P.211 Presented at the 2023 MDA Clinical and Scientific Conference; March 19–22, 2023; Dallas, TX, and Virtual

Interim Analysis of EVOLVE: Evaluating Eteplirsen, Golodirsen, or Casimersen Treatment in Patients <7 Years Old in Routine Clinical Practice

Shannon Grabich,[1] Sourav Santra,[1] Megan A. Waldrop,[2] Katherine Mathews,[3] Farida Abid,[4] Leigh Maria Ramos-Platt,[5] Rebecca Scharf,[6] Craig Zaidman,[7] Ihor Sehinovych,[1] Craig McDonald,[8] on behalf of the Study 403 EVOLVE investigators

[1]Sarepta Therapeutics, Inc., Cambridge, MA; [2]Center for Gene Therapy, Nationwide Children's Hospital and Ohio State University Wexner Medical Center, Columbus, OH; [3]The University of Iowa, Iowa City, IA; [4]Texas Children's Hospital, Houston, TX; [5]Children's Hospital Los Angeles and Keck School of Medicine University of Southern California, Los Angeles, CA; [6]UVA Children's Hospital, Charlottesville, VA; [7]Washington University School of Medicine, St Louis, MO; [8]University of California, Davis, Sacramento, CA

Please scan QR code for full study details

Objective

To describe the treatment patterns, safety, and functional assessments of eteplirsen, golodirsen, or casimersen in patients with DMD <7 years old in routine clinical practice

Key Findings

Real-world data from an interim analysis of EVOLVE support the safety of PMOs in patients <7 years old to date

BACKGROUND

- Current clinical recommendations for Duchenne muscular dystrophy (DMD) emphasize the importance of early diagnosis and treatment[1-3]
- Eteplirsen, golodirsen, and casimersen are phosphorodiamidate morpholino oligomers (PMOs) that are FDA-approved for the treatment of DMD in patients who are amenable to exon 51, 53, and 45 skipping, respectively
- Previous studies in boys >4 years old indicated eteplirsen is well tolerated and attenuates pulmonary and ambulatory decline compared with matched natural history cohorts[4-8]
- Study 4658-102 (NCT03218995) demonstrated the safety and tolerability of eteplirsen in the youngest population of patients with DMD (6 to 48 months) in a clinical trial setting[9]
- EVOLVE is an ongoing, phase 4, multicenter, prospective, observational study to collect available data on patients with DMD receiving PMOs in routine clinical practice
- This interim analysis of the EVOLVE study evaluated the use of PMO therapies in patients with DMD <7 years old

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; protocol was amended to expand eligibility criteria following FDA approval of golodirsen and casimersen
- In this analysis, patients were stratified by age at PMO treatment initiation: <24, 24 to <48, and 48 to <84 months

Outcomes

- Treatment patterns, safety, functional assessments (loss of ambulation [LOA])

CONCLUSIONS

- Real-world studies in rare diseases such as DMD are key as they follow patients longitudinally post clinical trials, capturing valuable data on the patient journey and disease progression; notwithstanding, they are also prone to confounding factors, bias, and data missingness
- These interim results from the first real-world PMO registry indicate that eteplirsen was well tolerated in young patients (<7 years) with DMD in routine clinical practice; insufficient number of golodirsen- and casimersen-treated patients enrolled so far for analysis
- Safety experience was consistent with the known safety profile of eteplirsen; there were no treatment-related discontinuations or treatment interruptions in patients <7 years old
  - 3 SAEs were reported, none of which were determined to be related to treatment
- Previous analyses have shown that eteplirsen is associated with significant and clinically meaningful delays in time to LOA; shorter follow-up and small sample size limit interpretation of age at LOA in this younger age cohort
- The safety and clinical outcomes of eteplirsen, golodirsen, and casimersen will continue to be evaluated in this ongoing study

RESULTS

- As of December 2021,[a] 144 patients have enrolled in EVOLVE, with most patients (N=123) receiving eteplirsen[10]
- Of the enrolled patients <7 years old, 30/32 (93.8%) are receiving eteplirsen, 1 (3.1%) is receiving golodirsen, and 1 (3.1%) is receiving casimersen; all 32 patients were ambulatory at PMO initiation
- To date, patients <7 years old received eteplirsen treatment for an average of 2.5 years in the youngest age group (<24 months) to 4.6 years in the oldest age group (48 to <84 months)
- Steroid usage before eteplirsen initiation was 0/3 (0%), 1/7 (14.3%), and 12/20 (60.0%) for the <24-, 24- to <48-, and 48- to <84-month-old groups receiving eteplirsen, respectively

Patient Characteristics

Parameter[a]	<24 months (N=3)	24 to <48 months (N=7)	48 to <84 months (N=22)		
	Eteplirsen (N=3)	Eteplirsen (N=7)	Eteplirsen (N=20)	Golodirsen (N=1)	Casimersen (N=1)
Age at PMO initiation, years	1.8 (0.05)	3.3 (0.42)	5.7 (0.74)	6.4	6.2
Age at study enrollment, years	2.7 (1.53)	4.3 (1.11)	8.5 (1.64)	7.0	6.0
Time from DMD diagnosis to PMO initiation, years	0.3 (0.07)	1.1 (1.27)	2.2 (1.78)	1.9	1.1
PMO treatment, years					
Total duration	2.5 (1.45)	2.8 (1.66)	4.6 (1.54)	0.7	0.7
At study enrollment	1.7 (1.5)	1.6 (1.06)	3.1 (1.37)	0.6	0.5
Corticosteroid use, n (%)					
Prior to PMO initiation	0	1 (14.3)	12 (60.0)	0	0
At or after PMO initiation	1 (33.3)	4 (57.1)	20 (100)	1 (100)	1 (100)

[a]Data are not final until study completion and database lock occur; values are mean (SD) unless otherwise noted. DMD=Duchenne muscular dystrophy; PMO=phosphorodiamidate morpholino oligomer.

Eteplirsen was well tolerated with no treatment-related discontinuations or treatment interruptions in this young cohort of patients

- 3 serious adverse events (SAEs) occurred in 2/30 (6.7%) eteplirsen-treated patients; all were determined to be unrelated to treatment
- There were no SAEs reported in either golodirsen- or casimersen-treated patients (0/2)

Summary of SAEs

Patient	Age at SAE Onset	SAE	Outcome	Severity	Related to Treatment	Actions Taken
Patient 1	12	Acute myocarditis	Recovered/resolved	Moderate	No	No interruption
Patient 2	6	Catheter-site erythema	Recovered/resolved	Moderate	No	No interruption
		Pyrexia	Recovered/resolved	Moderate	No	No interruption

SAE=serious adverse event.

- Port use was reported in the physician notes or AE listing in at least 20/30 (66.7%) of eteplirsen-treated patients and both (100%) golodirsen- and casimersen-treated patients; patients as young as 1 year old have received a port
- As port use was not a mandatory collected observation, this may be an underestimation of port use in this population
  - 13 patients experienced a total of 16 port-related AEs
  - 3/16 port-related AEs were considered related to PMO treatment (port placement, improper port position, port malfunction); none were serious, and all were mild in severity
  - There were no port-related infections related to treatment

The majority of patients initiating eteplirsen in this young cohort continue to be ambulatory to date
The short follow-up and small size preclude accurate analysis of age at LOA in this age group

- In total, 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[10]
- Of the 31 eteplirsen-treated patients who have lost ambulation, 5 initiated PMO treatment between 48 and 84 months; all other patients initiated eteplirsen >7 years old
  - The age at PMO initiation for those 5 patients was ~1 year later (median, 6.5 years) than those who remain ambulatory (median, 5.4 years) in the same age group (48 to <84 months)
- All 5 patients remained on PMO treatment after LOA

REFERENCES

1. Mendell JR, et al. *Ann Neurol*. 2012;71:304-13. **2.** Aartsma-Rus A, et al. *J Pediatr*. 2019;204:305-13. **3.** Birnkrant DJ, et al. *Lancet Neurol*. 2018;17:251-67. **4.** Mendell JR, et al. *J Neuromusc Dis*. 2021;8(4):469-479. **5.** McDonald CM, et al. *J Neuromusc Dis.* 2021; **6.** Mendell JR, et al. *Ann Neurol*. 2016;79:257-71. **7.** Mendell JR, et al. *Ann Neurol.* 2013;74:637-47. **8.** clinicaltrials.gov. NCT02420379. **9.** Muntoni F, et al. Poster presentation at MDA 2022. **10.** Ricchetti-Masterson, et al. Poster presentation at WMS 2022.

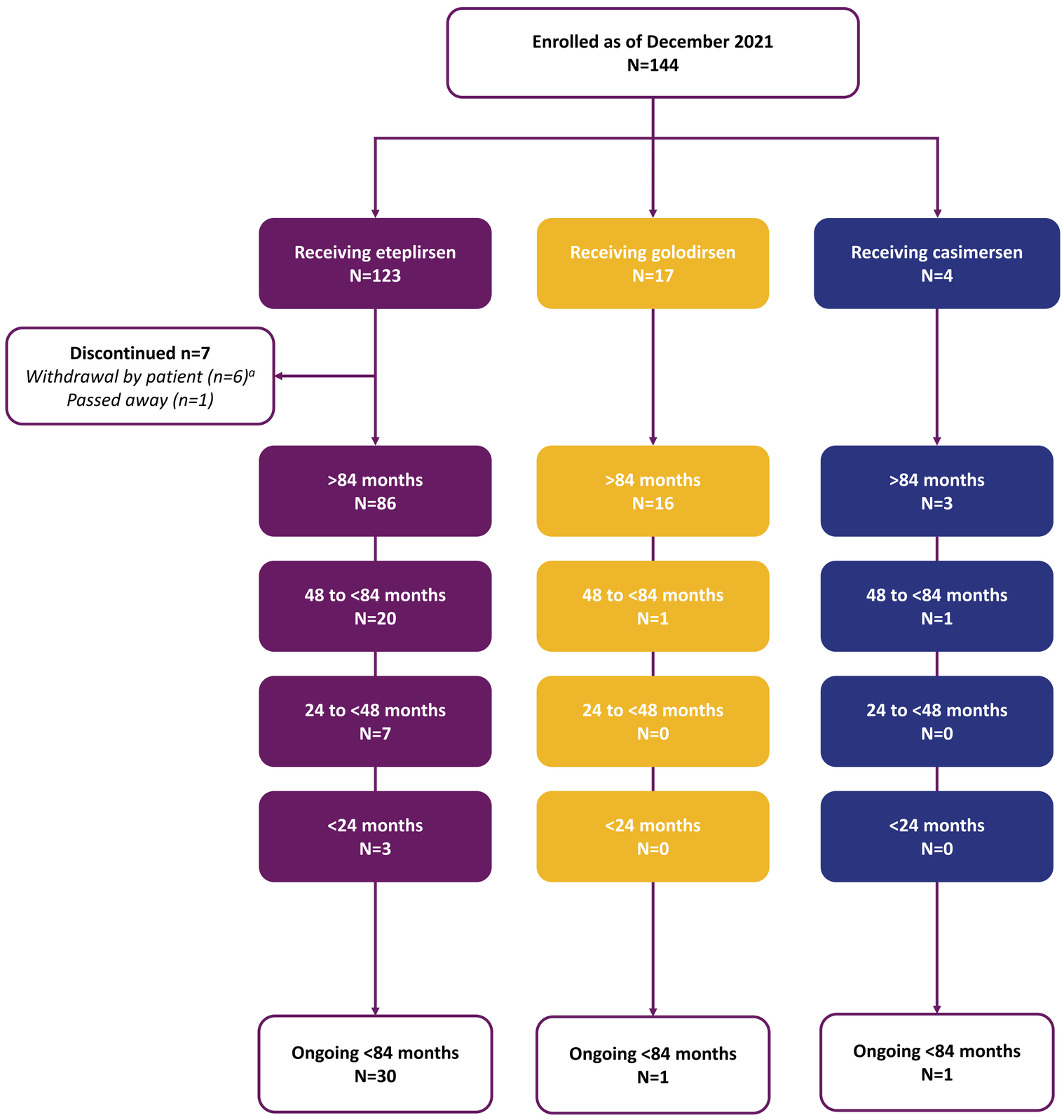
ACKNOWLEDGMENTS & DISCLOSURES

The authors would like to thank the following for their previous contributions in initiating the EVOLVE 403 Study: 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 Paraskevi Briassouli, PhD, of Eloquent Scientific Solutions and was funded by Sarepta Therapeutics, Inc. **Disclosures: SG, SS, IS:** Employees of Sarepta Therapeutics, Inc. **MAW:** Received research funding as site or study Principal Investigator from Sarepta Therapeutics, Inc., Novartis Gene Therapies, and Alcyone Therapeutics, Inc., and serves as consultant for Sarepta Therapeutics, Inc. **KM:** Received research support as site Principal Investigator from Sarepta Therapeutics, Inc., Italfarmaco, Retrotope, Reata, Catabasis, and Santhera, and received research support from NIH (5 U54 NS053672, U24 NS-10718), CDC (U01 DD001248), and FARA. **FA:** Served on advisory boards for NS Pharma, PTC Therapeutics, Santhera Pharmaceuticals, Mallinckrodt, and Sarepta Therapeutics, Inc. **LMR-P:** Served on advisory boards for NS Pharma, PTC Therapeutics, Santhera Pharmaceuticals, Mallinkrodt, and Sarepta Therapeutics, Inc., and received research support as Principal Investigator from Capricor, PTC Therapeutics, Catabasis, Fibrogen, Santhera Pharmaceuticals, and Sarepta Therapeutics, Inc. **RS:** Received research funding from Genentech, Sarepta Therapeutics, Inc., Novartis, Fibrogen, Capricor, argenx BVBA, and Biohaven. **CZ:** Received research support from Biogen and Novartis, served on advisory boards for Biogen, Optum, and Sarepta Therapeutics, Inc. **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.

PATIENT DETAILS

Patient disposition

- Of the 144 patients initially enrolled, 32 patients were <84 months old at PMO initiation
  - 1 patient from the 48- to <84-month-old group receiving eteplirsen discontinued due to patient withdrawal (N=1)



[a]One patient from the 48- to <84-month-old group receiving eteplirsen discontinued due to patient withdrawal.

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