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CLINICAL RESEARCH ARTICLE

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Survival among patients receiving eteplirsen for up to 8 years for the treatment of Duchenne muscular dystrophy and contextualization with natural history controls

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Abstract

Introduction/Aims: Eteplirsen, approved in the US for patients with Duchenne muscular dystrophy (DMD) with exon 51 skip-amenable variants, is associated with attenuated ambulatory/pulmonary decline versus DMD natural history (NH). We report overall survival in a US cohort receiving eteplirsen and contextualize these outcomes versus DMD NH.

Methods: US patients with DMD receiving eteplirsen were followed through a patient support program, with data collected on ages at eteplirsen initiation and death/end of follow-up. Individual DMD NH data were extracted by digitizing Kaplan–Meier (KM) curves from published systematic and targeted literature reviews. Overall survival age was analyzed using KM curves and contextualized with DMD NH survival curves; subanalyses considered age groups and duration of eteplirsen exposure. Overall survival time from treatment initiation was also evaluated.

Results: A total of 579 eteplirsen-treated patients were included. During a total follow-up of 2119 person-years, median survival age was 32.8 years. DMD NH survival curves extracted from four publications (follow-up for 1224 DMD NH controls) showed overall pooled median survival age of 27.4 years. Eteplirsen-treated patients had significantly longer survival from treatment initiation versus age-matched controls (age-adjusted hazard ratio [HR], 0.65; 95% confidence interval [CI], 0.44–0.98; $p < .05$). Longer treatment exposure was associated with improved survival (HR, 0.15; 95% CI, 0.05–0.41; $p < .001$). Comparisons using different DMD NH cohorts to address common risks of bias yielded consistent findings.

Abbreviations: CI, confidence interval; DMD, Duchenne muscular dystrophy; DRG, Data Resources Group; FDA, Food and Drug Administration; HR, hazard ratio; KM, Kaplan–Meier; NH, natural history; PMO, phosphorodiamidate morpholino oligonucleotide; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature review; TLR, targeted literature review.

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Discussion: Data suggest eteplirsen may prolong survival in patients with DMD across a wide age range. As more data become available, the impact of eteplirsen on survival will be further elucidated.

KEYWORDS
Duchenne muscular dystrophy, eteplirsen, exon skipping, natural history, PMO, survival

1 | INTRODUCTION

Duchenne muscular dystrophy (DMD) is a rare, fatal, X-linked degenerative neuromuscular disease affecting 1 in 3500–5000 boys worldwide,[1,2] which causes premature death.[3–6] DMD is currently considered incurable, and early treatments focus on managing disease symptoms using a multidisciplinary strategy of systemic corticosteroids, physiotherapy, cardiac medication, and ventilation support.[7–11] Exon skipping using phosphorodiamidate morpholino oligonucleotides (PMOs) has recently emerged as a DMD treatment strategy that addresses the underlying cause of disease by restoring the open reading frame and enabling translation of an internally shortened, yet functional dystrophin protein.[12,13] As a result, disease progression is slowed. To date, multiple PMOs have received accelerated approval by the U.S Food and Drug Administration (FDA) for the treatment of DMD in patients with confirmed *DMD* pathogenic gene variants amenable to exon 51 (eteplirsen), exon 53 (golodirsen, viltolarsen), or exon 45 (casimersen) skipping.[14–17]

Eteplirsen was the first PMO approved in 2016, targeting the most frequent group of exon-skippable pathogenic variants, which represent approximately 13% of the DMD population.[18] FDA approval was based on data demonstrating increased dystrophin levels in skeletal muscle tissue after treatment in clinical trial patients initially dosed as early as 2011.[14,19] Based on clinical data, eteplirsen has been shown to have a favorable safety profile and to slow disease progression, delaying deterioration of ambulatory and respiratory function compared with variant-matched external controls.[20–22] This study describes overall survival among the majority of patients receiving eteplirsen in the US since approval, with contextualization relative to published natural history (NH) cohorts.

2 | METHODS

2.1 | Patients

SareptAssist, the manufacturer's (Sarepta Therapeutics, Inc., Cambridge, MA) patient support program, collects administrative information on the majority of commercially and government-insured eteplirsen-treated US patients since the drug's approval (September 2016). Data for each patient include date of eteplirsen initiation and discontinuation, date of patient death or last date known to be alive, age at treatment initiation, and prior participation in specified clinical trials of eteplirsen (studies: 201/NCT01396239,[21] 202/NCT01540409,[20,21] 203/NCT02420379, 204/NCT02286947, and 301/NCT02255552).[23] No data are collected on patient clinical characteristics or functional assessments. Only de-identified data were available to the researchers of the present study.

2.2 | Literature review

DMD NH controls in this analysis consisted of reproduced patient-level data from published literature, including US and non-US populations (Figure 1). A recent systematic literature review (SLR) by Broomfield et al.,[24] conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, was used to identify studies with survival data for NH patients with DMD.[25] This included patients from publications available via PubMed and those published before July 31, 2020, with no exclusions based on region, language, study period, or publication date. An updated targeted literature review was conducted to identify additional articles published after July 31, 2020, to June 30, 2022, that reported overall survival in patients with DMD fulfilling the Broomfield et al. PRISMA search criteria, while limiting to studies published in English.

Publications identified in these reviews were subjected to additional selection criteria to identify those suitable for contextualization of the eteplirsen-treated cohort. Specifically, studies were included when patients were born after 1980 and when observation occurred under NH conditions. In addition, survival data were required to be reported in a Kaplan–Meier (KM) curve of suitable digital quality, calculated as overall survival with age as the timescale, and reporting the number of patients at risk. No requirements were imposed on the represented *DMD* pathogenic variants (Table S1). Included survival curves were digitized and converted to patient-level survival data to form an NH control cohort using software and approaches as in Broomfield et al. (Supplemental Methods in Supporting Information S1 and Figure S1).

2.3 | Study measures

Age at death, and those alive at the end of follow-up (i.e., without death, administrative censoring), were calculated directly from variables available in the administrative database for eteplirsen-

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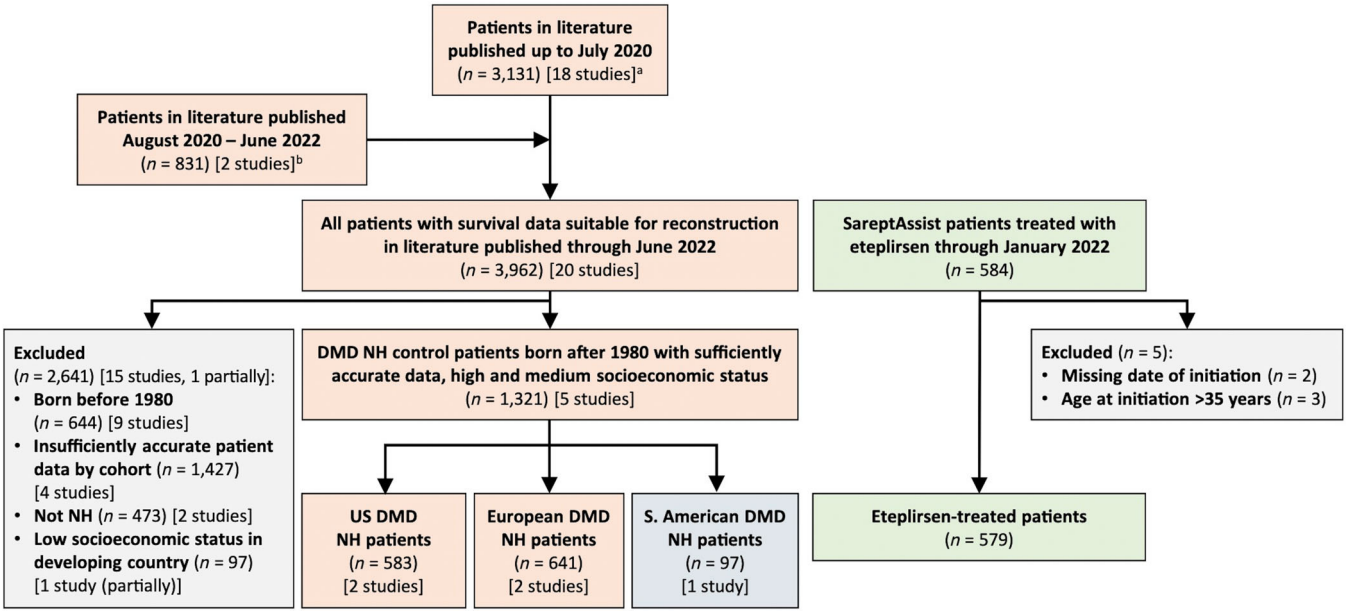

FIGURE 1 Flow diagram of patients included in the study. DMD, Duchenne muscular dystrophy; NH, natural history; SLR, systematic literature review; TLR, targeted literature review. [a]Studies identified by Broomfield et al.[24] SLR, which was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. [b]Studies identified by TLR conducted by authors using the same search terms as Broomfield et al.'s[24] study.

treated patients. Deaths collected after treatment discontinuation were included in the analysis, that is, those patients were not censored. Age at eteplirsen initiation and the total duration of exposure were extended when applicable to account for clinical trial participation based on the specific trial and its protocol-specified duration of exposure (Supplemental Methods in Supporting Information S1). Stratified analysis of survival age was also conducted by duration of eteplirsen exposure (<2, 2–4, and 4+ years).

2.4 | Statistical analysis

The distribution of overall survival age was estimated using KM curves for the eteplirsen-treated cohort and for the patient-level data generated from published survival curves. KM curves were compared using log-rank tests. Separately, time from eteplirsen initiation to death was described using KM curves, with age at eteplirsen initiation serving as the baseline and the subsequent time from baseline to death or censoring serving as the outcome. To contextualize this outcome, an approximately 3:1 baseline age-matched DMD NH control population was generated. Specifically, for each eteplirsen-treated patient, up to three NH controls who were alive at the treated patient's baseline age were sampled from the control population (Supplemental Methods in Supporting Information S1). Survival time from baseline was then compared between the eteplirsen-treated and age-matched control cohorts using Cox proportional hazards regression.

2.5 | Sensitivity analyses

Several sensitivity analyses were conducted to assess the robustness of the findings to use of different NH control sources (e.g., using US patients only), exclusion of patients who first received eteplirsen in clinical trials, application of eteplirsen exposure thresholds, minimum follow-up requirements, and use of different statistical methods (Supplemental Methods in Supporting Information S1 and Table S2).

2.6 | Standard protocol approvals, registrations, and patient consent

This article is based on previously published studies and does not contain any studies with human participants performed by the authors. This analysis received an exemption in accordance with FDA 21 CFR 56.104 and DHHS 45 CFR 46.104 regulations "Secondary Research Uses of Data or Specimens" from the PearlIRB Institutional Review Board (Protocol #22-ANGR-120).

3 | RESULTS

3.1 | Patient characteristics

A total of 579 eteplirsen-treated patients were included. Patients were born between 1985 and 2020, and initiated eteplirsen at ages ranging from 1 to 35 years, with an average age of 11.9 (SD 6.4)

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TABLE 1 Characteristics of eteplirsen-treated patients for the overall sample and by duration of exposure.[a]

		Duration of exposure to eteplirsen		
	Total	<2 years	2–4 years	4+ years
	n = 579	*n* = 130	*n* = 162	*n* = 287
Age at treatment initiation, years[a]				
Mean ± SD	11.9 ± 6.4	11.9 ± 8.2	11.8 ± 6.5	11.9 ± 5.4
Median	11.0	9.0	11.0	11.0
Range	(1.0–35.0)	(1.0–35.0)	(1.0–33.0)	(1.0–32.0)
Prior trial participation, *n* (%)				
No	436 (75.3)	125 (96.2)	151 (93.2)	160 (55.8)
Yes	143 (24.7)	5 (3.8)	11 (6.8)	127 (44.2)
Duration of eteplirsen exposure (continuous), years				
Mean ± SD	3.7 ± 1.9	1.0 ± 0.6	3.2 ± 0.6	5.2 ± 1.0
Median	4.0	1.0	3.3	4.8
Range	0.0–8.6	0.0–2.0	2.0–4.0	4.0–8.6
Duration of eteplirsen exposure (categorical), *n* (%)				
<2 years	130 (22.4)	130 (22.4)	N/A	N/A
2–4 years[b]	162 (28.0)	N/A	162 (28.0)	N/A
4+ years	287 (49.6)	N/A	N/A	287 (49.6)
Study outcome				
Died, *n* (%)	29 (5.0)	16 (12.3)	8 (4.9)	5 (1.7)
Censored, *n* (%)	550 (95.0)	114 (87.7)	154 (95.1)	282 (98.3)
Birth year				
Median	2005	2011	2007	2004
Range	1985–2020	1985–2020	1986–2018	1985–2016

Abbreviation: N/A, not applicable.
[a]Age at treatment initiation was rounded to integer numbers in the SareptAssist data made available for the study.
[b]4.0 not included in the interval.

years at initiation. The duration of exposure ranged from 0.0 to 8.6 years, with a mean (SD) of 3.7 (1.9) years; a total of 143 (24.7%) patients had participated in a prior eteplirsen clinical trial (Table 1).

3.2 | Characteristics of studies contributing to reproduced individual patient data for DMD NH controls

DMD NH controls were identified from studies published up to June 30, 2022, with survival data suitable for reconstruction ($N = 3962$ patients, $N = 20$ studies; Figure 1). Five of twenty studies identified met the inclusion criteria ($n = 1321$ DMD NH controls; Table 2), and four of the five studies were included in the primary analysis, as they described cohorts of patients with DMD in the US and Europe. A total of 307 deaths were observed among the 1224 patients included in the primary DMD NH control cohort. *DMD* pathogenic variants reported in the DMD NH studies are shown in Table S3.

3.3 | Overall survival age contextualized with DMD NH pooled survival curves

During a total follow-up of 2119 person-years, a total of 29 deaths was observed among eteplirsen-treated patients. The KM estimated median survival age was 32.8 years (Figure 2). Overall pooled median survival age in the DMD NH published cohorts was 27.4 years (range 23.7–34.5 years), significantly shorter than in the eteplirsen-treated cohort (5.4 years' difference; Figure 2A). Cox proportional hazards model estimates were consistent with these findings, showing that eteplirsen-treated patients had a 66% lower hazard of death compared with DMD NH controls (hazard ratio [HR], 0.34; 95% confidence interval [CI], 0.23–0.50). Sensitivity analyses comparing eteplirsen-treated patients with different DMD NH control subgroups yielded results consistent with those of the main analysis (Figure 2B–D), with greater median survival ages for the eteplirsen cohorts by a range of 2.1–8.6 years. Wang et al.'s[26] US study and van den Bergen et al.'s[27] and Wahlgren et al.'s[28] European studies were included in sensitivity analysis 3 (Figure 2D); however, Paramsothy et al.'s[29] US study was excluded due to lower overall survival versus other DMD NH studies included in the main

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TABLE 2 Characteristics of studies contributing to reproduced individual patient data for DMD NH controls.

Study	Paramsothy[a,b,c]	Wang[a,b,c,d]	van den Bergen[a,b,d]	Wahlgren[a,b,d]	San Martin[c]
Publication year	2022	2018	2014	2022	2018
Country	United States	United States	Netherlands	Sweden	Chile
Region	AZ, CO, IA, NY, GA, HI	Greater Cleveland, OH	Entire country	Entire country	Entire country
Total patients included	526	57	336	305	97
Total deaths	136	27	41	103	52
Total censored, *n* (%)	390 (74.1)	30 (52.6)	295 (87.8)	202 (66.2)	45 (43.7)
Age at study entry	–	18.1 ± 6.7	–	–	7.2 (6.8–7.7) (1993–2002 cohort) 6.1 (5.7–6.5) (2003–2013 cohort)
Median survival age (95% CI), years	23.7 (22.3, 24.2)	31.7 (27.4, 36.0)	29.0[e]	29.9 (27.1, 31.2)	High SES: 22.7[e] Medium SES: 23.3
Source	TLR	SLR	SLR	TLR	SLR
Birth cohort[f]	1982–1999 (data cut 2011)	>15 years old 2003–2015, at least 3 ECHO[g]	1980–2006 (data cut approx. 2013)	1980–2009 (data cut 2019)	Admitted 1993–2013[g] (data cut July 30, 2014)
Corticosteroid use, *n* (%)	220 (43.7)[h]	15 (26.3)	165 (49.1)	–	–
ACEI or ARB use, *n* (%)	262 (52.0)[h,i]	51 (89.5)	41 (12.2)	–	–
Beta-blocker use, *n* (%)	262 (52.0)[h,i]	33 (57.9)	18 (5.4)	–	–
Ventilation assistance, *n* (%)	191 (37.9)[h]	50 (87.7)	93 (27.7)	–	–
SES, *n* (%)					
High income	–	–	–	–	15 (15.5%)
Medium–high income	–	–	–	–	82 (84.5%)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; CI, confidence interval; DMD, Duchenne muscular dystrophy; ECHO, echocardiogram; NH, natural history; SES, socioeconomic status; SLR, systematic literature review; TLR, targeted literature review.
[a]Reproduced individual patient data were included in the natural history 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]Reproduced individual patient data were included in the external control sample for sensitivity analysis 2 only.
[e]95% CIs not reported.
[f]The "post-1990" birth cohort analyzed by Broomfield et al. included a small number of patients born between 1980 and 1990 as some of the survival data in the original studies did not specify birth cohort. The studies included in this cohort were Wang et al., van den Bergen et al., and San Martin et al.
[g]Birth cohort not reported.
[h]Reported for $N = 504$ in the cohort analyzed for time to death since age 10.
[i]Cardiac medication use reported in aggregate.

analysis. The results of additional sensitivity analyses (e.g., not extending the exposure to eteplirsen using the clinical trial periods, excluding patients with prior trial exposure) were consistent with those of the primary analysis (data not shown).

3.4 | Overall survival time from eteplirsen treatment initiation

Analysis of survival from eteplirsen treatment initiation showed that eteplirsen-treated patients had significantly longer survival compared with age-matched DMD NH controls (Figure 3A). Consistent with the KM results, HR estimates from Cox proportional hazards models adjusting for baseline age indicated that eteplirsen-treated patients had 35% lower hazard of death compared with age-matched DMD NH controls (HR, 0.65; 95% CI, 0.44–0.98; Table 3). When adjusted for baseline age and eteplirsen-baseline age interaction, results indicated that the youngest eteplirsen-treated patients had 80% higher survival compared with age-matched controls. The coefficient of the interaction term indicated that the difference in survival between eteplirsen-treated patients and DMD NH controls was more pronounced with lower age at initiation (Table 3). In the subgroup of

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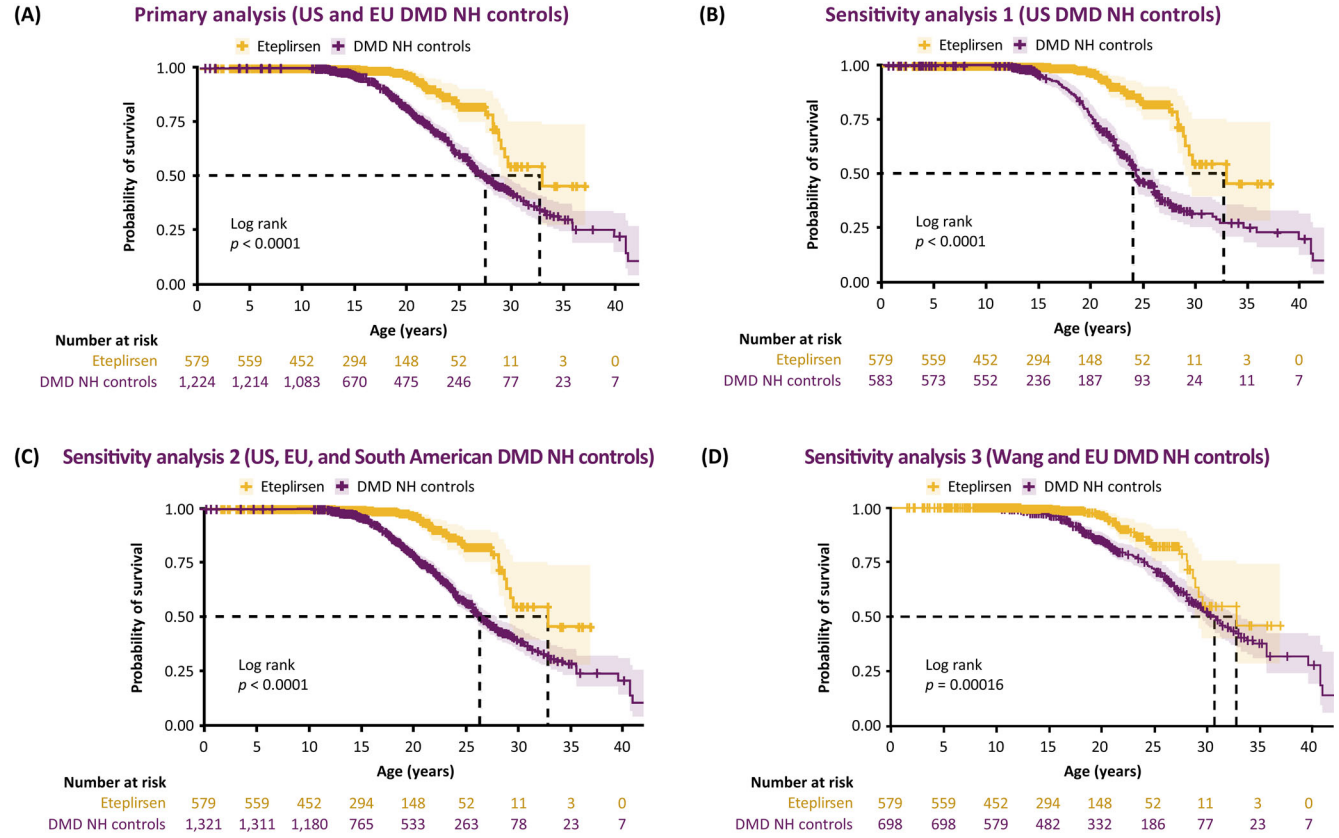

	Primary analysis	Sensitivity analysis 1	Sensitivity analysis 2	Sensitivity analysis 3
Δ Median age of death, years (eteplirsen vs. NH)	5.4 (32.8 vs. 27.4)	8.6 (32.8 vs. 24.2)	6.4 (32.8 vs. 26.4)	2.1 (32.8 vs. 30.7)
HR (95% CI), *p* value	0.34 (0.23, 0.50) <0.001	0.25 (0.17, 0.38) <0.001	0.31 (0.22, 0.46) <0.001	0.47 (0.32, 0.70) <0.001

FIGURE 2 Kaplan–Meier analysis of survival age for eteplirsen-treated patients and DMD NH controls. CI, confidence interval; DMD, Duchenne muscular dystrophy; NH, natural history; NR, not reached. The Kaplan–Meier estimated median survival age for eteplirsen-treated patients was 32.8 years, and pooled median survival age in the DMD NH cohorts was 27.4 years (5.4 years difference) (A). Sensitivity analyses comparing eteplirsen-treated patients with different DMD NH control subgroups yielded results consistent with those of the main analysis (B–D). Shaded areas represent 95% confidence bands. Tick marks represent censored patients.

patients 10–28 years for whom deaths are most likely to be observed, significantly higher probability of survival was observed for eteplirsen-treated patients versus DMD NH controls (HR, 0.58; 95% CI, 0.38–0.89), although the median survival time was not reached in either group (Figure 3B).

3.5 | Overall survival age by duration of eteplirsen exposure

Patients treated with eteplirsen for <2 years had a median survival age of 28.1 years (Figure 4). KM estimates showed that patients treated with 2–4 years or >4 years of eteplirsen had not reached the median survival time, indicating that longer eteplirsen treatment was associated with longer survival time (Figure 4). Patients with >4 years of eteplirsen treatment had an 85% lower risk of death compared with patients with <2 years of treatment exposure (HR, 0.15; 95% CI, 0.05–0.41; Figure 4).

4 | DISCUSSION

This study reports overall survival outcomes from a large cohort of patients receiving eteplirsen. Median survival age appeared to be greater when compared with multiple published DMD NH controls from similar birth cohorts representing the US and other regions. When compared with age-matched DMD NH controls, eteplirsen treatment was associated with a lower hazard of death. Sensitivity analyses of survival that included DMD NH data from different geographic regions yielded similar results.

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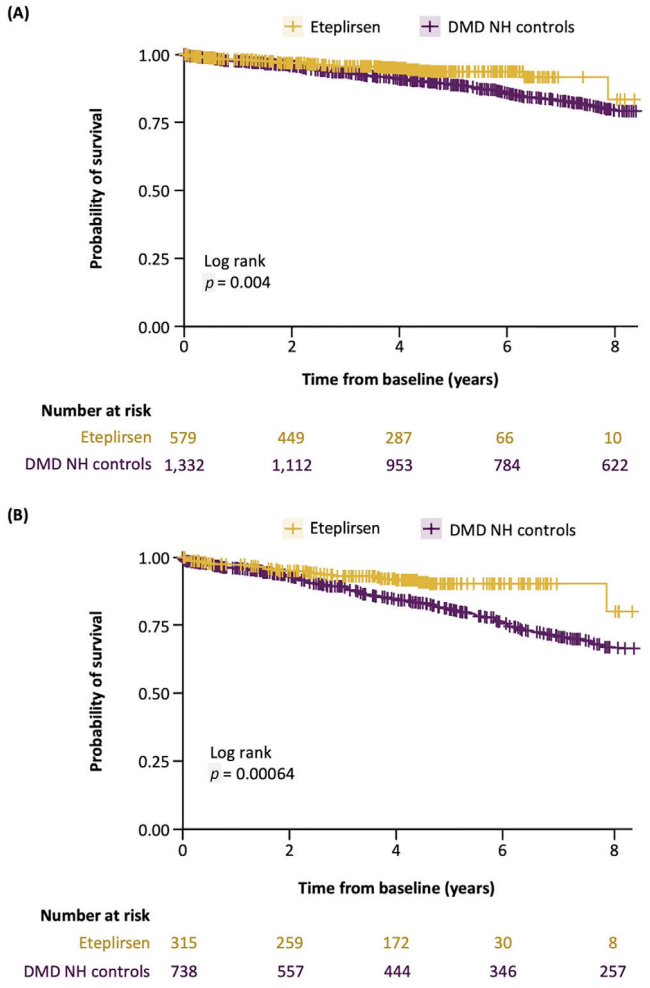

FIGURE 3 Kaplan–Meier analysis of survival from eteplirsen treatment initiation among eteplirsen-treated patients and age-matched DMD NH controls (A) all patients (b) patients ages 10–28 at treatment initiation (eteplirsen-treated) or baseline (DMD NH). Analysis of survival from eteplirsen treatment initiation showed that eteplirsen-treated patients had significantly longer survival compared with age-matched DMD NH controls (A). Significantly higher probability of survival in the 10–28 years subgroup was observed for eteplirsen-treated patients versus DMD NH controls, although the median survival time was not reached in either group (B). Tick marks represent censored patients.

TABLE 3 Estimates for Cox proportional hazards models[a] for survival time from baseline comparing eteplirsen-treated patients with age-matched DMD NH controls.

	Cox model 1[b] HR estimate (95% CI)	Cox model 2[c] HR estimate (95% CI)
Eteplirsen	0.65* (0.44–0.98)	0.20** (0.06–0.59)
Age at baseline	1.15*** (1.13–1.17)	1.14*** (1.12–1.16)
Eteplirsen × age at baseline		1.07* (1.01–1.12)

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a]Global Schoenfeld residual tests indicated that there is overall evidence of nonproportionality of hazards; this suggests that the HR estimates should be interpreted cautiously as average values over the entire follow-up period, as there is evidence of significant heterogeneity for *Age at baseline* across different follow-up segments. However, the partial Schoenfeld test for the *Eteplirsen* variable is not significant, indicating that there is no evidence of nonproportionality of hazards by treatment arm (Figure S2).
[b]Cox proportional hazards model controlled for eteplirsen and baseline age.
[c]Cox proportional hazards model controlling for eteplirsen, baseline age, and the interaction of the two.
*$p < .05$; **$p < .01$; ***$p < .001$.

Clinical studies so far have demonstrated the positive effect of eteplirsen on slowing disease progression, but survival has not yet been assessed; this is due to the need for large patient numbers and lengthy follow-up for a clinical endpoint to be demonstrated in clinical trials. Evidence from several other clinical trials and the present study reinforces the hypothesis that changes at a molecular level can translate into meaningful clinical benefits.[20–22] In a small ($n = 12$) randomized, double-blind, placebo-controlled study,[21] longer exposure to eteplirsen led to an increased percentage of dystrophin-positive fibers (i.e., an increase of 23% at 24 weeks and 52% at 48 weeks), as well as an increase in 6-min walk test distance relative to patients who received placebo or delayed eteplirsen treatment. A larger phase 3, multicenter, open-label study of eteplirsen showed dystrophin protein accumulation over time (i.e., a 7.02-fold increase at 96 weeks from baseline) as well as slowing of functional decline over 96 weeks.[23] In two longitudinal studies comparing data from eteplirsen-treated patients enrolled in clinical trials with data from NH controls,[20,22] eteplirsen was associated with significantly longer median time to loss of ambulation and significantly attenuated rates of pulmonary decline during follow-up of up to 7 years. The evidence that eteplirsen slows ambulatory and pulmonary decline suggests that an impact on survival may be reasonably expected, given that most deaths in patients with DMD occur due to cardio-pulmonary failure.[30]

The present study provides an analysis of long-term survival data from a large cohort of patients treated with a therapy targeting the underlying cause of DMD, contextualized with survival estimates from the literature. Despite data not being available to adjust for differences in baseline functional characteristics, comparisons of these treated patients with age-matched controls suggest that eteplirsen may indeed provide survival benefits, in line with prior evidence on its effects of dystrophin expression and clinical function.

The statistical comparisons of age at disease milestone event, while common in DMD literature,[11,31] were conducted between non-randomized groups and did not match patients with similar characteristics at treatment initiation, potentially leading to selection bias and unobserved confounding. For instance, patients in the DMD NH cohorts came mainly from studies of mortality in different countries with different procedures and selection criteria, and thus varied in their ability to select cohorts' representative of the overall DMD population. While the analyses of time from treatment initiation allowed accounting for baseline age, they were based on a matching procedure that randomly selected subgroups of DMD NH patients still alive at each age of treatment initiation, in effect mimicking the

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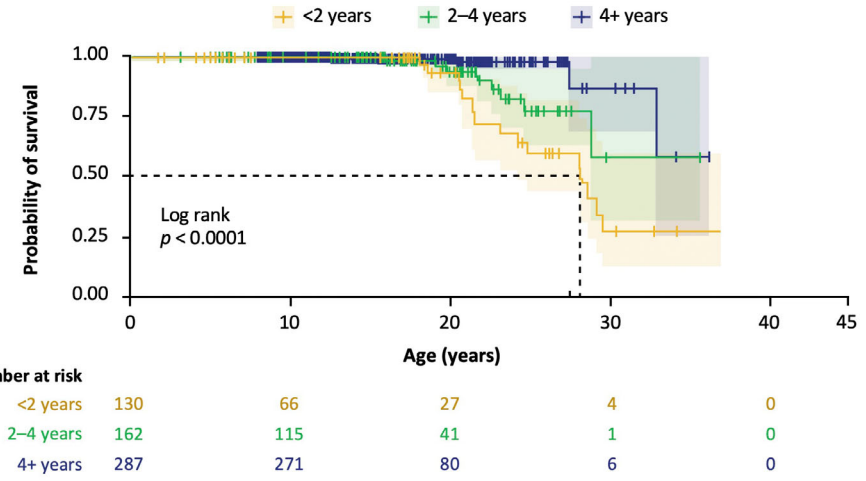

FIGURE 4 Kaplan–Meier analysis of survival age stratified by duration of exposure to eteplirsen in eteplirsen-treated patients. CI, confidence interval; DMD, Duchenne muscular dystrophy; NR, not reached. Kaplan–Meier estimates indicated that longer eteplirsen treatment was associated with greater survival. A median survival age of 28.1 years was estimated for eteplirsen treatment duration of <2 years, and median survival time had not been reached for eteplirsen treatment duration of 2–4 years or >4 years. Shaded areas represent 95% confidence bands. Tick marks represent censored patients.

Exposure duration	HR	95% CI	*p*
<2 years (ref.)	–	–	–
2–4 years	0.47	(0.20, 1.13)	0.09
4+ years	0.15	(0.05, 0.41)	<0.001

Exposure duration	Median survival age (years)	95% CI
<2 years	28.1	(24.2, NR)
2–4 years	NR	(28.9, NR)
4+ years	NR	(32.8, NR)

construction of a synthetic placebo group. Moreover, while selecting the most comparable group of DMD NH patients from the available published literature was sought, some studies[32] did not report sufficient data to allow for curve digitization and reproduction of patient data. Sensitivity analyses were conducted to explore the potential effect of attrition bias by excluding patients who discontinued eteplirsen, given that patients who discontinued eteplirsen could in theory do so right before death due to the observational nature of the data; however, the findings were consistent with those in the primary analysis.

Patients were included in the present study only if they survived up to the point of enrollment in the SareptAssist program, which may introduce immortal time bias.[33] However, this is not only a potential issue in the eteplirsen-treated group but also for the DMD NH studies identified, which were generally cohort studies with incomplete coverage of the entire DMD population in a given geographic region. Furthermore, in the stratified analysis of survival age by duration of eteplirsen exposure, patients with longer exposure times had longer survival, while the mean age at eteplirsen initiation was similar for patients in each of the exposure categories (Table 1).

The potential difference in DMD genotype between the groups could have biased the survival comparison as genotype differences in DMD have been linked to different clinical trajectories.[3,34] Patients in the SareptAssist database all have *DMD* pathogenic variants amenable to exon 51 skipping, while NH studies include patients with all pathogenic variants (Table S3). However, given that several studies have found that patients with exon 51 skip-amenable pathogenic variants tend to exhibit faster disease progression with respect to loss of ambulatory function[35] compared with other genotypes,[3,34–37] it is expected that the genotype composition may have slightly biased the study results in favor of the DMD NH cohort. Therefore, the estimated effect of eteplirsen on survival in this analysis is likely conservative.

Adherence to treatment guidelines and other aspects of standards of care for DMD may have differed between eteplirsen-treated and DMD NH patients, including the use of corticosteroids, noninvasive ventilatory assistance, physical therapy, and spine scoliosis surgery, which may have affected disease progression and survival.[1,11,38–40] In particular, prior research reported a significant 76% reduction in mortality rates associated with long-term steroid therapy in patients with DMD.[11,39] However, patients treated with corticosteroids in this study had similar survival rates to US DMD NH patients in the present study, thereby further illustrating the mortality rates that can be expected even among corticosteroid-treated patients.

Patients who access eteplirsen in the US via health insurance may not be entirely representative of the overall DMD patient population. For example, these patients may have better access to care compared with patients with less insurance coverage, which could bias the findings toward a higher impact of eteplirsen. We addressed this limitation by conducting a descriptive analysis of the Data Resources Group (DRG) Real-World Data Repository (Supplemental Methods in Supporting Information S1), a healthcare claims database with national US coverage. The results of this analysis suggest that the corticosteroid

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and ventilatory assistance use rates were similar in eteplirsen-treated and nontreated patients with DMD in the US. The corticosteroid use rate in the DRG database, in particular, was very similar between the 2 groups: eteplirsen-treated ($n = 546$), 216 (39.6%); not eteplirsen-treated ($n = 1583$), 602 (38.0%). Nevertheless, we cannot entirely rule out the possibility that changes in treatment patterns, such as variations in corticosteroid treatment rates over time, may confound our analysis.

The relatively low overall treatment exposure time may limit the detection of survival benefits. Although almost half of eteplirsen-treated patients had been exposed to treatment for 4+ years, a significant number of patients had <2 years of exposure, which may not be sufficient time for the impact of eteplirsen to be evident. Moreover, due to limited follow-up in both the SareptAssist database and in the DMD NH studies, only a limited number of patients were observed beyond the age of 25, and the different follow-up lengths across the studies may affect the results.

Because a subset of eteplirsen-treated patients ($n = 143$) was exposed to eteplirsen in prior trials, but patient identifiers were unavailable, there was also a possibility of misclassification bias for exposure imputation. However, extensive sensitivity analyses were conducted removing prior trial participants from analysis or foregoing the extension of exposure based on trial duration to mitigate this bias, and findings supported the main results. Furthermore, for eteplirsen-treated patients, only age at treatment initiation rounded to the nearest integer was available from SareptAssist, which introduced some uncertainty in the estimates of survival age.

While the timing of the NH studies makes it highly unlikely that any of the DMD NH patients were treated with eteplirsen for some period of time, this possibility that a small number of patients received in clinical studies cannot be completely excluded. Some of the patients in the US studies had exon 51 skip-amenable pathogenic variants, and the data cut for Wang et al.'s study is 2015, when there was no commercial eteplirsen but when eteplirsen clinical trials (initiated in 2011) were ongoing. However, it is important to note that any potential bias resulting from this treatment contamination is likely to be minimal due to the small number of patients who might have received treatment (e.g., Wang et al.'s study only included 5 patients with exon 51 deletions) and the short treatment duration in question. Additionally, any such bias would also likely lead to an attenuated treatment effect, making the estimates in the current study more conservative.

Nonetheless, future research may benefit from the assessment of other factors affecting survival among eteplirsen-treated patients relative to DMD NH controls.

5 | CONCLUSIONS

The clinical data presented in the current study suggest that eteplirsen may prolong survival in patients with DMD across a wide age range in both unadjusted and treatment initiation age-adjusted analyses. However, acknowledging the rare nature of disease, multiple confounding variables, and evolving standard of care, further analyses should be conducted on survival impact of DMD therapies as more data become available.

AUTHOR CONTRIBUTIONS

Joel Iff: Conceptualization; writing – review and editing; writing – original draft; methodology; validation. **Nicolae Done:** Conceptualization; methodology; validation; writing – review and editing; formal analysis. **Edward Tuttle:** Conceptualization; formal analysis; methodology; validation; writing – review and editing. **Yi Zhong:** Conceptualization; visualization; formal analysis; writing – review and editing. **Fangzhou Wei:** Conceptualization; writing – review and editing; formal analysis. **Basil T. Darras:** Writing – review and editing. **Craig M. McDonald:** Writing – review and editing. **Eugenio Mercuri:** Writing – review and editing. **Francesco Muntoni:** Writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

Joel Iff: Employee of Sarepta Therapeutics, Inc., and may own stock/options in the company. Nicolae Done, Edward Tuttle, Yi Zhong, and Fangzhou Wei: Employees of Analysis Group, Inc., a consultancy, which received payment from Sarepta Therapeutics, Inc., for participation in this analysis. Basil T. Darras: Honoraria from Sarepta Therapeutics, Inc., for advisory board participation. Craig M. McDonald: Grants from Capricor, Catabasis, Edgewise, Epirium Bio, Italfarmaco, Pfizer, PTC Therapeutics, Santhera Pharmaceuticals, Sarepta Therapeutics, Inc., and other remuneration from Capricor, Catabasis, PTC Therapeutics, Santhera Pharmaceuticals, and Sarepta Therapeutics, Inc. Consultancies for advisory boards from Sarepta Therapeutics, Santhera Pharmaceuticals, Biomarin, and Edgewise. Honoraria for symposia from Sarepta Therapeutics and PTC Therapeutics. Eugenio Mercuri: Consultant fees from Sarepta Therapeutics, Inc. Francesco Muntoni: Consultancies for advisory boards and symposia participation from Sarepta Therapeutics, Inc., and consultancies from PTC, Dyne Therapeutics, Roche, Santhera Pharmaceuticals, and Pfizer.

DATA AVAILABILITY STATEMENT

Individual de-identified patient data will not be available in a publicly accessible repository to protect the interests of the patients, in accordance with the policies of Sarepta Therapeutics, Inc., and in line with the General Data Protection Regulation.

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ETHICAL PUBLICATION STATEMENT

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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