Center Director's Remarks

Janet Woodcock, MD
Director
Center for Drug Evaluation and Research
Food and Drug Administration

Eteplirsen for treatment of Duchenne muscular dystrophy in patients who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping therapy

Billy Dunn, M.D.
Director
Division of Neurology Products
Center for Drug Evaluation and Research

Peripheral and Central Nervous System Drugs Advisory Committee
April 25, 2016

Duchenne Muscular Dystrophy (DMD)

- Serious and devastating disease with profound unmet medical need and no approved treatment
- FDA highly sensitive to urgency of situation
- FDA will use all available pathways to approval for a safe and effective drug to treat DMD

Eteplirsen

- Developed to treat patients with DMD who have a confirmed mutation of the dystrophin gene amenable to exon 51 skipping.
- Eteplirsen's intended mechanism of action is by removal of exon 51 of the pre-messenger RNA, thereby restoring the dystrophin mRNA reading frame, which may increase the production of a truncated form of dystrophin, hopefully leading to a clinical benefit for patients.

Eteplirsen Proposed Path to Approval

- Applicant proposes approval based on:
  - Clinical results from a single open-label study in 12 patients (Study 201/202), using a comparison to a historical control.
  - Biomarker results from Study 201/202, and from two exploratory studies (28 and 33).

Issues for which FDA is Seeking PCNS Input (1)

- Discuss and vote on whether there is substantial evidence from adequate and well-controlled studies, as required under the Food, Drug and Cosmetic Act, that eteplirsen induces production of dystrophin to a level that is reasonably likely to predict clinical benefit.

Issues for which FDA is Seeking PCNS Input (2)

- Discuss and vote on whether substantial evidence of effectiveness has been provided, as required under the Food, Drug and Cosmetic Act, by the clinical results of the single historically-controlled efficacy study (Study 201/202) conducted by the applicant.

Substantial Evidence of Effectiveness (1)

- 1962 Kefauver-Harris Amendments to the Food, Drug and Cosmetic Act included a provision requiring manufacturers of drug products to establish a drug's effectiveness by "substantial evidence"
- *Substantial evidence* was defined in section 505(d) of the Act as
  - "evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and responsibly be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof."

Substantial Evidence of Effectiveness (2)

- It has long been FDA's position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness.
- The usual requirement for more than one adequate and well-controlled investigation reflects the need for *independent substantiation* of experimental results.
  - Independent substantiation of a favorable result protects against the possibility that a chance occurrence in a single study will lead to an erroneous conclusion that a treatment is effective.

Substantial Evidence of Effectiveness based on a Single Study (1)

- In 1997, the FDA Modernization Act (FDAMA) amended section 505(d) of the Act to make it clear that the Agency may consider "data from one adequate and well-controlled clinical investigation and confirmatory evidence" to constitute substantial evidence if FDA determines that such data and evidence are sufficient to establish effectiveness.

Substantial Evidence of Effectiveness based on a Single Study (2)

- FDA has relied on only a single adequate and well controlled efficacy study to support approval, generally, only in cases in which a single multicenter study of excellent design provided highly reliable and statistically strong evidence of an important clinical benefit, such as an effect on survival, and a confirmatory study would have been difficult to conduct on ethical grounds.

Substantial Evidence of Effectiveness based on a Single Study (3)

- Characteristics of a single adequate and well-controlled study that could make the study adequate support for an effectiveness claim include:
  - Large multicenter study
  - Consistency across study subsets
  - Multiple studies in a single study
  - Multiple endpoints involving different events
  - Statistically very persuasive finding

Substantial Evidence of Effectiveness based on a Single Study (4)

- It is critical that the possibility of an incorrect outcome be considered and that all the available data be examined for their potential to either support or undercut reliance on a single trial.

Accelerated Approval (1)

- FDA may grant accelerated approval for a product for a serious or life-threatening disease or condition upon a determination that the product has an effect:
  - On a surrogate endpoint that is reasonably likely to predict clinical benefit, or
  - On a clinical endpoint that can be measured earlier than irreversible morbidity or mortality and that is reasonably likely to predict an effect on irreversible morbidity or mortality or other clinical benefit (intermediate clinical endpoint).

Accelerated Approval (2)

- FDA has indicated* that biomarkers that reliably reflect the health and amount of skeletal muscle may, if supported by sufficient scientific evidence and acceptable analytical methods, be used as surrogate endpoints to support accelerated approval of a new DMD drug.
- Such a biomarker would have to be "reasonably likely to predict clinical benefit" in order to be acceptable as a basis for accelerated approval.

*Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment Guidance for Industry.

•http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM450229.pdf

Accelerated Approval (3)

- Importantly, the evidentiary standards for effectiveness are not lower for biomarker or intermediate clinical endpoints used to support accelerated approval.
- Substantial evidence of an effect on those biomarker or intermediate clinical endpoints must be demonstrated.
- Accelerated approval cannot be used to compensate for weak or inconsistent clinical findings.

External Control Historical Studies (1)

- Under the proper circumstances, FDA regulations (21 CFR 314.126) recognize that historical control studies can be considered adequate and well-controlled studies, and used to support approval.

- There are many issues to consider with the interpretability of such studies (as discussed in ICH E10).
  - These will be discussed by Dr. Temple.

Eteplirsen PCNS Drug Advisory Committee Meeting

- **Applicant presentations (Sarepta Therapeutics, Inc.)**
- **FDA presentations**
  - **Center Director's Remarks**
    Janet Woodcock, MD
  - **Issues to Consider with External Control Studies**
    Robert Temple, MD
  - **FDA Efficacy Review**
    Ronald Farkas, MD, PhD
    Ashutosh Rao, PhD
  - **Concluding Remarks**
    Eric Bastings, MD

Eteplirsen PCNS Drug Advisory Committee Meeting

- **Open Public Hearing**
- **Questions to the Committee/Committee Discussion**

Historically Controlled Trials

Robert Temple, MD
Deputy Center Director For Clinical Science
Center for Drug Evaluation and Research
Food and Drug Administration

PCNS AC Meeting
April 25, 2016

Overview

Brief discussion of history of FDA use of historically controlled studies and concerns associated with this design.

N.B. Will not specifically address eteplirsen data (Study 201/202). That will come in subsequent presentations.

Historical Control

Section 505(d) of the FD & C Act, defining standards for drug approval, calls for substantial evidence of effectiveness, meaning evidence "consisting of adequate and well-controlled investigations, including clinical investigations. . . on the basis of which it could fairly & responsibly be concluded. . . that the drug will have the effect it. . . is represented to have."

Adequate and well-controlled studies were first described in regulations in 1970, now included in 21 CFR 314.126, and have always included as one kind of adequate & well-controlled study the "Historical Control."

Historical Control - Regulation

(v) Historical Control: The results of treatment with the test drug are compared with experience historically derived from the adequately documented natural history of the disease or condition, or from the results of active treatment, in comparable patients or populations. Because historical control populations usually cannot be as well assessed with respect to pertinent variables as can concurrent control populations, historical control designs are usually reserved for special circumstances. Examples include studies of diseases with high and predictable mortality (for example, certain malignancies) and studies in which the effect of the drug is self-evident (general anesthetics, drug metabolism).

Note that a baseline control trial, where a single-arm treatment is compared with what would have been expected in the absence of an intervention, is a kind of historical control.

Historical Control – ICH E-10

Renames “historical control” as one of a kind“ external control” and notes several kinds of external control groups:

- Population treated earlier (historical control)
- Population treated contemporaneously at another institution
- A group treated outside the study within same institution
- Baseline control, where the patient’s course is compared with the “expected” course, based on general knowledge of specific experience, or, sometimes, with a prior period of observation.

The design works most clearly when effect is dramatic and rapid: general anesthesia, cardioversion, tumor shrinkage.

Historical Control - ICH E-10 (cont)

The “inability to control bias is a major and well-recognized limitation of externally controlled trials and is sufficient in many cases to make the design unsuitable.”

Really two distinct aspects of bias: bias before the trial; bias during and after the trial.

1. Bias before the trial – patient selection. But this is really two issues.
   - Non-comparability of the groups; i.e., they may differ in important characteristics that may influence outcome.
   - Selection bias – the control patients are worse, (sicker or destined to have worse outcomes than the treated patients).

Historical Control - ICH E-10 (cont)

Non-comparability can go in either direction, favoring or disfavoring the treatment. The guidance points out, however, that “it is well-documented that untreated historical-control groups tend to have worse outcomes than an apparently similarly chosen control group in a randomized study, possibly reflecting a selection bias.”

ICH E-10 Selection Bias

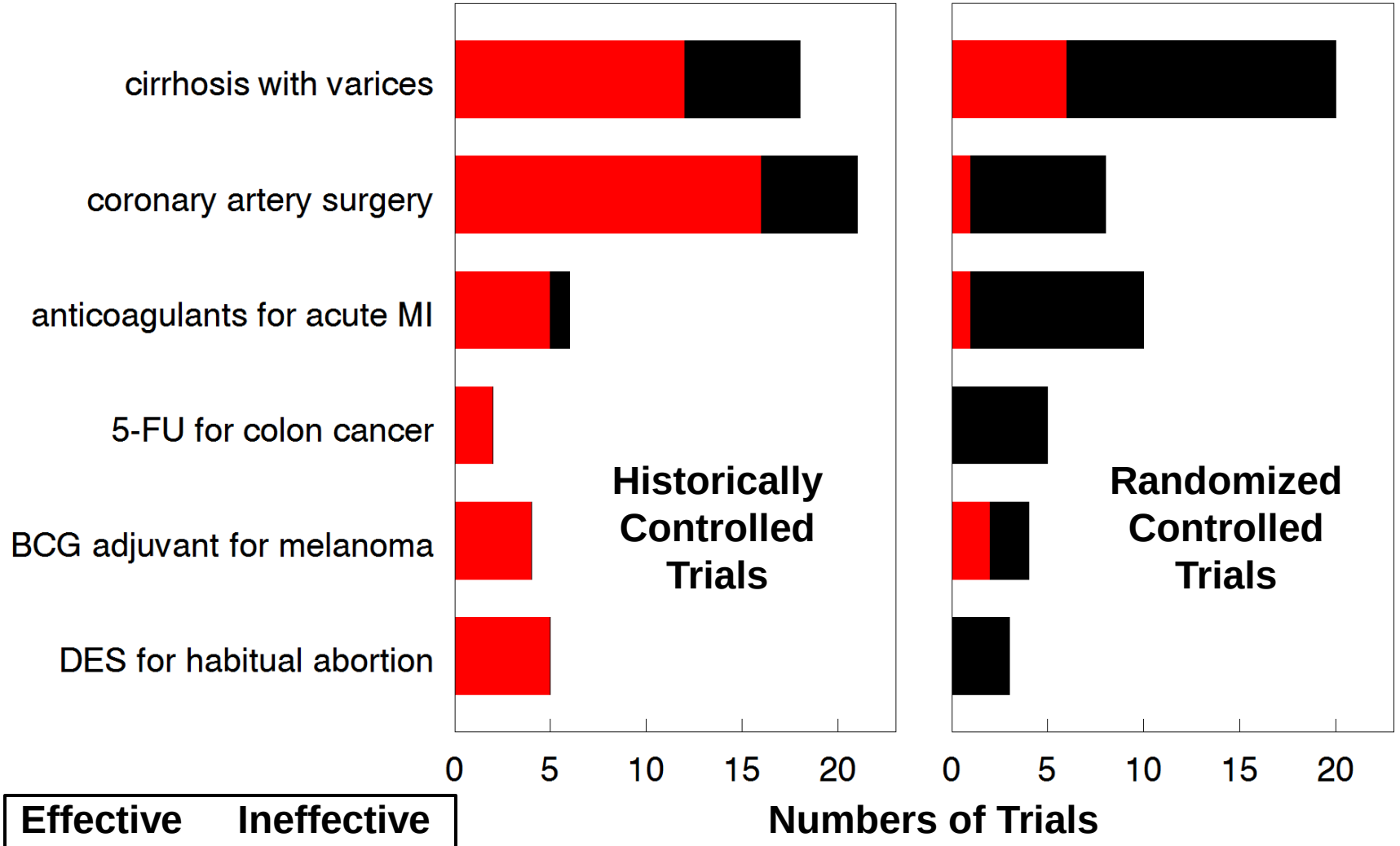
Classic Analysis

Sacks, Chalmers, Smith. Am. J Med (1982); 72: 233-240.

Compared RCTs and HCTs for same disease, finding results regularly more favorable for HCTs.

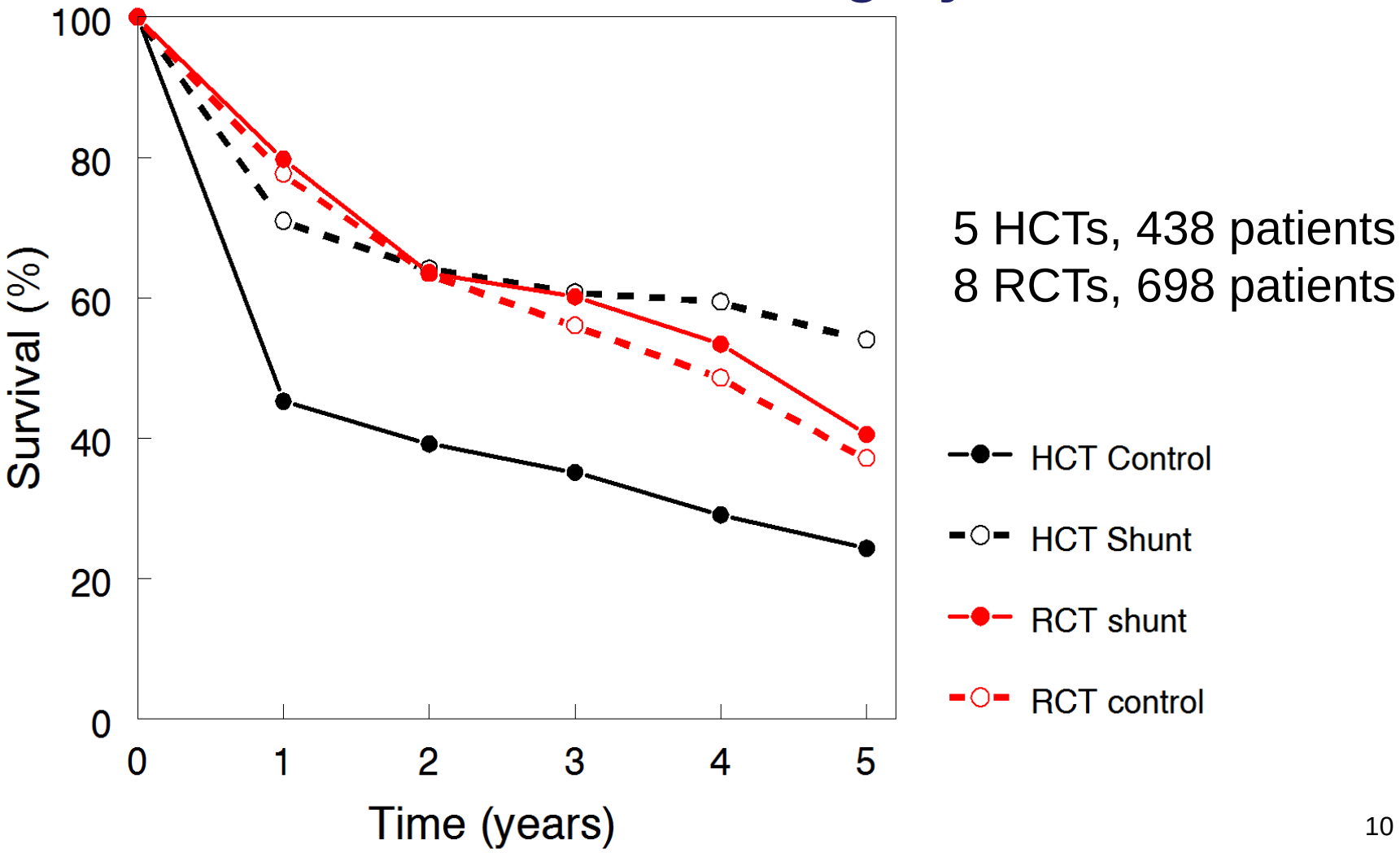
In following figure, it is clear that results of RCTs are regularly less positive than HCTs (10/50 favorable for RCTs vs 44/56 favorable for HCTs).

Conclusions on RCTs and HCTs on 6 Therapeutic Questions



Adapted from Sacks H. *et al* Am J Med (1982); 72:233

Survival of Treated and Control Groups in Clinical Trials of Shunt Surgery for Cirrhosis:



5 HCTs, 438 patients
8 RCTs, 698 patients

Selection Bias

It seems likely that the historical control untreated patients were sicker and that the surgical candidates in the HCT's were in better shape. In the RCTs they appeared very similar. Selection bias in this case (patients different at baseline) is the only real source of potential bias, as mortality is objective, but the finding was very powerful.

ICH E-10 specifically notes that selection of the control retrospectively, i.e., with results known and in hand, poses a particular problem.

ICH E-10
Other Bias

2. Bias during and after the trial.

Apart from selection bias, the lack of blinding and the investigators' knowledge of treatment in patients getting the test treatment (and those getting the control treatments if they are being newly analyzed) can also allow bias to affect endpoints if they are subjective. Most endpoints, even those seemingly objective, have subjective (judgment) elements, including presence of absence of AMI, cause of hospitalization, and most other endpoints. You will later hear a discussion of subjectivity of ability to ambulate. Importantly, expectation bias and motivation can affect symptoms and performance.

ICH E-10
Other Bias

Another potential source of bias is choice of endpoint (when there are several possibilities), including whether to use a composite endpoint, time-to-event or cumulative events, decisions about which patients to include, etc. These problems can be seen in RCTs as well, but expectations for a prospective statistical analysis plan are higher for RCTs; indeed, they are a virtual requirement.

ICH E-10 Bottom Line(s)

The overall tone is skeptical about use of external controls for most situations, as is our adequate and well-controlled studies regulation, but both accept them as credible in particular situations. ICH E-10 urges:

- Selection of a control group for which there is detailed information (demographic, baseline state, concomitant medications, and study course).
- Try to assure similar Rx, other than test drug, and similar observations in the treatment and control groups.
- Use of multiple external control groups.
- Consideration of blinded endpoint reassessment in treatment and external control group.

ICH E-10 Bottom Line(s) (cont)

ICH E-10 also suggests that the main credible use of external controls is when there is an ethical difficulty in doing the RCT. The suggested remedy is to randomize the earliest studies: “The concurrently controlled trial can detect extreme effects very rapidly and, in addition, can detect modest, but still valuable, effects that would not be credibly demonstrated by an externally controlled trial.”

ICH E-10 again notes that external control trials are most likely to be persuasive when the effect is very large.

A Few More Examples

A. Fulminant Hepatitis B

Gocke. Fulminant hepatitis treated with serum containing antibody to Australia antigen. NEJM (1971): 284; 919, letter to the editor.

- Nine consecutive cases of acute fulminant hepatitis B; all fatal despite exchange Tx, steroids, support.
- Eight hepatic coma patients given usual Rx plus anti-Australia antigen serum; 5/8 survived.

Considered reaching a conclusion that the treatment was effective, BUT realized it could be better care, earlier Rx, so urged a RCT in severe hepatitis.

Examples (cont)

Hepatitis RCT

Acute Hepatic Failure Study Group: Failure of specific immunotherapy in fulminant Type B hepatitis. Ann Int Med (1977); 86: 272-277.

30 centers, 53 patients

Survival: placebo vs hepatitis B immune globulin (HBIG)

Placebo 9/28 (32%)

HBIG 7/25 (28%)

Examples (cont)

Renal Artery Denervation

B. Widely publicized renal artery denervation device was studied in three trials:

Open-label single-arm study (Symplicity HTN-1 Trial) found an average 3-year fall in BP of 33/19 mmHg

RCT (device vs no device) with no sham control, i.e., open label (Symplicity HTN-2) found at 6 months a change of -32/12 vs 1/0 in the control.

RCT with sham control (Symplicity HTN-3) found at 6 months a change of -14 mmHg (denervation) vs -12 mmHg (sham), p= 0.26.

Examples

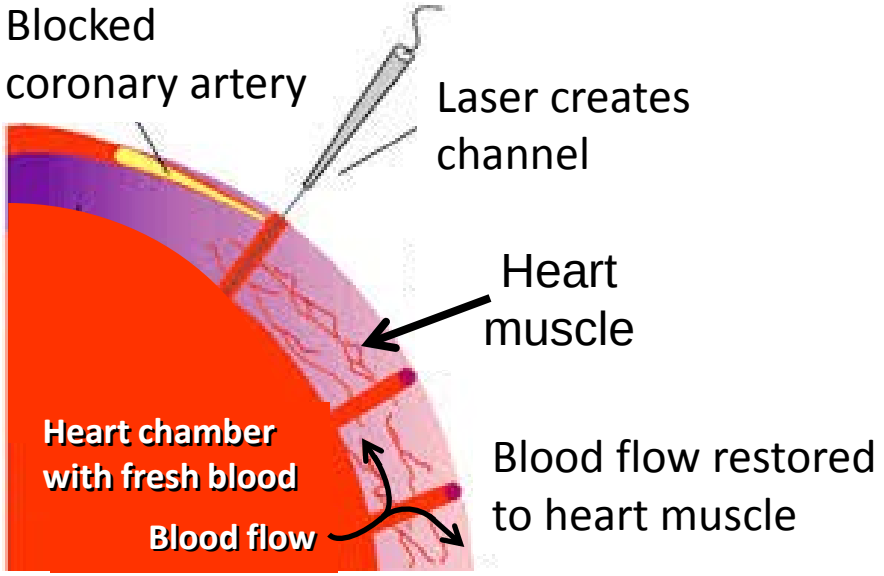
Transmyocardial Laser Revascularization (TMLR).

Dr. Unger has provided 3 slides illustrating a case with a motivationally dependent endpoint, exercise ability, using both a baseline control and a randomized control.

Uncontrolled (Baseline-Controlled) Studies of Transmyocardial Laser Revascularization (TMLR)

- Many cardiac centers experimented with TMLR in the 1990s.
- Patients with coronary artery disease, severe angina, and no treatment options (poor candidates for bypass surgery/ angioplasty)

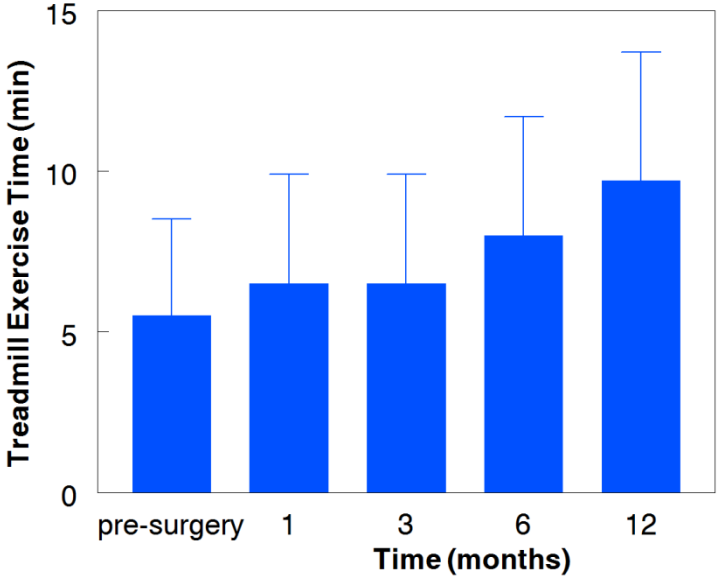
Procedure: open-heart surgery; use laser to create channels through the heart muscle, allowing blood to flow to the muscle directly from the inside the heart.



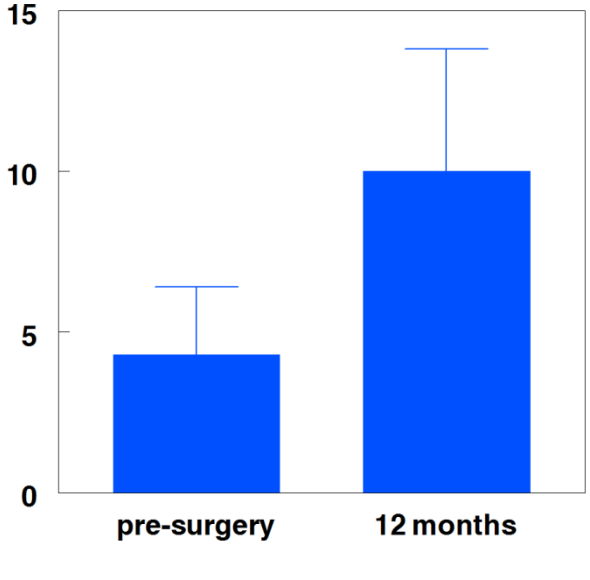
- No way to conduct a placebo-controlled trial to assess efficacy
- One cannot give patients SHAM open-heart surgery!

Many Centers: Extraordinary Results on Exercise

- Observed treatment effects were based on historical comparisons
- Typical results, reported by many investigators, generally small studies:



Ann Thorac Surg 1999;67:432-6



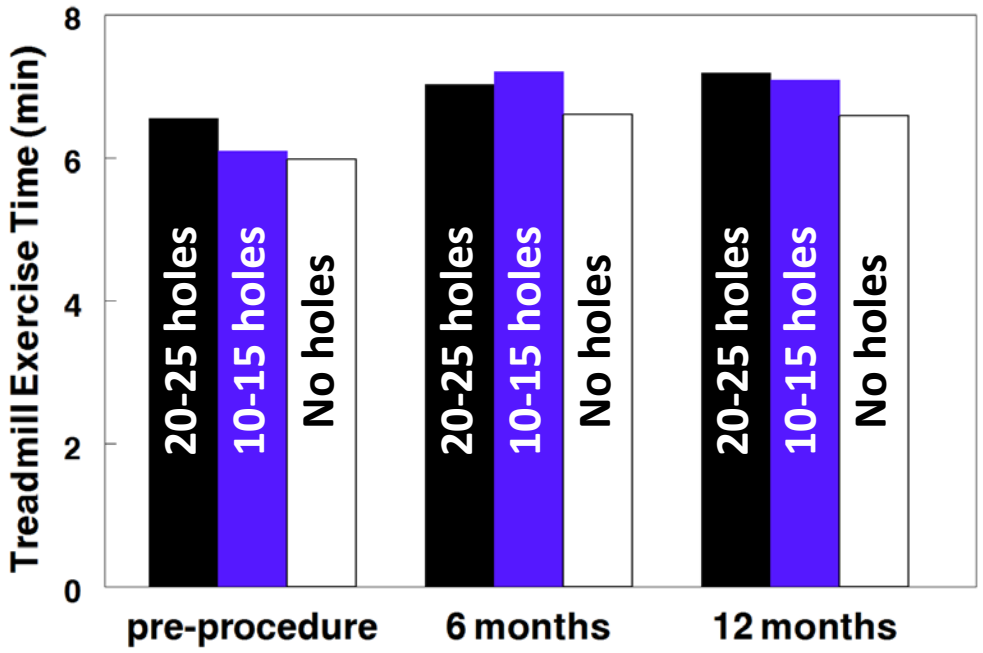
J Thorac Cardiovasc Surg 1996;111:791-9

- Marked increases in exercise time, sustained for a year in sick patients, seemed fantastic – too good (and long-lasting) to be "placebo" effect.
- Many were not willing to attribute the improvement to chance or expectation bias, i.e., they believed that the procedure worked.

***Many patients underwent this operation for angina.

Double-Blind Placebo-Controlled Trial: No Effect of TMLR on Exercise

- With new catheters, laser revascularization could be conducted through arteries, without need for open-heart surgery
- Multicenter, double-blind, placebo-controlled trial in 298 subjects
- Compared "low-dose" and "high dose" laser treatments to a sham procedure, under sedation



Results:

- No improvement in exercise time after 6 or 12 months
- Effects of TMLR on exercise, observed in many uncontrolled studies, was probably due to expectation bias – patients with few options; many hopes from a radical procedure.

J Am Coll Cardiol 2005;46:1812-9

But We Do Use Them, As Contemplated in Regulations

I. Obvious case: tumor response in oncology and, not commonly, cures.

a. Some treatments of some leukemias and lymphomas give a cure rate.

a. It is certain that cannot happen absent therapy, so effect is demonstrated.

b. The first 3 treatments for metastatic testicular cancer, cis-platinum, ifosfamide, and etoposide, were all based on success rates (1 year tumor-free survival in patients with metastatic disease) > 90% for cis-platinum, and about 10% for ifosfamide and etoposide in cis-platinum failures.

Given the unequivocal expected 1-year tumor-free survival of 0%, this was a straightforward use of a baseline control, single-arm design.

Uses of Historical Controls

2. Stone Cases

   Many years ago (late 70's, early 80's) drugs for stone disease were approved based on a comparison of monthly stone rates in patients for the months preceding treatment compared with rates in treatment. Differences were large (would we do that today? Not sure). Premise: patients had a disease that would not spontaneously change.

3. Many orphan diseases (described in various NORD publications) use these designs.

   Alglucosidase ALFA for Pompe disease (2006).

   Endpoint: 1 year ventilator free survival in 18 treated patients vs 62 historical controls.

Orphans (cont)

- Lomitapide was approved to reduce LDL cholesterol in patients with homozygous familial hypercholesterolemia (2012) based on treatment of 29 patients for 26 weeks in a single-arm trial. The 40% fall in LDL was plainly a change that would not occur spontaneously in this genetic disorder.
- Pasireotide diaspartate was approved (2012) for the treatment of Cushing Disease based on two-arm trial comparing two doses in 162 patients. It was considered unethical to leave patients untreated and the endpoint, one that clearly would not have occurred spontaneously, was normalization of mean urinary free cortisol.
- Deferiprone was approved (2011) for treatment of transfusional iron overload associated with thalassemia syndromes. Evidence of effectiveness came from a 236 patient pooled analysis using a historical control and showing reduced ferritin.

Orphans

A number of approvals of anti-infectives (anti-fungals, especially) where there was no needed comparison to existing therapy, have compared treatment with literature-based natural history. Isavuconazonium for invasive mucormycosis was approved on this basis.

Uses of Historical Controls

The cases cited are typically ones involving well-defined diseases with VERY predictable outcomes, thought not to be susceptible to effects of treatments other than the test drug and thought to be relatively non-variable from one patient to the next.

There are, however, cases in which there can be debate about how predictable the course of the disease is in the absence of treatment and, thus, whether historical control approaches can be considered and would be well-supported, as stressed in ICH E-10.

Eteplirsen

Duchenne Muscular Dystrophy in Patients with Mutations Amenable to Skipping Exon 51

FDA Efficacy Review

Peripheral and Central Nervous System Drugs Advisory Committee Meeting
April 25, 2016

Ashutosh Rao, Ph.D.
Acting Chief, Laboratory
of Applied Biochemistry
Division of Biotechnology
Review and Research III
Office of Biotechnology Products

Ronald Farkas, M.D., Ph.D.
Clinical Team Leader
Division of Neurology Products
Office of Drug Evaluation I
Office of New Drugs

1. Biomarker evidence
   - Bioassay methods: Dr. Rao
   - Bioassay findings: Dr. Farkas

2. Clinical evidence
   - 24 week controlled trial
   - Open label treatment vs. external controls

Lack of Dystrophin is the Cause of DMD

- FDA DMD Guidance – particular interest in dystrophin as a biomarker and potential surrogate for accelerated approval based on a conclusion of “reasonably likely” to predict clinical benefit

- “Reasonably likely” depends on quantity, location and function of dystrophin produced

- Reliable assays, and consistent findings across and within studies are critical for interpretation

Common Methods to Show Production of 'Skipped' Messenger RNA and Restored Dystrophin Protein

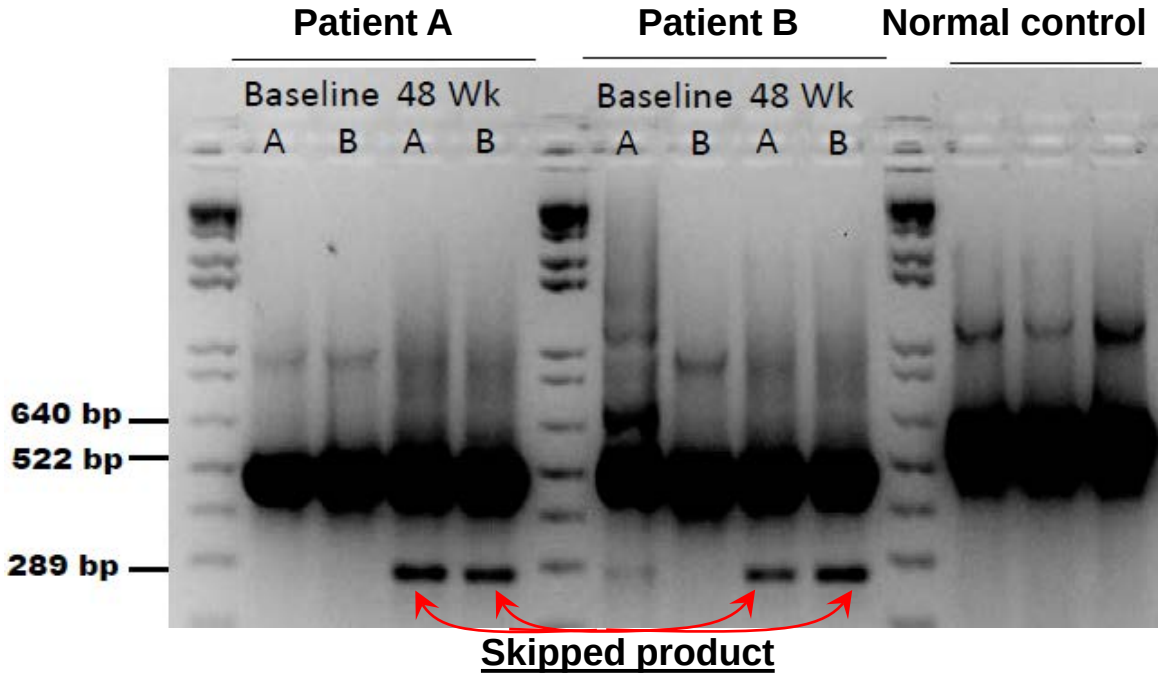
- RT-PCR – standard method; used to provide evidence that the desired messenger RNA is produced (i.e., exon 51 skipping)

- Western blot (WB) – standard immunoblotting method; used for relative protein quantification

- Immunofluorescence – standard microscopy method; used to localize protein; semi-quantitative for total immunoreactive signal

Methods Used by Applicant to Measure Effect of Eteplirsen on Dystrophin: RT-PCR

- Eteplirsen is designed to cause skipping of exon 51 in mRNA, which could increase production of a truncated but partially functional dystrophin protein



Methods Used by Applicant to Measure Effect of Eteplirsen on Dystrophin: RT-PCR

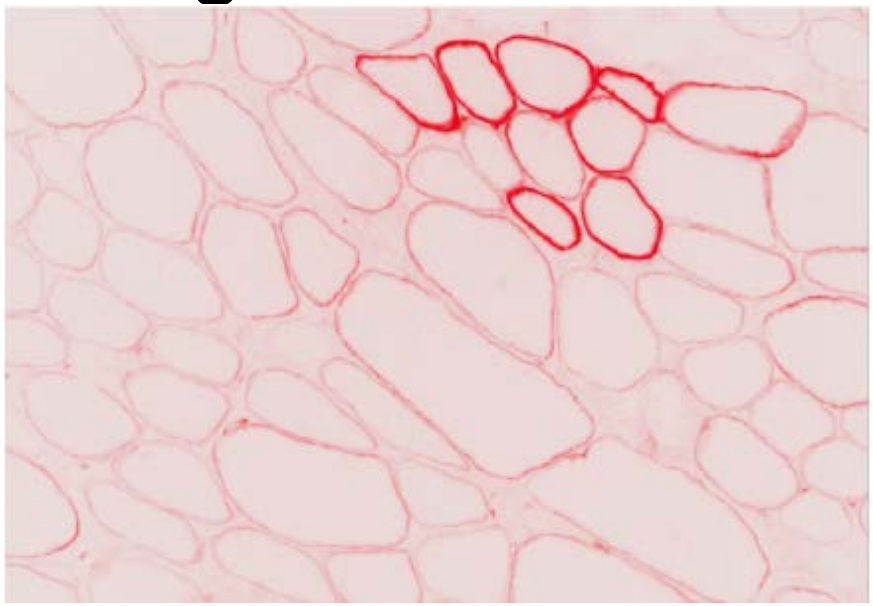
- Eteplirsen designed to cause skipping of exon 51 in mRNA, which could increase production of a truncated but partially functional dystrophin protein

- RT-PCR method can detect exon 51 skipped mRNA
  - "Positive" RT-PCR can be encouraging, but method does not measure *amount* of mRNA skipping, and can be positive if even a very small amount of skipping is occurring
  - Neither does RT-PCR measure how much, or even if, dystrophin *protein*, is being produced

Methods Used to Measure Effect of Eteplirsen on Dystrophin: Immunofluorescence

- Microscopy method most useful for showing location of dystrophin in the muscle
- Major shortcomings compared to WB for quantifying dystrophin protein levels
  - Lacks the type of internal control (reference dilution series) that is necessary for reliable quantification
  - Intensity measurements tend to overestimate dystrophin at the low levels present in untreated and eteplirsen-treated patients
    - *e.g.*, often shows **10%** of normal intensity in Duchenne, even though far less than 10% by WB

Immunofluorescence: Scoring Positive Fibers



- Processed image of muscle section, stained to identify dystrophin
- Staining localizes to the sarcolemma, as expected.
- Fibers are scored as positive or negative, but scoring based on staining intensity is not “all-or-nothing” – reading is subjective.
- Fibers can be classified as “positive” if stained only barely more than background.
- Fields are not uniform – mixture of many staining intensities
- Not possible to differentiate fibers with drug-induced dystrophin from revertant fiber dystrophin with this method

Immunofluorescence: Critical Factors in Analyses

- Investigators blinded to patient identity and treatment assignment
- Systematic and random selection of fields for analysis
- Use of positive, intermediate, and negative controls
- Careful control over conditions of observation (e.g., image processing, video display, ambient light)
- Reading by >1 pathologist, blinded to sequence, with assessment of intra- and inter-observer variability

Data generated from Study 28 and the first 3 biopsies of Study 201/202 were not consistent with all of these principles.

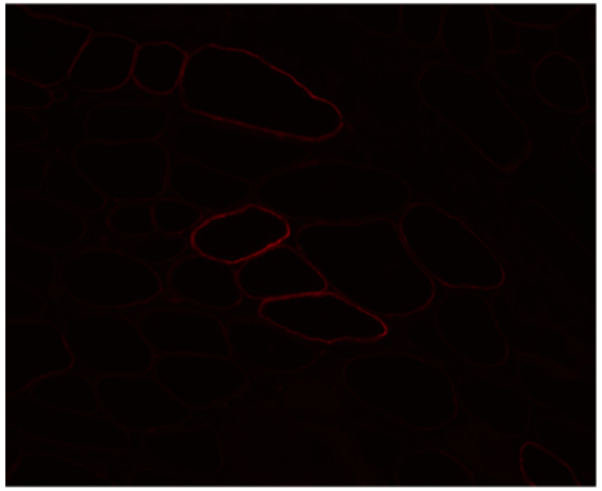
Prior to 4th Biopsy at Week 180, FDA Advice to Applicant on Assay Development and Validation

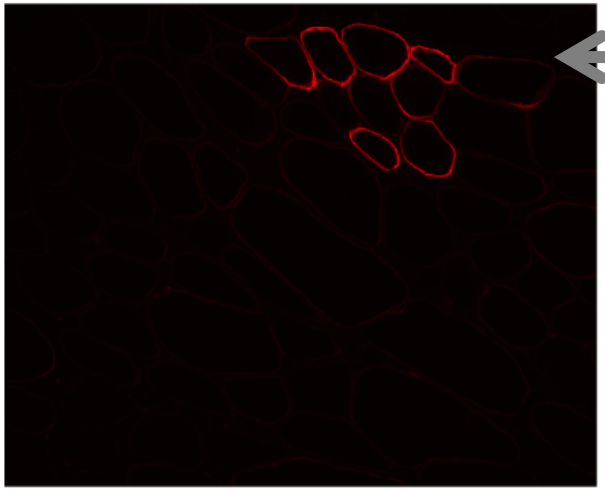
- FDA performed laboratory site visit to assess methodology:
  - Some issues identified
  - Technical advice provided
- NIH-FDA workshop on the current state of dystrophin methodologies
- Draft Guidance for Industry on developing therapies for DMD

Technically Satisfactory Methods Used for 4th Biopsy Immunofluorescence

- Systematic, random field acquisition
- Improved blinding and quality assurance procedures
- Independent re-assessment by three pathologists outside of primary test laboratory
- Positive/intermediate/negative control samples included

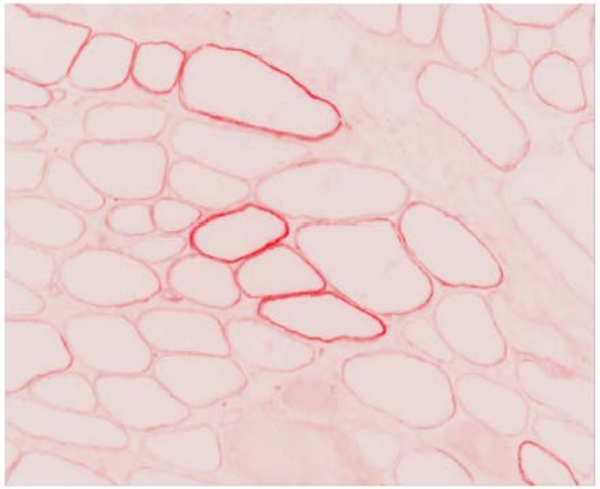
Immunofluorescence, 4th Biopsy

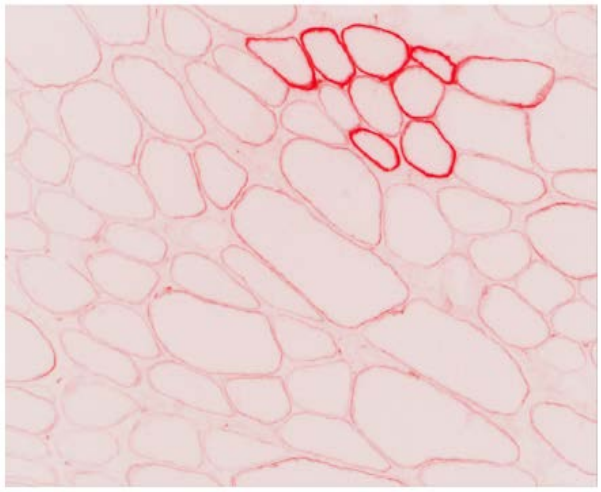




“Revertant Fibers” or newly expressed dystrophin?

Mandys106 immunofluorescence

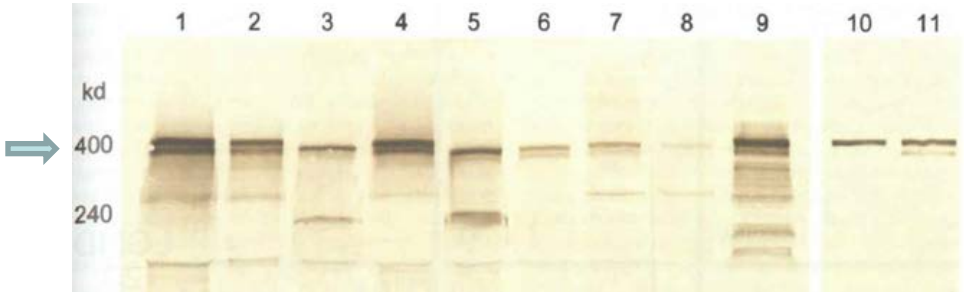




Inverted and amplified image for pathologist to identify total fibers

Methods Used by Applicant to Measure Effect of Eteplirsen on Dystrophin: Western Blot

- Standard method used for relative protein quantification
  - **But still a difficult method to perform well**

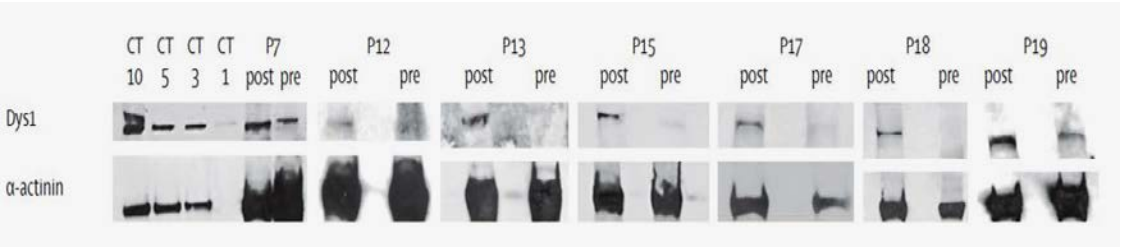


Hoffman EP et al, Neurology, 1989

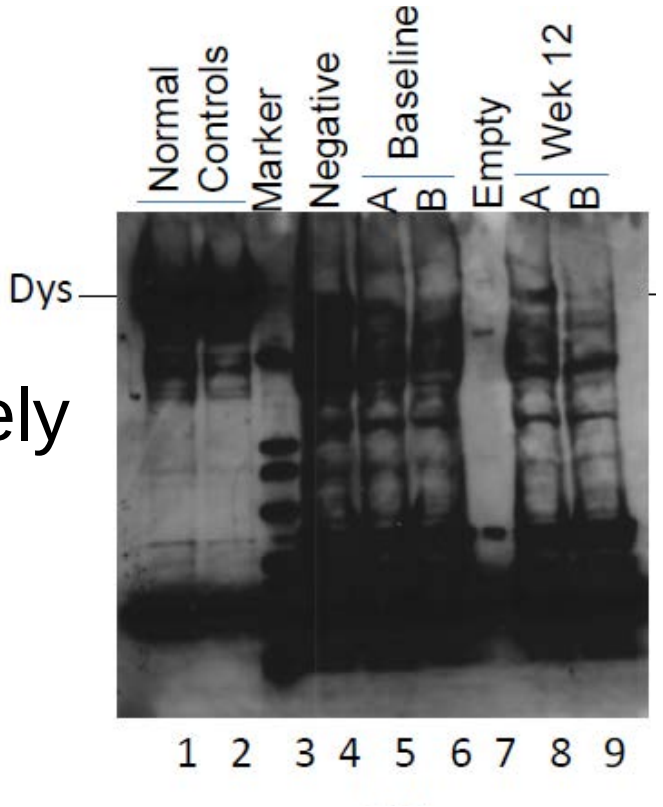
- Most quantitative method used by the applicant
- Allows comparison of relative levels of dystrophin in patients with DMD or Becker muscular dystrophy (BMD) to healthy controls

Technical Problems with Western Blots in Study 28 and First 3 Biopsies of Study 201/202

Example from Study 28



Example from first 3 Biopsies

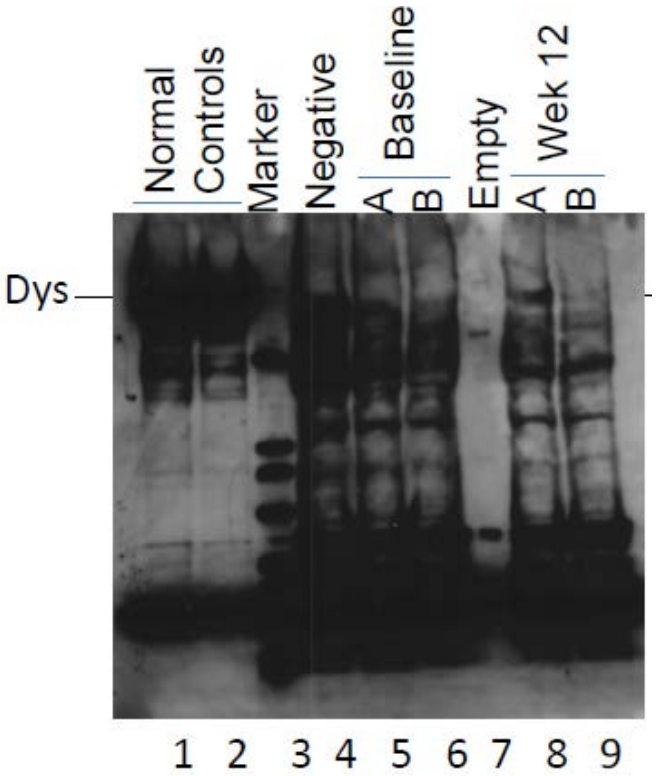


- Methods not validated and largely exploratory
- Bands are oversaturated
- Prevents reliable quantification

Mandys106WB

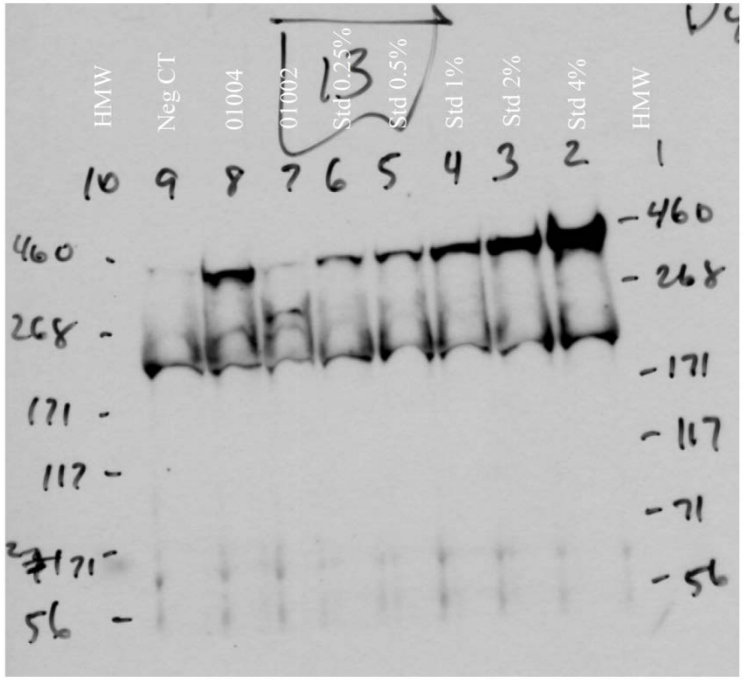
Western Blot with 4th Biopsy following FDA Advice

Example from first 3 Biopsies



Mandys106WB

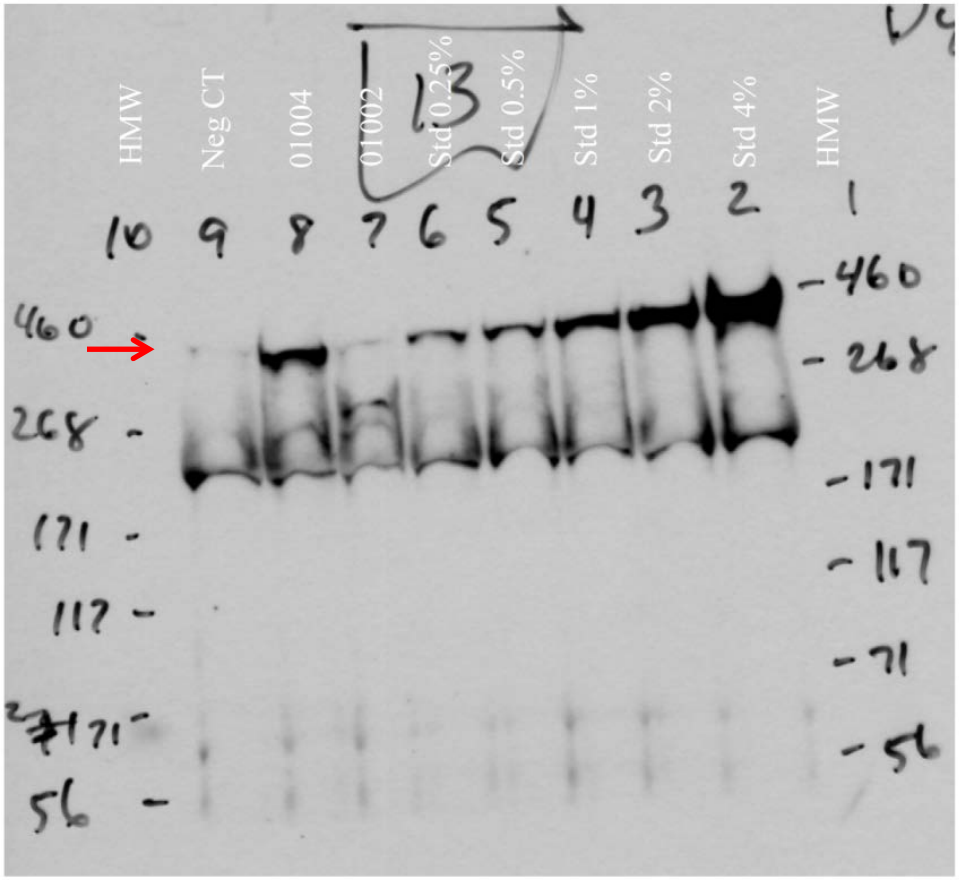
Example from 4th Biopsy



Source Image File Name: 01004_01002_50TT_30TT_180_D1_30minWB13.tif

Satisfactory to quantify relative protein levels

Technically Satisfactory Western Blot Used for 4th Biopsy of Study 201/202



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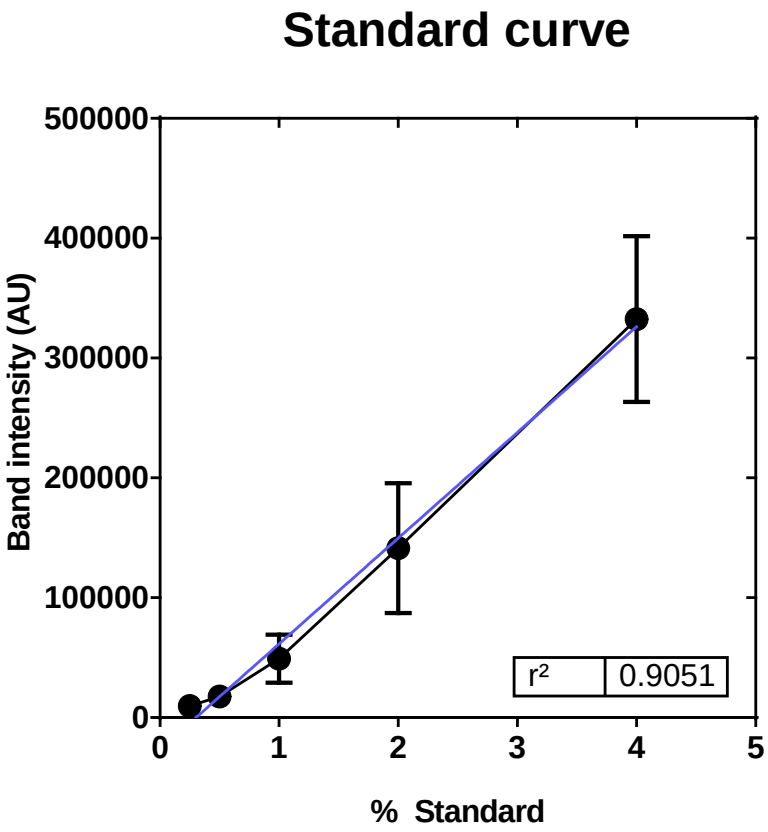


Fourth Biopsy was Acceptable, however…

- Problems with controls the make change in dystrophin challenging to interpret

- Ideally, the change in dystrophin would have been assessed by comparing pre-treatment and post-treatment samples

Shortcomings of Controls Used for 4th Biopsy

- Control samples from different muscle groups used - biceps, quadriceps, deltoid - and data combined for comparison to deltoid samples from 4th biopsy
- Baseline comparator only available from 2 DMD patients and from a different muscle group
- Healthy controls not sex-matched – one female and two male healthy controls combined for mean value
- Dystrophin variability in healthy controls (51%-95%)

Summary: Dystrophin Methods

- The applicant's 4th biopsy Western blot method from study 201/202 is adequate for determining relative levels of total dystrophin protein and is the most quantitative method that was used
  - **But controls were not well matched, such that small differences at low levels may not be reliably attributable to an effect of eteplirsen**

- Data from immunofluorescence can serve as support for the location of dystrophin protein

1. **Biomarker evidence**

   Bioassay methods: **Dr. Rao**

   Bioassay findings: **Dr. Farkas**

2. Clinical evidence

   24-week controlled trial

   Open-label treatment vs. historical controls

Study 28: Was the Right Dose and Dosing Frequency Identified?

- Phase 1 and 2 studies are important to develop a promising drug candidate
  - **For most new drugs, it is usual to increase the dose until limited by safety and tolerability, or no further increase of effect on the biomarker (dystrophin)**

- Doses in Study 28 ranged from 0.5 to 20 mg/kg/week, for 12 weeks, with 4 or fewer patients per dose cohort

Study 28: Results

- Study 28 investigators reported dystrophin levels of 0 to 5% of normal in untreated patients (by Western blot)
  - These levels consistent with expected trace dystrophin
- Reported that dystrophin levels increased after **12 weeks** of eteplirsen treatment to about **10 to 20%** of normal (by Western blot) at eteplirsen doses as low as 2 mg/kg/wk, into a range that might be encouraging for efficacy
  - No safety issues found that would limit higher dosing

Study 201/202: Was the Right Dose and Dosing Frequency Identified?

- Study 201/202 tested doses only modestly higher than 20 mg/kg/wk, and in a small number of patients (12)
  - 30 mg/kg/wk in 4 patients
  - 50 mg/kg/wk in 4 patients
  - Placebo in 4 patients

- Dystrophin measured at Week 12, as in Study 28, and at also at Weeks 24 and 48
  - These three time points referred to in briefing material and this presentation as the "1st 3 biopsies"

Study 201/202: Initial Results

- Study 201/202 investigators reported dystrophin increased at Week 24, but not at Week 12
  - Different from robust effect on dystrophin reported at Week 12 in Study 28
  - Consistency of findings of great concern in science and drug development; raises questions that should be explored
- High dystrophin levels initially reported by the applicant in all patients at Week 48, seemingly to 25 to 50% of normal or higher (Mendell et al., Ann Neurol 2013)
- Essentially marked the end of phase 1 and 2 studies

FDA Expressed Concerns Early and Consistently

- FDA learned more about the data on dystrophin levels in discussions about NDA filing, and became concerned about reliability and consistency, communicating this clearly to the applicant

- FDA nevertheless agreed to file the NDA based on assertions of both high levels of dystrophin and clear clinical stabilization

Study 201/202, 4th Biopsy

- FDA worked with the applicant on more reliable Western blot and immunofluorescence assays for dystrophin quantification

- The applicant obtained a 4th biopsy at Week 180 of eteplirsen treatment from 11 of 12 original patients and, as the NDA was being submitted, studied the biopsies with the more reliable assays

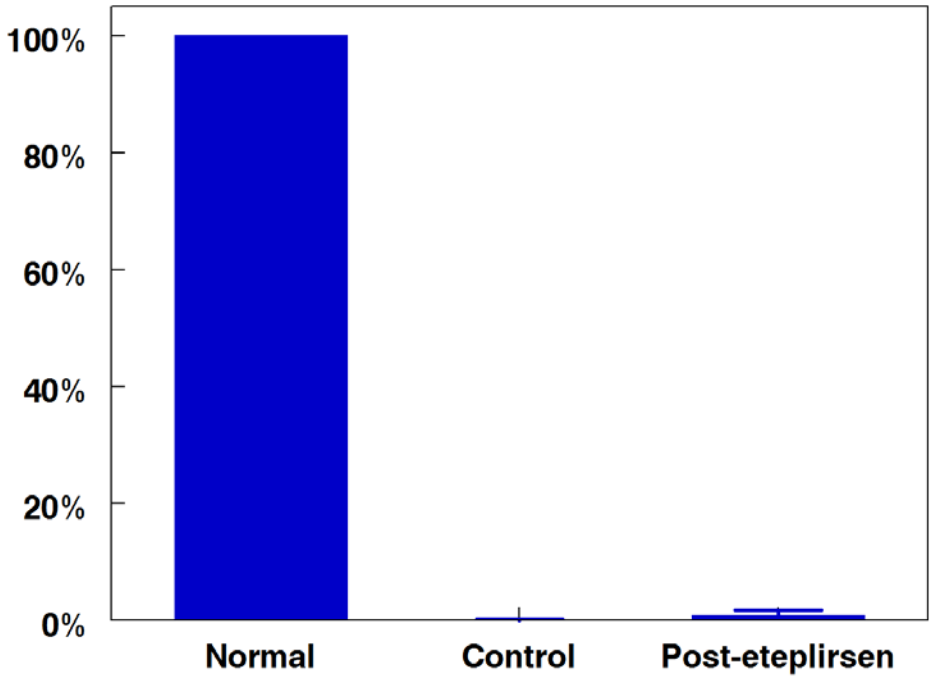
NDA Review of Dystrophin Data

- Detailed review of dystrophin data from Study 28 and the first 3 biopsies of Study 201/202 confirmed FDA concerns about problems with assay reliability, e.g.,
  - Western blot bands oversaturated
  - Immunofluorescence images captured and read in a way that might have been overly-subjective, with preferential capture of brighter-staining regions
    - Note that independent, blinded re-reading of positive fibers cannot address possible bias in the specific muscle regions that were selected for image capture

Study 201/202, 4th Biopsy Results

- The 4th biopsy results, obtained with more reliable assays, became available during the NDA review

Instead of the expected levels of 25 to 50% dystrophin, a very low level, **0.93 ± 0.84%,** was reported by WB, the most accurate method of quantification used by the applicant



Inconsistent Dystrophin Results

- The 4th biopsy dystrophin result is clearly inconsistent with earlier results, and appears to raise important questions
  - Highlights the reason for independent confirmation of important findings in science, including in drug development

The 4th biopsy result was based on one group of patients, at one investigative site; no matter how many times a single set of data is re-analyzed, it does not constitute independent confirmation of findings

Did Eteplirsen Produce Dystrophin?

- **0.08% ± 0.13%** dystrophin level in the selected controls
  - Noting that because the lower limit of sensitivity of the assay was 0.25%, more accurate to view the level in controls as "<0.25%"

- Clearly lower than in eteplirsen-treated patients but, as discussed by Dr. Rao, the controls were poorly matched (e.g., from different patients and muscle groups), such that the comparison may be "apples to oranges"

Did Eteplirsen Produce Dystrophin?

Because of poorly matched controls, the proportion of the ≈1% ± ≈1% dystrophin present in eteplirsen-treated patients that was produced by eteplirsen, as opposed to the dystrophin that can be present at baseline, appears to be uncertain

Percent Dystrophin Positive Fibers (PDPF) by Immunofluorescence

PDPF

- Not a helpful measure of the amount of dystrophin
  - "Positive" fiber does not mean a functional amount, only "an intensity judged by eye to be above background of the image."

Percent Positive Fibers in 4th Biopsy

- Applicant reported 17% ± 10% dystrophin positive fibers for eteplirsen-treated patients, and 1% ± 1% in the poorly-matched controls
  - Uncertain whether or to what degree this difference might have been due to eteplirsen, versus non-drug related differences between the samples

- It also remains difficult to find consistency in the percent positive fiber counts, even with the improved method of reading by 3 blinded readers

Standardized Reading by the 3 Blinded Readers (blue) Gave Much Lower Estimates Than the Original Reading (grey)

	Nationwide Children's Hospital analysis				Re-analysis by 3 blinded readers				
	Baseline	Week 12	Week 24	Week 48	Baseline	Week 12	Week 24	Week 48	Week 180 (n=11)
30 mg/kg (n=4)	18		41	70	14		27	23	
50 mg/kg (n=4)	11	12		54	15	17		25	eteplirsen 17
Placebo to 30 mg/kg (n=2)	24		24	58	10		10	9	
Placebo to 50 mg/kg (n=2)	7	7		49	11	9		10	

- Percent positive fibers did not consistently increase even at Week 24 according to the blinded reanalysis
- In patients treated with placebo for 24 weeks, followed by eteplirsen for 24 weeks, percent positive fibers did not increase

	Nationwide Children's Hospital analysis				Re-analysis by 3 blinded readers				
	Baseline	Week 12	Week 24	Week 48	Baseline	Week 12	Week 24	Week 48	Week 180 (n=11)
30 mg/kg (n=4)	18		41	70	14		27	23	
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Placebo to 30 mg/kg (n=2)	24		24	58	10		10	9	
Placebo to 50 mg/kg (n=2)	7	7		49	11	9		10	

- The 4th biopsy controls had **1%** positive fibers, vs. **10-15%** for the original baseline samples (rectangle)
- Difference in methods? Or difference in controls?

	Nationwide Children's Hospital analysis				Re-analysis by 3 blinded readers				
	Baseline	Week 12	Week 24	Week 48	Baseline	Week 12	Week 24	Week 48	Week 180 (n=11)
30 mg/kg (n=4)	18		41	70	14		27	23	
50 mg/kg (n=4)	11	12		54	15	17		25	eteplirsen 17
Placebo to 30 mg/kg (n=2)	24		24	58	10		10	9	
Placebo to 50 mg/kg (n=2)	7	7		49	11	9		10	

- Little difference in positive fibers between original baseline samples (rectangle) of treated patients and Week 180 (circle)
- Percent positive fibers is partly subjective, but still may increase concerns about whether eteplirsen increased positive fibers

	Nationwide Children's Hospital analysis				Re-analysis by 3 blinded readers				
	Baseline	Week 12	Week 24	Week 48	Baseline	Week 12	Week 24	Week 48	Week 180 (n=11)
30 mg/kg (n=4)	18		41	70	14		27	23	
50 mg/kg (n=4)	11	12		54	15	17		25	eteplirsen 17
Placebo to 30 mg/kg (n=2)	24		24	58	10		10	9	
Placebo to 50 mg/kg (n=2)	7	7		49	11	9		10	

Summary: Dystrophin Findings

- **0.93 ± 0.84%** of normal dystrophin levels, as measured by Western blot, after long-term treatment with eteplirsen, and **17% ± 10%** of muscle fibers with at least some detectable amount
  - Because of poorly matched controls, the proportion of the dystrophin that was produced by eteplirsen, as opposed to the dystrophin that can be present at baseline, appears to be uncertain
  - No independent confirmation provided by the applicant
  - Ratios of treated to control values presented by the applicant appear to be “apples to oranges” comparisons because of poorly matched controls, and lack reliability because of small and questionably calculated denominators

Dystrophin as a Surrogate Endpoint for FDA Accelerated Approval

Measuring Low-Level Dystrophin

- At the low dystrophin levels being discussed, literature reports may not be accurate
  - May state that a patient expressed no dystrophin, but may just mean that the patient had less than some lower limit of detection of the assay
- Literature reports may not be precise in describing low levels of dystrophin
  - “trace” dystrophin levels as detected by immunofluorescence often present in DMD, but this is not a defined or useful measure of amount

Quantity by Western Blot

- By the most reliable Western blot methods, dystrophin less than ≈3% of normal muscle appears to be associated with the typical DMD phenotype
  - Appears to be little evidence that disease is milder at the high vs. low end of this range
  - Appears to be some evidence that dystrophin levels need to be higher, perhaps >10%, with expression present in most muscle fibers, for a milder than average DMD clinical course

Percent Dystrophin Positive Fibers

- Typical DMD can be associated with detectable dystrophin staining in anywhere from 0 to 100% of muscle fibers

- The 17% dystrophin positive fibers in eteplirsen-treated patients appears to be more typical of untreated DMD than milder forms of dystrophinopathy

In Rare Patients, Absence of Dystrophin Does Not Cause Severe Disease

- Rare patients with the milder BMD phenotype have dystrophin levels near zero
- These unusual cases highlight that there is often a lack of clear relationship between dystrophin levels and severity
- Mild disease in these individuals is likely unrelated to, not the result of, trace levels of dystrophin
  - Active area of research to find the factors that compensate for missing dystrophin

Half-Brothers with the Same Mutation but Discordant Duchenne and Becker Phenotype

- In both, dystrophin negative except revertant fibers
- Younger half-brother (II) wheelchair-bound at age 9
- Older half-brother (I) normal walking ability at age 15

(Zatz et al., 2014)

1. Biomarker evidence
   - Bioassay methods: Dr. Rao
   - Clinical Findings: Dr. Farkas

2. **Clinical evidence**
   - **24-week controlled trial**
   - **Open-label treatment vs. historical controls**

Study 201/202

- Planned as a 24-week placebo-controlled study
  - 4 patients – eteplirsen 50 mg/kg/week
  - 4 patients – eteplirsen 30 mg/kg/week
  - 4 patients – placebo

- Primary endpoint: dystrophin expression

- Multiple clinical endpoints were measured including 6 minute walk distance (6MWT) and North Star Ambulatory Assessment (NSAA)

Study 201/202
Negative in placebo-controlled portion

- The prespecified clinical endpoints of Study 201 (Week 24) and Study 202 (Week 48) were negative

- The applicant performed a post-hoc analysis based on a number of major changes, including removing 2 patients treated with eteplirsen who deteriorated rapidly, and using a time point outside the controlled trial period

- FDA explained that these types of changes did not appear reasonable even for hypothesis generation, and were not interpretable, but the applicant announced the post-hoc results, generating considerable public attention

1. Biomarker evidence
   - Bioassay methods: Dr. Rao
   - Clinical Findings: Dr. Farkas

2. **Clinical evidence**
   - 24-week controlled trial
   - **Open-label treatment vs. external controls**

FDA Advice to Applicant (1)

- FDA consistently and strongly encouraged the applicant to perform an adequately powered randomized double-blind controlled trial, and expressed strong doubts regarding the interpretability of comparison to external controls

FDA Advice to Applicant (2)

- FDA is receptive to interpretable data from externally controlled trials

- FDA explained to the applicant that data from externally controlled studies “may only be interpretable if a relevant objective endpoint obviously insulated from bias demonstrated compelling data that are clearly outside the known variability range for DMD”

DMD experts have noted physical function may be affected by simply being in an efficacy study

Example from Fascioscapulohumoral Muscular Dystrophy

– "Whereas natural history data showed a **decrease** in strength over 1 year, there was an apparent **increase** in strength … in both the placebo and treatment groups"

– "Patients in clinical trials in FSHD may have **better outcomes** than those in natural history studies, regardless of treatment assignment, emphasizing the importance of placebo groups"

Statland et al., Neuromuscul Disord 2013

FDA Advice to Applicant (3)

- The observations of DMD experts guided FDA advice to the applicant that ambulation was a problematic endpoint in externally-controlled trials in DMD
  - e.g., in September 2014, FDA explained that preservation of ambulation and other skills is affected by subjective decision-making from families and caregivers about those skills, with factors such as risk of falls and injury from continued ambulation weighed against the safety and speed of allowing patients to use a wheelchair

Many possible sources of non-drug related differences, beyond those just mentioned, between patients in efficacy and observational studies

To understand if there is evidence of efficacy in an externally controlled trial, necessary to study the sources and possible sizes of these differences

A few examples of non-drug related differences between study arms follow, and others are described in the FDA memos

Impact of Subjective Decision-Making on Efficacy Endpoints

- The decision to ask a patient to attempt to perform a functional test such as 6MWT, versus deeming the patient unable, is based on the judgment and attitudes of the investigator, patient and caregivers

- There may have been differences in how such decisions were made for eteplirsen treated and external control patients

- Two of the applicant's 13 control patients were able to perform 10 meter run/walk reasonably well, but were deemed unable to attempt 6MWT
- Data for one of these patients is shown below

	Age 10	Age 11
10 meter run/walk	10 seconds	12 seconds
6MW Distance	356 meters	"deemed unable"

- In the eteplirsen group, decisions about whether to attempt 6MWT may have been made differently
- May have large effect on outcomes, including whether patient is considered "ambulatory" or "non-ambulatory"

Impact of Differences in Supportive Treatment

- Supportive treatment, including steroids, can have important effects on slowing functional decline, and there were some differences between eteplirsen treated patients and external controls
  - e.g., eteplirsen patients treated with steroids for about a year longer

- The key point is that experts in DMD have observed that seemingly small differences in supportive care or steroid use may have large effects on age of loss of ambulation

DMD experts have noted that seemingly small differences in care confound interpretation

Steroid/Regimen	Median loss of ambulation (years)	N
Deflazacort/Daily	14	80
Deflazacort/Switched*	16	8

"Differences in standards of care and dosing complicate interpretation…This study emphasizes the necessity of a randomized, blinded trial of GC regimens in DMD"

Bello et al., on behalf of CINRG investigators, 2015

Thus even a 2-year difference in age of loss of ambulation between eteplirsen treated patients and historical controls may not be a drug effect

*switched between daily, QOD, or weekly dosing

Other, Less Obvious, Sources of Differences Can Confound Externally Controlled Trials

- Patients who are not motivated, able or qualified to enroll in drug studies may remain in natural history studies
- Patients who have progressed more rapidly may be over-represented in natural history studies if they no longer meet eligibility requirements for drug studies

Difference Between Patients Selected for Registry Studies vs. Drug Studies

- One of the 13 eteplirsen controls lost ambulation after 1 year, and stayed in the observational study for several more years, long enough to enable matching to eteplirsen patients

- Two other exon-51 patients who were doing relatively well had similar baseline age and 6MWT values, but discontinued the observational study to participate in other drug studies, and were therefore not under observation long enough to be controls for the eteplirsen study

- The only patient who was available to be matched to the eteplirsen patients was therefore the one who definitely had a rapid decline.

Different Analysis Approach Needed for Externally Controlled Trials

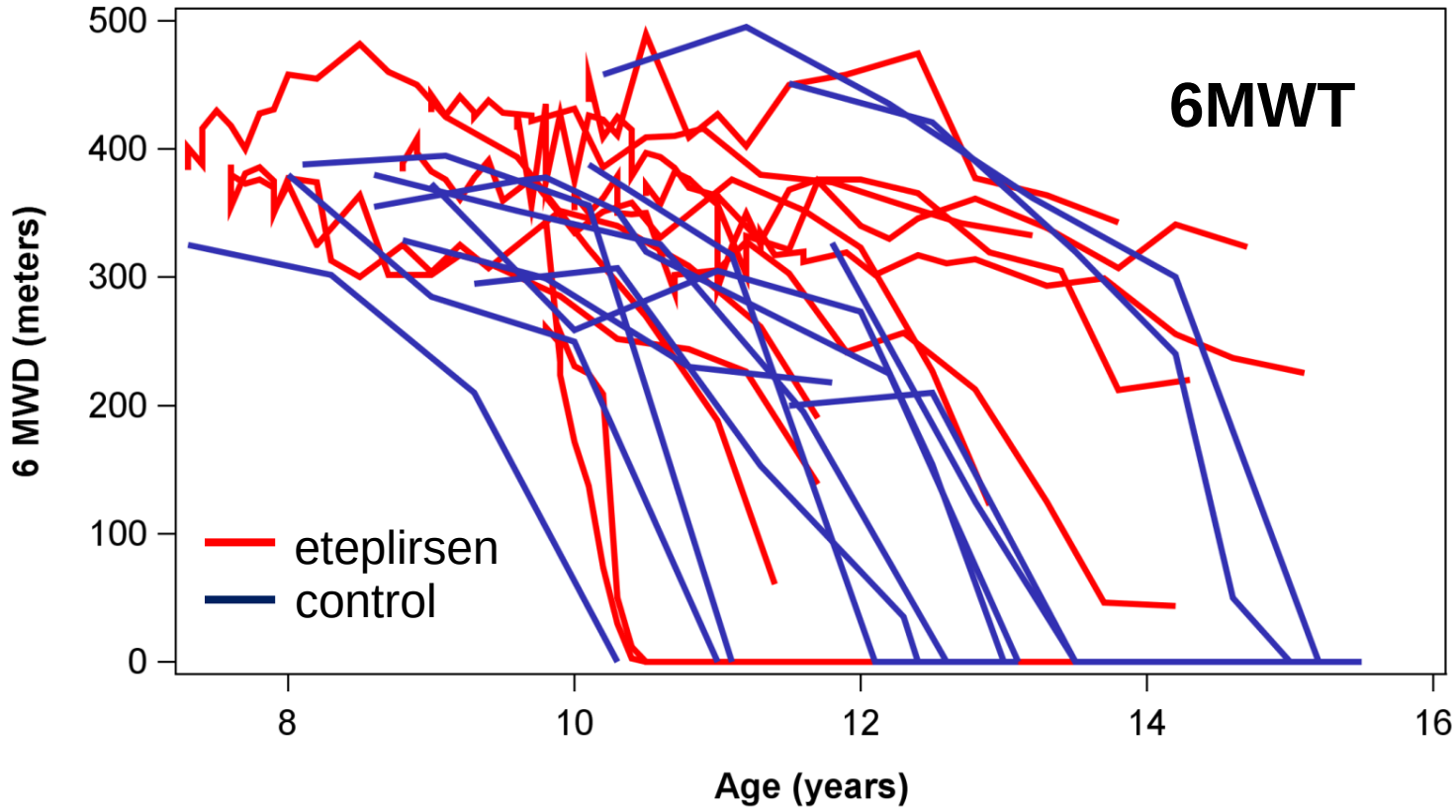
- In externally-controlled trials, data gathered differently from each group, and groups are different in ways that are impossible to fully understand or measure

- **p-values, sensitivity analyses, etc. can be misleading because only tell you data are different, not why they are different**

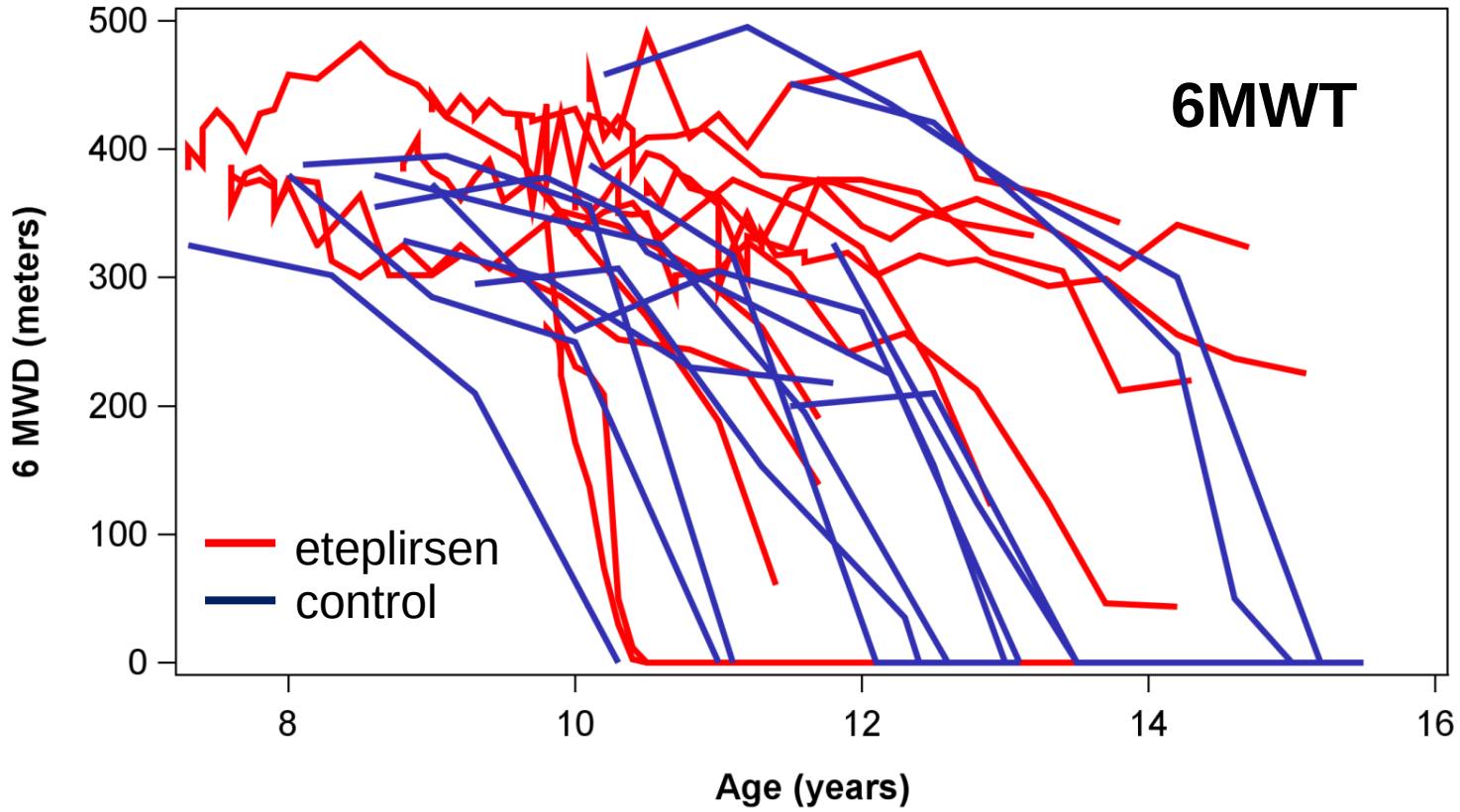
- Key question to ask is whether the endpoint difference was **so large** to be able to conclude it was from an effect of drug, not other differences, both known and unknown, at baseline or during observation

Eteplirsen Clinical Data Compared to Applicant's Historical Controls

The applicant has shown these 6-minute walk data as a function of time on study, but showing by age is more meaningful, because loss of ambulation is correlated with age in DMD, and important for comparing similar patients



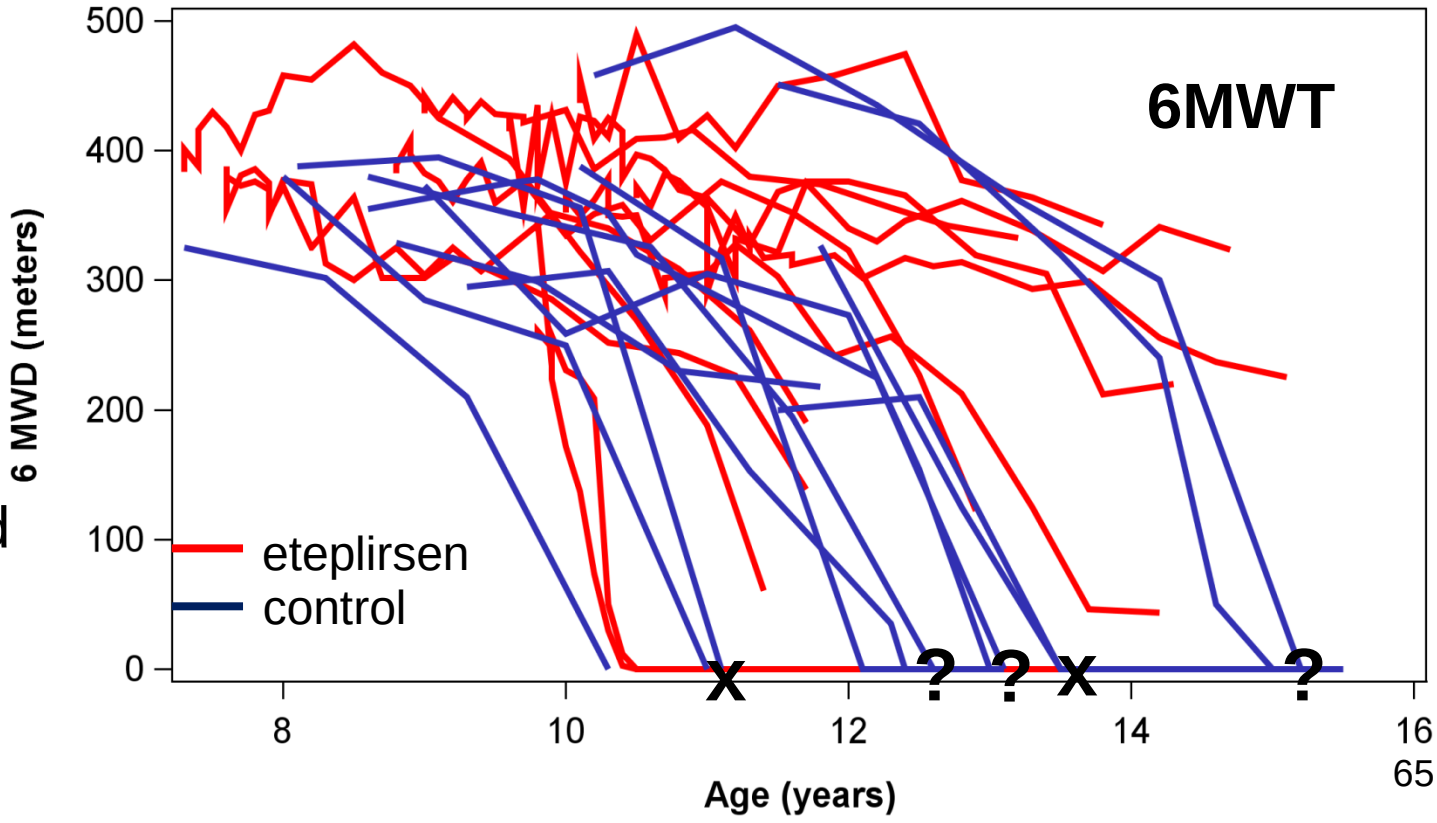
- The red lines show eteplirsen patients, and the blue lines show the applicant's external controls
- Each line begins at the patient's age at enrollment, and continues through 4 or 5 years, depending on the available data



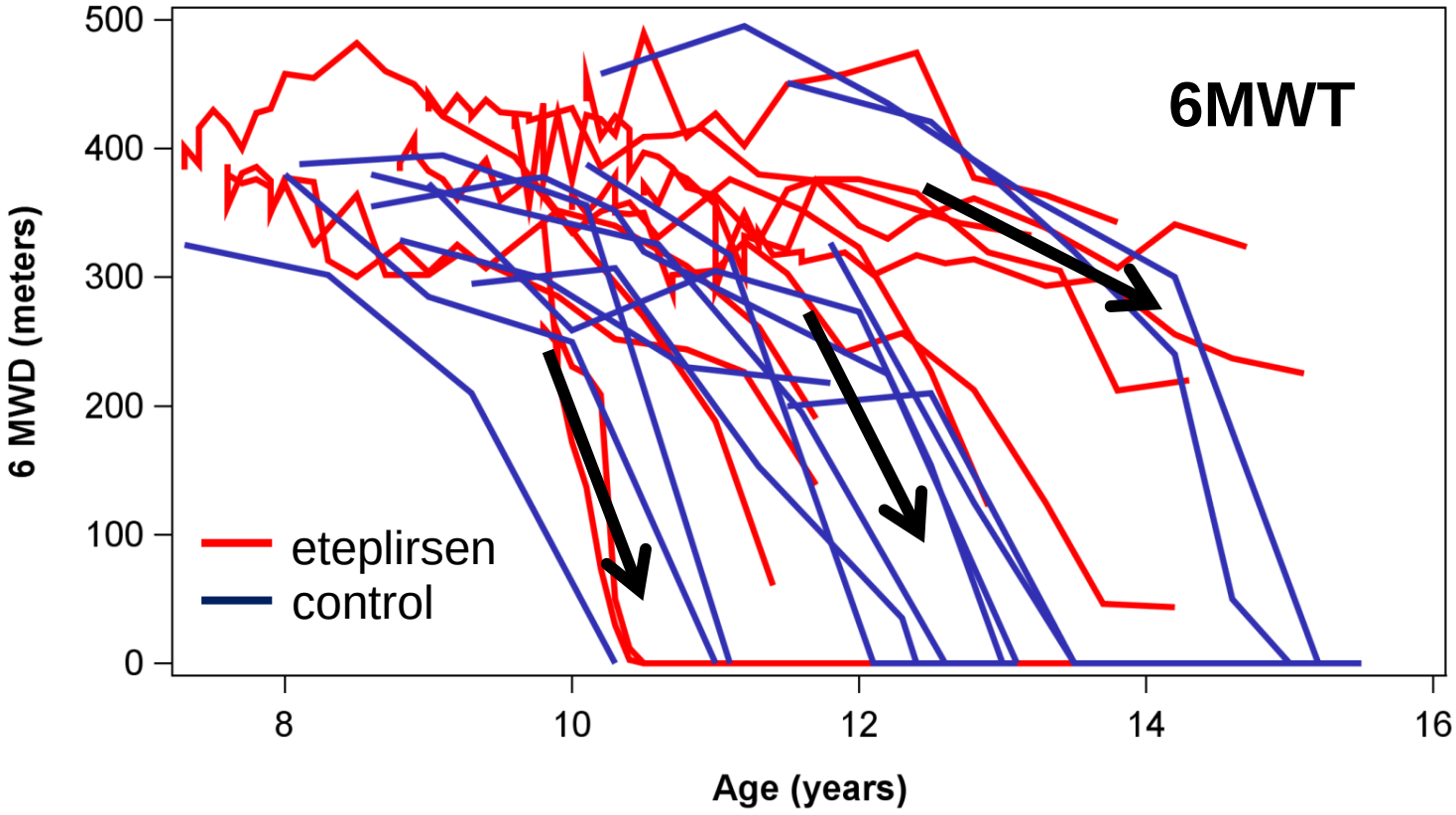
Because of many types of non-drug related differences, including the way endpoints assessed for eteplirsen treated patients and controls, these may be “apples to oranges” comparison

“x” = control patient able to perform 10m walk/run, but given zero value for 6MWT

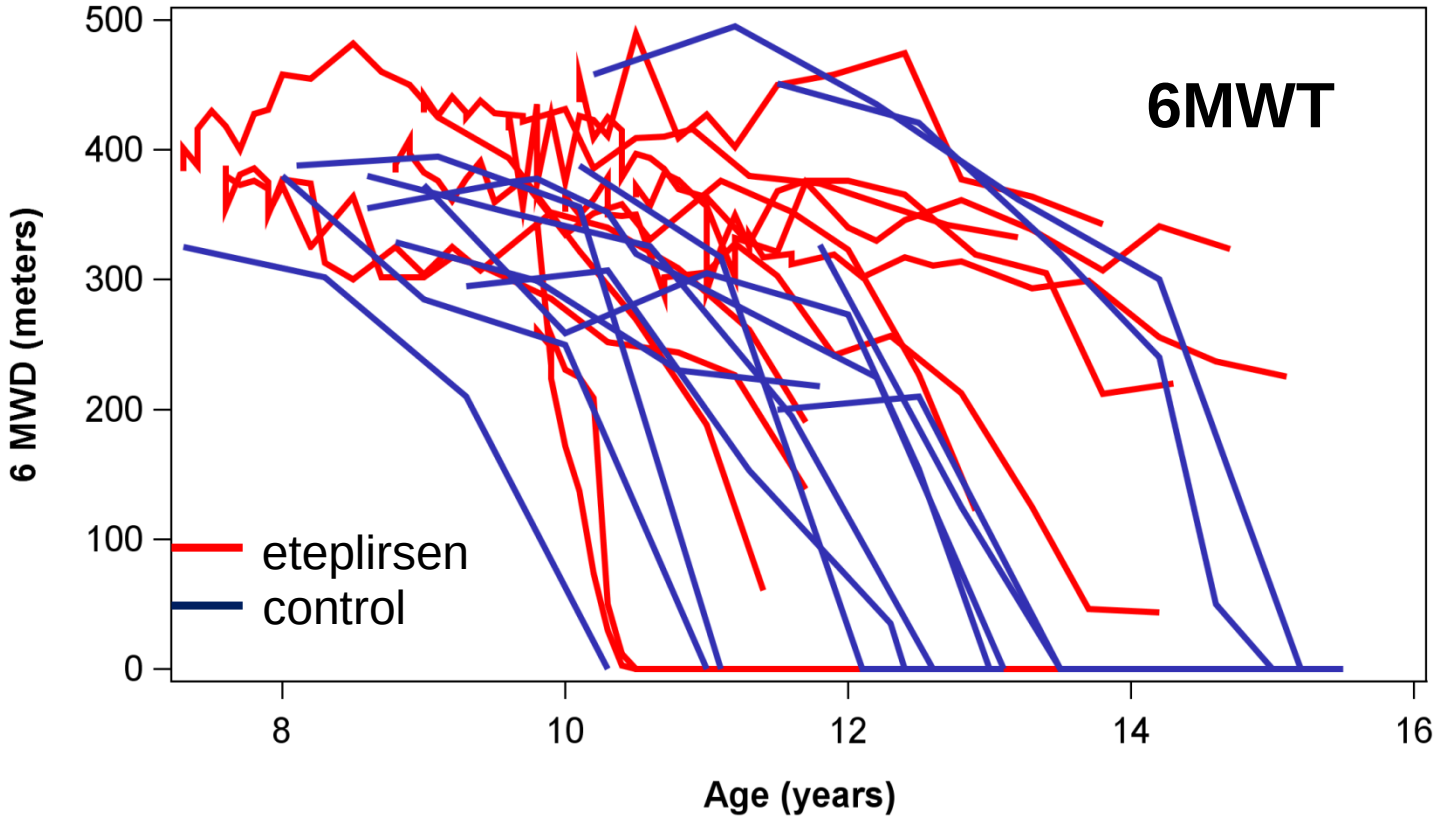
“?” = control patients assigned zero by asking if patient was ambulatory at Year 4



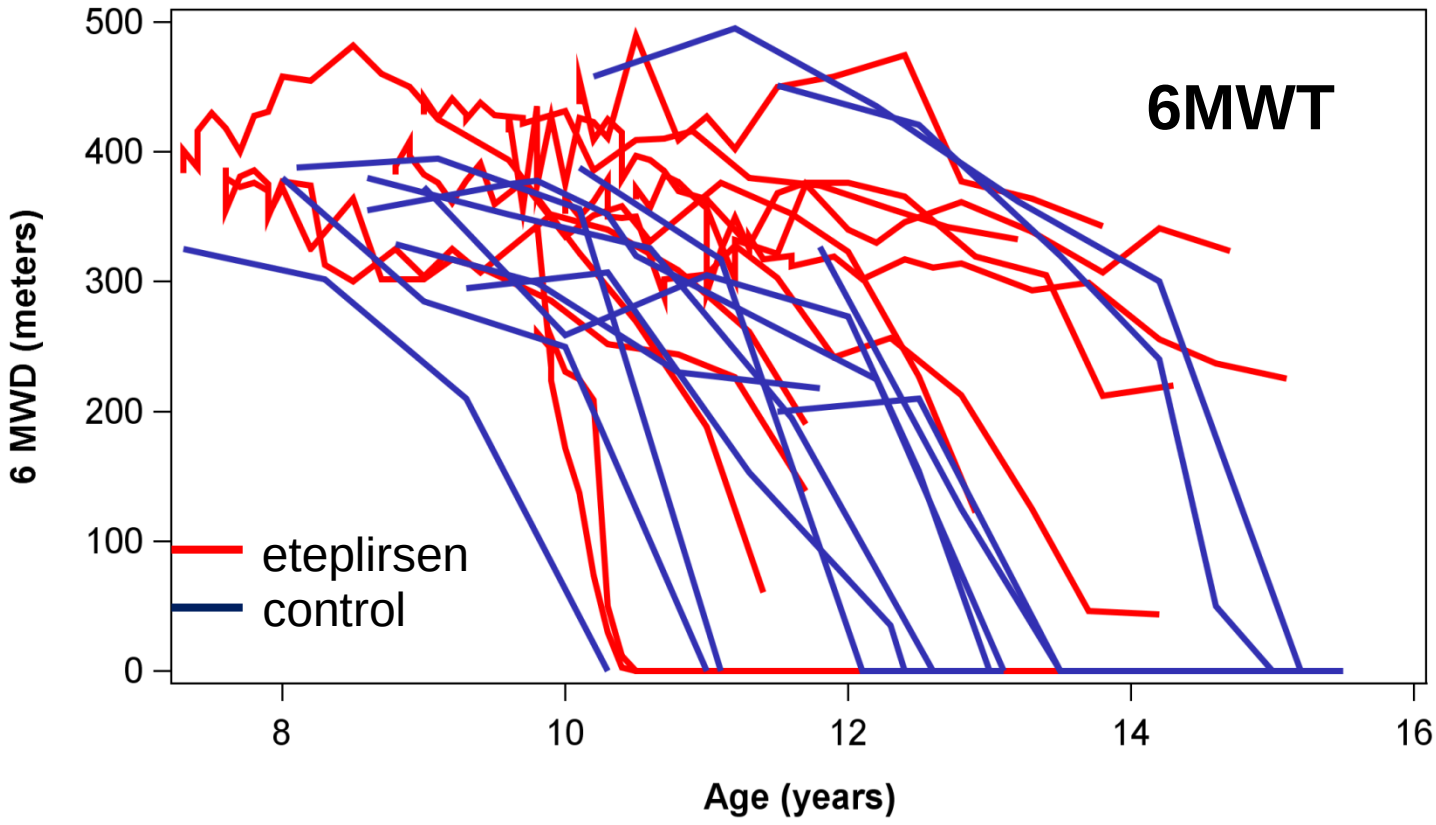
Importantly, appears to be general similarity of age at which eteplirsen and control patients begin to decline more sharply in 6MWT, and in the rate of that decline



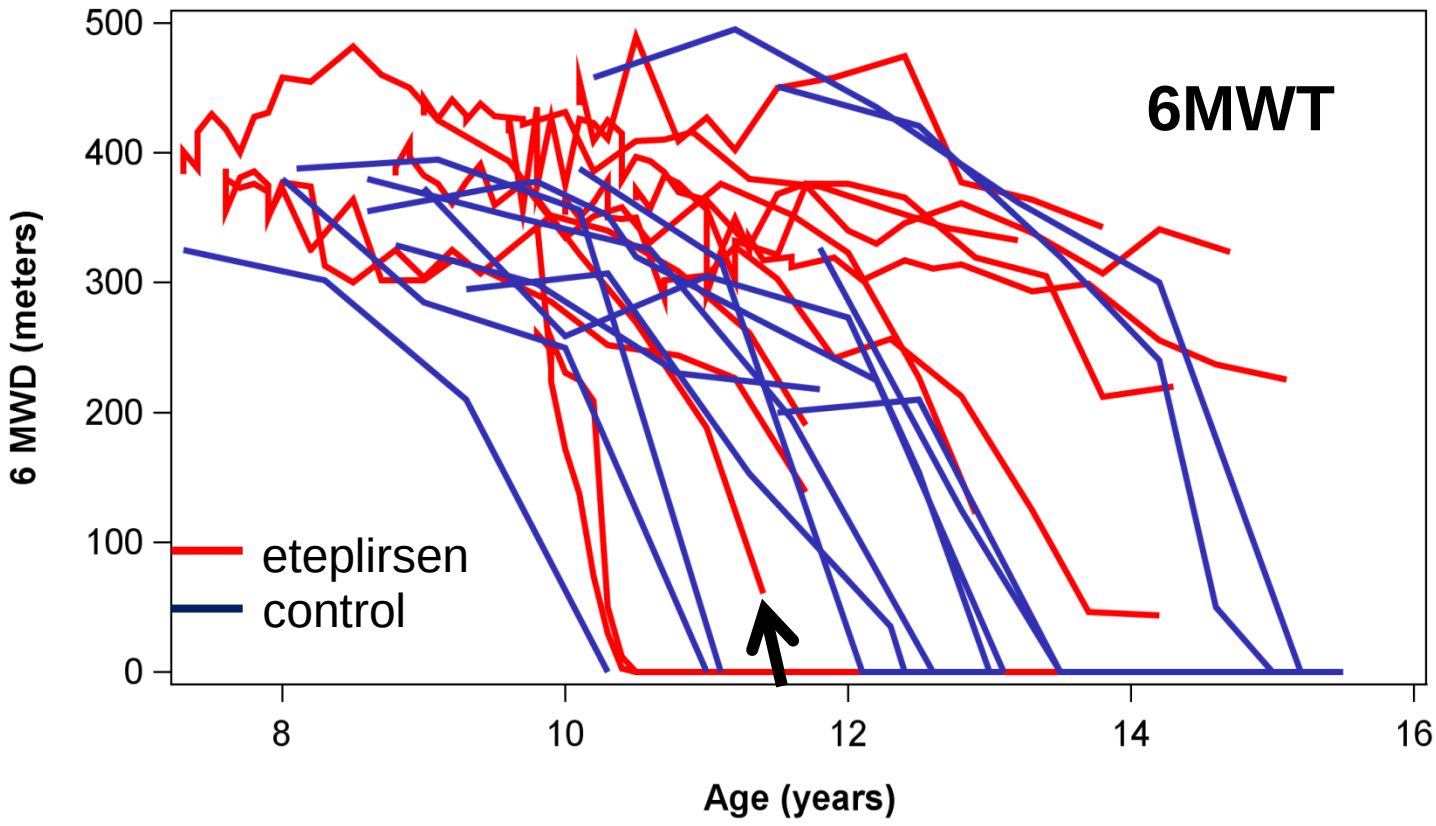
Contrary to what is suggested by some of the applicants analyses, there does not appear to be evidence of a difference in age (or future age) of loss of ambulation in the eteplirsen patients and controls



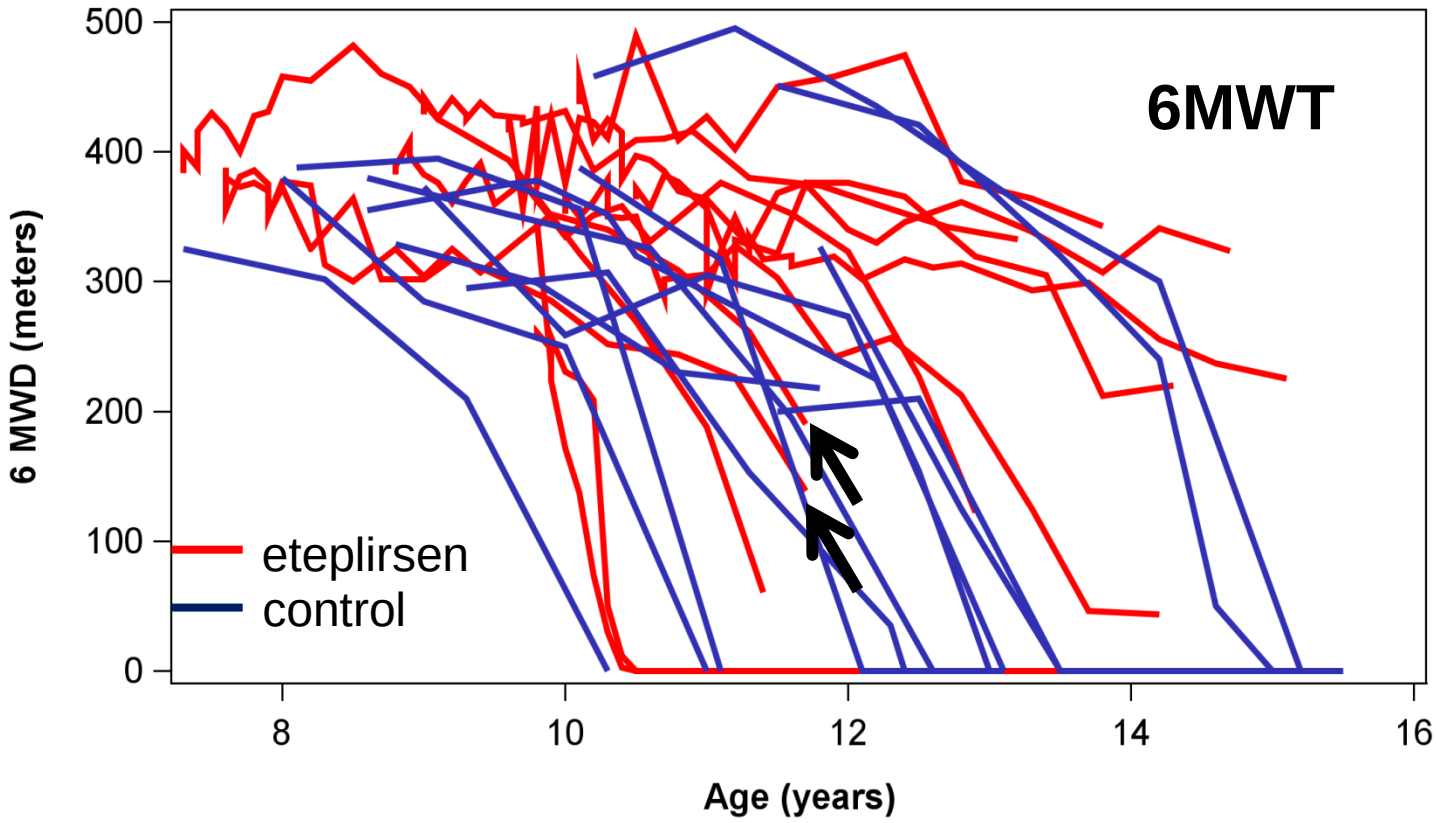
- There is no bigger “apples to oranges” comparison than comparing walking in an 11 year with DMD to walking in a 15 year old with DMD
- Need to compare eteplirsen patients to controls of similar age



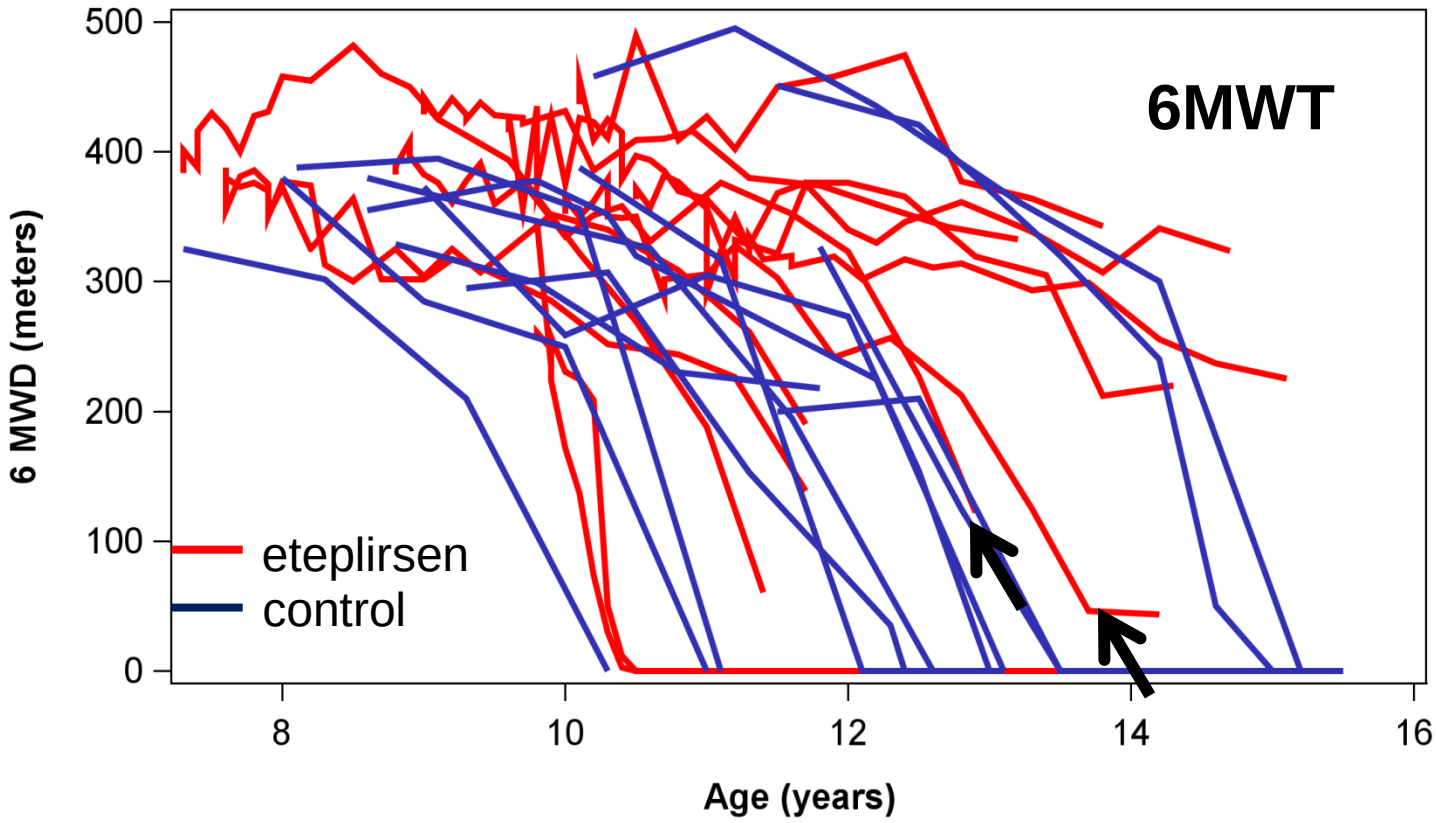
The 11 year old eteplirsen-treated patient indicated by the arrow appears to be progressing about the same as the controls on either side



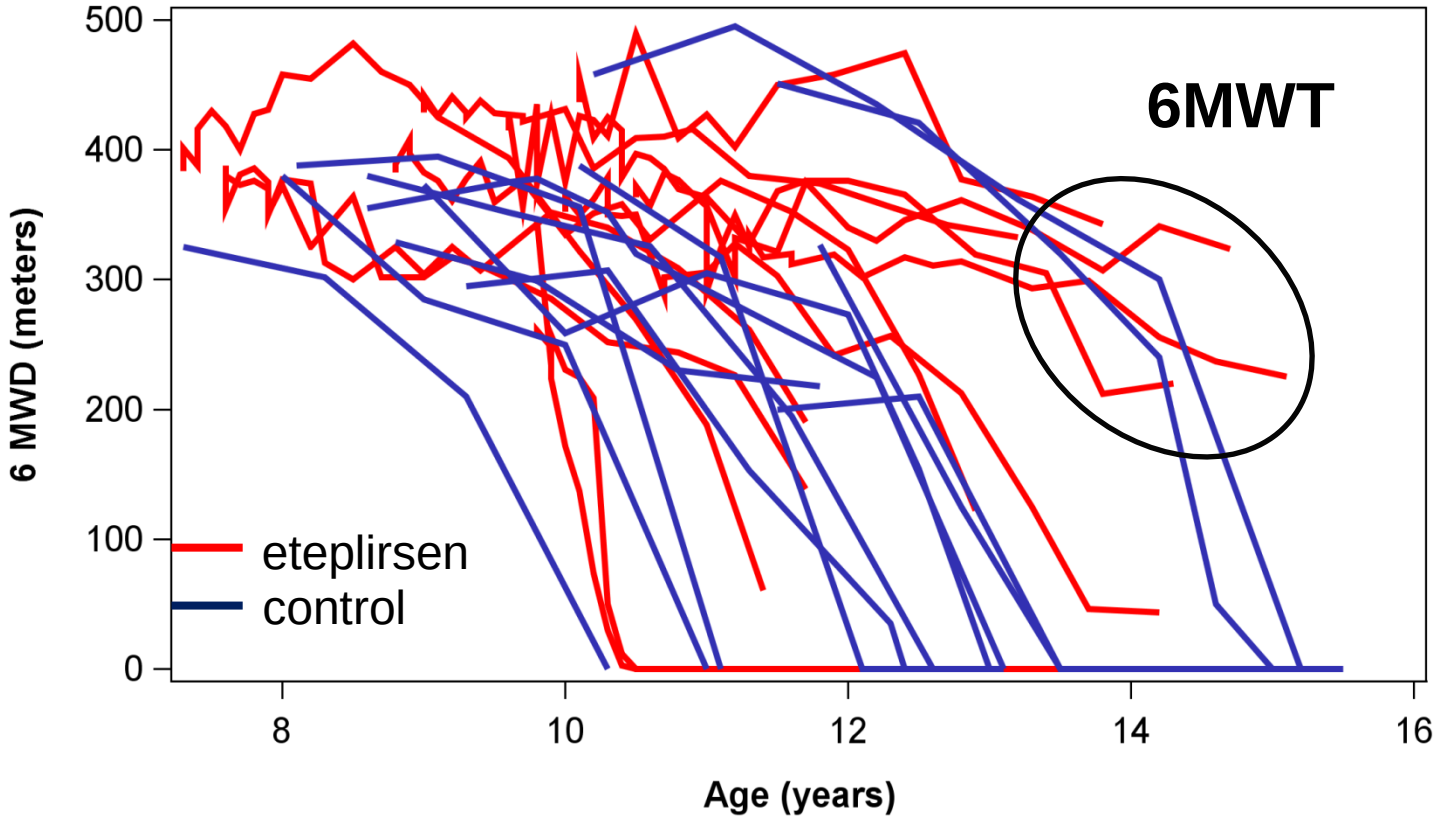
The same appears to be true for these two twelve year old eteplirsen-treated patients



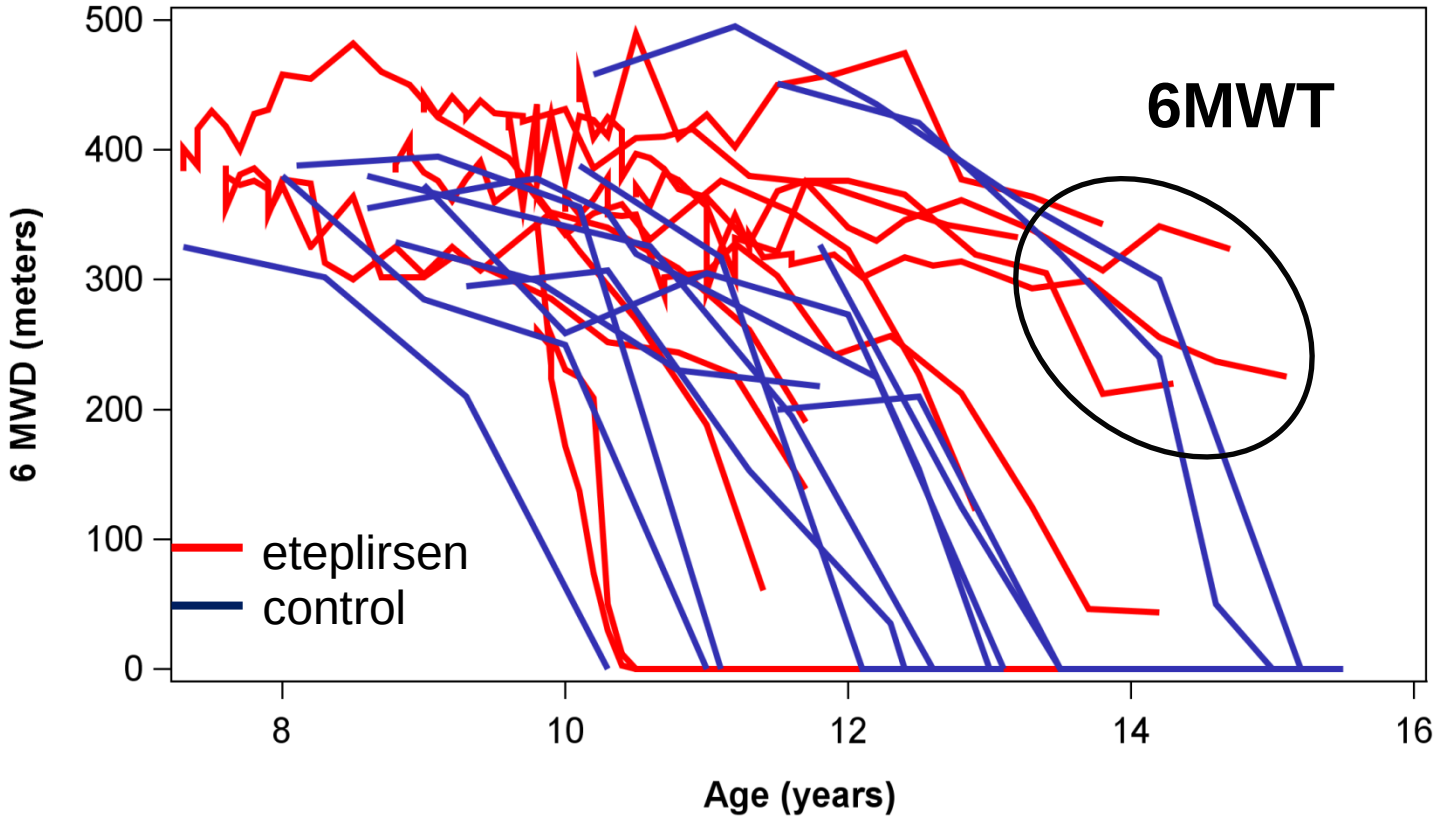
And the same appears to be true for these 13 and 14 year old eteplirsen-treated patients



There may be differences in the 6MWT values for eteplirsen treated and control patients in the circled area, remembering that this may be from non-drug related differences, including the way these values were assessed



It would be important to identify whether there were eteplirsen-treated patients who were ambulatory beyond an age that could be explained by the range of natural history, but recent data suggest that this is not the case

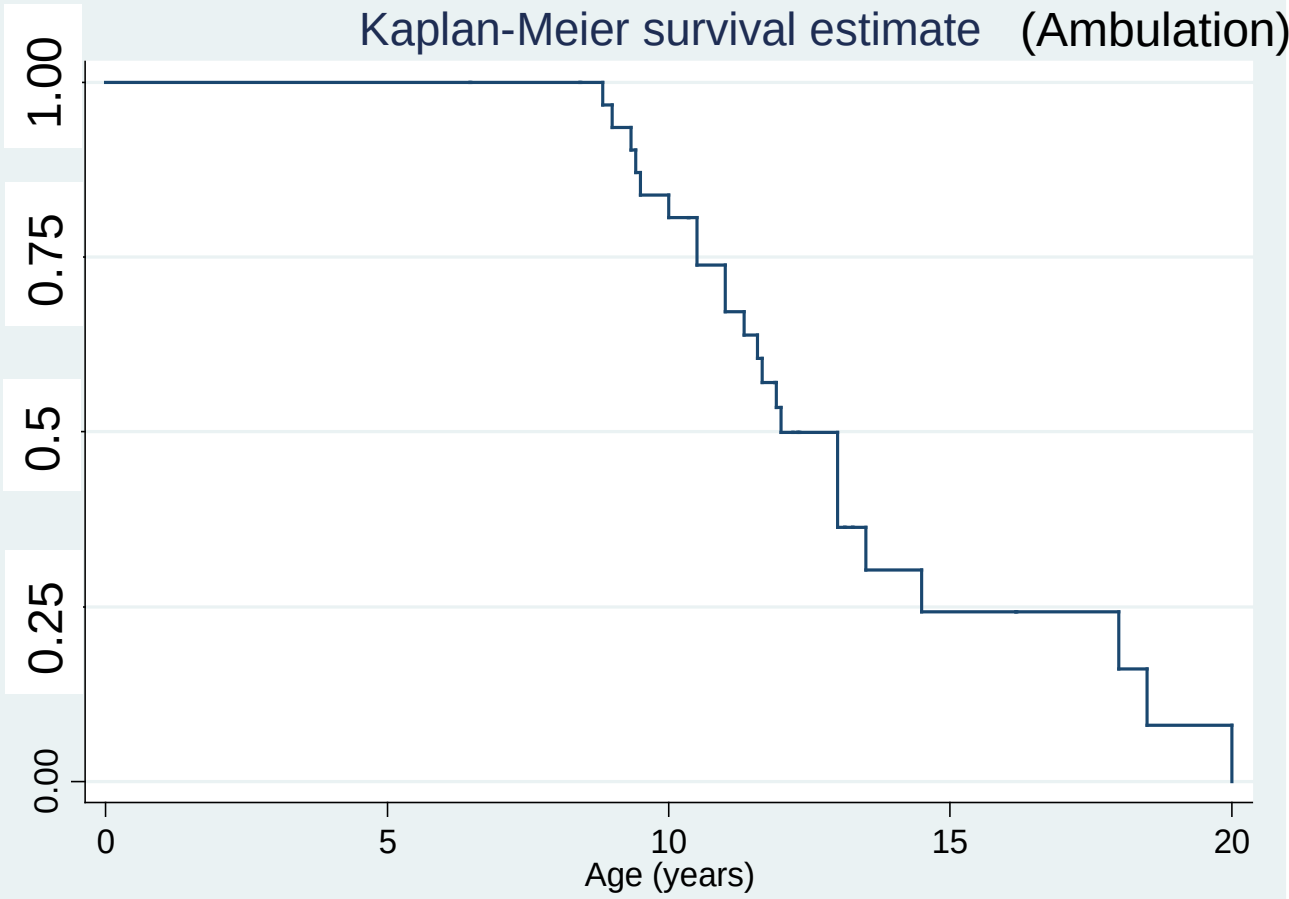


Age of loss of ambulation in exon-51 skippable patients may be older than sometimes realized

≈25% of exon 51 boys walking at 16 years

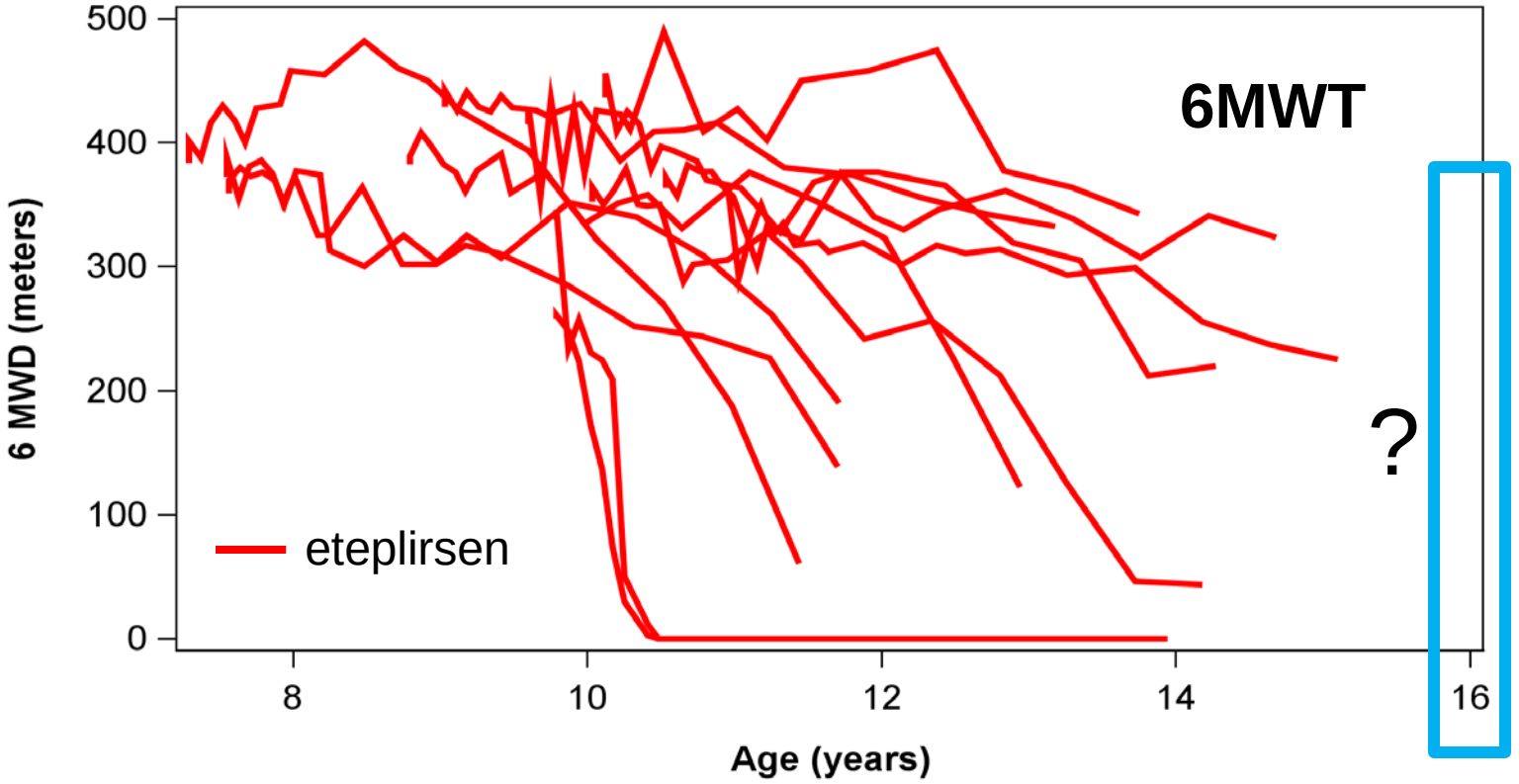
≈15% walking at 18 years

This analysis recently provided to FDA by CINRG for detailed review



*Cooperative International Neuromuscular Research Group

The estimate from CINRG of 25% of exon-51 skippable patients ambulant at 16 years appears similar to what might be expected for the group of eteplirsen-treated patients



Other Historical Data Appear to be Generally Consistent

- Exon-51 skippable patients in the placebo arms of recent randomized, placebo controlled studies of drisapersen
  - As detailed in the FDA memo, ambulation to 16+ years
  - Many patients >12 years continue to have relatively well-preserved rise-time and 6MWT

MD STAR*net*

(Muscular Dystrophy Surveillance Tracking and Research Network)

- MD STAR*net* is a population-based surveillance program for individuals with Duchenne and Becker muscular dystrophy (DBMD) in six states in the United States.
- Starting in 2004, MD STAR*net* identified all patients born with DBMD from 1982-2011 in the surveillance areas.
- Cases identified retrospectively before 2004, but new cases were identified after that date and follow-up abstraction was conducted.

Findings from MD STAR*net*

- 612 DBMD patients in 3 three MD STAR*net* sites (Colorado, Arizona and Georgia).
  - 510 (83%) had testing for deletion mutation
    - 47 patients (9.3%) with mutations amenable to exon 51 skipping.

- 26 patients with mutations amenable to exon 51 skipping and have taken or are taking steroids for at least one day prior to loss of ambulation or if they are still walking, prior to their last mobility entry

- Of these 26 patients, there are 15 patients who are still ambulant.

- Of these 15 patients who are still ambulant there are
  - 3 patients walking at or beyond 14 years
  - 2 of these 3 patients walking at or beyond 16 years.

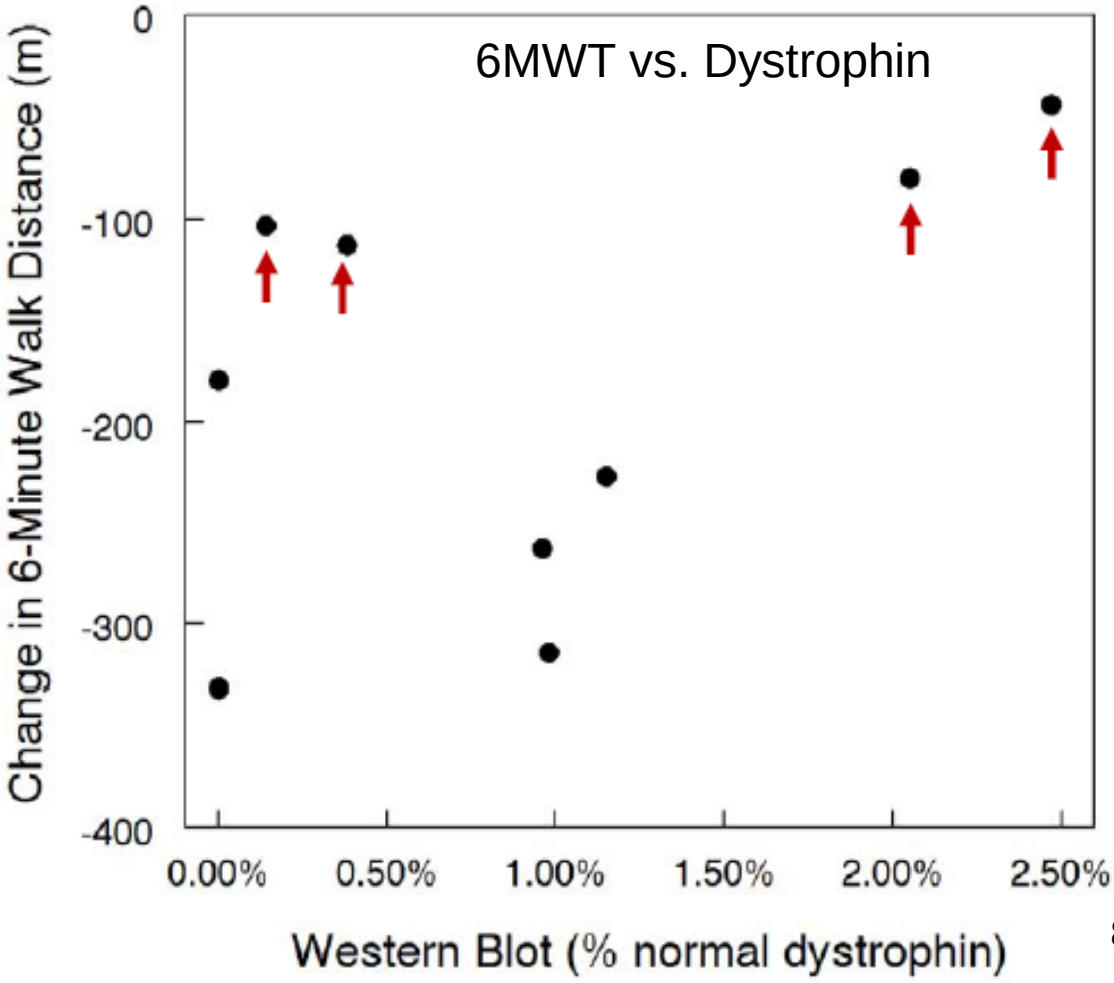
MD STAR*net* Limitations

- MD STAR*net* primarily captured individuals who sought clinical care at neuromuscular clinics.
- Cases born in the early to mid 1980's were less likely to have DNA testing in their records.
- Some patients may have been part of previous clinical trials

No Apparent Correlation Between Dystrophin Levels and Change in 6MWT

An exploratory analysis only, but a clearly positive correlation, if had been present, would have been important to identify

For the 4 patients with most preserved 6MWT, 2 had among the lowest levels, and 2 among the highest (arrows)



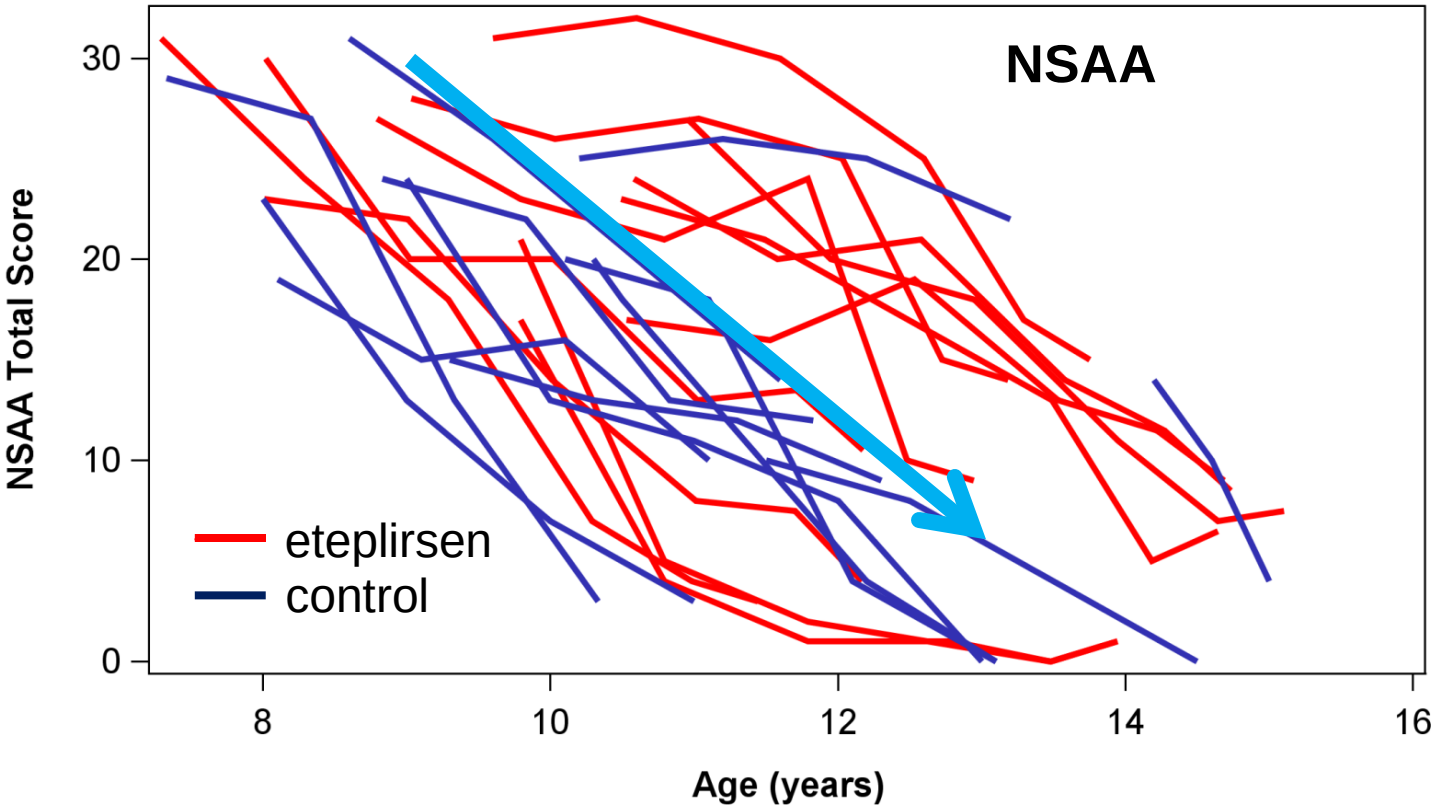
Other Functional Endpoints

North Star Ambulatory Assessment (NSAA)

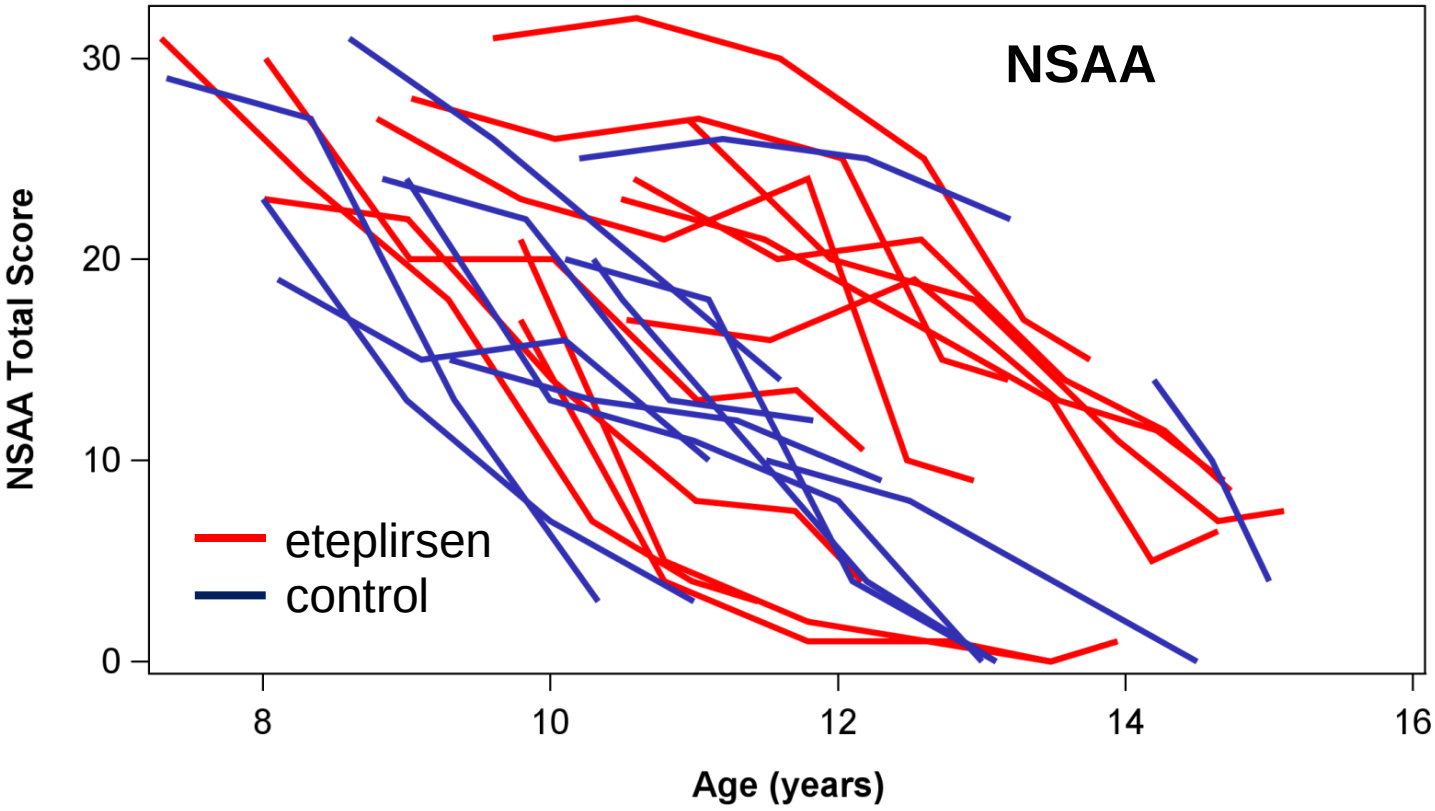
- NSAA may be a particularly important measure of disease progression in DMD because it measures a number of underlying abilities related to muscle strength, and to safe and practical walking

- **In the eteplirsen study, NSAA may be a more reliable measure than 6MWT because it was more consistently measured, with fewer (although still some) instances of "zero" assigned without measurement being conducted**

The arrow indicates what appears to be a generally similar slope of decline of NSAA for both treated and control patients

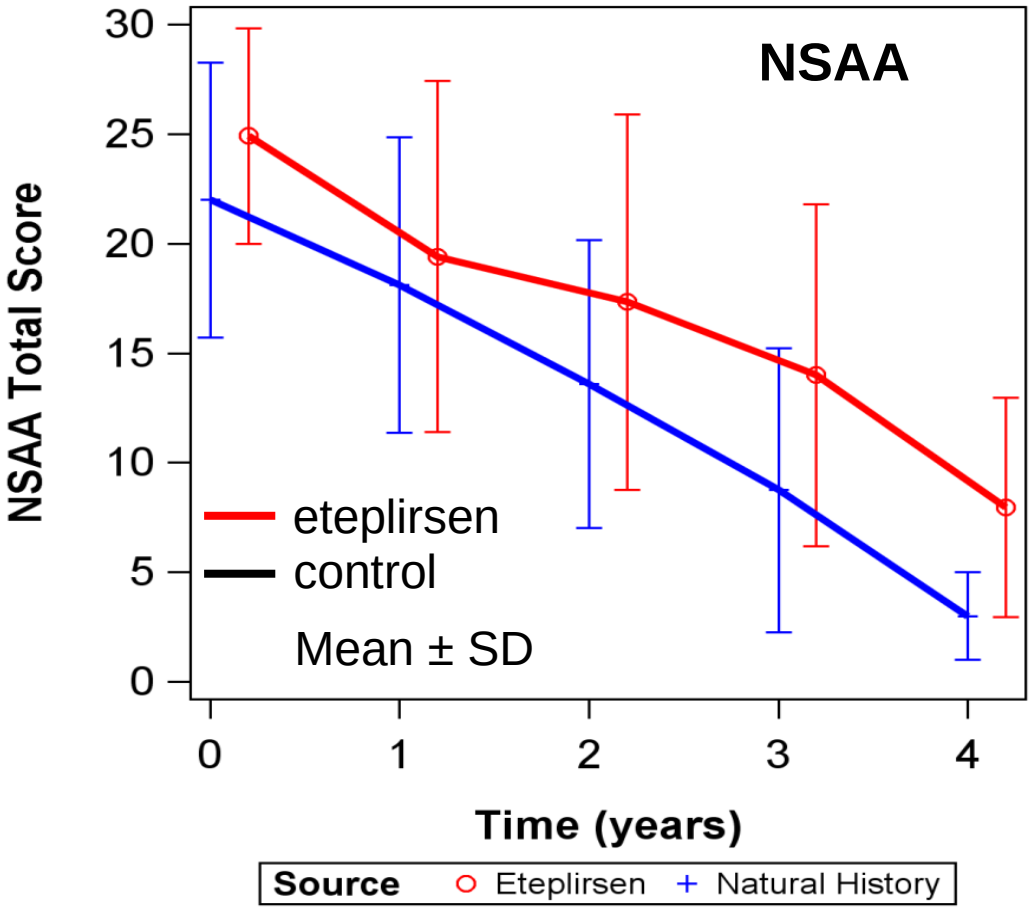


More control patients are to the left of the figure because of lower mean baseline scores in controls, and much missing data for NSAA for control patients at older ages

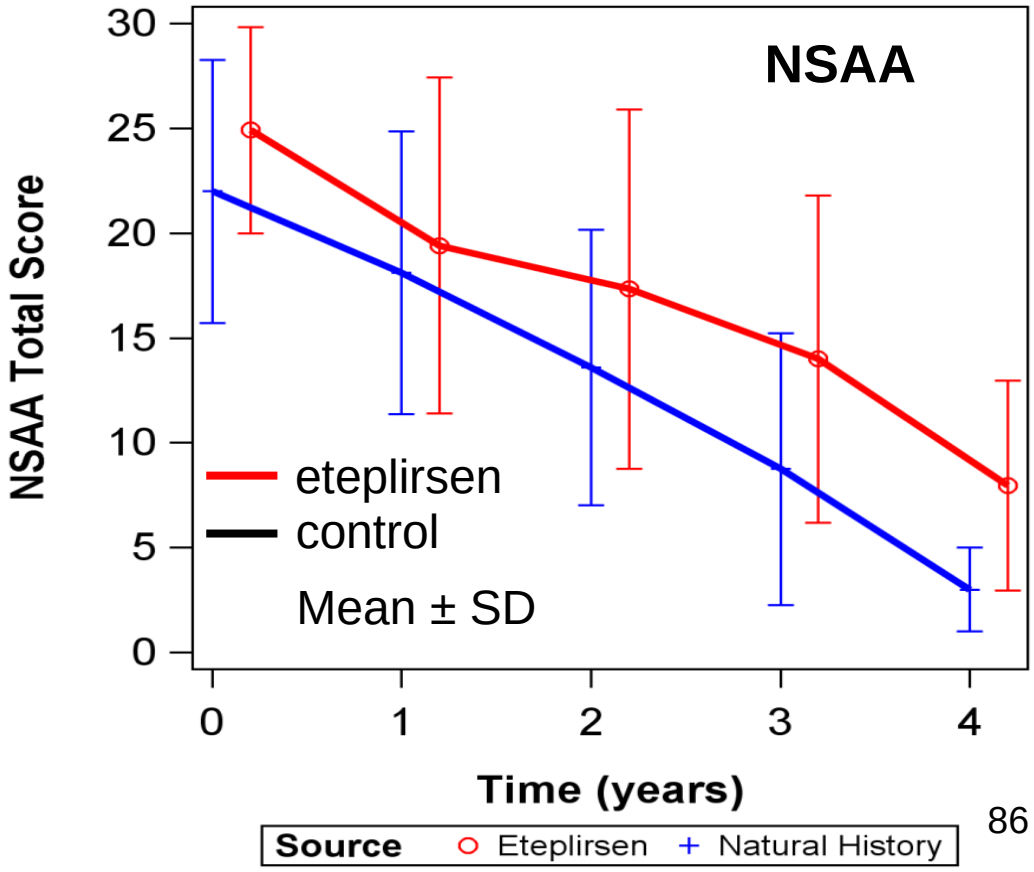


- Mean NSAA scores by time on treatment shows this baseline imbalance

- Control patients had lower (worse) mean NSAA score, which may predict earlier decline in ambulation

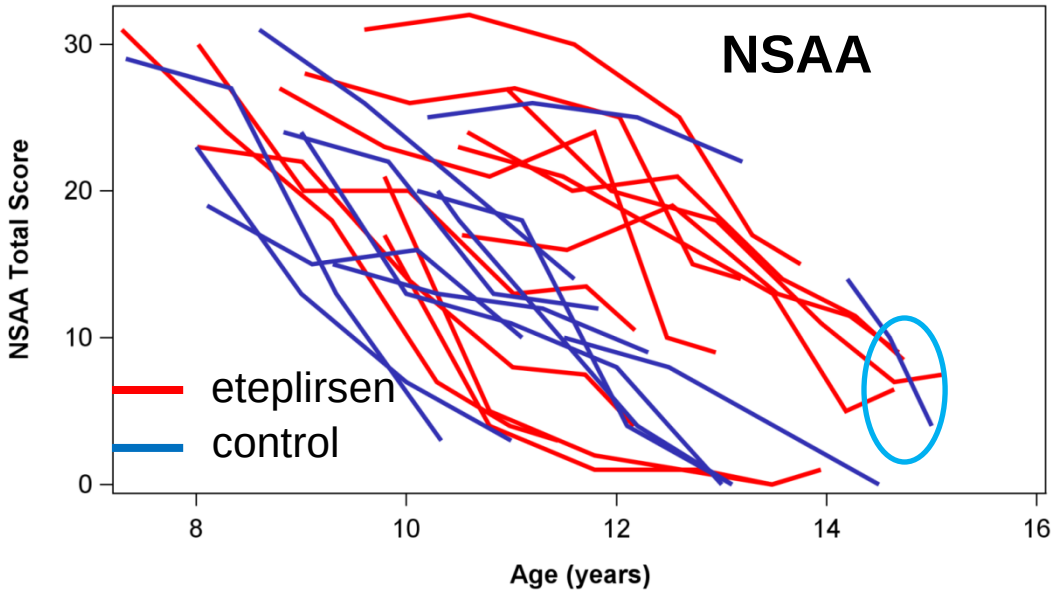


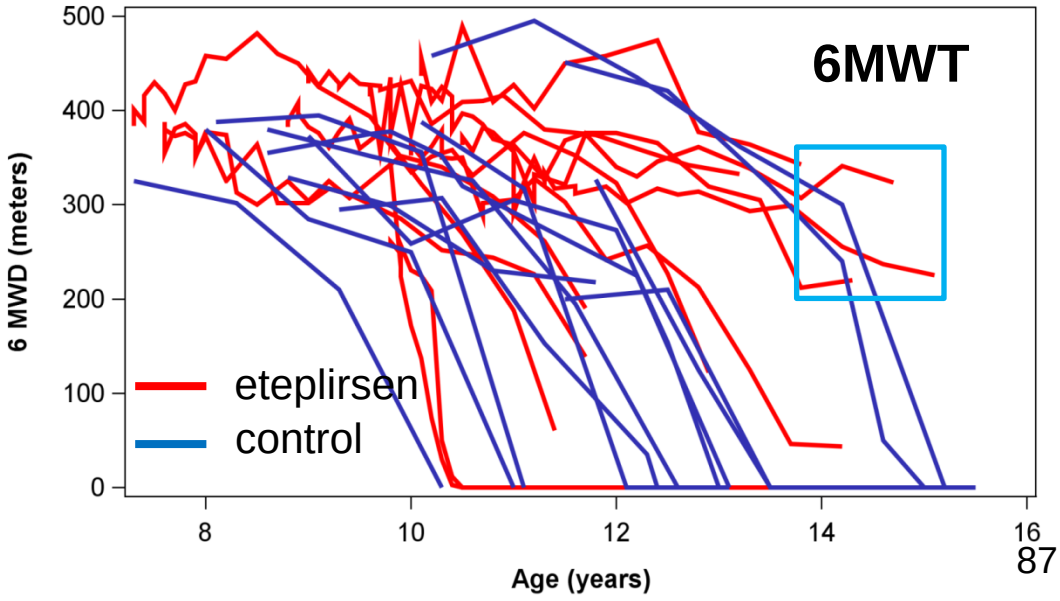
Separation between study arms appears to be generally similar over 4 years (as also indicated by the overlap of standard deviation bars) indicating general similarity of disease progression for eteplirsen-treated and control patients



All eteplirsen patients have declined substantially on NSAA, including the several older patients (oval) with more preserved 6MWT (square)

There appears to be little reason to believe that age at loss of ambulation for these patients will exceed the typical range in untreated patients with DMD

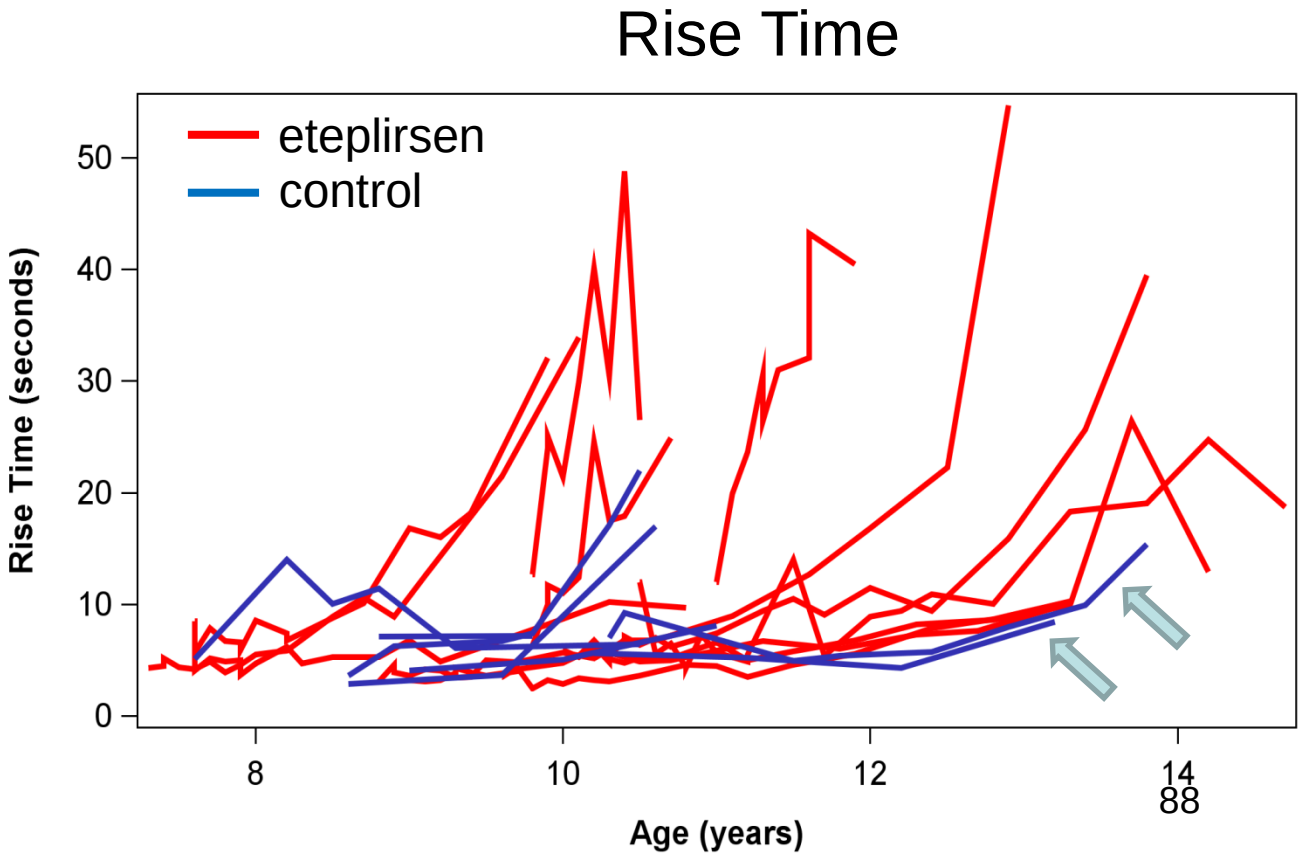




Ability to rise from the floor may be another useful measure of disease progression in DMD

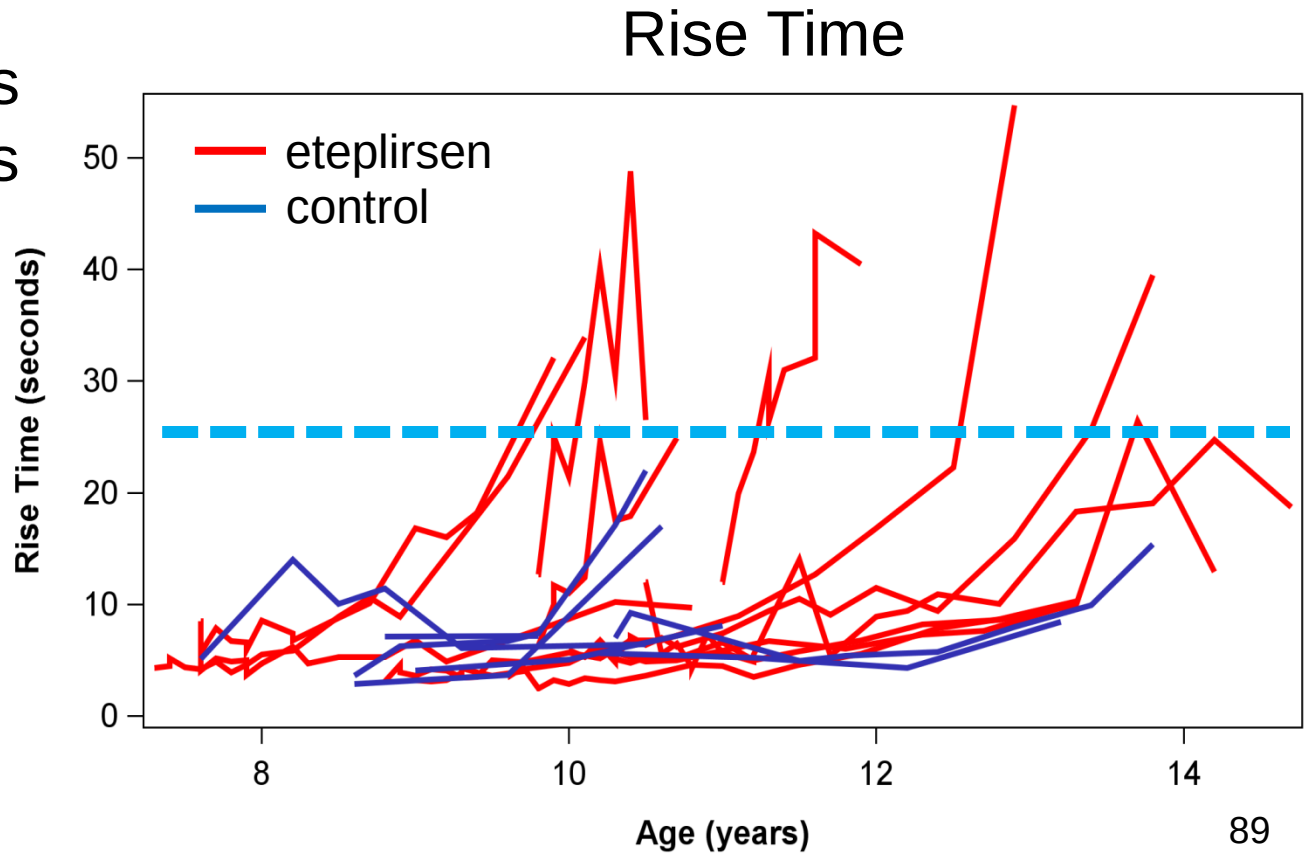
Lower values and more horizontal slope indicate better function and slower decline, respectively

Two of the patients with the most preserved rise time at older ages were historical controls (arrows)



May be differences in how endpoints were assessed for eteplirsen-treated and external control patients

- Eteplirsen patients recorded to values greater than 50 seconds
- Controls have no values larger than ≈25 seconds



Preliminary FDA Analyses of CINRG Functional Endpoint Data

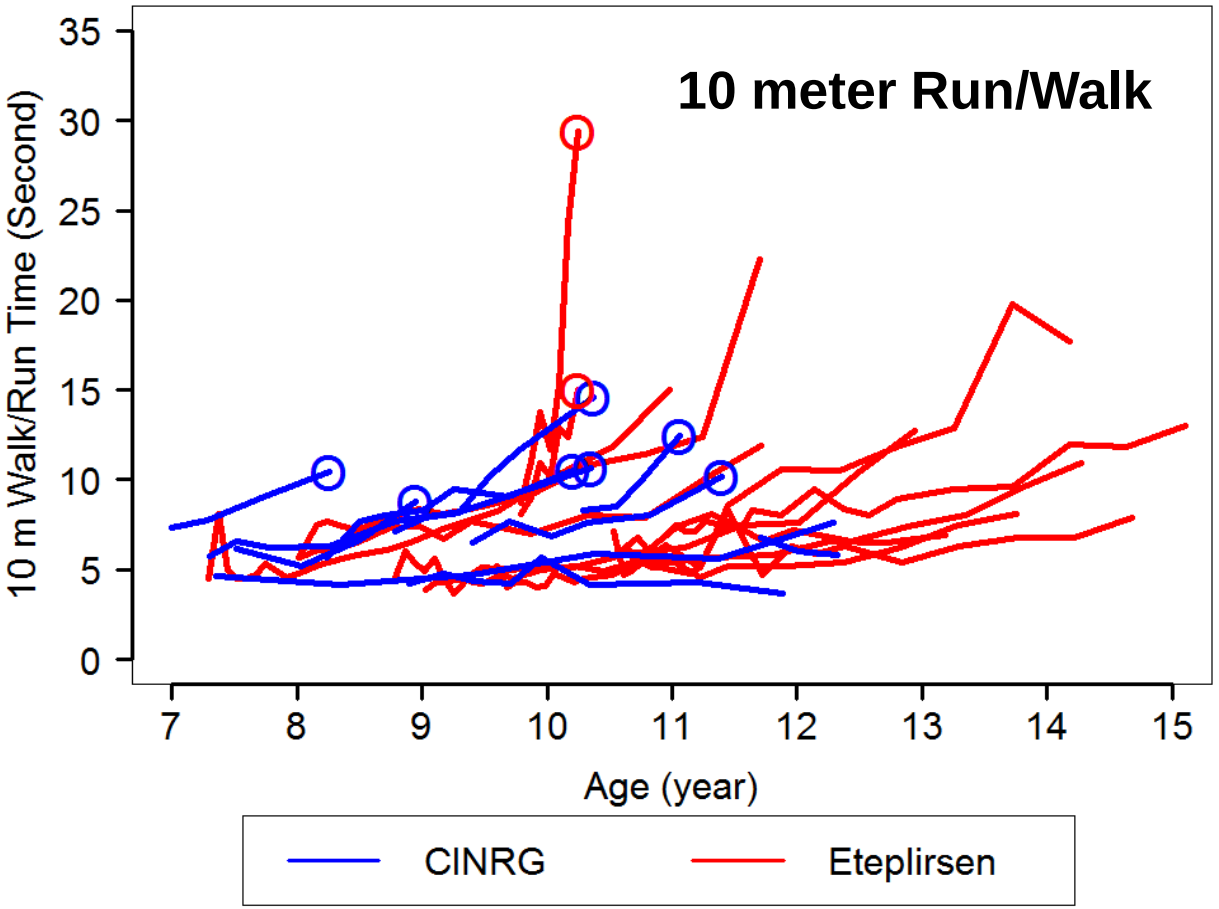
- 10 meter run/walk
- Rise time
- 4 step climb

FDA Analysis of CINRG Data

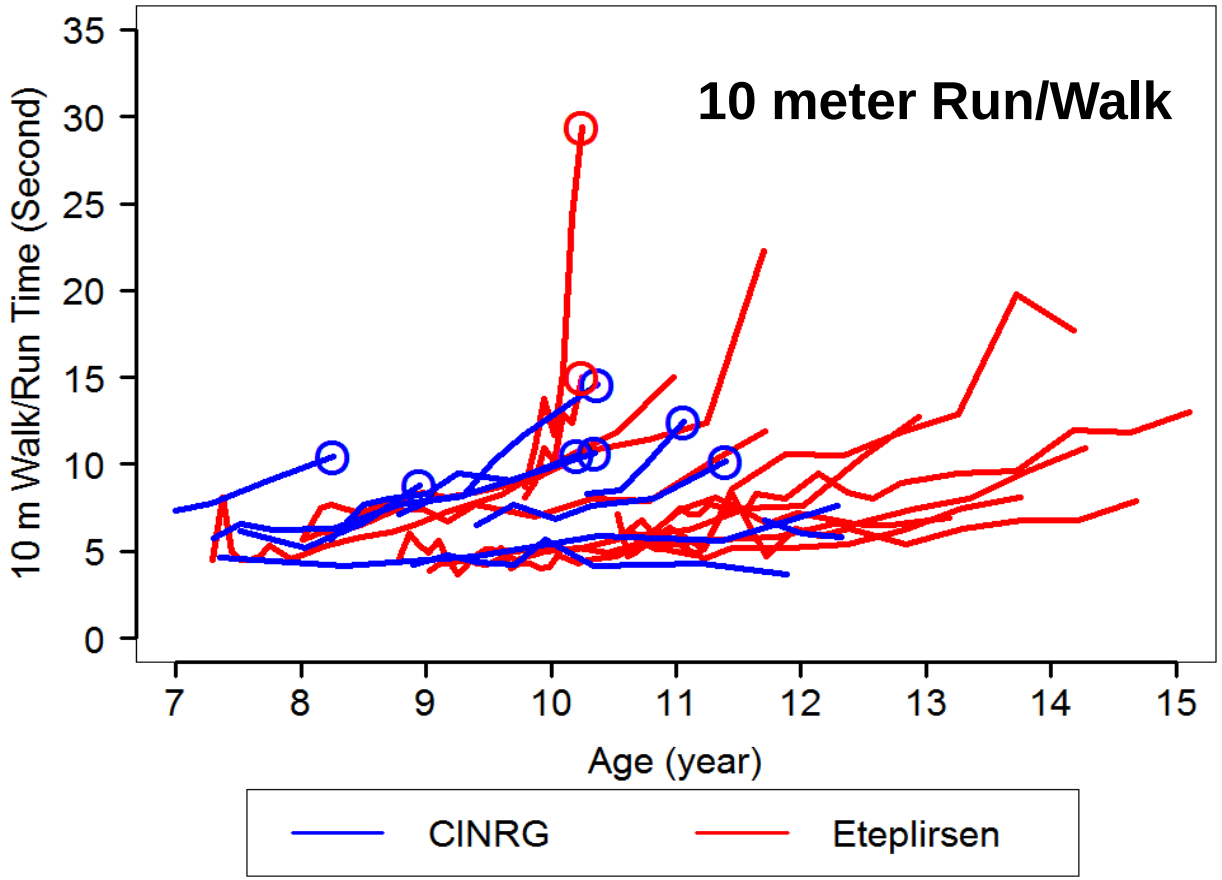
- Prior to receipt of the CINRG data, FDA pre-specified an analysis plan for matching patients, and identified FDA statisticians not involved in the review

- CINRG patients were matched to eteplirsen patients based on the following baseline characteristics
  - Exon-51 skippable
  - Ambulatory at baseline
  - Baseline age 6-12 years
  - 10 meter run/walk time less than 10 seconds

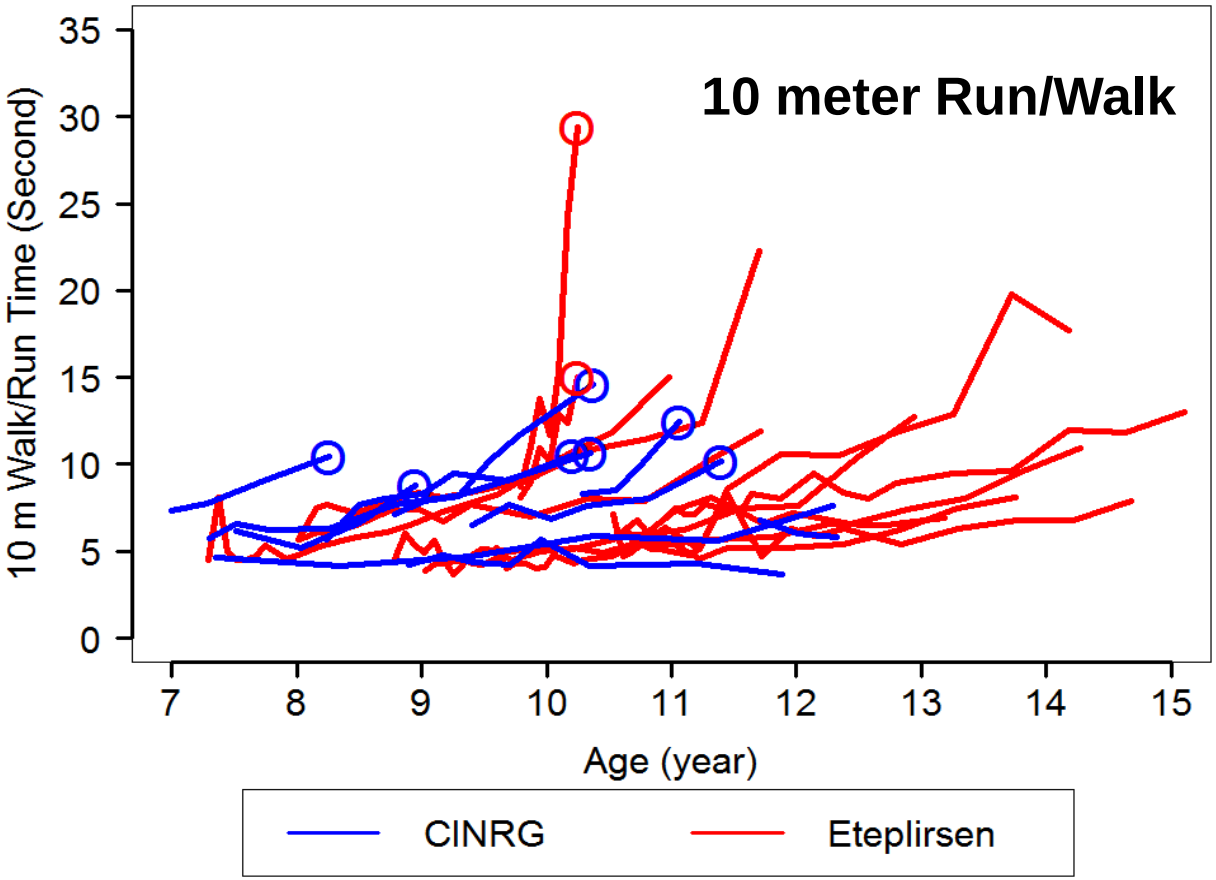
- 10 meter run/walk was considered the primary comparison because few long-term 6MWT data are currently available in the CINRG database



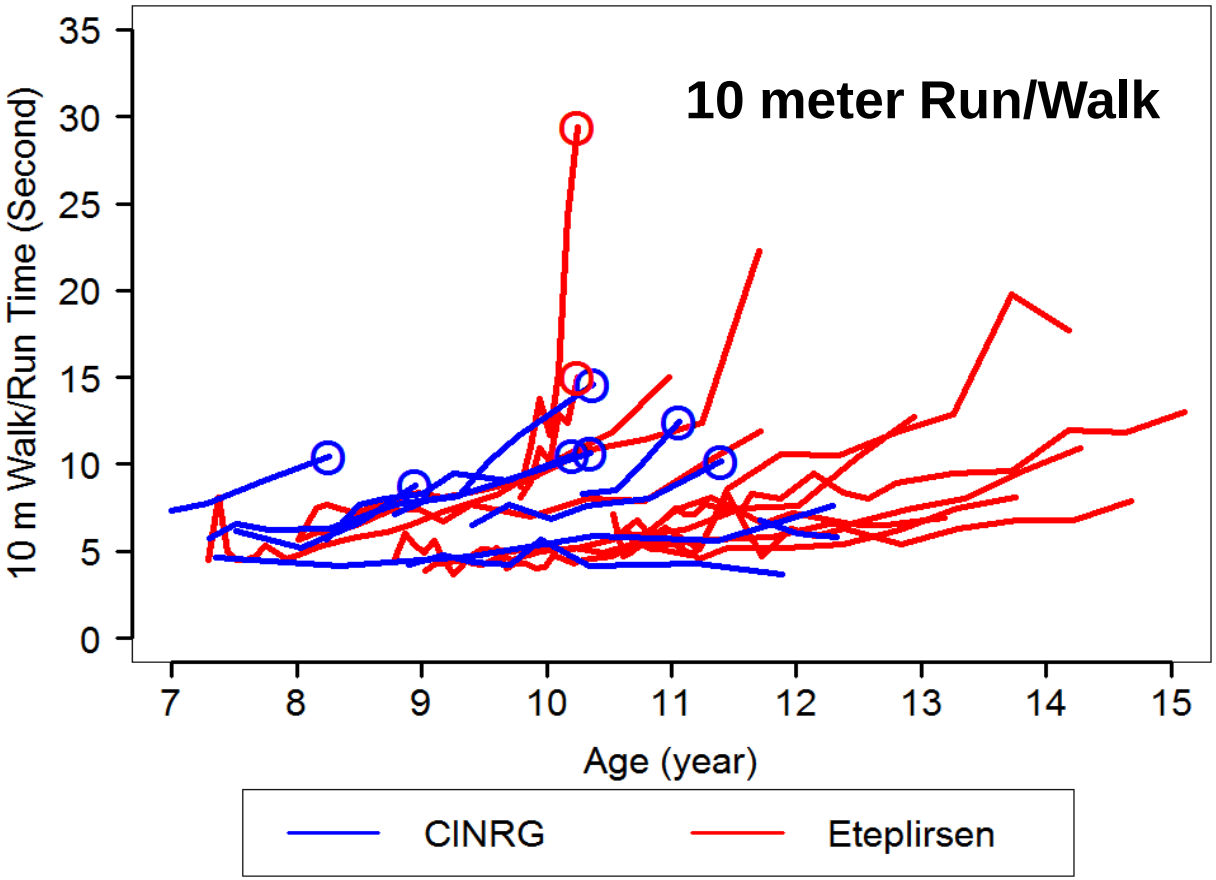
- The lines show results of 10 meter run/walk tests that were attempted – that is, had a numerical value
- Circles indicate patients in whom the next value was imputed as “unable”



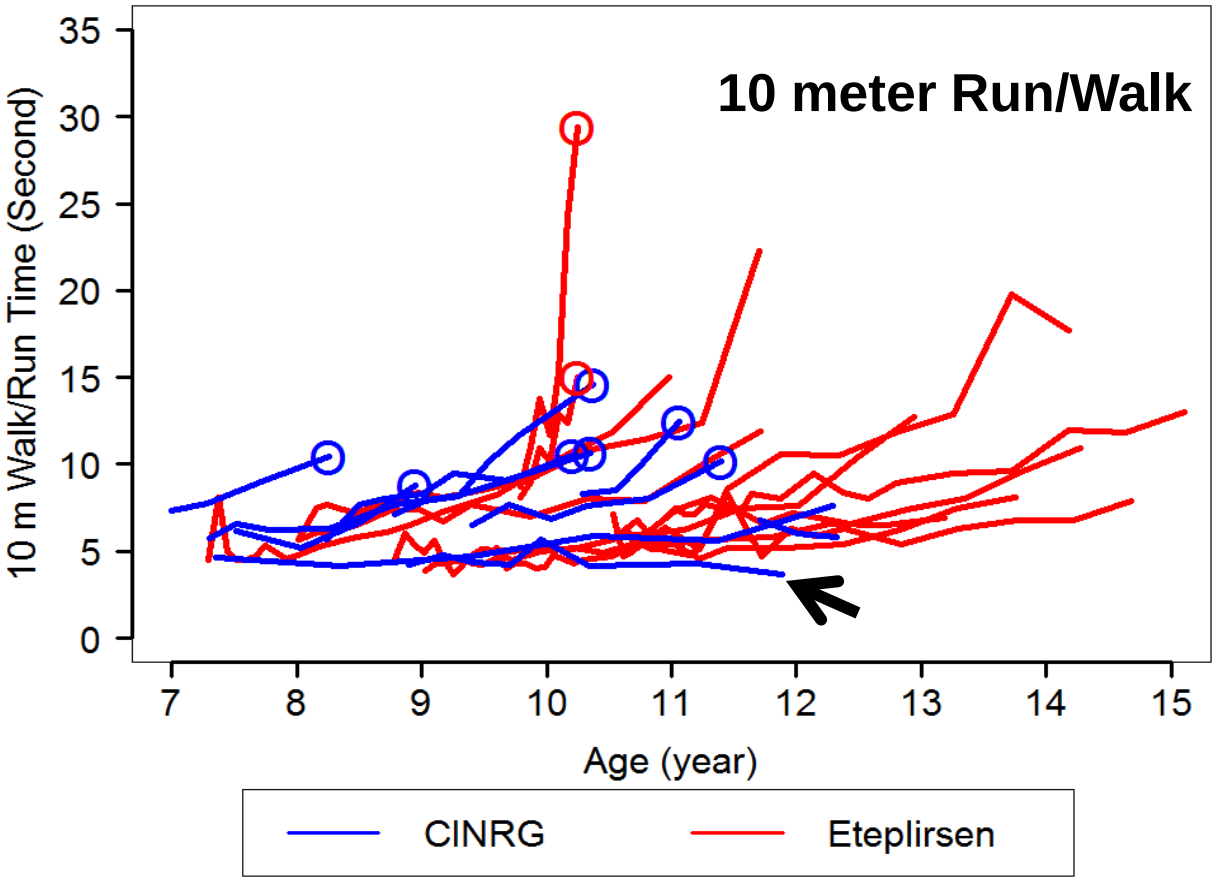
- Course of 10 meter run/walk appears to be a similar for eteplirsen-treated and CINRG patients for values that were measured



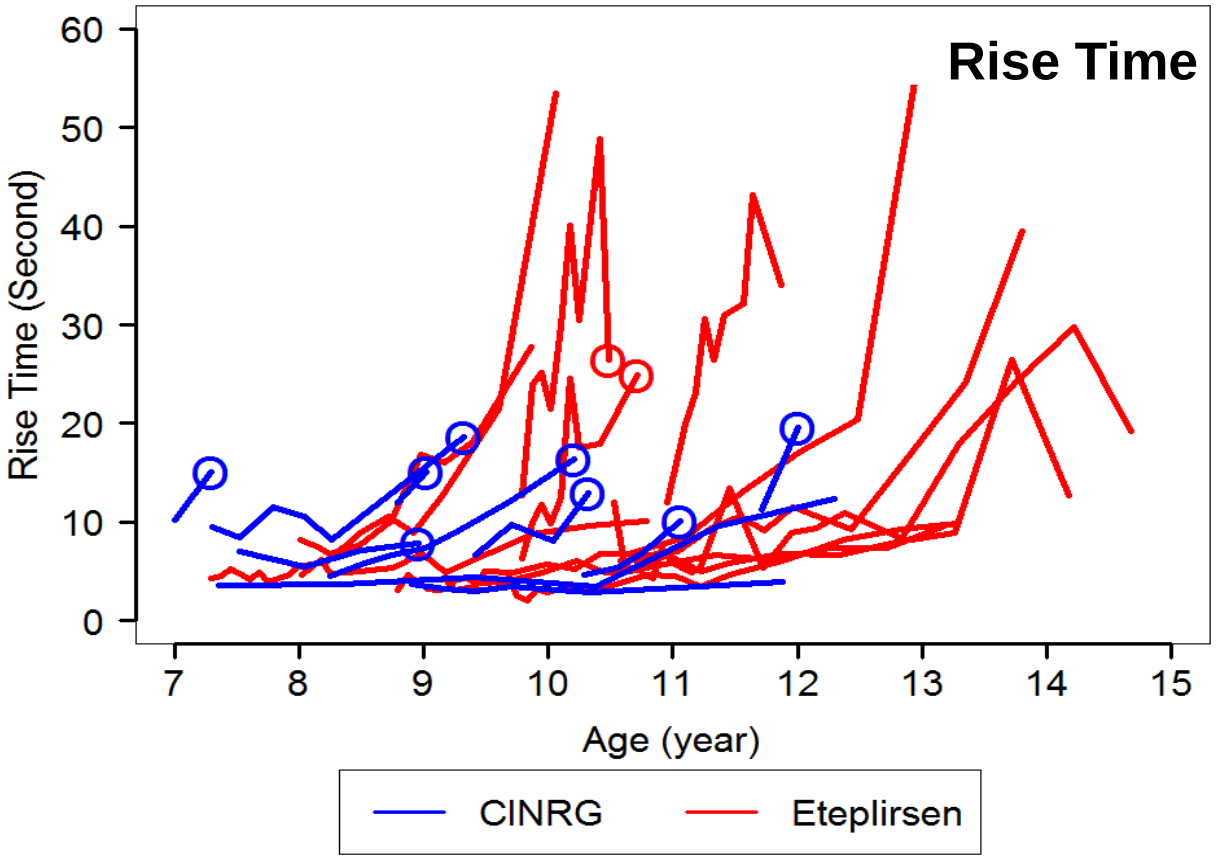
- For 10 meter run/walk, eteplirsen-treated patients were measured to higher values, but this may reflect differences in when patients were deemed unable to attempt the endpoint



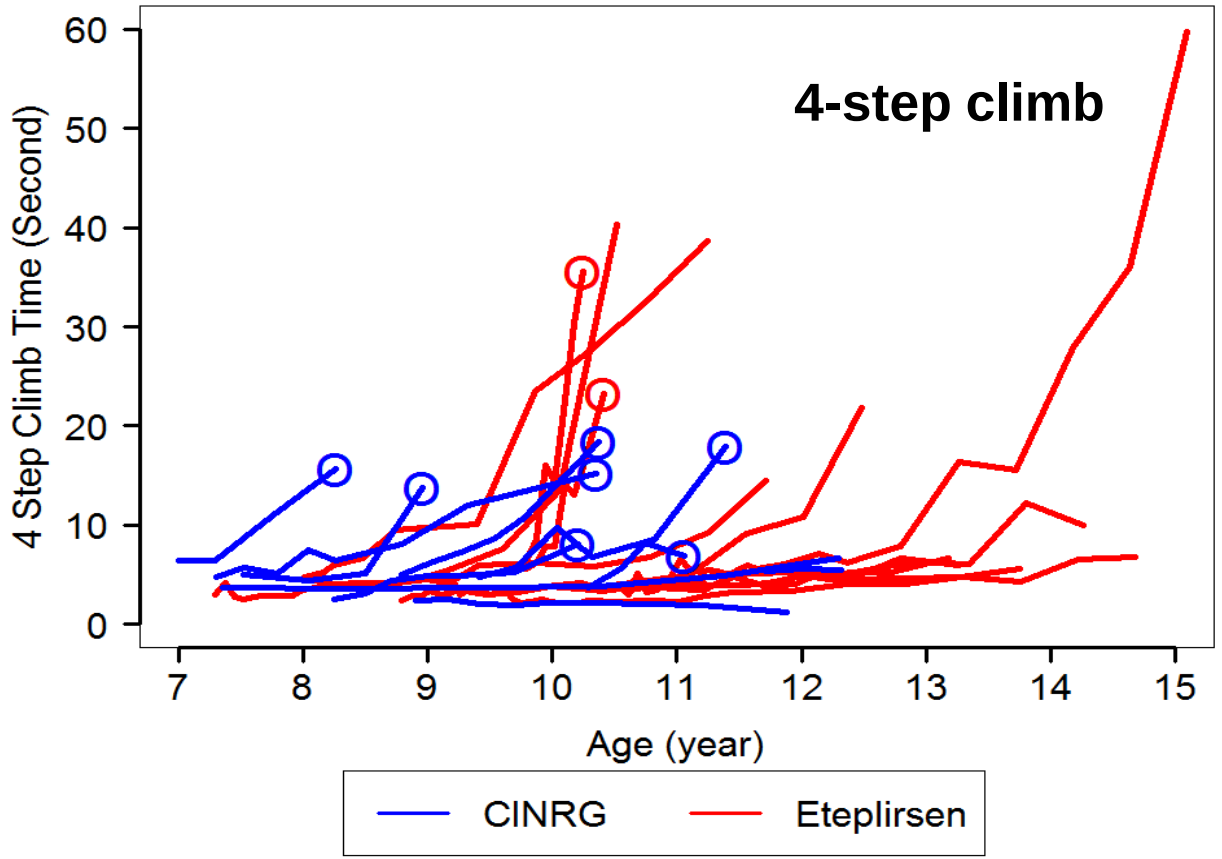
- Note the most preserved 10 meter run/walk time is an external control patient (arrow)



- Course of rise time also appears to be similar for eteplirsen-treated and CINRG patients, for values that were measured



- Course of 4-step climb also appears to be a similar for eteplirsen-treated and CINRG patients, for values that were measured



Conclusions

- From the placebo-controlled portion of Study 201/202, including from the applicant's post-hoc analyses, there does not appear to be any evidence of efficacy for eteplirsen

- Interpretation of the externally controlled portion of Study 201/202 must keep in mind the limitations of an externally-controlled study, which are well-known, and detailed in FDA guidance and international guidelines such as ICH E10

- Based on an assessment of all physical performance measures, disease progression appeared to be similar for eteplirsen-treated patients and external controls

- All eteplirsen patients who have maintained ambulation are still well within the age range in which exon 51 skippable patients appear commonly to walk

- It does not appear possible to conclude that differences in physical performance between eteplirsen-treated patients and external controls resulted from an effect of eteplirsen, instead of from other differences and influences, both known and unknown, between the groups, both at baseline and during conduct of the study

General Drug Development Considerations

- Dose-limiting toxicity from eteplirsen was not observed at the doses studied
- Higher doses and/or more frequent dosing could hold promise for the future

Concluding Remarks

Eric Bastings, M.D.
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Office of New Drugs

Center for Drug Evaluation and Research

Peripheral and Central Nervous System Drugs Advisory Committee
April 25, 2016

Great Hope for a Profound Unmet Medical Need

- Duchenne Muscular Dystrophy (DMD) is a serious and devastating disease with profound unmet medical need and no approved treatment
- Great hope raised by early reports by the Applicant and its academic associates that with eteplirsen treatment, dystrophin levels were increased to levels as high as 50% of normal, and that the course of the disease had stabilized, effects would have been unprecedented for DMD.

Extensive Discussions and FDA Guidance During Eteplirsen Development Program (1)

- Between 2013 and 2015, FDA held 13 meetings with the Applicant to discuss eteplirsen's development program
- FDA identified significant methodological concerns about the Applicant's biomarker assessments, and provided extensive guidance on methods for collection of additional biomarker data
- Extensive involvement and guidance from senior FDA management during eteplirsen development program

Extensive Discussions and FDA Guidance During Eteplirsen Development Program (2)

- Extensive discussions with Applicant about Study 201/202, which started as 24-week placebo-controlled study (Study 201)
- The Applicant conducted a number of post hoc analyses of Study 201/202, which FDA did not consider scientifically valid
- After Study 201 failed, FDA advised the Applicant to conduct an adequately powered, randomized, placebo-controlled trial to assess the clinical effect of eteplirsen
- Applicant instead continued open-label administration of eteplirsen, and is proposing approval primarily based on a post hoc comparison to an external control

Why is the public hearing about FDA's concerns regarding eteplirsen development program only after the NDA has been submitted?

- Because of laws governing trade secret, FDA is generally unable to provide any information to the public about its findings regarding drugs under development, and is unable to comment about information provided by the drug developer
- Because of those restrictions, some decisions or positions taken by FDA, or FDA's silence, might be construed by the public and the patient community as a lack of caring, understanding, or expertise, when they simply reflect a legal restriction against sharing commercial confidential information with the public

Biomarker Evidence

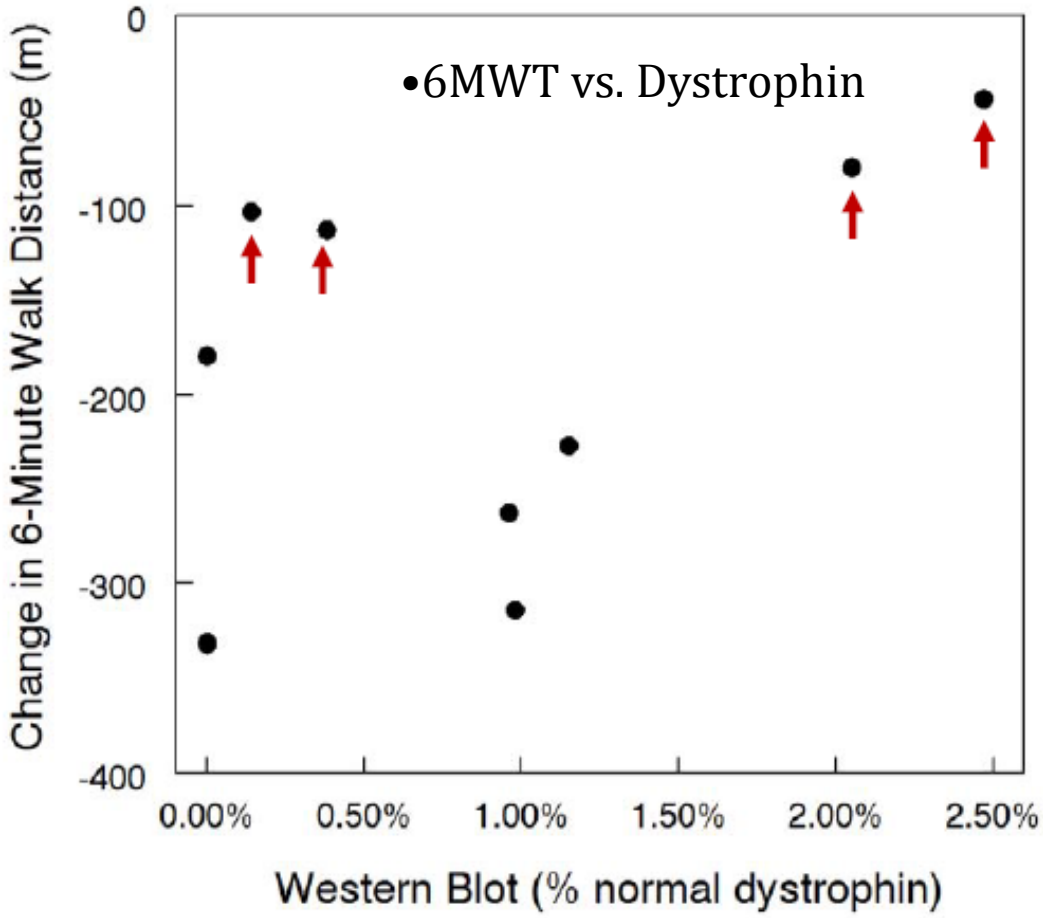
- There is evidence of production of exon 51 skipped mRNA with eteplirsen, supporting its proposed mechanism of action
  - Method does not show how much mRNA was produced or whether this mRNA led to production of dystrophin
- After 3.5 years of treatment, the proportion of muscle fibers with detectable dystrophin identified by immunofluorescence was 17% ± 10% of normal
  - It is not clear whether 17% constitutes an increase from baseline levels
  - This method is mostly useful for showing location of dystrophin in the muscle, and has major shortcomings for quantifying dystrophin
- After 3.5 years of treatment, the amount of dystrophin assessed by western blot, the most quantitative method, was 0.9% ± 0.8% of normal
  - It is not clear whether this constitutes an increase from baseline levels

Is the Biomarker Data Reasonably Likely to Predict Clinical Benefit?

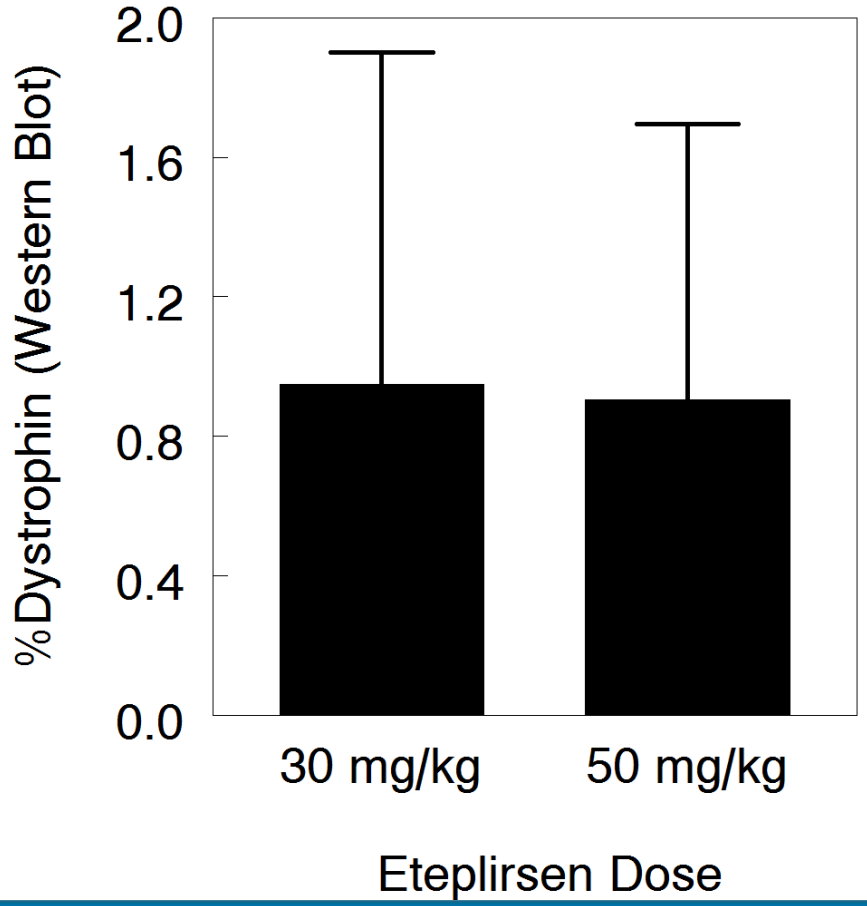
- Is there adequate evidence that eteplirsen produced dystrophin, and if so, what was the amount produced?
- Is the amount produced (if any) reasonably likely to predict of clinical benefit?

No Apparent Correlation between Dystrophin Levels and Change in 6MWT

For the 4 patients with most preserved 6MWT, 2 had among the lowest levels of dystrophin, and 2 among the highest (arrows)



No Evidence of Dose-response in Amount of Dystrophin at Week 180



Clinical Evidence (1)

- Study 201 did not show a significant difference between boys treated with eteplirsen and those treated with placebo for the prespecified clinical endpoint (6MWT - Week 24).
  - This endpoint was the only one assessed in a randomized controlled study in the entire development program
- Study 202 did not show a significant difference between boys initially treated with eteplirsen and those initially treated with placebo for the prespecified clinical endpoint (6MWT - Week 48).

Clinical Evidence (2)

- The Applicant describes highly statistically significant results in the comparison between boys treated with eteplirsen in Study 201/202, and external controls, presenting a difference of 162 m (p=0.005) between the groups
- The Applicant also describes that, in a comparison of eteplirsen to the external control over 4 years, only two of eteplirsen-treated boys lost ambulation, compared to 10 of the 13 untreated external controls

Clinical Evidence (3)

A 160-meter difference in 6-minute walk distance, if demonstrated in an adequate and well controlled study, would provide evidence of effectiveness.

But Study 202 was not a randomized controlled trial, and several lines of evidence raise concerns that the differences in ambulation between eteplirsen-treated boys and external controls are not related to a treatment effect, and may be due to other factors.

Clinical Evidence (4)

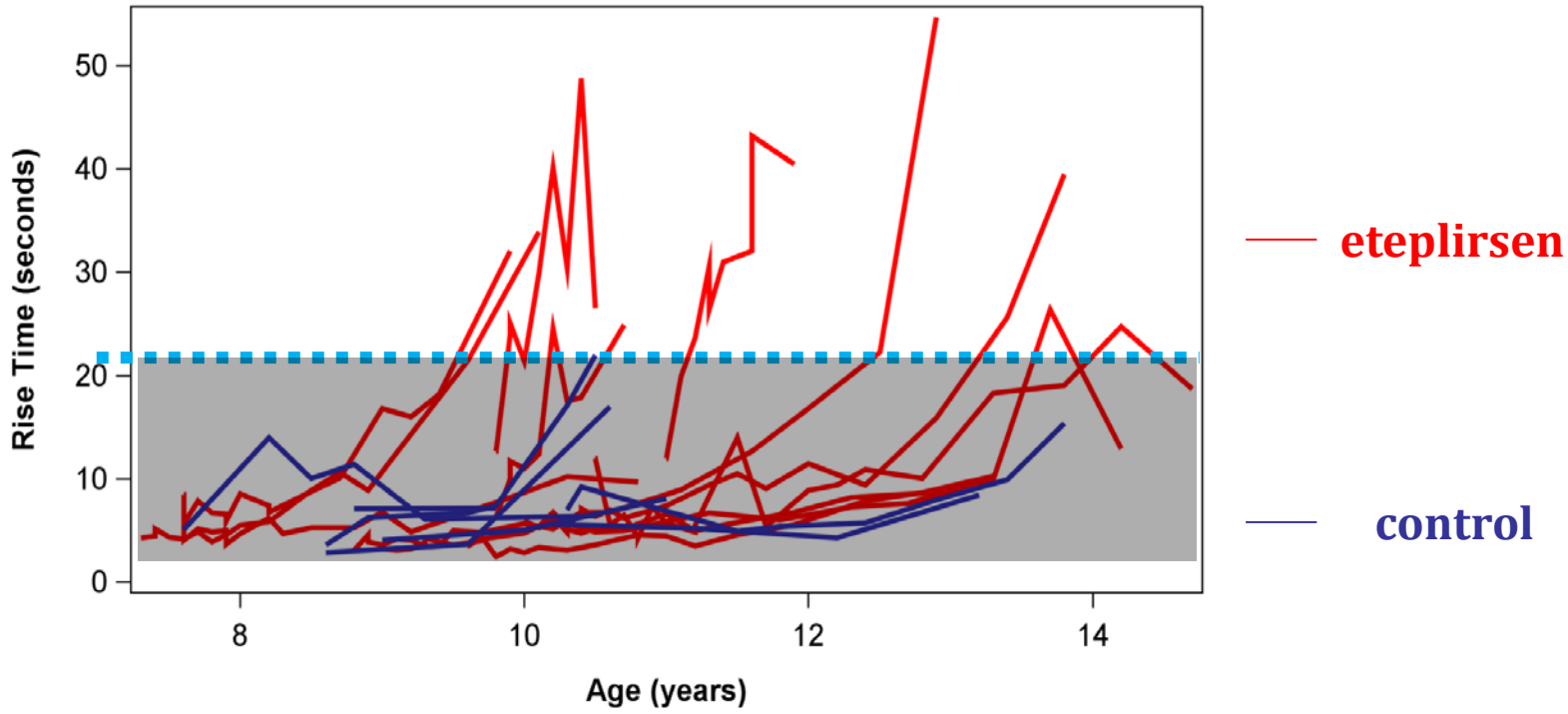
1. Differences between important baseline characteristics that could affect outcomes in boys enrolled in the eteplirsen study compared to those of the registries

   - Differences in steroid treatments (e.g., mean age at treatment initiation over one year earlier for eteplirsen)
   - Differential selection of patients for registry vs. drug study
   - Many other unrecognized, and potentially very important factors, were not balanced by randomization between the study and registry cohorts

Clinical Evidence (5)

2. Differences, either *apparent* or *unrecognized,* in the administration and/or performance of functional tests between eteplirsen-treated boys and external controls

– E.g., no boy in the Belgian or Italian registry had a recorded rise time greater than 22 seconds, while 8 eteplirsen-treated boys did



Clinical Evidence (6)

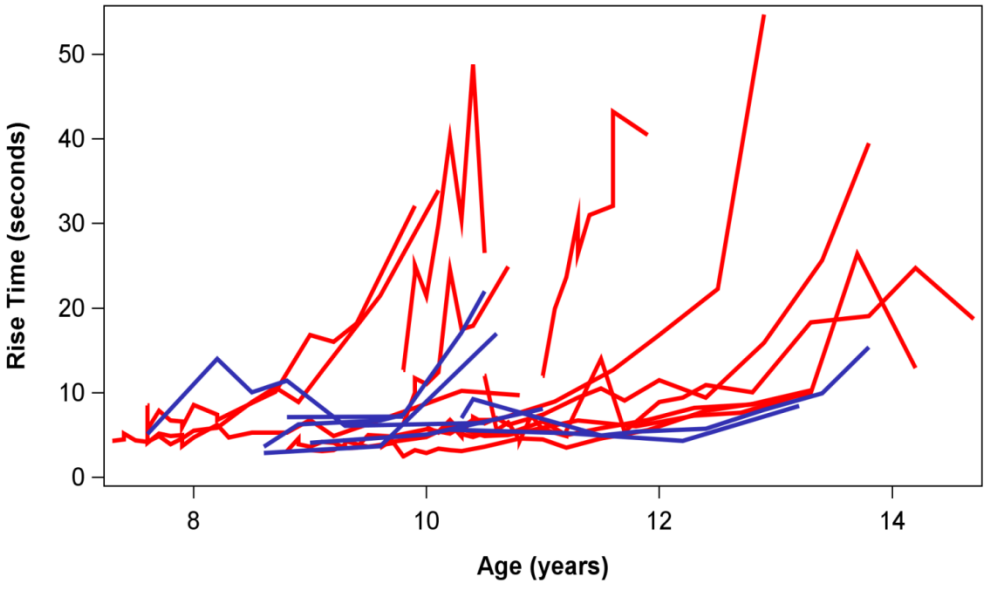
2. Differences, either *apparent* or *unrecognized,* in the administration and/or performance of functional tests between eteplirsen-treated boys and external controls

- Similarly, extreme results were recorded for the 4-step climb time for some eteplirsen-treated boys, but not for controls
- Some boys in the external control group had recorded 10-meter walk results but were declared unable to ambulate
- Functional tests are not as objective as one may hope, and may be influenced by decisions made by boys, caregivers, or investigators/health care providers
- No way to correct for this sort of issue statistically in an external control study

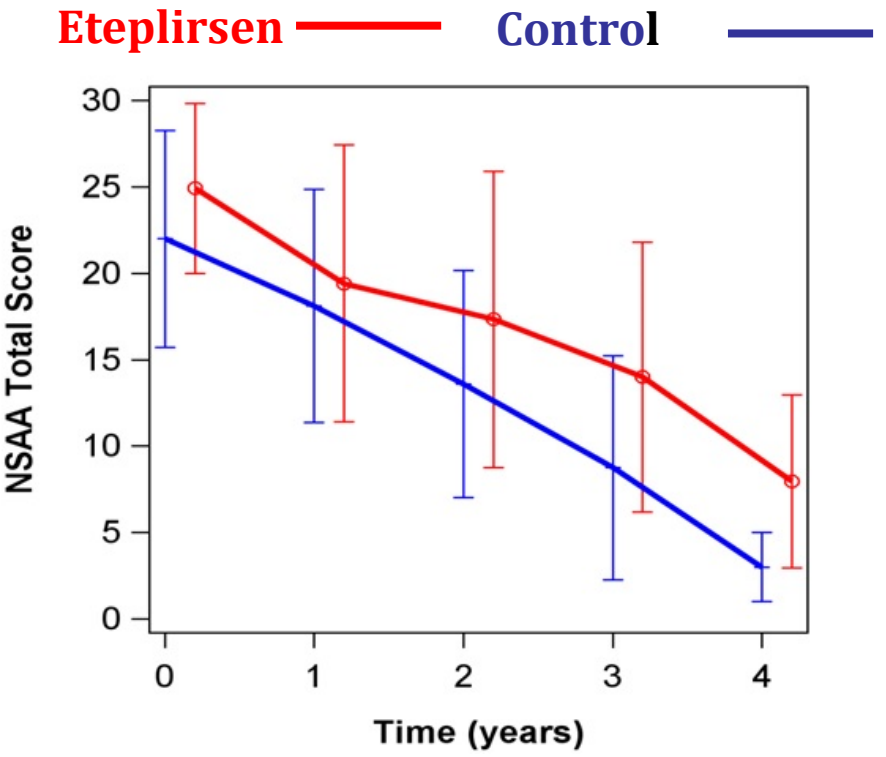
Clinical Evidence (7)

3. Inconsistencies between 6MWT results and other clinical endpoints in eteplirsen-treated boys

Rise time



North Star Ambulatory Assessment

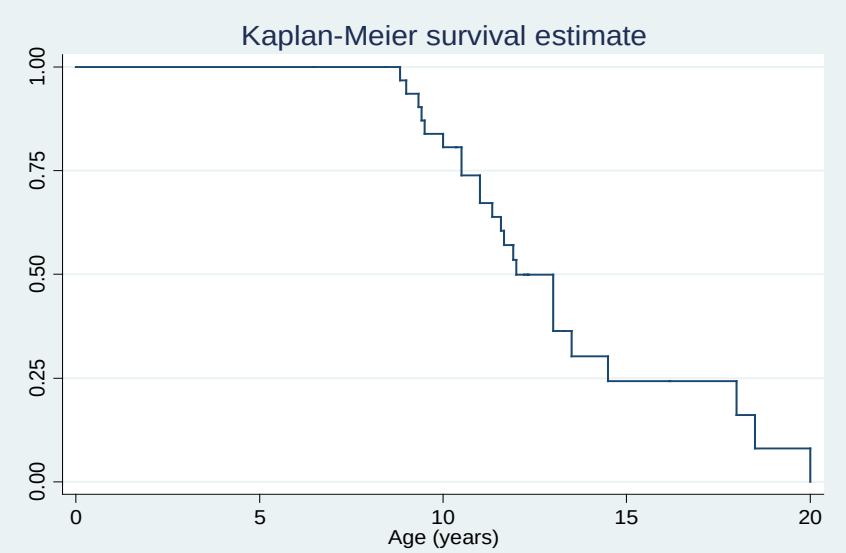


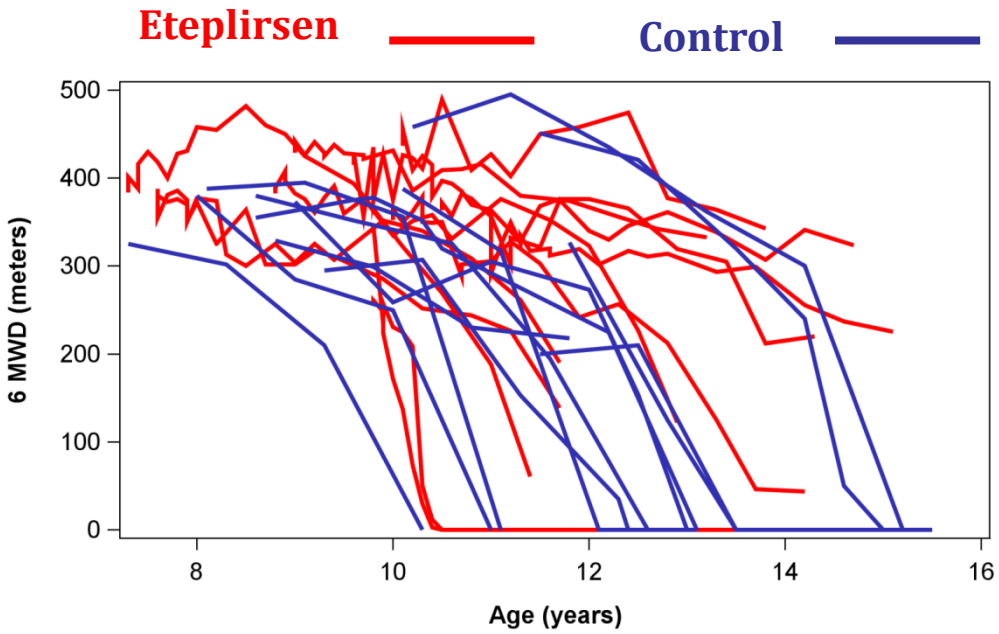
Clinical Evidence (8)

4. Substantial overlap of ambulation results between eteplirsen-treated boys, external controls, and natural history

- Proportion of eteplirsen-treated patients still ambulating after age 14 is not clearly different from what is expected by natural history, as shown in a comparison to loss of ambulation data from the CINRG database

Age of loss of ambulation in CINRG database





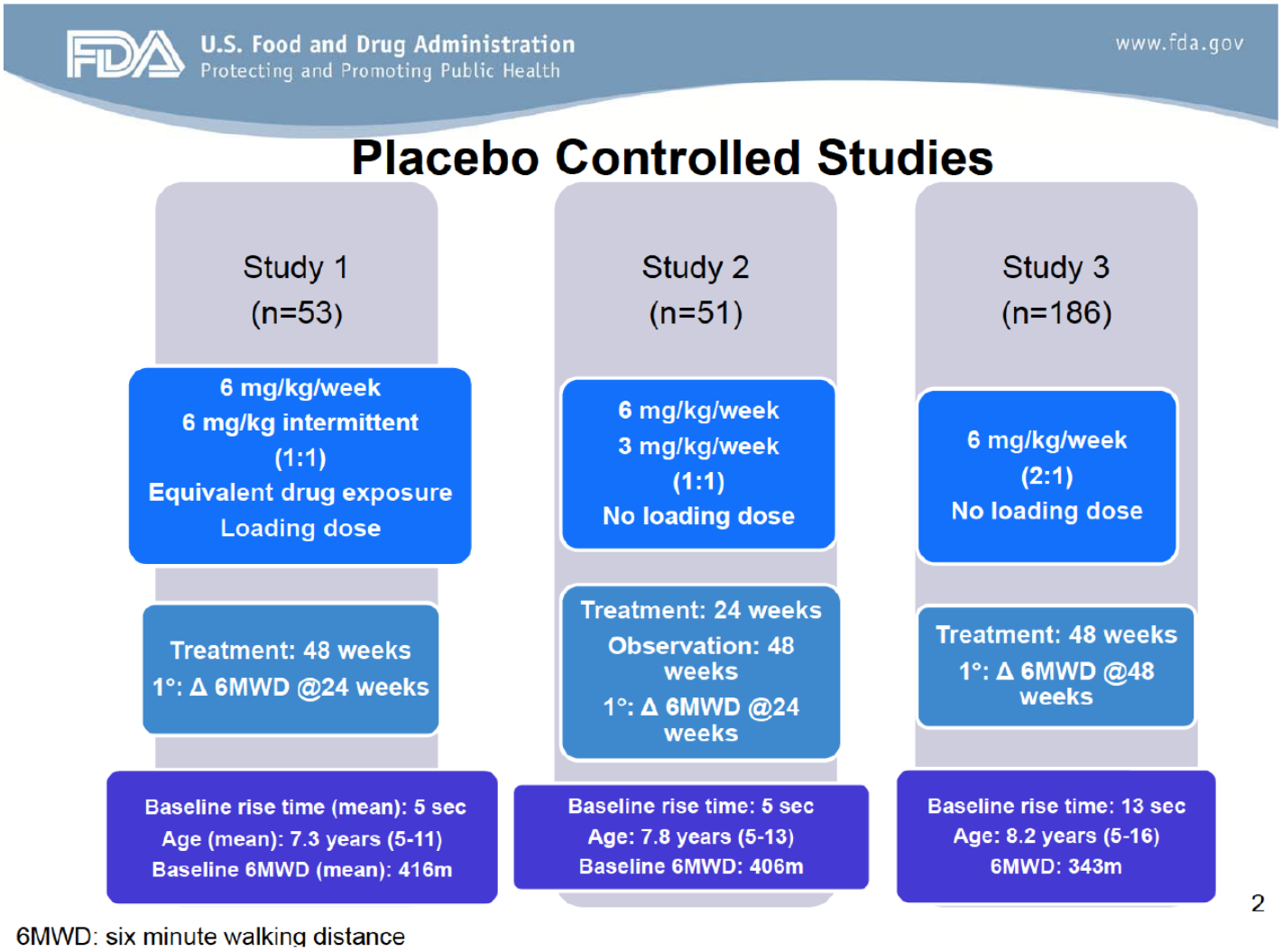
Issues to Consider with External Control Trials

- Bias before the trial
  - Difference in important characteristics between groups
  - Control patients are destined to have worse outcomes (in particular if control patients are selected with data in hand)
- Bias during and after the trial
  - Affects endpoints if they are subjective or have subjective elements
  - Choice of endpoint (e.g., NSAA vs. 6MWT or rise time)
- External control trials are most likely to be persuasive when the effect is very large, and when the natural history is highly predictable

FDA has serious concerns about all of the above issues regarding the comparison to external control conducted by the Applicant

DMD IS AN ORPHAN DISEASE: WAS IT POSSIBLE TO CONDUCT AN ADEQUATE AND WELL CONTROLLED STUDY IN THAT POPULATION?

Drisapersen PNCS Meeting (November 2015)



PCNS Comments about Study 1 (N=53) and Study 2 (n=51)

- "I think the data are very difficult to interpret with the small sample size"
- "These are two very small phase 2 studies with positive to marginally negative endpoints. They're potentially encouraging or potentially not encouraging."
- "I think that this is a phase 2 study. It has to be taken as an early phase study. I don't think that the p-value has any bearing on the result of this setting."
- "That being said, I just don't feel that the trial was large enough to get any really meaningful idea of its effect."
- "With the small sample size, I felt that it was an inconclusive study, and the discussion that we had just reinforced that it was an inconclusive study."
- "Sample size is small and inconclusive."

Eteplirsen Efficacy Database

- 12 patients
- Single site
- Single investigator
- Open-label
- External control

While there is no specific minimum number of patients that should be studied to establish effectiveness of a treatment for any rare disease, the number of patients must be sufficient to draw valid scientific conclusions.

Accelerated vs. Conventional Approval

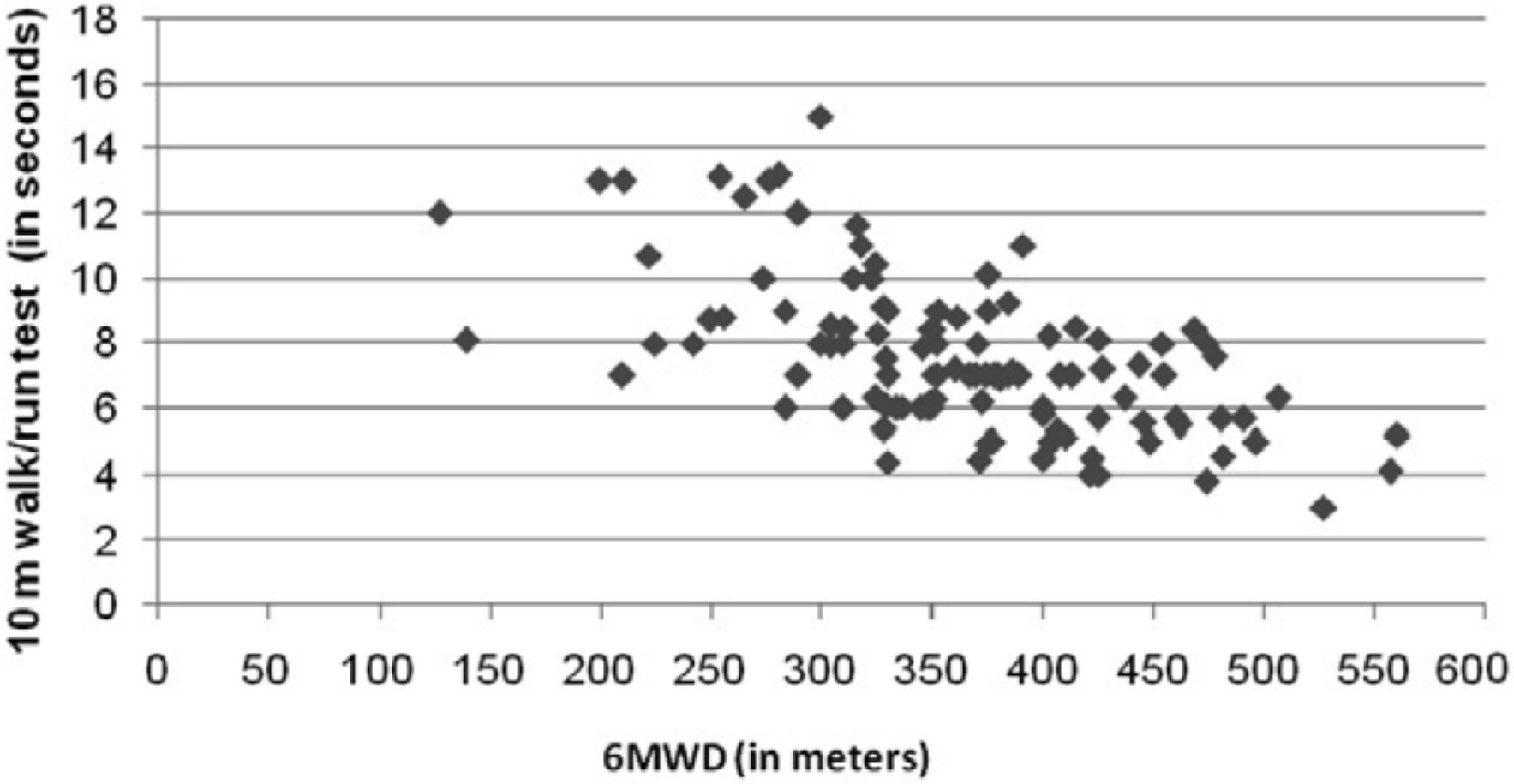
Difference between accelerated and conventional approval is the type of endpoint, not the strength of the evidence. Substantial evidence is required for both pathways.

Accelerated Approval	**Conventional Approval**
Biomarker, or Intermediate Clinical Endpoint reasonably likely to predict clinical benefit	Benefit to patients in how they feel, function, or survive

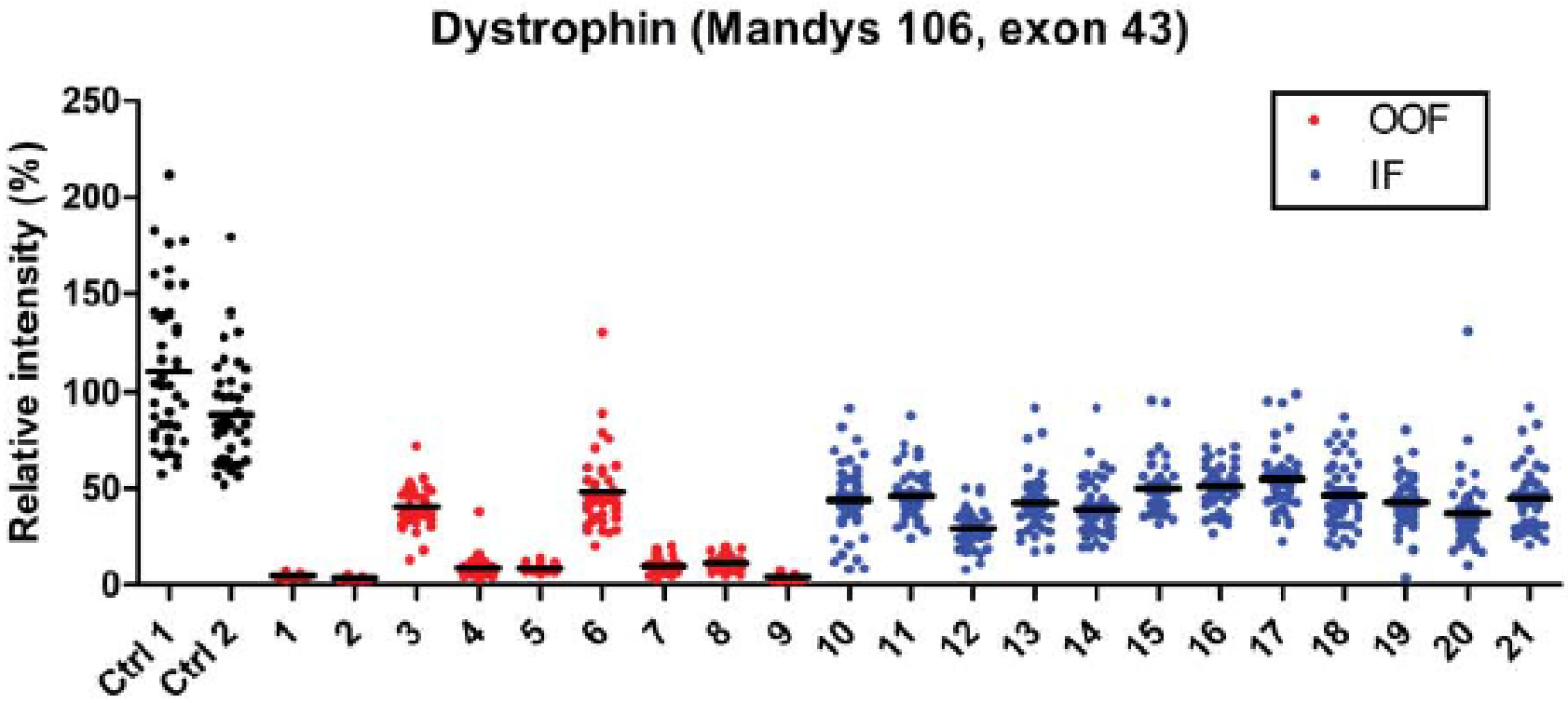
THANK YOU TO THE STUDY PARTICIPANTS AND THEIR FAMILIES

Backup Slides Shown

Figure 7: 10 m walk/run vs 6MWD, by individual patient, Italian natural history cohort



Comparative Immunohistochemical Analysis of Dystrophin Protein Expression in Patients With IF or OOF *DMD* Deletions Around Exons 44 and 45



Anthony et al., 2013 JAMA Neurology