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Real-world evidence of eteplirsen treatment effects in patients with Duchenne muscular dystrophy in the USA

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Aim: To evaluate treatment effects of eteplirsen among patients with Duchenne muscular dystrophy. **Methods:** Using real-world claims and electronic medical record data, this retrospective comparative analysis assessed eteplirsen-treated and control cohorts matched by age, disease progression state, and pre-index period healthcare resource utilization. Poisson regression was used to evaluate eteplirsen effects on healthcare resource utilization outcomes. **Results:** Eteplirsen was associated with statistically significant reductions in rates of hospital encounters (31%), emergency room visits (31%), need for pulmonary management (33%), cardiac management (21%), tracheostomy (86%), and assisted ventilation (39%) versus the control group. Other assessed outcomes favored eteplirsen numerically but did not all reach statistical significance. **Conclusion:** Eteplirsen-treated patients had reduced rates of multiple healthcare resource utilization measures versus matched controls.

Plain language summary: How eteplirsen treatment impacts the health of people living with Duchenne muscular dystrophy in the United States: What is this article about?: Duchenne muscular dystrophy (DMD) is a rare genetic disease. People with DMD do not make a protein called dystrophin. This leads to damage to all muscles, including the heart and the muscles used for breathing. Patients also lose the ability to walk and take care of themselves. Treatment for DMD is complex, and as the disease progresses, patients use more healthcare resources. Eteplirsen is a treatment for people with DMD, which is caused by mutations in a specific part of the gene, and helps produce shortened but functional dystrophin. Researchers looked at information from insurance claims and electronic medical records to compare healthcare resource use in people who received eteplirsen (n = 579) and those who received standard of care (n = 1296).
What were the results?: Patients receiving eteplirsen had significantly fewer hospital admissions (31%) and emergency room visits (31%). Patients also had a reduced need for special care of the lungs (pulmonary management) (33%), care for the heart (cardiac management) (21%), special surgery to access the windpipe (tracheostomies) (86%), and help with breathing (assisted ventilation) (39%) compared with patients who received standard of care.
What do the results mean?: These results suggest that people who received eteplirsen in routine clinical care settings used healthcare resources less often compared with patients who did not receive eteplirsen. Similar findings were seen in people receiving eteplirsen in clinical trials. These results suggest that eteplirsen treatment delays muscle damage in people with DMD.

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Keywords: disease burden • Duchenne muscular dystrophy • eteplirsen • real-world • treatment effects

Duchenne muscular dystrophy (DMD) is a rare, X-linked, neuromuscular disease characterized by muscle deterioration due to the lack of functional dystrophin protein, caused by mutations in the *DMD* gene [1]. Patients

with DMD have progressive muscle fiber damage from birth, which leads to functional impairments and loss of self-care skills over time [2–4], necessitating complex and resource-intensive multidisciplinary care [5–7]. On average, death occurs by the third decade of life, mostly from cardiopulmonary compromise, with median life expectancy estimated at 28.1 years (95% confidence interval [CI]: 25.1, 30.3) [8–10]. While survival of patients with DMD has improved with early use of molecular diagnostics, emerging innovative interventions, and updated standardization of care guidelines [5,11,12], it is still associated with a significant burden for patients [10,13] and reduced quality of life across physical, social, and psychological domains [14,15]. With loss of functional mobility and increasingly impaired cardiopulmonary function [16], the financial cost associated with DMD also climbs dramatically [13]. Reliance on caregivers also increases over time, especially with loss of ambulation and the need for ventilatory assistance due to deteriorating pulmonary function [10].

As muscle damage and loss of function in patients with DMD is irreversible, it is crucial to diagnose and treat the disease as early as possible. As such, currently available treatments for DMD focus on delaying disease progression [17,18]. Targeted therapies for patients with certain types of mutations have also been developed recently. Eteplirsen and the more recently approved golodirsen, casimersen, and viltolarsen are phosphorodiamidate morpholino oligomers (PMOs) approved for the treatment of patients with DMD with mutations amenable to exon 51 skipping (eteplirsen), exon 53 skipping (golodirsen and viltolarsen), or exon 45 skipping (casimersen) [13,19]. Specifically, these PMO treatments bind to exon 51, 53, or 45 of dystrophin pre-mRNA to induce skipping of the respective exon, thus restoring the reading frame and enabling translation of a truncated, but functional, dystrophin protein.

Clinical trials have shown that eteplirsen is well tolerated and associated with statistically significant and clinically meaningful attenuation of pulmonary and ambulatory declines compared with matched control patients from natural history data sets [20–23]. While these studies provide evidence of eteplirsen's efficacy in the trial population, real-world data for patients outside of the clinical trial setting are limited given the rarity of DMD and recency of PMO approvals. This study intended to bridge this data gap by comparing healthcare resource utilization (HRU) in various DMD-related measures from a real-world dataset of eteplirsen-treated patients from claims covering most of the US population and linked electronic medical records (EMRs) with those of a non-PMO-treated control matched cohort of patients.

Patients & methods

Data source

This study used data from the Clarivate Real-World Data repository, which includes open medical and pharmaceutical claims data from multiple electronic data interchanges and EMR data from a major EMR vendor that included more than 300 million patients representative of the population of all US states [24]. The data vendor matched all provider-based sources at the patient level by linking information from different pharmacy and clinic networks, thus enabling longitudinal tracking of patients over time and across multiple data sources, even if they had changed provider or health insurance during the course of receiving services or medications. Although there are systems in place to ensure data quality within any real-world dataset, it is possible that an open claims database may not fully capture all medical services that patients may have received from out of network providers. As such, potential data missingness may represent a limitation among this dataset if patient cohorts of interest are disproportionately affected. The Clarivate data provide a rich source of information on medical care utilization and health status for a large cohort of patients. Indeed, these data have been used in multiple studies evaluating medical costs and HRU [25,26]. Data were de-identified by the vendor in compliance with requirements of the Health Insurance Portability and Accountability Act. Data from January 2011 to June 2021 were extracted from the database by the vendor and were provided for this analysis.

Study design

This was a retrospective comparative analysis to assess rates of DMD-related HRU in eteplirsen-treated patients versus matched controls. Figure 1 illustrates the study design. For eteplirsen-treated patients, the index was defined as the time of eteplirsen initiation; for the control group, the index was defined as the time at which the patient was matched to an eteplirsen-treated patient (i.e., month-year; further detail is provided in the matching methods section). For both groups, the pre-index period was defined as the period from the earliest claim (or EMR record) that occurred within the 12-month window prior to index up to the index date. The follow-up period was defined as the period from index to the last claim or EMR record entry.

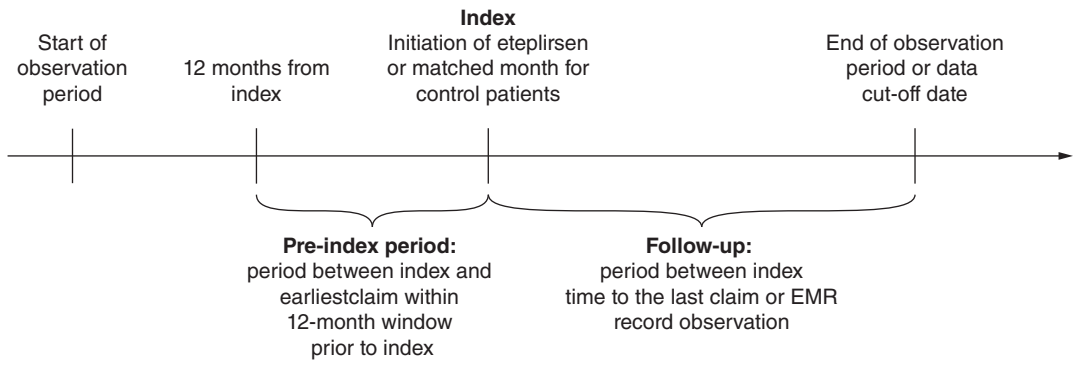

Figure 1. Study design.
EMR: Electronic medical record.

The design and reporting of this study aligned with the Structured Template and Reporting Tool for Real World Evidence framework [27] and relevant requirements of the US FDA guidance published in 2021 [28] by including research objectives, data source information, data collection, definition of index time, sample inclusion/exclusion criteria, covariates and outcome variable definition, and analysis specification. All data incorporated into the Clarivate Real-World Data repository and used in this study were de-identified at the original data source utilizing a third-party data encryption engine to tokenize each patient record with no reidentification possible by the researchers in this study.

Patients

Data provided by Clarivate were drawn from January 2011 to June 2021 for patients with: (1) at least one diagnosis code of muscular dystrophy (MD) identified by *International Classification of Diseases* 9th/10th revision (ICD-9/ICD-10) codes. Within this group of patients, the presence of Systematized Nomenclature of Medicine (SNOMED) clinical term code 76670001 (which is used to identify DMD specifically) or a record of eteplirsen treatment (NDC 60923-284-10 or 60923-363-02 or Healthcare Common Procedure Coding System [HCPCS] codes C9484 or J1428) was used to identify patients with DMD and to exclude potential Becker muscular dystrophy diagnoses included within the (ICD-9/ICD-10) code for MD.

Patients in the control group were required to be identified as having DMD and were not to be treated with eteplirsen or another approved novel DMD treatment: golodirsen (NDC 60923-465-02), viltolarsen (NDC 73292-011-01), or casimersen (NDC 60923-227-02). Forty-one percent of patients in the extracted dataset had EMR data that included the SNOMED code; thus, the proportion of patients with DMD available for inclusion in the control group was restricted to this subset.

Sample selection is shown in Figure 2. Patients from the Clarivate dataset were included in this analysis if they were younger than 40 years of age at the first observed diagnosis in the data (which may not be the actual clinical diagnosis) for DMD or the initiation of eteplirsen, golodirsen, or casimersen treatment. Only male patients receiving eteplirsen were included in the primary analysis and are reflected in Figure 2 below. Sensitivities, including those patients with golodirsen treatment (only males received golodirsen), casimersen treatment, or female sex are reported in Tables 5, 6, and 7. Treated patients included in this analysis were required to have a pre-index period observation (i.e., observation from earliest claim to index time) of 12 months and a follow-up period of at least 6 months. For patients in the control group (no predefined index date), a minimum of 18 months of observation was required.

Outcomes

DMD-related HRU procedures and events were identified using multiple ICD-9, ICD-10, HCPCS, and Current Procedural Terminology codes in the EMR and claims data. Place-of-service information was also used to identify hospital encounters and emergency room (ER) visits.

The HRU procedures and events assessed in this study and their definitions are detailed in Table 1. For a given patient on a given day, each HRU outcome was counted only once if any of the codes associated with the outcome were observed. For each patient, the average yearly rate for each outcome was calculated using the total number of events and number of years observed (including fractions of years based on days of observation). Hospital

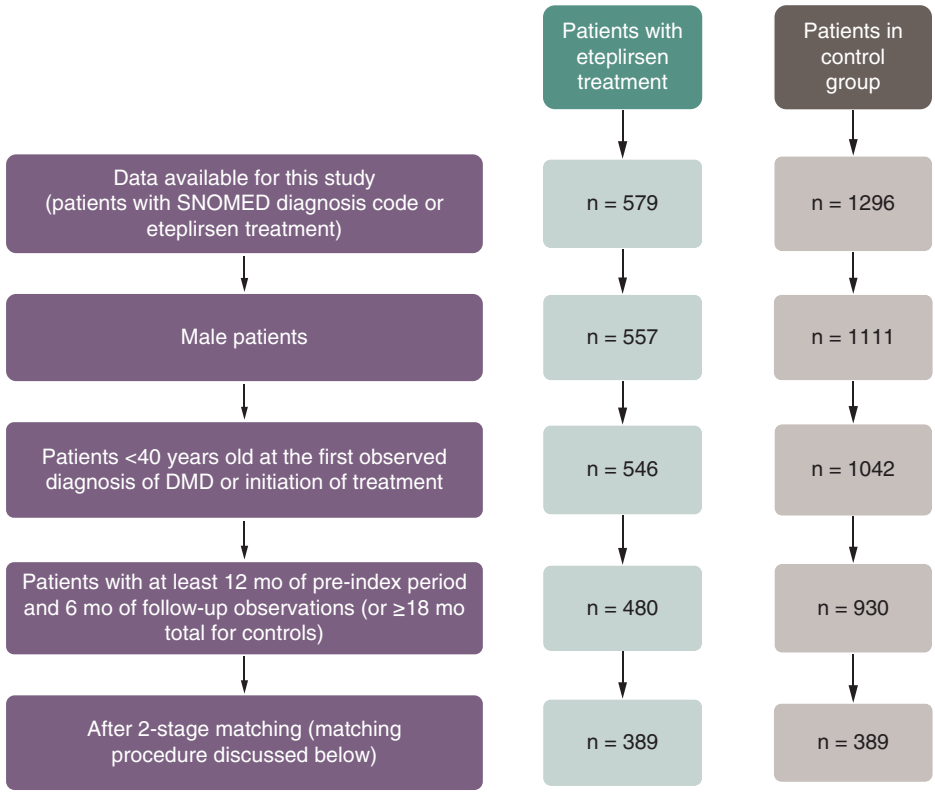

Figure 2. Sample selection.
Note: One eteplirsen-treated patient included in the final sample was observed to discontinue eteplirsen and initiate viltolarsen (potentially due to being amenable to both exon 51 and exon 53 skipping). Consistent with other patients discontinuing eteplirsen, the entire follow-up period for this patient was included in the analysis. There are 389 patient-month pairs from the control group matched to the 389 treated patients. The 389 patient-month pairs include 279 independent control patients.
DMD: Duchenne muscular dystrophy; mo: Month; SNOMED: Systematized Nomenclature of Medicine.

Table 1. Definitions of healthcare resource utilization procedure and event outcome variables.

Outcome	Definition
Hospital encounters	Total number of unique diagnoses and procedure codes per service day performed in the inpatient/hospitalization setting, identified by place of service
ER visits	Total number of unique diagnoses and procedure codes per service day performed in the ER setting, identified by place of service and procedure codes specific to the ER
ICU visits	Total number of unique diagnoses and procedure codes per service day performed in ICU, identified by procedure codes specific to ICU
Motorized wheelchair-related events	Total number of unique procedure codes per service day for motorized wheelchair and chair accessories
Scoliosis events	Total number of unique diagnosis and procedure codes per service day for scoliosis diagnoses, procedures, and devices
Cardiac management events	Total number of unique diagnosis and procedure codes per service day for cardiac-related monitoring, procedure, and diagnostic services
Pulmonary management events	Total number of unique procedure codes per service day for pulmonary management services that are typically needed to assist with normal functioning, such as nasal, positive airway, and other breathing devices
Cough assist device-related events	Total number of unique procedure codes per service day for cough stimulating or interface for cough stimulating devices
Assisted ventilation events	Total number of unique diagnosis and procedure codes per service day for assisted ventilation procedure or equipment prescription
Tracheostomy events	Total number of unique diagnosis and procedure codes per service day for tracheostomy procedure or equipment prescription

ER: Emergency room; ICU: Intensive care unit.

encounters, ER visits, and intensive care unit (ICU) stays were measured by length of stay, which was calculated as the number of consecutive days with any codes associated with hospitalization, ER, and ICU, respectively. In addition, hospitalization, ER, and ICU measures adjusted for the intensity of care (i.e., care-adjusted numbers) were also calculated based on the total number of distinct codes per day in each hospitalization, ER, or ICU encounter.

The DMD-related HRU procedures and events were measured at the pre-index period and during the follow-up period among the eteplirsen-treated and control patients.

Health stage algorithm to measure disease progression

Measuring DMD progression over time has always been challenging in real-world settings, but it is critical in order to select comparable treated and control cohorts for treatment effect evaluation. This study followed Iff *et al.* in classifying patients with DMD according to the four stages of disease progression: early ambulatory (stage 1), late ambulatory (stage 2), early non-ambulatory (stage 3), and late non-ambulatory (stage 4) [29]. This progression identification method was validated using natural history data containing both clinical and claims associated information [29], with each stage determined based on a combination of patient characteristics and markers of DMD progression. Disease stage using the four categories was assessed monthly for each patient in this analysis. The identified stage was carried forward until a more severe stage was identified and it was assumed that patients would not revert to an earlier stage.

Matching

Due to the nature of the study, patients with DMD receiving eteplirsen or, in sensitivity analyses selected other PMO treatment, may have differed from control patients in both observable and non-observable ways (e.g., age, disease stage, other morbidity, and HRU behavior). To minimize the effect of potential confounders and to establish more comparable treated and control cohorts at the pre-index period, a two-step matching approach was applied to balance characteristics among treated and control patients hierarchically. As described further below, this process includes a step of exact matching and a step of propensity score matching, resulting in a final analytical dataset in which each treated patient was matched 1:1 to the most comparable control patient at the most comparable month of disease progression (i.e., the patient-month pair with closest propensity score) based on observed patient characteristics at the pre-index period. The matched sample was used for the subsequent statistical analyses.

Step 1: exact matching on age & health stage

In the first step, each treated patient was matched to control patients with the same age (measured in months) and health stage at index. For eteplirsen-treated patients, index was defined as the earliest observed date with an eteplirsen prescription or injection. For control patients, any month that satisfies the pre-index period and follow-up requirements could serve as the index for matching a control patient to an eteplirsen-treated patient. Each underlying control patient is thus able to be defined at a given patient-month in which their pre-index period characteristics may be most closely matched to a treated patient at index, and their subsequent follow-up data can be used in the analysis. In this step, there was no limit on the number of control patients (or patient-months) to which each treated patient could be matched (the next step limits to one control patient-month matched to each treated patient). All control patients (or patient-months) who had the same age and health stage as a treated patient at index were included. For example, a control patient aged 12.5 years and at stage 3 in July 2019 could be matched to any treated patient who was aged 12.5 years and at stage 3 when they initiated eteplirsen, with July 2019 being the control patient's pseudo-index.

Step 2: propensity score matching on DMD-related HRU procedures & events at the pre-index period

Within the matched sets from step 1, a further level of matching was applied using propensity score matching to select the most comparable control patient-month for each treated patient based on the rates of the main DMD-related HRU procedures and events within a 12-month window before index. Specifically, a logistic regression was estimated using eteplirsen treatment as the dependent variable and matching criteria measures as independent variables. After sample selection, patients included for propensity score matching do not have missing data. A propensity score is then calculated for each treated patient and control patient-month based on the estimated coefficients. From the matched sets from step 1, each eteplirsen-treated patient was matched at index 1:1 to the control patient-month with the closest propensity score value to the treated patient. Matching was conducted without replacement in this step using "MatchIt" package in R software.

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DMD-related HRU procedures and events considered as criteria in the second step of matching included hospital encounters, ER visits, pulmonary management visits, motorized wheelchair, scoliosis visits, cardiac management visits, cough assist device, and assisted ventilation use during the pre-index period. If a patient did not have any degree of a particular event, zero was used for matching. Regarding motorized wheelchair outcomes, determination of whether the patient has ever had a claim is more meaningful than the rate of claims to reflect disease progression; thus, motorized wheelchair was treated as a progression event (i.e., observation at any point before index) in the matching. All other outcomes were treated as rates (i.e., frequency of observation over time during the pre-index period).

Statistical analysis

For each patient, the frequency of each outcome during the pre-index period and follow-up period was counted separately. The observed pre-index period rates (i.e., annualized rates at the pre-index period) for each HRU measure are reported for treated and control patients, and T-tests were used to assess differences in the pre-index period rates between the treated and control groups. Steroid usage in the pre- and post-index periods was also reported for treated and control cohorts.

Poisson regression models were used to compare the DMD-related HRU procedure and event outcomes in the follow-up period in treated and control patients. This was the most appropriate statistical model given that outcomes were measured as incidence counts. For each HRU outcome, a separate Poisson regression was estimated with controls for age and health stage at index as well as pre-index period rates of DMD-related HRU procedures and events to control for any remaining differences between the pre-index period characteristics of the treated and control patients after matching. The "exposure" function in STATA was used to address different lengths of follow-up periods, and therefore, the coefficients were estimated based on the annual rates of events. Additionally, the regressions were weighted by the length of pre-index periods to give patients with longer or more complete observation higher weights in the estimation. Robust standard errors were used. Using the estimated coefficients from the Poisson regressions, the average annualized incidence rates of each HRU outcome during the follow-up period for treated and control patients were predicted and reported. Specifically, the average annualized incidence for the treated group was fitted using estimated coefficients and observed values of covariates, while fixing the treatment variable to be true (1). The average annualized incidence for the control group is obtained similarly while fixing the treatment variable to be false (0). The estimated coefficients, standard errors, p-values, and 95% *CIs* of the Poisson regressions are reported in the Supplementary Tables.

Sensitivity analysis

Three sensitivity analyses were conducted. First, to assess whether the treatment effects can be generalized to other PMO treatments for different skip-amenable gene mutations (e.g., exon 53 skip amenable and exon 45 skip amenable mutations), the matching and Poisson regression analyses were repeated following inclusion of male patients receiving golodirsen (for exon 53 skip amenable mutations) in the treated group. There were not enough patients or sufficient follow-up time for casimersen (for exon 45 skip amenable mutations) given the proximity of its approval to the cut-off date of the dataset. Second, female patients with DMD receiving eteplirsen treatment and females in the control group were included. Previous studies including female patients with DMD have been limited, but this population is represented in the dataset and allows for inclusion. In this scenario, female sex was used as a matching criterion in the first step to ensure that treated female patients were matched to control female patients only. Lastly, the matching and Poisson regression analyses were repeated after limiting patients to those who were aged 28.1 years or younger at index to examine whether results were consistent after excluding patients who were older than the median life expectancy of patients with DMD reported in a recent systematic literature review [8].

Results

Patient characteristics

Following matching, the analytical sample included 389 treated and 389 control patients (Figure 2). The characteristics of the matched patients are presented in Table 2. Age and health stage were the same at index in both groups because patients were matched exactly for these characteristics in the first matching step. The mean (SD) age was 13.31 (6.31) years, 20% (81/389) of patients were in the early ambulatory stage, 17% (66/389) late ambulatory, 43% (169/389) early non-ambulatory, and 19% (73/389) late non-ambulatory. The proportion of patients with

Table 2. Age and health stage distribution at index among matched eteplirsen-treated and control patients.

	Eteplirsen-treated (n = 389)	Control (n = 389)	p-value
Age at index in years, mean (SD)	13.31 (6.31)	13.31 (6.31)	–
Health stage at index, n (%)			
Early ambulatory	81 (20.1)	81 (20.1)	–
Late ambulatory	66 (17.0)	66 (17.0)	–
Early non-ambulatory	169 (43.4)	169 (43.4)	–
Late non-ambulatory	73 (18.8)	73 (18.8)	–
Exposure to steroid treatment, n (%)			
Pre-index period	122 (31.4)	127 (32.6)	0.70
Follow-up	135 (34.7)	159 (40.8)	0.08
Length of pre-index period in months, mean (SD)	10.57 (1.76)	10.63 (1.67)	–
Length of follow-up period in months, mean (SD)	36.62 (15.84)	48.76 (26.85)	–
Length of treatment, mean (SD)	28.53 (20.10)	–	–

SD: Standard deviation.

prior exposure to steroids at the pre-index period was similar in both cohorts (31.4% for treated vs 32.6% for control), but during the follow-up period, a greater proportion of patients had used steroids in the control group (34.7% for treated vs 40.8% for control). The length of the pre-index period was similar in both cohorts, but the control cohort had a longer follow-up period. The mean (SD) duration of eteplirsen treatment was 28.5 (20.1) months, but the mean (SD) entire follow-up period of 36.6 (15.8) months was used in the analyses.

Table 3 reports DMD-related HRU procedures and events at the pre-index period after matching. There were no statistically significant differences between treated and control patients, suggesting that both groups were comparable at the pre-index period after matching. Patients in both cohorts had a mean (SD) of 3.7 (7.8) hospital encounters per year, or 1.8–2.0 (3.5–4.1) days of hospitalization, and had 0.7 (2.0–2.2) ER visits or 0.4 (1.1–1.2) days in the ER per year. Both treated and control patients had similarly low rates of ICU stays and similar levels of pulmonary management, motorized wheelchair, and cough assist device use at the pre-index period. Treated patients had slightly higher pre-index period rates of scoliosis and assisted ventilation than control patients.

Treatment effect evaluation

Poisson regression, controlling for age and health stage at index as well as pre-index period rates of all HRU measures, was estimated. Regressions were performed using observations in the follow-up period among matched treated and control patients. The estimated coefficients, standard errors, p-values, and 95% *CIs* are reported in Appendix Table 1. The estimated coefficients were used to estimate average annualized rates for each study HRU measure (Table 4). The estimated average (SD) yearly rate of hospital encounters/hospital days was 6.08 (0.76) / 2.86 (0.35) for control patients versus 4.17 (0.45) / 1.89 (0.18) for treated patients. The 1.91/0.97 difference between the cohorts represents a 31%/34% reduction in hospital encounters/hospital days for those treated with eteplirsen. Similarly, a 31% reduction in ER yearly rates (0.62 [0.08] treated vs 0.91 [0.09] control) and a 32% reduction in ER days (0.36 [0.05] treated vs 0.53 [0.06] control) were estimated for treated patients. Estimated pulmonary management visits, cardiac management visits, assisted ventilation visits, and tracheostomy were reduced by 33% (1.33 [0.18] treated vs 1.98 [0.29] control), 21% (1.39 [0.10] treated vs 1.76 [0.13] control), 39% (1.87 [0.19] treated vs 3.06 [0.53] control), and 86% (0.90 [0.17] treated vs 6.50 [3.47] control), respectively, in treated patients.

Sensitivity analyses

Table 5 reports the characteristics of eteplirsen, golodirsen, and female patients before matching, and Table 6 reports the characteristics of golodirsen and female patients after matching. The mean (SD) age at index in male golodirsen-treated patients was 13.1 (4.9) years, which was comparable to that of male eteplirsen patients, while the mean (SD) age of female eteplirsen patients at index was 15.6 (10.3) years, and the mean (SD) age of female control patients was 23.1 (10.8) years at the first SNOMED diagnosis. After matching, 25 male golodirsen patients and 6 female patients (3 treated and 3 control) were included in the matched sample.

Table 3. Pre-index period Duchenne muscular dystrophy-related healthcare resource utilization procedures and events in matched eteplirsen-treated and control patients.

	Pre-index period		
	Eteplirsen-treated (n = 389)	Control (n = 389)	*t*-test
Length of pre-index period in months, mean (SD)	10.57 (1.76)	10.63 (1.67)	–
Hospital encounters			
Yearly average care-adjusted number, mean (SD)	3.70 (7.75)	3.73 (7.77)	0.954
Yearly average days, mean (SD)	1.97 (4.12)	1.82 (3.47)	0.581
Emergency room			
Yearly average care-adjusted number, mean (SD)	0.71 (2.20)	0.65 (2.02)	0.681
Yearly average days, mean (SD)	0.42 (1.09)	0.39 (1.15)	0.741
Intensive care unit			
Yearly average care-adjusted number, mean (SD)	0.13 (1.13)	0.05 (0.51)	0.179
Yearly average days, mean (SD)	0.12 (1.05)	0.05 (0.43)	0.176
Pulmonary management			
Yearly average number, mean (SD)	0.96 (3.46)	0.85 (3.85)	0.661
Motorized wheelchair			
Yearly average number, mean (SD)	0.82 (2.30)	0.77 (2.19)	0.775
Ever have motorized wheelchair, n (%)	94 (24.16)	97 (24.94)	0.803
Scoliosis			
Yearly average number, mean (SD)	0.92 (6.04)	0.53 (1.89)	0.217
Cardiac management			
Yearly average number, mean (SD)	1.49 (2.93)	1.40 (2.70)	0.646
Tracheostomy			
Yearly average number, mean (SD)	0.98 (11.07)	0.80 (7.24)	0.785
Cough assist device			
Yearly average number, mean (SD)	0.41 (1.73)	0.45 (1.93)	0.759
Ever have cough assist device, n (%)	58 (14.91)	54 (13.88)	0.683
Assisted ventilation			
Yearly average number, mean (SD)	0.99 (6.78)	0.76 (6.41)	0.630

SD: Standard deviation.

Table 4. Observed pre-index period and estimated follow-up average rates of healthcare resource utilization events.

Outcome variable	Observed annualized pre-index period rates		Annualized follow-up rates	
	Treated mean (SD) (n = 389)	Control mean (SD) (n = 389)	Treated mean (SD) (n = 389)	Control mean (SD) (n = 389)
Care-adjusted hospital encounter	3.70 (7.75)	3.73 (7.77)	4.17 (0.45)†	6.08 (0.76)
Care-adjusted ER	0.71 (2.20)	0.65 (2.02)	0.62 (0.08)†	0.91 (0.09)
Assisted ventilation	0.99 (6.78)	0.76 (6.41)	1.87 (0.19)†	3.06 (0.53)
Cardiac management	1.49 (2.93)	1.40 (2.70)	1.39 (0.10)†	1.76 (0.13)
Cough assist device	0.41 (1.73)	0.45 (1.93)	0.67 (0.08)	0.76 (0.10)
ER days	0.42 (1.09)	0.39 (1.15)	0.36 (0.05)†	0.53 (0.06)
Hospital days	1.97 (4.12)	1.82 (3.47)	1.89 (0.18)†	2.86 (0.35)
Care-adjusted ICU	0.13 (1.13)	0.05 (0.51)	0.25 (0.05)	0.27 (0.07)
ICU days	0.12 (1.05)	0.05 (0.43)	0.22 (0.04)	0.24 (0.06)
Motorized wheelchair	0.82 (2.30)	0.77 (2.19)	0.94 (0.09)	0.96 (0.07)
Pulmonary management	0.96 (3.46)	0.85 (3.85)	1.33 (0.18)†	1.98 (0.29)
Scoliosis	0.92 (6.04)	0.53 (1.89)	0.99 (0.21)	1.24 (0.34)
Tracheostomy	0.98 (11.07)	0.80 (7.24)	0.90 (0.17)†	6.50 (3.47)

†Rates estimated from statistically significant model coefficients (i.e., $p < 0.05$).
ER: Emergency room; ICU: Intensive care unit; SD: Standard deviation.

Table 5. Age and health stage distribution among patients with Duchenne muscular dystrophy before matching.

	Male patients treated with eteplirsen before matching (n = 546)	Male patients treated with golodirsen before matching (n = 53)	Female patients treated with eteplirsen before matching (n = 10)	Female control patients before matching (n = 92)
Age at index (treated) or at first SNOMED (control), mean (SD)	13.08 (6.28)	13.09 (4.88)	15.60 (10.30)	23.10 (10.78)
Health stage at index (treated) or at first SNOMED (control), n (%)				
Early ambulatory	112 (20.5)	7 (13.2)	2 (20.0)	26 (28.3)
Late ambulatory	84 (15.4)	7 (13.2)	2 (20.0)	4 (4.3)
Early non-ambulatory	191 (35.0)	25 (47.2)	4 (40.0)	10 (10.87)
Late non-ambulatory	88 (16.1)	14 (26.4)	0 (0)	5 (5.4)
Missing	71 (13.0)	0 (0)	2 (20.0)	47 (51.1)
Length of observation in months, mean (SD)	83.10 (35.01)	97.44 (16.45)	71.65 (27.97)	81.23 (23.81)

SD: Standard deviation; SNOMED: Systematized Nomenclature of Medicine.

Table 6. Age and health stage distribution at index among golodirsen-treated and female patients after matching.

	Male patients treated with golodirsen after matching (n = 25)	Female patients treated with golodirsen (n = 3)	Female control patients after matching (n = 3)
Age at index in years, mean (SD)	13.04 (5.04)	15.33 (5.03)	15.33 (5.03)
Health stage at index, n (%)			
Early ambulatory	2 (8.0)	0 (0)	0 (0)
Late ambulatory	4 (16.0)	2 (66.7)	2 (66.7)
Early non-ambulatory	10 (40.0)	1 (33.3)	1 (33.3)
Late non-ambulatory	9 (36.0)	0 (0)	0 (0)
Length of pre-index period in months, mean (SD)	11.36 (0.88)	10.37 (1.88)	9.49 (0.66)
Length of follow-up period in months, mean (SD)	8.97 (1.92)	21.28 (13.99)	38.61 (30.25)
Length of treatment in months, mean (SD)	7.38 (3.32)	6.17 (10.51)	–

SD: Standard deviation.

The estimated follow-up average rates of HRU events for the three sensitivity analyses are reported in Table 7 (the estimated coefficients are reported in Appendix Table 2). For the scenario including male patients treated with golodirsen, the estimated average (SD) yearly rate of hospital encounters/hospital days was 5.87 (0.67) / 2.69 (0.23) for control patients versus 4.19 (0.43) / 1.96 (0.17) for treated patients. The 1.68/0.73 difference between the cohorts represents a 29%/27% reduction in hospital encounters/hospital days for those treated with eteplirsen or golodirsen. Similarly, a 28% reduction in ER yearly rates (0.63 [0.07] treated vs 0.88 [0.09] control) and a 29% reduction in ER days (0.36 [0.05] treated vs 0.51 [0.06] control) were estimated for treated patients. Estimated pulmonary management visits, cardiac management visits, assisted ventilation visits, and tracheostomy were reduced by 40% (1.37 [0.18] treated vs 2.29 [0.32] control), 23% (1.39 [0.10] treated vs 1.81 [0.12] control), 51% (1.80 [0.18] treated vs 3.64 [0.54] control), and 90% (0.85 [0.15] treated vs 8.13 [4.29] control), respectively, in treated patients. The other two sensitivity analyses yield similar estimates.

Discussion

Using a large claims and medical record dataset spanning 10 years, this study is among the first to provide real-world evidence regarding the impact of eteplirsen treatment on patient HRU outcomes. To address potential differences between patients who initiated eteplirsen and patients in the control group, this study applied a two-step matching to ensure that eteplirsen-treated and control cohorts were comparable at the pre-index period. Poisson regression analysis controlling for pre-index period characteristics showed a favorable treatment effect for eteplirsen versus control for all 13 HRU outcomes examined (care-adjusted hospital encounters and hospital days, care-adjusted ER visits and days in the ER, care-adjusted ICU and ICU days, pulmonary management visits, cardiac management visits, cough assist device, motorized wheelchair, scoliosis, tracheostomy, and assisted ventilation visits), with

Table 7. Sensitivity analyses estimated annualized follow-up rates of healthcare resource utilization events.

Outcome variable	Main study sample plus male patients treated with golodirsen		Main study sample plus female patients treated with eteplirsen		Main study sample excluding those aged >28.1 years	
	Treated mean (SD) (n = 828)	Control mean (SD) (n = 828)	Treated mean (SD) (n = 784)	Control mean (SD) (n = 784)	Treated mean (SD) (n = 766)	Control mean (SD) (n = 766)
Care-adjusted hospital encounter	4.19 (0.43)†	5.87 (0.67)	4.17 (0.45)†	6.05 (0.75)	4.11 (0.44)†	6.19 (0.76)
Care-adjusted ER	0.63 (0.07)†	0.88 (0.09)	0.62 (0.07)†	0.90 (0.09)	0.60 (0.07)†	0.90 (0.09)
Assisted ventilation	1.80 (0.18)†	3.64 (0.54)	1.86 (0.19)†	3.04 (0.53)	1.32 (0.15)†	2.62 (0.45)
Cardiac management	1.39 (0.10)†	1.81 (0.12)	1.38 (0.10)†	1.75 (0.12)	1.38 (0.10)†	1.76 (0.13)
Cough assist device	0.70 (0.08)	0.84 (0.12)	0.67 (0.08)	0.76 (0.10)	0.68 (0.08)	0.78 (0.10)
ER days	0.36 (0.05)†	0.51 (0.06)	0.36 (0.04)†	0.53 (0.06)	0.35 (0.04)†	0.53 (0.06)
Hospital days	1.96 (0.17)†	2.69 (0.23)	1.89 (0.18)†	2.85 (0.35)	1.87 (0.18)†	2.95 (0.36)
Care-adjusted ICU	0.22 (0.04)	0.37 (0.11)	0.25 (0.05)	0.27 (0.07)	0.22 (0.04)	0.27 (0.07)
ICU days	0.20 (0.04)	0.32 (0.08)	0.22 (0.04)	0.24 (0.06)	0.19 (0.04)	0.25 (0.06)
Motorized wheelchair	0.95 (0.09)	0.99 (0.07)	0.95 (0.09)	0.95 (0.07)	0.95 (0.10)	0.94 (0.07)
Pulmonary management	1.37 (0.18)†	2.29 (0.32)	1.32 (0.18)†	1.97 (0.28)	1.09 (0.14)†	1.95 (0.28)
Scoliosis	1.37 (0.34)	1.85 (0.61)	0.99 (0.21)	1.24 (0.33)	0.99 (0.22)	1.25 (0.34)
Tracheostomy	0.85 (0.15)†	8.13 (4.29)	0.89 (0.17)†	6.45 (3.45)	0.59 (0.12)†	4.67 (2.09)

†Indicates statistical significance.
ER: Emergency room; ICU: Intensive care unit; SD: Standard deviation.

statistically significant differences achieved for eight outcomes (care-adjusted hospital encounters and hospital days, care-adjusted ER visits and days in the ER, pulmonary management visits, cardiac management visits, tracheostomy, and assisted ventilation visits).

Pre-index period characteristics

After 1:1 matching, the mean age at index in both cohorts was 13.31 years. The standard deviation of 6.3 suggests that approximately 95% of patients in the analytical sample were aged younger than 26 years at index. This is consistent with a recent study reporting the median life expectancy of patients with DMD of 28.1 years [8]. Furthermore, findings from sensitivity analysis 3 confirm robust results after excluding patients older than 28.1 years.

The lack of significant pre-index period differences between the treated and matched control patients in HRU outcomes suggested that the matching process was successful. The mean follow-up period in eteplirsen-treated patients was longer than the mean duration of treatment. To the extent that some eteplirsen-treated patients did not receive eteplirsen for the entire duration of follow-up, the treatment effect observed may have been a conservative estimate.

As steroid use has demonstrated an impact on disease progression for patients with DMD, the proportion of patients using steroids at the pre-index period and during follow-up was examined. Results demonstrated that steroid experience was similar among eteplirsen-treated and control patients at the pre-index period, while a higher proportion of patients had used steroids in the control group during the follow-up period. Inasmuch as steroid use may confer benefits with respect to certain study HRU measures, such as pulmonary management, more frequent use of steroids among control patients versus treated patients could imply that the differences between groups in-treatment effect may represent a conservative estimate.

Eteplirsen treatment effects

Poisson regression analysis was used, controlling for any remaining differences between the two cohorts in baseline characteristics and baseline HRU procedure and event measures following the two-step matching process. Annualized rates for the 13 outcomes examined all favored eteplirsen treatment, and 8 of 13 reached statistical significance, consistent with favorable effects on disease progression and disease burden in eteplirsen-treated patients. Specifically, outcomes with significant favorable findings were: adjusted hospital encounter and hospital days, adjusted ER visits and days in the ER, pulmonary management visits, cardiac management visits, tracheostomy, and assisted ventilation visits. Given that these HRU procedures and events are typically linked to progressed patients with DMD that necessitate intensive care and incur higher healthcare expenses [7,30] the reduction in disease burden for patients with DMD may extend to reduced burden for caregivers of eteplirsen-treated patients. Although HRU

is required to treat DMD symptoms when patients progress to certain stages, prolonging the time before patients require these resources and reducing the level of care needed would also be beneficial. Furthermore, as patients receiving a novel treatment, such as eteplirsen, may be more closely connected with the healthcare system, they may also be more likely to use resources that are helpful for their symptoms. This suggests the observed reduced rates of HRU among eteplirsen-treated patients is not due to a lack of participation in required care.

Treatment effects on ICU outcomes did not reach statistical significance, which may be due to the rarity of ICU events. A large reduction in predicted tracheostomy events was observed in eteplirsen-treated patients; however, this may be attributable to the rarity of tracheostomy or to the recent trend toward a reduction in use of this procedure.

Sensitivity analyses for the small number of male patients receiving golodirsen treatment and female patients receiving eteplirsen treatment also supported the findings of the primary analysis, suggesting that PMOs may have a class effect on HRU outcomes.

Limitations

These results should be considered within the context of several limitations. First, the Clarivate dataset may have had incomplete coverage of patient medical care history. Use of both the EMR and claims data available in the Clarivate dataset helped to reduce the potential for missing observations, but the observed rates for each HRU measure may nonetheless be lower than the actual rates for some patients. Because this issue is expected to have impacted both eteplirsen-treated and control patients equally, the comparative analysis results are expected to be robust and valid. Alternatively, data missingness and underreported HRU would likely have impacted the standard of care (SoC) patients to a greater extent than the eteplirsen-treated patients because the eteplirsen-treated patients were likely to be more closely connected with the medical care system. This would constitute a conservative bias in estimating the effects of eteplirsen on reducing HRU rates. Future studies comparing the Clarivate data with other data sources to assess the missingness of HRU would also be helpful to understand the impact of data missingness on HRU for patients with DMD.

Incompleteness of data coverage may have resulted in the identified eteplirsen treatment initiation date being later than the actual initiation date, potentially causing underestimation of the eteplirsen treatment period. As SNOMED codes are available only in EMR data, the use of SNOMED codes to identify patients with DMD limited the control patients in these analyses to a subsample in the Clarivate dataset that had both available claims and EMR data that included the SNOMED code (41 percent of all patients in the extracted Clarivate dataset). Mutation status was also not available in the data and thus could not be controlled for when matching eteplirsen-treated with control patients. Eteplirsen is indicated for patients with DMD amenable to exon 51 skipping, which represents about 13 percent of all patients with DMD [29]. Eteplirsen-treated patients were assumed to meet this criterion, but the mutation types in control patients were not available. Because patients with DMD amenable to exon 51 skipping have been found to have more aggressive disease progression [31], the inclusion of patients with other mutation types in the control cohort would be expected to have a negative impact on the difference in treatment effects observed. If mutation status data become available in claims or EMR data sources, further studies using mutation-matched cohorts would be beneficial. The eteplirsen-treated population may also be affected by the recency of eteplirsen's approval, as some patients may have been previously enrolled in a clinical trial and may have had additional exposure to eteplirsen that was not accounted for in this analysis. Other patients initiating eteplirsen treatment shortly after approval may have represented a pent-up demand among potentially sicker or more progressed patients and may not be representative of a steady-state population (who are more homogeneous to the clinical trial population). Other unidentifiable differences in factors, such as health coverage or socioeconomic status, could also influence the initiation of eteplirsen treatment. Lastly, in the matched sample, the average follow-up period was slightly longer for matched control patients compared with eteplirsen-treated patients. If control patients had more frequent events in the most recent months of follow-up, the true treatment effects may be smaller than the estimated coefficients in the study. As longer follow-up becomes available for treated patients, future studies may have more balanced follow-up periods for comparison.

Conclusion

Using a large real-world dataset covering the period from 2011 to 2021, this study evaluated the effect of eteplirsen treatment among patients with DMD and found that eteplirsen was associated with statistically significant reductions in the rates of clinically meaningful HRU procedure and event measures, such as hospitalization, compared with a control group. Given the real-world data source, a two-step matching approach was applied to balance char-

acteristics among eteplirsen-treated and control patients at the pre-index period and to establish more comparable cohorts. With a 1:1 matched sample of 389 treated patients and 389 control patients, Poisson regression analysis indicated that eteplirsen treatment was associated with improved rates in all HRU outcomes assessed, including statistically significant effects for care-adjusted hospital encounters and hospital days, care-adjusted ER visits and days in the ER, pulmonary management visits, cardiac management visits, tracheostomy, and assisted ventilation visits. These results demonstrated that eteplirsen treatment was associated with benefits for multiple DMD-related HRU outcomes, reducing disease burden for patients, and by extrapolation for caregivers and healthcare systems.

Summary points

- Recent improvements in the management of Duchenne muscular dystrophy (DMD) include the approval of targeted therapies, such as eteplirsen.
- Clinical studies have shown that eteplirsen is well tolerated and associated with statistically significant and clinically meaningful attenuation of pulmonary and ambulatory decline in patients with DMD.
- A retrospective comparative analysis was conducted using a large claims and electronic medical record dataset to evaluate outcomes in the real-world setting in patients treated with eteplirsen compared with a control group receiving standard of care.
- A two-step matching approach was applied to balance characteristics in the eteplirsen-treated and control groups prior to analysis.
- Poisson regression was used to evaluate treatment effects on healthcare resource utilization (HRU) events and procedures.
- In the real-world setting, eteplirsen-treated patients had improved outcomes in multiple DMD-related HRU measures versus control patients.
- Statistically significant results were seen favoring eteplirsen versus control for care-adjusted hospital encounters, days in hospital, care-adjusted emergency room (ER) visits, days in the ER, pulmonary management visits, assisted ventilation visits, cardiac management visits, and tracheostomies.
- There remains a significant unmet need in DMD, as identified by the HRU events observed in this study, and further research on the HRU and health-related quality-of-life impact among DMD patients and caregivers is needed.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: https://bpl-prod.literatumonline.com/doi/10.57264/cer-2023-0086

Author contributions

J Iff, Y Zhong, E Tuttle, D Gupta, X Paul and E Henricson participated in the study design, interpretation of results, and review of this manuscript. Y Zhong, E Tuttle, D Gupta and X Paul coordinated the data collection. Y Zhong, E Tuttle and X Paul conducted the data analysis.

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Ethical conduct of research

The ethics approval and informed consent for this study are covered by the ethics approvals and consent forms for Decision Resources Group data.

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