The “ESSENCE” Clinical Trial: Protocol Design and Challenges

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Relevant Disclosures

Have served as a Consultant on an Ad Hoc Advisory Board for Sarepta Therapeutics

Serve as a site-Investigator for clinical trials sponsored by Sarepta Therapeutics, including the ESSENCE clinical trial, which is the subject of this meeting

Travel for today’s meeting supported by the FDA
Outline

• Background of Duchenne Muscular Dystrophy
• SRP-4045 and SRP-4053: Rationale for Exon Skipping
• Highlights of the ESSENCE Protocol
• Challenges in implementing the ESSENCE Protocol
Background

Duchenne Muscular Dystrophy

• DMD is a disease of boys who have a mutation in a gene called dystrophin
• Because of their inability to make the dystrophin protein, their muscles degenerate
DMD: Progression of Disease

Age (years)

Walking problems
Wheelchair
Limited use of arms
Nocturnal ventilation
24-hour ventilation
Death
Predicting Severity of Disease: The Reading Frame Rule

• Becker Muscular dystrophy is also caused by mutations in dystrophin, but is characterized by a milder course than Duchenne Muscular Dystrophy

• Monaco AP, et al., proposed the reading frame hypothesis\(^1\) that predicts the severity of disease

• Aartsma-Rus A, et al., found (in a database of 4700 patients) that the rule holds true in 91% of patients\(^2\)

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Codons and the reading frame

- Each 3-letter codon encodes an amino acid
The Reading Frame

DADPETTHTHEFATDOG

DAD PET THE FAT DOG
ADP ETT HEF ATD OG
DPE TTH EFA TDO G
The Role of Dystrophin

nNOS, neuronal nitric oxide synthase.
Mutations in Dystrophin (cont’d)

Mutations may be:

- Large deletions: 68%
- Large duplications: 11%
- Small deletions/duplications
- Single-nucleotide substitutions
- Nonsense mutations: 10%
- Splice-site mutations: <1%
- Intronic mutations: 3%

7%

DMD Versus BMD

Mutations that have a more severe phenotype (DMD) generally:

- **Disrupt** the reading frame
- **Remove critical regions** of the dystrophin protein
DMD Versus BMD

Mutations that **preserve** the reading frame (especially mutations in the central rod domain) generally have a milder phenotype (BMD)
Exon Skipping

Exon skipping is a treatment strategy designed to restore the reading frame.

Eteplirsen: Morpholino anti-sense oligonucleotides directed against critical splicing sequences within exon 51
Deletion of exon 50

CUA-GCG-UAC-CAG-GGA-ACU-UCC-CCG-UGA

Leu  Ala  Tyr  Gln  Gly  Thr  Ser  Pro

STOP

Truncated Dystrophin
Exon Skipping

Deletion of exon 50

DNA

Pre-mRNA

mRNA (In-frame transcript)

CUA-GCG-UAC-CAG-AAC-CCG-CAG-UAG-CAU-UCA-GAG

Shorter, but functional dystrophin
6MWT data from eteplirsen treated patients vs. external control cohort

**Eteplirsen-treated (N=12)**
- Δ = 148 m†
- N = 13

**External Control: Exon 51 Amenable (N=13)**
- Δ = 162 m†
- N = 13

†Difference in mean change from baseline, Day 1 values used for eteplirsen.
Patients who lost ambulation contributed a score of 0 to the mean.
Individual time points missing: ECM2 Year 4, ECG3 Year 3 & 4.
ESSENCE: Protocol Highlights

Study of patients with genotypes that are amenable to exon 45 and exon 53 skipping

- SRP-4045
- SRP-4053

Similar to eteplirsen, these investigational products are designed to block sequences within these respective exons that are required for splicing
ESSENCE: Protocol Highlights

The protocol combines all of the lessons learned from previous clinical trials on exon skipping:

• Double blind, placebo controlled design
• Adequate power (n = ~99 subjects), combining two different exon skipping investigational products: SRP-4045 and SRP-4053
• 2 year double-blind period was based on guidance provided by FDA¹

ESSENCE: Protocol Highlights

4 year study
- 2 year double-blind phase
- 2 year open label phase
ESSENCE: The Protocol

Operational Details

• Randomized 2:1 - active vs. placebo
• Weekly IV infusion of investigational product
• Open muscle biopsy at baseline and at week 48

• At present time, no implantable IV access device is allowed at U.S. sites
ESSENCE: The Protocol

Key Outcome measures

- Primary Outcome: 6 minute walk distance at 48 weeks (interim) and 96 weeks (final) vs. baseline
- Secondary Outcome: Dystrophin quantification (Western Blot of muscle tissue) 48 weeks vs. baseline
Protocol Challenges

• Screening began August 2016
• First patient randomized September 28, 2016
• The most common complaint has been the difficulty of IV access

• Methods used to mitigate IV access problems:
  – Lidocaine Cream prior to placement of IV access
  – Infrared Vein finder
Concerns

• Among patients with difficult IV access: Psychological and physical suffering of patients and psychological suffering of family members

• Among patient with adequate IV access: Potential progressive worsening of IV access with repeated attempts during the course of the clinical trial

• Among patient with behavior issues, autism or OCD (which are common among DMD patients) – IV access can be a struggle, even among patients who should have good IV access
Alternatives to peripherally placed IV

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

CVC — central venous catheter, PICC — peripherally inserted central venous catheter, SVC — superior vena cava, TPN — total parenteral nutrition, TIVAP — totally implantable venous-access port.
Proposed alternative: Port-a-Cath

• Port-a-Cath placement has been used among many of our patients who have required frequent IV access.
• It has been used in other clinical trials, including previous Sarepta Exon Skipping clinical trials, to facilitate IV access.
Port-a-Cath

http://www.bardpv.com/portfolio/titanium-low-profile/#prettyPhoto
Experience with Port-a-Cath

- Port-placement requires a surgical procedure under anesthesia with laryngeal mask airway or endotracheal tube.
- The port is placed under the skin of the chest.
- The catheter tunneled under the skin to the entry point of the jugular or subclavian vein.
- The tip of the catheter is most commonly placed in the junction of SVC-right atrium.

http://www.uwmedicine.org/health-library/Pages/chest-port.aspx
Experience with ports

• Our Nurses at UCLA have experience with using port-a-caths for clinical care and for clinical trials
• They are easy to use and do not typically create significant discomfort to our patients.
• Port-a-caths can be used instead of phlebotomy for routine laboratory work as well
Risks of port-a-cath

The procedure of placing the port-a-cath carries the risk of:

- Surgical complications
  - e.g. hematoma
- Procedural sedation

Patients with Port-a-caths are at risk for:

- Infection
- Thrombosis

Risks of port-a-cath: comments

• For subjects that are enrolled in the future, UCLA and the other surgical centers identified in the ESSENCE study can perform muscle biopsies and port-a-cath procedures during the same surgical encounter, minimizing the risk of procedural sedation
Alternative Risk-Benefit Analysis

- Using component analysis, it has been the opinion of the FDA and several IRBs that the ESSENCE protocol fell within 21 CFR 50.53 (45 CFR 46.406)
- However, this does not account for the prospect of benefit of the open label extension
Alternative Risk-Benefit Analysis

• Research subjects that are randomized to active treatment – there is a prospect of direct benefit of 4 years of treatment

• Research subjects that are randomized to placebo – prospect of direct benefit of two years of treatment

• Since the risks of the port lie mostly with the surgical procedure of placing the port, essentially a fixed risk with different degrees of benefit.
Conclusions

• This ESSENCE study is designed to establish the efficacy of an promising investigational medication in a severe pediatric disease with an unmet need.

• The study is well designed and based on currently accepted recommendations and standards

• The enrollment interest of this study speaks to the importance of this study to patients and their families
Additional Comment

• If one considers the study over the course of 4 years (including the open label extension), the study may be considered to have a prospect of direct benefit to the research subjects
21 CFR 50.54

- 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.
- The clinical investigation will be conducted in accordance with sound ethical principles.
- 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.
Thank you for your attention

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