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CLINICAL PROTOCOL

A Phase 2 Study of the Safety, Pharmacokinetics, and Pharmacodynamics of Ataluren (PTC124®) in Patients Aged ≥2 to <5 Years Old with Nonsense Mutation Dystrophinopathy

Protocol Number PTC124-GD-030-DMD

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Version 2.0

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PROTOCOL IDENTIFIERS AND STUDY PERSONNEL

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PRINCIPAL INVESTIGATOR AGREEMENT AND SIGNATURE

I have read the protocol document and, on behalf of my institution, agree to comply with the protocol and all applicable regulations.

_____ _____

Principal Investigator **Date**

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ABBREVIATIONS

Abbreviation	Definition
6MWT	6-minute walk test
AE	Adverse event(s)
ALT	Alanine aminotransferase
AR	Accumulation Ratio
AST	Aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
AUC_{0-t}	Area under the plasma concentration time curve from time zero to the time of last quantifiable concentration
AUC_{0-10}	Area under the plasma concentration time curve from time zero up to 10 hours after the morning dosing
AUC_{0-24}	Area under the concentration curve versus time curve from time zero to 24 hours
BMI	Body mass index
BCRP	Breast Cancer Resistant Protein
BUN	Blood urea nitrogen
CD-ROM	Compact disc read-only memory
CF	Cystic fibrosis
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CK	Creatine kinase
CI	Confidence interval
CL/F	Apparent clearance
CLd/F	Apparent distribution clearance
C_{max}	Maximum observed plasma concentration
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
$C_{trough@6h}$	Concentration at the end of the first (morning) dosage interval
CV%	Coefficient of variation
DLT	Dose-limiting toxicity
DMC	Data monitoring committee
DMD	Duchenne muscular dystrophy
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
ET	Early termination
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
HPLC-MS/MS	High performance liquid chromatography-mass spectrometry
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
ICJME	International Committee of Medical Journal Editors

Abbreviation	Definition
ICTRP	International Clinical Trials Registry Platform
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IV	Intravenous
ka	Rate constant of absorption
LOQ	Limit of quantitation
MedDRA	Medical Dictionary for Regulatory Activities
MMA	Methylmelonic acidemia
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
NCA	Non-compartmental analysis
nmDMD	Nonsense mutation Duchenne muscular dystrophy
nmCF	Nonsense mutation cystic fibrosis
NSAA	North Star Ambulatory Assessment
OAT1	Organic anion transporter 1
OAT3	Organic anion transporter 3
OATP1B3	Organic anion transporting polypeptide 1B3
PD	Pharmacodynamic(s)
PIP	Pediatric Investigation Plan
PK	Pharmacokinetic(s)
popPK	Population PK
PTC124	Ataluren
SAS	Statistical Analysis System
SAE	Serious adverse event
$t_{½}$	Terminal half-life
TEAE	Treatment-emergent adverse event
TFTs	Timed function tests
TID	3 times per day
t_{max}	Time of maximum observed plasma concentration
UGT	Uridine diphosphate glucuronosyltransferase
UGT1A9	Uridine diphosphate glucuronosyltransferase 1 family, polypeptide A9
US	United States
Vc/F	Apparent central volume of distribution
Vp/F	Apparent peripheral volume of distribution
WHODRUG	World Health Organization Drug Dictionary

1. OVERVIEW

Duchenne muscular dystrophy (DMD) is a disabling and life-threatening X-linked genetic disorder [Worton 2001, Khurana 2003] caused by defects in the gene for dystrophin, a protein that stabilizes muscle cell membranes [Lapidos 2004]. Due to muscle fragility, boys with DMD develop muscle weakness that leads to deterioration of ambulation, wheelchair dependency, and eventual respiratory and cardiac failure with death by 15 to 22 years of age [Brooke 1989, McDonald 1995, Worton 2001]. Only chronic administration of corticosteroids has slowed progression of DMD. However, corticosteroids do not address the underlying cause of DMD, are typically associated with serious sequelae, and are not always employed. There is no current therapy for the underlying cause of DMD. In approximately 13% of boys with DMD, the causative defect in the dystrophin gene is a nonsense mutation that truncates dystrophin protein production by introducing a premature stop codon into the dystrophin messenger ribonucleic acid (mRNA) [Dent 2005]. Nonsense mutation (nm) DMD is estimated to affect approximately 1,700 boys in the United States (US) and approximately 2,200 boys in Europe [Hirawat 2004a, Hirawat 2004b].

Ataluren is an orally bioavailable, investigational new drug that promotes ribosomal readthrough of premature stop codons [Welch 2007, Du 2008, Wang 2010, Goldmann 2011, Tan 2011, Kayali 2012]. In reporter assays, as well as in nonclinical models of genetic disease, ataluren demonstrates the ability to specifically and selectively enable ribosomal readthrough of mRNA containing a premature stop codon, inducing production of protein that localizes to the appropriate cellular location and is functionally active [Welch 2007, Du 2008, Wang 2010, Goldmann 2011, Tan 2011, Kayali 2012]. In vitro and in vivo studies in nmDMD have shown that ataluren can restore production of the missing dystrophin [Welch 2007, Kayali 2012]. Ataluren (Translarna) is currently available in Europe and Israel for treatment of nmDMD in patients older than 5 years.

Ataluren has been administered to patients with nonsense mutation cystic fibrosis (nmCF) as young as 6 years of age, patients with nmDMD as young as 5 years of age, and patients with nonsense mutation methlymelonic acidemia (nmMMA) as young as 3 years of age. No obvious differences have been apparent in the activity or safety profiles of ataluren in children relative to adults. Although patients <3 years of age have not been included in clinical studies, chronic toxicology studies in weanling rats and dogs support dosing of pediatric patients as young as 2 years of age. Refer to the Ataluren Investigator's Brochure (IB) for current information on use in pediatric patients.

This protocol describes a Phase 2, multiple-dose, open-label study evaluating the safety, pharmacokinetics (PK), and pharmacodynamics (PD) of ataluren in patients aged ≥2 to <5 years old with nmDMD. In nmDMD, early start of treatment is important and necessary and, therefore, it is relevant to understand the correct and tolerable dose in this age group, particularly since ataluren is dosed by weight. The study will include a 4-week screening period, a 4-week study period, and a 48-week extension period for patients who complete the 4-week study period (52 weeks total treatment). The objective of the extension period is to assess the long-term safety of chronic administration of ataluren in this patient population.

The primary objective of this study is to evaluate the safety of ataluren as measured by type, frequency, severity, timing, and relationship to study drug of treatment-emergent adverse events (TEAEs), laboratory abnormalities, and electrocardiograms (ECGs).

The secondary objectives are to determine the plasma PK of ataluren in patients aged ≥2 to <5 years old with nmDMD, to monitor proximal muscle function using timed function tests (TFTs), to monitor physical function using the North Star Ambulatory Assessment (NSAA), to determine the effect of ataluren on weight, height, and body mass index (BMI), and to assess the palatability of ataluren.

This study provides ongoing safety review during open-label ataluren treatment. Furthermore, a planned interim safety analysis will be conducted by an independent data monitoring committee (DMC) when all patients have completed 12 weeks of treatment and additionally as needed.

2. BACKGROUND

2.1. Disease Indication

DMD is an X-linked disorder caused by defects in the gene for dystrophin, a protein that is critical to the structural stability of myofibers in skeletal, diaphragmatic, and cardiac muscle [Worton 2001, Khurana 2003]. The prevalence is estimated at approximately 13,000 males in the US and approximately 17,000 boys in the European Union (EU) [Hirawat 2004a, Hirawat 2004b].

Dystrophin is a high-molecular-weight cytoskeleton protein localized at the inner surface of the muscle membrane [Worton 2001]. It is part of a dystrophin-glycoprotein complex that also includes dystroglycan and sarcoglycans. This complex provides a bridge across the muscle membrane in which dystrophin couples actin in the cytoplasm with dystroglycan. Dystrophin deficiency destabilizes the dystrophin-glycoprotein complex, impairing localization of the dystroglycan and sarcoglycans to the muscle membrane, and compromising the structural integrity of the membrane. The absence of normally functioning dystrophin results in sarcolemmal breakdown, calcium ion influx, phospholipase activation, oxidative muscle injury, and, ultimately, myonecrosis. As muscle damage progresses, connective tissue and fat replace muscle fibers.

In patients with DMD, the age at which the earliest sign or symptom of the disease is noted ranges from infancy to approximately 6 years old [Ciafaloni 2009]. Initial signs and symptoms of DMD include lordosis, a waddling gait, and the Gowers' sign (a characteristically abnormal method of rising from a supine to a standing position) [Brooke 1989, McDonald 1995, Boland 1996, Worton 2001]. Inexorable progressive weakness is seen, particularly in the proximal musculature. Ambulation becomes increasingly abnormal. By the age of 8 years, most boys have difficulty rising from the floor and ascending stairs and they often fall while walking. Boys with the disease spend less time walking and walk more slowly than healthy boys [McDonald 2005a], and are significantly less active than normal boys of similar age [McDonald 2002, McDonald 2005b]. By 10 to 14 years of age, most are wheelchair-bound. In ambulatory boys with DMD, the most frequent cardiac abnormality is sinus tachycardia and heart rate variability, occurring from childhood and persisting throughout life [Finsterer 2003, Gulati 2005]. Pulmonary function is usually normal before 10 years of age and is well maintained into adolescence in boys receiving corticosteroids [Mendell 1989, Griggs 1991, Phillips 2001, Tangsrud 2001, Biggar 2001, Biggar 2006]. Later in adolescence, cardiac and diaphragmatic muscles become progressively weaker and patients require treatment for cardiac insufficiency and ventilatory support. Patients usually die of cardiac or pulmonary failure by 15 to 22 years of age [Brooke 1989, McDonald 1995, Simonds 1998, Worton 2001, Eagle 2002].

Presently, ataluren is the only therapy available to restore dystrophin protein production and preserve muscle function. The current standard of care is corticosteroids, which do not address the underlying cause of the disease and are not typically initiated prior to the age of 5 years old.

2.2. Ataluren (PTC124®)

2.2.1. Therapeutic Concept

Among the several types of disease-causing mutations, a nonsense mutation is a single-point alteration in one of the nucleotides of deoxyribonucleic acid (DNA) that, when copied to mRNA, is interpreted as a stop signal by the ribosomal cellular translational machinery. The presence of such a premature stop signal within the protein-coding region of the mRNA for dystrophin signals the ribosomes to halt production of the protein before the full-length protein is completed. The resulting truncated dystrophin is too short to serve its necessary function and causes disease. It is estimated that approximately 10-15% of all boys with DMD have a nonsense mutation as the basis for the disorder [Dent 2005], resulting in a prevalence of approximately 1,700 boys in the US and approximately 2,200 boys in Europe.

It has been known for some time that drugs with translation-modifying mechanisms of action, such as the aminoglycoside antibiotics (eg, gentamicin), can ameliorate the effects of nonsense mutations in experimental systems. By binding to the ribosomes, such agents permit the ribosomes to reinterpret the nonsense mutation stop signal in mRNA such that they can move through the obstruction by inserting an amino acid and continuing the translation process to produce a full-length functional protein. In experimental animal systems and in pilot studies in nmDMD, treatment with high concentrations of gentamicin has restored production of functional dystrophin [Barton-Davis 1999, Politano 2003]. Similarly, nonclinical and clinical studies in cystic fibrosis (CF) have demonstrated restoration of the CF transmembrane conductance regulator, the epithelial chloride channel that is defective in that disease [Clancy 2001, Du 2002, Wilschanski 2003]. Data suggest that the geometry of mRNA and associated initiation-termination proteins is critically different at a premature stop compared with a normal stop. This may explain why a drug can permit the ribosomes to selectively read through the premature stop codon, but will not allow the ribosomes to read through the normal stop codon at the end of the mRNA protein-coding region [Sachs 2000, Welch 2000, Amrani 2004]. Because serious renal and otic toxicities and the need for parenteral administration preclude the long-term clinical use of gentamicin, there has been considerable interest in the identification of safer and more conveniently administered, low-molecular-weight, synthetic compounds with the ability to promote readthrough of disease-causing nonsense mutations.

PTC Therapeutics is a biopharmaceutical company involved in the discovery and development of new therapies for genetic diseases. Based on the clear medical need in dystrophinopathy and other genetic disorders, and the unacceptable toxicity that would be associated with chronic systemic aminoglycoside use, scientists at the company have conducted a drug discovery program with the objective of finding and developing new agents that overcome the effects of nonsense mutations. A high-throughput screening program identified sets of novel, non-aminoglycoside chemical structures that selectively induce ribosomal readthrough of premature stop codons in mRNA. Chemical optimization, pharmacologic characterization, and toxicological evaluation have led to identification of ataluren as an orally bioavailable, small molecule with potential clinical utility in treating genetic disorders through induction of readthrough of nonsense mutations and production of full-length, functional proteins [Welch 2007, Du 2008]. In the subset of patients whose disease is mediated by a nonsense mutation, ataluren may offer a definitive therapy by overcoming the basic cause for dystrophinopathy and other disabling and life-threatening genetic disorders.

2.2.2. Chemical Description

Ataluren is a new chemical entity with a chemical formula of $C_{15}H_9FN_2O_3$ and a molecular weight of 284.2 Daltons. Ataluren is a Biopharmaceutical Classification System Case 2 compound, possessing low aqueous solubility (<31 μg/mL) but high permeability across gastrointestinal epithelium, consistent with its high oral bioavailability.

2.2.3. Clinical Studies

In total, >750 subjects, including healthy subjects as well as adult and pediatric patients with several nonsense mutation genetic disorders, have been exposed to ataluren in Phase 1 [Hirawat 2007], Phase 2 [Kerem 2008, Sermet-Gaudelus 2010, Wilschanski 2011, Finkel 2013] and Phase 3 [Kerem 2014, Bushby 2014] clinical studies. Refer to the Ataluren IB for a detailed presentation of safety, efficacy, and PK data from these clinical studies.

3. STUDY OBJECTIVE AND ENDPOINTS

3.1. Primary Objective

The primary objective of this study is to:

- Evaluate the safety of ataluren as measured by type, frequency, severity, timing, and relationship to study drug of TEAEs, laboratory abnormalities and ECGs

3.2. Secondary Objectives

The secondary objectives of this study are to:

- Evaluate the plasma PK of ataluren in patients aged ≥2 to <5 years old with nmDMD
- Assess proximal muscle function using TFTs
- Assess change in physical function using the NSAA
- Determine the effect of ataluren on weight, height, and BMI
- Assess the palatability of ataluren

3.3. Primary Endpoint

The primary endpoints of this study are:

- Overall safety profile in terms of the type, frequency, severity, timing, and relationship to study therapy of any adverse events (AEs) or abnormalities of physical findings, laboratory tests, or ECGs
- Occurrence of any dose-limiting toxicities (DLTs)
- Drug discontinuations due to AEs
- Serious adverse events (SAEs)

3.4. Secondary Endpoints

The secondary endpoints are:

- Pharmacokinetic parameters (t_{max}, $t_{1/2}$, C_{max}, $C_{trough@6h}$, AUC_{0-10}), CL/F, and Vc/F based on frequent blood sampling for PK on Days 1 and 28 of ataluren treatment. On each of these days, blood samples for ataluren concentration assessments will be collected immediately pre-dose and at specified time points following the morning, midday, and evening doses. Ataluren concentrations in plasma will be analyzed using a validated HPLC-MS/MS method.
- TFTs (time to walk/run 10 meters, time to climb 4 stairs, time to descend 4 stairs, and time to stand up from a supine position)
- NSAA
- Changes in body weight, height, and BMI
- Ataluren palatability characteristics as determined by a parent/caregiver questionnaire

4. SUBJECT SELECTION CRITERIA

4.1. Overview

This clinical study can fulfill its objectives only if appropriate patients are enrolled. The following eligibility criteria are designed to select patients for whom study participation is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular patient. Eligibility criteria may not be waived and conformance to the eligibility criteria is subject to review in the case of a Good Clinical Practice (GCP) audit or a regulatory authority inspection. Any questions regarding a patient's eligibility should be discussed with the PTC Therapeutics medical monitor or designee prior to enrollment.

4.2. Inclusion Criteria

Patients must meet all of the following conditions to be eligible for enrollment into the study:

General inclusion criteria

1. Evidence of signed and dated informed consent document(s) indicating that the study candidate (and/or a parent/legal guardian) has been informed of all pertinent aspects of the study. *Note: As all study candidates are considered children under local regulation, at least one parent or legal guardian must provide written consent prior to initiation of study-related procedures, in accordance with local regulation, and the study candidate may be required to provide written assent. The rules of the responsible institutional review board/independent ethics committee (IRB/IEC) regarding whether one or both parents must provide consent and the appropriate ages for obtaining consent and assent from the patient should be followed.*
2. Males ≥2 to <5 years of age
3. Body weight ≥12 kg
4. Willingness and ability to comply with scheduled visits, drug administration plan, study procedures, and study restrictions.
5. No clinically significant abnormality based upon laboratory assessments during the screening period, in the opinion of the Investigator; good general health, as determined during the screening period by medical history and physical examination (including vital sign measurements).

DMD inclusion criteria

6. Diagnosis of DMD based on an elevated serum CK and genotypic evidence of dystrinopathy. *Medical documentation of phenotypic evidence of dystrophinopathy needs to be provided upon request by the PTC Therapeutics medical monitor.*
7. Documentation of the presence of a nonsense mutation in at least 1 allele of the dystrophin gene.
8. Verification that a blood sample has been drawn for sequencing of the dystrophin gene. *Note: A patient who has written documentation of a nonsense mutation as the cause of dystrophinopathy need not wait for confirmatory results to start study drug.*

4.3. Exclusion Criteria

The presence of any of the following conditions will exclude a patient from study enrollment:

General exclusion criteria

1. Patients participating in any drug or device clinical investigation or having received an investigational drug within 3 months prior to Visit 1 (Screening) or who anticipate participating in any other drug or device clinical investigation or receiving any other investigational drug within the duration of this study.
2. Expectation of a major surgical procedure during the study period.
3. Prior or ongoing medical condition, medical history, physical findings, or laboratory abnormality that, in the Investigator's opinion, could adversely affect the safety of the patient, or makes it unlikely that the course of study drug administration or follow-up would be completed, or could impair the assessment of study results.
4. Known hypersensitivity to any of the ingredients or excipients of the study drug (polydextrose, polyethylene glycol 3350, poloxamer 407, mannitol 25C, crospovidone XL10, hydroxyethyl cellulose, vanilla, colloidal silica, or magnesium stearate).

Drug therapies

5. Ongoing use of the following drugs:

   Drugs metabolized by CYP2C8 (eg, paclitaxel) or CYP2C9 (eg, coumarin anticoagulants [warfarin], phenytoin, or tolbutamide)
   Drugs that are inhibitors of breast cancer resistant protein (BCRP) (eg, cyclosporine, eltrombopag, geftinib)
   Drugs that are substrates of UGT1A9 (eg, propofol, mycophenolate mofetil), OAT1, OAT3, or OATP1B3 (eg, oseltamivir, acyclovir, captopril, furosemide, bumetanide, valsartan, pravastatin, rosuvastatin, atorvastatin, pitavastatin)
   Drugs that are general inhibitors of UGT (eg, probenecid, valproic acid)

6. Treatment with systemic aminoglycoside antibiotics within 3 months prior to start of study treatment
7. Prior therapy with ataluren

5. ENROLLMENT PROCEDURES

5.1. Source and Number of Subjects

At least 12 patients will be enrolled. Patients will be recruited from dystrophinopathy populations who receive care or are referred for evaluation at the investigational site. The principal Investigator or sub-investigator will discuss the possibility of participation directly with parent(s)/legal guardian in the clinic.

5.2. Screening and Study Drug Dispensation

The Investigator must inform each parent/legal guardian and study candidate of the nature of the study, explain the potential risks, and obtain written informed consent/assent from the parent(s)/legal guardian and/or study candidate (as required by local regulations) prior to performing any study-related screening procedures. Once written informed consent/assent has been obtained, a site representative should access Medrio (the electronic data capture [EDC] system) to indicate that a candidate is being screened. The user will need to supply the EDC system with the required information to permit study drug dispensation. Refer to the CRF Completion Guidelines for additional details.

Using forms in the Medrio system, the EDC system will document all screening that has occurred. The Medrio Randomization module will be used to assign kit numbers and email notifications for shipment of investigational drug kits. Forms in the Medrio system will be used to track receipt of the drug shipment at the site.

6. INVESTIGATIONAL MEDICINAL PRODUCT

6.1. Study Drug Supply

Ataluren drug product will be provided as a white to off-white powder for oral suspension, also referred to as ataluren granules. The drug substance and drug product are manufactured under current Good Manufacturing Practices (cGMP) conditions. The formulation includes matrix and suspending agents, surfactants, and various excipients that aid in the manufacturing process. Ataluren granules are packaged in aluminum foil, child-resistant sachets and supplied in dose strengths containing 125 or 250 mg of the active drug substance.

Ataluren will be supplied free of charge to the investigational site by PTC Therapeutics for appropriate distribution to the patients/caregivers.

6.1.1. Study Drug Packaging and Labeling

Sachets and cartons will be color-coded to indicate dosage strength (125 mg – yellow, 250 mg - pink). Labels will be provided in appropriate languages as required by each country in which the study is conducted. The content of the labeling will be in accordance with local regulatory specifications and requirements.

6.1.2. Study Drug Storage

Sachets of ataluren will be shipped to the investigational sites, and stored and monitored at room temperature (~15 to 30°C). The available stability data from representative samples support the use of the drug product for 48 months when stored at room temperature.

Study personnel must ensure that all ataluren supplies are kept in a secure locked area with access limited to authorized personnel. The study product must not be used outside the context of this protocol. Under no circumstances should the Investigator or site personnel supply ataluren to other investigators or clinics, or allow the ataluren supplies to be used other than as directed by this protocol.

6.1.3. Study Drug Dispensing

Dosing of ataluren will be based on milligrams of drug per kilogram of patient body weight assessed every 12 weeks and will be calculated to allow for dosing with the appropriate dose strengths (125 mg or 250 mg).

The clinic staff (eg, pharmacist or other qualified person) will be responsible for dispensing ataluren at the beginning of the study and every 12 weeks during the extension period according to the instructions in the study manual.

6.1.4. Study Drug Preparation

Once at the investigational site and/or with the patient/caregiver, ataluren sachets should be stored at room temperature, away from the reach of children, until the time of reconstitution. The appropriate sachet strength will be used to prepare each dose. The full contents of each sachet should be mixed with at least 30 mL (1 ounce) of liquid, or 3 tablespoons of semi-solid

food. The prepared dose should be mixed well before administration. The amount of the liquid or semi-solid food can be increased based on patient preference.

Each prepared dose is best administered immediately after preparation. The prepared dose should be discarded if not consumed within 3 hours (if kept at room temperature) or within 24 hours of preparation (if kept refrigerated).

Detailed written drug mixing and dosing instructions will be provided to the patient/caregiver when ataluren supplies are dispensed. A copy of these instructions will be maintained in the Investigator site study file.

6.1.5. Study Drug Accountability

The Investigator and/or the responsible site personnel must maintain accurate records of the receipt of all ataluren shipped by PTC Therapeutics or its designee, including, but not limited to, the date received, lot number, amount received, and the disposition of all ataluren. Current reconciliation and dispensing records must also be maintained that include the date and amount of ataluren dispensed, relevant batch numbers, and patient's assigned study number. Caregivers should return all unused sachets of ataluren to the investigational site at the end of each 12-week treatment interval for inventory. The eCRF will serve as the source document for drug supply to the patients and will document the return of any unused drug for compliance assessments.

Depending upon the decision of PTC Therapeutics, unused clinical supplies must be destroyed or returned to PTC Therapeutics (or its designee) after the study is completed and drug accountability has been verified by the monitor. Records documenting the date of study drug destruction or shipping, relevant batch numbers, and amount destroyed or shipped should be kept in the investigational site study file.

The Medrio EDC system will be used to track drug accountability.

6.1.6. Overdose Precautions

For any patient experiencing an overdose (see Section 9.1.1 for the definition of overdose), observation for any symptomatic side effects should be instituted, and vital signs and biochemical and hematological parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. Pending the acquisition of sufficient human experience with the drug, use of gastric lavage or induction of emesis is not specifically recommended or contraindicated.

The PTC Therapeutics medical monitor must be contacted if an overdose occurs. Under applicable regulations, overdosing may be considered a SAE and should be reported accordingly (see Sections 9.1.1 and 9.1.2).

6.1.7. Inadvertent Exposure and Spill Precautions

Based on available data from nonclinical studies, ataluren does not appear to be acutely toxic or genotoxic at levels that are likely to result from inadvertent exposure to the contents of the packet, if opened. Based on general experience with the drug during manufacturing, it does not appear that exposure to formulated ataluren is likely to be irritating to skin or eyes. However, personnel handling the drug should use reasonable precautions to avoid eye contact, skin contact,

inhalation, or ingestion of the material in the packets. Refer to the Ataluren IB for current information on inadvertent exposures and spill precautions.

6.2. Study Drug Treatment

6.2.1. Study Drug Dosing

Dosing of ataluren will be based on milligrams of drug per kilogram of patient body weight assessed every 12 weeks. All patients will receive approximately 10, 10, 20 mg/kg ataluren 3 times daily (TID) for 4 weeks during the PK portion and for 48 weeks during the extension period.

6.2.2. Duration of Treatment

The study duration will be 4 weeks during the PK portion and 48 weeks during the extension period (52 weeks total). Initial data assessment and reporting will be after all patients complete first 4 weeks (safety and PK) to satisfy Pediatric Investigation Plan (PIP) requirements and an additional report will be issued after completion of 48 weeks extension). The study may be terminated by the sponsor at any time and for any reason, eg, the clinical development of ataluren in dystrophinopathy is discontinued.

6.2.3. Schedule of Administration

As noted in Table 1, 3 doses should be taken per day – the 1st dose in the morning, the 2nd dose during the middle of the day (midday), and the 3rd dose in the evening. Intervals for dosing should be ~6 hours (±1 hour) between morning and midday doses, ~6 hours (±1 hour) between midday and evening doses, and ~12 hours (±1 hour) between evening doses and the morning dose on the next day.

Table 1: Suggested Daily Dosing Schedule

Dose Designation	Example Dosing Times
Morning	~7:00 AM – 0700 hours (±1 hour)
	↑ ~6 hours ↓
Mid-day	~1:00 PM – 1300 hours (±1 hour)
	↑ ~6 hours ↓
Evening	~7:00 PM – 1900 hours (±1 hour)
	↑ ~12 hours ↓
Next Day Morning	7:00 AM – 0700 hours (±1 hour)

6.2.4. Instructions for Delays in Dosing

Dosing delays should be handled as follows:

- If there is a delay in the administration of ataluren of **<3 hours** after the morning or midday doses or **<6 hours** after the evening dose, the planned dose should be taken with no changes to the subsequent dose schedules.
- If there is a delay in the administration of ataluren of **>3 hours** after the morning or midday doses or **>6 hours** after the evening dose, the planned dose should **not** be taken and patients should resume their usual dosing schedule.

6.3. Safety Monitoring and Study Drug Dose Interruption/Modification

6.3.1. Laboratory Abnormalities and Adverse Events Requiring Evaluation and Potential Drug Interruption/Modification

Patients must be monitored closely for AEs or laboratory abnormalities during the course of the study.

For AEs or laboratory abnormalities, the Investigator will use judgment in determining whether the event or abnormality is clinically significant, whether diagnostic evaluation is warranted, and whether potential interruption of study drug treatment is appropriate. In general, life-threatening (Grade 4) or severe (Grade 3) AEs or laboratory abnormalities should be considered clinically significant, although recurrent or persistent moderate events (Grade 2) may also be considered clinically significant in certain circumstances. Reference should be made to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (see http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf) for grading the severity of AEs and laboratory abnormalities.

6.3.2. Evaluation of Adverse Events or Laboratory Abnormalities

While specific monitoring, diagnostic testing, and supportive care measures must be instituted based on the clinical judgment of the Investigator, Investigators are encouraged to contact either the PTC Therapeutics medical monitor (or designee) to obtain guidance and to ascertain whether similar events are being seen at other investigational sites. The PTC Therapeutics medical monitor should be notified of any AE or laboratory abnormality that leads to dose interruption and should be apprised of ancillary laboratory or other diagnostic findings and the evolving data from any work-up of the initial abnormality. The PTC Therapeutics medical monitor may suggest review of the case with gastroenterology or nephrology consultants or with other experts (either at the site or retained by PTC Therapeutics).

Clinical evaluations for potential hepatic and renal toxicities may include the following:

- **Hepatic:** The medical history, hepatitis screening results, all clinical blood values (particularly serum bilirubin, gamma-glutamyl transferase [GGT], aspartate aminotransferase [AST], and alanine aminotransferase [ALT] values), and all concomitant medications should be reviewed. Depending upon changes observed, the recommended diagnostic workup may include more frequent monitoring or further evaluations for viral hepatitis and immune disorders; tests for cholelithiasis; or abdominal ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), or other imaging methods.
- **Renal:** The medical history, all clinical blood and urine renal values, serum electrolytes, medications, and potential pre- or post renal conditions should be reviewed. Depending upon the changes observed, recommended diagnostic workup may include further evaluations of blood or urine; tests of glomerular filtration rate (GFR), concentrating ability, or other renal functions; CT, MRI, or other imaging methods; and/or renal biopsy. Transient reversible mild (Grade 1) hypercreatinemia was seen in ~15% of patients in Study 009. Therefore, renal function should be monitored and only if sustained (ie, >4 weeks) should dose adjustment or discontinuation be considered after discussion with the PTC Therapeutics medical monitor.

6.3.3. Instructions for Resuming Study Drug Administration after an Interruption for Safety Concerns

In deciding whether to re-institute study drug after a dose interruption for any clinically significant safety concern, the Investigator in consultation with PTC Therapeutics should consider factors such as the following:

- Type and severity of the AE or laboratory abnormality
- The potential causal relationship of study drug
- The patient's status in terms of dystrophinopathy and other health conditions
- The ability to monitor for recurrence of the event

For hepatic or renal events, the level of Investigator certainty that an abnormality leading to drug interruption is drug-related should be considered strongly in deciding if and when to re-institute ataluren treatment. If the Investigator considers the hepatic or renal event that led to ataluren interruption as probably related to ataluren, restarting ataluren is not advised. In this case, the

patient should be discontinued from the study (see Section 10). If the Investigator considers the hepatic or renal event that prompted ataluren interruption to be possibly related or unlikely related to ataluren, the Investigator should use best judgment in determining whether to restart ataluren. If the hepatic or renal event is considered unrelated to ataluren, re-institution of ataluren is recommended.

If the Investigator believes it is appropriate to do so and the PTC Therapeutics medical monitor has been consulted, ataluren may be re-initiated. If the event was determined to be unrelated to ataluren, the treatment may be resumed at full dose. Otherwise, if the drug is resumed, it should be initially re-initiated at half of the original dose. The appropriate clinic staff should instruct the patient/caregiver about the revised number of study drug sachets to be used per dose according to the new schedule. Re-challenge at half dose should be initiated only as a bridge to full dosing. If a patient cannot tolerate the full dose, he/she should be discontinued from study participation.

If further evaluation reveals that the AE that led to dose reduction was not related to the ataluren, the dose should be escalated to the original dose level.

If after dose reduction, the patient experiences a recurrence of a previous abnormality that led to ataluren dose interruption or experiences a new occurrence of an unacceptable AE or laboratory abnormality, the Investigator should interrupt ataluren and confer with the PTC Therapeutics medical monitor regarding the potential need to discontinue ataluren permanently and discontinue the patient from the study.

6.3.4. Instructions for Discontinuation of Study Drug Administration for Safety Concerns

Study drug should be permanently discontinued following appropriate consideration of study drug interruption/modification and consultation with the PTC Therapeutics medical monitor or designee. If permanent discontinuation of study drug is the result of an SAE, then a follow-up SAE report form must be completed (see Section 9.7). In the case of treatment discontinuation due to an AE that is not an SAE, the PTC Therapeutics medical monitor or designee should be notified (see Section 10). In addition, details regarding the reasons for discontinuation and the AEs leading to the discontinuation should be recorded in the source documents and in the appropriate eCRF. The Early Termination (ET) Visit eCRF should be completed and appropriate follow-up (at ~4 weeks post extension period as per protocol or until recovery from or stabilization of the AE, whichever comes last) should be instituted.

7. CONCOMITANT AND SUPPORTIVE THERAPY

7.1. Concomitant Medications

Other than the study drug, any treatments taken by a patient from the screening period through the 4-Week Follow-Up are defined as concomitant medications.

To the extent possible, administration of any treatment other than the study drug should be minimized during the study period. Patients should be discouraged from use of herbal remedies, growth hormone, self-prescribed drugs, street drugs, tobacco products, or alcohol at any time during the study.

If considered necessary for the patient's well-being, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the Investigator. The decision to authorize the use of any other drug(s) should take into account patient safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more relevant underlying event, and whether use of a concomitant medication will compromise the outcome or integrity of the study.

Parents/caregivers should be instructed about the importance of informing the clinic staff of the patient's use of any drugs or remedies (whether prescribed, over-the-counter, or illicit) before and during the course of the study. Information regarding all concomitant medications will be collected and documented in the concomitant medication page of the eCRF.

7.1.1. Corticosteriods

To date, corticosteroid use is the only pharmacological intervention that has demonstrated benefit in DMD [Mendell 1989, Fenichel 1991a, Fenichel 1991b, Griggs 1991, Biggar 2001, Beenakker 2005, Biggar 2006, Pradhan 2006]. Subjects who require corticosteroid interruption, dose modification, or reinstitution may remain on study drug therapy.

Co-administration of systemic corticosteroids with ataluren may cause more frequent instances of hypertension than does systemic corticosteroid use alone (without ataluren). However, the blood pressure data available to date are not definite about any contributory role of ataluren in development of hypertension in patients who are taking corticosteroids.

7.1.2. Nephrotoxic Medications

Renal abnormalities were observed in a Phase 3 trial evaluating ataluren in patients ≥6 years of age with nonsense mutation cystic fibrosis (nmCF) who were receiving concomitant IV aminoglycosides and IV vancomycin (as described in the Ataluren IB). Caution should therefore be exercised during concomitant use of study drug and potentially nephrotoxic agents.

In patients who require treatment for serious infections, investigators should substitute other antibiotics for systemic aminoglycosides or vancomycin when clinically appropriate, if possible. If IV aminoglycosides or IV vancomycin are administered, study drug must be interrupted during the course of antibiotic therapy. Patients requiring IV aminoglycoside or vancomycin therapy should be closely monitored in an appropriate setting, such as a hospital. Investigators should be particularly vigilant with patients experiencing nausea, vomiting, diarrhea, fever, or laboratory

evidence of dehydration. Treatment with ataluren may be resumed no earlier than 2 days after administration of these antibiotics has ceased.

In patients receiving such agents, antibiotic drug levels and serum creatinine and blood urea nitrogen (BUN) should be monitored closely as follows:

- Creatinine and BUN should be measured:
    - Prior to initiating IV aminoglycoside or vancomycin therapy
    - Within 24 to 48 hours of the first antibiotic administration (and further antibiotic dosing should be based on these results)
    - At least twice a week during the course of antibiotic treatment (if possible)
- Antibiotic trough levels should be measured:
    - Within 24 to 48 hours of the first antibiotic administration (and further antibiotic dosing should be based on these results)
    - At intervals during the course of antibiotic treatment based on clinical need

7.2. Non-Drug Therapy

7.2.1. Physical Therapy

There are neither restrictions nor prescriptions for physical therapy during the study. Sites should use local best practices in providing physical therapy support for patients participating in the study.

7.2.2. Hydration

Because of the potential risk of renal dysfunction during periods of dehydration in patients receiving ataluren, it is important to encourage study patients to maintain adequate hydration throughout the study. Patients should be adequately hydrated prior to receiving any potentially nephrotoxic agents, and hydration status should be carefully monitored throughout the administration of any agent with nephrotoxic characteristics. Investigators should be particularly vigilant with patients who are experiencing nausea, vomiting, diarrhea, fever, or laboratory evidence of dehydration.

7.2.3. Dietary Restrictions

There are no specific dietary restrictions in the study.

8. SCHEDULE OF EVENTS AND STUDY PARAMETERS

8.1. Schedule of Events

The types and timing of data to be recorded are summarized in Table 2. Please see Section 8.2 for explanations of the study procedures outlined.

Table 2: Schedule of Events

	Screening	Ataluren Treatment						4-Week Follow-Up
Day (±2)	**-28**	**1[a]**	**28**	**112**	**196**	**280**	**364**	**392**
Weeks	**-4**	**0**	**4**	**16**	**28**	**40**	**52/ET[b]**	**56**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Informed consent	X							
Clinical and medication history	X							
Vital signs	X	X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X
Physical examination	X	As clinically indicated						X
Hematology	X	X	X	X	X	X	X	X
Blood sample for gene sequencing [c]	X							
Biochemistry[d]	X	X	X	X	X	X	X	X
Urinalysis	X	X	X	X	X	X	X	X
12-lead ECG	X		X				X	X
Timed function tests		X			X		X	
North Star Ambulatory Assessment		X			X		X	
Blood for ataluren PK[e]		X	X					
Palatability questionnaire			X					
Drug administration		X---------- X						
Adverse events	X---------- X							
Concomitant medications	X---------- X							
Non-DMD-related adverse events	X							

[a] All study and laboratory assessments on the first day of treatment must be done prior to ataluren dosing.

[b] Patients who terminate the study early should complete all assessments required for Week 52/ET (Visit 7) and will be required to return 4 weeks from the final dose of study medication for the 4-Week Follow-up Visit.

[c] Verification that a blood sample has been drawn for sequencing of the dystrophin gene. A patient who has written documentation of a nonsense mutation as the cause of DMD need not wait for confirmatory results to start study drug as long as the confirmatory blood sample for gene sequencing was drawn.

[d] Biochemistry laboratory assessments will include hepatic transaminases and additional parameters as specified in Section 8.2.7.2.

[e] On Days 1 and 28, blood samples for PK assessment will be drawn pre-dose and 1 (±15 min), 2 (±15 min), 4 (±30 min), 6 (±30 min), 8 (±30 min), and 10 (±30 min) hours post-dose.

Abbreviations: ECG = electrocardiogram, ET = early termination, PK = pharmacokinetics

8.2. Explanation of Study Procedures

8.2.1. Study Visits

8.2.1.1. Screening (Visit 1)

No study-related procedures should be performed prior to the signing of the informed consent/ assent document(s). Thereafter, patients should undergo the initial set of screening procedures as noted in Table 2.

Study participants will report to the clinic on the morning of each on-site visit and will remain in the clinic until released by the Investigator after all the study-related procedures have been completed and the patient and/or parent(s)/caregiver have been instructed regarding drug storage, reconstitution, and administration.

8.2.1.2. Treatment Visits

During the treatment period, each patient will return to the clinical research facility during Week 0 (Visit 2) and Week 4 (Visit 3) for PK testing, and Week 16 (Visit 4), Week 28 (Visit 5), Week 40 (Visit 6), and Week 52 (Visit 7/ET).

8.2.1.3. End of Treatment

If the patient discontinues treatment prematurely, the procedures required for Week 52 (Visit 7/ET) should be performed before the patient leaves the study and the patient should return for the 4-Week Post-Treatment Follow-up Visit.

Please refer to Section 10 for further details regarding patient withdrawal procedures.

8.2.2. Informed Consent

The Investigator/study staff member must inform each study candidate of the nature of the study, explain the potential risks, and obtain written informed consent from the parent(s)/legal guardian and/or study candidate (as required by local regulations) prior to performing any study-related screening procedures.

8.2.3. Clinical/Medication History

The Investigator or a qualified designee should review the patient's clinical history, including details relating to DMD and any other medical conditions. Information regarding clinical history and current medications must be captured on the medical history and prior/concomitant medication eCRFs, respectively.

8.2.4. Vital Signs

Vital signs (pulse rate and body temperature) will be monitored at all protocol-required study visits. Pulse rate determinations will be performed with the patient in a sitting position after a 5-minute rest.

8.2.5. Height, Weight and Physical Examination

Height (in cm) and weight (in kg) will be measured at all study visits. A full physical

examination (including evaluation of the cardiovascular system, chest and lungs, thyroid, abdomen, nervous system, skin and mucosae, musculoskeletal system, eyes, ears, nose, mouth, throat, spine, lymph nodes, and extremities) will be conducted at Screening (Visit 1) and 4-week Follow-up (Visit 8), 4 weeks after discontinuation of study drug.

Physical examinations may also be performed at any time during the study as clinically indicated.

8.2.6. Confirmatory Gene Sequencing

A blood sample for dystrophin gene sequencing will be drawn at Screening (Visit 1). The study manual should be referenced for collection, processing, and shipping information.

8.2.7. Central Laboratory Assessments

All laboratory samples will be analyzed by a central laboratory. Please refer to the study manual for instructions regarding collection, processing, and shipment of all laboratory samples.

8.2.7.1. Hematology Laboratory Assessment

Hematology laboratory assessments will include white blood cell count with differential, hemoglobin, hematocrit, other red cell parameters, and platelet count. These parameters will be measured at every protocol-specified study visit. The study manual should be referenced for collection, processing, and shipping information.

8.2.7.2. Biochemistry Laboratory Assessment

Biochemistry laboratory assessments will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, magnesium, calcium, phosphorus, uric acid, glucose, total protein, albumin, bilirubin (total, direct, and indirect), AST, ALT, GGT, CK, lactate dehydrogenase, alkaline phosphatase, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, and cystatin C. These parameters will be measured at every protocol-specified study visit. The study manual should be referenced for collection, processing, and shipping information.

8.2.7.3. Urinalysis

Urinalysis will include analysis for pH, specific gravity, glucose, ketones, blood, protein, urobilinogen, bilirubin, nitrite, and leukocyte esterase. These parameters will be measured at every protocol-specified study visit. The study manual should be referenced for collection, processing, and shipping information.

8.2.8. 12-Lead ECG

A 12-lead ECG will be obtained at screening, Week 4 (Visit 3), Week 52 (Visit 7/ET), and 4-week Follow-up (Visit 8). ECGs will be read locally at investigational sites and interpreted for clinical significance. The findings will be captured in source documents and within the eCRF.

8.2.9. Timed Function Tests

Timed function tests will include the time taken to run/walk 10 meters, time to climb 4 stairs, time to descend 4 stairs, and time to stand up from a supine position [Mendell 1989, Griggs 1991, Beenakker 2005a, Pradhan 2006] (see Study Manual for detailed instructions). These parameters will be assessed prior to ataluren dosing on the first day of treatment (Visit 2), Week 28 (Visit 5), and Week 52 (Visit 7/ET).

8.2.10. North Star Ambulatory Assessment

The NSAA will be used to evaluate physical function, using standardized procedures (see Study Manual for detailed instructions). The NSAA will be performed prior to ataluren dosing on the first day of treatment (Visit 2), Week 28 (Visit 5), and Week 52 (Visit 7/ET).

8.2.11. Pharmacokinetic Assessment

During PK assessment on Days 1 and 28, patients will remain in the clinic until all blood draws are complete. On Days 1 and 28, blood samples for PK assessment will be drawn pre-dose and 1 (±15 min), 2 (±15 min), 4 (±30 min), 6 (±30 min), 8 (±30 min), and 10 (±30 min) hours post- dose. These samples will be sent to a central bioanalytical laboratory for analysis of ataluren levels. Please refer to the study manual for instructions regarding the collection, processing and shipment of all PK samples to the bioanalytical laboratory.

8.2.12. Palatability Questionnaire

The palatability questionnaire assessing characteristics of the study drug such as smell and taste will be administered at Week 4 (Visit 3). A parent/caregiver may respond on the patient's behalf after discussing each item with the patient, age permitting.

8.2.13. Ataluren Administration

Refer to Section 6.2. The clinic staff will administer the first dose of the study drug at Day 1 (Visit 2).

8.2.14. Adverse Events

Systemic AEs must be assessed and documented at each scheduled clinic visit, beginning at Day 1. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE should be obtained when clinically indicated. Patients must be followed for AEs for at least 28 days after the last dose of ataluren administration, or until any drug-related AEs and/or ongoing SAEs have resolved or become stable, whichever is later.

8.2.15. Concomitant Medications

Concomitant medication information will be collected and documented at each scheduled clinic visit, beginning at Screening. Any concomitant drugs (prescribed or over-the-counter) used during the course of the study and the reason for their use will be recorded. Information regarding the timing, type, and amount will be recorded in the eCRF.

8.3. Blood Collection Summary

Assuming a patient completes the study, the maximum amount of blood to be drawn at a visit is approximately 12 mL at screening, 24 mL during the 2 PK assessments, and 5 mL during the remaining visits. The total amount of blood to be drawn over the entire study (including the screening visit, treatment period, and post-treatment follow-up period) is approximately 61 mL.

9. ADVERSE EVENT ASSESSMENTS

9.1. Adverse Event Definitions

9.1.1. Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug (investigational medicinal product) in humans, whether or not it is considered related to the drug. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease in a study patient who is administered study drug in this study.

For this protocol, untoward medical occurrences that should be reported as AEs include the following:

- All AEs that are suspected or are not suspected to be due to study drug
- Overdose (administration of a study drug dose >4 times the intended total daily dose level for this protocol [>160 mg/kg/day]) of study drug
- All reactions from medication misuse, abuse, withdrawal, sensitivity, or toxicity
- All reactions that result from medication errors or uses of the study drug outside what is described in the protocol
- Apparently unrelated illnesses, including the worsening of a preexisting illness
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate AEs. The outcome of the accident (hip fracture secondary to the fall) should be recorded in source documents.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test)
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (eg, elevated liver enzymes in a patient with jaundice) should be captured in the source documents. Laboratory abnormalities not requiring clinical intervention or further investigation will be captured as part of overall laboratory monitoring, and should not be reported as AEs.
- A pre-existing condition (eg, allergic rhinitis) must be noted on the appropriate eCRF for Visit 1, but should not be reported as an AE unless the condition worsens or episodes increase in frequency during the AE reporting period. Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE and the resulting appendectomy should be recorded in the source documents. If a surgical procedure was planned prior to entry into the study, and the surgery is not performed because of a worsening of a baseline condition, this should not be reported as an AE. Note that, as

described in Section 9.1.2, any inpatient hospitalization occurring as the consequence of an AE during the study period should be reported as an SAE.

Each AE is to be classified as serious or non-serious by the Investigator using medical and scientific judgment.

9.1.2. Serious Adverse Events (SAEs)

An SAE is an untoward medical occurrence or effect associated with the use of a study drug at any dose, regardless of whether it is considered to be related to the study drug, which results in one of the following:

- Death (ie, all deaths on treatment or within 4 weeks after last study drug administration), including deaths due to disease progression. Any death occurring later than 4 weeks following the last dose need not be reported as an SAE unless it is a result of an event that started within the period covered by the on-study definition. The reported AE should be the event that caused the death. In addition, any AE resulting in death that occurs subsequent to the AE-reporting period and that the Investigator assesses as possibly related to the study drug should also be reported as serious.
- Life-threatening AE. This is an event that, in the view of either the Investigator or the sponsor, places the patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, hypothetically might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (eg, excluding hospitalizations for administration of the study drug, procedures required by the study protocol, or dystrophinopathy-related diagnostic procedures; other planned hospitalizations; or hospitalizations related only to progression of disease). Treatments in the emergency room for procedures such as hydration that do not require admitting the patient to the hospital and observational durations in the emergency room for less than 24 hours are not considered serious.
- Persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions, not related to dystrophinopathy.
- Any other medically important event that the Investigator or the sponsor judges to be serious or which is defined as serious by the regulatory agency in the local country. Medical judgment should be exercised in deciding whether a reaction is serious in other situations. Important medical events that do not result in death, are not immediately life-threatening, and do not require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment administration in an emergency room or at home, newly diagnosed malignancy, or blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- An event need not be reported as a SAE if it exclusively represents a relapse or an expected change or progression of the baseline dystrophinopathy. This type of event need only to be reported as an AE.

Note that any SAEs occurring after the end of the patient's participation in the study should be reported to the sponsor if the Investigator becomes aware of them.

9.1.3. Unexpected Adverse Events

Unexpected AEs are defined as those events that were not previously reported with study drug as referenced in the most current Investigator Brochure, or that are symptomatically and pathophysiologically related to a known toxicity but differ because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Ataluren IB only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the IB only listed cerebral vascular accidents. "Unexpected," as used in this definition, also refers to an AE that is mentioned in the most current IB as occurring with the class of drugs or as anticipated from the pharmacological properties of the study drug, but is not specifically mentioned as occurring with the medicinal product.

For the purposes of considering expectedness, the Ataluren IB provides a summary of the safety profile of ataluren based on available clinical information (also referred to as the reference safety information).

9.2. Eliciting Adverse Event Information

The Investigator is to report all directly observed AEs and all AEs spontaneously reported by the study patient or parent/guardian in case of a child. In addition, each study patient will be questioned about AEs at each scheduled clinic visit after study drug administration or during any telephone contact with the patient or parent/guardian in case of a child. The type of question asked should be open-ended, eg, "*How has your child been feeling?*" or a similar type of query.

9.3. Adverse Event Recording

All AEs (both serious and non-serious) that occur in patients during the AE reporting period must be recorded, whether or not the event is considered drug related. In addition, any known untoward event that occurs subsequent to the AE reporting period that the Investigator assesses as possibly related to the investigational drug/product should also be recorded as an AE.

All AEs are to be recorded in the source documents and on the eCRF using concise medical terminology; whenever possible terms contained in Medical Dictionary for Regulatory Activities (MedDRA) should be employed. In addition, the following information should be recorded:

- Indication of whether the event is serious or non-serious (see Section 9.1.2)
- Relationship to study drug (see Section 9.4)
- Severity of the event (see Section 9.5)
- Onset date
- Resolution date, or date of death
- Action taken
- Outcome of the event

Classification of the event as serious or non-serious determines the reporting procedures to be followed.

9.4. Describing Adverse Event Relationship to Study Drug

Based on the considerations outlined in Table 3 the Investigator should provide an assessment of the relationship of the AE to the study drug, ie, whether there is a reasonable possibility that the study drug caused the AE.

Table 3: Relationship of Study Drug to Adverse Event

Relationship	Description
Probable	A clinical event in which a relationship to the study drug seems probable because of such factors as consistency with known effects of the drug; a clear temporal association with the use of the drug; improvement upon withdrawal of the drug; recurrence upon rechallenge with the drug; lack of alternative explanations for the event.
Possible	A clinical event occurring coincident with administration of the study drug and which may or may not be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal or rechallenge may be lacking.
Unlikely	A clinical event with a temporal relationship to the study drug exposure that does not preclude causality but for which there is a clear alternate cause that is more likely to have caused the AE than study drug. Such alternatives include a concomitantly administered drug, the patient's disease state, other medical conditions, or environmental factors.
Unrelated	A clinical event, for which a relationship to the study drug seems improbable because of factors such as inconsistency with known effects of the study drug, lack of a temporal association with study drug administration, lack of association of the event with study drug withdrawal or rechallenge, and/or presence of alternative explanations for the event. Alternative explanations might include a known relationship of the AE to a concomitant drug, medical history of a similar event, the patient's disease state, other medical conditions, or environmental factors.

9.5. Grading of Severity of Adverse Events

The severity of AEs will be graded using CTCAE v 4.0 (refer to the study manual). For each episode, the highest severity grade attained should be reported.

If a CTCAE criterion does not exist, the Investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the AE. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 4.

Table 4: Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the patient's overall health and well-being, does not interfere with the subject's usual function, and is not likely to require medical attention
Grade 2	Moderate	Sign or symptom causes interference with usual activity or affects clinical status, and may require medical intervention
Grade 3	Severe	Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow up
Grade 4	Life-threatening	Sign or symptom results in a potential threat to life
Grade 5	Fatal	Sign or symptom results in death

Note the distinction between the seriousness and the severity of an AE. Severity is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity but would not be classified as serious unless it met one of the criteria for serious events listed in Section 9.1.2.

9.6. Follow-Up of Unresolved Adverse Events

All AEs should be followed up by the Investigator until they are resolved, or the Investigator assesses them as chronic or stable. Follow-up of any SAE that is fatal or life-threatening should be provided within one additional calendar week. The Investigator should consider protocol guidelines and use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events. In the event of additional investigations, the PTC Therapeutics Safety Department or designee should be informed via e-mail or fax. A patient withdrawn from the study because of an AE must be followed by the Investigator until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. Follow-up may need to continue after the patient has discontinued from the study, and additional investigations may be requested by the medical monitoring team.

9.7. Adverse Event Reporting Period

The first day of AE reporting will coincide with the day the first dose of study drug is administered. The AE reporting period for this study ends with the 4-week post-treatment follow-up visit, except as described in Section 9.3. In addition, SAEs occurring in a patient after the study period should be reported to the sponsor if the Investigator becomes aware of them.

9.8. Investigator Site Adverse Event Reporting Requirements

Classification of an event as serious or non-serious (see Section 9.1.2) determines the reporting procedures to be followed. Investigator site reporting requirements for AEs are summarized in Table 5.

Table 5: Investigational Site Requirements for Reporting Adverse Events

Classification	Reporting Time	Reporting Action
Serious	Within 24 hours	E-mail, fax or telephone call to the PTC Therapeutics Safety Department/designee within 24 hours.
	Within 5 calendar days	Provide photocopies or document scan of relevant source documents[a] (eg, progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries) as requested by the PTC Therapeutics Safety Department/designee.
	Per CRF submission procedure	Record and submit information on appropriate CRFs (eg, Medical History and Concomitant Medications CRFs)
AESI	Within 24 hours	E-mail, fax or telephone call to the PTC Therapeutics Safety Department/designee within 24 hours.
	Within 5 calendar days	Provide photocopies of relevant source documents[a] (eg, progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries) as requested by the PTC Therapeutics Safety Department/designee.
	Per CRF submission procedure	Record and submit information on appropriate CRFs (eg, Medical History and Concomitant Medications CRFs)
Nonserious	Per CRF submission procedure	Record and submit information on appropriate CRFs (eg, Adverse Events, Medical History and Concomitant Medications CRFs)

a Patient name, address, and other personal identifiers should be obscured.
Abbreviations: AESI = AEs of special interest, eCRF = electronic case report form, IRB/IEC = Institutional Review Board/Independent Ethics Committee, SAE = Serious Adverse Event

For SAEs, in addition to completing the AE eCRF, the SAE report form must also be completed. The SAE report form should be signed by the Investigator; however, if the Investigator is unable to sign at the time of the event or within 24 hours, the form should be signed by the clinical staff member reporting the SAE (eg, the study coordinator). The SAE report form must be faxed or emailed to the PTC Therapeutics Safety Department or designee and to the site IRB/IEC (if required by local regulations) within 24 hours. Follow-up information to the SAE should be clearly documented as "follow up" in the SAE report form and must also be faxed or emailed to the same parties. All follow up SAE report forms for the event must be signed by the Investigator. Any source documents (eg, progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries) provided to the sponsor must be redacted so that the patient's name, address, and other personal identifiers are obscured. Only the patient's study number and initials are to be provided (in regions where the provision of such information is permitted). The information in the AE eCRF and the SAE report form(s) must match or be reconciled. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms.

In the rare event that the Investigator does not become aware of the occurrence of an SAE immediately (for example, if a patient initially seeks treatment elsewhere), the Investigator is to document his/her first awareness of the AE and report the event within 24 hours after learning of it.

The PTC Therapeutics Safety Department/designee contact information for reporting SAEs is provided below. This information is also provided in the Investigator File and the back-up paper SAE report form.

PTC Therapeutics Safety Department
Attention: [redacted]
Telephone [redacted]
Facsimile: [redacted]
E-mail: [redacted]

9.9. PTC Therapeutics Adverse Event Reporting Requirements

As the sponsor of the study, PTC Therapeutics is responsible for reporting certain safety information, particularly SAEs and patient deaths related to participation in the study, to each Investigator in an expedited manner. If notification of an AE requiring expedited reporting to investigators is received, PTC Therapeutics or its designated representative will contact each investigational site participating in this study by e-mail, fax, and/or overnight mail such that the Investigator can promptly notify the site IRB/IEC per their local requirements. The initial expedited safety report will be provided as required according to local regulations (eg, within 15 days) after the earliest date PTC Therapeutics or an agent of PTC Therapeutics (eg, a site monitor) becomes aware of an AE. This awareness date is the date the regulatory reporting clock begins and the date is considered Day 0.

10. WITHDRAWAL OF SUBJECTS

All patients who receive ataluren should remain in the study whenever possible. However:

- The parent/caregiver has the right to withdraw consent and discontinue ataluren at any time.
- If the patient's condition substantially worsens after initiating ataluren, the patient will be carefully evaluated by the Investigator. The patient will be withdrawn from treatment if continuing would place them at risk.
- The Investigator may withdraw the patient from ataluren, if, in the Investigator's clinical judgment, it is not in the patient's best interest to continue.
- In the event that the patient becomes significantly noncompliant with ataluren administration, study procedures, or study requirements, the patient should be withdrawn from ataluren when the circumstances surrounding noncompliance increase risk to the patient or are anticipated to substantially compromise the interpretation of study results.
- This study may be discontinued by the relevant regulatory authority, IRB/EC, and/or PTC Therapeutics at any time.

The date ataluren is discontinued and the reason for discontinuation will be recorded in the source documents and in the eCRF. The PTC medical monitor (or designee) should be informed via e-mail of when a patient discontinues study drug.

When ataluren is discontinued (regardless of the reason), the Investigator is expected to capture all of the evaluations required at the end of treatment or Follow-up and any additional evaluations should be completed that may be necessary to ensure that the patient is free of untoward effects. The patient should be encouraged to seek appropriate follow-up for any continuing health problems.

11. STATISTICAL CONSIDERATIONS

11.1. Sample Size

The sample size of 12 patients for this study is not based on formal statistical considerations. However, preliminary results from population PK (popPK) simulation indicate that the current study design (sample size and sparse sampling strategy) will provide adequate precision for the prediction of PK parameters (apparent clearance and volume of distribution) even considering the usual potential for subject dropouts and/or missing samples [Wang 2012, FDA General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products 2014].

11.2. Analysis Populations

All patients who receive at least 1 dose of ataluren will be included in the analyses of safety. For each outcome measure, evaluable populations of patients will be considered to comprise all patients who have sufficient baseline and on-study measurements to provide interpretable results for the test of interest.

11.3. General Statistical Considerations

By-subject listings will be created for each eCRF module. Summary tables for continuous variables will contain the following statistics: N, mean, median, standard deviation, standard error, minimum, maximum, and 95% confidence intervals (CIs) as appropriate. Summary tables for categorical variables will include N and percentage. Graphical techniques will be used when such methods are appropriate and informative.

Transformations of the data may be explored if warranted by the distribution of the data.

All analyses will be performed using Statistical Analysis System (SAS® Version 9.0 or higher).

The primary analysis will be conducted on data obtained during the 4-week PK period of the study and may be reported separately from the extension study data.

11.4. Subject Disposition and Baseline Characteristics

The numbers of patients screened and enrolled will be summarized. Reasons for screen failures will be presented. The number of patients receiving ataluren will be described. Patients who do not complete the planned observations will be described and evaluated separately. Patients receiving ataluren who are found not to have fully met the eligibility criteria will be described. On-study protocol violations will also be presented. Reasons for study discontinuation and dates of withdrawal from study will be described.

Patient characteristics at baseline will be summarized using appropriate descriptive statistics.

11.5. Efficacy Endpoints

Observed values and changes from baseline in timed function tests, NSAA total score and composite score will be summarized descriptively.

11.6. Pharmacokinetic Parameters

PK parameters of ataluren on Day 1 and 28 will be derived using non-compartmental analysis (NCA) methods. The PK parameters of ataluren listed below will be derived following the morning dose on Day 1 and 28 using NCA methods.

Parameters	Definition
AUC_{0-t}	Area under the plasma concentration time curve from time zero to the time of last quantifiable concentration (C_{trough}) using the linear trapezoidal rule during the ascending portion of the curve and the log-trapezoidal rule during the descending portion of the curve
AUC_{0-10}	Area under the plasma concentration time curve from time zero up to 10 hours after the morning dosing using the linear trapezoidal rule during the ascending portion of the curve and the log-trapezoidal rule during the descending portion of the curve
C_{max}	Maximum observed plasma concentration
$C_{trough@6h}$	Concentration at the end of the first (morning) dosage interval
t_{max}	Time of maximum observed plasma concentration
λ_z	Terminal rate constant
$t_{1/2}$	Terminal half-life, calculated as $\ln(2) / \lambda_Z$

The accumulation ratio on Day 28 will be calculated as follows:

Parameter	Description
AR(AUC)	$AR(AUC) = (AUC_{0-t})Day28 / (AUC_{0-t})$ Day 1
$AR(C_{max})$	$AR(C_{max}) = (C_{max})$ Day28 / (C_{max})Day 1

Individual PK parameters will be derived using actual sampling and dosing times. Concentrations below the limit of quantitation (LOQ) will be set to zero for the calculation of NCA parameters. PK parameters will be summarized with descriptive statistics on Day 1 and 28 (eg, n, arithmetic mean, standard deviation, standard error, median, minimum, and maximum, CV% mean, geometric mean, and CV% geometric mean). The analysis will be performed with a fully validated version of Phoenix WinNonlin V6.3.

In addition, a popPK analysis will be performed by simultaneously assessing concentrations on Days 1 and 28 in order to explore the potential time-dependency of ataluren and derive the following additional PK parameters.

Parameter	Description
ka	Rate constant of absorption
CL/F	Apparent clearance
CLd/F	Apparent distribution clearance
Vc/F	Apparent volume of distribution
Vp/F	Apparent peripheral volume of distribution

The above PopPK model will be used to simulate rich concentration-time profiles and derive the area under the curve over 24 hours (AUC_{0-24}).

A two-compartment model with time-dependent clearance (between the morning and midday dose), was previously used to assess the concentration-time profiles of ataluren in adult patients with nonsense-mutation Duchenne-Becker muscular dystrophy. If required, data collected in the current study (≥2 to <5 year old nmDMD patients) may be merged with data collected in adult patients with nmDMD to assess potential effect of age and/or body weight on PK parameters of ataluren.

Additional information will be provided in the PK analysis plan.

11.7. Safety

11.7.1. Adverse Events

Adverse events will be tabulated by using the MedDRA classification system. The severity of the AE will be graded using the CTCAE whenever possible. For AEs that are not included in the CTCAE, the grading categories (mild, moderate, severe, life-threatening, and fatal) described in Table 4 will be used. The frequency of patients experiencing a specific AE will be tabulated by system organ class; preferred term; seriousness (serious vs nonserious; see Section 9.1.2); timing of occurrence, outcome, and relationship to study drug (see Section 9.4); and worst severity (see Section 9.5) In the by-subject analysis, a patient having the same event more than once will be counted only once and will be classified at the highest severity and/or relatedness for those events.

Adverse events classified as CTCAE Grade ≥3; study-drug-related events; hepatic, and renal events leading to special diagnostic evaluations; events leading to discontinuation of ataluren, events leading to death, and SAEs will be considered with special attention.

11.7.2. Laboratory Parameters

Hematological and biochemistry data will be summarized by visit and will be graded according to CTCAE severity grade, when applicable. The frequencies of the worst severity grade observed will be displayed. For variables graded according to CTCAE severity grade, the frequencies of

the worst severity grade observed will be displayed. For parameters for which a CTCAE scale does not exist, the frequency of patients with values below, within, and above the normal ranges will be summarized. In the by-subject analysis, a patient having the same abnormality more than once will be counted only once based on the worst severity grade observed.

11.7.3. Vital Signs and ECGs

Vital signs (height, weight, BMI, pulse rate, and body temperature) and ECGs will be listed and summarized by visit. Where appropriate, changes from baseline will be presented by visit.

11.7.4. Other Safety Parameters

Physical examination data will be described. Where appropriate, changes from baseline will be presented by visit.

11.7.5. Interim Safety Review

An interim safety analysis is planned with the assistance of the DMC; the analysis will be a safety review when all patients have completed ≥12 weeks of treatment. If this review indicates potential safety concerns, the DMC may elect to have additional safety reviews for specific patients or all patients.

11.8. Treatment Administration and Drug Compliance

Study drug compliance will be assessed by unused study drug reporting. Compliance will be analyzed as a percentage of drug actually taken relative to the amount that was specified to be taken during the study.

11.9. Use of Concomitant Medication and Supportive Therapy

Concomitant medications will be coded by means of the World Health Organization Drug Dictionary (WHODRUG) into Anatomical-Therapeutic-Chemical (ATC) classification codes. The type and timing of use of specific concomitant medications will be listed and summarized.

The frequency, timing, type, and amount of any other therapies for dystrophinopathy will be considered with special interest.

11.10. Palatability Questionnaire

Palatability data will be summarized descriptively.

11.11. Exploration of Correlations

Correlations between patient characteristics and outcome measures, and correlations among outcomes measures may be explored using regression models or other appropriate techniques.

12. STUDY COMMITTEES

A DMC, operating autonomously from the sponsor and the clinical investigators, will be responsible for providing independent recommendations to PTC Therapeutics about evolving risk-benefit observed in the course of the study and any modifications required during the course of the study. The DMC will comprise appropriately qualified personnel as detailed in the DMC charter. The DMC will be chaired by one of those individuals. DMC members must not be actively involved in study design, conduct, or daily management of this study and must not have financial, proprietary, professional, or other interests that may affect impartial, independent decision-making. Specialists may be invited to participate as non-voting members at any time if additional expertise is desired.

13. OBLIGATIONS OF THE INVESTIGATOR AND THE SPONSOR

13.1. Compliance with Ethical and Regulatory Guidelines

The Investigator is responsible for ensuring that the clinical study is performed in accordance with the International Council on Harmonisation (ICH) GCP guidance documents and the Declaration of Helsinki.

13.2. Institutional Review Board/Independent Ethics Committee

Prior to enrollment of patients into the study, as required by regulatory authorities, the protocol and informed consent document will be reviewed and approved by an appropriate IRB/IEC. By signing the protocol, the Investigator assures that approval of the protocol will be obtained from the IRB/IEC and that all aspects of the IRB/IEC review will be conducted in accordance with current regulations. Amendments to the protocol will be subject to the same IRB/IEC review requirements as the original protocol. Only changes necessary to eliminate apparent immediate hazards to the patients may be initiated prior to IRB/IEC approval. In that event, the Investigator must notify the IRB/IEC and PTC Therapeutics in writing within 5 working days after implementation. The Investigator will also promptly notify the IRB/IEC of any serious, unexpected AEs or any other information that may affect the safe use of the drug during the course of the study.

A letter documenting the IRB/IEC approval and a list of the names and titles of the IRB/IEC members must be received by PTC Therapeutics prior to the initiation of the study. All correspondence with the IRB/IEC should be retained in the Investigator's study file.

The Investigator shall submit a progress report, at least once yearly, to the IRB/IEC, and must provide a copy to PTC Therapeutics. As soon as possible after completion or termination of the study, the Investigator will submit a final report to the IRB/IEC and to PTC Therapeutics. This report should include the dates of initiation and completion of the study, a description of any changes in study procedures or amendments to the protocol, any deviations from the protocol, the number and type of patients evaluated, the number of patients who discontinued (and the reasons for discontinuation), the number of patients who completed the study, and the results of the study, including a description of any AEs. PTC Therapeutics will assist the Investigator in the preparation of this report, as needed.

13.3. Informed Consent/Assent

By signing the protocol, the Investigator assures that informed consent/assent will be obtained from each patient and/or parent/legal guardian prior to study entry and that the informed consent/assent will be obtained in accordance with current regulations.

The Investigator or sub-investigator will give each patient and/or parent/guardian full and adequate verbal and written information regarding the objectives and procedures of the study and the possible risks involved. An informed consent/assent document will be provided to each patient and/or parent/guardian in a language in which the patient or parent/guardian is fluent. This information must be provided to the patient or parent/guardian prior to undertaking any study-related procedure. Adequate time should be provided for the patient and/or

parent/guardian to read the informed consent, to understand the risks and benefits of participating in the study, and to ask any questions that the patient and/or parent/guardian may have about the study. The patient and/or parent/guardian should be able to ask additional questions as and when needed during the conduct of the study. The patient's and/or parent(s)/guardian signature (as required by local regulations) on the informed consent form should be obtained at the investigational site in the presence of the Investigator or a qualified representative (eg, sub-investigator). Where applicable, the patient will sign an age-appropriate assent form.

Each patient or parent/guardian will be given a copy of the signed consent/assent form. The original signed informed consent forms will be retained by the Investigator with the study records.

The written patient information must not be changed without prior approval by PTC Therapeutics and the IRB/IEC.

13.4. Case Report Forms

An eCRF is required and must be completed for each patient, with all required study data accurately recorded such that the information matches the data contained in medical records (eg, physicians' notes, nurses' notes, clinic charts, and other study-specific source documents). The eCRFs exist within a Web-based EDC system managed by the data management CRO for this study. After the Investigator or the Investigator's designees (eg, research coordinators) have been appropriately trained, they will be given access to the EDC system and will enter the data required by the protocol into the EDC system. Any change of data will be made via the EDC system, with all changes tracked by the system to provide an audit trail.

With an electronic signature, the Investigator certifies that the data are complete and accurate prior to database lock. This electronic signature serves to attest that the information contained in the eCRFs is true. After database lock, the investigational site will receive a CD-ROM and/or paper copies of the patient data for archiving at the investigational site. At all times, the principal Investigator has final responsibility for the accuracy and authenticity of all clinical data entered onto the eCRFs and/or reported to PTC Therapeutics from the investigational site.

13.5. Study Records

During the study, the Investigator will maintain adequate records for the study, including medical records, source document records detailing the progress of the study for each patient, laboratory reports, a CD-ROM or paper copy of the data that have been captured in the EDC for each patient (electronic equivalents of CRFs), paper CRFs, signed informed consent forms, ataluren reconciliation and dispensing records, correspondence with the IRB/IEC, AE reports, and information regarding patient discontinuation and completion of the study. Current regulations require PTC Therapeutics (or an authorized designee) to inspect all documents and records required to be maintained by the Investigator, including but not limited to medical records (office, clinic, or hospital) for the patients enrolled in this study. These regulations also allow the same records to be inspected by authorized representatives of the FDA, Health Canada, or other regulatory authorities.

13.6. Confidentiality

Research records will be collected and stored in a manner that protects the confidentiality of patient information. The names and identities of all research patients will be kept in strict confidence and will not appear on eCRFs, paper CRFs, or other records provided to or retained by PTC Therapeutics (or its authorized designee). The names and identities of the patients need not be divulged; however, the records must nevertheless be inspected. This will be accomplished by redacting the patient's name and replacing the name with the patient's study identification number on any record provided to or retained by PTC Therapeutics. The informed consent form must include appropriate statements explaining these requirements.

By signing this protocol, the Investigator affirms to PTC Therapeutics that the Investigator will maintain, in confidence, information furnished by PTC Therapeutics and will divulge such information to the IRB/IEC under an appropriate understanding of confidentiality with such board.

13.7. Retention of Records

To enable evaluations and/or audits from regulatory authorities or PTC Therapeutics, the Investigator agrees to keep accurate and complete records, including the identity of all participating patients (sufficient information to link eCRFs and clinic records), all original signed informed consent forms, CD-ROM or paper copies of the data that have been captured in the EDC for each patient (electronic equivalents of CRFs), and detailed records of ataluren disposition. All records and documents pertaining to the study (including but not limited to those outlined in Section 13.5 above) will be maintained by the Investigator until notification is received from PTC Therapeutics that the records no longer need to be retained.

The Investigator must obtain written permission from PTC Therapeutics before disposing of any records. In order to avoid any possible errors, the Investigator will contact PTC Therapeutics prior to the destruction of any study records. The Investigator will promptly notify PTC Therapeutics in the event of accidental loss or destruction of any study records. If the Investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another Investigator, another institution, or to PTC Therapeutics.

13.8. Monitoring and Auditing

In accordance with 21 CFR Part 312.56 and/or relevant ICH guidelines, PTC Therapeutics or a designee will periodically inspect all eCRFs (see Section 13.4), study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times, before, during, and after completion of the study. As required by applicable regulations (Responsibilities of Sponsors and Investigators), the monitoring visits provide PTC Therapeutics with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of data in the eCRFs; ensure that all protocol requirements, other relevant regulations, and Investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records required to be maintained by the Investigator, including but not limited to medical records (office, clinic, or hospital) for the patients in this study. The names and identities of all research subjects will be kept in strict

confidence and will not appear on eCRFs or other records provided to or retained by

PTC Therapeutics. The Investigator/institution guarantees direct access to source documents by PTC Therapeutics and appropriate regulatory authorities.

The investigational site may also be subject to review by the IRB/IEC, to quality assurance audits performed by PTC Therapeutics or a designee, and/or to inspection by regulatory authorities. The GCP regulations also require the Investigator to allow authorized representatives of the regulatory authorities to inspect and make copies of the same records.

It is important that the Investigator and relevant institutional personnel are available during the monitoring visits and possible audits or inspections, and that sufficient time is devoted to the process.

13.9. Termination of the Study

PTC Therapeutics reserves the right to discontinue the study prior to inclusion of the intended number of subjects. The Investigator, after consultation with the PTC Therapeutics medical monitor, reserves the right to discontinue the study at the investigational site for safety reasons at any time.

After a decision to terminate the study, investigators must contact all subjects who are continuing their participation in the study and must do so within a time period set by PTC Therapeutics. As directed by PTC Therapeutics, all study materials must be collected and all electronic data entry forms completed to the greatest extent possible.

13.10. Public Notification of Study Conduct

Consistent with requirements of the International Committee of Medical Journal Editors (ICJME) as a condition of consideration for publication of study results, PTC Therapeutics will be responsible for ensuring that this protocol is listed at the ClinicalTrials.gov website. PTC Therapeutics will also be responsible for ensuring that information at this website relating to study design and conduct is appropriately updated during the course of the study. In order to facilitate this process, investigators will need to supply PTC Therapeutics with appropriate contact information for investigational site personnel.

13.11. Dissemination of Results

The information developed during the conduct of this clinical study is considered confidential by PTC Therapeutics. This information may be disclosed as deemed necessary by PTC Therapeutics.

To allow for the use of the information derived from this clinical study and to ensure compliance with current regulations, the Investigator is obliged to provide PTC Therapeutics with complete test results and all data developed in this study. The information obtained during this study may be made available by PTC Therapeutics to other physicians who are conducting similar studies and to the FDA, Health Canada, or other regulatory authorities. Such information may be disclosed as deemed necessary by PTC Therapeutics.

PTC Therapeutics intends for the data from this study to be presented and published. The PTC Therapeutics staff under the direction of the PTC Therapeutics chief medical officer in collaboration with the Investigator will be responsible for writing presentations and manuscripts

for publication. Investigators will not be allowed to publish or present the data from this study without prior agreement with PTC Therapeutics.

13.12. Communication with Regulatory Authorities

PTC Therapeutics will assume responsibility for regulatory interactions with the FDA, Health Canada, and/or other regulatory authorities. In fulfilling this responsibility, PTC Therapeutics (or a designee) will collect, assemble, and communicate all required regulatory documents (eg, Investigator financial disclosure forms, protocol and protocol amendments, investigator brochures, informed consent documents, annual reports) as required by regulation.
PTC Therapeutics (or a designee) will also assume responsibility for AE reporting to regulatory authorities as described in Section 9.9.

14. RATIONALE FOR STUDY DESIGN FEATURES

14.1. Subject Selection

14.1.1. General

This study is an open-label PK, efficacy, and safety study of ataluren in subjects with nmDMD. Consistent with GCP guidelines, parents/guardians and subjects must provide informed consent/assent before initiation of any study procedures. To minimize missing data and premature discontinuations, subjects must have the personal and family resources to comply with study procedures and restrictions. In addition, subjects must not have serious concomitant conditions that would compromise safety, compliance, or evaluation.

14.1.2. Inclusion of Minors

Inclusion of children ≥2 to <5 years old in this protocol is appropriate and necessary. The benefit-risk ratio is enhanced by the known severity of the disease phenotype in patients with dystrophinopathy caused by nonsense mutations, the generally favorable safety profile of ataluren, and the limited population of patients with nonsense-mutation-mediated disease (~13% of the total dystrophinopathy population). Inclusion of young children will allow an understanding of how age-dependent disease characteristics may affect PK parameters and, therefore, dosing.

In standard toxicology studies, dosing is initiated in young adult rats (6 to 8 weeks old) and in 4- to 6-month old dogs. However, the chronic toxicology studies conducted with ataluren initiated dosing in weanling animals (approximately 4- to 5-week-old rats, and dogs <3 months of age) to support dosing of pediatric subjects as young as 2 years of age. A detailed summary of methods and results of these chronic toxicity studies is provided in Section 7 of the Ataluren IB.

In the clinic, ataluren has previously been administered to patients as young as 3 years old. A Phase 2 study of ataluren in patients with methylmelonic acidemia (MMA) enrolled 11 patients, including 2 patients who were 3 years old and 1 patient who was 4 years old. All 3 of these patients completed the study as planned, receiving ataluren 5, 5, 10 mg/kg for 28 days in Cycle 1 and ataluren 10, 10, 20 mg/kg for 28 days in Cycle 2; there was a washout period of 21 days between the cycles.

Ataluren was well tolerated by the 3 patients <6 years old in the MMA study. Treatment-emergent AEs in these patients were vomiting, pyrexia, nasopharyngitis, cough, flatulence, and rash. All treatment-emergent AEs were mild or moderate in severity, and none were serious or led to discontinuation of treatment. Overall, the ataluren safety profile was similar in patients <6 years old and ≥6 years old.

Twenty-four hour blood sampling for ataluren PK assessments was performed on Day 28 of each cycle; the data from Cycle 2, in which a dose of 10, 10, 20 mg/kg was administered, are of particular relevance to the proposed study. Ataluren plasma concentrations in the 3 patients <6 years old were comparable to ataluren plasma concentrations in the 8 patients ≥6 years old who participated in the MMA study. Mean $AUC_{0\text{-}24h}$ was 279.3 h•µg/mL and 358.4 h•µg/mL for patients <6 and ≥6 years old, respectively, on Day 28 of Cycle 2. Mean C_{max} was 28.2 µg/mL

and 29.9 µg/mL for patients <6 and ≥6 years old, respectively, on Day 28 of Cycle 2 (10, 10, 20 mg/kg). These data suggest similar ataluren PK profiles in patients <6 and ≥6 years old.

In Phase 2 clinical studies, ataluren has demonstrated comparable PD activity and safety, as well as PK profiles similar to adult patients, in children >6 years old with CF [Clancy 2006, Kerem 2008, Sermet-Gaudelus 2010, Wilschanski 2011]. The drug has also shown PD activity and was generally well-tolerated at the dose used in that study and a higher dose level in children with DMD [Finkel 2013].

During study conduct, patients will be monitored closely for adverse clinical and laboratory events. This protocol clearly defines the actions to be taken if AEs occur. Procedures have been established for defining AEs, eliciting AE information, recording AEs, evaluating the relationship of AEs to the study drug, grading the severity of AEs, following up on unresolved AEs, and reporting AEs. These procedures are fully detailed in Section 9. Additional risk/benefit information that becomes available during the conduct of the study will be provided to each investigational site as a "letter to the Investigator" or safety alert. In addition, pain and discomfort will be prevented as much as possible, and investigations will be limited to a minimum necessary to provide meaningful data and performed using size/age appropriate material and devices.

14.1.3. Reproductive Considerations

Ataluren is not genotoxic, did not affect fertility in male and female rats, and was not teratogenic in rats and rabbits. In addition, lack of sexual maturity in the subjects enrolled in this study limits reproductive risks.

14.1.4. Prior and Concomitant Therapies

Conventional supportive therapies will be permitted; however, efforts will be made to avoid use of concomitant medications that might confound interpretation of study results or pose a safety risk. Ataluren has not proved allergenic in studies performed to date, but review of known allergies to excipients containing in the formulation is prudent. As substantial modification of corticosteroid dosing due to manifestation of undesirable side effects such as osteoporosis during the study may confound study results, investigators and subjects are encouraged to maintain corticosteroid dosing as uniformly as possible.

In vitro studies have suggested that ataluren is potentially an inhibitor of CYP450, 2C8 and 2C9 at concentrations that may be achieved in the clinic. Because ataluren may slow the clearance of medications that are primarily metabolized by CYP2C8 or CYP2C9, investigators should pay specific attention to use of drugs that are known substrates of this enzyme, particularly when such drugs may have a low therapeutic index.

While no clinical evidence of drug-drug interactions has been demonstrated, the potential for ataluren interactions with other drugs has been assessed. Based on in vitro studies, ataluren is a substrate of UGT1A9 and BCRP. The clinical drug-drug interaction study for ataluren with a strong UGT1A9 inducer (eg, rifampin) has been conducted. Although the average ataluren C_{max} and AUC were reduced posttreatment of rifampin (~11% and ~29%, respectively), these changes are considered not to be clinically important. Caution should be exercised when ataluren is co-administered with drugs that are inhibitors of BCRP.

In vitro data indicate that ataluren is an inhibitor of UGT1A9, OAT1, OAT3 and 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 increased concentration of these drugs.

Physicians and subjects are encouraged to avoid the use of extraneous drugs or alternative therapies in order to minimize the possibility that drug-drug interactions might occur. In particular, physicians are advised to closely monitor subjects when drugs of low therapeutic index that are cleared by CYP2C9 are administered concomitantly with ataluren.

Specific drugs that are prohibited during the study are listed in the Exclusion Criteria (see Section 4.3).

14.2. Treatment Rationale

14.2.1. Ataluren Schedule and Dose Selection

Dosing based on body weight will be employed. Such dosing is common in pediatrics and reduces variability in exposure by accommodating differences in patient size across the span of ages of the patients who will participate in the clinical study. The preliminary results from a popPK simulation indicated that the current study design of 10, 10, 20 mg/kg dose in 12 patients with 7-point sampling after the morning dose would provide good precision of the estimates of CL/F and Vd/F, according to FDA recommendation.

The schedule of drug administration was derived directly from Phase 1 PK modeling and from Phase 2 exposure information. The intent of administering 2 smaller doses at 6-hour intervals during the day and a larger dose at a 12-hour interval overnight (eg, at 7:00 AM, 1:00 PM, and 7:00 PM) is to optimally sustain target plasma concentrations while minimizing total exposures. This schedule is likely to fit well with daily patterns of living for patients, thus enhancing compliance. As confirmation of that premise, compliance with ataluren dosing in Phase 2 and Phase 3 testing has been excellent.

In clinical studies of ataluren in nmDMD, ataluren has been studied most extensively at the 10, 10, 20 mg/kg dose level. In the Phase 2b, randomized, double-blinded, placebo-controlled study of ataluren in nmDMD (Study 007), 57 patients received ataluren 10, 10, 20 mg/kg for 48 weeks. In addition, all patients in the ongoing open-label safety studies of ataluren in nmDMD (Studies 016 and 019) are receiving the 10, 10, 20 mg/kg dose level. As of 31 January 2015, the estimated median duration of exposure was 196.6 weeks for Study 016 (N=108) and 102.4 weeks for Study 019 (N=93). Across the Phase 3, randomized, double-blinded, placebo-controlled study of ataluren in nmCF (Study 009) and its open-label extension (009e), a total of 164 nmCF patients have received ataluren 10, 10, 20 mg/kg for ≥48 weeks, including 45 patients who have received ataluren 10, 10, 20 mg/kg for ≥96 weeks. The controlled studies in nmDMD (Study 007) and nmCF (Study 009) have documented a favorable risk-benefit at the 10, 10, 20 mg/kg dose level in these indications [Bushby 2014, Kerem 2014]. In nmDMD, ataluren has been conditionally approved at a dose of 10, 10, 20 mg/kg for the treatment of nmDMD. Based on the collective clinical experience with ataluren 10, 10, 20 mg/kg, this dose level will be evaluated in patients with dystrophinopathy aged 2 to <5 years.

14.2.2. Duration of Therapy

The primary objective of this Phase 2 study is to determine whether ataluren can be safely administered as a chronic treatment for patients 2 to <5 years of age. In patients ≥6 years old, ataluren has been generally well tolerated when administered chronically for >4 years. Therefore, exposure to ataluren for 52 weeks in this study is not expected to pose undue safety risk.

14.2.3. Selection of Endpoint Measures

The proposed safety PK and PD evaluations were chosen based on relevance to the pathophysiology and clinical manifestations of the disease, and past experience that these tests can be performed with acceptable accuracy in this young patient population.

14.2.3.1. Timed Function Tests

Commonly employed over many years [Brooke 1989, McDonald 1995] TFTs are relevant to the disease in that they assess functional aspects of proximal muscle strength required for everyday activities. TFTs are substantially abnormal in boys with DMD compared to healthy boys [Beenakker 2005b]. Worsening values have been correlated with time to wheelchair dependency and these tests can be sensitive to medical intervention [Mendell 1989, Griggs 1991, Beenakker 2005b]. Given their long-standing use, there is substantial experience with the conduct of the tests, the analyses of the data, and very high reproducibility has been demonstrated [Mayhew 2007].

14.2.3.2. North Star Ambulatory Assessment

The NSAA is a functional scale specifically designed for ambulant DMD patients. The scale was developed and piloted in the United Kingdom by the North Star Clinical Network for Paediatric Neuromuscular Disease Management with good intra- and inter-observer reliability and has recently been used in a large multicenter study [Mazzone 2011]. The scale includes items assessing abilities that are necessary to remain functionally ambulant, ie, ability to rise from the floor, ability to get from lying to sitting and sitting to standing, and that are known to progressively deteriorate in untreated patients. The scale also includes items assessing head raise and standing on heels that can be partly present in the early stages of the disease and a number of activities such as hopping, jumping, and running [Mazzone 2011].

14.2.3.3. Ataluren Plasma Concentrations

Collection of blood for ataluren plasma concentration analysis is critical for evaluating exposure-safety relationships in this population. Based on the preliminary popPK simulation results, sampling pre-dose and then at 1, 2, 4, 6, 8, and 10 hours post-dose on Days 1 and 28 will provide information about single-dose and steady-state after 28-day ataluren PK parameters in this population. Additionally, the ataluren PK profile has been well characterized in existing Phase 2a and Phase 3 studies in patients with CF.

The high performance liquid chromatography with tandem mass spectrometry (HPLC/MS-MS) method that will be used to quantify ataluren plasma concentrations has been fully validated in the context of the prior Phase 1 and Phase 2 studies.

14.2.4. Safety Monitoring

In defining therapeutic activity in a particular clinical setting, it is imperative that the drug's safety profile be fully characterized. As is conventional in all clinical studies, proper description of each AE or laboratory abnormality requires an understanding of the type, incidence, timing, severity, and relatedness to study drug. In this study, particular focus will be placed on monitoring for renal adverse findings. For consistency of interpretation, AEs will be coded using the standard MedDRA, and the severity of these events will be graded using the well-defined CTCAE Version 4.0. Standard definitions for seriousness will be applied. Particular attention will be paid to any AEs causing discontinuation of ataluren and to SAEs requiring rapid regulatory reporting.

15. BENEFITS AND RISKS

15.1. Benefits and Risks: Non-Clinical

Nonclinical safety pharmacology and toxicology studies indicate that ataluren has an acceptable safety profile. The findings seen pose a low human safety risk and the program supports chronic administration of ataluren for the treatment of nmCF in patients as young as 2 years of age.

15.2. Benefits and Risks: Clinical

Multiple Phase 2 and Phase 3 trials have now shown the potential benefit and safety of ataluren in the treatment nmDMD in adults and children (details are provided in the Ataluren IB).

Decline in ambulation is the hallmark of dystrophinopathy, and the major goal of intervention during the ambulatory phase of dystrophinopathy is to maintain ambulation for as long as possible. Ataluren at a dose of 10, 10, 20 mg/kg slowed the decline in ambulation in nmDMD patients. In the placebo-controlled study, Study 007, the targeted difference of 30 meters between ataluren 10, 10, 20 mg/kg and placebo in the 6-minute walk test (6MWT) was achieved (Δ=31.3 meters). The 30-meter distance meets the threshold for minimal clinically important difference in dystrophinopathy and other diseases, and is in the range of the 6MWT results for approved therapies in a variety of conditions. The 30-meter distance is meaningful to dystrophinopathy patients, providing greater ability to walk in their daily lives, for example, walking to and from the school bus and taking part in social activities.

The time-to-event analysis of 6MWT progression further showed that ataluren 10, 10, 20 mg/kg slowed disease progression in patients with nmDMD. Only 26% of patients who received ataluren 10, 10, 20 mg/kg, compared with 44% of the patients who received placebo, had persistent 10% worsening in the 6MWT at Week 48. Delaying ambulatory decline provides direct clinical benefit by affording boys with nmDMD a longer period of self-sufficiency before transitioning to full-time wheelchair use. Maintenance of ambulatory capacity can prevent, delay the onset of, or reduce the severity of scoliosis, a debilitating complication of dystrophinopathy, and is beneficial to the patient's pulmonary status.

Positive trends in secondary endpoints in Study 007 support the 6MWT results. Patients who were treated with ataluren 10, 10, 20 mg/kg trended toward less decline in muscle function than patients who were treated with placebo and met the threshold (~1.5 seconds) for clinically meaningful differences. Among the TFTs, the largest effect for ataluren 10, 10, 20 mg/kg was seen in stair climbing, which is one of the most difficult activities of daily living for patients with dystrophinopathy. Positive trends, favoring ataluren 10, 10, 20 mg/kg over placebo were also observed for TFT method grading, accidental fall frequency, activity and wheelchair use in the community setting, myometry, and patient-reported physical functioning domain of the Pediatric Quality of Life Inventory. The consistency of these findings across outcome measures supports a treatment effect of ataluren 10, 10, 20 mg/kg in patients with nmDMD.

15.3. Benefit/Risk Conclusions

Dystrophinopathy is a disabling and life-threatening genetic disorder resulting from mutations in the gene encoding the dystrophin gene. Dystrophin dysfunction leads to multiple organ

dysfunction starting in early childhood. An urgent unmet medical need exists for a therapy that addresses the underlying cause of nmDMD, a condition with high unmet medical need. Ataluren 10, 10, 20 mg/kg represents the first potentially disease-modifying therapy for a subset of patients with this severely disabling, progressive, and ultimately fatal disease.

The collective nonclinical and clinical data provide the basis for the continued development of ataluren treatment for nmDMD. The clinical efficacy data, in addition to an overall generally favorable safety profile collected from Phase 2 and 3 clinical trials supports a positive benefit-risk profile for ataluren. Appropriate safety monitoring and laboratory evaluation, as detailed in Section 14, is incorporated in this protocol in order to minimize risk to study participants. The current trial (Study 030) is feasible and will provide additional safety, PK, efficacy, and exposure data of ataluren in young children with nmDMD.

Participants in this trial have the potential for direct benefit from treatment with ataluren, which justifies the known and potential risks. Substantial nonclinical and clinical safety experience provides appropriate risk-benefit information that supports the conduct of this study. This information is detailed in the Ataluren IB and is summarized in Section 9.8 of the IB. The potential risks (real and theoretical) have been weighed against the expected benefits for the children enrolled in the clinical trial. It is believed that the balance of risks versus expected benefits will be positive for the clinical trial.

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