

**CBER CMC BLA Review Memorandum**

**BLA STN 125781**

**delandistrogene moxeparvovec-rokl  
ELEVIDYS**

**Reviewers**

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**1. BLA#: STN 125781**

**2. APPLICANT NAME AND LICENSE NUMBER**

Sarepta Therapeutics, License No. 2308

**3. PRODUCT NAME/PRODUCT TYPE**

Non-Proprietary/Proper/USAN: delandistrogene moxeparvovec-rokl  
Proprietary Name: ELEVIDYS  
Company codename: SRP-9001  
UNII Code: 2P6QV2ZE52  
NDC Code (vial): 60923-501-10

**4. GENERAL DESCRIPTION OF THE FINAL PRODUCT**

Pharmacological category: Adeno-associated virus vector-based gene therapy  
Dosage form: Suspension for injection  
Strength/Potency:  $1.33 \times 10^{13}$  vector genome copies (vg)/mL  
Route of administration: Intravenous infusion  
Indication: For the treatment of ambulatory patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the DMD gene.

**5. MAJOR MILESTONES**

BLA Milestone	Dates
IND received from Dr. Jerry Mendell (Nationwide Children's Hospital)	5-Oct-17
IND transferred to Sarepta Therapeutics, Inc.	21-Sep-18
(b) (4)	(b) (4)
Fast Track designation granted	4-Jun-20
Type B End of Phase 2	27-Jul-21
Original BLA submission-Accelerated approval	28-Sep-22
First Committee Meeting	24-Oct-22
Filing Meeting	14-Nov-22
60-day filing date	25-Nov-22
Internal Mid-cycle Meeting	9-Jan-23
Mid-cycle Applicant t-con	24-Jan-23
Internal Late-cycle Meeting	21-Feb-23
Late-cycle Meeting	13-Mar-23
Original PDUFA Action Date	26-May-23
Extended PDUFA Action Date	22-June-23

**6. CMC/QUALITY REVIEW TEAM**

Reviewer/Affiliation	Section/Subject Matter
Lilia Lei Bi, PhD, OTP/OGT/DGT1/GTB1	DS manufacturing process and process validation/ DP manufacturing process and process validation/ Viral clearance study

Emmanuel Adu-Gyamfi, PhD, OTP/OGT/DGT1/GTB1	Elucidation of Structure and Other Characteristics/Impurities/Specification(s)/Justification of Specification(s)/Analytical methods and validation /Batch Analysis/Container closure/reference standard/ Physicochemical and Biological Properties/pharmaceutical development/Environmental assessment/Batch records/ Analytical Procedures for Assessment of Clinical and Animal Study Endpoints
Sukyoung Sohn, PhD, OTP/OGT/DGT1/GTB1	Control of materials/ Shipping validation/ DP manufacturer/ DP batch formular/ Control of excipients/ Stability
Brian Stultz, MS, OTP/OGT/DGT1/GTB3	Analytical Procedures for Assessment of Clinical Endpoint
Andrey Sarafanov PhD, OTP/OPPT/DH/HB2	Process / Storage Leachables assessment in DP

**7. INTER-CENTER CONSULTS REQUESTED: N/A**

**8. SUBMISSION(S) REVIEWED**

Date Received	Submission	Comments/ Status
9/28/2022	125781/0	Original submission
10/24/2022	125781/2	Response to DMPQ IR sent on 10/19/2022
12/6/2022	125781/4	Response to DMPQ IR sent on 11/29/2022
12/8/2022	125781/5	Response to DMPQ IR sent on 11/28/2022
12/22/2022	125781/6	Response to DMPQ IR sent on 12/14/2022
12/29/2022	125781/8	Response to CMC IR sent on 12/21/2022
1/11/2023	125781/12	Response to DBSQC IR sent on 1/6/2023
1/12/2023	125781/13	Response to DMPQ IR sent on 12/27/2022
1/19/2023	125781/14	Response to DMPQ IR sent on 1/17/2023
1/20/2023	125781/15	Response to DBSQC IR sent on 1/10/2023
1/24/2023	125781/16	Response to DMPQ IR sent on 1/10/2023
2/3/2023	125781/19	Response to CMC IR sent on 1/20/2023
2/17/2023	125781/20	Response to CMC IR sent on 2/16/2023
2/21/2023	125781/22	Response to CMC IR sent on 2/13/2023
3/1/2023	125781/24	Response to CMC IR sent on 2/13/2023
3/3/2023	125781/27	Response to CMC IR sent on 2/24/2023
3/17/2023	125781/29	Commitments in response to CMC IRs sent on 2/13/2023, 2/16/2023
4/14/2023	125781/38	Commitment in response to DMPQ IR sent on 12/14/2022

4/17/2023	125781/40	Response to CMC IRs sent on 4/12/2023, 4/13/2023
4/21/2023	125781/43	Commitment for PMC in response to CMC IR sent on 1/20/2023
4/21/2023	125781/44	Response to CMC IR sent on 4/13/2023
4/26/2023	125781/46	Response to DBSQC IR sent on 4/19/2023
4/27/2023	125781/47	Response to CMC IR sent on 4/20/2023
5/3/2023	125781/50	Response to CMC IR sent on 4/27/2023
5/10/2023	125781/52	Response to DBSQC IR sent on 5/8/2023, Updated Lot Release Protocol (LRP)
5/11/2023	125781/53	Response to CMC IR sent on 4/27/2023, DP Method Validation
5/16/2023	125781/54	Response to CMC IRs sent on 4/27/2023, 5/11/2023
5/19/2023	125781/59	Response to Form FDA 483 observations from the pre-license inspection of Catalent BWI
5/30/2023	125781/60	Response to CMC postmarketing commitments (PMCs) sent on 5/24/2023
6/7/2023	125781/66	Response to CMC IR sent on 6/2/2023
6/8/2023	125781/68	Response to CMC postmarketing commitments (PMCs) sent on 6/5/2023
6/14/2023	125781/70	Response to CMC IR sent on 6/12/2023
6/20/2023	125781/73	Response to CMC IR sent on 6/16/2023
6/15/2023	125781/75	Response to CMC IR sent on 6/14/2023
6/21/2023	125781/77	Response to Vial-Carton Label request sent on 6/20/2023

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

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
DMF (b) (4)	(b) (4)	(b) (4) Vial	Yes	Information supports section (3.2.P.7.2) of BLA
DMF (b) (4)	(b) (4)	Vial Sterilization of (b) (4) vials	Yes	Information supports section (3.2.P.5.1) of BLA
MF (b) (4)	(b) (4)	Sterilization validation results for Stopper	Yes	Information supports section (3.2.P.5.2) of BLA
STN (b) (4)	(b) (4)	Stopper, elastomeric formulations, coatings, films	Yes	Section 3.2.P.7

## 10. REVIEWER SUMMARY AND RECOMMENDATION


### A. EXECUTIVE SUMMARY

Based on the review of the collective CMC information submitted in the BLA by the Applicant and subsequent information requests reviewed throughout the review period, the CMC review team concludes that the manufacturing and controls for delandistrogene moxeparvovec-rokl (also referred to as SRP-9001; ELEVIDYS) are capable of yielding the drug product with consistent quality attributes and therefore, deemed acceptable for commercial manufacturing under the accelerated approval for this BLA.

Description of the product: SRP-9001 (rAAVrh74.MHCK7.micro-dystrophin) consists of a 4.7 Kb codon-optimized DNA vector genome encapsidated in a simian AAV serotype rh74 capsid. Each virion potentially contains a single copy of the vector genome. The vector genome expresses micro-dystrophin ( $\mu$ -Dys), a novel, engineered protein consisting of select domains from the full-length dystrophin protein, which are essential for muscle contractions and turnover. The vector genome expression cassette contains essential elements to control gene expression, including AAV2 inverted terminal repeats (ITRs), a chimeric (SV40) intron, and a synthetic polyadenylation (Poly A) signal (See Figure 1). Expression of the micro-dystrophin protein is under the control of the  $\alpha$ -myosin heavy-chain creatine kinase 7 (MHCK7) promoter to restrict expression to skeletal and cardiac muscle.

*Manufacturing and process validation:*

(b) (4)



The delandistrogene moxeparvovec drug product (DP) is manufactured at the Catalent Pharma Solutions facility (BioPark), Baltimore, Maryland. Each DP vial contains an extractable volume of not less than 10 mL, with a nominal concentration of  $1.33 \times 10^{13}$  vector genome (vg)/mL formulated in 7 mM Tromethamine / 13 mM Tromethamine HCl, 200 mM Sodium chloride, 1 mM Magnesium chloride, 0.001% Poloxamer 188, at (b) (4)

(b) (4). The DP manufacturing process includes formulation buffer preparation, (b) (4), sterile filtration, aseptic filling, stoppering, and capping. After visual inspection, the vials are packed, stored at (b) (4), and shipped to the labeling and secondary

packaging site. Validation of the DP manufacturing process included three PPQ runs. The DP manufacturing process is validated for commercial manufacturing.

The manufacturers accept raw materials based on specified quality attributes, including (b) (4). Raw materials derived from animals are appropriately controlled to ensure the absence of microbial contaminants.

**Control and testing:** The manufacturing steps, (b) (4), and final DP are controlled and characterized by a panel of analytical methods that are used for characterization and release. These include quantitative assays that assess critical measures of product quality, safety, purity, strength (vg/mL), and potency attributes. The potency test measures the ability of the SRP-9001 to successfully transduce a dystrophin (b) (4) and express the miniaturized micro-dystrophin, which is measured via quantitative (b) (4). There is a (b) (4) potency tests that ensure the (b) (4) of the microdystrophin to the (b) (4). Collectively, the assays used as part of the overall controls for the manufacturing process were found to be fit-for-purpose. Release and characterization test methods are discussed in detail in this BLA memo.

**Stability:** The DS is stable for (b) (4) when stored at the long-term storage condition of (b) (4). The DP is stable for 12 months at the storage condition of  $\leq -60^{\circ}\text{C}$ . During administration of the DP in the clinic, the DP is thawed and aspirated into an infusion syringe to be infused with a syringe pump. Based on the stability data submitted in the BLA, the thawed DP is stable for up to 24 hours at room temperature ( $15^{\circ}\text{C}$  to  $25^{\circ}\text{C}$ ) and stable for up to 14 days at  $2^{\circ}\text{C}$  to  $8^{\circ}\text{C}$ .

**Comparability:** Two manufacturing processes were utilized to generate purified DP to support the clinical program. For early clinical trials (Study SRP-9001-101 and Study 102), the DP was made using manufacturing **Process A** at Nationwide Children's Hospital (Ohio State University). Process A used a (b) (4)-based purification process to achieve a near complete removal of empty AAV capsids from the final formulated product. For late-stage clinical trials (Study SRP-9001-103 and ongoing Phase 3 trial [Study 301]), the DP was purified using the to-be-commercialized manufacturing process, referred to as **Process B** at Catalent Pharma Solutions (Baltimore, MD). Process B utilizes a scaled-up purification method that incorporates chromatography-based methods purification of the DP, including separation of the empty capsid residuals from the full capsids. The Process B purification method results in less efficient separation of empty AAV capsids from full AAV capsids (b) (4) full capsids), which contain the SRP-9001 micro-dystrophin DNA.

Based on both the Applicant's and FDA's assessment, it was concluded that the Process A and Process B materials are not analytically comparable relative to the levels of empty capsid residuals. The percent (%) full capsids of Process A and Process B material were found to be significantly different with a statistical probability t-test with p value = 0.0002.

## **B. RECOMMENDATION**

### **I. APPROVAL**

This biological license application (BLA) provides an adequate description of the manufacturing process and characterization of the new drug product delandistrogene moxeparvovec-rokl to support accelerated approval. 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 attributes. This information, along with post-marketing commitments (PMC) from Sarepta, fulfills 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 and thus, we recommend approval under the accelerated approval pathway requested by the Applicant. When the confirmatory study is completed, the applicant will submit additional CMC data that may require revision of some aspects of this approval memo (e.g., specifications, etc based on additional manufacturing data).

Post-Marketing Commitments (PMCs):

1. Sarepta Therapeutics, Inc. commits to performing (b) (4) [REDACTED] as a “Postmarketing Commitment- Final Study Report” by July 31, 2024
2. Sarepta Therapeutics, Inc. commits to submitting a final report for the supplemental (b) (4) [REDACTED] manufacturing runs for (b) (4) [REDACTED] at the Catalent facility as a “Postmarketing Commitment - Final Study Report” by June 30, 2024.
3. Sarepta Therapeutics, Inc. commits to submitting a final report of the (b) (4) [REDACTED] as a “Postmarketing Commitment - Final Study Report” by March 31, 2024.
4. Sarepta Therapeutics, Inc. commits to revising the system suitability criteria set in the SOP for (b) (4) [REDACTED] to reflect the assay variability (percent coefficient of variation; %CV) observed in intermediate precision during assay validation and to submitting the revised SOP as a “Postmarketing Commitment - Final Study Report” by December 31, 2023
5. Sarepta Therapeutics Inc. commits to revising the system suitability in the SOP for the (b) (4) [REDACTED] assay to include a parameter determining (b) (4) [REDACTED] and to submitting the revised SOP as a “Postmarketing Study Commitment – Final Study Report” by June 30, 2024.
6. Sarepta Therapeutics Inc. commits to reassessing the commercial acceptance criterion for the release testing of potency of SRP-9001 drug product after data have been collected on (b) (4) [REDACTED] commercial lots and submit a “Postmarketing Study Commitment – Final Study Report” by June 30, 2024.
7. Sarepta Therapeutics Inc. commits to implementing the following CMC change for the SRP-9001 (b) (4) [REDACTED] . The CMC change will be submitted as a “Postmarketing Commitment - Final Study Report” by December 31, 2024.
8. Sarepta Therapeutics Inc. commits to performing (b) (4) [REDACTED] . The final report will be submitted as a “Postmarketing Study Commitment – Final Study Report” by December 31, 2024.

## II. COMPLETE RESPONSE (CR)

Clinical and clinical pharmacology Review teams are recommending complete response, due to their assessment that the data provided for the accelerated endpoint, micro-dystrophin expression, does not meet the requirement that this endpoint is reasonably likely to predict clinical benefit. This decision was overruled by Dr. Peter Marks, Director CBER and he approved this accelerated endpoint, and the BLA.

## III. SIGNATURE BLOCK

<b>Reviewer/Title/Affiliation</b>	<b>Concurrence</b>	<b>Signature and Date</b>
Lilia Lei Bi, Ph.D. Biologist OTP/OGT/DGT1/GTB1	Concur	
Emmanuel Adu-Gyamfi, Ph.D. Biologist OTP/OGT/DGT1/GTB1	Concur	
Sukyoung Sohn, Ph.D. Biologist OTP/OGT/DGT1/GTB1	Concur	
Brian Stultz, M.S. Biological Reviewer OTP/OGT/DGT1/GTB3	Concur	
Andrey Sarafanov, Ph.D. Chemist OTP/OPPT/DH/HB2	Concur	
Andrew Harmon, Ph.D. Lead Biologist OTP/OGT/DGT1/GTB1	Concur	
Denise Gavin, Ph.D. Chief, Gene Therapy Branch 1 OTP/OGT/DGT1	Concur	
Kimberly L.W. Schultz, Ph.D. Chief, Gene Therapy Branch 4 OTP/OGT/DGT2	Concur	
Denise Gavin, Ph.D. Director, Office of Gene Therapy OTP/OGT	Concur	



## Review of CTD

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### 3.2.S DRUG SUBSTANCE

#### 3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties

Reviewed by Emmanuel Adu-Gyamfi (EAG)

#### Nomenclature

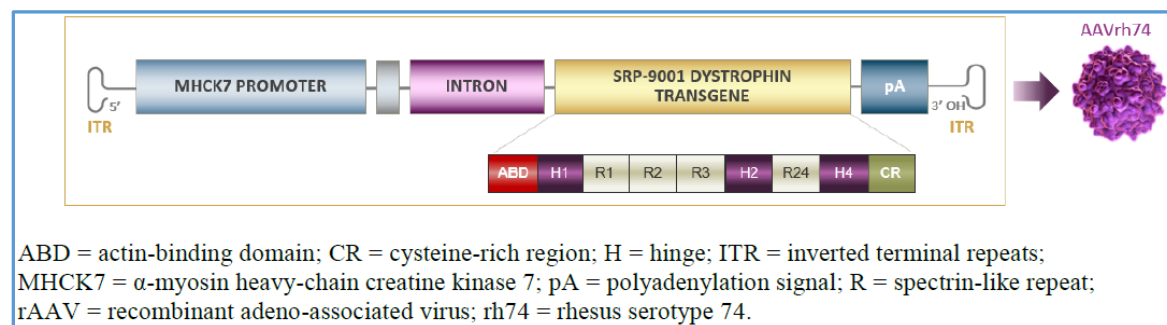
**Table 1: Nomenclature of SRP-9001**

International Nonproprietary Name (INN)	delandistrogene moxeparvovec-rokl
United States Adopted Name (USAN)	delandistrogene moxeparvovec-rokl
Proprietary name:	ELEVIDYS
Company code	SRP-9001
Chemical Abstracts Service (CAS) registry number	2305040-16-6
Chemical name (CAS Index Name)	DNA (Recombinant adeno-associated virus AAVrh74 vector SRP-9001 MHCK7 promoter plus micro-dystrophin-specifying)
Unique Ingredient Identifier (UNII)	2P6QV2ZE52
World Health Organization (WHO) Number	11631
Other Names	Micro-dystrophin, SRP-9001-micro-dystrophin

#### Structure

The drug substance (DS) vector genome is 4.7 kb in size. It is encapsidated in a rhesus AAV serotype rh74 capsid, with each virion potentially containing one copy of the viral genome. The vector genome contains a codon-optimized microdystrophin transgene (b) (4) derived from minimal elements of the full length wild-type human dystrophin gene. The vector genome also contains genetic elements required for gene expression, including AAV2 inverted terminal repeats (ITR), chimeric (SV40) intron, and synthetic polyadenylation (Poly A) signal, all under the control of the  $\alpha$ -myosin heavy-chain creatine kinase 7 (MHCK7) promoter to restrict expression to skeletal and cardiac muscles. (b) (4). Elements of the vector genome are schematically summarized under Figure 1 and discussed under Table 2

**Figure 1: SRP-9001 Vector Design**



#### General Properties

The SRP-9001 vector expresses a miniaturized version of the full-length dystrophin protein described above. This protein is truncated from the mild Becker Dystrophin (see Figure 2) used

to design the expression cassette. The dystrophin elements selected as well as the Applicant's rationale for the design of SRP-9001 construct is summarized under Table 2

**Table 2: SRP-9001-micro-dystrophin vector elements**

(b) (4)

(b) (4)

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



(b) (4)

(b) (4)

(b) (4)

### 3.2.P DRUG PRODUCT

#### 3.2.P.1 Description and Composition of the Drug Product

*Reviewed by LB*

The SRP-9001 Drug Product (DP) is a sterile suspension for intravenous (IV) administration, containing  $1.33 \times 10^{13}$  vg/mL of delandistrogene moxeparvovec formulated in a buffered solution of Tromethamine/Tromethamine-HCl, Magnesium chloride, Sodium chloride, and Poloxamer 188. Each vial contains an extractable volume of not less than 10.0 mL. The total recommended dosage is based on patient weight and requires multiple vials per dose.

**Table 77: Composition of the SRP-9001 Drug Product**

Component	Quantity per 10 mL <sup>a</sup>	Concentration	Reference to Standard(s)	Function
Delandistrogene moxeparvovec	$1.33 \times 10^{14}$ vector genomes (vg)	$1.33 \times 10^{13}$ vector genomes (vg)/mL	In-house specification <sup>b</sup>	Active ingredient
Sodium chloride	(b) (4)	200 mM	(b) (4)	(b) (4)
Tromethamine HCl (b) (4)	(b) (4)	13 mM	In-house specification <sup>c</sup>	Buffer agent

Tromethamine (b) (4)	(b) (4)	7 mM	(b) (4)	Buffer agent
Magnesium chloride (Magnesium chloride) (b) (4)	(b) (4)	1 mM	(b) (4)	(b) (4)
Poloxamer 188 (b) (4)	(b) (4)	0.001% (b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	q.s.	(b) (4)	(b) (4)
<sup>a</sup> Vial contains a target overfill of (b) (4) mL per vial to allow complete withdrawal of 10.0 mL dose. <sup>b</sup> Specification is provided in Section 3.2.S.4.1. <sup>c</sup> Manufactured for supplier under GMP using Tromethamine, (b) (4) is provided in Section 3.2.P.4.1 – Tromethamine HCl / (b) (4) q.s. = quantity sufficient to achieve final volume				

### 3.2.P.2 Pharmaceutical Development

#### 3.2.P.2.1 Components of the Drug Product

##### 3.2.P.2.1.1 Drug Substance

The drug substance (delandistrogene moxeparvovec) is (b) (4)

in order to prepare the drug product. The drug substance is stored at (b) (4)

##### 3.2.P.2.1.2 Excipients

The drug product is formulated in 7 mM Tromethamine (b) (4) / 13 mM Tromethamine HCl (b) (4) 200 mM Sodium chloride, 1 mM Magnesium chloride (Magnesium chloride (b) (4) 0.001% Poloxamer 188, at (b) (4)

#### 3.2.P.2.2 Drug Product

##### 3.2.P.2.2.1 Formulation Development

The components of the formulation are commonly used as ingredients of intravenous formulations and were selected to provide stability and compatibility of the drug product for the intended route of administration.

Development of SRP-9001 DP formulation was based on available knowledge of physicochemical properties of recombinant AAV serotypes. The same formulation has been used from initial clinical trials through to the commercial product.

##### 3.2.P.2.2.2 Overages

There are no overages in the formulation of the DP.

##### 3.2.P.2.2.3 Physicochemical and Biological Properties

*Reviewed by EAG*

The composition of the DS (b) (4)

DP titer of 1.33 e13 vg/mL. According to the Applicant, the quality target product profile (QTPP) for the SRP-9001 program was compiled by a cross-functional team which included input from gene therapy research, process development, formulation development and analytical development, provides a comprehensive listing of the desired drug substance (DS)/ drug product (DP) quality attributes for the finished product. Subsequent assessment of critical quality attributes (CQAs) was performed. The QTPP for SRP-9001 is summarized below under Table 78.

**Table 78: SRP-9001 Quality Target Product Profile**

Category of Attribute	Quality Target Product Profile
Drug Product Attributes (General)	
Description	SRP-9001-micro-dystrophin is a recombinant gene therapy product designed to deliver the gene encoding the SRP-9001-micro-dystrophin protein. It is a non-replicating, recombinant, adeno-associated virus (AAV) serotype rh74 (AAVrh74) based vector containing the SRP-9001-micro-dystrophin expression cassette, under the control of the MHCK7 promoter.
Intended use in clinical setting	Adeno-associated virus gene therapy for the treatment of patients aged 4 through 5 with a confirmed diagnosis of Duchene Muscular Dystrophy (DMD).
Dosage form	SRP-9001 1.33 × 10 <sup>13</sup> vg/mL suspension for infusion is supplied as a single-use, clear to opalescent, colorless, preservative-free, sterile, aqueous solution for intravenous infusion, that may contain white to off-white particles. Multiple vials will be thawed and pooled at the clinical site and prepared for I.V. infusion to achieve the therapeutic dose per patient body weight in kg (1.33E14 vg/kg).
Route of administration	Intravenous. The product will be administered as a single IV infusion.
Delivery system	Microbore infusion set with syringe pump
Dose/Dose frequency	1.33E14 vg/kg, SRP-9001 administered as single (one time) peripheral venous infusion.
Container	SRP-9001 drug product is stored as a sterile frozen liquid formulation in a cyclic olefin polymer vial closed with a rubber stopper and sealed with an aluminum seal and plastic flip-off cap.
Shelf life	drug product shelf-life is 12 months.
Formulation biocompatibility	(b) (4) formulation buffer, containing generally regarded as safe (GRAS) excipients (20 mM Tris, 200 mM NaCl, 1 mM MgCl <sub>2</sub> , (b) (4) 0.001% (b) (4) Poloxamer 188.
Primary sequence and therapeutic moiety integrity	SRP-9001-micro-dystrophin is a recombinant gene therapy product designed to deliver the gene encoding the 9001-micro-dystrophin protein. It is a non-replicating, recombinant, adeno-associated virus (AAV) serotype rh74 (AAVrh74) based vector containing the 9001-micro-dystrophin expression cassette, under the control of the MHCK7 promoter.

**Reviewer Comment:**

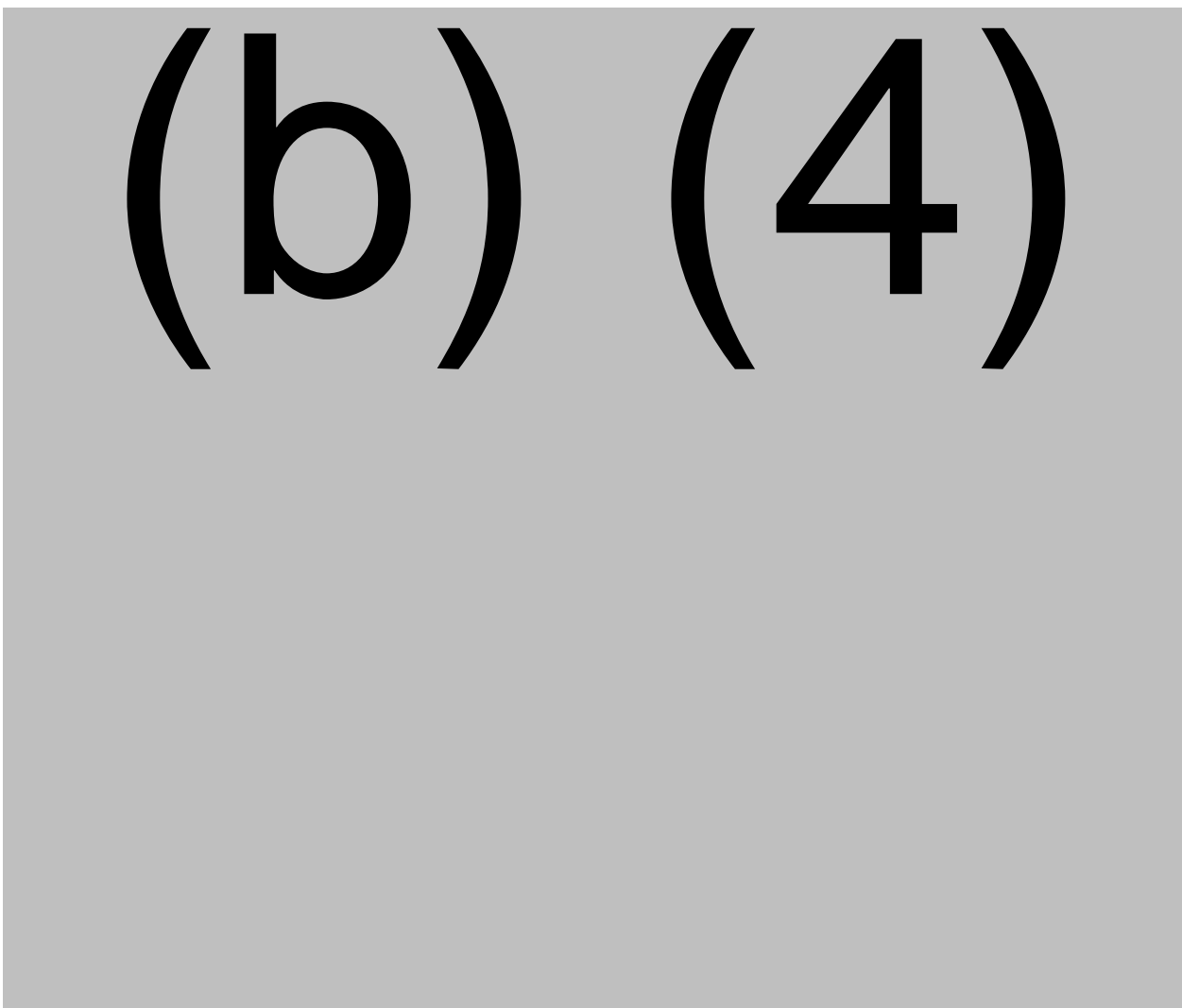
- The QTPP does not fully specify Drug product quality criteria (e.g., sterility, purity, stability, and drug release) appropriate for an intended marketed product. However, these are clearly indicated in release specification.
- Although (b) (4) guideline on QTPP summary is not explicit about content, the QTPP should incorporate a summary on handling and storage as this is critical to product and process quality. Table 78 reflects the revised QTPP table submitted by the Applicant under Amendment #70 submitted 2023.06.14. This is acceptable.

**Assessment of SRP-9001 Product Criticality**

Critical quality attributes (CQAs) for the drug substance and drug product have been designated based on product and process development experience, nonclinical, as well as published literature and publicly available information on other AAV product (CQAs) were evaluated in process development and characterization studies. Manufacturing process steps were evaluated to understand their impact on CQAs, and relevant methods were chosen for specific studies evaluating safety, purity, potency and identity. *These have been discussed and summarized under 3.2.P.3.5 Process Validation* and/or Evaluation. CQAs are grouped mainly under safety, purity, potency and identity See table below. Purity was further divided into

process and product related impurities. *Note: Practically, all attributes reported on release CoA are classified as CQA and are monitored at release or as in-process steps.*

**Table 79: Categorization of critical quality attributes**



(b) (4)

***Reviewer Comment:** The rationale for criticality assignments did not include any dedicated criticality scoring scheme that considers all the information gathered from manufacturing, known safety concerns in the literature as well as regulatory and compendial requirements. However, the assignments of product criticality is consistent with current understanding of AAV products in the field. Also, practically every measured attribute reported on release is considered critical and is thus monitored accordingly. Hence, this is acceptable.*

### **3.2.P.2.3 Manufacturing Process Development**

*Reviewed by EAG and AS*

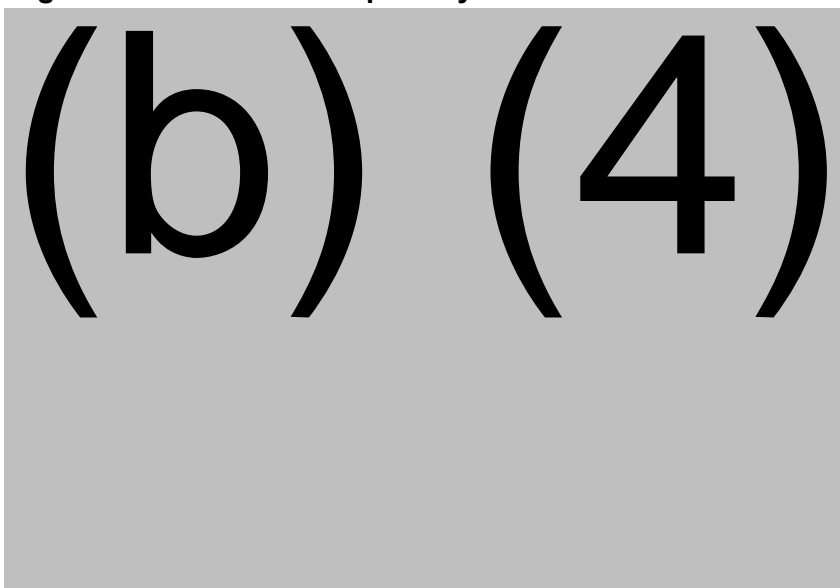
Two manufacturing processes have been utilized during the clinical trial stages for SRP-9001 program: early clinical manufacturing Process A and late-stage Process B. *The comparability study to support the drug product Process A to Process B manufacturing change already discussed under 3.2.S.2.6 Manufacturing Process Development.* Process B clinical DP is manufactured at Catalent BioPark and has been validated as the intended commercial process, while Process A was not validated.

### 3.2.P.2.4 Container Closure System

Reviewed by EAG and Andrey Sarafanov (AS)

**Primary Container:** SRP-9001 is supplied in a 10-mL (b) (4) cyclic olefin polymer (b) (4) vial with a rubber stopper and capped with an aluminum seal. According to the Applicant, all components are received in pre-sterilized, ready-to-use configurations. The components and schematic of the container closure system (CCS) are summarized under Figure 21 and Table 80 below.

**Figure 21: Schematics of primary container closure of SRP-9001**



**Table 80: Summary of DP primary container closure description**

Component	Description	Manufacturer	MF/DMF <sup>a</sup>	Reference to Standards
Vial	10-mL, cyclic olefin polymer (b) (4)	(b) (4)	(b) (4) (letter of authorization to DMF (b) (4))	(b) (4)
Stopper	20-mm, (b) (4) grey chlorobutyl rubber stopper with (b) (4) barrier on product contact side, (b) (4) on non-product side	(b) (4)	STN (b) (4) (letter of authorization to DMF STN (b) (4))	(b) (4)
Seal	20-mm, aluminum shell with polypropylene flip- off cap overseal	(b) (4)	Not applicable (no product contact)	Not applicable (no product contact)

<sup>a</sup> DMFs containing the sterilization information for components listed in the table are located in [Section 3.2.P.3.5](#).

<sup>b</sup> (b) (4)

(b) (4)

**Container Closure System Extractable and Leachables Substances Determination**

(b) (4)

[Redacted text block]

[Redacted text block]

[Redacted text block]

**Secondary Packaging:** The secondary packaging consists of an opaque, tamper-evident, rigid paperboard carton. The carton provides physical protection for the vials during storage and shipping. *Reviewer Note: During PLI for the DP (at Catalent-BioPark, Baltimore MD), the secondary packaging container was inspected to be acceptable. Details can be found in the EIR report for the drug product manufacturing site.*

### 3.2.P.2.5 Microbiological Attributes

Reviewed by EAG

SRP-9001 DP is manufactured by aseptic processing, for intravenous infusion to avoid microbial contamination. The DP is supplied as single-use vials free of preservative. As part of processing, DP solution is filtered through (b) (4) filters. DP is aseptically filled using a process that has been validated. Components that have direct contact with the DP are either received sterile or sterilized during the process. DP is subject to sterility and endotoxin testing as part of the release process. For assurance of container closure system (CCS) integrity, the DP vial is tested for CCS integrity during stability testing, in lieu of sterility testing via (b) (4) method and has been developed according to the principles in (b) (4). *This is acceptable. Also, for detailed microbial containment strategy see DBSQC memo.*

### 3.2.P.2.6 Compatibility

Reviewee by EAG

SRP-9001 drug product (DP) is supplied as single-use, preservative-free, sterile, aqueous solution for infusion, to be administered with a 0.2 µm in-line dosing filter. Studies to assess for potential change in (b) (4) were performed during clinical development. (b) (4) independent compatibility studies were performed using representative DP (lot (b) (4) in which the DP was (b) (4)

[REDACTED]

### Dosing Filter Compatibility Study (Study 3)

According to the Applicant, low levels of visible particles were observed in SRP-9001 drug product vials during the 100% visual inspection process in some batches and were rejected. Based on investigations conducted, the Applicant concluded that the formulated DP has the propensity to also form inherent (b) (4)-related particles. Therefore, as a risk mitigation strategy, a dosing filter is needed in the infusion line to reduce the level of inherent subvisible and visible particles in the dosing solution. A study to assess the in-use compatibility and effectiveness of a 0.2 µm in-line filter as part of DP administration to remove potential intrinsic particulates in the DP, was conducted using the delivery device components listed in the table below. *(Note: delivery device components were requested during BLA review under Amendment # 27, 2023.03.03). The Applicant also clarified that the in-line filter was introduced in Study SRP-9001-103 and the ongoing pivotal trial (SRP-9001-301). Clinical studies SRP-9001-101 and 102 did not use the in-line filter for administration.*

**Table 81: Description of Delivery Device Set Used in Compatibility Studies**

Component	Description	Manufacturer	Part Number	Sarepta In-Use Compatibility Study Number	Material of Construction
Study 3					

Syringe	60 mL plastic syringe (b) (4)	(b) (4)	(b) (4)	RPT-02108	Siliconized polypropylene
IV infusion extension set	Non-DEHP IV infusion extension set	(b) (4)	(b) (4)		PVC (non-DEHP)
IV catheter	(b) (4) Catheter	(b) (4)	(b) (4)		Polyurethane
Needle	21-G Precision Glide needle	(b) (4)	(b) (4)		Stainless steel
In-line dosing filter	Non-DEHP in-line filter extension set (0.2 μm PES filter)	(b) (4)	(b) (4)		PVDF (hydrophobic air vent filter membrane), Copolyester (housing material), PVC (non-DEHP, tubing), PES (filter)
DEHP = Di(2-ethylhexyl)phthalate PES = polyethersulfone PVC = polyvinyl chloride PVDF = (b) (4)					

(b) (4)

(b) (4)

(b) (4)



(b) (4)

**Reviewer Comment:**

- (b) (4)

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

- Information provided to describe pharmaceutical development together with the additional IR responses are acceptable.
- State if deficiencies were identified and how they were resolved.
  - Limited information regarding description of the delivery device components used in the assessment of device compatibility study was present in the BLA. This was resolved with the Applicant through an IR request (Amendment 27).
  - Absence of assessment of cumulative process leachables in DP. Upon FDA request, the Applicant committed performing such assessment (PMC #1). The study details, recommended by FDA (see review memo of Dr. Andrey Sarafanov), were communicated to the Applicant on January 20, 2023 (Question 24).

**3.2.P.3 Manufacture**

**3.2.P.3.1 Manufacturer(s)**

DP Manufacturers are summarized the table below.

**Table 83: Description of DP Manufacturers**

Site Name and Address	FEI	DUNS	Responsibility	Testing Performed (if applicable)
Catalent Pharma Solutions <sup>a</sup> Catalent Maryland (BioPark) 801 West Baltimore Street, Suite 302, Baltimore, MD 21201, USA	3015558590	618890289	Manufacture	(b) (4), Bioburden, Filter integrity, Fill weight check
(b) (4)	(b) (4)	(b) (4)	Labeling Secondary packaging	n/a

(b) (4)			DP storage	
(b) (4)	(b) (4)	(b) (4)	Release testing Stability testing	Release: All methods except Vector genome concentration and Potency  Stability: All methods except Vector genome concentration, Potency, and Container closure integrity test
(b) (4)	(b) (4)	(b) (4)	Release testing	All methods except Vector genome concentration, Potency, Percent full capsid, and Identity (vector capsid)
Sarepta Therapeutics 100 Federal Street, Andover, MA 01810, USA	3012807588	072827382	Release testing Stability testing	Potency and Vector genome concentration
(b) (4)	(b) (4)	(b) (4)	Stability testing	Container closure integrity test

<sup>a</sup> Previously Paragon Bioservices, Inc.

**Reviewer's comment:** The updated list of DP manufacturers was submitted under Amendment #19 dated 02/17/2023.

### 3.2.P.3.2 Batch Formula

Each DP batch is prepared according to the formula summarized in Table 84. A batch consists of (b) (4) (approximately (b) (4) vials) of pre-sterilized DP.

**Table 84: DP Batch Formula**

Component	Quantity	
	Min Batch Size (b) (4)	Max Batch Size (b) (4)
Delandistrogene moxeparvovec	(b) (4)	(b) (4)
Sodium chloride	(b) (4)	(b) (4)
Tromethamine HCl (b) (4)	(b) (4)	(b) (4)
Tromethamine (b) (4)	(b) (4)	(b) (4)
Magnesium chloride	(b) (4)	(b) (4)
(Magnesium chloride (b) (4)	(b) (4)	(b) (4)
Poloxamer 188	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

<sup>a</sup> Target DP titer of  $1.33 \times 10^{13}$  vg/mL multiplied by the batch (b) (4), is presented. The total vg per batch for each DP formulation is calculated from the (b) (4), which is determined by (b) (4) during DS release testing.  
q.s. = quantity sufficient to achieve final (b) (4)

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

☐ Descriptions of DP manufacturers and the DP batch formula are acceptable.

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

(b) (4)

- **Visual Inspection**

All filled vials are manually inspected for container closure and solution defects. The inspection process is qualified to remove container integrity defects which may compromise the sterility of the product, and to remove other container and product characteristic defects such as variations in fill level, discoloration or clarity. Vials found to have defects, including visible particles are removed. Vials passing the 100% manual visual inspection process are then sampled for an Acceptable Quality Limit (AQL) visual inspection.

- **Freezing and Storage**

The drug product vials are frozen and stored at  $\leq -60^{\circ}\text{C}$ .

- **Labeling and Packaging**

Drug product is transferred to the secondary packaging site. Labeling and packaging operations are performed at (b) (4) under GMP on qualified equipment according to standard operating procedures.

**Long-Term Storage:** The final drug product vials are stored at  $\leq -60^{\circ}\text{C}$ .

**Reprocessing:** No reprocessing is allowed during the manufacturing of the drug product.

**Reviewer Comment:** *In response to IRs, the Applicant provided information on DP labeling and packaging in amendment #19 of 03Feb2023 and in amendment #27 of 03Mar2023. The provided information is acceptable.*

**DP Labeling and Packaging**

The unlabeled vials are shipped from Catalent BioPark to (b) (4) for vial labeling and secondary packaging. In summary, after the drug product vials are manufactured and inspected, they are packaged directly into (b) (4). These (b) (4)

**The Primary (vial) and Secondary (carton) Labeling Procedures:**

Drug product vials are labeled in a room maintained at (b) (4). The primary vial labels are manually applied to the vials and visually inspected. Labeled vials are transferred into (b) (4) secondary carton. The carton is sealed with tamper evident seals to maintain product identity. Finished goods are (b) (4). The established labeling procedures and controls are supported by the (b) (4) study summarized under stability section 3.2.P.8 Stability).

Identity testing by (b) (4) is performed at (b) (4) to ensure identity of the product in accordance with 21CFR 610.14. Confirmation of the passing ID test by QA is required. The labeled DP is packed and shipped for distribution (of the commercial finished goods) to Sarepta customers from the same packaging site (b) (4) and will only be sent to the clinical site when a DP administration is scheduled. Drug product will not be stored at the dosing site long term. These commercial shipments are completed using qualified, temperature-controlled shipping processes and shippers that utilize dry ice to maintain temperature. Temperature is continuously monitored for these shipments using specialty logistics courier. Instructions for the storage of the product at the dosing sites are provided in the USPI to customers. *Reviewer Comment: Description of labeling and shipping procedures are acceptable.*

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

The description of DP manufacturing process is acceptable. In response to IRs, the Applicant provided the information on DP labeling and packaging in amendment #19 of 03Feb2023 and in amendment #27 of 03Mar2023. The provided information is acceptable.

**3.2.P.3.4 In-process Controls**

*Reviewed by LB*

Throughout the SRP-9001 manufacturing process, multiple process parameters are controlled and monitored. The controls of the critical steps of the commercial manufacturing process for SRP-9001 Drug Product are summarized in following tables:

**Table 86: Critical Process Parameters in SRP-9001 DP Manufacture**

(b) (4)
---------

**Table 87: In-Process Controls for SRP-9001 DP**

(b) (4)
---------

(b) (4)

**Table 88: DP In-Process Hold Times**

(b) (4)

(b) (4)

### **3.2.P.3.5 Process Validation and/or Evaluation**

*Reviewed by LB and AS*

#### **Process Validation Overview**

The Applicant states that the Process Validation of the SRP-9001 drug product (DP) manufacturing process has been carried out with adherence to current regulatory guidelines. Process validation is executed through a methodical sequence of cross-functional activities that incorporate the evolving knowledge of the drug product and its characteristics with an understanding of the production process gained through experimentation, experience and GMP manufacturing activities. The process validation lifecycle links product and process development, validation of the commercial manufacturing process and on-going verification to ensure the process remains in a state of control throughout routine commercial production. The process validation program follows written guidelines aligned with ICH guidance. The various aspects of process qualification include:

- (b) (4) studies



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

The DP manufacturing process validation results generated from the PPQ runs are acceptable. The results of (b) (4) will be submitted by March 31, 2024 – PMC #3.

**3.2.P.4 Control of Excipients**

*Reviewed by SS*

**3.2.P.4.1 Specifications**Compendial excipient

The compendial excipients are summarized in Table 98 and comply with the quality standards as referenced in Table 99.

**Table 98: Compendial Excipients**

Excipient	Complies with
Sodium chloride	(b) (4)
Tromethamine (b) (4)	
Magnesium chloride (Magnesium chloride (b) (4))	
Poloxamer 188	
(b) (4)	

Non-compendial excipient

Tromethamine HCl ((b) (4)) is a non-compendial excipient which is made from (b) (4). The specifications for Tromethamine HCl are summarized in Table 99.

**Table 99: Specifications for Tromethamine HCl (b) (4)**

(b) (4)
---------

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

The analytical procedures used for compendial excipients testing are performed according to the appropriate compendial monographs. The analytical procedures used to test Tromethamine HCl (b) (4) are summarized in Table 99. The assay methods are either compendial or validated except for the assays for (b) (4) and (b) (4) test is an



(b) (4) test and (b) (4) are not likely to be introduced during the manufacturing process.

#### 3.2.P.4.4 Justification of Specifications for Excipients

The specifications of the compendial excipients are consistent with those required by the respective compendial monographs. The specifications of Tromethamine HCl are designed to confirm the identity and (b) (4)

#### 3.2.P.4.5 Excipients of Human or Animal Origin

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

#### 3.2.P.4.6 Novel Excipient

There are no novel excipients in 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.

#### 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 EAG

*The specification for SRP-9001 drug product release is summarized under the Table 100 below. The justification for individual product attributes is summarized and discussed.*

**Table 100: SRP-9001 Drug product release specification**

Attribute	Analytical Procedure	Specification	Reviewer Comment
Appearance Clarity Color Visible particles Cap color	(b) (4)     , visual inspection Visual inspection	Clear, colorless liquid, may have some opalescence, (b) (4)  Cap color: Blue	<i>Acceptable, see discussion below. Amendment # 22 and 27</i>
(b) (4)	(b) (4)	(b) (4)	<i>Acceptable</i>
(b) (4)	(b) (4)	(b) (4)	<i>Acceptable</i>
Identity (vector genome)	(b) (4)	(b) (4)	<i>Acceptable</i>
Identity (vector capsid)	(b) (4)	(b) (4)	<i>Acceptable</i>

Sterility	(b) (4)	No growth	Acceptable
Bacterial Endotoxin	(b) (4)	(b) (4)	Acceptable
Capsid Purity	(b) (4)	(b) (4)	Revise to (b) (4) (Amendment 22)
(b) (4)	(b) (4)	(b) (4)	Revise to (b) (4) under Amendment#22
Percent Full Capsid	(b) (4)	(b) (4)	Acceptable based on data and statistical analysis of process B lots
Particulate Matter	Based on (b) (4)	(b) (4)	Acceptable compendial limits
(b) (4)	(b) (4)	(b) (4)	Criterion based on (b) (4)
Potency	(b) (4)	(b) (4)	Applicant did not revise potency spec under Amendment 22. FDA recommend (b) (4) relative potency based study 103 DP lots with consideration for method variability
		-- (b) (4) SRP-9001-micro-dystrophin: (b) (4)	Attribute not stability indicating and can not detect degraded DP. Therefore acceptable.
Vector Genome Concentration	(b) (4)	(b) (4)	Revised based on IR response in Amendment 67 Acceptable see discussion
Extractable volume	(b) (4)	(b) (4)	Acceptable see DBSQC memo.

**Appearance: Release Acceptance Criterion:** Clear, colorless liquid, may have some opalescence, (b) (4). Cap color: Blue

**Justification:** Filled vials are manually inspected. Defective vials including those with particulates are rejected during 100% visual inspection release test as described in (b) (4)



**Container Closure Integrity:** Container closure integrity testing (CCIT) is used in lieu of sterility testing during the (b) (4) stability time points. A deterministic (b) (4) test is utilized as described in (b) (4). The acceptance criterion is based on the (b) (4)

*See full detailed review under DMPQ memo. The method was found to be acceptable.*

(b) (4) : According to the applicant, this attribute is being replaced with the (b) (4) assay. *Note: The assay was used in the assessment of process A material with no specified limit. After the switch to process B, an acceptance criterion of (b) (4). This criterion was not informative as it was still wide (b) (4) relative to actual manufacturing data. Note: this method has been discontinued under the commercial Process B.*

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

- ☐ The release specification for the drug product and justifications are acceptable.

**3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures**  
Reviewed by EAG

Compendial Analytical methods:

*Note: For compendial methods such as (b) (4) Appearance, (b) (4), Sterility bacterial endotoxins, the description of the assay and verification information are reviewed in adequate details by DBSQC. Please see DBSQC review memo. The description and validation Product specific non-compendial analytical methods used for the release of SRP-9001 are summarized below.*

*Product specific, non-compendial release methods have been discussed under DS section 3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures) for Identity (vector genome), Identity (Vector capsid, Protein Identity), Capsid Purity and (b) (4)*

- ☐ **Percent Full Capsids by** (b) (4)

(b) (4)



(b) (4)

(b) (4)

(b) (4)

**Extractable volume:** *This compendial method was reviewed and found acceptable. See DBSQC memo for details.*

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

The description of DP release methods and validation is acceptable.

(b) (4)

**3.2.P.5.4 Batch Analyses**

*The information submitted to support batch analysis include process A and process B batches. Except for process B PPQ batches, all batches made were processed through to DP without a discrete DS storage stage. Because Process A has been discontinued and was unvalidated, the CMC review team's assessment of batch analysis was done primarily with process B batches which is the commercial representative process. Process A batches, used for Phase 1 Clinical trial(study101) have been reviewed and discussed under IND 17763. Drug product batch made from Catalent Process B process are summarized below.*

(b) (4)

(b) (4)

(b) (4)

(b) (4)

### 3.2.P.5.5 Characterization of Impurities

*The DS and DP are identical except* (b) (4)

*DS batches are* (b) (4) *. The description of product and process-related impurities, their clearance and control was discussed under. 3.2.S.3.2 Impurities.*

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

- ☐ Description of DP batch analysis and impurity and is acceptable.

**3.2.P.6 Reference Standards or Materials**

*Refer to section 3.2.S.5 Reference Standards or Materials) for information on Reference Standards or Materials. Reference standard information is acceptable.*

**3.2.P.7 Container Closure System**

*Reviewed by EAG and AS*

- Refer to information under section 3.2.P.2.4 Container Closure System.*

**Overall Reviewer's Assessment of Section 3.2.P.7:**

- ☐ Information submitted and the proposed PMC are acceptable.

**3.2.P.8 Stability**

*Reviewed by SS*

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

The intended storage condition for the DP is  $\leq -60^{\circ}\text{C}$ . DP stability studies include storage conditions of  $\leq -60^{\circ}\text{C}$  (up to (b) (4) months), (b) (4) (up to 6 months), and  $2-8^{\circ}\text{C}$  (up to 14 days), (b) (4). The CCS used for DP stability studies is the same as the one used for commercial production. The proposed DP shelf life is 12 months at  $\leq -60^{\circ}\text{C}$ , and the DP is recommended to "Do not refreeze" and "Do not shake".

Data from the assays listed in the Table 112 were analyzed to determine the DP shelf life. The (b) (4) assay was replaced by the in (b) (4) potency assay during the clinical development and was discontinued. The Applicant proposed to revise the AC for DP stability studies in Amendment #19 (2/3/2023), Amendment #50 (5/3/2023), Amendment #66 (6/7/2023), and Amendment #70 (6/14/2023). The DP stability specification for clinical and PPQ batches and the revised stability specification submitted under Amendment #70 (6/14/2023) are summarized in the table below. The changes are shown in bold.

**Table 112: DP Stability Acceptance Criteria**

Attribute	Acceptance Criteria for Clinical and PPQ Batches	Acceptance Criteria for Commercial Batches
Appearance	Clear, colorless liquid, may have some opalescence, May contain white to off-white particles	Clear, colorless liquid, may have some opalescence, May contain white to off-white particles
(b) (4)	(b) (4)	(b) (4)
Vector Genome Concentration	(b) (4)	(b) (4)
Potency-(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	N/A
Capsid Purity	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Particulate Matter	(b) (4)	(b) (4)
Particles (b) (4)	(b) (4)	(b) (4)
Particles (b) (4)	(b) (4)	(b) (4)



Bacterial Endotoxin	(b) (4)	(b) (4)
Sterility	No growth	No growth
Container Closure Integrity Test (CCIT)	(b) (4)	(b) (4)
* The (b) (4) assay was replaced by the in (b) (4) potency assay during the clinical development.		

**Reviewer comment:**

- Vector genome titer: The Applicant proposed to revise the AC for vector genome titer for DP stability studies from (b) (4) (Amendment #19 dated 2/3/2023), to (b) (4) of the target titer (Amendment #50 dated 5/3/2023), and then again to (b) (4) vg/mL (b) (4) (Amendment #66 dated 6/7/2023). Based on the stability data submitted, there are no changes in vector genome titer. FDA requested to revise the AC to be consistent with DP release, which is (b) (4) (6/8/2023). The Applicant accepted FDA recommendation and submitted the updated specification for the post-approval stability protocol under Amendment #70 (6/14/2023).
- The revised AC for (b) (4), potency (b) (4), capsid purity, and (b) (4) have been submitted under Amendment #66 (6/7/2023). This is acceptable.

**DP stability at the long-term  $\leq -60^{\circ}\text{C}$  storage condition**

The long-term stability study has been conducted using (b) (4) DP batches (Process B) as summarized in Table 113. The DP shelf-life was determined based on data collected from (b) (4) registration DP batches. The Applicant provided updated stability data under Amendment #19 (2/3/2023).

**Table 113: DP batches on long-term ( $\leq -60^{\circ}\text{C}$ ) stability studies**

(b) (4)

**Reviewer's comment:**

- In Amendment #47 submitted on 4/20/2023, the Applicant clarified that the DP vials used in the stability studies have not undergone the same labeling process as the proposed commercial DP at (b) (4). Although the Applicant submitted stability data

for the (b) (4) study that mimics the labeling process, the current stability protocol does not represent the long-term storage condition of commercial DP vials. In Amendment #66 (6/7/2023), the Applicant agreed to include (b) (4) to mimic the commercial labeling and packaging process before the DP vials are stored at  $\leq -60^{\circ}\text{C}$  and submitted the updated post-approval protocol.

- The stability samples are shipped from the DP manufacturing site, Catalent BioPark, to (b) (4), where they are (b) (4). Upon receipt vials are placed in  $\leq -60^{\circ}\text{C}$  storage until tested. (b) (4) for CCIT and to Sarepta Andover for potency and vector genome titer. All other stability tests are performed at (b) (4)

There are no concerns related to shipping and handling of the stability samples.

- Vector genome concentration

A plot of registration and PPQ stability data without a fit is shown in the figure below. The vector genome concentration results for the DP stored at  $\leq -60^{\circ}\text{C}$  for up to (b) (4) months conform to the proposed AC.

**Reviewer's comment:** Based on the data provided, no significant decreases in vector genome titer were observed. However, the assay results are highly variable, and a statistical evaluation of stability trends was not possible due to this high variation. Regarding (b) (4) assay re-validation, see Section 3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures.

(b) (4)

- (b) (4)

(b) (4)

**Reviewer comment:**

- The stability data for (b) (4) potency are highly variable. The Applicant stated that due to limited timepoints for each stability batch available (only (b) (4) stability timepoints for each lot), a statistical evaluation of stability data and stability trends using the available stability data is not possible (Amendment #47 dated 4/27/2023). Regarding assay controls and PMCs related to the potency assay, see (b) (4) Potency Assay.
  - The AC for (b) (4) potency is (b) (4) and it is too wide to ensure the product stability. After several rounds of IRs, the Applicant agreed to revise the AC to (b) (4) in Amendment #66 (6/7/2023).
  - During the PLI, it was discovered that the Applicant did not investigate multiple assay errors associated with (b) (4) potency testing on stability samples. This led to Observation 1 on the 483. See the EIR for the Sarepta Andover facility for additional information.
- (b) (4) / Capsid purity  
(b) (4) capsid highest impurity in all timepoints analyzed met the AC but showed a potential trend with time during storage at  $\leq -60^{\circ}\text{C}$ . According to the Applicant, all prediction results were within the specification (b) (4) at (b) (4) months, based on the prediction model using the data from registration batches. The Applicant commits (b) (4).

(b) (4)

**Stability at the accelerated storage condition (b) (4)**

(b) (4)

**Stability at the stressed condition (2-8°C)**

The stability study for the stressed condition was conducted to support potential brief storage of the DP at 2-8°C prior to administration at the clinics. This study was conducted using (b) (4) Process B DP (b) (4) stored at  $5 \pm 3$  °C condition in an upright orientation for 3, 7, and 14 days. Appearance, (b) (4) vector genome titer, (b) (4), capsid purity, and (b) (4) were not changed up to 14 days. The count of particles larger than (b) (4) per container was increased from (b) (4) particles/container at T=0 to (b) (4) particles/container at 14-day, but all data points still met the proposed AC.

*Reviewer's comment: While the (b) (4) potency data for (b) (4) micro-dystrophin at 7-day and 14-day were unavailable due to operator errors, this potency assay is not stability indicating and the (b) (4) potency data measuring total micro-dystrophin at 7-day and 14-day*

met the AC. Therefore, it is acceptable to demonstrate that the DP is stable for up to 14 days when held at  $5 \pm 3^\circ\text{C}$  in the final DP container. However, the study was conducted using the DP vials held only in an upright configuration. FDA recommended to indicate that the DP is stable for up to 14 days at  $5 \pm 3^\circ\text{C}$  when the vial is held in an upright position in the package insert. A commitment to (b) (4) is demonstrated in Section 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment.

(b) (4)

[Redacted]

[Redacted]

[Redacted]

[Redacted]

[Redacted]

(b) (4)

[Redacted]

(b) (4)

[Redacted]



(b) (4)

(b) (4)

### 3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

The Applicant commits to continuing and completing the ongoing stability studies for the registration lots to (b) (4) months at  $\leq 60^{\circ}\text{C}$  storage conditions. The Applicant may extend the DP shelf life based on real-time data generated from three representative lots according to the ongoing stability study protocol. The shelf life will be updated in the annual report.

#### Annual stability

Annual stability studies will be performed on at (b) (4) at  $\leq 60^{\circ}\text{C}$  and (b) (4) storage condition in alignment with ICH Q7. The post-approval stability protocol for the  $\leq 60^{\circ}\text{C}$  storage condition is summarized in the table below. If no DP is manufactured during a given year, no stability study will be initiated. The Applicant also commits to placing a DP batch manufactured with major DS or DP manufacturing changes on stability.

**Table 119: DP Stability Protocol for  $\leq 60^{\circ}\text{C}$  Storage Condition**

Test Name	Acceptance criteria	Time Point (month)					(b) (4)
		0	3	6	9	12	
Appearance	Clear, colorless liquid, May have some opalescence. May contain white to off white particles.	X	X	X	X	X	
Capsid Purity	(b) (4)	X	X	X	X	X	
Vector Genome Concentration	(b) (4)	X	X	X	X	X	

(b) (4)	(b) (4)	X	X	X	X	X	(b) (4)
(b) (4)	(b) (4)	X	X	X	X	X	
(b) (4) potency	(b) (4)	X	X	X	X	X	
	(b) (4)	X	X	X	X	X	
Particulate Matter							
Particles (b) (4)	(b) (4)	X	--	--	--	X	
Particles (b) (4)	(b) (4)						
Endotoxin	(b) (4)	X	--	--	--	X	
Sterility	No grow	X	--	--	--	--	
Container Closure Integrity Testing	(b) (4)	--	--	--	--	X	
-- Not tested							

### In-use stability

The in-use DP compatibility study was performed on DP lots less than 12 months old at the time of the study provided in Section 3.2.P.2.6 Compatibility. The Applicant commits to (b) (4)

### Stressed (5±3°C) stability

The stressed stability study was performed on (b) (4) potency results at 7-day and 14-day were invalidated due to operator error. The Applicant commits (b) (4)

**Reviewer's comment:** The Applicant agreed to include (b) (4) to mimic the commercial labeling and packaging process and submitted the updated post-approval protocol under Amendment #66 (6/7/2023). Applicant's post-approval stability plan and stability commitments are acceptable.



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

(b) (4) registration lots and (b) (4) PPQ lots were evaluated for DP stability. After multiple rounds of IRs, the Applicant agreed to revise the stability AC for vector genome titer to be consistent with DP release, which is (b) (4) and submitted the updated post-approval stability protocol under Amendment #70 (6/14/2023). The revised AC for (b) (4) potency (b) (4) capsid purity, (b) (4) were also submitted under Amendment #66 (6/7/2023). The stability data for (b) (4) potency are highly variable, and a statistical evaluation of stability data and stability trends using the available stability data is unavailable due to limited timepoints for each stability batch (only (b) (4) stability timepoints for each lot). FDA recommended that the Applicant tighten the AC for in (b) (4) potency (b) (4), and the Applicant agreed to revise the AC to (b) (4) and submitted the updated post-approval protocol in Amendment #66 (6/7/2023).

The DP vials used in the stability studies have not undergone the same labeling process as the proposed commercial DP, which does not represent the long-term storage condition of commercial DP vials. The Applicant agreed to include (b) (4) to mimic the commercial labeling and packaging process before the DP vials are stored at  $\leq -60^{\circ}\text{C}$  and submitted the updated post-approval protocol under Amendment #66 (6/7/2023).

Based on data from (b) (4) registration lots, the Applicant proposed a 12-month shelf life for the DP at  $\leq -60^{\circ}\text{C}$ . Additional data from the ongoing stability study will be provided as it becomes available in order to extend the DP shelf life. This is acceptable.

The stability data for the stressed condition were provided to support potential brief storage of the DP at  $2-8^{\circ}\text{C}$  and room temperature ( $25^{\circ}\text{C}$ ) prior to administration at the clinics. The results support that the DP is stable for up to 14 days when held at  $5 \pm 3^{\circ}\text{C}$  and stable for up to 24 hours at room temperature ( $25^{\circ}\text{C}$ ). However, the studies were conducted using the DP vials held only in an upright configuration. Following FDA's recommendation, the package insert was revised to indicate the position of DP vials. In addition, (b) (4), and (b) (4) studies were performed appropriately.

**3.2.A APPENDICES****3.2.A.1 Facilities and Equipment**

*Reviewed by DMPQ*

**3.2.A.2 Adventitious Agents Safety Evaluation**

*Reviewed by SS*

The strategy to control adventitious agent comprises of:


1. Ensuring adequate control of raw materials, especially those of biological origin that are used in the generation of cell banks and DS manufacturing.
2. Testing of cell banks and unprocessed bulk harvest for adventitious agents (bacteria, fungi, mycoplasma, and viruses)
3. Viral clearance by spike-recovery studies using (b) (4) model viruses to demonstrate that the downstream purification process can effectively clear viruses exhibiting a broad range of biochemical and biophysical properties.

**Reviewer's comment:** *Materials of Biological Origin including cell banks, (b) (4) were reviewed in 3.2.S.2.3 Control of Materials. The materials are satisfactorily controlled.*


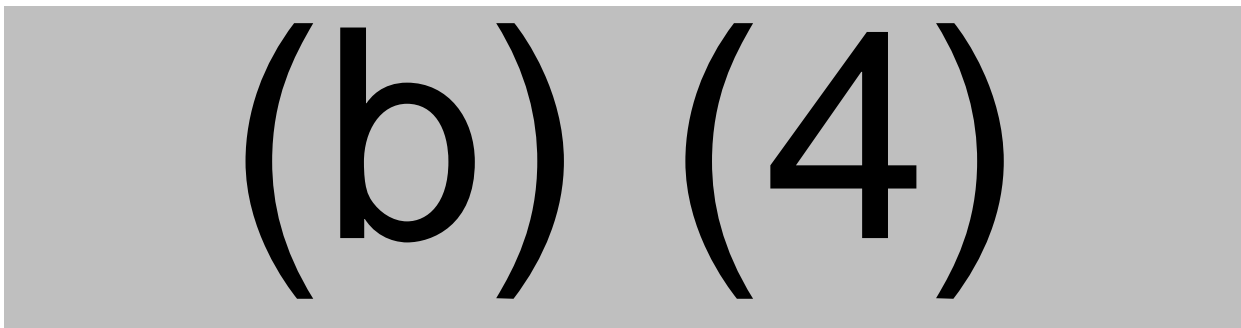
#### ❑ **Viral Clearance Studies**

*Reviewed by LB*

(b) (4)



(b) (4)

#### **Reviewer's Assessment:**

*The viral clearance study results are acceptable.*

#### **Overall Reviewer's Assessment of Section 3.2.A.2:**

- ❑ The information provided in Module 3.2.A.2 demonstrates negligible risk posed by materials of biological origin and demonstrates robust viral clearance. This is acceptable.

#### **3.2.A.3 Novel Excipients**

*There are no novel excipients.*

#### **3.2.R Regional Information (USA)**

##### ❑ **Executed Batch Records**

*Reviewed by EAG and LB*

A representative set of executed DS upstream and downstream batch records are provided for all steps in the DS manufacturing process described (under 3.2.S.2.2 Description of Manufacturing Process). The batch record for DS PV/PPQ DS batch (b) (4) was submitted in the BLA. The batch record contained detailed step-by-step executed instruction and data of manufacturing activities of all the steps involved in DS manufacture; from (b) (4) for SRP-9001.

A representative batch record for the preparation of the formulation buffer used during DS and DP manufacture (Lot No. (b) (4)) was also submitted and reviewed to be adequate. Additionally, a copy of an executed batch record for the DP detailing the manufacture of DP PV/PPQ batch # (b) (4) was submitted and reviewed to be generally acceptable.

**Reviewer Note:** During pre-license inspection (PLI) at the DS site (March 6-10, 2023, BWI-Harman Maryland). I(EAG) reviewed additional post PPQ executed batch records for DS Lot#(b) (4) and Lot#(b) (4). Also, during PLI for the DP (Feb 24-27, Biopark -Baltimore Maryland), additional executed batch records for DP lots (b) (4) and formulation buffer lots (b) (4) were reviewed. No concerns were found. The executed batch records for SRP-9001 DS and DP are acceptable.

**Overall Reviewer's Assessment of Combination Products Section:**

- ❑ Executed batch records submitted for review are acceptable.

**❑ Method Validation Package**

Method validation package provided in the BLA was reviewed and discussed at the appropriate sections of this memo: 3.2.S.4.2 Analytical Procedures and 3.2.S.4.3 Validation of Analytical Procedures (for drug substance) and 3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures (for Drug Product).

**❑ Combination Products**

Not applicable

**❑ Comparability Protocols**

This is not applicable to this BLA. The Sponsor did not propose a future comparability study.

**Other eCTD Modules**

**Module 1**

**A. Environmental Assessment or Claim of Categorical Exclusion**

Reviewed by EAG

The Applicant submitted environmental (EA) assessment under section 1.12.14 of the BLA, in accordance with 21 CFR 25 requirement. The applicant does not make a claim of categorical exclusion for EA. This application is not eligible for categorical exclusion.

The product delandistrogene moxeparvovec-rokl is derived from rhesus serotype 74 [rh74] AAV (AAVrh74), a nonpathogenic human DNA virus that is incapable of self-replication. The natural DNA genome of AAVrh74 has been replaced with SRP-9001 DNA for the expression of the miniaturized dystrophin protein. Vector mobilization theoretically may occur in the rare setting of a helper virus infected patient because of complementation and recombination between the viral vector, WT AAV and a helper virus. A worst-case scenario (presence of all helper functions plus AAV vector) would yield very low levels of additional vector, which is non-pathogenic. The replication of recombinant AAVrh74 in an infected host cell is dependent on co-infection with a WT AAV virus and a helper virus such as adenovirus. The generation time of Wt AAV in a natural ecosystem will be significantly very high, depending on the timing of the coinfection. The generation of replication competent AAV (rcAAV) at the time of SRP-9001 is not relevant since it lacks the rep and cap genes that are required for replication.

The manufacturing process is designed to minimize the potential that DNA recombination might result in a virus that contains viral DNA. The product is tested for the presence of (b) (4)

Certain wild-type AAVs can integrate at a specific locus of the host cell genome (AAVS1 in human chromosome 19 long arm); in these cases of integration, they remain non-pathogenic. The oncogenicity due to integration and insertional mutagenesis is a potential risk of AAV vectors, based on findings of tumors in mice and hepatocyte clonal expansion in the livers of hemophilic dogs years after administration of an AAV vector, with insertions noted near genes that control cell growth (Nguyen 2021). In contrast, recombinant AAVs have lost the ability to integrate at specific sites in the host cells. Theoretical insertional mutagenesis, caused by non-site-specific integration of the SRP-9001 genome into the host cell genome, can occur in transfected cells. Also, the simian virus 40 [SV40] sequence present in the construct may, in theory, allow interaction of SRP-9001 viral sequences with viruses present in the patient or non-target individual, the lack of intact MHCK7 in other WT viruses makes recombination/mutagenesis a theoretical safety concern.

Germline transmission was evaluated in 2 nonclinical studies in DMD<sup>MDX</sup> and WT mice, respectively per study #SR-20-014. Analysis of testes and ovaries using (b) (4) assay (b) (4) showed no staining above the negative control background for the AAV vector MHCK7 or the SRP-9001 transgene. SRP-9001 is indicated for use in male children. the applicant concludes that vertical transmission, via germline transmission is negligible.

Shedding occurs through patient excreta. Caregivers and patient's families will be advised on the proper handling of patients' bodily fluids and waste. Standard precautions are recommended to the health care providers, including the pharmacy personnel preparing SRP-9001, and waste should be disposed of as regulated medical waste. For caregivers, standard hygiene measures are recommended for caregivers and treated subjects after SRP-9001 treatment.


Data from a clinical study demonstrate that patients who are treated with delandistrogene moxeparvovec will shed vector DNA in saliva, urine, feces for around 4 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.

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 delandistrogene moxeparvovec-rokl will shed vector DNA in saliva, urine, feces for around 4-weeks. Viral shedding peaks in the first 48 hours post SRP-9001 administration in saliva and urine) and first month in the feces, then decreases rapidly to a level below the LOD. The half-lives (mean range) are ~57 to ~68 hours in saliva, ~38 to ~45 hours in urine, and ~54 to ~57 hours in feces. The data from the viral shedding assessment in clinical patients also show decrease in shedding from peak to week 4 was greater than 99% for saliva, urine, and feces.

*Reviewer Comment:*

- *The information provided in the environmental assessment demonstrate that the SRP-9001 poses no significant environmental risk from its approval. As such, a finding of no significant impact (FONSI) will be prepared.*

**B. (b) (4)**

A large rectangular area of the document is redacted with a solid grey box, covering several lines of text.

**C. Labeling Review**

**Full Prescribing Information (PI):**

**Reviewed by EAG**

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

ELEVIDYS is supplied as a frozen suspension of adeno-associated virus (AAV) vector-based gene therapy for a single intravenous infusion with a nominal concentration of  $1.33 \times 10^{13}$  vg/mL. It is supplied to the clinic as a customized commercial kit containing ten(10) to seventy (70) 10 mL single-dose vials. Each kit constitutes 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  $1.33 \times 10^{14}$  vector genomes per kilogram (vg/kg) of body weight (or 10 mL/kg body weight) and it is administered as a single intravenous infusion without dilution at a rate of less than 10 mL/kg/hour.

Prior to administration, the number of single-dose vials and volume of product needed (based on patient weight) is calculated and verified. The dose needed is transferred into the recommended syringe using aseptic techniques. (Multiple syringes maybe be prepared depending on the patient weight). The dose is administered via a syringe infusion pump, IV infusion tubing and catheter equipped with a 0.2-micron PES in-line filter. The intravenous access line is flushed with 0.9% Sodium Chloride Injection before and after the infusion.

**Section 11 (Description)**

ELEVIDYS (delandistrogene moxeparvovec-rokl) is a recombinant gene therapy designed to deliver the gene encoding the ELEVIDYS micro-dystrophin protein. ELEVIDYS is a non-replicating, recombinant, adeno-associated virus serotype rh74 (AAVrh74) based vector containing the ELEVIDYS micro-dystrophin transgene under the control of the MHCK7 promoter. The micro-dystrophin protein expressed by ELEVIDYS is a shortened version of dystrophin (138 kDa, compared to 427 kDa size of dystrophin expressed in normal muscle cells) that contains selected domains of dystrophin expressed in normal muscle cells.

ELEVIDYS is a preservative-free, sterile, clear, colorless liquid that may have some opalescence and may contain white to off-white particles. ELEVIDYS is a suspension for intravenous infusion with a nominal concentration of  $1.33 \times 10^{13}$  vg/mL and supplied in a single-dose 10 mL vial. Each vial contains an extractable volume of 10 mL and the following excipients: 200mM sodium chloride, 13 mM tromethamine HCl, 7 mM tromethamine, 1mM magnesium chloride, 0.001% poloxamer 188.

**Section 12 (Clinical Pharmacology)**

ELEVIDYS is designed to include MHCK7 promoter/enhancer that drives transgene expression in skeletal muscle cells. In nonclinical studies, ELEVIDYS micro-dystrophin protein was expressed predominantly in skeletal muscle (including diaphragm) and cardiac muscle cells. In clinical studies, muscle biopsy analyses confirmed ELEVIDYS micro-dystrophin expression in skeletal muscle of patients. *Note: This section of the PI also contains adequate description of the biodistribution of the vector including the shedding of the virus 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)

ELEVIDYS is shipped frozen ( $\leq -60^{\circ}\text{C}$  [ $-76^{\circ}\text{F}$ ]) in 10 mL single-dose vials. It can be refrigerated for up to 14 days when stored at  $2^{\circ}\text{C}$  to  $8^{\circ}\text{C}$  ( $36^{\circ}\text{F}$  to  $46^{\circ}\text{F}$ ) in the upright position. It is supplied as a customized kit to meet dosing requirements for each patient. Each kit contains ten (10) to seventy (70) single-dose vials of ELEVIDYS and one alcohol wipe per vial. Each ELEVIDYS kit may contain a maximum of two different drug product lots.

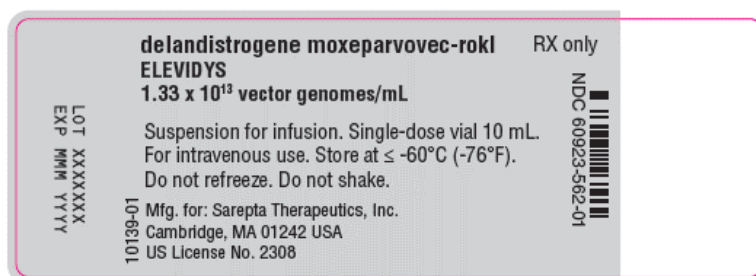
*Reviewer Note: If vials from two different lots are kitted, the expiry is assigned based on the lot with the shortest shelf-life. The instructions provided in the PI is supported by the information submitted and reviewed in the BLA. This includes stability and storage conditions prior to and during use in the clinic*

## Carton and Container Label:

Reviewed by EAG

After labeling, the primary vials are kitted(packaged) into a carton. The carton size ranges from 10 vial-carton to 70 vial-carton. Each kit bears unique NDC code#. Individual vial labels have NDC codes (and nominal titer). See below.

**Figure 35: SRP-9001 Container/vial sample label**



## Reviewer Comment:

*The primary vial and carton sample labels were reviewed and found acceptable per the requirements under 21 CFR Sec. 610.60-63 Container label. The Applicant under Amendment #70 (2023.06.14) revised the term 'single-use' vial to 'single-dose' vial to reflect the current FDA guidance (<https://www.fda.gov/media/117883/download>) and also included the language 'Do not shake' to the vial and carton labels. See additional schematic details about the kit configuration and Carton sample label under Figure 36, Figure 37 and Figure 38. Finally, the Applicant provided a sample of the carton printed label that will be attached to the configured Kit (Amendment # 77, dated 2023.06.21) which included an updated suffix (Figure 39). This is acceptable.*

An example of carton(kit) label which will include a printed carton label (specifying the number of vials in a specific configured kit, product identifying information) are shown below in Figure 38 and Figure 39.

**Figure 36: SRP-9001 One pack carton sample label**

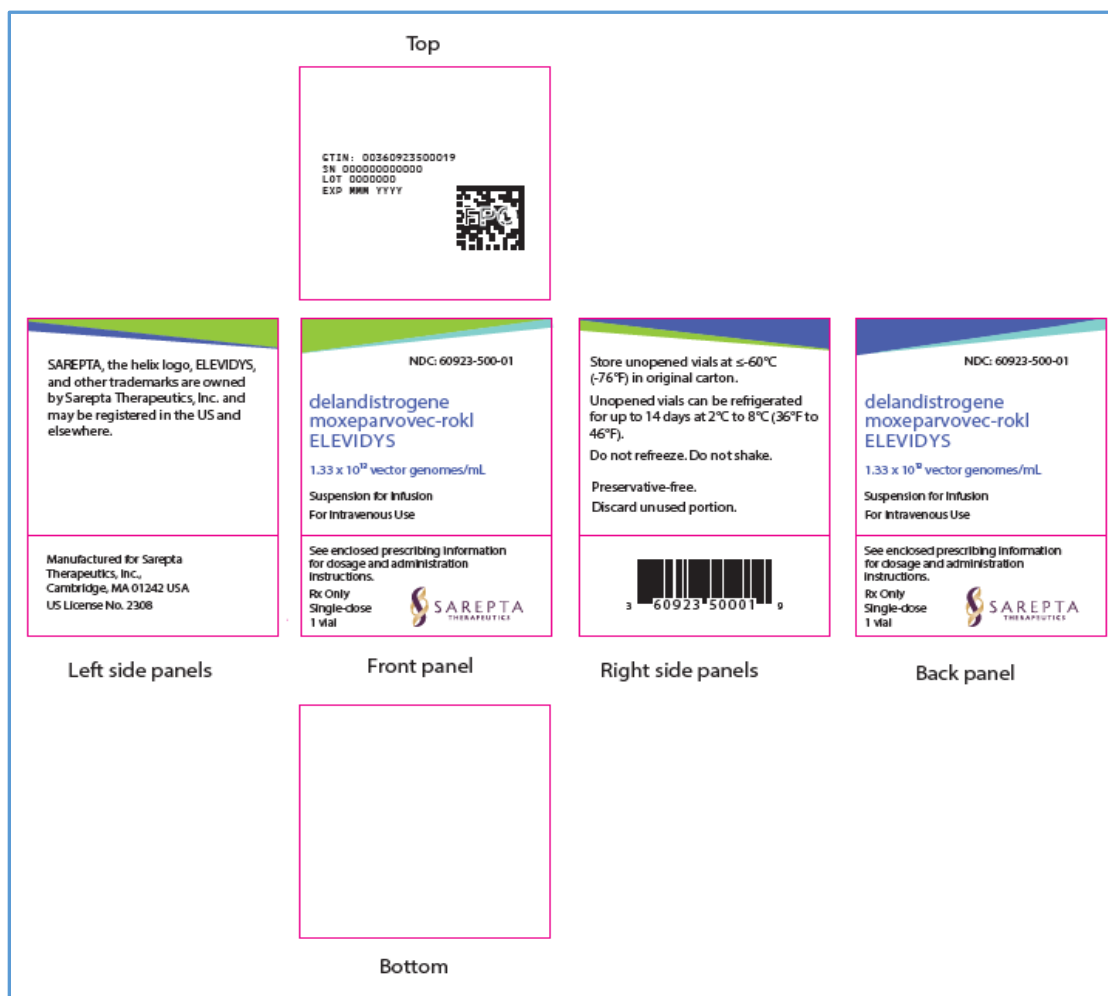




Figure 37: Example of Carton (kit) configuration

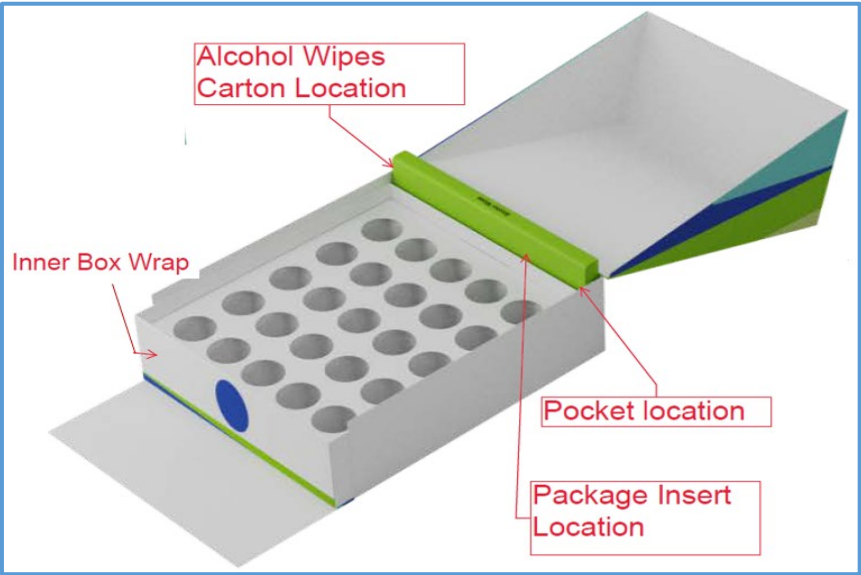


Figure 38: Example of Carton (Kit) front label





**Figure 39: Printed ELEVIDYS Kit label**

NDC: 60923-501-10 <b>delandistrogene moxeparvovec-rokl ELEVIDYS</b>	Patient Weight: 10.0 - 10.4 kg Kit Contents: 10 x 10 mL vials 10 alcohol swabs
 3 60923 50110 8	Date of refrigeration: <div style="border: 1px solid black; height: 30px; width: 100%;"></div>
GTIN 00360923501108 SN 000000000000 LOT 0000000 EXP MMM YYYY	

Date: 18 Feb 2023

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**SRP-9001 Carton Label** Market(s): US ■ Black  
Proof #: 4 Part no: 10087-01  
Size: 2.75 in x 2.75 in Supplier/Drawing #: N/A  
Fonts: Helvetica Neue LT Std Family, OCRB  
Minimum font size: 7pt  
GSP: (b) (4)

**Modules 4 and 5**

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

**Fluorescent Immunohistochemistry Assays**

*Reviewed by Brian Stultz (BS)*

The Applicant, in coordination with (b) (4), has developed fluorescent immunohistochemistry assays to monitor changes to the dystrophin associated protein complex (DAPC), dystrophin expression, and muscle content between pre- and post-treatment muscle biopsies as a biomarker for SRP-9001 efficacy. The Applicant has established a (b) (4)

(b) (4) fluorescent immunohistochemistry assay including muscle sectioning, antibody staining, image acquisition, image handling, and analysis algorithms to generate data. Antibodies are validated and fit for purpose for each assay. Muscle section antibody staining, and imaging protocols are optimized and validated. Imaging and analysis are mostly automated to ensure consistency across all samples with pathologist verification. Overall, the assay methodology is suitable to produce reliable data on comparison between pre- and post-treatment muscle biopsies. An example of assay performance for inter-run precision (intra-class correlation coefficient = (b) (4) is provided in the figure below.

**Figure 40: Dystrophin Assay Repeatability**



(b) (4) independent pathologist and analyst teams annotated and analyzed (b) (4) samples labeled on (b) (4) different days. The scores are highly clustered for each sample supporting the conclusion that myofiber MSD was not impacted by different days, different pathologists, or analyst teams.

**Microdystrophin Western Blot Assay (Method v2, DOC-03106)**

*Reviewed by EAG*

This method measures the absolute amount of SRP-9001 expressed microdystrophin via western blot. The method is performed in Andover and was performed to support clinical trial testing in the Phase I/II Clinical Trial for Duchenne Muscular Dystrophy using SRP-9001 (NCT03375164).

**Table 121: Summary of Clinical Western Blot Assay description**

<b>Bioanalytical method</b>	VAL-RPT-01333 Translational Development Microdystrophin Western Blot Method Version-2
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(b) (4)

**Table 122: Summary of Clinical Western Blot Assay Validation**

(b) (4)

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

*Western blot assay will not be used as primary endpoint or for clinicals decision in the ongoing Phase 3 confirmatory trial.*

**Summary Method Performance for Biodistribution VGC ddPCR (DOC-03188)**

DOC-02886:	Muscle DNA Isolation Method – for Muscle Tissue for ddPCR
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(b) (4)

(b) (4)

(b) (4)

**Vector Shedding (Vector Genome Copies Assay):** Analysis performed to measure the levels of vector genome copies shed into human stool, urine and saliva were conducted per the following:

- Vector Shedding (b) (4) (Vector Shedding in Stool method-SOP-DOC-(b) (4)
- Vector Shedding (b) (4) (Vector shedding in Urine and Saliva- SOP-DOC-(b) (4)

Briefly, the (b) (4) assay detects the viral genome DNA in a single reaction. The assay detects and quantify the absolute copy numbers of the viral genome present in certain amount of saliva, urine, and stool collected from patients who have received the SRP-9001 PRODUCT. The reaction relies on a (b) (4)

**Critical reagents used:**

- (b) (4)

- (b) (4)

The extraction of vector DNA (using sample specific commercial kits) and the (b) (4) reaction are described appropriately under the following documents submitted to the BLA:

**Table 123: Viral Shedding method summary and Validation**

(b) (4)

(b) (4)

**AAVrh74 humoral immune response by ELISA**

Reviewed and documented Dr Natasha Thorne, DIHD/OHT7(OIR)/OPEQ/CDRH.

- srp-9001-doc-02845.pdf – a “Test Method”/assay protocol for an ELISA Assay conducted at “the Gene Therapy Center of Excellence (GTCOE), at Sarepta, OH.”
- srp-9001-doc-02867.pdf – a protocol for the validation studies “to demonstrate the validity” of the ELISA Assay conducted at “the Sarepta Gene Therapy laboratory located at 5200 Blazer Parkway, Building 4, Dublin, OH 43017.”



- srp-9001-doc-02992.pdf – the results from the validation studies described in the srp-9001-doc-02867 document for the ELISA Assay as conducted at “the Sarepta Gene Therapy Center of Excellence (GTCOE) laboratory located at 5200 Blazer Parkway, Building 4, Dublin, OH 43017.”

*Excerpts from Consults Review: She concludes that:*

- *there is insufficient information to fully understand the validation studies conducted*
- *The device as described in the “Test Method” document is different than the device evaluated in these method validation studies,*
- *samples are diluted at (b) (4), that there is no evaluation of performance of the assay at higher dilutions (b) (4) or greater). The Applicant set the screening cut off at 1:400 or greater which is not supported by the validated cut off point.*
- *CDRH concludes that based on the information provided it is unable to determine the reliability of the assay.*

**Overall Reviewer’s Assessment of Relevant Sections of Module 4 and 5:**

- ❑ Description and validation of assays for the assessment of clinical surrogate endpoint (WB assessment of microdystrophin) and viral shedding are acceptable.
- ❑ The ELISA assay for screening patients who will receive the drug is not adequate per consults review from Dr Natasha Thorne. The Applicant has submitted a PMR for consideration by the clinical review team. Defer review to clinical team.