CRISPR THERAPEUTICS

CTX001 Clinical Data Update

November 19, 2019

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

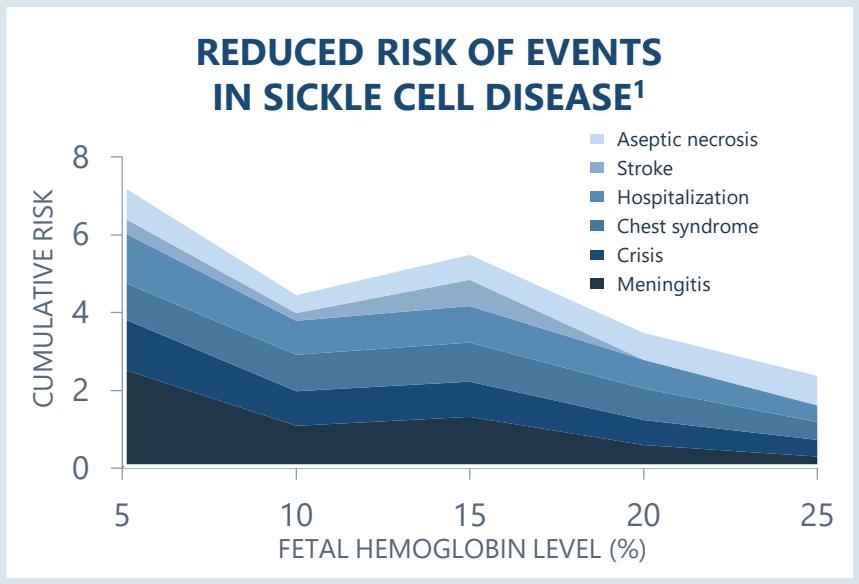
High morbidity and mortality

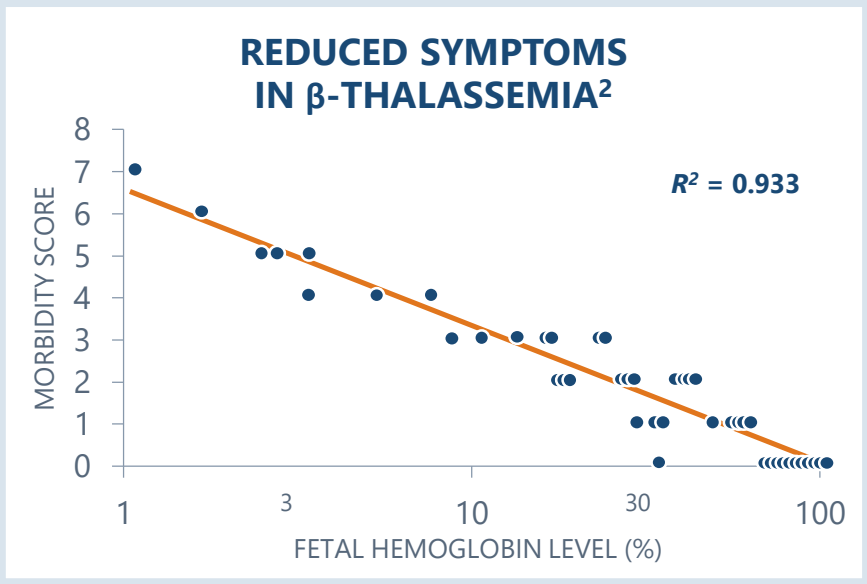
Anemia | Pain | **Early death**

Heavy burden of patient care

Frequent transfusions & hospitalizations

Persistence of fetal hemoglobin alleviates symptoms

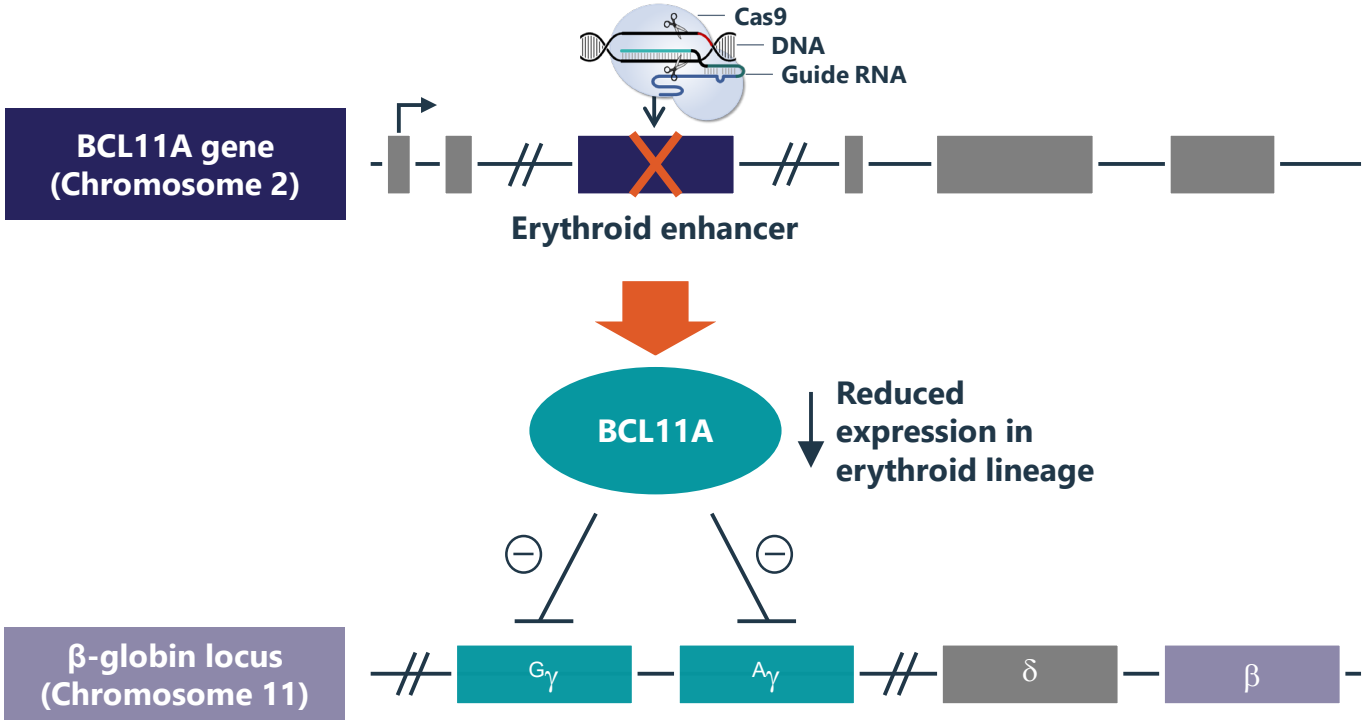




› **Rare patients continue to express HbF into adulthood,** a condition known as hereditary persistence of fetal hemoglobin (HPFH), and these patients experience **reduced or no symptoms**

1. Powars, *et al.* Blood 1984; 2. Musallam, *et al.* Blood 2012

CTX001 edits the BCL11A erythroid enhancer region

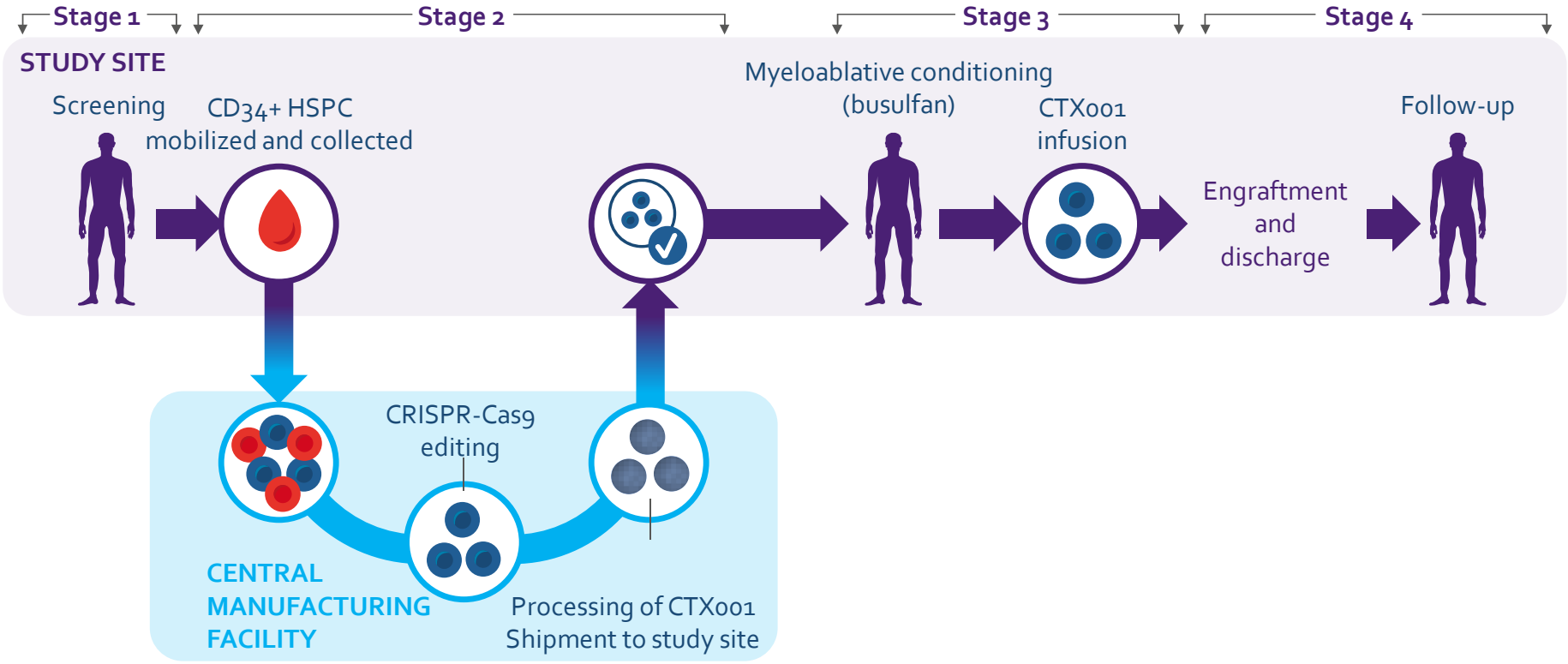


Editing of the erythroid enhancer region of BCL11A causes induction of γ-globin, a subunit of fetal hemoglobin (HbF)

CLIMB 111 and CLIMB 121: Phase 1/2 studies in patients with β-thal and SCD, respectively

	CLIMB THAL-111	CLIMB SCD-121
Design	Phase 1 / 2, international, multi-center, open-label, single arm study	Phase 1 / 2, international, multi-center, open-label, single arm study
Target enrollment	45 patients between 18 – 35 years of age with transfusion dependent thalassemia (TDT), including β0/β0 genotypes	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
Primary endpoint	Proportion of patients achieving sustained transfusion reduction for at least 6 months starting 3 months after CTX001 infusion	Proportion of patients with HbF ≥ 20%, sustained for at least 3 months starting 6 months after CTX001 infusion

Trials involve a stem cell transplant using CTX001 – an investigational treatment



CLIMB THAL-111: Patient baseline and treatment characteristics

Patient baseline

Genotype	**β^0/IVS-I-110**
Gender	**F**
Age at consent, *years*	**19**
Pre-study pRBC transfusions *Episodes/year*[2]	**16.5**

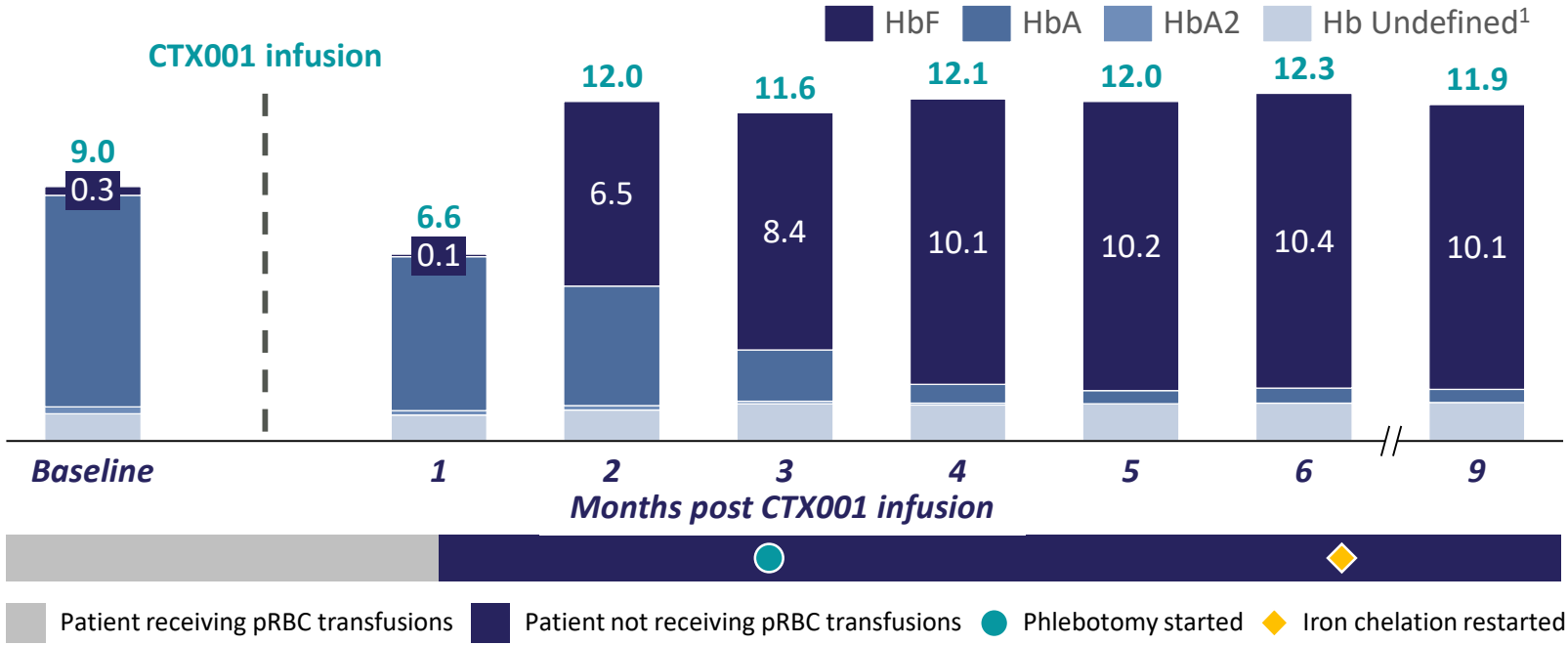
Treatment characteristics

- 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

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)

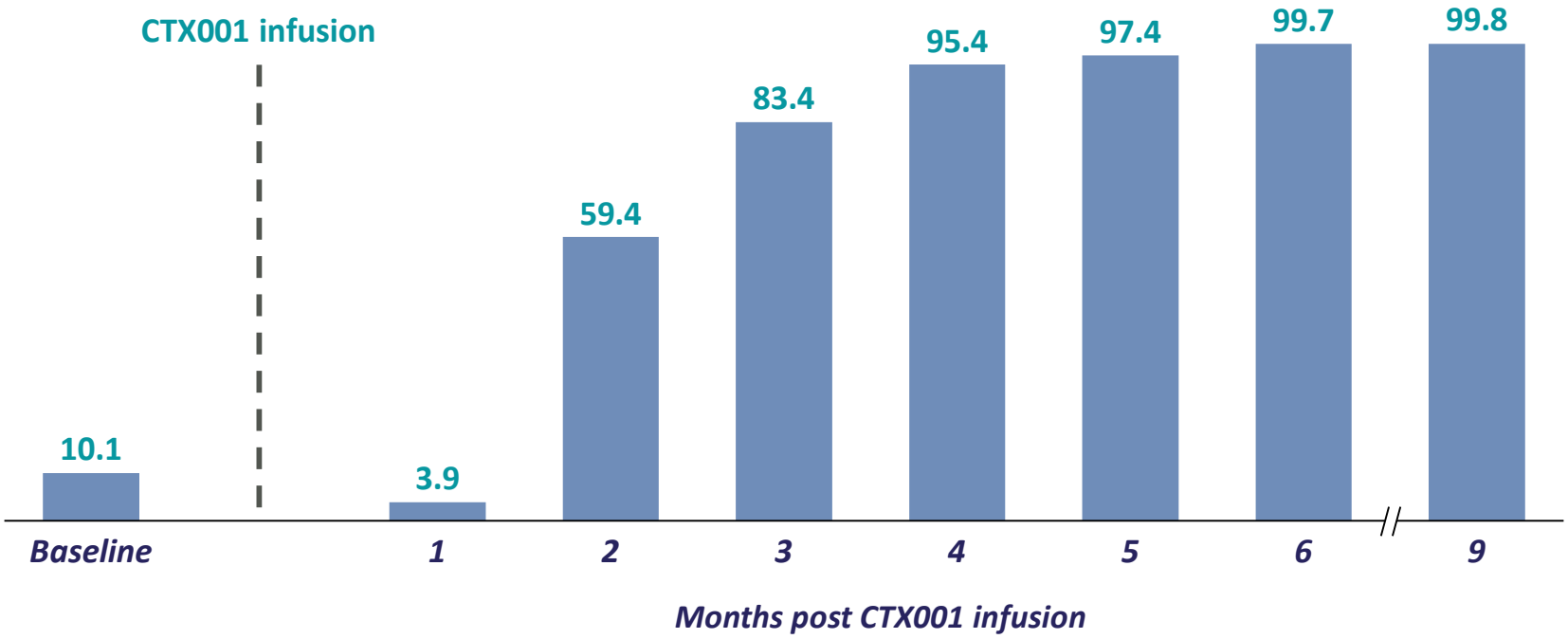


1 Hb Undefined: Hb adducts and other variants.

HbF is highly pancellular in peripheral RBCs

Peripheral RBC F-cells

% F-cells (circulating RBCs expressing fetal hemoglobin)



CLIMB SCD-121: Patient baseline and treatment characteristics

Patient baseline

Genotype	**β^S/β^S**
Gender	**F**
Age at consent, *years*	**33**
Pre-study VOCs, *VOCs / year*[2]	**7**

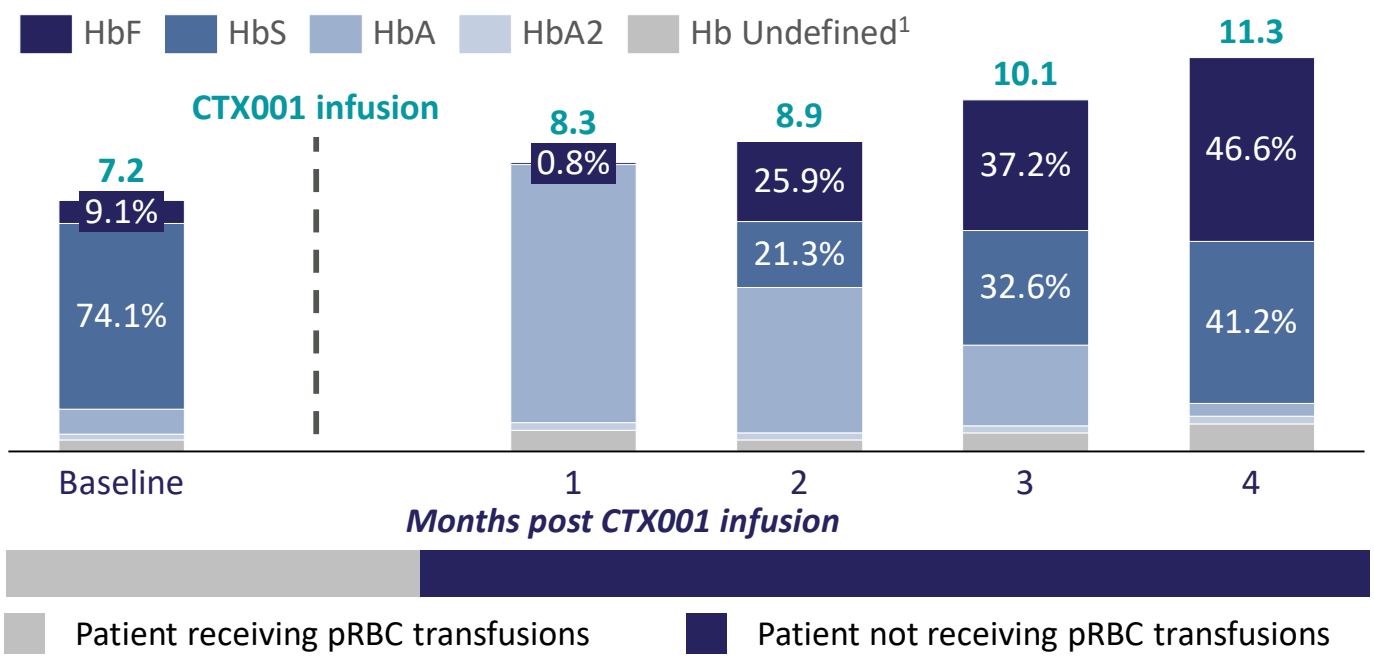
Treatment characteristics

- 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

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



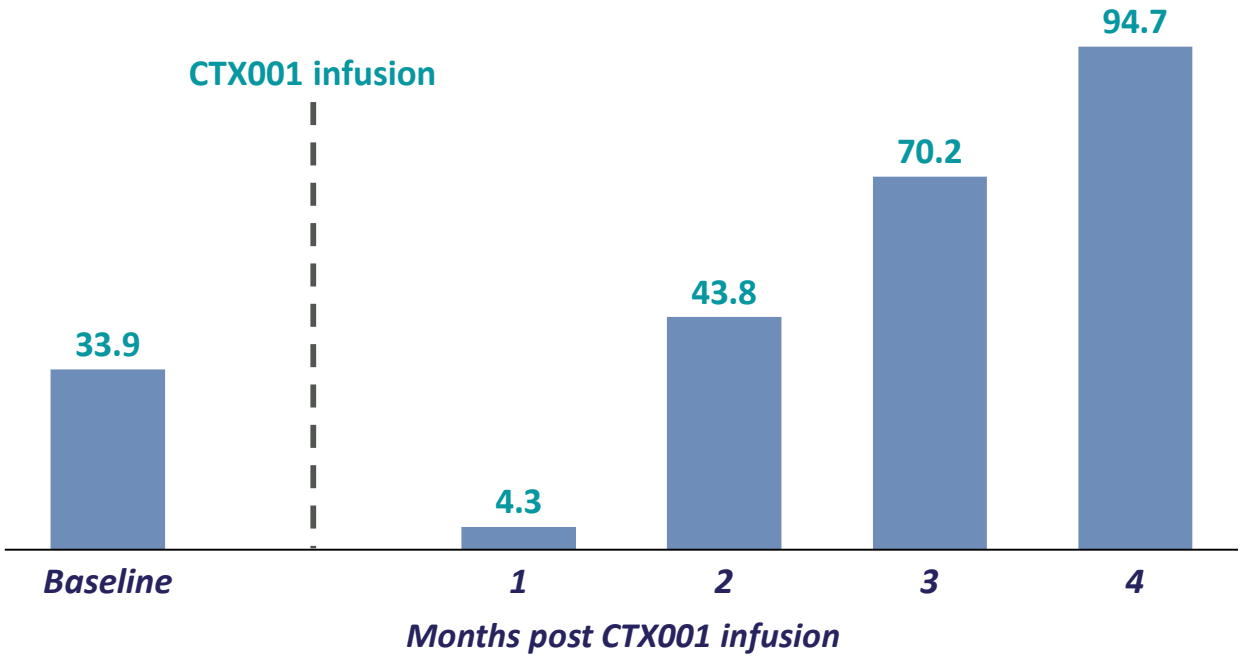
Patient has had no reported VOCs since CTX001 infusion

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)



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 β^0/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