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CLINICAL PROTOCOL

AN OPEN-LABEL STUDY FOR PREVIOUSLY TREATED ATALUREN (PTC124®) PATIENTS WITH NONSENSE MUTATION DYSTROPHINOPATHY

Protocol Number PTC124 -GD-019-DMD

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PROTOCOL IDENTIFIERS AND STUDY PERSONNEL

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PRINCIPAL INVESTIGATOR AGREEMENT AND SIGNATURE

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

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ABBREVIATIONS

Abbreviation	Definition
6MWD	6-minute walk distance
6MWT	6-minute walk test
^{99m}-Tc-DTPA	99m-diethylenetriamine pentaacetic acid
ACE	Angiotensin converting enzyme (inhibitor)
ACTH	Adrenocorticotropic hormone
ALT	Alanine aminotransferase
ARB	Angiotensin receptor blocker
AST	Aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
AUC	Area under the concentration versus time curve
AUC_{0-24}	Area under the concentration versus time curve from time 0 to 24 hours
BID	Bis in die (2 times per day)
BMD	Becker muscular dystrophy
BUN	Blood urea nitrogen
CF	Cystic fibrosis
CFR	Code of Federal Regulations
CFTR	Cystic fibrosis transmembrane conductance regulator
cGMP	Current Good Manufacturing Practices
CHF	Congestive heart failure
CI	Confidence Interval
CK	Creatine kinase
C_{max}	Maximum plasma concentration
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
D/C	Discontinuation
DMC	Data monitoring committee
DBMD	Duchenne and Becker muscular dystrophy
DMD	Duchenne muscular dystrophy
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRFs	Electronic case report forms
EDC	Electronic data capture
EDTA	Ethylenediaminetetraacetic acid
EK	Egen Klassifikation
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FDAMA	Food and Drug Modernization Act of 1997
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma glutamyl transferase

Abbreviation	Definition
HDL	High-density lipoprotein
hERG	Human ether-à-go-go-related gene
HPA	Hypothalamic-pituitary-adrenal
ICH	International Conference on Harmonisation
ICJME	International Committee of Medical Journal Editors
IND	Investigational New Drug (Application)
IRB/IEC	Institutional Review Board/Institutional Ethics Committee
IV	Intravenous
IWR	Interactive Web Response
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
nmDBMD	Nonsense mutation Duchenne and Becker muscular dystrophy
NSAA	North Star Ambulatory Assessment
PK	Pharmacokinetic(s)
QT	Ventricular depolarization-repolarization interval on ECG
SAE	Serious adverse event
SD	Standard deviation
$t_{1/2}$	Plasma half-life
TID	Ter in die (3 times per day)
Tx	Treatment
UE	Upper extremity
ULN	Upper limit of normal
US	United States
WHODRUG	World Health Organization Drug Dictionary
WNL	Within normal limits

1. OVERVIEW

1.1. Background

Duchenne muscular dystrophy (DMD) is a disabling and life-threatening X-linked genetic disorder affecting males. A small subset of boys and men (1 out of 10) are classified as having Becker muscular dystrophy (BMD), a phenotypically milder form of the dystrophic muscle disease that is associated with later manifestation of symptoms. In essence, DMD and BMD represent a continuum of the same disease caused by mutations in the gene for dystrophin, a protein that stabilizes muscle cell membranes. Boys with DBMD (Duchenne and Becker muscular dystrophy) develop progressive proximal muscle weakness that leads to deterioration of ambulation, wheelchair dependency, and eventual respiratory and cardiac failure. Only chronic administration of corticosteroids has slowed progression of the disease. However, because of serious side effects, corticosteroids are not always employed, especially in nonambulatory patients. There is no current therapy for the underlying cause of DBMD.

In ~10 to 15% of boys and men with DBMD, the causative defect in the dystrophin gene is a nonsense mutation that truncates dystrophin protein production by introducing a premature stop codon into the dystrophin messenger ribonucleic acid (mRNA). Ataluren (PTC124) is a novel, orally bioavailable, small-molecule drug that promotes ribosomal readthrough of mRNA containing a premature stop codon. Through this mechanism of action, ataluren has the potential to overcome the genetic defect in patients with nonsense mutation DBMD (nmDBMD).

A previous Phase 2a study (PTC124-GD-004-DMD) enrolled 38 boys with nmDMD, including ambulatory and nonambulatory patients, to receive 28 days of ataluren treatment. The study demonstrated ataluren-related increases in in vitro and in vivo dystrophin expression and statistically significant reductions in serum concentrations of muscle-derived creatine kinase (CK). Of the 38 patients, 36 patients subsequently enrolled into a Phase 2a open label extension study (PTC124-GD-004e-DMD). These patients received the 20-, 20-, 40-mg/kg dose level of ataluren for a median [range] of 70 [53 to 81] weeks.

A Phase 2b, international, multicenter, randomized, double-blind, placebo-controlled, dose-ranging, efficacy, and safety study (Study PTC124-GD-007-DMD; Study 007) evaluating ataluren in patients with nmDBMD was conducted. Patients were 5 to 20 years of age and were ambulatory at baseline. They were randomized 1:1:1 to receive placebo; ataluren at a low dose of 10 mg/kg (morning), 10 mg/kg (midday), 20 mg/kg (evening); or ataluren at a high dose of 20 mg/kg (morning), 20 mg/kg (midday), 40 mg/kg (evening). Patients completing this study continued to receive high-dose ataluren in an open-label extension to this study (PTC124-GD-007e-DMD; Study 007e). The safety data from Study 007 revealed a favorable ataluren safety profile across both ataluren dose levels. Efficacy data indicated that patients receiving low-dose ataluren experienced a slower loss of walking ability relative to patients receiving placebo. Efficacy in the high-dose ataluren arm was not better than observed in the placebo arm. Given these data suggesting the potential for an inverse dose-response relationship favoring the lower dose of ataluren, the data monitoring committee (DMC) for the ataluren DBMD program recommended discontinuation of ongoing studies evaluating high-dose ataluren. Consequently, ataluren administration in the open-label extension studies (004e and 007e) and in an additional

open-label study assessing the safety and exposure profiles of ataluren in nonambulatory patients with nmDBMD (Study PTC124-GD-008-DMD; Study 008) was halted in March 2010.

At the end of Study 007 (Week 48), the mean change from baseline in 6-minute walk distance (6MWD) was ~30 meters greater in patients treated with low-dose ataluren than in patients treated with placebo, consistent with the 30-meter change specified in the study protocol as being clinically relevant. The improvement among patients treated with low-dose ataluren compared to patients treated with placebo was generally consistent regardless of age, use of corticosteroids, or walking ability at the beginning of the study. There was no difference between high-dose ataluren and placebo in change in 6MWD over 48 weeks.

Positive trends in muscle function, as measured by timed function tests, were observed at Week 48 in patients treated with low-dose ataluren when compared to patients treated with placebo. In addition, over the 48-week study, patients treated with low-dose ataluren had a reduction in the frequency of accidental falls compared to patients treated with placebo. Mean changes in other secondary outcome measures were generally small; the meaningfulness of these results is unclear given the lack of prior experience in DBMD and/or other known limitations associated with these evaluations.

1.2. Study Design

This study comprises a Phase 3, open-label study of ataluren in patients with nmDBMD who previously received ataluren at an investigator site in a prior PTC-sponsored clinical study. A separate open-label study (PTC124-GD-016-DMD) is being conducted for nmDBMD patients who previously received ataluren at an investigator site in the United States (US).

All participating sites must have had at least 1 patient that received ataluren treatment in a prior PTC-sponsored clinical study in DBMD. It is planned that up to ~96 patients will be enrolled.

Subjects will receive ataluren 3 times per day (TID) at respective morning, midday, and evening doses of 10 mg/kg, 10 mg/kg, and 20 mg/kg, for approximately 240 weeks. Study assessments will be performed at clinic visits during screening, on the first day of ataluren dosing, and then every 12 weeks during the ataluren treatment period.

2. INTRODUCTION

2.1. Disease Indication

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

Dystrophin is a high-molecular-weight cytoskeleton protein localized at the inner surface of the muscle membrane [Worton 2001]. It is part of a dystrophin-glycoprotein complex that also includes dystroglycan and sarcoglycans. This complex provides a bridge across the muscle membrane; dystrophin couples actin in the cytoplasm with dystroglycan. Dystrophin deficiency destabilizes the dystrophin-glycoprotein complex, impairing localization of the dystroglycan and sarcoglycans to the muscle membrane, and compromising the structural integrity of the

membrane. The absence of normally functioning dystrophin results in sarcolemmal breakdown, calcium ion influx, phospholipase activation, oxidative muscle injury, and, ultimately, myonecrosis. As muscle damage progresses, connective tissue and fat replace muscle fibers.

DBMD usually first manifests in boys ~3 to 7 years of age when they are noted to develop lordosis, a waddling gait, and the Gowers' sign (a characteristically abnormal method of rising from a supine to a standing position) [Brooke 1989, McDonald 1995, Boland 1996, Worton 2001]. Inexorable progressive weakness is seen, particularly in the proximal musculature. Ambulation becomes increasingly abnormal. By the age of 8 years, most boys have difficulty rising from the floor and ascending stairs and they often fall while walking. Boys with the disease spend less time walking and walk more slowly than healthy boys [McDonald 2005a] and are significantly less active than normal boys of similar age [McDonald 2002, McDonald 2005b]. By 10 to 14 years of age, most are wheelchair-bound. In ambulatory DMD boys, the most frequent cardiac abnormality is sinus tachycardia and heart rate variability, occurring from childhood and persisting throughout life [Finsterer 2003, Gulati 2005]. Pulmonary function is usually normal before 10 years of age and is well maintained into adolescence in boys receiving corticosteroids [Mendell 1989, Griggs 1991, Phillips 2001, Tangsrud 2001, Biggar 2001, Biggar 2006]. Later in adolescence, cardiac and diaphragmatic muscles become progressively weaker and patients require treatment for cardiac insufficiency and ventilatory support. Patients usually die of cardiac or pulmonary failure by 15 to 22 years of age [Brooke 1989, McDonald 1995, Simonds 1998, Worton 2001, Eagle 2002].

2.2. Ataluren (PTC124)

2.2.1. Therapeutic Concept

Among the several types of disease-causing mutations, a nonsense mutation is a single-point alteration in one of the nucleotides of deoxyribonucleic acid (DNA) that, when copied to mRNA, is interpreted as a stop signal by the ribosomal cellular translational machinery. The presence of such a premature stop signal within the protein-coding region of the mRNA for dystrophin tells the ribosomes to halt production of the protein before the full-length protein is completed. The resulting truncated dystrophin is too short to serve its necessary function and causes disease. It is estimated that ~10-15% of all boys with DMD and BMD have a nonsense mutation as the basis for the disorder [Dent 2005], resulting in a prevalence of nmDBMD of ~1700 boys in the United States and ~2200 boys in Europe.

It has been known for some time that drugs with translation-modifying mechanisms of action, such as the aminoglycoside antibiotics (eg, gentamicin), can ameliorate the effects of nonsense mutations in experimental systems. By binding to the ribosomes, such agents permit the ribosomes to reinterpret the nonsense mutation stop signal in mRNA such that they can move through the obstruction by inserting an amino acid and continuing the translation process to produce a full-length functional protein. In experimental animal systems and in pilot studies in nmDBMD, treatment with high concentrations of gentamicin has restored production of functional dystrophin [Barton-Davis 1999, Politano 2003]. Similarly, nonclinical and clinical studies in cystic fibrosis (CF) have demonstrated restoration of the cystic fibrosis transmembrane conductance regulator (CFTR), the epithelial chloride channel that is defective in that disease

[Clancy 2001, Du 2002, Wilschanski 2003]. Current data suggest that the geometry of mRNA and associated initiation-termination proteins is critically different at a premature stop than at a normal stop. This may explain why a drug can permit the ribosomes to selectively read through the premature stop codon, but will not allow the ribosomes to read through the normal stop codon at the end of the mRNA protein-coding region [Sachs 2000, Welch 2000, Amrani 2004]. Because serious renal and otic toxicities and the need for parenteral administration preclude the long-term clinical use of gentamicin, there has been considerable interest in the identification of safer and more conveniently administered, low-molecular-weight, synthetic compounds with the ability to promote readthrough of disease-causing nonsense mutations.

Ataluren as an orally bioavailable, small molecule with potential clinical utility in treating genetic disorders through induction of readthrough of nonsense mutations and production of full-length, functional proteins. Ataluren does not promote readthrough of normal stop codons, alter mRNA levels, or affect the process of nonsense-mutation-mediated mRNA decay. In the subset of patients whose disease is mediated by a nonsense mutation, clinical development of ataluren may offer a definitive therapy by overcoming the basic cause for DBMD and other disabling and life-threatening genetic disorders.

2.2.2. Chemical Description

Ataluren is a new chemical entity with a chemical formula of $C_{15}H_9FN_2O_3$ and a molecular weight of 284.2 Daltons. Ataluren is a Biopharmaceutical Classification System Case 2 compound, possessing low aqueous solubility (<31 μg/mL) but high permeability across gastrointestinal epithelium, consistent with its high oral bioavailability. The drug has been manufactured and formulated under current Good Manufacturing Practices (cGMP) and is provided as a vanilla-flavored, white to off-white powder for suspension.

2.2.3. Clinical Studies

2.2.3.1. Phase 1 Studies

Two Phase 1 safety and pharmacokinetic (PK) studies of ataluren were conducted in 62 healthy adult male and female volunteers ranging in age from 18 to 30 years [Hirawat 2007]. Single doses of ataluren administered orally at dose levels ranging from 3 to 100 mg/kg were palatable and generally well tolerated. Mild adverse events of mild headache, dizziness, nausea, vomiting, diarrhea, and abdominal pain at dose levels of 150 and 200 mg/kg appeared to be coincident with achieving the maximum concentration (C_{max}). Elevations of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed in 1 subject receiving a single dose of 200 mg/kg. With repeated doses through 50 mg/kg/dose 2 times per day (BID), reversible, low-grade (<2 times the upper limit of normal [ULN]) transaminase elevations were observed in some patients. No bilirubin increases were observed. In addition, no notable BUN, creatinine, or urinalysis abnormalities were observed. PK analyses indicated rapid oral absorption, generally dose-proportional PK, an effective plasma half-life ($t_{1/2}$) in the range of 2 to 6 hours, and no relevant drug accumulation with repeated dosing. The data also demonstrated that ataluren can be given with or without food and that trough plasma concentrations exceeding the ~2-μg/mL to ~10-μg/mL target values active in the *mdx* mouse model of DMD might best be achieved with TID dosing after meals.

The mass balance, absorption, excretion, and metabolism profiles of ataluren after a single dose of unlabeled and [^{14}C]-labeled ataluren oral suspension were determined in 7 healthy male subjects in an additional Phase 1 study. Each subject received 1375 mg [18.5 mg/kg] of unlabeled ataluren and 96.6 μCi of [^{14}C]ataluren (~0.5 mg). Whole blood and plasma samples, and urine and feces were collected up to 264 hours after dosing. The results showed that the majority of circulating total radioactivity in plasma was associated with unchanged ataluren. Ataluren was not highly associated with red blood cells. The only metabolite detected in plasma after oral administration of ataluren was ataluren acyl glucuronide, which represented ~8%, on average, of the exposure (area under the concentration-time curve [AUC]) relative to ataluren. The total mean recovery of the administered radioactive dose was complete (~102%), with 55% recovery in urine and 47% in feces. Based on the mean urinary recovery of radioactivity, the absolute bioavailability of ataluren is estimated to be ≥55%. The majority of the radioactivity recovered in urine represented ataluren acyl glucuronide (~49% of the administered dose); unchanged ataluren in urine represented <1% of the administered dose. The primary drug-related moiety in feces was a metabolite (M2) formed as a result of a reductive cleavage of the oxadiazole ring of ataluren, followed by hydrolysis; unchanged ataluren in feces represented ~0.4% of the radioactive dose. M2 is presumably the product of metabolism of ataluren by fecal microorganisms. The elimination of ataluren is likely dependent on hepatic glucuronidation of ataluren followed by renal excretion of the resulting glucuronide metabolite.

2.2.3.2. Phase 2 Clinical Studies in Duchenne/Becker Muscular Dystrophy

2.2.3.2.1. Phase 2a Study

The initial evaluation of ataluren in nmDMD was a Phase 2a, open-label, sequential dose-ranging, activity, safety, and PK study PTC124-GD-004-DMD (Study 004) conducted at 3 centers in the United States. Participants in the study were 38 boys with nmDMD ranging in age from 5 to 17 years. Cohorts received sequential, escalating dose levels of ataluren in a single 56-day cycle, comprising 28 days of drug administration and 28 days of follow-up. The first cohort of 6 patients received drug TID at morning, midday, and evening doses of 4-, 4-, and 8-mg/kg. A second cohort of 20 patients received drug TID at doses of 10-, 10-, and 20-mg/kg. Thereafter, a further cohort of 12 patients received drug TID at doses of 20-, 20-, and 40-mg/kg.

The primary outcome measure was muscle dystrophin expression. As assessed by quantitative immunohistochemistry, ataluren induced a mean [SD] 11.1 [24.3] % increase in muscle dystrophin expression over the 28 days of treatment, with 23/38 (61%) of patients showing a response (positive change). Serum CK reductions were observed in 92% (35/38) of patients during ataluren administration. With cessation of ataluren treatment, mean serum CK concentrations reverted toward baseline. Changes in myometry scores and timed function tests were small and not statistically significant with 28 days of ataluren treatment. However, parents and teachers of several boys noted evidence of greater activity, increased endurance, and less fatigue during ataluren administration; these effects waned after the cessation of ataluren. The timing of the onset and reversion of CK and symptomatic effects provided additional support for ataluren pharmacological activity.

Mild treatment-emergent adverse events of transient headache and gastrointestinal complaints were observed at all 3 dose levels and appeared consistent with background symptoms

commonly observed in clinical trials. No clearly dose-dependent increases in frequency or severity were evident. Episodes of nausea and vomiting were primarily related to anesthesia administered at the time of muscle biopsies. No drug-related serious adverse events (SAEs) were reported. There were no safety concerns identified in patients' physical examinations, vital sign measurements, or electrocardiograms (ECGs), and none of the patients had clinically concerning laboratory abnormalities. Consistent with this safety profile, compliance was excellent; on average, boys received >99% of the planned ataluren doses and no patient discontinued ataluren due to an adverse event.

Mean values for C_{max} and area under the concentration-time curve through 24 hours (AUC_{0-24}) for ataluren plasma concentrations on Days 1 and 28 showed no drug accumulation and no change in ataluren exposures in boys receiving or not receiving corticosteroids as treatment for DMD. At the 10-, 10-, 20-mg/kg and 20-, 20-, 40-mg/kg dose levels, mean trough plasma concentrations exceeding target values active in the *mdx* mouse model of DMD were achieved.

2.2.3.2.2. Phase 2b Study

Based on the Phase 2a results, a Phase 2b, randomized, double-blind, placebo-controlled study PTC124-GD-007-DMD (Study 007) of ataluren in nmDBMD was conducted at 37 centers in 11 countries. Participants in the study were 174 boys with nmDBMD ranging in age from 5 to 20 years. Patients were randomized 1:1:1 so that 57 received placebo, 57 received the low-dose level of ataluren (10-, 10-, 20-mg/kg), and 60 received the high-dose level of ataluren (20-, 20-, 40-mg/kg) for a duration of 48 weeks.

At the end of Study 007 (Week 48), the mean change from baseline in 6MWD was ~30 meters greater in patients treated with low-dose ataluren than in patients treated with placebo, consistent with the 30-meter change specified in the study protocol as being clinically relevant. The improvement among patients treated with low-dose ataluren compared to patients treated with placebo was generally consistent regardless of age, use of corticosteroids, or walking ability at the beginning of the study. There was no difference between high-dose ataluren and placebo in change in 6MWD over 48 weeks.

Positive trends in muscle function, as measured by timed function tests, were observed at Week 48 in patients treated with low-dose ataluren when compared to patients treated with placebo. In addition, over the 48-week study, patients treated with low-dose ataluren had a reduction in the frequency of accidental falls compared to patients treated with placebo. Mean changes in other secondary outcome measures were generally small; the meaningfulness of these results is unclear given the lack of prior experience in DBMD and/or other known limitations associated with these evaluations.

Measurement of muscle dystrophin expression was included in this study as an exploratory secondary endpoint. However, the data are compromised by poor sample quality and inadequacies in currently available methods. Consequently, no conclusions can be drawn from the analyses of muscle dystrophin expression.

Ataluren was well tolerated at both the low- and high-dose levels. The majority of treatment-emergent adverse events were mild (Grade 1) to moderate (Grade 2). The most frequent adverse events were vomiting (46.6%), headache (29.3%), and diarrhea (24.1%). The

only adverse event that showed potential dose-relatedness was abdominal pain, occurring in 7% of patients receiving placebo, 12.3% of patients receiving low-dose ataluren, and 16.7% of patients receiving high–dose ataluren. Investigators' attributions of drug-relatedness were similar across the placebo- and ataluren-treated groups. None of the patients prematurely discontinued treatment because of adverse events. No ataluren-related SAEs were reported. There were no safety concerns identified in patients' physical examinations, vital sign measurements, or ECGs, and none of the patients had clinically concerning laboratory abnormalities.

Median study drug compliance was >97% in each treatment arm. Ataluren plasma concentrations were obtained prior to the morning dose (trough) and 2 hours after the morning dose at each visit. These plasma concentrations were dose-proportional and well-maintained over time.

2.2.3.2.3. Other Completed Studies

Subjects completing Study 007 were eligible to enroll in an open-label extension trial PTC124-GD-007e-DMD (Study 007e). Of the 174 patients participating in the blinded Phase 2b study, 173 patients enrolled in this study. These patients received the 20-, 20-, 40-mg/kg dose level of ataluren for a median [range] of 22 [11 to 57] weeks before the study was discontinued on 03 March 2010. The safety findings from this study confirmed that ataluren was well tolerated; there were no concerning safety signals evident in the patients participating in this trial.

Subjects completing Study 004 were eligible to enroll in an open-label extension trial. Of the 38 patients participating in the prior Phase 2a study, 36 patients enrolled in an open-label extension study PTC124-GD-004e-DMD (Study 004e). These patients received the 20-, 20-, 40-mg/kg dose level of ataluren for a median [range] of 70 [53 to 81] weeks before the study was discontinued on 03 March 2010. The safety results from this trial also documented good tolerability for ataluren; there were no worrisome ataluren-related adverse events reported for the patients participating in this trial.

In addition, an open-label Phase 2a study PTC124-GD-008-DMD (Study 008) was conducted in nonambulatory patients with nmDBMD; this study was discontinued on 03 March 2010. At the time of discontinuation, 6 patients had received the 20, 20, 40 mg/kg dose level of ataluren for periods ranging from1 week to 6 weeks. While no safety concerns were identified during this study, with the small number of patients and short duration of dosing, no definitive conclusions can be drawn from this study regarding the safety profile of ataluren 20, 20, and 40 mg/kg in nonambulatory boys with nmDBMD.

The results of the nmDBMD program were reviewed by an independent DMC on 24 February 2010. It was the DMC opinion that there were no safety concerns based on the available data.

2.2.3.2.4. Ongoing Studies

A Phase 3 open-label, study PTC124-GD-016-DMD (Study 016) to assess the safety of ataluren in patients who participated in one of the 5 previous ataluren nmDBMD studies at an investigator site in the US is ongoing. As of 01 September 2015, this study had enrolled 108 patients who

received ataluren for a median of 227 weeks (range, 4 to 249 weeks). To date in this study, ataluren has been well tolerated. Further details on the safety results are found in the IB.

A Phase 3 extension study (Study 020e) of ataluren (PTC124) in patients with nonsense mutation dystrophinopathy, that is being conducted at 54 sites in 18 countries. As of 31 July, 2015, this study had enrolled 199 patients who received ataluren for a median of 24 weeks (range, 0.2 to 71 weeks). To date in this study, ataluren has been well tolerated. Further details on the safety results are found in the IB.

2.2.3.3. Safety Experience in Other Indications

Ataluren is also being evaluated in children and adults with other nonsense mutation genetic disorders Safety information from other indications are provided in the Ataluren Investigator Brochure.

3. STUDY OBJECTIVE AND ENDPOINTS

3.1. Primary Objective

The primary objective of this study is to assess the long-term safety and tolerability of 10, 10, 20 mg/kg ataluren in patients with nmDBMD who had prior exposure to ataluren in a PTC-sponsored clinical trial.

3.2. Secondary Objectives

Secondary objectives include the following:

- Ambulatory patients (able to run/walk 10 meters in ≤30 seconds) - To determine the effect of ataluren on ambulation and other aspects of physical function
- Nonambulatory patients (unable to run/walk 10 meters in ≤30 seconds) - To assess the effect of ataluren on activities of daily living, upper limb function, and pulmonary function
- All patients – To assess patient and/or parent/caregiver reports of changes in disease status:
    - Retrospectively during and after participation in previous studies (Studies 007 and 007e)
    - Prospectively during the current study

3.3. Clinical Endpoints

Primary

- Safety profile characterized by type, frequency, severity, timing, and relationship to ataluren of any adverse events or laboratory abnormalities

Secondary

- In ambulatory patients, change from baseline in 6MWD as measured by the 6-minute walk test (6MWT)

- In ambulatory patients, change from baseline in physical function as measured by the North Star Ambulatory Assessment (NSAA)
- In ambulatory patients, change from baseline in timed function tests (time to stand from supine and time to run/walk 10 meters)
- In nonambulatory patients, change from baseline in pulmonary function as measured by spirometry
- In nonambulatory patients, change from baseline in patient and parent/caregiver-reported activities of daily living, as measured by the Egen Klassifikation (EK) scale
- In all patients, changes in patient and/or parent/caregiver reports of disease status as measured by a standardized survey administered by site personnel

4. SUBJECT SELECTION CRITERIA

4.1. Overview

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

4.2. Inclusion Criteria

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

1. Evidence of signed and dated informed consent/assent document(s) indicating that the subject (and/or his parent/legal guardian) has been informed of all pertinent aspects of the trial. ***Note: If the study candidate is considered a child under local regulation, a parent or legal guardian must provide written consent prior to initiation of study screening procedures and the study candidate may be required to provide written assent. The rules of the responsible Institutional Review Board/Independent Ethics Committee (IRB/IEC) regarding whether one or both parents must provide consent and the appropriate ages for obtaining consent and assent from the subject should be followed.***
2. History of exposure to ataluren in a prior PTC study in nmDBMD . ***Note: Patients are considered eligible only if they received ataluren during their participation in one or more prior PTC-sponsored studies of ataluren in nmDBMD. Note: Subjects who have participated in a prior or ongoing PTC study with ataluren in nmDBMD at a trial site in the US or Canada, but reside outside of the US and Canada, may be eligible for this study (with the approval of the PTC Therapeutics Medical Monitor).***
3. Male sex.

4. Confirmed screening laboratory values within the central laboratory ranges specified in Table 1 below. ***Note: Confirmation should be performed for out-of-range values to determine if the abnormality is real or artifactual. Values used to establish eligibility should be the last measurements obtained within the screening period.***

Table 1. Required Screening Laboratory Values

Organ System	Parameter	Required Value
Hepatic	Serum total bilirubin	≤1.5 x ULN
	Serum GGT	≤1.5 x ULN
	Hepatitis B core antibody and Hepatitis C antibody	Negative
Renal	Serum creatinine	≤ULN
	Serum BUN	≤ULN
	Urine blood (by dipstick)	≤1+
Serum Electrolytes	Serum sodium (Na^+)	<Grade 2
	Serum potassium (K^+)	<Grade 2
	Serum bicarbonate (HCO_3^-)	<Grade 2
	Serum magnesium (Mg^{2+})	<Grade 2
	Serum calcium (Ca^{2+})	<Grade 2
	Serum phosphorus	<Grade 2

Abbreviations: BUN = blood urea nitrogen, GGT = gamma glutamyl transferase, ULN = upper limit of normal

5. In patients who are sexually active, willingness to abstain from sexual intercourse or employ a barrier or medical method of contraception during ataluren administration and the 6-week follow-up period.
6. Willingness and ability to comply with scheduled visits, drug administration plan, study procedures, laboratory tests, and study restrictions. ***Note: Psychological, social, familial, or geographical factors that might preclude adequate study participation should be considered***.

4.3. Exclusion Criteria

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

1. Exposure to another investigational drug within 1 month prior to start of study treatment.
2. Eligibility for another ataluren clinical trial that is actively enrolling study participants.
3. Known hypersensitivity to any of the ingredients or excipients of ataluren (Litesse® Ultra™ [refined polydextrose], polyethylene glycol 3350, Lutrol® micro F127 [poloxamer 407], mannitol 25C, crospovidone XL10, hydroxyethyl cellulose, vanilla, Cab-O-Sil® M5P [colloidal silica], magnesium stearate).
4. Ongoing use of the following medications:
    a. Coumarin-based anticoagulants (eg, warfarin), phenytoin, tolbutamide, or paclitaxel.
    b. Systemic aminoglycoside therapy
5. Ongoing uncontrolled medical/surgical condition, ECG findings, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the patient or make it unlikely that follow-up would be completed.

5. ENROLLMENT PROCEDURES

5.1. Source and Number of Subjects

Up to ~96 patients with nmDBMD each received ataluren treatment in a prior PTC-sponsored clinical trial; these patients are all potential candidates for this study.

It is anticipated that patients will be enrolled from investigator sites in countries including Belgium, France, Germany, Italy, Spain, United Kingdom, Sweden, Israel, and Australia.

5.2. Screening and Study Drug Allocation

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

The subject number used in the prior ataluren DBMD study shall be retained for use in this study. This subject number must be used for subject identification on all study-related documents (case report forms [CRFs], laboratory samples, etc).

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

The relevant site staff will need to supply the Interactive Web Response (IWR) system with the information required by the system (eg, site number, subject number, subject weight in kilograms) to permit study drug allocation.

6. STUDY DRUG ADMINISTRATION

6.1. Investigational Product

6.1.1. Ataluren (PTC124)

Ataluren will be provided as a vanilla-flavored, white to off-white powder for oral suspension. The drug has been manufactured and formulated under cGMP conditions. The formulation includes matrix and suspending agents, surfactants, and various minor excipients that aid in the manufacturing process. The powder for oral suspension is packaged in aluminum-foil, child-resistant sachets and is supplied in dose strengths containing 125, 250, or 1000 mg of the active drug substance. For administration, the powder in the sachet may be mixed with water, milk (skim, 1% fat, 2% fat, whole milk, or lactose-free milk), fruit juice (except apple juice), fruit punch, or in semi-solid food (yogurt, pudding, or applesauce).

6.1.2. Drug Source

Ataluren will be supplied free of charge to the investigator site by PTC Therapeutics for appropriate distribution to the patients/caregivers. It is intended that ataluren will be provided in sufficient supply for a 12-week study period. However, in the event of pending commercial availability of ataluren, drug may be supplied for a treatment period of less than 12 weeks. Resupply may be obtained via the IWR system.

6.1.3. Study Drug Packaging and Labeling

Sachets will be color-coded to indicate dosage strength (125 mg – yellow, 250 mg – pink, 1000 mg – blue). The labeling will bear the text "CAUTION – New Drug – limited by Federal (USA) law to investigational use."

6.1.4. Study Drug Dispensing

Dosing of ataluren will be based on milligrams of drug per kilogram of subject body weight at Screening/Baseline (Visit 1) and will be adjusted to allow for dosing with the available sachet dose strengths. The sachet dosage strengths and number of sachets to be taken per dose will be provided by the EDC system.

The clinic staff (eg, pharmacist or other qualified person) will be responsible for dispensing study drug according to the EDC system directions.

Because of potential changes in subject body weight over time, weight-based dose adjustment will occur every 6 months. Depending upon the magnitude of change in subject body weight since baseline, the number and type of sachets to be used by the subject may remain the same or may be adjusted.

6.1.5. Return of Study Drug

Subjects should return all unused sachets of ataluren to the investigator site at the end of each visit for inventory. The case report forms will serve as the source document for drug supply to the patients and will document the return of any unused drug for compliance assessments.

6.1.6. Storage and Stability

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

6.1.7. Study Drug Accountability

Study personnel must ensure that all ataluren 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 other 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 ataluren shipped by PTC Therapeutics or its designee, including, but not limited to, the date received, lot number, amount received, and the disposition of all ataluren. Current reconciliation and dispensing records must also be maintained that include the date and amount of drug dispensed, relevant batch and sachet numbers, and subject's assigned study number.

Depending upon the decision of PTC Therapeutics, unused clinical supplies must be destroyed or must be returned to PTC Therapeutics or its designee after the study is completed.

Accountability must be verified by the site monitor prior to return or destruction. Records documenting the date of study drug destruction or shipping, relevant sachet numbers, and amount destroyed or shipped should be kept in the investigator site study file.

6.1.8. Overdose Precautions

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

The PTC Therapeutics medical monitor should be contacted if an overdose occurs. Under applicable regulations, overdosing may be considered an SAE and should be reported accordingly (see Sections 8.1.1 and 8.1.2).

6.1.9. Inadvertent Exposure and Spill Precautions

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

6.2. Study Drug Treatment

6.2.1. Duration of Therapy

Treatment with ataluren in the context of this protocol is anticipated to occur for 240 weeks. The actual duration of ataluren treatment under this protocol will be subject to the following conditions:

- The patient has the right to withdraw consent and discontinue ataluren at any time.
- If the patient's condition substantially worsens after initiating ataluren treatment, the patient will be carefully evaluated by the investigator in consultation with the PTC Therapeutics medical monitor. The patient will be withdrawn from treatment if continuing would place them at risk.
- Upon consultation with the PTC Therapeutics medical monitor, the investigator may withdraw the patient from ataluren treatment, if, in the investigator's clinical judgment, it is not in the patient's best interest to continue.
- The patient will be withdrawn from treatment if he is unable to tolerate ataluren.
- The patient may be withdrawn from this study if he is eligible to participate in another ataluren - nmDBMD clinical study or program.
- This study may be discontinued by the relevant regulatory authority and/or PTC Therapeutics at any time.
- This study may be stopped upon ataluren marketing authorization within the relevant country.

6.2.2. Schedule of Administration

As noted in Table 2 below, 3 doses should be taken per day – the first dose in the morning (10 mg/kg), the second dose during the middle of the day (mid-day – 10 mg/kg), and the third dose in the evening (20 mg/kg). 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). If possible, intervals for dosing should be ~6 hours (±1 hour) between morning and midday doses, ~6 hours (±1 hour) between midday and evening doses, and ~12 hours (±1 hour) between evening doses and the morning dose on the next day.

Table 2. Suggested Daily Dosing Schedule

Dose Designation	Preceding Meal	Example Dosing Times[a]
Morning	Breakfast	~7:00 AM – 0700 hours (±1 hour)
		↑ ~6 hours ↓
Midday	Lunch	~1:00 PM – 1300 hours (±1 hour)
		↑ ~6 hours ↓
Evening	Dinner	~7:00 PM – 1900 hours (±1 hour)
		↑ ~12 hours ↓
Next Day Morning	Breakfast	7:00 AM – 0700 hours (±1 hour)

a Dosing times are examples and may be varied to suit each subject's schedule. However, the time between morning and midday doses and between midday and evening doses should be maintained at ~6-hour intervals, while the time between the evening and next morning dose should be maintained at an ~12-hour interval.

6.2.3. Instructions for Delays in Dosing

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

6.2.4. Study Drug Preparation and Storage

Study drug sachets should be stored and monitored at room temperature away from the reach of children until time of reconstitution. The suspension (powder in the sachet) may be mixed with water, milk (skim, 1% fat, 2% fat, whole milk, or lactose free milk), fruit juice (except apple juice), 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. The full contents of each packet should be mixed with at least 30 mL (1 ounce) of

liquid, or 3 tablespoons of semi-solid food. The prepared dose should be mixed well before administration. The amount of the liquid or semi-solid food can be increased based on patient preference.

6.3. Safety Monitoring and Study Drug Dose Interruption/Modification

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

Subjects must be monitored closely for adverse events or laboratory abnormalities during the course of the study.

For adverse events or laboratory abnormalities, the investigator will use judgment in determining whether the event or abnormality is clinically significant, whether diagnostic evaluation is warranted, and whether potential interruption of ataluren treatment is appropriate. In general, life-threatening (Grade 4) or severe (Grade 3) adverse events or laboratory abnormalities should be considered clinically significant, although recurrent or persistent moderate events (Grade 2) may also be considered clinically significant in certain circumstances. Reference should be made to the Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 (see *http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf*) for grading the severity of adverse events and laboratory abnormalities.

If the patient experiences a dose-limiting adverse event related to ataluren, then drug administration can be interrupted, as necessary, until the adverse event resolves or stabilizes to an acceptable degree. If further evaluation reveals that the adverse event is not related to ataluren, treatment will be continued at the original dose level. Alternatively, until full resolution of the ataluren related adverse event, ataluren may be continued at a reduced dose level of 5 mg/kg in the morning, 5 mg/kg at midday, and 10 mg/kg in the evening. If the patient continues to experience dose-limiting adverse events at this lower dose level, ataluren will be discontinued. If the ataluren adverse event is fully resolved, the ataluren dose may be increased back to 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening. The PTC Therapeutics medical monitor will be notified of any SAE or any adverse event that leads to dose reduction, interruption, or treatment discontinuation. In addition, the MAPI Safety Department will be notified any SAEs.

Table 3 below provides information on actions to be taken in the event that abnormalities are noted in specified laboratory parameters. Thresholds are provided for interrupting ataluren immediately, for interrupting ataluren after confirmation of a value beyond the threshold, or for continuing ataluren while evaluating for potential drug-related toxicity. For adverse events or laboratory abnormalities not listed in Table 3 below, the investigator should use his/her judgment in determining whether the event or abnormality is clinically significant, whether diagnostic evaluation is warranted, and whether potential interruption of ataluren therapy is appropriate.

Table 3. Safety Monitoring Parameters and Actions To Be Taken

Organ System and Laboratory Parameter	Stop Study Drug Immediately, Confirm Abnormal Value, and Then Start Work-Up	Stop Study Drug After Confirming[a] Abnormal Value, and Then Start Work-Up	Continue Study Drug, Confirm Abnormal Value, and then Start Work-Up[a]
Hepatic			
Serum total bilirubin	≥Grade 3 (≥3.0 x ULN)	Grade 2 (1.5 – 3.0 x ULN)	---
Serum GGT	≥Grade 3 (≥5.0 x ULN)	Grade 2 (>2.5 – 5.0 x ULN)	---
Serum ALT			↑ of > 150 U/L with stable or ↓ CK
Adrenal			
Plasma ACTH	---	>ULN (and plasma cortisol <LLN)	>ULN (and cortisol WNL)
Renal			
Serum cystatin C	>2.00 mg/L	>1.33 – 2.00 mg/L	---
Serum creatinine	≥ Grade 2 (≥1.5 x ULN for age)	Grade 1 (>ULN – 1.5 x ULN for age)	---
Serum BUN	≥3.0 x ULN	≥1.5 – 3.0 x ULN	---
Urine protein: urine creatinine (spot)	---	>0.40 mg:mg	---
Urine protein: urine osmolality (spot)	---	>0.30 mg/L:mOsm/kg	---
Urine blood (by dipstick)	4+ (Large)	3+ (Moderate)	2+ (Small)
Serum electrolytes	**Grade 3-4**	**Grade 2**	**Grade 1**
Serum Na+, high	>155 mmol/L	>150 – 155 mmol/L	---
Serum Na+, low	<130 mmol/L	---	---
Serum K+, high	>6.0 mmol/L	>5.5 – 6.0 mmol/L	---
Serum K+, low	<3.0 mmol/L	---	---
Serum Mg^{2+}, high	>1.23 mmol/L	---	---
Serum Mg^{2+}, low	<0.4 mmol/L	<0.5 – 0.4 mmol/L	---
Total serum Ca^{2+}, high	>3.1 mmol/L	>2.9 – 3.1 mmol/L	---
Total serum Ca^{2+}, low	<1.75 mmol/L	<2.0 – 1.75 mmol/L	---
Serum phosphorous	<0.6 mmol/L	<0.8 – 0.6 mmol/L	---
Serum HCO_3-	<11 mmol/L	<16 – 11 mmol/L	---

a Laboratory abnormalities may be confirmed immediately or at the next scheduled clinic visit based on investigator judgment.
Abbreviations: ACTH = adrenocorticotropic hormone, ALT = alanine aminotransferase, BUN = blood urea nitrogen, Ca^{2+} = calcium, CK = creatine kinase, GGT = gamma glutamyl transferase, HCO_{3-} = bicarbonate, K+ = potassium, Mg^{2+} = magnesium, Na+ = sodium, ULN = upper limit of normal, WNL = within normal limits

It should be noted that blood samples for renin and aldosterone determinations will also be obtained at screening, and, as necessary, for patients with treatment-emergent evidence of adrenal dysfunction. Changes in these laboratory parameters alone will not be exclusionary or reason for study drug discontinuation because renin and aldosterone values are markedly affected by age and normal reference ranges are too narrow to reliably use as guidance for treatment discontinuation in this study population. In addition, renin and aldosterone values may be affected by angiotensin-converting enzyme (ACE) inhibitors, and angiotensin-receptor blockers (ARBs). Changes in renin and aldosterone will be viewed in context with other laboratory findings.

6.3.2. Evaluation of Adverse Events or Laboratory Abnormalities

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

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

- **Hepatic:** The medical history, hepatitis screening results, all clinical blood values (particularly serum bilirubin, GGT, AST, and ALT values), and all concomitant medications should be reviewed. Depending upon changes observed, the recommended diagnostic workup may include more frequent monitoring or further evaluations for viral hepatitis and immune disorders; tests for cholelithiasis; or abdominal ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), or other imaging methods.
- **Adrenal:** The medical and family history, all clinical blood values (particularly previous adrenocorticotropic hormone (ACTH), cortisol, renin, and aldosterone values and serum potassium and sodium concentrations), and all concomitant medications (particularly corticosteroids, ACE inhibitors, and ARBs) should be reviewed. Depending upon the changes observed, recommended diagnostic workup may include further evaluations of plasma ACTH, cortisol, and aldosterone levels; serum electrolytes; ACTH stimulation testing; reassessment of plasma renin and aldosterone after interruption of ACE inhibitor or ARB treatment; CT, MRI, or other imaging methods; and/or adrenal biopsy.
- **Renal:** The medical history, baseline ultrasound data, all clinical blood and urine renal values, serum electrolytes, medications, and potential pre- or post renal conditions should be reviewed. Depending upon the changes observed, recommended diagnostic workup may include further evaluations of blood or urine; tests of glomerular filtration rate (GFR), concentrating ability, or other renal functions; CT, MRI, or other imaging methods; and/or renal biopsy.

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

In deciding whether to reinstitute therapy after a dose interruption for any clinically significant safety concern, the investigator should consider factors such as the type and severity of the adverse event or laboratory abnormality, the potential causal relationship of ataluren therapy, the subject's status in terms of DBMD or other health conditions, and the ability to monitor for recurrence of the event.

For hepatic, adrenal, or renal events (refer to Table 3), the level of investigator certainty that an abnormality leading to drug interruption is drug-related should be considered strongly in deciding

whether or not to reinstitute ataluren treatment. If the investigator considers the hepatic, adrenal, or renal event to that led to ataluren interruption to be probably related to ataluren, restarting the ataluren is not advised. In this case, the subject should be discontinued from the study (see Sections 6.3.4 and 9). If the investigator considers the hepatic, adrenal, or renal event that prompted ataluren interruption to be possibly related or unlikely related to ataluren, the investigator should use best judgment in determining whether to restart ataluren. If the hepatic, adrenal, or renal event is considered unrelated to ataluren, reinstitution of ataluren is recommended.

If the investigator believes it is appropriate to do so and the PTC Therapeutics medical monitor has been consulted, ataluren may be re-initiated. If the event was determined to be unrelated to ataluren, the study drug may be resumed at full dose. Otherwise, if the drug is resumed, it should be reinitiated at half of the original dose (5-, 5-, 10-mg/kg). The appropriate clinic staff should instruct the subject/caregiver about the revised number of ataluren sachets to be used per dose according to the new schedule.

In general, after dose reduction, the dose should not be returned to the original dose level. However, if further evaluation reveals that the adverse event that led to dose reduction was not related to the ataluren, the dose may be returned to the original dose level. The appropriate clinic staff should instruct the subject/caregiver about the revised number of ataluren sachets to be used per dose according to the schedule provided by the IWR system.

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

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

If after appropriate consideration of ataluren interruption/modification and consultation with the PTC Therapeutics medical monitor, it is not appropriate for a subject to continue with study treatment, then ataluren should be permanently discontinued. After permanent discontinuation of ataluren for a safety concern, and if the initial event was reported as a SAE, then a follow-up SAE report form should be completed. In the case of a treatment discontinuation due to an event that is not an SAE, the PTC Therapeutics medical monitor should be notified (see Section 9). In addition, details regarding the reasons for discontinuation and the adverse events leading to the discontinuation should be recorded in the source documents and in the appropriate CRF. The End of Treatment Visit CRF should be completed and appropriate follow-up (at ~6 weeks as per protocol or until recovery from or stabilization of the adverse event, whichever comes last) should be instituted.

6.4. Concomitant and Supportive Therapy

Other than ataluren, any treatments (including prescription and non-prescription drugs, health foods, herbal remedies, self-prescribed drugs, street drug, tobacco products, or alcohol) that are

taken by a subject during the screening period, during ataluren administration, and for ≥6 weeks after discontinuation of ataluren are considered concomitant medications. Information regarding any concomitant medications will be recorded in the source documents and in the concomitant medication CRF.

6.4.1. Aminoglycosides or Other Potentially Nephrotoxic Agents

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

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

6.4.2. Hydration

Because of the potential risk of renal dysfunction during periods of dehydration in patients receiving ataluren, it is important to encourage study patients to maintain adequate hydration throughout the study. Patients should be adequately hydrated prior to receiving 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 patients who are experiencing nausea, vomiting, diarrhea, or fever, or who have laboratory evidence of dehydration.

6.4.3. Cardiac Drugs for CHF Prophylaxis/Treatment

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

In patients who are receiving an ACE inhibitor or ARB, monitoring of plasma renin and aldosterone values in patients with treatment-emergent evidence of adrenal dysfunction should be conducted with the understanding that high renin values or low aldosterone values may not

represent definitive evidence of adrenal toxicity. In patients on these drugs who develop other evidence for primary adrenal insufficiency (eg, elevated plasma ACTH concentration), reassessment of plasma renin and aldosterone after interruption of ACE inhibitor or ARB treatment may be warranted.

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

6.4.4. Drugs Metabolized by Cytochrome P450 Enzymes

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 enzymes (CYPs) are unlikely. In particular, ataluren is not an inhibitor of CYP1A2, CYP2B6, CYP2C19, CYP2D6, and CYP3A4/5, and does not have induction potential on the major CYP enzymes.

In vitro, ataluren is a weak inhibitor of CYP2C8 and CYP2C9, but in vivo drug-drug interactions mediated by these enzymes are not expected according to the criteria described in the EMA guideline on the investigation of drug interactions [EMA 2012]. As an added measure of safety, investigators should pay specific attention to use of drugs that are known substrates of these enzymes, particularly when such drugs may have a low therapeutic index. The study manual includes a list of clinically available drugs that are metabolized by CYP2C8 or CYP2C9 so that investigators may use appropriate judgment in deciding how to monitor patients who may be receiving such substrates.

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 and patients who require the use of these drugs will not be enrolled to the study. Coumarin anticoagulants are cleared by CYP2C9 and increases in plasma concentrations of coumarin anticoagulants may result in serious clinical consequences. For patients 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 patients 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; thus, investigators should be aware that administration of ataluren may hypothetically change losartan effectiveness. However, concomitant use of losartan and inhibitors of CYP2C9 has not been examined.

6.4.5. Other Potential Drug Interactions

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, phenobarbital, rifampin), or inhibitors of BCRP (eg, cyclosporine, eltrombopag, gefitinib), as these drugs may affect ataluren plasma concentrations.

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 concentrations of these drugs.

Based on in vitro studies, ataluren is not expected to be an inhibitor or a substrate of p-gp mediated transport.

Pharmacokinetic data indicate that no ataluren dose adjustment is required when ataluren is co-administered with systemic corticosteroids (deflazacort, prednisone, or prednisolone), and no corticosteroid dose adjustments are required when they are co-administered with ataluren. Co-administration of systemic corticosteroids with ataluren may cause more frequent instances of hypertension than does systemic corticosteroid use alone (without ataluren). However, the blood pressure data available to date are not unequivocal about any contributory role of ataluren in development of hypertension in patients who are taking corticosteriods.

6.4.6. Other Concomitant Medications

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

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

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

6.5. Physical and Respiratory Therapy

There are neither restrictions nor prescriptions for physical or respiratory therapy during the study. Investigator sites should use local best practices in providing physical therapy support for patients participating in the study. Respiratory care guidelines as suggested by the American Thoracic Society should be followed [ATS 2004].

6.6. Dietary Restrictions

There are no specific dietary restrictions in the study.

7. SCHEDULE OF EVENTS AND STUDY PARAMETERS

7.1. Schedule of Events

The proposed types and timing of data to be recorded are described in Table 4 below. Please see Section 7.2 for cross-referenced explanations of the study procedures described in the tables.

Table 4. Schedule of Events

Period	Screening[a]	Baseline [a]	Ataluren Treatment					Post-Treatment
Study Week (±7 days)	-4 to -1	Week 1	Every 60 Weeks	Every 12 Weeks	Every 24 Weeks	Every 48 Weeks	End of Tx Week 240	6 Week Post D/C
Informed Consent {7.2.2}	X							
Clinical/medication history {7.2.3}	X							
Hepatitis screen {7.2.4}	X							
Vital signs {7.2.5}	X	X		X			X	X
Brooke UE Functional Rating Scale {7.2.6}	X							
Height/Ulna length/Arm Span {7.2.7}	X				X		X	
Physical examination {7.2.8}	X					X	X	
Weight {7.2.9}	X	X		X			X	X
Hematology {7.2.10}	X	X		X			X	X
Biochemistry {7.2.11}	X	X		X			X	X
ACTH and cortisol {7.2.12}	X	X		X			X	X
Renin and aldosterone {7.2.12}	X	As Indicated						
Urinalysis {7.2.13}	X	X		X			X	X
12-lead ECG {7.2.14}	X	As Indicated						
Echocardiogram {7.2.15}	X		X			X		X[b]
6-minute walk test {7.2.16}	X				X		X	
Timed Function Tests {7.2.17}	X					X	X	
North Star Ambulatory Assessment {7.2.18}	X					X	X	
Egen Klassifikation Scale {7.2.19}	X					X	X	
Spirometry {7.2.20}	X				X		X	
Disease status survey {7.2.21}	X	X		X			X	
Drug administration {7.2.22}		X		X				
Drug compliance {7.2.23}				X			X	
Adverse events {7.2.24}		X		X			X	X
Concomitant medications {7.2.25}	X	X		X			X	X

a Ataluren may be initiated as soon as the investigator confirms patient eligibility. Baseline procedures (excluding drug administration) do not need to be performed if Screening procedures have been performed within 7 days of anticipated initiation of ataluren treatment.

b Only applies to patients who discontinue the study after 240 weeks of treatment.

Abbreviations: ACTH = adrenocorticotropic hormone, D/C = discontinuation, ECG = electrocardiogram, Tx = treatment, UE = upper

extremity

7.2. Explanation of Study Procedures

7.2.1. Pretreatment, Treatment, and Follow-Up Periods

7.2.1.1. Screening/Baseline Period

No study-related procedures should be performed prior to the signature of the informed consent/assent document(s). Thereafter, study candidates should undergo the initial set of screening procedures as noted in Table 4. If a subject has successfully completed the necessary screening assessments and has been confirmed to be eligible by the investigator, the baseline visit for the subject can be conducted and ataluren treatment may be initiated. Ataluren may be initiated as soon as the investigator confirms patient eligibility. Baseline procedures do not need to be performed if screening procedures have been performed within 7 days of anticipated initiation of ataluren treatment. The subject will remain at the clinic until after study drug for the next 12 weeks has been dispensed and the subject/caregiver has been instructed regarding study drug storage, compliance, and administration.

7.2.1.2. Treatment Visits during Study

Each subject will subsequently return to the clinical research facility during Week 12 (Visit 3), Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 84 (Visit 9), Week 96 (Visit 10), Week 108 (Visit 11), Week 120 (Visit 12), Week 132 (Visit 13),Week 144 (Visit 14), Week 156 (Visit 15), Week 168 (Visit 16), Week 180 (Visit 17), Week 192 (Visit 18), Week 204 (Visit 19), Week 216 (Visit 20), Week 228 (Visit 21) and Week 240 (Visit 22) .

7.2.1.3. End of Treatment

It is planned that each subject will return to the clinical research facility at Week 240 (Visit 22) for the End-of-Treatment Visit. However, this study duration may be altered per the conditions noted in Section 6.2.1. In this case, the timing of the End-of-Treatment Visit, will be adjusted appropriately. If the patient terminates the study early because ataluren is commercially available in that country, then the patient only needs to return for the End-of-Treatment Visit.

If the subject discontinues prematurely, except patients switching to commercial ataluren (ie, before Week 240) and the last visit to the investigator site occurred >3 weeks previously, the procedures that would normally be performed at Week 240 should be performed as a Premature Discontinuation Visit before the subject leaves the study.

7.2.1.4 Post-Treatment Visits

All patients who discontinue ataluren must return for a Post-Treatment Visit at the investigator site 6 weeks (±7 days) after the last dose of ataluren for final study-related evaluations. If the End-of-Treatment Visit occurs >6 weeks after the last dose of ataluren, the Post-Treatment Visit does not need to be performed. For patients discontinuing the study to transition to commercially available ataluren, an End-of-Treatment visit should be performed for that patient. However, a 6-Week Post-Treatment Visit is not required for these patients.

7.2.2. Informed Consent

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

7.2.3. Clinical/Medication History

The investigator should review the study candidate's clinical history, including details relating to DBMD and any other medical conditions. Information regarding current medications must be recorded in the source documents and on the concomitant medication CRF.

7.2.4. Hepatitis Screen

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

7.2.5. Vital Signs

Vital signs (including systolic and diastolic blood pressure, pulse rate, and body temperature) will be monitored at Screening (Visit 1), Week 1 (Visit 2), Week 12 (Visit 3), Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 84 (Visit 9), Week 96 (Visit 10), Week 108 (Visit 11), Week 120 (Visit 12), Week 132 (Visit 13), Week 144 (Visit 14), Week 156 (Visit 15), Week 168 (Visit 16), Week 180 (Visit 17), Week 192 (Visit 18), Week 204 (Visit 19), Week 216 (Visit 20), Week 228 (Visit 21) and Week 240 (Visit 22 End-of-Treatment/Premature Discontinuation) and at the Post-Treatment Visit (6 weeks post discontinuation of ataluren). The pulse rate and blood pressure determinations will be performed with the subject in a sitting position after a 5-minute rest.

7.2.6. Brooke Upper Extremity Functional Rating Scale

Upper extremity function will be assessed in all patients who are nonambulatory at study entry using the Brooke Upper Extremity Functional Rating Scale [Brooke 1981, Lue 2006, Florence 1984]; this evaluation will be performed at Screening (Visit 1). The Study Manual provides additional information regarding the performance of this procedure.

7.2.7. Height/Ulna Length/Arm Span

Height (in cm) will be measured at Screening (Visit 1), at Week 24 (Visit 4), Week 48 (Visit 6), and Week 72 (Visit 8), Week 96 (Visit 10), Week 120 (Visit 12), Week 144, Week 168 (Visit 16), Week 192 (Visit 18), Week 216 (Visit 20) and Week 240 (Visit 22 End-of-Treatment/Premature Discontinuation) in ambulatory patients.

For nonambulatory patients, due to the difficulty in obtaining an accurate standing height measurement, ulna length and arm span will be used, as a surrogate measure for height (see Study Manual). Ulna length and arm span (in cm) will be measured at Screening (Visit 1),Week

24 (Visit 4), Week 48 (Visit 6), and Week 72 (Visit 8), Week 96 (Visit 10), Week 120 (Visit 12), Week 144, Week 168 (Visit 16), Week 192 (Visit 18), Week 216 (Visit 20) and Week 240 (Visit 22 End-of-Treatment/Premature Discontinuation).

7.2.8. Physical Examination

A full physical examination (including evaluation of cardiovascular system, chest and lungs, thyroid, abdomen, nervous system, skin and mucosae, musculoskeletal system, eyes, ears, nose, mouth, throat, spine, lymph nodes, extremities, and genitourinary) will be conducted at Screening (Visit 1), at Week 48 (Visit 6), Week 96 (Visit 10), Week 144 (Visti 14), Week 192 (Visit 18), and Week 240 (Visit 22 End-of-Treatment/Premature Discontinuation).

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

7.2.9. Weight

Weight (in kg) will be measured at Screening (Visit 1), Week 1 (Visit 2), Week 12 (Visit 3), Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 84 (Visit 9), Week 96 (Visit 10), Week 108 (Visit 11), Week 120 (Visit 12), Week 132 (Visit 13), Week 144 (Visit 14), Week 156 (Visit 15), Week 168 (Visit 16), Week 180 (Visit 17), Week 192 (Visit 18), Week 204 (Visit 19), Week 216 (Visit 20), Week 228 (Visit 21), Week 240 (Visit 22 End-of-Treatment/Premature Discontinuation) and at the Post-Treatment Visit (6 weeks post discontinuation of ataluren).

7.2.10. Hematology Laboratory Assessment

Hematology laboratory assessments will include white blood cell count with differential, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, total red cell count with morphology, and platelet count. These parameters will be measured at Screening (Visit 1), Week 1 (Visit 2), Week 12 (Visit 3), Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 84 (Visit 9), Week 96 (Visit 10), Week 108 (Visit 11), Week 120 (Visit 12), Week 132 (Visit 13), Week 144 (Visit 14),Week 156 (Visit 15), Week 168 (Visit 16), Week 180 (Visit 17), Week 192 (Visit 18), Week 204 (Visit 19), Week 216 (Visit 20), Week 228 (Visit 21), Week 240 (Visit 22 End-of-Treatment/Premature Discontinuation) and at the Post-Treatment Visit (6 weeks post discontinuation of ataluren). Hematology parameters will be analyzed by the central laboratory. The Covance Central Laboratory Manual should be consulted for collection, processing, and shipping details.

7.2.11. Serum Biochemistry Laboratory Assessment

Biochemistry laboratory assessments will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen, creatinine, magnesium, calcium, phosphorus, uric acid, glucose, total protein, albumin, globulin, albumin:globulin ratio, bilirubin (direct and indirect), AST, ALT, GGT, CK, lactate dehydrogenase (LDH), alkaline phosphatase, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and cystatin C. These parameters will be measured at Screening (Visit 1), Week 1 (Visit 2), Week 12 (Visit 3), Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 84 (Visit 9), Week 96 (Visit 10), Week 108 (Visit 11), Week 120 (Visit 12), Week 132

(Visit 13), Week 144 (Visit 14), Week 156 (Visit 15), Week 168 (Visit 16), Week 180 (Visit 17), Week 192 (Visit 18), Week 204 (Visit 19), Week 216 (Visit 20), Week 228 (Visit 21), Week 240 (Visit 22 End-of-Treatment/Premature Discontinuation) and at the Post-Treatment Visit (6 weeks post discontinuation of ataluren). Subjects should have fasted for at least 8 hours prior to blood collection. Biochemistry parameters will be analyzed by the central laboratory. The Covance Central Laboratory Manual should be consulted for collection, processing, and shipping details.

7.2.12. Adrenal Laboratory Assessments

A plasma sample for ACTH and cortisol assessments will be collected. These parameters will be measured at Screening (Visit 1), Week 1 (Visit 2), Week 12 (Visit 3), Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 84 (Visit 9) , Week 96 (Visit 10), Week 108 (Visit 11), Week 120 (Visit 12), Week 132 (Visit 13), Week 144 (Visit 14, Week 156 (Visit 15), Week 168 (Visit 16), Week 180 (Visit 17), Week 192 (Visit 18), Week 204 (Visit 19), Week 216 (Visit 20), Week 228 (Visit 21), Week 240 (Visit 22 End-of-Treatment/Premature Discontinuation) and at the Post-Treatment Visit (6 weeks post discontinuation of ataluren). These parameters will be analyzed by the central laboratory. The Central Laboratory Manual should be consulted for collection, processing, and shipping details.

Aldosterone and renin pre-treatment values will be measured at Screening (Visit 1), and, as necessary, for patients with treatment emergent evidence of adrenal dysfunction. These parameters will be analyzed by the central laboratory. The Covance Central Laboratory Manual should be consulted for collection, processing, and shipping details.

7.2.13. Urinalysis

Urinalysis will include analysis for pH, specific gravity, glucose, ketones, blood, protein, urobilinogen, bilirubin, nitrite, and leukocytes. These parameters will be measured at Screening (Visit 1), Week 1 (Visit 2), Week 12 (Visit 3), Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 84 (Visit 9), Week 96 (Visit 10), Week 108 (Visit 11), Week 120 (Visit 12), Week 132 (Visit 13), Week 144 (Visit 14), Week 156 (Visit 15), Week 168 (Visit 16), Week 180 (Visit 17), Week 192 (Visit 18), Week 204 (Visit 19), Week 216 (Visit 20), Week 228 (Visit 21), Week 240 (Visit 22 End-of-Treatment/Premature Discontinuation) and at the Post-Treatment Visit (6 weeks post discontinuation of ataluren). These parameters will be analyzed by the central laboratory. Urine samples will also be collected and shipped to central laboratory for assessment of urine protein, creatinine, osmolality and urinalysis. The Covance Central Laboratory Manual should be consulted for collection, processing, and shipping details.

7.2.14. 12-Lead ECG

A 12-lead ECG will be obtained at Screening (Visit 1) to establish a baseline tracing. Thereafter during the study, ECGs should be obtained as clinically indicated.

7.2.15. Echocardiogram

An echocardiogram will be obtained at Screening (Visit 1), Week 60 (Visit 7), Week 108 (Visit 11), Week 156 (Visit 15) and Week 216 (Visit 20). In addition, an echocardiogram will be

obtained at the Post-Treatment Visit (6 weeks post discontinuation of ataluren) in patients who discontinue the study after 240 weeks of treatment.

7.2.16. 6-Minute Walk Test

6MWD will be assessed in those patients who are ambulatory (able to run/walk 10 meters in ≤30 seconds) at study entry, using standardized procedures [McDonald 2010] (see Study Manual). The 6MWT will be performed at Screening (Visit 1), Week 24 (Visit 4), Week 48 (Visit 6), Week 72 (Visit 8), Week 96 (Visit 10), Week 120 (Visit 12), Week 144 (Visit 14), Week 168 (Visit 16), Week 192 (Visit 18), Week 216 (Visit 20) and Week 240 (Visit 22 End-of-Treatment/Premature Discontinuation).

7.2.17. Timed Function Tests

Timed function tests will performed in those patients who are ambulatory at study entry, and include the time taken to stand from supine and time taken to run/walk 10 meters [Mendell 1989, Griggs 1991, Beenakker 2005a, Pradhan 2006] (see Study Manual). These parameters will be monitored at Screening (Visit 1), Week 48 (Visit 6), Week 96 (Visit 10), Week 144 (Visit 14), Week 192 (Visit 18) and Week 240 (Visit 22 End-of-Treatment/Premature Discontinuation).

7.2.18. North Star Ambulatory Assessment

The NSAA will be used to evaluate physical function in those patients who are ambulatory at study entry, using standardized procedures (see Study Manual). The NSAA will be performed at Screening (Visit 1), Week 48 (Visit 6), Week 96 (Visit 10), Week 144 (Visit 14), Week 192 (Visit 18) and Week 240 (Visit 22 End-of-Treatment/Premature Discontinuation).

7.2.19. Egen Klassifikation Scale

Activities of daily living will be measured using the EK scale [Steffensen 2001] in nonambulatory patients (unable to run/walk 10 meters in ≤30 seconds). The EK scale will be completed at Screening (Visit 1), Week 48 (Visit 6), Week 96 (Visit 10), and Week 144 (Visit 14), Week 192 (Visit 18), and Week 240 (Visit 22 End-of-Treatment/Premature Discontinuation).

Please refer to the Study Manual for further details on how to administer the EK scale.

7.2.20. Spirometry

Spirometry will be conducted in nonambulatory patients. Spirometry will be performed at Screening (Visit 1), Week 24 (Visit 4), Week 48 (Visit 6), Week 72 (Visit 8), Week 96 (Visit 10), Week 120 (Visit 12), Week 144 (Visit 14), Week 168 (Visit 16), Week 192 (Visit 18), Week 216 (Visit 20) and Week 240 (Visit 22 End-of-Treatment/Premature Discontinuation).

7.2.21. Disease Status Survey

For all patients, a disease status survey will be administered at Screening (Visit 1) to collect retrospective information on patient and/or parent-reported changes in disease status during and after their participation in the prior PTC Therapeutics Studies 007 and 007e.

A separate survey will be administered at Week 1 (Visit 2), Week 12 (Visit 3), Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 84 (Visit 9), Week 96 (Visit 10), Week 108 (Visit 11), Week 120 (Visit 12), Week 132 (Visit 13), Week 144 (Visit 14), Week 156 (Visit 15), Week 168 (Visit 16), Week 180 (Visit 17), Week 192 (Visit 18), Week 204 (Visit 19), Week 216 (Visit 20), Week 228 (Visit 21), Week 240 (Visit 22 End-of-Treatment/Premature Discontinuation) to collect prospective information on patient and/or parent-reported changes in disease status.

7.2.22. Study Drug Administration

Subjects should take ataluren TID as described in Section 6.2.2. Ataluren supply sufficient for each 12-week treatment period will be supplied to the subject or caregiver, as appropriate. The patient is still required to be at the site for the 24-week (6-month) re-weigh visit. The amount of study drug supplied to the subject may be altered in the event of pending commercial availability or other reasons as noted in Section 6.2.1. Sufficient drug will be provided at each of these visits to lessen the likelihood that patients will experience drug shortages due to inadvertent loss of some of the sachets or scheduling delays for return visits.

Because of potential changes in subject body weight over time, an investigator site representative should enter the subject's current body weight into the IWR system at Week 24, Week 48, Week 72, Week 96, Week 120, Week 144, Week 168, Week 192 and Week 216 to obtain study drug dosing instructions. Depending upon the magnitude of change in subject body weight since baseline, the number and type of sachets to be used by the subject may remain the same or may be adjusted.

7.2.23. Study Drug Compliance

Ataluren compliance will be assessed using the electronic case report forms. The system will document the return of any unused drug sachets for compliance assessments.

Subjects or caregivers will return all unused sachets of ataluren to the investigator site for full compliance assessments.

7.2.24. Adverse Events

Adverse events must be assessed and documented at each clinic visit. This information will be collected at Week 1 (Visit 2), Week 12 (Visit 3), Week 24 (Visit 4), Week 36 (Visit 5),Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 84 (Visit 9), Week 96 (Visit 10), Week 108 (Visit 11), Week 120 (Visit 12), Week 132 (Visit 13), Week 144 (Visit 14), Week 156 (Visit 15), Week 168 (Visit 16), Week 180 (Visit 17), Week 192 (Visit 18), Week 204 (Visit 19), Week 216 (Visit 20), Week 228 (Visit 21), Week 240 (Visit 22 End-of-Treatment/Premature Discontinuation) and at the Post-Treatment Visit (6 weeks post discontinuation of ataluren). In

addition, patients/caregivers will be encouraged to report adverse events of concern at any time in the intervals between visits.

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

7.2.25. Concomitant Medications

Information regarding any concomitant medications administered, as well as information regarding all non-drug therapies, will be collected throughout the study. This information will be collected at Screening (Visit 1), Week 1 (Visit 2), Week 12 (Visit 3), Week 24 (Visit 4), Week 36 (Visit 5), Week 48 (Visit 6), Week 60 (Visit 7), Week 72 (Visit 8), Week 84 (Visit 9), Week 96 (Visit 10), Week 108 (Visit 11), Week 120 (Visit 12), Week 132 (Visit 13), Week 144 (Visit 14), Week 156 (Visit 15), Week 168 (Visit 16), Week 180 (Visit 17), Week 192 (Visit 18), Week 204 (Visit 19), Week 216 (Visit 20), Week 228 (Visit 21), Week 240 (Visit 22 End-of-Treatment/Premature Discontinuation) and at the Post-Treatment Visit (6 weeks post discontinuation of ataluren).

7.3. Blood Collection Summary

Information regarding the types and approximate amounts of blood samples to be collected in the study is provided in Table 5. Assuming a 240-week treatment of ataluren, the approximate maximum amount of blood to be drawn at a visit is 22.5 mL and the total amount of blood to be drawn over the entire 240-week study period (including the Screening visit, the 240-week treatment period, and the 6-week follow-up period) is approximately 264.5 mL. Additional blood collection may be required in the event of an adverse events or laboratory abnormality.

Table 5. Blood Drawing Requirements

Test	Sample Type	Tube Type	Tube Top (Color)	Tube Size (mL)	Blood Per Tube (mL)	Number of Tubes		Total Blood (mL)
						Per Visit	Total	
Hematology	Whole blood	EDTA	Lavender	2	2	1	23	46
Hepatitis screen	Serum	Clot	Gold	3.5	3.5	1	1	3.5
Biochemistry	Serum	Clot	Gold	5	5	1	23	115
ACTH	Plasma	EDTA	Lavender	2	2	1	23	46
Cortisol	Plasma	EDTA	Lavender	2	2	1	23	46
Aldosterone and Renin	Plasma	EDTA	Lavender	8	8	1	1	8
Maximum Total								264.5

Abbreviations: ACTH = adrenocorticotropic hormone, EDTA = ethylenediaminetetraacetate

8. ADVERSE EVENT ASSESSMENTS

8.1. Adverse Event Definitions

8.1.1. Adverse Events

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

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

- All adverse events that are suspected to be due to ataluren.
- Overdose (administration of an ataluren dose >4 times the highest intended total daily dose level for this protocol [>160 mg/kg/day]) of ataluren.
- All reactions from medication misuse, abuse, withdrawal, sensitivity, or toxicity.
- All reactions that result from medication errors or uses of the study drug outside what is described in the protocol.
- Apparently unrelated illnesses, including the worsening of a preexisting illness.
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate adverse events. 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 (eg, elevated liver enzymes in a subject with jaundice) should be captured in the source documents. Laboratory abnormalities not requiring clinical intervention or further investigation will be captured as part of overall laboratory monitoring, and should not be reported as adverse events.
- A preexisting condition (eg, allergic rhinitis) must be noted on the appropriate electronic CRF (eCRF) for Visit 1, but should not be reported as an adverse event unless the condition worsens or episodes increase in frequency during the adverse event reporting period. Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as

the adverse event and the resulting appendectomy should be recorded in the source documents. If a surgical procedure was planned prior to entry into the study, and the surgery is not performed because of a worsening of a baseline condition, this should not be reported as an adverse event. Note that, as described in Section 8.1.2, any inpatient hospitalization occurring as the consequence of an adverse event during the study period should be reported as an SAE.

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

8.1.2. Serious Adverse Events (SAEs)

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

- Death (ie, all deaths on treatment or within 6 weeks after last ataluren administration), including deaths due to progression of DBMD. Any death occurring later than 6 weeks following the last dose need not be reported as a serious adverse event unless it is a result of an event that started within the period covered by the on-study definition. The reported adverse event should be the event that caused the death. In addition, any adverse event resulting in death that occurs subsequent to the adverse event-reporting period and that the investigator assesses as possibly related to ataluren should also be reported as serious.
- Life-threatening adverse event. This is an event that, in the view of either the investigator or the sponsor, places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, hypothetically might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (excluding hospitalizations for administration of ataluren, procedures required by the study protocol, or DBMD-related diagnostic procedures; other planned hospitalizations; or hospitalizations related only to progression of disease). Treatments in the emergency room for procedures such as hydration that do not require admitting the subject to the hospital and observational durations in the emergency room for less than 24 hours are not considered serious.
- Persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions, not related to DBMD.
- Any other medically important event that the investigator or the sponsor judges to be serious or which is defined as serious by the regulatory agency in the local country. Medical judgment should be exercised in deciding whether a reaction is serious in other situations. Important medical events that do not result in death, are not immediately life-threatening, and do not require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment administration in an emergency room or at home, newly diagnosed malignancy, or blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

An event need not be reported as a SAE if it exclusively represents a relapse or an expected change or progression of the baseline DBMD. This type of event need only to be reported as an adverse event.

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

8.1.3. Unexpected Adverse Events

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

For the purposes of considering expectedness, Section 9 of the ataluren investigator brochure provides a summary of the safety profile of ataluren based on available clinical information (also referred to as the reference safety information).

8.2. Eliciting Adverse Event Information

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

8.3. Adverse Event Recording

All adverse events (both serious and nonserious) that occur in patients during the adverse event 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 adverse event reporting period that the investigator assesses as possibly related to the investigational drug/product should also be recorded as an adverse event.

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

- Indication of whether the event is serious or nonserious (see Section 8.1.2)

- Relationship to ataluren (see Section 8.4)
- Severity of the event (see Section 8.5)
- Onset date
- Resolution date, or date of death
- Action taken
- Outcome of the event

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

8.4. Describing Adverse Event Relationship to Study Drug

Based on the considerations outlined in Table 6 below, the investigator should provide an assessment of the relationship of the adverse event to the study drug, ie, whether there is a reasonable possibility that the study drug caused the adverse event.

Table 6. 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.

8.5. Grading of Severity of Adverse Events

The severity of adverse events will be graded using the CTCAE, Version 3.0 (refer to Study Manual or to http://ctep.cancer.gov/forms/CTCAEv3.pdf). For each episode, the highest severity grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the adverse event. For purposes of consistency with the CTCAE, these intensity grades are defined in Table 7.

Table 7. 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 adverse event. Severe is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in Section 8.1.2 above.

8.6. Pregnancy of Female Partners

PTC Therapeutics should be notified in the event that a female partner of a subject becomes pregnant at any time after the subject's first dose of ataluren. Any such pregnancy occurring on-study or within 60 days of the last administration of ataluren must be reported on a Pregnancy Notification Form (see Study Manual for details). This must be done whether or not an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of birth or pregnancy termination.

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

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

If the outcome of the pregnancy meets the criteria for immediate classification as a serious adverse event (ie, spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator should follow the procedures for reporting serious adverse events, ie, report the event to the PTC Therapeutics Safety Department and follow up by submission of appropriate adverse event CRFs (see Section 8.9).

8.7. Follow-Up of Unresolved Adverse Events

All adverse events should be followed up by the investigator until they are resolved, or the investigator assesses them as chronic or stable. Follow-up of any SAE that is fatal or life-threatening should be provided within one additional calendar week. The investigator should consider protocol guidelines and use his/her discretion in ordering additional tests as necessary to monitor the resolution of such events. In the event of additional investigations, the PTC Therapeutics Safety Department should be informed via e-mail or fax. A subject withdrawn from the study because of an adverse event 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.

8.8. Adverse Event Reporting Period

The first day of adverse event reporting will coincide with the day the first dose of ataluren is administered. The adverse event reporting period for this study ends with the 6-week (± 7 days) Post-Treatment Visit, except as described in Section 8.7 above. In addition, SAEs occurring in a subject after the study period should be reported to the sponsor if the investigator becomes aware of them.

8.9. Investigator Site Adverse Event Reporting Requirements

Classification of an event as serious or nonserious (see Section 8.1.2) determines the reporting procedures to be followed. Investigator site reporting requirements for adverse events are summarized in Table 8 below.

Table 8. Investigator Site Reporting Requirements for Adverse Events

Classification	Reporting Time	Reporting Action
Serious	Within 24 hours	Telephone call, fax, or e-mail to the PTC Therapeutics Safety Department
	Within 24 hours	Fax report or document scan on designated SAE report form to the PTC Therapeutics Safety Department and to site IRB/IEC, as per local IRB/IEC requirements
	Within 5 calendar days	Photocopies or document scan of relevant CRFs (eg, adverse event form, medical history form, concomitant drug/therapy form) and source documents[a] (eg, progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries) to the PTC Therapeutics Safety Department
	Per CRF submission procedure	Record and submit information on appropriate CRFs
Nonserious	Per CRF submission procedure	Record and submit information on appropriate CRFs

a Subject name, address, and other personal identifiers should be obscured.

Abbreviations: CRF = case report form, IRB/IEC = Institutional Review Board/Independent Ethics Committee, SAE = Serious Adverse Event

For SAEs, in addition to completing the adverse event portion of the CRF, the SAE report form must also be completed. The SAE report form should be signed by the investigator; however, if the investigator is unable to sign at the time of the event or within 24 hours, the form should be signed by the clinical staff member reporting the SAE (eg, the study coordinator). The SAE report form must be faxed or emailed to the PTC Therapeutics Safety Department and to the site IRB/IEC (if required by local regulations) within 24 hours. Follow up information to the SAE should be clearly documented as "follow up" in the SAE report form and must also be faxed or emailed to the same party. All follow up SAE report forms for the event must be signed by the investigator. Any source documents (eg, progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries) provided to the sponsor should be redacted so that the patient's name, address, and other personal identity information are obscured. Only the patient's study number and initials are to be provided. The information in the adverse event portion of the CRF and the SAE report form(s) must match or be reconciled. Where the same data are collected, the

forms must be completed in a consistent manner. For example, the same adverse event 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 adverse event.

The PTC Therapeutics Safety Department contact information for reporting serious adverse events is provided below. This information is also provided in the Study Manual and in the SAE report form.

8.10. PTC Therapeutics Adverse Event Reporting Requirements

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

9. WITHDRAWAL OF PATIENTS

All patients who receive ataluren should remain in the study whenever possible. Treatment with ataluren in the context of this protocol is anticipated to occur for 240 weeks. The actual duration of ataluren treatment under this protocol will be subject to the following conditions:

- The patient has the right to withdraw consent and discontinue ataluren at any time.
- If the patient's condition substantially worsens after initiating ataluren treatment, the patient will be carefully evaluated by the investigator in consultation with the PTC Therapeutics medical monitor. This worsening may include cardiac events such as QTc interval limits, new evidence of symptomatic cardiomyopathy and significant decrease in left ventricular ejection fraction. The patient will be withdrawn from treatment if continuing would place them at risk.
- Upon consultation with the PTC Therapeutics medical monitor, the investigator may withdraw the patient from ataluren treatment, if, in the investigator's clinical judgment, it is not in the patient's best interest to continue.
- The patient will be withdrawn from treatment if he is unable to tolerate ataluren.
- The patient may be withdrawn from this study if he is eligible to participate in another ataluren - nmDBMD clinical study or program.
- This study may be discontinued by the relevant regulatory authority and/or PTC Therapeutics at any time.
- This study may be stopped upon ataluren marketing authorization within the relevant country.

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

When study treatment is discontinued, (regardless of the reason), the investigator should encourage that all of the evaluations required at the End of Treatment Visit be performed and that any additional evaluations be completed that may be necessary to ensure that the patient is free of untoward effects. The patient should be encouraged to seek appropriate follow-up for any continuing health problems.

10. STATISTICS AND DATA MANAGEMENT

10.1. Sample Size Calculation for the Primary Endpoint

The pool of patients potentially eligible for this study is described by inclusion criterion 2 of Section 4.2. Hence the sample size is determined by how many such patients satisfy all inclusion/exclusion criteria when applying for participation in this study and not by any formal statistical hypothesis.

10.2. Study Population Definition

10.2.1. As-Treated Population

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

10.3. General Statistical Considerations

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

Summary tables for continuous variables, overall and by corticosteroid use, will contain the following statistics: n, mean, standard deviation, standard error, 95% confidence intervals (CIs) on the mean, median, minimum, and maximum. In addition, changes from baseline will be likewise summarized.

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

In addition to a stand-alone analysis of data from this study, the data may be interpreted in conjunction with corresponding data from other alaluren studies.

10.4. Specific Statistical Analyses

10.4.1. Study Conduct and Subject Disposition

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

10.4.2. Baseline Characteristics

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

10.4.3. Study Treatment Administration

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

10.4.4. Use of Concomitant Medication and Supportive Therapy

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

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

10.4.5. Primary Variables

10.4.5.1. Adverse Events

Adverse events will be classified using the MedDRA classification system. The severity of adverse events will be graded by the investigator according to the CTCAE, Version 3.0 whenever possible. A treatment-emergent adverse event is defined as an adverse event that occurs or worsens in the period extending from the day of a patient's first ataluren dose in this study to 6 weeks after the last ataluren dose in this study.

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

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

10.4.5.2. Laboratory Data

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

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

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

10.4.5.3. Physical Findings

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

10.4.6. Secondary Variables

10.4.6.1. 6-Minute Walk Test

The distance walked at each visit and the change from baseline in the distance walked at each

postbaseline visit, as obtained from the 6MWT, will be summarized descriptively. Only the results of the patient's best valid test at each visit will be included in the analysis. Changes from baseline in 6MWD at each postbaseline visit will be analyzed using paired t-tests. All data from the 6MWTs, valid or invalid, will be listed by patient and visit, with invalid results flagged.

The 6MWD at each visit will be converted into a percent-predicted 6MWD value through the use of a relevant reference equation. The percent-predicted 6MWD value at each visit and the change from baseline in the percent-predicted 6MWD value will be summarized descriptively. Only the results of the patient's best valid test at each visit will be included in the analysis. Changes from baseline at each postbaseline visit will be analyzed using paired t-tests. All percent-predicted 6MWD values, valid or invalid, will be listed by patient and visit, with invalid results flagged.

10.4.6.2. Timed Function Tests

Timed function test data (time taken to stand from supine and time taken to run/walk 10 meters) will be summarized by visit and the changes in the variable from baseline to each post-baseline visit and summarized descriptively. The changes from baseline to each postbaseline visit will be analyzed using paired t-tests.

10.4.6.3. North Star Ambulatory Assessment

Data from the North Star Ambulatory Assessment will be summarized by visit and the changes in the variable from baseline to each postbaseline visit and will be summarized descriptively. The changes from baseline to each postbaseline visit will be analyzed using paired t-tests.

10.4.6.4. Egen Klassifikation Scale

EK scale results will be summarized by visit and the changes in the variable from baseline to each postbaseline visit and will be summarized descriptively. The changes from baseline to each postbaseline visit will be analyzed using paired t-tests.

10.4.6.5. Spirometry

Pulmonary function parameters (adjusted as appropriate for gender, age, and height (using ulna length and arm span) and their changes from baseline will be described by subject and visit and summarized by visit. Ulna length and arm span will be used for separate calculation of %-predicted parameters. The within-subject changes from baseline will be tested for each applicable visit using the t-test. Repeated measure analysis may also be used to estimate the effect of treatment duration on pulmonary function parameters.

10.4.6.6. Disease Status Survey

Disease status survey data will be listed by subject and visit; these data will be summarized by visit. For the prospective survey data, changes from baseline to each scheduled visit and to the final visit will be summarized descriptively. Data from the retrospective survey will be summarized and compared with other subject characteristic and outcome measure data generated from this study and Studies 007 and 007e.

10.4.7. Exploration of Correlations

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

11. STUDY COMMITTEE

11.1. Data Monitoring Committee

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

The DMC will operate under a charter developed as a collaborative document between the DMC and PTC Therapeutics. The primary responsibility of the DMC is to protect the safety and welfare of subjects participating in this clinical study and to ensure the integrity of the clinical study.

In general, the DMC will be responsible for:

- Examining accumulated safety, efficacy, and other relevant data at prespecified points during the course of the study in order to make recommendations concerning continuation, termination, or modification of the study
- Reviewing major study design modifications proposed prior to implementation of those modifications
- Reviewing the general progress of the study
- Providing expert advice to the PTC Therapeutics members on an ad hoc basis regarding matters such as safety concerns or diagnostic evaluations in individual subjects

Based on the results of its deliberations, the DMC can recommend continuation of the study unchanged, study interruption, study termination, modification of the study, or alteration in the DMC monitoring plan.

12. OBLIGATIONS OF THE INVESTIGATOR AND THE SPONSOR

12.1. Compliance with Ethical and Regulatory Guidelines

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

12.2. Institutional Review Board/Independent Ethics Committee

Prior to enrollment of patients 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 patients may be initiated prior to IRB/IEC approval. In that event, the investigator must notify the IRB/IEC and PTC Therapeutics in writing within 5 working days after implementation. The investigator will also promptly notify the IRB/IEC of any serious, unexpected adverse events, or any other information that may affect the safe use of the drug during the course of the study.

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

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

12.3. Informed Consent/Assent

By signing the Statement of Investigator (FDA Form 1572), the investigator assures that informed consent/assent will be obtained from each patient and/or parent/legal guardian prior to study entry and that the informed consent/assent will be obtained in accordance with current regulations.

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

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

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

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

12.4. Case Report Forms

An eCRF is required and must be completed for each enrolled patient, with all required study data accurately recorded such that the information matches the data contained in medical records (eg, physicians' notes, nurses' notes, clinic charts, and other study-specific source documents). The eCRFs exist within a Web-based electronic data capture (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 patient data for archiving at the investigator site. At all times, the principal investigator has final responsibility for the accuracy and authenticity of all clinical data entered onto the eCRFs and/or reported to PTC Therapeutics from the investigator site.

12.5. Study Records

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

12.6. Confidentiality

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

Attention is drawn to the regulations promulgated by the FDA under the Freedom of Information Act providing, in part, that information furnished to clinical investigators and the IRB/IEC will be kept confidential by the FDA only if maintained in confidence by the clinical investigator and the IRB/IEC. By signing this protocol, the investigator affirms to PTC Therapeutics that the investigator will maintain, in confidence, information furnished by PTC Therapeutics and will divulge such information to the IRB/IEC under an appropriate understanding of confidentiality with such board.

12.7. Retention of Records

To enable evaluations and/or audits from regulatory authorities or PTC Therapeutics, the investigator agrees to keep accurate and complete records, including the identity of all participating patients (sufficient information to link eCRFs and clinic records), all original signed informed consent forms, CD-ROM or paper copies of the data that have been captured in the EDC for each patient (electronic equivalents of CRFs), and detailed records of ataluren disposition. All records and documents pertaining to the study (including but not limited to those outlined in Section 12.5 above) will be maintained by the investigator until notification is received from PTC Therapeutics that the records no longer need to be retained.

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

12.8. Monitoring and Auditing

In accordance with 21 CFR Part 312.56 and/or relevant ICH guidelines, PTC Therapeutics or a designee will periodically inspect all eCRFs (see Section 12.4), study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times, before, during, and after completion of the study. As required by applicable regulations (Responsibilities of Sponsors and Investigators), the monitoring visits provide PTC Therapeutics with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of data in the eCRFs; ensure that all protocol requirements, applicable FDA and other relevant

regulations, and investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records required to be maintained by the investigator, including but not limited to medical records (office, clinic, or hospital) for the patients in this study. The names and identities of all research patients will be kept in strict confidence and will not appear on eCRFs or other records provided to or retained by PTC Therapeutics. The investigator/institution guarantees direct access to source documents by PTC Therapeutics and appropriate regulatory authorities.

The investigator site may also be subject to review by the IRB/IEC, to quality assurance audits performed by PTC Therapeutics or a designee, and/or to inspection by the FDA and/or other regulatory authorities. The 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.

12.9. Termination of the Study

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

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

12.10. Public Notification of Study Conduct

Consistent with Section 113 of the Food and Drug Modernization Act of 1997 (FDAMA) and with requirements of the International Committee of Medical Journal Editors (ICJME) as a condition of consideration for publication of study results, PTC Therapeutics will be responsible for ensuring that this protocol is listed at the ClinicalTrials.gov website and that information at the website relating to study design and conduct is appropriately updated during the course of the study. In order to facilitate this process, investigators will need to supply PTC Therapeutics with appropriate contact information for investigator site personnel.

12.11. Dissemination of Results

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

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

and to the FDA or other regulatory authorities. Such information may be disclosed as deemed necessary by PTC Therapeutics.

PTC Therapeutics intends that the data from this study will be presented and published. The PTC Therapeutics staff under the direction of the PTC Therapeutics chief medical officer in collaboration with the investigator will be responsible for writing presentations and manuscripts for publication. Investigators will not be allowed to publish or present the data from this study without prior agreement with PTC Therapeutics.

12.12. Communication with Regulatory Authorities

PTC Therapeutics will assume responsibility for regulatory interactions with the FDA, the European Medicines Agency (EMA), and/or other regulatory authorities. In this regard, PTC Therapeutics will maintain an IND for ataluren in support of the study. In fulfilling this responsibility, PTC Therapeutics (or a designee) will collect, assemble, and communicate all required regulatory documents (eg, Form FDA 1572, investigator financial disclosure forms, protocol and protocol amendments, investigator brochures, informed consent documents, annual reports) as required by regulation. PTC Therapeutics (or a designee) will also assume responsibility for adverse event reporting to regulatory authorities as described in Section 8.10.

13. RATIONALE FOR STUDY DESIGN FEATURES

13.1. Patient Selection

13.1.1. General

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

13.1.2. Required Laboratory Values

In general, the required laboratory values for eligibility are necessary in order to implement the safety monitoring plan described in Section 6.3.1.

13.1.3. Reproductive Considerations

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

13.1.4. Prior and Concomitant Therapies

Conventional supportive therapies will be permitted; however, efforts will be made to avoid use of concomitant medications that might confound interpretation of study results (eg, aminoglycosides) or pose a safety risk (immunosuppressive therapy other than corticosteroids). Ataluren has not proved allergenic in studies performed to date, but review of known allergies to excipients contained in the formulation is prudent.

Pharmacokinetic data indicate that no ataluren dose adjustment is required when ataluren is co-administered with systemic corticosteroids (deflazacort, prednisone, or prednisolone), and no corticosteroid dose adjustments are required when they are co-administered with ataluren. Co-administration of systemic corticosteroids with ataluren may cause more frequent instances of hypertension than does systemic corticosteroid use alone (without ataluren). However, the blood pressure data available to date are not unequivocal about any contributory role of ataluren in development of hypertension in patients who are taking corticosteriods.

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 enzymes (CYPs) are unlikely. In particular, ataluren is not an inhibitor of CYP1A2, CYP2B6, CYP2C19, CYP2D6, and CYP3A4/5, and does not have induction potential on the major CYP enzymes.

In vitro, ataluren is a weak inhibitor of CYP2C8 and CYP2C9, but in vivo drug-drug interactions mediated by these enzymes are not expected according to the criteria described in the EMA guideline on the investigation of drug interactions [EMA 2012]. As an added measure of safety, consideration should be given when ataluren is administered concomitantly with drugs that have narrow therapeutic indices and are primarily metabolized by CYP2C8 (eg, paclitaxel) or CYP2C9 (eg, warfarin and phenytoin), to avoid any risk of increased concentrations of these drugs. Coumarin anticoagulants are cleared by CYP2C9 and increases in plasma concentrations of coumarin anticoagulants may result in serious clinical consequences. For patients 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 patients 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.

Based on in vitro studies, ataluren is not expected to be an inhibitor or a substrate of p-gp mediated transport.

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, phenobarbital, rifampin), or inhibitors of BCRP (eg, cyclosporine, eltrombopag, gefitinib), as these drugs may affect ataluren plasma concentrations.

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 concentrations of these drugs.

Other restrictions relating to recent use of experimental drugs or surgery allow candidates sufficient time to recover before proceeding to ataluren dosing. Restrictions against enrollment of patients expected to have major surgical procedures during the course of the study or who have substantial respiratory or cardiac compromise are intended to avoid safety problems or gaps in ataluren administration in patients who require intensive supportive care.

13.2. Treatment Rationale

13.2.1. Ataluren Schedule and Dose Selection

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

The schedule of drug administration is derived directly from Phase 1 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 administration plan capitalizes on the effect of food in maintaining ataluren plasma concentrations and on nocturnal increase in plasma exposures observed in the Phase 1 studies [Hirawat 2007]. This schedule is likely to fit well with daily patterns of living for patients, thus enhancing compliance. As confirmation of that premise, compliance with ataluren dosing in Phase 2a and Phase 2b testing has been excellent.

13.2.2. Duration of Therapy

Because ataluren therapy will be administered chronically if the compound receives regulatory authority approval, it is important to continue to collect long-term safety and efficacy data during the ataluren development program. This open-label study is expected to generate additional long-term safety and efficacy information at the planned dosed level. This information will supplement data obtained in patients with nmDBMD who received ataluren in a prior PTC clinical study.

13.2.3. Safety Monitoring

In response to the occurrence of mild transaminase elevations in healthy volunteers participating in Phase 1 studies, and adrenal and renal findings in individual toxicology species, a specific safety monitoring plan for the target organs that these types of abnormalities represent has been established in this study. In addition, thresholds for evaluation and intervention have been established for other types of adverse events or laboratory abnormalities observed in the study. The intent is to protect patients, obtain a thorough assessment of any clinically relevant adverse events or laboratory abnormalities, and to offer recommendations for interruption and dose modification of ataluren in response to potential safety signals. The nature of these risks and the measures to monitor for them are to be reflected in the informed consent form.

As noted in Section 6.3.1, patients must be monitored closely for adverse events or laboratory abnormalities during the course of the study; safety findings deserving particular attention include hepatic, adrenal, renal, and electrolyte abnormalities. Section 6.3.1 provides information on actions to be taken in the event that abnormalities are noted on specified monitoring studies. Thresholds are provided for interrupting ataluren immediately, for interrupting ataluren after confirmation of a value beyond the threshold, or for continuing ataluren while evaluating for potential drug-related toxicity.

13.2.3.1. Hepatic Abnormalities

13.2.3.1.1. Overview

While toxicology studies in mice, rats, and dogs did not indicate adverse changes in hepatic pathology or serum aminotransferase levels, ataluren administration during Phase 1 studies in healthy volunteers was associated with Grade 1, reversible transaminase elevations in ALT and AST [Hirawat 2007]. During Phase 2a testing, serum transaminase levels have tended to improve in both DMD and cystic fibrosis patients (perhaps indicating evidence of response to

treatment). Thus, while clinical risk appears low, specific follow-up of markers of liver injury in this study is warranted.

13.2.3.1.2. Hepatic Monitoring Plan

Muscle breakdown results in ALT and AST values that are commonly 10- to 20-fold > ULN (Grade 3-4) in patients with DBMD. Consequently, it is not practical to exclude patients with high serum AST or ALT concentrations from enrollment in this study, and monitoring for hepatotoxicity must rely primarily on following patients for increases in bilirubin or GGT. Consistent with well-established guidelines [Abboud 2007] applied in this disease setting, even modest (Grade 2) alteration in bilirubin or GGT values should prompt interruption of ataluren. While serum ALT or AST values cannot routinely serve as measures of hepatic injury in boys with DBMD, significant increases in ALT (>150 U/L) in conjunction with a stable or falling CK should prompt increased frequency of laboratory monitoring and possibly an evaluation for potential hepatotoxicity.

13.2.3.2. Adrenal Abnormalities

13.2.3.2.1. Overview

Adrenal findings were noted in dogs receiving ataluren for ≥20 weeks. Anatomic findings included decreased adrenal weights and lymphohistiocytic infiltration with adjacent foci of parenchymal degeneration in the adrenal cortex. The morphology was not consistent with an immune-mediated hypoadrenalism (Addison's disease) and the dogs were asymptomatic throughout the entire study duration. These findings did not reverse at the end of 4 and 8 weeks of recovery following 20 and 52 weeks of dosing. An increase in serum basal adrenocorticotropic hormone (ACTH) values was observed and ACTH stimulation testing indicated that all dogs showed responses with increases in serum cortisol levels. However, because the magnitude of the cortisol response was not as great in animals receiving the mid- and high-dose of ataluren (500 and 1000 mg/kg/day) in comparison to controls, a no observed adverse effect level (NOAEL) for adrenal cortical function at the lowest ataluren dose level (250 mg/kg/day) was established. Consistent with lack of involvement of the zona glomerulosa, serum aldosterone values were unaffected and no serum electrolyte changes were seen. Steady state exposure in dogs at 250 mg/kg/day is ~0.8-fold the exposure in patients administered ataluren at the morning, midday, and evening doses of 10, 10 and 20 mg/kg/day, respectively. No drug-related effects on the adrenal gland have been seen in mice dosed for 26 weeks or in rats dosed for 24 months.

It is possible that patients participating in the ataluren studies could experience events similar to those occurring in animals. Pending the acquisition of further clinical safety information, a program of adrenal monitoring for patients receiving ataluren is being instituted using well-established techniques.

13.2.3.2.2. Adrenal Monitoring Plan

Adrenal monitoring in boys with DBMD presents unique challenges given the prevalence of chronic corticosteroid use in this population. While assessments of adrenal function in boys who are not using corticosteroids is straightforward, regular administration of prednisone or deflazacort to boys with DBMD is expected to induce secondary adrenal atrophy and reductions

in circulating glucocorticoids that may obscure the biochemical detection of potential ataluren-mediated adrenal toxicity. While this situation might seem concerning, it should be realized that boys who are receiving supraphysiological doses of corticosteroids are protected against endogenous hypoproduction of cortisol due to any cause [Ten 2001, Kyriazopoulou 2007].

In this context, the proposed monitoring plan for adrenal toxicity relies upon repeated assessment of tandem plasma markers – ACTH and cortisol to assess functional changes in glucocorticoid production, and secondary assessments of renin and aldosterone to measure mineralocorticoid production. Such use of these markers builds on evolving paradigms for semi-annual or annual monitoring adrenal function in individuals at high risk of primary autoimmune adrenal failure [Barker 2005, Coco 2006] and the well-established physiology of the adrenal gland and associated endocrine organs [Oelkers 1996].

In the evaluation of glucocorticoid function, it is understood that progressive primary failure of the adrenal gland results in decreased cortisol production and diminished negative feedback on pituitary gland generation of ACTH. In humans with an intact hypothalamic-pituitary-adrenal (HPA) axis, the pituitary gland compensates by progressively increasing plasma ACTH to maintain plasma cortisol levels. Cortisol production is preserved until adrenal cortical reserves become so low that ACTH hyperstimulation is no longer sufficient and cortisol concentrations finally fall. Thus, an early harbinger of a failure of primary glucocorticoid production is the detection of an elevated plasma ACTH concentration with a normal or falling cortisol level [Ketchum 1984, Oelkers 1992, De Bellis 1993, Blevins 1994]. Similar negative feedback loops exist for the renin-angiotensin-aldosterone system. In this situation, primary loss of aldosterone production in the adrenal results in compensatory hyperproduction of renin by the kidney. Thus, the earliest sign of a failure of mineralocorticoid production is the detection of an elevated plasma renin concentration with a normal or falling plasma aldosterone level [Ketchum 1984, De Bellis 1993, Betterle 2002].

Based on the findings of ataluren-associated effects on the ACTH-cortisol axis in the dog, assessments of plasma ACTH and cortisol are clearly warranted, especially in patients who are not receiving exogenous corticosteroids. In patients who are taking corticosteroids, endogenous plasma ACTH and cortisol levels will generally be low and the diagnostic sensitivity will be blunted. However, abnormal elevations of ACTH in this circumstance would still be a specific indication of glucocorticoid insufficiency and so should be monitored during ataluren dosing [Ten 2001].

The dog toxicology data do not indicate an ataluren-related risk of compromised mineralocorticoid production. Additionally, clinical measures of renin and aldosterone are markedly affected by age and normal reference ranges are very narrow. In boys who are taking ACE inhibitors or ARBs as prophylaxis/treatment of CHF, plasma renin values may be elevated and plasma aldosterone levels may be low due to these drugs [Azizi 1997, Hansen 1999]. For such patients, plasma renin and aldosterone concentrations may not prove useful as adrenal monitoring tools. Given these limitations, reliance will primarily be placed on monitoring of ACTH and cortisol values; routine assessment of the renin-aldosterone axis will only be performed if evidence of compromised corticosteroid production is observed. To facilitate

assessment of the renin-aldosterone axis in patients with treatment-emergent evidence of adrenal dysfunction, baseline renin and aldosterone values will be obtained in all patients prior to initiating treatment with study drug.

Based on these considerations, elevations of plasma ACTH should prompt confirmation of the elevated value, reassessment of cortisol levels, further diagnostic evaluation (potentially including ACTH stimulation testing [Dorin 2003]), and possible interruption of ataluren dosing. If patients who are not already receiving corticosteroids develop ataluren-related adrenal insufficiency, physiological replacement therapy with corticosteroids and/or mineralocorticoids can be instituted according to well-established protocols [Oelkers 1992, Ten 2001, Kyriazopoulou 2007].

13.2.3.3. Renal Abnormalities

13.2.3.3.1. Overview

Renal findings were seen in mice receiving 1 or 2 doses through 26 weeks of doses of ataluren. A NOAEL for the renal toxicity findings in mice has not been identified; the lowest observed adverse effect level (LOAEL) = 75 mg/kg/day. Exposure in mice at 75 mg/kg/day is 0.3-fold the exposure in patients administered ataluren at the morning, midday, and evening doses of 10, 10 and 20 mg/kg/day, respectively. The renal finding was seen primarily in the distal nephron and involved some degenerative changes (apoptosis) and proliferation of renal epithelium. Renal tubular dilatation and proteinaceous material within the tubules also were seen. The structural integrity of the nephron was maintained, as degenerative/necrotic changes of large numbers of cells were not seen. A few glomeruli in the upper cortex were shrunken but the overall lesion did not primarily involve the glomeruli. The finding was occasionally accompanied by individual increases in serum blood urea nitrogen (BUN) and/or creatinine, however, a dose relationship for these parameters was not observed. The kidney findings were partially to completely reversible as soon as 2 weeks after cessation of dosing. The renal toxicity was observed in mice only, and has not been seen in rats dosed for 24 months or in dogs dosed for 52 weeks despite achievement of exposures in rats and dogs that were comparable to or greater than those observed in mice. In Phase 1 studies in healthy volunteers and Phase 2 studies in patients with DMD and cystic fibrosis, renal laboratory abnormalities have been infrequent.

During the Phase 2b double-blind study of ataluren in nmDMD (PTC124-GD-007-DMD), small increases in mean serum creatinine, BUN, and cystatin C were observed. The values tended to stabilize early in the study and did not increase further with continued treatment.

Renal abnormalities were observed in an international, multicenter, double-blind, placebo-controlled Phase 3 trial evaluating ataluren in patients ≥6 years of age with nonsense mutation cystic fibrosis in patients receiving concomitant ataluren and IV aminoglycosides (as described in the Ataluren Investigator Brochure). In patients who require treatment for serious infections, investigators should substitute other antibiotics for systemic aminoglycosides when clinically appropriate. If IV aminoglycosides are administered, study drug must be interrupted during the course of these antibiotics.

Study drug interruption should be considered with concomitant use of other potentially nephrotoxic antibiotics (eg, vancomycin). Caution should be exercised during concomitant use of other potentially nephrotoxic agents.

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

Overall, the renal monitoring program included in this protocol considers nonclinical and clinical findings with ataluren, past experience with known nephrotoxicants, manifestations of DBMD, and current knowledge regarding exploratory renal toxicity biomarkers. A focus is placed on well-established clinical indictors of renal dysfunction for making diagnostic decisions and prompting treatment interruptions/ modifications in individual patients. The rationale for each of the decision-making parameters is discussed below.

13.2.3.3.2. Renal Monitoring Plan

- **Serum Cystatin C:** GFR is a requisite component of renal testing to evaluate glomerular and nephron integrity. While "gold standard" methods of determining GFR (eg, infusions of inulin, iohexol, iothalamate, or technetium 99m-diethylenetriamine pentaacetic acid [^{99m}-Tc-DTPA] with timed blood and urine assessments) can be employed, these methods are cumbersome and are often reserved for renal physiology laboratories at specialized centers [Guignard 2004, Stevens 2007]. In clinical practice, assessments of GFR have more typically relied upon determination of creatinine clearance during 24-hour urine collections or calculation based on nomograms using only serum creatinine. It is generally acknowledged that 24-hour urine collection in children is inaccurate and impractical due to compliance issues [Guignard 2004]. Calculation of GFR using only measurement of serum creatinine has long been standardized for children [Schwartz 1987]. However, because it is both filtered and secreted by the kidney, serum creatinine is acknowledged to be relatively imprecise and insensitive marker of renal damage [Herget-Rosenthal 2007, Schwartz 2007]. Moreover, serum creatinine is subject to variation based on endogenous and exogenous factors. This problem is particularly concerning in boys with DMD because the majority of creatinine in serum is derived from muscle [Wang 1996] and boys with DMD have decreased serum creatinine concentrations due to reduced muscle mass. A review of baseline serum creatinine values among the 38 boys with DMD participating in the ataluren Phase 2a study indicates low serum creatinine values (median 0.3, range 0.1-0.5 mg/dL). Additional sources of variability for boys with DMD may include ingestion of creatine (a substrate for creatinine production) [Escolar 2005] and treatment-mediated alterations in muscle fragility [Mendell 1989].

As an alternative to assessing GFR based on serum creatinine, serum cystatin C offers substantial advantages in the context of this protocol. Cystatin C is a low-molecular-weight [~13 kDa] proteinase inhibitor derived from all cells that is filtered by the glomerulus and degraded in the renal tubules [Herget-Rosenthal 2007]. The serum cystatin C concentration is almost solely dependent upon GFR and appears relatively unaffected by muscle mass or other conditions. An additional advantage is that circulating cystatin C changes more rapidly in response to multiple types of renal injury than creatinine [Herget-Rosenthal 2007]. Methods for measuring cystatin C are standardized and the correlations between serum cystatin C and GFR have been derived and confirmed in large studies involving healthy children and adults and those with renal dysfunction [Dharnidharka 2002, Grubb 2005, Zappitelli 2007]. Based on these considerations, values of serum cystatin above 1.33 mg/L should prompt diagnostic evaluation and interruption/modification of ataluren if required per protocol.

- **Serum Creatinine**: Given the widespread clinical familiarity with serum creatinine as a marker of renal dysfunction and as a monitoring tool for nephrotoxins in clinical practice [Gilead 2002, Gilead 2006, Novartis 2005], characterization of serum creatinine provides an appropriate frame of reference relative to other experiences. Because most participating boys with DMD are expected to have low normal values of serum creatinine due to reduced muscle mass, any values higher than the normal range may be cause for concern. Caveats regarding interpretation of serum creatinine in boys with DMD (particularly if there are food- or treatment-induced changes in serum creatinine values) dictate that an increase in serum creatinine above the age-specific normal range should prompt reevaluation of other safety parameters and potential interruption/modification of ataluren dosing.
- **Serum Blood Urea Nitrogen:** Considering its role in maintaining urine-concentrating ability, urea has major importance in renal physiology and its clinical measurement as a marker of renal dysfunction is long established. In the context of nephrotoxicity, elevations in BUN suggest disruption of tubular integrity [Vonderscher 2007]. In the nonclinical mouse studies of ataluren in which nephrosis was observed, BUN was elevated in some of the affected animals, confirming that this marker should also be measured in clinical studies of ataluren. Monitoring serum BUN, like monitoring creatinine, provides an additional frame of reference relative to other markers assessed within this study and in other studies of known nephrotoxicants. However, an elevation in BUN is not a specific signal of renal tubular injury, but also may reflect compromised renal tubular blood flow due to depressed cardiac output, medications, or dehydration [Guignard 2004, Stevens 2007]. For these reasons, a BUN increase ≥1.5 x ULN should prompt a review of potential pre-renal, renal, and post-renal causes for the abnormality as well as consideration of potential interruption/modification of ataluren dosing.
- **Urine Protein:Creatinine and Urine Protein:Osmolality Ratio:** Proteinuria can be an early marker for renal injury in experimental models [Amin 2004] and is commonly observed with even modest clinical decreases in renal function [National Kidney Foundation 2002]. Glomerular disease (eg, diabetic nephropathy) is often associated with albuminuria due to defects in exclusion of plasma proteins in the glomerular filtrate. Tubular injury (eg, as

observed in mice receiving ataluren) more often leads to increases in low-molecular-weight proteins (eg, beta-2 microglobulin, β2-microglobulin, α1-microglobulin retinol-binding protein, lysozyme) as tubular protein catabolism is compromised or proteins of injury are produced [Guignard 2004, Stevens 2007]. Because mice that developed nephrosis while receiving ataluren had proteinaceous material in the renal tubules on histological examination, monitoring of urine protein in humans receiving ataluren is additionally warranted.

Dipstick methods of protein screening are only semiquantitative, are relatively insensitive, and are confounded by exogenous substances and subjective interpretation [Kim 2007]. The presence of urinary protein may be masked in dilute urine or exaggerated in concentrated urine. For these reasons, a quantitative method of accessing proteinuria is planned in this study. Two methods will be assessed: urinary protein concentration relative to urinary creatinine concentration [Ginsberg 1983, Schwab 1987]. and urinary protein concentration relative to urine osmolality [Wilson 1993, Morgenstern 2003]. These methods of screening, using spot urine samples, have been found to be as accurate as and more practical than quantification of urine protein during a 24-hour collection. Values for protein:creatinine of ≥0.2 mg/dL:mg/dL and of protein:osmolality of ≥0.15 mg/L:mOsm/kg have been established as abnormal [Morgenstern 2003]. While measurement of protein:creatinine is generally the preferred method in children [Morgenstern 2003], it is possible that low urinary creatinine excretion in boys with DMD may falsely elevate protein:creatinine ratios. For this reason, confirmed evidence that both measures are abnormal should stimulate further evaluation and intervention. Follow-up methods such as urine electrophoresis may be useful in discriminating among the types of proteins present and may suggest a site of injury (eg, an albumin-specific pattern with glomerular damage versus a diffuse multiple low-molecular-weight protein pattern with tubular damage) [Stevens 2007]. Confirmed proteinuria should prompt consideration of interruption/modification of ataluren dosing.

- **Urine Blood:** Blood in the urine may indicate pathology of the renal parenchyma or of the urinary collecting system (eg, ureters, bladder, and urethra). Like proteinuria, hematuria is commonly found in patients with minimal changes in GFR due to renal (particularly glomerular) dysfunction [National Kidney Foundation 2002]. Confirmed, persistent evidence of urinary blood by dipstick and/or microscopic examination will prompt further evaluation. Ultrasound or other imaging can evaluate for a potential renal cause for bleeding. Urology consultation can be obtained to assess for post-renal sources of hematuria. Clotting function and use of drugs that may impair platelet function will be reviewed. Confirmed, persistent hematuria in the absence of a post-renal source of bleeding or a bleeding diathesis will prompt potential interruption/modification of ataluren dosing.

- **Serum Electrolytes:** Assessments of serum electrolytes (sodium, chloride, potassium, bicarbonate, magnesium, calcium, and phosphorus) provide information regarding renal function that may supplement more primary assessments. Derangements in serum concentrations may reflect altered tubular handling of these ions. With worsening renal function, hyperphosphatemia and hypocalcemia may develop and reductions in serum bicarbonate or elevations in potassium may suggest an impaired ability of proximal tubules or collecting ducts to maintain acid-base balance [National Kidney Foundation 2002].

Given the cardiovascular and neurological consequences of severe derangements of serum potassium, calcium, or magnesium, evaluation of these ions is important to avoid potential secondary complications. Because transient Grade 1 alterations in the concentrations of electrolytes are very unlikely to be associated with significant secondary side effects, alterations to ≥Grade 2 are considered appropriate to prompt potential interruption/modification of ataluren dosing.

13.2.3.4 Lipid Profile

During the Phase 2b double-blind study of ataluren in nmDMD (PTC124-GD-007-DMD), mean total cholesterol and triglycerides were in the upper range of normal at baseline and increased on study, reaching borderline high or high values. Although the values tended to stabilize early in the trial and did not increase further with continued use of ataluren, monitoring the changes in patients' lipid profile is warranted. For this reason, total cholesterol, LDL, HDL, and triglycerides will be evaluated at each visit to monitor for changes in lipid profile values.

13.2.3.5 Blood Pressure Assessment

During the Phase 2b double-blind study of ataluren in nmDMD (PTC124-GD-007-DMD), 6 patients – all receiving corticosteroids – had hypertension (or increased blood pressure) reported as adverse events (0 for ataluren 20, 20, 40 mg/kg, 5 for ataluren 10, 10, 20 mg/kg, and 1 for placebo). For this reason, blood pressure will be monitored via standardized procedures at each visit.

13.2.3.6 Other Non-Clinical Findings

Single lipomatous, non metastatic tumors, determined to be malignant hibernomas originating in brown adipose tissue were identified in 6 rats during a 26 week toxicity study. In a second 26 week rat study, no malignant hibernomas were observed in any dose group, including the high dose group (1200 mg/kg/day). The exact correlative relevance of this finding is unclear given the lack of reproducibility in rats, the different physiology of brown fat in rats relative to humans [Cannon 2004, Iatropoulos 2004], the very young age of the rats used in these studies, the lack of ataluren genotoxicity, and the extreme rarity and generally benign course of hibernomas in humans [Furlong 2001].

Urinary bladder tumors were observed in 3/60 females at the high dose of 300 mg/kg/day in the 24-month carcinogenicity study in rats. This dose exceeded the maximum tolerated dose (MTD), based on an average 23% reduction in body weight gain in comparison to vehicle controls throughout the study. In addition, the proposed mode of urinary bladder tumor formation (presence of calculi) in rats is not considered relevant to humans. Mean steady state exposures in female rats at the mid-dose of 100 mg/kg/day and in male rats at the high-dose of 300 mg/kg/day were 4 and 6 times, respectively, the steady state exposure in patients administered ataluren at the morning, midday and evening doses of 10, 10 and 20 mg/kg/day, respectively.

Long-term post-treatment follow-up safety data currently available from the patients dosed with ataluren to date in the clinical studies, some for over 7 years, indicate no increased risk of tumors.

13.2.4 Other Abnormalities

Recommendations for interruption of dosing are provided in Section 6.3.1, with the general intent that a Grade 4 (life-threatening) event should result in immediate cessation of dosing while awaiting confirmation of the abnormal laboratory value, a Grade 3 (severe) event may require confirmation of the abnormal laboratory value before cessation of dosing, and a Grade 2 (moderate) event may prompt further evaluation while ataluren dosing continues. It is intended that these recommendations be viewed flexibly; the type and context for any adverse event or laboratory abnormality must be considered in taking action.

13.2.5 Actions to be Taken in Response to Safety Signals

The intent of the recommendations to investigators regarding response to safety signals is to encourage a medically appropriate and consistent approach to adverse events and laboratory abnormalities. While specific monitoring, diagnostic testing, and supportive care measures must be instituted based on the clinical judgment of the investigator, investigators are encouraged to contact the MAPI or PTC Therapeutics medical monitor to obtain guidance and to ascertain whether similar events are being seen at other investigator sites. The availability of advice from hepatology, endocrinology, and nephrology experts retained by PTC Therapeutics is intended to provide a uniformly high level of consultation in support of the investigators and the PTC medical monitor.

The dose interruption and modification provisions are designed to balance a primary concern for patient safety with the potential for observing efficacy in circumstances under which a patient experiencing an adverse event may still be able to continue with dosing at a lower ataluren dose. Interruption of dosing is advocated as the primary response in order to determine reversibility of the adverse finding. Rechallenge permits a patient to proceed with potentially beneficial treatment and enhances understanding of the relatedness of the adverse event to ataluren.

13.2.6 Efficacy Measurements

13.2.6.1 6-Minute Walk Test

Loss of ambulation is one of the most serious complications of DBMD. The 6MWT is an established outcome measure reflecting the global status of all the systems involved in walking, including the neuromuscular, pulmonary, and cardiovascular systems [Takeuchi 2008].

Based on precedent in other neuromuscular disorders [Rubin 2002, Wraith 2004, Muenzer 2006], the 6MWT represents an appropriate approach to assessing ambulatory ability in boys with DBMD. A change in performance on the 6MWT constitutes a clinically meaningful endpoint and improvements would be a direct reflection of benefit to boys with DBMD. The 6MWT is feasible, accurate, and reproducible in the target population [McDonald 2010].

13.2.6.2 Timed Function Tests

These tests provide additional measures of ambulatory capability in boys with DMD who can still walk. Commonly employed over many years [Brooke 1989, McDonald 1995], these tests are relevant to the disease in that they assess functional aspects of proximal muscle strength required for everyday ambulation. Timed function tests are substantially abnormal in boys with DMD compared to healthy boys [Beenakker 2005b]. Worsening values have been correlated with time to wheelchair dependency [Brooke 1989, McDonald 1995]. These tests can be sensitive to medical intervention; corticosteroid therapy has documented improvements in all 3 parameters [Mendell 1989, Griggs 1991, Beenakker 2005a]. Given their long-standing use and simplicity, there is substantial experience with the conduct of the tests and the analyses of the data and very high reproducibility has been demonstrated [Mayhew 2007].

13.2.6.3 North Star Ambulatory Assessment

The NSAA is a functional scale specifically designed for ambulant DMD boys. The scale has been developed and piloted in the United Kingdom by the North Star Clinical Network for Paediatric Neuromuscular Disease Management with good intra and interobserver reliability and has recently been used in a large multicenter study [Mazzone 2011].

The scale includes items assessing abilities that are necessary to remain functionally ambulant, ie, ability to rise from the floor, ability to get from lying to sitting and sitting to standing, and that are known to progressively deteriorate in untreated DMD patients. The scale also includes items assessing head raise and standing on heels that can be partly present in the early stages of the disease and a number of activities such as hopping, jumping, and running [Mazzone 2010].

13.2.6.4 Egen Klassifikation

For nonambulatory patients with DMD, the EK scale has been selected to assess functional ability after loss of ambulation [Steffensen 2001]. The EK scale has previously been shown to be highly reliable when tested for intra- and inter-rater reliability among patients with DMD [Steffensen 2002a, Steffensen 2002b].

13.2.6.5 Spirometry

Progressive pulmonary dysfunction is a major source of disability and shortened survival associated with DMD and represents an important target for therapeutic intervention. Natural

history data in DMD show that pulmonary values decline more precipitously once patients lose ambulation [Steffensen 2002b].

Based on experience at measuring pulmonary function in randomized trials [Mendell 1989, Griggs 1991], it is clear that spirometry testing can be performed practically in multicenter studies enrolling study populations comparable to those to be enrolled into this study. Standard operating procedures for spirometry performance, requiring that spirometric effort is sufficient and that each test is consistent with American Thoracic Society/European Respiratory Society guidelines [Miller 2005a, Miller 2005b] will be used.

13.2.6.6 Disease Status Surveys

Information on patient and/or parent-reported changes in disease status (eg. disease symptoms and activities of daily living) during and after their participation in the prior PTC Therapeutics Studies 007 and 007e will be collected retrospectively through the use of a standardized survey administered by site personnel.

A separate survey will be administered by site personnel during the study to collect prospective information on patient and/or parent-reported changes in disease status.

14 BENEFITS AND RISKS

14.1 Benefits and Risks – Non-Clinical

Ataluren is an orally bioavailable small molecule intended for the treatment of nonsense Duchenne muscular dystrophy (nmDMD) resulting from a nonsense mutation in the dystrophin gene. In cellular assays and animal models of genetic disease, ataluren demonstrated the ability to specifically and selectively enable readthrough of mRNA containing a premature stop codon, inducing production of full-length protein that localizes to the appropriate cellular location and is functionally active. Ataluren consistently enabled mRNA readthrough and functional full-length protein production from mRNAs that contain a premature stop codon without promoting readthrough of normal stop codons.

Ataluren was shown to be selective for translation. Ataluren did not alter levels of mRNA with premature stop codons or wild type mRNA demonstrating that ataluren does not modify transcription or mRNA stability. In cell-free translation assays, ataluren functions at the level of translation and not transcription. Ataluren does not produce a functional protein by promoting readthrough of premature stop codons due to frameshift mutations (insertions or deletions) or of mRNAs harboring multiple sequential premature stop codons. Ataluren is selective for premature stop codons and does not promote readthrough of normal stop codons. In cellular models of nonsense mutation genetic diseases, ataluren exhibited a bell-shaped concentration response with maximal activity at 10 μg/mL. At ataluren concentrations above 20 μg/mL a reduction in activity is observed, indicating a bell-shaped dose response. Cytotoxicity was not observed at any concentration tested. In animal models, ataluren exhibited a bell-shaped dose-response. In vitro and in vivo nonclinical efficacy pharmacology data indicate that concentrations that range from ~1 to 20 μg/mL were associated with pharmacodynamic activity.

Specifically, in the *mdx* mouse model, efficacy was associated with concentrations ranging from 2 to 10 µg/mL.

Toxicokinetic data were obtained in toxicity studies conducted in mice, rats, rabbits and dogs. Consistent with the short t½, there was no accumulation of drug in plasma upon repeated daily dosing. In all species, ataluren exposure increased with increasing dose, but the increase was generally less than dose proportional. There were no sex-related differences in ataluren exposure in dogs, but in rats and mice, exposure was slightly higher in females than in males. The major metabolite seen in mice, rats and dogs was ataluren acyl glucuronide; exposure to this metabolite in the toxicology species at LOAELs, NOAELs, and NELs in the toxicology program was greater than the exposure observed in humans administered the clinical dose of 10, 10 and 20 mg/kg/day at morning, midday, and evening, respectively. Ataluren is highly bound (> 97%) to plasma proteins in all species, including human. Ataluren is neither a substrate for nor an inhibitor of p-glycoprotein. Enzyme inhibition studies with human liver microsomes showed that ataluren has a weak potential for direct inhibition of CYP2C8 and CYP2C9. As an added measure of safety, investigators should pay specific attention to use of drugs that are known substrates of these enzymes, particularly when such drugs may have a narrow therapeutic index. Enzyme induction evaluations in human hepatocytes showed that ataluren did not induce the activities of CYP450 enzymes. Induction of metabolism by ataluren is not expected since slight increases in CYP2B6 and CYP2C9 activity are observed only at an ataluren concentration that is 3- to 5-fold higher than the average peak concentration after a 20 mg/kg dose.

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, phenobarbital, rifampin), or inhibitors of BCRP (eg, cyclosporine, eltrombopag, gefitinib).

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.

Ataluren was evaluated in safety pharmacology studies and found to have no effects on the cardiovascular system, respiratory system, or central nervous system. In the toxicology program, the major findings observed were species-specific, ie, observed in one toxicology species only. These findings included kidney findings in mice (nephrosis, predominantly in the distal nephron, reversible following cessation of dosing) and adrenal gland cortical findings in dogs (lymphohistiocytic infiltrates with focal parenchymal cell degeneration in regions responsible for synthesis of glucocorticoids). Chronic studies were conducted in weanling rats and dogs to support dosing in children as young as 2 years of age. Ataluren was not genotoxic, and was not teratogenic in rats and rabbits. In rats and rabbits, fetal toxicity was observed only at materno-toxic doses. Ataluren had no effect on the fertility of male and female rats. In rats, postnatal developmental effects were observed only at materno-toxic doses. Maternal administration of

ataluren in rats had no effect on F_1 reproduction or F_2 embryo/fetal development. Ataluren did not increase the incidence of tumors in a 26-week carcinogenicity study in Tg.rasH2 mice. Tumors observed in rats in the toxicology program occurred at exposures that exceeded clinical exposure and were not considered relevant to humans. The structurally identified process impurities of the ataluren drug substance were qualified in rats at doses 29- to 33-fold higher than would be administered in the clinic at the proposed morning, midday, and evening doses of 10, 10 and 20 mg/kg/day, respectively. Ataluren is a small molecular weight compound, and therefore, is not expected to produce anti-drug antibodies. Ataluren had no effect on the immune system in the toxicology program and in the clinical trials; therefore, immunotoxicity studies were not performed with ataluren.

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

The nonclinical evaluation of ataluren presented in this summary support its use for the treatment of nmDMD.

14.2 Benefits and Risks - Clinical Efficacy

Duchenne muscular dystrophy (DMD) is a rare (1 in 3500 male births) disabling, relentlessly progressive, and ultimately fatal X-linked genetic disorder that primarily affects males. Currently, treatment is palliative. No therapies that address the underlying cause of the disease are available.

Decline in ambulation is the hallmark of DMD, and the major goal of intervention during the ambulatory phase of DMD is to maintain ambulation for as long as possible. Ataluren at a dose of 10, 10, 20 mg/kg slowed the decline in ambulation in nonsense mutation DMD patients. In the placebo-controlled study, Study 007, the targeted difference of 30 meters between ataluren 10, 10, 20 mg/kg and placebo in the 6-minute walk distance (6MWD) was achieved (Δ=31.3 meters, adjusted p=0.0561, cITT analysis). The 30-meter distance meets the threshold for minimal clinically important difference in DMD and other diseases, and is in the range of the 6MWD results for approved therapies in a variety of conditions. The 30-meter distance is meaningful to DMD patients, providing greater ability to walk in their daily lives, for example, walking to and from the school bus and taking part in social activities.

The time-to-event analysis of 6MWD progression further showed that ataluren 10, 10, 20 mg/kg slowed disease progression in patients with nmDMD. Only 26% of patients who received ataluren 10, 10, 20 mg/kg, compared with 44% of the patients who received placebo, had persistent 10% worsening in the 6MWD at Week 48 (adjusted p=0.0652, cITT analysis). Delaying ambulatory decline provides direct clinical benefit by affording boys with nmDMD a longer period of self-sufficiency before transitioning to full-time wheelchair use. Maintenance of

ambulatory capacity can prevent, delay the onset of, or reduce the severity of scoliosis, a debilitating complication of DMD, and is beneficial to the patient's pulmonary status.

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

The higher dose in Study 007, 20, 20, 40 mg/kg, did not differentiate from placebo in the primary endpoint, 6MWD. The inverse dose response prompted an analysis of efficacy measures by ataluren plasma concentration in the ataluren clinical trials. Across 3 clinical trials (placebo-controlled Study 007 and open-label Studies 007e and 004e), ataluren concentration-response analyses in patients who were treated with ataluren 20, 20, 40 mg/kg showed better results for the 6MWT and timed function tests (TFTs) in patients whose plasma ataluren concentrations were in the range of those observed with ataluren 10, 10, 20 mg/kg, than in patients with higher plasma concentrations. This inverse concentration-response relationship is supported by the population PK-PD model of 6MWT data. These clinical findings are consistent with nonclinical studies of ataluren (in the DMD mouse model and other disease models) as well as other nonsense mutation read-through drugs, which show a bell-shaped concentration-response relationship. These analyses explain the inverse dose-response seen in Study 007 and support the proposed dose of ataluren 10, 10, 20 mg/kg.

Collectively, the 6MWD data in Study 007, supported by secondary outcome measures, and the concentration-response analyses across nmDMD studies, demonstrate the beneficial effect of ataluren 10, 10, 20 mg/kg in patients with nmDMD. Ataluren thus offers an important advance in the genetic-based treatment of nmDMD in patients aged 5 years and older.

14.3 Benefits and Risks - Clinical Safety

Ataluren was well tolerated by patients with nmDMD at the proposed recommended dose of 10, 10, 20 mg/kg, as well as at the higher dose of 20, 20, 40 mg/kg, when taken daily for 48 weeks in the Phase 2b placebo controlled study (Study 007). Most adverse events were mild or moderate, transient, and did not require medical intervention. None of the patients discontinued treatment because of adverse events. Few serious adverse events were reported, none was attributed to ataluren, and no deaths occurred.

The adverse-event profile of ataluren was comparable to that of placebo. Vomiting, headache, diarrhea, nasopharyngitis, pyrexia, cough, and upper abdominal pain were the most commonly

reported adverse events in the placebo, ataluren 10, 10, 20 mg/kg, and ataluren 20, 20, 40 mg/kg treatment arms. Many of the reported adverse events were those that are typically associated with pediatric illnesses.

In Study 007, no clinically meaningful effects of ataluren, at either dose level, were observed in clinical laboratory assessments, vital signs, physical examinations, or ECGs. Six patients – all receiving corticosteroids - had hypertension (or increased blood pressure) reported as adverse events (0 for ataluren 20, 20, 40 mg/kg, 5 for ataluren 10, 10, 20 mg/kg, and 1 for placebo). In this study, mean total cholesterol and triglycerides were in the upper range of normal at baseline and increased, reaching borderline high or high values. The values tended to stabilize early in the study and did not increase further with continued treatment. Small increases in mean serum creatinine, BUN, and cystatin C were observed. Similarly, the values tended to stabilize early in the study and did not increase further with continued treatment.

The safety profiles observed in other nmDMD studies and in nmCF studies were generally similar to that observed in Study 007. Renal adverse reactions, primarily creatinine elevations, occurred more frequently in nmCF than in nmDMD, in particular with concomitant administration of IV aminoglycosides.

Based on evidence of decreased renal function in patients with nmCF who received coadministration of ataluren and IV aminoglycosides, ataluren should not be coadministered with IV aminoglycosides. Since some of the cases of decreased renal function were also associated with dehydration, patients receiving ataluren are encouraged to maintain adequate hydration.

Collectively, the safety data from clinical trials demonstrate that ataluren has a favorable safety profile for the treatment of patients with nmDMD.

14.4 Benefit/Risk Conclusions

An urgent unmet medical need exists for a therapy that addresses the underlying cause of nmDMD, a condition for which no approved treatment exist. Ataluren 10, 10, 20 mg/kg represents the first disease-modifying therapy for this severely disabling, progressive, and, ultimately fatal disease.

This is one of the largest studies ever conducted in DMD. Moreover, Study 007 was a well designed placebo controlled study conducted with excellent compliance and with high quality. The pre-specified and clinically meaningful target of a 30 meter difference in the primary endpoint, 6MWD, was achieved. The study approached statistical significance in the primary endpoint after necessary correction of baseline data and refinement of the statistical analysis. Furthermore, ataluren demonstrated slowing of disease progression in several outcome measures. The positive trends in the analysis of percent of patients whose 6MWD progressed by Week 48, as well as in many secondary endpoints, support the clinical benefit of ataluren treatment in nmDMD.

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APPENDIX A. DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th World Medical Association General Assembly Helsinki, Finland, June 1964 and amended by the 29th World Medical Association General Assembly, Tokyo, Japan, October 1975 35th World Medical Association General Assembly, Venice, Italy, October 1983 41st World Medical Association General Assembly, Hong Kong, September 1989 48th World Medical Association General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd World Medical Association General Assembly, Edinburgh, Scotland, October 2000

A. Introduction

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the etiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will

not benefit personally from the research and for those for whom the research is combined with care.

9. Research investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. Basic Principles for All Medical Research

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, PTC Therapeutics, or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any SAEs. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to

outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
11. The subjects must be volunteers and informed participants in the research project.
12. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.
13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the

research should be obtained as soon as possible from the individual or a legally authorized surrogate.

18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. Additional Principles for Medical Research Combined with Medical Care

19. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.
20. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
21. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
22. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
23. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgment it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.