CTX001™ for Transfusion-Dependent β-Thalassemia: Safety and Efficacy Results from the Ongoing CLIMB THAL-111 Study of Autologous CRISPR-Cas9-Modified CD34+ Hematopoietic Stem and Progenitor Cells

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INTRODUCTION

- In patients with transfusion-dependent β-thalassemia (TDT), a reduction in the level of fetal hemoglobin (HbF) shortly after birth is associated with the onset of symptoms and transfusion dependence[1]
- Naturally occurring genetic polymorphisms in *BCL11A*, a repressor of HbF, are associated with elevated HbF and decreased severity of TDT[2,3]
- Editing of *BCL11A* results in reactivation of γ-globin expression and formation of HbF (α2γ2) in animal models[3,4]
- CTX001™ is a genetically modified cell therapy that uses non-viral, ex vivo CRISPR-Cas9 gene editing in autologous CD34+ hematopoietic stem and progenitor cells (HSPCs) at the erythroid enhancer region of the *BCL11A* gene to reduce expression of BCL11A and reactivate HbF production[5]
- Early results from the Phase 1/2 CLIMB THAL-111 study of patients with TDT and the Phase 1/2 CLIMB SCD-121 study of patients with sickle cell disease (SCD) infused with CTX001 demonstrate clinically meaningful increases in total hemoglobin (Hb) and HbF that occurred early and were maintained over time, and a safety profile generally consistent with myeloablative conditioning. Elimination of transfusion requirements within 2 months of CTX001 infusion in patients with TDT and elimination of vaso-occlusive crises in patients with SCD were also observed[6]

OBJECTIVE

- To present updated data from the CLIMB THAL-111 study for patients (N=15) with ⩾3 months of follow-up after CTX001 infusion from a data cut on 30 March 2021. As of 26 May 2021, a total of >40 patients with TDT and SCD have been dosed with CTX001

METHODS

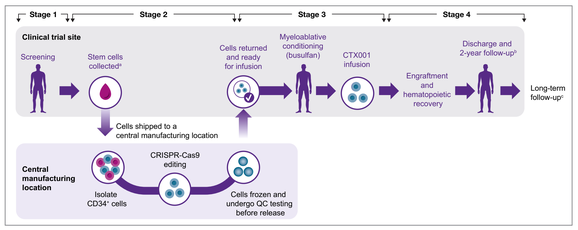
Study Design and Patient Population

- CLIMB THAL-111 (NCT03655678) is a Phase 1/2, international, multicenter, open-label, single-arm study investigating the safety and efficacy of autologous CD34+ CRISPR-Cas9-modified HSPCs (CTX001) in patients with TDT
- Patients aged 12 to 35 years with a diagnosis of TDT, defined as a history of ⩾100 mL/kg/year or ⩾10 units/year of packed red blood cell (pRBC) transfusions in the previous 2 years, were eligible

CTX001 Manufacturing and Infusion (Figure 1)

- CD34+ HSPCs were collected from patients by apheresis following mobilization with filgrastim and plerixafor
- CTX001 was manufactured from these CD34+ cells by editing at the erythroid enhancer region of *BCL11A* with a specific single-guide RNA and Cas9 nuclease
- Patients received myeloablative conditioning with pharmacokinetically adjusted busulfan, followed by a one-time infusion of CTX001
  - Patients were monitored for engraftment, hematopoietic recovery, adverse events (AEs), Hb production, HbF and F-cell expression, and pRBC transfusion requirements occurring during follow-up
  - Bone marrow aspirates were obtained at 6, 12, and 24 months after CTX001 infusion and next-generation sequencing was used to measure the fraction of on-target allelic editing in CD34+ bone marrow cells

Figure 1. CTX001 Infusion Process



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QC, quality control.

[a]Patients enrolled in CLIMB THAL-111 received a combination of plerixafor and filgrastim for mobilization. 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 overall in a long-term follow-up study (NCT04208529) after completion of or withdrawal from CLIMB THAL-111.

RESULTS

Table 1. Patient Baseline Demographics and Treatment Characteristics

Patient Demographics, N=15	
Genotype, n	
β^0/β^0	2
β^0/IVS-I-110	2
IVS-I-110/IVS-I-110	2
β^0/β^E	2
β^0/β^+	4
β^+/β^+	3
Gender, n	
Female/male	9/6
Age in years, median (range)	23 (18–32)
Pre-study pRBC transfusions[a]	
Units per year, median (range)	34 (20.5–61)
Treatment Characteristics, N=15	**Median (Range)**
Drug product cell dose, CD34+ cells × 10^6/kg	6.5 (3.5–16.6)
Neutrophil engraftment[b], Study Day[c]	29 (19–39)
Platelet engraftment[d], Study Day[c]	40 (29–56)
Duration of follow-up, months	8.7 (4.0–26.2)

pRBC, packed red blood cell.

[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]Study Day 1 is the day of CTX001 infusion; [d]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.

Safety

- The safety profile of CTX001 is generally consistent with myeloablation and autologous hematopoietic stem cell transplant
- As previously reported, 1 patient had 4 serious AEs (SAEs) assessed by the investigator as related or possibly related to CTX001: headache, haemophagocytic lymphohistiocytosis (HLH), acute respiratory distress syndrome, and idiopathic pneumonia syndrome (latter also related to busulfan), all in the context of HLH[6]
- 3 patients experienced SAEs assessed as related or possibly related to busulfan only: venoocclusive liver disease (2 patients), febrile neutropenia (1 patient), colitis (1 patient), and pneumonia (1 patient). All were previously reported, except for the SAE of pneumonia
- All of these SAEs have resolved

Table 2. Summary of Adverse Events

Months of follow-up, median (range)	8.7 (4.0–26.2)

	Patients with non-serious AEs, n	Patients with SAEs, n
Relationship[a]		
Related to plerixafor and/or G-CSF	10	0
Related to busulfan only	15	3
Related to CTX001 only	1[b]	1
Related to busulfan and CTX001	3[c]	1
Not related to any study drug	9	1

AEs, adverse events; G-CSF, granulocyte colony-stimulating factor; SAEs, serious adverse events; WBC, white blood cell.

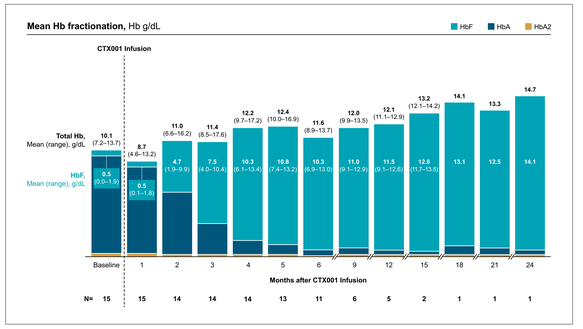
[a]Includes related, possibly related, and missing relationship AEs; [b]1 patient experienced a non-serious AE of anaemia possibly related to CTX001 (resolved); [c]3 patients experienced non-serious AEs related or possibly related to busulfan and CTX001: petechiae, pyrexia, epistaxis, lymphocyte count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

- In addition to the safety data presented above, which includes all patients dosed with CTX001 with ⩾3 months of follow-up as of the data cut of 30 March 2021, an additional SAE is included here, in a patient with <3 months of follow-up as of the data cut of 30 March 2021. This patient experienced an SAE of cerebellar hemorrhage, assessed by the investigator to be life-threatening, related to busulfan-induced thrombocytopenia, and not related to CTX001. The SAE has since resolved

Efficacy

- Increases in total Hb and HbF occurred early and were maintained over time (**Figure 2**)

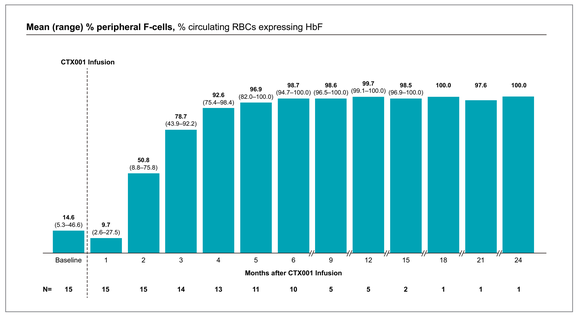
Figure 2. All Patients Demonstrated Increased Total Hb and HbF



Hb, hemoglobin; HbA, adult hemoglobin; HbF, fetal hemoglobin.

- Pancellular expression of HbF following CTX001 infusion demonstrates homogenous distribution of HbF
  - The mean proportion of circulating RBCs expressing HbF (F-cells) increased to >95% (**Figure 3**)

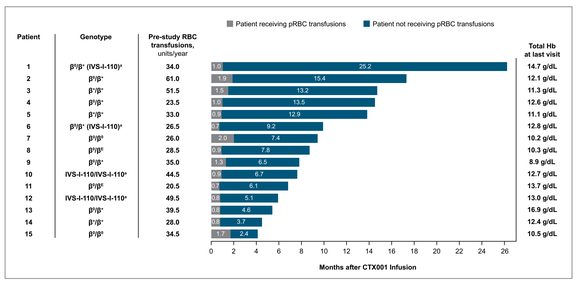
Figure 3. Pancellular Expression of HbF is Maintained



F-cells, HbF-containing cells; HbF, fetal hemoglobin; RBCs, red blood cells.

- All 15 patients were transfusion-free at the time of this analysis (within a median of 0.9 months after CTX001 infusion [range: 0.7 to 2.0 months]), with up to 26.2 months of total follow-up (**Figure 4**)

Figure 4. Patients Have Stopped Receiving Transfusions Within 2 Months of CTX001 Infusion



Hb, hemoglobin; pRBC, packed red blood cell; RBC, red blood cell.

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

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

- In the 10 patients with data available at 6 months post CTX001 infusion, the mean proportion of edited alleles in CD34+ bone marrow cells was 70.5% (range: 41.8% to 91.4%) at 6 months; in the 5 patients with at least 12 months of follow-up, the mean proportion of edited alleles in CD34+ bone marrow cells was 71.4% (range: 41.8% to 88.1%) at 6 months and 73.6% (range: 53.3% to 88.2%) at 12 months
- The proportion of edited alleles has been maintained in bone marrow cells over the duration of follow-up post CTX001 infusion (**Figure 5**)

Figure 5. Durable BCL11A Editing Observed in CD34+ Bone Marrow Cells in Patients with ⩾12 Months of Follow-Up

	Proportion of edited alleles in CD34+ bone marrow cells[a], %		
	6-month visit	12-month visit	24-month visit
Patient 1	78.1	76.1	80.9
Patient 2	41.8	53.3	
Patient 3	72.6	69.5	
Patient 4	76.6	81.0	
Patient 5	88.1	88.2	

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

CONCLUSIONS

- All patients (N=15) stopped transfusions within 2 months of CTX001 infusion, with a follow-up of 4.0 to 26.2 months
- The safety profile of CTX001 is generally consistent with that of myeloablative conditioning and autologous hematopoietic stem cell transplant
- All patients demonstrated clinically meaningful increases in total Hb and HbF which occurred early and have been maintained over time
- After CTX001 infusion, high levels of *BCL11A* edited alleles in CD34+ bone marrow cells were maintained
- The updated data reported here are consistent with previous reports and support continued investigation of CTX001 as a potential functional cure for patients with TDT

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AUTHOR DISCLOSURES

This study was sponsored by Vertex Pharmaceuticals Incorporated and CRISPR Therapeutics AG.

S A-L, **YB**, **TWH**, **LP**, **AS**, and **PS** are employees of CRISPR Therapeutics and hold stock/stock options. **MDC** is on the advisory boards for Sanofi Genzyme, Novartis, BMS/Celgene, Vifor, CRISPR, and Silence. **AL** reports consultancy for Novartis Canada. **J de la Fuente** is on the advisory board for Jazz Pharmaceuticals. **WH**, **YL**, and **NS** are employees of Vertex Pharmaceuticals Incorporated and hold stock/stock options. **AK** has received grants from Novartis, personal fees from Novartis, Chiesi, BMS/Celgene, and Agios Pharmaceuticals, and is on the advisory boards for Vertex/CRISPR, BMS/Celgene, Ionis, and Vifor. **SS** has received grants from Agios, La Jolla, Terumo, DisperSol, Novartis, and Celgene, is a consultant for Agios, Celgene, bluebird bio, Acceleron, and Chiesi, and is on the steering committee for Vertex/CRISPR. **HF** is on the study Data and Safety Monitoring Board for Rocket Pharma and the steering committee for CTX001-121. **FL**, **SC**, **JD**, **J Foell**, **RH**, and **DW** have nothing to declare.