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Comparative Analysis of Loss of Ambulation in Eteplirsen-Treated Patients With DMD in the EVOLVE Study and Propensity Score–Weighted External Controls

Katherine Mathews[1], Shannon Grabich[2], Sai Dharmarajan[2], Kathryn DeYoung[2], Craig M. Zaidman[3], Megan A. Waldrop[4], Craig M. McDonald[5], on behalf of the EVOLVE study group

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Background

- Loss of ambulation (LOA) is a critical milestone in Duchenne muscular dystrophy (DMD) progression, significantly impacting patients' clinical outcomes and quality of life[1]
- Eteplirsen is an FDA-approved phosphorodiamidate morpholino oligomer (PMO) for the treatment of DMD in patients with mutations amenable to exon 51 skipping[2]
  - Clinical studies and post hoc analyses have demonstrated clinically meaningful improvements in age at LOA in eteplirsen-treated patients compared with mutation-matched controls[3–8]
- EVOLVE (NCT06606340) is an ongoing phase 4, multicenter, prospective, observational study evaluating male patients with DMD receiving PMOs in routine clinical practice[9]

Objective

To examine the effect of eteplirsen on LOA by comparing patients with DMD amenable to exon 51 skipping from an interim analysis of EVOLVE with propensity score–weighted external controls (ECs) in a real-world setting

Methods

Study population

- Male patients ≥4 years of age with DMD amenable to exon 51 skipping
- Ambulant at baseline
- Receiving treatment with eteplirsen and/or glucocorticoids (GCs)

Primary endpoint

- Age at LOA
  - LOA was defined as the earliest date of patient-/caregiver-reported continuous wheelchair use, verified by attending physician, North Star Ambulatory Assessment walk score of 0 or 10-meter walk/run (10MWR) score of ≥30 (if available), or inability to perform 10MWR, and not a temporary event due to injury

Inverse probability treatment weighting (IPTW)

- IPTW was applied to create a pseudo-population where EVOLVE and EC cohorts were balanced across key prognostic covariates, making direct comparison feasible
  - A fractional weight was assigned to individuals based on their probability of receiving treatment (propensity score) given their covariate values
- Prognostic covariates included:
  - Age group (4–7 years, 8+ years)
    - Younger patients (4–7 years) are at lower risk of LOA than those >7 years, at which point ambulatory function typically begins to decline[1,6,10]
  - 10MWR velocity at baseline (10MWR ≤30 sec)
  - Rise from floor (RFF) velocity at baseline (RFF ≤20 sec)
  - GC duration group (≥1 year, <1 year)
    - ≥1 year of steroid use is associated with improved LOA outcomes[1,10]
- Propensity score model:
  - *Probability (treatment | covariates) = age group + 10MWR velocity + RFF velocity + GC duration group + (10MWR velocity × RFF velocity)*
- Smaller standardized differences (≤0.20) indicate better balance between groups[11]
- After IPTW, a Cox proportional hazard regression model was fit to estimate the effect of eteplirsen treatment on LOA
  - Model included treatment, and age as a continuous covariate to correct for some moderate residual imbalance after weighting

Supportive analyses

- Supportive analyses were conducted using the Kaplan-Meier (KM) estimator to capture treatment impact at critical points of disease progression given the median age at LOA in patients with DMD amenable to exon 51 skipping
  - 15 years was used as the cutoff, as this was the oldest age with appropriate EC data available
- Along with probability of remaining ambulant, restricted mean ambulation time (RMAT) was calculated as the area under the KM curve to estimate the average time a patient will remain ambulant at a given age

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Results

Patient characteristics

- A total of 33 eteplirsen-treated patients from EVOLVE and 75 ECs met inclusion criteria as of October 2023 (**Supplemental Table 1**)
- Mean (SD) follow-up time for unweighted eteplirsen-treated patients and ECs was 4.7 (2.82) years and 2.9 (1.69) years, respectively

Pre-weighted patient characteristics (Supplemental Table 2)

- Prior to weighting, eteplirsen-treated patients were slightly older than ECs at baseline (mean [SD]: 8.9 [2.62] vs 7.0 [1.61] years)
- Baseline functional tests were comparable between the eteplirsen-treated patients and ECs
  - Pre-weighted standardized differences for 10MWR and RFF velocities were -0.156 and -0.163, respectively

IPTW: post-weighting differences (Table 1)

- IPTW successfully balanced age group, duration of GC use, and 10MWR and RFF velocities at baseline with standardized differences <0.15 after weighting
- Age as a continuous variable had a moderate residual imbalance and was thus included as a covariate in the Cox proportional hazard regression model

Table 1 *Baseline Patient Characteristics and Standardized Differences Between EVOLVE and Weighted EC Cohorts*

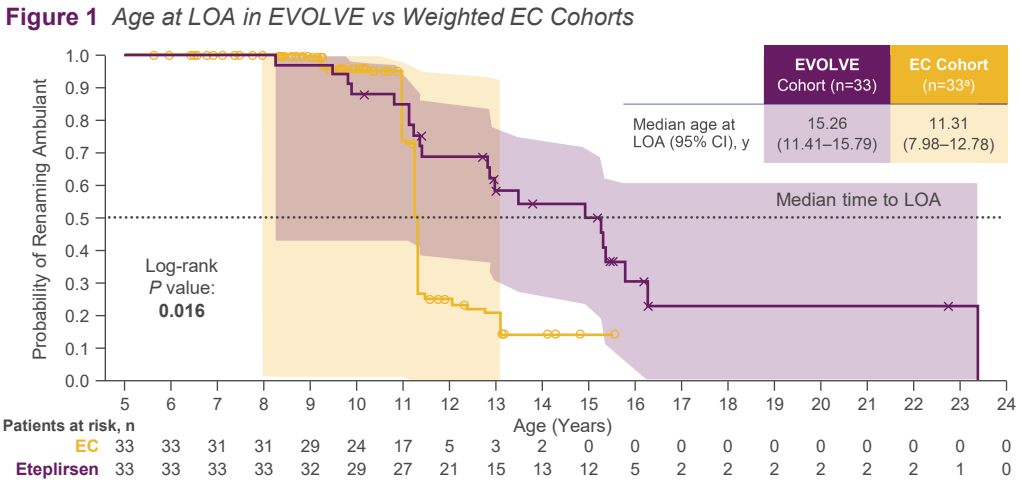
Baseline Patient Characteristics[a]	EVOLVE Cohort (n=33)	EC Cohort (Weighted) (n=33[b])	Post-Weighted Standardized Difference
Age, years			0.392[c]
Mean (SD)	8.88 (2.62)	8.03 (1.59)	
Median	8.77	8.50	
Age group, n (%)			-0.028
4–7 years	14 (42.4)	14.6 (43.8)	
8+ years	19 (57.6)	18.7 (56.2)	
Duration of GC use, n (%)			0.013
<1 year	6 (18.2)	5.9 (17.7)	
≥1 year	27 (81.8)	27.4 (82.3)	
10MWR velocity, m/s			0.130
Mean (SD)	1.77 (0.46)	1.71 (0.55)	
Median	1.72	1.40	
RFF velocity, rises/s			-0.100
Mean (SD)	0.19 (0.10)	0.20 (0.09)	
Median	0.18	0.21	

[a]Baseline is defined as treatment initiation for EVOLVE patients and first visit at matched parameters for ECs; data are not final until study completion and database lock occur. [b]The actual total number of weighted ECs is 33.3, which represents the sum of the fractional contributions of individuals. [c]Standardized difference of >0.20 indicates moderate imbalance of age.
10MWR=10-meter walk/run; EC=external control; GC=glucocorticoid; m=meters; RFF=rise from floor; s=second.

Loss of ambulation

- LOA occurred in 21/33 eteplirsen-treated patients (13.5/100 patient-years [PY]) and 19/33 weighted ECs (20.8/100 PY)
- Median (95% CI) age at LOA was 15.3 (11.4–15.8) years in eteplirsen-treated patients vs 11.3 (8.0–12.8) years in ECs (*P*=0.016) by KM analysis (**Figure 1**)
- Cox proportional hazard regression analysis suggested eteplirsen reduced LOA risk by 62% (95% CI, 20–82; *P*=0.011) across the lifespan (**Supplemental Table 3**)

Figure 1 *Age at LOA in EVOLVE vs Weighted EC Cohorts*



[a]The actual total number of weighted ECs is 33.3, which represents the sum of the fractional contributions of individuals.
EC=external control; LOA=loss of ambulation; y=years.

Supportive analyses: LOA up to age 15 years (Table 2)

- Nonparametric analyses estimated the probability (95% CI) of remaining ambulant at age 15 was 0.50 (0.32–0.69) and 0.14 (-0.06, 0.34) for eteplirsen-treated patients and ECs, respectively
- Eteplirsen treatment increased the likelihood of remaining ambulant by age 15 by 36% (95% CI, 9–63)
- RMAT analyses estimated that by age 15, eteplirsen-treated patients had an average of 1.5 additional years of ambulation compared to ECs

Table 2 *Effect of Eteplirsen on LOA Up to Age 15 in EVOLVE vs Weighted EC Cohorts*

	Probability of Remaining Ambulant (95% CI)			RMAT (95% CI), years		
Age	EVOLVE Cohort (n=33)	EC Cohort (Weighted) (n=33[a])	Post-Weighted Standardized Difference	EVOLVE Cohort (n=33)	EC Cohort (Weighted) (n=33[a])	Post-Weighted Standardized Difference
10 years[b]	0.88 (0.77–0.99)	0.96 (0.83–1.09)	-0.08 (-0.25, 0.09)	9.9 (9.8–10.0)	10.0 (9.9–10.1)	0.0 (-0.2, 0.1)
12 years[b]	0.69 (0.53–0.85)	0.25 (-0.05, 0.55)	0.44 (0.10–0.78)	11.5 (11.2–11.8)	11.3 (10.9–11.7)	0.2 (-0.3, 0.7)
14 years	0.54 (0.36–0.72)	0.14 (-0.06, 0.34)	0.40 (0.13–0.67)	12.8 (12.2–13.3)	11.7 (10.9–12.5)	1.1 (0.1–2.1)
15 years	0.50 (0.32–0.69)	0.14 (-0.06, 0.34)	0.36 (0.09–0.63)	13.3 (12.6–14.0)	11.8 (10.9–12.8)	1.5 (0.3–2.7)

[a]The actual total number of weighted ECs is 33.3, which represents the sum of the fractional contributions of individuals. [b]Values at 10 and 12 years cross the null value at which no change is expected, indicating no divergence observed until age 14.
EC=external control; LOA=loss of ambulation; RMAT=restricted mean ambulation time.

Key Finding

This interim analysis shows a clinically and statistically significant delay in LOA in eteplirsen-treated patients vs ECs using advanced methods to reduce confounding in a real-world setting

Conclusions

This is the first study to compare eteplirsen-treated patients from the ongoing EVOLVE study with mutation-matched ECs

In those who lost ambulation, eteplirsen-treated patients had a difference in median age at LOA of ~4 years compared to ECs

Cox models indicate a statistically significant 62% reduction in risk of LOA across the lifespan, utilizing robust statistical methodology to account for possible confounding

Supportive analyses further underscore the benefit of eteplirsen treatment in delaying LOA

Limitations include potential unmeasured confounders, differences in follow-up time, and potential differences in how LOA is reported by physicians across EVOLVE and EC data sources

This interim analysis informs the real-world benefits of eteplirsen for patients with DMD

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Methods (cont)

EC data sources

- Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS)[12]
- Finding the Optimum Regimen for Duchenne Muscular Dystrophy (FOR-DMD)[13]
- PRO-DMD-01 study[14]
- The Italian DMD Telethon[15]
- The Belgium Leuven NeuroMuscular Reference Center (NMRC)[16]

Results (cont)

Supplemental Table 1 *Patient Disposition of the EVOLVE Eteplirsen and EC Cohorts*

EVOLVE Cohort Attrition (Mutually Exclusive), n (%)	EVOLVE Eteplirsen Cohort
Total eligible patients	126/126 (100)
Initiated treatment as part of EVOLVE or prior clinical trial, with baseline function data available	48/126 (38.1)
Ambulant at treatment initiation	40/126 (31.7)
≥4 years of age at treatment initiation	37/126 (29.4)
No missing values for key measures[a]	33/126 (26.2)
EVOLVE analysis cohort	**33/126 (26.2)**

EC Cohort Attrition (Mutually Exclusive), n (%)	CINRG DNHS (n=440)	FOR-DMD (n=194)	Belgium Leuven NMRC (n=89)	PRO-DMD (n=269)	Italian DMD Telethon (n=97)	Overall EC Cohort
Exon 51 skip-amenable	59/59 (100)	25/25 (100)	16/16 (100)	17/17 (100)	12/12 (100)	129/129 (100)
≥1 visit with no missing values for key measures[a]	28/59 (47.5)	24/25 (96.0)	13/16 (81.3)	11/17 (64.7)	9/12 (75.0)	85/129 (65.9)
≥1 ambulant visit	28/59 (47.5)	24/25 (96.0)	13/16 (81.3)	11/17 (64.7)	9/12 (75.0)	85/129 (65.9)
Met EVOLVE entry criteria on key measures[a]	24/59 (40.7)	24/25 (96.0)	13/16 (81.3)	7/17 (41.2)	7/12 (58.3)	75/129 (58.1)
EC analysis cohort	**24/59 (40.7)**	**24/25 (96.0)**	**13/16 (81.3)**	**7/17 (41.2)**	**7/12 (58.3)**	**75/129 (58.1)**

[a]Key measures include age, steroid use duration, 10MWR, RFF, height, and weight.
10MWR=10-meter walk/run; CINRG DNHS=Cooperative International Neuromuscular Research Group Duchenne Natural History Study; DMD=Duchenne muscular dystrophy; EC=external control; FOR-DMD=Finding the Optimum Regimen for Duchenne Muscular Dystrophy; NMRC=NeuroMuscular Reference Center; RFF=rise from floor.

Supplemental Table 2 *IPTW Diagnostics: Pre-Weighting*

Baseline Patient Characteristics[a]	EVOLVE Cohort (n=33)	EC Cohort (Unweighted) (n=75)	Pre-Weighted Standardized Difference
Age, years			0.868
Mean (SD)	8.88 (2.62)	6.99 (1.61)	
Median	8.77	6.47	
Age group, n (%)			-0.659
4–7 years	14 (42.4)	55 (73.3)	
8+ years	19 (57.6)	20 (26.7)	
Duration of steroid use, n (%)			-1.573
<1 year	6 (18.2)	60 (80.0)	
≥1 year	27 (81.8)	15 (20.0)	
10MWR velocity, m/s			-0.156
Mean (SD)	1.77 (0.46)	1.84 (0.48)	
Median	1.72	1.89	
RFF velocity, rises/s			-0.163
Mean (SD)	0.19 (0.10)	0.21 (0.10)	
Median	0.18	0.21	

[a]Baseline is defined as treatment initiation for EVOLVE patients and first visit at matched parameters for ECs; data are not final until study completion and database lock occur.
10MWR=10-meter walk/run; EC=external control; m=meters; IPTW=inverse probability treatment weighting; RFF=rise from floor; s=second.

Supplemental Table 3 *Weighted Cox Regression Analysis of Age at LOA*

Variable, Adjusting for Baseline Age	Hazard Ratio (95% CI)	*P* value
Treatment = eteplirsen	0.38 (0.18–0.80)	0.011
Age at baseline	0.99 (0.87–1.12)	0.860

LOA=loss of ambulation.