CTX001™ INVESTOR EVENT

DECEMBER 9, 2020

AGENDA

Reshma Kewalramani, M.D.,
Vertex CEO and President

Scientific Achievements and Recent Progress for CTX001

Haydar Frangoul, M.D.,
Medical Director of Pediatric Hematology and Oncology at Sarah Cannon Research Institute, HCA Healthcare's TriStar Centennial Medical Center

CTX001 Data Presentation from ASH Conference

Samarth Kulkarni, Ph.D.,
CRISPR Therapeutics CEO

Commercial Opportunity and Future Outlook for CTX001

Q&A

David Altshuler, M.D., Ph.D.,
Vertex's EVP, Global Research, and Chief Scientific Officer

VERTEX | CRISPR THERAPEUTICS

FORWARD-LOOKING STATEMENTS

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RESHMA KEWALRAMANI, M.D., VERTEX CEO AND PRESIDENT

Scientific Achievements and Recent Progress for CTX001

SCIENTIFIC MILESTONES FOR CRISPR/CAS9 AND CTX001

2012 - 2018

Landmark *Science* Publication of CRISPR/Cas9 as Gene-Editing Tool

CRISPR Therapeutics & Vertex Collaboration

Initiation of CTX001 Clinical Development

2019 - 2020

First Positive Safety & Efficacy Data for CTX001 in Two Patients

Presentation at EHA Conference for Three Patients

Nobel Prize in Chemistry Awarded to Emmanuelle Charpentier, Ph.D., CRISPR Therapeutics' co-founder, and Jennifer Doudna, Ph.D.

Presentation at ASH Conference for 10 Patients

***NEJM* Publication**

KEY PROGRAM HIGHLIGHTS FOR CTX001 IN BETA THALASSEMIA AND SICKLE CELL DISEASE

Remarkable Results

10 patients with ≥3 months of follow-up are transfusion-independent or free of vaso-occlusive pain crises

Durable and Consistent Responses Across All Patients

Rapid and sustained increase in Hb and HbF

Increasing Momentum in Enrolling and Dosing Patients

20 patients dosed to date

Advancing Toward Regulatory Submissions

Multiple regulatory designations allow for increased regulatory interaction and input

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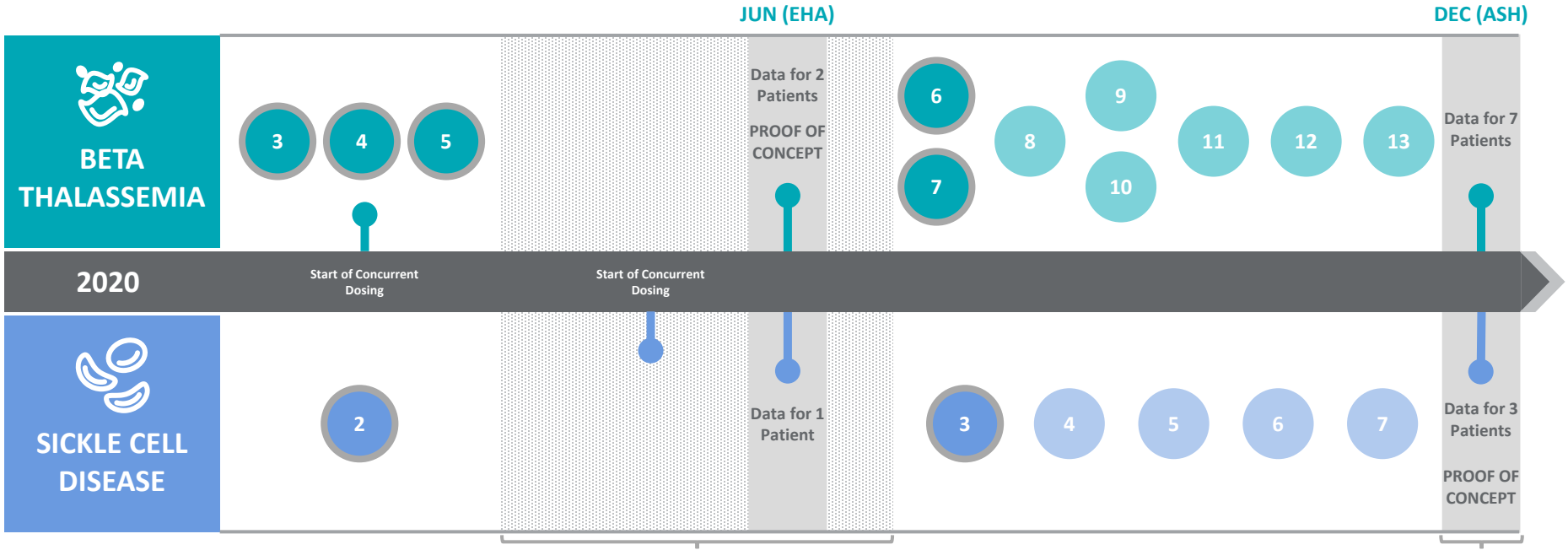
Note: ≥3 months of follow-up after CTX001 dosing

CTX001 PROGRAM GAINING MOMENTUM



Patients Dosed; Data Reported at ASH 2020

Additional Patients Dosed; Data for Medical Meeting in 2021

Note: Dosing dates are approximations

KEY REGULATORY DESIGNATIONS

RMAT

Fast Track & Breakthrough Therapy Designation benefits, including increased interactions with FDA to expedite development and review of the therapy

PRIME

Increased interactions with EMA Committees for Medicinal Products for Human Use (CHMP) and Advanced Therapies (CAT) to optimize development and speed evaluation of the therapy

ODD

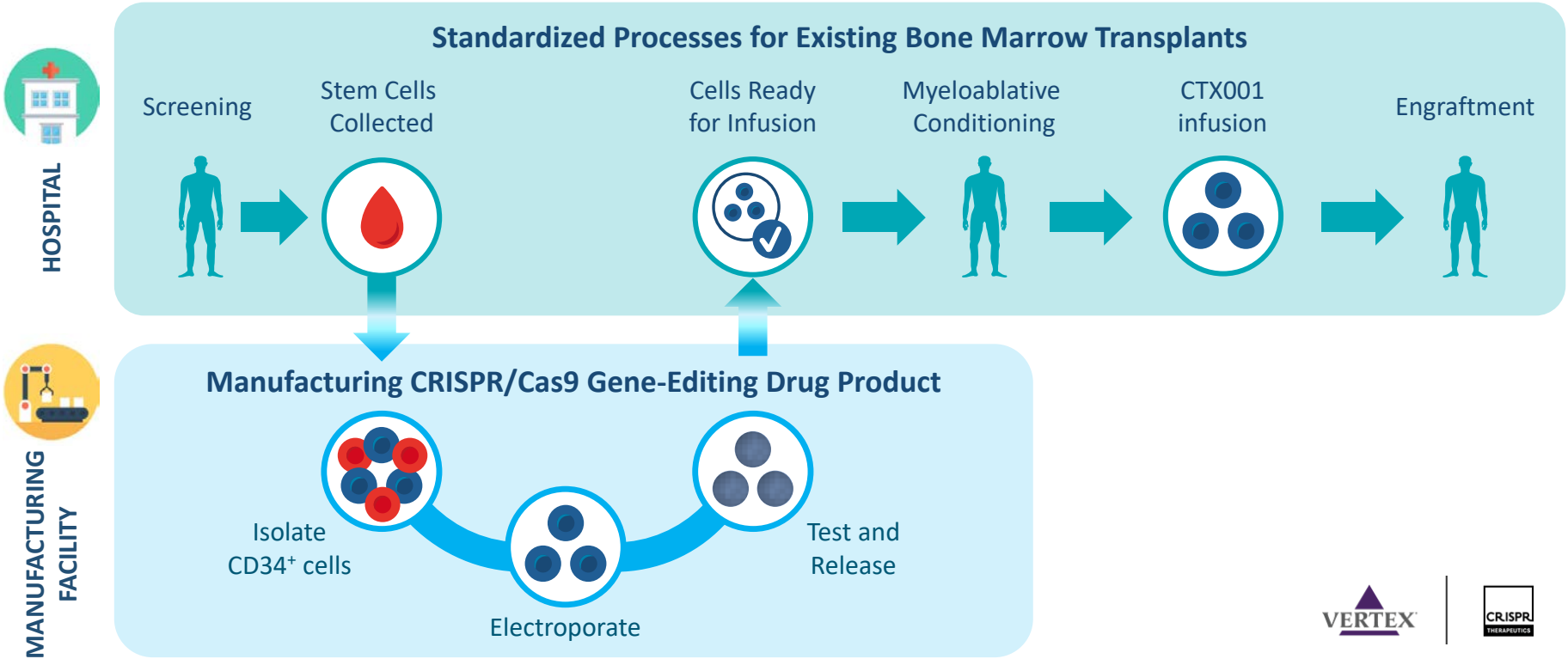
Reduction or waiver of MAA/BLA application fees

Additional market exclusivity
(7 years U.S.; 10 years EU)

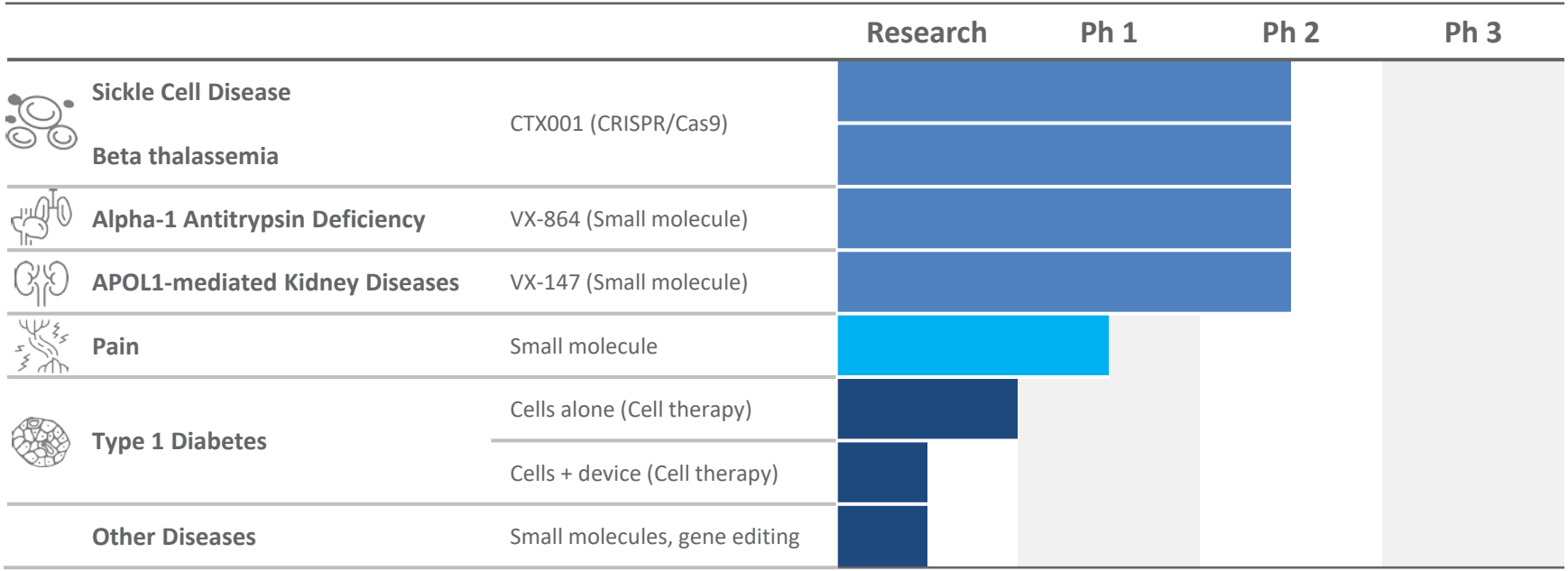
Rare Pediatric Disease

Potential to receive FDA priority review vouchers upon approval of the therapy

ROBUST MANUFACTURING PROCESS DESIGNED FOR CONSISTENCY FROM DEVELOPMENT TO COMMERCIALIZATION



PIPELINE OF POTENTIALLY TRANSFORMATIVE MEDICINES



There is no guarantee that the investigational compounds listed will be approved by a Health Authority or will be marketed. Safety and effectiveness of investigational medicines have not been established.

VERTEX CELL AND GENETIC THERAPIES

Gene Editing	Cell Therapy	mRNA
Sickle Cell Disease, Beta thalassemia, Cystic Fibrosis, DMD, DM1	***Type 1 Diabetes***	***Cystic Fibrosis***
People & Expertise, Enzymes, Guide RNA, Manufacturing, Targeted Conditioning, AAV Capsids and IP	People & Expertise, Cells, Devices, Manufacturing and IP	People & Expertise, Delivery, mRNA Chemistry and IP

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Expanding toolkit of scientific technologies, platforms and people with critical scientific and manufacturing expertise

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HAYDAR FRANGOUL, M.D., MEDICAL DIRECTOR OF PEDIATRIC HEMATOLOGY AND ONCOLOGY AT SARAH CANNON RESEARCH INSTITUTE, HCA HEALTHCARE'S TRISTAR CENTENNIAL MEDICAL CENTER

CTX001 Data Presentation from ASH Conference

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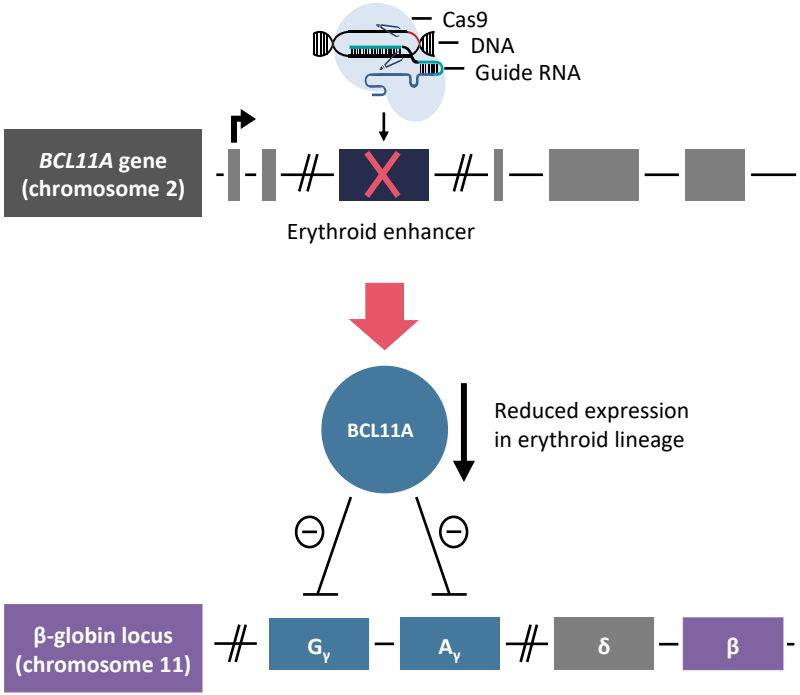
Studies in Patients With Transfusion-dependent β-Thalassemia (TDT) and Sickle Cell Disease (SCD) Are Ongoing

	CLIMB THAL-111	CLIMB SCD-121
Design	Phase 1 / 2, international, multicenter, open-label, single-arm study (NCT03655678)	Phase 1 / 2, international, multicenter, open-label, single-arm study (NCT03745287)
Target enrollment	45 patients aged 12 to 35 years with TDT, including β^0 / β^0 genotypes, defined as a history of at least 100 mL/kg/year or 10 units/year of pRBC transfusions in the previous 2 years	45 patients aged 12 to 35 years with severe SCD and a history of ≥2 vaso-occlusive crises per year over the previous 2 years
Primary endpoints	Proportion of patients achieving sustained transfusion reduction of 50% 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

Here, we present safety and efficacy results from the first 10 patients infused with CTX001

HbF: fetal hemoglobin; pRBC: packed red blood cell; SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia.

CRISPR-Cas9-Mediated Editing of *BCL11A* Increases HbF Levels[1]



- Naturally occurring genetic polymorphisms in *BCL11A* are associated with elevated HbF and decreased severity of TDT and SCD[2-4]
- BCL11A suppresses expression of HbF
- Editing of *BCL11A* results in reactivation of γ-globin expression and formation of HbF ($\alpha 2\gamma 2$) in mouse models
- CTX001 is produced using ex vivo editing of the erythroid enhancer region of *BCL11A* in $CD34^+$ HSPCs and reduces erythroid-specific expression of BCL11A
- Infusion of CTX001 leads to an increase in HbF levels in erythroid cells in vivo

HbF: fetal hemoglobin; HSPCs: hematopoietic stem progenitor cells; SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia.

1. Figure modified from Canver MC, Orkin SH. *Blood.* 2016;127:2536-2545; 2. Murray N, et al. *Br J Haematol*. 1988;69:89-92; 3. Conley CL, et al. *Blood*. 1963;21:261-281; 4. Bank A. *Blood.* 2006;107:435-443.

TDT: Patient Baseline and Treatment Characteristics

Patients with ≥3-month follow-up (n=7)

Patient characteristics		
Genotype, n	**β^+ / β^+**	**2**
	β^0 / β^+ (not IVS-I-110)	**2**
	β^0 / β^+ (IVS-I-110)[a]	**2**
	β^0 / β^0	**1**
Gender, Female/Male, n		**5/2**
Age at consent, years Median (range)		**23** (19 – 26)
Pre-study pRBC transfusions[b]		
Units/year, median (range)		**33.0** (23.5–61.0)
Transfusions episodes/year, median (range)		**15.0** (12.5–16.5)

Treatment characteristics	Median (range)
Drug product cell dose, $CD34^+$ cells × 10^6/kg	**11.6** (4.5 – 16.6)
Neutrophil engraftment,[c] Study Day[d]	**32** (20 – 39)
Platelet engraftment,[e] Study Day[d]	**37** (29 – 52)
Duration of follow-up, Months	**8.9** (3.8 – 21.5)

pRBC: packed red blood cell; TDT: transfusion-dependent β-thalassemia.

[a]IVS-I-110 phenotype is severe and similar to β^0 / β^0; [b]Annualized number during the 2 years before consenting to study participation; [c]Defined as the first day of 3 measurements of absolute neutrophil count ≥500 cells/µL on 3 consecutive days; [d]Study day defined as day after CTX001 infusion; [e]Defined as the first day of 3 consecutive measurements of platelet count ≥20,000/µL on 3 different days after CTX001 infusion, without a platelet transfusion in the past 7 days.

TDT: Summary of Adverse Events

Patients with ≥3-month follow-up (n=7)

AEs were generally consistent with myeloablation and autologous stem cell transplant

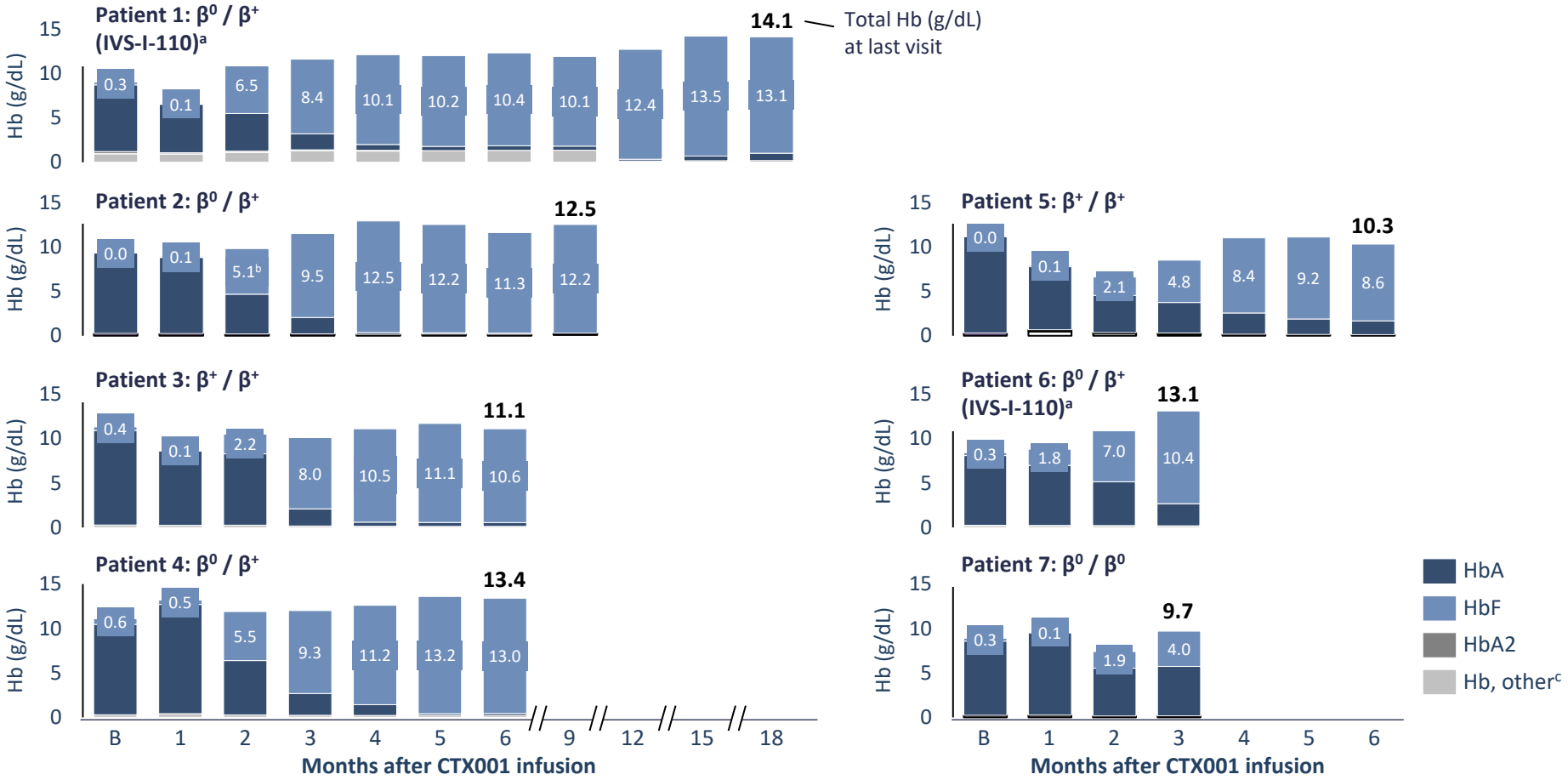
Months of follow-up, median (range)	8.9 (3.8–21.5)	
	Patients with non-serious AEs, n	**Patients with SAEs, n**
Relationship[a]		
Related to plerixafor and/or G-CSF	6	0
Related to busulfan only	7	2
Related to CTX001 only	1[b]	1
Related to busulfan and CTX001	3[c]	1
Not related to any study drug	7	4

- Majority of AEs occurred within first 60 days after CTX001 infusion
- 2 patients experienced a combined total of 5 SAEs related or possibly related to busulfan only: venoocclusive liver disease (in both patients), febrile neutropenia (2 events in 1 patient), and colitis; all resolved
- One patient experienced 4 SAEs related or possibly related to CTX001: headache, haemophagocytic lymphohistiocytosis (HLH), acute respiratory distress syndrome, and idiopathic pneumonia syndrome (latter also related to busulfan). All SAEs occurred in the context of HLH and have resolved.
- No CTX001-related SAEs were reported in the other patients

AEs: adverse events; G-CSF: granulocyte colony-stimulating factor; SAEs: serious adverse events.

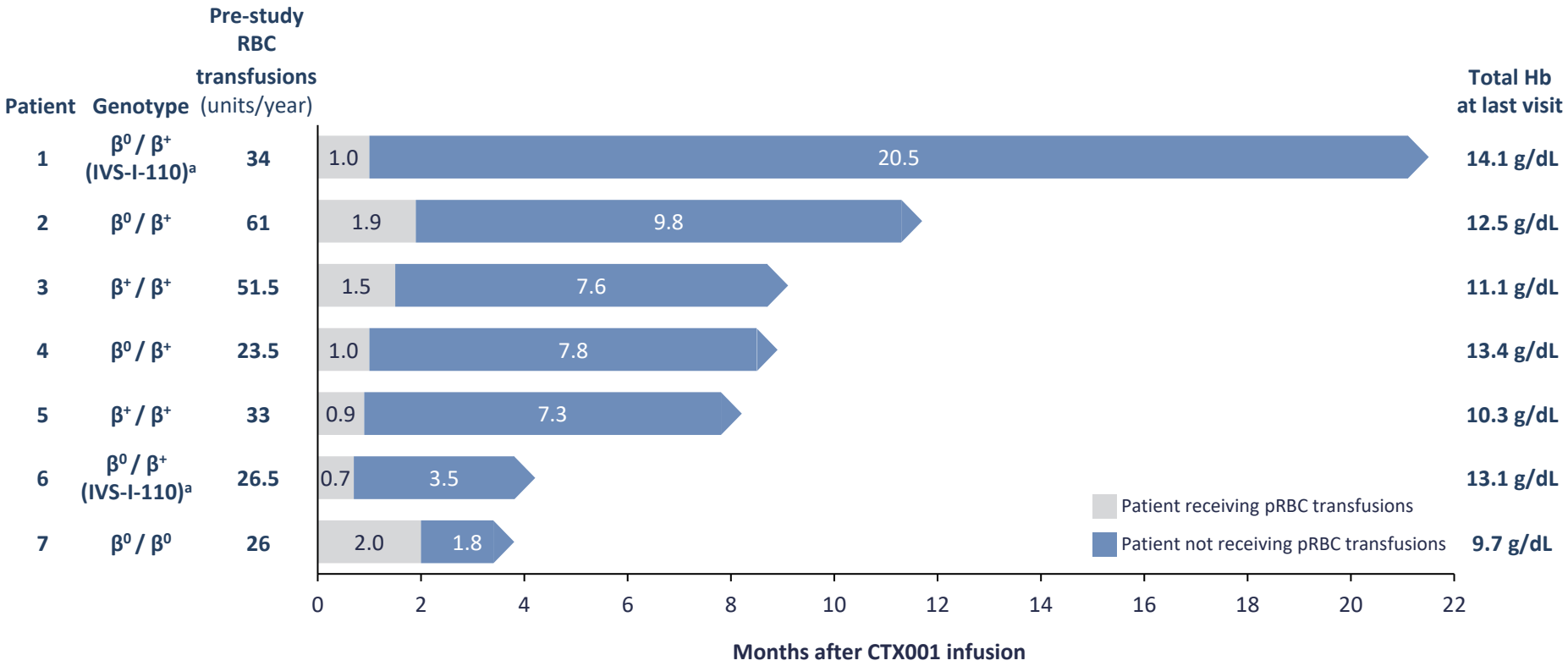
[a]Includes related and possibly related AEs. [b]1 patient experienced a non-serious AE of anaemia possibly related to CTX001 (resolved). [c]3 patients experienced non-serious AEs related or possibly related to busulfan and CTX001: petechiae, pyrexia, epistaxis, lymphocyte count decreased, neutrophil count decreased, WBC count decreased, and platelet count decreased.

TDT: Early, Sustained Increases in Total Hb & HbF Across Genotypes



B: Baseline, Hb: hemoglobin; HbA: adult hemoglobin; HbF: fetal hemoglobin; TDT: transfusion-dependent β-thalassemia. [a]Total Hb from local laboratory and Hb fraction from central laboratory.
[a]IVS-I-110 phenotype is severe and similar to β⁰ / β⁰ [c]Hb adducts and other variants

TDT: Duration of Transfusion Independence After CTX001



[a]IVS-I-110 phenotype is severe and similar to β^0 / β^0.
Hb: hemoglobin; pRBC: packed red blood cell; RBC: red blood cell; TDT: transfusion-dependent β-thalassemia.

SCD: Patient Baseline and Treatment Characteristics

Patients with ≥3-month follow-up (n=3)

Patient characteristics		
Genotypes, n	β^S / β^S	**3**
Gender, Female/Male, n		**2/1**
Age at consent, years Median (range)		**22** (22 – 33)
Pre-study VOCs VOCs/year[a], Median (range)		**7** (4.0 – 7.5)

Treatment characteristics	**Median** (range)
Drug product cell dose,[b] $CD34^+$ cells × 10^6/kg	**3.8** (3.1 – 3.9)
Neutrophil engraftment,[c] Study Day[d]	**22** (17 – 30)
Platelet engraftment,[e] Study Day[d]	**30** (30 – 33)
Duration of follow-up, Months	**7.8** (3.8 – 16.6)

SCD: sickle cell disease; VOCs: vaso-occlusive crises.

[a]Annualized rate during the 2 years before consenting to study participation; [b]Across multiple drug product lots per patient; [c]Defined as the first day of 3 measurements of absolute neutrophil count ≥500 cells/µL on 3 consecutive days; [d]Study day defined as day after CTX001 infusion [e]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.

SCD: Summary of Adverse Events

Patients with ≥3-month follow-up (n=3)

AEs were generally consistent with myeloablation and autologous stem cell transplant

Months of follow-up, *median (range)*	7.8 (3.8 – 16.6)	
	Patients with non-serious AEs, n	**Patients with SAEs,** n
Relationship[a]		
Related to plerixafor only	3	1
Related to busulfan only	3	1
Related to CTX001 only	0	0
Related to busulfan and CTX001	2[b]	0
Not related to any study drug	3	2

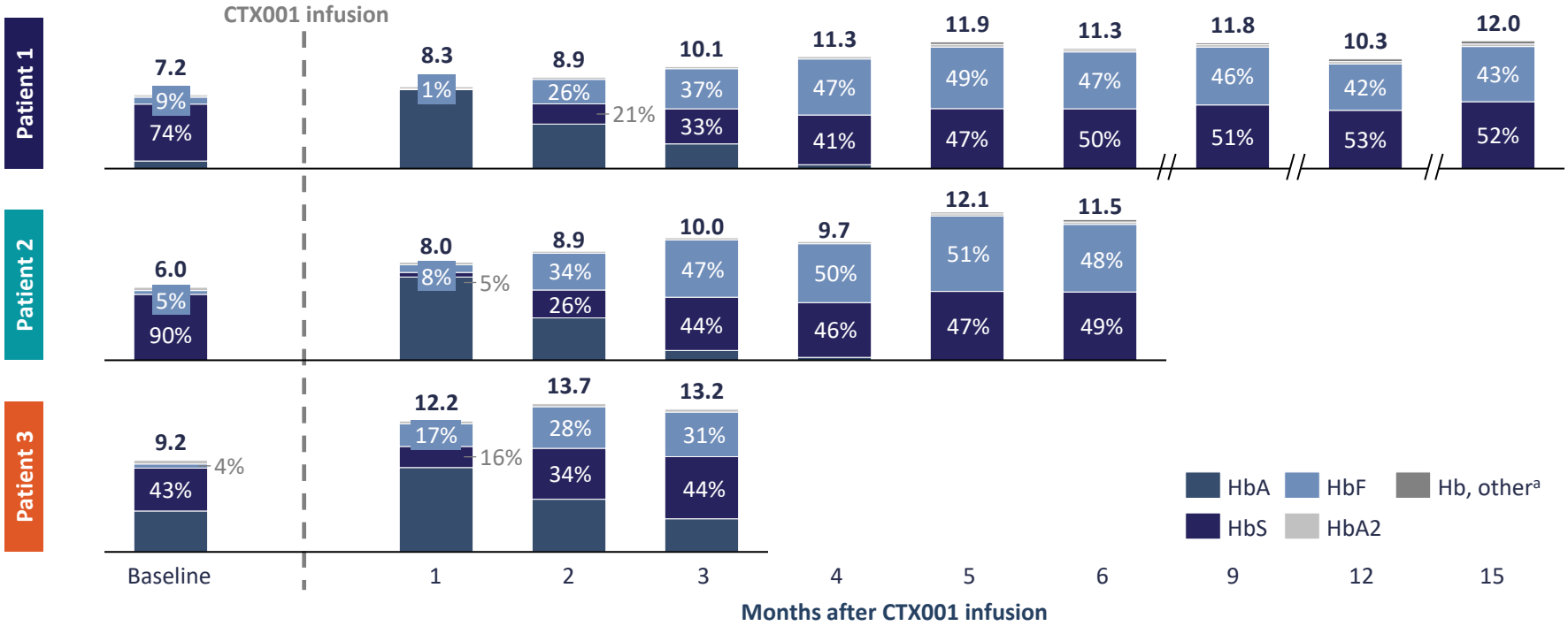
- Majority of AEs occurred within first 60 days after CTX001 infusion
- 1 patient experienced SAEs related to plerixafor: chest pain, neck pain, headache, and abdominal pain; all resolved
- Post-CTX001, only 1 patient experienced SAEs: sepsis (related to busulfan), cholelithiasis, and abdominal pain (both unrelated to any study drug); all resolved
- There were no SAEs related to CTX001

AEs: adverse events; SAEs: serious adverse events.

[a]Includes related and possibly related AEs. [b]2 patients experienced non-serious AEs related or possibly related to busulfan and CTX001: lymphopenia and dermatitis.

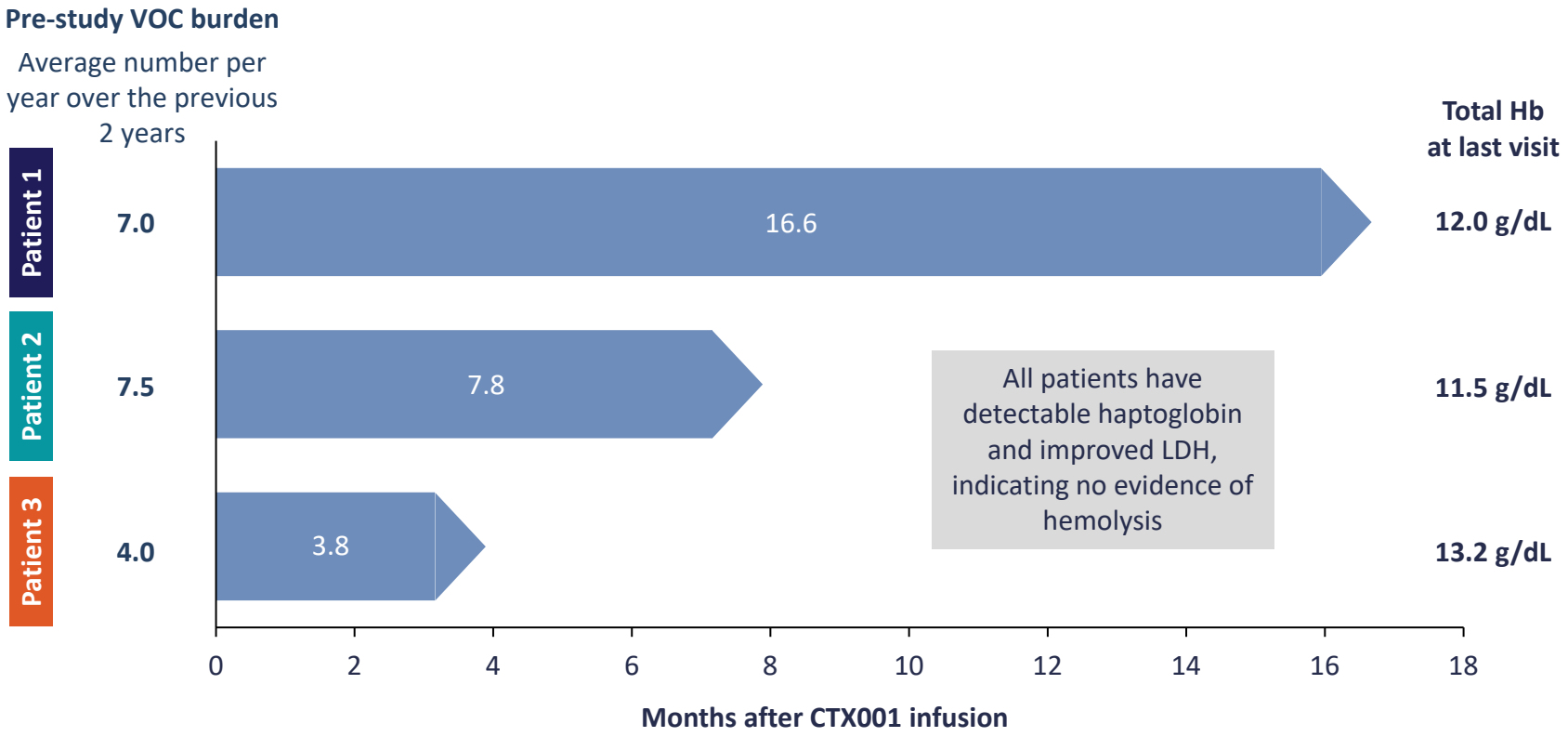
SCD: Clinically Meaningful HbF and Total Hb Are Achieved Early and Maintained

Hb fractionation[a], Hb g/dL



Hb: hemoglobin; HbA: adult hemoglobin; HbF: fetal hemoglobin; HbS: sickle hemoglobin; SCD: sickle cell disease.
[a]Hb adducts and other variants.

SCD: Duration VOC-free After CTX001



SCD: sickle cell disease; VOCs: vaso-occlusive crises.

Conclusions

The first 10 patients treated with CTX001 have been followed for 3.8 to 21.5 months and have stopped transfusions (TDT) and are VOC-free (SCD)

- Overall safety profile is generally consistent with myeloablative conditioning and autologous bone marrow transplant
- Clinically meaningful HbF and total hemoglobin levels are observed early and maintained across all 10 patients
- Clinical proof-of-concept for CTX001 has now been demonstrated for both TDT and SCD
- These data demonstrate that CTX001 is a potential functional cure for the treatment of TDT and SCD

HbF: fetal hemoglobin; SCD: sickle cell disease; TDT: transfusion-dependent β-thalassemia; VOCs: vaso-occlusive crises.

SAMARTH KULKARNI, PH.D., CRISPR THERAPEUTICS CEO

Commercial Opportunity and Future Outlook for CTX001

CRISPR PLATFORM: THE PROMISE OF CRISPR BECOMING A REALITY

- ✓ Translating CRISPR/Cas9 platform into transformative medicines
- ✓ Lead programs have achieved clinical PoC
- ✓ Rapidly advancing pipeline across four pillars
- ✓ Building a global fully integrated biopharma company

Ex vivo
hemoglobinopathies

Ex vivo
immuno-oncology

Ex vivo
regenerative medicine

In vivo
approaches

CTX001: POTENTIAL TO TRANSFORM THE LIVES OF PATIENTS WITH SEVERE SCD AND TDT

Potential to be Best-in-Class

Based on reawakening a naturally occurring form of hemoglobin

Simple, precise and durable single-edit approach using CRISPR

Significant Market Opportunity

Potential to treat large number of patients in the near-term in the U.S. and EU

Addressable market becomes larger with gentler conditioning regimens

Strong Case for Benefit

Need for new therapies that address the underlying cause of disease

Significant value to patients and to health system due to reduced chronic healthcare utilization

Competitively Well-Positioned

Leverage combined resources and capabilities of CRISPR and Vertex

Ability to scale manufacturing and commercial infrastructure globally

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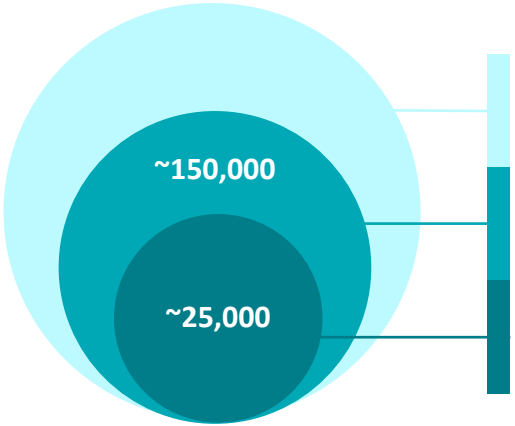
CTX001: >30,000 POTENTIAL PATIENTS IN THE NEAR-TERM ACROSS THE U.S. AND EU

SICKLE CELL DISEASE

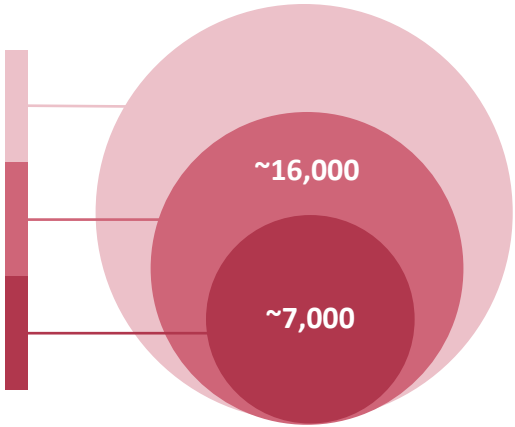


Expansion into other international markets

Total patients in the U.S. and EU – *potential for expansion with gentler conditioning regimens*

Likely candidates for gene-editing therapy in the U.S. and EU based on disease severity

BETA THALASSEMIA



*Potential to treat **a large number of patients** with severe forms of these diseases in the U.S. and EU **in the near-term with CTX001***
Larger addressable market with gentler conditioning regimens

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THANK YOU

Q&A

