P.185 Presented at the 2023 MDA Clinical and Scientific Conference; March 19–22, 2023; Dallas, TX, and Virtual

# Interim Analysis of EVOLVE: A Long-term Observational Study Evaluating Eteplirsen, Golodirsen, or Casimersen in Routine Clinical Practice

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## Objective

To describe the usage, safety, and clinical outcomes of long-term use of eteplirsen, golodirsen, or casimersen in patients with Duchenne muscular dystrophy (DMD) in routine clinical practice

## Key Findings

**Real-world data from an interim analysis of EVOLVE support the safety and will continue to describe long-term clinical outcomes of eteplirsen, golodirsen, and casimersen**

## CONCLUSIONS

- Consistent with previous clinical studies, eteplirsen, golodirsen, and casimersen were well tolerated in patients with DMD in routine clinical practice to date
- Median age at LOA for eteplirsen-treated patients was consistent with prior clinical trial post hoc results
- These real-world data from the interim analysis of EVOLVE, the first and largest registry of patients treated with PMOs to date, support the safety profiles and will continue to describe long-term clinical outcomes of eteplirsen, golodirsen, and casimersen

## STUDY DESIGN

**EVOLVE: A phase 4, multicenter, prospective, observational study to collect available data on patients with DMD receiving eteplirsen, golodirsen, or casimersen in routine clinical practice**

### Patient population

- Receiving or initiating treatment with eteplirsen, golodirsen, or casimersen at time of study enrollment as prescribed by treating physicians as part of standard of care
- Enrollment of eteplirsen-treated patients began in 2019; following FDA approval of golodirsen and casimersen, protocol was amended to expand eligibility criteria

### Outcomes of interest

- Safety, functional assessments (loss of ambulation [LOA])

## RESULTS

- As of December 2021,[a] 144 patients have enrolled, with most patients receiving eteplirsen
- Across the 3 phosphorodiamidate morpholino oligomers (PMOs), patient age at treatment initiation ranged from 1 to 33 years old
- The mean total duration of PMO treatment received was equal to 4.7 years for eteplirsen-treated, 1.3 years for golodirsen-treated, and 0.3 years for casimersen-treated patients

[a]Data are not final until study completion and database lock occur.

### Baseline Patient Characteristics

| Parameter | Eteplirsen (N=123) | Golodirsen (N=17) | Casimersen (N=4) |
|---|---|---|---|
| **Age at PMO initiation, years, mean (SD)** | 10.3 (5.18) | 12.9 (4.15) | 16.3 (11.67) |
| **Range** | 1–24 | 6–19 | 6–33 |
| **Age at study enrollment, years, mean (SD)** | 13.7 (5.50) | 13.5 (4.27) | 16.3 (11.67) |
| **Range** | 1–28 | 7–20 | 6–33 |
| **Race, n (%)** | | | |
| White | 93 (75.6) | 14 (82.4) | 4 (100) |
| Other | 30 (24.4) | 3 (17.6) | |
| **Ethnicity, n (%)** | | | |
| Hispanic or Latino | 27 (22.0) | 4 (23.5) | 0 |
| Not Hispanic or Latino | 83 (67.5) | 11 (64.7) | 4 (100) |
| Not reported/unknown | 13 (10.6) | 2 (11.8) | 0 |
| **BMI, kg/m², mean (SD)** | 24.3 (8.4)[a] | 23.2 (5.6)[b] | 22.8 (12.6)[c] |
| **Nonambulatory, n (%)** | | | |
| At PMO initiation | 38[d] (30.9) | 10 (58.8) | 2 (50) |
| At last available visit | 69[d] (56.1) | 10 (58.8) | 2 (50) |
| **PMO treatment, years (SD)** | | | |
| Total duration | 4.7 (1.88) | 1.3 (0.45) | 0.3 (0.22) |
| At study enrollment | 3.4 (1.90) | 0.6 (0.57) | 0.2 (0.17) |
| **Corticosteroid use, n (%)** | | | |
| Prior to PMO initiation | 71 (57.7) | 14 (82.4) | 2 (50.0) |
| At or after PMO initiation | 109 (88.6) | 15 (88.2) | 3 (75.0) |
| In the past 12 mo prior to study enrollment | 108 (87.8) | 15 (88.2) | 2 (50.0) |

[a]N=85. [b]N=12. [c]N=2. [d]3 additional patients were described as nonambulatory at PMO initiation but were excluded from these counts as their LOA dates were not available at the time of this interim data cut. BMI=body mass index; PMO=phosphorodiamidate morpholino oligomer.

**Favorable safety profiles were observed for eteplirsen, golodirsen, and casimersen to date (as of December 2021)**

- Safety data were collected starting from study enrollment
- 21/123 (17.1%) of eteplirsen-treated and 1/17 (5.9%) of golodirsen-treated patients experienced a treatment-emergent adverse event (TEAE) of special interest; no patients receiving casimersen have reported any TEAEs of special interest to date
- The percentage of patients experiencing treatment-emergent serious adverse events (TESAEs) decreased over time for patients receiving eteplirsen; no TESAEs were reported for golodirsen or casimersen
- None of the TESAEs were considered related to treatment
- Most common TEAE of special interest was infusion-related reaction (IRR), occurring in 11/123 (8.9%) of eteplirsen-treated patients and 1/17 (5.9%) of golodirsen-treated patients
- 4 TEAEs of special interest reported were considered related to treatment (3 catheter issues, 1 proteinuria); none resulted in treatment interruption or discontinuation; none were considered serious events

### Summary of TESAEs

| | Eteplirsen (N=123) |
|---|---|
| **Any TESAE, n/total (%)** | |
| Year 1 | 10/123 (8.1) |
| Year 2 | 4/71 (5.6) |
| Year 3 | 1/28 (3.6) |
| **TESAEs by system organ class, n (%)** | |
| Blood/lymphatic disorders | 1 (0.8) |
| Cardiac disorders | 1 (0.8) |
| Gastrointestinal disorders | 2 (1.6) |
| General disorders | 1 (0.8) |
| Infections | 5 (4.1) |
| Injury/poisoning | 2 (1.6) |
| Musculoskeletal disorders | 1 (0.8) |
| Psychiatric disorders | 1 (0.8) |
| Respiratory disorders | 2 (1.6) |
| Uncoded[a] | 1 (0.8) |
| Vascular disorders | 1 (0.8) |

[a]Preferred term=acute myocarditis. TESAE=treatment-emergent serious adverse event.

### Summary of TEAEs of Special Interest

| TEAEs of Special Interest, by System Organ Class (preferred term) n (%) | Eteplirsen (N=123) |
|---|---|
| **Catheter issues** | 10 (8.1) |
| **Hepatotoxicity (hepatic steatosis)** | 1 (0.8) |
| **Hypersensitivity** | 8 (6.5) |
| **IRR[a]** | 11 (8.9) |
| **Nephrotoxicity (proteinuria)** | 1 (0.8) |
| **Rhabdomyolysis** | 2 (1.6) |
| **Serious blood stream infections[b] (pneumonia)** | 1 (0.8) |

[a]IRRs were defined as events reported with a start during or within 24 hours after an infusion that were medically reviewed by a pharmacovigilance specialist and physician to determine if they met the criteria for IRR. [b]Serious bloodstream infection was suspected but later not confirmed from blood culture leading to final designation of aspiration pneumonia. IRR=infusion-related reaction; TEAE=treatment-emergent adverse event.

**Median age at LOA for eteplirsen-treated patients was 15.32 years, consistent with prior clinical trial post hoc results[1,2]**

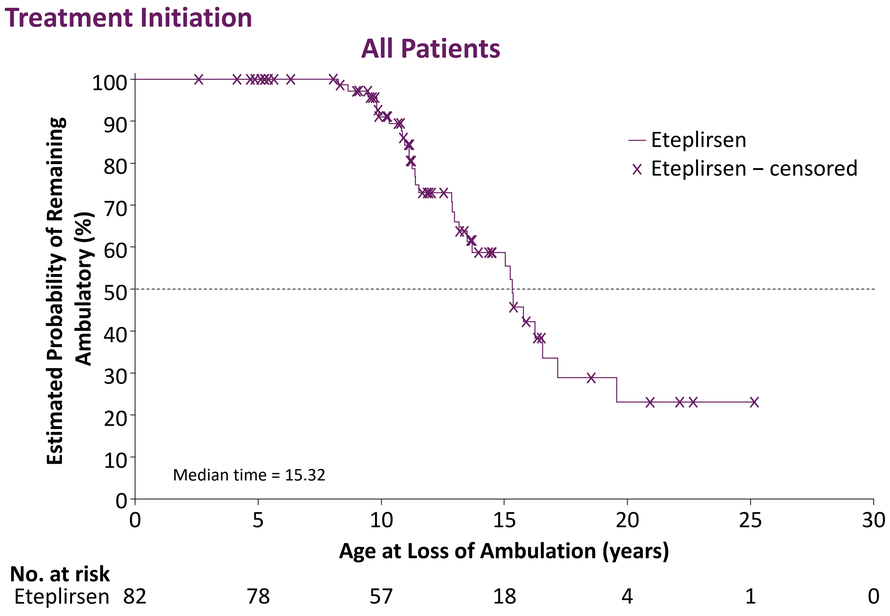
- Of the ambulatory patients at PMO initiation, 31/82 eteplirsen-treated, 0/7 golodirsen-treated, and 0/2 casimersen-treated patients have since lost ambulation
  - Sample size to date precludes analysis of age at LOA for golodirsen- or casimersen-treated patients
- Shorter follow-up of eteplirsen-treated patients aged <7 years and small sample size may preclude accurate analysis of age at LOA in this age group

### Summary of Eteplirsen Use by Age Group of Ambulatory Patients at PMO Treatment Initiation

| Age Group, years[a] | Time From Confirmed Diagnosis of DMD to PMO Initiation, years | Duration of PMO Treatment at Study Enrollment, years | Total Duration of PMO Treatment, years | Received Eteplirsen in Clinical Trial? |
|---|---|---|---|---|
| <7 (N=30) | 1.7 (1.69) | 2.6 (1.46) | 4.0 (1.76) | Yes: 7 (23.3%) No: 23 (76.7%) |
| 7 to <13 (N=43) | 4.2 (2.63) | 4.4 (2.27)[b] | 5.6 (2.22) | Yes: 26 (59.1%) No: 18 (40.9%) |
| 13 to <18 (N=6) | 10.6 (3.43) | 3.1 (0.97) | 4.7 (0.91) | Yes: 2 (33.3%) No: 4 (66.7%) |
| ≥18 (N=2) | 13.9 (7.16) | 4.1 (0.002) | 4.9 (0.002) | Yes: 0 (0) No: 2 (100%) |

Values are mean (SD) unless otherwise specified. [a]Age at study enrollment. [b]N=44. DMD=Duchenne muscular dystrophy; PMO=phosphorodiamidate morpholino oligomer.

### Age at LOA in Eteplirsen-Treated Patients Ambulatory at PMO Treatment Initiation

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**ACKNOWLEDGMENTS & DISCLOSURES**

The authors would like to thank the following for their previous contributions in initiating the EVOLVE Study 403: Daisy Dai, Ashish Dugar, Zohal Ghiaszada, Alaina Keane, Olga Mitelman, Elizabeth Smyth, Katherine Tsai. **Funding:** This study was funded by Sarepta Therapeutics, Inc. Editorial support was provided by Meghan Jones, PhD, of Eloquent Scientific Solutions and was funded by Sarepta Therapeutics, Inc. **Disclosures: KR-M, SS, SH, IS, DM:** Employees of Sarepta Therapeutics, Inc. **BB:** Has nothing to disclose. **AK**: Received research support from AveXis/Novartis, FibroGen, MDA, NIH, NINDS – U01 NS061799-01A2, PPMD, PTC Therapeutics, Sarepta Therapeutics, Inc., served as consultant/advisory board member for Audentes, AveXis/Novartis, Biogen, PTC Therapeutics, Roche, and Sarepta Therapeutics, Inc., and served on the speakers' bureau for PTC Therapeutics. **KM**: Received research support as site Principal Investigator from Catabasis, Italfarmaco, Reata, Retrotope, Santhera Pharmaceuticals, and Sarepta Therapeutics, Inc., and received research support from CDC (U01 DD001248), FARA, and NIH (5 U54 NS053672, U24 NS-10718). **LMR-P:** Served on advisory boards for Mallinckrodt, NS Pharma, PTC Therapeutics, Santhera Pharmaceuticals, and Sarepta Therapeutics, Inc., and received research support as Principal Investigator from Capricor, Catabasis, FibroGen, PTC Therapeutics, Santhera Pharmaceuticals, and Sarepta Therapeutics, Inc. **MAW:** Received research funding as site or study Principal Investigator from Alcyone Therapeutics, Inc., Novartis Gene Therapies, and Sarepta Therapeutics, Inc., and serves as a consultant for Sarepta Therapeutics, Inc. **CZ:** Received research support from and serves on advisory boards for Biogen and serves as consultant for Optum. **CM:** Serves as consultant for Astellas/Mitobridge, Bristol-Myers Squibb, Capricor, Catabasis Pharmaceuticals, Edgewise Therapeutics, Eli Lilly, Epirium Bio (formerly Cardero Therapeutics), Gilead, Halo Therapeutics, Italfarmaco, Novartis, Pfizer, Prosensa, PTC Therapeutics, Santhera Pharmaceuticals, and Sarepta Therapeutics, Inc., and receives research funding and speaking fees from Sarepta Therapeutics, Inc. Previously presented at the 27th International Hybrid Annual Congress of the World Muscle Society; October 11–15, 2022; Halifax, Nova Scotia, Canada.

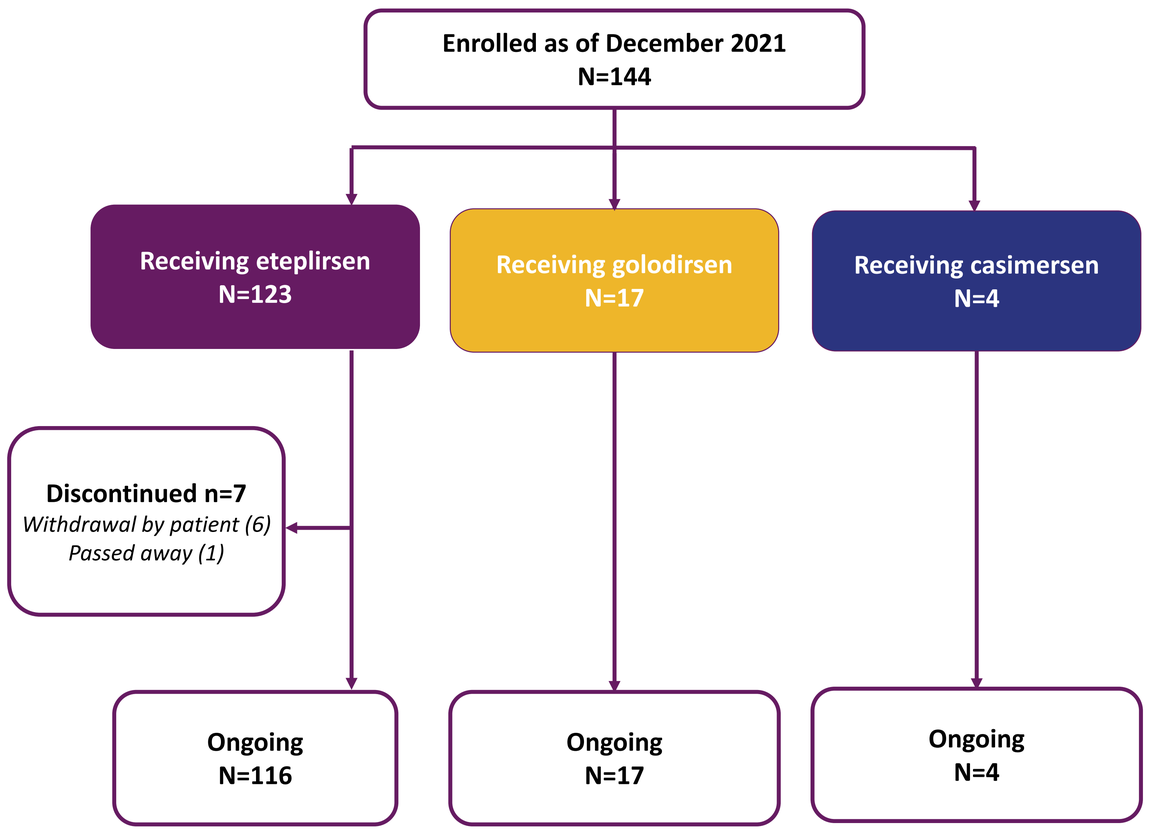
## BACKGROUND

- DMD is a fatal, X-linked neuromuscular disease caused by mutations in the dystrophin gene[3,4]
  - LOA in patients with DMD occurs at approximately 12 years[5-7]
- Eteplirsen, golodirsen, and casimersen are PMOs approved for the treatment of patients with DMD with mutations amenable to 51, 53, and 45 exon skipping, respectively
- Clinical studies have shown that eteplirsen is associated with significant and clinically meaningful delays in time to LOA,[2,4,8] whereas a post hoc analysis in golodirsen-treated patients suggests attenuation of ambulatory function loss compared with mutation-matched external controls[9]
- Accumulation of PMO experience and recent approvals have led to the availability and access of real-world data sources that allow assessment of long-term safety, tolerability, and/or effectiveness of PMOs for DMD

## PATIENT DETAILS

### Patient disposition

- Of the 144 patients initially enrolled, 137 are continuing participants in the study
  - 7 patients receiving eteplirsen discontinued due to patient withdrawals (n=6) or death (n=1)




### Summary of Treatment Use by Age Group

| Parameter | Eteplirsen (N=123) | Golodirsen (N=17) | Casimersen (N=4) |
|---|---|---|---|
| **Time from confirmed diagnosis of DMD to start of PMO treatment, years** | | | |
| Overall | (N=122)<br>6.0 (4.74) | (N=17)<br>8.2 (3.76) | (N=3)<br>13.5 (14.04) |
| <7 years | (n=30)<br>1.7 (1.69) | (n=1)<br>1.9 | (n=1)<br>1.1 |
| 7 to <13 years | (n=53)<br>4.6 (2.72) | (n=6)<br>5.9 (2.99) | (n=0)<br>NA |
| 13 to <18 years | (n=26)<br>10.2 (2.72) | (n=7)<br>9.1 (2.56) | (n=1)<br>10.6 |
| ≥18 years | (n=13)<br>13.2 (4.73) | (n=3)<br>12.8 (0.70) | (n=1)<br>28.8 |
| **Total duration of PMO treatment at study enrollment, years** | | | |
| Overall | (N=123)<br>3.4 (1.90) | (N=17)<br>0.6 (0.57) | (N=4)<br>0.2 (0.17) |
| <7 years | (n=30)<br>2.6 (1.46) | (n=1)<br>0.6 | (n=1)<br>0.5 |
| 7 to <13 years | (n=54)<br>4.2 (2.27) | (n=6)<br>0.5 (0.66) | (n=1)<br>0.2 |
| 13 to <18 years | (n=26)<br>2.8 (0.98) | (n=7)<br>0.8 (0.65) | (n=1)<br>0.2 |
| ≥18 years | (n=13)<br>2.9 (1.19) | (n=3)<br>0.4 (0.29) | (n=1)<br>0.04 |
| **Total duration of PMO treatment, years** | | | |
| Overall | (N=123)<br>4.7 (1.88) | (N=17)<br>1.3 (0.45) | (N=4)<br>0.3 (0.22) |
| <7 years | (n=30)<br>4.0 (1.76) | (n=1)<br>0.7 | (n=1)<br>0.7 |
| 7 to <13 years | (n=54)<br>5.4 (2.16) | (n=6)<br>1.3 (0.43) | (n=1)<br>0.2 |
| 13 to <18 years | (n=26)<br>4.3 (0.82) | (n=7)<br>1.6 (0.31) | (n=1)<br>0.3 |
| ≥18 years | (n=13)<br>4.1 (1.41) | (n=3)<br>0.8 (0.33) | (n=1)<br>0.2 |

Values are mean (SD) unless otherwise specified. DMD=Duchenne muscular dystrophy; NA=not available; PMO=phosphorodiamidate morpholino oligomer.

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