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CURRENT OPINION

Opinion of the Italian Association of Myology on Ataluren for the Treatment of Nonsense Mutation Duchenne Muscular Dystrophy

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Abstract
The Italian Duchenne muscular dystrophy expert clinicians, gathered in the Italian Association of Myology (AIM), intend to express a position against the suspension of the Marketing Authorization of ataluren (Translarna®) for the treatment of nonsense mutation Duchenne muscular dystrophy. The marketing authorization has been recently withdrawn by the European Commission following a recommendation from the Committee for Medicinal Products for Human Use of the European Medicines Agency. This negative recommendation was based on the fact that three randomized controlled trials of ataluren in nonsense mutation Duchenne muscular dystrophy (007, 020, and 041) have failed to show statistically significant differencs in favor of the treatment in the selected primary outcomes for each individual study, i.e., 6-min walk distance, in the intent-to-treat population for 007 and 020 and in a subgroup for 041. However, observed differences always favored treatment, and several clinically meaningful secondary outcomes were positive and statistically significant across studies. Importantly, the largest and longest phase III study (041) showed a statistically significant effect in favor of ataluren in the wider intent-to-treat population. Furthermore, a long-term registry of "real-world" ataluren treatment data (Strategic Targeting of Registries and Database of Excellence, STRIDE), in addition to confirming a reassuring safety profile, suggested a prolonged maintenance of ambulatory, upper limb, and respiratory function. We deem that a withdrawal of ataluren from the European market would harm not only patients with nonsense mutation Duchenne muscular dystrophy, but the whole neuromuscular field, in which clinical trials are challenging because of the heterogenous complex slow-progressing nature of the disorders.

1 Introduction

The expert Italian clinicians in the field of neuromuscular diseases and especially Duchenne muscular dystrophy (DMD), gathered in the Italian Association of Myology (AIM), intend to express a position against the suspension of the marketing authorization (MA) of ataluren (Translarna®) for the treatment of nonsense mutation DMD (nmDMD). Suspension of the MA has been recently recommended to the European Commission (EC) by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA). An Italian language version of this paper has been sent as an open letter to the EC in December 2024. Our position is based on a scientific background, a review of major clinical trials, and considerations regarding the regulatory process to date, as detailed below.

2 Scientific Background

Duchenne muscular dystrophy is a rare (incidence of about 1:5000 male individuals), severe, progressive neuromuscular disorder, caused by mutations in the *DMD* gene, located on the X chromosome. Duchenne muscular dystrophy mutations abolish the expression of the protein dystrophin in skeletal muscle fibers (including respiratory muscles) and in the myocardium [1, 2]. With current standards of care, the course of DMD involves loss of ambulation by teenage years, followed by loss of upper limb function, and respiratory and cardiac failure with severe reduction in life expectancy [3–5]. In about 10–15% of patients with DMD, the cause of the disease is a point mutation that causes the insertion of a premature termination codon, or nonsense mutation, into the coding sequence [6].

Ataluren (Translarna®) is a molecule bioavailable by oral administration, developed by PTC Therapeutics with the aim of promoting a ribosomal read-through of nonsense

Key Points

Clinical trials of ataluren have failed to show significant effects on primary outcomes, but do show consistent efficacy signals on secondary outcomes, and a good safety profile.

Marketing authorization for Translarna® in the European Union is being withdrawn following a negative assessment by the European Medicines Agency Committee for Medicinal Products for Human Use.

The authors (Duchenne muscular dystrophy clinicians from the Italian Association of Myology [AIM]) express an opinion against discontinuation of ataluren because of the evidence of an effect in slowing the progression of a degenerative disease.

Reasons behind the failure to reach statistically significant primary endpoints include a relatively short trial duration, and the insufficient development of standardized outcome measures.

mutations. Pharmacodynamic proof of concept was reached in cellular and animal models, in particular in the *mdx* mouse model [7].

3 Review of Major Clinical Trials

3.1 Open-Label, Phase IIa Trial (004) [8]

This "open-label" study treated 38 children with nmDMD at escalating doses of ataluren of 16 mg/kg/day ($n=6$), 40 mg/kg/day ($n=20$), and 80 mg/kg/day ($n=12$), with planned muscle biopsies at baseline and after 28 days of treatment, with the aim of demonstrating the pharmacodynamic effect of dystrophin expression. Immunofluorescence analyses showed an increase in dystrophin-positive fibers, relative to baseline levels, of 33%, 40%, and 25% in the three dose groups, respectively. Quantitatively, a dystrophin/spectrin ratio calculation (a control cytoskeletal protein) showed an average increase of 11% ($p=0.008$) relative to baseline after treatment.

3.2 Randomized, Controlled, Phase IIb Trial (007) [9]

This study compared 60 patients with nmDMD treated with ataluren 80 mg/kg/day, 57 treated with ataluren 40 mg/kg/day, and 57 treated with placebo for 48 weeks, the primary outcome being the change in 6-min walk distance (6MWD). Inclusion criteria were age (5 years and older), 6MWD (> 75 m), and stable glucocorticoid (GC) therapy. While the 80-mg/kg/day dose, which was subsequently abandoned, demonstrated results similar to placebo, the ataluren 40-mg/kg/day population showed a 31.3-m advantage over placebo ($p=0.056$) in the corrected intent-to-treat (ITT) population. The corrected ITT comprised the entire population, with the replacement of baseline 6MWD values with screening values in two patients (in the placebo and 80-mg/kg/day arms) who had experienced lower limb trauma immediately prior to baseline. Secondary endpoints (timed function tests [TFTs]: standing from supine, walking 10 m, climbing and descending four standard steps) showed numerical differences in favor of Translarna® 40 mg/kg/day. A prespecified analysis of patients with 6MWD at baseline < 350 m, a predictor of faster disease progression, showed a 40-mg/kg/day treatment advantage of 68.2 m compared with placebo ($p=0.0053$).

3.3 Randomized, Controlled, Phase III Trial (020) [10]

This study recruited patients with nmDMD already receiving GC therapy, aged 7–16 years, and with a 6MWD range from 150 m to 80% of the predicted value by age, comparing 115 patients treated with ataluren 40 mg/kg/day with 115 patients treated with placebo, with 6MWD at 48 weeks as the primary outcome. In the ITT population, there was a difference in favor of ataluren of 13 m, which was not statistically significant; while in a prespecified population of patients with 6MWD at baseline between 300 and 400 m (characterized by greater sensitivity of 6MWD to identify treatment effects), a difference in favor of ataluren of 42.9 m ($p=0.007$) was detected. Secondary endpoints (TFTs and North Star Ambulatory Assessment [NSAA]) showed numerical differences in favor of Translarna® in the ITT population and statistically significant differences in the 300–400 m population. A post hoc analysis, concerning the risk of loss of clinically significant functions that constitute the items of the NSAA scale, showed a reduction in the risk of functional loss of 31% ($p=0.010$) in the ITT population. Despite the statistical limitation related to the post hoc nature of this analysis, we consider it particularly relevant from a clinical point of view, given that the preservation of motor function is the main objective of DMD treatments.

3.4 Randomized, Controlled, Phase III Trial (041) [11]

This new phase III study recruited patients with nmDMD already receiving GC therapy, aged ≥ 5 years, and able

to walk at least 150 m in the 6MWD, and compared 184 patients treated with ataluren 40 mg/kg/day with 176 patients treated with placebo, for an extended observation period of 72 weeks. The primary outcome remained 6MWD, but, crucially, on this occasion the primary outcome was not defined in the entire ITT population, but only in a subgroup for which maximum sensitivity of the 6MWD measure was expected, i.e., those patients with 6MWD of at least 300 m, but who took more than 5 seconds to get up from supine (92 patients treated vs 93 receiving placebo). The subgroup of patients with 6MWD at baseline between 300 and 400 m (86 treated and 83 receiving placebo), which had appeared particularly sensitive to the effects of treatment in previous studies, was also included among the predefined (secondary) analyses in the statistical analysis plan. This study design followed a specific recommendation from the EMA when renewing the conditional MA in 2016, where the main condition was to conduct study 041 (see below). The EMA's recommendation was to define the primary outcome on a population with "mid-range" function, to be chosen "arbitrarily" between the two subgroups mentioned above, while still recruiting a wider range of patients with nmDMD in the ITT population, more representative of the treatment indication in clinical practice.

The ataluren versus placebo differences in terms of a change in 6MWD were distributed as follows in the various populations, always remaining numerically in favor of ataluren: entire ITT population: 14.4 m ($p=0.0248$); 6MWD subpopulation > 300 m and time to rise from supine ≥ 5 s (primary outcome): 8.3 m ($p=0.36$); 6MWD subpopulation between 300 and 400 m: 24.2 m ($p=0.031$).

In all secondary endpoints, the numerical differences were in favor of Translarna®, with statistical significance in the ITT population for NSAA, walking 10 m, climbing steps; in the "> 300 m ≥ 5 s" subpopulation for climbing steps; and in the "300–400 m" subpopulation for linearized NSAA, walking 10 m, and climbing four steps, as well as the performance of upper limbs test for upper limb function.

4 Meta-analysis of Randomized Controlled Trials [12]

A meta-analysis of data from the three randomized trials 007, 020, and 041, considering the outcomes at 48 weeks in 354 patients treated with ataluren versus 347 treated with placebo, provides the following differences in favor of ataluren: 6MWD: 15.8 m, $p=0.0032$; walk 10 m: 1.1 seconds, $p=0.0026$; climb four steps: 1.3 seconds, $p=0.0025$; go down four steps: 1.3 seconds, $p=0.0021$; raw NSAA: 1.1 points, $p=0.0010$; linearized NSAA: 2.6 points, $p=0.0036$. In those with 6MWD 300–400 m at baseline, the difference in favor of ataluren was 33.7 m ($p<0.0001$). In 2020, a two-study meta-analysis of studies 007 and 020 was published [13], showing that the ITT populations of the two studies combined to demonstrate statistical significant effects of Translarna®, and recommending the subpopulation of patients with baseline 6MWD 300–400 m as ideal to inform future studies.

We should also consider that Translarna® functioned as a "trailblazer" for modern clinical trials in DMD, beginning recruitment at a time when 6MWD was the only validated clinical outcome. More recent trials have adopted NSAA or TFTs as primary outcomes [14, 15]; in fact, these measures were more frequently positive and statistically significant for Translarna® effects in ITT populations and relevant subpopulations in the various studies described above.

5 STRIDE Post-marketing Registry (025) [16]

Still following a recommendation from the EMA, data on the efficacy and safety of patients treated with commercially available Translarna® were entered into a longitudinal registry (Strategic Targeting of Registries and International Database of Excellence [STRIDE]) with a follow-up of up to 5 years and the possibility of entering data from "retrospective" visits, i.e., performed at the participating centers before recruitment. At the most recent data cut-off (January 2023), 298 male patients with nmDMD had been recruited. Uncontrolled data, but with prolonged observation periods, in which the use of placebo would be unethical or impractical, are relevant not only for safety, but also for long-term clinical outcomes, or disease "milestones," such as, for DMD, loss of autonomous ambulation, as well as loss of respiratory and upper limb function. The DMD population of the Cooperative International Research Group Duchenne Natural History Study (CINRG-DNHS) [17] was used as an external control, after a propensity score matching procedure based on covariates predicted to influence outcomes. These included: age at symptom onset; age at initiation of GCs; and duration of GC use (prednisone or deflazacort). The Kaplan–Meier analysis of median age at loss of ambulation showed a median value of 16.5 years in 277 STRIDE patients with all available data for the calculation of the propensity score, compared with 13.0 years in 277 CINRG-DNHS propensity-score-matched patients, estimating a delay in loss of ambulation of 3.5 years (log-rank $p<0.0001$). Similar analyses were conducted for other events, including the median time to reaching a forced vital respiratory capacity below 60% (17.7 vs 15.6 years, estimated delay of 2.1 years,

$p = 0.0085$), or the loss of the ability to raise the upper limbs above the head (15.8 vs 12.7 years, estimated delay of 3.1 years, $p = 0.0095$).

6 Phase II, Open-Label Study (045) [18]

This study, whose results are available online but not as a peer-reviewed article, evaluated dystrophin expression in 18 patients treated with 40 mg/kg/day of ataluren, with muscle biopsies at baseline and after 40 weeks, using quantitative methods based on electrochemiluminescence and immunohistochemistry validated by the US Food and Drug Administration. Increases in dystrophin levels of 9.2% (electrochemiluminescence) and 7.0% (immunohistochemistry) relative to baseline levels were observed in the entire evaluable population; in a subset of patients ($n = 8$), in whom the second biopsy was delayed to 62–70 weeks, the increases appeared greater (23.9% with electrochemiluminescence and 10.8% with immunohistochemistry).

7 Safety

All the studies cited above, and especially the STRIDE registry, which provides data for 1636 patient-years of ataluren exposure, show a reassuring safety profile with a substantial absence of severe drug-related adverse effects, as recognized at all stages of the regulatory process (see below).

8 Highlights of the European Regulatory Process [19]

In 2014, based on the results of the phase IIb study (007), which did not achieve the primary outcome in a statistically significant manner (see above), but showed signs of efficacy in the prespecified population with 6MWD at baseline < 350 m, the EMA granted a conditional MA for Translarna®, in patients with nmDMD ≥ 5 years of age and ambulatory, with the condition of completing the phase III study (020).

In 2016, given the results of the phase III study (020), which still did not reach the primary outcome in a statistically significant manner (see above), but showed signs of efficacy in the prespecified population with 6MWD at baseline between 300 and 400 m, as well as in various secondary outcomes, with an excellent tolerability profile, the EMA extended the MA; provided that the MA holder carry out a phase III, randomized controlled trial of longer duration (18 months), for which it was explicitly recommended to define the primary outcome on a "mid-range" subpopulation (6MWD 300–400 m or 6MWD >300 m and time to get up from supine ≥ 5 seconds) with increased sensitivity for treatment effects on 6MWD, while still recruiting a larger ITT population, which would better reflect the clinical indication of Translarna®.

In September 2023, given the negative result of the 6MWD primary outcome, predefined in the subpopulation with baseline 6MWD > 300 m and time to get up from supine ≥ 5 seconds, and despite positive and statistically significant results in the ITT population and in the 6MWD 300–400 m subpopulation, the CHMP judged study 041 as "failed". This judgment represents the basis of the recommendation against renewal of the MA, with the motivation that signals of efficacy in secondary outcomes, or in subpopulations different (albeit predefined) from the one defined for the primary outcome, represent only supportive criteria, and cannot replace the main criterion consisting of the achievement of a statistically significant primary endpoint. The same reasoning applied for uncontrolled registry data, such as STRIDE data, for which there are a number of potential confounders, such as calendar time in which the studies were carried out ("calendar bias"), different selection criteria (e.g., inclusion of patients who are mainly still ambulatory in STRIDE, "immortal time bias"), a different genotype (i.e., nmDMD in STRIDE and global DMD in CINRG-DNHS, "genotype bias"), and potential preferential inclusion in STRIDE of patients with a more benign course ("selection bias").

In January 2024, following a review procedure requested by the MA holder, the CHMP reached unchanged conclusions, and forwarded its recommendation to the EC to ratify the withdrawal of MA. In May 2024, the EC rejected the CHMP's recommendation to suspend the MA for Translarna®, requiring the CHMP to fully re-evaluate, and explicitly suggesting to carefully consider data from the STRIDE registry.

Between June and October 2024, a further evaluation procedure of Translarna® by the CHMP took place, during which the MA holder corroborated the conclusions on efficacy obtained by the STRIDE registry by presenting literature data and new analyses that addressed potential bias [20], in particular: no changes in standards of care related to motor function in the period between the collection of CINRG and STRIDE data [21, 22]; evidence that the type of mutation (in particular nonsense vs deletions) does not represent a relevant predictor of outcome, compared to GC therapy and functional status [23]; median age at loss of ambulation unchanged in the STRIDE subpopulations from

Italy and the UK, countries that included 98% of patients treated in the registry (i.e., no "selection bias"); and pairing via a propensity score only with ambulatory CINRG-DNHS patients at the time of recruitment (i.e., no "immortal time bias"), which showed unchanged results.

In October 2024, the CHMP again forwarded to the EC, the recommendation to not renew the Translarna® MA, with motivations that were still substantially unchanged. In all evaluation procedures at the EMA, the safety profile of Translarna® has always been rated as very good and has never raised concerns.

During the regulatory process, the CHMP, on the basis of indications from the Scientific Advisory Group Neurology (SAG-N), has always evaluated clinical data as more relevant than data on dystrophin expression, considering the quantitative relationships between pharmacodynamic dystrophin data and clinical outcomes unclear, and therefore not essential for decision making. In fairness, it should be observed that dystrophin expression data for Translarna® is overall quite scarce, as data collected within study 004 suffered from methodological limitations and biopsy quality issues, and study 025 data are not available as a peer-reviewed publication.

As we were drafting this article in December 2024, a meeting of the Standing Committee of the EC was awaited, which would vote on the recent negative recommendation from the CHMP. During this meeting, the CHMP's assessment was deemed "robust," but a high unmet need for treatment was recognized in nmDMD, so that in these "very special circumstances," therapeutic continuity should be managed in patients already under treatment. In March 2025, the EC definitively adopted the CHMP's recommendation, effectively withdrawing the MA for Translarna®, while indicating that "individual countries within the European Union can leverage Articles 117(3) and 5(1) of the EU Directive 2001/83 to allow continued use of Translarna®". These Articles regulate in EU countries the temporary and exceptional use of an unauthorized drug in individual patients who were already receiving treatment before the suspension of the MA, under the direct responsibility of the healthcare professional.

9 Comments and Opinions

Evaluating the available scientific data in their entirety, with an approach aimed at considering the totality of the evidence, it seems clear that Translarna® is effective in slowing the loss of motor function measured with 6MWT, NSAA, and TFTs in ambulatory patients with nmDMD. This evidence derives from more than 700 patients with nmDMD randomized 1:1 and followed for at least 48 weeks. The estimated magnitude of the effect may seem small (e.g., 15 m for 6MWD), but the short duration of the observation period should be kept in mind, in patients who at the beginning of treatment have already experienced years of progressive disease with fibrofatty replacement of muscle tissue and loss of motor function. We consider this short time span the main reason for the failures of Translarna® studies to reach statistically significant results in the primary outcomes; a second reason being the yet incomplete development of clinical outcomes at the time of inception of the various studies.

However, the crucial goal in the treatment of patients with DMD, and other unilaterally progressive neuromuscular diseases, as often indicated by patients and their representatives (e.g., https://buysometime.eu), is to slow down the progression of the disease, and preserve function over the time of several years. For example, in study 041, it was shown that the median time to permanently lose 10% of 6MWD is prolonged from 48 to 74 weeks with treatment. This perspective on the data highlights its clinical relevance, in our opinion, more than the assessment of average numerical changes.

In this context, the relevance of the results from the STRIDE registry becomes more evident. On the one hand, we agree with the CHMP's methodological considerations, which rightly point to potential bias in externally controlled, non-randomized studies. On the other hand, it should be considered that long-term outcomes are not explorable with randomized trials, and that the MA holder has performed every possible analysis to account for possible known confounding factors (e.g., time of data collection, standard of care, selection of ambulatory patients at baseline, possible selection of patients with a benign course, GC dosage, genotype-related variables) obtaining consistent results in any case. In support of the consistency of the STRIDE data with those deriving from controlled trials, there is also the fact that the progression at 48 weeks of 6MWD, NSAA, and TFTs in STRIDE patients, compared with the meta-analysis of the active arms in the three studies 007, 020, and 041, is very similar (e.g., −25.4 m vs −25.7 m 6MWD; −2.10 vs −2.10 NSAA points; and +0.95 vs +0.86 seconds to walk 10 m). Finally, it seems reasonable, based on current knowledge on the progression of DMD, that an average difference of 15–30 m in 6MWD in the first year of treatment can translate, in the long term, into a maintenance of autonomous walking in the order of 3–4 years. However, as the variability in age at loss of ambulation in nonsense dystrophinopathy is much larger than 3–4 years [24, 25], the effect of Translarna® may be hardly appreciated in single cases (by clinicians or patients), or in small case series followed at individual centers, possibly leading to impressions of low or no efficacy.

The CHMP's criteria, which relied strictly on the failure to achieve the primary outcome in the three randomized trials 007, 020, and 041, appear to us to be overly formalistic in this particular context, and in contrast with the totality of the evidence. In particular, with regard to study 041, the

one with the largest sample size and an extended duration of 72 weeks, it seems clear to us that the selection as a subgroup for primary analysis of patients with 6MWD > 300 m and time to get up from supine ≥ 5 seconds represented a methodological mistake, influenced by recommendations from the regulatory bodies themselves; whereas the global ITT population, which inherently provides a more faithful representation of the clinical treatment indication, as well as the 6MWD 300–400 m subpopulation, already identified as sensitive in previous studies, showed statistically significant effects of ataluren.

We also consider the CHMP's refusal to consider data from the meta-analysis of the three randomized studies as excessively formalistic, and in contrast with the totality of the evidence, as none of these is considered "positive". We do recognize that accumulating several negative studies could lead to identifying, in the combined data, false associations, which, although statistically significant, would not be clinically meaningful. This, however, does not seem to be the case of Translarna®, which has always and consistently, in various studies, demonstrated numerical differences in favor of treatment, with difficulty in meeting the primary statistical objective related to the relatively short duration of the studies, the ultra-rare nature of the disease, and the heterogeneity of clinical progression. All these challenges are well known in the field of clinical research in DMD [26].

In conclusion, we reiterate our position against the discontinuation of the MA for Translarna®, which will deprive European patients with nmDMD of an effective and safe treatment, just as many of them begin to experience, after some years of treatment, the long-term benefits shown by scientific data, and which we as clinicians appreciate in our daily practice. In addition, it will deprive newly diagnosed young patients of a possibility to access a safe drug, with a concrete possibility of modifying the history of the disease over years of treatment; all this, in a landscape where therapeutic alternatives are extremely limited. In particular, nmDMD may not benefit from exon skipping drugs currently being experimented, while microdystrophin gene transfer therapy could be ideally associated with stop codon read-through, rather than representing an alternative. Participation in clinical trials of these and other therapeutic approaches may be hindered by Translarna® treatment, but considerations about such treatment plans should be made individually, on a case-by-case basis.

Finally, we believe that the withdrawal of the MA for Translarna® will harm not only patients with nmDMD, but the entire field of rare neuromuscular diseases, all of which are characterized by slow progression over time, difficulty in developing outcome measures and sensitive biomarkers, clinical heterogeneity, poor knowledge of natural history, and difficulty in recruiting homogeneous groups of patients. It is evident that this field requires regulatory principles that are rigorous, but innovative, starting with a principle of evaluation based on the totality of evidence, rather than on a formalistic hierarchy of primary and secondary outcomes.

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Authors' Contributions LB drafted the manuscript. All authors reviewed and edited the manuscript for intellectual content, and approved the final version.

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