD: sickle cell disease.

SCD: Duration VOC-free After CTX001



SCD: sickle cell disease; VOCs: vaso-occlusive crises.

Durable *BCL11A* Editing Observed in Bone Marrow CD34^{+} Cells

Patients with ≥6-month follow-up (n=5 TDT patients, n=2 SCD patients)[a]

	Total follow-up, months	Allelic editing in CD34^{+} bone marrow cells, %	
		6-month visit	12-month visit
1	21.5	78.1	76.1
2	11.7	41.8	
3	9.1	72.6	
4	8.9	76.6	
5	8.2	88.1	
1	16.6	81.4	80.4
2	7.8	87.3	

TDT

SCD

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

[a]Bone marrow editing assessments performed starting at 6 months, 12 months, and 24 months of follow-up.

Conclusions

The first 10 patients treated with CTX001 have been followed for 3.8 to 21.5 months and have stopped transfusions (TDT) and are VOC-free (SCD)

- Overall safety profile is generally consistent with myeloablative conditioning and autologous bone marrow transplant
- Clinically meaningful HbF and total hemoglobin levels are observed early and maintained across all 10 patients
- Clinical proof-of-concept for CTX001 has now been demonstrated for both TDT and SCD
- These data demonstrate that CTX001 is a potential functional cure for the treatment of TDT and SCD

HbF: fetal hemoglobin; SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia; VOCs: vaso-occlusive crises.

Thank You to Study Participants and Their Families

CLIMB THAL-111 and CLIMB SCD-121 sites

Both

- Lucille Packard Children's Hospital of Stanford University, Palo Alto
- Columbia University Medical Center, New York
- The Children's Hospital at TriStar Centennial Medical Center / Sarah Cannon Center for Blood Cancers, Nashville
- The Hospital for Sick Children, Toronto
- Regensburg University Hospital, Clinic and Polyclinic for Paediatric and Adolescent Medicine, Paediatric Haemotology, Oncology and Stem Cell Transplantation
- Dipartimento di Onco-Ematologia e Terapia Cellulare e Genica Ospedale Pediatrico Bambino Gesù – IRCCS, Rome
- Imperial College Healthcare, London

SCD-121

- University of Illinois at Chicago Hospitals and Health Systems
- Children's Hospital of Philadelphia
- St. Jude Children's Research Hospital, Memphis
- Methodist Children's Hospital / Texas Transplant Institute, San Antonio
- Hôpital Universitaire des Enfants Reine Fabiola, Brussels

THAL-111

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- University Hospital Tübingen

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