22 May 2014
EMA/369266/2014
Committee for Medicinal Products for Human Use (CHMP)

Translarna

(ataluren)

Procedure No. EMEA/H/C/002720

Applicant: PTC Therapeutics Limited

Assessment report for initial marketing authorisation application

Assessment report as adopted by the CHMP with all commercially confidential information deleted

7 Westferry Circus ● Canary Wharf ● London E14 4HB ● United Kingdom
Telephone +44 (0)20 7418 8400 **Facsimile** +44 (0)20 7523 7455
E-mail info@ema.europa.eu **Website** www.ema.europa.eu

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List of abbreviations

6MWD	6-minute walking distance
6MWT	6-minute walking test
AUC	area under curve
ACTH	adrenocorticotrophic hormone
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AP	alkaline phosphatase
AST	aspartate aminotransferase
BCRP	breast cancer resistant protein
BCS	biopharmaceutics classification system
BID	twice a day
BUN	blood urea nitrogen
CF	cystic fibrosis
CFTR	cystic fibrosis transmembrane conductance regulator
Chol	cholesterol
cITT	corrected intention to treat (population)
CK	creatine kinase
CNS	central nervous system
ECG	electrocardiogram
EC	European Commission
EU	European Union
DBMD	Duchenne/Becker muscular dystrophy
DMC	data monitoring committee
DMD	Duchenne muscular dystrophy
DMF	*N*,*N*-dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
DSC	differential scanning calorimetry
EC	European Commission
EU	European Union
F	female
GC	gas chromatography
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
Gluc	Glucose
GMP	Good Manufacturing Practice
GRAS	generally recognised as safe
Hb	haemoglobin
Hct	haematocrit
HDPE	high density polyethylene
HEK293	human embryonic kidney (cells)
hERG	human ether-a-go-go related gene
HPLC	high performance liquid chromatography
HRQL	health-related quality of life
ICH	International Conference on Harmonization (of technical requirements for registration of pharmaceuticals for human use)
IP	intraperitoneal
IR	infra-red spectroscopy
ITT	intention-to-treat (population)
IVR/IWR	interactive voice response/interactive web response (system)
KF	Karl-Fischer titration
LD50	lethal dose, 50%
LOCF	last observation carried forward
LOEL	low-observed-effect level
M	male
MCH	mean corpuscular haemoglobin
MCHC	mean corpuscular haemoglobin concentration

MCID	minimal clinically important difference
MCV	mean corpuscular volume
MEFs	mouse embryonic fibroblasts
MMRM	mixed-model repeated-measures
mRNA	messenger ribonucleic acid
nm	non-sense mutation
NMR	nuclear magnetic resonance spectroscopy
NOEL	No-observed-effect level
NOAEL	No-observed-adverse-effect level
OAT	organic anion transporter
PBMC	peripheral blood mononuclear cells
PBT	persistent, bioaccumulative and toxic
PCR	polymerase chain reaction
PD	pharmacodynamics
PE	polyethylene
PedsQL	paediatric quality of life
Ph. Eur.	European Pharmacopoeia
PIB	powder in bottle
PK	pharmacokinetics
PPI	proton pump inhibitors
PTT	partial thromboplastin time
QC/QA	quality control/quality assurance
RBC	red blood cells
RH	relative humidity
RMP	risk management plan
RNA	ribonucleic acid
ROI	residue on ignition
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	summary of product characteristics
TFTs	timed function tests
TGA	thermogravimetric analysis
TID	three times a day
TSQM	Treatment Satisfaction Questionnaire for Medication
UGT	uridine diphosphate glucuronosyltransferase
UV	ultra-violet spectroscopy
Vss	volume of distribution at steady state
WBC	white blood cells
XRPD	X-ray powder diffraction

1. Background information on the procedure

1.1. Submission of the dossier

The applicant PTC Therapeutics Limited submitted on 29 October 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Translarna, through the centralised procedure falling within the Article 3(1) and point 4 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 April 2012.

The applicant applied for the following indication:

Treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in patients aged 5 years and older

The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing.

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

Following the CHMP positive opinion on this marketing authorisation, the Committee for Orphan Medicinal Products (COMP) reviewed the designation of Translarna as an orphan medicinal product in the approved indication. The outcome of the COMP review can be found on the Agency's website: ema.europa.eu/Find medicine/Rare disease designations.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that ataluren was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0202/2012 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0202/2012 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.

Applicant's request(s) for consideration

Conditional Marketing Authorisation

The applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14(7) of the above mentioned Regulation based on the following claim(s):

- The product will address unmet medical need in a life-threatening and chronically debilitating condition where no satisfactory methods of treatment exist.
- The risk-benefit balance of the product is positive.
- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required.
- It is likely that the Applicant will be able to provide comprehensive data based on confirmatory study in nmDMD patients.

New active Substance status

The applicant requested the active substance ataluren contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Protocol Assistance

The applicant received Protocol Assistance from the CHMP on 19 July 2007 and on 24 May 2012. The Protocol Assistance pertained to clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Almac Pharma Services Ltd.
Seagoe Industrial Estate
Craigavon
Co. Armagh BT63 5UA
United Kingdom

1.3. Steps taken for the assessment of the product

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

Rapporteur: Johann Lodewijk Hillege

Co-Rapporteur: Concepcion Prieto Yerro

CHMP Peer reviewer: Ian Hudson

- The application was received by the EMA on 29 October 2012.
- The procedure started on 21 November 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 12 February 2013. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 9 February 2013.
- During the PRAC meeting on 4-7 March 2013, the PRAC adopted an RMP Advice and assessment overview.
- During the meeting on 21 March 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 March.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 23 July 2013.
- The Integrated Inspection Report (IIR) of the inspections carried out at the following site(s): Clinical Investigator sites in UK and USA, Sponsor site in USA and Central Pathology lab in USA, between 2 April and 7 May 2013 was issued on 5 July 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 29 August 2013.
- During the PRAC meeting on 2-5 September 2013, the PRAC adopted an RMP assessment report.
- During the CHMP meeting on 19 September 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 21 October 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 5 November 2013.
- During the PRAC meeting on 4-7 November 2013, the PRAC adopted an RMP assessment report.
- During a meeting of a SAG on 5 December 2013, experts were convened to address questions raised by the CHMP.
- During the PRAC meeting on 2-5 December 2013, the PRAC adopted an RMP Advice and assessment overview.
- During the CHMP meeting on 17 December 2013, outstanding issues were addressed by the applicant during an oral explanation.
- During the meeting on 23 January 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a negative opinion for granting a Marketing Authorisation to Translarna.

1.4. Steps taken for the re-examination procedure

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

Rapporteur: Martina Weise

Co-Rapporteur: Greg Markey

- The applicant submitted written notice to the EMA on 28 January 2014 to request a re examination of Translarna CHMP opinion of 23 January 2014.
- During its meeting on 17-20 February 2014, the CHMP appointed Martina Weise as Rapporteur and Greg Markey as Co-Rapporteur.
- The applicant submitted the detailed grounds for the re-examination on 25 March 2014. The re-examination procedure started on 26 March 2014.
- The Rapporteur's Assessment Report was circulated to all CHMP members on 17 April 2014. The Co Rapporteur's Assessment Report was circulated to all CHMP members on 22 April 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's detailed grounds for re-examination to all CHMP members on 8 May 2014.
- During the CHMP meeting on 19-22 May 2014, the detailed grounds for re-examination were addressed by the applicant during oral explanations before the CHMP.
- During the meeting on 19-22 May 2014, the CHMP, in the light of the scientific data available and the scientific discussion within the Committee, the CHMP re-examined its initial opinion and in its final opinion concluded that the application satisfied the criteria for authorisation and recommended the granting of the conditional marketing authorisation.

2. Scientific discussion

2.1. Introduction

Duchenne muscular dystrophy (DMD) is a rare (1 in 3500 male newborns), 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].

DMD is caused by several types of mutations in the dystrophin gene such as deletions, insertions and point mutations. Approximately 13% of patients with DMD have the disorder due to a nonsense mutation [Dent 2005]. A nonsense mutation is a change in the nucleotide sequence of DNA that is transcribed into a premature stop codon in the messenger RNA (mRNA) for dystrophin. This stop codon causes the ribosome complex to terminate translation prematurely and results in a truncated, non-functional protein.

The overall prevalence of DMD in the European Union (EU) is of the order of 0.37 per 10,000 [Orphanet 2011], accounting for approximately 18,600 individuals (current EU population estimated at 503,500,000) [Eurostat 2012]. Based on the estimation that in about 13% of all DMD

patients the disease is due to a nonsense mutation (nmDMD) [Dent 2005], it is estimated that there are approximately 2,400 patients with nmDMD in the EU.

The majority of genetic defects in subjects with Duchenne and Becker muscular dystrophy are large deletions or insertions in the dystrophin gene. Point mutations leading to a nonsense codon are relatively rare and are found in about 7-13% of the DMD/BMD patient population. In DMD the disease is caused by the lack of a functional dystrophin - a structural protein from the sarcoglycan complex important for stability of skeletal and cardiac muscle cell, but also expressed in the CNS and smooth muscle. The concept of treating DMD subjects with a nonsense mutation is to promote production of a full-length dystrophin protein and hence restore its function in muscle cells.

There are no curative therapies available for DMD and the current management of the disease is based on prevention and management of complications [Bushby 2010]. Corticosteroids (e.g. prednisone or deflazacort) are the only pharmacologic therapy that have been demonstrated to temporarily reduce the decline in motor function in patients with DMD [Mendell 1989, Griggs 1991, Fenichel 1991a, Fenichel 1991b, Biggar 2001, Beenakker 2005a, Biggar 2006, Pradhan 2006].

Ataluren is a first-in-class oral drug which is claimed to enhance ribosomal read-through of non-sense mutations in different genes. The mode of action of ataluren is believed to be related to the ability of this compound to interfere with the ribosomal translational machinery in such a way that premature nonsense stop codons in the mRNA are read through by the translational machinery and this results in the translation of the entire mRNA and hence production of a full-length protein product.

The applicant applied for the following indication:

Translarna is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in patients aged 5 years and older (see section 5.1).

The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing (see section 4.4).

The recommended dose of ataluren is 40 mg/kg/day, divided in 3 doses (10 mg/kg in the morning, 10 mg/kg at midday and 20 mg/kg in the evening) within 30 minutes of a meal.

2.2. Quality aspects

2.2.1. Introduction

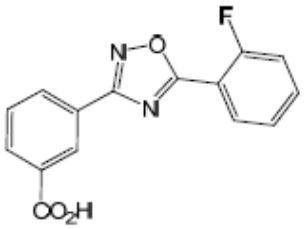
The finished product is presented as granules for oral suspension containing 125, 250, or 1000 mg of Ataluren as active substance.

Other ingredients are: Polydextrose (E1200), polyethylene glycol, poloxamer, mannitol (E421), crospovidone, hydroxyethyl cellulose, artificial vanilla flavour, colloidal silicon dioxide (E551) and magnesium stearate.

The product is available in child-resistant heat-sealed laminated aluminium foil sachets.

2.2.2. Active Substance

The chemical name of Ataluren is 3-[5-(2-fluorophenyl)-1,2,4-oxadiazol-3-yl]-benzoic acid and has the following structure:



The structure of Ataluren was unambiguously confirmed by ^{1}H and ^{13}C NMR, UV spectroscopy, IR spectroscopy, mass spectrometry and elemental analysis. Physical properties were investigated using DSC, TGA, XRPD, KF (to determine water content and hygroscopicity) and particle size distribution.

Ataluren is a white to off-white non-hygroscopic crystalline solid, practically insoluble in pH 1 and sparingly soluble at pH 6.6 in aqueous medium. Solubility is much higher in aqueous borate buffer at pH 8 due to the carboxylic acid functionality. Ataluren is also slightly soluble in acetonitrile and ethanol and freely soluble in DMSO, 1,4-dioxane and DMF. Although dosed as a suspension, the active substance is milled to increase solubility *in vivo*.

Ataluren is achiral. Polymorphism has been observed for Ataluren. The most thermodynamically stable form is routinely made by the proposed manufacturing process.

Manufacture

Ataluren is synthesized from well-defined starting materials with acceptable specifications. Enough of the manufacturing process is described and the physicochemical properties of the active substance are well controlled by the process. A particle size reduction step is required to ensure robust dissolution following formulation. Detailed information about the manufacturing process and process development has been provided. Since the manufacturing process is considered as standard, validation will be performed ahead of release of commercial supplies. A validation protocol was provided. Separate manufacturing sites are used which carry out identical processes with the exception of differences in scale.

The manufacturing process is adequately described. The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Impurities present at higher than the qualification threshold according to ICH Q3A were qualified by toxicological and clinical studies and appropriate specifications have been set.

All relevant impurities, including genotoxins, degradation products, by-products derived from impurities in the starting materials, synthetic intermediates, reaction by-products and residual solvents have been appropriately characterised and are controlled by the active substance specifications. Sufficient information on two genotoxic impurities is provided and these are controlled well below the TTC limit. The overall control strategy is traditional and includes adherence to process description parameters, a series of in-process controls during each synthetic step, appropriate specifications for starting materials, intermediates, solvents and reagents, and active substance release testing. Therefore, the manufacturer has good control over the

manufacturing process and the described control strategy is considered adequate to ensure the required quality active substance.

Specification

The active substance specification includes tests for appearance, identity (IR), assay (HPLC), impurities (HPLC), residual solvents (GC), water content (KF), heavy metals (Ph. Eur.), residue on ignition (Ph. Eur.) and particle size distribution (laser diffraction).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Batch analysis data from 21 batches of active substance from the proposed manufacturers on commercial scale are provided. Batch analysis on a further 11 batches ranging from development scale to commercial scale from a previous (no longer used) manufacturer are also provided as supporting data. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on three commercial batches of active substance from one proposed manufacturer, and three pilot scale batches from the other proposed manufacturer, stored in the intended commercial package for up to 48 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. Additionally, stability data on six additional pilot scale batches of active substance from a previous (no longer used) manufacturer stored in the intended commercial package for up to 60 months under long term conditions at 25 ºC / 60% RH and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided as supportive data. No changes to any of the measured parameters were observed over the course of the studies under either long term or accelerated conditions.

The active substance was also exposed to thermal, humidity, photolytic, acidic, basic, and oxidative stress conditions following ICH guideline Q1B. These studies further establish the stability of Ataluren and demonstrate that the analytical methods are stability indicating.

The parameters tested are the same as for release with the omission of those unaffected by storage (heavy metals, ROI and residual solvents) and the addition of microbial testing. The analytical methods used were the same as for release.

The stability results indicate that the drug substance manufactured by the proposed suppliers is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

2.2.3. Finished Medicinal Product

Pharmaceutical development

The objectives of formulation development were to develop an immediate release solid oral dosage form of Ataluren suitable for consumption by paediatric patients and young adults. After initial clinical studies using powder in bottle formulation, granules for suspension were selected as the commercial dosage form since these would allow reconstitution in liquid media (water, milk, fruit juice) or semi-solid media (yoghurt, pudding, or apple sauce) for ease of administration to the youngest patients.

The active substance shows pH dependent dissolution characteristics due to the ionisable carboxylic acid group, being practically insoluble in acidic or neutral pH and soluble in basic aqueous media. It has been shown to be highly permeable in *in vitro* assays (BCS class II). Ataluren has a bitter taste. Excipients were chosen to improve powder flow properties for large scale granulation, to aid formation of a homogeneous suspension given the poor wetting properties of the active substance, and to mask the active substance taste.

All excipients are well known pharmaceutical ingredients or food additives and their quality is compliant with Ph. Eur. standards, tested to be suitable for pharmaceutical use, or generally recognised as safe (GRAS). There are no novel excipients used in the finished product formulation. The full list of excipients is included in section 6.1 of the SmPC.

Compatibility studies between active substance and a range of potential excipients tested in formulation development were carried out under accelerated conditions (40 ºC / 75% RH) over 12 weeks. The active substance was shown to be compatible with all tested excipients.

The granules are stored in moisture-excluding aluminium sachets to prevent clumping of the granules over time.

The formulation evolved during development from a powder to granules, which is also the commercial formulation. Comparative dissolution data indicate that all previously used clinical formulations and the commercial formulation have similar dissolution profiles, with >85% dissolution in <15 minutes. The discriminatory power of the dissolution method has been demonstrated.

The primary packaging is child-resistant heat-sealed laminated aluminium foil sachets. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

No excipients derived from animal or human origin have been used in the formulation. Magnesium stearate is derived from a vegetable source.

Manufacture of the product

The manufacturing process is considered standard for the production of granules. Key steps in the process include roller compaction, milling and blending. Adequate process controls are in place for each of these steps to ensure the quality of the finished product. The formal validation of the process in the production facilities has not yet been completed but will be carried out prior to release of Translarna to the market. A process validation scheme has been provided and the applicant will validate the process before commercialisation.

Product specification

The finished product release specifications include validated tests for appearance (visual description), identification (HPLC and UV), assay (HPLC), degradants (HPLC) content uniformity (HPLC), dissolution (HPLC), water content (KF) and microbial limits (Ph. Eur.) appropriate for this kind of dosage form.

Batch analysis results are provided for three batches of 125 mg strength, nine batches of 250 mg strength and four batches of 1000 mg strength, confirming the consistency and uniformity of the manufacturing process and its ability to manufacture the finished product to the intended specifications.

Stability of the product

A bracketing strategy was used to investigate stability: the 125 mg and 1000 mg strengths were tested but not the intermediate 250 mg strength. This is considered acceptable. Stability data from three commercial scale batches of both 125 mg and 1000 mg strengths of finished product stored under long term conditions (25 ºC / 60% RH) for 48 months, under intermediate conditions (30 ºC / 75% RH) for 36 months at and for up to 6 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. The batches of Translarna were identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

In addition, finished product in the proposed commercial packaging was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products.

Samples were tested for appearance, assay, degradants, dissolution, moisture content, microbial limits, granule particle size and average deliverable powder weight. The analytical procedures used are stability indicating.

None of the parameters tested showed any observable trends over the course of the stability and photostability studies.

Since finished product granules can be reconstituted in liquid media (water, milk, fruit juice) and semi-solid media (yoghurt, pudding, apple sauce), in-use stability data have been provided which indicate the preparation in water at ambient conditions or that in other liquid or semi-solid media under refrigerated conditions should be used within 24 hours. The stability data also supports transient excursion to room temperature for 3 hours in milk or yoghurt or 6 hours in fruit juice, pudding, or apple sauce.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

The applicant will conduct stability studies on the first 3 commercial production batches under long-term (25 ºC / 60% RH) and accelerated (40 ºC / 75% RH) conditions, and 1 commercial production batch per year thereafter.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

Not applicable.

2.3. Non-clinical aspects

2.3.1. Introduction

Ataluren (PTC124) is an orally bioavailable small molecule intended for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene. Ataluren is the first investigational new drug designed to enable ribosomal readthrough of premature stop codons, resulting in the formation of a full-length functional protein in patients with nonsense mutation genetic disorders.

The summary of the pharmacology, pharmacokinetics and toxicology of ataluren provided below is based on the non-clinical summary submitted by the Applicant and available information on the published scientific literature.

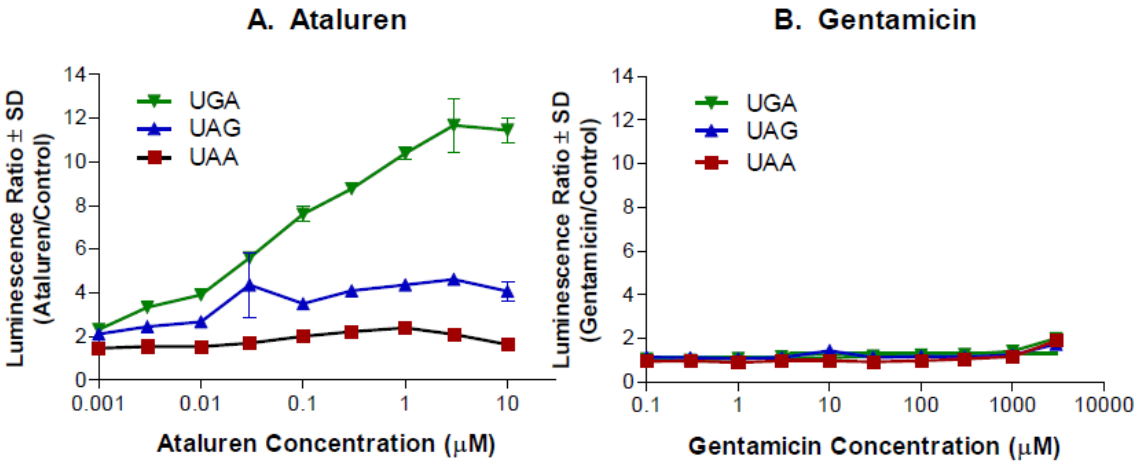
Safety pharmacology studies and all pivotal toxicity studies were performed under GLP.

2.3.2. Pharmacology

Primary pharmacodynamic studies

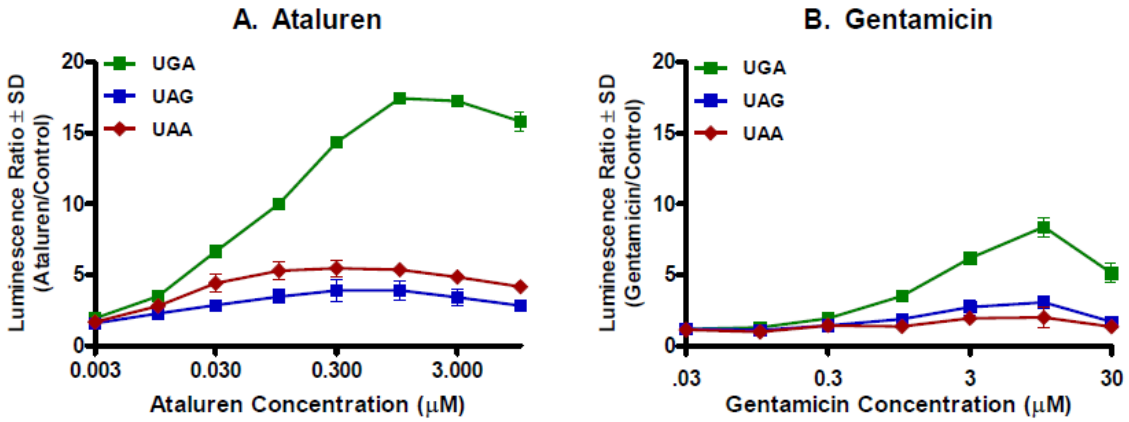
A series of *in vitro* studies were conducted in different model systems to characterise the primary pharmacodynamics of ataluren. In HEK293 cells transfected with the luciferase gene engineered to have premature stop codons at codon 190, increasing concentrations of ataluren resulted in dose-dependent readthrough of full-length, functional luciferase as measured by chemiluminescence in the HEK293 LUC-190 cell-based assays (Fig. 1).

Fig. 1



A dose-dependent readthrough and production of full-length, functional luciferase was also seen in a cell-free translation assay (LUC-190 mRNA with a cytoplasmic translation extract from HeLa cells (Fig. 2).

Fig. 2



In myotubes isolated from the mouse model of nonsense mutation DMD (*mdx* mice) testing ataluren concentrations of 0.1 to 30 µg/ml and in cultured human myotubes from nmDMD patients testing concentrations of 0.1 to 40 µg/ml, a bell-shaped dose response was observed, with maximal induction of dystrophin at an ataluren concentration of 10 µg/ml.

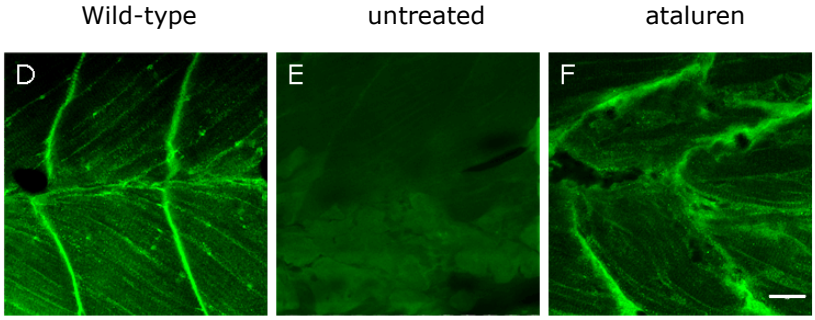
In mouse embryonic fibroblasts (MEFs) isolated from the mouse model of nonsense mutation Hurler syndrome (Idua-W392X mice), reduction in tissue glycosaminoglycan levels due to production of a full-length functional enzyme was evaluated. The maximal induction of enzyme activity was seen at an ataluren concentration of 10 µg/ml, indicating a bell-shaped response.

The ability of ataluren to read through premature stop codons, thus enabling production of full length functional protein, was further investigated *in vivo* in nonsense mutation mouse models: nmDMD mdx mice, Cftr-/- FABP-hCFTR-G542X mice (a mouse model of nonsense mutation cystic fibrosis) and Idua-W392X mice (a mouse model of nmHurler syndrome).

In the mdx mouse model of nmDMD testing three dosing regimens- oral, intraperitoneal (IP) and combination of both, the optimal efficacy was observed with a combined oral and IP dosing (1.8 mg/ml via a liquid diet and 33 mg/kg IP TID). Pharmacokinetics were performed and this dosing regimen resulted in a trough concentration of approximately 10 µg/ml. Doses that would result in higher plasma concentrations were not assessed and the potential for a bell-shaped response could not be determined in this model. Overall, ataluren administration resulted in protection from eccentric contraction injury and in reduced serum CK, indicating reduced muscle fragility. Dystrophin was seen to be located in the cell appropriately, with levels accounting to 20% of the normal levels.

During the procedure, the Applicant submitted additional data from an nmDMD zebrafish model indicating promotion of nonsense mutation readthrough (fig. 3).

Fig. 3 Effect of ataluren treatment on dystrophin expression in nmDMD zebrafish model



Li, et al, In Press

In an *in vivo* model of CF (Cftr-/-FABP-hCFTR-G542X mice) ataluren administration dose-dependently increased expression of appropriately located full-length CFTR and restored CFTR-dependent chloride channel function. When ataluren was administered to Idua-W392X mice, a bell-shaped dose response was observed with maximal induction of Idua enzyme activity at an ataluren dose of 0.1% (in brain, spleen, heart, and lung) or 0.3% (3.7 to 19 µg/ml) (in liver), with less activity at 1.0% (w/w).

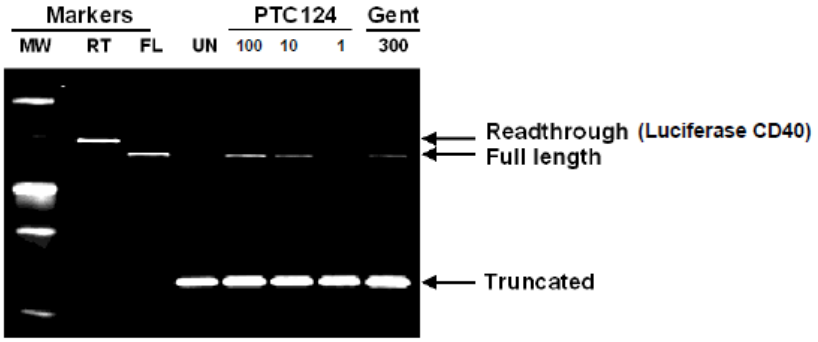
Secondary pharmacodynamic studies

In an RT-PCR assay, LUC-190 (UGA) mRNA transcripts were monitored to determine whether ataluren might affect cellular mRNA levels. Data obtained with HEK293 LUC-190 (UGA) cells incubated with ataluren at a concentration of 30 µM showed that LUC-190 mRNA levels were not altered. In a microarray analysis of mRNA levels assessing the effect of ataluren treatment, some transcripts (22 out of >54000) were different from control cells at an ataluren concentration of 5 µM. Results of both analyses indicated that ataluren did not globally affect the synthesis or stability of the mRNA at concentrations that enable readthrough of a premature stop codon.

A series of studies was conducted, both *in vitro* and *in vivo* to evaluate the potential of ataluren to promote readthrough of normal stop codons.

In a nonsense mutation luciferase-CD40 reporter assay, no readthrough of normal stop codons was seen at any of the ataluren concentrations tested (fig. 4)

Fig. 4



Cultured transfected HEK293 LUC-190 CD40 cells were treated with ataluren (PTC124) at 1, 10, and 100 µM (0.28, 2.8, and 28 µg/mL) or gentamicin at 300 µM for 72 hours. Luciferase protein was purified and analyzed by Western blotting. The control read-through Luciferase-CD40 protein (lane labeled RT) was produced by replacing the normal stop codon in the luciferase gene to CGA to generate the luciferase CD40 UTR fusion protein.
Abbreviations: FL=full length luciferase protein, GENT=gentamicin, MW=molecular weight markers, RT=readthrough product positive control luciferase-CD40 fusion extended protein produced by mutating the normal stop codon of luciferase, UN=untreated, UTR=untranslated region.

Similarly, no readthrough of normal stop codons was observed in a wild-type luciferase-CD40 reporter assay, with the normal UAA luciferase stop codon changed to a UGA stop codon. This was documented by the absence of the luciferase-CD40 extended protein product in cells treated with ataluren at concentration of 1, 10 and 100 µM.

In a 2D gel analysis of ataluren effect on normal stop codons, HEK293 LUC-190 (UGA) cells were incubated with ataluren at a concentration of 5 µM. The only noted difference in the electrophoretic pattern of proteins from cells incubated with ataluren compared to those from vehicle treated cells was a protein with a molecular weight and charge corresponding to the luciferase protein. No aberrantly elongated proteins were produced.

In order to evaluate the potential for off-target pharmacologic activity, evaluation of the ability of ataluren to block binding of ligand to 62 diverse receptors or enzymes (neurotransmitter receptors, enzymes, steroids, ion channels, secondary messengers, prostaglandins, growth factors or hormones and brain and gut peptides) was conducted. Ataluren did not significantly block ligand binding to any of the targets (inhibition of >50% was considered significant) at concentrations of 10 µM (2.84 µg/mL) and 30 µM (8.52 µg/mL).

Safety pharmacology programme

Ataluren was evaluated in stand-alone and GLP-compliant safety pharmacology studies.

The effects of ataluren on general activity and behaviour in the rat were evaluated at several time-points after a single oral dose and after 7 consecutive daily doses of vehicle or 500, 1000 or 2000 mg/kg/day of ataluren. There were no behavioural or physiological changes in rats when compared to vehicle control rats. A slight decrease (5%) in body weight on Day 2 was observed in the 2000 mg/kg/day dose group.

The effects on respiratory parameters of ataluren in single oral doses up to 2000 mg/kg were evaluated in rat. Ataluren did not elicit any statistically significant or biologically important changes in respiratory parameters of tidal volume, respiratory rate and minute volume.

The potential for effects on cardiovascular function were evaluated *in vitro* in a human ether-a-gogo-related gene (hERG) assay and *in vivo*, in a single dose cardiovascular safety pharmacology study in telemetered dogs (in doses up to 1500 mg/kg) and the 4-week and 52-week toxicology studies in dogs (in doses up 1500 and 1000 mg/kg/day, respectively). All studies were conducted

in accordance with GLP. *In vitro*, ataluren inhibited hERG current by 0.2±0.1% at 10 µM and 4.1±0.1% at 100 µM. In the *in vivo* studies in dogs, ataluren had no effect on the ECG morphology, heart rate and ECG intervals at any dose.

Pharmacodynamic drug interactions

The potential pharmacodynamic interaction of ataluren and representative aminoglycoside antibiotics was explored in an *in vitro* model system of ribosomal readthrough. The ability of ataluren to enable readthrough was reduced in the presence of antibiotics that are known to interact with ribosomal RNA (gentamicin and tobramycin) but not in the presence of antibiotics that act through alternative mechanisms (aztreonam and colistin).

2.3.3. Pharmacokinetics

The pharmacokinetic characteristics of ataluren were characterised after single- and repeat-dose administration in mice. The toxicokinetics of ataluren were assessed after single- and repeat-dose administration to animal species used in the toxicological evaluation, i.e. Tg.rasH2 wild type mice, rats, dogs and rabbits.

Following oral administration of ataluren to mice, rats, dogs and rabbits, the drug was rapidly absorbed and eliminated in all species, with peak concentrations after single doses occurring 0.25 to 4 hours post dose. The T_{max} tended to increase with increasing dose and with multiple doses. The half-life was similar across the non-clinical species tested and ranged within 1.1 to 7.6 hours. There was no accumulation of drug in plasma upon repeated daily dosing. In rats, two peak plasma concentrations were observed, indicating entero-hepatic recirculation. Plasma exposure to ataluren in all species, based on C_{max} and AUC, was less than dose proportional. After multiple dosing, plasma exposure (in particular the AUC values) decreased after Day 1. Ataluren showed a high plasma protein binding (98.4% in mouse, 98.7% in rat and 97.5 in dog).

Following intravenous administration of a single dose to dogs, the systemic clearance averaged 123 ml/kg.hr and the volume of distribution at steady state (V_{ss}) was 0.21 l/kg. In a bioavailability study conducted in dogs with intravenous and oral dosing, low bioavailability (7%) was seen, which corresponded to the observed low urinary excretion in this species (12% of the dose). In mice and rats, the excretion via urine and bile indicated high bioavailability (40% urinary excretion in mice and 90% urinary and bile excretion in rats).

After oral administration of radio-labelled ataluren to rats, high concentrations were found in the gastrointestinal tract, the secretion organs (liver and kidney), adrenal gland, brown fat and lung. Low radioactivity concentrations were observed in the brain. The blood-to-plasma ratio of ataluren radioactivity was less than one, indicating that ataluren does not accumulate in erythrocytes. At 24 hours after dosing, radioactivity was still observed in brown fat, skin and the Harderian and preputial glands.

In rats, placental transfer of radio-labelled ataluren and excretion in milk were observed. At a single maternal dose of 30 mg/kg, the concentration of foetal radioactivity was ≤ 27% of the maternal concentration. At the same maternal dose, the highest measured concentration of radioactivity in rat milk was 37% of the maternal plasma concentration. Presence of radioactivity in pup plasma confirmed absorption from the milk by the pups. The composition of this radioactivity (parent compound and/or metabolites) was not investigated.

The major biotransformation pathway of ataluren included acyl glucuronidation, reductive oxadiazole ring cleavage, oxidative deamination and hydrolysis. In all species, unchanged ataluren was the major component in plasma (ranging from 70 to 91%).

Ataluren was not metabolised by CYP isozymes, but was directly glucuronidated via UGT1A9 in human liver microsomes. No non-clinical studies were performed by the applicant to evaluate potential drug-drug interaction, but based on the *in vitro* data, inhibitors of UGT1A9 or drugs metabolised by UGT1A9 may have a clinically relevant effect on the metabolism of ataluren.

In vitro studies indicated that ataluren was not a substrate for P-glycoprotein.

Following a single oral dose of radio-labelled ataluren, the majority of the administered radioactivity was excreted in faeces: 54% by mice, 84% by rats and 80% by dogs. Most of the dose was excreted within 48 hours. The total recovery was >93% in the three species.

2.3.4. Toxicology

Single dose toxicity

Single dose toxicity studies of ataluren were conducted in rats and dogs. The oral LD_{50} in rats was >2000 mg/kg, the highest dose tested. In an oral escalating dose study in dogs, ataluren was well tolerated up to the highest dose of 1600 mg/kg. No macroscopic abnormalities were noted at necropsy.

Repeat dose toxicity

Repeat dose toxicity studies of ataluren were conducted in mice for up to 29 days, in rats for up to 26 weeks and in dogs for up to 52 weeks. Both 26-week toxicology studies in rats and the 52-week toxicology study in dogs initiated dosing in weanling animals to support dosing in children.

The major findings are summarised in Table 1.

Study ID	**Species/Sex/ Number/Group**	**Dose/ Route**	**Duration**	**NOEL/ NOAEL (mg/ kg/ day)**	**Major findings**
AB19LA.2G3R.04.BTL (GLP)	CByB6F1 (Tg.rasH2 non-transgenic littermates) hybrid mice Main study: 10 mice/sex/dose and 44 mice/sex/dose level for toxicokinetics	Oral gavage Final study: 0, 600, 1200, or 1800 mg/kg/day	29 days	N/A	29 day study: 1800: ↓ Hb (F), Hct (F), MCV (F), ↑ segm neutrophils (F); ↓ Gluc (M), ↑ AP (M), ↑ Creat (M) 1200-1800: ↓ body weight, ↓ body weight gain, small ↓ d-r MCH, small ↑ total bilirubin 600-1800: d-r ↑ deaths, temporary ↑ food intake (M), ↑ BUN, ↓ Cl, both attributed to renal nephrosis or dehydration, ↑ liver weight , ↓ abs and ↑ rel weight of brain, kidneys, heart, ovaries and testes (possibly due to ↓ body weight) Histopathology: nephrosis, thymus atrophy

Study ID	Species/Sex/ Number/Group	Dose/ Route	Duration	NOEL/ NOAEL (mg/ kg/ day)	Major findings
7470-122 (GLP)	Weanling (5 week old) rats 36 (control and high dose) and 24 (low and mid dose)/sex/group and 10/sex/group (for toxicokinetics)	Oral gavage 0, 150, 300, or 1200 mg/kg/day	26 weeks	< 150 mg/kg/ day	1200 mg/kg: ↓ body weight, ↓ body weight gain, ↓ food intake (first week), ↑ Urea nitrogen (M), Ca (F), inorg phosph., ↓ mean mandibular salivary gland weights (possibly due to ↓ food intake), ↓ mean prostate weight 300-1200 mg: ↓ RBC, Hb (F), Hct, ↑ MCHC, WBC (F), LC, ↓ PTT, ↓ glucose, ↑ albumin (M), ↓ Trigl (M), ↓ AST (F), ↑ K, ↑ urine volume 150-1200 mg: ↑ total protein, ↑ Chol, AP, ↑ liver and kidney weight (without histopath correlate) Malignant hibernomas in 6 animals (1200 mg group: 2M + 1F at 20 weeks and 2 M at 26 weeks and 150 mg group: 1M at 26 weeks) 150-300 mg/kg/day: ↓ body weight, ↓ body weight gain
1144-002 (GLP)	Weanling (4 week old) rats, 22/sex/dose and 18/sex/dose (for toxikokinetics)	Oral gavage 0, 30, 60, 120 or 1200 mg/kg/ day	26 weeks	NOAEL 120 mg/kg/ day; NOEL 30 mg/kg/ day	1200 mg: ↓ body weight, food intake, ↓ RBC, Hb, Hct, ↑ Ret + anisocytosis/ hyperchromia, ↑ AP, ↓ Trigl (M), ↑ erosion/ulcer (2M + 2F) in glandular stomach. 120-1200 mg: ↓ neutrophils, ↑ adrenal weight without microsc correlate 60 – 1200 mg: ↓ Gluc, ↑ renal weight without microsc correlate, ↑ liver weight without microsc correlate
7470-123 (GLP)	Dog 16/sex/dose (0, 1000 mg); 10/sex/dose (250,500 mg).	Oral gavage: 0, 250, 500, 1000 mg/kg/day	52 week with an 8-week recovery period Age at start of treatment: 68-83 days.	< 250 mg/kg/ day	1000 mg: ↑ AP, ↑ basal serum ACTH. 500-1000 mg: ↓ serum cortisol response to ACTH stimulation, ↑ aldosterone. 250-1000 mg: ↓ RBC, Hb, Ht, ↑ PLT, ↑ Chol, Trigl, ↓ adrenal weight, ↑ liver/gallbladder weight, ↓ spleen weight, ↑ thyroid/ parathyroids weight , ↑ hepatocellular glycogen histopathological findings adrenals: multifocal lymphohistiocytic infiltrates in adrenal cortex and focal degeneration of individual or small groups of adjacent parenchymal cells *Terminal recovery*: 1000 mg: ↓ red blood cell parameters and ↑ PLT not fully recovered, ↑ AP not fully recovered, ↓ adrenal weight, ↑ liver/ gallbladder weight, ↓ spleen weight, ↑ thyroid/ parathyroid weight; histopathological findings in adrenals not

Study ID	Species/Sex/ Number/Group	Dose/ Route	Duration	NOEL/ NOAEL (mg/ kg/ day)	Major findings
					fully recovered. 250-500 mg: histopathological findings in adrenals not fully recovered

Genotoxicity

Ataluren genotoxicity was evaluated *in vitro* in gene mutation tests in bacteria and in mammalian cells *and* and *in vivo* in rat. The studies and their results are summarised in Table 2.

Table 2

Type of Study/ Study Number /GLP	Species and Strain	Concentrations/ Concentration range/ Metabolising system	Results: Positive/negative/ equivocal
Gene mutations in bacteria /7470-106 /GLP Yes	*Salmonella* and E. *coli* Strains	33.3 to 5000 µg/plate (± S9)	Negative
Gene mutations in mammalian cells /7470-105 /GLP Yes	Chinese hamster ovary (CHO) cells	Initial Assay: 141 to 412 (-S9) and 98.8, to 288 µg/mL (+S9); Confirmatory Assay: 12.5, to 100 (-S9) and 100 to300 µg/mL (+S9)	Negative
Chromosomal aberrations in vivo / 7470-118 /GLP YES	Polychromatic erythrocytes (PCEs) /rat	Initial Assay: 368 - 1470 mg/kg; Repeat Assay: 323 -1620 mg/kg Initial Assay: 1470 mg/kg; Repeat Assay: 1620 mg/kg	Negative
Chromosomal aberrations in vivo / 7470-124 /GLP YES	PCEs / rat	450, 900, 1800 mg/kg	Negative

Carcinogenicity

Carcinogenicity potential of ataluren was tested in mice and rats. In a GLP-compliant 26-week carcinogenicity study in Tg.rasH2 mice, ataluren did not increase the incidence of tumours up to the highest doses tested in males (600 mg/kg/day) and in females (300 mg/kg/day). The non-neoplastic findings included endometrial hyperplasia and nephropathy in females. In a GLP-compliant 24-month carcinogenicity study in rats, urinary bladder tumours (benign urothelial cell papilloma [2 rats] and malignant urothelial cell carcinoma [1 rat]) were seen in 3/60 female rats dosed at 300 mg/kg/day. In addition, one case of malignant hibernoma was observed in 1/60 male rats at the dose of 300 mg/kg/day. The non-neoplastic toxicity consisted of a decrease of body weight.

Reproduction Toxicity

The package of reproduction toxicity studies consisted of a male/female fertility study in rats, embryo-foetal developmental toxicity studies in rats and rabbits and a peri/postnatal toxicity study in rats. In the fertility study, no effects on male/female fertility were observed at a dose of 300 mg/kg/day, the highest dose tested, and the NOAEL for early embryonic toxicity was the same as in the rat embryo-foetal toxicity study. In the embryo-foetal toxicity study in rat, embryo-foetal toxicity consisted of increased early resorptions, post-implantation loss and decreased viable foetuses and signs of developmental delay (increased skeletal variations). The NOAEL for embryo-

foetal toxicity was 100 mg/kg/day, giving an exposure margin of factor 4 compared to human exposure. The NOAEL for maternal toxicity was 30 mg/kg/day.

Placental transfer of ataluren and distribution in the rat foetus was investigated with radiolabelled ataluren. At a maternal dose of 30 mg/kg/day, the concentration of foetal radioactivity was ≤ 1/3 of the maternal concentration.

In the rabbit embryo-foetal toxicity study, maternal and embryo-foetal toxicity was seen at the highest tested dose of 100 mg/kg/day. Embryo-foetal toxicity consisted of decreased mean foetal weight and increased skeletal variations. At the maternal and embryo-foetal NOAEL, there was no exposure margin compared to human exposure.

In the rat pre/postnatal developmental toxicity study, significant effects on maternal food intake and body weight and on offspring body weight and ambulatory activity were observed at a dose of 150 mg/kg/day, i.e. at an exposure 5 times higher than the human exposure. The maternal systemic exposure at the NOEL for neonatal toxicity was <3 and at the LOEL <4.

Toxicokinetic data

The toxicokinetics of ataluren were characterised after single and repeated daily doses of 75-1800 mg/kg/day to mice (including the mouse carcinogenicity study), 30-2000 mg/kg/day in rats (including the rat carcinogenicity study), 25-200 mg/kg/day in pregnant rabbits (in support of embryo-fetal development toxicology studies) and 200-1500 mg/kg/day in dogs. The toxicokinetic data indicated a short t½ and also showed that there was no significant drug accumulation in plasma upon repeated daily dosing. Ataluren exposure increased with increasing dose, but it was less than dose proportional at higher doses. There were no sex-related differences in ataluren exposure in dogs, but in rats and mice, exposure was slightly higher in females than in males. The major metabolite seen in mice, rats and dogs was ataluren acyl glucuronide.

Local Tolerance

No local tolerance studies were performed (see section 2.3.6).

Other toxicity studies

No juvenile toxicity studies were performed (see section 2.3.6).

2.3.5. Ecotoxicity/environmental risk assessment

Table 3 Summary of main study results

Substance (INN/Invented Name): ataluren			
CAS-number (if available): 775304-57-9			
PBT screening		Result	**Conclusion**
Bioaccumulation potential – log K_{ow}	OECD107	4.15 at pH 3.23 2.19 at pH 5.40 0.94 at pH 7.12 0.41 at pH 8.46	Not PBT
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	4.15 at pH 3.23 2.19 at pH 5.40 0.94 at pH 7.12 0.41 at pH 8.46	Not PBT
PBT-statement	Not PBT, nor vPvB		

Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, refined (prevalence)	0.0067	µg/L	> 0.01 threshold No
Other concerns (e.g. chemical class)			No

The maximal measured logKow of ataluren is 4.15 at pH 3.23) which is below the PBT screening criterion of 4.5. A full PBT assessment has therefore not been conducted. The refined $PEC_{surfacewater}$, based on the prevalence of Duchenne muscular dystrophy (DMD) originating from nonsense (premature stop codon) mutations (nmDMD) is calculated to be 0.0067 µg/L, which is below the threshold for progression to phase II ERA studies. It is concluded that Ataluren is not considered to cause a potential risk to the environment.

2.3.6. Discussion on non-clinical aspects

The CHMP considered a series of studies were conducted by the applicant to characterise the primary pharmacology of ataluren. These comprised *in vitro* studies in different cell model systems including transfected human embryonic kidney, a cell-free translation system, myoblasts isolated from *mdx* mice and nmDMD patients and mouse embryonic fibroblasts isolated from the *Idua-W392X* mice. The ability of ataluren to read through premature stop codons was also investigated *in vivo* using nonsense mutation mouse models of DMD, cystic fibrosis and Hurler syndrome. In the course of the procedure, the applicant submitted results from an additional study in zebrafish to further support the mechanism of action of ataluren. While these data suggested a plausible readthrough effect of ataluren on the premature stop codons under certain conditions, the CHMP also considered recent publications, e.g. by Mc Elroy et al. 2013[1], which indicated a lack of translational read-through activity for ataluren. The CHMP highlighted the conflicting nature of the data available and the fact that the variability of results across test systems was not sufficiently characterised. Nevertheless, it was concluded that the limited understanding of the variability in the non-clinical setting would not be critical if sufficient clinical efficacy was shown.

The lack of readthrough of normal stop codons was supported by *in vitro* and *in vivo* studies. Overall, the CHMP considered that the experimental data provided some reassurance that no readthrough occurs at terminal stop codons level. Moreover, it was noted that a proteomic analysis of HEK293 cells, treated and untreated with ataluren, will be performed by the applicant, in order to further evaluate the potential of ataluren to promote readthrough of normal stop codons. The CHMP recommended that these data should be submitted for review once available, as appropriate.

The bell-shaped dose response hypothesis (discussed further in the Clinical section) was supported by data obtained from a number of *in vitro* test systems and in zebrafish larvae in ataluren solution. Additional circumstantial evidence was obtained in *in vivo* models relevant for other diseases. However, the CHMP considered that the bell-shaped curve was not seen in the *in vivo* model of the DMD, i.e. the *mdx* mouse. Therefore, the applicant´s hypothesis that clinical efficacy follows a bell-shaped dose-response curve was only partly supported by the non-clinical data.

Safety pharmacology studies were carried out in order to assess ataluren effects on the central nervous system, respiratory system and cardiovascular system. No relevant effects on the CNS and respiratory systems were observed in rats at doses up to 2000 mg/kg/day. Cardiovascular safety of ataluren was assessed *in vitro* and in vivo. No relevant inhibition of ataluren on cloned hERG

[1] http://www.plosbiology.org/article/info:doi/10.1371/journal.pbio.1001593

channels expressed in mammalian cells was observed up to a free concentration of 100 µM. The results of *in vivo* studies in dogs assessing cardiovascular safety indicated that ataluren dosed up to 1500 mg/kg did not elicit any biologically important changes in cardiovascular parameters.

The potential pharmacodynamic interactions of ataluren were explored. Of note, ataluren readthrough effect was reduced in the presence of antibiotics known to interact with ribosomal RNA. These studies suggested that there was no benefit to co-administration of systemic or inhaled aminoglycoside antibiotics during treatment with ataluren and moreover, that the efficacy of ataluren would be reduced during such co-administration.

The CHMP considered that the pharmacokinetics of ataluren were adequately characterised in the non-clinical programme.

The applicant conducted an adequate toxicology programme for ataluren. All pivotal toxicity studies were performed in compliance with GLP. Only the oral route of administration was investigated in all tested species, which was considered acceptable by the CHMP.

The most important toxicity identified in mice after repeated dosing was nephrotoxicity. No NOEL and no significant exposure margin compared to human exposure could be established. Although this toxicity was not seen in the other species tested, i.e. rat and dog, since its mechanism in mice is not known, the CHMP was of the view that its relevance for humans could not be ruled out.

One of the main concerns discussed was the finding of malignant hibernomas in rat. While this finding was made only in this species, similarly to renal toxicity in mice, the CHMP concluded that occurrence of similar effects in humans could not be excluded, particularly in the young population, where the quantity of the brown adipose tissue is higher. In particular, the CHMP considered that malignant hibernomas could be related to the effects of ataluren on fat tissue metabolism and to effects on plasma lipid parameters, which were observed in rats, dogs and humans. Thus, hibernomas were reflected in the proposed risk management plan of ataluren. The CHMP also noted that the applicant will perform a β3 adrenergic binding assay with ataluren and one of its metabolites to further investigate their potential effects in the brown adipose tissue in rats.

In addition to the above mentioned effects, several other less adverse effects were found in the repeat dose studies; in particular decreased body weight gain, food intake and increased liver weight without a histological correlate.

An adequate battery of genotoxicity tests was conducted and the data did not reveal any special hazard for humans.

No evidence of carcinogenicity was seen in mice. In rats, cases of hibernomas were observed in the carcinogenicity- and repeat dose toxicity studies. In addition, an increase of rare urinary bladder tumours was found in rats, but the systemic exposure margin for these tumours compared to the human exposure was considered sufficiently high and the finding hence of unlikely significance.

The CHMP considered that a GLP-compliant full reproductive toxicology programme consisting of fertility and early embryonic development study, embryo/foetal development studies and a pre-/postnatal development study was conducted.

The lack of formal local tolerance studies was considered acceptable by the CHMP, as ataluren is intended for oral use and investigating the potential local gastro-intestinal effects was covered by the oral repeated dose studies.

The CHMP considered that while no juvenile toxicity studies were performed, the repeated dose 26-week rat studies started at the age of 4-5 weeks and the repeated dose 52-week dog study at the

age of 68-83 days. The CHMP was of the view that these studies were supportive of use in children older than 4-5 years (based on the studies in rats) or slightly younger, 3-4 years (based on the study in dogs). Overall, the CHMP concluded that the level of evidence available was, from the perspective of non-clinical toxicity testing, sufficient to justify ataluren administration to patients 5 years and older, i.e. the patient population covered by the indication applied for.

ERA studies did not indicate potential risks to the environment linked to ataluren.

2.3.7. Conclusion on the non-clinical aspects

Overall, the CHMP concluded that despite the identified weaknesses of the pharmacology data (on mechanism of action and bell-shaped dose-response hypothesis), the limitations within the non-clinical package could be considered acceptable, if sufficiently compensated by compelling clinical evidence.

2.4. Clinical aspects

2.4.1. 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.

Table 4: Overview of clinical studies

Study ID (M5 Section)	No. of Sites Country	Study Dates (Start–Completion)	Design / Control	Route and Regimen	Indication	No. of Patients by Treatment (Entered/ Completed)	Treatment Duration	Sex (M/F) Age Range (years)
Clinical Pharmacology (Healthy Volunteers)								
PTC124-GD-001-HV, (001) Stage 1 (5.3.3.1)	1 USA	14 Jun 2004 – 25 Jul 2004	Randomized, double-blind, placebo-controlled, dose-escalation	Oral, 3, 10, 30, 100, 150, 200 mg/kg	NA	18/14	Single dose	10/8 18-30
PTC124-GD-001-HV, (001) Stage 2 (5.3.3.1)	1 USA	30 Jul 2004 – 12 Aug 2004	Randomized, open-label crossover evaluation of food effect	Oral, 50 mg/kg with or without food	NA	13/12	Single dose	7/6 22-30
PTC124-GD-002-HV, (002) Stage 1 (5.3.3.1)	1 USA	18 Oct 2004 – 9 Dec 2004	Open-label dose-escalation	Oral, 10, 20, 30, 50 mg/kg BID	NA	24/24	7 days	12/12 18-30
PTC124-GD-002-HV, (002) Stage 2 (5.3.3.1)	1 USA	10 Jan 2005 – 3 Feb 2005	Open-label	Oral, 50 mg/kg BID	NA	7/5	14 days	4/3 18-30
PTC124-GD-010-HV, (010) (5.3.3.1)	1 USA	12 Aug 2008 – 3 Oct 2008	Open-label AME study	Oral, single-dose (1375 mg ataluren + ~ 100 µCi [^{14}C]-ataluren)	NA	14/7 [a]	Single dose	14/0 19-50
Adequate and Well-Controlled Studies in nmDMD Patients								
PTC124-GD-007-DMD (007) (5.3.5.1)	37 Australia Canada Europe Israel USA	28 Feb 2008 – 17 Dec 2009	Randomized, placebo-controlled, 3-arm study	Oral, TID Placebo, ataluren 10, 10, 20 or 20, 20, 40 mg/kg	nmDBMD	Placebo: 57/57 10/10/20: 57/57 20/20/40: 60/59 Total: 174/173	48 weeks	174/0 5-20
Uncontrolled Studies in nmDMD Patients								
PTC124-GD-007e-DMD (007e)[b] (5.3.5.2)	37 Australia Canada Europe Israel USA	30 Jan 2009 – 24 May 2010	Open-label extension	Oral, TID Ataluren 20, 20, 40 mg/kg	nmDBMD	173/0	Median: 21.9 weeks Range: 10.7 to 61.3 weeks	173/0 6-21
PTC124-GD-004e-DMD (004e)[b] (5.3.5.2)	3 USA	13 Aug 2008 – 17 May 2010	Open-label extension	Oral, TID Ataluren 20, 20, 40 mg/kg	nmDMD	20/20/40: 36/0	Median: 70.9 weeks Range: 54.0 to 88.3 weeks	36/0 7-19
PTC124-GD-004-DMD (004) (5.3.4.2)	3 USA	21 Dec 2005 – 3 May 2007	Open-label, dose-escalation	Oral, TID Ataluren 4, 4, 8 mg/kg; 10, 10, 20 mg/kg; or 20, 20, 40 mg/kg	nmDMD	4/4/8: 6/6 10/10/20: 20/20 20/20/40: 12/12 Total: 38/38	4 weeks	38/0 5-17
PTC124-GD-008-DMD (008)[b] (5.3.5.2)	2 USA	13 Jan 2010 – 23 Mar 2010	Open-label	Oral, TID Ataluren 20, 20, 40 mg/kg	nmDBMD	6/0	2 to 7 weeks	6/0 12-20

2.4.2. Pharmacokinetics

Absorption

Although ataluren is practically insoluble in water, it is readily absorbed after oral administration as a suspension. Ataluren was rapidly absorbed with Tmax between 0.5 and 2.5 h after single doses in fasted adult healthy volunteers. Peak plasma levels were attained approximately 1.5 hours after dosing in subjects who received medicinal product within 30 minutes of a meal. Based on the urinary recovery of radioactivity in a single-dose study of radiolabeled ataluren under fasting conditions, the oral bioavailability of ataluren was estimated to be ≥55%.

The effect of food on ataluren bioavailability was investigated in study 001, using a formulation (powder in bottle) different from the phase 2a/2b formulation. Based on PK modelling in healthy volunteers and data from patients with nmDMD, no significant effect of food was detected on either the rate or extent of ataluren absorption.

Ataluren plasma concentrations at steady state were dose-proportional for ataluren doses between 10 and 50 mg/kg. No accumulation was observed after repeated dosing.

Distribution

In vitro, ataluren was 99.6% bound to human plasma proteins and the binding was independent of plasma concentration. Ataluren did not distribute into red blood cells.

Ataluren volume of distribution (Vz/F) varied between 393 and 689 l when single doses between 3 and 200 mg/kg were administered in healthy volunteers. A lower volume of distribution (around 50 l for a 70 kg adult) was determined in the population pharmacokinetic analysis.

Elimination

In vitro, ataluren was metabolized by conjugation via uridine diphosphate glucuronosyltransferase (UGT) enzymes, predominantly UGT1A9 in liver and intestine. Cytochrome P450 system was not involved in the metabolism of ataluren.

In vivo, the only metabolite detected in plasma after oral administration of radio-labelled ataluren was the ataluren-O-1β-acyl glucuronide; exposure to this metabolite in humans was approximately 8% of the plasma AUC of ataluren.

Ataluren plasma half-life ranged from 2-6 hours and was unaffected either by dose or repeated administration. The elimination of ataluren was likely dependent on hepatic and intestinal glucuronidation of ataluren followed by renal excretion of the resulting glucuronide metabolite.

After a single oral dose of radiolabeled ataluren, approximately half of the administered radioactive dose was recovered in the faeces and the remainder was recovered in the urine. In the urine, unchanged ataluren and the acyl glucuronide metabolite accounted for <1% and 49%, respectively, of the administered dose.

Dose proportionality and time dependencies

In study 001 conducted under fasting conditions, more than a dose proportional increase in $AUC_{0-\infty}$ of ataluren was observed over the studied dose range, i.e. 3mg/kg to 200 mg/kg. In study PTC124-GD-002-HV under fed conditions, dose proportional increase in AUC and Cmax was seen for ataluren between doses 10 and 50 mg/kg. After BID dosing for 7 days, plasma exposure of ataluren increased also in a more than dose-proportional manner. In healthy volunteers, after BID

dosing of 50 mg/kg for 14 days, plasma ataluren concentrations appeared to decrease over time with the linearity factor decreasing to 0.6, suggestive of non-linear PK at 50 mg/kg dose in this study. Data from clinical trials on plasma concentration indicated that the steady state is maintained from Week 6 (the earliest measurement time) through more than two years of treatment and based on the proposed popPK analysis it was estimated that 95% of the decrease to the steady-state value occurs within the first two weeks of therapy.

Special populations

Age

Based on data from subjects ranging in age from 5 years to 57 years, there was no apparent effect of age on ataluren plasma exposure.

Gender

Females were not studied in nmDMD clinical trials. However, there were no apparent effects of gender on ataluren plasma exposure in other populations.

Race

The pharmacokinetic properties of ataluren were not considered to be significantly affected by UGT1A9 polymorphisms in a Caucasian population. Due to the low number of other races included in the clinical studies, no conclusions were drawn on the effect of UGT1A9 in other ethnic groups.

Renal or hepatic impairment

No studies were conducted in patients with renal or hepatic impairment.

Non-ambulatory

There were no apparent differences in steady-state relative bioavailability and clearance due to loss of ambulation.

Pharmacokinetic interaction studies

Effect of other drugs on ataluren pharmacokinetics

Based on *in vitro* studies, ataluren was a substrate of UGT1A9 and breast cancer resistant protein (BCRP). Caution should be exercised when ataluren is co-administered with drugs that are inducers of UGT1A9 or inhibitors of BCRP.

Ataluren is practically insoluble in the pH range of 1.02 to 5.7, with only limited pH-dependent solubility within this range. Since at the therapeutically recommended dose, PPIs have been shown to increase gastric pH from average of 1.4 to median values of 3.5 to 5, no relevant interactions with PPIs and other drugs altering gastric pH are expected.

In vitro, ataluren was not a substrate for the p-glycoprotein transporter. The pharmacokinetics of ataluren are unlikely to be affected by medicinal products that inhibit the p-glycoprotein transporter.

Effect of ataluren on pharmacokinetics of other drugs

In vitro, ataluren was an inhibitor of UGT1A9, organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3) and organic anion transporting polypeptide 1B3 (OATP1B3). Caution should

be exercised when ataluren is co-administered with drugs that are substrates of UGT1A9, OAT1, OAT3 or OATP1B3 because of the risk of increase in concentration of these drugs.

Based on the *in vitro* data, ataluren is not expected to inhibit *in vivo* the following transporters: BCRP, MRP2, BSEP, OATP1B1, MATE1, MATE2-K and OCT2.

Furthermore, based on *in vitro* studies, ataluren was not expected to be an inhibitor of either p-gp mediated transport or of cytochrome P450 mediated metabolism. Similarly, ataluren is not expected *in vivo* to be an inducer of cytochrome P450 isoenzymes.

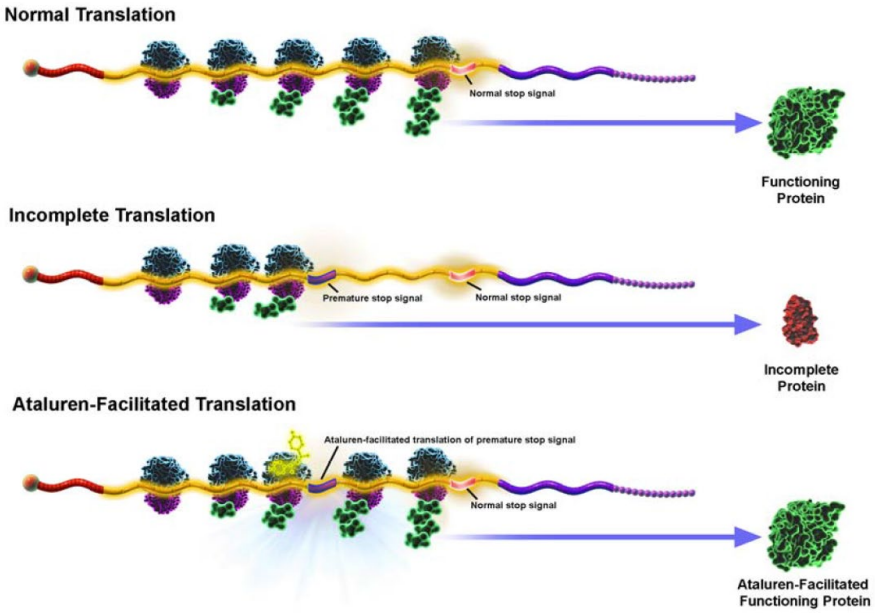
Potential interaction between ataluren and corticosteroids was investigated by analysing pharmacokinetics in Phase 2 nmDMD patients receiving corticosteroids, and adverse events by corticosteroid usage in the long-term studies in nmDMD patients. Coadministration of corticosteroids with ataluren did not affect the plasma concentrations of ataluren. No clinically relevant change in the plasma concentrations of corticosteroids was seen with co-administration of ataluren. These data indicated no apparent drug-drug interaction between corticosteroids and ataluren and no dose adjustments were required.

2.4.3. Pharmacodynamics

Mechanism of action

Ataluren was claimed to enable ribosomal readthrough of mRNA containing a premature stop codon, resulting in production of a full-length protein (dystrophin). A premature stop codon within an mRNA is a result of a nonsense mutation in DNA and causes disease by terminating translation before a full-length protein is generated. A nonsense mutation is an underlying genetic defect in approximately 13% of DMD patients.

Fig. 5 Mechanism of action of ataluren



Primary and Secondary pharmacology

Given ataluren's mechanism of action, pharmacodynamic activity cannot be assessed in healthy subjects because they do not have disease-causing premature stop codons. Therefore, quantification of dystrophin in muscle biopsies was included as a pharmacodynamic marker in two clinical trials of nmDMD patients.

In Study 004, muscle dystrophin expression was evaluated as the primary endpoint. This proof-of-concept open-label study had a treatment period of 4 weeks. The extensor digitorum brevis muscle was sampled pre- and post-treatment to improve the ability to quantify dystrophin expression. 61% of patients showed an increase in dystrophin staining in 28 days of ataluren treatment. A mean change from baseline to Week 4 of 11.0% in dystrophin expression was observed in the overall study population (p=0.008, paired t-test comparing pre-treatment to post-treatment). The mean per cent change in dystrophin expression was generally similar across the dose levels (4, 4, 8 mg/kg [n=6]; 10, 10, 20 mg/kg [n=20]; 20, 20, 40 mg/kg [n=10]) and no clear dose-response relationship was observed, which was attributed by the Applicant to the small and unequal numbers of patients in each group and the short duration of the study.

Muscle biopsies were also collected in the pivotal Study 007, which had a treatment period of 48 weeks. In this study, biopsy of the biceps brachii was performed from one arm at baseline (pre-treatment sample) and from the other arm at Week 36 ±14 days (post-treatment sample) to assess the production of dystrophin. Based on a quantitative analysis of patients with pre- and post-treatment muscle biopsy samples, a mean change (from pre-treatment to post-treatment) of 2.8% in dystrophin expression was observed in the ataluren 10, 10, 20 mg/kg dose group, 1.3% in the ataluren 20, 20, 40 mg/kg dose group, and 0.09% in the placebo group. These differences were not statistically significant.

The analysis of muscle dystrophin expression in Study 007 was compromised by limitations in the available assay methods to sensitively measure changes in dystrophin expression at low levels and by poor sample quality in the majority of muscle biopsy samples (primarily due to artefacts introduced in the handling and shipping of the samples). Only 19 (~11%) paired pre- and post-treatment biopsy samples met the criteria of an optimal sample, defined as no or mild freeze artefact, good cross orientation and no more than mild or moderate fibrotic replacement. Of these 19 optimal paired samples, there were similar positive and negative changes in dystrophin expression across all 3 treatment groups.

Other evidence of ataluren' s pharmacologic action was provided from the open-label Phase 2 studies of ataluren in paediatric, adolescent and adult patients with nmCF. This disease is caused by nonsense mutations in the gene for the cystic fibrosis transmembrane conductance regulator (CFTR). In these studies, the activity of ataluren to restore CFTR in nmCF patients was supported by improvements of transepithelial potential difference, which directly measures CFTR function in the nasal mucosa.

2.4.4. Discussion on clinical pharmacology

The pharmacokinetic profile (absorption, distribution, metabolism and elimination) of ataluren was studied in healthy volunteers and nmDMD patients and was considered sufficiently characterised in the intended patient population.

Three formulations of ataluren were used in the programme, but no bioequivalence studies were performed. Because of the ataluren BCS classification, the differences between the formulations in terms of composition (excipients) were considered critical and bioequivalence could not be

established. The CHMP considered that the varying results regarding bioavailability could be attributed to the disease status, as claimed by the MAH, but due to uncertainties in the pop-PK modelling, this could not be confirmed.

The CHMP considered that the study 001 evaluating the effect of food was performed with Phase I PIB formulation which could not be assumed to be bioequivalent with Phase 2a/2b formulation. However, since clinical studies, including the pivotal Study 007 in patients with nmDMD, were standardized regarding the food intake, i.e. Translarna was taken with food, the CHMP agreed that the product can be recommended to be taken with food.

The CHMP considered that the data on dose- and time linearity/non-linearity were inconclusive, but the clinical trial data suggesting that the steady state is maintained from week 6 through more than two years of treatment were re-assuring.

With respect to special populations, the CHMP was of the view that age-adjusted dosing would not be required and that the data available on patients of other than Caucasian population were limited to allow any conclusions regarding use in different ethnic groups. In the absence of specific studies in patients with renal or hepatic impairment, the CHMP considered the pharmacokinetic properties of ataluren. As it is extensively metabolized in liver and renal excretion accounts for 50% of the drug elimination, hepatic and renal impairment can be expected to result in ataluren/ataluren glucuronide accumulation. The CHMP concluded that close monitoring would be required in clinical practice, should these patients be treated. Furthermore, additional studies addressing the pharmacokinetics and safety in these patients were considered necessary, as described in the proposed Risk Management Plan.

The CHMP discussed the interaction potential of ataluren and was of the view that this should be further explored by the Applicant. Of note, as ataluren was shown to inhibit UGT1A9 *in vitro*, the CHMP requested that *in vivo* studies with a sensitive probe substrate be conducted. Furthermore, because of the observed time dependency, interaction study with UGT1A9 inducer should be performed. Since ataluren may be expected to inhibit OAT1, OAT3 and OATP1B3 *in vivo*, *in vivo* studies with sensitive probe substrates for these transporters were also deemed necessary. The CHMP also considered that *in vitro* studies showed that ataluren was a substrate of BCRP and consequently requested that the potential interactions between ataluren and a BCRP selective inhibitor should be evaluated also in an *in vivo* study.

In order to characterise the mechanism of action of ataluren, a series of studies were conducted *in vitro* and *in vivo*, as detailed in the non-clinical section. While the CHMP acknowledged that the data from the presented studies were supportive of the readthrough ability of ataluren, recent literature provided some evidence indicating lack of translation readthrough, rendering the Applicant´s data less convincing. Furthermore, the CHMP questioned whether the oral administration of ataluren in humans could lead to sufficient levels of ataluren in muscles, considering that the available non-clinical data were based on models with intramuscular administration or models with direct contact with ataluren solution, as was the case in zebrafish. The CHMP considered that the most appropriate way of addressing this issue would be providing evidence of a pharmacodynamic effect in muscles and therefore, data on dystrophin expression from muscle biopsies were discussed by the CHMP in greater detail. Of note, the fact that data from biopsies on dystrophin production would serve as supportive evidence was also highlighted by the SAG Neurology experts.

In the proof-of-concept study 004, increase in dystrophin levels (mean increase of approximately 11%) was observed in about 60% of the subjects, indicating that not all subjects responded to

treatment, or at least not within 28 days. Importantly, there was no dose response relationship and results of this study did not support the bell-shaped dose-response hypothesis of the Applicant.

The pharmacodynamic effect suggested by the study 004 was not confirmed in the pivotal study 007. Considerable variability in the dystrophin assay was exemplified by the finding that positive changes occurred in the placebo group, to the same extent as the ataluren treatment groups. The CHMP considered that the lack of observed effect could be due to the poor quality of the muscle biopsies. The GCP inspection looked into the reasons for failure to provide results from samples obtained at the start and the end of the study and identified particularly wrong biopsy orientation and freezing artefacts. In addition, approximately half of the biopsies exhibited moderate to severe replacement of muscle with fat or fibrotic tissue.

In the context of these data, the CHMP concluded that the pharmacodynamic effect of ataluren, i.e. production of dystrophin in muscle cells of DMD patients treated with ataluren, could not be considered confirmed. Secondly, even if dystrophin were produced in cells with advanced stage of fibrosis, it could be questioned whether newly produced dystrophin may restore the disrupted sarcoglycan complex which plays a role in muscle fibre stability and protection from damage. Examples from other clinical studies with products inducing dystrophin production in muscle cells indicated that this may not translate into convincing clinical efficacy. Overall, the lack of a pharmacodynamic effect in study 007 was considered a weakness of the dossier and is also limiting the external validity of the efficacy results.

2.4.5. Conclusions on clinical pharmacology

Overall, the pharmacological profile of ataluren in human studies was not adequately documented. In particular, the CHMP concluded that there was a lack of relevant data on the pharmacodynamic effects of ataluren in humans reinforcing the uncertainties raised on its mechanism of action and the dose-response relationship.

2.5. Clinical efficacy

2.5.1. Dose response studies

No dose response studies were performed. Instead the preclinical data in combination with data from the phase 2a study 004 with three doses tested (4/4/8 mg/kg, 10/10/20 mg/kg and 20/20/40 mg/kg) and a PD endpoint, were used for further determination of the dose in the phase 2b and the extension studies.

The treatment plan in the Phase 2b study built on the Phase 2a experience in DBMD and cystic fibrosis (CF) and on the available toxicokinetic and pharmacokinetic data from previous non-clinical and clinical studies. Because the observed ataluren pharmacodynamic activity had not exhibited clear dose-response over the tested dose range and because the correlations between short-term pharmacodynamic effects and long-term clinical benefit were unknown, further exploration of dose and duration of therapy in study 007 was necessary.

The disabling and life-threatening nature of DBMD, the lack of approved therapies to treat the underlying cause of this disease and the serious consequences of chronic corticosteroid administration in boys with DBMD mandated that the highest tolerable dose be explored in order

to maximize the potential for benefit. Nonclinical animal data and dose-response data from the *in vitro* myotube dystrophin expression experiments performed as part of the Phase 2a DMD study (Study 004) suggested that maintaining trough ataluren plasma concentrations of >2 to 10 mcg/ml may be important to achieve optimal efficacy [Welch 2007].

The 20, 20, 40 mg/kg dosage regimen in Study 004 was associated with maximum concentration (C_{max}) and area under the concentration-time curve through 24 hours (AUC_{0-24}) values that were lower than and/or comparable to the mean C_{max} and AUC_{0-24} values in nonclinical toxicity studies, either at the 600 mg dose associated with recoverable renal lesions in mice or at the NOAEL in rats and dogs in the 4-week toxicology studies. The mean C_{max} and AUC_{0-24} values were also lower than the mean values observed with the NOAEL in the 26-week rat studies and similar to the mean values observed at the NOAEL for adrenal cortical function in the 52-week dog study.

The exposure values were also comparable to those that were generally well tolerated in adults with CF participating in the Phase 2a study program – including patients who received ataluren treatment for 12 weeks. These exposures were generally well tolerated in boys participating in the Phase 2a DMD study (Study 004) for 28 days. Collectively, these considerations supported inclusion of the 20-, 20-, 40-mg/kg dose level in the Phase 2b study.

The 10, 10, 20 mg/kg dose tested in Study 004 showed clinical pharmacodynamic activity and, unlike the 4-, 4-, 8-mg/kg dose level, achieved trough exposure levels within the target range of 2 to 10 μg/mL associated with activity in nonclinical models. The C_{max} and AUC_{0-24} values associated with this dose level suggested favourable exposure ratios relative to animal toxicokinetic data. Clinically, these exposures were safe across the Phase 2a DMD and CF experience. For these reasons, the 10, 10, 20 mg/kg dose level was also evaluated in the Phase 2b study.

2.5.2. Main study

A phase 2b efficacy and safety study of PTC124 in subjects with non-sense-mutation-mediated Duchenne and Becker muscular dystrophy

Methods

Study Participants

To be eligible to participate in the study, patients had to be males ≥5 years of age who had a diagnosis of (nonsense mutation Duchenne/Becker muscular dystrophy - nmDBMD) based on phenotypic evidence of DBMD and a nonsense mutation in the dystrophin gene as confirmed by gene sequencing. Patients were required to have the ability to walk ≥75 meters unassisted. Adequate baseline renal, adrenal and hepatic function, as established by serum markers was required. Key exclusion criteria included prior or ongoing clinically significant illness or severe complications of DBMD, serologic evidence of hepatitis B or C and change in prophylaxis/treatment for congestive heart failure within 3 months prior to start of study treatment. Patients receiving corticosteroid therapy were required to have stabilization of such therapy prior to study entry.

Treatments

Patients received placebo, ataluren 10, 10, 20 mg/kg (total daily dose 40 mg/kg) or ataluren 20, 20, 40 mg/kg (total daily dose 80 mg/kg) every day during the treatment period using a TID

schedule comprising morning, midday and evening doses. Approximate intervals for dosing were to be 6 hours between morning and midday doses, 6 hours between midday and evening doses and 12 hours between the evening dose and the morning dose on the next day.

Administration within 30 minutes after a meal was recommended. Study drug dosing was based on milligrams of drug per kilogram of body weight. The planned duration of treatment was 48 weeks.

The use of corticosteroids was to be standardized as much as possible during the study in order to minimize potential confounding effects. In patients not on corticosteroids at the beginning of the study, initiation of corticosteroid therapy during the study was discouraged unless there was a strong medical need. For patients on corticosteroids at the beginning of the study, a stable corticosteroid regimen was to be maintained during the study. Adjustments in corticosteroid dosage for increases in body weight were permitted but were not mandatory.

Objectives

The primary objective was to determine the effect of ataluren on ambulation. The secondary objectives were to evaluate the effects of ataluren on physical function, patient-reported outcomes, cognitive function, cardiac function and pharmacodynamics. Safety, compliance with study drug treatment and ataluren plasma exposure were also assessed.

Outcomes/endpoints

The primary efficacy endpoint was change in 6MWD from baseline to Week 48. The secondary endpoints comprised changes in proximal muscle function as assessed by timed function tests; change in force exerted during knee flexion and extension, elbow flexion and extension and shoulder abduction as assessed by myometry; change in activity in the community setting as assessed by step activity monitoring; change in the patient-reported wheelchair use; change in patient and parent/caregiver reported HRQL as measured by the Pediatric Quality of Life Inventory (PedsQL); change in parent/caregiver-reported treatment satisfaction as measured by the Treatment Satisfaction Questionnaire for Medication (TSQM); change in the rate of accidental falls per day as recorded by patients and/or parent/caregivers in a daily diary; change in verbal memory and attention as assessed by the digit span task; change in heart rate before, during, and after each 6MWT as assessed by heart rate monitoring; change in serum concentration of CK; and change in biceps muscle dystrophin expression as determined by immunofluorescence.

The safety endpoints were the type, frequency, severity, timing and relationship to study drug of adverse events, laboratory abnormalities, vital sign changes, electrocardiogram (ECG) abnormalities, renal ultrasound and physical exams.

The planned doses were compared to the actual doses (as reported by the patients) to determine compliance.

Pre-dose (C_{0h}) and 2-hour post-dose (C_{2h}) ataluren plasma concentrations after morning drug administration were assessed by a validated bio-analytical method.

Sample size

The hypothesis of this study was that the mean change in 6MWD from baseline to 48 weeks would be 30 meters longer in at least one of the ataluren arms than in the placebo arm. Assuming a common standard deviation of ~50 meters in each arm and a 1:1:1 randomization, 150 patients were required (50 patients in each of the 3 arms) to detect a difference of 30 meters in

the 6MWD with >85% power using a 2-sided Dunnett' s t-test at the 0.042 significance level. Assuming a premature discontinuation rate of ~10%, it was planned that ~165 patients (~55 patients in each of the 3 arms) be enrolled.

Randomisation

Eligible patients were randomized in a 1:1:1 ratio and stratified based on age (<9 vs ≥9 years), use of corticosteroids at baseline (yes vs no) and 6MWD (≥350 meters vs <350 meters).

At the time of randomization, the IVR/IWR system provided the clinic pharmacist or other qualified person with the patient randomization number and the Component ID numbers designating the kits to be dispensed.

Blinding (masking)

Patients, parents/caregivers, investigational site personnel, PTC Therapeutics employees and all other study personnel were to remain blinded to the identity of the treatment assignments until every patient had completed study treatment and the database had been locked. The identity of the study treatments were concealed by the use of a placebo that was identical to the active drug in appearance, taste, odour, packaging, labelling and schedule of administration. Unblinding was only to occur in the case of patient emergencies, if requested by the DMC at the time of the interim analyses, and at the conclusion of the study. During the study, the treatment assignments were to be available only to an independent biostatistician and to the DMC.

Statistical methods

A mixed-model repeated-measures (MMRM) analysis of the change in 6MWD from baseline to Week 48 was performed in the intent-to-treat (ITT) population (all randomized patients with a valid 6MWT at baseline and ≥1 post-baseline visit). Included in the model were treatment, baseline 6MWD, age (<9 or ≥9 years), corticosteroid use (yes or no), visit, and treatment-by-visit interaction. Because baseline 6MWD was included in the model as a covariate, the stratification factor of baseline 6MWD was excluded from this model. Least-squares means and variance estimates of changes in 6MWD at Week 48 were generated from the model. These estimates were then used to compare the changes in 6MWD at 48 weeks between each ataluren treatment arm and the placebo arm. Normality was tested using the Shapiro-Wilks W-test at the 0.05 significance level. Because a significant degree of non-normality was observed, rank-transformed data were used in the pre-specified analysis.

Sensitivity analyses were performed to assess the potential for induction of bias due to lack of patient conformance to the protocol, inclusion of sibling pairs, and missing data (analysis after multiple imputation and last observation carried forward [LOCF]) and dynamic randomization in an MMRM setting (permutation test). A sensitivity analysis to assess robustness of the primary efficacy results to missing data was based on the LOCF concept, by applying an analysis of covariance (ANCOVA) model to the last available post-baseline 6MWD observation, with covariates as defined in the SAP.

As specified in the SAP, time to persistent 10% 6MWT worsening (last time that 6MWD was not 10% worse than baseline) and time to persistent 10% 6MWT improvement (last time that 6MWD was not 10% improved over baseline) were evaluated as supportive analyses of the primary endpoint. Differences between each ataluren treatment arm and the placebo arm were assessed using Kaplan-Meier methods and the stratified log-rank test.

In general, secondary variables were analysed using the final MMRM that was used for the primary analysis of the 6MWD data, except that the baseline value of the secondary variable of interest served as the covariate and baseline 6MWD was added to the model as an independent variable. In cases where an MMRM analysis was not appropriate for the secondary variable of interest, alternative statistical methods were used as necessary.

Post-hoc:

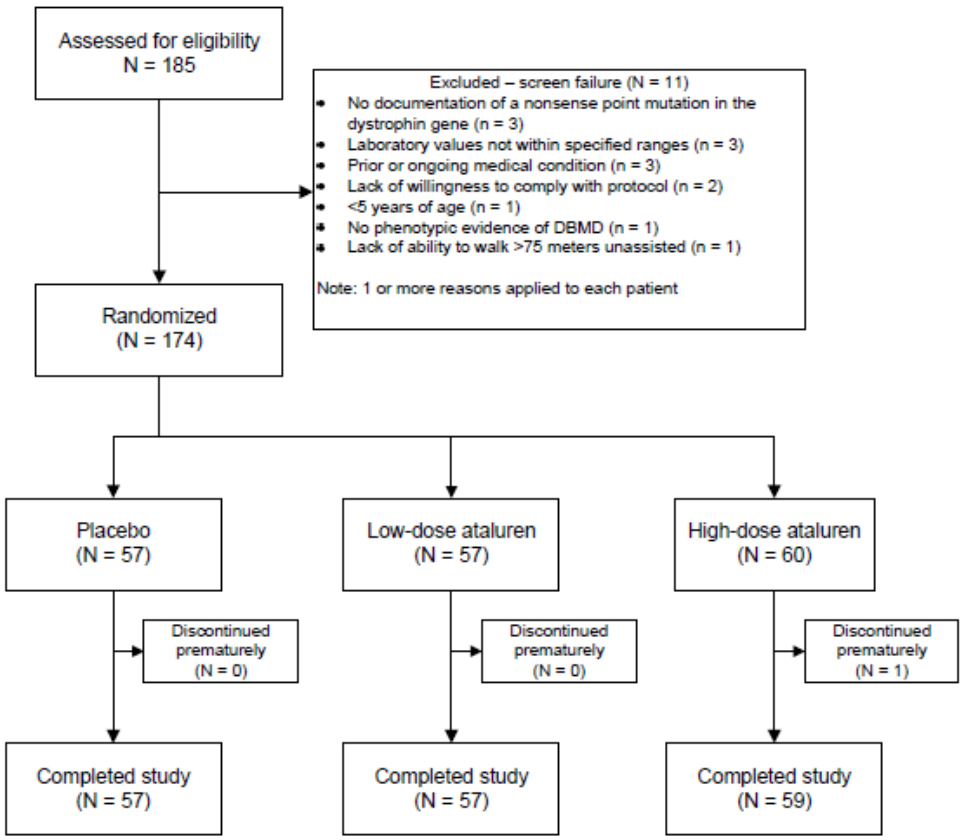
Post-hoc refined MMRM, including baseline-by-visit interaction term, analysis of 6MWD as well as stair-climbing, stair-descending, running/walking 10 meters, and rising from supine to stand were performed in the corrected ITT population. It was recognized after unblinding that 2 patients had baseline 6MWTs that were incorrectly classified as valid. In fact, these 2 patients suffered from recent lower leg injuries that reduced their baseline 6MWD when compared to their prior 6MWD at Screening or subsequent 6MWD at Week 6. These 2 patients should not have been included in the ITT population without a valid baseline test. To address this issue their baseline values were replaced with screening values, creating a corrected ITT population.

Results

Participant flow

The study participant flow is shown in figure 6.

Fig. 6



Recruitment

The study took place between 28 February 2008 (first patient first visit) and 17 December 2009 (last patient last visit).

Conduct of the study

The most common protocol deviations involved variations from protocol-specified collection times for safety and efficacy assessments, particularly laboratory evaluations (urinalysis, haematology and blood chemistries). Patients who did not have an evaluation that was needed for a particular statistical analysis (e.g. missing baseline data in evaluations of change from baseline) were excluded from that analysis. With regard to eligibility, seven of the 174 patients had laboratory abnormalities at screening that should have excluded their participation in the study. However, a decision had already been mad to amend the protocol to allow for inclusion of patients with clinically insignificant laboratory abnormalities and thus, waivers were granted allowing these patients into the study and the planned protocol amendment was subsequently implemented. None of the patients received excluded concomitant medication and no patients were withdrawn from the study due to developing any of the withdrawal criteria (as assessed by the adverse event data).

Baseline data

A summary of the patient population enrolled in the study is presented in the tables below:

Table 5 Patient demographics

Characteristic	Treatment Arm		
	Placebo	Ataluren 10, 10, 20 mg/kg	Ataluren 20, 20, 40 mg/kg
	N=57	N=57	N=60
Age, years			
Mean (SD)	8.3 (2.33)	8.8 (2.91)	8.4 (2.53)
Median	8.0	8.0	8.0
Range	5-15	5-20	5-16
Sex, n (%)			
Male	57 (100.0)	57 (100.0)	60 (100.0)
Female	0 (0.0)	0 (0.0)	0 (0.0)
Race, n (%)			
Caucasian	54 (94.7)	53 (93.0)	50 (83.3)
Black	0 (0.0)	1 (1.8)	1 (1.7)
Asian	1 (1.8)	1 (1.8)	4 (6.7)
Hispanic	1 (1.8)	1 (1.8)	2 (3.3)
Other	1 (1.8)	1 (1.8)	3 (5.0)
Body height, cm			
Mean (SD)	123.4 (11.8)	124.5 (15.3)	126.2 (13.8)
Median	122.1	121.1	125.9
Range	104-163	99-173	99-173
Body weight, kg			
Mean (SD)	28.6 (9.1)	31.2 (12.1)	31.9 (12.8)
Median	25.6	27.0	27.6
Range	16-55	16-76	17-84
Body mass index, kg/m^2			
Mean (SD)	18 (3.7)	19 (3.5)	19 (4.8)
Median	17.4	18.8	18.2
Range	13-29	14-31	14-41
Sibling pairs[a], n	4	1	1

[a] The second sibling enrolled was assigned to the same treatment arm as the first sibling.
Abbreviation: SD = standard deviation

Table 6 Patient disease-related characteristics

Characteristic	Treatment Arm		
	Placebo	Ataluren 10, 10, 20 mg/kg	Ataluren 20, 20, 40 mg/kg
	N=57	N=57	N=60
Age at diagnosis, years			
Mean (SD)	3.9 (2.3)	3.3 (1.8)	3.8 (2.0)
Median	4.0	3.0	3.5
Range	0-10	0-9	0-8
Time from diagnosis to randomization, years			
Mean (SD)	4.4 (2.5)	5.4 (3.4)	4.6 (3.1)
Median	5.0	5.0	4.0
Range	0-11	0-17	0-14
Phenotype diagnosis, n (%)			
Proximal muscle weakness	50 (88)	49 (86)	52 (87)
Waddling gait	44 (77)	43 (75)	49 (82)
Gowers' maneuver	47 (83)	50 (88)	51 (85)
Calf hypertrophy	56 (98)	48 (84)	55 (92)
Other[a]	12 (21)	19 (33)	13 (22)
Baseline 6MWD[b], m			
Mean (SD)	359.6 (87.7)	350.0 (97.6)	358.2 (104.0)
Median	354.0	362.1	368.0
Range	159-533	75-525	90-554

[a] Other phenotypic diagnoses included toe walking, muscle cramps, lordosis, and developmental delay.
[b] Two patients (1 randomized to placebo and 1 randomized to ataluren 20, 20, 40 mg/kg) had lower-limb injuries at baseline that affected their baseline 6MWD (see Section 11.4.1.1.2.1); for post-hoc analyses, their baseline 6MWD and timed function test values were replaced with screening values. Following this approach, mean (SD) baseline 6MWD was 361.1 (87.5) for placebo, 350.0 (97.6) for ataluren 10, 10, 20 mg/kg, and 361.2 (99.7) for ataluren 20, 20, 40 mg/kg.
Abbreviations: 6MWD = 6-minute walk distance, SD = standard deviation

Table 7 Patient genetic characteristics

Characteristic, n (%)	Treatment Arm		
	Placebo	Ataluren 10, 10, 20 mg/kg	Ataluren 20, 20, 40 mg/kg
	N=57	N=57	N=60
Stop codon[a]	57 (100.0)	57 (100.0)	60 (100.0)
Agreement between central vs local analyses[a]			
Stop codon type	57 (100.0)	56 (98.2)	57 (95.0)
Exon location	57 (100.0)	54 (94.7)	58 (96.7)
Stop codon type			
UGA	31 (54.4)	29 (50.9)	23 (38.3)
UAG	12 (21.1)	17 (29.8)	19 (31.7)
UAA	14 (24.6)	11 (19.3)	18 (30.0)
Exon location			
1 to 39	33 (57.9)	25 (43.9)	36 (60.0)
40 to 79	24 (42.1)	32 (56.1)	24 (40.0)

[a] Documentation of the presence of a nonsense mutation in the dystrophin gene as determined by gene sequencing from a laboratory certified by CAP, CLIA, or an equivalent organization was required prior to enrollment; the genetic mutation was subsequently confirmed by a central dystrophin gene sequencing laboratory.
Abbreviations: CAP = College of American Pathologists, CLIA = Clinical Laboratory Improvement Act/Amendment, UAA = uridine-adenosine-adenosine, UAG = uridine-adenosine-guanosine, UGA = uridine-guanosine-adenosine

Numbers analysed

Available data for all 57 patients who received placebo, 57 patients who received ataluren 10, 10,

20 mg/kg and 60 patients who received ataluren 20, 20, 40 mg/kg were included in analyses of efficacy. The only patients excluded from all analyses of efficacy were those who failed screening (see fig. 7 above).

Outcomes and estimation

Primary outcome

The model-estimated difference (pre-specified analysis) in the mean change in 6MWD from baseline to Week 48 between the ataluren 10, 10, 20 mg/kg and placebo arm was 26.4 meters (95% CI -4.2,57.1).

Further results of the pre-specified efficacy analysis in the ITT population, i.e. analysis of the change in 6MWD at Week 48 is presented in table 8 below.

Table 8 Pre-specified MMRM analyses of change in 6MWD (ITT)

Endpoint[a,b]	Ataluren 10, 10, 20 mg/kg vs Placebo				Ataluren 20, 20, 40 mg/kg vs Placebo			
	Δ		p-value[c]		Δ		p-value[c]	
	Mean	95% CI	Nominal	Adjusted	Mean	95% CI	Nominal	Adjusted
Untransformed 6MWD	26.4	-4.2, 57.1	0.0905	0.1592	-0.1	-30.4, 30.2	0.9956	1.0000
Rank-transformed 6MWD	--	--	0.1490	0.2539	--	--	0.4756	0.6959

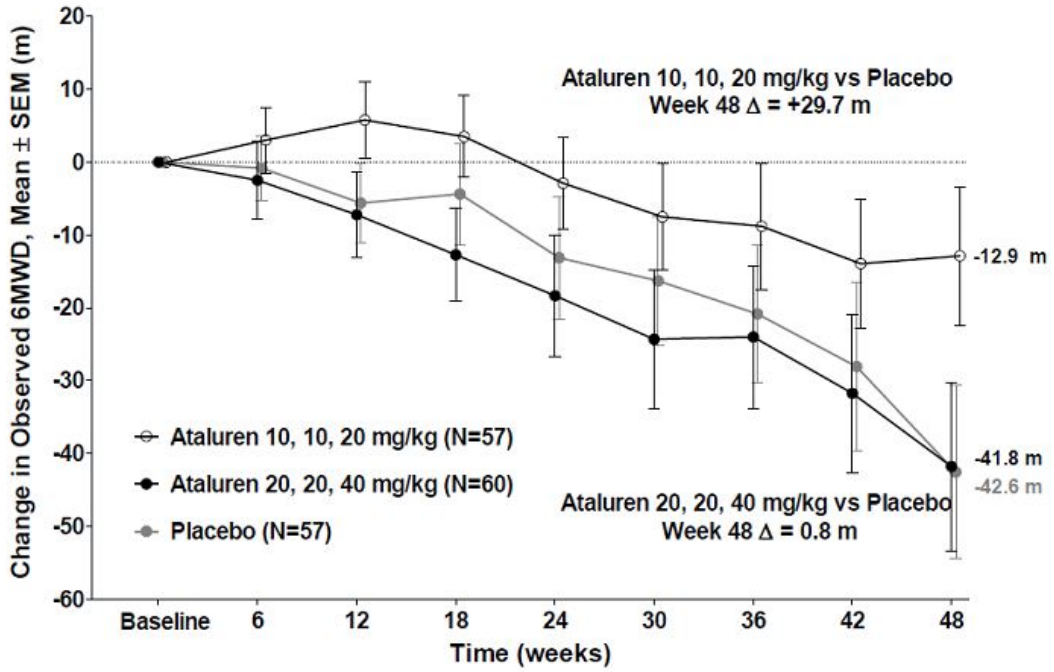
[a] The analysis of rank-transformed 6MWD was considered primary due to non-normal distribution of the untransformed 6MWD data.

[b] MMRM model: 6MWD = baseline 6MWD (covariate) + arm + visit + visit*arm + age group (<9 vs ≥9 years) + corticosteroid (yes vs no); unstructured variance/covariance matrix

[c] Dunnett's test was applied to adjust for the comparison of 2 dose levels vs placebo

The observed difference between the ataluren 10, 10, 20 mg/kg and placebo arms in mean change in observed 6MWD from baseline to Week 48 was 29.7 meters (Figure 8).

Figure 8, Mean change in observed 6MWD by Visit (ITT)



Abbreviations: 6MWD = 6-minute walk distance, ITT = intent-to-treat population, SEM = standard error of the mean

A *post hoc* statistical analysis was performed on the cITT population (see section "Statistical methods") and presented by the Applicant to support the efficacy of ataluren. The observed difference in the mean change in the 6MWD from baseline to Week 48 between placebo and the lower dose of ataluren (10, 10, 20 mg/kg) was 31.3 metres, while the model-estimated difference was 31.7 (nominal p=0.0281, adjusted p=0.0561) Essentially no difference was observed between the higher dose (20, 20, 40 mg/kg) and placebo. The results are shown in figure 9 and table 8 below).

Fig. 9 Mean change in observed 6MWD by visit (cITT)

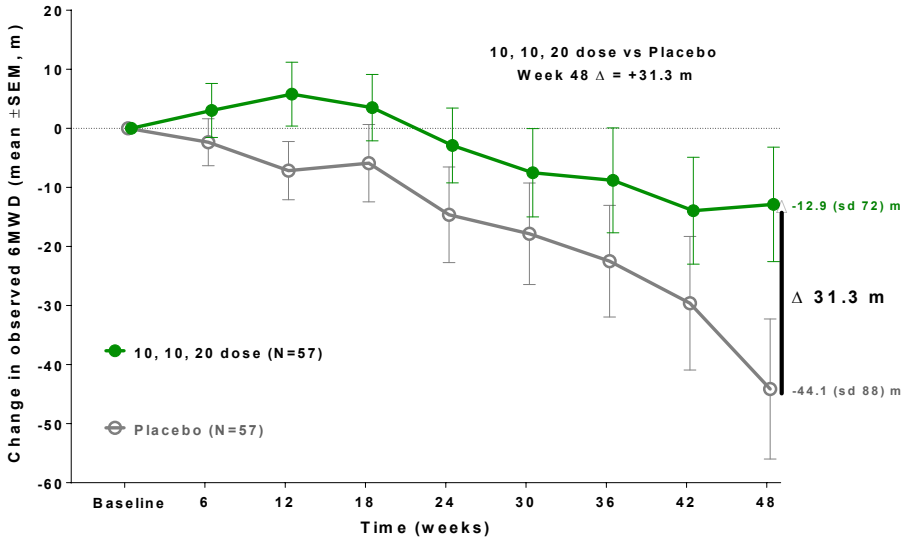


Table. 8. *Post Hoc* MMRM Analysis of Change in Untransformed 6MWD based on Permutation test (Corrected ITT).

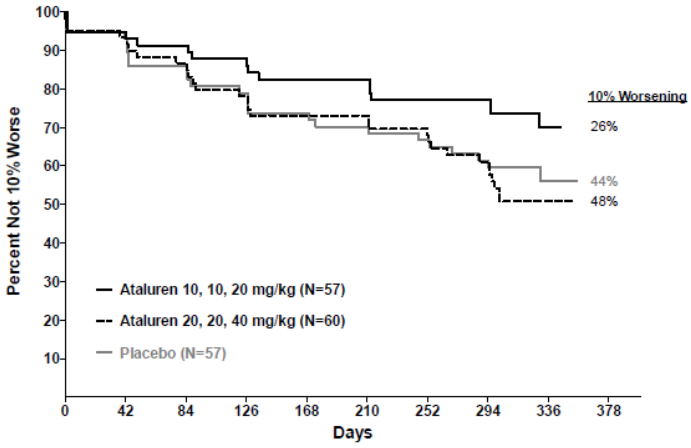
Analysis	Ataluren 10, 10, 20 mg/kg vs Placebo				Ataluren 20, 20, 40 mg/kg vs Placebo			
	Δ		p-value		Δ		p-value	
	Mean	95% CI	Nominal	Adjusted	Mean	95% CI	Nominal	Adjusted
MMRM[a]	31.7	5.1, 58.3	0.0197	0.0367[b]	-1.62	-27.8, 24.6	0.9031	0.9891[b]
Permutation test[c]	--	--	0.0281	0.0561[d]	--	--	0.9118	0.9910[d]

[a] MMRM model: 6MWD = baseline 6MWD (covariate) + arm + visit + visit*arm + baseline 6MWD*visit + age group (<9 vs ≥9 years) + corticosteroid (yes vs no); unstructured variance/covariance matrix.
[b] Dunnett's test was applied to adjust for the comparison of 2 dose levels vs placebo.
[c] Permutation test of 10,000 re-randomizations. For each re-randomization, patients were dynamically re-randomized in the same order as they originally entered the study (starting seed = 14576).
[d] Based on the proportion of the 10,000 permutations in which the maximum effect size among the 2 comparisons (10, 10, 20 mg/kg vs placebo and 20, 20, 40 mg/kg vs placebo) exceeded the observed maximum effect size
Abbreviations: 6MWD = 6-minute walk distance, ITT = intent-to-treat population, MMRM = mixed-model repeated-measures

As pre-specified, the proportions of patients with at least 10% worsening in 6MWD at Week 48 were assessed. At Week 48, 44% and 48% of patients in the placebo and 20, 20, 40 mg/kg ataluren arms, respectively, were progressors, with no statistically significant difference between these arms. In the 10, 10, 20 mg/kg ataluren arm, 26% of patients were progressors (nominal p=0.0326, adjusted p=0.0652).

The hazard ratio for ataluren 10, 10, 20 mg/kg vs placebo was 0.51 representing a 49% reduction in the risk of 10% 6MWD worsening.

Fig. 10 Time to persistent 10% 6MWD worsening (cITT)



Secondary outcomes

Timed function tests

The results on timed function tests of muscle function (table 9) indicated positive trends for climbing and descending four stairs and running/walking 10 metres, as evidenced by less decline over 48 weeks; these differences were more prominent in the lower dose. No difference between ataluren and placebo was observed for the stand to supine test.

Table 9 Timed function tests and functional method scores (cITT)

Endpoint[a]	Placebo		Ataluren 10, 10, 20 mg/kg				Ataluren 20, 20, 40 mg/kg			
	Baseline, mean	Δ at Wk 48, mean	Baseline, mean	Δ at Wk 48, mean	Difference, mean (95% CI)	% Difference, mean[b]	Baseline, mean	Δ at Wk 48, mean	Difference, mean (95% CI)	% Difference, mean
Climb 4 stairs										
Time, s	6.0	4.8	6.9	2.4	-2.4 (-4.9, 0.0)	-50%	7.5	3.7	-1.2 (-3.6, 1.2)	-23%
Method score	4.0	-0.4	3.6	0.1	0.4 (0.1, 0.9)	--	3.9	-0.3	0.04 (-0.4, 0.5)	--
Descend 4 stairs										
Time, s	5.5	4.1	6.1	2.4	-1.6 (-4.3, 1.0)	-41%	6.7	3.1	-1.0 (-3.6, 1.6)	-24%
Method score	3.7	-0.1	3.3	0.2	0.2 (-0.2, 0.6)	--	3.6	-0.2	-0.1 (-0.5, 0.3)	--
Run/walk 10 m										
Time, s	6.7	3.2	7.5	1.7	-1.5 (-3.7, 0.7)	-47%	7.4	2.7	-0.4 (-2.6, 1.7)	-16%
Method score	4.8	-0.6	4.7	-0.4	0.2 (-0.1, 0.6)	--	4.6	-0.4	0.2 (-0.1, 0.6)	--
Supine to stand										
Time, s	11.5	3.2	10.8	3.2	-0.01 (-2.3, 2.3)	0%	12.3	3.0	-0.2 (-2.5, 2.1)	-6%
Method score	3.6	-0.4	3.7	-0.3	0.1 (-0.2, 0.5)	--	3.6	-0.3	0.1 (-0.3, 0.4)	--

[a] For timed function tests, negative differences between ataluren and placebo represent better outcomes in ataluren-treated patients. For functional method scores, positive differences between ataluren and placebo represent better outcomes in ataluren-treated patients.
[b] % Difference, mean calculation = ataluren Week 48 Δ - placebo Week 48 Δ / placebo Week 48 Δ

Upper and lower extremity myometry tests

Over 48 weeks, ataluren-treated patients generally showed less decline in muscle strength, as evidenced by smaller decreases in most myometry parameters relative to placebo (table 10). These trends were more prominent at the 10, 10, 20 mg/kg dose.

Table 10 Myometry (ITT)

Endpoint, lbs	Placebo		Ataluren 10, 10, 20 mg/kg			Ataluren 20, 20, 40 mg/kg		
	Base-line, mean	Δ at Wk 48, mean	Base-line, mean	Δ at Wk 48, mean	Difference[a], mean (95% CI)	Base-line, mean	Δ at Wk 48, mean	Difference[a], mean (95% CI)
Knee flexion	11.06	0.38	12.08	-0.07	-0.46 (-1.66, 0.75)	12.45	0.39	0.01 (-1.19, 1.20)
Knee extension	12.96	-1.85	12.81	-0.63	1.22 (-0.15, 2.59)	12.71	-0.59	1.26 (-0.10, 2.62)
Elbow flexion	8.14	-0.35	7.66	-0.10	0.25 (-0.41, 0.91)	8.72	-0.50	-0.15 (-0.80, 0.51)
Elbow extension	6.77	-0.51	6.19	0.10	0.60 (-0.05, 1.26)	6.81	-0.28	0.22 (-0.43, 0.87)
Shoulder abduction	5.76	-0.28	5.81	-0.08	0.21 (-0.50, 0.90)	6.37	-0.96	-0.68 (-1.39, 0.02)

[a] Positive differences between ataluren and placebo represent better outcomes in ataluren-treated patients.

Step activity monitoring

Step activity monitoring was performed in the community setting. Patients wore a device monitoring and recording the numbers of steps taken. Differences in changes in mean steps taken from baseline to Week 48 favoured ataluren and placebo at both dose levels. The proportions of

time during which the patient is moving at 0 (no activity), 1-15 (low activity), 16-30 (medium activity) and above 30 (high activity) steps/minute were also assessed (table 11).

Table 11 Proportions of time spent at no, low, medium and high activity (ITT)

Endpoint, %[a]	Placebo		Ataluren 10, 10, 20 mg/kg			Ataluren 20, 20, 40 mg/kg		
	Base-line, mean	Δ at Wk 48, mean	Base-line, mean	Δ at Wk 48, mean	Difference[b], mean (95% CI)	Base-line, mean	Δ at Wk 48, mean	Difference[b], mean (95% CI)
No activity	48.17	4.08	51.88	2.78	-1.30 (-5.51, 2.90)	49.41	4.07	-0.01 (-4.16, 4.13)
Low activity	32.86	-1.11	32.38	-1.12	-0.01 (-2.90, 2.88)	32.91	-2.06	-0.95 (-3.80, 1.90)
Medium activity	11.84	-1.92	10.00	-0.69	1.23 (-0.25, 2.71)	11.11	-1.35	0.57 (-0.89, 2.03)
High activity	7.17	-1.03	5.78	-0.96	0.07 (-1.18, 1.31)	6.59	-0.66	0.37 (-0.87, 1.60)

[a] No activity = 0 steps/minute; low activity = ≤15 steps/minute; medium activity = 16-30 steps/minute; high activity = >30 steps/minute

[b] For no activity, negative differences between ataluren and placebo represent better outcomes in ataluren-treated patients. For medium and high activity, positive differences between ataluren and placebo represent better outcomes in ataluren-treated patients.

Wheelchair use

Patient-reported wheelchair use showed a positive trend favouring ataluren 10, 10, 20 mg/kg vs placebo. Mean percentage of day of wheelchair use (95%CI) increased from baseline to Week 48 by 11.5% (4.36, 18.54) for placebo, 4.0% (-2.77, 10.68) for ataluren 10, 10, 20 mg/kg and 9% (0.7, 17.38) for ataluren 20, 20, 40 mg/kg. The treatment differences were not statistically significant.

Frequency of accidental falls

Over 48 weeks, reductions in the frequency of accidental falls were seen at both dose levels compared to placebo. The absolute numbers showed a decrease from baseline to Week 48 of -0.04 falls per day in the 10, 10, 20 mg/kg ataluren arm vs increase of 0.18 falls per day in the placebo arm (table 12).

Table 12 Change in falls/day

Treatment arm	Falls/Day (SD)	
	Baseline	Week 48
Placebo	0.54 (0.94)	0.72 (1.28)
Ataluren 10, 10, 20 mg/kg	0.27 (0.48)	0.23 (0.53)
Ataluren 20, 20, 40 mg/kg	0.40 (0.60)	0.28 (0.53)

Quality of life measures

Positive trends in PedsQL favoured ataluren vs placebo in the physical function domain in a pre-specified analysis. The difference in the mean change in physical functioning score, favouring ataluren 10, 10, 20 mg/kg over placebo, was 3.4 at Week 48. As with the other endpoints, this was more pronounced in a post-hoc analysis of the decline phase subgroup; within this subgroup a difference of 6.1 in the mean change in physical functioning score, favouring ataluren 10, 10,

20 mg/kg over placebo, was observed at Week 48.

Other secondary endpoints

Changes in the other secondary outcome measures not directly related to physical functioning (patient-reported psychosocial functioning, treatment satisfaction, digit span task, heart rate monitoring and serum CK) were generally small and no clear differentiation between ataluren and placebo was observed.

Muscle dystrophin expression

The muscle dystrophin expression data were compromised by poor sample quality and inadequacies in currently available methods for quantification of dystrophin expression.

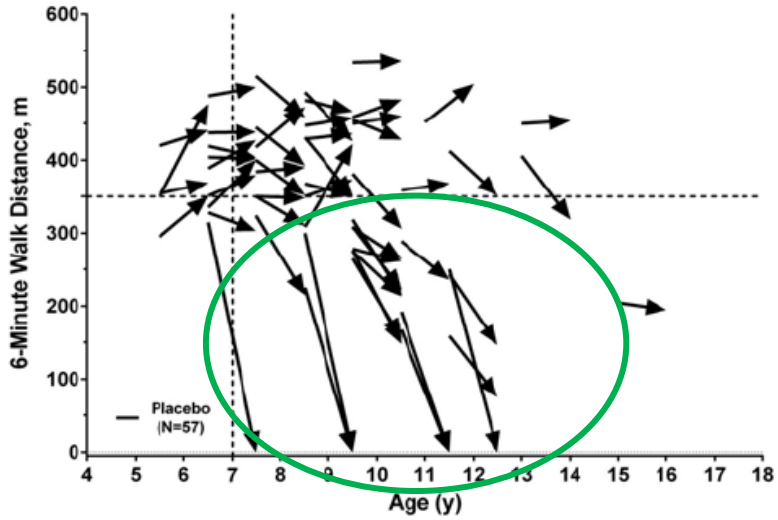
Ataluren plasma concentration

Ataluren plasma concentration before and 2 hours following the morning dose were dose-proportional and well-maintained over time. All patients who received 10, 10, 20 mg/kg ataluren had a mean C_{2h} across all visits less or equal to 19.3 mcg/ml. Consistent with the analysis by treatment arm, patients who received 20, 20, 40 mg/kg ataluren but had mean C_{2h} below or equal to 19.3 mcg/ml showed a better response to ataluren as measured by 6MWD, timed function tests and frequency of accidental falls than those who received the higher dose and had C_{2h} above 19.3 mcg/ml.

Ancillary analyses

Subgroup analyses were performed in patients who were in the decline of the disease. Criteria for this subgroup were identified based on the results from the placebo arm which helped to define the natural history of 6MWT in DMD (fig. 11).

Fig. 11 The natural history of DMD as defined by 6MWT data from the placebo group in study 007

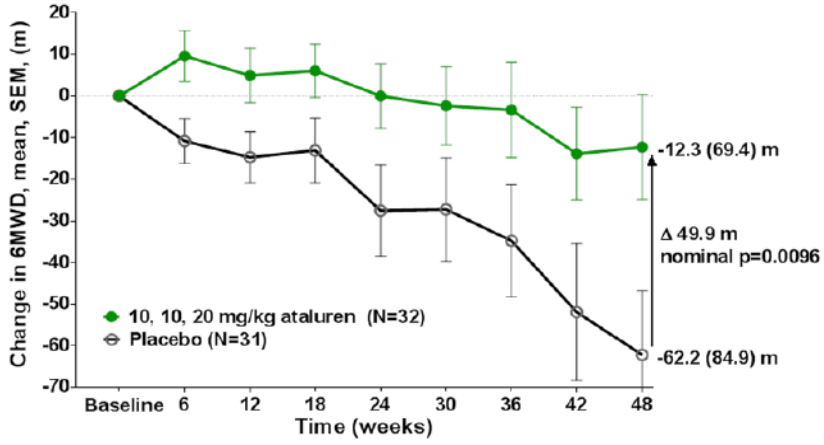


This figure shows that patients younger than 7 years tend to increase their 6MWD over 48 weeks (maturational improvements). Patients who have higher baseline 6MWD (above 350 m) tend to be stable over the 48-week period, whereas those patients with lower baseline 6MWD (below 350 m) show decline in their walking ability over 48 weeks.

Based on the natural history data, the applicant considered that the ability to measure a

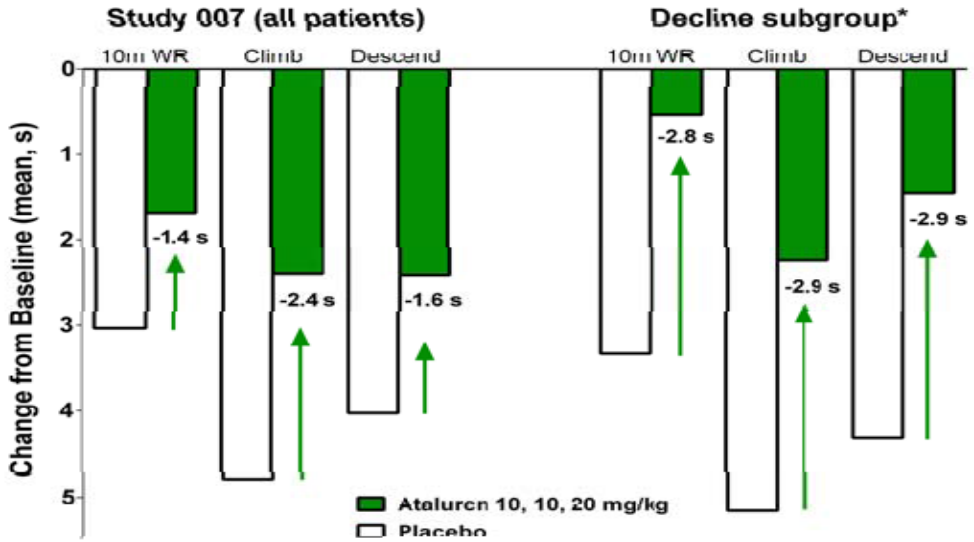
treatment effect over a shorter period (48 weeks) would be greater in the decline-phase patients (7-16 years, baseline 6MWD ≥150 metres and <80% of predicted 6MWD). This was reflected in the design of the planned confirmatory phase 3 trial (inclusion criteria) as well as in the "decline phase" subgroup analyses of the primary and secondary endpoints of study 007 (fig. 12 and fig. 13).

Figure 12 Mean change in the observed 6MWD by visit (decline phase subgroup)



*In patients on corticosteroids, between 7 and 16 years of age, with baseline 6MWD ≥150 m and ≤80% of predicted

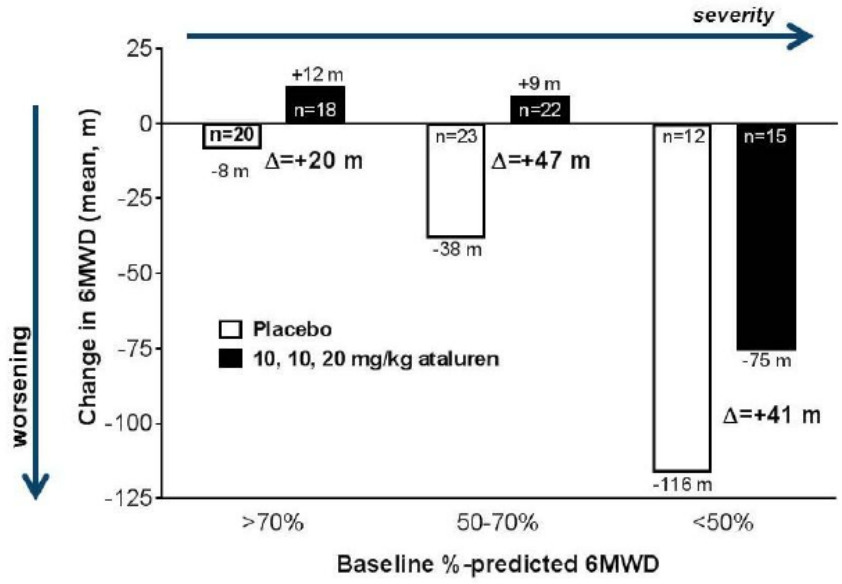
Fig. 13 TFT results in the phase 2b overall population vs decline phase subgroup



*On corticosteroids, age 7-16, Baseline 6MWD ≥150m and Baseline %-predicted 6MWD ≤ 80%
Abbreviations: 10m WR = 10-meter walk/run; s = seconds

Figure 14 presents the activity of ataluren observed in patients at different ambulatory stages, categorised based on %-predicted 6MWD at baseline, indicating a favourable effect of ataluren across the disease spectrum, including milder patients (i.e. baseline values above 70% predicted 6MWD).

Fig. 14 Response by category of ambulatory capacity



Abbreviation: 6MWD = six-minute walk distance

Furthermore, evidence of a correlation between the plasma concentration achieved and the effect in terms of 6MWT and TFTs was presented by the Applicant to support the robustness of the effect of the selected dose (fig. 15) and a scatter plot with change in 6MWT and plasma concentration on an individual patent level (fig. 16).

Fig. 15 Inverse concentration response in clinical data: Phase 2b study

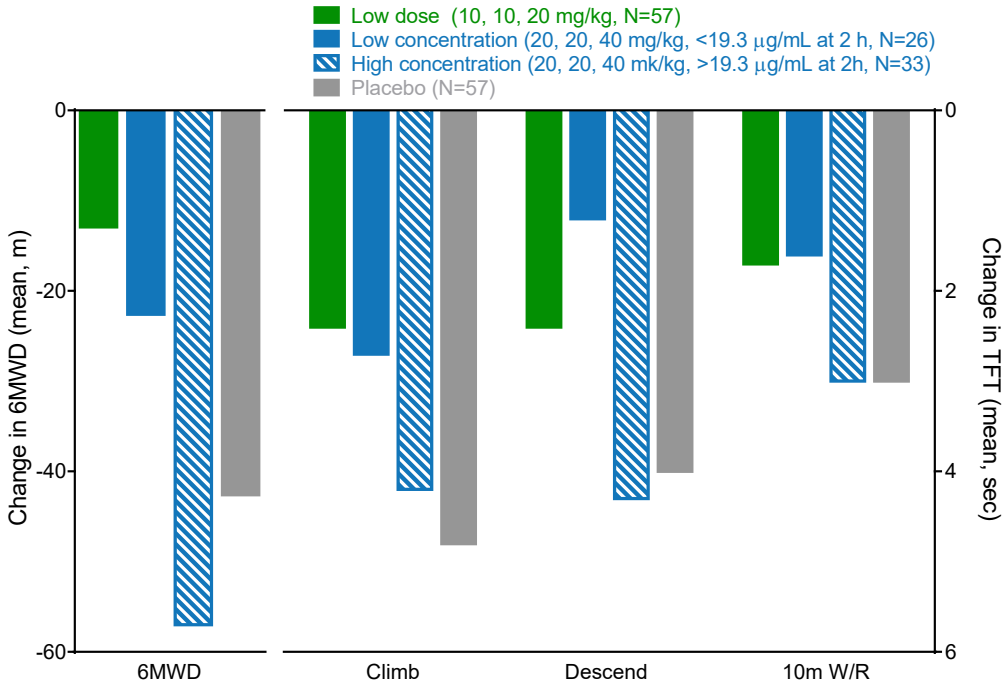
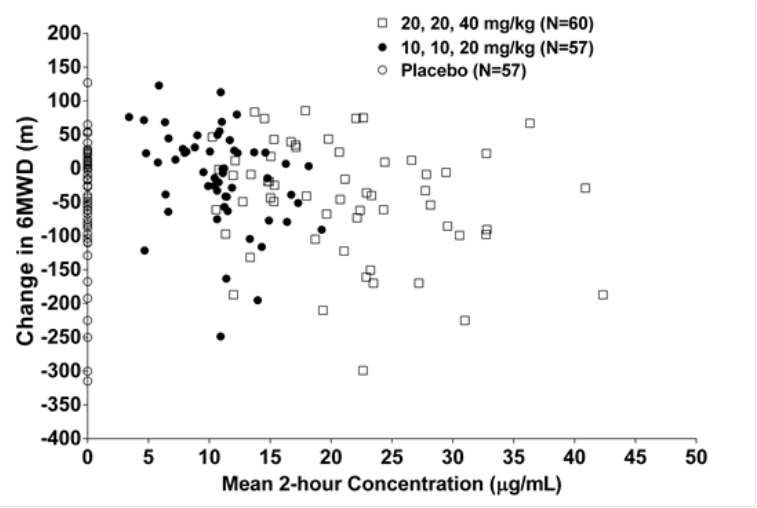


Fig. 16 Plasma concentration versus change on 6MWT



Summary of main study

The following table summarises the efficacy results from the main study 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 13 Summary of Efficacy for trial PTC124-GD-007-DMD

Title: A Phase 2b Efficacy and Safety Study of PTC124 in Subjects with Nonsense-Mutation-Mediated Duchenne and Becker Muscular Dystrophy			
Study identifier	PTC124-GD-007-DMD		
Design	multicenter, international, randomized (1:1:1), double-blind, placebo-controlled, dose-ranging study, stratified by age, corticosteroid use and baseline 6MWD		
	Duration of main phase: Duration of screening phase: Duration of extension phase:		48 weeks n.a. n.a. (subject to a separate protocol)
Hypothesis	Superiority		
Treatments groups	Placebo		taken orally three times a day (morning, midday, evening) N= 57/57 (randomized/ treated)
	Ataluren 10-10-20 mg/kg		taken orally three times a day (morning, midday, evening) N= 57/57 (randomized/ treated)
	Ataluren 20-20-40 mg/kg		taken orally three times a day (morning, midday, evening) N= 60/59 (randomized/ treated) Note: 1 patient was withdrawn at W6 due to protocol non-compliance.
Endpoints and definitions	Primary endpoint	6MWD	Change in 6-minute walk distance from baseline to Week 48
Results and Analysis			

Analysis description	**Primary Analysis** A mixed-model repeated-measures (MMRM) analysis of the change in 6MWD from baseline to Week 48 was performed in the intent-to-treat (ITT) population (all randomized patients with a valid 6MWT at baseline and ≥1 post-baseline visit). Included in the model were treatment, baseline 6MWD, age (<9 or ≥9 years), corticosteroid use (yes or no), visit, and treatment-by-visit interaction. Because baseline 6MWD was included in the model as a covariate, the stratification factor of baseline 6MWD (≥350 or <350 meters) was excluded from this model.			
Analysis population and time point description	Intent to treat population; time point – week 48			
Descriptive statistics	Treatment group	Placebo	Ataluren 10-10-20 mg/kg	Ataluren 20-20-40 mg/kg
	Number of subjects	57	57	60
	Baseline	359.5 (87.7)	350.0 (97.6)	358.2 (104.0)
	Change in observed 6MWD Mean (SD) Median Min, max	 -42.6 (90.1) -17.0 -314.5, 127.2	 -12.9 (72.0) -0.5 -248.5, 123.1	 -41.8 (89.2) -36.0 -299.0, 172.1
Effect estimate per comparison	The model-estimated difference in mean change in untransformed 6MWD at Week 48	Comparison groups	Ataluren 10-10-20 mg/kg vs Placebo	
		Difference (meters)	26.4	
		95% CI	-4.2, 57.1	
		p-value	nominal -0.0905 adjusted – 0.1592	
	the model-estimated difference in mean change in untransformed 6MWD at Week 48	Comparison groups	Ataluren 20-20-40 mg/kg vs Placebo	
		Difference (meters)	- 0.1	
		95% CI	-30.4, 30.2	
		p-value	nominal - 0.9956 adjusted – 1.0000	

Clinical studies in special populations

The target patient population for the treatment with ataluren is predominantly paediatric and the majority of subjects in the studies were children, with the exception of the phase 1 studies in healthy volunteers. Ataluren was not evaluated in elderly patients, which is in line with the short life expectancy of the patient population.

No studies in patients with renal or hepatic impairment were performed (see the Clinical pharmacology discussion, section 2.4.4).

Supportive studies

With the exception of the pivotal 007, all studies presented in the dossier were conducted as uncontrolled:

PTC124 GD 004 DMD (as Study 004) - an open-label Phase 2a trial assessing 3 dose levels of Translarna (4, 4, 8 mg/kg; 10, 10, 20 mg/kg; and 20, 20, 40 mg/kg) evaluating muscle dystrophin expression as the primary endpoint.

The results of study 004 are summarised and discussed in the Clinical Pharmacology section (2.4).

PTC124 GD 004e DMD (Study 004e) - an open-label Phase 2a extension trial assessing Translarna 20, 20, 40 mg/kg

PTC124 GD 007e DMD (study 007e) - an open label Phase 2b extension trial assessing Translarna 20, 20, 40 mg/kg

PTC124 GD 008 DMD, referred to as Study 008 - an open-label Phase 2a trial assessing Translarna 20, 20, 40 mg/kg

After unbinding of study 007 and the observation of no separation of the high dose from placebo, studies 004e, 007e and 008 were some prematurely stopped since patients were treated with the 20/20/40 mg/kg dose.

Two open-label studies were ongoing at the time of this marketing authorisation application:

PTC124-GD-016-DMD (Study 016) - an open-label Phase 3 safety trial of ataluren in ambulatory and non-ambulatory patients who originally participated in Studies 007, 007e, 004, 004e or 008. Patients were treated with ataluren 10, 10, and 20 mg/kg for an open duration.

PTC124-GD-019-DMD (Study 019) - an open-label Phase 3 safety trial of ataluren in ambulatory and non-ambulatory patients who originally participated in Studies 007 and 007e Patients were treated with 10, 10, and 20 mg/kg for 48 weeks.

2.5.3. Discussion on clinical efficacy

Design and conduct of clinical studies

The clinical programme of ataluren for nmDMD consisted of phase 1 single and multiple dose studies, a phase 2a proof-of-concept study (004), one phase 2b efficacy and safety study (007) and open label extension studies 004e and 007e. The phase 2b study was the only placebo-controlled study and was presented by the Applicant as pivotal. The CHMP considered that claims of efficacy based on a single study could be acceptable in the context of a rare disease provided that results of the study were sufficiently robust and compelling.

The main clinical study 007 was performed as multicentre, randomised, double-blind and placebo-controlled. The CHMP considered that the choice of placebo for the reference arm of the trial was justified, as ataluren represents a first-in-class approach to DMD and no approved standard therapy exists. This approach was also in line with a protocol assistance provided by the CHMP on the product.

With respect to the choice of the inclusion and exclusion criteria, the CHMP noted that as the distribution of age at study recruitment was wide (i.e. the age of diagnosis ranged from 0 – 10 years and the age range of recruited subject ranged from 5 to 20 years) and patients with DMD as well as BMD could be enrolled, the population was rather heterogeneous. Furthermore, as the study included only ambulant boys, since the primary endpoint was the 6MWT, the CHMP considered that extrapolation of efficacy results to the entire DMD patient population might be difficult.

The applicant provided a justification as to why the 6MWT is considered the most appropriate and relevant measurement tool for DMD and for the objectives of the study. The CHMP acknowledged

that the 6MWT is one of the most commonly applied tools for this condition and that ambulation is a very important aspect for individuals affected by the disease. However, as discussed in literature, the 6MWT has in itself several deficiencies, such as high inter- and intra-individual variability. Furthermore, the results can be influenced by several factors, e.g. behaviour, motivation, fatigue and a learning effect. Therefore, the CHMP highlighted during their follow-up protocol assistance that clinically meaningful effects should be seen in the domains of disability and muscle strength. Since the study was already performed with the 6MWT as the only primary endpoint, the CHMP pointed out in this protocol assistance that the outcomes of the timed functional tests, myometry and the other secondary endpoints should be supportive of efficacy, i.e. pointing in the same direction.

The 48 week duration of the clinical trial was in general considered adequate to investigate the efficacy of the test product. Still, based on the data available (and discussed below), the CHMP noted that the ability to measure a treatment effect in 1 year was lower in patients with stable ambulatory ability, as compared to the population of patients in the decline phase of ambulation, which might have impacted the efficacy observed in the overall population of the study.

With respect to GCP compliance and data verification, a routine inspection and an additional inspection requested by CHMP were performed. The inspections were conducted at the sponsor site, two clinical investigator sites and at the central pathology laboratory where the biopsies were analysed. The main findings pertained to archiving, AE reporting, lack of oversight (at the investigator sites); lack of oversight and QC/QA issues (at the sponsor site) and limited GCP-awareness regarding documentation and archiving (at the laboratory). With respect to the acceptability of the clinical trial data, the inspection team considered that the data presented in the clinical study reports were reliable and suitable for assessment in the MAA.

Efficacy data and additional analyses

The primary analysis of the data resulted in a difference of -0.1 m (95% CI -30.4, 30.2; nominal p-value= 0.9956, adjusted p-value=1.0000) between placebo and the high dose arm and a difference of 26.4 m (95% CI -4.2, 57.1; nominal p value=0.0905, adjusted p-value = 0.1592) between placebo and the low dose arm. As the results were not statistically significant, the study 007 was formally considered negative. Two subjects had invalid baseline measurements; analyses with these invalid baseline data, without these subjects or with corrected baseline values were performed to assess the impact of different approaches. P-values varying between 0.05 and 0.09 were observed, with sometimes substantially overlapping confidence intervals in the different analyses, but comparable results in terms of point estimates (25-35m) were seen. Taken together with the fact that the variation in 6MWD turned out to increase over visits and exceeded the variation accounted for in the sample size calculation, the lack of statistical significance was assumed to be a consequence of under-powerment of the trial. Overall, the effect was considered consistent, but the confidence intervals were too wide to be perceived as conclusive.

Further analyses and discussions were made on the corrected ITT population (cITT), which from a methodological point of view might be considered acceptable, although the CHMP flagged the fact that the results were post-hoc derived. In the post-hoc analysis of the primary endpoint, the 10/10/20 mg/kg group had an observed mean of 31.3 meters less deterioration on the 6MWT, as compared to the placebo group, while the 20/20/40 mg/kg group was not distinguishable from placebo. The model-estimated mean showed a value of 31.7 m (95 % CI 5.1,58.3) with a nominal p value= 0.0281 and an adjusted p value = 0.0561. The CHMP also considered the results of a progressor analysis which was discussed during the protocol assistance and which showed that the

proportion of subjects with 10% deterioration on the 6MWT (indicating disease progression) at week 48 was 26% in the low dose group versus 44% in the placebo and 48% in the high dose group.

To further support the robustness of the efficacy data the applicant was requested to discuss the outcomes on the secondary endpoints, particularly on the timed function tests and patient reported quality of life outcomes. The results indicated trends towards better outcome on some endpoints, e.g. 4 stair ascend, 4 stair descend, 10-m run/walk, smaller increase in time at the end of the study was seen in the ataluren arms as compared to placebo. These differences were more pronounced in the low dose group but being expressed in (mili)seconds were difficult to interpret.

The frequency of patient/parent-reported accidental falling was also considered a relevant endpoint by the CHMP, since it is related to limb fractures which further reduce the activity and may accelerate the transition to permanent loss of ambulation. Moreover, the fact that this endpoint did not highly correlate with the 6MWT indicated that the rate of falls is measuring a different activity than the 6MWT. Since accidental fall rate was included in the study protocol as a secondary endpoint, it was surprising that a rather high number of subjects had no baseline values. On request of the CHMP the absolute figures were presented indicating that the low dose arm had milder (on this parameter) subjects (0.27 falls/day) as compared to placebo (0.54) and high dose arm (0.40). The absolute rates of accidental falls indicated that the population in the low dose arm was milder in this respect. Therefore, the data on "change in accidental falls" (decrease from baseline to Week 48 of -0.04 falls per day in the 10, 10, 20 mg/kg ataluren arm, vs an increase of 0.18 falls per day in the placebo arm) were not considered as indicating a true effect of ataluren on this parameter.

With respect to the mean percentage of wheelchair use, the CHMP considered the baseline data and the respective increases observed in each treatment groups at week 48 and requested additional information on the way the wheel chair use was registered. As the questionnaire did not take into account total duration of use of a wheelchair, but only a day in which it was used, it was considered that the variability in performance and the actual need for use of a wheelchair could not be completely captured.

The data from the step activity monitoring indicated less increase in time spent in no activity in the 10/10/20 group, but the results were considered inconclusive. The clinical relevance of spending 2% less of the time in no activity was not substantiated.

The CHMP paid specific attention to evaluation of muscle strength, which is considered as an important outcome for this disorder. Over 48 weeks, ataluren-treated patients generally showed less decline in muscle strength, as evidenced by smaller decreases in most myometry parameters relative to placebo. However, observed differences were considered to be below the level of clinical meaningfulness. The CHMP considered the applicant´s argumentation that in the course of the disease there is severe disorganisation within the muscle (at the level of muscle fibres and fibre bundles) as well as fibrosis and aberrant innervation. Thus, in case of new production of functional dystrophin the regeneration processes and restoration of muscle strength may indeed be time consuming and may not be seen in a study of a shorter duration. Furthermore, as indicated by the SAG Neurology experts, while minimal increase in dystrophin production could lead to functional improvement, much higher levels of dystrophin in muscular fibres would have to be achieved for an effect on strength to be seen. In this context, i.e. little supportive evidence of effect on muscle strength, the CHMP considered that robust and convincing results on the functional outcomes (6MWD and functional timed tests) are of even greater importance and in the absence thereof, the entire body of evidence of efficacy is considered weak.

Overall, the CHMP considered that the results on the secondary endpoints did not support the primary endpoint. The view that there was little supportive evidence of effect from the data on the secondary endpoints was also shared by the SAG Neurology experts.

In an additional post-hoc analysis of a subgroup of patients in the decline phase (older than 7 years, treated with corticosteroids, baseline 6MWD ≥150 metres and <80% predicted 6MWD) a difference in mean 6MWD of -50 metres was seen, favouring ataluren 10, 10, 20 mg/kg. This result was considered to be a clinically meaningful improvement in terms of stabilisation of walking. A similar effect was also consistently observed in the key secondary endpoints, i.e. time function tests, which provided reassurance to the global results. The applicant discussed this finding making reference to the natural history data on 6MWD in DMD patients and concluded that over a shorter period of time, subjects in the decline phase of their walking ability may show a greater effect than patients with stabilised ambulation. At the same time, the applicant argued that in light of its mechanism of action, i.e. production of dystrophin, ataluren should provide protection from further damage and hence be more efficacious in less damaged muscle cells. While this would imply that treatment should start earlier than in the decline phase, which was also supported by the SAG Neurology experts, the CHMP maintained that the potential effect in earlier stages of the disease was not evidenced. Overall, the CHMP considered that the patients in the decline phase of their ambulation constituted only a subset of the study 007 population and the analysis should be seen as exploratory. Therefore, the results to be generated in the ongoing confirmatory trial enriched with a population of patients in the decline phase were seen as critical to addressing this issue.

The CHMP considered that even if the lack of statistical significance was disregarded, there is an outstanding issue pertaining to the absence of effect seen in the higher dose. The applicant argued that the finding is explained by the bell-shaped curve dose response, supporting their position by a combination of non-clinical and clinical data. In order to further address this issue, the applicant submitted a correlation between the plasma concentration achieved and the effect in terms of 6MWT and TFTs supporting the robustness of the effect of the selected dose (fig. 15 above). While patients with lower concentrations appeared to show better results on 6MWD as well as across TFTs, the CHMP considered that a scatter plot with change in 6MWT and plasma concentration on an individual patient level would have been of greater value. This data were additionally presented by the applicant (fig. 16 above). However, the CHMP was of the view that no specific pattern could be identified to provide additional evidence in support of the bell shape concentration response curve.

The data in support of the bell-shape curve hypothesis were considered to be inconsistent and not allowing a reliable assessment. The CHMP also took into consideration the SAG Neurology comment that additional non-clinical *in vivo* data would have been useful. The evidence was mainly limited to *in vitro* data from myotubes derived from DMD patients and similar findings were not demonstrated to occur *in vivo*. The mechanistic explanation provided by the Applicant was not considered as sufficient level of evidence. Overall, the CHMP concluded that the effect observed in the lower dose only could be a chance finding.

Additional expert consultation

In the course of the procedure, the CHMP identified need for input from the SAG Neurology on the three following questions:

- **Question 1**

Does the SAG consider that the evidence for the mechanism of action of ataluren (nonsense mutation read-through) is convincing, and the results on dystrophin

production could be seen as supportive of the pharmacodynamics of ataluren?

The SAG considered that mechanism of action seemed plausible, but the experts felt that the provided data were still not convincing enough, and that they would need more information in order to be certain. The same was true for the data provided on dystrophin production in this case, that at least the data from the available biopsies, limited as they may be, should be provided. Thus, the SAG considered that presently the available data on dystrophin production cannot be used as supportive of the pharmacodynamics of ataluren.

- **Question 2**

Does the SAG agree that the presented pre-clinical and clinical evidence supports the bell-shaped dose-response curve and hence, the absence of efficacy at the higher dose studied?

The SAG considered that the proposed hypothesis for the bell-shaped dose response curve seemed likely, but once again the experts felt that additional information was needed. More specifically, it was noted that while evidence on the bell-shape dose-response curve was available in several pre-clinical models, no data were generated in the mdx mouse model, relating the production of dystrophin to the levels of ataluren in the muscle fibres. Such evidence would be considered of relevance, as the available data describe only the relationship between plasmatic levels of ataluren and dystrophin production.

Overall, the SAG was of the view that no clear-cut conclusions could be derived on the bell-shaped dose-response hypothesis and the absence of efficacy in the higher dose studied in the Ph II trial.

- **Question 3**

Does the SAG consider, based on the data presented by the Applicant, that the observed effects are sufficiently robust and clinically meaningful taking into account the results on the primary and secondary endpoints? This should be discussed within the context of starting treatment at all stages of the disease (as now claimed by the MAH) or in the subgroup of patients with more advanced disease (where effects appear to be different).

The SAG considered that although the results were not sufficiently robust, the demonstrated effects were encouraging. The robustness of the results was challenged because of the observed variability in the primary efficacy data, the fact that many of the important conclusions supporting the efficacy of the drug were derived from the performed post hoc analyses, and the fact that there was little supportive evidence of effect from the data on the secondary endpoints. At the same time it was recognized that at the time the study was designed the knowledge of the natural history of the disease was different from what we now know. It was agreed that the applicant has performed the post hoc analyses in line with the most current knowledge about the natural history of the disease, and in this respect the definition of the sub-groups in these analyses is clinically and scientifically justified. The SAG experts considered that the results derived from these may be considered clinically relevant, especially in the sub-group of patients with more advanced disease. Additionally, it was considered that the lack of effect on the secondary endpoints could be explained by the expected mechanism of action of the drug i.e. partial restoration of dystrophin production. Most of the secondary endpoints are of such nature that any effect will have to be driven by an increase in strength, rather than an improvement of function. The experts were presented with the latest available data, showing that minimal increase in dystrophin production could lead to functional improvement, but not to improvement

of strength, and for the latter to occur, levels of dystrophin close to the ones in normal muscular fibres must be achieved. The SAG experts agreed that this could be a valid explanation of the lack of concordance between the primary and secondary endpoints' efficacy data. It was also the position of the group that despite the fact that efficacy was most prominently shown in the sub-group of patients with more advanced disease, there were trends of efficacy in all the sub-groups by severity, although of a different magnitude. This effect is to be expected, as according to the data presented by the experts, the decline in function of Duchenne patients is not linear, but rather the speed of functional decline increases with the duration of the disease. In that respect, it would be very difficult to show a significant functional improvement in milder patients in the frame of a controlled clinical trial with duration of 1 or 2 years. On the contrary, in the most severe patients even a small effect on function would be detectable and clinically meaningful. The patients and representatives in the room, in their statements, defended the position that at that late stage of the disease even small effects providing longer independent use of arms and hands, or preserving the ability to feed and drink from a cup on their own, would represent a significant and important effect. Taking all of the above in consideration, the SAG experts felt that there should be no scientific reason for the drug not to be given to milder patients if efficacy is established in more severe ones. The long term benefit on this population could be documented by a follow-up of data collected in specific registries.

Overall, considering the totality of the evidence available to date, the SAG was of the view that while ataluren can be considered as a potentially efficacious drug, the data from the confirmatory phase III trial are necessary before final conclusions on efficacy can be made.

This conclusion was shared by the CHMP.

2.5.4. Conclusions on the clinical efficacy

While the effects observed in the pivotal study were considered generally encouraging, the CHMP considered that the clinical efficacy data submitted were not adequate and did not provide sufficient evidence to support the indication of ataluren for the treatment of patients with Duchenne muscular dystrophy.

2.6. Clinical safety

Patient exposure

As of 12 May 2012, a total of 588 subjects had been exposed to ataluren in completed or ongoing clinical trials. This number comprised 76 healthy male and female volunteers, 218 male patients with nmDMD, 270 male and female patients with nmCF and 24 male and female patients with nmHA/HB or nmMMA (table 14).

Table 14 Patient exposure to ataluren by age group, nmDMD and other indications

Indication	Study Number	Ataluren Patients[a]	Naïve Patients Treated with Ataluren	Patients by Age Subgroup, N (% of Total for Each Row)		
				3 to ≤11 years	12 to ≤17 years	≥18 years
nmDMD	004	38	38	33 (86.8)	5(3.2)	0
	004e	36	0	0	0	0
	007	117	117	103 (88.0)	13 (11.1)	1 (0.9)
	007e	173	57	48 (84.2)	9 (15.8)	0
	008	6	6	6 (100)	0	0
	016[b]	106	0	0	0	0
TOTAL nmDMD			**218**	**190 (87.2)**	**27 (12.4)**	**1 (0.5)**
nmCF	003	24	**24**	0	0	24 (100)
	005	23	**23**	0	0	23 (100)
	005e	19	**0**	0	0	0
	006	30	**30**	11 (36.7)	18 (60.0)	1 (3.3)
	009	120	**107**	11 (10.4)	24 (22.4)	72 (67.3)
	009e[b]	96	**86**	4 (4.7)	22 (25.6)	60 (69.8)
TOTAL nmCF			**270**	**26 (9.6)**	**64 (23.7)**	**180 (66.7)**
nmHA/HB	011[b]	13	**13**	0	0	13 (100)
nmMMA	012[b]	11	**11**	5 (45.5)	4 (36.4)	2 (18.2)
TOTAL Other			**24**	**5 (20.8)**	**4 (16.7)**	**15 (62.5)**
Overall TOTAL			**512**	**221 (43.2)**	**95 (18.5)**	**196 (38.3)**

[a] All patients who received ataluren in each study without regard to participation in other studies.
[b] Ongoing study; exposure is estimated as of 12 May 2012.
Abbreviations: nmCF = nonsense mutation cystic fibrosis; nmDMD = nonsense mutation Duchenne muscular dystrophy; nmHA/HB = nonsense mutation hemophilia A or B; nmMMA = nonsense mutation methylmalonic acidemia

In the completed studies in patients with nmDMD, ataluren was administered three times a day at one of three dose levels: 4, 4, 8 mg/kg; 10, 10, 20 mg/kg and 20, 20, 40 mg/kg. In the completed studies in patients with nmCF, patients received ataluren three times a day at one of two dose levels: 4, 4, 8 mg/kg and 10, 10, 20 mg/kg. Healthy volunteers received single doses of ataluren up to 200 mg/kg and repeated doses up to 50 mg/kg BID for 7 days or 14 days.

Adverse events

The adverse-event profile of ataluren was comparable to that of placebo in patients with nmDMD in the main study 007. The adverse events that were reported in ≥5% of patients in any treatment arm are summarized in Table 15. The AEs which occurred twice as frequently in the ataluren groups as compared to placebo are highlighted. None of the patients discontinued treatment with ataluren or withdrew from the study because of a treatment-related adverse event.

Table 15 Treatment-emergent AEs with a patient frequence of ≥5% by SOC (study 007)

MedDRA System Organ Class/ Preferred Term[a],	Treatment Arm		
	Placebo	Ataluren 10, 10, 20 mg/kg	Ataluren 20, 20, 40 mg/kg
	N=57	N=57	N=60
	n (%)	n (%)	n (%)

MedDRA System Organ Class/ Preferred Term[a],	Treatment Arm		
	Placebo	Ataluren 10, 10, 20 mg/kg	Ataluren 20, 20, 40 mg/kg
	N=57	N=57	N=60
	n (%)	n (%)	n (%)
Gastrointestinal disorders	**37 (64.9)**	**42 (73.7)**	**44 (73.3)**
Vomiting	22 (38.6)	32 (56.1)	27 (45.0)
Diarrhoea	14 (24.6)	11 (19.3)	17 (28.3)
Abdominal pain upper	9 (15.8)	9 (15.8)	13 (21.7)
Nausea	7 (12.3)	8 (14.0)	10 (16.7)
Abdominal pain	4 (7.0)	7 (12.3)	10 (16.7)
Flatulence	4 (7.0)	5 (8.8)	7 (11.7)
Stomach discomfort	0	4 (7.0)	5 (8.3)
General disorders	**21 (36.8)**	**23 (40.4)**	**20 (33.3)**
Pyrexia	12 (21.1)	14 (24.6)	7 (11.7)
Disease progression	6 (10.5)	4 (7.0)	5 (8.3)
Asthenia	2 (3.5)	3 (5.3)	4 (6.7)
Infections and infestations	**43 (75.4)**	**38 (66.7)**	**39 (65.0)**
Nasopharyngitis	13 (22.8)	13 (22.8)	10 (16.7)
Upper respiratory tract infection	10 (17.5)	9 (15.8)	11 (18.3)
Influenza	8 (14.0)	6 (10.5)	7 (11.7)
Gastroenteritis	4 (7.0)	9 (15.8)	3 (5.0)
Rhinitis	2 (3.5)	6 (10.5)	3 (5.0)
Ear infection	3 (5.3)	3 (5.3)	4 (6.7)
Gastroenteritis viral	3 (5.3)	4 (7.0)	3 (5.0)
Injury, poisoning and procedural complications	**26 (45.6)**	**28 (49.1)**	**31 (51.7)**
Fall	7 (12.3)	11 (19.3)	6 (10.0)
Procedural pain	7 (12.3)	6 (10.5)	8 (13.3)
Contusion	3 (5.3)	6 (10.5)	4 (6.7)
Joint sprain	1 (1.8)	4 (7.0)	4 (6.7)
Investigations	**4 (7.0)**	**10 (17.5)**	**6 (10.0)**
Weight decreased	1 (1.8)	5 (8.8)	3 (5.0)
Metabolism and nutrition disorders	**3 (5.3)**	**7 (12.3)**	**6 (10.0)**
Decreased appetite	2 (3.5)	5 (8.8)	5 (8.3)
Musculoskeletal and connective tissue disorders	**19 (33.3)**	**25 (43.9)**	**28 (46.7)**
Pain in extremity	6 (10.5)	7 (12.3)	8 (13.3)
Back pain	5 (8.8)	9 (15.8)	6 (10.0)
Arthralgia	2 (3.5)	2 (3.5)	6 (10.0)
Muscle spasms	5 (8.8)	3 (5.3)	1 (1.7)
Muscular weakness	1 (1.8)	3 (5.3)	5 (8.3)
Nervous system disorders	**17 (29.8)**	**25 (43.9)**	**18 (30.0)**
Headache	14 (24.6)	22 (38.6)	15 (25.0)
Dizziness	4 (7.0)	3 (5.3)	3 (5.0)

MedDRA System Organ Class/ Preferred Term[a],	Treatment Arm		
	Placebo	Ataluren 10, 10, 20 mg/kg	Ataluren 20, 20, 40 mg/kg
	N=57	N=57	N=60
	n (%)	n (%)	n (%)
Respiratory, thoracic and mediastinal disorders	**18 (31.6)**	**20 (35.1)**	**22 (36.7)**
Cough	11 (19.3)	9 (15.8)	13 (21.7)
Nasal congestion	4 (7.0)	5 (8.8)	6 (10.0)
Oropharyngeal pain	4 (7.0)	6 (10.5)	4 (6.7)
Rhinorrhoea	6 (10.5)	4 (7.0)	0
Skin and subcutaneous tissue disorders	**18 (31.6)**	**19 (33.3)**	**14 (23.3)**
Rash	5 (8.8)	4 (7.0)	8 (13.3)
Scar	3 (5.3)	4 (7.0)	5 (8.3)

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities

[a] Adverse events with a frequency of ≥5% across all 3 treatment arms are displayed alphabetically by MedDRA System Organ Class and from highest to lowest incidence across all 3 treatment arms within each System Organ Class. Patients who had the same adverse event more than once are counted only once for that adverse event. Adverse events with a frequency of ≤5% across all 3 treatment arms are not shown.

The combined safety dataset for nmDMD was based on studies 007, 007e, 004e, 016 and 019. Patients in this dataset ranged in age from 5 to 22 years and the median age was 9 years. The combined long-term ataluren exposure was achieved in 179 nmDMD patients who received ataluren for ⩾48 weeks. Ataluren was generally well tolerated and the most common adverse events (those reported in ⩾20% of patients) included headache (40.7%), diarrhoea (27.3%), nasopharyngitis (26.4%), cough (25.0%), upper abdominal pain (21.8%), pyrexia (21.8%), fall (20.8%) and upper respiratory tract infection (20.8%).

Serious adverse event/deaths/other significant events

Deaths

There were no deaths during the completed clinical studies of ataluren in nmDMD patients. In the ongoing open-label safety study for previously treated ataluren patients with nmDMD, study 016 (PTC124-GD-016-DMD), three cases of death were reported: a male patient treated with ataluren for ~9 months, a male patient treated with ataluren for ~14 months and a male patient treated with ataluren for ~18 months. Causal relationship between the fatal outcomes and treatment with ataluren was not found.

Serious AEs

In study 007, serious adverse events were reported in 5.3% (3 of 57) subjects in the placebo arm, in 3.5% (2 of 57) patients in the ataluren 10, 10, 20 mg/kg arm and in 3.3% (2 of 60) patients in the ataluren 20, 20, 40 mg/kg arm. None of the serious adverse events in either ataluren arm was considered by the investigator to be related to ataluren (Table 16).

Table 16: Serious Adverse Events in nmDMD Placebo-controlled study 007

MedDRA Preferred Term	Treatment Duration[a], weeks	Relationship per Investigator	Treatment Arm
Abdominal pain	7.6	Possibly[b]	Placebo
Appendicitis	27.6	Unrelated	Ataluren 10, 10, 20 mg/kg
Dehydration	0[c]	Unrelated	Placebo
Dehydration	25.9	Unrelated	Ataluren 10, 10, 20 mg/kg
Femur fracture	47.9	Unlikely	Placebo
Grand mal convulsion	44.6	Unlikely[d]	Placebo
Influenza	47.9	Unlikely	Placebo
Internal fixation of fracture	0[c]	Unrelated	NA
Lower limb fracture	32.7	Unrelated	Ataluren 20, 20, 40 mg/kg
Supraventricular tachycardia	46.1	Unlikely	Ataluren 20, 20, 40 mg/kg
Varicella	23.9	Unrelated	Placebo

[a]Treatment duration at start date of event
[b]Event expected and not reported in expedited fashion
[c]Event occurred during screening
[d]Event unexpected and initially reported as possibly related.

There were 21 SAEs reported from studies 007,007e, 004 and 004e. Fourteen of these SAEs were reported in patients receiving ataluren and only one (hypertension) was considered by the applicant as likely related to the ataluren. The case of paroxysmal supraventricular tachycardia was considered unlikely related to study drug by the applicant, because the patient had previously experienced similar symptoms and self-limiting episodes.

There were three SAE cases of hypertension (1 in 007e and 2 in 004e) of which one was considered as related to ataluren. In addition, there were five cases of bone fractures reported (four fractures of femur and one of lower limb) of which one occurred in the placebo arm and 4 in patients treated with ataluren; none of these cases was considered by the investigators to be related to ataluren.

Laboratory findings

Data obtained in healthy volunteers indicated that exposure to ataluren could cause elevation of liver enzymes (but not bilirubin), serum cholesterol and triglycerides. These changes seemed to be dose-dependent and reversible after exposure to ataluren was stopped.

No significant haematology findings or signals of renal toxicity and effects on adrenal function were seen in studies 007 and 007e. The only finding was hepatic toxicity, which was expected given the data from healthy volunteers. There were ten ataluren-treated patients and one placebo-treated patient with isolated Grade 1 (mild) elevations in GGT or total bilirubin. Mean cholesterol and triglycerides levels were in the upper range of normal at baseline and increased to borderline-high or high levels in the ataluren arms and, to a lesser extent, in the placebo treatment arm during treatment, primarily in patients who were receiving corticosteroids (Table 17).

Table 17 Mean Change in Cholesterol and Triglycerides by Treatment Arm and Corticosteroid use in nmDMD Placebo-Controlled Study 007.

Visit/Parameter, mmol/L*	Treatment Arm					
	Placebo (N=57)		Ataluren 10, 10, 20 mg/kg (N=57)		Ataluren 20, 20, 40 mg/kg (N=60)	
Baseline, mean (SD)						
Cholesterol	4.22 (0.86)		4.50 (0.70)		4.45 (0.75)	
Triglycerides	1.41 (0.79)		1.38 (0.57)		1.34 (0.60)	
Week 48, mean (SD)						
Cholesterol	4.40 (0.75)		4.82 (0.85)		5.05 (0.91)	
Triglycerides	1.48 (0.81)		1.64 (0.59)		1.67 (0.78)	
Change, mean (SD)						
Cholesterol	0.18 (0.64)		0.34 (0.48)		0.51 (0.57)	
Triglycerides	0.08 (0.76)		0.27 (0.51)		0.25 (0.62)	
	Corticosteroid Use		Corticosteroid Use		Corticosteroid Use	
	Yes (N=40)	No (N=17)	Yes (N=41)	No (N=16)	Yes (N=43)	No (N=17)
Baseline, mean (SD)						
Cholesterol	4.46 (0.9)	3.64 (0.5)	4.65 (0.7)	4.09 (0.6)	4.56 (0.7)	4.17 (0.7)
Triglycerides	1.49 (0.7)	1.20 (1.0)	1.45 (0.6)	1.19 (0.5)	1.43 (0.6)	1.13 (0.4)
Week 48, mean (SD)						
Cholesterol	4.57 (0.7)	3.96 (0.6)	5.04 (0.8)	4.26 (0.6)	5.29 (0.9)	4.47 (0.6)
Triglycerides	1.62 (0.9)	1.14 (0.5)	1.77 (0.6)	1.33 (0.3)	1.83 (0.8)	1.26 (0.6)
Change, mean (SD)						
Cholesterol	0.10 (0.6)	0.34 (0.7)	0.39 (0.5)	0.21 (0.4)	0.61 (0.6)	0.30 (0.5)
Triglycerides	0.11 (0.6)	-0.01 (1.1)	0.31 (0.6)	0.17 (0.4)	0.29 (0.7)	0.15 (0.4)

* Conversion factors for mmol/L to mg/dL are 39 for cholesterol and 89 for triglycerides.
Abbreviation: SD = standard deviation
Reference: [PTC124-GD-007-DMD Table 49; Table 14.3.3.2]

No clear relationship was identified between pulse rate, respiration rate or temperature and the use of ataluren, but increased blood pressure was observed (table 18). This increase was slightly higher in the subgroup using corticosteroids than in the subgroup not using corticosteroids. There was also a slight increase in the diastolic blood pressure in all treatment arms.

Table 18: Mean Change in Blood Pressure in nmDMD Placebo-Controlled Study 007.

Parameter/ Visit, mmHg	Placebo N=57	Ataluren 10, 10, 20 mg/kg N=57	Ataluren 20, 20, 40 mg/kg N=60
Blood Pressure Values Collected as Part of Vital Sign Assessments			
Systolic			
Baseline	103.7 (N=57)	105.2 (N=57)	104.4 (N=60)
Week 48	105.8 (N=56)	111.8 (N=57)	110.1 (N=59)
Change (SD)	2.2 (11.3) (N=56)	6.6 (12.7) (N=57)	5.6 (11.5) (N=59)
Diastolic			
Baseline	63.4 (N=57)	64.4 (N=57)	62.8 (N=60)
Week 48	64.5 (N=56)	67.6 (N=57)	66.4 (N=59)
Change (SD)	1.3 (10.1) (N=56)	3.3 (10.5) (N=57)	3.6 (10.4) (N=59)
Blood Pressure Values Collected Before the 6MWT			
Systolic			
Baseline	101.9 (N=57)	102.6 (N=57)	102.7 (N=60)
Week 48	105.6 (N=49)	107.9 (N=53)	106.9 (N=55)
Change (SD)	4.8 (11.7) (N=49)	5.6 (15.1) (N=53)	4.4 (13.5) (N=55)
Diastolic			
Baseline	62.2 (N=57)	64.9 (N=57)	64.6 (N=60)
Week 48	64.9 (N=49)	66.5 (N=53)	65.7 (N=55)
Change (SD)	3.6 (7.5) (N=49)	2.1 (10.2) (N=53)	0.9 (11.5) (N=55)

Abbreviations: 6MWT = 6-minute walk test, SD = standard deviation
Reference: [PTC124-GD-007-DMD Table 53; Table 14.3.5.13.2, Table 14.3.5.13.4]

Safety in special populations

Age-related differences in frequency of some of the frequent adverse events were observed. Vomiting, pyrexia, abdominal pain, influenza and viral gastroenteritis were more frequent in children aged 5 to 6 years than in older children. Headache, diarrhoea, upper abdominal pain, nausea, falls, procedural pain, pain in extremity, back pain, rash, flatulence, disease progression, oropharyngeal pain and dizziness occurred more frequently in the older categories.

No studies were conducted in patients with renal or hepatic impairment and safety in these populations was not fully established. These safety concerns were proposed by the Applicant to be reflected as "Missing information" in the RMP and the use of ataluren in these patients was proposed to be subject to close monitoring.

Safety related to drug-drug interactions and other interactions

Specific drug-drug interaction studies of ataluren were not conducted. Potential interaction between ataluren and corticosteroids was investigated by analysing pharmacokinetics in Phase 2 nmDMD patients receiving corticosteroids and adverse events by corticosteroid usage in the long-term studies in nmDMD patients. Of note, hypertension was reported in some patients concomitantly treated with systemic corticosteroids.

In the long-term studies of ataluren in nmDMD patients (Studies 007, 007e, and 004e), concomitant use of warfarin was not allowed because ataluren may slow the clearance of medications that are primarily metabolized by cytochrome P450 2C9.

Safety results from the placebo-controlled study 009 in nmCF patients suggested a potential interaction of ataluren with intravenous aminoglycosides. Serious adverse events related to renal dysfunction, which occurred only in the ataluren arm, included three patients with acute renal failure, three patients with renal failure and one patient with hypercreatininemia. These events were characterised by elevated creatinine (Grade 1 to Grade 4), which resolved over days to weeks. All seven events were associated with concomitant systemic treatment with aminoglycosides or other potentially nephrotoxic antibiotics (e.g. vancomycin) that were generally administered as treatment for pulmonary exacerbations. No patient required dialysis. This issue was recognized during the conduct of this study and changes were made in the protocol (prohibition of concomitant use of intravenous aminoglycosides or other potentially nephrotoxic antibiotics), which successfully addressed the issue.

Discontinuation due to adverse events

A total of 6 of the 216 nmDMD patients (2.8%) discontinued treatment because of one or more adverse events. Vomiting was reported as the reason for discontinuation of treatment in two patients. One patient discontinued due to a Grade 1 micturition disorder, indicated as unlikely related to study drug. After the interim database cut-off date for Study 016, one additional patient discontinued due to abnormal cystatin C and BUN values.

Discontinuation due to adverse events was also seen in the nmCF studies (e.g. due to renal and urinary disorders).

2.6.1. Discussion on clinical safety

The safety profile of ataluren was based on data from phase 1 studies in healthy volunteers, phase 2 studies in DMD patients and their extensions. Upon request from the CHMP during the course of the procedure, the Applicant also provided an analysis on a combined safety data from the nmDMD patients. Of note, more than 50% of patients were exposed to ataluren for at least 96 weeks, which was considered to constitute a sufficient long-term safety database, especially taking into account the nature of the condition. The CHMP also considered that additional information on safety was derived from studies in other conditions (nmCF, nmHA/HB and nmMMA).

With respect to data from the phase 1 studies, next to headache and gastrointestinal adverse events, there were signals that exposure to ataluren could lead to elevation of liver enzymes as well as serum cholesterol and triglycerides. Cases of hepatic toxicity (elevated liver enzymes) were seen also in DMD patients in the pivotal phase 2 study 007. While these changes seemed to be reversible after exposure to ataluren was stopped, the CHMP considered that ataluren was intended for continuous life-long use and hence, reversibility of elevated liver enzymes was seen as less relevant for the target population. Overall, the CHMP considered hepatotoxicity as an important potential risk.

Similarly, the effect of ataluren on cholesterol and triglyceride levels was also documented in DMD patients. In study 007, mean cholesterol and triglyceride levels increased to borderline-high or high levels in both ataluren treatment arms and to a lesser extent in the placebo arm and the increase was more prominent in patients who received corticosteroid therapy. The CHMP considered that this would be the case in the majority of DMD patients in clinical practice and considered this finding as a safety concern.

The treatment-related adverse events reported most commonly in the study 007 (i.e. in $\geqslant$5% of

patients across all 3 treatment arms) were vomiting, diarrhoea, upper abdominal pain, flatulence, nausea, headache and decreased appetite. The CHMP considered that most of these occurred with similar frequency in the placebo and ataluren arms. The adverse events vomiting, flatulence, stomach discomfort and fatigue were seen to increase in frequency from placebo to ataluren 10, 10, 20 mg/kg to ataluren 20, 20, 40 mg/kg.

Increase in systolic and to a less extent in diastolic blood pressure was observed in subjects treated with ataluren and there were three cases of hypertension, some of which required antihypertensive treatment. The CHMP considered that the use of corticosteroids may have contributed to these cases. However, if authorised, ataluren would be used mostly in combination with corticosteroids and thus, the potential risk of hypertension with concomitant use of corticosteroids was considered as a safety concern by the CHMP, particularly in the context of a disease with frequent development of cardiomyopathy.

Based on the combined safety dataset analysis, i.e. data from patients in studies 007, 007e, 004e, 016 and 019, the CHMP considered that ataluren was generally well tolerated by patients with nmDMD, with the most common adverse events (those reported in $\geqslant$20% of patients) being those that are typical of paediatric illnesses or DMD complications, e.g. headache (41%), diarrhoea (27%), nasopharyngitis (26%), cough (25%), upper abdominal pain (22%), pyrexia (22%), fall (21%) and upper respiratory tract infection (21%).

Additionally, the safety analysis indicated the changes in the lipid profile, hypertension, renal and hepatic events need to be considered as safety concerns and reflected in the Risk Management Plan.

The CHMP considered there were only few treatment-related serious adverse events. Femur fracture (4.2%) was the most frequently reported serious adverse event, but none of these fractures which met the criteria for a serious adverse event was considered by the investigators to be related to ataluren. Although the causal relationship was not suggested by the investigators, the CHMP paid attention to this signal, considering that lower limb fractures in DMD patients may lead to immobilization which may become permanent, i.e. transition to non-ambulation. Further to their review of additional data on lower limb and on all fractures both in nmDMD and in nmCF patients, the CHMP concluded that over comparable periods, there was no signal of higher frequency of fractures in subjects exposed to ataluren, as compared to placebo.

With respect to specific patient populations, the CHMP considered that no studies were conducted in patients with renal or hepatic impairment and safety in these populations was not fully established. Since renal excretion accounts for ~ 50% of the drug elimination, renal impairment is likely to result in accumulation of ataluren and/or ataluren glucuronide. Similarly, since ataluren is extensively metabolized in liver, hepatic impairment is expected to result in ataluren increased plasma concentrations. Taken together with the uncertainties around the claimed bell-shaped dose-response curve, the CHMP considered that without clinical data, understanding of both efficacy and safety profile of ataluren in subjects with renal or hepatic impairment remains limited.

The CHMP considered that no immunological events were reported in the DMD patients treated with ataluren. Although immunological reactions are not expected for this type of compound, the Applicant was requested to review all available data, including those from the CF clinical programme. Two CF patients receiving ataluren had allergic reactions possibly related to the investigational drug, as compared to one patient on placebo. Based on the data available, ataluren's potential for immunogenicity was considered low by the CHMP.

Despite substantial differences between the DMD and CF patient populations (differences in demographics, concomitant medications, complications of the disease, overall health status/ need for hospitalisations), the safety data from the combined nmCF population was considered supportive of the safety profile for ataluren in nmDMD. Ataluren was generally well tolerated by the nmCF patients, who were exposed to ataluren in the two long-term studies for up to two years. The adverse events were typical of CF and included cystic fibrosis pulmonary exacerbation (84%), cough (32%), viral upper respiratory tract infection (28%) and pyrexia (22%) as the most frequently reported treatment-emergent adverse events (reported in ⩾20% of patients). Most of the adverse events were Grade 1 or Grade 2 in severity, were not attributed to ataluren and did not lead to discontinuation of treatment with ataluren. The data generated in the CF patients also provided evidence of interactions between ataluren and i.v. aminoglycosides, which was considered of relevance and supportive of a respective contraindication should the product be authorised. Ultrasound examinations (in nmDMD and nmCF studies) identified cases of abnormal renal ultrasound findings. In particular, the nmCF study data suggested a clear effect of ataluren on renal abnormalities. Of note, five events of renal disorders were reported as serious adverse events in nmCF patients. The CHMP considered that although the mechanism of a potential contribution of ataluren to the reported cases of nephrotoxicity was not known, this signal in the clinical development appeared to reinforce the non-clinical findings seen in mice. Based on the clinical data available, renal toxicity was assumed to occur less likely in DMD patients but was still perceived as a safety concern. The CHMP concluded that it should be considered as a potential important risk.

The CHMP pointed out a theoretical concern about possible effects of ataluren on reading through normal stop codons and hence producing abnormally elongated proteins. This was investigated in healthy volunteers and the results did not confirm that this would be the case. This was considered re-assuring by the CHMP. However, these analyses were performed on a number of selected proteins and on pooled samples from peripheral blood of healthy volunteers. Moreover, the CHMP noted that the non-specific read through of normal stop codons should be examined in a range of plasmatic concentrations which are expected to bring about the read-through in DMD patients. In response to this concern, lysates from muscle biopsies obtained from 48 nmDMD patients treated with ataluren 10, 10, 20 mg/kg for 36 weeks (Study 007) were analysed by Western blotting. Two muscle proteins were examined (GAPDH and β-actin) without further evidence of protein elongation. Nevertheless, the CHMP was of the view that the theoretical risk of non-specific read-through of normal stop codons still remains an uncertainty.

Furthermore, the CHMP flagged a theoretical concern that ataluren could enhance read through of non-sense mutations in other genes. The applicant discussed the potential endogenous nonsense codons substrates for ataluren presenting theoretical arguments why no effect on these would be expected. However, no data were submitted in support of these statements. Overall, the CHMP concluded that the potential off-target effects were an uncertainty about the risks related to the mechanism of action of ataluren.

2.6.2. Conclusions on the clinical safety

Overall, the CHMP was of the view that the Applicant performed a comprehensive safety analysis and that the safety profile of ataluren could be considered acceptable, although it was based on a rather limited patient exposure.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

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

PRAC Advice

Based on the PRAC review of the applicant´s response to the previous list of questions referring to the Risk Management Plan version 1.2, the PRAC considered by consensus that the risk management plan for Translarna (ataluren) in the proposed treatment of Duchenne muscular dystrophy, resulting from a nonsense mutation in the dystrophin gene (nmDMD) in ambulatory patients aged 5 years and older, could be acceptable provided that an updated risk management plan is submitted before final CHMP opinion, addressing the following issues:

- Hepatic toxicity should be included as an important potential risk. In addition, all corresponding sections throughout the RMP require revision accordingly.

- The summary table of risk minimisation measures should be edited, as no additional risk minimisation measures are planned for any of the safety concerns in the RMP. In the absence of educational materials, the relevant sections of the RMP should be edited to clarify how health-care professionals (and patients if needed) will be advised about the need for monitoring of the patient's lipid profile, renal and hepatic function monitoring and for the monitoring of blood pressure. Genetic testing might also be considered. Furthermore, the reported risk minimisation measures in the summary table should be limited to SmPC (i.e. no Package Leaflet references are expected).

- Please note that amendments are needed in the proposed SmPC to ensure monitoring requirements on the above mentioned issues.

- Part VI of the RMP (Summary of activities in the risk management plan by product) – table VI.I.2 – the objectives of the imposed PASS should be included.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

Summary of safety concerns	
Important identified risks	• Potentiation of aminoglycoside renal toxicity • Changes in lipid profile
Important potential risks	• Hypertension with concomitant use of systemic corticosteroids • Renal toxicity • Hibernoma • Malignancies in general

Summary of safety concerns	
Missing information	• Effect of co-administration of ataluren with nephrotoxic drugs other than intravenous aminoglycosides • Use in patients with moderate to severe hepatic impairment • Use in patients with moderate to severe renal impairment • Potential use in children from 6 months to 5 years • Use in patients whose ethnic origin is other than Caucasian • Extended long-term safety • Off-label use in patients who do not have DMD caused by a nonsense mutation in the dystrophin gene • Effect of co-administration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies

- **Pharmacovigilance plans**

Activity/Study title (type of activity, study title [if known] category 1-3)*	**Objectives**	**Safety concerns addressed**	**Status Planned, started,**
Post-approval registry(s) Working title: 'Long-Term Observational Study of Ataluren Safety and Effectiveness in Usual Care' Category 1	Continue to document the long-term safety profile of ataluren Obtain additional information on the long-term effectiveness of ataluren Evaluate the safety and effectiveness of ataluren in subgroups not traditionally included in clinical trials Evaluate changes in lipid profile Determine the incidence and frequency of: o Hypertension with use of concomitant corticosteroids o Renal toxicity (without concomitant aminoglycosides or other nephrotoxic drugs) Evaluate the safety of ataluren • in patients with moderate to severe renal or hepatic impairment • when used with nephrotoxic	Changes in lipid profile Hypertension with use of concomitant systemic corticosteroids Renal toxicity Effect of co-administration of ataluren with nephrotoxic drugs other than intravenous aminoglycosides Use in patients with moderate to severe hepatic impairment Use in patients with moderate to severe renal impairment Potential use in children from 6 months to 5 years	Planned

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,
	drugs (other than aminoglycosides) Evaluate the safety and effectiveness of ataluren in the context of certain concomitant drugs. Monitor the utilization pattern of ataluren	Use in patients whose ethnic origin is other than Caucasian Extended long-term safety Off-label use in patients who do not have DMD caused by a nonsense mutation in the dystrophin gene Effect of co-administration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies	
7-day tolerability and pharmacokinetic study in neonatal dogs Category 3		Potential use in children from 6 months to 5 years	Planned
1-month juvenile dose range-finding toxicology and toxicokinetic study planned in neonatal dogs (age correlating with dosing in newborn paediatric patients to 2 years of age), Study 2 of EMA/PDCO/476743/2012 PDCO document. Category 3		Potential use in children from 6 months to 5 years	Planned
3-month juvenile toxicology and toxicokinetic study planned in neonatal dogs (age correlating with dosing in newborn paediatric patients to 2 years of age), Study 3 of EMA/PDCO/476743/2012 PDCO document Category 3		Potential use in children from 6 months to 5 years	Planned
β3 adrenergic binding assay with ataluren and the M4 metabolite, if such a study is technically feasible Category 3		Further investigation of ataluren's potential effect in the development of hibernomas	Planned
Plan to investigate further postauthorisation the potential effects of		Further investigation of ataluren's potential effect in the development of	Planned

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,
ataluren and metabolite M4 in brown adipose tissue of rats. Category 3		hibernomas	
Open-label safety and PK study in children age 6 months to 5 years, Study 6 of EMA/PDCO/476743/2012 PDCO document Category 3		Potential use in children from 6 months to 5 years	Planned
Safety and PK study in patients with moderate to severe hepatic impairment Category 3	To evaluate the safety and PK of ataluren in subjects with different degrees of hepatic impairment, in order to provide guidance for ataluren dosing in patients with moderate to severe hepatic impairment.	Use in patients with moderate to severe hepatic impairment	Planned
Safety and PK study in patients with moderate to severe renal impairment Category 3	To evaluate the safety and PK of ataluren in subjects with different degrees of renal impairment, in order to provide guidance for ataluren dosing in patients with moderate to severe renal impairment.	Use in patients with moderate to severe renal impairment	Planned
Safety and PK study of co-administration of ataluren and a sensitive probe for induction of UGT1A9 Category 3	To evaluate the safety and PK of ataluren and/or the appropriate sensitive probe substrate, in order to provide guidance for dosing ataluren with the specific concomitant medication.	Effect of coadministration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies	Planned
Safety and PK study of co-administration of ataluren and a sensitive probe for substrates of UGT1A9 Category 3	To evaluate the safety and PK of ataluren and/or the appropriate sensitive probe substrate, in order to provide guidance for dosing ataluren with the specific concomitant medication.	Effect of coadministration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies	Planned
Safety and PK study of co-administration of ataluren and a sensitive probe for inhibitors of the transporter breast cancer resistant protein (BCRP) Category 3	To evaluate the safety and PK of ataluren and/or the appropriate sensitive probe substrate, in order to provide guidance for dosing ataluren with the specific concomitant medication.	Effect of coadministration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies	Planned
Safety and PK study of co-administration of ataluren and a sensitive probe substrate of organic anion transporter 1 (OAT1) Category 3	To evaluate the safety and PK of ataluren and/or the appropriate sensitive probe substrate, in order to provide guidance for dosing ataluren with the specific concomitant medication.	Effect of coadministration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies	Planned
Safety and PK study of co-administration of ataluren and a sensitive probe	To evaluate the safety and PK of ataluren and/or the appropriate sensitive probe substrate, in order to provide	Effect of coadministration of ataluren with certain drugs not yet	Planned

Activity/Study title (type of activity, study title [if known] category 1-3)*	Objectives	Safety concerns addressed	Status Planned, started,
substrate for organic anion transporter 3 (OAT3) Category 3	guidance for dosing ataluren with the specific concomitant medication.	evaluated in formal drug-drug interaction studies	
Safety and PK study of co-administration of ataluren and a sensitive probe substrate organic anion transporting polypeptide 1B3 (OATP1B3) Category 3	To evaluate the safety and PK of ataluren and/or the appropriate sensitive probe substrate, in order to provide guidance for dosing ataluren with the specific concomitant medication.	Effect of coadministration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies	Planned

- **Risk minimisation measures**

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Potentiation of aminoglycoside renal toxicity	**SmPC section 4.3 (Contraindications)** Concomitant use of intravenous aminoglycosides (see section 4.5). **SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction)** <u>Aminoglycosides</u> Translarna should not be co-administered with intravenous aminoglycosides, based on cases of decreased renal function observed in a clinical trial in patients with nonsense mutation cystic fibrosis (nmCF) (see section 4.3). Elevations of serum creatinine occurred in several nmCF patients treated with Translarna and intravenous aminoglycosides together with other antibiotics for cystic fibrosis exacerbations. The serum creatinine elevations resolved in all cases, with discontinuation of the intravenous aminoglycoside, and either continuation or interruption of the study drug. These findings suggested that co-administration of Translarna and intravenous aminoglycosides may potentiate the nephrotoxic effect of the	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	aminoglycosides. Treatment with Translarna can be resumed 2 days after administration of the aminoglycoside has ended. The effect of co-administration of ataluren with other nephrotoxic drugs is unknown. Dehydration may be a contributing factor in some of these cases. Patients should maintain adequate hydration while taking Translarna. **PIL section 2** **(What you need to know before you take Translarna)** Do not take Translarna if you are taking injection by vein for antibiotics, such as gentamicin, tobramycin, or streptomycin. (Other medicines and Translarna) Tell your doctor if you are taking, have recently taken, or might take any other medicines. In particular do not take Translarna with gentamicin, tobramycin, or streptomycin injections. These may affect your kidney function.	
Changes in lipid profile	**SmPC section 4.8 (Undesirable effects)** Change in lipid profile (increased triglycerides and cholesterol) are included in Table 1. **(Description of selected adverse reactions)** *Serum lipids* During the controlled study of nmDMD, mean total cholesterol and triglycerides were in the upper range of normal at baseline and increased, reaching borderline high or high values. The values tended to stabilize early in the study and did not increase further with continued treatment.	Monitoring of the patient's lipid profile on an annual basis.
Hypertension with concomitant use of corticosteroids	**SmPC section 4.8 (Undesirable effects)** Hypertension is included in Table 1	Monitoring of resting systolic and diastolic blood pressure every 6 months, or more frequently as needed based on the patient's clinical status.
Renal toxicity	**SmPC section 4.8 (Undesirable effects)** Change in renal function tests (increased	Monitoring of the renal laboratory tests

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	creatinine, BUN, cystatin C) are included in Table 1. **(Description of selected adverse reactions)** *Renal function tests* During the controlled study of nmDMD, small increases in mean serum creatinine, blood urea nitrogen (BUN), and cystatin C were observed. The values tended to stabilize early in the study and did not increase further with continued treatment.	(serum creatinine, BUN, cystatin C) every 6 to 12 months.
Hibernoma	**PIL Section 4 (Possible side effects)** **Reporting of side effects** If you have any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.	None proposed
Malignancies in general	**PIL Section 4 (Possible side effects)** **Reporting of side effects** If you have any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.	None proposed
Use of ataluren in nmDMD patients who co-administered ataluren with nephrotoxic drugs	**SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction)** The effect of co-administration of ataluren with other nephrotoxic medicinal products is unknown. **PIL section 2 (other medicines and translarna)** Tell your doctor if you are taking, have recently taken, or might take any other medications.	None proposed
Use of ataluren in nmDMD patients	**SmPC section 4.2 (Posology and method**	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
with moderate to severe hepatic impairment	**of administration)** *Renal and hepatic impairment* Safety and efficacy of ataluren in patients with renal and hepatic impairment have not been established. **SmPC section 4.4 (Special warnings and precautions for use)** Patients with renal and hepatic impairments should be closely monitored. **SmPC section 5.2 (Pharmacokinetic properties)** Renal or hepatic impairment No studies have been conducted with Translarna in patients with renal or hepatic impairment. Patients with renal or hepatic impairment should be monitored closely. **PIL section 2. (What you need to know before you take Translarna)** **Warnings and precautions** If you have any liver or kidney problem, your doctor should check your liver and kidney functions regularly.	
Use of ataluren in nmDMD patients with moderate to severe renal impairment	**SmPC section 4.2 (Posology and method of administration)** *Renal and hepatic impairment* Safety and efficacy of ataluren in patients with renal and hepatic impairment have not been established. **SmPC section 4.4 (Special warnings and precautions for use)** Patients with renal and hepatic impairments should be closely monitored. **SmPC section 5.2 (Pharmacokinetic properties)** Renal or hepatic impairment No studies have been conducted with Translarna in patients with renal or hepatic impairment. Patients with renal or hepatic impairment should be monitored closely.	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	PIL section 2. (What you need to know before you take Translarna) **Warnings and precautions** If you have any liver or kidney problem, your doctor should check your liver and kidney functions regularly.	
Potential use in children from 6 months to 5 years old	**SmPC section 4.1 (Therapeutic indications)** Translarna is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older. Efficacy has not been demonstrated in non-ambulatory patients. **SmPC section 4.2 (Posology and method of administration)** The safety and efficacy of Translarna in children and infants less than 5 years old have not yet been established. **PIL Section 1 (What Translarna is and what it is used for)** Children and adolescents This medicine has not been tested in children under 5 years.	None proposed
Use of ataluren in patients whose ethnic origin is other than Caucasian	**SmPC section 5.2 (Pharmacokinetic properties)** It is unlikely that the pharmacokinetics of ataluren are significantly affected by UTG1A9 polymorphisms in a Caucasian population. Due to the low number of other races included in the clinical studies, no conclusions can be drawn on the effect of UTG1A9 in other ethnic groups.	None proposed
Extended long-term Safety	None proposed	None proposed
Off-label use of ataluren in patients who do not have DMD caused by a nonsense mutation in the dystrophin gene	**SmPC section 1 (Therapeutic indications)** The presence of a nonsence mutation in the dystrophin gene should be determined by genetic testing. **PILsection 2 (Warnings and precautions)**	Central certification of nonsense mutation in the dystrophin gene required for prescription to be filled.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Your doctor must have results of a blood test to confirm that Translarna may be helpful in treating your abnormal muscle function.	
Effect of coadministration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies	**SmPC section 4.4 (Special warnings and precautions for use)** Caution should be exercised when ataluren is co-administered with medicinal products that are substrates or inducers of UGT1A9, inhibitors of BCRP, or substrates of OAT1, OAT3, or OATP1B3. **SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction)** Based on *in vitro* studies, ataluren is an inhibitor of UGT1A9, organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3) and organic anion transporting polypeptide 1B3 (OATP1B3). Caution should be exercised when ataluren is coadministered with drugs that are substrates of UGT1A9, OAT1, OAT3, or OATP1B3 **Information in PIL 2 (What you need to know before you take Translarna)** Tell your doctor if you are taking any of the following medicines: propofol, mycophenolate mofetil, phenobarbital, rifampin, cyclosporine, eltrombopag, gefitinib, adefovir, captopril, furosemide, lamivudine, methotrexate, oseltamivir, tenofovir, zalcitabine, zidovudine, acyclovir, bumetanide, ciprofloxacin, famotidine, penicillin G, sitagliptin, pravastatin, rosuvastatin, atorvastatin, pitavastatin, telmisartan, valsartan, or olmesartan. These medicines were not tested together with Translarna and your doctor may decide to monitor you closely.	None proposed

The CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider pharmacovigilance activities and risk minimisation measures at this time.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Ataluren is a first-in-class drug designed to enable ribosomal readthrough of premature stop codons, resulting in the formation of a full-length functional protein in patients with nonsense mutation genetic disorders. In the proof of concept study in *mdx* mice ataluren was seen to promote formation and adequate localization of dystrophin, resulting in increased muscle strength and prevention of loss of strength following repeated contractions.

In the clinical setting, beneficial effects of the lower dose (10, 10, 20 mg/kg) were claimed in both primary and secondary endpoints of physical functioning.

With respect to 6MWD, ataluren was observed to slow disease progression in nmDMD patients. The post-hoc analysis in the cITT population indicated an estimated difference in the Change in 6MWD at Week 48 of 31.7 metres (nominal p=0.0281, adjusted p=0.0561, observed mean difference in 6MWD=31.3 metres) between the 10, 10, 20 mg/kg dose and placebo. Looking at the proportions of patients with at least 10% worsening in 6MWD at Week 48, 44% vs 26% of patients in the placebo and the 10, 10, 20 mg/kg ataluren arm, respectively were progressors (nominal p=0.0326, adjusted p=0.0652) .

A greater effect over 48 weeks was seen in patients in the "ambulatory decline" phase, i.e. patients between 7 and 16 years of age, with baseline 6MWD ≥150m and ≤80% of predicted value. Based on a post-hoc subgroup analysis in this population, a difference in the change in 6MWD at Week 48 of 49.9 metres (p=0.0096) between the 10, 10, 20 mg/kg dose and placebo was seen.

In terms of secondary endpoints of physical functioning, only limited effects of ataluren were observed: ataluren patients had fewer falls/week than placebo-dosed patients; increase of wheelchair use from baseline was less in ataluren than placebo; ataluren patients spent less time in "no activity" (based on Step activity monitoring) and a minor positive trend was observed in myometry tests.

Uncertainty in the knowledge about the beneficial effects

The CHMP was of the view that the main uncertainties about the claimed beneficial effects pertained to the robustness of efficacy data in general, the dose-response curve (and hence the appropriate dose) and the applicability of the data to the overall target population.

Uncertainties about robustness of efficacy data

The primary analysis of the pivotal study 007 indicated an estimated difference of 26.4 m between placebo and the low dose arm; this, however, was not statistically significant (nominal p=value 0.0905, adjusted p value=0.1592) and by the usual statistical standards, the study was

formally negative. In order to explain the findings in study 007, the Applicant performed a number of post hoc analyses. These consistently showed a similar difference in 6MWD, but the wide confidence intervals reflected the uncertainty in the estimate.

The CHMP was of the view that the results on the secondary endpoints provided only limited support for the primary endpoint outcomes, as they were inconsistent, difficult to interpret and needed to be seen only as trends. Nevertheless, in line with the input from the SAG Neurology, the CHMP acknowledged that most of the secondary endpoints were of such nature that any effect would have to be driven by an increase in strength and for this to occur, higher levels of dystrophin in muscular fibres would have to be achieved.

Pharmacodynamic confirmation of efficacy was not provided by the pivotal study, despite the fact that biopsies were collected. While the technical problems with dystrophin quantification were recognised by the CHMP, the quality of the biopsies supplied was of concern. The GCP inspection identified that several steps were underestimated, namely instructions for performing the muscle biopsies and the storage/ shipping logistics. Since the mechanism of action of ataluren is claimed to be by promoting production of a full-length dystrophin, more prominent evidence of dystrophin in muscle of patients treated for 48 weeks would be expected. Considering the limitations of data on clinical efficacy, the CHMP pointed out that the dossier would have benefited from supportive data on pharmacodynamics and their absence was seen as adding to the uncertainties.

Uncertainties about the dose-response curve and dose

The CHMP considered that one of the critical issues was the absence of effect in patients treated with the higher dose. The applicant argued that the finding could be explained by the bell-shaped curve dose response, supporting their position by a combination of *in vitro* data (e.g. human myotube cultures, nmDMD mouse myotubes and nmDMD zebrafish) and clinical data (studies 004e, 007 and 007e). The bell-shape response curve was however not obvious based on the *in vivo* preclinical data and the phase 2a clinical data, i.e. before the design and start of the clinical studies 004e, 007 and 007e.

In order to further address this issue, the applicant submitted a correlation between the plasma concentration achieved and the effect in terms of 6MWT and TFTs supporting the robustness of the effect of the selected dose. While patients with lower concentrations appeared to show better results on 6MWD as well as across timed function tests, the CHMP considered that a scatter plot with change in 6MWT and plasma concentration on an individual patient level would have been of greater value. This data were additionally presented by the applicant, but no specific pattern could be identified to provide additional evidence in support of the bell shape concentration response curve.

Overall, the data in support of the bell-shape curve hypothesis were considered to be inconsistent and not allowing a reliable assessment. The CHMP concluded that the effect observed in the lower dose only could be a chance finding.

Validity of data for the entire nmDMD patient population

Since efficacy was investigated in a subgroup of ambulant DMD boys and documented mainly on ambulation parameters, extrapolation to the broader nmDMD patient population (including non-ambulant subjects) was not supported by sufficient evidence.

Risks

Unfavourable effects

Ataluren was generally well tolerated by patients with nmDMD, with the most common adverse events being headache and gastrointestinal disorders such as nausea, vomiting, (upper) abdominal pain, flatulence, diarrhoea, stomach discomfort, constipation and regurgitation.

The laboratory data indicated that exposure to ataluren could cause elevation of serum cholesterol and triglycerides. Mean cholesterol and triglycerides levels were in the upper range of normal at baseline and increased to borderline-high or high levels in the ataluren arms, primarily in patients who were receiving corticosteroids. The values tended to stabilize early and did not increase further with continued treatment. "Changes in the lipid profile" were considered as an important identified risk in the proposed Risk Management Plan.

Of note, elevations of serum creatinine occurred in several patients with nonsense mutation cystic fibrosis treated concomitantly with intravenous aminoglycosides. In all cases, the elevations resolved with discontinuation of the aminoglycosides indicating that co-administration of ataluren and intravenous aminoglycosides may potentiate the nephrotoxic effect of the aminoglycosides. Based on this evidence of decreased renal function, "potentiation of aminoglycoside renal toxicity" was determined as an important identified risk.

There were no deaths during the placebo controlled study. Three fatal cases were seen in one open-label study, but the fatal outcomes were not considered related to treatment with ataluren.

Uncertainty in the knowledge about the unfavourable effects

From the non-clinical database, the finding of malignant hibernomas in rat raised the concern as to whether occurrence of similar effects could be expected in humans, particularly in the paediatric population where the quantity of the brown adipose tissue is higher. In particular, the CHMP considered that malignant hibernomas could be related to the effects of ataluren on fat tissue metabolism and to effects on plasma lipid parameters, which were observed in rats, dogs and humans. Thus, "hibernomas" were reflected in the proposed risk management plan of ataluren as an important potential risk.

Considering the mechanism of action of ataluren, the CHMP pointed out a theoretical concern about possible effects of ataluren on reading through normal stop codons (and thus producing abnormally elongated proteins) and a concern that ataluren could enhance read through of non-sense mutations in other genes. Although such effects were not seen in the data available, the CHMP was of the view that the potential off-target effects were an uncertainty about the risks of ataluren.

Based on results of *in vitro* studies, ataluren was expected to have an interaction potential, which the CHMP considered necessary to be explored further *in vivo*. This pertained to ataluren interactions with a BCRP inhibitor, UGT1A9 substrate, OAT1, OAT3 and OATP1B3 substrates and UGT1A9 selective inducer.

Increase in blood pressure including cases of hypertension requiring antihypertensive treatment was observed in subjects treated with ataluren. While this could have been due to the use of corticosteroids administered concomitantly, this issue was considered an uncertainty and captured as a potential risk in the proposed Risk Management Plan.

The preclinical data as well as data from healthy volunteers and DMD patients indicated that exposure to ataluren may lead to increase in transaminases. While these changes seemed to be

reversible after exposure to ataluren was stopped and a clear hepatotoxic effect was not confirmed, the CHMP considered hepatotoxicity as an important potential risk.

The nmCF study data suggested an effect of ataluren on renal abnormalities. Although the mechanism of a potential contribution of ataluren to the reported cases of nephrotoxicity was not known, this signal in the clinical development appeared to reinforce the non-clinical findings seen in mice. Based on the clinical data available, renal toxicity was assumed to occur less likely in DMD patients, but was still perceived as a potential important risk.

Treatment of patients with renal or hepatic impairment is another area of uncertainty, as no specific studies were performed and potential safety concerns are implied by the pharmacokinetics of ataluren. Since renal excretion accounts for ~ 50% of the drug elimination, renal impairment is likely to result in accumulation of ataluren and/or ataluren glucuronide. Similarly, since ataluren is extensively metabolized in liver, hepatic impairment is expected to result in ataluren increased plasma concentrations. Taken together with the uncertainties around the claimed bell-shaped dose-response curve, the CHMP considered that without clinical data, understanding of both efficacy and safety profile of ataluren in subjects with renal or hepatic impairment remains limited.

Benefit-risk balance

Importance of favourable and unfavourable effects

Several lines of evidence support the clinical relevance of a 30-meter difference in 6MWT, including a report[2] showing that a 30-meter change in 6MWD over 48 weeks can be considered a clinically meaningful change based on the patient/parent-reported quality of life measures in DMD patients. This is also supported by results of longitudinal LMWT natural history data in DMD, indicating that each 30-meter decrease in baseline 6MWD predicts increasing risk of loss of ambulation over the following 2 years.

Ability to climb and descend a short grouping of stairs, abililty to run in short bursts, or to walk a short distance unaided, e.g. to a bathroom, reflect the typical activities important in the lives of DMD patients. Importantly, recent data indicated that timed function tests evaluating these abilities are, similarly to 6MWT, predictive of the time for a patient to become non-ambulatory. Natural history data from the Cooperative International Neuromuscular Group indicated that changes in these parameters are predictive of the likelihood of loss of ambulation over 1 year. Falls commonly lead to fractures in DMD patients and the injuries sustained may accelerate loss of ambulation. Decreasing the rate of accidental falls and hence the risk of fractures, pain and other trauma would be of benefit to the patients. With respect to decrease in wheel chair use, benefits can be attributed not only in terms of ambulation itself, but also by positively impacting on the respiratory function and minimalisation of scoliosis. Thus, if sufficiently documented these effects would be considered of high importance.

The most commonly reported treatment-related adverse events vomiting, diarrhoea, abdominal pain upper, flatulence, nausea, headache and decreased appetite were not considered to raise major safety concerns in a seriously debilitating and life-threatening condition such as DMD.

[2] Henricson E, Abresch R, Han JJ, Nicorici A, Goude Keller E, de Bie E, McDonald CM. The 6-Minute Walk Test and Person-Reported Outcomes in Boys with Duchenne Muscular Dystrophy and Typically Developing Controls: Longitudinal Comparisons and Clinically-Meaningful Changes Over One Year. PLOS Currents Muscular Dystrophy. 2013 Jul 8; 5:ecurrents.md.9e17658b007eb79fcd6f723089f79e06. doi: 10.1371/currents.md.9e17658b007eb79fcd6f723089f79e06

The effect of ataluren on the lipid profile (cholesterol and triglyceride levels) was considered of importance, especially in a situation where long-term administration of corticosteroids is expected. Nevertheless, the values tended to stabilize early in the study and did not increase further with continued treatment, which was considered re-assuring. Similarly, the risk of hypertension during concomitant use of corticosteroids and ataluren was seen as of importance to the target population, considering that such co-administration would occur in the majority of patients in the clinical practice.

In the context of the age group targeted, the potential risk of hibernoma was considered relevant, due to higher proportion of brown fat tissue in children.

Discussion on the benefit-risk balance

The CHMP considered that the data presented in the dossier had several deficiencies which impacted on the benefit-risk assessment. In particular, the Applicant conducted only a single pivotal trial and with the formal failure of its primary analysis, the efficacy discussion was based on post hoc analyses. It was agreed that these analyses were performed in line with the most current knowledge about the natural history of the disease (gained during the conduct of study 007), and in this respect the definition of the subgroups in these analyses was clinically and scientifically justified (e.g. patients in decline phase of their ambulation). While the effects observed in the pivotal study were considered generally encouraging, as supported also by the SAG Neurology, the CHMP was of the view that they still need to be seen as failing to provide compelling evidence of efficacy (due to the failure of the primary analysis).

Considering the limitations of data on clinical efficacy, the CHMP pointed out that the dossier would have benefited from supportive data on pharmacodynamics, i.e. data on dystrophin production in human muscle and evidence supporting the bell-shape dose response hypothesis. In this respect, the CHMP noted that while dystrophin production was observed in the phase IIa study 004, the limited data from the pivotal study (due to the low quality of muscle biopsies) precluded confirmation of a pharmacodynamic effect. Even though it was acknowledged that dystrophin is not a valid biomarker for efficacy, the mechanism of action is directly linked to its production and the limited data from study 007 on dystrophin production contributed to the overall uncertainties.

As discussed above, the bell-shape dose response hypothesis was used by the Applicant to explain why effects were only seen with the lower dose (10, 10, 20 mg/kg). The CHMP considered that unless the hypothesis is supported by sufficient (non)-clinical data, the observation of an effect in the lower dose and no effect in higher dose could be considered as a chance finding. Taking into account all available evidence, the CHMP was of the view that the bell-shaped dose response hypothesis was not confirmed.

Furthermore, the CHMP was of the view that the results on the secondary endpoints provided only limited support for the primary endpoint outcomes, as they were inconsistent, difficult to interpret and could be considered only as trends. In particular, the fact that endpoints more directly linked to the daily living activities or those reflecting the negative impact of the condition (falls, level of physical activity or wheelchair use) did not show a re-assuring effect was of concern.

All these aspects taken together were considered as having a negative impact on the robustness of the data in a broader sense, i.e. in addition to the statistical considerations.

In their discussion, the CHMP also focused on the fact that ataluren was evaluated only in ambulatory patients, whereas the product was intended for a broader patient population. Furthermore, considering that the beneficial effects were most prominent in a sub-population of

ambulatory patients in the decline phase of their walking ability (effect size of approximately 50 metres on the 6MWD), the CHMP discussed whether the benefit-risk balance could be considered favourable in this population, and whether this should lead to a restriction of the proposed indication. Of note, the SAG experts felt that scientifically there should be no reason for the drug not to be given to milder patients if efficacy had been established in more severe ones. This was considered by the CHMP, but the overall conclusion was that based on the level of uncertainties, efficacy could not be reliably established even in this subpopulation.

Although the safety data identified some safety concerns, in general these were considered manageable through the implementation of adequate pharmacovigilance activities and risk minimisation measures as described in the proposed Risk Management Plan. The lack of serious toxic effects and the oral administration were also considered to represent clear advantages for a population of mainly paediatric patients.

Overall, the CHMP was of the view that the risks of the product could be considered acceptable if there were data providing sufficient level of evidence that ataluren may be beneficial in delaying disease progression in nmDMD. However, considering the totality of data available and the uncertainties described above, the CHMP concluded that a favourable benefit-risk balance could not be established at this point.

The applicant applied for a conditional marketing authorisation with the proposal that additional data would be generated post-authorisation in the confirmatory phase 3 study PTC124-GD-020-DMD (Study 020). Therefore, the CHMP also discussed the criteria that would need to be met for a conditional approval and made the following conclusions:

- DMD is a life-threatening and chronically debilitating condition where no satisfactory methods of treatment exist and it was considered that the product would thus address an unmet medical need.

- The CHMP pointed out that while in case of an orphan condition the clinical dataset might not be fully comprehensive, the evidence of efficacy should be sufficient to allow assessment and concluding on a favourable benefit-risk balance. As discussed above, a favourable benefit risk balance of ataluren was not considered established at this point.

- The criterion that the benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required was not considered fulfilled since the benefits to public health were not substantiated by the data presented in the dossier.

- With respect to generating additional data post authorisation, the CHMP considered that the Applicant intends to conduct a confirmatory randomized placebo-controlled Phase 3 study (Study 020) with the 10, 10, 20 mg/kg/day dose in patients with nmDMD. The CHMP agreed that this clinical trial may provide data alleviating the current uncertainties, but noted that although it will presumably be well advanced by the time the product is launched, its conduct (specifically retention of patients) might be affected by the availability of an authorised product. This impact was considered specifically in the context of the paediatric setting. Thus, the marketing authorisation might jeopardise feasibility of completing the study and hence the quality of the results.

Overall, the CHMP concluded that conditions for granting a conditional marketing authorisation were not met.

Divergent positions are appended to this report.

4. Recommendations

Based on the CHMP review of data on quality, safety and efficacy for Translarna in the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in patients aged 5 years and older the CHMP considers by majority decision that the efficacy of the above mentioned medicinal product is not sufficiently demonstrated and therefore recommends the refusal of the granting of the conditional Marketing Authorisation for the above mentioned medicinal product. The CHMP considers that:

- The single study fails to demonstrate persuasive evidence of therapeutic efficacy of Translarna in terms of the primary endpoint (6MWT) and further efficacy parameters confirming functional improvement and activities of daily living. Furthermore, the mechanism of action and the bell shape dose-response relationship of Translarna were not conclusively established, which adds further uncertainty on the overall robustness of the efficacy data.

Therefore, the CHMP was of the opinion that pursuant to Article 12 of Regulation (EC) No 726/2004, the efficacy of the above mentioned medicinal product is not properly or sufficiently demonstrated.

- Furthermore, the CHMP considered that the Applicant has not convincingly shown that comprehensive data can be obtained from the confirmatory placebo-controlled trial if the product is authorised and available on the market.

Due to the aforementioned concerns a satisfactory summary of product characteristics, package leaflet and risk management plan to address other concerns as outlined in the list of outstanding issues cannot be agreed at this stage.

Furthermore, the CHMP, in light of the negative recommendation, is of the opinion that it is not appropriate to conclude on the new active substance status at this time.

Divergent positions to the majority recommendation are appended to this report.

Re-examination of the CHMP opinion of 22 May 2014

Following the CHMP conclusion that Translarna was not approvable due to the lack of established efficacy, the applicant submitted detailed grounds for the re-examination of the grounds for refusal.

Detailed grounds for re-examination submitted by the applicant

The applicant presented their detailed grounds for re-examination in writing and at an oral explanation.

A summary of the applicant´s grounds for re-examination is presented below.

The Applicant requested a re-examination of the CHMP opinion on Translarna, claiming that substantial evidence is available for granting a conditional marketing authorisation in the following indication:

"Translarna is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older. Efficacy has not been demonstrated in non-ambulatory patients.

The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing."

Overall, the Applicant was of the view that ataluren has a favourable benefit-risk profile in nmDMD patients, which is a population suffering from a fatal disease with high unmet medical need, and maintained that criteria for a conditional marketing authorisation were fulfilled.

Ground 1: *The single study fails to demonstrate persuasive evidence of therapeutic efficacy of Translarna in terms of the primary endpoint (6MWT) and further efficacy parameters confirming functional improvement and activities of daily living. Furthermore, the mechanism of action and the bell shape dose-response relationship of Translarna were not conclusively established, which adds further uncertainty on the overall robustness of the efficacy data.*

The applicant re-iterated that the ataluren phase 2b study (Study 007) was the first registration-directed trial in DMD. The lack of an accepted primary endpoint in DMD prior to the conduct of this study required that the company establish the 6MWT as the primary endpoint, as a result of which the 6MWT is now an accepted primary outcome measure in DMD clinical trials. In Study 007, the 6MWD results met the MCID for 6MWD in DMD, demonstrating clinical meaningfulness in a heterogeneous population (estimated 31.7 meters 6MWD benefit over placebo, in the cITT analysis (post-hoc analysis), adjusted p=0.056). One indication of the robustness of the results was that slowing of disease progression was also shown in the pre-specified analysis of time to 10%-worsening in 6MWD, in which only 26% of patients who received ataluren 10, 10, 20 mg/kg experienced disease progression, compared with 44% of the patients who received placebo. The applicant claimed that the difference between the ataluren 10, 10, 20 mg/kg treatment group and the placebo group was apparent as early as Week 24 in this analysis.

The applicant highlighted that, given the role of dystrophin in stabilizing muscles and the natural history of ambulation based on the 6MWT, the effect of ataluren is most evident in patients who are in the ambulatory decline phase of the disease in a 48-week clinical trial. The eligibility criteria for the ongoing confirmatory Phase 3 study (study 020) were designed on this basis: age ≥7 and ≤16 years; baseline 6MWD ≤80% of predicted for age and height, (and, to enhance uniformity, on corticosteroids, and baseline 6MWD ≥150 meters). Applying these criteria to the Study 007 population, a larger ataluren effect in 6MWD was seen in this "decline phase" subgroup (49.9 meters, p=0.0096). These data were further supported by the results in patients with more advanced disease, with baseline 6MWD <350 meters, which indicated a difference for the primary outcome measure as well as trends favouring ataluren in the TFTs on the lower limb, wheelchair usage, and the HRQL patient-reported physical function domain.

Furthermore, the robustness of the 6MWT results was in the Applicant´s view supported by the positive trends seen in the key secondary endpoints, i.e. TFTs, that represent daily activities and also predict risk of loss of ambulation. As seen in the 6MWT, the trends in TFTs on the lower limb were larger in the subgroup enriched for the decline phase than in the overall study population. The internal consistency of the 6MWD and TFT results was demonstrated in Monte Carlo simulations, in which 10% of patients were randomly removed from each treatment arm, and the analysis repeated 1000 separate times. The Monte Carlo analyses and other sensitivity analyses (such as removal of best/worst patients and the randomization-based ANCOVA analysis) demonstrated that the results of the study were robust.

Further evidence of the robustness of the data seen was constituted by the positive trends observed in other secondary endpoints, which pointed in the same direction as the 6MWT and TFTs: step activity monitoring, wheelchair use, accidental falls, and the QOL child physical function domain. The results for wheelchair use and the QOL child physical function domain, like

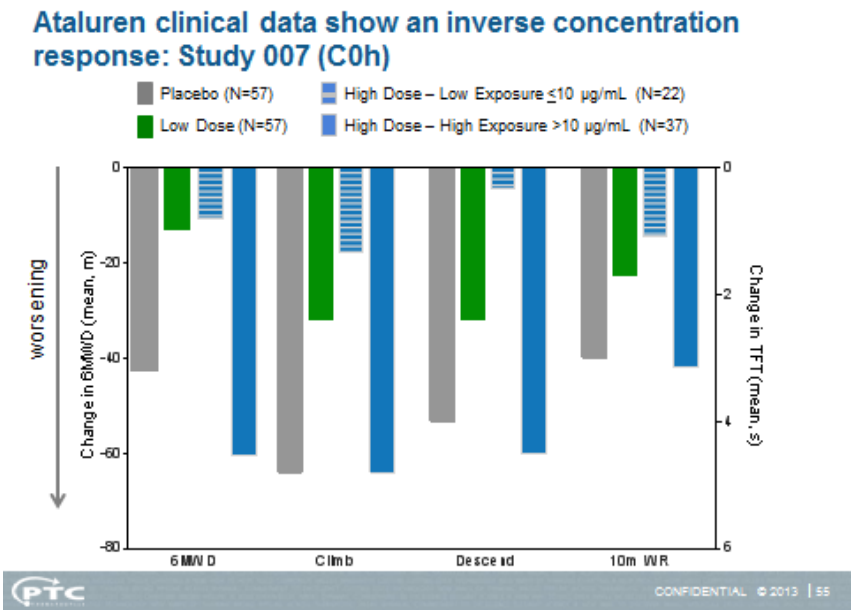
the 6MWT and TFTs, showed larger effect sizes in the subgroup of patients in the ambulatory decline phase. The totality of the data was considered compelling by the Applicant when looking at the aggregately positive trends for ataluren vs placebo across outcome measures. With respect to muscle strength, the applicant pointed out that its measurement is not a relevant outcome for the evaluation of a dystrophin restoration therapy, making reference to studies using the *mdx* mouse which indicated that dystrophin levels correlate with changes in muscle function but not with muscle strength.

In terms of dystrophin production, positive differences in dystrophin expression were seen in ataluren-treated patients in the Phase 2a study. These data were considered by the Applicant to support the bell-shaped dose response since the majority of patients had plasma concentrations less than 20 µg/ml. The Applicant acknowledged that those results were not replicated in the Study 007, giving a variety of reasons, including biopsy sample issues, technical problems, and shipping and handling-introduced artefacts. Of note, despite considerable technical limitations in the Phase 2b study, the largest %-increase in dystrophin and the largest number of patients who exceeded the value of 40% increase were in the 10, 10, 20 mg/kg group, compared to the 20, 20, 40 mg/kg and placebo groups. To put the limited evidence into perspective, the Applicant made reference to the EMA draft guideline [EMA 2013], specifically to sections recognising that dystrophin is not a validated biomarker and may provide only complementary information during diagnosis, and the fact that muscle biopsies are debatable regarding the robustness and the precise quantification of extremely low levels of dystrophin.

The published *in vivo* demonstration of ataluren's readthrough ability was considered by the Applicant to be corroborated by the efficacy of ataluren in both the *mdx* mouse and zebrafish model of nmDMD. Furthermore, the Applicant documented that ataluren's readthrough activity was thoroughly verified by a number of independent investigators in other disease models (Hurler syndrome, cystic fibrosis).

With respect to the bell-shaped dose response, several lines of evidence were submitted by the Applicant in its support, including observations of a bell shaped response in muscle cell cultures from *mdx* mice and nmDMD patients, mouse embryonic fibroblasts (MEFs) of nmHurler mice and in a zebrafish nmDMD model in vivo (sapje mutant). In addition, the Applicant pointed at similarities between the ribosomal binding mechanism of ataluren and aminoglycosides, which also show a bell-shaped response, highlighting that the dose-response relationship is not caused by adverse effects of ataluren. Furthermore, the bell-shaped dose-response curve observed in concentration-based analyses of ataluren in the clinical studies was presented as consistent with the bell-shaped dose-response hypothesis. In particular, the Applicant presented additional analyses based on C0h (fig. 17) documenting that the same trend is observed as within the analyses based on C2h, i.e. higher efficacy in patients with lower concentrations.

Fig. 17 Inverse concentration response – C0h data from study 007



In terms of safety, ataluren was generally well-tolerated by patients with nmDMD at the proposed recommended dose of 10, 10, 20 mg/kg, as well as at the higher dose of 20, 20, 40 mg/kg, when taken daily for 48 weeks in the Phase 2b Study 007. The adverse event profile of ataluren was comparable to that of placebo. Most adverse events were mild or moderate, transient, and did not require medical intervention. None of the patients discontinued treatment because of adverse events. Few serious adverse events were reported, none was considered related to ataluren, and no deaths occurred. Of note, an observational registry study was proposed by the Applicant to collect additional long-term safety data.

Ground 2: *The Applicant has not convincingly shown that comprehensive data can be obtained from the confirmatory placebo-controlled trial if the product is authorised and available on the market.*

With regard to the completion of the Phase 3 confirmatory trial PTC124-GD-020-DMD (Study 020), the Applicant stated that as of 20 March 2014, 48 study sites were activated, with 163 patients screened and 125 patients randomized. The Applicant committed to completing the study in a timely manner, allowing availability of results in 3Q 2015. Based on the advanced state of study enrolment and a careful analysis of when market access to commercial drug would likely occur in the concerned EU member states, the Applicant was of the view that only a very small number of patients would be at risk of withdrawing, and maintained that the granting of the conditional marketing authorisation should not jeopardize the completion or integrity of this critical study. In this context, the Applicant referred to support from DMD patient advocacy groups, existing patient-physician relationships and the option of continuing in a separate open-label extension study as tools encouraging patients to complete the confirmatory trial. Furthermore, the Applicant argued that the study 020 sample size was sufficiently large to allow high integrity of conclusions even if some premature patient discontinuations should occur and also flagged that their successful completion of the study 020 was critical in order to pursue approval in other regions.

Overall CHMP conclusion on grounds for re-examination

The CHMP assessed all the detailed grounds for re-examination and argumentations presented by the applicant in writing and in the oral explanation and considered the views expressed by the Scientific Advisory Group in the initial phase of the procedure.

Ground 1

Following review of the non-clinical evidence available, the CHMP considered that effective promotion of translation across premature nonsense stop codons was documented in various cell culture systems as well as *in vivo*. In particular, the effects of ataluren observed in the zebrafish sapje mutant and in the different genetic mouse models *in vivo* were considered of relevance in terms of the mechanism of action claimed. With respect to the conflicting nature of some of the results that was pointed out in the initial phase, the CHMP acknowledged that it may be attributed to methodological differences of the respective assays. Overall, the mechanism of action of ataluren (nonsense mutation readthrough) was considered plausible. Furthermore, the CHMP noted that the maximum activity of ataluren in the non-clinical setting was mostly observed at concentrations overlapping with the efficacious plasma levels of ataluren in the clinical studies 004 and 007, i.e. < 20 µg/ml.

The CHMP considered that the activity of ataluren in cultures of myotubes from *mdx* mice and nmDMD patients or MEFs of nmHurler mice *in vitro* and in mutant zebrafish larvae *in vivo* followed a bell-shaped dose-response curve. In addition, results in nmHurler mice showed an inverse dose-response relationship with the lowest dose being most effective, which was also indicative of the above hypothesis of a bell shape. While some of the previous uncertainties related to the lack of verification of the findings by additional non-clinical *in vivo* data were maintained, overall, the CHMP concluded that the bell-shaped dose-response could be considered implied by investigations of ataluren's activity *in vitro* and supported by data from *in vivo* study in *sapje* mutant zebrafish, which constitutes a valuable complement to disease models in mammals.

With respect to clinical evidence of the bell-shaped dose response hypothesis, specific attention was paid by the CHMP to the re-analyses of the treatment response in correlation to human plasma concentrations of ataluren. The cut off value of < 19.3 µg/ml used for categorization of patients in low/high plasma level subjects was considered justified, as it was based on the range of C2h seen in the low dose group (10, 10, 20 mg/kg). The results of this analysis indicated that patients in study 007 who had lower plasma ataluren concentrations (< 19.3 µg/ml) experienced less decline in 6MWT than patients who had higher plasma ataluren concentrations. Furthermore, in their oral explanation the Applicant presented additional analysis based on C0h values of plasma concentration of ataluren, i.e. a parameter which approximately reflects the trough concentration. Importantly, when looking at the efficacy by concentration, similarly to the observation based on the C2h data, patients with low concentrations of ataluren performed better than those with high concentration (both in terms of 6MWD and a across TFTs). Of note, the magnitude of the effect size observed in patients with lower plasma concentration on the high dose and the one observed in the patients on the low dose was similar in both instances, i.e. in the analyses based on C0h and C2h data. This evidence was considered to provide support to the bell-shaped dose-response hypothesis from the clinical point of view.

Overall, the CHMP was of the view that the bell-shaped dose response hypothesis was plausible and that despite some limitations of the findings, the available evidence could provide a rationale for the observed differences in efficacy between the two doses tested, i.e. higher efficacy seen in the 10, 10, 20 mg/kg dose and minimal efficacy in the 20, 20, 40 mg/kg dose.

In light of the revised position of the CHMP on the mechanism of action and the bell-shaped dose-response hypothesis, which were both parts of the initial grounds for refusal, the CHMP looked into the available clinical efficacy data.

The CHMP maintained their initial position that there were limitations of the dataset in terms of robustness, namely the observation of the variability of the primary efficacy data and the fact that many of the conclusions supporting efficacy were derived from the post hoc analyses. However, taking into account that the mechanistic concerns and concerns pertaining to the dose-response were alleviated during the re-examination, as discussed above, the CHMP was of the view that the observed results could reflect a true effect. This was considered to adequately reduce the concern expressed during the initial phase, i.e. that the observed effects could be only chance findings. With respect to the magnitude and clinical relevance of the observed effects, the CHMP referred to their previous position, i.e. that there were several lines of evidence supporting the clinical relevance of a 30-meter difference in 6MWT, including a report showing that a 30-meter change in 6MWD over 48 weeks can be considered a clinically meaningful change based on the patient/parent-reported quality of life measures in DMD patients. This was also supported by results of natural history data in DMD, indicating that 30-meter decrease in baseline 6MWD significantly increases the risk of loss of ambulation over the following 2 years.

As in the initial phase of the MAA review, the CHMP discussed the appropriate target population for the use of ataluren. Considering that the beneficial effects were most prominent in a sub-population of ambulatory patients in the decline phase of their walking ability (effect size of approximately 50 metres on the 6MWD), the CHMP discussed whether this finding would imply the need for restricting the indication to a population defined accordingly, i.e. patients in ambulatory decline phase. In line with the previous position of the SAG, the CHMP agreed that scientifically there should be no reason for the drug not to be given to milder patients if efficacy had been established in more severe ones. Furthermore, the CHMP considered that while less prominent, a clinically meaningful effect was seen also in the overall population studied. Thus, the CHMP concluded that ataluren can be authorised in the indication that the company claimed in the re-examination:

"Translarna is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older. Efficacy has not been demonstrated in non-ambulatory patients.

The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing."

Of note, the indication initially applied for, covering also non-ambulatory patients was not pursued by the Applicant in their Grounds for re-examination. This was considered appropriate by the CHMP, since ataluren was evaluated only in ambulatory patients.

The CHMP considered that the ground for refusal No. 1 was resolved with a specific obligation to conduct the confirmatory clinical trial 020. The results of this trial were expected to further reduce the uncertainties about benefits and support the favourable benefit-risk balance.

Ground 2

The CHMP reviewed the Applicant´s discussion about the feasibility of the confirmatory trial, including the progress on recruitment, expected timelines and actions proposed to minimise patient withdrawals and to ensure successful completion of the trial. Based on the assumptions made by the Applicant, the CHMP agreed that conducting the confirmatory study 020 and submitting the final study results by 4Q 2015 could be feasible independently of the status of approval. In

particular, the CHMP took into consideration the additional tools presented by the Applicant to ensure that patients complete the confirmatory trial. These included existing patient-physician relationships, the option of continuing participation in a separate open-label extension study and also support from DMD patient advocacy groups which will be leveraged by the Applicant to conduct outreach programmes for patients, emphasising the importance of remaining in study 020 through its completion. Furthermore, the CHMP considered that a protocol amendment will be implemented by the Applicant allowing for additional recruitment, replacing patients who withdraw from the study for reasons linked to the availability of the product on the market.

The CHMP concluded that the strategy of the Applicant was re-assuring and considered that the ground for refusal No. 2 was resolved.

Overall conclusion

The Applicant applied for a conditional marketing authorisation with the proposal that additional data would be generated post-authorisation in the confirmatory phase 3 study (020). Therefore, the CHMP also re-discussed the criteria that would need to be met for a conditional approval according to Articles 2 and 4 of the Regulation (EC) no 507/2006, and made the following conclusions upon re-examination of the initial CHMP Opinion:

- DMD is a life-threatening and chronically debilitating condition where no satisfactory methods of treatment exist and it was considered that the product would thus address an unmet medical need.

- Upon review of the Applicant´s grounds for re-examination, the CHMP considered that despite the uncertainties discussed above and the fact that the dataset was not comprehensive, sufficient efficacy was seen to conclude on a favourable benefit-risk balance. Of note, this conclusion was to a great extent supported by the safety profile of ataluren, which does not pose any major safety concerns.

- The criterion that the benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required was considered fulfilled since the benefits to public health were substantiated by providing a treatment for a serious disease, characterised by gradual deterioration of the condition and a fatal outcome.

- With respect to generating additional data post authorisation, the CHMP considered that the Applicant will complete a confirmatory randomized placebo-controlled Phase 3 study PTC124-GD-020-DMD (Study 020) with the 10, 10, 20 mg/kg/day dose in patients with nmDMD. The CHMP agreed that this clinical trial may provide data alleviating the current uncertainties and acknowledged the timelines planned for its conduct and submission of its results (4Q 2015). With respect to the study feasibility, the position of the CHMP changed at the time of the re-examination Opinion; specifically, the CHMP considered that performing the study was plausible per se, independent of the marketing authorisation status, as discussed above.

A favourable benefit-risk balance was established based on the data available at the time of this MAA and the CHMP concluded that the confirmatory evidence from study 020 was acceptable to be generated post authorisation.

4.1. Risk Management Plan

At the end of the initial procedure, the CHMP, having considered the data submitted in the application was of the opinion that it was not appropriate to consider pharmacovigilance activities and risk minimisation measures.

During the re-examination procedure, the Applicant addressed the open issues described in the PRAC RMP assessment dated 03 December 2013. A review of the Applicant's responses and of the updated RMP (submitted as part of the re-examination file) concluded that the RMP in the proposed treatment of Duchenne muscular dystrophy, resulting from a nonsense mutation in the dystrophin gene (nmDMD) in ambulatory patients aged 5 years and older, could be acceptable provided that an updated risk management plan is submitted before final CHMP opinion, addressing the following issues:

1. Hepatic toxicity should be included as an important potential risk;
2. The summary table of risk minimisation measures should be edited to reflect the routine risk minimisation measures planned for each safety concern (e.g. SmPC);
3. Amendments are needed in the proposed SmPC to ensure accurate communication on the monitoring requirements.

Of note, as requested by the PRAC during the initial phase of the MAA procedure, the PASS study 'Long-Term Observational Study of Ataluren Safety and Effectiveness in Usual Care' was classified by the Applicant as a category 1 study. With respect to the scope of this PASS study, following a review of the Applicant´s responses, it was concluded that it had been satisfactorily expanded to obtain additional information on the long-term effectiveness of ataluren.

The Applicant addressed the above issues and produced an RMP based on the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	• Potentiation of aminoglycoside renal toxicity • Changes in lipid profile
Important potential risks	• Hypertension with concomitant use of systemic corticosteroids • Renal toxicity • Hepatic toxicity • Hibernoma • Malignancies in general
Missing information	• Effect of co-administration of ataluren with nephrotoxic drugs other than intravenous aminoglycosides • Use in patients with moderate to severe hepatic impairment • Use in patients with moderate to severe renal impairment • Potential use in children from 6 months to 5 years • Use in patients whose ethnic origin is other than Caucasian • Extended long-term safety • Off-label use in patients who do not have DMD caused by a nonsense mutation in the dystrophin gene

Summary of safety concerns	
	• Effect of co-administration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies

Pharmacovigilance plans

Study/activity type, title and category	Objectives	Safety concern addressed	Status (planned /started)	Date for submission of interim or final reports (planned or actual)
Post-approval registry [Working title: Long-Term Observational Study of Ataluren Safety and Effectiveness in Usual Care] Category 1* *re-classified to category 3 at the request of the CHMP, see p. 93	Continue to document the long-term safety profile of ataluren Obtain additional information on the long-term effectiveness of ataluren Evaluate the safety and effectiveness of ataluren in subgroups not traditionally included in clinical trials Evaluate changes in lipid profile Determine the incidence and frequency of: ○ Hypertension with use of concomitant corticosteroids ○ Renal toxicity (without concomitant aminoglycosides or other nephrotoxic drugs) ○ Hepatic toxicity	Changes in lipid profile Hypertension with use of concomitant systemic corticosteroids Renal toxicity Hepatic toxicity Effect of co-administration of ataluren with nephrotoxic drugs other than intravenous aminoglycosides Use in patients with moderate to severe hepatic impairment Use in patients with moderate to severe renal impairment Potential use in children from 6 months to 5 years Use in patients whose ethnic origin is other than Caucasian Extended long-term safety Off-label use in patients who do not have DMD caused by a nonsense mutation in the dystrophin gene Effect of co-administration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies	Planned	4Q2015 (1-year interim) 4Q2016 (2-year interim) 4Q2017 (3-year interim) 4Q2018 (4-year interim) 4Q2019 (5-year interim) 4Q2020 (6-year interim) 4Q2021 (7-year interim) 4Q2022 (final)

Study/activity type, title and category	Objectives	Safety concern addressed	Status (planned /started)	Date for submission of interim or final reports (planned or actual)
	Evaluate the safety of ataluren • in patients with moderate to severe renal or hepatic impairment • when used with nephrotoxic drugs (other than aminoglycosides) Evaluate the safety and effectiveness of ataluren in the context of certain concomitant drugs Monitor the utilization pattern of ataluren			
7-day tolerability and pharmacokinetic study in neonatal dogs Category 3		Potential use in children from 6 months to 5 years	Planned	December 2014
1-month juvenile dose range-finding toxicology and toxicokinetic study planned in neonatal dogs (age correlating with dosing in newborn paediatric patients to 2 years of age), Study 2 of EMA/PDCO/476743/2012 PDCO document. Category 3		Potential use in children from 6 months to 5 years	Planned	December 2014

Study/activity type, title and category	Objectives	Safety concern addressed	Status (planned /started)	Date for submission of interim or final reports (planned or actual)
3-month juvenile toxicology and toxicokinetic study planned in neonatal dogs (age correlating with dosing in newborn paediatric patients to 2 years of age), Study 3 of EMA/PDCO/476743/2012 PDCO document Category 3		Potential use in children from 6 months to 5 years	Planned	December 2014
β3 adrenergic binding assay with ataluren and the M4 metabolite, if such a study is technically feasible Category 3		Further investigation of ataluren's potential effect in the development of hibernomas	Planned	December 2014
Plan to investigate further post-authorisation the potential effects of ataluren and metabolite M4 in brown adipose tissue of rats. Category 3		Further investigation of ataluren's potential effect in the development of hibernomas	Planned	4Q2015
Open-label safety and PK study in children age 6 months to 5 years, Study 6 of EMA/PDCO/476743/2012 PDCO document Category 3		Potential use in children from 6 months to 5 years	Planned	December 2016
Safety and PK study in patients with moderate to severe hepatic impairment Category 3	To evaluate the safety and PK of ataluren in subjects with different degrees of hepatic impairment, in order to provide guidance for ataluren dosing in patients with moderate to severe hepatic impairment.	Use in patients with moderate to severe hepatic impairment	Planned	3Q2017

Study/activity type, title and category	Objectives	Safety concern addressed	Status (planned /started)	Date for submission of interim or final reports (planned or actual)
Safety and PK study in patients with moderate to severe renal impairment Category 3	To evaluate the safety and PK of ataluren in subjects with different degrees of renal impairment, in order to provide guidance for ataluren dosing in patients with moderate to severe renal impairment.	Use in patients with moderate to severe renal impairment	Planned	4Q2017
Safety and PK study of co-administration of ataluren and a sensitive probe inducer of UGT1A9 Category 3	To evaluate the safety and PK of ataluren and/or the appropriate sensitive probe, in order to provide guidance for dosing ataluren with the specific concomitant medication.	Effect of co-administration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies	Planned	2Q2015
Safety and PK study of co-administration of ataluren and a sensitive probe substrate of UGT1A9 Category 3	To evaluate the safety and PK of ataluren and/or the appropriate sensitive probe substrate, in order to provide guidance for dosing ataluren with the specific concomitant medication.	Effect of co-administration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies	Planned	4Q2015
Safety and PK study of co-administration of ataluren and a sensitive probe inhibitor of the transporter breast cancer resistant protein (BCRP) Category 3	To evaluate the safety and PK of ataluren and/or the appropriate sensitive probe, in order to provide guidance for dosing ataluren with the specific concomitant medication.	Effect of co-administration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies	Planned	2Q2016

Study/activity type, title and category	Objectives	Safety concern addressed	Status (planned /started)	Date for submission of interim or final reports (planned or actual)
Safety and PK study of co-administration of ataluren and a sensitive probe substrate of organic anion transporter 1 (OAT1) Category 3	To evaluate the safety and PK of ataluren and/or the appropriate sensitive probe substrate, in order to provide guidance for dosing ataluren with the specific concomitant medication.	Effect of co-administration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies	Planned	4Q2016
Safety and PK study of co-administration of ataluren and a sensitive probe substrate of organic anion transporter 3 (OAT3) Category 3	To evaluate the safety and PK of ataluren and/or the appropriate sensitive probe substrate, in order to provide guidance for dosing ataluren with the specific concomitant medication.	Effect of co-administration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies	Planned	2Q2017
Safety and PK study of co-administration of ataluren and a sensitive probe substrate of organic anion transporting polypeptide 1B3 (OATP1B3) Category 3	To evaluate the safety and PK of ataluren and/or the appropriate sensitive probe substrate, in order to provide guidance for dosing ataluren with the specific concomitant medication.	Effect of co-administration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies	Planned	2Q2018

Risk minimisation measures

Safety concerns	Routine risk minimisation measures	Additional risk minimisation measures
Potentiation of aminoglycoside renal toxicity	**SmPC section 4.3 (Contraindications)** Concomitant use of intravenous aminoglycosides (see section 4.4 and 4.5). **SmPC section 4.4 (Special warnings and precautions for use)** <u>Aminoglycosides</u> Aminoglycosides have been shown to reduce the readthrough activity of ataluren *in vitro*. In addition, ataluren was found to increase nephrotoxicity of intravenous aminoglycosides. The co-administration of these medicinal products with ataluren should be avoided (see section 4.3). Since the mechanism by which ataluren increases nephrotoxicity of intravenous aminoglycosides is not known, concomitant use of other nephrotoxic medicinal products with ataluren is not recommended. If this is unavoidable (e.g. vancomycin to treat MRSA) careful monitoring of renal function is advised (see section 4.5) **SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction)** <u>Aminoglycosides</u> Ataluren should not be co-administered with intravenous aminoglycosides, based on cases of decreased renal function observed in a clinical trial in patients with nonsense mutation cystic fibrosis (nmCF) (see section 4.3). Elevations of serum creatinine occurred in several nmCF patients treated with ataluren and intravenous aminoglycosides together with other antibiotics for cystic fibrosis exacerbations. The serum creatinine elevations resolved in all cases, with discontinuation of the intravenous aminoglycoside, and either continuation or interruption of Translarna . These findings suggested that co-administration of Translarna and intravenous aminoglycosides may potentiate the nephrotoxic effect of the aminoglycosides. Therefore, if treatment with intravenous aminoglycosides is necessary the treatment with Translarna should be stopped and can be resumed 2 days after administration of the aminoglycoside has ended. The effect of co-administration of ataluren with other nephrotoxic medicinal products is unknown. Dehydration may be a contributing factor in some of these cases. Patients should maintain adequate hydration while taking ataluren (see section 4.4).	None proposed

Safety concerns	Routine risk minimisation measures	Additional risk minimisation measures
Changes in lipid profile	**SmPC section 4.4 Special warnings and precautions for use** Changes in lipid profile Because changes in lipid profile (increased triglycerides and cholesterol) were reported for some patients in clinical trials, it is recommended that total cholesterol, LDL, HDL, and triglycerides be monitored on an annual basis in nmDMD patients receiving ataluren, or more frequently as needed based on the patient's clinical status. **SmPC section 4.8 (Undesirable effects)** Change in lipid profile (increased triglycerides and cholesterol) are included in Table 1. (Description of selected adverse reactions) Serum lipids During the controlled study of nmDMD, mean total cholesterol and triglycerides were normal at baseline and increased, reaching borderline high or high values. The values tended to stabilize early in the study and did not increase further with continued treatment.	None proposed
Hypertension with use of concomitant corticosteroids	**SmPC section 4.4 Special warnings and precautions for use** Hypertension with use of concomitant systemic corticosteroids Because hypertension with use of concomitant systemic corticosteroids was reported in some patients in clinical trials, it is recommended that resting systolic and diastolic blood pressure be monitored every 6 months in nmDMD patients receiving ataluren concomitantly with corticosteriods, or more frequently as needed based on the patient's clinical status. **SmPC section 4.8 (Undesirable effects)** Hypertension is included in Table 1.	None proposed

Safety concerns	Routine risk minimisation measures	Additional risk minimisation measures
Renal toxicity	**SmPC section 4.4 Special warnings and precautions for use** Renal function monitoring Because small increases in mean serum creatinine, blood urea nitrogen (BUN), and cystatin C were observed in the controlled study of nmDMD, it is recommended that serum creatinine, BUN, and cystatin C be monitored every 6 to 12 months in nmDMD patients receiving ataluren, or more frequently as needed based on the patient's clinical status. **SmPC section 4.8 (Undesirable effects)** Change in renal function tests (increased creatinine, blood urea nitrogen, cystatin C) is included in Table 1. **(Description of selected adverse reactions)** *Renal function tests* During the controlled study of nmDMD, small increases in mean serum creatinine, blood urea nitrogen (BUN), and cystatin C were observed. The values tended to stabilize early in the study and did not increase further with continued treatment.	None proposed
Hepatic toxicity	None proposed	None proposed
Hibernoma	None proposed	None proposed
Malignancies in general	None proposed	None proposed
Use of ataluren in nmDMD patients who co-administered ataluren with nephrotoxic drugs	**SmPC section 4.4 Special warnings and precautions for use** Aminoglycosides Since the mechanism by which ataluren increases nephrotoxicity of intravenous aminoglycosides is not known, concomitant use of other nephrotoxic medicinal products with ataluren is not recommended. If this is unavoidable (e.g. vancomycin to treat MRSA) careful monitoring of renal function is advised (see section 4.5). **SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction)** The effect of co-administration of ataluren with other nephrotoxic medicinal products is unknown.	None proposed

Safety concerns	Routine risk minimisation measures	Additional risk minimisation measures
Use of ataluren in nmDMD patients with moderate to severe hepatic impairment	**SmPC section 4.2 (Posology and method of administration)** *Renal and hepatic impairment* Safety and efficacy of ataluren in patients with renal and hepatic impairment have not been established (see section 4.4). **SmPC section 4.4 Special warnings and precautions for use)** Hepatic and renal impairment Patients with renal and hepatic impairments should be closely monitored. **SmPC section 5.2 Pharmacokinetic properties** Renal or hepatic impairment No studies have been conducted with Translarna in patients with renal or hepatic impairment. Patients with renal or hepatic impairment should be monitored closely.	None proposed
Use of ataluren in nmDMD patients with moderate to severe renal impairment	**SmPC section 4.2 Posology and method of administration** *Renal and hepatic impairment* Safety and efficacy of ataluren in patients with renal and hepatic impairment have not been established. **SmPC section 4.4 Special warnings and precautions for use** Hepatic and renal impairment Patients with renal and hepatic impairments should be closely monitored. **SmPC section 5.2 Pharmacokinetic properties** Renal or hepatic impairment No studies have been conducted with Translarna in patients with renal or hepatic impairment. Patients with renal or hepatic impairment should be monitored closely.	None proposed
Potential use in children from 6 months to 5 years old	**SmPC section 4.1 (Therapeutic indications)** Translarna is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older. **SmPC section 4.2 (Posology and method of administration)** The safety and efficacy of Translarna in children and infants less than 5 years old have not yet been established.	None proposed

Safety concerns	Routine risk minimisation measures	Additional risk minimisation measures
Use of ataluren in patients whose ethnic origin is other than Caucasian	**SmPC section 5.2 Pharmacokinetic properties** It is unlikely that the pharmacokinetics of ataluren are significantly affected by UTG1A9 polymorphisms in a Caucasian population. Due to the low number of other races included in the clinical studies, no conclusions can be drawn on the effect of UTG1A9 in other ethnic groups.	None proposed
Extended long-term safety	None proposed	None proposed
Off-label use of ataluren in patients who do not have DMD caused by a nonsense mutation in the dystrophin gene	**SmPC section 1 (therapeutic indications)** Translarna is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older. Efficacy has not been demonstrated in non-ambulatory patients.	None proposed

Safety concerns	Routine risk minimisation measures	Additional risk minimisation measures
Effect of co-administration of ataluren with certain drugs not yet evaluated in formal drug-drug interaction studies	**SmPC section 4.4 Special warnings and precautions for use** Potential interactions with other medicinal products Caution should be exercised when ataluren is co-administered with medicinal products that are substrates or inducers of UGT1A9, inhibitors of BCRP, or substrates of OAT1, OAT3, or OATP1B3 (section 4.5). **SmPC section 4.5 (Interaction with other medicinal products and other forms of interaction)** *Effect of other medicinal products on ataluren pharmacokinetics* Based on in vitro studies, ataluren is a substrate of UGT1A9 and breast cancer resistant protein (BCRP). Caution should be exercised when ataluren is co-administered with medicinal products that are inducers of UGT1A9 (e.g. mycophenolate mofetil), or inhibitors of BCRP (e.g. ciclosporin). *Effect of ataluren on pharmacokinetics of other medicinal products* Based on in vitro studies, ataluren is an inhibitor of UGT1A9, organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3) and organic anion transporting polypeptide 1B3 (OATP1B3). Caution should be exercised when ataluren is co-administered with drugs that are substrates of UGT1A9, OAT1, OAT3, or OATP1B3 because of the risk of increase concentration of these medicinal products (eg, oseltamivir, aciclovir, ciprofloxacin, captopril, furosemide, bumetanide, valsartan, pravastatin, rosuvastatin, atorvastatin, pitavastatin). Based on the *in vitro* studies, ataluren is not expected to be an inhibitor of neither p-gp mediated transport nor of cytochrome P450 mediated metabolism. Similarly, ataluren is not expected *in vivo* to be an inducer of cytochrome P450 isoenzymes.	None proposed

The CHMP endorsed the PRAC advice with changes.

These changes concerned the following elements of the Risk Management Plan:

The CHMP considered that the PASS study 'Long-Term Observational Study of Ataluren Safety and Effectiveness in Usual Care' should be classified as a category 3 study, rather than a category 1 study.

The CHMP justified these changes as follows:

The CHMP considered that the scope of this observational study is to look into the long-term safety and effectiveness of ataluren, rather than to focus on a specific issue key to the benefit-risk balance of ataluren.

5. Benefit-Risk Balance

Benefits

Beneficial effects

Ataluren is a first-in-class drug designed to enable ribosomal readthrough of premature stop codons, resulting in the formation of a full-length functional protein in patients with nonsense mutation genetic disorders. In the proof of concept study in *mdx* mice ataluren was seen to promote formation and adequate localization of dystrophin, resulting in increased muscle strength and prevention of loss of strength following repeated contractions.

In the clinical setting, beneficial effects of the lower dose (10, 10, 20 mg/kg) were claimed in both primary and secondary endpoints of physical functioning.

With respect to 6MWD, ataluren was observed to slow disease progression in nmDMD patients. The post-hoc analysis in the cITT population indicated an estimated difference in the Change in 6MWD at Week 48 of 31.7 metres (nominal p=0.0281, adjusted p=0.0561) between the 10, 10, 20 mg/kg dose and placebo. Looking at the proportions of patients with at least 10% worsening in 6MWD at Week 48, 44% vs 26% of patients in the placebo and the 10, 10, 20 mg/kg ataluren arm, respectively were progressors (nominal p=0.0326, adjusted p=0.0652) .

A greater effect over 48 weeks was seen in patients in the "ambulatory decline" phase, i.e. patients between 7 and 16 years of age, with baseline 6MWD ≥150m and ≤80% of predicted value. Based on a post-hoc subgroup analysis in this population, a difference in the change in 6MWD at Week 48 of 49.9 metres (p=0.0096) between the 10, 10, 20 mg/kg dose and placebo was seen.

In terms of secondary endpoints of physical functioning, only limited effects of ataluren were observed: ataluren patients had fewer falls/week than placebo-dosed patients; increase of wheelchair use from baseline was less in ataluren than placebo; ataluren patients spent less time in "no activity" (based on Step activity monitoring) and a minor positive trend was observed in myometry tests.

Uncertainty in the knowledge about the beneficial effects

The CHMP was of the view that the main uncertainties about the claimed beneficial effects pertained to the dose-response curve (and hence the appropriate dose), the robustness of efficacy data in general and the applicability of the data to the overall population of nmDMD patients.

Uncertainties about the dose-response curve and dose

The CHMP considered that the activity of ataluren in cultures of myotubes from *mdx* mice and nmDMD patients or MEFs of nmHurler mice *in vitro* and in mutant zebrafish larvae *in vivo* followed a bell-shaped dose-response curve. In addition, results in nmHurler mice showed an inverse dose-response relationship with the lowest dose being most effective, which was also indicative of the above hypothesis of a bell-shape dose-response. While some of the uncertainties related to the lack of verification of the findings by additional non-clinical *in vivo* data were maintained, overall, the CHMP concluded that the bell-shaped dose-response could be considered implied by investigations of ataluren's activity *in vitro* and supported by data from *in vivo* study in *sapje* mutant zebrafish, which constitutes a valuable complement to disease models in mammals.

With respect to clinical evidence of the bell-shaped dose response hypothesis, specific attention was paid by the CHMP to the re-analyses of the treatment response in correlation to human plasma concentrations of ataluren. The cut off value of < 19.3 µg/ml used for categorization of patients in low/high plasma level subjects was considered justified, as it was based on the range of C2h seen in the low dose group (10, 10, 20 mg/kg). The results of this analysis indicated that patients in study 007 who had lower plasma ataluren concentrations (< 19.3 µg/ml) experienced less decline in 6MWT than patients who had higher plasma ataluren concentrations. Furthermore, in their oral explanation the Applicant presented additional analysis based on C0h values of plasma concentration of ataluren, i.e. a parameter which approximately reflects the trough concentration. Importantly, when looking at the efficacy by concentration, similarly to the observation based on the C2h data, patients with low concentrations of ataluren performed better than those with high concentration (both in terms of 6MWD and a across TFTs). Of note, the magnitude of the effect size observed in patients with lower plasma concentration on the high dose and the one observed in the patients on the low dose was similar in both instances, i.e. in the analyses based on C0h and C2h data. This evidence was considered to provide support to the bell-shaped dose-response hypothesis from the clinical point of view.

Uncertainties about robustness of efficacy data

The CHMP was of the view that there were limitations of the dataset in terms of robustness, namely the observation of the variability of the primary efficacy data and the fact that many of the conclusions supporting efficacy were derived from the post hoc analyses. However, taking into account that the mechanistic concerns and concerns pertaining to the dose-response were alleviated during the re-examination, as discussed above, the CHMP concluded that the observed results could reflect a true effect. This was considered adequate to reduce the concern expressed during the initial phase, i.e. that the observed effects could be only chance findings.

The CHMP was of the view that the results on the secondary endpoints provided only limited support for the primary endpoint outcomes and needed to be seen only as trends. Nevertheless, in line with the previous input from the SAG, the CHMP acknowledged that most of the secondary endpoints were of such nature that any effect would have to be driven by an increase in strength and for this to occur, higher levels of dystrophin in muscular fibres would have to be achieved.

Pharmacodynamic confirmation of efficacy was not provided by the pivotal study, despite the fact that biopsies were collected. While the technical problems with dystrophin quantification were recognised by the CHMP, the quality of the biopsies supplied was of concern. The GCP inspection identified that several steps were underestimated, namely instructions for performing the muscle biopsies and the storage/ shipping logistics. Since the mechanism of action of ataluren is claimed to be by promoting production of a full-length dystrophin, more prominent evidence of dystrophin in muscle of patients treated for 48 weeks would be expected. Considering the limitations of data on clinical efficacy, the CHMP pointed out that the dossier would have benefited from supportive data on pharmacodynamics.

With respect to the actual mechanism of restoring dystrophin production, the CHMP considered that promotion of the translation process at the ribosomal level was plausible, despite the fact that positive results were not seen in all assays reported.

Validity of data for the entire nmDMD patient population

Of note, the indication initially applied for, covering also non-ambulatory patients was not pursued by the Applicant in their Grounds for re-examination. This was considered appropriate by the CHMP, since ataluren was evaluated only in ambulatory patients.

Risks

Unfavourable effects

Ataluren was generally well tolerated by patients with nmDMD, with the most common adverse events being headache and gastrointestinal disorders such as nausea, vomiting, (upper) abdominal pain, flatulence, diarrhoea, stomach discomfort, constipation and regurgitation.

The laboratory data indicated that exposure to ataluren could cause elevation of serum cholesterol and triglycerides. Mean cholesterol and triglycerides levels were in the upper range of normal at baseline and increased to borderline-high or high levels in the ataluren arms, primarily in patients who were receiving corticosteroids. The values tended to stabilize early and did not increase further with continued treatment. "Changes in the lipid profile" were considered as an important identified risk in the proposed Risk Management Plan.

Of note, elevations of serum creatinine occurred in several patients with nonsense mutation cystic fibrosis treated concomitantly with intravenous aminoglycosides. In all cases, the elevations resolved with discontinuation of the aminoglycosides indicating that co-administration of ataluren and intravenous aminoglycosides may potentiate the nephrotoxic effect of the aminoglycosides. Based on this evidence of decreased renal function, "potentiation of aminoglycoside renal toxicity" was determined as an important identified risk.

There were no deaths during the placebo controlled study. Three fatal cases were seen in one open-label study, but the fatal outcomes were not considered related to treatment with ataluren.

Uncertainty in the knowledge about the unfavourable effects

From the non-clinical database, the finding of malignant hibernomas in rat raised the concern as to whether occurrence of similar effects could be expected in humans, particularly in the paediatric population where the quantity of the brown adipose tissue is higher. In particular, the CHMP considered that malignant hibernomas could be related to the effects of ataluren on fat tissue metabolism and to effects on plasma lipid parameters, which were observed in rats, dogs and humans. Thus, "hibernomas" were reflected in the proposed risk management plan of ataluren as an important potential risk.

Considering the mechanism of action of ataluren, the CHMP pointed out a theoretical concern about possible effects of ataluren on reading through normal stop codons (and thus producing abnormally elongated proteins) and a concern that ataluren could enhance read through of non-sense mutations in other genes. Although such effects were not seen in the data available, the CHMP was of the view that the potential off-target effects were an uncertainty about the risks of ataluren.

Based on results of *in vitro* studies, ataluren was expected to have an interaction potential, which the CHMP considered necessary to be explored further *in vivo*. This pertained to ataluren interactions with a BCRP inhibitor, UGT1A9 substrate, OAT1, OAT3 and OATP1B3 substrates and UGT1A9 selective inducer.

Increase in blood pressure including cases of hypertension requiring antihypertensive treatment was observed in subjects treated with ataluren. While this could have been due to the use of corticosteroids administered concomitantly, this issue was considered an uncertainty and captured as a potential risk in the proposed Risk Management Plan.

The preclinical data as well as data from healthy volunteers and DMD patients indicated that

exposure to ataluren may lead to increase in transaminases. While these changes seemed to be reversible after exposure to ataluren was stopped and a clear hepatotoxic effect was not confirmed, the CHMP considered hepatotoxicity as an important potential risk.

The nmCF study data suggested an effect of ataluren on renal abnormalities. Although the mechanism of a potential contribution of ataluren to the reported cases of nephrotoxicity was not known, this signal in the clinical development appeared to reinforce the non-clinical findings seen in mice. Based on the clinical data available, renal toxicity was assumed to occur less likely in DMD patients, but was still perceived as a potential important risk. Of note, data from a clinical trial investigating ataluren in cystic fibrosis were published at the time of the re-examination CHMP Opinion (May 2014). Upon request of the CHMP, these results were discussed by the Applicant in their oral explanation. In their conclusions, the CHMP highlighted that while the evidence did not indicate increased risk for the DMD population, as a precautionary measure, additional wording should be implemented in the Product Information to discourage concomitant use of ataluren and nephrotoxic medicinal products.

Treatment of patients with renal or hepatic impairment is another area of uncertainty, as no specific studies were performed and potential safety concerns are implied by the pharmacokinetics of ataluren. Since renal excretion accounts for ~ 50% of the drug elimination, renal impairment is likely to result in accumulation of ataluren and/or ataluren glucuronide. Similarly, since ataluren is extensively metabolized in liver, hepatic impairment is expected to result in ataluren increased plasma concentrations. Taken together with the uncertainties around the claimed bell-shaped dose-response curve, the CHMP considered that without clinical data, understanding of both efficacy and safety profile of ataluren in subjects with renal or hepatic impairment remains limited.

Benefit-risk balance

Importance of favourable and unfavourable effects

Several lines of evidence support the clinical relevance of a 30-meter difference in 6MWT, including a report[3] showing that a 30-meter change in 6MWD over 48 weeks can be considered a clinically meaningful change based on the patient/parent-reported quality of life measures in DMD patients. This is also supported by results of longitudinal LMWT natural history data in DMD, indicating that each 30-meter decrease in baseline 6MWD predicts increasing risk of loss of ambulation over the following 2 years.

Ability to climb and descend a short grouping of stairs, ability to run in short bursts, or to walk a short distance unaided, e.g. to a bathroom, reflect the typical activities important in the lives of DMD patients. Importantly, recent data indicated that timed function tests evaluating these abilities are, similarly to 6MWT, predictive of the time for a patient to become non-ambulatory. Natural history data from the Cooperative International Neuromuscular Group indicated that changes in these parameters are predictive of the likelihood of loss of ambulation over 1 year. Falls commonly lead to fractures in DMD patients and the injuries sustained may accelerate loss of ambulation. Decreasing the rate of accidental falls and hence the risk of fractures, pain and

[3] Henricson E, Abresch R, Han JJ, Nicorici A, Goude Keller E, de Bie E, McDonald CM. The 6-Minute Walk Test and Person-Reported Outcomes in Boys with Duchenne Muscular Dystrophy and Typically Developing Controls: Longitudinal Comparisons and Clinically-Meaningful Changes Over One Year. PLOS Currents Muscular Dystrophy. 2013 Jul 8; 5:ecurrents.md.9e17658b007eb79fcd6f723089f79e06. doi: 10.1371/currents.md.9e17658b007eb79fcd6f723089f79e06

other trauma would be of benefit to the patients. With respect to decrease in wheel chair use, benefits can be attributed not only in terms of ambulation itself, but also by positive impact on the respiratory function and minimisation of scoliosis. Thus, if sufficiently documented these effects would be considered of high importance.

The most commonly reported treatment-related adverse events vomiting, diarrhoea, abdominal pain upper, flatulence, nausea, headache and decreased appetite were not considered to raise major safety concerns in a seriously debilitating and life-threatening condition such as DMD.

The effect of ataluren on the lipid profile (cholesterol and triglyceride levels) was considered of importance, especially in a situation where long-term administration of corticosteroids is expected. Nevertheless, the values tended to stabilize early in the study and did not increase further with continued treatment, which was considered re-assuring. Similarly, the risk of hypertension during concomitant use of corticosteroids and ataluren was seen as of importance to the target population, considering that such co-administration would occur in the majority of patients in the clinical practice.

In the context of the age group targeted, the potential risk of hibernoma was considered relevant, due to higher proportion of brown fat tissue in children.

Discussion on the benefit-risk balance

The CHMP considered that the data presented in the dossier had some deficiencies which impacted on the benefit-risk assessment. In particular, the Applicant conducted only a single pivotal trial and with the formal failure of its primary analysis, the efficacy discussion was based on post hoc analyses. It was agreed that these analyses were performed in line with the most current knowledge about the natural history of the disease (gained during the conduct of study 007), and in this respect the definition of the subgroups in these analyses was clinically and scientifically justified (e.g. patients in decline phase of their ambulation). The effects observed in the pivotal study were considered generally encouraging, as also supported by the previous input from the SAG, and in the context of a revised position on the mechanism of action and on the issue of dose-response relationship, the CHMP was of the view that the observed results could reflect a true effect and thus constitute evidence of efficacy.

As discussed above, the bell-shape dose response hypothesis was used by the Applicant to explain why effects were only seen with the lower dose (10, 10, 20 mg/kg). Following re-examination of the initial opinion the CHMP was of the view that, despite some limitations of the findings, the bell-shaped dose response hypothesis was plausible and the available evidence could provide a rationale for the observed differences in efficacy between the two doses tested, i.e. higher efficacy seen in the 10, 10, 20 mg/kg dose and minimal efficacy in the 20, 20, 40 mg/kg dose.

The CHMP was of the view that the results on the secondary endpoints provided only limited support for the primary endpoint outcomes and needed to be seen only as trends. Nevertheless, in line with the previous input from the SAG, the CHMP acknowledged that most of the secondary endpoints were of such nature that any effect would have to be driven by an increase in strength and for this to occur, higher levels of dystrophin in muscular fibres would have to be achieved.

Although the safety data identified some safety concerns, in general these were considered manageable through the implementation of adequate pharmacovigilance activities and risk minimisation measures as described in the proposed Risk Management Plan. The lack of serious toxic effects and the oral administration were also considered to represent clear advantages for a population of mainly paediatric patients.

Overall, the CHMP was of the view that the risks of the product could be considered acceptable and that the data provided sufficient level of evidence that ataluren may be beneficial in delaying disease progression in nmDMD. Therefore, the CHMP concluded that a favourable benefit-risk balance could be established at this point.

As in the initial phase of the MAA review, the CHMP discussed the appropriate target population for the use of ataluren. Considering that the beneficial effects were most prominent in a sub-population of ambulatory patients in the decline phase of their walking ability (effect size of approximately 50 metres on the 6MWD), the CHMP discussed whether this finding would imply the need for restricting the indication to a population defined accordingly, i.e. patients in ambulatory decline phase. In line with the previous position of the SAG, the CHMP agreed that scientifically there should be no reason for the drug not to be given to milder patients if efficacy had been established in more severe ones. Furthermore, the CHMP considered that while less prominent, a clinically meaningful effect was seen also in the overall population studied. Thus, the CHMP concluded that ataluren can be authorised in the indication:

"Translarna is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older. Efficacy has not been demonstrated in non-ambulatory patients.

The presence of a nonsense mutation in the dystrophin gene should be determined by genetic testing."

The Applicant applied for a conditional marketing authorisation with the proposal that additional data would be generated post-authorisation in the confirmatory phase 3 study PTC124-GD-020-DMD (study 020). Therefore, the CHMP also re-discussed the criteria that would need to be met for a conditional approval according to Articles 2 and 4 of the Regulation (EC) no 507/2006, and made the following conclusions upon re-examination of the initial CHMP Opinion:

- DMD is a life-threatening and chronically debilitating condition where no satisfactory methods of treatment exist and it was considered that the product would thus address an unmet medical need.

- Upon review of the Applicant´s grounds for re-examination, the CHMP considered that despite the uncertainties discussed above and the fact that the dataset was not comprehensive, sufficient efficacy was seen to conclude on a favourable benefit-risk balance. Of note, this conclusion was to a great extent supported by the safety profile of ataluren, which does not pose any major safety concerns.

- The criterion that the benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required was considered fulfilled since the benefits to public health were substantiated by providing a treatment for a serious disease, characterised by gradual deterioration of the condition and a fatal outcome.

- With respect to generating additional data post authorisation, the CHMP considered that the Applicant will complete a confirmatory randomized placebo-controlled Phase 3 study (study 020) with the 10, 10, 20 mg/kg/day dose in patients with nmDMD. The CHMP agreed that this clinical trial may provide data alleviating the current uncertainties and acknowledged the timelines planned for its conduct and submission of its results (4Q 2015). With respect to the study feasibility, the position of the CHMP changed at the time of the re-examination Opinion; specifically, the CHMP considered that performing the study was plausible per se, independent of the marketing authorisation status.

A favourable benefit-risk balance was established based on the data available at the time of this MAA and the CHMP concluded that the confirmatory evidence from study 020 was acceptable to be generated post authorisation.

Overall, the CHMP concluded that conditions for granting a conditional marketing authorisation were met.

Recommendations following re-examination

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 concluded by majority decision that the risk-benefit balance of Translarna indicated for

"Translarna is indicated for the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older. Efficacy has not been demonstrated in non-ambulatory patients.

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is favourable and therefore recommends the granting of the conditional marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;

- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Specific Obligation to complete post-authorisation measures for the conditional marketing authorisation

This being a conditional marketing authorisation and pursuant to Article 14(7) of Regulation (EC) No 726/2004, the MAH shall complete, within the stated timeframe, the following measures:

Description	Due date
To complete a multicentre, randomised, double-blind, placebo-controlled confirmatory study to examine efficacy and safety of ataluren 10, 10, 20 mg/kg in patients with non-sense mutation Duchenne muscular dystrophy (Study PTC124-GD-020-DMD)	Submission of the final report: By 4Q 2015

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that ataluren is qualified as a new active substance.

Divergent positions to the majority recommendation are appended to this report.

DIVERGENT POSITION DATED 23 JANUARY 2014

The undersigned members of the CHMP did not agree with the CHMP's negative opinion recommending the refusal of the granting of a conditional approval of Translarna in the indication "treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in patients aged 5 years and older".

The reasons for the divergent opinion are as follows:

Translarna was developed to address the unmet medical need of the small fraction of patients with Duchenne muscular dystrophy (DMD) caused by a nonsense mutation, estimated to be 2500 patients (13%) of the European DMD population (~19000 patients). There are no remaining issues from the *Quality* point of view, and although some *Non-clinical* issues are still identified, they can be followed-up post approval. Considering the *Clinical* data, although the results are not sufficiently robust for a full Marketing Authorisation, the demonstrated effects are considered to be encouraging. The robustness of the results was challenged because of the observed variability in the primary efficacy data, the fact that many of the important conclusions supporting efficacy were derived from post hoc analyses and the fact that there was little supportive evidence of effect from the data on the secondary endpoints. It is recognized that at the time the study was designed the knowledge of the natural history of the disease was different from what we currently know. Therefore, the post hoc analyses reflecting the most current knowledge about the natural history of the disease, and in this respect the definition of the sub-groups in these analyses is clinically and scientifically justified. In agreement with the SAG experts, results derived from these analyses may be considered clinically relevant, especially in the sub-group of patients with more advanced disease. Additionally, the lack of effect on the secondary endpoints could be explained by the expected mechanism of action of the drug i.e. partial restoration of dystrophin production. Most of the secondary endpoints are of such nature that any effect will have to be driven by an increase in strength, rather than by an improvement of function. The latest available data suggest that minimal increase in dystrophin production could lead to functional improvement, but not to improvement of strength. For the latter to occur, levels of dystrophin close to the ones in normal muscular fibres may need to be achieved. This could be a valid explanation of the lack of concordance between the results on the primary and secondary efficacy endpoints. The group also noted that, despite the fact that efficacy was most prominently shown in the sub-group of patients with more advanced disease, there were trends of efficacy in all the sub-groups by severity, although of a different magnitude. This finding may be expected since the decline in function of DMD patients is not linear, but rather the speed of functional decline increases with the duration of the disease. In that respect, it would be very difficult to show a significant functional improvement in mildly affected patients in the frame of a controlled clinical trial with duration of 1 or 2 years. On the contrary, in more severely affected patients even a small effect on function could be detectable and clinically meaningful. It should be acknowledged that, in these patients, even small effects providing longer independent use of arms and hands, or preserving the ability to feed and drink from a cup on their own, would represent a significant and important achievement.

Taking all of the above into consideration and in the absence of major safety concerns, the minority view was that a positive benefit/risk relationship of ataluren has been reasonably established in Duchenne patients with nonsense mutations and, consequently, treatment with

ataluren should not be withheld from these patients. A conditional approval with the ongoing phase III trial as condition was considered acceptable. In addition, the long-term benefit of ataluren in this population could be documented by following patients up in specific registries.

Overall, and under the scope of a conditional approval, the B/R balance is considered to be positive in the following indication: "Duchenne muscular dystrophy (nmDMD) caused by nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 and older".

London, 23 January 2014

Jan Mueller-Berghaus	Bruno Sepodes
Jean-Louis Robert	Natalja Karpova
Jan Mazag	Daniela Melchiorri
Jens Heisterberg	Pierre Demolis
Harald Enzmann	Jacqueline Genoux-Hames

DIVERGENT POSITION DATED 22 MAY 2014

The undersigned member(s) of the CHMP did not agree with the CHMP's positive opinion recommending the granting of the marketing authorisation of Translarna indicated in the treatment of Duchenne muscular dystrophy resulting from a nonsense mutation in the dystrophin gene, in ambulatory patients aged 5 years and older.

The reason for the divergent opinion was as follows:

- The single study fails to demonstrate evidence of therapeutic efficacy of Translarna either on the primary endpoint (6MWD) or on secondary efficacy measures. The study failed on its primary endpoint analysis and efficacy claims are based on post hoc revisions to the analysis and on subgroup analyses. The argument that efficacy could be shown more easily in the decline phase subgroup seems plausible, based on data on the natural history of the disease, and it is agreed that confirmation of efficacy in these patients could be in principle extrapolated to support a general indication in DMD. However there are concerns that the presented analyses in this subgroup might be data driven i.e. the inclusion or exclusion from the subgroup of a few patients with a large change in 6MWD (depending on how the population is defined) could substantially affect the analysis. In this context it is noted that the corresponding analysis in the pre-specified <350 metre (baseline 6MWD) subgroup was much less impressive than in the *post* hoc defined decline phase subgroup. The mechanism of action of Translarna and an effect on a relevant pharmacodynamic measure have not been conclusively established, which adds further uncertainty. There is some evidence for the bell shape dose-response relationship but still some uncertainty. The numerous assumptions that need to be made to accept the claim that efficacy is shown for the low dose (but not the high dose) in the decline phase subgroup is considered problematic. Confirmatory data from on-going phase 3 trial are considered necessary and a positive benefit-risk balance has not been established at the present time due to a lack of evidence of efficacy.

London, 22 May 2014

Nela Vilceanu	Alar Irs
Karsten Bruins Slot	Sol Ruiz
Robert Hemmings	Ondrej Slanar
Daniel Brasseur	David Lyons
Greg Markey	Dinah Duarte
Pieter de Graeff	Concepcion Prieto Yerro
Reynir Arngrimsson	Romaldas Maciulaitis