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A Real-World Target Trial Emulation of Eteplirsen, Casimersen, and Golodirsen to Evaluate Survival Among Patients With Duchenne Muscular Dystrophy

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Background

- Duchenne muscular dystrophy (DMD) is an X-linked, degenerative neuromuscular disease caused by pathogenic variants in the *DMD* gene estimated to affect roughly 1 in 5,000 newborn boys worldwide[1] and 9,000 to 12,000 males in the US[2]
- The phosphorodiamidate morpholino oligomers (PMOs) eteplirsen, casimersen, and golodirsen are approved treatments for patients with DMD[3-5]
- Previous research showed eteplirsen prolonged survival compared with unadjusted natural history data[6]
- However, the survival benefit of eteplirsen has not been evaluated in analyses that control for glucocorticoids (GCs) use and prognostic factors, and no survival data are currently published for casimersen or golodirsen

Objectives

- Describe the unadjusted time to death in patients taking the PMOs eteplirsen, casimersen, or golodirsen and GCs (PMO+GCs), and in patients taking GCs-only
- Assess the survival effect of receiving PMO+GCs vs GCs-only in patients with DMD using causal inference methods for analysis of real-world data
- Describe the frequency of comorbidities prior to death in patients with available data

Methods

Data sources and tokenization

- Retrospective data from insured US patients in the Inovalon closed claims database (including all US states and covering Medicaid, Medicare, and commercial coverage) were de-identified and combined via tokenization with mortality data from Datavant (**Supplement, Figure S1**)
  - Tokenization enables linking patient data across different databases while keeping their identities and health information protected and in compliance with the Health Insurance Portability and Accountability Act (HIPAA)

Study population

- The study population included patients with DMD who met criteria for having a DMD diagnosis based on a validated claims-based algorithm[7] (**Supplement, Figure S2**) or had a record of treatment with a commercial DMD-specific therapy
- Only patients with evidence of treatment with systemic GCs were included
- Patients with evidence of DMD gene therapy or viltolarsen were excluded or censored upon initiation of these treatments

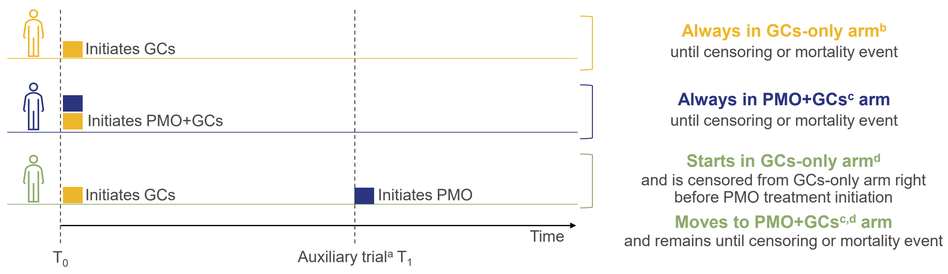
Target trial emulation with sequential trial design

- Studies with real-world data often lack a clear T_0 for the control group; TTE addresses this by aligning eligibility, treatment, and follow-up to mimic a randomized trial, thereby avoiding biases common to observational studies[8,9] (for more information on TTE, see **Supplement**)
- This study used TTE with a sequential trial design to enable patients who became newly eligible over time to enter auxiliary trials (**Figure 1**)
  - T_0 was defined as the time when the patient first initiated injectable or oral GCs treatment lasting ≥30 days or the time when the patient initiated PMO treatment; if a patient had multiple dates satisfying the T_0 criteria, the earliest date was used
  - Starting from T_0, an auxiliary trial was emulated each month when patients initiated treatment with PMOs
  - In each auxiliary trial new initiators of PMOs were compared to all patients still in GCs-only arm, thus ensuring perfect alignment on the length of GCs use in the PMO+GCs vs GCs-only comparison

Figure 1 *Sequential Trial Design*

A. Emulated target trial design

B. Example time progression for 3 patients in sequential trial design



C. Patient populations in sequential trial study

	Always in the **GCs-only** arm	Always in the **PMO+GCs** arm[c]	Start in the GCs-only arm, **move** to the PMO+GCs arm[d]
N	2,656	112	260
T_0	First observed date of ≥30 days of GCs use	First observed date of PMO use	First observed date of ≥30 days of GCs use[c]
Initiates PMO treatment	Not observed	At T_0	On auxiliary trial T_x, which occurs after T_0

[a]A new auxiliary trial started each month new patients began PMO treatment. [b]Patients in the GCs-only arm could enroll in auxiliary trials in the GCs-only arm. [c]In the PMO+GCs arm, patients were not required to be taking PMOs and GCs concurrently. [d]Patients who had a first date of PMO use after the first observed date of ≥30 days of GCs use that qualified as T_0. T_x indicates a new sequential trial (defined in month since T_0) where new PMO initiators from that month are compared with all patients still in the GCs-only arm. Note, patients in the GCs-only arm can be included in multiple trials up until they are censored or have an event.
GC, glucocorticoid; PMO, phosphorodiamidate morpholino oligomer.

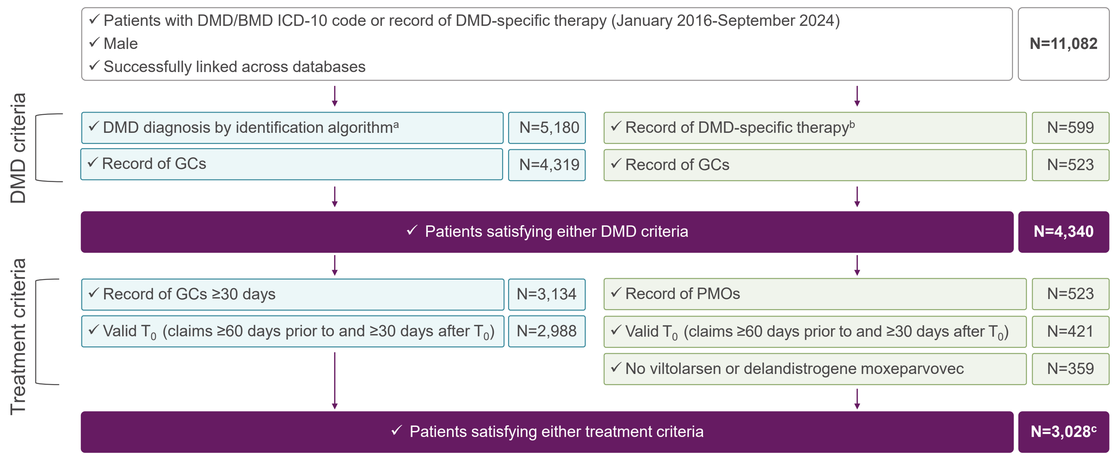
- The data across the sequentially emulated trials were pooled to generate an estimate of the hazard ratio (HR) of PMO+GCs vs GCs-only treatment
- To ensure that the comparison of PMO+GCs vs GCs-only controlled for key confounders, inverse probability of treatment weighting was used to balance the two groups in sequentially emulated trials on key covariates (**Supplement**, **Figure S3**)
- Covariates included age, concomitant therapies, and comorbidities, among others (see **Supplement** for full list of covariates)
- Additionally, inverse probability of censoring weighting was used to account for the informative censoring of patients in the GCs-only arm when they initiated PMOs

Results

Study population

- A total of 3,028 patients met either of the 2 enrollment criteria (**Figure 2**)

Figure 2 *Study Population*



[a]Algorithm criteria included male, aged ≤40 years at G71.01 ICD-10 claim, ≥2 claims with G71.01 ICD-10 code, aged <30 years at first ventilation claim, and ≥1 of the following: prescription for GCs at any time, claim for gene or exon-skipping therapy, evidence of ventilation support.[c] Because a record of GCs was required for this study, the criterion "prescription for GCs at any time" was removed from the DMD algorithm step and applied on the subsequent step. [b]Approved PMO or gene therapy and aged ≤40 years. [c]319 patients met both sets of treatment criteria.
T_0 is defined as the time when the patient first initiates injectable or oral GCs treatment lasting ≥30 days or the time when the patient initiated PMO treatment.
BMD, Becker muscular dystrophy; DMD, Duchenne muscular dystrophy; GC, glucocorticoid; ICD-10, International Classification of Diseases, Tenth Revision; PMO, phosphorodiamidate morpholino oligomer.

Unadjusted data

- Throughout the study, 2,656 patients were treated with GCs-only (**Tables 1, 2**)
  - In total, 260 patients were treated with GCs-only at T_0 and subsequently initiated PMO therapy
  - A total of 112 patients started PMO treatment at T_0
- Most patients in the PMO+GCs group were treated with eteplirsen (83/112, 74%) at T_0 (**Table 1**)
- In the PMO+GCs group, 3% (12/372) of patients died vs 4% (114/2,656) in the GCs-only group (**Table 2**)
- Unadjusted time to death from Kaplan-Meier analysis could not be calculated due to insufficient events and accumulated time (**Supplement, Figure S4**)

Table 1 *Patient Demographics and Baseline Characteristics*

Treatment status at T_0	GCs-only N=2,916	PMO+GCs N=112
Age at T_0 Median (Q1, Q3)	11 (8, 16)	10 (7, 15)
Age at 1st GC Median (Q1, Q3)	10 (7, 16)	9 (6, 15)
Age at 1st record of G71.01[a] Median (Q1, Q3)	11 (8, 16)	9 (6, 13)
Follow-up time, y Median (Q1, Q3)	4.8 (2.6, 6.9)	4.6 (2.7, 6.6)
PMO type, n (%)		
Eteplirsen	0	83 (74)
Casimersen	0	21 (19)
Golodirsen	0	8 (7)

[a]ICD-10 code for DMD/BMD, G71.01.
BMD, Becker muscular dystrophy; DMD, Duchenne muscular dystrophy; GC, glucocorticoid; ICD-10, International Classification of Diseases, Tenth Revision; PMO, phosphorodiamidate morpholino oligomer; Q, quartile.

Table 2 *Patient Characteristics Across all Follow-Up Time*

Treatment status across all follow-up	GCs-only N=2,656	PMO+GCs N=372
Treatment at T_0, n (%)		
GCs-only	2,656 (100)	260 (70)
PMO+GCs	0	112 (30)
Age at PMO or GCs initiation Median (Q1, Q3)	11 (8, 16)	12 (8, 16)
PMO type, n (%)		
Eteplirsen	0	208 (56)
Casimersen	0	123 (33)
Golodirsen	0	41 (11)
Died after T_0, n (%)	114 (4.3)	12 (3.2)

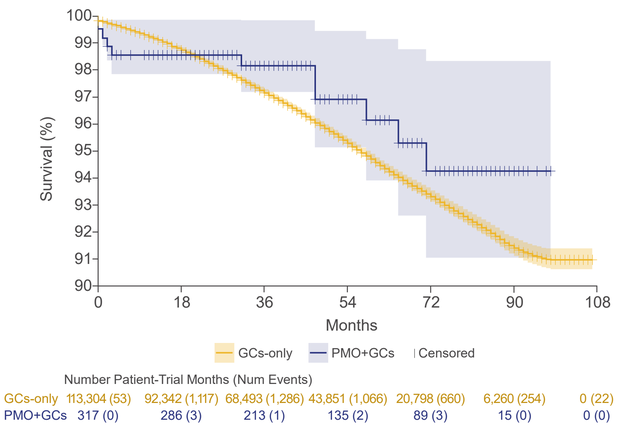
GC, glucocorticoid; PMO, phosphorodiamidate morpholino oligomer; Q, quartile.

Sequential target trial emulation

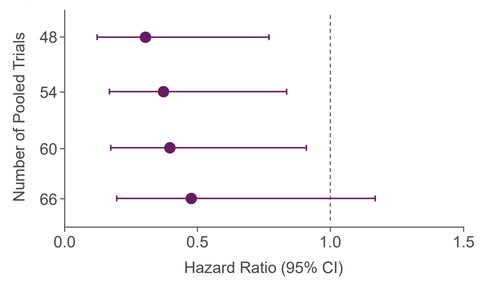
- The HR estimated using data from 48 sequential trials showed that treatment with PMO+GCs reduced mortality risk by 69.7% vs the GCs-only group (**Figure 3A**)
- The HR estimated using data from 66 sequential trials showed that PMO+GCs reduced mortality risk by 52.3% vs the GCs-only group (**Figure 3B**)
  - As very few PMO users (~6%) initiated PMO therapy beyond 66 months after initiating GCs and had limited follow-up, these data could not be used in the sequential TTE analysis

Figure 3 *Survival in Patients Treated With PMO+GCs vs GCs-Only*

A. Survival data pooled from 48 sequentially emulated trials



B. Survival hazard ratios from pooled sets of sequentially emulated trials



N pooled trials	HR (95% CI)	*P* value
48	0.303 (0.119-0.769)	0.012
54	0.373 (0.167-0.834)	0.016
60	0.397 (0.173-0.909)	0.029
66	0.477 (0.194-1.169)	0.105

Shading on panel A represents 95% confidence interval. CI, confidence interval; GC, glucocorticoid; HR, hazard ratio; PMO, phosphorodiamidate morpholino oligomer; TTE, target trial emulation.

Comorbidities experienced by patients who died

- For evaluation of comorbidities prior to death, a subset of patients with 3 months of continuous claims data prior to death were evaluated (84 of 126 patients who died; **Table 3**)
- Over 75% of patients who died had circulatory or respiratory claims within 3 months of death (**Table 3**)

Table 3 *Comorbidities Prior to Mortality Events (N=84)[a]*

ICD-10 chapters	ICD code description	n (%)
I00-I99	**Diseases of the circulatory system**	**71 (85)**
I469	Cardiac arrest, cause unspecified	35 (42)
I420	Congestive cardiomyopathy	27 (32)
I429	Cardiomyopathy (primary) (secondary) NOS	26 (31)
J00-J99	**Diseases of the respiratory system**	**64 (76)**
J984	Calcification of lung	39 (46)
J9601	Acute respiratory failure with hypoxia	30 (36)
J9610	Chronic respiratory failure, unspecified with hypoxia or hypercapnia	28 (33)
E00-E89	**Endocrine, nutritional and metabolic diseases**	**56 (67)**
E876	Hypokalemia	23 (27)
E871	Hypo-osmolality and hyponatremia	14 (17)
E860	Dehydration	13 (15)
M00-M99	**Diseases of the musculoskeletal system and connective tissue**	**51 (61)**
M419	Scoliosis, unspecified	13 (15)
M6281	Muscle weakness (generalized)	9 (11)
M4145	Neuromuscular scoliosis, thoracolumbar region	8 (10)
K00-K95	**Diseases of the digestive system**	**48 (57)**
K219	Esophageal reflux NOS	18 (21)
K5900	Constipation, unspecified	14 (17)
K567	Ileus, unspecified	12 (14)

[a]Only ICD-10 chapters with claims from ≥50% of patients are shown; below the ICD-10 chapters, only the 3 codes with most claims are shown.
ICD-10, International Classification of Diseases, Tenth Revision; NOS, not otherwise specified.

Conclusions

- This is the first study to estimate the effect of treatment with eteplirsen, casimersen, or golodirsen on survival using trial emulation causal methods and data tokenization
  - These results are consistent with a previous study assessing the effect of eteplirsen treatment in patients with DMD on survival,[6] and expands the generalizability of these findings to casimersen and golodirsen while controlling for GC use and prognostic factors
- The high prevalence of circulatory or respiratory claims within 3 months of death helps characterize common late-stage patient characteristics prior to mortality in DMD
- A key limitation of this study is that later emulated trials had less follow-up time, fewer events, and fewer patients, which made groups less balanced and estimates of the survival benefit less statistically efficient as more trials were added
- Data with longer follow-up periods are needed to shed further light on the effect of eteplirsen, casimersen, and golodirsen on survival in patients with DMD

Target trial emulation analyses indicate that during the study period, the mortality rate in patients with DMD receiving PMOs and GCs is approximately 50%-70% lower than in patients receiving GCs-only

Acknowledgments & Disclosures

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Presented at the Muscular Dystrophy Association (MDA) Clinical and Scientific Conference, March 8–11, 2026, Orlando, FL

References

1. Crisafulli S, et al. *Orphanet J Rare Dis*. 2020;15:141. **2.** Mendell JR, et al. *J Neuromuscul Dis*. 2021;8:469. **3.** Eteplirsen. Prescribing Information. Sarepta Therapeutics, Inc.; 2024. **4.** Casimersen. Prescribing Information. Sarepta Therapeutics, Inc.; 2024. **5.** Golodirsen. Prescribing Information. Sarepta Therapeutics, Inc.; 2024. **6.** Iff J, et al. *Muscle Nerve*. 2024;70:60. **7.** Grabich S, et al. Poster presented at: ISPE, August 22-26, 2025; Washington DC, USA. Poster C-201. **8.** Hernán MA, et al. *Am J Epidemiol*. 2016;183:758. **9.** Nguyen VT, et al. *BMC Med*. 2021;19:279. **10.** Schrader R, et al. *J Manag Care Spec Pharm*. 2023;29:1033. **11.** Gooch KL, et al. *Adv Ther*. 2024;41:3615.

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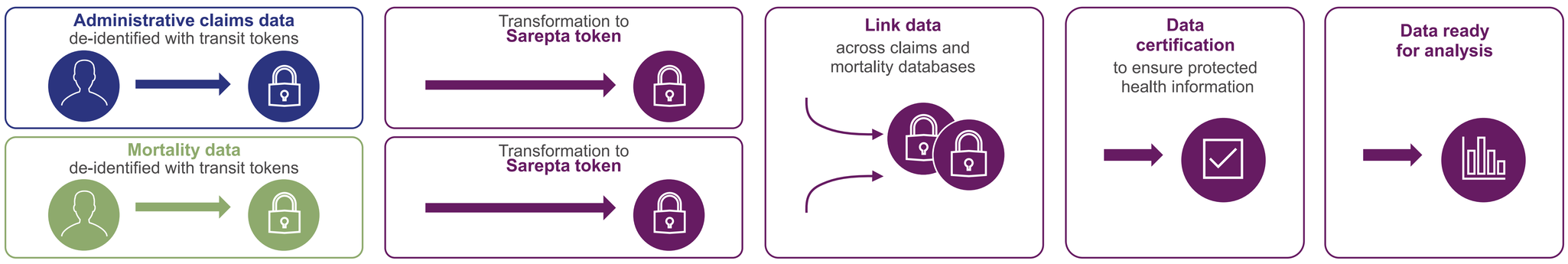
Supplement

Data sources

- In this study, tokenization was used to merge data across an administrative claims database and a mortality database while protecting patient identity and protected health information (**Figure S1**)

Figure S1 *Process of Generating De-Identified Linked Dataset*



Why tokenization?

- Data linkage and/or tokenization of health care data is a process by which patient identifiers are de-identified through generation of a patient-specific "token" that is encrypted
- Tokenization helps researchers link real-world data from a patient's previous medical history, including diverse sources, and aids in tracking events across the health care system and minimizing the risk of a breach in the patient's privacy
- Tokenization can also be used to link real-world data to patients who participated in clinical trials, facilitating an accurate understanding of post-clinical trial treatment patterns and health care resource utilization, and can also provide information on long-term effectiveness and safety

Identifying patients with Duchenne muscular dystrophy in claims data

- There is no specific International Classification of Diseases code for Duchenne muscular dystrophy (DMD), as the G71.01 code includes both DMD and Becker muscular dystrophy, making identification of patients with DMD from administrative claims data challenging[10,11]
- To address this issue, a DMD identification algorithm was used to identify the patients most likely to have DMD from the Inovalon closed claims dataset[7]
  - The DMD identification algorithm used here is a modified version of the "narrow DMD definition" published by Schrader et al., 2023,[10] and reported a positive predictive value >80% in Inovalon claims data with genetic diagnostic data used as the reference standard[7] (**Figure S2**)

Figure S2 *Definition of the Validated Claims-Based DMD Identification Algorithm*[7]

Claims-based DMD identification algorithm

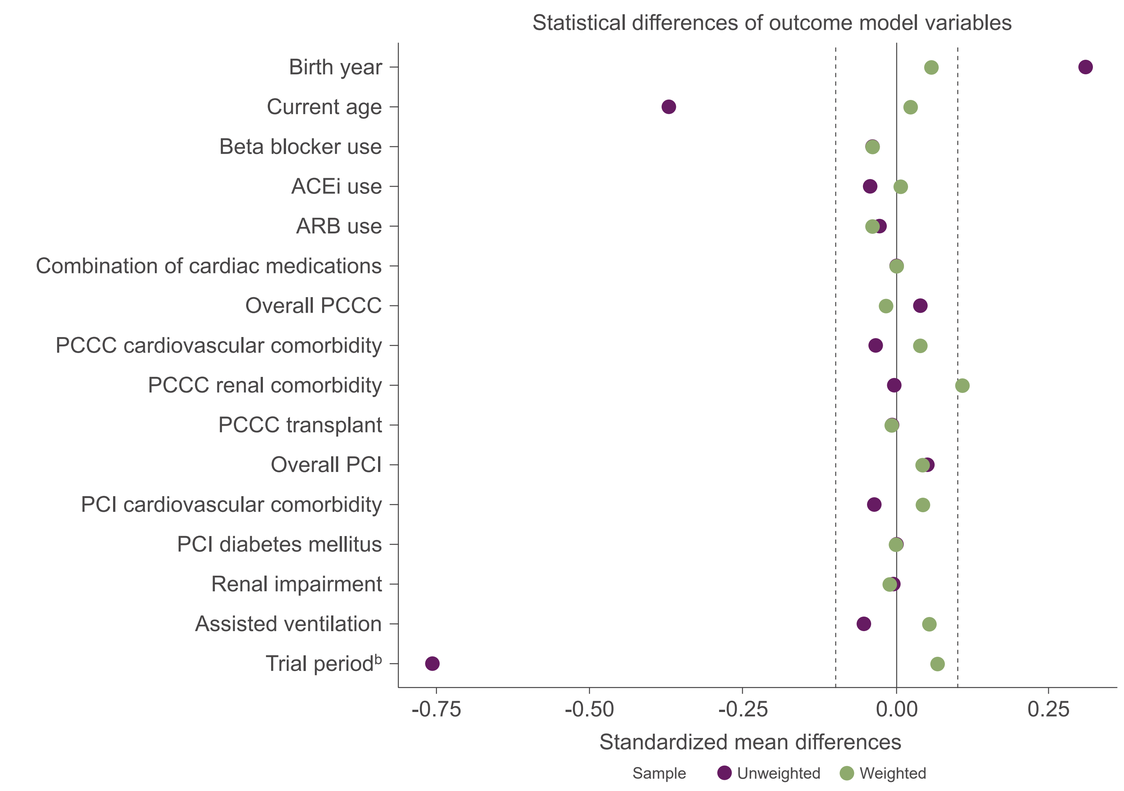
- Male
- Age ≤40 at first DMD/BMD ICD-10 diagnosis code[a]
- ≥2 claims with DMD/BMD ICD-10 diagnosis code
- Had ≥1 of the below:
  - Prescription for GCs[b] at any time
  - Claim for exon-skipping therapy[c] or gene therapy[d]
  - Evidence of ventilation support or dependence at any age
- Patients ≥30 years of age were required to have evidence of ventilation support or dependence on or before their 30th year

[a]ICD-10 diagnosis code for BMD and DMD is G71.01. [b]GCs included betamethasone, budesonide, cortisone, deflazacort, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, or triamcinolone. [c]Exon-skipping therapy included casimersen, eteplirsen, golodirsen, or viltolarsen. [d]Gene therapy included delandistrogene moxeparvovec-rokl.
BMD, Becker muscular dystrophy; DMD, Duchenne muscular dystrophy; GCs, glucocorticoids; ICD-10, International Classification of Diseases, Tenth Revision.

Sequential TTE and additional confounding control

- The target trial emulation (TTE) provides a formal framework to help avoid self-inflicted biases common to observational studies, such as selection bias and immortal time bias[8,9]
- Defining a clear index date (T_0) for a real-world evidence study ensures that patients are eligible before treatment starts and that outcomes are only counted after treatment begins, avoiding accidentally comparing patients with different starting points, which can lead to biased or misleading results[8]
- In this study, all enrolled patients met criteria for a T_0 at some point in the observation period (January 2016 to September 2024), in which they initiated treatment either with glucocorticosteroids (GCs) only or with a phosphorodiamidate morpholino oligomer (PMO)
- In addition to sequential TTE, inverse probability of treatment weighting was used to ensure covariate balance in both treatment arms (**Figure S3**)

Figure S3 *Covariates Balance (Standardized Mean Differences) Pre- and Post-Weighting*[a]

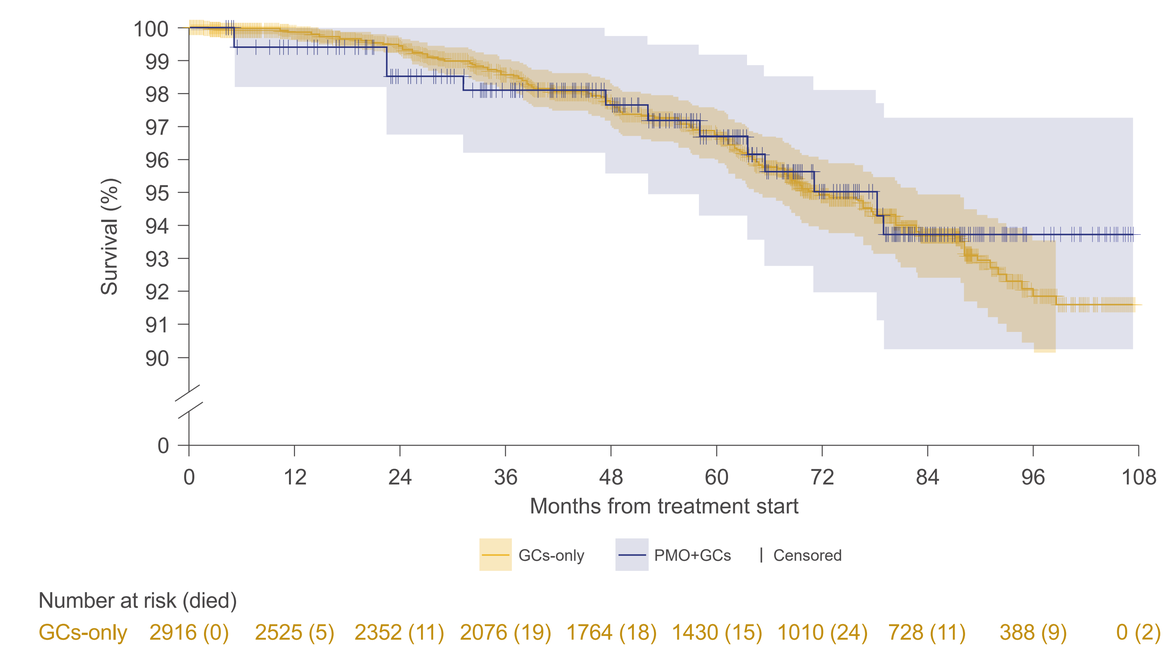


[a]All variables were measured in the previous 12 months, except for birth year, current age, and trial period. [b]Trial period is equivalent to glucocorticosteroids treatment duration.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; PCCC, Pediatric Complex Chronic Conditions; PCI, Pediatric Comorbidity Index.

Unadjusted time to mortality

- Due to the small number of deaths in the PMO+GCs cohort, the primary objective of unadjusted time to mortality was not calculated (**Figure S4**)

Figure S4 *Unadjusted Survival from Treatment Initiation*



Number at risk (died)										
GCs-only	2916 (0)	2525 (5)	2352 (11)	2076 (19)	1764 (18)	1430 (15)	1010 (24)	728 (11)	388 (9)	0 (2)
PMO+GCs	112 (0)	184 (1)	217 (2)	232 (1)	219 (1)	189 (2)	155 (3)	116 (2)	65 (0)	0 (0)

Shading represents 95% confidence interval. GCs, glucocorticoids; PMO, phosphorodiamidate morpholino oligomer.

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