U.S. FOOD & DRUG ADMINISTRATION

Memorandum

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Deputy Commissioner for Medical Products and Tobacco
Office of the Commissioner

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Date: May 25, 2017

Subject: Recommendation for Permitting the Use of a Totally Implantable Central Venous Access Device in the 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)." (IND 118,086 (SRP-4045) and 119,982 (SRP-4053))

Issue:

This document provides a recommendation by the Office of Pediatric Therapeutics (OPT) that the Food and Drug Administration (FDA) determine that the revised 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)" may proceed with the use of a totally implantable central venous access device (TICVAD), provided certain conditions are met as detailed below. The protocol is currently 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 is specifically to consider whether placement of a central venous access device (CVAD), which includes a TICVAD and other types of central venous catheters (CVC), for study drug infusion (including for the placebo control group) would be acceptable during the initial 96-week study period.

The University of California at Los Angeles (UCLA) Institutional Review Board (IRB) referred the protocol to the FDA on March 15, 2017 for consideration under 21 CFR 50.54, which is one of FDA's regulations concerning the Additional Safeguards for Children in Clinical Investigations (21 CFR part 50 subpart D). Pursuant to the procedures outlined at 21 CFR 50.54, on May 18, 2017, OPT convened a joint meeting of the Pediatric Advisory Committee (PAC) and the Pediatric Ethics Subcommittee (PES) to provide an opportunity for public review and comment as well as expert advice to inform a determination regarding whether the clinical investigation may proceed under the revised protocol. The PAC/PES roster, meeting agenda, FDA briefing information, and presentations are available on the FDA website (www.fda.gov/AdvisoryCommittees) under the 2017 meeting

materials for the PAC. When available, the meeting transcripts and minutes will also be found at this site. In making this recommendation, OPT has reviewed the proposed modification of the clinical investigation, considered the opinions of experts in pertinent disciplines, and reviewed all public comments received.

Regulatory Background:

21 CFR Part 50, Subpart D, Additional Safeguards for Children in Clinical Investigations, sets forth requirements that must be met in order for an IRB to approve clinical investigations involving children as subjects. In general, each intervention and procedure in a protocol must be evaluated separately (i.e., "component analysis") for approvability under Subpart D.

Under 21 CFR 50.51, a clinical investigation in which no greater than minimal risk to children is presented may involve children as subjects only if the IRB finds that: no greater than minimal risk to children is presented; and adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians.

21 CFR 50.52 provides that a clinical investigation in which more than minimal risk to children is presented by an intervention or procedure 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 alternative approaches; and adequate provisions are made for soliciting assent of the children and permission of their parents or guardians.

21 CFR 50.53 provides that a clinical investigation in which more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit to 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 subjects 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.

If an IRB does not believe that a clinical investigation meets the criteria for approval under 21 CFR 50.51, 21 CFR 50.52, or 21 CFR 50.53, it may only proceed if the IRB finds that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children, and the Commissioner of Food and Drugs, after consultation with a panel of experts in pertinent disciplines and following an opportunity for public review and comment, determines either (1) that the clinical investigation in fact satisfies the conditions of 50.51, 50.52, or 50.53, as applicable, or (2) that the following conditions are met: (i) the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; (ii) the clinical investigation will be conducted in accordance with sound ethical principles; and (iii) adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians. Consistent with the general redelegation of authority reflected in FDA Staff Manual Guide 1410.21.B, the responsibility for making this determination for the current referral has been delegated to the Deputy Commissioner for Medical Products and Tobacco.

In the context of the ESSENCE clinical trial, the use of a CVAD, including a TICVAD, 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, absent referral under 21 CFR 50.54, the risks to this group must not exceed a minor increase over minimal risk for the IRB to be able to approve the protocol that includes the use of this intervention under 21 CFR 50.53. Placement of a CVAD, including a TICVAD, 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.

Protocol Overview:

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 Duchenne Muscular Dystrophy (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.

The Division of Neurology Products (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 by an IRB under 21 CFR 50.51, 50.52 or 50.53. 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. 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.

Protocol Referral:

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 port 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 to FDA for review by an FDA panel under 21 CFR 50.54.

The sponsor revised the protocol to allow for the use of additional venous access methods: "In the event it becomes necessary, venous access methods such as midline catheter, central line, or portacath may be used at the Investigator's discretion, contingent upon approval by local and/or country-specific regulatory body(ies)." The revised protocol was submitted to the respective INDs 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 in the revised protocol, a "central line" generally includes percutaneously inserted central catheter (PICC) lines, CVC and tunneled CVCs. A portacath is a specific example of a TICVAD.

Public Review and Comment:

There were 3 comments submitted to the docket prior to the AC meeting. A pediatric anesthesiologist commented on the risk of anesthesia in boys with DMD and included recommendations to mitigate those risks when implanting a TICVAD. Another pediatric anesthesiologist submitted comments on behalf of Parent Project Muscular Dystrophy, supporting the use of a TICVAD in DMD patients in the ESSENCE study. The Jett Foundation commented on the difficulties DMD patients have had with peripheral venous access in the study and requested that a TICVAD be allowed. The latter two comments emphasized that a decision on the need for placement of a TICVAD in the study should be left to the family and the treating physician involved in the patient's care.

The comments provided during the open public hearing were in unanimous support for the use of a TICVAD (or port) in the ESSENCE clinical trial. This included testimony from 13 speakers, including 2 healthcare providers and 10 parents of a boy with DMD. One boy with DMD provided testimony. Several parents stated that the peripheral venous access issues that developed during the course of the trial were not anticipated at study entry. These issues were attributed to the trauma to the veins as a result of the weekly intravenous (IV)

infusions and blood draws required in the study. The anticipatory anxiety as well as the pain associated with multiple attempts to obtain peripheral IV access was a repeated concern. Speakers were also concerned that if venous access were lost, the boys may no longer be able to participate in the trial. As a result, boys allow continued attempts to obtain IV access despite considerable pain and discomfort. Additionally, if boys are forced to leave the study because of an inability to obtain venous access, the interpretability or completion of the entire study may be jeopardized. Speakers expressed that the decision for use of a TICVAD should be made in consultation with family and the treating physician, and not mandated by specific requirements in a protocol. Although the use of a TICVAD has potential serious risks, speakers indicated that the families were aware of the risks and were willing to take those risks to reduce the psychological and physical pain associated with the multiple IV attempts needed to obtain IV access.

Review by FDA Panel of Experts:

Following the presentations and any clarifying questions, the PAC/PES voting members were asked to vote on the following question:

(1) "Use of an indwelling central venous access device in the ESSENCE clinical trial should be allowed. A "yes" means that there are circumstances in which an indwelling central venous access device should be allowed in the ESSENCE clinical trial. A "no" vote means that there are no circumstances in which an indwelling central venous access device should be allowed in the ESSENCE clinical trial."

The PAC/PES members voted unanimously (14 yes; 0 no) to allow the use of an indwelling central venous access device in the clinical trial.

The PAC/PES members were then asked to discuss the following question:

(2) "If the ESSENCE protocol, as 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)?"

This question was framed as a discussion question, given the difficulty in framing a series of voting questions to cover all of the possible permutations of potential criteria for determining DIVA. Nevertheless a consensus emerged from the PAC/PES discussion on the following points:

(1) A TICVAD should be used instead of other CVADs, such as a percutaneously inserted or tunneled CVC, as it is less susceptible to infection and can remain in place for an extended period of time. For example, a TICVAD placed during the initial 96-week blinded placebo-controlled phase would have a significantly higher probability of remaining in place during the open label phase of the clinical trial. Nevertheless, there may be rare clinical circumstances where other options could be considered based on surgical consultation.

(2) The timing of the placement of the TICVAD should be at the discretion of the parent(s)/guardian, in consultation with the local clinical investigator and consulting surgeon. The PAC/PES did not believe that it was necessary to wait until a boy qualified as having DIVA. To minimize the risks of anesthesia for placement of the TICVAD, it could be combined with the muscle biopsies to be obtained at week 0 or 48. However, this is not required and may be difficult to coordinate if an initial decision to use a peripheral IV was made, and found to be difficult to sustain prior to week 48. Although local study sites may want to put in place DIVA criteria (as proposed by UCLA), the specification of any criteria in the study protocol was rejected explicitly by the PAC/PES.

(3) The consulting surgeon should have sufficient expertise in the placement of TICVADs in pediatric patients, having placed at least 30 TICVADs in a comparable pediatric patient population. In order for the risks of TICVAD placement to be minimized, the ideal setting for the placement of a TICVAD is in the operating room under general anesthesia to allow for direct visualization of the site of venous access.

(4) The risks of the TICVAD need to be adequately described in the parental permission and child assent documents, including the admittedly rare possibility of death from an infection (i.e., sepsis). The PAC/PES acknowledged that these risks can be mitigated by timely removal of the TICVAD, if clinically necessary, and that the frequent weekly monitoring of the injection site and patient helps to ensure patient safety.

OPT Findings and Recommendations:

OPT agrees with the recommendation of the PAC/PES that the use of a TICVAD be allowed in the protocol "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)" (conducted under IND 118,086 for SRP-4045 and IND 119,982 for SRP-4053). Although the use of a TICVAD for patients receiving the investigational product is approvable under 21 CFR 50.52, the risks of the TICVAD are not justified by any prospect of direct benefit for patients randomized to placebo. As such, the use of the TICVAD for patients randomized to placebo can only proceed if the criteria under 21 CFR 50.54 are satisfied.

If use of a CVAD becomes necessary or if use of a CVAD is preferred by the parents/guardian (in consultation with the investigator and consulting surgeon), a TICVAD should be used unless contraindicated. Absent a contraindication for the use of a TICVAD, the use of other CVADs would present "an unreasonable and significant risk of illness or injury" (21 CFR 312.42(b)(2)(i)) given the higher incidence of infection, thrombosis and other complications.

Provided the stipulations below are satisfied, OPT believes that the following conditions are met for the use of a TICVAD in the clinical protocol for all patients regardless of whether they are randomized to receive the investigational product or placebo, given that it is a blinded trial:

(1) The clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children;

(2) The clinical investigation will be conducted in accordance with sound ethical principles; and

(3) Adequate provisions are made for soliciting the assent of children and the permission of their parents or guardians as set forth in 21 CFR 50.55.

Stipulations for Allowing the Protocol to Proceed:

(1) Version 6 (Amendment 5) of the ESSENCE protocol, dated 03 April 2017, includes the following language in the Study Synopsis (page 10) and in Section 9.2 Treatments Administered (page 51): "In the event it becomes necessary, venous access methods such as midline catheter, central line, or portacath may be used at the Investigator's discretion, contingent upon approval by local and/or country-specific regulatory body(ies)."

This language must be replaced with: "In the event it becomes necessary, or at the discretion of the parents/guardian, in consultation with the investigator and consulting surgeon and following adequately informed and voluntary parent/guardian permission and child assent, a totally implantable central venous access device (i.e., port) may be used, contingent upon approval by local and/or country-specific regulatory body(ies). "

(2) The revised protocol may provide for the use of alternative methods of central venous access, such as a percutaneously inserted or tunneled central venous catheter, as long as the patient has a documented contraindication in the opinion of the consulting surgeon for the placement of a TICVAD.

(3) Consistent with 21 CFR Part 56, the revised protocol must be approved by the responsible local and/or country-specific regulatory body for each investigational site. At their discretion, the responsible

regulatory body may consider further requirements on the use of a TICVAD, such as criteria for DIVA. While permissible, under FDA's regulations these local requirements may be considered site-specific amendments, and would not require a modification of the protocol nor notification, review and approval at other study sites.

(4) Consistent with 21 CFR 50.55, the sponsor must revise the parental permission and child assent templates to include the possibility, risks and benefits of using a TICVAD. Consistent with 21 CFR 312.60 and Parts 50 and 56, these templates should be provided to the responsible investigator at each investigational site for use in developing the parental permission and child assent documents to be submitted to the local and/or country-specific regulatory body at the time of the review of the amended protocol.

(5) The sponsor should obtain documentation from the local investigator of the expertise of the consulting surgeon in the placement of TICVAD, and incorporate monitoring of the safety and use of the TICVAD into the study protocol.

(6) The revised protocol with the language about the use and safety monitoring of TICVADs, and the revised sponsor template for the parental permission and child assent documents, must be submitted to the respective INDs for SRP-4045 and SRP-4053. Once those documents have been submitted to the INDs, and approval by responsible local and/or country-specific regulatory body(ies) has been obtained, the revised protocol may be implemented at that site.

OPT Recommendations:

(1) The use of a TICVAD in the 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)" is allowable under 21 CFR 50.54(b)(2), subject to the stipulations as outlined above, and therefore the protocol as modified to include the use of a TICVAD may proceed.

(2) This determination should be made available to the public through (a) placing this document on the Pediatric Advisory Committee website for the May 18th meeting and (b) posting it to the corresponding docket for that meeting.

FDA Determination:

(1) Subject to the stipulations as outlined above, the conditions in 21 CFR 50.54(b)(2) are met and therefore the 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)" may proceed with the inclusion of the use of a totally implantable central venous access device (TICVAD).

Approved Rachel Sherman Disapproved _____ Date 5/25/2017

(2) This determination should be made available to the public through (a) placing this document on the Pediatric Advisory Committee website for the May 18th meeting and (b) posting it to the corresponding docket for that meeting.

Approved Rachel Sherman Disapproved _____ Date 5/25/2017