Comparing the change in 6-minute walk distance in nmDMD patients receiving ataluren: STRIDE Registry compared with phase 3 clinical trial

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Poster #164

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 primary endpoint was the effect of ataluren on disease progression, as assessed by change in 6-minute walk distance (6MWD), from baseline to week 48.[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) experienced a similar decline in 6MWD as 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 6MWD analyses because these patients are still in the maturational phase of DMD.[9]

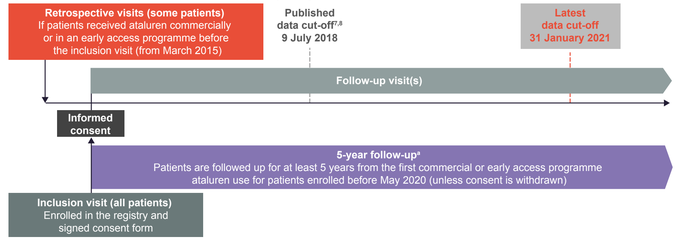
ACT DMD

- 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 their first 48-week change in 6MWD (i.e. the difference between their first assessment and their first '48-week assessment' [between 40 and 72 weeks]).
- ACT DMD patients (ataluren and placebo-controlled groups) were assessed by change in 6MWD over 48 weeks.
- Only ambulatory patients from the STRIDE Registry and ACT DMD with a 6MWD of ≥ 300 m to ≤ 400 m at first assessment who provided written informed consent, were included in the analysis.
- For patients who lost ambulation during the 48-week period analysed, 6MWD was imputed as 0 m 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

- All patients assessed had a 6MWD of ≥ 300 m to ≤ 400 m at first assessment. Characteristics for STRIDE Registry patients (≥ 5-year old evaluable subgroup) and ACT DMD ataluren and placebo groups were comparable (**Table 1**).
  - Mean (standard deviation [SD]) ages at first assessment were 9.6 (3.1) years (ataluren, n = 42) in STRIDE, and 8.9 (1.8) years (ataluren, n = 47) and 9.0 (1.5) years (placebo, n = 52) in ACT DMD.

Change in 6MWD

- The mean (95% confidence interval [CI]) first baseline 6MWD assessment for STRIDE patients (349.7 [341.4, 358.0] m, n = 42) was comparable to that for patients in ACT DMD ataluren and placebo groups (ataluren, 356.7 [348.9, 364.5] m, n = 47; placebo, 354.5 [346.3, 362.8] m, n = 52) (**Figure 2**).
- STRIDE patients experienced a mean (95% CI) decline in 6MWD of 3.5 (−13.8, 20.9) m between their first assessment and their first '48-week assessment', thus performing better than ataluren-treated ACT DMD patients (−28.3 [−45.1, −11.5] m). Placebo-treated patients in ACT DMD experienced the greatest decline in 6MWD (−75.5 [−105.7, −45.3] m) (**Figure 2**).
  - The mean duration of the first '48 weeks' for the STRIDE Registry is shown in **Figure 2**.

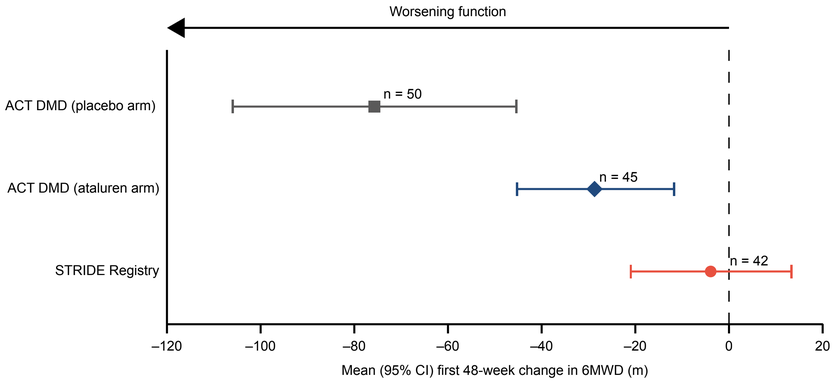
Table 1. Demographics and characteristics of patients assessed for 6MWD with ≥ 300 m to ≤ 400 m at first assessment in the STRIDE Registry and ACT DMD.

	STRIDE Registry n = 42	ACT DMD (ataluren arm) n = 47	ACT DMD (placebo arm) n = 52
Age at first assessment, years	9.6 (3.1)	8.9 (1.8)	9.0 (1.5)
Age at first symptoms, years	2.8 (1.8)	–	–
Age at nmDMD diagnosis, years	5.4 (2.6) n = 40	4.6 (2.1)	4.5 (2.6)
Patients naive to ataluren trials, n (%)	37 (88.1)	47 (100)	52 (100)
Corticosteroid use, n (%)	39 (92.9)	47 (100)	52 (100)
Weight, kg	28.9 (10.6) n = 31	30.4 (11.2)	30.7 (10.2)
Height, cm	121.9 (13.1) n = 24	123.8 (10.8)	126.7 (9.5)
BMI, kg/m²	17.8 (3.3) n = 24	19.4 (4.8)	18.8 (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 as-treated patients excluding female patients, those with a frameshift mutation and those with missing mutation data).
6MWD, 6-minute walk distance; 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.

Figure 2. Mean first 48-week change[a] in 6MWD for patients with a 6MWD of ≥ 300 m to ≤ 400 m at first assessment in the STRIDE Registry and ACT DMD.

	STRIDE Registry n = 42	ACT DMD (ataluren arm) n = 47	ACT DMD (placebo arm) n = 52
First 6MWD assessment, m	349.7 (341.4, 358.0)	356.7 (348.9, 364.5)	354.5 (346.3, 362.8)
Duration of first '48 weeks',[a] weeks	52.1 (49.5, 54.6)	48.0	48.0
First 48-week change,[a] m	−3.54 (−20.87, 13.78)	−28.32 (−45.14, −11.50) n = 45	−75.48 (−105.68, −45.27) n = 50



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, 6MWD was imputed as 0 m on the day they became non-ambulatory.
[a]STRIDE patients were assessed by their first 48-week change in 6MWD (i.e. the difference between their first assessment and their first '48-week assessment' [between 40 and 72 weeks]); ACT DMD patients were assessed by change in 6MWD over 48 weeks.
6MWD, 6-minute walk distance; 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.

4. CONCLUSIONS

- Patients with nmDMD receiving ataluren in the STRIDE Registry and in ACT DMD showed a delay in motor function decline 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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