

## CENTER DIRECTOR DECISIONAL MEMO

**BLA 125781**

**Product Name:** ELEVIDYS (delandistrogene moxeparvovec-rokl)

**Indication:** Duchenne Muscular Dystrophy (DMD) in Ambulatory Individuals

**Applicant:** Sarepta Therapeutics, Inc.

**Author:** Peter Marks, M.D., Ph.D., Director, Center for Biologics Evaluation and Research (CBER), FDA

### SUMMARY

This memorandum explains CBER's final decision on BLA 125781 for ELEVIDYS (delandistrogene moxeparvovec-rokl) from Sarepta Therapeutics, Inc. I have read the reviews and recommendations by staff of the Office of Therapeutic Products (OTP) the Office of Biostatistics and Pharmacovigilance (OBPV), the Office of Compliance and Biologics Quality (OCBQ), as well as the consult from the Center for Drug Evaluation and Research (CDER) Division of Pharmacometrics and have discussed issues surrounding manufacturing quality, safety, and efficacy with the review team. In addition to the review memoranda, I have reviewed pertinent portions of the Applicant's submission, the Advisory Committee materials and transcript, and multiple scientific statements and video testimony submitted by the public to the docket (FDA-2023-N-1190). I have also discussed this file with senior staff within CBER and with senior colleagues at CDER.

Although I agree with the review team's conclusions regarding product quality and safety, I disagree with certain interpretations of the efficacy data and come to a different conclusion regarding individuals ages 4 through 5 years. The clinical efficacy outcome using the North Star Ambulatory Assessment (NSAA) among 4- and 5-year-olds showed an average 4.3-point increase in the least square mean change from baseline in the SRP-9001 group compared to a 1.9-point increase in the placebo group and in the subset of these individuals for which data are available, this outcome correlated with the level of ELEVIDYS micro-dystrophin protein expression. I therefore find that the data contained in BLA 125781, including from Study 102, provide substantial evidence of effectiveness of ELEVIDYS by demonstrating an effect on the surrogate endpoint of expression of ELEVIDYS micro-dystrophin protein that is reasonably likely to predict clinical benefit in the specific population of individuals ages 4 through 5 years. Accordingly, I find that the data and information in BLA 125781 meet the standard for accelerated approval under section 506(c) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR 601.41 for the treatment of individuals ages 4 through 5 years with DMD who do not have significant pre-existing antibody titers against the AAV rh74 vector or have other contraindications based on the inclusion criteria of the clinical trials.

### DISCUSSION

#### Disease background and unmet medical need

DMD is a severe progressive X-linked recessive disease of muscle caused by a spectrum of mutations in the *DMD* gene encoding dystrophin that are associated with progressive muscle weakness, eventually leading to respiratory failure and death. With best supportive care, adults are wheelchair bound,

experience many complications, and even with additional recent advances in supportive care are noted to only have a median life expectancy of 41 years.<sup>1</sup>

Glucocorticoids such as prednisone and deflazacort (the only drug that has received traditional approval from FDA for treatment of DMD) were the first drugs found to have some benefit in individuals with DMD, apparently delaying disease progression when given when motor development stops or declines. With the administration of glucocorticoids and best supportive care, individuals with DMD may have improvement of motor function for a few years. However, after peaking at approximately 6 years of age, even on corticosteroids, the muscle function of individuals with DMD deteriorates due to progressive muscle injury potentially caused by a variety of pathophysiologic mechanisms.<sup>1</sup>

Antisense oligonucleotides (ASOs) have been developed to facilitate exon skipping for specific out-of-frame deletions in the *DMD* gene leading to restoration of dystrophin function. Because of the nature of the genetic mutations, the ASOs can only address a minority of the existing gene mutations, such as a mutation in exon 51 that affects about 14% of individuals with DMD.<sup>2</sup> Additionally, these drugs require repeated administration, and confirmatory clinical trials have yet to be completed for the four ASOs available for the treatment of DMD in the United States.

Gene therapy has been considered as a potential option to address the treatment of DMD. However, the remarkably large size of the *DMD* gene encoding the dystrophin protein, which serves to link the muscle membrane and cytoskeleton, has precluded consideration of introduction of the entire contiguous coding region of the gene using the current generation of adenoviral-associated virus (AAV) vectors. For this reason, alternative strategies have been taken. These include strategies like Sarepta's, which involve trying to introduce shortened length dystrophin molecules attempting to mimic the situation seen in individuals with milder forms of muscular dystrophy, such as Becker Muscular Dystrophy. However, to date, no gene therapy for DMD has been approved by the FDA.

#### Summary of key data

SRP-9001 (delandistrogene moxeparvovec-rokl) is an AAVrh74 vector-based gene therapy designed to treat DMD by replacement of the dysfunctional or missing dystrophin protein with a shortened dystrophin protein about one-third the molecular size of the normal dystrophin protein, called by the Applicant ELEVIDYS SRP-9001 dystrophin (further described here as ELEVIDYS micro-dystrophin). The Applicant, Sarepta Therapeutics, has submitted three clinical studies for consideration:

1. Study 101, a study in individuals ages 4 to 7 (n=4) with an initial version of the product (Process A SRP-9001)
2. Study 102, a randomized, double-blind, placebo-controlled crossover trial in individuals ages 4 to 7 (n=41) using a version of the product not intended for commercialization (Process A SRP-9001)
3. Study 103, a single-arm study in individuals ages 4 to 7 (n=40) using the version of the product intended for commercialization (Process B SRP-9001)

Additionally, as part of their Biologics License Application (BLA) submission, the Applicant also provided data from external controls to help facilitate the interpretation of the uncontrolled studies (Study 101 and Study 103). Following initial review by the FDA, a decision was ultimately made to hold an advisory

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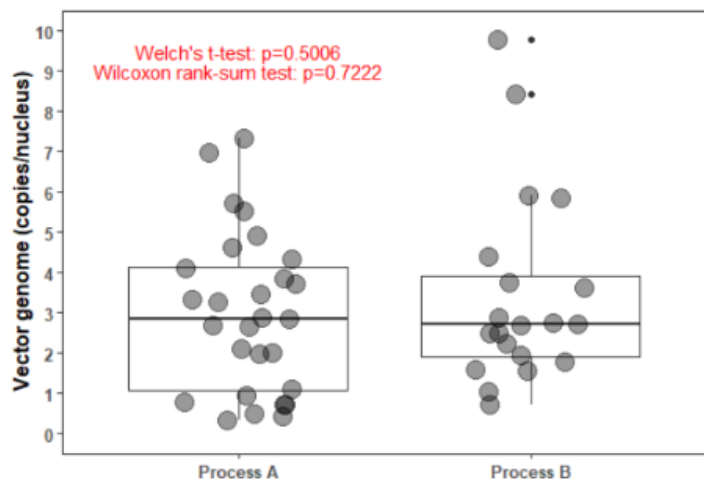
<sup>1</sup> Duan D, Goemans N, Takeda S, Mercuri E, Aartsma-Rus A. Duchenne muscular dystrophy. *Nat Rev Dis Primers*. 2021 Feb 18;7(1):13. doi: 10.1038/s41572-021-00248-3. PMID: 33602943.

<sup>2</sup> Takeda S, Clemens PR, Hoffman EP. Exon-Skipping in Duchenne Muscular Dystrophy. *J Neuromuscul Dis*. 2021;8(s2):S343-S358. doi: 10.3233/JND-210682. PMID: 34180420; PMCID: PMC8673534.

committee meeting, and the Cell, Tissue, and Gene Therapy Advisory Committee (CTGTAC) convened on May 12, 2023, to discuss the application. During the meeting, in addition to sponsor and FDA presentations, several providers and family members testified at the open public hearing showing videos indicating apparent improvement of individuals following the administration of SRP-9001. Ultimately, the committee voted 8-6 in favor of accelerated approval of this gene therapy. However, even some of the advisors who voted in favor of approval, noting the compelling patient testimony and video evidence shown, expressed concerns about the strength of the clinical evidence.

I have carefully reviewed the documentation on the evaluation of the submission provided by the different review disciplines and largely agree with the reviewers' assessments. I have no disagreement with the assessment of product quality, comparability, or safety. Although different processes were used to manufacture the product used in Study 101 and Study 102 (Process A) than in Study 103 (Process B, the commercial product proposed for marketing), the higher number of empty capsids present in Process B do not appear to significantly affect the number of viral genomes present in cells in those treated with the product manufactured by the two different processes as noted in the following figure from the CDER Office of Pharmacology, Division of Pharmacology Review Consult memorandum:

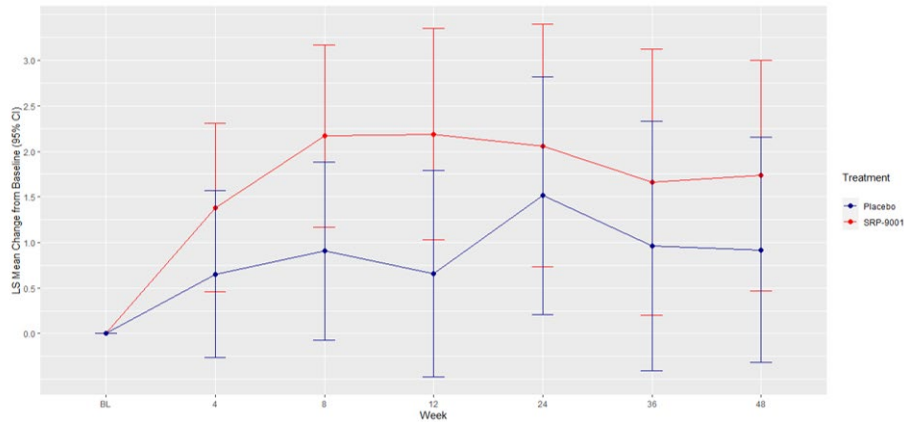
**Boxplot SRP-9001 Vector Genome Exposures Observed in Patients After ELEVIDYS Administration Using Formulations Manufactured by Process A and Process B at the Proposed Dose ( $1.33 \times 10^{14}$  vg/kg)**



Source: Reviewer's Analysis

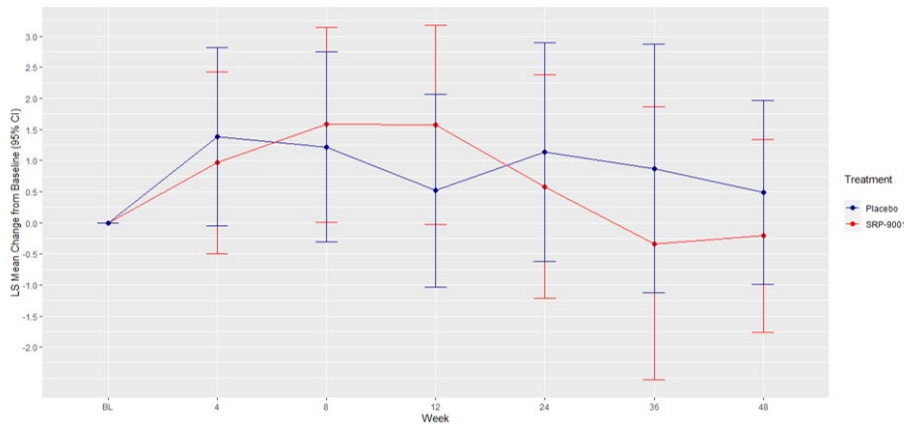
Additionally, in reviewing the documentation provided in the CBER Clinical Review, Clinical Pharmacology Review, and the Statistical Review, which do not recommend approval based upon their overall evaluation of the data submitted, as well as in reviewing the CDER Division of Pharmacometrics consult, I agree in large part with the efficacy assessments provided. Specifically, because of the variable nature of DMD and the evolution and variation in supportive care provided, Study 101, Study 103, and the use of external controls for analysis are not helpful in determining whether ELEVIDYS micro-dystrophin protein expression is reasonably likely to predict clinical benefit in individuals with DMD. Additionally, I agree with the review team that the data in Study 102 shown in the figures below taken from the Clinical Review memo for the overall population and for individuals ages 6 through 7 years for the primary clinical endpoint of the NSAA do not indicate clinical benefit for administration of the product independently based on outcome, nor do they support an accelerated approval based upon the proposed surrogate marker of ELEVIDYS micro-dystrophin protein expression.

### LS Mean Change in NSAA Total Score From Baseline Over Time



Source: FDA statistical reviewer’s analysis  
 Abbreviation: LS, least square; NSAA, North Star Ambulatory Assessment.

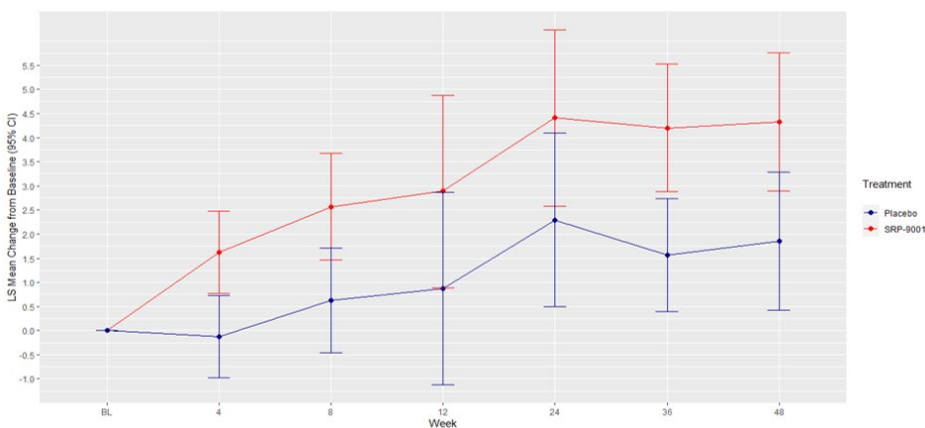
### LS Mean Change in NSAA Total Score From Baseline Over Time in 6-7 Year Age Group



Source: FDA statistical reviewer’s analysis  
 Abbreviation: LS, least square; NSAA, North Star Ambulatory Assessment.

However, an analysis of Study 102 confined to individuals ages 4 through 5 years supports clinical benefit.

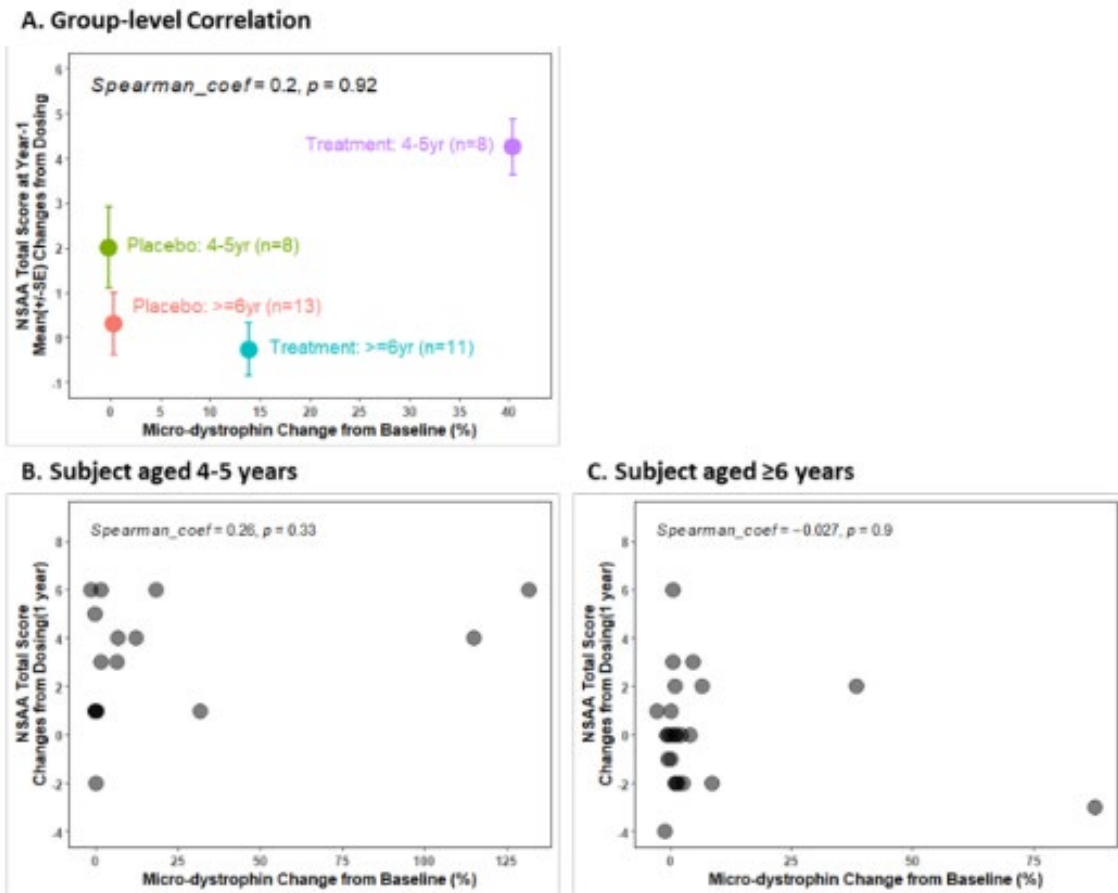
### LS Mean Change in NSAA Total Score From Baseline Over Time in 4-5 Year Age Group



Source: FDA statistical reviewer’s analysis  
 Abbreviation: LS, least square; NSAA, North Star Ambulatory Assessment.

Although I agree with the Statistical Review that it is not appropriate to note p-values for the outcomes of the NSAA in Study 102, the clinical efficacy outcome among 4- and 5-year-olds showed an average 4.3-point increase (standard error [SE] of 0.7) in the least square mean change from baseline in the SRP-9001 group compared to a 1.9-point increase (SE 0.7) in the placebo group. While this may not be sufficient on its own to demonstrate clinical benefit because of the sample size, this outcome correlates with the proposed surrogate endpoint of ELEVIDYS micro-dystrophin protein expression. Although the data for treated participants are limited (n=8), ELEVIDYS micro-dystrophin protein expression in individuals ages 4 through 5 years shows this correlation with their outcome on NSAA. This is noted in the following figure from the CDER Division of Pharmacometrics review (purple dot below):

**Relationship Between Week 12 ELEVIDYS Micro-dystrophin Changes From Baseline and NSAA Total Score at Year 1 by Age Group Using SRP-9001-102 Part 1 Data Only**



Source: Reviewer’s Analysis  
 Abbreviations: NSAA, North Star Ambulatory Assessment; SE, standard error.

**Integrated Assessment**

In summary, I agree with the review team regarding their evaluation of product quality and safety, and largely agree with their assessment of the clinical efficacy data. However, accounting for the totality of the available evidence, and noting the high unmet medical need in a serious disease affecting a relatively small number of individuals, I conclude that the data provided in Study 102 for individuals ages 4 through 5 years along with other supporting information meet the standard for accelerated approval because they show that the product has an effect on a surrogate endpoint that is reasonably likely to

predict clinical benefit in this population. After carefully considering the totality of the available data and information, I have determined that accelerated approval is appropriate.

As noted in the figures above, despite the lack of benefit in the overall population of individuals enrolled in Study 102, the data in the subgroup of individuals ages 4 through 5 years is compelling, even though hypothesis testing in this age group was not pre-specified. In particular, the results of ELEVIDYS micro-dystrophin protein expression and the results of the NSAA in this age group supports an association between the two, such that ELEVIDYS micro-dystrophin protein expression is reasonably likely to predict clinical outcome in individuals ages 4 through 5 years eligible for this treatment.

A change in the disease course of DMD is observed on average at approximately age 6 years. Prior to this age, there is often improvement in physical function with corticosteroid treatment and best supportive care. However, following this age, a decline in physical function often begins.<sup>3,4</sup> Because this clinical observation of physical decline after age 6 years may reflect a change in the underlying disease pathology related to any one of several different potential mechanisms of irreversible muscle injury, an analysis of the data confined to ages 4 through 5 years is not unreasonable.

Regarding the larger population of ambulatory patients with DMD, the externally controlled data provided are challenging to interpret and the randomized data from Study 102 in children ages 6 through 7 years do not provide compelling data regarding the ability of the expression of the ELEVIDYS micro-dystrophin protein to predict clinical benefit in children ages 6 through 7 years with DMD. In older children, it is at least theoretically plausible that the product may be less effective. Additionally, the administration of a potentially ineffective AAV gene therapy, which may preclude administration of a subsequent AAV gene therapy because of the development of high titer antibodies, presents significant concerns. These concerns may be even greater in older children receiving an ineffective AAV gene therapy, as they might not have time to wait for the development of a subsequent generation of gene therapy that could be given prior to their significant physical decline if such high titer AAV antibodies develop. The possibility that older individuals with DMD may not benefit from treatment with SRP-9001 because of irreversible lesions in muscles that develop with age also supports granting accelerated approval at this time for children ages 4 through 5, as some individuals in this younger age range might otherwise irreversibly miss a window of opportunity for the product to provide clinical benefit.

The approach described above meets the statutory standard for accelerated approval set forth in section 506(c) of the FD&C Act and is consistent with FDA's regulations and policies, including as articulated in guidance. As FDA has explained in regulations and draft guidance, FDA exercises its scientific judgment to determine the kind and quantity of data and information an applicant is required to provide for a particular drug to meet the applicable statutory standards. FDA must reach the conclusion that there is substantial evidence of effectiveness to approve a drug; however, the degree of certainty supporting such a conclusion may differ, depending on clinical circumstances (e.g., severity and rarity of the disease and unmet medical need). This reflects the longstanding awareness that, in certain

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<sup>3</sup> Mercuri E, Signorovitch JE, Swallow E, Song J, Ward SJ; DMD Italian Group; Trajectory Analysis Project (CTAP). Categorizing natural history trajectories of ambulatory function measured by the 6-minute walk distance in patients with Duchenne muscular dystrophy. *Neuromuscul Disord*. 2016 Sep;26(9):576-83. doi: 10.1016/j.nmd.2016.05.016. Epub 2016 May 27. Erratum in: *Neuromuscul Disord*. 2017 May;27(5):e1. PMID: 27423700; PMCID: PMC5026045.

<sup>4</sup> Miller NF, Alfano LN, Iammarino MA, Connolly AM, Moore-Clingenpeel M, Powers BR, Tsao CY, Waldrop MA, Flanigan KM, Mendell JR, Lowes LP. Natural History of Steroid-Treated Young Boys With Duchenne Muscular Dystrophy Using the NSAA, 100m, and Timed Functional Tests. *Pediatr Neurol*. 2020 Dec;113:15-20. doi: 10.1016/j.pediatrneurol.2020.08.013. Epub 2020 Aug 27. PMID: 32979653.

settings, a somewhat greater risk of false positive conclusions (compared to placebo-controlled or other randomized superiority trials)—and, therefore, less certainty about effectiveness—may be acceptable, when balanced against the risk of rejecting or delaying the marketing of an effective therapy for an unmet medical need. The data supporting effectiveness could, despite the greater risk of error, support a conclusion in certain circumstances that there is substantial evidence of effectiveness. See, e.g., 21 CFR 601.41, and FDA’s Draft Guidance on Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products (December 2019).<sup>5</sup> Here, given the unmet medical need, the serious nature of the underlying disease entity, and the progressive and irreversible nature of the disease with onset in early childhood, it is reasonable to accept less certainty about effectiveness than in other circumstances. An additional randomized clinical trial will be required as a condition of accelerated approval to verify and describe the predicted clinical benefit. The trial is fully enrolled at this time and data from the study will be available by fall of 2023 as a condition of accelerated approval.

## CONCLUSIONS

I find that the data contained in BLA 125781 meet the standard for accelerated approval under section 506(c) of the FD&C Act and 21 CFR 601.41 for the treatment of individuals ages 4 through 5 years with DMD who do not have significant pre-existing antibody titers against the AAVrh74 vector or have other contraindications based on the inclusion criteria of the clinical trials. The data and information in BLA 125781, including data from the submitted randomized clinical trial (Study 102), provide substantial evidence of effectiveness of ELEVIDYS by demonstrating an effect on a surrogate endpoint—expression of ELEVIDYS micro-dystrophin protein at week 12 following administration of ELEVIDYS—that is reasonably likely to predict clinical benefit in this specific population for a serious disease with high unmet medical need. Therefore, and after reviewing other materials regarding product manufacturing quality and safety, and other relevant issues, as discussed above, it will be the regulatory decision of the Center to grant the application accelerated approval for the treatment of individuals ages 4 through 5 years with DMD who do not have significant pre-existing antibody titers against the AAVrh74 vector or have other contraindications based on the inclusion criteria of the clinical trials.

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<sup>5</sup> US Food and Drug Administration. [Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products | FDA](#). December 2019.