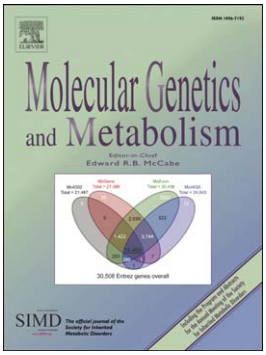

The case for eteplirsen: Paving the way for precision medicine

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The case for eteplirsen: paving the way for precision medicine

Duchenne muscular dystrophy (DMD) is the most common lethal genetic diseases of childhood. In 1986, the causal gene was identified and revealed that large deletions in *DMD* typically interrupt mRNA reading frame, thus preventing dystrophin protein expression. Dystrophin is a key sub-sarcolemmal protein that protects the muscle membrane from contraction-induced injury. Without dystrophin, young boys experience skeletal muscle deterioration and become progressively more disabled over time, often succumbing to pulmonary or heart failure before their twenty-fifth year. By 1988, Becker muscular dystrophy, a substantially more mild muscular dystrophy, was recognized to also be caused by large deletions in *DMD*, but these mutations preserve the open reading frame and result in the expression of an internally deleted dystrophin protein with partial functionality (reviewed in 1). This biologic observation provided the rationale for a therapeutic strategy, antisense-mediated "exon skipping"; in which sequence specific oligonucleotides are designed to promote exon exclusion from mature *DMD* mRNA in order to restore reading frame and rescue the expression of an internally deleted Becker-like dystrophin protein.

Eteplirsen (Sarepta Therapeutics), a phosphoramidite morpholino sequence complementary to a portion of exon 51, is designed to force the exclusion of exon 51 from the mature *DMD* mRNA. This drug is relevant for approximately 13% of the DMD population harboring specific *DMD* mutations. Similar drugs targeting other *DMD* exons are under development and could theoretically restore reading frame in up to 80% of patients. The fact that these drugs rely on specific sequence information and target the proximate cause of the disease make this one of the first examples of precision genetic medicine.

The promise of personalized medicines is enormous, particularly for rare disease. However, their approval relies on the application of regulatory tools designed to specifically empower the FDA to use flexibility in approvals for severely debilitating rare disease with unmet need, like Duchenne. Thus, DMD exon skipping trials are drawing considerable attention from the drug industry, rare disease advocates, patients, physicians and scientists.

A FDA Peripheral and Central Nervous System Advisory Committee Meeting (AdComm) was originally scheduled for Jan 22, 2016, in order for the FDA to obtain independent assessment and expert advice regarding the New Drug Application of Eteplirsen for Accelerated Approval. In advance of this meeting, three briefing documents were released (2,3,4). Sarepta initially presented data from studies involving 12 boys who have been administered intravenous eteplirsen weekly over three years. While the first 24 weeks consisted of a randomized placebo controlled dose finding study with 4 boys each receiving 30mg/kg or 50mg/kg of eteplirsen or placebo (Study 201), all patients were rolled

over to open label eteplirsen treatment and some have now been treated for over 4 and a half years (Study 202). Since there was no pre-specified long-term control group, after considerable guidance from FDA, Sarepta is seeking regulatory approval for eteplirsen based on comparison to controls external to the study. Sarepta compared disease progression in the 12 boys treated with eteplirsen relative to 13 boys from available contemporary longitudinal natural history studies, where key variables such as age, functional ability, and mutation were systematically well-matched (5). This comparison demonstrated a clinically significant 153 meter benefit in 6 minute walk distance after 3 years of treatment with eteplirsen relative to external controls. Evidence of persistent dystrophin induction in serial muscle biopsies from treated boys establishes mechanism of action and provided further support for a treatment effect.

The FDA Briefing Document (3) questioned the appropriateness of the selected external control group, suggested an alternate external comparison group, and erroneously indicated that there was little evidence that eteplirsen has any effect at slowing the progression of DMD. In response to FDA reviewer criticism, Sarepta submitted an addendum (4) addressing many of these issues in a point-by-point written rebuttal that also provided updated clinical data after 4 years on study drug. The clinical significance of these additional data is underscored by year four study data reporting that only two of twelve eteplirsen-treated boys have lost ambulation, compared with ten of eleven who lost ambulation in the external control group.

A massive snowstorm on January 22nd forced the postponement of the AdComm, which has now been rescheduled for April 25th. Further, the four year data in the addendum was deemed “a major amendment”, requiring additional consideration by FDA, and the PDUFA date has been extended to May 26, 2016. This sequence of events has lead to the unusual circumstance wherein briefing documents are available for an extended period of time, providing a unique opportunity for Duchenne experts to thoughtfully consider all of the released data and criticisms in order to provide independent commentary on the evidence of efficacy of eteplirsen.

The three year, and the now four year, data make a compelling case that there is substantive evidence of effectiveness, which seems in stark contrast to conclusions reached in the FDA Briefing Document (3). This has prompted a group of 36 leading Duchenne experts to provide written commentary to clarify several issues while the FDA deliberates on the approval of eteplirsen. This expert commentary, in the form of a letter (6), was sent to the Director of the Division of Neurology Products, CDER. The signatories include leaders in DMD biology, therapy development, patient care and natural history.

In considering whether disease progression in the eteplirsen treated boys is substantially deviating from the expected disease course, the group of Duchenne experts comments “The collective signatories note that the group of

12 eteplirsen treated boys, even accounting for daily deflazacort usage or twice-weekly prednisone, is clearly performing better than our collective clinical experience and the published literature would predict. Collectively, a portion of us represent a group of physicians who have observed over 5,000 DMD patients in our practices over an average of more than 15 years. Published external natural history data and our clinical experience strongly support that the 12 boys treated for over 4 years show a milder clinical progression, likely due to a positive treatment effect of eteplirsen."

The group of Duchenne experts also considered whether the drug showed any convincing evidence of dystrophin protein induction. The letter states "In considering that eteplirsen promotes on average 0.93% of normal control levels of dystrophin (range 0%-2.47%), concentrated within an average of 16% "dystrophin positive" fibers (range 1.4%-33.5%), it is reasonable to expect that levels of dystrophin expressed in some positive fibers could be as high as 5-12% of normal; levels clearly predicted to impart some, albeit incomplete, protection of myofibers from contraction induced damage. We conclude that the findings of this trial are sufficiently robust to support the proposed mechanism of action of eteplirsen, to provide a plausible explanation for the relative gain in function observed within the treatment group, and serve to bolster confidence that there is a positive treatment effect."

Serious consideration of data generated using non-traditional trial paths, such as these, is especially important for rare diseases where small populations challenge the ability to robustly test drugs using the generally preferred large randomized double blind placebo controlled trials. In 2012, Congress enacted the Food and Drug Administration Safety and Innovation Act (FDASIA) to encourage and empower the FDA to grant accelerated approval in cases of rare disease with dire consequences and unmet need. The expert commentary concludes, "We suggest that the most scientifically robust way forward and the most ethical choice for the Duchenne community is in the context of an accelerated approval followed by a confirmatory trial." We are hopeful that the flexibility provided by FDASIA and other regulations will be exercised in the case of eteplirsen to ensure timely patient access and accelerate discovery as we usher in the era of personalized genetic medicine for rare disease.

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1. LM Kunkel, 2004 William Allan Award address. Cloning of the DMD gene (2005) Am J Hum Genet 2:205-14 (2005).

2.available at www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/peripheralandcentralnervoussystemdrugsadvisorycommittee/ucm481912.pdf
3. available at

www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/peripheralandcentralnervoussystemdrugsadvisorycommittee/ucm481911.pdf
4.available at www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/peripheralandcentralnervoussystemdrugsadvisorycommittee/ucm481913.pdf

5. JR Mendell, N Goemans, LP Lowes, LN Alfano, K Berry, J Shao, EM Kaye, E Mercuri ; Eteplirsen Study Group and Telethon Foundation DMD Italian Network. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne Muscular Dystrophy. Ann Neurol. 79(2):257-71 (2016)

6. available at www.cdmd.ucla.edu/FDA_ETEPLIRSEN_LETTER_02242016.pdf

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