Background Document
Joint Meeting of the Pediatric Advisory Committee and Pediatric Ethics Subcommittee
May 18, 2017

Protocol Referral

The Office of Pediatric Therapeutics (OPT) received a referral on March 15, 2017 from the University of California at Los Angeles (UCLA) Institutional Review Board (IRB) for federal panel review under 21 CFR 50.54 of a protocol entitled "A Double-Blind, Placebo-Controlled, Multicenter Study With an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients with Duchenne Muscular Dystrophy (ESSENCE)."(UCLA-IRB, 2017) The protocol currently is underway using a peripheral intravenous line for study drug infusion placed every week (with two lines placed when the protocol calls for pharmacokinetic studies) for the initial 96-week study period, which is then followed by open-label administration of the investigational product. The protocol referral specifically is to consider whether placement of central venous catheters for study drug infusion (including for the placebo control group) would be acceptable during the initial 96-week study period.

The protocol referral was precipitated by "a subject complaint about the line placement that the investigator says reflects the difficulties faced by all five subjects enrolled at UCLA." (UCLA-IRB, 2017) On February 24, 2017, a parent asked the UCLA investigator to permit the use of a central venous access port because of continued peripheral venous access issues for her son who is enrolled in the ESSENCE trial. According to the investigator, the placement of peripheral intravenous lines "has been very difficult for the subjects due to the stress placed on them and the difficulty in accessing veins for some of them. One subject has extensive scar tissue and deep veins and on multiple visits it has required over 5 attempts at accessing a vein, causing significant pain and stress for the subject and the family. This patient is no exception. All 5 subjects enrolled in this study at UCLA are struggling with the discomfort of IV placement. Also, many DMD patients are autistic. Among the 5 subjects enrolled into this protocol at UCLA, 3 of them are autistic. This makes it particularly difficult for these subjects to tolerate IV placement, especially by nurses that are unfamiliar to them." (Report of Protocol Incident, March 15, 2017)

The UCLA IRB met on March 9, 2017 to consider this request, along with clarification from the investigator about the criteria that would be used to offer portacath placement. At that meeting, the IRB determined that the use of venous catheter placement (portacath) was not approvable under 21 CFR 50.51, 50.52 or 50.53, and was "unanimous in finding that the clinical investigation (including potential use of central venous catheters) represents a reasonable opportunity to further understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children." (21 CFR 50.54) (UCLA-IRB, 2017)

The sponsor revised the protocol to allow for "venous access methods such as midline catheter, central line, or portacath" (central venous access port) for study treatment administration at the discretion of the site investigator, and submitted it to the IND as version 6 (Amendment 5), dated April 3, 2017. The revised protocol also was submitted by the UCLA investigator to the UCLA IRB, which forwarded it to FDA on April 13, 2017, to be included in the IRB referral package. The revised protocol has not yet been implemented pending the results of the 21 CFR 50.54 panel review.

21 CFR 50, subpart D, the additional safeguards for children in FDA-regulated clinical investigations, restricts IRB approval to interventions and procedures that either present minimal risk (21 CFR 50.51) or a minor increase over minimal risk absent any prospect of direct clinical benefit (21 CFR 50.53), or that provide a sufficient prospect of direct benefit to justify the risks, the balance of which is comparable to the available alternatives (21 CFR 50.52).

Each intervention and procedure in a protocol must be evaluated separately (i.e., "component analysis") for approvability under one of these three categories. The use of a central venous catheter for administration of active product may be approvable under 21 CFR 50.52, as those children have a prospect of direct benefit. Children receiving placebo do not have a prospect of direct benefit, and thus the risks to this group must not exceed a minor increase over minimal risk (21 CFR 50.53) for the IRB to be able to approve the intervention absent referral under 21 CFR 50.54.(Food and Drug Administration, 2013) Placement of a central venous catheter or port for placebo administration exceeds a minor increase over minimal risk, and thus is not approvable by an IRB without a determination by the FDA Commissioner following review by a panel of experts. As such, OPT is convening a joint meeting of the Pediatric Advisory Committee (PAC) and the Pediatric Ethics Subcommittee (PES) for this purpose. The advisory committee process also provides an opportunity for public review and comment on the protocol and referral. Following the joint meeting, OPT will draft a decisional memorandum to the FDA Commissioner that will include a recommended course of action based on an analysis of the issues, the PAC/PES discussion and public comments.

Description of the Disease Process

Duchenne Muscular Dystrophy (DMD) is an X chromosome linked genetic disorder, with an estimated pooled prevalence worldwide of 4.78 cases (95% CI, 1.94-11.81) per 100,000 males. (Mah et al., 2014) Based on the estimated population of males worldwide in 2017, the overall prevalence of DMD is approximately 1780 cases. The gene defect occurs at chromosome Xp21; the specific DMD gene that codes for dystrophin, a 427kDa protein of the muscle sarcolemma (locus Xp21.2). (Bushby et al., 2010a) Without dystrophin, the muscle membrane is destabilized which results in the clinical features of motor delay, joint contractures, calf hypertrophy, and muscle weakness which are characteristic of the disease. (Mah, 2016) Systemic effects of muscle weakness include the development of cardiomyopathy and a requirement for respiratory support in the late teens to early adult years, leading to death in adolescence or early adulthood. (McDonald, Henricson, Abresch, Han, et al., 2013) A multidisciplinary approach to management has been shown to improve survival, including involvement of specialists in rehabilitation, cardiovascular and respiratory disease, gastroenterology, nutrition, orthopedics and surgery. Interventions such as nocturnal ventilation and early recognition and treatment of cardiac disease, in particular, have had significant impact. (Bushby et al., 2010b) More than 50% of patients are managed with glucocorticoid therapy, which has been shown to increase muscle strength and reduce the development of scoliosis, but has also been associated with a variety of adverse effects, including weight gain, Cushingoid appearance and vertebral body fractures. (Manzur, Kuntzer, Pike, & Swan, 2008) Recently (February 2017), FDA approved the use of the corticosteroid deflazacort (EMFLAZA™) for the treatment of patients 5 years and older with DMD. ("Approval Letter Deflazacort (EMFLAZA™) NDA 208684 & 208685,")

Although recent advances in management and treatment have resulted in delays in disease progression, no treatments to date have been shown to significantly improve survival in patients with DMD. Several products are in development and one product is approved that are intended to address the defect in the dystrophin gene. DMD patients have mutations in specific regions of the DMD gene, and products designed to target these regions may result in a potentially functional dystrophin protein. Eteplirsen (EXONDYS 51™), a morpholino antisense oligonucleotide appropriate for patients with a DMD gene that is amenable to exon 51 skipping, was approved by the FDA on September 19, 2016, under the accelerated approval regulations (21 CFR 314.510). ("Approval Letter Eteplirsen (EXONDYS 51) NDA 206488," 2016) The approval was based on an increase in the dystrophin level in skeletal muscle in some patients treated with eteplirsen. ("Eteplirsen (EXONDYS 51) Labeling," 2016) However, the studies failed to establish a significant change in clinical outcome as measured by the 6 minute walk test (6MWT). Accordingly, a confirmatory postmarketing study is required under 21 CFR 314.510 to verify and describe the clinical benefit of the product. Ataluren (TRANSLARNA™), a product that targets nonsense mutations that prevent production of dystrophin in a subset of patients with DMD, was given conditional approval in the European Union (EU) in August 2014 for use in patients 5 years of age and older with DMD who can walk and have the specific genetic defect targeted by the product. A confirmatory trial of clinical benefit is required in the EU for the sponsor to maintain approval. ("European public assessment report (EPAR) for Translarna," 2014) The website

ClinicalTrials.gov lists several studies which are underway by different sponsors that are designed either to address the defect in the DMD gene or to stimulate muscle mass and strength by inhibiting myostatin. ClinicalTrials.gov also lists Phase I/II studies which have been completed exploring the use of recombinant adeno associated viral (rAAV) vector dystrophin cDNA gene transfer in treatment of DMD. Challenges to be overcome in gene transfer trials include developing low-immunogenic AAV vectors capable of packaging the full-length dystrophin coding sequence, the requirement for whole-body gene delivery, and the translatability of nonclinical study results to DMD patients. (Jarmin, Kymalainen, Popplewell, & Dickson, 2014; Nance & Duan, 2015)

Product Description

SRP-4045 and SRP-4053 are phosphorodiamidate morpholino oligomers (PMO) or synthetic versions of naturally occurring nucleic acids designed to bind to targeted pre-mRNA sequences and modulate gene expression. Patients with DMD have mutations in the gene that codes for dystrophin. As mRNA decodes the gene to produce the dystrophin protein, misalignment in the exon boundaries or coding triplets in the gene sequence results in a premature stop codon during transcription and subsequent decay of the RNA transcripts. (Yokota, Duddy, & Partridge, 2007) PMOs bind to regulatory sites in the pre-mRNA, causing the areas of exon deletion to be skipped and allowing further production of protein by restoring the reading frame. The protein that is produced is a shortened, but potentially functional protein. The proteins produced appear to be structurally similar to those seen with milder forms of muscular dystrophy. Approximately 80% of DMD patients may have mutations that are amenable to exon skipping of pre-mRNA. (Aartsma-Rus et al., 2009)

SRP-4045 selectively binds to a target site in the dystrophin pre-mRNA, which presumably would force the exclusion of exon 45 from the final mRNA transcript. SRP-4053 selectively binds to a target site in the dystrophin pre-mRNA, which presumably would force the exclusion of exon 53 from the final mRNA transcript. The skipping of exons 45 and 53 allows for an internally deleted but potentially functional form of dystrophin to be produced. (van Roon-Mom & Aartsma-Rus, 2012) These products are appropriate for patients who have mutations that allow skipping of exon 45, or 53, both which occur in approximately 8% of patients with DMD. (Aartsma-Rus et al., 2009)

Nonclinical Studies

SRP-4045

In *in vitro* studies supported by the sponsor, SRP-4045 was shown to result in a high level of exon skipping activity (Sarepta, 2016a) which led to further study in a dystrophic *mdx* mouse model. Because PMOs intended for human use are not pharmacologically active in normal animals, a murine surrogate PMO was produced. The surrogate PMO restored the reading frame by skipping exon 23 of mouse dystrophin pre-mRNA, in a manner similar to the intended effect of SRP-4045 in humans. Mice chronically administered PMO for 1 year at clinically applicable doses demonstrated a dose-dependent improvement in muscle strength compared to untreated mdx mice. The locomotor activity in treated mice was significantly improved such that it was indistinguishable from that of wild-type mice. (Alter et al., 2006; Fletcher et al., 2006; Gebski, Mann, Fletcher, & Wilton, 2003; Malerba et al., 2011; Wilton et al., 1999; Wu et al., 2011)

A number of nonclinical studies have been completed to support safety. Cardiovascular and neurologic safety was evaluated in male cynomolgus monkeys. Intravenous doses up to 320 mg/kg did not identify in any safety concerns based on mortality, food consumption, body weight, respiratory rate, neurologic effects, body temperature, heart rate, electrocardiographic (ECG) or hemodynamic parameters. The product has low protein binding and is expected to have minimal drug/drug interactions when used with other agents. (P. Sazani, 2015) Good Laboratory Practice (GLP)-compliant multiple dose toxicity studies have been completed in mice and non-human primates, and juvenile animal toxicity studies have been completed in rats. Given that the drug is renally excreted, the kidney appears to be the main target organ for product toxicity. No adverse effects were seen in the cardiovascular or neurologic systems. No immunogenicity was seen in juvenile animals or non-human primates. Plasma exposure increased with dose. (Sarepta, 2016a, 2017a)

SRP-4053

In *in vitro* studies supported by the sponsor, SRP-4053 was shown to result in a high level of exon skipping activity in a dose dependent manner. (Sarepta, 2016b) The dystrophic *mdx* mouse model referenced above was used as supportive evidence of the pharmacodynamic effects of this product.

No cardiovascular, neurologic or immunogenicity effects were seen in nonclinical safety studies. Renal excretion is the main elimination pathway for this product. Consequently, the kidney is the main target organ for the product. No renal or bladder findings were observed in the 12-week study in NHPs. The NOAEL was the highest dose tested at 320 mg/kg. (P. Sazani, 2015; Sarepta, 2016b, 2017a)

Clinical Studies/Regulatory History

The sponsor received approval through the accelerated approval process on September 19, 2016 for eteplirsen (EXONDYS 51™), an exon 51 skipping oligonucleotide.

Eteplirsen is the first product in this oligomer class that has been approved. Eteplirsen received orphan designation for the indication of "treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping." The sponsor was granted a rare pediatric disease priority review voucher, as provided under section 529 of the FDCA, at the time of product approval of eteplirsen.

Three studies supported the accelerated approval of eteplirsen. The following descriptions of the completed studies are included in the approved labeling for eteplirsen (EXONDYS 51™) (Drugs@FDA, 2016):

> "EXONDYS 51 was evaluated in three clinical studies in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping.
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> In Study 1, patients were randomized to receive weekly infusions of EXONDYS 51 (30 mg/kg, n=4); EXONDYS 51 (50 mg/kg, n=4), or placebo (n=4) for 24 weeks. The primary endpoint was dystrophin production; a clinical outcome measure, the 6-minute walk test (6MWT), was also assessed. The 6MWT measures the distance that a patient can walk on a flat, hard surface in a period of 6 minutes. Patients had a mean age of 9.4 years, a mean 6-minute walk distance (6MWD) at baseline of 363 meters, and were on a stable dose of corticosteroids for at least 6 months. There was no significant difference in change in 6MWD between patients treated with EXONDYS 51 and those treated with placebo."(Drugs@FDA, 2016) Patients, study staff, and the investigators were blinded to whether a patient received eteplirsen or placebo in this study. In addition, two patients in the 30 mg/kg/week treatment group become unable to ambulate soon after the clinical trial began.
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> "All 12 patients who participated in Study 1 continued treatment with open-label EXONDYS 51 weekly for an additional 4 years in Study 2. The 4 patients who had been randomized to placebo were re-randomized 1:1 to EXONDYS 30 or 50 mg/kg/week such that there were 6 patients on each dose. Patients who participated in Study 2 were compared to an external control group. The primary clinical efficacy outcome measure was the 6MWT. Eleven patients in Study 2 had a muscle biopsy after 180 weeks of treatment with EXONDYS 51, which was analyzed for dystrophin protein level by Western blot. Study 2 failed to provide evidence of a clinical benefit of EXONDYS 51 compared to the external control group. The average dystrophin protein level after 180 weeks of treatment with EXONDYS 51 was 0.93% of the dystrophin level in healthy subjects. Because of insufficient information on dystrophin protein levels before treatment with EXONDYS 51 in Study 1, it is not possible to estimate dystrophin production in response to EXONDYS 51 in Study 1."(Drugs@FDA, 2016)
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> "In Study 3, 13 patients were treated with open-label EXONDYS 51 (30 mg/kg) weekly for 48 weeks and had a muscle biopsy at baseline and after 48 weeks of treatment. Patients had a mean age of 8.9 years and were on a stable dose of corticosteroids for at least 6 months. Dystrophin levels in muscle tissue were assessed by Western blot. In the 12 patients with evaluable results, the pre-treatment dystrophin level was 0.16% ± 0.12% (mean ± standard deviation) of the dystrophin level in a healthy subject and 0.44% ± 0.43% after 48 weeks of treatment with EXONDYS 51 ($p < 0.05$). The median increase after 48 weeks was 0.1%." (Drugs@FDA, 2016)

Under the requirements of accelerated approval, the sponsor has a postmarketing requirement to complete a 2-year randomized, double-blind, controlled trial of eteplirsen in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping to verify the clinical benefit of eteplirsen. The study randomizes patients to the approved dosage of eteplirsen (30 mg/kg weekly) or to a dosage that provides significantly higher exposure, e.g., 30 mg/kg daily. The primary endpoint is specified as the North Star Ambulatory Assessment (NSAA). ("Approval Letter Eteplirsen (EXONDYS 51) NDA 206488," 2016) The NSAA is a functional scale designed for ambulant boys with DMD consisting of 17 items that assess skills needed to remain functionally ambulant. Items on the NSAA may be timed, but these items are not part of the global score. (Mazzone et al., 2010) The six minute walk test (6MWT) was used in the eteplirsen trials. This test is a timed test measuring the distance that a patient can cover in 6 minutes. The 6MWT has been validated for use in DMD patients. (American Thoracic Society, 2002; McDonald, Henricson, Abresch, Florence, et al., 2013)

DMD patients vary in terms of the expression of severity of disease and loss of functional capacity, even when they have similar deletion mutations. These differences may be due to environmental factors, whether corticosteroids are used, extent of physical therapy, etc. Consequently, either large patient numbers or an extended trial are needed to clearly establish a difference between groups in regards to treatment. FDA has recommended clinical trials of at least 18 months to 2 years to increase the statistical power of a study to demonstrate efficacy. (Bello et al., 2015; Bushby et al., 2010a, 2010b; Food and Drug Administration, 2015a)

Three studies are active and/or recruiting for SRP-4045 and SRP-4053:

1) A randomized, double-blind, placebo-controlled, dose-titration, safety, tolerability, and pharmacokinetics study followed by an open-label safety and efficacy evaluation of SRP-4045 in advanced-stage patients with DMD amenable to exon 45 skipping (Study 4045-101). This study is listed on ClinicalTrials.gov as active but not recruiting participants (NCT02530905). Patients may be on SRP-4045 or placebo in the first 12 weeks of the study after which patients are provided open-label SRP-4045.

2) A randomized, double-blind, placebo-controlled, dose-titration, safety, tolerability, and pharmacokinetics study followed by an open-label efficacy and safety evaluation of SRP-4053 in patients with DMD amenable to exon 53 skipping (Study 4053-101). This study is listed on ClinicalTrials.gov as active but not recruiting participants (NCT02310906). Patients may be on SRP-4053 or placebo in the first 12 weeks of the study after which patients are provided open-label SRP-4053. This study is being conducted in the United Kingdom, France and Italy.

3) A double-blind, placebo-controlled, multicenter study with an open-label extension to evaluate the efficacy and safety of SRP-4045 and SRP-4053 in patients with DMD (ESSENCE). This study is listed on ClinicalTrials.gov as recruiting patients (NCT02500381). The study will enroll patients to 1 of 3 arms, SRP-4045 and SRP-4053 or placebo, and patients will remain on treatment for up to 96 weeks. **This protocol is the subject of this referral under 21 CFR 50.54.**

SRP-4045 and SRP-4053 were granted fast track designation status in 2014, which provides for more frequent interactions with the FDA review team and an option for a “rolling review” of portions of a Biological Licensing (BLA) or New Drug (NDA) Application. (Food and Drug Administration, 2014)

Protocol Review

ESSENCE is a randomized double-blind, multi-center, 96-week study (followed by a 96 week open label phase) to evaluate the efficacy and safety of SRP-4045 and SRP-4053 in approximately 99 DMD patients with genotypically confirmed deletion mutations that are amenable to skipping exons 45 or 53. The study will include a placebo group with 2:1 randomization. After an 8-week screening period, patients will be placed on weekly intravenous infusions of 30 mg/kg of SRP-4045 or SRP-4053 or placebo for up to 96 weeks.

Although the study currently is open to enrollment using peripheral intravenous infusions, the revised protocol being considered by the PAC/PES would allow for the use of “venous access methods such as midline catheter,

central line, or portacath" (venous access port) for study treatment administration at the discretion of the site investigator.

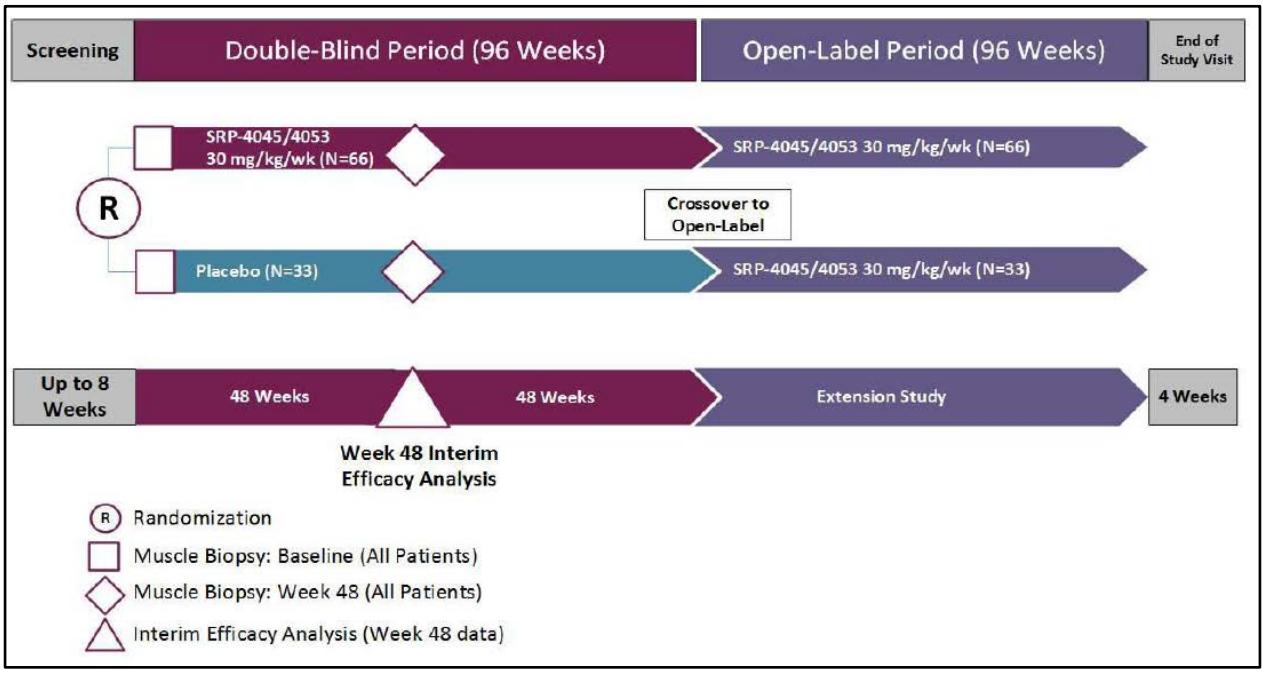
The DNP reviewed the ESSENCE protocol on November 6, 2015. At that time, the study specified that a venous access port could be used as the discretion of the investigator; other venous access methods were not specified. The DNP informed the sponsor that implantation of a venous access port for patients in the placebo arm of the study exceeded a minor increase over minimal risk and offered no prospect of direct benefit, and consequently was not approvable under 21 CFR 50.51, 50.52 or 50.53. This advice was based on a "component analysis" of the protocol, through which each component of the protocol (e.g., treatments, procedures, use of placebo, etc.) is analyzed separately and independently evaluated in terms of whether the intervention/procedure either offers a prospect of direct benefit (21 CFR 50.52) or does not and is no more than a minor increase over minimal risk (21 CFR 50.53) or should be referred to a federal panel for review (21 CFR 50.54). The sponsor subsequently amended the protocol to preclude use of a port during the double-blind placebo controlled period at study sites in the United States.

On February 24, 2017, the UCLA investigator received a request from a parent that a venous access port be allowed because of continued peripheral venous access issues for her son who is enrolled in the ESSENCE trial. The UCLA IRB met on March 9, 2017 to consider this request, along with clarification from the investigator about the criteria that would be used to offer portacath placement, and was "unanimous in finding that the clinical investigation (including potential use of central venous catheters) represents a reasonable opportunity to further understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children." In a letter dated March 15, 2017, the IRB referred the protocol for review by an FDA panel under 21 CFR 50.54. (UCLA-IRB, 2017) The sponsor revised the protocol to allow the use of alternative venous access methods such as a midline catheter, central line, or portacath, and submitted it to the IND as version 6 (Amendment 5), dated April 3, 2017. The revised protocol also was submitted by the UCLA investigator to the UCLA IRB, which forwarded it to FDA on April 13, 2017, to be included in the IRB referral package. The revised protocol has not yet been implemented pending the results of the 21 CFR 50.54 panel review. Although not specified, central lines generally include percutaneously inserted central catheter (PICC) lines, central venous catheters (CVC) and tunneled CVCs.

All patients will have a muscle biopsy at baseline and at Week 48. Muscle biopsies and the associated need for sedation/anesthesia generally have been allowed under 21 CFR 50.53. The Pediatric Ethics Subcommittee of the Pediatric Advisory Committee opined on the use of sedation for non-therapeutic procedures at a meeting in March 2015, and was unable to reach consensus on whether one or more approaches to procedural sedation should be considered a minor increase over minimal risk. However, the committee did make recommendations to minimize risk (discussed below in more detail under the heading "Sedation for Non-therapeutic Procedures" in the Analysis section). These recommendations should be taken into account when considering any non-therapeutic procedure in a pediatric patient, including the placement of a venous access port or central line.(Food and Drug Administration, 2015b)

Safety assessments include collection of adverse events, electrocardiograms (EKGs), echocardiograms, vital signs, laboratory assessments and physical exams. An additional 96-week open-label treatment period may follow the 96-week placebo period for a total of 204 weeks of patient participation. A complete schedule of study events is included in the protocol.

Study Schematic (page 40 of 99 of the protocol):



Major Inclusion Criteria:

- Male between the ages of 7 to 13 years of age, with an established diagnosis of DMD and out of frame deletion amenable to exon 45 or exon 53 skipping
- Stable pulmonary function with no requirement for nocturnal ventilation (FVC≥50%)
- Intact right and left biceps muscles or alternative upper arm groups (for biopsy)
- Stable dose of corticosteroids for at least 24 weeks
- Achieved a mean 6MWT distance of ≥300 to ≤450 meters
- Willing to use contraceptives if sexually active (male condom and female contraception)

Major Exclusion Criteria:

- Treatment at any time with utrophin upregulating agent, except PRO045 or PRO053
- Previous treatment with PRO045, PRO053 within last 24 weeks prior to Week 1
- Use of any pharmacologic treatment other than corticosteroids within 12 weeks prior to Week 1 of study participation
- Major surgery within the last 3 months or planned surgery during the study
- Left ventricular ejection fraction (LVEF) <50% on the screening echocardiogram (ECHO)
- Any other genetic disease other than DMD
- Clinically significant illness or ongoing medical condition that might make it difficult for patients to compete the study or adversely affect the safety of the patient

Primary Objective during the Double-blind Study Period:

To evaluate the effect of SRP-4045 and SRP-4053 (combined-active group) to placebo on ambulation, endurance, and muscle function as measured by the 6MWT

Secondary Objectives:

To evaluate the effect of SRP-4045 and SRP-4053 (combined-active group) on:

- Dystrophin protein expression as measured by WB and IHC fiber intensity
- Safety and tolerability

Primary Objective of the Open-label Study Period:

- Evaluate the long-term effects of SRP-4045 and SRP-4053 treatment on functional status up to 192 weeks.
- Evaluate the long-term safety and tolerability of SRP-4045 and SRP-4053

Pharmacokinetic Objective:

To evaluate the PK properties of SRP-4045 and SRP-4053 via a population PK model

Primary Efficacy Endpoint:

- Change from baseline at Week 96 on the 6MWT

Secondary Efficacy Endpoints:

- Change from baseline at Week 48 in quantity of dystrophin protein expression as measured by WB in biopsied muscle tissue
- Change from baseline at Week 48 in the intensity of dystrophin protein expression as measured by IHC in biopsied muscle tissue
- Ability to rise independently from the floor (without external support) at Week 96
- LOA status at Week 96
- Change from Baseline at Week 96 in NSAA total score, FVC% predicted, frequency of falls and LVEF

Primary Safety Endpoints:

Assessed through review and evaluation of AEs, Serious AEs, deaths and discontinuations throughout the study as determined through laboratory testing, immunologic assessments, EKGs, vital signs and physical exams.

Primary PK Endpoints:

A population PK analysis will be performed.

Safety Assessments and Monitoring:

An independent Data Monitoring Committee (DMC) will periodically monitor safety in the study. An interim efficacy analysis will be performed after the Week 48 6MWT data are available for 75% of patients. The first DMC meeting will be held 6 months after treatment initiation for the first patient in the study and then every 6 months throughout the study. Based on the results of the interim analysis, all patients may enter the open-label period of the study and receive active treatment, or patients must continue on double-blind placebo-controlled treatment through week 96.

Statistical Considerations (as per the protocol):

"At the interim analysis, the primary efficacy endpoint will be the change from Baseline at Week 48 in 6MWT. At the final analysis, the primary efficacy endpoint will be the change from Baseline at Week 96 in 6MWT (Sarepta, 2017a)."

"An interim analysis of efficacy will be performed when Week 48 6MWT data are available for 75% of the patients."

Patient Withdrawal:

Patients may withdraw at any time. The sponsor may withdraw a patient because they do not meet eligibility criteria, because of intolerable or unacceptable adverse events (AE), patient compliance or because patient is participating in another clinical trial without sponsor consent. Patients who received at least one dose of study treatment and withdraw within 28 days after a functional assessment visit will be asked to return for an end of study visit. If patients are withdrawn more than 28 days after a functional assessment visit, they will be asked to return for both an early termination visit (Week 96 visit) and an End of Study Visit (Week 100 visit).

Study Stopping Criteria:

The study may be terminated or a site closed for the following reasons:

- An unexpected, serious, or unacceptable risk to patients enrolled in the study
- Sponsor elects to suspend or discontinue testing, evaluation, or development of the investigational product
- Unacceptably slow enrollment at the site
- Failure of the Investigator to comply with pertinent regulations of IRB/IEC or appropriate regulatory authorities or the protocol
- Purposely submitting false information by the site to the sponsor, the study monitor, IRB/IEC or regulatory authority
- Insufficient adherence to protocol requirements as per 21 CFR 312 or the EU Clinical Trial Directive 2001/20/EC

Previous Data and Rationale Supplied by the Sponsor for the Use of a Venous Access Port

At the time of the initial FDA review of the ESSENCE protocol in 2015, the sponsor provided justification in a communication to the IND for including a venous access port in the study.

> "This Confirmatory Study is a double blind placebo-controlled study with 6MWT as the primary efficacy endpoint. As previously discussed with FDA, functional clinical endpoints with motivational aspects such as the 6MWT, when assessed in an open-label design, are not sufficiently protected against bias. A placebo-controlled design is therefore necessary to provide interpretable data. Therefore, maintaining the blind is essential for the integrity and validity of this study, and precludes any differentiation in how participants are treated based on randomization group. Since use of longer-term IV access methods such as midline catheters, central venous lines, or ports cannot be kept blinded from participants, families, investigators, or clinical evaluators, any such alternate access would need to be an option for both placebo and active-treated patients." [Emphasis in the original]
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> "The necessity of a placebo-controlled, double-blind study design to generate interpretable data on functional clinical endpoints, along with the particular needs and challenges of the DMD patient population with respect to IV access, support the appropriateness of offering optional longer-term IV access methods to all participants - both active and placebo, based on the investigator's best medical judgment, the clinical and psychological status of the individual patient, and parental prerogative."

> "Please note that in the Sarepta DMD clinical trial experience to date, over half the study participants (52%, N=56) have had a port placed for infusions. Of these, approximately 40% (N=21) were placed due to loss of peripheral IV access during the course of the study, requiring implementation of an alternate longer-term access route (e.g. portacath). In many cases, parents have been the driving force for port placement based of the escalating trauma and pain experienced by their sons as peripheral IV access becomes more and more challenging. For patients who enroll in the 4045-301 study, prohibition of alternate access methods would mean that patients who lose peripheral IV access during the study would have to withdraw from treatment and from the study." OPT has been informed of at least one boy with DMD who has been withdrawn from the clinical study due to failure of peripheral intravenous access. We have not verified this information.

In response, DNP asked Sarepta to "kindly confirm/explain the basis of the investigator's judgment and local best clinical practices to only use peripheral IV and portacath (venous access port). Please also address if PICC lines or Midline catheters are alternative options." Sarepta replied:

> "PICC lines or midline catheters are options in addition to peripheral IVs and portacaths. In clinical trials of eteplirsen in DMD patients, Sarepta has provided no requirement or guidance regarding type of IV access to be used for administration of weekly infusions. As such, data regarding the rationale for selection of a particular access method have not been systematically captured across studies. Based on feedback received from investigators and parents of participants in eteplirsen studies, the choice of intravenous access method has taken multiple factors into consideration and has differed for individual investigators, institutions, and families."
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> "Overall, it is often parents who provide the impetus to seek an alternative to weekly peripheral IV insertion, based on the individual child's experience as a patient and his emotional and physical state. However, some parents have expressly declined placement of central venous access for their child even when suggested by the investigator."
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> "For investigators, the threshold for moving to a more long-lasting IV access method and the choice of appropriate method varies considerably. This is reflected in the language regarding alternatives to peripheral IVs provided in individual institutional ICFs. In some cases, the ICF outlines a hierarchy of preferred options (e.g. peripheral IV; implanted port if peripheral access becomes difficult; other form of central line if port placement is not feasible); in other cases, a portacath alone is cited as the "go-to" option should peripheral access be problematic."

The information from the sponsor provides justification for use of a central venous access port in both the placebo and active treatment arms in order to maintain blinding. This is an important consideration in regards to maintaining the scientific integrity of the study and reducing bias, as the primary outcome variable, the 6MWT, is prone to variation based on factors such as motivation and/or coaching. Additionally, the sponsor states that not allowing a venous access port may undermine the feasibility of the study because of patients who can no longer maintain peripheral venous access dropping out of the study. These points are valid, but do not alter the risk determination associated with the intervention (e.g., placement of a port). In general, the use of a midline catheter in the placebo arm of a clinical study is approvable under 21 CFR 50.53, but a PICC line or other form of central venous access is not approvable under 21 CFR 50.53. Further discussion on this point can be found later in this document.

Additionally, in 2015, the sponsor provided information on the types of venous access that are available for pediatric patients, and advantages and disadvantages for use in DMD patients. The protocol at the time of the 2015 review only specified the alternative use of a central venous access port when peripheral access cannot be maintained; PICC and non-tunneled and tunneled CVC were not included in the protocol as options. As noted in Table 1 (on page 11), venous access ports appear to have a lower rate of infection. Midline catheters are not included in this analysis. (Chesshyre, Goff, Bowen, & Carapetis, 2015) The disadvantages of venous access ports include difficulties with insertion and need for surgical placement and removal. However, the advantage is that they

can be maintained for extended periods without a need for replacement. See Table 2 (see below). (Westergaard et al., 2013)

Table 1 – from (Chesshyre, Goff, Bowen, & Carapetis, 2015)

Table 1 Types of Central Venous Catheter (CVC).[10,18,34,36,112,113,116,127]

Catheter type	Features	Uses	Duration of use	Infection risk
Peripherally inserted CVC (PICC lines)	Inserted peripherally into basilic, cephalic or brachial veins and enter superior vena cava (SVC)	Blood sampling Fluid, blood product and total parenteral nutrition (TPN) administration Medication (such as inotropes, antibiotics, chemotherapy)	4 weeks–6 months	Similar, or lower rates of infection to non-tunnelled CVCs[18,113,114]
Non-tunnelled CVC	Percutaneously inserted into subclavian, internal jugular or femoral vein	Blood sampling Fluid and blood product and TPN administration Medication Haemodialysis	7–10 days	Highest risk of infection[18]
Tunnelled CVC (Hickman, Broviac, Grohong)	Surgically or radiologically implanted into subclavian, internal jugular or femoral vein	Blood sampling Blood product and TPN administration Medication including antibiotics and chemotherapy Haemodialysis	Months – years	Tunnelling reduces rate of infection compared to non-tunnelled CVCs[10,127]
Totally implantable venous-access port (TIVAP)	Tunnelled beneath the skin with subcutaneous port accessed with a needle. Implanted by surgical/radiological placement into subclavian or internal jugular vein	Infrequent access on long term basis such as for antibiotics (such as for patients with cystic fibrosis), chemotherapy	Months – years	Lowest risk of infection[10,113,116]

CVC – central venous catheter, PICC – peripherally inserted central venous catheter, SVC – superior vena cava, TPN – total parenteral nutrition, TIVAP – totally implantable venous-access port.

Table 2 - from (Westergaard, Classen, & Walther-Larsen, 2013)

Comparison of PICCs with other IV access devices.

	PICC	PIV	CVC	TCVC or implantable port
Necessitate GA	Sometimes	Rare	Always	Always
Serious insertion complications	Very rare	No	Potential	Potential
Serious systemic complications	Potential	No	Potential	Potential
Mechanical problems*	Sometimes	Often	Sometimes	Sometimes
Patency	Weeks	Days	Weeks	Months
Catheter cost	+++	+	++	++++
Patient compliance	++	+	+	+++
Necessitate surgical removal	No	No	No	Yes
Insertion difficulty	Easy	Easy	Difficult	Difficult

*Occlusion, dislodgment, fracture.
CVC, central venous catheter; GA, general anaesthesia; IV, intravenous; PICC, peripherally inserted central catheter; PIV, peripheral IV catheter; TCVC, tunnelled CVC.

As previously mentioned, the portacath can be maintained for an extended period, but is more invasive and requires sedation for placement and removal. The information in Table 3 (on page 12), although highlighting the

advantages of a venous access port for pediatric patients with DMD, clearly indicates that the placement of a port exceeds a minor increase over minimal risk.

Table 3: Overview and Comparison of Pediatric IV Access Methods for Use in DMD Patients

Access Option	Pros	Cons
Standard peripheral IV line *(option used in Sarepta DMD studies)*	Routinely used for temporary IV access	Peripheral IV access is challenging in DMD patient population due to many factors including: --- DMD-associated changes including muscle atrophy, contractures, etc. --- Cushingoid features and vein fragility associated with chronic corticosteroid use --- Needle phobia and other psychological, cognitive and behavioral issues [1] New IV line must be inserted each week for study infusions = 48 IV placements required for each participant over the course of the study Pediatric patients, particularly those with chronic diseases, are especially prone to physical and emotional stress associated with painful medical procedures, which can lead to permanent adverse physiological changes.[2, 3]
Peripherally Inserted Central Catheter (PICC) *(not used in Sarepta DMD studies)*	Can be used up to several months (4 wk-6 mo) General anesthesia not required for line placement	Shorter lifetime than implanted port; would need to be replaced at least once during the study[4,5] Higher complication rate than implanted port (e.g. infection, occlusion)[6] Harder to manage in pediatric population (site must be kept dry; entry site covering/dressing requires frequent maintenance; catheter tail with cap protrudes and is subject to mechanical tension/manipulation by patient, etc.).
Central Venous Catheter (CVC) *(not used in Sarepta DMD studies)*	Tunneled CVC may stay in place for years; non-tunneled CVC limited to 7-10 days of use General anesthesia not required for line placement	Difficult to perform in pediatric patients due to catheter size and small vessel diameter. [2,4] Harder to manage in pediatric population (site must be kept dry; entry site covering/dressing requires frequent maintenance; catheter tail with cap protrudes and is subject to mechanical tension/manipulation by patient, etc.). Higher complication rate (breakage, infection) vs PICC or indwelling port [6]
Portacath (port) *(option available per investigator discretion in Sarepta DMD studies)*	Can be used for up to 2000 punctures (chest port); estimated lifetime of port is 2-6 years Lowest complication rate (infection, occlusion, breakage) and replacement rate, compared to PICC or CVC devices Lower replacement rate than PICC or CVC devices[6] Eliminates unnecessary pain and stress accompanying repeated procedures for venous access.[2]	General anesthesia used for indwelling port placement in pediatric population[7] More invasive than other options[4]

[1] Cirak S, et al. Exon skipping and dystrophin restoration in patients with Duchenne muscular dystrophy after systemic phosphorodiamidate morpholino oligomer treatment: an open-label, phase 2, dose-escalation study. Lancet. 2011; 378: 595–605
[2] Barczykowska E, et al. Review: The Use of Central Venous Lines in the Treatment of Chronically Ill Children. Adv Clin Exp Med. 2014; 23: 1001–1009
[3] Pervanidou P, et al. Metabolic consequences of stress during childhood and adolescence. Metabolism. 2012; 61: 611-19
[4] Chesshyre E, et al. The prevention, diagnosis and management of central venous line infections in children. J Infect. 2014; 71: S59-S75
[5] The Children's Hospital of Philadelphia; http://www.chop.edu/treatments/peripherally-inserted-central-catheter-picc#.Vfcd_k3bKt5 (accessed 14 Sep 2015)
[6] Bratton J, et al. Outpatient Management of Vascular Access Devices in Children Receiving Radiotherapy: Complications and Morbidity. Pediatr Blood Cancer. 2014; 61: 499–501
[7] Holland A. Port-a-cath Fact Sheet. National MPS Society. 2006/2014

The sponsor also provided data on the extent and duration of use of ports in another Sarepta study requiring weekly infusions. In that study 8 of 12 patients required port placement. Ports were placed between Weeks 68 to 183 with a mean of 109 weeks. For all patients, the reason stated for using a port was difficult peripheral venous access. No other venous access options were used. These data suggest that study participants may be able to maintain peripheral infusions for the initial 48 weeks of the ESSENCE study but may need another venous access option if they remain in the study through Week 96 (randomized phase) and Week 192 (open-label phase). At Week 96, the risk determination of port placement for individual patients in the study would change, because all patients will be receiving open-label product. As such, after week 96, port placement may be approvable under 21 CFR 50.52 (as offering a sufficient prospect of direct benefit through administration of active study drug to justify the risks).

In addition, the UCLA principle investigator provided the following information in support of the UCLA IRB consideration of the requested protocol modification (Report of Protocol Incident, March 15, 2017):

> "Sarepta performed an analysis of safety related to the use of ports in its DMD studies. To identify adverse events (AEs) that were potentially related to a portacath, a search was conducted within the clinical databases for trials evaluating eteplirsen, SRP-4045, or SRP-4053. This search combined standardized Medical Dictionary for Regulatory Activities (MedDRA) queries (SMQs) and groupings of MedDRA terms as well as an additional search for "port", "central venous", and "central line" in the verbatim AE term. Data [were] summarized only for patients who had a portacath placed after entering the study and only those AEs that were reported after the placement of a portacath were included."
>
> "As of 03 June 2016, 85 patients had received eteplirsen administered via a portacath. Among these 85 patients, aside from 1 severe event of incision site hemorrhage (bleeding after swimming), the remaining events have all been mild to moderate in severity. In addition, the majority of AEs were considered by the Investigator to be unrelated to study drug. There have been no serious or severe reports of infection with usage of a central venous port with eteplirsen. A single event of mild catheter site cellulitis has been reported, which was considered mild in severity and unrelated to eteplirsen. Overall descriptions of the AEs coincident with usage of a portacath include catheter site pain, bruising, or pruritus, and are consistent with the application or placement of a portacath device"
>
> "As of 03 October 2016, 11 of the 12 patients treated with SRP-4045 in Study 4045-101 had the study drug administered via a portacath. Of these 11 patients, 4 experienced a portacath-related AE. None of the events were reported in more than 1 patient. With the exception of 3 events that were serous and moderate to severe in intensity, all other events were non-serious and mild. All reported events, serious and non-serious, were considered unrelated to study treatment. One non-ambulatory patient with advanced DMD experienced 3 SAEs (bacteremia, septic embolus, and vena cave thrombosis). These SAEs were considered moderate to severe in intensity, unrelated to SRP-4045, and definitely related to study procedure (use of a portacath). The patient temporarily interrupted study drug, missing 1 dose, and had the portacath removed."
>
> "As of 03 October 2016, 7 of the 25 patients treated with SRP-4053 in Study 4053-101 had study drug administered via a portacath. Of these 7 patients, 3 experienced a portacath-related AE. Events included catheter site pain and catheter site bruise (2 patients, each) and device related infection (1 patient). All events were considered unrelated to study treatment. Two events were considered moderate in seventy and the remaining events were considered mild.
>
> "Additional Precautions:
>
> "DMD patients have special medical, surgical and anesthesia needs that must be addressed in order to reduce risks associated with surgical procedures in this population (Bushby et al., 2010b) Accordingly, port placement will be performed only (a) at select surgical sites that have been extensively vetted by the Sponsor and that have pediatric intensive care units; (b) by surgeons with whom the Sponsor has worked during multiple prior DMD trials and who have extensive experience with port placement in DMD patients. This past experience helps ensure that site staff and the surgical teams at these institutions are familiar with the precautions that need to be taken with respect to anesthetic, surgical and medical management of DMD patients in order to reduce the risk of procedural complications."

The UCLA principle investigator, in an e-mail to the UCLA IRB dated March 9, 2017, indicated that "we will not offer portacath placement to all subjects. The default procedure for IV access for IP infusion is venipucture with cutaneous anesthesia and will continue to be used for subjects who do not have difficulty of access. Portacaths would only be used for subjects for which peripheral IV access presents significant difficulty. In the case that either a subject requires 3 or more attempts at venipuncture access at 2 consecutive visits or 5 or more attempts at any one visit, we would offer portacath placement for the subject."

Previous FDA Experience in the Review of a Protocol using a PICC line in a Placebo-Controlled Study

In 2010, FDA became aware of use of PICC lines in a placebo-controlled clinical trial of a monoclonal antibody product under study in recent onset diabetics as young as 8 years of age. The study required daily infusions of active product or placebo for up to 14 days. Of the 119 sites that enrolled patients in the study, only 16 sites allowed for the use of a PICC line based on the approval by 12 IRBs. It is not known whether any of the IRBs at the sites that did not use PICC lines considered and rejected that approach. The Division provided the following feedback to the sponsor and asked for additional information from the IRBs to evaluate how 21 CFR subpart D was applied to the protocol:

> "From review of the protocol and consent documents, there is concern that this procedure is not in compliance with 21 CFR 50, subpart D Additional Safeguards for Children in Clinical Investigations."
>
> "Unlike research in adults, the allowable risks of research [interventions] involving children that are approvable by an IRB are capped at either minimal risk (21 CFR 50.51) or a minor increase over minimal risk (21 CFR 50.53), absent the prospect for direct benefit to the enrolled child. Alternatively, research [interventions] allowable under 21 CFR 50.52 must present risks that are justified by anticipated direct benefits to the child and are as favorable as any available alternatives. Minimal risk is defined as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests." (21 CFR 56.102i)"
>
> "The risks of an experimental intervention or procedure must also be justified by the prospect of direct benefit from that same intervention or procedure, and not by other interventions or procedures included in the protocol. In this case, the risks of the administration of an infusion via PICC placement must be justified by the prospect of direct benefit from that same infusion. If there is no direct benefit from the infusion, the risks of the infusion itself must be restricted to a minor increase over minimal risk, regardless of other direct benefits the protocol may offer to the enrolled child. This approach is often called "component analysis" and is meant to avoid the practice of justifying a risky and non-beneficial intervention merely by including ancillary benefits in the same protocol (such as other therapeutic procedures and/or health care)."
>
> "Insertion of a PICC requires sedation in pediatric patients which carries its own inherent risks. In addition, there are risks of thrombosis, infection, and distal migration of catheter tips from the indwelling PICC. The infusion of [active study drug] offers the prospect of direct benefit to the enrolled child that appears to be sufficient to justify the risks of PICC placement. However, none of these risks is counterbalanced by direct benefits from the infusion of placebo to children. As such, we have concluded that the risks of PICC use in combination with procedural sedation for placebo infusion into children represent greater than minimal risk without direct benefit to the pediatric patient and the trial, therefore, is not in compliance with 21 CFR 50 subpart D."

A review of the information submitted by the IRBs revealed that several of the IRBs assessed the prospect of direct benefit prior to randomization (pre-randomization analysis of benefit). This method of assessment does not allow an analysis of each of the components of the research as was recommended by the National Commission in 1978. "To determine the overall acceptability of the research, the risk and anticipated benefit of activities described in the protocol must be evaluated individually as well as collectively..." In order to assess the risk and direct benefit of each component, a risk/benefit analysis for each component/intervention/procedure must be performed separately. One IRB stated that PICC catheter insertion was appropriate if parents choose to use it. This IRB did not consider the protections provided by 21 CFR 50 subpart D to place a limit on the risks that parents might allow their child to bear for non-therapeutic procedures. Two IRBs used component analysis to evaluate the trial. One IRB incorrectly compared placebo and the active product to best available treatments and determined that since there was reasonable uncertainty to the merits of either treatment arm that 21 CFR 50.52 was satisfied. This approach confuses the question of whether the active product is efficacious (even though there are data to support a prospect of direct benefit) with the question of whether the risk of placebo exposure was justified given the

absence of direct benefit. Finally one IRB correctly applied the concept of component analysis to their review, determining that insertion of a PICC line was approvable under 21 CFR 50.53. Although FDA does not agree with this determination, the analysis was done appropriately.

FDA drafted a letter to the sponsor and to the involved IRBs to provide feedback on the analysis and concluded:

1. "The risks of an experimental intervention or procedure must be justified by the prospect of direct benefit from that same intervention or procedure. In other words, the use of "component analysis" is required by FDA regulations found at 21 CFR 50, subpart D. As such, the control and experimental arms of a clinical trial should be evaluated separately, and may receive different determinations under 21 CFR 50, subpart D.
2. The administration of placebo does not offer any prospect of direct benefit to pediatric subjects, so the risks of placebo administration should be no greater than a minor increase over minimal risk (21 CFR 50.53). The insertion of PIC catheters represents greater than a minor increase over minimal risk to enrolled subjects, and thus must not be used for placebo administration."

The sponsor of this study subsequently contacted the Division to ask if midline catheters were acceptable for use in a study. Following internal consultation, the Division responded that midline catheters were approvable as a minor increase over minimal risk (21 CFR 50.53). Midline catheters have a lower risk of infection that PICC lines, do not require sedation for placement, and migration of catheter tips is less of a concern.

Parental Permission Form and Child Assent

The parental permission form includes all the basic elements of consent as per 21 CFR 50.25(a). Additional elements of consent (21 CFR 50.25(b)) are added as appropriate. Risks associated with the muscle biopsy and non-procedural sedation are included in the parental permission form. Pediatric patients 13 and older will sign the parental permission form. A separate assent form is used for ages 7 to 12 years. The risks and benefits of central venous access methods, including ports, are not included in the documents. As the use of central venous access methods are not permitted pending a determination by the FDA Commissioner following the PAC/PES review under 21 CFR 50.54, revised parental permission and child assent forms were not requested.

ANALYSIS

The Additional Safeguards for Children in Clinical Investigations (21 CFR part 50 subpart D) must be considered when pediatric patients will be enrolled in a clinical trial. In order for a protocol to be approvable by a local IRB, under 21 CFR 50 subpart D, the IRB must find that the protocol satisfies the criteria in subpart D.

21 CFR 50.52 provides that an intervention or procedure presenting more than minimal risk that holds out the prospect of direct benefit for the individual subject is only approvable if the IRB finds that: the risk is justified by the anticipated benefit to the subjects; the relation of the anticipated benefit to the risk is at least favorable to the subjects as that presented by available alternative approaches; and adequate provisions are made for soliciting assent of the children and permission of their parents or guardians as set forth in 21 CFR 50.55. Thus, the administration of SRP-4045 and SRP-4053 to subjects in this clinical investigation must satisfy these conditions.

21 CFR 50.53 provides that an intervention or procedure presenting more than minimal risk that does not hold out the prospect of direct benefit for the individual subject is only approvable if the IRB finds that: the risk represents a minor increase over minimal risk; the intervention or procedure presents experiences to subject that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations; the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition that is of vital importance for understanding or amelioration of the subjects' disorder or condition; and adequate provisions are made for soliciting assent of the children and permission of their parents or guardians as set forth in 21 CFR 50.55. Thus, the administration of placebo to subjects, as well as the other non-beneficial procedures in the protocol, such as the muscle biopsy, must satisfy these conditions (along with the

necessary procedural sedation). Alternatively, the IRB may refer the clinical investigation for federal panel review under 21 CFR 50.54.

This approach to the analysis of placebo-controlled trials is consistent with the recommendation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (created under the 1974 National Research Act, Public Law 93–348) that the interventions that do and do not offer a prospect of direct benefit in any given protocol must be analyzed separately (often called a component analysis of risk) (43 FR 2084 at 2086 (January 13, 1978)).

In the protocol being reviewed (version 6 (Amendment 5), dated April 3, 2017), the sponsor has proposed that alternative venous access methods (midline catheter, PICC, CVC, venous access port) may be placed to administer SRP-4045 and SRP-4053 or placebo in patients where peripheral venous access proves difficult. Patients receiving active product have a prospect of direct benefit from the receipt of the product and as such can be exposed to more risk. Consequently, the use of any of these venous access methods for patients receiving active product would be acceptable under 21 CFR 50.52. However, patients on placebo do not directly benefit from administration of placebo, and as such, risks to these patients must be limited to a "minor increase over minimal risk" to be approvable under 21 CFR 50.53. Minimal risk has been defined in FDA's regulations as "the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (21 CFR 56.102(i))." There is variability in the interpretation of what constitutes a minor increase over minimal risk (Wendler & Emanuel, 2005), although the U.S. National Commission believed that the increase in risk allowable under this category was intended to be "a slight increase in the potential for harms or discomfort beyond minimal risk (as defined in relation to the normal experiences of average, healthy, normal children)." More recently, the Institute of Medicine opined that "what constitutes 'a bit more' risk in research involving children is not relative and does not allow a higher threshold for children with high-risk or high-burden conditions than for children with less serious conditions."(Field & Behrman, 2004) Placement of a PICC line, CVC or venous access port solely for research purposes in patients with DMD is more than a minor increase over minimal risk. Venous access issues are a common problem for these patients.(Cripe & Tobias, 2013) Since placement of PICC line, CVC or venous access port in these patients for research purposes does not meet criteria as a "minor increase over minimal risk" under 21 CFR 50.53, the revised protocol must be reviewed by a federal panel under 21 CFR 50.54 in order for the use of these interventions in the protocol to be allowed proceed. A midline catheter is approvable as a minor increase over minimal risk (21 CFR 50.53).

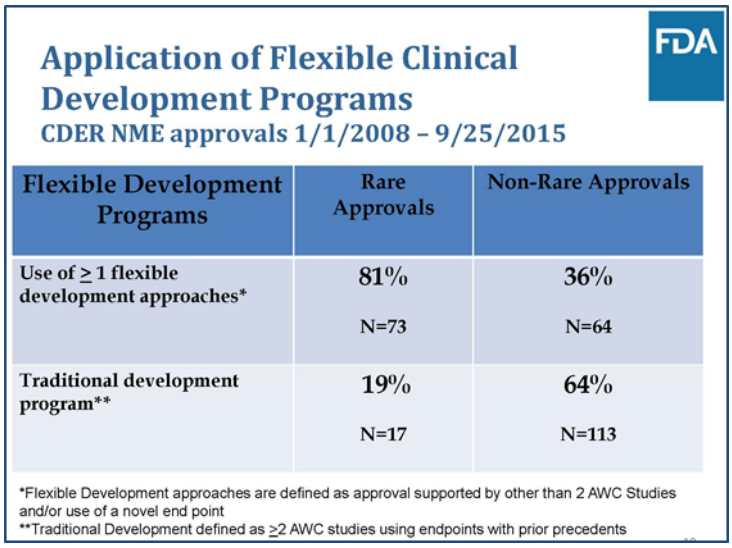
Additional Background

The context for considering whether the use of central venous access methods should be permitted includes: the requirement for a placebo arm, the length of the study, the suitability of the proposed venous access methods in this population, and the need for procedural sedation. This patient population also undergoes a protocol-driven muscle biopsy, a procedure that generally has been approved by IRBs as a "minor increase over minimal risk" for patients who do not benefit directly from the procedure.

Rationale for a Placebo-Controlled Study

In general, at least two adequate and well-controlled studies are required to establish effectiveness (see Section 505(d) of the Food, Drug & Cosmetic Act). However, FDA has been flexible, broadly interpreting the statutory requirements to the extent possible where the data on a particular drug are convincing. In 1997, Congress amended section 505(d) to make it clear that FDA may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness. In doing so, Congress confirmed FDA's interpretation of the statutory requirements for approval. (Food and Drug Administration, 1998a) This flexibility has been used by FDA to approve drugs for rare diseases. In a review of CDER new molecular entity (NME) approvals from January 2008 through September 2015, 81% (N=73) of NMEs for rare diseases were approved using one or more flexible

approaches, compared to 36% of NME's for non-rare diseases (see table below). ("Presentation by John Jenkins to NORD Summit Meeting, Arlington VA. ," October 18, 2016)



Application of Flexible Clinical Development Programs

CDER NME approvals 1/1/2008 – 9/25/2015

Flexible Development Programs	Rare Approvals	Non-Rare Approvals
Use of ≥ 1 flexible development approaches*	81% N=73	36% N=64
Traditional development program**	19% N=17	64% N=113

*Flexible Development approaches are defined as approval supported by other than 2 AWC Studies and/or use of a novel end point

**Traditional Development defined as ≥2 AWC studies using endpoints with prior precedents

The major purpose of a control group is to be able to differentiate whether a change in a patient outcome has been caused by the study drug or by some other factor, such as the natural progression of the disease, observer or patient expectations, or other treatment. "Control groups in clinical trials can be classified on the basis of two critical attributes: (1) the type of treatment used and (2) the method of determining who will be in the control group. The type of control treatment may be any of the following four: (1) placebo, (2) no treatment, (3) different dose or regimen of the study treatment, or (4) a different active treatment. The principal methods of determining who will be in the control group are by randomization or by selection of a control population separate from the population treated in the trial (external or historical control)." (Food and Drug Administration, 2000) The use of an external or historical control group raises concerns about the ability of such trials "to ensure comparability of test and control groups and their ability to minimize important biases." The other four types of control treatments are concurrently controlled, in that "the control group and test groups are chosen from the same population and treated concurrently." (Food and Drug Administration, 2000) Randomization allows for impartial assignment to a treatment group, and impartial assessment of treatment results as the study progresses. (Food and Drug Administration, 1998b) Random assignment of the enrolled subject population to test and control groups "avoids systematic differences between groups with respect to known or unknown baseline variables that could affect outcome. Inability to eliminate systematic differences between treatment groups is a major problem of studies without a concurrent randomized control." (Food and Drug Administration, 2000) Randomization may not require blinding to treatment assignment (such as a no treatment control). However, the use of blinding so that subjects and investigators are unaware of treatment assignment "is intended to minimize the potential biases resulting from differences in management, treatment, or assessment of patients, or interpretation of results that could arise as a result of subject or investigator knowledge of the assigned treatment."(Food and Drug Administration, 2000) Blinding reduces any unconscious expectations of the participants or providers that may influence the results if treatment assignment is known. (Schulz, 1995)

Elimination of the placebo arm and/or blinding to treatment assignment so that it was known which boys were on placebo would allow the use of a PICC line, CVC or venous access port under 21 CFR 50.52 for those boys receiving active product. Other than a placebo control, the other options for the study of SRP-4045 and SRP-4053 include: an external (historical) control; an active-comparator control; a dose-ranging control; and a no treatment control.

Nonconcurrent External or Historical Control

Although an external (historical) control might be considered for trials of SRP-4045 and SRP-4053, there are data to suggest that patients with neuromuscular disorders may improve in efficacy studies regardless of whether they are on placebo or active treatment when compared to natural history studies. (Statland et al., 2013) With a historically controlled study, there is no randomization or blinding. This simplifies the design, but also increases the chance of selection bias where the population chosen for comparison is not representative of the treatment group in the study. (Lachin, 1988) For studies submitted to support approval of eteplirsen, use of an external control was problematic, because it was difficult to ensure that patients used for comparison had similar characteristics, similar disease severity and had received similar treatments. Additionally, since functional outcomes such as the 6MWT are affected by motivation and coaching, patients who knew they were on eteplirsen may have been more motivated to complete

the 6MWT than patients known not to be on eteplirsen, which also would impact on the outcome. Generally the "use of external controls should be limited to cases in which the endpoints are objective and the impact of baseline and treatment variables on the endpoint is well characterized." (Food and Drug Administration, 2000)

Different Active Treatment as a Concurrent Control

There are no active treatments against which a comparison of SRP-4045 and SRP-4053 would be appropriate. The boys enrolled in the ESSENCE study are required to be on corticosteroids. The corticosteroid deflazacort has been available even prior to the recent FDA approval of deflazacort (EMFLAZA™) for the treatment of patients 5 years and older with DMD. Eteplirsen (EXONDYS 51™) is only approved for patients with a mutation in the DMD gene that is amenable to exon 51 skipping. Even if there were an appropriate comparator, the study would either need to be designed as a superiority study (potentially placing the investigational drug at a disadvantage) or as a non-inferiority (i.e., equivalence) study (for which a creditable and clinically meaningful non-inferiority margin would be difficult to establish since anticipated changes in clinical outcomes, such as the 6MWT and the NSAA have not been determined). "The margin chosen for a non-inferiority trial cannot be greater than the smallest effect size that the active drug would be reliably expected to have compared with placebo in the setting of the planned trial."(Food and Drug Administration, 2000) In addition, a non-inferiority study would require a larger sample size than a placebo-controlled study, which might impact the feasibility of study completion in a rare disease population. (Hahn, 2012)

Different Dose or Regimen of the Study Treatment as a Concurrent Control

A dose-ranging trial may use differences in dose-response relationship to establish efficacy and does not always require a placebo arm. In order to use this design, predetermined procedures must be in place to estimate the relationship between dose and response and establish appropriate confidence intervals. (Food and Drug Administration, 1998b) However, the trial risks the possibility that if the doses chosen are too high, too low or too close together, efficacy will not be established because all doses appear equivalent. (Marchetti & Schellens, 2007) This is a serious concern since the trial would ultimately be uninformative, and considered unethical as it would be exposing children to the risks of product exposure in a study design unable to provide informative scientific data. For eteplirsen, no difference in the dose-response for the amount of dystrophin produced between a 30 mg/kg and 50mg/kg weekly dose was seen in the conducted studies at Week 180, which suggests that this approach may not be successful for other exons. (Food and Drug Administration, 2016) If the lower dose selected is too low, there may be an insufficient prospect of direct benefit to justify the risks of either the study drug administration or use of central venous access (i.e., effectively a "placebo" dose). If the lower dose is too high, there may be no difference in dystrophin production and/or clinical outcome between the two doses, rendering the study uninformative (i.e., no different from using an external historical control).

No Treatment as a Concurrent Control

The principle difference between a no treatment control and placebo control is the absence of blinding the patient/parent (i.e., single blind) and the investigator (i.e., double blind) to the treatment assignment. (Food and Drug Administration, 2000) If the study endpoints are not susceptible to the bias introduced by the lack of blinding (such as mortality), a no treatment control group may be appropriate. Randomization can still be used to assign eligible patients to the treatment arms. However, knowledge of the treatment assignment also may bias the study results by introducing differences between the two groups post-randomization. The eteplirsen (EXONDYS 51™) approval letter states: "A double-blind, placebo-controlled trial design should be used, if feasible, as this would be most informative. If it is not feasible to include a placebo group, an untreated concurrent control group may be considered, with appropriate care to reduce bias in outcome assessments given the lack of randomization and blinding." However, until the use of dystrophin levels has been established as a validated surrogate biomarker for meaningful clinical changes in motor function (such as the 6MWT), it is not clear how the bias introduced by the lack of blinding and randomization would be reduced to the point of being able to draw meaningful conclusions from short-term clinical trials (i.e., ≤ two years in duration). The letter notes that the sponsor and the FDA would need to agree on the protocol prior to initiation of the clinical trial.

Placebo as a Concurrent Control

"The placebo control design, by allowing blinding and randomization and including a group that receives an inert treatment, controls for all potential influences on the actual or apparent course of the disease other than those arising from the pharmacologic action of the test drug. These influences include spontaneous change (natural history of the disease and regression to the mean), subject or investigator expectations, the effect of being in a trial, use of other therapy, and subjective elements of diagnosis or assessment." (Food and Drug Administration, 2000) As such, a placebo (i.e., inert treatment) is the ideal comparer for use as a control, especially given the susceptibility of assessments of motor function such as the 6MWT to factors such as motivation or coaching. If the population treated with placebo has similar characteristics and like treatments except for exposure to the therapy or placebo, then the presumed change in outcome as a result of study participation can be attributed to the therapeutic intervention. Use of a placebo in a study requires that some uncertainty exists regarding the efficacy of the experimental treatment and that there are no known alternative treatments outside of the trial or if treatments are known, that use of the placebo will not expose the patient to serious harm. A placebo would be inappropriate in cases where known treatment might be delayed and result in significant harm to the patient. (Food and Drug Administration, 2000) Other than the use of deflazacort (EMFLAZA™), which is allowed in the study, there are no known effective treatments for DMD patients with genotypically confirmed deletion mutations that are amenable to skipping exons 45 or 53.

The sponsor's clinical development plans include testing different PMO products that would target DMD patients with specific mutations in other exons (apart from 45, 51 and 53)(Sarepta, 2017b). If a clinical response is seen using a strong study design for eteplirsen (in the required post-marketing study to verify clinical benefit) and SRP-4045 and SRP-4053 (blinded, randomized, placebo-controlled study), then these data could potentially be used to support additional studies for other (more rare) exons using dystrophin as a surrogate marker of response. Once dystrophin has been established as a surrogate marker, such studies may not require randomization to different treatment arms or blinding of treatment assignment. The patient populations under study to date, eteplirsen, SRP-4045 and SRP-4053, represent the most frequent deletion mutations at 13%, 8.1% and 7.7% respectively. (Aartsma-Rus et al., 2009) Future studies of exons for other less frequently encountered deletions may be more difficult to complete, given there will be less available patients. Consequently, a streamlined development program for these additional DMD populations would be advantageous.

Justification for the Study Duration

The protocol involves a 96-week randomized double-blind placebo-controlled phase followed by up to a 96-week open-label extension phase to assess clinical outcome measures, based on the rate of decline in functional capacity and the lack of any appreciable increase in trials of lesser duration based on the eteplirsen data. There is considerable variability in terms of the phenotypic expression of disease in DMD patients. Some patients progress rapidly while others remain ambulatory until late adolescence and beyond. Some of these changes may be related to environmental factors, differences in clinical care including steroid use, and contracture management and fracture prevention. (Bello et al., 2015; Bushby et al., 2010a, 2010b) However, change in functional capacity is not associated with the specific deletion mutation and siblings with the same genetic defect can vary in presentation and progression. (Zatz et al., 2014) Current FDA draft guidance on the development of drugs for DMD states the following: "For drugs expected to slow functional decline, study length necessarily is affected by rate of progression in addition to predicted drug efficacy. Although studies of 1 year's duration have been conducted in DMD, the duration of studies should be based on scientifically justifiable sample size calculations that include, when appropriate, the predicted rate of functional decline in the placebo group, the anticipated effect size, the variability around these estimates, and the desired statistical power. Efficacy studies of 18 to 24 months' duration may substantially increase statistical power, while only modestly increasing overall development time." (Food and Drug Administration, 2015a)

Changes in 6MWT have been evaluated in natural history studies. Age and baseline walking ability impact change in function over time. The 6MWT may improve in children less than 7 years of age if they are followed for 48 weeks

compared to a decline seen in older patients. Steroid use may also have more of an impact in younger patients. There appears to be a threshold for continued decline and loss of ambulation (LOA). At a 6MWT of 55% predicted or approximately 325 m, DMD patients are likely to continue to decline at a rate of greater than 10% of 6MWT over the next year or may lose walking ability entirely. (McDonald, Henricson, Abresch, Florence, et al., 2013) This variability supports the need for longer study durations to account for the variability between groups.

The sponsor has proposed a blinded interim analysis at 48 weeks. The inclusion of an interim analysis ensures that patients are not continued in the study unnecessarily should there be sufficient data to make an efficacy determination prior to the 96-week study endpoint.

Rationale for the Use of Alternative Venous Access Methods

The revised ESSENCE protocol under consideration allows for the use of alternative venous access methods (midline catheter, PICC, CVC, venous access port) for study treatment administration at the discretion of the investigator if peripheral venous access becomes problematic for participants in the study. Even for children without chronic disease, establishing intravenous (IV) access can be difficult; 45% to 75% of peripheral IV insertions are successful on the first attempt. (Rauch et al., 2009) DMD patients are known to have venous access issues, which may arise because of contractures, positioning issues, fragile veins due to steroid use and scarred veins from multiple previous IV insertions. (Cripe & Tobias, 2013; Kuensting et al., 2009) Obesity may also be a contributing factor. (Nafiu et al., 2010) Continued peripheral venous access in the ESSENCE study may be possible, but patients are likely to have problems with peripheral venous access over the course of the ESSENCE study, especially beyond 48 weeks (as noted from information provided above from the sponsor). A difficult intravenous access (DIVA) score has been developed in the emergency department setting using four variables (vein visible after tourniquet, vein palpable after tourniquet, age category and history of prematurity). (Yen, Riegert, & Gorelick, 2008) The DIVA score was validated (O'Neill, Dillane, & Hanipah, 2012) and also simplified to a three-variable rule, deleting the history of prematurity. (Riker, Kennedy, Winfrey, Yen, & Dowd, 2011) However, the applicability of the DIVA score to pediatric populations other than those children presenting to the emergency department is unknown, although one would expect the scoring variables to be independent of the clinical care setting. Imaging techniques such as the use of ultrasound-guided placement may improve the success rate for patients with DIVA. (Benkhadra et al., 2012; Partovi-Deilami, Nielsen, Moller, Nesheim, & Jorgensen, 2016) However, there are conflicting data in the literature about the usefulness of some imaging techniques. (Kim et al., 2012; Szmuk et al., 2013)

The sponsor has submitted data to the IND to indicate that venous access ports may be less likely to become infected than PICC lines or central venous catheters (CVC) and tunneled CVCs. (Chesshyre et al., 2015) This infection risk can further be reduced by preventing colonization at the time of insertion, adequate training of staff who access the port and reducing the frequency of handling the port to only what is absolutely necessary. (Lebeaux et al., 2014) Pediatric patients may be at increased risk of infection when compared to adults, although most of the available data is in pediatric cancer patients. (Penel et al., 2007) The sponsor did not provide data to the IND on midline catheters; infection rates of these catheters are reported to be similar to peripheral IVs and lower than any of the central venous options ((PIV 0.2/1000, MC 0.5/1000, PICC 2.1-2.3/1000, CVC 2.4-2.7/1000 catheter days). (Adams, Little, Vinsant, & Khandelwal, 2016)

Venous access ports and CVCs may be more difficult to insert and require sedation for insertion. PICC lines are easier to insert, but may require sedation to reduce discomfort with placement and to optimize positioning at the insertion site. Insertion of PICC lines may require use of techniques such as ultrasound or fluoroscopy to visualize the vein. Complication issues related to PICC lines, in addition to infection, include dislodgement, occlusion, breakage or leakage of the catheter and venous thrombosis. (Duesing, Fawley, & Wagner, 2016) Mechanical issues with PICC lines may be greater than that seen with CVC and ports. (Westergaard et al., 2013) (Hussain, Gomez, Wludyka, Chiu, & Rathore, 2007) Both PICC lines and CVC carry an equal risk of venous thrombotic events. (Male, Julian, Massicotte, Gent, & Mitchell, 2005) Venous access ports carry early complication risks related to the surgical procedure: bleeding, embolism, catheter tip migration, pneumothorax and wound dehiscence. Late complications consist of thrombotic issues and infection. (Walser, 2012)

Average PICC and midline catheter dwell times are 7 to 17 days, but PICC lines may be commonly used up to 6 weeks. (Adams et al., 2016) CVC dwell time varies based on the type of CVC; short term "neck" lines may only be suitable for 10 days, tunneled lines may remain in place longer. (Drewett, 2000) Venous access ports are intended for longer term therapy and are generally maintained for much longer periods of time; a dwell time of 2 years is not uncommon, with one article reporting a dwell time of 5114 days. Difficulty in removing ports are reported as uncommon in pediatric patients, but there may be more issues with removal in patients who had ports placed at a young age, had acute lymphoblastic leukemia or longer port dwell time. Interestingly, the patient with a reported time of 5114 days did not have a difficult removal. (Patel et al., 2016)

Given the anticipated length of study treatment in ESSENCE and lower reported rates of infection, a venous access port may be a better option for DMD patients, since other forms of central venous access and midline catheters may require re-insertion during the course of the study. The benefits of these alternative venous access methods must be weighed against the need for surgical placement for a CVC or port, and sedation risks for PICC lines, CVCs and ports. DMD patients require special considerations with the use of anesthesia because of reduced respiratory and cardiac function related to their disease and may require a longer recovery time after surgery.(Cripe & Tobias, 2013)

Rationale for Use of Muscle Biopsies

One of the secondary objectives of this study is to evaluate the effect of SRP-4045 and SRP-4053 (combined-active group) on the level of dystrophin protein as measured by WB and IHC in muscle tissue. From a scientific perspective, this comparison is necessary to determine if administration of SRP-4045 and SRP-4053 results in an increase in dystrophin when compared to the placebo-control group. However, since testing of dystrophin in the muscle is not used for treatment or diagnostic purposes in this study, neither the patients in the active treatment or placebo group directly benefit as a result of the procedure. Consequently, the procedure must be determined to be no more than a minor increase over minimal risk (21 CFR 50.53).

Generally, a muscle biopsy has been considered to be a minor increase over minimal risk. Muscle biopsies are commonly done in children to diagnose neuromuscular disorders and the incidence of complications is low. (Gibreel et al., 2014; Shapiro, Athiraman, Clendenin, Hoagland, & Sethna, 2016) The sedation/anesthesia must also be considered in the risk analysis, as discussed below. If a muscle biopsy is performed for non-diagnostic purposes, the sponsor should provide additional assurance that any risks and discomforts have been minimized (21 CFR 56.111(a)(1)) and that those risks and discomforts are described in the parental permission and assent forms (21 CFR 50.55). FDA has been supportive of developing new technologies for biomarker measurement which may only require needle biopsies or other biological materials, or other non-invasive testing.

Sedation for Non-therapeutic Procedures

Both insertion of a venous access port and the muscle biopsies collected in this study require the use of procedural sedation. As previously stated, muscle biopsies have been determined to be approvable under 21 CFR 50.53 for patients who require the procedure for non-diagnostic purposes as a "minor increase over minimal risk."

The Pediatric Ethics Subcommittee (PES) of the Pediatric Advisory Committee (PAC) met in in March 2015 to discuss the use of procedural sedation for non-therapeutic research interventions and was unable to reach consensus on whether one or more approaches to procedural sedation should be considered a minor increase over minimal risk. (Food and Drug Administration, 2015b) The PES was asked to discuss the factors which should be taken into account when designing a protocol to provide procedural sedation for nontherapeutic procedures in pediatric clinical investigations, and on how the risks of procedural sedation may be minimized.

The PES generally agreed on the following when considering the use of procedural sedation for a non-therapeutic procedure:

1. "procedures should be performed at a high volume center with a dedicated pediatric sedation service;

2. there should be rigorous scientific justification for the need for the nontherapeutic procedures;
3. the approach to procedural sedation and risk minimization procedures should be described in the protocol;
4. children with chronic conditions that may place them at higher risk from procedural sedation should be carefully evaluated and potentially excluded from the protocol;
5. the nontherapeutic procedure should be terminated if complications of sedation arise or the level of sedation is inadequate as it would be inappropriate to escalate the approach to procedural sedation beyond what would be considered a minor increase over minimal risk rather than to stop the procedure;
6. if a particular procedure in a particular patient population is normally accompanied by sedation when performed for clinical reasons, sedation should not be withheld in the nontherapeutic research setting to avoid its risks and thereby enhance the procedure's approvability under federal research regulations; and
7. there should be clear communication with potential subjects (and their parents) regarding the nontherapeutic nature of the procedures and procedural sedation in child assent and parental permission documents."

However, the PES was not able to agree on whether one or more approaches to procedural sedation would present no more than a minor increase over minimal risk, assuming the risks have been minimized (YES: 7; NO 9). In light of this result, the above recommendations should be included in any protocol that includes a non-therapeutic procedure that requires procedural sedation so that FDA and the responsible IRB may evaluate whether the sedation presents no more than a minor increase over minimal risk. Additionally, the risks and discomforts of procedural sedation should be described in the parental permission and assent forms.

SUMMARY

1. The Office of Pediatric Therapeutics (OPT) received a referral on March 15, 2017 from the University of California at Los Angeles (UCLA) Investigational Review Board (IRB) for federal panel review under 21 CFR 50.54 of a protocol entitled "A Double-Blind, Placebo-Controlled, Multicenter Study With an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients with Duchenne Muscular Dystrophy (ESSENCE)."(UCLA-IRB, 2017) The protocol currently is underway using a peripheral intravenous line for study drug infusion placed every week (with two lines placed when the protocol calls for pharmacokinetic studies) for the initial 96-week study period, which is then followed by open-label administration of the investigational product. The protocol referral specifically is to consider whether placement of central venous catheters for study drug infusion (including for the placebo control group) would be acceptable during the initial 96-week study period.
2. The UCLA IRB met on March 9, 2017 to consider this request, along with clarification from the investigator about the criteria that would be used to offer portacath placement. At that meeting, the IRB determined that the use of venous catheter placement (portacath) was not approvable under 21 CFR 50.51, 50.52 or 50.53, and was "unanimous in finding that the clinical investigation (including potential use of central venous catheters) represents a reasonable opportunity to further understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children." (21 CFR 50.54) (UCLA-IRB, 2017) The sponsor revised the protocol to allow for "venous access methods such as midline catheter, central line, or portacath" (central venous access port) for study treatment administration at the discretion of the site investigator, and submitted it to the IND as version 6 (Amendment 5), dated April 3, 2017. The revised protocol also was submitted by the UCLA investigator to the UCLA IRB, which forwarded it to FDA on April 13, 2017, to be included in the IRB referral package. The revised protocol has not yet been implemented pending the results of the 21 CFR 50.54 panel review. OPT is convening a joint meeting of the Pediatric Ethics Subcommittee (PES) and the Pediatric Advisory Committee (PAC) to review the protocol and provide consultative advice to the FDA Commissioner to inform a determination under 21 CFR part 50 subpart D

regarding the acceptability of this protocol (version 6 (Amendment 5), dated April 3, 2017) to proceed.

3. In order for this protocol to be approvable under 21 CFR part 50 subpart D, the administration of SRP-4045 and SRP-4053 must be approvable under 21 CFR 50.52 and the administration of the placebo either must be approvable under 21 CFR 50.53 or must be referred for federal panel review under 21 CFR 50.54. This approach to the analysis of placebo-controlled trials is consistent with the recommendation of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (created under the 1974 National Research Act, Public Law 93–348) that the interventions that do and do not offer a prospect of direct benefit in any given protocol must be analyzed separately (often called a component analysis of risk) (43 FR 2084 at 2086 (January 13, 1978)).
4. The referred protocol ESSENCE involves an initial 96-week phase in patients with DMD comparing SRP-4045 and SRP-4053 to placebo, followed by a 96 week open label phase. A randomized, double-blind, placebo controlled study will help ensure that the change in clinical outcome is attributable to the study intervention, since the population chosen for comparison will be representative of the treatment group and the functional measures used as clinical outcomes (6MWT, NSAA, etc.) are subject to such factors as motivation and coaching.
5. There is variability in the rate of progression of patients with DMD, likely related to environmental factors and differences in clinical management. This variability in progression necessitates study durations of sufficient length to detect clinical differences between the treatment and placebo groups. Current FDA draft guidance recommends study durations for DMD indications of at least 18 to 24 months.
6. The protocol under reviewed (version 6 (Amendment 5), dated April 3, 2017) allows for the use of alternative venous access methods such as midline catheter, central line, or central venous access port at the site investigator's discretion. Although midline catheters do not carry the same risks as CVCs and venous access ports, reinsertion would be necessary. Given the length of the study, venous access ports and tunneled CVCs may be more practical; venous access ports are less likely to become infected and may have an advantage over other CVCs.
7. Muscle biopsies are commonly done in children to diagnose neuromuscular disorders and the incidence of complications is low. As such, the procedure itself represents a minor increase over minimal risk. If a muscle biopsy is performed for non-diagnostic purposes, the sponsor should provide additional assurance that any risks and discomforts have been minimized (21 CFR 56.111(a)(1)) and that those risks and discomforts are described in the parental permission and assent forms (21 CFR 50.55).
8. Insertion of CVCs, PICC lines, central venous access ports and muscle biopsies require the use of procedural sedation. As previously stated, muscle biopsies generally have been approved under 21 CFR 50.53 for patients who require the procedure for non-diagnostic purposes. In assessing the acceptability of central venous access methods, the use of procedural sedation must also be considered and present no more than a minor increase over minimal risk.
9. Currently the parental permission and child assent documents do not include a discussion of the risks and benefits of central venous access methods, including ports. If the use of these methods is approved, these documents must be updated to include this information (21 CFR 50.25; 21 CFR 50.55). Revisions in the current documents were not requested at this time pending the results of the federal panel review under 21 CFR 50.54.

VOTING AND DISCUSSION QUESTIONS

Question One (voting):

Use of an indwelling central venous access device in the clinical trial "A Double-Blind, Placebo-Controlled, Multicenter Study With an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients with Duchenne Muscular Dystrophy (ESSENCE)" (version 6 (amendment 5), dated April 3, 2017) should be allowed.

Yes - There are circumstances in which an indwelling central venous access device should be allowed in the ESSENCE clinical trial.

No - There are no circumstances in which an indwelling central venous access device should be allowed in the ESSENCE clinical trial.

Question Two (non-voting):

If version 6 (amendment 5) of the ESSENCE clinical trial (dated April 3, 2017), amended to include the use of an indwelling central venous access device, is allowed to proceed, please discuss the following issues:

(a) Should the choice and timing of placement of a clinically-appropriate central venous access device be left to the discretion of the study site investigator?
(b) Should the protocol include criteria for deciding when an individual study participant has difficulties with peripheral intravenous access (DIVA) such that use of a central venous access device may be appropriate?
(c) If the protocol should include such criteria, what type of criteria ought to be specified (e.g., number of failed attempts at establishing peripheral intravenous access, number of visits where there was difficulty establishing peripheral intravenous access, use of alternative visualization technologies)?
(d) How should the burden of undergoing multiple failed attempts at establishing peripheral intravenous access be taken into account (e.g., anticipatory anxiety, post-traumatic stress)?

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