Hemoglobinopathies – sickle cell disease (SCD) and β-thalassemia (β-thal)

**Blood disorders** caused by *mutations* in the β-globin gene

- Sickle Cell
- Normal Cell
- β-thalassemia

**Significant worldwide burden**

- 300,000 Annual births in SCD and β-thal, respectively
- 60,000

**High morbidity and mortality**

- Anemia
- Pain
- Early death

**Heavy burden of patient care**

- Frequent transfusions & hospitalizations
Persistence of fetal hemoglobin alleviates symptoms

Rare patients continue to express HbF into adulthood, a condition known as hereditary persistence of fetal hemoglobin (HPFH), and these patients experience reduced or no symptoms

CTX001 edits the BCL11A erythroid enhancer region

Editing of the erythroid enhancer region of BCL11A causes induction of γ-globin, a subunit of fetal hemoglobin (HbF)
CLIMB 111 and CLIMB 121: Phase 1/2 studies in patients with β-thal and SCD, respectively

<table>
<thead>
<tr>
<th></th>
<th>CLIMB 111 (THAL-111)</th>
<th>CLIMB 121 (SCD-121)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Phase 1 / 2, international, multi-center, open-label, single arm study</td>
<td>Phase 1 / 2, international, multi-center, open-label, single arm study</td>
</tr>
<tr>
<td><strong>Target enrollment</strong></td>
<td>45 patients between 18 – 35 years of age with transfusion dependent thalassemia (TDT), including β0/β0 genotypes</td>
<td>45 patients between 18 – 35 years of age with severe SCD and a history of ≥2 vaso-occlusive crises/yr over the previous two years</td>
</tr>
<tr>
<td><strong>Primary endpoint</strong></td>
<td>Proportion of patients achieving sustained transfusion reduction for at least 6 months starting 3 months after CTX001 infusion</td>
<td>Proportion of patients with HbF ≥ 20%, sustained for at least 3 months starting 6 months after CTX001 infusion</td>
</tr>
</tbody>
</table>
Trials involve a stem cell transplant using CTX001 – an investigational treatment

Stage 1
Screening

Stage 2
CD34+ HSPC mobilized and collected

CENTRAL MANUFACTURING FACILITY

Stage 3
Myeloablative conditioning (busulfan)
CTX001 infusion

Stage 4
Engraftment and discharge
Follow-up

CRISPR-Cas9 editing
Processing of CTX001
Shipment to study site
### CLIMB THAL-111: Patient baseline and treatment characteristics

#### Patient baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>$\beta^0$/IVS-I-110</td>
</tr>
<tr>
<td>Gender</td>
<td>F</td>
</tr>
<tr>
<td>Age at consent, years</td>
<td>19</td>
</tr>
<tr>
<td>Pre-study pRBC transfusions Episodes/year$^2$</td>
<td>16.5</td>
</tr>
</tbody>
</table>

#### Treatment characteristics

- **Successful engraftment$^1$**
  - Neutrophil engraftment at study day 33
  - Platelet engraftment at study day 37
- **Initial safety profile consistent with myeloablative busulfan conditioning and autologous HSCT**
- **2 SAEs occurred, neither considered related to CTX001 by study investigator, both resolved:**
  - Veno-occlusive liver disease attributed to busulfan conditioning
  - Pneumonia in the presence of neutropenia

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1. Neutrophil engraftment defined as absolute neutrophil count ≥500 cells/µL for three consecutive days, and platelet engraftment defined as unsupported platelet count ≥ 20,000/µL
2. Annualized rate during the two years prior to consenting for the study
First TDT patient treated is transfusion free with sustained HbF > 10 g/dL

Hemoglobin fractionation over time pre and post CTX001 infusion, Hemoglobin (g/dL)

<table>
<thead>
<tr>
<th>Months post CTX001 infusion</th>
<th>Baseline</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbF</td>
<td>9.0</td>
<td>6.6</td>
<td>12.0</td>
<td>11.6</td>
<td>12.1</td>
<td>12.0</td>
<td>12.3</td>
<td>11.9</td>
</tr>
<tr>
<td>HbA</td>
<td>0.3</td>
<td>6.5</td>
<td>8.4</td>
<td>10.1</td>
<td>10.2</td>
<td>10.4</td>
<td>10.1</td>
<td></td>
</tr>
<tr>
<td>HbA2</td>
<td>0.1</td>
<td>4.0</td>
<td>8.4</td>
<td>10.1</td>
<td>10.2</td>
<td>10.4</td>
<td>10.1</td>
<td></td>
</tr>
<tr>
<td>Hb Undefined</td>
<td>6.6</td>
<td>4.0</td>
<td>8.4</td>
<td>10.1</td>
<td>10.2</td>
<td>10.4</td>
<td>10.1</td>
<td></td>
</tr>
</tbody>
</table>

1 Hb Undefined: Hb adducts and other variants.
HbF is highly pancellular in peripheral RBCs

Peripheral RBC F-cells
% F-cells (circulating RBCs expressing fetal hemoglobin)

<table>
<thead>
<tr>
<th>Months post CTX001 infusion</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>10.1</td>
<td>3.9</td>
<td>59.4</td>
<td>83.4</td>
<td>95.4</td>
<td>97.4</td>
<td>99.7</td>
</tr>
</tbody>
</table>

CTX001 infusion
## Patient baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genotype</td>
<td>$\beta^s/\beta^s$</td>
</tr>
<tr>
<td>Gender</td>
<td>F</td>
</tr>
<tr>
<td>Age at consent, years</td>
<td>33</td>
</tr>
<tr>
<td>Pre-study VOCs, VOCs / year$^2$</td>
<td>7</td>
</tr>
</tbody>
</table>

## Treatment characteristics

- Successful engraftment$^1$
  - Neutrophil engraftment at study day 30
  - Platelet engraftment at study day 30
- Initial safety profile consistent with myeloablative busulfan conditioning and autologous HSCT
- 3 SAEs occurred, none considered related to CTX001 by study investigator, all resolved:
  - Sepsis in the presence of neutropenia
  - Cholelithiasis
  - Abdominal pain

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1 Neutrophil engraftment defined as absolute neutrophil count ≥500 cells/µL for three consecutive days, and platelet engraftment defined as unsupported platelet count ≥ 50,000/µL
2 Annualized rate during the two years prior to consenting for the study
First patient treated in CLIMB SCD-121 had 46.6% HbF at 4 months after CTX001 infusion

Hemoglobin fractionation over time pre and post CTX001 infusion, % of total g/dL hemoglobin

<table>
<thead>
<tr>
<th>Months post CTX001 infusion</th>
<th>Baseline</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbF</td>
<td>7.2</td>
<td>8.3</td>
<td>8.9</td>
<td>10.1</td>
<td>11.3</td>
</tr>
<tr>
<td>HbS</td>
<td>9.1%</td>
<td>0.8%</td>
<td>25.9%</td>
<td>37.2%</td>
<td>46.6%</td>
</tr>
<tr>
<td>HbA</td>
<td>74.1%</td>
<td>21.3%</td>
<td>32.6%</td>
<td>41.2%</td>
<td></td>
</tr>
<tr>
<td>HbA2</td>
<td>4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hb Undefined (^1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Hb Undefined: Hb adducts and other variants.

Patient has had no reported VOCs since CTX001 infusion

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Patient receiving pRBC transfusions

Patient not receiving pRBC transfusions
HbF is highly pancellular in peripheral RBCs

Peripheral RBC F-cells
% F-cells (circulating RBCs expressing fetal hemoglobin)

![Graph showing HbF levels post CTX001 infusion](image)

- **Baseline**: 33.9%
- **1 month post CTX001**: 4.3%
- **2 months post CTX001**: 43.8%
- **3 months post CTX001**: 70.2%
- **4 months post CTX001**: 94.7%
Conclusions

- Initial safety profile of CTX001 is consistent with myeloablative busulfan conditioning and autologous hematopoietic stem cell transplant

- First patient with transfusion dependent β-thalassemia and β0/IVS-I-110 genotype in CLIMB THAL-111 has stopped pRBC transfusions
  - HbF sustained >10 g/dL at 9 months post infusion

- First patient with severe sickle cell disease in CLIMB SCD-121 has had no vaso-occlusive crises (VOC) since CTX001 treatment and has stopped pRBC transfusions
  - HbF of 46.6% at 4 months post infusion