INTRODUCTION

- In patients with SCD, high levels of HbS (>90%) reduce the level of fetal hemoglobin (HbF)
  shortly after birth is associated with the onset of symptoms.
- Naturally occurring genetic polymorphisms in BCL11A, a repressor of HbF, are associated with elevated HbF and decreased severity of SCD.
- Editing of BCL11A results in reactivation of δ-globin expression and formation of HbF (α2δ2) in animal models.1
- 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 increase HbF production.2
- Early results from the Phase 1/2 CLIMB SCD-121 study of patients with SCD and the Phase 1/2 CLIMB THAI-121 study of patients with transfusion-dependent β-thalassemia (TDT) [TDT] treated 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 pre-existing clone (PXC) 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.3

OBJECTIVE

- To present updated data from the CLIMB SCD-121 study for patients (N=7) with SCD and 2 years of follow-up.
- To present updated data from the CLIMB THAI-121 study for patients (N=7) with TDT and 2 years of follow-up.
- To present updated data from the CLIMB SCD-121 study for patients (N=7) with SCD and 12 months of follow-up.
- To present updated data from the CLIMB THAI-121 study for patients (N=7) with TDT and 12 months of follow-up.

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 hematopoietic stem and progenitor cells (HSPCs) collected from patients by apheresis following mobilization with up to 22.4 months of total follow-up (4.9–22.4 months).

CTX001 Manufacturing and Infusion (Figure 1)

- CD34+ cells were collected from patients after mobilization mobilization
- CTX001 was manufactured in these CD34+ cells by using the erythroid enhancer region of the BCL11A gene with a single-guide RNA (sgRNA) and Cas9 nuclease
- Patients received myeloablative conditioning with trimethylolpropane sulfobenzyl ether sulfosuccinate (TME) before infusion of CTX001.

RESULTS

Table 1. Patient Baseline Demographics and Treatment Characteristics

<table>
<thead>
<tr>
<th>Patient Demographics, N=7</th>
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<tbody>
<tr>
<td>Genotype, n</td>
<td>7</td>
</tr>
<tr>
<td>HbS</td>
<td>7</td>
</tr>
<tr>
<td>HbA</td>
<td>7</td>
</tr>
<tr>
<td>Gender, n/f/m</td>
<td>2/9</td>
</tr>
<tr>
<td>Age in years, median (range)</td>
<td>22 (19–24)</td>
</tr>
<tr>
<td>Pre-study VOCs</td>
<td>S5 (5.8–6.1)</td>
</tr>
</tbody>
</table>

Treatment Characteristics, N=7

- Drug product cell dose, CTX001 cells: 107/kg
- Neutrophil engraftment: Study Day +37 to +54
- Patient enrollment: Study Day −30 to +58
- Duration of follow-up, months: 7.6 (9.5–20.6)

Safety

- The safety profile of CTX001 is generally consistent with that of myeloablative conditioning and autologous hematopoietic stem cell transplant.
- No SAEs related to CTX001 were reported.
- As previously reported, post-CTX001 infusion, 1 patient experienced a serious AE (SAE).

CONCLUSIONS

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


AUTHOR DISCLOSURES

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M Mapara is on the advisory board for Vertex.

MHS and M Mapara have nothing to disclose.