CLINICAL PROTOCOL

AN OPEN-LABEL STUDY EVALUATING THE SAFETY AND PHARMACOKINETICS OF ATALUREN IN CHILDREN FROM ≥6 MONTHS TO <2 YEARS OF AGE WITH NONSENSE MUTATION DUCHENNE MUSCULAR DYSTROPHY

PTC124-GD-048-DMD

06 MAY 2022

VERSION 4.0

PTC THERAPEUTICS, INC.
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PROTOCOL IDENTIFIERS AND STUDY PERSONNEL

Project Code	PTC124-GD
Therapeutic Area	Genetic Disorders - Duchenne Muscular Dystrophy
PTC Therapeutics Substance Identifier	Ataluren (PTC124)
IND Number	068431
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Protocol Number	PTC124-GD-048-DMD
Protocol Version	Version 4.0
Protocol Version Date	06 May 2022
Protocol Phase	Phase 2
Protocol Title	An Open-Label Study Evaluating the Safety and Pharmacokinetics of Ataluren in Children From ≥6 Months to <2 Years of Age with Nonsense Mutation Duchenne Muscular Dystrophy
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PRINCIPAL INVESTIGATOR AGREEMENT AND SIGNATURE

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

Principal Investigator Full Name & Signature	**Date**

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SYNOPSIS

Name of Sponsor/Company	PTC Therapeutics
Study Number	PTC124-GD-048-DMD
Name of Investigational Product	Ataluren (PTC124)
Title of Study	An Open-Label Study Evaluating the Safety and Pharmacokinetics of Ataluren in Children From ≥6 Months to <2 Years of Age with Nonsense Mutation Duchenne Muscular Dystrophy
Proposed Indication	For the treatment of nonsense mutation Duchenne muscular dystrophy (nmDMD) in children <2 years of age
Number of Study Sites	≤3 sites
Trial Phase	Phase 2
Study Objectives	***Primary*** • To assess the safety and tolerability of ataluren in male children with nmDMD aged ≥6 months to <2 years old ***Secondary*** • To assess the pharmacokinetics (PK) of ataluren in male children with nmDMD aged ≥6 months to <2 years old ***Exploratory*** • To assess changes from baseline in creatine kinase (CK) levels
Study Endpoints	***Primary*** • Overall safety profile of ataluren in terms of type, frequency, severity, seriousness, timing, and relationship to study therapy of any treatment-emergent adverse event (TEAE) during the 24 weeks of treatment ***Secondary*** • Evaluation of PK parameters after 24 weeks of treatment as follows: – Area under the concentration curve from a time of 0 to 24 hours post first morning dose (AUC_{0-24}) and AUC between dose interval ($AUC_{0-\tau}$) – T_{max} – C_{max} – Trough concentration (Plasma concentration pre morning dose) (C_{trough}) ***Exploratory*** • Change from baseline in CK levels after 24 weeks of treatment
Study Population	Male subjects with nmDMD aged ≥6 months to <2 years

Sample Size	Up to 10 subjects (minimum of 6 subjects)
Methodology/Study Design	Study 048 is a Phase 2, open-label study to evaluate safety, tolerability, and PK of ataluren in male children with nmDMD aged ≥6 months to <2 years of age treated TID for 24 weeks with orally administered ataluren 10, 10, 20 mg/kg (morning, mid-day, and evening dose, respectively). Safety evaluations will include TEAEs, serious adverse events (SAEs), adverse events (AEs) leading to discontinuation, laboratory evaluations, EGCs, vital signs, and physical examination. The study will include 3 PK profile assessments (baseline, Week 4, and end of treatment at Week 24). At these visits, PK parameters will be investigated based on blood sampling at pre-dose, and 1-, 2-, 3-, and 4-hours post-dose following both the morning and mid-day ataluren doses, and immediately pre-dose, and 1-, 2-, 3-, 4- and 12- (before the next day morning dose) hours post-dose following the evening dose. The PK parameters, including $AUC_{0\text{-}24}$ and $AUC_{0\text{-}\tau}$, T_{max}, C_{max}, C_{trough} will be assessed after each dose. If feasible, apparent clearance (CL/F), and $T_{1/2}$ will also be assessed after each dose.
Main Inclusion Criteria	1. Signed and dated informed consent document indicating that the parent(s)/caregivers(s) of the subject has been informed of all pertinent aspects of the study prior to initiation of any study-related procedures. 2. Males ≥6 months to <2 years of age. 3. Body weight ≥7.5 kg 4. Willingness and ability of the subject's parent/caregiver to comply with scheduled visits, drug administration plan, study procedures, and study restrictions. 5. Diagnosis of Duchenne muscular dystrophy (DMD) based on an elevated serum CK and genotypic evidence of dystrophinopathy. 6. Documentation of the presence of a nonsense mutation of the dystrophin gene as determined by gene sequencing confirmed by a PTC Therapeutics (PTC) designee is required prior to enrollment.

Main Exclusion Criteria	1. Subject who is participating in any drug or device clinical investigation (or whose sibling is currently participating in a blinded portion of another ataluren study) or received an investigational drug within 3 months prior to the Screening Visit or who anticipate participating in any other drug or device clinical investigation or receiving any other investigational drug within the duration of this study. 2. Expectation of a major surgical procedure during the study period. 3. Prior or ongoing medical condition, medical history, physical findings, or laboratory abnormality that, in the Investigator's opinion, will adversely affect the safety of the subject, or will make it unlikely that the course of study drug administration or follow-up will be completed, or will impair the assessment of study results. 4. Known hypersensitivity to any of the ingredients or excipients of the study drug (polydextrose, polyethylene glycol 3350, poloxamer 407, mannitol 25C, crospovidone XL10, hydroxyethyl cellulose, vanilla, colloidal silica, or magnesium stearate). 5. Ongoing use of the following drugs: a. Systemic aminoglycoside therapy and/or intravenous vancomycin. b. Coumarin-based anticoagulants (eg, warfarin), phenytoin, tolbutamide, or paclitaxel. c. Inducers of UGT1A9 (eg, rifampicin), or substrates of OAT1 or OAT3 (eg, ciprofloxacin, adefovir, oseltamivir, aciclovir, captopril, furosemide, bumetanide, valsartan, pravastatin, rosuvastatin, atorvastatin, pitavastatin).

Study Treatment	All subjects will receive 10, 10, 20 mg/kg ataluren TID in the morning, at mid-day, and in the evening, respectively, for 24 weeks. **Study Drug Description:** Ataluren will be provided as white to off-white granules for oral suspension. The granules for oral suspension are packaged in aluminum foil, child-resistant sachets and supplied in dose strengths containing 125 or 250 mg of the active drug substance. **Study Drug Storage and Preparation**: Entire content of the sachets: Study drug sachets should be stored at labeled storage conditions until time of reconstitution. For administration, the powder in the sachet may be mixed with water, milk (skim, 1% fat, 2% fat, whole milk, chocolate milk, or lactose free milk), breast milk, fruit juice, or fruit punch, or in semi-solid food (yogurt, pudding, or applesauce). For subjects with body weight <10 kg, a NeoMed oral dosing syringe (12 mL) will be used to administer an aliquot of a 25 mg/mL concentration suspension in water or milk, including breast milk. Ataluren remains stable for up to 1 hour at ambient temperature in the NeoMed oral syringe. For subjects with body weight ≥10 kg, the full contents of each sachet should be well-mixed with at least 30 mL (1 ounce) of liquid, or 3 tablespoons of semi-solid food. Please reference the dosing instructions for further information. The constituted ataluren suspension may be kept for up to 24 hours under refrigeration or 3 hours at room temperature.
Treatment Duration	This study includes a 4-week screening period followed by 24 weeks of treatment with ataluren. PTC will ensure that subjects who complete the 24-week treatment period are offered participation to a follow-up extension period for at least 52 weeks from the date of first administration of ataluren in this parent study. The subjects who roll over into the extension study will be followed-up for long-term safety and efficacy as an exploratory endpoint.
Safety Monitoring	Subjects will be monitored closely for AEs, vitals, and laboratory and electrocardiogram abnormalities during the study.
Serious Adverse Event Reporting	All SAEs should be reported via the SAE report form to PTC within 24 hours of becoming aware of the event(s).

Pharmacokinetic Sampling	Blood sampling for PK will occur at baseline, Week 4, and end of treatment at Week 24. On each of these days, blood samples for ataluren PK assessments will be collected immediately pre-dose and at 1-, 2-, 3-, and 4-hours post-dose following both the morning and mid-day doses, and immediately pre-dose and 1-, 2-, 3-, 4- and 12 (before the next day morning dose) hours post-dose following the evening dose. Blood/plasma partition will be determined at baseline, Week 4, and end of treatment at Week 24. Blood samples will be collected at 2.5 hours and 4.5 hours post morning dose.
Statistical Methods	All subjects who receive ≥1 dose of ataluren will be included in the safety analyses. All subjects who receive ≥1 dose of ataluren and have at least 1 PK concentration datum will be included in the PK population. Subject characteristics at study entry will be summarized with frequency tables for categorical variables and with descriptive statistics, as appropriate, for quantitative variables. Frequencies of TEAEs will be tabulated by Medical Dictionary of Regulatory Activities System Organ Class, Preferred Term, severity, timing, outcome of the event, relationship to study drug, and seriousness.
Timing of Assessments	See Schedule of Assessments (Table 2, Section 7.1)

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation or Specialized Term	Explanation
6MWD	6-minute walk distance
AE	Adverse event
$AUC_{0-\tau}$	Area under the plasma concentration curve between dose interval
AUC_{0-24}	Area under the plasma concentration curve from time zero following the morning dose up to hour 24
BCRP	Breast cancer resistant protein
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
C_{trough}	Trough concentration (Plasma concentration pre morning dose)
CK	Creatine Kinase
CL/F	Apparent clearance
CRF (eCRF)	Case Report Form (electronic CRF)
CRO	Contract Research Organization
CTCAE	Common terminology criteria for adverse events
CV%	Coefficient of variation
CYP	Cytochrome P450
DMD	Duchenne muscular dystrophy
EC	Ethics Committee
ECG	Electrocardiogram
EDC	Electronic data capture
EOS	End of study
EOT	End of treatment
ET	Early termination
FDA	Food and Drug Administration
FU	Follow-up
GCP	Good clinical practice
HDL	High-density lipoprotein
HR	Heart rate
IB	Investigator brochure
ICH	International Conference on Harmonization
ICF	Informed consent form
IEC	Independent Ethics Committee
IND	Investigational New Drug
IRB	Institutional Review Board
IV	Intravenous
LC-MS/MS	Liquid chromatography with tandem mass spectrometry
LDL	Low-density lipoprotein
mRNA	Messenger ribonucleic acid
MedDRA	Medical Dictionary for Regulatory Activities
NeoMed syringe	Neonatal oral syringe
nmDMD	Nonsense mutation Duchenne muscular dystrophy
OAT	Organic anion transporter
OATP	Organic anion transporting polypeptide
PIP	Pediatric investigation plan
PK	Pharmacokinetics
PTC124	Ataluren
RSI	Reference safety information
SAE	Serious adverse event
SmPC	Summary of Product Characteristics

Abbreviation or Specialized Term	Explanation
SUSAR	Serious adverse reactions
TEAE	Treatment-emergent adverse event
VAMS	Volumetric absorptive microsampling

1. INTRODUCTION

1.1. Investigational Product

Ataluren (also known as PTC124) is a novel, orally bioavailable, small-molecule drug being developed for the treatment of nonsense mutation Duchenne muscular dystrophy (nmDMD).

A nonsense mutation in DNA results in a premature stop codon within the corresponding messenger ribonucleic acid (mRNA) that causes disease by terminating translation before a functional protein is generated. Duchenne muscular dystrophy (DMD) is a rare, X-linked genetic muscle disorder that is debilitating, progressive, and ultimately fatal . Duchenne muscular dystrophy is caused by a mutation in the dystrophin gene. Dystrophin is a 427 kDa structural protein present at the muscle sarcolemma that provides stability to the muscle and is expressed in skeletal, respiratory, and cardiac muscle, . Dystrophin acts as a shock absorber during muscle contraction by linking the actin of the contractile apparatus to the layer of connective tissue that surrounds each fiber .

Dystrophin mutations disrupt the connection with the actin cytoskeleton and connective tissue resulting in chronic muscle damage, inflammation, and eventual replacement of muscle fibers by fat and fibrotic tissue resulting in progressive and irreversible loss of muscle function . The culmination of muscle function loss leads to early death; the average life expectancy of DMD patients is about 25 years of age.

Approximately 10% to 15% of boys with DMD have the disease due to a nonsense mutation in the dystrophin gene , resulting in a premature stop codon in the dystrophin mRNA. Consequently, ribosomal translation of nonsense codon-containing mRNA results in premature termination of translation before a full-length, functional protein is generated.

To date, no medications cure or reverse the effects of DMD. The goal of current interventions is to help slow or stabilize disease progression, prolong patients' ability to manage activities of daily living, and to delay the onset of subsequent deterioration. Recent clinical guidelines recommend treatment with glucocorticoids, which address the inflammatory component of the disease, and have beneficial effects on prolonging ambulation and muscle and respiratory function .

The progressive and irreversible effects of nmDMD underscore the importance of early intervention with treatments that have the potential to slow physical deterioration and delay the natural course of this fatal disease. While treatment with corticosteroids target the inflammatory component of the disease, additional treatments are needed to address the loss of dystrophin, the underlying cause of the disease. Because of the role of the dystrophin protein, dystrophin restoration therapy would be expected to stabilize or slow disease progression in patients with DMD.

1.2. Nonclinical Findings

The mechanism by which ataluren restores dystrophin has been established in comprehensive preclinical studies and supported in clinical evaluations. Ataluren promotes ribosomal readthrough of mRNA containing premature stop codons, resulting in production of a functional protein . In reporter assays, as well as in nonclinical models of genetic disease, ataluren demonstrates the ability to specifically and selectively enable ribosomal readthrough of mRNA containing a premature stop codon, inducing production of protein that localizes to the appropriate cellular location and is functionally active . Ataluren does not promote readthrough of normal stop codons, does not alter mRNA levels, and does not affect the process of nonsense-mutation-mediated mRNA decay. In vitro and in vivo studies in nmDMD have shown that ataluren can restore production of the missing dystrophin protein.

In support of administering ataluren to children from ≥6 months to <2 years of age, a 3-month juvenile dog study was performed (Test Facility Study 9001126). The administration of ataluren by once daily oral gavage for 3 months at doses of 125, 250, and 500 mg/kg/day (up to steady state systemic exposures equivalent to the steady state area under the concentration curve [AUC] in patients) was well tolerated in juvenile beagle dogs when dosed from post-natal day 7 to post-natal day 97. Cytoplasmic alteration of the brown adipose tissue, considered likely ataluren-related and nonadverse, was observed in 1 male at 125 mg/kg/day, 2 males at 500 mg/kg/day, and 1 female each at 125 and 250 mg/kg/day. Following the 3-month recovery period, the cytoplasmic alteration of brown adipose tissue was not present, suggesting recovery of the change. No other ataluren-related macroscopic or organ weight changes were observed. Based on these results, the no-observed-adverse-effect level was considered to be 500 mg/kg/day.

Nonclinical safety pharmacology and toxicology studies, including the completed juvenile toxicology study, indicate that ataluren has an acceptable safety profile. Findings pose a low human safety risk, and the overall program supports chronic administration of ataluren for the treatment of nmDMD in patients as young as neonates.

1.3. Risk/Benefit Assessment

1.3.1. Clinical Studies

The clinical efficacy and safety of ataluren for the treatment of nmDMD were assessed in 2 randomized, double-blind, placebo-controlled, 48-week studies (PTC124-GD-007-DMD [NCT00592553] [Study 007] and PTC124-GD-020-DMD [NCT01826487] [Study 020]).

Study 007 was a Phase 2b, international, multicenter, randomized, double-blind, placebo-controlled, dose-ranging study of ataluren in 174 male subjects ≥5 years old with nmDMD. Subjects were randomized 1:1:1 to receive placebo, low-dose level of ataluren (10, 10, 20 mg/kg), or high-dose level of ataluren (20, 20, 40 mg/kg) TID for a duration of 48 weeks. At the end of Week 48, the mean change from baseline in 6-minute walk distance (6MWD) was approximately 30 meters greater in subjects treated with low-dose ataluren than in subjects treated with placebo, while there was no difference between high-dose ataluren and placebo in change in 6MWD over 48 weeks. Plasma concentrations were dose-proportional and well-maintained over time. Ataluren was well tolerated at both the low- and high-dose levels.

None of the subjects prematurely discontinued treatment because of adverse events (AEs), and no ataluren-related serious adverse events (SAEs) were reported.

Study 020 was a Phase 3, international, multicenter, randomized, double-blind, placebo-controlled efficacy and safety study of ataluren in ambulatory males ≥7 to ≤16 years old with nmDMD. A total of 230 subjects were randomized (1:1) to receive placebo or ataluren 10, 10, 20 mg/kg TID. Ataluren-treated subjects experienced clinical benefit as measured by numerically favorable differences versus placebo across all efficacy endpoints. The difference between the ataluren and placebo arms in mean change in observed 6MWD from baseline to Week 48 was 15.4 meters favoring ataluren. In a subgroup analysis of subjects with baseline 6MWD ≥300 to <400 meters, the Week 48 treatment difference in mean change in 6MWD was 47.2 meters (p=0.007). Ataluren was well tolerated and slowed the decline in physical functioning in subjects with nmDMD.

Small increases in mean serum creatinine, blood urea nitrogen (BUN), and cystatin C, changes in lipid profile (increased triglycerides and cholesterol), and hypertension with use of concomitant systemic corticosteroids were reported for some subjects in clinical studies. Monitoring serum creatinine, BUN, and cystatin C, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, and resting systolic and diastolic blood pressure (BP) in subjects receiving ataluren concomitantly with corticosteroids is recommended every 6 to 12 months, or more frequently as needed based on the subject's clinical status (Ataluren, SmPC 2019).

Data from Studies 007 and 020 supported conditional marketing authorization of ataluren for the treatment of nmDMD in ambulatory subjects aged ≥5 years in Europe on 31 Jul 2014. Subsequently, the indication was extended to ≥2 years of age based on pharmacokinetic (PK) extrapolation from study PTC124-GD 030-DMD (Study 030).

Study 030 was a Phase 2, open-label study of ataluren safety, PK, and pharmacodynamics in 14 male subjects with nmDMD, aged ≥2 to <5 years. Ataluren was administered at 10, 10, 20 mg TID for 52 weeks. The PK analysis demonstrated ataluren exposures similar to that observed in older subjects. Improvements were seen in physical functioning across all assessments. Ataluren was well tolerated by all subjects. The treatment-emergent adverse events (TEAEs) classified as possibly related to ataluren were rash, flatulence, nausea, and vomiting and were all classified as mild in severity, except for 2 occurrences of vomiting that were classified as moderate. No subjects experienced an SAE or prematurely discontinued study drug due to a TEAE.

This study (Study 048) is designed to evaluate the safety and pharmacokinetics of ataluren exposure in male children ≥6 months to <2 years old with nmDMD. Ataluren has been administered to subjects with nmDMD as young as 2 years of age. There were no obvious differences in the activity or safety profiles of ataluren in children relative to adults. Given that ataluren, in children <5 years old, has demonstrated an ataluren PK profile that is similar to that observed in older subjects, has shown improvements in physical functioning assessments, and exhibited a favorable safety profile, the benefit-risk profile of ataluren is positive. Hence, the study design and the importance of confirming a similar PK profile, and the safety and tolerability in children ≥6 months to <2 years old results in a positive risk/benefit.

Known and potential risks associated with ataluren: The potentiation of aminoglycoside renal toxicity is a clearly documented risk for ataluren. Other potential risks include long-term cardiovascular effects including changes in lipid profile, hypertension with use of concomitant systemic corticosteroids, renal toxicity, hepatic toxicity, hibernoma, and general malignancies.

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

1.3.2. Risk-Benefit Conclusion

Any benefit of ataluren depends on the presence of a nonsense mutation. Participants in this study have the potential for direct, early benefit from treatment with ataluren. This theoretical early benefit justifies the known and potential risks as detailed in the SmPC and ataluren IB. Substantial nonclinical and clinical safety experience provides appropriate risk-benefit information that supports the conduct of this study. This information is detailed in the ataluren IB. The potential risks (real and theoretical) have been weighed against the expected benefits for the children enrolled in the clinical study. It is believed that the balance of risks versus expected benefits will be positive for the clinical study.

2. STUDY OBJECTIVE AND ENDPOINTS

2.1. Objectives

2.1.1. Primary Objective

The primary objective of this study is to assess the safety and tolerability of ataluren in male children with nmDMD aged ≥6 months to <2 years old.

2.1.2. Secondary Objective

The secondary objective of this study is to assess the PK of ataluren in male children with nmDMD aged ≥6 months to <2 years old.

2.1.3. Exploratory Objective

The exploratory objective of this study is to assess changes from baseline in creatine kinase (CK) levels.

2.2. Endpoints

2.2.1. Primary Endpoint

The primary endpoint of this study is the overall safety profile of ataluren in terms of type, frequency, severity, seriousness, timing, and relationship to study therapy of any TEAE during the 24 weeks of treatment.

2.2.2. Secondary Endpoint

The secondary endpoint of this study is the evaluation of PK parameters after 24 weeks of treatment as follows:

- AUC from a time of 0 to 24 hours post first morning dose (AUC_{0-24}) and AUC between dose interval ($AUC_{0-\tau}$)
- T_{max}
- C_{max}
- C_{trough} (concentration prior to the morning dose)

2.2.3. Exploratory Endpoints

- Change from baseline in CK levels after 24 weeks of treatment

3. STUDY DESIGN

3.1. Overall Design

Study 048 is a Phase 2, open-label study to evaluate safety, tolerability, and PK of ataluren in male children with nmDMD aged ≥6 months to <2 years of age treated TID for 24 weeks with orally administered ataluren 10, 10, 20 mg/kg (morning, mid-day, and evening dose, respectively).

3.2. Scientific Rationale for Study Design

At the request of the European Medicines Agency, Paediatric Committee, and as agreed upon by PTC Therapeutics (PTC), Study 048 is being conducted as part of a Paediatric Investigation Plan (PIP) as PIP Study 7.

Translarna was granted a conditional marketing authorization on 31 July 2014 for the treatment of nmDMD in ambulatory patients aged 5 years and older. On 23 July 2018, the expansion of the indication to include patients aged ≥2 to <5 years old with nmDMD was approved on the basis of comparable pharmacokinetics and consistency with the known safety profile of ataluren in PTC124-GD-030-DMD (Study 030 - PIP Study 6).

Study 048 is designed to evaluate the safety, tolerability, and PK of ataluren in male children aged ≥6 months to <2 years old with nmDMD.

3.3. Justification of Dose

Participants in the study will be administered ataluren 10, 10, 20 mg/kg (morning, mid-day, and evening dose, respectively), orally or via a neonatal oral syringe (NeoMed syringe). Dosing is based on body weight, a common practice in pediatric studies that reduces variability in exposure by accommodating differences in subject size across the span of ages of the subjects who will participate in the clinical study.

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

In clinical studies of ataluren in nmDMD, ataluren has been studied most extensively at the 10, 10, 20 mg/kg dose level. In the Phase 2b, randomized, double-blinded, placebo-controlled study of ataluren in nmDMD (Study 007), 57 subjects received ataluren 10, 10, 20 mg/kg for 48 weeks with a favorable risk-benefit at this dose level . Ataluren has been conditionally approved at a dose of 10, 10, 20 mg/kg for the treatment of nmDMD. Based on the collective clinical experience with ataluren 10, 10, 20 mg/kg, this dose level will be evaluated in male children ≥6 months to <2 years old with nmDMD.

4. STUDY POPULATION

4.1. Overview

The study will include up to 10 subjects (minimum of 6 subjects) selected according to the following inclusion and exclusion criteria.

4.2. Inclusion Criteria

1. Signed and dated informed consent document indicating that the parent(s)/caregiver(s) of the subject has been informed of all pertinent aspects of the study prior to initiation of any study-related procedures.
2. Males ≥6 months to <2 years of age.
3. Body weight ≥7.5 kg.
4. Willingness and ability of the subject's parent(s)/caregiver(s) to comply with scheduled visits, study drug administration plan, study procedures, and study restrictions.
5. Diagnosis of DMD based on an elevated serum CK and genotypic evidence of dystrophinopathy.
6. Documentation of the presence of a nonsense mutation of the dystrophin gene as determined by gene sequencing confirmed by a PTC designee is required prior to enrollment.

4.3. Exclusion Criteria

1. Subject who is participating in any drug or device clinical investigation or whose sibling is currently participating in a blinded portion of another ataluren study or received an investigational drug within 3 months prior to the Screening Visit or who anticipate participating in any other drug or device clinical investigation or receiving any other investigational drug within the duration of this study.
2. Expectation of a major surgical procedure during the study period.
3. Prior or ongoing medical condition, medical history, physical findings, or laboratory abnormality that, in the investigator's opinion, will adversely affect the safety of the subject, or will make it unlikely that the course of study drug administration or follow-up will be completed, or will impair the assessment of study results.
4. Known hypersensitivity to any of the ingredients or excipients of the study drug (polydextrose, polyethylene glycol 3350, poloxamer 407, mannitol 25C, crospovidone XL10, hydroxyethyl cellulose, vanilla, colloidal silica, or magnesium stearate).
5. Ongoing use of the following drugs:
    a. Systemic aminoglycoside therapy and/or intravenous (IV) vancomycin.
    b. Coumarin-based anticoagulants (eg, warfarin), phenytoin, tolbutamide, or paclitaxel.
    c. Inducers of UGT1A9 (eg, rifampicin), or substrates of OAT1 or OAT3 (eg, ciprofloxacin, adefovir, oseltamivir, aciclovir, captopril, furosemide, bumetanide, valsartan, pravastatin, rosuvastatin, atorvastatin, pitavastatin).

4.4. Strategies for Recruitment and Retention

A minimum of 6 male subjects will be enrolled. Subjects will be recruited from dystrophinopathy populations who receive care or are referred for evaluation at the investigational site. Subjects who have siblings with nmDMD who have a history of ataluren exposure or a nmDMD treatment plan may be eligible for this study. The principal investigator or sub-investigator will discuss the possibility of participation directly with subject's parent(s)/caregiver(s) in the clinic. Participant's sibling cannot be participating in the blinded portion of another ataluren study at the time of subject's enrollment in this study.

Advertisements approved by IRBs/ECs and investigator databases may be used as recruitment procedures.

PTC will have an opportunity to review in advance and approve the content of any study recruitment materials provided to potential study subjects' parent(s) or caregiver(s).

5. STUDY INTERVENTION

5.1. Study Intervention Administration

Ataluren will be the only study medication administered in this open-label study.

Ataluren will be supplied to the investigational site(s) by PTC for appropriate distribution to the subject's parent(s)/caregiver(s).

5.1.1. Study Intervention Description

Ataluren will be provided as white to off-white granules for oral suspension.

5.1.2. Dosing and Administration

Subjects in the study will be administered ataluren 10, 10, 20 mg/kg (morning, mid-day, and evening dose, respectively), orally or via a NeoMed syringe. Dosing will be based on body weight, a common practice in pediatric studies that reduces variability in exposure by accommodating differences in subject size across the span of ages of the subjects who will participate in the clinical study. The subject's parent(s)/caregiver(s) will be provided a Study Drug Administration Record (dosing sheet) to document daily subject compliance.

5.1.2.1. Dose and Dosing Regimen

Dosing of ataluren will be on a milligram of drug per kilogram of subject body weight at baseline (Visit 2). A subsequent weight-based dose adjustment may be necessary over time (see Section 5.1.2.2). All subjects will receive approximately 10, 10, 20 mg/kg ataluren TID in the morning, at mid-day, and in the evening, respectively, for 24 weeks. Ataluren will be administered orally immediately after preparation.

The amount of study drug administered to each subject, any missed doses, and the reason for noncompliance will be recorded in the source documents and electronic Case Report Form (eCRF).

5.1.2.2. Dose Adjustments and Modifications

Because of changes in subject body weight over time, a weight-based dose adjustment may be necessary. Weight will be re-assessed at Week 12 and ataluren dosing adjusted accordingly.

5.1.2.3. Schedule of Drug Administration

Ataluren administration will begin at baseline (Visit 2) and continue for up to 24 weeks.
As noted in Table 1, three ataluren doses should be taken per day; the first dose in the morning, the second dose during the middle of the day (mid-day), and the third dose in the evening. Ideally each dose should be taken within ~30 minutes after a meal (eg, ~7:00 AM after breakfast, ~1:00 PM after lunch, and ~7:00 PM after dinner). Intervals for dosing 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. While it is realized that variations in dosing schedule may occur in the outpatient setting, the prescribed regimen (including dosing intervals and the relationship of dosing to meals) should be followed closely on the day preceding PK sample collection in the clinic.

Table 1: Suggested Daily Dosing

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

5.1.2.4. Instructions for Delays in Dosing

Dosing delays will be handled as follows:

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

5.1.2.5. Overdose Precautions

For any subject experiencing an overdose (administration of a study drug dose >4 times the highest intended total daily dose level for this protocol [ie, >160 mg/kg/day]), observation for any symptomatic side effects should be instituted, and vital signs and biochemical and hematological parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. Pending the acquisition of sufficient human experience with the drug, use of gastric lavage or induction of emesis is not specifically recommended nor contraindicated.

The PTC medical monitor must be contacted if an overdose occurs. Under applicable regulations, overdosing may be considered an SAE and should be reported accordingly (see Section 7.6.2 and Section 7.6.8).

5.1.2.6. Hydration

Dehydration is a condition that occurs when the body loses too much water and other fluids that it needs to work normally. Dehydration is usually caused by severe diarrhea and vomiting, but it may also be caused by not drinking enough water or other fluids, sweating too much, fever, urinating too much, or taking certain medicines. Signs and symptoms include thirst, dry mouth, headache, fatigue, dark-colored urine, urinating less than normal, sunken eyes or cheeks, dry and cool skin, dizziness, fainting, muscle cramps, rapid heartbeat, and rapid breathing. Dehydration can be severe, especially in young children and older adults. 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. Frequent sipping or drinking of water is recommended to prevent dehydration. Subjects should be adequately hydrated prior to receiving potentially nephrotoxic agents such as aminoglycosides or vancomycin, and hydration status should be carefully monitored throughout the administration of these agents. Investigators should be particularly vigilant with subjects who are experiencing nausea, vomiting, diarrhea, or fever, or who have laboratory evidence of dehydration.

During the course of the study, breastfeeding and milk formula are allowed as part of a normal alimentation regime.

5.1.3. Formulation

Ataluren is manufactured under current good manufacturing procedures conditions.
The formulation includes matrix and suspending agents, surfactants, and various excipients that aid in the manufacturing process.

5.1.4. Packaging and Labeling

Ataluren granules for oral use will be packaged in aluminum foil, child-resistant sachets (packets) and supplied in dose strengths containing 125 or 250 mg of the active drug substance. Sachets and cartons will be affixed with color-coded labels to indicate dosage strength (125 mg - yellow, 250 mg - pink).

Labels will be provided in appropriate languages as required by each country in which the study is conducted. The content of the labeling will be in accordance with local regulatory specifications and requirements.

5.1.5. Study Drug Preparation and Storage

Sachets of study drug will be shipped at labeled storage conditions and stored at room temperature (15 to 30°C [59 to 86°F]). Upon receipt at the study site, study drug(s) will be stored in a safe and secure area with restricted access and stored at room temperature 15 to 30°C (59 to 86°F).

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 will be monitored to support the clinical study.

Ataluren Suspension in a NeoMed Oral Syringe: Ataluren, suspended in either milk or water, remains stable for up to 1 hour at ambient temperature in the NeoMed oral syringe.

Entire content of the sachets: Study drug sachets should be stored at labeled storage conditions, away from the reach of children until time of reconstitution. For administration, the powder in the sachet may be mixed with water, milk (skim, 1% fat, 2% fat, whole milk, chocolate milk, or lactose free milk), breast milk, fruit juice, or fruit punch, or in semi-solid food (yogurt, pudding, or applesauce). The number of sachets to be taken for a dose should be separated from the total number of sachets dispensed for the subject.

For subjects with body weight <10 kg, a NeoMed oral dosing syringe (12 mL) will be used to administer an aliquot of a 25 mg/mL concentration suspension in water or milk, including breast milk. Ataluren remains stable for up to 1 hour at ambient temperature in the NeoMed oral syringe.

For subjects with body weight ≥10 kg, the full contents of each sachet should be well-mixed with at least 30 mL (1 ounce) of liquid, or 3 tablespoons of semi-solid food. The prepared dose should be mixed well before administration. The amount of the liquid or semi-solid food can be increased based on subject preference. Please reference the dosing instructions for further information.

The constituted ataluren suspension may be kept for up to 24 hours under refrigeration or 3 hours at room temperature.

The clinic staff will instruct each subject's parent(s)/caregiver(s) on the specific number of sachets to be taken from each kit at 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's parent(s)/caregiver(s) when drug supplies are dispensed. The clinic staff should attempt to follow-up with the parent(s)/caregiver(s) regarding the drug preparation and dosing procedures within an appropriate interval (eg, 1 week) after initiation of study treatment.

5.1.6. Study Drug Accountability

Upon receipt of the study drug(s), the investigator or designee will maintain accurate records of study drug delivery to the study center, the inventory at the study center, the use by each subject, the reconciliation of all study drug(s) received from the sponsor, and the return to the sponsor's or its designated depot/vendor of unused study drug(s).

Study personnel must ensure that all study drug supplies are temperature monitored and kept in a secure locked area with access limited to authorized personnel. This study product must not be used outside the context of this protocol. Under no circumstances should the investigator or site personnel supply study product to other investigators or clinics; or allow the 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 or its designee, including, but not limited to, the date received, lot number, amount received, and the disposition of all study drug. Current reconciliation and dispensing records must also be maintained that include the date and amount of drug dispensed, and subject's assigned study number.

Unused clinical supplies must be returned to PTC or its designated depot/vendor after the study is completed. Accountability must be verified by the site monitor prior to return. Records documenting the date of study drug shipped, relevant sachet numbers, and amount shipped should be kept in the investigator site study file.

5.2. Measures to Minimize Bias: Randomization and Blinding

This is an open-label study.

5.3. Study Intervention and Compliance

Subject's parent(s)/caregiver(s) should return all remaining study drug (all unused sachets and drug kits) to the study site at Week 4 (Visit 3), Week 12 (Visit 4), and end of treatment (EOT) at Week 24 (Visit 5). The dosing sheet provided to subject's parent(s)/caregiver(s) will serve as a source document for subject compliance and will help the investigator determine how much unused drug should be returned upon study completion.

5.4. Concomitant Therapy

Other than the study drug, any treatments (including prescription and non-prescription drugs, health foods, herbal remedies, or self-prescribed drugs) that are taken by or given to a subject during the screening period, during study drug administration, and for 4 to 6 weeks after discontinuation of study drug are considered concomitant medications.

To the extent possible, administration of any treatment other than the study drug is to be minimized during the study period. The subject's parent(s)/caregiver(s) are discouraged from providing "health supplements" (eg, creatine, glutamine, coenzyme Q), herbal remedies, growth hormone, or self-prescribed drugs, at any time during the study.

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) must 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 would compromise the outcome or integrity of the study.

The subject's parent(s)/caregiver(s) will be instructed about the importance of informing the clinic staff of the subject's use of any drugs or remedies (whether prescribed, over the counter, or illicit) before and during the course of the study. Information regarding all concomitant medications will be collected and documented in the concomitant medication page of the eCRF and in the source documents by the clinic staff. Concomitant therapies will be recorded, reviewed, and updated at each visit.

Any new concomitant therapy or modification of an existing therapy can be linked to an AE. A corresponding AE Form is to be completed to account for the change in therapy, except in some cases, such as therapy used for prophylaxis and dose modification for a chronic condition.

5.4.1. Concomitant Use of Corticosteroids

Although it is recognized that corticosteroid use has demonstrated benefit in DMD patients , because of their potential to influence changes in BP measurements and cholesterol and triglyceride levels, corticosteroid use is strongly discouraged in this study in order to minimize potential confounding effects on the interpretation of study results. If the investigator deems it necessary for the benefit of the subject to continue use of a corticosteroid during the study, a stable and standardized regimen must be maintained for at least 30 days prior to randomization, and throughout the duration of the study.

5.4.2. Concomitant Use of Systemic Aminoglycoside Therapy and/or Intravenous Vancomycin

Ataluren should not be co-administered with IV aminoglycosides. Cases of decreased renal function were observed in a clinical study of subjects with nonsense mutation cystic fibrosis receiving concomitant ataluren and IV aminoglycosides (as described in the Ataluren IB).

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

5.4.3. Coumarin-Based Anticoagulants

As the primary route of ataluren metabolism is via glucuronidation by UGT1A9, clinically significant interactions between ataluren and co-administered drugs metabolized by cytochrome P450 (CYP) enzymes are unlikely. In particular, ataluren is not an inhibitor of CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4/5, and does not have induction potential on the major CYP enzymes. Based on in vitro studies, ataluren is also not expected to be an inhibitor or a substrate of p-gp mediated transport.

As an added measure of safety, investigators should pay specific attention to use of drugs that are known substrates of this enzyme, particularly when such drugs may have a low therapeutic index.

Drugs that are metabolized by CYP2C8 or CYP2C9 that have low therapeutics indices (in particular, paclitaxel for CYP2C8 and coumarin anticoagulants [eg, warfarin], phenytoin, or tolbutamide for CYP2C9) may be of particular concern. Coumarin anticoagulants are cleared by CYP2C9 and increases in plasma concentrations of coumarin anticoagulants may result in serious clinical consequences. For subjects who require anticoagulation during the study, use of an alternative form of anticoagulation (eg, fractionated heparin) should be considered. Phenytoin is metabolized by CYP2C9 and concomitant use with ataluren may be of potential concern. For subjects who require anticonvulsant therapy during the study, use of alternative anticonvulsant drugs should be considered.

The metabolism of losartan to its active metabolite may, in part, be mediated by CYP2C9. However, concomitant use of losartan and inhibitors of CYP2C9 have not been examined. Because this drug does not have a narrow therapeutic window, the potential for mild to moderate changes in activity does not require a dose modification.

5.4.4. Inducers of UGT1A9 or Substrates of OAT1, OAT3, or OATP1B3

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

In vitro data indicate that ataluren is an inhibitor of UGT1A9, organic anion transporter 1 (OAT1), organic anion transporter 3 (OAT3) and organic anion transporting polypeptide 1B3 (OATP1B3). Caution should be exercised when ataluren is co-administered with drugs that are substrates of UGT1A9 (eg, propofol, mycophenolate mofetil), OAT1, OAT3, or OATP1B3 (eg, oseltamivir, acyclovir, ciprofloxacin, captopril, furosemide, bumetanide, valsartan, pravastatin, rosuvastatin, atorvastatin, pitavastatin) because of the risk of increased concentration of these drugs.

6. STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

6.1. Discontinuation of Study Intervention

If after appropriate consideration of study drug interruption/modification and consultation with the PTC 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 medical monitor should be notified. 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 Early Termination (ET) Visit CRF should be completed and appropriate follow-up, ie, at ~4 weeks as per protocol or until recovery from or stabilization of the AE, whichever comes last.

6.2. Participant Discontinuation/Withdrawal from the Study

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

1. The subject's parent(s)/caregiver(s) has the right to withdraw consent and discontinue ataluren at any time.
2. If the subject's condition substantially worsens after initiating ataluren, the subject will be carefully evaluated by the investigator. The subject will be withdrawn from treatment if continuing would place them at risk.
3. The investigator may withdraw the subject from ataluren, if, in the investigator's clinical judgment, it is not in the subject's best interest to continue.
4. In the event the subject becomes significantly noncompliant with ataluren administration, study procedures, or study requirements, the subject should be withdrawn from ataluren when the circumstances surrounding noncompliance increase risk to the subject or are anticipated to substantially compromise the interpretation of study results.
5. This study may be discontinued by the relevant regulatory authority, Institutional Review Board/Independent Ethics Committee (IRB/IEC), and/or PTC at any time.

6.2.1. Collection of Data from Withdrawn Subjects

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

When ataluren is discontinued (regardless of the reason), the investigator is expected to capture all of the evaluations required at the EOT or follow-up and any additional evaluations should 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.

6.2.2. Subject Replacement

Subjects will only be replaced, if necessary, to meet study objectives.

6.2.3. Subject Follow-Up

Investigators will make every effort to obtain follow-up assessments within 4 weeks ±7 days from the date of the last ataluren treatment for all subjects withdrawing from study treatment prematurely.

7. STUDY ASSESSMENTS AND PROCEDURES

7.1. Schedule of Events and Study Parameters

Subjects may be in the study for up to 4 weeks prior to receiving study drug at the baseline visit (Visit 2) and for 4 weeks ±7 days after last study drug administration (Visit 5).

The timing and types of procedures and assessments for this study are specified below in Table 2.

Table 2: Schedule of Assessments

Study Period	**Screening**[a]	**Baseline/ Start of Treatment**[b]	**Treatment Phase**		**EOT/ET**[c]	**Post-Treatment Follow-Up/ EOS**[d]
Visit	**Visit 1**	**Visit 2**[e]	**Visit 3**[e]	**Visit 4**	**Visit 5**[e]	**Visit 6**
Week	**-**	**Week 0**	**Week 4**	**Week 12**	**Week 24**	**Week 28**
Visit Window (days)	**(-28 to -1)**	**0**	**±7**	**±7**	**±7**	**±7**
Eligibility						
Informed Consent[f]	X					
Inclusion/Exclusion	X	X				
Medical/Surgical History	X	X				
Demographics	X					
Safety Assessments						
Physical Examination[g]	X	X	X	X	X	
Clinical Labs[h]	X	X	X	X	X	
Blood Sample for Gene Sequencing[i]	X					
Height/Weight[j]/BMI	X	X	X	X	X	
Vitals (HR and BP)[k]	X	X	X	X	X	
ECG[l]	X	X	X		X	
AE/SAE Monitoring	X	X	X	X	X	X
Concomitant Medications[m]	X	X	X	X	X	X
PK Blood Sampling (VAMS)[n]		X	X		X	
Blood/Plasma Partition Sampling[o]		X	X		X	
Study Drug Administration						
Dispense Drug		X		X		
Unused Drug Return/Compliance			X	X[p]	X	

Abbreviations: AE, adverse event; BMI, body mass index; BP, blood pressure; CL/F, apparent clearance; C_{trough}, trough concentration (plasma concentration pre morning dose); ECG, electrocardiogram; EOS, end of study; EOT, end of treatment; ET, early termination; HR, heart rate; PK, pharmacokinetic; SAE, serious adverse event; VAMS, volumetric absorptive microsampling

[a] Screening procedures must take place within 28 days of baseline (Visit 2).

[b] Any screening procedure completed within and including 14 days of baseline (Visit 2) can serve as baseline assessment and does not need to be repeated at Visit 2.

[c] Subjects who terminate the study early are to complete all assessments required for EOT/ET (Visit 5) prior to leaving the study and will be contacted by phone 4 weeks from the final dose of study medication for the post-treatment follow-up/EOS (Visit 6).

[d] Post-treatment follow-up will be conducted by phone 4 weeks ± 7 days from last day of study treatment for review of adverse events and concomitant medications. Post-treatment follow-up is not required if subjects are transitioning to another ataluren clinical trial.

[e] Visits 2, 3, and 5 will be conducted over the course of 24 hours due to the timing of the collection of PK samples and will require an overnight stay.

[f] A signed and dated informed consent must be obtained before conducting any study procedures. Remote informed consent is permitted consistent with local policies and procedures.

[g] A full physical examination will include evaluation of the cardiovascular system, chest and lungs, thyroid, abdomen, nervous system, skin and mucosae, musculoskeletal system, eyes, ears, nose, mouth, throat, spine, lymph nodes, and extremities.

[h] Blood and urine collection will be obtained locally and submitted to the local or central laboratory for analysis. Use of standard of care labs is permitted when samples were obtained within the visit window. Clinical labs will include hematology, biochemistry, and urinalysis parameters as follows: Hematology laboratory assessments will include white blood cell count with differential, hemoglobin, hematocrit, other red cell parameters, and platelet count. Biochemistry laboratory assessments will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, magnesium, calcium, phosphorus, uric acid, glucose, total protein, albumin, bilirubin (total, direct, and indirect), aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, creatinine kinase, lactate dehydrogenase, alkaline phosphatase, total cholesterol, high density lipoprotein, low density lipoprotein, triglycerides, and cystatin C. Urinalysis assessments will include analysis for pH, specific gravity, glucose, ketones, blood, protein, urobilinogen, bilirubin, nitrite, urine protein: urine creatinine ratio (spot), and leukocyte esterase.

[i] This is to ensure a blood sample has been drawn for sequencing of the dystrophin gene. The sample will be sent to a central laboratory for analysis.

[j] Weight-based dose adjustment will be assessed at Week 12.

[k] Heart rate and BP determinations will be performed with the subject in a supine position after a 5-minute rest.

[l] ECGs will be read locally at investigational sites and interpreted for clinical significance.

[m] Concomitant medication information will need to be collected starting 28 days prior to the first dose of study drug (Screening, Visit 1).

[n] PK samples (VAMS method) will be drawn at baseline (Visit 2), Week 4 (Visit 3), and Week 24 (EOT/ET) for evaluation. Samples will be drawn immediately pre-dose, and at 1-, 2-, 3-, and 4-hours post-dose following both the morning and mid-day doses and immediately pre-dose and at 1-, 2-, 3-, 4-, and 12- (before the next day morning dose) hours post-dose following the evening dose.

[o] Blood sampling via venous draw will be conducted at Visits 2, 3, and 5. These additional samples will be taken at 2.5 -hours and 4.5 -hours post morning dose (1.5 ml each timepoint). Out of the 1.5 mL blood sample collected, at the 2.5 hour and 4.5 hour timepoints, 1 mL blood sample will be processed to plasma and the remaining 0.5 mL blood will be processed to dried blood sample using a VAMS device.

[p] Parent(s)/caregiver(s) will record daily dose administration on a Study Drug Administration Record (dosing sheet) and Subjects are required to return any unused study drug.

7.1.1. Screening (Visit 1)

The Screening phase of the study will occur from Day -28 to Day -1 prior to the first dose of study medication. Screening procedures must take place within 28 days of the baseline visit (Visit 2). No study-related procedures should be performed prior to the signing of the informed consent document. Thereafter, subjects should undergo the initial set of screening procedures as noted in Table 2.

7.1.2. Baseline/ Start of Treatment (Visit 2)

Information will be gathered, and assessments performed for each subject at baseline (Visit 2) according to the schedule in Table 2 Any screening procedure completed within and including 14 days of Visit 2 can serve as baseline and does not need to be repeated at Visit 2. Ataluren will be administered at Visit 2 (See Section 5.1.2.3) and treatment will continue for up to 24 weeks.

Study participants will report to the clinic on the day of each on-site visit as directed by the investigator and will remain in the clinic until released by the investigator after all the study -related procedures have been completed and the parent(s)/caregiver(s) have been instructed regarding drug storage, reconstitution, and administration. Visit 2 will be conducted over the course of 24 hours due to the timing of the collection of PK samples and will require an overnight stay.

7.1.3. Treatment Phase (Visits 3-4)

During the treatment period, each subject will return to the clinical research facility at Week 4 ±7 days (Visit 3) and at Week 12 ±7 days (Visit 4) for procedures and assessments according to Table 2. Visit 3 will be conducted over the course of 24 hours due to the timing of the collection of PK samples and will require an overnight stay.

7.1.4. End of Treatment/Early Termination (Visit 5)

Subjects will return to the clinic for the EOT visit (Visit 5) after 24 weeks ±7 days of treatment and assessments will be performed according to the schedule in Table 2. Visit 5 will be conducted over the course of 24 hours due to the timing of the collection of PK samples and will require an overnight stay.

If the subject discontinues treatment prematurely, the procedures required for the EOT visit (Visit 5) should be performed before the subject leaves the study and the subject should be contacted by phone for the 4-week post-treatment follow-up (Visit 6). PTC will ensure that subjects who complete the 24-week treatment period in this study are offered participation to a follow-up extension period for at least 52 weeks from the date of first administration of ataluren in this parent study. These subjects will be followed-up for long-term safety and efficacy as an exploratory endpoint in the extension study.

See Section 6.2 for details regarding subject withdrawal procedures.

7.1.5. Post-treatment Follow-Up/End of Study (Visit 6)

The subject's parent/guardian will be contacted by phone 4 weeks ±7 days from the last day of study treatment for review of AEs and concomitant medications (see Table 2). Post-treatment follow-up is not required if subjects are transitioning to another ataluren clinical trial.

7.1.6. Unscheduled Visits

An unscheduled visit may take place at any time during the study at the request of the subject's parent/guardian, or as deemed necessary by the investigator due to medical conditions. The date and reason for the unscheduled visit will be recorded. Adverse event monitoring and concomitant medications will be recorded. Other procedures and assessments will be completed as deemed necessary by the investigator and may include (but not be limited to) safety laboratory tests, electrocardiogram (ECG), vital signs, and physical examination.

7.2. Eligibility Procedures

7.2.1. Informed Consent

The investigator/study staff member must inform each study candidate's parent(s)/caregiver(s) of the nature of the study, explain the potential risks, and obtain written informed consent from the parent(s)/caregiver(s) prior to performing any study-related screening procedures. Remote informed consent is permitted per local policies and procedures.

No study-related procedures should be performed prior to the signing of the informed consent document. Thereafter, subjects should undergo the initial set of screening procedures as noted in Table 2. Please refer to Section 4.2 and Section 4.3 respectively for study inclusion and exclusion criteria.

7.2.2. Medical History

The investigator or a qualified designee should review the subject's clinical history, including details relating to nmDMD and any other medical conditions. Information regarding clinical history and current medications must be captured on the medical history and prior/concomitant medication eCRFs, respectively. Concomitant medications information will need to be collected starting 28 days prior to first dose of study drug.

7.2.3. Demographic Information

Demographic information will be gathered and recorded in source documents and within the eCRF.

7.3. Safety Assessments

7.3.1. Physical Examination

A full physical examination (including evaluation of the cardiovascular system, chest and lungs, thyroid, abdomen, nervous system, skin and mucosae, musculoskeletal system, eyes, ears, nose, mouth, throat, spine, lymph nodes, and extremities) will be conducted at all protocol-required study visits.

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

7.3.2. Clinical Laboratory Assessments (hematology, biochemistry, urinalysis)

Fasting will not be required for laboratory assessments. Laboratory assessments are as follows:

- **Hematology:** white blood cell count with differential, hemoglobin, hematocrit, other red cell parameters, and platelet count.
- **Biochemistry**: sodium, potassium, chloride, bicarbonate, BUN, creatinine, magnesium, calcium, phosphorus, uric acid, glucose, total protein, albumin, bilirubin (total, direct, and indirect), aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transferase, CK, lactate dehydrogenase, alkaline phosphatase, total cholesterol, HDL, LDL, triglycerides, and cystatin C.
- **Urinalysis**: pH, specific gravity, glucose, ketones, blood, protein, urobilinogen, bilirubin, nitrite, urine protein: urine creatinine ratio (spot), and leukocyte esterase.

Please refer to Section 7.5 for further details.

7.3.3. Confirmatory Gene Sequencing

A blood sample for dystrophin gene sequencing to confirm the presence of a nonsense mutation will be drawn at screening (Visit 1). This sample will be sent to a central laboratory for analysis. The sample will be destroyed by the central laboratory after test completion and generation of a final report. The study manual should be referenced for collection, processing, and shipping information.

Please refer to Section 7.5 for further details.

7.3.4. Pharmacokinetic Assessment

The PK parameters will be evaluated based on frequent blood sampling. During PK assessments at baseline (Visit 2), Week 4 (Visit 3), and EOT at Week 24 (Visit 5), subjects will remain in the clinic until all blood draws are complete. At each assessment period, blood sampling will occur immediately pre-dose, and at 1-, 2-, 3-, and 4-hours post-dose following the morning and mid-day doses and immediately pre-dose and at 1-, 2-, 3-, 4-, and 12- (before the next day morning dose) hours post-dose following the evening ataluren dose. Blood PK samples will be collected by dried blood sampling via volumetric absorptive microsampling (VAMS) technology by utilizing the Mitra microsampling device (Neoteryx, CA, USA). An ~80 µL blood sample will be collected for each of the 16 time points during each assessment period. These samples will be sent to a bioanalytical laboratory for analysis of ataluren levels. The concentration of ataluren in the VAMS dried blood sample will be assessed using validated liquid chromatography with tandem mass spectrometry (LC-MS/MS) method. Please refer to the laboratory manual for instructions regarding the collection, processing, and shipment of all PK samples to the bioanalytical laboratory.

The blood/plasma partition sampling will occur at 2.5 hour and 4.5 hour post morning dose at baseline (Visit 2), Week 4 (Visit 3), and EOT at Week 24 (Visit 5).

Please refer to Section 7.5 for further details.

7.3.5. Weight, Height, and Body Mass Index

Height (in cm), weight (in kg) and body mass index (BMI) (kg/m^2) will be measured at all study visits.

7.3.6. Vital Signs

Vital signs (heart rate and systolic and diastolic BP) will be monitored at all protocol -required study visits. Heart rate and BP determinations will be performed with the subject in a supine position after a 5-minute rest.

7.3.7. Electrocardiogram

A 12-lead ECG will be obtained at screening (Visit 1), baseline (Visit 2), Week 4 (Visit 3), and EOT at Week 24 (Visit 5). The ECGs will be read locally at investigational sites and interpreted for clinical significance. The findings will be captured in source documents and within the eCRF.

7.3.8. Adverse Events/Serious Adverse Events

AEs must be assessed and documented at each scheduled clinic visit, beginning at screening (Visit 1). Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an AE should be obtained when clinically indicated. Subjects must be followed for AEs for at least 4 weeks after the last dose of ataluren administration, or until any drug-related AEs and/or ongoing SAEs have resolved or become stable, whichever is later. Please refer to Section 7.5.1 for further details.

7.3.9. Concomitant Medications

Concomitant medication information will be collected and documented at each scheduled clinic visit, from screening (Visit 1) through EOT at Week 24 (Visit 5). Any concomitant drugs (prescribed or over the counter) used during the course of the study and the reason for their use will be recorded. Information regarding the timing, type, and amount will be recorded in the eCRF.

7.4. Study Drug Administration Procedures

7.4.1. Study Drug Administration

Ataluren will be supplied at baseline and Week 12 (Visit 4). Because of potential changes in subject body weight over time, the subject's body weight will be assessed and documented at Week 12 and dose modifications made as appropriate.

The PTC medical monitor should be notified of any AE or laboratory abnormality that leads to dose interruption and should be apprised of ancillary laboratory or other diagnostic findings and the evolving data from any work-up of the initial abnormality. The return of any unused drug sachets will be documented for compliance assessments. The subject's parent(s)/caregiver(s) will return all unused sachets of ataluren as instructed for full compliance assessments.

Please see Section 5 for further information on Study Intervention Procedures, including study intervention and compliance.

7.5. Laboratory Procedures/ Sample Preparation, Handling, Storage and Shipment

Clinical labs, including hematology, biochemistry, and urinalysis parameters, are to be collected following the standard institutional procedures for blood and urine collection and submitted to the local or central laboratory by the investigative site for analysis. Please refer to the laboratory manual for instructions regarding collection, processing, and shipment of gene sequencing and PK blood samples to the central laboratory.

7.5.1. Blood Collection Summary

Blood collection procedures and total amounts of blood to be drawn over the entire study are discussed in the laboratory manual and summarized in Table 3.

Table 3: Summary of Estimated Total Blood Volume by Assessment and Visit

Study Period	**Screening**	**Baseline/ Start of Treatment**	**Week 4**	**Week 12**	**Week 24 EOT/ET**
Visit	**Visit 1**	**Visit 2**	**Visit 3**	**Visit 4**	**Visit 5**
Clinical Labs	8.5 mL	8.5 mL	8.5 mL	8.5 mL	8.5 mL
Blood Sample for Gene Sequencing	6 mL				
PK Blood Sampling[a]		1.28 mL	1.28 mL		1.28 mL
Blood/Plasma Partition Sampling[b]		3ml	3ml		3ml

Abbreviations: EOT, end of treatment; ET, early termination; PK, pharmacokinetic; VAMS, volumetric absorptive microsampling

[a] ~80µL blood sample will be collected by dried blood sampling using VAMS technology for each of the 16 time points during each assessment period.

[b] 1.5 ml blood sample will be collected for each of the 2 timepoints during each assessment period.

7.6. Adverse Events and Serious Adverse events

Information about AEs, whether reported by the subject's parent/guardian, discovered by the investigator by questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded on the AE form and followed-up as appropriate. Information about SAEs should be reported within 24 hours of obtaining knowledge of the event.

7.6.1. Definition of 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

- Apparently unrelated illnesses, including worsening of a preexisting illness
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate AEs. The outcome of the accident (hip fracture secondary to the fall) should be recorded in source documents
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test)
- Laboratory 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 CRF for Visit 1 but should not be reported as an AE unless the condition worsens, or episodes increase in frequency during the AE reporting period. Diagnostic and therapeutic noninvasive 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 eCRF. 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 any hospitalization occurring as the consequence of an AE during the study period should be reported as an SAE.

Each AE is to be classified as serious or nonserious by the investigator using medical and scientific judgment.

7.6.2. Definition of Serious Adverse Events

An SAE is an untoward medical occurrence or effect associated with the use of a study drug at any dose, regardless of whether it is considered related to the study drug, which 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. In addition, any AE resulting in death that occurs subsequent to the AE reporting period and that the investigator assesses as possibly related to the study drug should also be reported as serious.

- 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 hospitalization or prolongation of existing hospitalization (excluding hospitalizations for administration of the study drug, procedures required by the study protocol, or treatment-related diagnostic procedures; other planned hospitalizations; or hospitalizations related only to progression of disease). Emergency room visits that do not require admission to the hospital do not fall into this category, although the event may still be serious due to another seriousness criterion.
- Results in persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions, not related to cancer.
- Any other medically important event that the investigator or the sponsor judges to be serious or which is defined as serious by the regulatory agency in the local country. 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 hospitalization, or development of drug dependency or drug abuse.

7.6.3. Unexpected Adverse Events

The IB contains the Reference Safety Information (RSI) which will be used for assessing expectedness. If an event is not listed in the RSI, it should be considered unexpected or if the AE occurs at a greater severity, specificity, or frequency, it should be considered unexpected.

7.6.4. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject's parent(s)/caregiver/legally acceptable representative. In addition, each study subject's parent(s)/caregiver/legally acceptable representative will be questioned about AEs at each scheduled clinic visit after study drug administration or during any telephone contact with the subject's parent(s)/caregiver/legally acceptable representative. The type of question asked should be open-ended, for example, "*How have you been feeling*?" or a similar type of query.

7.6.5. Recording Nonserious Adverse Events and Serious Adverse Events

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. In addition, any known untoward event that occurs subsequent to the AE reporting period that the investigator assesses as possibly related to the investigational drug/product should also be recorded as an AE.

All AEs are to be recorded in the source documents and on the eCRF using concise medical terminology; whenever possible, terms contained in the 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 7.6.2)
- Relationship to study drug (see Section 7.6.6)
- Severity of the event (see Section 7.6.7)
- 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.

7.6.6. Describing Adverse Event Relationship to Study Drug

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, using the considerations outlined in Table 4.

Table 4: Relationship of Study Drug to Adverse Event

Relationship	Description
Probable	A clinical event in which a relationship to the study drug seems probable because of such factors as consistency with known effects of the drug; a clear temporal association with the use of the drug; improvement upon withdrawal of the drug; recurrence upon 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 adverse event than study drug. Such alternatives include a concomitantly administered drug, the subject's disease state, other medical conditions, or environmental factors.
Unrelated	A clinical event, for which a relationship to the study drug seems improbable because of factors such as inconsistency with known effects of the study drug, lack of a temporal association with study drug administration, lack of association of the event with study drug withdrawal or rechallenge, and/or presence of alternative explanations for the event. Alternative explanations might include a known relationship of the adverse event to a concomitant drug, medical history of a similar event, the subject's disease state, other medical conditions, or environmental factors.

An AE is considered causally related to the use of the study product when the relationship assessment is probable or possible. Events assessed as unlikely related or unrelated to the use of study product will be considered as having no relationship to treatment.

7.6.7. Grading of Severity of Adverse Events

The severity of AEs will be graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 (refer to the study manual). For each episode, the highest severity grade attained should be reported.

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

Table 5: Grading of Adverse Event Severity

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

Note the distinction between the seriousness and the severity of an AE. Severity is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity but would not be classified as serious unless it met one of the criteria for serious events listed in Section 7.6.2.

7.6.8. Adverse Event Reporting

Investigator site reporting requirements for AEs are summarized in Table 6.

Table 6: Investigator Site Requirements for Reporting Adverse Events

Event	Recorded on the eCRF	Reported on the SAE Report Form to PTC Pharmacovigilance Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Occupational Exposure	None	Occupational exposure (regardless of whether associated with an AE)

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

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 medical monitor or designee should be informed via e-mail A subject withdrawn from the study because of an AE must be followed by the investigator until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. Follow-up may need to continue after the subject has discontinued from the study, and additional investigations may be requested by the PTC medical monitoring team.

The first day of AE reporting will coincide with the date of signing of informed consent and including a minimum of 4 weeks after the last administration of study drug.

7.6.9. Serious Adverse Event Reporting

All SAEs should be reported via the SAE report form to PTC Therapeutics Pharmacovigilance Department 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 e-mailed to the PTC Therapeutics Pharmacovigilance Department or designee and to the site IRB/Ethics Committee (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 e-mailed 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 eCRF and the SAE report form(s) must match or be reconciled. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (for example, if a 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 SAE.

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.

PTC Therapeutics Pharmacovigilance Department
E-mail: [redacted]
Fax: [redacted]

7.6.10. Reporting Pregnancy

Subjects enrolled in this trial will have not reached sexual maturity; therefore, there are no requirements for pregnancy avoidance for study participants.

7.6.11. PTC Therapeutics Adverse Event Reporting Requirement

As the sponsor of the study, PTC is responsible for reporting certain safety information, such as suspected unexpected serious adverse reactions (SUSARs) and other significant safety findings, per local reporting requirements, to each investigator in an expedited manner. If notification of a SUSAR requiring expedited reporting to investigators is received, PTC or its designated representative will contact each investigational site participating in this study by e-mail, fax, and/or overnight mail such that the investigator can promptly notify the site IRB/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 or an agent of PTC (eg, a site monitor) becomes aware of the event. This awareness date is the date the regulatory reporting clock begins, and the date is considered Day 0.

7.6.12. Describing Outcome of Adverse Event

The outcome of an AE is assessed by the investigator using the following definitions:

- **Recovered:** Fully recovered, or by medical or surgical treatment the condition has returned to the level observed at the first study-related activity after the parent/guardian signed the informed consent.
- **Recovering:** The condition is improving, and the subject is expected to recover from the event.
- **Recovered with sequelae:** As a result of the AE the subject suffered persistent and significant disability/incapacity (eg, became blind, deaf, paralyzed). Any AE recovered with sequelae should be classified as SAE.
- **Not recovered:** The subject's condition has not improved, and the symptoms are unchanged.
- **Fatal**.
- **Unknown:** The subject's condition is unknown. This term should only be used when no other definition is possible, eg, the subject is lost to follow-up.

7.6.13. Follow-up of Unresolved Adverse Events

All AEs should be followed-up by the investigator until they are resolved, or the investigator assesses them as chronic or stable.

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

8. STATISTICAL METHODS AND DATA ANALYSIS

8.1. Statistical Methods

Detailed methodology for summary and statistical analyses of the data collected in this study will be documented in a statistical analysis plan.

By-subject listings will be created for each eCRF module. Statistical methods will be descriptive in nature. Summary tables for continuous variables will contain the following statistics: N, mean, standard deviation, minimum, and maximum as appropriate. Summary tables for categorical variables will include N, n, and percentage. Graphic displays will be used when such methods are appropriate and informative.

No interim analyses are planned.

8.2. Sample Size Determination

Sample size is not based on any formal statistical hypothesis for this study. It is anticipated that up to 10 subjects (minimum of 6 subjects) will be enrolled.

8.3. Statistical Significance

Statistical analyses will be descriptive in nature.

8.4. Population for Analyses

Two analysis populations are planned for this study, the Safety population and the PK population defined as follows:

- The **Safety Population** will include all subjects who receive at least one dose of ataluren and will be used for all safety analyses.
- The **PK Population** will include all subjects who receive at least 1 dose of ataluren and have at least 1 PK concentration datum. The PK Population will be used for all PK analyses.

8.5. Specific Planned Statistical Analyses

8.5.1. Subject Disposition and Baseline Characteristics

The number of subjects in each analysis population will be summarized using frequency count.

The number of subjects who completed or discontinued from the study and the reasons of discontinuation will be summarized based on both the Safety and the PK populations.

Reasons for screening failures and early discontinuations, and time of withdrawal from study will be described.

8.5.2. Use of Concomitant Medication and Supportive Therapy

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

8.5.3. Primary Variables – Safety

The primary safety analysis will use the Safety population and assess the type, frequency, severity (Section 7.6.7), seriousness (Section 7.6.2), timing, and relationship (Section 7.6.6) of TEAEs to study therapy.

All TEAEs will be tabulated using the MedDRA classification system (Version 22.1 or higher). The severity of TEAEs will be graded using the CTCAE (Version 5.0 or higher) whenever possible. For TEAEs that are not included in the CTCAE, the grading categories (mild, moderate, severe, life-threatening, and fatal) described in Table 5 will be used. The frequency of subjects experiencing a specific TEAE will be tabulated by system organ class; preferred term; seriousness (serious vs nonserious); timing of occurrence, outcome, relationship to study drug; and worst severity. In the by-subject analysis, a subject having the same event more than once will be counted only once and will be classified at the highest severity and/or relatedness for those events.

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

8.5.4. Secondary Variables - PK Parameters

The PK analyses will be performed using the PK population defined above (Section 8.4). The PK parameters will be summarized and described using descriptive statistics and results placed into context with PK data from previous studies.

The following PK parameters will be derived, when appropriate and data permitting, using noncompartmental analysis methods following the morning dose at baseline (Visit 2), Week 4 (Visit 3), and EOT at Week 24 (Visit 5):

- AUC will be derived using the linear trapezoidal rule during the ascending portion of the curve and the log-trapezoidal rule during the descending portion of the curve. $AUC_{0\text{-}24}$ after the morning dose and $AUC_{0\text{-}\tau}$ following every dose will be derived.
- C_{max}
- T_{max}
- C_{trough} (concentration prior to the morning dose)

Apparent clearance (CL/F) and $T_{1/2}$ may also be assessed, if feasible.

The PK parameters will be investigated based on frequent blood sampling. At each assessment period, blood sampling will occur at pre-dose, and 1-, 2-, 3-, and 4-hours post-dose following the morning and mid-day ataluren doses, and at pre-dose, 1-, 2-, 3-, 4-, and 12- (before the next day dose) hours after the evening ataluren dose.

Blood/plasma partitioning will be determined at 2.5 hour and 4.5 hour post morning ataluren dose at each visit.

8.5.4.1. PK Analysis Methods

Observed values of plasma concentrations for ataluren will be summarized at baseline (Visit 2), Week 4 (Visit 3), and EOT at Week 24 (Visit 5).

Individual PK parameters will be derived using actual sampling and dosing times. The PK parameters will be summarized with descriptive statistics at baseline (Visit 2), Week 4 (Visit 3), and EOT at Week 24 (Visit 5).(eg, n, arithmetic mean, standard deviation, standard error, median, min, and max, CV% mean, geometric mean, and CV% geometric mean). The analysis will be performed with a fully validated version of Phoenix WinNonlin V6.3 or higher.

Additional information will be provided in the PK analysis plan.

8.5.5. Other Variables

8.5.5.1. Vital Signs and Physical Examination

Vital signs (height, weight, BMI, systolic and diastolic BP, and heart rate) and physical examination data will be listed and summarized by visit and overall. Where appropriate, changes from baseline will be summarized by visit.

8.5.5.2. Laboratory Values

Laboratory data (hematology, biochemistry, and urinalysis) will be summarized by treatment visit and overall. Where appropriate, changes from baseline will be presented by visit.

8.5.5.3. Electrocardiogram

All ECG data will be listed and summarized by treatment visit and overall. Where appropriate, changes from baseline will be presented by visit.

8.5.6. Treatment Administration and Drug Compliance

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

Study drug administration data and compliance will be presented in a by-subject listing from data reported in the electronic data capture (EDC).

9. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

9.1. Regulatory, Ethical, and Study Oversight Considerations

9.1.1. Informed Consent Process

By signing the protocol, the investigator assures that written informed consent will be obtained from each subject's parent(s)/caregiver(s) prior to study entry and that the informed consent will be obtained in accordance with current regulations.

The investigator or sub-investigator must inform each subject's parent(s)/caregiver(s) of the nature of the study, explain the potential risks, and obtain written informed consent from the subject's parent(s)/caregiver(s) (as required by local regulations) prior to performing any study -related screening procedures.

Each subject's parent(s)/caregiver(s) must be given full and adequate verbal and written information regarding the objectives and procedures of the study and the possible risks involved. An informed consent document will be provided to each parent(s)/caregiver(s) in a language in which the parent(s)/caregiver is fluent. This information must be provided to the parent(s)/caregiver(s) prior to undertaking any study-related procedure. Adequate time should be provided for the parent(s)/caregiver(s) to read the informed consent, to understand the risks and benefits of participating in the study, and to ask any questions that the parent(s)/caregiver(s) may have about the study. The parent(s)/caregiver(s) should be able to ask additional questions as and when needed during the conduct of the study.

Each subject's parent(s)/caregiver(s) will be given a copy of the signed informed consent 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 and the IRB/IEC.

9.1.2. Study Discontinuation and Closure

PTC reserves the right to discontinue the study prior to inclusion of the intended number of subjects. The investigator, after consultation with the PTC 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 time-period set by PTC. As directed by PTC, all study materials must be collected, and all electronic data entry forms completed to the greatest extent possible.

9.1.3. Confidentiality and Privacy

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 (or its authorized designee). The names and identities of the subjects need not be divulged; however, the records must nevertheless be inspected. This will be accomplished by blanking out the subject's name and replacing the name with the subject's study identification number on any record provided to or retained by PTC. The informed consent form must include appropriate statements explaining these requirements.

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

9.1.4. Clinical Monitoring

In accordance with 21 Code of Federal Regulations Part 312.56 and/or relevant International Council on Harmonization (ICH) guidelines, PTC or a designee will periodically inspect all eCRFs (see Section 9.1.10), 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 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. The investigator/institution guarantees direct access to source documents by PTC and appropriate regulatory authorities.

The investigator site may also be subject to review by the IRB/IEC, to quality assurance audits performed by PTC or a designee, and/or to inspection by the Food and Drug Administration (FDA) and/or other regulatory authorities. The Investigational New Drug (IND) regulations also require the investigator to allow authorized representatives of the FDA 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.

9.1.5. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, the protocol, and the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for good clinical practice (GCP) (ICH 1996 and revisions), and the Declaration of Helsinki (World Medical Association).

The investigator is responsible for ensuring that the clinical study is performed in accordance with applicable legal and regulatory requirements, the Declaration of Helsinki, the ICH GCP guidance documents, and the protocol.

9.1.6. Study Discontinuation and Closure

PTC reserves the right to discontinue the study prior to inclusion of the intended number of subjects. The investigator, after consultation with the PTC 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 time-period set by PTC. As directed by PTC, all study materials must be collected, and all electronic data entry forms completed to the greatest extent possible.

9.1.7. Quality Assurance and Quality Control

To ensure compliance with GCP and all applicable regulatory requirements, PTC, PTC's representatives, a regulatory authority or and Institutional Review board may conduct a quality assurance audit. Reasons for quality assurance audit may include but are not limited to random selection, geographic proximity, suspected GCP violation, high enrolling site, recurring protocol deviations, etc. The purpose of a sponsor audit or inspection is to systematically and independently examine all study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP guidelines of the ICH, and any applicable regulatory requirements. The investigator should contact the sponsor immediately if contacted by a regulatory agency about an inspection.

9.1.8. Institutional Review Board/Independent Ethics Committee

Prior to enrollment of subject into the study, as required by the FDA and other regulatory authorities, the protocol and informed consent document will be reviewed and approved by an appropriate IRB/IEC. By signing the Statement of Investigator Form (FDA Form 1572), the investigator assures that approval of the study protocol will be obtained from the IRB/IEC and that all aspects of the IRB/IEC review will be conducted in accordance with current regulations. Amendments to the protocol will be subject to the same IRB/IEC review requirements as the original protocol. Only changes necessary to eliminate apparent immediate hazards to the subjects may be initiated prior to IRB/IEC approval. In that event, the investigator must notify the IRB/IEC and PTC in writing within 5 working days after implementation. The investigator will also promptly notify the IRB/IEC of any serious, unexpected AEs, or any other information that may affect the safe use of the drug during the study.

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

The investigator shall submit a progress report, at least once yearly, to the IRB/IEC, and must provide a copy to PTC. As soon as possible after completion or termination of the study, the investigator will submit a final report to the IRB/IEC and to PTC. 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 will assist the investigator in the preparation of this report, as needed.

9.1.9. Data Handling and Record Keeping

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 (electronic equivalents of CRFs), paper CRFs, signed informed consent forms, study drug disposition records, correspondence with the IRB/IEC, AE reports, and information regarding subject discontinuation and completion of the study. Current regulations require PTC (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 authorized representatives of the FDA or other regulatory authorities.

9.1.10. Case Report Forms

An eCRF is required and must be completed for each enrolled subject, with all required study data accurately recorded such that the information matches the data contained in medical records (eg, reasons for screen failure, 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 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 from the investigator site.

9.1.11. Protocol Deviations

A protocol deviation is defined as any intentional or unintentional change to, or noncompliance with, the approved protocol procedures or requirements.

Deviations may result from the action or inaction of the subject, investigator, or site staff. Examples of deviations include, but are not limited to:

- Failure to adhere to study exclusion and inclusion criteria
- Use of medications that are specifically prohibited in the protocol
- Missed or out-of-window visits
- Failure to adhere to test requirements, including vital signs, laboratory tests, physical examinations, PK blood draws, medical history, etc. - either tests not done, incorrect tests done, or not done within the time frame specified in the protocol
- Procedural deviations such as failure to update the Informed Consent Form (ICF) when new risks become known, or failure to obtain IRB approvals for the protocol and ICF revisions

Major deviations are any deviations that impact subject eligibility (ie, protocol inclusion/exclusion violations), subject safety or a subject's ability to continue in the clinical study.

At the outset of the study, a process for defining and handling protocol deviations will be established with the CRO. This will include determining which deviations will be designated major; thus, requiring immediate notification to the PTC medical monitor and the sponsor.

Prospective deviations (eg, protocol waivers) are prohibited per PTC policy.

The investigator is responsible for seeing that any known protocol deviations are recorded handled as agreed.

9.1.12. Publication and Data Sharing Policy

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

PTC intends that the data from this study will be presented and published. The PTC staff under the direction of the PTC 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.

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

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the Clinical Study Site Agreement. In the event of any discrepancy between the protocol and the Clinical Study Site Agreement, the Clinical Study Site Agreement will prevail.

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

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

9.2. Additional Considerations

Not applicable

9.3. Protocol Amendment History

Version 1.0: 14 April 2020

Amendment 1: 29 April 2021 (Version 2.0)

Amendment 2: 01 July 2021 (Version 3.0)

Amendment 3: 06 May 2022 (Version 4.0)

9.3.1. Amendment 1: 29 April 2021 (Version 2.0)

No.	Protocol Section	Version 2.0/Update	Reason/ Rationale
1	Protocol identifiers and study personnel, Protocol approval signatures	Study personnel and protocol approvers were updated	Update
2	Synopsis	Synopsis was updated to reflect the changes in the protocol	
3	List of Abbreviations	List of abbreviations was updated to reflect the changes in the protocol	Update
4	Protocol	Document date/version were updated	Update
5	Protocol	Minor clarifications and editorial/formatting updates	Update
6	Protocol	Updated the end of treatment timepoint to occur at Week 24 instead of Week 52	Update

No.	Protocol Section	Version 2.0/Update	Reason/ Rationale
7	Protocol	Removed efficacy endpoint from this study (ie, change in motor development). Removed the exploratory endpoint "abnormalities of physical findings, clinical laboratory tests, or electrocardiograms (ECGs)" since this information will be captured as part of the primary endpoint	Update
8	Protocol	Clarified that AUC would also be derived from time zero up to hour 6. The definition of C_{trough} was clarified to trough concentration (plasma concentration pre morning dose). It was clarified that apparent volume of distribution (Vc/F) would not be assessed.	Clarification
9	Protocol	The following sections were removed: "End of Study Definition" "Motor Development" Section added on home care services at week 4.	Update
10	Section 2.1	The exploratory objective of "to assess changes from baseline in CK levels after 24 weeks of ataluren treatment" was added	Update
11	Section 2.2	The exploratory endpoint of "change from baseline in CK levels" was added	Update
12	Section 3.2	The following text was added: "A new request for modification is currently being reviewed by the agency."	Update
13	Section 3.1 and Section 8.2	Clarified the planned sample size for this study	Clarification

No.	Protocol Section	Version 2.0/Update	Reason/ Rationale
14	Section 3.2	Removed the following language from criterion 2 as this information is included in Exclusion Criterion 1: "Participant's sibling, if enrolled in another ataluren study, must be on open-label study drug at the time of subject's enrollment in this study". Removed "Good general health, as determined by the investigator during the screening period based on medical history and physical examination (including vital sign measurements), as no clinically significant abnormal laboratory assessments" as this information is included in Exclusion Criterion 3. Removed the following language in relation to the diagnosis of Duchenne muscular dystrophy: "Medical documentation of phenotypic evidence of dystrophinopathy needs to be provided upon request by the PTC Therapeutics medical monitor" Clarified that the presence of a nonsense mutation of the dystrophin gene needs to be confirmed by a PTC designee prior to enrollment. Removed "verification that a blood sample was drawn for sequencing of the dystrophin gene" as an inclusion criterion	Update
15	Section 3.3	Removed "prior and concomitant use of corticosteroids" as an exclusion criterion. Clarified that subjects whose sibling is currently participating in a blinded portion of another ataluren study are excluded from this study	Update
16	Section 5.1.2.1	Duration of treatment was changed from "52 weeks" to "24 weeks"	Update
17	Section 5.1.2.2	Updated text to "weight will be reassessed at Week 12 and ataluren dosing adjusted accordingly" in line with the change to duration of treatment	Update
18	Section 5.1.2.3	Duration of treatment was changed from "52 weeks" to "24 weeks"	Update
19	Section 5.1.2.6	The following text was added: "During the course of the study, breastfeeding and milk formula are allowed as part of a normal alimentation regime."	Update
20	Section 5.1.5	Removed exclusion of orange juice for the constitution of ataluren Language regarding study drug preparation was modified for clarity.	Update
21	Section 5.3	Updated text to ""Parents/caregivers should return all remaining study drug (all unused sachets and drug kits) to the study site at Week 12 (Visit 4), if the visit is conducted on-site, and EOT at Week 24 (Visit 5)."	Update
22	Section 5.4.1	Provided additional information regarding corticosteroid use in the study	Update

No.	Protocol Section	Version 2.0/Update	Reason/ Rationale
23	Section 7.1.2	Duration of treatment was changed from “52 weeks” to “24 weeks” The following text was added for clarification: “Visit 2 will be conducted over the course of 24 hours due to the timing of the collection of PK samples and will require an overnight stay.”	Update
24	Section 7.1.3 and Table 2	Updated the treatment phase to include Visit 3 (Week 4) and Visit 4 (Week 12)	Update
25	Section 7.1.4	Added that subjects who completed the 24-week treatment period in this study were offered participation to a follow-up extension period for at least 52 weeks from the date of first administration of ataluren in this parent study.	Update
26	Section 7.3.3	Added additional information related to confirmatory gene sequencing	Update
27	Section 7.3.4	Revised the process by which blood PK samples will be collected	Update
28	Section 7.3.6 and Table 2	Clarified that heart rate and blood pressure determinations will be performed with the subject in a supine position	Clarification
29	Section 7.4.1	Clarified that “ataluren will be supplied at baseline and Week 12 (Visit 4)”	Clarification
30	Section 7.5	Clarified that clinical labs will be analyzed locally at the investigational sites	Clarification
31	Section 7.5.1	Updated to reflect the revisions to the study timepoints and updated the volume and process by which blood PK samples will be collected	Update
32	Section 7.6.2	It was clarified that emergency room visits that do not require admission to the hospital would not be reported as SAEs on that basis alone.	Clarification
33	Section 7.6.11	Details regarding PTC adverse event reporting were clarified.	Clarification
34	Section 8.5.6	Clarified that study drug administration will be presented in a by-subject listing	Clarification
35	Section 9.3	Updated protocol version history to reflect Version 2.0	Update

9.3.2. Amendment 2: 01 July 2021 (Version 3.0)

Protocol Section	Version 3/Update	Reason/ Rationale
Protocol	The version number and date were updated throughout. Editorial and administrative revisions (eg, typographical error, punctuation, tenses, abbreviations) were incorporated to provide clarity. The synopsis and Schedule of Assessments were updated to be consistent with changes in the protocol.	Update
Section 5.1.2 Section 5.3	Details on the Study Drug Administration Record were clarified.	Clarification
Section 7.1.7	Section on Home Care Services at Visit 4 was removed	Update
Section 7.3.4	Blood/plasma partition sampling was added.	Update

9.3.3. Amendment 3: 06 May 2022 (Version 4.0)

Protocol Section	Version 3/Update	Reason/ Rationale
Protocol	The version number and date were updated throughout. Editorial and administrative revisions (including, personnel changes, and the addressing of minor editorial issues) were incorporated to provide clarity. The synopsis and Schedule of Assessments were updated to be consistent with changes in the protocol.	Update
Section 3.2	Text, previously included in error, referring to agency review of a modification was deleted.	Correction
Section 7.1 , Table 2	The window during which screening procedures can serve as baseline assessments was revised from 7 days to 14 days prior to baseline. Language was added to explicitly permit obtaining informed consent remotely in keeping with local policy and procedures. Urine protein: urine creatinine ratio (spot) was added to the list of clinical laboratory assessments. Language was added to allow for clinical laboratory assessments in keeping with standard of care to serve as the clinical laboratory assessments if conducted within the visit window.	Update
Section 7.1.2	The window during which screening procedures can serve as baseline assessments was revised from 7 days to 14 days prior to baseline.	Update
Section 7.2.1	Language was added to explicitly permit obtaining informed consent remotely in keeping with local policy and procedures.	Update
Section 7.3.2	Urine protein: urine creatinine ratio (spot) was added to the list of clinical laboratory assessments.	Update
Section 7.5	The phrase “or central” was added to clarify that either central or local laboratory analysis of clinical laboratory specimens is permitted.	Clarification
Section 8.5.4	Clarification was provided regarding the pharmacokinetic analysis.	Clarification

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