Washington State Health Care Authority

Exondys 51® Clinical Policy

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Clinical Quality and Care Transformation
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Washington State Health Care Authority

Overview

- Review of Exondys51
- Review of FDA findings
- Recommended changes to the policy

Exondys 51® (eteplirsen)

- Eteplirsen is an antisense oligonucleotide that binds to exon 51 of the dystrophin mRNA, blocking its translation during protein synthesis. This 'skipping' allows for production of internally truncated dystrophin proteins[4].
  - Approximately 13% of patients have DMD genes that are amenable to exon 51 skipping[5].
- Eteplirsen is administered by intravenous infusion at a dose of 30 mg/kg per week[4]. There is no defined end-point for when to stop therapy.

Exondys 51® (eteplirsen)

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EXONDYS 51™ safely and effectively. See full prescribing information for EXONDYS 51.

EXONDYS 51 (eteplirsen) injection, for intravenous use
Initial U.S. Approval: 2016

INDICATIONS AND USAGE

EXONDYS 51 is an antisense oligonucleotide indicated for the treatment of Duchenne muscular dystrophy (DMD) in patients who have a confirmed mutation of the DMD gene that is amenable to exon 51 skipping. This indication is approved under accelerated approval based on an increase in dystrophin in skeletal muscle observed in some patients treated with EXONDYS 51 *[see Clinical Studies (14)]*. A clinical benefit of EXONDYS 51 has not been established. Continued approval for this indication may be contingent upon verification of a clinical benefit in confirmatory trials. (1)

Dystrophin Positive Fibers - Study 201/202

- 12 patients were randomized (4 in each arm) to receive 30 mg/kg/week vs. 50 mg/kg/week vs. placebo x 24 wk; then 4 patients in the placebo group were divided and assigned to 30 mg or 50 mg/kg/week for an additional 24 weeks
- Patients underwent muscle biopsies at baseline and weeks 12, 24, 48, 11 of 12 also received a 4th biopsy at 180 weeks.

Study 201/202 - Results

- **Dystrophin-positive fiber levels:**
  - Subjects in the 30mg/kg/wk cohort and 50mg/kg/wk cohort were evaluated at 48 weeks and found to have a statistically significant increase in dystrophin-positive fibers compared to pretreatment ($p < 0.001$)
  - Subjects in the placebo cohort randomized to receive either 30mg/kg/wk or 50mg/kg/wk at 24 weeks and were evaluated at 48 weeks and found to have a statistically significant increase in dystrophin-positive fibers compared to pretreatment (mean: 37.7%, range: 28.4% to 55.1%, $p < 0.008$)
  - *"Substantial increases in dystrophin in Study 201 were initially reported in a publication, which stated '…percentage of dystrophin-positive fibers was increased to 23% of normal; no increases were detected in placebo-treated patients ($p \leq 0.002$). Even greater increases occurred at week 48 (52% and 43% in the 30 and 50 mg/kg cohorts respectively…' "*

Re-analysis of first 3 biopsies using blinded reviewers

- 50mg/kg arm: mean percent change in DPF increased from 15% at baseline to 17% at week 12, and 25% at week 48
- Placebo to 50mg/kg/week: no increase in percent DPF between baseline and week 48.
- No difference between 50mg/kg/week vs placebo at week 12
- 30mg/kg/week significantly higher than placebo at week 24
- "*However, the nominal p-value (0.002) for the comparison between eteplirsen 30mg/kg group and the placebo group can only be considered exploratory, as there was no plan to control the type-1 error due to multiple comparisons, and because the other primary endpoint comparison between the 50mg/kg group and placebo was negative.*"

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Study 201 Immunofluorescence results for first three muscle biopsies (% positive fibers)

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

Study 201/202 – Western Blot

- "…the Western blots from first 3 biopsies had over saturated bands, did not have appropriate controls or quality control metrics and were essentially uninterpretable."

Study 201/202 – External Controls

- Of the 3 patients that had available base-line samples, only two had a biopsy at week 180 (patient 13 and patient 15)
- Week 180 biopsy (n=11) were compared to three eteplirsen-treated patients and 6 external controls
  - untreated controls 1% DPF
  - 3 eteplirsen patient had 1.1%, 2.6%, 0.2% DPF at baseline (original analysis 11.7%, 17%, 18.9% at baseline)
- The mean dystrophin level after about 3.5 years (week 180) was 0.93%.

Study 201/202 – External Controls cont'd

- **Week 180 biopsies came from the deltoid while biopsies for the external controls and preserved baseline muscle samples came from the biceps in all but one patient.**
  - **Deltoid and calf muscles are known to atrophy in DMD**
- ***"It is not clear to what extent differences in the dystrophin expression between muscle groups may have contributed to the change in dystrophin reported in the 4th biopsy."***
- **Untreated controls in the fourth biopsy were not selected at random they came from the ongoing eteplirsen phase 3 trial confirmatory study 4658-301**

PROMOVI

- **Type:** non-randomized, open-label, untreated control arm
- **Treatment groups: Eteplirsen** 30 mg/kg/week in DMD patients amenable to exon 51 skipping vs. untreated group of DMD patients not amenable to exon 51 skipping
- **Demographics:** N = 13 (still enrolling)
- **Endpoints:** 48 weeks and ongoing
- **Inclusion:** male 7-16 years old; diagnosed with DMD; stable dose of corticosteroids for at least 24 weeks; intact right and left alternative upper muscle groups; mean 6MWT greater than 300m; stable pulmonary and cardiac function; predicted FVC equal to or greater than 50% and LVEF of greater than 50%
- **Exclusion:** previous treatment with any gene therapy within the last 6 months; previous treatment with any RNA antisense agent; major surgery within 3 months; presence of clinically significant illness

PROMOVI - Results

- Western blot analysis between baseline and week 48 showed an increase from a mean of 0.16% to a mean of 0.44% of healthy normal subjects
- Change in a mean 0.28% (p=0.008).
- Most patients ~60% had no increase in dystrophin levels or an increase less than detectable (<0.25%)
- One patient had an increase in dystrophin greater than 1%
- No patient had an increase in dystrophin greater than 2%

Effect on Functional Status

- Study 201: secondary endpoint was change in 6MWT from baseline to week 24
- Study 202: comparison of 6MWT at week 48 between patients originally randomized to eteplirsen vs. those originally randomized to placebo

6MWT Results - Study 201/202

- **Study 201:**
  - **no statistically significant difference on the change from baseline to week 24 in the 6MWT between eteplirsen 50mg/kg/wk, 30mg/kg/wk, or placebo**
- **Study 202:**
  - **No statistically significant difference in the 6MWT between eteplirsen treated patients and placebo**
  - **3 patients in the 30mg/kg group were unable to ambulate soon after study initiation and were excluded from the analysis**

6MWT Study 202 Post-Hoc

- Post Hoc analysis looking at the 6 patients able to ambulate compared to the placebo-eteplirsen group
  - *"48 weeks of treatment with eteplirsen resulted in an unprecedented and clinically meaningful 67.3 meter clinical benefit on the 6MWT compared to placebo for 24 weeks followed by eteplirsen for 24 weeks."*
- However, FDA determined no evidence of clinical benefit
  - Post-hoc analysis
  - post- randomization exclusion of two patients that lost ambulation
  - Challenges with bias from open-label design

Study 202 participants compared to DMD Registry

- Post-hoc comparison of patients in study 202 (up to week 144) to a natural history cohort of untreated patients from the "Italian DMD Registry" and the "Leuven Neuromuscular Reference Center" registry
- 13 external controls were matched on:
  - Corticosteroid use at baseline (use/non-use)
  - Sufficient longitudinal data for 6MWT available (Y/N)
  - Age ≥ 7 years (Y/N)
  - Genotype amenable to any exon skipping therapy (Y/N)
  - Genotype amendable to exon 51 skipping therapy (Y/N)
- Patients did not have to match for baseline 6MWT distance

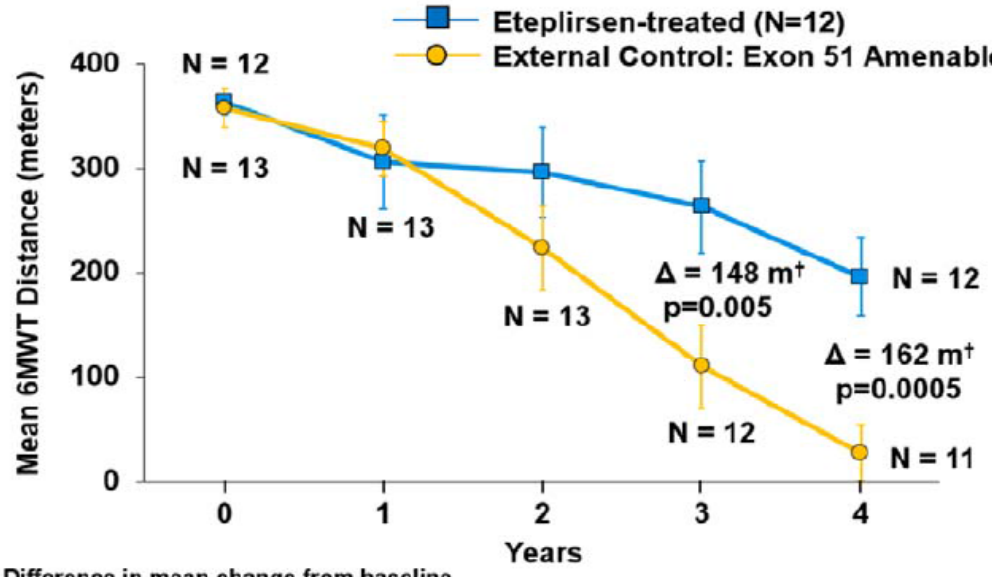
Study 202 participants compared to DMD Registry

- Baseline characteristics between eteplirsen-treated patients and external controls were reasonably well matched by:
  - Age
  - Height
  - Weight
- Areas of concern:
  - mean age of initiation of corticosteroid therapy was 1 year older in the control group compared to eteplirsen group (6.4 years vs 5.2 years)
  - Many control group subjects were on sub-optimal steroid regimens
  - North Star Ambulatory Assessment (NSAA) scores at baseline were lower in the control group

Study 202 vs DMD Registry - Results

Reported highly statistically significant difference of 162 meters ($p<0.0005$) between eteplirsen treated patients compared to external control

Figure 2: Mean 6MWT Distance over Time in Eteplirsen-Treated Patients vs. External Controls (copied from applicant's Advisory Committee Briefing materials, page 64)



†Difference in mean change from baseline
Patients who lost ambulation contributed a score of 0 to the mean
1 EC Subject was missing data at Year 3 & 4, 1 EC Subject was missing data at Year 4 only

Study 202 vs DMD Registry - Concerns

- Identification of the registries and selection of the control group occurred 3 years after completion of Study 201/202
- Differences in disease severity at baseline could effect outcomes
- Interventional clinical trials were enrolling DMD patients during the same period of the observational study. Patients in the observational study who qualified to enroll in the clinical trial may have dropped out of the observational study
- Considerable overlap between the 6MWT results for eteplirsen-treated patients and external controls

Figure 3: 6MWT distance vs. duration of observation in eteplirsen-treated patients in Study 201/202 and external control from the "Italian DMD Registry" and the "Leuven Neuromuscular Reference Center" registry (copied from Dr. Farkas' review)

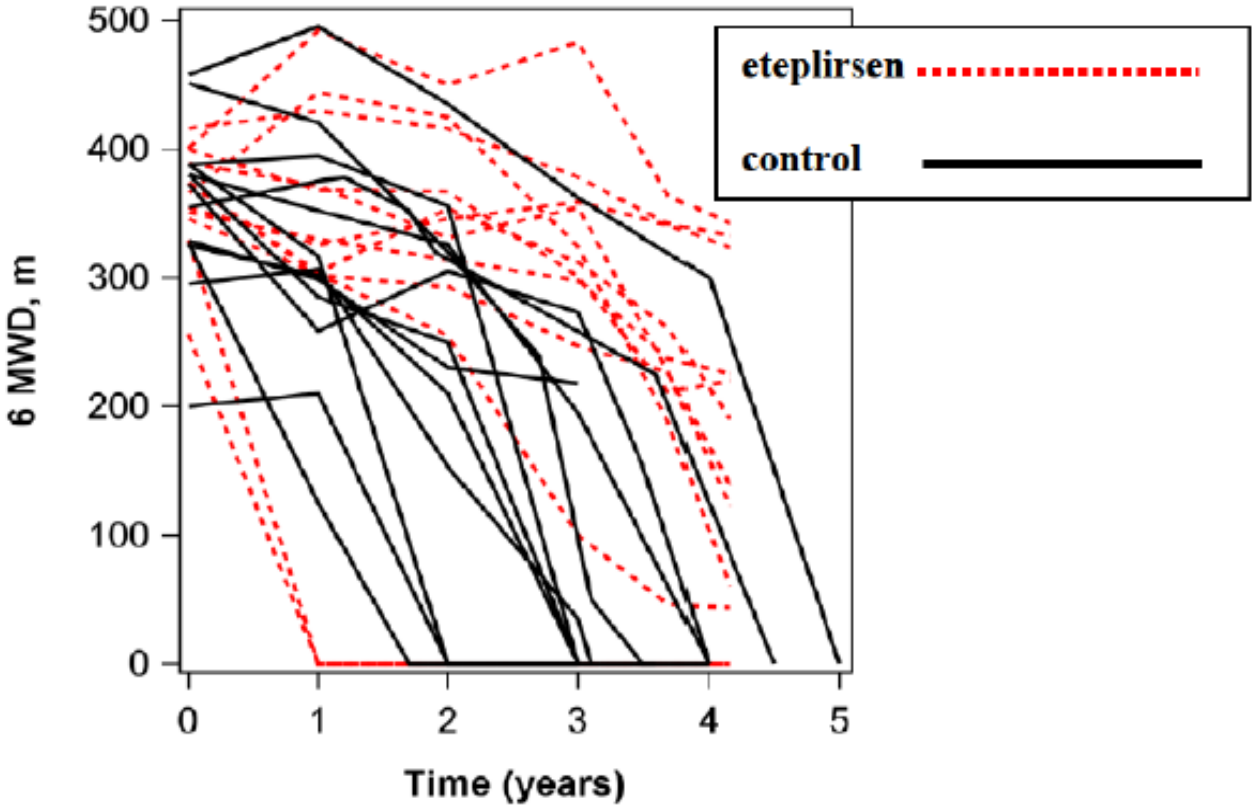
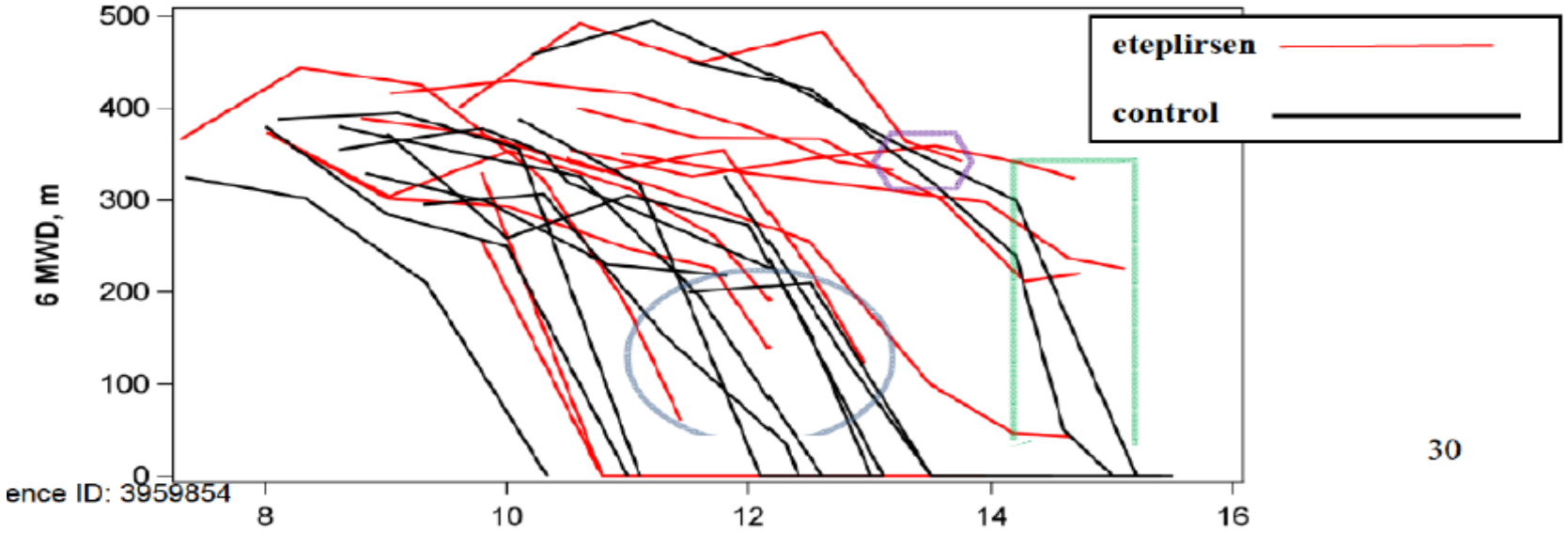


Figure 4: 6MWT distance vs. age in eteplirsen-treated patients in Study 201/202 and external control from the "Italian DMD Registry" and the "Leuven Neuromuscular Reference Center" registry (adapted from Dr. Farkas' memo)



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It is noteworthy that, although only two eteplirsen-treated patients have lost ambulation by the time of data cutoff for NDA submission, four patients younger than age 14 at the time of their last observations (identified by a blue oval shape on Figure 4) appear to have a disease course extremely close to that of controls of similar age, and appear very likely to be on a path to loss of ambulation before or by age 14 (in fact, one of them recently did, as reported in a data update submitted by the applicant after the April 25 Advisory Committee meeting, and another patient has a 6MWT distance of 31 meters, which, as discussed below, would be considered as loss of ambulation in the registry studies). Two eteplirsen-treated patients (identified in the purple hexagon of Figure 4), still ambulatory after age 13, but having not yet reached age 14 at the time of their last observations, appear to have a course no different than the two control patients still ambulatory at age 14.

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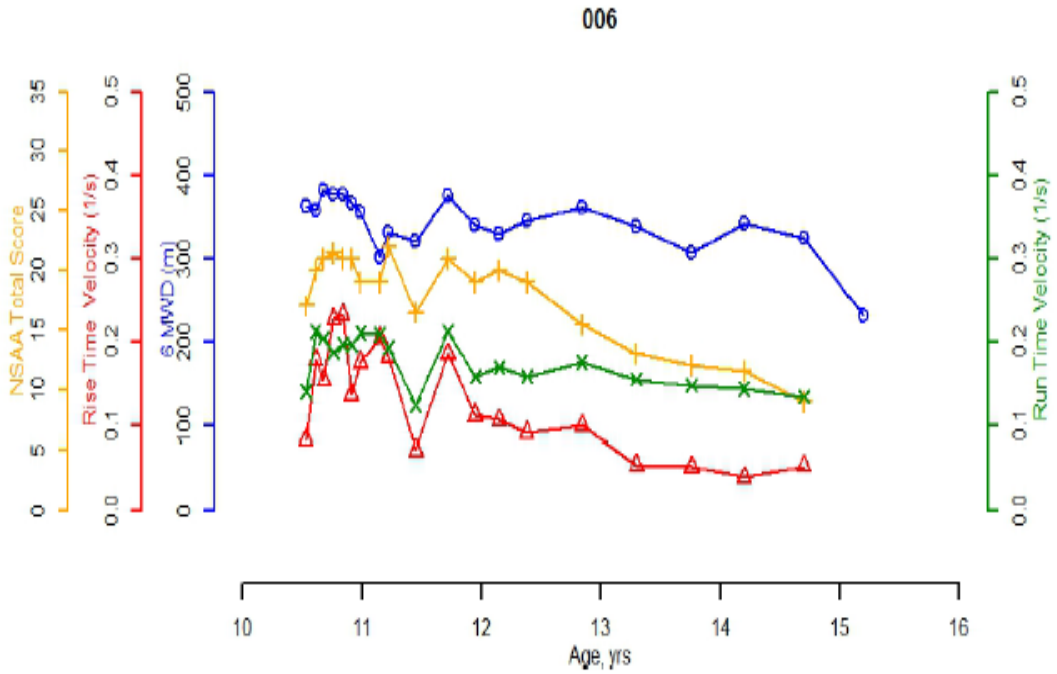
Review of eteplirsen-treated patient with highest 6MWT after age 14

Figure 5: Clinical profile of Patient 006



- Eteplirsen 30mg/kg
- highest 6MWT after age 14
- Marked decline in NSAA starting about age 12.5 years.
- Rise time velocity is slowly but steadily decreasing (> 20 seconds at last observation)
- Decline of 80 meters in 6MWT from week 216 to week 240
- Dystrophin by Western blot at week 180 was 2.47% of normal
- No baseline sample retained so cannot tell if this is an increase from baseline

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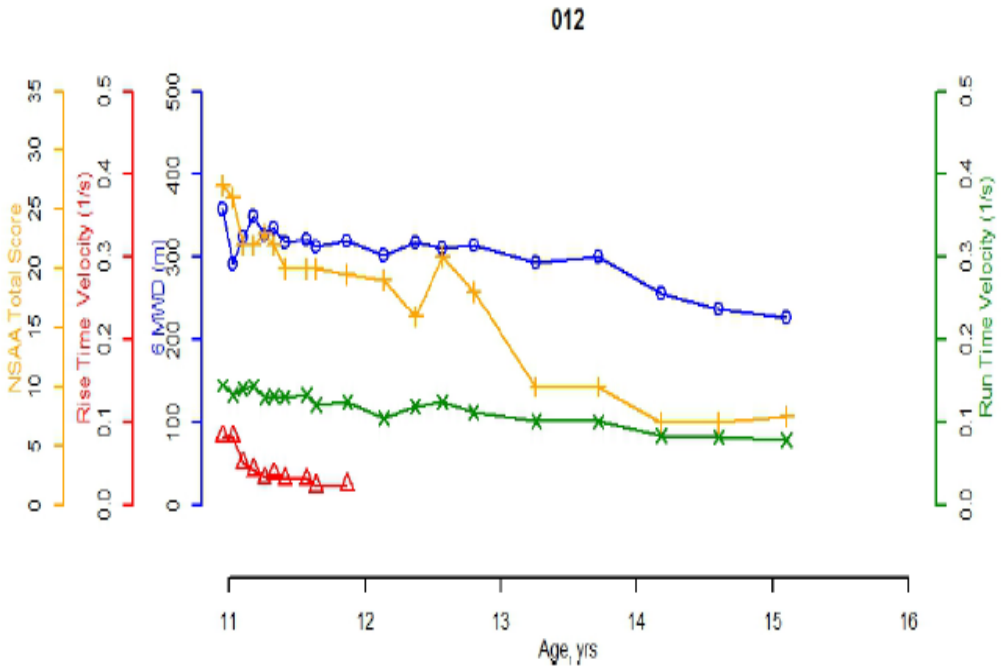
Review of eteplirsen-treated patient with second highest 6MWT after age 14

Figure 6: Clinical Profile of Patient 012



- Eteplirsen 50mg/kg/wk
- Second highest 6MWT after age 14
- Marked decline in NSAA at age 12.5 years
- Lost ability to rise at age 12
- Week 240 6MWT distance unknown due to femur fracture
- Dystrophin by Western blot at week 180 was 0.375% of normal
- Baseline is unknown

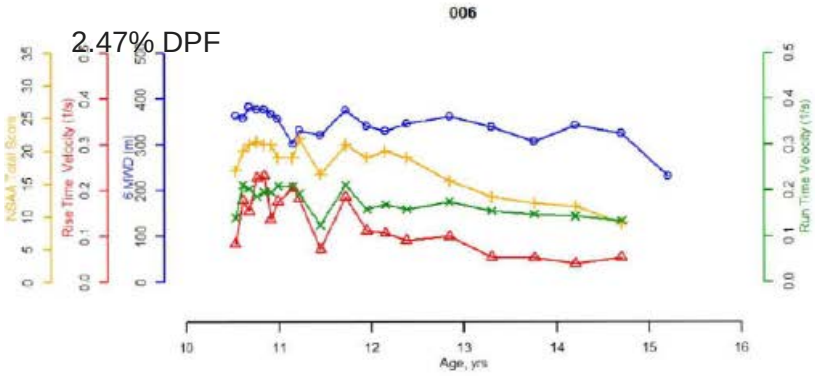
180 in Patient 006 was 0.375% of normal. The low level of dystrophin in this patient assessed at Week 180 does not suggest that eteplirsen could have produced any significant amount dystrophin for this patient (who was on the highest dose of eteplirsen tested), and that the maintenance of relatively high 6MWT distance values at age 15 is not related to a drug effect, and instead illustrates the variability in the natural history of DMD.

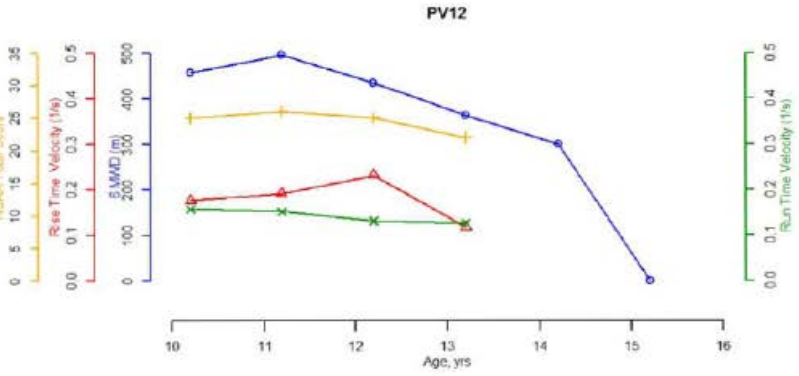
Patient 6 and Patient 12

For Patient 006 and Patient 012, the similarity in 6MWT distance, NSAA, and Run Time between age 11 years and age 15 years is striking (Figure 7). While Patient 006 had one of the highest dystrophin levels observed in eteplirsen-treated patients, Patient 012 had one of the lowest, in fact barely above the limit of quantification. These two patients illustrate that the temptation to assign the relative stability of Patient 006 to his dystrophin level must be restrained by the very similar progression of Patient 012 who, in fact, had extremely low dystrophin. That concern is reinforced by similar observations in other patients, as will be described below. In addition, a comparison with matched patients from the historical cohort (Patient PV12 and KB) shows that the course of Patient 006 and 012 is not exceptional for a DMD patient, and is compatible with the natural history of the disease (Figure 7). Specifically, the comparison of eteplirsen-treated Patient 006 to historical control Patient PV12, who both entered the study or registry around age 10 years and a half, shows the following:

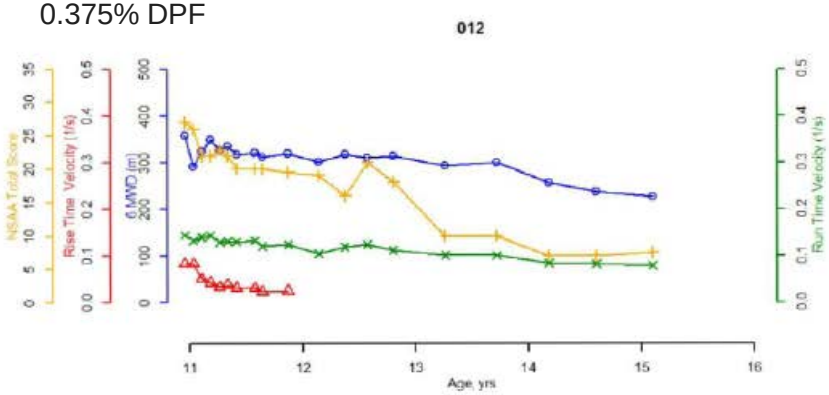
Figure 7: Comparison of Patient 012 and Patient 006 (from Study 201/202) with each other, and with Patient PV12 and KB from the historical patient registries

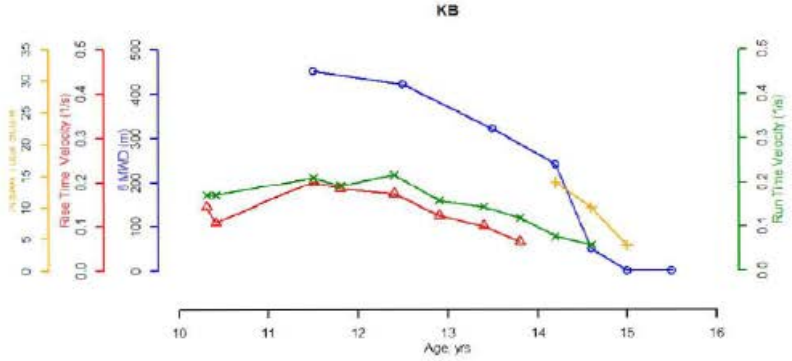
2.47% DPF





0.375% DPF

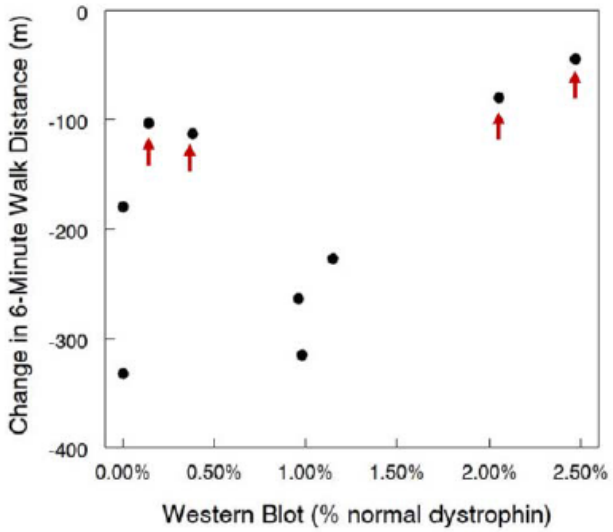




This detailed comparison of Patient 006 (the best performing patient of Study 006 up to age 14 years and a half) with Patient PV12 illustrates that the overall course of the disease is very similar in both patients, and that the course of Patient 006 is clearly within the boundaries of DMD natural history. This alone, in my opinion, is nearly sufficient to reject that a historical control design is capable of establishing the efficacy of eteplirsen, as the best performing eteplirsen-treated patient, in Study 201/202, does not have a course clearly different from natural history.

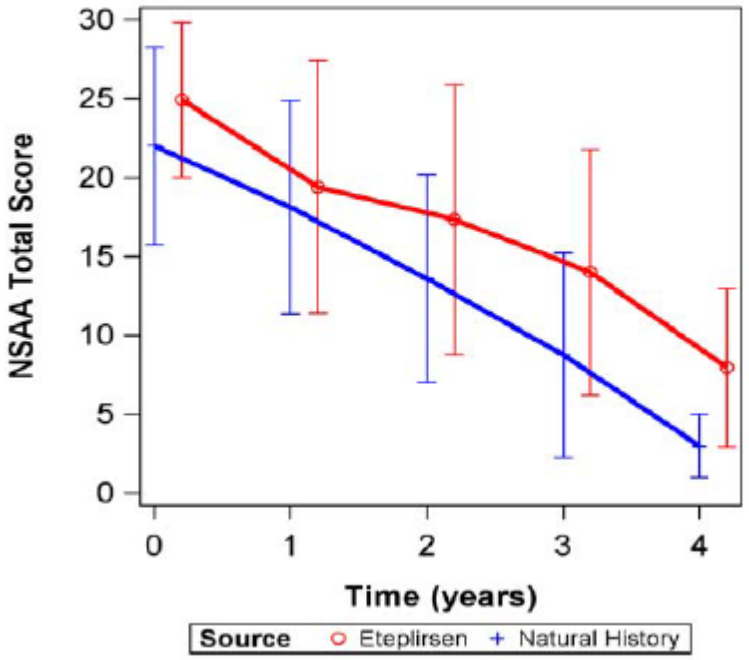
Correlation between dystrophin and clinical outcome Study 201/202

Figure 13: Change in 6-minute walk distance (Week 180 minus Baseline) versus dystrophin level as determined by Western blot Study 201/202. (Two patients who lost ambulation are omitted.)



If production of dystrophin protein is reasonably likely to predict clinical benefit, one would expect a correlation between the level of dystrophin and ambulation in eteplirsen-treated patients. In Study 201/202, there were too few patients to perform a rigorous analysis. But for the nine patients who were able to ambulate and had a biopsy at Week 180, it is apparent that for the four patients whose 6MWT distances were best preserved, two had very low levels of dystrophin, and two had the highest levels. Thus, there is no apparent correlation between 6MWT and dystrophin levels in eteplirsen-treated patients (Figure 13).

Figure 12: Mean NSAA scores over time



It is also remarkable that mean NSAA values over time show a very similar decline in eteplirsen-treated boys and external controls. As illustrated in Figure 12, patients in the external control group had a worse mean NSAA score at baseline, suggesting a worse prognosis in these patients. The curves are then similar over time, with large overlaps in confidence intervals.

Other Potential Sources of Bias

- No boy in the Belgian or Italian registry had a rise time greater than 22 seconds, whereas 2/3 of the eteplirsen group did some as long as 40 seconds
- Boys in the eteplirsen group that reached a certain rise time were allowed to receive external support for the test which was not known to the review team up to the advisory committee meeting, and was NOT specified in the protocol.
- Some boys in the Belgian or Italian registry had recorded 10-meter run/walk results and at the same time were declared unable to ambulate. **The FDA learned that it was standard in the control protocols to categorize a patient as non-ambulatory if they could not finish the 6MWT.**
- Eteplirsen patients had two opportunities on consecutive days to perform the functional tests, whereas the natural history patients had only one.

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Other Potential Sources of Bias

Subsequent to the release of the previous version of this memo, FDA has determined that for at least two or three[46] of the 13 exon-51 skippable natural history patients selected by the applicant as controls, a value of zero was recorded for 6-minute walk distance apparently prior to loss of ambulation as documented by ability to perform the 10 meter walk/run test. Similar discordance between 6MW distance and 10 m walk/run was identified for at least 6 patients in the group of external control patients. Importantly, for both the exon-51 skippable patients and larger group of external controls, 10 m walk/run data were not available for many patients, limiting ability to assess discordance of results.

The applicant has recently provided FDA with source documents from the clinical sites for this patient and the other historical controls. These documents appear to indicate that at a follow-up visit 6 months later, 6MWT was not attempted because the patient was judged to be unable to walk. At the next visit 6 months later (1 year after the 327 m was recorded), a 6MWT was attempted, with the patient walking 125 m in about 3½ minutes. The examiner at the time noted that the patient "no longer wanted to continue (could still continue, had back pain)." *The examiner's comment appears to underscore the importance of motivation in 6MWT.*

Other Potential Sources of Bias

- In the study manual 6MWT evaluators were encouraged to walk along directly behind the patient at a distance of about 2 meters, giving positive verbal encouragement at approximately 15 second intervals. Encouragement should be similar to any of the following phrases: "You're doing a great job (participant name)! Keep it up!," Remember walk as fast as you can!," "Fantastic job (participant name), Keep going!," or "Keep up the good work!".
- The manual also stated that if the patient fell or could not rise from the floor, the test was over and the distance should be recorded. On the other hand the protocols for the historical controls were very scant and included no time how rise time test was to be performed, **no mention with respect to encouragement during performance of the 6MWT, and no discussion about the situations under which boys should be declared unable to perform the test without even attempting it.**

g. Conclusions, Clinical Endpoints

In the context of the above, the major conclusions with regard to clinical endpoints are listed below:

1. The natural history of DMD in patients amenable to exon 51 skipping has been characterized in a number of observational natural history studies and controlled trials, and the range of age at loss of ambulation is very wide, currently between about 8 and 18 years for most patients. Eteplirsen patients have experienced a sequential loss of ambulatory abilities and increasing muscle weakness, as measured by rise time from floor, NSAA, 6MWT, and other tests. In the context of this considerable variability among patients, the clinical course of eteplirsen patients over more than 3 ½ years of treatment with eteplirsen has been generally similar to expected natural history of patients provided with intensive supportive care.

Cross discipline team lead reviewer

Overall Conclusions

The overall conclusion of this review is that the applicant has not provided the substantial evidence of effectiveness required by law [see 21 CFR 314.126(a)(b)] to support approval, based on either endpoints measuring clinical benefit, or biomarker endpoints that might be considered reasonably likely to predict benefit under accelerated approval provisions.

Dystrophin protein could be considered under the accelerated approval provisions as a biomarker endpoint reasonably likely to predict benefit in DMD, but the amount, localization, and functionality would be key considerations. There is some evidence that eteplirsen increases the expression of a functional Becker-type dystrophin protein, to a level ≈1% of normal, but the evidence is less than the amount that is generally considered "substantial evidence." Additional independent substantiation of dystrophin production would be necessary to reach the level of evidence generally considered substantial evidence.

The amount of Becker-type dystrophin that may be produced by eteplirsen, ≈1% of normal, is low enough that a conclusion that the amount would be reasonably likely to predict clinical benefit would have to be based on a low threshold for reasonably likely. The level is well within the range of dystrophin levels of untreated DMD patients, and appears to be substantially lower than dystrophin levels in patients with less severe forms of dystrophinopathy.

Determination Of Medical Necessity

(6) The agency uses the following processes to determine whether a requested service described in subsection (1) is medically necessary:

(a) **Hierarchy of evidence - How defined.** The agency uses a hierarchy of evidence to determine the weight given to available data. The weight of medical evidence depends on objective indicators of its validity and reliability including the nature and source of the evidence, the empirical characteristics of the studies or trials upon which the evidence is based, and the consistency of the outcome with comparable studies. The hierarchy (in descending order with Type I given the greatest weight) is:

(i) Type I: Meta-analysis done with multiple, well-designed controlled studies;

(ii) Type II: One or more well-designed experimental studies;

(iii) Type III: Well-designed, quasi-experimental studies such as nonrandomized controlled, single group pre-post, cohort, time series, or matched case-controlled studies;

(iv) Type IV: Well-designed, nonexperimental studies, such as comparative and correlation descriptive, and case studies (uncontrolled); and

(v) Type V: Credible evidence submitted by the provider.

Determination of Medical Necessity

(i) **"A" level evidence:** Shows the requested service or equipment is a proven benefit to the client's condition by strong scientific literature and well-designed clinical trials such as Type I evidence or multiple Type II evidence or combinations of Type II, III or IV evidence with consistent results (An "A" rating cannot be based on Type III or Type IV evidence alone).

(ii) **"B" level evidence:** Shows the requested service or equipment has some proven benefit supported by:

(A) Multiple Type II or III evidence or combinations of Type II, III or IV evidence with generally consistent findings of effectiveness and safety (A **"B"** rating cannot be based on Type IV evidence alone); or

(B) Singular Type II, III, or IV evidence in combination with agency-recognized:

(I) Clinical guidelines;

(II) Treatment pathways; or

(III) Other guidelines that use the hierarchy of evidence in establishing the rationale for existing standards.

(iii) **"C" level evidence:** Shows only weak and inconclusive evidence regarding safety, or efficacy, or both. For example:

(A) Type II, III, or IV evidence with inconsistent findings; or

(B) Only Type V evidence is available.

(iv) **"D" level evidence:** Is not supported by any evidence regarding its safety and efficacy, for example that which is considered investigational or experimental.

Determination of Medical Necessity

(c) **Hierarchy of evidence - How applied.** After classifying the available evidence, the agency:

(i) Approves **"A"** and **"B"** rated requests if the service or equipment:

(A) Does not place the client at a greater risk of mortality or morbidity than an equally effective alternative treatment; and

(B) Is not more costly than an equally effective alternative treatment.

(ii) Approves a **"C"** rated request only if the provider shows the requested service is the optimal intervention for meeting the client's specific condition or treatment needs, and:

(A) Does not place the client at a greater risk of mortality or morbidity than an equally effective alternative treatment

(B) Is less costly to the agency than an equally effective alternative treatment; and

(C) Is the next reasonable step for the client in a well-documented tried-and-failed attempt at evidence-based care.

(iii) Denies **"D"** rated requests unless:

(A) The requested service or equipment has a humanitarian device exemption from the Food and Drug Administration (FDA); or

(B) There is a local institutional review board (IRB) protocol addressing issues of efficacy and safety of the requested service that satisfies both the agency and the requesting provider.

Requests for Exondys 51®

- I move that the Medicaid program determine the medical necessity for use of Exondys 51® to treat DMD on a case by case basis using our medical necessity criteria

Motion: Johnson

2nd: Flatebo

Passed, 1 opposed

- Exondys 51® will be carved out of the MCO contracts and paid for by the HCA Medicaid program.

Citations

1. Breder CD, Farkas RH. NDA 206488 Sarepta eteplirsen DMD. Clinical Review. Center for Evaluation and Research. US Department of Health & Human Services. May 9, 2016.

Questions?

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