Eteplirsen Delays Time to Loss of Ambulation in Patients With Duchenne Muscular Dystrophy Compared With Patients Receiving Standard of Care

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BACKGROUND

- Duchenne muscular dystrophy (DMD) is a severe, X-linked neuromuscular disease caused by mutations in the *DMD* gene[1]
- The most common mutations are deletions flanking exon 51, which account for 13% of all DMD patients[2]
  - Eteplirsen (EXONDYS 51®; Sarepta Therapeutics, Inc.) is indicated for the treatment of DMD in patients who have mutations amenable to exon 51 skipping
- Previous analyses reported slower declines in ambulation in 12 eteplirsen-treated patients compared with natural history controls[3]
- Additional data has since accrued for a larger number of eteplirsen-treated patients, allowing for a more comprehensive assessment of delay in long-term functional milestones, such as loss of ambulation (LOA)
- LOA is a critical milestone in DMD, marking progression to a disease stage associated with greater disability and cost[4,5]
  - A recent study estimated total average annual costs were £47,160 ($74, 385 USD) in the early non-ambulatory stage of the disease, compared with £30,950 ($48,817 USD) in the late ambulatory stage
- In this post hoc analysis, we assessed time to LOA, which was defined as the ability to perform the 6-minute walk test (6MWT)

OBJECTIVE

- To compare the time to LOA between patients with DMD treated once weekly with intravenous eteplirsen 30 or 50 mg/kg and patients with DMD receiving standard of care (SOC) treatment (eg, glucocorticoids, TREAT NMD guidelines)

METHODS

Data sources

- Data were obtained for DMD patients with exon 51–skippable mutations (**Table 1**)

Table 1. Data sources

Source	Description	N
Standard of care		**72**
DEMAND III Study[6]	Placebo arm data from a 48-week, randomized, double-blind, placebo-controlled, phase 3 trial of drisapersen in boys with DMD with mutations amenable to exon 51 skipping	60
Telethon	Natural history data from the Fondazione Telethon DMD Italian Network Registry, a database of tertiary care centers in Italy	9
Leuven	Natural history data from routine clinical care of patients at the pediatric neurology clinic at the Leuven Neuromuscular Reference Center in Leuven, Belgium	3
Eteplirsen		**83**
Sarepta Study 301[7]	Eteplirsen-treated patients from PROMOVI, an ongoing, open-label efficacy study of eteplirsen in DMD patients	71
Sarepta Studies 201/202[8]	Eteplirsen-treated patients from the initial pivotal study of eteplirsen in DMD	12

Statistical analyses

- LOA was defined as loss of the ability to complete the 6MWT (6MWT=0)
- Time to 6MWT=0 was compared between eteplirsen-treated patients and patients receiving SOC treatment, using Kaplan-Meier analyses and log-rank tests
- A parametric survival regression model using a Weibull distribution was used to estimate the association between treatment groups and time to occurrence of 6MWT=0, adjusting for baseline differences between groups
  - The Weibull model allows for description of treatment effects in terms of the treatment-associated relative increase or decrease in event time[9,10]
  - It offers a directly interpretable, easy to understand estimate of the extent to which treatment slows disease progression
  - As a parametric survival model, the Weibull model also allows for further extrapolation of the time-to-event curves beyond the observed range of follow-up time
- Using this regression-based approach, models were adjusted for baseline age and baseline 6MWT, and included interactions of both baseline age and 6MWT with treatment group

METHODS continued

- Adjusted, model-based projections were obtained for:
  - Median time to 6MWT=0 in each group and the difference between groups
  - The proportion of patients by group with 6MWT>0 after 1, 2, 3, and 4 years

RESULTS

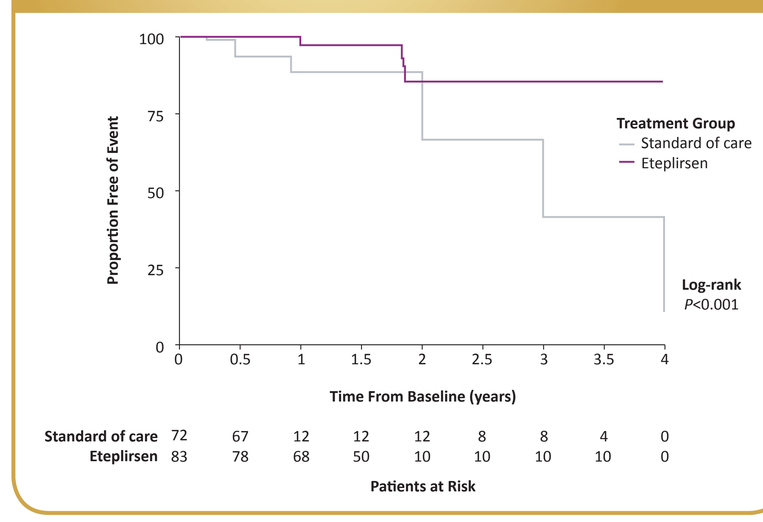
Sample characteristics

- The analyses included 83 eteplirsen-treated patients and 72 SOC patients
- Median follow-up time was 1.13 years
- At baseline, compared with SOC patients, eteplirsen-treated patients, on average:
  - Were slightly older (mean age, 9.4 vs 8.6 years)
  - Had greater 6MWT distances (mean, 389 vs 351 meters) at baseline
- Seven eteplirsen patients and 15 SOC patients experienced 6MWT=0 over the course of follow-up

Kaplan-Meier analyses

- Eteplirsen was associated with significantly longer time (P<0.001) to 6MWT=0 than SOC in unadjusted Kaplan-Meier analyses (**Figure 1**)
- The observed median time to 6MWT=0 in the SOC group was 3 years; the median was not reached for the eteplirsen group

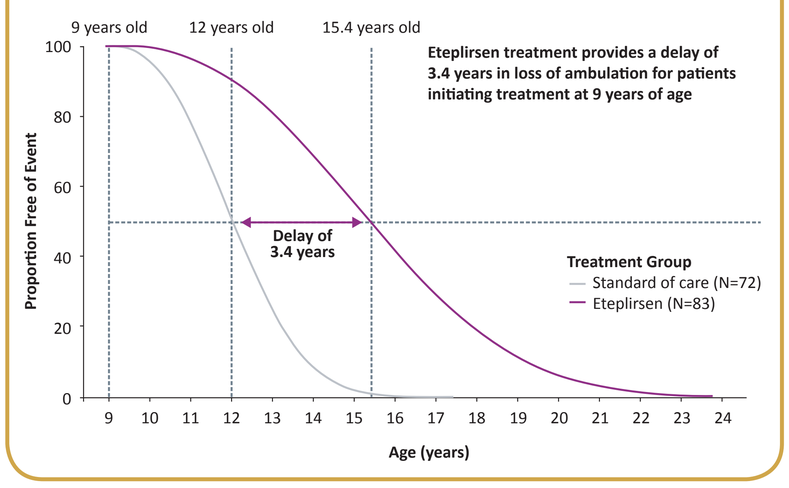
Figure 1. Time to loss of ambulation was longer in eteplirsen-treated patients vs SOC (Kaplan-Meier analysis)



Weibull analyses

- In Weibull analyses adjusted for baseline age and walking distance, eteplirsen was associated with 2.07 times longer time to 6MWT=0 than patients receiving SOC treatment (P=0.010) (**Figure 2**)
- For a patient with population-average baseline age and 6MWT (age, 9.0 years, 6MWT, 371.4 meters), this corresponds to a projected delay in median time to 6MWT=0 of 3.4 years (6.5 vs 3.1 years) in eteplirsen-treated vs SOC patients

Figure 2. Eteplirsen treatment was associated with a longer time to loss of ambulation compared with SOC (Weibull analysis)

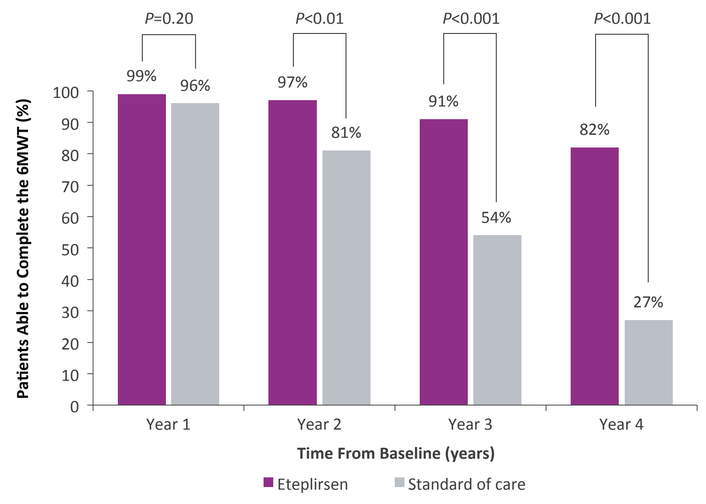


- Based on model-based projections, 27% of patients receiving SOC treatment are able to complete the 6MWT after 4 years compared with 82% of patients receiving eteplirsen, which is a 3-fold increase (P<0.001) (**Figure 3**)

CONCLUSIONS

- Based on the most current and comprehensive follow-up data with adjusted comparisons to SOC treatment, eteplirsen was associated with significant and clinically meaningful delays in time to loss of ambulation
- These delays associated with the use of eteplirsen potentially have important implications for DMD patients. Studies indicate that such delays are associated with delays in other disease milestones, including scoliosis,[11] the need for ventilation, and survival,[12,13] and with lower costs[5]

Figure 3. Significantly more eteplirsen-treated patients were able to complete the 6MWT after 4 years compared with SOC



Study limitations

- The comparisons conducted here are between non-randomized treatment groups, and results may be confounded by unobserved or unadjusted baseline differences between the groups
- Duration of follow-up for most patients included in this analysis was approximately 1 year; longer-term follow-up data are needed to confirm these findings

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