VERTEX

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# Administration of Exagamglogene autotemcel (exa-cel), also known as CTX001™

SEPTEMBER 13, 2022

# EXAGAMGLOGENE AUTOTEMCEL
(exa-cel)

**Exa-cel is an investigational therapy that has not been approved by any regulatory authority. The safety and effectiveness of exa-cel has not yet been established.**

# EXA-CEL IS AN INVESTIGATIONAL CELL THERAPY THAT USES NON-VIRAL, *EX VIVO* CRISPR/CAS9-MEDIATED EDITING OF *BCL11A* TO INCREASE 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 γ-globin and thus HbF
- Editing of BCL11A reactivates γ-globin expression and formation of HbF (α2γ2) in mouse models[4]
- Exa-cel is produced using non-viral, *ex vivo* editing of the erythroid-specific enhancer region of *BCL11A* in CD34⁺ HSPCs and reduces erythroid-specific expression of BCL11A
- Infusion of exa-cel leads to an increase in HbF levels in erythroid cells *in vivo*

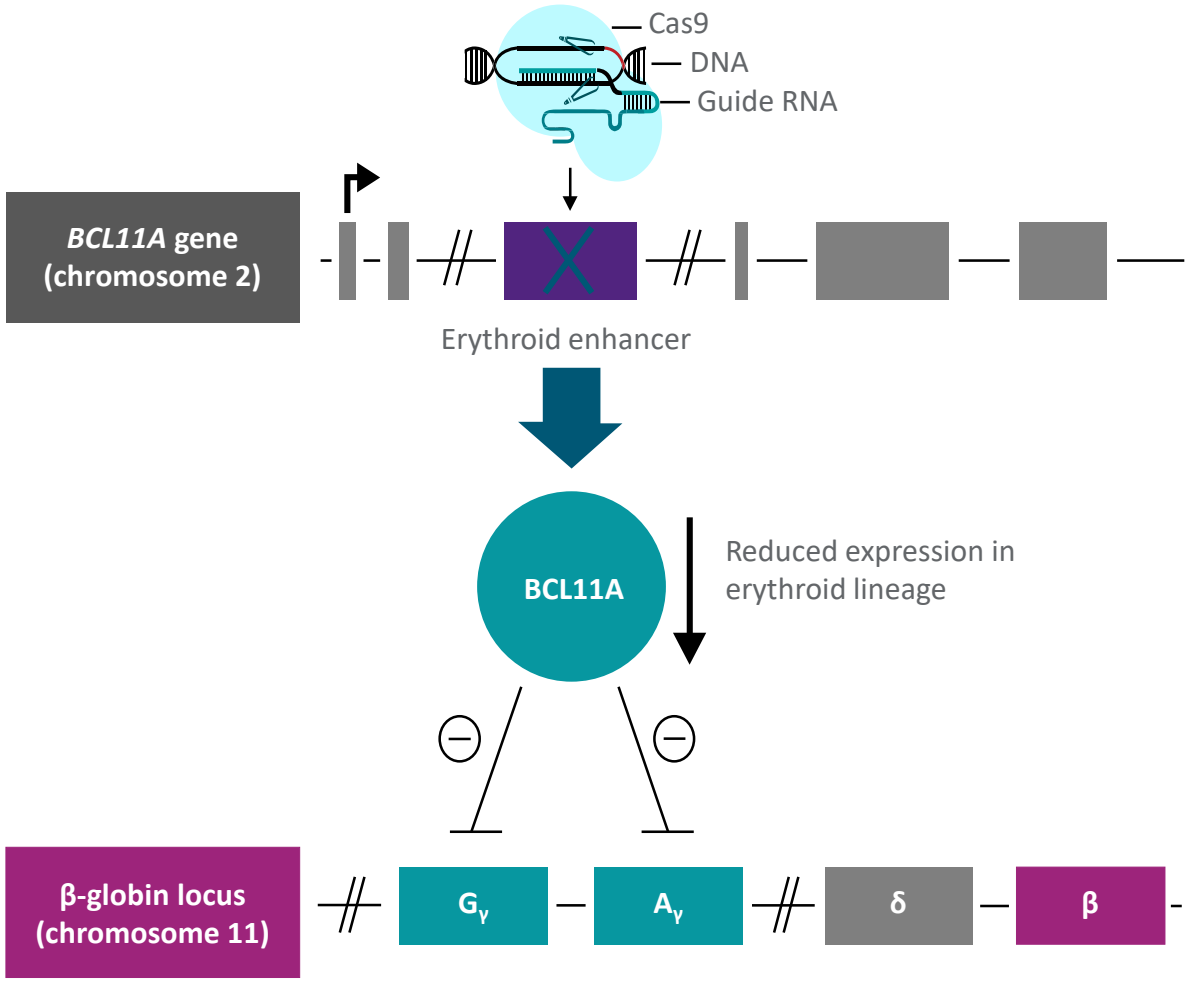
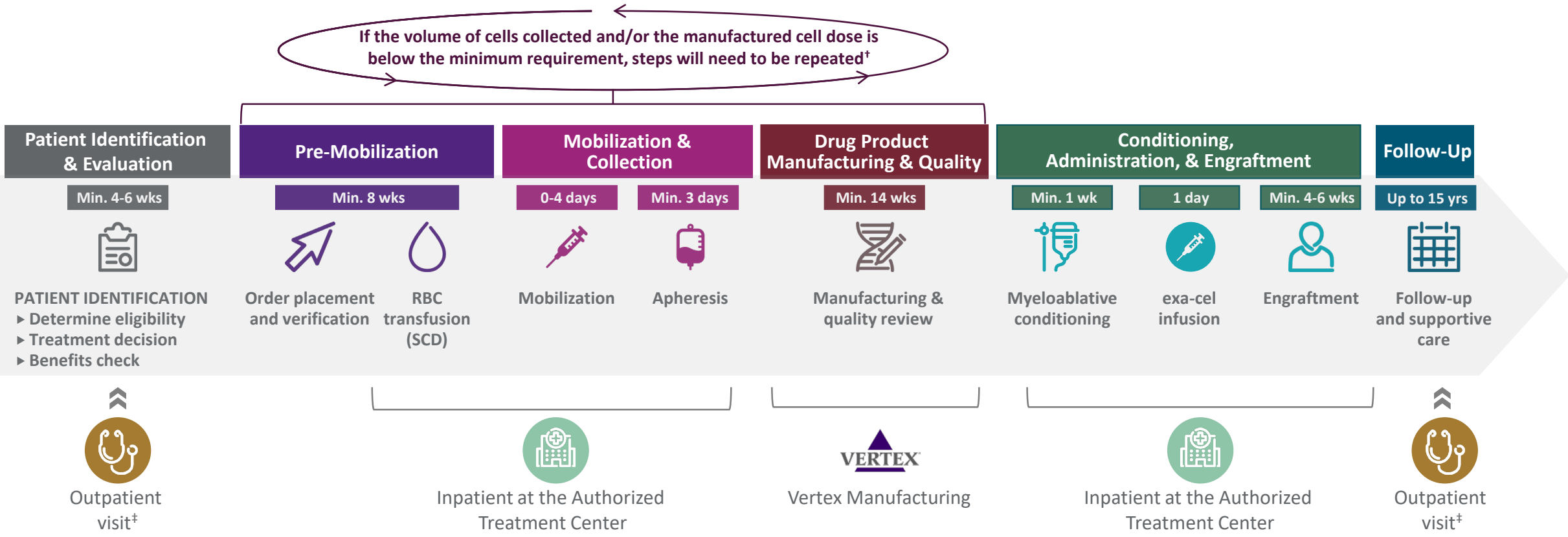



Figure modified from Canver, et al.[1]

*BCL11A*, B-cell lymphoma/leukemia 11A; CRISPR, clustered regularly interspaced short palindromic repeats; DNA, deoxyribonucleic acid; HbF, fetal hemoglobin; HSPC, hematopoietic stem and progenitor cell; RNA, ribonucleic acid; SCD, sickle cell disease; TDT, transfusion dependent β-thalassemia.

1. Canver MC, et al. *Blood*. 2016;127:2536-2545; 2. Murray N, et al. *Br J Haematol*. 1988;69:89-92; 3. Bank A. *Blood*. 2006;107:435-443; 4. Bauer DE, et al. *Science*. 2013;342:253-257.

# ANTICIPATED EXA-CEL TREATMENT JOURNEY[1-4*]




**Exa-cel is an investigational therapy that has not been approved by any regulatory authority. The safety and effectiveness of exa-cel has not been established. Treatment journey timing may be subject to change based on FDA approved product label.**

*Treatment journey timing may vary by patient. Timing illustrated in the chart is based on clinical trial experience to date and may change upon commercialization and final product label.

† The average number of collection cycles for TDT is 1; the average number of collection cycles for SCD is 2.

‡ Visits may be at local hematologist or Authorized Treatment Center based on physician and patient discretion.

1. Data on file. Vertex Pharmaceuticals Incorporated. Boston, MA. REF-15461 (v1.0); 2022. 2. Grupp S, et al. Abstract EP736. Presented at the 26th EHA Annual Congress; June 9-17, 2021. 3. Locatelli F, et al. Abstract EP733. Presented at the 26th EHA Annual Congress; June 9-17, 2021. 4. U.S. National Institutes of Health. ClinicalTrials.gov. A Long-term Follow-up Study in Subjects Who Received CTX001. Accessed May 16, 2022. https://clinicaltrials.gov/ct2/show/NCT04208529.

# CLIMB THAL-111 AND CLIMB SCD-121 PIVOTAL TRIALS OF EXA-CEL IN PATIENTS WITH TDT AND SEVERE SCD ARE ONGOING

| | CLIMB THAL-111 | CLIMB SCD-121 |
|---|---|---|
| Design | International, multicenter, open-label, single-arm pivotal study of exa-cel (NCT03655678) | International, multicenter, open-label, single-arm pivotal study of exa-cel (NCT03745287) |
| Key Inclusion Criteria | Twelve to 35 years of age with TDT, including $\beta^0/\beta^0$ genotypes, defined as a history of ≥100 mL/kg/year or ≥10 units/year of pRBC transfusions in the previous 2 years | Twelve to 35 years of age with severe SCD and a history of ≥2 VOCs per year in the previous 2 years |
| Primary Endpoint | *Primary efficacy endpoint:* Proportion of patients achieving a maintained weighted average Hb ≥9 g/dL without RBC transfusions for at least 12 consecutive months after exa-cel infusion | *Primary efficacy endpoint:* Proportion of patients who have not experienced any severe VOC for at least 12 consecutive months after exa-cel infusion |
| Clinical Assessments | Engraftment, total Hb, HbF, *BCL11A* edited alleles, transfusions, and AEs | Engraftment, total Hb, HbF, *BCL11A* edited alleles, transfusions, VOCs, and AEs |

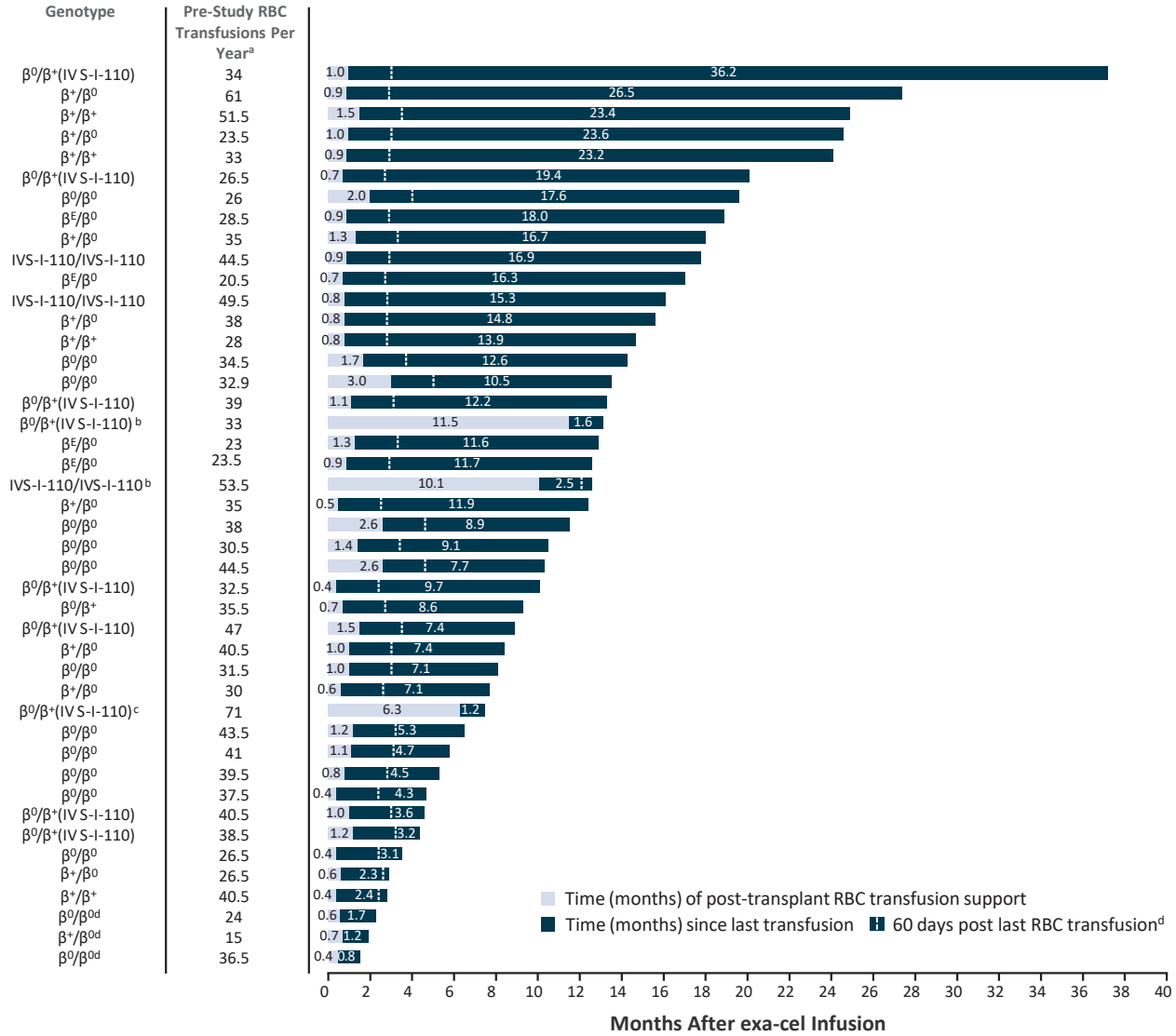
**Data presented on all patients infused with exa-cel who have TDT (n = 44) or severe SCD (n = 31) as of February 2022**

AE, adverse event; *BCL11A*, B-cell lymphoma/leukemia 11A; Hb, hemoglobin; HbF, fetal hemoglobin; pRBC, packed red blood cell; RBC, red blood cell; SCD, sickle cell disease; TDT, transfusion dependent β-thalassemia; VOC, vaso-occlusive crisis.

# FORTY-TWO OF 44 PATIENTS WITH TDT TREATED WITH EXA-CEL ARE TRANSFUSION-FREE

- Time (months) of post-transplant RBC transfusion support is indicated by the light blue bar and time (months) since last transfusion is indicated by the dark blue bar
- 42 of 44 patients stopped RBC transfusions (duration from 0.8 to 36.2 months)
- Two patients had not yet stopped transfusions but have 75% and 89% reductions in transfusion volume

## Transfusion-Free Period After exa-cel Infusion




Hb, hemoglobin; RBC, red blood cell; TDT, transfusion-dependent β-thalassemia.

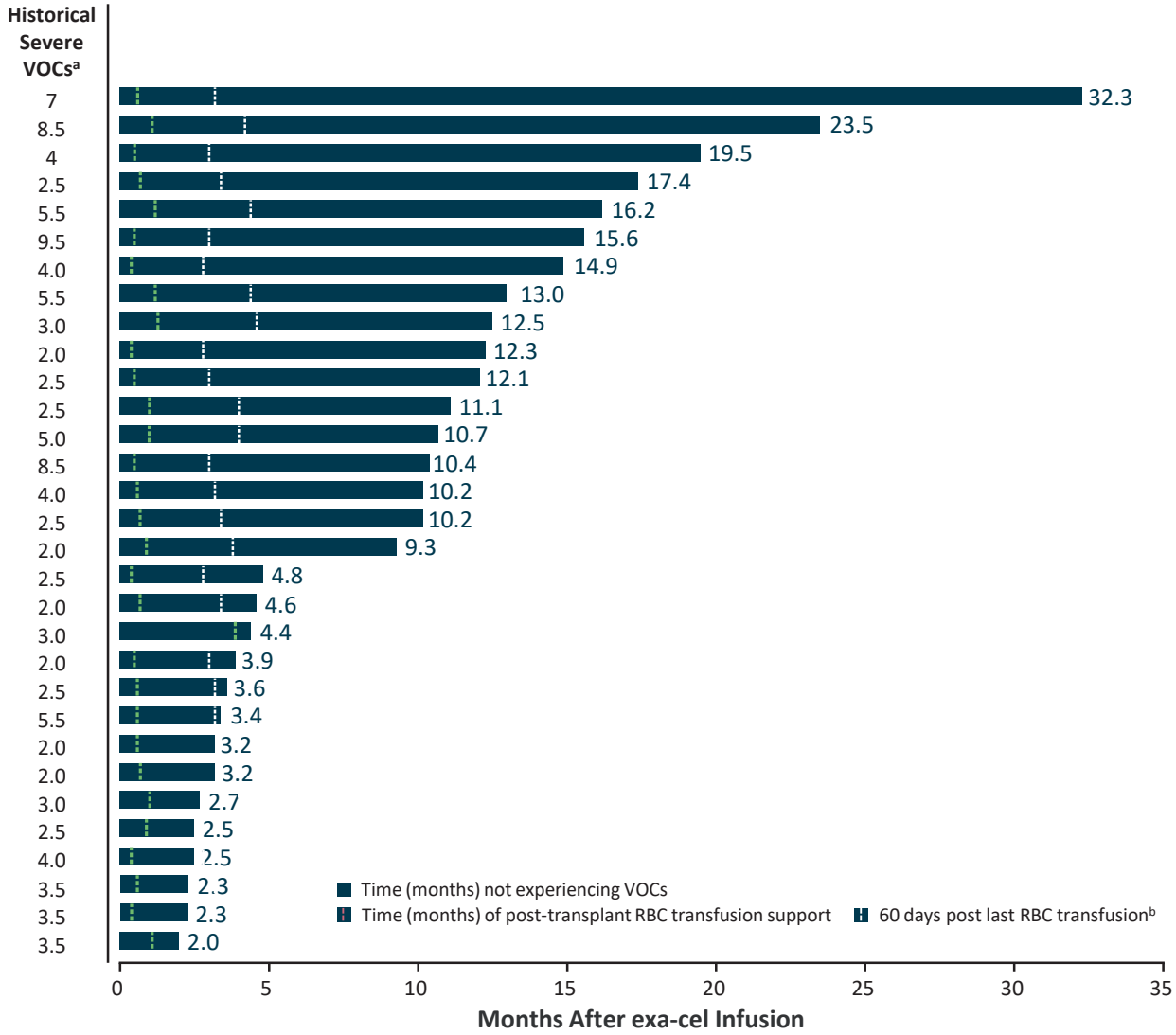
Each row in the figure on the right represents an individual patient.

[a]Number of transfusion units annualized over 2 years; [b]Received RBC transfusions at or after data cut; [c]Patient stopped transfusions after data cut; [d]Patients are evaluable for elimination of transfusions starting 60 days after their last transfusion.

# ALL PATIENTS WITH SCD TREATED WITH EXA-CEL ARE VOC-FREE

- Time (months) since exa-cel infusion is indicated by the dark bar
- 31 of 31 patients were VOC-free after exa-cel infusion (duration from 2.0 to 32.3 months)

## VOC-Free Period After exa-cel Infusion




RBC, red blood cell; SCD, sickle cell disease; VOC, vaso-occlusive crisis.

Each row in the figure on the right represents an individual patient.

[a]Pre-study severe VOCs annualized over 2 years; [b]Patients are evaluated for elimination of VOCs starting 60 days after their last transfusion.

# OVERVIEW OF EXA-CEL AES

| Post-exa-cel AE Overview | TDT (n = 44) | SCD (n = 31) |
|---|---|---|
| Patient-time exposure, Patient-months | 520.2 | 288.6 |
| Patients with any AEs, n (%) | 44 (100.0) | 31 (100.0) |
| Patients with AEs related to exa-cel, n (%)[a] | 12 (27.3) | 9 (29.0) |
| Patients with AEs related to busulfan, n (%)[a] | 43 (97.7) | 31 (100.0) |
| Patients with AEs Grade 3/4, n (%) | 38 (86.4) | 31 (100.0) |
| Patients with SAEs, n (%) | 15 (34.1) | 10 (32.3) |
| Patients with SAEs related to exa-cel, n (%)[a] | 2 (4.5) | 0 |
| Patients with AEs leading to death, n (%) | 0 | 0 |

AE, adverse event; HSCT, hematopoietic stem cell transplantation; SAE, serious adverse event; SCD, sickle cell disease; TDT, transfusion-dependent β-thalassemia.

[a]Includes related and possibly related AEs.

# EXA-CEL RELATED SAES

- One patient with TDT had 3 SAEs related to exa-cel of hemophagocytic lymphohistiocytosis (HLH; macrophage activation syndrome), acute respiratory distress syndrome, and headache, and 1 SAE of idiopathic pneumonia syndrome related to both exa-cel and busulfan
  - All began peri-engraftment and occurred in the context of HLH. Events fully resolved with steroid and immunosuppressant treatment
  - HLH is a systemic hyperinflammatory non-infectious syndrome that has been reported after autologous HSCT
- One patient with TDT had SAEs related to both exa-cel and busulfan of delayed neutrophil engraftment and thrombocytopenia
  - Both SAEs resolved. Neutrophil engraftment was achieved on Day 56 without use of backup cells
  - All other patients in both exa-cel trials achieved neutrophil engraftment within 43 days of exa-cel infusion
- No patients with SCD had an SAE considered related or possibly related to exa-cel

HLH, hemophagocytic lymphohistiocytosis; HSCT, hematopoietic stem cell transplant; SAE, serious adverse event; SCD, sickle cell disease; TDT, transfusion-dependent β-thalassemia.

# SUMMARY OF THE CLINICAL TRIALS (TO DATE)

- Data from 75 patients with TDT and severe SCD shows a **single dose of exa-cel leads to early increases in HbF and total Hb** that are durable up to 3 years
- 42 of 44 patients with TDT **stopped RBC transfusions** and all 31 patients with severe SCD are **free of VOCs**
- Patients with ≥1 year of follow up have stable proportions of *BCL11A* edited alleles in bone marrow and peripheral blood, **indicating successful and durable editing** of long-term HSCs
- **Safety profile of exa-cel is consistent** with that of busulfan myeloablative conditioning and autologous hematopoietic stem cell transplantation
- Exa-cel has the potential to be the first CRISPR/Cas9-based therapy to provide a **potential functional cure for patients with TDT and severe SCD**

**Investigational treatment with exa-cel is associated with early, consistent, and durable increases in HbF levels leading to elimination of transfusions in almost all patients with TDT and elimination of VOCs in all patients with SCD**

Hb: hemoglobin; HbF: fetal hemoglobin; HSC: hematopoietic stem cell; RBC: red blood cell; SCD: sickle cell disease; TDT, transfusion-dependent β-thalassemia; VOCs: vaso-occlusive crises.

# EXA-CEL

Procedure Description

Documentation

Code Request

## Procedure Description

- Exa-cel is a gene-edited biological product prepared from a patient's own hematopoietic stem cells (HSCs), which are collected from the patient. The cells are edited at a manufacturing facility, cryopreserved and shipped back to the authorized treatment center (e.g., hospital). Once the cells are received at the authorized treatment center, the patient undergoes myeloablative conditioning with busulfan before the cells are infused.

- The single dose of exa-cel is infused through a central venous catheter at least 48 hours and within 7 days after the last busulfan dose. Monitoring for adverse events and engraftment occurs along with the administration of any supportive therapy that may be required. Once engraftment occurs, the cells begin production of red blood cells that express fetal hemoglobin.

## Documentation

- The administration of the biological product, exa-cel, will be documented either as a pharmacy order or a cellular laboratory order.
- The clinical documentation of the administration of exa-cel will likely be in the transplant clinician's note in the patient's medical record. Vertex expects a patient's medical record to include notes from the physician and nursing staff that describe the conditioning of the patient, the administration of the biological product, and time to engraftment. The procedure note will likely indicate that the patient received the exa-cel gene-edited therapy via an autologous transplant.

## Code Request

- There are no precise codes available to describe the administration of exa-cel. The current coding options do not specifically identify the administration of exa-cel, which is necessary to track utilization, outcomes, and resources associated with the biological product.

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# THANK YOU