CLINICAL PROTOCOL

A PHASE 3, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED EFFICACY AND SAFETY STUDY OF ATALUREN IN PATIENTS WITH NONSENSE MUTATION DUCHENNE MUSCULAR DYSTROPHY AND OPEN-LABEL EXTENSION

PTC124-GD-041-DMD

21 JULY 2020

VERSION 4.0

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PROTOCOL IDENTIFIERS AND STUDY PERSONNEL

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PRINCIPAL INVESTIGATOR AGREEMENT AND SIGNATURE

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

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF APPENDICES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

Term	Definition
6MWD	6-minute walk distance
6MWT	6-minute walk test
ACE	angiotensin-converting enzyme
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ARB	angiotensin receptor blockers
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BB	Beta-blocker
Bi-PAP	bi-level positive airway pressure
BUN	blood urea nitrogen
CD40	cluster of differentiation 40
CD-ROM	compact disk read-only memory
cGMP	current good manufacturing practice
CI	confidence interval
CK	creatine kinase
CRF	case report form
CRO	contract research organization
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450 enzyme
DMD	Duchenne muscular dystrophy
DMDSAT	DMD Functional Ability Self-Assessment Tool
DNA	deoxyribonucleic acid
EC	ethics committee
ECG	Electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
EMA	European Medicines Agency
EQ-5D	EuroQoL 5-Dimension
FDA	Food and Drug Administration
FVC	forced vital capacity
GCP	good clinical practice
GGT	gamma-glutamyl transferase
HDL	high-density lipoprotein
HRQL	health-related quality of life
ICH	International Council for Harmonisation
ID	Identification
IRB	institutional review board
IRT	interactive response technology
ITT	intention-to-treat
IV	intravenous
LDH	lactate dehydrogenase
LDL	low-density lipoprotein
LTBP4	latent TGF-beta binding protein 4
MAR	missing at random
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intention-to-treat
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
MRS	magnetic resonance spectroscopy

Term	Definition
mRNA	messenger ribonucleic acid
nmCF	nonsense mutation cystic fibrosis
nmDMD	nonsense mutation Duchenne muscular dystrophy
NSAA	North Star Ambulatory Assessment
OAT1	organic anion transporter 1
OAT3	organic anion transporter 3
OATP1B3	organic anion transporting polypeptide 1B3
PROM	Patient-Reported Outcome Measure
PUL	Performance of Upper Limb
RSI	reference safety information
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SOP	standard operating procedure
SPP1	secreted phosphoprotein 1
TEAE	treatment-emergent adverse event
TFTs	timed function tests
ULN	upper limit of normal
WHODRUG	World Health Organization Drug Dictionary

1 INTRODUCTION

1.1 Disease Background

Duchenne muscular dystrophy (DMD) is a rare genetic disorder caused by mutations in the gene encoding dystrophin, a protein expressed in skeletal, respiratory, and cardiac muscle [Bushby 2010a, Bushby 2010b]. The role of the dystrophin protein is to act as a shock absorber, bearing the mechanical stresses that occur during muscle contraction, stabilizing muscle cell membranes, and protecting muscles from injury [Petrof 1993]. In the absence of dystrophin, the stress placed on the membranes during contractions causes them to tear. Degeneration of muscle fibers attracts inflammatory cells, ultimately resulting in the replacement of healthy muscle with fatty and fibrosis tissue.

Muscle weakness in the lower-extremity muscles generally becomes apparent in the first few years of life, with delays in motor milestones such as attainment of independent walking [Bushby 2010a]. Deterioration of ambulation occurs in the first decade of life and wheelchair dependency in the teen years [Bushby 2010a]. Muscle weakness eventually develops in the upper-extremity muscles as well as respiratory and cardiac muscles, and respiratory or cardiac failure typically results in death by the third decade [Passamano 2012].

There is no cure for DMD. Treatments aimed at maintaining ambulation for as long as possible and managing the musculoskeletal complications of DMD include corticosteroids, physical therapy interventions involving gentle exercise and activity, and surgery to prevent or minimize lower-limb contractures and deformities [Bushby 2010a, Bushby 2010b]. The use of corticosteroids, previously controversial due to side effects, has increased since the publication of clinical management guidelines in 2010 strongly urging consideration of glucocorticoid therapy in all patients with DMD [Bushby 2010a, Bushby 2010b]. As the disease progresses, respiratory (eg, mechanical ventilation) and cardiac (eg, angiotensin-converting-enzyme inhibitors) interventions are employed [Bushby 2010a, Bushby 2010b].

Approximately 10 to 15% of boys with DMD have the disease due to a nonsense mutation [Aarstma-Rus 2006, Bladen 2015]. A nonsense mutation in deoxyribonucleic acid (DNA) results in a premature stop codon in the protein-coding region of the corresponding messenger ribonucleic acid (mRNA). When a premature stop codon is present, ribosomal translation of mRNA is interrupted before a full-length, functional protein is generated.

1.2 Ataluren

Ataluren promotes ribosomal readthrough of premature stop codons, enabling the formation of full-length, functional dystrophin protein [Welch 2007]. Because of the role of the dystrophin protein, dystrophin restoration therapy would be expected to stabilize or slow disease progression in patients with DMD [Merlini 2015].

The efficacy and safety of ataluren as a treatment for nonsense mutation Duchenne muscular dystrophy (nmDMD) previously were assessed in 2 randomized, double-blind, placebo-controlled, 48-week trials (NCT00592553 and NCT01826487, respectively). Data from these studies supported conditional marketing authorization of ataluren for the treatment of nmDMD in ambulatory patients aged ≥5 years in Europe, with a specific obligation to confirm the efficacy and safety of ataluren in this population by conducting a randomized, double-blind, placebo-controlled, 72-week study followed by a 72-week open-

label extension. This protocol describes the randomized, double-blind, placebo-controlled, 72-week study and its 72-week open-label extension.

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

2 STUDY OBJECTIVE AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objective

The primary objective of this study is to determine the effect of ataluren on ambulation and endurance as assessed by the 6-minute walk test (6MWT).

2.1.2 Secondary Objectives

The secondary objectives of this study are to:

- Determine the effects of ataluren on ambulation and burst activity as assessed by timed function tests
- Determine the effects of ataluren on lower-limb muscle function as assessed by the North Star Ambulatory Assessment (NSAA)
- Assess the safety profile of ataluren
- Evaluate the correlation between plasma concentration of ataluren and functional outcomes
- Evaluate the plasma pharmacokinetic (PK) profile of ataluren

2.1.3 Exploratory Objectives

The exploratory objectives of this study are to:

- Determine the effects of ataluren on upper-limb muscle function strength as assessed by the Performance of Upper Limb (PUL) and by the DMD Upper Limb PROM (in subjects ≥7 years old at baseline)
- Determine the effects of ataluren on muscle strength as assessed by myometry (in subjects <7 years old at baseline)
- Determine the effects of ataluren on skeletal muscle integrity as assessed by magnetic resonance imaging (MRI) (at pre-qualified sites only)
- Determine the effects of ataluren on subject- and parent/caregiver-reported health-related quality of life (HRQL) as assessed by at-home questionnaire
- Determine the effects of ataluren on pulmonary function as assessed by forced vital capacity (FVC)

2.2 Endpoints

2.2.1 Double-Blind Treatment Period

The efficacy endpoints below focus on the comparison of ataluren versus placebo in the double-blind treatment period (baseline to Week 72).

2.2.1.1 Primary Endpoint

The primary endpoint of this study is slope of change in 6-minute walk distance (6MWD) over 72 weeks.

2.2.1.2 Secondary Endpoints

- Change from baseline to Week 72 in 6MWD
- Composite of average change in times to run/walk 10 meters, climb 4 stairs, and descend 4 stairs at Week 72
- Change from baseline to Week 72 in time to run/walk 10 meters
- Change from baseline to Week 72 in time to climb 4 stairs
- Change from baseline to Week 72 in time to descend 4 stairs
- Change from baseline to Week 72 in NSAA total score
- Time to loss of ambulation over 72 weeks
- Time to loss of stair-climbing over 72 weeks
- Time to loss of stair-descending over 72 weeks
- Risk of loss of NSAA items over 72 weeks
- Ataluren safety profile characterized by type, frequency, severity, and relationship to study drug of any adverse events (AEs), or of abnormalities of laboratory tests, vital signs, physical examinations, or electrocardiograms (ECGs)

2.2.1.3 Exploratory Endpoints

- Changes from baseline to Week 72 in PUL total score and domain subscores (in subjects ≥7 years old at baseline)
- Change from baseline to Week 72 in DMD Upper Limb PROM total score (in subjects ≥7 years old at baseline)
- Risk of loss of DMD Upper Limb PROM items over 72 weeks (in subjects ≥7 years old at baseline)
- Change from baseline to Week 72 in myometry parameters (in subjects <7 years old at baseline)
- Change from baseline to Week 72 in muscle fat fraction as assessed by MRI (at pre-qualified sites only)
- Changes from baseline to Week 72 in HRQL as assessed by EQ-5D

- Change from baseline to Week 72 in FVC

2.2.2 Open-Label Treatment Period

The efficacy endpoints below focus on the comparison of early-start ataluren (subjects receiving ataluren from baseline to Week 144) versus delayed start ataluren (subjects receiving ataluren from Week 72 to Week 144) across the double-blind and open-label treatment periods.

2.2.2.1 Secondary Endpoints

- Slope of change in 6MWD over 144 weeks
- Change from baseline to Week 144 in 6MWD
- Composite of average change in times to run/walk 10 meters, climb 4 stairs, and descend 4 stairs at Week 144
- Change from baseline to Week 144 in time to run/walk 10 meters
- Change from baseline to Week 144 in time to climb 4 stairs
- Change from baseline to Week 144 in time to descend 4 stairs
- Change from baseline to Week 144 in NSAA total score
- Time to loss of ambulation over 144 weeks
- Time to loss of stair-climbing over 144 weeks
- Time to loss of stair-descending over 144 weeks
- Risk of loss of NSAA items over 144 weeks
- Ataluren safety profile characterized by type, frequency, severity, and relationship to study drug of any AEs, or of abnormalities of laboratory tests, vital signs, physical examinations, or ECGs
- Plasma PK at pre-morning dose and 2 hours post-morning dose at Week 144

2.2.2.2 Exploratory Endpoints

Exploratory endpoints will include the following:

- Changes from baseline to Week 144 in PUL total score and domain subscores (in subjects ≥7 years old at baseline)
- Change from baseline to Week 144 in DMD Upper Limb PROM total score (in subjects ≥7 years old at baseline)
- Risk of loss of DMD Upper Limb PROM items over 144 weeks (in subjects ≥7 years old at baseline)
- Change from baseline to Week 144 in myometry parameters (in subjects <7 years old at baseline)
- Change from baseline to Week 144 in muscle fat fraction as assessed by MRI (at pre-qualified sites only)

- Changes from baseline to Week 144 in HRQL as assessed by EQ-5D
- Change from baseline to Week 144 in FVC

3 SUBJECT SELECTION CRITERIA

3.1 Overview

The eligibility criteria are designed to allow entry of 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 must 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.

3.2 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/ethics committee (IRB/EC) 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. Male sex.
3. Age ≥5 years. When Version 3 is implemented or approximately 270 subjects have enrolled in the study, only subjects aged ≥7 to ≤16 who meet the mITT criteria will be eligible to enroll.
4. Phenotypic evidence of DMD based on the onset of characteristic clinical symptoms or signs (eg, proximal muscle weakness, waddling gait, and Gowers' maneuver) by 6 years of age and an elevated serum creatine kinase (CK). ***Medical documentation of phenotypic evidence of DMD needs to be provided upon request by the PTC Therapeutics medical monitor.***
5. Documentation of the presence of a nonsense point mutation in the dystrophin gene as determined by gene sequencing. ***Note: Review and approval of documentation by sponsor or designee is required prior to enrollment.***

6. Use of systemic corticosteroids (prednisone/prednisolone or deflazacort) for a minimum of 12 months immediately prior to start of study treatment, with no significant change in dosage or dosing regimen for a minimum of 3 months immediately prior to start of study treatment and a reasonable expectation that dosage and dosing regimen will not change significantly for the duration of the study. ***Note: Daily, every other day, high-dose weekend, and intermittent regimens permitted only. The doses recommended or required are shown in Table 1. Increases in corticosteroid dose to adjust for increases in body weight will not exclude a subject from participation.***

Table 1. Corticosteroid Regimens and Doses Recommended or Required

Regimen	Prednisone/Prednisolone	Deflazacort
Daily	0.75 mg/kg (recommended) At least 0.3 mg/kg (required)	0.9 mg/kg (recommended) At least 0.3 mg/kg (required)
Every other day	0.75-1.25 mg/kg (recommended)	2 mg/kg (recommended)
High-dose weekend	5 mg/kg given each Friday and Saturday (recommended)	
Intermittent	0.75 mg/kg for 10 days alternating with 10-20 days off medication (recommended)	0.6 mg/kg on days 1-20 and none for the remainder of the month (recommended)

For the daily regimen, 0.3 mg/kg is the minimum acceptable dose but either 0.75 (prednisone/prednisolone) or 0.5 (deflazacort) mg/kg is preferred. For the other regimens, a recommended dose or dose range is provided in the table although no set dose or dose ranges have been clearly accepted as optimum.
Reference: Bushby 2010a

7. 6MWD ≥150 meters at screening, baseline Day 1, and baseline Day 2. When Version 3 is implemented or approximately 270 subjects have enrolled in the study, only subjects who meet the mITT criteria, 6MWD ≥300 meters at Baseline Day 1 or Day 2, and time to stand from supine ≥5 seconds at Baseline Day 1, will be eligible to enroll. ***Note: Personal assistance or use of assistive devices for ambulation (eg, short leg braces, long leg braces, or walkers) will not be permitted during the 6MWT.***
8. Results of the two Baseline 6MWD results must be determined as valid and results of the Day 2 Baseline 6MWD must be within 20% of the Day 1 Baseline 6MWD.
9. Baseline 6MWD (maximum of valid Day 1 and Day 2 values) must be no more than a 20% reduction from the valid Screening 6MWD.
10. Ability to perform timed function tests (run/walk 10 meters, climb 4 stairs, descend 4 stairs, stand from supine) within 30 seconds at screening and baseline.
11. In subjects who are sexually active, willingness to abstain from sexual intercourse or employ a barrier or medical method of contraception during the study drug administration and 4-week follow-up period.
12. Willingness and ability to comply with scheduled visits, drug administration plan, study procedures, laboratory tests, and study restrictions. ***Note: Psychological, social, familial, or geographical factors that might preclude adequate study participation (in particular, the ability to satisfactorily perform the 6MWT) should be considered.***

3.3 Exclusion Criteria

Prior to study drug administration, it will be confirmed that the subject meets none of the following conditions:

1. Any change (initiation, change in type of drug, dose modification, schedule modification, interruption, discontinuation, or reinitiation) in prophylaxis/treatment for cardiomyopathy within 1 month prior to start of study treatment.
2. Ongoing intravenous (IV) aminoglycoside or IV vancomycin therapy.
3. Prior or ongoing therapy with ataluren.
4. Known hypersensitivity to any of the ingredients or excipients of the study drug [eg, refined polydextrose, polyethylene glycol 3350, poloxamer 407, mannitol 25C, crospovidone XL10, hydroxyethyl cellulose, colloidal silica, magnesium stearate].
5. Exposure to another investigational drug within 6 months prior to start of study treatment, or ongoing participation in any interventional clinical trial. ***Note: This does not apply to patients receiving deflazacort through an expanded access program.***
6. History of major surgical procedure within 12 weeks prior to start of study treatment, or expectation of major surgical procedure (eg, scoliosis surgery) during the 72-week placebo-controlled treatment period.
7. Ongoing immunosuppressive therapy (other than corticosteroids).
8. Requirement for daytime ventilator assistance or any use of invasive mechanical ventilation via tracheostomy. ***Note: Evening non-invasive mechanical ventilation such as use of bi-level positive airway pressure (Bi-PAP) therapy is allowed.***
9. Uncontrolled clinical symptoms and signs of congestive heart failure (American College of Cardiology/American Heart Association Stage C or Stage D) [Hunt 2001].
10. Elevated serum creatinine or cystatin C at screening. ***Note: If the initial test result is abnormal, it is permissible to re-test serum creatinine or cystatin C and randomize the subject if the re-test result is normal.***
11. Positive for hepatitis B core antibody or hepatitis C antibody at screening.
12. Prior or ongoing medical condition (eg, concomitant illness, psychiatric condition, behavioral disorder, alcoholism, drug abuse), medical history, physical findings (eg, lower-limb injury that may affect 6MWT performance), ECG findings, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of treatment or follow-up would be completed, or could impair the assessment of study results.

4 ENROLLMENT PROCEDURES

4.1 Source and Number of Subjects

Study candidates comprise patients with nmDMD who are being followed at the participating study sites or are referred to the participating study sites. Subjects will be enrolled at investigator sites worldwide and will undergo study-specific screening procedures prior to enrollment. Approximately 340 subjects, who meet all inclusion criteria and none of the exclusion criteria, will be enrolled. A sample size of approximately 340 subjects will include approximately 162 subjects who meet the criteria for inclusion in the primary analysis population (defined as the modified intention-to-treat [mITT] population in Section 9.2.2).

4.2 Screening

The investigator must inform each prospective subject and/or the parent/legal guardian 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. At the time the study candidate signs the informed consent/assent and completes the Screening 6MWT, a site representative should access the interactive response technology (IRT) system to indicate that a candidate is being screened. The site representative will need to supply the IRT system with information, including:

- Site number as previously assigned by PTC Therapeutics
- Subject number
- Subject initials (if permitted per local privacy regulations)
- Subject date of birth
- Date of Screening (Visit 1)
- Results of valid 6MWT obtained at Screening

The IRT system will use this information to maintain a central screening log documenting that screening occurred. Upon successful entry of the subject in the IRT system and confirmation of all subject eligibility requirements, the subject may proceed to baseline procedures.

4.3 Randomization and Stratification

After a subject has completed all screening and baseline assessments and has been confirmed to be eligible by the investigator in accordance with the inclusion and exclusion criteria, the subject can be randomized into the study.

In order to obtain a treatment arm assignment for a subject, a site representative will access the IRT system. The user will need to supply the IRT system with at least the following information so that the system can assign the subject to a treatment group.

- Site number as previously assigned by PTC Therapeutics
- Subject number as previously entered into the IRT system
- Subject initials

- Subject date of birth
- Type of corticosteroid
- Results of the baseline Day 1 and Day 2 6MWTs in meters
- Result of the baseline time to stand from supine in seconds
- Brother already randomized into the study: yes or no; if yes, subject number of the previously randomized brother
- Subject's weight at baseline in kg

The IRT system will provide instructions for dispensing study drug (see Section 5.1.4).

Subjects will be randomized in a 1:1 ratio to 1 of 2 possible treatment assignments:

- Placebo
- Ataluren (10, 10, 20 mg/kg)

In order to balance treatment allocation by potentially important predictive factors for the 6MWT, the following stratification factors will be used:

- Type of concomitant corticosteroid use at baseline: (deflazacort versus prednisone/prednisolone)
- Maximum of the Day 1 and Day 2 6MWTs performed at baseline: <300 meters versus ≥300 to <350 meters versus ≥350 to <400 meters versus ≥400 meters
- Time to stand from supine at baseline: <5 seconds versus ≥5 seconds

4.4 Blinding

During the double-blind treatment period, the identity of the treatments will be concealed by the use of a placebo that is matched to the active drug in appearance, taste, odor, packaging, labeling, and schedule of administration. Unblinding will only occur in the case of subject emergencies before study completion and at the conclusion of the study. Except for emergency unblinding, individual subjects, parents/caregivers, and site personnel will not be informed of the randomized treatment assignments until the implications of revealing such data for the overall ataluren clinical development program have been determined by PTC Therapeutics.

Emergency unblinding should only occur after the principal investigator deems the subject's emergency warrants the unblinding of the treatment. Unblinding of the treatment can only be performed by the principal investigator in the IRT system. Unblinding instructions are provided in the IRT system instruction manual.

5 STUDY DRUG ADMINISTRATION

5.1 Investigational Product

5.1.1 Ataluren (PTC124)

Blinded ataluren (treatment through Week 72) as well as open-label ataluren (treatment from Week 73 to Week 144) will be provided as white to off-white granules for oral suspension. The drug substance and drug product are manufactured under current good manufacturing practice (cGMP) conditions. The formulation includes matrix and suspending agents, surfactants, and various 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 granules in the sachet may be mixed with water, fruit juice, fruit punch, or milk (skim, 1% fat, 2% fat, whole milk, chocolate milk, soy milk, or lactose-free milk), or semi-solid food (yogurt, pudding, or applesauce).

5.1.2 Placebo

A white to off-white granules placebo formulation will be provided for oral suspension. The placebo formulation has been manufactured under cGMP conditions. The dry granules and the liquid suspension of the drug match the active formulation in appearance, odor, and taste. The placebo formulation contains excipients similar to those used in the active product. The placebo is packaged in the same aluminum-foil, child-resistant sachets using weights and volumes to match each of the 125, 250, and 1000 mg dose strengths of active drug sachets.

5.1.3 Packaging and Labeling

Drug kits will be provided, each of which contains sachets of one of the dose strengths (125, 250, or 1000 mg or matching placebo [during the double-blind treatment period]). Sachets and cartons will be color-coded to indicate dosage strength (125 mg - yellow, 250 mg - pink, 1000 mg - blue). Each kit will have a unique kit identification (ID) number. 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.

5.1.4 Study Drug Dispensing

During both treatment periods (double-blind and open-label), dosing of study drug will be based on milligrams of drug per kilogram of subject body weight and will be adjusted to allow for dosing with up to 2 of the available sachet dose strengths (125 mg, 250 mg, and/or 1000 mg). The sachet dose strengths and number of sachets to be taken per dose will be calculated and provided by the IRT system.

The clinic staff (eg, pharmacist or other qualified person) will be responsible for dispensing study drug according to the IRT system directions. At the time of randomization, the IRT system will provide the clinic staff with the subject randomization number and the kit ID numbers designating the kits to be dispensed. Multiple kits may be dispensed at a single visit (maximum of 2 different strengths).

During the double-blind treatment period, study drug will be provided for each 12-week study period. During the open-label treatment period, study drug will be provided for each 24-week study period.

Because of potential changes in subject body weight over time, at Week 24 (Visit 4) and every 24 weeks thereafter, a dose adjustment may be made based on the subject's body weight at that visit. Depending upon the magnitude of change in subject body weight since baseline, the number and strengths of sachets to be used by the subject may remain the same or may be adjusted.

5.1.5 Return of Study Drug

Subjects and/or parents/caregivers should return all used and unused kits, as well as all unused sachets, to the study site at each onsite study visit. Study drug dispensing to the subjects and the return of any unused study drug for compliance assessments will be documented.

5.1.6 Storage and Stability

Kits containing sachets of study drug will be stored at room temperature. The available stability data from representative samples support the use of the drug product for 48 months when stored at room temperature. The stability of the clinical study samples or representative samples may be monitored, as appropriate, to support the clinical study.

5.1.7 Study Drug Accountability

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

The investigator and/or the responsible site personnel must maintain accurate records of the receipt of all study drug shipped by PTC Therapeutics or its designee, including, but not limited to, the date received, lot number, amount received, amount returned, and the disposition of all study drug product. Drug accountability records must also be maintained by the site that include the subject's assigned study number, date and amount of study drug dispensed, and relevant lot and sachet numbers.

Study drug must be returned to PTC Therapeutics or its designee, except where sites are required to destroy study drug per their local standard operating procedures (SOPs). Records documenting the date of study drug destruction or shipping, relevant sachet numbers, and amount shipped should be kept in the investigator site study file.

5.1.8 Overdose Precautions

For any subject experiencing an overdose (administration of a study drug dose >4 times the 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. Use of gastric lavage or induction of emesis is not specifically recommended nor contraindicated.

The PTC Therapeutics medical monitor or designee must be contacted if an overdose occurs, and the overdose must be reported as an AE according to Section 7.1.1 (or as a serious adverse event [SAE] if it meets the applicable criteria for an SAE in Section 7.1.2).

5.1.9 Inadvertent Exposure and Spill Precautions

Reference can be made to the Ataluren Investigator Brochure for current information on inadvertent exposures and spill precautions.

5.2 Study Drug Treatment

5.2.1 Duration of Treatment

Treatment will comprise continuous daily administration of double-blind ataluren or placebo for 72 weeks followed by continuous daily administration of open-label ataluren for an additional 72 weeks.

5.2.2 Schedule of Administration

Throughout the study (ie, during the double-blind treatment period and the open-label treatment period), study drug should be taken TID – the 1st dose (10 mg/kg) in the morning, the 2nd dose (10 mg/kg) at mid-day, and the 3rd dose (20 mg/kg) in the evening. Intervals for dosing ideally should be ~6 hours (±1 hour) between morning and mid-day doses, ~6 hours (±1 hour) between mid-day and evening doses, and ~12 hours (±1 hour) between evening doses and the morning dose on the next day.

5.2.3 Instructions for Delays in Dosing

If a subject experiences a delay in the administration of study drug 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 study drug of >4 hours, the dose should not be taken. Study drug administration may continue but the missed dose should not be made up and the planned timing of subsequent study drug dosing should not be altered.

5.2.4 Study Drug Preparation and Storage

Study drug sachets should be stored at room temperature, away from the reach of children until time of reconstitution and should only be opened at the time of dose preparation. The full contents of the sachets 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). 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 on the specific number of sachets to be taken from each kit 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 when drug supplies are dispensed.

5.3 Safety Monitoring and Study Drug Dose Interruption/Modification

5.3.1 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.

For AEs or laboratory abnormalities, the investigator will use judgment in determining whether the event or abnormality is clinically significant, whether diagnostic evaluation is warranted, and whether potential interruption of study drug treatment is appropriate. In general, life-threatening (Grade 4) or severe (Grade 3) AEs or laboratory abnormalities should be considered clinically significant, although recurrent or persistent moderate events (Grade 2) may also be considered clinically significant in certain circumstances. Reference should be made to the latest version of the Common Terminology Criteria for Adverse Events (CTCAE) for grading the severity of AEs and laboratory abnormalities.

Cases of decreased renal function have been observed in patients with nonsense mutation cystic fibrosis (nmCF) receiving ataluren and IV aminoglycosides together with other antibiotics for cystic fibrosis exacerbations (Section 5.4.2). As a precaution, Table 2 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 2, 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.

Table 2. 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.

5.3.2 Evaluation of Adverse Events or Laboratory Abnormalities

The PTC Therapeutics medical monitor or designee 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.

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

- **Hepatic**: The medical history, hepatitis screening results, all clinical blood values (particularly serum bilirubin, gamma-glutamyl transferase [GGT], aspartate aminotransferase [AST], and alanine aminotransferase [ALT] values), and all concomitant medications should be reviewed. Depending upon changes observed, the recommended diagnostic workup may include more frequent monitoring or further evaluations for viral hepatitis and immune disorders; tests for cholelithiasis; or abdominal ultrasound, computed tomography, MRI, or other imaging methods.
- **Renal**: The medical history, all clinical blood and urine renal values, serum electrolytes, medications, and potential pre or- post renal conditions should be reviewed. Depending upon the changes observed, recommended diagnostic workup may include further evaluations of blood or urine; tests of glomerular filtration rate, concentrating ability, or other renal functions; computed tomography, MRI, or other imaging methods; and/or renal biopsy.

5.3.3 Instructions for Resuming Study Drug Administration after an Interruption for Safety Concerns

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

- Type and severity of the AE or laboratory abnormality
- The potential causal relationship of study drug
- The subject's status in terms of DMD and 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.

5.3.4 Instructions for Discontinuation of Study Drug Administration for Safety Concerns

If after appropriate consideration of study drug interruption/modification and consultation with the PTC Therapeutics medical monitor, it is not appropriate for a subject to continue with study treatment, then study drug should be permanently discontinued. After permanent discontinuation of study drug for a safety concern, and if the initial event was reported as a SAE, then a follow-up SAE report form should be completed. In the case of a treatment discontinuation due to an event that is not an SAE, the PTC Therapeutics medical monitor should be notified (see Section 7). In addition, details regarding the reasons for discontinuation and the AEs leading to the discontinuation should be recorded in the source documents and in the appropriate case report form (CRF). The End of Treatment Visit CRF should be completed and appropriate follow-up (at ~4 weeks as per protocol or until recovery from or stabilization of the AE, whichever comes last) should be instituted.

5.4 Concomitant and Supportive Therapy

Other than the study drug, 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 study drug administration, and for 4 weeks after discontinuation of study drug 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.

5.4.1 Corticosteroids

Corticosteroid therapy in DMD improves muscle strength and function in the short term [Matthews 2016]. To minimize potential confounding effects of changes in corticosteroid therapy on the interpretation of study results, the use of these medications must be standardized as much as possible during the study.

A stable and standardized corticosteroid regimen should be maintained during the 72 weeks of double-blind study drug treatment. Adjustments in corticosteroid dosage for increases in body weight are permitted (only once during the 72-week double-blind study treatment) but are not mandatory. Upward adjustments in corticosteroid dose for increases in body weight or other reasons should follow recommendations provided in Appendix A.

If a subject experiences a concerning AE related to systemic corticosteroid use, interventions or potential adjustments in the corticosteroid dosage may be considered, as detailed in Appendix A. It should be emphasized that reductions in corticosteroid dosage for cosmetic or other minor reasons should be avoided. Subjects who require corticosteroid interruption, dose modification, or reinstitution may remain on blinded study drug therapy.

5.4.2 Aminoglycosides and Vancomycin

Ataluren should not be co-administered with IV aminoglycosides (eg, tobramycin, gentamicin, amikacin, kanamycin and/or IV vancomycin), based on cases of decreased renal function observed in a clinical trial of ataluren in patients with nmCF. Elevations of serum creatinine occurred in several nmCF patients treated with ataluren and IV aminoglycosides/vancomycin together with other antibiotics for cystic fibrosis exacerbations. The serum creatinine elevations resolved in all cases, with discontinuation of the IV aminoglycoside/vancomycin, and either continuation or interruption of ataluren. These findings suggested that co-administration of ataluren and IV aminoglycosides/vancomycin may potentiate the nephrotoxic effect of these antibiotics. For additional details, refer to the Investigator Brochure.

In subjects who require treatment for serious infections, investigators should substitute other antibiotics for systemic aminoglycosides/vancomycin when clinically appropriate. For subjects requiring systemic antibiotic therapy, IV aminoglycosides/vancomycin may be used when medically necessary. However, consideration should be given to use of alternative agents if appropriate. If IV aminoglycosides/vancomycin) are administered, study drug must be interrupted during the course of these antibiotic treatments. Subjects requiring IV aminoglycoside or IV vancomycin therapy should be closely monitored in an appropriate setting, such as a hospital. In subjects receiving potentially nephrotoxic agents such as IV aminoglycosides or IV vancomycin, antibiotic drug levels (if appropriate) and serum creatinine and blood urea nitrogen (BUN) should be followed closely. The antibiotic trough level (if appropriate) 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. Creatinine and BUN should be measured prior to initiating IV aminoglycoside or vancomycin therapy and at least weekly during the course of antibiotic treatment.

5.4.3 Hydration

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

5.4.4 Cardiac Drugs for Cardiomyopathy Prophylaxis/Treatment

The use of angiotensin-converting enzyme (ACE) inhibitors for the management of DMD-associated cardiomyopathy has become widespread in the DMD population [El-Aloul 2016]. In subjects who are unable to tolerate ACE inhibitors, angiotensin receptor blockers (ARBs) are sometimes used. Beta-blocker (BB) therapy is sometimes initiated after ACE inhibitor/ARB therapy for progressive cardiac decline. Finally, the use of an aldosterone antagonist (AA) has recently demonstrated favorable effects on cardiac function in DMD [Raman 2015]. Because changes in the use of cardiac drugs could introduce confounding influences on the interpretation of efficacy results, such changes should be minimized during study drug therapy.

For subjects who are not on cardiac drugs for the prophylaxis/treatment of cardiomyopathy, initiation of such drugs during the 72 weeks of blinded study drug treatment is discouraged unless there is a strong medical need.

For subjects who are on cardiac drugs, they should be on a stable dose for at least 1 month prior to randomization and a stable regimen should be maintained during the 72 weeks of blinded study drug treatment. Adjustments in dosage or type of drug are permitted to avoid symptoms (eg, cough associated with ACE inhibitors) but attempts should be made to avoid entirely removing subjects from cardiomyopathy prophylaxis/treatment. Subjects who require initiation, interruption, dose modification, or reinstitution of cardiomyopathy prophylaxis/treatment may remain on blinded study drug therapy.

5.4.5 Drugs Metabolized by Cytochrome P450 Enzymes

As the primary route of ataluren metabolism is via glucuronidation by UDP-glucuronosyltransferase 1-9 (UGT1A9), clinically significant interactions between ataluren and co-administered drugs metabolized by cytochrome P450 enzymes (CYPs) are unlikely. In particular, ataluren is not an inhibitor of CYP1A2, CYP2B6, CYP2C19, CYP2D6, and CYP3A4/5, and does not have induction potential on the major CYP enzymes.

In vitro, ataluren is a weak inhibitor of CYP2C8 and CYP2C9, but in vivo drug-drug interactions mediated by these enzymes are not expected according to the criteria described in the European Medicines Agency (EMA) guideline on the investigation of drug interactions [EMA 2012]. As an added measure of safety, however, investigators should pay specific attention to use of drugs that are known substrates of these enzymes, particularly when such drugs may have a low therapeutic index.

5.4.6 Other Potential Drug Interactions

Based on in vitro studies, ataluren is a substrate of UGT1A9. Coadministration with rifampin, a strong inducer of metabolic enzymes, including UGT1A9, decreased ataluren exposure by 30%. The significance of these findings is unknown. Caution should be exercised when ataluren is coadministered with medicinal products that are inducers of UGT1A9 (eg, rifampicin).

In vitro data indicate that ataluren is an inhibitor of organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3) and organic anion transporting polypeptide 1B3 (OATP1B3). Caution should be exercised when ataluren is co-administered with e.g.OAT1, OAT3, or OATP1B3 (e.g., oseltamivir, acyclovir, ciprofloxacin, captopril, furosemide, bumetanide, valsartan, pravastatin, rosuvastatin, atorvastatin, pitavastatin) because of the risk of increased plasma concentration of these drugs.

The investigator is encouraged to consult the PTC medical monitor or designee with questions relating to specific drugs and their potential for interactions with ataluren.

5.4.7 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" (eg, creatine, glutamine, coenzyme Q), herbal remedies, growth hormone, 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 other drug(s) 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-thecounter-, or illicit) before and during the course of the study. Information regarding 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 concomitant medication CRF.

5.5 Assistive Devices

During study-specified 6MWTs, timed function tests, and NSAA evaluations, subjects must not use assistive devices (eg, short leg braces, long leg braces, or walkers).

5.6 Physical and Respiratory Therapy

There are neither restrictions nor prescriptions for physical or respiratory therapy during the study. Sites should follow recommendations by the DMD Care Considerations Working Group [Bushby 2010b] in providing physical therapy support for subjects participating in the study. Respiratory care guidelines for DMD as suggested by the American Thoracic Society should be followed [Finder 2004]. If changes in the physical or respiratory therapy regimen are planned, sites are encouraged to initiate these changes prior to randomization and to maintain the same general level of support throughout the duration of the study.

5.7 Dietary Restrictions

There are no specific dietary restrictions in the study.

6 SCHEDULE OF EVENTS AND STUDY PARAMETERS

6.1 Schedule of Events

The proposed types and timing of data to be recorded are described in Table 3 (double-blind treatment period) and Table 4 (open-label treatment period). Refer to Section 6.2 for cross-referenced explanations of the study procedures described in the tables.

Table 3. Schedule of Events (Double-Blind Treatment Period)

Study Period	**Screening**	**Double-Blind Treatment**									**Notes**
Study Week	**-2 weeks**	**1**		**12**	**24**	**36**	**48**	**60**	**72**		2-week screening period may be extended by 1 week if necessary to schedule pretreatment MRI
Visit Window (days)				±7	±7	±7	±7	±7	±7		
Visit Number	**1**	**2**		**3**	**4**	**5**	**6**	**7**	**8**		At Visit 2, complete assessments before first dose
Visit Day		**1**	**2**						**1**	**2**	2-day visits only at Visit 2 and Visit 8
Informed consent	X										May be obtained prior to Visit 1 (eg, by phone)
Enter subject in IRT system	X										Access IRT system to enter subject
Clinical and medication history	X										
Hepatitis screen	X										
Urinalysis sample	X	X			X		X		X		
EQ-5D and DMDSAT	X	X		X	X	X	X	X	X		Provided to subject at Visit 1 for at-home completion between visits and reviewed for compliance in clinic
DMD Upper Limb PROM		X		X	X	X	X	X	X		Performed only in subjects ≥7 years at baseline
Height	X	X		X	X	X	X	X	X		
Weight	X	X		X	X	X	X	X	X		
Physical examination	X	X			X		X		X		Full (Visit 1, 8) or symptom-directed (Visit 2, 4, 6)
Concomitant medications	X	X		X	X	X	X	X	X		
Adverse events	X	X		X	X	X	X	X	X		
Genotyping sample		X									
Hematology sample	X	X			X		X		X		
Biochemistry sample	X	X			X		X		X		To be collected in fasted state (except Visit 1)
Vital signs	X	X		X	X	X	X	X	X		
Myometry	X	X		X	X	X	X	X	X		Performed only in subjects <7 years at baseline
PUL	X	X		X	X	X	X	X	X		Performed only in subjects ≥7 years at baseline
6-minute walk test (1st test)	X	X		X	X	X	X	X	X		
6-minute walk test (2nd test)			X							X	
NSAA	X	X		X	X	X	X	X	X		
Timed function tests	X	X		X	X	X	X	X	X		
Study drug dispensed			X	X	X	X	X	X		X	Open-label study drug dispensed at Visit 8
Study drug compliance				X	X	X	X	X	X		
12-lead ECG	X				X		X		X		
Spirometry	X	X							X		Required at all visits after subject loses ambulation
Echocardiogram	X								X		
Randomization			X								Access IRT system to randomize subject
Upper leg imaging		X			X		X		X		Performed only at pre-qualified sites. May be done between Visits 1 and 2 (pre-treatment assessment) or ±4 weeks of visit (post-treatment assessments).

Abbreviations: DMD = Duchenne Muscular Dystrophy, DMDSAT = DMD Functional Ability Self-Assessment Tool, ECG = electrocardiogram, EQ-5D = EuroQoL 5-Dimension, IRT = interactive response technology, NSAA = North Star Ambulatory Assessment, PROM = Patient-Reported Outcome Measure, PUL = Performance of Upper Limb

Table 4. Schedule of Events (Open-Label Treatment Period)

Study Period	**Open-Label Treatment**			**Follow-Up**	**Notes**
Study Week	**96**	**120**	**144**	**148**	
Visit Window (days)	±7	±7	±7	±7	
Visit Number	**9**	**10**	**11**	**12 (by phone)**	Subjects who discontinue prematurely should complete Visit 11 and Visit 12 (by phone). Post treatment follow-up is not required if subjects are transitioning to another ataluren clinical trial.
Urinalysis	X	X	X		
EQ-5D and DMDSAT	X	X	X		Provided to subject at Visit 1 for at-home completion between visits and reviewed for compliance in clinic
DMD Upper Limb PROM	X	X	X		Performed only in subjects ≥7 years old at baseline
Height	X	X	X		
Weight	X	X	X		
Physical examination			X		Full (Visit 11)
Concomitant medications	X	X	X	X	
Adverse events	X	X	X	X	
Hematology sample	X	X	X		
Biochemistry sample	X	X	X		To be collected in fasted state
PK sample			X		Pre-morning dose and 2 hours post-morning dose
Vital signs	X	X	X		
PUL	X	X	X		Performed only in subjects ≥7 years old at baseline
Myometry	X	X	X		Performed only in subjects <7 years old at baseline
6-minute walk test	X	X	X		
NSAA	X	X	X		
Timed function tests	X	X	X		
Study drug dispensed	X	X			Open-label study drug dispensed at Visit 8
Study drug compliance	X	X	X		
12-lead ECG			X		
Spirometry			X		Required at all visits after subject loses ambulation
Echocardiogram			X		
Upper leg imaging			X		Performed only at pre-qualified sites. May be assessed ±4 weeks of visit date

Abbreviations: DMD = Duchenne muscular dystrophy, DMDSAT = DMD Functional Ability Self-Assessment Tool, ECG = electrocardiogram, EQ-5D = EuroQoL 5-Dimension, NSAA = North Star Ambulatory Assessment, PK = pharmacokinetic; PROM = Patient-Reported Outcome Measure, PUL = Performance of Upper Limb

6.2 Explanation of Study Procedures

6.2.1 Pretreatment, Treatment, and Follow-Up Periods

No study-related procedures should be performed prior to the signature of the informed consent/assent document(s). To accommodate subjects who must travel a long distance to visit the site, a subject may be consented by phone prior to Visit 1 if this is allowed by local regulation; in this situation, the screening period of up to 2 weeks will begin on the date of Visit 1. After a subject has completed the necessary screening assessments and has been confirmed to be eligible by the investigator, the baseline visit (Visit 2) for the subject can be scheduled.

To the extent possible, excessive physical activity should be avoided on the day prior to a clinic visit; if the subject will be undergoing MRI, then excessive physical activity should be avoided for 3 days prior to the imaging procedure. All clinic visits should occur in the morning, at approximately the same time of day throughout the study. Ideally, the procedures should be performed in the same sequence at each visit. A recommended sequence of procedures is provided in the Study Reference Manual; however, feedback from the parent/caregiver may be considered in determining whether an alternative sequence may be more appropriate for an individual subject based on factors such as attention span, anxiety about blood tests, etc. For subjects on an intermittent treatment regimen of a corticosteroid, clinic visits ideally should be scheduled such that study-related evaluations are performed at the same approximate timepoint within a subject's corticosteroid regimen in order to avoid confounding effects due to the corticosteroids.

6.2.1.1 Screening Period

Following signature of the informed consent/assent document(s), subjects will report to the clinic for the performance of screening procedures (Visit 1) as noted in Table 3. The screening period is up to 2 weeks in duration; if necessary to schedule the baseline MRI (Section 6.2.26), the screening period may be extended by up to 1 additional week. Following the completion of these procedures, availability of the corresponding procedure results, and successful completion of the Screening entry to the electronic data capture (EDC)/IRT system, eligible subjects will return to the clinic for the performance of baseline procedures (Visit 2).

6.2.1.2 Baseline Treatment Visit (Visit 2)

Before initiating treatment, each study participant will report to the clinic no later than the morning of Day 1 (Visit 2). Fasting for at least 8 hours prior to blood collection is required. On Day 1, the DMD Upper Limb PROM should be administered (if the subject is ≥7 years old) prior to the performance of the other study-related procedures. The subject will return to the clinic the next day for the 2nd 6MWT. After the completion of the 2nd baseline 6MWT (Day 2), the investigator must confirm eligibility. Following investigator confirmation of eligibility, a site representative should access the IRT system and supply the necessary information to obtain a subject randomization number and treatment assignment (see Section 4.3). Study drug will be dispensed on Day 2 of the baseline visit and the subject

and/or parent/caregiver will be instructed regarding study drug storage, reconstitution, and administration. The subject will remain at the clinic until released by the investigator.

6.2.1.3 Treatment Visits During Study

Each subject will subsequently return to the clinical research facility at Week 12 (Visit 3) Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 96 (Visit 9), and Week 120 (Visit 10). Fasting for at least 8 hours prior to blood collection is required; blood collection will be performed at Week 24 (Visit 4), Week 48 (Visit 6), Week 72 (Visit 8), Week 96 (Visit 9), and Week 120 (Visit 10). At these visits, the DMD Upper Limb PROM should be administered (if the subject is ≥7 years old) prior to the performance of the other study-related procedures.

Because of potential changes in subject body weight over time, at Week 24 (Visit 4), Week 48 (Visit 6), Week 72 (Visit 8), Week 96 (Visit 9), and Week 120 (Visit 10), a dose adjustment may be made based on the subject's body weight at that visit. Depending upon the magnitude of change in subject body weight since baseline, the number and strengths of sachets to be used by the subject may remain the same or may be adjusted. If the dose is adjusted, then the new IRT system-determined dose will be initiated on the morning immediately after the applicable visit.

6.2.1.4 End of Treatment

The subject will return to the clinical research facility at Week 144 (Visit 11) for the End-of-Treatment Visit. If the subject discontinues prematurely (ie, before Week 144) and the last visit to the investigational site occurred >3 weeks previously, the procedures that would normally be performed at Week 144 should be performed as a Premature-Discontinuation Visit before the subject leaves the study. Fasting for at least 8 hours prior to blood collection is required. The DMD Upper Limb PROM should be administered (if the subject is ≥7 years old) prior to the performance of the other study-related procedures.

6.2.1.5 Post-Treatment Follow-Up Phone Visit

The subject will be contacted by phone 4 weeks (±7 days) after the last dose of study drug for assessment of AEs and concomitant medications. If the End-of-Treatment Visit occurs >4 weeks after the last dose of study drug, the Post-Treatment Follow-Up Phone Visit does not need to be performed. Post-treatment follow-up s not required for subjects who will continue to receive post-study access to ataluren.

6.2.2 Informed Consent

The investigator, or a sub-investigator listed on the Statement of Investigator Form Food and Drug Administration (FDA) 1572, 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 re-consented with the appropriate age related-documents as needed, if required by local regulations.

6.2.3 Clinical/Medication History

The investigator should review the subject's clinical history, including details relating to DMD and any other medical conditions. Information regarding current medications must be captured on the concomitant medication CRF. Details regarding corticosteroid use within 12 months prior to study entry will be collected on a specific CRF.

6.2.4 Hepatitis Screen

Tests include hepatitis A antibody, hepatitis B core antibody, and hepatitis C antibody. The Central Laboratory Manual should be consulted for collection, processing, and shipping details. ***Note: Only hepatitis B and C results are required for eligibility determination.***

6.2.5 Vital Signs

Vital signs (including systolic and diastolic blood pressure, pulse rate, and body temperature) will be monitored at Screening (Visit 1), baseline (Visit 2), Week 12 (Visit 3) Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 96 (Visit 9), Week 120 (Visit 10), and Week 144 (Visit 11 - End of Treatment/ Premature Discontinuation). The pulse rate and blood pressure determinations will be performed with the subject in a sitting position after a 5-minute rest. Blood pressure will be measured in triplicate and the average will be recorded, as described in the study reference manual.

6.2.6 Height, Weight, and Physical Examination

Height (in cm) and weight (in kg) will be measured at Screening (Visit 1), Baseline (Visit 2), Week 12 (Visit 3), Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 96 (Visit 9), Week 120 (Visit 10), and Week 144 (Visit 11 - End of Treatment/Premature Discontinuation). If the subject is unable to stand, sitting arm span and ulna length should be assessed as surrogate measurements for height.

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 at Screening (Visit 1), Week 72 (Visit 8), and Week 144 (Visit 11 - End of Treatment/Premature Discontinuation).

A symptom-directed physical examination will be conducted at Baseline (Visit 2), Week 24 (Visit 4), and Week 48 (Visit 6).

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

6.2.7 Genotyping

Blood for genotyping of genetic modifier candidates (latent TGF-beta binding protein 4 [LTBP4], secreted phosphoprotein 1 [SPP1], cluster of differentiation 40 [CD40]) and thrombospondin 1 [TBHS1] will be collected at Baseline (Visit 2). Sequencing of the dystrophin gene to confirm the presence of a nonsense mutation also will be performed. This sample will be stored at the central laboratory. This blood sample will be destroyed after the

test is completed and a final report is generated by the designated central laboratory. The Study Manual should be consulted for collection, processing, and shipping details.

6.2.8 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 at Screening (Visit 1), baseline (Visit 2), Week 24 (Visit 4), Week 48 (Visit 6), Week 72 (Visit 8), Week 96 (Visit 9), Week 120 (Visit 10), and Week 144 (Visit 11 - End of Treatment/Premature Discontinuation). Hematology parameters will be analyzed by the central laboratory. The Central Laboratory Manual should be consulted for collection, processing, and shipping details.

6.2.9 Serum Biochemistry Laboratory Assessment

Biochemistry laboratory assessments will include sodium, potassium, chloride, bicarbonate, BUN, creatinine, magnesium, calcium, phosphorus, uric acid, glucose, total protein, albumin, globulin, albumin:globulin ratio, bilirubin (direct and indirect), AST, ALT, GGT, CK, lactate dehydrogenase (LDH), alkaline phosphatase, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and cystatin C. These parameters will be measured at Screening (Visit 1), Baseline (Visit 2), Week 24 (Visit 4), Week 48 (Visit 6), Week 72 (Visit 8), Week 96 (Visit 9), Week 120 (Visit 10), and Week 144 (Visit 11 - End of Treatment/Premature Discontinuation). Subjects should have fasted for at least 8 hours prior to blood collection; this is not necessary at screening (Visit 1). Biochemistry parameters will be analyzed by the central laboratory. The Central Laboratory Manual should be consulted for collection, processing, and shipping details.

6.2.10 Pharmacokinetic Assessment

Ataluren concentrations in PK samples will be determined using a validated LC-MS/MS method. The Central Laboratory Manual should be consulted for timing of collection, processing, and shipping details.

6.2.11 Urinalysis

Urinalysis will include analysis for pH, specific gravity, glucose, ketones, blood, protein, urobilinogen, bilirubin, nitrite, and leukocytes. These parameters will be measured at Screening (Visit 1), Baseline (Visit 2), Week 24 (Visit 4), Week 48 (Visit 6), Week 72 (Visit 8), Week 96 (Visit 9), Week 120 (Visit 10), and Week 144 (Visit 11 - End of Treatment/Premature Discontinuation). These parameters will be analyzed by the central laboratory. Urine samples will also be collected and shipped to central laboratory for assessment of urine protein, creatinine, osmolality, and urinalysis. The Central Laboratory Manual should be consulted for collection, processing, and shipping details.

6.2.12 12-Lead ECG

A 12-lead ECG will be obtained at Screening (Visit 1), Week 24 (Visit 4), Week 48 (Visit 6), Week 72 (Visit 8), and Week 144 (Visit 11 - End of Treatment/Premature Discontinuation). The ECG will be performed and interpreted locally. The findings will be captured in source documents and with the CRF.

A follow-up ECG may also be performed at any time during the study as clinically indicated at the discretion of the investigator. The PTC medical monitor must be informed via e-mail that an additional ECG was obtained and the SAE reporting process should be followed, if applicable.

6.2.13 Spirometry

Spirometric evaluation of FVC and other parameters (eg, maximal inspiratory and expiratory pressures, peak expiratory flow) in the sitting position will be performed at screening (Visit 1), Baseline (Visit 2), Week 72 (Visit 8), and Week 144 (Visit 11 - End of Treatment/Premature Discontinuation). If a patient loses ambulation as determined by inability to perform the 10-meter run/walk test within 30 seconds at a clinic visit, then spirometry will be performed at that visit and at all subsequent visits.

6.2.14 Echocardiogram

An echocardiogram will be obtained at Screening (Visit 1), Week 72 (Visit 8), and Week 144 (Visit 11 – End of Treatment/Premature Discontinuation).

6.2.15 Study Drug Randomization

After the completion of the 2nd baseline 6MWT at Week 1, Day 2 (Visit 2, Day 2), a site representative should access the IRT system, following investigator confirmation of eligibility and supply the necessary information to obtain a subject randomization number and treatment assignment (see Section 4.3) in anticipation of administration of the first dose of study drug on the morning or afternoon on Day 2 of the Baseline visit (Visit 2, Day 2). If there is a delay in starting of study drug administration, all subsequent visits will be timed relative to the date that dosing is initiated.

6.2.16 Study Drug Administration

Refer to Section 5.2.

6.2.17 Study Drug Compliance

Subjects and/or parents/caregivers will return unused study drug (sachets and kits) to the study site for full compliance assessments.

6.2.18 Adverse Events

AEs must be assessed and documented at each clinic visit. This information will be collected at Screening (Visit 1), Baseline (Visit 2), Week 12 (Visit 3) Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 96 (Visit 9), Week 120 (Visit 10), and Week 144 (Visit 11 - End of Treatment/Premature Discontinuation). AEs also will be assessed during the Post-Treatment Follow-Up Phone Call (4 weeks post discontinuation of study drug). In addition, subjects and patients/caregivers will be encouraged to report AEs of concern at any time in the intervals between visits.

6.2.19 Concomitant Medications

Information regarding any concomitant medications administered, as well as information regarding all non-drug therapies, will be collected throughout the study. This information will be collected at Screening (Visit 1), Baseline (Visit 2), Week 12 (Visit 3) Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 96 (Visit 9), Week 120 (Visit 10), and Week 144 (Visit 11 - End of Treatment/ Premature Discontinuation). Concomitant medication information also will be collected during the Post-Treatment Follow-Up Phone Call (4 weeks post discontinuation of study drug).

6.2.20 Myometry

Myometry will be performed only in subjects who are <7 years old at baseline.

Upper and lower extremity myometry will be performed using a myometer following standardized procedures (see Study Manual for detailed instructions). Muscle groups to be evaluated include knee extensors and elbow flexors. Bilateral assessments should be done and 3 measurements should be recorded from each muscle group on each side if possible. These parameters will be monitored at screening (Visit 1), Baseline (Visit 2), Week 12 (Visit 3) Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 96 (Visit 9), Week 120 (Visit 10), and Week 144 (Visit 11 - End of Treatment/Premature Discontinuation).

6.2.21 Performance of Upper Limb

PUL will be assessed only in subjects who are ≥7 years old at baseline.

PUL will be administered using standardized equipment and procedures (see Study Manual for detailed instructions) at screening (Visit 1), Baseline (Visit 2), Week 12 (Visit 3) Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 96 (Visit 9), Week 120 (Visit 10), and Week 144 (Visit 11 - End of Treatment/Premature Discontinuation).

6.2.22 6-Minute Walk Test

Ambulation and endurance will be assessed via the 6MWT following standardized procedures (see Study Manual for detailed instructions). The 6MWT will be performed at Screening (Visit 1), Baseline (Visit 2, two 6MWTs performed), Week 12 (Visit 3) Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8, two 6MWTs performed), Week 96 (Visit 9), Week 120 (Visit 10), and Week 144 (Visit 11 - End of Treatment/Premature Discontinuation).

6.2.23 North Star Ambulatory Assessment

The NSAA will be used to evaluate physical function, using standardized procedures (see Study Manual for detailed instructions). The NSAA will be performed at Screening (Visit 1), Baseline (Visit 2), Week 12 (Visit 3) Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 96 (Visit 9), Week 120 (Visit 10), and Week 144 (Visit 11 - End of Treatment/Premature Discontinuation).

6.2.24 Timed Function Tests

Timed function tests of peak physical capacity, including the times taken to climb 4 stairs, and descend 4 stairs, will be performed using standardized procedures (see Study Manual for detailed instructions). These assessments will be performed at Screening (Visit 1), Baseline (Visit 2), Week 12 (Visit 3) Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 96 (Visit 9), Week 120 (Visit 10), and Week 144 (Visit 11 - End of Treatment/Premature Discontinuation).

Time to run/walk 10 meters and time to stand from supine will be assessed as part of the NSAA (Section 6.2.23).

6.2.25 DMD Upper Limb PROM

DMD Upper Limb PROM will be assessed only in subjects who are ≥7 years old at baseline.

The DMD Upper Limb PROM questionnaire will be available in all languages relevant for this study and will be completed by the parent/caregiver. If possible, the same parent/caregiver should complete the questionnaire each time. The DMD Upper Limb PROM questionnaire will be completed at Baseline (Visit 2), Week 12 (Visit 3) Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 96 (Visit 9), Week 120 (Visit 10), Week 144 (Visit 11 - End of Treatment/Premature Discontinuation). Refer to the Study Manual for further details on how to administer the DMD Upper Limb PROM questionnaire.

6.2.26 Magnetic Resonance Imaging/Spectroscopy

MRI and/or magnetic resonance spectroscopy (MRS) will be conducted at a subset of sites that have been pre-qualified by a central imaging vendor to perform this assessment. To be pre-qualified, a site must have access to a whole-body scanner and appropriate personnel at the site must have been trained on the procedure for data acquisition. A list of qualified sites and documentation of equipment and training, as well as whether the site is performing MRI only or MRI and MRS, will be maintained. MRI/MRS data will be analyzed centrally. MRI/MRS will be performed at Baseline (Visit 2), Week 24 (Visit 4), Week 48 (Visit 6),

Week 72 (Visit 8), and Week 144 (Visit 11 – End of Treatment/Premature Discontinuation). The baseline imaging may be performed during the screening period, and post-baseline imaging may be performed ±4 weeks of visit date. To the extent possible, excessive physical activity should be avoided for 3 days prior to imaging assessments.

Subjects with a contraindication to imaging (eg, subjects with a fear of closed spaces or with metal objects in the body that are not scanner-safe) should not undergo imaging but can participate in the rest of the study.

6.2.27 At-Home Questionnaires

HRQL will be measured using the EQ-5D and patient-reported functional ability will be measured using the DMD Self-Assessment Tool [Landfeldt 2015]. These questionnaires will only be completed where validated versions in the local language are available. The questionnaires will be completed by the subject (where possible) and a parent/caregiver. If possible, the same parent/caregiver should complete the questionnaire each time. The questionnaires will be provided at Visit 1 and completed at home by the subject and a parent/caregiver between Visit 1 and Visit 2 (pre-treatment) and approximately once per month for the rest of the study. Site personnel will assess subject compliance with the questionnaires at Baseline (Visit 2), Week 12 (Visit 3) Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 96 (Visit 9), Week 120 (Visit 10), and Week 144 (Visit 11 - End of Treatment/Premature Discontinuation). Refer to the Study Manual for further details on the at-home questionnaires.

6.3 Blood Collection Summary

Assuming a patient completes the study, the maximum amount of blood to be drawn at a visit is approximately 20 mL and the total amount of blood to be drawn over the entire study period is approximately 81 mL.

7 ADVERSE EVENT ASSESSMENTS

7.1 Adverse Event Definitions

7.1.1 Adverse Events

An AE is any untoward medical occurrence associated with the use of a drug 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 study drug 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 study drug administration.
- All AEs resulting from medication misuse, abuse, withdrawal, or overdose, of study drug.
- 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.
- 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 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 (eg, allergic rhinitis) must be noted on the appropriate electronic CRF (eCRF) for Visit 1, but should not be reported as an AE unless the condition worsens or episodes increase in frequency during the AE reporting period. Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that 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 7.1.2, any inpatient hospitalization occurring as the consequence of an AE during the study period should be reported as an SAE.

7.1.2 Serious Adverse Events (SAEs)

An AE that results in one of the following:

- Results in death. This includes all deaths on treatment or within 4 weeks after last study drug administration, including deaths due to disease progression. Any death occurring later than 4 weeks following the last dose need not be reported as an SAE unless it is a result of an event that started within the period covered by the on-study definition. The reported AE should be the event that caused the death.
- 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, hypothetically might have caused death.
- Requires inpatient hospitalization or prolongation of existing hospitalization (excluding hospitalizations for administration of the study drug, procedures required by the study protocol, or DMD-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 disability or incapacity or substantial disruption of the ability to conduct normal life functions, not related to DMD.
- Important medical event: These are AEs that might not be immediately life-threatening or result in death or hospitalization but might jeopardize the subject 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 home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or development of drug dependency or drug abuse.
- A pregnancy resulting in spontaneous abortion, stillbirth, neonatal death, or congenital anomaly (including that in an aborted fetus).

7.1.3 Unexpected Adverse Events

Unexpected AEs are 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 example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the Investigator Brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator Brochure only listed cerebral vascular accidents.

For the purposes of considering expectedness, the Ataluren Investigator Brochure provides a section referred to as the Reference Safety Information.

7.2 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 study drug administration or during any telephone contact with the subject or parent/guardian in case of a child. The type of question asked should be open-ended, eg-, *"How has your child been feeling?"* or a similar type of query.

7.3 Adverse Event Recording

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

- Indication of whether the event is serious or nonserious (see Section 7.1.2)
- Relationship to study drug (see Section 7.4)
- Severity of the event (see Section 7.5)

- Onset date
- Resolution date, or date of death
- Action taken
- Outcome of the event

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

7.4 Describing Adverse Event Relationship to Study Drug

Based on the considerations outlined in Table 5, the investigator should provide an assessment of the relationship of the AE to the study drug, ie, whether there is a reasonable possibility that the study drug caused the AE.

Table 5. Relationship of Study Drug to Adverse Event

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

7.5 Grading of Severity of Adverse Events

The severity of AEs will be graded using the CTCAE Version 4.0. 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 6.

Table 6. 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 affects clinical status, and may require medical intervention
Grade 3	Severe	Sign or symptom is incapacitating or significantly affects clinical status and likely requires medical intervention and/or close follow-up
Grade 4	Life-threatening	Sign or symptom results in a potential threat to life
Grade 5	Fatal	Sign or symptom results in death

Note the distinction between the seriousness and the severity of an AE. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious event. 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 7.1.2.

7.6 Pregnancy of Female Partners

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 and PTC Pharmacovigilance of the outcome within 24 hours. 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 (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including in an aborted fetus]), the investigator should follow the procedures for reporting SAEs, ie, report the event to the PTC Therapeutics Safety Department or designee and follow up by submission of appropriate AE CRFs (see Section 7.9).

7.7 Follow-Up of Unresolved Adverse Events

All AEs should be followed up by the investigator until they are resolved, or the investigator assesses them as chronic or stable. The investigator should consider protocol guidelines and use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events. In the event of additional investigations, the PTC Therapeutics Pharmacovigilance Department or designee should be informed via email or fax. 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.

7.8 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 with the 4-week (± 7 days) Post-Treatment Visit, except as described in Section 7.7. In addition, SAEs occurring in a subject after the study period should be reported to the sponsor if the investigator becomes aware of them.

7.9 Investigator Site Adverse Event Reporting Requirements

Classification of an event as serious or non-serious (see Section 7.1.2) determines the reporting procedures to be followed. Investigator site reporting requirements for AEs are summarized in Table 7.

Table 7. Investigator 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

7.10 Serious Adverse Event Reporting

All SAEs should be reported via the SAE report form to PTC Therapeutics within 24 hours of becoming aware of the event(s). In addition, the AE portion of the eCRF must also be completed.

The SAE report form should be signed by the investigator; however, if the investigator is unable to sign at the time of the event or within 24 hours, the form should be signed by the clinical staff member reporting the SAE (eg, the study coordinator). The SAE report form must be faxed or emailed to the PTC Therapeutics Pharmacovigilance Department or designee and to the site IRB/EC (if required by local regulations) within 24 hours. Follow-up information to the SAE should be clearly documented as "follow-up" in the SAE report form and must also be faxed or emailed to the same party. All follow-up SAE report forms for the

event must be signed by the investigator. Any source documents (eg, progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries) provided to the sponsor 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 (in regions where the provision of such information is permitted). 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 Pharmacovigilance Department contact information for reporting SAEs is provided below. This information is also provided in the Study Manual and in the SAE report form. In Japan only, send to both email addresses.

E-mail: **Pharmacovigilance@ptcbio.com**
prj-as-ptc124-pv@eps.co.jp
SAE Fax Line: **1-908-325-0355**

7.11 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 or its designated representative 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/EC per their local requirements. The initial expedited safety report will be provided as required according to local regulations (eg, within 15 days) after the earliest date PTC Therapeutics or an agent of PTC Therapeutics (eg, a site monitor) becomes aware of an AE. This awareness date is the date the regulatory reporting clock begins and the date is considered Day 0.

8 WITHDRAWAL OF SUBJECTS

All subjects who receive study drug should remain in the study whenever possible, including after loss of ambulation. However:

- The subject has the right to withdraw consent and discontinue study drug at any time.
- If the subject's condition substantially worsens after initiating study drug, 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.
- Upon consultation with the PTC Therapeutics medical monitor, the investigator may withdraw the subject from study drug, if, in the investigator's clinical judgment, it is not in the subject's best interest to continue.
- If the subject becomes significantly noncompliant with study drug administration, study procedures, or study requirements. In this event, the subject should be withdrawn from study treatment when the circumstances surrounding noncompliance increase risk to the subject or are anticipated to substantially compromise the interpretation of study results.
- The subject will be withdrawn from treatment if he is unable to tolerate study drug.
- The subject may be withdrawn from this study in circumstances where the blind is intentionally or accidentally broken.
- This study may be discontinued by the relevant regulatory authority and/or PTC Therapeutics at any time.

The date study drug is discontinued and the reason for discontinuation will be recorded in the source documents and in the eCRF.

When study drug is discontinued (regardless of the reason), the investigator should encourage that all of the evaluations required at the End of Treatment Visit be performed 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.

Subjects may be replaced if they withdraw from the study because ataluren has become commercially available in their country. Subjects removed from the study for any other reason will not be replaced.

9 STATISTICS AND DATA MANAGEMENT

Statistical considerations for this international study are described below. Any country-specific statistical considerations, if requested by regulatory authorities, will be described in a separate statistical analysis plan.

9.2 Study Population Definition

9.2.1 Intention-to-Treat (ITT) Population

This population will include all subjects who are randomized, with treatment assignments designated according to initial randomization, regardless of whether subjects receive a different study treatment from the one randomized. In addition, subjects in this population must have a valid 6MWT at baseline, and at least one valid post-baseline 6MWT. This population will be used for summary and analysis of efficacy endpoints.

9.2.2 Modified Intention-to-Treat (mITT) Population

This population will include all subjects in the ITT population who meet the following additional criteria: ≥7 to ≤16 years old with 6MWD ≥300 meters and time to stand from supine ≥5 seconds at baseline. This population will be used for the primary endpoint analysis, and other supportive analyses.

9.2.3 As Treated - Population

The as-treated population consists of all randomized subjects who receive study treatment, with treatment assignments designated according to actual treatment received. This population will be used for summary and analysis of safety endpoints.

9.2.4 Per-Protocol Population

This population will include all subjects in the mITT population who meet the following additional criteria: received study treatment in agreement with randomization, completed the 72-week double-blind treatment period, had drug compliance between 75% and 125%, inclusive, and had no inclusion or exclusion criteria violations and no major protocol violations. This population will be used for supportive efficacy analyses.

9.2.5 Evaluable Populations

In general, evaluable populations consist of all as-treated subjects who have sufficient data to assess the measure of interest (eg, HRQL questionnaire). These populations may be evaluated in the analysis of other secondary endpoints.

9.3 General Statistical Considerations

By-subject listings will be created for each CRF module. Summary tables for continuous variables will contain the following statistics: n, mean, standard deviation, standard error, 95% confidence intervals (CIs) on the mean, median, minimum, and maximum. Summary tables for categorical variables will include N (population), n (subgroup), percentage, and 95% CIs on the percentage. Where applicable, the summary data (mean, standard error) will be presented in graphical form against time of visit. Unless otherwise specified, all inferential analyses will be 2-sided at the alpha (α) 0.05 level of significance.

9.4 Specific Statistical Analyses

9.4.1 Study Conduct and Subject Disposition

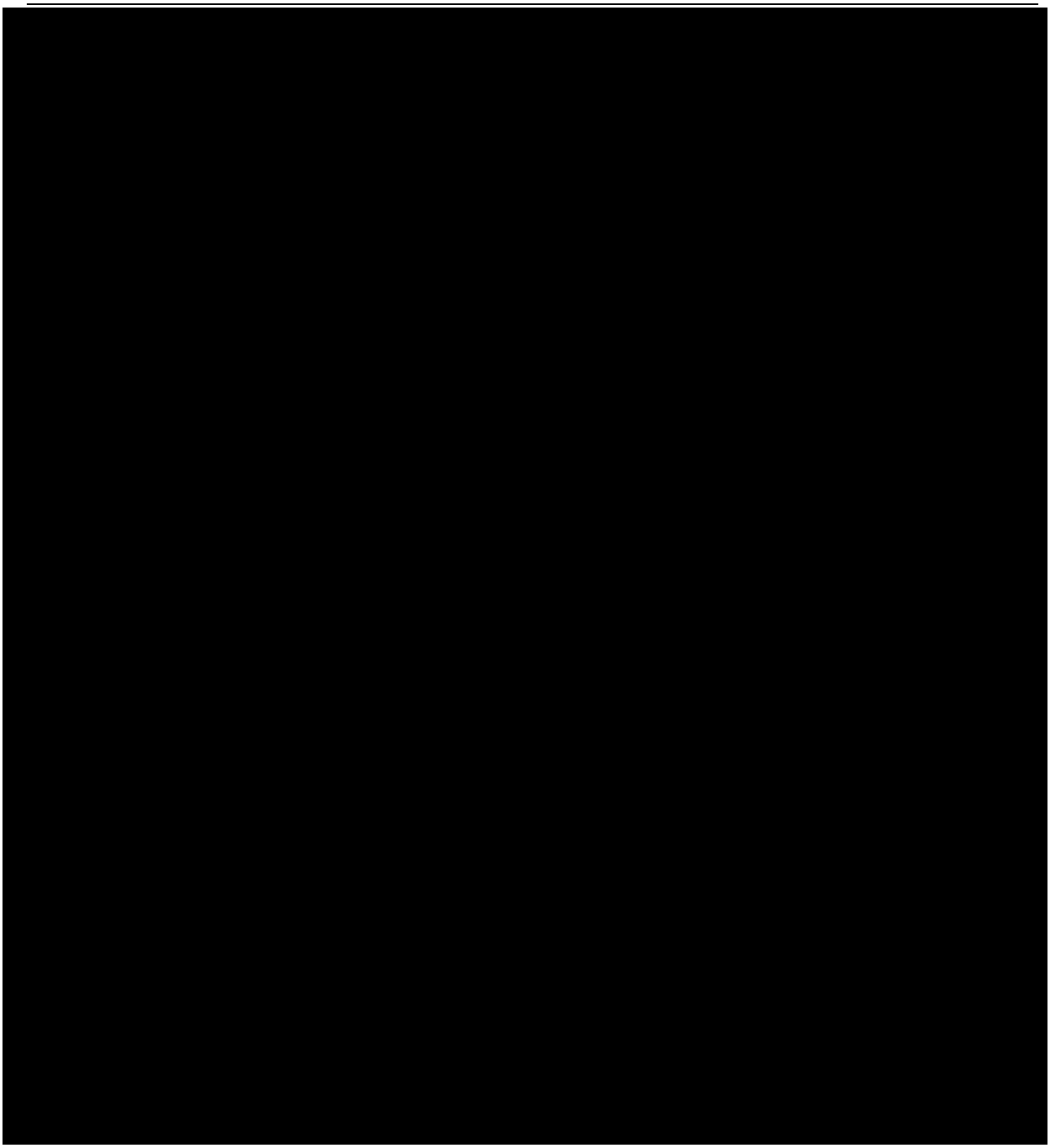
The number of subjects screened and randomized, and the number of subjects completing all planned study assessments, will be summarized by treatment. Subjects who discontinue study drug or are removed from the study prematurely will be summarized by reason for discontinuation and treatment. Randomization errors, and timing of withdrawal from the study will be described.

9.4.2 Baseline Characteristics and Treatment Group Comparability

Baseline subject characteristics for each study population, and for each phase of the study, will be summarized using frequency tables for categorical variables and descriptive statistics for quantitative variables.

9.4.3 Use of Concomitant Medication and Supportive Therapy

Concomitant medications will be coded using the World Health Organization Drug Dictionary (WHODRUG), using Anatomical Therapeutic Chemical classification (ATC) codes. The incidence of specific concomitant medications will be summarized by treatment group, for the pre-treatment, double-blind, and open-label periods. Specific attention will be given to corticosteroids, and to drugs for prophylaxis and/or treatment of congestive heart failure. The type and timing (pre-treatment, double-blind, and open-label) of such drugs will be summarized by treatment group. The incidence of changes in regimen for such drugs will also be summarized for the double-blind and open-label periods.



9.4.5 Secondary Endpoints

9.4.5.1 Timed Function Tests

Timed function tests (10-meter run/walk, 4-stair stair-climb, and 4-stair stair descend) will be analyzed using the analysis methods outlined for the primary efficacy variable (MMRM and ANCOVA), for both the mITT and ITT populations, at the end of the double-blind and open-label phases. A separate analysis will evaluate 10-meter run/walk results in subjects with a baseline 6MWD <300 meters. An additional analysis will evaluate a composite endpoint of average change in times to run/walk 10 meters, climb 4 stairs, and descend

4 stairs. Subjects who cannot perform a timed function test within 30 seconds will be assigned a value of 30 seconds for the analysis.

[redacted]

9.4.5.3 North Star Ambulatory Assessment

The NSAA consists of 17 activities, each scored as 0, 1, or 2. The sum of these 17 scores will be used to form a total score. This total score will be analyzed using the ANCOVA analysis method outlined for the primary efficacy variable, for both the mITT and ITT populations, at the end of the double-blind and open-label phases. A separate analysis for the open-label phase will evaluate changes in total score in subjects with a baseline 6MWD ≥400 meters and <7 years of age. Transformation of the total score to a linear scale [Mayhew 2013a] also will be performed. In addition, the odds of losing one or more of the NSAA items (score of 1 or 2 at baseline transitioning to a 0 score post-baseline) will be evaluated for ataluren versus placebo subjects using a risk ratio derived via re-sampling based analysis methods; the "lifts head" item will be excluded from this analysis because it does not fit the original construct of the NSAA based on Rasch analysis [Mayhew 2013a].

[redacted]

[redacted]

9.4.7 Safety

Vital sign results, including height and weight, will be summarized by treatment group, and by double-blind and open-label phases. Physical examination results will be listed. AEs will be classified using MedDRA, according to system organ class and preferred term. The severity of AEs will be graded according to the latest version of the CTCAE whenever possible. A treatment-emergent adverse event (TEAE) is defined as an AE that occurs or worsens in the period extending from the first dose of study drug to 4 weeks after the last dose of study drug in this study. The incidence of subjects experiencing specific TEAEs will be tabulated by treatment group, and by double-blind and open-label phases. Subjects experiencing the same event more than once will be counted only once. AEs will be summarized by worst CTCAE grade. AEs classified as CTCAE Grade 3 or higher, study-drug-related events, renal events leading to special diagnostic evaluations, events leading to discontinuation from treatment, and SAEs will be considered with special attention. Hematological data, serum biochemistry, and urine data will be summarized by treatment group, and by double-blind and open-label phases. Values will be graded according to CTCAE severity grade, when applicable. For variables graded according to CTCAE severity grade, the incidence of the worst severity grade observed will be displayed. 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 by treatment group, and by double-blind and open-label phases. ECG data will be summarized by treatment group, and by double-blind and open-label phases.

9.4.8 Pharmacokinetic analyses

Plasma concentration collected at the last visit (Week 144) will be summarized with descriptive statistics (eg, n, arithmetic mean, standard deviation, standard error, median, minimum, and maximum, CV% mean, geometric mean, and CV% geometric mean). Additionally, the SAP will be developed to include evaluation of correlation between plasmatic concentrations of ataluren and 6MWD and TFT, including time to run/walk 10 meters, time to 10% worsening in 6MWD and other outcomes that are sufficiently sensitive.

9.5 Description and Timing of Analysis

When all subjects have completed the study and data entry is complete, the database will be locked, archived, unblinded, and analyzed.

10 OBLIGATIONS OF THE INVESTIGATOR AND THE SPONSOR

10.1 Compliance with Ethical and Regulatory Guidelines

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

10.2 Institutional Review Board/Independent Ethics Committee

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

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

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

10.3 Informed Consent/Assent

By signing the protocol, the investigator assures that informed consent/assent will be obtained from each subject and/or parent/legal guardian prior to performing any study-related activities and that the informed consent/assent will be obtained in accordance with current regulations.

The investigator, or a sub-investigator listed on the Statement of Investigator Form FDA 1572, 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 studyrelated- 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 and/or parent/guardian should be able to ask additional questions as and when needed during the conduct of the study. The subject's and/or parent(s)/guardian signature (as required by local regulations) on the informed consent form should be obtained at the investigator site in the presence of the investigator or a qualified representative (eg, sub-investigator). Where applicable, the subject will sign an age-appropriate assent form.

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/EC.

10.4 Electronic Case Report Forms

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

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

10.5 Study Records

During the study, the investigator will maintain adequate records for the study, including medical records, source document records detailing the progress of the study for each subject, laboratory reports, a CD-ROM or paper copy of the data that have been captured in the EDC for each subject (eCRFs), paper CRFs, signed informed consent forms, study drug disposition records, correspondence with the IRB/EC, AE reports, and information regarding subject discontinuation and completion of the study. Current regulations require PTC Therapeutics (or an authorized designee) to inspect all documents and records required to be maintained by the investigator, including but not limited to medical records (office, clinic, or hospital) for the subjects enrolled in this study. These regulations also allow the same records to be inspected by regulatory authorities.

10.6 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 eCRFs, paper 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 redacting the subject's name and replacing the name with the subject's study ID 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/EC under an appropriate understanding of confidentiality with such board.

10.7 Retention of Records

To enable evaluations and/or audits from regulatory authorities or PTC Therapeutics, the investigator agrees to keep accurate and complete records, including the identity of all participating 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 (eCRFs), and detailed records of study drug disposition. All records and documents pertaining to the study (including but not limited to those outlined in Section 10.5) will be maintained by the investigator until notification is received from PTC Therapeutics that the records no longer need to be retained.

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

10.8 Monitoring and Auditing

In accordance with 21 Code of Federal Regulations Part 312.56 and/or relevant ICH guidelines, PTC Therapeutics or a designee will periodically inspect all eCRFs (see Section 10.4), study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times, before, during, and after completion of the study. As required by applicable regulations (Responsibilities of Sponsors and Investigators), the monitoring visits provide PTC Therapeutics with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of data in the eCRFs; ensure that all protocol requirements, 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.

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

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

10.9 Termination of the Study

PTC Therapeutics reserves the right to discontinue the study prior to inclusion of the intended number of subjects. The investigator, after consultation with the PTC Therapeutics medical monitor, reserves the right to discontinue the study at the investigator 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 timeperiod- 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.

10.10 Public Notification of Study Conduct

Consistent with requirements of the International Committee of Medical Journal Editors as a condition of consideration for publication of study results, PTC Therapeutics will be responsible for ensuring that this protocol is listed in the applicable clinical trials registry(s) and that information in the clinical trials registry(s) relating to study design and conduct is appropriately updated during the course of the study. In order to facilitate this process, investigators will need to supply PTC Therapeutics with appropriate contact information for investigator site personnel.

10.11 Dissemination of Results

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

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

10.12 Communication with Regulatory Authorities

PTC Therapeutics (or designee) will assume responsibility for regulatory interactions with the applicable regulatory authorities. In fulfilling this responsibility, PTC Therapeutics (or a designee) will collect, assemble, and communicate all required regulatory documents (eg, investigator financial disclosure forms, protocol and protocol amendments, investigator brochures, informed consent documents, annual reports) as required by regulation. PTC Therapeutics (or a designee) will also assume responsibility for AE reporting to regulatory authorities as described in Section 7.11.

11 RATIONALE FOR STUDY DESIGN FEATURES

11.1 Endpoint Selection

11.1.1 Overview

Endpoints have been selected based upon their ability to measure important aspects of DMD according to the scientific literature, their inclusion in regulatory guidance documents on clinical trials in DMD, their use in previous trials of ataluren and other investigational therapies for DMD, and/or their applicability across the age range of this study. Scientific advice from regulatory authorities and the efficacy results of Study 007 and Study 020 have also been considered in the selection of endpoints.

11.1.2 6-Minute Walk Test

The 6MWT is an established outcome measure reflecting the global status of all the systems involved in walking, including the neuromuscular, pulmonary, and cardiovascular systems [Takeuchi 2008]. The 6MWT assesses walking ability and endurance, both of which are important in measuring the disease status of patients with DMD. Based on precedent for using the 6MWT as a primary outcome measure in registration-directed trials of other neuromuscular disorders [Rubin 2002, Wraith 2004, Muenzer 2006], PTC Therapeutics collaborated with the University of California-Davis to adapt the 6MWT to accommodate the physical and behavioral characteristics of children with DMD [McDonald 2010a]. Standardized guidelines for conduct of the 6MWT in the DMD population and multicenter training procedures for use in DMD clinical trials were developed [McDonald 2010a]. The 6MWT was shown to be validated, feasible, accurate, and reproducible in the target population [McDonald 2010b]. Subsequently, the 6MWT has been extensively evaluated in DMD clinical trials and natural history studies [Mazzone 2011, Goemans 2013, Henricson 2013, Mazzone 2013, McDonald 2013a, McDonald 2013b, Pane 2014a, Pane 2014b, Pane 2014c, Mazzone 2016, Mercuri 2016, Willcocks 2016].

11.1.3 Timed Function Tests

Timed function tests of running/walking 10 meters, climbing 4 stairs, and descending 4 stairs have been used for decades in DMD to monitor the progression of the disease and guide management of the patient [Brooke 1989, McDonald 1995]. Clinical evaluators in a multicentric setting are able to obtain highly reliable measurements [Mayhew 2007]. Worsening values have been correlated with time to wheelchair dependency and sensitivity to medical intervention has been shown [Mendell 1989, Griggs 1991, Beenakker 2005]. In addition, significant correlations between timed function test values and actual participation in daily life physical and social activities have been established [Bendixen 2014].

11.1.4 North Star Ambulatory Assessment

The NSAA is a functional scale specifically designed for ambulant DMD patients. The scale has been developed and piloted in the United Kingdom by the North Star Clinical Network for Paediatric Neuromuscular Disease Management with good intra- and inter-observer reliability and has recently been used in a large multicenter study [Mazzone 2011]. The scale consists of 17 items, ranging from standing (item 1) to running (item 17). It includes several items assessing abilities that are necessary to remain functionally ambulant; items assessing abilities, such as head raise and standing on heels, that can be partly present in the early stages of the disease; and a number of activities, such as hopping or running, that are generally never fully achieved in untreated boys with DMD but that have been found in those treated with daily steroids.

11.1.5 Myometry

Myometric evaluation of limb strength is less sensitive than timed function tests to changes in disease status [Beenakker 2005]. Changes in muscle strength (as assessed by myometry) are most likely to be seen in DMD boys <7 years of age, while patients ≥7 years old show small changes in muscle strength by year, indicative of a floor effect. Because muscle strength is lost predominantly during earlier stages of the disease, a clearer effect of dystrophin replacement therapy on muscle strength may be expected in younger patients. For these reasons, myometry will be performed only in subjects <7 years of age. (Note: Upper limb function will be assessed in subjects ≥7 years old [Section 11.1.6]).

In subjects <7 years of age, hand-held myometry will be employed to test knee extension and elbow flexion. These two muscle groups have shown the greatest test-retest reliability for quantitative myometry in boys with DMD [Mayhew 2007].

11.1.6 Performance of Upper Limb (PUL)

The PUL is a scale designed to measure motor performance of the upper limbs in DMD. The PUL was created within a conceptual framework reflecting the progression of weakness and natural history of functional decline evident in both the ambulant and non-ambulant stages of DMD. Modern psychometric methods were used to create a scale with robust internal reliability, validity, and hierarchical scalability; males with DMD and their families were involved iteratively throughout the process of the clinician-reported outcome assessment tool development to establish clinical meaningfulness and relevance of individual PUL items to activities of daily living [Mayhew 2013b]. The PUL includes 22 items (with an entry item to define starting functional level to avoid testing functional dimensions in which the patient

lacks the lower limit of function, and 21 items subdivided into shoulder level (4 items), elbow level (9 items), and distal level (8 items) dimensions.

11.1.7 DMD Upper Limb PROM

The DMD Upper Limb PROM has been developed to assess disease progression in the upper limbs, beginning in the ambulatory stage of the disease through the transition to the non-ambulatory stage of the disease [Klingels 2016]. Thus, this outcome measure can provide information on the efficacy of ataluren even after subjects in the study lose ambulation. In addition, the DMD Upper Limb PROM provides information on activities of daily living that cannot otherwise be observed in a clinical or research setting (eg, feeding, washing, and leisure activities). This DMD-specific questionnaire includes 32 items categorized in 4 domains of daily life: food (7 items), self-care (8 items), household and environment (6 items), and leisure and communication (11 items). The 32 items were selected, with input from DMD patients, physicians, physiotherapists, and sponsors, to cover a wide range of upper limb activities in daily life, from unimanual to bimanual activities and dexterity. The DMD Upper Limb PROM was designed for patients ≥7 years old, the age at which the maximum score is achieved by typically developing children. However, it is completed by a parent/caregiver until the patient is ≥16 years old. Excellent test-retest reliability (ICC=0.99) has been demonstrated [Klingels 2016].

11.1.8 Magnetic Resonance Imaging

Progressive fatty and fibrotic replacement of muscle due to an absence of dystrophin underlies the phenotypic manifestations of muscle weakness in boys with DMD. Quantitative MRI enables non-invasive, objective measurement of muscle pathophysiology in patients with DMD [Willcocks 2016]. 3-point Dixon imaging separates muscle fat and water based on phase difference (chemical shift) and provides measurement of muscle fat without any confounding effect of muscle edema. A standardized MRI protocol has been developed to facilitate image acquisition across multiple sites. Using centralized data analysis, quantitative evaluations of muscle fat fraction can be derived for leg muscles with important functional roles, such as the vastus lateralis. Inclusion of MRI in this trial offers the potential for tying an imaging biomarker to clinical benefit. Due to the need for specific equipment and trained operators, MRI will be conducted only at sites that have been qualified to perform this assessment based on access to the necessary equipment and trained operators. Although only a subset of sites will participate, it has been reported in the literature that the sensitivity of MRI may reduce the sample size needed to demonstrate a treatment effect, compared to functional outcome measures such as the 6MWT [Bonati 2015, Willcocks 2016]; this hypothesis remains to be confirmed. A limited number of MRI sites will also assess muscle fat fraction by MRS to explore the correlation between MRI and MRS.

11.1.9 At-Home Questionnaires

Regulatory guidelines for DMD clinical trials recommend assessment of subject- and parent/caregiver-reported HRQL [EMA 2015, FDA 2015]. Such information may help to confirm more objective measures of patient benefit, and document how drug activity translates to improved well-being outside of the clinic. The EQ-5D is a simple generic instrument developed by a multidisciplinary group of researchers, has been validated in many countries, and has been used to evaluate HRQL in patients with DMD [Cavazza 2016]. The DMD Self-Assessment Tool is a patient-reported outcome scale designed to measure functional ability in patients with DMD [Landfeldt 2015]. Both questionnaires will be completed at home, which may more accurately reflect the subject's routine experience compared to in-clinic completion. These questionnaires will only be completed where validated versions in the local language are available. The questionnaires will be completed by the subject (where possible) and a parent/caregiver.

11.1.10 Safety Profiling

As is conventional, safety will be characterized in terms of the type, incidence, timing, severity, drug-relatedness, and seriousness of AEs and laboratory abnormalities. For consistency of interpretation, AEs will be coded using the MedDRA, the severity of these events and laboratory abnormalities will be graded using the well-defined CTCAE and concomitant medications will be coded with the WHODRUG dictionary.

11.1.11 Study Drug Compliance

Evaluation of study drug compliance provides context for assessments of efficacy and safety, and may offer a general indication of subject acceptance of therapy, integrating factors of tolerability, palatability, and convenience. The compliance of the subject will be verified by counting used drug study sachets.

11.1.12 Timing of Assessments

The timing of study assessments is appropriate in the context of a chronic study. The 12-week interval of subject visits permits inclusion of 6 post-baseline evaluations of efficacy during the randomized study period, ensuring that time trends can be adequately assessed and that sporadically missing data do not have a substantial impact on data analysis. Visits are paced sufficiently closely so that subjects and sites can become familiar with the routine of the study, but are sufficiently spaced so that learning and carryover effects are unlikely. Consideration has been given to the prospect that many subjects will need to travel considerable distances to study sites and that sites may achieve limiting capacity to accomplish study visits and data flow once multiple subjects are being followed simultaneously at a single site.

Study activities have been mapped across the study as outlined in the Schedule of Events (see Table 3 and Table 4) and within each study visit (see Study Manual); the intent is minimize variability by maintaining a clear and consistent approach to evaluations for each subject, across subjects at a site, and across sites. In particular, patient- and parent/caregiver-reported questionnaires are administered early, before later events in the day may influence reporting.

11.2 Subject Selection

11.2.1 General

The eligibility criteria are designed to limit enrollment to subjects who clearly have DMD based on clinical, laboratory, and genetic findings but are sufficiently well (both in terms of DMD and in terms of concomitant illness) to safely participate in study procedures and provide interpretable results. Consistent with GCP guidelines, parents and subjects must provide informed consent/assent before initiation of any study procedures. To minimize missing data and premature discontinuations, subjects must have the personal and family resources to comply with study procedures and restrictions. In addition, subjects must not have serious concomitant conditions that would compromise safety, compliance, or evaluation.

11.2.2 DMD Diagnosis

It is essential that subjects have a definite clinical and genetic diagnosis of DMD to justify the potential risks and inconvenience of involvement in the study. Mild patients are excluded by the requirement for disease presentation prior to age 6, in order to avoid difficulties in measuring a treatment effect within the 72-week treatment period. Restriction of enrollment to subjects with a nonsense mutation as the basis for DMD avoids the therapy of subjects who have no chance of benefit; it is known from prior studies with gentamicin that full-length protein production was seen only in subjects harboring a nonsense mutation as the exclusive basis for disease [Clancy 2001, Wilschanski 2003].

11.2.3 Age

This study will enroll patients ≥5 years old, consistent with the conditionally approved indication in Europe. However, the primary analysis will be conducted in a subset of patients who are ≥7 and ≤16 years old and meet additional criteria, as defined in Section 9.2.2.

In DMD, disease-related progressive loss of muscle function occurs against the background of normal growth and development, where initial gains attributable to normal growth and development are eventually outpaced by losses due to disease progression [Henricson 2012]. A 1-year observational study of the 6MWT in patients with DMD and healthy controls (conducted by PTC Therapeutics in collaboration with Craig McDonald, MD, University of California-Davis) demonstrated that 6MWD in boys with DMD tends to improve up to age 7 and decline due to disease progression thereafter [McDonald 2010a; McDonald 2010b]. This tendency for 6MWD to increase prior to age 7 and to decrease in older DMD patients was confirmed in a separate natural history study [Mazzone 2011]. In subjects who are 5 and 6 years old, a treatment benefit may be obscured due to the confounding effect of normal

growth and development. Therefore, patients who are 5 and 6 years old are eligible for the study but will not be included in the primary analysis.

Patients who are ≥16 years old and ambulatory at baseline may be considered to have a milder phenotype and a slower trajectory of disease progression. To limit the variability of study results, these patients will not be included in the primary analysis population.

11.2.4 Baseline 6MWD

This study will enroll subjects with 6MWD ≥150 meters at pretreatment assessments. However, the primary analysis will be conducted in a subset of patients who have with 6MWD ≥300 meters at pretreatment assessments and meet additional criteria, as defined in Section 9.2.2.

The requirements that subjects enrolled in the study be able to walk 150 meters during the screening 6MWT provides an objective means to ensure that subjects are truly ambulatory, as ataluren is indicated for ambulatory patients with nmDMD. Assessing this distance is convenient because it constitutes 6 laps of a 25-meter course.

Patients with baseline 6MWD <300 meters have a high muscle fat fraction and therefore a high risk of near-term loss of ambulation [Sweeney 2014]. To limit the variability of study results, these patients will not be included in the primary analysis population.

11.2.5 Baseline Timed Function Tests

This study will enroll patients who are able to complete several timed function tests (run/walk 10 meters, climb 4 stairs, descend 4 stairs, and stand from supine) within 30 seconds at pretreatment assessments. This inclusion criterion ensures that patients will be evaluable for changes from baseline in the timed function tests, which are important secondary endpoints in this study.

Time to stand from supine significantly predicts for change in 6MWD, as demonstrated in two separate natural history studies [Goemans 2016, Mazzone 2016]. Patients who are able to stand from supine in <5 seconds are likely to remain relatively stable over the 72-week double-blind treatment period, potentially obscuring a treatment benefit in these patients. Therefore, these patients will not be included in the primary analysis population as defined in Section 9.2.2.

11.2.6 Reproductive Considerations

Ataluren is not genotoxic, did not affect fertility in male and female rats, and was not teratogenic in rats and rabbits. In addition, lack of sexual maturity in most of the subjects likely to be enrolled in this study limits reproductive risks. However, restriction on eligibility relating to willingness to avoid unprotected sexual intercourse in any subjects known to be sexually active is included as a general precaution.

11.2.7 Prior and Concomitant Therapies

11.2.7.1 Corticosteroids

Although not specifically approved by regulatory authorities for treatment of DMD, corticosteroids are commonly employed in this subject population [Matthews 2016]. Recently, a Centers for Disease Control and Prevention working group strongly urged consideration of corticosteroid therapy in all patients with DMD [Bushby 2010a]. A completed Phase 3 study of exon-skipping therapy in a subset of patients with DMD required corticosteroid use as an entry criterion [http://clinicaltrials.gov/ct2/show/NCT01254019]. Limiting eligibility to patients receiving a stable corticosteroid regimen of prednisone/prednisolone or deflazacort is expected to reduce the variability of slope of change in 6MWD (the primary endpoint), thereby minimizing the required sample size to demonstrate a statistically significant treatment effect and enhancing study feasibility.

11.2.7.2 Other Prior and Concomitant Therapies

Conventional supportive therapies will be permitted; however, efforts will be made to avoid use of concomitant medications that might confound interpretation of study results (eg, aminoglycosides) or pose a safety risk (immunosuppressive therapy other than corticosteroids). Ataluren has not proven to be allergenic in studies performed to date, but review of known allergies to excipients contained in the formulation is prudent. Other restrictions relating to recent use of experimental drugs or surgery allow candidates sufficient time to recover before proceeding to study drug dosing. Subjects are not permitted to enroll who have had changes in the use of ACE inhibitors or ARBs for the prophylaxis/treatment of cardiomyopathy within 1 month to start of study due to the potential to confound study results. Restrictions against enrollment of patients expected to have major surgical procedures during the course of the study or who have substantial respiratory or cardiac compromise are intended to avoid safety problems or gaps in study drug administration in patients who require intensive supportive care.

11.3 Methods to Reduce Bias

11.3.1 Randomization

Randomization is an accepted means to reduce bias and allows for the highest standard of evidence in documenting a treatment effect. The stratified, block randomization approach will be used. The system will assign the next available randomization number, within the list for the stratum, to the patient. Such a method allows treatment arms to be balanced with respect to the predefined stratification factors as well as for the number of subjects in each arm. The process will be established and performed centrally by an experienced CRO through an IRT system to maximize the integrity and security of the randomization and ensure appropriate access and convenience-of-use by the investigational sites.

11.3.2 Stratification

The 3 stratification factors (type of concomitant corticosteroid use at baseline [deflazacort versus prednisone/prednisolone], baseline 6MWD [<300 meters versus ≥300 to <350 meters versus ≥350 to <400 meters versus ≥400 meters], and baseline time to stand from supine [<5 seconds versus ≥5 seconds]) are included to balance allocation of patients into treatment groups by these important parameters.

Although not specifically approved by regulatory authorities for the treatment of DMD, the DMD Care Considerations Working Group strongly urges consideration of corticosteroid therapy in all patients who have DMD [Bushby 2010a]. Types of corticosteroids used in DMD included deflazacort, prednisolone, and prednisone. As prednisone is metabolized to prednisolone, prednisone and prednisolone are equipotent [Matthews 2016]. There is mixed evidence with respect to the comparative efficacy of deflazacort versus prednisone/prednisolone as treatments for DMD. Some reports have indicated that deflazacort and prednisone/prednisolone may be equivalent in improving motor function [Gloss 2016], while longer-term natural history data have associated use of deflazacort with later loss of ambulation [Bello 2015]. On the basis of the latter finding, stratification by deflazacort versus prednisone/prednisolone in DMD clinical trials has been recommended [Bello 2015].

DMD natural history studies have documented that baseline 6MWD is a significant predictor of change in 6MWD [Mazzone 2011, Goemans 2013, Mazzone 2013, McDonald 2013a, McDonald 2013b, Pane 2014a]. Therefore, it is important to ensure that the treatment arms are well balanced by baseline 6MWD. In the previous Phase 3 trial of ataluren for nmDMD, subgroup analyses showed a large treatment difference in patients with baseline 6MWD ≥300 meters to <400 meters. Within the ≥300 meters to <400 meters stratum, further stratification by <350 vs ≥350 meters may be important to achieve the desired balance between treatment arms. In patients with less advanced disease severity (>400 meters at baseline), 6MWD is likely to remain stable over 1 year and therefore a treatment effect of disease stabilization/slowing can be obscured. In patients with more advanced disease severity (<300 meters at baseline), there is a high risk of loss of ambulation and loss of ability to perform functional outcome measures.

Baseline time to stand from supine also significantly predicts for change in 6MWD, independently of baseline 6MWD [Goemans 2016, Mazzone 2016], with poor performance on the time to stand from supine assessment increasing the risk of markedly negative changes in 6MWD and loss of ambulation. These results have identified time to stand from supine as an important additional prognostic factor of changes in 6MWD and more generally of disease progression [Mazzone 2016]. A threshold value of approximately 5 seconds appears to differentiate between patients who are likely to show stability or improvement versus those who are likely to decline [Goemans 2016]. These observations from natural history studies have been corroborated by analyses of data from our own previous placebo-controlled trials of ataluren.

11.3.3 Blinding

Double-blind administration of study treatments is utilized to provide additional and substantial protection against motivational bias on the part of subjects, caregivers, clinic staff, and other study personnel, with respect to assessment of efficacy and safety parameters.

Several steps have been taken in the proposed protocol design to minimize the prospect of systematic unblinding. Placebo is available that is an excellent match for both unmixed and mixed ataluren in terms of appearance, texture, taste, and odor. Brothers participating in the study will receive the same treatment group designation to minimize potential compromise of study drug blinding and to reduce the chance of dosing errors within families.

Packaging and labeling is identical for both the active drug and placebo. Blinding will be done centrally rather than at sites. Access to randomization information during the course of the study will be restricted to the IRT system CRO. The focus of the interim safety reviews will be on blinded data without segregation by treatment group. The final unblinded analysis of the randomized phase of the study will only be performed when the data set is complete, and a snapshot has been frozen and archived.

Unblinding in individual subjects who experience AEs is rarely required to provide effective intervention and support. Thus, disincentives for unblinding for AEs are included in the study. Investigational personnel will not have access to information at the site that would permit unblinding, and the individual subject randomization codes will only be obtainable through an auditable process involving the IRT system. Clinic staff will be made aware that such unblinding will preclude a subject from continuing with study drug administration. Unblinding will also require discussion between the investigator and the PTC Therapeutics medical monitor; this provision is not intended to prevent an investigator from proceeding with unblinding, but to ensure that appropriate consultation is obtained, that the investigator is aware of the consequences of the unblinding for the subject's continued participation in the study, and that appropriate permission is granted to the IRT system to release the treatment assignment only for that subject.

11.4 Treatment and Safety Monitoring Plan

11.4.1 Reference Therapy

Selection of placebo as the reference arm in the proposed study is clearly appropriate given that no other approved standard therapy for nmDMD exists. Use of placebo provides an opportunity to obtain additional information regarding the full treatment effect size for ataluren.

11.4.2 Schedule and Dose Selection

Dosing based on body weight will continue to be employed. Such dosing is common in pediatrics and reduces variability in exposure by accommodating differences in subject size across the span of ages of the boys who will participate in the clinical study program.

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

The dose of 40 mg/kg/day is the conditionally approved dose of ataluren for DMD in Europe.

11.4.3 Duration of Therapy

Duration of therapy in this confirmatory study is consistent with the EMA and FDA guidelines for DMD clinical trial, which indicate that a duration of therapy >1 year may be necessary to demonstrate a treatment effect. Use of a placebo control beyond 72 weeks would likely be discouraging to subjects and could compromise subject participation and retention. After the double-blind treatment period ends, subjects will receive an additional 72 weeks of open-label treatment to evaluate long-term effects of ataluren on patients with this progressive disorder.

11.4.4 Safety Monitoring

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

11.4.5 Concomitant Therapies

As substantial modification of corticosteroid dosing due to manifestation of undesirable side effects such as osteoporosis during the study may confound study results, investigators and subjects are encouraged to maintain corticosteroid dosing as uniformly as possible. Specific recommendations for maintaining, modifying, or discontinuing corticosteroids are provided with the protocol (see Appendix 1).

Cases of decreased renal function have been observed in patients with nmCF receiving ataluren and IV aminoglycosides together with other antibiotics for cystic fibrosis exacerbations (Section 5.4.2). As a precaution, guidance has been provided to the investigator with respect to actions to be taken in the event that abnormalities are noted in renal laboratory parameters.

The investigator is encouraged to consult the PTC medical monitor with questions relating to specific drugs and their potential for interactions with ataluren.

11.5 Open-Label Treatment Period

The inclusion of a 72-week open-label treatment period following 72 weeks of double-blind treatment will allow for collection of long-term efficacy data and add to the long-term safety database.

The open-label treatment period is important for subject recruitment, retention, and compliance in this double-blind study. The assurance that all subjects can eventually receive open-label ataluren if they participate in the double-blind study will stimulate subject recruitment. The knowledge that subjects must be reasonably compliant with study procedures and persist with therapy throughout the double-blind study unless medical contraindications supervene provides strong incentives for subject reliability and retention. The understanding by parents that actions to break the blind (eg, having study medication chemically analyzed) will result in forfeiture of participation in the open-label treatment period will help to preserve the integrity of the blinding.

12 PROTOCOL VERSION HISTORY

Version 1: 23 February 2017

Version 2: 04 October 2017

Version 3: 01 August 2019

Version 4: 21 July 2020

12.1 Version 4.0: 21 July 2020

Item No.	Protocol Section	Version 4/Update	Reason/Rationale
1	Protocol Identifiers and Study Personnel	Revised list of study personnel and protocol number and date	Clarification
2	3.2	Revised phrasing of assessment timepoints	Clarification
3	4.1	Revised text to indicate enrollment targets are approximate	Clarification
4	6.1	Updated Schedule of Events to reflect that subjects transitioning to another ataluren study do not require a post-treatment follow-up visit	Clarification
5	6.2.1.5	Added language indicating that subjects who continue to receive post-study access to ataluren are not required to have a follow-up visit.	Clarification
6	6.2.10	Clarified that the Central Laboratory Manual provides detail on the timing of collection of pharmacokinetic samples	Clarification
7	7.6	Added that PTC Pharmacovigilance is also to be notified of pregnancy outcomes and that this notification is to occur within 24 hours.	Update
8	9.1	Added the word “approximately” for consistency with Section 4.1	Clarification
9	12	Updated protocol version history to reflect version 4	Update

12.2 Version 3.0: 01 August 2019

The overall reason for Version 3: The overall reasons for Version 3 were to address regulatory feedback and to provide updates.

Item No.	Protocol Section	Version 3/Update	Reason/Rationale
1	Protocol	Document date/version were updated	Update
2	Protocol Identifiers and Study Personnel	Study personnel updated	Update
3	2.1.2	Added secondary objectives: • Evaluate the correlation between plasma concentration of ataluren and functional outcomes • to evaluate plasma pharmacokinetic (PK) profile of ataluren	Update
4	2.2.2.1	Added: • Plasma PK at pre-morning dose and 2 hours post-morning dose at Week 144	Update
5	3.2, #3, #7	3. Added: "When Version 3 is implemented or approximately 270 subjects have enrolled in the study, only subjects aged ≥7 to ≤16 who meet the mITT criteria will be eligible to enroll." 7. Added: "When Version 3 is implemented or approximately 270 subjects have enrolled in the study, only subjects who meet the mITT, 6MWD ≥300 meters at screening, Baseline Day 1, and Baseline Day 2 and time to stand from supine ≥5 seconds at Baseline Day 1 and Baseline Day 2, will be eligible to enroll."	Update
6	4.1	Number enrolled/sample size increased from ~250 to a maximum of 340 subjects; the maximum sample size of 340 subjects will include up to 162 subjects who meet the mITT criteria; deleted phrase that subjects who do not meet the mITT will be included in the ITT.	Update
7	6.1, Table 4	Added PK samples on Day 144	Update
8	6.2.7	Added thrombospondin 1 (THBS1) as a marker	Update
9	6.2.10	Added PK analysis method and sampling details	Update
10	6.3	Increased the amount of blood drawn	Update
11	7.9, Table 7	Table of AE reporting revised	Update
12	7.10	SAE reporting contact information updated	Update
13	9.1	Increased sample size	Update
14	9.4.8	Added PK statistical analysis methods	Update
15	9.5	Revised timing of analyses	Update
16	12	Added Protocol Version History	Update

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APPENDIX 1 MANAGEMENT OF CORTICOSTEROIDS

A. Initiating Alternate Corticosteroids During the Study

If a subject does require initiation of an alternate corticosteroid therapy (ie. switching from prednisone to deflazacort or vice-versa) during the study, total doses should not exceed 0.75 mg/kg for prednisone and 0.9 mg/kg for deflazacort. General recommendations for corticosteroid dosing are provided in Table A below.

Table A. Guidance for Initiating Alternate Corticosteroid Treatment

Weight Range	Prednisone Dose (0.75 mg/kg)	Deflazacort Dose (0.9 mg/kg)
15-19 kg	12 mg	15 mg
20-25 kg	17 mg	21 mg
26-32 kg	22 mg	27 mg
33-39 kg	27 mg	33 mg
40 kg+	30 mg	36 mg

Subjects who require alternate corticosteroid initiation may remain on blinded study drug therapy. Changing the type of corticosteroid or the corticosteroid schedule during the study is strongly discouraged.

B. Maintaining Corticosteroid Dosage During the Study

Adjustments in corticosteroid dosage for increases in body weight are permitted but are not mandatory. If it is the practice of the investigator to adjust subjects' corticosteroid doses for changes in body weight, total doses should not exceed 0.75 mg/kg for prednisone and 0.9 mg/kg for deflazacort (see Table A above).

In addition, consistent with the standards proposed for the planned international corticosteroid optimization study [Bushby 2007], increases in total dose for any reasons should not exceed 5 mg for prednisone or 6 mg for deflazacort. For example, if a subject is receiving 22 mg QD of prednisone and it is elected to increase the dose, the total prednisone dose should not be increased beyond 27 mg QD. In addition, for subjects ≥40 kg, total doses should be capped at 30 mg of prednisone or 36 mg of deflazacort unless the subject was already receiving a higher dose of corticosteroids than these limits at study entry [Bushby 2007].

Subjects who require corticosteroid increases may remain on blinded study drug therapy.

C. Modifying Corticosteroid Dosage During the Study

Discontinuation of corticosteroid therapy during the study should be avoided unless clinically necessary. In the case of the development of predictable corticosteroid-related side effects, appropriate supportive care should be provided and corticosteroid dosage can be maintained (ie, not increased for the normal increase in body weight). If unacceptable corticosteroid side effects persist, the dosage can be reduced in decrements of ≤5 mg total dose for prednisone (≤6 mg total dose for deflazacort). Finally, corticosteroid administration can be stopped altogether. Specific recommendations for precautionary interventions for specific corticosteroid-related AEs are given below.

Acne

In the event of bothersome acne that may be attributable to corticosteroids, the following interventions are recommended:

- Corticosteroids should not to be increased to adjust for increases in body weight and the subject should be provided with consultation from a dermatologist for institution of appropriate conventional therapy for acne.
- If the acne is so severe it cannot be managed with appropriate anti-acne measures, dosage reductions of ≤5 mg total dose for prednisone (≤6 mg total dose for deflazacort) at ~6-week intervals can be considered.
- Every attempt should be made to avoid stopping corticosteroids solely for acne; if the subject/family demands that corticosteroids be stopped, see Section D below for procedures for withdrawal of corticosteroids.

Behavior Changes

Where behavior changes are disruptive to family/school life, the following interventions are recommended:

- The subject and the family should be provided with behavioral support from a child psychologist.
- If the subject is already receiving behavioral advice under the guidance of a child psychologist, the corticosteroid dosage should not to be increased to adjust for increases in body weight. Consideration can be given to administering the corticosteroid dose at night instead of in the morning.
- If there is no improvement despite behavioral advice under the guidance of a child psychologist, dosage reductions of ≤5 mg total dose for prednisone (≤6 mg total dose for deflazacort) at ~6-week intervals can be considered.
- If the severe behavioral problems continue to cause unacceptable disruption to school/ family life, corticosteroids may be stopped. See Section D below for procedures for withdrawal of corticosteroids.

Bone Fractures Due to Osteoporosis

Subjects who experience limb fractures should have fixation as directed by an orthopedic surgeon. Subjects who develop vertebral fractures can be treated with bisphosphanates (eg, pamidronate, 0.5 to 1 mg/kg/day IV for 3 days every 4 months). Subjects should not have a corticosteroid dosage adjustment due to the occurrence of fractures.

Cataracts

The development of cataracts should prompt referral to an ophthalmologist for evaluation. Subjects should not have a corticosteroid dosage adjustment due to the occurrence of cataracts.

Cushingoid Appearance

If the subject develops a Cushingoid appearance, that is unacceptable to the subject/family, the following actions are recommended:

- Corticosteroid dosage should not be increased to adjust for increases in body weight
- Reassurance and support should be provided. Counseling from a child psychologist should be considered.
- If the Cushingoid appearance remains unacceptable to child/family, dosage reductions of ≤5 mg total dose for prednisone (≤6 mg total dose for deflazacort) at ~6-week intervals can be considered.
- Every attempt should be made to avoid stopping corticosteroids solely for Cushingoid appearance; if the subject/family demands that corticosteroids be stopped, see Section D below for procedures for withdrawal of corticosteroids.

Gastrointestinal Irritation

In the event of the development of symptoms consistent with esophagitis, gastritis, or duodenitis, the following interventions are recommended:

- Treatment with supportive care (H2 antagonists, proton pump inhibitors, antacids) should be initiated and corticosteroid dosage should not be increased to adjust for increases in body weight.
- If symptoms persist for ≤6 weeks despite supportive care (H2 antagonists, proton pump inhibitors, antacids), a gastroenterology consultation should be obtained
- If symptoms persist despite continued supportive care (H2 antagonists, proton pump inhibitors, antacids) and gastroenterology evaluation, dosage reductions of ≤5 mg total dose for prednisone (≤6 mg total dose for deflazacort) at ~6-week intervals can be considered.
- If the gastroenterologist recommends discontinuation of corticosteroids for frank gastrointestinal ulceration, bleeding, etc, corticosteroids may be stopped. See Section D below for procedures for withdrawal of corticosteroids.

Height Gain Inhibition

In the event of an inhibition of body height increases that is unacceptable to the subject/family, the following interventions are recommended:

- Corticosteroid dosage should not be increased to adjust for increases in body weight
- Reassurance and support should be provided. Counseling from a child psychologist should be considered.
- If the failure to gain height remains unacceptable to child/family, dosage reductions of ≤5 mg total dose for prednisone (≤6 mg total dose for deflazacort) at ~6-week intervals can be considered.

- Every attempt should be made to avoid stopping corticosteroids solely for failure to gain height; if the subject/family demands that corticosteroids be stopped, see Section D below for procedures for withdrawal of corticosteroids.

Hyperglycemia or Glycosuria

Evidence of fasting hyperglycemia or ≥1+ glycosuria persisting for ≥6 weeks should prompt the following interventions:

- Institute monitoring of glycosylated hemoglobin (hemoglobin A1c) to evaluate for evidence of chronic hyperglycemia.
- If hyperglycemia or glucosuria is only episodic and chronic hyperglycemia is not present by hemoglobin A1c, corticosteroids should not to be increased to adjust for increases in body weight.
- If chronic hyperglycemia is present by hemoglobin A1c, consultation should be arranged with an endocrinologist regarding diagnostic evaluation and potential intervention for hyperglycemia
- If hyperglycemia persists and corticosteroid dose reduction is warranted, dosage reductions of ≤5 mg total dose for prednisone (≤6 mg total dose for deflazacort) at ~6-week intervals can be considered.
- If the endocrinologist recommends corticosteroid discontinuation, corticosteroids may be stopped. See Section D below for procedures for withdrawal of corticosteroids.

Hypertension

Evidence of substantial hypertension (blood pressure elevation at 99th percentile + 15 mmHg for age) persisting for ≥6 weeks should prompt the following interventions:

- Corticosteroids should not to be increased to adjust for increases in body weight. Dietary recommendations (weight reduction/sodium reduction) should be considered.
- If substantial hypertension persists, appropriate blood pressure management (eg, diuretics, beta blockers, calcium channel blockers) can be considered. If they can be avoided, angiotensin converting enzyme inhibitors or angiotensin receptor blockers should not be instituted during study drug therapy because such drugs may elevate plasma renin values and obscure monitoring for potential ataluren hypoaldosteronism.
- If hypertension persists despite continued antihypertensive therapy, dosage reductions of ≤5 mg total dose for prednisone (≤6 mg total dose for deflazacort) at ~6-week intervals can be considered.
- If hypertension persists despite continued antihypertensive support and corticosteroid dosage reductions, corticosteroids may be stopped. See Section D below for procedures for withdrawal of corticosteroids.

Infections Potentially Related to Corticosteroid-Mediated Immunosuppression

Unusual opportunistic infections or unusual responses to infection potentially consistent with corticosteroid-mediated immunosuppression should prompt the following interventions:

- Corticosteroids should not to be increased to adjust for increases in body weight and consultation with an infectious disease expert should be obtained.
- If infections cannot be managed with appropriate antibiotic prophylaxis or treatment, dosage reductions of ≤5 mg total dose for prednisone (≤6 mg total dose for deflazacort) at ~6-week intervals can be considered.
- If infections are clinically severe and/or persistent despite corticosteroid dosage reductions, corticosteroids may be stopped. See Section D below for procedures for withdrawal of corticosteroids.

Weight Gain

In the event of a body weight increase that is unacceptable to the subject/family, the following interventions are recommended:

- Corticosteroid dosage should not be increased to adjust for increases in body weight
- Reassurance and support should be provided. Counseling from a nutritionist should be considered.
- If the body weight increase remains unacceptable to child/family, dosage reductions of ≤5 mg total dose for prednisone (≤6 mg total dose for deflazacort) at ~6-week intervals can be considered.
- Every attempt should be made to avoid stopping corticosteroids solely due to increase in weight; if the subject/family demands that corticosteroids be stopped, see Section D below for procedures for withdrawal of corticosteroids.

D. Withdrawal of Corticosteroids

Corticosteroids should not be stopped suddenly. A tapered reduction in dosage is required to avoid risks of adrenal insufficiency. Tapering of drug dosage should follow the normal clinical practice of taking ½ the regular dose for the first week, ¼ the regular dose for the second week, 1/8 the regular dose for the third week and no study drugs thereafter. All adverse effects possibly due to corticosteroid should be monitored until resolved and subjects should be followed closely for symptoms consistent with adrenal insufficiency. Subjects who require corticosteroid discontinuation may remain on blinded study drug therapy.

E. Reinstitution of Corticosteroids

In subjects who discontinue corticosteroids after following the recommended interventions and corticosteroid dosage modification procedures, reinstitution of corticosteroids is not generally recommended unless adrenal insufficiency is detected. However, if reinstitution of corticosteroids is deemed necessary, the corticosteroid dosage should be lower than the lowest total dose that previously proved intolerable. Subjects who require corticosteroid reinstitution may remain on blinded study drug therapy.