CTX001™ for Sickle Cell Disease: Safety and Efficacy Results from the Ongoing CLIMB SCD-121 Study of Autologous CRISPR-Cas9-Modified CD34⁺ Hematopoietic Stem and Progenitor Cells

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INTRODUCTION

- In patients with sickle cell disease (SCD), a reduction in the level of fetal hemoglobin (HbF) shortly after birth is associated with the onset of symptoms[1]
- Naturally occurring genetic polymorphisms in *BCL11A*, a repressor of HbF, are associated with elevated HbF and decreased severity of SCD[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 SCD-121 study of patients with SCD and the Phase 1/2 CLIMB THAL-111 study of patients with transfusion-dependent β-thalassemia (TDT) 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 vaso-occlusive crises (VOCs) in patients with SCD infused with CTX001 and elimination of transfusion requirements within 2 months of CTX001 infusion in patients with TDT were also observed[6]

OBJECTIVE

- To present updated data from the CLIMB SCD-121 study for patients (N=7) with ⩾3 months of follow-up after CTX001 infusion from a data cut on 15 March 2021. As of 26 May 2021, a total of >40 patients with SCD and TDT have been dosed with CTX001

METHODS

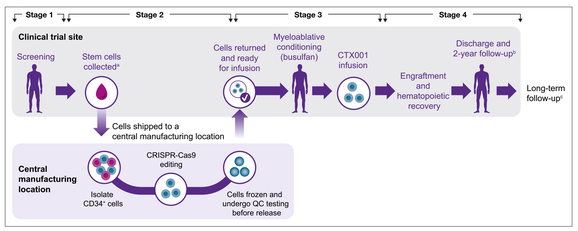
Study Design and Patient Population

- CLIMB SCD-121 (NCT03745287) 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 SCD
- Patients aged 12 to 35 years with severe SCD, defined as a history of ⩾2 VOCs per year in the previous 2 years, were eligible

CTX001 Manufacturing and Infusion (Figure 1)

- CD34⁺ HSPCs were collected from patients by apheresis following mobilization with 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, hemolysis, HbF and F-cell expression, and number of VOCs occurring during follow-up
  - Bone marrow aspirates were obtained at 6 and 12 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 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 overall in a long-term follow-up study (NCT04208529) after completion or withdrawal from CLIMB SCD-121.

RESULTS

Table 1. Patient Baseline Demographics and Treatment Characteristics

Patient Demographics, N=7	
Genotype, n	
β⁰/β⁰	7
Gender, n	
Female/male	3/4
Age in years, median (range)	22 (19–34)
Pre-study VOCs[a]	
VOCs per year, median (range)	5.5 (2.5–9.5)
Treatment Characteristics, N=7	**Median (Range)**
Drug product cell dose, CD34⁺ cells × 10^6/kg	3.3 (3.1–3.9)
Neutrophil engraftment[b], Study Day[c]	25 (17–33)
Platelet engraftment[d], Study Day[c]	33 (30–53)
Duration of follow-up, months	7.6 (4.9–22.4)

VOCs, vaso-occlusive crises.
[a]Annualized rate 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 ⩾50,000/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, post-CTX001 infusion, 1 patient experienced a serious AE (SAE) related to busulfan: sepsis; resolved[6]
- No SAEs related to CTX001 were reported

Table 2. Summary of Adverse Events

Months of follow-up, median (range)	7.6 (4.9–22.4)

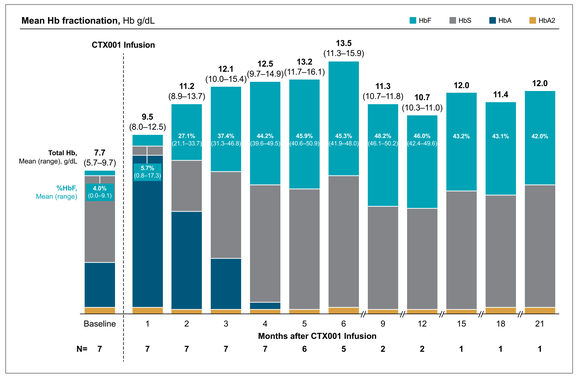
	Patients with non-serious AEs, n	Patients with SAEs, n
Relationship[a]		
Related to plerixafor	6	2
Related to busulfan only	7	1
Related to CTX001 only	0	0
Related to busulfan and CTX001	3[b]	0
Not related to any study drug	7	6

AEs, adverse events; SAEs, serious adverse events.
[a]Includes related, possibly related, and missing relationship AEs; [b]3 patients experienced non-serious AEs related or possibly related to busulfan and CTX001: dermatitis, lymphopenia, and CD4 lymphocytes decreased.

Efficacy

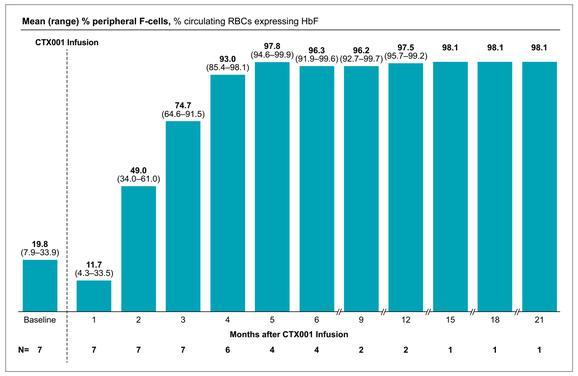
- Increases in total Hb and HbF occurred early and were maintained over time; mean %HbF increased to >30% by 3 months following infusion (**Figure 2**)
- Pancellular expression of HbF following CTX001 infusion demonstrates homogenous distribution of HbF
  - The mean proportion of circulating red blood cells expressing HbF (F-cells) increased to >95% (**Figure 3**)
- All 7 patients have remained VOC-free from CTX001 infusion to the time of this analysis, with up to 22.4 months of total follow-up (**Figure 4**)

Figure 2. All Patients Demonstrated Increased Total Hb and HbF



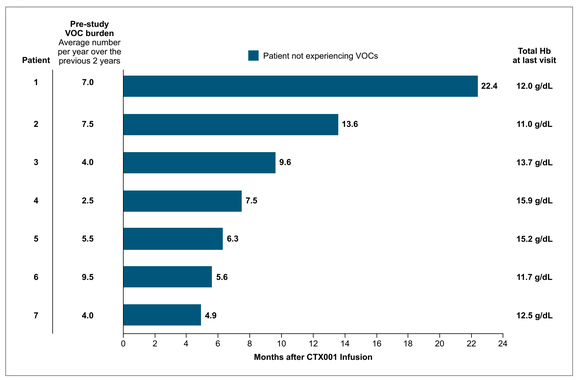
Hb, hemoglobin; HbA, adult hemoglobin; HbF, fetal hemoglobin; HbS, sickle hemoglobin.
Bars show mean Hb in g/dL, labels indicate mean proportion of HbF as a percentage of total Hb.

Figure 3. Pancellular Expression of HbF is Maintained



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

Figure 4. All Patients Infused with CTX001 Remain VOC-Free



Hb, hemoglobin; VOC, vaso-occlusive crisis.

Hemolysis

- Improvements in markers of hemolysis (serum lactate dehydrogenase and haptoglobin) were observed. Haptoglobin was detectable by Month 6 in all 4 patients with Month 6 values

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

- Bone marrow editing assessments were performed at 6 months and 12 months of follow-up
- The mean proportion of edited alleles in CD34⁺ bone marrow cells was 85.5% (range: 80.4% to 93.1%) in the 4 patients with data available at 6 months post CTX001 infusion
- In the 2 patients with at least 12 months of follow-up post CTX001 infusion, the proportion of edited alleles was maintained in bone marrow cells over the duration of follow-up (in the first patient, 81.4% and 80.4% at Months 6 and 12, respectively [22.4 months of total follow-up]; and in the second patient, 87.3% and 87.1% at Months 6 and 12, respectively [13.6 months of total follow-up])

CONCLUSIONS

- All patients (N=7) have been VOC-free from the time of CTX001 infusion, with a follow-up of 4.9 to 22.4 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 SCD

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AUTHOR DISCLOSURES

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