Summary Basis for Regulatory Action

Date:	November 22, 2022
From:	Anurag Sharma, Chair of the Review Committee, Office of Tissues and Advanced Therapies (OTAT), Division of Cellular and Gene Therapies (DCGT)
BLA STN:	BL125772/0
Applicant:	CSL Behring LLC
Submission Receipt Date:	March 24, 2022
PDUFA Action Due Date:	November 22, 2022
Proper Name:	etranacogene dezaparvovec-drlb
Proprietary Name:	HEMGENIX
Indication:	Indicated for the treatment of adults with Hemophilia B (congenital Factor IX deficiency) who: currently use Factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes.

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

Director, Office of Tissues and Advanced Therapies

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)	Anurag Sharma, CBER/OTAT/DCGT Mikhail Ovanesov, CBER/OTAT/DPPT Ronit Mazor, CBER/OTAT/DCGT Emmanuel Adu-Gyamfi; CBER/OTAT/DCGT Massoud Motamed, CBER/OTAT/DCGT Alifiya Ghadiali, CBER/OCBQ/DMPQ Christian Lynch, CBER/OCBQ/DMPQ Debbie Vause, CBER/OCBQ/DMPQ Hsiaoling Wang, PhD, CBER/OCBQ/DBSQC Simleen Kaur, CBER/OCBQ/DBSQC Esmeralda Alvarado Facundo, CBER/OCBQ/DBSQC Marie Anderson, CBER/OCBQ/DBSQC Varsha Garnepudi CBER/OCBQ/DBSQC Unnee Ranjan, ORA/OMPTO/OBPO
Clinical • Clinical (Product Office) • Postmarketing safety epidemiological review (OBPV/DE) • BIMO	Megha Kaushal, CBER/OTAT/DCEPT Courtney Johnson, CBER/OTAT/DCEPT Leah Crisafi, CBER/OTAT/DCEPT Bethany Baer, CBER/OBPV Triet Tran, CBER/OCBQ/DIS
Statistical Clinical data (OBPV/DB)	Yuqun Abigail Luo, CBER/OBPV
Non-clinical/Pharmacology/Toxicology • Toxicology (Product Office)	Margaret Benny Klimek, CBER/OTAT/DCEPT
Clinical Pharmacology	Million Tegenge, CBER/OTAT/DCEPT
Labeling • Promotional (OCBQ/APLB)	Benjamin Cyge, CBER/OCBQ/DCM/APLB Shalini Seetharaman, CBER/OTAT/DRPM Leyish Minie, CBER/OTAT/ DRPM
Other Reviews not captured above categories, for example: • Consults • Devices • Software • Human Factors • FONSI	Oluchi Elekwachi, CBER/OCBQ/DCM/APLB Lisa Stockbridge, CBER/OCBQ/DCM/APLB Natasha Throne, CDRH/OPEQ/OHTVII/DIHD
Advisory Committee Summary	N/A

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1. Introduction

CSL Behring LLC submitted a Biologics License Application (BLA), STN 125772, for licensure of etranacogene dezaparvovec-drlb, with the proprietary name of HEMGENIX. HEMGENIX is an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with Hemophilia B (congenital Factor IX deficiency) who: currently use Factor IX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or have repeated, serious spontaneous bleeding episodes.
Deficiency of the essential blood coagulation Factor IX results in impaired hemostasis and increased bleeding tendency. HEMGENIX is designed to deliver a copy of a gene

encoding the Padua variant of human coagulation Factor IX (hFIX-Padua) to patients with Hemophilia B to restore Factor IX activity.

This document summarizes the basis for regular approval of HEMGENIX. An ongoing Phase 3 clinical trial and a completed Phase 2b clinical trial provide the primary evidence of safety and effectiveness for the treatment of adult patients with Hemophilia B. Our recommendation for approval is based on the reduction in annualized bleeding rate (ABR) and an increase in Factor IX activity, demonstrated in the ongoing Phase 3 clinical trial. The more serious risks of HEMGENIX include infusion reactions and hepatotoxicity (elevation of liver enzymes (e.g., alanine aminotransferase [ALT], aspartate aminotransferase [AST]).

The applicant has provided substantial evidence of effectiveness and safety based on a single adequate and well controlled clinical investigation providing compelling evidence of clinical benefit, supported by the initial clinical investigation and preclinical studies. The review team recommends regular approval of this BLA with the Clinical Postmarketing Requirements (PMRs), and Chemistry, Manufacturing, and Control (CMC) Postmarketing Commitments (PMCs) listed in Section 11.c of this document.

2. Background

Disease background
Hemophilia B is a recessive X-linked congenital bleeding disorder, caused by mutations in the factor IX (FIX) gene. It is the second most common coagulation factor deficiency. Most FIX deficiency occurs in males as expected for an X-linked disease, but females comprise 3% of affected persons. More than 50% of all patients with Hemophilia B have no known family history of the disease, and these are called sporadic cases. Deficiency or absence of FIX results in impaired hemostasis, prolonged bleeding, and rebleeding.

The severity of symptoms can vary and the severe forms of Hemophilia B become apparent early in life. About one-third of individuals with Hemophilia B have a severe disorder characterized by functional FIX levels that are less than 1% of normal, and have at least monthly bleeds, most frequently in joints without preceding trauma. Moderate and mild Hemophilia B, with 1 to 5% or 5 to <40% of normal FIX activity level, respectively, are each observed in about one-third of patients. Subjects with moderate Hemophilia B have bleeds associated with mild trauma, and their bleeding frequency is less often than severe subjects. Subjects with mild deficiency of FIX activity levels of ≥5-40% have prolonged bleeding with worse than mild trauma as well as with surgery, and since females are almost exclusively in this group, with menstruation.

A goal of modern Hemophilia management is to prevent spontaneous bleeds by supplying replacement factor that will maintain higher FIX activity levels, i.e., in the range of subjects with the moderate form of the disease. This approach is known as routine prophylaxis. This treatment option has limitations including regular intravenous (IV) injections and risk of infection. Periodic infusion resulting in variable FIX activity may result in breakthrough bleeding episodes.

The most serious complication of replacement therapy is inhibitor development. FIX inhibitors are allogenic antibodies to FIX that reduce or eliminate the activity of FIX.

Approximately 1−3% of patients with Hemophilia B develop inhibitors following exposure to FIX. Among patients with severe Hemophilia B the percentage has, however, been reported to be as high as 9%.

Product Description
HEMGENIX (etranacogene dezaparvovec-drlb) is a suspension of an adeno-associated virus (AAV) vector-based gene therapy for intravenous infusion. The active ingredient is a recombinant AAV vector, where the vector DNA genome is enclosed in a capsid that consists of (b) (4) serotype 5 AAV capsid proteins. The vector DNA lacks all AAV genes. The vector DNA contains a transgene encoding the Padua variant of human coagulation Factor IX (hFIX-Padua), under the control of a liver-specific promoter (LP1). The hFIX-Padua (R338L substitution) represents a naturally occurring gain-of-function variant that displays increased specific activity compared to wild-type hFIX.

The regulatory history of HEMGENIX is outlined in Table 1.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
1. Pre-IND meeting	December 12, 2013
2. IND submission	November 14, 2014
3. Orphan Drug designation granted	April 17, 2019
4. Breakthrough Therapy designation granted	January 25, 2017
5. Pre-BLA meeting	June 4, 2021
6. BLA 125772/0 submission	March 24, 2022
7. BLA filed	May 23, 2022
8. Mid-Cycle communication	July 15, 2022
9. Late-Cycle meeting	September 30, 2022
10. Action Due Date	November 22, 2022

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

The CMC review team concludes that the HEMGENIX manufacturing process and controls can yield a product with consistent quality attributes, and the CMC review team recommends approval.

Manufacturing Summary

Etranacogene dezaparvovec-drlb is produced using a (b) (4) requiring (b) (4) vectors that are used to (b) (4) The (b) (4) vectors serve to deliver the essential components (hFIX-Padua transgene, AAV rep and cap genes) to produce AAV5 containing the hFIX-Padua transgene (AAV5-hFIX-Padua) in the (b) (4) the AAV5-hFIX-Padua virus is (b) (4)

(b) (4)
excipients as the drug product (DP) and stored (b) (4)

The DP is manufactured by (b) (4)
The DP manufacturing process does not introduce any process-related impurities and does not include any manufacturing steps that further remove impurities. After sterile filtration, the DP is filled aseptically into vials and stored at +5°C ± 3°C.

The DP has a nominal concentration of 1 x 10^{13} genomic copies (gc)/mL. Each vial of DP contains an extractable volume of not less than 10 mL. DP formulation consists of 5% sucrose (w/v), 0.02% polysorbate-20, (b) (4) potassium chloride, (b) (4) potassium phosphate monobasic, (b) (4) sodium chloride, and (b) (4) sodium phosphate (b) (4) . The DP is sterile and contains no preservative. The secondary packaging is a carton that contains 10-48 vials (depending on the weight of the patient). The carton is shipped at +5°C ± 3°C, and after receipt the carton is stored refrigerated and protected from light until the time of dilution and administration.

Manufacturing Control strategy

Manufacturing process consistency is controlled by (b) (4) . The manufacturer accepts (b) (4) based on specified (b) (4) The control strategy includes testing of the (b) (4), DP, and in-process materials for microbial (b) (4), identity, purity, strength, and potency. (b) (4) DP quality are controlled and characterized by several release tests (see Table 2). These tests include (b) (4) In addition, the applicant committed to add a (b) (4) potency control that measures the amount of (b) (4) This assay will be developed as a post-marketing commitment and submitted as a supplement.

Process Validation
(b) (4) cells.
Process validation for the DP manufacturing process was conducted by manufacturing (b) (4) PPQ DP lots at commercial scale, at uniQure, Inc (Lexington, MA). The data demonstrate that the thawing, filtration, mixing, filling, and storage steps of the manufacturing process are controlled effectively to produce DP that consistently meets the established product quality acceptance criteria. Additional validation studies,

including aseptic process simulation and shipping validation studies, were also performed.

Impurity profile
Impurities can be classified into product-related and process-related impurities. Product-related impurities include (b) (4) Process-related impurities may include (b) (4) and reagents used for product manufacturing that are not intended to be present in the final product. Most process-related impurities are removed; however, (b) (4), and (b) (4) from the (b) (4) The levels of these DNA impurities are controlled by lot release specifications. The typical level of cellular DNA in the (b) (4) is approximately (b) (4) of the total vector DNA, and the typical level of (b) (4) DNA is approximately (b) (4).

Manufacturing Risks
The risk of product contamination with other adventitious agents is minimized by ensuring adequate control of raw materials, especially those of biological origin that are used in the generation of cell banks, viral banks, and DP manufacturing; testing of the cell banks, viral banks, cells at limit of age, and unprocessed bulk harvest for adventitious agents; and demonstration of robust viral clearance by the (b) (4) process.

Stability
The DP is stable for 24 months when stored at +5°C ± 3°C. The DS is stable for (b) (4) when stored at (b) (4). Prior to administration, the DP is diluted with 0.9% normal saline solution in infusion bags. Once diluted, the DP in the infusion bag protected from light is stable for up to 24 hours at room temperature (15°C to 25°C).

Comparability

Throughout clinical trials the manufacturing process was optimized and (b) (4). The current manufacturing process produces the DP with critical quality attributes that are comparable to those of clinical lots used in phase 3 studies.

b. Testing Specifications

The analytical methods and their validations and/or qualifications for the HEMGENIX DS and DP were found to be adequate for their intended purpose. The final lot release specifications for the DP are shown in the table below.

Table 2. Drug Product Specifications

Attribute	Method	Acceptance Criteria
General Tests		
Appearance - Color - Clarity - Visible Particulates	- (b) (4)	- Colorless liquid - < Reference Suspension IV - Essentially free of visible particulates
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Sucrose Concentration	(b) (4)	(b) (4)
Polysorbate-20 Concentration	(b) (4)	(b) (4)
(b) (4)	(b) (4) (b) (4)	(b) (4)
	(b) (4)	(b) (4)
Extractable Volume	(b) (4) .	(b) (4)
Safety		
Sterility	(b) (4)	No growth
Bacterial Endotoxins	(b) (4)	(b) (4)
Identity		
Vector DNA Identity	(b) (4)	Confirmed
Content		
Genome Copies Concentration	(b) (4)	(b) (4)
Total Particle (tp) Concentration	(b) (4)	(b) (4)
Biological Activity		
Potency	(b) (4)	(b) (4)
Infectivity: (b) (4)	(b) (4)	(b) (4)
Purity		
(b) (4)	(b) (4)	(b) (4)
(b) (4) Purity	(b) (4)	(b) (4)

CSL Behring has provided a written commitment to validate and implement a suitable method for (b) (4) for (b) (4) ,

and (b) (4) assay for DP release testing, and to complete the (b) (4) validation for assays for (b) (4) CSL Behring also committed to re-evaluate the acceptance criteria for release testing after manufacturing (b) (4) DS and (b) (4) DP commercial batches. CSL Behring has also committed to perform long-term leachables study of the intended DP (b) (4) container closures at the intended storage conditions. (See Section 11.c for CMC PMCs).

c. CBER Lot Release

The lot release protocol template for HEMGENIX was submitted to CBER for review and found to be acceptable after revisions. A Laboratory Quality Product Testing Plan was developed by CBER and will be used for routine lot release.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be sufficient and acceptable. The activities and inspectional histories for facilities involved in the manufacture of etranacogene dezaparvovec-drlb are summarized in the table below.

Table 3. Manufacturing Facilities Table for HEMGENIX (etranacogene dezaparvovec-drlb)

Name/Address	FEI Number	DUNS number	Inspection/ waiver	Justification/ Results
uniQure, Inc. 113 Hartwell Avenue Lexington, MA 02421, USA *Drug Substance and Drug Product manufacturing, Drug Product release testing (except sterility)*	3011357564	052841733	Pre-License Inspection	CBER August 15-19, 2022 VAI
CSL Behring (b) (4) *Drug Product labeling and packaging*	(b) (4)	(b) (4)	Waived	ORA (b) (4) VAI
(b) (4) *Drug Product release testing (sterility)*	(b) (4)	(b) (4)	Waived	ORA (b) (4) VAI

CBER conducted a pre-license inspection at the uniQure, Inc. facility in August 2022 and an FDA Form 483 was issued. All 483 issues were resolved, and the inspection was classified as voluntary action indicated (VAI).

Office of Regulatory Affairs (ORA) performed a surveillance inspection of CSL Behring (b) (4) . All 483 issues were resolved, and the inspection was classified as VAI.

ORA performed a surveillance inspection of (b) (4) . All 483 issues were resolved, and the inspection was classified as VAI.

e. Container/Closure System

The primary container closure system for HEMGENIX (etranacogene dezaparvovec-drlb) is a 10 mL single-dose filled in a 10 mL (b) (4) clear glass vial with a 20 mm opening (Afton Scientific), stoppered with a (b) (4) ready-to-use (b) (4) serum stopper, (b) (4) gray chlorobutyl rubber base with (b) (4) and sealed with an aluminum flip-off cap. The container closure integrity testing (CCIT) was performed by (b) (4) using the (b) (4) method and testing results were acceptable. An additional CCIT using a more sensitive (b) (4) analysis was implemented. This testing is performed by (b) (4) and results indicate that the primary container closure is able to maintain the integrity under normal use, storage, and transportation conditions.

f. Environmental Assessment

The applicant submitted an environmental assessment (EA) pursuant to 21 CFR part 25.20(l). The EA provided an assessment of HEMGENIX environmental exposure based on known biology of parental virus (adeno-associated virus serotype 5; AAV5), genetic modifications made to the vector, data from biodistribution and shedding studies, lot release testing, and related nonclinical studies, and a worst-case assumption in each case. The Agency determined that approval of HEMGENIX will not result in any significant environmental impact. A Finding of No Significant Impact memorandum has been prepared.

4. Nonclinical Pharmacology/Toxicology

The early nonclinical development program evaluated a predecessor of HEMGENIX (AMT-060) expressing the wild-type codon-optimized human Factor IX (hFIXco). At 4 weeks following intravenous (IV) administration of $5x10^{11}$ to $2.3x10^{14}$ gc/kg of AMT-060 in the *B6.129P2-F9^{tm1Dws}* mouse model of Hemophilia B, dose-dependent increases in vector transduction in the liver, plasma hFIX protein levels, and plasma hFIX activity were observed.

Intravenous administration of HEMGENIX in healthy male mice at dose levels ranging from $5x10^{10}$ to $5x10^{13}$ gc/kg, resulted in dose-dependent increases in plasma hFIX protein expression. Higher levels of mean plasma hFIX enzymatic and clotting activity were observed compared to mice administered the HEMGENIX predecessor. One out of 10 healthy mice administered 5×10^{13} gc/kg of the HEMGENIX predecessor or HEMIGENIX developed pulmonary thrombi at 13 weeks post-dose. This dose level is

2.5-fold higher than the recommended dose level for HEMGENIX. The identified no-observed-adverse-effect-level was $5x10^{13}$ gc/kg.

Intravenous administration of HEMGENIX in male nonhuman primates (NHPs) at dose levels ranging from $5x10^{12}$ to $9x10^{13}$ gc/kg, was well tolerated and resulted in dose-dependent transgene expression in the liver and increased mean plasma FIX enzymatic and clotting activity compared to concurrent controls. Findings in animals dosed at $9x10^{13}$ gc/kg included prolonged prothrombin time, decreased activated partial thromboplastin time, and decreased heart rates; however, these changes were not statistically significant, and no adverse effects were observed. This dose level is 4.5-fold higher than the recommended dose level for HEMGENIX. By 13 weeks post-dose, anti-hFIX antibodies developed in 5 out of 12 NHPs dosed with HEMGENIX, which correlated with a decline in plasma hFIX protein levels and decreased FIX clotting activity. The identified no-observed-adverse-effect-level was $9x10^{13}$ gc/kg.

The biodistribution of HEMGENIX was evaluated in mice and NHPs. At 13 weeks following IV administration of $5x10^{13}$ gc/kg HEMGENIX in mice, the highest vector DNA concentration was detected in the liver, followed by the adrenal glands, heart, kidney, and spleen. Mean plasma vector DNA levels were highest in the mice on Day 1 post-dose followed by decreasing vector levels for the remainder of the study. At 26 weeks following IV administration of $5x10^{12}$ to $9x10^{13}$ gc/kg HEMGENIX in NHPs, high levels of vector DNA were detected in a dose-dependent manner in the liver. Vector DNA was also identified in the adrenal glands and spinal cord, followed by limited vector presence in various tissue types. At 26 weeks post-dose, vector DNA was detected in the testis, epididymis, and seminal vesicles at all dose levels.

The risk of germline transmission of the HEMGENIX predecessor was evaluated in healthy male mice administered $2.3x10^{14}$ gc/kg and mated with healthy naïve female mice on Day 6 post-dose. High levels of vector DNA were detected in the male reproductive tissues (epididymis, seminal vesicles, and testes) and sperm at 20 days post-dose. However, there were no adverse effects on mating rates or fertility indices. In addition, vector DNA was not detected in female reproductive tissues following mating. There were no adverse effects on pregnancy performance parameters or fetal weights.

Integration site analysis was performed on host genomic DNA isolated from liver tissue collected at 180 days (healthy mice) and 26 weeks (NHPs) following IV administration of the HEMGENIX predecessor. For both species, the majority of the identified vector DNA sequences represented episomal forms that were not integrated into the host DNA. A low level of integrated vector DNA was distributed throughout the host genome with no predilection to specific integration sites, including in genes associated with malignant transformation in humans.

Studies to evaluate the carcinogenicity/tumorigenicity of HEMGENIX were not conducted. These studies are not warranted based on the nonclinical safety profile.

5. Clinical Pharmacology

The clinical pharmacology of HEMGENIX is supported by two clinical studies employing the Padua variant of a codon-optimized human Factor IX gene (Study CT-AMT-061-01

and Study CT-AMT-061-02). The supporting clinical data from the predecessor product that used a similar vector (AAV5) as HEMGENIX was used to inform dosing for later clinical studies, and assessments of vector viral kinetics.

Viral Vector DNA Biodistribution and Shedding

Vector DNA in biological matrices was measured using a (b) (4) assay with limit of detection (LOD) of (b) (4). The vector DNA kinetic profile in blood exhibited a rapid distribution phase followed by slow elimination and a higher inter-individual variability.

Following administration of the HEMGENIX predecessor at doses of 5×10^{12} (N = 5) and 2×10^{13} gc/kg (N = 5) in a clinical study, the pharmacokinetics of vector DNA in blood and viral shedding in saliva, nasal secretions, semen, urine, and feces were characterized. Clearance of vector DNA was confirmed by 3 subsequent measurements below limit of detection (LOD), achieved in all subjects at both dose levels from all the matrices except for semen, where clearance was achieved in 9/10 subjects. One subject was unable to produce semen due to a historical medical condition and, therefore, shedding from semen could not be assessed. The maximum time to clearance of vector DNA was 22 weeks for urine, 26 weeks for saliva and nasal secretions, 40 weeks for feces, 52 weeks for semen, and 159 weeks for blood.

Subsequently, the pharmacokinetics of vector DNA in blood, and viral shedding in semen following HEMGENIX administration was characterized in 2 clinical studies. In the initial clinical study, Study CT-AMT-061-01 (N = 3), clearance of vector DNA from semen and blood (i.e., confirmed with 3 subsequent measurements below LOD of vector DNA) was achieved in 2/3 subjects, and in all subjects, respectively, after 3 years post-administration. One subject did not return the required number of semen samples to assess the shedding status as per the definition of 3 subsequent measurements below LOD of vector DNA.

In the clinical efficacy study, Study CT-AMT-061-02 (N = 54), a total of 56% (30/54) of subjects achieved absence of vector DNA from blood and 69% (37/54) from semen by Month 24. Several subjects did not return the required number of blood and semen samples to assess the shedding status as per the definition of 3 subsequent measurements below the LOD of vector DNA. Considering results obtained from 2 available consecutive samples below the LOD, a total of 40/54 (74%) and 47/54 (87%) subjects were identified to have reached absence of vector DNA from blood and semen, respectively, at 24 months post-administration.

FIX Activity and Protein Expression

Single intravenous infusion of HEMGENIX resulted in cell transduction and increase in circulating Factor IX activity in patients with Hemophilia B. The one-stage activated partial thromboplastin time (aPTT-based) assay was used as a primary assay for pharmacodynamic assessment of FIX protein expression and FIX activity. FIX activity values that were measured more than 5 half-lives after the most recent FIX-replacement administration are used to support the efficacy evaluation and referred to as “uncontaminated FIX levels”. The FIX activity measured by chromogenic assay was

consistently resulted in lower values with the mean of chromogenic assay to one-stage FIX activity ratio ranging from 0.4 to 0.6 across all the clinical studies.

In Study CT-AMT-061-01, at Week 52 following AMT-061 administration, the mean uncontaminated FIX activity level was 41 ± 9 % of normal measured by the one-stage assay and all three subjects achieved a FIX activity > 30%. The FIX protein expression was detected within one week following administration of AMT-061.

In Study CT-AMT-061-02, at 6 months post-AMT-061 treatment, the mean FIX activity was 39 ± 19% (range: 8 to 97%). The FIX activity was maintained through Month 12, with a mean FIX activity of 41 ± 22% (range: 6 to 113%). At Month 18, the mean FIX activity was 37 ± 21% (range: 4 to 123%). The time to onset of FIX protein expression occurred at Week 3 as evaluated by first uncontaminated measurement. FIX protein levels during the post-treatment period followed a similar trend as FIX activity by one-stage (aPTT-based) activity; however, more variability was observed in the protein concentrations.

Effect of Intrinsic and Extrinsic Factors on FIX Activity

Although limited sample size and confounding factors preclude definitive conclusions, the following are major summary of the effects of intrinsic and extrinsic factors on FIX activity:

- A trend of higher mean FIX activity was observed with increased age. The mean FIX activity levels were 1.5 to 2-fold lower in the < 40 years subgroup compared to ≥ 60 years of age at the evaluated time points. It should be noted that all treated subjects were adults (41± 16 years of age).
- The FIX activity increased by 32 % in overweight (BMI 25-29, n=29 subjects) and by 49 % in obese (BMI ≥ 30, n=10 subjects) as compared to normal BMI (<25, n=11 subjects).
- Subjects with mild renal impairment (N = 7/53) had higher mean FIX activity (up to 37% higher) compared to those with normal renal function during Month 6 to 18 post-dose period. However, confounding factors such as age and BMI should be considered in interpreting the effects of mild renal impairment. For example, 5 out of 7 subjects with mild renal impairment are ≥ 60 years of age and 6 out of 7 subjects have BMI ≥ 25 kg/m^2.
- A trend for lower FIX activity with liver impairment (about 31% lower FIX activity) was observed.
- Based on the applicant analysis, subjects with ALT elevation (13 out of 53; 24%) had approximately 44% lower mean FIX activity at Month 18 compared to those that did not have ALT elevation.
- The 9/53 subjects (17%) that were treated with corticosteroid for ALT elevations exhibited approximately 63% lower mean FIX activity at Month 18 compared to those who did not receive corticosteroid coadministration.

Immunogenicity Assessments

A (b) (4) neutralization clinical trial assay with limit of detection (LOD) of 1:7 titer was used for detection of anti-AAV5 neutralizing antibodies (NAbs) for both Studies

CT-MT-061- 01 and CT-MT-061- 02. Based on this clinical trial assay, the following is a summary of the NAbs:

- In Study CT-MT-061- 01, all 3 subjects had anti-AAV5 NAbs before dosing. However, the NAb titer level was below 50 and all three subjects achieved FIX activity >30%.
- In Study CT-MT-061- 02, 38.9 % (21/54 subjects) had anti-AAV5 NAbs before dosing with a median titer of 1:57 (range: 1:9 to 1:3,212).
- After HEMGENIX administration, all subjects in both studies developed detectable anti-AAV5 NAbs within 2-3 weeks.
- The mean uncontaminated FIX activity at Month 12 was 42 ± 22 % in subjects with NAbs titer ≤ 1:100 (n=45) and FIX activity was 36 ± 17% in subjects with NAbs titer >1:100 to < 1:700 (n=5). The mean FIX activity at Month 12 was 42 ± 22% in subjects with NAb titers ≤ 1:350 (n=47) and 27 ± 17% in subjects with NAb titers >1:350 to <1:700 (n=3). It should be noted that only one subject had a titer > 700 and the uncontaminated FIX activity for this subject was 1.5%.

Overall, limited data (n=5) are available with a target threshold > 1:350 NAb of which uncontaminated FIX activity data was analyzed from only three subjects. The Month 12 uncontaminated FIX activity was lower by 36% in subjects with NAb titers >1:350. However, the anti-AAV NAb titer assay used in these studies is not validated; therefore, the results should be interpreted with caution.

6. Clinical/Statistical

The clinical review team's recommendation for regular approval of HEMGENIX for the treatment of Hemophilia B who currently use FIX prophylaxis therapy, or have current or historical life-threatening hemorrhage, or repeated serious spontaneous bleeding episodes is based on 2 clinical studies, Study CT-AMT-061-01 (Safety) and Study CT-AMT-061-02 (Safety and Efficacy).

a. Clinical Program

Study CT-AMT-061-01 was a Phase 2b, open-label, single-dose, single-arm, multi-center trial to confirm the factor IX activity level of the serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5-hFIXco-Padua, AMT-061) administered to adult subjects with severe or moderately severe Hemophilia B.

Study CT-AMT-061-02 was a Phase 3, open-label, single-dose, multi-center, multinational trial investigating a serotype 5 adeno-associated viral vector containing the Padua variant of a codon optimized human Factor IX gene (AMT-061) administered to adult subjects with severe or moderately severe Hemophilia B. Subjects completed a lead-in period of at least six months receiving FIX prophylaxis therapy. These 54 subjects received a single dose of AMT-061 and were followed for up to 18 months after treatment.

Efficacy was based on annualized bleeding rate (ABR) during Months 7-18 after treatment with AMT-061 compared with the ABR during the lead-in period. The mean ABR during Months 7-18 was 1.9 bleeds/year with a 95% confidence interval (95% CI) of

(1.0, 3.4), compared with a mean ABR of 4.1 [95% CI: 3.2, 5.4] during the lead-in period. The ABR ratio (Months 7 to 18 post-treatment / lead-in) was 0.46 [95% CI: 0.26, 0.81], demonstrating non-inferiority of ABR during Months 7 to 18 compared to the lead-in period. The mean Factor IX activity levels over time, as measured by one-stage [activated Partial Thromboplastin Time (aPTT)-based] assay were 39% (± 19), 42% (± 22), 37% (± 21) and 37% (± 19) of normal, respectively, at 6, 12, 18, and 24 months.

In AAV-vector based gene therapies, preexisting neutralizing anti-AAV antibodies may impede transgene expression at desired therapeutic levels. In the clinical studies with HEMGENIX, an unvalidated clinical trial assay was used to assess preexisting neutralizing anti-AAV5 antibodies. These titers were measured at baseline prior to infusion of the gene therapy product. There were 21 subjects with a positive neutralizing antibody (NAb) to AAV5. These NAb titers were in the range of 1:8.5-3212. Twenty of the subjects had titer values up to 700 (Range 8.5-678). The subject with the highest titer of 1:3212 had no human FIX expression and was not able to discontinue routine prophylaxis after HEMGENIX treatment due to bleeding events. As the clinical trial assay was not validated and the data are limited, no conclusion can be reached regarding correlation between positive NAb titers and efficacy. However, as there was one subject with very high NAb titers who had significant bleeding post-treatment, a safety PMR study will be required to assess the association between serious risk of bleeding due to failure of expected pharmacological action of HEMGENIX and pre-existing high anti-AAV 5 NAb titers.

The basis of FDA's conclusion of substantial evidence of effectiveness comes from a single adequate and well controlled trial with highly persuasive results on the benefit of ABR at Months 7-18 post-treatment compared to baseline ABRs. Therefore, the evidence supports regular approval for HEMGENIX.

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

Bioresearch Monitoring (BIMO) inspections were issued for one foreign and four domestic clinical study sites that participated in the conduct of Study CT-AMT-061-02: A Phase III, open-label, single-dose, multi-center multinational trial investigating a serotype 5 adeno-associated viral vector containing the Padua variant of a codon-optimized human factor IX gene (AAV5-hFIXco- Padua, AMT-061) administered to adult subjects with severe or moderately severe Hemophilia B. The inspections did not reveal significant issues impacting the data submitted in support of this application.

c. Pediatrics

This application is exempt from Pediatric Research Equity Act (PREA) because it is intended for a biologic product for which orphan designation has been granted. This product is not indicated in pediatric subjects.

d. Other Special Populations

The efficacy of HEMGENIX has not been studied in any special populations.

7. Safety and Pharmacovigilance

Safety

The safety population consists of 57 subjects who received HEMGENIX, to include 3 subjects treated in Study CT-AMT-061-01, a Phase 2b trial and 54 subjects treated in the Phase 3 trial, CT-AMT-061-02. In the Phase 3 trial, 53 subjects received the planned dose of HEMGENIX and 1 subject received a partial (10%) dose of HEMGENIX due to a hypersensitivity reaction.

A total of 613 treatment-emergent adverse events (TEAEs) were reported. Most subjects reported mild or moderate TEAEs. Of subjects reporting TEAEs, 39 (68%) experienced at least 1 treatment-related event. Eleven (19%) subjects experienced at least 1 TEAE which was rated severe. Fifteen (2%) subjects experienced serious TEAEs (serious adverse events [SAEs]). No treatment-related SAEs were reported in either study. FDA agreed with the applicant that none of the SAEs were attributed to treatment.

The most common adverse reactions (incidence ≥5%) were elevated ALT/AST, headache, blood creatine kinase elevations, flu-like symptoms, infusion-related reactions, malaise and fatigue.

Individual infusion reactions occurred in 7 subjects during the infusion and in 12 subjects after the infusion. Symptoms were comprised of dizziness, flu-like symptoms, abdominal pain, infusion site reaction, chills and headaches. All symptoms resolved without sequelae. Two subjects had hypersensitivity reactions shortly after HEMGENIX infusion, and one of these subjects received epinephrine.

Five subjects had ALT elevations >2-3x ULN (range = 89 IU/L – 130 IU/L), one subject had an ALT elevation > 3-5x ULN (193 IU/L) and one subject had an ALT elevation > 5x ULN (275 IU/L). The ALT elevation >5x ULN occurred 3 weeks after HEMGENIX administration.

Five subjects had AST elevations > 2-3x ULN (range = 71 IU/L – 118 IU/L), three subjects had AST elevations > 3-5x ULN (range = 127 IU/L – 163 IU/L) and one subject had an AST elevation > 5x ULN (327 IU/L). The AST elevation > 5x ULN occurred 11 months post-HEMGENIX administration.

Nineteen of the 24 subjects with ALT elevations also had related AST elevations.

Nine subjects with ALT elevations received a tapered course of corticosteroids. The mean duration of corticosteroid treatment for elevated ALT was 81 days. There were no SAEs caused by prolonged corticosteroid use. There were no adverse events of thrombosis. Twenty-one subjects had elevated transaminase levels and were not treated with corticosteroids.

There was no clear difference in AEs between subjects who had positive anti-AAV5 NAb titers and negative anti-AAV5 NAb titers at Baseline, with the exception of one subject with Baseline NAb titers of 1:3212 who had no transgene expression and experienced increased bleeds post-treatment.

There was one subject who developed hepatocellular carcinoma (HCC) and underwent tumor resection on Study Day 443. The HCC was investigated thoroughly and the relationship to AAV was not proven, particularly as the integration site analysis did not indicate a dominant integration site, as would be expected if there were AAV vector integration that led to clonal expansion of the tumor cells. The HCC was not likely related to vector integration, and was more likely a result of pre-existing risk factors to include Hepatitis B, Hepatitis C, and alcoholic liver. However, as HEMGENIX targets transgene expression in the liver, there may be a potential risk of HCC. The PI notes potential risks of hepatotoxicity and HCC.

Pharmacovigilance

Anti-AAV5 neutralizing antibodies (NAb) may decrease or prevent expression of the FIX-transduced gene product. There were 24 (45.6%) of 57 subjects who were positive for anti-AAV5 NAb at Baseline. One of the subjects had a titer over 1:700 and that subject did not express Factor IX following HEMGENIX treatment. Exogenous Factor IX prophylaxis was restarted for bleeding episodes in that high-titer patient. As discussed earlier, there are limitations in interpretability of the results of the clinical trial assay; however, there was no consistent, clear association between anti-AAV5 NAbs and ABR or safety. Nonetheless, there is uncertainty regarding potential risk of increased bleeding due to high anti-AAV5 NAb titers based on observations from a single subject.

(HEMGENIX has not been previously approved or used outside of the clinical trials, so there are no prior marketed safety data.)

The Sponsor will conduct routine pharmacovigilance in accordance with 21 CFR 600.80 and enhanced pharmacovigilance with follow-up questionnaires for liver toxicity, liver malignancy, and thromboembolic events.

In addition to routine and enhanced pharmacovigilance, the postmarketing safety monitoring of HEMGENIX will include two safety-related postmarketing requirement (PMR) studies under 505 (o) of the Federal Food, Drug, and Cosmetic Act (FDCA) to assess the unexpected serious risk of bleeding due to failure of expected pharmacological action of HEMGENIX in the presence of pre-existing anti-AAV5 neutralizing antibodies:

- PMR#1: To validate a sensitive and accurate assay for the detection of anti-AAV5 neutralizing antibodies, specifically to detect anti-AAV5 NAb titers up to 1:1400 or higher.
- PMR#2: A postmarketing study to assess the association between the serious risk of bleeding related to the failure of expected pharmacological action of HEMGENIX and pre-existing anti-AAV5 NAb to the AAV5 capsid of HEMGENIX with a validated assay (required in PMR 1). The study will evaluate at least 35 Hemophilia B patients treated with HEMGENIX, to include at least 10 patients with high (1:1400 or higher) pre-treatment anti-AAV5 NAb titers.

Additionally, a prospective, observational postmarketing study in 250 Hemophilia B patients treated with HEMGENIX, will be conducted as a voluntary sponsor study, to collect long-term safety data; the enrolled patients will be followed for 15 years after product administration.

Please refer to Section 11c regarding Post-Marketing Requirements and Post-Marketing Commitments for additional details and study milestone dates.

8. Labeling

The proposed proprietary name, HEMGENIX, was reviewed by the Advertising and Promotional Labeling Branch (APLB) on May 26, 2022 and was found acceptable. CBER communicated the acceptability of the proprietary name to the applicant on June 15, 2022. The proper name suffix, -drlb, was designated on October 31, 2022, making (etranacogene dezaparvovec - drlb) the proper name.

APLB reviewed the proposed prescribing information and package and container labels on October 24, 2022 and found them acceptable from a promotional and comprehension perspective.

9. Advisory Committee Meeting

No advisory committee meeting was held because initial review of information submitted in the BLA did not raise concerns or controversial issues that would have benefited from an advisory committee discussion.

10. Other Relevant Regulatory Issues

HEMGENIX has received Orphan and Breakthrough Designation, and this submission was reviewed under priority review.

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

The Applicant has provided substantial evidence of effectiveness based on a single adequate and well controlled clinical trial with supportive evidence from the initial clinical investigation and preclinical studies. The compelling evidence of treatment effect in the single adequate and well controlled trial is based on a highly persuasive clinically meaningful benefit in Annualized Bleed Rates in a sufficient number of subjects using the subjects' own ABRs 6-months prior to HEMGENIX administration as the control.

The Applicant has met the statutory requirements for regulatory approval and the review team recommends regular approval of HEMGENIX, an adeno-associated virus vector-based gene therapy indicated for the treatment of adults with Hemophilia B (congenital Factor IX deficiency) who:

- Currently use Factor IX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated, serious spontaneous bleeding episodes.

b. Benefit/Risk Assessment

HEMGENIX has demonstrated efficacy with reduction in ABRs. The mean ABR during Months 7-18 was 1.9 bleeds/year with a 95% confidence interval (95% CI) of (1.0, 3.4), compared with a mean ABR of 4.1 [95% CI: 3.2, 5.4] during the lead-in period.

The most common adverse events included elevations in ALT/AST, infusion reactions, malaise and fatigue. There is a concern related to increased risk of bleeding in patients with pre-existing anti-AAV 5 NAbs based on data from a single subject with very high NAb titers. This risk will be evaluated in a safety PMR study using a validated assay (see Section 11c). There is a potential for hepatocellular carcinoma, which is adequately described in the label, and will be evaluated in the 15-year long-term extension study. The safety profile is acceptable.

Thus, considering the magnitude of the effect on bleeding events, and the fact that the risks are generally mild, infrequent, and/or easily mitigated, the overall benefit-risk profile favors approval of HEMGENIX in patients with Hemophilia B who:

- Currently use Factor IX prophylaxis therapy, or
- Have current or historical life-threatening hemorrhage, or
- Have repeated, serious spontaneous bleeding episodes.

c. Recommendation for Postmarketing Activities

The sponsor will conduct routine and enhanced pharmacovigilance activities as outlined in the Pharmacovigilance Plan, version 2, and two safety-related PMRs under section 505(o) of the FDCA, to assess the unexpected serious risk of bleeding due to failure of expected pharmacological action of HEMGENIX in the presence of pre-existing anti-AAV5 neutralizing antibodies (PMRs listed below). The sponsor is also planning a voluntary, 15-year observational study and a long-term clinical extension study. The review team determined that a Risk Evaluation and Mitigation Strategy (REMS) is not required for this product.

The Applicant agreed to the following safety PMRs:

1. To validate a sensitive and accurate assay for the detection of anti-AAV5 neutralizing antibodies (NAb), specifically to detect anti-AAV5 NAb titers up to 1:1400 or higher.

   Assay and methodology for reportable titers up to 1:1100
   Study Report Submission: February 10, 2023

   Assay and methodology for reportable titers ≥ 1:1100 including above 1:1400
   Final Study Report Submission: May 31, 2023

2. A post-marketing study to assess the association between the serious risk of bleeding related to the failure of expected pharmacological action of HEMGENIX and pre-existing anti-AAV5 NAb to the AAV5 capsid of HEMGENIX with a validated assay (required in PMR 1). The study will evaluate at least 35 Hemophilia B patients treated with HEMGENIX, to include at least 10 patients with high (1:1400 or higher) pre-treatment anti-AAV5 NAb titers. The assessment will compare pre- and post-treatment annualized bleeding rates (ABRs), with a lead-in period to establish the

patients' baseline ABR on routine treatment and 18-month follow up after HEMGENIX administration.

Final Protocol Submission: Feb. 10, 2023
Study Completion: Dec. 31, 2028
Final Report Submission: May 31, 2029

The Applicant agreed to the following CMC PMCs:

3. CSL Behring commits to validate a suitable method for release testing of etranacogene dezaparvovec-drlb drug product for (b) (4) . A final assay validation report will be submitted in conjunction with the introduction of release testing with appropriate acceptance criteria as a "PMC Submission – Final Study Report."

   Final report submission: December 31, 2023

4. CSL Behring commits to validate (b) (4) for release testing of etranacogene dezaparvovec-drlb drug product for (b) (4) . A final assay validation report will be submitted in conjunction with the introduction of release testing with appropriate acceptance criteria as a "PMC Submission – Final Study Report."

   Final report submission: December 31, 2023

5. CSL Behring commits to include (b) (4) assay for release testing of etranacogene dezaparvovec-drlb drug product. A final assay validation report will be submitted in conjunction with the introduction of release testing with appropriate acceptance criteria as a "PMC Submission – Final Study Report."

   Final report submission: July 30, 2023

6. CSL Behring commits to perform a long-term leachables study of the intended drug product (b) (4) container closures at the intended storage conditions. A final leachables report will be submitted as a "PMC Submission – Final Study Report."

   Final report submission: April 30, 2024

7. CSL Behring commits to complete (b) (4) validation for (b) (4) assays. A final report will be submitted as a "PMC Submission – Final Study Report."

   Final report submission: December 31, 2022

8. CSL Behring commits to re-evaluate the acceptance criteria for release testing of etranacogene dezaparvovec-drlb drug substance and drug product based on manufacturing experience when additional data from (b) (4) drug substance and (b) (4) drug

product commercial batches are available and revise if appropriate. A final acceptance criteria report after re-assessment will be submitted as a “PMC Submission – Final Study Report.”

Final report submission: June 30, 2024