Summary Basis for Regulatory Action

Date:	January 16, 2024
From:	Anna Kwilas, PhD, Review Committee Chair, Center for Biologics Evaluation and Research (CBER), Office of Therapeutic Products (OTP), Office of Gene Therapy (OGT)
BLA STN:	BLA 125785
Parent BLA STN Note: this is only applicable if the STN will be merged with a Parent STN	**BLA 125787**
Applicant:	Vertex Pharmaceuticals, Inc
Submission Receipt Date:	March 31, 2023
PDUFA Action Due Date:	March 30, 2024
Proper Name:	exagamglogene autotemcel
Proprietary Name:	CASGEVY
Indication:	Treatment of patients aged 12 years and older with transfusion-dependent ß-thalassemia (TDT)

***** PDUFA=Prescription Drug User Fee Act

Recommended Action: The Review Committee recommends approval of this product.

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Director, Product Office

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC • CMC Product (Product Office and OCBQ/DBSQC) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC)	Anna Kwilas, PhD, CBER/OTP/OGT Jessica Chery, PhD, CBER/OTP/OGT Elena Gubina, PhD, CBER/OTP/OGT Eric Levenson, PhD, CBER/OTP/OGT Komudi Singh, PhD, CBER/OTP/OCTHT Brian Stultz, MS, CBER/OTP/OGT Zhaohui Ye, PhD, CBER/OTP/OGT Greg Price, PhD, CBER/OCBQ/DMPQ Carl Perez, CBER/OCBQ/DMPQ Hyesuk Kong, PhD, CBER/OCBQ/DBSQC Most Nahid Parvin, PhD, CBER/OCBQ/DBSQC Tao Pan, PhD, CBER/OCBQ/DBSQC
Pre-License Inspection	Gregory Price, PhD, CBER/OCBQ/DMPQ Carl Perez, CBER/OCBQ/DMPQ Hoda Abadeer, MS, CBER/OCBQ/DMPQ Prajakta Varadkar, PhD, CBER/OCBQ/DMPQ Wei Wang, PhD, CBER/OCBQ/DMPQ Jessica Chery, PhD, CBER/OTP/OGT Elena Gubina, PhD, CBER/OTP/OGT Zhaohui Ye, PhD, CBER/OTP/OGT
Clinical • Clinical (Product Office) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • BIMO	Kavita Natrajan, MD, CBER/OTP/OCE Muhammad (Umer) Choudhry, MD, CBER/OTP/OCE Srinivas Ayyala, MD, CBER/OBPV/DPV Triet M. Tran, PharmD, BCSCP, CBER/OCBQ/DIS
Statistical • Clinical data (OBPV/DB) • Non-clinical data	Shuya (Joshua) Lu, PhD, CBER/OBPV/DB Tianjiao Dai, PhD, CBER/OBPV/DB
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office) • Developmental toxicology (Product Office) • Animal pharmacology	Theresa Chen, PhD, CBER/OTP/OPT
Clinical Pharmacology	Xiaofei Wang, PhD, CBER/OTP/OCE
Labeling • Promotional (OCBQ/APLB) • Container/carton	Benjamin Cyge, PhD, CBER/OCBQ/DCM/APLB Danielle Bauman, MPH, CBER/OTP/ORMRR Anna Kwilas, PhD, CBER/OTP/OGT
Other Review(s) not captured above categories, for example: • Bioinformatics • Consults • Devices • Software • Human Factors • FONSI	Tianjiao Dai, PhD, CBER/OBPV/DB Komudi Singh, PhD, CBER/OTP/OCTHT Elin Cho, MS, CBER/OBPV/DB
Advisory Committee Summary	N/A

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1. Introduction

Vertex Pharmaceuticals Inc. (Applicant) submitted Biologics License Application (BLA) 125785 for licensure of exagamglogene autotemcel (exa-cel, hereafter referred to as CASGEVY, the proprietary name) on March 31, 2023, for treatment of patients aged 12 years and older with transfusion-dependent ß-thalassemia (TDT). After the submission of STN 125785, CASGEVY also came under review under a separate BLA (STN 125787) for a different indication, under which it was subsequently approved on December 8, 2023, for the treatment of patients aged 12 years and older with sickle cell disease (SCD) with recurrent vaso-occlusive crises (VOCs). Upon approval, BLA STN 125785 will be administratively closed, and future regulatory activity for both indications will be conducted under BLA STN 125787.

CASGEVY is an autologous, hematopoietic, stem cell-based gene therapy consisting of an autologous, CD34+ cell-enriched population containing the patient's own hematopoietic stem and progenitor cells (HSPCs), which are genome edited ex vivo using clustered regularly interspaced short palindromic repeats-associated protein 9 (CRISPR/Cas9) and the SPY101 single guide RNA to disrupt the GATA1 transcription factor binding domain of the B-cell lymphoma/leukemia 11A (BCL11A) gene erythroid enhancer. CASGEVY is supplied frozen in 20 mL vials as a suspension for intravenous (IV) infusion. Each vial contains between 4 and 13×10^6 CD34+ cells/mL, frozen in 1.5 to 20 mL of cryopreservation solution. The minimum dose is ≥ 3.0×10^6 CD34+ cells/kg of patient weight.

Each patient undergoes a period of red blood cell transfusions during the premobilization and for at least 60 days prior to conditioning to maintain Hb ≥11 g/dL to suppress ineffective erythropoiesis. The patients then undergo hematopoietic stem cell mobilization with plerixafor and G-CSF, followed by apheresis to harvest the cells. The collected cells are shipped to one of two contract manufacturing sites, where CD34+ cells are selected and then edited with the Cas9/*SPY101* ribonucleoprotein (RNP) complex to manufacture CASGEVY. After full myeloablative conditioning and CASGEVY infusion, edited HSPCs engraft in the bone marrow and differentiate to reconstitute the hematopoietic system, including red blood cells, which manifest augmented expression of fetal hemoglobin (HbF) which increases total Hb and eliminates the need for transfusion, which is therapeutic for TDT.

This document summarizes the basis for approval of CASGEVY. Thirty-five of 52 CASGEVY-treated subjects in one single-arm, Phase 1/2/3 study, Study 111, and the rollover long-term follow-up study, Study 131, provide the primary evidence of effectiveness and all 52 subjects serve as the basis of the safety review. The recommendation for approval is based on demonstration of efficacy in the primary efficacy outcome (TI12 response), maintaining weighted average Hb ≥9 g/dL without red blood cell (RBC) transfusions for at least 12 consecutive months during the 24-month follow-up period in Study 111 after CASGEVY infusion. Efficacy evaluation started after a 60-day washout period following the last red blood cell transfusion for post-transplant support or TDT disease management. The major risk of treatment with CASGEVY is the potential for off-target, unintended genome editing by CRISPR/Cas9.

The review team recommends approval of this BLA with safety postmarketing requirement (PMR) studies to assess the off-target editing risks associated with the product and the long-term safety of CASGEVY, including risk of malignancy.

2. Background

Beta (ß)-thalassemia is an inherited autosomal recessive disorder caused by mutations in the ß-globin gene leading to reduced or absent expression of ß-globin in erythropoietic cells. These genetic mutations reduce or eliminate the expression of β-globin, which results in an alpha to non-alpha-globin chain imbalance and decrease in adult hemoglobin (HbA) tetramers in red blood cells (RBCs). Unpaired α-globin chains precipitate inside RBCs, leading to destruction of erythroid precursors and ineffective erythropoiesis and peripheral hemolysis.

Transfusion-dependent ß-thalassemia (TDT) is the most severe form of β-thalassemia associated with life-long anemia requiring frequent red blood cell (RBC) transfusions, and is complicated by organopathy related to iron overload, reduced quality of life, and shortened survival. Treatment options for TDT include regular red blood cell (RBC) transfusions with iron chelation, allogenic hematopoietic stem cell transplant (HSCT), Luspatercept- an activin A receptor IIA (ActRIIA) ligand approved for adults with TDT in 2019, and betibeglogene autotemcel- a lentiviral vector (LVV) based cellular gene therapy which was approved in pediatric and adult subjects with TDT in 2022. Drawbacks of currently available therapy include need for continued therapy with transfusion and Luspatercept, thromboembolism, hypertension, EM hematopoiesis, and teratogenicity with Luspatercept along with modest efficacy, lack of suitable donors and transplant-related morbidity and mortality with allogenic HSCT, and risk of insertional oncogenesis with betibeglogene autotemcel. Thus, there still continues to be a significant unmet need for treatment of TDT.

Product Description

CASGEVY is a biological product containing genetically modified autologous HSPCs that are edited with CRISPR/Cas9/*SPY101*, leading to disruption of *BCL11A* expression in erythroid cells, thus alleviating the *BCL11A*-mediated block of HbF expression. Increased HbF expression is designed to correct the lack of beta-globin expression and coincident HbA in erythroid cells of patients with TDT. Reactivation of HbF increases the total Hb levels in TDT patients and has the potential to reduce or eliminate the need for RBC transfusions by decreasing the severity of the anemia.

The regulatory history of CASGEVY is outlined in Table 1.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. IND submission	April 27, 2018
2. Fast Track designation granted	April 8, 2019
3. Orphan Drug designation granted	April 27, 2020
4. Regenerative Medicine Advanced Therapy designation granted	May 05, 2020
5. Pre-BLA meeting	Aug 09, 2022
6. Rare Pediatric Disease designation granted	September 27, 2020
7. BLA 125785/0 submission	March 31, 2023
8. BLA filed	May 30, 2023
9. Mid-Cycle communication	September 28, 2023
10. Late-Cycle meeting	December 18, 2023
11. Action Due Date	March 30, 2024

3. Chemistry Manufacturing and Controls (CMC)

This BLA includes an adequate description of the manufacturing process and characterization of CASGEVY. The chemistry, manufacturing, and controls review team concludes that the manufacturing process, along with associated test methods and control measures, is capable of yielding a product with consistent quality characteristics.

a. Product Quality

Manufacturing Summary

To manufacture CASGEVY, autologous HSPCs obtained by apheresis are collected from each patient. The apheresis material is shipped to (b) (4) for drug substance and drug product (DP) manufacturing. CD34+ cells are selected using the CliniMACS Prodigy System. Briefly, the apheresis material is enriched for cells expressing CD34 by labeling CD34+ cells with paramagnetic microbeads conjugated to a monoclonal antibody directed against CD34 using an automated cell processor. The labeled CD34+ cells are then selected in the presence of a magnetic field using an automated cell separation system. The enriched CD34+ cells are then cultured in the presence of (b) (4) . The expanded, enriched CD34+ cells are then electroporated with CRISPR/Cas9/*SPY101* RNP complexes. After electroporation, the cells (b) (4) To produce the CASGEVY DP, the drug substance is formulated in (b) (4) cryopreservation solution containing 5% dimethyl sulfoxide at a target concentration of (b) (4) . The formulated DP is passed through an (b) (4) before being filled into one to nine 20 mL (b) (4) vials, depending on the number of cells produced. Filled vials are visually inspected then cryopreserved using a (b) (4) and stored at ≤-135°C in vapor phase liquid nitrogen until lot release testing is complete. Once the minimum dose has been met, CASGEVY is shipped in a vapor-phase, liquid nitrogen dry shipper to the administration site for administration back to the same patient.

The Cas9 used in CASGEVY manufacturing was derived from *Streptococcus pyogenes*. The (b) (4) Cas9 is manufactured (b) (4)

The *SPY101* single guide RNA used in CASGEVY manufacturing is a 100 base pair synthetic oligonucleotide. (b) (4) *SPY101* is manufactured (b) (4)

Manufacturing Control Strategy

The CASGEVY manufacturing control strategy consists of (1) raw material, component, and reagent qualification programs; (2) in-process monitoring; (3) in-process control testing; (4) lot release and stability testing; (5) manufacturing process validation and continuous process verification; and (6) traceability through chain of identity and chain of custody (COI/COC). The raw material, component, and reagent qualification program consists of source material risk assessment, vendor qualification, confirmation of the certificate of analysis, and material testing. Raw materials derived from animals and humans are controlled to ensure the absence of microbial contaminants and adventitious agents. The manufacturing process has been adequately validated using a combination of healthy donor- and patient-derived starting material. Critical process parameters are established for unit operations based on process characterization and risk assessment studies. In-process monitoring and controls are implemented throughout the process to support process consistency. The manufacturing process validation demonstrated removal of process-related impurities, including Cas9 and *SPY101*. The Cas9 and *SPY101* manufacturing processes were also validated. Additional validation studies, including aseptic process simulation and shipping validation studies, were also performed. Lot release test methods are suitably validated or verified. CASGEVY specifications are adequate to ensure product quality and consistency with DP used in the clinical study. Manufacturing and testing comply with Current Good Manufacturing Practice (GMP) requirements. COI/COC are established at the time of apheresis collection and maintained throughout the manufacturing process to administration to ensure that the patient receives the correct autologous lot.

Comparability Assessments

During the BLA review, comparability of products that were manufactured at different manufacturing facilities was assessed to enable pooling of clinical data and allow manufacture of commercial product at multiple facilities. Two manufacturing facilities were utilized to manufacture CASGEVY for the clinical studies: (b) (4) (clinical and commercial site) and (b) (4) (clinical and reference site). A third manufacturing facility, (b) (4), was added as the (b) (4) commercial manufacturing site. The acceptance criteria for the initial comparability assessment were not adequately justified. During the review period, the Applicant provided a supplemental comparability analysis with consideration of FDA comments. The supplemental comparability analysis demonstrated equivalence between DPs manufactured at (b) (4) and (b) (4) for the majority of the CASGEVY critical quality attributes assessed, except for Viability (%) and (b) (4) . However, FDA determined that the observed differences were not biologically or clinically significant. The supplemental comparability analysis also demonstrated equivalence between DPs manufactured at (b) (4) and (b) (4) with DPs manufactured at (b) (4) for all the CASGEVY critical quality attributes assessed. Thus, the DPs manufactured at (b) (4) are considered comparable.

Manufacturing Risks, Potential Safety Concerns, and Management

Product Mix-Up

CASGEVY is an autologous product manufactured in a multiproduct manufacturing facility; as such, product mix-ups, either of autologous lots or with other stem cell products manufactured at the same facility, would result in potential risks. The COI/COC ensures that the patient receives their autologous lot. COI/COC is established at the point of apheresis collection, checkpoints are indicated throughout the manufacturing process, and patient identifiers are confirmed prior to administration. The COI/COC is maintained through integrated computer-based programs with human-readable identifiers present on all labels as well. Additionally, only a single product lot is manufactured in a production suite at any given time. Prior to electroporation, the Cas9 and *SPY101* labels are confirmed to ensure the correct materials are used. Lot release testing also confirms product identity and activity.

Off-Target Editing

The risk of off-target editing in CASGEVY was evaluated in nonclinical studies. These studies are described in Section 4 of this document.

CMC PMCs

The following issues were identified but could not be resolved during the review cycle. These issues will be resolved through postmarketing commitments by December 31, 2024.

- There were deficiencies in the CASGEVY shipping validation studies: 1) one of the Liquid Nitrogen shippers used for shipping CASGEVY DP to clinical sites, the (b) (4) shipper, was not evaluated in the shipping simulation study; 2) the study did not evaluate potency-related quality attributes; and 3) pre-transportation DP testing data were not available for a complete evaluation of stability during shipping.

- The (b) (4) manufacturing process includes in-process hold times with normal operating ranges and proven acceptable ranges. The in-process hold time proven acceptable ranges were not adequately assessed for the effect on final vialed (b) (4) quality.

b. Testing Specifications

The final CASGEVY lot release specifications are shown in Table 2.

Table 1: Final Commercial CASGEVY Release Specifications

Attribute	Test	Method	Acceptance Criteria
General	Appearance	Visual assessment	Translucent cell suspension, essentially free of visible foreign particles
Identity	CD34 expression	Flow Cytometry	Positive
-	On-Target Editing Frequency	TIDE	Positive
Purity	CD34 Purity	Flow Cytometry	(b) (4)
Potency	On-Target Editing Frequency	TIDE	(b) (4)
-	(b) (4)	(b) (4)	(b) (4)
-	(b) (4)	(b) (4)	(b) (4)
Quantity and Content	Viable Cell Count	(b) (4)	(b) (4)
-	Cell Viability	(b) (4)	(b) (4)
Safety	Sterility	(b) (4)	Drug Product: No growth (b) (4)
-	Mycoplasma	(b) (4)	Negative
-	Endotoxin	(b) (4)	(b) (4)

Abbreviations: (b) (4); NLT, not less than; NMT, not more than; (b) (4); TIDE, Tracking of Indels by Decomposition; (b) (4).

CASGEVY lot release analytical methods, and their validations and/or verifications, were found to be adequate for their intended use.

Impurity Profile

The active ingredient in CASGEVY is a viable CD34+ cell enriched population, containing HSPCs, genome edited at the *GATA1* binding site of the *BLC11A* gene by CRISPR/Cas9/*SPY101*. Impurities in CASGEVY can be divided into product-related impurities (nonviable cells and viable non-CD34+ cells derived from the apheresis material) and process-related impurities (residuals derived from raw materials and manufacturing components, Cas9 and *SPY101*, not intended to be in the final product). Impurities were evaluated in CASGEVY process characterization studies. The levels of all evaluated impurities in CASGEVY were acceptable, and the calculated possible impurity per dose was below the maximum permissible single exposure level outlined in literature, as applicable.

Stability

Long-term stability studies have been completed and support a CASGEVY shelf life of 18 months when stored at ≤-135°C in vapor phase of liquid nitrogen. The stability studies utilized CASGEVY manufactured at-scale from normal healthy donor starting material. Accelerated and stress studies were also performed. In-use stability testing supported the proposed post-thaw expiry of (b) (4) minutes.

A shelf life of (b) (4) was supported for Cas9 when stored at (b) (4), and a shelf life of (b) (4) was supported for *SPY101* when stored at (b) (4).

c. CBER Lot Release

CBER Lot Release, including the submission of product samples to CBER, is not required. The basis for this decision is that CASGEVY is an autologous product; as such, each lot will treat a single patient. Failure of a single lot will have minimal potential impact on public health.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The facilities involved in the manufacture of CASGEVY are listed in the table below. The activities performed and inspectional histories are noted in Table 3 below.

Table 2. Facilities Involved in the Manufacture and Testing of CASGEVY

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Justification/ Results
(b) (4) *DS and DP manufacturing, labeling, release and stability testing, primary packaging, and storage*	(b) (4)	(b) (4)	Pre-License Inspection	CBER/DMPQ (b) (4) VAI
(b) (4) *DS and DP manufacturing, labeling, release and stability testing, primary packaging, and storage*	(b) (4)	(b) (4)	Pre-License Inspection	CBER/DMPQ (b) (4) VAI

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Justification/ Results
(b) (4) (b) (4) *labeling, packaging, release, and stability testing*	(b) (4)	(b) (4)	Pre-License Inspection	CBER/DMPQ (b) (4) VAI
(b) (4) (b) (4) *labeling, and packaging*	(b) (4)	(b) (4)	Pre-License Inspection	CBER/DMPQ (b) (4) NAI
(b) (4) (b) (4) *labeling, packaging, release, and stability testing*	(b) (4)	(b) (4)	704(a)(4) Records Request in lieu of Inspection	CBER/DMPQ (b) (4) 704(a)(4) Records Request Acceptable MRA Inspection (b) (4) Assessed by ORAHQ: VAI
(b) (4) *DP release testing*	(b) (4)	(b) (4)	Waived	ORA/OPQO (b) (4) NAI
(b) (4) *DP release testing*	(b) (4)	(b) (4)	Waived	(b) (3), (b) (4) Inspection (b) (3), (b) (4) Assessed by ORA/OPQO: VAI
(b) (4) *DP release testing*	(b) (4)	(b) (4)	Waived	ORA/OPQO (b) (4) NAI
(b) (4)	(b) (4)	(b) (4)	Waived	(b) (4) GMP Inspection (b) (4)

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Justification/ Results
(b) (4) *DP release testing*				
(b) (4) *DP release testing*	(b) (4)	(b) (4)	Waived	(b) (4) GMP Inspection (b) (4) Assessed by ORA/OPQO: VAI
(b) (4) *DP release testing*	(b) (4)	(b) (4)	Waived	(b) (4) GMP Inspection (b) (4)

Abbreviations: (b) (4); CBER, Center for Biologics Evaluation and Research; DMPQ, Division of Manufacturing and Product Quality; DP, drug product; DS, drug substance; DUNS, Data Universal Numbering System; (b) (4); FEI, FDA Establishment Identifier; GMP, Good Manufacturing Practice; (b) (4) MRA, Mutual Recognition Agreement; NAI, No Action Indicated; OPQO, Office of Pharmaceutical Quality Operations; ORA, Office of Regulatory Affairs; ORAHQ, Office of Regulatory Affairs headquarters; VAI, Voluntary Action Indicated.

The Division of Manufacturing and Product Quality (DMPQ) conducted a pre-license inspection (PLI) of the DP manufacturer, (b) (4), in (b) (4), and a Form FDA 483 was issued at the end of the inspection. The firm's response to the observations and the corrective actions were reviewed and found to be adequate. The inspection was classified as Voluntary Action Indicated (VAI).

DMPQ conducted a PLI of the DP manufacturer, (b) (4), from (b) (4), and a Form FDA 483 was issued at the end of the inspection. The firm's response to the observations and the corrective actions were reviewed and found to be adequate. The inspection was classified as VAI.

DMPQ conducted a PLI of the (b) (4) manufacturer, (b) (4), in (b) (4), and a Form FDA 483 was issued at the end of the inspection. The firm's response to the observations and the corrective actions were reviewed and found to be adequate. The inspection was classified as VAI.

DMPQ conducted a PLI of the (b) (4) manufacturer, (b) (4), in (b) (4). No Form FDA 483 was issued at the end of the inspection, and the inspection was classified as No Action Indicated (NAI).

DMPQ performed a 704(a)(4) Records Request in lieu of an inspection of the (b) (4) manufacturer, (b) (4). Following review of the quality systems and (b) (4) manufacturing and facility documents, no objectionable conditions were noted, and the outcome was acceptable.

The Office of Regulatory Affairs (ORA)/Office of Pharmaceutical Quality Operations (OPQO) conducted a surveillance inspection of (b) (4) in (b) (4). No Form FDA 483 was issued, and the inspection was classified as NAI.

(b) (4) performed an inspection of (b) (4) in (b) (4). ORA/OPQO reviewed the (b) (4) inspection report under the Mutual Recognition Agreement in (b) (4) and classified the inspection as VAI.

ORA/OPQO performed a surveillance inspection of (b) (4) in (b) (4). No Form FDA 483 was issued, and the inspection was classified as NAI.

(b) (4) performed an inspection of (b) (4) in (b) (4). A GMP Certificate was issued.

(b) (4) performed an inspection of (b) (4) in (b) (4). ORA/OPQO reviewed the (b) (4) inspection report under the Mutual Recognition Agreement in (b) (4) and classified the inspection as VAI.

(b) (4) performed an inspection of (b) (4) in (b) (4). A GMP Certificate was issued.

e. Container/Closure System

CASGEVY DP is filled and stored in 20 mL (b) (4) manufactured by (b) (4) The vial is made of (b) (4) and the stoppers are (b) (4), which are pre-assembled and sterilized prior to DP fill. The top ring and cap (nonproduct contact) are composed of (b) (4) (b) (4), respectively, also manufactured by (b) (4) Container closure integrity testing was performed by (b) (4) using the (b) (4) and (b) (4) methods. All acceptance criteria were met.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 Code of Federal Regulations (CFR) 25.31. This request and supporting information provided by Vertex are acceptable to conclude that CASGEVY poses a negligible risk to the environment or to the general public. There are no significant environmental or public health impacts posed by the product or its manufacturing. The potential for CASGEVY to persist in the environment is negligible because these cells have stringent nutritional requirements for survival and therefore are not viable in the environment. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

The *in vitro* pharmacology studies conducted with healthy donor CD34+ cells edited using the *SPY101*-RNP used in the manufacture of CASGEVY showed editing at the

target genomic locus of the *BCL11A*/*GATA1* binding site, with genome editing frequencies ranging from 60% to 92%. Subsequent upregulation of gamma-globin transcripts and HbF levels was observed compared to that of unedited cells, and on-target editing frequencies were stable during erythroid differentiation. There were no significant editing-related changes to cell viability, cell growth, erythroid differentiation, enucleation, and distribution profile across various lineage progenitor subpopulations compared to that of unedited CD34+ human hematopoietic stem and progenitor cells (hHSPCs). Edited CD34+ hHSPCs from healthy donors and patients with transfusion dependent beta-thalassemia (TDT) showed similar on-target editing frequencies and upregulation of gamma-globin transcript and HbF protein.

The *in vivo* pharmacology of *SPY101*-RNP-edited CD34+ hHSPCs from healthy donors was evaluated in irradiated NOD/SCID/IL2Rg null (NSG) mice. Engraftment of transplanted cells and the on-target editing frequencies were evaluated. Single IV administration of edited CD34+ hHSPCs at 1×10^6 cells/mouse resulted in similar levels of chimerism of CD34+ hHSPCs in whole blood, bone marrow, and spleen, as well as multilineage differentiation to B-, T-, and myeloid cells in whole blood, bone marrow, and spleen in studies of 16- and 20-week duration compared to that of unedited cells. At 16 weeks post administration, engrafted cells in NSG mice demonstrated >90% on-target editing frequencies in whole blood, bone marrow, and spleen. Erythroid progenitor cells that were differentiated from bone marrow-engrafted cells isolated at 16 weeks post administration had an average of 90% on-target editing frequency.

An *in vivo* pharmacokinetic study of *SPY101*-RNP-edited CD34+ hHSPCs from healthy donors was conducted in irradiated NSG mice. Human DNA was detected in most of the examined tissues in mice that received a single IV administration of 1×10^6 cells/mouse, with the highest levels detected in the bone marrow, followed by spleen, blood, lung, liver, and kidney. Low levels of human DNA were detected at the injection site and in the heart, mammary gland, jejunum, pancreas, brain, and skeletal muscle. Human DNA levels were minimal to below the limit of quantification in the prostate, uterus, ovary, and testis at 8 weeks post administration. Editing frequencies of 87.4±1.5% were observed in the spleen and bone marrow at 8- and 20-weeks post administration.

An *in vivo* toxicology and tumorigenicity study of *SPY101*-RNP-edited CD34+ hHSPCs from healthy donors was conducted in irradiated NSG mice. Mice received single IV administration of 1×10^6 cells/mouse and were followed for 20 weeks. There were no significant adverse findings or tumor formation.

The potential for *SPY101*-RNP-mediated off-target editing and chromosomal aberrations was evaluated for CD34+ hHSPCs from healthy donors, patients with sickle cell disease (SCD), and patients with TDT. No off-target editing was detected following hybrid-capture confirmatory testing of the candidate off-target sites identified from in silico and cell-based analysis. A variant-aware analysis accounting for genomic heterogeneity was performed. Although no off-target editing was reported, only some variants harboring potential off-target loci were empirically tested due to sample limitations. No chromosomal aberrations for *SPY101*-RNP-edited CD34+ hHSPCs from healthy donors were observed based on karyotyping, long-range polymerase chain reaction sequencing, and hybrid capture sequencing analyses.

Developmental and reproductive toxicity studies and carcinogenicity studies were not conducted with CASGEVY. These studies are not warranted based on the characteristics and safety profile of the product.

5. Clinical Pharmacology

The clinical pharmacology evaluation of this biologics license application (BLA) includes one ongoing Phase 1/2/3 study (Study CTX001-111), one long-term follow-up study (Study CTX001-131), and a population pharmacodynamic (PD) study (Study T067). Based on the nature of CASGEVY, conventional studies on pharmacokinetics, absorption, distribution, metabolism, and elimination cannot be used to monitor the presence of the drug product and are not applicable. Clinical pharmacology review focuses on the pharmacodynamic responses after administration of CASGEVY.

After CASGEVY infusion, the edited $CD34^+$ cells engraft in the bone marrow and differentiate to erythroid lineage cells with reduced BCL11A expression. Reduced BCL11A expression results in an increase in γ-globin expression and HbF protein production in erythroid cells. In subjects who received CASGEVY, the mean proportion of alleles with the intended genetic modification in CD34+ cells of bone marrow remained stable (>75%) at Month 6 onward. Allelic editing in the peripheral blood was detectable at Month 1 and remained stable (> 62%) from Month 2 onwards. Increases in mean (SD) total hemoglobin (total Hb) and fetal hemoglobin (HbF) levels were observed as early as Month 3 after CASGEVY infusion and continued to increase to 12.2 (SD: 2.0) g/dL and 10.9 (SD: 2.8) g/dL respectively at Month 6. After Month 6, levels of total Hb and HbF were maintained thereafter, with HbF comprising ≥ 88% of total Hb. Consistent with the increase in HbF levels, the mean (SD) proportion of circulating erythrocytes expressing HbF (F-cells) at Month 3 was 73.8% (SD: 19.7%) and continued to increase over time to 95.9% (SD: 15.2%) at Month 6, with levels remaining stable thereafter, indicating sustained pan-cellular expression of HbF. The durability of pharmacodynamic responses was observed up to Month 42 post infusion of CASGEVY. Durability of PD responses was also supported by correlation analysis of PD biomarkers at different visits and population pharmacodynamic modeling. No dose-response relationship was identified for clinical efficacy (transfusion independence). The proposed minimum dose of CASGEVY (3.0×10^6 CD34+ cells/kg) is acceptable.

From clinical pharmacology standpoint, the BLA is acceptable to support approval.

6. Clinical/Statistical

a. Clinical Program

The evaluation of CASGEVY in transfusion-dependent thalassemia (TDT) was based on the interim analysis of the ongoing Study 111 and the long-term follow-up Study 131. Study 111 is a multinational, single-arm, open-label, Phase 1/2/3 study to evaluate the efficacy and safety of a single dose of CASGEVY (minimum dose of 3×10^6 CD34+ cells/kg) in subjects 12-35 years of age (inclusive) with TDT. Enrolled subjects had

homozygous or compound heterozygous β-thalassemia including β-thalassemia/Hb E with genotype confirmation in a central laboratory and with a transfusion requirement of at least 100 mL/kg/year or 10 units/year of RBC transfusion in the 2 years prior to screening. Subjects had to meet eligibility criteria for autologous hematopoietic stem cell transplantation following myeloablative conditioning with busulfan and lack a 10/10 HLA-matched related donor.

The primary endpoint was the proportion of subjects who achieved transfusion independence (TI)12, defined as maintaining a weighted average Hb ≥ 9 g/dL without red blood cell (RBC) transfusions for at least 12 consecutive months any time after CASGEVY infusion during the 24-month followup. The evaluation of TI12 starts 60 days after the last RBC transfusion for post-transplant support or TDT disease management. The key secondary endpoint was the proportion of subjects who achieved TI6, defined as maintaining a weighted average Hb ≥ 9 g/dL without RBC transfusions for at least 6 consecutive months any time after CASGEVY infusion. Other secondary endpoints presented here include transfusion-free duration in subjects who achieved TI12, total and fetal hemoglobin (HbF) over time, and bone marrow (BM) and peripheral blood (PB) allelic editing percentage over time.

Data for the interim analysis with a cutoff date of January 16, 2023, were submitted in this BLA. A total of 52 subjects were dosed with CASGEVY at the time of this analysis, of whom 35 subjects had an adequate duration of follow-up (at least 16 months following CASGEVY and at least 14 months since last RBC transfusion post-transplant) for evaluation of efficacy.

Efficacy Results

Thirty-two of 35 (91.4%) efficacy evaluable subjects achieved the primary efficacy endpoint of TI12 with a 1-sided 98.3% confidence interval (CI) of (75.7, 100).

All subjects who achieved TI12 achieved the key secondary endpoint of TI6.

The median duration of follow-up for the 35 efficacy evaluable subjects is 23.6 months (range 16.1 to 26.4 months). The median (range) transfusion free duration in the 32 subjects with TI12 is 20.4 (13.3, 23.7) months; no subject has resumed transfusions after achievement of TI12. All 3 subjects considered as non-responders for TI12 at the interim analysis are transfusion-free as of the latest data cutoff of September 18, 2023. Mean (SD) total and fetal hemoglobin are ≥11 g/dL and ≥10 g/dL respectively from month 6 through follow up. Mean bone marrow and peripheral blood editing have remained stable for the duration of follow-up.

In summary, Study 111 provides substantial evidence of effectiveness of CASGEVY for the treatment of TDT in subjects 12 years and older.

b. Bioresearch Monitoring (BIMO) – Clinical/Statistical/Pharmacovigilance

Given the robust inspection histories for the clinical study sites participating in the conduct of the pivotal study supporting this application, the review team has determined

that Bioresearch Monitoring (BIMO) inspections are not warranted to support the review of this BLA.

c. Pediatrics

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Since this biological product for TDT indication has an orphan drug designation, this application is exempt from this requirement.

The Applicant evaluated pediatric subjects 12 years and older in their clinical development program. The clinical data support the safety and effectiveness of CASGEVY in the studied pediatric subgroup.

d. Other Special Populations

CASGEVY has not been studied in other special populations.

7. Safety and Pharmacovigilance

Safety

The primary safety population in Study 111 included 52 subjects who received busulfan myeloablation conditioning and CASGEVY at a median (min, max) dose of 7.5 (3.0, 19.7) $\times 10^6$ cells/kg as an IV infusion by the data cutoff of January 16, 2023. Treatment-emergent adverse events were defined as all adverse events occurring after initiation of CASGEVY administration up to Month 24 visit. Subjects were followed for a median (min, max) duration of 20.4 (2.1, 48.1) months post CASGEVY, including the long-term follow-up Study 131.

Summary of Safety Findings

Treatment-emergent adverse events were mostly related to hematologic, gastrointestinal, and mucosal sequelae of myeloablative conditioning required immediately prior to CASGEVY. Serious adverse reactions after CASGEVY infusion were observed in 32.7% of subjects with TDT. The most common serious adverse reactions (≥2 subjects) were veno-occlusive liver disease, pneumonia, covid-19, hypoxia, thrombocytopenia, upper respiratory tract infection, and viral infection. There were no deaths or discontinuations reported due to adverse events in Studies 111 and 131.

Neutrophil engraftment was defined as the first day of 3 consecutive measurements of ANC ≥500/μL on 3 different days, achieved within 42 days post CASGEVY infusion, without additional use of the unmodified CD34+ cells. The median (min, max) time to neutrophil engraftment was 29 (12, 56) days (N=52). One subject failed to achieve neutrophil engraftment by day 42 but later achieved engraftment on day 56 without use

of backup cells. Platelet engraftment was defined as three consecutive measurements of platelet counts ≥20×10^9/L, obtained on three different days after CASGEVY infusion, without administration of platelet transfusions for 7 days. The median (min, max) time to platelet engraftment was 44 (20, 200) days (N=52). There were five subjects who had delayed platelet engraftment (range: 110-200 days) post infusion, despite the use of thrombopoietin (TPO) mimetics and remained thrombocytopenic during safety follow-up, based on the data cutoff date January 16,2023. In one subject the ASXL1 gene mutation was detected (at month 12, next generation sequencing (NGS) report) but no evidence of malignancy has been identified.

The overall safety profile of CASGEVY therapy was as expected with autologous transplant but was associated with delayed platelet engraftment in some subjects.

Pharmacovigilance Plan

The CASGEVY US pharmacovigilance plan (PVP) for SCD and TDT Version 1.0 includes the Applicant's assessment of identified and potential risks and missing information based on the pre-licensure clinical trial data, published literature, known product-class effects, and other relevant sources of safety information. The Applicant will conduct routine pharmacovigilance in accordance with 21 CFR 600.80, and enhanced pharmacovigilance for secondary malignancies and off-target effects following genome editing. Enhanced pharmacovigilance will include expedited (15-day) reporting of secondary malignancies and any clinical manifestations associated with off-target effects following genome editing (regardless of seriousness or label status). The Applicant will also provide a safety assessment of secondary malignancies and off-target effects following genome editing in periodic safety reports.

Off-target analysis accounting for heterogeneity in the intended patient population included in the BLA was performed using a variant database with sequencing information from only a limited number of individuals in the United States. Several off-target loci contributed by variants were not empirically tested by the Applicant. Therefore, to enable clinical safety evaluation of off-target editing, the review team required a post-marketing bioinformatics study for CASGEVY to adequately assess potential off-target editing risks arising from heterogeneity in the patient population.

Consequently, in addition to the routine and enhanced pharmacovigilance, the postmarketing safety risk evaluation of CASGEVY will include the above-described bioinformatics study and a 15-year observational safety study to assess the long-term safety risks, including the risk of secondary malignancies (Study VX22-290-101). These studies will be required as two postmarketing requirements (PMRs) under 505(o) of the Federal Food, Drug, and Cosmetic Act. The Applicant will also conduct routinely recommended long-term follow-up of clinical trial subjects in the ongoing Study 131. The above studies are in alignment with FDA guidance for industry Long Term Follow-up After Administration of Human Gene Therapy Products (January 2020).

8. Labeling

The proposed proprietary name, CASGEVY, was reviewed by the Advertising and Promotional Labeling Branch (APLB), on June 14, 2023, and was found acceptable.

CBER communicated the acceptability of the proprietary name to the applicant on June 23, 2023.
APLB reviewed the proposed Prescribing Information, Patient Package Insert, and package and container labels on November 3, 2023.

9. Advisory Committee Meeting

An advisory committee meeting was held for CASGEVY for treatment of patients 12 years and older with sickle cell disease (SCD) who have recurrent vaso-occlusive crises (VOCs) under BLA 125787 on October 31, 2023, to address the off-target editing risks. Therefore, it was not deemed to be necessary to hold an advisory committee meeting for CASGEVY for the TDT indication.

10. Other Relevant Regulatory Issues

CASGEVY was granted Orphan Drug, Fast Track, and Regenerative Medicine Advanced Therapy designations. The BLA was reviewed under standard review.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Applicant has provided substantial evidence of effectiveness and reasonable assurance of safety based on adequate clinical investigation.

The review team recommends approval of CASGEVY for the treatment of patients aged 12 years and older with transfusion-dependent beta thalassemia (TDT).

b. Benefit/Risk Assessment

CASGEVY administration resulted in 91.4% of subjects with TDT achieving transfusion independence while maintaining a weighted average Hb of ≥ 9g/dL for a period of at least 12 consecutive months during the study. No subject who has achieved the primary efficacy endpoint of TI12 has resumed transfusions. The clinical benefit appears to be durable with stable total and fetal hemoglobin levels and stable bone marrow and peripheral blood allelic editing. Important safety risks include the potential of off-target editing by CRISPR/Cas9 and delayed platelet engraftment. There are no cases of malignancies reported and delayed platelet engraftment appears to be a manageable risk. Thus, the overall benefit-risk is favorable.

c. Recommendation for Postmarketing Activities

The Applicant will conduct routine and enhanced pharmacovigilance activities as outlined in the pharmacovigilance plan, and the following safety studies as PMRs under section 505(o) of the Federal Food, Drug, and Cosmetic Act to assess the serious risks of secondary malignancies and off-target effects following genome editing:

1. A postmarketing, prospective, multi-center, observational study, to assess and characterize the risks of secondary malignancies and off-target effects following genome editing occurring after treatment with CASGEVY, and to assess the long-term safety of CASGEVY. This study will include 150 patients with transfusion-dependent β-thalassemia (TDT), and each enrolled subject will be followed for 15 years after product administration. The study design will include monitoring (at pre-specified intervals) with adequate testing strategies (Study Protocol VX22-290-101).

   Final Protocol Submission: March 31, 2024
   Study Completion: December 31, 2042
   Final Study Report Submission: December 31, 2043

2. A bioinformatics study and respective analyses to comprehensively assess and screen for the impact of sequence heterogeneity on the risk of off-target editing in the patient population that would use CASGEVY. Specifically:
   a. Perform a new in silico off-target analysis using publicly available databases/datasets to allow for inclusion of more variants. Specifically, perform the analysis using all variants with at least 0.5% allele frequency in at least one of the five continental groups (Africa, Europe, East Asia, South Asia, and the Americas).
   b. Perform confirmatory testing, as appropriate and feasible, of all the off-target loci nominated from the new in silico analysis in study (i), as well as those that were not accounted for in the previous study using appropriate samples harboring variants. Specifically:
      i. Screen for the presence of all previously identified variants (e.g., CPS1), as well as any variants identified in study (i) and (ii) in the patients treated in Studies 121, 111, 141, 151, 161, and 171.
      ii. For patients with a confirmed variant(s), assess for indels and chromosomal changes at each respective locus in appropriate samples.

Final Protocol Submission (submitted): December 01, 2023
Study Completion Date: June 30, 2032
Final Report Submission: June 30, 2032

The Applicant also agreed to the following chemistry, manufacturing, and controls postmarketing commitments:

1. Vertex Pharmaceuticals Inc commits to performing a supplemental shipping validation study of CASGEVY assessing the quality attributes, including (b) (4) for (b) (4) and (b) (4) transportation samples using the (b) (4) (b) (4) commercial shippers. The final validation study report will be submitted as a Postmarketing Commitment-Final Study Report by May 31, 2024.

   Final Report Submission: May 31, 2024

2. Vertex Pharmaceuticals Inc commits to performing a supplemental (b) (4) hold time stability study in which additional data are obtained to support the current hold time proven acceptable ranges, including the cumulative proven acceptable hold time. The final validation study report will be submitted as a Postmarketing Commitment-Final Study Report by December 31, 2024.

   Final Report Submission: December 31, 2024