

A Primer On Eteplirsen For Duchenne Muscular Dystrophy

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Summary

- Duchenne muscular dystrophy is a rare, debilitating, degenerative disease that causes children to be confined to wheelchairs in their teens and to die in their teens to twenties.
- There is no cure available, and the current treatments have limited effect.
- A new drug, eteplirsen, has shown great potential to stabilize and reverse the course of Duchenne in a clinical trial, and showed no safety issues.
- One of our sons, Max, participated in the trial; his life has improved dramatically. We think it is a wonder drug. Media coverage of the experience of other boys in the trial show that Max is not alone.
- Congress has given the FDA the power to expedite the review of novel treatments for rare and serious diseases for which there are no adequate treatments, and stated its intention that the FDA use these provisions.
- If the FDA does not accelerate the review of eteplirsen, then other children, including our son Austin, are destined to see their mobility and the quality of life decline and to die far too early.
- We would like you to let the FDA know that eteplirsen is the kind of drug for which Congress intended that the FDA expedite review, and also to help mobilize the support of other Senators and Representatives in conveying this message.

About Duchenne Muscular Dystrophy

Duchenne muscular is a genetic disease in which patients, almost all boys, experience rapid deterioration in muscle function.

Duchenne is the most common form of muscular dystrophy, affecting around 1 in 3,500 male births. There are around 20,000 Americans living with this disease. Duchenne is classified as a rare disease by the Office of Rare Diseases of the National Institutes of Health.

After around age 7 or 8, these patients do not get better, and evidence indicates that, after the disease reaches a more advanced state, the damage may be irreversible.

Most Duchenne patients are wheelchair bound by their early teens, and most die from respiratory failure or heart failure in their teens to mid-20s.

There is no cure. The most common drug therapy is steroids, which delay progression of the disease by around 1-3 years. Patients also receive respiratory and physical therapy.

More information:

http://www.cdc.gov/ncbddd/actearly/pdf/parents_pdfs/Duchenne.pdf;

<http://www.ninds.nih.gov/disorders/md/md.htm>,

<http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001724>

The Science of Duchenne

Persons with Duchenne produce little or no dystrophin, a protein that helps to bind muscle cells together. The gene that codes for the dystrophin protein normally has 53 separate regions, called exons.

In Duchenne muscular dystrophy, the DNA in one of these exons is shifted, which causes everything after the location of that shift to be eliminated when the patient's cells make dystrophin. For example, someone with a shift in exon 51 will not produce the portions of the protein that relate to exons 52 and 53.

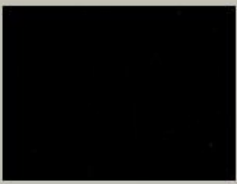
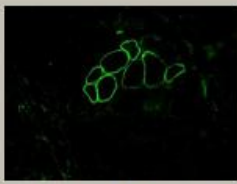

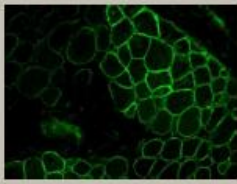

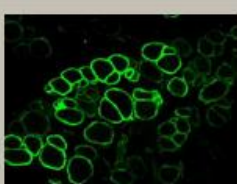
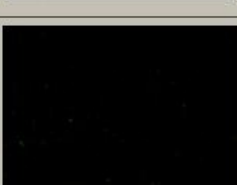
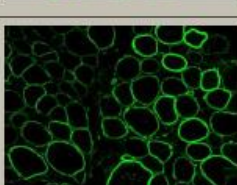
Dystrophin is not functional without both ends of the protein, so the dystrophin that Duchenne patients produce does not hold the muscle cells together.

Exon skipping is a technology in which a small molecule that is chemically similar to DNA is given to patients. This molecule causes the cells to skip over the exon with the DNA shift. While this does not restore the exon that contains the DNA shift, it does restore the rest of the missing portions of the protein.

Eteplirsen

Eteplirsen is an exon skipping drug that Sarepta Therapeutics is developing. They just reported fantastic results from a clinical trial with this drug.

Although the trial was small, the results showed significant production of dystrophin in all patients receiving the drug. You can see this graphically in these slides, which show dystrophin in samples of muscle cells from patients before the clinical study began and at 48 weeks:

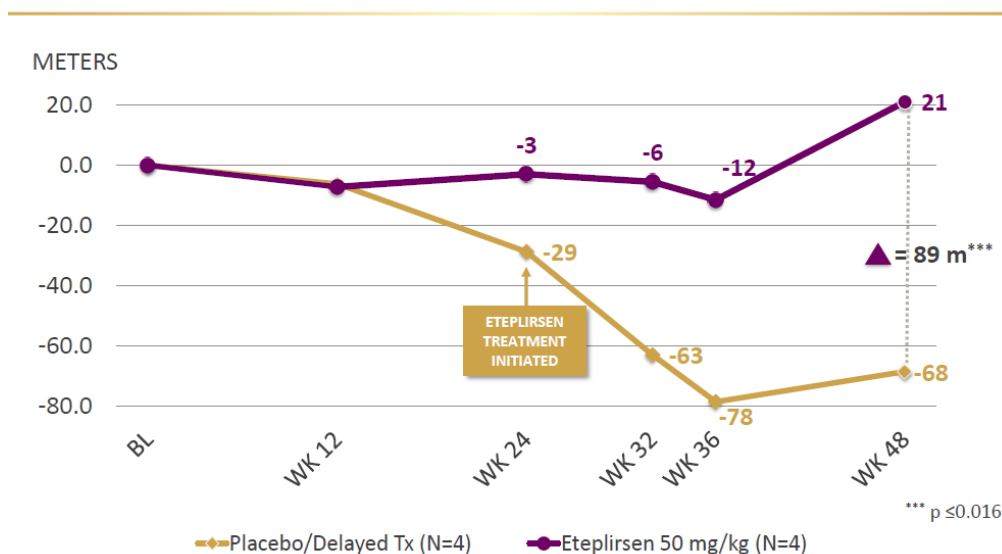
50 MG/KG		
Patient	Pre-Tx	48 wks of Tx
03		
04		
12		
15		

Our son, Max, is patient 15. Compare these to dystrophin levels in a boy without muscular dystrophy:



The study also measured the ability of patients to walk in a six minute period. Here you can see that patients who received placebos walked an average of 68 meters less after 48 weeks than they did when the trial began, whereas patients who received the largest dose of the drug were able to walk 21 meters more on average:

6MWT CHANGE FROM BASELINE TO WEEK 48:
INTENT-TO-TREAT POPULATION: ETEPLIRSEN 50MG/KG VS PLACEBO



Note: Statistical analysis based on Intent-To-Treat Population using ANCOVA test

These results were statistically significant and confirm that the dystrophin these boys produce after they have taken eteplirsen is working. Note that the boys in the placebo group began receiving eteplirsen after 24 weeks, and their Duchenne seems to have stabilized, too.

None of the children in the trial suffered any serious adverse effect.

Source: Mendell, JR *et al.*, *Results At 48 Weeks Of A Phase IIB Extension Study Of The Exon-Skipping Drug Eteplirsen In Patients With Duchenne Muscular Dystrophy (DMD)*, presented at World Muscle Society conference, Oct. 13, 2012, <http://phx.corporate-ir.net/External.File?item=UGFyZW50SUQ9MTU2ODE3fENoaWxkSUQ9LTF8VHlwZT0z&t=1>. See also Sarepta’s press release announcing the top-line 48-week data, <http://investorrelations.sareptatherapeutics.com/phoenix.zhtml?c=64231&p=irol-newsArticle&ID=1741044> and the transcript from their conference call at

<http://seekingalpha.com/article/902741-sarepta-therapeutics-ceo-discusses-48-week-results-from-the-phase-iib-dmd-study-transcript>.

Stories Of Children In The Trial

Charts and graphs are important, but, to appreciate what this means in human terms, you need to see the incredible effect this drug has had on the lives of boys in the trial. We, and the families of two other patients who received eteplirsen from the beginning of the trial, have gone public with stories of dramatic improvements in the lives of our sons. I understand that this is unprecedented.

<http://www.wcax.com/story/19277658/2-vt-brothers-battle-deadly-disorder-only-1-can-get-treatment>

<http://www.wcvb.com/A-Miracle-drug/-/9849586/17080266/-/8dm27v/-/index.html>

<http://www.youtube.com/watch?v=LblpXPbJMqU>

<http://www.kfvs12.com/story/19411932/clinical-trial-shows-promise-for-jackson-12-year-old-with-duchenne-muscular-dystrophy>

What's truly amazing is the things that these boys can do now that they could not do before. For example, our son Max can open bottles, get around school without a wheel chair, jumps, climbs, none of which he could do before he started receiving eteplirsen, and bounds down stairs when he used to have to use an elevator. One patient, Justin Trovillion, even competed in a 5K run to support the organization that provides some of his physical therapy.

What We Need Now

Normally, the FDA requires at least two positive studies before approving a drug. The FDA has the power to grant an "accelerated approval" where there is less data available to expedite novel treatments for rare, serious, and life-threatening diseases for which there is no adequate treatment under Section 506 of the Food, Drug, and Cosmetic Act. Note that the FDA can, if it grants accelerated approval, require a follow-up study to confirm the results, and Sarepta has committed to perform the follow-up study.

Section 901 of the Food and Drug Administration Safety and Innovation Act, which passed both houses with wide bipartisan support, Congress enhanced the FDA's ability to accelerate development and review of these drugs. Congress also clearly stated its intention that the FDA do so. See <http://www.gpo.gov/fdsys/pkg/BILLS-112s3187enr/pdf/BILLS-112s3187enr.pdf>, pp. 90-92 (other sections of Title IX of

the Act add other programs and resources to help with the development of these drugs, but accelerated approval is the key provision for eteplirsen).

Eteplirsen meets all of the criteria that Congress set forth in Section 901.

The choice here is stark. If the FDA requires the completion of another study before it reviews eteplirsen, then we know that the children who might benefit from the drug will lose their ability to walk, see their quality of life decline, and be destined to die young. Set against this we have a new drug that has shown remarkable results in one study and no safety issues.

As the parents of a boy in the trial, we can tell you that we think this is a wonder drug. As the parents of another boy who was not eligible for the trial, we can tell you that we and Austin want this drug available as soon as possible for him and all of the other patients it might help. These boys deserve this chance.

We Need Your Help!

We are not asking anyone to tell the FDA to approve eteplirsen. Reviewing the science and balancing risks against benefits is their job, and they're good at it.

We would, however, like support from the members of the Senate HELP committee, the House Subcommittee on Health, any other interested Senator or Representative, and their staffs, to let the FDA know that eteplirsen is exactly the kind of drug that Congress intended to be eligible for accelerated review under the amended Section 506 of the Food, Drug, and Cosmetic Act.

Need More Information?

We can put you in touch with other parents, physicians who treat Duchenne, medical researchers who work every day to find a cure, advocacy groups, and others who can provide additional background if you would like it.