CLINICAL PROTOCOL

AN OPEN-LABEL, SAFETY STUDY FOR ATALUREN (PTC124) PATIENTS WITH NONSENSE MUTATION DYSTROPHINOPATHY

PTC124-GD-016-DMD

12 NOVEMBER 2021

VERSION 7.0

PTC THERAPEUTICS, INC.
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PROTOCOL IDENTIFIERS AND STUDY PERSONNEL

Project Code	PTC124-GD
Therapeutic Area	Genetic Disorders - Duchenne Muscular Dystrophy
PTC Therapeutics Substance Identifier	Ataluren (PTC124)
IND Number	68,431
EudraCT Number	Not Applicable
Included in clinical trials.gov Database	Yes
Protocol Number	PTC124-GD-016-DMD
Protocol Version	Version 7.0
Protocol Version Date	12 November 2021
Protocol Phase	Phase 3
Protocol Title	An Open-label, Safety Study for Ataluren (PTC124) Patients with Nonsense Mutation Dystrophinopathy
PTC Clinical Lead/PTC Medical Monitor	[redacted]
PTC Biostatistician	[redacted]
PTC Study Manager	[redacted]

PTC THERAPEUTICS PROTOCOL APPROVAL SIGNATURES

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Date

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Date

The eSignature page is located on the last page.

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**

Institution: _____

Address: _____

City: _____

State/Province: _____

Country: _____

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SYNOPSIS

Name of Sponsor/Company: PTC Therapeutics		
Name of Investigational Product: Ataluren (PTC124)		
Name of Active Ingredient: Ataluren		
Protocol Number: PTC124-GD-016-DMD	**Phase:** 3	**Country:** US and Canada
Title of Study: An Open-label, Safety Study for Ataluren (PTC124) Patients with Nonsense Mutation Dystrophinopathy		
Duration of Study: Approximately 13 years		
Objectives: The objective of this study is to assess the safety and tolerability of 10, 10, and 20 mg/kg ataluren in subjects with nonsense mutation Duchenne and Becker muscular dystrophy (nmDBMD) who had prior exposure to ataluren in a PTC-sponsored clinical trial or treatment plan, and siblings of those patients (provided those patients have completed the placebo-controlled portion of the trial). **Study Design:** This study comprises an open-label, safety study of ataluren in subjects who previously received ataluren at an investigational site in a prior PTC-sponsored clinical study or treatment plan and siblings of those subjects.		
Methodology: This study will be performed at investigational sites in the US and Canada. Subjects will receive ataluren 3 times per day (TID) at respective morning, midday, and evening doses of 10, 10, and 20 mg/kg. Study assessments will be performed during screening, on the first day of ataluren dosing, and then every 12, 24, and 48 weeks as described in the Schedule of Events. For subjects from Study 048 only, study assessments will be performed and motor development will be assessed using the Peabody Developmental Motor Scale, second edition (PDMS-2) at baseline/Day 1, Week 14, and Week 28. After the Week 28 visit, study assessments will be performed every 12, 24, and 48 weeks as described in the Schedule of Events for PTC124-GD-048-DMD Subjects. **Sample Size Justification:** The sample size for this study is based on the number of subjects in previous ataluren Duchenne and Becker muscular dystrophy (DBMD) studies and is not based upon any formal statistical hypothesis.		
Number of Patients (Planned): It is planned that approximately 270 subjects will be enrolled.		
Diagnosis and Main Criteria for Inclusion: 1. Evidence of signed and dated informed consent/assent document(s) indicating that the subject (and/or his parent/legal guardian) has been informed of all pertinent aspects of the trial. ***Note: If the study candidate is considered a child under local regulation, a parent or legal guardian must provide written consent prior to initiation of study screening procedures and the study candidate may be required to provide written assent. The rules of the responsible Institutional Review Board/Independent Ethic Committee (IRB/IEC) regarding whether one or both parents must provide consent and the appropriate ages for obtaining consent and assent from the subject should be followed.***		

2. Subjects with nmDBMD and a history of exposure to ataluren in a prior PTC study or treatment plan and affected nmDBMD siblings of those subjects (provided those subjects have completed the placebo-controlled portion of the trial).
3. Male sex.
4. Fertile men, as defined in (CTFG 2020), who are sexually active with women of childbearing potential and who have not had a vasectomy, must agree to use a barrier method of birth control during the study and for up to 50 days after the last dose of study drug.
5. Willingness and ability to comply with scheduled visits, drug administration and return plan, study procedures, laboratory tests, and study restrictions. ***Note: Psychological, social, familial, or geographical factors that might preclude adequate study participation should be considered***.

Investigational Product, Dosage, and Mode of Administration:
Ataluren will be provided as white to off-white granules for oral suspension. Subjects will receive ataluren 3 times per day (TID) at respective morning, midday, and evening doses of 10, 10, and 20 mg/kg.

Duration of Treatment:
The actual duration of ataluren treatment under this protocol will be subject to the following conditions:

- The subject has the right to withdraw consent and discontinue ataluren at any time.
- The subject's condition substantially worsens after initiating ataluren treatment. In such a case, the subject will be carefully evaluated by the investigator in consultation with the PTC Therapeutics medical monitor. The subject will be withdrawn from treatment if continuing would place them at risk.
- The investigator may withdraw the subject from ataluren treatment, if, in the investigator's clinical judgment, it is not in the subject's best interest to continue or if the subject is not complying with the protocol (ie, per protocol visits, return of unused study drug).
- If the subject is unable to tolerate ataluren, he will be withdrawn from treatment.
- The subject is eligible to participate in another ataluren nmDBMD clinical trial program initiated by PTC Therapeutics.
- This study is discontinued by the relevant regulatory authority and/or PTC Therapeutics.
- Ataluren becomes commercially available.

Reference Therapy, Dosage, and Mode of Administration:
Not applicable

Criteria for Evaluation:
The safety profile of ataluren will be characterized by type, frequency, severity, timing, and relationship to ataluren of any adverse events (AEs) or laboratory abnormalities.

Statistical Methods:
The as-treated population consists of all subjects who receive at least 1 dose of ataluren. This population will be evaluated in the analyses of safety (the primary endpoint) and treatment administration.
Adverse events will be classified using the MedDRA classification system. The severity of AEs will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0 whenever possible. The frequency of subjects experiencing a specific

AE will be tabulated by visit, body system, and MedDRA term. Adverse events classified as CTCAE Grade 3 or higher; study-drug-related events; adrenal, hepatic, and renal events leading to special diagnostic evaluations; events leading to discontinuation from treatment; and SAEs will be considered with special attention.

Hematological, serum biochemistry, adrenal laboratories, and urine data and their changes (only for continuous laboratory parameters) from baseline will be summarized by visit. Hematological, serum biochemistry, adrenal laboratories, and urine data will be graded according to CTCAE severity grade when applicable. For parameters for which a CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized. Summary tables will be presented for each relevant assay to show the number of subjects by severity grade with corresponding percentages. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during the time period of interest.

Shift tables for hematology, serum biochemistry, adrenal laboratories, and urine data will also be presented showing change in CTCAE severity grade from baseline to each visit. For parameters for which a CTCAE scale does not exist, shift tables will be presented showing change in results from baseline (normal, low, and high [or abnormal]) to each visit (normal, low, and high [or abnormal]).

Physical findings (weight, physical examination data, systolic and diastolic blood pressure, radial pulse rate, and body temperature) will be listed and summarized by visit. Where appropriate, changes from baseline at each visit will be summarized and tested using the paired t-test or a nonparametric alternative.

Motor development as assessed by the PDMS-2 for subjects enrolled from PTC124-GD-048-DMD will be summarized by visit.

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialized Term	Explanation
ACE	Angiotensin converting enzyme (inhibitor)
AE	Adverse event
ARB	Angiotensin receptor blocker
ATC	Anatomical-Therapeutic-Chemical
BUN	Blood urea nitrogen
CFR	Code of Federal Regulations
cGMP	Current Good Manufacturing Practices
CHF	Congestive heart failure
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DBMD	Duchenne and Becker muscular dystrophy
DMD	Duchenne muscular dystrophy
ECG	Electrocardiogram
eCRF(s)	Electronic case report form(s)
EDC	Electronic data capture
FDA	Food and Drug Administration
FVC	Forced vital capacity
GCP	Good Clinical Practice
IB	Investigator's Brochure
ICH	International Council for Harmonisation
IRB/IEC	Institutional Review Board/Institutional Ethics Committee
IV	Intravenous
LDL	Low density lipoprotein
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
nmDBMD	Nonsense mutation Duchenne and Becker muscular dystrophy
OAT1	Organic anion transporter 1
OAT3	Organic anion transporter 3
OATP1B3	Organic anion transporting polypeptide 1B3
PDMS-2	Peabody Developmental Motor Scale, second edition
SAE	Serious adverse event
TID	Ter in die (3 times per day)
ULN	Upper limit of normal
US	United States
WHODRUG	World Health Organization Drug Dictionary

1. INTRODUCTION

1.1. Disease Background

Duchenne and Becker muscular dystrophy (DBMD) is an X-linked disorder caused by defects in the gene for dystrophin (Worton 2001, Khurana 2003). 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; 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.

DBMD usually first manifests in boys ~3 to 7 years of age when they are noted to develop 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 2018b). By 10 to 14 years of age, most are wheelchair-bound. In ambulatory Duchenne muscular dystrophy (DMD) boys, 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, Biggar 2001, Phillips 2001, Tangsrud 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).

Corticosteroids, working through unknown mechanisms, have been the only medications to demonstrate a benefit in ameliorating the manifestations of DBMD (Mendell 1989, Griggs 1991, Fenichel 1991a, Fenichel 1991b, Biggar 2001, Beenakker 2005a, Biggar 2006, Pradhan 2006). Clinical improvement, primarily measured by muscle strength testing and timed function tests (standing from supine, climbing stairs, and running 10 meters), is seen within ~2 months after starting treatment and disease progression appears to be slowed (Beenakker 2005a, Biggar 2006, Pradhan 2006). In addition, corticosteroid usage appears to slow the rate of forced vital capacity (FVC) decline, substantially reducing decreases in any 6- to 12-month period (Mendell 1989, Griggs 1991, Biggar 2001, Biggar 2006). Most boys receiving corticosteroids experience physically and socially distressing growth inhibition, interruption of pubertal changes, and disfiguring Cushingoid facies and habitus (Manzur 2008). Many boys have weight gain (which is problematic given the need to reduce muscle load-bearing). Behavioral problems, osteopenia with a high rate of fractures (Biggar 2006), gastric ulceration, rashes, glucose intolerance, and cataracts are also observed. Because chronic corticosteroid use in children with DBMD is

typically associated with serious sequelae, corticosteroids are not universally employed. No treatment is currently available to address the underlying cause of the disease by restoring the missing dystrophin in muscle.

1.2. Ataluren

Ataluren is a small molecule being developed for the treatment of nonsense mutation Duchenne muscular dystrophy (nmDMD). Ataluren promotes ribosomal readthrough of premature stop codons, enabling the formation of full-length, functional dystrophin protein (Welch 2007).

The efficacy and safety of ataluren for the treatment of nmDMD were assessed in 2 randomized, double-blind, placebo-controlled, 48-week trials (PTC124-GD-007-DMD [NCT00592553] [Study 007] and PTC124-GD-020-DMD [NCT01826487] [Study 020]). Data from these studies supported conditional marketing authorization of ataluren for the treatment of nmDMD in ambulatory patients aged ≥5 years in Europe and subsequently extended to ≥2 years of age based on pharmacokinetic extrapolation from study PTC124-GD-030-DMD.

A detailed description of the chemistry, pharmacology, efficacy, and safety of ataluren is provided in the Investigator's Brochure (IB).

1.3. Risk/Benefit Assessment

Under the current standard of care, nmDMD remains a disease with devastating consequences and bleak prognosis. The progressive and irreversible effects of nmDMD underscore the importance of early intervention with treatments that have the potential to slow physical deterioration and delay the natural course of this fatal disease. While treatment with corticosteroids target the inflammatory component of the disease, additional treatments are needed to address the loss of dystrophin, the underlying cause of the disease.

The mechanism by which ataluren restores dystrophin has been established in comprehensive preclinical studies and supported in clinical evaluations. Moreover, the clinical benefit of ataluren has been demonstrated in 2 large randomized controlled trials Study 007 and Study 020.

The unmet medical need in this devastating disease, in which there is no available therapy that addresses its underlying cause, justifies clinical treatment with this novel treatment. Given that ataluren has a favorable safety profile, the benefit-risk profile of ataluren is positive.

2. STUDY OBJECTIVE AND ENDPOINTS

The objective of this study is to assess the safety and tolerability of 10, 10, 20 mg/kg ataluren in subjects with nmDBMD who had prior exposure to ataluren in a PTC-sponsored clinical trial or treatment plan, and siblings of those patients (provided those patients have completed the placebo-controlled portion of the trial). The safety profile of ataluren will be characterized by type, frequency, severity, timing, and relationship to ataluren of any adverse events (AEs) or laboratory abnormalities.

3. STUDY DESIGN

This study comprises an open-label, safety study of ataluren in subjects who previously received ataluren at an investigational site in a prior PTC-sponsored clinical study or treatment plan and siblings of those subjects. Only subjects enrolling in the current study from PTC124-GD-048-DMD (Study 048) will have efficacy assessments (ie, Peabody Developmental Motor Scale, second edition [PDMS-2]) performed for up to 52 weeks from the date of first dosing in Study 048.

This study will be performed at investigational sites in the US and Canada. It is planned that approximately 270 subjects will be enrolled. Subjects will receive ataluren 3 times per day (TID) at respective morning, midday, and evening doses of 10 mg/kg, 10 mg/kg, and 20 mg/kg. Study assessments will be performed during screening, on the first day of ataluren dosing, and then every 12, 24, and 48 weeks as described in Table 2.

For subjects from Study 048 only, study assessments will be performed and motor development will be assessed using the PDMS-2 at baseline/Day 1, Week 14, and Week 28. After the Week 28 visit, study assessments will be performed every 12, 24, and 48 weeks as described in Table 3.

4. SUBJECT SELECTION CRITERIA

4.1. Overview

The eligibility criteria are designed to select subjects 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 subject. Eligibility criteria may not be waived by the investigator and conformance to the eligibility criteria is subject to review in the case of a Good Clinical Practice (GCP) or a regulatory authority audit. Any questions regarding a subject's eligibility should be discussed with the PTC Therapeutics medical monitor prior to enrollment.

4.2. Inclusion Criteria

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

1. Evidence of signed and dated informed consent/assent document(s) indicating that the subject (and/or his parent/legal guardian) has been informed of all pertinent aspects of the trial. ***Note: If the study candidate is considered a child under local regulation, a parent or legal guardian must provide written consent prior to initiation of study screening procedures and the study candidate may be required to provide written assent. The rules of the responsible Institutional Review Board/Independent Ethic Committee (IRB/IEC) regarding whether one or both parents must provide consent and the appropriate ages for obtaining consent and assent from the subject should be followed.***
2. Subjects with nmDBMD and a history of exposure to ataluren in a prior PTC study or treatment plan and affected nmDBMD siblings of those subjects (provided those subjects have completed the placebo-controlled portion of the trial).
3. Male sex.
4. Fertile men, as defined in (CTFG 2020), who are sexually active with women of childbearing potential and who have not had a vasectomy, must agree to use a barrier method of birth control during the study and for up to 50 days after the last dose of study drug.
5. Willingness and ability to comply with scheduled visits, drug administration and return plan, study procedures, laboratory tests, and study restrictions. ***Note: Psychological, social, familial, or geographical factors that might preclude adequate study participation should be considered***.

4.3. Exclusion Criteria

Prior to treatment with ataluren, it will be confirmed that the subject meets none of the following criteria:

1. Exposure to another investigational drug within 1 month prior to start of study treatment.
2. Eligibility for another ataluren clinical trial that is actively enrolling study participants.
3. Positive for Hepatitis B core antibody or Hepatitis C antibody at screening for ataluren-naïve subjects (siblings) or subjects who have a temporary treatment gap of 1 year before entering study.

4. Known hypersensitivity to any of the ingredients or excipients of ataluren (refined polydextrose, polyethylene glycol 3350, poloxamer 407, mannitol 25C, crospovidone XL10, hydroxyethyl cellulose, colloidal silica, magnesium stearate).
5. Ongoing intravenous (IV) aminoglycoside or IV vancomycin therapy.
6. Ongoing uncontrolled medical/surgical condition, electrocardiograph (ECG) findings, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject or make it unlikely that follow-up would be completed.

5. ENROLLMENT PROCEDURES

5.1. Source and Number of Subjects

Subjects with nmDBMD who received ataluren treatment in a prior PTC-sponsored clinical trial or treatment plan at a study site and siblings of those subjects are all potential candidates for this study. Approximately 270 subjects will be enrolled.

It is anticipated that subjects will be enrolled from investigator sites in the US and Canada.

5.2. Screening and Study Drug Allocation

The investigator must inform each prospective subject of the nature of the study, explain the potential risks, and obtain written informed consent/assent from the subject and/or the parent/legal guardian prior to performing any study related screening procedures.

All subjects will be assigned a unique subject identification number for this study. This subject number must be used for subject identification on all study related documents (case report forms [CRFs], clinic notes, laboratory samples, etc.).

Any questions regarding the eligibility of a subject should be discussed with the PTC Therapeutics medical monitor.

In addition, the user will need to supply the electronic data capture (EDC) system with the information required by the system (e.g., site number, subject number).

6. STUDY DRUG ADMINISTRATION

6.1. Investigational Product

6.1.1. Ataluren (PTC124)

Ataluren will be provided as white to off -white granules for oral suspension. The drug has been manufactured and formulated under cGMP conditions. The formulation includes matrix and suspending agents, surfactants, and various minor excipients that aid in the manufacturing process. The granules for oral suspension are packaged in aluminum-foil, child-resistant sachets (packets) and supplied in dose strengths containing 125, 250, or 1000 mg of the active drug substance. For administration, the full contents of the sachet should be mixed with at least 30 mL (1 ounce) of liquid (water, milk, fruit juice, fruit punch) or 3 tablespoons of semi-solid food (yogurt, pudding, or applesauce) and administered with food. The prepared dose should be mixed well and stirred for approximately 30 to 60 seconds before administration. The amount of the liquid can be increased based on subject preference.

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

The clinic staff will instruct each subject or parent/caregiver or legal guardian on the specific number of sachets to be taken for each dose and will provide detailed oral directions regarding drug preparation. In addition, detailed written drug mixing and dosing instructions will be provided to the subject or parent/caregiver or legal guardian when drug supplies are dispensed.

6.1.2. Drug Source

Ataluren will be supplied free of charge and dispensed directly to subjects or parent(s)/legal guardian(s), as appropriate. Distribution of ataluren directly to the subject or parent(s)/legal guardian(s) will be coordinated through the clinical site or designated study pharmacy, where approved. It is intended that ataluren will be provided in sufficient supply for a 12-week study period. However, in the event of pending commercial availability of ataluren, drug may be supplied for a treatment period of less than 12-weeks.

6.1.3. Study Drug Packaging and Labeling

Sachets will be color coded to indicate dosage strength (125 mg- yellow, 250 mg- pink, 1000 mg- blue). 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.

6.1.4. Study Drug Dispensing

Dosing of ataluren will be based on milligrams of drug per kilogram of subject body weight at screening/baseline (Visit 1) and will be adjusted to allow for dosing (as shown in Table 2 and Table 3) with the available sachet dose strengths. A form (CRF) containing pertinent information for the subject's ataluren dispensing will be provided to the designated study pharmacy by the clinical site staff.

The designated study pharmacy (e.g., central pharmacy, pharmacist or other qualified person) will be responsible for dispensing study drug according to the Investigator's directions. The clinical site staff will contact the subject or parent(s)/caregiver(s) or legal guardian(s) to confirm availability to receive study drug shipment, including confirmation of receipt of study drug. Sufficient study drug will be provided for each study period at the beginning of the period.

Depending upon the magnitude of change in subject body weight since baseline, the number and type of sachets to be used by the subject may remain the same or may be adjusted.

6.1.5. Return of Study Drug

Subjects or parent(s)/caregiver(s) or legal guardian(s) should return all used and unused cartons and unused sachets of ataluren as instructed. Study drug dispensing to the subjects and the return of any unused study drug for compliance assessments will be documented.

6.1.6. Storage and Stability

Sachets containing ataluren will be shipped and stored 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.

6.1.7. Study Drug Accountability

Study drug must not be used outside the context of this clinical trial.

The investigator/site personnel and/or designated study pharmacy must maintain accurate records of the receipt of all ataluren shipped by the designated study pharmacy, including, but not limited to, the date received, lot number, amount received, amount returned, and the disposition of all study drug. Current reconciliation and dispensing records must also be maintained that include the date and, relevant lot number and number of cartons and sachets dispensed, and number of unused cartons and sachets returned, and subject's assigned study number.

Study drug must be returned to PTC Therapeutics designee, except where sites are required to destroy study drug per their local standard operating procedures.

6.1.8. Overdose Precautions

For any subject experiencing an overdose (administration of an ataluren dose >4 times the highest intended total daily dose level for this protocol [>160 mg/kg/day]), 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 nor contraindicated.

The PTC Therapeutics medical monitor should be contacted if an overdose occurs. Under applicable regulations, overdosing may be considered a serious adverse event (SAE) and should be reported accordingly (see Section 8.9).

6.1.9. Inadvertent Exposure and Spill Precautions

Reference can be made to the current ataluren IB for information on inadvertent exposures and spill precautions.

6.2. Study Drug Treatment

6.2.1. Duration of Therapy

The actual duration of ataluren treatment under this protocol will be subject to the following conditions:

- The subject has the right to withdraw consent and discontinue ataluren at any time.
- The subject's condition substantially worsens after initiating ataluren treatment. In such a case, the subject will be carefully evaluated by the investigator in consultation with the PTC Therapeutics medical monitor. The subject will be withdrawn from treatment if continuing would place them at risk.
- The investigator may withdraw the subject from ataluren treatment, if, in the investigator's clinical judgment, it is not in the subject's best interest to continue or if the subject is not complying with the protocol (ie, per protocol visits, return of unused study drug).
- If the subject is unable to tolerate ataluren, he will be withdrawn from treatment.
- The subject is eligible to participate in another ataluren nmDBMD clinical trial program initiated by PTC Therapeutics.
- This study is discontinued by the relevant regulatory authority and/or PTC Therapeutics.
- Ataluren becomes commercially available.

6.2.2. Schedule of Administration

Three doses should be taken per day - the first dose in the morning (10 mg/kg), the second dose during the middle of the day (mid-day - 10 mg/kg), and the third dose in the evening (20 mg/kg). It is suggested that each dose should be taken within ~30 minutes after a meal.

6.2.3. Instructions for Delays in Dosing

If a subject experiences a delay in the administration of ataluren of ≤1 hour, the planned dose should be taken with no changes to the subsequent dose schedules. For a subject who has a delay of >1 hour but ≤4 hours, the planned dose should be taken; however, all future doses for that day should be shifted later by an approximately corresponding amount. For a subject who has a delay in administration of ataluren of >4 hours, the dose should not be taken. Ataluren administration may continue but the missed dose should not be made up and the planned timing of subsequent ataluren dosing should not be altered.

6.2.4. Study Drug Preparation and Storage

For administration, the full contents of the sachet should be mixed with at least 30 mL (1 ounce) of liquid (water, milk, fruit juice, fruit punch) or 3 tablespoons of semi-solid food (yogurt, pudding, or applesauce) and administered with food. The prepared dose should be mixed well and stirred for approximately 30 to 60 seconds before administration. The amount of the liquid can be increased based on subject preference.

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

The clinic staff will instruct each subject or parent/caregiver or legal guardian on the specific number of sachets to be taken for each dose and will provide detailed oral directions regarding drug preparation. In addition, detailed written drug mixing and dosing instructions will be provided to the subject or parent/caregiver or legal guardian when drug supplies are dispensed.

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

Subjects must be monitored closely for AEs or laboratory abnormalities during the course of the study. Monitoring and capturing of AEs will be conducted approximately every 12 weeks through phone conversations (post-drug dispensing) or through visits to site.

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 ataluren 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 5 (see https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf) for grading the severity of AEs and laboratory abnormalities.

If the subject experiences a dose-limiting AE related to ataluren, then drug administration can be paused, as necessary, until the AE resolves or stabilizes to an acceptable degree. If further evaluation reveals that the AE is not related to ataluren, treatment will be continued at the original dose level. The PTC Therapeutics Pharmacovigilance Department will be notified of any SAE or any AE that leads to dose reduction or treatment discontinuation.

Cases of decreased renal function have been observed in patients with nonsense mutation cystic fibrosis (nmCF) receiving ataluren and intravenous aminoglycosides together with other antibiotics for cystic fibrosis exacerbations (Section 6.4.1). As a precaution, Table 1 provides information on actions to be taken in the event that abnormalities are noted in specified renal laboratory parameters. Thresholds are provided for interrupting study drug immediately or for interrupting study drug after confirmation of a value beyond the threshold. For AEs or laboratory abnormalities not listed in Table 1, the investigator should use his/her judgment in determining whether the event or abnormality is clinically significant, whether diagnostic evaluation is warranted, and whether potential interruption of study drug 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 (Grade 2 events) may also be considered clinically significant in certain circumstances.

Table 1: Renal Monitoring Parameters and Actions To Be Taken

Laboratory Parameter	Stop Study Drug Immediately, Confirm Abnormal Value, and Then Start Work-Up	Stop Study Drug After Confirming[a] Abnormal Value, and Then Start Work-Up
Serum cystatin C	>2.00 mg/L	>1.33-2.00 mg/L
Serum creatinine	≥ Grade 2 (≥1.5 x ULN for age)	Grade 1 (>ULN - 1.5 x ULN for age)
Serum BUN	≥3.0 x ULN	≥1.5-3.0 x ULN

Abbreviations: BUN, blood urea nitrogen; ULN, upper limit of normal
[a]Laboratory abnormalities may be confirmed immediately or at the next scheduled clinic visit based on investigator judgment.

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 the medical monitor to obtain guidance and to ascertain whether similar events are being seen at other 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, endocrinology, or nephrology consultants or with other experts (either at the site or retained by PTC Therapeutics).

Clinical evaluations for potential renal toxicities may include the following:

Renal: The medical history, baseline ultrasound data, 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, concentrating ability, or other renal functions; CT, MRI, or other imaging methods; and/or renal biopsy.

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

When deciding whether to reinstitute therapy after a dose interruption for any clinically significant safety concern, the investigator should consider factors as the following:

- Type and severity of the AE or laboratory abnormality,
- The potential causal relationship of ataluren therapy,
- The subject's status in terms of DBMD or other health conditions,
- The ability to monitor for recurrence of the event.

If further evaluation reveals that the AE that led to dose interruption was not related to the study drug, study drug may be restarted.

If the subject experiences a recurrence of a previous abnormality that led to study drug dose interruption or experiences the new occurrence of an unacceptable AE or laboratory abnormality, the investigator should interrupt study drug and confer with the PTC Therapeutics medical monitor or designee regarding the potential need to discontinue study drug permanently.

6.4. Concomitant and Supportive Therapy

Other than ataluren, any treatments (including prescription and non-prescription drugs, health foods, herbal remedies, self-prescribed drugs, street drug, tobacco products, or alcohol) that are taken by a subject during the screening period, during ataluren administration, and for 6 weeks after discontinuation of ataluren are considered concomitant medications. Information regarding any concomitant medications will be collected and documented in the concomitant medication CRF page and in the source documents by the clinic staff.

6.4.1. Aminoglycosides

Renal abnormalities were observed in an international, multicenter, double-blind, placebo-controlled Phase 3 trial evaluating ataluren in subjects ≥6 years of age with nonsense mutation cystic fibrosis in subjects receiving concomitant ataluren and IV aminoglycosides (as described in the ataluren IB). In subjects who require treatment for serious infections, investigators should substitute other antibiotics for systemic aminoglycosides when clinically appropriate.

If IV aminoglycosides or other nephrotoxic antibiotics (e.g., vancomycin) are administered, study drug must be interrupted during the course of these antibiotics. Subjects requiring IV aminoglycoside or vancomycin therapy should be closely monitored in an appropriate setting. In subjects receiving potentially nephrotoxic antibiotics such as IV aminoglycosides or vancomycin, antibiotic drug levels and serum creatinine and BUN should be followed closely. The antibiotic trough level and creatinine and BUN should be measured within 24 to 48 hours of administration of the first antibiotic dose, and further antibiotic dosing should be based on these results. Trough levels should be measured at intervals during the course of antibiotic treatment. Creatinine and BUN should be measured prior to initiating IV aminoglycoside or vancomycin therapy and at least twice a week during the course of antibiotic treatment.

6.4.2. Hydration

Because of the potential risk of renal dysfunction during periods of dehydration in subjects receiving ataluren, it is important to encourage study subjects to maintain adequate hydration throughout the study. Subjects should be adequately hydrated prior to receiving potentially nephrotoxic antibiotics such as aminoglycosides or vancomycin, and hydration status should be carefully monitored throughout the administration of these agents. Investigators should be particularly vigilant with subjects experiencing nausea, vomiting, diarrhea, or fever, or who have laboratory evidence of dehydration.

6.4.3. Cardiac Drugs for CHF Prophylaxis/Treatment

Cardiac drugs (e.g., ACE inhibitors, ARBs, beta-blockers, etc.) may be used in the treatment of CHF in nonambulatory subjects with DMD and may increasingly be considered for use as prophylaxis against symptomatic cardiac dysfunction in younger boys with the disease (Bosser 2004, American Academy of Pediatrics 2005, Duboc 2005, Kajimoto 2006, Ramaciotti 2006).

Subjects who require initiation, interruption, dose modification, or reinstitution of CHF prophylaxis/treatment may continue ataluren dosing.

Potential Drug Interactions

Based on in vitro studies, ataluren is a substrate of UGT1A9. Coadministration of rifampicin, a strong inducer of metabolic enzymes including UGT1A9, decreased ataluren exposure by 29%. The significance of these findings for humans is unknown. Caution should be exercised when ataluren is coadministered with medicinal products that are inducers of UGT1A9 (e.g., rifampicin).

Based on in vitro studies, ataluren has the potential to inhibit UGT1A9, organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3), and organic anion transporting polypeptide 1B3 (OATP1B3). Coadministration with mycophenolate mofetil in healthy subjects did not affect the exposure of its active metabolite, mycophenolic acid (a substrate of UGT1A9). No dose adjustment is required when ataluren is coadministered with medicinal products that are substrates of UGT1A9 (e.g., propofol, mycophenolate mofetil).

In a clinical study to evaluate the potential for ataluren to inhibit the OATP1B3 transport system using a single-dose of 80 mg telmisartan, an in vitro selective OATP1B3 substrate, ataluren increased the exposure to telmisartan by 28%. This effect is considered clinically not relevant. However, the magnitude of this effect could be larger for the 40 mg dose of telmisartan. Caution should be exercised when ataluren is coadministered with medicinal products that are substrates of OAT1 or OATP1B3 because of the risk of increased concentration of these medicinal products (e.g., oseltamivir, acyclovir, captopril, furosemide, bumetanide, valsartan, pravastatin, rosuvastatin, atorvastatin, pitavastatin).

Caution should also be exercised when ataluren is coadministered with OAT3 substrates (e.g., ciprofloxacin), especially those OAT3 substrates with a narrow therapeutic window. In a clinical study, the extent of exposure for ciprofloxacin was 32% higher in the presence of ataluren. In a separate clinical study, the extent of exposure for adefovir was 60% higher in the presence of ataluren. Caution should be exercised when ataluren is co-administered with adefovir.

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

Coadministration of corticosteroids (deflazacort, prednisone, or prednisolone) with ataluren did not affect the plasma concentrations of ataluren. No clinically relevant change in the plasma concentrations of corticosteroids was seen with coadministration of ataluren. These data indicate no apparent drug-drug interaction between corticosteroids and ataluren, and no dose adjustments are required.

6.4.4. Other Concomitant Medications

To the extent possible, administration of any prescription or over-the-counter drug products other than study medication should be minimized during the study period. Subjects should be discouraged from use of "health supplements" (e.g., creatine, glutamine, coenzyme Q), herbal remedies, self-prescribed drugs, street drugs, tobacco products, or alcohol at any time during clinical studies of ataluren.

If considered necessary for the subject'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 drug other than ataluren should take into account subject 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.

Subjects should be instructed about the importance of the need to inform the clinic staff of the use of any drugs or remedies (whether prescribed, over-the-counter, or illicit) before and during the course of the study. Any concomitant drugs taken by a subject during the course of the study and the reason for use will be recorded in the source documents and in the CRFs.

6.5. Physical and Respiratory Therapy

There are neither restrictions nor prescriptions for physical or respiratory therapy during the study. Sites should use local best practices in providing physical therapy support for subjects participating in the study. Respiratory care guidelines as suggested by the American Thoracic Society should be followed (Finder 2004).

6.6. Dietary Restrictions

There are no specific dietary restrictions in the study.

7. SCHEDULE OF EVENTS AND STUDY PARAMETERS

7.1. Schedule of Events

Study assessments will be performed as described in Table 2 and Table 3. Please see Section 7.2 for detailed explanations of the study procedures and data collection identified in the tables.

Table 2 includes the schedule of events for all subjects enrolled in the current study, except for those subjects who enrolled in the current study following completion of Study 048, for whom the schedule of events is included in Table 3.

Table 2: Schedule of Events

Study Period	**Screening**	**Baseline**	**Treatment**				**6 Weeks Post D/C**
Study Week (±7 Days)	**Day 1[a]**	**Day 1[a]**	**Every 12 Weeks**	**Every 24 Weeks**	**Every 48 Weeks[b]**	**End of TX**	
Informed consent[c]	X	X					
Clinical history[d]	X	X					
Vital signs	X				X	X	X
Height	X						
Weight	X	X		X[e]	X	X	X
Physical examination	X						
Hepatitis B and C[f]	X						
Hematology	X				X	X	X
Biochemistry	X				X	X	X
Drug dispensed		X	X[g]	X[g]	X[g]		
Pre-/post-shipment communication			X[h]	X[h]	X[h]		
Drug compliance			X[i]	X[i]	X[i]	X	
Adverse events	X	X	X[j]	X[j]	X[j]	X	X
Concomitant medication	X	X	X[j]	X[j]	X[j]	X	X

Abbreviations: D/C, discontinuation; TX, treatment

[a] Subjects who have not participated in an ataluren study in the past year are required to complete all assessments identified under screening. Subjects who have participated in an ataluren study within the past year only need to compete the assessments identified under baseline.

[b] Annual visits will occur every 48 weeks (ie, Weeks 48, 96, 144, 192, 240, 288, 336, 384, 432, 480, 528, 576, 624, 672, 720, etc).

[c] Informed consent will be signed before any study procedures are performed.

[d] Clinical history will be collected for ataluren-naïve subjects (siblings). For subjects enrolling from another ataluren clinical study, only clinical history reported since the last dose of ataluren in the prior DBMD study will be collected.

[e] Reminders will be communicated prior to every 24 week visit for subject to obtain a weight check-in between the annual visits at sites. This communication will be documented in the source.

[f] Hepatitis B and C testing is only required for ataluren-naïve subjects (siblings) or subjects who have a temporary treatment gap of 1 year before entering Study 016.

[g] Drug will be dispensed to the subject every 12 weeks.

[h] Clinical site staff will contact the subject or parent(s)/legal guardian(s) to confirm details and timing of the upcoming study drug shipment. Post-shipment contact will confirm receipt of and condition of study drug.

[i] Subjects or parent(s)/caregiver(s) or legal guardian(s) should return all used and unused cartons and unused sachets of ataluren as instructed in order to assess study drug compliance.

[j] Clinical site staff will contact subject or parent(s)/legal guardian(s) every 12 weeks (by phone, email, or text if there is no clinic visit) to assess adverse events and concomitant medications.

Table 3: Schedule of Events for PTC124-GD-048-DMD Subjects

Study Period	**Scr/Baseline**	**Treatment**						**6 Weeks Post D/C**
Study Week (±7 Days)	**Day 1[a]**	**Week 14[b]**	**Week 28[b]**	**Week 40 Through End of TX**				
				Every 12 Weeks[c]	**Every 24 Weeks[c]**	**Every 48 Weeks[c]**	**End of TX**	
Informed consent[d]	X							
Clinical history[e]	X							
Vital signs	X		X			X	X	X
Height	X	X	X					
Weight	X	X	X		X[f]	X	X	X
Physical examination	X							
Hepatitis B and C[g]	X							
Hematology		X	X			X	X	X
Biochemistry		X	X			X	X	X
Drug dispensed	X	X[h]	X[h]	X[i]	X[i]	X[i]		
Pre-/post-shipment communication		X		X[j]	X[j]	X[j]		
Drug compliance	X	X	X	X[k]	X[k]	X[k]	X	
Adverse events	X	X	X	X[l]	X[l]	X[l]	X	X
Concomitant medication	X	X	X	X[l]	X[l]	X[l]	X	X
PDMS-2	X	X	X					

Abbreviations: D/C, discontinuation; PDMS-2, Peabody Developmental Motor Scale, second edition; Scr, screening; TX, treatment

[a] Screening/baseline (Day 1) of the current study may be the same day as visit 5 (Week 24) in Study PTC124-GD-048-DMD, in which case, corresponding assessments in the two studies do not need to be repeated.

[b] Weeks 14 and 28 of the current study represent 38 and 52 weeks, respectively, of ataluren treatment for these Study 048 subjects.

[c] After the Week 28 visit, assessments will be conducted as outlined in the table every 12 weeks, every 24 weeks, and every 48 weeks. These visits will be anchored by the visit date for Week 28. The visit following Week 28 should be the first every 12 week visit at approximately Week 40 post-enrollment. Annual visits will occur every 48 weeks (ie, Weeks 76, 124, 172, etc).

[d] Informed consent will be signed before any study procedures are performed.

[e] Clinical history reported since the last dose of ataluren in Study 048 will be collected.

[f] Reminders will be communicated prior to every 24 week visit for subject to obtain a weight check-in between the annual visits at sites. This communication will be documented in the source.

[g] Hepatitis B and C testing is only required for ataluren-naïve subjects (siblings) or subjects who have a temporary treatment gap of 1 year before entering Study 016.

[h] Drug will be dispensed manually at the Week 14 and Week 28 visits.

[i] After the Week 28 visit, drug will be dispensed to the subject every 12 weeks.

[j] Clinical site staff will contact the subject or parent(s)/legal guardian(s) to confirm details and timing of the upcoming study drug shipment. Post-shipment contact will confirm receipt of and condition of study drug.

[k] Subjects or parent(s)/caregiver(s) or legal guardian(s) should return all used and unused cartons and unused sachets of ataluren as instructed in order to assess study drug compliance.

[l] Clinical site staff will contact subject or parent(s)/legal guardian(s) every 12 weeks (by phone, email, or text if there is no clinic visit) to assess adverse events and concomitant medications.

7.2. Explanation of Study Procedures

7.2.1. Study Periods

7.2.1.1. Screening/Baseline Period

Study related-procedures and data collection may only be performed once the informed consent/assent document(s) have been reviewed and signatures have been obtained. Thereafter, study candidates may undergo screening/baseline procedures as noted in the Schedule of Events (Section 7.1).

Subjects who have not participated in an ataluren study in the past 1 year are required to complete screening assessments identified in Table 2. Once the investigator has confirmed eligibility, ataluren may be initiated. Baseline procedures (weight, adverse events, and concomitant medications) do not need to be performed for these subjects.

Subjects who have participated in an ataluren study within the past 1 year are not required to complete screening assessments. Subjects will either complete the baseline visit in Table 2 or Table 3 based on previous study participation. Baseline assessments must be completed within 7 days of initiation of ataluren treatment.

The subject will remain at the clinic following the completion of screening or baseline assessments until the subject/caregiver has been instructed regarding study drug storage, compliance, and administration.

7.2.1.2. Treatment Visits during Study

Study visits will occur every 12 weeks, 24 weeks, and 48 weeks during the treatment period. The subject is required to complete a visit at the clinical research facility every 48 weeks. Every 24 weeks, the subject is required to have a weight check. A study drug shipment will be sent to the subject/caregiver's home every 12 weeks. Clinical site staff will contact the subject (pre-and post-study drug dispensing) to notify of upcoming study drug shipment and to confirm study drug receipt. Phone conversations will be conducted to monitor and capture AEs and use of concomitant medications.

Subjects previously enrolled in PTC124-GD-048-DMD will complete 2 additional visits as indicated in Table 3. Subjects will report to the clinical research facility for a Week 14 and Week 28 visit. After the Week 28 visit, study visits will follow the 12 weeks, 24 weeks, and 48 weeks schedule.

7.2.1.3. End of Treatment

The study duration is contingent upon the conditions noted in Section 6.2.1. Upon discontinuation of ataluren treatment, each subject will return to the clinical research facility for an End-of-Treatment Visit.

7.2.1.4. Post-Treatment Visits

All subjects who discontinue ataluren must return to the clinical research facility for a Post-Treatment Visit 6 weeks (±7 days) after the last dose of ataluren for final study-related evaluations. If the End-of-Treatment Visit occurs >6 weeks after the last dose of ataluren, the Post-Treatment Visit does not need to be performed.

7.2.2. Study Assessments

7.2.2.1. Informed Consent

The investigator or sub-investigator must inform each prospective subject of the nature of the study, explain the potential risks, and obtain written informed consent/assent from the subject and/or the parent/legal guardian prior to performing any study-related screening procedures. Subjects will be reconsented with the appropriate age-related documents as needed, if required by local regulations.

7.2.2.2. Clinical/Medication History

The investigator should review the study candidate's clinical history, including details relating to DBMD (ie, history of genotype confirmation and phenotype presentation, if any) and any other medical conditions, as well as any surgical or medical treatment. Information regarding current medications must be captured on the concomitant medication CRF.

7.2.2.3. Hepatitis Screen

Tests include hepatitis A antibody, hepatitis B core antibody, and hepatitis C antibody. The Laboratory Manual should be consulted for collection, processing, and shipping details. Note: Only hepatitis B and C results are required for eligibility determination. Testing is only required for ataluren-naïve subjects (siblings) or subjects who have a temporary treatment gap of 1 year before entering the current study.

7.2.2.4. Vital Signs

Vital signs (including systolic and diastolic blood pressure, pulse rate, and body temperature) will be monitored as per the schedule of events (Table 2 and Table 3). The pulse rate and blood pressure determinations will be performed with the subject in a sitting position after a 5 minute rest.

7.2.2.5. Height, Weight and Physical Examination

Standing height (in cm) will be measured at as per the schedule of events (Table 2 and Table 3).

For nonambulatory subjects, due to the difficulty in obtaining an accurate standing height measurement, ulna length and arm span will be used as a surrogate measure for height (see Study Manual). Ulna length and arm span (in cm) will be measured at screening/baseline.

Weight (in kg) will be measured as per the schedule of events (Table 2 and Table 3). As noted in Table 2 and Table 3, when not at the clinical site, the subjects will be reminded to obtain their weight.

A full physical examination (including evaluation of cardiovascular system, chest and lungs, thyroid, abdomen, nervous system, skin and mucosae, musculoskeletal system, eyes, ears, nose, mouth, throat, spine, lymph nodes, extremities, and genitourinary) will be conducted as per the schedule of events (Table 2 and Table 3).

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

7.2.2.6. Hematology Laboratory Assessment

Hematology laboratory assessments will include white blood cell count with differential, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, total red cell count with morphology, and platelet count. These parameters will be measured as per the schedule of events (Table 2 and Table 3). Hematology parameters will be analyzed by the central laboratory. The Laboratory Manual should be consulted for collection, processing, and shipping details.

7.2.2.7. Serum Biochemistry Laboratory Assessment

Biochemistry laboratory assessments will include blood urea nitrogen, creatinine, cystatin C, total cholesterol, high density lipoprotein, low density lipoprotein (LDL) and triglycerides. These parameters will be measured as per the schedule of events (Table 2 and Table 3). Subjects should have fasted for at least 8 hours prior to blood collection. Biochemistry parameters will be analyzed by the central laboratory. The Laboratory Manual should be consulted for collection, processing, and shipping details.

7.2.2.8. Peabody Developmental Motor Scale, Second Edition (Study 048 subjects only)

The PDMS-2 is a validated instrument used to measure motor skills and developmental milestone achievement in infants and children (Folio 2000).

The PDMS-2 will only be performed in subjects entering the study from PTC124-GD-048-DMD (Study 048).

The PDMS-2 will be performed at the site as per the schedule of events (Table 3). Please see the study reference manual for detailed instructions.

The PDMS-2 score sheet is provided in Appendix 1.

7.2.2.9. Study Drug Administration

Subjects should take ataluren TID as described in Section 6.2. Ataluren will be supplied as per the schedule of events (Table 2 and Table 3).

The amount of study drug supplied to the subject may be altered in the event of pending commercial availability or other reasons as noted in Section 6.2.

Because of potential changes in subject body weight over time, a site representative should enter the subject's current body weight into the EDC system to obtain study drug dosing instructions.

7.2.2.10. Study Drug Compliance

Ataluren compliance will be assessed by the clinical site throughout the study.

Subjects or parent(s)/caregiver(s) or legal guardian(s) should return all used and unused cartons and unused sachets of ataluren as instructed in order to assess study drug compliance.

7.2.2.11. Adverse Events

Adverse events will be assessed and documented as per the schedule of events (Table 2 and Table 3). This information will be collected at all visits. In addition, subjects/caregivers will be encouraged to report AEs of concern at any time.

In addition, AEs should be evaluated after the Post-Treatment Visit (6 weeks post discontinuation of ataluren) until any drug-related AEs and/or ongoing SAEs have resolved or become stable, whichever occurs later.

7.2.2.12. Concomitant Medications

Information regarding any concomitant medications administered, as well as information regarding all non-drug therapies, will be collected throughout the study, as per the schedule of events (Table 2 and Table 3).

8. ADVERSE EVENT ASSESSMENTS

8.1. Adverse Event Definitions

8.1.1. 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 subject who is administered ataluren in this study.

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

- All AEs during the course of treatment with ataluren.
- All AEs resulting from medication misuse, abuse, withdrawal or overdose of ataluren.
- All AEs resulting from medication errors such as dispensing or administration error outside of what is described in the protocol.
- 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.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Laboratory or ECG 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 (e.g., elevated liver enzymes in a subject 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 preexisting condition (e.g., allergic rhinitis) must be noted on the appropriate CRF 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 occurs during the treatment with study drug should be reported as the AE and the resulting appendectomy should be recorded in the source documents and CRF. 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 8.1.2, 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.

8.1.2. Serious Adverse Events

An AE, which results in one of the following:

- Results in death (i.e., all deaths on treatment or within 6 weeks after last ataluren administration), including deaths due to progression of DBMD. Any death occurring later than 6 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.
- Is life-threatening. This refers to an event in which the subject was at risk of death at the time of the event. It does not include an event that, had it occurred in a more severe form, might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospitalizations for administration of ataluren, procedures required by the study protocol, or DBMD-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 subject to the hospital and observational durations in the emergency room for less than 24 hours do not fall into this category.
- Results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, not related to DBMD.
- Important medical event: These are AEs that might not be immediately life-threatening or results in death or hospitalization but might jeopardize the subjects or might require intervention to prevent one of the other outcomes listed above. Medical judgment should be exercised in deciding whether an AE is serious based on above definition. Examples of such events are intensive treatment in an emergency room or at a home for allergic bronchospasm blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All SAEs that occur after any subject has been consented must be recorded on the CRF.

8.1.3. Unexpected Adverse Events

Unexpected AEs are those events that are not consistent with the Reference Safety Information (RSI) for the medicinal product, or the nature, severity, or outcome of which is not consistent with the expected events as per the RSI. For ataluren, the RSI is the Table of Adverse Reactions in Section 4.8 of the SmPC

A copy of the SmPC (version dated 17 June 2021) is included in the current protocol in Appendix A.

8.2. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject or parent/guardian in case of a child. In addition, each study subject will be questioned about AEs at each scheduled clinic visit after ataluren administration or during each

telephone contact with the subject or parent/guardian in case of a child. The type of question asked should be open-ended, e.g., *"How has your child been feeling?"* or a similar type of query.

8.3. Adverse Event Recording

All AEs (both serious and non-serious) that occur in subjects during the AE reporting period must be recorded, whether or not the event is considered drug related. All AEs are to be recorded in the source documents and the CRF 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 8.1)
- Relationship to ataluren (see Section 8.4)
- Severity of the event (see Section 8.5)
- 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.

8.4. Describing Adverse Event Relationship to Study Drug

Based on the considerations outlined in Table 4 below, the investigator should provide an assessment of the relationship of the AE to the study drug, i.e., whether there is a reasonable possibility that the study drug caused the AE.

Table 4: 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 re-challenge 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 re-challenge 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 adverse event than study drug. Such alternatives include a concomitantly administered drug, the subject'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 re-challenge, and/or presence of alternative explanations for the event. Alternative explanations might include a known relationship of the adverse event to a concomitant drug, past medical history of a similar event, the subject's disease state, other medical conditions, or environmental factors.

8.5. Grading of Severity of Adverse Events

The severity of AEs will be graded using the CTCAE, Version 5.0 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8.5x11.pdf). 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 5.

Table 5: 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 subject'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 affect 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. Severe 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 8.1 above.

8.6. Follow-up of Unresolved Adverse Events

All AE 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 medical monitor should be informed via e-mail. A subject 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 subject has discontinued from the study, and additional investigations may be requested by the medical monitoring team.

8.7. Adverse Event Reporting Period

The first day of AE reporting will coincide with the day the informed consent is signed. The AE reporting period for this study ends 6 weeks after the last administration of the ataluren.

8.8. Site Adverse Event Reporting Requirements

Classification of an event as serious or non-serious (see Section 8.1) determines the reporting procedures to be followed. Site reporting requirements for AEs are summarized in Table 6 below.

Table 6: Site Reporting Requirements for Adverse Events

Event	Recorded on the eCRF	Reported on the SAE/Pregnancy Report Form to PTC Pharmacovigilance Within 24 Hours of Awareness
Serious AE	All	All
Non-Serious AE	All	None
Other, eg, paternal exposure before/during pregnancy, or occupational exposure	All (regardless of whether associated with an AE), except occupational exposure	All (regardless of whether associated with an AE)

Abbreviations: AE, adverse event; eCRF, electronic case report form; SAE, serious adverse event

8.9. Serious Adverse Event Reporting

All SAEs should be reported via the SAE form to PTC Therapeutics within 24 hours of becoming aware of the event(s).

In addition to completing the AE portion of the CRF, 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 (e.g., the study coordinator). The SAE report form must be emailed or faxed to the PTC Therapeutics Pharmacovigilance Department 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 emailed or faxed to these same parties. All follow up SAE report forms for the event must be signed by the investigator. Any source documents (e.g., progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries) should be redacted so that the subject's name, address, and other personal identity information are obscured. Only the subject's study number and initials are to be provided. The information in the AE portion of the CRF 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 subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and to document his/her first awareness of the AE.

The PTC Therapeutics contact information for reporting SAEs is listed below and is also provided in the Study Manual and in the SAE report form.

PTC Therapeutics Safety Department
Attention: Pharmacovigilance
E-mail: Pharmacovigilance@ptcbio.com
Facsimile: 1 (908) 325-0355

8.10. Reporting Pregnancy

PTC Therapeutics should be notified in the event that a female partner of a subject becomes pregnant at any time after the subject's first dose of study drug. Any such pregnancy occurring on study or within 30 days of the last administration of study drug must be reported on a Pregnancy Notification Form. This must be done whether or not an AE has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of birth or pregnancy termination.

Written consent is required prior to collecting and reporting any information on a female partner of a subject.

If possible, the investigator should follow the pregnant female partner of the subject until completion of the pregnancy and notify the PTC Therapeutics medical monitor of the outcome within 5 days or as specified below. The investigator will provide this information as a follow--up to the initial Pregnancy Notification Form via the Pregnancy Outcome Form (see Study Manual for details).

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator should follow the procedures for reporting SAEs, i.e., report the event to the PTC Therapeutics Safety Department or designee and follow up by submission of appropriate AE CRFs.

8.11. PTC Therapeutics Adverse Event Reporting Requirements

As the sponsor of the study, PTC Therapeutics is responsible for reporting certain safety information, particularly SAEs and subject 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 will contact each investigator 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 (e.g., within 15 days) after the earliest date PTC Therapeutics or an agent of PTC Therapeutics (e.g., 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.

9. WITHDRAWAL OF SUBJECTS

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

- The subject has the right to withdraw consent and discontinue ataluren at any time.
- If the subject's condition substantially worsens after initiating ataluren treatment, the subject will be carefully evaluated by the investigator. The subject will be withdrawn from treatment if continuing would place them at risk.
- The investigator may withdraw the subject from ataluren treatment, if, in the investigator's clinical judgment, it is not in the subject's best interest to continue or if the subject is not complying with the protocol (ie, per protocol visits, return of unused study drug).
- If the subject is unable to tolerate ataluren, he will be withdrawn from treatment.
- The subject is eligible to participate in another ataluren - nmDBMD clinical trial program initiated by PTC Therapeutics.
- The relevant regulatory authority and/or PTC Therapeutics may discontinue the study at any time.
- The study will be stopped once ataluren becomes commercially available.

The date the subject is withdrawn from the study and the reason for discontinuation will be recorded in the source documents and in the CRFs. The PTC medical monitor should be informed via e-mail of when a subject is withdrawn from the study.

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

10. STATISTICS AND DATA MANAGEMENT

10.1. Sample Size Calculation for the Primary Endpoint

The sample size for this study is based on the number of subjects in previous ataluren DBMD studies and is not based upon any formal statistical hypothesis.

10.2. Study Population Definition

10.2.1. As-Treated Population

The as-treated population consists of all subjects who receive at least 1 dose of ataluren. This population will be evaluated in the analyses of safety (the primary endpoint) and treatment administration.

10.3. General Statistical Considerations

By-subject listings will be created for each CRF module.

Summary tables for continuous variables, overall and by corticosteroid use, will contain the following statistics: n, mean, standard deviation, standard error, 95% confidence intervals on the mean, median, minimum, and maximum. In addition, changes from baseline will be likewise summarized. If continuous data have substantial non-normality, log-transformed data or nonparametric tests may be employed, as appropriate.

Summary tables for categorical variables, overall and by corticosteroid use, will include N, n, and percentages.

Unless otherwise specified, all analyses will be 2-sided at the 0.05 level of significance.

10.4. Specific Statistical Analyses

10.4.1. Study Conduct and Subject Disposition

Subjects who discontinue ataluren or are removed from the study prematurely will also be reported. Reasons for screening failures and early discontinuations, and time of withdrawal from study will be described.

10.4.2. Baseline Characteristics

Subject characteristics at entry into the study will be summarized in frequency tables and descriptive statistics will be provided for quantitative variables.

10.4.3. Study Treatment Administration

For each subject, ataluren administration will be described in terms of the total duration of therapy, dose modifications, dose delays, and dose omissions; and reasons for deviations from planned therapy.

10.4.4. Use of Concomitant Medication and Supportive Therapy

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

Specific attention will be focused on corticosteroid use and use of drugs for prophylaxis/treatment of CHF. The type and duration of pre-study use will be described. The type, dose, schedule, duration of use, dose modifications, dose omissions, and reasons for deviations from initial therapy will be described.

10.4.5. Primary Variables

10.4.5.1. Adverse Events

Adverse events will be classified using the MedDRA classification system. The severity of AEs will be graded according to the CTCAE, Version 5.0 whenever possible. A treatment-emergent adverse event is defined as an AE that occurs or worsens in the period extending from a subject's first ataluren dose in this study to 6 weeks after the last ataluren dose in this study.

The frequency of subjects experiencing a specific AE will be tabulated by visit, body system, and MedDRA term. In the by-subject analysis, a subject having the same event more than once will be counted only once using the worst CTCAE grade.

Adverse events classified as CTCAE Grade 3 or higher; study-drug-related events; adrenal, hepatic, and renal events leading to special diagnostic evaluations; events leading to discontinuation from treatment; and SAEs will be considered with special attention.

10.4.5.2. Laboratory Data

Hematological, serum biochemistry, adrenal laboratories, and urine data and their changes (only for continuous laboratory parameters) from baseline will be summarized by visit. Hematological, serum biochemistry, adrenal laboratories, and urine data will be graded according to CTCAE severity grade when applicable. For parameters for which a CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges will be summarized. Summary tables will be presented for each relevant assay to show the number of subjects by severity grade with corresponding percentages. Subjects will be characterized only once for a given assay, based on their worst severity grade observed during the time period of interest.

Shift tables for hematology, serum biochemistry, adrenal laboratories, and urine data will also be presented showing change in CTCAE severity grade from baseline to each visit. For parameters for which a CTCAE scale does not exist, shift tables will be presented showing change in results from baseline (normal, low and high [or abnormal]) to each visit (normal, low and high [or abnormal]).

Separate listings and tables will be created for parameters for assessment of adrenal, hepatic, and renal monitoring based on the conditions listed in Section 6.3.

10.4.5.3. Physical Findings

Physical findings (weight, physical examination data, systolic and diastolic blood pressure, radial pulse rate, and body temperature) will be listed and summarized by visit. Where appropriate, changes from baseline at each visit will be summarized and tested using the paired t-test or a nonparametric alternative.

10.4.5.4. Peabody Developmental Motor Scale, Second Edition

The PDMS-2 assessments will be summarized by visit for subjects enrolled from Study 048.

11. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1. Informed Consent/Assent

By signing the protocol, the investigator assures that informed consent/assent will be obtained from each subject and/or parent/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 subject 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 subject and/or parent/guardian in a language in which the subject or parent/guardian is fluent. This information must be provided to the subject or parent/guardian prior to undertaking any study related procedure. Adequate time should be provided for the subject 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 subject and/or parent/guardian may have about the study. The subject should be able to ask additional questions as and when needed during the conduct of the study. The subject's signature on the informed consent form should be obtained at the investigational site in the presence of the investigator or a qualified representative (e.g., subinvestigator).

Each subject 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 subject information must not be changed without prior approval by PTC Therapeutics and the IRB/IEC.

11.2. Confidentiality

Research records will be collected and stored in a manner that protects the confidentiality of subject information. The names and identities of all research subjects will be kept in strict confidence and will not appear on CRFs or other records provided to or retained by PTC Therapeutics (or its authorized designee). The names and identities of the subjects need not be divulged; however, the records must nevertheless be inspected. This will be accomplished by blanking out the subject's name and replacing the name with the subject'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.

11.3. 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 subjects (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 subject (electronic equivalents of CRFs), and detailed records of ataluren disposition. All records and documents pertaining to the study 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. 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 as applicable.

11.4. Clinical Monitoring

In accordance with 21 CFR Part 312.56 and/or relevant ICH guidelines, PTC Therapeutics or a designee will periodically inspect all eCRFs, 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, applicable FDA and 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 subjects 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.

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.

11.5. 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 investigator's 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.

11.6. 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.

PTC Therapeutics intends that the data from this study will be presented and published. The PTC Therapeutics staff under the direction of the PTC Therapeutics chief medical officer or designee 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.

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the clinical study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results, other than study recruitment materials and/or advertisements, is the sole responsibility of the Sponsor.

Data from all sites participating in the study will be pooled and analyzed by the sponsor or the sponsor's designee. The first publication of the study results shall be made in conjunction with the results from other study sites as a multicenter publication. If a multicenter publication is not forthcoming within 24 months of completion of the study at all sites, the investigator may publish or present the results generated at his or her site.

The investigator will provide the sponsor with a copy of any proposed publication or presentation for review and comment at least 60 days prior to such presentation or submission for publication. The sponsor shall inform the investigator in writing of any changes or deletions in such presentation or publication required to protect the sponsor's confidential and proprietary technical information and to address inaccurate data or inappropriate interpretations in the context of any pooled multicenter results. At the expiration of such 60-day period, the investigator may proceed with the presentation or submission for publication unless the sponsor has notified the institution or the investigator in writing that such proposed publication or presentation discloses the sponsor's confidential and proprietary technical information. Further, upon the request of the sponsor, the investigator will delay the publication or presentation for an additional 90 days to permit the sponsor to take necessary actions to protect its intellectual property interests.

12. PROTOCOL AMENDMENT HISTORY

12.1. Amendment 6: 12 November 2021 (Version 7.0)

Overall reason for Amendment 6: The overall reason for the amendment was to provide details regarding the schedule of assessments for subjects transitioning from Study 048.

Protocol Section	Amendment/Update	Reason/ Rationale
Protocol	Document date/version was updated; minor grammatical and format changes were made throughout for clarity	Update
Protocol Identifiers and Study Personnel	Study personnel and approvers were updated where relevant	Update
Synopsis	Synopsis was updated to reflect changes to the protocol since Version 2.0; synopsis is now included within the body of the protocol	Update
Section 3	It was clarified that siblings of subjects who previously received ataluren at an investigational site in a prior PTC sponsored clinical study or treatment plan could also participate in this study. The following text was added "Only subjects enrolling in the current study from PTC124-GD-048-DMD (Study 048) will have efficacy assessments (ie, Peabody Developmental Motor Scale, second edition [PDMS-2]) performed for up to 52 weeks from the date of first dosing in Study 048. The number of subjects was updated to be approximately 270 subjects (from "a minimum of 160 subjects"). It was clarified that for subjects in the present study (except for subjects from Study 048), study assessments will be performed during screening on the first day of ataluren dosing, and then every 12, 24, and 48 weeks as described in Table 2. The following text was added "For subjects from Study 048 only, study assessments will be performed and motor development will be assessed using the PDMS-2 at baseline/Day 1, Week 14, and Week 28. After the Week 28 visit, study assessments will be performed every 12, 24, and 48 weeks as described in Table 3".	Update/ Clarification
Section 4.2	Inclusion criterion 2 was updated to clarify that subjects are required to be diagnosed with nmDBMD; inclusion criterion 4 was updated to "fertile men, as defined in (CTFG 2020), who are sexually active with women of childbearing potential and who have not had a vasectomy, must agree to use a barrier method of birth control during the study and for up to 50 days after the last dose of study drug"	Update/ Clarification
Section 4.3	Exclusion criterion #3 was updated to "Positive for Hepatitis B core antibody or Hepatitis C antibody at screening for ataluren-naïve subjects (siblings) or subject who have a temporary treatment gap of 1 year before entering study"	Update
Section 5.1	The number of subjects was updated to be approximately 270 subjects (from "a minimum of 160 subjects")	Update
Section 6.2.1	It was clarified that the investigator may withdraw a subject if they are not complying with the protocol (ie, per protocol visits, return of unused study drug)	Clarification
Section 7.1	It was clarified that Table 2 includes the schedule of events for all subjects enrolled in the current study, except for those subjects who enrolled in the current study following completion of Study 048, for whom the schedule of events is included in Table 3	Clarification

Protocol Section	Amendment/Update	Reason/ Rationale
Section 7.1	It was clarified in Table 2 that assessments completed every 12 weeks would also be completed during the "every 24 weeks" and "every 48 weeks" visits; it was clarified which subjects would require a baseline visit; it was clarified that subsequent annual visits would occur every 48 weeks (ie, Weeks 48, 96, 144, 192, 240, 288, 336, 384, 432, 480, 528, 576, 624, etc); it was clarified that clinical history would be collected for ataluren-naïve subjects (siblings) and that for subjects enrolling from another ataluren clinical study, only clinical history reported since the last dose of ataluren in the prior DBMD study will be collected	Clarification
Section 7.1	Table 3 was added and details the schedule of events for subjects enrolling from Study 048	Update
Section 7.2.1.1	Details regarding the screening and baseline assessments were clarified	Clarification
Section 7.2.1.2	It was clarified that study visits would occur every 12 weeks, 24 weeks, and 48 weeks during the treatment period. It was also added that "Subjects previously enrolled in PTC124-GD-048-DMD will complete 2 additional visits as indicated in Table 3. Subjects will report to the clinical research facility for a Week 14 and Week 28 visit. After the Week 28 visit, study visits will follow the 12 weeks, 24 weeks, and 48 weeks schedule."	Update/ Clarification
Section 7.2.2.2	Additional details regarding clinical/medication history was added	Update
Section 7.2.2.3	It was clarified that hepatitis testing is only required for ataluren-naïve subjects (siblings) or subjects who have a temporary treatment gap of 1 year before entering the study	Clarification
Section 7.2.2.4 Section 7.2.2.5 Section 7.2.2.6 Section 7.2.2.7 Section 7.2.2.8 Section 7.2.2.9 Section 7.2.2.11 Section 7.2.2.12	Cross-references to the Schedule of Events tables (Table 2 and Table 3) were added in place of details regarding timing of study procedures in each section	Update
Section 7.2.2.8	Details regarding the PDMS-2 assessment were added	Update
Section 8.1.2	It was added that all SAEs that occurred after any subject has been consented must be recorded on the CRF. The following was removed as part of the definition of a SAE as this study only includes males: "A pregnancy resulting in spontaneous abortion, stillbirth, neonatal death or congenital anomaly (included that in an aborted fetus)"	Update
Section 8.1.3	It was clarified that for ataluren, the RSI is the Table of Adverse Reactions in Section 4.8 of the SmPC and that the SmPC (version dated 17 June 2021) was included in the current protocol in Appendix A	Clarification
Section 9	It was clarified that the investigator may withdraw a subject if they are not complying with the protocol (ie, per protocol visits, return of unused study drug)	Clarification
Section 10.4.5.4	It was added that PDMS-2 will be summarized by visit for subjects enrolled from Study 048	Update
Appendix 1	The PDMS-2 Score Sheet was added in Appendix 1.	Update

12.2. Amendment 5: 13 Jan 2020 (Version 6.0)

Overall reason for Amendment 5: The overall reason for the amendment was to clarify about siblings entry criteria, to include vancomycin in the exclusion criteria, to remove the requirement for weight to be measured by the primary care physician, to add collection of used cartons for a more accurate assessment of study drug compliance, and to update communication by the clinical site to the subject or parent/legal guardian.

Item No.	Protocol Section	Amendment/Update	Reason/Rationale
1	Protocol	Document date/version and abbreviations were updated; small grammatical and format changes were made throughout	Update
2	Protocol Identifiers and Study Personnel	Clinical Development approver updated	Update
3	3 7.2.1.2 7.2.6	Removed requirement for weight to be measured by the primary care physician	Update
4	4.2, #2	Siblings entry criteria updated to specify “effected nmDBMD siblings”	Update
5	4.3, #5	Exclusion criteria updated to add intravenous vancomycin therapy	Update
6	6.1.5 7.1, Table 2, footnote g 7.2.10	Added collection of used cartons for a more accurate assessment of study drug compliance	Updated
7	7.1, Table 2, footnote c	Updated that reminders will be communicated prior to Week 24 for subject to obtain a weight check-in between the annual visits at sites and that this communication will be documented in the source	Update
8	7.1, Table 2, footnote f 7.2.1.2	Updated that the clinical site staff will contact the subject (pre-and post-study drug dispensing) to notify of upcoming study drug shipment and to confirm study drug receipt	Update
9	7.1, Table 2, footnote h	Updated that the clinical site staff will contact subject or parent(s)/legal guardian(s) every 12 weeks (by phone if there is no clinic visit) to assess adverse events and concomitant medications	Update
10	7.2.1.2	Updated that phone conversations will be conducted to monitor and capture AEs and use of concomitant medications	Update

12.3. Amendment 4: 13 Aug 2019 (Version 5.0)

The overall reason for Amendment 4: The overall reason for the amendment was to permit enrollment of siblings, to update information on concomitant use of cardiac drugs for cardiomyopathy prophylaxis/treatment, to update the protocol format and to remove redundant/out of date information.

Item No.	Protocol Section	Amendment/Update	Reason/Rationale
1	Protocol	Document date/version and abbreviations were updated; small grammatical and format changes were made throughout	Update
2	Protocol Identifiers and Study Personnel	Study title revised to remove “Previously Treated”; study personnel updated	Update
3	Overview and Background	Sections deleted	Improve clarity
4	1	Brief introduction	Context for current study
5	2	Revisions regarding nmDBMD siblings	Update
6	3	Study design summarized	Improve clarity
7	4.2, #2	Adding sibling program to permit enrollment of eligible siblings of subjects	Update
8	5.1	Enrollment redefined; added siblings of subjects as potential candidates	Allow additional subjects
9	5.2	Reference to Interactive Web Response replaced with EDC); unique subject identification numbers will be assigned for this study	Update
10	6.1.1	Updated drug description from powder to granules; added that study drug may be taken with juice/fruit punch; added that study drug is administered with food; added directions for preparation and use after preparation	Clarification and update
11	6.1.2	Updated study drug dispensing procedure	Update
12	6.1.4	Added that the designated study pharmacy will manage study drug dispensing according to investigator instructions; EDC will not be used; deleted need to enter subject weight into EDC	Update
13	6.1.5	Added that unused cartons will be returned as instructed; dispensing and study drug return will be documented	Update
14	6.1.6	Stability revised from 36 to 48 months	Update
15	6.1.7	Removed requirement for temperature monitoring; added site personnel and designated study pharmacy will manage study drug dispensing; updated information on reconciliation and dispensing records, and drug return	Update
16	6.2.2	revision to timing of dosing; deletion of Table 1	Update
17	6.2.4	Reworded drug preparation and storage section	Update
18	6.3.1	Deleted reference to 5 mg/5 mg/10 mg dosing; CTCAE version updated	Update

Item No.	Protocol Section	Amendment/Update	Reason/Rationale
19	6.3.4	Deleted section re instructions on drug discontinuation	Update
20	6.4.3	Deleted paragraph on monitoring aldosterone and plasma renin in subjects who are receiving an ACE inhibitor or ARB	Update
21	6.4.4	Combined 6.4.4 and 6.4.5; aligned with June2019 EU SmPC	Update
22	7.1	Aligned schedule of events to match protocol revisions	Update
23	7.2.1.1, Table 1	Defined Screening/Baseline visit, revised wording re: screening procedures	Update
24	7.2.1.2	Added wording re: phone visit to notify of upcoming drug shipment	Update
25	7.2.1.4	Deleted wording re visit as investigator site	Update
26	7.2.6	Added wording re: subjects reminded via phone call to obtain weight from primary care physician	Update
27	7.2.9	Added reference to designated study pharmacy and timing of drug supply	Update
28	7.2.10	Wording revised re: subjects to return drug as instructed	Update
29	7.2.11	Deleted wording that AE was to be reported in the interval between visits	Update
30	7.3	Blood collection summary deleted; current data are in the Laboratory Manual	Remove outdated information
31	8.1	Added classification of each AE as serious or non-serious	Update
32	8.1.2	Deleted wording re: reporting AEs post study to PTC	Update
33	8.5	CTCAE version updated	Update
34	8.8, Table 5	Table 5 AE Reporting Requirements updated	
35	8.9	SAE reporting contact updated	Update
36	8.10	Pregnancy reporting added	Update
37	9	Withdrawal information updated	Update
38	10.4.5	Deleted ECG as a variable (not collected)	Correction
39	11	Supporting documentation and operational considerations condensed/updated	Update
40	12	Added Protocol Amendment History	Clarification
41	13	References updated	Update
42	Appendix 1	Deleted	Update

Amendment 3: 30 Jan 2017 (Version 4.0)
Amendment 2: 17 Mar 2014 (Version 3.0)
Amendment 1: 25 May 2011 (Version 2.0)
Original Protocol: 08 Oct 2010 (Version 1.0)

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APPENDIX 1. PDMS-2 SCORE SHEET

Signature Page for PTC124-GD-016-DMD Clinical Protocol V7.0 - 12NOV2021 v2.0

Clinical Approval	[redacted] I approve the document(s) 15-Nov-2021 21:59:38 GMT+0000

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