Demographic and safety data from patients with nonsense mutation Duchenne muscular dystrophy receiving ataluren in the STRIDE Registry

Francesco Muntoni,[1,2] Filippo Buccella,[3] Isabelle Desguerre,[4] Janbernd Kirschner,[5] Andrés Nascimento Osorio,[6] Már Tulinius,[7] Joel Jiang,[8] Allan Kristensen,[8] Panayiota Trifillis[8] and Claudio L Santos,[8] on behalf of the STRIDE investigators

[1]Dubowitz Neuromuscular Centre and MRC Centre for Neuromuscular Diseases, University College London, Institute of Child Health and Great Ormond Street Hospital for Children Foundation Trust, London, UK; [2]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; [3]Parent Project Italy APS, Rome, Italy; [4]APHP Necker – Enfants Malades Hospital, Paris V Descartes University, Neuromuscular Network FILNEMUS, Paris, France; [5]Department of Neuropediatrics, University Hospital Bonn, Bonn, Germany; [6]Hospital Sant Joan de Déu Unidad de Patología Neuromuscular, Universidad de Barcelona, CIBERER, ISCIII, Barcelona, Spain; [7]Department of Pediatrics, Gothenburg University, Queen Silvia Children's Hospital, Gothenburg, Sweden; [8]PTC Therapeutics Inc., South Plainfield, NJ 07080-2449, USA

1. Background

- Duchenne muscular dystrophy (DMD) is a severe, X-linked, recessive neuromuscular disorder affecting approximately 1 in every 3600–6000 live male births.[1–3]
- Owing to the absence of functional dystrophin, patients with DMD experience a progressive decline in functional ability, including loss of ambulation, and respiratory and cardiac complications, which lead to premature death.[1]
- In approximately 10–15% of patients, the disorder is caused by a nonsense mutation (nm) in the *DMD* gene, leading to a premature stop codon in the dystrophin mRNA, which prevents translation of a full-length, functional dystrophin protein.[4,5]
- Ataluren is an orally bioavailable drug that is designed to promote readthrough of the in-frame premature stop codon to produce full-length dystrophin.[6]
- Ataluren 40 mg/kg/day is indicated for the treatment of nmDMD in ambulatory patients aged ≥ 2 years[7] in member states of the European Union, and Iceland, Israel, Kazakhstan, Liechtenstein, Norway and the Republic of Korea, or aged ≥ 5 years in Brazil and Chile.[8]
  - Efficacy has not been demonstrated in non-ambulatory patients.
  - The presence of a nonsense mutation in the *DMD* gene should be determined by genetic testing.[7]
- The **S**trategic **T**argeting of **R**egistries and **I**nternational **D**atabase of **E**xcellence (STRIDE; ClinicalTrials.gov identifier: NCT02369731) is an ongoing, multicenter, observational registry providing real-world evidence regarding the use of ataluren in patients with nmDMD in routine clinical practice.
- Here, we describe the demographic data and interim safety results for patients in the STRIDE Registry as of the latest data cut-off date of January 31, 2019.

2. Methods

Study design

- The STRIDE Registry is a post-approval safety study of ataluren use in patients with nmDMD in routine clinical practice, requested by the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency.
  - The study design is shown in **Figure 1**.
  - The registry can only be implemented in countries where ataluren is commercialized or available through an early access program (if applicable).
  - Patients will be followed up for ≥ 5 years, or until study withdrawal.

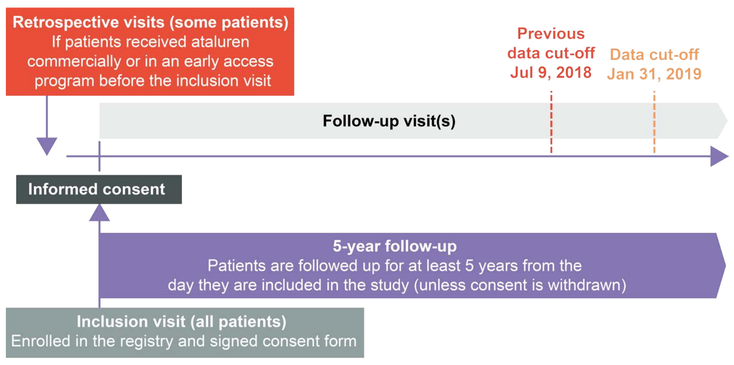
Study population and data collection

- Patients were eligible if they received ataluren as a commercial supply or as part of an early access program and provided written informed consent before participating in this study.
  - Dosage of ataluren received: 40 mg/kg/day (10, 10 and 20 mg/kg for morning, midday and evening doses, respectively).
- 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 program that prevented participation in this study.
- Data from enrolled patients were collected at the consent date; for patients who initiated ataluren as part of a commercial or early access program before enrollment, data for the period before enrollment were obtained retrospectively.

Statistical analysis

- Demographic and safety data were captured in the STRIDE Registry.
- Descriptive statistics, including percentages, means and standard deviations (SDs), were calculated for the demographic and safety data, when appropriate.

Figure 1. STRIDE Registry post-approval safety study design.



STRIDE, Strategic Targeting of Registries and International Database of Excellence.

3. Results

STRIDE Registry patient disposition

- As of January 31, 2019, 224 patients with DMD had been enrolled in STRIDE at 55 sites in 11 countries; of these, 3 patients were female, and 1 patient failed screening (**Figures 2** and **3**).
- All the 220 male patients who provided informed consent and did not fail screening (the evaluable/safety population) received at least one dose of ataluren.
- Overall, the total mean (SD) exposure to ataluren was 822.0 (367.9) days, equivalent to 495.1 patient-years.
  - 59.5% of patients (131/220) had been receiving ataluren for more than 672 days.
- Fourteen of the 220 boys discontinued the study owing to the following reasons determined by the investigator: lost to follow-up (n = 1), withdrawal of consent (n = 1) and other reasons (n = 12).
- Twelve of the 220 boys discontinued ataluren owing to the following reasons determined by the investigator: adverse events (n = 1), the family's/patient's decision (n = 3), the physician's decision (n = 3) and other reasons (n = 5).

Safety and tolerability of ataluren

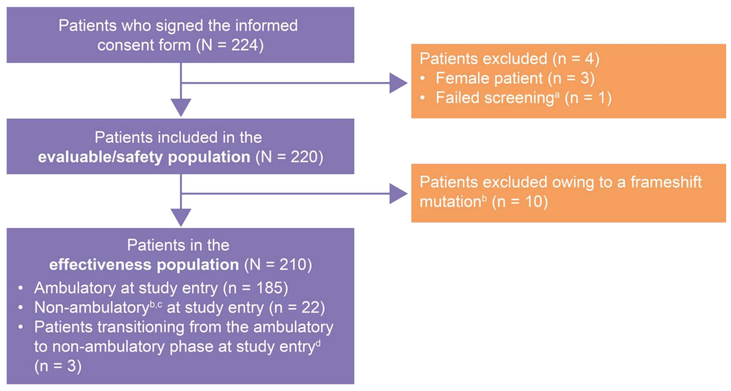
- Safety outcomes were consistent with the known safety profile of ataluren (**Table 1**).[9–11]
- Five patients (2.3%) experienced a treatment-emergent adverse event (TEAE) deemed related to ataluren, and six patients (2.7%) experienced a TEAE that led to discontinuation of ataluren.
- Fourteen patients (6.4%) had a total of 19 serious adverse events (SAEs), all of which were either considered not related to the study medication (n = 18) or of unknown relationship to the study medication (n = 1).
  - Seven of the 14 patients had an SAE relating to hospitalization owing to respiratory complications (n = 1; pneumonia, acute respiratory failure and bronchial secretion retention) or bone fractures (n = 6; of the humerus, femur or tibia).
  - The following events were reported in one patient each: appendicitis, orchidopexy, rhabdomyolysis with myoglobinuria, left ventricular dysfunction, joint surgery, gastroenteritis, varicella and osteosynthesis.
- The majority of TEAEs were mild to moderate in severity, and no life-threatening TEAEs were reported.

3. Results (continued)

Demographics and characteristics of STRIDE Registry patients

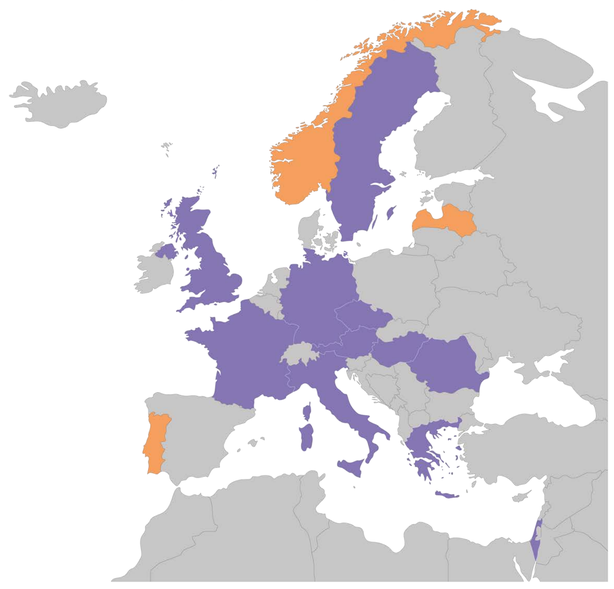
- Of the 220 patients in the evaluable/safety population, 210 patients with genetically confirmed nmDMD were included in the effectiveness population; 10 patients with frameshift mutations were excluded from the analysis (**Figure 2**).
- Most patients were white (140/210 [66.7%]), and the mean (SD) age at consent date was 10.6 (3.6) years (**Table 2**).
- The majority of patients used concomitant corticosteroids (191/220 [86.8%]) (**Table 1**).
- The mean (SD) age at treatment start date was 9.9 (3.7) years; at data cut-off (January 31, 2019) it was 12.2 (3.6) years (**Table 2**).
- The mean (SD) age at first symptoms was 2.8 (1.8) years (n = 193); at nmDMD confirmation it was 5.2 (2.9) years (n = 200) (**Table 3**).
- The median time between first symptoms and genetic confirmation of diagnosis was 1.6 years (n = 186) (**Table 3**).

Figure 2. STRIDE Registry patient disposition.



[a]Screening failure due to a frameshift mutation.
[b]Ataluren is not indicated in non-ambulatory patients or patients with a frameshift mutation. The safety and efficacy of ataluren in non-ambulatory patients have not been established.
[c]Defined as full-time wheelchair use.
[d]Patients with a first 10-m run/walk test result of ≥ 30 seconds.
STRIDE, Strategic Targeting of Registries and International Database of Excellence.

Figure 3. Number of male patients in the evaluable population of the STRIDE Registry and study sites by country.



Country	Number of sites, n	Patients in the evaluable population, as of Jan 31, 2019 N = 220 Number of patients, n (%)
Austria	2	4 (1.8)
Czech Republic	2	6 (2.7)
France	16	54 (24.5)
Germany	9	33 (15.0)
Greece	1	1 (0.5)
Hungary	1	2 (0.9)
Israel	1	5 (2.3)
Italy	11	49 (22.3)
Romania	2	11 (5.0)
Sweden	2	12 (5.5)
United Kingdom	8	43 (19.5)
Latvia	1	0 (0.0)
Norway	1	0 (0.0)
Portugal	1	0 (0.0)

Countries in which study sites are actively recruiting patients are shown in purple, and countries in which study sites are yet to recruit any patients are shown in orange.
STRIDE, Strategic Targeting of Registries and International Database of Excellence.

Table 1. TEAEs[a] experienced by patients in the STRIDE Registry evaluable/safety population, overall and stratified by corticosteroid use.

AEs	Corticosteroid use: Yes (n = 199)	No (n = 21)	All patients (N = 220)
Number of TEAEs[a]	141	26	167
Patients with at least one of the following, n (%)			
TEAE	61 (30.7)	7 (33.3)	68 (30.9)
TEAE related to ataluren	4 (2.0)	1 (4.8)	5 (2.3)
TEAE leading to discontinuation of ataluren	5 (2.5)	1 (4.8)	6 (2.7)
SAE	12 (6.0)	2 (9.5)	14 (6.4)
TEAE with maximum severity[b]			
Mild	23 (11.6)	1 (4.8)	24 (10.9)
Moderate	20 (10.1)	4 (19.0)	24 (10.9)
Severe	5 (2.5)	1 (4.8)	6 (2.7)
Life-threatening	0 (0.0)	0 (0.0)	0 (0.0)
Not reported	4 (2.0)	0 (0.0)	4 (1.8)
Unknown	9 (4.5)	1 (4.8)	10 (4.5)

[a]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.
[b]For patients with two or more AEs, the event with the maximum severity, as classified by the CTCAE, was reported. The order of severity is: 'Not reported', 'Unknown', 'Mild', 'Moderate', 'Severe' and 'Life-threatening'.
AE, adverse event; CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event; STRIDE, Strategic Targeting of Registries and International Database of Excellence; TEAE, treatment-emergent adverse event.

3. Results (continued)

Table 2. Patient demographics and characteristics of the STRIDE Registry effectiveness population, overall and stratified by corticosteroid use.

Characteristic	Corticosteroid use: Yes (n = 191)	No (n = 19)	All patients (N = 210)
Weight, kg	n = 165	n = 16	n = 181
Mean (SD)	31.7 (13.5)	31.9 (18.9)	31.7 (14.0)
95% CI	29.6–33.8	21.8–42.0	29.7–33.8
Median (min, max)	28.0 (13.5, 78.0)	24.3 (15.0, 87.0)	27.7 (13.5, 87.0)
Height, cm	n = 142	n = 13	n = 155
Mean (SD)	124.2 (15.6)	126.5 (22.9)	124.4 (16.2)
95% CI	121.6–126.8	112.7–140.3	121.8–127.0
Median (min, max)	122.5 (94.3, 177.0)	116.0 (102.0, 178.0)	122.0 (94.3, 178.0)
BMI, kg/m²	n = 142	n = 13	n = 155
Mean (SD)	19.4 (4.5)	17.3 (4.1)	19.2 (4.5)
95% CI	18.6–20.1	14.9–19.8	18.5–19.9
Median (min, max)	18.3 (13.7, 40.5)	16.3 (13.7, 27.5)	18.1 (13.7, 40.5)
Race, n (%)			
White	128 (67.0)	12 (63.2)	140 (66.7)
Arab/Middle Eastern	6 (3.1)	0 (0.0)	6 (2.9)
Arab/Middle Eastern, Asian	1 (0.5)	0 (0.0)	1 (0.5)
Asian	6 (3.1)	0 (0.0)	6 (2.9)
Black	2 (1.0)	0 (0.0)	2 (1.0)
Mixed race, black/white	1 (0.5)	0 (0.0)	1 (0.5)
North African	1 (0.5)	0 (0.0)	1 (0.5)
Latin	1 (0.5)	0 (0.0)	1 (0.5)
Unknown	1 (0.5)	0 (0.0)	1 (0.5)
Age at consent date, years			
Mean (SD)	10.6 (3.5)	10.4 (4.3)	10.6 (3.6)
95% CI	10.1–11.1	8.3–12.5	10.1–11.1
Median (min, max)	10.2 (5.2, 22.8)	9.8 (5.0, 19.4)	10.2 (5.0, 22.8)
Age at treatment start date, years			
Mean (SD)	9.9 (3.6)	9.8 (4.3)	9.9 (3.7)
95% CI	9.3–10.4	7.7–11.8	9.4–10.4
Median (min, max)	9.3 (4.0, 22.8)	8.3 (5.0, 19.4)	9.2 (4.0, 22.8)
Age at cut-off date, years			
Mean (SD)	12.2 (3.5)	12.1 (4.5)	12.2 (3.6)
95% CI	11.7–12.7	10.0–14.3	11.7–12.7
Median (min, max)	12.1 (6.1, 24.7)	12.1 (6.3, 21.1)	12.1 (6.1, 24.7)

CI, confidence interval; max, maximum; min, minimum; SD, standard deviation; STRIDE, Strategic Targeting of Registries and International Database of Excellence.

Table 3. Patient demographics relating to diagnosis and symptoms for the STRIDE Registry effectiveness population, overall and stratified by corticosteroid use.

Characteristic	Corticosteroid use: Yes (n = 191)	No (n = 19)	All patients (N = 210)
Age at genetically confirmed nmDMD diagnosis, years[a]	n = 184	n = 16	n = 200
Mean (SD)	5.2 (2.9)	4.8 (2.8)	5.2 (2.9)
95% CI	4.8–5.6	3.3–6.3	4.8–5.6
Median (min, max)	4.9 (−0.4, 15.6)	5.2 (1.1, 11.1)	4.9 (−0.4, 15.6)
Age at first symptoms, years	n = 179	n = 14	n = 193
Mean (SD)	2.8 (1.7)	2.7 (2.4)	2.8 (1.8)
95% CI	2.5–3.0	1.3–4.1	2.5–3.0
Median (min, max)	2.5 (0.0, 8.0)	2.0 (0.1, 8.0)	2.5 (0.0, 8.0)
Time between nmDMD diagnosis and first symptoms, years[a]	n = 173	n = 13	n = 186
Mean (SD)	2.4 (2.5)	1.7 (1.6)	2.3 (2.4)
95% CI	2.0–2.8	0.7–2.7	2.0–2.7
Median (min, max)	1.7 (−3.4, 12.6)	1.4 (−0.2, 6.1)	1.6 (−3.4, 12.6)

[a]A minimum age value of zero or a negative minimum age value is due to a prenatal diagnosis.
CI, confidence interval; max, maximum; min, minimum; nmDMD, nonsense mutation Duchenne muscular dystrophy; SD, standard deviation; STRIDE, Strategic Targeting of Registries and International Database of Excellence.

4. CONCLUSIONS

- The STRIDE Registry constitutes the first drug registry for patients with DMD and is the largest real-word study of patients with nmDMD to date.
- Analyses of effectiveness data from patients in the STRIDE Registry will provide insights into the real-world, long-term effectiveness and safety of ataluren.

References

1. Birnkrant DJ *et al. Lancet Neurol* 2018;17:251–67.
2. Bushby K *et al. Lancet Neurol* 2010;9:77–93.
3. Ellis JA *et al. Neuromuscul Disord* 2013;23:682–9.
4. Bello L, Pegoraro E. *Acta Myol* 2016;35:122–7.
5. Pichavant C *et al. Mol Ther* 2011;19:830–40.
6. Roy B *et al. Proc Natl Acad Sci USA* 2016;113:12508–13.
7. PTC Therapeutics International Ltd. Summary of product characteristics, Translarna. European Medicines Agency, 2018. Available from: www.ema.europa.eu/documents/product-information/translarna-epar-product-information_en.pdf (Accessed January 9, 2020).
8. Data on file.
9. Bushby K *et al. Muscle Nerve* 2014;50:477–87.
10. Finkel RS *et al. PLoS One* 2013;8:e81302.
11. McDonald CM *et al. Lancet* 2017;390:1489–98.

Disclosures

The STRIDE Registry is sponsored by PTC Therapeutics. Medical writing support was provided by Emily Colbeck, PhD, of PharmaGenesis London, London, UK, and was funded by PTC Therapeutics.
FM has received consultancy fees from Akashi Therapeutics, Biogen, BioMarin, Capricor, Catabasis Pharmaceuticals, Italfarmaco, Pfizer, PTC Therapeutics, Roche, Sarepta Therapeutics, Tivorsan Pharmaceuticals and Wave Therapeutics, and is supported by the National Institute for Health Research Biomedical Research Centre at Great Ormond Street Hospital for Children National Health Service Foundation Trust and University College London. **FB** has received consultancy fees from Pfizer, PTC Therapeutics, Santhera Pharmaceuticals and Sarepta Therapeutics. **ID** has received consultancy fees from AveXis, Biogen, BioMarin and PTC Therapeutics. **JK** has acted as a consultant for AveXis, Biogen, PTC Therapeutics, Roche and Sarepta Therapeutics, and has received research support for taking part in clinical research from AveXis, Biogen, Novartis, PTC Therapeutics, Roche and Santhera Pharmaceuticals. **ANO** has received speaker and consultancy fees from Biogen, PTC Therapeutics and Sarepta Therapeutics, and is an investigator on clinical trials sponsored by Biogen, F. Hoffmann-La Roche, Italfarmaco, Sarepta Therapeutics and TAMDMD. **MT** has received lecture fees from Biogen and PTC Therapeutics, has acted as a consultant on DMD clinical trials for BioMarin, Catabasis Pharmaceuticals, PTC Therapeutics, ReveraGen BioPharma and Sarepta Therapeutics, and as an advisory board member for AveXis, Biogen, PTC Therapeutics and Sarepta Therapeutics. **JJ**, **AK**, **PT** and **CLS** are employees of PTC Therapeutics, Inc.

Acknowledgments

We thank the patients and their families for their participation in this study, and individuals involved in the conduct of this study and the collection of data, particularly the principal investigators, clinical evaluators and study coordinators of the STRIDE Registry.

Scan QR code for poster

COPYRIGHT © 2020 PTC THERAPEUTICS INC., ALL RIGHTS RESERVED
TRANSLARNA™ IS A TRADEMARK OF PTC THERAPEUTICS, INC.