Comparison of timed function test results in nmDMD patients receiving ataluren: STRIDE Registry vs phase 3 clinical trial

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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]).

Studies and aim

- The **S**trategic **T**argeting of **R**egistries and **I**nternational **D**atabase of **E**xcellence (STRIDE; ClinicalTrials.gov identifier: 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.[6]
  - The secondary efficacy endpoint was the effect of ataluren on disease progression, as assessed by the following timed function tests (TFTs): change from baseline to week 48 in time to run/walk 10 m, climb four stairs, descend four stairs and stand from supine.[6]
- We investigated whether patients receiving ataluren in real-world practice in STRIDE (as of the latest data cut-off date of 31 January 2021) performed similarly in TFTs to patients who received ataluren in ACT DMD.

2. Methods

Study design

- The STRIDE Registry study design is shown in **Figure 1**.[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 the 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.[7,8]
- Patients aged < 5 years were excluded from the TFT analyses because these patients are still in the maturational phase of DMD.[9]

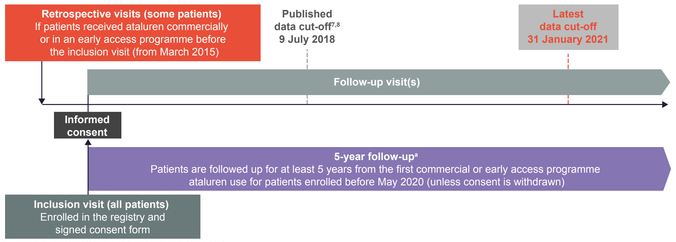
ACT DMD

- Patients aged 7–16 years with confirmed nmDMD and phenotypic evidence of dystrophinopathy were eligible to participate.[6]
  - They were also required to have used systemic corticosteroids (prednisone, prednisolone or deflazacort) for ≥ 6 months before the start of the study, with no significant change in dose or dose regimen for ≥ 3 months before treatment start.
- Exclusion criteria included prior therapy with ataluren or another investigational drug within 3 months before the start of study treatment.[6]

Analysis

- STRIDE patients (aged ≥ 5 years) from the evaluable population (all as-treated patients excluding female patients, those with a frameshift mutation and those with missing mutation data) were assessed by the first 48-week change in time to complete TFTs (i.e. the difference between the first assessment and the first '48-week assessment' [between 40 and 72 weeks]).
- ACT DMD patients (ataluren and placebo-controlled groups) were assessed by the change in time to complete TFTs over 48 weeks.
- Only ambulatory patients from the STRIDE Registry and ACT DMD who provided written informed consent were included in the analysis.
- For patients who lost ambulation during the 48-week period analysed, time to complete TFTs was imputed as 30 seconds from the day they became non-ambulatory.

Figure 1. 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]

3. Results

Demographics and characteristics of STRIDE Registry patients versus ACT DMD patients

- Characteristics for patients assessed for TFTs in the STRIDE Registry (≥ 5-year-old evaluable subgroup) and the ACT DMD ataluren and placebo groups were comparable (**Table 1**).

Change in time to complete TFTs

- In ACT DMD, ataluren-treated patients experienced a smaller mean increase in time to complete TFTs compared with placebo-treated patients over 48 weeks (**Figure 2**).
- STRIDE patients consistently experienced smaller mean increases in time to perform TFTs than placebo-treated ACT DMD patients between the first assessment and the first '48-week assessment' (**Figure 2**).
  - The mean duration of the first '48 weeks' for the STRIDE Registry is shown in **Table 2**.

Table 1. Demographics and characteristics of patients assessed for TFTs in the STRIDE Registry and ACT DMD.

	STRIDE (run/walk 10 m) n = 113	STRIDE (climb four stairs) n = 73	STRIDE (descend four stairs) n = 59	STRIDE (stand from supine) n = 93	ACT DMD (ataluren arm) n = 114	ACT DMD (placebo arm) n = 114
Age at first assessment, years	8.9 (3.1)	9.0 (3.3)	9.3 (3.4)	8.5 (3.0)	8.9 (1.8)	9.0 (1.7)
Age at first symptoms, years	2.8 (1.8) n = 104	2.8 (1.9) n = 70	2.6 (1.9) n = 56	2.8 (1.8) n = 85	3.3 (1.8)	3.7 (2.0)
Age at nmDMD diagnosis, years	5.2 (2.7) n = 107	5.3 (2.9) n = 72	5.4 (2.9) n = 58	5.0 (2.6) n = 90	4.4 (2.1)	4.4 (2.5)
Patients naive to ataluren trials, n (%)	97 (85.8)	60 (82.2)	49 (83.1)	80 (86.0)	114 (100)	114 (100)
Corticosteroid use, n (%)	108 (95.6)	78 (95.1)	55 (93.2)	89 (95.7)	114 (100)	114 (100)
Weight, kg	26.9 (9.8) n = 95	26.9 (9.6) n = 63	27.2 (9.8) n = 51	25.8 (9.1) n = 76	31.4 (10.8)	30.7 (10.5)
Height, cm	118.7 (13.1) n = 82	118.4 (13.3) n = 52	119.5 (14.2) n = 41	116.8 (12.3) n = 67	126.0 (10.6)	126.3 (10.4)
BMI, kg/m²	18.3 (3.7) n = 82	18.0 (3.3) n = 59	17.8 (3.0) n = 41	17.9 (3.5) n = 67	19.3 (4.4)	18.9 (4.1)

All data are mean (SD) unless otherwise specified.
STRIDE patients included in the analysis were aged ≥ 5 years from the evaluable population (all screened patients excluding female patients, those with a frameshift mutation and those with missing mutation data).
ACT DMD, Ataluren Confirmatory Trial in Duchenne Muscular Dystrophy; BMI, body mass index; nmDMD, nonsense mutation Duchenne muscular dystrophy; SD, standard deviation; STRIDE, Strategic Targeting of Registries and International Database of Excellence; TFT, timed function test.

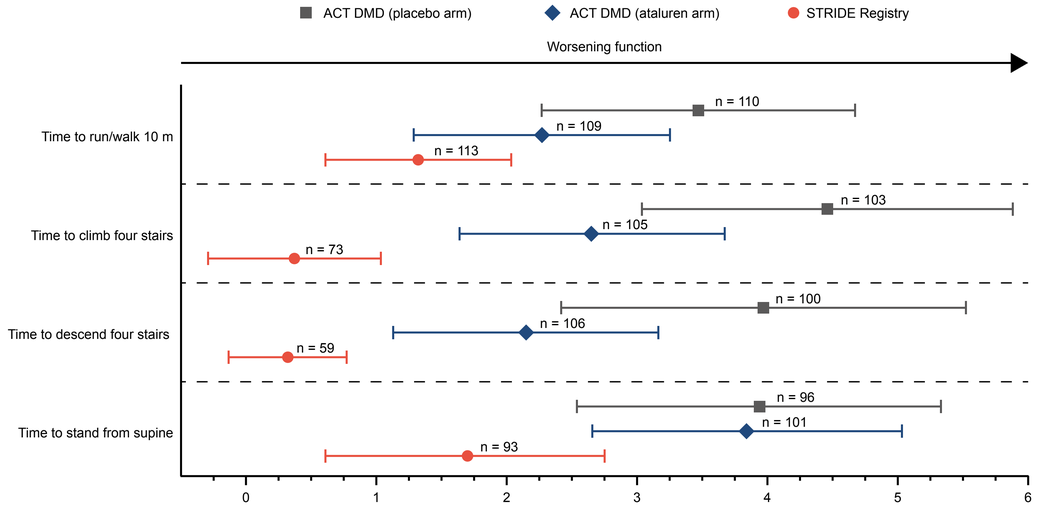
Table 2. Mean duration of follow-up[a] for the STRIDE Registry.

	Run/walk 10 m	Climb four stairs	Descend four stairs	Stand from supine
Duration of first '48 weeks',[a] weeks	52.7 (51.3, 54.0) n = 113	51.6 (49.9, 53.3) n = 73	51.8 (49.7, 53.8) n = 59	52.7 (51.2, 54.2) n = 93

All data are mean (95% CI).
STRIDE patients included in the analysis were aged ≥ 5 years from the evaluable population (all as-treated patients excluding female patients, those with a frameshift mutation and those with missing mutation data).
[a]STRIDE patients were assessed by the first 48-week change in TFTs (i.e. the difference between the first assessment and the first '48-week assessment' [between 40 and 72 weeks]).
CI, confidence interval; n, number of patients who had non-missing data for both assessments; STRIDE, Strategic Targeting of Registries and International Database of Excellence; TFT, timed function test.

Figure 2. Mean first 48-week change[a] in TFTs for patients in the STRIDE Registry and ACT DMD.

	Time to run/walk 10 m			Time to climb four stairs			Time to descend four stairs			Time to stand from supine		
	STRIDE Registry n = 113	ACT DMD (ataluren arm) n = 114	ACT DMD (placebo arm) n = 114	STRIDE Registry n = 73	ACT DMD (ataluren arm) n = 114	ACT DMD (placebo arm) n = 114	STRIDE Registry n = 59	ACT DMD (ataluren arm) n = 114	ACT DMD (placebo arm) n = 114	STRIDE Registry n = 93	ACT DMD (ataluren arm) n = 114	ACT DMD (placebo arm) n = 114
First TFT assessment, s	6.4 (5.9, 6.8)	6.6 (6.1, 7.2)	6.8 (6.3, 7.3)	5.2 (4.2, 6.2)	5.9 (5.0, 6.9) n = 111	6.4 (5.3, 7.4) n = 111	4.0 (3.0, 5.0)	5.0 (4.1, 6.0) n = 111	4.8 (3.9, 5.6) n = 108	6.5 (5.5, 7.5)	9.1 (7.7, 10.6) n = 109	9.6 (8.1, 11.1) n = 110
First 48-week change,[a] s	1.3 (0.6, 2.0)	2.3 (1.3, 3.3) n = 109	3.5 (2.3, 4.7) n = 110	0.4 (−0.3, 1.0)	2.7 (1.6, 3.7) n = 105	4.5 (3.0, 5.9) n = 103	0.3 (−0.1, 0.8)	2.2 (1.1, 3.2) n = 106	4.0 (2.4, 5.5) n = 100	1.7 (0.6, 2.8)	3.8 (2.7, 5.0) n = 101	3.9 (2.5, 5.3) n = 96



All data are mean (95% CI).
STRIDE patients included in the analysis were aged ≥ 5 years from the evaluable population (all as-treated patients excluding female patients, those with a frameshift mutation and those with missing mutation data).
Only patients who had a duration between first and last assessments of ≥ 40 weeks were included in these analyses. For patients who lost ambulation, time to complete TFTs was imputed as 30 seconds.
[a]STRIDE patients were assessed by the first '48-week change' in TFTs (i.e. the difference between the first assessment and the first '48-week assessment' [between 40 and 72 weeks]). ACT DMD patients were assessed by the change in TFTs over 48 weeks.
ACT DMD, Ataluren Confirmatory Trial in Duchenne Muscular Dystrophy; CI, confidence interval; n, number of patients who had non-missing data for both assessments; STRIDE, Strategic Targeting of Registries and International Database of Excellence; TFT, timed function test.

4. CONCLUSIONS

- Patients with nmDMD receiving ataluren in the STRIDE Registry and in ACT DMD showed a delay in decline in performance of TFTs compared with patients in the placebo group in ACT DMD.
- These results demonstrate that in both the real-world and clinical trial setting, ataluren delays the decline in motor function in patients with nmDMD, indicating that ataluren delays disease progression.

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Disclosures

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