EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 May 2018
EMA/431114/2018
Committee for Medicinal Products for Human Use (CHMP)

CHMP extension of indication variation assessment report

Invented name: Translarna

International non-proprietary name: ataluren

Procedure No. EMEA/H/C/002720/II/0037

Marketing authorisation holder (MAH): PTC Therapeutics International Limited

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1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, PTC Therapeutics International Limited submitted to the European Medicines Agency on 30 August 2017 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include a new population (children from 2 to less than 5 years of age) for Translarna; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and RMP (version 7.1) is updated in accordance.

The variation proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Translarna was designated as an orphan medicinal product EU/3/05/278 on 27 May 2005. Translarna was designated as an orphan medicinal product in the following indication: treatment of Duchenne Muscular Dystrophy.

The new indication, which is the subject of this application, falls within the above mentioned orphan designation.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included EMA Decisions P/83/2009 issued on 15 May 2009, P/123/2010 issued on 28 July 2010, P/0069/2012 issued on 4 April 2012, P/0202/2012 issued on 30 August 2012, P/0132/2015 issued on 12 June 2015, P/0002/2016 issued on 14 January 2016, P/0122/2016 issued on 29 April 2016 and P/0283/2016 issued on 4 November 2016 on the granting of a (product-specific) waiver and a class waiver.

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Protocol assistance

The MAH did receive Protocol Assistance at the CHMP in January 2017 (EMEA/H/SA/918/3/2016/PA/SME/II).

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: N/A

Timetable	Planned dates	Actual dates
Start of procedure:	16 September 2017	16 September 2017
CHMP Co-Rapporteur Assessment Report	10 November 2017	n/a
CHMP Rapporteur Assessment Report	10 November 2017	14 November 2017
PRAC Rapporteur Assessment Report	17 November 2017	16 November 2017
PRAC members comments	22 November 2017	22 November 2017
Updated PRAC Rapporteur Assessment Report	23 November 2017	n/a
PRAC Outcome	30 November 2017	30 November 2017
CHMP members comments	4 December 2017	4 December 2017
Updated CHMP Rapporteur(s) (Joint) Assessment Report	7 December 2017	8 December 2017
Request for Supplementary Information (RSI)	14 December 2017	14 December 2017
Submission	22 December 2017	22 December 2017
Procedure Restart	25 December 2017	25 December 2017
CHMP Rapporteur Assessment Report	23 January 2018	24 January 2018
PRAC Rapporteur Assessment Report	26 January 2018	29 January 2018
PRAC members comments	31 January 2018	31 January 2018
Updated PRAC Rapporteur Assessment Report	01 February 2018	n/a
PRAC Outcome	08 February 2018	08 February 2018
CHMP members comments	12 February 2018	12 February 2018
Updated CHMP Rapporteur(s)Assessment Report	15 February 2018	n/a
2nd Request for Supplementary Information	22 February 2018	22 February 2018
Submission	23 February 2018	26 February 2018
Procedure Restart	26 February 2018	26 February 2018
CHMP Rapporteur Assessment Report	26 March 2018	29 March 2018
PRAC Rapporteur Assessment Report	28 March 2018	29 March 2018
PRAC members comments	04 April 2018	04 April 2018
Updated PRAC Rapporteur Assessment Report	05 April 2018	n/a
PRAC Outcome	12 April 2018	12 April 2018
CHMP members comments	16 April 2018	16 April 2018
Updated CHMP Rapporteur(s)Assessment Report	19 April 2018	20 April 2018
3rd Request for Supplementary Information	26 April 2018	26 April 2018

Timetable	Planned dates	Actual dates
Submission	03 May 2018	03 May 2018
Procedure Restart	04 May 2018	04 May 2018
CHMP Rapporteur Assessment Report	16 May 2018	17 May 2018
CHMP members comments	22 May 2018	22 May 2018
Updated CHMP Rapporteur(s)Assessment Report	24 May 2018	25 May 2018
Opinion	31 May 2018	31 May 2018

2. Scientific discussion

2.1. Introduction

Ataluren is conditionally approved in the European Union (EU) since 31 July 2014 for the following indication:
"Treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older."

Ataluren is a first-in-class oral orphan drug designed to enable ribosomal read through of premature stop codons, resulting in the formation of a full-length functional protein in patients with nonsense mutation genetic disorders. Ataluren is available in granules for oral suspension in sachets of different strength (125 mg, 250 mg, and 1000 mg).

On 31 July 2014, the European Commission issued a conditional Marketing Authorisation (MA) for ataluren. This implied that the Marketing Authorisation Holder (MAH) had to complete ongoing studies, and to conduct (PTC124-GD-020-DMD [Study 020]) as a Specific Obligation, in order to confirm that the risk-benefit balance is positive and to provide additional data. These data formed the basis of the renewal of the conditional MA. The benefit/risk was re-evaluated during the renewal procedure in 2016. In November 2016, the CHMP concluded that the conditional marketing authorisation could be renewed considering that the totality of the clinical data available continued to support the positive B/R of ataluren 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 a specific obligation to answer the remaining uncertainties in the context of conditional marketing authorisation.

In the current application the MAH proposes to lower the age limit. Originally the MAH proposed to perform clinical studies in children from 6 months – 5 years. However, the PDCO concluded that due to possible different PK and safety concerns, the clinical studies should be split into two different groups; 6 months - 2 years and 2 - 5years. Taken the concerns from the PDCO into account the MAH has performed a clinical study in 2-5 years. The current proposal is to change the indication to patients ≥ 2years because, from a disease pathology perspective, that treatment for DMD would be most effective when initiated as early as possible in the course of the disease.

In summary, the current submission concerns the request for the extension of indication to include a new population (children from 2 to less than 5 years of age) for Translarna 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 proposed recommended dose and schedule of ataluren in children 2-5 years of age is the same as that approved for children ≥ 5 years of age, i.e. 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).

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application, which is considered acceptable.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trial supporting this application was performed in accordance with GCP as claimed by the applicant.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.3.2. Pharmacokinetics

The basis of this submission is Study PTC124-GD-030-DMD (study 030) - a multiple-dose, open-label study evaluating the safety and PK of ataluren in patients aged ≥ 2 to <5 years old with nmDMD for a period of 28 days (4 weeks). In order to collect longer-term safety and some efficacy functional endpoint information (i.e, TFTs and NSAA assessments), a 48-week extension phase was added.

The role of the pharmacokinetic data in this application is to show comparable ataluren pharmacokinetics in children 2-5 years with the pharmacokinetics in older children in order to bridge the efficacy and safety from children ≥ 5 years of age to children 2-5 years of age. For that purpose an updated popPK analysis was presented.

Study design

Study 030 was a Phase 2, multiple-dose, open-label study evaluating the safety and PK 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 pharmacokinetics, a 48-week extension period, and a 4-week follow-up period (60 weeks total). The PK evaluation was conducted in the first 4 weeks (day 1 and day 28), which also included safety assessments.

The results from a population PK simulation supported that a study design of 12 patients with 7-point sampling after the morning dose (sample size and sparse sampling strategy) would provide adequate data to assess PK in children with nmDMD aged ≥2 to <5 years. This design was agreed upon by the

Paediatric Committee (PDCO) as well as the Modelling and Simulation Working Group (MSWG) through a Scientific Advice Working Party (SAWP) consultation (EMA/CHMP/SAWP/34612/2017).

Patients were administered ataluren 3-times per day (10, 10, 20 mg/kg). The drug product lots used were the granules for oral suspension formulation, which is the same as the marketed formulation in the European Union (EU), and the one used in Phase 2b PTC124-GD-007-DMD and Phase 3 PTC124-GD-020-DMD studies.

Blood samples were collected pre-dose and at 1, 2, 4, 6, 8, and 10 hours post morning dose on Days 1 and 28 to provide information about Day 1 and steady-state ataluren plasma concentrations.

Conventional PK parameters of ataluren on Day 1 and 28 were derived by non-compartmental analysis (NCA), using Phoenix WinNonlin® v6.4 software (Certara, LP, Princeton, NJ, USA). PK parameters such as AUC_{0-6}, AUC_{0-10}, C_{max} (0-6 hr), $C_{trough@6h}$, t_{max} (0-6 hr) were calculated as appropriate for Day 1 and Day 28. The accumulation ratio (AR) on Day 28, AR(AUC) and AR(C_{max}) were also calculated.

Using the nmDMD Relative F Model (2017) with pooled data from healthy volunteers, patients with nmDMD, and patients from Study 030, ataluren plasma exposures and other PK parameters such as AUC_{0-24}, C_{max}, and C_{ave}, CL/F, and V_{ss}/F were estimated and compared with those estimated for nmDMD patients aged ≥5 years who received the same dosing regimen (studies PTC124-GD-004-DMD and PTC124-GD-007-DMD) (as discussed in the population PK modelling below).

Population PK analysis

The population pharmacokinetic (PK) model for ataluren has been refined over time based upon the availability of data from various studies. The data from a recently completed study in patients with nmDMD aged 2-5 years (Study 030) and from study 026 (interaction study with rifampin) in healthy volunteers were pooled with data from healthy volunteers (studies 001 and 002) and patients with nmDMD who had participated in Studies 004/004e and 007/007e, which had been used to previously develop a population PK model for ataluren (ICPD 00321-2). The population PK model has been refined using the pooled data. In addition, several activities were performed to comply with scientific advice that was provided by the SAWP in January 2017 (EMA/CHMP/SAWP/34612/2017). The primary goals of the analysis were as follows:
☐ Refine the previous population PK model to incorporate the data from younger patients (ages 2 – 5),

☐ Confirm the driver for the decrease in ataluren exposure with time (i.e., time-dependent relative bioavailability or time-dependent clearance),

☐ Conduct a covariate analysis to identify any other patient characteristics that are associated with the inter-individual variability in ataluren PK (including confirmation of the previously derived coefficients governing the relationship between body weight and clearance or volume), and

☐ Refine the presentation of prediction-corrected visual predictive check plots to mimic those most commonly presented in the literature

In the above mentioned 6 studies, ataluren was administered orally with doses ranging from 3 to 200 mg/kg. PK data from 76 healthy volunteers and 226 nmDMD patients were included in the model. PK data from study 15, 24 Japanese and 24 non-Japanese healthy volunteers administered a single dose 5, 10 or 20 mg/kg of ataluren granules formulation were used as external validation.

PK model structure

The PK structural model used rich data from healthy volunteers. The primary structural model was a two-compartment model with first-order absorption and linear elimination. The impact of food on both

the rate (ka) and extent (relative bioavailability or F) of absorption, as well as the impact of diurnal variation (e.g., impact of morning vs. evening dosing) on CL/F, were assessed a priori as part of the structural PK model.

The structural model parameters were then re-estimated after pooling the data from the healthy volunteers, nmDMD patients and cystic fibrosis patients to allow for testing for potential differences between the three populations. Absorption rate dependent on dose and relative bioavailability dependent on time with time), formulation (day 1), or disease state (at steady-state) were included into the model.

This population PK (popPK) model was the base model and refined with the pooled data from the 6 studies in healthy volunteers (N= and nmDMD patients. PK data from cystic fibrosis patients were not longer included in order to enrich the PK dataset for nmDMD patients.

The decrease in ataluren exposure over time was evaluated by time-dependent relative bioavailability and a time dependent clearance model. A model using allometric scaling i.e. 0.75 or clearance and 1.0 for volume of the central compartment, was tested but found unstable.

Covariate analysis

After updating the Expanded Model (2013/2014) using the additional PK data, a formal covariate analysis was initiated in NONMEM using stepwise forward selection. Continuous descriptors that were evaluated for their potential to explain a portion of the inter-individual variability in PK parameters included age in years, weight in kg, height in cm, BSA in m^2, BMI in kg/m^2, and calculated CLcr in mL/min/1.73 m^2. Categorical covariates that were evaluated include sex, race, patient status (healthy subjects, nmDMD), formulation, and potentially study if warranted.

Stepwise forward (6.635 change in the MVOF (α = 0.01, 1 df) and backward elimination (at least a 10.83 increase in the MVOF (α = 0.001, 1 df) was applied to select the covariates.

Model Evaluation

Model evaluation was assessed by graphical evaluation of standard goodness-of-fit plots, as well as plots of the observed and predicted concentration-time profiles, examination of the predicted parameter estimates and their precision (standard error of the mean) and comparison of these values to historical results. A prediction-corrected visual predictive check (pcVPC) was also used to assess the ability of the fixed and random effects components of the final PK model to adequately describe the observed ataluren concentration-time data.

The fit of the time-dependent relative bioavailability and a time dependent clearance model were compared by graphical evaluation of standard goodness-of-fit plots, examination of the predicted parameter estimates and their precision (standard error of the mean). Further the models were used to predict the plasma concentration-time profiles for the subjects from study 026 when ataluren was given in combination with rifampin.

Generation of PK Exposure Measures

The individual, Bayesian post-hoc PK parameters from the most appropriate model were used to simulate plasma ataluren concentration-time profiles in order to estimate Day 1 and steady-state exposure (Cmax, AUC0-24, and Cave) for the patients from Study 030 (≥2 and <5 years age) included in the analysis as well as the patients from Study 004 and 007 (>5 years age) who received the same dose regimen as those in Study 030 (10/10/20 mg/kg). Note that, due to the sparse sampling employed in Study 030, the simulated profile contained augmented times in order to provide a more relevant comparison to the profile from patients in Study 004, who were sampled relatively intensively on Day 1 and at steady-state (e.g., Day 28).

Model-Based Simulations

The final population PK model will be used as the basis for model-based simulations of PK results from Study PTC124-GD-030-DMD (Study 030), a Phase 2, open-label study of the safety, pharmacokinetics, and pharmacodynamics of ataluren in patients with nmDMD aged two to five years. The objective of the simulation exercises will be to assess the expected exposure to ataluren in children aged two to five years of age receiving the labelled daily dose of 40mg/kg/day (as administered in 3 doses of 10/10/20 mg/kg) to assure that exposure is consistent across the age continuum.

POPPK ANALYSIS RESULTS

Parameter estimates and associated standard errors from the fit of the nmDMD Relative F Model (2017) to the data from healthy subjects and nmDMD patients are provided in Table 1. The parameters relative bioavailability at steady-state (FSS) for healthy subjects (0.568 or 56.8%) and kdec (0.0113 hr-1) were fixed to the final estimate from the healthy subject models in the previous report. An attempt was made to fit the value for TSTART but the resultant value was consistent with the previous estimate of 60 hr and was estimated with poor precision. Thus, this parameter was also fixed. Similarly, the values for F0 and FSS for the POS and granules formulations were fixed to the prior estimates. The final estimate of F0 was 0.642 (64.2%) for the POS formulation and 0.898 (89.8%) for the granules formulation. The estimate of FSS was 0.568 (56.8%) for healthy subjects, and was slightly lower (FSS = 0.414 or 41.4%) for nmDMD patients.

Table 1 Parameter estimates and associated standard errors from the nmDMD

Parameter	Final estimate	%SEM
Absorption rate-constant, k_a (hr^{-1})		
k_a (for a 70 kg subject given 20 mg/kg)	0.932	9.72
k_a-Dose power	-0.501	0.776
Clearance, CL/F (L/hr)		
CL/F coefficient for evening doses and a 70 kg adult	3.83	3.29
CL/F-Weight power	0.580	6.92
Proportional shift in CL/F for morning or midday doses	0.493	3.94
Central volume of distribution, V_c/F (L)		
V_c/F coefficient (for a 70 kg subject)	25.9	7.39
V_c/F-Weight power	0.308	26
Peripheral volume of distribution, V_p/F (L)	0.425	13.5
Distribution clearance, CL_d/F (L/hr)	0.0189	7.13
Initial relative bioavailability, F_0		
F_0 for PIB formulation	1	FIXED[a]
F_0 for POS formulation	0.642	FIXED[a]
F_0 for Granule formulation	0.898	FIXED[a]
Relative bioavailability at steady-state F_{SS}		
F_{SS} for healthy subjects	0.568	FIXED[a]
F_{SS} for nmDMD patients	0.414	FIXED[a]
First-order rate constant for decline in F_0 to F_{SS}, k_{dec} (hr^{-1})	0.0113	FIXED[a]
Delay in the onset of the decline in F_0 to F_{SS}, T_{START} (hr)	60	FIXED[b]
$\omega^2_{CL/F}$	0.0741 (27.2 %CV)	11.5
$\omega^2_{Vc/F}$	0.267 (51.6 %CV)	11.2
ω^2_{ka}	0.836 (91.4 %CV)	22.6
$\omega^2_{Vp/F}$	0.161 (40.1 %CV)	28.3
ω^2_{Fss}	0.0616 (24.8% CV)	23.4
Residual variability (σ^2)		
Log error (SD) for healthy subjects	0.172 (0.415)	1.1
Log error (SD) for nmDMD patients	0.349 (0.591)	0.914

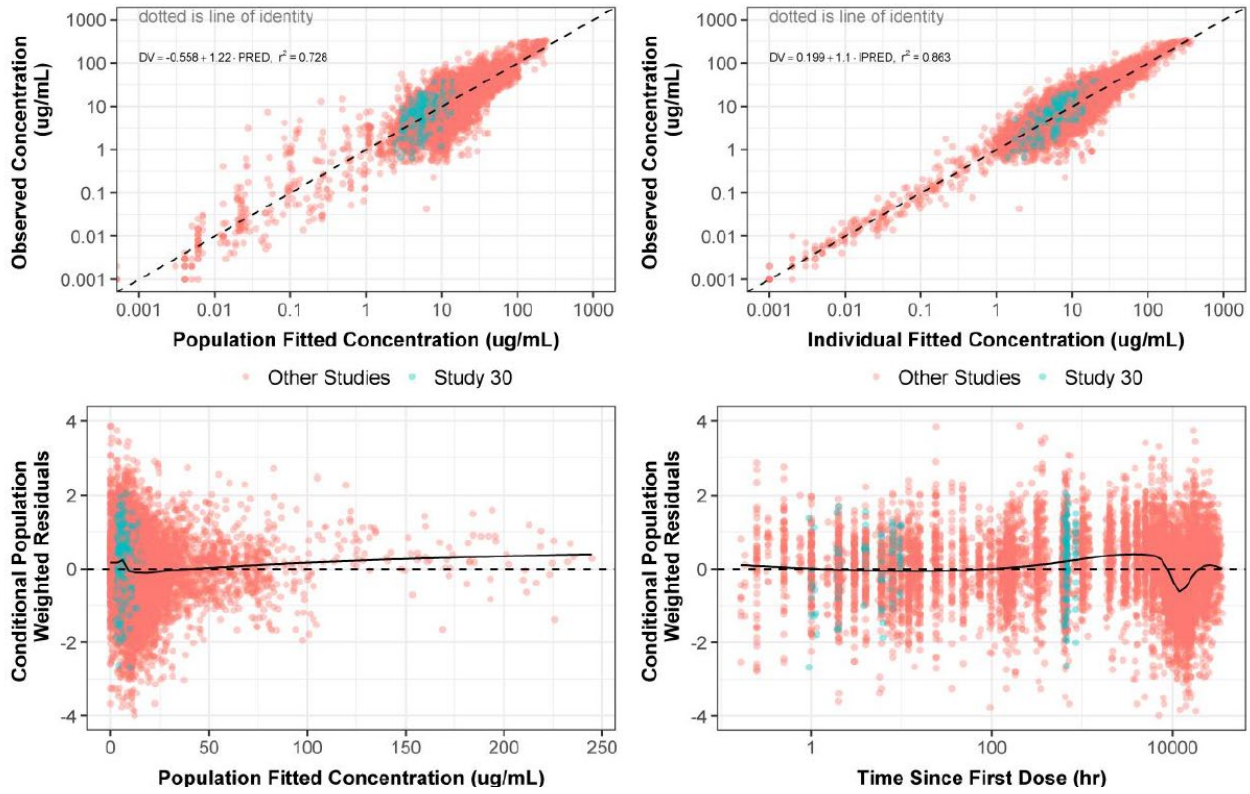
Note: Abbreviations are provided in the Abbreviation Listing.
a. These parameters were fixed to the final estimates from the previous analysis [1].
b. This parameter was initially fit to the updated dataset. The resultant estimate was nearly identical to the previous estimate but was estimated with poor precision. Thus the parameter value was fixed to the final estimate from the previous analysis [1].

Below are equations describing the population mean relationships for ka, CL/F, Vc/F and relative bioavailability (F) of the time-dependent relative bioavailability model.

- k_a (hr^{-1}) = $0.878 \bullet (Dose/1400)^{-0.485}$
- CL/F (L/hr) = $3.81 \bullet (WTKG/70)^{0.589} \bullet (1+0.445 \cdot AM)$ where AM = 0 for an evening dose and 1 for a morning or midday dose
- V_c/F (L/hr) = $26.5 \bullet (WTKG/70)^{0.359}$
- Relative bioavailability (F) at any given time:
  - When TSFD < T_{START}, $F = F_0$;
  - When TSFD ≥ T_{START}, $F = F_{SS} - (F_{SS} - F_0) \bullet \exp^{(-kdec*(TSFD-T_{START}))}$

The primary goodness-of-fit plots for the fit of the existing population PK model to the updated dataset are provided in Figure 1.

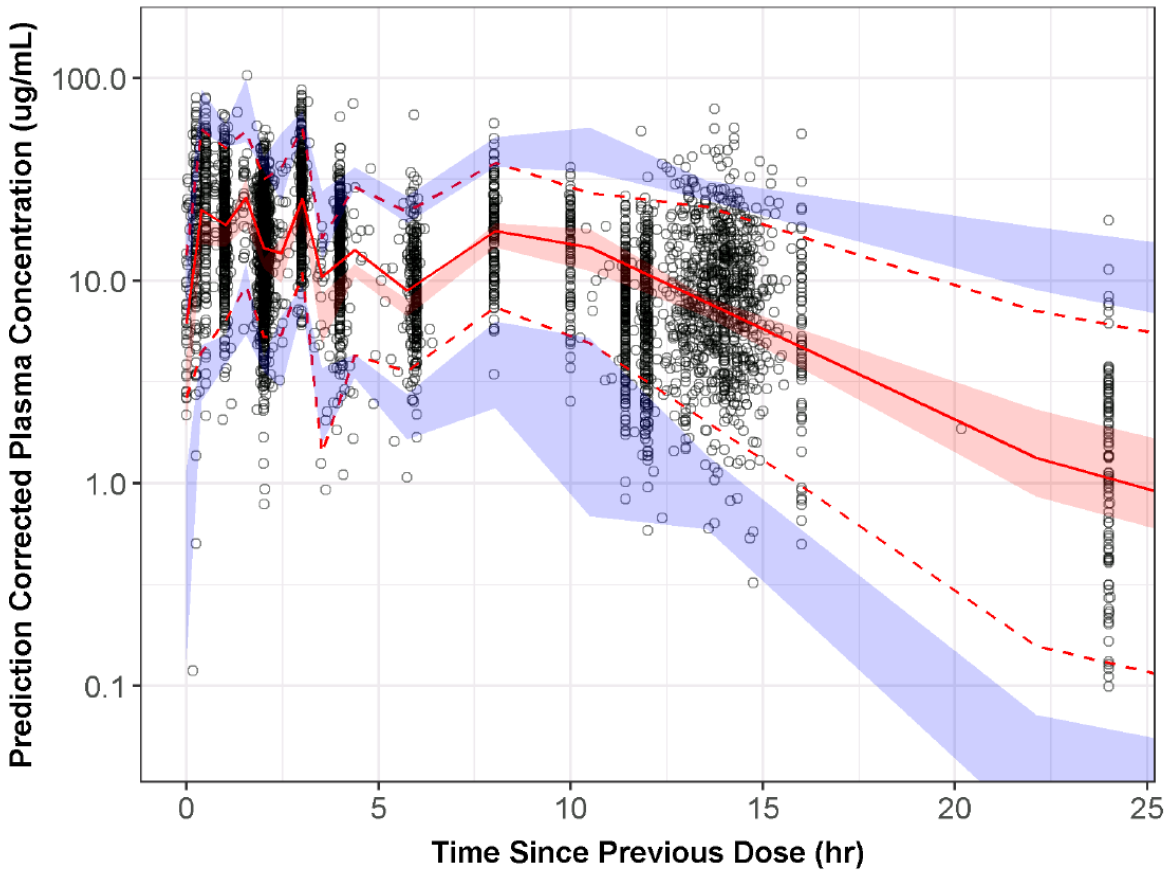
Figure 1 Goodness-of-fit plots for the application of the nmDMD Relative F Model (2017) to the pooled dataset



The pc-VPC plots are provided in Figure 2**,**Figure 3**,** and Figure 4 for all subjects/patients, nmDMD patients only, and Study 030 patients only, respectively.

Note that the data from the extension studies (004e and 007e) were not included in the pc-VPC plots due to the extremely long time of treatment, which resulted in file size issues. However, these plots are considered sufficient for assessing the predictive ability of the model at steady state as all patients received at least 28 days of treatment.

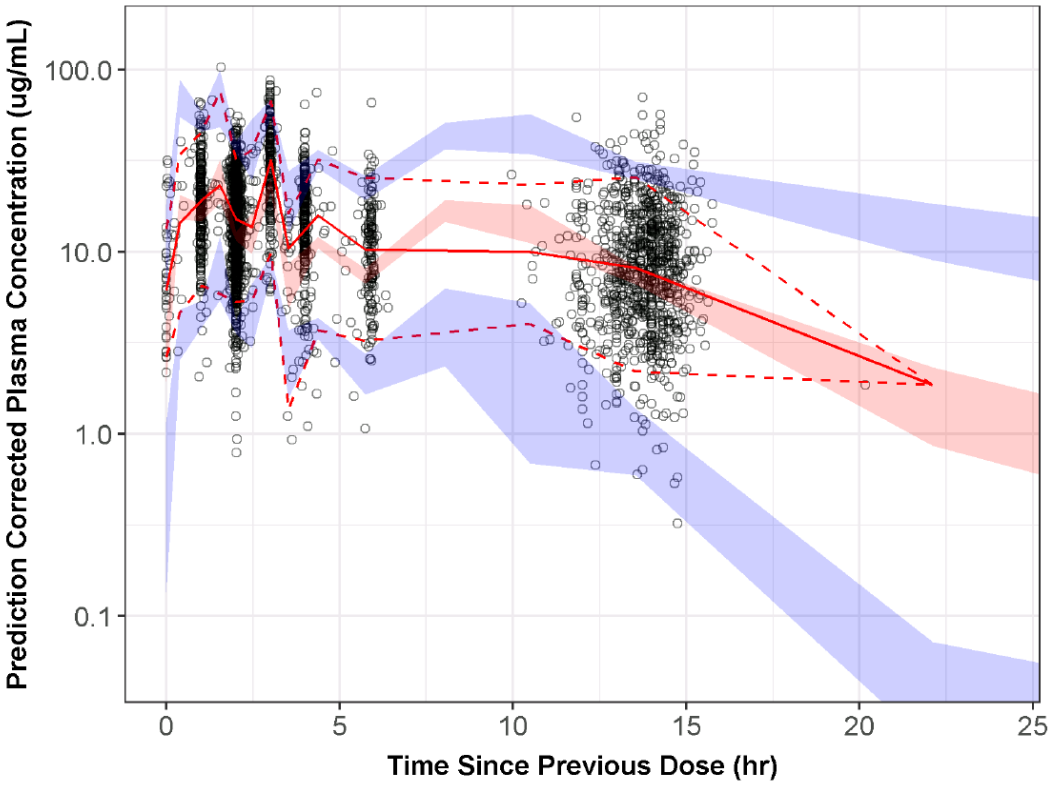
Figure 2 Prediction-corrected visual predictive check plot for the final population PK model (time-dependent relative bioavailability) using data from healthy volunteers and patients with nmDMD



Note: Abbreviations are provided in the Abbreviation Listing.

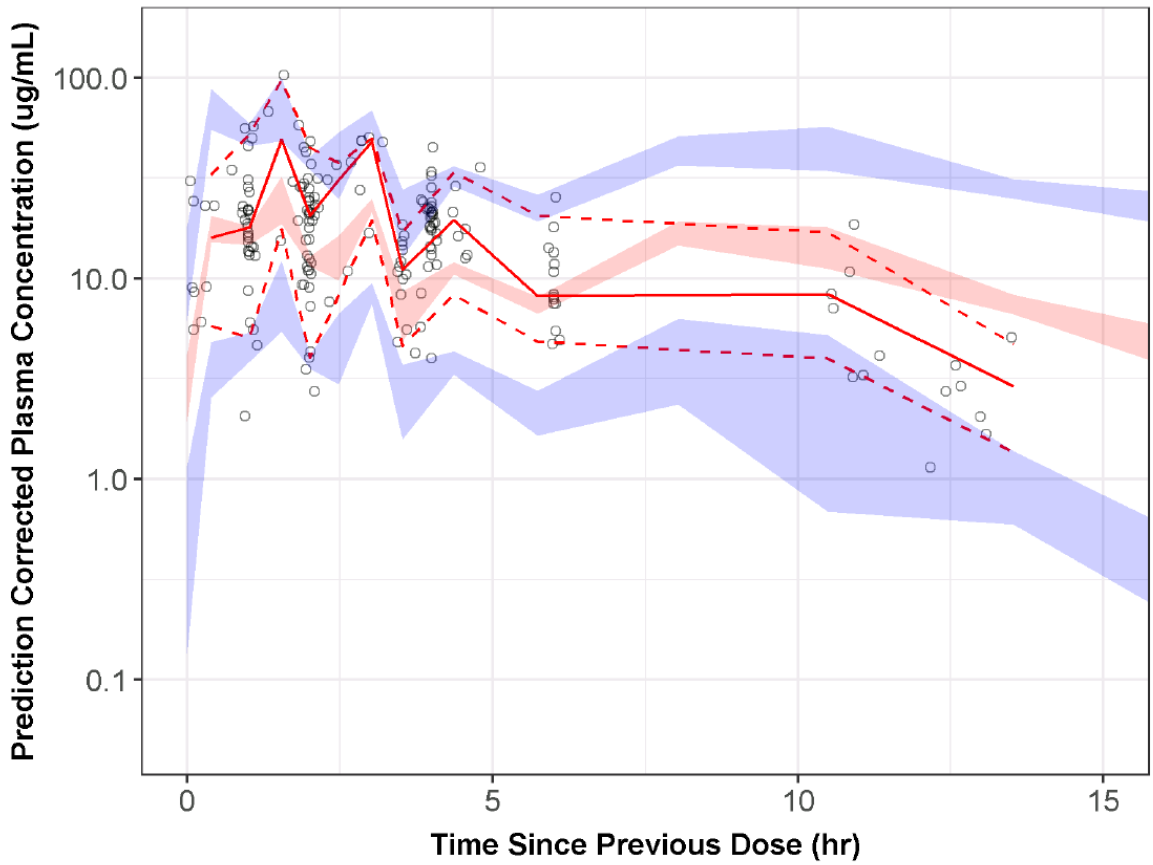
Plot definition: open circles show the prediction-corrected observed ataluren concentrations with the median and 5th/95th percentiles of the prediction-corrected observed data shown in solid and dashed red lines, respectively. The red shaded region is the 90% prediction interval for the median simulated prediction-corrected concentrations and the blue shaded regions are the 90% prediction interval for the 5th and 95th percentiles of the prediction-corrected simulated data.

Figure 3 Prediction-corrected visual predictive check plot for the final population PK model (time-dependent relative bioavailability) using data from patients with nmDMD only



Note: Abbreviations are provided in the Abbreviation Listing.
Plot definition: open circles show the prediction-corrected observed ataluren concentrations with the median and 5th/95th percentiles of the prediction-corrected observed data shown in solid and dashed red lines, respectively. The red shaded region is the 90% prediction interval for the median simulated prediction-corrected concentrations and the blue shaded regions are the 90% prediction interval for the 5th and 95th percentiles of the prediction-corrected simulated data.

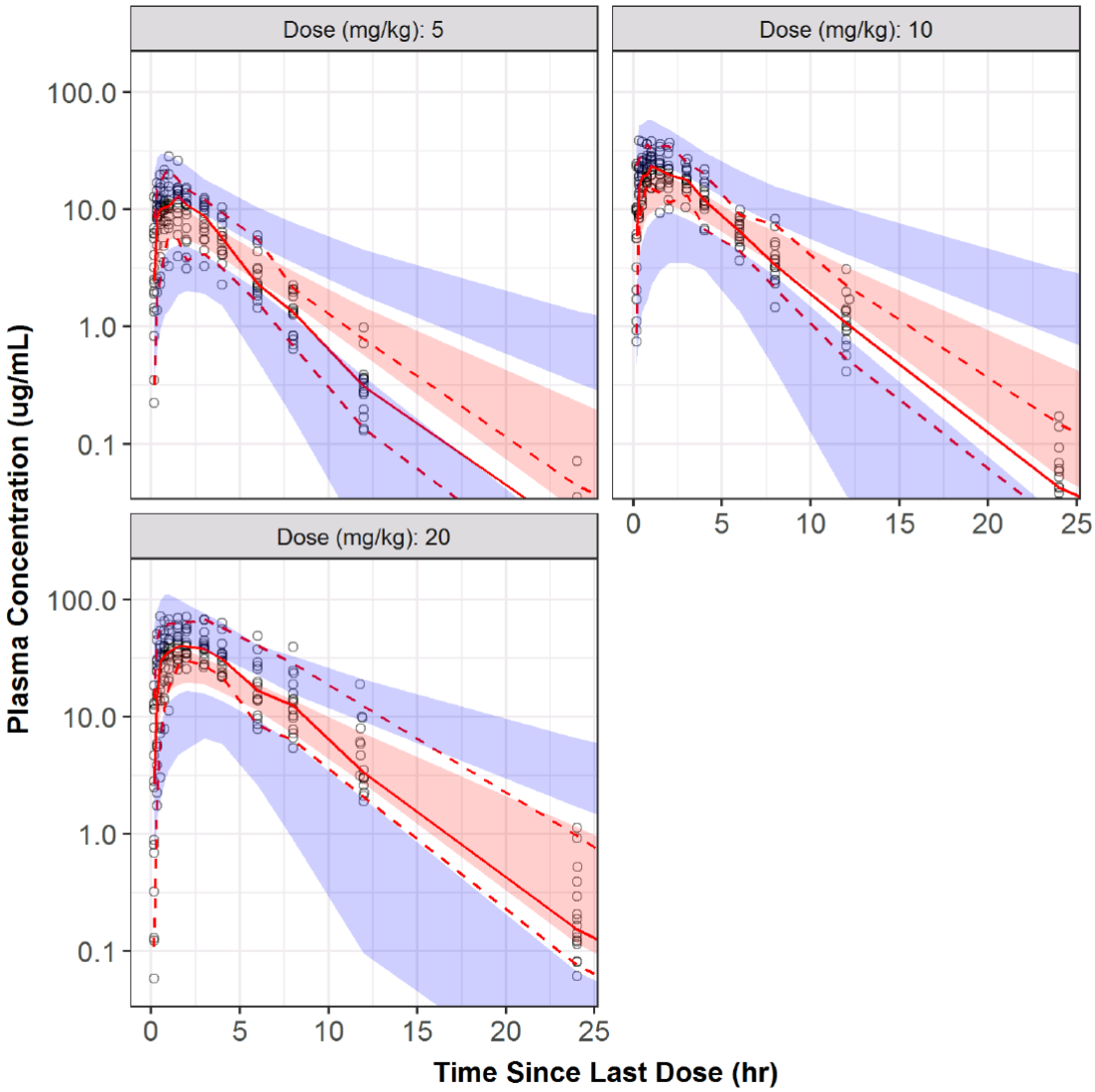
Figure 4 Prediction-corrected visual predictive check plot for the final population PK model (time-dependent relative bioavailability) using data from patients with nmDMD enrolled in Study 030 only



Note: Abbreviations are provided in the Abbreviation Listing.
Plot definition: open circles show the prediction-corrected observed ataluren concentrations with the median and 5th/95th percentiles of the prediction-corrected observed data shown in solid and dashed red lines, respectively. The red shaded region is the 90% prediction interval for the median simulated prediction-corrected concentrations and the blue shaded regions are the 90% prediction interval for the 5th and 95th percentiles of the prediction-corrected simulated data.

External Validation using single-dose adult data in order to assess the ability of the nmDMD Relative F Model (2017) to capture single-dose data obtained from adults that were not included in the development of the model, a traditional visual predictive check (VPC) was constructed. This involved the replication of the Study 015 dataset 500 times in order to simulate concentration-time profiles for the 48 subjects while incorporating the inter-individual and residual variability from the final population PK model. The resultant VPC plots are provided in Figure 5.

Figure 5 Visual predictive check plots for the application of the nmDMD Relative F Model (2017) to the data from Study 015



Note: Abbreviations are provided in the Abbreviation Listing.
Plot definition: open circles show the observed ataluren concentrations with the median and 5th/95th percentiles of the observed data shown in solid and dashed red lines, respectively. The red shaded region is the 90% prediction interval for the median simulated concentrations and the blue shaded regions are the 90% prediction interval for the 5th and 95th percentiles of the simulated data.

Bioanalytical assay

The quantitation of ataluren in human plasma in the clinical studies was carried out using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays with high sensitivity and specificity, as previously described for the MAA procedure. The validation studies demonstrated that the procedures for the determination of ataluren in human K3EDTA and K2EDTA plasma are accurate, and reproducible. Tabulated below is the summary of validated bioanalytical method used for study 030. The method was partially revalidated to reduce the sample aliquot volume from 0.100 mL to 0.0250 mL in support of pediatric studies.

Table 2 Assay Validation Parameters for Bioanalytical Method Used to Assay Plasma Samples Collected in Ataluren Clinical Study, PTC124-GD-030-DMD

Parameter	inVentiv Health
	Plasma ataluren
Validation Reports	10189.070215[a]
Method	LC-MS/MS
Regression/ weighting	Linear, $1/x^2$
IS	ataluren-D4
Sensitivity range	0.5–200 µg/mL
LLOQ	0.5 µg/mL
Analyte recovery (mean)	35.5%[b]
IS recovery (mean)	33.4%[b]
Cal Std inter-assay precision (%CV)	3.75 to 6.05%
Cal Std inter-assay accuracy (%RE)	-2.20 to 6.00%
QC samples	0.500, 1.50, 20.0 and 150 µg/mL
QC intra-assay precision (%CV)	1.07 to 14.6%
QC intra-assay accuracy (%RE)	-12.2 to 12.6%
QC inter-assay precision (%CV)	1.32 to 13.6%
QC inter-assay accuracy (%RE)	-0.667 to 0.00%
Dilution linearity	10-fold (0.1 dilution)[c]
Freeze/thaw stability	4 cycles at -20°C
Benchtop stability	26 hours at ambient temperature
Refrigeration stability/Post- Preparative Stability	99 hours at 5°C
Long-term stability	1510 days at -20°C (K_2EDTA)[c]

[a] Partial validation

[b] Established during partial validation using TM.895 in inVentiv Report No. 5768.050709

[c] Established during partial validation using TM.895 in inVentiv Report No. 8458.073014

Abbreviations: CV = coefficient of variation; IS = internal standard; LC-MS/MS = liquid chromatography/tandem mass spectrometry; LLOQ = lower limit of quantitation; QC = quality control; RE = relative error

Study 030. Human plasma samples were received between August 31, 2016 and February 28, 2017. These included 195 samples for analysis and 166 duplicates (1 duplicate sample analyzed in place of primary sample since primary sample tube was empty). All study samples were received in acceptable condition, frozen on dry ice. Study samples, blanks, standards and QC samples were kept at approximately -20°C. The interval from first sample draw date to last analysis date was 233 days. Adequate long-term stability (1510 days) has been established to cover the clinical samples storage period (233 days). In study performance showed a precision of 5.6 to 7.9% and accuracy within -4.0

to -2.5 %. Incurred sample reanalysis showed that all values are within the reproducibility criteria of the reference value.

Results

Summary statistics of the demographic and clinical laboratory information for the patients from Study 030 are provided in Table 3 Summary statistics of the continuous demographic and clinical laboratory. The subjects from Study 030 were predominantly Caucasian (11/14, 78%); the remaining 3 patients were Asian.

Table 3 Summary statistics of the continuous demographic and clinical laboratory information for healthy subjects from Study 030

Variable	N	Mean (SD)	Median	Minimum	Maximum
Age (yr)	14	3.43 (0.756)	4.00	2.00	4.00
Weight (kg)	14	17.0 (3.26)	16.4	13.2	25.2
BSA (m^2)	14	0.671 (0.0734)	0.660	0.570	0.830
BMI (kg/m^2)	14	17.1 (2.22)	16.6	14.8	22.9
CLcr ($mL/min/1.73\ m^2$)[a, b]	14	196 (36.6)	201	127	247

Note: Abbreviations are provided in the Abbreviation Listing.

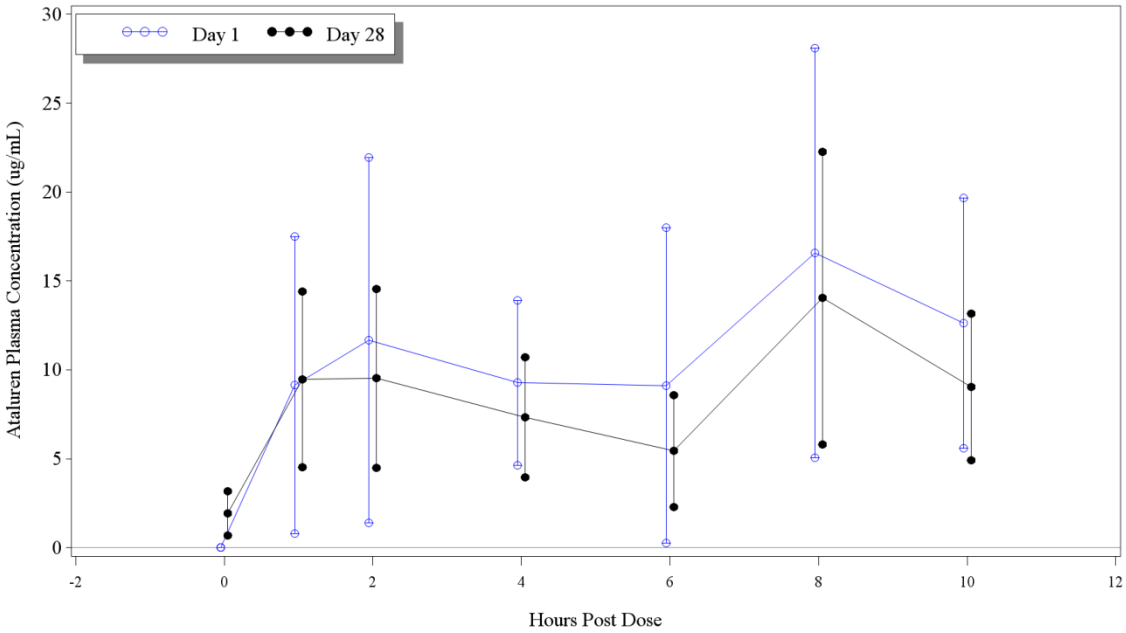
a. Calculated for adults ≥ 18 years of age using Cockcroft and Gault Formula after substituting IBW for WTKG if WTKG > IBW and then multiplying by BSA/1.73. To prevent unreasonable CLcr estimates in adults, a value of 0.7 was substituted for Scr for the calculation of CLcr if Scr < 0.7.

b. Calculated in pediatrics and adolescents < 18 years of age using revised Schwartz equation. To prevent unreasonable CLcr estimates in children, a value of 0.4 was substituted for Scr for the calculation of CLcr if Scr < 0.4.

PK analysis using NCA methods in patients ≥2 to <5 years of age

All 14 patients completed the PK portion of the study. Mean (SD) plasma ataluren concentration-time profiles at Day 1 and Day 28 are presented in Figure 6. The mean plasma concentration-time curves follow a similar pattern on Day 1 and Day 28. Peak concentrations are seen around 2 hours post the morning dose and 2 hours post the second dose for most patients. The second (midday) dose of ataluren was administered 6 hours after the first dose.

Figure 6 Mean (SD) Plasma Ataluren Concentration-Time Profiles Following Administration of Ataluren to Patients Aged ≥2 to <5 Years Old with nmDMD (N=14, Study 030)



Ataluren PK parameters are presented in Table 4. Mean [SD] AUC_{0-6}, AUC_{0-10}, and C_{max} (0-6 hrs) for Day 1 were 53.03 [30.18] hr*µg/mL, 101.64 [58.52] hr*µg/mL, and 15.95 [9.51] µg/mL, respectively. Mean [SD] AUC_{0-6}, AUC_{0-10}, and C_{max} (0-6hr) for Day 28 at steady state were 43.63 [14.65] hr*µg/mL, 82.13 [27.43] hr*µg/mL, and 12.54 [4.43] µg/mL, respectively. Median t_{max} (0-6 hr) was 3.97 hrs (1.92 to 6.02) on Day 1 and 2.00 hrs (1.00 to 6.05) on Day 28. The mean plasma concentration pre-dose (C_{0h}) at Day 28 was 1.929 µg/mL, and individual patient C_{0h} values on Day 28 ranged from 0.66 µg/mL to 5.29 µg/mL. The accumulation ratios for AUC_{0-6} and C_{max}(0-6 hrs) were 0.99 and 1.02, respectively, indicating no apparent drug accumulation up to 6 hours post the morning dose.

Table 4 Ataluren plasma pharmacokinetics in nmDMD patients 2-5 years of age using NCA (study 030)

	Dose (mg)*	AUC $_{0\text{-}6h}$ **(hr*µg/mL)**	AUC $_{0\text{-}10h}$ **(hr*µg/mL)**	Cmax$_{0\text{-}6h}$ **(µg/mL)**	C_{6h} **(µg/mL)**	Cpredose **(µg/mL)**	AUC $_{0\text{-}6h}$ **(hr*µg/mL)**	AUC $_{0\text{-}10h}$ **(hr*µg/mL)**	Cmax$_{0\text{-}6h}$ **(µg/mL)**	C_{6h} **(µg/mL)**	Accumlation ratio AUC0-6	Accumulation ratio Cmax
patient		Day 1				Day 28						
1	125	20.7	34.9	6.4	1.5	0.9	11.9	26.5	4.9	4.9	0.58	0.76
2	125	29.1	49.7	7.6	2.8	0.7	47.7	87.7	20.5	1.8	1.64	2.71
3	125	63.4	83.3	20.1	2.8	2.4	35.5	56.4	10.9	1.8	0.56	0.54
4	125	43.9	98.2	9.3	6.8	1.6	52.0	95.6	13.8	5.4	1.19	1.49
5	125	33.5	68.6	8.7	2.4	0.7	34.4	66.3	14.5	1.8	1.03	1.67
6	125	20.8	49.4	11.8	5.9	5.3	42.9	67.2	14.3	4.2	2.07	1.21
7	125	24.9	50.5	9.9	6.0	2.0	33.8	71.2	9.1	9.1	1.36	0.91
8	250	67.4	144.4	20.5	20.5	1.4	63.6	84.5	18.9	9.9	0.94	0.92
9	250	56.8	80.9	13.9	6.0	3.1	63.0	108.8	15.2	7.4	1.11	1.09
1	250	83.7	178.4	18.6	18.6	2.2	66.8	137.1	15.9	10.0	0.80	0.85
10	250	45.5	102.9	18.8	5.0	2.4	35.6	73.3	7.9	4.9	0.78	0.42
11	250	35.0	78.6	7.8	4.2	1.0	35.6	67.7	8.1	2.9	1.02	1.03
12	250	105.6	170.6	37.9	3.3	2.4	46.3	93.6	9.4	9.4	0.44	0.25
13	250	112.3	232.6	32	32	0.9	41.8	114.3	12.2	2.6	0.37	0.38
Mean		53.0	101.6	16.0	9.1	1.9	43.6	82.1	12.5	5.4	0.99	1.02
sd		30.2	58.5	9.5	8.9	1.2	14.7	27.4	4.4	3.2	0.47	0.64

*Patients <16.5kg were dosed 125 mg in morning and at midday, patients≥ 16.5 kg were dosed 250 mg in morning and at midday.

Table 5 Summary statistics of patient age and ataluren PK parameter and exposure estimates in patients receiving

Variable	Occasion	Age ≥ 5 yr			Age ≥2 to <5 yr
		Study 004 (n = 20)	Study 007 (n = 57)	Pooled 004/007 (n = 77)	Study 030 (n = 14)
Age (yr)	—	8.50 (20.0) 8.50 (6.00 – 12.0)	8.81 (33.2) 8.00 (5.00 – 20.0)	8.73 (30.4) 8.00 (5.00 - 20.0)	3.43 (22.0) 4.00 (2.00 – 4.00)
CL (L/hr)[a]	Morning	3.14 (31.9) 3.03 (1.91 – 6.33)	3.93 (21.0) 3.95 (2.58 – 6.38)	3.70 (26.1) 3.82 (1.91 - 6.38)	2.36 (19.6) 2.31 (1.62 – 3.39)
	Evening	2.10 (31.9) 2.03 (1.28 – 4.24)	2.62 (20.9) 2.60 (1.73 – 4.27)	2.47 (26.0) 2.53 (1.28 - 4.27)	1.58 (18.7) 1.48 (1.09 – 2.27)
Vss/F (L)[a]	—	20.9 (46.3) 19.3 (8.71 – 44.5)	21.5 (41.9) 22.1 (9.46 – 54.6)	21.3 (42.8) 21.8 (8.71 - 54.6)	13.0 (50.5) 11.6 (6.78 – 31.0)
AUC_{0-24} (µg•hr/mL)	Day 1	244 (30.5) 262 (151 – 389)	302 (27.3) 313 (103 – 470)	286 (29.5) 293 (103 - 470)	253 (33.0) 254 (142 – 418)
	Steady-state	231 (31.1) 247 (144 – 401)	147 (37.0) 157 (58.9 – 366)	163 (40.4) 167 (58.9 - 401)	151 (38.5) 150 (59.0 – 244)
C_{ave} (µg/mL)	Day 1	10.1 (30.5) 10.9 (6.30 – 16.2)	12.6 (27.3) 13.1 (4.28 – 19.6)	11.9 (29.5) 12.2 (4.28 - 19.6)	10.6 (33.0) 10.6 (5.92 – 17.4)
	Steady-state	9.64 (31.1) 10.3 (5.99 – 16.7)	6.11 (37.0) 6.55 (2.45 – 15.2)	6.79 (40.4) 6.96 (2.45 - 16.7)	6.30 (38.5) 6.23 (2.46 – 10.2)
C_{max} (µg/mL)	Day 1	18.6 (31.4) 18.8 (10.9 – 29.4)	26.6 (32.6) 28.7 (6.31 – 43.6)	24.2 (35.7) 25.5 (6.31 - 43.6)	23.0 (38.2) 22.7 (13.7 – 38.3)
	Steady-state	14.9 (33.4) 15.2 (9.05 – 25.5)	11.5 (40.3) 12.4 (3.32 – 21.3)	12.2 (40.1) 12.6 (3.32 - 25.5)	12.6 (44.6) 13.3 (5.25 – 23.8)

Note: Abbreviations are provided in the Abbreviation Listing.

Note: Summary statistics presented as mean (CV%) and median (min. – max.) for age and geometric mean (geometric CV%) and median (Min. – Max.) for CL/F, Vss/F, AUC_{0-24}, C_{ave}, and C_{max}

a. CL/F has values for morning and evening due to the inclusion of diurnal variation in the model. Vss/F only has one value for each patient.

Comparison between nmDMD patients 2-5 years of age and ≥ 5 years of age

PopPK analysis was used to estimate the ataluren exposure in the population of ≥2 to <5 years (study 030) and compare it with the exposure in the population of patients aged ≥5 (studies 004 and 007). Table 5 summarises ataluren PK parameter and exposure estimates in patients receiving the 10/10/20 mg/kg regimen by study. The median steady-state ataluren Cave in the 14 patients from Study 030 was 6.23 µg/mL, which is slightly lower but consistent with that seen in the older nmDMD patients (median steady-state ataluren Cave of 10.3 in Study 004 and 6.55 in Study 007).

Visual comparisons of exposure in the patients from Study 030, Study 004, and Study 007 are provided in Figure 7, Figure 8, and Figure 9.

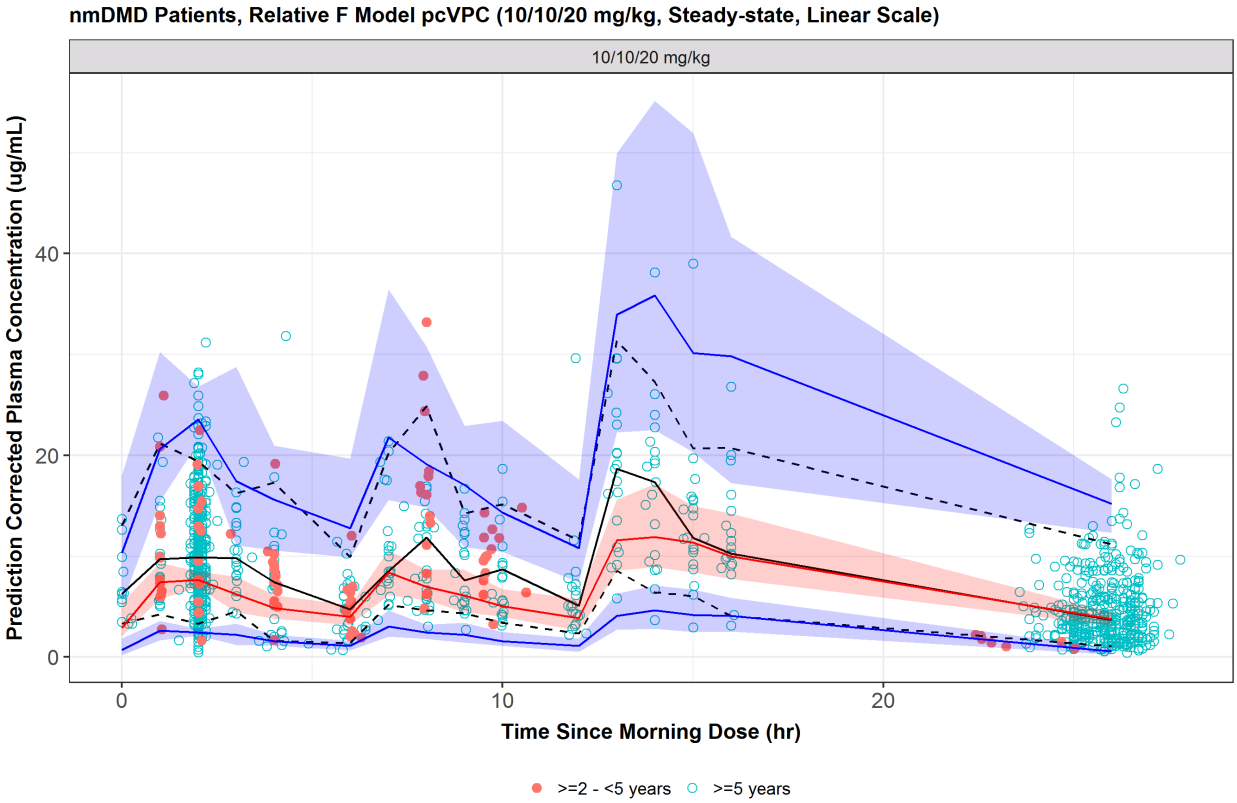
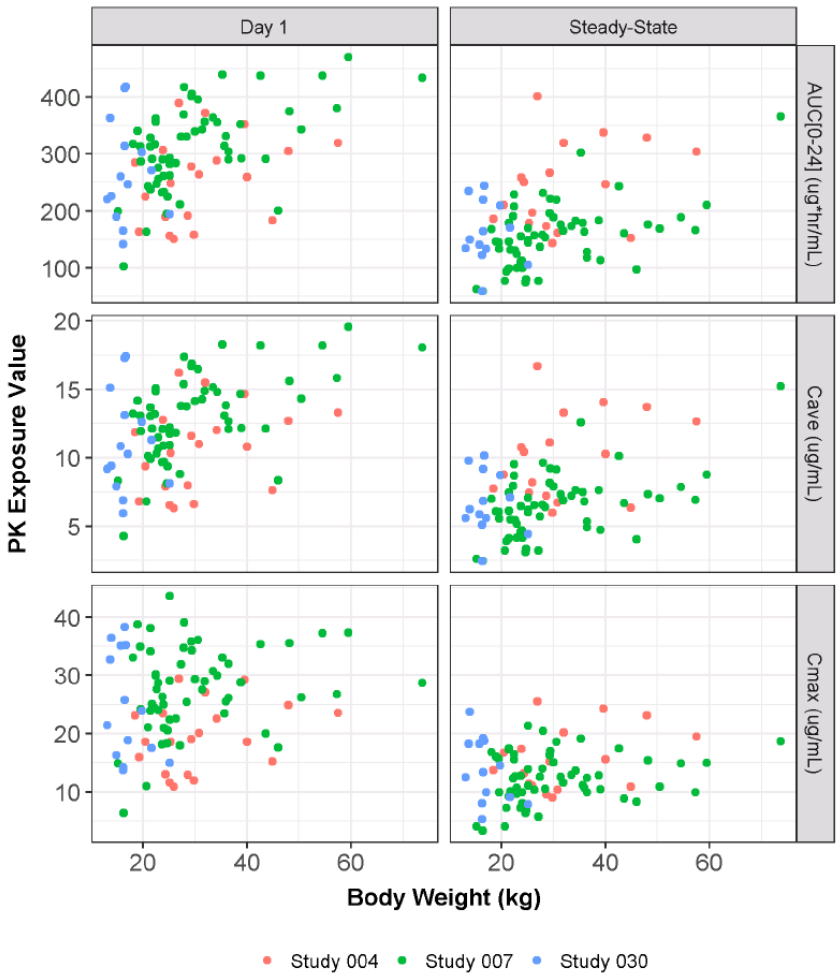


Figure 7 Ataluren plasma concentrations in nmDMD patients dosed 10/10/20 mg/kg. nmDMD patients in Study 004 and 007 were ≥ 5 years of age while patients in study 30 were ≥ 2 and<5 years of age.

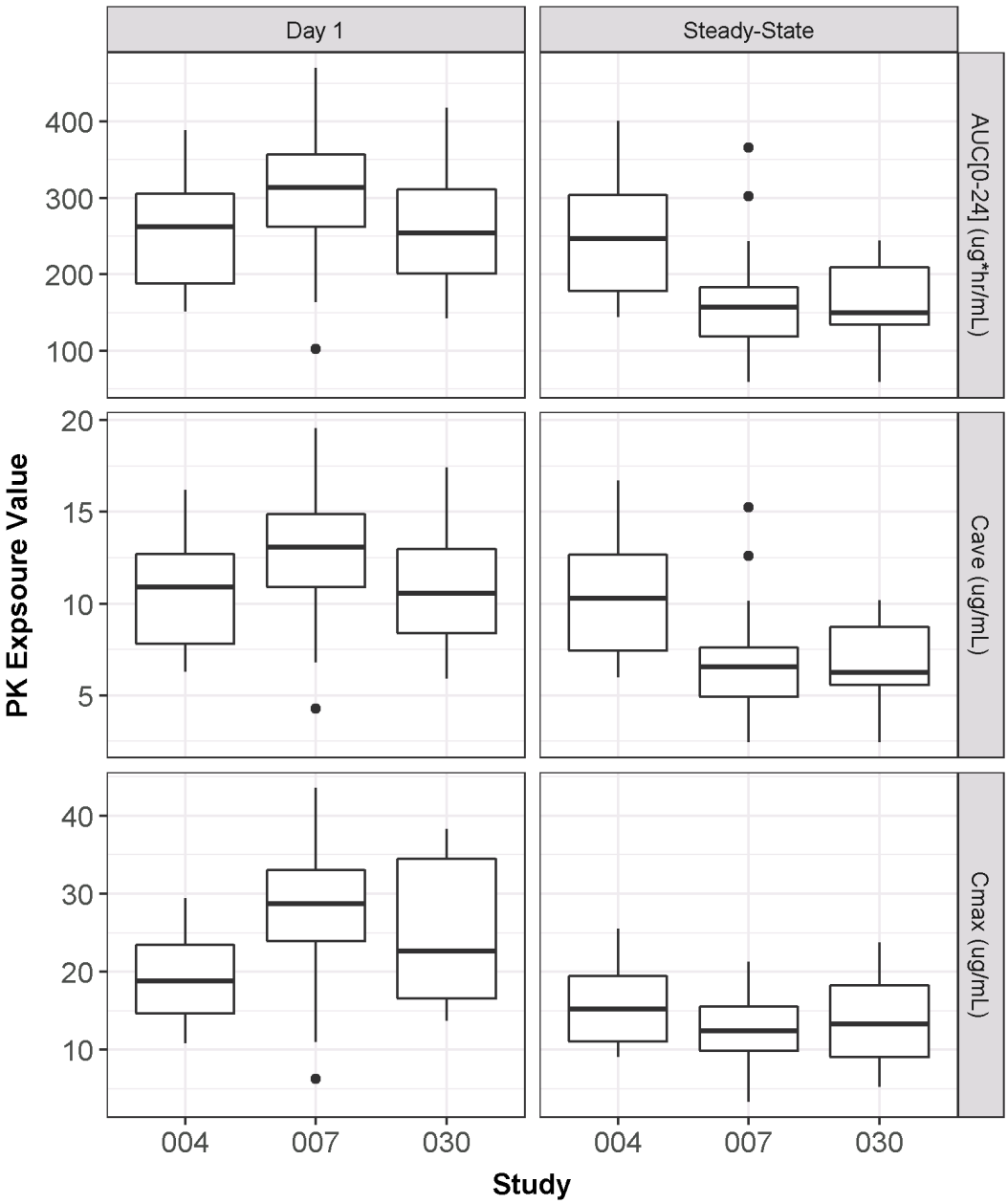
Observed data is shown in circles (open circles ≥ 5 years of age, closed circles 2-5 years of age. Median of the observed data is shown as a black, solid line. The 5th and 95th percentiles of the observed data are shown as black, dashed lines. The percentiles of the simulated data are shown as: Median of median values for each replicate: red, solid line 90% prediction interval around the median line: red, shaded region Median of the 5th/95th percentiles for each replicate: blue, solid line 90% prediction intervals around the 5th/95th percentile lines: blue, shaded regions

Figure 8 Scatterplot of individual estimates of ataluren PK exposure parameters versus patient body weight, coloured by study and panelled by parameter and occasion (Day 1 and steady-state)



Note: Abbreviations are provided in the Abbreviation Listing. PK exposures were derived from the fit of the nmDMD Relative F Model (2017) to the pooled dataset.

Figure 9 Box-and-whisker plots showing the distributions of ataluren PK exposure parameter estimates, stratified by study and paneled by parameter and occasion (Day 1 and steady-state)



Note: Data for the 004 and 007 studies are results from patients (≥5 years of age) treated with 10, 10, 20 mg/kg. PK exposures were derived from the fit of the nmDMD Relative F Model (2017) to the pooled dataset.
Plot definition: Horizontal line is the median, box shows the 25th-75th percentiles, and whiskers extend to the 1.5 times the interquartile range below and above the 25th and 75th percentiles, respectively. Solid circles indicate values outside of the whiskers.

Abbreviations: AUC $_{(0\text{-}24)}$, area under the concentration-time curve from 0 to 24 hours; C_{ave}, average concentration; C_{max}, maximum observed concentration

2.3.3. Pharmacodynamics

There are no pharmacodynamics data submitted by the applicant. The MAH performed only PK studies and relied on the claim of a PK-PD correlation from the previous study.

2.3.4. PK/PD modelling

Based on previous PK-PD analyses [17], a target ataluren Cave,ss of >0.970 and <17.6 µg/mL is aimed for. All of the patients 2-5 years of age had an ataluren Cave of >0.970 and <17.6 µg/mL suggesting that the dose of ataluren 10/10/20 mg/kg is appropriate for nmDMD patients aged ≥2 to <5 years.

2.3.5. Discussion on clinical pharmacology

The basis of this submission for the extension of indication to include a new population (children from 2 to less than 5 years of age) for Translarna for the treatment of nmDuchenne muscular dystrophy is one multiple-dose, open-label study 030, evaluating the safety and PK of ataluren in patients aged ≥ 2 to <5 years old with nmDMD for a period of 28 days (4 weeks). It was intended to show comparable ataluren pharmacokinetics in children 2-5 years with the pharmacokinetics in older children in order to provide basis for a conclusion on the expected the efficacy and safety in children 2-5 years of age.

Ataluren is mainly eliminated by intestinal and hepatic glucuronidation. Maturation rates of hepatic UGTs vary between the UGTs, but may extend beyond the age of two years. UGT1A9 is the main UGT enzyme involved in metabolism of ataluren. Hepatic UGT1A9 levels reached adult values well before the age of two years (Strassburg et al. 2002, Miyagi et al. 2012). Therefore, no age related differences in glucuronidation other than difference in body size between patients ≥2 to <5 years and ≥5 years of age are to be expected.

Pharmacokinetic data were collected at day 1 and day 28. The treatment dose was 10/10/20 mg/kg for morning/midday/evening dose. Using the available data on the observed plasma values, ataluren exposure appears to be similar in nmDMD patients ≥2 to <5 years of age compared to those ≥5 years of age.

Flat dosing is recommended per predefined weight groups (SmPC section 4.2). As a consequence, children <31 kg were dosed 125 mg or 250 mg, dose range 7.7 mg/kg to 15.1 mg/kg. Ataluren exposure varied dose proportionally, hence there was considerable variability between subjects due to the difference in dosing. Using the dosing regimen currently proposed (multiples of sachets of 125 mg, 250 mg and 1000 mg), this resulted in almost a 1.6-fold difference in predicted ataluren exposure in nmDMD patients 2-5 years old: patients 2-5 years old with low body weight <17 kg had a lower exposure than nmDMD patients ≥ 17 kg. Further, the predicted exposure in patients <17 kg was lower compared to nmDMD patients ≥ 5 years of age in study 004 without an overlap in ataluren exposure. Additional data analysis showed that the trend was not universal and the intersubject variability in ataluren exposure cannot be fully attributed to the different dosing regimen. As body weight was a covariate on clearance with a power coefficient less than 1, a lower exposure in subjects with a low body weight can be expected applying a mg/kg dosing regimen.

The MAH proposal to use PopPK analysis was to estimate the ataluren exposure in the population of ≥2 to <5 years and compare it with the exposure in the population of patients aged ≥5. However, the CHMP concluded that there were too many shortcomings in the proposed model, bringing about uncertainties about the ability of the popPK model to adequately describe the pharmacokinetics of ataluren in children 2-5 years of age.

These uncertainties related to model development and presentation of the data and included e.g.: external validation using single dose data in healthy volunteers from study 15 indicates that the model does not capture well the dose dependent elimination; a time-dependent bioavailability was included in the model while PK data from study 30 in nmDMD patients 2-5 years of age did not indicate time dependent pharmacokinetics. Empirical adjustments have been made to the model to fit the measured steady-state data without a mechanistic basis. Despite the efforts by the MAH, ultimately the popPK model can provide little additional value over measured plasma concentration data.

In terms of the expected pharmacodynamics of ataluren, it is plausible to assume that a similar pharmacodynamic effect in boys 2-5 years old should be expected as in patients >5 years old, provided similar exposure levels are achieved. The MAH did not submit new PD data, but rather reiterated the position that due to the specific exposure-response behaviour of ataluren, a dose of 10/10/20 mg/kg could be appropriate for nmDMD patients aged ≥2 to <5 years, as it is assumed that it would result in target concentrations of ataluren that are likely to provide the expected PD effect. In their conclusion the CHMP agreed with the proposed approach.

2.3.6. Conclusions on clinical pharmacology

The CHMP concluded that the presented popPK model had inherent flaws not allowing it to serve the initially intended purpose of demonstrating comparable ataluren exposure in patients aged 2-5 years with that of nmDMD patients aged ≥5 years of age. Despite all the efforts by the MAH, the concerns regarding the model remain, and ultimately it was seen as unable to provide additional value over measured plasma concentration data. With that in mind, the Committee reviewed the available pharmacokinetic results from paediatric study 030 in nmDMD patients aged ≥2 to <5 years old dosed 10/10/20 mg/kg ataluren, and considered that the analysis of the observed plasma values can constitute another approach in verifying the comparability of exposure between the two groups. Recognizing the potential uncertainties in this approach, the Committee ultimately agreed that ataluren exposure appears to be similar in nmDMD patients ≥2 to <5 years of age compared to those ≥5 years of age, after administration of 10/10/20 mg/kg ataluren.

2.4. Clinical efficacy

2.4.1. Main study

PTC124-GD-030-DMD (Study 030) is multiple-dose, open-label study evaluating the safety and PK of ataluren in patients aged ≥2 to <5 years old with nmDMD for a period of 28 days (4 weeks). In order to collect longer-term safety and functional endpoint information (i.e, TFTs and NSAA assessments), a 48-week extension phase was added. All patients received approximately 10-, 10, 20-mg/kg ataluren 3 times daily (TID) for 4 weeks during the PK portion and continue to receive the same dose for an additional 48 weeks during the ongoing extension period. Ataluren is administered orally immediately after preparation.

During the treatment period, each patient returned to the clinical research facility during Week 0 and Week 4 for PK testing, and at Week 16, Week 28 for safety and efficacy assessments. Subsequent visits are scheduled for Week 40 and Week 52.

The following tables summarise the efficacy results from the main studies supporting the present application.

Table 6 Summary of Efficacy for trial Study 030

Title: Study 030 (PTC124-GD-030-DMD)					
Study identifier	030 (PTC124-GD-030-DMD)				
Design	a phase 2, multiple-dose, open-label study in patients aged ≥2 to <5 years old with nmDMD				
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	4 weeks not applicable 28-weeks			
Hypothesis	Clinical benefit of Ataluren in patients ≥2 and < 5 years of age				
Treatments groups	Study 030	10,10,20mg/kg Ataluren, 28-weeks, 14 patients aged ≥2 and < 5, average age 3.4 , 6 patients received concomitant steroid treatment (42.9%)			
	National history of DMD Cooperative International Neuromuscular Research Group (CINRG)	31 patients, average age 3.52 , 9 patients received concomitant steroid treatment (29%)			
Endpoints and definitions	Functional endpoint	TFTs	The time taken to run or walk 10 meters, to climb 4 standard stairs, and to stand from a supine starting position were assessed		
	Functional endpoint	NSAA	8 items were selected (85% of typically developing boys are able to fully perform 8 of the 17 items) 3 items were assessed (100% of boys age 3 are typically to perform these).		
Results and Analysis					
Analysis description	**Primary Analysis**				
Effect estimate per comparison	Changes from baseline to week 28 _time to run or walk 10 meters	CINRG n=31 -0.32 (1.579) (Mean(SD)) -0.30 (median) -3.6, 4.3 (min, max)	Study 030 N=12 -0.6 (1.44) (mean (SD)) -0.5 (median) -2, 2 (min, max)	Mean δ -0.3	
	Time to Climb 4 Stairs from Baseline to Week 28	N=28 -1.3 (3.479) (mean (SD)) -0.36 (median) -15,-2.9 (min, max)	N=12 -2.1(5.07) (mean (SD)) 0.0 -17, 1 (SD)	-0.8	
	Change in Time to Stand from a Supine Position from Baseline to week 28	N=25 -0.65 (2.618) (mean(SD)) -0.36 (median) -9.6, 5.2 (min, max)	N=12 -3.3 (6.70) (mean(SD)) -0.5 (median) -18,1 (min,max)	-2.65	

	Change in North Star Ambulatory Assessment 8-item Score from Baseline to Week 28	N=11 0.00(1.612) (mean(SD)) 0.00 (median) -3.0, 3.0 (min, max)	N=12 1.5 (1.446) (mean(SD)) 2.00 (median) -1.0, 3.0 (min, max)	+1.5
	Change in North Star Ambulatory Assessment 3-item Score from Baseline to Week 28	N=11 0.09(0.3015) (mean(SD)) 0.00 (median) 0.0, 1.0 (min, max)	N=12 0.5 (0.7977) (mean(SD)) 0.50 (median) -1.0, 2.0 (min, max)	+0.5
	Change in North Star Ambulatory Assessment total Score from Baseline to Week 28	N=11 0.64(3.779) (mean(SD)) 1.00 (median) -6.0, 7.0 (min, max)	N=12 3.4 (4.19) (mean(SD)) 4.0 (median) -4, 9 (min, max)	+3

Methods of Assessing Muscle Function

Muscle function was assessed through timed function tests (TFTs) and the North Star Ambulatory Assessment. The time taken to run or walk 10 meters, to climb 4 standard stairs, and to rise from supine has predictive value for clinically meaningful loss of function, including ambulation, in DMD [McDonald 2013].

The NSAA is a functional assessment tool designed for ambulant patients affected by DMD [Mazzone 2010]. In its original form, it consists of 17 activities (including, for example, standing upright, rising to standing from a seated position, standing on one leg, walking, running, hopping, and jumping) each scored as 0, 1, or 2, with a higher score indicating better function and a maximum total score of 34. The full 17-item scale has been validated for use in children above the age of 5 years [Mercuri 2016].

Before the age of 4, many of the items (for example, standing on one leg and hopping) are not yet reliably performed by typically developing boys. At age 3, 85% of typically developing boys are able to fully perform 8 of the 17 items and 100% are able to perform 3 of them. It is only at age 4 that 85% of typically developing boys are able to achieve full scores in all 17 items [Mercuri 2016]. As a result, revised NSAA scales that include the subsets of items reliably performed by boys in the ≥ 2 and < 5 year age group are the most appropriate approach for this age group. The results for these developmentally appropriate 8- and 3-item scales, as well as the full 17-item NSAA scale, are presented here.

These assessments were scheduled to be performed at baseline (Week 0), Week 28, and Week 52.

Patient Demographics and Baseline Characteristics

The patients ≥2 and < 5 years of age in the CINRG study and the patients in Study 030 were similar across a range of demographic and baseline characteristics.

The mean age among patients in the selected age range of the CINRG study and in Study 030 was 3.5 years and 3.4 years, respectively. Patients in Study 030 are slightly taller and heavier than their CINRG counterparts, but the BMI in both groups is comparable.

In Study 030, 6 (43%) patients (5 of whom are included in the evaluable population) received corticosteroid treatment at baseline, in comparison with 9 (29%) patients in the CINRG dataset. Given the effects of chronic administration of steroids on the slowing of disease progression in DMD, in Study 030 investigators were encouraged to maintain as uniform a steroid regimen as possible. All 6 patients who received corticosteroids at baseline in Study 030, continued to do so concomitantly in stable regimens (Listing 16.2.8.7).

Patient Disposition

All 14 patients who were enrolled in Study 030 completed the 4-week PK phase and entered into the 48-week extension phase. As of the 21 July 2017 cut-off date, 2 patients have completed the extension phase and no patients have discontinued prematurely from the study.

Table 7 Demographics and Baseline characteristics (all patients)

Patient Characteristic Statistic	CINRG (N = 31)	Study 030 10, 10, 20 mg/kg Ataluren (N = 14)
Age (years)		
n	31	14
Mean (SD)	3.52 (.6256)	3.4 (0.76)
Median	4.00	4.0
Min, Max	2.0, 4.0	2, 4
Sex n (%)		
Male	31 (100.0)	14 (100.0)
Ethnicity n (%)		
Caucasian	23 (74.2)	11 (78.6)
African-American	0 (0.0)	0 (0.0)
Asian	6 (19.4)	3 (21.4)
Hispanic[a]	0 (0.0)	3 (21.4)
Other	2 (6.5)	0 (0.0)
Missing	0 (0.0)	0 (0.0)
Weight (kg)		
n	31	14
Mean (SD)	15.91 (1.804)	16.99 (3.26)
Median	15.60	16.40
Min, Max	13.2, 20.2	13.2, 25.2
Height (cm)		
n	30	14
Mean (SD)	96.88 (4.951)	99.43 (5.28)
Median	97.30	98.55
Min, Max	83.0, 106	88.8, 108.0
BMI (kg/m^2)		
n	30	14
Mean (SD)	16.94 (1.614)	17.09 (2.22)
Median	16.71	16.64
Min, Max	14.1, 22.6	14.78, 22.94
Baseline Steroid Use		
None	22 (71.0)	8 (57.1)
Prednisone	1 (3.2)	2 (14.3)
Deflazacort[b]	1 (3.2)	3 (21.4)
Prednisolone	7 (22.6)	1 (7.1)

Results

Time to run or walk 10 meters

In the CINRG natural history dataset, for the 31 patients with both baseline and Week 28 assessments for the time to run or walk 10 meters, the mean time in seconds was slightly improved from the 7.32 second baseline, as is expected among patients in this age group, with a mean decrease of 0.32 seconds (a mean improvement of approximately 4% from baseline). Among the 12 patients in Study 030 with valid baseline and Week 28 assessments, the mean improvement was 0.6 seconds from the 6.7 second baseline, an 8.9% improvement over baseline. The relative improvement from baseline compared with that of natural history data (8.9% versus 4%) is evidence of clinical benefit of ataluren in younger patients.

Table 8 Change in Time to Run or Walk 10 Meters from Baseline to Week 28 in CINRG Natural History Dataset and Study 030 (Evaluable Population)

Timepoint	Time to Run or Walk 10 Meters (seconds)	
Statistic	CINRG	Study 030
Baseline		
n	31	12[a]
Mean (SD)	7.32 (2.311)	6.7 (2.46)
Median	6.97	6.5
Min, Max	4.1, 12.6	4, 12
Week 28		
n	31	12
Mean (SD)	7.00 (2.193)	6.1 (2.23)
Median	6.44	5.0
Min, Max	4.3, 14.7	4, 11
Change from Baseline to Week 28		
n	31	12
Mean (SD)	-0.32 (1.579)	-0.6 (1.44)
Median	-0.30	-0.5
Min, Max	-3.6, 4.3	-2, 2

Abbreviations: CINRG=Cooperative International Neuromuscular Research Group natural history dataset; Max = maximum; Min = minimum; SD = standard deviation.
[a]One patient was excluded from this analysis due to a baseline assessment deemed invalid by the investigator, while a second patient did not have reported functional assessments at Week 28.

Time to climb 4 stairs

Clinical benefit is further supported by the results for the time to climb 4 stairs. In the CINRG natural history dataset, for the 28 patients with both baseline and Week 28 assessments for the time to climb 4 stairs, the mean time in seconds was improved from the 7.30 seconds at baseline to 6.00 seconds at Week 28 (a mean decrease of 1.30 seconds and an improvement of approximately 18% from baseline). Among the 12 patients in Study 030 with valid baseline and Week 28 assessments, the mean time in seconds was also improved from the 7.4 seconds at baseline to 5.3 seconds at Week 28 (a mean decrease of 2.1 seconds and an improvement of approximately 28% from baseline). The magnitude of the relative improvement from baseline over natural history data (28% versus 18%) is further evidence of clinical benefit.

Table 9 Change in Time to Climb 4 Stairs from Baseline to Week 28 in CINRG Natural History Dataset and Study 030 (Evaluable Population)

Timepoint	Time to Climb 4 Stairs (seconds)	
Statistic	CINRG	Study 030
Baseline		
n	28	12
Mean (SD)	7.30 (5.137)	7.4 (7.49)
Median	6.36	5.5
Min, Max	3.2, 30.0	2, 30
Week 28		
n	28	12
Mean (SD)	6.00 (2.835)	5.3 (3.23)
Median	4.99	4.0
Min, Max	2.8, 14.7	3, 13
Change from Baseline to Week 28		
n	28	12
Mean (SD)	-1.30 (3.479)	-2.1 (5.07)
Median	-0.36	0.0
Min, Max	-15, 2.9	-17, 1

Abbreviations: CINRG=Cooperative International Neuromuscular Research Group natural history dataset; Max = maximum; Min = minimum; SD = standard deviation.
[a]One patient was excluded from this analysis due to a baseline assessment deemed invalid by the investigator, while a second patient did not have reported functional assessments at Week 28.

The time to stand from a supine position

The time to stand from a supine position is an established early predictor of disease progression in boys with DMD over the age of 7 [Mazzone 2016] and is also of important clinical validity in younger boys, since it is the first milestone to be lost in DMD patients. In the CINRG natural history dataset, for the 25 patients with both baseline and Week 28 assessments for the time to stand from a supine position, the mean time in seconds was slightly improved from the 5.68 second baseline, with a mean decrease of 0.65 seconds, as is expected among patients in this age group. Among the 12 patients in Study 030 with valid

baseline and Week 28 assessments, the mean time in seconds was also improved from the 7.6 seconds at baseline to 4.3 seconds at Week 28 (a mean decrease of 3.3 seconds and an improvement of approximately 43% from baseline). The magnitude of the improvement over natural history data (43% versus 11%) is notable.

Table 10 Change in Time to Stand from Supine Position from Baseline to Week 28 in CINRG Natural History Dataset and Study 030 (Evaluable Population)

Timepoint Statistic	Time to Stand from Supine (seconds)	
	CINRG	Study 030
Baseline		
n	25	12
Mean (SD)	5.68 (2.571)	7.6 (7.79)
Median	5.19	4.5
Min, Max	3.3, 15.8	3, 26
Week 28		
n	25	12
Mean (SD)	5.03 (1.875)	4.3 (1.50)
Median	4.98	4.0
Min, Max	2.5, 11.4	3, 8
Change from Baseline to Week 28		
n	25	12
Mean (SD)	-0.65 (2.618)	-3.3 (6.70)
Median	-0.36	-0.5
Min, Max	-9.6, 5.2	-18, 1

Abbreviations: CINRG=Cooperative International Neuromuscular Research Group natural history dataset; Max = maximum; Min = minimum; SD = standard deviation.
[a]One patient was excluded from this analysis due to a baseline assessment deemed invalid by the investigator, while a second patient did not have reported functional assessments at Week 28.

NSAA

At 3 years of age, at least 85% of typically developing boys are able to reliably perform 8 of the 17 functions on the full NSAA scale: stand, walk 10 meters, go from sitting in a chair to standing, climb a step (with the right and left foot), get to a sitting position, jump, and run. [Mercuri 2016] In order to more accurately assess functional improvement in patients ≥2 and <5 years of age, the 8-item scale based on only these functions was used. In the CINRG natural history data, for the 11 patients with both baseline and Week 28 assessments for the NSAA, the 8-item score was unchanged from the 14.00 baseline. Among the 12 patients in Study 030 with a valid baseline and Week 28 assessment, the mean NSAA 8-item score was improved from the 10.42 baseline by 1.5 points, providing further support for clinical benefit of ataluren in this population, in a developmentally appropriate subset of functions.

Table 11 Change in North Star Ambulatory Assessment 8-item Score from Baseline to Week 28 in CINRG Natural History Dataset and Study 030 (Evaluable Population)

Timepoint Statistic	Revised 8-item NSAA Score	
	CINRG	Study 030
Baseline		
n	11	12
Mean (SD)	14.00 (2.145)	10.42 (2.746)
Median	15.00	10.50
Min, Max	10.0, 16.0	6.0, 15.0
Week 28		
n	11	12
Mean (SD)	14.00 (1.612)	11.92 (3.204)
Median	14.00	13.00
Min, Max	11.0, 16.0	7.0, 16.0
Change from Baseline to Week 28		
n	11	12
Mean (SD)	0.00 (1.612)	1.50 (1.446)
Median	0.00	2.00
Min, Max	- 3.0, 3.0	-1.0, 3.0

There are 3 items that 100% of typically developing boys are able to perform from the age of 3 years: the ability to stand, walk 10 meters, and go from sitting in a chair to standing [Mercuri 2016]. In order to further evaluate functional improvement in patients ≥2 and < 5 years of age in the CINRG dataset and Study 030, a 3-item scale assessing only these items was also analyzed. In the CINRG natural history dataset, for the 11 patients with both baseline and Week 28 assessments for the NSAA, the 3-item score increased by 0.09 points from the baseline of 5.91. Among the 12 patients in Study 030 with a valid baseline and Week 28 assessment, the mean NSAA 3-item score was improved from the 5.33 baseline by 0.5 points.

While the populations in the ≥2 and < 5 age group in the CINRG dataset and Study 030 are generally comparable, the subset of 11 CINRG patients for whom NSAA assessments are available is not representative of the larger CINRG population in this age group. All 11 CINRG patients with both baseline and Week 28 assessments for the NSAA were 4 years old at baseline, an age at which at least 85% typically developing 4 year olds are able to perform all 17 functions of the full NSAA scale [Mercuri 2016]. The 12 patients in Study 030 with both baseline and Week 28 assessments included 4 patients who were 3 years old at baseline and 1 patient who was 2 years old at baseline. This reflected in the more than 7-point difference in the baseline NSAA total scores for this subset of CINRG patients and the 12 patients in Study 030 with valid baseline and Week 28 assessments. In the CINRG natural history dataset, for the 11 patients with both baseline and Week 28 assessments for the NSAA, the total score was slightly improved from the 24.00 baseline, with a mean increase of 0.64 points. Among the 12 patients in Study 030 with valid baseline and Week 28 assessments, the mean NSAA total score was improved from the 16.8 baseline by 3.4 points. The difference in the improvement in NSAA total score among CINRG patients and the ataluren-treated patients in Study 030 (0.64 points versus 3.4 points, respectively) is notable, despite the limitations of the comparison for this endpoint, and represents another indication of clinical benefit.

Table 12 Change in North Star Ambulatory Assessment Total Score from Baseline to Week 28 in CINRG Natural History Dataset and Study 030 (Evaluable Population)

Timepoint	NSAA Total Score	
Statistic	CINRG	Study 030
Baseline		
n	11	12
Mean (SD)	24.00 (5.532)	16.8 (5.10)
Median	26.00	17.5
Min, Max	14.0, 33.0	7, 23
Week 28		
n	11	12
Mean (SD)	24.64 (4.456)	20.3 (6.94)
Median	25.00	21.5
Min, Max	15.0, 32.0	10, 30
Change from Baseline to Week 28		
n	11	12
Mean (SD)	0.64 (3.776)	3.4 (4.19)
Median	1.00	4.0
Min, Max	-6.0, 7.0	-4, 9

Abbreviations: CINRG = Cooperative International Neuromuscular Research Group; Max = maximum; Min = minimum; SD = standard deviation.

The linear transformation of NSAA scores to a scale of 0 to 100 has also been performed. An increase of 4.0 linearized units per year has been reported in the literature for boys with DMD prior to age 7 [Ricotti 2015].

Table 13 Change in North Star Ambulatory Assessment Linear Score from Baseline to Week 28 in CINRG Natural History Dataset and Study 030 (Evaluable Population)

Timepoint	NSAA Linear Score	
Statistic	CINRG	Study 030
Baseline		
N	10	12
Mean (SD)	66.10 (11.56)	51.2 (9.75)
Median	67.00	52.5
Min, Max	52.0, 91.0	32, 63
Week 28		
N	10	12
Mean (SD)	66.50 (8.209)	59.3 (15.73)
Median	65.00	60.0
Min, Max	57.0, 85.0	38, 85
Change from Baseline to Week 28		
N	10	12
Mean (SD)	0.40 (8.682)	8.2 (10.54)
Median	-1.00	8.0
Min, Max	-13.0, 13.0	-8, 26

Abbreviations: CINRG = Cooperative International Neuromuscular Research Group; Max = maximum; Min = minimum; SD = standard deviation.

Note: One patient in the CINRG dataset was missing Week 28 assessments for "lifts head" and "stand on heels" preventing calculation of the linear score for this patient

In the CINRG natural history dataset, for the 11 patients with both baseline and Week 28 assessments for the NSAA, the linear score was slightly improved from the 66.10 baseline, with a mean increase of 0.40 points. Among the 12 patients in Study 030 with a valid baseline and Week 28 assessment, the mean NSAA linear score was improved from the 51.2 baseline by 8.2 points. Again with the caveat that the age-related difference in baseline complicates the comparison, this represents a notable and potentially clinically meaningful increase in function in relative to the change seen among the patients in the CINRG dataset.

2.4.2. Discussion on clinical efficacy

A phase II, multi-dose open label study was conducted to perform PK analysis. The study included patients between 2 and 5 years. Patients were treated with 40mg/kg/day ataluren for 4 weeks in this initial phase. To further assess the efficacy and safety profile of the product in the population, the study was extended to 48 weeks. As, this study was originally intended as a PK study, there was no placebo-controlled arm included, and the data are prone to different kinds of bias because of the open-label structure of the study.

The MAH has used historical data set from CINRG to provide for a comparison of efficacy. In general, motor function development and disease progression in DMD subjects are subject to significant variability. For that reason the use of any historical data in the form of a treatment control group could only be accepted if the strict comparability of the included patients is guaranteed. In the specific case here, the selected CINRG population did not differ from the patients included in study 030 in terms of age, sex, height and BMA. Importantly though, the two groups showed differences in patient weight and the recorded baseline steroid use. Although a higher mean body weight did not result in a difference in BMI between groups, it cannot be excluded that it might have an effect on the dose which each individual patient has received. In terms of concomitant steroid use, there were more patients in the study 030 that were treated with steroids (42.9%), than those in the CINRG data set (29%). Since treatment with corticosteroids has a proven effect on disease progression in DMD (particularly notable in the first years of treatment), the efficacy and safety results in the 030 study subjects may be influenced by this, and should be interpreted with caution.

The extension phase is for 48 weeks, the study 030 is currently ongoing and in the application the MAH has provided data after 28 weeks of treatment. In light of the described mechanism of action of ataluren, and the results presented in the previous phase III studies (007 and 020), there is an increasing body of evidence that suggests that longer time may be needed for any effect of the product to be observed in clinical terms. The effect on the 6MWT and the TFTs was not convincing after 48 weeks in the studies mentioned above and the CHMP has recommended 1.5 years phase III study in order to account for the fact that clinical effect may need longer periods to be robustly demonstrated. Therefore the presented 28 weeks' data on efficacy could at best be considered as supportive information, and on their own will be insufficient to provide the basis for a robust conclusion on the efficacy of ataluren in the target population.

Considering the described mechanism of action of ataluren, the MAH maintained the position that favourable effects of treatment could be expected on patient functioning and less likely on muscle strength. In support of this, the data presented in this extension of the indication application focused on parameters and endpoints that describe functioning. It is recognized that the 6MWT is not a reliable outcome measurement tool in children <5years, and therefore in study 030 the efficacy outcomes were selected to be three measures of timed function tests (TFTs) and a revised version of the NSAA. Although in principle it is agreed that these may represent a more appropriate way to measure efficacy in this young patient population, it has to be kept in mind that the clinical relevance of the observed differences should be appropriately justified. Additionally, the interpretation of the clinical value of the observed difference is hindered by the short study duration and the lack of an appropriate control, in the form of a placebo or fully matched historical control group. In addition, supportive evidence from muscle strength and PD outcome measures is still considered insufficient.

From the results presented for the three TFTs, it was evident that there were minor differences between the CINRG controls and the study 030 population. The effect size of the observed difference is such that it fell within the variety range of both groups. For both the time to climb 4 stairs and the time to stand from a supine position, a difference in baseline levels was noted, which is more prominent in the stand from supine position, and may influence the interpretation of the results. As mentioned before, the clinical

relevance of an improvement of 0.3 seconds in the time to run/walk 10 meters and an improvement of 0.8 seconds in the time to descent 4 stairs has to be properly justified, preferably by a clear correlation to a clinical event signifying a clear effect on disease progression.

The MAH performed the full NSAA test and 2 revised subsets – of 3 and 8 items. It has to be highlighted that the results provided represent an overlap, since the 3 items are also included in the 8 items subtest and in the full NSAA. Taking the clinical experts' opinion into account, the most relevant test would be the revised 8-item NSAA as it can be performed reliably by patients aged 4 years (the average age of Study 030 population). Based on this evaluation, the CINRG patients showed no improvement or deterioration, while for the subjects in study 030 there was an observed improvement of 1.5 points. The interpretation of this result should be made with caution as there are confounding factors that may have significantly contributed to it, like the inherent variability in the disease course, or the abovementioned differences in the patients' characteristics in the two groups.

The demographics of the 11 subjects from CINRG were not provided, but the fact that these have a higher mean NSAA score at baseline (14.0 versus 10.4) might suggest that these are older boys (i.e. able to perform more items on the 8 item NSAA). This assumption is also supported by the difference in baseline as provided on the total NSAA – 24.0 versus 16.8 on the total score and 66.1 versus 51.2 on the linear score respectively. The lack of any improvement in the CINRG (on the 8 item and the total NSAA) as compared to some improvement in the 030 subjects might also be due to the fact that the historical control group was not completely matched, as these were older boys able to perform more of the items on the NSAA, who were compared to younger boys still acquiring new skills and functions.

2.4.3. Conclusions on the clinical efficacy

Although the efficacy data from study 030 present a trend in favour of ataluren treated DMD patients aged 2-5 years old, when compared to a group of controls, taken from the CINRG database, there are a number of inconsistencies in the matching of the historical controls were noted, and have to be taken into consideration in the evaluation of the observed differences between the groups. Additionally, the effect size and its clinical relevance remain to be fully ascertained in terms of their importance for the functioning of patients and the expected potential benefit from ataluren treatment. Despite the abovementioned irregularities, it cannot be denied that a trend favouring ataluren was observed when measuring the functional performance of DMD boys, using clinically valid and established instruments like the TFTs and NSAA and its variants. Although the level of robustness of these data is insufficient to serve on their own as the basis for a conclusion that efficacy in DMD patients, aged 2-5 years has been unequivocally demonstrated, in the context of the available PK data they do provide additional support that efficacy is expected to be similar in these patients and the ones aged >5 years, as demonstrated in the previous development steps.

2.5. Clinical safety

Introduction

The most common side effects with ataluren (seen in more than 5 in 100 people) are vomiting, diarrhoea, nausea (feeling sick), headache, stomach ache and flatulence. Side effects are usually mild or moderate in severity.

Ataluren must not be used at the same time as certain antibiotics known as aminoglycosides when these are given by injection into a vein.

Patient exposure

Study 030 began with a 4-week PK phase assessing short-term safety and PK, followed by a 48-week extension phase to provide long-term safety and efficacy information in this population. Safety and pharmacokinetic data from the 4-week PK phase are available in a final PK CSR dated 21 April 2017. The cut-off date of the PK CSR was 10 February 2017.

This summary presents safety data with a cut-off date of 21 July 2017 (the date by which data for the 28 Week visit was captured in the database for all 14 patients), and includes events with a start date on or before that date.

After the PK CSR cut-off date, the database was updated to include 6 additional adverse events experienced by 3 patients during the PK phase not previously reported in the PK CSR.

These TEAEs (2 patients with events of flatulence, and one patient with events of pyrexia, contusion, constipation, and rash) are reflected in this summary.

During development, 2 doses of ataluren: 10, 10, 20 mg/kg per day and 20, 20, 40 mg/kg per day were evaluated (Study 007). While both doses were well tolerated, clinical benefit was observed at the 10, 10, 20 mg/kg dose, which was selected for the Phase 3 study 020 and subsequently granted marketing authorisation. This addendum thus summarizes safety data for the 172 patients administered the 10, 10, 20 mg/kg dose from the two pooled nmDMD pivotal studies in patients aged ≥5 years (Study 007 and Study 020, the Pooled Studies) for the first 28 days of treatment.

Adverse events

Adverse Events During the First 28 Days of Treatment

To allow for a comparison of safety in patients 5 and older with those < 5 years old in the 28-day PK phase of the ongoing Study 030, adverse event data from the first 28 days of treatment in Study 007 and 020 (the two randomized, double-blind, placebo-controlled, 48-week trials in patients with nmDMD aged ≥5 years) were pooled and summarized. The adverse-event profile of ataluren in Study 030 was comparable to that of patients aged 5 and older in the pooled studies.

The overall frequency of treatment-emergent adverse events (TEAEs) was slightly higher among patients in PK phase of Study 030 (10 patients; 71.4%) than among ataluren-treated patients the first 28 days of treatment in the Pooled Studies (81 patients; 47.1%). Treatment emergent events considered to be related to ataluren were infrequent in both Study 030 and the Pooled Studies. Within the first 28 days of treatment in the Pooled Studies, 3 patients receiving 10, 10, 20 mg/kg ataluren experienced TEAEs with a maximum Common Terminology Criteria for Adverse Events (CTCAE) grade of severe (events of constipation, ileus, and disease progression). All TEAEs in the PK phase of Study 030 were mild or moderate in CTCAE-grade of severity.

Table 14 Overview of Treatment Emergent Adverse Events by Study for First 28 Days of treatment Reported for More than One Patient in the Pooled studies (Study 007 and study 020) or Study 030 (Safety Population)

	Study 007/020 Pooled Placebo (N = 172) n (%)	Studies 007/020 10, 10, 20 mg/kg Ataluren (N = 172) n (%)	Study 030 10, 10, 20 mg/kg Ataluren (N = 14) n (%)
Number of TEAE	**104**	**196**	**26**
Patients with 1 or more:			
TEAE	52 (30.2)	81 (47.1)	10 (71.4)
TEAE related to study drug[a]			
Not related	37 (21.5)	44 (25.6)	5 (35.7)
Related	15 (8.7)	37 (21.5)	5 (35.7)
TEAE leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
SAE	1 (0.6)	0 (0.0)	0 (0.0)
TEAE with a maximum CTCAE grade of:			
Mild	37 (21.5)	58 (33.7)	6 (42.9)
Moderate	15 (8.7)	20 (11.6)	4 (28.6)
Severe	0 (0.0)	3 (1.7)	0 (0.0)
Life-threatening	0 (0.0)	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; SAE = serious adverse event; TEAE = treatment-emergent adverse event

[a]Events deemed by the investigator to have a possible or probable relationship to study drug are considered "related" while those deemed to have an unlikely or unrelated relationship are considered "not related".

Note: A treatment-emergent adverse event (TEAE) was defined as an adverse event that occurs or worsens in the period extending from the first dose of study drug to 6 weeks (in the pooled studies) and 4 weeks (in Study 030) after the last dose of study drug.

There were no serious TEAEs among ataluren-treated patients in the first 28 days of the Pooled Studies or in the PK phase of Study 030. The most frequently occurring TEAEs among patients in the Pooled Studies treated with the 10, 10, 20 mg/kg dose of ataluren during the first 28 days of treatment were vomiting (15.1% of patients), diarrhea (8.7% of patients), headache (5.8% of patients), nausea (5.2% of patients).

Table 15 Summary of TEAEs by SOC and Preferred term

Table 17: Summary of Treatment-emergent Adverse Events by System Organ Class and Preferred Term Experienced by at Least One Placebo- or 10, 10, 20 mg Ataluren-treated Patient During the First 28 Days of Treatment in the Pooled Studies (Study 007 and Study 020) or Study 030 (Safety Population)

System Organ Class Preferred Term	Study 007/020 Pooled Placebo (N = 172) n (%)	Studies 007/020 10, 10, 20 mg/kg Ataluren (N = 172) n (%)	Study 030 10, 10, 20 mg/kg Ataluren (N = 14) n (%)
Patients with at least 1 TEAE	**52 (30.2)**	**81 (47.1)**	**10 (71.4)**
Cardiac Disorders	**1 (0.6)**	**1 (0.6)**	**0 (0.0)**
Left ventricular dysfunction	0 (0.0)	1 (0.6)	0 (0.0)
Myocardial fibrosis	0 (0.0)	1 (0.6)	0 (0.0)
Myocarditis	1 (0.6)	0 (0.0)	0 (0.0)
Ear and Labyrinth Disorders	**2 (1.2)**	**2 (1.2)**	**0 (0.0)**
Ear pains	1 (0.6)	1 (0.6)	0 (0.0)
Ear congestion	0 (0.0)	1 (0.6)	0 (0.0)
Tinnitus	1 (0.6)	0 (0.0)	0 (0.0)
Eye disorders	**1 (0.6)**	**1 (0.6)**	0 (0.0)
Eyelid cyst	0 (0.0)	0 (0.0)	0 (0.0)
Eye pain	0 (0.0)	1 (0.6)	0 (0.0)
Eye swelling	1 (0.6)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	**20 (11.6)**	**47 (27.3)**	**4 (28.6)**
Diarrhoea	5 (2.9)	15 (8.7)	0 (0.0)
Vomiting	8 (4.7)	26 (15.1)	0 (0.0)
Flatulence	2 (1.2)	4 (2.3)	2 (14.3)
Nausea	2 (1.2)	9 (5.2)	0 (0.0)
Abdominal pain upper	2 (1.2)	8 (4.7)	1 (7.1)
Abdominal pain	1 (0.6)	6 (3.5)	0 (0.0)
Abdominal discomfort	1 (0.6)	3 (1.7)	0 (0.0)
Constipation	1 (0.6)	1 (0.6)	1 (7.1)
Frequent bowel movements	1 (0.6)	0 (0.0)	0 (0.0)
Anal pruritus	0 (0.0)	1 (0.6)	0 (0.0)
Dyspepsia	0 (0.0)	1 (0.6)	0 (0.0)
Hemorrhoids	0 (0.0)	1 (0.6)	0 (0.0)
Ileus	0 (0.0)	1 (0.6)	0 (0.0)
Aerophagia	2 (1.2)	0 (0.0)	0 (0.0)
Gastroesophageal reflux disease	1 (0.6)	0 (0.0)	0 (0.0)
Lip dry	1 (0.6)	0 (0.0)	0 (0.0)

System Organ Class Preferred Term	Study 007/020 Pooled Placebo (N = 172) n (%)	Studies 007/020 10, 10, 20 mg/kg Ataluren (N = 172) n (%)	Study 030 10, 10, 20 mg/kg Ataluren (N = 14) n (%)
General disorders and administration site conditions	**4 (2.3)**	**8 (4.7)**	**5 (35.7)**
Malaise	1 (0.6)	0 (0.0)	1 (7.1)
Pyrexia	0 (0.0)	5 (2.9)	4 (28.6)
Disease progression	0 (0.0)	1 (0.6)	0 (0.0)
Thirst	1 (0.6)	0 (0.0)	0 (0.0)
Fatigue	0 (0.0)	1 (0.6)	0 (0.0)
Influenza like illness	0 (0.0)	1 (0.6)	0 (0.0)
Energy increased	1 (0.6)	0 (0.0)	0 (0.0)
Non-cardiac chest pain	1 (0.6)	0 (0.0)	0 (0.0)
Immune system disorders	**0 (0.0)**	**1 (0.6)**	**0 (0.0)**
Seasonal allergy	0 (0.0)	1 (0.6)	0 (0.0)
Infections and infestations	**16 (9.3)**	**19 (11.0)**	**3 (21.4)**
Ear infection	0 (0.0)	0 (0.0)	1 (7.1)
Nasopharyngitis	5 (2.9)	7 (4.1)	1 (7.1)
Respiratory tract infection	0 (0.0)	1 (0.6)	1 (7.1)
Rhinitis	0 (0.0)	3 (1.7)	1 (7.1)
Upper respiratory tract infection	2 (1.2)	1 (0.6)	1 (7.1)
Viral rash	0 (0.0)	0 (0.0)	1 (7.1)
Sinusitis	3 (1.7)	1 (0.6)	0 (0.0)
Hordeolum	0 (0.0)	1 (0.6)	0 (0.0)
Gastroenteritis	0 (0.0)	2 (1.2)	0 (0.0)
Influenza	1 (0.6)	1 (0.6)	0 (0.0)
Tonsillitis	1 (0.6)	1 (0.6)	0 (0.0)
Fungal skin infection	0 (0.0)	1 (0.6)	0 (0.0)
Gingivitis	0 (0.0)	1 (0.6)	0 (0.0)
Lower respiratory tract infection	0 (0.0)	1 (0.6)	0 (0.0)
Paronychia	0 (0.0)	1 (0.6)	0 (0.0)
Pharyngitis	0 (0.0)	1 (0.6)	0 (0.0)
Varicella	0 (0.0)	1 (0.6)	0 (0.0)
Skin infection	2 (1.2)	0 (0.0)	0 (0.0)
Oral herpes	1 (0.6)	0 (0.0)	0 (0.0)
Otitis media	1 (0.6)	0 (0.0)	0 (0.0)
Pharyngitis streptococcal	1 (0.6)	0 (0.0)	0 (0.0)
Urinary tract infection	1 (0.6)	0 (0.0)	0 (0.0)

System Organ Class Preferred Term	Study 007/020 Pooled Placebo (N = 172) n (%)	Studies 007/020 10, 10, 20 mg/kg Ataluren (N = 172) n (%)	Study 030 10, 10, 20 mg/kg Ataluren (N = 14) n (%)
Injury, poisoning, and procedural complications	**4 (2.3)**	**5 (2.9)**	**1 (7.1)**
Contusion	0 (0.0)	0 (0.0)	1 (7.1)
Fall	3 (1.7)	2 (1.2)	0 (0.0)
Limb injury	1 (0.6)	1 (0.6)	0 (0.0)
Ligament sprain	0 (0.0)	1 (0.6)	0 (0.0)
Spinal compression fracture	0 (0.0)	1 (0.6)	0 (0.0)
Post-traumatic pain	1 (0.6)	0 (0.0)	0 (0.0)
Investigations	**1 (0.6)**	**1 (0.6)**	**0 (0.0)**
Blood alkaline phosphatase increased	0 (0.0)	1 (0.6)	0 (0.0)
Weight increased	1 (0.6)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	**1 (0.6)**	**4 (2.3)**	**2 (14.3)**
Decreased appetite	1 (0.6)	3 (1.7)	1 (7.1)
Metabolic acidosis	0 (0.0)	0 (0.0)	1 (7.1)
Fluid retention	0 (0.0)	1 (0.6)	0 (0.0)
Musculoskeletal and connective tissue disorders	**3 (1.7)**	**8 (4.7)**	**0 (0.0)**
Pain in extremity	1 (0.6)	1 (0.6)	0 (0.0)
Myalgia	0 (0.0)	1 (0.6)	0 (0.0)
Back pain	1 (0.6)	2 (1.2)	0 (0.0)
Arthralgia	1 (0.6)	1 (0.6)	0 (0.0)
Joint swelling	0 (0.0)	1 (0.6)	0 (0.0)
Muscle atrophy	0 (0.0)	1 (0.6)	0 (0.0)
Scoliosis	0 (0.0)	1 (0.6)	0 (0.0)
Tendinous contracture	0 (0.0)	1 (0.6)	0 (0.0)
Nervous system disorders	**9 (5.2)**	**13 (7.6)**	**1 (7.1)**
Headache	8 (4.7)	10 (5.8)	1 (7.1)
Psychomotor hyperactivity	1 (0.6)	1 (0.6)	0 (0.0)
Autism	0 (0.0)	1 (0.6)	0 (0.0)
Migraine	0 (0.0)	1 (0.6)	0 (0.0)
Psychiatric disorders	**2 (1.2)**	**2 (1.2)**	**1 (7.1)**
Enuresis	0 (0.0)	0 (0.0)	1 (7.1)
Attention deficit/hyperactivity disorder	0 (0.0)	1 (0.6)	0 (0.0)
Abnormal behavior	0 (0.0)	1 (0.6)	0 (0.0)
Aggression	0 (0.0)	1 (0.6)	0 (0.0)
Negativism	0 (0.0)	1 (0.6)	0 (0.0)
Mood swings	2 (1.2)	0 (0.0)	0 (0.0)
Anxiety	1 (0.6)	0 (0.0)	0 (0.0)
Sleep disorder	1 (0.6)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	**0 (0.0)**	**1 (0.6)**	**0 (0.0)**
Pruritus genital	0 (0.0)	1 (0.6)	0 (0.0)

System Organ Class Preferred Term	Study 007/020 Pooled Placebo (N = 172) n (%)	Studies 007/020 10, 10, 20 mg/kg Ataluren (N = 172) n (%)	Study 030 10, 10, 20 mg/kg Ataluren (N = 14) n (%)
Renal and Urinary disorders	**3 (1.7)**	**4 (2.3)**	**0 (0.0)**
Enuresis	1 (0.6)	3 (1.7)	0 (0.0)
Urine abnormality	1 (0.6)	1 (0.6)	0 (0.0)
Polyuria	0 (0.0)	1 (0.6)	0 (0.0)
Strangury	0 (0.0)	1 (0.6)	0 (0.0)
Urinary incontinence	1 (0.6)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**8 (4.7)**	**10 (5.8)**	**1 (7.1)**
Cough	2 (1.2)	3 (1.7)	1 (7.1)
Oropharyngeal pain	3 (1.7)	2 (1.2)	0 (0.0)
Nasal congestion	2 (1.2)	2 (1.2)	0 (0.0)
Rhinorrhea	0 (0.0)	2 (1.2)	0 (0.0)
Epistaxis	2 (1.2)	1 (0.6)	0 (0.0)
Skin and subcutaneous tissue disorders	**4 (2.3)**	**9 (5.2)**	**4 (28.6)**
Hypertrichosis	0 (0.0)	0 (0.0)	1 (7.1)
Rash	2 (1.2)	2 (1.2)	3 (21.4)
Rash erythematous	0 (0.0)	3 (1.7)	0 (0.0)
Dry skin	1 (0.6)	1 (0.6)	0 (0.0)
Ecchymosis	0 (0.0)	1 (0.6)	0 (0.0)
Erythema	0 (0.0)	1 (0.6)	0 (0.0)
Hair texture abnormal	0 (0.0)	1 (0.6)	0 (0.0)
Keratosis pilaris	0 (0.0)	1 (0.6)	0 (0.0)
Skin burning sensation	0 (0.0)	1 (0.6)	0 (0.0)
Skin exfoliation	1 (0.6)	0 (0.0)	0 (0.0)
Vascular disorders	**2 (1.2)**	**0 (0.0)**	**0 (0.0)**
Flushing	2 (1.2)	0 (0.0)	0 (0.0)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

Safety events for the Pooled Studies were coded using MedDRA version 15.1. Safety events for Study 030 were coded using MedDRA version 19.0. In the Pooled Studies, events with the preferred term "enuresis" were coded as occurring in the Renal and Urinary Disorders system organ class, while in Study 030 these events were coded as occurring in the Psychiatric Disorders system organ class.

In the previous submission package, the as-treated population is the population for safety analyses.

A patient who experienced 2 or more events with the same preferred term is counted only once for that term. A patient who experienced 2 or more adverse events with different preferred terms within the same system organ class is counted only once in that system organ class total.

Reference: Table 14.3.1.2.1 and Table 4.2.1.1-d28

During the PK phase of Study 030, 4 patients (28.6%) experienced TEAEs of pyrexia, 4 patients (28.6%) experienced TEAEs of rash (3 [21.4%] with events with the preferred term "rash" and 1 [7.1%] with an event with the preferred term "viral rash") and 2 patients experienced TEAEs of flatulence (14.3%).

In the PK phase of Study 030, all 4 events of rash began within the first 27 days of treatment(one event each on Day 6, Day 12, Day 22, and Day 27) and were mild in severity. (The event with the preferred term of "viral rash" was considered to be unlikely related to ataluren treatment.) The 3 events with a preferred term of "rash" were considered possibly related to ataluren. Study treatment was not changed in response to any of these events, which resolved within 1 to 15 days.

All other individual adverse events were experienced by 1 patient each.

There were no deaths in the Pooled Studies or during Study 030 during the PK phase or as of the cut-off date, and no ataluren-treated patients experienced a serious adverse event (SAE) during the first 28 days of treatment in the Pooled Studies or in the PK phase of Study 030.

Table 16 Overview of TEAEs

Table 18 Overview of Treatment Emergent Adverse Events for the Pharmacokinetic Phase, Extension Phase, and Overall for Study 030 (Safety Population)

	PK Phase (N = 14) n (%)	Extension Phase (N = 14) n (%)	Overall (N = 14) n (%)
Number of TEAE	**26**	**36**	**62**
Patients with 1 or more:			
TEAE	10 (71.4)	10 (71.4)	14 (100.0)
TEAE related to study drug[a]			
Not related	5 (35.7)	9 (64.3)	9 (64.3)
Related	5 (35.7)	1 (7.1)	5 (35.7)
TEAE leading to discontinuation	0 (0.0)	0 (0.0)	0 (0.0)
SAE	0 (0.0)	0 (0.0)	0 (0.0)
TEAE with a maximum CTCAE grade of:			
Mild	6 (42.9)	6 (42.9)	7 (50.0)
Moderate	4 (28.6)	4 (28.6)	7 (50.0)
Severe	0 (0.0)	0 (0.0)	0 (0.0)
Life-threatening	0 (0.0)	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: CTCAE = Common Terminology Criteria for Adverse Events; MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event

[a]Events deemed by the investigator to have a possible or probable relationship to study drug are considered "related" while those deemed to have an unlikely or unrelated relationship are considered "not related".

Reference: Table 14.3.1.1.

Adverse Events During the Extension Phase

As of 21 July 2017, all 14 patients have completed the Week 28 visit. Adverse events beginning on or before this date are included in this submission.

As of the cut-off date, all 14 patients (100.0%) experienced at least one TEAE, including 10 (71.4%) patients who experienced TEAEs in the PK phase and 10 (71.4%) patients who experienced TEAEs in the extension phase. The most commonly occurring treatment-emergent adverse events were pyrexia (6 patients; 42.9%), rash (5 patients in total, 3 [21.4%] with events with the preferred term "rash", 1 [7.1%] with and event with the preferred term "viral rash", and 1 [7.1%] with an event with the preferred term "rash generalized"), ear infection (4 patients; 28.6%), nasopharyngitis (3 patients; 21.4%), and flatulence, vomiting, and cough (2 patients each; 14.3%). All other TEAEs were experienced by 1 (7.1%) patient each as of the cut-off date.

Table 17 Summary of TEAEs for study 030

Table 19: Summary of Treatment-emergent Adverse Events in Study 030 by System Organ Class and Preferred Term in Study 030 (Safety Population)

System Organ Class Preferred Term	PK Phase (N = 14) n (%)	Extension Phase (N = 14) n (%)	Overall (N = 14) n (%)
Patients with at least one TEAE	**10 (71.4)**	**10 (71.4)**	**14 (100.0)**
Gastrointestinal Disorders	**4 (28.6)**	**2 (14.3)**	**6 (42.9)**
Flatulence	2 (14.3)	0 (0.0)	2 (14.3)
Vomiting	0 (0.0)	2 (14.3)	2 (14.3)
Abdominal pain upper	1 (7.1)	0 (0.0)	1 (7.1)
Constipation	1 (7.1)	0 (0.0)	1 (7.1)
General disorders and administration site conditions	**5 (35.7)**	**3 (21.4)**	**6 (42.9)**
Pyrexia	4 (28.6)	3 (21.4)	6 (42.9)
Fatigue	0 (0.0)	1 (7.1)	1 (7.1)
Malaise	1 (7.1)	0 (0.0)	1 (7.1)
Infections and Infestations	**3 (21.4)**	**7 (50.0)**	**8 (57.1)**
Ear infection	1 (7.1)	3 (21.4)	4 (28.6)
Nasopharyngitis	1 (7.1)	3 (21.4)	3 (21.4)
Bronchitis viral	0 (0.0)	1 (7.1)	1 (7.1)
Conjunctivitis	0 (0.0)	1 (7.1)	1 (7.1)
Croup infectious	0 (0.0)	1 (7.1)	1 (7.1)
Gastroenteritis norovirus	0 (0.0)	1 (7.1)	1 (7.1)
Hordeolum	0 (0.0)	1 (7.1)	1 (7.1)
Pharyngitis streptococcal	0 (0.0)	1 (7.1)	1 (7.1)
Respiratory tract infection	1 (7.1)	0 (0.0)	1 (7.1)
Rhinitis	1 (7.1)	0 (0.0)	1 (7.1)
Upper respiratory tract infection	1 (7.1)	0 (0.0)	1 (7.1)
Viral rash	1 (7.1)	0 (0.0)	1 (7.1)
Injury, poisoning and procedural complications	**1 (7.1)**	**3 (21.4)**	**3 (21.4)**
Arthropod bite	0 (0.0)	2 (14.3)	2 (14.3)
Contusion	1 (7.1)	0 (0.0)	1 (7.1)
Tibia fracture	0 (0.0)	1 (7.1)	1 (7.1)
Metabolism and nutrition disorders	**2 (14.3)**	**1 (7.1)**	**3 (21.4)**
Decreased appetite	1 (7.1)	0 (0.0)	1 (7.1)
Hyperlipidemia	0 (0.0)	1 (7.1)	1 (7.1)
Metabolic acidosis	1 (7.1)	0 (0.0)	1 (7.1)

System Organ Class Preferred Term	PK Phase (N = 14) n (%)	Extension Phase (N = 14) n (%)	Overall (N = 14) n (%)
Nervous system disorders	**1 (7.1)**	**0 (0.0)**	**1 (7.1)**
Headache	1 (7.1)	0 (0.0)	1 (7.1)
Psychiatric disorders	**1 (7.1)**	**1 (7.1)**	**2 (14.3)**
Abnormal behavior	0 (0.0)	1 (7.1)	1 (7.1)
Enuresis	1 (7.1)	0 (0.0)	1 (7.1)
Insomnia	0 (0.0)	1 (7.1)	1 (7.1)
Renal and urinary disorders	**0 (0.0)**	**1 (7.1)**	**1 (7.1)**
Chromaturia	0 (0.0)	1 (7.1)	1 (7.1)
Respiratory, thoracic, and mediastinal disorders	**1 (7.1)**	**3 (21.4)**	**4 (28.6)**
Cough	1 (7.1)	1 (7.1)	2 (14.3)
Epistaxis	0 (0.0)	1 (7.1)	1 (7.1)
Rhinorrhoea	0 (0.0)	1 (7.1)	1 (7.1)
Tonsillar hypertrophy	0 (0.0)	1 (7.1)	1 (7.1)
Skin and subcutaneous tissue disorders	**4 (28.6)**	**1 (7.1)**	**5 (35.7)**
Rash	3 (21.4)	0 (0.0)	3 (21.4)
Hypertrichosis	1 (7.1)	0 (0.0)	1 (7.1)
Rash generalized	0 (0.0)	1 (7.1)	1 (7.1)
Urticaria	0 (0.0)	1 (7.1)	1 (7.1)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.
Safety events were coded using MedDRA version 19.0.
A patient who experienced 2 or more events with the same preferred term is counted only once for that term. A patient who experienced 2 or more adverse events with different preferred terms within the same system organ class is counted only once in that system organ class total.
Cut-off date: 21 July 2017
Reference: Table 14.3.1.2.1

All TEAEs in both the PK phase and the extension phase were mild or moderate in severity. Of the 10 (71.4%) patients who experienced TEAEs during the extension phase, 6 (42.9%) experienced TEAEs with a maximum CTCAE grade of mild, and 4 (28.6%) experienced TEAEs with a maximum CTCAE grade of moderate. Cumulatively, of the 14 (100%) patients who experienced a TEAE during the PK phase and the extension phase combined as of the cut-off date, 7 (50.0%) experienced TEAEs with a maximum CTCAE grade of mild and 7 (50.0%) experienced TEAEs with a maximum CTCAE grade of moderate.

Table 18 Summary of TEAEs by SOC experienced by at least 1 patient sor the furst 28days of treatment.

Table 20: **Summary of Treatment-related Treatment-emergent Adverse Events by System Organ Class and Preferred Term Experienced by at Least One 10, 10, 20 mg Ataluren-treated Patient During the First 28 Days of Treatment in the Pooled Studies (Study 007 and Study 020) or Study 030 (Safety Population)**

System Organ Class Preferred Term	Study 007/020 Pooled Placebo (N = 172) n (%)	Studies 007/020 10, 10, 20 mg/kg Ataluren (N = 172) n (%)	Study 030 10, 10, 20 mg/kg Ataluren (N = 14) n (%)
Patients with at least one related TEAE[a]	**15 (8.7)**	**37 (21.5)**	**5 (35.7)**
Ear and labyrinth disorders	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**
Tinnitus	1 (0.6)	0 (0.0)	0 (0.0)
Gastrointestinal Disorders	**8 (4.7)**	**24 (14.0)**	**2 (14.3)**
Diarrhoea	4 (2.3)	6 (3.5)	0 (0.0)
Vomiting	2 (1.2)	8 (4.7)	0 (0.0)
Nausea	0 (0.0)	5 (2.9)	0 (0.0)
Abdominal Pain	0 (0.0)	5 (2.9)	0 (0.0)
Flatulence	1 (0.6)	4 (2.3)	2 (14.3)
Abdominal discomfort	1 (0.6)	3 (1.7)	0 (0.0)
Abdominal pain upper	0 (0.0)	3 (1.7)	0 (0.0)
Aerophagia	2 (1.2)	0 (0.0)	0 (0.0)
Frequent bowel movements	1 (0.6)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	**1 (0.6)**	**2 (1.2)**	**1 (7.1)**
Malaise	0 (0.0)	0 (0.0)	1 (7.1)
Fatigue	0 (0.0)	1 (0.6)	0 (0.0)
Pyrexia	0 (0.0)	1 (0.6)	0 (0.0)
Energy increased	1 (0.6)	0 (0.0)	0 (0.0)
Infections and Infestations	**0 (0.0)**	**2 (1.2)**	**0 (0.0)**
Gastroenteritis	0 (0.0)	1 (0.6)	0 (0.0)
Lower respiratory tract infection	0 (0.0)	1 (0.6)	0 (0.0)
Injury, poisoning and procedural complications	**0 (0.0)**	**1 (0.6)**	**0 (0.0)**
Limb injury	0 (0.0)	1 (0.6)	0 (0.0)
Investigations	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**
Weight increased	1 (0.6)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	**1 (0.6)**	**3 (1.7)**	**0 (0.0)**
Decreased appetite	1 (0.6)	3 (1.7)	0 (0.0)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**2 (1.2)**	**0 (0.0)**
Back pain	0 (0.0)	1 (0.6)	0 (0.0)
Muscle atrophy	0 (0.0)	1 (0.6)	0 (0.0)
Pain in extremity	0 (0.0)	1 (0.6)	0 (0.0)
Nervous system disorders	**3 (1.7)**	**6 (3.5)**	**0 (0.0)**
Headache	2 (1.2)	5 (2.9)	0 (0.0)
Migraine	0 (0.0)	1 (0.6)	0 (0.0)
Psychomotor hyperactivity	1 (0.6)	0 (0.0)	0 (0.0)

System Organ Class Preferred Term	Study 007/020 Pooled Placebo (N = 172) n (%)	Studies 007/020 10, 10, 20 mg/kg Ataluren (N = 172) n (%)	Study 030 10, 10, 20 mg/kg Ataluren (N = 14) n (%)
Psychiatric disorders	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**
Mood swings	1 (0.6)	0 (0.0)	0 (0.0)
Sleep disorder	1 (0.6)	0 (0.0)	0 (0.0)
Renal and urinary disorders	**0 (0.0)**	**3 (1.7)**	**0 (0.0)**
Enuresis	0 (0.0)	1 (0.6)	0 (0.0)
Polyuria	0 (0.0)	1 (0.6)	0 (0.0)
Urine abnormality	0 (0.0)	1 (0.6)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	**1 (0.6)**	**1 (0.6)**	**0 (0.0)**
Cough	0 (0.0)	1 (0.6)	0 (0.0)
Epistaxis	1 (0.6)	0 (0.0)	0 (0.0)
Skin and subcutaneous tissue disorders	**0 (0.0)**	**2 (1.2)**	**3(21.4)**
Rash	0 (0.0)	0 (0.0)	3 (21.4)
Rash erythematous	0 (0.0)	2 (1.2)	0 (0.0)
Skin burning sensation	0 (0.0)	1 (0.6)	0 (0.0)
Vascular disorders	**1 (0.6)**	**0 (0.0)**	**0 (0.0)**
Flushing	1 (0.6)	0 (0.0)	0 (0.0)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; TEAE = treatment-emergent adverse event.

[a]Events deemed by the investigator to have a possible or probable relationship to study drug are considered "related" while those deemed to have an unlikely or unrelated relationship are considered "not related".

Safety events for the Pooled Studies were coded using MedDRA version 15.1. Safety events for Study 030 were coded using MedDRA version 19.0.

In the previous submission package, the as-treated population is the population for safety analyses.

A patient who experienced 2 or more events with the same preferred term is counted only once for that term. A patient who experienced 2 or more adverse events with different preferred terms within the same system organ class is counted only once in that system organ class total.

Reference: Table 14.3.1.5 and Table 4.2.1.5A-d28

Treatment-related adverse events are those deemed by the investigator to have a possible or probable relationship to study drug. In the PK phase, 3 events of rash and 2 events of flatulence were considered related to ataluren treatment by the investigator. In the extension phase as of the cut-off date, one event of fatigue was considered related to ataluren treatment by the investigator.

No patient to date discontinued from the study due to a TEAE. In addition, there were no SAEs or deaths in the PK phase or the extension phase of Study 030 as of the cut-off date.

Laboratory findings

No clinically meaningful trends in hematology, clinical chemistry, or urinalysis parameters were observed during the 28-day PK phase of Study 030 or the extension phase as of the cutoff date, and shifts from normal values at baseline to abnormal values at Week 4 and Week 28 were infrequent. Laboratory abnormalities were similar to those seen in the Pooled Studies and attributable to the underlying disease.

Duchenne muscular dystrophy is associated with elevated total cholesterol and triglycerides [Srivastava 2010] in part attributable to the use of corticosteroids, and changes in lipid profile are an identified risk associated with ataluren treatment for DMD [SmPC April 2017]. Most patients in Study 030 had normal values for HDL, LDL, total cholesterol, and triglycerides at baseline and at Week 28. At Week 28, there were mean increases from baseline in cholesterol and HDL levels of 13%, while LDL levels increased by 18%. Mean triglyceride levels were decreased more than 8% from baseline at Week 28. Shifts from normal baseline values to abnormal values at Week 28 for lipid parameters were infrequent and experienced by 4 patients for total cholesterol (two of whom were receiving concomitant treatment with steroids), 1 patient for LDL, and 2 patients for triglycerides (1 of whom was receiving concomitant steroid treatment). In general, these patients had values at the higher end of the normal range at baseline and experienced relatively small increases to values above the upper limit of normal at Week 28.

Table 19 Changes in lipid parameters

Table 21: Mean Changes in Lipid Parameters from Baseline at Week 4 and Week 28 for Patients with Baseline and Post-baseline Assessments in Study 030 (Safety Population)

Parameter / Statistic	Study 030 10, 10, 20 mg/kg Ataluren (N = 14)	
	Week 4	Week 28
Total Cholesterol, mmol/L	(n = 13)	(n = 14)
Baseline, mean (SD)	4.542 (1.1543)	4.446 (1.1656)
Postbaseline, mean (SD)	4.916 (1.4167)	5.044 (1.4521)
Change from baseline, mean (SD)	0.375 (0.6521)	0.599 (0.5792)
Change from baseline, Median (range)	0.320 (-0.30, 2.27)	0.720 (-0.58, 1.38)
HDL, mmol/L	(n = 13)	(n = 14)
Baseline, mean (SD)	1.175 (0.2537)	1.171 (0.2442)
Postbaseline, mean (SD)	1.234 (0.3149)	1.320 (0.2489)
Change from baseline, mean (SD)	0.059 (0.3737)	0.149 (0.2460)
Change from baseline, Median (range)	-0.020 (-0.58, 0.80)	0.160 (-0.44, 0.56)
LDL, mmol/L	(n = 13)	(n = 14)
Baseline, mean (SD)	2.741 (1.0151)	2.679 (1.0020)
Postbaseline, mean (SD)	3.239 (1.1161)	3.169 (1.2374)
Change from baseline, mean (SD)	0.498 (0.4984)	0.489 (0.4301)
Change from baseline, Median (range)	0.430 (-0.11, 2.00)	0.485 (-0.36, 1.23)
Triglycerides, mmol/L	(n = 13)	(n = 14)
Baseline, mean (SD)	2.108 (0.9387)	2.019 (0.9616)
Postbaseline, mean (SD)	1.683 (0.7684)	1.847 (0.7587)
Change from baseline, mean (SD)	-0.425 (0.5881)	-0.172 (0.8877)
Change from baseline, Median (range)	-0.470 (-1.45, 0.90)	-0.180 (-1.74, 1.66)

Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein; SD = standard deviation.
Note: Baseline is the last assessment recorded prior to the first dose of study drug.
Reference: Table 14.3.6.2

Table 22: **Shifts in Serum Lipid Profile Clinical Laboratory Assessments from Baseline to Week 4 in Study 030 (Safety Population)**

Parameter (n)	Baseline Result	Post-baseline Result (Week 4)[a]		
		Low n (%)	Normal n (%)	High n (%)
Total Cholesterol (n = 13)	Low	0 (0.0)	0 (0.0)	0 (0.0)
	Normal	0 (0.0)	9 (69.2)	2 (15.4)
	High	0 (0.0)	0 (0.0)	2 (15.4)
	Total	0 (0.0)	9 (69.2)	4 (30.8)
HDL (n = 13)	Low	2 (15.4)	3 (23.1)	0 (0.0)
	Normal	1 (7.7)	7 (53.8)	0 (0.0)
	High	0 (0.0)	0 (0.0)	0 (0.0)
	Total	3 (23.1)	10 (76.9)	0 (0.0)
LDL (n = 13)	Low	0 (0.0)	0 (0.0)	0 (0.0)
	Normal	0 (0.0)	9 (69.2)	1 (7.7)
	High	0 (0.0)	0 (0.0)	3 (23.1)
	Total	0 (0.0)	9 (69.2)	4 (30.8)
Triglycerides (n = 13)	Low	0 (0.0)	0 (0.0)	0 (0.0)
	Normal	0 (0.0)	8 (61.5)	0 (0.0)
	High	0 (0.0)	3 (23.1)	2 (15.4)
	Total	0 (0.0)	11 (84.6)	2 (15.4)

Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein.
[a]Percentages are calculated with the denominator as the number of patients who had non-missing values for both baseline and the Week 4 post-baseline assessment.
Reference: Table 14.3.6.5

Table 23: Shifts in Serum Lipid Profile Clinical Laboratory Assessments from Baseline in Study 030 (Safety Population)

Parameter (n)	Baseline Result	Post-baseline Result (Week 28)[a]		
		Low n (%)	Normal n (%)	High n (%)
Total Cholesterol (n = 14)	Low	0 (0.0)	0 (0.0)	0 (0.0)
	Normal	0 (0.0)	8 (57.1)	4 (28.6)
	High	0 (0.0)	0 (0.0)	2 (14.3)
	Total	0 (0.0)	8 (57.1)	6 (42.9)
HDL (n = 14)	Low	1 (7.1)	4 (28.6)	0 (0.0)
	Normal	0 (0.0)	9 (64.3)	0 (0.0)
	High	0 (0.0)	0 (0.0)	0 (0.0)
	Total	1 (7.1)	13 (92.9)	0 (0.0)
LDL (n = 14)	Low	0 (0.0)	0 (0.0)	0 (0.0)
	Normal	0 (0.0)	10 (71.4)	1 (7.1)
	High	0 (0.0)	0 (0.0)	3 (21.4)
	Total	0 (0.0)	10 (71.4)	4 (28.6)
Triglycerides (n = 14)	Low	0 (0.0)	0 (0.0)	0 (0.0)
	Normal	0 (0.0)	7 (50.0)	2 (14.3)
	High	0 (0.0)	3 (21.4)	2 (14.3)
	Total	0 (0.0)	10 (71.4)	4 (28.6)

Abbreviations: HDL = high-density lipoprotein; LDL = low-density lipoprotein.
[a]Percentages are calculated with the denominator as the number of patients who had non-missing values for both baseline and the Week 28 post-baseline assessment.
Reference: Table 14.3.6.5

As is characteristic of patients with DMD due to the leakage of enzymes from the muscle in the absence of dystrophin [Tay 2000], elevated levels of AST and ALT were common at baseline in Study 030. Low baseline levels of bilirubin were also common, while GGT levels were typically normal at baseline and on treatment. At Week 28, small mean decreases in AST and bilirubin, and small mean increases in GGT and ALT were observed. These changes were not clinically significant. There were no patients with shifts from normal baseline values to abnormal values for ALT or AST at Week 28. One patient with a normal value at baseline for GGT experienced a shift to a low value for that parameter at Week 28; 2 patients with normal baseline values for bilirubin also experienced a shift to low values at Week 28.

Table 20 Changes in hepatic parameters

Table 24: Mean Changes in Hepatic Parameters from Baseline to Week 4 and Week 28 for Patients with Baseline and Post-baseline Assessments in Study 030 (Safety Population)

Parameter / Visit	Study 030 10, 10, 20 mg/kg Ataluren (N = 14)	
	Week 4	Week 28
AST, u/L	(n = 10)	(n = 12)
Baseline, mean (SD)	348.1 (102.62)	327.2 (106.18)
Postbaseline, mean (SD)	319.5 (75.22)	289.7 (101.22)
Change from baseline, mean (SD)	-28.6 (81.79)	-37.5(107.61)
Change from baseline, Median (range)	-23.0 (-194, 105)	-49.5 (-226, 159)
ALT, u/L	(n =12)	(n = 14)
Baseline, mean (SD)	428.1 (119.03)	426.4 (110.21)
Postbaseline, mean (SD)	423.0 (139.58)	432.2 (164.33/)
Change from baseline, mean (SD)	-5.1 (159.75)	5.9 (139.37)
Change from baseline, Median (range)	-14.0 (-389, 286)	0 (-268, 247)
GGT, u/L	(n = 13)	(n = 14)
Baseline, mean (SD)	5.8 (1.99)	5.8 (1.93)
Postbaseline, mean (SD)	6.0 (2.08)	6.8 (3.58)
Change from baseline, mean (SD)	0.2 (1.52)	1.0 (3.16)
Change from baseline, Median (range)	0.0 (-2, 3)	0 (-2, 11)
Bilirubin, µmol/L	(n =11)	(n = 12)
Baseline, mean (SD)	3.4 (1.21)	3.7 (1.56)
Postbaseline, mean (SD)	3.5 (0.93)	3.3 (0.62)
Change from baseline, mean (SD)	0.2 (1.66)	-0.4 (1.00)
Change from baseline, Median (range)	0.0 (-4, 3)	0.0 (-3, 0)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase.
Reference: Table 14.3.6.2

Table 25: Shifts in Hepatic Enzyme Clinical Laboratory Assessments from Baseline to Week 4 in Study 030 (Safety Population)

Parameter (n)	Baseline Result	Post-baseline Result (Week 4)		
		Low n (%)[a]	Normal n (%)	High n (%)
AST (n = 10)	Low	0 (0.0)	0 (0.0)	0 (0.0)
	Normal	0 (0.0)	0 (0.0)	0 (0.0)
	High	0 (0.0)	0 (0.0)	10 (100.0)
	Total	0 (0.0)	0 (0.0)	10 (100.0)
ALT (n = 12)	Low	0 (0.0)	0 (0.0)	0 (0.0)
	Normal	0 (0.0)	0 (0.0)	0 (0.0)
	High	0 (0.0)	0 (0.0)	12 (100.0)
	Total	0 (0.0)	0 (0.0)	12 (100.0)
GGT (n = 13)	Low	0 (0.0)	1 (7.7)	0 (0.0)
	Normal	0 (0.0)	12 (92.3)	0 (0.0)
	High	0 (0.0)	0 (0.0)	0 (0.0)
	Total	0 (0.0)	13 (100.0)	0 (0.0)
Bilirubin (n = 11)	Low	4 (36.4)	4 (36.4)	0 (0.0)
	Normal	1 (9.1)	2 (18.2)	0 (0.0)
	High	0 (0.0)	0 (0.0)	0 (0.0)
	Total	5 (45.5)	6 (54.4)	0 (0.0)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase.

[a]Percentages are calculated with the denominator as the number of patients who had non-missing values for both baseline and the Week 4 post-baseline assessment.

Reference: Table 14.3.6.5

Table 26: Shifts in Hepatic Enzyme Clinical Laboratory Assessments from Baseline to Week 28 in Study 030 (Safety Population)

Parameter (n)	Baseline Result	Post-baseline Result (Week 28)		
		Low n (%)[a]	Normal n (%)	High n (%)
AST (n = 12)	Low	0 (0.0)	0 (0.0)	0 (0.0)
	Normal	0 (0.0)	0 (0.0)	0 (0.0)
	High	0 (0.0)	0 (0.0)	12 (100.0)
	Total	0 (0.0)	0 (0.0)	12 (100.0)
ALT (n = 14)	Low	0 (0.0)	0 (0.0)	0 (0.0)
	Normal	0 (0.0)	0 (0.0)	0 (0.0)
	High	0 (0.0)	0 (0.0)	14 (100.0)
	Total	0 (0.0)	0 (0.0)	14 (100.0)
GGT (n = 14)	Low	0 (0.0)	1 (7.1)	0 (0.0)
	Normal	1 (7.1)	12 (85.7)	0 (0.0)
	High	0 (0.0)	0 (0.0)	0 (0.0)
	Total	1 (7.1)	13 (92.9)	0 (0.0)
Bilirubin (n = 12)	Low	5 (41.7)	3 (25.0)	0 (0.0)
	Normal	2 (16.7)	2 (16.7)	0 (0.0)
	High	0 (0.0)	0 (0.0)	0 (0.0)
	Total	7 (58.3)	5 (41.7)	0 (0.0)

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma glutamyl transferase.
[a]Percentages are calculated with the denominator as the number of patients who had non-missing values for both baseline and the Week 4 post-baseline assessment.
Reference: Table 14.3.6.5

Low levels of serum creatinine can be characteristic of patients with DMD, since creatinine is produced in skeletal muscle, and patients with compromised muscle mass have correspondingly low levels of serum creatinine [Zhang 2015]. At Week 28, the mean values for serum creatinine and cystatin C were slightly increased from baseline. These changes were not clinically significant. The mean BUN value was unchanged from baseline to Week 28. All patients had normal values for cystatin C at both baseline and Week 28. Five patients had low serum creatinine values at baseline; 3 also had low values for serum creatinine at Week 28, while 2 had normal values at the latter timepoint. Nine patients had normal values for serum creatinine at baseline, 4 of whom had a shift to a low value at Week 28. One patient experienced a shift from a normal baseline value to an elevated BUN value at Week 28. Creatinine levels and urinalysis were normal for this patient throughout the treatment. No patients had elevated values for creatinine or cystatin C.

There were no patients with shifts from normal values at baseline to abnormal values at Week 28 for albumin, alkaline phosphatase, calcium, creatine kinase, direct bilirubin, glucose, indirect bilirubin, lactate dehydrogenase, protein, or sodium.

Table 21 Changes in renal parameters

Table 27: Mean Changes in Renal Parameters from Baseline to Week 4 and Week 28 for Patients with Baseline and Post-baseline Assessments in Study 030 (Safety Population)

Parameter / Statistic	Study 030 10, 10, 20 mg/kg Ataluren (N = 14)	
	Week 4	Week 28
Serum creatinine, µmol/L	(n = 13)	(n = 14)
Baseline, mean (SD)	19.4 (4.21)	19.3 (4.07)
Postbaseline, mean (SD)	18.6 (3.62)	22.6 (7.66)
Change from baseline, mean (SD)	-0.8 (3.14)	3.3 (7.02)
Change from baseline, Median (range)	-1.0 (-6, 6)	2.0 (-4, 22)
BUN, mmol/L	(n = 13)	(n =14)
Baseline, mean (SD)	4.15 (1.124)	4.10 (1.093)
Postbaseline, mean (SD)	3.90 (0.796)	4.12 (1.244)
Change from baseline, mean (SD)	-0.25 (0.942)	0.02 (1.357)
Change from baseline, Median (range)	0.10 (-1.7, 0.7)	0.00 (-2.0, 3.2)
Cystatin C, mg/L	(n = 13)	(n = 14)
Baseline, mean (SD)	0.807 (0.1017)	0.809 (0.0981)
Postbaseline, mean (SD)	0.885 (0.1628)	0.916 (0.1207)
Change from baseline, mean (SD)	0.078 (0.1111)	0.107 (0.0906)
Change from baseline, Median (range)	0.050 (-0.14, 0.28)	0.110 (-0.03, 0.22)

Abbreviation: BUN = blood urea nitrogen
Reference: Table 14.3.6.2

Table 28: Shifts in Renal Clinical Laboratory Assessments from Baseline to Week 4 in Study 030 (Safety Population)

Parameter (n)	Baseline Result	Post-baseline Result (Week 4)		
		Low n (%)a	Normal n (%)	High n (%)
Serum creatinine (n = 13)	Low	3 (23.1)	1 (7.7)	0 (0.0)
	Normal	3 (23.1)	6 (46.2)	0 (0.0)
	High	0 (0.0)	0 (0.0)	0 (0.0)
	Total	6 (46.2)	7 (53.8)	0 (0.0)
BUN (n = 13)	Low	0 (0.0)	0 (0.0)	0 (0.0)
	Normal	0 (0.0)	13 (100.0)	0 (0.0)
	High	0 (0.0)	0 (0.0)	0 (0.0)
	Total	0 (0.0)	13 (100.0)	0 (0.0)
Cystatin C (n = 13)	Low	0 (0.0)	0 (0.0)	0 (0.0)
	Normal	0 (0.0)	13 (100.0)	0 (0.0)
	High	0 (0.0)	0 (0.0)	0 (0.0)
	Total	0 (0.0)	13 (100.0)	0 (0.0)

Abbreviation: BUN = blood urea nitrogen
[a]Percentages are calculated with the denominator as the number of patients who had non-missing values for both baseline and the Week 4 post-baseline assessment.
Reference: Table 14.3.6.5

Table 29: Shifts in Renal Clinical Laboratory Assessments from Baseline to Week 28 in Study 030 (Safety Population)

Parameter (n)	Baseline Result	Post-baseline Result (Week 28)		
		Low n (%)a	Normal n (%)	High n (%)
Serum creatinine (n = 14)	Low	3 (21.4)	2 (14.3)	0 (0.0)
	Normal	4 (28.6)	5 (35.7)	0 (0.0)
	High	0 (0.0)	0 (0.0)	0 (0.0)
	Total	7 (50.0)	7 (50.0)	0 (0.0)
BUN (n = 14)	Low	0 (0.0)	0 (0.0)	0 (0.0)
	Normal	0 (0.0)	13 (92.9)	1 (7.1)
	High	0 (0.0)	0 (0.0)	0 (0.0)
	Total	0 (0.0)	13 (92.9)	1 (7.1)
Cystatin C (n = 14)	Low	0 (0.0)	0 (0.0)	0 (0.0)
	Normal	0 (0.0)	14 (100.0)	0 (0.0)
	High	0 (0.0)	0 (0.0)	0 (0.0)
	Total	0 (0.0)	14 (100.0)	0 (0.0)

Abbreviation: BUN = blood urea nitrogen
[a]Percentages are calculated with the denominator as the number of patients who had non-missing values for both baseline and the Week 4 post-baseline assessment.
Reference: Table 14.3.6.5

At Week 28, shifts from normal to low for bicarbonate and chloride and from normal to high for magnesium, potassium, and urate were experienced by 1 patient each. Two patients with normal values at baseline had high values for phosphate at Week 28 (Table 14.3.6.5). These shifts were not clinically meaningful.

Vital Signs, Physical Findings and Other Observations Related to Safety

There were no clinically meaningful trends in vital sign parameters in Study 030 as of the cut-off date.

Electrocardiograms

Per protocol, ECGs are performed at baseline, Week 4, and Week 52 or End of Treatment. There were no clinically significant electrocardiogram (ECG) abnormalities at baseline or Week 4 in Study 030.

Other Studies Enrolling Patients Less Than 5 Years of Age

Study 012 enrolled 11 patients ≥2 years of age with nonsense mutation methylmalonic acidemia (nmMMA) to receive ataluren 5, 5, 10 mg/kg for a 28 day cycle, followed by a period of 21 to 42 days without ataluren treatment before a second cycle of ataluren at a 10, 10, 20 mg/kg dose for 28 days.

Three of the 11 patients were <5 years old at the time of enrollment; 2 patients were 3 years of age and 1 patient was 4 years of age. Ataluren treatment was well tolerated by these patients at both dose levels. Vomiting was the most frequently reported TEAE. All TEAEs were mild in severity and resolved without concomitant treatment or dose modification. No patients discontinued treatment due to a TEAE.

Table 22 TEAEs in patients < 5 years of age in Patients with Nonsense Mutation Methylmalonic Acidemia

Patient	Start Date -Stop Date	Adverse Event	Severity	Relationship To Ataluren	Action Taken	Outcome
14	27 Jul 2011– 28 Jul 2011	Cold	Mild	Unlikely related	None	Resolved
15	15 Jul 2011– 16 Jul 2011	Fever	Mild	Unlikely related	None	Resolved
	15 Jul 2011– 15 Jul 2011	Vomiting	Mild	Unlikely related	None	Resolved
	22 Aug 2011– 22 Aug 2011	Vomiting	Mild	Unlikely related	None	Resolved
	26 Jul 2011– 28 Jul 2011	Cold	Mild	Unlikely related	None	Resolved
16	2 Aug 2011– 4 Aug 2011	Coughing	Mild	Probably related	None	Resolved
	2 Aug 2011– 4 August 2011	Flatulence	Mild	Possibly related	None	Resolved
	4 Oct 2011– 12 Oct 2011	Rash	Mild	Possibly related	None	Resolved
	7 Oct 2011– 7 Oct 2011	Vomiting	Mild	Probably related	None	Resolved
	9 Aug 2011– 9 Aug 2011	Vomiting	Mild	Possibly related	None	Resolved
	12 Sept 2011– 12 Sept 2011	Vomiting	Mild	Unlikely related	None	Resolved

2.5.1. Discussion on clinical safety

The reported adverse events are in line with the reported events for the patient population >5 years.

However, in the first 28 days of exposure the overall frequency of TEAEs in Study 030 was higher than in the pooled studies 007 and 020 (10 patients; 71.4% versus 81 patients; 47.1%). The higher frequency seems to be driven by a higher frequency of malaise(7,1%), pyrexia (42.9%), ear infection (28,6%) and rash (21,4%), which may be considered as more frequent in younger children in general.

For the 28 week cut off, the most common TEAEs were vomiting, diarrhoea, headache, nausea.

All patients experienced at least one TEAE, however, these were all mild to moderate in nature.

The laboratory test analysis showed an increase in cholesterol and triglycerides, shifting into the abnormal range. At 4 weeks 2 patients shifted from normal to the high range. At 28 weeks an additional 2, leading to a total of 4 patients shifted to the high range of cholesterol. This could indicate that the cholesterol levels increase over time. Therefore, data from longer exposure is required. The increase in triglyceride was observed after 28 weeks and was not detected yet at 4 weeks.

The cholesterol and triglyceride increase is observed in patients both with and without corticosteroid treatment. This indicates that ataluren treatment alone may result in elevated cholesterol and triglycerides reaching abnormal high levels. Furthermore, the renal parameters tested show an increase in blood urea nitrogen. This could indicate an effect on renal function over time. Both these safety concerns are mentioned in the SmPC and are part of the RMP.

2.5.2. Conclusions on clinical safety

The available data on the safety of ataluren in the target population confirm the known safety profile of the product and do not raise any new concerns. They can be used to support the conclusion that there are reasons to believe that from a safety perspective, ataluren would behave similarly in DMD patients 2-5-year-old as in those >5 years old.

2.5.3. PSUR cycle

The PSUR cycle remains unchanged.

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan (RMP):

The PRAC considered that the RMP version 7.1 dated 23 February 2018 is acceptable.

The CHMP endorsed this advice without changes.

Summary of Safety concerns

Important identified risks	• Potentiation of aminoglycoside renal toxicity
Important potential risks	• Long-term cardiovascular effects including changes in lipid profile[1] • Hypertension with use of concomitant systemic corticosteroids • Renal toxicity • Hepatic toxicity • Hibernoma • Malignancies in general
Missing information[2,3,4]	• Effect of co-administration of ataluren with nephrotoxic drugs other than intravenous aminoglycosides • Use in patients with moderate to severe renal impairment • Potential use in children from 6 months to less than 2 years • Extended long-term safety • Off-label use in patients who do not have DMD caused by a nonsense mutation in the dystrophin gene • Effect of co-administration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies

[1]Change in lipid profile was previously classified as an important identified risk however due to the signfiicant overlap between the risk and the important potential risk of long-term cardiovascular effects, the risk has been reclassified and is presently encompassed within the important potential risk: long-term cardiovascular effects.

[2]Use in patients with moderate to severe hepatic impairment is no longer considered missing information based on enhanced understanding through PTC124-GD-033-HV, a study that evaluated the safety and PK of ataluren in patients with moderate to severe hepatic impairment (PRAC recommendation on PSUSA/00010274/201707 – 08 February 2018). The study was conducted to develop guidance for ataluren dosing in this population. Chronic hepatic impairment is an uncommon baseline comorbidity among nmDMD patients. The study completed in Q32017 and it was concluded no dose adjustments are necessary.

[3]The use in patients whose ethnic origin is other than Caucasian is no longer considered missing information. The MAH has evaluated the evidence base to date and has found no meaningful difference in efficacy or safety with ataluren use in patients of non-Caucasian ethnic origin.

[4]Safety with use in patients who do not have DMD caused by a nonsense mutation in the dystrophin gene is not established and there are no studies planned to evaluate off-label use. As such, off-label use of this type will continue to be classified and monitored as missing information.

Pharmacovigilance plan

Summary Table of Ongoing and Planned Additional Pharmacovigilance Activities

Study/activity type, title and category	Objectives	Safety concern addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
Post-approval registry Protocol PTC124-GD-025o-DMD, "Long-Term Observational Study of Translarna Safety and Effectiveness in Usual Care" **Category 3**	To assess long term safety and effectiveness in usual care	All potential risks and missing information for ataluren.	Started	Annual reports starting April 2016 April 2023 (final)
Extension to Open-label safety and PK study in children 2 years to 5 years of age, Study 6 of the current PIP for dystrophinopathy Protocol PTC124-GD-030 DMD, "A Phase 2 Study of the Safety, Pharmacokinetics, and Pharmacodynamics of Ataluren (PTC124) in Patients Aged ≥2 to <5 Years Old with Nonsense Mutation Dystrophinopathy" **Category 3**	To evaluate the safety and PK of ataluren in children from 2 years to 5 years of age	Potential use in children from 2 years to 5 years of age	Ongoing	3Q 2017
Safety and PK study in patients with moderate to severe renal impairment, Protocol PTC124-GD-032-HV, "A Phase 1, Open-Label, Single Dose, Parallel-Group Study to Evaluate the Pharmacokinetics and Safety of Ataluren (PTC124) in Subjects With Severe Renal Impairment and Healthy Matched Control Subjects" **Category 3**	To evaluate the safety and PK of ataluren in subjects with different degrees of renal impairment, in order to provide guidance for ataluren dosing in patients with moderate to severe renal impairment.	Use in patients with moderate to severe renal impairment	Started	2Q2018
Safety and PK study of co-administration of ataluren and a sensitive probe substrate of OATP1B3 **Category 3**	To evaluate the safety and PK of ataluren and/or the appropriate sensitive probe substrate, in order to provide guidance for dosing ataluren with the specific concomitant medication.	Effect of co-administration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies	Started	2Q2018
Study 041: A phase 3 efficacy and safety study of ataluren in patients with nonsense mutation Duchenne muscular dystrophy and open-label extension **Category 2**	To confirm the efficacy and safety of ataluren in the treatment of ambulant patients with nmDMD aged 5 years or older.	To confirm the efficacy and safety of ataluren in the treatment of ambulant patients with nmDMD aged 5 years or older	Started	Final study report: September 2021

Risk Minimisation Measures

Summary Table of the Risk Minimisation Measures

Safety Concern	**Routine Risk Minimisation Measures**	**Additional risk minimisation measures**
Long-term cardiovascular effects including changes in lipid profile	SmPC section 4.4, 4.8	None proposed
Potential for aminoglycoside renal toxicity	SmPC section 4.3, 4.4, 4.5	None proposed
Hypertension with concomitant use of corticosteroid	SmPC section 4.4, 4.8	None proposed
Renal toxicity	SmPC section 4.4, 4.8	None proposed
Hepatic toxicity	None proposed	None proposed
Hibernoma	None proposed	None proposed
Malignancies in general	None proposed	None proposed
Use of ataluren in nmDMD patients who co-administered ataluren with nephrotoxic drugs	SmPC section 4.4, 4.5	None proposed
Use of ataluren in nmDMD patients with moderate to severe renal impairment	SmPC section 4.2, 4.4, 5.2	None proposed
Potential use in children from 6 months to <2 years old	SmPC section 4.1, 4.2, 5.1 Therapeutic indications	None proposed

Extended long-term safety	None proposed	None proposed.
Off-label use of ataluren in patients who do not have DMD caused by a nonsense mutation in the dystrophin gene	SmPC section 4.1, 4.4	None proposed.
Effect of co-administration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies	SmPC section 4.4, 4.5	None proposed.

The MAH is reminded that, within 30 calendar days of the receipt of the Opinion, an updated version of Annex I of the RMP template, reflecting the final RMP agreed at the time of the Opinion should be submitted to h-eurmp-evinterface@emea.europa.eu.

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Translarna (Ataluren) is included in the additional monitoring list as

- It contains a new active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.
- It is approved under a conditional marketing authorisation [REG Art 14(7)]

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

Main clinical study

The extension of the indication in children aged ≥ 2 to <5 years old with nmDMD is supported by data from one clinical study - Study 030. This was a Phase 2, multiple-dose, open-label study evaluating the safety, PK, and pharmacodynamics (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 pharmacokinetics, a 48-week extension period, and a 4-week follow-up period (60 weeks total). The proposed dose and schedule of ataluren in children 2-5 years of age was the same as those approved for children ≥ 5 years of age, i.e. 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).

Favourable effects

The results from Study 030 were used to demonstrate that ataluren plasma levels in nmDMD patients in

the age range ≥ 2 to <5 years old overlapped with the ataluren plasma levels in children ≥ 5 years of age (studies 004 and 007) when dosed according to the regimen 10/10/20 mg/kg. There was complete overlap in plasma concentrations between patients ⩾2 to <5 years of age (study 30) compared to those ⩾5 years of age (study 007, pivotal for PKPD relationship) at day 1 and at steady-state. Although the popPK model had inherent flaws which prevented use for its initially intended purpose, the plasma level data allowed the CHMP to positively conclude that the ataluren exposure in both age groups was comparable.

Uncertainty in the knowledge about the beneficial effects

Initially, a PopPK analysis was to be used to estimate the ataluren exposure in the population of ≥2 to <5 years and compare it with the exposure in the population of patients aged ≥5. However, a number of uncertainties with the model hindered a reliable and accurate description of the pharmacokinetics of ataluren. Thus the data from the modelling alone were not considered sufficient to support the proposed dosing recommendations in children 2-5 years of age.

The MAH did not provide any PD data, that may support the dosing in nmDMD patients ≥2 to <5 years. Hence, there was no actual confirmation that steady state levels in patients ≥2 to <5 years are sufficient to achieve the same magnitude of a PD effect and subsequent clinical improvement.

Additional results, describing effects of ataluren in the target population, were provided for a treatment period of 28 weeks, using a comparison with historical control data from the CINRG (n=14 and n=11 to 31 for the study group and historical data group, respectively). From this comparison, the results obtained from on 3 out of 4 possible TFTs showed a trend for stabilisation or improvement. The differences were 0.3 sec., 0.8 sec., 2.65 sec., respectively on time to run/walk 10 m, time to climb 4 stairs, time to stand from supine tests. A similar trend was also observed for the NSAA and the revised NSAA results, both favouring the ataluren-treated patients. The differences observed for the NSAA were 2.0 points, 0.5 points and 3.0 points respectively on the 8-item, 3-item and total NSAA score.

With regard to efficacy, the robustness of the observed results and conclusions is significantly affected from both the open label study design and a comparison with the external control CINRG data. The open label study design makes it susceptible to all types of bias, known to be present in unblinded studies, while the comparison to the CINRG data has several known drawbacks including pitfalls of indirect comparisons, large variability, some baseline differences between the two groups (e.g. treatment with corticosteroids), and short study duration.

Additionally, the effect size of the observed differences on the TFTs and NSAA scores make it difficult to conclude whether they were of true clinical relevance, and therefore these results can only be interpreted as being supportive for efficacy in the young age group of 2-5 years, but will be insufficient on their own if presented outside of the context of the effects observed in the group of DMD patients >5 years of age.

Risks

Unfavourable effects

Most adverse events as reported from study 030 are already known from previous experience with exposure to ataluren.

However, in the first 28 days of exposure the overall frequency of TEAEs in Study 030 was higher than in the pooled studies 007 and 020 (10 patients; 71.4% versus 81 patients; 47.1%). The higher frequency seems to be driven by a higher frequency of malaise (7,1%), pyrexia (42.9%), ear infection (28,6%) and rash (21,4%), which may be considered as more frequent in younger children in general.

For the 28 week cut off, the most common TEAEs were vomiting, diarrhoea, headache, nausea. All patients experienced at least one TEAE; however, these were all mild to moderate in nature.

The laboratory test analysis showed an increase in cholesterol and triglycerides, shifting into the abnormal range. Change in cholesterol levels was observed at 4 weeks already, while for the triglycerides – only at week 28. Since changes in lipid profile have been observed in patients both with and without corticosteroid treatment, this is the first time that it can be concluded with certainty ataluren treatment alone may result in elevated cholesterol and triglycerides reaching abnormal levels.

Uncertainty in the knowledge about the unfavourable effects

The additional safety data of exposure of the younger age group is with a maximum of 28 weeks. Longer exposure data is missing. Therefore it is uncertain what the long term safety of children 2- 5 years would be.

The observed elevation in lipid cholesterol and triglyceride levels are in line with the data from nmDMD children aged >5 years old. As it is unknown whether these levels will continue to increase, the nmDMD children aged 2-5 years old need to be monitored similarly to the nmDMD children aged >5 years.

Furthermore, although renal function seems in line with the data of nmDMD children aged > 5 years, the renal function needs to be monitored in both age groups as the long term effects remain unknown.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

Ataluren has been approved for ambulant children with DMD who are older than 5 years. Due to the progressive nature of the disease, from a biological and clinical perspective, it is agreed that it would be beneficial to start early treatment in DMD patients, if the beneficial effects outweigh the unfavourable effects. In order to expand the indication in younger children, it was recommended clinical studies in children aged 2-5 years should be performed, in order to collect as much PK and clinical efficacy and safety data as possible in this population. The MAH provided the results from such a study (Study 030) and argued that the observed PK behaviour and the positive trends registered in the measured clinical outcomes, together with the benign safety profile of the product, warrant the extension of the indication in younger DMD patients. The provided clinical data focused on patient functioning only, without direct measurement of the effects on muscle strength. This may be acceptable, as the mechanism of action of ataluren suggests at best stabilisation and reduction of the rate of loss of function, rather than a direct effect on muscle strength.

Regarding the outcome measures used, it is accepted that the 6MWT is not a reliable way of measuring effect in DMD children younger than 5 years, as they are still in the development phase of their walking ability. Therefore it is acceptable that in study 030 the efficacy outcome measures were 3 TFTs and a revised NSAA tool. It was difficult for the CHMP to conclude on the actual clinical relevance of the observed differences in the endpoints, but the registered positive trend could not be ignored.

With regard to the unfavourable effects, some TEAEs have always been of special interest, especially in the context of a lifelong treatment. The safety profile data from study 030 confirms that the already identified risks related to treatment with ataluren in older DMD patients are also relevant in patients 2-5 years old. Additionally, in this study was the first time that subjects treated with ataluren only show an increase in glycerol and triglycerides and after a 28 week exposure. This is an indication that ataluren may increase the cardiovascular risk and has to be considered in the decision on the time to start treatment in young nmDMD boys.

The concerns regarding the suitability of the popPK model to provide reliable quantifiable estimation of ataluren exposure remain, and thus it was concluded that the model could not be used to support the proposed dosing in paediatric patients ≥2 to <5 years. Instead the comparison of ataluren exposure in nmDMD patients ≥ 2 to <5 years old with those ≥ 5 years of age has been mainly based on comparison of plasma concentrations.

Benefit-risk balance

For this extension of the indication to nmDMD children aged 2-5 years, the applicant presented data from a single study in the target population, building upon the clinically justified approach that treating as early as possible in a neuro-muscular, progressive condition is meant to provide the most benefit for the treated patients. The applicant continues to defend that based on the available PK data, it can be reasonably assumed that similar exposure can be observed in older and younger DMD patients, providing for a similar efficacy and safety in both groups. Additionally, the observed positive trends in efficacy data can be used as supportive, and taking into account the generally mild safety profile of ataluren, can justify a positive benefit/risk ratio conclusion.

The CHMP acknowledged that comprehensive assessment of efficacy in children ≥2 and <5 years of age is not feasible due to the rarity of diagnosed nmDMD patients <5 years of age. Thus, the Committee agreed with the above argumentation, concluding that assumption about the similarity of the efficacy and safety established in nmDMD children in both groups (≥5 years and below 5 years of age) can be made, provided that comparable exposure has been demonstrated in both age groups.

The background of this position is that the disease process and pathogenesis of nmDMD, which is loss of muscle due to the absence of dystrophin, is independent of age. Also the mechanism of action of ataluren, to enable ribosomal read-through of mRNA containing a premature stop codon, resulting in production of a full-length protein (dystrophin), is expected to be the same in both age groups. Additionally, comparable ataluren exposure in patients ≥2 to <5 years of age with those ≥5 years of age could be assumed, based on the observed full overlap in ataluren plasma concentrations in patients from both groups.

It was recognised that the results from the clinical data on TFTs and NSAA as provided, were not robust on their own. There are too many factors which influence the interpretation and put in question the effect size and clinical relevance of the observed results. Nevertheless the observed positive trends cannot be ignored. On the other hand, the preliminary short term safety data seems in line with the patient population aged >5 years, and confirms the generally benign safety profile of the drug. No major unexpected safety issues were encountered in patients aged ≥2 to <5 years, and ataluren is well tolerated.

In conclusion, taking into account the totality of the presented data up to this moment, the CHMP agreed that they allow to reasonably assume that the efficacy and safety profile of ataluren in children with DMD 2- 5 years old could be expected to be similar to the one in patients older than 5 years, thus providing for a conclusion on a positive B/R ratio in this population.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of Indication to include a new population (children from 2 to less than 5 years of age) for Translarna; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and RMP (version 7.1) is updated in accordance.

The variation leads to amendments to the Summary of Product Characteristics, Package Leaflet and to the Risk Management Plan (RMP).

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of Indication to include a new population (children from 2 to less than 5 years of age) for Translarna; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet and RMP (version 7.1) is updated in accordance.

Summary

Please refer to the published Assessment Report Translarna H-2720-II-37.

Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 31 May 2018.