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Survival in Eteplirsen-Treated vs Duchenne Muscular Dystrophy (DMD) Natural History Controls: An Indirect Treatment Comparison Using Real-world Data

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Please scan QR code for full study details

Objective

To compare the survival of patients with Duchenne muscular dystrophy (DMD) receiving eteplirsen as part of routine care with recently published DMD natural history (NH) controls

Key Takeaway

These real-world data suggest eteplirsen may prolong survival in patients with DMD across a wide age range

CONCLUSIONS

- Real-world data from patients treated with eteplirsen had significantly longer survival compared to reproduced patient-level data on DMD NH controls, with a median difference of at least 5.4 years
- Patients treated with eteplirsen for longer exposure periods may experience increasing survival benefits
- Patients who initiate eteplirsen at younger ages may have higher survival benefits compared to those initiating at older ages (survival differences were most evident for those initiating eteplirsen between ages 10–28 years and were attenuated beyond >28 years)
- The findings are generally robust to sensitivity analyses with different cohorts included in the DMD NH control group

METHODS

Objectives

- To investigate whether patients initiating eteplirsen at a younger age or with a longer duration of exposure have longer all-cause survival compared with patients who initiate eteplirsen at an older age
- To compare all-cause survival age between eteplirsen-treated patients vs DMD NH controls
- To compare all-cause survival measured from treatment initiation (baseline) in eteplirsen-treated patients and DMD NH controls

Data sources

- **Eteplirsen-treated patients (N=579)**
  - Collected as part of SareptAssist, Sarepta's US patient support program for real-world eteplirsen treatment covering most commercially insured skip-51 patients
  - Age/date of eteplirsen initiation, discontinuation, and death were available; data on prognostic factors, other treatments used, or outcomes were not collected
- **DMD NH controls (N=1224; *scan QR code for details*)**
  - A recent systematic literature review (SLR)[1] of the published literature on survival in DMD was used to extract data for comparable NH patients (ie, "post-1990" birth cohort, with some patients born in 1980s)
  - A targeted literature review using the same search terms used in Broomfield et al[1] was used to identify other NH survival studies published after the SLR search end date (July 2020) with the most comparable patients suitable to serve as external controls[2-6]
  - The Kaplan-Meier curves were digitized and individual patient data were reproduced using the method proposed by Guyot et al[15]

Statistical analysis

- **Survival age** was compared between eteplirsen-treated patients and DMD NH controls using different survival methods:
  - Nonparametric analyses: Kaplan-Meier curves, 95% confidence bands and log-rank tests
  - Semiparametric analyses: Cox proportional hazards models and Schoenfeld residuals tests
  - Parametric analyses: accelerated failure time models and piecewise-constant hazard models
- **Time from baseline to death** was analyzed by comparing eteplirsen-treated patients with age-matched controls obtained based on the following procedure:
  - Up to 15 age-matched controls were identified among DMD NH patients still alive at each age of treatment initiation among eteplirsen-treated patients
  - Time to death (or censoring) for DMD NH controls was calculated from the age of a randomly generated baseline date to the age of the event
  - Time from baseline to death was compared between the age-matched eteplirsen-treated patients and the NH controls (N=3690, with some patients selected as comparators at multiple ages), adjusted for baseline age and age-treatment interaction

RESULTS

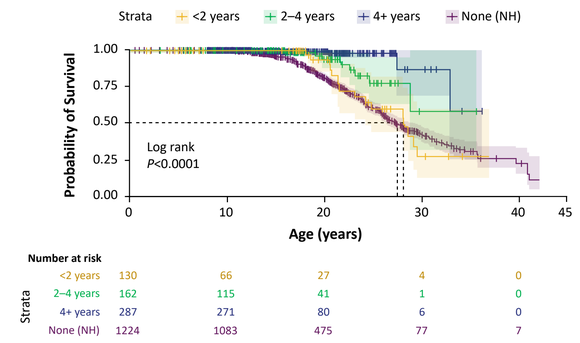
Characteristics of Eteplirsen-Treated Patients

Characteristic	Total (N=579)
Duration of eteplirsen exposure, years	
Mean (SD)	3.7 (1.9)
Median	4.0
Range	0.0, 8.6
Categorical duration of eteplirsen exposure, n (%)	
<2 years	130 (22.4)
2–4 years	162 (28.0)
4+ years	287 (49.6)
Age at treatment initiation, years	
Mean (SD)	11.9 (6.4)
Median	11.0
Range	1.0, 35.0
Trial participation, n (%)	
Prior trial experience	143 (24.7)

Values are mean SD unless otherwise stated.

Patients treated with eteplirsen for longer periods of time tend to have longer survival

- Among 579 patients, **mean age at eteplirsen initiation was 11.9 years** (range, 1.0–35.0) and mean exposure was 3.7 years (range, 0.0–8.6)
- **Patients treated with ≥2 years of eteplirsen had higher median survival ages** than DMD NH controls
- Patients treated with <2 years of eteplirsen had similar median survival age vs DMD NH controls (28.1 vs 27.4), suggesting that patients with low eteplirsen exposure were similar to the unexposed DMD NH cohort



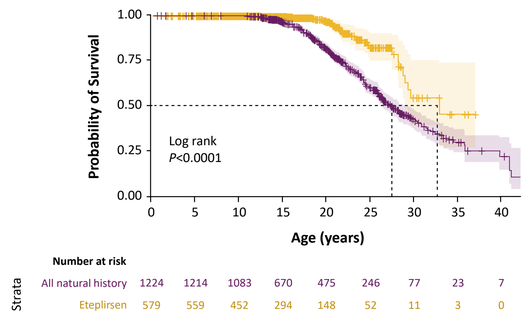
Categorical Eteplirsen Exposure Duration vs US and EU DMD NH Controls[2,3]

Eteplirsen Exposure Group	HR [95% CI]	*P* value
<2 years	0.89 [0.54, 1.46]	0.64
2–4 years	0.36 [0.18, 0.74]	0.005
4+ years	0.11 [0.05, 0.27]	<0.001

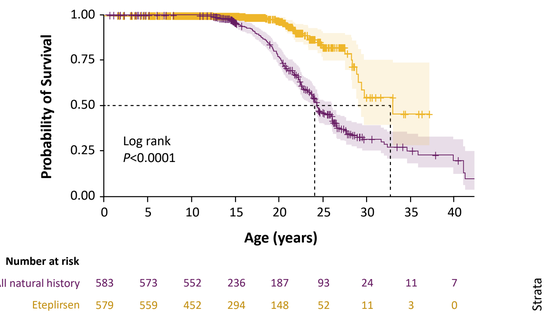
DMD=Duchenne muscular dystrophy; HR=hazard ratio; NH=natural history.

Eteplirsen-treated patients had statistically significant longer survival compared with DMD NH controls

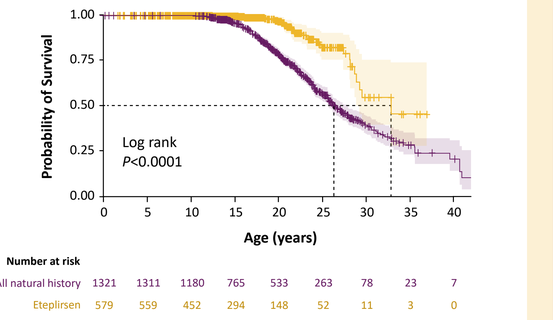
Primary Analysis (US and EU DMD NH Controls[2,3])



Sensitivity Analysis 1 (US DMD NH Controls[2-5])



Sensitivity Analysis 2 (US, EU, and South America DMD NH Controls[2-6])



- Nonparametric and semiparametric analyses showed that **eteplirsen-treated patients appeared to have a 66% higher survival compared with DMD NH controls** (hazard ratio [HR], 0.34, 95% CI, 0.23, 0.50; *P*<0.0001)
- **Median survival age was higher for eteplirsen-treated patients** vs DMD NH controls, **resulting in prolonged median survival of 5.4 years for eteplirsen-treated patients**
- Results were robust to different combinations of NH controls (Sensitivity Analysis 1 and 2)

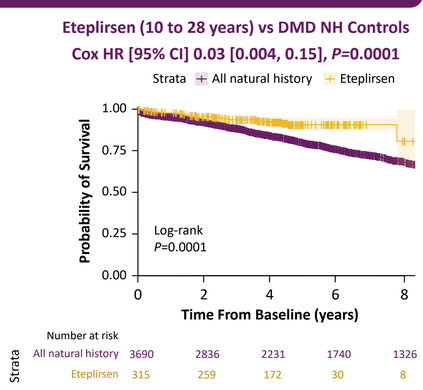
	Primary Analysis	Sensitivity Analysis 1	Sensitivity Analysis 2
Δ Median age of death, years (eteplirsen vs NH)	5.4 (32.8 vs 27.4)	8.6 (32.8 vs 24.2)	6.4 (32.8 vs 26.4)
HR [95% CI], *P* value	0.34 [0.23, 0.50] <0.001	0.25 [0.17, 0.38] <0.001	0.31 [0.22, 0.46] <0.001

HR=hazard ratio; NH=natural history.

Eteplirsen-treated patients experienced prolonged survival from baseline vs age-matched DMD NH synthetic controls

- Analysis of survival from baseline showed that **eteplirsen-treated patients had significantly longer survival compared with DMD NH controls** (*P*=0.0011)
  - This finding was consistent in the subgroup of patients aged 10–28 years at baseline, for whom deaths are most likely to be observed (*P*=0.0001)
- **Older age at initiation was independently associated with lower survival benefits** (eteplirsen × baseline age interaction HR, 1.07; *P*<0.05)
  - Similar results were observed in the subgroup of patients aged 10–28 years (eteplirsen × baseline age interaction HR, 1.17; *P*<0.001)

Eteplirsen (10 to 28 years) vs DMD NH Controls
Cox HR [95% CI] 0.03 [0.004, 0.15], *P*=0.0001

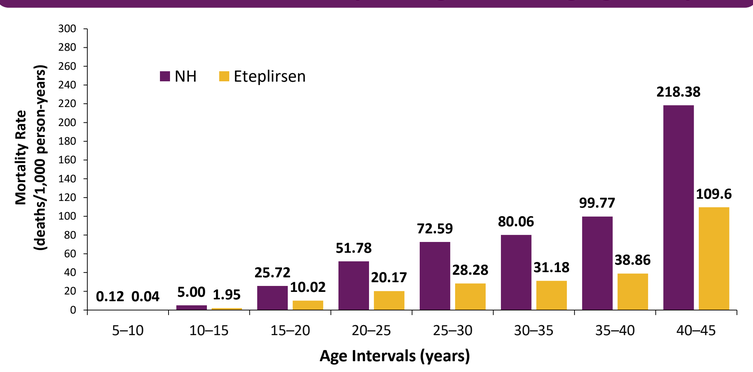


Patients initiating eteplirsen at younger ages had greater survival benefits vs age-matched DMD NH controls compared to patients initiating at older ages

	HR [95% CI]	*P* value
Eteplirsen	0.19 [0.07, 0.55]	<0.01
Baseline age	1.14 [1.13, 1.15]	<0.001
Eteplirsen × age	1.07 [1.02, 1.12]	<0.05

DMD=Duchenne muscular dystrophy; HR=hazard ratio; NH=natural history.

Mortality rates were lower for eteplirsen-treated patients vs DMD NH controls across all 5-year segments ranging 5–45 years



- **Mortality rates predicted from piecewise-constant hazard model** were lower for eteplirsen-treated patients vs DMD NH controls for all segments between 10–30 years (when data are most reliable)
- **The results indicated an overall 61% lower risk of death among eteplirsen-treated patients** vs DMD NH controls (HR, 0.39; *P*<0.05) in the age range studied

Limitations

- Data limitations do not allow for adjusted comparisons controlling for prognostic factors, such as baseline function, corticosteroid exposure, mutation type, geographic area, and other patient characteristics
- Analyses of age at event, while common in DMD literature, do not match patients with similar characteristics at treatment initiation, potentially leading to selection bias and unobserved confounding
- Analyses of time from baseline are based on matching DMD NH patients still alive at each age of treatment initiation with eteplirsen-treated patients in an indirect comparison
- Several eteplirsen-treated patients (N=143) were exposed to eteplirsen in prior trials, but due to unavailability of patient IDs only average exposure was imputed; results were robust to removing prior trial participants from analysis
- Although almost half of the eteplirsen-treated patients have been exposed to treatment for 4+ years, overall exposure time is relatively low for the purpose of detecting survival benefits
- It was not possible to assess whether patients discontinuing eteplirsen deceased shortly after discontinuation; however, the results did not qualitatively change after removing patients who discontinued eteplirsen from the sample
- There are limited mortality data in the published literature that can be used for comparison, particularly for exon 51 skip-amenable patients; moreover, data are heterogeneous and not all studies published all potential confounders

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1. Broomfield JJ, et al. *Neurology.* 2021;97:e2304-14; **2.** Wang M, et al. *Open Heart.* 2018;5:e000783; **3.** Paramsothy P, et al. *Neuromuscul Disord.* 2022;32:468-76; **4.** van den Bergen JC, et al. *J Neuromuscul Dis.* 2014;1:91-4; **5.** Wahlgren L, et al. *Eur J Epidemiol.* 2022;37:147-56; **6.** San Martín PP, et al. *Rev Chil Pediatr.* 2018;89(4):477-83; **7.** Birnkrant DJ, et al. *Lancet Neurol.* 2018;17(3):251-67; **8.** Koeks Z, et al. *J Neuromuscul Dis.* 2017;4:293-306; **9.** Ryder S, et al. *Orphanet J Rare Dis*. 2017;12:79; **10.** Passamano L, et al. *Acta Myol.* 2012;31:121-5; **11.** Mayer OH, et al. *US Neurology.* 2017;13(1):35-41; **12.** Mendell JR, et al. *Ann Neurol.* 2016;79:257-71; **13.** Iff J. *Muscle Nerve.* 2022;66:262-69; **14.** https://apps.automeris.io/wpd/; **15**. Guyot P, et al. *BMC Med Res Methodol.* 2012;12:9; **16.** Debray TPA, et al. *Res Synth Methods.* 2015;6:293-309; **17.** Crowther MJ, et al. *BMC Med Res Methodol*. 2012;12:34; **18.** Moher D, et al. *PLoS Med*. 2009;6(7):e1000097.

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BACKGROUND

- Duchenne muscular dystrophy is a rare, fatal genetic disorder caused by a lack of dystrophin protein, which leads to progressive and irreversible muscle damage from birth[7]
- Loss of ambulation occurs at approximately age 12 years in patients treated with corticosteroids[8,9]
- Median age of death with standard of care is 26–28 years,[10,11] with major causes of death being respiratory insufficiency and cardiomyopathy[7,10]
- Studies have established a linear decline in pulmonary function between ages 10–18 years, irrespective of ambulatory status[11]
- Eteplirsen induces dystrophin production and results in delayed loss of ambulatory and pulmonary function in exon 51 skip-amenable patients with DMD vs NH patients[12,13]
- Impact of eteplirsen treatment on prolonging patient survival is unknown

METHODS DETAILS

Characteristics of Studies Contributing to Reproduced Individual Patient Data for DMD NH Controls

First author	Wang[a,b,c]	Paramsothy[a,b,c]	van den Bergen[a,b]	Wahlgren[a,b]	San Martin[c]
Publication year	2018	2022	2014	2022	2018
Country	United States	United States	Netherlands	Sweden	Chile
Region	Greater Cleveland, OH	AZ, CO, IA, NY	Entire country	Entire country	Santiago
Total patients included	57	526	336	305	97
Total deaths	27	136	41	103	52
Source	Broomfield et al (2021) SLR	TLR (authors)	Broomfield et al (2021) SLR	TLR (authors)	Broomfield et al (2021) SLR
Birth cohort	>15 years old 2003–2015, at least 3 ECHO[d]	1982–1999 (data cut 2011)	1980–2006 (data cut approx. 2013)	1980–2009 (data cut 2019)	Admitted 1993–2013[d] (data cut July 20, 2014)
Corticosteroid use, n (%)	15 (26.3)	220 (43.7)[e]	165 (49.1)	–	–
ACEI or ARB use, n (%)	51 (89.5)	262 (52.0)[e,f]	41 (12.2)	–	–
Beta-blocker use, n (%)	33 (57.9)	262 (52.0)[e,f]	18 (5.4)	–	–
Ventilation assistance, n (%)	50 (87.7)	191 (37.9)[d]	93 (27.7)	–	–
Socioeconomic status, n (%)					
High income	–	–	–	–	15 (15.5)
Medium-high income	–	–	–	–	82 (84.5)
Mutation types	• Exon 44 deletion (n=9) • Exon 51 deletion (n=5) • Various mutations (n=43)	–	• Exon deletion (n=212) • Duplication (n=42) • Premature stop codon (n=49) • Splice site mutation (n=18) • Unknown mutation (n=12)	–	–

[a]Reproduced individual patient data were included in the NH sample for the main analysis. [b]Reproduced individual patient data were included in the external control sample for Sensitivity Analysis 1 only. [c]Reproduced individual patient data were included in the external control sample for Sensitivity Analysis 2 only. [d]Birth cohort not reported. [e]Reported for N=504 in the cohort analyzed for time to death since age 10 years. [f]Cardiac medication use reported in aggregate.
ACEI=angiotensin-converting enzyme inhibitor; ARB=angiotensin receptor blocker; DMD=Duchenne muscular dystrophy; ECHO=echocardiogram; NH=natural history; SLR=systematic literature review; TLR=targeted literature review.

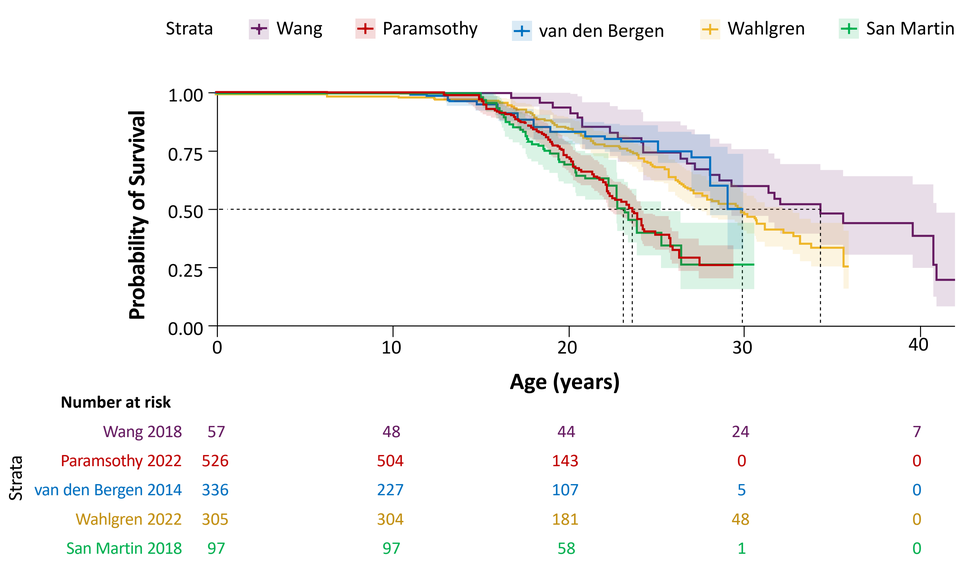
Data processing

- Main outcome (survival age in years[a]) for eteplirsen-treated patients was calculated as:

$$\text{Survival age} = \text{Age at eteplirsen initiation} + \frac{\text{Date of death or discontinuation} - \text{Date of initiation}}{365.25}$$

- Exposure to eteplirsen was extended for patients in prior eteplirsen clinical trials by:
  - 192 weeks for 12 patients who participated in studies 201/202
  - 96 weeks for 123 patients who participated in studies 203 (n=24), 204 (n=21), and 301 (n=78)
- Reproduced individual patient data for DMD NH controls, consisting of survival ages, were obtained by:
  - Digitizing the Kaplan-Meier survival curves using WebPlotDigitizer[14] to estimate the survival probabilities at different time points
  - Generating reproduced individual patient data on survival age using the methodology described by Guyot et al,[15] a recognized method of reconstructing individual data from aggregate summaries,[16] and also used by Broomfield et al[1]; reproduced data for the 3 digitized papers closely matched reproduced data obtained from the corresponding author of Broomfield et al[1]
  - Validating the reproduced individual patient data with respect to the original articles by reproducing Kaplan-Meier curves, event rates, and median time to event, when provided in each publication

Kaplan-Meier Analysis of DMD NH Survival Studies Considered



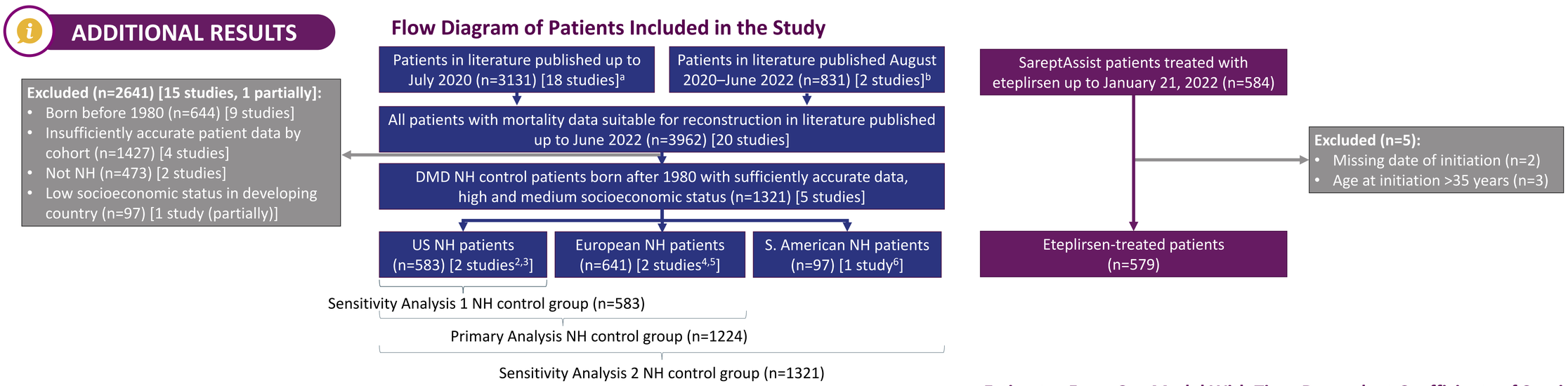
- The Paramsothy and the San Martin high income (n=15) and medium-high income (n=82) cohorts have the lowest survival times
- The Wang, van den Bergen, and Wahlgren cohorts are in the "middle of the pack"
- Note that the Paramsothy, van den Bergen, and Wahlgren cohorts include some patients born in the 1980s

Additional statistical analysis details

- Accelerated failure time models:
  - Several distributions were tested (exponential, Weibull, Gompertz, log-logistic, log-normal, generalized gamma, generalized F)
  - Model fit was assessed via Akaike Information Criterion and Bayesian Information Criterion, and graphically by juxtaposition with the respective nonparametric Kaplan-Meier curve; the model with the highest fit was selected as primary
- Piecewise-constant hazard models with study-level frailty terms[17]
  - Mortality rates in deaths per 1000 patient-years were predicted for each 5-year segment
- DMD NH control group data were censored at 8.62 years of follow-up, in line with the maximum follow-up period of 8.62 years in the eteplirsen group after imputation of exposure for patients participating in prior clinical trials

ADDITIONAL RESULTS

Flow Diagram of Patients Included in the Study



[a]Studies identified by Broomfield et al[1] SLR, which was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18]
[b]Studies identified by TLR conducted by authors using the same search terms as the Broomfield et al[1] study.
DMD=Duchenne muscular dystrophy; NH=natural history.

Effect of eteplirsen on survival is most evident between 10–28 years of age and is attenuated in patients who initiate eteplirsen beyond age 28 years

- Eteplirsen treatment effect on survival using a Cox model with time-varying coefficients indicates:
  - 92.9% reduction in risk of death between 0–15 years ($P<0.01$)
  - 82.1% reduction in risk of death between 15–20 years ($P<0.001$)
  - 47.4% reduction in risk of death between 20–25 years ($P<0.05$)
- Past age 28 years, risk reductions with eteplirsen treatment vs DMD NH controls are not statistically significant

Estimates From Cox Model With Time-Dependent Coefficients of Survival Age Comparing Eteplirsen-Treated Patients With DMD NH Controls

	HR [95% CI]
Eteplirsen × age (0–15) years	0.07 [0.01, 0.52]**
Eteplirsen × age (15–20) years	0.18 [0.08, 0.41]***
Eteplirsen × age (20–25) years	0.53 [0.30, 0.92]*
Eteplirsen × age (25–30) years	0.71 [0.32, 1.56]
Eteplirsen × age (30+) years	0.38 [0.05, 2.84]

*$P<0.05$; **$P<0.01$; ***$P<0.001$. DMD=Duchenne muscular dystrophy; HR=hazard ratio; NH=natural history.

Rates of ventilatory assistance and corticosteroid use were similar for eteplirsen-treated patients and overall patients with DMD in the United States up to 2017

- Based on exploratory analysis of Clarivate Decision Resources Group Real-World Data Repository (not shown) up to December 31, 2017, rates of corticosteroid use were similar for eteplirsen-treated patients vs overall patients with DMD in the United States (39.6% vs 38.0%), providing support for the comparison of eteplirsen-treated patients and DMD NH controls
- Rates of having ever used ventilatory assistance were also similar before the age of 25, when the data are most reliable: 12.2% vs 9.9% (0–14 years), 38.5% vs 38.7% (15–20 years), 54.5% vs 53.3% (21–25 years); rates for older ages are also comparable but are less reliable given the small sample sizes

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