M180

Interim Analysis of EVOLVE: Evaluating Eteplirsen Treatment in Nonambulatory Patients in Routine Clinical Practice From a Phase 4 Observational Study

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Objective

To describe treatment patterns, safety, and functional assessments in nonambulatory participants with Duchene muscular dystrophy (DMD) receiving long-term eteplirsen treatment in routine clinical practice

Methods

EVOLVE: A phase 4, multicenter, prospective, observational study to collect available data on participants with DMD receiving phosphorodiamidate morpholino oligomers (PMOs) in routine clinical practice

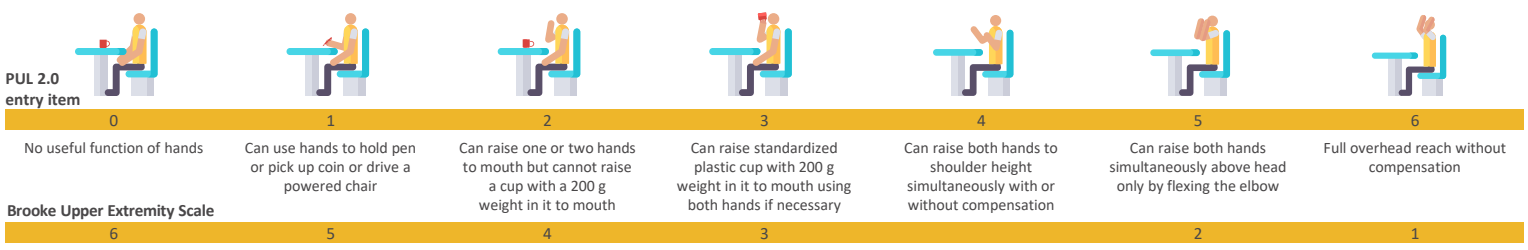
Study analysis

- Data from this interim analysis are presented for the eteplirsen-treated participants who either were nonambulatory at eteplirsen treatment initiation or became nonambulatory after treatment initiation
- In EVOLVE, nonambulatory was defined as continuous wheelchair use, approximated to the nearest month, verified by an attending physician

Outcomes of interest

- Safety and treatment patterns
- Loss of ambulation (LOA)
- Brooke Upper Extremity Scale (Brooke) and Performance of Upper Limb (PUL) Module for DMD 2.0 (PUL 2.0) Entry Item A (**F1**)

F1 *PUL 2.0 Entry Items and Brooke Upper Extremity Scale[1,2]*



Results

- As of December 2021, 123 participants enrolled and received eteplirsen as part of the EVOLVE study (**SF1**)
  - 41 (33%) were nonambulatory at eteplirsen initiation
  - 31 (25%) became nonambulatory after eteplirsen initiation
  - 51 (41%) were ambulatory at eteplirsen initiation and through follow-up
- Of the 82 participants who were ambulatory at treatment initiation, the median age at loss of ambulation was 15.32[3]
- Participants who were nonambulatory at treatment initiation started treatment ranging from 9.1–24.4 years of age (**T1**)
  - Age range for participants who were ambulatory at eteplirsen initiation and remained ambulatory through follow-up started treatment 1.7–20.3 years of age
  - Age range for participants who became nonambulatory after eteplirsen initiation started treatment 5.5–19.2 years of age
- Seven participants discontinued from the study (withdrawal by participant [n=6], passed away [n=1]; **SF1**)
- Most ambulatory and nonambulatory participants (n=109, 88.6%) were receiving corticosteroids at or after eteplirsen initiation (**T1**)

Summary of eteplirsen use by ambulatory status

- At time of this analysis, the mean duration of treatment was 4.2 years for participants who were ambulatory (N=51) and nonambulatory (N=41) at treatment initiation, and 6.1 years for participants who became nonambulatory after treatment initiation (N=31; **T1**)
- Most participants who either were nonambulatory at treatment initiation or lost ambulation after eteplirsen initiation persisted on eteplirsen treatment (95.8%, N=69/72)*
  - Mean (SD) duration of treatment: 5.0 (1.8) years; mean (SD) duration of follow-up in EVOLVE: 1.1 (0.8) years
  - The 3 participants who had discontinued treatment at the time of this analysis were for reasons unrelated to treatment
- All ambulatory participants (51/51) persisted on treatment through the time of this analysis

*This statement has been revised since the submitted abstract.

Safety in nonambulatory participants

- Safety data were collected starting from EVOLVE study enrollment
- Treatment-emergent serious adverse events (TESAEs) by system organ class are shown in **T2**
- No treatment-related TESAEs were observed in any eteplirsen-treated participants
- The safety profile in nonambulatory participants is consistent with that observed in previous clinical trials[4,5]

Upper extremity data collection in participants receiving eteplirsen

- Across all participants (ambulatory and nonambulatory), Brooke scores were reported more frequently than PUL 2.0 Entry Item A in EVOLVE (72/123 [58%] vs 23/123 [19%], respectively)
- Both outcomes had upper limb data reported in nonambulatory participants (53/72, 73.6%) more frequently than ambulatory participants (28/51, 54.9%)

Upper extremity scores in participants receiving eteplirsen by ambulatory status

- In all nonambulatory participants, 33/72 (46%) had ≥2 Brooke assessments (**T3**)
  - In participants nonambulatory at eteplirsen initiation with ≥2 Brooke assessments (n=18):
    - 13 (72%) maintained or showed improvement (n=1) in function and 4 (22%) had a decline in upper limb entry items over an average follow-up period of 1.1 years (**T4A**)
    - 8 (44%) were unable to raise hand to mouth (Brooke Score of 5) at the start of EVOLVE to last follow-up (**T4A**)
  - In participants nonambulatory after eteplirsen initiation with ≥2 Brooke assessments (n=15):
    - 9 (60%) maintained or showed improvement (n=3) in function and 3 (20%) had a decline in upper limb entry items over an average follow-up period of 1.0 year (**T4B**)
- Brooke upper extremity scores varied not only across different ages, but also within similarly aged participants, highlighting the heterogeneity of the disease (**SF2**)

T1 *Participant Characteristics by Ambulatory Status*

	Ambulatory at Eteplirsen Initiation and Through Follow-up (N=51)	Nonambulatory at Eteplirsen Initiation (N=41)	Nonambulatory After Eteplirsen Initiation (N=31)
Age at eteplirsen initiation, years			
N	51	41	31
Mean (SD)	7.4 (3.9)	15.7 (3.8)	10.0 (2.9)
Range	1.7–20.3	9.1–24.4	5.5–19.2
Age at study enrollment, years			
N	51	41	31
Mean (SD)	10.3 (4.8)	18.4 (4.0)	14.7 (3.5)
Range	1.7–24.4	10.6–28.6	7.2–23.2
Time from confirmed diagnosis of DMD to eteplirsen initiation (years)			
N	50	41	31
mean (SD)[a]	3.4 (3.5)	10.0 (4.0)	4.9 (3.8)
Duration of eteplirsen treatment (years), mean (SD)			
N	51	41	31
Total duration	4.2 (1.9)	4.2 (1.2)	6.1 (1.9)
At study enrollment	3.0 (1.8)	2.8 (1.3)	4.8 (2.0)
Corticosteroid use, n (%)			
In the past 12 months prior to study enrollment	44 (86.3)	34 (82.9)	30 (96.8)
At or after eteplirsen initiation	44 (86.3)	34 (82.9)	31 (100.0)
Age at first documented use of corticosteroid treatment, years			
N	43	35	31
Mean (SD)	7.3 (3.8)	10.4 (4.6)	9.7 (3.7)
Range	3–22	3–23	2–19

[a]Enrollment of participants treated with eteplirsen began in 2019. DMD=Duchenne muscular dystrophy.

T2 *Summary of TESAEs in Nonambulatory Participants*

TESAEs by System Organ Class, n (%)	Total Nonambulatory (N=72)[a]
Infections	4 (5.6)
Gastrointestinal disorders	2 (2.8)
Injury/poisoning	2 (2.8)
Respiratory disorders	2 (2.8)
Blood/lymphatic disorders	1 (1.4)
Cardiac disorders	1 (1.4)

TESAEs by System Organ Class, n (%) (cont)	Total Nonambulatory (N=72)[a]
Musculoskeletal disorders	1 (1.4)
Product issues[b]	1 (1.4)
Psychiatric disorders	1 (1.4)
Uncoded[c]	1 (1.4)
Vascular disorders	1 (1.4)

[a]Includes 41 participants who were nonambulatory at treatment initiation and 31 who became nonambulatory after treatment initiation. All events in this table occurred after loss of ambulation during the EVOLVE study. [b]Malfunctioning venous access port. [c]Preferred term = acute myocarditis. TESAE=treatment-emergent serious adverse event.

T3 *Brooke Assessments in Nonambulatory Participants*

	Nonambulatory at Eteplirsen Initiation (N=41)	Nonambulatory After Eteplirsen Initiation (N=31)	Total Nonambulatory (N=72)
≥1 Brooke assessment, n (%)	21 (51.2)	18 (58.1)	39 (54.2)
≥2 Brooke assessments, n (%)	18 (43.9)	15 (48.4)	33 (45.8)
Time from first to last assessment, years			
N	18	15	33
Mean (SD)	1.3 (0.69)	1.1 (0.69)	1.2 (0.69)

T4A *Shift Table of Brooke Scores in Nonambulatory Participants at Eteplirsen Initiation With ≥2 Data Points*

Nonambulatory **at** Eteplirsen Initiation	Latest Observation Value	First Observation					
		1, n (%)	2, n (%)	3, n (%)	4, n (%)	5, n (%)	6, n (%)
n=18 out of 41 total	1	1 (5.6)	0	0	0	0	0
= Improvement	2	0	2 (11.1)	0	0	0	0
= Maintenance	3	0	0	0	0	0	0
= Decline	4	1 (5.6)	0	1 (5.6)	2 (11.1)	1 (5.6)	0
	5	0	0	1 (5.6)	1 (5.6)	8 (44.4)	0
	6	0	0	0	0	0	0

T4B *Shift Table of Brooke Scores in Nonambulatory Participants After Eteplirsen Initiation With ≥2 Data Points*

Nonambulatory **After** Eteplirsen Initiation	Latest Observation Value	First Observation					
		1, n (%)	2, n (%)	3, n (%)	4, n (%)	5, n (%)	6, n (%)
n=15 out of 31 total	1	2 (13.3)	1 (6.7)	0	0	0	0
= Improvement	2	0	3 (20.0)	0	1 (6.7)	0	0
= Maintenance	3	0	3 (20.0)	2 (13.3)	1 (6.7)	0	0
= Decline	4	0	0	0	1 (6.7)	0	0
	5	0	0	0	0	1 (6.7)	0
	6	0	0	0	0	0	0

Key Findings

Interim real-world data from nonambulatory EVOLVE participants show persistence of therapy and support the safety of eteplirsen

Conclusions

Most (95.8%) participants who were nonambulatory at treatment initiation or lost ambulation after treatment initiation persisted on eteplirsen therapy through the time of this analysis

The safety profile of eteplirsen in nonambulatory participants is consistent with that observed in previous clinical trials; no treatment-related TESAEs were observed in any participants to date

Upper limb function as measured by Brooke score was recorded in 80% of nonambulatory participants treated with eteplirsen, with an average follow-up period of approximately 1.1 years

While the Brooke score has been more frequently used in EVOLVE to date, sites will be capturing upper limb function by the PUL 2.0 entry item moving forward

- Recent guidelines suggest that PUL 2.0 entry items can be reliably used for longitudinal assessment of upper limb function and its progressive impairment in both ambulatory and nonambulatory participants with DMD[6]

These real-world data from a subgroup analysis of EVOLVE, the first and largest phase 4 study of participants treated with PMOs to date, support the safety of eteplirsen and will continue to describe long-term clinical outcomes

Acknowledgments & Disclosures

Acknowledgments: This study was sponsored by Sarepta Therapeutics, Inc. Editorial support was provided by Kimberly Fischer, PhD, of Eloquent Scientific Solutions, and was funded by Sarepta Therapeutics, Inc.

Disclosures: SG, SS, SH, IS are employees of Sarepta Therapeutics, Inc., and may own stock/options in the company. **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. **RS:** Received research funding from Genentech, Sarepta Therapeutics, Inc., Novartis, FibroGen, Capricor, argenx BVBA, and Biohaven. **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.

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Presented at the 2024 MDA Clinical and Scientific Conference; March 3–6, 2024; Orlando FL

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Background

- DMD is a fatal, X-linked neuromuscular disease caused by mutations in the dystrophin gene[7]
  - Irreversible muscle damage caused by DMD leads to a decline in upper limb strength and function[7]
- Eteplirsen is a PMO approved by the US Food and Drug Administration (FDA) used in the treatment of DMD in participants with mutations amenable to exon 51 skipping[8]
- While eteplirsen has been shown to attenuate ambulatory and pulmonary decline compared with mutation-matched natural history controls, accumulation of data in more advanced participant populations allows further understanding of treatment impact[4-6]
- EVOLVE is an ongoing real-world, phase 4, multicenter, observational study involving participants with DMD receiving PMOs in routine clinical practice
- Enrollment of eteplirsen-treated patients began in 2019; following FDA approval of golodirsen and casimersen, protocol was amended to expand eligibility criteria
- The objective of this interim analysis is to describe safety and clinical outcomes, including upper limb function, in eteplirsen-treated nonambulatory participants with DMD

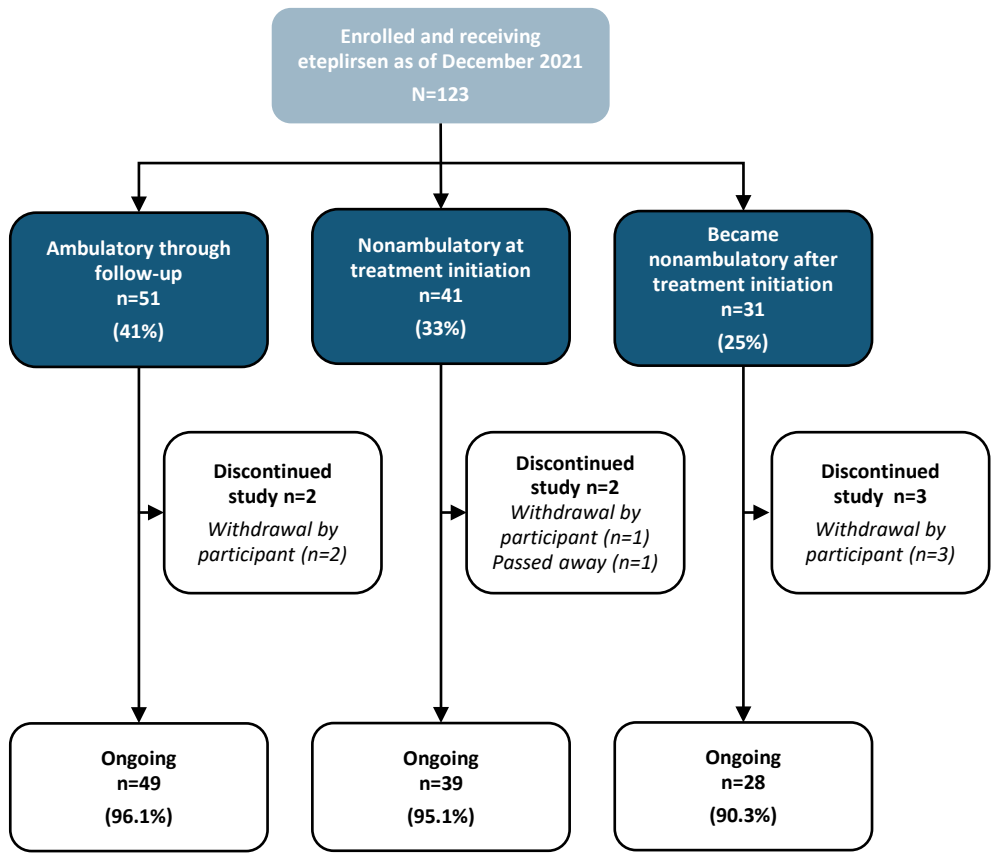
Participant population

- Receiving or initiating treatment with eteplirsen at time of study enrollment as prescribed by treating physicians as part of standard of care[3]
- Enrollment of eteplirsen-treated participants began in 2019[3]

Participant disposition

- Of the 123 participants who had been included in the eteplirsen treatment group, 116 continued through study follow-up (**SF1**)

SF1 *Participant Disposition*

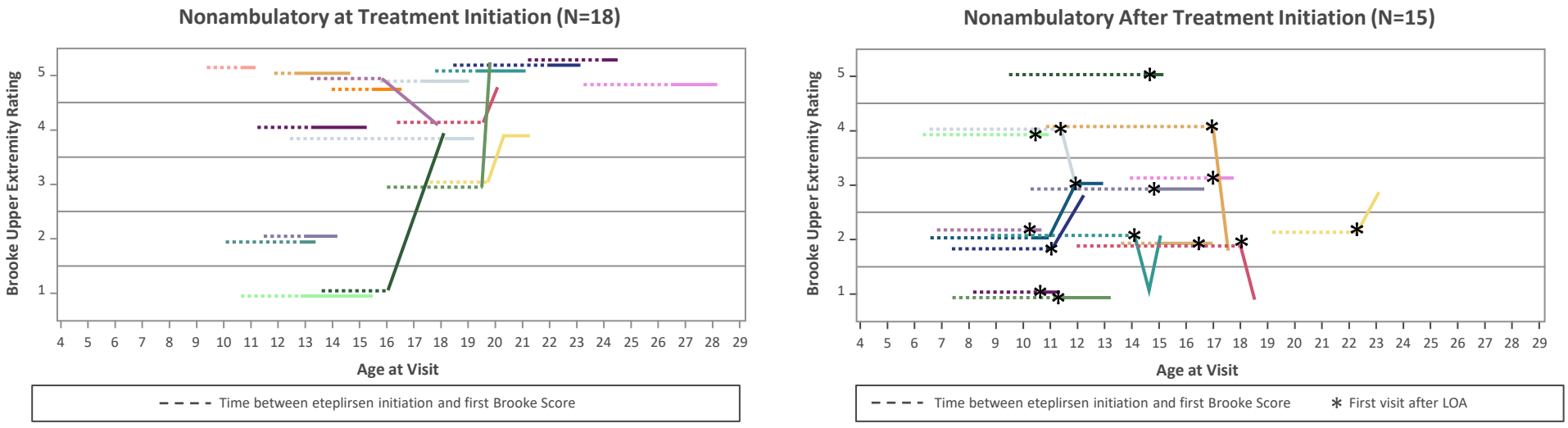


ST1 *Additional Participant Demographics and Disease Characteristics*

	Ambulatory at Eteplirsen Initiation and Through Follow-up (N=51)	Nonambulatory at Eteplirsen Initiation (N=41)	Nonambulatory After Eteplirsen Initiation (N=31)
Weight (kg), mean (SD)	33.6 (15.8)	61.9 (19.2)	67.9 (20.3)
BMI (kg/m^2), mean (SD)	20.9 (6.1)	26.7 (8.4)	31.5 (9.3)
Ethnicity, n (%)			
Hispanic or Latino	10 (19.6)	11 (26.8)	6 (19.4)
Not Hispanic or Latino	36 (70.6)	26 (63.4)	21 (67.7)
Not reported/unknown	5 (9.8)	4 (9.8)	4 (12.9)
Race, n (%)			
Asian	3 (5.9)	4 (9.8)	2 (6.5)
Black	1 (2.0)	1 (2.4)	0
White	37 (72.5)	32 (78.0)	24 (77.4)
Other/Missing	10 (19.6)	4 (9.8)	5 (16.1)

BMI=body mass index.

SF2 *Spaghetti Plot of Brooke Score in Eteplirsen-Treated Participants vs Age at Visit in Nonambulatory Participants With ≥2 Data Points*



LOA=loss of ambulation.