Pulmonary function in Duchenne muscular dystrophy patients from the STRIDE Registry and CINRG Natural History Study: a matched cohort analysis

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Poster #169

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 **C**ooperative **I**nternational **N**euromuscular **R**esearch **G**roup **D**uchenne **N**atural **H**istory **S**tudy (CINRG DNHS; ClinicalTrials.gov identifier: NCT00468832) 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 centres in nine countries.[6,7]
- We aimed to examine, as of the latest STRIDE data cut-off date of 31 January 2021, whether STRIDE patients with nmDMD receiving ataluren plus SoC experienced a change in disease progression (as measured by decline in pulmonary function) compared with CINRG DNHS patients with DMD receiving SoC alone using propensity-score matched analyses.

2. Methods

Study design

- The STRIDE Registry study design is shown in **Figure 1**.[8]
  - Patients are followed up for ≥ 5 years or until study withdrawal.
- Data from CINRG DNHS patients receiving SoC were used as a control to provide context for assessing the effects of ataluren plus SoC on patients in the STRIDE Registry.

Study populations

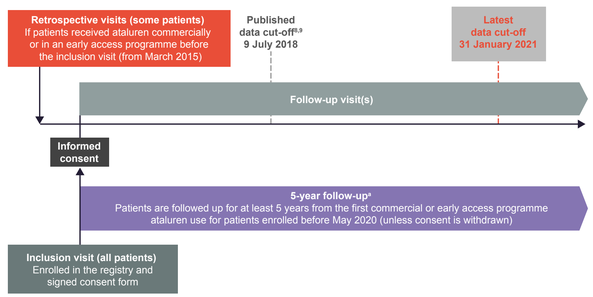
STRIDE Registry

- 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.[8,9]
- 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.[8,9]

CINRG Duchenne Natural History Study

- Patients aged 2–28 years were included if they had a diagnosis of DMD.[6,7]
- Patients were excluded from the present analysis if they had participated in clinical trials of ataluren or received any other mutation-specific investigational drug for DMD, or if they had missing data.[9]

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.[8]

2. Methods (continued)

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.[7,9–11]
- Kaplan–Meier analyses estimated the distribution of age at transition to the following endpoints ('events'): predicted forced vital capacity (FVC) < 60% and predicted FVC < 30% among STRIDE Registry patients and matched CINRG DNHS patients.[9]
  - Lung volume recruitment is indicated by the International Care Considerations for DMD at predicted FVC ≤ 60%.[12]
  - Once patients with DMD have declined to a predicted FVC of < 30%, they are considered to have severe respiratory insufficiency, for whom non-invasive ventilation is necessary.[12,13]
- The hazard ratio (HR; STRIDE Registry:CINRG DNHS) and the corresponding 95% confidence intervals (CIs) were calculated using a Cox proportional hazard model stratified by durations of corticosteroid use, with study (i.e. the STRIDE Registry or the CINRG DNHS), age at first symptoms and age at first corticosteroid use as covariates.[9]

3. Results

STRIDE Registry patient disposition

- As of 31 January 2021, a total of 288 patients with DMD had been enrolled in STRIDE at 64 sites in 13 countries (**Figure 2**).
- 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.
- Of these 269 patients, 241 with confirmed nmDMD were included in the effectiveness population (23 patients with missing data for age at loss of ambulation or age at first symptoms and 5 patients with an age at first symptoms equal to 0 years were excluded).

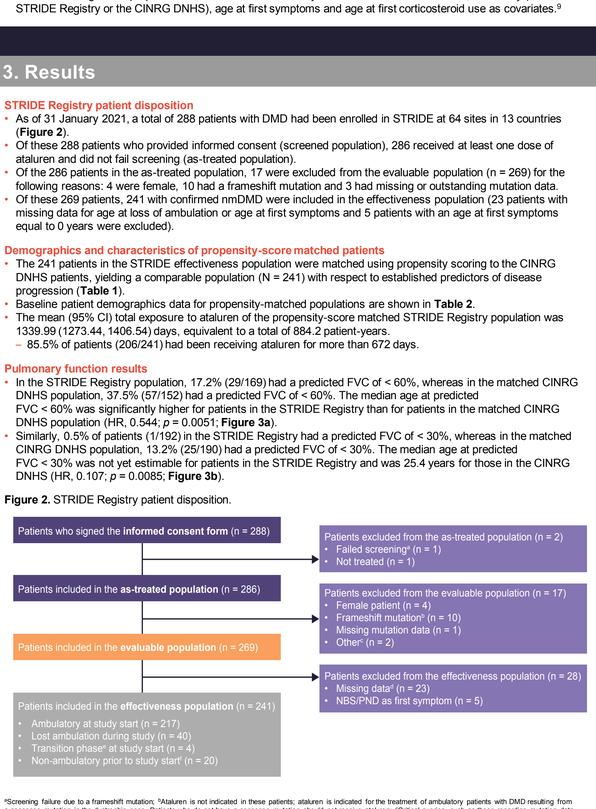
Demographics and characteristics of propensity-score matched patients

- The 241 patients in the STRIDE effectiveness population were matched using propensity scoring to the CINRG DNHS patients, yielding a comparable population (N = 241) with respect to established predictors of disease progression (**Table 1**).
- Baseline patient demographics data for propensity-matched populations are shown in **Table 2**.
- The mean (95% CI) total exposure to ataluren of the propensity-score matched STRIDE Registry population was 1339.99 (1273.44, 1406.54) days, equivalent to a total of 884.2 patient-years.
  - 85.5% of patients (206/241) had been receiving ataluren for more than 672 days.

Pulmonary function results

- In the STRIDE Registry population, 17.2% (29/169) had a predicted FVC of < 60%, whereas in the matched CINRG DNHS population, 37.5% (57/152) had a predicted FVC of < 60%. 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 (HR, 0.544; $p = 0.0051$; **Figure 3a**).
- Similarly, 0.5% of patients (1/192) in the STRIDE Registry had a predicted FVC of < 30%, whereas in the matched CINRG DNHS population, 13.2% (25/190) had a predicted FVC of < 30%. The median age at predicted FVC < 30% was not yet estimable for patients in the STRIDE Registry and was 25.4 years for those in the CINRG DNHS (HR, 0.107; $p = 0.0085$; **Figure 3b**).

Figure 2. STRIDE Registry patient disposition.



[a]Screening failure due 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; [d]Data were missing for age at loss of ambulation or age at first symptoms; [e]Patients were in the transition phase if they completed the first 10-m walk/run test in ≥ 30 seconds; [f]Non-ambulatory patients were defined as such if using a wheelchair full-time or bedridden; patients who were non-ambulatory "prior to study start" were all ambulatory at ataluren initiation in previous clinical trials.
NBS, newborn screening; PND, prenatal diagnosis; STRIDE, Strategic Targeting of Registries and International Database of Excellence.

3. Results (continued)

Table 1. Demographics and characteristics of patients in the STRIDE Registry and CINRG DNHS before and after propensity score matching.

Characteristics	Unmatched population		Propensity-score matched population	
	STRIDE (N = 241)	CINRG DNHS (N = 398)	STRIDE (N = 241)	CINRG DNHS (N = 241)
Age at first symptoms, years				
Mean (SD)	2.74 (1.66)	3.23 (1.68)	2.74 (1.66)	2.78 (1.50)
Median	2.50	3.00	2.50	3.00
Minimum, maximum	0.10, 8.00	0.08, 8.00	0.10, 8.00	0.08, 8.00
p value	0.0004		0.8187	
Age at first corticosteroid use (excluding treatment-naive patients),[a] years	n = 212	n = 315	n = 212	n = 212
Mean (SD)	6.61 (2.16)	6.74 (2.05)	6.61 (2.16)	6.41 (2.01)
Median	6.18	6.57	6.18	6.22
Minimum, maximum	2.93, 15.31	1.99, 14.25	2.93, 15.31	1.99, 13.89
p value	0.4832		0.3111	
Deflazacort duration,[b] n (%)				
< 1 month	124 (51.5)	234 (58.8)	124 (51.5)	120 (49.8)
≥ 1 to < 12 months	12 (5.0)	20 (5.0)	12 (5.0)	12 (5.0)
≥ 12 months	105 (43.6)	144 (36.2)	105 (43.6)	109 (45.2)
p value	0.1697		0.9322	
Other corticosteroid duration,[b] n (%)				
< 1 month	128 (53.1)	204 (51.3)	128 (53.1)	123 (51.0)
≥ 1 to < 12 months	13 (5.4)	35 (8.8)	13 (5.4)	14 (5.8)
≥ 12 months	100 (41.5)	159 (39.9)	100 (41.5)	104 (43.2)
p value	0.2669		0.8980	

[a]Treatment-naive patients were excluded to calculate the true age at first corticosteroid use; [b]Corticosteroid duration is calculated from the date at which corticosteroid use was started and the loss of ambulation/censor date.
CINRG DNHS, Cooperative International Neuromuscular Research Group Duchenne Natural History Study; SD, standard deviation; STRIDE, Strategic Targeting of Registries and International Database of Excellence.

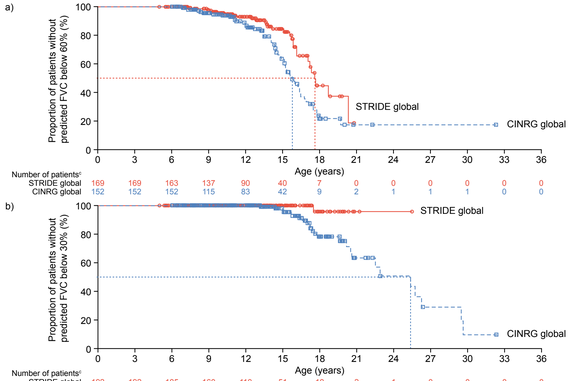
Table 2. Baseline demographics and characteristics of patients in the STRIDE Registry and CINRG DNHS effectiveness population.

Assessment	STRIDE N = 241	CINRG DNHS N = 241
Age at first assessment, years	9.05 (3.71)	10.18 (5.50)
Age at last assessment, years	12.20 (4.21)	14.65 (6.50)
Any corticosteroid duration, n (%)		
< 1 month	31 (12.9)	32 (13.3)
≥ 1 to < 12 months	18 (7.5)	17 (7.1)
≥ 12 months	192 (79.7)	192 (79.7)
Lifetime corticosteroid use, n (%)		
< 1 month	28 (11.6)	30 (12.4)
≥ 1 to < 12 months	18 (7.5)	14 (5.8)
≥ 12 months	195 (80.9)	197 (81.7)
Weight, kg	n = 200 29.6 (12.9)	33.3 (19.3)
Height, cm	n = 173 121.8 (16.0)	n = 171 115.8 (12.7)
BMI, kg/m²	n = 172 19.0 (4.5)	n = 171 17.9 (3.7)

All data are mean (SD) unless otherwise specified.
BMI, body mass index; CINRG DNHS, Cooperative International Neuromuscular Research Group Duchenne Natural History Study; SD, standard deviation; STRIDE, Strategic Targeting of Registries and International Database of Excellence.

3. Results (continued)

Figure 3. Age at predicted FVC a) < 60%[a] and b) < 30%[b] for propensity-score matched patients in the STRIDE Registry and CINRG DNHS.



Assessment	Predicted FVC < 60%[a]		Predicted FVC < 30%[b]	
	STRIDE (SoC + ataluren) N = 241	CINRG DNHS (SoC) N = 241	STRIDE (SoC + ataluren) N = 241	CINRG DNHS (SoC) N = 241
Patients, n (%)				
Assessed	169	152	192	190
With events[d]	29 (17.2)	57 (37.5)	1 (0.5)	25 (13.2)
Censored	140 (82.8)	95 (62.5)	191 (99.5)	165 (86.8)
Age at event, years				
25% quartile (95% CI)	**15.8** (14.1, 17.1)	**14.2** (13.2, 14.7)	**NA** (17.5, NA)	**20.2** (17.2, 22.5)
Median (95% CI)	**17.6** (16.2, NA)	**15.8** (15.1, 16.5)	**NA** (NA, NA)	**25.4** (20.6, 29.4)
Minimum, maximum[e]	5.0*, 20.8*	6.0*, 32.3*	5.0*, 20.8*	6.0*, 32.3*
p value[f]	**0.0051**		**0.0085**	
Hazard ratio[g] (95% CI)	**0.544** (0.343, 0.863)		**0.107** (0.014, 0.813)	

[a]Lung volume recruitment is indicated by the International Care Considerations for DMD at predicted forced vital capacity of ≤ 60%;[12] [b]Once patients with DMD have declined to a predicted FVC of < 30%, they are considered to have severe respiratory insufficiency, for whom non-invasive ventilation is necessary;[12,13] [c]Number of patients at risk of having the event (predicted FVC < 60% or < 30%); [d]Event = predicted FVC < 60% or < 30%; [e]* indicates a censored observation; [f]p value is from a log-rank test stratified by deflazacort and other corticosteroid usage durations. [g]HR is from stratified (by durations of deflazacort and other corticosteroid use) Cox regression with study (STRIDE Registry or CINRG DNHS), age at first symptoms and age at first corticosteroid use as covariates. HR is STRIDE Registry:CINRG DNHS.
Patients were censored when they left the study (e.g. were lost to follow-up, withdrew consent) before the event had occurred, or when the patient had not yet had the event by the date of data cut-off.
CI, confidence interval; CINRG DNHS, Cooperative International Neuromuscular Research Group Duchenne Natural History Study; FVC, forced vital capacity; NA, not available; SoC, standard of care; STRIDE, Strategic Targeting of Registries and International Database of Excellence.

4. CONCLUSIONS

- Although there were few loss of pulmonary function events observed in STRIDE patients, the percentage of patients who reached the different pulmonary function disease milestones (predicted FVC < 60% and predicted FVC < 30%) was smaller for those receiving ataluren plus SoC (STRIDE Registry) than for matched patients receiving SoC alone (CINRG DNHS).
- Loss of pulmonary function was delayed in STRIDE patients compared with CINRG DNHS patients.
- These data show that treatment with ataluren in addition to SoC in routine clinical practice may delay disease progression in patients with nmDMD.
- Future comparisons of data from the STRIDE Registry at a later cut-off date with CINRG DNHS data, in addition to the accumulation of more pulmonary function events, will provide further real-world insights into the long-term effectiveness of ataluren for the treatment of patients with nmDMD.

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