



IVD Companion Diagnostic Device Memorandum BLA 125781

Date: June 16, 2023
To: FILE
From: Lei Xu, MD, PhD, CBER/OTP/OCE/DCEGM/GMB2
Subject: IVD Companion Diagnostic Device for BLA 125781

BLA Applicant: Sarepta Therapeutics, Inc.

Product: Delandistrogene moxeparvovec-rokl (Proprietary Name: ELEVIDYS; SRP-9001)

I. Purpose and Background

It will be the regulatory decision of the Center Director to grant BLA 125781 accelerated approval for the treatment of ambulatory patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation in the *DMD* gene.¹ Only patients with baseline anti-AAVrh74 total binding antibody titers <1:400 and without any deletion in exon 8 and/or exon 9 of the *DMD* gene can receive ELEVIDYS. The purpose of this memorandum is to document CBER's assessment of the testing associated with SRP-9001 as mentioned in the labeling.

II. AAVrh74 total antibody screening assay:

CDRH/OPEQ/OHT7(OIR)/DIHD provided consultation to CBER for ICCR 00884656 in a memorandum dated January 25, 2023, regarding information submitted in BLA125781 for an ELISA-based assay as conducted at Sarepta, OH, USA and used to detect total binding antibodies to AAVrh74 in 3 clinical studies (SRP-9001-101, -102 and -103). CDRH determined that a companion diagnostic should be contemporaneously approved with ELEVIDYS. (b) (4) AAVrh74 ELISA assay. Further, the review of the validation studies for the Sarepta AAVrh74 ELISA assay were found to be inadequate to support a premarket submission or approval.

(b) (4)

III. Definition of an In Vitro Companion Diagnostic Device

Per the final [In Vitro Companion Diagnostic Device Guidance](#) (August 6, 2014), section III:

An in vitro companion diagnostic device (IVD companion diagnostic device) is an in vitro diagnostic device that provides information that is essential for the safe and effective use of a corresponding therapeutic product. The use of an IVD companion diagnostic device with a therapeutic product is stipulated in the instructions for use in the labeling of both the diagnostic device and the corresponding therapeutic product, including the labeling of any generic equivalents of the therapeutic product.

¹ See Center Director Decisional Memo for BLA# 125781

An IVD companion diagnostic device could be essential for the safe and effective use of a corresponding therapeutic product to:

- Identify patients who are most likely to benefit from the therapeutic product
- Identify patients likely to be at increased risk for serious adverse reactions as a result of treatment with the therapeutic product
- Monitor response to treatment with the therapeutic product for the purpose of adjusting treatment (e.g., schedule, dose, discontinuation) to achieve improved safety or effectiveness
- Identify patients in the population for whom the therapeutic product has been adequately studied, and found safe and effective, i.e., there is insufficient information about the safety and effectiveness of the therapeutic product in any other population

FDA does not include in this definition in vitro diagnostic tests that are not essential to the safe and effective use of a therapeutic product.

CBER determines that the AAVrh74 total binding antibody screening assay meets the definition of an IVD companion diagnostic device and is essential for the safe and effect use of SRP-9001.

The labeling reflects that patients will be selected for treatment with ELEVIDYS with anti-AAVrh74 total binding antibody titers <1:400. Baseline testing will be performed to determine the presence of anti-AAVrh74 total binding antibodies to evaluate pre-existing immunity against AAVrh74 prior to administration of ELEVIDYS.

IV. Non-Contemporaneous Approval

Per the final [In Vitro Companion Diagnostic Device Guidance](#) (August 6, 2014), Section IV.B.1:

FDA may decide to approve a therapeutic product even if an IVD companion diagnostic device is not yet approved or cleared when the therapeutic product is intended to treat a serious or life-threatening condition for which no satisfactory alternative treatment exists and the benefits from the use of the therapeutic product are so pronounced as to outweigh the risks from the lack of an approved or cleared IVD companion diagnostic device. This will be determined by FDA during product review.

Additionally, the guidance states:

In general, if a therapeutic product is approved without approval or clearance of an IVD companion diagnostic device, FDA expects that an IVD companion diagnostic device that is intended for use with the therapeutic product will be subsequently approved or cleared through an appropriate device submission, and the therapeutic product labeling will be revised to stipulate the use of the IVD companion diagnostic device. In addition, FDA will consider whether additional protections are necessary to address the safety issues presented by the use of the therapeutic product without an approved or cleared IVD companion diagnostic device.

CBER determines the IVD companion diagnostic device for AAVrh74 total antibody screening meets the scenario for non-contemporaneous marketing authorization:

- A. ELEVIDYS is an adeno-associated virus vector-based gene therapy indicated for the treatment of ambulatory patients aged 4 through 5 years with Duchenne muscular dystrophy (DMD) with a confirmed mutation of the *DMD* gene. This indication will be approved under accelerated approval.²
- B. The benefits from the use of SRP-9001 outweigh the risks from lack of an authorized IVD companion diagnostic device for AAVrh74 total antibody screening.
- i. DMD is a serious and life-threatening condition for which there is substantial unmet need for additional safe and effective therapies. DMD results from deficiency of the cytoskeletal protein dystrophin due to mutation of the *DMD* gene and is associated with progressive muscle weakness, eventually leading to respiratory failure and death. With best supportive care, adults are wheelchair bound, experience many complications, and have a median life expectancy about 41 years.
 - ii. The Center Director finds the data contained in BLA 125781 from Study 102 Part 1 to meet the standard for accelerated approval under 21 CFR 601.41 for the treatment of individuals ages 4 through 5 years with DMD based on data submitted for the surrogate endpoint of ELEVIDYS micro-dystrophin protein production, in which the evidence in this specific population, though not pre-specified in the randomized clinical trial and with limited number of study subjects that was submitted, appears reasonably likely to predict clinical benefit in this specific population of DMD, a serious disease with high unmet medical need.
 - iii. The scientific rationale for screening patients for anti-AAVrh74 total binding antibodies is to assess for levels of pre-existing immunity against AAVrh74 serotype to identify patients with DMD who may benefit from SRP-9001 therapy. The labeling reflects that patients will be selected for treatment with ELEVIDYS with anti-AAVrh74 total binding antibody titers <1:400. Anti-AAVrh74 total binding antibody titers of <1:400 are indicative of a relatively low level of pre-existing immunity against AAVrh74 serotype and such a low level may have a low potential for immune interference leading to reduced efficacy of the product. Among the enrolled study subjects (all with anti-AAVrh74 total binding antibody titer <1:400), there was no clear association between the anti-AAVrh74 total binding antibody titer and the level of expressed ELEVIDYS micro-dystrophin based on available data.
 - iv. In all ELEVIDYS clinical studies, patients with anti-AAVrh74 total binding antibody titers >1:400 using investigational assays (b) (4)

² The accelerated approval provisions of FDASIA in section 506(c) of the FD&C Act provide that FDA may grant accelerated approval to:

... a product for **a serious or life-threatening disease or condition** ... upon a determination that the product has an effect on a surrogate endpoint that is reasonably likely to predict clinical benefit, or on a clinical endpoint that can be measured earlier than irreversible morbidity or mortality, that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit, taking into account the severity, rarity, or prevalence of the condition and the availability or **lack of alternative treatments**.

CDRH) were not treated with ELEVIDYS. (b) (4)

Thus, the Center Director considers the potential benefits of the therapy, currently indicated only for patients ages 4 through 5 and under accelerated approval, to outweigh the risks from lack of an authorized IVD companion diagnostic device, considering an assay is undergoing validation (b) (4)

V. Postmarketing Commitment

The following postmarketing commitment (PMC) subject to reporting requirements under section 506B was cleared by CDRH and communicated by CBER to the Applicant on June 2, 2023:

Conduct adequate analytical and clinical validation testing to establish an in-vitro diagnostic device developed to accurately and reliably detect anti-AAVrh74 total binding antibodies that can be used to identify patients with DMD who may benefit from delandistrogene moxeparvovec-rokl therapy. The results of the validation study are intended to inform product labeling. The clinical validation should be supported by a clinical bridging study comparing the in-vitro diagnostic device and the clinical trial enrollment assays.

Per timetable submitted on May 30, 2023, the Applicant will conduct this study according to the following schedule:

Final Report Submission Date: 1/30/2025

(b) (4)

In an amendment 125781/65, received June 6, 2023, the Applicant confirmed agreement with the proposed PMC.

VI. DMD Genetic Tests:

CBER does not recommend issuing a post marketing commitment for the development of in vitro diagnostic tests for the detection mutations and/or deletions in the *dystrophin (DMD)* gene for the purposes of diagnosis (mutation confirmation) or patient selection (deletion detection), accordingly. This is based on multiple factors, including the course of diagnostic work-up and diagnosis for monogenic disorders such as DMD, the currently available laboratory developed testing (LDT) and genetic screening and testing landscape, and existing precedence for not requiring IVD companion diagnostic device development (not limited to CBER).