
EUROPEAN
HEMATOLOGY
ASSOCIATION
EHA25
VIRTUAL
25th Congress of the European Hematology Association
VIRTUAL EDITION

Initial Safety and Efficacy Results with a Single Dose of Autologous CRISPR-Cas9-Modified CD34+ Hematopoietic Stem and Progenitor Cells in Transfusion-Dependent β-Thalassemia and Sickle Cell Disease

Selim Corbacioglu[1], Maria Domenica Cappellini[2], John Chapin[3], Nicole Chu-Osier[4], Christine Marie Fernandez[3], Juergen Foell[1], Josu de la Fuente[5], Stephan Grupp[6], Tony W. Ho[3], Antonis Kattamis[7], Julie Lekstrom-Himes[4], Franco Locatelli[8], Yimeng Lu[4], Mariane de Montalembert[9], Damiano Rondelli[10], Ainsley Ross[3], Niraj Shanbhag[4], Sujit Sheth[11], Sandeep Soni[12], Martin H. Steinberg[13], Donna A. Wall[14], Haydar Frangoul[15]

[1]Paediatric Haemotology, Oncology and Stem Cell Transplantation, Regensburg University Hospital, Clinic and Polyclinic for Paediatric and Adolescent Medicine, Regensburg, Germany; [2]Department of Clinical Sciences and Community, University of Milan, IRCCS Ca' Granda Foundation Maggiore Policlinico Hospital, Milan, Italy; [3]CRISPR Therapeutics, Cambridge, United States; [4]Vertex Pharmaceuticals Incorporated, Boston, United States; [5]Imperial College Healthcare NHS Trust, Hammersmith Hospital, London, United Kingdom; [6]Department of Pediatrics, University of Pennsylvania Perelman School of Medicine, Philadelphia, United States; [7]Division of Pediatric Hematology-Oncology, First Dept of Pediatrics, University of Athens, Athens, Greece; [8]IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy; [9]Hôpital Universitaire Necker-Enfants Malades, Paris, France; [10]University of Illinois at Chicago, Chicago, United States; [11]Division of Pediatric Hematology / Oncology, Weill Cornell Medicine, New York, United States; [12]Lucile Packard Children's Hospital, Palo Alto, United States; [13]Boston University, Boston, United States; [14]Blood and Marrow Transplant/Cellular Therapy, Division of Haematology / Oncology, The Hospital for Sick Children and the University of Toronto, Toronto, Canada; [15]The Children's Hospital at TriStar Centennial Medical Center / Sarah Cannon Center for Blood Cancers, Nashville, United States

June 12, 2020
Session topic: 25. Gene therapy, cellular immunotherapy and vaccination - Clinical

Disclosures

- This study was sponsored by Vertex Pharmaceuticals Incorporated and CRISPR Therapeutics AG
- JC is a shareholder of CRISPR Therapeutics and was an employee of CRISPR Therapeutics at the time this research was conducted. NC-O, JL-H, YL, and NS are employees of Vertex Pharmaceuticals Incorporated and hold stock and / or stock options in that company. CMF, TWH, and AR are employees of CRISPR Therapeutics and hold stock and / or stock options in that company. SG receives study support from Novartis, Kite, and Servier, consults for Novartis, Roche, GSK, Cure Genetics, Humanigen, CBMG, and Janssen / J&J, participates in study steering committees or scientific advisory boards for Jazz, Adaptimmune, TCR2, Eureka, Cellectis, Juno, and Vertex, and has a patent (Toxicity management for anti-tumor activity of CARs, WO2014011984A1) that is managed according to the University of Pennsylvania patent policy. AK has participated in advisory boards for Vertex Pharmaceuticals Incorporated / CRISPR Therapeutics, Novartis, Vifor, Ionis, and BMS / Celgene, has participated in a steering committee for Vertex Pharmaceuticals Incorporated / CRISPR Therapeutics, has received research support from Novartis, and has received speaker fees from BMS / Celgene. MM has participated in advisory boards for Addmedica, Bluebird Bio, and Novartis. MHS has participated in advisory boards for Vertex Pharmaceuticals Incorporated / CRISPR Therapeutics, Fulcrum Therapeutics, DSMB, and Imara. S. Sheth has served as a consultant for Acceleron, Agios, Bluebird Bio, Celgene, and Novartis, has received research support from Agios, Celgene, Dispersol, LaJolla, Novartis, and Terumo, and has participated in a steering committee for Vertex Pharmaceuticals Incorporated / CRISPR Therapeutics. S. Soni and HF have participated in a steering committee for Vertex Pharmaceuticals Incorporated / CRISPR Therapeutics. SC, MDC, JF, J de la F, FL, DR, and DAW have no conflicts to disclose
- Medical writing support was provided by Katie L. Beski, PhD of Complete HealthVizion, Inc., Chicago, IL, USA, funded by Vertex Pharmaceuticals Incorporated. Development and review coordination was provided by Leah Eardley, PhD of Vertex Pharmaceuticals Incorporated, who holds stock and / or stock options in that company

Transfusion-Dependent β-Thalassemia (TDT) and Sickle Cell Disease (SCD) Cause Significant Morbidity and Mortality

	TDT	SCD
Blood disorders caused by mutations in the β-globin gene[1,2]	Loss-of-function mutations reduce the level of β-globin, lowering total Hb 	Single-point mutation causes hemoglobin to polymerize, leading to sickling of RBCs 
Significant worldwide burden[1,2]	**60,000** ANNUAL BIRTHS[a]	**300,000** ANNUAL BIRTHS
Significant morbidity and mortality, and heavy burden of patient care[1-4]	Severe anaemia, frequent transfusions, complications related to iron overload 	Pain, anaemia, frequent hospitalizations, end-organ damage, early death 

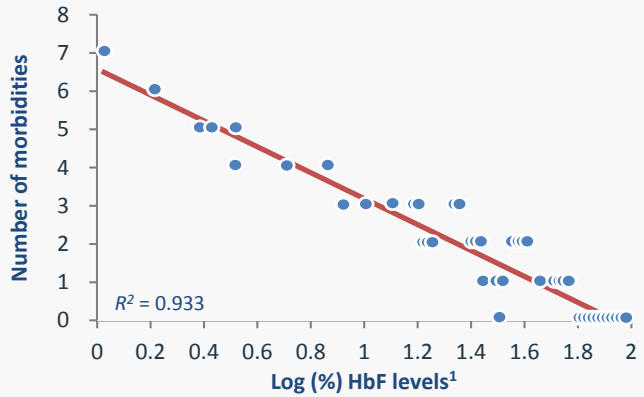
Hb, hemoglobin; RBC, red blood cell

[a]Symptomatic individuals (not all are transfusion-dependent)

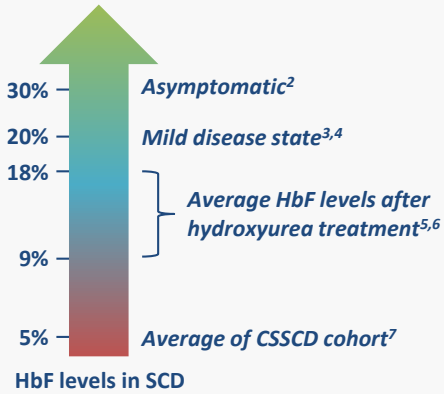
1. Kato et al. *Nat Rev Dis Primers*. 2018;4:18010; 2. Galanello, Origo. *Orphanet J Rare Dis*. 2010;5:11; 3. Taher et al. *Lancet.* 2018;391:155-167; 4. Ware et al. *Lancet*. 2017;390:311-323

Elevated Fetal Hemoglobin (HbF) is Associated With Decreased Disease Severity

TDT



SCD

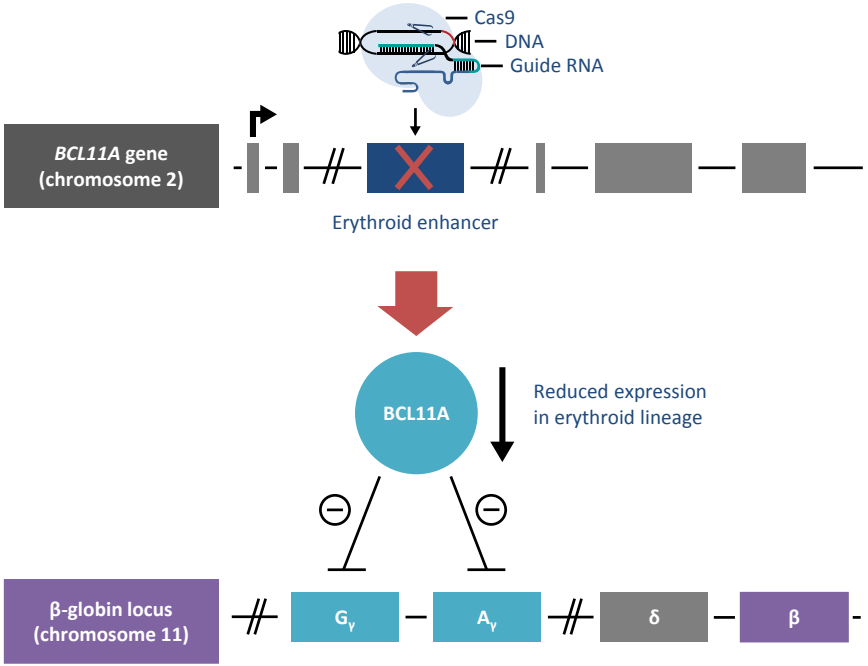


Rare patients with β-thalassemia or SCD continue to express HbF into adulthood, a condition known as hereditary persistence of HbF, and these patients experience **reduced or no symptoms**[8-10]

CSSCD, Cooperative Study of Sickle Cell Disease

1. Musallam et al. *Blood*. 2012;119:364-367; 2. Ngo et al. *Brit J Haematol*. 2012;156:259-264; 3. Akinsheye et al. *Blood*. 2011;118:19-27; 4. Alsultan et al. *Am J Hematol*. 2012;87:824-826; 5. Nevitt et al. *Cochrane Database Syst Rev*. 2017;4:CD002202; 6. Fitzhugh et al. *PLoS One*. 2015;10:e0141706; 7. Sebastiani P et al. *Am J Hematol.* 2008;83:189-195; 8. Murray et al. *Br J Haematol*. 1988;69:89-92; 9. Conley et al. *Blood*. 1963;21:261-281; 10. Bank. *Blood*. 2006;107:435-443

Disruption of *BCL11A* Expression Increases HbF Levels



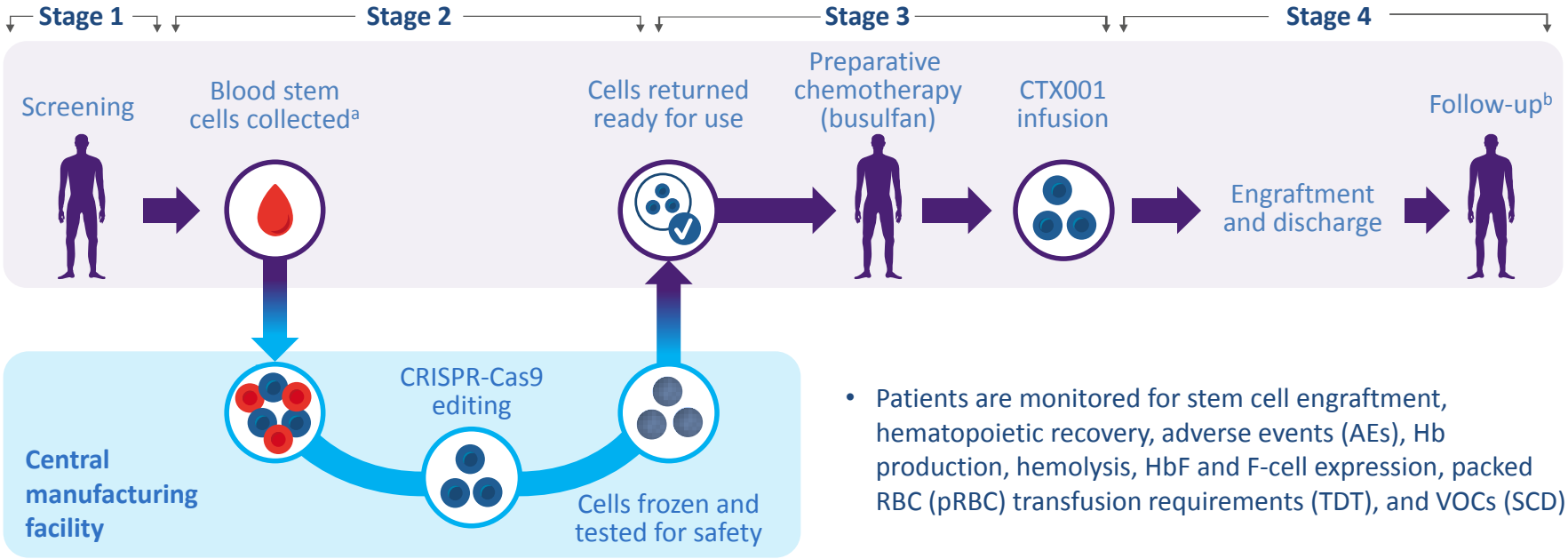
- BCL11A suppresses expression of the γ-globin subunit of HbF
- Naturally occurring genetic polymorphisms in *BCL11A* are associated with elevated HbF
- CTX001: CD34+ cells gene edited with CRISPR-Cas9, resulting in reduction of erythroid-specific expression of BCL11A
- *In vivo,* infusion of CTX001 leads to an increase in HbF levels in erythroid cells
- Here we report preliminary results of the first-in-human therapeutic trial of CRISPR-Cas9 editing in TDT and SCD

Modified from Canver, Orkin. *Blood*. 2016;127:2536-2545

Phase 1 / 2 Studies in Patients with TDT and SCD

	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 between 18 and 35 years with TDT, including β0 / β0 genotypes, defined as a history of at least 100 mL/kg/year or 10 units/year of packed RBC transfusions in the previous 2 years	45 patients aged between 18 and 35 years with severe SCD and a history of ≥2 vaso-occlusive crises (VOCs)/year over the previous 2 years
Primary endpoint	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

CTX001 Infusion Process



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

[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;
[b]Patients will be followed for 24 months after CTX001 infusion with physical exams, laboratory and imaging assessments, and AE evaluations. 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

Patient baseline	Patient 1	Patient 2
Genotype	**β0 / β+ (IVS-I-110)**	**β0 / β+ (IVS-II-745)**
Age at consent, *years*	**19**	**26**
Gender	**Female**	**Male**
Pre-study pRBC transfusions[a] *Units/year* *Transfusion episodes/year*	 **34** **16.5**	 **61** **15**
Treatment characteristics		
Cell dose, *CD34+ cells/kg*	**17.0×10^6**	**12.3×10^6**
Neutrophil engraftment[b]**,** *Study day*	**33**	**36**
Platelet engraftment[c]**,** *Study day*	**37**	**34**

Phenotype associated with genotype of Patient 1 (IVS-I-110) is severe and similar to that of β0/β0

[a]Annualized number during the 2 years before consenting to study participation; [b]Defined as the first day of 3 measurements of absolute neutrophil count ≥500 cells/μL on 3 consecutive days; [c]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

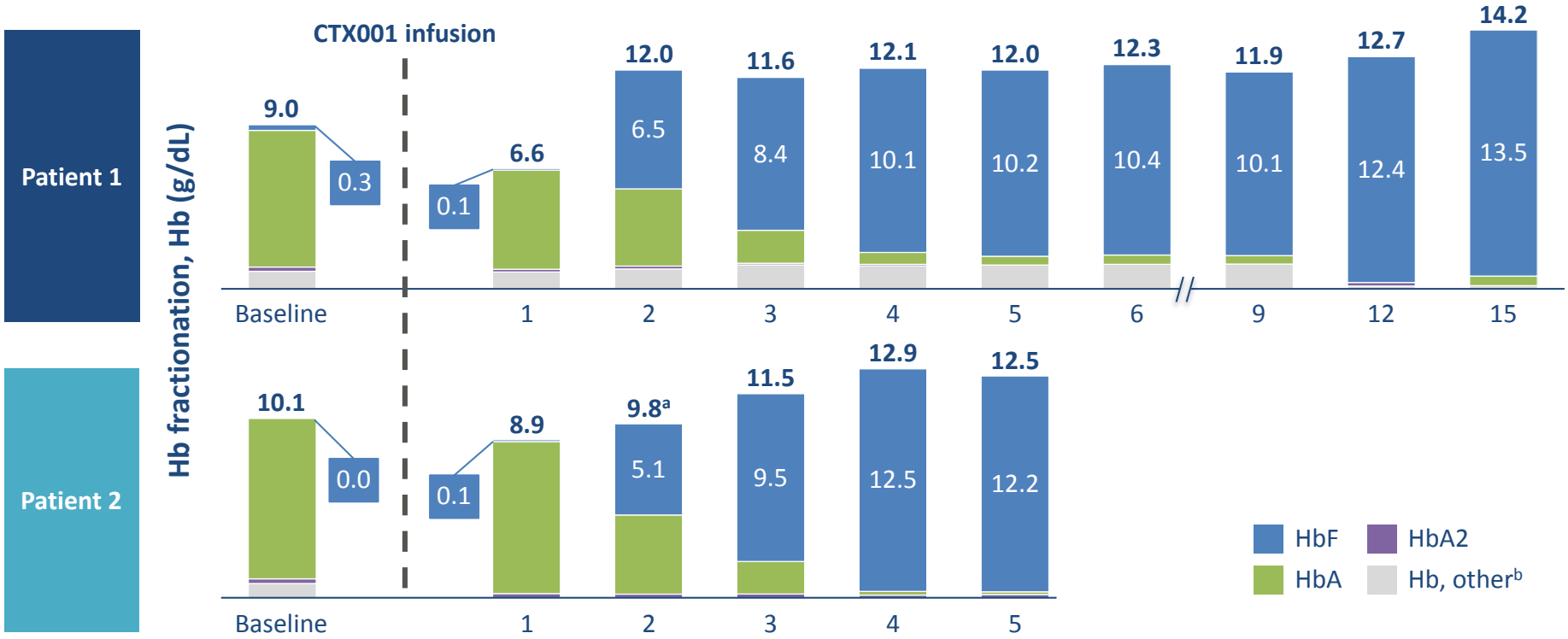
TDT: Adverse Events

	Patient 1	Patient 2
Screening to CTX001 infusion		
AEs	12	8
Serious AEs	0	0
Post-CTX001 infusion		
AEs	32	34
Serious AEs	2[a]	2[b]
Weeks of follow-up	66.6	24.7
AE relationship[c]		
Related to filgrastim only	4[d]	2
Related to plerixafor and filgrastim	0	2
Related to busulfan only	8[e]	15[f]
Related to CTX001 only	0	1[g]
Related to busulfan and CTX001	0	3[h]
Not related to any study drug	32	19

AEs were generally consistent with myeloablation and autologous stem cell transplant

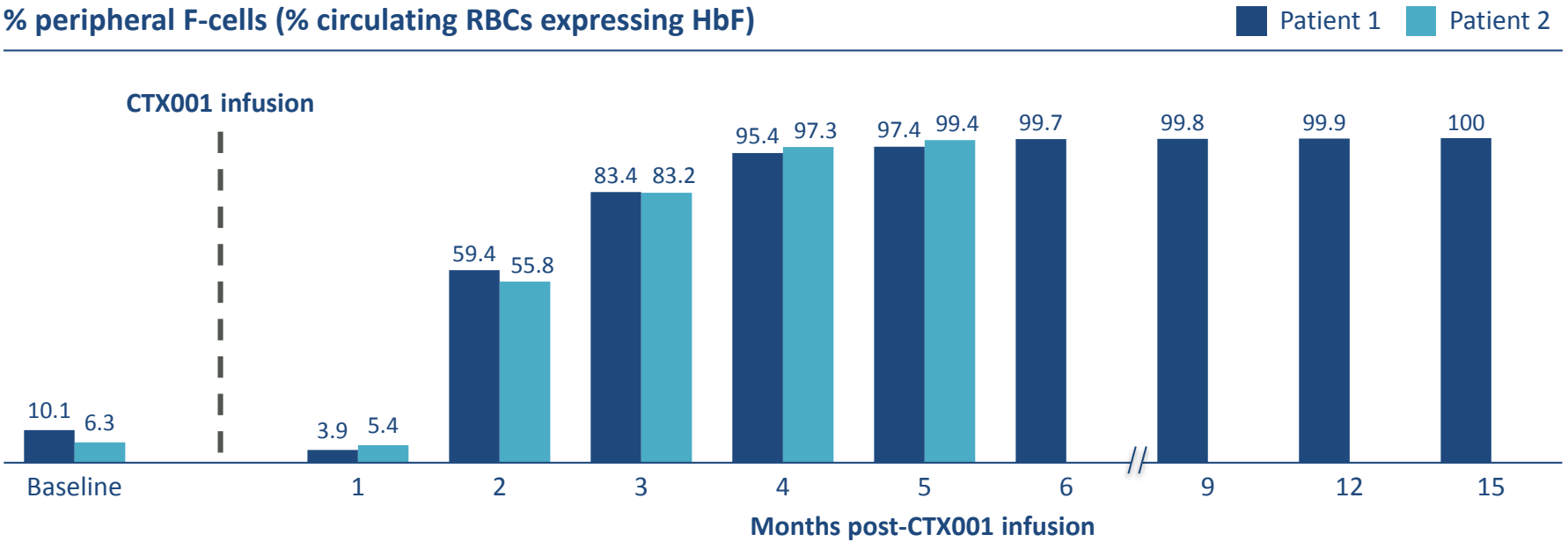
[a]Venoocclusive liver disease (related to busulfan only) and pneumonia (not considered related to CTX001 or other study drug), both resolved; [b]Pneumonia and upper respiratory tract infection, both not considered related to CTX001 or other study drug, both resolved; [c]Includes both related and possibly related AEs. Only those AEs which occurred ≥2 times are described in the footnote for all AE listings except for "Related to CTX001" AEs where all are listed; [d]Bone pain (×2); [e]Stomatitis (×3); [f]Vomiting (×2), stomatitis (×2); [g]Anaemia; [h]Pyrexia (×2), petechiae

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

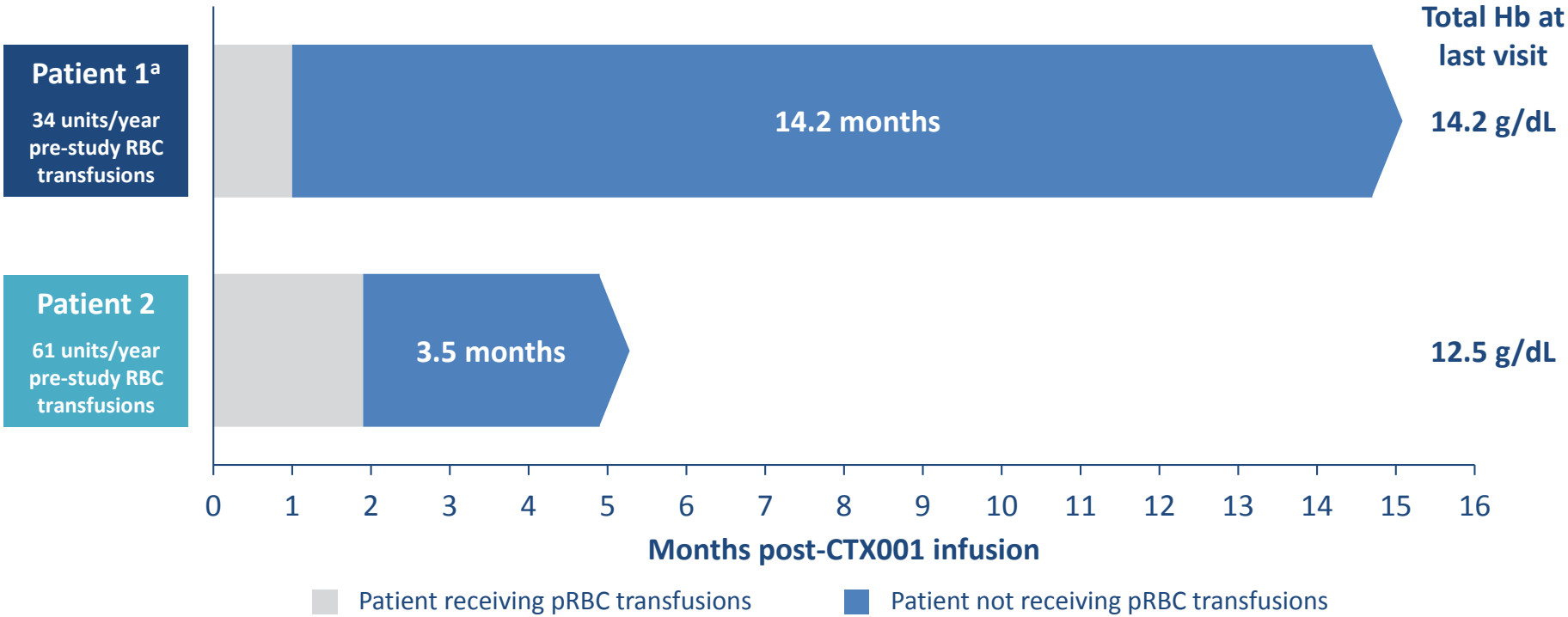


[a]Total Hb from local laboratory and Hb fraction from central laboratory;
[b]Hb adducts and other variants

TDT: Pancellular Expression of HbF is Maintained



Both TDT Patients Have Stopped pRBC Transfusions



[a]In the 15 months after CTX001 infusion, phlebotomy for iron reduction occurred on Study Days 98, 147, 170, and 191. Iron chelation therapy received from Study Day 205 to Study Day 316

SCD Patient Baseline and Treatment Characteristics

Patient baseline[a]

Genotype	**βS / βS**
Age at consent, *years*	**33**
Gender	**Female**
Pre-study VOCs, *VOCs/year*[b]	**7**

Treatment characteristics

Cell dose, *CD34+ cells/kg*	**3.3×10^6**
Neutrophil engraftment[c]**,** *Study day*	**30**
Platelet engraftment[d]**,** *Study day*	**30**

[a]Patient had received hydroxyurea treatment from 2016 to November 22, 2018 (Study Day −222); [b]Annualized rate 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 for 3 consecutive days; [d]Defined as the first of 3 consecutive measurements on 3 separate days with platelet count ≥50,000/μL without a platelet transfusion for 7 consecutive days

SCD: Adverse Events

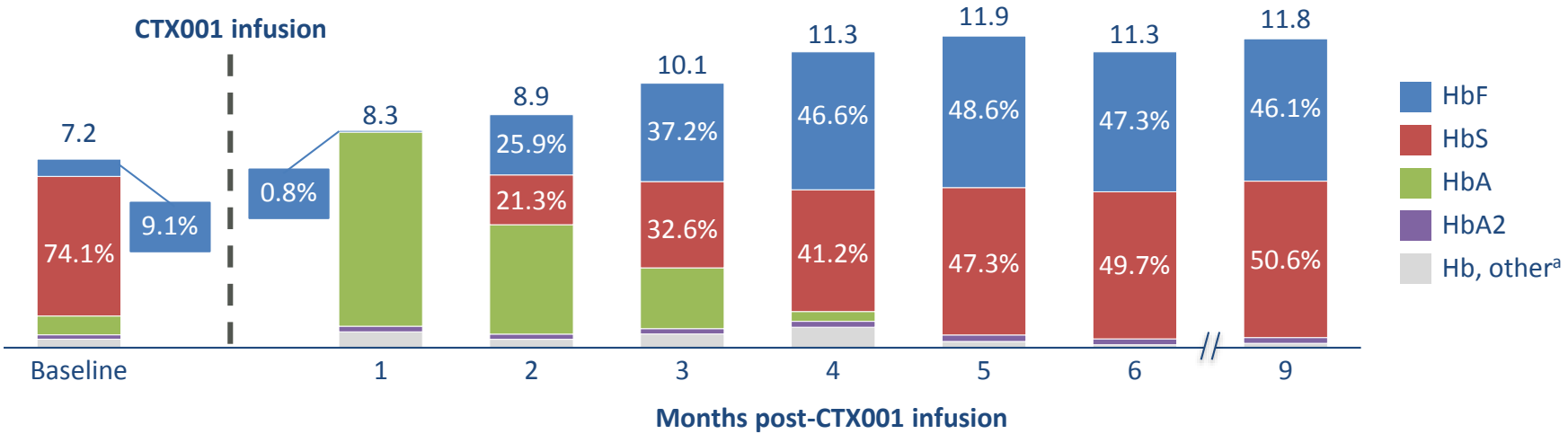
	SCD Patient
Screening to CTX001 infusion	
AEs	35
Serious AEs	11
Post-CTX001 infusion	
AEs	91[a]
Serious AEs	3[b]
Weeks of follow-up	45.1
AE relationship[c]	
Related to plerixafor only	6
Related to busulfan only	21[d]
Related to CTX001 only	0
Related to busulfan and CTX001	5[e]
Not related to any study drug	94

AEs were generally consistent with myeloablation and autologous stem cell transplant

[a]Most common grade ≥3 AEs (occurring ≥2 times) post-CTX001: headache, neck pain, cholelithiasis, oesophagitis, leukopenia, musculoskeletal chest pain, non-cardiac chest pain, stomatitis; [b]Sepsis (related to busulfan), cholelithiasis and abdominal pain (both not related to CTX001 or other study drug), all resolved; [c]Includes related and possibly related AEs. Only those AEs which occurred ≥2 times are described in the footnote except for "Related to CTX001" AEs where all are listed; [d]Oesophagitis (×3), leukopenia (×2), vulvovaginal inflammation (×2), stomatitis (×2); [e]Lymphopenia (×5), attributed to the CD34+ hematopoietic stem cell enrichment of the CTX001 product

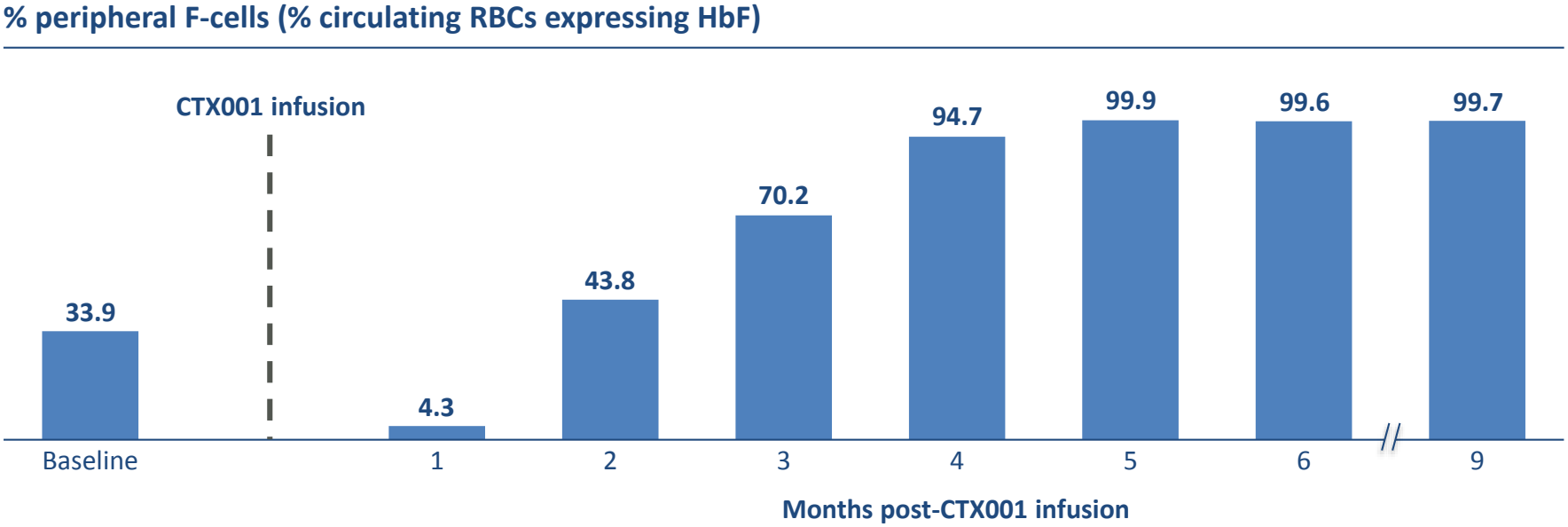
SCD: Clinically Meaningful HbF is Achieved Early and Maintained

Hb fractionation, Hb (g/dL)

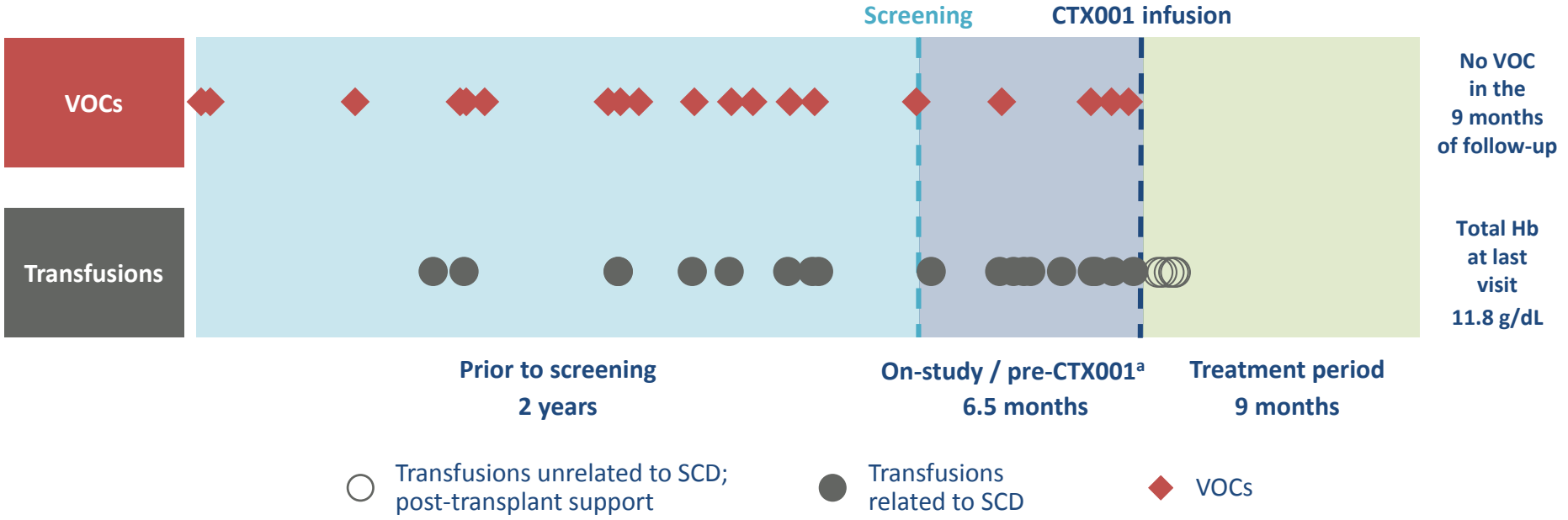


HbS, sickle hemoglobin
[a]Hb adducts and other variants

SCD: Pancellular HbF Expression is Maintained



SCD: No VOCs Post-CTX001 Infusion

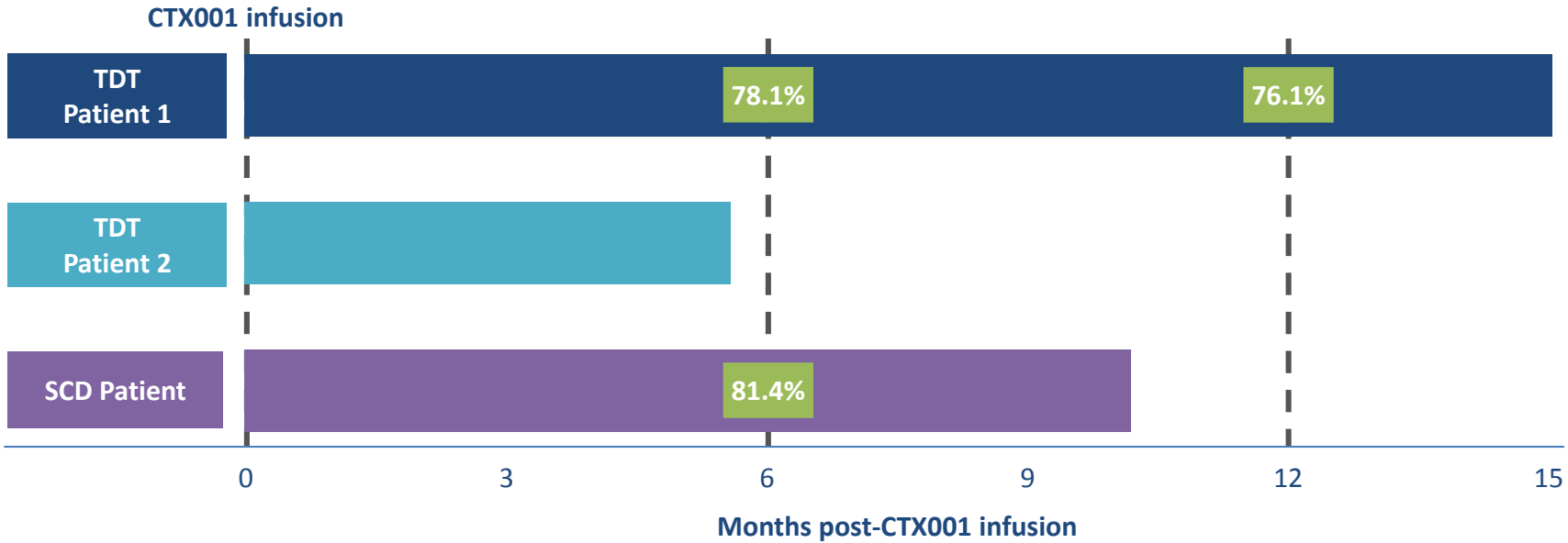


No pRBC transfusions have occurred since Study Day 19

[a]Exchange transfusions per study protocol occurred during the on-study / pre-CTX001 period (not included here)

Durable *BCL11A* Editing Observed in Bone Marrow CD34+ Cells

Allelic editing in CD34+ bone marrow cells[a]



[a]Allelic editing in CD34+ bone marrow cells assessed every 6 months

Conclusions

- These studies are the first demonstration of the clinical impact of CRISPR-Cas9-based gene editing for hemoglobinopathies and establish proof of concept for TDT
- Overall safety is consistent with myeloablative conditioning and autologous transplant
- Clinically meaningful HbF and total Hb levels, as well as pancellular expression of HbF in red blood cells, are observed early and maintained in TDT and SCD
- First 2 TDT patients have been free of pRBC transfusions for >14 and >3 months respectively; first SCD patient has had no VOCs in >9 months
- Sustained engraftment of edited hematopoietic stem cells is supportive of long-term clinical efficacy
- Enrollment and manufacturing of CTX001 for TDT and SCD are ongoing with further dosing planned in 2020

CTX001 has been granted Regenerative Medicine Advanced Therapy (RMAT) designation from the FDA, Orphan Drug Designation from both the FDA and the EMA, and Fast Track Designation from the FDA

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

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

- BC Children's Hospital, Vancouver
- University Hospital Tübingen
- Imperial College Healthcare, London

Thank you to study participants and their families, as well as **sites, investigators, nurses, and the entire CTX001 team** from CRISPR Therapeutics and Vertex Pharmaceuticals