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SCIENCE MEDICINES HEALTH

17 October 2019
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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Translarna

International non-proprietary name: ataluren

Procedure No. EMEA/H/C/002720/II/0047

Note

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

Medicinal product no longer authorised

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List of abbreviations

Abbreviation	Term
6MWD	6-minute walk distance
6MWT	6-minute walk test
ACE	Angiotensin converting enzyme
ACTH	Adrenocorticotrophic hormone
ADL	Activities of daily living
AE	Adverse event
ALT	Alanine aminotransferase
ARB	Angiotensin receptor blockers
AST	Aspartate aminotransferase
AT	As treated
ATC	Anatomic therapeutic class
BCRP	Breast cancer resistant protein
BMD	Becker muscular dystrophy
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CHF	Congestive heart failure
CI	Confidence interval
CINRG	Cooperative International Neuromuscular Research Group
CK	Creatinine kinase
CRF (eCRF)	Case report form (electronic CRF)
cGMP	Current good manufacturing procedures
CS	Clinically significant
CTCAE	Common terminology criteria for adverse events
CYP	Cytochrome P450 subtypes
DBMD	Duchenne/Becker muscular dystrophy
DBP	Diastolic blood pressure
DMC	Data monitoring committee
DMD	Duchenne muscular dystrophy
DNA	Deoxyribonucleic acid
eCRF	Electronic Case Report Forms
EOS	End of study
EOT	End of treatment
ECG	Electrocardiogram
ECMO	Extracorporeal membrane oxygenation
EDC	Electronic data capture
FEV1	Forced expiratory volume in 1 second
EF	Ejection fraction
EK	Egen Klassifikation Scale
FVC	Forced vital capacity
GCP	Good clinical procedures
GGT	Gamma glutamyl transferase

Abbreviation	Term
HDL	High density lipoprotein
IB	Investigator brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IRB	Institutional Review Board
IV	Intravenous
IWR	Interactive web response
KM	Kaplan-Meier
LDH	Lactate dehydrogenase
LDL	Low density lipoprotein
LLN	Lower limit of normal
Max	Maximum
MedDRA	Medical dictionary for regulatory activities
MI	Myocardial infarction
Min	Minimum
MMRM	Mixed model for repeated measures
MRI	Magnetic response image
mRNA	Messenger ribonucleic acid
NCS	Not clinically significant
Neuro-QoL	Quality of Life in Neurological Disorders
nmDBMD	Nonsense mutation Duchenne/Becker muscular dystrophy
NSAA	North Star Ambulatory Assessment
OAT1	Organic anion transporter 1
OAT3	Organic anion transporter 3
OATPIB3	Organic anion transporting polypeptide 1B3
PCF	Peak cough flow
PedsQL	Pediatric Quality of Live inventory
PEF	Peak expiratory flow
PK	Pharmacokinetic
POSNA	Pediatric Orthopaedic Society of North America
PT	Preferred Term
PTC	PTC Therapeutics, Inc.
RBC	Red blood cell
RIVA	Ramus interventricularis anterior
SAE	Serious adverse event
SAP	Statistical analysis plan
SBP	Systolic blood pressure
SD	Standard deviation
SE	Standard error
SOC	System organ class
SOP	Standard operating procedure
SUSAR	Suspected unexpected serious adverse reaction

Abbreviation	Term
TEAE	Treatment-emergent adverse event
TFT	Timed Function Test
TID	Three times a day
UGT1A9	UDP glucuronosyltransferase family 1 member A9
ULN	Upper limit of normal
URTI	Upper respiratory tract infection
WBC	White blood cell
WHO	World Health Organization
WHO QOL	World Health Organization Quality of Life
WNL	With-in normal limits

Medicinal product no longer authorised

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 29 August 2018 an application for a variation.

The following variation was requested:

Variation requested		Type	Annexes affected
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 non-ambulatory patients with Duchenne muscular dystrophy; This variation additionally presents, as supportive data, the final results of the long term clinical study PTC-124-GD-019-DMD (an Open-Label Study for Previously Treated Ataluren (PTC124) Patients with Nonsense Mutation Dystrophinopathy), submitted in line with the requirements of Article 46 of Regulation (EC) No 1901/2006.

The requested variation included amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP):

The MAH applied for an update of sections 4.1, 4.2, 4.8, and 5.1 of the SmPC The Package Leaflet was proposed to be updated accordingly

The RMP version 8.0 has also been submitted.

Translarna was designated as an orphan medicinal product EU/3/05/278 on 31 May 2005, 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 an EMA Decision(s) P/0393/2017 on the agreement of a paediatric investigation plan (PIP). At the time of submission of the application, the PIP P/0393/2017 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 Applicant did not seek Protocol Assistance at the CHMP.

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: Maria Concepcion Prieto Yerro

Timetable	Actual dates
Submission date	29 August 2018
Start of procedure:	15 September 2018
CHMP Rapporteur Assessment Report	15 November 2018
CHMP Co-Rapporteur Assessment Report	15 November 2018
PRAC Rapporteur Assessment Report	15 November 2018
PRAC Outcome	29 November 2018
CHMP members comments	3 December 2018
Updated CHMP Rapporteur(s) (Joint) Assessment Report	7 December 2018
1 st Request for supplementary information (RSI)	13 December 2018
CHMP Rapporteur Assessment Report	6 February 2019
PRAC Rapporteur Assessment Report	6 February 2019
PRAC Outcome	14 February 2019
CHMP members comments	18 February 2019
Updated CHMP Rapporteur Assessment Report	21 February 2019
2 nd Request for supplementary information (RSI)	28 February 2019
PRAC Rapporteur Assessment Report	7 June 2019
CHMP, PRAC Rapporteurs' Joint Assessment Report	14 June 2019
PRAC Outcome	13 June 2019
CHMP members comments	19 June 2019
Updated CHMP Rapporteur Assessment Report	21 June 2019
An Oral explanation took place on	25 June 2019
CHMP Opinion	27 June 2019

1.3. Steps taken for the re-examination procedure

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

Rapporteur: Kristina Dunder Co-Rapporteur: Alexandre Moreau

Timetable	Actual dates
Written notice to the EMA to request a re-examination of Translarna CHMP opinion of 27 June 2019	05 July 2019
Rapporteur's appointment	25 July 2019
Detailed grounds for the Re-examination submitted on	26 August 2019

Timetable	Actual dates
Start of procedure:	27 August 2019
Rapporteur's preliminary assessment report and LoQ for SAG circulated on:	11 September 2019
Co-Rapporteur assessment report	11 September 2019
CHMP MS comments	16 September 2019
CHMP Request for supplementary information + adoption of LoQ of SAG	19 September 2019
CHMP Rapporteur updated assessment report (uAR)	07 October 2019
CHMP MS comments	10 October 2019
The SAG meeting considered the grounds for re-examination	11 October 2019
An Oral explanation on the detailed grounds for re-examination took place on:	15 October 2019
CHMP adoption of opinion	17 October 2019

2. Scientific discussion

2.1. Executive summary

Ataluren (Translarna) is indicated for the treatment of Duchenne muscular dystrophy (DMD) resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged ≥ 2 years.

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.

On 31 July 2014, ataluren was granted a conditional marketing authorisation (CMA) under the tradename Translarna for the treatment of nonsense mutation Duchenne muscular dystrophy (nmDMD) in ambulatory patients aged ≥ 5 years. The approval was based on data from a randomized, double-blind, placebo-controlled, dose-ranging, multi-centre study in 174 subjects with nmDMD (Study 007).

In the initial conditional marketing authorisation application, the MAH submitted also data on non-ambulatory patients. However, the indication was restricted to ambulatory nmDMD patients, because:

- It was questioned whether the increase in dystrophin levels would result in restoration of the muscle function in the environment of fatty and fibrotic degeneration.
- The evaluation of efficacy mainly focused on ambulation and the extrapolation to non-ambulant subject was not supported by sufficient evidence.

The conditional marketing authorisation was renewed on 29th May 2019 (CHMP Opinion) based on the totality of the clinical data available, including the results of a confirmatory randomized placebo-controlled Phase 3 trial (Study 020) as a Specific Obligation. Despite this study failed to reach statistical significance on its primary endpoint (6MWD), efficacy was demonstrated in a subgroup of patients with baseline 6MWD between 300-400 meters. A new Specific Obligation was imposed and is still ongoing.

The current application concerns an extension of the indication to non-ambulatory nmDMD patients. The following amendments of the indication were proposed by the Applicant:

"*Translarna is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 2 years and older (see section 5.1). Efficacy has not been demonstrated in non-ambulatory patients.*"

In support of this variation, the MAH originally submitted data from PTC-124-GD-019-DMD (study 019). In order to support their position, MAH claimed that the extension of indication should be accepted based on extrapolation from the efficacy in ambulatory patients given comparable pharmacokinetics (PK) and safety comparable between ambulatory and non-ambulatory patients and submitted analyses supporting efficacy data in non-ambulatory. Although it was agreed that the underlying pathology is similar regardless of ambulatory status, and that PK and safety may be considered as comparable in ambulatory and non-ambulatory patients, the CHMP was not convinced that any ataluren treatment effects on the remaining muscle tissue would translate into clinically meaningful effects on function in this specific patient population. The position of the MAH that the data from Study 019 provide supportive evidence of clinical benefit was not endorsed due to severe methodological concerns including the design and conduct of the study and the appropriateness of the selected control group. Moreover, the additional propensity score matched analyses the MAH submitted in response to the major objections were considered exploratory at best, since there were concerns that they may have been influenced by data, and methodologically were not sufficiently justified, thus questioning the validity of the results. Together with the additional analyses, the Applicant provided letters of support from clinical experts. These letters seem to indicate that ataluren might be used safely in real world conditions, according to these experts' views. However, these reports cannot replace the necessary robust data required to support an extension of indication.

2.2. Non-clinical aspects

No new non-clinical data was submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the Applicant.

The Applicant 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.

- Tabular overview of clinical studies

Study Number Region	Objective / Developmental Need	Study Population; Study Type	Dose
PTC124-GD 019-DMD Worldwide	Primary: Long term safety study in ambulatory and non-ambulatory nmDMD patients Secondary: Efficacy in terms of FVC and EK in non-ambulatory nmDMD patients compared to CINRG historical data set	multicenter, open-label safety study (openable extension Study of 007e)	Morning dose 10mg/kg Afternoon dose 10mg/kg Evening dose 20mg/kg dose

See section 2.4 Clinical efficacy for further details.

2.3.2. Pharmacokinetics

No new data were submitted. Reference is made to the previous assessment in the context of the extension of indication below 5 years of age, where it was shown that the PK of ataluren does not differ between ambulatory and non-ambulatory patients. This was considered acceptable.

2.3.3. Pharmacodynamics

Mechanism of action

There are no specific pharmacodynamics data submitted by the Applicant. This was accepted by the CHMP.

2.3.4. Discussion and conclusions on clinical pharmacology

With respect to PK, no new data were provided. Instead, the MAH referred to the CHMP's prior conclusions that the PK and safety of ataluren are similar between ambulatory and non-ambulatory patients as also stated in the SmPC. Based on actual plasma levels obtained, this argument is accepted. In terms of the expected pharmacodynamics of ataluren, it is plausible to assume that a similar pharmacodynamic effect in non-ambulatory boys should be expected, 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 non-ambulatory nmDMD patients, as the MAH assumed that it would result in target concentrations of ataluren that are likely to provide the expected PD effect. However, this assumption has not been supported with any data in the non-ambulatory patient population.

2.4. Clinical efficacy

2.4.1. Dose response studies

No dose-response studies were conducted. The Applicant relied on extrapolation from PK data, which was an acceptable approach.

2.4.2. Main study

Study PTC-124-GD-019-DMD (Study 019)

Study PTC124-GD-019-DMD (Study 019) was a long-term multicenter, open-label safety study in male patients with nmDBMD who had previously received ataluren in one or more prior PTC-sponsored studies specifically, the Phase 2b double-blind, placebo-controlled study (Study 007) and its open-label extension (Study 007e) and in PTC124-GD-004-DMD (Study 004). One patient had no prior experience with ataluren.

All eligible patients received ataluren 10 mg/kg in the morning, 10 mg/kg at mid-day, and 20 mg/kg in the evening. Follow-up was up to 240 weeks (336 weeks in Canada).

Study assessments were performed at clinic visits during screening, the first day of ataluren dosing, and every 12 weeks thereafter. See Table 1.

All patients who discontinued ataluren had to return for a Post-Treatment Visit 6 weeks (± 7 days) after the last dose of ataluren for final evaluations.

Table 1. Schedule of Procedures and Assessments

Period Study Week (±7 days)	Screening ^A	Baseline ^A		Ataluren Treatment			Post- Treatment
	-4 to -1	Week 1	Every 12 Weeks	Every 24 Weeks	Every 48 Weeks	End of Treatment Week 336	6 Weeks Post D/C
Procedures / Assessments							
Informed consent	X						
Demographics	X						
Inclusion/Exclusion criteria	X						
Clinical/medication history	X						
Hepatitis screen	X						
Vital signs	X	X			X	X	X
Brooke UE Functional Rating Scale [1]	X						
Height/Ulna length/Arm Span [1]	X			X			
Physical examination [1]	X						
Weight	X	X		X ^B		X	X
Hematology	X	X			X	X	X
Biochemistry	X	X			X	X	X
ACTH and cortisol [1]	X	X				X ^C	X
Renin and aldosterone [1]	X				As Indicated		
Urinalysis [1]	X	X				X ^C	X
12-lead ECG [1]	X				As Indicated		
Echocardiogram [1]	X				X		X ^D
6-minute walk test [1]	X			X		X ^C	
Timed Function Tests [1]	X				X	X ^C	
North Star Ambulatory Assessment [1]	X				X	X ^C	
Egen Klassifikation Scale [1]	X				X	X ^C	
Spirometry [1]	X			X		X ^C	
Disease status survey [1]	X	X	X			X ^C	
Drug administration		X	X ^E				
Phone call pre-drug shipment				X			
Phone call post shipment			X ^G				
Drug Compliance			X ^H			X	
Adverse events		X	X ^I			X	X
Concomitant medications		X	X ^I			X	X

Abbreviations: ACTH, adrenocorticotropic hormone; D/C, discontinuation, ECG, electrocardiogram; Tx, treatment; UE, upper

^AAtaluren was initiated as soon as the investigator confirmed patient eligibility. Baseline procedures (excluding drug administration) did not need to be performed if Screening procedures had been performed within 7 days of anticipated initiation of ataluren treatment.

^BPatient was expected to visit a primary care physician who recorded the weight and communicated it to the investigator site between the annual visits.

^CEfficacy assessments were conducted through 240 weeks.

^DOnly applies to patients who discontinue the study after 240 weeks of treatment.

^EDrug was shipped by the site to the patient every 12 weeks for a total of 4 times per year.

^FA pre-shipment phone call (4 to 6 weeks prior to Week 24) was made to remind the patient to visit his PCP for a weight check in between the annual visits at sites.

^GPost-shipment phone calls were made 2 to 4 weeks after drug shipments to confirm drug receipt and record adverse events and concomitant medications.

^HUnused drug was shipped back to sites by the patients in order to assess compliance.

^IAdverse events and concomitant medications were monitored and captured by phone every 12 weeks between the annual visits.

[1] NOTE: Certain baseline and screening assessments were discontinued in Protocol version 6.0 (dated 21 November 2016). Additionally, all efficacy assessments were removed from Protocol version 6.0 (dated 21 November 2016) since efficacy measures were no longer being captured, reflective the new purpose of the study as a long-term focused safety study. Since efficacy was analysed in this clinical study report, all efficacy assessments are included in the schedule of assessments above.

Study participants

Main inclusion criteria were exposure to ataluren in prior PTC-sponsored studies i.e. study 007/700e and 008.

Subjects were excluded if they were exposed to other investigational drugs within 1 month prior to study treatment, if they were eligible for another ataluren clinical trial, if there were ongoing uncontrolled medical conditions or laboratory findings that would adversely affect the safety of the patient.

Treatments

Patients received continuous daily treatment with ataluren TID; the first dose in the morning (10 mg/kg), the second dose during the middle of the day (mid-day – 10 mg/kg), and the third dose in the evening (20 mg/kg). Intervals for dosing were approximately 6 hours (±1 hour).

Dosing was based mg/kg based in the patient's body weight at Screening/Baseline and adjusted to allow for dosing with the available sachet dose strengths. Weight-based dose adjustment occurred every 24 weeks as required.

Objectives

The primary study objective was to assess the long-term safety and tolerability of a 10 mg/kg, 10 mg/kg, and 20 mg/kg ataluren regimen in patients ≥ 5 years of age with nmDBMD who had prior exposure to ataluren in PTC-sponsored clinical trials.

The secondary objectives were exploratory of efficacy:

- To determine the effect of ataluren on ambulation and other motor functions in ambulatory patients (i.e., those able to run/walk 10 meters in ≤ 30 seconds).
- To assess the effect of ataluren on activities of daily living (ADL), upper limb function, and pulmonary function in non-ambulatory patients (i.e. in those unable to run/walk 10 meters in ≤ 30 seconds).
- To assess patient and/or parent/caregiver reports of changes in disease status for all patients, using the Disease status Survey:
 - o Retrospectively during and after participation in previous studies (Studies 007 and 007e).
 - o Prospectively during the current study

Outcomes/endpoints

As this was a safety study, the primary endpoints of this study were **safety endpoints** assessed through Week 240:

- AEs
- Laboratory abnormalities

Safety assessments included scheduled vital sign measurements, laboratory tests, and AE reporting. Safety analyses were performed for all patients having received at least one dose of ataluren and who had at least 1 post-dosing safety evaluation. The study used the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 for reporting all AEs.

Since the focus of the study was long-term safety, collection of efficacy endpoint data was discontinued in protocol amendment version 6.0 dated 21 November 2016 that extended the duration of the study to 336 weeks. Efficacy was assessed as a secondary objective through 240 weeks.

Clinical efficacy endpoints for non-ambulatory patients included:

- Change from baseline in pulmonary function as measured by spirometry.
- Change from baseline in patient and parent/caregiver-reported ADL, as measured by the Egen Klassifikation (EK) scale.

Spirometry

Pulmonary function parameters included percent-predicted forced vital capacity (FVC), percent-predicted forced expiratory volume in 1 second (FEV1) (adjusted using ulna length and age), peak expiratory flow (PEF), and peak cough flow (PCF) and their absolute and relative changes from baseline were summarized by visit for non-ambulatory patients and the as treated (AT) population. Similarly, the observed values of the endpoints were summarized for each actual age.

The time to event approach was applied as well i.e. age at FVC < 1 litre. If patients did not have FVC < 1 litre, the age at the last non-missing FVC assessment was chosen as the censor age.

Egen Klassifikation Scale (EK) in non-ambulatory subjects

The ADLs were measured using the EK scale (Steffensen 2001), i.e. control electric chair, transfer from chair, stand, sit up, use arms, use arms for eating, turn in bed, cough, talk and general wellbeing in non-ambulatory patients (defined as unable to run/walk 10 meters in ≤ 30 seconds). The total score of EK scale and change from baseline to each post-baseline visit was summarized descriptively by visit for non-ambulatory patients all subjects enrolled in the study (i.e. including ambulatory subjects at baseline) and by age with intervals of 0.5 years.

Disease Status Survey

For all patients, a disease status survey was administered at Screening (Visit 1) to collect retrospective information on patient and/or parent-reported changes in disease status during and after their participation in the prior PTC Studies 007 and 007e. Separate surveys were administered at Week 1 (Visit 2), Week 12 (Visit 3), and every 12 weeks through Week 240 (Visit 22 EOT/Premature Discontinuation) to collect prospective information on patient and/or parent-reported changes in disease status.

Sample size

The as treated (AT) population, including any patients that received one or more doses of ataluren, was used for all analyses unless otherwise specified.

Randomisation

NA

Blinding (masking)

NA, as this was an open-label study.

Statistical methods

Summary tables for continuous variables included: n, mean, standard deviation (SD), standard error (SE), 95% CIs on the mean, median, minimum (min), and maximum (max). Changes from baseline were likewise summarized. Summary tables for categorical variables included absolute numbers of the included population (N), absolute numbers of the groups (n), and percentages (%). Patient demographics and baseline characteristics were presented by ambulatory status at baseline (Yes, n=50; No, n=44) and by corticosteroid (Yes, n=84; No, n=10).

A. Propensity score matched analyses for dynamics of FVC over age and age at FVC<1 litre

To compare Cooperative International Neuromuscular Research Group (CINRG) with Study 019, the matched populations for different endpoints and analyses were defined in Table 2. Matching criteria could be adjusted if imbalance demographics and baseline characteristics were observed.

Table 2. Study 019 and CINRG Dataset Matching Criteria for Pulmonary Endpoints

Endpoint/ Analysis	Age (years) at Study Entry	Age (years) At Assessment	Steroid Use	Ambulation Status	Exclude Exon 51 and 44	Baseline FVC value	Visit Year
Age at FVC <1 litre	9-18	Not applicable	Sensitivity performed with steroid use	Non-ambulatory at study entry	Yes	1-3.08	Not applica ble
Piecewise regression based on FVC	Not applicable	≤25	Cumulative Steroid use duration at each assessment ≥24 months	Non-ambulatory at each assessment	Yes	Not applicable	≥2012

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital capacity

According to the Statistical Analysis Plan (SAP), demographics and baseline characteristics (age, race, ambulation status, corticosteroid use (yes or no), duration of corticosteroid use, corticosteroid type, baseline 6MWD, baseline time to run/walk 10 meters, baseline time to stand from supine, baseline %-predicted FEV1, %-predicted FVC, PEF, EK score, NSAA total score) were summarized descriptively for CINRG and Study 019 matched populations. The summary were displayed by corticosteroid use (yes vs. no) and cumulative steroid use (≥12 months vs. <12 months) for baseline ambulatory and non-ambulatory subjects separately. In general, the baseline was defined as the first visit in CINRG data. The baseline age in the FVC analysis using piece-wise regression models was the age at the first FVC assessments for both CINRG and Study 019.

The comparison to the natural history data (i.e., CINRG data) based on matched subjects was performed in FVC using piece-wise regression models and in age to loss of ambulation and age to FVC <1 litre using Kaplan-Meier method.

Piece-wise regression models were applied to log FVC in CINRG and Study 019 data, separately, using different ages as the change point. The most possible change point in terms of age is chosen at the best model fit (i.e., corrected Akaike information criterion (AICc) value is the maximal). Scatter plots of log FVC and the most fitted piece-wise regression line were generated for CINRG and Study 019, separately. Comparison between the observed and predicted FVC in Study 019 were performed using repeated measures analysis of variance to account for within-subject correlations, where the predicted values were based on the regression equation estimated by the best fit regression model based on CINRG data.

The Kaplan-Meier method was applied to the age to loss of ambulation the analysis of age to FVC <1 litre. The median age to loss of ambulation and median age to FVC<1 litre were reported. The comparison between Study 019 and CINRG was conducted via log-rank test by corticosteroid use at baseline (yes or no) and overall. The Kaplan-Meier curves were also displayed.

In Study 019, the loss of ambulation was defined as the disease progression reported as the adverse event or the time to run/walk 10 meters >30 seconds, whichever occurred earlier. The event age was the one on the AE start date. The subjects who were ambulatory at the end of study were censored on the last valid timed function tests assessment date. Age on that date was used in the analysis. In the CINRG data, the age at the earliest report of the non-ambulation or the time to run/walk 10 meters >30 seconds, whichever earlier, was picked as the event age. If subjects in CINRG data did not report non-

ambulation, the age at the last report of ambulation was chosen as the censor age. A sensitivity analysis was performed based on the loss of ambulation defined only by disease progression AE.

Similarly, the age at FVC<1 litre was the one at the first time FVC<1 litre. If subjects did not have FVC<1 litre, the age at the last non-missing FVC assessment was chosen as the censor age.

For CINRG data only, the observed values were summarized descriptively for each actual age on 6MWT, time to run/walk 10 meters, time to stand from supine, NSAA total and linear scores, %-predicted FVC, %-predicted FEV1, PEF and EK total scores by corticosteroid use at baseline (yes or no) and overall based on the matched populations. NSAA score derivation algorithms in Study 019 were applied to CINRG data

The Applicant did not submit results for end-point of age to loss of ambulation in the first analyses.

B. Propensity score matched analyses for age at percentage predicted FVC<60%, age at percentage predicted FVC<50% and age at FVC<1 litre

Kaplan Meier time to event analyses were undertaken for key pulmonary functional milestones: age at percent predicted FVC <60%, age at percent predicted FVC <50%, and age at FVC <1 litre. In Study 019, FVC was assessed only for non-ambulatory patients, thus only non-ambulatory subjects were included in these analyses. These analyses included all subjects with recorded values for age at first symptom and age at loss of ambulation who did not experience a decline below one of these FVC milestones prior to Study 019 entry.

B1. Building and selecting the final model for the propensity score

In order to build the model for the propensity score used for the matching between Study 019 and natural history patients, the Applicant considered the following candidate variables as proxies of the underlying disease and the standard of care a patient receives:

- Standard of care:
 - Duration of deflazacort use
 - Duration of other steroid use
- Disease severity:
 - Age at first symptom
 - Age at loss of ambulation
- Baseline Disease Stage:
 - Age at study entry
 - Time to run/walk 10m
 - Time to stand from supine
 - Time to climb 4 stairs

Then, the Applicant chose age at loss of ambulation as end-point of the propensity score model to select the appropriate the model among five candidate models (1-5 with 2a and 2b see below). Once the propensity score was calculated on the basis of these criteria, a randomly selected first Study 019 subject was matched to the CINRG subject with the absolute closest value in their propensity score (nearest neighbour search approach). CINRG subjects selected as the matching control was no longer available for further matching. This procedure was repeated for all subjects for a 1-to-1 match.

1. Standard of care (Duration of deflazacort use and duration of other steroid use) alone
2. Standard of care (Duration of deflazacort use and duration of other steroid use) + disease severity
 - a. Disease severity as age at first symptom
 - b. Disease severity as age at loss of ambulation (sensitivity analysis)

3. Standard of care + disease severity + age and time to run/walk 10m at study entry
4. Standard of care + disease severity + age and time to stand from supine at study entry
5. Standard of care + disease severity + age and time to climb 4 stairs at study entry

For all matching models (Figures 1-5) the subject level propensity score was created using logistic regression with duration of deflazacort use (<1 month, ≥1 month and <12 months, ≥12 months at time to event of censoring), duration of other steroid use (<1 month, ≥1 month and <12 months, ≥12 months at time to event of censoring) and any additional variables as covariates in the model.

In the view of the Applicant and to confirm the appropriateness of the propensity score match model, an analysis was undertaken of the subset of 58 of the 85 patients with a date for loss of ambulation, age at first symptom and corticosteroid use data who entered Study 019 as having never received treatment in the previous placebo-controlled studies with the established effective dose of ataluren (10, 10, 20 mg/kg) (Applicant refers to them as effectively treatment naïve population).

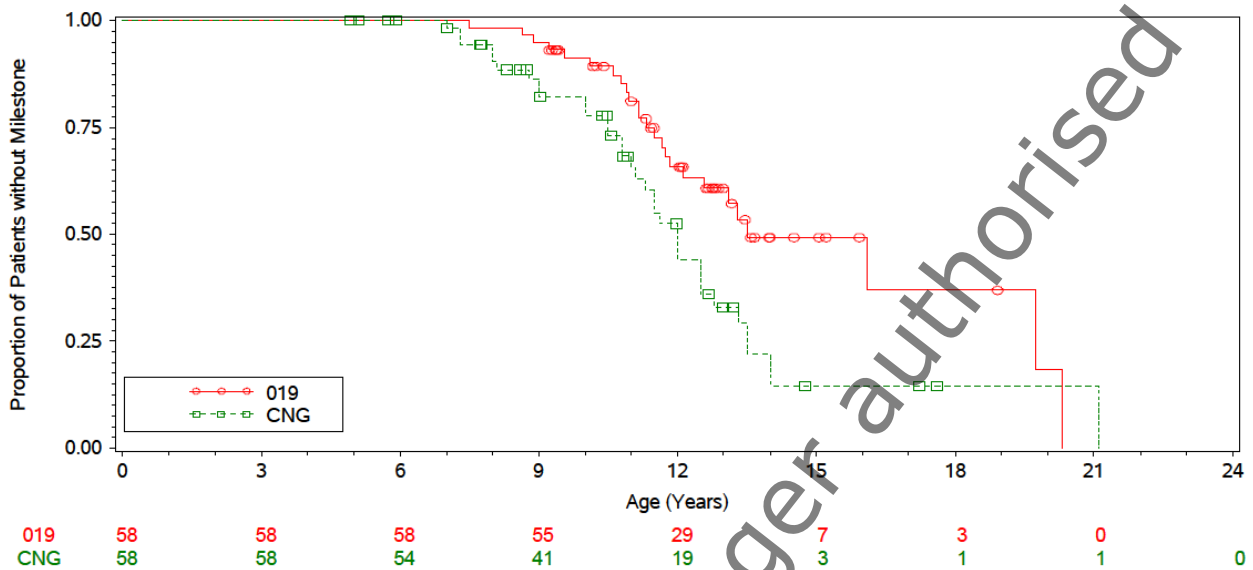
Table 3. Patient disposition by Ambulatory Status at 019 Study Entry and Previous Treatment Groups (019 As-Treated Population with Propensity Score Matched for Loss of Ambulation Analyses for models 1-5)

First Study Randomization	Ambulatory at Study at 019 Entry		Overall (N=85)
	YES (N=49)	NO (N=36)	
Ataluren 10/10/20mg/kg	16	11	27
Placebo/Ataluren 20/20/40 mg/kg	33	25	58
Total	49	36	85

The duration of steroid use and duration of deflazacort use are key factors known to alter the course of the disease and was the base case included in all matchings (McDonald 2018). In the view of the Applicant, the best match was found using Model 2, which included standard of care (duration of deflazacort use and duration of other steroid use) and disease severity. Age at first symptom was used as the criterion for disease severity in the primary model (Model 2a). In a Kaplan Meier analysis of age at loss of ambulation, this subgroup of Study 019 experienced a disease trajectory similar to that of the matched CINRG population. The median age of loss of ambulation was 13.5 years among Study 019 naïve patients and 13.0 years in CINRG, providing additional evidence that the matched populations were comparable in disease severity and standard of care (ie, steroid use) and those differences in outcome could be solely attributed to ataluren treatment (Figure 2). An additional approach matching on age at loss of ambulation instead of age at first symptom was also performed as a sensitivity analysis (Model 2b). In the view of the Applicant, matching on age at loss of ambulation ‘forces’ the selection of less severe untreated natural history patients with the same age at loss of ambulation as ataluren treated patients. The purpose of this analysis was to assess additional benefit of ataluren on disease progression after the time of loss of ambulation over and above the established benefit in the delay in time to loss of ambulation.

In the view of the Applicant, matching only on type and duration of steroid use (Model 1) yielded a match that selected for patients in CINRG with a more severe phenotype (Figure 1), whereas adding baseline disease stage (age and timed function at study entry - Model 3 through Model 5) led to overfitting and selection of milder phenotype patients from the CINRG database (Figure 3, Figure 4, Figure 5). However, model 3 should have been chosen taking into account how the models fit the overall population both visual and statistically. This model matched for the entire population and not just <14 years of age.

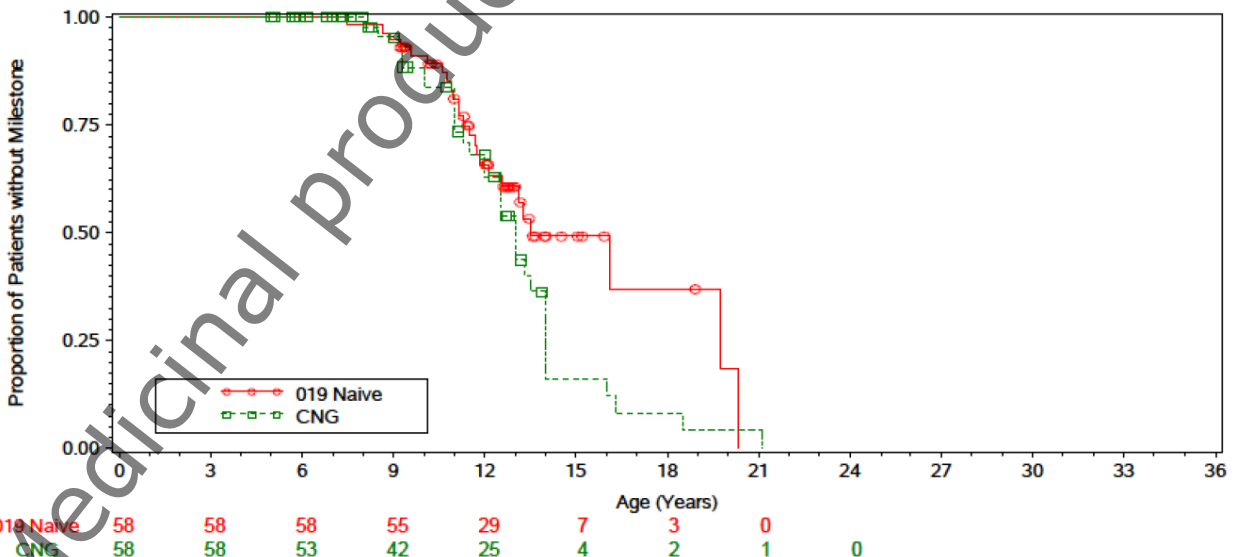
Figure 1. Kaplan-Meier Plot: Age at Loss of Ambulation (Study 019 Patients as having never received treatment in the previous placebo-controlled studies with the established effective dose of ataluren (10, 10, 20 mg/kg) and CINRG Data on 19 MAR2018 with Propensity Score Matched Using Model 1)



Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group

Note: Set 1 of Propensity Score model covariates includes duration of Deflazacort, and duration of steroid other than Deflazacort. A total of 58 subjects never received ataluren 10, 10, 20 mg/kg prior to Study 019. For this analysis, the 33 of these subjects who were ambulatory at Study 019 were censored at Study 019 entry (ie, prior to receiving their first dose of ataluren 10, 10, 20 mg/kg). Numbers shown at bottom of graph are numbers of patients at risk.

Figure 2. Kaplan-Meier Plot: Age at Loss of Ambulation (Study 019 Patients as having never received treatment in the previous placebo-controlled studies with the established effective dose of ataluren (10, 10, 20 mg/kg) and CINRG Data on 19 MAR2018 with Propensity Score Matched Using Model 2a)

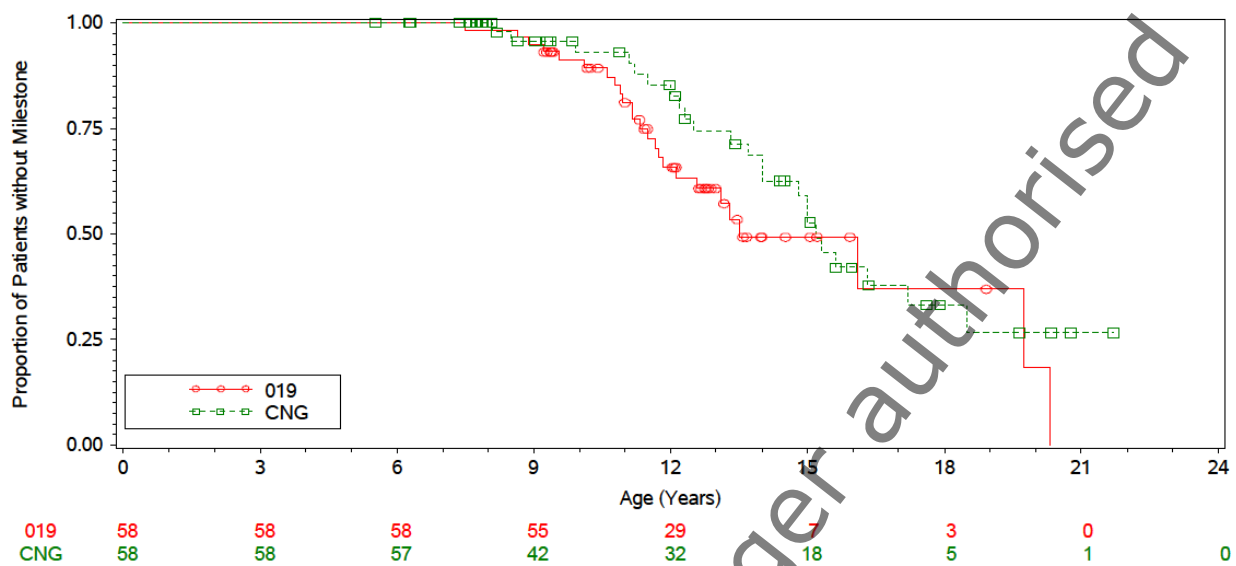


Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group

Note: Set 2a of Propensity Score model covariates includes age at first symptom and duration of Deflazacort, and duration of steroid other than Deflazacort

A total of 58 subjects never received ataluren 10, 10, 20 mg/kg prior to Study 019. For this analysis, the 33 of these subjects who were ambulatory at Study 019 were censored at Study 019 entry (ie, prior to receiving their first dose of ataluren 10, 10, 20 mg/kg). Numbers shown at bottom of graph are numbers of patients at risk.

Figure 3. Kaplan-Meier Plot: Age at Loss of Ambulation (Study 019 Patients as having never received treatment in the previous placebo-controlled studies with the established effective dose of ataluren (10, 10, 20 mg/kg and CINRG Data on 19MAR2018 with Propensity Score Matched Using Model 3)



Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group

Note: Set 3 of Propensity Score model covariates includes age at first symptom, baseline age and baseline time for 10m run/walk from 007/004 and study entry of CINRG, duration of Deflazacort, and duration of steroid other than Deflazacort

A total of 58 subjects never received ataluren 10, 10, 20 mg/kg prior to Study 019. For this analysis, the 33 of these subjects who were ambulatory at Study 019 were censored at Study 019 entry (ie, prior to receiving their first dose of ataluren 10, 10, 20 mg/kg). Numbers shown at bottom of graph are numbers of patients at risk.

Figure 4. Kaplan-Meier Plot: Age at Loss of Ambulation (Study 019 Patients as having never received treatment in the previous placebo-controlled studies with the established effective dose of ataluren (10, 10, 20 mg/kg and CINRG Data on 19MAR2018 with Propensity Score Matched Using Model 4)

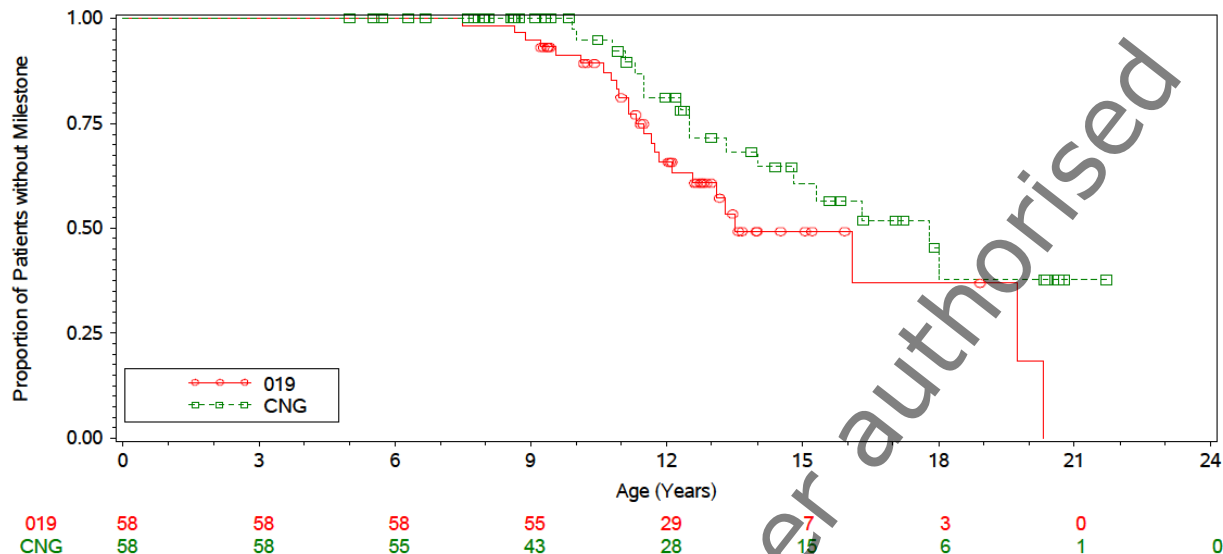


Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group

Note: Set 4 of Propensity Score model covariates includes age at first symptom, baseline age and baseline time for stand from supine from 007/004 and study entry of CINRG, duration of Deflazacort, and duration of steroid other than Deflazacort

A total of 58 subjects never received ataluren 10, 10, 20 mg/kg prior to Study 019. For this analysis, the 33 of these subjects who were ambulatory at Study 019 were censored at Study 019 entry (ie, prior to receiving their first dose of ataluren 10, 10, 20 mg/kg). Numbers shown at bottom of graph are numbers of patients at risk.

Figure 5. Kaplan-Meier Plot: Age at Loss of Ambulation (Study 019 Patients as having never received treatment in the previous placebo-controlled studies with the established effective dose of ataluren (10, 10, 20 mg/kg and CINRG Data on 19MAR2018 with Propensity Score Matched Using Model 5)



Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group

Note: Set 5 of Propensity Score model covariates includes age at first symptom, baseline age and baseline time for climb 4 stairs from 007/004 and study entry of CINRG, duration of Deflazacort, and duration of steroid other than Deflazacort

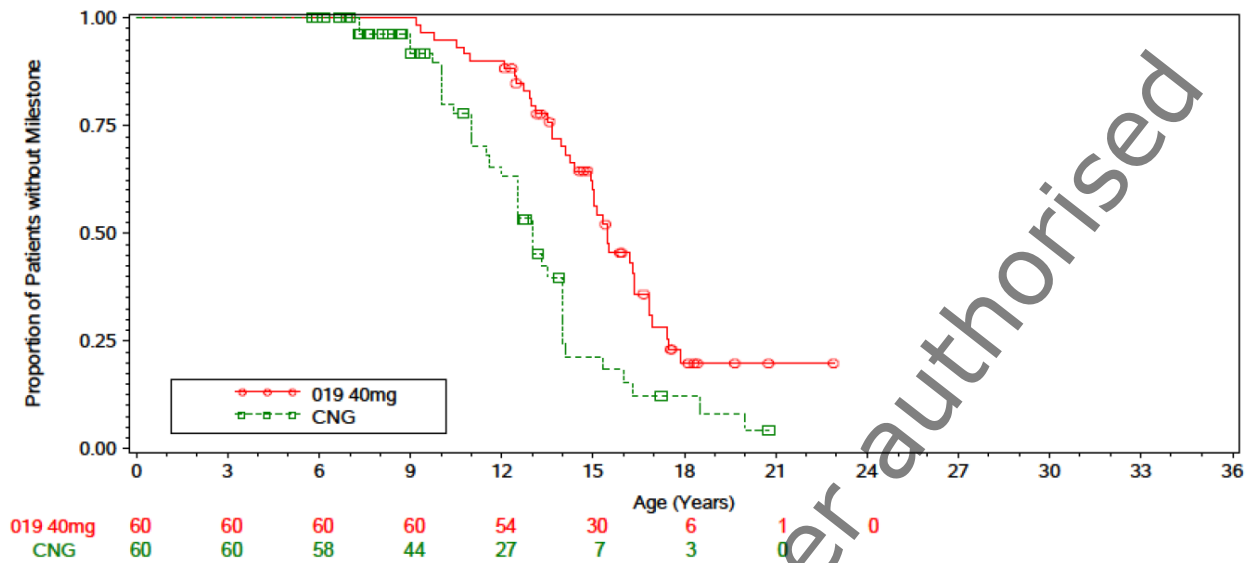
A total of 58 subjects never received ataluren 10, 10, 20 mg/kg prior to Study 019. For this analysis, the 33 of these subjects who were ambulatory at Study 019 were censored at Study 019 entry (ie, prior to receiving their first dose of ataluren 10, 10, 20 mg/kg). Numbers shown at bottom of graph are numbers of patients at risk.

B2. Assessing the appropriateness model using age at loss of ambulation

Kaplan Meier Analyses of Age at Loss of Ambulation of Propensity-score Matched Populations

In the position of the Applicant, age at loss of ambulation was a suitable end-point to validate the appropriateness of the model 2a. In the Figure 6 and Table 4 the Applicant provided a propensity-score based analysis comparing 60 subjects treated with 10, 10, 20 mg/kg and 60 matched participants from the CINRG cohort. The 60 subjects treated with 10, 10, 20 mg/kg ataluren had a median age at loss of ambulation of 15.5 years in Study 019 while matched CINRG cohort had 13.0 years as median age at loss of ambulation, representing a statistically significant difference in favour of ataluren (p value=0.0079). The 10, 10, 20 mg/kg treated population included the 27 subjects who received this dose in the preceding clinical trials 007/004 and the 33 subjects who began treatment at this dose upon entry into Study 019. In the position of the Applicant, these analyses underlined the appropriateness of the match and the clear clinical benefit of ataluren treatment. However, the efficacy regarding the age of loss of ambulation was not at discussion, as this is covered by the current indication.

Figure 6. Kaplan-Meier Plot: Age at Loss of Ambulation (Study 019 Patients treated with 10, 10, 20 mg/kg ataluren and CINRG Data on 19MAR2018 with Propensity Score Matched Using Model 2a)



Abbreviations: CNG/CINRG Cooperative International Neuromuscular Research Group

Note: Set 2a of Propensity Score model covariates includes age at first symptom and duration of Deflazacort, and duration of steroid other than Deflazacort

The 60 treated patients in this analysis are comprised of the 27 subjects received 10, 10, 20 mg/kg ataluren in Studies 004/007 and the 33 patients who were ambulatory at entry to Study 019 and who began treatment with 10, 10, 20 mg/kg ataluren upon entry to Study 019. For this analysis, the 33 of these subjects who were ambulatory at Study 019 were censored at Study 019 entry (ie, prior to receiving their first dose of ataluren 10, 10, 20 mg/kg)

Numbers shown at bottom of graph are numbers of patients at risk.

Table 4. Kaplan Meier Analysis of the Age of loss of ambulation (Study 019 Patients treated with 10, 10, 20 mg/kg ataluren and CINRG Data on 19MAR2018 with Propensity Score Matched Using Model 2a)

	019 40 mg (N=60)	CNG (N=60)
Loss of Ambulation		
Number of Patients Assessed	60	60
Number of Patients with Events [2]	39 (65.0%)	36 (60.0%)
Number of Patients Censored	21 (35.0%)	24 (40.0%)
Age (Years) at Loss of Ambulation		
25% Quantile (95% CI)	13.6 (12.5, 14.9)	11.0 (10.0, 12.5)
Median (95% CI)	15.5 (14.9, 16.4)	13.0 (11.6, 14.0)
75% Quantile (95% CI)	17.5 (16.4, NA)	14.0 (13.5, 18.5)
Minimum, Maximum [3]	9.2, 22.9+	5.8+, 20.8+
p-value [4]	0.0079	

Abbreviations: CNG/CINRG Cooperative International Neuromuscular Research Group

Note: Set 2a of Propensity Score model covariates includes age at first symptom and duration of Deflazacort, and duration of steroid other than Deflazacort

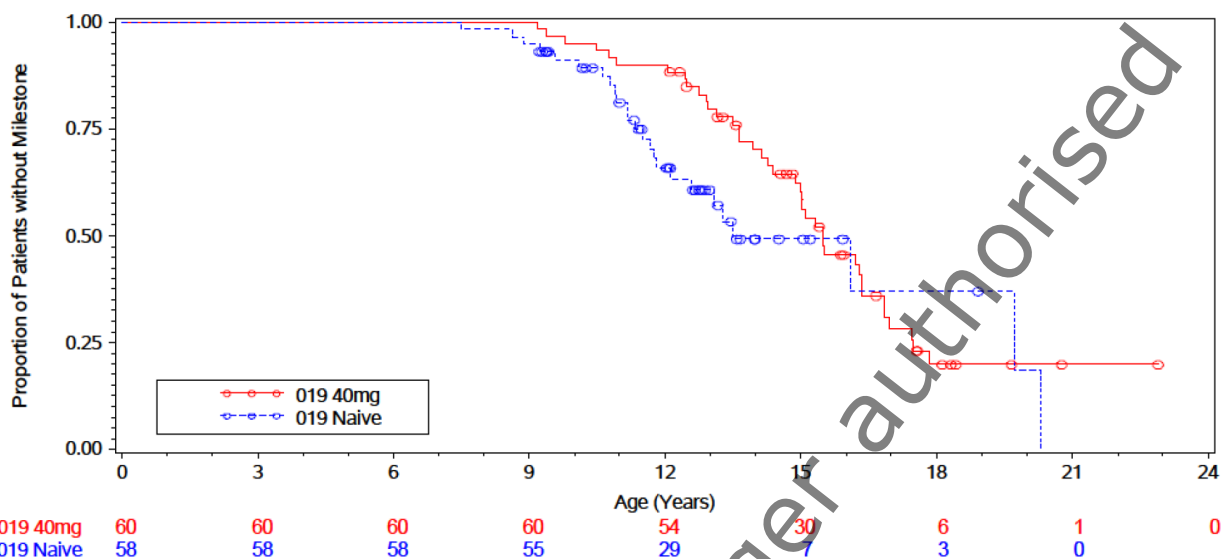
[1, 2] Event = Lost of Ambulation.

[3] '+' indicates censored observation.

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

The Applicant presented an additional analysis including the results of a Kaplan Meier analysis of age at loss of ambulation for patients who were received the effective 10, 10, 20 mg/kg dose of ataluren in Study 007/004 and those who received either placebo or a non-efficacious dose of ataluren prior to Study 019. In this analysis, ataluren treatment was associated with prolonging ambulation for 2 years, with a median age at loss of ambulation of 15.5 years among subjects randomized to 10, 10, 20 mg/kg ataluren and 13.5 years for the effectively naïve patients (Figure 7 and Table 5).

Figure 7. Kaplan-Meier Plot: Age at Loss of Ambulation (019 Patients treated with 10, 10, 20 mg/kg ataluren and Study 019 Patients as having never received treatment in the previous placebo-controlled studies with the established effective dose of ataluren (10, 10, 20 mg/kg) with Propensity Score Matched Using Model 2a)



Abbreviations: CINRG, Cooperative International Neuromuscular Research Group
 The 60 treated patients in this analysis are comprised of the 27 subjects received 10, 10, 20 mg/kg ataluren in Studies 004/007 and the 33 patients who were ambulatory at entry to Study 019 and who began treatment with 10, 10, 20 mg/kg ataluren upon entry to Study 019. The 58 naïve subjects never received ataluren 10, 10, 20 mg/kg prior to Study 019. Patients who began receiving the 10, 10, 20 mg/kg ataluren dose upon entry to Study 019 are included in both the treated and naïve groups
 Numbers shown at bottom of graph are numbers of patients at risk.

Table 5. Kaplan Meier Analysis of the Age of loss of ambulation (Study 019 Patients treated with 10, 10, 20 mg/kg ataluren and Study 019 Patients as having never received treatment in the previous placebo-controlled studies with the established effective dose of ataluren (10, 10, 20 mg/kg) with Propensity Score Matched Using Model 2a)

	019 40 mg (N=60)	19 Naive (N=58)
Loss of Ambulation		
Number of Patients Assessed	60	58
Number of Patients with Events [2]	39 (65.0%)	25 (43.1%)
Number of Patients Censored	21 (35.0%)	33 (56.9%)
Age (Years) at Loss of Ambulation		
25% Quantile (95% CI)	13.6 (12.5, 14.9)	11.3 (10.8, 12.6)
Median (95% CI)	15.5 (14.9, 16.4)	13.5 (12.1, 20.3)
75% Quantile (95% CI)	17.5 (16.4, NA)	19.7 (16.1, 20.3)
Minimum, Maximum [3]	9.2, 22.9+	7.5, 20.3

Note: Set 2a of Propensity Score model covariates includes age at first symptom and duration of Deflazacort, and duration of steroid other than Deflazacort
 [1, 2] Event = Lost of Ambulation.
 [3] '+' indicates censored observation.

Study 019 Patients as having never received treatment in the previous placebo-controlled studies with the established effective dose of ataluren (10, 10, 20 mg/kg) who were ambulatory at Study 019 were censored at Study 019 entry

Importantly, it should be noted that the patients included in the 40mg group include patients that were also included in the naïve treatment arm. The patients in the naïve arm were censored when switching to ataluren 40mg treatment. This introduced the steep decline in the naïve group, the blue line. The effect was exaggerated as patients were removed from the blue group and introduced in the red group. Moreover, before the switch, both arms were comparable, i.e. no differences between groups up to 11 years of age. However, as mentioned previously the efficacy of ataluren on the loss of ambulation is covered by the current indication and thus not at discussion.

Methodological considerations on the Propensity score-based models

Propensity score-matching analysis should be performed carefully following general consideration and acknowledging the limitations.

1. Matching on Propensity score method allows for adjusting for known baseline confounders. Therefore, it cannot correct for other bias in the study design or unmeasured/unknown baseline confounders. Additionally, as opposite to other propensity score-based methods such as inverse probability weighting, propensity score matching does not allow controlling for time-varying confounding.
2. Propensity score method usually relies on larger datasets, both in number of patients and number of variables. In a small dataset, as is the case here, the added value of propensity score matching is considered small at best, since perfect matches will not be found. In large datasets, it is also possible to impose some restriction on the matching criteria (i.e. a caliper such as 0.20 SD of the logit transformation of the propensity score) to minimize residual confounding within the categories of propensity score.
3. In order to build an appropriate propensity score model, the selection of variables should be carefully considered. The optimal propensity score model should include all variables associated with the outcome, irrespective of their potential association with treatment. In this study, it was unclear how the variables that were used in the propensity score models were selected. There were relevant variables such as TFT items that were not included.
4. In addition to the appropriate variables, avoiding model misspecification in the model for propensity score is needed for achieving causal inference throughout a propensity score-based method. Testing the performance of the model is a good practice. However, information on residual variance of covariates was not provided, which could inform on misspecification of the models.
5. The Applicant used a different end-point (age of loss of ambulation) to select and validate the final propensity score model applicable to pulmonary function end-points. The underlying assumption that could be questioned was whether a model with loss of ambulation as dependent variable could be extrapolated to a model with FVC as a dependent variable. Additionally, the final model chosen by the Applicant was the one with the largest effect and the most visually appealing. However, another model (model 3) showed a closer match.
6. The Applicant combined both placebo arm and high dose ataluren arm in the population to validate the matching models. The so-called *treatment naïve population* is not a truly naïve population as subjects could have been on placebo or high dose ataluren treatment. The assumption that the high dose ataluren has no effect at all was not justified. It was unclear if these two cohorts could indeed be pooled. If not, data from the placebo arm would be <20 , and thus the outcomes would have been more questionable.
7. The methods used for the propensity score matching appeared data driven, as results were already known. This may have affected variable and model selection. The MAH indicated that models 3-5 led to overfitting of the data as the CINRG group performed better than the ataluren group, although this has not been substantiated other than visual comparison. Given the low number of patients on which the propensity scores were calculated, overfitting may have been present in all models. However, statistically models 3-5 indicated a closer match. The p-values were $p=0.002$ (model 1), $p=0.093$ (model 2a), $p=0.424$ (model 3), $p=0.412$ (model 4) and $p=0.291$ (model 5). Therefore statistically, model 3 appeared to be the best model. Selection of the model is not based only on statistics but also should take into account how well the overall population matches visually, although it could not be excluded that model choice was (partly) based on knowing the final results, making the analyses explorative at most.

Results

Participant disposition

The number of subjects included in study 019 is 94, which includes ambulatory and non-ambulatory subjects at baseline.

- A total of 90 of the 96 ex-US patients who completed Study PTC124-GD-007-DMD 007 enrolled in Study 019; subjects continued into the extension trial regardless of the nature of their treatment response. The Study 019 population thus very closely reflects the population of the randomized placebo-controlled predecessor Study 007.
- Four subjects had not participated in the Study 007: 3 subjects had participated in PTC124-GD-004-DMD (Study 004) and 1 patient had no prior ataluren clinical trial experience.

A total of 37 out of 94 patients enrolled in the study 019 (39.4%) completed the study and 57 (60.0%) discontinued. Of the 57 subjects who discontinued, 40 (42.6%) did so due to the commercial availability of ataluren. While per protocol these patients could no longer be followed in Study 019, a total of 19 such subjects (6 of whom were non-ambulatory at baseline in Study 019) enrolled into the post-approval observational study PTC124-GD-025o-DMD (Study 025o), a registry in which they will be followed for a period of 5 years while treated with commercial ataluren (PTC124-GD-025o-DMD). The registry study is voluntary and therefore, not all subjects elected to participate, only a half of them decided to enrol. The full patient disposition including completed study and discontinuation and reasons for discontinuation are presented in Table 6. Per protocol, treatment under Study PTC124-GD-019-DMD (Study 019) was to discontinue once ataluren became commercially available.

Table 6. Patient disposition in Study 019.

	Ambulatory at Study Entry		Corticosteroid Use		Overall
	Yes	No	Yes	No	
Enrolled, n	50	44	84	10	94
As Treated (AT) Population, n [1]	50	44	84	10	94
Gap (days) between 007/007e and 019 [2]					
n	47	43	81	9	90
Mean (SD)	1045.7 (138.32)	1096.5 (185.38)	1071.1 (164.35)	1060.2 (165.60)	1070.0 (163.57)
Median	1066.0	1074.0	1070.0	1074.0	1070.0
Min, Max	801, 1334	809, 1863	801, 1863	856, 1302	801, 1863
Completed Study, n (%) [3]	22 (44.0)	15 (34.1)	36 (42.9)	1 (10.0)	37 (39.4)
Discontinued from study, n (%) [3]	28 (56.0)	29 (65.9)	48 (57.1)	9 (90.0)	57 (60.6)
Primary reasons for study discontinuation					
Withdrew Consent, n (%) [3]	1 (2.0)	8 (18.2)	8 (9.5)	1 (10.0)	9 (9.6)
Lost to follow up, n (%) [3]	1 (2.0)	4 (9.1)	3 (3.6)	2 (20.0)	5 (5.3)
Adverse Event, n (%) [3] ^[4]	1 (2.0)	2 (4.5)	2 (2.4)	1 (10.0)	3 (3.2)
Transitioned into commercial drug product (other), n (%) [3-4]	25 (50.0)	15 (34.1)	35 (41.7)	5 (50.0)	40 (42.6)

Abbreviations: Max, maximum; min, minimum; SD, standard deviation.

[1] AT population consists of all patients who had at least one dose of ataluren.

[2] The gap was calculated as (Study 019 baseline date -Studies 007/007e last dose +1).

[3] Percentages are calculated based on the total number of patients in the AT population.

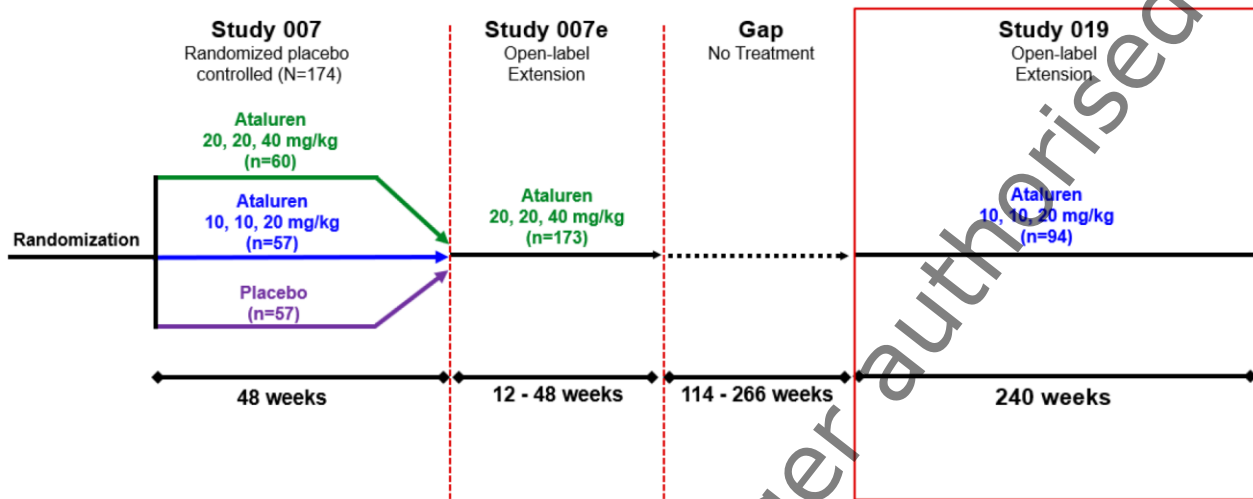
[4] All 40 patients discontinued study due to the commercial availability of ataluren.

Conduct of the study

Subjects in Study 007 were randomized to one of three arms: placebo, 10, 10, 20 mg/kg ataluren, or 20, 20, 40 mg/kg ataluren. Study 007 was followed immediately by an extension study PTC124-GD-007e-DMD (Study 007e) at the 20, 20, 40 mg/kg dose. After Study 007e, there was a treatment gap between the date of administration of the last dose of ataluren in PTC-sponsored studies and the date of administration of the first dose of ataluren in Study 019 that ranged from 114.43 to 266.14 weeks (801 to 1863 days). During this period, patients were not treated with ataluren. Then, they enrolled in the

open-label extension Study 019 at the 10, 10, 20 mg/kg dose (Figure 8). At the conclusion, the median (min., max.) duration of treatment with 10, 10, 20 mg/kg ataluren was 1670 (294, 2185) days, overall.

Figure 8. Clinical Study Participation History of Patients in Study 019



Note: A total of 4 patients enrolled in Study 019 without having participated in Study 007: Three had participated in Study 004 and one had not participated in a previous clinical trial of ataluren.

Six amendments to the original protocol were made, i.e. the ataluren treatment period was extended from 48 to 96 weeks, 96 to 144 weeks, 144 to 192 weeks, 192- to 240 weeks, 240- 366 weeks (Canada) respectively. Further, the End-of-Treatment visit for patients switching to commercially available ataluren was amended.

A total of 349 protocol deviations occurred in 77/94 (81.9%) patients (Table 7). Protocol deviations classified as "other" included, but were not limited to, out of window visits; missed visits; and lack of spirometry, ECHO, and other tests that were not performed as indicated in the protocol at specific visits.

One patient was classified as a screen failure as he had not participated in any prior ataluren studies. However, this patient was enrolled in the study and included in the data analyses of the study.

Table 7. Protocol Deviations in Study 019

Protocol Deviation Category	Ambulatory at Study Entry		Corticosteroid Use		Overall N=94
	Yes n=50	No n=44	Yes n=84	No n=10	
Total number of protocol deviations	140	209	308	41	349
Number of Patients with ≥1 Protocol Deviations, n (%)	38 (76.0)	39 (88.6)	68 (81.0)	9 (90.0)	77 (81.9)
Patients who developed withdrawal criteria during the study but were not withdrawn	0	0	0	0	0
Patients who entered the study even though they did not satisfy the entry criteria	0	0	0	0	0
Patients who received an excluded concomitant treatment	0	0	0	0	0
Patients who received the wrong treatment or incorrect dose, n (%)	3 (6.0)	3 (6.8)	6 (7.1)	0	6 (6.4)
Other, n (%)	38 (76.0)	39 (88.6)	68 (81.0)	9 (90.0)	77 (81.9)

Baseline data

Patient demographics and baseline characteristics by ambulatory status and by corticosteroid use are presented in table 8a.

All patients were between the ages of 9 to 21 years at entry of study 019. Overall, the median age was 13 years; for ambulatory and non-ambulatory patients, the median age was 12 years and 14 years, respectively. The majority of patients (69.1%) were ≥ 12 and ≤ 17 years of age and Caucasian (92.6%). Patients who were non-ambulatory were heavier, had a higher body mass index (BMI) and were taller than ambulatory patients. The mean 6MWD for ambulatory patients at baseline was 341.63 meters.

Demographic and baseline characteristics were generally balanced between corticosteroid types (deflazacort vs. prednisone/prednisolone) for ambulatory and non-ambulatory patients. The mean percent-predicted FVC was higher in the prednisone/prednisolone group as compared to the deflazacort group (81.27% vs. 66.34%) for non-ambulatory patients. Demographic and baseline characteristics by cumulative corticosteroid use (<12 months vs. ≥ 12 months) at study entry were comparable between ambulatory and non-ambulatory boys. The majority of subjects were on corticosteroids for ≥ 12 months, e.g. 40 ambulatory boys and 30 non ambulatory boys.

The disease characteristics and the concomitant corticosteroid medications use at study entry are presented in Table 8b. Of the 94 subjects in Study 019, all (47 ambulatory and 37 non-ambulatory) but 10 (3 ambulatory and 7 non-ambulatory) received concomitant treatment with corticosteroids.

Table 8a. Demographics and baseline characteristics (AT population) in Study 019

	Ambulatory at Study Entry		Corticosteroid Use		Overall N=94
	Yes N=50	No N=44	Yes N=84	No N=10	
Age (years)					
n	50	44	84	10	94
Mean (SD)	12.1 (2.07)	13.7 (2.46)	12.8 (2.30)	13.1 (3.14)	12.8 (2.38)
Median	12.0	13.0	13.0	12.5	13.0
Min, Max	9, 18	9, 21	9, 21	9, 19	9, 21
Age Groups, n (%)					
6 - ≤ 11	18 (36.0)	6 (13.6)	22 (26.2)	2 (20.0)	24 (25.5)
12 - ≤ 17	31 (62.0)	34 (77.3)	59 (70.2)	6 (60.0)	65 (69.1)
≥ 18	1 (2.0)	4 (9.1)	3 (3.6)	2 (20.0)	5 (5.3)
Sex, n (%)					
Male	50 (100)	44 (100)	84 (100)	10 (100)	94 (100)
Race, n (%)					
Caucasian	46 (92.0)	41 (93.2)	77 (91.7)	10 (100)	87 (92.6)
Asian	3 (6.0)	1 (2.3)	4 (4.8)	0	4 (4.3)
Other	0	2 (4.5)	2 (2.4)	0	2 (2.1)
Weight (kg)					
n	50	44	84	10	94
Mean (SD)	39.50 (9.491)	53.05 (14.951)	45.09 (13.312)	52.16 (18.779)	45.84 (14.039)
Median	38.45	50.35	42.00	52.10	42.05
Min, Max	26.3, 71.6	23.8, 92.6	26.3, 92.6	23.8, 77.8	23.8, 92.6
Height (cm)					
n	50	8	55	3	58
Mean (SD)	131.57 (11.120)	135.04 (7.011)	130.96 (8.240)	151.97 (27.974)	132.05 (10.667)
Median	129.45	133.00	130.00	146.70	130.50
Min, Max	113.5, 182.2	127.8, 150.0	113.5, 150.0	127.0, 182.2	113.5, 182.2
BMI (kg/m ²)					
n	50	8	55	3	58
Mean (SD)	22.81 (4.634)	26.66 (4.793)	23.64 (4.669)	17.86 (4.641)	23.34 (4.804)
Median	21.70	27.08	22.11	16.78	22.08
Min, Max	13.8, 33.7	19.8, 33.0	16.7, 33.7	13.8, 22.9	13.8, 33.7

Baseline six-minute walk distance (m)					
n	49	1*	47	3	50
Mean (SD)	341.63 (108.106)	11.00 (.)	337.83 (119.297)	291.00 (60.258)	335.02 (116.768)
Median	355.00	11.00	361.00	302.00	352.50
Min, Max	36.0, 552.0	11.0, 11.0	11.0, 552.0	226.0, 345.0	11.0, 552.0
Baseline six-minute walk distance (m) group, n (%)					
<300	14 (28.0)	1 (2.3)*	14 (16.7)	1 (10.0)	5 (16.0)
≥300 - <400	18 (36.0)	0	16 (19.0)	2 (20.0)	18 (19.1)
≥400	17 (34.0)	0	17 (20.2)	0	17 (18.1)
Baseline time of 10-meter walk/run (s)					
n	50	1*	48	3	51
Mean (SD)	8.35 (4.693)	37.00 (.)	8.88 (6.329)	9.43 (0.379)	8.91 (6.138)
Median	7.21	37.00	6.50	9.60	7.32
Min, Max	3.5, 26.4	37.0, 37.0	3.5, 37.0	9.0, 9.7	3.5, 37.0
Baseline time of rise from supine (s)					
n	38	1*	36	3	39
Mean (SD)	18.56 (34.349)	98.00 (.)	19.97 (37.522)	26.13 (13.068)	20.60 (36.202)
Median	6.80	98.00	6.03	26.60	7.20
Min, Max	0.0, 190.0	98.0, 98.0	0.0, 190.0	15.9, 41.9	0.0, 190.0
Baseline time of rise from supine (s) group, n (%)					
<5	11 (22.0)	0	11 (13.1)	0	11 (11.7)
≥5	27 (54.0)	1 (2.3)*	25 (29.8)	3 (30.0)	28 (29.8)
Age at Diagnosis [1] (years)					
n	49	44	83	10	93
Mean (SD)	3.65 (2.185)	3.5 (1.62)	3.59 (1.874)	3.5 (2.46)	3.58 (1.930)
Median	3.00	3.0	3.00	3.0	3.00
Min, Max	0.0, 10.0	0, 7	0.0, 9.0	1.0, 10.0	0.0, 10.0
Time since diagnosis [2] (years)					
n	49	44	83	10	93
Mean (SD)	8.45 (2.292)	10.2 (2.89)	9.22 (2.673)	9.6 (3.20)	9.26 (2.718)
Median	8.00	10.0	9.00	9.0	9.00
Min, Max	5.0, 14.0	6, 19	5.0, 19.0	6, 18	5.0, 19.0
Stop Codon Type n (%)					
UAA	7 (14.0)	10 (22.7)	15 (17.9)	2 (20.0)	17 (18.1)
UGA	32 (64.0)	17 (38.6)	45 (53.6)	4 (40.0)	49 (52.1)
UAG	10 (20.0)	17 (38.6)	23 (27.4)	4 (40.0)	27 (28.7)
Missing	1 (2.0)	0	1 (1.2)	0	1 (1.1)
Phenotypic Diagnosis [3] n (%)					
Gowers Maneuver	38 (76.0)	39 (88.6)	68 (81.0)	8 (80.0)	77 (81.9)
Waddling Gait	37 (74.0)	37 (84.1)	66 (78.6)	9 (90.0)	74 (78.7)
Calf Hypertrophy	41 (82.0)	41 (93.2)	73 (86.9)	9 (90.0)	82 (87.2)
Genetic Results	47 (94.0)	43 (97.7)	81 (96.4)	9 (90.0)	90 (95.7)
Elevated CK	46 (92.0)	43 (97.7)	80 (95.2)	9 (90.0)	89 (94.7)
Proximal Muscle Weakness	40 (80.0)	41 (93.2)	73 (86.9)	8 (80.0)	81 (86.2)
Other	10 (20.0)	11 (25.0)	18 (21.4)	3 (30.0)	21 (22.3)
Exon Location n (%)					
1 - 39	21 (42.0)	27 (61.4)	42 (50.0)	6 (60.0)	48 (51.1)
40 - 80	28 (56.0)	17 (38.6)	41 (48.8)	4 (40.0)	45 (47.9)

Abbreviations: AT, as treated; BMI, body mass index; CK, Creatinine Kinase; Max, maximum; min, minimum; SD, standard deviation.

[1] Age at diagnosis = (Diagnosis date - Date of birth + 1) / 365.25

[2] Time since Diagnosis = (First dose date - Diagnosis Date + 1) / 365.25.

[3] Patients could have multiple diagnoses

*Even though one patient was classified as non-ambulatory per the SAP definition of being unable to run/walk 10 meters in ≤30 seconds; however, he completed assessments intended for ambulatory patients. Note: AT Population consists of all patients who had at least one dose of ataluren. All percentages are calculated based on the number of patients in the AT Population.

Height values for some non-ambulatory patients were not collected.

Table 8b. Concomitant corticosteroid medications at study entry (AT population) in Study 019

ATC level 3 Preferred Term	Ambulatory at Study Entry		Overall N=94 n (%)
	Yes N=50 n (%)	No N=44 n (%)	
Patients with any concomitant corticosteroid medication	47 (94.0)	37 (84.1)	84 (89.4)
Corticosteroids for systemic use	47 (94.0)	36 (81.8)	83 (88.3)
Deflazacort	35 (70.0)	16 (36.4)	51 (54.3)
Prednisone/prednisolone	14 (28.0)	21 (47.7)	35 (37.2)
Hydrocortisone	3 (6.0)	2 (4.5)	5 (5.3)
Betamethasone	1 (2.0)	1 (2.3)	2 (2.1)
Triamcinolone acetonide	0	1 (2.3)	1 (1.1)

Abbreviations: AT, as treated; ATC, anatomic therapeutic response. AT Population consists of all patients who had at least one dose of ataluren. Concomitant corticosteroid medications were coded with the WHO Drug Dictionary dated 2017 Dec 01 and defined as any

medications that patients took after/on first dose date. Patients may have more than one medication per ATC level 3 category and preferred name. At each level of patient summarization, a patient is counted once if the patients reported one or more medications.

A. Propensity score matched analyses for dynamics of FVC over age and age at FVC<1 litre

Baseline characteristics in Study 019 and CINRG matched population by FVC

The FVC by age was analysed based on a piecewise regression model for the matched Study 019 and CINRG populations, with matching criteria, as summarized in Table 2. According to the Applicant, the resulting populations, which included patients who were non-ambulatory at baseline as well as those who lost ambulation during the study, were comparable across a range of demographic and baseline pulmonary function characteristics presented (baseline FVC). According Table 9, matched cohort of participants in Study 019 had a median age of 14.1 years while matched cohort of CINRG participants had a median age of 10.7 years. Additionally, matched cohort of participants in Study 019 had a median baseline percentage predicted FVC of 72.2 litres and matched cohort of CINRG participants had a median baseline percentage predicted FVC of 77.3 litres.

Table 9. Summary of Demographics and Baseline Characteristics in Study 019 and CINRG (Matched Population for FVC Piecewise Regression Analysis)

	Study 019 n=60	CINRG n=91
Age (years)		
N	60	91
Mean (SD)	14.1 (2.22)	10.7 (3.52)
Age Groups, n (%)		
6 - ≤11	6 (10.0)	57 (62.6)
12 - ≤17	51 (85.0)	29 (31.9)
≥18	3 (5.0)	5 (5.5)
Sex, n (%)		
Male	60 (100)	91 (100)
Race, n (%)		
Caucasian	54 (90.0)	75 (82.4)
Black or African American	0 (0.0)	0 (0.0)
Pacific Islander	0 (0.0)	1 (1.1)
Asian	4 (6.7)	7 (7.7)
Native American	0 (0.0)	0 (0.0)
Other	2 (3.3)	8 (8.8)
Unknown	0 (0.0)	0 (0.0)
Baseline FVC		
n	60	91
Mean (SD)	1.91 (0.556)	1.70 (0.607)
Baseline %-predicted FVC		
n	48	91
Mean (SD)	72.75 (17.157)	77.3 (24.17)

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital capacity; SD, standard deviation
 Note: The matching is not on subjects but on the FVC assessments. The matched FVC assessments are the non-missing FVC meeting the following criteria: at those assessments, subjects are non-ambulatory, cumulative corticosteroid use duration ≥24 months, age ≤25 years, and visit year ≥2012. The cumulative corticosteroid use duration in study 019 is from the earliest corticosteroid use date of studies 004, 007 and 019 to those visits. All percentages are calculated based on the number of subjects in the matched population.

The demographic and baseline characteristics of the matched cohort for the analysis of age at FVC <1 litre are summarized in Table 10. All subjects included in this analysis were non-ambulatory with FVC ≥1L and ≤3.08L and age ≥9 and ≤18 at baseline. Subjects in Study 019 who were non-ambulatory at baseline had a mean treatment gap of 1096.5 days between the prior placebo-controlled studies and the start of Study 019. While demographic characteristics were generally comparable for the matched populations, patients in the CINRG dataset had a lower percent predicted FVC value at baseline than those in the Study 019 population and were more frequently not receiving corticosteroid. Two sensitivity analyses were undertaken to determine the effects of these imbalances on the primary Kaplan Meier analysis of age at FVC <1 litre.

Table 10. Summary of Demographics and Baseline Characteristics in Study 019 and CINRG (Matched Population Kaplan Meier Analysis of age at FVC Less Than 1 Litre)

	Study 019 n=37	CINRG n=52
Age (years)		
N	37	52
Mean (SD)	13.48 (1.650)	13.46 (2.270)
Age Groups, n (%)		
6 - ≤11	6 (16.2)	8 (15.4)
12 - ≤17	31 (83.8)	44 (84.6)
≥18		
Sex, n (%)		
Male	37 (100)	52 (100)
Race, n (%)		
Caucasian	34 (91.9)	30 (57.7)
Black or African American	0 (0.0)	1 (1.9)
Pacific Islander	0 (0.0)	0 (0.0)
Asian	1 (2.7)	12 (23.1)
Native American	0 (0.0)	0 (0.0)
Other	2 (5.4)	9 (17.3)
Unknown	0 (0.0)	0 (0.0)
Baseline corticosteroid use		
None	8 (21.6)	29 (55.8)
Deflazacort	13 (35.1)	11 (21.2)
Prednisone/ Prednisolone	16 (43.2)	12 (23.1)
Corticosteroid treatment duration		
<12 month	8 (21.6)	20 (38.5)
≥12 month	29 (78.4)	32 (61.5)
Baseline FVC		
N	35	52
Mean (SD)	2.00 (0.458)	1.77 (0.463)
Baseline %-predicted FVC		
N	31	52
Mean (SD)	76.97 (15.200)	57.5 (16.65)

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; FVC, Forced vital capacity; SD, standard deviation
 Note: Corticosteroid treatment duration is defined as cumulative steroid treatment duration prior to study entry, including prior corticosteroid use for patients who discontinued steroid treatment prior to baseline. The cumulative baseline corticosteroid use duration in study 019 is from the earliest corticosteroid use date of studies 004, 007 and 019 to the baseline visit date. Corticosteroid use at study entry is yes if the study entry visit date is between the corticosteroid start and stop dates.
 Matched population are those non-ambulatory subjects at study entry, with baseline FVC ≥1L and ≤3.08L, and baseline age ≥9 and ≤18. All percentages are calculated based on the number of subjects in the matched population.

In the matched populations for Study 019 and CINRG for age at FVC <1 litre, there was an imbalance in baseline absolute and percent-predicted FVC. This imbalance was driven largely by patients with a baseline FVC >2 litres. A sensitivity analysis excluding patients with baseline FVC >2 litres was undertaken to determine the effect of this imbalance. The baseline characteristics and demographics for the populations for this sensitivity analysis are summarized in Table 11. When these patients were excluded, the resulting population became comparable in absolute FVC and more comparable in percent-predicted FVC than the full matched population. However, mean percent-predicted FVC was 68.21 litres for participants in the Study 019 and 54.1 litres for participants in CINRG study.

Table 11. Summary of Demographics and Baseline Characteristics in Study 019 and CINRG for Patients with Baseline FVC <2 litre (Matched Population Kaplan Meier Analysis of age at FVC <1 litre)

	Study 019 n=20	CINRG n=41
Age (years)		
N	20	41
Mean (SD)	13.10 (1.842)	13.38 (2.415)
Age Groups, n (%)		

	Study 019 n=20	CINRG n=41
6 - ≤11	5 (25.0)	7 (17.1)
12 - ≤17	15 (75.0)	34 (82.9)
≥18	0 (0.0)	0 (0.0)
Sex, n (%)		
Male	20 (100)	41 (100)
Race, n (%)		
Caucasian	19 (95.0)	22 (53.7)
Black or African American	0 (0.0)	1 (2.4)
Pacific Islander	0 (0.0)	0 (0.0)
Asian	0 (0.0)	10 (24.4)
Native American	0 (0.0)	0 (0.0)
Other	1 (5.0)	8 (19.5)
Unknown	0 (0.0)	0 (0.0)
Baseline corticosteroid use		
None	6 (30.0)	23 (56.1)
Deflazacort	8 (40.0)	9 (22.0)
Prednisone/prednisolone	6 (30.0)	9 (22.0)
Baseline corticosteroid duration		
<12 month	5 (25.0)	14 (34.1)
≥12 month	15 (75.0)	27 (65.9)
Baseline FVC		
N	18	41
Mean (SD)	1.62 (0.233)	1.57 (0.255)
Baseline %-predicted FVC		
N	14	41
Mean (SD)	68.21 (12.299)	54.1 (16.68)

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital capacity; SD, standard deviation

Note: Corticosteroid treatment duration is defined as cumulative steroid treatment duration prior to study entry, including prior corticosteroid use for patients who discontinued steroid treatment prior to baseline. The cumulative baseline corticosteroid use duration in study 019 is from the earliest corticosteroid use date of studies 004, 007 and 019 to the baseline visit date. Corticosteroid use at study entry is yes if the study entry visit date is between the corticosteroid start and stop dates.

Matched population are those non-ambulatory subjects at study entry, with baseline FVC ≥1L and ≤3.08L, and baseline age ≥9 and ≤18.

In order to ensure that the effect seen in the analysis of age at FVC <1 litre could not be attributed to steroid use a sensitivity analysis was undertaken in the subsets of patients with and without corticosteroid use at baseline. The baseline characteristics and demographics for the corticosteroid use sensitivity analysis populations are summarized in Table 12.

Table 12. Summary of Demographics and Baseline Characteristics in Study 019 and CINRG for Patients with No Corticosteroid Use at Baseline (Matched Population Kaplan Meier Analysis of age at FVC Less Than 1 litre)

	Study 019 No corticosteroids n=8	CINRG No corticosteroids n=29
Age (years)		
N	8	29
Mean (SD)	13.15 (1.273)	13.71 (2.571)
Age Groups, n (%)		
6 - ≤11	1 (12.5)	5 (17.2)
12 - ≤17	7 (87.5)	24 (82.8)
≥18	0 (0.0)	0 (0.0)
Sex, n (%)		
Male	8 (100)	29 (100)
Race, n (%)		
Caucasian	8 (100.0)	14 (48.3)
Black of African American	0 (0.0)	1 (3.4)
Pacific Islander	0 (0.0)	0 (0.0)
Asian	0 (0.0)	8 (27.6)
Native American	0 (0.0)	0 (0.0)
Other	0 (0.0)	6 (20.7)
Unknown	0 (0.0)	0 (0.0)

	Study 019 No corticosteroids n=8	CINRG No corticosteroids n=29
Baseline corticosteroid use		
No	8 (100.0)	29 (100.0)
Yes	0 (0.0)	0 (0.0)
Cumulative baseline corticosteroid duration		
<12 month	7 (87.5)	20 (69.0)
≥12 month	1 (12.5)	9 (31.0)
Baseline FVC		
N	8	29
Mean (SD)	1.92 (0.498)	1.78 (0.465)
Baseline %-predicted FVC		
N	6	29
Mean (SD)	75.69 (16.102)	51.2 (15.56)

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital capacity; SD, standard deviation

Note: Corticosteroid treatment duration is defined as cumulative steroid treatment duration prior to study entry, including prior corticosteroid use for patients who discontinued steroid treatment prior to baseline. The cumulative baseline corticosteroid use duration in study 019 is from the earliest corticosteroid use date of studies 004, 007 and 019 to the baseline visit date. Corticosteroid use at study entry is yes if the study entry visit date is between the corticosteroid start and stop dates.

Matched population are those non-ambulatory subjects at study entry, with baseline FVC ≥1L and ≤3.08L, and baseline age ≥9 and ≤18.

B. Propensity score matched analyses for age at percentage predicted FVC<60%, age at percentage predicted FVC<50% and age at FVC<1 litre

There were no statistically significant differences between the matched populations for models 2a (Table 13) and 2b (Table 14) across a range of important baseline demographic and disease state characteristics. For the model 2a, the baseline values were generally comparable, however, looking at the TFT item time to climb 4 stairs; the CNRG group performed worse at baseline. This may have impacted the outcomes in favour of ataluren treatment (. For the model 2b, both groups showed comparable baseline values, however, very limited variables were compared. No other functional assessments, e.g. items on the time function test were included. As the functional baseline characteristics are also indicative for the disease stage, they should have been included (Table 14).

Table 13. Demographic and Disease Characteristics - 019 and CINRG Propensity Matched Population Using Model 2a

	Study 019 (N=45)	CINRG (N=45)	p value
Age at First Symptoms, years			
Mean (SD)	3.778 (1.757)	3.752 (1.529)	0.9405
SEM	0.262	0.228	
95% CI	(3.250, 4.306)	(3.292, 4.211)	
Median	3.000	3.170	
Min, Max	1.00, 9.00	1.00, 8.00	
DEFLAZACORT Duration, n (%)			
<1 month	22 (48.9)	25 (55.6)	0.5267
≥12 month	23 (51.1)	20 (44.4)	
Other Steroid Duration, n (%)			
<1 month	26 (57.8)	25 (55.6)	0.9762
≥1 to <12 month	2 (4.4)	2 (4.4)	
≥12 month	17 (37.8)	18 (40.0)	

First Assessment of 4 Stair Climb in Study 004/007/CINRG, n (%)			
Mean (SD)	7.131 (7.686)	10.384 (7.752)	0.1212
SEM	1.146	1.733	
95% CI	(4.822, 9.440)	(6.756, 14.012)	
Median	4.300	6.560	
Min, Max	1.50, 30.00	2.03, 28.33	
First Assessment of 10m r/w in Study 004/007/CINRG, n (%)			
Mean (SD)	8.169 (5.714)	8.588 (3.875)	0.7486
SEM	0.852	0.791	
95% CI	(6.452, 9.886)	(6.952, 10.224)	
Median	6.600	8.000	
Min, Max	3.20, 30.00	3.62, 22.63	
First Assessment of Stand from Supine in Study 004/007/CINRG, n (%)			
Mean (SD)	12.416 (11.050)	11.173 (8.101)	0.6904
SEM	1.647	2.092	
95% CI	(9.096, 15.735)	(6.686, 15.659)	
Median	6.300	7.220	
Min, Max	1.80, 30.00	3.78, 30.00	

Abbreviations: CI, confidence interval; CINRG, Cooperative International Neuromuscular Research Group; Max, maximum; Min, minimum; SEM, standard error of the mean; SD, standard deviation
Propensity score model covariates include age at first symptom, duration of Steroid-DEFLAZACORT, and duration of Steroid-Other. Data for six-minute walk distance are not summarized here due to the insufficient number of patients (n=3) in the CINRG population with values for this endpoint at study entry.
Steroid duration is calculated from starting use of steroid to FVC <1 L/censored date.
P value is calculated based on 2-sample t-test.

Table 14. Demographic and Disease Characteristics - 019 and CINRG Propensity Matched Population Using Model 2b

	Study 019 (N=45)	CINRG (N=45)	p value
Age at LoA, years			
Mean (SD)	12.833 (2.635)	12.804 (2.465)	0.9579
SEM	0.393	0.368	
95% CI	(12.041, 13.624)	(12.064, 13.545)	
Median	12.750	12.500	
Min, Max	7.49, 17.85	8.10, 18.50	
DEFLAZACORT Duration, n (%)			
<1 month	22 (48.9)	22 (48.9)	1.000
≥12 month	23 (51.1)	23 (51.1)	
Other Steroid Duration, n (%)			
<1 month	26 (57.8)	25 (55.6)	0.7929
≥1 to <12 month	2 (4.4)	1 (2.2)	
≥12 month	17 (37.8)	19 (42.2)	
%pFVC (First Assessment Relevant to LoA), n (%)			
Mean (SD)	78.766 (10.795)	77.467 (13.382)	0.7287
SEM	2.544	2.443	
95% CI	(73.398, 84.134)	(72.470, 82.464)	
Median	77.345	78.000	
Min, Max	61.90, 103.83	57.00, 115.00	

Abbreviations: %pFVC, percent predicted forced vital capacity; CI, confidence interval; CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital capacity; LoA, loss of ambulation; Max, maximum; Min, minimum; SEM, standard error of the mean; SD, standard deviation
Propensity score model covariates include age at loss of ambulation, duration of Steroid-DEFLAZACORT, and duration of Steroid-Other. Steroid duration is calculated from starting use of steroid to FVC <1 L/censored date.
P value is calculated based on 2-sample t-test.

Numbers analysed

A total of 94 patients who had previously received ataluren in a prior PTC Therapeutics clinical study were enrolled at 21 sites in Australia, Belgium, Canada, France, Germany, Israel, Italy, Spain, Sweden, and United Kingdom. Patients received ataluren TID (10, 10, 20 mg/kg) for a total daily dose of 40 mg/kg. At the EOT (240 weeks), 37/94 (39.4%) patients had completed the study.

Outcomes and estimation

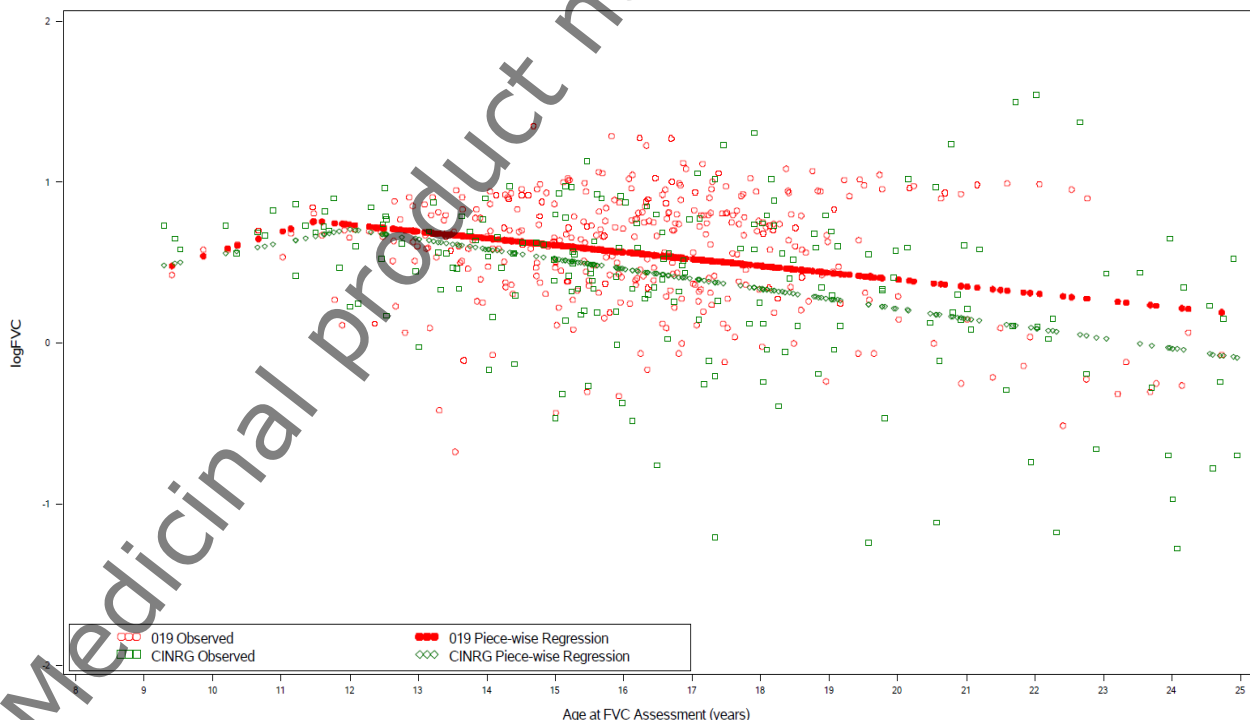
A. Propensity score matched analyses for dynamics of FVC over age and age at FVC<1 litre

A1. Dynamics of FVC over age

According to the Applicant, this analysis revealed CINRG patients reached an average maximum FVC at 12 years of age followed by the onset of progressive pulmonary decline. In contrast, patients taking ataluren experienced relative stability in pulmonary function, with no true inflection point occurring during the nearly 4 years of study duration.

The relative stability of FVC values for ataluren-treated subjects in Study 019 made discerning an inflection point through this piecewise-regression model difficult. The sample-size corrected AICc value was very similar for ages that range from 11 to 15 years, and there was no significant decline (indicated by the lack of a statistically significant slope $p=0.0749$). In comparison, after the age of 12, the age determined as the inflection point by the best fitting piecewise regression model for subjects in the CINRG dataset in this analysis, CINRG subjects experienced a decline in FVC represented by a statistically significant slope ($p=0.0212$). Furthermore, on the basis of an analysis that estimated absolute FVC for a given age using data of untreated nmDMD patients from CINRG, ataluren therapy in this analysis was associated with 13% higher absolute FVC than no treatment ($p=0.0038$) (Figure 9). All patients included in this analysis were on concomitant corticosteroids; thus, the difference in the rate of decline in FVC observed between the Study 019 and CINRG cohorts could not be driven by the effect of the use of concomitant corticosteroids, provided the use is similar across cohorts (type, dose and time).

Figure 9. Scatter Plot Forced Vital Capacity (log transformed) vs Age and Best Fitting Piece-Wise Regression Model for Non-ambulatory patients in Study 019 and CINRG Data on 18NOV2016 (Matched Population for Piece-wise Regression Analysis on FCV)



Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; FVC, Forced vital capacity
For study 019, change point from piece-wise regression is at age 11.5. For study CINRG, change point is at age 12.

A2. Time to FVC below 1 litre

In the CINRG dataset, 22 (42.3%) of subjects experienced a decline of FVC to <1 litre. In comparison, 4 (10.8%) ataluren-treated subjects experienced an FVC below this crucial threshold. The median age of FVC <1 litre among CINRG subjects was 19.3 years. Due to the infrequency of events of FVC <1 in the ataluren-treated population, the median age could not be estimated (Table 15).

Table 15. Kaplan-Meier Analysis of age at FVC <1 Liter (Study 019 and CINRG)

	Study 019 n=37	CINRG n=52
FVC <1 Liter		
Patients Assessed	37 (100.0)	52 (100)
Patients with Events	4 (10.8)	22 (42.3)
Patients Censored	33 (89.2)	30 (57.7)
Age at FVC < 1 Liter (years)		
25% Quantile (95% CI)	NA (16.3, NA)	16.3 (15.3, 18.9)
Median (95% CI)	NA (NA, NA)	19.3 (18.5, 22.6)
75% Quantile (95% CI)	NA (NA, NA)	22.6 (22.0, 24.0)
Minimum, Maximum	10.4+, 20.0+	12.4, 24.0
Log-rank p value		0.1083
Wilcoxon p value		0.1821

Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; CI, Confidence interval; FVC, forced vital capacity; NA, not applicable

Note: An event is defined as a subject who has FVC <1 L.

[1] "+" indicates a censored observation.

Matched subjects are those non-ambulatory subjects at study entry, with baseline FVC \geq 1L and \leq 3.08L, and baseline age \geq 9 and \leq 18.

Sensitivity Analysis for Patients with Baseline FVC < 2 litres

A sensitivity analysis excluding patients with baseline FVC >2 litres was undertaken to determine the effect of this imbalance. The result was similar to that of the primary analysis. The Kaplan-Meier analysis of age at FVC <1 litre for patients with baseline FVC <2 litres is summarized in Table 16.

Table 16. Kaplan-Meier Analysis of age at FVC <1 Liter for Patients with a Baseline FVC <2 L (Study 019 and CINRG)

	Study 019 n=20	CINRG n=41
FVC <1 Liter		
Patients Assessed	20 (100.0)	41 (100.0)
Patients with Events	3 (15.0)	19 (46.3)
Patients Censored	17 (85.0)	22 (53.7)
Age at FVC < 1 Liter (years)		
25% Quantile (95% CI)	18.0 (13.7, NA)	17.0 (14.4, 18.5)
Media (95% CI)	NA (18.0, NA)	18.9 (18.3, 22.0)
75% Quantile (95% CI)	NA (NA, NA)	22.3 (19.2, NA)
Minimum, Maximum	10.4+, 19.2+	12.4, 22.8+
Log-rank p value		0.3932
Wilcoxon p value		0.3817

Abbreviation: CINRG, Cooperative International Neuromuscular Research Group; CI, Confidence interval; FVC, forced vital capacity; NA, not applicable.

Note: An event is defined as a subject who has FVC <1 L.

[1] "+" indicates a censored observation.

Note: Matched subjects are those non-ambulatory subjects at study entry, with baseline FVC \geq 1L and \leq 3.08L, and baseline age \geq 9 and \leq 18.

Sensitivity Analysis for Patients without Baseline Corticosteroid Use

A sensitivity analysis was undertaken in the subsets of patients with and without corticosteroid use at baseline. The Kaplan-Meier analysis of age at FVC <1 litre for patients with no baseline corticosteroid use is summarized in Table 17 and Kaplan-Meier curves for no baseline corticosteroid use and baseline corticosteroid are displayed in Figure 10 and Figure 11, respectively.

Table 17. Kaplan-Meier Analysis of age at FVC <1 Liter for Patients with No Corticosteroid Use at Baseline (Study 019 and CINRG)

	Study 019 n=8	CINRG n=29
FVC <1 Liter		
Patients Assessed	8 (100.0)	29 (100.0)
Patients with Events	1 (12.5)	13 (44.8)
Patients Censored	7 (87.5)	16 (55.2)
Age at FVC < 1 Liter (years)		
25% Quantile (95% CI)	NA (15.2, NA)	18.3 (14.4, 19.2)
Media (95% CI)	NA (15.2, NA)	19.2 (18.3, 22.6)
75% Quantile (95% CI)	NA (NA, NA)	22.6 (19.2, 24.0)
Minimum, Maximum	14.2+, 17.7+	12.4, 24.0
Log-rank p value		0.9188
Wilcoxon p value		0.9111

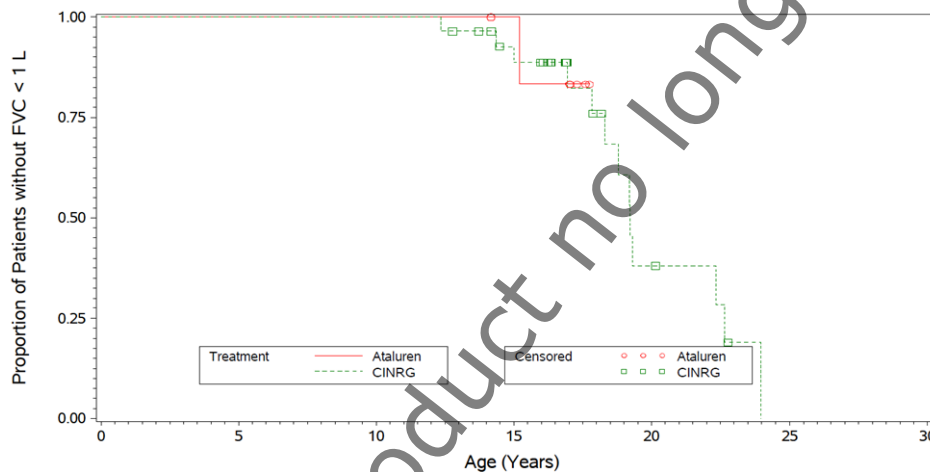
Abbreviations: CINRG, Cooperative International Neuromuscular Research Group; CI, Confidence interval; FVC, forced vital capacity; NA, not applicable

Note: An event is defined as a subject who has FVC < 1 L.

[1] "+" indicates a censored observation.

Matched subjects are those non-ambulatory subjects at study entry, with baseline FVC $\geq 1L$ and $\leq 3.08L$, and baseline age ≥ 9 and ≤ 18 .

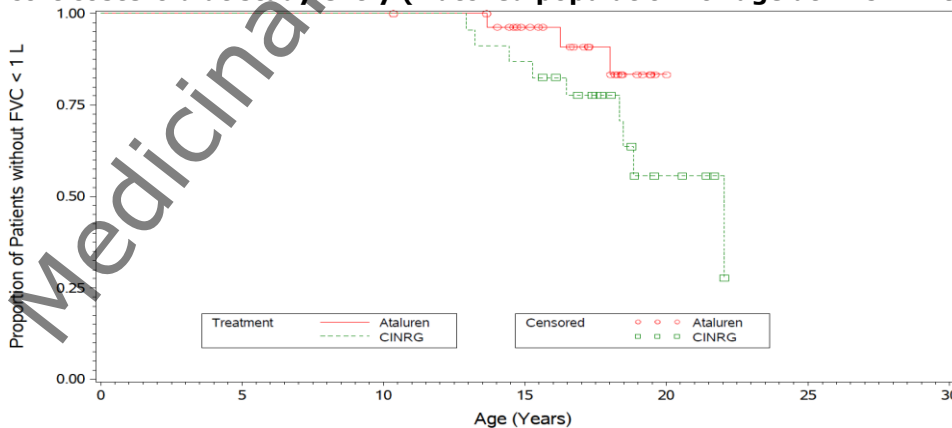
Figure 10. Kaplan-Meier Plot: Age at FVC<1 L for study 019 vs CINRG for subjects who did not use corticosteroid at study entry (Matched population for age at FVC <1litre analysis)



Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group

Matched subjects are those non-ambulatory subjects at study entry, with baseline FVC $\geq 1L$ and $\leq 3.08L$, and baseline age ≥ 9 and ≤ 18 and no baseline corticosteroid use. The Applicant did not provide the numbers of patients at risk

Figure 11. Kaplan-Meier Plot: Age at FVC<1 L for study 019 vs CINRG for subjects who used corticosteroid at study entry (Matched population for age at FVC <1litre analysis)



Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group

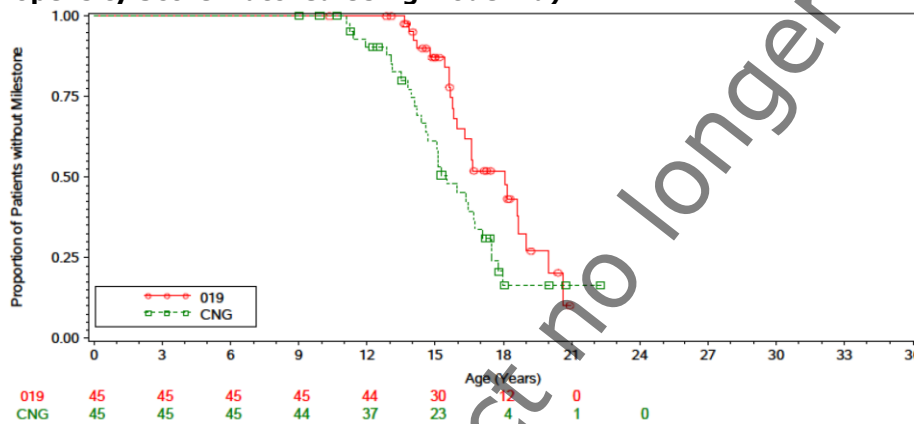
Matched subjects are those non-ambulatory subjects at study entry, with baseline FVC $\geq 1L$ and $\leq 3.08L$, and baseline age ≥ 9 and ≤ 18 and baseline corticosteroid use. The Applicant did not provide the numbers of patients at risk

B. Analyses Based on Matched Populations of CINRG and Study 019 for age at % predicted FVC<60%, age at % predicted FVC<50% and age at % predicted FVC<1 L

B1. Age at % predicted FVC<60%

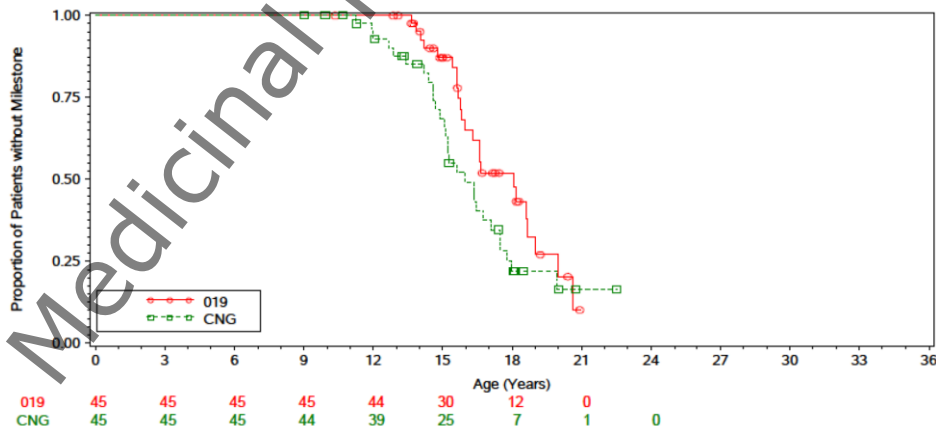
In the populations matched using age at first symptom as a disease severity criterion, 23 (51.1%) patients in Study 019 and 30 (66.7%) patients in CINRG experienced a decline below the 60% percent predicted FVC threshold. The median age for this milestone was 18.1 years in Study 019 and 15.5 years in CINRG (Figure 12), representing a delay in progression of over 2.5 years with ataluren treatment. In addition, this analysis was undertaken with another match using age at loss of ambulation instead of age at first symptoms as the index of disease severity (Figure 13). In the view of the Applicant, the resulting analysis isolated the benefit of ataluren treatment after loss of ambulation (most conservative approach) as Applicant pointed that the benefit of ataluren on the delay of loss of ambulation was removed after matching for disease severity based upon age at loss of ambulation. In the matched populations, 23 (51.1%) patients in Study 019 and 29 (64.4%) patients in CINRG experienced a decline below 60% percent predicted FVC.

Figure 12. Kaplan-Meier Plot: Age at % Predicted FVC <60% (Study 019 and CINRG with Propensity Score Matched Using Model 2a)



Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital Capacity.
 Note: Set 2a of Propensity Score model covariates includes age at first symptom and duration of Deflazacort, and duration of steroid other than Deflazacort
 A total of 45 subjects with recorded values for age at first symptom and age at loss of ambulation who did not experience a decline below one of these FVC milestones prior to Study 019 entry.
 Numbers shown at bottom of graph are numbers of patients at risk. P=0.0376. P-value is from log-rank test stratified by deflazacort and other steroid usage durations.

Figure 13. Kaplan-Meier Plot: Age at % Predicted FVC <60% (Study 019 and CINRG with Propensity Score Matched Using Model 2b)



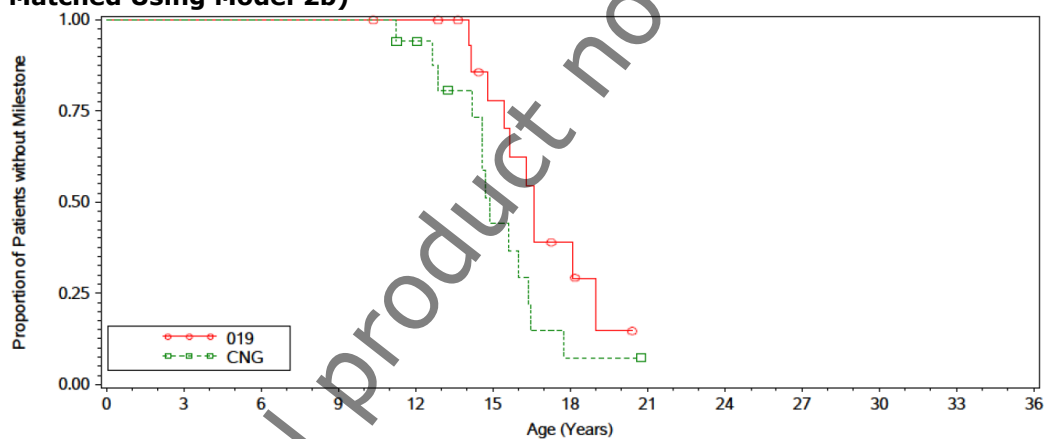
Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital Capacity
 Note: Set 2b of Propensity Score model covariates includes age at loss of ambulation and duration of Deflazacort, and duration of steroid other than Deflazacort
 A total of 45 subjects with recorded values for age at first symptom and age at loss of ambulation who did not experience a decline below one of these FVC milestones prior to Study 019 entry.

Numbers shown at bottom of graph are numbers of patients at risk. P=0.0817. P-value is from log-rank test stratified by deflazacort and other steroid usage durations.

The comparison between Figure 12 and Figure 13 shows the effect size was affected when the patients were matched to age at loss of ambulation instead of age at first symptom. The difference in median age at % predict FVC <60% was 2.5 years and statistically significant (P=0.0376), when the groups were matched for disease severity defined as age at first symptoms. However, when the disease severity was defined as age at loss of ambulation the difference in median age at % predict FVC <60% was 2 years and no longer statistically significant (P=0.0817). Although, both analyses did point in the same direction, it was questioned if the effect observed was a true effect as there were major methodological issues regarding the propensity score match variable and model selection as previously indicated. These precluded a firm conclusion. The data was therefore, considered explorative at the most and could not confirmative as intended by the Applicant.

The Applicant also showed an analysis of age at FVC <60% including only for 17 patients who entered Study 019 as non-ambulatory and received their first dose of 10, 10, 20 mg/kg ataluren after loss of ambulation using age at loss of ambulation as the disease severity matching criterion. In the matched populations, 10 (58.8%) patients in Study 019 and 13 (76.5%) patients in CINRG experienced FVC <60%, with median ages at that milestone of 16.6 years and 14.9 years, respectively. In the view of the Applicant, ataluren effectively prolonged pulmonary function and delayed the need for mechanical ventilation by more than 1 year with treatment begun after the loss of the ability to walk, (Figure 14). However, the numbers presented were too low to draw a meaningful conclusion out of them.

Figure 14. Kaplan-Meier Plot: Age at % Predicted FVC <60% (Study 019 who never took ataluren 10, 10, 20 mg/kg dose prior to loss of ambulation and CINRG with Propensity Score Matched Using Model 2b)



Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital Capacity. Note: Set 2b of Propensity Score model covariates includes age at loss of ambulation and duration of Deflazacort, and duration of steroid other than Deflazacort

A total of 17 subjects who never took ataluren 10, 10, 20 mg/kg dose prior to loss of ambulation with recorded values for age at first symptom and age at loss of ambulation who did not experience a decline below one of these FVC milestones prior to Study 019 entry. Numbers shown at bottom of graph are numbers of patients at risk.

P=0.0472. P-value is from log-rank test stratified by deflazacort and other steroid usage durations.

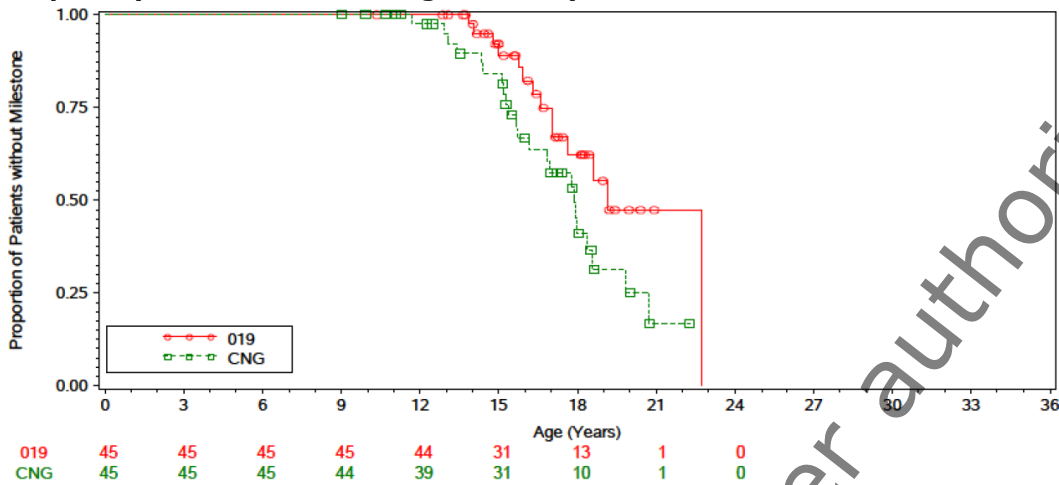
B2. Age at % predicted FVC<50%

In the matched populations, 14 (31.1%) patients in Study 019 and 23 (51.1%) patients in CINRG experienced a decline below the 50% percent predicted FVC threshold at a median age of 19.1 years in Study 019 and 17.9 years in CINRG (Figure 15) (p-value 0.3013).

Figure 16 and Figure 17 showed the analysis for the model 2b for this outcome and the model 2b for treatment naïve at loss of ambulation, respectively. The previous comments regarding the selection of the propensity score match method and baseline characteristics also applied to this data. However, in contrast to the age at % predictive FVC<60%, no effect was observed for the age at % predictive FVC

<50% for all analysis presented. This thus further questioned the validity of the analysis, as different outcomes were generated for two close related assessments.

Figure 15. Kaplan-Meier Plot: Age at % Predicted FVC <50% (Study 019 and CINRG with Propensity Score Matched Using Model 2a)



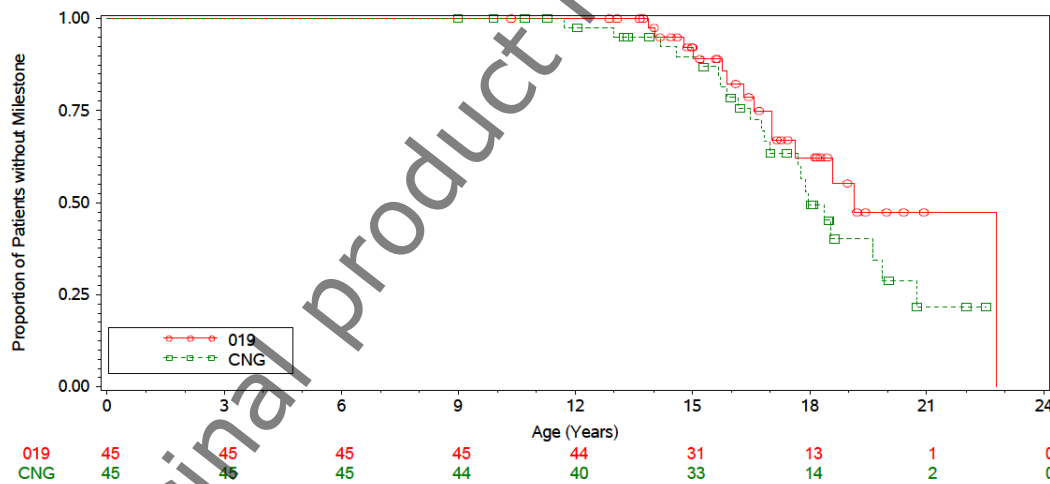
Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital Capacity
 Note: Set 2a of Propensity Score model covariates includes age at first symptom and duration of Deflazacort, and duration of steroid other than Deflazacort

A total of 45 subjects with recorded values for age at first symptom and age at loss of ambulation who did not experience a decline below one of these FVC milestones prior to Study 019 entry.

Numbers shown at bottom of graph are numbers of patients at risk.

P=0.3013. P-value is from log-rank test stratified by deflazacort and other steroid usage durations.

Figure 16. Kaplan-Meier Plot: Age at % Predicted FVC <50% (Study 019 and CINRG with Propensity Score Matched Using Model 2b)

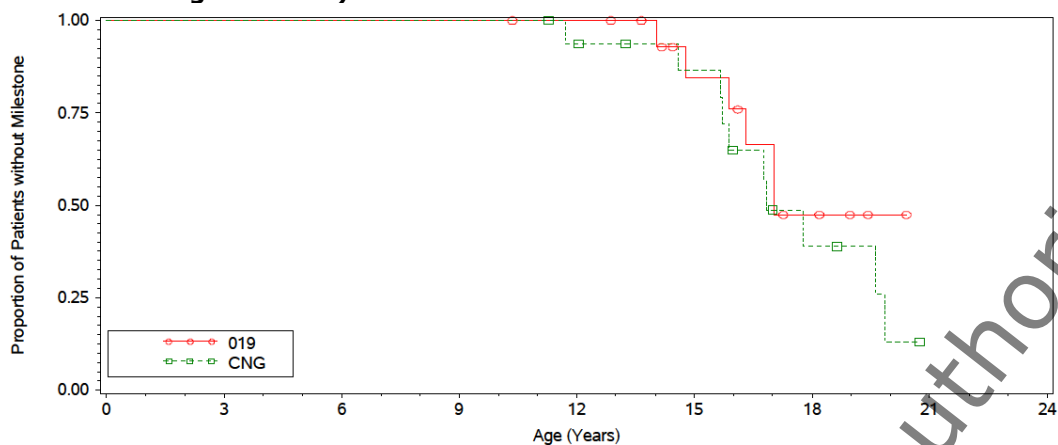


Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital Capacity
 Note: Set 2b of Propensity Score model covariates includes age at loss of ambulation and duration of Deflazacort, and duration of steroid other than Deflazacort.

A total of 45 subjects with recorded values for age at first symptom and age at loss of ambulation who did not experience a decline below one of these FVC milestones prior to Study 019 entry.

Numbers shown at bottom of graph are numbers of patients at risk.

Figure 17. Kaplan-Meier Plot: Age at % Predicted FVC <50% (Study 019 who never took ataluren 10, 10, 20 mg/kg dose prior to loss of ambulation and CINRG with Propensity Score Matched Using Model 2b)



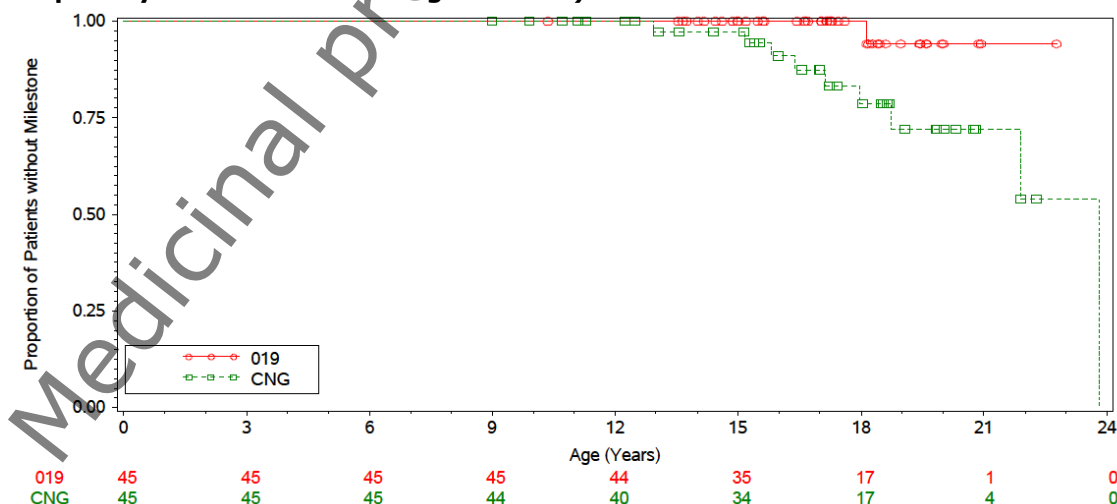
Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital Capacity
 Note: Set 2b of Propensity Score model covariates includes age at loss of ambulation and duration of Deflazacort, and duration of steroid other than Deflazacort.

A total of 17 subjects who never took ataluren 10, 10, 20 mg/kg dose prior to loss of ambulation with recorded values for age at first symptom and age at loss of ambulation who did not experience a decline below one of these FVC milestones prior to Study 019 entry. Numbers shown at bottom of graph are numbers of patients at risk.

B3 Age at FVC<1 litre

One (2.2%) patient in Study 019 and 9 (20.0%) patients in CINRG experienced a decline in FVC< 1 litre (Figure 18). Due to the infrequency of events for this advanced-stage disease milestone among ataluren-treated patients, median age for this milestone was not estimable in Study 019. The smaller proportion of ataluren-treated subjects (a treatment difference of 18%) experiencing a decline in FVC to <1 litre was additional evidence of the clinical benefit of ataluren in delaying disease progression in non-ambulatory subjects. KM curves should be interpreted with caution when low numbers of subjects were included and when the majority of patients were censored. Therefore, no conclusions could be drawn, as for all 3 graphs (Figure 18, Figure 19, Figure 20) presented >80% of patients in both arms censored. Thus, the numbers were too low to draw a meaningful conclusion.

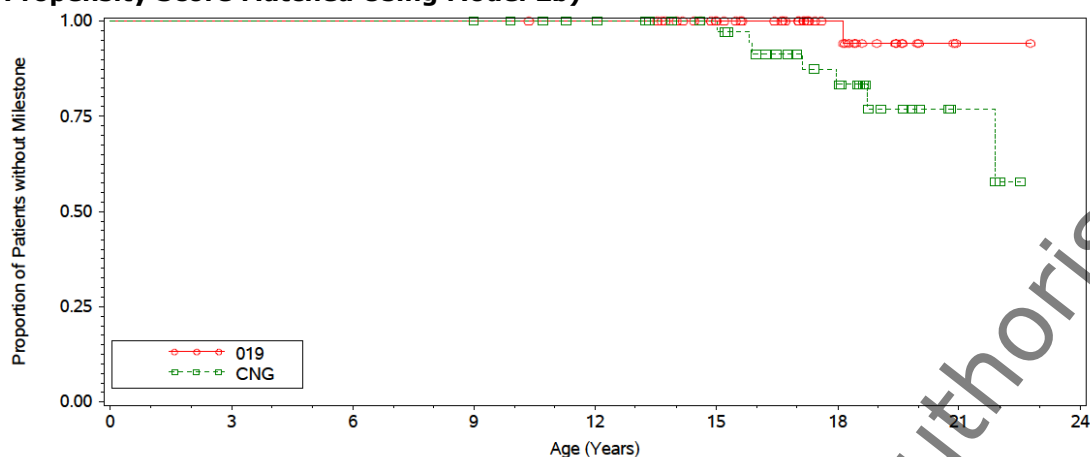
Figure 18. Kaplan-Meier Plot: Age at % Predicted FVC <1 Litre (Study 019 and CINRG with Propensity Score Matched Using Model 2a)



Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital Capacity. Note: Set 2a of Propensity Score model covariates includes age at first symptom and duration of Deflazacort, and duration of steroid other than Deflazacort.

A total of 45 subjects with recorded values for age at first symptom and age at loss of ambulation who did not experience a decline below one of these FVC milestones prior to Study 019 entry. Numbers shown at bottom of graph are numbers of patients at risk.

Figure 19. Kaplan-Meier Plot: Age at % Predicted FVC <1 Litre (Study 019 and CINRG with Propensity Score Matched Using Model 2b)



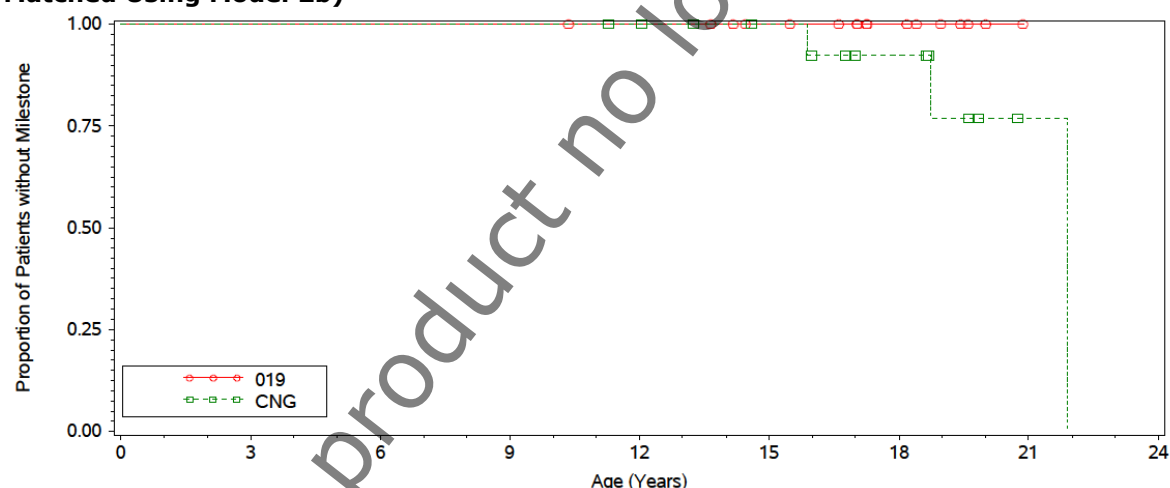
019	45	45	45	45	44	35	17	1	0
CNG	45	45	45	44	41	36	20	4	0

Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital Capacity. Note: Set 2b of Propensity Score model covariates includes age at loss of ambulation and duration of Deflazacort, and duration of steroid other than Deflazacort.

A total of 45 subjects with recorded values for age at first symptom and age at loss of ambulation who did not experience a decline below one of these FVC milestones prior to Study 019 entry.

Numbers shown at bottom of graph are numbers of patients at risk.

Figure 20. Kaplan-Meier Plot: Age at % Predicted FVC <1 Litre (Study 019 who never took ataluren 10, 10, 20 mg/kg dose prior to loss of ambulation and CINRG with Propensity Score Matched Using Model 2b)



019	17	17	17	17	16	13	7	0	0
CNG	17	17	17	17	16	13	8	1	0

Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital Capacity.

Note: Set 2b of Propensity Score model covariates includes age at loss of ambulation and duration of Deflazacort, and duration of steroid other than Deflazacort.

A total of 17 subjects who never took ataluren 10, 10, 20 mg/kg dose prior to loss of ambulation with recorded values for age at first symptom and age at loss of ambulation who did not experience a decline below one of these FVC milestones prior to Study 019 entry.

Numbers shown at bottom of graph are numbers of patients at risk.

C. Other assessments

Egen Klassifikation Scale

Among patients who were ambulatory at study entry, mean (SD) baseline EK was 7.3 (3.55) for corticosteroid users (n=34), 10.7 (3.93) for non-corticosteroid users (n=6), and 7.8 (3.76) for the overall population (n=40). The mean change from baseline in EK score at Week 48 for the 35 subjects with baseline and week 48 assessments was 2.0 points. As detailed in the SAP, a comparison of the results for the EK scale scores from Study 019 was initially planned, however, in the matched CINRG population,

there were only 2 subjects with baseline EK scale score, and no matching subjects with both baseline and post-baseline EK scale scores. As a result, a comparison of EK scale scores in Study 019 with the CINRG dataset was not undertaken.

Surveys

Changes in disease status were surveyed at each visit. Prospective survey results were in line with expectations for a progressive disease and generally indicated worsening over the duration of the study period. Retrospective survey results (study 007/007e) indicated that 32/94 (34.0%) of patients/parents saw some degree of improvement during study 007 and that those improvements persisted for a mean (SD) of 51.2 (55.72) weeks following the end of study 007. Improvements persisted for a mean (SD) of 10.0 (2.83) weeks following the end of study 007e. Additionally, a majority of participants of study 007 were ambulatory at entry so it was not clear whether this improvement was actually driven by non-ambulatory patients.

Ancillary analyses

Not applicable

Summary of main study

The following table summarises the efficacy results from the main studies supporting the present application. This summary should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18. Summary of Efficacy for trial PTC124-GC-019-DMD

Title: An open-label study for previously treated ataluren patients with nonsense mutation dystrophinopathy			
Study identifier	PTC124-GC-019-DMD		
Design	Open-label, multi-centre, long-term safety study		
	Duration of main phase:	Approximately 240 weeks	
	Duration of Run-in phase:	N.A	
	Duration of Extension phase:	N.A	
Hypothesis	Observational open-label safety study		
Treatments groups	Study 019	Ataluren treatment Up to approximately 240 weeks 94 subject, 60 matched to control	
	CINRG	Historical control. Followed for at least 5 years 91 Matched to ataluren based on FVC	
Endpoints and definitions	Primary endpoint	safety	
	Secondary	FVC	Decline in FVC for ages 11 to 15 years of age Estimated FVC for given age based on CINRG Proportion of subjects experiencing an FVC of <1L Age at % predicted FVC <60%, indicative for mechanic ventilation Number of patients with FVC<1L, indicative for time to death
	Secondary	Egen Klassification	Control electric chair, transfer from chair, stand, sit up, use arms, use arms for eating, turn in bed, cough, talk and general wellbeing in non-ambulatory patients (defined as unable to run/walk 10 meters in ≤30 seconds).
Results and Analysis			

Analysis description	Primary Analysis		
Analysis population and time point description	Matched on FVC		
Descriptive statistics and estimate variability	Treatment group	Study 019	CINRG
	Number of subject	60	91
	Decline in FVC for ages 11-15 years of age	P=0.079	P=0.0212
	Subjects with FVC <1L	4 (10.8%) *	22 (42.3%)*
Effect estimate per comparison	Estimated FVC for given age based on CINRG	Comparison groups	Study 019 versus CINRG
		Estimated FVC values	13% higher than CINRG
		P-value	0.0038
Notes	<p>Non-ambulatory patients were defined as unable to run/walk 10 meters in ≤ 30 seconds.</p> <p>The initial population of n=60 (Study 019) and n=91 (CINRG) is matched based on medical history.</p> <p>*The further matched population is based on age at study entry (between 9 and 18 years of age), baseline FVC (between 1 and 3.08L) and ambulation status. N =37 for study 019 and n=52 for CINRG.</p>		
Analysis description	<p>The study concerns an open-label safety study and is inappropriate to support extension of the indication. The statistical analysis plan adjusted after completion of the trial, indicating that the analysis was data driven and thus is only exploratory.</p> <p>There are differences in baseline values for mean age (subjects of CINRG were younger mean age of 10.7, while in Study 019 the mean age was 14.4 years of age), FVC (a larger proportion in study 019 had a FVC of >2L than in the CINRG), and Corticosteroid use (differences in duration on corticosteroids and proportion on corticosteroids). All these affect the outcomes in favour of ataluren.</p>		
Analysis description	Secondary analyses (response to RSI)		
Descriptive statistics and estimate variability	Treatment group	Study 019	CINRG
	Number of subject	45	45
	Median age at % predicted FVC <60%	18.1 years	15.5 year (p=0.037) ^a 16 years (p=0.082) ^a
	Number of patients with FVC<1L	1 (2.2%)	9 (20%) ^b
Notes	<p>Concerns for both analyses</p> <p>Match naïve population includes high dose ataluren.</p> <p>Extrapolation beyond 14 years and other variables unknown</p> <p>Validity of model questioned</p> <p>^a Effect not shown for age at % predict FVC <50%</p> <p>^b Median age not determined. >80% of patients censored in both groups</p>		

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable

Clinical studies in special populations

Not applicable

Supportive studies

Not applicable

2.4.3. Discussion on clinical efficacy

Design and conduct of clinical studies

In support of the extension of the indication to non-ambulatory nmDMD patients, the Applicant submitted Study 019. Study 019 was an open-label uncontrolled long-term safety study, which included patients from studies 007(e) and 004. As the study concerned was a safety study the main outcome was safety. Some exploratory endpoints, i.e. EK score and FVC, were included.

A limited number of subjects completed the study. The main reason for drop out was the commercially available ataluren. It remains unexplained why subjects switching from the investigational product to the commercial product could not have been followed-up for longer.

Upper extremity function was not assessed as an efficacy variable. For the assessment of motor function in non-ambulatory DMD subjects the Egen Klassifikation Scale may be helpful. However, a comparative analysis was not possible due to the low number of subjects available for analysis.

A historical control, derived from the CINRG-database, was used to compare efficacy in study 019 to the 'natural course' of DMD. The SAP was updated at the end of the study. Therefore, data-driven decisions cannot be excluded, and efficacy results can thus only be considered as exploratory.

Efficacy data and additional analyses

The CINRG dataset was used to create a matched historical control group. Subjects in the CINRG database had generally a more severe condition, when matched for FVC and ambulatory status. The mean age of the subjects selected in study 019 was 14.1 years, while the mean age of the subjects in the CINRG database was 10.7 years. Moreover, the baseline FVC in the subjects of the CINRG group was generally already <2 litres (baseline predicted % FVC (72.75 litres for Study 019 and 77.3 litres for CINRG) and there were more subjects not using concomitant corticosteroids. Although the variables were provided, the exact matching was unclear.

The Applicant indicated that the decline in FVC in patients treated with ataluren was not statistically significant ($p=0.0749$). The decline in the CINRG subjects was statistically significant different ($p=0.0212$). However, severe differences in the baseline characteristics between Study 019 and CINRG may explain the observed outcome including differences in age and FVC. On the basis of an analysis that estimated absolute FVC for a given age using data of untreated nmDMD patients from CINRG, ataluren therapy in this analysis was associated with 13% higher absolute FVC than no treatment ($p=0.0038$). Again, the manner in which the matching was taken into account in the model was unclear and the comparison may not be unbiased.

The Applicant indicated that the subjects that experienced a decline in FVC to <1 litre was 22 (42.3) in the CINRG group and 4 (10.8%) in Study 019. However, the lengths of follow-up time in the CINRG group and ataluren group were different, and it appeared that this could have been the sole explanation for the differences.

The Applicant performed several subgroup and sensitivity analyses but only presented baseline data and outcomes for some of the groups, e.g. for non-users of corticosteroids, but not for corticosteroid use. However, analyses should have been presented for the subgroups: ambulatory + corticosteroid users, ambulatory + no corticosteroids, non-ambulatory + corticosteroids, non-ambulatory + no corticosteroids, including a graphical representation of the KM estimates. As these sensitivity analyses were performed *a posteriori* it was impossible to exclude data-driven decisions in the choice of subgroups and analyses.

The Applicant provided letters of support from clinical experts. These letters seem to indicate that ataluren might be used safely in real world conditions, according to these experts' views. However, these reports cannot replace the necessary robust data required to support an extension of indication.

Regarding the results, the Applicant showed that in matched cohort, 23 (51.1%) patients in Study 019 and 30 (66.7%) patients in CINRG experienced a decline below the 60% percent predicted FVC threshold (p-value=0.0376). The effect size was affected when the patients were matched to age at loss of ambulation instead of age at first symptom. The difference in median age at percent predict FVC <60% was 2.5 years and statistically significant (P=0.0376), when the groups were matched for disease severity defined as age at first symptoms. More importantly, no effect was observed for the age at % predictive FVC <50% for all analyses presented. One (2.2%) patient in Study 019 and 9 (20.0%) patients in CINRG experienced a decline in FVC < 1 litre. However, the numbers were too low to draw a meaningful conclusion out of them.

The Applicant performed a disease status survey; however, it was unclear which population survey this entailed. In addition, the presented data contained mainly ambulatory patients, and the retrospective nature of the assessment should be particularly noted. The improvement observed in the study could have been driven by the outcomes reported by the ambulatory patients and may not have been reliable as it was a retrospective questionnaire. Finally, there were no data submitted on functional outcomes, i.e. how the efficacy outcome correlated to a clinically meaningful improvement or benefit of the ataluren treatment in the non-ambulant status.

The Applicant argued in their conclusion that the extension of the indication to include non-ambulatory patients with Duchenne muscular dystrophy could be justified based on:

1. The CHMP's prior conclusions that the PK and safety of ataluren are similar between ambulatory and non-ambulatory patients. Extrapolation of efficacy based on PK is supported by the guideline "Concept Paper on Extrapolation of Efficacy and Safety in medicinal products" [EMA/129698/2012] and "Guideline on the Role of PK in the development of medicinal products in the paediatric population" [EMA/CHMP/EWP/147013/2004].
2. The mechanism of action of ataluren and the underlying cause of the disease do not differ between ambulatory and non-ambulatory patients.
3. The CHMP stated in the Day 180 Joint Response Assessment (JAR180) of the EMA that non-ambulant should not be precluded from the use of Translarna.
4. Efficacy comparisons between non-ambulatory patients in Study 019 and matched CINRG natural history database support the long-term effectiveness of ataluren in this patient population. This concerned the final results of the long-term clinical study PTC-124-GD-019-DMD (an Open-Label Study for Previously Treated Ataluren (PTC124) Patients with Nonsense Mutation Dystrophinopathy), submitted in line with the requirements of Article 46 of Regulation (EC) No 1901/2006.
5. The safety profile, the plasma PK similarity between ambulatory and non-ambulatory patients, and the observed effectiveness of ataluren in non-ambulant nmDMD patients collectively support a favourable benefit-risk profile in this patient population.

However, the following comments were made with regard to these arguments (numbers correspond to the numbering of the MAH above):

1. It was agreed that the plasma levels are reasonably comparable between ambulatory and non-ambulatory patients and no new PK data was required. In the EPAR and SmPC, it is stated that there were no apparent differences in steady-state relative bioavailability and clearance due to loss of ambulation.

2. Both arguments, i.e. that underlying cause of DMD and the mechanism of action of ataluren do not differ between ambulatory and non-ambulatory DM patients, were agreed. However, the discussion was whether the effect is the same in a more advanced stage of the disease where the effect may plateau as there is less functional muscle tissue left. According to the guideline "Guideline on the clinical investigation of medical products for the treatment of Duchenne and Becker muscular dystrophy" [EMA/CHMP/236981/2011, Corr. 1] section 7.7 "The extent of extrapolation that might be accepted will depend on the demonstrated mechanism of action of the product and the efficacy data available" and "supported by the mechanism of action, extrapolation from older to younger (or from younger to older) patients might be discussed in the context of additional real life data needed to be collected post-authorisation". Therefore, extrapolation would require data supporting efficacy (see point 4).

3. This statement had not been stated in the JAR180 or EPAR. This seems to be a free interpretation by the Applicant of the following statement:

"In the context of a progressive and severely debilitating disorder with shortened life expectancy as in the case of DMD, any treatment which may offer some effect on disease stabilization or delay in progression to the next stage of disease would be considered as favourable. Also improvement in daily functioning which may offer a better quality of life is relevant for these patients. In this respect slowing deterioration on functionality and delaying the transition from ambulatory to non-ambulatory phase as well as the use of supportive care (cardiac medication, orthopaedic support, assisted ventilation, etc.) may be considered as critical indicators.

As part of the initial MAA, the CHMP decided that based on the data submitted it was not possible to extrapolate the efficacy from ambulatory to non-ambulatory DMD patients and a conditional approval was given for ambulatory patients. The non-ambulatory patient was no longer pursued in the indication by the Applicant in the re-examination procedure as the CHMP considered efficacy non-ambulatory patients not demonstrated".

4. The data referred to were considered insufficient in support of this efficacy claim. See sections: "Discussion on clinical efficacy" and "Conclusions on the clinical efficacy.

5. The data referred to were considered insufficient in support of this B/R in non-ambulatory DMD patients. See above and below (under the B/R assessment).

Additional expert consultation

Not applicable

2.4.4. Conclusions on the clinical efficacy

The submitted data i.e. study 019 did not allow a reliable and valid assessment of the efficacy of ataluren in the non-ambulatory boys with DMD:

1. The study is an open label long term safety study, primary focusing on safety.
2. A Historical control, derived from the CINGR-database, was used to compare efficacy in study 019 to the 'natural course' of DMD. The SAP plan was updated at the end of the study. Therefore, data-driven decisions could not be excluded, and efficacy results could thus only be exploratory.
3. The matching with the historical control data from the CINRG database was inappropriate and contained multiple sources of bias in favour of ataluren.
4. There were no other functional assessments of non-ambulatory motor function than FVC. Thus, a correlation to clinically meaningful improvement or benefit of the ataluren treatment compared to standard of care could not be made.

In conclusion, the efficacy of ataluren in non-ambulatory subjects has not been robustly demonstrated.

2.5. Clinical safety

Introduction

The ataluren safety profile up to 336 weeks in this open-label safety study was consistent with other ataluren studies; no new risks were identified.

Patient exposure

Overall, the mean (SD) duration of study drug treatment was 197.25 (62.67) weeks. Those who were ambulatory and those who used corticosteroids tended to stay in the study longer than those who were not ambulatory and those who did not use corticosteroids (Table 19). Overall study drug compliance was 88.4% and similar between groups.

Table 19. Treatment Duration and Drug Compliance (AT Population)

	Ambulatory Status		Corticosteroid Use		Overall N=94
	Yes N=50	No N=44	Yes N=84	No N=10	
Treatment Duration (weeks) [1]					
Mean (SD)	212.43 (48.69)	180.00 (72.26)	199.14 (61.62)	181.41 (72.51)	197.25 (62.67)
95% CI for Mean	198.59, 226.27	158.04, 201.97	185.77, 212.51	129.54, 233.28	184.42, 210.09
Median	222.50	202.15	216.80	192.35	214.60
Min, Max	42.0, 268.1	29.6, 267.0	29.6, 267.0	44.1, 268.1	29.6, 268.1
Overall Study Drug Compliance					
Mean (SD)	89.0 (5.54)	87.6 (8.46)	88.4 (7.20)	88.0 (6.00)	88.4 (7.05)
95% CI for Mean	87.43, 90.57	85.06, 90.21	86.84, 89.97	83.71, 92.29	86.92, 89.81
Median	90.0	89.5	90.0	89.0	90.0
Min, Max	70, 96	48, 103	48, 103	76, 95	48, 103

Abbreviations; AT, As treated; CI, confidence interval; Max, maximum; Min, minimum; SD, standard deviation.

[1] Treatment Duration (in weeks) = (Last dose date – First dose date +1)/7, if date of study drug intake was not known (Last visit date – First dose date + 1)/7

Adverse events

At least 1 treatment-emergent adverse event (TEAE) was reported in 91/94 (96.8%) for the overall population, with a similar incidence in ambulatory and non-ambulatory patients (49/50 [98%] and 42/44 [95.5%], respectively) (Table 20). The TEAEs were mild in 23 (24.5%) patients, moderate in 31 (33.0%) patients, and severe in 35 (37.2%) patients. Two (2.1%) patients had fatal TEAEs (see section Serious adverse event/deaths/other significant events for further discussion). There were no life-threatening TEAEs.

Table 20. Overall Summary of Adverse Events (AT Population)

	Ambulatory Status		Overall N=94 n (%)
	Yes N=50 n (%)	No N=44 n (%)	
Total number of AEs	740	556	1296
Total number of TEAEs	737	545	1282
Patients with ≥1 TEAE	49 (98.0)	42 (95.5)	91 (96.8)
Patients with related TEAE	14 (28.0)	12 (27.3)	26 (27.7)
Patients with severe TEAEs	23 (46.0)	12 (27.3)	35 (37.2)
Patients with serious TEAE	18 (36.0)	13 (29.5)	31 (33.0)
Patients with related, serious TEAE	1 (2.0)	0	1 (1.1)
Patients with severe, serious TEAEs	11 (22.0)	9 (20.5)	20 (21.3)
Patients with TEAEs Leading to Death	0	2 (4.5)	2 (2.1)
patients with TEAEs Leading to Discontinuation	1 (2.0)	2 (4.5)	3 (3.2)

Abbreviations; AT, As treated; AE, adverse event; SOC, system organ class; TEAE, treatment emergent adverse event.

[1] TEAE defined as an AE that occurs or worsens in the period extending from the day of the patients first dose of study drug to 6 weeks after the last dose of study drug in this study. A patient who reported 2 or more AEs with the same preferred term was counted only once for that term. A patient who reported 2 or more AEs with different preferred terms within the same SOC was counted only once in the SOC.

Common (Occurring in $\geq 10\%$ of Patients) Treatment Emergent Adverse Events

The most frequent TEAEs for the overall population during the treatment period were nasopharyngitis (42.6%), headache (30.9%), vomiting (29.8%), and disease progression (28.7%). Additionally, fall was reported in 23.4% of patients in the overall population and was most common among ambulatory patients versus non-ambulatory (40.0% versus 4.5%, respectively) (Table 21). This difference in incidence of falls was consistent with ambulatory patients being more active and prone to falls.

Table 21. Treatment-Emergent Adverse Events with a Frequency of $\geq 10\%$ by Preferred Term in Descending Order (AT Population)

Preferred Term [1]	Ambulatory Status		Overall N=94 n (%)
	Yes N=50 n (%)	No N=44 n (%)	
Patients with at Least one TEAE [2]	49 (98.0)	42 (95.5)	91 (96.8)
Nasopharyngitis	20 (40.0)	20 (45.5)	40 (42.6)
Headache	17 (34.0)	12 (27.3)	29 (30.9)
Vomiting	16 (32.0)	12 (27.3)	28 (29.8)
Disease progression	27 (54.0)	0	27 (28.7)
Fall	20 (40.0)	2 (4.5)	22 (23.4)
Back Pain	12 (24.0)	9 (20.5)	21 (22.3)
Gastroenteritis	10 (20.0)	10 (22.7)	20 (21.3)
Pyrexia	9 (18.0)	10 (22.7)	19 (20.2)
Upper respiratory tract disease	14 (28.0)	5 (11.4)	19 (20.2)
Femur fracture	11 (22.0)	6 (13.6)	17 (18.1)
Cough	5 (10.0)	11 (25.0)	16 (17.0)
Abdominal pain Upper	9 (18.0)	5 (11.4)	14 (14.9)
Oropharyngeal pain	8 (16.0)	6 (13.6)	14 (14.9)
Diarrhoea	5 (10.0)	8 (18.2)	13 (13.8)
Arthralgia	5 (10.0)	4 (9.1)	9 (9.6)
Constipation	2 (4.0)	7 (15.9)	9 (9.6)
Influenza	6 (12.0)	3 (6.8)	9 (9.6)
Rhinitis	5 (10.0)	4 (9.1)	9 (9.6)
Scoliosis	2 (4.0)	7 (15.9)	9 (9.6)
Nausea	2 (4.0)	5 (11.4)	7 (7.4)
Abdominal pain	1 (2.0)	5 (11.4)	6 (6.4)
Joint injury	5 (10.0)	0	5 (5.3)
Ligament sprain	5 (10.0)	0	5 (5.3)

Abbreviations: AE, adverse event; AT, as treated; medDRA, medical dictionary for regulatory activities; SOC, system organ class; TEAE, treatment emergent adverse events

[1] AEs were coded using MedDRA, Version 20.1

[2] TEAEs were defined as an AE that occurs or worsens in the period extending from the day of the patients first dose of study drug to 6 weeks after the last dose of study drug in this study. A patient who reported 2 or more AEs with the same preferred term was counted only once for that term. A patient who reported 2 or more AEs with different preferred terms within the same SOC was counted only once in the SOC.

Comparison of Common TEAE Rates

A comparison of common TEAEs between Study 019 and pooled data from prior PTC Studies PTC124-GD-007-DMD (Study 007) and PTC124-GD-020-DMD (Study 020) demonstrated favourable outcomes for Study 019.

Studies 007 and 020 were both double-blind, placebo-controlled 48-week studies in male patients with nmdMD. As shown in (Table 22), the TEAEs in Study 019 remain within the known and predictable safety profile of ataluren.

Table 22. Summary of Common TEAEs (Subject Frequency >5%) by SOC and Preferred Term (AT Population)

System Organ Class Preferred Term [1]	Study 019						Studies 007/020	
	Ataluren 10,10,20 mg/kg (N=94)						Ataluren 10,10,20 mg/kg (N=172)	Placebo (N=172)
	Period 1 (N=94)	Period 2 (N=89)	Period 3 (N=84)	Period 4 (N=78)	Period 5 (N=68)	Period 6 (N=21)		
Subjects with ≥1 TEAE [2]	62 (66.0)	57 (64.0)	56 (66.7)	38 (48.7)	27 (39.7)	7 (33.3)	143 (83.1)	140 (81.4)
Gastrointestinal disorders	28 (29.8)	21 (23.6)	12 (14.3)	8 (10.3)	6 (8.8)	1 (4.8)	87 (50.6)	76 (44.2)
Abdominal pain	5 (5.3)	1 (1.1)	0	1 (1.3)	0	0	14 (8.1)	9 (5.2)
Abdominal pain upper	8 (8.5)	4 (4.5)	4 (4.8)	3 (3.8)	2 (2.9)	0	18 (10.5)	22 (12.8)
Constipation	2 (2.1)	3 (3.4)	3 (3.6)	1 (1.3)	0	0	5 (2.9)	12 (7.0)
Diarrhoea	8 (8.5)	5 (5.6)	1 (1.2)	2 (2.6)	1 (1.5)	0	31 (18.0)	24 (14.0)
Nausea	6 (6.4)	3 (3.4)	1 (1.2)	1 (1.3)	0	0	15 (8.7)	14 (8.1)
Vomiting	18 (19.1)	10 (11.2)	6 (7.1)	2 (2.6)	3 (4.4)	1 (4.8)	58 (33.7)	43 (25.0)
General disorders and administration site conditions	14 (14.9)	15 (16.9)	10 (11.9)	5 (6.4)	3 (4.4)	1 (4.8)	40 (23.3)	44 (25.6)
Disease progression	5 (5.3)	7 (7.9)	8 (9.5)	4 (5.1)	2 (2.9)	1 (4.8)	13 (7.6)	20 (11.6)
Pyrexia	9 (9.6)	8 (9.0)	3 (3.6)	1 (1.3)	1 (1.5)	0	30 (17.4)	24 (14.0)
Infections and infestations	30 (31.9)	31 (34.8)	29 (34.5)	20 (25.6)	19 (27.9)	4 (19.0)	78 (45.3)	77 (44.8)
Ear infection	2 (2.1)	1 (1.1)	2 (2.4)	1 (1.3)	1 (1.5)	0	9 (5.2)	4 (2.3)
Gastroenteritis	9 (9.6)	7 (7.9)	4 (4.8)	2 (2.6)	2 (2.9)	0	14 (8.1)	9 (5.2)
Influenza	3 (3.2)	2 (2.2)	1 (1.2)	3 (3.8)	1 (1.5)	0	9 (5.2)	13 (7.6)
Lower respiratory tract infection	0	2 (2.2)	2 (2.4)	4 (5.1)	1 (1.5)	0	5 (2.9)	1 (0.6)
Nasopharyngitis	16 (17.0)	14 (15.7)	19 (22.6)	9 (11.5)	6 (8.8)	3 (14.3)	37 (21.5)	35 (20.3)
Respiratory tract infection	0	1 (1.1)	0	1 (1.3)	4 (5.9)	0	2 (1.2)	1 (0.6)
Rhinitis	4 (4.3)	4 (4.5)	2 (2.4)	1 (1.3)	2 (2.9)	1 (4.8)	14 (8.1)	6 (3.5)
Upper respiratory tract infection	5 (5.3)	6 (6.7)	4 (4.8)	4 (5.1)	6 (8.8)	0	20 (11.6)	16 (9.3)
Injury, poisoning and procedural complications	7 (7.4)	14 (15.7)	13 (15.5)	7 (9.0)	8 (11.8)	3 (14.3)	36 (20.9)	31 (18.0)
Contusion	0	1 (1.1)	1 (1.2)	0	0	0	9 (5.2)	7 (4.1)
Fall	3 (3.2)	11 (12.4)	7 (8.3)	6 (7.7)	5 (7.4)	2 (9.5)	32 (18.6)	27 (15.7)
Femur fracture	4 (4.3)	4 (4.5)	6 (7.1)	1 (1.3)	4 (5.9)	1 (4.8)	0	2 (1.2)
Musculoskeletal and connective tissue disorders	7 (7.4)	6 (6.7)	11 (13.1)	5 (6.4)	3 (4.4)	0	34 (19.8)	32 (18.6)
Back pain	7 (7.4)	3 (3.4)	10 (11.9)	3 (3.8)	2 (2.9)	0	20 (11.6)	13 (7.6)
Pain in extremity	1 (1.1)	3 (3.4)	1 (1.2)	2 (2.6)	1 (1.5)	0	17 (9.9)	20 (11.6)
Nervous system disorders	16 (17.0)	14 (15.7)	13 (15.5)	8 (10.3)	3 (4.4)	2 (9.5)	43 (25.0)	35 (20.3)
Headache	16 (17.0)	14 (15.7)	13 (15.5)	8 (10.3)	3 (4.4)	2 (9.5)	43 (25.0)	35 (20.3)
Respiratory, thoracic and mediastinal disorders	14 (14.9)	7 (7.9)	9 (10.7)	9 (11.5)	4 (5.9)	0	47 (27.3)	38 (22.1)
Cough	6 (6.4)	4 (4.5)	4 (4.8)	3 (3.8)	3 (4.4)	0	28 (16.3)	24 (14.0)
Epistaxis	3 (3.2)	1 (1.1)	0	1 (1.3)	0	0	9 (5.2)	5 (2.9)
Oropharyngeal pain	6 (6.4)	4 (4.5)	4 (4.8)	5 (6.4)	2 (2.9)	0	13 (7.6)	10 (5.8)
Rhinorrhoea	2 (2.1)	0	1 (1.2)	0	0	0	7 (4.1)	9 (5.2)

Study 019								
Ataluren 10,10,20 mg/kg (N=94)							Studies 007/020	
System Organ Class Preferred Term [1]	Period 1 (N=94)	Period 2 (N=89)	Period 3 (N=84)	Period 4 (N=78)	Period 5 (N=68)	Period 6 (N=21)	Ataluren 10,10,20 mg/kg (N=172)	Placebo (N=172)
Skin and subcutaneous tissue disorders	0	4 (4.5)	3 (3.6)	1 (1.3)	0	0	8 (4.7)	9 (5.2)
Rash	0	4 (4.5)	3 (3.6)	1 (1.3)	0	0	8 (4.7)	9 (5.2)

Abbreviations: AT, as treated; SOC, system organ class; medDRA, medical dictionary for regulatory activities; TEAE, treatment emergent adverse events

[1] For study 007 and 020, MedDRA version is 15.1. For study 019 MedDRA version is 20.1.

[2] TEAE = Treatment-emergent adverse event defined as an adverse event that occurs or worsens during study.

For study 019, TEAE are summarized for each 48-week interval of study for AE onset. Period 1 shows AE onset during the first 48 weeks of study. Period 2 shows AE onset from Week 49 to Week 96, Period 3 from Week 97 to Week 144, etc. Each Period is defined by calendar time, not by visit. Study 019 TEAE is summarized in period 1 if onset date is completely missing. When only onset day is missing, onset period is determined with onset day imputed as first day of the month.

A patient who reported 2 or more adverse events with the same preferred term was counted only once for that term.

A patient who reported 2 or more adverse events with different preferred terms within the same system organ class was counted only once in the system organ class.

Treatment Related Treatment Emergent Adverse Events

A total of 26/94 (27.7%) patients reported at least one possibly/probably related TEAE. The rate of treatment related TEAEs was similar between ambulatory and non-ambulatory patients (Table 23). Vomiting was the only related preferred term occurring in $\geq 5\%$ of patients (7.4%, n=7/94).

Of the 26 patients with related TEAEs, the events were classified as mild in 19 patients and moderate in 5 patients. Two patients experienced three related Grade 3 (severe) TEAEs (vomiting and myocardial infarction [MI] in a corticosteroid user and abdominal pain in a corticosteroid non-user); both patients were ambulatory.

Upon review of the MI by the Data Monitoring Committee paediatric cardiologist, the MI was considered not related to ataluren.

Table 23. Treatment-Related Treatment-Emergent Adverse Events by SOC and Preferred Term (AT Population)

System Organ Class Preferred Term	Ambulatory Status		Overall N=94 n (%)
	Yes N=50 n (%)	No N=44 n (%)	
Patients with at least one TEAE [1]	49 (98.0)	42 (95.5)	91 (96.8)
Patients with at least one related TEAE	14 (28.0)	12 (27.3)	26 (27.7)
Gastrointestinal disorders	10 (20.0)	4 (9.1)	14 (14.9)
Vomiting	6 (12.0)	1 (2.3)	7 (7.4)
Abdominal pain upper	2 (4.0)	1 (2.3)	3 (3.2)
Flatulence	2 (4.0)	1 (2.3)	3 (3.2)
Nausea	1 (2.0)	2 (4.5)	3 (3.2)
Abdominal pain	1 (2.0)	1 (2.3)	2 (2.1)
Diarrhoea	2 (4.0)	0	2 (2.1)
Abdominal discomfort	1 (2.0)	0	1 (1.1)
Faeces soft	1 (2.0)	0	1 (1.1)
Frequent bowel movement	1 (2.0)	0	1 (1.1)
Irritable bowel syndrome	1 (2.0)	0	1 (1.1)
Investigations	4 (8.0)	6 (13.6)	10 (10.6)
Monocyte count decreased	0	2 (4.5)	2 (2.1)
Red blood cells urine	2 (4.0)	0	2 (2.1)
Blood bilirubin increased	0	1 (2.3)	1 (1.1)
Blood cholesterol increased	0	1 (2.3)	1 (1.1)
Blood magnesium increased	0	1 (2.3)	1 (1.1)
Blood sodium decreased	0	1 (2.3)	1 (1.1)
Blood urine present	0	1 (2.3)	1 (1.1)
Cardiac function test abnormal	1 (2.0)	0	1 (1.1)
Cortisol decreased	0	1 (2.3)	1 (1.1)
Cystatin C increased	1 (2.0)	0	1 (1.1)

System Organ Class Preferred Term	Ambulatory Status		Overall N=94 n (%)
	Yes N=50 n (%)	No N=44 n (%)	
Gamma-glutamyl transferase increased	0	1 (2.3)	1 (1.1)
High density lipoprotein increased	0	1 (2.3)	1 (1.1)
Monocyte count increased	0	1 (2.3)	1 (1.1)
Protein urine present	0	1 (2.3)	1 (1.1)
Urinary lipids present	0	1 (2.3)	1 (1.1)
Metabolism and nutrition disorders	1 (2.0)	2 (4.5)	3 (3.2)
Decreased appetite	1 (2.0)	0	1 (1.1)
Hypercholesterolaemia	0	1 (2.3)	1 (1.1)
Overweight	0	1 (2.3)	1 (1.1)
Renal and urinary disorders	0	3 (6.8)	3 (3.2)
Proteinuria	0	3 (6.8)	3 (3.2)
Cardiac disorders	1 (2.0)	0	1 (1.1)
Myocardial infarction	1 (2.0)	0	1 (1.1)
Ear and labyrinth disorders	1 (2.0)	0	1 (1.1)
Vertigo	1 (2.0)	0	1 (1.1)
General disorders and administration site conditions	1 (2.0)	0	1 (1.1)
Asthenia	1 (2.0)	0	1 (1.1)
Infections and infestations	0	1 (2.3)	1 (1.1)
Gastroenteritis	0	1 (2.3)	1 (1.1)
Injury, poisoning and procedural complications	0	1 (2.3)	1 (1.1)
Administration related reaction	0	1 (2.3)	1 (1.1)
Nervous system disorders	1 (2.0)	0	1 (1.1)
Headache	1 (2.0)	0	1 (1.1)
Skin and subcutaneous tissue disorders	1 (2.0)	0	1 (1.1)
Eczema	1 (2.0)	0	1 (1.1)

Abbreviations: AT, as treated; SOC, system organ class; medDRA, medical dictionary for regulatory activities; TEAE, Treatment-emergent adverse event

AEs were coded using MedDRA, Version 20.1.

[1] TEAEs were defined as an AE that occurs or worsens in the period extending from the day of the patients first dose of study drug to 6 weeks after the last dose of study drug in this study. A patient who reported 2 or more AEs with the same preferred term was counted only once for that term with the most related incidence. A patient who reported 2 or more AEs with different preferred terms within the same SOC was counted only once in the SOC.

Serious adverse event/deaths/other significant events

During the reporting period for this study, two patients experienced 2 serious adverse events (SAEs) each that led to death. One patient (age 14 years) experienced cardiac failure and aspiration pneumonia, another patient (age 13 years) experienced cardiogenic shock and ventricular arrhythmia. None of these events were considered related to study drug.

Suspected Unexpected Serious Adverse Reaction

MI was the only serious TEAE that was classified by the investigator as both treatment-related and as being Grade 3 in severity. This patient was ambulatory and reported corticosteroid use. Steroids were also reported to have a suspected causal relationship to the event.

Upon review by the Data Monitoring Committee paediatric cardiologist, the event was assessed as focal myofibrosis, a known complication of DMD (Petrie 2005) and considered not related to ataluren. Therefore, the sponsor assessed the MI as unrelated to ataluren. The event was reported as a suspected unexpected serious adverse reaction.

Serious Adverse Events

A total of 31/94 (33%) patients experienced 40 serious TEAEs (Table 21). Of the 40 serious events only 1 event (the MI as described above) was considered by the investigator as related but was considered by the sponsor as unrelated. The only serious events that occurred in more than 1 patient were femur fracture, tibia fractures, pneumonia and ventricular arrhythmia which are known complications of DMD.

The femur fractures were most frequently reported preferred term in ambulatory patients and in corticosteroid users (Table 24).

Twenty of 31 patients had SAEs classified as severe in intensity; 9 patients had moderate TEAEs and two patients had SAEs that were classified as fatal.

Table 24. Serious Treatment Emergent Adverse Events by SOC and Preferred Term (AT Population)

System Organ Class Preferred Term	Ambulatory Status		Overall N=94 n (%)
	Yes N=50 n (%)	No N=44 n (%)	
Total Number of TEAE [1]	22	18	40
Patients with ≥1 serious TEAE [1]	18 (36.0)	13 (29.5)	31 (33.0)
Injury, poisoning and procedural complications	14 (28.0)	5 (11.4)	19 (20.2)
Femur fracture	10 (20.0)	5 (11.4)	15 (16.0)
Tibia fracture	2 (4.0)	0	2 (2.1)
Back injury	1 (2.0)	0	1 (1.1)
Fall	1 (2.0)	0	1 (1.1)
Spinal fracture	1 (2.0)	0	1 (1.1)
Infections and infestations	2 (4.0)	5 (11.4)	7 (7.4)
Pneumonia	0	3 (6.8)	3 (3.2)
Actinomycosis	1 (2.0)	0	1 (1.1)
Gastroenteritis	1 (2.0)	0	1 (1.1)
Postoperative Abscess	0	1 (2.3)	1 (1.1)
Urinary tract infection	0	1 (2.3)	1 (1.1)
Cardiac disorders	1 (2.0)	4 (9.1)	5 (5.3)
Ventricular arrhythmia	0	2 (4.5)	2 (2.1)
Cardiac failure	0	1 (2.3)	1 (1.1)
Cardiogenic shock	0	1 (2.3)	1 (1.1)
Myocardial infarction	1 (2.0)	0	1 (1.1)
Tachycardia	0	1 (2.3)	1 (1.1)
Gastrointestinal disorders	0	1 (2.3)	1 (1.1)
Rectal haemorrhage	0	1 (2.3)	1 (1.1)
Nervous system disorders	1 (2.0)	0	1 (1.1)
Intracranial pressure increased	1 (2.0)	0	1 (1.1)
Respiratory, thoracic and mediastinal disorders	0	1 (2.3)	1 (1.1)
Pneumonia aspiration	0	1 (2.3)	1 (1.1)

Abbreviations: AE, adverse event; AT, as treated; medDRA, medical dictionary for regulatory activities; SOC, system organ class; TEAE, Treatment-emergent adverse event

AEs were coded using MedDRA, Version 20.1

[1] TEAEs were defined as an adverse event that occurs or worsens in the period extending from the day of a patient's first dose of study drug to 6 weeks after the last dose of study drug in this study. A patient who reported 2 or more adverse events with the same preferred term was counted only once for that term. A patient who reported 2 or more adverse events with different preferred terms within the same SOC was counted only once in the SOC. SOC and Preferred Term are sorted by descending order of Overall column.

Renal and Hepatic Events

TEAEs of special interest included serum Cystatin C; unwanted increases in serum blood urea nitrogen (BUN)/ serum creatinine; urine protein:creatinine and urine protein:osmolality ratio; urine blood; and serum electrolytes (sodium, chloride, potassium, bicarbonate, magnesium, calcium, and phosphorus). There was no pattern of events to suggest hepatic or renal injury.

Laboratory findings

Assessment of laboratory parameters did not reveal any safety concerns with up to 268 weeks of ataluren use. There was no ≥ Grade 3 laboratory value abnormalities. No clinically important effects of ataluren were observed in any haematology, serum biochemistry or urine assays.

Protocol-Specified Thresholds for Safety Monitoring of Hepatic, Adrenal, Renal and Serum Electrolytes

Laboratory abnormalities meeting pre-defined protocol-specified thresholds for safety monitoring of hepatic, adrenal, renal and serum electrolyte abnormalities were generally infrequent.

Two hepatic abnormalities (total bilirubin and gamma glutamyl transferase elevations) meeting the pre-defined criteria were reported as TEAEs. Both events were classified as being related to study drug. Neither event was classified as severe.

None of the adrenocorticotrophic hormone elevations were reported as TEAEs and thus not considered clinically relevant.

None of the protocol-defined safety monitoring thresholds for renal assessment for urine protein: urine creatinine ratio or urine protein: urine osmolality ratio was reported as AEs.

Protocol-defined safety monitoring thresholds for serum cystatin C and for serum BUN occurred in one and two patients, respectively. No patient exceeded protocol-defined safety monitoring thresholds for serum creatinine, and no patients shifted from normal at baseline to above the upper limit of normal (ULN) at any creatinine assessment during the study.

For serum cystatin C, 6 (6.9%) patients shifted from normal at baseline to above the ULN at Week 48; at Week 192, 12 (18.8%) patients shifted from normal at baseline to above the ULN. There were no cystatin C increases \geq Grade 3. A moderate (Grade 2) cystatin C increase was reported as an AE in one patient at week 192. This increase was within normal range on retest.

No electrolyte abnormalities were report as AEs and none were considered clinically relevant. No pattern of serum electrolyte abnormalities was observed.

Lipid Levels

The mean high-density lipoprotein (HDL), low density lipoprotein (LDL), total cholesterol, and triglycerides levels were in the upper range of normal/borderline high at baseline. Increases in lipids were small, not clinically relevant, and in line with what was previously reported in controlled studies with ataluren. Changes from baseline for total cholesterol at 48 weeks ranged from 1.00 to 2.13 mmol/litre and at Week 240 ranged from -0.85 to 1.50 mmol/litre. There was one TEAE of hypercholesterolemia. The patient's baseline cholesterol was 4.60 nmol/litre and ranged from a low of 3.77 nmol/litre at Week 228 to a high of 5.47 mmol/litre at Weeks 84 and 96.

For the AT population, the lipid profile values shifted from normal at baseline to above the ULN at Week 48 in 18 (20.5%) patients for total cholesterol, 14 (15.9%) patients for LDL, and 15 (17.0%) patients for triglycerides. All patients were using corticosteroids. For HDL, 8 (9.1%) patients shifted from normal at baseline to above the ULN at 48 weeks. All but one of these patients used corticosteroids.

By Week 240, shifts from normal at baseline to above the ULN post baseline occurred in 4 (16.0%) patients for total cholesterol, and 2 (8.0) patients each for HDL, LDL and triglycerides (Table 25).

All of these shifts occurred in patients who used corticosteroids. No patients shifted from normal or high at baseline to low post baseline for any lipid parameter, however some patients who reported high lipid values at baseline shifted to normal values by Week 240: 3 (12.0%) patients each for HDL, LDL and triglycerides and 2 (8.0%) patients for total cholesterol; all were corticosteroid users. Additionally, one patient who did not use corticosteroids shifted from high triglyceride values at baseline to normal values at 240 weeks. Hypercholesterolemia was reported as a Grade 1 AE in 1 patient. The patient's baseline cholesterol was 4.60 nmol/litre and ranged from a low of 3.77 nmol/litre at Week 228 to a high of 5.47 nmol/litre at Weeks 84 and 96. There were no AEs reported for hypertriglyceridemia.

Table 25. Shifts from Baseline at Week 240 in Lipid Parameters (AT Population)

Week 240 Level	Corticosteroid Use					
	Yes N=84			No N=10		
	Baseline Level [1]					
	Low	Normal	High	Low	Normal	High
HDL	M=25 [2]	M=25 [2]	M=25 [2]	M=2 [2]	M=2 [2]	M=2 [2]
Low	0	0	0	0	0	0
Normal	0	15 (60.0)	3 (12.0)	0	2 (100)	0
High	0	2 (8.0)	5 (20.0)	0	0	0
LDL	M=25 [2]	M=25 [2]	M=25 [2]	M=2 [2]	M=2 [2]	M=2 [2]
Low	0	0	0	0	0	0
Normal	1 (4.0)	15 (60.0)	3 (12.0)	0	2 (100)	0
High	0	2 (8.0)	4 (16.0)	0	0	0
Total cholesterol	M=25 [2]	M=25 [2]	M=25 [2]	M=2 [2]	M=2 [2]	M=2 [2]
Low	0	0	0	0	0	0
Normal	0	13 (52.0)	2 (8.0)	0	2 (100)	0
High	0	4 (16.0)	6 (24.0)	0	0	0
Triglycerides	M=25 [2]	M=25 [2]	M=25 [2]	M=2 [2]	M=2 [2]	M=2 [2]
Low	0	0	0	0	0	0
Normal	0	15 (60.0)	3 (12.0)	0	0	1 (50.0)
High	0	2 (8.0)	5 (20.0)	0	0	1 (50.0)

Abbreviations: AT, as treated; HDL, high density lipoprotein; LDL, low density lipoprotein; M, Number of patients who had non-missing values for both baseline and post-baseline at the given visit

[1] Baseline is defined as last available assessment on or prior to the first dose of study medication.

[2] M = Number of patients who had non-missing values for both baseline and post-baseline at the given visit. Percentages are calculated as n/M*100.

Vital signs, physical finding and other observations related to safety

Blood pressure (BP) was elevated at baseline in 7/59 (11.9%) patients who were pre hypertensive and 13/59 (22.0%) patients who were hypertensive (Table 26). There was no apparent pattern of an increase in the number of patients with hypertension over time. The proportion of patients who were pre-hypertensive or hypertensive at Weeks 192 and 240 were similar to that at baseline. Through Week 240 of the study, the largest mean increases in systolic BP were -2.5 mmHg at Week 204 and +2.5 mmHg at Week 228. No patients discontinued the study due to hypertension.

Mean changes from baseline for diastolic BP, pulse rate, respiration rate, and temperature values were small and not clinically meaningful through Week 240.

Mean body weight increased from baseline to Week 48 by 2.57 kg and by 12.39 kg at Week 240.

Table 26. Vital Sign Results Meeting Hypertension Criteria (AT Population)

Visit Criteria [1]	Corticosteroid Use		Overall N=94 n (%)
	Yes N=84 n (%)	No N=10 n (%)	
Baseline	56	3	59
Normal	37 (66.1)	2 (66.7)	39 (66.1)
Pre-hypertensive	6 (10.7)	1 (33.3)	7 (11.9)
Hypertensive	13 (23.2)	0	13 (22.0)
Week 48	43	4	47
Normal	28 (65.1)	4 (100)	32 (68.1)
Pre-hypertensive	5 (11.6)	0	5 (10.6)
Hypertensive	10 (23.3)	0	10 (21.3)
Week 96	36	3	39
Normal	26 (72.2)	2 (66.7)	28 (71.8)
Pre-hypertensive	5 (13.9)	1 (33.3)	6 (15.4)
Hypertensive	5 (13.9)	0	5 (12.8)
Week 144	37	2	39
Normal	22 (59.5)	1 (50.0)	23 (59.0)
Pre-hypertensive	13 (35.1)	1 (50.0)	14 (35.9)
Hypertensive	2 (5.4)	0	2 (5.1)
Week 192	34	2	36
Normal	23 (67.6)	1 (50.0)	24 (66.7)
Pre-hypertensive	8 (23.5)	1 (50.0)	9 (25.0)
Hypertensive	3 (8.8)	0	3 (8.3)
Week 240	17	1	18
Normal	14 (82.4)	1 (100)	15 (83.3)
Pre-hypertensive	3 (17.6)	0	3 (16.7)

Abbreviations: AT, as treated; DBP, diastolic blood pressure; SBP, systolic blood pressure

[1] If age <18 years old, the hypertension criteria are based on age, gender, and height-adjusted systolic blood pressure (SBP) and diastolic blood pressure (DBP) percentile results (Hypertensive: \geq 95th percentile; Pre-hypertensive: 90 to <95th percentile; Normal: <90th percentile). If age \geq 18 years old, hypertensive: SBP \geq 140 mmHg or DBP \geq 90 mmHg; pre-hypertensive: SBP 120 to 139 mmHg or DBP 80 to 89 mmHg; Normal: SBP 90 to 119 mmHg and DBP 60 to 79 mmHg.

For the 43 patients with baseline height measurements, the overall mean increase from baseline in height was 2.00 cm at 48 weeks and 9.79 cm at Week 240.

No safety concerns were identified based on physical examinations. Physical findings were consistent with disease progression.

Three patients had clinically significant ECG abnormalities that were related to cardiomyopathy in two patients and left ventricular hypertrophy, which was reported as part of the patient's medical history in another patient. At week 240 these abnormalities were not clinically significant.

Safety in special populations

Not applicable.

Safety related to drug-drug interactions and other interactions

Not applicable, the Applicant did not submit drug-drug interaction studies as part of this variation.

Discontinuation due to adverse events

Three patients had five TEAEs leading to study discontinuation (Table 27). One patient experienced an MI of severe intensity and was considered related to study medication by the investigator and unrelated by the sponsor. The other four events (cardiac failure, pneumonia aspiration, cardiogenic shock and ventricular arrhythmia) were considered unrelated to study medication and led to a fatal outcome in two patients (Table 27).

Table 27. Incidence of Adverse Events Leading to Study Discontinuation by SOC and Preferred Term (AT Population)

System Organ Class Preferred Term	Ambulatory Status		Overall N=94 n (%)
	Yes N=50 n (%)	No N=44 n (%)	
Patients with ≥1 TEAE [1] leading to discontinuation	1 (2.0)	2 (4.5)	3 (3.2)
Cardiac disorders	1 (2.0)	2 (4.5)	3 (3.2)
Cardiac failure	0	1 (2.3)	1 (1.1)
Cardiogenic shock	0	1 (2.3)	1 (1.1)
Myocardial infarction	1 (2.0)	0	1 (1.1)
Ventricular arrhythmia	0	1 (2.3)	1 (1.1)
Respiratory, thoracic and mediastinal disorders	0	1 (2.3)	1 (1.1)
Pneumonia aspiration	0	1 (2.3)	1 (1.1)

Abbreviations: AE, adverse event; AT, as treated; SOC, system organ class; medDRA, medical dictionary for regulatory activities; TEAE, treatment-emergent adverse event

AEs were coded using MedDRA, Version 20.1

[1] TEAEs were defined as an adverse event that occurs or worsens in the period extending from the day of a patient's first dose of study drug to 6 weeks after the last dose of study drug in this study. A patient who reported 2 or more adverse events with the same preferred term was counted only once for that term. A patient who reported 2 or more adverse events with different preferred terms within the same system organ class was counted only once in the SOC.

SOC and Preferred Term are sorted by descending order of Overall column.

Post marketing experience

No data was submitted by the Applicant.

2.5.1. Discussion on clinical safety

There were no new adverse events reported during the clinical trial. The reported adverse events were also in line with the more severe stage of the condition in non-ambulatory subjects compared to ambulatory subjects for which ataluren is currently approved.

During the assessment, the Applicant was requested to address the benefit-risk of ataluren in respiratory compromised nmDMD patients considering the potential increase in risk for aspiration, in the light of the high frequency of cough, vomiting and nausea.

Cough, vomiting, and nausea were identified as adverse drug reactions (ADRs) in the Summary of Product Characteristics (SmPC), with a frequency of very common (vomiting) or common (nausea and cough).

In Study PTC124-GD-019-DMD (Study 019), the mean duration of study drug treatment was 197.25 weeks. During this long-term study, a total of 28 (29.8%) subjects experienced TEAEs of vomiting, 16 (17%) subjects experienced TEAEs of cough, and 7 (7.4%) subjects experienced TEAEs of nausea. All TEAEs of cough were mild (n=13) or moderate (n=3) in severity and were considered unrelated to ataluren therapy. No TEAEs of cough were associated with events of nausea or vomiting.

In order to enable a comparison of the incidence rates in the long-term Study 019 with the 48-week studies PTC124-GD-007-DMD (Study 007) and PTC124-GD-020-DMD (Study 020), TEAEs were summarized for the first 48 weeks of study treatment. The frequencies of cough (6.4% (6/94)), nausea (6.4% (6/94)), and vomiting (19.1% (18/94)) in 48 weeks of treatment were lower in Study 019 than in pooled studies 007/020 [17.7% (41/232) for cough, 10.8% (25/232) for nausea and 36.6% (85/232) for vomiting]. The lower incidence of nausea and vomiting in the open-label extension study Study 019 was consistent with an analysis that found the rates of these events decreased with duration of treatment, as subjects come to better tolerate ataluren treatment. Given the more advanced disease state in the subjects in the open-label extension trial Study 019, the lower rates of these events

suggested that there was no additional risk of aspiration due to nausea and vomiting for respiratory compromise ataluren-treated patients.

Study 019 included subjects who were ambulatory at baseline, as well as those who had lost ambulation prior to study entry. The overall frequency of cough, and to a lesser extent nausea, was higher among the 44 subjects who were non-ambulatory at baseline, while the vomiting occurred slightly more frequently among subjects who were ambulatory at baseline. It is well documented that DMD patients develop a respiratory muscle weakness that results in weakened cough and airway clearance impairment (Camela 2018); therefore, the increased incidence of cough in non-ambulatory patients is not unexpected. In addition, patients with DMD typically receive multiple concomitant medications, some of which are themselves associated with risk of cough.

Table 28. Summary of Treatment-Emergent Adverse Events by Preferred Term in in Study 019 by Baseline ambulatory Status in the first 48 weeks of treatment and Overall (As-treated population).

Preferred Term	Baseline Ambulatory Status			
	Yes n=50 n (%)		No n=44 n (%)	
	Onset ≤48 Weeks	Overall	Onset ≤48 Weeks	Overall
Cough	1 (2.0)	5 (10.0)	5 (11.4)	11 (25.0)
Nausea	2 (4.0)	2 (4.0)	4 (9.1)	5 (11.4)
Vomiting	12 (24.0)	16 (32.0)	6 (13.6)	12 (27.3)

Of the 16 patients who experienced TEAEs of cough in Study 019, 10 (63%) were receiving concurrent treatment with ACE inhibitors, which are known to commonly cause cough as a side effect. Table 29 summarizes the incidence of cough, nausea, and vomiting by baseline ambulatory status for Study 019 for the first 48 weeks and overall.

Inefficient coughing is a known characteristic of DMD, which worsens with the progression of the disease, and which can lead to mucus plugging and atelectasis or pneumonia. Difficulty swallowing and prolongation of the time taken to eat a meal also worsens during the course of the disease, which can also result in aspiration. A thorough evaluation of cumulative safety data was conducted to determine whether cough, vomiting, and nausea were associated with a potential increase in the risk of aspiration in respiratory-compromised nmDMD patients.

As of 31 July 2018, an estimated 1,415 unique subjects have been exposed to ataluren in clinical trials and an estimated total of 768 patients have been exposed to ataluren in post-marketing experience (Periodic Safety Update Report 7).

To date, 4 cases of aspiration or aspiration pneumonia have been received, none of which were considered related to ataluren. All 4 cases occurred in clinical studies; there have been no reports of aspiration from post-marketing sources. Two cases were associated with trauma (one in study PTC124-GD-019-DMD [Study 019], a case of vomiting and aspiration under nerve block, and one in study PTC124-GD-020e [Study 020e], a case of vomiting immediately following a femoral fracture). The two other cases were associated with the act of eating (one in the cystic fibrosis study PTC124-GD-021e-CF and one in the DMD open-label extension study PTC124-GD-016-DMD [Study 016]).

In the view of the Applicant, there was no association between events of cough, vomiting, nausea and events of aspiration after evaluation of the aspiration cases received by the Applicant stated that all cases of aspiration had been unrelated to ataluren treatment and associated with clear alternative

aetiologies.

While it should be noted that the common adverse events nausea, vomiting and cough may be more critical in a respiratory compromised population, e.g. non-ambulatory nmDMD subjects, as it may lead to aspiration, no causality between the use of ataluren and aspiration or adverse events leading to treatment withdrawal could be established.

2.5.2. Conclusions on clinical safety

No new safety concerns were identified

2.5.3. PSUR cycle

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.

2.5.4. Direct Healthcare Professional Communication

Not applicable

2.6. Risk management plan

The CHMP and the PRAC having considered the data submitted in the application were of the opinion that due to the concerns identified with this application, the risk management plan for Translarna cannot be agreed.

2.7. Update of the Product information

In relation to the new claimed indication, sections 4.1, 4.2, 4.8, 5.1 of the SmPCs have been proposed to be updated by the Applicant. In light of the negative recommendation, the proposed changes to the SmPC and Package Leaflet for Translarna cannot be agreed.

2.7.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

2.7.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Translarna is included in the additional monitoring list as the product has a conditional approval.

Therefore, the summary of product characteristics and the package leaflet include 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.

2.8. Significance - Non-Conformity of paediatric studies

Not applicable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

Ataluren is an oral drug which is claimed to enhance ribosomal read-through of nonsense mutations in messenger RNA (mRNA) resulting in full-length protein production.

3.1.1. Disease or condition

DMD is a rare (1 in 3500 male newborn), disabling and ultimately fatal X-linked genetic disorder that primarily affects males (Emery 1991, Worton 2001, Khurana 2003). The disease is caused by mutations in the gene for dystrophin, a protein that is critical to the structural stability of myofibers in skeletal, diaphragmatic and cardiac muscle and is also of importance for the central nervous system and smooth muscles (Worton 2001, Khurana 2003). Approximately 13% of patients with DMD have the disorder due to a nonsense mutation which introduces a premature stop codon in the messenger mRNA for dystrophin, leading to non-functional protein.

3.1.2. Available therapies and unmet medical need

Ataluren is indicated for the treatment of DMD resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 2 years and older. Corticosteroids are also used to temporarily reduce the decline in motor function. For the non-ambulatory patients, the focus of treatment is on the prevention and management of complications.

3.1.3. Main clinical studies

Inclusion of non-ambulatory subjects with nmDMD in the indication is claimed based on results of one clinical study, i.e. study 019. This was a non-randomised open-label, uncontrolled multicentre study evaluating primarily the tolerability and long-term safety of ataluren over approximately 240 weeks of use. The dose regime of ataluren was the same as that approved for the ambulatory patients aged >2 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).

Secondary outcomes included spirometry variables and the EK in non-ambulatory patients, assessed at screening (visit 1), week 48 (visit 6), and week 48 through week 240 or premature discontinuation. These efficacy outcomes were compared to a matched historical control, derived from the CINRG-database.

3.2. Favourable effects

The subjects that experienced a decline in FVC to <1 litre was 22 (42.3%) in the CINRG group and 4 (10.8%) in Study 019.

The median age at predicted FVC% <60% was 18.1 years in Study 019 non-ambulatory patients. For the propensity score-matched CNRG population this was 15.5 years (P=0.0376) or 16 years, matching for corticosteroid use and duration, deflazacort use and duration either age at first symptom or age at loss of ambulation, respectively.

One (2.2%) patient in Study 019 and 9 (20.0%) patients in CINRG experienced a decline in FVC <1 litre.

3.3. Uncertainties and limitations about favourable effects

The Applicant argued that a full extrapolation to non-ambulant DMD patients, based on PK and safety data similarity in the two populations (ambulatory and non-ambulatory) and additional efficacy data in non-ambulatory patients, should be allowed. The CHMP were of the opinion that a full extrapolation was not possible, as the subjects in question were in a more advanced stage of the disease, and it could not be assumed without the presentation of appropriate data that meaningful, clinically relevant effects on function would still be present in the context of the muscle degeneration and fibrosis in these patients. No new data was provided to address the shortcomings in the trial. An additional post hoc analysis was performed by the Applicant.

The CHMP was of the opinion that the study was not appropriate to assess the efficacy of ataluren in non-ambulant patients. There was no direct control group. An estimation of efficacy based on a comparison to a historical control group could in principle be accepted, provided that the methods used handle bias carefully, to the highest extent possible in estimates of efficacy. However, in this case, it was impossible to exclude data-driven decisions. In the first analysis, severe differences in baseline characteristics between the CINRG population and Study 019 were noted, there were unclarities regarding the matching procedure, results were confounded by a difference in length of observation time, and the sensitivity analysis was defined *a posteriori*. In summary, these analyses could only be considered as exploratory rather than confirmative.

In response to the CHMP objections, the Applicant submitted additional propensity score matched analyses. Similar to the previous ones, these analyses were considered exploratory at best, since there were several uncertainties regarding the propensity score methods, questioning the validity of the results:

- Matching on propensity score methods can correct for known baseline differences but not for flaws in study design or unmeasured confounding. Additionally, for an optimal performance these models usually rely on larger datasets than in this case.
- Furthermore, it was unclear how the variables for the model were selected. Not all covariates, e.g. TFT, relevant to the outcome were included when the model was designed, questioning thus the validity of the model selected.
- It was unclear how the optimal model was chosen. No information was provided on model characteristics, e.g. C-statistics and patients propensity scores.
- The model selected for FVC outcomes was validated on a model with age at loss of ambulation as a dependent variable with age at first symptoms and corticosteroid use as independent variables. The underlying assumption that the same combination of independent variables predicts age at loss of ambulation as well as FVC was not further justified. A second underlying assumption of this approach, which is that the dependent variable used to validate the model (age at loss of ambulation) can be included as independent in the model of FVC, was not justified.
- As opposite to FVC60%, when the FVC50% was used as dependent variable and the same model was used, the difference between the CNRG and study 019 disappeared. The model did not appear very robust when an almost similar dependent variable was used (FVC60% vs. FVC50%).
- Note that the control group of the double-blind phase of Study 007 was used for the validation. This population was referred to as the naïve population. However, this was not a truly naïve population as subjects could have been on placebo or high dose ataluren treatment. The assumption that the high dose ataluren had no effect at all was not justified.
- The model did not include the entire age range. The underlying claim that the model also applies for the age outside the observed age range is an assumption that had not been justified.
- Since the data were already known, it was impossible to exclude data-driven decisions in variable and model selection.

- The substantial loss to follow-up allowed no conclusion on the efficacy of an open-label, long term safety trial.

3.4. Unfavourable effects

The adverse events as reported in study 019 were found in similar frequencies when comparing non-ambulatory boys with ambulatory boys, and when comparing to frequencies in the placebo-controlled trial 007. Moreover, they were in line with the expectations of the severity of the conditions. No new safety concerns were identified.

3.5. Uncertainties and limitations about unfavourable effects

Due to the severity of the condition, it was difficult to determine whether the adverse events observed were contributed by ataluren or the progression of DMD.

Incidence of nausea and vomiting is frequent and increases the risk of aspiration in patients with an impaired ability to cough and to control movements. These events have a greater impact in the non-ambulatory subjects as compared to ambulatory patients. Aspiration is a life-threatening event, especially in patients with respiratory insufficiency. It remains unknown if this was due to ataluren or was related to disease progression.

3.6. Effects Table in non-ambulatory patients

Effect	Short description	Unit	Treatment (ataluren)	CINRG selected control	Uncertainties / Strength of evidence	References
Favourable Effects						
FVC <1L	Decline of FVC to <1L	%	10.8%	42.8%	-Unclear matching -Baseline differences in corticosteroids use and FVC -Difference in follow up time -Results not stat. sig. -Exploratory rather than confirmatory	Study 019
FVC <60%	Age at % predicted FVC <60%, indicative for mechanic ventilation	Median age	18.1 years	15.5 ^a (p=0.037)/16 ^b years (p=0.082)	- Match naïve population includes high dose ataluren. - Extrapolation beyond 14 years and other variables unknown -Validity of model questioned - Effect not shown for age at % predict FVC <50%	Study 019, 2 nd RfSI
FVC <1L	Number of patients with FVC <1L, indicative for time to death	n (%)	1 (2.2%)	9 (20%)	Median age not determined. >80% of patients censored in both groups	Study 019, 2 nd RfSI)
Unfavourable Effects						
Nausea, cough, vomiting	Ambulatory vs non-ambulatory	(%)	4%, 10%, 32% vs 11%, 25%, 27%		AEs related to either ataluren or disease progression	Study 019

Abbreviations: CINRG= Cooperative International Neuromuscular Research Group, FVC = forced vital capacity, n.s. = not significant

^a propensity score matched, based on age at first symptoms and corticosteroid use

^p propensity score matched, based on age at loss of ambulation and corticosteroid use

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The MAH claimed a delay progression of FVC under ataluren treatment as compared to a matched historical control. The uncertainty of how the control group was constructed, uncertainties with respect to the analysis methods, lack of supportive evidence from other non-respiratory motor function, did not allow for a definite conclusion that efficacy has been shown. It was impossible to exclude data-driven decisions and Applicant included a more severe control group. Moreover, the concomitant corticosteroid use in the ataluren group was higher than that in the subjects selected as control.

In support of efficacy, the Applicant submitted data on pulmonary function. No upper limb or other non-ambulation motor functions were submitted. In this respect, other relevant outcomes for the patients such as residual leg function, residual upper limb function or cardiac function would have also been helpful in order to provide further support to any observed effect.

3.7.2. Balance of benefits and risks

The overall benefit of ataluren in non-ambulant DMD patients, though, remains unclear and was not robustly demonstrated. The effect on pulmonary function should be considered exploratory at most as the analysis had methodological flaws. There were concerns on potential data-driven decisions in the post hoc analysis, and on the fact that the model chosen was the model that provided the largest effect, while other models showed a closer match. Not all variables were included that are relevant to the outcome, therefore the results were considered non-robust. In addition, it was questioned if the model with loss of ambulation as the dependent variable can be extrapolated to a model with FVC as a dependent variable and a population with a larger age range. Finally, the propensity score models were based on a small number of patients compared to the number of variables. In conclusion, efficacy in the target population has not been sufficiently demonstrated, as the data and the methods relied upon by the Applicant were not sufficiently robust.

In addition, nausea, cough, and vomiting, are known and frequently occurring adverse events of ataluren, and should be weighted differently in respiratory compromised nmDMD patients considering the increased risk for aspiration. It remains unclear if these AEs were due to ataluren or due to the disease progression.

3.7.3. Additional considerations on the benefit-risk balance

The Applicant argued that the application for extension of indication of ataluren was primarily based on extrapolation from the demonstrated efficacy in ambulatory patients given the comparable pharmacokinetics (PK), as well as safety, in the two populations and indicated that this was a position endorsed in the past by the CHMP. In this context the Applicant refers to the CHMP concept paper on extrapolation of efficacy and safety in medicinal development [EMA/129698/2012] in which is stated:

"...in situations where the feasibility of studies is restricted, extrapolation principles may be applied for rational interpretation of the limited evidence in the target population in the context of data from other sources."

The Applicant further indicated that: given the (i) previously agreed comparable PK and safety in the two populations, (ii) substantial methodological obstacles to directly demonstrate efficacy in non-ambulatory patients with nmDMD, (iii) the change of clinically relevant endpoints in non-ambulatory patients, a full extrapolation strategy, as defined in the concept paper, was selected to justify treatment with ataluren in a non-ambulatory patient population. This was further warranted by the understanding of the mechanism of action of ataluren. Further, they continued to claim that data presented from Study PTC124-GD-019-DMD (Study 019) showed a better course of FVC as compared to a cohort of patients untreated with ataluren (CINRG). This was intended as supportive, complementing and validating the PK extrapolation with results consistent with clinical benefit.

However, extrapolation solely based on comparable PK and safety was not considered sufficient. The CHMP considered that efficacy in ambulatory subjects cannot be extrapolated to non-ambulatory subjects. In contrast to DMD subjects below 5 years of age, extrapolating of efficacy from ambulatory to non-ambulatory DMD patients is not straightforward as in a more advantaged stage of the disease the effect size may be limited as there is less functional muscle tissue left. During the review of the initial marketing authorisation application of ataluren it was already questioned if there was still an added benefit in DMD patients moving from the ambulatory to the non-ambulatory phase and the time of terminating treatment was extensively discussed. It was agreed that efficacy in non-ambulatory patients should be established separately. Clinically relevant efficacy in the non-ambulatory nmDMD patient needs to be predefined and demonstrated in a well-designed controlled trial. A well designed and well conducted propensity score-based study, capable of controlling for known and measured confounding, should be considered capable of supporting efficacy. The flaws in the design of Study 019, however, did not allow a valid conclusion that efficacy can be demonstrated. Moreover, the current data lack supporting functional assessments other than FVC, and the overall clinical relevance was therefore questioned. Finally, the validity of the findings was severely compromised due to the limited number of subjects that completed the study, essentially due to patients switching to commercially-available ataluren. It remains unexplained why subjects switching from the investigational product to the commercial product could not have been followed-up for longer.

3.8. Conclusions

The overall B/R of Translarna in non-ambulant DMD patients is negative.

The position of the Applicant of an extrapolation approach from ambulant to non-ambulant DMD patients, solely based on comparable PK and safety in these two populations was not endorsed. According to the mentioned guidelines for DMD [EMA/CHMP/236981/2011, Corr. 1], extrapolation approach needs efficacy data. This is because due to the more advanced stage of the disease, the value judgment and benefit/risk assessment may differ in these two populations. Hence, further support is needed to substantiate that the benefit/risk balance is still favourable at later stages. The supportive analysis using propensity match model, presented by the Applicant to support efficacy in non-ambulant was not appropriate due to several methodological flaws. The efficacy of ataluren in non-ambulatory subjects cannot be considered as sufficiently demonstrated and, as a consequence, the benefit-risk balance for treatment with ataluren in this group was considered negative.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation not acceptable and therefore does not recommend, by consensus, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation rejected		Type
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

Extension of Indication to include non-ambulatory patients with Duchenne muscular dystrophy; This variation additionally presents, as supportive data, the final results of the long term clinical study PTC-124-GD-019-DMD (an Open-Label Study for Previously Treated Ataluren (PTC124) Patients with Nonsense Mutation Dystrophinopathy), submitted in line with the requirements of the Article 46 of Regulation (EC) No 1901/2006.

Due to the methodological flaws of study PTC-124-GD-019-DMD, the SmPC and the Package Leaflet were not updated to include these results, and consequently no update of the RMP was required.

Grounds for refusal:

The CHMP was of the opinion that a robust clinically relevant efficacy of ataluren in non-ambulant Duchenne muscular dystrophy (DMD) patients has not been demonstrated. The submitted post-hoc analysis did not allow for a reliable and valid assessment of the efficacy of ataluren in the non-ambulant patients with DMD. The submitted data and analyses suffered from multiple severe methodological issues including critical uncertainties in the way the study was conducted and the comparability of the control group. Therefore, the CHMP concluded that the indication of ataluren should not be extended to the non-ambulant Duchenne muscular dystrophy (DMD) patients.

The CHMP has recommended the refusal of the variation to the terms of the marketing authorisation.

5. Re-examination of the CHMP opinion of 27 June 2019

Following the CHMP conclusion that Translarna was not approvable due to severe methodological concerns including the design and conduct of the study and the appropriateness of the selected control group, the Applicant submitted detailed grounds for the re-examination of the grounds for refusal.

5.1. Detailed grounds for re-examination submitted by the Applicant

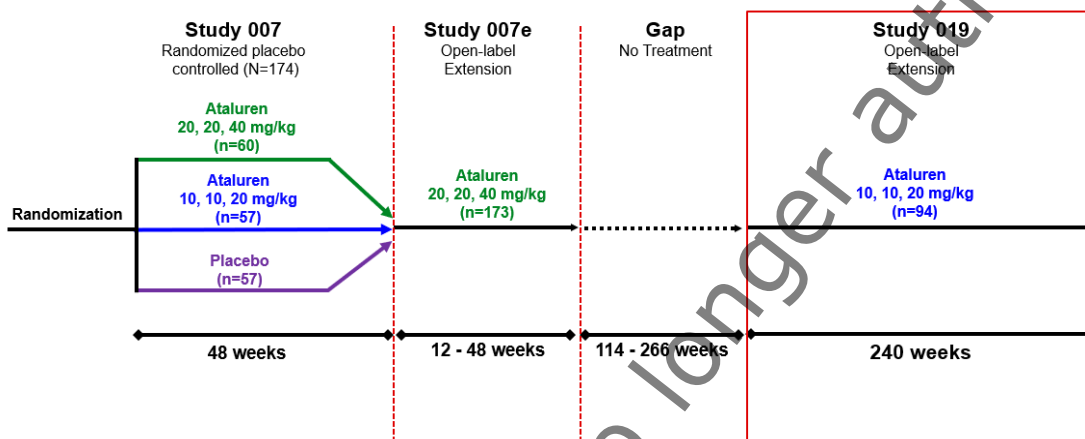
The MAH presented in writing arguments refuting the grounds for refusal. The MAH argumentation was as follows:

Ground #1: PROPENSITY-SCORE METHODOLOGY MIMICS RANDOMIZATION AND PROVIDES A RELIABLE BASIS FOR COMPARISON OF STUDY 019 PATIENTS WITH NATURAL HISTORY PATIENTS

1.1 Study 019 is an Important Source of Long-term Longitudinal Data

All but 4 subjects in Study 019 had participated in the placebo-controlled trial PTC124-GD-007-DMD (Study 007); 3 subjects had participated in PTC124-GD-004-DMD (Study 004) and 1 subject had no prior ataluren clinical trial experience. Subjects in Study 007 were randomized to one of three arms: placebo, 10, 10, 20 mg/kg ataluren, or 20, 20, 40 mg/kg ataluren. Study 007 was followed immediately by an extension study PTC124-GD-007e-DMD (Study 007e) at the 20, 20, 40 mg/kg dose. After Study 007e, patients had a treatment gap ranging from 114 to 266 weeks, after which they enrolled in the open-label extension trial Study 019 at the 10, 10, 20 mg/kg dose (Figure 21). At the conclusion of Study 019, the median (minimum, maximum) duration of treatment with 10, 10, 20 mg/kg ataluren was 1670.0 (294, 2185) days, overall and the mean follow-up period was more than 8 years.

Figure 21. Clinical Study Participation History of Patients in Study 019



Note: A total of 4 patients enrolled in Study 019 without having participated in Study 007: Three had participated in Study 004 and one had not participated in a previous clinical trial of ataluren.

A total of 90 of the 96 ex-US patients who completed Study 007 (Study 007) enrolled in Study 019, ensuring that Study 019 isn't affected by enrichment bias; subjects continued into the extension trial regardless of the nature of their treatment response. The Study 019 population thus very closely mirrors the population of the randomized placebo-controlled predecessor Study 007.

Of the 94 patients in Study 019, 64 were non-ambulatory, 45 of whom had values for age at first symptom and did not experience a decline below percent predicted FVC 60% prior to Study 019 entry.

1.2 Comparability of Study 019 and CINRG Natural History Study Populations

Study 019 was run contemporaneously with the CINRG natural history study. The CINRG history study enrolled more than 400 patients and provides longitudinal DMD data from more than 400 ambulatory and non-ambulatory patients aged 2 to 28 years, making it a rich source of natural history data.

The use of CINRG as a comparator for Study 019 is grounded in the similarity of the populations each study enrolled. As noted, both studies were run contemporaneously, and both had similar follow-up periods, an average of more than 8 years and up to 10 years for Study 019 and CINRG, respectively. Both studies enrolled patients at dedicated DMD centers in the United States and European Union, ensuring that enrolled patients experienced similar standards of care.

1.3 A Propensity-score Match Strategy Was Selected to Mimic Randomization

A propensity score is a numerical representation of the probability of an individual unit (in this case a patient) being assigned to a particular cohort (in this case an interventional study or a natural history study). Propensity scores were used in this procedure in order to mitigate for any imbalances in prognostic factors between the non-randomized populations of Study 019 and CINRG to derive an

unbiased estimate of treatment effect that is not confounded by any baseline difference in the populations. There are several methods for applying propensity scores to reduce confounding variables. On the basis of the advantages and disadvantages of each method and the suitability of these methods for the time to event analyses that would be used to assess the effect of ataluren on pulmonary function, it was determined that a propensity score matching method would be used (Table 29).

Table 29. Selection of a Propensity Score Adjustment Method

Method	Definition	Characteristics	Applicability (Yes/No)
Matching	Patients are paired based on proximity of propensity scores	Widely and commonly used, Straight-forward If propensity score distributions don't overlap for the treatment and control groups, many units from the sample will be dropped	Yes (Selected Method)
Subclassification (Stratification)	Samples are divided into strata by propensity score	Each resulting stratum contains participants from treatment and control groups Conversion of continuous propensity scores to a categorical matching variable reduces the precision of the matched units	No
Weighting	Observations are multiplied by a derivative of the propensity score (commonly, the inverse of the propensity score)	Enables balancing of the treatment and control groups Some uncertainty of application to an analysis of age at event	Yes (Performed as Sensitivity Analysis)
Covariate Adjustment	Propensity score is used as a covariate in the analysis	Cannot be used for a KM analysis because covariates cannot be added to the modeling.	No

Abbreviations: KM, Kaplan Meier

As noted in Table 29, a disadvantage of the propensity-score matching method is that it requires that propensity scores be distributed with enough overlap throughout the comparator populations in order to match enough pairs with suitably close propensity scores. As discussed in Section 6, however, not only were the distributions of the propensity scores similar, they were nearly identical between the Study 019 and the CINRG populations.

In addition to propensity score matching, a weighting method is the other use of propensity scores that could be applicable to this Study 019 and CINRG comparison. Under the inverse propensity treatment weight (IPTW) method, the average treatment effect of the ataluren-treated group is weighted by the inverse of the propensity score and the CINRG patients are weighted by the inverse of one minus of the propensity score (Xie 2005). This method was performed as a sensitivity analysis, the results of which were consistent with the propensity-score match method.

In summary, it was determined that a propensity score matching method applies to Study 019 and the CINRG natural history dataset would allow for a reliable analysis of treatment effect minimizing bias and mimicking randomization.

Ground #2: THE SELECTED PROPENSITY-SCORE MATCHING CRITERIA EFFECTIVELY CONTROL FOR DISEASE SEVERITY AND STANDARD OF CARE

The rate of disease progression in DMD is a function of two elements: standard of care and underlying disease severity. DMD has a high degree of variability in the severity of the underlying disease. A key indicator of disease severity is the age at disease onset, with the most severely affected patients experiencing symptoms at a younger age (Ciafaloni 2016). In addition, the duration and type of steroid

use are the two quantifiable variables in standard of care that most clearly influence the trajectory of DMD. Thus, in order to identify ataluren-treated patients from Study 019 and untreated patients in the CINRG database who were comparable for these factors, the following variables were explored as potential propensity-score match criteria: standard of care (as indexed by duration of corticosteroid use and duration of deflazacort use), disease severity (as indexed by age of first symptom), and, in order to account for baseline disease state, age at study entry and timed function test (TFT) results. These variables were combined to create the following potential propensity-score match models:

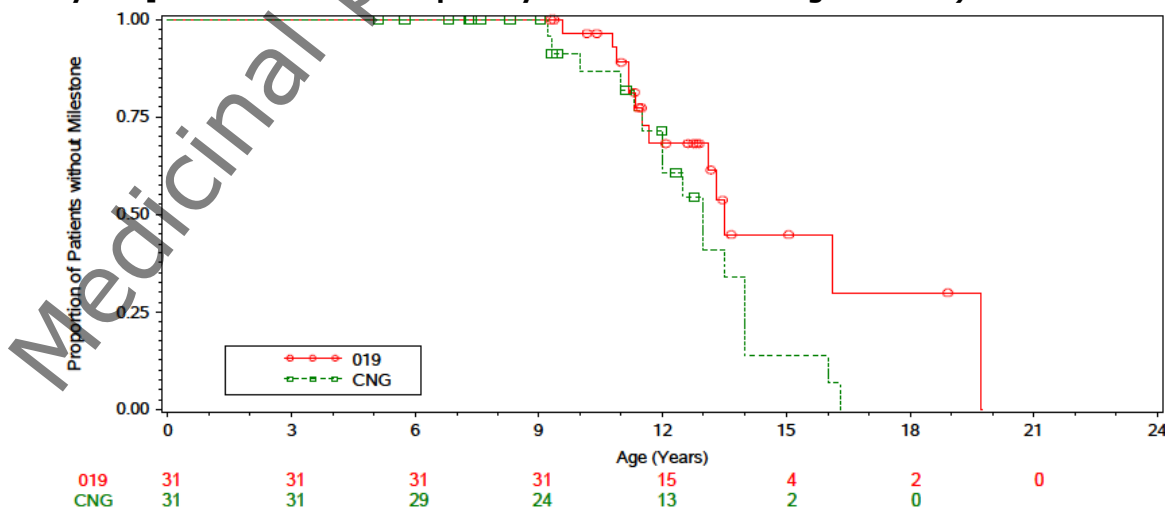
1. Standard of care (Duration of deflazacort use and duration of other steroid use) alone
2. Standard of care (Duration of deflazacort use and duration of other steroid use) + disease severity
 - a) Disease severity as age at first symptom
 - b) Disease severity as age at loss of ambulation (sensitivity analysis)
3. Standard of care + disease severity + age and time to run/walk 10m at study entry
4. Standard of care + disease severity + age and time to stand from supine at study entry
5. Standard of care + disease severity + age and time to climb 4 stairs at study entry

2.1 The Populations Defined by Each Propensity-Score Model Were Assessed for Comparability

The placebo-controlled predecessor Study 007 provided an opportunity to compare the disease trajectory of subgroup of patients in the selected matched comparison population who had not yet received a dose of ataluren with the untreated patients in CINRG. If the match criteria effectively selected suitably comparable populations for disease severity, the placebo-treated subgroup from Study 019 should experience a similar disease trajectory for loss of ambulation to that of the selected CINRG matched population.

Kaplan-Meier (KM) analyses were thus undertaken of age at loss of ambulation using the CINRG population selected by Models 1 through 5 in comparison with the subset of the 31 matched Study 019 patients who had received placebo in the preceding randomized controlled study PTC124-GD-007-DMD (Study 007). The resulting analyses showed that placebo-treated patients in Study 007 experienced a disease trajectory most similar to the matched CINRG population when Model 2a, using age at first symptom, steroid treatment duration, and deflazacort treatment duration was applied. The trajectories of placebo-treated patients and their CINRG counterparts showed a high-degree of overlap, and only began to separate when the numbers of patients at risk became too small for meaningful interpretation (Figure 22).

Figure 22. Kaplan-Meier Plot: Age at Loss of Ambulation (Study 019 Placebo Subjects [from Study 007] and CINRG with Propensity Score Matched Using Model 2a)



Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group

Note: Set 2a of Propensity Score model covariates includes age at first symptom and duration of Deflazacort, and duration of steroid other than Deflazacort

A total of 31 subjects assigned to Placebo group in Study 019. Note as opposite to figure number 2 only participants were included in this analysis

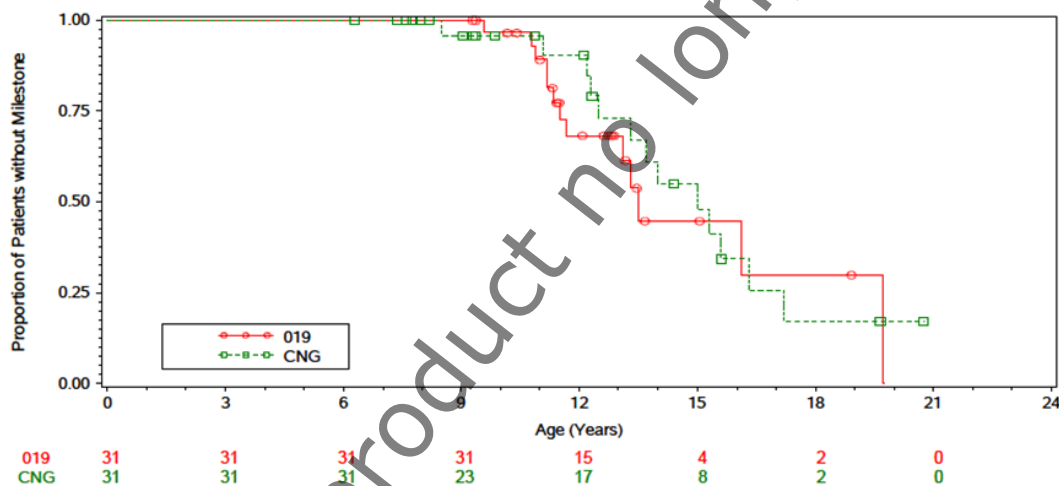
Patients who were ambulatory at Study 019 were censored at Study 019 entry (ie, prior to receiving their first dose of ataluren 10, 10, 20 mg/kg).

Numbers shown at bottom of graph are numbers of patients at risk.

Models 3 through 5, which added age at study entry and TFT results (10m run/walk, time to stand from supine, and time to climb stairs) to the variables used in Model 2a, proved problematic due to the nature of patients in CINRG for whom TFTs were assessed. It was determined that TFT values were generally collected in CINRG for patients with milder disease. CINRG patients with an assessment for any TFT experienced loss of ambulation at age 14, while those without any TFT datapoint lost ambulation 3.5 years sooner, when they were 10.5 years of age.

Accordingly, when age at baseline and time to run/walk 10 meters was added to the match model, the trajectories of placebo-treated patients and their CINRG counterparts separated early, and only began to overlap when the numbers of patients at risk became too small for meaningful interpretation (Figure 23). In this model, CINRG patients were thus progressing at a slower rate than their Study 019 counterparts.

Figure 23. Kaplan-Meier Plot: Age at Loss of Ambulation (Study 019 Placebo Subjects [from Study 007] and CINRG with Propensity Score Matched using Model 3)



Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group

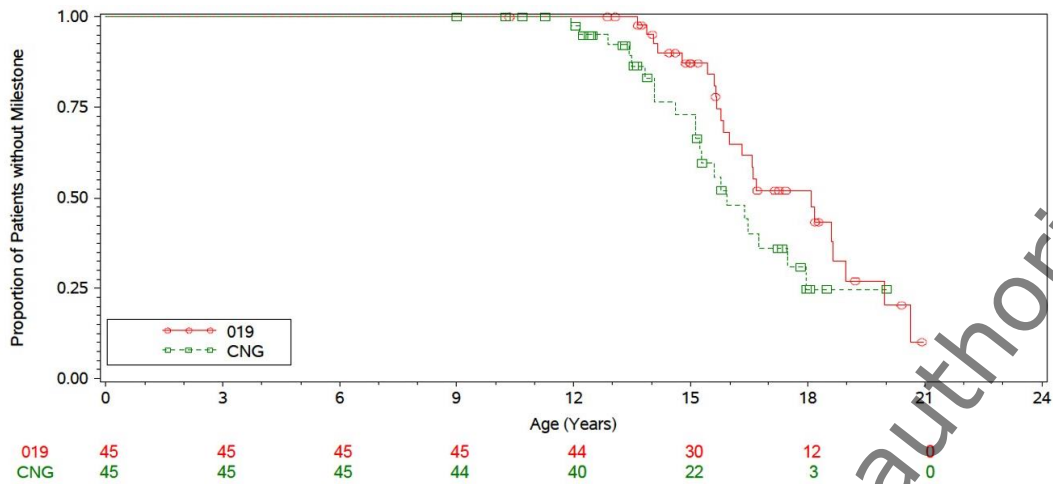
Note: Set 3 of Propensity Score model covariates includes age at first symptom, baseline age and baseline time for 10m run/walk from 007 and study entry of CINRG, duration of Deflazacort, and duration of steroid other than Deflazacort

A total of 31 subjects assigned to Placebo group in Study 019. Note as opposite to figure number 3 only participants assigned to Placebo group in Study 019 were included in this analysis.

Patients who were ambulatory at Study 019 were censored at Study 019 entry (ie, prior to receiving their first dose of ataluren 10, 10, 20 mg/kg). Numbers shown at bottom of graph are numbers of patients at risk.

Notably however, though this provided a concrete representation of why a match using TFTs was not selected, KM analyses for age at FVC <60% were still favourable for ataluren using age and time to run/walk (Figure 24), age and time to stand from supine and age and time to climb 4 stairs. These results persisted despite a more conservative match comparing Study 019 patients with more slowly progressing patients in CINRG.

Figure 24. Kaplan-Meier Plot: Age at Percent Predicted FVC <60% (Study 019 and CINRG with Propensity Score Matched Using Model 3)



Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital capacity.
 Note: Set 3 of Propensity Score model covariates includes age at first symptom, baseline age and baseline time for 10m run/walk from 007 and study entry of CINRG, duration of Deflazacort, and duration of steroid other than Deflazacort
 A total of 45 subjects with recorded values for age at first symptom and age at loss of ambulation who did not experience a decline below percent-predicted FVC <60% prior to Study 019 entry. Numbers shown at bottom of graph are numbers of patients at risk.

2.2 Baseline Demographic Characteristics Are Comparable for the Matched Populations

Additional confirmation of the appropriateness of the selected match was the comparability of the baseline demographic and disease characteristics in the resulting matched populations for FVC analyses. These analyses included all 45 non-ambulatory subjects with recorded values for age at first symptom who did not experience a decline below percent-predicted FVC <60% prior to Study 019 entry. Table 30 summarizes these for the population matched using the selected Model 2a, along with the associated p-values, indicating that there were no significant differences for the matched patients in functional status at the time of first assessment.

Table 30. Demographic and Disease Characteristics – Study 019 and CINRG Propensity Matched Population Using Model 2a

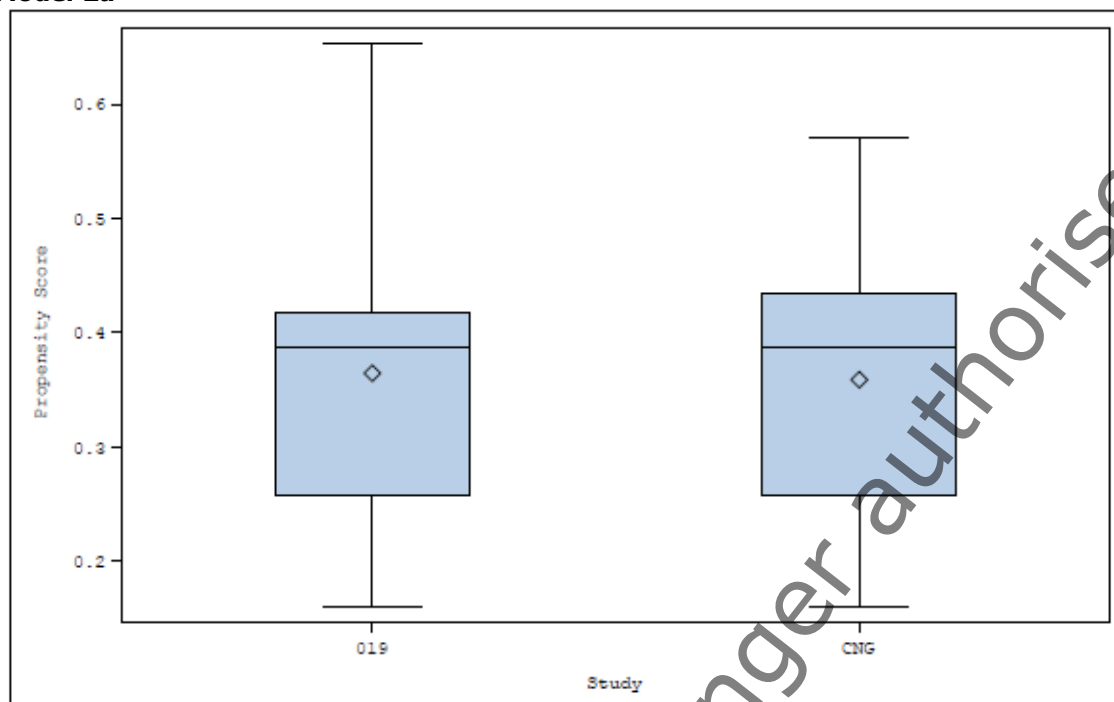
	Study 019 (N=45)	CINRG (N=45)	p value
Age at First Symptoms, years			
Mean (SD)	3.778 (1.757)	3.752 (1.529)	0.9405
SEM	0.262	0.228	
95% CI	(3.250, 4.306)	(3.292, 4.211)	
Median	3.000	3.170	
Min, Max	1.00, 9.00	1.00, 8.00	
DEFLAZACORT Duration, n (%)			
<1 month	22 (48.9)	25 (55.6)	0.5267
≥12 month	23 (51.1)	20 (44.4)	
Other Steroid Duration, n (%)			
<1 month	26 (57.8)	25 (55.6)	0.9762
1 to <12 month	2 (4.4)	2 (4.4)	
≥12 month	17 (37.8)	18 (40.0)	
First Assessment of 4 Stair Climb in Study 004/007/CINRG, n (%)			
Mean (SD)	7.131 (7.686)	10.384 (7.752)	0.1212
SEM	1.146	1.733	
95% CI	(4.822, 9.440)	(6.756, 14.012)	
Median	4.300	6.560	
Min, Max	1.50, 30.00	2.03, 28.33	
First Assessment of 10m run/walk in Study 004/007/CINRG, n (%)			
Mean (SD)	8.169 (5.714)	8.588 (3.875)	0.7486
SEM	0.852	0.791	
95% CI	(6.452, 9.886)	(6.952, 10.224)	
Median	6.600	8.000	
Min, Max	3.20, 30.00	3.62, 22.63	
First Assessment of Stand from Supine in Study 004/007/CINRG, n (%)			
Mean (SD)	12.416 (14.050)	11.173 (8.101)	0.6904
SEM	1.647	2.092	
95% CI	(9.096, 15.735)	(6.686, 15.659)	
Median	6.300	7.220	
Min, Max	1.80, 30.00	3.78, 30.00	

Abbreviations: CI, confidence interval; CINRG, Cooperative International Neuromuscular Research Group; Max, maximum; Min, minimum; SEM, standard error of the mean; SD, standard deviation
Propensity score model covariates include age at first symptom, duration of Steroid-DEFLAZACORT, and duration of Steroid-Other.
Data for six-minute walk distance are not summarized here due to the insufficient number of patients (n=3) in the CINRG population with values for this endpoint at study entry.
Steroid duration is calculated from starting use of steroid to FVC <1 L/censored date.
P value is calculated based on 2-sample t-test.

Ground #3: THE PROXIMITY OF PATIENT PROPENSITY SCORES FURTHER CONFIRM THE APPROPRIATENESS OF THE MATCH

As described before, propensity score matching requires a considerable overlap of the distribution of propensity scores between the populations to be matched. For the selected match model, the scores were distributed very comparably between the two populations (Figure 25) with the majority of patients in both groups falling between 0.25 and 0.44, resulting in matched populations with a mean (median) difference in propensity scores of 0.0090 (0.0011). This provided yet further confirmation of the appropriateness of the match.

Figure 25. Boxplot of Propensity Scores for Matched Study 019 and CINRG Populations Using Model 2a



Note: Set 2a of Propensity Score model covariates includes age at first symptom and duration of Deflazacort, and duration of steroid other than Deflazacort

Ground #4: THE TOTALITY OF AVAILABLE DATA SUPPORTS THE BENEFIT OF ATALUREN IN NON-AMBULATORY PATIENTS; THIS FINDING IS SHOWN TO BE REPRODUCIBLE WITH ADDITIONAL MATCH TYPES UNDERTAKEN AS SENSITIVITY ANALYSES ALL SHOWING A CONSISTENT ATALUREN TREATMENT EFFECT

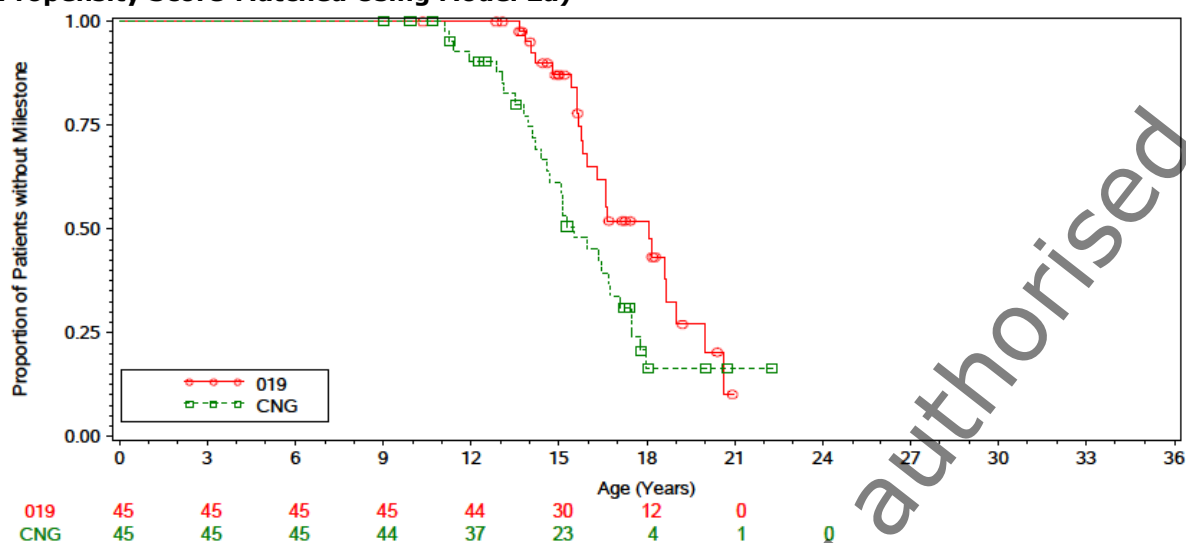
The effect of ataluren on pulmonary function was robust and reproducible, as illustrated with analyses of age at percent predicted FVC <60% for the primary match, as well as a series of analyses using alternative match types that were undertaken as sensitivity analyses. In addition, other available data also provided confirmation of the benefit of ataluren for patients who are non-ambulatory.

4.1 Ataluren Preserves Pulmonary Function (Primary Match, Previously Submitted)

As noted, a percent-predicted FVC of <60% is indicative of the first need for respiratory support intervention in the form of mechanical ventilation (through a manual ventilation bag or an insufflation-exsufflation device) in order to preserve lung function (Birnkranz 2018).

In the populations matched using age at first symptom, steroid duration, and deflazacort duration (ie, the match selected as primary), 23 (51.1%) patients in Study 019 and 30 (66.7%) patients in CINRG experienced a decline below the 60% percent-predicted FVC threshold. The median age for this milestone was 18.1 years in Study 019 and 15.5 years in CINRG (Figure 26), representing a delay in progression of 2.6 years with ataluren treatment.

Figure 26. Kaplan-Meier Plot: Age at % Predicted FVC <60% (Study 019 vs CINRG with Propensity Score Matched Using Model 2a)



Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital capacity
 Note: Set 2a of Propensity Score model covariates includes age at first symptom and duration of Deflazacort, and duration of steroid other than Deflazacort
 A total of 45 subjects with recorded values for age at first symptom and age at loss of ambulation who did not experience a decline below one of these FVC milestones prior to Study 019 entry.
 Numbers shown at bottom of graph are numbers of patients at risk.

4.2 Additional Match Types Undertaken as Sensitivity Analyses All Confirm Ataluren Treatment Effect

As described above, a rigorous process was undertaken to select and validate the best propensity-score match model. In addition, the same KM analyses were also performed using alternative match types and methods, some suggested by the CHMP, in order to further address concerns regarding potential bias.

The resulting analyses function as sensitivity analyses and demonstrate that the treatment effect observed in the primary analysis was reproduced consistently and repeatedly, when different matching methodologies were applied.

Table 31 summarizes the match type used in the selected primary match and the sensitivity analysis alternatives undertaken here.

Table 31. Primary and Alternative Match Types

Matching Type Options	Type used in Selected Match	Type Used in Sensitivity
Local versus Global	Local (nearest neighbor)	Global (optimal)
Caliper	Without caliper	With 0.2 SD caliper
Matching Ratio	1:1	1:2
Sorting Order	Arbitrary random seed number	100 iterations of randomly selected seed numbers

Abbreviations: SD, standard deviation

4.2.1 Sorting Order

When propensity scores are used to match populations, a randomly selected first Study 019 subject (ie, the "seed") is matched to the CINRG subject with the absolute closest value in their propensity scores. In order to explore the effect of this sorting order on the resulting analysis, 100 simulations were performed using a different randomly selected seed as a starting point for matching. The results were remarkably consistent with the primary analysis, indicating that the treatment effect persists without regard to sorting order (Table 32).

Table 32. Summary of Median Age and Difference in Median Age at FVC <60% in 100 Simulations of Match Sorting Order

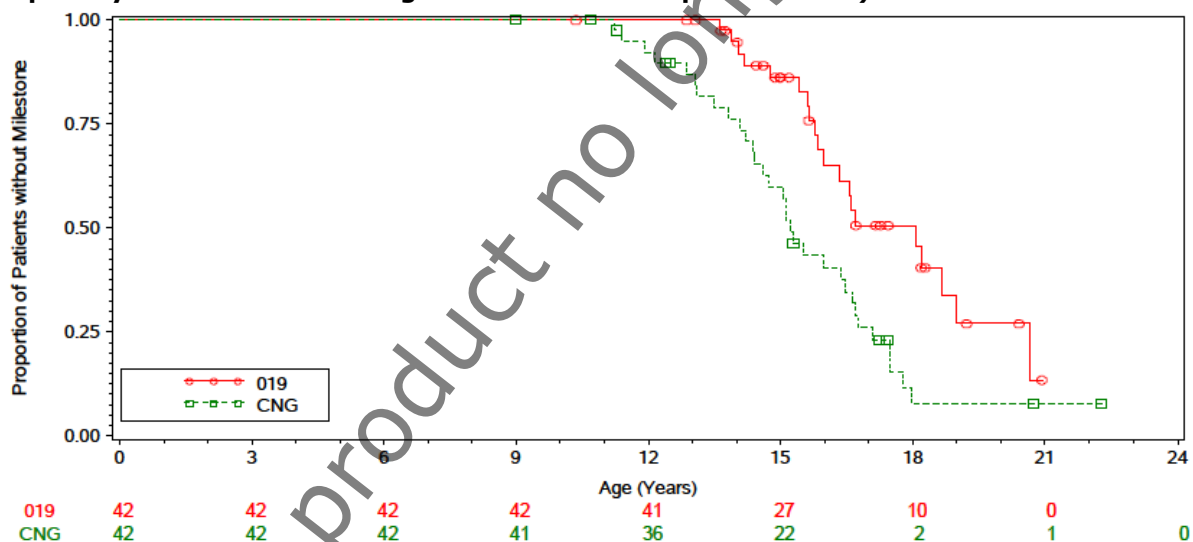
Statistic	Mean	SD	Min	Max
019 Median Age at FVC <60%	18.1	0	18.1	18.1
CNRG Median Age at FVC <60%	15.2	0	15.2	15.2
Difference in Median Ages (019 v CNRG)	2.9	0	2.9	2.9
P value	0.005359	0.0034729	0.002	0.0109

Abbreviations: CNRG, Cooperative International Neuromuscular Research Group; FVC, forced vital capacity; SD, standard deviation

4.2.2 Primary Match with Caliper Applied

A KM analysis of time to FVC <60% was undertaken using the selected propensity-score criteria (age at first symptom, steroid duration, deflazacort duration) in a 1:1 match with a caliper of 0.2 SD of the propensity scores. Application of the 0.2 SD caliper resulted in the exclusion of 3 patients from the matched populations. Patients in Study 019 again showed preservation of pulmonary function (Figure 27), with a median age of 18.1 years for the FVC <60% milestone, in contrast with a median of 15.2 years for CINRG, indicating that the use of a caliper did not impact the conclusion of a treatment effect for ataluren.

Figure 27. Kaplan-Meier Plot: Age at % Predicted FVC <60% (Study 019 vs CINRG with Propensity Score Matched Using 1:1 Match with Caliper Model 2a)



Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital capacity.

Note: Set 2a of Propensity Score model covariates includes age at first symptom and duration of Deflazacort, and duration of steroid other than Deflazacort.

A total of 42 subjects with recorded values for age at first symptom and age at loss of ambulation who did not experience a decline below one of these FVC milestones prior to Study 019 entry and were matched using a 0.2 SD caliper.

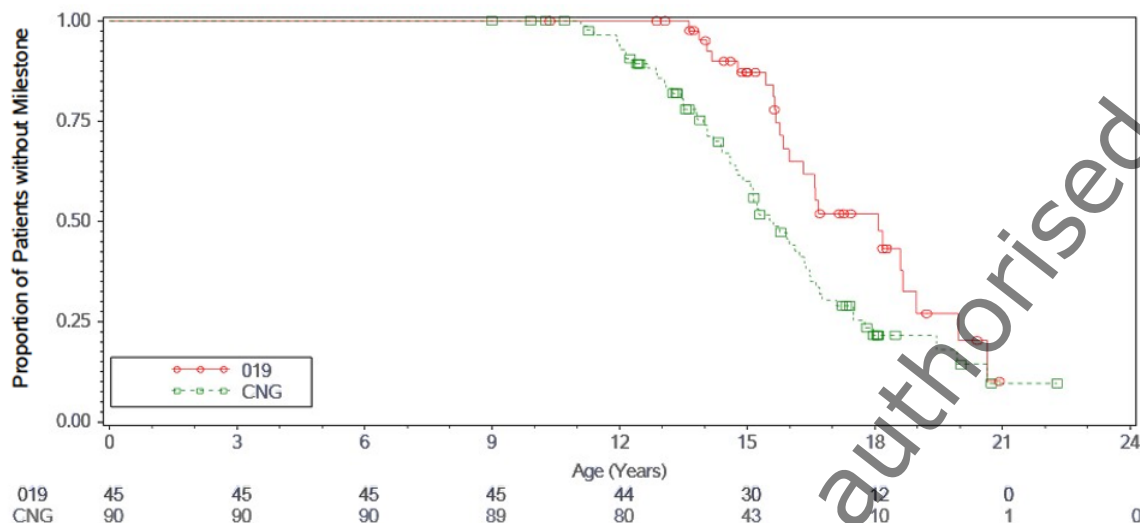
Numbers shown at bottom of graph are numbers of patients at risk.

4.2.3 1:2 Ratio Match

A KM analysis of time to FVC <60% was undertaken using the selected propensity-score criteria (age at first symptom, steroid duration, deflazacort duration), with patients in Study 019 matched in a 1:2 ratio with subjects from CINRG.

When a 1:2 matching ratio was performed, patients in Study 019 still showed marked preservation of pulmonary function (Figure 28), with a median age of 18.1 years for the FVC <60% milestone, in contrast with a median of 15.6 years for CINRG, again echoing the result of the primary match despite the use of the 1:2 ratio.

Figure 28. Kaplan-Meier Plot: Age at % Predicted FVC <60% (Study 019 vs CINRG with Propensity Score Matched Using 1:2 Ratio Model 2a)

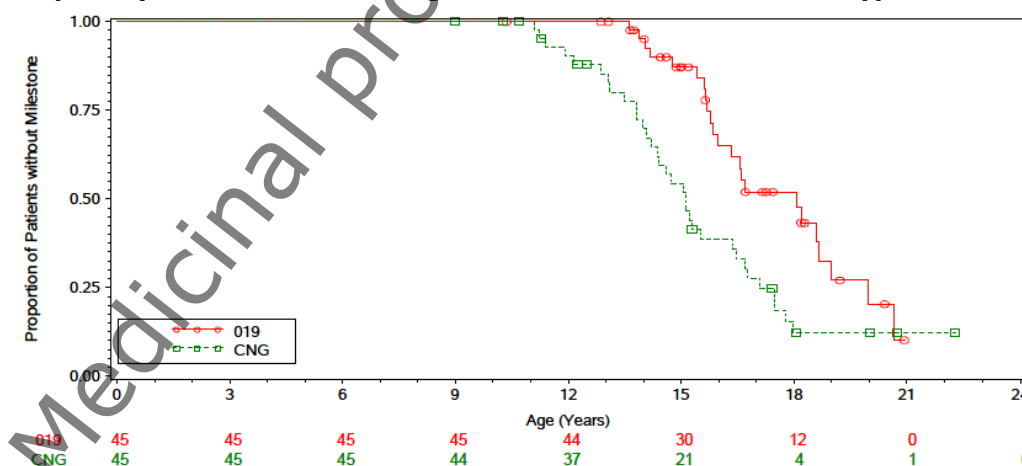


Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital capacity.
 Note: Set 2a of Propensity Score model covariates includes age at first symptom and duration of Deflazacort, and duration of steroid other than Deflazacort
 A total of 45 subjects with recorded values for age at first symptom and age at loss of ambulation who did not experience a decline below one of these FVC milestones prior to Study 019 entry and were matched 2:1 without caliper.
 Numbers shown at bottom of graph are numbers of patients at risk.

4.2.4 Global Match Type

A match was also performed using the selected match criteria (ie, age at first symptom, steroid duration, and deflazacort duration) in a global (optimal) type method. In this analysis, patients in Study 019 again showed preservation of pulmonary function, with a median age of 18.1 years for the percent-predicted FVC <60% milestone, in contrast with a median of 15.1 years for CINRG. This confirmed that whether nearest neighbour or global matching was employed, the results showed a consistent treatment effect for ataluren (Figure 29).

Figure 29. Kaplan-Meier Plot: Age at % Predicted FVC <60% (Study 019 vs CINRG with Propensity Score Matched Using 1:1 Match with Global Match Type Model 2a)



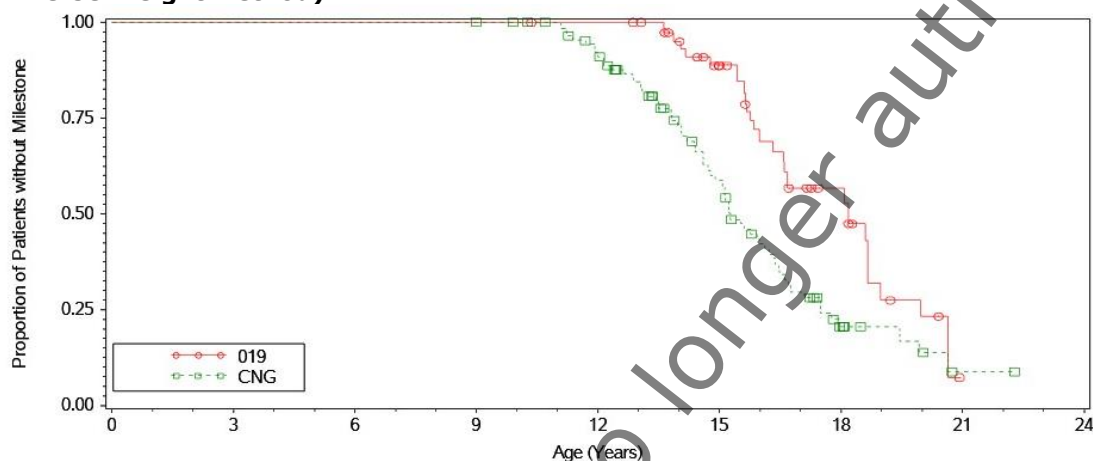
Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital capacity.
 Note: Set 2a of Propensity Score model covariates includes age at first symptom and duration of Deflazacort, and duration of steroid other than Deflazacort
 A total of 45 subjects with recorded values for age at first symptom and age at loss of ambulation who did not experience a decline below one of these FVC milestones prior to Study 019 entry and were matched 1:1 with global match.
 Numbers shown at bottom of graph are numbers of patients at risk.

4.2.5 Inverse Weighting

Under the IPTW method, the average treatment effect of the ataluren-treated group was weighted by the inverse of the propensity score and the CINRG patients were weighted by the inverse of one minus of the propensity score.

A KM analysis of age at percent-predicted FVC <60% found that ataluren treated patients in Study 019 reached that milestone at 18.2 years, in comparison with 15.3 years for their CINRG counterparts. This confirmed that the use of inverse weighting instead of propensity-score matching still yielded a consistent treatment effect for ataluren on pulmonary function (Figure 30).

Figure 30. Kaplan-Meier Plot: Age at % Predicted FVC <60% (Study 019 vs CINRG Using Inverse Weight Method)



Abbreviations: CNG/CINRG, Cooperative International Neuromuscular Research Group; FVC, forced vital capacity.

Note: Set 2a of Propensity Score model covariates includes age at first symptom and duration of Deflazacort, and duration of steroid other than Deflazacort

A total of 45 subjects with recorded values for age at first symptom and age at loss of ambulation who did not experience a decline below one of these FVC milestones prior to Study 019 entry and were matched 1:1 with global match.

The Applicant did not provide number of patients at risk

4.3 The Registry (Study 025o) Allows for Additional Follow-up Time for Study 019 Patients

Among the 45 patients in the matched FVC analysis population for Study 019, 10 patients were enrolled in the post-approval registry Study 025o and had additional long-term FVC data from that study. Of these 10 patients, 8 patients had data allowing for additional follow-up before censoring.

A KM analysis of time to FVC <60% incorporating these additional data points determined that this milestone continued to be reached at a median of 18.1 years among ataluren-treated subjects in Study 019, compared with 15.5 years for CINRG.

4.4 Additional Upper Limb Functional Data is Consistent with Preservation of Function in Non-ambulatory Patients (Study 020e)

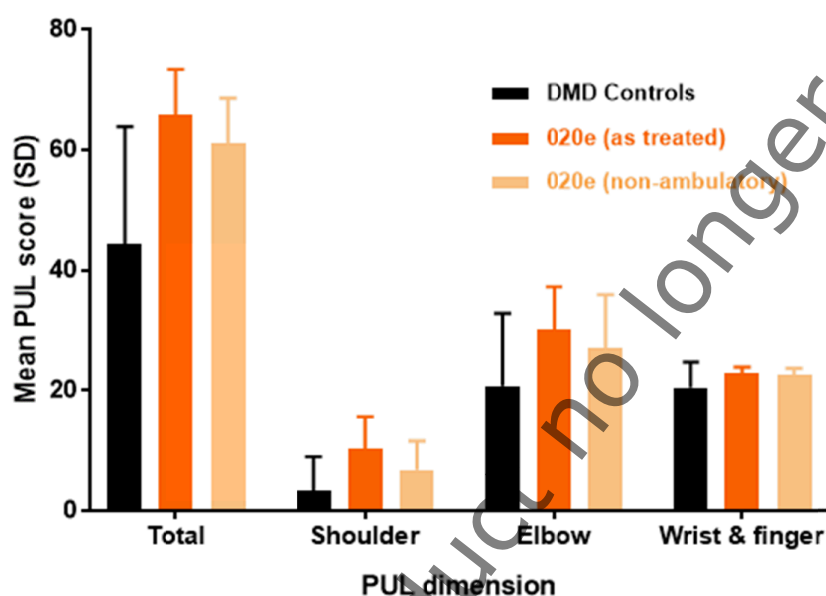
Study 020e “A Phase 3 Extension Study of Ataluren (PTC124) in Patients with Nonsense Mutation Dystrophinopathy” was a Phase 3, international, open-label, single group, extension study of patients who completed the placebo-controlled study PTC124-GD-020-DMD study (Study 020).

An analysis was performed on the performance of the upper limb (PUL) results for the last available assessment for total score and the shoulder, elbow, and wrist and finger dimensions in comparison with natural history controls (Pane 2014) for the As-treated Population and the subset of patients who were non-ambulatory at the time of the last assessment. The mean PUL total score for the last visit was 65.9 among ataluren-treated patients in the As-treated Population between the ages of 13 and 21.9. For the

subset of patients in this age group who were non-ambulatory at their last visit, the mean total last visit PUL score was 61.1. In comparison, the total PUL score for the last visit for DMD natural history controls (a population which included ambulatory and non-ambulatory subjects) was 44.43, suggesting that ataluren treatment is associated with preservation of upper body function.

In DMD, upper limb involvement progresses from proximal to distal, with shoulder function thus affected first, followed by the elbow, and lastly wrist and finger function. Accordingly, when PUL scores were analysed at the dimensional level, a notable separation was observed between ataluren-treated patients and natural history control subjects for the shoulder and elbow, the dimensions most affected in this age group. For the wrist and finger dimension, a smaller separation was observed, reflecting that subjects in the natural history cohort had not yet begun to lose function in this dimension (Figure 31).

Figure 31. Mean Performance of Upper Limb Scores at Time of Last Assessment for Study 20e Patients Versus Duchenne Muscular Dystrophy Natural History Control



Ground #5: A SUBSTANTIAL EXPANSION OF THE ONGOING POST-APPROVAL REGISTRY (STUDY 0250) WILL PROVIDE FURTHER EVIDENCE OF EFFICACY OF ATALUREN IN NON- AMBULATORY PATIENTS

Study PTC124-GD-025o-DMD (Study 025o), the Registry, is the ongoing, observational, multicenter study of patients receiving commercial ataluren (Translarna) in accordance with standard of care. Study 025o, a post-approval commitment and part of the current Translarna risk management plan, was initiated on 30 March 2015 and achieved its target enrolment of 200 patients on 6 March 2018.

It is understood that despite the rigorous methodology applied, the analyses without randomized groups can be associated with uncertainty of the magnitude of the established treatment effect. It is also acknowledged that additional information regarding the effect size on upper limb function would be beneficial. Given the small number of non-ambulatory nonsense mutation DMD patients and the duration of follow-up that would be required to show a treatment effect in this population, the Applicant thus proposes an expansion of the registry Study 025o, to allow for collection of additional long-term data in on-ambulatory patients and prospectively defined analyses in comparison with CINRG natural history data.

Study 025o currently collects information on the effectiveness of ataluren in routine clinical care, with assessments that include the PUL scale and FVC. With the inclusion of 57 newly non-ambulatory subjects aged 13 to 21.9 years, 90% power will be achieved for change from baseline in percent-predicted FVC

over a period of 4 years in comparison with a CINRG natural history control. Considering a potential 15% drop-out rate, an additional 70 non-ambulatory patients would be enrolled to attain the required 57 patients. It is estimated that will require an enrolment period of approximately 2 years, for a total study duration of 6 years.

The primary endpoint to assess the effectiveness of ataluren in non-ambulatory patients will be the change from baseline (defined relative to loss of ambulation) in percent-predicted FVC at Month 48 in non-ambulatory patients. Since Study 0250 does not have a control group, a subset of patients in CINRG database will be identified as the control group in the data analysis using the propensity-score matching method. The change from baseline in percent-predicted FVC at Month 48 for the ataluren-treated non-ambulatory patients will be compared with that of the matching CINRG patients using analysis of covariance. The age at which non-ambulatory patients decline to percent-predicted FVC < 60% and <50% and FVC <1litre will also be compared between ataluren-treated patients and the matched CINRG patients using the KM estimators.

In addition to pulmonary function, the upper body function of the non-ambulatory patients will also be assessed using PUL. The mean and change from baseline in PUL total score and domain subscores will be summarized for non-ambulatory patients. Since there is no natural history database available for the PUL assessment, the PUL total and domain subscores will also be summarized by age groups, and the PUL total scores and the domain subscore for the shoulder dimension of the ataluren-treated non-ambulatory patients between age of 13 to 21.9 years old will be compared with PUL results for untreated patients in the published literature (Pane 2014).

The details of the propensity score matching modeling and the data analysis methods will be prespecified in the Study Protocol and the SAP.

5.2. Scientific Advisory/Expert Group-Neurology consultation

Following a request from the Applicant at the time of the re-examination, the CHMP convened a Scientific Advisory Group (SAG) inviting the experts to provide their views on the CHMP grounds for refusal, taking into account the Applicant's response.

The following questions were adopted in the CHMP 15th-19th September meeting and answered during the SAG on 11 October 2019:

Question 1: In the primary assessment of the current variation, the CHMP was of the opinion that a robust clinically relevant efficacy of ataluren in non-ambulant Duchenne muscular dystrophy (DMD) patients had not been demonstrated by the results of study 019 since the submitted data and analyses suffered from multiple severe methodological issues including critical uncertainties in the way the study was conducted and the comparability of the control group.

a. Please discuss if these methodological issues have been resolved by the argumentation provided by the Applicant (consider in particular the potential selection bias in the comparison to the CINRG controls, and to what extent the few variables used in the propensity score can reflect the severity of disease with sufficient accuracy)

- Generally, the goal of a propensity score model is to achieve conditional exchangeability (treated and non-treated comparable in all features except for exposure/intervention). The main limitation of the approach used in the above procedure is that variable model selection was likely based on data availability in Study019 and Natural history cohorts. According to SAG, the possibility of confounding remains, and it is particularly troublesome in this setting with a modest effect size as showed by the Applicant. Overall, the SAG was not convinced that both matching cohorts were comparable. The construction of the PS model has some methodological limitations as some relevant variables were

not included in the logistic model leading to PS model including steroid regimes (daily vs. intermittent) or posology (cumulative dose of steroids), age at loss of ambulation as indicator of disease severity in addition to age at onset, region of origin, baseline FVC at baseline (unavailable in Study019) or specific genetic mutation. Other variables such as duration of steroids were modelled as categorical variables using cut-offs (<1M 1-12M >12M) instead of a continuous variable. The SAG particularly highlighted the absence of steroid regime and age at loss of ambulation in the model.

- The SAG agrees that the Applicant may have done almost the best with available data. In fact, SAG recognized that the natural history cohort the Applicant used as reference may not be detailed enough (enough variables and measures) to provide an appropriate reference.
- There were concerns about data quality that was thought to be heterogeneous depending on the participating center which was not considered into the model that lead to PS.
- Relative to the participation of different centers, the role of measurement bias was also discussed. It was agreed that there may be different investigators assessing measures in the clinical setting which may introduce a non-differential observational bias.
- Other concerns were that all analyses were post-hoc and therefore, exploratory. In the same line, it was highlighted that the fact that it is unusual that all sensitivity analyses decreased size effect which may invoke a data-driven analyses.

b. If resolved, does the SAG consider that the submitted efficacy data from study 019 are sufficiently robust to establish a clinically relevant efficacy in non-ambulant nmDMD patients?

Overall, the SAG is not convinced about the robustness of efficacy data due to two main reasons.

- First and most important, even though the SAG considered that Applicant tried his best according to available data, there are still relevant methodological issues (please see discussion above) that negatively impact the evaluation of efficacy in non-ambulatory patients.
- Second, efficacy data on non-ambulatory patients was limited to FVC. There was an absence of lung function endpoints other than FVC (PEP, and PCF) and other non-ambulatory assessment (PUL or EK scale) were also missing. The statement done by the Applicant that lung function is the outmost important endpoint in non-ambulatory patients and that there is a linear correlation between lung function and other measures in non-ambulatory patients was not fully endorsed by SAG. However, the SAG overall agrees that a reasonable association and correlation likely exists between lung function endpoints and other non-ambulatory endpoints (upper limb, others). So, the limitation of scarce efficacy data could have been overcome if there were not methodological issues.

Conclusion for Question 1: The SAG is not convinced about the robustness of efficacy data because the analyses suffered from relevant methodological issues. Additionally, the SAG considers that data provided by Applicant in non-ambulatory patients lack some relevant endpoints including measures of upper limb function and ventilatory function other than FVC, endpoints that should have been investigated in this group of patients.

Question 2: Considering the disease mechanism, the course of disease in DMD, the pharmacodynamic effects of ataluren as well as the documented effect in ambulatory patients, which are the arguments for and against expecting a clinically relevant effect in non-ambulatory patients with a more advanced disease stage?

- The SAG agrees that pathophysiology of DMD is the same across the entire disease course. The assumption that an effect on one function is transportable/transferable towards other function ("what

works for leg should work for arm”) is reasonable. The SAG agrees that although loss of ambulation is a relevant milestone, DMD is a continuum and kind of limited muscle function do remain after loss of ambulation but will decrease progressively. Thus, the non-ambulatory group is likely to be heterogeneous with regards to many outcomes (such as motor and respiratory functions). Therefore, some degree of efficacy could be expected after loss of ambulation at least for patients in certain stages. However, the SAG considered that, based on available data during ambulatory phase, it seems impossible to identify these stages at an individual level.

- Overall, the SAG, highlights that some level of restricted efficacy in non-ambulatory stages could be expected. However, it was not clearly documented in the Applicant’s results. Specifically, SAG suggests that other motor function effects (upper limb function) would have been desirable in this particular setting. Alternatively, the SAG considered that some signal in muscle biopsies (specifically by tests other than western blots) could have been useful. In this context, the role of other non-invasive markers such as magnetic resonance imaging was discussed but agreed that at this stage its contribution may not be as relevant as it is for other primary neurodegenerative disorders.
- The SAG discussed about the expected magnitude of effect in later stages and the stage beyond which further efficacy should not be expected. The SAG was of the opinion that there is not enough evidence to provide quantities for these aspects. From Patient’s perspective, any level of efficacy, although not clinically visible nor objectively measurable, would be considered as clinically meaningful.

Conclusion for Question 2: The SAG agrees that it is reasonable to assume that loss of ambulation may not be a signal of loss of efficacy at least for some stages (no patient stratification proposed). However, the SAG could not quantify the expected magnitude of efficacy in non-ambulatory stages that could be considered clinically relevant and could not identify a milestone/stage beyond which further efficacy would not be expected. From Patient’s perspective, any efficacy would be considered as clinically meaningful. Few experts and patients’ representative expressed their concerns on discontinuation of the drug at the time of loss of ambulation.

Question 3: Does the SAG believe a randomised controlled trial investigating efficacy of ataluren compared to standard of care in non-ambulatory nmDMD patients to be feasible in the context of an already approved product in ambulatory patients? What would be relevant and sensitive outcome measures?

The SAG discussed the factors that may hamper feasibility of a trial with ataluren in DMD:

- The current use of ataluren (including relevant off-label use in some EU countries) may complicate the enrolment. In fact, the proposal of a trial design allocating ataluren-treated patients to either continue or discontinue treatment after loss of ambulation was not considered feasible due to the off-label use of the ataluren, and to the existence of competing trials. The idea of running a trial in the US was discussed and was considered possible although with some limitations.
- Ethical reasons according to some SAG members.
- Time-constraints: the trial may take several years to provide results.

The SAG considered that two different situations may need two different settings:

- Continuation of ataluren (frequent situation in EU): the SAG considered that the performance of a RCT in non-ambulatory patients is not feasible. SAG discussed the option of a new open-label

prospective study including treated patients with a historical control as reference with an improved design, a pre-specified statistical plan that improves current methodological issues in presented analyses.

- Initiation of ataluren in naïve patients (rare situation in EU): The Applicant could have performed a RCT. There was not a 100% agreement on the situation. There were experts that consider that the Applicant could explore feasibility of a RCT (two year duration) in some EU countries (NL) or US. Other experts considered that an approach similar to the previous situation was the most feasible option.

Conclusion for Question 3: Overall, the SAG considered that feasibility of randomized placebo-controlled trial (at least in EU) may be limited by the ongoing use of ataluren, ethical concerns and likely time constraints. For assessing B/R of continuation of ataluren, a RCT is considered unfeasible. A potential proposal was a new open-label observational study in non-ambulatory patients with a historical control natural history and registry cohorts as reference. Standardised outcome measures should be agreed between the open-label observational study and natural history studies as much as possible. For assessing B/R of ataluren in naïve patients, the most feasible option is a similar approach, probably more feasible in the US and other countries where ataluren is not commercially available, although the Applicant could explore the feasibility of a RCT.

5.3. Discussion and overall conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the Applicant and considered the views of the SAG. As a response to the grounds for refusal, the Applicant provided further analyses and clarifications during an oral explanation on 15 October 2019. According to the Applicant's position, the selected methodology provided unbiased evidence supporting efficacy in non-ambulatory patients.

Assessment of the response to the grounds for refusal

One fundamental problem with comparing the study population in study 019, namely patients selected to participate in a randomised trial, with the external controls from the CINRG population, namely patients that had not been selected for participation in a randomised trial, is selection bias. This is often a problem that is difficult to resolve as such a selection bias can induce important imbalances between measured and unmeasured covariates. Although measured covariates can be adjusted for in the analysis, the problem of an imbalance in unmeasured covariates is not one that can be as easily resolved,

The Applicant stated that since both studies enrolled patients at dedicated DMD centres in the United States and European Union, this ensures that enrolled patients experienced similar standards of care. This was an unsubstantiated statement and differences in standard of care and outcomes between centres and geographic regions, also in diseases/conditions with highly standardized treatments, are expected.

Compared samples from study 019 (n=45) and the CINRG database (45 and 90) constituted further selection. According to the study report PTC-124-GD-019-DMD, 28 patients lost ambulation during the study. Together with those who were non-ambulatory at study start (n=44) this would add up to 72 patients for additional selection based on availability of data for age at first symptom, and FVC > 60% at study start. Overall 61% of patients discontinued study 019. In the CINRG database there were 418 patients, from which individually matched controls were drawn.

Addressing the selection bias problem analytically, requires accurate measurement of variables that determine selection. If such accurately measured variables are available, the propensity score may be

an appropriate tool to reduce confounding. The choice of method to adjust for the propensity score is unlikely to be of importance, unless there is effect-modification (Lunt, M., et al. (2009). "Different methods of balancing covariates leading to different effect estimates in the presence of effect modification." *Am J Epidemiol* 169(7): 909-917). The propensity score approach is intended to improve the balance of important risk factors between the two groups. That this would "mimic randomisation" is an overly enthusiastic statement. While randomisation creates balance of both measured and unmeasured confounders, the propensity score can only address confounding from adequately measured risk factors. The statement that covariate adjustment is not possible in a KM analysis is correct, but it is unclear why a time-to-event regression model (such as Cox PH regression) would not have been applicable. This is, however, as stated above, likely a minor issue.

The Applicant argued that the selected propensity-score matching criteria effectively control for disease severity and standard of care. This was not substantiated by the arguments put forward.

The process for selection of propensity score model was questionable. Few baseline variables were available. An initial screening of potential confounders should be solely based on clinical and biological considerations and current understanding of causal relations. There are good arguments for including all the potential confounders in the propensity score model (Austin, P. C. (2011). "An Introduction to Propensity Score Methods for Reducing the Effects of Confounding in Observational Studies." *Multivariate Behav Res* 46(3): 399-424). The exercise of identifying potential confounders should not be restricted by which variables are available in the dataset. This is important in order to identify potentially important confounders that are unmeasured. Using tools such as directed acyclic graphs (DAG) may be helpful. It should also be noted that it is rarely necessary to restrict the number of covariates in the propensity score model.

It was agreed that rate of disease progression in DMD is a function of underlying disease severity and standard of care. Disease severity is in published literature clearly related to age at loss of ambulation (LoA). This is because LoA is an important milestone at about half of the expected lifetime, and it correlates with later disease events. Thus, it captures more of the effect of identified and unknown disease modifiers than does age at first symptom. It was noted that age at first symptom for the 45 patients in Study 019 was 3.78 years on average while age at diagnosis in the overall population of Study 019 was 3.58 years on average. It was agreed with the Applicant that for standard of care corticosteroid treatment should be included. A recent prospective cohort study based on the CINRG population, shows that deflazacort might be more effective than other steroids (McDonald et al (2018). "Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study" *Lancet* 391:451-461). Other standard of care factors of significance are scoliosis treatment, non-invasive ventilation and early medication of heart failure.

Having comparable propensity score distributions after matching is the aim of matching. What could be interesting is the degree of lack of overlap of the distributions of the estimated propensity score for Study 019 patients and the totality of CINRG populations. Few covariates were included in the model, the set of treated patients to match was small, and the pool of untreated patients used for comparison was much larger. It was noted that there was a good degree of proximity in propensity scores between matched pairs, but, this did not address the fundamental uncertainties regarding the model.

The approach used for balancing diagnostics was not optimal. It is an important step in the analysis to examine whether the propensity score model has been adequately specified. An expected presentation would have been the standardized difference to compare the mean of continuous and binary variables between treatment groups without being biased by the sample size. Arguments based on absence of statistical significance are not appropriate.

The Applicant stated that the models 3 through 5, which added age at study entry and TFT results to the propensity score model, proved problematic due to a pattern of informative missingness in CINRG. It

should be noted that the results presented for age at LoA were based on 31 exposed patients at risk, and results for age at percent predicted FVC <60% were based on 45 exposed patients at risk. There were in total 64 non-ambulatory patients in study 019. There were clear indications of problematic and extensive missingness that was informative of the outcome and differing between 019 and CINRG. Sensitivity analyses to explore boundaries for the bias this missing data problem could introduce were not presented.

The added value of propensity score weighting (using the same selected propensity-score criteria) on matching method was not clearly reported. It was also unclear how many subjects of the untreated group were used in this analysis. Nevertheless, propensity score weighting is very sensitive to the misspecification of the model and could yield biased treatment effect when score weights are estimated from mis-specified models. The weighting method performed instead of matching does not address the uncertainties regarding the propensity score estimation selection model, unmeasured confounders or the flaws in the study design.

In accordance with Article 62(1) of Regulation (EC) No 726/2004, data from study 020e could not be assessed in the context of a re-examination procedure since they were not available at the time of the initial CHMP opinion.

The Applicant proposed an expansion of the ongoing post-approval observational study 025o to provide further evidence of efficacy of ataluren in non-ambulatory patients. The primary endpoint would be the change from baseline (defined relative to loss of ambulation) in percent-predicted FVC at month 48 in non-ambulatory patients. A subset of patients in CINRG database would be identified as the control group in the data analysis using the propensity-score matching method. In addition, the upper body function would also be assessed. This could provide further exploratory information on the effect of ataluren in non-ambulant patients. However, in such a study, it is very difficult to have appropriate robust confirmatory efficacy data. Handling bias to the highest extent possible in estimating efficacy is very challenging and there may be an apprehension for data-driven decisions. It is also very important to assess carefully whether the assumption of strong ignorability could be met before the application of propensity score techniques.

Conclusion

The data provided for the re-examination of the grounds for refusal were claimed by the Applicant to show that ataluren-treated subjects reach an FVC <60% at the age of 18.1 years, while matched historical controls reach this limit at the age of 15.5 years. Notable issues with selection bias and missing data precluded a sufficiently robust comparison to conclude on whether there was true efficacy of ataluren provided also after loss of ambulation, or if the difference seen in the age for initiation of respiratory decline, was mainly due to unknown, unmeasured and/or uncontrolled characteristics of the compared study groups, and/or were the result of treatment with ataluren provided before loss of ambulation. The strength of evidence provided was not sufficient to outweigh these concerns that benefit in non-ambulant patients has not been robustly demonstrated. Data were not sufficiently robust to support an indication in non-ambulatory patients, and the wording of the indication should therefore presently remain unchanged.

5.4. Risk Management Plan

The CHMP and the PRAC having considered the data submitted in the application were of the opinion that due to the concerns identified with this application, the risk management plan for Translarna cannot be agreed.

5.5. Update of the Product information

In relation to the new claimed indication, sections 4.1, 4.2, 4.8, 5.1 of the SmPCs have been proposed to be updated by the Applicant. In light of the negative recommendation, the proposed changes to the SmPC and Package Leaflet for Translarna could not be agreed.

5.5.1. User consultation

No justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the Applicant. However, the changes to the package leaflet are minimal and do not require user consultation with target patient groups.

5.5.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Translarna is included in the additional monitoring list as the product has a conditional approval.

Therefore, the summary of product characteristics and the package leaflet include 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.

6. Updated Benefit-risk balance (after re-examination)

6.1. Therapeutic Context

Ataluren is an oral drug which is claimed to enhance ribosomal read-through of nonsense mutations in messenger RNA (mRNA) resulting in full-length protein production.

6.1.1. Disease or condition

DMD is a rare (1 in 3500 male newborn), disabling and ultimately fatal X-linked genetic disorder that primarily affects males (Emery 1991, Worton 2001, Khurana 2003). The disease is caused by mutations in the gene for dystrophin, a protein that is critical to the structural stability of myofibers in skeletal, diaphragmatic and cardiac muscle and is also of importance for the central nervous system and smooth muscles (Worton 2001, Khurana 2003). Approximately 13% of patients with DMD have the disorder due to a nonsense mutation which introduces a premature stop codon in the messenger mRNA for dystrophin, leading to non-functional protein.

Duchenne muscular dystrophy is a progressive and ultimately fatal disease characterised by muscle degeneration and atrophy. DMD patients generally lose ambulation before age of 12 and develop respiratory or cardiac complications in their late teenage years. Advances in medical management, including corticosteroid use, contracture treatment, cardiac therapy, and ventilatory support, have increased life expectancy for young men with DMD. Although individuals with DMD begin to experience weakness in the upper limbs when they are still ambulant, muscle strength and function of upper extremities is maintained for variable periods of time once boys with DMD become non-ambulatory. Maintaining this function or slowing the progression leading to their loss (essential for functional activities such as self-feeding or ability to perform positional transfers) is likely to have a significant impact on their activities of daily living and on their overall quality of life.

Pulmonary function is known to decline over the second decade of life in boys with DMD and this decline is a major source of disability and shortened life span. As the disease progresses, the myocardium fails

to meet physiological demands and clinical heart failure develops. The failing myocardium is also at risk of life-threatening rhythm abnormalities. Cardiovascular complications are a leading cause of disease-related morbidity and mortality among individuals with DMD.

6.1.2. Available therapies and unmet medical need

Ataluren is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 2 years and older. Corticosteroids are also used to temporarily reduce the decline in motor function. For the non-ambulatory patients, the focus of treatment is on the prevention and management of complications.

6.1.3. Main clinical studies

The proposal to include non-ambulatory subjects with nmDMD in the indication was claimed based on results of study 019, a non-randomised, open-label, uncontrolled, multicentre, extension study evaluating primarily the tolerability and long-term safety of ataluren over approximately 240 weeks of use. 90 out of 96 subjects in study 007 rolled-over to study 019. 64 of these were non-ambulatory. The dose regime of ataluren was the same as that approved for the ambulatory patients aged >2 years of age. Secondary outcomes included spirometry variables and the EK in non-ambulatory patients, assessed at screening (visit 1), week 48 (visit 6), and week 48 through week 240 or premature discontinuation. 45 non-ambulatory patients had non-missing information on age at first symptom and age at percent-predicted FVC <60%. They formed the basis for the main analyses. The efficacy outcomes were compared to historical controls, derived from the CINRG-database. A propensity-score approach was made to adjust the comparisons for confounding.

6.2. Favourable effects

In the populations matched using age at first symptom, steroid duration, and deflazacort duration, 23 (51.1%) patients in Study 019 and 30 (66.7%) patients in CINRG experienced a decline below the 60% percent-predicted FVC threshold. The median age for this milestone was 18.1 years in Study 019 and 15.5 years in CINRG, suggesting a delay in progression of 2.6 years with ataluren treatment. Regarding FVC < 1litre, this was reached by 10.8 and 42.8% in study 019 and CINRG, respectively.

6.3. Uncertainties and limitations about favourable effects

One fundamental problem when comparing the study population in Study 019, patients selected to participate in a randomised trial, with the external controls from the CINRG population, patients that had not been selected for participation in a randomised trial, is selection bias. This is often a methodological problem that is difficult to resolve. Differences in standard of care and outcomes between centres and geographic regions, also in diseases/conditions with highly standardized treatments, are expected. Compared subsets from study 019 (n=45) and the CINRG database (n=45 and n=90) constitutes further selection.

To address the selection bias problem analytically requires accurate measurement of variables that determine selection. If such accurately measured variables are available, the propensity score may be an appropriate tool to reduce confounding. While randomisation creates balance of both measured and unmeasured confounders, however, the propensity score can only address confounding from adequately measured risk factors. The Applicant argued that the selected propensity-score matching criteria effectively control for disease severity and standard of care. This was not substantiated by the arguments put forward.

The process for selection of propensity score model was questionable. Few baseline variables were available. An initial screening of potential confounders should be solely based on clinical and biological considerations and current understanding of causal relations. There are good arguments for including all the potential confounders in the propensity score model. The exercise of identifying potential confounders should not be restricted by which variables are available in the dataset. This is important in order to identify potentially important confounders that are unmeasured. It should also be noted that it is rarely necessary to restrict the number of covariates in the propensity score model.

The approach used for balancing diagnostics to assess if the propensity score model has been adequately specified was not optimal. An expected presentation would have been the standardized difference to compare the mean of continuous and binary variables between treatment groups without being biased by the sample size. Arguments based on absence of statistical significance were not appropriate.

The Applicant states that the models 3 through 5, which added age at study entry and TFT results to the propensity score model, proved problematic due to a pattern of informative missingness in CINRG. It should be noted that the results presented for Age at LoA were based on 31 exposed patients at risk, and results for Age at percent predicted FVC <60% are based on 45 exposed patients at risk. There were in total 64 non-ambulatory patients in study 019. There were clear indications of problematic and extensive missingness that was informative of the outcome and differing between 019 and CINRG. Sensitivity analyses to explore boundaries for the bias this missing data problem could introduce were not presented.

6.4. Unfavourable effects

No new safety concerns were identified in study 019.

6.5. Uncertainties and limitations about unfavourable effects

Some adverse drug reactions (ADR) may have a greater impact on patients in a more advanced stage of the disease. Nausea (a common ADR) and vomiting (a very common ADR) bear a greater risk of aspiration in patients with impaired ability to cough and to control movements. The seriousness of this event increases in more advanced stages of the disease, when respiratory muscles are affected, and scoliosis has progressed to a degree that impairs cough and respiratory function. This may not only increase the risk for aspiration, but there may also be more serious consequences of aspiration in advanced disease stages. Aspiration is a life-threatening event, especially in patients with respiratory insufficiency. Aspiration is also not necessarily clinically overt but may be seen as recurrent lower respiratory tract infections and progression of respiratory impairment. In the safety data there is a case of fatal aspiration that has been stated as "not related" to ataluren. This categorisation is questioned.

6.6. Effects Table

Effect	Short description	Unit	Treatment (ataluren)	CINRG selected control	Uncertainties / Strength of evidence	References
Favourable Effects						
FVC <1L	Decline of FVC to <1L	%	10.8%	42.8%	-Unclear matching -Baseline differences in corticosteroids use and FVC -Difference in follow up time -Results not stat. sig. -Exploratory rather than confirmatory	Study 019

FVC <60%	Age at % predicted FVC <60%, indicative for mechanic ventilation	Median age	18.1 years	15.5 ^a (p=0.037)/16 ^b years (p=0.082)	- Match naïve population includes high dose ataluren. - Extrapolation beyond 14 years and other variables unknown - Validity of model questioned - Effect not shown for age at % predict FVC <50%	Study 019, 2 nd RSI
FVC<1L	Number of patients with FVC<1L, indicative for time to death	n (%)	1 (2.2%)	9 (20%)	Median age not determined. >80% of patients censored in both groups	Study 019, 2 nd RSI)
Unfavourable Effects						
Nausea, cough, vomiting	Ambulatory vs non-ambulatory	(%)	4%, 10%, 32% vs 11%, 25%, 27%		AEs related to either ataluren or disease progression	Study 019

6.7. Benefit-risk assessment and discussion

6.7.1. Importance of favourable and unfavourable effects

A delay in the progression of respiratory impairment in patients with DMD would be of clinical importance. The Applicant claimed a delay in the progression of respiratory impairment in patients treated with ataluren, as compared to matched historical controls. However, methodological issues did not allow a sufficiently robust conclusion that effects were related to treatment and not due to other factors.

In addition, no data reflecting upper limb or other non-ambulation motor functions were submitted. In this respect, other relevant outcomes for the patients such as residual leg function, residual upper limb function or cardiac function would also have been important as supportive evidence.

Nausea, cough, and vomiting are known adverse events of ataluren, which may be of higher importance in respiratory compromised nmDMD patients considering the increased risk for aspiration.

6.7.2. Balance of benefits and risks

The data provided in this procedure, and specifically within the grounds for re-examination, were claimed by the Applicant to show efficacy in ataluren-treated non-ambulant subjects. Notable issues with selection bias and missing data precluded a sufficiently robust comparison to conclude on whether there was true efficacy of ataluren provided also after loss of ambulation, or if the difference seen in the age for initiation of respiratory decline, was mainly due to unknown, unmeasured and/or uncontrolled characteristics of the compared study groups, and/or are the result of treatment with ataluren provided before loss of ambulation. Data were not sufficiently robust to support a full indication in non-ambulatory patients, and the wording of the indication should therefore presently remain unchanged.

6.7.3. Additional considerations on the benefit-risk balance

In addition to discussing the grounds for refusal, the *ad hoc* SAG group was asked to consider arguments for and against expecting a clinically relevant effect in non-ambulatory patients with a more advanced disease stage taking into account the disease mechanism, the course of disease in DMD, the pharmacodynamic effects of ataluren and the documented effect in ambulatory patients.

The SAG was of the opinion that the pathophysiology of DMD is the same across the entire disease course. The assumption that an effect on one function is transportable/transferable towards other function was considered as reasonable. The SAG agreed that although loss of ambulation is a relevant milestone, DMD is a continuum and muscle function does remain after loss of ambulation but will decrease progressively. Thus, the non-ambulatory group is likely to be heterogeneous with regards to many outcomes (such as motor and respiratory functions). Therefore, some degree of efficacy could be expected after loss of ambulation at least for patients in certain stages. Similar positions were put forward by the Applicant at the oral explanation held in front of the CHMP stating that patients retain, after loss of ambulation, sufficient muscle tissue for dystrophin restoration via ataluren to have clinically meaningful impact on disease progression.

The CHMP agreed that loss of ambulation represents an arbitrary milestone for effects of a disease-modifying therapy and acknowledged that some effect would be expected also in non-ambulatory patients based on the argumentation put forward by the SAG and the Applicant. However, since the efficacy of ataluren is mainly documented by the 6MWD, it is not possible to quantify and characterize the expected effect in non-ambulatory patients. Therefore, whether the effect of ataluren translates into a clinically meaningful effect needs to be supported by reliable clinical data.

The currently approved indication for Translarna is;

"Translarna is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 2 years and older (see section 5.1). Efficacy has not been demonstrated in non-ambulatory patients."

The Applicant's proposal to extend the indication to non-ambulatory patients was not accepted (see section 6.7.2). The CHMP discussed whether the following sentence of the approved indication '*Efficacy has not been demonstrated in non-ambulatory patients*' could be deleted. This was not considered as acceptable in the context of the current procedure since the submitted data were not able to support any changes to the wording of the indication.

6.8. Conclusions

The overall B/R of Translarna remains unchanged. Data presented on efficacy in non-ambulant DMD were not sufficiently robust to support an extension of the indication to include non-ambulatory patients, and the wording of the indication should therefore presently remain unchanged.

7. Recommendations following re-examination

Final outcome

Based on the arguments of the Applicant and all the supporting data on quality, safety and efficacy, the CHMP re-examined its initial opinion and in its final opinion considers the following variation not acceptable and therefore refuses by consensus, the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation rejected		Type
C.I.6.a	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II

Extension of Indication to include non-ambulatory patients with Duchenne muscular dystrophy; This variation additionally presents, as supportive data, the final results of the long term clinical study PTC-124-GD-019-DMD (an Open-Label Study for Previously Treated Ataluren (PTC124) Patients with Nonsense Mutation Dystrophinopathy), submitted in line with the requirements of the Article 46 of Regulation (EC) No 1901/2006.

Due to the methodological flaws of study PTC-124-GD-019-DMD, the SmPC and the Package Leaflet were not updated to include these results, and consequently no update of the RMP was required.

Grounds for refusal:

The CHMP was of the opinion that robust clinically relevant efficacy of ataluren in non-ambulant Duchenne muscular dystrophy (DMD) patients has not been demonstrated. The methodological issues concerning study conduction and comparability of the groups remained after the re-examination procedure. Therefore, the CHMP concluded that the indication of ataluren should not be extended to the non-ambulant Duchenne muscular dystrophy (DMD) patients.

The CHMP has refused the variation to the terms of the marketing authorisation.

8. 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 non-ambulatory patients with Duchenne muscular dystrophy; This variation additionally presents, as supportive data, the final results of the long term clinical study PTC-124-GD-019-DMD (an Open-Label Study for Previously Treated Ataluren (PTC124) Patients with Nonsense Mutation Dystrophinopathy), submitted in line with the requirements of the Article 46 of Regulation (EC) No 1901/2006.

Summary

Please refer to the Scientific Discussion of Ataluren EMEA/H/C/002720/II/0047.