INTRODUCTION

• Patients with transfusion-dependent β-thalassemia (TDT), a reduction in the level of total hemoglobin (Hb) shortly after birth is associated with the onset of symptoms and transfusion dependence*

• Naturally occurring genetic polymorphisms in β2+1bp, a repressor of Hb, are associated with the increased levels of fetal hemoglobin (HbF) and decreased severity of TDT**

• Editing of BC1L114 results in the restoration of γ-globin expression and increased HbF levels in normal cells***

• 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 BC1L114 to create the expression of BC1L114 and activate HbF production

• Early results from the Phase 2 CLIMB THAL-111 study of patients with TDT and the Phase 2 CLIMB (TDT-112) 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 auto-immune crises in patients with SCD was also observed

OBJECTIVE

• To present updated data from the CLIMB THAL-111 study for patients (N=15) with transfusion-dependent β-thalassemia (TDT). A total of 10 patients with TDT and SCT have been infused with CTX001

METHODS

Study Design and Patient Population

- CLIMB THAL-111 (NCT03503587) is a Phase 1/2, international, multicenter, open-label, single-arm study investigating the safety and efficacy of autologous CTX001™ CAR-T cells modified with CRISPR (CTX001) in patients with TDT

- Patients aged 12 to 35 years with a diagnosis of TDT, defined as a history of transfusion dependence and/or a transfusion requirement of >10 units/year of packed red blood cell (pRBC) transfusions in the previous 2 years, were eligible

- Modified HSPCs (CTX001) in patients with TDT

- CTX001™ for Transfusion-Dependent β-Thalassemia: Safety and Efficacy Results

RESULTS

Table 1. Patient Baseline Demographics and Treatment Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
<th>Patient 4</th>
<th>Patient 5</th>
<th>Patient 6</th>
<th>Patient 7</th>
<th>Patient 8</th>
<th>Patient 9</th>
<th>Patient 10</th>
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<th>Patient 12</th>
<th>Patient 13</th>
<th>Patient 14</th>
<th>Patient 15</th>
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<tbody>
<tr>
<td>Gender</td>
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<td>M</td>
<td>M</td>
<td>M</td>
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<td>F</td>
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<td>F</td>
<td>M</td>
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<td>Age, year</td>
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<td>30</td>
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<td>33</td>
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<td>Total Hb, g/dL</td>
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<td>7.6</td>
<td>7.5</td>
<td>7.3</td>
<td>7.4</td>
<td>7.4</td>
<td>8.0</td>
<td>7.6</td>
<td>7.5</td>
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<td>7.8</td>
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<td>HbF, g/dL</td>
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<td>0.6</td>
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</table>

Safety

• The safety profile of CTX001™ is generally consistent with myeloablative and autologous hematopoietic stem cell transplant

• As previously reported, 1 patient had a serious adverse event (SAE) related to busulfan and CTX001: headache, haemophagocytic lymphohistiocytosis (HLH), acute respiratory distress syndrome, and splenic pyknocytotic syndrome (latter also related to busulfan), all in the context of HLH

• A patient experienced SAEs assessed as related or possibly related to busulfan only: headache, hemophagocytic lymphohistiocytosis (HLH).

• The safety profile of CTX001 is generally consistent with myeloablation and autologous hematopoietic stem cell transplant

• All patients demonstrated clinically meaningful increases in total Hb and HbF which occurred early and were maintained over time

• After CTX001 infusion, high levels of BC1L114 edited alleles in β-thalassemia bone marrow stem cells

• 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

ACKNOWLEDGMENTS

The authors and their respective organizations and their families, as well as co-investigators and collaborators, were funded by Vertex Therapeutics AG, ACE Therapeutics Ltd, and Vertex Pharmaceuticals Incorporated, which conduct research and development activities. Medical writing support was provided by S. Zaki, PhD, of Complete HealthCare, Inc., Chicago, IL. Support was funded by Vertex Pharmaceuticals Incorporated. The study was conducted via a investigator sponsored trial administered by Amgen, Inc. Marseille, France, and Vertex Pharmaceuticals Incorporated, who holds stock and/or stock options in that company.

REFERENCES


AUTHOR DISCLOSURES

The authors and their respective organizations and their families, as well as co-investigators and collaborators, were funded by Vertex Therapeutics AG, ACE Therapeutics Ltd, and Vertex Pharmaceuticals Incorporated, which conduct research and development activities. Medical writing support was provided by S. Zaki, PhD, of Complete HealthCare, Inc., Chicago, IL. Support was funded by Vertex Pharmaceuticals Incorporated. The study was conducted via a investigator sponsored trial administered by Amgen, Inc. Marseille, France, and Vertex Pharmaceuticals Incorporated, who holds stock and/or stock options in that company.

Efficacy

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

• All patients demonstrated increased Total Hb and HbF

• Patients have stopped receiving transfusions within 2 months of CTX001 infusion (Figure 2)

• Patients have stopped receiving transfusions within 2 months of CTX001 infusion

• Pancreatic expression of HbF following CTX001 infusion demonstrates homogeneous distribution

• The mean proportion of circulating BCEs expressing HbF (δ cells) increased to >100% (Figure 3)

• Patients have stopped receiving transfusions within 2 months of CTX001 infusion

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 were maintained over time

• After CTX001 infusion, high levels of BC1L114 edited alleles in β-thalassemia bone marrow stem cells

• 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

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 91.1%) at 6 months; in the 1 patient with data at 12 months of follow-up, the mean proportion of edited alleles in CD34+ bone marrow cells was 71.4% (range: 41.8% to 86.2%) at 4 months and 71.3% (53.3% to 86.2%) at 12 months

- The proportion of edited alleles has been maintained in bone marrow cells over the duration of follow-up post-infusion (Figure 4)

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

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

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