Comparison of North Star Ambulatory Assessment score change in nmDMD patients receiving ataluren: STRIDE Registry vs phase 3 clinical trial

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Poster #170

1. Background

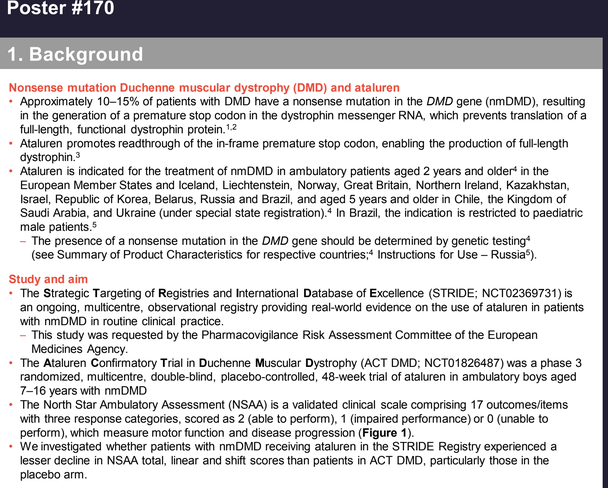
Nonsense mutation Duchenne muscular dystrophy (DMD) and ataluren

- Approximately 10–15% of patients with DMD have a nonsense mutation in the *DMD* gene (nmDMD), resulting in the generation of a premature stop codon in the dystrophin messenger RNA, which prevents translation of a full-length, functional dystrophin protein.[1,2]
- Ataluren promotes readthrough of the in-frame premature stop codon, enabling the production of full-length dystrophin.[3]
- Ataluren is indicated for the treatment of nmDMD in ambulatory patients aged 2 years and older[4] in the European Member States and Iceland, Liechtenstein, Norway, Great Britain, Northern Ireland, Kazakhstan, Israel, Republic of Korea, Belarus, Russia and Brazil, and aged 5 years and older in Chile, the Kingdom of Saudi Arabia, and Ukraine (under special state registration).[4] In Brazil, the indication is restricted to paediatric male patients.[5]
  - The presence of a nonsense mutation in the *DMD* gene should be determined by genetic testing[4] (see Summary of Product Characteristics for respective countries;[4] Instructions for Use – Russia[5]).

Study and aim

- The **S**trategic **T**argeting of **R**egistries and **I**nternational **D**atabase of **E**xcellence (STRIDE; NCT02369731) is an ongoing, multicentre, observational registry providing real-world evidence on the use of ataluren in patients with nmDMD in routine clinical practice.
  - This study was requested by the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency.
- The **A**taluren **C**onfirmatory **T**rial in **D**uchenne **M**uscular **D**ystrophy (ACT DMD; NCT01826487) was a phase 3 randomized, multicentre, double-blind, placebo-controlled, 48-week trial of ataluren in ambulatory boys aged 7–16 years with nmDMD
- The North Star Ambulatory Assessment (NSAA) is a validated clinical scale comprising 17 outcomes/items with three response categories, scored as 2 (able to perform), 1 (impaired performance) or 0 (unable to perform), which measure motor function and disease progression (**Figure 1**).
- We investigated whether patients with nmDMD receiving ataluren in the STRIDE Registry experienced a lesser decline in NSAA total, linear and shift scores than patients in ACT DMD, particularly those in the placebo arm.

Figure 1. North Star Ambulatory Assessment (NSAA).



Adapted from: Straub V *et al. Neuromuscul Disord* 2018;28:690–701.[6]

2. Methods

Study design

- The STRIDE Registry study design is shown in **Figure 2**.[7]
  - Patients are followed up for ≥ 5 years or until study withdrawal.

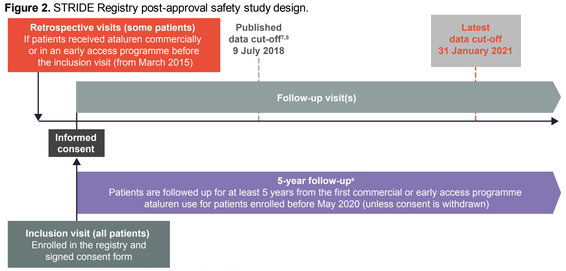
Study populations

STRIDE Registry

- Patients were eligible if they received ataluren as a commercial supply or as part of an early access programme and provided written informed consent before participating in this study.[7,8]
- Patients were not eligible if they were receiving:
  - ataluren or placebo in an ongoing, blinded, randomized clinical trial
  - ataluren in any other ongoing clinical trial or early access programme that prevented participation in this study.
- Patients were excluded from the NSAA analyses if they were aged < 5 years because these patients are still in the maturational phase of DMD.[9]

2. Methods (continued)

Figure 2. STRIDE Registry post-approval safety study design.



[a]Patients enrolled after May 2020 will be followed up through March 2025.
STRIDE, Strategic Targeting of Registries and International Database of Excellence.
Adapted from: Muntoni F *et al. J Comp Eff Res* 2019;8:1187–200.[7]

ACT DMD

- Ambulatory boys aged 7–16 years with confirmed nmDMD were enrolled.
- Key inclusion criteria included:
  - stable corticosteroid use for ≥ 6 months before enrolling in the trial (with no significant change in dose or dose regimen for ≥ 3 months before treatment start)
  - a 6-minute walk distance of ≥ 150 m and ≤ 80% of that predicted for patients according to their age or height.

Statistical analysis

- To evaluate the first 48-week change in total and linear NSAA scores:
  - STRIDE patients were assessed by their first 48-week score change (i.e. the difference between their first '48-week assessment' [between weeks 40 and 72] and their first assessment)
  - ACT DMD patients receiving either ataluren or placebo were assessed by their score change over 48 weeks.
- To evaluate the shift in each NSAA item score to 'failure' to perform:
  - the proportion of patients losing the ability to perform individual NSAA items was assessed over the first 48-week study period in the STRIDE Registry and ACT DMD; 'failure' to perform an NSAA item was recorded by a shift from a score of either 2 (able) or 1 (impaired) to 0 (unable).

3. Results

Study population

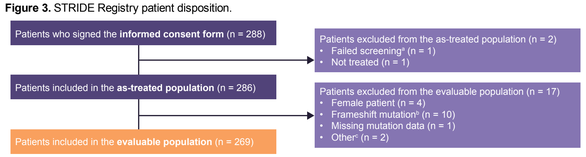
STRIDE Registry

- As of 31 January 2021, a total of 288 patients had been enrolled in STRIDE at 64 sites in 13 countries (**Figure 3**).
- Of these 288 patients who provided informed consent (screened population), 286 received at least one dose of ataluren and did not fail screening (as-treated population).
- Of the 286 patients in the as-treated population, 17 were excluded from the evaluable population (n = 269) for the following reasons: 4 were female, 10 had a frameshift mutation and 3 had missing or outstanding mutation data.

ACT DMD

- In total, 230 patients were eligible for the study.
- Patients were randomized 1:1 to placebo:ataluren (115 in each treatment arm).
  - Two patients (one in each treatment arm) were excluded from the intention-to-treat (ITT) population; neither patient had at least one valid post-baseline 6-minute walk distance test result, a requirement for inclusion in the ITT population, because they were prematurely discontinued from the study when gene sequencing results did not confirm nmDMD.
- Overall, 228 patients were randomized to receive either placebo or ataluren (114 per group).

Figure 3. STRIDE Registry patient disposition.



[a]Screening failure owing to a frameshift mutation.
[b]Ataluren is not indicated in these patients; ataluren is indicated for the treatment of ambulatory patients with DMD resulting from a nonsense mutation in the dystrophin gene. Patients who do not have a nonsense mutation should not receive ataluren.
[c]Critical queries, such as those regarding mutation data, are still outstanding.
DMD, Duchenne muscular dystrophy; STRIDE, Strategic Targeting of Registries and International Database of Excellence.

3. Results (continued)

Table 1. Demographics and characteristics of patients assessed for NSAA linear and total scores in the STRIDE Registry and ACT DMD.

	STRIDE Registry (aged ≥ 5 years) n = 116	ACT DMD (ataluren arm) n = 114	ACT DMD (placebo arm) n = 114
Age at first assessment, years			
Mean (SD)	9.9 (3.3)	8.9 (1.8)	9.0 (1.7)
Median (min, max)	9.4 (5.0, 18.6)	8.5 (7, 14)	9.0 (7, 14)
Age at nmDMD diagnosis, years	n = 111	n = 114	n = 114
Mean (SD)	5.1 (2.6)	4.4 (2.1)	4.4 (2.5)
Median (min, max)	4.9 (0.3, 14.1)	4.0 (0, 9)	4.0 (0, 11)
Patients naive to ataluren, n (%)	94 (81.0)	114 (100)	114 (100)
Corticosteroid use, n (%)	110 (94.8)	114 (100)	114 (100)
Weight, kg	n = 101	n = 114	n = 114
Mean (SD)	28.6 (11.1)	31.4 (10.8)	30.7 (10.5)
Median (min, max)	26.0 (13.5, 74.0)	29.3 (15.8, 63.0)	27.0 (18.1, 68.0)
Height, cm	n = 89	n = 114	n = 114
Mean (SD)	120.7 (14.2)	126.0 (10.6)	126.3 (10.4)
Median (min, max)	120.0 (94.3, 177.0)	125.6 (93.9, 163.5)	125.8 (101.8, 151.0)
BMI, kg/m²	n = 89	n = 114	n = 114
Mean (SD)	18.7 (3.9)	19.3 (4.4)	18.9 (4.1)
Median (min, max)	17.9 (13.0, 30.4)	18.3 (11.3, 36.2)	18.0 (13.0, 36.0)

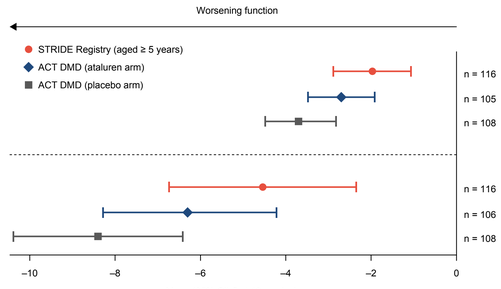
ACT DMD, Ataluren Confirmatory Trial in Duchenne Muscular Dystrophy; BMI, body mass index; max, maximum; min, minimum; nmDMD, nonsense mutation Duchenne muscular dystrophy; SD, standard deviation; STRIDE, Strategic Targeting of Registries and International Database of Excellence.

Table 2. Comparison of NSAA scores between patients in the STRIDE Registry and ACT DMD.

	NSAA total score			NSAA linear score		
	STRIDE Registry (aged ≥ 5 years)	ACT DMD (ataluren arm)	ACT DMD (placebo arm)	STRIDE Registry (aged ≥ 5 years)	ACT DMD (ataluren arm)	ACT DMD (placebo arm)
First assessment	20.1 (18.8, 21.3) n = 142	22.2 (20.7, 23.6) n = 114	21.9 (20.4, 23.3) n = 114	58.6 (55.6, 61.6) n = 142	60.9 (57.6, 64.3) n = 114	60.2 (56.8, 63.6) n = 114
First 48-week change[a]	−2.0 (−2.9, −1.1) n = 116	−2.7 (−3.5, −1.9) n = 105	−3.7 (−4.5, −2.8) n = 108	−4.5 (−6.8, −2.3) n = 116	−6.3 (−8.3, −4.2) n = 106	−8.4 (−10.4, −6.4) n = 108

All data are mean (95% CI).
[a]The first 48-week change is the difference between the first 48-week assessment (during weeks 40 and 72) and the first assessment. Patients without a second assessment or those for whom the first and last assessments were < 40 weeks apart were excluded.
ACT DMD, Ataluren Confirmatory Trial in Duchenne Muscular Dystrophy; n, number of patients who had non-missing data for both first and last assessments; NSAA, North Star Ambulatory Assessment; STRIDE, Strategic Targeting of Registries and International Database of Excellence.

Figure 4. Forest plot showing first 48-week change[a] in NSAA linear and total scores for the STRIDE Registry versus ACT DMD.



Only patients with ≥ 40 weeks between first and last assessments were included in these analyses.
[a]The first 48-week change is the difference between the first 48-week assessment (during weeks 40 and 72) and the first assessment. Patients without a second assessment or those for whom the first and last assessments were < 40 weeks apart were excluded. The mean (95% CI) duration of the first 48 weeks for the STRIDE Registry (n = 116) was 52.99 (51.77, 54.21) weeks.
ACT DMD, Ataluren Confirmatory Trial in Duchenne Muscular Dystrophy; CI, confidence interval; n, number of patients who had non-missing data for both first and last assessments; NSAA, North Star Ambulatory Assessment; STRIDE, Strategic Targeting of Registries and International Database of Excellence.

3. Results (continued)

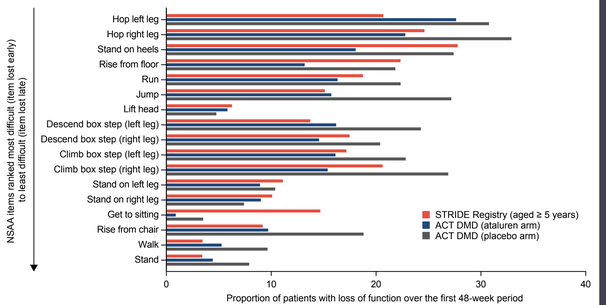
Demographics and characteristics of STRIDE Registry patients versus ACT DMD patients

- In total, 116 STRIDE Registry patients aged ≥ 5 years had non-missing NSAA data for both the first and last assessments, which were ≥ 40 weeks apart.
  - Demographics and characteristics were similar between the STRIDE population and the patients in the ataluren and placebo arms of ACT DMD (**Table 1**).

First 48-week change in NSAA total and linear scores and shift in total NSAA score

- In ACT DMD, ataluren-treated patients experienced a lesser mean decline in NSAA total and linear scores than patients who received placebo over 48 weeks (total score [95% confidence interval (CI)]: ataluren, −2.7 [−3.5, −1.9] and placebo, −3.7 [−4.5, −2.8]; linear score [95% CI]: ataluren, −6.3 [−8.3, −4.2] and placebo, −8.4 [−10.4, −6.4]). Consistently, STRIDE patients experienced mean (95% CI) declines in NSAA total and linear scores of −1.97 (−2.90, −1.05) and −4.54 (−6.75, −2.33) respectively, over their first 48-week assessments (**Table 2** and **Figure 4**).
- The proportion of patients who lost the ability to perform NSAA items was greater for patients who received placebo in ACT DMD than for ataluren-treated patients in both ACT DMD and the STRIDE Registry (**Figure 5**).

Figure 5. Proportion of patients losing ability to perform individual NSAA items over the first 48-week study period in the STRIDE Registry and ACT DMD.



For the STRIDE Registry, loss of function was defined as patients with a score of 1 or 2 at the first assessment and a score of 0 at the first '48-week assessment'; for ACT DMD, it was defined as patients with a score of 1 or 2 at baseline and a score of 0 at week 48. Patients with a score of 0 at the first assessment in the STRIDE Registry or at baseline in ACT DMD were not at risk of loss of function, and therefore are not included in this analysis. The first '48-week assessment' in the STRIDE Registry is the assessment during weeks 40 and 72, after the first assessment.
ACT DMD, Ataluren Confirmatory Trial in Duchenne Muscular Dystrophy; NSAA, North Star Ambulatory Assessment; STRIDE, Strategic Targeting of Registries and International Database of Excellence.

4. CONCLUSIONS

- These results demonstrate that in a real-world setting, ataluren treatment delays decline in performance of NSAA items in nmDMD patients, when compared with placebo in a randomized clinical trial.
  - A limitation of these analyses is that comparisons were between populations with slightly different age ranges (STRIDE patients were aged ≥ 5 years and ACT DMD patients were aged 7–16 years).
- These data suggest that ataluren delays nmDMD disease progression in routine clinical practice.

References

1. Bello L *et al. Acta Myol* 2016;35:122–7.
2. Pichavant C *et al. Mol Ther* 2011;19:830–40.
3. Roy B *et al. Proc Natl Acad Sci USA* 2016;113:12508–13.
4. PTC Therapeutics International Ltd. Summary of product characteristics. European Medicines Agency, 2018. Available from: www.ema.europa.eu/documents/product-information/translarna-epar-product-information_en.pdf (Accessed 7 September 2022).
5. Data on file.
6. Straub V *et al. Neuromuscul Disord* 2018;28:690–701.
7. Muntoni F *et al. J Comp Eff Res* 2019;8:1187–200.
8. Mercuri E *et al. J Comp Eff Res* 2020;9:341–60.
9. Mercuri E *et al. PLoS One* 2016;11:e0160195.

Disclosures

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