Real-World Benefit of Ataluren Treatment in Milestones Not Related to Ambulatory Function in Nonsense Duchenne Muscular Dystrophy Versus Standard of Care

Daiana Machado[1] , Anderson Luiz Machado Freitas[1], Ana Paula Carneiro dos Santos[1], Ellen Paula[1], Isabel de Lima Bretas[1] and Marcia Treglia[1]

[1] PTC Farmacêutica, São Paulo, São Paulo, Brazil

CO29

1. BACKGROUND

Duchenne muscular dystrophy (DMD) and ataluren

- Duchenne muscular dystrophy (DMD) is a lethal X-linked recessive neuromuscular disorder caused by mutations in the dystrophin gene that result in absent or insufficient functional dystrophin, a cytoskeletal protein that enables the strength, stability, and functionality of myofibres.[1,2]
- Progressive muscular damage occurs in people with DMD, resulting in muscular weakness, motor delays, loss of ambulation, respiratory impairment, and cardiomyopathy. It is important to highlight that patients 'death is due to cardiac and respiratory impairment.[1,2]
- Around 10–15% of patients with DMD have a nonsense mutation in the DMD gene (nmDMD), which results in a premature stop codon in the protein-coding region of the mRNA.[3,4]
- Current standard of care for DMD include oral glucocorticoids, cardiac management, pulmonary management, vaccinations, physical therapy and orthopedic care, nutritional management, and bone health.[1,5]
- Currently there is no cure for DMD but there are therapies that can slow down the progression of the disease.[6]

Ataluren

Ataluren promotes readthrough of the in-frame premature stop codon, enabling the production of full-length dystrophin in patients with nmDMD.[7]

Translarna is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 2 years and older in the European Member States and Iceland, Liechtenstein, Norway, Great Britain, Northern Ireland, Kazakhstan, Israel, Republic of Korea, Belarus, Russia, Brazil, Peru, Chile, Macedonia, Uruguay and Serbia, and aged 5 years and older in the Kingdom of Saudi Arabia and Ukraine (under special state registration). In Brazil, the indication is specific to male pediatric patients. The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing[8]

2. OBJECTIVE AND METHODS

The objective of this work is to raise data on patients taking ataluren in milestones not related to ambulatory function, such as upper limb and respiratory function.

We performed a search literature at EMBASE and Medline, on June 28th, 2023, using the terms: [ataluren + pulmonary or respiratory function]; [ataluren + upper limb] [ataluren] and [standard of care]. The same search was performed on the abstracts of the main and latest congress in this area: the 27th Annual Congress of the World Muscle Society (WMS), October 2022.

3. RESULTS

- **References found and selected**

The literature search at EMBASE and Medline brought 177 results and 3 relevant references (McDonald, 2022; Michael, 2021 and Tulinius, 2022) were selected, which presented ataluren benefits on milestones related to respiratory and upper limb function. The reason for not considering the other 174 references is detailed below. The search performed on the abstracts of the 27th Annual Congress of the WMS, brought 1 additional relevant reference (McDonald, LSVP #26).

174 non considered references

142	30	02
non applicable (Eg: review article, non DMD related)	previous data from a selected study	same selected posters presented at another conference

The references selected and some details on each of them is listed below:

Reference selected	Study presented at the reference
1. McDonald CM, Muntoni F, Penematsa V, et al. Ataluren delays loss of ambulation and respiratory decline in nonsense mutation Duchenne muscular dystrophy patients. J Comp Eff Res. 2022;11(3):139-155. doi:10.2217/cer-2021-0196	Study 019 (NCT01557400), a phase 3, international, multicenter, open-label, long-term safety study of ataluren that enrolled patients with nmDMD, most of whom were from a prior ataluren clinical trial.
2. Michael E, Sofou K, Wahlgren L, Kroksmark AK, Tulinius M. Long term treatment with ataluren-the Swedish experience. BMC Musculoskelet Disord. 2021;22(1):837. Published 2021 Sep 30. doi:10.1186/s12891-021-04700-z	A Swedish experience on ataluren long term treatment is a retrospective, longitudinal case-series study of all male nmDMD patients who have been treated with ataluren and followed at the Queen Silvia Children's Hospital in Gothenburg, Sweden, from 2008 to 2020.
3. Tulinius et al. Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Duchenne Natural History Study: a matched cohort analysis. Poster #23. Presented at the 27th International Annual Congress of the World Muscle Society (WMS), Halifax, NS, Canada, October 11–15, 2022	Registry Study Strategic Targeting of Registries and International Database of Excellence (STRIDE), an ongoing, multicenter, observational registry providing real-world evidence on use of ataluren in patients with nmDMD in routine clinical practice.
4. McDonald et al. Ataluren preserves upper limb function in nmDMD patients from Study 041, a phase 3 placebo-controlled trial, and the STRIDE Registry. LSVP #26. Presented at the 27th International Annual Congress of the World Muscle Society (WMS), Halifax, NS, Canada, October 11–15, 2022	Comparison between the STRIDE Registry described above and Study 041 (NCT03179631), an international, phase 3, randomized, double-blind, placebo-controlled 72-week trial of ataluren in patients with nmDMD, followed by a 72-week open-label period.

These 4 references bring data on nmDMD patients taking ataluren on other milestones not only related to ambulatory function but also respiratory and upper limb functions.

Three of the four references (1, 3 and 4) compare ataluren studies data with data from the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG DNHS; ClinicalTrials.gov identifier: NCT00468832) which was a prospective, longitudinal study of a total of 440 patients with DMD receiving standard of care (SoC; corticosteroid or palliative therapies) who were followed up between 2006 and 2016 at 20 centers in 9 countries.

- **Analyzing references data**

Reference 1 – Study 019

Study populations

- Study 019: Patients were eligible if they were male, diagnosed with nmDMD and had received ataluren in prior PTC Therapeutics-sponsored studies at investigational sites outside the United States.
- CINRG: Patients were included if they had a confirmed diagnosis of DMD and were aged 2–28 years.

Statistical analysis

- Propensity score matching (PSM) was performed to identify CINRG DNHS patients who were similar to Study 019 patients in the following four covariates, which are established predictors of disease progression:
  - age at first symptoms
  - age at initiation of corticosteroid use
  - duration of deflazacort use
  - duration of other corticosteroid use

3. RESULTS

In Study 019, age at first symptoms was not recorded; therefore, age at diagnosis was used as a conservative proxy for age at first symptoms in PSM.

The risk assumed with this approach accepts the probability of Study 019 patients declining in functional capabilities sooner than those in the CINRG DNHS cohort, because the Study 019 patients are likely to have a more severe disease phenotype.

Lung function analysis: Population criteria

- Patients who were non-ambulatory and had available data for age at loss of ambulation (LoA), the four respiratory outcome measures assessed, and the four covariates used for propensity score matching, and had not experienced a decline in one of these FVC milestones before Study 019 entry.

Results

- Ataluren treatment resulted in a significant 3.0-year delay in decline of predicted FVC <60% compared with matched controls. The median age for this milestone was 18.1 years in Study 019 and 15.1 years in the CINRG DNHS.

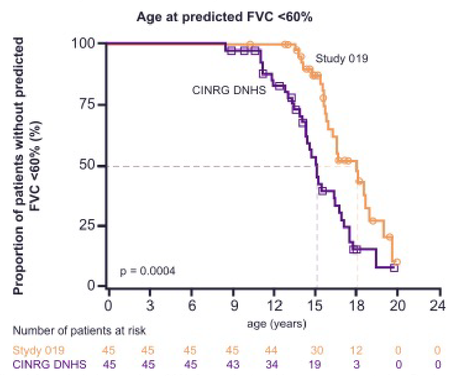

Figure 1. Age at predicted forced vital capacity <60% for patients with nonsense mutation Duchenne muscular dystrophy who received ataluren 40 mg/kg/day plus standard of care in at least Study 019 (all n = 45), compared with propensity-score matched patients with Duchenne muscular dystrophy who received SoC alone in the CINRG DNHS (n = 45). FVC: Forced vital capacity. Adjusted from McDonald et al. 2022

- Besides that, Ataluren + SoC was also associated with a delay of approximately 1 year in the age at predicted FVC declining to <50%, compared with SoC alone. In addition, 1 patient (2.2%) from Study 019 and 9 patients (20.0%) from the CINRG DNHS experienced a FVC decline below the critical threshold of < 1 L.

Reference 2 – Swedish experience

Study population

- 11 patients who initially received ataluren as part of previous clinical trials (007, 019 and 020) and since ataluren was granted approval by the EMA in 2017, all of them continued to receive their treatment through their country hospital, having regular follow-ups at the clinic with the same array of tests, as part of the STRIDE registry follow-up protocol.

Statistical analysis

- The statistical evaluations performed were mainly descriptive. Due to the small number of patients, frequencies were presented as median and minimum/maximum scores.

- **Lung function analysis**
- Forced vital capacity (FVC) was measured with a spirometer. The value, FVC%, was given as percentage of reference value correlated to sex, age and height.

Results

- In the non-ambulatory group, most patients declined over time, but were still above the predicted decline according to Mayer et al. The authors speculate that the cumulative effect of ataluren could lead to higher FVC values before lung function begins to deteriorate and thus it would take longer to reach below 1L, delaying the age at which continuous ventilatory support is needed. This statement is strengthened by the fact that the majority of patients (9 of 10 pts) maintained a pulmonary decline above the expected over time.

Performance of Upper Limb (PUL) analysis

- Assessment of upper limb function was performed with the Performance of the Upper Limb module (PUL 1.2). The test comprises modules for shoulder, elbow and wrist and hand dimensions with a total score of 74 points. This function test was first introduced in 2013 for patients who have lost ambulation.

Results

- PUL assessments were mainly performed in the non-ambulatory patients (n = 6). Following loss of ambulation, 4 of 6 patients had PUL scores above the expected mean values over time.

Reference 3 – STRIDE Registry Study

Study populations

- Patients were eligible if they received ataluren as a commercial supply or as part of an early access program and provided written informed consent before participating in this study.

CINRG Duchenne Natural History Study:

- Patients aged 2–28 years were included if they had a diagnosis of DMD.

Statistical analysis

- Propensity score matching was performed to identify CINRG DNHS patients who were comparable to STRIDE patients in the following established predictors of disease progression:
  - age at onset of first symptoms
  - age at initiation of corticosteroid use
  - duration of deflazacort use
  - duration of other corticosteroid use

Lung function Results

- In the STRIDE Registry, the median age at predicted FVC < 60% was significantly higher for patients in the STRIDE Registry than for patients in the matched CINRG DNHS population: 17.7 years vs 15.9 years, respectively (HR: 0.539; p= 0.0021).

Similar, the median age at predicted FVC < 30% was not yet estimable for patients in the STRIDE Registry, as those patients had not yet reached that disease milestone and was 22.5 years for those in the CINRG DNHS population (HR: 0.333; p= 0.0165).

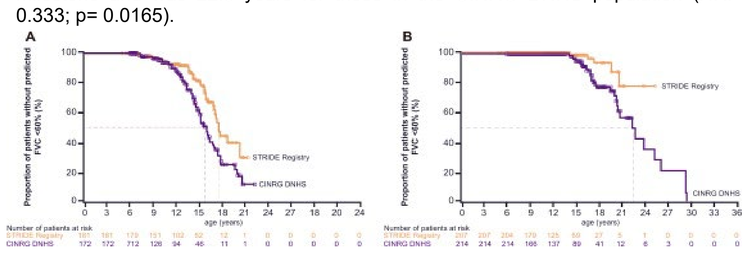

Figure 2. Age at predicted FVC **(A)** < 60% and **(B)** < 30% for propensity-score matched patients in the STRIDE Registry and CINRG DNHS population. Adjusted from Tulinius, 2022.

3. RESULTS

Reference 4: STRIDE Registry and 041 Studies

Study populations

- **STRIDE Registry:** Patients were eligible if they received ataluren as a commercial supply or as part of an early access program and provided written informed consent before participating in this study.
- **CINRG Duchenne Natural History Study:** Patients aged 2–28 years were included if they had a diagnosis of DMD.
- **041 Study:** Boys with nmDMD aged ≥ 5 years, on a stable corticosteroid regimen, and with a 6-minute walk distance (6MWD) of ≥ 150 m were eligible. Key subgroup analysis included patients with a 6MWD of 300–400 m.

Statistical analysis

- Propensity score matching was performed to identify CINRG DNHS patients who were comparable to STRIDE patients as described previously.
- A mixed-model repeated measures (MMRM) analysis was employed using a random intercept to interpret results from Study 041.
- In Study 041, upper limb function was assessed using the PUL module that provides a score based on performance across multiple upper limb dimensions.
- In the STRIDE Registry, the PUL (1.2 and 2.0) entry-level items were compared with the Brooke scale, which has been shown to be comparable and was used in the CINRG DNHS.
- For STRIDE and CINRG DNHS results, Kaplan–Meier analyses estimated age at loss of upper limb function and at persistent loss of upper limb function.

Performance of Upper Limb (PUL) analysis

Results

Ataluren treatment preserved upper limb function in the Study 041 300–400 m 6MWD subgroup and STRIDE Registry patients.

- Ataluren significantly preserved upper limb function compared with placebo in the 300–400 m 6MWD subgroup, as shown by the high-level shoulder, mid-level elbow and total score results (p = 0.0446, p = 0.0276, p = 0.0178, respectively).

Table 1. Performance of upper limb score change from baseline to week 72 for the Study 041 ITT and 300–400 m 6MWD populations.

		300-400 m 6MWD	
		Ataluren (N = 86)	Placebo (N = 83)
High-level shouder score	LS mean change (95%CI)	-0.47 (-0.79, -0.16)	-0.92 (-1.23, -0.61)
	Treatment difference[a]	0.45	
	P value	0.00446	
Mid-level elbow score	LS mean change (95%CI)	-0.20 (-0.49, -0.09)	-0.66 (-0.94, -0.37)
	Treatment difference[a]	0.46	
	P value	0.0276	
Distal weist and hand score	LS mean change (95%CI)	-0.02 (-0.15, -0.20)	-0.03 (-0.20, -0.14)
	Treatment difference[a]	0.05	
	P value	0.6803	
Total score	LS mean change (95%CI)	-0.6 (-1.14, -0.05)	-1.065 (-2.23, -1.07)
	1.00	0.05	
	P value	0.0178	

[a]Treatment difference (ataluren – placebo).
Mean change from baseline to week 72 analyzed by MMRM. Baseline defined as the maximum measurement of a valid day 1 or day 2 6MWD value.
The MMRM model for the ITT population and the 300–400 m 6MWD subgroup includes baseline concomitant corticosteroid type (deflazacort vs prednisone/prednisolone); baseline 6MWD category (< 300 m, ≥ 300 to < 350 m, ≥ 350 to < 400 m, ≥ 400 m); baseline PUL score; treatment week (as a categorical variable); the interaction of week and baseline PUL score, and the interaction of week and treatment. The Toeplitz covariance matrix was assumed.
CI, confidence interval; LS, least squares; MMRM, mixed-model repeated measures.

For matched STRIDE and CINRG DNHS populations ataluren slowed the decline:

- Hand-to-mouth function by 3.4 years (p = 0.0046)
- Similar results were seen for median age at persistent loss of upper limb function for STRIDE versus CINRG DNHS patients, further demonstrating the favorable effects of ataluren.

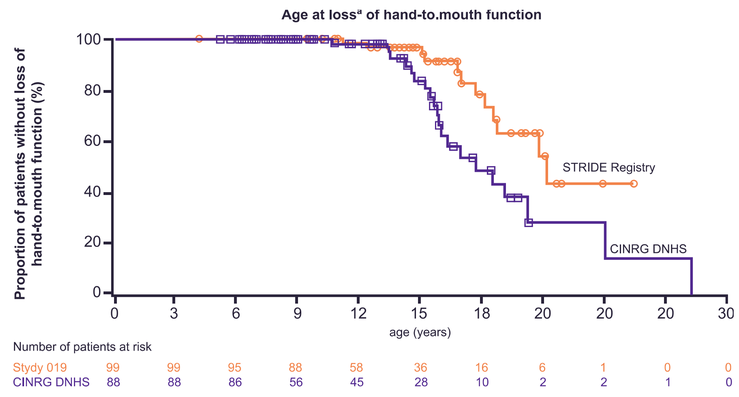

Figure 4. Patients receiving ataluren in the STRIDE Registry had preserved upper limb function versus matched patients receiving SoC alone in the CINRG DNHS.
For STRIDE Registry vs CINRG DNHS patients, performance of upper limb function was assessed by entry level items of PUL versus Brooke scale. Propensity score model covariates include age at first symptom, age at initiation of corticosteroid use, duration of deflazacort use and duration of other corticosteroid use. Age at loss of function is defined as the first time loss of function was documented (but might be regained at a later measurement).

4. DISCUSSION/CONCLUSION

- In the 019 Study, ataluren + SoC was associated with a 3.0-year delay in decline of predicted forced vital capacity to <60% in non-ambulatory patients, versus SoC alone.
- In the Swedish case report, ataluren was associated with a slower decline in FVC and in upper limb motor function.
- In the STRIDE Study, ataluren + SoC data demonstrated a significant delay in pulmonary function decline as assessed by FVC < 60% for STRIDE patients compared with CINRG DNHS patients.
- The results of STRIDE Registry and 041 Studies, indicate that ataluren+SoC may help to preserve upper limb function in patients with nmDMD, as demonstrated in a relatively young patient cohort in Study 041 and in a relatively older patient cohort in the STRIDE Registry.

Disclosure:

This work was prepared by PTC Farmacêutica do Brasil and the poster layout was prepared by Origin Health.

REFERENCES

1. Birnkrant DJ, Bushby K, Bann CM, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management [published correction appears in Lancet Neurol. 2018 Apr 4;:]. Lancet Neurol. 2018;17(3):251-267.
2. van Ruiten HJ, Straub V, Bushby K, Guglieri M. Improving recognition of Duchenne muscular dystrophy: a retrospective case note review. Arch Dis Child. 2014;99(12):1074-1077.
3. Bello L, Pegoraro E. Genetic diagnosis as a tool for personalized treatment of Duchenne muscular dystrophy. Acta Myol. 2016;35(3):122-127
4. Pichavant C, Aartsma-Rus A, Clemens PR, et al. Current status of pharmaceutical and genetic therapeutic approaches to treat DMD. Mol Ther. 2011;19(5):830-840
5. Shieh PB. Emerging Strategies in the Treatment of Duchenne Muscular Dystrophy. Neurotherapeutics. 2018;15(4):840-848. doi:10.1007/s13311-018-00687-z
6. Sun C, Shen L, Zhang Z, Xie X. Therapeutic Strategies for Duchenne Muscular Dystrophy: An Update. Genes (Basel). 2020;11(8):837. Published 2020 Jul 23
7. Roy B, Friesen WJ, Tomizawa Y, et al. Ataluren stimulates ribosomal selection of near-cognate tRNAs to promote nonsense suppression. Proc Natl Acad Sci U S A. 2016;113(44):12508-12513.
8. Translarna Summary of Product Characteristics for respective countries

SCAN QR CODE FOR ADDITIONAL RESULTS