EMA/CHMP/116346/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Translarna

International non-proprietary name: Ataluren

Procedure No. EMEA/H/C/002720/II/0074

Note

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

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1. Background information on the procedure

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, PTC Therapeutics International Limited submitted to the European Medicines Agency on 29 September 2023 an application for a variation.

The following changes were proposed:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to change posology information in paediatric population, to update the summary of safety profile and to update efficacy, safety and pharmacokinetic information on paediatric population based on the final results from study PTC124-GD-048-DMD "A Phase 2, multiple-dose, open-label study evaluating the safety and PK of ataluren in patients with nmDMD aged ≥6 months to <2 years old" (MEA-018). The Package Leaflet is updated accordingly. In addition, the MAH took this opportunity to introduce editorial changes to the PI.

The requested variation proposed amendments to the Summary of Product Characteristics and Package Leaflet.

2. Overall conclusion and impact on the benefit/risk balance

In the current variation the MAH proposes amendments to the SmPC to inform physicians on the use/posology in patients aged ≥6 months to <2 years of age, outside the currently authorised use of the medicinal product, i.e. patients aged 2 years and older.

Translarna (ataluren) exerts its efficacy through enabling ribosomal read through when a premature stop codon is generated in the mRNA by nonsense mutations in the dystrophin DNA.

Translarna is administered orally every day with a recommended dose of 10 mg/kg body weight in the morning, 10 mg/kg body weight at midday, and 20 mg/kg body weight in the evening (for a total daily dose of 40 mg/kg body weight).

Translarna obtained conditional approval in 2014 for "*the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older (see section 5.1). The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing (see section 4.4)*".

In 2016 the conditional marketing authorisation was renewed with the obligation to perform a second efficacy study, i.e., study PTC124-GD-041-DMD (study 041). In 2018 the indication was extended to include nmDMD patients aged 2-5 years of age. In 2019 the extension of the indication to non-ambulatory patients was rejected. Data of the SOB study 041 was assessed as part of variation EMEA/H/C/002720/II/0069. Further results were assessed during the annual renewal EMEA/H/C/002720/R/071 in which a re-assessment of the benefit—risk balance of Translarna was performed, taking into account the totality of the data. Negative opinions were concluded for both variation II/069 and annual renewal R/071 in September 2023. Following the re-examination of the annual renewal R/071 requested by the MAH, the CHMP recommended in January 2024 to not renew the conditional marketing authorisation for Translarna.

In support of the proposed updates of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC the MAH has submitted

data of an open label study in 6 nmDMD subjects aged≥6 months to <2 years of age, who were followed for at least 24 weeks. The study included PK assessment and tolerability/ safety assessment.

Blood samples for PK assessments were drawn using the volumetric absorptive micro-sampling method at baseline (Visit 2), Week 4 (Visit 3), and Week 24 (Visit 5; end of treatment/early termination). The samples were drawn immediately pre-dose and at 1, 2, 3, and 4 hours post-dose following both the morning and midday doses and immediately pre-dose and at 1, 2, 3, 4, and 12 (before the next day morning dose) hours post-dose following the evening dose.

The PK data was compared to data from nmDMD patients age 2-5 years of age (study 030) and to patients >5years of age (Study 004).

The safety analysis following 24 weeks of treatment did not show unexpected findings. The results were in line with the known effects of ataluren and with frequent occurring childhood illness as was also seen in the children aged 2-5 years of age. Six patients ranging from to with a mean age of 14 months (range 7 months; 23months), however, is considered too limited a sample to allow for a meaningful conclusion. The proposed changes to SmPC sections 4.2, 4.8, 5.1 and 5.2 are supported by the data submitted.

However, in view of the CHMP opinion for the annual renewal EMEA/H/C/002720/R/071 adopted on 24 January 2024 to not renew the marketing authorisation of Translarna, as a favourable benefit-risk balance has not been confirmed in the treatment of ambulant patients with nmDMD aged 2 years or older, no changes to the marketing authorisation can be recommended. The European Commission decision on the non-renewal of the conditional marketing authorisation is awaited.

3. Recommendations

Based on the review of data submitted in this application, concerning the following change:

Variation requested		**Type**	**Annexes affected**
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I and IIIB

The CHMP is of the opinion that the requested update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC in order to change posology information in paediatric population, to update the summary of safety profile and to update pharmacokinetic information on paediatric population based on the final results from study PTC124-GD-048-DMD "A Phase 2, multiple-dose, open-label study evaluating the safety and PK of ataluren in patients with nmDMD aged ≥6 months to <2 years old" (as well as the subsequent updates to the Package Leaflet and the additional editorial changes to the PI) are supported by the data submitted. However, in view of the CHMP opinion for the annual renewal EMEA/H/C/002720/R/071 adopted on 24 January 2024 to not recommend the renewal of the marketing authorisation of Translarna, as a favourable benefit-risk balance was not confirmed in the treatment of ambulant patients with nmDMD aged 2 years or older, no changes to the marketing authorisation can be recommended at this stage.

4. EPAR changes

The table in Module 8b of the EPAR will be updated as follows:

Scope

Please refer to the Recommendations section above

Summary

Not applicable

Please refer to Scientific Discussion ‘Translarna-H-C-002720-II-74’

Annex: Rapporteur’s assessment comments on the type II variation

5. Introduction

The MAH conducted a clinical study in children with nmDMD between 6 months and 2 years of age (study 048), as part of the PIP requirements. The number of subjects for this age group (n=6) was agreed upon in the PIP. Updates of the study, i.e. recruitment, enrolment etc, has been presented in the annual PSUR updates.

The original protocol, dated 14 April 2020, was amended on 29 April 2021 (version 2.0), 01 July 2021 (version 3.0) and 06 May 2022 (version 4.0). The most significant changes to the study protocol were implemented in Version 2.0 and included the following:

- The duration of treatment was changed from "52 weeks" to "24 weeks" and the end of treatment (EOT) timepoint was updated to occur at Week 24 instead of Week 52 following discussion and agreement with the EMA PDCO on PIP RfM#11 (EMEA-000115-PIP01-07-M11)
- Removal of the efficacy endpoint (change in motor development)
- Removal of the exploratory endpoint "abnormalities of physical findings, clinical laboratory tests, or electrocardiograms (ECGs)" since this information is captured as part of the primary endpoint
- The exploratory objective of "to assess changes from baseline in creatine kinase (CK) levels after 24 weeks of ataluren treatment" and the exploratory endpoint of "change from baseline in CK levels" were added
- Updates were made to the volume and process by which blood PK samples are collected

In addition, blood/plasma partition sampling was added in Version 3.0 and urine protein: urine creatinine ratio (spot) was added to the list of clinical laboratory assessments in Version 4.0.

The MAH indicates that no extension of the indication for patients with nmDMD ≥6 months to <2 years of age is sought. Instead, it is proposed to update the SmPC based on the data from study 048. More specifically the following updates are proposed (strike trough indicates text removed, bold underlined is newly added)

Section 4.2 Posology and Method of Administration	~~"The safety and efficacy of Translarna in children <12kg and aged 6 months to 2 years have not yet been established. No data are available.~~ **Translarna is not recommended for use in patients aged <2 years due to insufficient data on safety and efficacy (see section 4.8 and 5.1)**
Section 4.8 Undesirable effects	"**In an open-label study to evaluate safety and PK in patients ≥6 months to <2 years of age (n=6), safety data from 24 weeks of therapy showed that study drug is well tolerated with no adverse effects specific to the younger population. There are no safety concerns or safety signals from the study, and none of the adverse events were considered treatment related. The only events that occurred in more than 1 patient were gastroenteritis and diarrhoea, which occurred in 2 patients (33.3%) each. These higher frequency events are considered unrelated. The study safety results did not alter or change the existing safety profile of ataluren.**
Section 5.1 Pharmacodynamic Properties	"The safety, pharmacokinetics and exploratory effectiveness of Translarna were assessed in ~~an~~ **two** open-label studies~~y~~ in children between **6 months** and 5 years of age with nmDMD. **Study 30 (PTC124-GD-030-DMD)**

	assessed Translarna in children aged 2 to 5 years old, with the efficacy of T~~ranslarna in children aged 2-5 years has been~~ established on extrapolation from patients aged >5 years, **and Study 48 (PTC124-GD-048-DMD) assessed Translarna in children aged 6 months to 2 years old."** ~~The European Medicines Agency has deferred the obligation to submit the results of studies with ataluren in one subset of the paediatric population aged 6 months to less than 2 years old in nmDMD, as per Paediatric Investigation Plan (PIP) decision in the granted indication (see section 4.2 for information on paediatric use).~~
Section 5.2 Pharmacokinetic Properties	"Based on data from subjects ranging in age from **6 months** ~~2 years~~ to 5 years, there is no apparent effect of age on ataluren plasma exposure. Age-adjusted dosing is not required. The pharmacokinetics of ataluren has been evaluated in **DMD patients 6 months and above receiving the 10/10/20 mg/kg dose regimen. Ataluren plasma concentrations were maintained consistently across age groups at steady state.** ~~study PTC124-GD-030 over a duration of 4 weeks. Ataluren plasma concentrations in patients from 2 to less than 5 years old were consistent with those seen in patients above the age of 5 years receiving the 10/10/20 mg/kg dose regimen.~~"

6. Clinical Pharmacology aspects

Study 048 was designed as a Phase 2, open-label study to evaluate the safety, tolerability, and PK of ataluren in 6 male children with nonsense mutation Duchenne muscular dystrophy (nmDMD) ≥6 months to <2 years of age.

Subjects received 3 times daily for 24 weeks orally administered ataluren 10, 10, 20 mg/kg (morning, midday, and evening dose, respectively).

6.1. Methods – analysis of data submitted

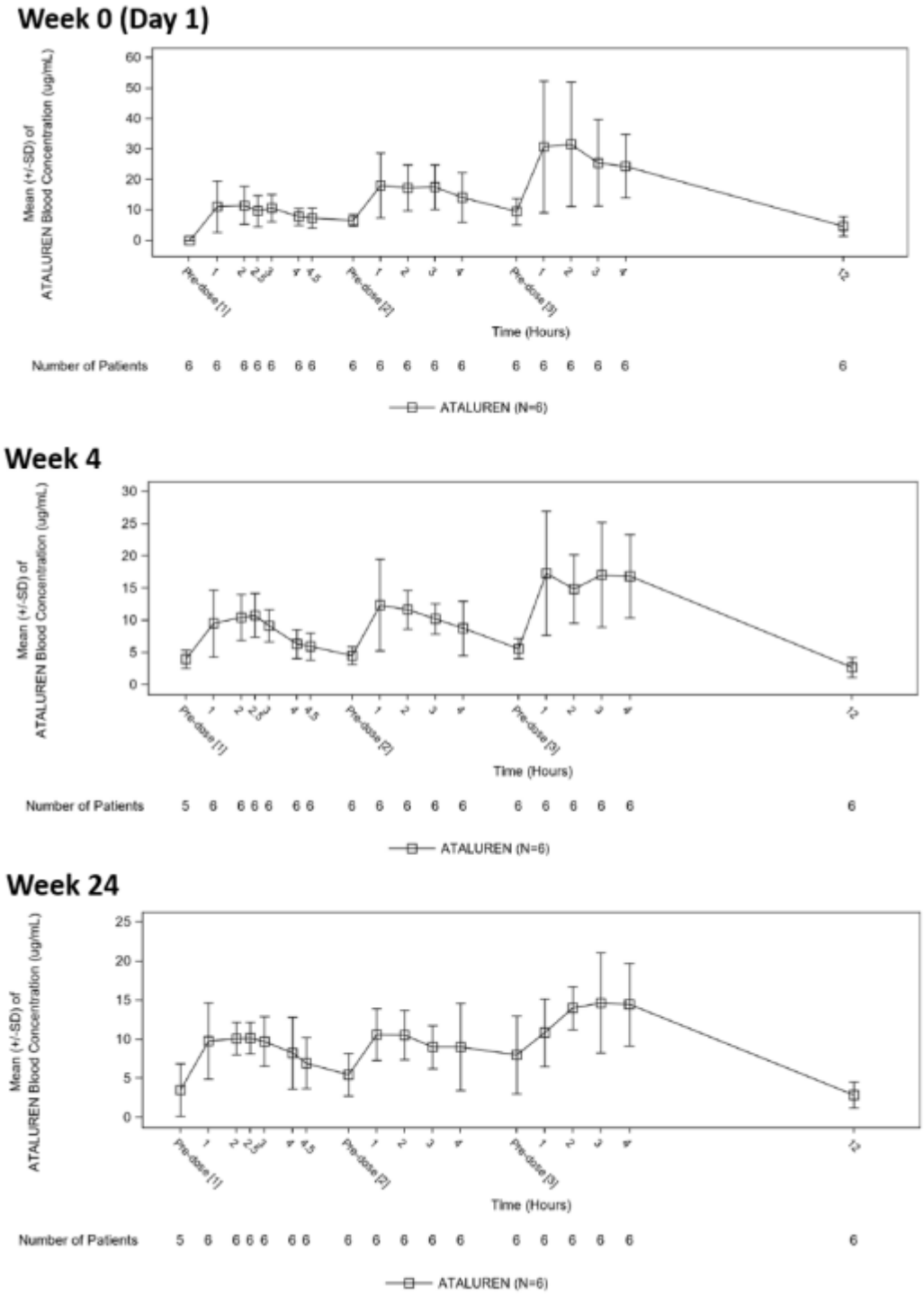
Blood samples for the measurement of ataluren levels and PK assessments were drawn using the volumetric absorptive microsampling method at baseline (Visit 2), Week 4 (Visit 3), and Week 24 (Visit 5; end of treatment/early termination) for evaluation using a bioanalytical method (Module 2.7.1). Samples were drawn immediately predose and at 1, 2, 3, and 4 hours postdose following both the morning and midday doses and immediately predose and at 1, 2, 3, 4, and 12 (before the next day morning dose) hours postdose following the evening dose. In addition, blood sampling via venous draw was conducted at Visits 2, 3, and 5 for the assessment of blood/plasma partitioning.

All 6 participants enrolled were included in the PK analysis.

6.2. Results

Mean concentration-time profiles for ataluren in blood at Week 0 (Day 1), Week 4, and Week 24 are shown in Figure 1. The mean concentration-time curves of ataluren in blood follow a similar pattern at Weeks 0, 4, and 24.

Figure 1: Mean (±SD) Blood Concentrations of Ataluren by Week – Linear Scale (PK Population)



Abbreviations: BLQ, below the limit of quantitation; CSR, clinical study report; PK, pharmacokinetic; SD, standard deviation
[1] Predose of morning dose
[2] Predose of midday dose
[3] Predose of evening dose
Note: Concentration values reported as BLQ were set to zero.
Source: PTC124-GD-048-DMD CSR, Figure 14.2.1.1, Figure 14.2.1.2, and Figure 14.2.1.3

Ataluren PK parameters in blood following the morning dose at Weeks 0, 4, and 24 are presented in Table 1.

The accumulation ratios for area under the concentration-time curve from time zero to 24 hours after the morning dose (AUC0-24h) and maximum observed concentration at Week 4 were 0.633 and 1.18,

respectively, and at Week 24 were 0.542 and 1.08, respectively, indicating no apparent accumulation following treatment with orally administered ataluren 10, 10, 20 mg/kg.

Table 1: Summary of Mean (SD) Pharmacokinetic Parameters of Ataluren in Blood After the Morning Dose at Week 0 (Day 1), Week 4, and Week 24 (PK Population)

Parameter, Unit	Mean (SD)		
	Week 0 (Day 1) (Visit 2) (N=6)	Week 4 (Visit 3) (N=6)	Week 24 (Visit 5) (N=6)
C_{trough}, µg/mL	NA	3.96 (1.39)[a]	3.48 (3.36)[a]
C_{max}, µg/mL[b]	13.7 (7.55)	12.6 (3.58)	12.6 (3.64)
T_{max}, h[b,c]	1.48 (0.95-3.12)	2.03 (0.92-3.02)	2.08 (1.00-4.13)
$AUC_{0-\tau}$, h•µg/mL[b]	NC[d]	46.7 (9.33)[e]	NC[d]
AUC_{0-24}, h•µg/mL	339 (159)[a]	201 (38.0)[e]	167 (23.8)[f]
CL/F, L/h[b]	NC[d]	2.16 (0.639)[e]	NC[d]
$T_{1/2}$, h[b]	NC[d]	1.58 (0.196)[g]	NC[d]
Accumulation ratio - C_{max}[b]	NA	1.18 (0.662)	1.08 (0.430)
Accumulation ratio – AUC_{0-24}	NA	0.633 (0.0868)[g]	0.542 (0.0355)[g]

Abbreviations: AUC0-τ, area under the concentration-time curve of the dosing interval; AUC0-24h, area under the concentration-time curve from time zero to 24 hours after the morning dose; CL/F, apparent oral clearance; C_{max}, maximum observed concentration; CSR, clinical study report; C_{trough}, trough concentration (concentration prior to the morning dose); N, number of participants; NA, not applicable; NC, not calculated; PK, pharmacokinetic; SD, standard deviation; T1/2, apparent terminal elimination half-life; T_{max}, time to maximum observed concentration
a N=5.
b Data reported from the dosing interval of 0-6 hours following the morning dose and prior to the midday dose. c Median (minimum, maximum).
d Parameter not calculated due to rules stating that the linear regression of concentration in the logarithmic scale versus time must be performed using at least 3 data points spanning 1.5 T1/2 and adjusted R2 must be >0.8. e N=3.
f N=4.
g N=2.

When corrected for blood/plasma partitioning, ataluren steady-state exposure and PK parameters in participants with nmDMD ≥6 months to <2 years of age were generally consistent with those observed in plasma from older nmDMD patients (≥2 years of age) (Table 2).

Table 2: Cross-Study Comparison of PK Parameters in Participants With nmDMD

Study ID	Study 048		Study 030[a]	Study 004[b]
Age range (years)	0.6-1.9		2-4	6-12
Dose (mg/kg)	10/10/20		10/10/20	10/10/20
N	6		14	20
Matrix	Blood		Plasma	Plasma
Timepoint	Week 4	Week 24	Week 4	Week 4
Mean (SD) PK Parameters				
C_{trough}, µg/mL	3.96 (1.39)[c] [6.58 in plasma]	3.48 (3.36)[c] [5.78 in plasma]	1.93 (1.24)	5.99 (4.00)[d]
C_{2h}, µg/mL	10.4 (3.58) [17.3 in plasma]	10.1 (2.08) [16.8 in plasma]	9.53 (5.03)	11.8 (4.75)
AUC_{0-24h}, h•µg/mL	201 (38.0)[e] [334 in plasma]	167 (23.8)[f] [277 in plasma]	NA	244 (88.2)

Abbreviations: AUC0-24h, area under the concentration-time curve from time zero to 24 hours after the morning dose; C_{2h}, concentration at 2 hours after the morning dose; CSR, clinical study report; C_{trough}, trough concentration (concentration prior to the morning dose); N, number of participants; NA, not applicable; nmDMD, nonsense mutation Duchenne muscular dystrophy; PD, pharmacodynamics; PK, pharmacokinetics; SD, standard deviation
a PTC124-GD-030-DMD (Study 030) was a Phase 2, multiple-dose, open-label study to evaluate the safety, PK, and PD of ataluren in patients aged ≥2 to <5 years with nmDMD. The study included a 4-week screening period, a 4-week treatment period to evaluate

safety and PK, a 48-week extension period, and a 4-week follow-up period (60 weeks total). The PK evaluation was conducted using a sparse sampling strategy (predose and 1, 2, 4, 6, 8, and 10 hours after the morning dose) at Day 1 and Day 28 in the first 4-week treatment period.
b PTC124-GD-004-DMD (Study 004) was a Phase 2a, multicentre, open-label, sequential dose-ranging, challenge-dechallenge study to evaluate the clinical activity, safety, and PK of ataluren in 38 male children and adolescents with nmDMD aged 5 to 17 years (20 participants 6 to 12 years of age received ataluren 10/10/20 mg/kg). Plasma samples for PK determinations were obtained on Days 1 and 27 predose and at 1, 2, 3, and 4 hours after the morning dose.
c N=5 (predose sample missed in 1 participant)
d N=19 (predose sample missed in 1 participant)
e N=3 (predose sample missed in 1 participant and insufficient terminal phase data in 2 participants)
f N=4 (predose sample missed in 1 participant and insufficient terminal phase data in 1 participant)
Note: Mean plasma equivalent parameters in Study 048 were derived using blood:plasma ratio (□~0.602)

Discussion

The proposed changes to section 5.2 of the SmPC are not agreed. The MAH has merged data from two clinical studies, while the data should be presented separately. Study 030 had greater numbers of subjects included and an extrapolation was considered possible. For the current study in nmDMD subjects between 6 months and 2 years of age the data are rather limited (n=6). Moreover, the statement "*age adjusted dosing is not required*" should be removed for patients aged six months to 2 years. The proposed text is a dose recommendation and 1) Section 5.2 is not the appropriate place for a dose recommendation this should be done in SmPC section 4.2 the posology, and more important 2) a dose recommendation should not be included if the population is not included in the indication.

For the study description of study 048, the number of subjects should be included with the mean age and the range (minimum age, and upper age) to provide context to the treating physician on the available data.

7. Clinical Safety aspects

Study 048 also assessed the safety and tolerability of ataluren exposure in 6 male subjects with nmDMD aged ≥6 months to <2 years of age treated 3 times daily for 24 weeks with orally administered ataluren 10, 10, 20 mg/kg (morning, midday, and evening dose, respectively).

All 6 participants completed the 24-week treatment period and rolled over to the long-term open-label safety study for follow-up of at least 52 weeks from the date of first administration of ataluren.

7.1. Methods – analysis of data submitted

The 6 participants received ataluren 10, 10, 20 mg/kg (morning, midday, and evening dose, respectively) for durations of 162, 163, 169, 169, 169, and 174 days.

7.2. Results

Treatment-emergent adverse events (TEAEs) were experienced by 5 (83.3%) participants (Table 3). A total of 18 TEAEs were reported in 5 participants overall (Listing 16.2.7.1).

A total of 2 (33.3%) participants experienced TEAEs that were mild in severity, and 3 (50.0%) participants experienced TEAEs that were moderate in severity. There were no TEAEs classified as severe (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 or higher).

There were no TEAEs during the study that were considered possibly or probably related to the study drug. There were no serious TEAEs or TEAEs leading to discontinuation or death.

Table 3. Overview of Treatment-Emergent Adverse Events (Safety Population)

Category	Ataluren 10, 10, 20 mg/kg (N=6) n (%)
Participants with any TEAEs	5 (83.3)
Participants with any serious TEAEs	0
Participants with any TEAEs leading to death	0
Participants with any TEAEs classified as CTCAE Grade 3 or higher	0
Participants with any study drug related TEAEs	0
Participants with any TEAEs leading to study drug withdrawal	0
Participants with any TEAEs by maximum severity	
Mild	2 (33.3)
Moderate	3 (50.0)
Severe	0
Life Threatening	0
Fatal	0

Abbreviations: %, percentage of participants with an adverse event (n/N×100); AE, adverse event; CSR, clinical study report; CTCAE, Common Terminology Criteria for Adverse Events; n, number of participants with an adverse event; N, number of participants; TEAE, treatment-emergent adverse event
Note: A TEAE was defined as an AE that occurred or worsened while on ataluren (on or after first dose of ataluren) up to 4 weeks after the last dose.
A study drug related TEAE was defined as a TEAE with a relationship of possibly or probably related to the study drug, as determined by the investigator.
For severity, if multiple grades of AE occur in the same participant, then that participant was counted into the worst severity.

7.2.1. Display of Adverse Events

The most common TEAEs were infections and infestations: gastroenteritis was experienced by 2 (33.3%) participants and body tinea, enterovirus infection, hand-foot-and-mouth disease, otitis media, upper respiratory tract infection, and viral upper respiratory tract infection were experienced by 1 participant each (Table 4).

Gastroenteritis and diarrhoea (2 [33.3%] participants each) were the only TEAEs reported in more than 1 participant.

The AEs were consistent with the age of participants and their underlying condition.

Table 4. Treatment-Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Ataluren 10, 10, 20 mg/kg (N=6) n (%)
Subjects with any TEAEs	5 (83.3)
Infections and infestations	4 (66.7)
Gastroenteritis	2 (33.3)
Body tinea	1 (16.7)
Enterovirus infection	1 (16.7)
Hand-foot-and-mouth disease	1 (16.7)
Otitis media	1 (16.7)
Upper respiratory tract infection	1 (16.7)
Viral upper respiratory tract infection	1 (16.7)
Gastrointestinal disorders	3 (50.0)
Diarrhoea	2 (33.3)
Teething	1 (16.7)
Vomiting	1 (16.7)
Skin and subcutaneous tissue disorders	2 (33.3)
Eczema	1 (16.7)
Skin plaque	1 (16.7)
Urticaria	1 (16.7)
Injury, poisoning, and procedural complications	1 (16.7)
Fall	1 (16.7)
General disorders and administration site conditions	1 (16.7)
Pyrexia	1 (16.7)
Metabolism and nutrition disorders	1 (16.7)
Decreased appetite	1 (16.7)

Abbreviations: %, percentage of participants with an adverse event (n/N×100); CSR, clinical study report; MedDRA, Medical Dictionary for Regulatory Activities; n, number of participants with an adverse event; N, number of participants; TEAE, treatment-emergent adverse event
Note: Adverse events were coded using the MedDRA Version 26.0.
A TEAE was defined as an adverse event that occurred or worsened while on ataluren (on or after first dose of ataluren) up to 4 weeks after the last dose.

7.2.2. Analysis of Adverse Events

A total of 3 (50.0%) participants experienced TEAEs that were moderate in severity. One participant experienced a TEAE of otitis media, 1 participant experienced TEAEs of urticaria and decreased appetite, and 1 participant experienced TEAEs of teething, skin plaque, eczema, body tinea, and enterovirus infection (Listing 16.2.7.1). All other TEAEs were mild. There were no TEAEs classified as CTCAE Grade 3 or higher.

All TEAEs were transient and had resolved with the exception of teething, eczema, and body tinea in 1 participant (Listing 16.2.7.1).

There were no TEAEs during the study that were considered possibly or probably related to the study drug, and there were no serious TEAEs or TEAEs leading to discontinuation or death (Table 14.3.1.1). No participants had dose-limiting toxicities.

There were no deaths, serious TEAEs, or other significant AEs in this study (PTC124-GD-048-DMD CSR, Table 14.3.1.1 and Listing 16.2.7.1).

7.2.3. Clinical Laboratory Evaluation

There were no clinically meaningful trends in clinical laboratory values during the study related to chemistry parameters, haematology parameters, and urinalysis parameters. There were no TEAEs associated with any clinical laboratory value.

The mean (standard deviation [SD]) baseline value for creatine kinase was 24901.5 (10069.12) U/L (n=6). The mean (SD) change from baseline at Week 4 (n=4), Week 12 (n=5), and Week 24 (n=6) was -4358.5 (10283.15), -6946.6 (7363.86), and -1537.8 (11057.99) U/L, respectively.

7.3. Discussion

The safety analysis following 24 weeks of treatment did not reveal unexpected findings. The results were in line with the known effects of ataluren and with frequent occurring childhood illness as was also seen in the children aged 2-5 years of age. However, 6 patients ranging from 7 months to 23 months with a mean age of 14 months is considered too limited to allow the conclusions drawn by the MAH. The proposed changes to section 4.2, 4.8 and 5.1 are therefore not agreed. The SmPC should adequately present the limited data to inform treating physicians. See section 9 for further details.

8. PRAC advice

Not applicable

9. Changes to the Product Information

As part of this variation, the Applicant requested updates in section(s) 4.2, 4.8, 5.1 and 5.2 of the SmPC (see below). The Package Leaflet (PL) is proposed to be updated accordingly.

The proposed updates are not agreed. See below for Rapporteurs comment on each section.

SmPC section	**Proposed wording**	**Rapporteurs comment**
Section 4.2 Posology and Method of Administration	~~"The safety and efficacy of Translarna in children <12kg and aged 6 months to 2 years have not yet been established. No data are available.~~ Translarna is not recommended for use in patients aged <2 years due to insufficient data on safety and efficacy (see section 4.8 and 5.1)	The proposed changes are not agreed. Previous wording should be reinstalled. Reference to section 4.8 and 5.1 is considered a disguised extension of the indication. The text should be changed to read: *"The safety and efficacy of Translarna in children <12kg and ~~aged 6 months to~~ <2 years have not been established. Currently available data are described ~~Limited data are available (see~~ in section 4.8 and 5.2."*
Section 4.8 Undesirable effects	"In an open-label study to evaluate safety and PK in patients ≥6 months to <2 years of age (n=6), safety data from 24 weeks of therapy showed that study drug is well tolerated with no adverse effects specific to the younger population. There are no safety concerns or safety signals from the study, and none of the adverse events were considered treatment related. The only events that occurred in more than 1 patient were gastroenteritis and diarrhoea, which occurred in 2 patients (33.3%) each.	The proposed wording of the study description is not agreed. Inclusion of most common adverse events based on frequencies are not truly representative as adverse events occurring once contribute to 16.7% of the cases. The relevance of this information is questioned.

	These higher frequency events are considered unrelated. The study safety results did not alter or change the existing safety profile of ataluren.	The following could be acceptable: *The safety and PK of ataluren was evaluated in a 24 week open-label study in 6 nmDMD patients aged ≥ 6 months to <2 years of age (mean age xxx; range xx - xx). In this study, the safety profile was comparable to that seen in nmDMD patients aged >2 years of age, even though the number of patients is small.*
Section 5.1 Pharmacodynamic Properties	"The safety, pharmacokinetics and exploratory effectiveness of Translarna were assessed in ~~an~~ **two** open-label studies~~y~~ in children between **6 months** and 5 years of age with nmDMD. **Study 30 (PTC124-GD-030-DMD) assessed Translarna in children aged 2 to 5 years old, with** the efficacy of T~~ranslarna in children aged 2-5 years has been~~ established on extrapolation from patients aged >5 years, **and Study 48 (PTC124-GD-048-DMD) assessed Translarna in children aged 6 months to 2 years old."** ~~The European Medicines Agency has deferred the obligation to submit the results of studies with ataluren in one subset of the paediatric population aged 6 months to less than 2 years old in nmDMD, as per Paediatric Investigation Plan (PIP) decision in the granted indication (see section 4.2 for information on paediatric use).~~	The proposed alteration to merge the study description in children <5 years of age is not agreed. Only the wording of the study in children 2-5 years may remain. The wording as proposed by the MAH may be perceived by the reader that efficacy data is available for the nmDMD patients aged *≥6 months to <2 years* of age efficacy. Furthermore, as no specific efficacy or pharmacodynamic outcomes are included, no additional information for section 5.1 relevant for prescribers is provided. A study description in 4.8 and 5.2 may be acceptable, provided these are done as indicated. The removal of the PIP obligation is agreed. The following text can be included in section 5.1: A study is conducted in children aged 6 months to 2 years in accordance with the Paediatric Investigation Plan (PIP) as requested by the European Medicine Agency. This study included PK and safety assessments (see section 4.8 and 5.2)

Section 5.2 Pharmacokinetic Properties	Based on data from subjects ranging in age from **6 months** ~~2 years~~ to 5 years, there is no apparent effect of age on ataluren plasma exposure. Age-adjusted dosing is not required. The pharmacokinetics of ataluren has been evaluated in **DMD patients 6 months and above receiving the 10/10/20 mg/kg dose regimen. Ataluren plasma concentrations were maintained consistently across age groups at steady state.** ~~Study PTC124-GD-030 over a duration of 4 weeks. Ataluren plasma concentrations in patients from 2 to less than 5 years old were consistent with those seen in patients above the age of 5 years receiving the 10/10/20 mg/kg dose regimen.~~"	The MAH has merged data from two clinical studies. This is not agreed. The data should be presented separately. Study 030 had greater numbers of subjects included and an extrapolation was considered possible. For the current study, the data is limited. Moreover, the statement "*age adjusted dosing is not required*" should be removed for patients aged 6 months to 2 years. The proposed text is a dose recommendation and 1) Section 5.2 is not the appropriate place for a dose recommendation this should be done in SmPC section 4.2 the posology and 2) a dose recommendation should not be included if the population is not included in the indication. For the study description of study 048, the number of subjects should be included with the mean age and the range (minimum age, and upper age). In addition comparative relevant PK data should be included in this section (e.g., AUC and C_{trough}) for the three age groups for which there are PK data available (6 months to 2 years, 2 years to 5 years and 6 years to 17 years) in order to provide useful information to the prescribers.

Package leaflet

2. What you need to know before you take Translarna
Children and adolescents
Do not give this medicine to children under the age of 2 years or weighing less than 12 kg, ~~as it has not been tested in this group of patient~~ **as there is not enough data in this group of patients.**

(bold=new ~~removed~~**)**

Please find below the table including all changes in sections 4.2, 4.8, 5.1 and 5.2 that are supported on the data submitted.

SmPC section	**Wording**

<table>
<tr><td>Section 4.2 Posology and Method of Administration</td><td><u>The safety and efficacy of Translarna in children <12kg and ~~aged 6 months to~~ <2 years have not been established. Currently available data are described ~~Limited data are available (see~~ in section 4.8 and 5.2)</u></td></tr>
<tr><td>Section 4.8 Undesirable effects</td><td>The safety and PK of ataluren was evaluated in a 24-week open-label study in 6 nmDMD patients aged ≥ 6 months to < 2 years of age (mean age was 14 months, age range 7 – 23 months). In this study, the safety profile was comparable to that seen in nmDMD patients aged >2 years of age, even though the number of patients is small.</td></tr>
<tr><td>Section 5.1 Pharmacodynamic Properties</td><td>~~The European Medicines Agency has deferred the obligation to submit the results of studies with ataluren in one subset of the paediatric population aged 6 months to less than 2 years old in nmDMD, as per Paediatric Investigation Plan (PIP) decision in the granted indication (see section 4.2 for information on paediatric use).~~

A study is conducted in children aged 6 months to 2 years in accordance with the Paediatric Investigation Plan (PIP) as requested by the European Medicine Agency. This study included PK and safety assessments (see section 4.8 and 5.2)</td></tr>
<tr><td>Section 5.2 Pharmacokinetic Properties</td><td>The pharmacokinetics of ataluren has been evaluated in study PTC124 GD-048 over a duration of 24 weeks. Ataluren plasma concentrations were determined in 6 patients from 7 to 23 months old (mean 14 months).

Steady state plasma concentrations from samples collected before dosing (Ctrough) and 2 hours after the morning dose (C2h) are presented for three paediatric age groups in Table 2. The mean concentrations for all three age groups are within the concentration range in which ataluren treatment benefit has been demonstrated.

Table 5: Steady-State Ataluren Concentrations by Paediatric Age Group
<table>
<tr><td></td><td>Study 048 (n=6)</td><td>Study 030 (n=14)</td><td>Study 007 (n=57)</td></tr>
<tr><td>Nominal age group</td><td>6 months to <2 years</td><td>2 to 5 years</td><td>6 to 17 years</td></tr>
<tr><td>Subject age (years), mean (range)</td><td>1.15 (0.58 to 1.92)</td><td>3.4 (2 to 4)</td><td>8.8 (5 to 20)</td></tr>
<tr><td>Ataluren Dose (mg/kg)</td><td>10/10/20</td><td>10/10/20</td><td>10/10/20</td></tr>
<tr><td>Matrix</td><td>Blood</td><td>Plasma</td><td>Plasma</td></tr>
<tr><td>Timepoint</td><td>Week 4</td><td>Week 4</td><td>Week 48</td></tr>
<tr><td colspan="4">Mean (SD) Pharmacokinetic Parameters</td></tr>
<tr><td>Ctrough, µg/mL</td><td>3.96 (1.39)a [6.58 in plasma]</td><td>1.93 (1.24)</td><td>4.5 (3.44)</td></tr>
<tr><td>C2h, µg/mL</td><td>10.4 (3.58) [17.3 in plasma]</td><td>9.53 (5.03)</td><td>12.5 (6.71)</td></tr>
</table>
Abbreviations: C_{2h}, concentration at 2 hours after the morning dose; C_{trough}, trough concentration (concentration before the morning dose); SD, standard deviation

a N=5 (predose sample missed in 1 participant</td></tr>
</table>

The finally proposed changes to SmPC sections 4.2, 4.8, 5.1 and 5.2 included in the above table are supported by the data submitted and could have been agreed. However, in view of the CHMP opinion for the annual renewal EMEA/H/C/002720/R/071 adopted on 24 January 2024 to not renew the marketing authorisation of Translarna, as a favourable benefit-risk balance has not been confirmed in the treatment of ambulant patients with nmDMD aged 2 years or older, no changes to the marketing authorisation can be recommended.

10. Assessment of the responses to the 2nd request for supplementary information

10.1. Major objections

None.

10.2. Other concerns

Clinical aspects

Question 1

The proposed changes are not agreed. Data from 6 patients is too limited to allow for meaningful information for the prescribers. The current SmPC text is sufficient. An update to section 4.8 and 5.2 may be acceptable, provided the amendments are made as indicated by the Rapporteur.

Summary of the MAH's response

Text has been proposed according to the Agency's proposal.

Assessment of the MAH's response

As a result of this variation, section(s) 4.2, 4.8, 5.1 and 5.2 of the SmPC are being updated (see below). The Package Leaflet (PL) is updated accordingly.

The proposed updates are not agreed. See below for Rapporteurs comment on each section. The MAH has generally amended the SmPC as indicated by the Rapporteur. However, the age is indicated as years, while months is more appropriate for this age range. This should be corrected.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance

SmPC section	Initial Proposed wording	Rapporteurs comment 1st round	MAH response 1st RfSI	Rapporteurs Assessment 1st RfSI
Section 4.2 Posology and Method of Administration	~~"The safety and efficacy of Translarna in children <12kg and aged 6 months to 2 years have not yet been established. No data are available.~~ Translarna is not recommended for use in patients aged <2 years due to insufficient data on safety and efficacy (see section 4.8 and 5.1)	The proposed changes are not agreed. Previous wording should be reinstalled. Reference to section 4.8 and 5.1 is considered a disguised extension of the indication. The last part can be changed to Limited data are available with a reference to section 4.8 and 5.2. More specifically, the text should read: *"The safety and efficacy of Translarna in children <12kg and ~~aged 6 months to~~ <2 years have not been established. Currently available data are described ~~Limited data are available (see~~ in section 4.8 and 5.2)"*	The safety and efficacy of Translarna in children <12kg and ~~aged 6 months to~~ <2 years have not been established. Currently available data are described ~~Limited data are available (see~~ in section 4.8 and 5.2)	The changes are in line with the text indicated by the Rapporteur. Issues solved
Section 4.8 Undesirable effects	"In an open-label study to evaluate safety and PK in patients ≥6 months to <2 years of age (n=6), safety data from 24 weeks of therapy showed that study	The proposed wording of the study description is not agreed. Inclusion of most common adverse events based on	*The safety and PK of ataluren was evaluated in a 24 week open-label study in 6 nmDMD patients aged ≥6 months to <2 years of age (mean age **was 1.15**; age range **0.58 – 1.92) years**. In this study, the safety profile was comparable to that seen in nmDMD patients*	The MAH has generally changed the wording as indicated by the Rapporteur. However, the actual age of patient included in

	drug is well tolerated with no adverse effects specific to the younger population. There are no safety concerns or safety signals from the study, and none of the adverse events were considered treatment related. The only events that occurred in more than 1 patient were gastroenteritis and diarrhoea, which occurred in 2 patients (33.3%) each. These higher frequency events are considered unrelated. The study safety results did not alter or change the existing safety profile of ataluren.	frequencies are not truly representative as adverse events occurring once contribute to 16.7% of the cases. The relevance of this information is questioned. The following could be acceptable: *The safety and PK of ataluren was evaluated in a 24 week open-label study in 6 nmDMD patients aged ≥6 months to <2 years of age (mean age xxx; range xx - xx). In this study, the safety profile was comparable to that seen in nmDMD patients aged >2years of age, even though the number of patients is small.*	*aged >2years of age, even though the number of patients is small.*	study is written in years instead of months. This is not agreed. Indicating the age in months corresponds to the use in clinical practice (i.e. 7 months instead of 0.58 years). The MAH should change the mean age and age range expressed in years to the closest month, i.e. meant age of 13months and age range of 7 to 23months
Section 5.1 Pharmacodynamic Properties	"The safety, pharmacokinetics and exploratory effectiveness of Translarna were assessed in ~~an~~ **two** open-label studies~~y~~ in children between **6 months** and 5 years of age with nmDMD. **Study 30 (PTC124-GD-030-DMD) assessed Translarna in**	The proposed alteration to merge the study description in children <5years of age is not agreed. Only the wording of the study in children 2-5 years may remain. The wording as proposed by the MAH may be perceived by	Text reverted back to original one, as proposed by the Agency A study is conducted in children aged 6 months to 2 years in accordance with the Paediatric Investigation Plan (PIP) as requested by the European Medicine Agency. This study included	The changes are agreed

	children aged 2 to 5 years old, with the efficacy of T~~ranslarna in children aged 2-5 years has been~~ established on extrapolation from patients aged >5 years, **and Study 48 (PTC124-GD-048-DMD) assessed Translarna in children aged 6 months to 2 years old."** ~~The European Medicines Agency has deferred the obligation to submit the results of studies with ataluren in one subset of the paediatric population aged 6 months to less than 2 years old in nmDMD, as per Paediatric Investigation Plan (PIP) decision in the granted indication (see section 4.2 for information on paediatric use).~~	the reader that efficacy data is available for the nmDMD patients aged *≥6 months to <2 years* of age efficacy. Furthermore, no specific efficacy or pharmacodynamic outcomes are included, therefor no added information for prescribers is provided. A study description in 4.8 and 5.2 may be acceptable, provided these are done as indicated. The removal of the pip obligation is agreed. A study is conducted in children aged 6 months to 2 years in accordance with the Paediatric Investigation Plan (PIP) as requested by the European Medicine Agency. This study included PK and safety assessments (see section 4.8 and 5.2)	PK and safety assessments (see section 4.8 and 5.2)	
Section 5.2 Pharmacokinetic Properties	Based on data from subjects ranging in age from **6 months** ~~2 years~~ to 5 years,	The MAH has merged data from 2 clinical studies. This is not agreed. The data	The pharmacokinetics of ataluren has been evaluated in study PTC124 GD-048 over a duration of 24 weeks. Ataluren plasma	In the study description the age should be mentioned

<table>
<tr>
<td></td>
<td>there is no apparent effect of age on ataluren plasma exposure. Age-adjusted dosing is not required.

The pharmacokinetics of ataluren has been evaluated in <u>DMD patients 6 months and above receiving the 10/10/20 mg/kg dose regimen. Ataluren plasma concentrations were maintained consistently across age groups at steady state.</u> <s>study PTC124-GD-030 over a duration of 4 weeks. Ataluren plasma concentrations in patients from 2 to less than 5 years old were consistent with those seen in patients above the age of 5 years receiving the 10/10/20 mg/kg dose regimen.</s>”</td>
<td>should be presented separately. Study 030 had greater numbers of subjects included and an extrapolation was considered possible. For the current study, the data is limited. Moreover, the statement “age adjusted dosing is not required” should be removed for patients aged 6months to 2 years. The proposed text is a dose recommendation and 1) Section 5.2 is not the appropriate place for a dose recommendation this should be done in SmPC section 4.2 the posology and 2) a dose recommendation should not be included if the population is not included in the indication.

For the study description of study 048, the number of subjects should be included with the mean age and the range (minimum age, and upper age). <u>In addition</u> comparative relevant pk</td>
<td>concentrations were determined in 6 patients from 0.58 to 1.92 years old (mean 1.15 years).

Steady state plasma concentrations from samples collected before dosing (Ctrough) and 2 hours after the morning dose (C2h) are presented for three paediatric age groups in Table 2. The mean concentrations for all three age groups are within the concentration range in which ataluren treatment benefit has been demonstrated.

Table 6: Steady-State Ataluren Concentrations by Paediatric Age Group
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</table>
</td>
<td>in months rather than years for children <2years of age. See comments regarding section 4.8.</td>
</tr>
</table>

		data should be included in this section (e.g., AUC and C_{trough}) for the 3 groups of age for which there are pk data available (6 months to 2 years, 2 years to 5 years and 6 years to 17 years) in order to provide useful information to the prescribers. ~~to provide context to the treating physician on the available data~~.	<table><tr><td>C2h, µg/mL</td><td>10.4 (3.58) [17.3 in plasma]</td><td>9.53 (5.03)</td><td>12.5 (6.71)</td></tr></table> Abbreviations: C2h, concentration at 2 hours after the morning dose; Ctrough, trough concentration (concentration before the morning dose); SD, standard deviation a N=5 (predose sample missed in 1 participant	

11. Request for supplementary information

11.1. Major Objections

None.

11.2. Other concerns

Clinical aspects

1. The MAH has generally amended the SmPC as indicated by the Rapporteur. However, the age is indicated as years, while months is more appropriate for this age range. This should be corrected.

12. Assessment of the responses to the request for supplementary information

12.1. Major objections

None.

12.2. Other concerns

Clinical aspects

Question 1
The MAH has generally amended the SmPC as indicated by the Rapporteur. However, the age is indicated as years, while months is more appropriate for this age range. This should be corrected.

Summary of the MAH's response
The MAH has updated the text in SmPC section 4.8 and 5.2 to include age as months instead of years:
Section 4.8
The safety and PK of ataluren was evaluated in a 24-week open-label study in 6 nmDMD patients aged ⩾ 6 months to < 2 years of age ***(mean age was 14 months, age range 7 – 23 months).*** *In this study, the safety profile was comparable to that seen in nmDMD patients aged >2 years of age, even though the number of patients is small.*
[…]
Section 5.2
The pharmacokinetics of ataluren has been evaluated in study PTC124 GD-048 over a duration of 24 weeks. Ataluren plasma concentrations were determined in 6 patients from ***7 to 23 months old (mean 14 months).***

Assessment of the MAH's response

Age is indicated as months which is considered more appropriate for this age range. The proposed updates are agreed.

Conclusion

☒Overall conclusion and impact on benefit-risk balance has/have been updated accordingly

☐No need to update overall conclusion and impact on benefit-risk balance