#P79

# Association Between Exon-Skipping Therapy With Eteplirsen and Cardiac Outcomes in Duchenne Muscular Dystrophy

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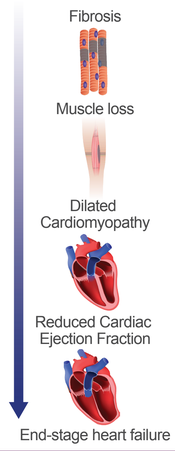
## Background

- Duchenne muscular dystrophy (DMD) is caused by mutations in the *DMD* gene that result in the absence of functional dystrophin protein[1]

**Pathophysiology of DMD**




DMD leads to progressive decline in cardiac functions, development of dilated cardiomyopathy, and progression to terminal heart failure during the teenage years or young adulthood[1]

- Eteplirsen is a phosphorodiamidate morpholino oligonucleotide (PMO) approved for the treatment of patients with DMD with mutations amenable to exon 51 skipping[2]
- Studies quantifying the potential of eteplirsen to attenuate the decline in cardiac function for patients with DMD who are amenable to exon 51 skipping are lacking[3]

## Objectives

- This analysis evaluated and compared risk of reaching left ventricular ejection fraction (LVEF) thresholds indicative of cardiac function decline, and annual rate of decline in cardiac function via LVEF over time between eteplirsen-treated and natural history (NH) control patients with exon 51 skip-amenable DMD

## Methods

### Data sources

- The data for eteplirsen-treated patients were obtained from clinical trials performed at US-based clinical sites: Study 201 (NCT01396239),[4] Study 202 (NCT01540409),[4] Study 203 (NCT02420379),[5] Study 204 (NCT02286947),[6] and Study 301 (NCT02255552)[7]
- The data for control patients were obtained from the Cooperative International Neuromuscular Research Group DMD Natural History Study (CINRG-DNHS; NCT00468832),[8] a Prospective Natural History Study of Progression of Subjects With Duchenne Muscular Dystrophy (PRO-DMD-01; NCT01753804),[9] and the French DMD Heart Registry (NCT03443115)[10]
- Requirements for clinical trial and NH data sources included the availability of genotype information and patient baseline and medication characteristics related to cardiac function
- LVEF was the most systematically available and clinically relevant cardiac function measure across all data sets that could be compared directly

### Patient selection

- Inclusion criteria for patients with exon 51 skip-amenable DMD administered eteplirsen and/or standard of care treatment:
  1. Availability of LVEF at baseline and ≥1 post-baseline visit and
  2. Complete information on patient's age and use of concomitant medications, including cardiac medications and corticosteroids at the baseline visit
- Baseline visit was defined as the screening or initial treatment visit for eteplirsen-treated patients, and as the first visit with non-missing LVEF for NH control patients
- Patients with baseline LVEF <50% were excluded

### Study endpoints

- Time to reach LVEF threshold values of <50%, <55%, and <60%
- Rate of LVEF decline
- LVEF was measured by echocardiography; all studies from which data were drawn allowed for practitioners' choice to derive LVEF

### Statistical analyses

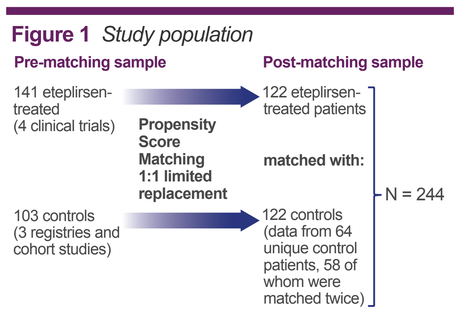
- Propensity score (PS) matching was conducted to mitigate patient differences from the use of multiple data sources and to align baseline characteristics and prognostic factors that potentially influence LVEF
- Each eteplirsen-treated patient (at their baseline visit) was matched with a control patient with the closest PS at a qualifying visit
  - Each control patient could be matched a maximum of two times
- Baseline characteristics used in this analysis were age, LVEF, prophylactic ACE inhibitor/ARB use prior to the first LVEF <50% event, and stable corticosteroid use
- Time-to-event and trajectory analyses were performed using Kaplan-Meier curves and linear mixed effects models (LMEM), respectively
- Cox proportional hazard models were used to evaluate the impact of eteplirsen on the risk of reaching LVEF decline thresholds
- Validation analyses evaluated potential sources of bias, including geographic imbalance, an E-value analysis, and a restricted mean survival time (RMST) analysis

## Results

### Study population and patient characteristics

- 122 eteplirsen-treated patients were matched with 122 NH controls (**Figure 1**)

**Figure 1** *Study population*




## Results *(cont)*

- Baseline characteristics were well-matched between the eteplirsen-treated and NH controls (**Table 1**)

**Table 1** *Baseline and matched characteristics*

| Characteristics | Pre-matched samples | | | Matched samples | | |
|---|---|---|---|---|---|---|
| | Eteplirsen-treated (n=141) | NH controls (n=103) | *P*-value | Eteplirsen-treated (n=122) | NH controls (n=122) | *P*-value |
| Age | 9.3 ± 3.2 | 9.1 ± 5.2 | 0.68 | 9.1 ± 3.1 | 9.6 ± 5.3 | 0.33 |
| LVEF | 68.1 ± 5.5 | 63.2 ± 7.4 | <0.01 | 67.4 ± 5.3 | 67.7 ± 5.9 | 0.70 |
| <50% | 0 (0.0) | 4 (3.9) | 0.02 | 0 (0.0) | 0 (0.0) | N/A |
| <55% | 1 (1.0) | 13 (12.6) | <0.01 | 1 (0.8) | 4 (3.3) | 0.18 |
| <60% | 8 (5.7) | 22 (21.4) | <0.01 | 8 (6.6) | 7 (5.7) | 0.79 |
| Prophylactic ACE/ARB | 66 (46.8) | 65 (63.1) | 0.01 | 62 (50.8) | 69 (56.6) | 0.37 |
| Prophylactic beta blocker or other cardiac medication | 25 (17.7) | 25 (24.3) | 0.21 | 24 (19.7) | 17 (13.9) | 0.23 |
| Stable corticosteroid[a] | 112 (79.4) | 47 (45.6) | <0.01 | 93 (76.2) | 84 (68.9) | 0.20 |

Values are mean ± SD or number (%).
ACE, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker; LVEF, left ventricular ejection fraction; NH, natural history.
[a]Defined as any type of corticosteroid medication, including prednisone, prednisolone, or deflazacort, recorded in ≥30% of visits over ≥18 months.

**Table 2** *Follow-up characteristics*

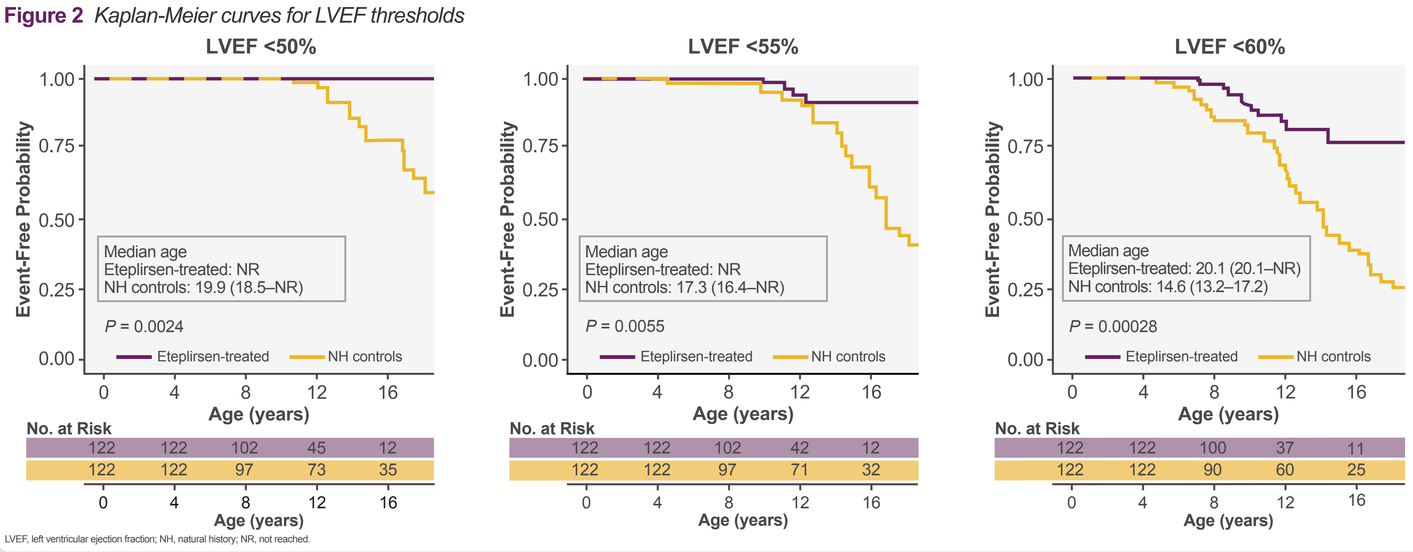
| Characteristics | Pre-matched samples | | Matched samples | |
|---|---|---|---|---|
| | Eteplirsen-treated (n=141) | NH controls (n=103) | Eteplirsen-treated (n=122) | NH controls (n=122) |
| Length of follow-up, months | 26.4 ± 9.4 | 118.7 ± 91.2 | 26.5 ± 9.7 | 69.3 ± 71.1 |
| No. of visits with LVEF recorded | | | | |
| Average | 6.3 ± 3.1 | 6.3 ± 3.8 | 6.4 ± 3.2 | 4.5 ± 3.0 |
| Minimum–Maximum | 3–16 | 2–15 | 3–16 | 2–13 |
| Duration between visits,[a] months | 4.9 ± 1.5 | 20.5 ± 20.4 | 4.9 ± 1.5 | 19.5 ± 21.1 |
| LVEF | | | | |
| <50% | 0 (0.0) | 39 (37.9) | 0 (0.0) | 27 (22.1) |
| <55% | 5 (3.6) | 52 (50.5) | 4 (3.3) | 33 (27.1) |
| <60% | 15 (10.6) | 73 (70.9) | 13 (10.7) | 60 (49.2) |

Values are mean ± SD or number (%).
LVEF, left ventricular ejection fraction; NH, natural history.
[a]With LVEF recorded.

### Time-to-event analysis

- Mean duration of follow-up was 26.5 months and 69.3 months among the 122 eteplirsen-treated and 122 NH controls, respectively (**Table 2**)
- In the pre-matched samples, no eteplirsen-treated patients reached LVEF <50% and the proportion of patients reaching <55% and <60% thresholds was significantly lower for eteplirsen-treated patients compared with NH controls (**Table 2**)
- In the matched cohort, no eteplirsen-treated patients and 22.1% of NH control patients reached LVEF <50%; 3.3% of eteplirsen-treated and 27.1% of NH controls reached LVEF <55%; and 10.7% of eteplirsen-treated and 49.2% of NH controls reached LVEF <60% (**Table 2**)
- The median age of reaching LVEF thresholds between eteplirsen-treated and NH controls is illustrated in **Figure 2**

**Figure 2** *Kaplan-Meier curves for LVEF thresholds*




LVEF, left ventricular ejection fraction; NH, natural history; NR, not reached.

- The hazard ratio (HR) for time to the first LVEF <55% event in eteplirsen-treated patients relative to matched NH controls was 0.22 (95% CI = 0.07–0.66; *P* < 0.01), and for LVEF <60% was 0.40 (95% CI = 0.22–0.76; *P* < 0.01), respectively, thus demonstrating a significantly lower risk of reaching LVEF thresholds among eteplirsen-treated patients relative to matched NH controls (**Table 3**)

**Table 3** *Multivariable Cox proportional hazard models*

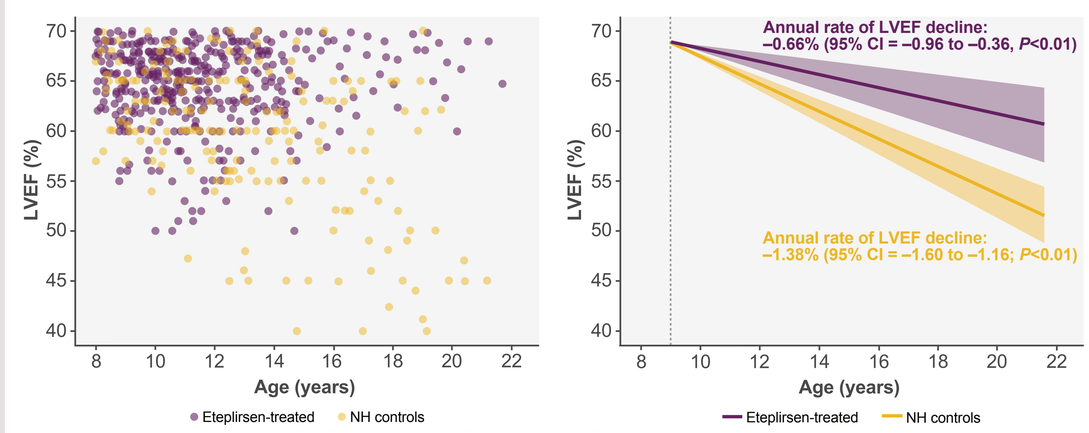
| | LVEF <55% | | LVEF <60% | |
|---|---|---|---|---|
| Variable in the model | HR (95% CI) | *P*-value | HR (95% CI) | *P*-value |
| Eteplirsen | 0.22 (0.07–0.66) | <0.01 | 0.40 (0.22–0.76) | <0.01 |
| Baseline age | 1.06 (0.99–1.14) | 0.11 | 1.04 (0.99–1.10) | 0.16 |
| Baseline LVEF | 0.82 (0.76–0.89) | <0.01 | 0.84 (0.79–0.89) | <0.01 |
| Prophylactic ACE/ARB | 1.22 (0.49–3.08) | 0.67 | 1.40 (0.77–2.51) | 0.27 |
| Stable corticosteroid[a] | 0.83 (0.32–2.16) | 0.70 | 0.77 (0.38–1.54) | 0.46 |

Note: The Cox model for the LVEF <50% is not reported due to limited events: no eteplirsen-treated patients reached this milestone; only three NH control patients reached this milestone within a similar (median or the third quantile) time period of follow-up as eteplirsen-treated patients.
ACE, angiotensin-converting enzyme; ARB, angiotensin-receptor blocker; CI, confidence interval; HR, hazard ratio; LVEF, left ventricular ejection fraction.
[a]Defined as any type of corticosteroid medication, including prednisone, prednisolone, or deflazacort, recorded in ≥30% of visits over ≥18 months.

### Trajectory analysis

- The linear rate of LVEF decline in the eteplirsen-treated and the NH control patients was –0.66 (95% CI = – 0.96 to – 0.36; *P* < 0.01) and – 1.38 (95% CI = – 1.60 to – 1.16; *P* < 0.01) percentage points per year, respectively
- A scatter plot for LVEF over time and the projected LVEF decline over time for a hypothetical patient with and without treatment started at age 9 are displayed in **Figure 3**

**Figure 3** *Estimated rate of LVEF decline*




Left panel: scatter plot, and right panel: decline extrapolation in the LMEM. LVEF 50: est. 14.35 years' delay. LVEF 55: est. 10.4 years' delay. LVEF 60: est. 6.44 years' delay.
LMEM, linear mixed effects model; LVEF, left ventricular ejection fraction; NH, natural history.

**Table 4** *RMST analysis - comparison between matched eteplirsen-treated and NH control patients*

| Characteristics | LVEF 50% | | | LVEF 55% | | | LVEF 60% | | |
|---|---|---|---|---|---|---|---|---|---|
| Time point | Treatment (year) | Control (year) | *P*-value | Treatment (year) | Control (year) | *P*-value | Treatment (year) | Control (year) | *P*-value |
| 12-year | 12.00 | 11.98 | 0.15 | 11.95 | 11.81 | 0.14 | 11.68 | 11.16 | <0.01 |
| 14-year | 14.00 | 13.83 | <0.01 | 13.80 | 13.56 | 0.15 | 13.35 | 12.40 | <0.01 |
| 16-year | 16.00 | 15.47 | <0.01 | 15.65 | 15.05 | 0.03 | 14.95 | 13.35 | <0.01 |
| 18-year | 18.00 | 16.95 | <0.01 | 17.49 | 16.16 | <0.01 | 16.50 | 14.07 | <0.01 |
| 20-year | 20.00 | 18.13 | <0.01 | 19.33 | 17.04 | <0.01 | 18.06 | 14.63 | <0.01 |
| 22-year | 21.66 | 18.83 | <0.01 | 20.86 | 17.75 | <0.01 | 18.76 | 15.08 | <0.01 |

Note: The RMST analysis was performed to examine treatment effects across different age intervals. The findings of the analysis provide the average survival time during a defined age range until each LVEF threshold is reached.
LVEF, left ventricular ejection fraction; NH, natural history; RMST, restricted mean survival time.

### Analyses to address potential sources of bias

- No statistically significant geographic imbalance was observed between treated and control patients in the rate of LVEF decline by age (coefficient of the interaction term between age and region: 0.18; *P* = 0.58)
- The E-value of the point estimate in the Cox model for time required to reach the first LVEF <55% threshold was 8.66 (95% CI upper bound = 2.38), indicating robust results
- Results of RMST analysis suggested that eteplirsen-treated patients had a significantly lower risk of reaching LVEF thresholds at ≥16 years of age compared with matched NH controls (**Table 4**)

***All results were consistent with a sensitivity analysis using an alternate PS matching approach in which each eteplirsen-treated patient was matched with a unique control patient with the closest matching PS at a qualifying visit (data not shown)***

## Key Finding

**In this retrospective study of patients with exon 51 skip-amenable DMD, eteplirsen-treated patients were observed to have a significantly lower risk of reaching LVEF thresholds indicative of cardiac function decline, and a significant attenuation of the rate of LVEF decline compared with matched controls**

## Conclusions

All results consistently indicated a positive association between eteplirsen and significantly lower risk of LVEF decline for patients with DMD, including the post-matching time-to-event and trajectory analysis with adjustment for key cardiac prognostic factors

Validation analyses for potential sources of bias also suggested the estimated effects of the treatment were robust

Data sources from multiple studies that may vary in underlying populations, follow-up periods, study inclusion criteria, and standard of care were used, though all statistical tools available were used to limit the influence of such biases

LVEF measurement by echocardiogram entails some subjective evaluation, though it has been a primary outcome considered in other studies of cardiac function in DMD[11,12]

This study is the first to demonstrate significant change in measured cardiac function with an innovative therapy that aims to increase dystrophin expression, suggesting clinically meaningful multi-year delays in reaching cardiomyopathy milestones for treated patients

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