



Real-world phosphorodiamidate morpholino oligomer treatment patterns in Duchenne muscular dystrophy: a claims-based analysis

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Aim: Phosphorodiamidate morpholino oligomers (PMOs) are exon-skipping therapies administered through once-weekly intravenous infusions used to treat Duchenne muscular dystrophy (DMD). This study assessed treatment patterns among patients with DMD receiving PMOs using administrative claims data while accounting for limitations in claims data for these therapies. **Materials & methods:** This study used Inovalon[®] public and private closed claims data (1 June 2016–31 March 2024). Male patients with ≥ 1 claim for a PMO approved for DMD in the US (eteplirsén, casimersén, golodirsén and viltolarsén) were included. Index date was the first PMO claim. All available follow-up data were used to assess continuous PMO claims coverage, ≥ 60 -day and ≥ 30 -day gaps in PMO claims and PMO re-initiation after a gap. Adherence during 1 year after index was measured using proportion of days covered (PDC). Treatment patterns were also assessed in patients stratified by baseline algorithm-defined nonambulatory status (inferred from claims). **Results:** Among 397 patients included, median (IQR) follow-up time was 788 (484, 1109) days. Gaps in PMO claims coverage occurred in 190 (47.9%) and 254 (64.0%) patients using ≥ 60 -day and ≥ 30 -day gaps, respectively, among whom 110 (57.9%) and 176 (69.3%) had PMO re-initiation. Using ≥ 60 -day and ≥ 30 -day gap lengths, median (IQR) time to first gap in PMO claims was 25.5 (22.3, 32.9) months and 13.5 (10.2, 17.7) months, respectively and median (IQR) time to PMO re-initiation (not including gap time) was 4.4 (2.8, 8.7) months and 2.5 (1.7, 3.2) months. Median (IQR) PDC was 78.8% (38.8, 94.0) during 1 year after index. PMO treatment patterns were generally similar in patients stratified by algorithm-defined nonambulatory status. **Conclusion:** In an analysis of administrative claims data, adherence to PMO treatment for DMD was high. For patients with a gap in PMO claims, most subsequently re-initiated treatment, indicating lower discontinuation rates than previously reported.

Plain language summary: Phosphorodiamidate morpholino oligomers in patients with Duchenne muscular dystrophy: how long are these treatments used?

Why was this study done? Duchenne muscular dystrophy (DMD) is a debilitating disease involving muscle weakness that starts in the first years of life and worsens over time. Most affected children lose their ability to walk by their teens. Phosphorodiamidate morpholino oligomers (PMOs) are a type of treatment used in certain patients with DMD. However, it is not well known how long patients stay on these treatments.

What did this study look at? This study used information from health insurance claims to look at how long patients with DMD stay on PMO treatment, how many patients have a longer-than-expected gap in PMO claims and whether patients who have a gap in claims eventually re-initiate PMO treatment after a gap.

What were the results? Nearly 400 patients were included in the study. On average, patients stayed on PMO treatment without any gaps in claims for more than 2 years. Overall, about 80% of the patients in the study either stayed on PMO treatment without a gap in claims through to the end of the study or re-initiated PMO treatment after a gap. The results were similar between patients who were not able to

walk (nonambulatory patients) and those who may have been able to walk (ambulatory patients) when they started PMO treatment.

What do the results mean? The results show that patients with DMD who are taking PMOs stay on the treatment for a long period of time and that patients with a gap in claims often continue their treatment.

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Duchenne muscular dystrophy (DMD) is a rare progressive disease that primarily affects males [1–3]. DMD is caused by pathogenic variants in the *DMD* gene as a result of frame-shift mutations [1,2,4–8]. The variants lead to the absence of functional dystrophin protein, resulting in progressive muscle deterioration, weakness and loss of independent ambulation [1,2,4–7].

Exon-skipping therapies are approved in the US for patients with DMD who are amenable to certain exon skipping [8–10]. These treatments work by modifying the *DMD* gene-splicing process to shift an out-of-frame mutation into an in-frame mutation in patients with DMD, increasing dystrophin expression [11–15]. Phosphorodiamidate morpholino oligomers (PMOs) are exon-skipping therapies that are chronically administered as weekly infusions [16–19]. To date, four PMOs have been approved by the US FDA for the treatment of DMD under the Accelerated Approval Program: eteplirsen (2016), golodirsen (2019), viltolarsen (2020) and casimersen (2021) [16–19]. Each of these therapies binds to a specific exon of the *DMD* gene and is indicated for patients with a confirmed variant amenable to skipping of the exon targeted by the PMO [16–19].

Treatment persistence, discontinuation and adherence are commonly assessed measures of treatment patterns that are often associated with clinical and health outcomes [20–27], including among patients with neuromuscular diseases prescribed injectable therapies [28,29]. These metrics are often assessed using healthcare administrative claims data, with persistence typically defined as the duration from initiation to discontinuation of therapy, discontinuation defined as time without therapy exceeding a context-specific and predefined threshold and adherence defined as the extent to which a patient acts in accordance with the prescribed dosing regimen [20,22,24,26,30–34]. These measures are all dependent on claims being captured in a timely and accurate manner and are limited when gaps in claims coverage are present [27,30,32,35].

Conclusions based on claims-based analyses for PMO therapies are impacted if the methodology used does not account for barriers that cause gaps in coverage [36]. The current published real-world evidence for PMO treatment patterns is limited to two studies, both of which analyzed data from claims databases but showed significant heterogeneity of methods and treatment pattern outcomes [36,37]. Hong *et al.* assessed a fixed 1-year follow-up period after PMO initiation and defined discontinuation as a 30-day gap in claims without considering claims occurring after a gap, concluding that approximately one-third of patients discontinued treatment after a mean follow-up time of 7 months [37]. In contrast, Klimchak *et al.* used all available follow-up data and assessed ≥ 30 -day gaps in claims as well as claims occurring after a gap, showing that approximately 85% of patients had either continuous PMO claims coverage or a subsequent PMO claim after a gap over a mean follow-up time of ~ 22 months [36]. These analyses demonstrate a need to optimize assessment and improve understanding of treatment patterns for these therapies.

The objective of this study was to assess PMO treatment patterns in US administrative claims data by characterizing continuous PMO claims coverage, total days' supply and the frequency and timing of claims occurring after a gap in coverage (PMO re-initiation) among patients with DMD treated with any PMO. These outcomes are similar to the conventional measures of persistence and discontinuation, but more comprehensively capture episodic claim profiles and gaps between claims that may not represent true discontinuation of treatment [36]. In addition, loss of ambulation (LOA) is widely acknowledged as an important measure of disease progression in DMD [38]. Nonambulatory patients with DMD may have reduced access to PMO therapy as many payer policies restrict authorization and reauthorization to ambulatory patients only [39–52]. Therefore, the study outcomes were also assessed in the cohort stratified by baseline nonambulatory status.

Materials & methods

Study design & data source

This retrospective, observational cohort study used the Inovalon[®] health administrative closed claims database, which includes fully adjudicated medical and pharmacy closed payer claims from more than 160 sources spanning all 50 states in the US, DC and Puerto Rico [53]. The database comprises claims data covering more than half of the US insured population across Medicaid, Medicare and commercial coverage, with more than 1 million providers [53]. Inovalon data were chosen based on the quantity of patients with DMD covered and the heterogeneous population as evidenced by inclusion of both public and private payer coverage.

Ethics

This study was performed in accordance with ethical principles consistent with the Declaration of Helsinki and Good Pharmacoepidemiology Practice [54]. Institutional review board (IRB) exemption was sought from Advarra IRB and received on 28 November 2023. Advarra IRB is registered with the Office for Human Research Protections and FDA under IRB#00000971. Data were de-identified and compliant with Health Insurance Portability and Accountability Act regulations thus meeting determination for exemption.

Study population

Patients with at least 1 claim for a PMO approved by the FDA for the treatment of DMD (eteplirsén, golodirsén, casimersén or viltolarsén) from the time of FDA approval to 31 December 2023 were included. Since treatment of DMD is the only approved indication for PMO therapies and eligible patients must have a confirmed mutation of the *DMD* gene amenable to certain exon skipping [16–19], a diagnosis code is not required to confirm DMD in claims data when the study population only includes PMO-treated patients. This approach is consistent with other recent claims analyses of PMO therapies [36,37].

PMO claims were captured in the dataset using Healthcare Common Procedure Coding System (HCPCS) J-codes and National Drug Codes codes (Supplementary Table 1). Female patients and those without continuous medical and prescription benefit enrollment during the 60 days prior to the index date were excluded.

The index date was defined as the first eligible medical/pharmacy claim of a PMO after its FDA approval date between 19 September 2016 and 31 December 2023. The study period was between 1 June 2016 and 31 March 2024, allowing for a minimum 60-day pre-index period with no observed PMO claim and a minimum 3-month post-index follow-up period. A 60-day pre-index continuous enrollment period was selected to allow for sufficient capture of patient attributes without substantially reducing sample size and amplifying survival biases. All available follow-up data were used in the primary analysis, with patients followed from the index date until the last data availability date prior to a gap in continuous insurance enrollment with medical and pharmacy benefits.

Continuous enrollment in Inovalon data was defined as insurance enrollment periods that included both prescription and medical coverage, overlapped with the index date and continued for the required amount of time before or after the index date. Patients who changed insurance plans without a >1-day gap in coverage continued to have the same insurance enrollment period. For multiple concurrent plans, the period started with the earliest plan and ended with the latest plan. Coverage end dates beyond the available data were truncated to the end of the data.

One-year post-index subgroup

In a subgroup analysis, the required follow-up period for a sub-cohort was defined as at least 1 year after index to understand PMO treatment patterns within a fixed time frame of the first year after initiating therapy, consistent with a previously published study [37]. In the subgroup analysis, claims extending beyond 1 year were truncated to include only the portion of days' supply captured within the 1-year window.

Stratification by nonambulatory status

Patients were stratified based on nonambulatory status at the time of exon-skipping therapy initiation, as inferred from claims data. A recently published algorithm was used to identify patients who were determined to be nonambulatory in claims data based on HCPCS J-codes, International Classification of Diseases, Tenth Revision (ICD-10) diagnosis and procedure codes and Common Procedural Terminology (CPT) codes [55]. Several newer and/or revised codes were added to the previously published algorithm for use in this study (Supplementary Table 2). Nonambulatory status was defined as ≥ 1 claim for a power wheelchair or bed confinement or ≥ 1 claim

indicating ventilation dependence. In the source publication, the nonambulatory status algorithm yielded a positive predictive value (PPV; 95% confidence interval [CI]) of 88.4% (80.2, 94.1) among patients with DMD identified in claims data and confirmed in electronic health records (EHRs) [55]. When patients with insufficient EHR notes to confirm DMD diagnosis were included, the PPV (95% CI) decreased to 79.3% (70.3, 86.5) [55]. It was noted that the algorithms accurately identified the majority of nonambulatory patients with DMD, but the PPV was likely limited by patient numbers [55]. In the present study, patients who were not identified as nonambulatory within the 60-day required baseline period using the published algorithm had no evidence of nonambulatory status in claims. As such, the stratum of patients with absence of algorithm-defined nonambulatory status (hereafter referred to as the ambulatory stratum) may have included nonambulatory patients who were not identified using the algorithm in the defined baseline period.

Study outcomes

Total days' supply in PMO claims, follow-up time and adherence (measured using proportion of days covered [PDC]) were calculated. A gap in PMO claims was defined as a period of ≥ 60 days or ≥ 30 days after the run-out of the previous claim. Gap length definitions of ≥ 60 days and ≥ 30 days were used to assess continuous PMO claims coverage without a gap in PMO claims, total number of patients with a gap in PMO claims, time to first gap in PMO claims, total number of patients who re-initiated PMO treatment after a gap in claims (≥ 1 PMO claim after a gap) and time to PMO re-initiation. These outcomes were assessed in the primary analysis using all available follow-up data, in the analysis stratifying patients by pre-index nonambulatory status using all available follow-up data and in the subgroup analysis using a ≥ 1 -year post-index follow-up period. The definitions of continuous PMO claims coverage and time to first gap in PMO claims are similar to the conventional measure of persistence; however, the conventional definition of persistence assumes that a gap in claims represents discontinuation. The terminology and definitions for outcomes measured in this study along with the assessment of PMO re-initiation account for episodic claim profiles in which gaps between claims may not represent true discontinuation of treatment with PMOs.

Rules used to calculate total days' supply (covered days) are presented in the [Supplementary Methods](#). PDC was calculated during the first year post index among patients with continuous enrollment. PDC was capped at 100%, where the numerator was total number of days on index therapy and the denominator was 365 days [30,31,56]. If the run-out date of the final claim extended beyond the 1-year follow-up period, it was truncated to the end of 1 year. If a patient refilled a prescription or infused early, any days overlapping from the early refill or infusion were added to the calculated coverage duration. Two definitions of adherence based on PDC were used: a dichotomous definition with PDC $\geq 80\%$ considered adherent and PDC $< 80\%$ considered nonadherent and granular ordinal PDC cutoffs with adherence defined as low (PDC $< 50\%$), moderate (PDC 50% to $< 80\%$), high (PDC 80% to $< 90\%$) and very high (PDC $\geq 90\%$). The medication possession ratio (MPR) was also evaluated but not presented due to the high frequency of overlapping days' supply, as MPR does not take overlapping fill days into account or truncate the last fill to the end of the follow-up period.

Statistical analysis

Baseline demographics (age, sex, US region, race/ethnicity and health insurance type) and study outcomes were assessed using descriptive statistics including mean and standard deviation (SD), minimum and maximum, and median and interquartile range (IQR) for continuous variables and frequency and proportion for categorical variables. Time to first gap in PMO claims and time to PMO re-initiation after a gap were analyzed using the Kaplan–Meier (KM) method. In the analysis stratified by nonambulatory status, the KM curves for the nonambulatory status strata were visually inspected to assess the proportional hazards assumption. Log-rank tests were planned if the proportional hazards assumption was upheld and descriptive analyses were planned if the assumption was violated. All statistical analyses were conducted using SAS version 9.4.

Results

Patient characteristics

Five hundred eighty-one patients with an eligible PMO claim during the study period were identified. Thirty patients were excluded based on sex, leaving 551 male patients, of whom 154 did not meet the continuous pre-index enrollment criteria. The remaining 397 patients were included in the primary analysis using all available follow-up data. The mean (SD) age was 12.9 (6.3) years, 37.0% of patients were White and 23.9% were Hispanic

Table 1. Characteristics of the overall cohort – all available follow-up (n = 397).

Baseline demographics	Overall (n = 397)
Age, years	
Mean (SD)	12.9 (6.3)
Median (IQR)	12 (8, 17)
Age groups, n (%)	
<7	61 (15.4)
7–12	146 (36.8)
13–17	104 (26.2)
18–24	69 (17.4)
≥25	16 (4.0)
Missing [†]	1 (0.3)
Gender, n (%)	
Male	397 (100)
Geographic region, n (%)	
Midwest	75 (18.9)
Northeast	54 (13.6)
South	170 (42.8)
West	96 (24.2)
Missing	2 (0.5)
Race/Ethnicity, n (%)	
Asian or Pacific Islander	22 (5.5)
Black or African-American	15 (3.8)
Hispanic or Latino	95 (23.9)
White	147 (37.0)
Other race	24 (6.0)
Unknown	94 (23.7)
Health insurance type, n (%)	
Medicaid	322 (81.1)
Commercial	61 (15.4)
Dual (Medicaid + commercial)	12 (3.0)
Medicare/other/unknown	2 (0.5)
Treatment characteristics	
Index PMO, n (%)	
Eteplirsen	218 (54.9)
Casimersen	114 (28.7)
Golodirsen	35 (8.8)
Viltolarsen	30 (7.6)
Total days' supply	
Mean (SD)	605.2 (505.8)
Median (IQR)	504 (196, 812)
Follow-up time, days	
Mean (SD)	875.4 (554.0)
Median (IQR)	788 (484, 1109)

[†] One patient had reported age markedly outside of the range; therefore, age for this patient was set to missing.
 IQR: Interquartile range; PMO: Phosphorodiamidate morpholino oligomer; SD: Standard deviation.

or Latino (Table 1). Most patients had Medicaid (81.1%) coverage at index, followed by commercial (15.4%) or dual (3.0%) coverage. The majority of index PMO claims were for eteplirsen (54.9%), followed by casimersen (28.7%), golodirsen (8.8%) and viltolarsen (7.6%). Two (0.5%) patients had a claim for a PMO during follow-up that was different than their index PMO.

Among patients in the primary analysis population, 120 (30.2%) were nonambulatory (as defined based on the algorithm used) and 277 (69.8%) were ambulatory before index (Table 2). Ambulatory patients were younger than nonambulatory patients (mean [SD] age: 12.0 [6.3] vs 14.8 [6.0] years). Geographic distribution across US regions differed between nonambulatory strata, with a higher proportion of nonambulatory patients located in the Northeast (20.0% vs 10.8%) and a higher proportion of ambulatory patients located in the West (27.8% vs 15.8%). All other demographics were similar between patients stratified by nonambulatory status. In both the nonambulatory and ambulatory strata, most of the PMO claims were for eteplirsen (47.5% and 58.1%, respectively), followed by casimersen (35.8% and 25.6%), golodirsen (10.0% and 8.3%) and viltolarsen (6.7% and 7.9%).

Patient characteristics were generally similar between the primary analysis population and the subgroup that required a 1-year follow-up period (Supplementary Table 3).

Table 2. Characteristics stratified by index nonambulatory status – all available follow-up (n = 397).

Baseline demographics	Ambulatory [‡] (n = 277)	Nonambulatory (n = 120)
Age, years		
Mean (SD)	12.0 (6.3)	14.8 (6.0)
Median (IQR)	11 (7, 16)	14 (11, 18)
Age groups, n (%)		
<7	54 (19.5)	7 (5.8)
7–12	107 (38.6)	39 (32.5)
13–17	67 (24.2)	37 (30.8)
18–24	38 (13.7)	31 (25.8)
≥25	10 (3.6)	6 (5.0)
Missing [†]	1 (0.4)	0 (0.0)
Gender, n (%)		
Male	277 (100)	120 (100)
Geographic region, n (%)		
Midwest	50 (18.1)	25 (20.8)
Northeast	30 (10.8)	24 (20.0)
South	119 (43.0)	51 (42.5)
West	77 (27.8)	19 (15.8)
Missing	1 (0.4)	1 (0.8)
Race/Ethnicity, n (%)		
Asian or Pacific Islander	13 (4.7)	9 (7.5)
Black or African-American	13 (4.7)	2 (1.7)
Hispanic or Latino	64 (23.1)	31 (25.8)
White	106 (38.3)	41 (34.2)
Other race	13 (4.7)	11 (9.2)
Unknown	68 (24.5)	26 (21.7)
Health insurance type, n (%)		
Medicaid	221 (79.8)	101 (84.2)
Commercial	45 (16.2)	16 (13.3)
Dual (Medicaid + commercial)	10 (3.6)	2 (1.7)
Medicare/other/unknown	1 (0.4)	1 (0.8)
Treatment characteristics		
Index PMO, n (%)		
Eteplirsén	161 (58.1)	57 (47.5)
Casimersén	71 (25.6)	43 (35.8)
Golodirsén	23 (8.3)	12 (10.0)
Viltolarsén	22 (7.9)	8 (6.7)
Total days' supply		
Mean (SD)	605.0 (516.5)	605.8 (482.4)
Median (IQR)	483 (182, 847)	529 (207, 795)
Follow-up time, days		
Mean (SD)	902.4 (575.3)	813.2 (497.9)
Median (IQR)	799 (480, 1210)	756 (491, 970)

[†] One patient had reported age markedly outside of the range; therefore, age for this patient was set to missing.
[‡] Refers to patients with absence of algorithm-defined nonambulatory status within the 60-day baseline period.
IQR: Interquartile range; PMO: Phosphorodiamidate morpholino oligomer; SD: Standard deviation.

Primary analysis: PMO treatment patterns over the entire follow-up period

The median (IQR) total days' supply was 504 (196, 812) and the median (IQR) follow-up time was 788 (484, 1109) days (Table 1). In the primary analysis, 52.1% and 36.0% of patients had continuous claims coverage without a ≥60-day or ≥30-day gap, respectively (Table 3). Gaps in PMO claims coverage during follow-up (from nonparametric KM curves) occurred in 47.9% and 64.0% of patients using ≥60-day and ≥30-day gap definitions, respectively (Table 3). The median (IQR) time to first gap in PMO claims was 25.5 (22.3, 32.9) months using the ≥60-day gap definition and 13.5 (10.2, 17.7) months using the ≥30-day gap definition (Table 3 & Figure 1A & C).

Among patients who had a gap in PMO claims, 57.9% and 69.3% re-initiated PMO treatment (from nonparametric KM curves) using ≥60-day and ≥30-day gap definitions, respectively (Table 3), with a median (IQR) time to PMO re-initiation (not including gap time) of 4.4 (2.8, 8.7) months and 2.5 (1.7, 3.2) months, respectively (Table 3 & Figure 1B & D). Approximately 80% of patients had continuous PMO claims coverage or PMO re-initiation during follow-up, regardless of gap length definition (Table 3).

Table 3. Gaps in PMO claims and PMO re-initiation after a gap in the overall cohort – all available follow-up (n = 397).

	Overall (n = 397)	
	60-day gap	30-day gap
Total patients with continuous PMO claims coverage during follow-up, n (%) [†]	207 (52.1)	143 (36.0)
Total patients with a gap during follow-up, n (%) [†]	190 (47.9)	254 (64.0)
Median time to first gap, months (95% CI)	25.5 (22.3, 32.9)	13.5 (10.2, 17.7)
Total patients with PMO re-initiation, n (%) [‡] / Median time to PMO re-initiation, months (95% CI) [§]	110 (57.9) / 4.4 (2.8, 8.7)	176 (69.3) / 2.5 (1.7, 3.2)
Total patients with continuous PMO claims coverage or PMO re-initiation during follow-up, n (%) [†]	317 (79.8)	319 (80.4)

[†]Denominator is the total number of patients in the overall cohort.

[‡]Denominator is the total number of patients with a gap at the end of follow-up.

[§]Time to PMO re-initiation does not include the gap time (i.e., begins after the 60- or 30-day gap).

CI: Confidence interval; NR: Not reached; PMO: Phosphorodiamidate morpholino oligomer.

PMO treatment patterns in nonambulatory status strata over the entire follow-up period

Total days' supply (median [IQR]: 483 [182, 847] vs 529 [207, 795] days) and follow-up length (median [IQR]: 799 [480, 1210] vs 756 [491, 970] days) were similar between ambulatory and algorithm-defined nonambulatory patients (Table 2). The proportion of patients with a gap in PMO claims during follow-up showed separation between ambulatory and nonambulatory strata using the ≥ 60 -day gap definition (52.0% vs 38.3%) but was similar between strata using the ≥ 30 -day gap definition (64.3% vs 63.3%) (Table 4).

Visual inspection of the KM curves for the nonambulatory status strata showed violation of the proportional hazards assumption; therefore, results of KM analyses were assessed descriptively. The median (IQR) time to first gap in PMO claims appeared longer in the nonambulatory stratum (not reached [NR] [22.6, NR]) than in the ambulatory stratum (24.7 [15.6, 29.1] months) using the ≥ 60 -day gap definition, with a similar but less pronounced difference using the ≥ 30 -day gap definition (14.9 [11.3, 20.6] months vs 12.0 [7.7, 18.7] months) (Table 4 & Figure 2A & C).

Among ambulatory and algorithm-defined nonambulatory patients who had a gap in PMO claims during follow-up, the proportion of patients with PMO re-initiation was similar between strata using both ≥ 60 -day (57.6% vs 58.7%) and ≥ 30 -day (67.4% vs 73.7%) gap definitions (Table 4). The median (IQR) time to PMO re-initiation (not including gap time) appeared longer among ambulatory patients than among nonambulatory patients using both the ≥ 60 -day gap definition (6.3 [3.8, 11.7] months vs 2.8 [1.9, 4.8] months) and the ≥ 30 -day gap definition (2.9 [2.0, 4.5] months vs 1.3 [0.8, 2.7] months) (Table 4 & Figure 2B & D).

Proportion of days covered

Analysis of PDC included 324 patients with at least 1 year of follow-up data available after index. The median (IQR) PDC for PMO claims in the first year after index was 78.8% (38.8, 94.0) (Table 5). Using a dichotomous definition of adherence, 49.7% of patients were considered adherent to PMO therapy (PDC $\geq 80\%$) and 50.3% were considered nonadherent (PDC $< 80\%$). Using more granular PDC cutoffs, 70.7% of patients exhibited moderate or better (PDC $\geq 50\%$) adherence, including 13.9% with high adherence (PDC 80% to $< 90\%$) and 35.8% with very high adherence (PDC $\geq 90\%$).

Subgroup analysis: PMO treatment patterns over 1-year follow-up

In the subgroup analysis, the median (IQR) total days' supply was 301 (147, 350) and was higher among algorithm-defined nonambulatory patients than among ambulatory patients (median [IQR]: 319 [228, 364] vs 277 [119, 343] days; Supplementary Table 3). The overall trends in the subgroup analysis using only the first year of follow-up after index (n = 324) were similar to those of the primary analysis, although the proportion of patients with a gap in PMO claims coverage was lower with the shorter follow-up period. The proportion of patients with continuous claims coverage during the first year after initiating PMO therapy was 65.1% using the ≥ 60 -day gap definition and 53.4% using the ≥ 30 -day gap definition (Supplementary Table 4). At least 85% of patients had either continuous PMO claims coverage or PMO re-initiation during the first year of follow-up, regardless of gap definition.

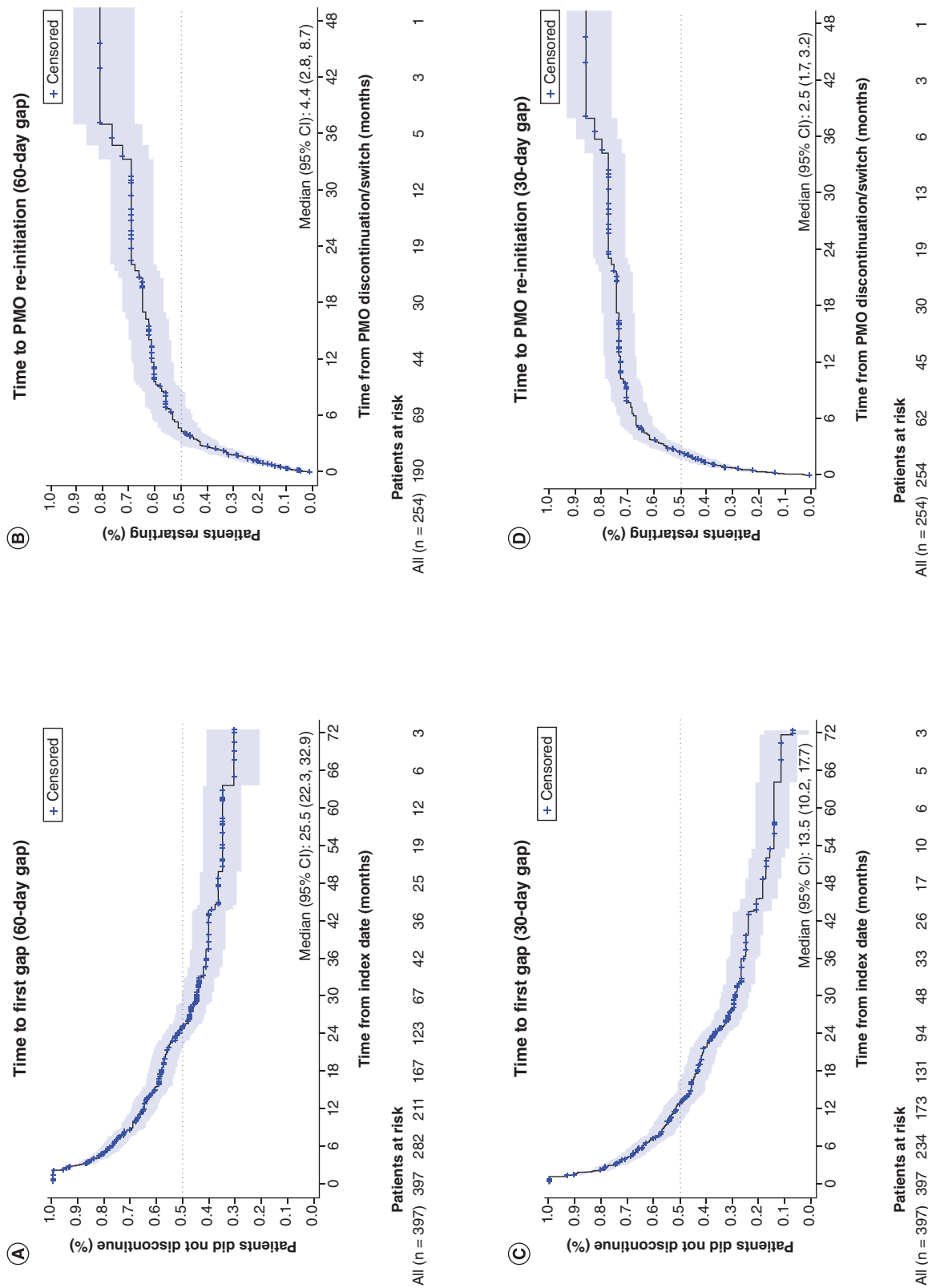


Figure 1. Time to first gap in PMO claims coverage and PMO re-initiation after a gap. (A & B) Using 60-day or (C & D) 30-day gap definitions – all available follow-up data (n = 397).
CI: Confidence interval; PMO: Phosphorodiamidate morpholino oligomer.

Table 4. Gaps in PMO claims and PMO re-initiation after a gap stratified by index nonambulatory status – all available follow-up (n = 397).

	60-day gap		30-day gap	
	Ambulatory [¶] (n = 277)	Nonambulatory (n = 120)	Ambulatory [¶] (n = 277)	Nonambulatory (n = 120)
Total patients with continuous PMO claims coverage during follow-up, n (%) [†]	133 (48.0)	74 (61.7)	99 (35.7)	44 (36.7)
Total patients with a gap during follow-up, n (%) [‡]	144 (52.0)	46 (38.3)	178 (64.3)	76 (63.3)
Median time to first gap, months (95% CI)	24.7 (15.6, 29.1)	NR (22.6, NR)	12.0 (7.7, 18.7)	14.9 (11.3, 20.6)
Total patients with PMO re-initiation, n (%) [‡] / Median time to PMO re-initiation, months (95% CI) [§]	83 (57.6) / 6.3 (3.8, 11.7)	27 (58.7) / 2.8 (1.9, 4.8)	120 (67.4) / 2.9 (2.0, 4.5)	56 (73.7) / 1.3 (0.8, 2.7)
Total patients with continuous PMO claims coverage or PMO re-initiation during follow-up, n (%) [†]	216 (78.0)	101 (84.2)	219 (79.1)	100 (83.3)

[†] Denominator is the total number of patients in the ambulatory or nonambulatory strata.
[‡] Denominator is the total number of patients with a gap at the end of follow-up.
[§] Time to PMO re-initiation does not include the gap time (i.e., begins after the 60- or 30-day gap).
[¶] Refers to patients with absence of algorithm-defined nonambulatory status within the 60-day baseline period.
CI: Confidence interval; NR: Not reached; PMO: Phosphorodiamidate morpholino oligomer.

Discussion

This study provides a detailed analysis of PMO treatment patterns in patients with DMD using administrative claims data, with the largest sample size and longest follow-up time to date among claims-based PMO treatment patterns studies [36,37]. The analysis included data up to March 2024, allowing for more data accrual than previous studies, which is particularly noteworthy for the most recently approved PMOs.

For patients with DMD, access to PMO therapies may be impacted by insurance policies and reauthorization criteria [40–52], an observation that has been documented for other infusion therapies [57–61]. These authorization requirements could lead to delayed or denied treatment delivery, interrupted treatment processes and increased resource utilization [59,61]. Many other factors could also lead to interruptions or gaps in therapy, including changes in insurance coverage, lifestyle and personal reasons and other medical encounters [57–59,62–64]. Other plausible scenarios include logistical challenges such as difficulty securing home infusion support, moving further from an infusion center or clinical issues such as requiring a pause in treatment for venous port placement due to IV access issues. Nonetheless, by using methodology that accounts for treatment interruptions, the findings highlight that despite many patients having an apparent gap in PMO claims coverage, most patients re-initiate PMO treatment within a few months after the gap.

In a previous study by Hong *et al.*, PMO treatment patterns were assessed in commercial and Medicaid claims data (multiple databases) using a 1-year follow-up period and a 30-day gap duration to define treatment discontinuation [37]. The authors concluded that approximately one-third of patients with DMD discontinued PMO therapy after a mean follow-up time of 7 months [37]. However, limiting the follow-up period to 1 year from PMO therapy initiation does not allow for a complete assessment of PMO treatment patterns, as shown by the median time to first gap in PMO claims in our study, which was more than 1 year using a ≥ 30 -day gap definition and more than 2 years using a ≥ 60 -day gap definition. Further, the previous study's conclusion was likely impacted by the assumption that patients with a 30-day gap in claims discontinued PMO therapy since PMO claims occurring after a gap were not explored [37]. This current analysis of all available PMO claims data shows that limiting follow-up to 1 year and not including PMO claims that occur after gaps will lead to rates of apparent PMO discontinuation that are overstated compared with a more complete view of real-world care, in which the majority of patients continue to be treated with PMOs despite gaps in claims.

Recently, Klimchak *et al.* assessed PMO treatment patterns in MarketScan[®] commercial and Medicaid claims using all available follow-up data and a ≥ 30 -day gap definition and included an analysis of subsequent PMO claims after a gap (similar to PMO re-initiation in this study) in their study design [36]. In that analysis, more than half of all patients had continuous PMO claims coverage during a mean of approximately 22 months of continuous follow-up [36]. Similar to the present study, most patients with a gap in PMO coverage had a subsequent PMO claim after a gap [36]. The present study used a different closed claims data source, included more patients in the analysis, used a more recent data cutoff than the previous studies and considered multiple definitions to assess gaps in coverage and PMO re-initiation. Further, a greater proportion of patients had Medicaid coverage in this study

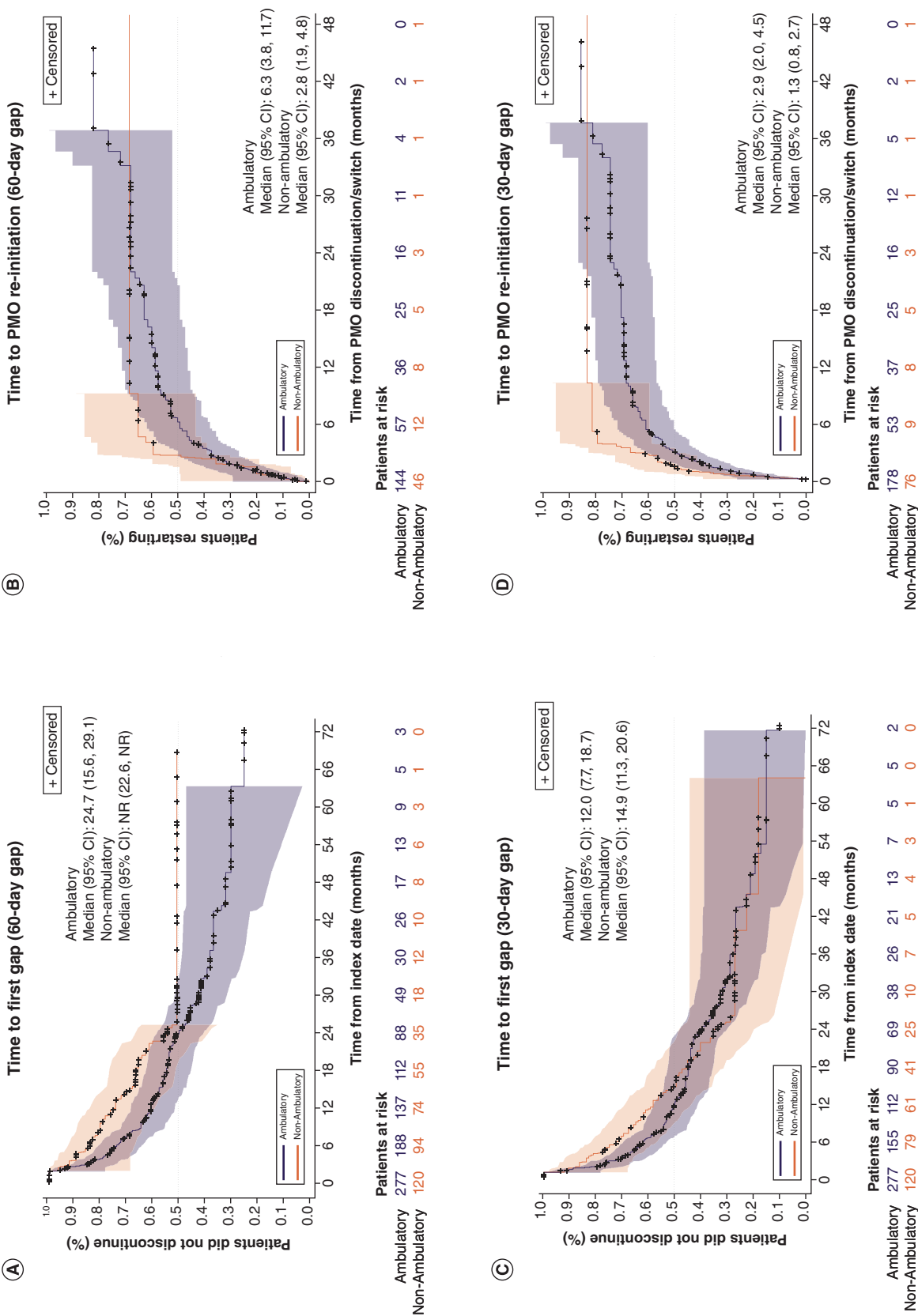


Figure 2. Time to first gap in PMO claims coverage and PMO re-initiation after a gap using 60-day (A & B) or 30-day (C & D) gap definitions by index nonambulatory status^a – all available follow-up data (n = 397).

^aRefers to patients with absence of algorithm-defined nonambulatory status within the 60-day baseline period.

CI: Confidence interval; PMO: Phosphorodiamidate morpholino oligomer.

Table 5. Proportion of days covered for PMO claims in the first year after index (n = 324).

Adherence	Overall (n = 324)
Proportion of days covered (PDC), %	
Mean (SD)	66.9 (31.1)
Median (IQR)	78.8 (38.8, 94.0)
Min, max	1.9, 100.0
PDC category no. 1, n (%)	
Adherent (PDC ≥80%)	161 (49.7)
Nonadherent (PDC <80%)	163 (50.3)
PDC category no. 2, n (%)	
Very high adherence (PDC ≥90%)	116 (35.8)
High adherence (PDC 80% to <90%)	45 (13.9)
Moderate adherence (PDC 50% to <80%)	68 (21.0)
Low adherence (PDC <50%)	95 (29.3)

†The PDC is defined broadly as the proportion of days that an individual has access to medication during a specified observation period, based on the fill dates and days' supply for each dispensing.
IQR: Interquartile range; PDC: Proportion of days covered; PMO: Phosphorodiamidate morpholino oligomer; SD: Standard deviation.

than in the previous studies [36,37]. Overall, the findings from this study expand the understanding of real-world PMO treatment patterns and when considered alongside the previous studies, support the need for robust methods to analyze PMO treatment patterns.

In the present study, applying a conventional, dichotomous definition of adherence based on a PDC of 80% or greater suggested that approximately 50% of patients were adherent to PMO therapy during the first year after treatment initiation. However, it is well recognized that this conventional approach is limited [22,26,30,32,56,65,66]; therefore, a more granular approach was also used to categorize adherence based on different levels ranging from low to very high. Using this approach, more than 70% of patients had at least moderate adherence (PDC of 50% or greater). Considering heterogeneity of PDC thresholds for different routes of administration may be warranted when assessing treatment patterns of infusion therapies.

Additional data sources such as phase IV studies provide useful insight into real-world PMO treatment patterns. Interim results from the ongoing, real-world, phase IV, multicenter EVOLVE study showed that 95.2% of patients treated with eteplirsén (n = 126) remained on treatment at the time of analysis, with a mean treatment duration of 6.4 years [67]. The proportion of patients continuing eteplirsén through follow-up was 95.8% among patients who were ambulatory at eteplirsén initiation (n = 48) and 97.6% among patients who were nonambulatory at eteplirsén initiation (n = 41) [67]. These interim findings show high rates of continuous treatment among patients with DMD who initiate PMO therapy [67]. Notably, the rate of continuous treatment in the EVOLVE study is higher than continuous claims coverage rates in the present study or in previously published claims-based analyses [36,37], highlighting the limitations of capturing PMO treatment patterns in claims data and the need to consider various data sources. This difference may also reflect other barriers to adherence related to real-world care and reimbursement, which should be considered by providers. Additionally, the EVOLVE study is assessing multiple patient-relevant functional measurements and may provide an opportunity to evaluate associations between continuous PMO treatment and functional outcomes in patients with DMD.

Limitations

Administrative claims data sources only capture insured patients; therefore, the findings may not be applicable to patients without insurance. Further, the majority (>80%) of patients included in the analysis had Medicaid insurance, whereas approximately 15% had commercial coverage. This may have influenced the findings since policies for PMO therapy coverage differ between Medicaid and commercial plans.

In terms of limitations specific to the data source, the Inovalon claims database has multiple records per claim line, which required consolidation algorithms to determine adjudicated claims. The data source also has multiple insurance enrollment periods, some of which extend beyond the available data cut; therefore, algorithms for continuous enrollment were required to cap enrollment to the end of the data period and avoid overestimating eligible patients. Additionally, dispensing of infusion drugs is observed in both pharmacy and medical settings, which can occur simultaneously in the Inovalon data, also requiring adjustment.

As with other claims-based analyses of PMO treatment patterns [36,37], drug codes for PMOs approved by the FDA for DMD were used to identify eligible claims, but ICD-10 codes were not used to verify the patient's DMD

diagnosis; therefore, the study assumes the drugs were used appropriately and on-label. The algorithm used to stratify patients' nonambulatory status only identifies nonambulatory patients and those not meeting the definition (i.e., without evidence of LOA within the 60-day baseline period) are considered ambulatory. Although the source publication validating the algorithm used in this study noted that the majority of nonambulatory patients with DMD are captured (with a PPV of 79.3–88.4%), it is possible that some nonambulatory patients were misclassified as ambulatory for the analysis. For example, some claims used in the nonambulatory status algorithm would occur very infrequently (e.g., power wheelchair claims) and may not have been captured in the 60-day baseline period, potentially leading to nonambulatory patients being classified as ambulatory. This represents a limitation of the ambulatory stratum, but the algorithm is highly sensitive for nonambulatory patients. The mean age of patients in the nonambulatory stratum in the present study was similar to that of nonambulatory patients initiating eteplirsen in the phase IV EVOLVE study (14.8 and 15.4 years, respectively), supporting classification of nonambulatory patients in the present study [67]. Although the mean age of the ambulatory stratum (12.0 years) was higher than expected in the present study, age at LOA is higher in some studies; for example, median age at LOA among patients who were ambulatory at the time of eteplirsen initiation in EVOLVE was 15.36 years based on KM analysis [67].

Additionally, the KM curves used to assess time-to-event outcomes in the nonambulatory and ambulatory strata showed violation of the proportional hazards assumption upon visual inspection; therefore, results were only summarized descriptively. Although restricted mean survival analyses could be applied in such cases, these were not used in this study given the limitations regarding the nonambulatory status stratification described above.

Finally, many different factors could lead to interruptions or gaps in therapy (e.g., insurance reauthorization processes, changes in insurance coverage/policies, lifestyle reasons, etc.) [57–59,62–64]. Although it is impossible to identify the specific cause(s) in claims data [64], future studies should explore the reasons underlying gaps in PMO therapy using other data sources that could provide this type of information.

Conclusion

The results of this claims-based cohort study show adherence to PMO treatment for DMD was high. Most patients (~80%) with DMD on PMO therapy either had continuous PMO claims coverage during follow-up or had a gap in claims followed by PMO re-initiation, indicating lower discontinuation rates than previously reported. The methodology used herein accounts for gaps in claims that may be caused by issues with patient access to PMO therapy, improving the current understanding of PMO treatment patterns. Future analyses using other data sources, including prospective studies (e.g., phase IV studies) may provide more detailed insights into real-world treatment patterns of PMO therapies for patients with DMD.

Summary points

- Phosphorodiamidate morpholino oligomers (PMOs) are exon-skipping therapies used to treat Duchenne muscular dystrophy (DMD).
- Few studies have assessed real-world PMO treatment patterns and the limited evidence to date is mixed, potentially related to differences in methodology of claims-based analyses.
- This retrospective cohort study sought to assess treatment patterns of PMOs among patients with DMD using Inovalon® administrative closed claims data (1 June 2016–31 March 2024).
- The methodology accounted for the limitations of conventional claims-based analyses of these infused therapies by considering gaps in PMO claims and PMO re-initiation after a gap in claims.
- All available follow-up data (median follow-up >2 years) were assessed for 397 patients.
- Gaps in PMO claims coverage occurred in 47.9% of patients using a ≥ 60 -day gap definition and 64.0% using a ≥ 30 -day gap definition, within a median of 25.5 and 13.5 months of PMO initiation, respectively.
- Among patients with a ≥ 60 -day or ≥ 30 -day gap in claims, 57.9% and 69.3% re-initiated PMO treatment after a gap within 4.4 and 2.5 months, respectively.
- Median proportion of days covered (PDC), used as a measure of adherence, was 78.8%.
- An analysis stratifying patients by nonambulatory status (as inferred from claims) showed generally similar treatment patterns regardless of baseline nonambulatory status stratification, with both algorithm-defined nonambulatory patients and ambulatory patients remaining on PMO therapy for long periods of time after treatment initiation.
- Most patients (~80%) receiving PMOs for DMD had continuous claims coverage or PMO-reinitiation. Other data sources, including prospective studies, may provide more detailed insight into real-world PMO treatment patterns.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: <https://becarispublishing.com/doi/epdf/10.57264/cer-2025-0037>

Author contributions

S Grabich, B Ung, A Nadkar, K DeYoung and J Signorovitch contributed to the study conception and design. Acquisition, analysis or interpretation of data were performed by all authors. All authors read and approved the final manuscript.

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Competing interests disclosure

S Grabich, B Ung, A Nadkar and K DeYoung are employees of Sarepta Therapeutics, Inc. and may own stock/options in the company. J Signorovitch is an employee of Analysis Group, Inc, which has received consulting fees from Sarepta Therapeutics, Inc. A Veerapandian has a consultancy/advisory role with AMO Pharma, AveXis, Biogen, Edgewise Therapeutics, FibroGen, Novartis, Pfizer, PTC Therapeutics, Sarepta Therapeutics, UCB Pharma, Catalyst and Scholar Rock; has received research funding from AMO Pharma, Capricor Therapeutics, Edgewise Therapeutics, FibroGen, the Muscular Dystrophy Association, Novartis, Parent Project Muscular Dystrophy, Pfizer, RegenxBio and Sarepta Therapeutics; and has other relationship(s) with MedLink Neurology for editorial services. The authors have no other competing interests or relevant affiliations with any organization or entity with the subject matter or materials discussed in the manuscript apart from those disclosed.

Writing disclosure

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Ethical conduct of research

This study was performed in accordance with ethical principles consistent with the Declaration of Helsinki and Good Pharmacoepidemiology Practice. Institutional review board (IRB) exemption was sought from Advarra IRB and received 28 November 2023. Advarra IRB is registered with the Office for Human Research Protections (OHRP) and FDA under IRB#00000971. Data were de-identified and compliant with Health Insurance Portability and Accountability Act regulations thus meeting determination for exemption.

Data sharing statement

The datasets generated and/or analyzed during the current study are not publicly available as they were used under license from Inovalon®.

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