EMA/CHMP/555483/2024 Corr [1]
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Translarna

International non-proprietary name: Ataluren

Procedure No. EMEA/H/C/002720/R/0071

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

[1] 30/10/2024

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Status of this report and steps taken for the assessment				
Current step[1]	**Description**	**Planned date**	**Actual Date**	**Need for discussion**[2]
☐	Start of procedure:	26 Feb 2023	26 Feb 2023	☐
☐	CHMP and PRAC Rapporteurs Joint Assessment Report	25 Apr 2023	03 May 2023	☐
☐	CHMP and PRAC members comments	02 May 2023	15 May 2023	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	12 May 2023	12 May 2023	
☐	Updated CHMP and PRAC Rapporteurs Joint Assessment Report	04 May 2023	19 May 2023	☐
☐	Request for Supplementary information	25 May 2023	25 May 2023	☐
☐	MAH responses to (RfSI) received on	14 Jul 2023	14 Jul 2023	☐
☐	Re-start of procedure	17 Jul 2023	17 Jul 2023	☐
☐	CHMP and PRAC Rapporteurs' joint assessment report	18 Aug 2023	18 Aug 2023	☐
☐	PRAC members comments	23 Aug 2023	n/a	☐
☐	Updated PRAC Rapporteurs Assessment Report	24 Aug 2023	n/a	☐
☐	PRAC endorsed relevant sections of the assessment report[3]	31 Aug 2023	31 Aug 2023	☐
☐	CHMP members comments	04 Sept 2023	04 Sept 2023	☐
☐	Scientific Advisory Group meeting[4]	05 Sept 2023	05 Sept 2023	☐
☐	Updated CHMP and PRAC Rapporteurs joint assessment report[4]	07 Sept 2023	n/a	☐
☐	An oral explanation took place on[4]	12 Sept 2023	12 Sept 2023	☐
☐	Initial Opinion[4]	14 Sept 2023	14 Sept 2023	☐
☐	Start of the re-examination procedure[4]	28 Nov 2023	28 Nov 2023	☐
☐	Preliminary re-examination CHMP Rapporteur Assessment Report[4]	22 Dec 2023	22 Dec 2023	☐
☐	Preliminary re-examination CHMP Co-Rapporteur Assessment Report[4]	22 Dec 2023	21 Dec 2023	☐
☐	Comments from CHMP[4]	09 Jan 2024	09 Jan 2024	☐
☐	N-SAG Meeting [4]	11 Jan 2024	11 Jan 2024	☐
☐	Updated re-examination Joint CHMP Rapporteurs Assessment Report[4]	11 Jan 2024	18 Jan 2024	☐
☐	Oral Explanation at CHMP[4]	23 Jan 2024	23 Jan 2024	☐
☐	Final opinion after re-examination[4]	24 Jan 2024	24 Jan 2024	☐
☐	The European Commission returned the Opinion to the Agency, requesting to: further	22 April 2024	22 April 2024	☐

Status of this report and steps taken for the assessment				
	consider whether the totality of the data including the additional data from patient registries and real-world evidence highlighted by Czechia are sufficiently comprehensive to conclude on the benefit/risk balance of Translarna and whether these additional data/evidence would impact the CHMP conclusion on the benefit/risk profile of Translarna; to consider the impact of the appellate judgment of the Court of Justice of the European Union in Case C-291/22 P and restart the the procedure from the point in time when the initial SAG was convened			
☐	Scientific Advisory Group meeting	10 June 2024	10 June 2024	☐
☐	Updated CHMP and PRAC Rapporteurs joint assessment revised report	17 June 2024	18 June 2024	☐
☐	An oral explanation took place on	25 June 2024	25 June 2024	☐
☐	A CHMP opinion, taking into account the European Commission aforementioned requests was adopted on	27 June 2024	27 June 2024	☐
☐	Submission of the MAH's grounds for re-examination	02 Sep 2024	02 Sep 2024	☐
☐	Start of the re-examination procedure	03 Sep 2024	03 Sep 2024	☐
☐	Preliminary re-examination CHMP Rapporteur Assessment Report	03 Oct 2024	02 Oct 2024	☐
☐	Preliminary re-examination CHMP Co-Rapporteur Assessment Report	03 Oct 2024	04 Oct 2024	☐
☐	Comments from CHMP	07 Oct 2024	07 Oct 2024	☐
☐	Updated re-examination Joint CHMP Rapporteurs Assessment Report	11 Oct 2024	11 Oct 2024	☐
☐	Oral Explanation at CHMP	16 Oct 2024	16 Oct 2024	☐
☒	Final opinion after re-examination	17 Oct 2024	17 Oct 2024	☐

[1] Tick the box corresponding to the applicable step – do not delete any of the steps. If not applicable, add n/a instead of the date.

[2] Criteria for PRAC plenary discussion: interim results/outcome of the SOB that is a non-interventional PASS study challenging the benefit/risk balance of the product; new imposed non-interventional PASS resulting from the annual renewal (annex II condition); divergent positions between the Committees (CHMP and PRAC Rapp and CHMP and PRAC members) on specific aspects with significant impact on the B/R and any other situation at the discretion of the PRAC rapporteur.

Criteria for CHMP plenary discussion: interim results/outcome of the SOB challenging the benefit/risk balance of the product; fulfilment of all SOBs; non-compliance with SOB(s); new imposed PASS/PAES resulting from the annual renewal (annex II condition or new SOB); divergent positions between the

Committees (CHMP and PRAC Rapp and CHMP and PRAC members) on specific aspects with significant impact on the B/R and any other situation at the discretion of the CHMP rapporteur.

[3] Sections related to data on non-interventional PASS imposed as an SOB, Risk Management Plan (safety concerns, Pharmacovigilance plans, Risk minimisation Measures), sections on issues originating from parallel/recent PSUR or signal assessment, additional monitoring, pharmacovigilance inspections and preliminary conclusions on the benefit/risk balance.

[4] Procedural steps annulled. Following the appellate judgment of the Court of Justice of the European Union in Case C-291/22 P, CHMP decided to convene a new scientific advisory group on neurology (SAG-N) for Translarna. The procedure step of the SAG-N conducted on 05 September 2023 was annulled and all subsequent procedural steps were considered invalid.

Table of contents

1. Background information on the annual renewal

The European Commission issued on 31 July 2014, a conditional marketing authorisation (MA) for Translarna. This implied that pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 5 of Commission Regulation (EC) No 507/2006, the marketing authorisation holder (MAH) has to complete ongoing studies, or conduct new studies, as listed in Annex II.E of the MA, the so-called Specific Obligations (SOBs). These data form the basis of the renewal of the conditional MA.

Translarna was designated as an orphan medicinal product EU/3/05/278 on 27 May 2005.

A conditional MA is valid for one year and may be renewed annually upon request by the MAH. Therefore, pursuant to Article 14-a of Regulation (EC) No 726/2004 and Article 6(2) of Commission Regulation (EC) No 507/2006, the MAH PTC Therapeutics International Limited, submitted to the Agency on 3 February 2023 an application for the annual renewal of the conditional MA for Translarna.

The period covered by this annual renewal is from 31 December 2021 to 31 December 2022.

Variation procedure II/69 and renewal procedure R-71 were assessed in parallel due to their submission dates. As a result, there is an overlap in the data submitted for both procedures. The CHMP reviewed the data within the scope of each procedure. Where the assessment of the type II variation application and that of the annual renewal application intersect, reference is made between the assessment reports of the two procedures.

On 14 September 2023, the CHMP issued a negative opinion for the annual renewal of the Conditional Marketing Authorisation of Translarna. On 27 November 2023, the MAH submitted the grounds for re-examination of the CHMP opinion and on 24 January 2024, the CHMP adopted its final opinion recommending to not renew the conditional marketing authorisation for Translarna.

During the decision-making process for issuing the Commission Implementing Decision, on 22 April 2024 a meeting of the Standing Committee had been convened at the request of Czechia which discussed the content of the CHMP opinion. As a result of this discussion, on 2 May 2024, the EC returned the opinion to the Agency and request the CHMP to further consider the following two scientific questions in a revised opinion:

- whether the totality of the data including the additional data from patient registries and real-world evidence highlighted by Czechia are sufficiently comprehensive to conclude on the benefit/risk balance of Translarna;

- whether these additional data/evidence would impact the CHMP conclusion on the benefit/risk profile of Translarna.

The additional real-world data brought to the attention of the Commission during the decision-making process were taken into account when re-evaluating the benefit-risk balance of Translarna.

In addition, in the Commission letter of 2 May 2024 returning the CHMP final opinion to EMA, the EC, taking into account the impact of the appellate judgment of the Court of Justice of the European Union in Case C-291/22 P, requested that the procedure was restarted from the point in time when the initial scientific advisory group was convened. Consequently, the procedure step of the SAG-N conducted on 05 September 2023 was annulled and all subsequent procedural steps were considered invalid. The assessment of the annual renewal was therefore reset to this stage of the initial annual renewal procedure, i.e. prior to the conduct of the SAG-N. A new SAG-N was conducted on 10 June 2024 and its outcome was taken into account by the CHMP when re-evaluating the benefit-risk balance of Translarna as part of the present annual renewal procedure.

2. Overall conclusions and benefit-risk balance

2.1. Specific Obligations (SOBs)

Compliance of SOB data submitted

During the period covered by this annual renewal, data on the SOBs were submitted that overall are compliant in terms of adherence to deadlines and in terms of acceptability of data submitted.

As part of this annual renewal, the CHMP has noted that the results of study 041 (i.e. the last SOB) were assessed in a parallel variation procedure (namely, EMEA/H/C/002720/II/069) and that the study was conducted as per the agreed protocol and timelines. However, study 041 did not meet its primary objective (was a failed study), and its impact on the benefit risk assessment of Translarna is re-evaluated in this annual renewal procedure, taking into account all available data, including study 041 results.

Description	Due date
In order to confirm the efficacy and safety of ataluren in the treatment of ambulant patients with nmDMD aged 5 years or older, the MAH will conduct and submit the results of a multicentre, randomised, double-blind, 18-month, placebo-controlled study, followed by an 18-month open-label extension, according to an agreed protocol.	Proposed by MAH: Final study report to be submitted Due date: September 2022.

Updated list of specific obligations (SOBs)

Not applicable.

2.2. Benefit-risk Balance

During the period covered by this annual renewal, new data have emerged, particularly the study 041 results related to the last SOB, which were also considered in the parallel variation procedure EMEA/H/C/002720/II/0069. These data are considered to have an impact on the benefit-risk of Translarna in the approved indication. Therefore, the benefit/risk of Translarna is re-assessed in the context of this annual renewal, based on the totality of the data, which includes the data at the time of the conditional approval, data generated as per the specific obligations (the data from study 020, as well as the data from study 041), data from STRIDE (study 025o) registry and additional real world data made available to the Committee as well as data on paediatric studies 045 and 046.

Regulatory/procedural context

Ataluren enables ribosomal readthrough of mRNA containing a premature stop codon induced by a nonsense mutation in the DNA. As a result of the ribosomal readthrough, a full-length protein is produced.

In 2014, a conditional market authorisation (CMA) was granted based on the results of phase II study 007, a multicentre, randomised, placebo-controlled study of 48 weeks duration in which two dose regimens of ataluren were compared to placebo in patients with nonsense mutation Duchenne muscular dystrophy (nmDMD). The low dose of ataluren was 10/10/20mg/day, and the high dose of ataluren was 20/20/40mg/day. As the results from the primary efficacy analysis were not statistically significant, Study 007 was considered inconclusive, i.e., non-confirmative. The MAH defined a corrected ITT population (cITT) created by the replacement of the value of 6 minutes walking distance (6MWD) at

baseline by the screening value in two patients who suffered from leg injuries limiting the performance of 6MWD at baseline, which showed a borderline beneficial effect on the 6MWD for the low dose only; however, this was not statistically significant. The high dose did not show a separation from placebo, and the MAH concluded that there is a bell-shaped dose-response curve. Efficacy was supported on the Timed Function Tests (TFT). The MAH identified a subgroup, i.e. patients with baseline 6MWD ≥150m and ≤80% of predicted value, referred to as ambulatory declined phase (ADP) subgroup. Effect size in this subgroup was larger. As this was a *post hoc* exercise, a confirmative study was considered needed. Thus, as a Specific Specific Obligation (SOB), the MAH was requested to perform an additional clinical efficacy study (study 020) to confirm the positive benefit/risk balance of ataluren in ambulatory subjects with DMD. Study 020 was a multicentre, randomised, double-blind, placebo-controlled, confirmatory study with 10, 10, and 20 mg/kg doses in nmDMD patients in the ambulatory decline phase, i.e., aged ≥7 years of age, 6MWD at baseline of ≥150m and ≤80% of predicted value. This study did not meet its primary objective, i.e., the effect on the 6MWD was 15.4m (p=0.213) in favour of ataluren with a p-value of 0.213, this difference is not statistically significant. This effect was also falling short of a generally regarded minimal clinical important difference of 30m (McDonald et al. 2023). Hence, the results of study 020 were considered insufficient to convert the CMA into a full MA (for further details, see favourable effects and uncertainties about unfavourable effects below). However, *post hoc* analyses in patients with a baseline 6MWD between 300 and 400 and with a 6MWD <350m showed meaningful treatment differences of 47.2m ($p_{nominal}$=0.007) and 68m ($p_{nominal}$=0.0053), respectively.

Considering that a potential beneficial effect was seen in *post hoc* derived groups, it was concluded that additional data were needed to confirm these favourable effects. Hence, CHMP agreed on renewing the CMA with the obligation to perform a second efficacy study, i.e., study 041 (2016) to confirm the positive benefit/risk (i.e., to confirm the findings of *post hoc* subgroup analyses of studies 007 and 020). This study focused on subjects in a more progressive phase of their disease; hence, this population (mITT) constituted the primary efficacy population for efficacy analysis. Due to the more progressive phase, this population was anticipated to be more sensitive to show a treatment effect. In addition, to further increase the sensitivity of the study, the duration of the double-blind placebo controlled period was extended from 48 to 72 weeks.

Additional data submitted

The MAH refers to the results of the double-blind phase **study 041** and some results from the **open-label extension** phase, initially submitted in variation procedure **EMEA/H/C/002720/II/69**. In addition, the results of studies 007, 020, and 041 were subject of a **pooled efficacy analysis**.

SOB study 041

Study 041 was a phase 3, randomised (1:1), double-blind, placebo-controlled trial for 72 weeks in 360 subjects with nmDMD. The double-blind phase was followed by an open-label extension of another 72 weeks wherein subjects who received placebo switched to ataluren. The primary endpoint was the change from baseline in the 6MWD at 72 weeks. "Key" secondary endpoints were the average change in the composite TFT (time to run/walk 10 metres + time to climb 4 stairs + time to descend 4 stairs) and the change in North Star Ambulatory Assessment (NSAA).

Other secondary outcomes included the linear NSAA, individual TFT, the time to persistent 10% worsening in 6MWD, the time to loss of ambulation (LoA), the time to loss of stair-climbing and stair-descending, and the risk of loss of NSAA items.

Based on *post hoc* subgroup analyses of studies 007 and 020, the MAH claimed an effect in the subgroup with a baseline 6MWD between 300-400 m. Based on this, the MAH defined a subpopulation that was considered even more sensitive to show an effect. The primary analysis was restricted to the mITT population (185 out of 359 randomised). The mITT population was defined as subjects ≥7 years of age,

able to perform the 6MWD >300 meters, and time to stand from the supine position to a standing position >5 seconds. This population and analysis were predefined and agreed upon by CHMP in the annual renewal procedure (EMEA/H/C/002720/R/0022) concluded on the 9th of January 2017.

Both studies were the subject of further evaluation within EMEA/H/C/002720/R/0022: https://www.ema.europa.eu/en/documents/variation-report/translarna-h-c-2720-r-0022-epar-assessment-report-renewal_en.pdf

Pooled efficacy analysis

In addition, a pooled analysis was performed using ITT population data from studies 007, 020 and 041, resulting in a total sample size of 701, from whom 354 were treated with ataluren. This was presented in variation procedure **EMEA/H/C/002720/II/69.** Given the shorter duration of studies 007 and 020, comparisons were made at week 48 which is acceptable. However, considering the differences between the studies regarding the patient population, length of follow-up and primary analysis population, the pooled analysis is not acceptable. As part of the responses to the request for supplementary information, the MAH submitted a random effect meta-analysis with results for the ITT, mITT and a subgroup with baseline 6MWD of 300 to 400m. Data from the high dose group from study 007 was also included using two approaches: the "including" approach included high dose, commercial dose and placebo and made separate comparisons versus placebo; and the "combined" approach compared all Translarna versus placebo. The "combined" approach is considered more conservative and might better reflects the requested analysis, including all available data from Translarna and is preferred. The meta-analysis of the ITT population is considered of most interest as this population best reflects the target population as reflected in the current indication. Further, the subgroup of 6MWD 300 to 400 m was *post hoc* defined based on a larger treatment effect in all studies. Therefore, this subgroup's meta-analysis is not considered valuable for confirmatory purposes.

Further, the MAH compared the data of ataluren used in a registry study "STRIDE" (Study 025o) to a historic "Cohort group (Cooperative International Neuromuscular Research Group (CINRG)) Duchenne Natural History Study (DNHS). The groups were propensity score matched for age at first symptoms, age at starting corticosteroid use, type of corticosteroid (deflazacort vs others) and duration of corticosteroid use (<1month, ≥1 to <12 months, ≥12months). During the Oral Examination data on matching for corticosteroid dose and a rational for the lack of matching for type of mutation were presented. The effect of calendar bias was also addressed by the MAH.

Favourable effects

Study 007 (initial CMA): For the ITT a difference of -0.1m 6MWD (95% CI -30.4, 30.2; $p_{nominal}$ =0.9956, adjusted p-value=1.0000) between placebo and the high dose arm (20/20/40 mg/kg per day) and a difference of 26.4 m 6MWD (95% CI -4.2, 57.1; $p_{nominal}$ =0.0905, adjusted p-value = 0.1592) between placebo and the low dose arm (10, 10, 20 mg/kg per day) was seen. The difference in the mean change in 6MWD at Week 48 between ataluren low dose and placebo in the cITT population was 31.7 metres (95 % CI 5.1,58.3; $p_{nominal}$ =0.0197, adjusted p-value=0.0367). A *post hoc* subgroup (patients with baseline 6MWD ≥150m and ≤80% of predicted value) analysis showed a difference in the change in 6MWD at Week 48 of 49.9 metres ($p_{nominal}$=0.0096) between the 10, 10, 20 mg/kg dose and placebo.

Study 020 (first SOB): The observed difference in the mean 6MWD at Week 48 between ataluren and placebo was 15.4 meters (p=0.213) for the ITT. The difference between ataluren and placebo for the time to 10m run/walk was -1.2 seconds (p=0.117), and the treatment difference for the 4 stair descend was 1.8-seconds (p=0.012). The HR for time to loss of ambulation in the ataluren group is 0.69 (p=0.404). The difference between ataluren and placebo on NSAA total score was 1.5 point (p=0.270). In a *post hoc* defined group, i.e. patients with a baseline 6MWD ⩾300 to < 400 meters, a difference of 47.2 meters was found in the ataluren group compared to placebo at week 48 ($p_{nominal}$ =0.007). Also in

patients with a baseline 6MWD <350m, a difference of 68m in favour of ataluren versus placebo was observed ($p_{nominal}$ =0.0053). The difference in total NSAA score was 4.5 points (p=0.030)

Study 041 (second SOB) was a phase 3, randomised (1:1), double-blind, placebo-controlled trial for 72 weeks in 360 subjects with nmDMD. In study 041, a non-significant difference of 8.26 meters ($CI_{95\%}$ -26.05; -9.53, p = 0.36) and a difference of 14.42 meters ($CI_{95\%}$ 1.83 – 27.01; $p_{nominal}$ = 0.025) were found in the mITT population (n=185) and ITT population (n=359), respectively. The differences for the TFT composite was -1.04 seconds (p= 0.0892) for the mITT population and -0.70 seconds (p=0.09) for the ITT population. The difference between placebo and ataluren was 0.9 points for both populations on the NSAA total score (p=0.13). More information on results from study 041 is found in variation EMEA/H/C/002720/II/0069 procedure.

Submitted meta-analysis: In the ITT population using the combined approach, the submitted meta-analysis shows a LS mean difference from placebo of 13.8 meters in 6MWD (95% CI: 3.51, 24.08), 1.26 seconds in the TFT composite score (95% CI: -1.91, -0.61), 1.07 points in the NSAA total score (95% CI: 0.433, 1.716), and 2.64 points in NSAA linear score (95% CI: 0.861, 4.412).

STRIDE Registry Study (study 025o): The propensity score matched analysis showed that subjects in the *STRIDE Registry Study (study 025o)* reached the milestones of FVC ⩽60% predicted at a median age of 17.7 years (95%CI 16.6; 19.9). For subjects in the CINRG-DNHS this milestone of FVC ⩽60% predicted was reached at a median age of 15.6 years (95%CI 15.1; 16.4). The milestone FVC ⩽50% predicted was reached at a median age of 19.2 years (95%CI 17.8; NA) in the STRIDE Registry subjects and at 17.7 years (95%CI 16.5; 18.6) in the subjects of the CINRG-DNHS.

The median age at loss of ambulation was 16.5 years (95%CI 14.4, 19.7) compared to 13.0 years (95%CI 12.3, 13.8) in the CINRG-DNHS (p<0.0001; HR 0.455 [95%CI 0.350, 0.593]).

Uncertainties about the favourable effects

In study 007, no effect of the high dose was seen. This was odd as a greater effect was anticipated. The MAH argued that there is a bell-shaped dose response curve which was however, not evident from the non-clinical data. This was not further pursued by the CHMP. Considering that a potential beneficial effect was seen in a *post hoc* derived group, it was concluded that additional data was needed to confirm these favourable effects. In the first SOB (study 020) the overall population, i.e., ambulatory DMD subjects, did not show a clinically meaningful difference from placebo. However, a new study was requested as a clinically meaningful difference was noted in *post hoc* defined sub-groups. An extension of study duration was recommended considering the effect size of 48 weeks may be too small to allow for a firm conclusions on the effect size.

The largest effects were seen in the *post hoc* defined groups of patients with baseline 6MWD ≥300 to <400 meters and patients with baseline 6MWD ≥150m and ≤80% of predicted value based on studies 007 and 020. It was argued that these subgroup apparently are the most rapid declining and therefore the most sensitive to show an effect. Accordingly, the MAH defined a mITT population anticipating the largest effect for this population. However, results from the mITT population in study 041 did not confirm the effect seen in the initial phase 2 study (i.e., study 007) that supported the conditional marketing authorisation in 2014 and the effect in the *post hoc* analyses of studies 007 and 020 that supported the renewal of the CMA in 2016. Additionally, the difference in 6MWD between placebo and ataluren found in the ITT population of the phase III study 041 (14.4 meters after 72 weeks of treatment), is comparable to that of the phase III study 020 (15.4 meters after 48 weeks of treatment), but considerably smaller than the effect seen in phase II study 007 (31.3 meters after 48 weeks treatment, p=0.056), i.e., there is uncertainty concerning the true effect size if there at all is an effect. Moreover, the effect on the key secondary outcomes, i.e., NSAA and TFT (including the individual items), is also uncertain in study 041.

Graphically, the rate of decline as measured by 6MWD and TFT in study 041 is comparable between the placebo and ataluren group during week 24-36 to week 144 as the curves run in parallel, which further increases the uncertainty concerning efficacy of ataluren.

As per the random meta-analysis, the integrated meta-analysis violated methodological principles (see benefit-risk assessment and discussion section) and in any case results are not capable of compensating or overruling the negative findings of the individual studies.

The STRIDE registry study (study 025o) has an open-label design following only nmDMD patients who are treated with ataluren. The interpretation of results from studies using an external control should be done with caution as this type of approach is prone to bias due to measured and unmeasured confounding. In this particular case, the controls from STRIDE were matched with participants in CINRG-DNHC using propensity score matching (see above the matching parameters of the logistic PS model).

Though the updated model presented at the oral explanation in June 2024 includes matching for dose and type of corticosteroid, uncertainties remain around the matter of corticosteroid use (on-off regimen) and the rationale for the matching categorisation as an equal effect on delaying the time to loss of ambulation for everyone beyond 12 month corticosteroid use is assumed. This is questioned.

DMD mutations were not considered in the PS model. The MAH argued during the oral explanation that this aspect is not influencing the STRIDE results based on the comparability of the time to LoA between a group of nmDMD and a group of non-nmDMD participants in two registries. However, for both comparisons differences in baseline characteristics and confounding could not be excluded. Further, it is unclear how the data showing no clear effect of mutation on decrease in NSAA and 10m velocity after 1 year of follow relate to time to Loss of Ambulation.

In addition, a 2-year difference in age at first assessment is noted hampering a match on functional outcome measures. Importantly, immortal time bias is introduced as patients in STRIDE were only allowed to enter the registry if prescribed Translarna requiring them to be still ambulatory at enrolment.

Further, as the ataluren-treated nmDMD patients were enrolled into the STRIDE cohort from 2015-2022, and the untreated DMD patients were recruited into the CINRG cohort from 2006-2016, a calendar bias cannot be fully excluded. During the oral explanation, the MAH claimed that the key elements of the standard of care remained consistent over the periods of enrolment. However, the MAH made reference to four guidelines and it was noted that neither physiotherapy nor scoliosis management were formally included in the Moxley et al 2005 publication. More importantly, the most comprehensive guideline promoting a multidisciplinary treatment strategy for DMD including interventions in different areas per the different stages of DMD was only available at 2018 (Birnkrant et al, 2018). Hence, the MAH´s claim is questioned. As opposed to well-conducted trials where randomization ensures exchangeability as per known and unknown confounders, the PS-matched methods only ensures exchangeability conditional to the variables included in the model and hence, by definition cannot account for unknown confounding.

Further, the STRIDE has an open-label design with is prone to observational bias as opposed to 007, 020 and 041 RCT that included a blinded-phase. Additional limitations and uncertainties were highlighted including the difference in the definition of loss of ambulation, unclear rules for censoring and substantial missing data for which the MAR pattern of missingness was used, which is questionable. The suggested delay of 3.5 years is based on data of 5-10% of the included population. Consequently, an open-label study with an external comparator cannot compensate or overrule the results of the individual RCTs, which by design produce the most valid results by design and the best approaches to isolate the true effect size.

Unfavourable effects

The most common adverse events across all studies were headache, upper respiratory infections and gastrointestinal disorders such as nausea, vomiting, (upper) abdominal pain, flatulence, diarrhoea, stomach discomfort, constipation and regurgitation.

Uncertainties about the unfavourable effects

As the safety has been monitored for approximately 10 years and the safety data was consistent across all studies, there are currently no uncertainties on unfavourable effects beyond the safety concerns included in the RMP. The safety concerns included in the RMP are currently managed by the established risk minimisation measures and additional pharmacovigilance activities described in the RMP.

Benefit-risk assessment and discussion

In 2014, Translarna received a CMA for the treatment of nmDMD in ambulatory patients based on *post hoc* results (cITT instead of ITT population) from a phase IIb study (Study 007) showing a borderline beneficial effect on the 6MWD test supported by numerical trends in TFT as secondary efficacy endpoints. The CMA was agreed upon the condition to conduct a confirmatory study in the post-authorisation phase as a SOB (first SOB / Study 020).

In Study 020, with an intended enriched population (i.e., different thresholds for eligibility based on the baseline performance on 6MWD), the treatment effect size on 6MWD in the primary efficacy analysis was much smaller than the one reported in the cITT population in Study 007 and not statistically significant. Hence, study 020 did not confirm the benefit/risk of Translarna in the approved indication.

Post hoc subgroup analyses from both Studies 007 and 020 showed beneficial effect sizes on patients with baseline 6MWD $\geqslant$150m and $\leqslant$80% of the predicted value in study 007 and patients with baseline 6MWD $\geqslant$300 to <400 meters in study 020. Though the original SOB failed to confirm the findings of study 007, the CMA was renewed in 2016 (EMEA/H/C/002720/R/0022) with a second condition (second SOB / Study 041) to confirm the B/R of Translarna taking into account the subgroup information in the study design. As such, the primary efficacy endpoint was defined as the difference in the change from baseline in the 6MWD at 72 weeks between the ataluren arm and placebo arm in the mITT population defined as patients able to perform the 6MWD >300 meters and time to stand from supine position >5 seconds.

Thus, it was anticipated that a more sensitive population (i.e., the mITT population, which was based on exploratory *post hoc* analyses of previous studies in DMD, including study 020) would be better able to show a treatment effect of ataluren. However, a statistically significant and beneficial effect could not be demonstrated in this mITT population. Therefore, Study 041 is a failed study.. The subsequent description of the findings in the ITT population reflects the attempt of the MAH to elicit a positive result from a failed study. Indeed, the ITT population reflects the population for which the CMA was granted. However, formal statistical testing is not allowed from a methodological perspective because the primary efficacy endpoint was specified to be tested in the mITT population and not the ITT population. Even ignoring this, the observed effect in 6MWD between ataluren and placebo in the ITT did not confirm the effect seen in the initial phase 2 study (i.e., study 007) that supported the conditional marketing authorisation in 2014 and the effect in the *post hoc* analyses of studies 007 and 020 that supported the renewal of the conditional marketing authorisation in 2016. For the NSAA, the 0.9-point difference does not exceed a category shift of the mean in any of the 16 items of the NSAA.

A *post hoc* conducted meta-analysis of the efficacy data from Studies 007, 020, and 041 submitted by the MAH shows a statistically significant but not beneficial effect at the 6MWD and TFTs, in the ITT population, which is considered of most interest as this best reflects the target population of the current

indication. However, the observed overall effect seems to be driven mainly by Study 007, which formally was a Phase 2 hypothesis-generating study. The confirmatory phase III studies (Studies 020 and 041) show a non-significant and marginal difference from placebo as compared to the Phase II study 007, which could, among others, be related to a regression-to-the-mean effect. Because studies 020 and 041 are confirmative phase III studies in a larger population imposed as SOBs for this CMA, they better estimate the true effect size than the hypothesis-generating phase II study 007. Notably, the applicability of the *post hoc* performed meta-analysis is questioned on methodological shortcomings violating methodological principles for a retrospective meta-analysis ((PtC "Points to consider on application with 1. Meta-analyses; 2. One pivotal study" CPMP/EWP/2330/99). The guideline lists the prerequisites for a retrospective meta-analysis. Among others, it specifies that some studies need to be clearly positive. Considering the primary efficacy analysis of the primary efficacy endpoint, the three studies (namely 007, 020 and 041) are formally negative. Further, it specifies that pooled 95% confidence interval needs to be well away from zero. For the primary efficacy endpoint (6MWD), the lower limit of the pooled 95% confidence interval for the least squares (LS) mean in the combined approach is 3.51 meters for the ITT population (see above). Note that for the NSAA (both total and linear) and the TFT (composite as well as individual items) the 95% confidence interval for the least squares (LS) mean in the combined approach were also close to 0. The effect is marginal and therefore inconsistent not only across studies, but also across several subgroups with also changes in direction in favour of the placebo group.

The comparison to a historical external cohort of the STRIDE registry is considered supportive, but cannot overrule the results of phase III placebo-controlled studies, which by default produce the most valid results by design and the best approaches to isolate the true effect size. Additionally, interpretability of results is hampered by the aforementioned limitations / uncertainties.

Third party interventions were received from several countries, which include letters from parents or caregivers, patient organisations, healthcare professionals organisations, and treating physicians. The interveners expressed the opinion on the large unmet medical need for DMD and the benefit of Translarna in nmDMD based on their experience in the clinical practice and their interpretation of the efficacy data of Translarna mainly the efficacy data from STRIDE registry. The unmet medical need for DMD is acknowledged and it has never been questioned. The CHMP noted the information on the experience in the clinical practice from health care professionals and health care professionals organisations shared through individual case reports. The information shared on quality of life difference between ambulatory DMD patients receiving ataluren, caregiver reported quality of life and a wider consideration of possible cost benefit of ataluren is also acknowledged. However, it is considered that these interventions do not impact the conclusion on the benefit-risk of ataluren in the view of the three failed clinical trials. The opinion on the value of RWE from STRIDE is also noted but the CHMP was concerned about the aforementioned limitations and uncertainties.

Another important issue in the assessment of efficacy of ataluren is the data on dystrophin expression. In the initial application, the data on dystrophin expression was inconclusive because of poor quality (Translarna EPAR Public assessment report EMA/369266/2014). In the Article 46 procedure EMEA/H/C/002720/P46/026, submitted in 2021, additional pharmacological data on dystrophin expression was submitted and assessed. The baseline median dystrophin level as measured by ECL was 0.42% of normal (range 0.00% to 41.85%). At the end of the study, the median dystrophin level was 0.33% of normal (range 0.04% to 48.55%). Hence dystrophin expression overall remained low and hardly changed following treatment. One would not expect efficacy in subjects in absence of overt myodystrophine expression. The product information was updated with this information in the variation procedure EMEA/H/C/002720/II/0068.

Discussion

The proof of demonstrating efficacy of Ataluren in Ambulatory DMD consists of several independent studies. The 2 phase III studies failed to confirm results of the phase II study that supported the conditional marketing authorisation. Study 041, that was performed in the population expected to be most sensitive to show an effect, failed to confirm the effect seen in the initial phase 2 study (i.e., study 007) that supported the conditional marketing authorisation in 2014 as well failed to confirm the effect of the *post hoc* analyses of studies 007 and 020 (the studies that supported the renewal of the conditional marketing authorisation in 2016). Importantly, although a statistically significant effect favouring ataluren over placebo is claimed in the meta-analysis, the (*post hoc* conducted) meta-analysis is questioned as it violates methodological principles. Further, it cannot compensate for or overrule the results of the individual RCTs, which produce the most reliable results by their predefined and alpha-controlled nature. Instead, in regulatory decision-making, an integrated meta-analytic approach is intended to understand better responses across studies, different populations (e.g., demographic, disease-related), and dosing regimens. It might provide a more precise estimate of the overall treatment effect and variability. The suggested result of 3.5 years delay in the loss of ambulation observed in participants in STRIDE registry compared to the external-controls from CINRG-DNH is difficult to interpret in the view of the mentioned limitations and uncertainties. Furthermore, apart from the uncertainty concerning the true effect size, both confirmatory studies show a mean effect size that is around half of the size of the accepted threshold for MCID i.e., 30 meters in the 6MWD (McDonald et al 2013). Moreover, separation between the placebo arm and ataluren arm does not increase further after 12 weeks of treatment with ataluren. Finally, PD studies showed that treatment with ataluren did hardly change dystrophin expression in the vast majority of the 20 patients evaluated. In general without a substantial dystrophin expression no efficacy is expected.

From a safety perspective, overall data support that ataluren is generally well-tolerated in ambulatory patients with nmDMD, with the most common adverse events being headache, upper respiratory infections and gastrointestinal disorders.

Conclusion

Considering that the data's totality is now considered as comprehensive, as opposed to when the CMA was first granted, and that the beneficial effect of the results from the phase 2 study could not be replicated in the two confirmatory phase 3 studies (020 and 041), and registry data were not considered interpretable for various reasons, including the fact that they are prone to bias such as confounding, and other bias as indicated in the prior sections and also to other uncertainties and, as such, are unable to overrule the negative findings from the studies, the benefit-risk of ataluren in DMD is negative.

Consultation to the Scientific Advisory Group of Neurology (SAG-N)

On 10 June 2024, a SAG Neurology was convened. Final minutes of the SAG -N are provided below.

SAG NEUROLOGY ANSWERS FOR TRANSLARNA

1. Given the failure of studies 020 and 041 to confirm the hypotheses tested, does the SAG-N consider that efficacy of ataluren is sufficiently established for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene in ambulatory patients aged 2 years and older?

The SAG-N experts agreed by consensus that the studies 020 and 041 were formally negative because the results from the primary endpoints did not reach statistical significance (were negative) Hence, all other results– including *post hoc* results from secondary endpoints– cannot confirm the efficacy of Translarna in nmDMD. One expert acknowledged the formally negative results but highlighted the value of *post hoc* results from the timed function tests as supporting efficacy at least for a conditional marketing authorisation.

The patient representatives expressed the view that if one considers the data from these trials, efficacy cannot be considered as sufficiently established. They highlighted, though, that these data are suggestive of some efficacy, especially if taken in the context of all available data, including real-world evidence.

2. Do you consider that the presented data from the STRIDE study 025 supports a relevant treatment effect of Translarna considering potential biases associated with open label studies with an external historical control?

The majority of the SAG-N experts agreed on the value of registries for regulatory purposes, but mainly as providing supporting evidence from positive randomized clinical trials. The experts stated that real world data from registries cannot fully substitute the ones from clinical trials. Overall, the majority of the experts agreed that the marketing authorisation holder has reasonably addressed the potential sources of bias but there was still the possibility of unknown confounding that can only be controlled by randomization. The majority of the experts expressed the opinion that in the present case a regulatory decision should not be based only on the registry data but consider these in the context of the data available from the controlled clinical trials. Nevertheless, all experts noted that the real-world data should not be ignored as they may represent a strong signal of efficacy.

The majority of the SAG-N experts noted the large discrepancy between the small effects in the randomized clinical trials (6MWT and TFT) and the large difference in the time to loss of ambulation (LoA) in the STRIDE registry. The underlying reasons for this discrepancy remain unclear to them. One potential reason they speculated about could be that the outcome measures are different (e.g., 6MWT and LoA are both ambulation outcomes but first one is a continuous outcome measure while the second one expressing the number of patients still capable to walk in each of the compared groups is a dichotomous outcome measure that is more easily interpretable in terms of clinical relevance).

Both patients' representatives highlighted that a delay of 3.5 years in the time of loss of ambulation is clearly a clinically relevant outcome. The patient representatives' view on this was that RWE should not only be used to confirm positive trial data, but also address uncertainties arising from these data. One patients' representative also noted the large discrepancy between effects in the trials and the STRIDE. Furthermore, one patient's representative stated that -in their views- the standard of care in DMD has only changed for the non-ambulatory phase of the DMD (e.g. ventilation, cardiac function control…).

3. In case the SAG-N does consider that there is sufficient certainty on the efficacy of ataluren, the SAG-N is invited to discuss if the results on the 6 Minutes Walking Distance (6MWD), Timed Function Test (TFT) and the North Star Ambulatory Assessment (NSAA) indicate a clinically meaningful benefit of treatment with ataluren in the short and long term in the intended population.

The majority of the experts considered that the differences in the above-mentioned tests are marginal at best and likely not clinically relevant. One expert disagreed and considered the effect sizes as clinically meaningful for the patients.

The patient's representatives commented that even a small difference demonstrating a reduction of the rate of decline in function, represents a clinically meaningful gain in the daily life of the patient and their families. Further, they noted that the data representing these small differences were all in favour of Translarna.

4. What is your view on the importance of the pharmacological data on dystrophin expression evaluated in study 045 including 20 subjects with nonsense mutation Duchenne muscular dystrophy (nmDMD) aged 2 to 7 years?

The SAG-N experts agreed by consensus that any clinical change is more important that any change in the dystrophin levels. Furthermore, the relationship between the dystrophin levels and functional outcome is unclear (i.e. it is unclear how much dystrophin needs to be increased to attain a clinical benefit). The SAG-N experts expressed the view that the role of dystrophin as marker of severity of prognosis is not clearly established. Thus, the pharmacological data are not essential for a decision-making process.

The patients' representatives shared the same views.

CHMP considerations on the SAG neurology

In brief, both the CHMP and the SAG are of opinion that the 2 specific obligation studies are failed trials.

The CHMP agrees that the MAH has addressed some of the concerns regarding corticosteroid bias and calendar bias. However, as also indicated by the SAG, 'in the matching one can only control for known biases'. It was also agreed that these data cannot replace the findings of the failed studies and should only be used to confirm or expand on beneficial effects observed in these trials. This is not the case here, as the RCTs consistently failed to demonstrate an effect in the predefined most sensitive treatment population.

One expert and the patients representatives' comment that for patients even a small improvement is clinically relevant. However, the CHMP is of the view that as the effect seen in the pivotal study for conditional market authorisation could not be repeated in 2 consecutive well designed trials, the beneficial effects of ataluren have not been properly demonstrated.

Finally, it is agreed with the SAG that functional benefit is more important than an effect on a biomarker. However, the mode of action of ataluren remains unconfirmed. The lack of effect on pharmacodynamic endpoint aligns with the lack of an effect on functional outcomes, i.e., 6MWD, NSAA and TFT in the clinical trials.

Third party interventions

Third party interventions were received from several countries, which include letters from parents or caregivers, patient organisations, healthcare professionals organisations, and treating physicians. The interveners expressed the opinion on the large unmet medical need for DMD and the benefit of Translarna in nmDMD based on their experience in the clinical practice and their interpretation of the efficacy data of Translarna mainly the efficacy data from STRIDE registry.

Among these interventions, a letter from a third party intervener from Ireland includes a reference to the United Kingdom NICE consultation and evaluation of ataluren focusing on the quality of life difference between ambulatory DMD patients receiving ataluren, caregiver reported quality of life and a wider consideration of possible cost benefit of ataluren. These documents are https://www.nice.org.uk/guidance/hst22/documents/committee-papers and https://www.nice.org.uk/guidance/hst22/documents/committee-papers-2.

CHMP considerations on the third party interventions

Third party interventions were received from several countries, which include letters from parents or caregivers, patient organisations, healthcare professionals organisations, and treating physicians.

The interveners expressed the opinion on the large unmet medical need for DMD and the benefit of Translarna in nmDMD based on their experience in the clinical practice and their interpretation of the efficacy data of Translarna mainly the efficacy data from STRIDE registry. The unmet medical need for DMD is acknowledged and it has never been questioned. The CHMP noted the information on the experience in the clinical practice from health care professionals and health care professionals organisations shared through individual case reports. The information shared on quality of life difference between ambulatory DMD patients receiving ataluren, caregiver reported quality of life and a wider consideration of possible cost benefit of ataluren is also acknowledged, However, it is considered that these interventions do not impact the conclusion on the benefit-risk of ataluren in the view of the three failed clinical trials. The opinion on the value of RWD from STRIDE is also noted but the CHMP was concerned about the aforementioned limitations and uncertainties.

The overall impact on the benefit-risk is included above.

Further considerations as requested by the European Commission

On 22 April 2024 a meeting of the Standing Committee had been convened at the request of Czechia which discussed the content of the CHMP opinion. As a result of this discussion, the EC decided to return the opinion to the Agency and to request, *inter alia*, the CHMP to further consider the following two scientific questions in a revised opinion:

- whether the totality of the data including the additional data from patient registries and real-world evidence highlighted by Czechia are sufficiently comprehensive to conclude on the benefit/risk balance of Translarna;

- whether these additional data/evidence would impact the CHMP conclusion on the benefit/risk profile of Translarna.

The following information was received from Czechia:

- An article By Atalaia *et al.* 2024. entitled EURO-NMD registry: Federated FAIR infrastructure, innovative technologies and concepts of a patient-centred registry for rare neuromuscular disorders. https://ojrd.biomedcentral.com/articles/10.1186/s13023-024-03059-3;
- A conference report by Isabelle Ciccone March 2024 entitled: Meta Analysis Shows Slow Decline of Muscle Function With Ataluren for Nonsense Mutation DMD. https://www.neurologylive.com/view/meta-analysis-slow-decline-muscle-function-ataluren-nonsense-mutation-dmd;
- An article entitled: the role of ataluren in the treatment of ambulatory and non-ambulatory children with nonsense mutation Duchenne Muscular Dystrophy - a consensus derived using a modified Delphi methodology in Eastern Europe, Greece, Israel and Sweden. This article was also mentioned in the letter requesting the EC SC meeting: https://bmcneurol.biomedcentral.com/articles/10.1186/s12883-024-03570-x.

A short summary with additional data from patients was provided as well:

- **Patient 01**, start of the treatment in the age of 13, 6MWT initially 346m, after 3 months of use 360m, after 9 and 12 months 405m, after 18 months 340m, after 24 months 398m, after 36 months 420m, after 3.5 years 450m, after 4 years still 415m, In our site last check in the spring of 2022 when he is still able to walk 450m, then transferred to an adult workplace. That is, at the time of handover, an adult patient, still walking, without breathing problems.
- **Patient 02**, start of the treatment in the age of 6, 6MWT initially 300m, after 6 months 338m, after 12 months 300m, 18 months 418m, after 2 years 435m, after 3 years 400m, after 4 years

gradual deterioration - 320m, after 5 years 300m, 5.5 years 280m, 6 years 105m, after 7 years only walking a very short distance.

- **Patient 03**, start of the treatment in the age of 2 - he is not capable of classic tests, but age - appropriate tests, he achieves the full number of points in all tests, the DMD phenotype is only minimal
- **Patient 04**, start of the treatment in the age of 2 - same as patient 02
- **Patient 05**, start of the treatment in the age of 6, 6MWT 350m, after 6 months 498m, after 1 year 503m, after 18 months 450m, after 24 months 440m, after 3 years 385m, after 4 years 260m, after 5 years 223m, then gradual progression. Now only able to walk a short distance
- **Patient 06**, start of the treatment in the age of 7, 6MWT 280m, after 6 months 270m, after 1 year 275m, after 1.5 years 250m, after 2 years 60m - significant deterioration, then no longer able to walk
- **Patient 07**, start of the treatment in the age of 8, 6MWT 350m, after 6 months 379m, after 18 months 402m, after 4 years 374m,
- All the boys show more energy since the start of the treatment, it is clear that the later they started the treatment, the smaller the effect is, The deterioration is very slow for all of them, none of them (not even an adult patient) have respiratory or cardiac problems. No one reported any serious side effects.

CHMP position on ***further considerations as requested by the European Commission***

The Atalaia *et al.* 2024 paper that is provided as additional evidence discusses a registry set- up which incorporates innovative technologies for rare neuromuscular disorders. The Registry Hub brings together data that are currently siloed and fragmented to improve healthcare and advance research for neuromuscular diseases. The efficacy of ataluren is not discussed.

The second additional paper (Ciccone) is a summary submitted to the Muscular Dystrophy Association conference (muscular Dystrophy Association Clinical and Scientific Conference) for either a poster presentation or oral presentation. This does not concern a peer reviewed article. It concerns a meta-analysis of 3 trials, i.e. study 041, Study 007 and Study 020. This meta-analysis was already discussed and reviewed by the CHMP It was concluded that there are several methodological concerns (i.e., (1) definition of ITT population differs in each study, and (2) the applicability of the *post hoc* performed meta-analysis is questioned on methodological shortcomings violating methodological principles for a retrospective meta-analysis (PtC CPMP/EWP/2330/99) and that results are not capable of compensating or overruling the negative findings of the individual studies.

The study by Golli et al (2024) concerns PTC sponsored interviews with clinicians on the use of ataluren in nmDMD subjects. Generally, the clinicians selected were positive about the role of ataluren in treatment of nmDMD subjects. The study does not provide any new data on efficacy of ataluren.

The individual subject data by Czechia as provided is very difficult to interpret and of limited value as these are retrospective case reports of a very small number of patients. These data do not indicate a treatment effect with reasonable certainty. Moreover, the observational data of 7 subjects cannot overrule the outcome of well-designed placebo controlled trials.

To specifically address the EC's questions:

The CHMP considers that the totality of the data including three randomized controlled trials including 753 subjects affected by nmDMD, hence a limited subset of a DMD, a rare condition (i.e., nmDMD represents less than 15% of DMD) as main sources of evidence and the additional data from STRIDE

(study 025o) registry including 277 subjects affected by nmDMD, additional real world data made available to the Committee including evidence highlighted by Czechia and studies 045 and 046 as complementary sources of evidence are sufficiently comprehensive to conclude on the benefit/risk balance of Translarna.

The additional data/evidence included three articles discussing a registry set up, the results from a meta-analysis of 3 trials (study 041, Study 007 and Study 020) already included in the assessment and a consensus article discussing role of ataluren in treatment of nmDMD subjects without providing any new data on efficacy of ataluren as well as case narratives from 7 CZ patients with nmDMD treated with Translarna. The CHMP considers that the limited additional data provided is insufficient evidence to allow for a conclusion on the efficacy of ataluren with reasonable certainty. Hence, the strength of the evidence from the newly provided data is very limited as compared with three formally negative randomized clinical trials that are considered the main sources of evidence and accordingly, these newly provided data do not impact the CHMP conclusion on the benefit/risk profile of Translarna.

Considering all the above, CHMP considers, the benefit of ataluren is not confirmed.

Grounds for non-renewal of the marketing authorisation

Whereas,

- The Committee re-assessed the benefit-risk of Translarna as part of the annual renewal procedure taking into account the totality of data, which includes the data available at the time of the conditional approval, data generated as per the specific obligations (the data from study 020, as well as the data from study 041), data from STRIDE registry (study 025o) and additional real world data made available to the Committee, as well as and on data on paediatric studies 045 and 046.

- The available data, in particular the results of study 041 conducted to fulfil the outstanding specific obligation with a view to confirming a favourable benefit-risk balance for the conditional marketing authorisation for Translarna, failed to confirm the efficacy of Translarna in the treatment of ambulant patients with nmDMD aged 2 years or older.

- Based on the above, the CHMP concluded, on the basis of the comprehensive set of data now available, that the efficacy of Translarna is not established and therefore a favourable benefit-risk balance has not been confirmed in the treatment of ambulant patients with nmDMD aged 2 years or older.

The CHMP therefore does not recommend the annual renewal of the conditional marketing authorisation for Translarna.

3. Recommendations

☒ Based on the review of the available information on the status of the fulfilment of Specific Obligations, the positive benefit-risk balance for Translarna in the treatment of ambulant patients with nmDMD aged 2 years or older is not confirmed and the annual renewal of the conditional marketing authorisation for Translarna is not recommended.

Amendments to the marketing authorisation

Not applicable.

Conditions of the marketing authorisation

Not applicable

4. EPAR changes

The table in the "Steps after" module of the EPAR will be updated as follows:

Scope

Renewal of conditional marketing authorisation.

Summary

Based on the review of the available information, the positive benefit-risk balance for Translarna in the treatment of ambulant patients with nmDMD aged 2 years or older is not confirmed and the annual renewal of the conditional marketing authorisation for Translarna is not recommended.

Annex: Rapporteurs' assessment comments on the renewal

PRAC input:

In this annual renewal,	**Yes**	**No**
- RMP submitted (If yes is ticked, discussion should be included in the Risk management plan section of the Annex)	☐	☒
- Outstanding SOB is a non-interventional PASS study (If yes is ticked, the relevant discussion should be included in the sub-section Outstanding Specific Obligations – status report for period covered of the Annex)	☐	☒
- There are issues originating from a parallel/recent PSUR or signal assessment to be flagged to the CHMP rapporteur (If yes is ticked, the relevant discussion should be included in the Clinical safety section of the Annex)	☐	☒
- PhV inspections have been conducted/are ongoing with an impact on the MA under annual Re-Assessment (If yes is ticked, the relevant discussion should be included in the Pharmacovigilance inspections section of the Annex)	☐	☒

5. Specific Obligations

5.1. Specific Obligations adopted with the initial marketing authorisation

Table 1: Full list of SOBs as adopted with the initial marketing authorisation

Number	Description	Status
PTC124-GD-020-DMD	To complete a multicenter, randomised, double-blind, placebo-controlled confirmatory study to examine the efficacy and safety of ataluren 10, 10, 20 mg/kg in patients with nonsense mutation Duchenne muscular dystrophy (Study PTC124-GD-020-DMD)	Submission of the final report: By 4Q 2015 Completed
PTC124-GD-041- DMD	In order to confirm the efficacy and safety of ataluren in the treatment of ambulant patients with nmDMD aged 5 years or older, the MAH should conduct and submit the results of a multicenter, randomised, double-blind, 18-month, placebo-controlled study, followed by an 18-month open label extension, according to an agreed protocol.	Submission of the final report: By 4Q 2022

Since the granting of the conditional MA, the MAH has submitted the following SOBs:

The Study 020 clinical study report was completed on 09 Dec 2015. Final results were submitted to the EMA on 07 Jan 2016 as a separate Type II variation application, hereafter referred to as SOB Type II variation (sequence 0040, Procedure No: EMEA/H/C/002720/II/0020).

Based on the totality of the data provided, the Committee recommended the renewal of the conditional marketing authorisation for Translarna, concluding that the MAH demonstrated that the criteria for the renewal of the conditional marketing authorisation continued to be met, including a positive benefit-risk balance of Translarna in the context of a conditional approval.

The Committee also took into account the fact that the MAH proposed an updated confirmatory study design, built upon the most current knowledge of the disease and its natural progression, as well as on the data gathered from the previous studies, and considered it appropriate to serve as an SOB to answer the remaining uncertainties in the context of conditional marketing authorisation. A new trial, PTC124-GD-041-DMD (Study 041), had to be performed as a specific obligation to answer remaining uncertainties. The protocol for Study 041 has been approved by the CHMP in January 2017.

The final study report was submitted by the MAH and reviewed by the CHMP in procedure EMEA/H/C/002720/II/0069. Results from study 041 were also submitted for this annual renewal application.

The results from this study did not confirm the observed effect in 6MWD between ataluren and placebo seen in the initial phase 2 study (i.e., study 007) that supported the conditional marketing authorisation in 2014 and the effect in the *post hoc* analyses of studies 007 and 020 that supported the renewal of the conditional marketing authorisation in 2016 despite the fact that the study included a population that was expected to be most sensitive to show an effect.

No new PD activity data or dose-response data was submitted. The MAH did submit a *post hoc* conducted meta-analysis. The meta-analysis of the efficacy data from studies 007, 020, and 041 did show a statistically significant difference at the 6MWD and TFTs, in the ITT population in favour of Ataluren. This is expected considering the larger population. It should be noted that the observed overall effect seems to be driven mainly by study 007, which formally was a phase 2 Hypothesis-generating study. The confirmatory phase III studies show a lesser effect which could be related to, i.e. regression to mean effects. Studies 020 and 041 are confirmative phase 3 studies in a larger population, so they better

approach the true effect size than hypothesis-generating study 007.

5.2. Outstanding Specific Obligations – status report for period covered

The results of the double-blind phase and some preliminary results from the open-label extension phase of the SOB 019/study 041 were submitted in the type II variation procedure EMEA/H/C/0027200/II/0069. A brief description is provided below.

SOB 019: Description

The SOB 019 was last revised in 2019 as follows:

Number	Description	Status
PTC124-GD-041- DMD	In order to confirm the efficacy and safety of ataluren in the treatment of ambulant patients with nmDMD aged 5 years or older, the MAH should conduct and submit the results of a multicentre, randomised, double-blind, 18-month, placebo-controlled study, followed by a 18-month open label extension, according to an agreed protocol.	Final study report to be submitted Due date: September 2022

Methods

PTC124-GD-041-DMD (Study 041) is a Phase 3, randomised, double-blind, placebo-controlled efficacy and safety study of ataluren (Translarna™) in patients with nonsense mutation Duchenne muscular dystrophy (nmDMD). The study consists of a 72-week randomised placebo-controlled phase followed by a 72-week open-label extension phase.

Study Participants

A total of 360 subjects with nmDMD were randomised (ITT), of which 185 met de mITT criteria. The mITT population is defined as all subjects in the intention-to-treat (ITT) population who meet the following additional criteria: ≥7 to ≤16 years old with a 6-minute walk distance ≥300 metres and time to stand from supine ≥5 seconds at baseline.

Treatments

During the randomised phase of the study, subjects receive continuous daily administration of double-blind ataluren (10, 10, and 20 mg/kg) or placebo for 72 weeks. During the open-label phase, all subjects receive continuous daily administration of ataluren 10, 10, and 20 mg/kg for an additional 72 weeks.

Objectives

The primary objective of this study is to determine the effect of ataluren on ambulation.

Outcomes/endpoints

The primary objective of this study is to determine the effect of ataluren on ambulation and endurance as assessed by the 6-minute walk test (6MWT).

The secondary objectives of this study are to:

- Determine the effects of ataluren on ambulation and burst activity as assessed by timed function tests

- Determine the effects of ataluren on lower limb muscle function as assessed by the North Star Ambulatory Assessment (NSAA)
- Assess the safety profile of ataluren
- Evaluate the correlation between plasma concentration of ataluren and functional outcomes
- Evaluate the plasma PK profile of ataluren

The exploratory objectives of this study are to:

- Determine the effects of ataluren on upper limb muscle function strength as assessed by the Performance of Upper Limb and by the DMD Upper Limb patient-reported Outcome Measure (in subjects ≥7 years old at Baseline)
- Determine the effects of ataluren on muscle strength as assessed by myometry (in subjects <7 years old at baseline)
- Determine the effects of ataluren on skeletal muscle integrity as assessed by magnetic resonance imaging (MRI) (at pre-qualified sites only)
- Determine the effects of ataluren on subject- and parent/caregiver-reported health-related quality of life as assessed by at-home questionnaire
- Determine the effects of ataluren on pulmonary function as assessed by forced vital capacity.

Randomisation

Randomisation was stratified by the following factors to balance treatment allocation:

• Type of concomitant corticosteroid use at Baseline (deflazacort versus prednisone/prednisolone)

• Maximum Day 1 and Day 2 6MWTs performed at Baseline: <300 metres versus ≥300 to <350 metres versus ≥350 to <400 metres versus ≥400 metres

• Time to stand from supine at Baseline: <5 seconds versus ≥5 seconds.

Subjects receive blinded, randomised treatment for 72 weeks. After the initial 72-week randomised treatment phase, all subjects receive open-label ataluren for an additional 72 weeks.

Blinding (masking)

The study is a double-blind study

Statistical methods/analysis

There will be 2 database locks for this study. The first database lock (soft lock) will occur when all subjects have completed double-blind treatment (Week 72). The final database lock will occur when all subjects have completed the open-label treatment phase.

Two separate analyses will be conducted for Study 041. The first analysis will be conducted after all subjects complete the 72-week randomised treatment phase and will focus on the comparison of efficacy measures between ataluren and placebo. The results of these analyses will be presented in a final CSR and submitted by September 2022 to fulfil the specific obligation. Available results generated during the open-label extension will also be presented in the final CSR using descriptive statistics.

The second analysis will be conducted after all subjects complete the open-label extension phase or withdraw from the study and will include results for all subjects over both the randomised and open-label phases. The results of these analyses will be provided in an addendum CSR by December 2023.

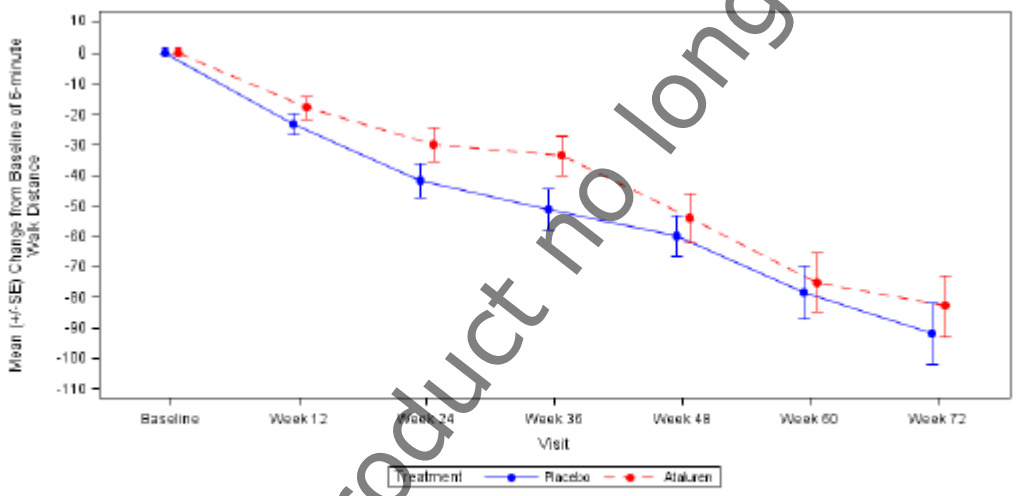
A pooled analysis was performed using ITT population data from studies 007, 020 and 041, resulting in a total sample size of 701, from whom 354 were treated with ataluren. Given the shorter duration of studies 007 and 020, comparisons were made at week 48. In the request for supplementary information, a meta-analysis instead of a pooled analysis was requested and submitted. The MAH included a meta-analysis of a subgroup with a 6MWD between 300-400 meters at baseline. Further, the MAH compared the data of ataluren used in a registry study to a historic cohort group (CINRG), which was propensity score matched.

Results

See procedure EMEA/H/C/002720/II/69 for more details on the efficacy data, assessment and discussion

For **mITT** population (n=185) the degree of worsening in 6MWD at week 72 was not statistically significantly different. The mean change from baseline was --81.8 meters in the ataluren group versus -90.01 meters in the placebo group, with a difference of 8.26 meters ($CI_{95\%}$ -26.05 ; -9.53, p=0.36) (Figure 1).

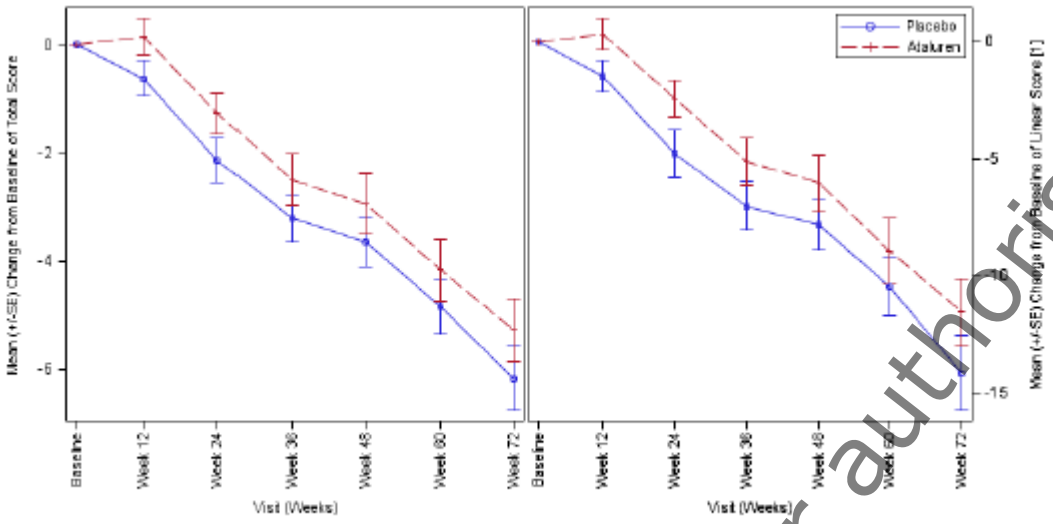
Figure 1: Change from baseline in 6-minute walk distance (mITT population, double-blind treatment period)



Abbreviations: 6MWD, 6-minute walk distance; mITT, modified intention-to-treat
Note: Baseline is defined as the maximum measurement of valid Day 1 and Day 2 6MWD values. Subjects who lost ambulation during the study were assigned a value of 0 for the first visit at which they lost ambulation and for all remaining visits while they participated in the study.
Source: Figure RSI_1_Q2_1.2

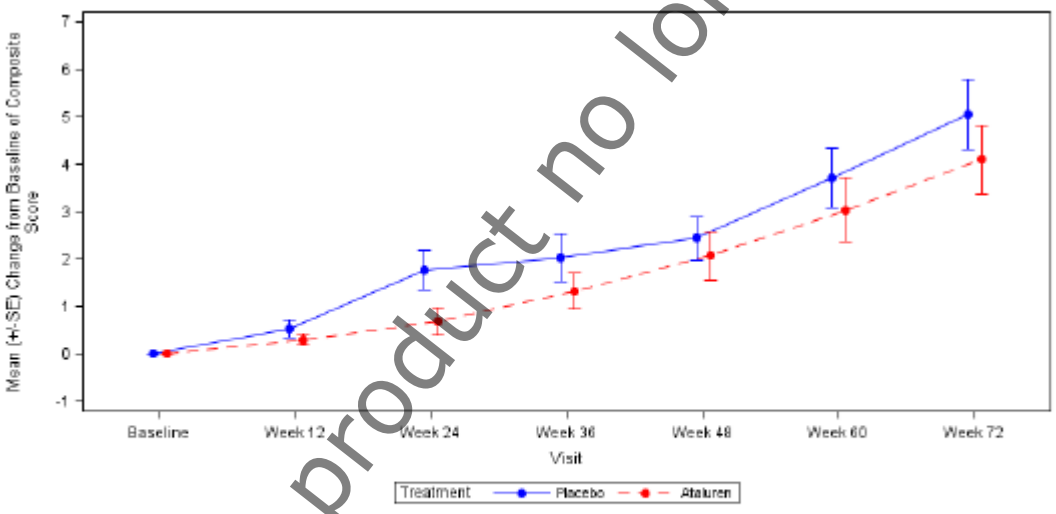
Formally the statistical interference testing should have stopped here in accordance with the predefined statistical analysis plan. The difference for the NSAA score was 0.9 points ($CI_{95\%}$ -0.22 ; 2.02, $p_{nominal}$=0.13) and the difference in the TFT composite score was -1.04 seconds ($CI_{95\%}$ -0.204 ; 5.204, $p_{nominal}$=0.09) (see Figure *2* and Figure 3, respectively).

Figure 2: Change in revised NSAA total and linear scores over time (mITT population, double-blind treatment period)



Abbreviations: mITT, modified intention-to-treat; NSAA, North Star Ambulatory Assessment
Source: Figure RSI_1_Q2_3.2

Figure 3: Change from baseline in timed function tests composit score (mITT population, double-blind treatment period)

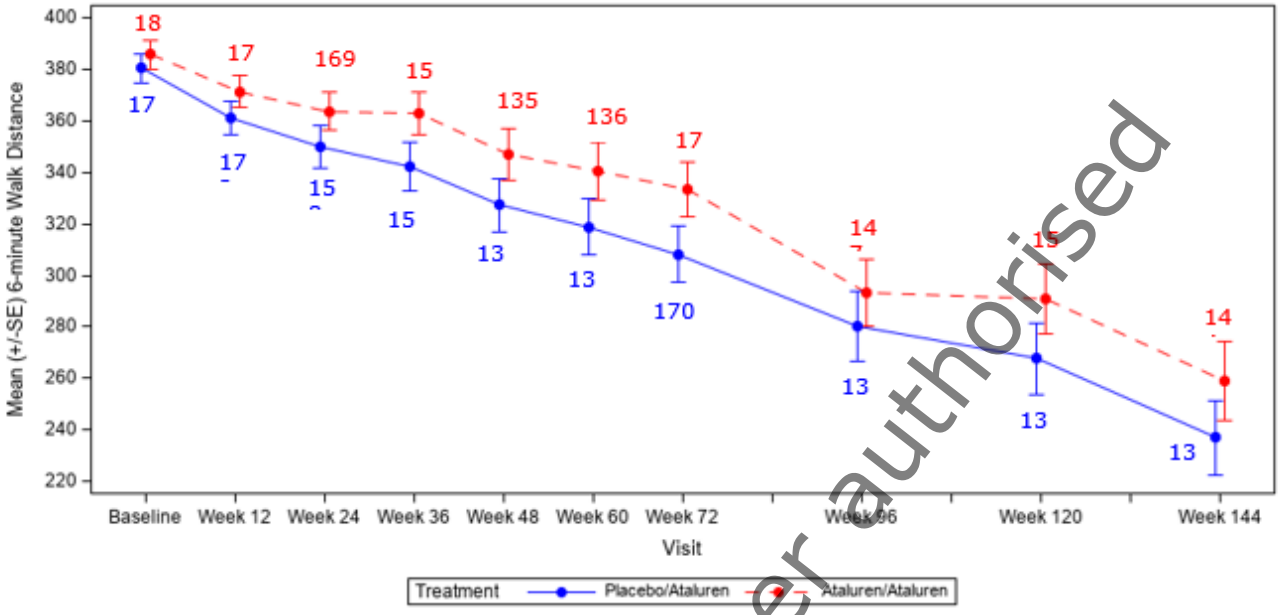


Abbreviations: mITT, modified intention-to-treat
Note: Baseline is defined as the last observed measurement on or prior to the first dose of study drug. Subjects who could not perform a timed function test within 30 seconds, including those who lost ambulation or had timed function test above 30 seconds, were assigned a value of 30 seconds for the respective test.
Source: Figure RSI_1_Q2_2.2

For the **ITT** population (n=359) the mean change in 6MWD was -53.01 meters in the ataluren group versus -67.43 meters in the placebo group (Diff. 14.42 meters, $CI_{95\%}$ 1.83; 27.01, $p_{nominal}$=0.025) (Figure 4). The difference for in the change in NSAA was 0.9 points ($CI_{95\%}$ 0.15; 1.64. $p_{nominal}$=0.024). The difference in the change in composite TFT score was -0.7 seconds ($CI_{95\%}$ -0.11; 11.5, $p_{nominal}$=0.090) (Figure 5).

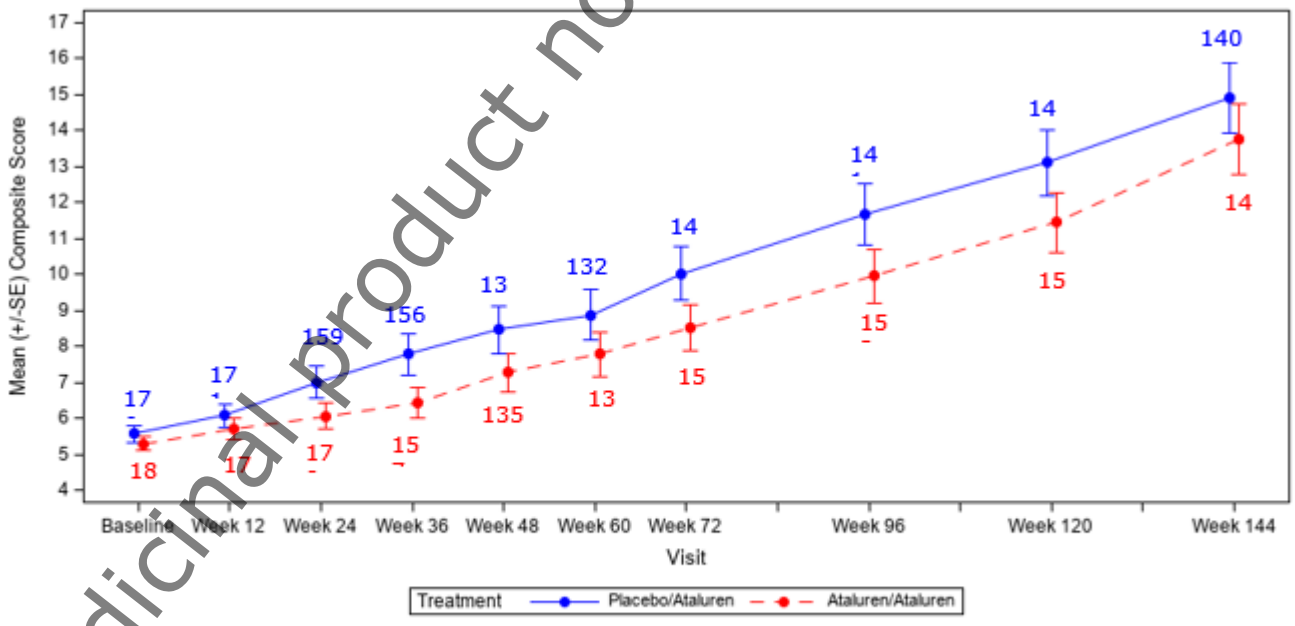
Open-label extension data of study 041 showed a comparable rate of decline in placebo-ataluren arm and ataluren-ataluren treatment arm from week 12 to week 144 for the 6MWD and the composite TFT score (see Figure 4 and Figure 5, respectively).

Figure 4: 6-Minute walk distance (ITT population, overall treatment period)



Abbreviations: 6MWD, 6-minute walk distance; ITT, intention-to-treat
Note: Baseline is defined as the maximum measurement of valid Day 1 and Day 2 6MWD values. Subjects who lost ambulation during the study were assigned a value of 0 for the first visit at which they lost ambulation and for all remaining visits while they participated in the study.
Source: Table RSI_1_Q14_1.2; Figure RSI_1_Q14_1.3

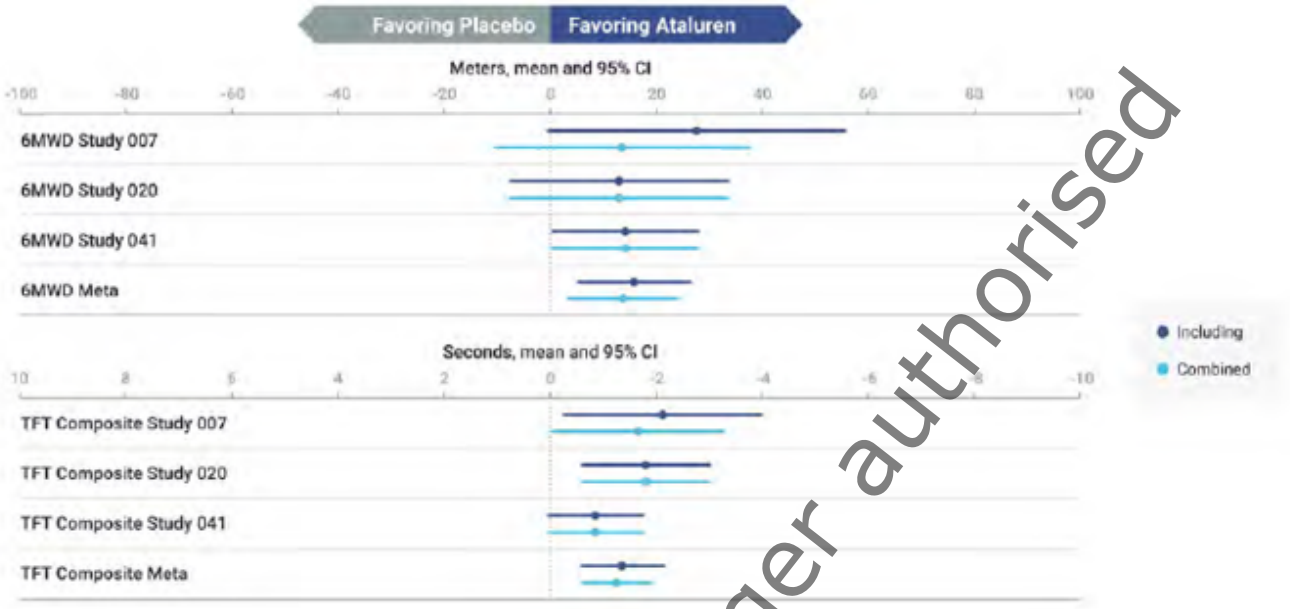
Figure 5: Timed function test composite score (ITT population, overall treatment period)



Abbreviations: ITT, intention-to-treat
Source: Table RSI_1_Q14_2.2, Figure RSI_1_Q14_2.3

The submitted random effect meta-analysis shows an LS mean difference from placebo of 15.81 meters in 6MWD (95% CI: 5.283, 26.330, nominal p=0.0032), 1.36 seconds in the TFT composite score (95% CI: -2.114, -0.600, nominal p=0.0004), 1.07 points in the NSAA total score (95% CI: 0.433, 1.716, nominal p=0.0010), and 2.64 points in NSAA linear score (95% CI: 0.861, 4.412, nominal p=0.0036).

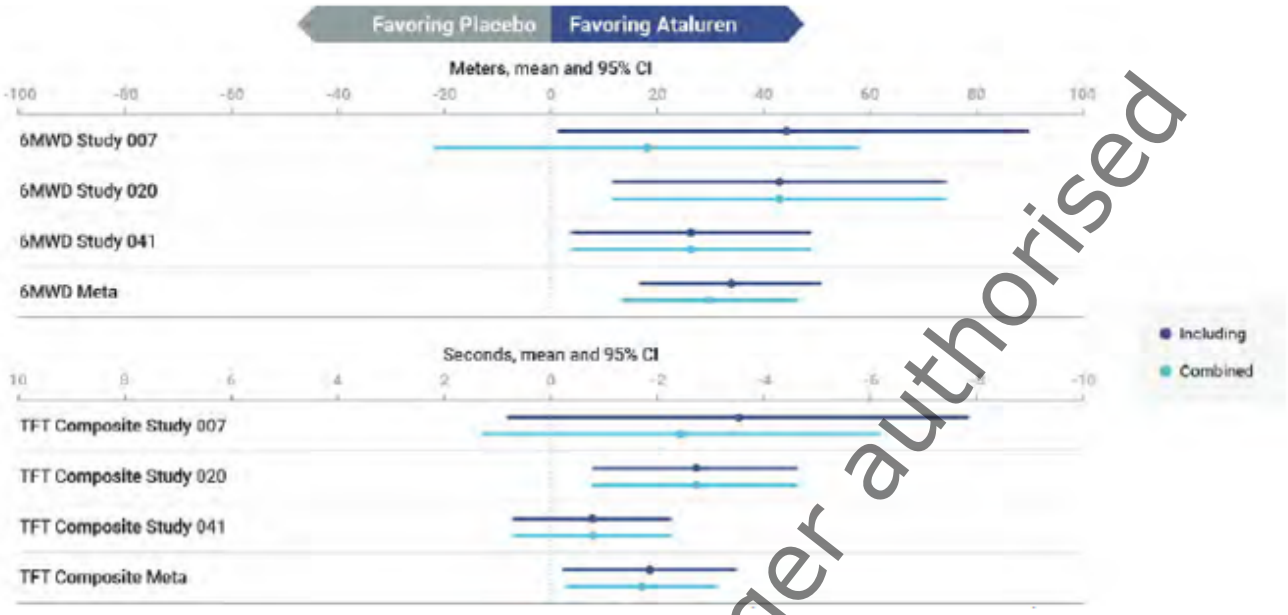
Figure 6: Meta-analysis of studies 007, 020, and 041 using random-effects model – ITT population week 48



Abbreviations: 6MWD, 6-minute walk distance; ANCOVA, analysis of covariance; ITT, intention-to-treat
Note: Including: comparison of ataluren commercial dose versus placebo used in the meta-analysis model.
Combined: comparison of combined ataluren doses and placebo used in the meta-analysis model.
ANCOVA models are applied after multiple imputation of missing data, assuming missing values were missing not at random and utilising the complete case missing value pattern.
In Study 007, the ANCOVA model for 6MWD includes factors of treatment, stratification factors of age, baseline 6MWD, and baseline corticosteroid use, and baseline 6MWD as a covariate.
In Study 020, the ANCOVA model for 6MWD includes factors of treatment, stratification factors of age, baseline 6MWD, and duration of prior corticosteroid use, and baseline 6MWD as a covariate.
For all other endpoints, the ANCOVA model includes factors of treatment, stratification factors of baseline 6WMD, baseline time to stand from supine, and baseline corticosteroid type, and baseline 6MWD as a covariate.
Source: Table RSI_1_Q15_1_1, Table RSI_1_Q15_2_1

The random effect meta-analysis in the new analysis population (6MWD 300-400m at baseline) shows an LS mean (95% CI) difference from placebo of 33.69 meters (16.9- 50.5 meters; p=0.0001) on 6MWD; -1.87 s (-3.5s - -0.3s; p=0.023) on TFT composite score, -1.46s (-2.5s - -0.4s; p=0.005) on TFT 10m walk/run, -2.24s (-4.3s - -0.2s; p=0.03) on TFT 4 stair ascent, -2.86s (-5.5s - -0.26s; p=0.031 on TFT 4 stair descent, and 1.3 points (-0.399s - 2.994s; p= 0.134) on NSAA total score.

Figure 7: Meta-analysis of studies 007, 020 and 041 using random-effects model – 300 to 400 metre subgroup, week 48



Abbreviations: 6MWD, 6-minute walk distance; ANCOVA, analysis of covariance; TFT, timed function test
Note: Including: comparison of ataluren commercial dose versus placebo used in the meta-analysis model.
Combined: comparison of combined ataluren doses and placebo used in the meta-analysis model.
ANCOVA models are applied after multiple imputation of missing data, assuming missing values were missing not at random and utilising the complete case missing value pattern.
In Study 007, the ANCOVA model for 6MWD includes factors of treatment, stratification factors of age, baseline 6MWD, and baseline corticosteroid use, and baseline 6MWD as a covariate.
In Study 020, the ANCOVA model for 6MWD includes factors of treatment, stratification factors of age, baseline 6MWD, and duration of prior corticosteroid use, and baseline 6MWD as a covariate.
For all other endpoints, the ANCOVA model includes factors of treatment, stratification factors of baseline 6WMD, baseline time to stand from supine, and baseline corticosteroid type, and baseline 6MWD as a covariate.
Source: Table RSI_1_Q15_5_1, Table RSI_1_Q15_6_1

Thus results for the 6MWD, the individual TFT items, and the NSAA total score were significantly different between placebo and ataluren, as expected, given the increased number of subjects.

In the Registry, ataluren-treated subjects reaching the milestones of FVC ≤60% predicted and FVC ≤50% predicted of 1.8 years (p=0.0021) and 2.3 years (p=0.0207), respectively, retain the ability to walk 4.0 years longer (p<0.0001) than their propensity-score matched CINRG counterparts.

CHMP comments

Results from the mITT population in study 041 did not confirm the findings of *post hoc* analyses of studies 007 and 020, neither in terms of statistical significance nor concerning clinical relevance

Additionally, the difference in 6MWD between placebo and ataluren found in the ITT population of the phase III study 041 (14.4 meters after 72 weeks of treatment) is comparable to that of the phase III study 020 (15.4 meters after 48 weeks of treatment, p = 0.213), but considerably smaller than the effect seen in phase II study 007 (31.3 meters after 48 weeks treatment, p=0.056). Thus, there is uncertainty concerning the true effect size on the primary endpoint. The effects on the key secondary endpoints, i.e., TFT and NSAA (including their individual items), are also smaller in study 041 compared to the previous studies.

In their response to the request for supplementary information adopted as part of the variation EMEA/H/C/002720/II/69, the MAH introduced **a new analysis population of study 041,** i.e., a population with subjects with a preserved 6MWD of 300-400m at baseline. Note that this was also the subgroup that was identified based on the data-driven analysis of studies 007 and 020, indicating that

this group might benefit most from treatment with ataluren. The MAH justified the relevance of this subgroup by stating that patients with a 6MWD < 300m would be in such a rapid decline phase that treatment may be too late, and those with 6MWD > 400 meter would be too good to show a treatment effect within the study period. Note that the mITT population of study 041 was defined as subjects who had a 6MWD > 300 m **and** TFT > 5 seconds. The random effects meta-analysis in this new analysis population showed an LS mean (95% CI) difference from placebo of 33.69 m (16.9 m - 50.5m; p=0.0001) on the 6MWD; -1.87 sec (-3.5 - -0.3; p=0.023) for the TFT composite, -1.46 sec (-2.5 - -0.4; p=0.005) on the 10m walk/run, -2.24 sec (-4.3 - -0.2; p=0.03) on 4-stair ascent; -2.86 sec (-5.5 - -0.26; p=0.031) on 4-stair descent, and 1.3 points (-0.399 - 2.994; p= 0.134) on NSAA total score. Although these data suggest statistical and clinical relevance, the analyses are **not acceptable**.

The statement by the MAH that *'the definition of the subgroup in study 041 selecting patients with DMD with a 6MWD > 300m was a mistake*' by hindsight is ill-justified. Falling back on a previous subgroup defined in other studies but not taken aboard in the protocol of study 041 has an element of *post hoc* convenience. Moreover, the biological plausibility of the rationale with which the MAH justifies this subgroup is questioned; one could also state that in those who decline rapidly, the effect of effective treatment may be picked up the earliest. Indeed, it may also be that for subjects < 300 mg, there is no point of return. The point to make is that both are assumptions that cannot be verified.Graphically, the rate of decline as measured by 6MWD and TFT in study 041 is comparable between the placebo and ataluren group during the course of week 12 to week 144 as the lines run in parallel, which further increases the uncertainty concerning the efficacy of ataluren.

There are several fundamental methodological concerns with the open-label registry study and the comparison to the external cohort.

Adverse events

See also procedure EMEA/H/C/002720/II/0069 for more details on the safety data and assessment

The most common individual TEAEs (occurring in ≥5% of all subjects) in the ataluren arm were vomiting (30 [16.3%] subjects), nasopharyngitis (27 [14.7%] subjects), upper respiratory tract infection (27 [14.7%] subjects), fall (19 [10.3%] subjects), and headache (19 [10.3%] subjects). Events that occurred in at least 5% of subjects in the ataluren arm and with greater frequency than in the placebo arm included nasopharyngitis, vomiting, diarrhoea, ligament sprain, pyrexia, rhinorrhea, and headache.

CHMP comments

The number of subjects with at least 1 TEAE is consistent with the findings of study 020. The reported adverse events align with the previous studies, though the frequencies changed slightly. Some adverse events appear to be related to concomitant corticosteroid use or disease progression. The majority of the events are mild to moderate in severity. The reported findings are in line with the known profile of ataluren.

Serious adverse event/deaths/other significant events

Maximum TEAE severity was mild or moderate for most subjects in both treatment arms during the double-blind treatment period. Maximum TEAE severity was mild for 67 (36.4%) subjects in the ataluren arm and 63 (35.8%) subjects in the placebo arm, and moderate for 77 (41.8%) subjects in the ataluren arm and 70 (39.8%) subjects in the placebo arm. Thirteen (7.1%) subjects in the ataluren arm and 16 (9.1%) subjects in the placebo arm had at least 1 TEAE that was classified as Grade 3 (severe). In both treatment arms, the most common severe TEAE was disease progression (8 [4.5%] subjects in the

placebo arm and 6 [3.3%] subjects in the ataluren arm). In both treatment arms, most subjects who experienced severe TEAEs of disease progression were older at study entry (≥9 years) and had baseline 6MWD values of <350 metres. None of the severe events was assessed as related to the study drug no life-threatening (Grade 4) or fatal (Grade 5) TEAEs were reported.

No deaths have been reported.

Subjects in the ataluren arm and 12 [6.8%] subjects in the placebo arm). The most common SAEs in both treatment arms were fractures. Two subjects in the ataluren arm had SAEs that were assessed by the investigator as related to study drug. . One subject had an SAE of moderate upper abdominal pain, and another one had an SAE of moderate vomiting. Both events were resolved without the need for permanent discontinuation of treatment.

CHMP comments

The severe adverse events appear to be related to disease progression or background corticosteroid use. Seizure was reported in a subject who suffered from epilepsy, and thus this is unrelated to ataluren treatment.

No treatment-related serious adverse events were reported in ataluren-treated patients in the two 48-week placebo-controlled studies.

Two treatment-related serious adverse events of upper abdominal pain and vomiting were reported in ataluren-treated subjects in the open-label extension. Both events were moderate in severity and resolved without the need for permanent discontinuation of ataluren.

One subject received concomitant treatment with famotidine and prednisolone at the time of the event. The patient was hospitalised for 1 day, and the event was reported as resolved. The event was assessed as possibly related to ataluren.

One subject experienced a moderate serious adverse event of vomiting and was administered an anti-nausea drip. As the symptoms did not resolve, the subject was hospitalised for suspected gastroenteritis and treated with metoclopramide hydrochloride for 1 day. The subject tested negative for rotavirus and adenovirus and showed no significant bacterial growth. The subject was discharged 1 day after hospitalisation, and the event was reported resolved on. The event was assessed as possibly related to ataluren.

The MAH proposes to amend section 4.8 based on these findings. The following is proposed:

Adverse reactions were generally mild or moderate in severity, and no treatment-related serious adverse events were reported among ataluren-treated patients in these 2 studies.

Adverse reactions were generally mild or moderate in severity. Two treatment-related serious adverse events of upper abdominal pain and vomiting were reported in ataluren-treated subjects. Both events were moderate in severity and resolved without the need for permanent discontinuation of treatment.

The need for inclusion of the events is questioned. The events were only possibly related to ataluren, presumably by lack of alternative explanation. These events, including the short hospitalisation and the aetiology of gastroenteritis not found, are not uncommon in the non-DMD population of the same age range

Laboratory findings

CHMP comments

Abnormal values of hyperuricemia were reported in 4 (2.2%) subjects in the ataluren group and 21 (12.0%) subjects in the placebo group in the double-blind period. This event is not likely associated with the use of ataluren.

The laboratory findings of interest are the increase in Cholesterol and Triglycerides. These data are provided in the section below. In brief, these findings correspond with the previous results, i.e. an increase in cholesterol and triglycerides from baseline. The SmPC already covers this, so no additional actions are required.

Discussion

See also procedure EMEA/H/C/002720/II/69

CHMP comments

Study 041 is a failed study; the results did not confirm the findings of the (*post hoc*) analyses of studies 007 and 020, neither in statistical significance nor clinical relevance. This is especially relevant since study 041 was performed in the population expected to be most sensitive to show an effect. The effect of ataluren was the largest in study 007, but this was a phase 2 study. Though a numerical effect favouring ataluren over placebo is observed in the meta-analysis, the credibility of the analysis is questioned, and a meta-analysis cannot compensate or overrule the results of the individual RCTs, which produce the most reliable results by their predefined and alpha-controlled nature. As important, the relevance of this effect is questioned, apart from the uncertainty concerning the true effect size. Moreover, this effect generally does not increase further after 12 weeks of treatment. In addition, PD studies showed that treatment with ataluren did not substantially change dystrophin production in the vast majority of 20 patients evaluated.

It was anticipated that a more sensitive population (i.e.. the mITT population, which was based on exploratory *post hoc* analyses of previous studies in DMD, including study 020) would be better able to show a treatment effect of ataluren. Despite this, a statistically significant and clinically relevant effect could not be demonstrated in this mITT population and study 041; therefore, in fact, is a failed study.

The subsequent description of the findings in the ITT population reflects the attempt of the MAH to elicit a positive study result from a failed study. Indeed, the ITT population reflects the population for which the CMA was granted, but formal statistical testing is not allowed from a methodological perspective. Despite ignoring this, the data showed a 14.4-meter difference in 6MWD between ataluren and placebo in this ITT population; this is substantially less than the generally accepted cut-off of 30 meters for clinical relevance. The clinical relevance of the difference in TFTs is difficult to interpret as a clear cut-off value has not formally been established; the differences are however perceived as marginal. For the NSAA, the 0.9 point difference does not exceed a category shift of the mean in any of the 16 items of the NSAA.

A *post hoc* defined and conducted Meta-analysis of the efficacy data from studies 007, 020, and 041 did not show a clinically relevant effect at the 6MWD and TFTs, in both the mITT and the ITT populations. However, considering the larger population, the results reach a statistically significant difference. It should be noted that the observed overall effect seems to be driven mainly by study 007, which formally was a phase 2 hypothesis-generating study. The confirmatory phase III studies show a smaller effect which could be related to the well-known 'regression-to-the-mean' effect. Studies 020 and 041 are confirmative phase 3 studies in a larger population, so they better approach the true effect size compared to hypothesis-generating study 007. Finally, the credibility and applicability of the post hoc conducted is questioned on principal methodological shortcomings violating methodological principles for a retrospective meta-analysis (PtC CPMP/EWP/2330/99

The comparison to a historical external cohort of the STRIDE registry is considered supportive, but cannot overrule the results of phase III placebo-controlled studies, which by default produce the most valid results by design and the best approaches to isolate the true effect size. Additionally, interpretability of results is hampered by limitations & uncertainties, due to differences in the case-mix and with regard to confounder control, incl. immortal time bias, calendar time bias, outcome assessment.

In the initial application, the data on dystrophin expression was inconclusive because of poor quality (Translarna EPAR Public assessment report EMA/369266/2014). In the Article 46 procedure EMEA/H/C/002720/P46/026, submitted in 2021, additional pharmacological data on dystrophin expression was submitted and assessed. The baseline median dystrophin level as measured by ECL was 0.42% of normal (range 0.00% to 41.85%). At the end of the study, the median dystrophin level was 0.33% of normal (range 0.04% to 48.55%). Hence dystrophin expression overall remained low and hardly changed following treatment. Reference is made to section 6 below. In subjects where an overt myodystrophine expression is absent one would not expect efficacy.

Overall, the database of ataluren has been expanded, and the totality of data is considered comprehensive for assessing efficacy and safety conclusively. Study 041 was specifically requested as a new SOB within EMEA/H/C/002720/R/0022 procedure in order to confirm the exploratory findings of the *post hoc* analyses of studies 007 and 020. The results from the 041 study did not confirm the findings of the *post hoc* analyses of studies 020 and 007, neither in terms of statistical significance nor concerning clinical relevance

Regarding the safety, the AEs reported and the elevation in serum cholesterol and triglycerides are consistent with the findings reported in studies 007, 020 and post-marketing surveillance data. Generally, the AEs reported are mild to moderate in severity. The adverse events reported as placebo versus ataluren were vomiting (9[5.1%] vs 30[16.3%]), nasopharyngitis (16[6.8%] vs 27[14.7%]), Upper respiratory tract infection (44[25%] vs 27 [14.7%]), fall (23[13.1%] vs 19[10.3]%), headache (15 [8.5%] vs 19[10.3%]), nausea (3[1.7%] vs 8[4.3%]), (upper) abdominal pain (6[3.4] vs 8[4.3]), diarrhoea (12 [6.8%] vs 15 [8.2%], and constipation (7 [4.0%] vs 9[4.9%]). These adverse events are included in section 4.8 of the SmPC.

Conclusion

Study 041 is a failed study; the results did not confirm the findings of the (*post hoc*) analyses of studies 007 and 020, neither in statistical significance nor clinical relevance. Though a numerical effect favouring ataluren over placebo is observed in the meta-analysis, the credibility of the analysis is questioned, and a meta-analysis cannot compensate or overrule the results of the individual RCTs, which produce the most reliable results by their predefined and alpha-controlled nature.

Considering that the data's totality is now considered comprehensive, it is considered that efficacy has not been demonstrated.

Overall, the safety of ataluren was consistent with previous findings and is already well described in the SmPC.

5.3. Overall conclusion on Specific Obligations

During the period covered by this annual renewal, new data regarding SOBs have emerged. The new data emerged are compliant in terms of adherence to deadlines and are not compliant in terms of the acceptability of data submitted.

During the period covered by this annual renewal, new data regarding the following SOB have emerged.

The SOB is considered fulfilled: **Number**	**Description**	**Status**
PTC124-GD-041- DMD	In order to confirm the efficacy and safety of ataluren in the treatment of ambulant patients with nmDMD aged 5 years or older, the MAH should conduct and submit the results of a multicentre, randomised, double-blind, 18-month, placebo-controlled study, followed by a 18-month open-label extension, according to an agreed protocol.	Final study report to be submitted Due date: September 2022

6. Additional scientific data provided relevant for the assessment of the benefit/risk balance

6.1. Quality

The marketing authorisation holder (MAH) confirms that all changes relating to the quality of the product have been made following the applications for variations and that the product conforms to current CHMP quality guidelines.

The quality of the product remains unchanged.

CHMP assessment/comment
No new data was provided.

6.2. Non-clinical

No new toxicology studies were conducted during the reporting period.

6.3. Clinical pharmacology

No new clinical pharmacology studies of relevance to the Translarna CMA were conducted during the reporting period.

However, the following data, which is included in the SmPC section 5.1 is considered relevant for the discussion on efficacy (EMA/H/C/002720/P46).

An open-label exploratory study (Study 045) was conducted in 20 subjects with nonsense mutation Duchenne muscular dystrophy (nmDMD) aged 2 to 7 years to explore quantitative levels of dystrophin in muscle tissue before and after 40 weeks of treatment with ataluren. Dystrophin was measured using the electrochemiluminescence (ECL) and immunohistochemistry (IHC) assays. From each subject 3 needle biopsies were taken from the gastrocnemius and the tibialis anterior at baseline and at the end of the treatment. Study 045 also included assessment of functional outcomes i.e. the revised North Star ambulatory assessment (rNSAA) and the Time Function Test (TFT).

The baseline dystrophin levels as measured by ECL was 0.42% of normal (range 0.00% ; 41.85%). At the end of study, dystrophin levels had a median of 0.33% of normal (range 0.04% ; 48.55%). For IHC, the median percentage of positive fibres at baseline was 73% (range 0.42% ;99.6%). At the end of the study, the median percentage of positive fibres was 66% (range 0.51% ; 99.77%).

6.4. Clinical efficacy

Three studies were ongoing during the reporting period:

• PTC-124-GD-041-DMD (Study 041): a Phase 3, randomised, double-blind placebo-controlled efficacy and safety study of ataluren in subjects with nmDMD and open-label extension.

• PTC124-GD-025o-DMD (Study 025o): a multicenter, observational study in patients with nmDMD who are being treated with ataluren in usual care (outside of a clinical study).

• PTC124-GD-048-DMD (Study 048): an open-label study evaluating the safety and pharmacokinetics of ataluren in children from 6 months to <2 years of age with nmDMD.

Study 041

PTC has been conducting a randomised, double-blind confirmatory study (Study 041) in patients with nmDMD as an SOB. Study recruitment (last subject first visit) in Study 041 concluded on 29 October 2020, and the last visit for the last subject is anticipated in July 2023.

The plan and timing for study completion and reporting is presented in Table 1. PTC provided the SOB final CSR in SOB Type II submission EMEA/H/C/002720/II/0069 on 30 September 2022.

Study 025o

One post-approval Registry for ataluren was ongoing during the reporting period. Study 025o is a long-term observational study of Translarna's safety and effectiveness in usual care. This Registry is ongoing in the European Union (EU), United Kingdom, Israel, and Brazil and was developed in consultation with regulatory authorities to monitor the safety, effectiveness, and utilisation patterns of ataluren.

As per the timelines, the submission of final study report of Study 025o would have been expected by 30 October 2025.

Study 048

Study 048 is an open-label study to evaluate the safety and pharmacokinetics of ataluren in children from 6 months to less than 2 years of age with nmDMD. The study is being conducted as part of the Translarna Paediatric Investigational Plan (ataluren; PIP EMEA-000115-PIP01-07-M12, EMA Decision P/04775/2022). As of the end of the reporting period, 4 subjects had been enrolled.

CHMP comment/assessment

Study 041 is briefly described above. The study was assessed in procedure EMEA/H/C/002720/II/0069 and results were also submitted for this renewal application. The efficacy in terms of effect size and clinical relevance seen in studies 007 and 020 could not be confirmed. The benefit-risk is at discussion. See above.

An interim report of study PTC124-GD-025o-DMD is annually provided as a PAM MEA-002. The study concerns comparison to an external cohort; hence no extensive description is provided. Data obtained from this study also contribute to the totality of the evidence. However, this data cannot replace the data from placebo-randomised controlled studies.

Study 048 was ongoing at the time of the submission of the renewal. No data was provided. The MAH submitted the study results in the in procedure EMEA/H/C/002720/II/0074 which has concluded. The Study 048 is a Phase 2, open-label study to evaluate the safety, tolerability, and PK of ataluren in 6 male subjects with nmDMD aged ≥6 months to <2 years of age. The study included PK and safety data but no efficacy or pharmacodynamic data. Further, the population included in this study, i.e. nmDMD patients aged ≥6 months to <2 years of age, is different from the population included in the authorised indication,

i.e. nmDMD patients aged ≥2 years of age. The MAH did not request for an extension of the indication based on the results of this study.

6.5. Clinical safety

6.5.1. Cumulative Estimated Exposure Data (as of 31 December 2022)

Cumulatively, as of 31 December 2022, 1795 unique subjects have been exposed to ataluren in interventional studies in the clinical development programme. An estimated 1616 patients have been exposed to ataluren in marketing experience between 31 July 2014 and 31 December 2022.

This includes 1410 patients receiving paid ataluren commercially or as part of expanded access programmes and 206 free-of-charge patients.

CHMP assessment/comment

The MAH provided the patient exposure covering the period of 31 December 2020 - 31 December 2021as requested previously by the PRAC. The number of subjects exposed to ataluren has increased to 48 subjects since the last report (31 July 2021). Also, the number of subjects receiving paid ataluren commercially or as part of expanded access programmes free-of-charge has increased. The number of subjects exposed to ataluren is sufficient to conclude upon the safety and long-term exposure to ataluren

6.5.2. Summaries of Significant Safety and Efficacy Findings From Clinical Studies and Non-interventional Studies

No new safety signals or trends were identified for ataluren after a cumulative review of all safety data from clinical studies and post-marketing surveillance. The totality of the safety data supports the favourable overall safety profile of Translarna.

CHMP assessment/comment

There were no new safety signals. The safety of ataluren in the population covered by the current indication is well known.

6.5.3. Study 041

The MAH claimed that the results of efficacy and safety assessments from Study 041 confirmed the positive benefit-risk profile of ataluren established in previous studies. Results of Study 041 were described in 2 reports submitted as part of a type II submission to fulfil the SOB (procedure EMEA/H/C/002720/II/0069).

CHMP assessment/comment

It can be agreed that the safety data of study 041 was in line with the safety profile of ataluren. There were no safety concerns raised in procedure EMEA/H/C/002720/II/0069. The MAH was requested to remove the statement in section 4.8 of the SmPC that the long-term safety is unknown, as the safety data set is comprehensive and subjects have been exposed to up to ~10 years. As per efficacy, see the above section.

6.5.4. Study 025o

As of the most recent database lock (31 January 2022), 306 patients in 14 countries had received Translarna as part of the registry study in usual care. The majority of treatment-emergent adverse events (TEAEs) were mild to moderate in severity. Events in 10 patients (3.3%) were assessed as related to treatment; 13 patients (4.2%) had TEAEs that led to the discontinuation of ataluren. Twenty-nine patients (9.5%) had 46 serious adverse events (AEs); 43 events were assessed as not related to ataluren, 2 had an unknown relationship, and the relationship of 1 event was not reported (Muntoni 2022).

The loss of ambulation and pulmonary milestones were significantly delayed relative to natural history controls from the Cooperative International Neuromuscular Research Group (CINRG) natural history study (Mercuri 2022, Tulinius 2022). Loss of ambulation was delayed by 4 years (hazard ratio [HR]: 0.375; p<0.0001), and the median age at predicted forced vital capacity (FVC) <60% was delayed by 1.8 years (17.7 years for patients in the Strategic Targeting of Registries and International Database of Excellence (STRIDE) Registry and 15.9 years for patients in the matched (HR: 0.539; p=0.0021).

CHMP assessment/comment

The MAH indicates that 13 patients (4.2%) had TEAEs that led to the discontinuation of ataluren; however, it is unknown what these TEAEs were. This issue is not pursued here as the sixth interim report is due to be submitted to the EMA by the end of April 2023, and the information will be provided there. As indicated, the safety of ataluren is now well known as the MAH was requested to remove the statement on long-term safety from the SmPC.

Regarding the significant delay relative to natural history controls, this is part of the discussion on efficacy.

6.5.5. Study 048

As of 31 December 2022, 4 subjects younger than 2 years of age were enrolled in Study 048. To date, 11 AEs have been reported across these 4 subjects. All events have been mild and assessed as unrelated to ataluren. Analysis of blood samples demonstrates that exposure is generally within the efficacious range and consistent with the established pharmacokinetic profile in older subjects.

6.5.6. Worldwide Marketing Authorisation Status

Translarna (ataluren) is conditionally approved in the EU under a centralised procedure. The date of EC decision of the last authorisation renewal was 20 June 2022. Translarna is currently authorised in the following countries: Belarus, Brazil, Chile, the European Union, Israel, Kazakhstan, the Kingdom of Saudi Arabia, Peru, the Russian Federation, South Korea, the United Kingdom, and Ukraine.

6.5.7. Actions Taken for Safety Reasons

No clinical studies of ataluren have been suspended or terminated for safety reasons. There have been no issues requiring communication to healthcare professionals. The benefit-risk profile of Translarna is unchanged since the initial marketing authorisation.

6.5.8. Significant Changes Made to the Reference Safety Information

On 04 March 2022, a corrigendum sequence was submitted to the EMA to correct discrepancies in the Translarna SmPC. This procedure only impacted Section 4.8, table 1 of the SmPC for the Bulgarian, Czech, French, Latvian, and Spanish versions of the Product Information. No updates were made to the English SmPC.

The date of last renewal in Section 9 of the SmPC (version dated 17 June 2021) was changed to 20 June 2022 to reflect the positive completion of the 8th Annual Renewal (procedure EMEA/H/C/002720/R/0067).

On 22 July 2022, a type II variation (EMEA/H/C/002720/II/0068) was submitted to the EMA to update the SmPC Section 5.1 following the EMA Assessment Report

EMEA/H/C/002720/P46/026 (dystrophin Study PTC124-GD-045-DMD). This procedure was still ongoing at the end of the reporting period.

On 30 September 2022, a type II variation (EMEA/H/C/002720/II/0069) was submitted to the EMA to fulfil the SOB and to propose a switch from a CMA to a full marketing authorisation.

CHMP comment

All the above mentioned procedures are now finalised. The dystrophin levels are included in section 5.1 of the SmPC. As study 041 is a failed study, the type II variation EMEA/H/C/002720/II/0069 is closed with a negative opinion.

6.5.9. Literature

During the full reporting period (31 December 2021 through 31 December 2022), several posters and abstracts describing the results of the ongoing ataluren Studies 041 and 025o (STRIDE Registry) were presented at the 2022 World Muscle Society (WMS) meeting in Halifax, Canada (Table 2).

Table 2: Ataluren presentations at the 2022 World Muscle Society meeting

First Author Year	Title
(Muntoni 2022)	Updated demographics and safety data from patients with nonsense mutation Duchenne muscular dystrophy receiving ataluren in the STRIDE Registry
(Tulinius 2022)	Pulmonary function in patients with Duchenne muscular dystrophy from the STRIDE Registry and CINRG Natural History Study: a matched cohort analysis
(Mercuri 2022)	Age at loss of ambulation in patients with DMD from the STRIDE Registry and the CINRG Natural History Study: a matched cohort analysis
(McDonald 2022a)	Ataluren preserves upper limb function in nmDMD patients from Study 041, a Phase 3, placebo-controlled trial, and the STRIDE Registry
(McDonald 2022b)	Safety and efficacy of ataluren in nmDMD patients from Study 041, a Phase 3, randomized, double-blind, placebo-controlled trial

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; nmDMD, nonsense mutation Duchenne muscular dystrophy; STRIDE, Strategic Targeting of Registries and International Database of Excellence

Across all of these publications, ataluren was shown to delay the progression of Duchenne muscular dystrophy (DMD) milestones compared to placebo or standard of care alone.

Safety results from the STRIDE Registry (Muntoni 2022) and Study 041 (McDonald 2022b) confirm the favourable safety profile of ataluren in treating nmDMD. Safety outcomes were consistent with the known

safety profile of ataluren established in previous studies. The majority of TEAEs were nonserious and mild to moderate in severity and infrequently resulted in treatment interruption or discontinuation. No new or unexpected events have been reported with long-term use.

An article describing the results of the STRIDE Registry as of the latest data cut-off of 31 January 2022 has been submitted to the Journal of Neurology. This article provides a comprehensive overview of the safety and efficacy results described in the various posters and abstracts presented at the WMS meeting in October 2022. The article is expected to be accepted for publication in February 2023.

Results from the STRIDE Registry at the time of a more recent data cut-off of 31 January 2023 was included in the sixth interim report of Study 025o submitted to the EMA in April 2023 (EMEA/H/C/002720/MEA/002.10). Published data from Study 041 are also described in the Study 041 CSRs that were submitted as part of a type II submission to fulfil the SOB (procedure EMEA/H/C/002720/II/0069).

CHMP comment

The MAH indicate that the safety in the Registry and study 041 were in line with the safety profile currently known. Consistent with previous studies, the majority of TEAEs were mild to moderate in severity. This is also reflected by the low number of subjects that discontinued treatment.

6.5.10. Periodic Benefit-Risk Evaluation Report

No new safety signals or trends were identified for ataluren. The MAH will continue to monitor all new safety data and safety concerns per the Risk Management Plan (RMP), which includes the important identified risk of "potentiation of aminoglycoside renal toxicity" and the following important potential risks: "long-term cardiovascular effects including changes in lipid profile"; "hypertension with use of concomitant systemic corticosteroids"; "renal toxicity"; "hepatic toxicity"; and "malignancies." The approved SmPC provides adequate information to minimise and mitigate these risks for ataluren.

6.5.11. Safety Assessment

The safety profile of ataluren remains unchanged during this reporting period.

6.5.12. Late-Breaking Information

No new significant safety or efficacy information was received by the MAH between the data cut-off date of 31 December 2022 and the submission of this document.

6.6. Pharmacovigilance inspections

One Regulatory Authority routine pharmacovigilance inspection was conducted during the period covered by this renewal. The Health Products Regulatory Authority (HPRA) conducted an inspection at PTC Therapeutics International Limited from 24 to 28 October 2022 and 01 to 03 November 2022. No critical findings were cited.

CHMP comment

The MAH reports that the HPRA conducted an inspection at PTC Therapeutics International Limited from 24 to 28 October 2022 and 01 to 03 November 2022. No critical findings were cited, according to the MAH. No information was provided on which site was inspected. Though the MAH is obliged to

provide this information as part of the renewal procedure, the issue will not be pursued as details on the inspection site and the full inspection report have been provided in the type II variation discussing study 041 (EMEA/H/C/002720/II/0069)

6.7. Discussion

No significant safety information has been received in the reporting period of this renewal. The findings reported are in line with the safety profile of ataluren as described in the SmPC and the EPAR.

7. Risk management plan

Version 11.1 (date of final sign-off 16 March 2023) of the Risk Management Plan (RMP) for Translarna was submitted in the type II variation to submit the CSR of Study 041 that fulfils the SOB of the CMA for Translarna, thus switching from a CMA to full marketing authorisation (procedure EMEA/H/C/002720/II/0069 submitted on 30 September 2022).

No other significant changes were made to version 11.1 of the RMP, and the list of safety concerns for ataluren remains the same as in the currently approved version of the RMP V10.0 (dated 11 March 2021) approved on 15 April 2021.

According to this version, the following are the safety concerns for ataluren:

Important identified risks

- Potentiation of aminoglycoside renal toxicity

Important potential risks

- Long-term cardiovascular effects including changes in lipid profile
- Hypertension with use of concomitant systemic corticosteroids
- Renal toxicity
- Hepatic toxicity
- Malignancies

Missing information

- Use in patients with severe renal impairment
- Extended long-term safety
- Effect of co-administration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies

CHMP comment

Within the procedure EMEA/H/C/002720/II/0069, the PRAC Rapporteur indicated that the re-categorisation of study PTC124-GD-041-DMD to a category 3 study is pending the CHMP's decision for granting a full MA. As this discussion would be further discussed in the current renewal procedure, the MAH was requested in variation II/0069 to provide a commitment to update the RMP after the finalisation of the renewal procedure. This updated RMP should include changes introduced in version 11.1 (pending outcome of granting a full MAA) compared to version 10.0 and remove pivotal clinical trial PTC124-GD-020-DMD from Annex 2.

8. Changes to the Product Information

No changes to the Product Information (PI) are introduced at this time.

9. Request for Supplementary Information - RfSI

The MAH should provide the following supplementary information in response to Day 60 RfSI:

9.1. Major objections

Clinical aspects

1. The submitted data and subsequently conducted analyses do not allow for isolating a beneficial and clinically relevant treatment effect that can be attributed to Translarna (ataluren). Comparison to an external control and a *post hoc* meta-analysis, violating methodological principles and targeting a subset of the licensed patient population, are not considered sufficient to provide evidence of a favourable effect (see also CPMP/EWP/2330/99).

   Notably, the meta-analysis cannot compensate for or overrule the results of the individual RCTs, which produce the most reliable results by their predefined and alpha-controlled nature.

   Considering that the data's totality is now regarded as comprehensive, the MAH is requested to justify that Translarna has demonstrated a beneficial and clinically relevant effect in the licensed patient population.

9.2. Other concerns

Clinical aspects

2. The MAH is requested to present a simplified version of figure 1 (from response OC15) in the product information of the effects in the target population (ITT) and show only the "combined" approach for the inclusion of the high dose arm of study 007 (former OC 15 in procedure EME/H/C/002720/69)

10. Assessment of the MAH responses to the RfSI

10.1. Major objections

Clinical aspects

1. The submitted data and subsequently conducted analyses do not allow for isolating a beneficial and clinically relevant treatment effect that can be attributed to Translarna (ataluren). Comparison to an external control and a *post hoc* meta-analysis, violating methodological principles and targeting a subset of the licensed patient population, are not considered sufficient to provide evidence of a favourable effect (see also CPMP/EWP/2330/99).

   Notably, the meta-analysis cannot compensate for or overrule the results of the individual RCTs, which produce the most reliable results by their predefined and alpha-controlled nature.

Considering that the data's totality is now regarded as comprehensive, the MAH is requested to justify that Translarna has demonstrated a beneficial and clinically relevant effect in the licensed patient population.

Summary of the MAH's response

CHMP comment:

In their response the MAH discusses how the beneficial effects are attributed to ataluren treatment and are of clinical relevance by discussing the consistency and replicability, the clinical meaningfulness and the safety profile. Below the MAH's conclusions are presented as summary. For the full response, please refer to the response document.

Duchenne muscular dystrophy is a relentlessly progressive and inevitably fatal disease characterised by a decline in muscle strength and function. Patients with DMD face year after year of decline, losing one motor function after another in a predictable stepwise pattern that culminates in death due to respiratory and cardiac compromise. These functional losses entail a loss of autonomy in nearly every activity of daily life. The goal of ataluren treatment is to alter this relentless trajectory by slowing the progression of the disease and the resulting loss of motor function. Despite the use of corticosteroids, there remains a critical need for therapies that target the underlying disease process. For the 10% to 15% of DMD patients who have the disease due to a nonsense mutation, ataluren is the only treatment to do so.

A Consistent and Replicable Treatment Benefit Has Been Demonstrated

The development of therapies for rare, progressive neurological and neuromuscular disorders poses many challenges, including patient heterogeneity (even for monogenic disorders), variable disease progression with periods of stability and rapid decline, and endpoints which may not be sensitive capturing key disease transition points over the time-limited course of a clinical trial.

Despite these methodological challenges, data from 3 randomised placebo-controlled studies, individually and combined in meta-analyses, confirm ataluren treatment is associated with consistent slowing of disease progression across multiple endpoints, providing clear evidence of a reliable and consistent treatment benefit in this rare, highly morbid, and ultimately fatal disease with no other disease-modifying treatment. The consistency of benefit recorded across 700 patients at the indicated dose support the fact that the treatment effect is not occurring by chance, but is a result of the beneficial effects of ataluren on several key aspects of disease pathology.

The Demonstrated Benefit is Clinically Meaningful

Firstly, the treatment benefits in highly relevant endpoints during the clinical trials translate to a slowing of the rate of disease progression and a preservation of important functions of daily life. Secondly, analyses of highly prognostic thresholds developed by DMD experts show how the observed slowing of progression is predictive of a delay in the key long-term morbid transition points of loss of ambulation and the need for respiratory intervention. Lastly, while it cannot provide the level of robustness of a placebo-controlled trial, the long-term follow-up in the STRIDE Registry allows for direct observation of the cumulative effects of ataluren on key disease outcomes.

Ataluren Has a Well-Established Favourable Safety Profile

The favourable safety profile of ataluren is also well established. In 12 completed clinical studies in subjects with nmDMD comprising over 1600 patient-years of exposure, ataluren was well tolerated across all age groups at an oral dose of 10, 10, 20 mg/kg and remained well tolerated in subjects on long-term ataluren treatment (exposures of >5 years). Study 041 itself provides confirmation of the established safety profile of ataluren over 72 weeks of treatment in more than 300 subjects throughout the disease lifecycle. The frequency and nature of TEAEs in Study 041 individually and the pooled data

for Study 007, Study 020, and Study 041 were consistent with the known safety profile of ataluren, with no new safety concerns identified.

Ataluren's Favourable Benefit/Risk Remains Unchanged

With the conclusion of Study 041, 3 randomised studies and the Registry provide clear and consistent evidence that ataluren therapy demonstrates a treatment benefit, results in clinically meaningful slowing of disease progression, and continues to show a highly favourable safety profile. Overall, the data, particularly given the context of the highly morbid, inevitably fatal nature of the disease and the lack of any other approved treatment, reaffirm that the benefit/risk profile of ataluren remains positive.

Assessment of the MAH's response

The unmet medical need for an effective treatment in the relentless progressive disabling and life-threatening Duchene Muscular Dystrophy is acknowledged and fully agreed. At discussion is the evidence provided whether ataluren can fulfill this unmet medical need.

Consistency of the effect

The MAH indicates that there is a consistent and replicable treatment benefit for the following reasons

(i) the endpoints may not be sensitive enough to capture the key disease transition points over the limited time course of a clinical trial

(ii) the data from 3 randomized placebo controlled trials confirmed a consistent slowing of disease progression across multiple endpoints both individually as well as in a combined meta-analysis

(iii) the effect is consistent across 700 patients as shown in subgroup analysis.

The following comments are made regarding these statements:

i. The endpoints were chosen based on clinical practice. Therefore study 020 and 041 also include the North Star Ambulatory Assessment, which was not part of the initial study 007. The sensitivity of the endpoints are not an issue as subjects deteriorate on the 6MWD, NSAA and TFT over the year there is sensitivity to change. Point is more are the endpoints sensitive to pick up a treatment effect, over the duration of a trial? This also depends on whether a treatment is highly effective (e.g. disease stabilization) or not.

   For Ataluren the results of the phase II study (007) triggered the decision to proceed in the phase III program, The phase III studies (020, 041) were not able to meet their primary endpoint in terms of both statistical significance and clinical relevance (see ii). This is especially disappointing for study 041 considering that this study was the largest one, in a sensitive population and had the longest study duration (72 weeks) in DMD so far. In fact, study 041 was designed as the one generating definitive decisive evidence. In fact, in this study the effect size was the smallest seen over the studies apart from not being statistically significant. Moreover, the separation from placebo did not increase beyond 12 weeks what would have been expected.

   Hence, the argument that the endpoints may not be sensitive enough to capture the key disease transition points over the limited time course of a clinical trial is not fully agreed. First, there is sensitivity to change of the endpoints for the duration of the study. Second, sensitivity to show a treatment effect over the time-frame of the study also depends on the effectiveness of the treatment. Third, it cannot be argued that if the study had been long enough such effect would have been seen. This requires verification by data.

ii. The MAH indicates that the effect is consistent, however, each study had a different primary efficacy population based on the results of the previous is study. In study 007, the difference in change from baseline at week 48 on the 6MWD was 26.4m ($p_{nominal}$=0.905), which was not clinically meaningful. The MAH therefore *post hoc* defined the subgroup (ambulatory decline population (ADP), i.e. patients aged7-16 years of age on corticosteroid with a baseline 6MWD≥150m and ≤80% predicted), which showed a statistically significant and clinically meaningful difference from placebo on the 6MWD of 49.9m ($p_{nominal}$=0.0096). In study 020 these results were not replicated as the difference from placebo on the 6MWD was 15m

(p=0.213). The MAH *post hoc* defined a new subgroup, i.e. subjects with a baseline 6MWD value of ≥300 to <400m. The difference between ataluren and the placebo arm was 47m ($p_{nominal}$=0.007). In study 041 the difference on the 6MWD between ataluren an the placebo in the 2nd defined sub group is 8.26m (P=0.3626). In the overall population the difference from placebo on the 6MWD is 14.42m (p=0.0248). Thus the effect of ataluren is not clearcut or straightforward.

iii. In contrast to the MAH's opinion the effect not considered consistent, as the greatest effect was seen in study 007 (49.9m ($p_{nominal}$=0.0096)), which could not be repeated in both SOB studies 020 (15m (p=0.213)) and 041 (14.42m (p=0.0248). The same applies to the TFT items, where also worse performance is seen with each study. Consistency over subgroups is questionable as each time a *post hoc* potential subgroup was identified (with different cut-off points) that possible might benefit the most, this could not be confirmed in the subsequent confirmatory study. This emphasis the general risk of data driven identification of subgroups with arbitrary cut-off point that have limited biological plausibility. Moreover, the performed subgroup analysis (on combined ITT data from study 007, 020 and 041) indicate that the effect is not consistent.

The SAG-N experts agreed by consensus that the studies 020 and 041 were formally negative because the results from the primary endpoints did not reach statistical significance (were negative). Hence, all other results– including *post hoc* results from secondary endpoints– cannot confirm the efficacy of Translarna in nmDMD. The patient representatives expressed the view that if one considers the data from these trials, efficacy cannot be considered as sufficiently established. They highlighted, though, that these data are suggestive of some efficacy, especially if taken in the context of all available data, including real-world evidence

Overall, it agreed that the beneficial effects seen in study 007, which was the basis for the conditional market authorization could not be confirmed. Moreover, the two specific obligation studies are considered formally negative.

Clinically relevant effect

Regarding the discussion on clinically meaningfulness, the MAH indicates that

i. the endpoints translate to a slowing of the rate of disease progression and a preservation of important functions of daily life

ii. slowing of disease progression leads to a delay in loss of ambulation and need for respiration support

iii. observation study allows for cumulative effect of ataluren on key disease outcomes.

The MAH statements are not agreed. It is questioned if differences are indeed attributed to ataluren treatment. The MAH argues that across 2 and 3 studies, ataluren treatment was associated with reductions in risk of experiencing a 10% worsening in 6MWD of 32% (HR=0.68,) and 34% (HR=0.66,), respectively. However, while differences from placebo are noted, it is questioned if this is attributed to ataluren treatment. If ataluren treatment indeed led to this benefit over time the difference from placebo would increase over time. However, the 72 week study showed more similarity to placebo. Moreover, this is demonstrated by data of figure 18, were at week 12 the separation from placebo occurs, but does not increase with increasing treatment. Further, when subjects from the placebo group switched to ataluren treatment there was no benefit from treatment detected i.e. no change in direction of the path of deterioration on any of the outcome measures. The data on the delay in 30m decline is also questioned as again the separation from placebo is not consistent across

the different trials, it does not increase with increase treatment with ataluren and when subjects switch to ataluren treatment no additional benefit is noted.

Comparison STRIDE registry

As indicated previously the data from an observational study cannot replace 3 well conducted clinical trials of which are all failed studies.

The interpretation of results from studies using an external control should be done with caution as this type of approach is prone to bias. In this particular case, the controls from CNRG-DNHC were matched with participants in STRIDE using propensity score matching (see above the logistic PS model).

First, neither dose nor the regimen of corticosteroid were considered in the original propensity score (PS) model. During the oral explanation, the MAH presented a PS model that also matched for type and daily dose of corticosteroid used, but with uncertainties remaining around the pattern of corticosteroid use. More specifically, the MAH included a categorical variable on duration of corticosteroid use. However, the rationale for this categorisation is unclear and does not match with other studies/recommendations (e.g. Kim et al. 2015). Moreover, the modelling decision assumes equal effects on delaying the time to loss of ambulation for everyone beyond 12 months of use (e.g., regardless of age). This is questioned.

Second, subjects in the ataluren group had a mean age of 8.845 years (95%CI 8.394-9.297), while subjects in the CINRG group had a mean age of 10.492 (95%CI 9.842 -11.143). This 2-year difference in age at first assessment hampers a match on functional outcome measures.

Third, although DMD mutations were not considered in the PS model, the MAH argued during the oral explanation that this aspect is not influencing the STRIDE results. The MAH presented data on a small subgroup of CINRG patients for whom it was known if they had or had not a nonsense DMD mutation and additionally data from the French Registry of Dystrophinopathies, both showing similar age of LoA of untreated nmDMD and non-nmDMD patients. However, for both comparisons differences in baseline characteristics and confounding could not be excluded. Therefore, conditional exchangeability of the groups is questionable. An additional justification provided by the MAH for not including matching based on genotype, was based on the lack of association between genotype class and 1 year change in NSAA and 10m walk/run velocity. This is questioned as it is unclear if this conclusion based on NSAA and 10m walk/run velocity can be extrapolated to time to LoA.

Further, as opposed to well-conducted trials where randomization ensures exchangeability as per known and unknown counfounders, the PS-matched methods only ensures exchangeability conditional to the variables included in the model and hence, by definition cannot account for unknown confounding.

Importantly as patients in STRIDE were only allowed to enter the registry if prescribed Translarna requiring them to be still ambulatory, this introduced immortal time bias.

Moreover, the impact of the calendar bias is unknown. The ataluren-treated nmDMD patients were enrolled into the STRIDE cohort from 2015-2022, and the untreated DMD patients were recruited into the CINRG cohort from 2006-2016. Therefore, differences in the standard or care could have also contributed to the better observed outcome. During the oral explanation, the MAH claimed that the key elements of the standard of care remained consistent over the periods of enrollment. However, the MAH made reference to four guidelines and it was noted that neither the physiotherapy nor scoliosis management are included in the therapeutic guideline by Moxley et al. 2005, the guideline available at the start of CINRG-NHS cohort in 2006. Further, the most comprenhensive guideline promoting a multidisciplinary treatment strategy for DMD including interventions in different areas (i.e., steroid dose, steroid regiment, physiotherapy, scoliosis management) per the different stages

of DMD (diagnosis, early ambulatory, late ambulatory, early non-ambulatory and late non-ambulatory) was only available at 2018 (Bimkrant et al, 2018). Hence, the MAH´s claim is questioned. As an additional justification, the MAH presented results from studies showing similar time to LoA over different study periods which spans from 10.8 years to 13.4 years of age at LoA. Thus, indicating that differences in baseline characteristics and confounding can lead to different age at LoA. Further limitations and uncertainties include unclear rules for censoring and substantial missing data for which the MAR pattern of missingness. Overall, there are many uncertainties related to the claimed delay of 3.5 years, particularly as this is based on data of 5-10% of the included population for whom also immortal time bias cannot be excluded.

The majority of the SAG-N experts agreed on the value of registries for regulatory purposes, but mainly as providing supporting evidence from positive randomized clinical trials. The patients' view on this was that RWE should not only be used to confirm positive trial data, but also address uncertainties arising from these data. The experts stated that real world data from registries cannot fully substitute the results from clinical trials. Overall, the majority of the experts agreed that the MAH has reasonably addressed the potential bias but there was still the possibility of unknown confounding that can only be controlled by randomization. The majority of the experts expressed the opinion that in the concrete case the regulatory a decision should not be based only on the registry data but consider these in the context of the data available from the controlled clinical trials. Nevertheless, all experts noted that the real-world data should not be ignored as they may represent a strong signal of efficacy.

It is agreed that the MAH has sufficiently addressed the concerns regarding corticosteroid bias and calendar-time bias. However, as also indicated by the SAG, in the matching one can only control for known biases. It is also agreed that these data cannot replace the findings of the failed studies and should only be used to confirm a beneficial effect observed in the trial. This is not the case here, as the RCTs consistently failed to demonstrate an effect in the predefined most sensitive treatment population.

Overall

The safety profile of ataluren is not at discussion. The issue is the unclear beneficial effects and clinical relevance of the effect size. This is particularly a concern as the MAH failed to demonstrate that clinically meaningful levels of dystrophin are produced following treatment with ataluren.

Without a substantial dystrophin expression no efficacy is expected.

The SAG-N experts and patient representatives agreed that any clinical change is more important that any change in the dystrophin levels. Furthermore, the relationship between the dystrophin levels and functional outcome is unclear (i.e., it is unclear how much dystrophin needs to be increased to attain a clinical benefit). The SAG-N experts expressed the view that the role of dystrophin as marker of severity of prognosis is not clearly established. Thus, the pharmacological data are not essential for a decision-making process.

It is acknowledged that functional benefits are more important than changes in dystrophin level, particularly if the studies would have shown a beneficial effect. However, here the mode of action was never confirmed. Moreover the lack of an effect on pharmacodynamics confirm the lack of functional benefit in the clinical trial. Therefore, the dystrophin data should not be ignored and is thus incorporated in the benefit-risk balance.

Conclusion

The Committee re-assessed the benefit-risk of Translarna as part of the annual renewal procedure, taking into account the totality of data, which includes the data available at the time of the conditional

approval, data generated as per the specific obligations (the data from study 020, as well as the data from study 041), data from STRIDE registry (study 025o) and additional real world data made available to the Committee, as well as and on data on paediatric studies 045 and 046.

The available data, in particular the results of study 041 conducted to fulfil the outstanding specific obligation with a view to confirming a favourable benefit-risk balance for the conditional marketing authorisation for Translarna, failed to confirm the efficacy of Translarna in the treatment of ambulant patients with nmDMD aged 2 years or older.

Based on the above, the CHMP concluded, on the basis of the comprehensive set of data, that the efficacy of Translarna is not established and therefore a favourable benefit-risk balance has not been confirmed in the treatment of ambulant patients with nmDMD aged 2 years or older.

10.2. Other concerns

Clinical aspects

2. The MAH is requested to present a simplified version of figure 1 (from response OC15) in the product information of the effects in the target population (ITT) and show only the "combined" approach for the inclusion of the high dose arm of study 007 (former OC 15 in procedure EME/H/C/002720/69)

MAH's response

The meta-analysis of efficacy data from the 3 randomised studies employed 2 approaches regarding the high dose (20, 20, 40 mg/kg) of ataluren used in Study 007:

- In approach 1 (referred to as the "including" approach), the ataluren high dose was included in the meta-analysis model, but the treatment comparison was made between the ataluren indicated dose of 10, 10, 20 mg/kg versus placebo.

- In approach 2 (referred to as the "combined" approach), both the ataluren indicated dose (10, 10, 20 mg/kg) and ataluren high-dose (20, 20, 40 mg/kg) treatment groups were combined into a single ataluren treatment group in the analysis model. The treatment comparison was made between this combined ataluren arm and placebo.

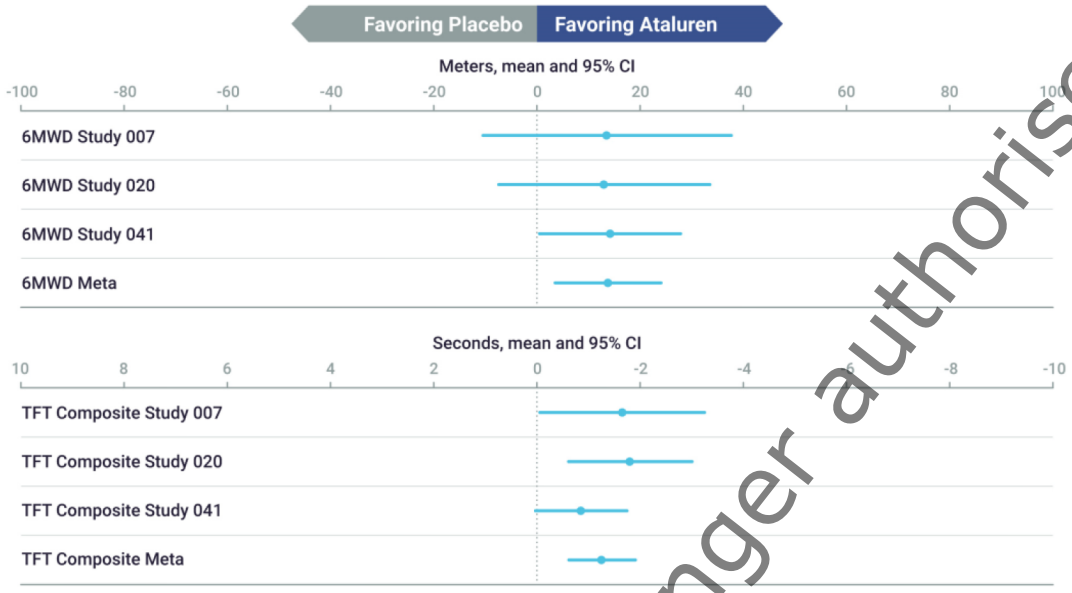
As would be expected, the point estimate for the treatment difference between ataluren and placebo in both Study 007 and the meta-analysis was smaller for approach 2, when results for the non-efficacious dose (ie, ataluren high dose) were combined with those of the indicated dose. In addition, the results for Study 007 and the meta-analysis using the combined approach 2 were more variable, with wider confidence intervals around the mean point estimate. As such, approach 2 represents the most conservative estimate of treatment effect in Study 007 and the meta-analysis as it dilutes the actual effect of the established indicated dose. Despite the more conservative approach, however, results of the meta-analysis for both endpoints consistently favour ataluren (Figure 8). Because the high dose was not used in Studies 020 and 041, both approaches yielded the same results for those studies.

As requested by EMA, the MAH will include results of the meta-analysis in section 5.1 of the Summary of Product Characteristics (SmPC) (Clinical efficacy and safety) with the following proposed text:

*"A meta-analysis was completed using all 761 patients randomised to ataluren 40 mg/kg/day (approved dose), ataluren 80 mg/kg/day, or placebo in Study 007, 020, or 041 (*Figure 8*). The meta-analysis included 354 patients on 40 mg/kg/day (approved dose), 60 patients on ataluren 80 mg/kg/day, and 347 patients on placebo. The mean change in 6MWD from baseline to Week 48 was 13.79 metres better*

in the treated arm than in the placebo arm (p=0.0086). The mean change in TFT composite score from baseline to Week 48 was 1.26 seconds better in the treated arm than in the placebo arm (p=0.0001).”

Figure 8: Meta-analysis of studies 007, 020, and 041 using random-effects model approach 2 (combined) – ITT population, week 48

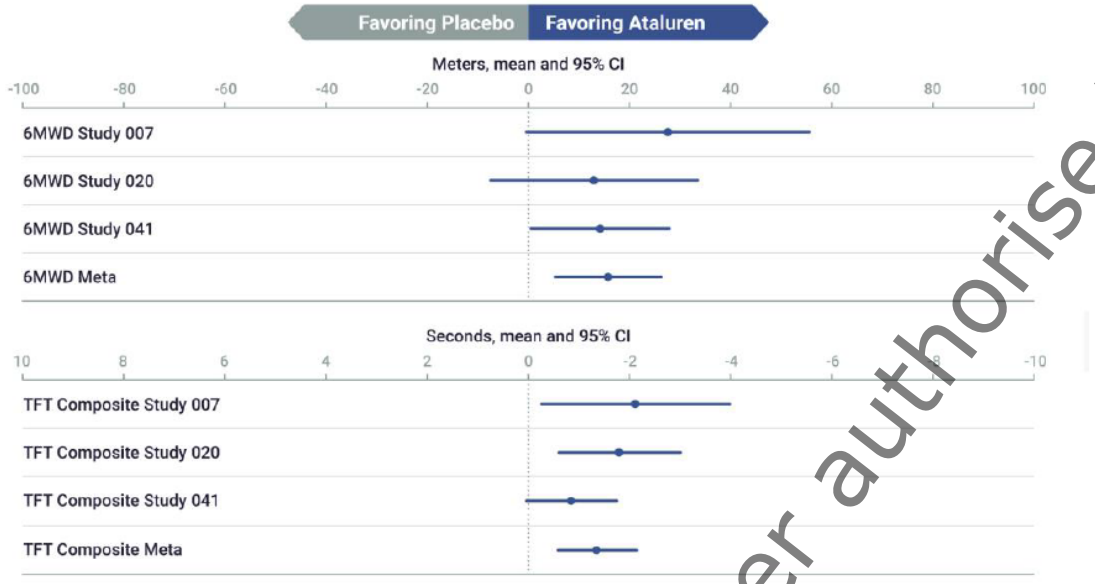


Abbreviations: 6MWD, 6-minute walk distance; ANCOVA, analysis of covariance; ITT, Intention-to-Treat; TFT, timed function test
Note: Combined: comparison of combined ataluren low and high doses and placebo used in the meta-analysis model across Studies 007, 020, and 041. The data for Study 007 and meta represent the treatment difference between placebo and ataluren when both doses of ataluren (10, 10, 20 mg/kg indicated dose and 20, 20, 40 mg/kg high dose) are combined.
ANCOVA models are applied after multiple imputation of missing data, assuming missing values were missing not at random and utilising the complete case missing value pattern.
In Study 007, the ANCOVA model for 6MWD includes factors of treatment, stratification factors of age, baseline 6MWD, and baseline corticosteroid use, and baseline 6MWD as a covariate.
In Study 020, the ANCOVA model for 6MWD includes factors of treatment, stratification factors of age, baseline 6MWD, and duration of prior corticosteroid use, and baseline 6MWD as a covariate.
For all other endpoints, the ANCOVA model includes factors of treatment, stratification factors of baseline 6WMD, baseline time to stand from supine, and baseline corticosteroid type, and baseline 6MWD as a covariate.
Source: Table RSI_1_Q15_2_1

Whilst approach 2 demonstrates consistent benefit favouring ataluren, the MAH considers that presentation of the data with combined high and low doses is potentially misleading to prescribers as it does not reflect the indicated commercial dose that patients will receive.

Therefore, the MAH proposes to include a figure that presents the data generated using approach 1 including), which is both representative of the 10, 10, 20 mg/kg dose that patients will receive and the overall treatment effect of the ataluren indicated dose demonstrated in clinical trials (Figure 9).

Figure 9: Meta-analysis of studies 007, 020, and 041 using random-effects model approach 1 (including) – ITT population, week 48



Abbreviations: 6MWD, 6-minute walk distance; ANCOVA, analysis of covariance; ITT, Intention-to-Treat; TFT, timed function test
Note: Including: comparison of ataluren commercial dose versus placebo used in the meta-analysis model across Studies 007, 020, and 041. The data represent the treatment difference between placebo and the indicated dose of ataluren (10, 10, 20 mg/kg).
ANCOVA models are applied after multiple imputation of missing data, assuming missing values were missing not at random and utilising the complete case missing value pattern.
In Study 007, the ANCOVA model for 6MWD includes factors of treatment, stratification factors of age, baseline 6MWD, and baseline corticosteroid use, and baseline 6MWD as a covariate.
In Study 020, the ANCOVA model for 6MWD includes factors of treatment, stratification factors of age, baseline 6MWD, and duration of prior corticosteroid use, and baseline 6MWD as a covariate.
For all other endpoints, the ANCOVA model includes factors of treatment, stratification factors of baseline 6WMD, baseline time to stand from supine, and baseline corticosteroid type, and baseline 6MWD as a covariate.
Source: Table RSI_1_Q15_1_1

Assessment of the MAH's response

The MAH was requested to present the data of the including and composite population separately and has presented this.

For a prescriber Figure 9 may be more relevant as this concerns the approved posology. For an SmPC it would have been helpful if also the overall effect excluding study 007 was presented, as study 007 is considered hypothesis generating and study 020 and 041 are considered pivotal. This is not further pursued.

Conclusion

Issue not pursued in view of the recommendation to not renew the conditional marketing authorisation.

11. Re-examination

11.1. Introduction

On 14 September 2023, the CHMP issued a negative opinion for the annual renewal of the Conditional Marketing Authorisation of Translarna. On 27 November 2023, the MAH submitted the grounds for re-examination of the CHMP opinion and on 24 January 2024, the CHMP adopted its final opinion recommending to not renew the conditional marketing authorisation for Translarna.

During the decision-making process for issuing the Commission Implementing Decision, on 22 April 2024 a meeting of the Standing Committee had been convened at the request of the Czech Republic which discussed the content of the CHMP opinion. As a result of this discussion, on 2 May 2024, the EC returned the opinion to the Agency and requested the CHMP to further consider the following two scientific questions in a revised opinion:

- whether the totality of the data including the additional data from patient registries and real-world evidence highlighted by Czechia are sufficiently comprehensive to conclude on the benefit/risk balance of Translarna;

- whether these additional data/evidence would impact the CHMP conclusion on the benefit/risk profile of Translarna.

The additional real-world data brought to the attention of the Commission during the decision-making process were taken into account when re-evaluating the benefit-risk balance of Translarna.

In addition, in the Commission letter of 2 May 2024 returning the CHMP final opinion to EMA, the EC, taking into account the impact of the appellate judgment of the Court of Justice of the European Union in Case C-291/22 P, requested that the procedure was restarted from the point in time when the initial scientific advisory group (SAG) was convened. Consequently, the procedure step of the SAG-Neurology conducted on 05 September 2023 was annulled and all subsequent procedural steps were considered invalid. The assessment of the annual renewal was therefore reset to this stage of the initial annual renewal procedure, i.e. prior to the conduct of the SAG-N.

A new SAG-N was conducted on 10 June 2024 and its outcome was taken into account by the CHMP when re-evaluating the benefit-risk balance of Translarna as part of the present annual renewal procedure.

Considering all the above, CHMP issued a negative opinion for renewal of the Conditional Marketing Authorisation to Translarna on 27 June 2024.

The MAH has requested a re-examination of the opinion adopted during the committee´s June 2024 meeting.

On 02 September 2024, the MAH submitted their documentation with grounds for re-examination according to Article 9 (2) of Regulation (EC) No. 726/2004.

11.2. Grounds for non-renewal of the marketing authorisation were the following:

Whereas,

- The Committee re-assessed the benefit-risk of Translarna as part of the annual renewal procedure taking into account the totality of data, which includes the data available at the time of the conditional approval, data generated as per the specific obligations (the data from study

020, as well as the data from study 041), data from STRIDE registry (study 025o) and additional real world data made available to the Committee, as well as and on data on paediatric studies 045 and 046.

- The available data, in particular the results of study 041 conducted to fulfil the outstanding specific obligation with a view to confirming a favourable benefit-risk balance for the conditional marketing authorisation for Translarna, failed to confirm the efficacy of Translarna in the treatment of ambulant patients with nmDMD aged 2 years or older.
- Based on the above, the CHMP concluded, on the basis of the comprehensive set of data now available, that the efficacy of Translarna is not established and therefore a favourable benefit-risk balance has not been confirmed in the treatment of ambulant patients with nmDMD aged 2 years or older.

The CHMP therefore did not recommend the annual renewal of the conditional marketing authorisation for Translarna.

12. Summary of the outcome of the original renewal-assessment procedure

12.1. Clinical aspects

12.1.1. Efficacy

The totality of the data included three randomized controlled trials, i.e., the initially performed phase IIb study 007 and two phase III studies performed after the CMA (studies 020 and 041). These studies, which were the main sources of evidence, included 753 subjects affected by nmDMD, hence a limited subset of DMD, a rare condition (i.e., nmDMD represents less than 15% of DMD). Additional data were generated from STRIDE (study 025o) registry which included 277 subjects affected by nmDMD, from real world data made available to the Committee including evidence highlighted by Czechia and the studies 045 and 046 as complementary sources of evidence. All these data were considered sufficiently comprehensive to conclude on the benefit/risk balance of Translarna.

The additional data provided by Czechia also included three articles discussing a registry set up, the results from a meta-analysis of 3 trials (study 041, Study 007 and Study 020) already included in the assessment and a consensus article discussing the role of ataluren in the treatment of nmDMD subjects without providing any new data on efficacy of ataluren as well as case narratives from 7 CZ patients with nmDMD treated with Translarna. The CHMP considered that the limited additional data provided is insufficient evidence to allow for a conclusion on the efficacy of ataluren with reasonable certainty. Hence, the strength of the evidence from the newly provided data is very limited as compared with three formally negative randomized clinical trials that are considered the main sources of evidence and accordingly, these newly provided data do not impact the CHMP conclusion on the benefit/risk profile of Translarna.

Considering all the above, it was considered that the benefit of ataluren is not confirmed.

12.1.2. Safety

From a safety perspective, overall data support that ataluren is generally well-tolerated in ambulatory patients with nmDMD, with the most common adverse events being headache, upper respiratory tract infections, and gastrointestinal disorders.

12.2. Benefit Risk assessment

Considering that the data's totality was considered as comprehensive, as opposed to when the CMA was first granted, and that the beneficial effect of the results from the phase 2 study could not be replicated in the two confirmatory phase 3 studies (020 and 041), and registry data were not considered sufficiently interpretable, it was considered that efficacy of ataluren is not established and therefore a favourable benefit-risk balance has not been confirmed in the treatment of ambulant patients with nmDMD aged 2 years or older.

13. Assessment of the MAH's responses to the grounds for non-renewal of the Marketing Authorisation

13.1. Introduction

The MAH PTC THERAPEUTICS addressed the formal grounds for non-renewal.

13.2. Ground #1

The MAH´s Grounds for re-examination:

GROUND 1: STUDY 041, PTC124-GD-041-DMD, CONFIRMS THE ATALUREN TREATMENT BENEFIT DEMONSTRATED IN THE PREVIOUS RANDOMISED STUDIES AND THUS SUPPORTS THE PREVIOUSLY ESTABLISHED FAVOURABLE BENEFIT-RISK PROFILE OF ATALUREN

The MAH fully acknowledges that Study 041 did not achieve statistical significance in the modified Intention-to-Treat (mITT) primary analysis subpopulation. This lack of statistical significance cannot, however, be equated to an absence of evidence of benefit. As discussed in this ground for re-examination, the results in the ITT Population and the 300- to 400-meter subgroup provide, according to the MAH, reliable evidence of a meaningful treatment benefit across multiple highly relevant endpoints assessing different aspects of ambulatory and neuromuscular function which are supportive of the established ataluren positive benefit-risk profile.

4.2.1. Study 041—the Largest and Most Recent RCT—Demonstrates Consistent Benefit Across Key Endpoints in Prespecified ITT Population

Study 041 included a broad population of nmDMD subjects with stratification for key baseline disease characteristics and the requirement for a stable corticosteroid regimen. In the ITT Population, ataluren treatment resulted in consistent, functional benefit as recorded by nominal significance in the primary endpoint and the key secondary endpoints capturing distinct aspects of disease pathology (Table 3, Figure 10). Since the ITT analysis includes all enrolled subjects, it is not subject to selection bias.

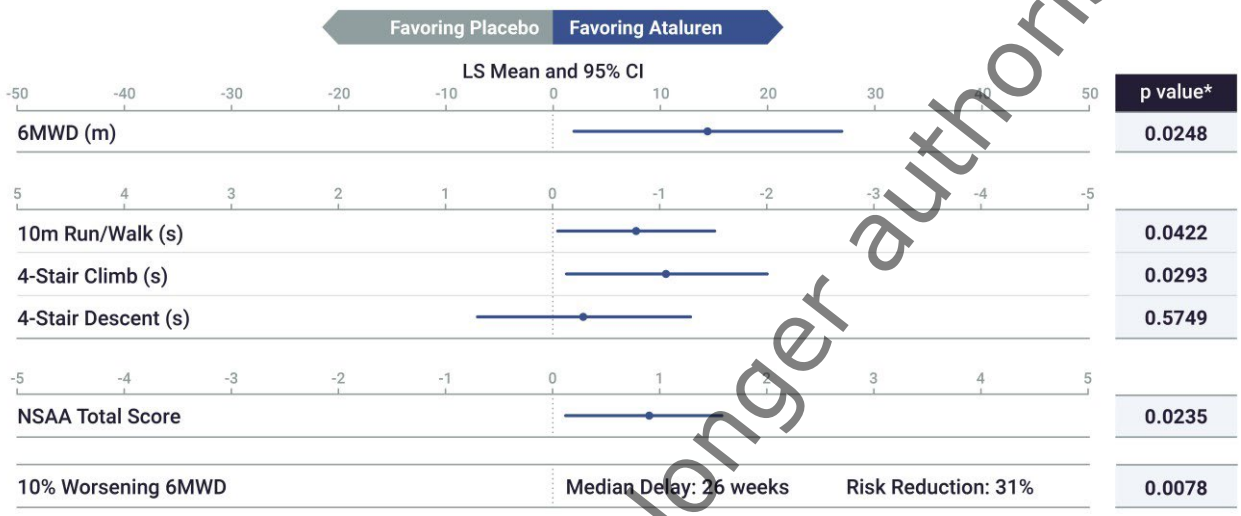
Table 3: Study 041 demonstrates consistent treatment benefit across endpoints at week 72 (study 041, ITT population, double-blind treatment period)

Endpoint	LS Mean (SE) Change Difference Ataluren vs Placebo	95% CI	Nominal p value
6MWD (metres)	14.42 (6.420)	(1.83, 27.01)	0.0248
10-metre run/walk (seconds)	-0.78 (0.383)	(-1.53, -0.03)	0.0422
4-stair climb (seconds)	-1.06 (0.488)	(-2.02, -0.11)	0.0293
4-stair descent (seconds)	-0.29 (0.516)	(-1.30, 0.72)	0.5749

NSAA total score	0.9 (0.38)	(0.1, 1.6)	0.0235
NSAA linear score	2.3 (1.02)	(0.3, 4.3)	0.0246

Abbreviations: 6MWD, 6-minute walk distance; CSR, clinical study report; ITT, intention-to-treat; LS, least squares; NSAA, North Star Ambulatory Assessment
Source: PTC124-GD-041-DMD CSR Table 14.2.1.1.12, Table 14.2.2.2.1.2, Table 14.2.2.4.1.30, Table 14.2.2.4.1.32, and Table 14.2.2.4.1.34

Figure 10: Study 041 demonstrates consistent benefit across key endpoints in prespecified ITT population



Abbreviations: 6MWD, 6-minute walk distance; CSR, clinical study report; ITT, intention-to-treat; NSAA, North Star Ambulatory Assessment * Nominal p value.
Source: Study 041 CSR Table 14.2.1.1.12, Table 14.2.2.2.1.2, Table 14.2.2.4.1.30, Table 14.2.2.4.1.32, Table 14.2.2.4.1.34, and Table 14.2.2.3.1.2

13.2.1.1. Ataluren Treatment Preserves Ambulatory Function

Change in 6MWD

In the ITT Population at Week 72, the least squares (LS) mean change in 6MWD was -53.01 metres in the ataluren group and -67.43 metres in the placebo group, a difference of 14.4 metres (nominal p=0.0248) representing a 21% slowing in the rate of decline.

Consistent with Studies 007 and 020, the greatest magnitude of treatment effect was again observed for 6MWD and other endpoints in the subset of subjects with a baseline walk distance between 300 and 400 metres. In this subgroup, there was a mean treatment difference of 26 metres in walk distance (83 metres of decline in the placebo group versus 57 metres of decline in the ataluren group), representing a 31% slowing of rate of decline. This finding of greatest magnitude of effect in this subgroup is consistent across the 3 studies. Importantly, the 300- to 400-metre subgroup had been previously identified and documented in peer-reviewed literature as a sensitive subgroup for 6MWD in trials of DMD patients.

Importantly, the overall benefit in the ITT Population is not driven exclusively by this subgroup; there is benefit across all categories of baseline severity supporting the robustness of the findings of benefit in 6MWD in the full ITT Population (Table 4).

Table 4: Subgroup analysis of change from baseline in 6MWD at week 72 by baseline 6MWD (ITT population)

Baseline 6MWD	Statistic	Placebo	Ataluren
<300 metres	N	21	19

	Mean (SD)	-143.07 (110.592)	-132.92 (121.004)
	Median (min, max)	-175.0 (-277, 106)	-148.7 (-282, 63)
≥300 and <400 metres	N	78	82
	Mean (SD)	-82.96 (114.034)	-57.05 (109.544)
	Median (min, max)	-55.0 (-337, 102.6)	-31.0 (-386.4, 112)
≥400 metres	N	71	73
	Mean (SD)	-38.46 (46.895)	-28.99 (57.704)
	Median (min, max)	-36.9 (-135, 54)	-26.0 (-143, 131)

Abbreviations: 6MWD, 6-minute walk distance; CSR, clinical study report; ITT, intention-to-treat; max, maximum; min, minimum; SD, standard deviation
Note: Baseline is defined as the maximum measurement of valid Day 1 and Day 2 6MWD values. Subjects who lost ambulation during the study were assigned a value of 0 for the first visit subjects lose ambulation and for all remaining visits while they participated in the study. **Source**: Study 041 CSR Table 14.2.1.3.8

Time to 10%

Time to 10% worsening in 6MWD, a secondary endpoint in Study 041, is another important endpoint assessing treatment effect on ambulatory function. This endpoint is predictive of time to LoA and thus has been used to inform potential longer-term treatment benefit given the understood limitations of clinical trial duration. Subjects with a ≥10% decline in ambulation over a 12-month period are significantly more likely to lose ambulation within 4 years (McDonald 2013a).

In Study 041, subjects in the ataluren group reached this critical milestone at a median of 74.3 weeks compared with a median of 48.0 weeks in the placebo group, for a median delay of 26 weeks (nominal p=0.0078) ,, representing a 31% reduction in risk of reaching this important threshold of decline (HR=0.69).

As expected, given the varying sensitivity of 6MWD with baseline function, the treatment effect in the time to 10% worsening in 6MWD was more pronounced in the subgroup of subjects with baseline 6MWD of ≥300 and <400 metres. In the 300- to 400-metre baseline subgroup, ataluren treatment reduced the risk of a persistent 10% worsening in 6MWD by 2-fold compared to placebo (HR=0.53). The median time to reach this critical milestone was 36 weeks in the placebo group and 74 weeks in the ataluren group, a difference of approximately 38 weeks observed within the relative short duration of a clinical trial and a 47% reduction in risk of this threshold (p=0.0011).

Loss of Ambulation

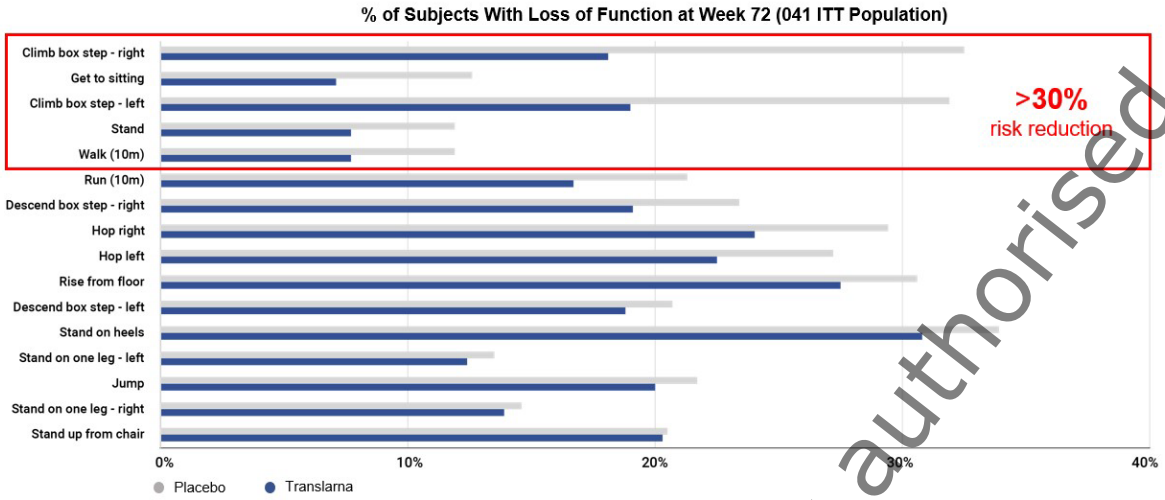
Consistent with the slowing of decline in 6MWD and the significant delay in the time to persistent 10% worsening and 30-metre decline in 6MWD, ataluren treatment also resulted in fewer subjects losing ambulation during the 72 weeks of Study 041. Nearly twice as many subjects in the placebo group (20 [11.4%] subjects) lost ambulation by Week 72 than in the ataluren group (12 [6.6%] subjects).

4.2.1.2 Ataluren Treatment Preserves Neuromuscular Function Key to Activities of Daily Living

NSAA

On the NSAA, a validated and highly relevant 16-item functional scale developed specifically for DMD, there were nominally statistically significant treatment differences of 0.9 points in total score (p=0.0235) and 2.3 points in linear score (p=0.0246). Critically, ataluren reduced the risk of losing the ability to perform all 16 individual functions in the scale, with an over 30% relative risk reduction for the tasks of standing, walking, box climbing, and getting to sitting position (Figure 11). According to the MAH, these NSAA results provide clear evidence of a meaningful ataluren treatment benefit in the preservation of neuromuscular functions important for patient autonomy.

Figure 11: Ataluren treatment reduces risk of loss of ability to perform NSAA functional tasks relevant to daily life



Abbreviations: CSR, clinical study report; ITT, intention-to-treat; NSAA, North Star Ambulatory Assessment
Source: PTC124-GD-041-DMD CSR Table 14.2.2.5.1.4 and Figure 14.2.2.5.1.2

In Figure 11, the percentage of ataluren-treated subjects in the ITT Population who lose the ability to perform each of the 16 NSAA tasks is shown in blue. Performance on the NSAA is predictive of loss of upper-limb muscle function, subsequent loss of lung function (Ekici 2011), and onset of cardiomyopathy (Ergul 2012). Ataluren treatment resulted in fewer subjects losing the ability to perform each of the 16 tasks.

When calculating a relative risk reduction of losing the ability to perform each task, ataluren treatment resulted in an at least 20% relative risk reduction of losing the ability to perform 12 of the 16 tasks and an over 40% relative risk reduction of losing the ability to perform 4 tasks. Thus, according to the MAH, ataluren treatment preserves the ability to perform important functional tasks in more subjects.

Given that the loss of even one function on the NSAA has been described by patients and families as meaningful, the meaningfulness of the risk reduction associated with ataluren treatment can be readily appreciated.

Timed Function Tests

Ataluren was favoured for each of the TFTs, secondary endpoints that measures the ability to perform standardised tasks that are important for functional activities in the daily life, and there were nominally statistically significant treatment differences of 0.78 seconds (p=0.0422) and 1.06 seconds (p=0.0293) for 10-metre run/walk and 4-stair climb, respectively. These treatment differences exceed the 1-second threshold established as clinically meaningful (Bendixen 2014).

4.2.2. Multiple Factors Support That Study 041 is a Reliable Source of Evidence of Benefit

A statistical test, based on randomisation and controlling the risk of a false-positive result, is arguably the most accepted way to establish that treatment difference is indicative of a true drug effect. However, absence of a statistically significant result in the primary analysis subpopulation does not indicate an absence of effect, according to the MAH. Other sources of evidence, including clinical data beyond the primary analysis, can also provide compelling evidence that a drug effect truly exists and mitigate against a chance finding of benefit. Consideration of the broader available data is particularly useful for rare, heterogeneous diseases, in which subjects progress at different rates of progression. Several important factors support that benefit can be reliably determined on the basis of Study 041 results.

4.2.2.1. Consistency of Favourable Findings Across Multiple Endpoint 3 Studies Supports Reliability of Conclusion of Benefit

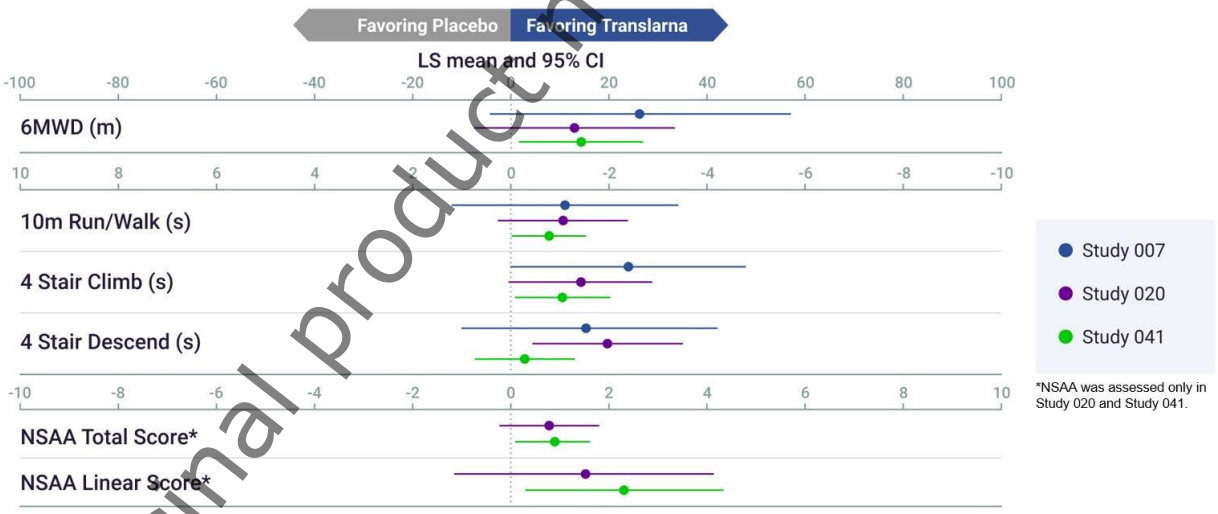
The ataluren clinical programme includes 3 randomised placebo-controlled trials in nmDMD that enrolled similar patient populations reflective of the broad ambulatory nmDMD population and the indication: Study PTC124-GD-007-DMD (Study 007), Study PTC124-GD-020-DMD (Study 020), and Study PTC124-GD-041-DMD (Study 041).

For the over 700 boys across the 3 studies, from study to study and endpoint to endpoint, the results favour ataluren. This treatment benefit is registered across primary and secondary endpoints from the placebo-controlled studies, including 6-minute walk distance (6MWD), 10-metre run/walk, 4-stair climb, 4-stair descent, and the North Star Ambulatory Assessment (NSAA) (with the last endpoint assessed only in Study 020 and Study 041), capturing distinct aspects of DMD disease pathology (Figure 12).

This replication of favourable results across 3 studies supports that the observed effect is real and not due to chance. In the absence of an ataluren treatment benefit, the results would be distributed randomly, with some endpoints in some studies favouring ataluren and some favouring placebo. Instead, there is a consistent identification of treatment benefit. From study to study and endpoint to endpoint, the results favour ataluren.

In addition, this consistency of benefit supports that the data collected in Study 041 do not challenge the previously established favourable benefit-risk assessment of ataluren, thus justifying the continued availability of ataluren treatment, according to the MAH.

Figure 12: Consistent treatment benefit in 3 randomised placebo-controlled studies at indicated dose provides assurance of reliability of findings (studies 007 [ITT], 020 [ITT], and 041 [ITT])



Abbreviations: 6MWD, 6-minute walk distance; CSR, clinical study report; ITT, intention-to-treat; LS, least squares; NSAA, North Star Ambulatory Assessment

* The NSAA was not established as an endpoint at the time Study 007 was designed. NSAA total score and linear score were thus assessed only in Studies 020 and 041.

Results at Week 48 for Study 007 and 020 and Week 72 for Study 041.

Source: Study 007 CSR Table 14.2.1.8.5B, Table 14.2.3.2.2B, Table 14.2.3.3.2B, and Table 14.2.3.4.2B; Study 020 CSR Table 14.2.1.3.1, Table 14.2.2.2.2, Table 14.2.2.3.2, Table 14.2.2.4.2, Table 14.2.3.2, and Table 14.2.3.4; Study 041 CSR Table 14.2.1.1.12, Table 14.2.2.2.1.2, Table 14.2.2.4.1.30, Table 14.2.2.4.1.32, and Table 14.2.2.4.1.34

4.2.2.2. Consistent Evidence of Benefit Demonstrated in Previously Identified 300- to 400 Metre Subgroup

Given the heterogeneity in DMD disease progression, efforts have been made to identify subgroups in whom the 6MWD may be more sensitive to treatment effect during the course of a randomised placebo-controlled study. It has been found that boys with greater than 400 metres in baseline walk distance tend to be stable over the course of a trial—making it challenging to capture treatment benefit on disease progression. Conversely, boys with less than 300 metres in baseline walk distance tend to progress too rapidly to enable a therapy to register a clear benefit on endpoints that assess ambulatory function. The population with a baseline walk distance between 300 and 400 metres is thus more sensitive to change in the timeframe of a clinical trial. The results of the two previous ataluren randomised studies, as well as other DMD studies, have supported that subjects with baseline 6MWD of 300 to 400 metres may be an optimal subgroup in whom to capture treatment effect. The renewal of the ataluren CMA in 2017 was based on the findings of greater benefit, relative to the ITT Population, in the 300- to 400-metre subgroup, which supported the renewal of the CMA in 2017. (Note: the selection of the mITT Population in Study 041 was a failed attempt to further refine this group.) In Study 041, nominally statistically significant benefit across 6MWD and other key endpoints was again demonstrated, with greater magnitude than in the ITT Population (Table 5).

Table 5: Study 041 demonstrates consistent treatment benefit across endpoints at week 72 in 300- to 400-metre subgroup (study 041, double-blind treatment period)

Endpoint	LS Mean (SE) Change Difference Ataluren vs Placebo	95% CI	Nominal p value
6MWD (metres)	24.21 (11.203)	2.22, 46.20	0.0310
10-metre run/walk (seconds)	-1.29 (0.636)	-2.54, -0.04	0.0429
4-stair climb (seconds)	-2.29 (0.813)	-3.88, -0.69	0.0050
4-stair descent (seconds)	-0.97 (0.879)	-2.69, 0.76	0.2714
NSAA total score	1.1 (0.65)	-0.1, 2.4	0.0837
NSAA linear score	3.3 (1.61)	0.1, 6.4	0.0419

Abbreviations: 6MWD, 6-minute walk distance; CSR, clinical study report; LS, least squares; NSAA, North Star Ambulatory Assessment
Source: Study 041 CSR Table 14.2.1.1.17, Table 14.2.2.4.1.31, Table 14.2.2.4.1.33, Table 14.2.2.4.1.35, Table 14.2.2.2.1.3

Importantly, since the 300- to 400-metre subgroup was previously identified as an important subgroup of interest, the results in this population are not prone to selection bias.

4.2.2.3. Multiple Sensitivity Analyses Confirm the Robustness of the Study 041 Results

The robustness of findings in the ITT Population are further supported by a set of sensitivity analyses that confirm the estimate of treatment effect obtained from the prespecified statistical analyses of the ITT Population.

The consistency in both point estimate and the associated p values all confirms the reliability of findings of benefit in the ITT Population, supporting that the observed ataluren treatment benefit is real and reliable and not affected by type of analysis model, endpoint definition, or missing data handling (Table 6).

Table 6: Consistency of primary and sensitivity analyses of change from baseline in 6MWD at week 72 confirms reliability of results

	Change From Baseline in 6MWD at Week 72 (Metres)			
Analysis	**Placebo**	**Ataluren**	**Treatment Difference (SE)**	**p value**
Primary Analysis				
MMRM categorical model[a]	-67.43	-53.01	14.42 (6.420)	0.025
Sensitivity Analyses				
Primary MMRM model using average 6MWD value at Baseline and Week 72[b]	-65.17	-50.35	14.82 (6.355)	0.020
Primary MMRM model excluding COVID-19 impacted visits	-66.60	-51.82	14.78 (6.549)	0.024
Primary MMRM model including first sibling only	-68.48	-54.71	13.78 (6.658)	0.039
Primary MMRM model with LOCF	-67.74	-51.89	15.85 (6.272)	0.012
Primary MMRM model with missing values imputed using MI method	-69.42	-54.07	15.35 (6.442)	0.017
Primary MMRM model with missing values imputed using control-based MI method	-69.58	-54.19	15.40 (6.463)	0.017
Primary MMRM model with missing values imputed using control-based MI method for informative dropouts[c]	-67.52	-53.09	14.43 (6.434)	0.025

Abbreviations: 6MWD, 6-minute walk distance; AE, adverse event; COVID-19, coronavirus 2019; CSR, clinical study report; LOCF, last observation carried forward; MI, multiple imputation; MMRM, mixed-model repeated measurement

[a] MMRM model includes random intercept, baseline concomitant corticosteroid type (deflazacort, prednisone/prednisolone), baseline 6MWD category (<300 metres, 300 to <350 metres, 350 to <400 metres, ≥400 metres), baseline time to stand from supine (<5 seconds, ≥5 seconds), baseline 6MWD, treatment, analysis visit (as a categorical variable), the interaction of analysis visit and baseline 6MWD, and the interaction of analysis visit and treatment with Toeplitz covariance matrix. [b] Average of valid Day 1 and Day 2 assessments is used for the baseline and Week 72 visits. [c] Control-based MI method is applied to missing values for subjects who withdrew from the study due to an AE, withdrawn consent, or investigator decision, in which the missing values are imputed using values from placebo subjects who completed the double-blind period of the study without any missing values. Note: In analyses, subjects who lost ambulation during the study were assigned a value of 0 at the first nonambulatory visit and for all remaining visits while they participated in the study.

Source: PTC124-GD-041-DMD CSR Table 14.2.1.1.12, Table 14.2.1.1.13, Table 14.2.1.1.14, Table 14.2.1.1.15, Table 14.2.1.1.16, and Table Ground2-1.1, Table Ground2-1.2, and Table Ground2-1.3

4.2.3. Ground 1 MAH Conclusions

The treatment benefit of ataluren in slowing disease progression and preserving ambulatory and neuromuscular function has been reliably demonstrated across multiple highly relevant endpoints in Study 041 in the ITT Population and the 300- to 400-metre baseline walk distance subgroup. These findings of benefit are consistent with the results of the prior randomised trials of ataluren in nmDMD. While there may be concerns regarding the interpretation of Study 041 results in the context of missing the study's primary endpoint, the findings of consistent benefit in the ITT Population across all study endpoints does not challenge the previous conclusion of a favourable benefit-risk profile. Rather, the findings in Study 041 support the established benefit-risk profile and the continued availability of ataluren.

Assessment of the MAH´s Ground #1 for re-examination

Ground for re-examination #1 refers to the efficacy results obtained in study 041 as well as multiple sensitivity analyses considered to confirm the robustness of these results.

Since the study 007, which was used to support the CMA and the first SOB study 020 have already been assessed the focus of this discussion is the second SOB, study 041. The design of this study was based on the experiences with studies 007 and 020 and input from DMD experts consulted in and *ad hoc* SAG-N convened by the CHMP to gain insight on the optimal design of the SOB to get comprehensive evidence.

While admitting that the main study 041 failed to show statistical significance in the pre-specified primary analysis population, i.e., the modified intention-to-treat (mITT) Population, the MAH raised the same arguments as during the initial renewal procedure, e.g., highlighting efficacy results obtained in the ITT population as well as in the 300-400 metre subgroup. According to the MAH, these results would be supportive of the established ataluren positive benefit-risk profile. However, in the context of the obtained CMA for Translarna (ataluren), study 041 (SOB 2) was necessary to confirm the findings of the (*post hoc*) analyses of the former studies 007 (initial) and 020 (SOB 1).

According to the CSR of study 041, the key inclusion criteria encompass male Duchenne patients with genetic evidence of nmDMD. Included patients were defined to be ≥5 years of age and treated with systemic corticosteroids for a minimum of 12 months with no significant change in dosage or regimen for a minimum of 3 months prior to study start. Additionally, they had a baseline 6MWD ≥150 meters and were able to perform TFTs (run/walk 10 metres, climb 4 stairs, descend 4 stairs, stand from supine) within 30 seconds.

While the ITT population included all randomised subjects (N= 176 for placebo, N= 183 for ataluren) the mITT population as targeted primary efficacy population only included those subjects from the ITT Population who were ≥7 to ≤16 years of age and who had a baseline 6MWD of ≥300 metres and a time to stand from supine of ≥5 seconds (N= 93 for placebo, N= 92 for ataluren).

Based on the study results and experiences (i.e. *post hoc* results) obtained from the previous studies 007 and 020, the mITT population was considered to be a more sensitive population for a possible treatment effect and was selected as the **pre-specified primary analysis population** in study 041 to **confirm** the effect obtained in the earlier studies. This also implicates several statistical considerations (see below) for the intention to demonstrate robustness of the effect, respectively confirmatory evidence of efficacy obtained from this phase III study and consequently to fulfil the outstanding SOB of the conditional MA.

Therefore, results from study 041 in the overall ITT population or additional subgroups can only be considered supportive in the context of this application. Although, it is agreed with the MAH that the ITT population is considered the population most closely aligned with the indication for Translarna, it has not been pre-specified as the primary analysis population for study 041.

While the 6MWD test was the primary efficacy outcome parameter, key secondary efficacy variables were the NSAA and TFTs (walk/run 10 meters and climb and descend 4 stairs). The change from baseline to week 72 in these parameters was compared between ataluren and placebo treatment arms.

In the grounds for re-examination, the MAH focuses again on the results in the ITT population as well as on those obtained in subgroups of the ITT population, e.g., the baseline 6MWD ≥300 - <400 m subgroup. This is not considered justified or appropriate.

As discussed above, not the ITT population but the mITT population was predefined as the analysis population for the primary hypothesis test to confirm for the primary outcome measurement, the 6MWD, the data of studies 007 and 020 *(the observed effect in 6MWD between ataluren and placebo seen in the initial phase 2 study (i.e., study 007) supported the conditional marketing authorisation in 2014 and the effect in the post hoc analyses of studies 007 and 020 supported the renewal of the conditional marketing authorisation in 2016).* The type I error rate is controlled only when adhering to the pre-specified testing strategy such that the analysis based on the ITT population does not provide confirmatory evidence of efficacy. *Post hoc* re-defining the testing strategy including a re-definition of the priority of analysis

populations in knowledge of the data results in additional chances for false positive conclusions with loss of control of type I error (furthermore, the point estimates are also biased as a consequence of data driven *post hoc* prioritisation of analysis populations). No further confirmatory conclusions are possible in a clinical trial where the primary null hypothesis cannot be rejected. Therefore, all additional findings need to be considered exploratory; particularly, claims of statistical significance are not valid but p-values can be considered descriptive/nominal only.

With regard to efficacy findings on the functional outcome measurements, i.e., 6MWD, the timed function tests (10 metre run/walk, 4 stairs climb and decent), NSAA total score and NSAA linear score, and taking the above-described statistical considerations into account, the results obtained in the ITT population reached nominal significance for a number of endpoints, with the exception of 4-stair descent.

Importantly, the prioritisation of the mITT population as the primary analysis population was based on the hypothesis that this subpopulation is more sensitive for demonstration of a treatment effect, i.e., that the treatment effect is larger in the mITT population in line with findings from the previous studies. However, the contrary was the case such that the credibility of the results in the ITT population is questionable. To demonstrate, that results based on the ITT population essentially differ from those based on the mITT population, both analyses sets are again presented in parallel in the following table (reference is made to variation EMEA/H/C/002720/II/0069).

Table 7: Analysis of primary and key secondary efficacy endpoints at week 72 (mITT and ITT populations, study 041, double-blind treatment period)

Endpoint	mITT		ITT	
	LS Mean (SE) Change Difference Ataluren – Placebo	p-value	LS Mean (SE) Change Difference Ataluren – Placebo	p-value
6MWD (metres)	8.26 (9.064)	0.3626	14.42 (6.420)	0.0248*
6MWD (metres/week)	0.11 (0.126)	0.3626	0.20 (0.089)	0.0248*
LoA (% subjects)	9.7% placebo 5.4% ataluren	0.4803	11.4% placebo 6.6% ataluren	0.1768
NSAA total score	0.9 (0.57)	0.1258	0.9 (0.38)	0.0235*
NSAA linear score	2.5 (1.38)	0.0656	2.3 (1.02)	0.0246*
TFT composite (seconds)	-1.04 (0.611)	0.0892	-0.70 (0.412)	0.0904
10-metre walk/run (seconds)	-0.73 (0.552)	0.1877	-0.78 (0.383)	0.0422*
4-stair ascent (seconds)	-1.73 (0.729)	0.0179*	-1.06 (0.488)	0.0293*
4-stair descent (seconds)	-0.19 (0.768)	0.7997	-0.29 (0.516)	0.5749

Abbreviations: 6MWD, 6-minute walk distance; ITT, intention-to-treat; LoA, loss of ambulation; LS, least squares; mITT, modified intention-to-treat; NSAA, North Star Ambulatory Assessment
Note: * indicates statistically significant p-values <0.05
Source: Table 14.2.1.1.2, Table 14.2.1.1.12, Table 14.2.2.1.1.3, Table 14.2.2.1.1.8, Table 14.2.2.2.1.1, Table 14.2.2.2.1.2, Table 14.2.2.4.1.30, Table 14.2.2.4.1.32, Table 14.2.2.4.1.34, Table 14.2.2.4.1.38, Table 14.2.2.4.1.39, Table 14.2.2.4.1.40, Table 14.2.2.6.1.1, Table 14.2.2.6.1.2

As shown in the table above, the pre-specified primary analysis population (mITT) failed to show statistical significance for the primary endpoint 6MWD and only showed a nominal statistically significant p-value for one of the secondary endpoints, i.e., for 4-stair ascent.

However, even in the ITT population, despite reaching nominal statistical significance, the result on the primary endpoint, the 6MWD, cannot be considered clinically relevant.

While in the mITT population a treatment difference of 8.26 meters was observed, the ITT population showed a treatment difference of 14.42 meters from baseline at week 72. In the context of a CMA, study 041 was imposed as a SOB with a view to confirm a favourable benefit / risk balance supporting the CMA. In this sense, it is important to note that none of these effect sizes is close to the 31.3 meters observed in the corrected ITT population (low dose and placebo arms only N=114) of the initial study 007. Additionally, these effect sizes are not within the observed values derived from *post hoc* subgroup

analyses in the 007 study (49.9 m in a subpopulation of participants aging 7-16 years with baseline 6MWD ≥150 and <80%pred N=63) and in the 020 study (47.2m in a subpopulation of participants aging 7-16 years with baseline 6MWD between 300-400m N=99) supporting the CMA renewal in 2016. Although it is acknowledged that published MCID can only serve as a landmark in interpreting the clinical relevance of obtained differences in change from baseline to end of study, it is noted that none of these effect sizes is close to the cut-off value for a clinically relevant effect, which has been defined as a MCID of at least 30 meters for 6MWT distance (McDonald et al, 2013).

The treatment difference of around 26 meters seen in the baseline 300-400 m 6MWD subgroup of the ITT population (N=78 for placebo, N=82 for ataluren) reflects what has been shown in the previous ataluren studies, namely that this subgroup is the most sensitive for changes in 6MWDT, while the subgroups of <300 meters and ≥400 meters 6MWD both had treatment differences of only around 10 meters. Importantly, also the baseline 300-400 m 6MWD subgroup had not been selected as the pre-specified primary analysis population for study 041 and therefore could only serve as supportive evidence. Of note, that treatment difference was around 47 meters in the 300-400 m 6MWD subgroup of study 020 (N=99).

Further subgroups according to baseline 6MWD, as well as time to 10% worsening in 6MWD and loss of ambulation, all based on the ITT population were again discussed by the MAH as other important measures to assess the treatment effect on ambulatory function. However, the time to 10% worsening of 6MWD is considered to represent a responder analysis derived from the 6MWD and does therefore not represent any novel data per se. Loss of ambulation, on the other hand, is acknowledged as an endpoint representing clinical relevance and could provide supportive information in the context of the obtained results. In study 041 loss of ambulation (LoA) has been defined as the inability to perform the 10-meter run/walk test within 30 seconds at any post-baseline visit and for all remaining visits (reference is made to the study protocol of study 041). Its definition differs from that used for the comparison between subjects from the STRIDE and the CINRG registries.

Change in NSAA total score was a key secondary efficacy endpoint and the NSAA is considered a relevant endpoint by experts in the field for DMD studies. It is noted that in the mITT population the treatment difference was neither statistically significant for the NSAA total score (p=0.126) nor for the NSAA linear score (p=0.066), whereas in the broader ITT population it reached nominal significance; NSAA total score (p=0.024) and linear score (p=0.025). Note that the p-values are descriptive only, i.e., no statistical significance can be claimed after the failure of the primary analysis (see above). These results therefore cannot be considered for confirmatory purposes, they should be regarded as exploratory or hypothesis generating only. From a statistical point of view, it is important that the analyses follow the predefined statistical analysis plan, to avoid loss of control of type I error and increased risk of chance findings and biased point estimates. Accordingly, the results from the broader ITT population may only be viewed as hypothesis-generating in this study 041.

Taking into account the aforementioned considerations about MCIDs, , the nominal treatment difference of 0.9 points on the NSAA total score both in the mITT and the ITT population is not a clinically meaningful change taking as reference the MCID of 2.32 points described by Haberkamp 2019 [using a distribution based approach that refers to the original NSAA raw scale; in addition the described MCID relates to the correlation between the NSAA total score and a new functional endpoint (Stride Velocity 95th Centile, Sv95C, and therefore needs primarily to be interpreted in this context] or to the MCID of 3.5 points proposed by Ayar Gupta 2023 (using an anchor based approach on the 6MWD).

The MAH also re-presented results on loss of NSAA functions, e.g. of all and of partial NSAA tasks relevant to patients' daily life, based on the ITT population but not based on the mITT population, thus again limiting the interpretation of the obtained results.

The additionally discussed results for the TFTs did not provide further support as they were nominally significant only for 10 metre run/walk and 4 stair climb based on the ITT population with only nominal significance for 4 stair climb in the mITT population.

Consistency of the observed findings across the three placebo-controlled clinical studies was claimed by the MAH by again showing results of the functional endpoints for the three studies (Figure 12). However, only for the study 020 the pre-defined primary efficacy population is presented. For study 007 a *post hoc* corrected ITT population is presented and for study 041 the ITT population is presented. In fact, these populations are not comparable in terms of age and 6MWD performance at study initiation (cITT for study 007 included patients aged ≥ 5 years and 6MWD ≥ 75 m at baseline; ITT for study 020 included patients aged 7-16 years and 6MWD ≥150m and <80%pred; ITT for study 041 included patients aged ≥ 5 years and 6MWD ≥150m and <80%pred). Further, the provided results do not support the claimed consistency of treatment effects. Figure 12 supports that on average the largest effect sizes are observed in study 007 while on average the smallest effect sizes are reported in study 041 in spite of its longer follow up (i.e. 72 weeks versus 48 weeks in study 007 and 020).

The MAH provided again results in the baseline 300 – 400 m 6MWD subgroup for different functional endpoints. However, it has not been selected to be the pre-specified primary analysis population in study 041 and therefore evidence of the results is limited.

To confirm robustness of obtained study 041 results, the MAH provided again pre-defined sensitivity analyses for change from baseline at week 72 in 6MWD in the ITT population, yielding comparable results as obtained in the primary analysis in the ITT population, which however was not the primary analysis population. The results of now provided additional sensitivity analyses (Table 6), i.e., primary MMRM model with LOCF, primary MMRM model with missing values imputed using MI method and primary MMRM model with missing values imputed using control-based MI method were in line with those already provided and implicate, that assumptions made for handling missing data had no relevant impact on the obtained results in the ITT population. However, the *post hoc* nature of these analyses has to be taken into account. Moreover, these additional sensitivity analyses were not provided in the primary analysis mITT population. It is noted, that results of predefined sensitivity analyses of the primary endpoint in the mITT population failed to show statistical significance with most of the mean differences between ataluren and placebo yielding even smaller differences than those observed in the primary analysis (i.e. <8.26 meters) (reference is made to Procedure No. EMEA/H/C/002720/II/0069).

Overall, the MAH provided a re-discussion of earlier submitted data, pointing out the consistency of favourable findings across (i) all endpoints in Study 041, (ii) the three RCTs in the ataluren clinical programme (iii) and previously identified 300- to 400-metre subgroup.

With the exception of three additional sensitivity analyses for study 041 on the primary outcome parameter, the 6MWD, performed in the ITT (but not in the mITT) population, no new analyses could be identified by the CHMP.

The MAH's discussion with respect to study 041 results again focused on the ITT population and a subpopulation, i.e. those patients with an initially preserved walking ability in the 6MWD of 300-400 metres. In light of the fact that the mITT population was defined to be the primary analysis population any references to a different population, cannot be agreed in the given context.

Taking the overall information and analyses from Study 041 into account with specific focus on results in the pre-specified mITT population that however failed to show statistical significance and clinical relevance with regard to the primary outcome parameter, this study could not confirm the benefit observed in the *post hoc* (cITT) analysis of the initial study 007 that formed the basis for the CMA and the *post hoc* subgroup analyses in the studies 007 and 020 supporting the CMA renewal in 2016 (EMEA/H/C/002720/R/0022).

Therefore, a benefit could not be confirmed based on the SOB2 study 041.

Ground #1 not resolved.

13.3. Ground #2

The MAH´s Grounds for re-examination:

GROUND 2: STRIDE REGISTRY PROVIDES RELIABLE SUPPORTIVE EVIDENCE OF LONG-TERM MEANINGFUL ATALUREN BENEFIT WITH RIGOROUS METHODS TO MITIGATE BIAS, AS VERIFIED BY AN EXTENSIVE SET OF SENSITIVITY ANALYSES

4.3.1. The STRIDE Registry Provides an Important Opportunity for Assessment of Long-Term Cumulative Benefit

Randomised placebo-controlled clinical studies, with a maximum duration of 1 to 1.5 years, can feasibly only evaluate a short segment of the decades-long progression of DMD. Thus, while these trials can inform short-term treatment benefit, they cannot fully inform the long-term cumulative treatment benefit of a DMD therapy on the key morbid disease transition points, like LoA and pulmonary function. This is particularly the case for DMD, which in addition to being rare, as discussed, has a highly heterogenous disease course.

Treatment registries, in contrast, allow for direct measurement of long-term treatment effects and thus can confirm that treatment benefits recorded over the short-term duration in clinical studies manifest cumulatively in long-term meaningful effect. The importance of treatment registries in informing regulatory decisions is increasingly recognised (McGettigan 2019, Jonker 2021).

As discussed in detail within this section, the rigorous design and conduct of STRIDE, the appropriateness of the CINRG natural history comparator, the use of propensity-score matching to ensure the comparability of the populations, and additional analyses and peer-reviewed literature addressing all known potential sources of bias, including those raised in the ataluren review procedure, make the STRIDE Registry a reliable source evidence of meaningful treatment benefit. Furthermore, the STRIDE Registry confirms that change in disease trajectory during the short-term duration of the clinical studies manifests cumulatively meaningful impact on the key morbid transition points of the disease.

4.3.2. Rigorous Design Supports Robustness of STRIDE Registry as a Data Source for Real-World Evidence of Treatment Effect

The STRIDE Registry was designed in close collaboration with EMA, DMD experts, and patient advocacy groups to enable rigorous assessment of the long-term safety and effectiveness of ataluren treatment.

STRIDE was designed with the following elements that support its reliability as a data source for long-term assessment of ataluren treatment:

- Inclusion criteria that require enrolled patients have genetically confirmed nmDMD
- Biopsy diagnosis to confirm that participants have DMD and not less severe forms of muscular dystrophy like Becker muscular dystrophy that could bias results (Note: this was a concern raised in the review procedure.)
- Standardised definitions for key study assessments, including LoA
- Regular assessment of key outcome measurements

- Procedures for data collection, data entry, and data monitoring to ensure data quality including a secure web-based data entry system and on-site data monitoring at regular intervals

In addition, the STRIDE Registry provides a comprehensive dataset of patients with nmDMD treated with ataluren, enabling the reliable assessment of long-term treatment effect.

- STRIDE includes a large population of over 300 nmDMD patients with average follow-up of 5.5 years, enabling the assessment of long-term treatment effects.
- Data for the primary endpoint of LoA are comprehensive because there is a high retention rate of enrolled patients, with approximately 85% of the population ongoing in the STRIDE Registry after 5.5 years and LoA is prospectively collected.
- The majority of patients in Europe who are prescribed ataluren were enrolled in STRIDE. In some countries, including Italy and the United Kingdom (UK), the vast majority of patients prescribed ataluren are included in the STRIDE Registry. As discussed in this ground, results from these countries corroborate the overall results, confirming that selection bias is not a concern.

STRIDE thus includes the key elements to ensure the data can enable reliable determination of the effects of ataluren on long-term disease progression and meaningfully inform regulatory decisions.

4.3.3. The CINRG Duchenne Natural History Study Dataset Provides a Robust and Appropriate Comparator Population

At the request of EMA at the time STRIDE was designed, PTC sought an appropriate rigorous natural history comparator population to contextualise the observed treatment effect of ataluren recorded in STRIDE.

The well-regarded CINRG Duchenne Natural History Study, the largest, prospective multicentre natural history study conducted at expert DMD centres primarily in North America and Europe, was selected for the quality and comprehensiveness of the data collected as well as its comparability to STRIDE on a number of key elements.

Multiple factors support the suitability of CINRG as the basis for establishing an external control:

- CINRG includes only patients with genetically confirmed DMD.
- CINRG, like STRIDE, is conducted at expert DMD centres, with optimised care and adherence to international practice guidelines. In particular, the guidelines for corticosteroid use (including regimen and dosing) under which all CINRG-enrolled patients were managed were the same as those used for the management of STRIDE patients.
- CINRG includes a sufficiently large population to allow for matching with the STRIDE dataset.
- CINRG data were collected prospectively, maximising the standardisation of data collection.
- The average of 5 years of follow-up time in CINRG is similar to that of the 5.5 years mean treatment duration captured in the STRIDE Registry.
- CINRG allowed for access to patient-level data to facilitate matching between the CINRG and STRIDE cohorts.
- Loss of ambulation, the key comparator analysis endpoint, was defined identically in CINRG and STRIDE as full-time wheelchair use.
- Ambulatory status was available for 98% of CINRG patients, minimising the risk of ascertainment bias.

Thus, a number of critical considerations informed the selection of CINRG (as endorsed by the expert steering committee and EMA) as the comparator population to support the reliability of the analyses with STRIDE. In addition, elements of STRIDE, including the design of the case report forms to mimic those in CINRG, were intended specifically to enable this planned comparison.

4.3.4. Propensity Matching Based on Key Factors Influencing Disease Progression Resulted in Comparable Populations From STRIDE and CINRG to Allow for Reliable Comparison of Ataluren Treatment Effect

Initial comparisons of the full populations of STRIDE and CINRG determined that the populations had a great deal of overlap in terms of standard of care and key disease characteristics. Importantly, the quality of both data sources was high for the primary endpoint of LoA, which was prospectively collected at expert sites in both studies, with an identical definition. Missing data were minimal, and subject-level data were comprehensive for key prognostic factors, including age at first symptom and age of steroid initiation, and steroid type, duration, dose, and regimen. It was also understood that functional status measures were not available for all subjects, that the two studies were not completely contemporaneous, and that while STRIDE included only nmDMD subjects, CINRG included subjects with a range of causative mutations, making it critical to ensure the comparability of the two populations.

Propensity-score matching was used to further ensure subject and disease characteristic covariates between individual subjects in each population were balanced (Inacio 2015). A propensity score is a numerical representation of the probability of an individual subject being assigned to a particular cohort (in this case STRIDE or CINRG). While the populations of STRIDE and CINRG were generally comparable, propensity scores were applied to match individual STRIDE and CINRG subjects to mitigate for any imbalances in prognostic factors between the nonrandomised populations and thus derive an unbiased estimate of treatment effect.

The propensity-score match model was established based on the core prognostic indicators of DMD progression identified in a systematic literature review that confirmed that the subject and disease factors most influential of disease trajectory include age of symptom onset, corticosteroid type, and duration of corticosteroid use (Moxley 2010, Ciafaloni 2016, McDonald 2017, Ferizovic 2022). Age of symptom onset is a critically important indicator of disease severity and future trajectory of DMD; the younger a boy with DMD is at the first clinical sign or symptom, the younger they are when they experience LoA (Ciafaloni 2016).

Corticosteroid use is the most impactful intervention influencing the trajectory of DMD progression. Accordingly, the propensity-score model incorporated not only age of initiation of corticosteroid use but also type of corticosteroid used and duration of corticosteroid use from the date of first systemic corticosteroid use until the date of LoA or the date of last assessment.

On this basis, a propensity score was created using a logistic regression with the following matching covariates:

- Duration of deflazacort use (<1 month, ≥1 month and <12 months, ≥12 months)
- Duration of other corticosteroid use (<1 month, ≥1 month and <12 months, ≥12 months)
- Age at onset of first symptom
- Age at initiation of corticosteroid use

The populations resulting from this primary match are comparable for the matched parameters, validating the match, and for other key disease characteristics, including corticosteroid dose and regimen and functional status at study entry (Table 7). Furthermore, the populations had equivalent baseline

function as assessed by 6MWD and 10-metre run/walk—despite not being matched on these criteria—validating that the propensity model parameters produced comparable populations in terms of disease severity and progression.

In the ataluren review procedure, reviewers had raised concerns that the STRIDE and CINRG populations were not matched for steroid use and dose, nor for baseline functional status. Table 8 clearly demonstrates that the prespecified matching algorithm results in populations that are highly similar for these parameters. In addition, as summarised above, when these factors are added to the matching model, the results confirm those of the primary analysis. Thus, these two concerns regarding the STRIDE analyses have been addressed.

Table 8: STRIDE registry and CINRG populations are comparable for disease severity, steroid use, and functional status at first assessment

Statistic	Propensity-Matched Population	
	STRIDE Registry (N=277)	**CINRG (N=277)**
Age at first symptom, years		
n	277	277
Mean (SD)	2.807 (1.6853)	2.885 (1.4867)
Median	2.600	3.000
Min, max	0.10, 8.00	0.08, 8.00
Age at corticosteroid initiation, years		
n	255	252
Mean (SD)	6.434 (2.0447)	6.573 (2.0256)
Median	5.940	6.360
Min, max	2.52, 15.31	2.22, 13.89
Average daily dose (deflazacort), mg/kg/d		
n	154	138
Mean (SD)	0.58 (0.224)	0.60 (0.212)
Median	0.62	0.62
Min, max	0.0, 1.0	0.0, 1.0
Average daily dose (other corticosteroids), mg/kg/d		
n	133	130
Mean (SD)	0.40 (0.170)	0.44 (0.205)
Median	0.39	0.47
Min, max	0.0, 0.8	0.0, 1.3
Time taken to run/walk 10 metres at first assessment, seconds		
n	214	187
Mean (SD)	7.19 (4.496)	6.93 (2.949)
Median	6.00	6.22
Min, max	0.0, 30.0	3.0, 22.6
6MWD, at first assessment, metres		
n	170	99
Mean (SD)	348.43 (100.824)	347.62 (108.824)
Median	361.50	347.00
Min, max	0.0, 595.0	75.0, 636.6

Abbreviations: 6MWD, 6-minute walk distance; CINRG, Cooperative International Neuromuscular Research Group;
CSR, clinical study report; max, maximum; Min, minimum; SD, standard deviation; STRIDE, Strategic Targeting of Registries and International Database of Excellence

Note: Propensity-score model covariates include age at first symptom, age at starting steroid, duration of deflazacort, and duration of steroid other than deflazacort. Steroid duration is calculated from starting use of steroid to loss of ambulation/censor date.
Source: Study 025o 6th Interim Report, Table 14.5.1.2.1a, Table 14.5.1.9.1a, 2023 grounds for re-examination Table 14.5.1.1.1.2, Table 14.5.1.1.1.3a

4.3.5. STRIDE Analyses Demonstrate Multiyear Benefit in Delay in Loss of Ambulation

Loss of ambulation is the first key morbid transition point for ambulatory DMD patients. Thus, understanding the long-term cumulative effects of ataluren on age at LoA provides important evidence of long-term treatment benefit and is of unequivocal meaningfulness.

The LoA analysis includes the 277 subjects from STRIDE. The average follow-up time of STRIDE patients is 5.5 years.

In the propensity-score matched populations, ataluren-treated patients in the STRIDE Registry retain the ability to walk 3.5 years longer (p<0.0001) than their propensity-score matched natural history counterparts, with a median age of LoA of 16.5 years for STRIDE patients compared with 13.0 years for CINRG patients (Table 9). This reduction in risk of LoA is consistent with the observation across the 3 placebo-controlled trials that fewer ataluren-treated subjects lost ambulation relative to those receiving placebo (25 subjects versus 40 subjects). Notably, this multiyear delay in LoA is on top of standard-of-care corticosteroid therapy.

Table 9: Age at loss of ambulation – STRIDE registry and CINRG propensity-score matched populations (primary match)

	STRIDE (N=277)	CINRG (N=277)
Number of patients		
Assessed, n	277	277
With events,[a] n (%)	94 (33.9)	147 (53.1)
Censored, n (%)	183 (66.1)	130 (46.9)
Age at loss of ambulation, years		
Median (95% CI)	16.5 (14.4, 19.7)	13.0 (12.3, 13.8)
Minimum, maximum[b]	2.1+, 25.0+	3.5, 21.7+
p value[c]	<0.0001	
Hazard ratio (95% CI)[d]	0.455 (0.350, 0.593)	

Abbreviations: 6MWD, 6-minute walk distance; CINRG, Cooperative International Neuromuscular Research Group; ECG, electrocardiogram; STRIDE, Strategic Targeting of Registries and International Database of Excellence
[a] Event=loss of ambulation. [b] + indicates censored observation. [c] p value is from log-rank test stratified by deflazacort and other steroid usage durations. [d] Hazard ratio is from stratified (by durations of deflazacort and other steroid use) Cox regression with covariates age at first symptom and age at starting steroid usage. Hazard ratio is STRIDE Registry over CINRG.
Note: Censor date is derived from the latest available date across treatment, physical examination, vital sign, 6MWD, timed function tests, North Star Ambulatory Assessments, pulmonary function tests, upper limb function tests, laboratory tests, ECG tests, and motor function measurements.
Steroid duration is calculated from starting use of steroid to loss of ambulation/censor date.
Source: Study 025o 6th Interim Report Table 14.5.2.1.1a

4.3.6. Propensity-Score Weighting Analyses Confirm Propensity-Score Match Analysis Results

During the review procedure, concerns regarding use of the propensity-matching model might be a source of bias, and the MAH was asked to look at other approaches to generating a comparator population for the STRIDE subjects. Thus, to confirm the reliability of results obtained through propensity-score matching, a sensitivity analysis was performed using the inverse probability of treatment weighting for the average treatment effect (IPTW-ATE) method.

Unlike the propensity-score match, which uses the best matched individuals (277) from the comparator population in a 1:1 ratio, weighting directly utilises data for all 398 CINRG subjects and corrects for potential differences in prognostic factors using the propensity score.

As summarised in Table 10, this analysis demonstrates that the treatment effect observed in the primary analysis is reproduced consistently when different matching methodologies are applied.

Table 10: Age at loss of ambulation – STRIDE registry and CINRG populations (ATE, inverse probability treatment weighting)

	STRIDE (N=277)	CINRG (N=398)
Number of subjects		
Assessed, n	277	398
With events,[a] n (%)	94 (33.9)	230 (57.8)
Censored, n (%)	183 (66.1)	168 (42.2)
Age at loss of ambulation, years		
Median (95% CI)	15.7 (14.0, 19.7)	12.5 (11.9, 13.0)
Minimum, maximum[b]	2.1+, 25.0+	3.5, 21.7+
p value[c]	<0.0001	
Hazard ratio (95% CI)[d]	0.418 (0.330, 0.530)	

Abbreviations: 6MWD, 6-minute walk distance; ATE, average treatment effect; CINRG, Cooperative International Neuromuscular Research Group; ECG, electrocardiogram; STRIDE, Strategic Targeting of Registries and International Database of Excellence

[a] Event=loss of ambulation. [b] + indicates censored observation.

[c] p value is from log-rank test stratified by deflazacort and other steroid usage durations.

[d] Hazard ratio is from stratified (by durations of deflazacort and other steroid use) Cox regression with covariates age at first symptom and age at starting steroid usage. Hazard ratio is STRIDE Registry over CINRG.

Note: Propensity-score model covariates include age at first symptom, age at starting steroid usage, duration of deflazacort, and duration of steroid other than deflazacort.

Censor date is derived from the latest available date across treatment, physical examination, vital sign, 6MWD, timed function tests, North Star Ambulatory Assessments, pulmonary function tests, upper limb function tests, laboratory tests, ECG tests, and motor function measurements.

Steroid duration is calculated from starting use of steroid to loss of ambulation/censor date.

Source: Table Ground2-3.1

A further analytical approach using propensity score as a covariate in the analysis (Cox regression) rather than as a factor in determining the control population was also performed. The results of this analysis were again consistent with the primary analysis, with the HR=0.44 (Table 16), again confirming the reliability of the results obtained with propensity-score matching.

4.3.7. New Analyses and Peer-Reviewed Literature Address Concerns of Potential Bias Raised During the Review Procedure

PTC undertook a systematic and multi-layered approach to identifying and minimising potential sources of bias.

This section describes these analyses and recent literature that support that all known potential sources of bias have been addressed so that the multiyear delay in LoA in the STRIDE/CINRG analyses can thus be reliably attributed to the effect of ataluren treatment.

During the R/0071 annual renewal re-examination procedure, concerns were raised regarding potential sources of bias that might limit the reliability of the evidence of long-term meaningful treatment effect in the STRIDE Registry. The MAH has performed a number of additional analyses and identified sources of peer-reviewed literature that confirm that all identified sources of potential bias do not change the

outcome of the STRIDE analyses. Many of the analyses presented herein were presented to the SAG-N held in June 2024 and the SAG-N concluded that identified sources of bias have been addressed, supporting the reliability of the STRIDE results.

4.3.8. Addressing Potential Selection Bias: The STRIDE Population is Representative of the Ataluren-Treated Population as a Whole

As described in ICH guidance, and raised during the ataluren review procedure, for real-world evidence to provide reliable evidence of benefit, it is necessary to evaluate potential differences between the source population and the study population. Accordingly, it was understood that for the STRIDE-CINRG analyses to serve as evidence of long-term treatment benefit, it would be necessary to determine that the population enrolled in STRIDE is representative of the ataluren treated population as a whole.

Since not all patients treated with ataluren get enrolled in STRIDE, it is theoretically possible that ataluren-patients who enrolled in STRIDE could differ from the overall treated population in some important way, for example, that less severe patients may be more likely to enrol, thus inflating the ataluren treatment effect recorded on the STRIDE versus CINRG analyses.

A subset of STRIDE allows for direct evaluation of the representativeness of the enrolled population. In the UK and Italy, almost all patients who are prescribed ataluren are enrolled in the Registry. In addition, UK and Italy centres follow uniform standards of treatment for DMD. A Kaplan Meier analysis of age at LoA for matched patients in the UK and Italy confirmed the multiyear treatment benefit of STRIDE and confirms the minimal risk of selection bias influencing the outcome of the STRIDE analyses (Table 11).

Table 11: Age at loss of ambulation – Italy and United Kingdom STRIDE registry patients and CINRG propensity-score matched populations

	STRIDE (N=120)	CINRG (N=120)
Number of patients		
Assessed, n	120	120
With events,[a] n (%)	35 (29.2)	56 (46.7)
Censored, n (%)	85 (70.8)	64 (53.3)
Age at loss of ambulation, years		
Median (95% CI)	16.7 (14.7, NE)	13.5 (12.5, 14.5)
Minimum, maximum[b]	2.1+, 22.6+	4.9+, 20.8+
p value[c]	<0.0006	
Hazard ratio (95% CI)[d]	0.464 (0.296, 0.728)	

Abbreviations: 6MWD, 6-minute walk distance; CINRG, Cooperative International Neuromuscular Research Group;
ECG, electrocardiogram; NE, not estimable; STRIDE, Strategic Targeting of Registries and International Database of Excellence [a] Event=loss of ambulation. [b] + indicates censored observation. [c] p value is from log-rank test stratified by deflazacort and other steroid usage durations.
[d] Hazard ratio is from stratified (by durations of deflazacort and other steroid use) Cox regression with covariates age at first symptom and age at starting steroid usage. Hazard ratio is Registry over CINRG.
Note: Propensity-score model covariates include age at first symptom, age at starting steroid usage, duration of deflazacort, and duration of steroid other than deflazacort. Steroid duration is calculated from starting use of steroid to loss of ambulation/censor date.
Censor date is derived from latest available date across treatment, physical examination, vital sign, 6MWD, timed function tests, North Star Ambulatory Assessments, pulmonary function tests, upper limb function tests, laboratory tests, ECG tests, and motor function measurements.
Source: 2023 grounds for re-examination Table 14.5.2.1.1a_IT_GB

4.3.9. Addressing Potential Mutation Bias: Mutation Type is Not a Meaningful Predictor of Disease Trajectory

Ataluren is indicated only for the treatment of DMD arising from a nonsense mutation. Thus, STRIDE includes only subjects with nonsense mutations. CINRG includes subjects with DMD caused by a range of mutation types, including nonsense mutations. It was thus important to determine that differences in disease severity arising from mutation type are not a source of bias in the STRIDE-CINRG analyses, and in particular that patients with nmDMD do not have a less severe form of the disease than those caused by other mutations. This subsection provides analyses and literature that confirm that nmDMD disease trajectory is comparable to that of the DMD population as a whole and thus that mutation type is not a meaningful source of bias in these analyses.

4.3.9.1. Both STRIDE and CINRG Require Immunohistochemical or Genetic Confirmation of Duchenne-Type Muscular Dystrophy

Dystrophinopathies (DYS) comprise a spectrum of disease severity, of which DMD, characterised by genetic defects that preclude the production of any or almost any functional dystrophin, is among the most severe.

Both STRIDE and CINRG required documentation of immunohistochemical or genetic confirmation of DMD, distinct from other less severe forms of muscular dystrophy, ensuring that subjects enrolled in both studies have a true DMD phenotype.

4.3.9.2. Literature Supports that Mutation Type is Not an Independent Predictor of Disease Severity

A review of peer-reviewed literature supports the comparison of nmDMD subjects in STRIDE with the mixed genotype DMD population of CINRG.

First, a recently published meta-analysis specifically addressed the question of influence of mutation subtype on DMD progression (Muntoni 2023). This multicentre study included over 700 patients with DMD and over 1600 patient-years of follow-up from 6 real-world/natural history data sources in Europe and the US. The purpose of this study was explicitly to support the pooling of patients with different mutations as a comparator group in interventional studies of a mutation-specific therapy. An evaluation of patient characteristics and disease progression as measured by the NSAA determined that genotype accounts for only ~2% of disease progression, supporting that mutation type is not a meaningful source of comparator bias and supporting the use of genotype-agnostic external comparator populations like CINRG.

Consistent with this, a 2022 study examined functional performance as assessed by 6MWD, 10-metre run/walk, and the NSAA for 193 patients with DMD, 10.4% of whom had nonsense mutations, and also determined that there were no statistically significant differences in functional measures associated with mutation type (Schiava 2022).

In addition, a number of publications look specifically at mutation type and age at LoA. One such publication determined that age of LoA for subjects with nmDMD is "generally comparable" to that of other mutations, confirming that mutation type did not influence the rate of ambulatory decline (Bello 2016).

Another study of mutation and age of LoA that included 765 patients also determined there was no statistically significant difference between nmDMD and the general DMD population for age at LoA, concluding that disease severity for nmDMD patients is comparable to the broader population and again explicitly supporting the appropriateness of comparison between an nmDMD population and the broader

DMD population (Wang 2018). A 2021 study of 358 patients drew the same conclusion; mutation type did not predict age at LoA (Haber 2021).

Each of these studies support not only that mutation type is not predictive of disease trajectory, but that age at first symptom and steroid use, the covariates in the propensity-score match model, are the key factors.

4.3.9.3. nmDMD CINRG vs CINRG Overall

An analysis of age of LoA by mutation type within the CINRG dataset itself corroborates the literature, providing additional support that DMD caused by a nonsense mutation is at least as severe as that caused by other mutations. A total of 16 subjects in CINRG have DMD due to a nonsense mutation. In the CINRG study, the median (95% CI) age of LoA for nmDMD subjects (N=16) was 11.1 (8.8, not estimable) years, compared with 12.0 (11.3, 12.5) years for those with other mutation types (N=382), providing further support that mutation type is not a meaningful source of bias (Table Ground 2-2.3.5).

4.3.9.4. nmDMD CINRG vs STRIDE

An additional analysis was conducted comparing age of LoA for the 16 nmDMD subjects in CINRG with subjects in STRIDE, all of whom have nmDMD. While the small number of nmDMD subjects in CINRG precludes optimal matching, the results of these analyses provide additional consistent evidence of a multiyear benefit when assessing nonsense mutation subjects alone.

Propensity-score matching was performed using the same model as that used in the primary analysis, and subjects were matched in a 3:1 ratio. As summarised in Table 12, the results confirm a multiyear treatment benefit when the nonsense mutation subjects in CINRG are matched to STRIDE nmDMD subjects.

Table 12: Age at loss of ambulation STRIDE registry subjects and CINRG propensity-score matched nmDMD population, 3:1 matching ratio

	STRIDE (N=48)	CINRG (N=16)
Number of subjects		
Assessed, n	48	16
With events,[a] n (%)	17 (35.4)	8 (50.0)
Censored, n (%)	31 (64.6)	8 (50.0)
Age at loss of ambulation, years		
Median (95% CI)	13.4 (11.9, NE)	11.1 (8.8, NE)
Minimum, maximum[b]	2.1+, 21.1+	5.2+, 18.5
p value[c]	0.1692	
Hazard ratio (95% CI)[d]	0.555 (0.189, 1.631)	

Abbreviations: 6MWD, 6-minute walk distance; CINRG, Cooperative International Neuromuscular Research Group;
ECG, electrocardiogram; NE, not estimable; nmDMD, nonsense mutation Duchenne muscular dystrophy; STRIDE, Strategic Targeting of Registries and International Database of Excellence [a] Event=loss of ambulation. [b] + indicates censored observation. [c] p value is from log-rank test stratified by deflazacort and other steroid usage durations. [d] Hazard ratio is from stratified (by durations of deflazacort and other steroid use) Cox regression with covariates age at first symptom and age at starting steroid usage. Hazard ratio is STRIDE Registry over CINRG.
Note: Propensity-score model covariates include age at first symptom, age at starting steroid usage, duration of deflazacort, and duration of steroid other than deflazacort. Steroid duration is calculated from starting use of steroid to loss of ambulation/censor date.
Censor date is derived from the latest available date across treatment, physical examination, vital sign, 6MWD, timed function tests, North Star Ambulatory Assessments, pulmonary function tests, upper limb function tests, laboratory tests, ECG tests, and motor function measurements. **Source**: Table Ground2-2.3.2

4.3.9.5. Nonsense Mutation Subjects in the French DYS Registry Have Similar Age at Loss of Ambulation to Those With Other Mutations

The French DYS Registry is a prospective registry that includes data for 504 subjects with confirmed DMD who were born after the year 2000 and were neither participants in a clinical study nor treated with ataluren. A Kaplan-Meier analysis was undertaken comparing age of LoA for the 43 subjects in the DYS Registry with a nonsense mutation with the 461 subjects with DMD due to other mutation types.

The median (95% CI) age of LoA for nmDMD subjects in the DYS Registry is 10.6 (10.04, 12.1) years, compared with 11.1 (10.96, 11.38) years for subjects overall. This finding provides further support that mutation type is not a meaningful source of bias.

4.3.10. Potential Calendar Bias: Calendar Year is Not a Meaningful Source of Bias During STRIDE-CINRG Study Periods

4.3.10.1. Standard of Care Consistent for CINRG and STRIDE Study Periods

The CINRG study enrolled subjects from 2006 to 2016. STRIDE enrolled subjects from 2015 to 2022. It was thus important to determine if standard of care remained consistent throughout the enrolment periods of both studies to ensure that differences in disease progression result from treatment rather than improvements in standard of care. This potential concern was addressed in several ways.

First, a comprehensive review of the DMD care guidelines for the study period was undertaken. This review determined that corticosteroid use was the only intervention proven to significantly affect disease trajectory and age of LoA over the study periods and that guidelines for steroid use were unchanged since 2005 (American Academy of Neurology Guidelines, 2005 and 2016, [(Moxley 2005, Gloss 2016)]). It was thus determined that differences in corticosteroid standard of care are not a meaningful source of bias. Given the importance of steroid use as a determinant of disease trajectory, as described throughout this document, additional analyses were employed to confirm that steroid use was comparable for the 2 populations.

While understood to be less impactful on disease progression than corticosteroid use, other aspects of care that could theoretically influence disease progression, such as physical therapy, scoliosis management, and nutritional recommendations, were likewise unchanged over the relevant period (Bushby 2010b, Birnkrant 2018a). Figure 13 summarizes care guidelines for steroid dose and regimen, physiotherapy, and scoliosis management for the periods of CINRG and STRIDE enrolment, confirming the consistency of these guidelines and the minimal risk of differences in standard of care as a source of bias.

Figure 13: Consistent DMD care guidelines from 2005 through 2022

Practice Area	2005 Guidelines (Moxley 2005)	2010 Guidelines (Bushby 2010)	2016 Guidelines (Gloss 2016)	2018 Guidelines (Birnkrant 2018)
Steroid dose: Prednisone: 0.75 mg/kg/d Deflazacort: 0.9 mg/kg/d	✓	✓	✓	✓
Steroid regimen: Daily	✓	✓	✓	✓
Physiotherapy: Stretching 4-6 days/week	N/A	✓	N/A	✓
Scoliosis management: Routine monitoring, surgical intervention to prevent progression and reduce pain	N/A	✓	N/A	✓

Standard-of-care did not change over the periods of CINRG and STRIDE confirming improvements in standard of care are not influencing results

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; DMD, Duchenne muscular dystrophy; N/A, not applicable; STRIDE, Strategic Targeting of Registries and International Database of Excellence
Source: (Moxley 2005, Bushby 2010a, Gloss 2016, Birnkrant 2018b)

4.3.10.2. Rate of Disease Progression Also Consistent Over STRIDE and CINRG Study Periods for Multiple Key Endpoints

Given the consistency of care guidelines over the study periods, it was anticipated that the rate of functional decline would also be consistent. A review of peer-reviewed literature confirms this is in fact the case.

Given the interest in using historical external comparators in studies of new potential therapies in DMD, several studies have directly assessed whether calendar bias would present a source of bias with the use of historical data from studies conducted over the periods of CINRG and STRIDE enrollment. These studies provide further evidence that calendar year is not a predictor of disease trajectory and thus that it is not a source of bias in the STRIDE and CINRG analyses.

6MWD

Goemans et al studied factors influencing decline in ambulatory function as assessed by 6MWD to assess the use of external natural history comparator populations to evaluate pharmacological treatment effect. In this analysis, the rate of decline in 6MWD for placebo-treated subjects was consistent over the period from 2006 to 2016, supporting that the rate of ambulatory decline was unchanged from the beginning of CINRG until the beginning of STRIDE (Goemans 2020).

NSAA

Another study sought to determine whether pooled placebo-group data from previous DMD randomised clinical studies could serve as a rigorous comparator population for future interventional studies without significant risk of bias. It thus specially addressed the risk of calendar bias in the use of external comparators in DMD. The analyses, which included 437 subjects from 9 different clinical studies, again confirmed that when adjusting for key prognostic factors, calendar year was not a meaningful driver of disease progression as assessed by the NSAA (Muntoni 2022).

Age of Loss of Ambulation

Szabo et al evaluated trends in age of LoA, the outcome in the STRIDE-CINRG primary analysis, following the introduction of corticosteroids into standard of care in the late 1990s. Corticosteroid use was

identified as the key driver of LoA, independent of calendar year of treatment, confirming that the risk of calendar bias is minimal when corticosteroid use is controlled for (Szabo 2021).

The unchanged rate of disease progression over this period further supports that the timing of study conduct is not a meaningful source of bias.

4.3.10.3. Comprehensive Literature Review Demonstrates Consistency of Median Age at Loss of Ambulation Over 2 Decades

To directly address whether age of LoA has changed over time, a recently published literature review of age of LoA from studies conducted from 2001 to 2023 confirms that age of LoA has remained consistent over this time period that extends beyond the period of STRIDE and CINRG data collection. Each study over this period of more than 2 decades determined that the median age of LoA ranged from 11 to 13.4 years in patients receiving corticosteroid therapy in accordance with standard of care (Figure 14). Notably, the median age of LoA in the CINRG dataset (to which STRIDE data are compared) was at the higher end estimate of median age of LoA reported in the literature, further supporting its appropriateness as a suitable comparator population representing current standard of care (Table 8).

Figure 14: Median age at loss of ambulation with glucocorticoid therapy

Publication	Year of Publication	Study Population (N)	Median Age at LoA (yrs)
Takeuchi et al.	2013	242	**11.00**
van den Bergen et al.	2014	165	**11.60**
Wang et al.	2014	633	**13.00**
Bello et al.	2015	277	**13.00**
Vry et al.	2016	792	**11.42**
Koeks et al.	2017	2658	**13.00**
McDonald et al.	2018	330	**13.40**
Chen et al.	2020	144	**11.67**
Zambon et al.	2022	48	**10.80**

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; LoA, loss of ambulation; STRIDE, Strategic Targeting of Registries and International Database of Excellence
Note: The same CINRG natural history database is used both in (McDonald 2018) and as the STRIDE propensity-score matched comparator. **Source**: Adapted from (Landfeldt 2024)

4.3.10.4. Placebo Group Trajectory During Span of Ataluren Clinical Studies Supports Consistency of Rate of Disease Progression Over the Study Periods

The randomised studies in the ataluren nmDMD clinical programme span the period from the outset of the CINRG study through 2022. Study 007, the earliest study in nmDMD, and Study 041, the most recent, had similar inclusion criteria, and all subjects were followed closely and prospectively evaluated using defined endpoint assessments. The rate of decline among placebo-treated subjects receiving standard-of-care steroid treatment thus provides valuable information about any change in disease trajectory over the study periods. As summarised in Table 13, the rate of disease progression for the placebo groups in Study 007 and Study 041 was consistent, providing additional direct evidence that calendar bias is not a meaningful factor during the study periods.

Table 13: Disease trajectory for placebo subjects in Ataluren studies consistent for study periods from 2008 through 2022

Assessment	2008-2009	2017-2022
	Study 007 N=40	Study 041 N=176
6MWD, change from baseline to Week 48 (m)	-46.19	-52.72
10-metre run/walk, change from baseline to Week 48 (sec)	3.09	3.01
Stair climb, change from baseline to Week 48 (sec)	4.70	4.59
Stair descent, change from baseline to Week 48 (sec)	4.00	4.10
NSAA total score, change from baseline to Week 48	N/A	-3.13

Abbreviations: 6MWD, 6-minute walk distance; ISE, Integrated Summary of Efficacy; N/A, not applicable; NSAA, North Star Ambulatory Assessment
Source: Table Ground2-3.1, ISE Table 3.3.1, Table 3.3.2, Table 3.3.3, Table 3.3.4, Table 3.3.5

4.3.11. Comparison of CINRG and RCT Placebo Subjects Further Validates Appropriateness of CINRG Comparator

Having thus established the consistency of change in the placebo group over the periods of the studies, a comparison was undertaken of pooled placebo subjects from the ataluren randomised studies and CINRG. The similarity of disease trajectory on functional endpoints in CINRG and the pooled placebo subjects provides further validation of the appropriateness of CINRG as a comparator and demonstrates that neither selection bias nor calendar bias are meaningful drivers of the observed treatment effect in the STRIDE-CINRG analyses (Table 14).

Table 14: Change from baseline for nmDMD placebo subjects and CINRG population are similar over 48 weeks

	Statistic	CINRG	RCT Placebo
10-metre run/walk	n	112	261
	Mean (SD)	1.20 (2.616)	1.15 (2.516)
4-stair climb	n	106	244
	Mean (SD)	2.18 (7.464)	2.11 (4.075)

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; nmDMD, nonsense mutation Duchenne muscular dystrophy; RCT, randomised controlled trial; SD, standard deviation
Source: Table Ground2-2.4.1 and Table Ground2-2.4.2

4.3.12. Potential Immortal Time Bias: Sensitivity Analyses Confirm Immortal Time is Not a Meaningful Source of Bias

At the June 2024 Oral Explanation, the concern of immortal time bias was raised. Two analyses were performed that directly address this concern

First, an analysis was performed excluding STRIDE subjects who began ataluren treatment after the median age of LoA in CINRG. Since initiating treatment with ataluren requires that subjects be ambulatory, the subjects who begin treatment after the median age of LoA could potentially inflate the treatment effect attributable to prolonged survival. However, as summarised in Table 15, the sensitivity analysis excluding these subjects confirms this is not the case.

Table 15: Age at loss of ambulation STRIDE registry subjects and CINRG propensity-score matched excluding subjects who started Ataluren treatment after 13 years of age

	STRIDE (N=236)	CINRG (N=236)
Number of subjects		
Assessed, n	236	236
With events,[a] n (%)	69 (29.2)	115 (48.7)
Censored, n (%)	167 (70.8)	121 (51.3)
Age at loss of ambulation, years		
Median (95% CI)	18.0 (14.1, NE)	13.3 (12.0, 14.0)
Minimum, maximum[b]	2.1+, 19.2+	4.5+, 21.7
p value[c]	<0.0001	
Hazard ratio (95% CI)[d]	0.480 (0.354, 0.650)	

Abbreviations: 6MWD, 6-minute walk distance; CINRG, Cooperative International Neuromuscular Research Group;
ECG, electrocardiogram; NE, not estimable; STRIDE, Strategic Targeting of Registries and International Database of Excellence [a] Event=loss of ambulation. [b] + indicates censored observation. [c] p value is from log-rank test stratified by deflazacort and other steroid usage durations. [d] Hazard ratio is from stratified (by durations of deflazacort and other steroid use) Cox regression with covariates age at first symptom and age at starting steroid usage. Hazard ratio is STRIDE Registry over CINRG.
Note: Propensity-score model covariates include age at first symptom, age at starting steroid usage, duration of deflazacort, and duration of steroid other than deflazacort. Steroid duration is calculated from starting use of steroid to loss of ambulation/censor date.
Censor date is derived from the latest available date across treatment, physical examination, vital sign, 6MWD, timed function tests, North Star Ambulatory Assessments, pulmonary function tests, upper limb function tests, laboratory tests, ECG tests, and motor function measurements. **Source**: 2023 grounds for re-examination Table 14.9.2.2

Concern about immortal time bias is also directly addressed by an analysis using a conditional match that requires that a CINRG subject still be ambulatory when the matched subject begins ataluren treatment. As summarised in Table 16, the consistency of this analysis with the primary analysis confirms that immortal time bias is not a significant driver of the observed treatment difference.

Table 16: Age at loss of ambulation, STRIDE registry subjects and CINRG propensity-score matched requiring that CINRG subject be ambulatory when matched STRIDE subject starts Ataluren

	STRIDE (N=277)	CINRG (N=277)
Number of subjects		
Assessed, n	277	277
With events,[a] n (%)	94 (33.9)	137 (49.5)
Censored, n (%)	183 (66.1)	140 (50.5)
Age at loss of ambulation, years		
Median (95% CI)	16.5 (14.4, 19.7)	13.5 (12.7, 14.0)
Minimum, maximum[b]	2.1+, 25.0+	4.5+, 21.7+
p value[c]	<0.0001	
Hazard ratio (95% CI)[d]	0.482 (0.369, 0.631)	

Abbreviations: 6MWD, 6-minute walk distance; CINRG, Cooperative International Neuromuscular Research Group; ECG, electrocardiogram; STRIDE, Strategic Targeting of Registries and International Database of Excellence [a] Event=loss of ambulation. [b] + indicates censored observation. [c] p value is from log-rank test stratified by deflazacort and other steroid usage durations. [d] Hazard ratio is from stratified (by durations of deflazacort and other steroid use) Cox regression with covariates age at first symptom and age at starting steroid usage. Hazard ratio is STRIDE Registry over CINRG.

Note: Propensity-score model covariates include age at first symptom, age at starting steroid usage, duration of deflazacort, and duration of steroid other than deflazacort. Steroid duration is calculated from starting use of steroid to loss of ambulation/censor date.
Censor date is derived from the latest available date across treatment, physical examination, vital sign, 6MWD, timed function tests, North Star Ambulatory Assessments, pulmonary function tests, upper limb function tests, laboratory tests, ECG tests, and motor function measurements.
Source: PTC124-GD-025o-DMD 6th Interim Report Table 14.5.3.1.1a

4.3.13. Additional Sensitivity Analyses

In addition to the analyses performed to address the specific concerns of bias discussed above, several additional sensitivity analyses were performed that addressed every other identified potential source of bias (Table 17). The results of these additional sensitivity analyses are consistent with the results of the primary analysis, supporting the robustness of the finding of multiyear treatment benefit in delay of LoA in STRIDE.

Table 17: Sensitivity analyses confirm robustness of primary analysis

Primary Analysis				
		Median Age at LoA (Years)		**Hazard Ratio**
		STRIDE	**CINRG**	
		16.5	13.0	0.46
Sensitivity Analyses				
Potential Source of Bias	**Analysis to Demonstrate Bias Mitigated**	**Median Age at LoA (Years)**		**Hazard Ratio**
		STRIDE	**CINRG**	
Standard of Care/Calendar Bias (Corticosteroid Use)				
Corticosteroid dose	Adding dose as covariate	16.5	12.7	0.45
Corticosteroid regimen	Adding dose and regimen as covariate	16.5	12.5	0.44
Functional Status at Study Entry				
Functional status assessment only available in a subset of subjects in STRIDE and CINRG	Adding 10-metre run/walk time and age at time of assessment as covariates	19.7	14.0	0.48
Selection Bias				
Starting ataluren requires that a subject be ambulatory	Conditional match required matched CINRG subjects to be ambulatory at the time the corresponding STRIDE subject initiated ataluren treatment	16.5	13.5	0.48
Starting ataluren late in life requires that a subject be ambulatory later than average	Excluding ataluren-treated subjects who start ataluren after 13 years of age (ie, median age of LoA for control subjects)	18.0	13.3	0.48
Additional Statistical Methods				
Covariate adjustment	Propensity score as covariate	N/A	N/A	0.44
Confirming quality of match	Match within 0.1 caliper	16.5	13.0	0.45
Missing Values and Censoring Rule Sensitivities				

Censor Date: STRIDE subjects who did not reach an event before their last assessment were censored at the age of their last assessment	LoA censor date is set as the last functional assessment indicating that the subject is still ambulatory	15.2	13.0	0.49
Initial symptoms might not reflect DMD disease severity	Excludes STRIDE subjects for whom initial symptoms only include elevated CK and/or	16.9	13.0	0.43

Primary Analysis				
		Median Age at LoA (Years)		**Hazard Ratio**
		STRIDE	**CINRG**	
		16.5	13.0	0.46
	liver enzymes, or prenatal diagnosis or neonatal screening			
STRIDE subjects who discontinue prior to losing ambulation are censored time of discontinuation	Discontinued subjects are conservatively assumed to have reached LoA on the day of discontinuation	15.2	13.0	0.53

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; CK, creatine kinase; DMD, Duchenne muscular dystrophy; LoA, loss of ambulation; N/A, not applicable; STRIDE, Strategic Targeting of Registries and International Database of Excellence
Source: STRIDE 6th Interim Report Table 14.5.2.1.1a, Table 14.5.3.1.1a, Table 14.5.4.1.1a; 2023 grounds for re-examination Table 14.9.1.1, Table 14.9.4.2.1, Table 14.9.2.2, Table 14.9.4.2.2, Table 14.9.5.2.1, Table 14.9.1.2, Table 14.5.2.1.1a-opt, Table Ground2-3.4

4.3.13.1. STRIDE Analysis Demonstrates That Ataluren Treatment Delays Need for Respiratory Support

In patients with DMD, the muscles of the diaphragm are compromised by the same dystrophic process as the muscles of the limbs. Disease progression thus entails progressive restriction of lung volume, resulting in the need for increasing levels of respiratory intervention and support, and the ultimate cause of death in DMD is most commonly respiratory failure. The effect of treatment on pulmonary function is thus of critical importance in understanding treatment benefit. However, the need for respiratory intervention occurs relatively late in the disease course and only after LoA.

While the STRIDE results on the protective effects of ataluren on pulmonary function are preliminary since the majority of patients in the STRIDE Registry have not yet progressed to the stage of requiring respiratory intervention, as of the current cutoff date in the Registry, ataluren treatment is associated with a multiyear slowing of decline in pulmonary function. In this preliminary analysis, ataluren treatment results in a delay of reaching the milestones of forced vital capacity (FVC) <60% predicted, a threshold indicating the first need for respiratory intervention, by 2.1 years (p=0.0086) when compared with their propensity-score matched CINRG counterparts. This suggests a delay in the need for respiratory intervention in initial data (Table 18), as when FVC dips below 60% predicted, manual ventilation or use of an insufflation-exsufflation device is necessary to preserve lung capacity (Birnkrant 2018a).

Over time, with a longer observation period, more patients will progress to a point where this analysis of pulmonary function can be more robust. Nonetheless, the early data support a potential ataluren treatment benefit on a highly morbid aspect of disease.

Table 18: Pulmonary function – STRIDE registry and CINRG propensity-score matched populations

Parameter	STRIDE (N=277)	CINRG (N=277)
% predicted FVC below 60%		
Patients assessed, n	207	179
Patients with events,[a] n (%)	57 (27.5)	70 (39.1)
Patients censored, n (%)	150 (72.5)	109 (60.9)
Median age (95% CI) at event, years	17.7 (16.9, 19.9)	15.6 (15.1, 16.4)
Minimum, maximum[b] age at event, years	5.0+, 22.1+	6.0+, 32.3+
p value[c]	0.0086	
Hazard ratio (95% CI)[d]	0.630 (0.440, 0.903)	

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital capacity; STRIDE, Strategic Targeting of Registries and International Database of Excellence [a] Event=% predicted FVC below 60%. [b] + indicates censored observation. [c] p value is from log-rank test stratified by deflazacort and other steroid usage durations.
[d] Hazard ratio is from stratified (by durations of deflazacort and other steroid use) Cox regression with covariates age at first symptom and age at starting steroid usage. Hazard ratio is Registry over CINRG.
Note: Propensity-score model covariates include age at first symptom, age at starting steroid usage, duration of deflazacort, and duration of steroid other than deflazacort. Censor date is derived from last assessment date. Steroid duration is calculated from starting use of steroid to loss of ambulation/censor date.
Source: PTC124-GD-025o-DMD 6th Interim Report Table 14.5.2.6.1a

4.3.14. Ground 2 MAH Conclusion

The STRIDE Registry provides critical support that the treatment effects recorded in the time-limited clinical trials manifest cumulatively in long-term meaningful treatment benefit.

The MAH has conducted numerous additional analyses to address the specific concerns that were raised regarding the reliability of the STRIDE analyses to support ataluren treatment benefit. In this formal grounds for re-examination document, the MAH has provided documentation supporting the robustness of the STRIDE analyses to support the favourable benefit-risk profile of ataluren, including a number of new analyses.

- The STRIDE and CINRG registries are both robust and employed specific measures to ensure data quality that have been recommended for the use of real-world evidence to support regulatory decisions.
- The MAH employed a propensity-matched approach based on key disease elements to ensure a suitable comparator population to address the well-understood risk for potential bias when using an external control group. The robustness of the propensity match is confirmed by the similarity between the comparator groups for key functional assessments not included in the matching model. In addition, inverse probability treatment weighting analysis also supports reliability of the multiyear ataluren treatment benefit.
- New analyses confirm that the treatment effect observed over 48 weeks in STRIDE on disease endpoints is consistent with the treatment effect recorded in the 3 ataluren RCTs. This directly addresses the concerns that the treatment effect in STRIDE is inconsistent with that observed in clinical trials and supports that the sometimes smaller treatment effect observed over 48 weeks in the RCTs can manifest cumulatively over time in a multiyear delay in LoA.
- New analyses and recent peer-reviewed literature support that bias due to mutation differences in the STRIDE and CINRG registries has been minimised.

- Recent literature supports that the risk of calendar bias over the periods of enrolment of STRIDE and CINRG is minimal. The most significant aspects of standard of care, the age of LoA, and the rate of functional decline across key disease assessments are unchanged over the past 2 decades.
- New analyses confirm that selection bias or "cherry picking" of STRIDE Registry enrolees is minimal.

While there may be unknown sources of bias not accounted for in our analyses, it is highly unlikely that a source of bias not identified in the DMD literature, by DMD experts, SAG-N experts, nor any of the reviewers participating in the review of ataluren, would change the findings of significant long-term treatment benefit of ataluren. While the MAH understands the potential concerns associated with real-world evidence providing confirmatory evidence of positive benefit-risk, these results nonetheless clearly support that ataluren treatment is associated with long-term meaningful effect on a key morbid transition point of disease. Indeed, the SAG-N in June 2024 concluded that the STRIDE Registry provides important evidence of treatment benefit that "should not be ignored."

As part of continued ataluren authorisation, PTC proposes to continue to collect data in the STRIDE Registry. With continued data collection, the LoA analyses will become more robust, and more data will be available to inform treatment effect on loss of pulmonary function, and ultimately, loss of cardiac function—endpoints of unequivocal meaningfulness of DMD patients that cannot be assessed in time-limited RCTs.

Assessment of the MAH´s Ground #2 for re-examination

The argumentation of the MAH is based on the following main points:

<u>The STRIDE Registry Provides an Important Opportunity for Assessment of Long-Term Cumulative Benefit</u>

The MAH again argues that the STRIDE Registry *is a reliable source evidence of meaningful treatment benefit* and would *confirm that change in disease trajectory during the short-term duration of the clinical studies manifests cumulatively meaningful impact on the key morbid transition points of the disease.*

However, as already delineated in the past and again discussed below, this is disagreed. Apart from concerns relating specifically to the STRIDE Registry (discussed below), general methodological shortcomings of STRIDE as an observational study limit STRIDE as a reliable source of evidence of treatment benefit.

<u>Rigorous Design Supports Robustness of STRIDE Registry as a Data Source for Real-World Evidence of Treatment Effect</u>

Although it is acknowledged that the registry study PTC124-GD-025o-DMD (STRIDE), a "Long-Term Observational Study of Translarna Safety and Effectiveness in Usual Care", was designed in collaboration with stakeholders in the field, it needs to be considered that according to the study CSR the registry was designed to evaluate the long-term safety and effectiveness and utilisation pattern of Translarna in routine clinical practice (also referred to as "usual care). Accordingly, the study objectives are as follows:

• Obtain additional information on all safety concerns being tracked in the RMP and long-term safety profile of Translarna

• Obtain additional information on the long-term effectiveness of Translarna

• Monitor the utilisation pattern of Translarna in usual care

limiting the overall possibility of the STRIDE study with respect to the provision of evidence of treatment effect per se as discussed below.

The CINRG Duchenne Natural History Study Dataset Provides a Robust and Appropriate Comparator Population

The MAH compared the data of ataluren in STRIDE to a natural history control (CINRG). The key elements of the CINRG study to serve as a comparator population are again provided by the MAH. However, the interpretability of results from studies using an external control is limited as discussed below.

Propensity Matching Based on Key Factors Influencing Disease Progression Resulted in Comparable Populations From STRIDE and CINRG to Allow for Reliable Comparison of Ataluren Treatment Effect

A number of 277 subjects from the STRIDE registry and from the CINRG registry each were propensity score matched for duration of deflazacort use, duration of other corticosteroid use, age at onset of first symptom and age at initiation of corticosteroid use.

It is acknowledged, that the populations resulting from this match are comparable for the matched parameters. Moreover, the MAH claims comparability of the populations in terms of baseline functional status (as measured by 6MWD or time required to walk /run 10 metres) (Table 8). However, as already earlier discussed, these findings need to be interpreted with caution as functional status assessment was only available in a subset of subjects in STRIDE and CINRG, i.e. time to run/walk 10 meters at first assessment only was provided for 214 and 187 subjects and the distance in the 6MWD test was only provided for 170 and 99 subjects from STRIDE and CINRG, respectively, representing only a subgroup of the compared populations, that might not have been representative for the full cohort.

Moreover, the sensitivity analysis using propensity-score match models that included age and the time required to run/walk 10 meters at study entry as covariates with the primary match criteria showed an age of loss of ambulation for both the STRIDE and CINRG cohorts later than in other analyses, i.e., 19.7 years and 14 years, respectively (reference is made to Table 17). Therefore, the provided analyses are not adequate to address uncertainties with regard to baseline function, i.e., whether potential differences with regard to baseline function might have introduced a source of bias in the analysis.

STRIDE Analyses Demonstrate Multiyear Benefit in Delay in Loss of Ambulation

The MAH again references the known propensity score matched analysis showing that the median age at loss of ambulation was 16.5 years (95%CI 14.4, 19.7) compared to 13.0 years (95%CI 12.3, 13.8) in the STRIDE Registry and CINRG-DNHS, respectively, ($p<0.0001$; HR 0.455 [95%CI 0.350, 0.593]). The MAH argues that this reduction in risk of LoA is consistent with the observation across the 3 placebo-controlled trials with fewer ataluren-treated subjects lost ambulation relative to those receiving placebo (25 subjects versus 40 subjects). However, whether the difference in time to loss of ambulation between treated and untreated patients in the registry trials can be clearly related to Translarna confounding or bias, cannot be concluded from this, especially when considering the large discrepancy between the difference in the time to LoA derived from the STRIDE registry compared to the small effects in the randomized controlled trials on functional outcome parameters, i.e. 6MWD and TFTs.

Propensity-Score Weighting Analyses Confirm Propensity-Score Match Analysis Results

The MAH again discusses that different propensity-score methods (matching, inverse probability of treatment weighting, including propensity score as covariate in the analysis) showed consistent results, confirming that results did not depend on the specific method how propensity scores were used in the analysis. However, all these analyses were still based on propensity scores derived based on the same set of covariates. Therefore, despite results were similar, this does not serve for evidence that results

are reliable and valid, given the uncertainties with respect to several important confounders not considered when deriving the propensity score.

New Analyses and Peer-Reviewed Literature Address Concerns of Potential Bias Raised During the Review Procedure

As stated by the MAH, many of the presented analyses and literature to address potential sources of bias have already been provided and/or discussed before. Additional analyses are discussed below. It is agreed that some of the concerns regarding corticosteroid bias and calendar-time bias, had already been addressed. However, as also stated by the SAG-N conducted in June 2024, in the matching one can only control for known bias. There is still the uncertainty regarding unknown confounding that can only be controlled by randomisation. That is why the results from the three randomised clinical trials are considered the key elements for the assessment of the benefit risk balance.

Addressing Potential Selection Bias: The STRIDE Population is Representative of the Ataluren-Treated Population as a Whole

To address the concern that the population enrolled in STRIDE could not be representative of the entire ataluren-treated population, e.g. less severe patients could be more likely to be enrolled, the MAH again presented a subgroup analysis (120 out of 277 subjects each for the STRIDE and the CINRG Population) from Italy and the United Kingdom. According to the MAH, in these countries almost all patients treated with ataluren are enrolled in the Registry, representing therefore the enrolled population with minimising the risk of selection bias. However, although results of the analysis were in line with the primary analysis, it remains unclear whether the entire nmDMD population was comprehensively covered.

Addressing Potential Mutation Bias: Mutation Type is Not a Meaningful Predictor of Disease Trajectory

As well known, a difference between the STRIDE and the CINRG registry relates to the fact that STRIDE included only patients with nmDMD, amenable to ataluren read through of stop codon treatment, whereas CINRG included DMD patients with any confirmed mutation as long as they satisfied all other eligibility criteria.

Although DMD mutations were not considered in the propensity score model, the MAH again argues that mutation type does not serve as meaningful source of bias in context of the STRIDE results. The MAH therefore provided a review of literature to support the comparison of nmDMD subjects in STRIDE with the mixed genotype DMD population of CINRG:

The published meta-analysis by Muntoni et al., 2023, addressing the question of influence of mutation subtype on DMD progression has already been provided by the MAH during the oral explanation in June 2024. However, as stated earlier, it is questioned, whether the conclusions based on the outcome on the NSAA score after 12 months, e.g., the lack of significant differences, can be extrapolated to the time in LoA. Further, although significant differences have not been shown based on the provided analyses, it cannot be postulated that they do not exist. The same pertains to the now provided publication by Schiava et al., 2022, who studied clinical and genetic characteristics in young, glucocorticoid-naïve boys with DMD. It is noted though that Schiava critically states that *Different factors might have contributed to the limited genotype-phenotype associations observed. The differences in motor outcomes might occur later in the disease course or may become easier to detect when symptoms become more severe because some functional outcomes might not be sensitive enough to capture differences when symptoms are mild or when the child is still developing.*

Overall, while no association between genotype class and change in some functional outcome parameters, e.g., NSAA and 10 metre walk/run, was found in the provided studies, it remains unclear whether these observations would also apply to time to LoA.

Further, the MAH again argues that age at LoA for subjects with nmDMD is comparable to that of other mutation types of DMD:

As reviewed earlier, Bello et al., 2016 reported in the very limited subgroup of patients with a nonsense mutation (N=16) from the CINRG registry, the median age of LoA was 11.1 (95% CI of 10.0–18.1) years. Further, in the very limited subpopulation of corticosteroid-treated nmDMD patients (N=10), the median age of LoA was 14.9 (95% CI of 9.3-∞) years.

As already assessed, Wang et al., 2018 used data with a data cut-off in 2016 from the Duchenne Registry. The authors evaluated patients for which they had genetic data, muscle function data, who were on current corticosteroid treatment and for whom the ambulatory status was known (N = 765). LoA was defined as full-time wheelchair use and ambulatory patients were included as right-censored data. The median age at LoA for the full cohort was 16 years, driven by two subgroups (subjects amenable to exon 8 and 44 skipping, respectively, 12% of total) with a LoA of ≥20 years. The N=71 patients with nonsense mutation DMD (nmDMD) had a median age at LoA of 14 years representing a somewhat higher age than in the mixed genotypes of the CINRG registry.

From these limited data on corticosteroid-treated nmDMD patients above, it is considered that there is an indication of a somewhat higher age of LoA (14.9 and 14 years) in the nmDMD subgroup than the broader DMD population from the CINRG registry (13 years) that does not fully solve the concern on possible mutation bias in favour of the ataluren cohort.

Haber et al., 2021 examined genetic and clinical data from the Muscular Dystrophy Surveillance, Tracking, and Research Network for 358 males born and diagnosed from 1982 – 2011. Although the provided results showed no differences in LoA across mutation type groups, i.e., deletions (N=259), duplications (N=34) and point mutations (N=65), no information was provided specifically with regard to nonsense-mutations. Moreover, the article states, that point mutation testing in the cohort was low, limiting the interpretation of the described results.

To further demonstrate that DMD mutations do not affect the overall results based on comparability of the time to LoA, the MAH again provided an analysis between the identified nmDMD subjects (N=16) versus the non-nmDMD subjects (N=382) from the CINRG Registry, showing a median age of LoA for nmDMD subjects of 11.1 years compared to 12.0 years for all other mutations.

In addition, the MAH presented again the results of an analysis from the French Registry of Dystrophinopathies (DYS) that included ataluren-naïve subjects. Included nmDMD subjects (N=43) were compared to the included subjects with DMD due to other mutation types (N=461), showing a median age of LoA for nmDMD subjects of 10.6 years compared to 11.1 years for non-nmDMD subjects.

However, although both comparisons show similar age of LoA of untreated nmDMD and non-nmDMD subjects as already stated earlier, for both comparisons differences in baseline characteristics and confounding could not be excluded.

The MAH also provides a sensitivity analysis between the nmDMD subjects from the CINRG Registry (N=16) versus nmDMD subjects from STRIDE (N= 48) with propensity-score matching using the same model as that used in the primary analysis, matching subjects in a 3:1 ratio, showing a median age of LoA for the STRIDE subjects of 13.4 years compared to 11.1 years for the nmDMD CINRG subjects, showing a difference in LoA of only 2.3 years.

In summary, based on the provided data, the concern that different underlying mutation types between the Registries could have biased the results in favour of the ataluren cohort could not further be solved. While no association between genotype class and change in some functional outcome parameters, e.g., NSAA and 10 metre walk/run, was found in the provided studies, it remains unclear whether these observations would also apply to time to LoA. Further, available literature suggests that certain mutation

groups (i.e. subjects amenable to exon 8 and 44 skipping) have a milder disease phenotype and a delayed time to loss of ambulation. Considering the unknown/unreported distribution of mutation types in the CINRG-NHS, the impact of mutation type cannot be elucidated. In any case, the MAH's position that mutations type is not a meaningful predictor of disease trajectory is not agreed based on the available data.

Potential Calendar Bias: Calendar Year is Not a Meaningful Source of Bias During STRIDE-CINRG Study Periods

As previously and in detail has been discussed, the ataluren-treated nmDMD patients were enrolled into the STRIDE cohort from 2015-2022 whereas the untreated DMD patients were recruited into the CINRG cohort from 2006-2016, a calendar bias could therefore not fully be excluded.

As stated earlier, the MAH again claims that the key elements of the standard of care remained consistent over the periods of subject enrolment. However, while referencing to four DMD Care Guidelines, neither physiotherapy nor scoliosis management were formally included in the guideline by Moxley et al., 2005, the guideline that has been available at the start of the CINRG cohort. More importantly, the most comprehensive guideline promoting a multidisciplinary treatment approach for DMD including interventions in different areas, e.g., steroid dose and regimen, physiotherapy, scoliosis management, and treatment per different disease stages (diagnosis, early ambulatory, late ambulatory, early non-ambulatory and late non-ambulatory including preventive measures for pulmonary and cardiac dysfunction starting early during the disease) was only available in 2018 (Birnkrant et al, 2018). Overall, regarding standard of care, since the publication of the Duchenne muscular dystrophy (DMD) care considerations in 2010, multidisciplinary care of this severe, progressive neuromuscular disease has evolved. In conjunction with improved patient survival, a shift to more anticipatory diagnostic and therapeutic strategies has occurred, with a renewed focus on patient quality of life. In 2014, a steering committee of experts from a wide range of disciplines was established to update the 2010 DMD care considerations, with the goal of improving patient care (Birnkrant 2018a). Hence, the MAH´s claim that differences in disease progression result from treatment rather than from improvements in standard of care is not considered demonstrated.

As additional justifications, the MAH again presented literature data showing consistent rates of functional decline in 6MWD (Goemans 2020), NSAA (Muntoni 2022) and age at LoA (Szabo 2021) from studies conducted over the periods of STRIDE and CINRG enrolment. However, these data have several limitations, i.e., while the analysis performed by Goermans only covered the period from the beginning of CINRG until the beginning of STRIDE, the studies included by Muntoni were performed in the timespan from 2004 until 2018. It was concluded that *mean changes in 48-week NSAA initially varied across calendar year categories. After adjustment for baseline prognostic factors, however, calendar year effects were attenuated and not statistically significant. There was no evidence of a trend towards improving NSAA change outcomes over time in the RWD/NHD after adjustment for baseline status.* Szabo 2021 evaluated trends in age at LoA on the basis of studies performed until 2018, representing again a period of time that does not cover the whole STRIDE period.

The MAH also again presented results from several studies with corticosteroid therapy showing time to LoA over different study periods which spans from 10.8 years to 13.4 years of age at LoA thus, not ruling out that differences in baseline characteristics and confounding can lead to different age at LoA.

Furthermore, to justify that calendar bias is not a meaningful factor during the study periods, the MAH provided again results on functional endpoints in the placebo arms for study 007 (performed from 2008-2009) in comparison to study 041 (performed from 2017-2022). Although the rate in progression based on the provided endpoints is overall comparable for these studies, these data are based on well-

controlled randomised studies. Therefore, they cannot justify that calendar bias is not a meaningful factor in relation to the comparison of observational studies, i.e., the CINRG and the STRIDE registries.

Overall, based on the provided data, the concern that calendar bias could have affected the obtained results in analyses between the Registries could not further be solved.

Comparison of CINRG and RCT Placebo Subjects Further Validates Appropriateness of CINRG Comparator

A comparison of a subset of pooled placebo subjects from the ataluren randomised studies to a subset from the CINRG registry showed comparable results in 10 metre run/walk and 4-stair climb. However, given the selected number of subjects, these data are not representative for the broader CINRG population, compared to the STRIDE Registry in the primary analysis; moreover, it is unclear why these data were not provided for the 6MWD.

Potential Immortal Time Bias: Sensitivity Analyses Confirm Immortal Time is Not a Meaningful Source of Bias

Immortal time refers to a period of follow-up during which, by design, the event of interest (i.e. loss of ambulation) cannot occur. In the MAH's analysis, all patients were considered to be at risk of losing ambulation from age 0. However, since initiating treatment with ataluren requires that subjects be ambulatory, the time between birth and initiation of ataluren treatment is immortal time. Considering immortal time in the analysis as time where an event could occur may lead to immortal time bias.

The MAH provided two analyses to address the concern of immortal time bias. According to the MAH, both analyses suggest that potential immortal time bias does not have a relevant influence on the conclusion from the study. However, these analyses, are not sufficient to address the concern of potential immortal time bias, considering that the analyses provided are still using a reference time of age 0.

In detail:

First, an analysis was performed excluding STRIDE subjects who began ataluren treatment after the median age of LoA in CINRG. However, while this analysis may reduce potential immortal time bias by excluding patients who began ataluren treatment at highest age (i.e. with longest immortal time), it still considers STRIDE subjects to be at risk of losing ambulation between birth and start of ataluren treatment (i.e. during the immortal time period). Therefore, it is still not excluded that immortal time bias occurred in this analysis.

Second, immortal time bias is addressed by an analysis using a conditional match that requires that the matched CINRG subject still be ambulatory when the matched subject from STRIDE begins ataluren treatment. I.e., an immortal time period is also introduced for the matched subject. The implicit assumption appears to be that immortal time bias is reduced when immortal times occurs in both treatment groups. However, this is still not an adequate approach as immortal time is misclassified as time at risk.

Generally, the calculation of median event time based on Kaplan-Meier curves is not valid when patients with immortal time are included in the analysis. The calculation of hazard ratio based on the Cox model is valid as long as patients are only included in the analysis from the time they were actually at risk of an event (i.e. when immortal time is excluded by truncation).

Additional Sensitivity Analyses

The MAH provided again a number of additional sensitivity analyses addressing several identified potential sources for bias. These analyses have been assessed previously or in the sections above. Although they are overall in line with the primary analyses, they can only be considered supportive. Moreover, there are several limitations in interpreting the results as discussed above.

The propensity score matched analysis showed that subjects in the *STRIDE Registry Study (study 025o)* reached the milestones of FVC ⩽60% predicted at a median age of 17.7 years (95%CI 16.6; 19.9). For subjects in the CINRG-DNHS this milestone of FVC ⩽60% predicted was reached at a median age of 15.6 years (95%CI 15.1; 16.4).

However, again it cannot be concluded with certainty that the obtained results are attributable to Translarna treatment.

Ground 2 Conclusion

In the Ground 2 Conclusion, the MAH refers amongst others to new analyses comparing the treatment over 48 weeks in STRIDE to the ataluren treated subjects from the 3 RCTs. These analyses have not been shown in the MAH´s Grounds for re-examination but were previously presented during the June 2024 oral explanation, showing comparable results. However, as only a small number of subjects from the STRIDE has been compared to those subjects from the RCTs, e.g. N= 71 and N=269, respectively for the 6MWD, their interpretation is limited.

Overall, the MAH addressed several of the earlier discussed concerns questioning that the STRIDE Registry provides reliable evidence of long-term benefit of Translarna on key disease milestones using the CINRG natural history study as comparator population.

This comparison was primarily based on propensity score matching that is sensitive to several bias, as discussed above. Overall, these uncertainties have not been sufficiently solved with the MAH´s Grounds for re-examination.

The Extensive set of sensitivity analyses and additional peer-reviewed literature to support that long-term benefit is reliably attributable to Translarna is acknowledged and overall in line with the primary analysis. However, these analyses also comprise a number of uncertainties as discussed above. In addition, the *post hoc* nature of these analyses reflecting several methodological limitations, has to be taken into account.

The fundamental concerns with regard to robustness of the efficacy conclusions from SOB 2, i.e., the phase III study 041, resulting from the way the analysis was performed (failure of primary analysis, introduction of *post hoc* subgroups) and taken the two other placebo-controlled studies also into account, who both also failed to meet their primary objective, cannot be resolved by further comparisons of observational data.

As stated earlier during the renewal procedure, opposed to well-conducted trials where randomisation ensures exchangeability as per known and unknown confounders, the PS-matched methods only ensure exchangeability conditional to the variables included in the model (if properly modelled) and hence, by definition cannot account for unknown confounding.

Therefore, reliable evidence that long-term Translarna treatment manifests cumulatively in a meaningful delay in loss of ambulation could not be provided.

Ground #2 not resolved.

13.4. MAH's conclusion: The benefit-risk-profile of Ataluren remains favourable supporting continued availability of ataluren for DMD patients

Study 041 Provides Clear, Reliable Evidence of Ataluren Treatment Benefit

Study 041 provides clear, reliable, and nominally statistically significant evidence of the meaningful slowing of disease progression associated with ataluren treatment as assessed by multiple highly relevant endpoints in the prespecified analyses of the ITT Population and in the previously identified sensitive

300- to 400-metre subgroup. These findings of benefit are consistent with the results of the prior randomised trials of ataluren in nmDMD, thus confirming the established favourable benefit-risk profile.

In conclusion, while Study 041 was formally negative, the results of the previous studies support the established favourable benefit-risk profile for ataluren in the treatment of nmDMD.

The STRIDE Registry Provides Credible Supportive Evidence That Benefit in the Clinical Trials Manifests Cumulatively as Delay in Loss of Ambulation

The STRIDE Registry provides reliable, real-world evidence that the treatment benefits observed in the clinical trials manifest cumulatively over the longer term as delays in key morbid disease transition points like LoA and the requirement for pulmonary intervention. While the use of an external comparator population carries a potential risk of bias, extensive sensitivity analyses and peer-reviewed literature confirm that the identifiable potential sources of bias have been appropriately controlled for and that the multiyear delay in LoA can be credibly attributed to ataluren treatment. On this basis, the STRIDE Registry was endorsed by the June 2024 Scientific Advisory Group experts as a source of evidence that "should not be ignored."

The Ataluren Safety Profile Remains Highly Favourable

As agreed with the CHMP and acknowledged in the assessment report, the safety profile of ataluren is not at issue. The results of Study 041 confirm the established safety profile of ataluren over 72 weeks of treatment. The frequency and nature of treatment-emergent adverse events in Study 041 individually and the pooled data for Studies 007, 020, and 041 were consistent with the known safety profile of ataluren, and no new safety concerns were identified.

In 12 completed clinical studies in subjects with nmDMD comprising over 1600 patient-years of exposure, ataluren was well tolerated across all age groups at an oral dose of 10, 10, 20 mg/kg and remained well tolerated in subjects on long-term ataluren treatment (exposures of >5 years).

In the ongoing STRIDE Registry, ataluren continues to be safe and tolerated in over 300 patients with nmDMD.

Conclusions of the MAH

Study 041 provides reliable evidence of treatment benefit of ataluren in slowing disease progression and preserving ambulatory and neuromuscular function across multiple highly relevant endpoints in the Study 041 ITT Population and the previously identified 300- to 400-metre subgroup. These findings of benefit are consistent with the results of the prior randomised trials of ataluren in nmDMD, thus confirming the established favourable benefit-risk profile.

In addition, the results of the STRIDE Registry provide credible evidence that the benefit recorded in the clinical trials manifests cumulatively in the slowing of progression as directly measured in multiyear delay in LoA. New analyses and peer-reviewed literature that confirm that identified sources of potential bias have been minimised and that the estimated treatment benefit can be reliably attributed to ataluren treatment.

As discussed in these formal grounds for re-examination, the evidence collected from Study 041 and the STRIDE Registry since the CMA renewal in 2017 provides further evidence of short- and long-term treatment benefit, and certainly provide no evidence that challenges the previous favourable benefit-risk ratio. The MAH acknowledges that CHMP may have remaining uncertainty regarding the benefit-risk profile of ataluren, and thus, PTC proposes to collect additional evidence as part of a continued CMA to confirm ataluren benefit.

Specifically, as discussed above, the MAH is committed to continuing STRIDE data collection to further inform treatment effect on LoA and loss of pulmonary function. The MAH is also open to inclusion of

additional functional endpoints that can provide more granular data on treatment effect on other measures of ambulatory and neuromuscular function such as NSAA and TFTs.

In addition, if CHMP agrees, PTC would commit to conducting a randomised placebo-controlled study with the sensitive subgroup of subjects with baseline walk distance of 300 to 400 metres that supported the 2017 renewal of the CMA as the primary analysis population. This study could feasibly be conducted at study sites globally and could provide robust and definitive evidence of ataluren treatment benefit.

Assessment of the MAH's conclusion

With respect to the benefit-risk profile, reference is made to section 14, Updated Benefit-risk balance.

It is noted that the MAH would commit to continuing STRIDE data collection to further inform treatment effect on LoA and loss of pulmonary function as well as to perform a further study, i.e., a randomised placebo-controlled study evaluating subjects with baseline 6MWD of 300 – 400 meters, former identified as the most sensitive subgroup, as the primary analysis population.

However, it needs to be considered that the 2 post-authorisation phase III confirmatory studies (020 and 041) which were imposed as SOBs in this CMA are formally negative and failed to confirm the results of the phase II study that supported the CMA. Given the fact that the CHMP considered the totality of data now comprehensive to reach a conclusion of the efficacy of ataluren (see also updated B/R balance section below and oral explanation), renewal of the CMA and imposition of a new SOB to perform a further study is not justified.

13.5. Oral Explanation

The MAH was invited to present its position during an Oral Explanation (OE). On October 16, 2024, a presentation to address the grounds for refusal was made in front of the CHMP plenary meeting.

As already proposed in the grounds for re-examination, the MAH suggested to perform an additional RCT of 48 weeks duration, with the 300 -400m baseline 6MWD subgroup, previously considered the most sensitive subgroup, as the primary analysis population, and to collect further data in the STRIDE Registry. In addition, the MAH also suggested to restrict the indication to 300m-400m baseline 6MWD for new patients. However, after this OE, the Committee concluded that the ground for non-renewal remain. The Committee's views on the MAH's proposal are further detailed above, in the assessment of the grounds for re-examination and below, in the updated benefit-risk section.

14. Updated Benefit-risk balance

During the period covered by this annual renewal, new data have emerged, in particular the results of study 041 related to the last SOB, which were also taken into account in the parallel variation procedure EMEA/H/C/002720/II/0069. These data are considered to be relevant for the benefit-risk balance of Translarna in the approved indication. Therefore, the benefit/risk balance of Translarna is re-assessed in the context of this annual renewal, based on the totality of the data, including the data at the time of the conditional approval, the data generated as per the specific obligations (the data from study 020, as well as the data from study 041), data from the STRIDE (study 025o) registry and additional real world data provided to the Committee, as well as data on paediatric studies 045 and 046.

Regulatory/procedural context

Reference is made to sections 2.2 and 11.1

SOB study 041

Study 041 was a 72-week, randomised (1:1), double-blind, placebo-controlled phase 3 trial in 360 subjects with nmDMD. The double-blind phase was followed by an open-label extension of another 72 weeks wherein subjects who received placebo switched to ataluren. The primary endpoint was the change from baseline in the 6MWD at 72 weeks. "Key" secondary endpoints were the average change in the composite TFT (time to run/walk 10 metres + time to climb 4 stairs + time to descend 4 stairs) and the change in North Star Ambulatory Assessment (NSAA).

Other secondary outcomes included the linear NSAA, individual TFT, the time to persistent 10% worsening in 6MWD, the time to loss of ambulation (LoA), the time to loss of stair-climbing and stair-descending, and the risk of loss of NSAA items.

Based on *post hoc* subgroup analyses of studies 007 and 020, the MAH claimed an effect in the subgroup with a baseline 6MWD between 300-400m. Based on this, the MAH defined a subpopulation that was considered even more sensitive to show an effect. The primary analysis was restricted to the mITT population (185 out of 359 randomised). The mITT population was defined as subjects ≥7 years of age, able to perform the 6MWD >300 meters, and time to stand from the supine position to a standing position >5 seconds. This population and analysis were predefined and approved by CHMP in the annual renewal procedure (EMEA/H/C/002720/R/0022), which was completed on January 9, 2017.

Both studies were the subject of further evaluation within EMEA/H/C/002720/R/0022: https://www.ema.europa.eu/en/documents/variation-report/translarna-h-c-2720-r-0022-epar-assessment-report-renewal_en.pdf

Pooled efficacy analysis

In addition, a pooled analysis was performed using ITT population data from studies 007, 020 and 041, resulting in a total sample size of 701, from whom 354 were treated with ataluren. This was presented in the variation procedure EMEA/H/C/002720/II/69. Given the shorter duration of studies 007 and 020, comparisons were made at week 48 which is acceptable. However, considering the differences between the studies regarding the patient population, length of follow-up and primary analysis population, the pooled analysis is not acceptable. As part of the responses to the request for supplementary information, the MAH submitted a random effect meta-analysis with results for the ITT, mITT and a subgroup with baseline 6MWD of 300 to 400m. Data from the high dose group of study 007 was also included using two approaches: the "including" approach with a high dose, commercial dose and placebo and separate comparisons versus placebo; and the "combined" approach in which all Translarna doses were compared with placebo. The "combined" approach is considered more conservative and might better reflect the requested analysis, including all available data from Translarna and is preferred. The meta-analysis of the ITT population is considered of most interest as this population best reflects the target population as reflected in the current indication. In addition, the subgroup of 6MWD 300 to 400m was defined *post hoc* based on a larger treatment effect across all studies. Therefore, this subgroup's meta-analysis is not considered valuable for confirmatory purposes.

Further, the MAH compared the data of ataluren used in a registry study "STRIDE" (Study 025o) to a historic Cohort group (Cooperative International Neuromuscular Research Group (CINRG)) Duchenne Natural History Study (DNHS). The groups were propensity score matched for age at first symptoms, age at starting corticosteroid use, type of corticosteroid (deflazacort vs others) and duration of corticosteroid use (<1month, ≥1 to <12 months, ≥12 months). During the oral explanation in October 2024, data on efficacy outcomes in STRIDE compared to Translarna RCT subjects and a rational for the lack of matching for type of mutation were presented. Some of the concerns regarding calendar bias and selection bias were also addressed by the MAH.

Favourable effects

Study 007 (initial CMA): For the ITT population a difference of -0.1m 6MWD (95% CI -30.4, 30.2; $p_{nominal}$ =0.9956, adjusted p-value=1.0000) between placebo and the high dose arm (20/20/40 mg/kg per day) and a difference of 26.4 m 6MWD (95% CI -4.2, 57.1; $p_{nominal}$ =0.0905, adjusted p-value = 0.1592) between placebo and the low dose arm (10, 10, 20 mg/kg per day) was seen. The difference in the mean change in 6MWD at Week 48 between ataluren low dose and placebo in the cITT population was 31.7 metres (95 % CI 5.1,58.3; $p_{nominal}$ =0.0197, adjusted p-value=0.0367). A *post hoc* subgroup (patients with baseline 6MWD ≥150m and ≤80% of predicted value) analysis showed a difference in the change in 6MWD at Week 48 of 49.9 metres ($p_{nominal}$=0.0096) between the 10, 10, 20 mg/kg dose and placebo.

Study 020 (first SOB): The observed difference in the mean 6MWD at Week 48 between ataluren and placebo was 15.4 meters (p=0.213) for the ITT population. The difference between ataluren and placebo for the time to 10m run/walk was -1.2 seconds (p=0.117), and the treatment difference for the 4 stair descend was 1.8-seconds (p=0.012). The HR for time to loss of ambulation in the ataluren group was 0.69 (p=0.404). The difference between ataluren and placebo on NSAA total score was 1.5 point (p=0.270). In a *post hoc* defined group, i.e. patients with a baseline 6MWD ⩾300 to < 400 meters, a difference of 47.2 meters was found in the ataluren group compared to placebo at week 48 ($p_{nominal}$ =0.007). Also in patients with a baseline 6MWD <350m, a difference of 68m in favour of ataluren versus placebo was observed ($p_{nominal}$ =0.0053). The difference in total NSAA score was 4.5 points (p=0.030).

Study 041 (second SOB) was a 72-week, randomised (1:1), double-blind, placebo-controlled phase 3 trial weeks in 360 subjects with nmDMD. In study 041, a non-significant small difference of 8.26 meters ($CI_{95\%}$ -26.05; -9.53, p = 0.36) and a difference of 14.42 meters ($CI_{95\%}$ 1.83 – 27.01; $p_{nominal}$ = 0.025) were found in the mITT population (n=185) and ITT population (n=359), respectively. The differences for the TFT composite was -1.04 seconds (p= 0.0892) for the mITT population and -0.70 seconds (p=0.09) for the ITT population. The difference between placebo and ataluren was 0.9 points for both populations on the NSAA total score (p=0.13). More information on results from study 041 is found in variation EMEA/H/C/002720/II/0069 procedure.

Submitted meta-analysis: In the ITT population using the combined approach, the submitted meta-analysis shows an LS mean difference from placebo of 13.8 meters in 6MWD (95% CI: 3.51, 24.08), 1.26 seconds in the TFT composite score (95% CI: -1.91, -0.61), 1.07 points in the NSAA total score (95% CI: 0.433, 1.716), and 2.64 points in NSAA linear score (95% CI: 0.861, 4.412).

STRIDE Registry Study (study 025o): The propensity score matched analysis showed that subjects in the *STRIDE Registry Study (study 025o)* reached the milestones of FVC ⩽60% predicted at a median age of 17.7 years (95%CI 16.6; 19.9). For subjects in the CINRG-DNHS this milestone of FVC ⩽60% predicted was reached at a median age of 15.6 years (95%CI 15.1; 16.4). The milestone FVC ⩽50% predicted was reached at a median age of 19.2 years (95%CI 17.8; NA) in the STRIDE Registry subjects and at 17.7 years (95%CI 16.5; 18.6) in the subjects of the CINRG-DNHS.

The median age at loss of ambulation was 16.5 years (95%CI 14.4, 19.7) compared to 13.0 years (95%CI 12.3, 13.8) in the CINRG-DNHS (p<0.0001; HR 0.455 [95%CI 0.350, 0.593]).

Uncertainties about the favourable effects

In study 007, no effect of the high dose was seen. This was odd as a greater effect compared to the low dose was anticipated. The MAH argued that there is a bell-shaped dose response curve which was, however, not evident from the non-clinical data. Considering that a potential beneficial effect was seen in a *post hoc* derived group, it was concluded that additional data was needed to confirm these favourable effects. In the first SOB (study 020) the overall population, i.e., ambulatory DMD subjects, did not show a statistically significant or clinically meaningful difference from placebo. However, a new study was requested as a clinically meaningful difference was noted in *post hoc* defined sub-groups. An extension of study duration was recommended considering the effect size after 48 weeks may be too small to draw

a well-founded conclusion about the effect size in terms of both clinical relevance and statistical significance.

The largest effects were seen in the *post hoc* defined groups of patients with baseline 6MWD ⩾300 to <400 meters and patients with baseline 6MWD ≥150m and ≤80% of predicted value based on studies 007 and 020. It was argued that these subgroups apparently are the most rapid declining and therefore the most sensitive to show an effect. Accordingly, the MAH defined a mITT population anticipating the largest effect for this population. However, results from the mITT population in study 041 did not confirm the effect seen in the initial phase 2 study (i.e., study 007) that supported the CMA in 2014 and the effect seen in the *post hoc* analyses of studies 007 and 020 that supported the renewal of the conditional marketing authorisation in 2016. This is also the case for the difference in 6MWD between placebo and ataluren found in the ITT population of the phase III study 041 (14.4 meters after 72 weeks of treatment). Considering that the study 041 failed to meet the primary efficacy endpoint, statistical significance claims cannot be accepted for any of the other efficacy endpoints. Furthermore, the effect sizes observed on the secondary outcomes, i.e., NSAA and TFT (including the individual items), are not within the range of the published MCIDs (when available). As per the individual items of the TFT that were performed in the three trials, the effect sizes observed in study 041 are the smallest in spite of being the longest trial.

The applicability of the *post hoc* performed meta-analysis is questioned on methodological shortcomings violating methodological principles for a retrospective meta-analysis (*PtC "Points to consider on application with 1. Meta-analyses; 2. One pivotal study" CPMP/EWP/2330/99*). The guideline lists the prerequisites for a retrospective meta-analysis. Among others, it specifies that some studies need to be clearly positive. Considering the primary efficacy analysis of the primary efficacy endpoint, the three studies (namely 007, 020 and 041) are formally negative. Further, it specifies that pooled 95% confidence interval needs to be well away from zero. For the primary efficacy endpoint (6MWD), the lower limit of the pooled 95% confidence interval for the least squares (LS) mean in the combined approach is 3.51 meters for the ITT population. Note that for the NSAA (both total and linear) and the TFT (composite as well as individual items) the 95% confidence interval for the least squares (LS) mean in the combined approach were also close to 0. In any case results are not capable of compensating or overruling the negative findings of the individual studies.

The STRIDE registry study (study 025) has an open-label design following only nmDMD patients who are treated with ataluren. In this particular case, the controls from STRIDE were matched with participants in CINRG-DNHC using propensity score matching. In spite of the observed difference in the loss of ability to walk in some patients treated with Translarna of about 3.5 years compared to those matched patients in the CINRG registry, comparison to an external control includes several biases due to measured and unmeasured confounding.

DMD mutations were not considered in the propensity score model. The MAH argued during the re-examination and the oral explanation in October 2024 that this aspect is not influencing the STRIDE results based on an extensive literature review and sensitivity analyses. The MAH presented results from studies where no associations between genotype class and change in some functional outcome parameters, e.g., NSAA and 10 metre walk/run were found after 12 months. However, it is unclear how the data relate to time to LoA. The MAH presented literature claiming that genotype does not have an impact on the phenotype and in particular on the time of LoA. However, available literature suggests that certain mutation groups (i.e. subjects amenable to exon 8 and 44 skipping) have a milder disease phenotype and a delayed time to loss of ambulation. Considering the unknown/unreported distribution of mutation types in the CINRG-NHS, the impact of mutation type cannot be elucidated. In any case, the MAH's position that mutations type is not a meaningful predictor of disease trajectory is not agreed based on the available data. Further, the MAH presented data from two registries and claimed comparability of

the time to LoA between a group of nmDMD and a group of non-nmDMD participants in two registries. However, for both comparisons differences in baseline characteristics and confounding could not be excluded. The sensitivity analyses presented by the MAH (i.e. nmDMD CINRG vs CINRG Overall and nmDMD CINRG vs STRIDE) were based on small sets and based on a suboptimal PS-matching as acknowledged by the MAH. The concern that different underlying mutation types between the Registries (STRIDE, CINRG-NHS) could have biased the results in favour of the ataluren cohort remained.

In addition, a 2-year difference in age at first assessment is noted hampering a match on functional outcome measures. The MAH claims comparability of the populations in terms of baseline functional status (as measured by 6MWD or time required to walk /run 10 metres). However, these findings need to be interpreted with caution as functional status assessment was only available in a subset of the compared populations that might not have been representative for the full cohort. The sensitivity analysis using propensity-score match models that included age and the time required to run/walk 10 meters at study entry as covariates with the primary match criteria showed an age of loss of ambulation for both the STRIDE and CINRG cohorts later than in other analyses, i.e., 19.7 years and 14 years, respectively. Therefore, the provided analyses are not adequate to address uncertainties with regard to baseline function, i.e., whether potential differences with regard to baseline function might have introduced a source of bias in the analysis. Thus, the CHMP maintained the concern.

Importantly, immortal time bias is introduced as patients in STRIDE were only allowed to enter the registry if prescribed Translarna requiring them to be still ambulatory at enrolment. Two analyses were provided to address the concern of immortal time bias. However, they are not sufficient to address the concern of potential immortal time bias, considering that the reference point for time to LoA remains age 0. During the oral explanation in October 2024 the MAH was requested to discuss whether alternative analysis approaches that may better address immortal time bias, e.g. by considering time to LoA from the start of patient follow-up with adequate matching/weighting by patient characteristics at inclusion, had been considered. However, the MAH confirmed that such alternative analyses have not been performed.

Further, as the ataluren-treated nmDMD patients were enrolled into the STRIDE cohort from 2015-2022, and the untreated DMD patients were recruited into the CINRG cohort from 2006-2016, a calendar bias cannot be fully excluded, this also refers to the provided data in the MAH´s Grounds for re-examination. The MAH claimed that the key elements of the standard of care remained consistent over the periods of enrolment. Treatment with steroids is a paramount strategy in the management of DMD. The PS model used by the MAH did not consider the dose and the regimen. However, it can be agreed that the results from the sensitivity analysis including these two variables in the PS model do not suggest that a difference in these aspects play a major role. The categorization of the duration of steroids treatment (<1 month, 1-12 months > 12 months) is still questionable as it assumes no further benefit beyond 12 months of use. Nevertheless, it is agreed that the concern on differences in the treatment with steroids was reasonably addressed by the MAH. However, the standard of care in DMD includes other measures. The MAH made reference to four guidelines, and it was noted that neither physiotherapy nor scoliosis management were formally included in the Moxley et al. 2005 publication. More importantly, the most comprehensive guideline promoting a multidisciplinary treatment strategy for DMD including interventions in different areas per the different stages of DMD was only available at 2018 (Birnkrant et al., 2018). As additional justifications, the MAH presented observational data showing consistent rates of decline in functional outcomes and age at LoA over different study periods. However, as discussed above, these data have limitations (differences in baseline features, confounding, periods that do not cover the whole STRIDE registry) and hence, do not allow to rule out the concern about calendar bias. The comparison of the results on functional endpoints in the placebo arms for study 007 (performed from 2008-2009) and study 041 (performed from 2017-2022) are based on randomised studies and

cannot justify that calendar bias is not a meaningful factor in relation to the comparison of observational studies. Hence, the MAH´s claim is not considered demonstrated and concern remains.

Selection bias was also discussed by the MAH in the grounds for re-examination and during the oral explanation in October 2024. The MAH presented a subgroup analysis from Italy and the United Kingdom. According to the MAH, in these countries almost all patients treated with ataluren are enrolled in the Registry, representing therefore the enrolled population with minimising the risk of selection bias. However, although results of the analysis were in line with the primary analysis, it remains unclear whether the entire nmDMD population was comprehensively covered. Then, the concern could not be sufficiently excluded.

Further, the STRIDE has an open-label design which is prone to observational bias as opposed to 007, 020 and 041 RCTs that included a blinded-phase. As opposed to well-conducted trials where randomisation ensures exchangeability as per known and unknown confounders, the PS-matched methods only ensures exchangeability conditional to the variables included in the model and hence, by definition cannot account for unknown confounding. Additional limitations and uncertainties were highlighted including unclear rules for censoring and substantial missing data for which the MAR pattern of missingness was used, which is questionable. The suggested delay of 3.5 years in loss of ambulation compared to the natural history registry is based on data of 5-10% of the included population. Consequently, an open-label study with an external comparator cannot compensate or overrule the results of the individual RCTs, which by design produce the most valid results and the best approaches to isolate a true effect size.

Unfavourable effects

The most common adverse events across all studies were headache, upper respiratory infections and gastrointestinal disorders such as nausea, vomiting, (upper) abdominal pain, flatulence, diarrhoea, stomach discomfort, constipation and regurgitation.

Uncertainties about the unfavourable effects

As the safety has been monitored for approximately 10 years and the safety data was consistent across all studies, there are currently no uncertainties on unfavourable effects beyond the safety concerns included in the RMP. The safety concerns included in the RMP are currently managed by the established risk minimisation measures and additional pharmacovigilance activities described in the RMP.

Benefit-risk assessment and discussion

In 2014, Translarna received a CMA for the treatment of nmDMD in ambulatory patients based on *post hoc* results (cITT instead of ITT population) from a phase 2b study (Study 007) showing with the lower dose a borderline beneficial effect on the 6MWD test supported by numerical trends in TFT as secondary efficacy endpoints. The CMA was approved under the condition to conduct a confirmatory study as SOB (first SOB / Study 020) in the post-authorisation phase.

In Study 020, with an intended enriched population (i.e., different thresholds for eligibility based on the baseline performance on 6MWD), the treatment effect size on 6MWD in the primary efficacy analysis was much smaller than the one reported in the cITT population in Study 007 and not statistically significant. Hence, study 020 did not confirm a favourable benefit/risk of Translarna in the approved indication.

Post hoc subgroup analyses from both Studies 007 and 020 showed potential beneficial effect sizes in patients with baseline 6MWD $\geqslant$150m and $\leqslant$80% of the predicted value in study 007 and patients with baseline 6MWD $\geqslant$300 to <400 meters in study 020. Though the original SOB failed to confirm the findings of study 007, the CMA was renewed in 2016 (EMEA/H/C/002720/R/0022) with a second condition (second SOB / Study 041) to confirm the positive B/R of Translarna taking into account the subgroup

information in the study design. As such, the primary efficacy endpoint was defined as the difference in the change from baseline in the 6MWD at 72 weeks between the ataluren arm and placebo arm in the mITT population defined as patients able to perform the 6MWD >300 meters and time to stand from supine position >5 seconds.

Thus, it was anticipated that a more sensitive population (i.e., the mITT population, which was based on exploratory *post hoc* analyses of previous studies in DMD, including study 020) would be more able to show a treatment effect of ataluren. However, a statistically significant and beneficial effect could also not be demonstrated in this mITT population. Therefore, Study 041 is considered a failed study. Please see more details on the assessment of Study 041 in procedure EMEA/H/C/002720/II/0069. The subsequent description of the findings in the ITT population reflects the attempt of the MAH to elicit a positive result from a failed study. Indeed, the ITT population is representative of the population for which the CMA was granted. However, formal statistical testing is not allowed from a methodological perspective because the primary efficacy endpoint was specified to be tested in the mITT population and not the ITT population. Even ignoring this, the observed effect in 6MWD between ataluren and placebo in the ITT did not confirm the effect seen in the initial phase 2 study (i.e., study 007and the effect in the *post hoc* analyses of studies 007 and 020. For the NSAA, the 0.9-point difference is not at the reported MCID.

Although a statistically significant effect favouring ataluren over placebo is claimed in a *post hoc* conducted meta-analysis, the applicability of the *post hoc* performed meta-analysis is questioned on methodological shortcomings violating methodological principles for a retrospective meta-analysis (PtC "Points to consider on application with 1. Meta-analyses; 2. One pivotal study" CPMP/EWP/2330/99). In any case, results are not capable of compensating or overruling the negative findings of the individual studies.

The comparison to a historical external cohort of the STRIDE registry is considered supportive, but cannot overrule the results of the placebo-controlled phase 3 studies, which by default produce the most valid results by design and the best approaches to isolate a true effect size. Additionally, interpretability of the results is hampered by the aforementioned limitations and uncertainties.

Third party interventions were received from several countries also during the re-examination procedure. These include letters from parents or caregivers, patient organisations, healthcare professional organisations, and treating physicians. The interventions expressed views on the large unmet medical need for DMD and the benefit of Translarna in nmDMD based on their experience in the clinical practice and their interpretation of the efficacy data of Translarna mainly the efficacy data from the STRIDE registry. The unmet medical need for DMD is acknowledged and has never been questioned. During the renewal procedure, the CHMP noted the information on the experience in the clinical practice from health care professionals and health care professional organisations shared through individual case reports. The information shared on quality of life difference between ambulatory DMD patients receiving ataluren, caregiver reported quality of life and a wider consideration of possible cost benefit of ataluren is also acknowledged. However, it is considered that these interventions do not impact the conclusion on the benefit-risk of ataluren in view of the three failed clinical trials.

Another important issue in the assessment of efficacy of ataluren is the data on dystrophin expression. In the initial application, the data on dystrophin expression was inconclusive because of poor quality (Translarna EPAR Public assessment report EMA/369266/2014). In the Article 46 procedure EMEA/H/C/002720/P46/026, submitted in 2021, additional pharmacological data on dystrophin expression was submitted and assessed. The baseline median dystrophin level as measured by ECL was 0.42% of normal (range 0.00% to 41.85%). At the end of the study, the median dystrophin level was 0.33% of normal (range 0.04% to 48.55%). Hence dystrophin expression overall remained low and

hardly changed following treatment. The product information was updated with this information in the variation procedure EMEA/H/C/002720/II/0068.

Discussion

In order to confirm the efficacy of Ataluren in ambulatory nmDMD two studies have been imposed as specific obligations and performed by the MAH. The two phase 3 studies (020 and 041) failed to confirm results of the phase 2 study (007) that supported the conditional marketing authorisation. Study 041, that was performed in the population expected to be most sensitive to show an effect, failed to confirm the effect seen in the initial phase 2 study 007 (cITT) and failed to confirm the effect of the *post hoc* analyses of studies 007 and 020 (that supported the renewal of the conditional marketing authorisation in 2016).

With respect to the registry-derived data, the suggested 3.5 years delay in the loss of ambulation observed in participants in STRIDE registry compared to the external-controls from CINRG-DNH is difficult to interpret in the view of the limitations and uncertainties related to external controls.

Finally, PD studies showed that treatment with ataluren did hardly change dystrophin expression in the vast majority of the 20 patients evaluated.

From a safety perspective, overall data support that ataluren is generally well-tolerated in ambulatory patients with nmDMD, with the most common adverse events being headache, upper respiratory infections and gastrointestinal disorders.

During the oral explanation in October 2024, the MAH claimed a treatment benefit to have been shown in a total number of subjects comparable to largest studies in a non-orphan indication based on the results from meta-analysis of the three RCT. As already explained, the applicability of the *post hoc* performed meta-analysis is questioned on methodological shortcomings violating methodological principles for a retrospective meta-analysis (PtC "*Points to consider on application with 1. Meta-analyses; 2. One pivotal study" CPMP/EWP/2330/99*). Nevertheless, the CHMP acknowledges the large number of subjects with nmDMD enrolled in the trials: 753 subjects (not all were included in the meta-analysis) affected by a limited subset (i.e., nmDMD represents less than 15% of DMD) of an already rare condition such as DMD. Furthermore, this large set of subjects were evaluated in three different randomised clinical trials all of them failing to meet the primary efficacy endpoint. It should be noted that it is considered that the study design of the trials overall follows the recommendations outlined in the EMA Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy (EMA/CHMP/236981/2011, Corr. 11). In particular for the study 041, the study was designed based on prior experiences from the other trials. Following the results from prior subgroup analyses supporting a greater treatment effect in subjects within a declining phase, this population (subjects ≥7 years of age, able to perform the 6MWD >300 meters, and time to stand from the supine position to a standing position >5 seconds) was selected as the primary efficacy study population while still other ambulatory subjects were included (ITT population) to gain understanding on the B/R in the target population in line with the recommendation that in confirmatory trials, the efficacy and safety of the product should be studied in the broad range of patients that the investigational product is intended to treat. In terms of study duration, study duration in 041 was increased to 18 months in line with the above-mentioned guideline that recommends at least one or two years and also in line with feedback received from the experts in a dedicated *ad hoc* SAG-N meeting. Also following the above-mentioned guidance, primary endpoints were focused on mobility, as recommended for clinical trials in ambulant boys that aim to demonstrate the efficacy of a disease modifying agent (e.g. enhancing some level of functional dystrophin or delaying muscle dystrophy). Hence, it is considered that the 020 and 041 phase III studies represent two failed opportunities to confirm the efficacy of Translarna as observed in the CMA. On the other hand, these trials confirmed the safety profile of Translarna. The CHMP considers that the totality of the data is now considered comprehensive for ambulatory nmDMD (and hence including

the ambulatory subpopulation of nmDMD with baseline 6MDW between 300 and 400 meters). Therefore, the need for a new study or further collection of STRIDE data is not agreed.

Moreover, the MAH´s proposal to restrict the indication in the SmPC for new patients to be treated with Translarna to a 300-400 m baseline 6MWD was not supported in the given context. It is not agreed that the efficacy of Translarna in nmDMD with a 300-400 m baseline 6MWD has been established. The estimates from this subpopulation pertain to subgroup analyses from trials for which the primary efficacy endpoint was not met. Hence, all other results from these trials can only be considered exploratory. Thus, the efficacy in nmDMD with baseline 6MWD between 300 and 400 m is not established. Thus, the newly proposed indication is not acceptable.

Conclusion

The CHMP considers that the totality of data from three randomized controlled trials including 753 subjects affected by nmDMD, which is a limited subset of DMD, an already rare condition (i.e., nmDMD represents less than 15% of DMD), as main sources of evidence, and the additional data from the STRIDE (study 025o) registry, which includes 277 subjects affected by nmDMD, as well as additional real world data provided to the Committee, including evidence highlighted by Czechia, and studies 045 and 046 as complementary sources of evidence, is now considered comprehensive, as opposed to when the CMA was first granted. Therefore, the renewal of the CMA and the provision of a new (fourth) RCT is not justified.

In fact, the beneficial effect resulting from *post hoc* analyses of the phase 2 study could not be replicated in two confirmatory phase 3 studies (020 and 041). Results derived from registry data are of limited interpretability and are considered only supportive, but cannot overrule the results of phase 3 placebo-controlled studies, which by default are designed to produce the most valid results and the best estimation of a true effect size. Therefore, efficacy of ataluren has not been established, neither in the indication currently approved, nor in a restricted indication as proposed by the MAH in the OE in October 2024, and a positive benefit-risk balance in DMD was not confirmed.

Grounds for non-renewal of the marketing authorisation

Whereas,

- The Committee re-assessed the benefit-risk of Translarna as part of the annual renewal procedure taking into account the totality of data, which includes the data available at the time of the conditional approval, data generated as per the specific obligations (the data from study 020, as well as the data from study 041), data from STRIDE registry (study 025o) and additional real world data made available to the Committee, as well as and on data on paediatric studies 045 and 046.
- The available data, in particular the results of study 041 conducted to fulfil the outstanding specific obligation with a view to confirming a favourable benefit-risk balance for the conditional marketing authorisation for Translarna, failed to confirm the efficacy of Translarna in the treatment of ambulant patients with nmDMD aged 2 years or older.
- Based on the above, the CHMP concluded, on the basis of the comprehensive set of data now available, that the efficacy of Translarna is not established and therefore a favourable benefit-risk balance has not been confirmed in the treatment of ambulant patients with nmDMD aged 2 years or older.

The CHMP therefore does not recommend the annual renewal of the conditional marketing authorisation for Translarna.

15. Conclusions and recommendation following re-examination

It is concluded that the benefit of ataluren has not been demonstrated. The grounds for refusal remain. Hence, renewal of the conditional marketing authorisation of Translarna (ataluren) is not recommended.