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

Kristen Ricchetti-Masterson,[1] Sourav Santra,[1] Shane Hornibrook,[1] Barry Byrne,[2] Ashutosh Kumar,[3] Katherine Mathews,[4] Leigh Maria Ramos-Platt,[5] Megan A. Waldrop,[6] Craig Zaidman,[7] Ihor Sehinovych,[1] David Miller,[1] Craig McDonald,[8] on behalf of the Study 403 EVOLVE investigators

[1]Sarepta Therapeutics, Inc., Cambridge, MA; [2]University of Florida, Gainesville, FL; [3]Penn State Health Milton S. Hershey Medical Center, Hershey, PA; [4]The University of Iowa, Iowa City, IA; [5]Children's Hospital Los Angeles and Keck School of Medicine, University of Southern California, Los Angeles, CA; [6]Center for Gene Therapy, Nationwide Children's Hospital and Ohio State University Wexner Medical Center, Columbus, OH; [7]Washington University School of Medicine, St Louis, MO; [8]University of California, Davis, Sacramento, CA

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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 PMO 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 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 (30.9)	10 (58.8)	2 (50)
At last available visit	69 (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.

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 any reported TEAEs of special interest to date
- 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
- The percentage of patients experiencing treatment-emergent serious AEs (TESAEs) decreased over time for patients receiving eteplirsen; no TESAEs were reported for golodirsen or casimersen

Summary of TEAEs of Special Interest

TEAEs of Special Interest, n (%)	Eteplirsen (N=123)
Catheter issues	10 (8.1)
Hepatotoxicity	1 (0.8)
Hypersensitivity	8 (6.5)
IRR[a]	11 (8.9)
Nephrotoxicity	1 (0.8)
Rhabdomyolysis	2 (1.6)
Serious blood stream infections	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. IRR=infusion-related reaction; TEAE=treatment-emergent adverse event.

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.

Median age at loss of ambulation 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

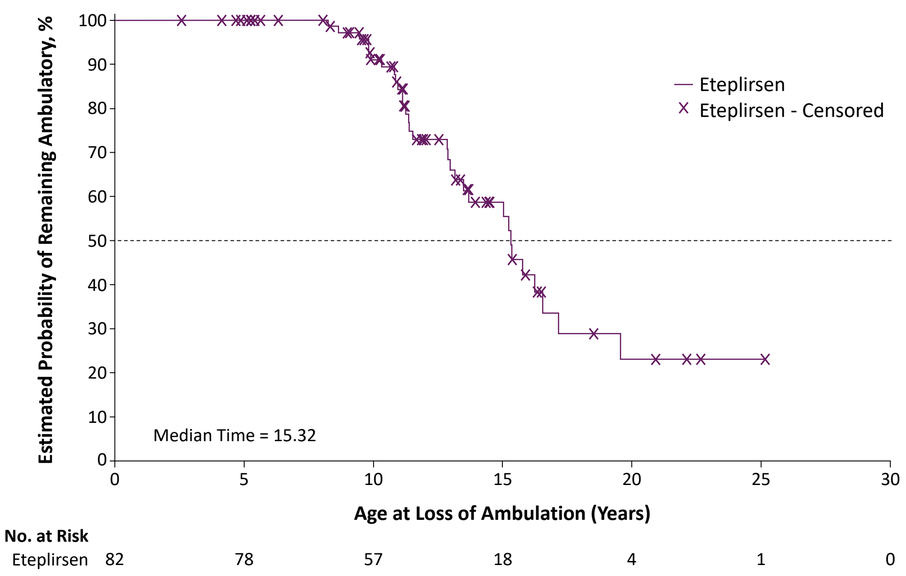
Summary of Eteplirsen Use by Age Group of Ambulatory Patients at PMO Treatment Initiation

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%)

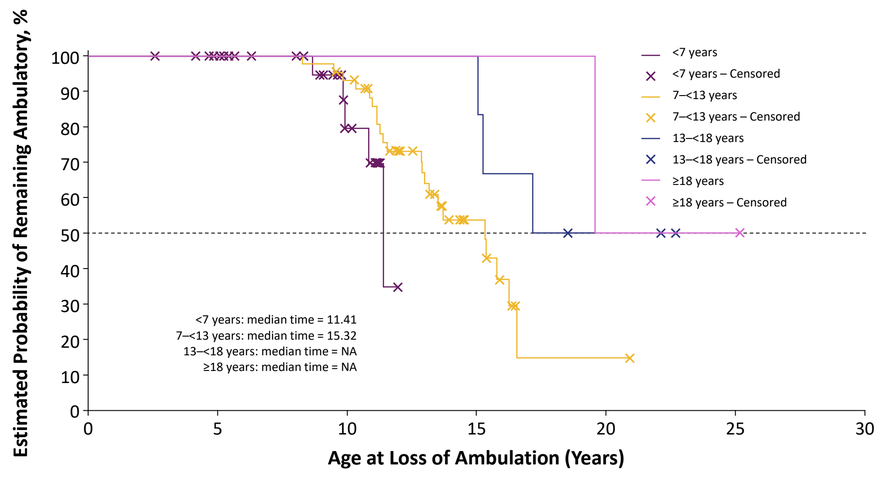
Values are mean (SD) unless otherwise specified. [a]Age at study enrollment; [b]N=44.

Age at Loss of Ambulation in Eteplirsen-treated Patients Ambulatory at PMO Treatment Initiation

All Patients



By Age Group



REFERENCES

1. Mitelman O, et al. *J Neuromuscul Dis*. 2022;9:39-52. **2.** Iff J, et al. MDA 2022, P128. 3. McDonald C, et al. *Lancet*. 2018;391:451-61. **4.** Mendell JR, et al. *Ann Neurol*. 2016;79(2):257-71. **5.** Mendell JR, et al. *J Neuromuscular Dis*. 2021;8:469-79. **6.** Servais LS, et al. *Nucleic Acid Ther.* 2022;32(1):29-39.

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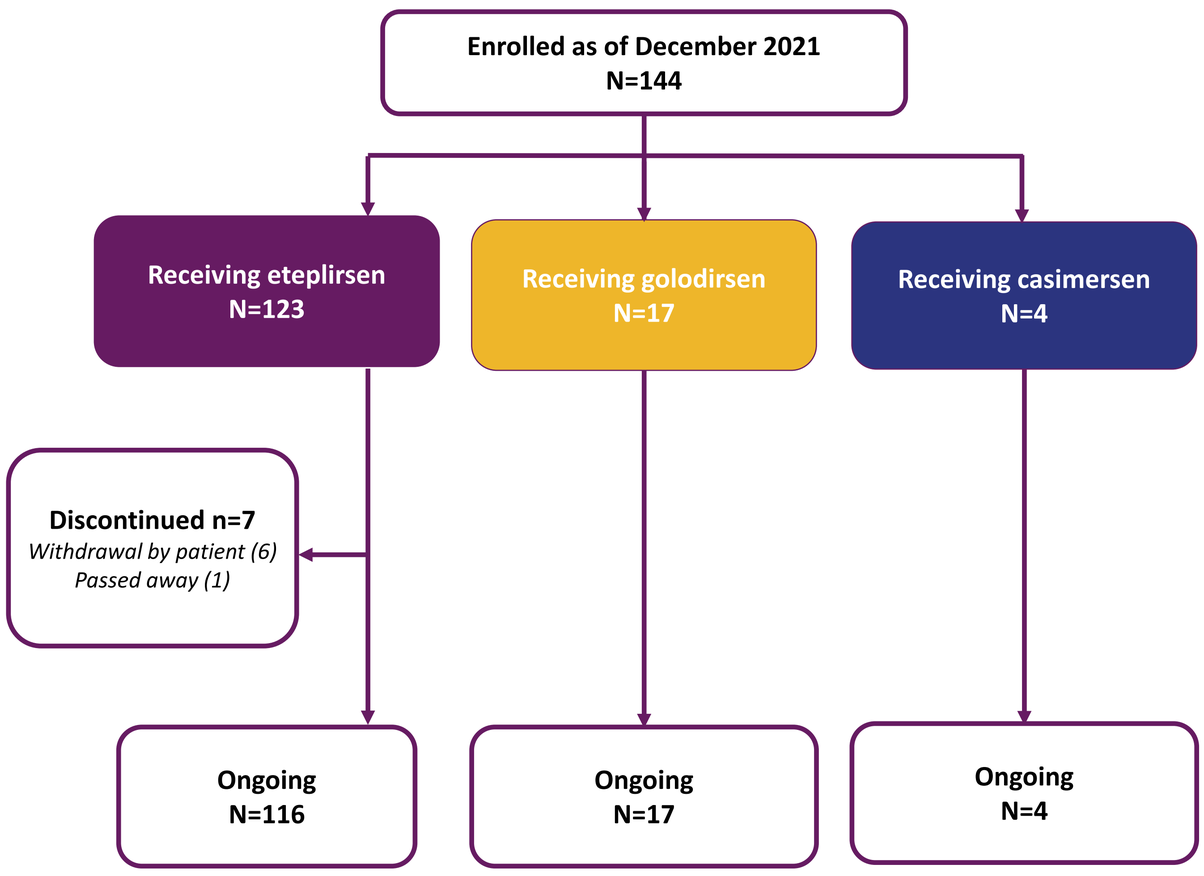
BACKGROUND

- Duchenne muscular dystrophy (DMD) is a fatal, X-linked neuromuscular disease caused by mutations in the dystrophin gene[3,4]
- Eteplirsen, golodirsen, and casimersen are phosphorodiamidate morpholino oligomers (PMOs) approved for the treatment of DMD in patients 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 loss of ambulation,[2,4,5] whereas a post hoc analysis in golodirsen-treated patients suggests attenuation of ambulatory function loss compared with mutation-matched external controls[6]
- 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	(N=122)	(N=17)	(N=3)
Overall	6.0 (4.74)	8.2 (3.76)	13.5 (14.04)
	(n=30)	(n=1)	(n=1)
<7 years	1.7 (1.69)	1.9	1.1
	(n=53)	(n=6)	(n=0)
7 to <13 years	4.6 (2.72)	5.9 (2.99)	NA
	(n=26)	(n=7)	(n=1)
13 to <18 years	10.2 (2.72)	9.1 (2.56)	10.6
	(n=13)	(n=3)	(n=1)
≥18 years	13.2 (4.73)	12.8 (0.70)	28.8
Total duration of PMO treatment at study enrollment, years	(N=123)	(N=17)	(N=4)
Overall	3.4 (1.90)	0.6 (0.57)	0.2 (0.17)
	(n=30)	(n=1)	(n=1)
<7 years	2.6 (1.46)	0.6	0.5
	(n=54)	(n=6)	(n=1)
7 to <13 years	4.2 (2.27)	0.5 (0.66)	0.2
	(n=26)	(n=7)	(n=1)
13 to <18 years	2.8 (0.98)	0.8 (0.65)	0.2
	(n=13)	(n=3)	(n=1)
≥18 years	2.9 (1.19)	0.4 (0.29)	0.04
Total duration of PMO treatment, years	(N=123)	(N=17)	(N=4)
Overall	4.7 (1.88)	1.3 (0.45)	0.3 (0.22)
	(n=30)	(n=1)	(n=1)
<7 years	4.0 (1.76)	0.7	0.7
	(n=54)	(n=6)	(n=1)
7 to <13 years	5.4 (2.16)	1.3 (0.43)	0.2
	(n=26)	(n=7)	(n=1)
13 to <18 years	4.3 (0.82)	1.6 (0.31)	0.3
	(n=13)	(n=3)	(n=1)
≥18 years	4.1 (1.41)	0.8 (0.33)	0.2

Values are mean (SD) unless otherwise specified.

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