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Dear Drs. Dunn and Woodcock,

As a group of physicians and scientists who have expertise in Duchenne muscular dystrophy (DMD), we respectfully request that you use the flexibility provided by FDASIA and available pathways to enable FDA accelerated approval for and allow patients with nonsense mutation DMD access to ataluren. We favor the granting of accelerated approval of ataluren in the U.S. to allow continued and broader access to patients while additional confirmatory data is collected.

Ataluren is an oral first-in-class dystrophin protein restoration therapy that has been assessed in two large double-blind, randomized, placebo-controlled trials[1,2]. The effect size was modest in the broader ITT population and statistical significance was not robust from each individual one-year trial, and this led the Advisory Committee to favor that more data was needed. However the treatment effect was substantial in the population of ambulatory DMD patients that is biologically most optimal to show a one-year treatment effect. Based on these clinical data, which are the most compelling to date for dystrophin restoration treatment in a one year placebo-controlled trial, and the absence of safety concerns from long term exposure, ataluren has been made available to large numbers of patients in Europe through a conditional approval pathway since 2014. The CHMP of the EMA again recently concluded that the totality of data from the two trials, which were designed prior to the availability of natural history data for the 6-minute walk test, showed substantial evidence of a treatment effect and merited conditional approval and a robust international confirmatory trial is now in progress.

As was clearly stated at the recent Advisory Committee, there remains an urgent need for treatments that slow the progression of this disease. DMD is a severe, progressive, and rare neuromuscular disorder caused by the lack of functional dystrophin protein. Due to the lack of dystrophin, muscle fibers are damaged with normal activities and are replaced by fat and connective tissue. Once this occurs, muscle tissue cannot be regained and clinically meaningful functions are progressively lost. Ataluren targets the proximate cause of disease and restores a small amount of appropriately localized dystrophin. Ataluren has clearly demonstrated in preclinical models an induction of dystrophin, and a majority of boys treated with ataluren had an observed increase in dystrophin as measured by immunofluorescence after 28 days of administration. While the amount of dystrophin produced is admittedly small, the induction of any dystrophin is likely therapeutically relevant and indeed was part of the basis for approval of eteplirsen.

The two large, double-blind, placebo-controlled trials included more than 400 subjects and all key clinical endpoints favor ataluren over placebo. As discussed at the Ad Com, there is less than a 1% probability that these findings favoring ataluren would occur by chance if there were no drug effect. Additionally, findings that atalurin delays in loss of ambulation and pulmonary function decline relative to natural history controls are consistent with the measured effect and strongly supports a therapeutic benefit of ataluren (discussed in detail below).

Testimony of the patients and parents at the Advisory Committee Meeting, in addition to statements from those that submitted letters to the docket, describe highly unusual disease courses where the patient perception is that ataluren had a meaningful benefit. While any one anecdote is difficult to interpret, the consistency of the stories is overall highly suggestive of a therapeutic benefit. The stories from affected men and families of children that have experience both on and off the drug, vividly described a typical decline when off drug and stabilization in the rate of functional decline once the drug was resumed. Patients with DMD in late teenage years and early adulthood clearly described a course of disease progression far different from what we typically see clinically when treating patients with steroids alone. These compelling testimonies are consistant with our observations of patients we have treated and highlight the tremendous need and the clear benefit of even modest slowing of disease progression to patients and their families.

While the package presented may not fulfill the conventional strict criteria for full approval, when considered in aggregate, these data do represent substantial evidence of efficacy that warrants accelerated approval. Using best clinical and scientific judgment, we believe the benefits of making ataluren available to a broader population of nonsense mutation DMD patients while confirmatory data is being collected is a public health benefit that far outweighs the risks.

Given that Ataluren has now been administered over multiple years to a relatively large group of Duchenne boys, it is possible to explore if there is a long-term benefit relative to the typical disease progression. The age at loss of ambulation is a hard and clinically meaningful endpoint recently linked to the rate of subsequent pulmonary decline in patients with DMD. The PTC extension Study 019 includes 49 ambulatory patients (94% on steroids at baseline) and showed a median age at loss of ambulation of 16.3 years (see Figure 1a). This is in substantial contrast to published data[3] from the Cooperative International Neuromuscular Research Group (CINRG) presented at the Advisory Committee meeting (Figure 1b) that show a median age at loss of ambulation in 330 steroid-treated DMD patients to be 13.4 years (95% confidence interval for the median of 12.4 – 14 years), and a median of 12.5 years for 809 steroid treated subjects in Duchenne Connect. This represents a *2-4-year longer ambulatory status in patients with ataluren treatment* over those treated with steroid therapy alone. A major criticism of this type of retrospective comparison is that the different control and ataluren-treated groups may have been functionally different prior to ataluren initiation, and thus the relatively higher age at loss of ambulation in the ataluren treated group simply reflects a more mild subject group. However, baseline characteristics between the CINRG and Study 019 cohorts were similar with no large bias towards more mild subjects in the treatment group (see Table 1). We note as well, that the 2-4-year prolongation in ambulation is actually predicted by the 48-week treatment effect of 1 to 1.5 seconds in 4-stair climb and 10M walk/run timed function tests observed with ataluren treatment in the ITT populations. This magnitude of treatment effect is similar to that of longterm steroid administration and has also been associated with an approximate 3-year prolongation in the age at loss of ambulation. These data also favor that the effect of ataluren is additive with the effect of steroids, widely prescribed for Duchenne.

The 95% confidence intervals for these median estimates from very large cohorts of DMD patients make the estimate of the ataluren treatment effects to be quite statistically robust and certainly clinically meaningful and substantial to a patient and family.

The FDA expressed concern regarding the need to control for mutation subtype in the use of natural history data. The FDA has data from the placebo controlled Biomarin drisapersen Study 044 and PTC studies 007 and 020 which provide additional comparison DMD patient cohorts. and the data clearly show that nonsense mutation patients have similar natural history to most other mutation subtypes. Based on 48-week changes in 6-minute walk test distance, the placebo groups from these studies indicate that nonsense mutation DMD patients (from PTC studies 007 and 020) look virtually identical to exon 51 skip-amenable patients (from Biomarin Study 044). . Other data[4] show nonsense mutation DMD patients to have similar rates of clinical disease progression in comparison to all other mutation subtypes (except exon 44 skip-amenable patients and exon 3-7 deletions). The published CINRG data on *the hard endpoint of age at loss of ambulation* was from a large cohort of patients (330 patients), 100% of whom were treated with steroids, and patients in the CINRG study had similar baseline characteristics to Study 019 patients. The Study 019 extension data of ataluren treated patients show the median age at loss of ambulation to be 2.3 years beyond the upper bounds of the 95% confidence interval for the median age at loss of ambulation in the CINRG cohort. This prolongation in age at loss of ambulation seen with ataluren treatment is clinically meaningful, a hard endpoint not attributable to motivational issues, and is also linked to time to subsequent progression to a critical 1 liter forced vital capacity (FVC) in DMD.[3] The FDA has been provided by PTC with both the CINRG data and the in press CINRG publication concerning age at loss of ambulation.

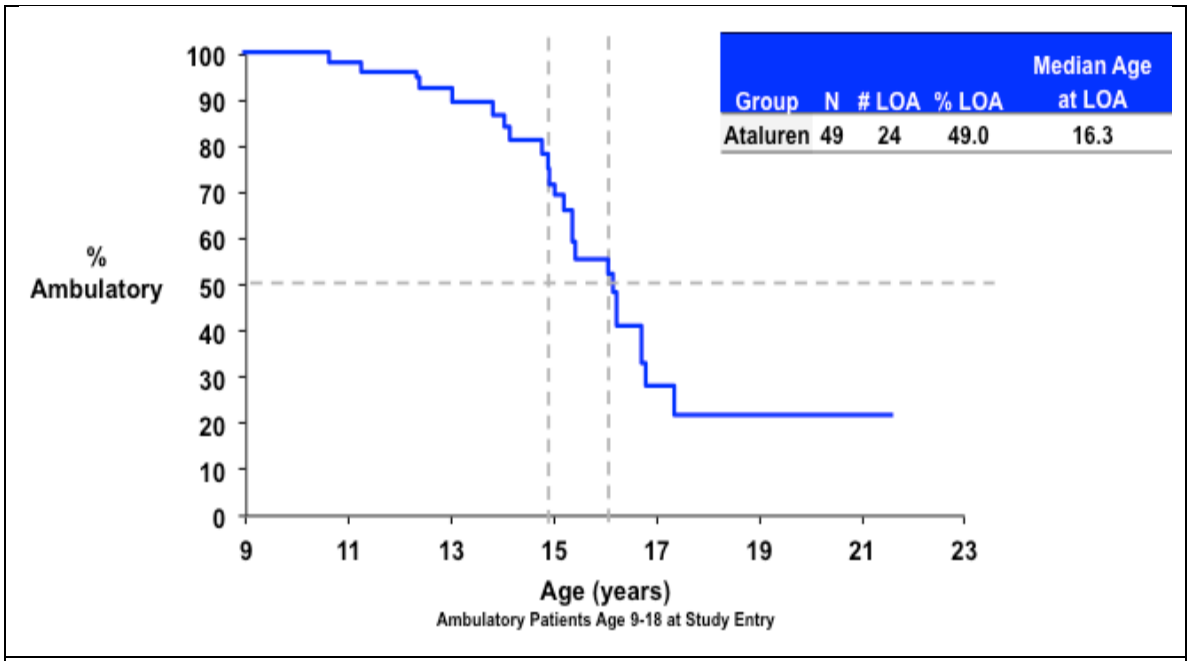

Figure 1a: Age at loss of ambulation in 49 ataluren treated patients from Study 019. (Data presented at September 28, Ad Com)

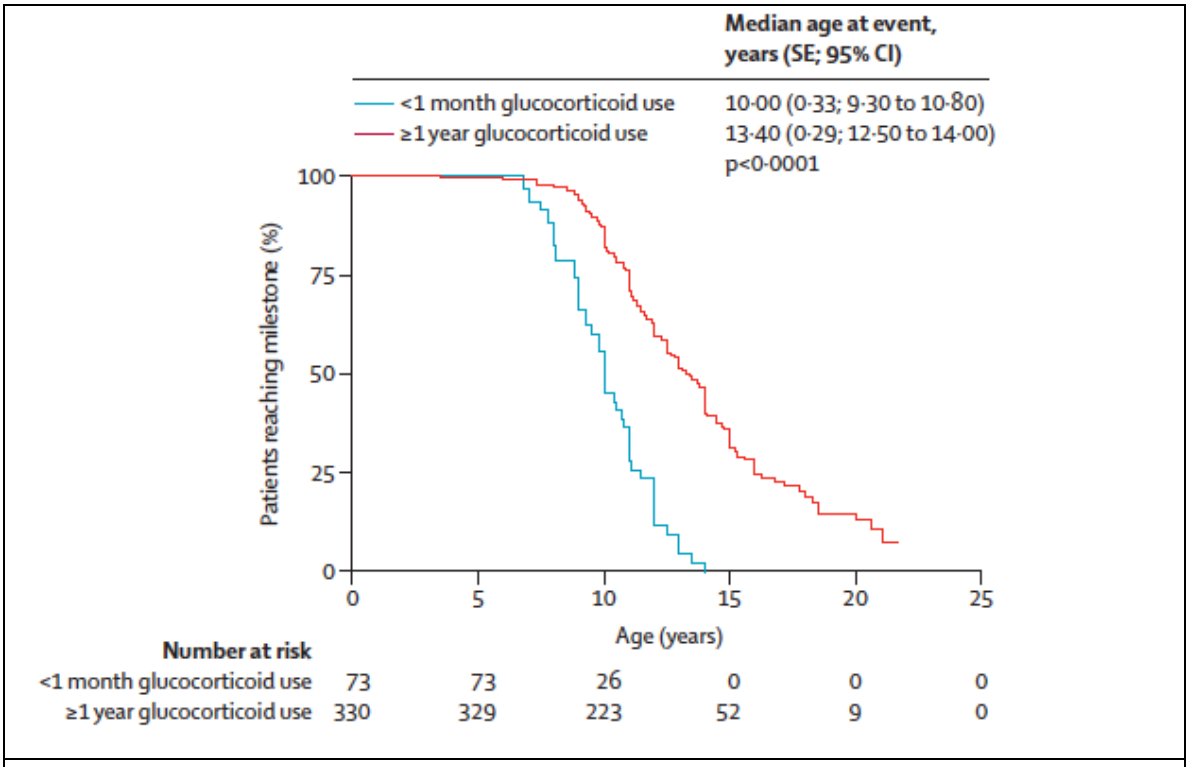

Figure 1b: Age at loss of ambulation in steroid treated DMD (red) from CINRG Duchenne Natural History Study.[1] (Data Presented at September 28, 2017 Ad Com)

Table 1: Baseline Demographics of Study 019 versus CINRG DNHS

	Ataluren Treated (Study 007 transitioning to 019)	**CINRG* DNHS (all mutations)**
N at study entry	49	330
Median Age at baseline Visit (95% CI)	8.00 (7.2-8.4)	8.76 (7.99 – 9.12)
% on Steroids	94%	100%
% on Deflazacort	61%	72%
Mean ± SEM 10 meter run/walk (95% CI)	8.37 ± 0.69 (6.98 – 9.78) beginning of Study 019	6.95 ± 0.21 (6.53 – 7.36)

Furthermore, this loss of ambulation data is corroborated by comparison of age at loss of ambulation of longterm treated ataluren on open label from 019 and 016, with age at loss of ambulation data from the Duchenne Connect Registry analyzed by Stanley Nelson, MD, Professor of Human Genetics at the David Geffen School of Medicine at UCLA and discussed during the OPH at the ataluren Ad Com on September 28, 2017 (see Figures 2a and 2b). Since there is no evidence that subjects enrolled into the ataluren trials that were rolled over to 019/016 were different from the overall Duchenne population, a direct comparison of contemporary patients is most relevant. All DuchenneConnect Registry data from October 2016 was retrieved which included age, age at loss of ambulation, steroid treatment, mutation type, and clinical trial participation. Since exon 44 skip-amenable patients are known to have milder disease severity and clinical trial participants may have a strong drug effect, these groups were removed from the comparator. A large group of 809 steroid treated subjects remained with a median age at loss of ambulation of 13 years. The median age at loss of ambulation in ataluren treated patients from PTC Studies 016 and 019 was 16.8 years shown in Figure 2a (log rank p = 3.2e-10). There was some trend towards more mild disease in the nonsense mutations subjects within DuchenneConnect, but even if we consider only nonsense mutation DMD patients on steroids (n=89), the median age at loss of ambulation was 14 years in steroid treated patients from Duchenne Connect, in comparison to 16.8 years in ataluren treated patients as shown in Figure 2b (log rank p = 1.9e-6). Both of these analyses from the Duchenne Connect Registry show a significant and clinically meaningful 2.8 to 3.8 year prolongation in the age at loss of ambulation in ataluren treated patients, which is very consistent with the prospective natural history data comparison from the CINRG Duchenne Natural History study.

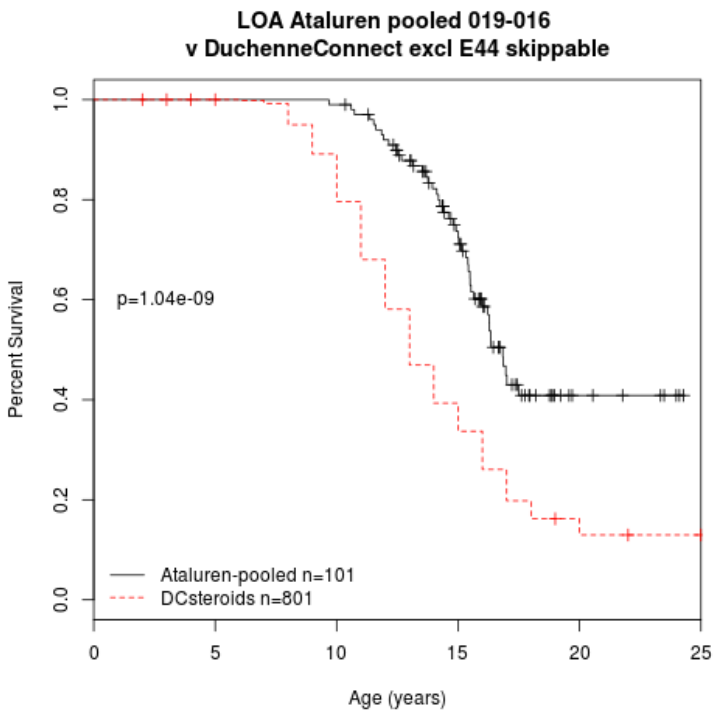

Figure 2a: Age at loss of ambulation in n=801 steroid treated DMD patients (excluding exon 44 skip amenable patients) from Duchenne Connect Registry (red) versus n=101 ataluren treated patients from Study 016 and 019 (black). Data Courtesy of Stanley Nelson, MD, UCLA

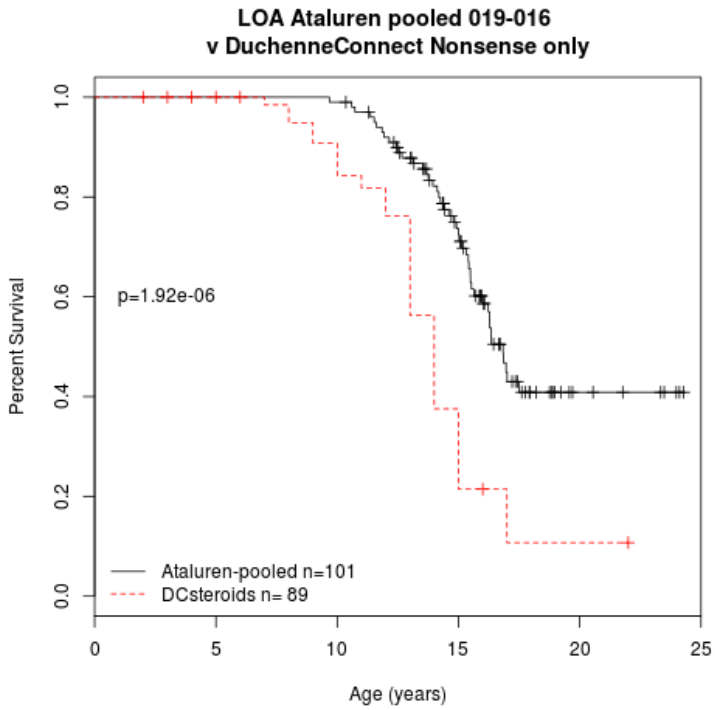

Figure 2b: Age at loss of ambulation in n=69 steroid treated nonsense mutation DMD patients from Duchenne Connect Registry (red) versus n=101 ataluren treated patients from Study 016 and 019 (black). Data Courtesy of Stanley Nelson, MD, UCLA

In support of a positive drug effect, an evaluation of non-ambulatory patients that have been treated with ataluren long-term shows a reduced rate of pulmonary decline in comparison to natural history data collected prospectively on DMD patients treated only with steroids from the CINRG Duchenne Natural History Study. This reduced rate of progression translates into a four-year prolongation in the onset of decline in absolute FVC. This benefit of lung function is particularly relevant for DMD as boys often die due to respiratory complications including respiratory failure. There is a delay in progression to a forced vital capacity of 1 liter when assessing progression rates by age (Figure 1a) and duration of follow-up (Figure 1b).

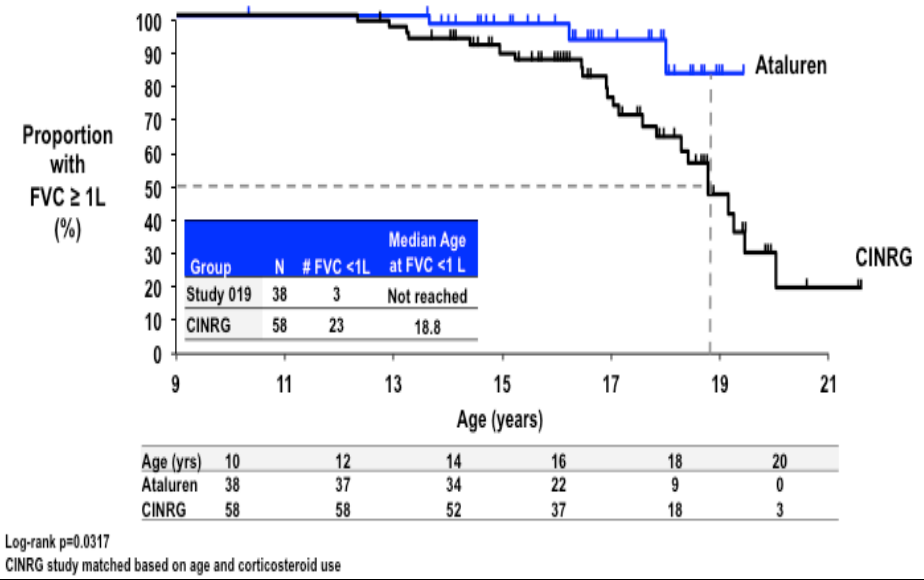

Figure 3a: Proportion of patients with FVC ≥ 1 liter by age in n=38 ataluren treated patients from Study 019 (blue) versus CINRG DNHS (black). Log-rank p=0.017. CINRG patients were matched based on age and corticosteroid use. Baseline age and baseline FVC were well balanced.

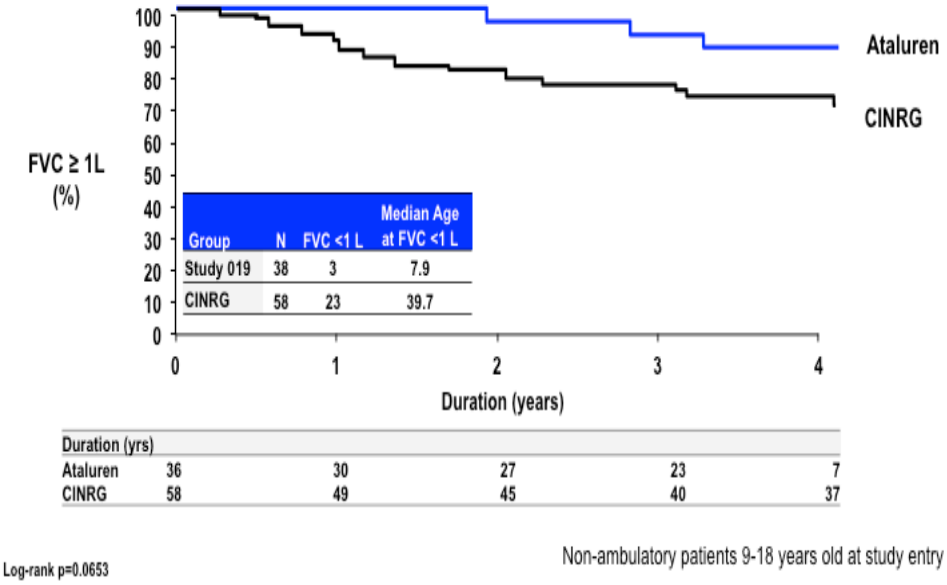

Figure 3b: Proportion of patients with FVC ≥ 1 liter by duration of follow-up in n=38 ataluren treated patients from Study 019 (blue) versus n=58 CINRG DNHS (black). Log-rank p=0.0653. CINRG patients were matched based on age and corticosteroid use. Baseline age and baseline FVC were well balanced.

This is particularly compelling because the CINRG Duchenne Natural History study shows an increased risk of death in those patients who drop below a 1 liter FVC.[3,5] The relationship between the risk of death and FVC was in the CINRG data set by calculating the hazard ratio of dying once reaching an FVC of 1 liter or less with a Cox proportional hazards model. Analysis was limited to participants who reached a FVC of 1L during the study to accurately define the age at event occurrence. In addition, they considered only those subjects with a PFT assessment within 12 months of the last study visit or death.

A total of 45 patients in the CINRG Duchenne Natural History Study died during the conduct of the study. The hazard ratio of death when reaching a FVC of 1 liter or less was 4.10 (95% CI 1.29 – 13.07, p=0.017), indicating that patients who reached this pulmonary milestone were more likely to die.[3,5] This is consistent with previous literature showing a reduced 5-year survival in DMD patients progressing below the critical threshold of a 1 liter FVC.[6]

The loss of ambulation comparisons, where ataluren treatment is associated with a 2-4 year prolongation in ambulation over matched patients in the CINRG database *and* the Duchenne Connect registry are compelling as they reflect long-term exposure and robust differences between untreated controls and ataluren treated study subjects. We use loss of ambulation as a key metric of disease severity, and it is accepted and documented that delaying loss of ambulation in DMD is linked to delay in subsequent loss of upper arm use, development of scoliosis, and need for mechanical ventilation.[3]

Future and ongoing post-marketing trials for ataluren can assess the long-term benefits in patients with nonsense mutation DMD. The delay in loss of ambulation reported in patients given ataluren will hopefully extend to longer-term benefits in both upper-limb and pulmonary function in non-ambulatory patients with DMD.

We ask you to use your clinical and scientific judgment and use available pathways (e.g. accelerated approval based on an intermediate endpoint) to allow patients to have access to ataluren now. We want to be able to prescribe ataluren to patients who may benefit as our European colleagues have had the privilege of doing for the last four years. From the totality of the data above, it is our collective opinion that our patients should benefit from access to Ataluren now while the necessary post-marketing confirmatory data is collected.

We thank you for your consideration.

Sincerely,

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