Minutes of a Joint Meeting of the Pediatric Advisory Committee and Pediatric Ethics Subcommittee

The Great Room, White Oak Campus
10903 New Hampshire Avenue
Silver Spring, MD 20993

May 18, 2017

The meeting convened at approximately 8:30 a.m.

Committee Members and Consultants
Marieann Brill, MBA, RAC, MT, ASCP
Mark Hudak, MD
Christy Turer, MD, MHS, FAAP, FTOS
Douglas Diekema, MD, MPH
Melody Cunningham, MD, FAAHPM
Aileen Foley, MD
Wael Sayej, MD
Steven Joffe, MD, MPH
Michael White MD, PhD, FACC, FAAP
Sarah Hoehn MD, MBe, FAAP
Maria Birzescu, MD, MS
Rodney Levine, MD, PhD
Norman Fost, MD, MPH
Amy Celento, BS
Richard Kryscio, PhD, MS
Samuel D. Maldonado, MD, MPH, FAAP
Marc Moon, MD

Speakers
Donna Snyder, MD
Perry Shieh, MD, PhD
James McGough, MD
Brett Bullers
Erin Bullers
Nicholas Bullers
Genevieve Laforet, MD, PhD

FDA Participants
Robert (Skip) Nelson, MD, PhD
Donna Snyder, MD

Open Public Hearing Speakers
A summary of comments posted to the docket were read by Mark Hudak MD.

Megan Polanin, PhD
Delanna Thomas
Anita Bullers
Christine McSherry
Suzanne Gaglianone
Rebecca Majors
Jenn McNary
Brian Denger
Erin Bullers
Jordan McSherry
Shelly Mays
Dr. Neera Gulati
Dr. Robert Dracker

Agenda

8:30 AM	Welcome and Introductions	Mark Hudak, MD Chair, Pediatric Advisory Committee (PAC)
8:35 AM	Opening Statement	Marieann Brill, MBA, RAC, MT (ASCP) Designated Federal Official, PAC Office of Pediatric Therapeutics (OPT), Office of the Commissioner (OC), FDA
8:30 AM	Opening Remarks and Review of the Agenda	Robert "Skip" Nelson, MD, PhD Deputy Director and Senior Pediatric Ethicist OPT/OC/FDA
8:45 AM	Additional Safeguards for Children in Research and Protocol Review Under 21 CFR 50.54	Donna Snyder, MD Pediatric Ethicist, OPT/OC/FDA
9:16 AM	The "Essence" Clinical Trial: Protocol Design and Obstacles	Perry Shieh, MD, PhD Associate Professor & Director of the Neuromuscular Program, Department of Neurology, David Geffen School of Medicine, UCLA
10:04 AM	UCLA IRB FDA Referral on the ESSENCE Trial for Duchenne Muscular Dystrophy	James McGough. MD Professor of Clinical Psychiatry, Semel Institute for Neuroscience and Human Behavior, and David Geffen School of Medicine, UCLA
10:34 AM	The Patient and Parent Perspective	Brett Bullers, Erin Bullers, and Nicholas Bullers
10:51 AM	Break	
11:10 AM	Open Public Hearing	
12:10 AM	Lunch	
1:20 PM	Sponsor Presentation	Genevieve Laforet, MD, PhD, Medical Director, Sarepta Therapeutics
1:54 PM	Presentation of Questions to the Committee	Robert "Skip" Nelson, MD, PhD Deputy Director and Senior Pediatric Ethicist OPT/OC/FDA
2:20 PM	Committee Discussion and Vote	Mark Hudak, MD Chair, PAC
3:28 PM	Adjournment	Mark Hudak, MD Chair, PAC

Introduction

The Pediatric Advisory Committee (PAC) and the Pediatric Ethics Subcommittee (PES) met jointly on May 18, 2017, to review a clinical investigation 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)." (ClinicalTrials.gov Identifier: NCT02500381) The review was requested by the University of California at Los Angeles (UCLA) Institutional Review Board (IRB) under 21 CFR 50.54. The committee's recommendations, deliberations, and vote are included below. The committee voted unanimously to allow approval of the protocol under 21 CFR 50.54. The committee's recommendation was then forwarded to the FDA Commissioner.

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 lead to misreading of the genetic code for dystrophin beginning at exons 45 or 53. Enrolled patients are randomly allocated to treatment or to placebo in a 2:1 ratio. After an 8-week screening period, patients are randomized to weekly intravenous infusions of 30 mg/kg of SRP-4045 or SRP-4053 or placebo for up to 96 weeks.

The Division of Neurologic Products (DNP) reviewed the ESSENCE protocol on November 6, 2015. At that time, the study protocol specified that a totally implantable central venous access device (TICVAD) could be used at the discretion of the investigator; other venous access methods were not specified. The DNP informed the sponsor that implantation of a TICVAD 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 TICVAD 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 to allow placement of a TICVAD because her son was experiencing significant issues with continued peripheral venous access during his participation 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 TICVAD 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. The sponsor revised the protocol to allow the use of alternative venous access methods such as a midline catheter, central line, or TICVAD, 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.

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 in the ESSENCE clinical trial. This included testimony from 13 speakers, including 2 healthcare providers and 10 parents/grandparents of a boy with DMD. Several speakers 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 might not be able to continue 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 entails potential serious risks, 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 even if a boy is randomized to placebo.

Issues Discussed

The committee discussed the ethics of the placement of a TICVAD in patients in the placebo arm of the ESSENCE study. Issues considered were risks related to the placement of a TICVAD, whether TICVAD could be placed prior to initiating study treatment, i.e. at the same time as the initial muscle biopsy, and the pain and suffering associated with multiple venous access attempts when obtaining venous access became difficult. The committee agreed that a 2-year placebo controlled trial was necessary, in order to obtain an adequate assessment of the efficacy of the product based on the expected decline in the clinical outcome measure, the 6 minute walk test (6MWT), over time.

The physical and psychological burden associated with multiple IV access attempts was discussed as a significant consideration for patients in the study. The potential for contributing to post-traumatic stress disorder (PTSD) in the patients increased the risk of study participation for these patients. One committee member noted that TICVAD placement would be considered standard of care in an oncology trial of a similar length with weekly infusions. The committee noted that a decision for a TICVAD must be considered within the context of the study population and disease. A TICVAD may not be appropriate for studies of shorter duration or for patients who have less difficulty with venous access.

A TICVAD was considered preferable over other forms of central venous access because of the lower rate of infection, thrombosis and complications, and because a TICVAD can be maintained for an extended period of time. However, the committee did note that if a patient had a contraindication that would preclude the use of a TICVAD, then other forms of central venous access could be considered. The committee agreed that a TICVAD could be placed at the time of the initial muscle biopsy, to take advantage of a single sedation anesthesia procedure, but that a TICVAD could be placed at some other time during the study. It would not be necessary for a patient to develop difficulties with peripheral intravenous access (DIVA) before a TICVAD could be considered. No particular criteria were determined to be necessary to define when a TICVAD could be placed. The timing of placement of the TICVAD should be a discussion between the family, the site investigator, and the consulting surgeon. The surgeon should have demonstrated expertise in placing a TICVAD with one member suggesting that prior successful placement of at least 30 TICVADs in a comparable pediatric patient population would be a reasonable level of experience that defined expertise.

The committee stated that both the parent and child should be fully informed of the risks with placement of a TICVAD or other central venous access device as part of the informed consent process and that both the consent of the parent and the assent of the child should be obtained.

Questions to the Committee:

(1) Use of an indwelling central venous access device in the ESSENCE clinical trial 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.

The PAC/PES voted unanimously (14 yes; 0 no) to allow the use of an indwelling central venous catheter in the ESSENCE protocol.

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

(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)?

These questions were framed to generate discussion rather than to elicit a vote, given the difficulty in framing a series of voting questions to cover all permutations of potential criteria for defining DIVA.

Nevertheless, a consensus emerged from the PAC/PES discussion on the following points:

(1) Committee members preferred the use of a TICVAD over other devices, such as a percutaneously inserted or tunneled central venous catheter. They noted that a TICVAD is less susceptible to infection and can remain in place for an extended period of time. Nevertheless, there may be rare clinical circumstances where the consulting surgeon might judge another option to be preferable.
(2) The timing of the placement of the TICVAD should be at the discretion of the parent(s)/guardian, following discussion between the local clinical investigator and consulting surgeon. The PAC/PES also believed that TICVAD placement could occur before a boy met criteria for DIVA. To minimize the risks of anesthesia for placement of the TICVAD, the protocol could allow placement of the TICVAD at the same time as the muscle biopsies at week 0 or 48; or could allow placement at another time. Although local study sites may choose to define DIVA criteria (as proposed by UCLA), the PAC/PES explicitly rejected specification of DIVA criteria in the study protocol.
(3) The consulting surgeon should have sufficient expertise in the placement of TICVADs in pediatric patients. The committee believed that a surgeon who had successfully placed a minimum of 30 TICVADs in a comparable pediatric patient population had sufficient expertise. 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 a device-related systemic 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 patient and the injection site would improve patient safety.

The meeting adjourned at approximately 3:28 p.m. on May 18, 2017.

Please see transcript for details.

I certify that I attended the May 18, 2017 meeting of the Pediatric Advisory Committee and Pediatric Ethics Subcommittee and that these minutes accurately reflect what transpired.

/S/
Marieann Brill, MBA, RAC, MT, ASCP
Designated Federal Officer

/S/
Mark Hudak, MD
Chairperson, PAC