Duchenne Parent Project aps

The Strategic Targeting of Registries and International Database of Excellence

STRIDE

THE STRIDE REGISTRY

Nonsense mutations:

A nonsense mutation is a point mutation, where a single nucleotide (or base of DNA) is replaced by a different one that creates what is called a premature stop codon. Stop codons give the specific instruction of terminating the synthesis of the protein at that site. When a nonsense mutation occurs, we therefore have a premature termination of the protein at that specific site preventing the production of a full-length, functional protein. Nonsense mutations in the DMD gene account for a proportion of 10-15% of boys with Duchenne.

Ataluren:

Ataluren is the first drug approved for Duchenne muscular dystrophy, resulting from a nonsense mutation in the dystrophin gene. It is currently indicated for ambulatory patients aged 5 years or older in Brazil, Chile and Ukraine. 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, Norway, Kazakhstan, and Republic of Korea. Ataluren is an oral treatment designed to promote readthrough of a premature stop codon due to a nonsense mutation. During the protein synthesis process this drug forces the cell to ignore the abnormal premature stop signal, thereby enabling the production of a full-length functional protein.

The **Strategic Targeting of Registries and International Database of Excellence (STRIDE)** Registry constitutes the first drug registry for patients with Duchenne muscular dystrophy (DMD) and represents the largest real-world study of DMD patients with **nonsense mutations** (nmDMD) to date.
STRIDE is a **post-approval**, **observational**, international study collecting long-term safety and effectiveness data on the use of **ataluren** in nmDMD patients in the real-world and in clinical practice. The Registry was requested by regulatory authorities for the post-marketing assessment of the use of ataluren and is underway in countries where ataluren is available commercially or through an early access program.

Why do we need a Registry like this?

As a rare genetic disease, DMD affects relatively few people. There is, therefore, little documented information on disease epidemiology, particularly for the different mutation subgroups of patients with DMD. In addition, it is often difficult to recruit large numbers of patients into clinical trials and the patients recruited in a clinical trial are usually a homogeneous population with well defined characteristics.
The STRIDE Registry is therefore important as it gathers and integrates data across a larger number of nmDMD patients for a longer period of time which is important for understanding real-world outcomes for diverse purposes, including the natural history of the disease and the effectiveness and safety of ataluren.
More specifically the STRIDE registry:

- Includes a more heterogeneous population of patients than those in a randomized clinical trial, including a wider range of ages, ambulatory ability and differences in steroid use. This means that the Registry will be more representative of the real-world setting and will help to improve our understanding of the treatment effects of ataluren, as well as provide more information on non-ambulatory patients, who are often omitted from clinical trials.
- Provides information on the long-term use of ataluren. This gives the opportunity to follow patients over a longer period of time with additional characterization and quantification of adverse events that may have a low incidence or occur following a long delay after exposure to ataluren, or that may be more likely to occur outside of the controlled setting of a clinical trial.

Post-approval study:

A study, generally required by regulatory authorities, to help assure continued safety and effectiveness of the approved product.

Observational study:

A study where investigators observe the effect of a treatment or other intervention, without trying to affect it by changing experimental conditions.

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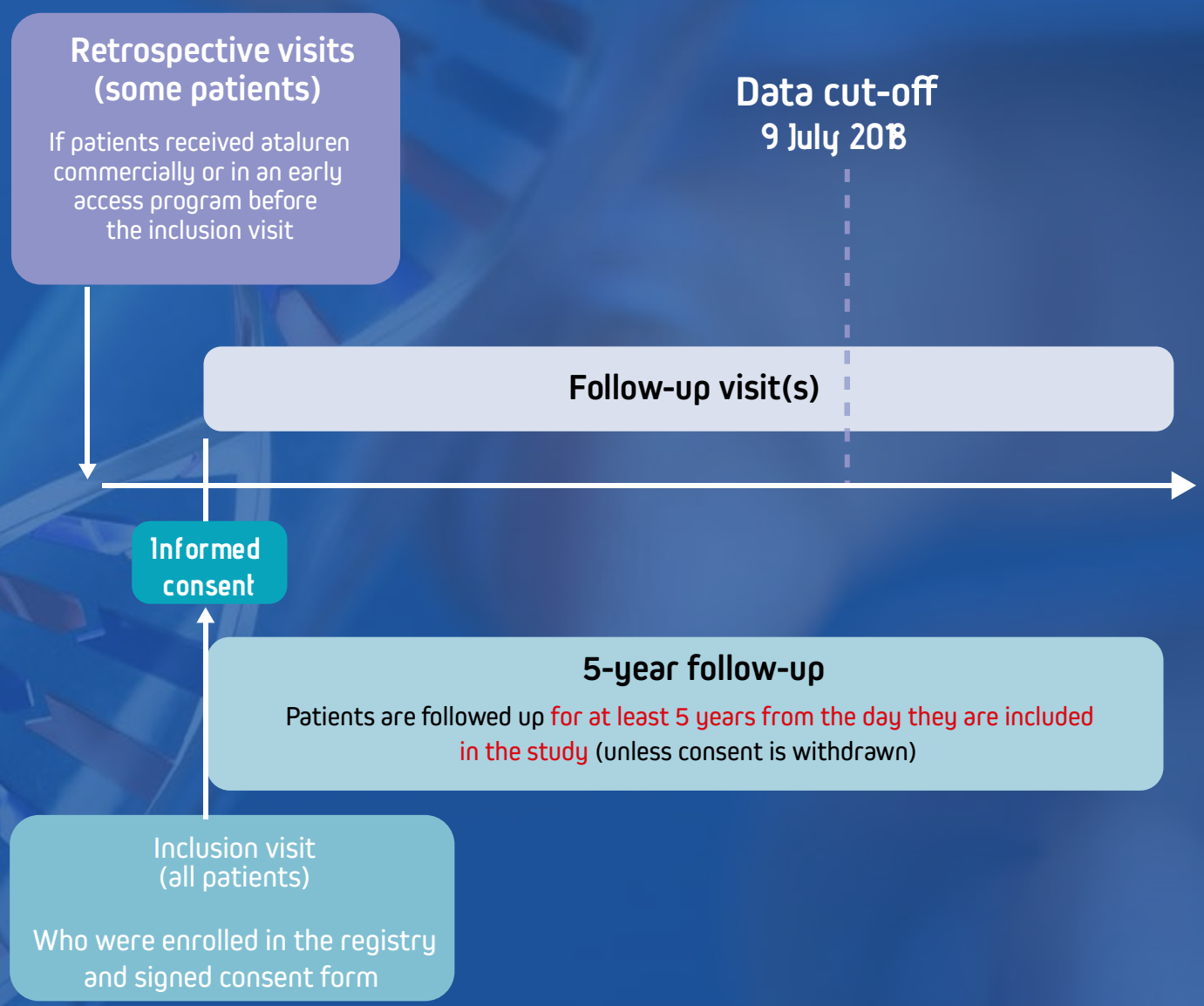
How the Registry operates

The STRIDE Registry includes genetically confirmed nmDMD patients, receiving treatment with ataluren outside of ataluren clinical trials, either through commercial supply or within an early access program.
At study entry, initial data is collected to include demographic characteristics, diagnosis information, ambulation status, previous and current exposure to ataluren, all concomitant medications, clinical information and symptoms.
All patients in the study are followed over a period of at least 5 years (or until withdrawal from the study).
During this period, routine follow-up visits, conducted as per usual care, are performed. Data collected during follow-up visits include routine clinical assessments of motor, cardiac and pulmonary function as well as safety data.

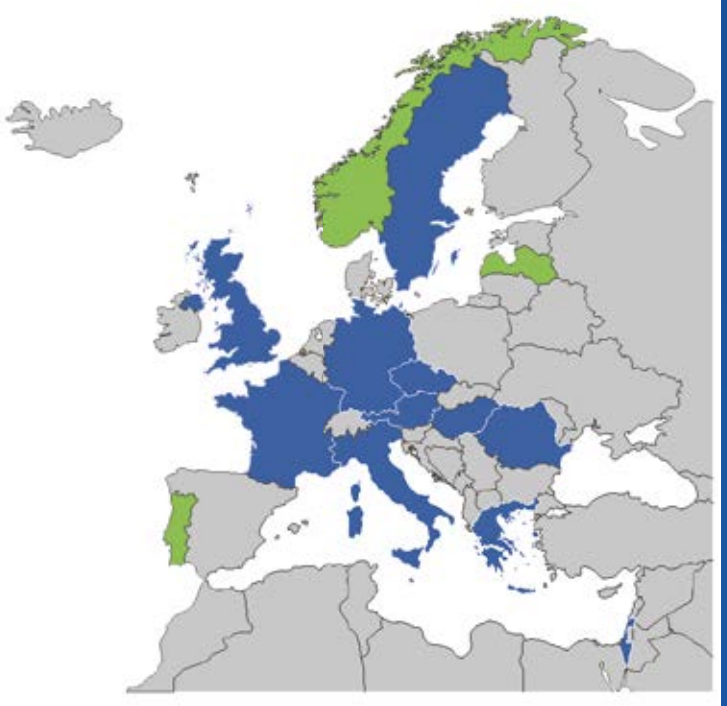
Study timeline:

Enrollment of patients in the STRIDE Registry began in March 2015. For the present analyses patients enrolled in the study until the 9th of July 2018 have been considered. All patients will be followed-up for at least 5 years from the date of their enrollment, or until withdrawal from the study.



Patients in the evaluable population, as of 9 July 2018
n = 213

Country	Number of sites, n	Number of patients, n (%)
Austria	2	4 (1.9)
Czech Republic	2	6 (2.8)
France	16	54 (25.4)
Germany	9	33 (15.5)
Greece	1	1 (0.5)
Hungary	1	2 (0.9)
Israel	1	5 (2.3)
Italy	11	49 (23.0)
Romania	2	11 (5.2)
Sweden	1	11 (5.2)
United Kingdom	7	37 (17.4)
Latvia	1	0 (0.0)
Norway	1	0 (0.0)
Portugal	1	0 (0.0)



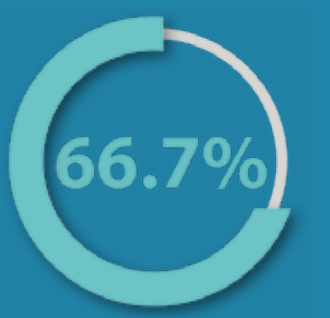
Patients distribution:

As of 9 July 2018, 213 male patients with DMD from 11 countries with 53 active study sites were enrolled in the STRIDE Registry.

Focus

Snapshot of the Registry at study entry:

Of the 213 boys in the registry:



142 were white

61 had participated in previous trials of ataluren

190 received corticosteroids during the study

119 had a muscle biopsy

At first visit captured within the registry:

22 were non ambulatory (but had previously received ataluren in a clinical trial) — 10,3%

88,3% — 188 were ambulatory

3 could not complete the 10-min walk/run test in less than 30 s — 1,4%

What are these numbers telling us?

There appears to be a longer mean time between first symptoms and genetic diagnosis in the STRIDE registry as compared to other studies. This suggests that patients with nonsense mutations are diagnosed later than those in the total DMD population. This is probably due to the longer diagnostic process required to identify a nonsense mutation, highlighting a potential unmet need for this patient group that should be addressed.

Data from the STRIDE Registry show that a muscle biopsy is routinely performed before genetic confirmation of DMD. This is a critical point that should raise awareness if we consider that international DMD guidelines recommend taking a muscle biopsy only if a genetic diagnosis is inconclusive.

Importantly, nine of the patients with DMD recruited into the registry carried frameshift mutations, due to misinterpretation of the genetic laboratory report by the treating physicians. This finding highlights the need for continuous professional development of the medical care team, especially when there are new personalized medications that require interpretation of complex genetic information.

Mean times between:

first symptoms and muscle biopsy: **1.6 years**

muscle biopsy and genetic nmDMD diagnosis: **1 year**

first symptoms and genetic nmDMD diagnosis: **2.4 years**

Mean age at:

first symptoms: **2.7 years**

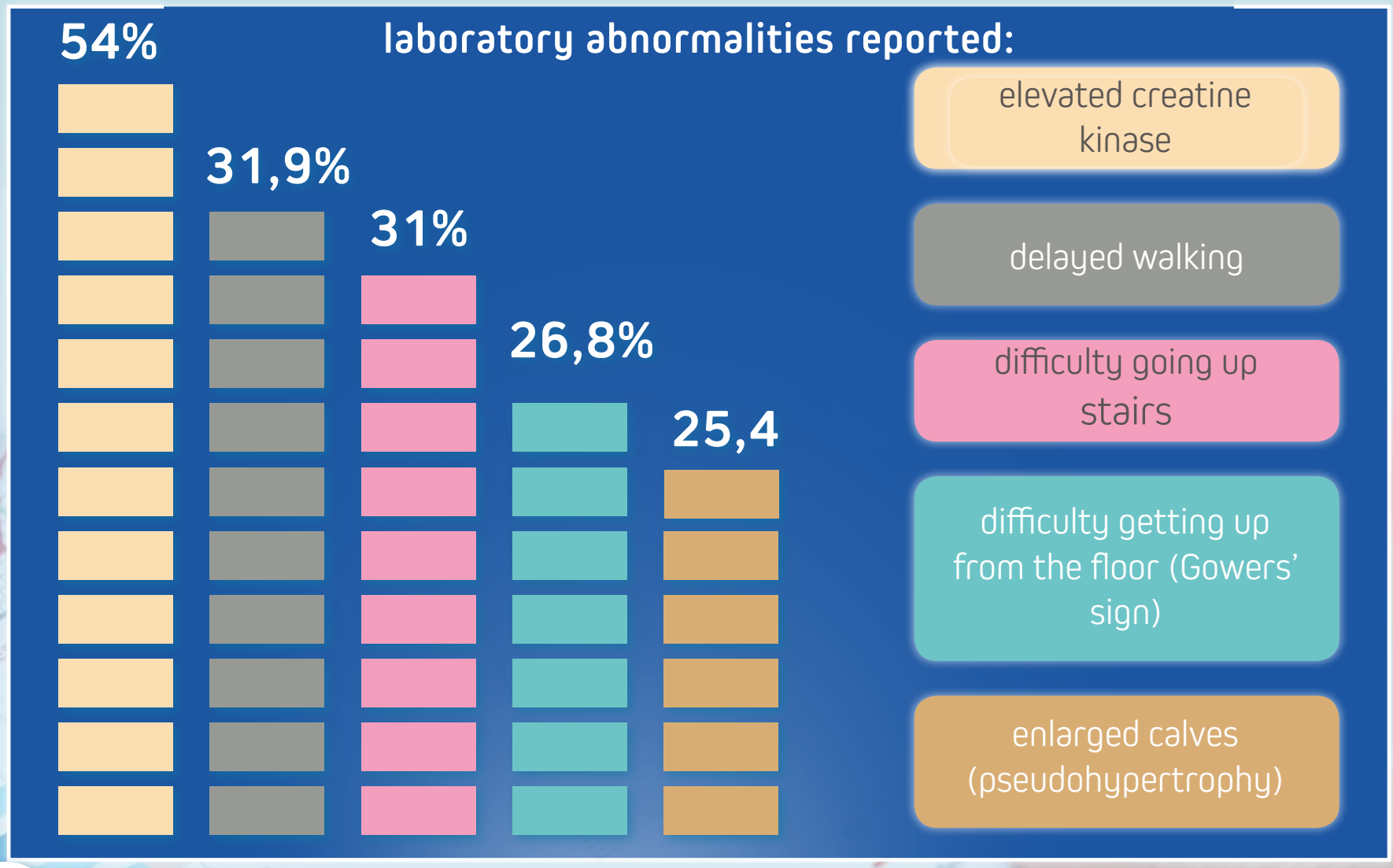
time of muscle biopsy: **4.5 years**

genetically confirmed diagnosis: **5.2 years**

Mean age of patients:

- at first capture in the registry: **9.8 years**
- at the inclusion visit: **10.5 years**
- at the cut-off date of 9 July 2018: **11.6 years**

Most common first clinical signs, symptoms and/or laboratory abnormalities reported:



Concomitant and prior medications

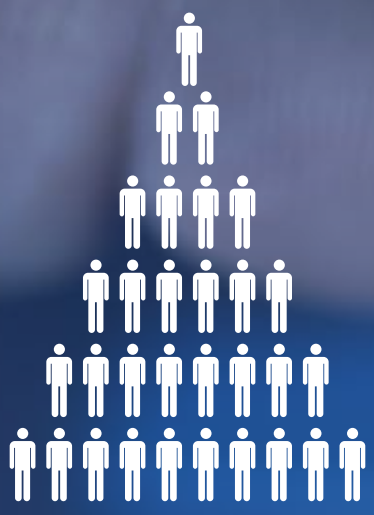
48 (22.5%) medications in use at study entry, including:

- corticosteroids (13.1%)
- vitamin D (3.8%)
- ACE inhibitors (2.3%)
- calcium (1.4%)

204 (95.8%) concomitant medications during the study, including:

- deflazacort (30.5%)
- prednisolone (19.7%)
- prednisone (19.7%)
- corticosteroids (67.1%):
- vitamin D (53.5%)
- proton pump inhibitors (10.8%)
- ACE inhibitors (26.8%)
- osmotic laxatives (6.1%).
- calcium (21.6%)

Of the 213 enrolled boys, 6 have withdrawn from the study and 8 have discontinued ataluren but remain in the registry.
The 213 patients used ataluren for a mean duration of 639 days while enrolled in the registry.



The reference population

The CINRG DNHS population includes over 400 DMD patients aged 2 to 28 years. who were followed up between 2006 and 2016 at 20 worldwide centers.
The CINRG DNHS serves as a useful comparator to the STRIDE Registry because it includes patients receiving standard of care who are experiencing the usual course of DMD disease progression.

Effect of DMD genotype on disease severity and ataluren treatment benefit

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, to evaluate a potential correlation between nonsense mutation location in the gene and disease severity, or type of stop codon and treatment efficacy.
Data analysis showed no significant relationship between disease severity (as assessed by age at first symptoms) and exon location of the nonsense mutation. Furthermore, no correlation between the type of the premature stop codon generated and age at loss of ambulation was observed, indicating that ataluren treatment benefit is not affected by stop codon type.

LESSONS LEARNED FROM THE REGISTRY

Safety of ataluren

Safety data collected from the 213 patients included in the study demonstrated that ataluren was well tolerated in patients with nmDMD and had a safety profile consistent with that shown in previous clinical trials.
Adverse events in most patients were mild or moderate and not usually related to ataluren.
Five patients **(2.3%)** experienced adverse events that were deemed related to ataluren treatment by the investigators. These included abdominal pain **(n=3)**, vomiting **(n=1)**, headache **(n=1)**, diarrhoea **(n=1)** and elevated serum lipids **(n=1)**. Four of these patients had received corticosteroids at some point in the study, one had not received corticosteroids at any point during the study.

Effectiveness of ataluren

The effectiveness of ataluren was evaluated in 181 of the 213 patients originally included in the STRIDE Registry. These 181 patients were those who had a confirmed nmDMD diagnosis, received at least one dose of ataluren and did not have missing data. This population was compared with patients in the Cooperative International Neuromuscular Research Group's (CINRG) Duchenne Natural History Study (DNHS).
Each of the 181 patients was matched with one patient from the CINRG DNHS, with respect to clinical features able to predict disease progression. These features include age at first clinical symptoms which was used as a measure of disease severity, the age at first corticosteroid use, corticosteroid type and duration.
The primary objective of this comparative analysis was the age at loss of ambulation, which is also used as a measure of treatment benefit.
When compared with the CINRG DNHS population, patients in the STRIDE Registry receiving ataluren had a significantly delayed loss of ambulation and delayed worsening of timed function test results, as measured by increases in times to stand from supine and to climb four stairs.
Comparative data also suggest a trend towards delayed worsening of pulmonary function for patients in STRIDE. However, given the low number of patients experiencing pulmonary dysfunction, and the shorter duration of follow-up in comparison to the CINRG DNHS cohort, it is premature to draw firm conclusions from these results.
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.

Adverse Events related to ataluren (5 patients, 2.3%)

- Abdominal pain
- Abdominal pain and diarrhea
- Abdominal pain and vomiting
- Headache
- Increased lipids

Age at loss of ambulation

Median age at loss of ambulation was:

14.5 years in STRIDE
11.0 years in CINRG DNHS

Number of patients who lost ambulation before 10:

3 (1.7%) in STRIDE
41 (22.7%) in CINRG DNHS

Number of patients who were still ambulatory after 15:

13 (7.2%) in STRIDE
6 (3.3%) in CINRG DNHS

TAKE HOME MESSAGE

Overall, the results obtained from the STRIDE Registry and from comparative analysis with CINRG DNHS corroborate previous evidence that ataluren treatment is well tolerated and can slow disease progression in patients with nmDMD.

The natural disease progression in DMD is characterized by the loss of motor, pulmonary and cardiac functions. The time of loss of one function is associated with the onset of subsequent disease milestones and indicative of disease progression. For example, age at loss of ambulation predicts age at future onset of complications of the lungs and heart.

The delay in loss of motor functions associated with ataluren treatment observed in the patients from the STRIDE Registry is important to patients and their families since it reflects a similar delay in the loss of basic daily functions as well as a prolongation of patient's autonomy and quality of life.

Moreover, this delay is also meaningful with respect to the onset of subsequent disease milestones. Indeed, data observed provides preliminary evidence towards associated delays in respiratory decline.

Duchenne muscular dystrophy (DMD) is a rare genetic disorder that affects 1 in 5,000 male newborns. It is the most serious form of muscular dystrophy, it occurs in children and it causes progressive muscle degeneration.

Becker muscular dystrophy (BMD) is a milder variant whose development varies, however, from patient to patient.

At the moment, there is no cure, although the progresses in research and clinical management by multidisciplinary teams have allowed, in recent decades, to increase life expectancy of young patients and to improve their quality of life.

Parent Project aps is the Italian association formed by patients and parents with children affected by Duchenne and Becker muscular dystrophy. Since 1996 the organization has been working to improve the available treatments, quality of life and long-term prospects of children and young people affected by the disease through research, education, training and awareness.

The basic objectives that made the association grow so far are those of supporting families through a network of Counseling Centers, promoting and financing scientific research and developing a collaborative network capable of sharing and disseminating key information.

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