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Applicant	Vertex Pharmaceuticals
Established Name	exagamglogene autotemcel
(Proposed) Trade Name	CASGEVY
Pharmacologic Class	Gene Therapy
Dosage Form(s) and Route(s) of Administration	A cell suspension for intravenous infusion
Dosing Regimen	One-time treatment. The minimum recommended dose is $3 \times 10^6$ CD34+ cells per kg of body weight, which may be composed of multiple vials.
Indication(s) and Intended Population(s)	Treatment of transfusion-dependent $\beta$ thalassemia in patients 12 years and older.

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GLOSSARY

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allo-HSCT	Allogeneic hematopoietic stem cell transplantation
ARDS	acute respiratory distress syndrome
beti-cel	Betibeglogene autotemcel
BLA	Biologics License Application
CRISPR/Cas9	Clustered Regularly Interspaced Short Palindromic Repeats-CRISPR associated 9 nuclease
EAC	endpoint adjudication committee
EES	Early Efficacy Set
exa-cel	exagamglogene autotemcel
FAS	Full Analysis Set
GVHD	graft-versus-host-disease
Hb	hemoglobin
HbA	adult hemoglobin
HbE	hemoglobin E
HbF	fetal hemoglobin
hHSPCs	human hematopoietic stem and progenitor cells
HLA	human leukocyte antigen
HLH	lymphohistiocytosis
HSPC	hematopoietic stem and progenitor cell
IA	interim analysis
ICF	informed consent form
IV	intravenous
LTFU	long-term follow-up
PES	Primary Efficacy Set
RBC	red blood cell
SAE	Serious Adverse Event
SCD	sickle cell disease
TDT	transfusion-dependent $\beta$ -thalassemia
TI	transfusion independence

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## 1. Executive Summary

This original Biologics License Application (BLA) is for the approval of a Clustered Regularly Interspaced Short Palindromic Repeats-CRISPR associated 9 nuclease (CRISPR/Cas9)-modified autologous CD34<sup>+</sup> hematopoietic stem and progenitor cell (HSPC) cellular therapy, CASGEVY (also referred to as exa-cel). The proposed indication is for the treatment of transfusion-dependent  $\beta$ -thalassemia (TDT) in patients 12 years and older.

The primary evidence is based on the results from a planned interim analysis (IA, the cut-off date was 16 January 2023) of the pivotal study CTX001-111: a single-

arm, open-label, multi-site, single dose, Phase 1/2/3 study in subjects 12 to 35 years of age (inclusive) who have TDT. The primary efficacy endpoint was the proportion of subjects achieving transfusion independence (TI)<sub>12</sub>, defined as maintaining weighted average Hb  $\geq$  9 g/dL without RBC transfusions for at least 12 consecutive months any time after CASGEVY infusion during the 24 month follow up.

The submission included 59 enrolled subjects from CTX001-111, and 52 of them received CASGEVY infusion. 35 of the infused subjects have been followed for at least 16 months post CASGEVY infusion and for at least 14 months after completion of the RBC transfusions for post-transplant support or TDT management. This population was defined as Primary Efficacy Set (PES) and was used for the primary efficacy evidence for the application. For the primary endpoint, 32 of 35 (91.4%) evaluable subjects achieved TI<sub>12</sub> (1-sided 98.3% CI: 75.7%, 100%).

All subjects who received CASGEVY infusion who completed or discontinued from CTX001-111 study were asked to participate in Study CTX001-131. CTX001-131 was an ongoing, multi-site, open-label, rollover study designed to evaluate the long-term safety and efficacy of CASGEVY in subjects who received CASGEVY in CTX001-111 study for a total follow-up of 15 years after CASGEVY infusion. The cut-off date for CTX001-131 was 16 January 2023 as well. Subjects who rolled over to Study 131, all of whom had achieved TI<sub>12</sub> in Study CTX001-111, maintained transfusion independence in Study CTX001-131. The results for the secondary endpoints also support the clinical effectiveness of CASGEVY.

For safety, no death was reported during the study as of the cut-off date of the IA (including the 120-day safety update). Among the subjects who completed myeloablative busulfan conditioning and received CASGEVY, 17 (32.7%) subjects had serious adverse events (SAEs). Veno-occlusive liver disease was the most common SAE (5 [9.6%]) subjects); these events were considered by the investigator(s) related to busulfan and not related to CASGEVY. Nine (17.3%) subjects had SAEs considered related or possibly related to busulfan. Two (3.8%) subjects had SAEs considered related or possibly related to CASGEVY (some of which were also related to busulfan).

In summary, the submitted data have provided sufficient evidence of clinical effectiveness of CASGEVY. Although the sample size (35) for the safety evaluation was lower than the 50 evaluable subjects recommended by FDA during pre-BLA communications, no unexpected safety concerns were identified. Therefore, I recommend the approval of CASGEVY for the proposed indication of the treatment of TDT in patients 12 years and older.

## 2. Clinical and Regulatory Background

### 2.1 Disease or Health-Related Condition(s) Studied

$\beta$ -thalassemia is an inherited autosomal recessive disorder caused by genetic mutations that reduce or eliminate the expression of  $\beta$ -globin, which results in an  $\alpha$ - to non- $\alpha$ -globin chain imbalance and decrease in adult hemoglobin (HbA) tetramers in RBCs. Unpaired  $\alpha$ -globin chains precipitate inside RBCs, leading to the destruction of erythroid precursors in the bone marrow, known as ineffective erythropoiesis, and destruction of RBCs in circulation, known as hemolysis.

TDT, a rare disease, is the most severe form of  $\beta$ -thalassemia, which is characterized by significant anemia requiring regular lifetime transfusions of RBCs (every 2 to 4 weeks). These transfusions carry risks of infection, iron overload, reduced quality of life, and reduced survival. TDT is associated with numerous comorbidities in nearly every organ system due to anemia and iron overload. Chronic anemia leads to reduced growth and development, and hemolysis leads to damage of the vasculature, thrombosis, and pulmonary hypertension. Iron overload from transfusions leads to end organ damage, cardiomyopathy, liver fibrosis and cirrhosis, and endocrinopathies in adolescents and adults. Even with optimal care including access to regular transfusions and iron chelation therapy, the overall survival of a patient with TDT is significantly reduced compared to people without the disease, with only 65% surviving to age 50.  $\beta$ -thalassemia is a rare disorder that is highly linked to ethnicity and is often associated with individuals originating from the Mediterranean, the Middle East, South Asia, and Southeast Asia. Across all age groups, the prevalence of  $\beta$ -thalassemia in the US is estimated to be ~2,600 individuals.

### 2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

The mainstay of current therapy for TDT is lifetime transfusion support with RBCs, which inevitably leads to iron overload and end-organ damage, and iron chelators to manage iron overload. Luspatercept (Reblozyl), an erythroid maturation agent, is approved in the US for adult patients with  $\beta$ -thalassemia to decrease RBC transfusion requirements.

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potential option for patients with TDT. However, allo-HSCT is limited in availability due to the paucity of human leukocyte antigen (HLA) matched related donors and associated with significant risks including transplant-related mortality, primary and secondary graft failure, acute and chronic graft-versus-host-disease (GVHD), and other severe complications related to the need for immunosuppressive therapies.

Betibeglogene autotemcel (beti-cel) was recently (2022) approved in the US under the trade name Zynteglo for the treatment of TDT. Beti-cel is a gene

therapy medicinal product consisting of autologous CD34+ cells transduced with a lentiviral vector encoding a modified  $\beta^{A-T87Q}$ -globin gene.

#### **2.4 Previous Human Experience with the Product (Including Foreign Experience)**

There is no previous human experience with the product in patients with TDT. CASGEVY was approved on December 18, 2023 for the indication of treatment of sickle cell disease in patients with recurrent vaso occlusive crises.

#### **2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission**

A meeting package was submitted on April 18, 2022 to seek FDA's comments on the proposal to combine the sickle cell disease (SCD) and TDT population safety and efficacy data into a single BLA for the two indications with 26 subjects in TDT and 17 subjects in SCD and only 50 subjects would have 12 months of follow-up to inform of short-term safety. In a meeting written response (CRMTS #14020) to the applicant on May 17, 2022, FDA commented that 26 subjects with TDT are likely inadequate to demonstrate evidence of efficacy or safety of CASGEVY, and recommended BLA submission with a minimum of 50 subjects with TDT followed  $\geq 18$  months. Meanwhile, FDA strongly recommend against combining the two indications into a single original BLA.

The applicant submitted another meeting request on June 10, 2022, to discuss and reach agreement on revised data package proposals at the time of BLA submission. The pre-meeting materials were submitted on July 8, 2022. FDA provided its preliminary meeting responses to the applicant on August 5, 2022. In the response, FDA commented that the adequacy of the applicant's proposed BLA submission package (42 subjects with TDT having  $\geq 16$  months follow up after CASGEVY) to provide sufficient evidence of effectiveness of CASGEVY remains uncertain and will ultimately be a review issue. In addition, the proposed data may not provide sufficient evidence of durability of effect.

### **3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES**

#### **3.1 Submission Quality and Completeness**

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

## 5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

### 5.1 Review Strategy

In this submission, one phase 3 clinical study, CTX001-111, and one long-term follow-up (LTFU) study, CTX001-131 were submitted in support of this application. Therefore, the efficacy and safety database consist of data from Study CTX001-111 and those from the TDT subjects in CTX001-131 is reviewed in detail in this memo.

### 5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

BLA	125785/0	
	Module 1.14	Labeling
	Module 1.6	Meetings
	Module 2.5	Clinical Overview
	Module 2.7	Clinical Summary
	Module 5.2	Tabular Listing of all Clinical Studies
	Module 5.3.5.2	Study Reports CTX001-111: study report body, protocol, statistical analysis plan. CTX001-131: study report body, protocol, statistical analysis plan.
	Module 5.3.5.2	Data Files
	125785/66	
	Module 5.3.5.2	Study Reports

### 5.3 Table of Studies/Clinical Trials

Table 1 Summary of clinical studies in the BLA

Study Identifier; Type of Study; Country; Study Status/ Location of Report	Study Design; Type of Control	Study Objectives	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects Dosed With Study Drug; Population	Duration of Treatment; Duration of Study
CTX001-111;  Phase 1/2/3 Safety and efficacy in subjects with TDT;	Single-arm, Open-label	Primary: • To evaluate the safety and efficacy of a single dose of autologous CRISPR/Cas9 modified CD34+	Exa-cel; single dose administration; minimum recommended dose of exacel is $3 \times 10^6$ CD34+ cells/kg; Intravenous use	52 subjects; Males and females with TDT aged 12 to 35 years (inclusive)	Single dose; up to 2 years after exa-cel infusion

<p>United States, United Kingdom, Italy, Germany, Canada;  Ongoing</p>		<p>hHSPCs (exacel) in subjects with TDT Secondary: • To quantify percentage of edited alleles in peripheral blood leukocytes and CD34+ cells of the bone marrow • To assess the production of HbF post-exa-cel infusion • To assess the effects of infusion of exa-cel on disease-specific events and clinical status</p>			
<p>VX18-CTX001-131; Long-term follow-up in subjects with either TDT or severe SCD;  United States, United Kingdom, Germany, Canada, Italy;  Ongoing</p>	<p>Single-arm, open-label</p>	<p>Primary: • Evaluate long-term safety up to 15 years after exacel infusion in subjects who received a single dose of exacel for treatment of TDT or SCD Secondary: • To evaluate efficacy of exacel up to 15 years after exacel infusion in subjects who received exacel for treatment of TDT or severe SCD</p>	<p>No study drug administration</p>	<p>No study drug administration; Subjects who complete or discontinue the parent study (CTX001-111, VX21-CTX001-141 [TDT]; CTX001-121, VX21-CTX001-151 [SCD])</p>	<p>No study drug administration; up to 15 years after exacel infusion in the parent study</p>

Source: Original BLA 125785/0; Module 5.2 Tabular Listing of all Clinical Studies.

## 5.4 Consultations

### 5.4.1 Advisory Committee Meeting

An advisory committee meeting was held on October 31, 2023, mainly to discuss the bioinformatics aspects of CASGEVY along with presentations of the safety

and efficacy of CASGEVY in patients with sickle cell disease. For more information, please refer to the website: <https://www.fda.gov/advisory-committees/advisory-committee-calendar/cellular-tissue-and-gene-therapies-advisory-committee-october-31-2023-meeting-announcement-10312023>.

## 6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

### 6.1 Trial CTX001-111

#### 6.1.1 Objectives

##### Primary Objective:

To evaluate the safety and efficacy of a single dose of autologous CRISPR/Cas9 modified CD34<sup>+</sup> hHSPCs (exagamglogene autotemcel [exa-cel]) in subjects with TDT.

##### Secondary Objectives:

- To quantify percentage of edited alleles in peripheral blood leukocytes and CD34<sup>+</sup> cells of the bone marrow
- To assess the production of fetal hemoglobin (HbF) after CASGEVY infusion
- To assess the effects of infusion of CASGEVY on disease-specific events and clinical status

#### 6.1.2 Design Overview

This was a single-arm, open-label, multi-site, single dose, Phase 1/2/3 study in subjects 12 to 35 years of age (inclusive) who have TDT. Transfusion dependence was defined as a history of at least 100 mL/kg/year or 10 units/year of packed RBC transfusions in the 2 years before the signing the informed consent form (ICF).

For each subject, the study was conducted in 4 stages: Stage 1 included Screening and the pre-mobilization period (approximately 1-3 months), Stage 2 included mobilization, autologous CD34<sup>+</sup> stem cell collection, and CASGEVY manufacture and disposition (approximately (b) (4) ), Stage 3 included myeloablative conditioning and CASGEVY infusion (approximately 1 month), and Stage 4 included post-infusion in-hospital follow-up (until neutrophil engraftment) and post-discharge follow-up (approximately 2 years).

#### 6.1.3 Population

Subjects 12 to 35 years of age (inclusive) with TDT as defined by:

- Documented homozygous  $\beta$ -thalassemia or compound heterozygous  $\beta$ -thalassemia including  $\beta$ -thalassemia/hemoglobin E (HbE).
- A history of at least 100 mL/kg/year or 10 units/year of packed RBC transfusions 2 years before signing the ICF or the last rescreening (if applicable).

#### 6.1.4 Study Treatments or Agents Mandated by the Protocol

CASGEVY is a cellular product consisting of autologous CD34<sup>+</sup> human hematopoietic stem and progenitor cells (hHSPCs) modified by CRISPR/Cas9-mediated gene editing. The target of the CRISPR/Cas9 gene editing is the erythroid lineage-specific enhancer region of the BCL11A gene located on intron 2 between exons 2 and 3 on chromosome 2. The median dose of CASGEVY was 7.5 (range: 3.0 to 19.7) × 10<sup>6</sup> CD34<sup>+</sup> cells/kg by intravenous (IV) infusion.

#### 6.1.6 Sites and Centers

Five study sites in US, three study sites in Germany, two study sites in UK, two study sites in Canada, and one study site in Italy.

#### 6.1.8 Endpoints and Criteria for Study Success

##### Primary Efficacy Endpoint

The primary endpoint was the proportion of subjects who achieved T112, defined as maintaining weighted average Hb ≥ 9 g/dL without RBC transfusions for at least 12 consecutive months any time after CASGEVY infusion. The evaluation of T112 starts 60 days after last RBC transfusion for post-transplant support or TDT disease management. A one-sided P value from a one-sample binomial test (against a 50% response rate) and 2-sided 95% exact Clopper-Pearson CI were planned to be provided.

##### Key Secondary Efficacy Endpoint

The key secondary endpoint was the proportion of subjects who achieved T16, defined as maintaining weighted average Hb ≥ 9 g/dL without RBC transfusions for at least 6 consecutive months any time after CASGEVY infusion. The evaluation of T16 starts 60 days after last RBC transfusion for post-transplant support or TDT disease management. A one-sided p-value from a one-sample binomial test (against a 50% response rate) and 2-sided 95% exact Clopper-Pearson CI were planned to be provided.

##### *Reviewer Comment:*

*There was no clinical evidence submitted to support the choice of a 50% null response rate for the primary or key secondary endpoints, therefore, I do not recommend reporting study results in terms of a p-value testing the T112 or T16 response rate against a null rate of 50%. Instead, reporting should focus on the observed point estimate and confidence interval.*

##### Other Secondary Efficacy Endpoints

- Duration of RBC transfusion free in subjects who have achieved T112.
- Total hemoglobin (Hb) concentration over time.
- HbF concentration (in absolute value and %) over time.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Determination of Sample Size

The planned sample size was 45 subjects dosed, and this sample size provided at least 95% power to rule out a response rate of 50% when the true response rate is 80% for both the primary and key secondary efficacy endpoints with one-sided alpha of 2.5%.

Three IAs were planned to be performed following a group sequential testing procedure in the expanded study to allow for early evaluation of efficacy. The operating characteristics under different scenarios of the true response rate for the primary and key secondary efficacy endpoints are shown in Table 2.

Table 2 Operating Characteristics of Efficacy Boundaries for Primary and Key Efficacy Endpoints

Analysis Stage	Efficacy Boundary	Boundary in Response Rate (95% CI)	Probability of Crossing Efficacy	Boundaries Under Different	True Response Rates (p1) <sup>a</sup>	Alpha spent at each IA
			p1=80%	p1=85%	p1=90%	
IA 1	14/17	82.4% (56.6%, 96.2%)	54.9%	75.6%	91.7%	0.636%
IA 2	18/24	75.0% (53.3%, 90.2%)	81.1%	94.3%	99.3%	0.780%
IA 3	22/30	73.3% (54.1%, 87.7%)	87.1%	97.2%	99.8%	0.275%
Final	31/45	68.9% (53.4%, 81.8%)	97.5%	99.8%	>99.9%	0.417%
Overall Power			98.0%	99.9%	>99.9%	
Overall $\alpha$ Spending						2.109%

a: Marginal probability of crossing the efficacy boundary at a specific interim analysis or final analysis.  
Source: Adapted from Original BLA 125785.0; Module 5.3.5.2, SAP, Table 7-1 and Table 9-1.

**Reviewer Comment:**

*In this submission, IA 1 and IA 2 were not conducted and the applicant stated the alpha planned for IA 1 and IA 2 was recovered at IA3 (current analyses). Therefore, the primary and key secondary efficacy endpoints based on the PES were considered as statistically significant if the corresponding 1-sided p-value was <0.01691(0.00636+0.00780+0.00275=0.01691). This alpha spending is also used for the response rate confidence intervals.*

Analysis Populations

Enrolled Set:

The Enrolled Set includes all enrolled subjects who have signed informed consent and met the eligibility criteria. Listing of the demographics and baseline characteristics will be provided based on the Enrolled Set.

*Safety Analysis Set:*

The Safety Analysis Set is a subset of the Enrolled Set that includes subjects who have started the mobilization regimen.

*Full Analysis Set:*

The Full Analysis Set (FAS) is a subset of the Enrolled Set that includes subjects who have received CASGEVY infusion. The demographics and baseline characteristics will be summarized based on FAS.

In the final analysis, the analysis of the primary efficacy endpoint will be based on the FAS.

*Primary Efficacy Set:*

The Primary Efficacy Set (PES) is a subset of FAS that includes all subjects who have been followed for at least 16 months post CASGEVY infusion and for at least 14 months after completion of the RBC transfusions for post-transplant support or TDT management. In addition, subjects who die or discontinue the study due to CASGEVY-related adverse events and have less than 16 months follow-up post CASGEVY infusion, or continuously receive RBC transfusions for more than 10 months post CASGEVY infusion will also be included in this set.

At the interim analyses, the analysis of the primary efficacy endpoint was to be based on the Primary Efficacy Set.

Primary Efficacy Endpoint Analysis

All transfusions post CASGEVY infusions were to be adjudicated by an endpoint adjudication committee (EAC). All analyses of the primary efficacy endpoint were to be based on RBC transfusions adjudicated for the purpose of post-transplant support or TDT management.

The weighted average Hb is calculated as:  $(\sum \Delta time_i \times (Hb_i + Hb_{i+1})/2) / (\sum \Delta time_i)$ ,  $i=1, \dots, I-1$ ,

where

$\Delta time_i$  = time (in days) between two consecutive available central lab Hb measurements ( $Hb_i$  and  $Hb_{i+1}$ ) post CASGEVY infusion. The day of measurement  $Hb_i$  is included while the day of measurement  $Hb_{i+1}$  is excluded.

$Hb_i$  =  $i^{\text{th}}$  available central lab Hb measurement in the evaluation period.

$Hb_1$  is the first available central lab Hb measurement in the evaluation period;  $Hb_I$  is the last available central lab Hb measurement in the evaluation period. The beginning of the evaluation period is 60 days after last RBC transfusion for post-transplant support or TDT management post CASGEVY infusion.

If a subject dies or discontinues the study before achieving T112 starting 60 days after the last RBC transfusion for post-transplant support or TDT management post CASGEVY infusion, due to reasons other than CASGEVY-related adverse events, the transfusion free status and weighted average Hb starting from 60 days after the last RBC transfusion of the subject were to be carried forward up to 24 months post CASGEVY infusion.

The proportion of subjects achieving T112 was to be provided, with one-sided p-value (against a null hypothesis of 50% response rate) and two-sided 95% exact Clopper-Pearson CI.

Subjects who die or discontinue the study due to CASGEVY-related adverse events before achieving T112, or continuously receive RBC transfusion for post-transplant support or TDT management after 10 months post CASGEVY infusion was to be considered non-responders for T112.

#### Key Secondary Efficacy Endpoint Analysis

The weighted average Hb was to be calculated the same way as in the primary efficacy endpoint. The proportion of subjects who meet the key secondary efficacy endpoint was to be provided, with one-sided p-value (against a null hypothesis of 50% response rate) and two-sided 95% exact Clopper-Pearson CI.

Subjects who die or discontinue the study due to CASGEVY-related adverse events before achieving T16 were to be considered non-responders for T16.

#### Interim Analysis

Three IAs were planned, and the first/second/third IA were to be conducted when the PES consisted of approximately 17/24/30 subjects, respectively. The familywise type I error rate was controlled by an alpha spending approach for tests at interim and final analyses and a sequential testing of the primary and key secondary efficacy endpoints (i.e., the key secondary efficacy endpoint was tested only if the primary efficacy endpoint has crossed an efficacy boundary).

#### Subgroup analyses planned

The following subgroup analyses of the primary efficacy endpoint were planned. Descriptive summary will be considered if a subgroup has a sample size < 5.

- Age at screening (<18, and ≥18 years)
- Genotype
  - β0-like genotype group: including β0/β0, IVS-I-110/IVS-I-110, or β0/IVS-I-110
  - Non-β0-like genotype group: all other genotypes
- Sex
- Race (Asian, White, or other races)

## 6.1.10 Study Population and Disposition

### 6.1.10.1 Populations Enrolled/Analyzed

Table 3 presents the numbers of subjects in different analysis sets at the time of IA.

Table 3 Numbers of subjects in different analysis sets

	Number of Subjects
Enrolled Set	59
Safety Analysis Set	59
FAS	52
PES	35
Never dosed with any study drug	0
Never dosed with CASGEVY	3

Source: Original BLA 125785.0; Module 5.3.5.2, Clinical Study Report, Table 10-1.

#### 6.1.10.1.1 Demographics

For the 52 subjects in the FAS, the median (range) age was 20 (12 to 35) years, with 18 (34.6%) subjects  $\geq 12$  and  $< 18$  years of age. For the 35 subjects in the PES, the median (range) age was 20 (12 to 33) years, with 11 (31.4%) subjects  $\geq 12$  and  $< 18$  years of age. Thirty-one (59.6%) subjects had  $\beta^0/\beta^0$ -like genotypes. Thirty-six (69.2%) subjects had an intact spleen. Baseline median (range) annualized units of TDT-related RBC transfusions per year was 35.0 (11.0 to 71.0) units. The baseline demographics and characteristics for the FAS and PES are presented in Table 4 and Table 5, respectively.

Table 4 Subject Demographics (FAS and PES)

Demographics	FAS (N=52)	PES (N=35)
Sex, n (%)		
Male	27 (51.9)	18 (51.4)
Female	25 (48.1)	17 (48.6)
Age at screening (years)		
n	52	35
Mean (SD)	21.5 (6.7)	21.1 (6.1)
Median	20.0	20.0
Min, max	12, 35	12, 33
Age category at screening, n (%)		
≥12 and <18 years	18 (34.6)	11 (31.4)
≥18 and ≤35 years	34 (65.4)	24 (68.6)
Race, n (%)		
White	18 (34.6)	15 (42.9)
Black or African American	0	0
Asian	22 (42.3)	13 (37.1)
American Indian or Alaska Native	0	0
Native Hawaiian or other Pacific Islander	0	0
Not collected per local regulations	7 (13.5)	4 (11.4)
Other	2 (3.8)	0
Multiracial	3 (5.8)	3 (8.6)
Ethnicity, n (%)		
Hispanic or Latino	1 (1.9)	1 (2.9)
Not Hispanic or Latino	46 (88.5)	31 (88.6)
Not collected per local regulations	5 (9.6)	3 (8.6)

<sup>a</sup> An RBC transfusion episode was defined as all transfusions within 5 days, starting from the first transfusion in the episode.

Source: Original BLA 125785.0; Module 5.3.5.2, Clinical Study Report, Table 10-2.

Table 5 Baseline Characteristics (FAS and PES)

Characteristics	FAS (N=52)	PES (N=35)
Genotype, n (%)		
$\beta^0/\beta^0$ -like	31 (59.6)	20 (57.1)
$\beta^0/\beta^0$	19 (36.5)	10 (28.6)
$\beta^0$ /IVS-I-110	9 (17.3)	7 (20.0)
IVS-I-110/ IVS-I-110	3 (5.8)	3 (8.6)
Non- $\beta^0/\beta^0$ -like	21 (40.4)	15 (42.9)
$\beta^+/\beta^+$	4 (7.7)	3 (8.6)
$\beta^+/\beta^0$	12 (23.1)	8 (22.9)
$\beta^E/\beta^+$	0	0
$\beta^E/\beta^0$	5 (9.6)	4 (11.4)
$\beta^E/\beta^E$	0	0
Other	0	0
Spleen intact, n (%)	36 (69.2)	26 (74.3)
Annualized volume of RBC transfusions (mL/kg)		
n	52	35
Mean (SD)	196.8 (63.0)	202.0 (57.1)
Median	201.0	205.2
Min, max	48.3, 330.9	115.2, 330.9
Annualized units of RBC transfusions		
n	52	35
Mean (SD)	36.0 (11.7)	37.1 (11.0)
Median	35.0	35.0
Min, max	11.0, 71.0	20.5, 71.0
Annualized number of RBC transfusion episodes <sup>a</sup>		
n	52	35
Mean (SD)	16.5 (5.3)	17.2 (5.2)
Median	16.5	16.5
Min, max	5.0, 34.5	10.5, 34.5
Total Hb concentration (g/dL)		
n	51	35
Mean (SD)	10.4 (2.0)	10.4 (1.9)
Median	10.1	10.1
Min, max	6.9, 14.2	6.9, 14.1
HbF concentration (g/dL)		
n	51	35
Mean (SD)	0.6 (1.0)	0.5 (0.6)
Median	0.3	0.3
Min, max	0.0, 5.8	0.0, 2.2
HbF concentration (%)		
n	52	35

Mean (SD)	6.6 (11.3)	5.5 (6.2)
Median	3.4	3.4
Min, max	0.0, 74.0	0.0, 21.3
Weight (kg)		
n	52	35
Mean (SD)	54.8 (14.2)	53.3 (11.5)
Median	52.0	52.0
Min, max	30.0, 96.0	34.0, 78.0

a An RBC transfusion episode was defined as all transfusions within 5 days, starting from the first transfusion in the episode.

Source: Original BLA 125785.0; Module 5.3.5.2, Clinical Study Report, Table 10-3.

### 6.1.10.1.3 Subject Disposition

A total of 59 subjects were enrolled at the time of the IA data cutoff date (January 16, 2023). All had started mobilization, 53 subjects had started myeloablative busulfan conditioning, and 52 subjects received CASGEVY infusion. No subjects discontinued from the study after starting busulfan conditioning or after CASGEVY infusion. Three subjects discontinued from the study after the start of mobilization but before conditioning: 1 subject discontinued due to withdrawing consent for undisclosed reasons, 1 subject discontinued due to wanting to undergo a second apheresis procedure and 1 subject discontinued due to concerns with continued study participation.

### 6.1.11 Efficacy Analyses

#### 6.1.11.1 Analyses of Primary Endpoint(s)

Table 6 presents the results of the primary efficacy analyses. Thirty-two of 35 (91.4%) subjects in the PES achieved TI12.

**Table 6 Proportion of Subjects Who Achieved TI12 (PES)**

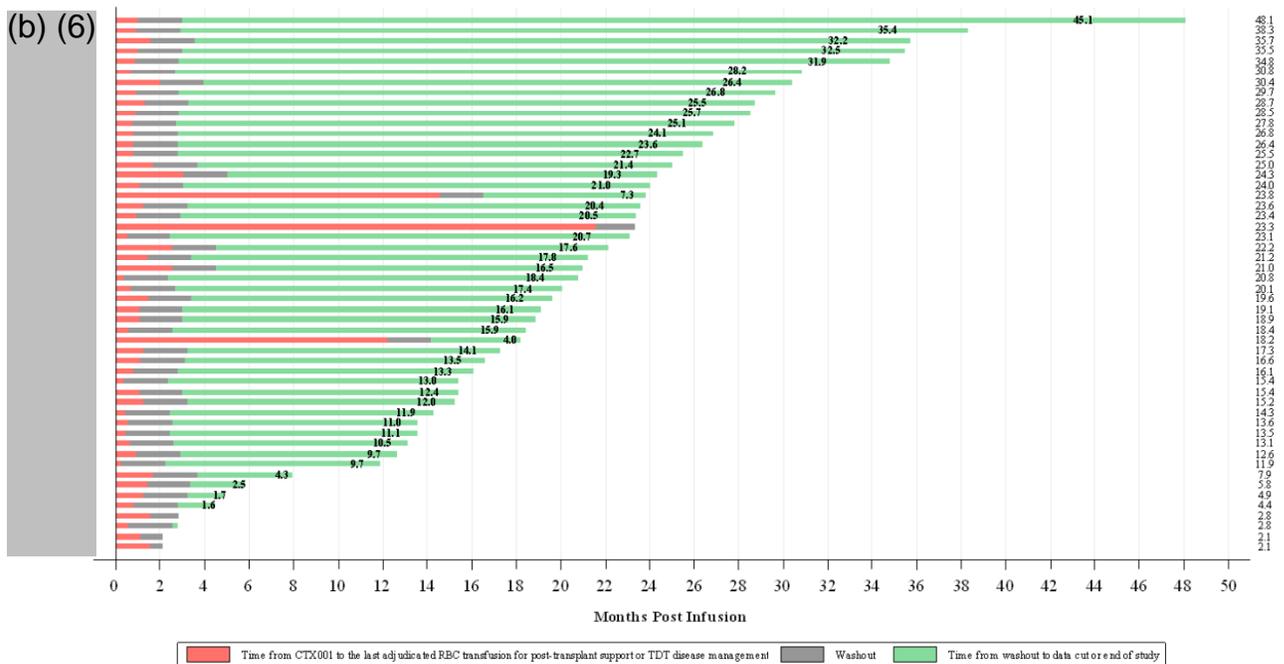
<b>Category</b>	<b>Total (N = 35)</b>
Subjects who achieved TI12	
n (%)	32 (91.4)
1-sided 98.3% CI <sup>a</sup>	(75.7, 100)

a The CI was calculated using the exact Clopper-Pearson method.

Source: Original BLA 125785.66; Module 1.11.3, Clinical Information Amendment, Table 1.

Figure 1 displays the transfusion free duration data (which starts 60 days after the last RBC transfusion, also including the follow-up information from Study CTX001-131) for the FAS by subjects.

Figure 1 Transfusion Free Duration (FAS, CTX001-111 and CTX001-131)



Source: Original BLA 125785.0; Module 5.3.5.2, CTX001-131 Interim CSR, Figure 11-1.

### 6.1.11.2 Analyses of Secondary Endpoints

Key Secondary Endpoint:

Thirty-two of 35 (91.4%) subjects in the PES achieved TI6. Table 7 presents the results of the key secondary efficacy analysis.

Table 7 Proportion of Subjects Who Achieved TI6 (PES)

Category	Total (N = 35)
Subjects who achieved TI6	
n (%)	32 (91.4)
1-sided 98.3% CI <sup>a</sup>	(75.7, 100)

<sup>a</sup> The CI was calculated using the exact Clopper-Pearson method.

Source: Original BLA 125785.66; Module 1.11.3, Clinical Information Amendment, Table 1.

#### Reviewer Comments:

- *The efficacy endpoint TI6 was intended solely as a surrogate endpoint to support the accelerated approval (AA) pathway. Since this endpoint itself is less clinically meaningful than TI12 and AA is not being considered for this application, the TI6 result presented here is for completeness only. The appropriateness of surrogacy of TI6 for TI12 is not evaluated.*

#### Other Secondary Endpoints:

Table 8 presents the results of three other secondary endpoints mentioned in Section 6.1.8. All subjects in the PES who achieved TI12 remained transfusion free for the duration of follow-up (including the data from Study CTX001-131) as of data cutoff at the IA; the median transfusion free duration while maintaining

weighted average Hb  $\geq 9$  g/dL was 20.8 months. The analyses of Hb and HbF show increases in mean total Hb, HbF levels, HbF % for subjects in the PES. Figure 3 presents the individual total Hb by subjects in the PES. Figure 2 displays the Total Hb and HbF concentrations over time. The increase in mean total Hb and HbF levels in the PES, which occurred early in Study CTX001-111 and were maintained over time throughout the study.

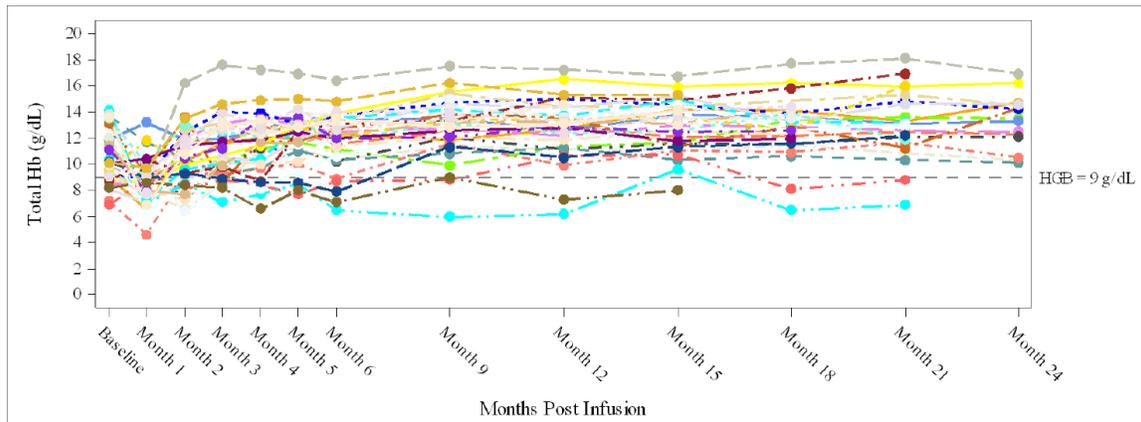
Table 8 Summary of Efficacy Secondary Endpoints

Endpoints	CASGEVY IA3 (PES, N=35)
<b>Duration of transfusion-independent period in patients who have achieved TI12 (months)<sup>a</sup></b>	
n	32
Mean (SD)	19.2 (2.8)
Median (min, max)	20.8 (13.3, 45.1)
<b>Total Hb (g/dL)<sup>b</sup></b>	
at Month 6	
n	35
Mean (SD)	11.9 (2.1)
at Month 12	
n	35
Mean (SD)	12.7 (2.2)
at Month 18	
n	30
Mean (SD)	12.9 (2.1)
at Month 24	
n	15
Mean (SD)	13.3 (2.0)
<b>HbF (g/dL)<sup>b</sup></b>	
at Month 6	
n	35
Mean (SD)	10.5 (3.0)
at Month 12	
n	34
Mean (SD)	11.4 (2.7)
at Month 18	
n	28
Mean (SD)	11.5 (2.4)
at Month 24	
n	15
Mean (SD)	12.0 (2.5)
<b>HbF (%)<sup>b</sup></b>	
at Month 6	
n	35
Mean (SD)	86.8 (19.4)
at Month 12	
n	34
Mean (SD)	89.0 (13.0)
at Month 18	
n	27
Mean (SD)	90.3 (10.8)
at Month 24	
n	15
Mean (SD)	89.1 (10.5)

<sup>a</sup> Source: Original BLA 125785.0; Module 5.3.5.2, CTX001-131 Interim CSR, Table 11-3.

<sup>b</sup> Source: Original BLA 125785.0; Module 5.3.5.2, CTX001-111 Interim CSR, Table 11-11.

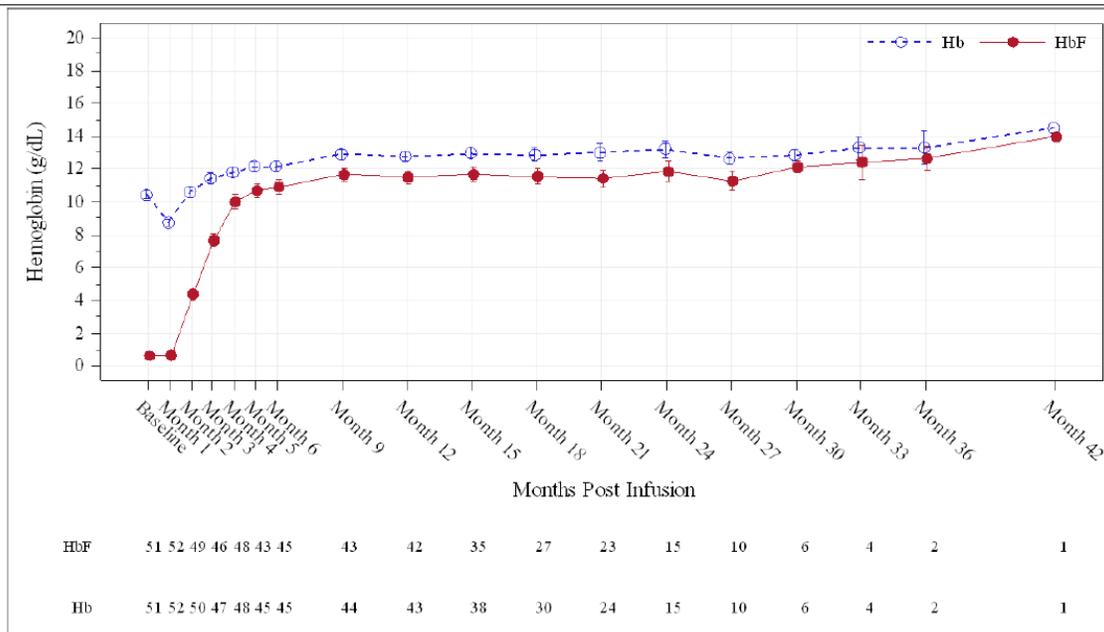
Figure 2 Individual Total Hb (g/dL) Over Time (PES, CTX001-111)



Source: Original BLA 125785.0; Module 5.3.5.2, CTX001-111 Interim CSR, Figure 14.2.3.1.

Another analysis in the FAS for the Total Hb and HbF concentrations over time after CASGEVY infusion were conducted. Figure 3 displays the results, and the pattern is consistent with what was observed in the PES of CTX001-111.

Figure 3 Summary of Total Hb (g/dL) and HbF (g/dL) Over Time (FAS, CTX001-111 and CTX001-131)



Source: Original BLA 125785.0; Module 5.3.5.2, CTX001-131 Interim CSR, Figure 11-4.

### 6.1.11.3 Subpopulation Analyses

Table 9 presents the results of the subgroup analyses for the primary endpoint TI12. For descriptive purpose, 95% CIs are presented.

Table 9 Subgroup Analysis: Proportion of Subjects Who Achieved T112 by Age, Genotype, Sex, and Race (PES)

Subgroup	Total (N = 35)
Age	
Subjects ≥12 and <18 years	11
Subjects ≥12 and <18 years achieved T112	
n (%)	10 (90.9)
2-sided 95% CI	(58.7, 99.8)
Subjects ≥18 and ≤35 years	24
Subjects ≥18 and ≤35 years achieved T112	
n (%)	22 (91.7)
2-sided 95% CI	(73.0, 99.0)
Genotype <sup>a</sup>	
Subjects with β <sup>0</sup> /β <sup>0</sup> -like	20
Subjects with β <sup>0</sup> /β <sup>0</sup> -like achieved T112	
n (%)	17 (85.0)
2-sided 95% CI	(62.1, 96.8)
Subjects with non-β <sup>0</sup> /β <sup>0</sup> -like	15
Subjects with non-β <sup>0</sup> /β <sup>0</sup> -like achieved T112	
n (%)	15 (100.0)
2-sided 95% CI	(78.2, 100.0)
Sex	
Male	18
Male achieved T112	
n (%)	16 (88.9)
2-sided 95% CI	(65.3, 98.6)
Female	17
Female achieved T112	
n (%)	16 (94.1)
2-sided 95% CI	(71.3, 99.9)
Race	
Asian	13
Asian achieved T112	
n (%)	11 (84.6)
2-sided 95% CI	(54.6, 98.1)
White	15
White achieved T112	
n (%)	14 (93.3)
2-sided 95% CI	(68.1, 99.8)
Other Race	7
Other Race achieved T112	
n (%)	7 (100%)
2-sided 95% CI	(59.0, 100.0)

<sup>a</sup> β<sup>0</sup>/β<sup>0</sup>-like genotypes included β<sup>0</sup>/β<sup>0</sup>, IVS-I-110/β<sup>0</sup>, and IVS-I-110/IVS-I-110. All other genotypes were considered non-β<sup>0</sup>/β<sup>0</sup>-like.

Source: Original BLA 125785.0; Module 5.3.5.2, Clinical Study Report, Table 11-4.

#### 6.1.11.4 Dropouts and/or Discontinuations

No subjects dropped out or discontinued after CASGEVY infusion prior to this IA analysis.

## 6.1.12 Safety Analyses

### 6.1.12.3 Deaths

Up to the time of this IA, no deaths occurred in the study.

### 6.1.12.4 Nonfatal Serious Adverse Events (SAEs)

Among the subjects who completed myeloablative busulfan conditioning and received CASGEVY, 17 (32.7%) subjects had SAEs. Veno-occlusive liver disease was the most common SAE (5 [9.6%] subjects); these events were considered by the investigator(s) related to busulfan and not related to CASGEVY. Nine (17.3%) subjects had SAEs considered related or possibly related to busulfan. Two (3.8%) subjects had SAEs considered related or possibly related to CASGEVY (some of which were also related to busulfan):

- One subject had SAEs of headache, hemophagocytic lymphohistiocytosis (HLH), and acute respiratory distress syndrome (ARDS) that were considered related or possibly related to CASGEVY only and an SAE of idiopathic pneumonia syndrome that was considered related to busulfan and possibly related to CASGEVY (all SAEs occurred in the context of HLH).
- One subject had SAEs of delayed engraftment (verbatim: delayed neutrophil engraftment) and thrombocytopenia that were considered related or possibly related to both busulfan and CASGEVY (no serious infections or bleeding events were reported; the subject engrafted neutrophils on Study Day 56 without the use of backup cells and achieved platelet engraftment).

### 6.1.12.5 Adverse Events of Special Interest (AESI)

No AE of special interest was found in the study.

#### *Reviewer Comment:*

*In the 120 Day safety update report, no additional safety concerns were identified during the reporting period from 17 January 2023 through 14 June 2023.*

## 10. CONCLUSIONS

### 10.1 Statistical Issues and Collective Evidence

The submission includes the primary evidence based on the results from a planned IA of the pivotal study CTX001-111: a single-arm, open-label, multi-site, single dose, Phase 1/2/3 study in subjects 12 to 35 years of age (inclusive) who have TDT. The primary efficacy endpoint is the proportion of subjects achieving TI12.

The submission included 59 enrolled subjects from CTX001-111, 52 of whom received CASGEVY infusion. Thirty-five of the infused subjects had been

followed for at least 16 months post CASGEVY infusion and for at least 14 months after completion of the RBC transfusions for post-transplant support or TDT management. This is the population that was used for the primary efficacy evidence for the application. For the primary endpoint, 32 of the 35 evaluable subjects achieved T112 (98.3% CI: 75.7%, 100%).

All subjects who received CASGEVY infusion who completed or discontinued from CTX001-111 study were asked to participate in Study CTX001-131. CTX001-131 was an ongoing, multi-site, open-label, rollover study designed to evaluate the long-term safety and efficacy of CASGEVY in subjects who received CASGEVY in CTX001-111 study for a total follow-up of 15 years after CASGEVY infusion. The cut-off date for CTX001-131 was 16 January 2023 as well. Subjects who rolled over to Study 131, all of whom had achieved T112 in Study CTX001-111, maintained transfusion independence in Study CTX001-131. The results for the secondary endpoints also support the clinical effectiveness of CASGEVY.

For safety, no death was reported during the study as of the cut-off date of the IA (including the 120-day safety update). Among the subjects who completed myeloablative busulfan conditioning and received CASGEVY, 17 (32.7%) subjects had SAEs. Veno-occlusive liver disease was the most common SAE (5 [9.6%] subjects); these events were considered by the investigator(s) related to busulfan and not related to CASGEVY. Nine (17.3%) subjects had SAEs considered related or possibly related to busulfan. Two (3.8%) subjects had SAEs considered related or possibly related to CASGEVY (some of which were also related to busulfan).

## **10.2 Conclusions and Recommendations**

In summary, the submitted data have provided sufficient evidence of clinical effectiveness of CASGEVY. Although the sample size (35) for the safety evaluation was lower than the 50 evaluable subjects recommended by FDA during pre-BLA communications, the overall safety profile has been favorable relative to the potential benefit of the treatment. Therefore, I recommend the approval of CASGEVY for the proposed indication of the treatment of TDT in patients 12 years and older.