

CBER CMC BLA Review Memorandum

BLA STN 125772

**etranacogene dezaparvovec-drlb
HEMGENIX**

Reviewers

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1. BLA#: STN 125772

2. APPLICANT NAME AND LICENSE NUMBER

CSL Behring, License # 1765

3. PRODUCT NAME/PRODUCT TYPE

Non-Proprietary/Proper/USAN: etranacogene dezaparvovec-drlb
 Proprietary Name: HEMGENIX
 Company codename: AMT-061, CSL222
 UNII Code: Z5XCD5Q9RL
 NDC Code (vial): 00053-0099-10

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

Pharmacological category: Adeno-associated virus vector-based gene therapy
Dosage form: Suspension for injection
Strength/Potency: 1×10^{13} genomic copies (gc)/mL
Route of administration: Intravenous infusion
Indication: For treatment of adults with moderately severe and severe Hemophilia B (congenital Factor IX deficiency)

5. MAJOR MILESTONES

Received: March 24, 2022
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PDUFA action due: November 22, 2022

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Anurag Sharma, PhD, OTAT/DCGT/GTB1	Control of materials, Impurities, Viral Clearance, Shedding, Environmental Assessment, Labeling, Reference standards
Emmanuel Adu-Gyamfi, PhD, OTAT/DCGT/GTB1	Manufacturing Process and Process Controls, Process Validation, Batch Analysis, Comparability
Ronit Mazor, PhD, OTAT/DCGT/GTIB	Analytical procedures, Validation of analytical procedures, Justification of Specification, Stability, Elucidation of Structure and Other Characterization, Clinical and Nonclinical bioanalytical assays
Massoud Motamed, PhD, OTAT/DCGT/GTB2	Container Closure System, Extractables and Leachables
Mikhail Ovanesov, PhD, OTAT/DPPT/HB	Validation of Potency Assay

7. INTER-CENTER CONSULTS REQUESTED: N/A

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
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03/24/20	125772/0	Original submission
5/5/2022	125772/4	Response to DMPQ/CMC IR dated 5/4/2022
5/12/2022	125772/7	Response to DMPQ/CMC IR dated 5/11/2022
5/17/2022	125772/8	Response to DMPQ/CMC IR dated 5/16/2022
6/7/2022	125772/11	Response to CMC filing letter comments dated 5/23/2022
6/21/2022	125772/13	Response to CMC IR dated 6/17/2022
7/1/2022	125772/16	Response to CMC IR dated 6/17/2022
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8/4/2022	125772/24	Response to CMC IR dated 7/14/2022
8/26/2022	125772/30	Response to CMC IRs dated 7/14/2022, 8/14/2022, & 8/16/2022
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9/19/2022	125772/41	Response to CMC IR dated 8/16/2022 & 9/14/2022
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11/1/2022	125772/57	Response to CMC IR dated 9/30/2022 & 10/28/2022
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11/7/2022	125772/61	Response to CMC IR dated 11/1/2022
11/9/2022	125772/65	Response to 11/7/2022 CMC PMCs
11/17/2022	125772/71	Response to 11/15/2022 CMC IR

9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

Submission type & #	Referenced Item	Holder	Letter of Cross-Reference	Comments/Status
DMF (b) (4)	(b) (4)	(b) (4)	Yes	No outstanding issues identified. Reviewed and assessed by Anurag Sharma in Section <u>3.2.S.2.3</u>
BB-MF (b) (4)	(b) (4)	(b) (4)	Yes	No outstanding issues identified. Pertinent information reviewed and assessed by Massoud Motamed in Section <u>3.2.P.2.4</u>
STN (b) (4)	(b) (4)	(b) (4)	Yes	No outstanding issues identified. Pertinent information reviewed and assessed by Massoud Motamed in Section <u>3.2.P.2.4</u>
IND (b) (4)	Entire IND	CSL Behring LLC (b) (4)	No; not required as the applicant is the holder of the IND	No outstanding issues
PMA (b) (4)	(b) (4)	(b) (4)	Yes	(b) (4)

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

Based on the review of the collective information submitted by the Applicant and subsequent information requests reviewed throughout the review period, the CMC review team concludes that the manufacturing and controls for etranacogene dezaparvovec (AMT-061; HEMGENIX) are capable of yielding the drug product with consistent quality attributes deemed acceptable for commercial manufacturing under the BLA.

Description of the product: Etranacogene dezaparvovec (AMT-061) is a suspension of an adeno-associated viral (AAV) vector-based gene therapy for intravenous infusion. The active ingredient is a recombinant AAV vector, where the DNA vector 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.

[illegible]

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, DP is filled aseptically into vials and stored at 2°C to 8°C.

The DP has a nominal concentration of 1×10^{13} genomic copies (gc)/mL. Each vial of DP contains an extractable volume of not less than 10 mL and excipients: 5% sucrose (w/v), 0.02% polysorbate-20, (b) (4) potassium chloride, (b) (4) potassium phosphate (b) (4), (b) (4) sodium chloride, (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 2°C to 8°C, and after receipt the carton is stored refrigerated protected from light until time of dilution and administration at the clinical site.

The manufacturer accepts raw materials based on specified quality attributes, including identity, concentration, and purity. Raw materials derived from animals and humans are appropriately controlled to ensure the absence of microbial contaminants.

The control strategy includes testing of the (b) (4), DP, and in-process materials for microbial contaminants, identity, purity, strength, and potency. Most process-related impurities are removed, however DNA impurities including the (b) (4)

The levels of these DNA impurities are controlled by lot release specifications. The typical level of cellular DNA in (b) (4) is approximately (b) (4) of the total vector DNA, and the typical level of (b) (4) is approximately (b) (4).

(b) (4) DP quality are controlled and characterized by several release tests. These tests include a quantitative assay that measures the concentration of (b) (4), an assay to measure vector infectivity, a potency assay that measures the ability of the DP to produce active FIX in a human hepatocyte cell line. 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.

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

Comparability: Throughout clinical trials the manufacturing process was optimized and scaled up. The current manufacturing process produces DP with critical quality attributes that are comparable to those of clinical lots used in phase 3 studies.

B. RECOMMENDATION

I. APPROVAL

This biological license application (BLA) provides an adequate description of the manufacturing process and characterization of the new drug product etranacogene dezaparvovec-drlb. The CMC review team has concluded that the manufacturing process, along with associated test methods and control measures, can yield a product with consistent quality characteristics. This information, along with post-marketing commitments (PMC) from CSL Behring, satisfies the CMC requirements for biological product licensure per the provisions of section 351(a) of the Public Health Service (PHS) Act controlling the manufacture and sale of biological products.

Post-Marketing Commitments (PMCs):

1. (b) (4)

CSL Behring commits to validate a suitable method for release testing of etranacogene dezaparvovec 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

2. (b) (4)

CSL Behring commits to validate (b) (4) for release testing of etranacogene dezaparovec 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

3. (b) (4)

CSL Behring commits to include (b) (4) assay for release testing of etranacogene dezaparovec 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

4. *Long-term leachables study*

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

5. (b) (4)

CSL Behring commits to complete robustness validation for (b) (4) assays. A final report will be submitted as a “PMC Submission – Final Study Report”. Final report submission: December 31, 2022

6. *Acceptance criteria*

CSL Behring commits to re-evaluate the acceptance criteria for release testing of etranacogene dezaparovec 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

II. **COMPLETE RESPONSE (CR)**

None

III. **SIGNATURE BLOCK**

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Steven Oh, Ph.D. Deputy Director DCGT/OTAT	Concur	
Heather Lombardi Director DCGT/OTAT	Concur	

Review of CTD

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Module 3

3.2.S DRUG SUBSTANCE¹

3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties (Reviewed by AS)

3.2.S.1.1 Nomenclature

Proper (non-proprietary) name: etranacogene dezaparvovec-drlb

Proprietary name: HEMGENIX

84 pages determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

3.2.P DRUG PRODUCT**3.2.P.1 Description and Composition of the Drug Product
(Reviewed by EAG)**

The AMT-061 drug product, also known by the proprietary name of HEMGENIX, is formulated at a nominal concentration of 1×10^{13} genome copies (gc)/mL in a single-use 10 mL glass vial in a sterile phosphate buffered saline (PBS) solution, (b) (4) containing 5% weight per volume (w/v) sucrose and polysorbate-20 (PS-20) 0.02% volume per volume (v/v). The nominal composition of DP is described under Table 26.

Table 26 Composition of the formulated AMT-061 drug product

Component	Nominal concentration	Quantity per mL	Quantity per vial ^a	Function	Quality standard
Etranacogene dezaparvovec	1×10^{13} gc/mL	1×10^{13} gc	1×10^{14} gc	Active ingredient	See Section 3.2.S.4.1
Polysorbate-20	0.02% v/v	0.22 mg	2.20 mg	(b) (4)	(b) (4)
Potassium chloride	(b) (4)	0.20 mg	2.00 mg	(b) (4)	(b) (4)
Potassium phosphate, (b) (4)	(b) (4)	0.20 mg	2.00 mg	(b) (4)	(b) (4)
Sodium chloride	(b) (4)	8.00 mg	80.00 mg	(b) (4)	(b) (4)

Sodium phosphate, (b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sucrose	5% w/v	50.00 mg	500.00 mg	(b) (4)	(b) (4)
(b) (4)					
a Each vial has a fill volume of 10.7 mL and extractable volume of ≥10.0 mL. The fill volume complies with excess volume recommendations for mobile and viscous liquids as per (b) (4) and per (b) (4)					

DP Container and Packaging

The filtered DP is vialled in a depyrogenated 10 mL (b) (4) glass vial stoppered with a 20 mm rubber stopper and sealed with an aluminum flip-off cap. Detailed assessment of DP container closure can be located at Section [3.2.P.7](#). The DP is packaged in kits containing 10 to 48 vials, each kit constituting a dosage unit based on the patient's body weight.

Diluent: The DP is intended for administration (as a single-dose intravenous infusion) after dilution in 0.9% compendial sodium chloride (saline). See section [3.2.P.2.6](#) for summary of compatibility studies and dose preparation.

Reviewer Comment:

- *Description of AMT-061 DP composition is acceptable.*

3.2.P.2 Pharmaceutical Development (Reviewed by AS)

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

The DP is formulated in a sterile phosphate buffered saline solution (PBS) containing sucrose (5% w/v) and polysorbate-20 (PS-20, 0.02% v/v), (b) (4). DP is prepared as a (b) (4) with a nominal viral genome concentration of 1×10^{13} gc/mL. The key physicochemical properties of the DS are described in Section [3.2.S.3.1](#).

3.2.P.2.1.2 Excipients

The excipients used in the DP are (b) (4). No additional excipients are added during the DP manufacture. The following excipients are used:

- Sodium chloride and potassium chloride are commonly used in PBS and are used as tonicity agents in the DP to regulate the DP (b) (4).
- Sucrose is added to the formulation at a concentration 5% w/v to act as a stabilizer.
- PS-20 (0.02% v/v) is included in the formulation to reduce the formation of visible and subvisible particles in the DP.
- (b) (4) is used as a (b) (4) to adjust the (b) (4)

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

The predecessor AMT-060, was formulated in (b) (4). Due to observation of (b) (4), surfactant PS-20 (optimized to concentration of 0.02% v/v) was included in the formulation to reduce formation of (b) (4) from phase 2b onwards. The DP formulation was

found to have satisfactory robustness at the recommended storage condition of 2-8°C. No further change was made, and the clinical and commercial formulations are same.

3.2.P.2.2.2 Overages

No overage is included for the DP.

3.2.P.2.2.3 Physicochemical and Biological Properties

DS and DP have the same formulation and same properties.

3.2.P.2.3 Manufacturing Process Development (Reviewed by EAG)

(b) (4)

3.2.P.2.4 Container Closure System (Reviewed by MM)

The DP container closure system is detailed in Table 27.

Table 27 Drug Product Container Closure

Component	Description	Supplier	Part #
10 mL Glass Vial	10 mL, ready-to-use, depyrogenated, (b) (4) class glass serum vial with 20 mm opening, 25 mm diameter × 54 mm height, complying with (b) (4).	(b) (4)	(b) (4)
Vial Stopper	20 mm ready-to-use serum stopper, gray (b) (4) rubber base with a (b) (4)	(b) (4)	(b) (4)

	(b) (4)		
Aluminum Seal	20 mm ready-to-use sterile aluminum cap with flip-off cap	(b) (4)	(b) (4)

Reviewer's Comment: The stopper is referenced to Master Files (b) (4) provided by (b) (4). This reference is acceptable.

Component Specifications

Vial

Vials are tested by the supplier and confirmed to be compliant with (b) (4), Glass Containers for Pharmaceutical Use, and (b) (4) Containers-Glass. The applicant assesses incoming vials for visual inspection and dimensional verification. Further, the applicant conducts tests representative samples from each lot of glass vials for sterility, particulate matter and endotoxin release testing at a contract laboratory.

Stopper

Stoppers are tested by the supplier and confirmed to be compliant with (b) (4) Rubber Closures, and the physicochemical tests described in (b) (4). Additionally, the supplier also tests for bacterial endotoxin, bioburden, and particulate matter. The applicant assesses incoming stoppers for visual inspection and dimensional verification. Further, the applicant conducts tests representative samples from each lot of stoppers for sterility, particulate matter, and endotoxin release testing at a contract laboratory.

Reviewer's Note: A Letter of Authorization for the stoppers, MF (b) (4), is provided. BLA (b) (4) also references MF and was found suitable. Communication with the reviewer (Rabia Ballica) indicates suitability for reference.

Seal

The seals do not undergo additional testing as part of the quality inspection and are released upon verification of the vendor's Quality Certificate. This includes testing for dimensional verification and sterility via a biological indicator.

Reviewer's Comment: The applicant was asked (IR dated July 14, 2022) to determine sterility and endotoxin levels. The applicant satisfactorily addressed the issue (Amendment #22, July 28, 2022).

Reviewer's Note: Section 3.2.P.2.4 includes a summary of the extractables and leachables (E&L) risk assessment of all materials of contact used in the DP manufacturing process.

Document RPT-1398 and RPT-4678 from (b) (4) titled "Extractables and Leachables Risk Assessment for the Rocker Reactor Platform Gene Therapy Product Manufacturing Process" dated 05-18-2021 provides an extractables and leachables (E&L) materials risk assessment for the entire manufacturing process and includes both (b) (4) DP manufacturing steps including (b) (4) processing steps. This risk assessment was purported to be based on vendor supplied information concerning the materials of construction and information concerning testing of equipment, as well as based on the actual conditions of use in the manufacturing of the therapeutic (time, temperature, and solvating properties of the process streams). Materials were determined to be low, moderate, or high E&L risk. Throughout the study, all materials were deemed low or moderate risk except for the vial stoppers (20 mm, sterile) from (b) (4), which was deemed "High".

Document AD-RPT-00140 from uniQure titled "AMT-061 Extractables & Leachables and DP compatibility with Contact of Material Risk Justification" dated 12-23-2021 provides a theoretical

justification to demonstrate the reasons why a moderate risk of leachables is deemed acceptable to uniQure, without conducting an E&L study.

Reviewer's Comment: AD-RPT-00140 is a theoretical assessment based on distance along the production stream, exposure temperature, exposure duration, process fluid interaction, and dilution ratio. It is notable that this theoretical assessment does not provide a comprehensive assessment of the cumulative impact of the process stream on the E&L profile (i.e., each aspect of the process is evaluated in (b) (4)).

In response to an IR sent on July 14, 2022, the applicant conducted an accelerated short-term simulation study with etranacogene dezaparovec formulation buffer to evaluate the E&Ls from the (b) (4) container (provided with Amendment 41 and discussed below as RPT-5702). In addition, to support DP manufacture, DP vials prepared from (b) (4) will be analyzed with extractables methods. Details are provided in document PRO-1577-BA titled Protocol for an Extractables and Leachables Study of AMT-061 Drug Substance Storage Container.

In the long term, CSLB commits (as PMC) to perform a formal study (E&L, (b) (4) long-term leachable study) to capture the potential carry-over and cumulative E&Ls obtained from the (b) (4) storage and DP manufacture. The long-term study is to be initiated in January 2023, with a final report will be submitted by March 30, 2024 (see PMC #4).

This response and commitment are suitable.

E&L studies are therefore limited to the drug product container closure (i.e., vial and stopper) and are listed in the reports tabulated in **Table 28**.

(b) (4)

(b) (4)

No extractable volatile compounds were detected in any of the (b) (4) that were unique to the extracts compared to the control for (b) (4). For non-volatile testing via (b) (4)

In response to a June 17, 2022 IR, the applicant provided report RPT-3346 (EXT-22-0022) (Amendment 16, dated July 1, 2022) to address the (b) (4) compounds listed

in report RPT-2070. This report identifies non-volatile organic compound (NVOC) unknowns from Report RPT-2070 as (b) (4)

(b) (4) of drug product, which was based on an acceptable intake of an individual impurity of (b) (4) based on ICH M7 guidance. .

Reviewer's Comment: This extractable assessment is conducted on placebo and solely represents the extractable profile of the drug product container closure. Other E&L Studies listed in Table 36 were found suitable without note.

As a part of Amendment 41, Document RPT-5702 from (b) (4) titled "Report for the Extractables and Leachables Study of AMT-061 (b) (4) Storage Container" dated 09-13-2022 provides an evaluation of extractable chemical entities from AMT-061 (b) (4) storage container, and compared them to extractable chemical entities from DP samples recently formulated from aged AMT-061 (b) (4).

Reviewer's Comment: This study was found suitable without note.

3.2.P.2.5 Microbiological Attributes (Reviewed by AS)

The drug product is sterile filtered and aseptically filled. Drug product is tested for sterility at the time of release. The stability study shows that the sterility is maintained on long-term storage. The acceptance criteria for endotoxin the drug product is (b) (4) . At this level, endotoxin exposure from drug product will not exceed (b) (4) . The formulation does not contain a preservative.

Please refer to the DMPQ review for further information on container closure integrity testing. The applicant also performed microbiological studies in support of the post-dilution storage time prior to the intravenous administration. The study demonstrates the microbial contamination control under the specified storage conditions (i.e., 24 hours at approximately 15-25°C with 0.9% normal saline). Please refer to DMPQ review for additional details on the microbial recovery study.

3.2.P.2.6 Compatibility (Reviewed by RM)

(b) (4)

1 page determined to be not releasable: (b)(4)

(b) (4)

(b) (4)

Reviewer's comment:

- The data are sufficient to demonstrate compatibility of DP with an acceptable range of administration sets for the times and temperatures that they will be used clinically. The fact that the DP was kept (b) (4) prior to the beginning of the study and not at $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ as the commercial product is a weakness. However, this discrepancy has minimal impact on the stability because the stability studies showed no change in viral genome throughout the stability testing duration (see section [3.2.P.8.1](#)).
- with regards to coverage of possible delivery devices, the PI describes that stability after dilution was established using Polyethylene/Polypropylene (PE/PP) copolymer, Polyvinyl Chloride (PVC)-free infusion bags with 0.9% normal saline. Furthermore, the PI specifies the filter PES 0.2 μm filter. The specific make of the remaining components (syringe, needle, infusion line or catheter) were not specified in the PI. In addition, there were no compatibility studies with polycarbonate syringes, but currently available polycarbonate syringes are small volume and very unlikely to be used to administer this product. This is acceptable.

Overall Reviewer's Assessment of Section 3.2.P.2:

(RM)

Compatibility studies were adequate to demonstrate the stability of DP when held in (b) (4) for up to 24 hours at room temperature, as well as compatibility with infusion sets and support the preparation conditions described in the package insert. These studies support the instructions in the package insert to use the product within 24h of diluting and drawing into a syringe.

3.2.P.3 Manufacture (Reviewed by EAG)

3.2.P.3.1 Manufacturer(s)

The manufacture, testing, labeling, packaging, release, storage, and distribution of the AMT-061 DP is performed in accordance with cGMP at the facilities presented in Table 30.

Table 30 Name and address of DP manufacturer and testing facilities

Facility	Responsibility
uniQure, Inc. 113 Hartwell Avenue, Lexington, MA 02421-3125 FEI: 3011357564 DUNS: 052841733	DP manufacture and filling In-process testing Release testing ^a Stability testing ^b Storage
CSL Behring (b) (4)	Labeling Packaging Release Storage
(b) (4)	Release and Stability Testing: Sterility
^a All release testing except sterility. ^b All stability testing except sterility.	

3.2.P.3.2 Batch Formula

The Batch formular for the DP is summarized in Table 31:

Table 31 Batch formular for the DP

Table of Batch Formulation for the Drug			
Component	Quality Standard	Amount per Minimum Batch Size ^a	Amount per Maximum Batch Size ^a
Etranacogene dezaparvovec	See Section 3.2.S.4.1	(b) (4)	(b) (4)
Hydrochloric acid	(b) (4)	(4)	
Polysorbate-20			
Potassium chloride			
Potassium phosphate, (b) (4)			
Sodium chloride			
Sodium phosphate, (b) (4)			
Sucrose			
Water for injections			
Each 10 mL glass vial is aseptically filled with 10.7 mL (11.0 g) of drug product (density = 1.024 g/mL). This overfill assures the specified extractable volume of ≥10.0 mL.			

Definition of DP batch:

Based on the drug product (DP) compounding performance qualification, minimum and maximum DP batch sizes along with theoretical number of vials are given in the Table 32 (b) (4) batches may be performed depending on the availability of (b) (4).

(b) (4)

(b) (4)

Overall Reviewer's Assessment of Sections 3.2.P.3.1 and 3.2.P.3.2:

□ *Description of drug product composition and batch formula are acceptable.*

**3.2.P.3.3 Description of Manufacturing Process
(Reviewed by EAG)**

The validated drug product process which comprises of (b) (4) steps are summarized as schematically under **Figure 34** below. Briefly, The (b) (4) DP are formulated in the same formulation buffer. (b) (4)

(b) (4)

The DP is aseptically filled into 10 mL (b) (4) glass vials with (b) (4) (corresponding to 10.7 mL) of DP (density = (b) (4) visually inspected (b) (4). A unique identifier is printed on each seal of each vial. Vials are placed into labeled storage boxes. Each filled storage box is sealed with tamper evident tape and is transferred to long-term storage at 2-8°C and shipped to labeling and packaging site.

(b) (4)

(b) (4)

Overall Reviewer's Assessment of Section 3.2.P.3.3:

- ☐ Detailed description of AMT-061 DP in the BLA was reviewed to be acceptable.
- ☐ State if deficiencies were identified and how they were resolved.

None

**3.2.P.3.4 Controls of Critical Steps and Intermediates
(Reviewed by EAG)**

Critical intermediate steps and controls (as described in the PPQ reports) are briefly summarized below.

(b) (4)

Overall Reviewer's Assessment of Section 3.2.P.3.4:

- In-process control strategy for AMT-061 DP is generally supported by manufacturing data.

3.2.P.3.5 Process Validation and/or Evaluation

(Reviewed by EAG)

Summary of Process Validation and PPQ study

The DP process validation was executed through a (b) (4) risk-based process validation lifecycle. (b) (4) (Continued Process Verification) are summarized below.

(b) (4)

(b) (4)

(b) (4)

Reviewer Comment: The CPV plan, as detailed in Doc No. MSAT-PROT-0004, is adequate to ensure consistency and monitoring of established process performance of DP process.

Overall Reviewer's Assessment of Section 3.2.P.3.5:

- ☐ *Collectively, the PPQ study and historical data together show that the AMT-061 DP manufacturing process can yield final DP that meets the predefined acceptance criteria of all measured product attributes.*
- ☐ *The continued validation process plan for monitoring of process parameters is acceptable.*
- ☐ State if deficiencies were identified and how they were resolved
 - ☐ None
- ☐ List any remaining deficiencies that should be included in a CR letter.
 - ☐ None

**3.2.P.4 Control of Excipients
(Reviewed by AS)**
3.2.P.4.1 Specifications

All excipients in the drug product comply with current compendial standards as listed in Table 40.

Table 40 Excipients in the Drug Product

Excipient	Quality Standard ¹
(b) (4)	(b) (4)
Polysorbate-20	
Potassium chloride	
Potassium phosphate, (b) (4)	
Sodium chloride	
Sodium phosphate, (b) (4)	

Sucrose	(b) (4)
Water for injections	

¹According to current version of the respective pharmacopoeia.

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

All excipients are tested per verified compendial methods and conform with the compendial requirements.

3.2.P.4.4 Justification of Specifications

Specifications of the excipients used in drug product comply with the monograph requirements of the current compendial standard.

3.2.P.4.5 Excipients of Human or Animal Origin

No excipients of human or animal origin are used in the drug product.

3.2.P.4.6 Novel Excipient

There are no novel excipients used in the manufacture of the DP.

Overall Reviewer's Assessment of Section 3.2.P.4:

There are no concerns regarding the control of excipients used in the DP.

There was a concern regarding the presence of beta-glucan impurities in sucrose batches that was satisfactorily addressed during the review process.

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s) (Reviewed by RM)

The statistical approach to setting limits for DP is the same as described in 3.2.S.4.5 for DS and is based on manufacturing experience of late phase lots and PV/PPQ lots. However, there was a limited number of DP lots (n=(b) (4)) in the original BLA submission, and therefore the TI approach yields wider intervals for the DP than for the (b) (4). Of the (b) (4) lots that were manufactured for phase III trials or for PV/PPQ, only (b) (4) lots were administered to patients during the pivotal trials (see **Table 41** below, DP (b) (4) lots used for determination of DP AC).

For certain quantitative assays for release of (b) (4) DP, the acceptance criteria are identical for (b) (4) DP (b) (4), sucrose, PS-20, endotoxin, vector DNA identity, potency, protein purity, infectivity, (b) (4) purity). In these cases, when the tolerance interval provided different results for the (b) (4) DP, the AC was determined based on the DP that had a wider AC with an exception for the (b) (4) test that was driven by a range that would accept (b) (4) DP.

Even after revision of the of the specifications during the time of the BLA review, some AC remained wider than the (b) (4) TI with a (b) (4) coverage. These include: (1) total particle concentration, (2) potency, (3) Infectivity, (4) (b) (4) and (5) (b) (4) purity and they are labeled with asterisks in **Table 42**. For those assays, the applicant set action limits to ensure internal investigation if the DP results exceed that limit to ensure additional investigation for results beyond the limit of the (b) (4) TI with a (b) (4) coverage. The SOP for the action limit process was provided in amendment #41, September 19, 2022. It includes an initiation of a three-phase investigation (outlined in QC-SOP-0081). Batch release will not occur until closure of the laboratory exception and will include an assessment of the laboratory exception conclusion. *Reviewer comment: In amendment #41, September 19, 2022, the applicant commits to further perform a post marketing reassessment, after they complete manufacturing of (b) (4) commercial DP lots and to further narrow the AC is necessary.*

(b) (4)

^b Information on the identity of the actual lots used in clinical trials was received in amendment #24, August 4, 2022.

Reviewer's comment. The FDA reanalyzed the specifications in the context of the (b) (4) that were used in the clinical and found that the AC would need to be widened for all specifications due to assay and lot-to-lot variation and due to the small sample size. Therefore, The FDA recommended to the applicant to include (b) (4) lots (including lots that were made for clinical use but never used) and including the PV/PPQ lots. Such analysis provides tighter AC that will results in safe and reproducible dosing. The AC and action limits for all DP specifications in this section rely on that recommendation with the exception of the viral genome titer.

Table 42 (Specification for Drug Product) below shows the release specification for the DP as well as the number of lots used for justification of the specification and the release AC for the (b) (4) All PV/PPQ lots passed all the specifications.

Table 42 Specification for Drug Product (updated 09/20)

Attribute Monitored	Method	Acceptance Criteria	Justification of Specification	DS Acceptance Criteria
General Tests			(b) (4)	(4)
Appearance ^a 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)		
Subvisible Particles ^a	(b) (4)	(b) (4)		
	(b) (4)	(b) (4)		
Extractable Volume	(b) (4)	(b) (4)		
Safety				
Sterility	(b) (4)	No growth		
Bacterial Endotoxins ^a	(b) (4)	(b) (4)		
Identity				
Vector DNA Identity	(b) (4)	Confirmed		
Content				
(b) (4)	(b) (4)	(b) (4)		
(b) (4)	(b) (4)	(b) (4)		
Biological Activity				
Potency ^a	(b) (4)	(b) (4)		

Infectivity: (b) (4)	(b) (4)	(b) (4) * action limit (b) (4)
Purity		
(b) (4)	(b) (4)	(b) (4) * action limit (b) (4)
(b) (4) Purity ^a	(b) (4)	(b) (4) * action limit (b) (4)

a Quality attribute included in stability specification for drug product.

EU = Endotoxin unit, gc = Genome copies, (b) (4)

Reviewer's comment: Overall, most of the assays had appropriate justification for specifications, with a few exceptions discussed below. A new specification for (b) (4) was added on amendment #24, August 4, 2022, per FDA request. This is acceptable.

PMC pertaining to DP justification of specifications:

- Currently, lot release testing of capsid content is performed by calculating the (b) (4) which is an indirect method for the assessment of capsid content. CSLB intends to introduce (b) (4) as a more suitable method for lot release testing as a prior approval supplement (PAS) in 2023. This is acceptable.
- (b) (4) assay for a secondary potency measurement will be developed and released in 2023.
- The Applicant committed to revisit the specification once additional data from (b) (4) commercial batches is available.

Appearance

In accordance with current (b) (4). Requirements, the specification was defined as "Colorless, liquid, < Reference Suspension IV, Essentially free of visible particulates". Per Referring to (b) (4) the term "essentially" is applied to a product that has undergone 100% inspection and zero particles detected. All (b) (4) DP lots were tested and met the criteria of appearance.

Reviewer's comment: This is acceptable

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Sucrose

The acceptance criterion for Sucrose of DP has been set at (b) (4) after exclusion of one statistical outlier and with an effort to keep the AC for this assay consistent for (b) (4) DP. The AC is wider than the DP TI with a confidence level of (b) (4) coverage. However, is acceptable based on the (b) (4) DP manufacturing experience.

(b) (4)

Reviewer's comment: Sucrose Concentration is an indicator of process consistency and does not represent a risk to patient safety or product efficacy. Therefore, this is acceptable. Also see section [3.2.S.4.1](#) justification of specifications for (b) (4).

Polysorbate-20

The acceptance criterion for Polysorbate-20 has been set at (b) (4). Only (b) (4) unique measurements were observed: (b) (4), due to rounding. The limited number of distinct measurements result in this attribute appearing like a discrete rather than continuous variable. Since the data are not normally distributed and behaving like a discrete variable, calculation of TI's was not performed.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Extractable volume

The acceptance criterion for extractable volume has been set according to (b) (4). Requirements, at “≥10.0 mL”. (b) (4) failed the specification with (b) (4) and was excluded from the statistical analysis.

(b) (4)

Reviewer’s comment: this is a non-critical assay which has a low risk for patients’ safety and efficacy. The AC is acceptable.

Vector DNA Identity

To confirm the identity of the DP, a (b) (4)

Reviewer’s comment: this is acceptable.

Genome Copy Concentration

The product will be dosed based on a nominal titer of 1.0×10^{13} vg/mL with no correction to the actual concentration of the specific batch. During the process of the BLA review, several IR and FDA feedback communications occurred with regards to this AC. The manufacturing experience and the assay itself have inherent variabilities that resulted in a very large range based on the statistical analysis (b) (4)

Therefore, the Applicant has not demonstrated safety or efficacy with lots that are in a lower or higher concentrations than these ranges. It is noteworthy that no statistically significant correlations between lots with a higher or lower concentrations within the (b) (4) and better or lower efficacy were identified.

(b) (4)

(b) (4)

(b) (4)


Reviewer's comment: This assay is very critical for safe and reproducible administration of the drug. The AC for the viral genome was (b) (4) which represents a target concentration of 1×10^{13} (b) (4) .. This range is in line with other approved AAV products such as Zolgensma and Luxterna with target titers of (b) (4) respectively. This is acceptable.

(b) (4)

(b) (4)

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(b) (4)

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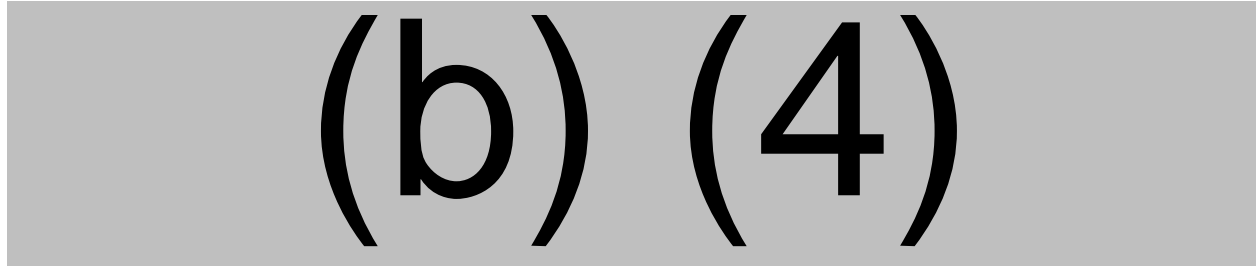
Potency

Only (b) (4) DP lots were used during the pivotal trials and those lots had a potency that ranged between minimum of (b) (4) and a maximum of (b) (4) Figure 41. Therefore, the Applicant has not demonstrated safety or efficacy with lots that are in a lower or higher concentrations than these ranges. It is noteworthy that no statistically significant correlations between lots with a higher or lower potency within the (b) (4) lots and better or lower efficacy were identified.

The DP potency specification was evaluated (b) (4)

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(b) (4)

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1 page determined to be not releasable: (b)(4)

(b) (4)

Reviewer's comment: The applicant's committed to revise this AC in a PMC after the complete manufacturing (b) (4) DP lots as well as the set of an action limit if (b) (4). This is acceptable.

Sterility

The acceptance criterion for Sterility has been set according to (b) (4) requirements. For the purpose of specification evaluation prior to PV/PPQ, a total of (b) (4) DP batches have been evaluated for Sterility. All of the batches met the specification "No growth".

Reviewer's comment: this is acceptable.

Bacterial Endotoxins

DP is tested for the presence of endotoxin using the (b) (4) assay. The specification limit was set at (b) (4). All of the batches met the specification (b) (4).

Reviewer's comment: the dosing of the DP will be (b) (4). This translates to (b) (4) because the nominal titer of the DP is 1E13vg/ml. Therefore, the specification of (b) (4) is in accordance with (b) (4) and acceptable.

Overall Reviewer's Assessment of Sections 3.2.P.5.1 and 3.2.P.5.6:

The DP specifications provide adequate control of the quality of the strength, identity, purity and potency of the DP. The approach to establish AC for DP release includes mostly appropriate statistical analysis of manufacturing experience in (b) (4) DP lots (including the PV/PPQ lots). Of the (b) (4) lots that were manufactured for phase III trials or for PV/PPQ, only (b) (4) lots were actually administered to patients during the pivotal trials and were demonstrated safe and efficacious. Consequently, for the two assays that have the chief impact on safety and efficacy (viral genome concentration and potency) and based on the FDA feedback, additional considerations were used to narrow the AC, such as the minimal and maximal results of the (b) (4) lots that were used in the pivotal clinical.

During the review of the BLA, the FDA negotiated modification to the acceptance criteria for (b) (4) assays based on review of the statistical analysis of the manufacturing experience and other considerations. (b) (4) of the (b) (4) was the viral genome assay (strength) which was changed and will be discussed below. The limit of the other (b) (4) assays that include (1) (b) (4) (2) potency, (3) Infectivity, (4) (b) (4) (5)

monomeric particle purity, were not changed. However, action limits were put in place to initiate an investigation on assay performance and manufacturing in cases where the DP results exceed the action limit. In addition, the applicant committed in a PMC to perform a post marketing reassessment of the AC after the applicant completes manufacturing of (b) (4) commercial DP lots.

(b) (4) important assays were not included in the original submission of the BLA and will be submitted as PMC based on the FDA feedback. One was an analytical assay to calculate the (b) (4). The applicant used a (b) (4)

as an indirect method to estimate this impurity. This ratio is informative, but not accurate or reproducible enough to reliably report this impurity. The applicant has a PMC to qualify and validate a (b) (4) assay to estimate amount of (b) (4). The (b) (4) assay that was not included in the submission is (b) (4) assay to detect FIX expression (using a commercial (b) (4) kit). The applicant has a PMC to qualify and both assays will be submitted in 2023.

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

All analytical procedures are described in section [3.2.S.4.2](#) Analytical procedures.

Overall Reviewer's Assessment of Sections 3.2.P.5.2 and 3.2.P.5.3:

See section [3.2.S.4.2](#).

3.2.P.5.4 Batch Analyses

(Reviewed by EAG)

The applicant submitted DP batch history that includes data from three AMT-061 DP batches made from the PV/PPQ studies, batches used in stability studies, Phase IIb and Phase III clinical studies and reference standard. Information submitted are summarized in **Table 41**.

Based on the assessment of the collective data submitted, product attributes such as appearance, visible particulates, (b) (4) sucrose concentration, Polysorbate-20 concentration, (b) (4), extractable volume, sterility, endotoxin and identity all met compendial requirement or were consistent (for non-compendial attributes). Note: that release data for these attributes are not shown in this memo.

Data on critical product attributes including DP potency, vector genome concentration, (b) (4) are summarized under just of specification (see 3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)).

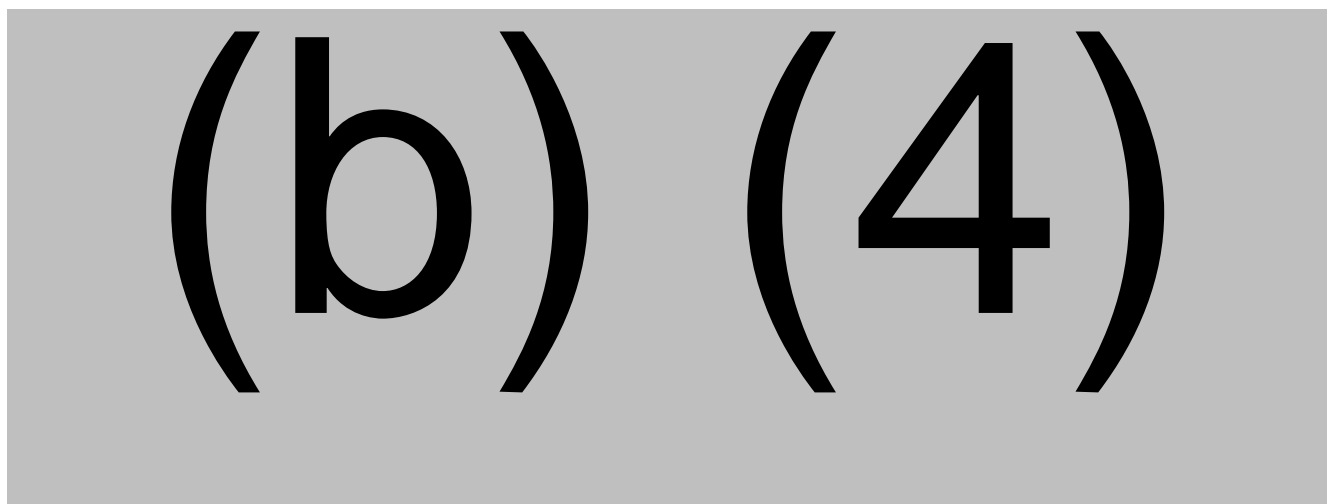

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)



3.2.P.5.5 Characterization of Impurities (Reviewed by AS)

No new process-related impurities are introduced during DP manufacture. Please refer to 3.2.S.3.2 for control of impurities. There is no indication of any change in protein purity between DS and DP.

Overall Reviewer's Assessment of Sections 3.2.P.5.4 and 3.2.P.5.5:

- ☐ The information provided to demonstrate consistency of commercial manufacturing is adequate. However, it is observed that the average vector potency is lower relative to historical clinical III and IIb manufacturing. Therefore, there is the need to closely monitor potency as part of Continuous process verification of the DP process to ensure improvements to justify risk of the therapy.
- ☐ Impurities are adequately controlled.

3.2.P.6 Reference Standards or Materials (Reviewed by AS)

Please reference Section 3.2.S.5 of this review memorandum.

3.2.P.7 Container Closure System (Reviewed by MM)


Please reference Section 3.2.P.2.4 of this review memorandum.

3.2.P.8 Stability (Reviewed by RM)

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

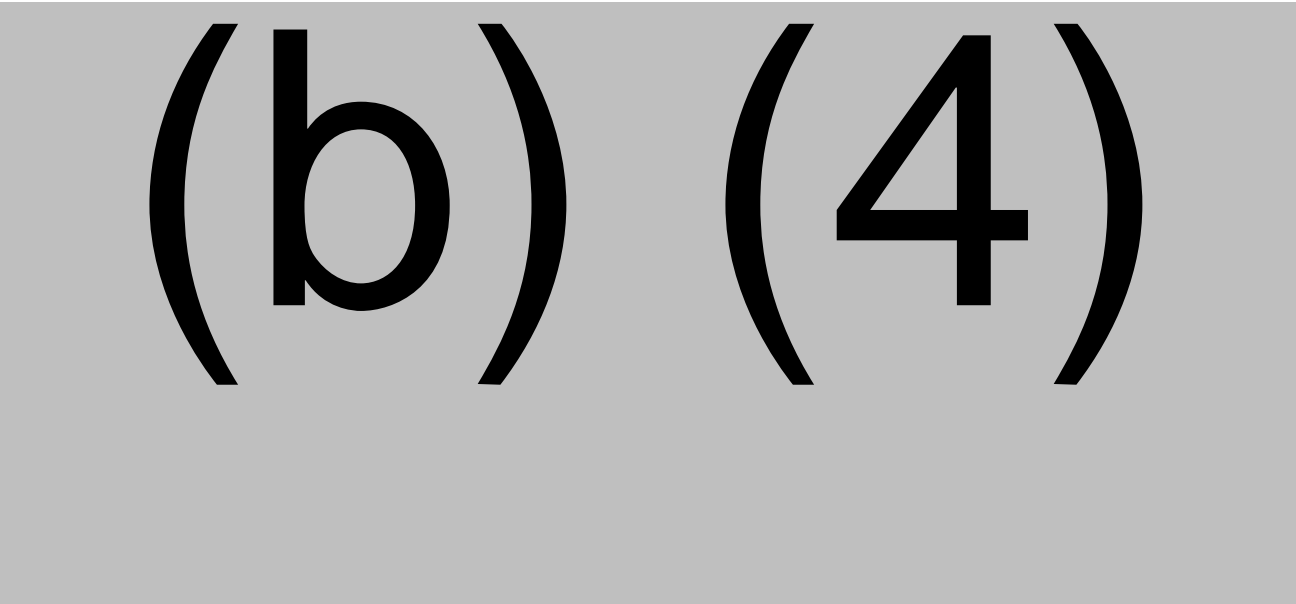
Selection of Batches

(b) (4)




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Potency

The results from 24 months DP stability show that all lots met the potency testing stability specification of (b) (4) reference units (RU). Visual inspection of the trend line at (b) (4) interval did not show any trends (Figure 44). Notedly, the potency assay (a (b) (4) assay comprised of cell line transfection with a tested sample in parallel with the reference standard followed by a (b) (4) assay to measure functional FIX protein in culture media samples) has a relatively high variability as evidenced by a coefficient of variation (CV) of (b) (4), which results in

apparent increase in potency at some time points. Notably, no major differences were observed between (b) (4) positioning of the vials over 9 months.

(b) (4)

(b) (4)


***Reviewer's comment.** Data over 9 months for PV/PPQ lots show no change in potency. Furthermore, supportive study over 24 months also did not show any increase or decrease in potency. Therefore, this is acceptable. It is noteworthy to mention that the stability study of (b) (4) lots showed a decrease in potency after 12 months of storage in (b) (4). However, this has not been observed in the DP stability in +5°C conditions. This is acceptable.*

Infectivity: (b) (4)

(b) (4)

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(b) (4)

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Safety attributes

Safety attributes including bacterial endotoxin and sterility were evaluated at the time point described in Table 44. All-long-term stability studies met the AC in all timepoints analyzed and support a shelf life of 24 months.

(b) (4)

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(b) (4)

Proposed shelf life

The selection and performance of analytical procedure to evaluate DP stability is appropriate. Based on the stability data from supporting stability study of three phase IIb/III clinical lots over 24 months and the data from the ongoing primary stability studies using three PV/PPQ lot over 9 months, the Applicant proposes a shelf-life of 24 months at $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ storage.

Reviewer comment. *All safety and physical attributes that were examined in long-term stability in the supporting stability study of three phase IIb/III clinical lots over 24 months and in the primary study of three PV/PPQ lot over 9 months (ongoing) have met the stability specifications. Out of specification results were identified once in the viral genome assay and three times in the infectivity assay. However, all out of specification results occurred in early time points and did not repeat in subsequent time points, indicating that those out of spec results were due to assay variability at the time, and not due to loss of stability. Therefore, I agree with the proposed shelf-life of 24 months.*

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment (Reviewed by RM)

The DP post-approval stability commitment is to continue the ongoing stability programs described in section 3.2.P.8.1 of the BLA. According to cGMP requirements, annual/routine stability studies will be performed on at least (b) (4) commercial batch of DP at the long-term storage condition each year a manufacturing campaign occurs.

A batch of DP produced with (b) (4) will undergo a stability study similar to the main stability study for PV/PPQ lots for future extension of (b) (4) DP shelf-life based on this cumulative stability study.

Reviewer comment. *This plan is acceptable*

Overall Reviewer's Assessment of Section 3.2.P.8:

The selection and performance of analytical procedure to evaluate DP stability are acceptable.

(b) (4) DP lots were evaluated including (b) (4) PV/PPQ lots that had data from 0, 1, 3, 5, 6 and 9 months and data from supporting stability study of (b) (4) clinical lots that had complete data from 24 months. Late in the review cycle, the applicant submitted stability data on 6 and 9 months the PV/PPQ DP lots at the long storage temperature of $+5^{\circ}\text{C} \pm 3^{\circ}\text{C}$ (amendment #38 September 13, 2022). Long term stability studies included both inverted and upright positioning of the vials to account for stability integrated with container closure. No major difference in stability was observed after the different positioning. In addition, accelerated stability, (b) (4) studies were performed appropriately.

The applicant committed to complete the stability program for the PV/PPQ lots over (b) (4) months post marketing. In addition, one additional batch of DP produced with aged drug substance (DS) will undergo a stability study for (b) (4) months for future extension of (b) (4) DP shelf-life based on this cumulative stability study (also see 3.2.S.7.1. DS stability).

The overall results from the supporting stability study of the DP clinical lots over 24 months indicate a stable product, with no trends of deterioration in viral genome, potency or infectivity. The stable potency is in contradiction to the DS stability studies that showed loss of potency and infectivity after (b) (4) months. This difference can be explained by the different storage conditions (DP stored in +5°C and DS stored at (b) (4)), the storage containers (DP is stored in (b) (4) vials and DS in (b) (4)) or by the additional filtration and compounding that the DP undergoes.

Based on the data from the supporting stability studies, the applicant proposed shelf life of 24 months for the DP. Additional data from the ongoing primary stability study will be provided as it becomes available in order to support the proposed shelf-life. This is acceptable.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Reviewed by DMPQ

3.2.A.2 Adventitious Agents Safety Evaluation

(Reviewed by AS)

The strategy to control adventitious agents comprises of:

(b) (4)

Reviewer's comment: Materials of Biological Origin including the insect cells-derived production cell banks, (b) (4) vector banks, (b) (4) culture media, (b) (4) antibody fragment were reviewed in 3.2.S.2.3 Control of Materials. The materials are of satisfactorily controlled.

Viral Clearance Studies

(Reviewed by AS)

Viral clearance studies were conducted to demonstrate the ability of multiple steps in etranacogene dezaparvovec manufacturing process to clear adventitious viruses. In particular, the (b) (4) is a known contaminant found within the (b) (4) cells used in upstream manufacture, and (b) (4) is used as a starting material in the manufacturing process. Therefore, it is critical that the (b) (4) are cleared by the manufacturing process.

(b) (4)

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(b) (4)

(b) (4)

(b) (4)

3.2.A.3 Novel Excipients

There are no novel excipients.

3.2.R Regional Information (USA)

Executed Batch Records

(Reviewed by EAG)

- (b) (4)

(b) (4)

Method Validation Package (Reviewed by EAG)

This BLA contained validation reports for assays that are used for release of (b) (4) DP. These validation reports are reviewed and discussed under appropriate sections of this memo (See sections 3.2.S.4.2, 3.2.S.4.3 , and 3.2.P.5. *The Applicant originally did not submit all relevant SOPs for the release assays. FDA requested assay SOPs in CMC IR #2, in amendment 16 (July 07, 22). SOPs provided were reviewed accordingly and are documented at respective sections in the memo.*

Combination Products

Not applicable.

Comparability Protocols (Post Approval) (Reviewed by EAG)

The applicant submitted post-approval analytical comparability protocol (CP) intended to support changes (scale-up) in the (b) (4) steps. However, the CP was deficient, and the applicant was advised (IR dated October 18, 2022) to remove the CP from the BLA and submit the CP as a prior approval supplement (PAS) after addressing FDA's concerns. In particular, the applicant was advised on type of statistical analysis to perform to demonstrate comparability of the pre-change and post-change products, inclusion of additional product attributes in CP, and prospective side-by-side testing. The applicant agreed (Amendment #50, dated October 20, 2022).

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion (Reviewed by AS)

The applicant's environmental assessment is provided in 1.12.14, in accordance with 21 CFR 25. This application is not eligible for categorical exclusion, and the applicant does not make a claim of categorical exclusion. The applicant does not propose any alternative action other than approval.

The product etranacogene dezaparvovec is derived from AAV5, a nonpathogenic human DNA virus that is incapable of autonomous replication. In this product, the DNA genome of

AAV5 has been replaced with a DNA genome that does not express any viral proteins. The product is capable of a single round of transduction (delivery of DNA to a cell), but there is no possibility of additional replication or infection. The manufacturing process is designed to minimize the potential that DNA recombination might result in a virus that contains viral DNA, and each lot of product is tested for the absence of replication-competent AAV (rcAAV). Even if rcAAV were to form, the virus would still be nonpathogenic and incapable of causing infectious disease.

The product is manufactured using insect cells and (b) (4) and therefore carries a theoretical risk of being contaminated with adventitious agents (viruses or bacteria). The manufacturing process efficiently inactivate and remove the (b) (4) and chances of (b) (4) to be present in the final product are very low. Even if present, recombinant (b) (4) are unable to replicate in humans and no adverse effects are expected. The production of potentially immunogenic (b) (4) proteins from the vector DNA fragments is highly unlikely. The insect cells are tested to ensure absence of adventitious agents, and each lot of products also undergoes (b) (4) testing to ensure absence of adventitious agents. The manufacturing process is also validated to remove or inactivate model viruses.

This product will be administered at hospitals or treatment centers using universal precautions, and unused product and product-contact materials will be disposed of as biohazardous medical waste. The product is relatively stable (compared to other viruses) at room temperature but will degrade over time into naturally-occurring materials.

Data from a clinical study demonstrate that patients who are treated with etranacogene dezaparvovec will shed vector DNA in saliva, nasal secretion, urine, feces for around 15-20 wks. DNA will also be shed in semen for extended period of time after administration. It is not known how much of the shed DNA is encapsidated in AAV capsids, as opposed to shedding of naked DNA. Even if encapsidated, the risk of causing infectious disease is zero because the product is inherently incapable of causing infectious disease, and there will be no direct toxic effects from exposure to small amounts of this vector, even if it is intact. The likelihood of germline transmission of vector DNA through semen is negligible. Animal studies showed no indication of paternal germline transmission to the offspring, even with high levels of vector DNA present in gonads. Please refer to pharmacology/toxicology memo for additional details. The AAV vector DNA in the semen is mainly present in the seminal fluid and not in the sperm cells, which is necessary for the germline transmission to the host progeny genome.

Reviewer's comment: It can be concluded that there will be no significant environmental impact from approval of etranacogene dezaparvovec-drlb, and a finding of no significant impact (FONSI) will be prepared.

Vector DNA Clearance (Shedding) (Reviewed by AS)

The vector shedding was investigated in studies CT-AMT-060-01 (using predecessor vector AMT-060), CT-AMT-061-01, and CT-AMT-061-02. In all the studies, levels of vector DNA were monitored using a validated (b) (4) assay (see below for assay details). The vector infectivity was not tested. A subject was considered to be no longer shedding vector DNA if they had a negative laboratory result for 3 or more consecutive time points.

In study CT-AMT-060-01, Vector DNA shedding was monitored in all subjects (n=10) and the median duration (in days) of shedding observed in the samples tested were (Median; Min, Max): saliva (92; 44,182), nasal secretion (77; 34,184), urine (60; 23,155), feces (111; 43,282), and semen (154; 65,365). The shedding in nasal secretion (10^6 copies/swab), saliva (10^7 copies/ml), and urine (10^5 copies/ml) was maximal at day 1, while the shedding in feces

(10^5 copies/mg) and semen (10^7 copies/ml) was maximal at 1-2 weeks post-dose, after which the vector DNA levels gradually declines to LOD.

Reviewer's comment: Considering the close similarities between the two vectors, AMT-061 is expected to follow the same shedding pattern as AMT-060.

In phase 3 study CT-AMT-061-02, vector DNA shedding was evaluated only in semen samples where the vector DNA was detected for extended period. Thirty two out of 54 (59.3%) subjects tested negative for vector DNA by 80 weeks post-treatment (median time to test negative = 47.3 weeks). The maximum level of vector DNA in semen was observed between weeks 5 and 27 post-dose. The remaining 12 subjects continue to test positive by week 96 (24 month; data cut-off time) and will continue to be monitored for vector shedding.

One of the concerns because of the prolonged shedding of vector in semen is the possibility of germline transmission. Based on published scientific literature, the vector DNA seems to reside in the seminal fluid and not in the cellular fraction of the semen samples. Likewise, paternal germline transmission was not observed in nonclinical germline transmission study performed with AMT-060, in alignment with other similar nonclinical studies with various AAV serotypes. In addition, AAV vector DNA is primarily maintained in episomal form, only rarely integrating to the host genome that is necessary for adverse event of germline transmission. Overall, the likelihood of germline transmission is negligible.

The assay used to monitor shedding used only measure vector DNA (see modules 4 and 5 for the assay information). Therefore, it is not known how much of the shed DNA is encapsidated in AAV capsids, as opposed to shedding of naked DNA. Even if encapsidated, the risk of causing infectious disease is negligible because the product is inherently incapable of causing infectious disease, and there will be no direct toxic effects from exposure to small amounts of this vector, even if it is intact.

B. Reference Product Designation Request (Reviewed by AS)

The applicant has requested reference product designation in section 1.3.5.3 of the CTD.

Reference Product Exclusivity Determination Board (meeting held on Oct 27, 2022) agreed to designate etranacogene dezaparvovec-drlb as reference product.

C. Labeling Review (Reviewed by AS)

Full Prescribing Information (PI):

The following sections were reviewed:

Sections 2 (Dose and Administration) and 3 (Dosage Forms and Strengths)

The product is supplied refrigerated (2-8°C) at a nominal concentration of 1.0×10^{13} gc/mL and each vial contain an extractable volume of 10 mL. The product is supplied in kits containing 10 to 48 single-use vials, each kit constituting a dosage unit based on the patient's body weight. The individual product vial and each of the possible kits has a separate NDC number. The recommended dose of the product is 2×10^{13} gc/kg of body weight, administered as a single intravenous infusion after dilution with 0.9% normal saline at a constant infusion rate of 500 mL/hour (8 mL/min).

To administer, the product is diluted with compendial 0.9% normal saline solution only prior to administration. Dose preparation involves significant manipulation. First the calculated product volume (in mL) is removed from the infusion bag(s) and then the volume of required product is dose is injected to the bag(s). For a 100 kg body weight patient, (b) (4) vials are needed to be

injected to the infusion bags. The diluted product in the bags can be stored at room temperature up to 24 hours after the dose preparation (supported by in-use stability study, section 3.2.P.8). The dose is prepared in biosafety cabinet or pharmaceutical isolators to prevent introduction of microbial contaminants. The product is administered through in-line filter (0.22µm). In original submission, the overall instructions in the PI to prepare and administer the product lacked detail. During the course of review, the Applicant subsequently provided more detailed and step-by-step instructions for the preparation and administration of the product.

Section 11 (Description)

HEMGENIX (etranacogene dezaparvovec-drlb) is a suspension of an adeno-associated viral vector-based gene therapy for intravenous infusion after dilution. The original PI refers HEMGENIX as solution. The applicant was asked to revise it to “suspension” (IR dated Nov 15, 2022). The applicant agreed (revised PI dated November 16, 2022).

Section 12 (Clinical Pharmacology)

Originally “mechanism of action (MoA)” in the PI contained promotional/unsubstantiated statements such as – The applicant was advised to rewrite the MoA based on the data-supported statements. Suggested MoA - HEMGENIX is an adeno-associated virus serotype 5 (AAV5) based gene therapy designed to deliver a copy of a gene encoding a Padua variant of human coagulation Factor IX (hFIX-Padua). Single intravenous infusion of HEMGENIX results in cell transduction and increase in circulating Factor IX activity in patients with Hemophilia B. The applicant agreed to the revised MoA (revised PI dated November 16, 2022).

The shedding studies are described in section 12.3 of the PI, based on review of shedding data from Phase 2b study (N=3) and Phase 3 study (N = 54). In line with FDA guidance, vector infectivity was not evaluated. A total of 47/54 (87%) subjects were identified to have reached absence of vector DNA from and semen, respectively, at 24 months post-administration. The applicant was asked to provide summary of shedding from other secretion/excretions (saliva, nasal secretion, urine, feces) from their phase 1/2 study using the predecessor product AMT-060, in the PI. The applicant agreed and updated the shedding data (revised PI dated November 16, 2022).

This section of the PI also contains a description of the biodistribution of vector, factor IX protein and factor IX activity after receiving the product. The assays used in the shedding, animal and human biodistribution studies are reviewed below in the sections for module 4/5.

Section 16 (How supplied / storage and handling)

The product is supplied in a kit of 10 to 48 vials, packaged into a carton. The number of vials depend on the weight of the patient, and there is a kit for every 5-kg of weight between 46 and 240 kg. Each kit contains one extra vial. Each kit size has a separate NDC number. The customized kit is accompanied with patient’s specific identifier number (Lot) on the outer carton. Each HEMGENIX kit may contain different drug product lots.

The product kit is shipped at 2°C to 8°C. Upon receipt, the vials are stored in refrigerator at 2°C to 8°C in the original carton protected from light until time of dilution and administration. The kit should not be stored frozen.

Reviewer’s comment: The information provided in the PI is consistent with the information in the BLA. This product is provided in a kit form based on the weight of the patient.

The PI contains adequate instructions for dose preparation and administration - the storage of the kit in a refrigerator, with appropriate instructions to use the diluted product in the infusion bags within 24 h of dose preparation.

The descriptions of shedding and biodistribution studies in the PI are based on sound methodology.

Carton and Container Label

(Reviewed by AS)

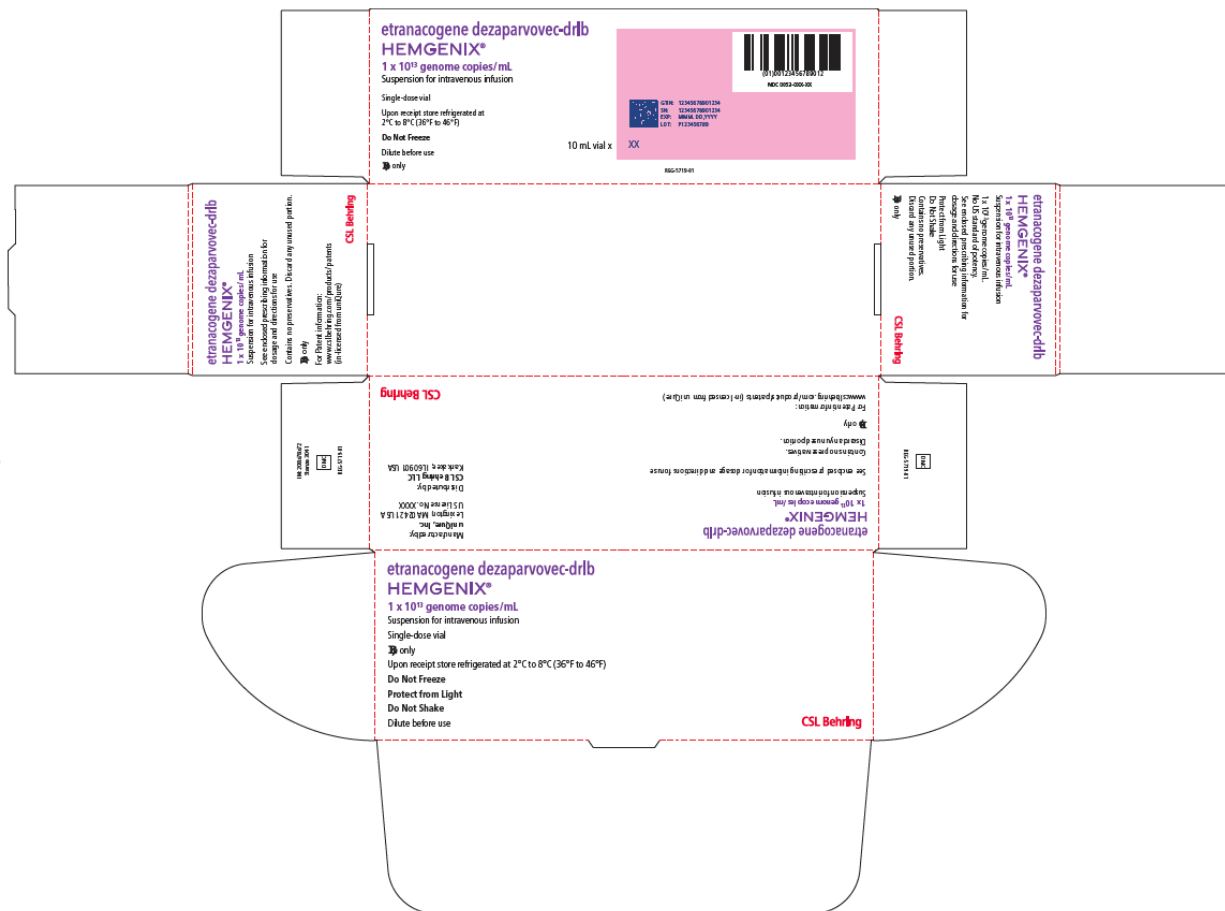
There were several mistakes on the container and carton labels and the applicant was asked (IR dated October 21, 2022 and November 1, 2022) to correct them. The applicant satisfactorily addressed the issues (Amendment #55, dated October 28, 2022, Amendment #60, dated November 4, 2022, and Seq #70, November 16, 2022).

Please refer to regulatory project manager (RPM)'s review memo for additional details.

Figure 47 Container/vial sample label



Figure 48 Carton sample label




Modules 4 and 5

(Reviewed by RM)


Analytical Procedures and Validation of Analytical Procedures for Assessment of Clinical and Animal Study Endpoints

(b) (4)

(b) (4)



(b) (4)



Measures of Product Potency (hFIX Activity)

The validation of the assay measuring product potency was validated in the context of Module 3. The same assays were used for analysis of clinical study endpoints. Review of these assays is cross-referenced to section 3.2.S.4.2-8.

Measures of hFIX transgene expression

A commercially available, (b) (4)

(b) (4) was used for the validation of quantitation of FIX. The (b) (4) used, branded as the (b) (4) FIX antigen kit, was sourced from (b) (4)

- ❑ The main assay used to assess in vitro potency is the same as the assay used to assess (b) (4) DP release and has been validated as fit for purpose.
- ❑ Other assays used in the clinical studies include detection of neutralizing antibodies to AAV5, IgG and IgM antibodies to AAV5, presence of FIX in the plasma, antibodies to FIX and inhibition of FIX. These assays have been validated and demonstrated to fit for the exploratory purpose.
- ❑ One assay to detect AAV5 reactive T-cells is not fit for its defined purpose due to a use of a full capsid to stimulate the cells, and not peptides. It is unlikely that the results of this assay show T cell activation and more likely that the results show activation of innate cells such as monocytes, neutrophils or NK cells and not T cells. Nevertheless, the applicant did not report any correlation between the results of this assay and efficacy or toxicity. Furthermore, the results of this assay are not described in the PI. Therefore, this reviewer does not feel strongly about requesting the Applicant to improve this assay. No further issues