Summary Basis for Regulatory Action

Date:	December 08, 2023
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:	125787
Applicant:	Vertex Pharmaceuticals Incorporated
Submission Receipt Date:	Monday, April 03, 2023
PDUFA Action Due Date:	Friday, December 08, 2023
Proper Name:	exagamglogene autotemcel
Proprietary Name:	CASGEVY
Indication:	Treatment of sickle cell disease (SCD) in patients 12 years and older with recurrent vaso-occlusive crises (VOCs)

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

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Director, Office of Therapeutic Products

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Director, Office of Compliance and Biologics Quality

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, 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, CBER/OCBQ/DMPQ Carl Perez, 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/DPV) • BIMO	Karl Kasamon, MD, CBER/OTP/OCE Alisha Thomas, MD, MPH, CBER/OBPV/DPV Triet M. Tran, PharmD, BCSCP, CBER/OCBQ/DIS
Statistical • Clinical data (OBPV/DB) • Non-clinical data	Yuqun Abigail Luo, 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	Million Tegenge (OTP/OCE)
Labeling • Promotional (OCBQ/APLB) • PNR • Container/carton	Benjamin Cyge, PhD, CBER/OCBQ/DCM/APLB Oluchi Elekwachi, PharmD, MPH, CBER/OCBQ/DCM/APLB Hosna Keyvan, CBER/OTP/ORMRR/DRMRR2/RMSB2 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
Advisory Committee Summary	Komudi Singh, PhD, CBER/OTP/OCTHT Karl Kasamon, MD, CBER/OTP/OCE

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1. Introduction

Vertex Pharmaceuticals Inc. (Applicant) submitted Biologics License Application (BLA) 125787 for exagamglogene autotemcel (exa-cel, hereafter referred to as CASGEVY, the proprietary name). CASGEVY is an autologous, hematopoietic, stem cell-based gene therapy indicated for treatment of patients 12 years and older with sickle cell disease (SCD) who have recurrent vaso-occlusive crises (VOCs). SCD is a rare disease manifested by recurrent VOCs, leading to life-threatening complications and decreased overall survival. Despite currently available treatments, a substantial unmet medical need remains.

CASGEVY consists 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 transfusion to dilute sickle hemoglobin (HbS) to <30% while keeping Hb no higher than 11 g/dL to optimize harvesting, and later, engraftment. The patients then undergo hematopoietic stem cell mobilization with single agent plerixafor, followed by apheresis to harvest the cells. The collected cells are shipped to (b) (4) of (b) (4) 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) and diminished expression of HbS, which is therapeutic for SCD.

This document summarizes the basis for approval of CASGEVY. Data from 44 CASGEVY-treated subjects from one single-arm Phase 1/2/3 study, Study 121, and the rollover long-term follow-up study, Study 131, provide the primary evidence of safety and effectiveness in this BLA. The recommendation for approval is based on demonstration of efficacy in the primary efficacy outcome (VF12 response), absence of severe vaso-occlusive crises (sVOCs) for a period of at least 12 consecutive months during the 24-month follow-up period in Study 121 after CASGEVY infusion. Efficacy evaluation started after a 60-day washout period following the last red blood cell transfusion for post-transplant support or SCD 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

SCD, a rare hemoglobinopathy affecting an estimated 80,000 patients in the United States (Jones and DeBaun 2021), is caused by a point mutation substituting valine for glutamic acid in the sixth codon of the beta-globin gene, leading to production of HbS. When deoxygenated, HbS polymerizes, creating rigid fibrils that occlude blood vessels and lead to hemolysis. The disease is characterized by debilitating, recurrent, painful VOCs and extensive organ damage involving the kidneys, cardiopulmonary system, and brain. Although a number of pharmaceuticals are approved to treat SCD, they offer a modest benefit to a fraction of patients with SCD and are noncurative. Allogeneic hematopoietic stem cell transplantation may offer a cure, but only for the small minority of patients with an available matched donor. Overall, treatment of patients with SCD remains an unmet medical need.

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 beta-like/alpha-globin imbalance in erythroid cells of patients with SCD who have recurrent sVOCs, and has the potential to diminish or prevent sVOCs and other complications.

The regulatory history of CASGEVY is outlined in Table 1.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Original IND Submission	April 27, 2018
2. Fast Track designation granted	January 02, 2019
3. Orphan Drug designation granted	May 11, 2020
4. Regenerative Medicine Advanced Therapy designation granted	May 05, 2020
5. Pre-BLA Meeting	Aug 09, 2022
6. BLA submitted	April 03, 2023
7. BLA filed	June 08, 2023
8. Mid-Cycle Meeting	July 31, 2023
9. Late-Cycle Meeting	October 19, 2023
10. Action Due Date	December 08, 2023

3. Chemistry Manufacturing and Controls

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) (b) (4) or (b) (4) (b) (4) for (b) (4) (b) (4) 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 (b) (4) (b) (4) (b) (4) using an automated cell processor. The labeled CD34+ cells are then selected in the presence of a (b) (4) using an automated cell separation system. The enriched CD34+ cells are then cultured in the presence of (b) (4) (b) (4) The expanded, enriched CD34+ cells are then electroporated with

CRISPR/Cas9/*SPY101* RNP complexes. After electroporation, the cells (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) (b) (4) To produce the CASGEVY DP, the (b) (4) is formulated in (b) (4) (b) (4) cryopreservation solution (b) (4) The formulated DP is passed through an (b) (4) before being filled into (b) (4) 20 mL (b) (4) (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. (b) (4) 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 (b) (4) 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) (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 2: 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)

Attribute	Test	Method	Acceptance Criteria
-	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 3. 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
(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) (b) (4) 704(a)(4) Records

Name/Address	FEI Number	DUNS Number	Inspection/ Waiver	Justification/ Results
				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)(4), (b)(3) 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) *DP release testing*	(b) (4)	(b) (4)	Waived	(b) (4) Inspection (b) (4)
(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) (b) (4) (b)(4), (b)(3) 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) (b) (4) manufacturer, (b) (4) (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) (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), (b)(3) performed an inspection of (b) (4) in (b)(4), (b)(3). 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 SCD 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 SCD, and patients with transfusion-dependent β-thalassemia. 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

After CASGEVY infusion, the edited autologous 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 gamma-globin expression and HbF protein production in erythroid cells. In patients with severe SCD, HbF expression reduces intracellular HbS concentration, preventing the red blood cells from sickling and addressing the underlying cause of disease, thereby eliminating VOCs.

The mean proportion of alleles with the intended genetic modification in peripheral blood was generally maintained at ≥70% from Month 2 onward, through the duration of follow-up in Studies 121 and 131. The mean (standard deviation) proportion of total Hb comprising HbF (%) was 36.9% (9.0%) at Month 3 and was maintained at ≥40% from Month 6 over the duration of follow-up. Correlative analysis demonstrates a correlation of the earlier timepoint (Month 6) with later timepoints (e.g., Month 12 and 24) for parameters such as HbF% and allelic editing in bone marrow and peripheral blood. The empirical population pharmacodynamic model reasonably described the observed HbF% versus time profile up to Month 24. No relevant dose-response relationship was identified

for HbF% and clinical efficacy (VF12). For a range of factors explored, no clinically relevant effects of intrinsic, extrinsic, or manufacturing factors were observed for HbF%.

Overall, dose response and correlative assessment did not identify CASGEVY dose as a factor affecting HbF% or clinical efficacy (VF12) based on the limited clinical data. The product allelic editing and percent net increase in gamma-globin expression appear to correlate with in vivo persistence of genome edited cells. However, the available data do not allow derivation of a threshold of in vivo persistence that correlates with HbF (%) or VF12. The recommended minimum single IV dose (3.0×10^6 CD34+ cells/kg) of CASGEVY for treatment of SCD is acceptable from a clinical pharmacology perspective. 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 patients with severe sickle cell disease, HbF expression reduces intracellular hemoglobin S (HbS) concentration, preventing the red blood cells from sickling and addressing the underlying cause of disease, thereby eliminating VOCs. Following successful engraftment, the effects of CASGEVY are expected to be over 24 Months based on the persistence of proportion of allelic edited CD34 cells and HbF. The mean proportion of alleles with the intended genetic modification in peripheral blood was generally maintained ≥70% from Month 2 onward, through the duration of follow-up in Studies 121 and 131. The mean (SD) proportion of total Hb comprised of HbF (%) was 36.9% (9.0%) at Month 3 and was maintained at ≥40% from Month 6 over the duration of follow-up. Correlative analysis demonstrates a correlation of the earlier timepoint (Month 6) with later timepoints (e.g., Month 12 & 24) for parameters such as HbF% and allelic editing in bone marrow and peripheral blood. The empirical population pharmacodynamic model reasonably described the observed HbF% vs time profile up to Month 24. No relevant dose-response relationship was identified for HbF% and clinical efficacy (VF12). For a range of factors explored no clinically relevant effects of intrinsic, extrinsic, or manufacturing factors are observed for HbF%.

Overall, dose-response and correlative assessment did not identify CASGEVY dose as a factor affecting HbF% or clinical efficacy (VF12) based on the limited clinical data. The product allelic editing and % net increase in gamma globin expression appears to correlate with in vivo persistence of gene edited cells. However, the available data don't allow to derive a threshold of in vivo persistence that correlates with HbF (%) or VF12. The recommended minimum single intravenous dose (3.0×10^6 CD34+ cells/kg) of CASGEVY for treatment of SCD is acceptable from clinical pharmacology perspective.

6. Clinical/Statistical

a. Clinical Program

The evaluation of CASGEVY efficacy was based on an interim analysis of the ongoing Study 121 and the long-term follow-up Study 131. Study 121 was a multinational, single-arm, Phase 1/2/3 study to evaluate the safety and efficacy of a single dose of CASGEVY in subjects 12 to 35 years old with SCD. Study 121 enrolled those with βS/βS, βS/β0, or βS/β+ genotypes and severe SCD phenotype (at baseline, documented to have at least two protocol-defined sVOCs for each year of a 2-year period preceding screening), and who lacked a matched marrow donor.

The primary efficacy outcome was VF12 response, defined as absence of protocol-defined sVOCs for at least 12 consecutive months within the 24-month follow-up period after CASGEVY infusion in Study 121. The key secondary endpoint was proportion of subjects who did not require hospitalization due to sVOCs for at least 12 consecutive months within the 24-month evaluation period (HF12). The evaluation of VF12 and HF12 began 60 days after the last red blood cell transfusion for post-transplant support or SCD management.

Data for an interim analysis with a database lock date of June 14, 2023 were submitted. A total of 44 SCD subjects were treated with CASGEVY, with 31 subjects having sufficient follow-up to be evaluable for the primary efficacy outcome.

Efficacy Results

A total of 31 subjects were evaluable for the primary efficacy outcome, of whom 29 (93.5%) were VF12 responders. The one-sided 98% confidence interval on the VF12 responder rate is (77.9%, 100%). An additional subject died during Month 8.9; the investigator reported that the cause was respiratory failure associated with COVID-19 pneumonia and busulfan lung injury. According to the statistical analysis plan, any death related to CASGEVY (the entire treatment regimen including conditioning agents) occurring before achievement of a VF12 response would be considered a VF12 non-response. However, FDA agreed with the Applicant's request to exclude this subject from efficacy analysis due to difficulty in determining, among multiple comorbidities, the extent to which busulfan contributed to the death.

Of the 31 subjects evaluable for VF12 response, 1 subject was not evaluable for HF12 response due to insufficient follow-up; the remaining 30 subjects (100% [98% one-sided confidence interval: 87.8%, 100.0%]) were HF12 responders.

All 31 subjects evaluable for VF12 response had sustained HbF ≥20% for at least 12 consecutive months.

In summary, Study 121 provides substantial evidence of effectiveness of CASGEVY in patients with SCD who have recurrent sVOCs. The results support approval for CASGEVY.

b. Bioresearch Monitoring – Clinical/Statistical/Pharmacovigilance

Bioresearch Monitoring inspections were conducted at two domestic clinical investigator sites participating in the conduct of Study 121. The inspections did not reveal any issues that impact the data submitted in this original 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.

Because the biological product for this 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 included 44 Study 121 subjects who received busulfan myeloablation and CASGEVY at a median (min, max) dose of 4.0 (2.9, 14.4)×10^6 cells/kg as an IV infusion by the data cutoff of June 14, 2023. Treatment-emergent adverse events were defined as all adverse events occurring after initiation of CASGEVY administration to Month 24 visit. Subjects were followed for a median (min, max) duration of 19.3 (0.8, 48.1) months post CASGEVY, including on 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 45% of subjects with SCD. The most common serious adverse reactions (≥2 subjects) were cholelithiasis, pneumonia, abdominal pain, constipation, pyrexia, abdominal pain upper, noncardiac chest pain, oropharyngeal pain, pain, and sepsis. One subject (2%) died of respiratory failure after COVID-19 infection compounded by busulfan lung injury. Neutrophil engraftment occurred by a median of (min, max) 27 (15, 40) days (N=44). Platelet engraftment was defined as three consecutive measurements of platelet counts ≥50×10^9/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 35 (23, 126) days (n=43). There was no association observed between bleeding events and time to platelet engraftment, but platelet engraftment was delayed compared with allogeneic hematopoietic stem cell transplant outcomes. The overall safety profile of CASGEVY therapy was largely as expected with autologous transplant but was associated with prolonged time to platelet engraftment.

Pharmacovigilance Plan

The pharmacovigilance plan (version 1.2) 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 postmarketing 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 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 for readability and comprehension on November 3, 2023.

9. Advisory Committee Meeting

A meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee was held on October 31, 2023, to discuss the Applicant's off-target safety assessment of CASGEVY

and to provide advice to FDA regarding adequacy of the off-target safety assessment and any additional studies needed to address safety of CASGEVY.

Summary of discussion:

- The Advisory Committee discussed the off-target safety risk and additional studies that could be implemented. Screening subjects for the CPS1 variant and additional methods for off-target analysis were also discussed.
- The Advisory Committee agreed that a 15-year follow-up of the patient population post approval would be sufficient.
- There was no voting question.

10. Other Relevant Regulatory Issues

CASGEVY was granted a Rare Pediatric Disease priority review voucher and Orphan Drug, Fast Track, and Regenerative Medicine Advanced Therapy designations. The BLA was reviewed under priority review.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Applicant 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 12 years and older with SCD who have recurrent VOCs.

b. Benefit/Risk Assessment

CASGEVY administration resulted in 93.5% of subjects with SCD and recurrent sVOCs achieving VF12 (freedom from sVOCs for ≥12 months after CASGEVY on Study 121). The most important risk identified with CASGEVY is potential off-target editing by CRISPR/Cas9, which is unknown at this time. There is substantial benefit of freedom from sVOC. Therefore, the overall benefit-risk profile of CASGEVY is favorable.

The clinical trial data do not suggest a safety concern that would necessitate a Risk Evaluation and Mitigation Strategy. However, PMR safety studies will be required to assess the long-term risk of hematologic malignancies and off-target genome editing effects by CRISPR/Cas9.

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, multicenter 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. The study will include 250 subjects with SCD, and each enrolled subject will be followed for 15 years after product administration. The study design will include monitoring (at prespecified intervals) with adequate testing strategies (Study Protocol VX22-290-101).

   Final protocol submission: March 31, 2024
   Study completion date: 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.

   Submit Draft Study Protocol for FDA review (completed): November 21, 2023
   Final Protocol Submission (completed): 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) -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

12. References

Jones, RJ and MR DeBaun, 2021, Leukemia after gene therapy for sickle cell disease: insertional mutagenesis, busulfan, both, or neither, Blood, 138(11):942-947.