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### Authors

Mercuri, Eugenio  
Muntoni, Francesco  
Osorio, Andrés  
et al.

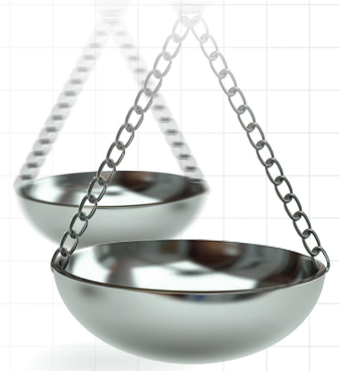
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# Safety and effectiveness of ataluren: comparison of results from the STRIDE Registry and CINRG DMD Natural History Study

Journal of **Comparative Effectiveness Research**

Eugenio Mercuri<sup>\*1,2</sup>, Francesco Muntoni<sup>3,4</sup>, Andrés Nascimento Osorio<sup>5</sup>, Már Tulinius<sup>6</sup>, Filippo Buccella<sup>7</sup>, Lauren P Morgenroth<sup>8</sup>, Heather Gordish-Dressman<sup>9</sup>, Joel Jiang<sup>10</sup>, Panayiota Trifillis<sup>10</sup>, Jin Zhu<sup>10</sup>, Allan Kristensen<sup>10</sup>, Claudio L Santos<sup>10</sup>, Erik K Henricson<sup>11</sup>, Craig M McDonald<sup>11</sup>, Isabelle Desguerre<sup>12</sup>, on behalf of the STRIDE<sup>‡</sup> & CINRG Duchenne Natural History Investigators<sup>§</sup>

<sup>1</sup>Department of Pediatric Neurology, Catholic University, Rome, Italy

<sup>2</sup>Centro Clinico Nemo, Policlinico Universitario A Gemelli IRCCS, Rome, Italy

<sup>3</sup>Dubowitz Neuromuscular Centre & MRC Centre for Neuromuscular Diseases, University College London, Institute of Child Health & Great Ormond Street Hospital for Children Foundation Trust, 30 Guildford Street, London, WC1N 1EH, UK

<sup>4</sup>NIHR Great Ormond Street Hospital Biomedical Research Centre, Great Ormond Street Institute of Child Health, University College London, Great Ormond Street Hospital Trust, London, UK

<sup>5</sup>Hospital Sant Joan de Déu Unidad de Patología Neuromuscular, Universidad de Barcelona, CIBERER, ISCIII, Barcelona, Spain

<sup>6</sup>Department of Pediatrics, Gothenburg University, Queen Silvia Children's Hospital, Gothenburg, Sweden

<sup>7</sup>Parent Project Italy APS, Rome, Italy

<sup>8</sup>Therapeutic Research in Neuromuscular Disorders Solutions, Pittsburgh, PA, USA

<sup>9</sup>Center for Genetic Medicine, Children's National Health System & the George Washington, Washington, DC, USA

<sup>10</sup>PTC Therapeutics Inc., South Plainfield, NJ 07080-2449, USA

<sup>11</sup>University of California Davis School of Medicine, Davis, CA, USA

<sup>12</sup>APHP Necker – Enfants Malades Hospital, Paris V Descartes University, Neuromuscular Network FILNEMUS, Paris, France

\*Author for correspondence: Tel.: +39 06 30155340; Fax: +39 06 30154386; [eumercuri@gmail.com](mailto:eumercuri@gmail.com)

‡STRIDE Registry Investigators (sorted by country): Austria: G Bernert, M Gosk-Tomek, A Ille, A Kellersmann, S Weiss (Vienna); V Pilshofer (Linz). Czech Republic: Z Bálintová, P Danhofer, P Fabulová, L Juřiková (Brno); P Fuchsová, J Haberlová (Prague). France: F Laffargue, C Sarret, B Pontier (Clermont Ferrand); R Bellance, E Sarrazin (Fort de France, Martinique); P Sabouraud (Reims); A Magot, S Mercier, Y Péréon (Nantes); J-M Cuisset, S Coopman-Degryse (former investigator) (Lille); E Enaud, M-L Jacquemont, A Perville, M Renouil (former investigator), V Trommsdorff, D Verheulpen (Saint-Pierre); S Fontaine-Carbonnel, C Vuillerot (Bron); S Peudenier, J Ropars (Brest); F Audic, B Chabrol (Marseille); S Chabrier, G Gousse (Saint-Etienne); E Lagrue (Tours); K Aragon (former investigator), C Barnerias, LV Brande, S De Lucia, I Desguerre, T Gidaro, A Seferian, L Servais (Paris); V Laugel (Strasbourg); C Espil-Taris (Bordeaux); H Mecili, E Raffo, S Ragot-Mandry (Vandoeuvre-lès-Nancy). Germany: S Borrell, J Kirschner (Freiburg); A Gangfuss, M Henrich, H Kölbl, U Schara, N Spönemann, E Temme (Essen); J Seeger (Frankfurt); A Hirsch (Fürth), J Denecke, J Johannsen, A Neu (Hamburg); D Osinski, S Rügner, S Schüssler, R Trollmann (Erlangen); A Kaindl, JB Schneider, C Stoltenburg, C Weiss (Berlin); G Schreiber (Kassel); A Hahn, M Grzybowski (Gießen). Greece: E Pavlidou, E Pavlou (Thessaloniki). Hungary: S Dobner, Z Liptai (Budapest). Israel: T Dor (Jerusalem). Italy: C Brogna, M Catteruccia, A D'Amico, E Mercuri, M Pane (Rome); L Bello, E Pegoraro, C Semplicini (Padua); E Albamonte, G Baranello, G Comi, A Govoni, A Lerario, F Magri, R Masson, E Mauri, V Sansone (Milan); C Brusa, T Mongini, F Ricci, M Vacchetti (Turin); C Bruno, C Paniucci, M Pedemonte (Genoa); M Giannotta, A Pini (Bologna); S Messina, M Sframenti, G Vita, G Vita (Messina); L Ruggiero, L Santoro (Naples). Romania: D Craiu (former investigator), C Motoescu, C Sandu, R Teleanu, D Vasile (Bucharest); Sweden: M Tulinius (Gothenburg). UK: I Hughes (Manchester), A-M Childs (Leeds), Z Alhaswani, H Roper (former investigator), D Parasuraman (Birmingham); C DeGoede (Preston); V Gowda, A Manzur, P Munot, A Sarkozky (London); C Charlesworth, J Lemon (former investigator), L Turner (former investigator), S Spinty (Liverpool).

§Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study Investigators (sorted by country): Argentina: A Dubrovsky (Buenos Aires). Australia: A Kornberg, M Ryan (Melbourne, VIC); R Webster (Sydney, NSW). Canada: WD Biggar, LC McAdam (Toronto, ON); JK Mah (Calgary, AB); H Kolski (Edmonton, AB). India: V Vishwanathan, S Chidambaranathan (Chennai). Israel: Y Nevo (Jerusalem). Italy: G Gorni (Milan). Puerto Rico: J Carlo (San Juan). Sweden: M Tulinius (Göteborg). USA: CM McDonald, EK Henricson, RT Abresch, NC Joyce (Sacramento, CA); A Cnaan, LP Morgenroth, R Leshner, C Tesi-Rocha, M Thangarajh, T Duong (Washington, DC); PR Clemens, H Abdel-Hamid (Pittsburgh, PA); AM Connolly, A Pestronk (St Louis, MO); J Teasley, A Harper (Richmond, VA); TE Bertorini (Memphis, TN); N Kuntz, S Driscoll (Rochester, MN); JW Day, P Karachunski (Minneapolis, MN); T Lotze (Houston, TX).

**Aim:** Strategic Targeting of Registries and International Database of Excellence (STRIDE) is an ongoing, multicenter registry providing real-world evidence regarding ataluren use in patients with nonsense mutation Duchenne muscular dystrophy (nmDMD). We examined the effectiveness of ataluren + standard of care (SoC) in the registry versus SoC alone in the Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS), DMD genotype–phenotype/–ataluren benefit correlations and ataluren safety. **Patients & methods:** Propensity score matching was performed to identify STRIDE and CINRG DNHS patients who were comparable in established disease progression predictors (registry cut-off date, 9 July 2018). **Results & conclusion:** Kaplan–Meier analyses demonstrated that ataluren + SoC significantly delayed age at loss of ambulation and age at worsening performance in timed function tests versus SoC alone ( $p \leq 0.05$ ). There were no DMD genotype–phenotype/ataluren benefit correlations. Ataluren was well tolerated. These results indicate that ataluren + SoC delays functional milestones of DMD progression in patients with nmDMD in routine clinical practice. **ClinicalTrials.gov identifier:** NCT02369731.

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**Keywords:** ataluren • dystrophin • effectiveness • nonsense mutation Duchenne muscular dystrophy • safety • STRIDE Registry

Duchenne muscular dystrophy (DMD) is a rare, progressive, X-linked neuromuscular disorder that is characterized by progressive muscle degeneration and weakness due to the absence of functional dystrophin protein [1,2]. Patients with DMD experience functional decline, loss of ambulation and ultimately premature death due to respiratory or cardiac failure [3]. DMD occurs in approximately 1 in every 3600–6000 live male births [1,3,4]. DMD is caused by either a deletion or duplication of one or more exons in the *DMD* gene, or by a small mutation in the gene, such as a small deletion or insertion, or a point (nonsense or missense), splice site or intronic mutation [5,6]. Deletions, insertions or duplications that result in a number of nucleotides that is no longer divisible by three shift the reading frame of the *DMD* gene, leading to the incorporation of aberrant amino acids into the dystrophin protein during translation, and often to the presence of premature stop codons in the dystrophin mRNA, resulting in a truncated protein [5]. In 10–15% of boys with DMD, the disorder is caused by a nonsense mutation in the *DMD* gene [2,6–8]. A nonsense mutation is a point mutation that does not affect the reading frame of the *DMD* gene, but creates a premature stop codon in the dystrophin mRNA, preventing the production of full-length, functional dystrophin protein [2,5–8]. Genetic testing is used to determine the presence of a nonsense mutation in the *DMD* gene [9].

Ataluren is an oral treatment for patients with nonsense mutation DMD (nmDMD), designed to promote ribosomal readthrough of an in-frame premature stop codon and thereby enable the production of full-length dystrophin protein [9–11]. It is indicated for the treatment of nmDMD in ambulatory patients aged 5 years or older in Brazil, Chile and Republic of Korea. More recently, the indication has expanded to include patients aged 2 years or older in member states of the European Union and Iceland, Israel, Liechtenstein and Norway [9]. Patients who do not have a nonsense mutation should not receive ataluren [9]. After an open-label Phase IIa study of ataluren (ClinicalTrials.gov identifier: NCT00264888) demonstrated increases in full-length dystrophin expression in patients with nmDMD treated with ataluren for 28 days [12], ataluren was evaluated in patients with nmDMD in Phase IIb (ClinicalTrials.gov identifier: NCT00592553) [13] and Phase III (ClinicalTrials.gov identifier: NCT01826487) randomized, double-blind, placebo-controlled trials [14]. These trials showed a benefit of ataluren (40 mg/kg per day) compared with placebo in a range of functional end points, including changes in 6-minute walk distance and timed function tests over 48 weeks, although the studies did not meet their primary end points [13,14]. Ataluren has been shown to be generally well tolerated and to have a favorable benefit–risk profile over a 48-week treatment period [13,14].

Strategic Targeting of Registries and International Database of Excellence (STRIDE; ClinicalTrials.gov identifier: NCT02369731) is an ongoing, observational, international registry of the safety and effectiveness of ataluren. STRIDE is the first drug registry for patients with nmDMD that will generate data on patterns of ataluren use and long-term patient outcomes in real-world routine clinical practice. Previously, we described the initial demographic characteristics of the study population in the STRIDE Registry, as of 9 July 2018 [15]. The Cooperative International Neuromuscular Research Group (CINRG) Duchenne Natural History Study (DNHS; ClinicalTrials.gov identifier:

NCT00468832) was a prospective, longitudinal study of more than 400 patients with DMD who were followed up between 2006 and 2016 at 20 worldwide centers as part of the academic clinical trial network, CINRG [16,17].

We aimed, first, to assess the safety of ataluren treatment in patients in the STRIDE Registry, as of the interim cut-off date of 9 July 2018; second, to assess the effectiveness of ataluren by comparing results from propensity score-matched patient populations from the STRIDE Registry and the CINRG DNHS. Third, we aimed to examine the link between DMD genotype and disease progression or ataluren treatment benefit in the STRIDE Registry, using age at first symptoms as a measure of disease progression and age at loss of ambulation as a measure of treatment benefit.

## Patients & methods

### Study design & methodology

Study design and data collection methodology for the STRIDE Registry and the CINRG DNHS have been described in full previously [15–17]. The STRIDE Registry is an ongoing, international, multicenter, observational, postapproval safety study of ataluren in patients with nmDMD, requested by the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency. It is underway in countries where ataluren is available commercially or through an early access program; additional countries may be added as ataluren becomes more widely accessible. Enrollment of patients in the STRIDE Registry began in March 2015, and all patients will be followed-up for at least 5 years from the date of their enrollment, or until withdrawal from the study or death [15]. The CINRG DNHS enrolled patients aged 2–28 years with DMD at 20 centers in nine countries from 2006 to 2016 [16,17]. Data from CINRG DNHS patients receiving standard of care (SoC) are used in the present analysis as a control to provide context for assessing the effects of ataluren plus SoC in patients in the STRIDE Registry. SoC refers to palliative therapies and corticosteroid treatment.

### Patient eligibility & enrollment

#### *STRIDE Registry*

Patient eligibility for the STRIDE Registry and information regarding the study size have been described in full previously [15]. Briefly, patients are eligible to participate in the STRIDE Registry if they have a confirmed genetic diagnosis of DMD and if they are, or will be, receiving usual care treatment with a commercial supply of ataluren (or receiving care within an early access program), and are willing to provide written informed consent for data collection procedures by themselves or a parent/legal guardian. Patients who are receiving ataluren or placebo in an ongoing, blinded, randomized clinical trial or ataluren in any other ongoing clinical trial or early access program that prevents participation in the current registry are not eligible to enroll in the STRIDE Registry, although those receiving ataluren can become eligible once they have completed the required follow-up, and fulfilled the conditions of the trial or early-access program. Data cut-off for inclusion in the present analyses was on 9 July 2018, the same date as that for the patient demographic analyses [15].

#### *CINRG DNHS*

Patient eligibility for the CINRG DNHS has been described previously [16,17]. Briefly, to be eligible to participate in the CINRG DNHS, patients aged 2–4 years were required to have a diagnosis of DMD confirmed by one or more of the following: dystrophin immunofluorescence, immunoblot, an out-of-frame deletion or complete dystrophin gene sequencing in the proband or sibling [16,17]. Patients aged 5–28 years were required to meet the same criteria or to have documented clinical symptoms referable to DMD. Direct support of the diagnosis by either a positive DNA analysis, a muscle biopsy showing abnormal dystrophin or a combination of increased creatine kinase levels (>five-times the upper limit of normal) in addition to an X-linked pedigree was also required [16,17]. In total, 440 patients were enrolled in the CINRG DNHS [16,17]. Patients were excluded from the present analyses if they received investigational drugs in previous clinical trials. Nonambulatory patients from the CINRG DNHS were defined in the same way as for those from the STRIDE Registry (requiring full-time use of a wheelchair).

### Statistical analyses

#### *Study populations*

In the STRIDE Registry, the evaluable population is defined as male patients who provided informed consent and did not fail screening, and the safety population is defined as all patients who received at least one dose of ataluren. The effectiveness population is defined as the subset of the evaluable population with confirmed nmDMD

(e.g., patients with a frameshift mutation are excluded) who received at least one dose of ataluren in the registry and did not have missing data for age at loss of ambulation, age at first symptoms, age at first corticosteroid use, duration of deflazacort use and duration of other corticosteroid use.

#### *STRIDE Registry safety & clinical laboratory data*

Adverse events (AEs) were coded using the Medical Dictionary for Regulatory Activities (version 20.1). A treatment-emergent AE (TEAE) is defined as an AE that occurs while the patient is receiving ataluren. Any AE with an end date before the date of first recorded use of ataluren, either commercially or through an early access program, was excluded from the TEAE summaries. Clinical laboratory, ECG and heart rhythm evaluations, as well as hypertension status and resting pulse categories were tabulated using frequency and percentage count. The clinical significance of abnormal biochemistry and ECG results was determined by the clinician. The hypertension status (normal, prehypertension and hypertension) was derived based on age, sex and height-adjusted systolic blood pressure and diastolic blood pressure percentile results (hypertensive:  $\geq 95$ th percentile; prehypertensive: 90th to  $< 95$ th percentile; normal:  $< 90$ th percentile) [18]. The resting pulses were classified into three categories (low, normal and elevated) based on the following normal ranges for different age groups: 3–4 years, 73–137 beats per minute (bpm); 5–7 years, 65–133 bpm; 8–11 years, 62–130 bpm; 12–15 years, 80–119 bpm;  $> 16$  years, 60–100 bpm.

#### *STRIDE Registry & CINRG DNHS data comparisons*

To eliminate bias and to enable a robust comparison between the STRIDE Registry and the CINRG DNHS, propensity score matching was performed to identify a subset of patients in the CINRG DNHS who were comparable to patients in the STRIDE Registry according to established predictors of disease progression. Propensity score matching is a method used to estimate the effect of receiving treatment when random assignment of patients to treatments is not possible [19], and has been used in recent studies to balance characteristics of patients according to covariates across cohorts to achieve comparable groups [20,21]. The propensity score was created using a logistic regression model with the following covariates: age at first clinical symptoms, age at first corticosteroid use, duration of deflazacort use ( $< 1$  month,  $\geq 1$  to  $< 12$  months,  $\geq 12$  months); and duration of other corticosteroid use ( $< 1$  month,  $\geq 1$  to  $< 12$  months,  $\geq 12$  months). Age at first symptoms is prognostic for severity of disease: the earlier the age of symptom onset, the more severe and rapid the course of disease progression. A 1-year increase in the age at onset of first symptoms was associated with a 10% reduction in annual risk of loss of ambulation for a cohort of patients with either DMD or Becker muscular dystrophy [22]. Age at first corticosteroid use, duration of corticosteroid use and duration of deflazacort use represent key factors that are known to alter the course of the disease [16,23]. Corticosteroid-naïve patients without age at first corticosteroid use data were captured in the propensity score calculations by imputing their age at first corticosteroid use as 30 years. Once the propensity score was calculated, a local optimal (greedy) algorithm based on the nearest neighbor approaches without replacement was used to find the matching controls [24]. Using the local optimal algorithms approach, patients from both the STRIDE Registry and the CINRG DNHS were first randomly sorted. The first patient from the STRIDE Registry was selected to find the closest matching patient from the CINRG DNHS, based on the absolute value of the difference between their propensity scores (predicted probability from the logistic regression model). The patient from the CINRG DNHS with the closest propensity score was selected as the matching control and was no longer available for further matching. This procedure was repeated for all patients from the STRIDE Registry for a one-to-one match.

The primary objective of the propensity score-matched analyses was to use Kaplan–Meier estimates and Cox regression to estimate the distribution of age at loss of ambulation (birth-to-event) among STRIDE Registry patients and matched CINRG DNHS patients. Kaplan–Meier estimates and Cox regression were also used to estimate the distribution of the following secondary time-to-event variables for propensity score-matched STRIDE and CINRG DNHS patients with available data: age when time to stand from supine was greater than or equal to 5 s or greater than or equal to 10 s, age when time to climb four stairs was greater than or equal to 5 s or greater than or equal to 10 s, age when predicted forced vital capacity (FVC) was less than 60%, age when predicted FVC was less than 50%, age when FVC was less than 1 l, age when left ventricular ejection fraction (LVEF) was less than 55% and age when shortening fraction (SF) was less than 28%. All of these milestones reflect the natural disease progression of DMD [16,25–27]. Patients were excluded from these analyses if they had already reached the event milestone before their first assessment in the study; if they did not reach the event milestone, they were

censored at the age of their last assessment. The age at event milestone for patients who did reach the event was defined as the age at the first time they reached the event. An FVC below a threshold of 1 l is strongly predictive of subsequent mortality in approximately 3 years and is associated with a fourfold increase in the risk of death [16,28]. Patients with a predicted FVC of less than 60% are considered to have clinically relevant lung volume restriction, and should be treated with lung volume recruitment [26]. Those with a predicted FVC of less than 50% are considered in the late nonambulatory stage of DMD, and should be treated with manual or mechanically assisted coughing [26]. Cardiomyopathy was defined as age when LVEF was less than 55% or age when SF was less than 28% [27]. For each of the time-to-event variables, the median was produced for the STRIDE Registry and CINRG DNHS populations separately, along with the 95% CI constructed based on log–log transformation. Distribution of the variables was compared between the STRIDE Registry and CINRG DNHS populations using a log-rank test stratified by the duration of deflazacort use and the duration of other corticosteroid use (<1 month, ≥1 to <12 months, ≥12 months). The corticosteroid durations are calculated up to the time at loss of ambulation or the latest time that the patient was still known to be ambulatory. Gaps between corticosteroid use were excluded, and the overlap of different corticosteroid use was not double counted. The hazard ratio (HR; STRIDE Registry vs CINRG DNHS) and the corresponding 95% CI were calculated using a Cox proportional hazard model stratified by durations of corticosteroid use, with study (CINRG DNHS or STRIDE), age at first symptoms and age at initiation of corticosteroid use as covariates.

### *Genotype–phenotype & genotype–treatment benefit analyses*

Using data from the STRIDE Registry, correlation analyses were performed to determine whether there is a relationship between the exon location of the nonsense mutation in the *DMD* gene and age at first symptoms, and between the type of stop codon and age at loss of ambulation. Age at first symptoms was used as a measure of disease severity and age at loss of ambulation as a measure of treatment benefit. A scatter diagram was used to graphically display the relative relationship between mutation location and disease severity, and differences in mean age at first symptoms across the mutation locations were analyzed using the analysis of variance method. Kaplan–Meier analyses were performed to determine whether ataluren treatment benefit, as assessed by the age at loss of ambulation, was dependent on the stop codon type. Age at loss of ambulation was evaluated using a log-rank test, and the median age at loss of ambulation was estimated using the Kaplan–Meier estimator. Exon locations and stop codon types were deduced from the STRIDE Registry mutation data collected using the online mutational analysis *DMD* Open-access Variant Explorer tool ([www.dmd.nl/DOVE/](http://www.dmd.nl/DOVE/)) [29].

## Results

### Patient disposition

As of 9 July 2018, 217 patients with nmDMD (Supplementary Figure 1) from 11 countries with 53 active study sites were enrolled in the STRIDE Registry; of these, three patients were girls and one patient failed screening. Of the 213 male patients who provided informed consent and did not fail screening (the evaluable population), all 213 patients received at least one dose of ataluren and were therefore included in the safety population. The 181 patients with confirmed nmDMD were included in the effectiveness population. The following 32 patients were excluded from the effectiveness population for the stated reasons: nine patients had frameshift mutations for which ataluren is not indicated [9], 18 patients had missing age at first symptoms data and five patients had an age at first symptoms equal to 0 years. Full details of the disposition of patients enrolled in the STRIDE Registry, the number of active countries, number of study sites and distribution of patients per country have been reported previously [15]. Data from 400 patients in the CINRG DNHS were utilized for comparisons with those from patients in the STRIDE Registry; 22 patients in the CINRG DNHS were excluded because they had participated in clinical trials of ataluren or had received eteplirsén, drisapersén or tadalafil. A further 18 patients were excluded because they had missing data for age at loss of ambulation and age at first symptoms.

### Safety of ataluren

TEAEs were reported for 43 patients (20.2%), who experienced a total of 117 TEAEs (Table 1). Of the 43 patients who experienced TEAEs, four did not use corticosteroids. TEAEs were mostly mild or moderate and were mostly not related to ataluren. None of the TEAEs were life-threatening, and there were no deaths as of the cut-off date. Three patients (1.4%), all of whom used corticosteroids, experienced TEAEs that led to discontinuation of ataluren.

**Table 1. Treatment-emergent adverse events<sup>†</sup> experienced by patients in the evaluable population of the STRIDE registry.**

| TEAEs   | Corticosteroid use |             |              |
|---|--------------------|-------------|--------------|
|   | Yes (n = 190)      | No (n = 23) | All (n= 213) |
| Number of TEAEs <sup>†</sup>  | 96                 | 21          | 117          |
| <b>Patients with at least one of the following</b>                  |                    |             |              |
| TEAE  | 39 (20.5)          | 4 (17.4)    | 43 (20.2)    |
| TEAE related to ataluren  | 4 (2.1)            | 1 (4.3)     | 5 (2.3)      |
| TEAE leading to discontinuation of ataluren                         | 3 (1.6)            | 0 (0.0)     | 3 (1.4)      |
| SAE   | 10 (5.3)           | 2 (8.7)     | 12 (5.6)     |
| <b>TEAE with maximum severity<sup>‡,§</sup></b>                     |                    |             |              |
| Not reported  | 2 (1.1)            | 0 (0.0)     | 2 (0.9)      |
| Unknown   | 2 (1.1)            | 0 (0.0)     | 2 (0.9)      |
| Mild  | 16 (8.4)           | 0 (0.0)     | 16 (7.5)     |
| Moderate  | 15 (7.9)           | 3 (13.0)    | 18 (8.5)     |
| Severe  | 4 (2.1)            | 1 (4.3)     | 5 (2.3)      |
| Life-threatening  | 0 (0.0)            | 0 (0.0)     | 0 (0.0)      |
| <b>Patients with at least one of the following<sup>‡,¶,#</sup></b>  |                    |             |              |
| Injury, poisoning and procedural complications <sup>‡</sup> :       | 11 (5.8)           | 1 (4.3)     | 12 (5.6)     |
| – Fall  | 2 (1.1)            | 0 (0.0)     | 2 (0.9)      |
| – Femur fracture  | 3 (1.6)            | 1 (4.3)     | 4 (1.9)      |
| – Humerus fracture  | 2 (1.1)            | 0 (0.0)     | 2 (0.9)      |
| – Ligament sprain   | 2 (1.1)            | 0 (0.0)     | 2 (0.9)      |
| Infections and infestations <sup>‡</sup> :                          | 8 (4.2)            | 2 (8.7)     | 10 (4.7)     |
| – Gastroenteritis   | 3 (1.6)            | 0 (0.0)     | 3 (1.4)      |
| – Nasopharyngitis   | 2 (1.1)            | 0 (0.0)     | 2 (0.9)      |
| – Upper respiratory tract infection                                 | 2 (1.1)            | 0 (0.0)     | 2 (0.9)      |
| General disorders and administration-site conditions <sup>‡</sup> : | 8 (4.2)            | 1 (4.3)     | 9 (4.2)      |
| – Gait inability  | 6 (3.2)            | 1 (4.3)     | 7 (3.3)      |
| – Pyrexia   | 2 (1.1)            | 0 (0.0)     | 2 (0.9)      |
| Gastrointestinal disorders <sup>‡</sup> :                           | 7 (3.7)            | 1 (4.3)     | 8 (3.8)      |
| – Abdominal pain  | 1 (0.5)            | 1 (4.3)     | 2 (0.9)      |
| – Diarrhea  | 4 (2.1)            | 0 (0.0)     | 4 (1.9)      |
| – Vomiting  | 3 (1.6)            | 1 (4.3)     | 4 (1.9)      |
| Musculoskeletal and connective tissue disorders <sup>‡</sup> :      | 8 (4.2)            | 0 (0.0)     | 8 (3.8)      |
| – Back pain   | 3 (1.6)            | 0 (0.0)     | 3 (1.4)      |
| – Rhabdomyolysis; myoglobinuria                                     | 2 (1.1)            | 0 (0.0)     | 2 (0.9)      |
| Respiratory, thoracic and mediastinal disorders <sup>‡</sup>        | 4 (2.1)            | 1 (4.3)     | 5 (2.3)      |
| Cough   | 4 (2.1)            | 0 (0.0)     | 4 (1.9)      |
| Nervous system disorders <sup>‡</sup>                               | 3 (1.6)            | 1 (4.3)     | 4 (1.9)      |
| Headache  | 2 (1.1)            | 1 (4.3)     | 3 (1.4)      |
| Investigations <sup>‡</sup>   | 3 (1.6)            | 0 (0.0)     | 3 (1.4)      |
| Increased lipids  | 2 (1.1)            | 0 (0.0)     | 2 (0.9)      |

Data represented as n (%).

<sup>†</sup>TEAE is defined as any AE with an end date on or after the first date of ataluren use. Events with missing severity are not reported.

<sup>‡</sup>TEAE categories.

<sup>§</sup>For patients with two or more AEs, the event with the maximum severity was reported. The order of severity is: ‘Not reported’, ‘Unknown’, ‘Mild’, ‘Moderate’, ‘Severe’ and ‘Life-threatening’.

<sup>¶</sup>AEs were coded using the Medical Dictionary for Regulatory Activities (version 20.1)

<sup>#</sup>A patient who reported at least one occurrence with the same preferred term was counted only once for that term.

AE: Adverse event; SAE: Serious adverse event; STRIDE: Strategic Targeting of Registries and International Database of Excellence; TEAE: Treatment-emergent adverse event.

The most common TEAEs (in >1% of patients) were gait inability (3.3% [seven patients]), cough, diarrhea, femur fracture, vomiting (1.9% [four patients] each), back pain, gastroenteritis and headache (1.4% [three patients] each).

12 patients (5.6%) experienced serious adverse events (SAEs; [Table 1](#)). Of these, ten used corticosteroids and two did not. Two patients reported humerus fractures and two patients reported femur fractures; of these, one patient with a femur fracture did not use corticosteroids. The following SAEs were reported in one patient each: appendicitis, orchidopexy, rhabdomyolysis, left ventricular dysfunction, joint surgery, gastroenteritis and fall. One patient experienced acute respiratory decompensation, pneumonia and secretion retention. All SAEs in all patients were determined by the investigator to be unrelated to ataluren treatment except for left ventricular dysfunction, of which the causal relationship to ataluren was determined as 'unknown' by the investigator.

TEAEs in five patients (2.3%) were considered to be related to ataluren; of these patients, four used corticosteroids and one did not. TEAEs considered related to ataluren included: abdominal pain (one patient), abdominal pain and diarrhea (one patient), abdominal pain and vomiting (one patient), headache (one patient) and increased lipids (one patient). TEAEs in five patients (2.3%) were considered severe; of these patients, four used corticosteroids and one did not. TEAEs considered severe included acute respiratory decompensation and secretion retention (one patient), femur fracture (one patient), femur fracture and gait inability (one patient), gait inability (one patient) and gastroenteritis (one patient); all were determined by the investigator to be unrelated to ataluren.

Laboratory results, including serum lipid profiles, vital signs and cardiac measurements, for patients receiving ataluren are shown in [Supplementary Tables 2–5](#). Clinically significant laboratory abnormalities were infrequent, and no clinically meaningful trends were observed in these laboratory assessments. The numbers of patients who experienced a shift in results from normal at the time of the first assessment to a value considered significantly abnormal by the investigator at subsequent assessments for HDL, LDL, triglycerides and total cholesterol were infrequent (HDL, 1 [1.2%] of 66; LDL, 2 [2.5%] of 67; triglycerides, 5 [4.8%] of 80; total cholesterol, 4 [3.4%] of 87; [Supplementary Table 2](#)). Owing to the potential confounding factor posed by corticosteroid use on lipid assessments, shifts in serum lipid parameters are also summarized for the subgroup of patients who did not use corticosteroids ([Supplementary Table 3](#)). No shifts in results from normal at the time of the first assessment to clinically significantly abnormal were noted in ataluren-treated patients who did not use corticosteroids.

Of the 75 patients (53.6%) who had normal blood pressure values at the time of the first assessment, 16 (11.4%) experienced a shift in values from normal to prehypertensive and 18 (12.9%) experienced a shift in values from normal to hypertensive ([Supplementary Table 4](#)). All but one of the patients with a shift in blood pressure values from normal to prehypertensive were patients who used corticosteroids. The same was true for patients with a shift in blood pressure from normal to hypertensive. Six patients (4.3%) who were prehypertensive at the time of the first assessment shifted to a normotensive status. Shifts in pulse rate from normal at the first assessment to elevated or low rates were infrequent and observed only in patients who used corticosteroids ([Supplementary Table 4](#)). Of the 90 patients (42.3%) with at least two ECG assessments, three patients experienced shifts in ECG results from normal at the first assessment to clinically significantly abnormal ([Supplementary Table 5](#)). There were no shifts from normal at the time of first assessment to clinically significant abnormalities in hepatic enzymes (AST, ALT, GGT and total bilirubin) or in renal test results for blood urea nitrogen and cystatin C ([Supplementary Table 6](#)). As expected for patients with DMD, many patients had abnormally low levels of serum creatinine at first assessment and throughout the study; one patient shifted from normal at the time of first assessment to a clinically significant abnormality [30].

### Patient demographics & characteristics

A comparison between the STRIDE Registry effectiveness population (n = 181) and the unmatched CINRG DNHS population (n = 400) revealed differences between the populations ([Table 2](#)). Propensity matching of the CINRG DNHS population yielded a population (n = 181) that was more comparable to the STRIDE Registry population (n = 181) with respect to age at first clinical symptoms, age at first corticosteroid use, duration of deflazacort use and duration of other corticosteroid use, which provided a relevant basis for comparison ([Table 2](#) & [Supplementary Figure 2](#)). Median durations of total exposure to corticosteroids in the unmatched populations from the STRIDE Registry and the CINRG DNHS were 568 days (n = 181; range, 0–5404; 95% CI: 822–1169) and 997 days (n = 400; range, 0–5970; 95% CI: 1154–1398), respectively; after matching, median durations were 568 days (n = 181; range, 0–5404; 95% CI: 822–1169) and 563 days (n = 181; range, 0–5254; 95% CI: 807–1149), respectively ([Table 2](#)). Most other patient demographic and disease characteristics were similar between the propensity score-matched populations of the STRIDE Registry and CINRG DNHS ([Supplementary](#)



**Table 2. Demographics of patients in the STRIDE Registry and CINRG DNHS before and after propensity-score matching.**

| Demographic  | Unmatched population |                         | Propensity-matched population |                         |
|--|----------------------|-------------------------|-------------------------------|-------------------------|
|  | STRIDE (n = 181)     | CINRG (n = 400)         | STRIDE (n = 181)              | CINRG (n = 181)         |
| <b>Age at first symptoms (years)</b>   |                      |                         |                               |                         |
| – Mean (SD)  | 2.80 (1.71)          | 3.22 (1.69)             | 2.80 (1.71)                   | 2.92 (1.64)             |
| – SE   | 0.13                 | 0.08                    | 0.13                          | 0.12                    |
| – 95% CI   | 2.55–3.05            | 3.05–3.38               | 2.55–3.05                     | 2.68–3.16               |
| – Median   | 2.50                 | 3.00                    | 2.50                          | 3.00                    |
| – Min–max  | 0.10–8.00            | 0.00 <sup>†</sup> –8.00 | 0.10–8.00                     | 0.00 <sup>†</sup> –8.00 |
| – p-value  | 0.0060               |                         | 0.4766                        |                         |
| <b>Age at first corticosteroid use (excluding corticosteroid-naïve patients)<sup>‡</sup> (years)</b> |                      |                         |                               |                         |
|  | n = 123              | n = 317                 | n = 123                       | n = 119                 |
| – Mean (SD)  | 6.87 (2.32)          | 6.74 (2.05)             | 6.87 (2.32)                   | 6.93 (2.27)             |
| – SE   | 0.21                 | 0.12                    | 0.21                          | 0.21                    |
| – 95% CI   | 6.46–7.29            | 6.51–6.97               | 6.46–7.29                     | 6.51–7.34               |
| – Median   | 6.47                 | 6.57                    | 6.47                          | 6.87                    |
| – Min–max  | 2.93–13.24           | 1.99–14.25              | 2.93–13.24                    | 2.71–14.25              |
| – p-value  | 0.5540               |                         | 0.8607                        |                         |
| <b>Deflazacort duration,<sup>§</sup> n (%)</b>   |                      |                         |                               |                         |
| – <1 month or corticosteroid-naïve   | 126 (69.6)           | 235 (58.8)              | 126 (69.6)                    | 131 (72.4)              |
| – ≥1 to <12 months   | 9 (5.0)              | 20 (5.0)                | 9 (5.0)                       | 4 (2.2)                 |
| – ≥12 months   | 46 (25.4)            | 145 (36.3)              | 46 (25.4)                     | 46 (25.4)               |
| – p-value  | 0.0331               |                         | 0.3642                        |                         |
| <b>Other corticosteroid duration,<sup>§</sup> n (%)</b>  |                      |                         |                               |                         |
| – <1 month or corticosteroid-naïve   | 107 (59.1)           | 205 (51.3)              | 107 (59.1)                    | 110 (60.8)              |
| – ≥1 to <12 months   | 11 (6.1)             | 35 (8.8)                | 11 (6.1)                      | 12 (6.6)                |
| – ≥12 months   | 63 (34.8)            | 160 (40.0)              | 63 (34.8)                     | 59 (32.6)               |
| – p-value  | 0.1795               |                         | 0.8976                        |                         |
| <b>Total exposure to corticosteroids (days)</b>  |                      |                         |                               |                         |
| – Mean (SD)  | 995 (1184)           | 1276 (1236)             | 995 (1184)                    | 978 (1166)              |
| – SE   | 88                   | 62                      | 88                            | 87                      |
| – 95% CI   | 822–1169             | 1154–1398               | 822–1169                      | 807–1149                |
| – Median   | 568                  | 997                     | 568                           | 563                     |
| – Min–max  | 0–5404               | 0–5970                  | 0–5404                        | 0–5254                  |
| – p-value  | 0.0105               |                         | 0.8882                        |                         |
| <b>Treatment follow-up duration (days)</b>   |                      |                         |                               |                         |
| – Mean (SD)  | 632 (363)            | 1655 (1023)             | 632 (363)                     | 1590 (1013)             |
| – SE   | 27                   | 51                      | 27                            | 75                      |
| – 95% CI   | 579–686              | 1554–1755               | 579–686                       | 1441–739                |
| – Median   | 616                  | 1796                    | 616                           | 1811                    |
| – Min–max  | 5–1453               | 0–3540                  | 5–1453                        | 0–3485                  |
| – p-value  | <0.0001              |                         | <0.0001                       |                         |

Propensity-score model covariates include age at first symptoms, age at first corticosteroid use, duration of deflazacort and duration of use of corticosteroids other than deflazacort.

<sup>†</sup>A minimum age value of 0 years is due to a prenatal diagnosis.

<sup>‡</sup>Corticosteroid-naïve patients were excluded to calculate the true age at first corticosteroid use. Corticosteroid-naïve patients without age at first corticosteroid use data were captured by imputing their age at first corticosteroid use as 30 years; these data were imputed into the propensity-score calculations.

<sup>§</sup>Corticosteroid duration is calculated from the date at which corticosteroid use was started to the date of loss of ambulation or the date of the last assessment. The same patient may be included in both the ‘deflazacort duration’ and ‘other corticosteroid duration’ groups if they had received both deflazacort or another corticosteroid at any one-time.

CINRG DNHS: Cooperative International Neuromuscular Research Group Duchenne Natural History Study; max: Maximum; min: Minimum; SD: Standard deviation; SE: Standard error; STRIDE: Strategic Targeting of Registries and International Database of Excellence.

Table 1). Age at the last assessment was higher for the matched population from the CINRG DNHS than for that from the STRIDE Registry, in line with a longer follow-up treatment period for patients in the CINRG DNHS. Median durations of treatment follow-up in the unmatched populations from the STRIDE Registry and the CINRG DNHS were 616 days (n = 181; range, 5–1453; 95% CI: 579–686) and 1796 days (n = 400; range, 0–3540; 95% CI: 1554–1755), respectively; after matching, median durations were 616 days (n = 181; range, 5–1453; 95% CI: 579–686) and 1811 days (n = 181; range, 0–3485; 95% CI: 1441–1739), respectively. The mean (standard deviation [SD]) exposure to ataluren of the propensity-matched STRIDE Registry population was 632.5 (362.9) days, a total of 313.4 patient-years. Patient demographics and disease characteristics of the STRIDE Registry evaluable population (n = 213) have been described previously [15].

## Effectiveness of ataluren

### *Age at loss of ambulation*

The median (95% CI) age at loss of ambulation for the matched STRIDE Registry and CINRG DNHS populations was 14.5 years (13.9, not available [NA]) and 11.0 years (10.5, 12.0), respectively, demonstrating a statistically significant difference in favor of ataluren treatment ( $p < 0.0001$ ; HR: 0.283; [Figure 1](#)). Of the 181 propensity-score matched patients, three patients in the STRIDE Registry (1.7%) and 41 patients in the CINRG DNHS (22.7%) lost ambulation before the age of 10 years. There were 13 patients in the STRIDE Registry (7.2%; as of 9 July 2018) and six patients in the CINRG DNHS (3.3%; as of 19 March 2018) who were still ambulatory after the age of 15 years.

### *Age at worsening of timed function test results*

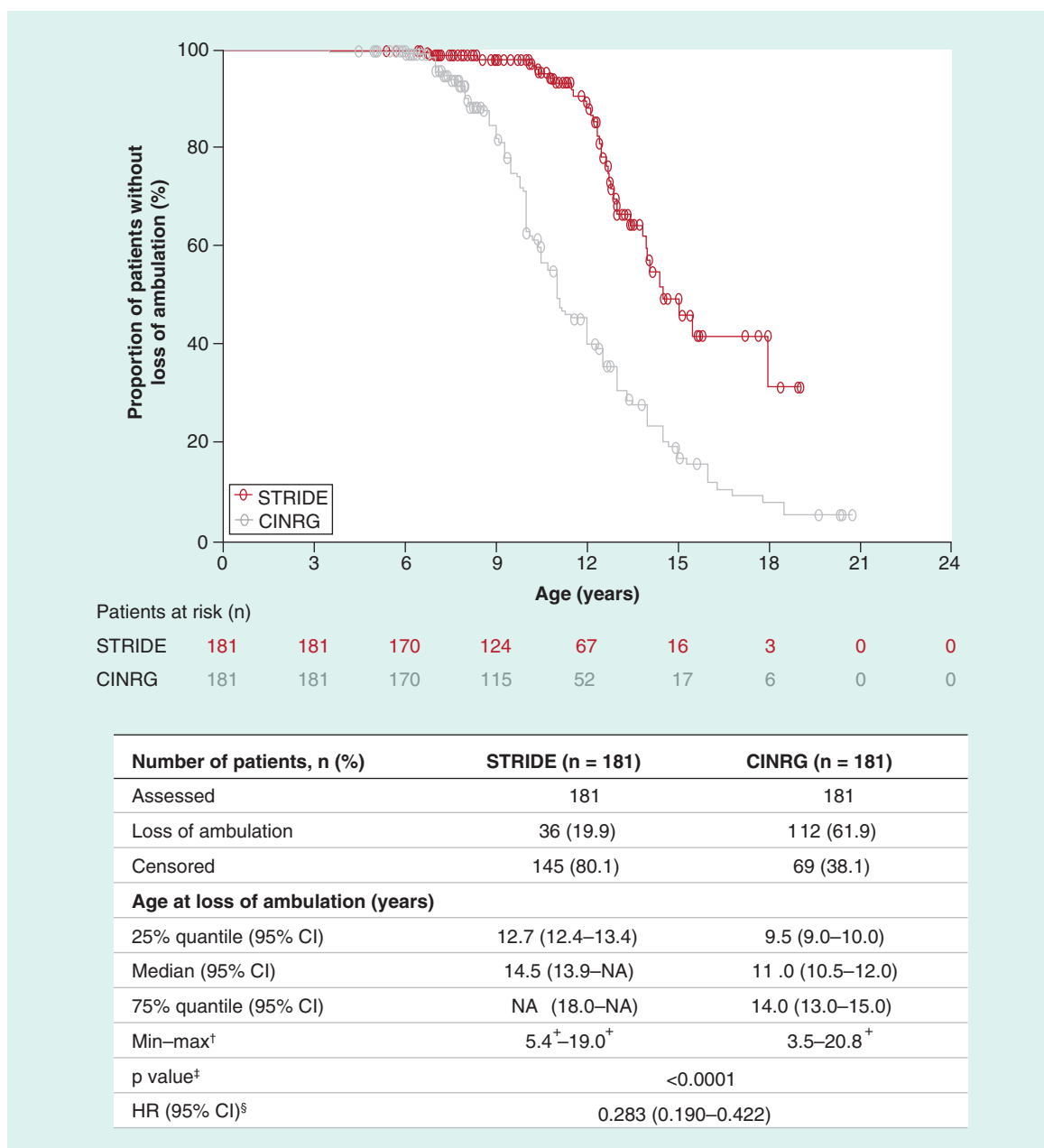
Compared with propensity score-matched patients from the CINRG DNHS, patients from the STRIDE Registry receiving ataluren were older when their time to stand from supine worsened to greater than or equal to 5 s (median age [95% CI]: STRIDE, 12.0 years [8.5, 16.8]; CINRG, 9.1 years [8.1, 9.7];  $p = 0.0031$ ; HR: 0.241) and greater than or equal to 10 s (median age [95% CI]: STRIDE, 14.0 years [11.8, 18.6]; CINRG, 9.9 years [9.6, 11.4];  $p = 0.0008$ ; HR: 0.290; [Figure 2](#)). Patients from STRIDE were also older than matched patients from CINRG when their time to climb four stairs worsened to greater than or equal to 5 s (median age [95% CI]: STRIDE, 12.3 years [10.9, 14.0]; CINRG, 10.9 years [8.7, 12.3];  $p = 0.0386$ ; HR, 0.400) and greater than or equal to 10 s (median not reached; 25% quantile [95% CI]: STRIDE, 13.4 years [9.9, NA]; CINRG, 9.8 years [9.0, 11.6];  $p = 0.0195$ ; HR: 0.385; [Figure 3](#)).

### *Age at worsening of pulmonary & cardiac functions*

The ages at worsening of pulmonary functions for patients in the propensity score-matched STRIDE Registry and CINRG DNHS populations, as measured by reductions in predicted FVC to lower than 60% or 50% and FVC to lower than 1 l are shown in [Table 3](#). These results suggest a trend toward delayed worsening of pulmonary function for patients in STRIDE compared with those in CINRG DNHS. However, given the low number of events, and the shorter duration of follow-up on ataluren treatment in the STRIDE Registry in comparison to the CINRG DNHS cohort, it is premature to draw firm conclusions from these results. The age at worsening of cardiac functions by echocardiography, as measured by reductions in LVEF to lower than 55% and SF to lower than 28%, are shown in [Supplementary Table 7](#). Similarly, owing to the short duration of follow-up and slow progression of cardiomyopathy in DMD, conclusions could not yet be made on the cardiac function results.

### *Effect of DMD genotype on disease severity & ataluren treatment benefit*

For patients with nmDMD in the effectiveness population of the STRIDE Registry (n = 181), no difference in age at first symptoms was observed among the DMD nonsense mutation locations ( $p = 0.4114$ ), indicating that the nonsense mutation location had no significant effect on disease severity ([Figure 4](#)). Furthermore, there was no significant effect observed of the type of premature stop codon on the age at loss of ambulation (point estimate for 25% quantile of age at loss of ambulation [95% CI]: UAA [n = 41], 12.72 [10.41–13.44] years; UAG [n = 68], 12.79 [12.20–14.52] years; UGA [n = 72], 12.46 [10.95–13.86] years;  $p = 0.1966$ ), demonstrating that the type of premature stop codon in patients with nmDMD did not influence their treatment benefit ([Figure 5](#)).



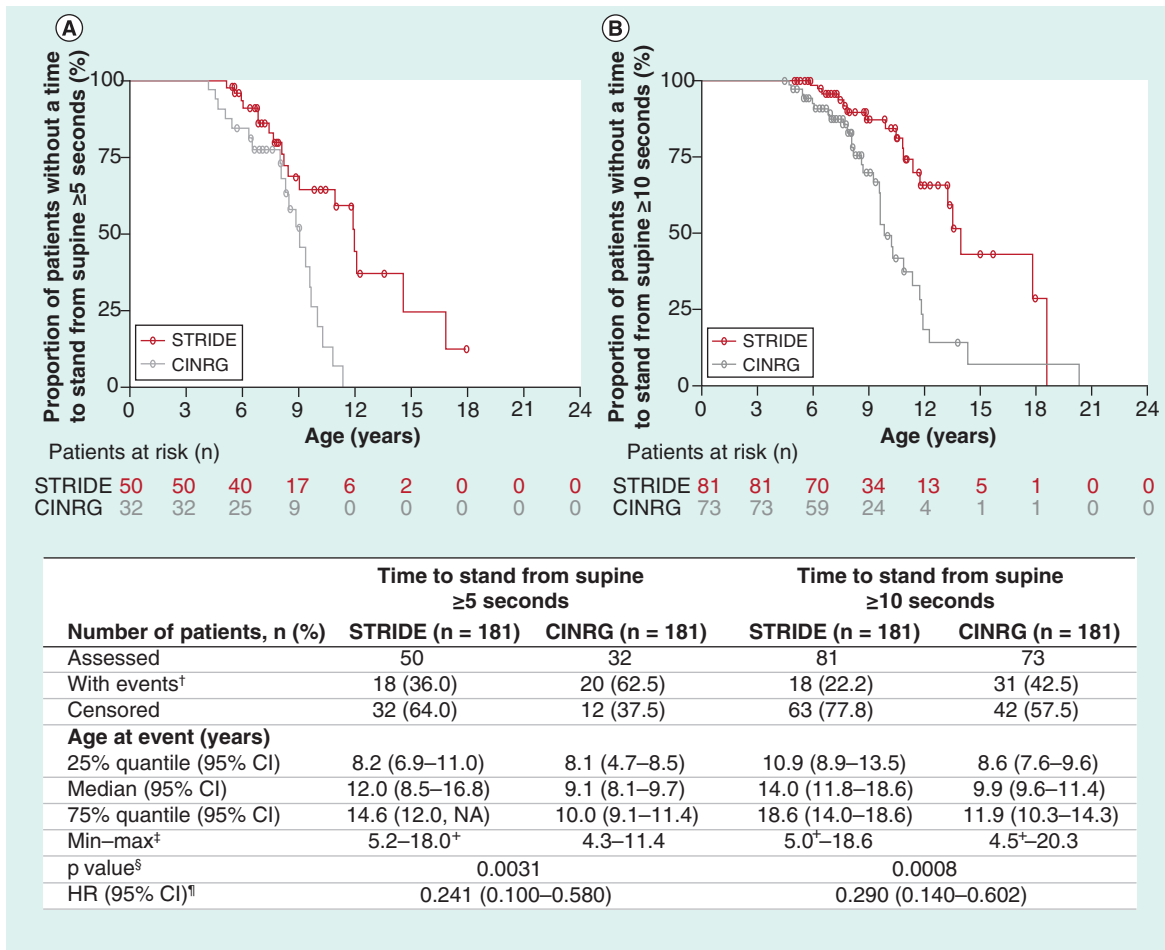
**Figure 1. Age at loss of ambulation for propensity-score matched patients from the STRIDE Registry and CINRG DNHS.** Propensity-score model covariates include age at first symptoms, age at first corticosteroid use, duration of deflazacort use and duration of use of corticosteroids other than deflazacort. Censor dates for censored patients in the STRIDE Registry were derived from the last assessment date across treatment, physical examination, vital signs, 6-minute walk distance, timed function tests, North Star Ambulatory Assessments, percentage of predicted FVC and upper limb function tests. Corticosteroid duration is calculated from the date at which corticosteroid use was started to the date of loss of ambulation or the date of the last assessment.

<sup>†††</sup> indicates a censored observation.

<sup>‡</sup>p-value is from a log-rank test stratified by deflazacort and other corticosteroid usage durations.

<sup>§</sup>HR is from stratified (by durations of deflazacort and other corticosteroid use) Cox regression with study, age at first symptoms and age at first corticosteroid use as covariates. The HR is STRIDE Registry versus CINRG DNHS.

CINRG DNHS: Cooperative International Neuromuscular Research Group Duchenne Natural History Study; FVC: Forced vital capacity; HR: Hazard ratio; max: Maximum; min: Minimum; NA: Not available; STRIDE: Strategic Targeting of Registries and International Database of Excellence.



**Figure 2. Age at time to stand from supine (A) ≥5 s and (B) ≥10 s for propensity-score matched patients from the STRIDE Registry and CINRG DNHS.** Propensity-score model covariates include age at first symptoms, age at first corticosteroid use, duration of deflazacort use and duration of use of corticosteroids other than deflazacort. Censor dates for censored patients in the STRIDE Registry were derived from the last assessment date across treatment, physical examination, vital signs, 6-minute walk distance, timed function tests, North Star Ambulatory Assessments, percentage of predicted FVC and upper limb function tests. Corticosteroid duration is calculated from the date at which corticosteroid use was started to the date of loss of ambulation or the date of the last assessment.

†Event = time to stand from supine ≥5 s or ≥10 s.

‡'+ indicates a censored observation.

§p-value is from a log-rank test stratified by deflazacort and other corticosteroid usage durations.

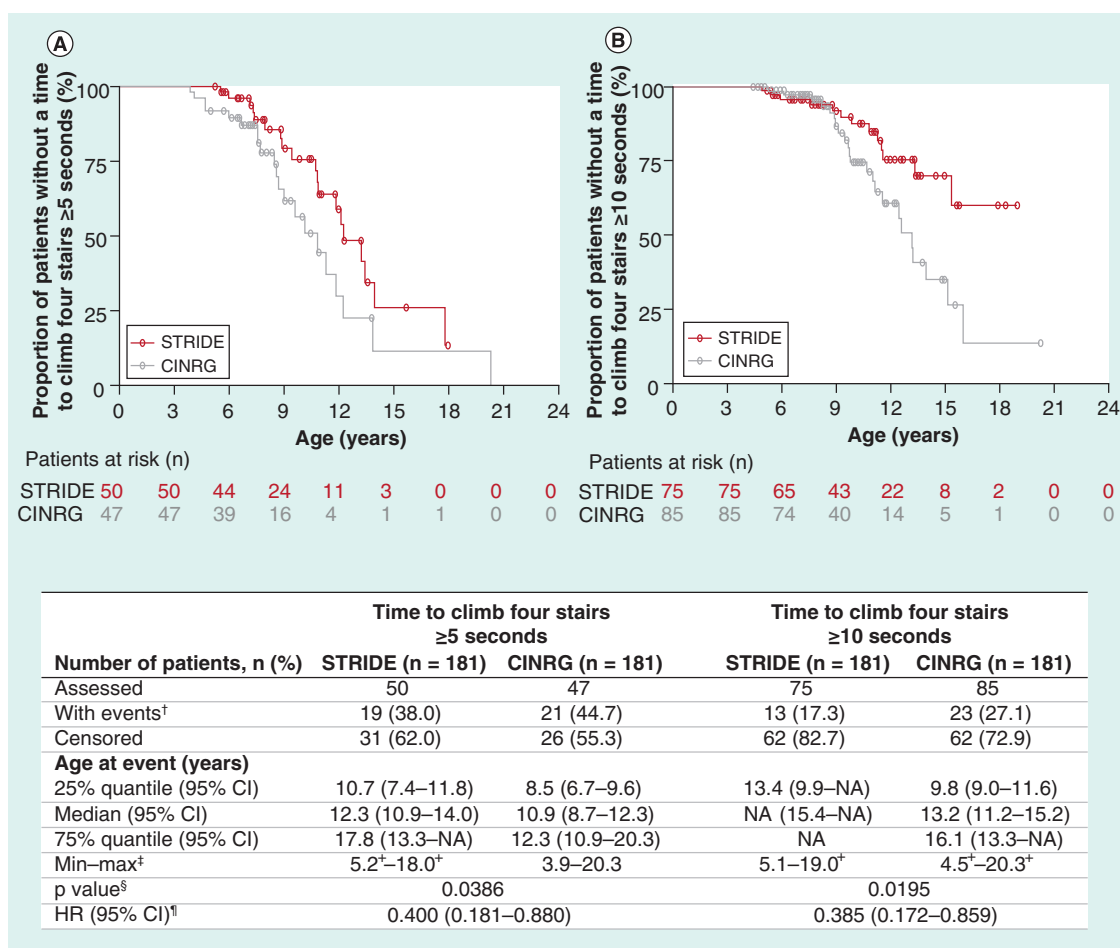
¶HR is from stratified (by durations of deflazacort and other corticosteroid use) Cox regression with study, age at first symptoms and age at first corticosteroid use as covariates. The HR is STRIDE Registry versus CINRG DNHS.

CINRG DNHS: Cooperative International Neuromuscular Research Group Duchenne Natural History Study; FVC: Forced vital capacity; HR: Hazard ratio; max: Maximum; min: Minimum; NA: Not available; STRIDE: Strategic Targeting of Registries and International Database of Excellence.

## Discussion

The STRIDE Registry provides real-world evidence on the long-term outcomes of patients with nmDMD receiving ataluren during routine clinical practice and therefore builds on evidence generated from previous clinical trials of ataluren, which were 48 weeks in duration [13,14]. Here, we have described the safety and effectiveness results of ataluren in patients with genetically confirmed nmDMD in the STRIDE Registry as of the cut-off date of 9 July 2018, and the results of correlation analyses of DMD genotype versus disease severity and DMD genotype versus ataluren treatment benefit.

Ataluren was well tolerated in patients with nmDMD and had a safety profile consistent with that shown in previous clinical trials, with TEAEs in most patients being mild or moderate and not related to ataluren [13,14]. To assess the real-world, long-term effectiveness of ataluren, we compared results between propensity score-matched



**Figure 3. Age at time to climb four stairs (A) ≥5 s and (B) ≥10 s for propensity score-matched patients from the STRIDE Registry and CINRG DNHS.** Propensity-score model covariates include age at first symptoms, age at first corticosteroid use, duration of deflazacort use and duration of use of corticosteroids other than deflazacort. Censor dates for censored patients in the STRIDE Registry were derived from the last assessment date across treatment, physical examination, vital signs, 6-minute walk distance, timed function tests, North Star Ambulatory Assessments, percentage of predicted FVC and upper limb function tests. Corticosteroid duration is calculated from the date at which corticosteroid use was started to the date of loss of ambulation or the date of the last assessment.

<sup>†</sup>Event = time to climb four stairs ≥5 s or ≥10 s.

<sup>‡</sup>†† indicates a censored observation.

<sup>§</sup>p-value is from a log-rank test stratified by deflazacort and other corticosteroid usage durations.

<sup>¶</sup>HR is from stratified (by durations of deflazacort and other corticosteroid use) Cox regression with study, age at first symptoms and age at first corticosteroid use as covariates. The HR is STRIDE Registry versus CINRG DNHS.

CINRG DNHS: Cooperative International Neuromuscular Research Group Duchenne Natural History Study; FVC: Forced vital capacity; HR: Hazard ratio; max: Maximum; min: Minimum; NA: Not available; STRIDE: Strategic Targeting of Registries and International Database of Excellence.

patient populations from the STRIDE Registry, which included patients with nmDMD receiving ataluren plus SoC and the CINRG DNHS, comprising data from patients with any DMD genotype receiving the SoC only. Propensity matching of all patients in the effectiveness population of the STRIDE Registry population with patients in the CINRG DNHS yielded populations that were comparable with respect to age at first corticosteroid use, duration of deflazacort use, duration of other corticosteroid use and age at first symptoms, which is predictive of age at loss of ambulation [22]. As of the STRIDE Registry cut-off date of 9 July 2018, patients in the CINRG DNHS had a longer median follow-up period than those in STRIDE (1811 vs 616 days), which is not surprising given that patients were enrolled in the CINRG DNHS for a period of up to 10 years (median of 1811 days, ~5 years).

Compared with propensity score-matched patients receiving SoC in the CINRG DNHS, patients in the STRIDE Registry receiving ataluren had significantly delayed loss of ambulation and delayed worsening of timed function

**Table 3. Age at predicted forced vital capacity <60%, predicted forced vital capacity <50% and forced vital capacity <1 l for propensity score-matched patients from the STRIDE Registry and CINRG DNHS.**

| Number of patients, n (%)   | Predicted FVC <60%                  |                                     | Predicted FVC <50%                  |                        | FVC <1 l                            |                        |
|-----------------------------|-------------------------------------|-------------------------------------|-------------------------------------|------------------------|-------------------------------------|------------------------|
|                             | STRIDE (n = 181)                    | CINRG (n = 181)                     | STRIDE (n = 181)                    | CINRG (n = 181)        | STRIDE (n = 181)                    | CINRG (n = 181)        |
| Assessed                    | 123                                 | 96                                  | 136                                 | 109                    | 129                                 | 130                    |
| With events <sup>†</sup>    | 4 (3.3)                             | 35 (36.5)                           | 3 (2.2)                             | 35 (32.1)              | 0 (0.0)                             | 31 (23.8)              |
| Censored                    | 119 (96.7)                          | 61 (63.5)                           | 133 (97.8)                          | 74 (67.9)              | 129 (100.0)                         | 99 (76.2)              |
| <b>Age at event (years)</b> |                                     |                                     |                                     |                        |                                     |                        |
| 25% quantile (95% CI)       | NA                                  | 13.4 (12.2–14.1)                    | NA (15.5–NA)                        | 14.3 (13.1–15.9)       | NA                                  | 19.1 (16.4–22.2)       |
| Median (95% CI)             | NA                                  | 15.1 (14.0–17.1)                    | NA                                  | 16.9 (15.4–19.6)       | NA                                  | 24.9 (20.8–29.5)       |
| 75% quantile (95% CI)       | NA                                  | 19.7 (16.7–NA)                      | NA                                  | 20.7 (18.4–25.1)       | NA                                  | 29.8 (25.3–33.9)       |
| Min–max <sup>‡</sup>        | 5.4 <sup>+</sup> –19.0 <sup>+</sup> | 6.0 <sup>+</sup> –20.7 <sup>+</sup> | 5.4 <sup>+</sup> –23.8 <sup>+</sup> | 6.0 <sup>+</sup> –25.1 | 5.4 <sup>+</sup> –23.8 <sup>+</sup> | 6.0 <sup>+</sup> –33.9 |
| p-value <sup>§</sup>        | <0.0001                             |                                     | 0.0008                              |                        | 0.0029                              |                        |
| HR (95% CI) <sup>¶</sup>    | 0.148 (0.052–0.426)                 |                                     | 0.169 (0.051–0.564)                 |                        | 0.000 (0.000–NA)                    |                        |

Propensity-score model covariates include age at first symptoms, age at first corticosteroid use, duration of deflazacort use and duration of use of corticosteroids other than deflazacort. Sensor dates for censored patients in the STRIDE Registry were derived from the last assessment date across treatment, physical examination, vital signs, 6-minute walk distance, timed function tests, North Star Ambulatory Assessments, percentage of predicted FVC and upper limb function tests. Corticosteroid duration is calculated from the date at which corticosteroid use was started to the date of the last assessment.

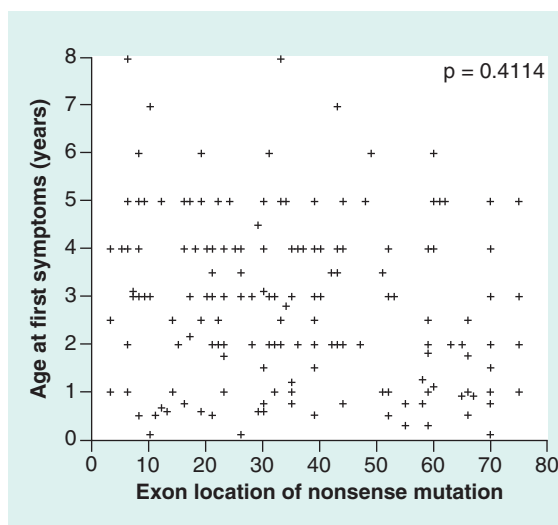
<sup>†</sup> Event = percentage predicted FVC <60%, FVC <50% or FVC <1 l.

<sup>‡</sup> '+' indicates a censored observation.

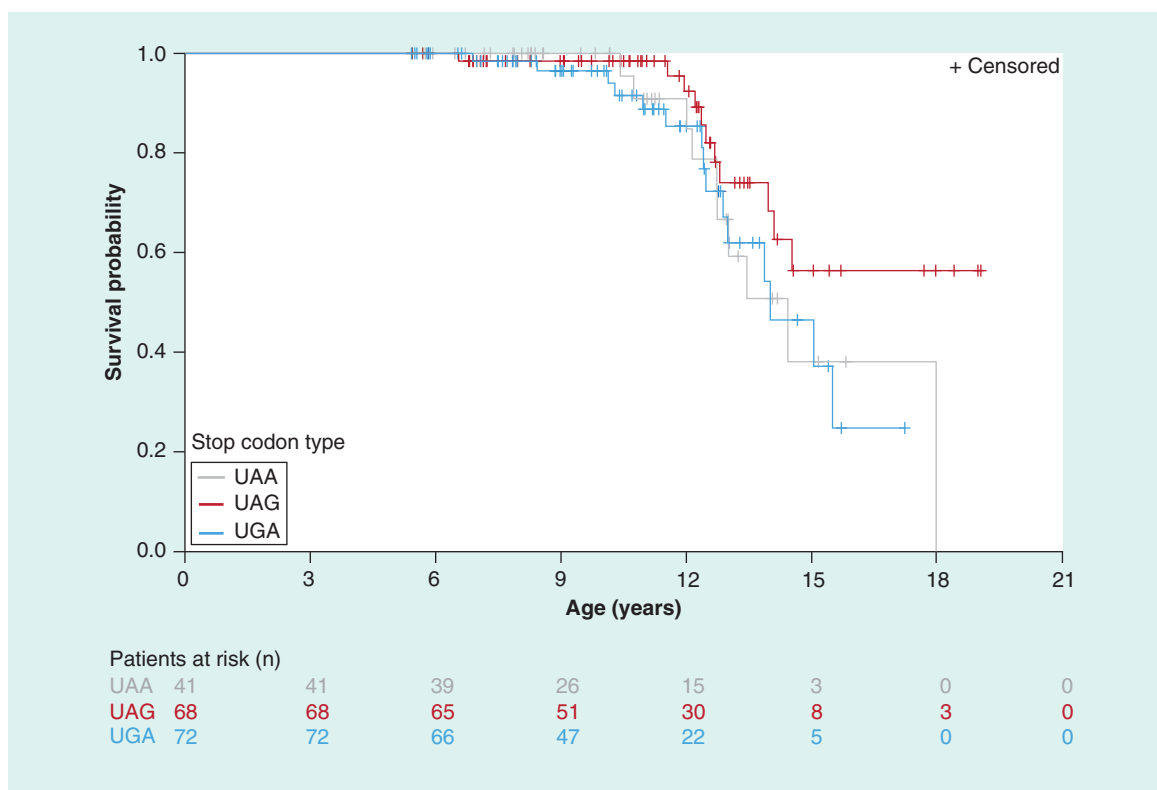
<sup>§</sup> p-value is from a log-rank test stratified by deflazacort and other corticosteroid usage durations.

<sup>¶</sup> HR is from stratified (by durations of deflazacort and other corticosteroid use) Cox regression with study, age at first symptoms and age at first corticosteroid use as covariates. The HR is STRIDE Registry versus CINRG DNHS.

CINRG DNHS: Cooperative International Neuromuscular Research Group Duchenne Natural History Study; FVC: Forced vital capacity; HR: Hazard ratio; max: Maximum; min: Minimum; NA: Not available; STRIDE: Strategic Targeting of Registries and International Database of Excellence.

**Figure 4. Correlation analysis of the effect of nonsense mutation exon location on disease severity (as measured by age at first symptoms) for patients from the STRIDE Registry (n = 181).**

test results, as measured by increases in times to stand from supine and to climb four stairs. The median age at loss of ambulation for patients with DMD in the CINRG DNHS has been reported previously for distinct subgroups [16,31,32]. Bello *et al.* [32] showed that 212 of the 340 CINRG patients enrolled between 2006 and 2009, who had available evidence of a *DMD* genetic mutation, had a median age at loss of ambulation of 12.0 years. A separate study by Bello *et al.* [31] showed that median age at loss of ambulation was approximately 3 years later in CINRG DNHS patients who were treated with corticosteroids for at least 1 year while they were ambulatory, compared with CINRG DNHS patients who were never treated or treated with corticosteroids for less than 1 year (13.0 vs 10.0 years; n = 252 vs 88). Median age at loss of ambulation was later in CINRG DNHS patients who received daily deflazacort than in those who received daily prednisone (13.9 vs 11.2 years; n = 80 vs 94) [31]. In a more recent analysis of CINRG DNHS patients enrolled between 2006 and 2009 or 2012 and 2016, McDonald *et al.* [16] also showed that the median age at loss of ambulation was later in patients who were treated with corticosteroids for at least 1 year than in those who were never treated or treated with corticosteroids for less than 1 month (13.4



**Figure 5. Kaplan–Meier analysis estimating the effect of the type of premature stop codon on ataluren treatment benefit as assessed by age at loss of ambulation for patients from the STRIDE Registry (n = 181).**  
 A: Adenine; G: Guanine; U: Uracil.

vs 10.0 years; n = 329 vs 73), and later in patients who received deflazacort than in those who received prednisone (14.0 vs 11.3 years). In the present analysis, median age at loss of ambulation for the unmatched CINRG DNHS population with DMD (n = 400) was 12.0 years, which is the same median age for patients with DMD as that reported by one of the CINRG DNHS articles by Bello *et al.* [32]. Furthermore, the median age at loss of ambulation for the unmatched population who received corticosteroids for at least 12 months (n = 275) was 13.5 years in the present analysis, which is similar to the median age of 13.4 years reported for the same subgroup by McDonald *et al.* [16]. Although the median age at loss of ambulation of 11.0 years for the propensity score-matched CINRG DNHS population in the present analysis was younger than that previously reported, this population has been matched to the STRIDE Registry population according to established predictors of disease progression, including corticosteroid type and duration, and is therefore a comparable group to the STRIDE Registry population. It should be noted, however, that propensity score matching can only adjust for measured covariates, and thus it cannot be guaranteed that confounding factors have been removed [19]. Furthermore, propensity score matching involves the assumption that the propensity score model has been correctly specified, and cannot account for unobserved variables [19].

Results showing the age at worsening of pulmonary function, as measured by reductions in predicted FVC to lower than 60% or 50% and FVC to lower than 1 l, for patients in the matched populations suggest a trend toward delayed worsening of pulmonary function for patients in STRIDE compared with those in the CINRG DNHS. A previous study by McDonald *et al.* [33] showed that patients in the CINRG DNHS treated with corticosteroids had delayed pulmonary disease progression (using measures including predicted and absolute peak expiratory flow rate, and predicted and absolute FVC), compared with those who were corticosteroid-treatment naive. However, predicted FVC declines were not consistent across all age groups regardless of corticosteroid use, suggesting that studies should be sufficiently long in duration in order to show meaningful pulmonary results [33]. It is important to note for the present study that relatively few patients in the STRIDE Registry reached the pulmonary and cardiac disease progression milestones of clinical significance because they were younger than CINRG DNHS patients,

and therefore not as far progressed in their disease. Furthermore, the follow-up treatment period in STRIDE was shorter than that for CINRG DNHS, so patients in STRIDE did not have as much time to decline and reach the pulmonary disease progression milestones. It would therefore be premature to draw any conclusions on these results. Data from a subsequent cut-off date may help to provide greater clarity on these endpoints.

Overall, our results corroborate previous evidence that ataluren treatment can slow disease progression in patients with nmDMD, which is considered an important benefit of therapy by the DMD patient community [34]. The motor disease progression milestones evaluated in the present study have previously been shown to be closely related to health-related quality of life measures [16,35]. The delay in loss of motor functions associated with ataluren treatment observed in routine clinical practice is clinically important and meaningful to patients and their families because the progressive loss of each function is usually irreversible. Preservation of motor function impacts a patient's autonomy and quality of life by postponing the loss of basic daily functions, such as climbing and descending stairs, and walking short distances independently. Furthermore, the time at loss of one function predicts the onset of subsequent disease milestones indicative of disease progression [16,36,37]. For example, age at loss of ambulation is associated with age at future onset of complications of the lungs and heart [16,38]. Corticosteroid treatment has been associated with delayed loss of ambulation [39]. Therefore, the delay in loss of ambulation for patients receiving ataluren compared with those receiving SoC alone represents not only a highly meaningful prolongation of autonomy in daily life but a delay in the onset of subsequent disease milestones and ultimately mortality. It is premature to draw conclusions from the pulmonary and cardiac function results at the STRIDE Registry cut-off date used for the present analysis. If analyses at a future cut-off date show that the age at worsening of these functions is significantly delayed with ataluren treatment in patients with nmDMD in routine clinical practice, then this result would be important because death usually occurs as a result of cardiac or respiratory compromise [1].

As part of the STRIDE Registry database, data were collected on the location of the nonsense mutation and the type of premature stop codon generated [15]. We therefore were interested in determining whether there is a correlation between the nonsense mutation location in the *DMD* gene and disease severity. Although previously published literature has suggested that nonsense mutation location may affect disease severity (e.g., nonsense mutations early in the *DMD* gene may sometimes lead to a milder DMD phenotype [5]), our correlation analyses showed no significant relationship between disease severity and exon location of the nonsense mutation. Additionally, the few patients who experienced first symptoms after 6 years of age had mutations spread across the *DMD* gene. To put our findings into context, we conducted a literature search to identify nonsense mutations that are reported in the literature as leading to a milder disease phenotype. We found only three instances, two of whom had a p.Arg1967\* mutation in exon 41 [40]. We conclude that, with the exception of mutations that affect exonic splicing enhancers and that result in exon skipping [32,41–49], there is no evidence for the location of nonsense mutation affecting the severity of disease.

Furthermore, no correlation was found between the type of the premature stop codon generated (UGA, UAA or UAG) and age at loss of ambulation, indicating that ataluren treatment benefit is not affected by stop codon type. These findings are caveated by the fact that age at loss of ambulation can be affected by SoC treatment, which was not the same across the STRIDE patients analyzed. As seen in the Phase IIb study of ataluren, in the registry, all three types of stop codon were represented [50]. In the STRIDE Registry, nonsense mutations were located across the length of the *DMD* gene. Our results showing no correlation between nonsense mutation location or type and disease severity/treatment benefit are aligned with findings from a study by Muntoni *et al.* [51], which showed no significant associations between the speed of disease progression (as assessed by North Star Ambulatory Assessment score trajectory) and the location of dystrophin nonsense mutations, nor any significant difference between the group of patients with nonsense mutations compared with those with deletions.

STRIDE is the first drug registry for patients with DMD and is the largest real-world study of patients with nmDMD to date. STRIDE contains patients with a wider range of ages and ambulatory ability than those in clinical trials, meaning that the data is representative of a broader range of real-world patient experiences in comparison with a short-duration randomized placebo-controlled clinical trial with narrowly defined inclusion criteria. Here, we have assessed the long-term safety of ataluren and conducted correlation analyses on the effect of nonsense mutation location on disease severity for the largest population of patients with nmDMD analyzed to date. Additionally, we have examined the effect of the nonsense mutation location and the type of premature stop codon generated on ataluren treatment benefit in this same population. We have placed the effectiveness results of ataluren from the registry into context by comparing results from patients in STRIDE with those from patients in the CINRG DNHS who have been successfully matched according to well-established predictors of disease progression using



propensity score. It should be acknowledged as a limitation of the study that the STRIDE and CINRG DNHS populations were not matched according to mutation type or location. However, the inclusion of patients in the CINRG DNHS with any DMD genotype rather than only patients with nmDMD should not be considered a source of bias because patients were matched based on several factors that are predictors of disease progression, such as age at onset of first symptoms, a known disease severity surrogate that is correlated with age at loss of ambulation for corticosteroid-naïve patients [22]. Moreover, the CINRG DNHS serves as a useful comparator to the STRIDE Registry because it includes patients receiving SoC who are experiencing the usual course of DMD disease progression.

## Conclusion

Ataluren treatment was well tolerated and was associated with clinical benefit when compared with patients who only received the SoC. The interim results of the STRIDE Registry reported here indicate the benefit of long-term treatment of nmDMD patients with ataluren as used in routine clinical practice in slowing disease progression. These benefits include clinically meaningful preservation of ambulation, which is predictive of disease progression in patients with DMD. Our results observed in routine clinical practice support the clinical benefit of ataluren in slowing nmDMD disease progression over a mean treatment period of 632 days. The interim findings of the STRIDE Registry indicate that ataluren is well tolerated and has favorable outcomes in patients with nmDMD over a longer period of time than can be afforded in clinical trials.

### Summary points

- Ataluren is an oral treatment for patients with nonsense mutation Duchenne muscular dystrophy (nmDMD) designed to promote readthrough of an in-frame premature stop codon and to enable the production of full-length dystrophin.
- Strategic Targeting of Registries and International Database of Excellence (STRIDE) is an ongoing registry of patients receiving ataluren in clinical practice.
- Ataluren was well tolerated in patients with nmDMD and had a safety profile consistent with that shown in previous clinical trials.
- Propensity score matching was performed to identify patients from STRIDE and the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG DNHS) who were comparable in established predictors of disease progression.
- Kaplan–Meier analyses demonstrated that patients receiving ataluren plus standard of care (SoC) in STRIDE had a significantly delayed age at loss of ambulation, worsening of performance in timed function tests and worsening of pulmonary function versus patients receiving SoC alone in the CINRG DNHS (all  $p \leq 0.0386$ ).
- Ataluren plus SoC was associated with delayed deterioration of cardiac function versus SoC alone, although this did not reach statistical significance.
- No correlation was observed between DMD genotype and disease progression or treatment benefit for patients with nmDMD.
- Our results indicate that ataluren plus SoC delays milestones of DMD progression in patients with nmDMD in routine clinical practice.

### Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: [www.futuremedicine.com/doi/suppl/10.2217/cer-2019-0171](http://www.futuremedicine.com/doi/suppl/10.2217/cer-2019-0171)

### Author contributions

E Mercuri, F Muntoni, A Nascimento Osorio, M Tulinius and I Desguerre are members of the STRIDE Registry Steering Committee and have enrolled patients at their study sites. F Buccella is a member of the STRIDE Registry Steering Committee and is an expert patient advocate. P Trifillis and CL Santos were involved in the design of the STRIDE Registry. J Jiang, J Zhu and A Kristensen were responsible for data analysis. EK Henricson has served as CINRG DNHS Study Co-Chair and contributed to the overall CINRG DNHS design. CM McDonald has served as CINRG DNHS Study Chair and contributed to the overall CINRG DNHS design. E Mercuri, F Muntoni, A Nascimento Osorio, M Tulinius, F Buccella, LP Morgenroth, H Gordish-Dressman, J Jiang, P Trifillis, J Zhu, A Kristensen, CL Santos, EK Henricson, CM McDonald and I Desguerre reviewed data, drafted and critically reviewed the manuscript, and approved the final version for submission.

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### Ethical conduct of research

Before any patient is enrolled and study-related data are collected, ethics committee approval of the protocol, informed consent form and all patient enrollment materials are obtained in each country and for each site, as applicable. The study is conducted in accordance with the ethical principles outlined in the Declaration of Helsinki, applicable privacy laws and local regulations for each participating site, as well as with the Guidelines for Good Pharmacoepidemiology Practices.

### Data sharing statement

The authors certify that this manuscript reports original real-world evidence data (NCT02369731). Individual patient data will not be made publicly available. The study protocol is available indefinitely to interested parties on request.

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## References

Papers of special note have been highlighted as: ● of interest; ●● of considerable interest

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. *Lancet Neurol.* 17(3), 251–267 (2018).
- **One article in a three-part overview of the 2018 standard of care guidelines for the management of patients with Duchenne muscular dystrophy (DMD).**
2. Pichavant C, Aartsma-Rus A, Clemens PR *et al.* Current status of pharmaceutical and genetic therapeutic approaches to treat DMD. *Mol. Ther.* 19(5), 830–840 (2011).
3. Bushby K, Finkel R, Birnkrant DJ *et al.* Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. *Lancet Neurol.* 9(1), 77–93 (2010).
4. Ellis JA, Vroom E, Muntoni F. 195th ENMC international workshop: newborn screening for Duchenne muscular dystrophy 14–16th December, 2012, Naarden, The Netherlands. *Neuromuscul. Disord.* 23(8), 682–689 (2013).
5. Aartsma-Rus A, Ginjaar IB, Bushby K. The importance of genetic diagnosis for Duchenne muscular dystrophy. *J. Med. Genet.* 53(3), 145–151 (2016).
6. Bladen CL, Salgado D, Monges S *et al.* The TREAT-NMD DMD global database: analysis of more than 7,000 Duchenne muscular dystrophy mutations. *Hum. Mutat.* 36(4), 395–402 (2015).
7. Bello L, Pegoraro E. Genetic diagnosis as a tool for personalized treatment of Duchenne muscular dystrophy. *Acta. Myol.* 35(3), 122–127 (2016).
8. Laing NG, Davis MR, Bayley K, Fletcher S, Wilton SD. Molecular diagnosis of duchenne muscular dystrophy: past, present and future in relation to implementing therapies. *Clin. Biochem. Rev.* 32(3), 129–134 (2011).
9. European Medicines Agency. Translarna™ (ataluren) summary of product characteristics (2019). [www.ema.europa.eu/en/documents/product-information/translarna-epar-product-information\\_en.pdf](http://www.ema.europa.eu/en/documents/product-information/translarna-epar-product-information_en.pdf)
10. Peltz SW, Morsy M, Welch EM, Jacobson A. Ataluren as an agent for therapeutic nonsense suppression. *Annu. Rev. Med.* 64, 407–425 (2013).
11. Roy B, Friesen WJ, Tomizawa Y *et al.* Ataluren stimulates ribosomal selection of near-cognate tRNAs to promote nonsense suppression. *Proc. Natl Acad. Sci. USA* 113(44), 12508–12513 (2016).
12. Finkel RS, Flanigan KM, Wong B *et al.* Phase IIa study of ataluren-mediated dystrophin production in patients with nonsense mutation Duchenne muscular dystrophy. *PLoS ONE* 8(12), e81302 (2013).
13. Bushby K, Finkel R, Wong B *et al.* Ataluren treatment of patients with nonsense mutation dystrophinopathy. *Muscle Nerve* 50(4), 477–487 (2014).
- **Describes the safety and efficacy results of ataluren in a Phase IIb randomized, double-blind, placebo-controlled trial.**
14. McDonald CM, Campbell C, Torricelli RE *et al.* Ataluren in patients with nonsense mutation Duchenne muscular dystrophy (ACT DMD): a multicentre, randomised, double-blind, placebo-controlled, Phase III trial. *Lancet* 390(10101), 1489–1498 (2017).
- **Describes the safety and efficacy results of ataluren in a Phase III randomized, double-blind, placebo-controlled trial.**
15. Muntoni F, Desguerre I, Guglieri M *et al.* Ataluren use in patients with nonsense mutation Duchenne muscular dystrophy: patient demographics and characteristics from the STRIDE Registry. *J. Comp. Eff. Res.* 8 (14) 1187–1200 (2019).
16. McDonald CM, Henricson EK, Abresch RT *et al.* Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study. *Lancet* 391(10119), 451–461 (2018).
- **Describes the long-term effects of corticosteroids on disease progression in patients with DMD in the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG DNHS).**
17. McDonald CM, Henricson EK, Abresch RT *et al.* The cooperative international neuromuscular research group Duchenne natural history study—a longitudinal investigation in the era of glucocorticoid therapy: design of protocol and the methods used. *Muscle Nerve* 48(1), 32–54 (2013).
- **Provides information on the study methodology of the CINRG DNHS in order to lay the groundwork for future analyses of these natural history data.**
18. National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents. The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. *Pediatrics* 114(Suppl. 2), 555–576 (2004).
19. Inacio MC, Chen Y, Paxton EW, Namba RS, Kurtz SM, Cafri G. Statistics in brief: an introduction to the use of propensity scores. *Clin. Orthop. Relat. Res.* 473(8), 2722–2726 (2015).
20. Badhiwala JH, Witiw CD, Wilson JR, Fehlings MG. Early versus late surgical decompression for central cord syndrome: a propensity score-matched analysis. *Neurosurgery* 66(Suppl.1), nyz310.447 (2019).
21. Lin WY, Lin MS, Weng YH *et al.* Association of antiviral therapy with risk of Parkinson disease in patients with chronic hepatitis c virus infection. *JAMA Neurol.* 76 (9) 1019–1027 (2019).

22. Ciafaloni E, Kumar A, Liu K *et al.* Age at onset of first signs or symptoms predicts age at loss of ambulation in Duchenne and Becker muscular dystrophy: data from the MD STARnet. *J. Pediatr. Rehabil. Med.* 9(1), 5–11 (2016).
23. Ricotti V, Ridout DA, Scott E *et al.* Long-term benefits and adverse effects of intermittent versus daily glucocorticoids in boys with Duchenne muscular dystrophy. *J. Neurol. Neurosurg. Psychiatry* 84(6), 698–705 (2013).
24. Coca-Perraillon M. Local and global optimal propensity score matching. SAS Global Forum 2007. Paper 185–2007 (2007). <https://support.sas.com/resources/papers/proceedings/proceedings/forum2007/185-2007.pdf>
25. McDonald CM, Henricson EK, Abresch RT *et al.* The 6-minute walk test and other endpoints in Duchenne muscular dystrophy: longitudinal natural history observations over 48 weeks from a multicenter study. *Muscle Nerve* 48(3), 343–356 (2013).
26. Birnkrant DJ, Bushby K, Bann CM *et al.* Diagnosis and management of Duchenne muscular dystrophy, part 2: respiratory, cardiac, bone health, and orthopaedic management. *Lancet Neurol.* 17(4), 347–361 (2018).
- **One article in a three-part overview of the 2018 standard of care guidelines for the management of patients with DMD.**
27. Spurney C, Shimizu R, Morgenroth LP *et al.* Cooperative International Neuromuscular Research Group Duchenne Natural History Study demonstrates insufficient diagnosis and treatment of cardiomyopathy in Duchenne muscular dystrophy. *Muscle Nerve* 50(2), 250–256 (2014).
28. Phillips MF, Quinlivan RC, Edwards RH, Calverley PM. Changes in spirometry over time as a prognostic marker in patients with Duchenne muscular dystrophy. *Am. J. Respir. Crit. Care Med.* 164(12), 2191–2194 (2001).
29. Bailey M, Miller N. DMD Open-access Variant Explorer (DOVE): a scalable, open-access, web-based tool to aid in clinical interpretation of genetic variants in the *DMD* gene. *Mol. Genet. Genomic Med.* 7(1), e00510 (2019).
30. Wang L, Chen M, He R *et al.* Serum creatinine distinguishes Duchenne muscular dystrophy from Becker muscular dystrophy in patients aged </=3 years: a retrospective study. *Front Neurol.* 8, 196 (2017).
31. Bello L, Gordish-Dressman H, Morgenroth LP *et al.* Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study. *Neurology* 85(12), 1048–1055 (2015).
- **Describes the results of an observational study of patients with DMD in the CINRG DNHS that assessed the age at loss of ambulation associated with different corticosteroid regimens.**
32. Bello L, Morgenroth LP, Gordish-Dressman H *et al.* DMD genotypes and loss of ambulation in the CINRG Duchenne Natural History Study. *Neurology* 87(4), 401–409 (2016).
- **Describes the results of a correlation analysis between different truncating DMD mutations and age at loss of ambulation in patients with DMD in the CINRG DNHS.**
33. McDonald CM, Gordish-Dressman H, Henricson EK *et al.* Longitudinal pulmonary function testing outcome measures in Duchenne muscular dystrophy: long-term natural history with and without glucocorticoids. *Neuromuscul. Disord.* 28(11), 897–909 (2018).
- **Describes results from an analysis of changes in pulmonary function measures across time in patients with DMD treated with corticosteroids for more than 1 year compared with corticosteroid-naïve patients in the CINRG DNHS.**
34. Peay HL, Hollin I, Fischer R, Bridges JF. A community-engaged approach to quantifying caregiver preferences for the benefits and risks of emerging therapies for Duchenne muscular dystrophy. *Clin. Ther.* 36(5), 624–637 (2014).
35. McDonald CM, McDonald DA, Bagley A *et al.* Relationship between clinical outcome measures and parent proxy reports of health-related quality of life in ambulatory children with Duchenne muscular dystrophy. *J. Child Neurol.* 25(9), 1130–1144 (2010).
36. Humbertclaude V, Hamroun D, Bezzou K *et al.* Motor and respiratory heterogeneity in Duchenne patients: implication for clinical trials. *Eur. J. Paediatr. Neurol.* 16(2), 149–160 (2012).
37. McDonald CM, Duong T, Henricson E, Abresch T, Hu F, Cnaan A. P.2.11 CINRG Duchenne Natural History Study: relationship of longitudinal measures of ambulatory timed function tests and loss of clinical milestones. *Neuromuscul. Disord.* 23(9), 752 (2013).
38. Passamano L, Taglia A, Palladino A *et al.* Improvement of survival in Duchenne muscular dystrophy: retrospective analysis of 835 patients. *Acta Myol* 31(2), 121–125 (2012).
39. King WM, Ruttencutter R, Nagaraja HN *et al.* Orthopedic outcomes of long-term daily corticosteroid treatment in Duchenne muscular dystrophy. *Neurology* 68(19), 1607–1613 (2007).
40. Nigro V, Nigro G, Esposito MG *et al.* Novel small mutations along the *DMD/BMD* gene associated with different phenotypes. *Hum. Mol. Genet.* 3(10), 1907–1908 (1994).
41. Aartsma-Rus A, Van Deutekom JC, Fokkema IF, Van Ommen GJ, Den Dunnen JT. Entries in the Leiden Duchenne muscular dystrophy mutation database: an overview of mutation types and paradoxical cases that confirm the reading-frame rule. *Muscle Nerve* 34(2), 135–144 (2006).
42. Daoud F, Angeard N, Demerre B *et al.* Analysis of Dp71 contribution in the severity of mental retardation through comparison of Duchenne and Becker patients differing by mutation consequences on Dp71 expression. *Hum. Mol. Genet.* 18(20), 3779–3794 (2009).
43. Ginjarr IB, Kneppers AL, vd Meulen JD *et al.* Dystrophin nonsense mutation induces different levels of exon 29 skipping and leads to variable phenotypes within one BMD family. *Eur. J. Hum. Genet.* 8(10), 793–796 (2000).

44. Juan-Mateu J, Gonzalez-Quereda L, Rodriguez MJ *et al.* Interplay between DMD point mutations and splicing signals in dystrophinopathy phenotypes. *PLoS ONE* 8(3), e59916 (2013).
45. Straathof CS, Van Heusden D, Ippel PF *et al.* Diagnosis of becker muscular dystrophy: results of re-analysis of DNA samples. *Muscle Nerve* 53(1), 44–48 (2016).
46. Takeshima Y, Yagi M, Okizuka Y *et al.* Mutation spectrum of the dystrophin gene in 442 Duchenne/Becker muscular dystrophy cases from one Japanese referral center. *J. Hum. Genet.* 55(6), 379–388 (2010).
47. Tuffery-Giraud S, Saquet C, Thorel D *et al.* Mutation spectrum leading to an attenuated phenotype in dystrophinopathies. *Eur. J. Hum. Genet.* 13(12), 1254–1260 (2005).
48. Wang L, Xu M, Li H *et al.* Genotypes and phenotypes of *DMD* small mutations in Chinese patients with dystrophinopathies. *Front. Genet.* 10, 114 (2019).
49. Sterne-Weiler T, Sanford JR. Exon identity crisis: disease-causing mutations that disrupt the splicing code. *Genome Biol.* 15(1), 201 (2014).
50. Bushby K, Finkel R, Wong B *et al.* Ataluren treatment of patients with nonsense mutation dystrophinopathy. *Muscle Nerve* 50(4), 477–487 (2014).
51. Muntoni F, Domingos J, Manzur AY *et al.* Categorising trajectories and individual item changes of the North Star Ambulatory Assessment in patients with Duchenne muscular dystrophy. *PLoS ONE* 14(9), e0221097 (2019).