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CLINICAL PROTOCOL

A PHASE 3 EXTENSION STUDY OF ATALUREN (PTC124) IN PATIENTS WITH NONSENSE MUTATION CYSTIC FIBROSIS

Protocol Number PTC124-GD-021e-CF

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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
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
ß-HCG	Beta human chorionic gonadotropin
BMI	Body mass index
BCRP	Breast Cancer Resistant Protein
BUN	Blood urea nitrogen
cAMP	Cyclic adenosine monophosphate
CD-ROM	Compact disc read-only memory
CF	Cystic fibrosis
CFQ-R	Cystic Fibrosis Questionnaire-Revised
CFR	Code of Federal Regulations
CFFT-TDN / CF-TDN	Cystic Fibrosis Foundation Therapeutics - Therapeutic Development Network
CFTR	Cystic fibrosis transmembrane conductance regulator
cGMP	Current Good Manufacturing Practices
CI	Confidence interval
CK	Creatine kinase
CRF	Case report form
CRO	Contract research organization
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DIOS	Distal intestinal obstruction syndrome
DMC	Data monitoring committee
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAMA	Food and Drug Modernization Act of 1997
FEF_{25-75}	Forced expiratory flow between 25% and 75% of expiration
FEV_1	Forced expiratory volume in 1 second
FVC	Forced vital capacity
GCP	Good Clinical Practices
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
HDL	High-density lipoprotein
HRQL	Health-related quality of life
ICH	International Conference on Harmonization
IL-8	Interleukin 8
IND	Investigational New Drug (Application)
ICJME	International Committee of Medical Journal Editors
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IVR/IWR	Interactive Voice Response/Interactive Web Response
LABA	Long-acting beta agonist
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
LS	Least square
MCID	Minimal clinically important difference

Abbreviation	Definition
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified intention-to-treat
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
nmCF	Nonsense mutation cystic fibrosis
nmDBMD	Nonsense mutation Duchenne/Becker muscular dystrophy
NOAEL	No-observed-adverse-effect level
PK	Pharmacokinetic(s)
PTCAD	PTC Therapeutics Awareness Date
PTC124	Ataluren
SABA	Short-acting beta agonist
TID	3 times per day
TIS	Tobramycin inhalation solution
TEPD	Transepithelial Potential Difference
ULN	Upper limit of Normal

1. OVERVIEW

Cystic fibrosis (CF) is a disabling and life-threatening genetic disorder resulting from mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR), an apical cell-surface epithelial chloride channel that promotes chloride efflux. CFTR dysfunction leads to epithelial mucous dehydration and viscous secretions, often causing chronic neutrophilic inflammation, occlusion of respiratory airways, and persistent pulmonary infections. Obstruction of pancreatic ducts, biliary tree, and vas deferens can occur. Patients typically develop progressive respiratory obstruction, coughing, dyspnea, and episodic infectious pulmonary exacerbations. They may have pancreatic insufficiency, diminished body weight, chronic hepatobiliary inflammation, and male infertility. Respiratory failure is the most common cause of death. Available medical therapies for treatment of the lung manifestations include inhaled aztreonam lysine, colistin, tobramycin (TOBI®), dornase alfa (Pulmozyme®), and hypertonic saline; and oral azithromycin and ibuprofen. Kalydeco, a recently approved potentiator for the G551D Class III mutation, does not address the underlying cause for patients with CF due to nonsense mutation (nmCF) (US Food and Drug Administration, 2013), one of the most severe forms of CF [Shoshani 1992, Cystic Fibrosis Genotype-Phenotype Consortium 1993, Kerem 1996, de Gracia 2005, McKone 2006].

In ~10% of patients with CF, the causative defect in the CFTR gene is a nonsense mutation that truncates CFTR protein production by introducing a premature stop codon into the CFTR messenger ribonucleic acid (mRNA). PTC Therapeutics, Inc., a biopharmaceutical company located in South Plainfield, NJ, USA has discovered and developed ataluren (PTC124®) as 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 for whom a nonsense mutation causes CF. Pharmacologic proof-of-concept has been demonstrated in animal models and Phase 2 clinical trials. A Phase 3, randomized, double-blind, placebo controlled clinical trial (Study 009) of patients ≥6 years of age with nmCF randomized to receive ataluren 10 mg/kg in the morning, 10 mg/kg mid-day and 20-mg/kg in the evening; or placebo for 48 weeks showed positive trends favoring ataluren vs placebo for both the primary endpoint, relative change in %-predicted forced expiratory volume in 1 second (FEV_1) at Week 48, and the secondary endpoint, pulmonary exacerbation rate over 48 weeks [Kerem 2014]. A subgroup effect in FEV_1 and pulmonary exacerbation rate showing larger differences favoring ataluren was observed in patients who were not receiving chronic inhaled antibiotics, which was driven by chronic inhaled tobramycin. This same study showed that ataluren was well tolerated; safety profiles were generally similar for ataluren and placebo, other than cases of reversible Grade 3-4 creatinine elevations, which were associated with the combination of potentially nephrotoxic antibiotics with ataluren.

These encouraging data led to the conduct of a confirmatory Phase 3, international, multicenter, randomized, double-blind, placebo-controlled, efficacy and safety study (Study PTC124-GD-021-CF). This ongoing Phase 3 study includes a treatment period of 48 weeks and an estimated recruitment period of 14 months at 93 investigational sites worldwide. The first patient in study PTC124-021-CF initiated study drug treatment on 15 August 2014.

All patients who successfully complete the Phase 3 double-blind, placebo-controlled study (PTC124-GD-021-CF) will be eligible for this Phase 3 open-label, extension study (PTC124-GD-021e-CF).

The primary objective of this Phase 3 extension study will be to obtain long-term safety data to augment the overall safety database. The secondary objectives will be to augment the efficacy data collected in the double-blind study (PTC124-GD-021-CF).

Screening and baseline procedures are structured to avoid a gap in treatment between the double-blind study (PTC124-GD-021-CF) and this extension study. When possible, Screening/Baseline (Visit 1) for this extension study should occur on the same day as the End-of-Study visit for the double-blind study (PTC124-GD-021-CF). During the treatment period, study assessments will be performed at clinic visits at Week 12 and thereafter every 12 weeks until the end of the study.

Planned interim safety analyses will be conducted by an independent data monitoring committee (DMC). The first safety review will occur when ~100 patients have completed >=36 weeks of treatment. The second safety review will occur when ~100 patients have completed >=72 weeks of treatment.

2. INTRODUCTION

2.1. Disease Indication

CF is one of the most common serious inherited diseases in the United States and Europe, with a prevalence estimated at ~30,000 patients in the United States and ~37,000 patients in Europe [Farrell 2008]. CF is an autosomal recessive disorder caused by defects in the gene for the CFTR, a protein that acts as a chloride channel and is regulated by cyclic adenosine monophosphate (cAMP) [Cheng 1991]. Loss of functional CFTR at membranes leads to abnormalities of cAMP-regulated chloride transport across epithelial cells on mucosal surfaces [O'Sullivan 2009]. The disruption of chloride transport, together with associated water transport abnormalities, results in viscous secretions in the respiratory tract, pancreas, gastrointestinal tract, sweat glands, and other exocrine tissues. Increased viscosity of these secretions makes them difficult to clear and patients develop exocrine gland dysfunction of multiple organ systems in childhood, resulting in chronic respiratory disease, pancreatic enzyme insufficiency, hepatic and biliary abnormalities, intestinal obstruction, and reduced fertility due to agenesis of the vas deferens in males and delayed menarche in females.

In the face of symptoms and/or a family history, the diagnosis of CF is based on evaluation of chloride secretion in sweat or on assessment of nasal transepithelial potential difference (TEPD) [Stern 1997, LeGrys 2000]. Total sequencing of the CFTR gene to confirm the presence of mutations is now available commercially [Ambry Genetics 2001, Danziger 2004].

Pulmonary involvement occurs in ~90% of patients, is usually among the most serious manifestations of the disease, and most commonly determines outcome [Ramsey 1996]. As early as 4 weeks of age, patients with CF begin to develop mucus plugging, bronchiectasis, neutrophilic invasion, and inflammation of airways [Khan 1995, Rosenfeld 2001]. High levels of the neutrophil chemoattractant interleukin-8 (IL-8) in the airways and sputum contribute to persistent neutrophilic inflammation and airway obstruction [Sagel 2007]. Over time, most patients develop chronic bacterial colonization/infection of the airways (characteristically with *Pseudomonas aeruginosa*, but also with *Burkholderia cepacia, Haemophilus influenzae*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and atypical mycobacterial species) resulting in infections and pulmonary dysfunction. Typically, CF pulmonary involvement manifests as an obstructive defect with air trapping and hyperinflation [Ramsey 1996, Tiddens 2002]. As the disease progresses, FEV_1 is reduced; it is estimated that FEV_1 declines by 1.9% per year in children and adolescents [FDA 1997]. Ultimately, chronic mucopurulent bronchiectasis leads to structural abnormalities and fibrosis, and the total lung capacity and forced vital capacity (FVC) decline. Progressive lung dysfunction leads to respiratory failure and death. The median age of survival is projected to be ~35 years of age if all genotypes are considered [Cystic Fibrosis Foundation 2003, Bellis 2006], but survival is generally shorter in patients with severe phenotypes [McKone 2006].

The primary goals of CF treatment are supportive, and include slowing the decline in lung function by clearing airways of mucus and by controlling respiratory infections, and maintaining nutritional status by providing pancreatic enzyme replacement therapy [Welsh 2001]. The first medical therapy approved by regulatory authorities for treatment/prophylaxis of the lung manifestations was dornase alfa (Pulmozyme®), a mucolytic enzyme that hydrolyzes neutrophil deoxyribonucleic acid (DNA) [Fuchs 1994]. Since that time, regulatory approval has been achieved for inhaled tobramycin (TOBI®) [Ramsey 1993, Ramsey 1999] and inhaled aztreonam

[Retsch-Bogart 2007, McCoy 2008, Oermann 2008, Retsch-Bogart 2008], antibiotics that suppress *Pseudomonas* colonization. Inhaled colistin and oral cephalosporins or fluoroquinolones are sometimes employed to reduce respiratory complications related to bacterial infection [Bell 2007]. Intravenous antibiotics are often administered in response to CF pulmonary exacerbations [Smyth 2008]. Clinical trial data from randomized studies also indicate that oral ibuprofen, oral azithromycin, and inhaled hypertonic saline have salutary effects on lung dysfunction and pulmonary complications [Konstan 1995, Saiman 2003, Elkins 2006].

Despite the advances in care offered by these types of drugs, and the recent approval of ivacaftor (Kalydeco®), a drug that targets the G551D gating mutation, there are no approved systemic therapies that address the underlying cause of CF caused by other mutations, such as premature stop codons. New agents are therefore needed that can overcome the fundamental genetic defect by restoring CFTR production and function.

2.2. Ataluren (PTC124)

2.2.1. Therapeutic Concept

Among the several types of disease-causing mutations, a nonsense mutation is an alteration in one of the nucleotides of 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 CFTR tells the ribosomes to halt production of the protein before the full-length protein is completed. The resulting truncated CFTR is too short to serve its necessary function and causes disease. It is estimated that nonsense mutations account for ~10% of the individual cases of CF [Bobadilla 2002, Du 2002, Cystic Fibrosis Genetic Analysis Consortium 2004, Bellis 2006], resulting in a prevalence of nonsense mutation-mediated disease of ~2800 patients in the United States and ~3600 patients in Europe (total ~6400 patients). However, in certain populations, the incidence of this type of mutation is much higher. For example, in Ashkenazi Jews, nonsense mutations (eg, R553X, G542X, or W1282X) account for ~65% of all abnormal CFTR alleles [Kerem 1995, Kerem 1997]. In CF, the presence of a nonsense mutation in the CFTR gene leads to little or no production of the CFTR chloride channel and has been associated with a particularly severe phenotype [Shoshani 1992, Cystic Fibrosis Genotype-Phenotype Consortium 1993, Kerem 1996, de Gracia 2005, McKone 2006].

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 clinical studies in nmCF, treatment with high concentrations of gentamicin has restored production of functional CFTR [Clancy 2001, Du 2002, Wilschanski 2003]. Similarly, preclinical and clinical studies in nonsense mutation Duchenne muscular dystrophy (nmDMD) have demonstrated gentamicin-induced restoration of dystrophin, the structural protein that is defective in that disease [Barton-Davis 1999, Politano 2003]. Current data suggest that the geometry of mRNA and associated initiation-termination proteins is critically different at a premature stop codon than at a normal stop codon. This may explain why a drug can permit the ribosomes to selectively read through the premature stop codon, but will not allow the ribosomes to read

through the normal stop codon at the end of the mRNA protein-coding region [Sachs 2000, Welch 2000, Amrani 2004]. Because serious renal and otic toxicities and the need for parenteral administration preclude the long-term clinical use of gentamicin, there has been considerable interest in the identification of safer and more conveniently administered, low-molecular-weight, synthetic compounds with the ability to promote readthrough of disease-causing nonsense mutations.

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

2.2.3. Nonclinical Studies

Refer to the Ataluren Investigator Brochure for a detailed presentation of efficacy pharmacology, safety pharmacology, toxicology, and PK data from ataluren nonclinical studies.

2.2.4. Clinical Studies

In total, ~700 patients, including healthy volunteers as well as patients with several nonsense mutation genetic disorders, have been exposed to ataluren in Phase 1 [Hirawat 2007], Phase 2 [Kerem 2008, Sermet-Gaudelus 2010, Wilschanski 2011, Finkel 2013] and Phase 3 [Kerem 2014, Bushby 2014] clinical studies. Refer to the Ataluren Investigator Brochure for a detailed presentation of safety, efficacy, and PK data from these clinical studies.

3. STUDY OBJECTIVE AND ENDPOINTS

3.1. Primary Objective

To evaluate the long-term safety of 10-, 10-, 20-mg/kg ataluren in patients with nonsense mutation cystic fibrosis (nmCF), who previously participated in pivotal study PTC124-GD-021-CF, as determined by adverse events and laboratory abnormalities.

3.2. Secondary Objectives

The secondary objectives are:

- To evaluate the long-term effect of ataluren on pulmonary function
- To evaluate the long-term effect of ataluren on pulmonary exacerbation
- To determine the long-term effect of ataluren on medical interventions
- To evaluate the long-term effect of ataluren on HRQL
- To evaluate the long-term effect of ataluren on general well-being
- To assess long-term ataluren plasma exposure

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

- Changes in FEV_1, FVC, and FEF_{25-75} as assessed by spirometry
- Rate, incidence, and duration of pulmonary exacerbations (modified Fuchs criteria)
- Incidences, rates, and durations of interventions (eg, antibiotic use and hospitalization) and disruptions to daily living (eg, missed school or work) resulting from pulmonary symptoms
- Changes in CFQ-R domains
- Changes in body weight and BMI
- New *Pseudomonas aeruginosa* lung infection
- Pre-dose ataluren plasma concentrations prior to morning ataluren administration at each clinic visit as assessed by a validated bioanalytical method
- Change from baseline in other safety parameters (eg, vital signs)

4. PATIENT SELECTION CRITERIA

4.1. Overview

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

4.2. Inclusion Criteria

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

1. Completion of study treatment (placebo or active) in the previous Phase 3, double-blind study protocol (Protocol PTC124-GD-021-CF).
2. Evidence of signed and dated informed consent/assent document(s) indicating that the patient (and/or his parent/legal guardian) has been informed of all pertinent aspects of the trial. ***Note: If the study candidate is considered a child under local regulation, a parent or legal guardian must provide written consent prior to initiation of study screening procedures and the study candidate may be required to provide written assent. The rules of the responsible Institutional Review Board/Independent Ethic Committee (IRB/IEC) regarding whether one or both parents must provide consent and the appropriate ages for obtaining consent and assent from the patient should be followed.***
3. In patients who are sexually active, willingness to abstain from sexual intercourse or employ a barrier or medical method of contraception during the study drug administration and 4-week follow-up period.
4. Willingness and ability to comply with scheduled visits, ataluren administration plan, study procedures, laboratory tests, and study restrictions.

4.3. Exclusion Criteria

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

1. Known hypersensitivity to any of the ingredients or excipients of the study drug (Litesse® UltraTM [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).
2. Ongoing participation in any other therapeutic clinical trial.
3. Prior or ongoing medical condition (eg, concomitant illness, psychiatric condition, behavioral disorder, alcoholism, drug abuse), medical history, physical findings, ECG findings, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the patient, makes it unlikely that the course of treatment or follow-up would be completed, or could impair the assessment of study results.

5. ENROLLMENT PROCEDURES

5.1. Source and Number of Patients

Approximately 200 patients for this Phase 3 extension study are derived only from those who completed blinded study drug in the Phase 3 study (PTC124-GD-021-CF).

5.2. Screening and Study Drug Allocation

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

The patient number used in the prior Phase 3 study (Protocol Number PTC124-GD-021-CF) shall be retained for use in this study. This patient number must be used for patient identification on all study-related documents (case report forms [CRFs], clinic notes, laboratory samples, etc).

The user will need to supply the Interactive Voice Response/Interactive Web Response (IVR/IWR) system with the information required by the system (eg, site number, patient number).

6. STUDY DRUG ADMINISTRATION

6.1. Investigational Product

6.1.1. Ataluren (PTC124)

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

6.1.2. Drug Kits

Drug kits will be provided, each of which contains 120 sachets of one of the dose strengths (125, 250, or 1000 mg.).

6.1.3. Study Drug Packaging and Labeling

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

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

6.1.4. Study Drug Dispensing

Dosing of ataluren will be based on milligrams of drug per kilogram of patient body weight at Screening/Baseline (Visit 1) and will be adjusted to allow for dosing with the available sachet dose strengths. All subjects will receive approximately 10-, 10-, 20-mg/kg ataluren TID for ~96 weeks. The sachet dosage strengths and number of sachets to be taken per dose will be provided by the IVR/IWR system.

The clinic staff (eg, pharmacist or other qualified person) will be responsible for dispensing study drug according to the IVR/IWR system directions. Sufficient study drug will be provided for each study period at the beginning of the period.

Because of potential changes in subject body weight over time, at Week 24 (Visit 3) and Week 60 (Visit 6), the possibility of a dose adjustment will be evaluated based on the subject's body weight at that visit. Depending upon the magnitude of change in subject body weight since baseline, the number and strengths of sachets to be used by the subject may remain the same or may be adjusted.

6.1.5. Return of Study Drug

Patients should return all remaining study drug (all unused sachets) to the study site at the end of each 12-week treatment period for inventory. The Subject Study Drug Accountability Log 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

Kits containing sachets of study drug will be stored at room temperature (~15 to 30°C). The available stability data from representative samples support the use of the drug product for 48 months when stored at room temperature. The stability of the clinical study samples or representative samples will be monitored to support the clinical study, as necessary.

6.1.7. Study Drug Accountability

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

The investigator and/or the responsible site personnel must maintain accurate records of the receipt of all study drug shipped by PTC Therapeutics or its designee, including, but not limited to, the date received, lot number, amount received, and the disposition of all study drug. Current reconciliation and dispensing records must also be maintained that include the date and amount of drug dispensed, and patient'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 patient experiencing an overdose (administration of a study drug 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 must be contacted if an overdose occurs. Under applicable regulations, overdosing may be considered an SAE and should be reported accordingly (see Sections 9.1.1 and 9.1.2).

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 Treatment

In this study, treatment will comprise continuous daily treatment with ataluren for up to 96 weeks (~2 years). This study may be further extended by amendment until either ataluren

becomes commercially available or the clinical development of ataluren in nmCF is discontinued.

6.2.2. Schedule of Administration

As noted in Table 1, 3 doses should be taken per day – the 1st dose in the morning, the 2nd dose during the middle of the day (mid-day), and the 3rd dose in the evening. Ideally each dose should be taken within ~30 minutes before or after a meal (eg, ~7:00 AM after breakfast, ~1:00 PM after lunch, and ~7:00 PM after dinner). Intervals for dosing should be ~6 hours (±1 hour) between morning and mid-day doses, ~6 hours (±1 hour) between mid-day and evening doses, and ~12 hours (±1 hour) between evening doses and the morning dose on the next day. While it is realized that variations in dosing schedule may occur in the outpatient setting, the prescribed regimen (including dosing intervals and the relationship of dosing to meals) should be followed closely on the day preceding PK sample collection in the clinic.

Table 1. Suggested Daily Dosing Schedule

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

a Dosing times are examples and may be varied to suit each patient'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 patient experiences a delay in the administration of study drug of ≤1 hour, the planned dose should be taken with no changes to the subsequent dose schedules. For a patient 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 patient who has a delay in administration of study drug of >4 hours, the dose should not be taken. Study drug administration may continue but the missed dose should not be made up and the planned timing of subsequent study drug dosing should not be altered.

6.2.4. Study Drug Preparation and Storage

Study drug sachets should be stored at room temperature, away from the reach of children until time of reconstitution and should only be opened at the time of dose preparation. The powder in the sachet may be mixed with water, milk (skim, 1% fat, 2% fat, whole milk, chocolate milk,

soy, or lactose free milk), or in semi-solid food (yogurt, pudding, or applesauce). The full contents of the sachets should be mixed with at least 30 mL (1 ounce) of liquid (water, milk [skim, 1% fat, 2% fat, whole milk, chocolate milk, or lactose-free milk], or 3 tablespoons of semi-solid food (yogurt, pudding, or applesauce). The prepared dose should be mixed well before administration. The amount of the liquid or semi-solid food can be increased based on patient preference.

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

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

6.3. Safety Monitoring and Study Drug Dose Interruption/Modification

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

Patients must be monitored closely for 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 study drug 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.

Table 2 provides information on actions to be taken in the event that abnormalities are noted in specified laboratory parameters. Thresholds are provided for interrupting study drug immediately, for interrupting study drug after confirmation of a value beyond the threshold, or for continuing study drug while evaluating for potential drug-related toxicity. For adverse events or laboratory abnormalities not listed in Table 2, the investigator should use his/her judgment in determining whether the event or abnormality is clinically significant, whether diagnostic evaluation is warranted, and whether potential interruption of study drug is appropriate.

Table 2. 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[a]	Stop Study Drug After Confirming Abnormal Value, and Then Start Work-Up[a]	Continue Study Drug, Confirm Abnormal Value, and then Start Work-Up[a]
Hepatic			
Serum total bilirubin[b]	≥Grade 3 (≥3.0 x ULN)	Grade 2 (1.5 – 3.0 x ULN)	---
Serum ALT	≥Grade 3 (≥5.0 x ULN)	Grade 2 (>2.5 – 5.0 x ULN)	---
Serum AST	≥Grade 3 (≥5.0 x ULN)	Grade 2 (>2.5 – 5.0 x ULN)	---
Serum GGT	≥Grade 3 (≥5.0 x ULN)	Grade 2 (>2.5 – 5.0 x ULN)	---
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	---

[a] Laboratory abnormalities may be confirmed immediately or at the next scheduled clinic visit based on investigator judgment.
[b] Patients with a diagnosis of Gilbert's syndrome need not confirm the laboratory parameter and/or stop study drug unless the total bilirubin value exceeds 3.0 x ULN.
Abbreviations: ALT = alanine aminotransferase, AST = aspartate aminotransferase, BUN = blood urea nitrogen, GGT = gamma glutamyl transferase, ULN = upper limit of normal

It should be noted that blood samples for cortisol, renin and aldosterone determinations will be obtained at screening, and, as necessary during the study, for patients with treatment-emergent evidence of adrenal dysfunction.

6.3.2. Evaluation of Adverse Events or Laboratory Abnormalities

While specific monitoring, diagnostic testing, and supportive care measures must be instituted based on the clinical judgment of the investigator, investigators are encouraged to contact either the PTC Therapeutics medical monitor (or designee) to obtain guidance and to ascertain whether similar events are being seen at other 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 or nephrology consultants or with other experts (either at the site or retained by PTC Therapeutics).

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

- **Hepatic:** The medical history, hepatitis screening results, all clinical blood values (particularly serum bilirubin, 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.
- **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.

Laboratory evaluation for adrenal function (cortisol, renin and aldosterone) will be performed at screening to determine normal clinical function. The results of placebo-controlled clinical trials with ataluren in nmCF and nmDBMD showed no meaningful imbalances in adrenal laboratory assessments between the ataluren and placebo arms; therefore, regular monitoring of function is not warranted and will not be performed routinely during study participation. However, adrenal function (via these or other parameters) may be tested in patients with evidence of adrenal dysfunction as clinically indicated.

The incidence of new onset nephrolithiasis was similar in both the ataluren and placebo arm in the previous double-blind study (4.2% on ataluren vs 3.4% on placebo). All cases involving the diagnosis of urinary tract calculi should be reported as adverse events of special interest to the CRO Pharmacovigilance Unit (see Section 9.1.2). Once it has been documented that a patient has symptomatic nephrolithiasis, determining the type of stone and the possible presence of either biochemical abnormalities or underlying conditions that predispose to stone formation are essential for guiding therapy to prevent recurrent disease. Patients should be encouraged to retrieve stones they pass or have removed for analysis. Analysis of the stone is an essential part of the evaluation. All patients presenting with their first stone should undergo a focused history, radiologic imaging, and at least a limited laboratory evaluation. A complete metabolic evaluation, in addition to the basic laboratory testing, is indicated in all patients with multiple stones at first presentation, in patients with a strong family history of stones, and in individuals with active stone disease, which is defined as recurrent stone formation, enlargement of existing stones, or the recurrent passage of gravel. The purpose of the focused history is to identify stone risk factors, such as a family history of stone disease and certain dietary habits. Adverse dietary habits include:

- Low fluid intake or a high fluid loss (eg, from sweating or gastrointestinal losses), which leads to a lower urine output and, therefore, a higher concentration of lithogenic factors.
- Higher animal protein diet, which can lead to hypercalciuria, hyperuricosuria, hypocitraturia, and elevated urinary acid excretion.
- Higher salt diet, which increases urinary calcium excretion.
- Increased intake of higher oxalate-containing foods, particularly spinach (the exact contribution of dietary oxalate to urinary oxalate is controversial and likely varies considerably from person to person).
- Lower calcium intake, which acts by increasing the absorption and subsequent excretion of oxalate due to decreased calcium oxalate complex formation within the intestinal lumen [Curhan 1997, von Unruh 2004]. The effect on oxalate more than counterbalances the decrease in calcium absorption and excretion.
- Excessive vitamin C and D supplementation.
- Excessive sugar (fructose) intake, which may increase calcium and/or oxalate excretion.

Because the risk of nephrolithiasis is influenced by urine composition, which can be affected by certain diseases and patient habits, a thorough clinical history and analysis of urine composition should be completed. For calcium oxalate stones, urinary risk factors include hypercalciuria, hyperoxaluria, hypocitraturia, and dietary risk factors such as a low calcium intake, high oxalate intake, high animal protein intake, high sodium intake, or low fluid intake. The patient should be

evaluated for possible underlying causes of stone disease, including hypercalcemia, hypercalciuria, hyperuricosuria, hypocitraturia, hyperoxaluria, and urine volume.

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

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

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

For hepatic or renal events (refer to Table 2), 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 re-institute study drug treatment. If the investigator considers the hepatic or renal event that led to study drug interruption to be probably related to study drug, restarting study drug is not advised. In this case, the patient should be discontinued from the study (see Sections 6.3.4 and 10). If the investigator considers the hepatic or renal event that prompted study drug interruption to be possibly related or unlikely related to study drug, the investigator should use best judgment in determining whether to restart study drug. If the hepatic or renal event is considered unrelated to study drug, re-institution of study drug is recommended.

If the investigator believes it is appropriate, after consultation with the PTC Therapeutics medical monitor , study drug may be re-initiated. If the event was determined to be unrelated to study drug, the treatment may be resumed at full dose. Otherwise, if the drug is resumed, it may be initially re-initiated at half of the original dose. If a patient cannot tolerate the full dose within 30 days of dosing re-initiation, then the patient is to be discontinued from study participation.

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

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

If after appropriate consideration of study drug interruption/modification and consultation with the PTC Therapeutics medical monitor, it is not appropriate for a patient to continue with study treatment, then study drug should be permanently discontinued. After permanent discontinuation of study drug for a safety concern, and if the initial event was reported as a SAE, then the SAE portion of the CRF should be updated. 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 ~4 weeks as per protocol or until recovery from or stabilization of the adverse event, whichever comes last) should be instituted.

7. CONCOMITANT AND SUPPORTIVE THERAPY

7.1. Concomitant Medications

Other than the study drug, any treatments (including prescription and non-prescription drugs, health foods, herbal remedies, self-prescribed drugs, street drug, tobacco products, or alcohol) taken by a patient during the screening period, during study drug administration, and for 4 weeks after discontinuation of study drug are considered concomitant medications. Information regarding all concomitant medications will be collected and documented in the concomitant medication page of the CRF.

7.1.1. Therapy/Prophylaxis for CF-Related Conditions

Study patients may receive existing therapy/prophylaxis for treatment of CF or CF-related conditions. To the extent possible, changes in drug regimens should be avoided because this may confound interpretation of study results. The decision to authorize the use of any drug other than ataluren should take into account patient safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more relevant underlying event, and whether use of a concomitant medication will compromise the outcome or integrity of the study.

For patients who are not on a particular type of CF-specific therapy/prophylaxis (eg, dornase alfa, hypertonic saline oral azithromycin or ibuprofen), initiation of such therapy/prophylaxis during ataluren treatment is discouraged unless there is a strong medical need. For patients who are on CF-specific therapy/prophylaxis at baseline, a stable regimen should be maintained during the 96 weeks of ataluren treatment. Adjustments in dosage or type of drug are permitted to avoid symptoms, but attempts should be made to avoid entirely removing or substituting CF treatments. However, patients who do require initiation, interruption, dose modification, or substitution of CF treatment may remain on ataluren therapy.

7.1.2. Therapy for CF Pulmonary Exacerbations or Other CF Complications

Patients should receive appropriate antibiotic or other therapy for CF pulmonary exacerbations or other CF-related complications (eg, DIOS) consistent with local best practices and guidelines. For patients requiring systemic antibiotic therapy, IV aminoglycosides may be used when medically necessary. However, given ataluren's ribosomal mechanism of action, and the possibility of aminoglycosides exhibiting a confounding effect upon study results, investigators should substitute other antibiotics for systemic aminoglycosides in patients who require treatment for serious infections whenever possible. For such severe infections, consideration should be given to use of appropriate alternative anti-pseudomonal agents including macrolide and glycopeptide antibiotics. Patients requiring IV therapy with an aminoglycoside or glycopeptide antibiotic (eg, vancomycin), should be closely monitored in an appropriate setting. Particular caution should be used for patients with a previous history of clinically significant creatinine elevations. Based on the increased incidence of creatinine elevation in patients treated with IV aminoglycosides and/or vancomycin, concomitant use of these medications with ataluren is contraindicated. If nephrotoxic antibiotics (eg, tobramycin or vancomycin) are administered, ataluren treatment must be interrupted for the duration of IV antibiotic treatment. In patients receiving any type of potentially nephrotoxic antibiotics, antibiotic drug levels, and renal function should be closely monitored. Creatinine and BUN should be measured prior to initiating IV aminoglycosides or other potentially nephrotoxic therapy, and at least twice a week during the course of such antibiotic treatment. The antibiotic trough level, 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 also be measured at intervals during the course of antibiotic treatment.

Additionally, patients should be adequately hydrated prior to receiving potentially nephrotoxic IV antibiotics, 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, fever, or who have laboratory evidence of dehydration. Treatment with ataluren may be resumed no earlier than 2 days after administration of nephrotoxic antibiotics has ceased.

In patients receiving non-nephrotoxic systemic antibiotics, creatinine and BUN should be measured at least once per week during the course of treatment for a pulmonary exacerbation.

It should be emphasized to patients/caregivers that they must always carry with them the existing 24-hour emergency card for the study to enable non-study physicians providing care at local hospitals or emergency facilities to communicate with the investigational site to ensure that appropriate supportive care and monitoring recommendations are followed.

Information regarding the types and durations of intervention for CF pulmonary exacerbations should be recorded on source documents and will be specifically collected in the CRFs in support of both the safety and efficacy analyses of the study.

Chronic use of inhaled aminoglycosides (eg, tobramycin and gentamicin) is prohibited during study participation based on the results of Study 009, although short regimens (up to 3 months total) are permitted for eradication of newly acquired *Pseudomonas aeruginosa* infection but must be completed during the first 12 weeks of treatment. However, eradication protocols with alternative antibiotics should be considered. Patients requiring *Pseudomonas aeruginosa* eradication protocols including inhaled tobramycin in the last 12 weeks of the study must be withdrawn from study participation. Start and stop dates for all inhaled antibiotics used during the study must be captured in the eCRF. If there is a time gap between the end of the pivotal 021 study and this 021 extension of longer than one month, the participating subjects must have been off inhaled tobramycin at least 4 weeks prior to screening into 021e.

7.1.3. 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. Patients should be discouraged from use of "health supplements" (eg, creatine, glutamine, coenzyme Q), herbal remedies, growth hormone, self-prescribed drugs, street drugs, tobacco products, or alcohol at any time during the study. Caution should be exercised during concomitant use of study drug and potentially nephrotoxic agents.

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

Patients/caregivers should be instructed about the importance of informing 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 patient during the course of the study and the reason for use will be recorded in the source documents and in the concomitant medication CRF.

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.

7.1.4. 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.

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. 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.

7.1.5. 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, geftinib).

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.

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

7.2. Non-Drug Therapy

7.2.1. Physical and Respiratory Therapy

There are neither restrictions nor prescriptions for physical or respiratory therapy during the study. Sites should use local best practices in providing physical therapy support for patients participating in the study. Respiratory care guidelines as suggested by the American Thoracic Society/European Thoracic Society should be followed [Miller 2005a, Miller 2005b]. If changes in the physical or respiratory therapy regimen are planned, sites are encouraged to initiate these changes prior to enrollment and to maintain the same general level of support throughout the duration of the study.

7.2.2. Dietary Restrictions

There are no specific dietary restrictions in the study.

7.2.3. Hydration

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

8. SCHEDULE OF EVENTS AND STUDY PARAMETERS

8.1. Schedule of Events

The proposed types and timing of data to be recorded are described in Table 3. Please see Section 8.2 for cross-referenced explanations of the study procedures described in the tables.

Table 3. Schedule of Events

Study Period	Screening/ Baseline	Treatment Period							Post-Treatment	
Study Week (±7 days)	Day 1	12	24	36	48	60	72	84	End of Tx/ Premature D/C 96	4 Weeks Post-Tx
Visit	1	2	3	4	5	6	7	8	9	10
Informed consent	X									
CFQ-R administration	X[a]	X	X	X	X	X	X	X	X	
Vital signs	X[a]	X	X	X	X	X	X	X	X	X
Height	X[a]	X	X	X	X	X	X	X	X	X
Weight	X[a]	X	X	X	X	X	X	X	X	X
Physical examination	X[a]				X				X	X
Hematology	X[a]	X	X	X	X	X	X	X	X	X
Biochemistry	X[a]	X	X	X	X	X	X	X	X	X
Urinalysis	X[a]	X	X	X	X	X	X	X	X	X
Renal ultrasound	X[a]				X				X	
12-lead ECG	X[a]				X				X	X
Study drug assignment	X									
Drug dispensed	X	X	X	X	X	X	X	X		
Drug compliance		X	X	X	X	X	X	X	X	
Adverse events	X	X	X	X	X	X	X	X	X	X
Concomitant medication	X	X	X	X	X	X	X	X	X	X
Spirometry	X[a]	X	X	X	X	X	X	X	X	X
Respiratory event evaluation[b]	X[a]	X	X	X	X	X	X	X	X	
P. aeruginosa in sputum	X[a]	X	X	X	X	X	X	X	X	
Pharmacokinetics			X		X		X		X	

[a] Study procedure need not be performed if Day 1 is within 14 days of the end of study evaluations at Week 48 (Visit 8) of the preceding Phase 3 double-blind study (PTC124-GD-021-CF). If Day 1 is >14 days from the end of study visit, study procedure must be performed; however, it is not required to assess serum electrolytes, urine protein; urine creatinine ratio (spot sample), or urine blood (by dipstick).
[b] Includes completion of the Respiratory Event Form.
[c] **Abbreviations**: D/C = discontinuation; ECG = electrocardiogram; F/U = follow up; Tx = treatment

8.2. Explanation of Study Procedures

8.2.1. Transition from the Phase 3 Study, Ataluren Treatment, and Follow-up Periods

Every effort should be made to conduct the Screening/Baseline visit (Visit 1) on the day of the End-of-Treatment visit (Visit 8/Week 48) of the Phase 3 double-blind study (PTC124-GD-021-CF) to avoid interruption in treatment with study drug. Signature of the informed consent/assent document(s) for this study should be obtained after completion of the study procedures at the End-of-Treatment visit (Visit 8/Week 48) of the Phase 3 double-blind study (PTC124-GD-021-CF).

8.2.2. Screening/Baseline Visit (Visit 1)

Following signature of the informed consent/assent document(s), the patient will complete the necessary screening evaluations. It should be noted that results from safety laboratory tests from End-of-Treatment visit (Visit 8/Week 48) of the Phase 3 study (PTC124-GD-021-CF) are not

required to determine eligibility. Patients who have been confirmed to be eligible by the investigator for this extension study should complete all Screening/Baseline (Visit 1) study procedures. Most of the data collected during the End-of-Treatment visit (Visit 8/Week 48) of the Phase 3 study (PTC124-GD-021-CF) can be utilized for the baseline assessments (see footnote "a" of Table 3. If the Baseline visit (Visit 1) is not completed within 14 days of the End-of-Treatment visit (Visit 8/Week 48) of the Phase 3 study (PTC124-GD-021-CF), all study procedures should be performed; however, it is not required to assess serum electrolytes, urine protein; urine creatinine ratio (spot sample), or urine blood (by dipstick).

After the completion of the baseline study procedures, a site representative should access the IVR/IWR system and supply the necessary information to obtain ataluren dosing instructions. The patient will remain at the clinic until ataluren supply for the next 12 weeks has been dispensed and the patient/caregiver has been instructed regarding ataluren storage, preparation, and administration.

8.2.3. Treatment Visits during Study (Visits 2 through 9)

Each patient will subsequently return to the clinical research facility during Week 12 (Visit 2), Week 24 (Visit 3), Week 36 (Visit 4), Week 48 (Visit 5), Week 60 (Visit 6), Week 72 (Visit 7), Week 84 (Visit 8), and Week 96 (Visit 9).

8.2.4. End of Treatment

The patient will return to the clinical research facility at Week 96 (Visit 9) for the End-of-Treatment visit. If the patient discontinues prematurely (ie, before Week 96), the procedures that would normally be performed at Week 96 should be performed as a Premature-Discontinuation Visit before the patient leaves the study.

8.2.5. Post-Treatment Visits

All patients who discontinue study drug must return for a Post-Treatment Visit at the investigator site 4 weeks (±7 days) after the last dose of study drug and the End of Treatment Visit, for final study-related evaluations. If the End-of-Treatment Visit occurs >4 weeks after the last dose of study drug, the Post-Treatment Visit does not need to be performed.

8.2.6. Informed Consent

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

8.2.7. Vital Signs

Vital signs (including systolic and diastolic blood pressure, pulse rate, pulse oximetry, and body temperature) will be monitored at Screening/Baseline on Visit 1, Week 12 (Visit 2), Week 24 (Visit 3), Week 36 (Visit 4), Week 48 (Visit 5), Week 60 (Visit 6), Week 72 (Visit 7), Week 84 (Visit 8), Week 96 (Visit 9 - End-of-Treatment/Premature Discontinuation), and at the Post-Treatment visit (4 weeks post discontinuation of study drug). The pulse rate and blood pressure determinations will be performed with the patient in a sitting position after a 5-minute rest.

8.2.8. Height, Weight, and Physical Examination

Height (in cm) and weight (in kg) will be measured at Screening/Baseline on Visit 1, Week 12 (Visit 2), Week 24 (Visit 3), Week 36 (Visit 4), Week 48 (Visit 5), Week 60 (Visit 6), Week 72 (Visit 7), Week 84 (Visit 8), Week 96 (Visit 9 - End-of-Treatment/Premature Discontinuation), and at the Post-Treatment visit (4 weeks post discontinuation of study drug).

A full physical examination (including general appearance, head, eyes, ears, nose, mouth, throat, heart, thyroid, chest and lungs, abdomen, extremities, neuromuscular system, skin, and lymph nodes) will be conducted at Screening/Baseline (Visit 1), Week 48 (Visit 5) and Week 96 (Visit 9 – End of Treatment/Premature Discontinuation) visit.

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

8.2.9. Pregnancy

Serum beta chorionic gonadotropin (β-HCG) will be measured at all study visits (females only).

8.2.10. 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/Baseline on Visit 1, Week 12 (Visit 2), Week 24 (Visit 3), Week 36 (Visit 4), Week 48 (Visit 5), Week 60 (Visit 6), Week 72 (Visit 7), Week 84 (Visit 8), Week 96 (Visit 9 - End-of-Treatment/Premature Discontinuation), and at the Post-Treatment visit (4 weeks post discontinuation of study drug). Hematology parameters will be analyzed by the central laboratory. The Central Laboratory Manual should be consulted for collection, processing, and shipping details.

8.2.11. 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 (total, direct and indirect), creatine kinase (CK), lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), alkaline phosphatase, total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, and cystatin C. These parameters will be measured at Screening/Baseline on Visit 1, Week 12 (Visit 2), Week 24 (Visit 3), Week 36 (Visit 4), Week 48 (Visit 5), Week 60 (Visit 6), Week 72 (Visit 7), Week 84 (Visit 8), Week 96 (Visit 9 - End-of-Treatment/Premature Discontinuation), and at the Post-Treatment visit (4 weeks post discontinuation of study drug). Patients should have fasted for at least 8 hours prior to blood collection. Biochemistry parameters will be analyzed by the central laboratory. The Central Laboratory Manual should be consulted for collection, processing, and shipping details.

8.2.12. Urinalysis

Urinalysis will include analysis for pH, specific gravity, glucose, ketones, blood, protein, creatinine, urobilinogen, bilirubin, nitrite, and leukocyte esterase. These parameters will be measured at Screening/Baseline on Visit 1, Week 12 (Visit 2), Week 24 (Visit 3), Week 36 (Visit 4), Week 48 (Visit 5), Week 60 (Visit 6), Week 72 (Visit 7), Week 84 (Visit 8), Week 96 (Visit 9

- End-of-Treatment/Premature Discontinuation), and at the Post-Treatment visit (4 weeks post discontinuation of study drug). These parameters will be analyzed by the central laboratory. Urine samples will also be collected and shipped to central laboratory for assessment of urine protein, creatinine, osmolality, and urinalysis. The Central Laboratory Manual should be consulted for collection, processing, and shipping details.

8.2.13. Renal Ultrasound

An ultrasound to examine the kidneys and collecting system will be performed at Screening/Baseline (Visit 1), Week 48 (Visit 5) and Week 96 (Visit 9 – End of Treatment/Premature Discontinuation) visit. The ultrasound examination will be performed according to local standards and a final interpretation and report will be provided by a local qualified expert. The findings will be captured in source documents and within the CRF.

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

8.2.14. 12-Lead ECG

A 12-lead ECG will be obtained at Screening/Baseline (Visit 1), Week 48 (Visit 5), Week 96 (Visit 9 – End of Treatment/Premature Discontinuation) visit, and at the Post-Treatment Visit (4 weeks post discontinuation of study drug). The ECG will be performed and interpreted locally for clinical significance. The findings will be captured in source documents and with the CRF.

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

8.2.15. Study Drug Administration

Patients should take study drug TID as described in Section 6.2.2 Study drug supply sufficient for each 12-week treatment period will be supplied to the patient at Screeing/Baseline (Visit 1), Week 12 (Visit 2), Week 24 (Visit 3), Week 36 (Visit 4), Week 48 (Visit 5), Week 60 (Visit 6), Week 72 (Visit 7), and Week 84 (Visit 8). Sufficient drug for 90 days (12 weeks + 6 days) will be provided at each of these visits so lessen the likelihood that patients will experience drug shortages due to inadvertent loss of some of the sachets or scheduling delays for return visits.

8.2.16. Study Drug Compliance

Study drug compliance will be assessed using a Subject Study Drug Accountability Log (to be completed by the investigational site pharmacist or delegate site staff), which will document the return of unused sachets for compliance assessments.

Patients or caregivers will return all unused sachets of study drug to the study site for full compliance assessments using the Subject Study Drug Accountability Log. Clinic staff will record the study drug dosing information including the actual clock time of each dose when the patient is dosed in the clinic.

8.2.17. Adverse Events

Adverse events must be assessed and documented at each clinic visit. This information will be collected at Screening/Baseline (Visit 1) – following initiation of study drug, Week 12 (Visit 2), Week 24 (Visit 3), Week 36 (Visit 4), Week 48 (Visit 5), Week 60 (Visit 6), Week 72 (Visit 7), Week 84 (Visit 8), Week 96 (Visit 9) and at the Post-Treatment Visit (4 weeks post discontinuation of study drug). In addition, patients/caregivers will be encouraged to report adverse events of concern at any time in the intervals between visits.

8.2.18. 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/Baseline (Visit 1) – following initiation of study drug, Week 12 (Visit 2), Week 24 (Visit 3), Week 36 (Visit 4), Week 48 (Visit 5), Week 60 (Visit 6), Week 72 (Visit 7), Week 84 (Visit 8), Week 96 (Visit 9) and at the Post-Treatment Visit (4 weeks post discontinuation of study drug).

8.2.19. Presence of *Pseudomonas aeruginosa* in Sputum

The results of standard-of-care sputum cultures obtained by each subject's treating CF physician will be collected throughout the study. Available data, including the presence of *Pseudomonas aeruginosa*, will be collected from each subject's treating CF physician at Week 12 (Visit 2), Week 24 (Visit 3), Week 36 (Visit 4), Week 48 (Visit 5), Week 60 (Visit 6), Week 72 (Visit 7), Week 84 (Visit 8), and Week 96 (Visit 9 - End-of-Treatment/Premature Discontinuation).

8.2.20. Spirometry

Lung function will be assessed by spirometry using standardized equipment and procedures (please refer to the Study Manual for detailed instructions). Spirometry will be performed at all study visits. Centralized review will be provided for all spirometry measurements.

Consistent with usual practice, it is important that all subjects withhold the following medications prior to spirometry testing in order to obtain an accurate assessment of baseline lung function:

- Short-acting beta agonists (SABAs) should not be administered within 4 hours prior to testing.
- Long-acting beta agonists (LABAs) should not be administered within 12 hours prior to testing.

Inhaled antibiotics prior to testing is permitted. If chronically used, and done for the baseline visit, the administration of inhaled antibiotic should be consistently administered before every study visit (as at the baseline visit).

Use of SABAs, LABAs, and inhaled antibiotic will be captured in the central spirometry vendor's system prior to start of testing.

In exceptional circumstances where the subject's lung function is too labile to tolerate the delay in the use of beta agonists, the investigator should confer with the PTC medical monitor to get approval to deviate from this requirement. In this instance, the subject should have all

spirometry measurements performed after use of the prescribed beta agonist(s) at the appropriate interval(s).

8.2.21. Pulmonary Exacerbation Rate

Signs and symptoms associated with respiratory events that may constitute a pulmonary exacerbation will be collected and documented by the investigator or other qualified medical personnel on a Respiratory Event Form. This assessment will be conducted on Visit 1, Week 12 (Visit 2), Week 24 (Visit 3), Week 36 (Visit 4), Week 48 (Visit 5), Week 60 (Visit 6), Week 72 (Visit 7), Week 84 (Visit 8), and Week 96 (Visit 9 - End-of-Treatment/Premature Discontinuation), and at the time of any unscheduled contact between the patient and the clinic. In addition to patient/caregiver and investigator discussion at scheduled study visits, patients/caregivers are encouraged to contact their investigator by telephone with all pulmonary exacerbation details for any events that occur between scheduled visits.

8.2.22. CFQ-R

The CFQ-R will be administered prior to performance of other study procedures with the exception of obtainment of informed consent. The questionnaire will be administered at all study visits.

8.2.23. Blood for Analysis of Pharmacokinetics

Blood for trough ataluren concentrations will be collected at Week 24 (Visit 3), Week 48 (Visit 5), Week 72 (Visit 7), and Week 96 (Visit 9 - End-of-Treatment/Premature Discontinuation immediately prior to the morning dose of study drug. The Central Laboratory Manual should be consulted for collection, processing, and shipping details.

Samples will be stored at the bioanalytical lab for analysis of ataluren parent drug using a validated high performance liquid chromatography with tandem mass spectrometry (HPLC/MS-MS) method. Thereafter, samples will be retained at the bioanalytical lab for potential follow-up analyses of ataluren metabolites.

8.3. Blood Collection Summary

Every effort has been made to minimize blood drawing to the minimum required to monitor patient safety during the trial. Assuming a 96-week treatment period and all visits completed as noted in Table 3, the maximum amount of blood to be drawn at a visit is ~12 mL and the total amount of blood to be drawn over the entire 96-week study period (including the Screening visit, the 96-week treatment period, and the 4-week follow-up period) is approximately 112 mL.

9. ADVERSE EVENT ASSESSMENTS

9.1. Adverse Event Definitions

9.1.1. 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 patient who is administered study drug 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 or are not suspected to be due to study drug.
- Overdose (administration of a study drug dose >4 times the highest intended total daily dose level for this protocol [>160 mg/kg/day]) of study drug.
- All reactions from medication misuse, abuse, withdrawal, sensitivity, or toxicity.
- All reactions that result from medication errors or uses of the study drug outside what is described in the protocol.
- Apparently unrelated illnesses, including the worsening of a preexisting illness.
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate 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 patient with jaundice) should be captured in the source documents. Laboratory abnormalities not requiring clinical intervention or further investigation will be captured as part of overall laboratory monitoring, and should not be reported as adverse events.
- A pre-existing condition (eg, allergic rhinitis) must be noted on the appropriate CRF 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 9.1.2, 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 non-serious by the investigator using medical and scientific judgment.

9.1.2. 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 4 weeks after last study drug administration), including deaths due to disease progression. Any death occurring later than 4 weeks following the last dose should be reported as a serious adverse event whether 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 the study drug 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 patient at immediate risk of death. It does not include an event that, had it occurred in a more severe form, hypothetically might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (eg. excluding hospitalizations for administration of the study drug, procedures required by the study protocol, or CF-related diagnostic procedures; other planned hospitalizations; or hospitalizations related only to progression of disease). Please note that CF pulmonary exacerbations should be reported if they meet this criterion. Treatments in the emergency room for procedures such as hydration that do not require admitting the patient to the hospital and observational durations in the emergency room for less than 24 hours are not considered serious.
- Persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions.
- Any other medically important event that the investigator or the sponsor judges to be serious or which is defined as serious by the regulatory agency in the local country. Medical judgment should be exercised in deciding whether a reaction is serious in other situations. Important medical events that do not result in death, are not immediately life-threatening, and do not require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment administration in an emergency room or at home, newly diagnosed malignancy, or blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- A pregnancy resulting in spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]).

Except for CF pulmonary exacerbations, an event need not be reported as a SAE if it exclusively represents a relapse or an expected change or progression of the baseline CF. This type of event need only to be reported as an adverse event.

Note that any SAEs occurring within 4 weeks of the date of last dose should be reported to the CRO Pharmacovigilance Unit if the investigator becomes aware of them.

In addition to serious adverse events, adverse events of special interest must be reported to the CRO Pharmacovigilance Unit within 24 hours. Adverse events of special interest include the following:

Laboratory abnormalities:

- Serum cystatin C >1.33 x ULN
- Serum creatinine > ULN for age
- Serum BUN >1.5 x ULN
- Urine dipstick with ≥2+ blood
- Urine dipstick with ≥2+ protein

Signs/symptoms:

- Dysuria
- Flank (renal) pain
- Nephrolithiasis or other urinary tract calculi

It should be noted that laboratory data sent to and analyzed by the Central Laboratory need not be reported through the CRO Pharmacovigilance Unit as these data will already be reported to PTC Therapeutics. Only those laboratory abnormalities meeting the protocol-defined criteria of an adverse event (ie, those that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test), see Section 9.1.1) should be reported as adverse events in the appropriate CRF, whether they were analyzed by the central laboratory or another laboratory.

9.1.3. Unexpected Adverse Events

Unexpected adverse events are defined as those events that were not previously reported with study drug as referenced in the most current investigator brochure, or that are symptomatically and pathophysiologically related to a known toxicity but differ because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the 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 the medicinal product.

For the purposes of considering expectedness, 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).

9.2. Eliciting Adverse Event Information

Each study patient will be questioned about adverse events at each post-screening study visit or during any telephone contact with the patient or parent/caregiver. The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the patient or parent/caregiver at each scheduled clinic visit after study drug administration or during any telephone contact with the patient or parent/guardian caregiver. The type of question asked should be open-ended, eg, *"How have you/ your child been feeling?"* or a similar type of query.

9.3. Adverse Event Recording

All adverse events (both serious and non-serious) 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 non-serious, 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 9.1.2)
- Relationship to study drug (see Section 9.4)
- Severity of the event (see Section 9.5)
- Onset date
- Resolution date, or date of death
- Action taken
- Outcome of the event

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

9.4. Describing Adverse Event Relationship to Study Drug

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

Table 4. Relationship of Study Drug to Adverse Event

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

9.5. Grading of Severity of Adverse Events

The severity of adverse events will be graded using the CTCAE, Version 3.0 (refer 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 6.

Table 5. Grading of Adverse Event Severity

Grade	Adjective	Description
Grade 1	Mild	Sign or symptom is present, but it is easily tolerated, is not expected to have a clinically significant effect on the patient's overall health and well being, does not interfere with the patient'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 9.1.2.

9.6. Pregnancy

PTC Therapeutics should be notified in the event that a female patient in the study becomes pregnant at any time after the patient's first dose of study drug. Any such pregnancy occurring on-study or within 60 days of the last administration of study drug must be reported on a Pregnancy Notification Form (see the 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.

If possible, the investigator should follow the patient 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 the 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 CRO Pharmacovigilance Unit and follow up by submission of appropriate adverse event CRFs (see Section 9.9).

9.7. 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 conducted within one 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 CRO Pharmacovigilance Unit should be informed via e-mail or fax. A patient 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 patient has discontinued from the study, and additional investigations may be requested by the medical monitoring team.

9.8. Adverse Event Reporting Period

The first day of adverse event reporting will coincide with the day the first dose of study drug is administered. The adverse event reporting period for this study ends with the 4-week (± 7 days) Post-Treatment Follow-up Visit, except as described in Section 9.7. In addition, SAEs occurring in a patient after the study period should be reported to the sponsor if the investigator becomes aware of them.

9.9. Investigator Site Adverse Event Reporting Requirements

Classification of an event as serious or non-serious (see Section 9.1.2) determines the reporting procedures to be followed. Investigator site reporting requirements for adverse events are summarized in Table 6.

Table 6. Investigator Site Reporting Requirements for Adverse Events

Classification	Reporting Time	Reporting Action
Serious	Within 24 hours	Complete AE and SAE portions of CRF and notify site IRB/IEC, as per local IRB/IEC requirements. If unable to enter event in EDC, call the CRO Pharmacovigilance Unit or fax the back-up paper SAE report form to the CRO Pharmacovigilance Unit, within 24 hours.
	Within 5 calendar days	Provide photocopies or document scan of relevant source documents[a] (eg, progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries) as requested by the CRO Pharmacovigilance Unit.
	Per CRF submission procedure	Record and submit information on appropriate CRFs (eg, Medical History and Concomitant Medications CRFs)
AESI	Within 24 hours	Complete AE and SAE portions of CRF and notify site IRB/IEC, as per local IRB/IEC requirements. If unable to enter event in EDC, call the CRO Pharmacovigilance Unit or fax the back-up paper SAE report form to the CRO Pharmacovigilance Unit, within 24 hours.
	Within 5 calendar days	Provide photocopies or document scan of relevant source documents[a] (eg, progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries) as requested by the CRO Pharmacovigilance Unit.
	Per CRF submission procedure	Record and submit information on appropriate CRFs (eg, Medical History and Concomitant Medications CRFs).
Nonserious	Per CRF submission procedure	Record and submit information on appropriate CRFs (eg, Adverse Events, Medical History and Concomitant Medications CRFs).

a Patient name, address, and other personal identifiers should be obscured.
Abbreviations: 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 portion of the CRF must also be completed. The SAE CRF must be completed within 24 hours of knowledge of the event. If the site is unable to enter the event in the EDC system within 24 hours, notification to the CRO Pharmacovigilance Unit should be conducted via telephone or fax using the back-up paper SAE report form. Follow up information for the SAE should be entered on the SAE CRF or clearly documented on the back-up paper SAE report form, as applicable, upon receipt, and must also be sent to the site IRB/IEC, as required. If a paper SAE report form is used to report follow up information, then it must be signed by the investigator. The SAE CRF should be signed by the investigator only after the data on the form has been finalized. Any source documents (eg, progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries) provided to the CRO Pharmacovigilance Unit should be redacted so that the subject's name, address, and other personal identifiers are obscured. Only the subject's study number and initials are to be provided (in regions where the provision of such information is permitted). The information in the adverse event and SAE portions of the CRF 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 document his/her first awareness of the adverse event and report the event within 24 hours after learning of it.

The CRO contact information for reporting serious adverse events and adverse events of special interest is provided below and may also be found in the Investigator File and the back-up paper SAE report form.

PPD North America, EU, and Israel
Toll-Free: [redacted]
Safety Fax Number: [redacted]

In addition, each site will be provided with a Verizon, country-specific calling code.

9.10. PTC Therapeutics Adverse Event Reporting Requirements

For regulatory reporting purposes, the event is classified as related if the investigator or PTC Therapeutics determines that the event is possibly or probably related to the study drug (see Section 9.4). An adverse event will be considered expected if the protocol or investigator brochure indicates that such an event of similar or greater severity has already been observed in association with use of the study drug.

As the sponsor of the study, PTC Therapeutics is responsible for reporting certain safety information, particularly SAEs and patient deaths related to participation in the study, to each investigator in an expedited manner. The event is classified as related if the investigator or PTC Therapeutics determines that the event is possibly or probably related to the study drug (see Section 9.4). An adverse event will be considered expected if the protocol or investigator brochure indicates that such an event of similar or greater severity has already been observed in association with use of the study drug. 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, as applicable, per their local requirements. The PTC Therapeutics Awareness Date (PTCAD) is the date the regulatory reporting clock begins and the date is considered Day 0. The initial expedited safety report will be provided as required according to local regulations after the earliest date PTC Therapeutics or an agent of PTC Therapeutics (eg, a site monitor) becomes aware of an adverse event (eg, within 7 calendar days for deaths or life-threatening events or within 15 calendar days for other reportable events from the PTCAD).

10. WITHDRAWAL OF PATIENTS

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

- The patient has the right to withdraw consent and discontinue study drug at any time.
- If the patient's condition substantially worsens after initiating study drug, 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 study drug, if, in the investigator's clinical judgment, it is not in the patient's best interest to continue.
- If the patient becomes significantly noncompliant with study drug administration, study procedures, or study requirements. In this event, the patient should be withdrawn from study treatment when the circumstances surrounding noncompliance increase risk to the patient or are anticipated to substantially compromise the interpretation of study results.
- The patient will be withdrawn from treatment if he is unable to tolerate study drug.
- 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 drug is discontinued and the reason for discontinuation will be recorded in the source documents and in the eCRF. The PTC medical monitor (and designee) should be informed via e-mail of when a patient is discontinues study drug.

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

11. STATISTICS AND DATA MANAGEMENT

11.1. Sample Size Calculation

The sample size for this extension study is not based upon any formal statistical hypothesis, but its upper bound is determined by the requirement that patients must have participated in the previous Phase 3 study of ataluren (PTC124-GD-021-CF) in which ~ 208 patients are expected to be enrolled.

11.2. Study Population Definition

11.2.1. As-Treated Population

The as-treated population consists of all subjects who took at least one dose of ataluren. This population will be used to analyze safety and treatment administration.

11.2.2. Evaluable Populations

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

11.3. General Statistical Considerations

By-subjects listings will be created for each CRF module. Summary tables for continuous variables will contain the following statistics: n, mean, standard deviation, standard error, 95% confidence intervals (CIs) on the mean, median, minimum, and maximum. Summary tables for categorical variables will include N, n, percentage, and 95% CIs on the percentage. Where applicable, the summary data (mean, standard error) will be presented in graphical form of against time of visit.

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

All analyses will be performed based on all observed data. For the efficacy endpoints, eg, FEV_1, FVC, FEF_{25-75}, and pulmonary exacerbation, the analyses will be performed for 48-week completers and the whole study completers as well.

11.4. Specific Statistical Analyses

11.4.1. Study Conduct and Subject Disposition

The number and percentage of subjects in each of the analyzed study populations and the subjects completing 96 weeks of planned assessments and those of all planned assessments during the study will be described. The number and percentage of subjects who prematurely discontinue from the study will also be reported.

Reasons for screening failures, reasons for discontinuation, and time of withdrawal from the study will be described.

11.4.2. Demographics and Baseline Characteristics

Subject demographics and baseline characteristics will be summarized in frequency tables and descriptive statistics will be provided for quantitative variables.

11.4.3. Study Treatment Administration

For each subject, ataluren administration will be described, inclusive of duration of therapy, dose modifications, dose delays and omissions, and reasons for any deviations from planned therapy.

11.4.4. Use of Concomitant Medication and Supportive Therapy

Concomitant medications will be coded by means of the World Health Organization Drug Dictionary (WHODRUG) dictionary into Anatomical-Therapeutic-Chemical classification (ATC) codes. The number and percentage of subjects who received specific concomitant medications and supportive therapy will be summarized descriptively for each drug within each drug class. Multiple drug usage by a subject in the same category will be counted only once. The by-subject listings of concomitant medication will be presented.

11.4.5. Primary Variables

11.4.5.1 *Adverse Event*

Adverse events will be classified using the MedDRA classification system. The severity of adverse events will be graded 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 severity in the period extending from the day of a subject's first ataluren dose in this study to 4 weeks after the last ataluren dose in this study.

The number and percentage of subjects experiencing a specific adverse event will be tabulated by body system and MedDRA term. A subject having the same event more than once will be counted only once. Adverse events will be summarized by worst CTCAE grade within a subject. Exposure-adjusted incidence rate will be reported.

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

11.4.5.2 *Laboratory Data*

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

Separate listings and tables will be created for assessment of hepatic and renal parameters.

11.4.6. Secondary Variables

11.4.6.1 *Spirometry*

Both absolute change and relative change in %-predicted FEV_1 from Baseline at each visit will be summarized descriptively. Pediatric equations for calculating %-predicted FEV_1 [Wang 1993] will be used from 6 to <16 years of age for female subjects and from 6 to <18 years of age for male subjects. For males or females >18 years of age, an adult equation for calculating

%-predicted FEV_1 [Hankinson 1999] will be used. Each %-predicted FEV_1 will be based on the height value obtained at the same study visit. The changes from baseline to each post-baseline visit will be analyzed using paired t-tests.

Above analyses will be repeated for FVC and FEF_{25-75}.

11.4.6.2 *Pulmonary Exacerbation*

A modified Fuchs' exacerbation is defined as an event requiring treatment with or without IV antibiotics for any 4 of the following 12 symptoms: change in sputum; new or increased hemoptysis; increased cough; increased dyspnea; fatigue; temperature >38°C; anorexia; sinus pain; change in sinus discharge; change in physical examination of the chest; decrease in pulmonary function by 10 percent or more from a previously recorded value; or radiographic changes indicative of pulmonary function [Fuchs 1994]. Modified Fuchs' (primary definition) exacerbation incidence will be summarized descriptively for each visit. Other pulmonary exacerbation definitions, including Fuchs and expanded Fuchs, will also be summarized.

11.4.7. Tertiary Variables

11.4.7.1 *Vital Signs, Renal Ultrasound, 12-Lead ECG, and Other Safety Parameters*

Vital signs (height, weight, BMI, systolic and diastolic blood pressure, pulse rate, pulse oximetry, and body temperature) and ECG will be listed and summarized by visit and overall. Physical examination findings will be listed. Where appropriate, changes from baseline at each visit will be presented by visit and overall.

The results of an ultrasound to examine the kidneys and collecting system will be listed and abnormal results will be noted and investigated in terms of their relation to other relevant subject outcome measurement.

11.4.7.2. *Ataluren Plasma Concentrations*

Ataluren plasma concentrations will be summarized via n, mean, standard deviation, standard error, median, minimum, and maximum, CV% mean, geometric mean, and CV% geometric mean for each visit. The relationship between ataluren plasma concentrations and selected efficacy and safety outcomes will be explored.

11.4.7.3. *CFQ-R*

Changes in CFQ-R domains will be summarized descriptively for each visit. The CFQ-R respiratory domain will be the major HRQL parameter.

11.4.7.4 *Respiratory Events*

Incidences, rates, and durations of interventions (eg, antibiotic use and hospitalization) and disruptions to daily living (eg, missed school or work) resulting from pulmonary symptoms will be summarized descriptively. The rate and durations will be adjusted forsubject exposure.

12. STUDY COMMITTEES

A DMC, operating autonomously from the sponsor, the clinical investigators, and the Study Steering Committee (SSC), 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 at least 2 physicians experienced in treating patients with CF, a nephrologist, 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 formally interact with the SSC through the sharing of meeting minutes. Informal interactions between the DMC and SSC will be limited.

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 patients participating in this clinical study and to ensure the integrity of the clinical study.

In general, the DMC will be responsible for:

- Examining accumulated data at pre-specified 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 prior to implementation of those modifications
- Reviewing the general progress of the study regarding such issues as patient accrual, study conduct, and protocol deviations
- Providing expert advice to PTC Therapeutics on an ad hoc basis regarding matters such as safety concerns or diagnostic evaluations in individual patients

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.

13. OBLIGATIONS OF THE INVESTIGATOR AND THE SPONSOR

13.1. Compliance with Ethical and Regulatory Guidelines

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

13.2. Institutional Review Board/Independent Ethics Committee

Prior to enrollment of patients into the study, as required by the Food and Drug Administration (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, per local IRB/IEC requirements.

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 or the sponsor shall submit a progress report, at least once yearly, to the IRB/IEC, as applicable, according to local regulations. A copy of any progress report submitted by the investigator must be provided to PTC Therapeutics. PTC Therapeutics will provide to the investigator a copy of any progress report submitted to the IRB/IEC. As soon as possible after completion or termination of the study, the investigator will submit a final report to the IRB/IEC, as applicable, and to PTC Therapeutics. This report should include the following:

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.

If this study is performed under a grant from the US government, PTC Therapeutics will also submit the protocol and informed consent documents to the company's IRB of record (Western Institutional Review Board [WIRB], Olympia, WA). PTC Therapeutics or its designee will be responsible for all interactions with WIRB relating to the study, including submission of protocol documents, consent forms, and amendments; submission of adverse event reports and annual reports; receipt of approval notices; and exchange of other correspondence.

13.3. 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.

13.4. Case Report Forms

An eCRF or paper CRF, as applicable, 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 EDC system managed by the data management contract research organization (CRO) for this study. After the investigator or the investigator's designees (eg, research coordinators) have been appropriately trained, they will be given access to the EDC system and will enter the data required by the protocol into the EDC system. Any change of data will be made via the EDC system, with all changes tracked by the system to provide an audit trail.

With an electronic signature, the investigator certifies that the data are complete and accurate prior to database lock. This electronic signature serves to attest that the information contained in the eCRFs is true. After database lock, the investigator site will retain read-only access to their respective eCRF data (as entered in the EDC system) for a period of up to 6 months following database lock. The investigator will have opportunity to review CD-ROM and/or paper copies of eCRF data against the read-only data (serving as a contemporaneous and independent copy of CRF). At all times, the principal investigator has final responsibility for the accuracy and authenticity of all clinical data entered onto the CRFs and/or reported to PTC Therapeutics from the investigator site.

13.5. Study Records

During the study, the investigator will maintain adequate records for the study, including the following:

- Medical records
- Source document records detailing the progress of the study for each patient
- Laboratory reports
- A CD-ROM or paper copies of the data that have been captured in the EDC for each patient
- Signed informed consent forms
- Delegation of Responsibility/Authority Log
- Ataluren drug accountability, reconciliation and disposition records
- Relevant equipment maintenance and calibration records
- Correspondence with the IRB/IEC
- Adverse event reports
- 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.

13.6. Confidentiality

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

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. In other countries where this clinical trial is conducted, the investigator and the sponsor will comply with the local data protection requirements, as applicable.

13.7. Retention of Records

To enable evaluations and/or audits from regulatory authorities or PTC Therapeutics, the investigator agrees to keep accurate and complete records, including the identity of all participating patients (sufficient information to link eCRFs and clinic records), all original signed informed consent forms, CD-ROM or paper copies of the data that have been captured in the

EDC for each patient (electronic equivalents of CRFs), and detailed records of study drug disposition. All records and documents pertaining to the study (including but not limited to those outlined in Section 13.5) will be maintained by the investigator until notification is received from PTC Therapeutics that the records no longer need to be retained.

The investigator must obtain written permission from PTC Therapeutics before disposing of any records. In order to avoid any possible errors, the investigator will contact PTC Therapeutics prior to the destruction of any study records. The investigator will promptly notify PTC Therapeutics in the event of accidental loss or destruction of any study records. If the investigator relocates, retires, or for any reason withdraws from the study, the study records may be transferred to an acceptable designee, such as another investigator or another institution. Precautions should be taken to ensure the integrity, security, and protection of these documents from damage or loss at all times during and after completion of the study.

13.8. Monitoring and Auditing

In accordance with 21 Code of Federal Regulations (CFR) Part 312.56 and/or relevant ICH guidelines, PTC Therapeutics or a designee will periodically inspect all eCRFs (see Section 13.4), study documents, research facilities, and clinical laboratory facilities associated with this study at mutually convenient times, before, during, and after completion of the study. As required by applicable regulations (Responsibilities of Sponsors and Investigators), the monitoring visits provide PTC Therapeutics with the opportunity to evaluate the progress of the study; verify the accuracy and completeness of data in the eCRFs; ensure that all protocol requirements, 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 Investigational New Drug (IND) regulations also require the investigator to allow authorized representatives of the FDA to inspect and make copies of the same records.

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

13.9. 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.

13.10. 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. Information from ClinicalTrials.gov is provided to other publically available and/or electronically linked databases, including the WHO International Clinical Trials Registry Platform (ICTRP).

The protocol will also be listed in the EU Clinical Trials Register, the EU clinical trials database, as extracted from EudraCT. The information provided by PTC Therapeutics is a component of its application to a national medicines regulatory authority for authorization to conduct the study. The information from PTC Therapeutics is loaded into the EudraCT database by the national medicines regulatory authority.

PTC Therapeutics will ensure that information on the websites 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.

13.11. Dissemination of Results

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

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

13.12. 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 9.10.

14. RATIONALE FOR STUDY DESIGN FEATURES

14.1. Patient Selection

14.1.1 Overview

Since this protocol describes an open-label extension study, enrollment is limited to the patients who successfully complete the double-blind, placebo-controlled Phase 3 study (PTC124-GD-021-CF). The eligibility criteria are designed to enable enrollment of patients who are sufficiently well (both in terms of CF and in terms of concomitant illness) to safely participate in study procedures and provide interpretable results. Consistent with GCP guidelines, patients and/or parent 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.

14.1.2 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 many 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. Because it is unknown if ataluren is excreted in breast milk, lactating female patients who are breast-feeding are excluded from participation.

14.1.3 Concomitant Therapies

Ataluren has not proved allergenic in studies performed to date, but review of known allergies to excipients contained in the formulation is prudent. The restriction on concurrent involvement in other therapeutic clinical trials is intended to avoid confounding effects.

14.1.4 Safety Profiling

As is conventional, safety will be characterized in terms of the type, incidence, timing, severity, drug-relatedness, and seriousness of adverse events and laboratory abnormalities. For consistency of interpretation, adverse events will be coded using the MedDRA, the severity of these events and laboratory abnormalities will be graded using the well-defined CTCAE, Version 3.0, and concomitant medications will be coded with the WHODRUG dictionary.

14.1.5 Study Drug Compliance

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

14.1.6 Trough Ataluren Plasma Concentrations

Collection of plasma for ataluren concentrations is important for confirming maintenance of exposure over time. Having these data may allow correlations of exposure with measures of efficacy and toxicity. Because the ataluren PK profile has been well characterized in existing Phase 2a and Phase 3 studies in patients with CF, plasma sampling will be limited to before

dosing relative to the morning dose at each clinic visit. This will provide information regarding ataluren trough concentrations. The high performance liquid chromatography with tandem mass spectrometry (HPLC/MS-MS) method that will be used to quantify ataluren plasma concentrations has been fully validated in the context of the prior Phase 1 and Phase 2 studies. Plasma samples will be retained for potential later analyses of ataluren metabolites or corticosteroid parent drug and metabolites.

14.1.7 Timing of Assessments

The timing of study assessments is appropriate in the context of a chronic study, permitting inclusion of 8 post-baseline evaluations during the study period, ensuring that time trends can be adequately assessed and that sporadically missing data do not have a substantial impact on data analysis. The visit frequency also give consideration the need for many patients to travel considerable distances to study sites and that sites may achieve limiting capacity to accomplish study visits and data flow once multiple patients are being followed simultaneously at a single site.

Study activities have been mapped across the study as outlined in the Schedule of Events (see Table 3).

14.2. Treatment and Safety Monitoring Plan

14.2.1. Schedule and Dose Selection

Dosing based on body weight will continue to be employed. Such dosing reduces variability in exposure by accommodating differences in patient size across the span of ages in patients 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 two smaller doses at 6-hour intervals during the day and a larger dose at a 12-hour interval overnight (eg, at 7:00 AM, 1:00 PM, and 7:00 PM) is to optimally sustain target plasma concentrations while minimizing total exposures. This schedule is likely to fit well with daily patterns of living for patients, thus enhancing compliance.

14.2.2. Duration of Therapy

This open-label study is expected to generate at least 96 weeks of safety information. This information will supplement safety data obtained from the randomized, placebo-controlled, double-blind study (PTC124-GD-021-CF), which has a planned treatment duration of 48 weeks.

14.2.3. Safety Monitoring Overview

In response to the occurrence of renal toxicology findings in the mouse and renal laboratory abnormalities in prior ataluren studies, the renal safety monitoring plan utilized for the previous Phase 3 study is also appropriate for renal monitoring of this study population. Thresholds for evaluation and intervention have been established for other types of adverse events or laboratory abnormalities observed in the study, including hepatic abnormalities. 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 study drug in response to potential safety signals. The nature of these risks and the measures to monitor for them will 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. 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 study drug immediately, for interrupting study drug after confirmation of a value beyond the threshold, or for continuing study drug while evaluating for potential drug-related toxicity.

14.2.4. Renal Monitoring Plan

Renal findings were seen in mice receiving one or two doses through 26 weeks of dosing with ataluren. A no-observed-adverse-effect level (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 regenerative changes (proliferation of renal epithelium) accompanied by tubular dilatation and proteinaceous material within the tubules. Rarely the tubules were mineralized. Fibrosis was not seen after 1 month of dosing, but an interstitial renal fibrosis was observed in the 26-week carcinogenicity study in mice. The finding was occasionally accompanied by individual increases in serum blood urea nitrogen (BUN) and/or creatinine, but a dose relationship for these parameters was not observed. The kidney findings were partially to completely reversible as soon as 2 to 6 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 the Phase 3 clinical trial (Study 009), serious adverse events related to renal dysfunction, which occurred only in the ataluren arm, included 3 patients with acute renal failure, 3 patients with renal failure, and 1 patient with hypercreatininemia. These events were characterized by elevated creatinine (Grade 1 to Grade 4), which resolved over days to weeks. Only 1 patient experienced symptoms of renal dysfunction (transient oliguria). All 7 events were associated with concomitant systemic treatment with potentially nephrotoxic antibiotics (eg, aminoglycosides, vancomycin) that were generally administered as treatment for pulmonary exacerbations. No patient required dialysis. One patient was unblinded and 1 patient chose not to continue study drug treatment; the remaining 5 of 7 patients restarted study medication and continued study participation without recurrent creatinine elevations. This issue was recognized during the conduct of the study and changes were made in the protocol (eg, prohibition of concomitant use of potentially nephrotoxic agents), which successfully addressed the issue.

Non-serious creatinine elevations occurred predominantly in the ataluren arm and were transient, generally mild, and resolved with or without interruption of study medication. The incidence of treatment emergent nephrolithiasis was similar in the ataluren and placebo groups.

Non-serious episodes of creatinine elevation in Study 009 occurred predominantly in the ataluren arm and were transient, generally mild, and resolved with or without interruption of study medication. However, there was no clinically meaningful difference in creatinine between the ataluren and placebo arms at Week 48, indicating that there was no cumulative effect of these transient elevations on renal function. The incidence of treatment-emergent nephrolithiasis was similar in the ataluren and placebo groups.

The renal monitoring program included in this protocol considers nonclinical and clinical findings with ataluren and past experience with known nephrotoxicants. Concomitant use of potentially nephrotoxic antibiotics with ataluren is prohibited. 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.

- **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.
- **Serum Cystatin C:** An alternative to assessing GFR based on serum creatinine, serum cystatin C offers advantages in the assessment of renal function 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 study drug if required per protocol.
- **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 were 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 study drug dosing.
- **Renal Ultrasound**: In considering the markers to be used for decision-making within the study, renal ultrasound is proposed because it is the central imaging modality for assessing the anatomy of the kidneys and urinary tract in children. The test can detect changes in kidney size, assess parenchymal cystic or mass lesions, evaluate the renal vasculature, and assess the collecting system [Avni 2004]. Renal ultrasound is a routine component of diagnostic algorithms for follow-up of serum or urinary abnormalities suggesting renal dysfunction [Barratt 2004] and will be among the diagnostic testing performed for this

protocol as part of the assessment for such findings. It is safe, painless and convenient, providing advantages over contrast-enhanced computed tomography (CT) scanning (which has contrast-mediated nephrotoxicity and radiation risks) and magnetic resonance imaging (MRI) (which requires contrast administration and potential sedation in young children). Obtaining a baseline ultrasound enhances the sensitivity of subsequent ultrasonography, offering context for any potential abnormalities emerging during study drug treatment. An end-of-study ultrasound offers further reassurance that the kidneys remain anatomically normal at the completion of this protocol.

14.2.5. Hepatic Monitoring Plan

CF-related hepatobiliary obstruction and inflammation may result in serum transaminase elevations. Consequently, it is not practical to exclude patients with modestly increased serum AST, ALT, or GGT concentrations from enrollment in the Phase 3 study, and monitoring for hepatotoxicity in patients with preexisting disease must rely on observing changes from baseline in these parameters while also looking for increases in bilirubin. Consistent with well-established guidelines [Abboud 2007] applied in this disease setting, even modest (Grade 2) alterations in bilirubin should prompt interruption of study drug, once abnormal value is confirmed (per Table 2).

In the Phase 2a experience with ataluren in nmCF, reductions in serum markers of hepatic injury (particularly ALT) were observed [Clancy 2006], although no significant changes were seen in a larger-scale Phase 3 study. Since no significant changes in hepatic serum markers were observed in the Phase 3 study, these markers are not included in this protocol as efficacy assessments. Therefore, the hepatic monitoring in this study is being performed as part of the general safety monitoring.

14.2.6. 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. During the double-blind Phase 3 study of nmCF (Study 009), changes in systolic and diastolic blood pressure were small and not clinically meaningful. No substantial shifts in systolic or diastolic blood pressure from below to above the 95th and/or 99th percentile (adjusted for age and height) from baseline to Week 48 were observed in the ataluren group. In this study, blood pressure will be monitored via standardized procedure at each visit.

14.2.7. Other Nonclinical 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, some for over 7 years, from the patients dosed with ataluren to date in the clinical studies, indicate no increased risk of tumors. Long-term outcomes will be collected by completion of long-term health surveys after completion of ataluren or through a post-approval registry.

14.2.8. 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 study drug 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 study drug 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.

14.2.9. 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 PTC Therapeutics medical monitor (or qualified designee) to obtain guidance and to ascertain whether similar events are being seen at other investigator sites. The availability of advice from medical experts retained by PTC Therapeutics is intended to provide a uniformly high level of consultation in support of the investigators and the PTC Therapeutics 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 on therapy at a lower study drug dose. Interruption of therapy is advocated as the primary response in order to determine reversibility of the adverse finding.

14.2.10. 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, inhaled aminoglycosides) or pose a safety risk. Ataluren has not proved allergenic in studies performed to date, but review of known allergies to excipients containing in the formulation is prudent. Precluding the accrual of patients who are participating in another therapeutic clinical trial prevents potential conflicts between protocols relating to assessments of efficacy and safety, or conduct of study procedures.

Concomitant use of potentially nephrotoxic systemic antibiotics (eg, aminoglycosides and vancomycin) with ataluren is prohibited.

Aminoglycosides, eg, tobramycin, are theorized to ribosomally interfere with ataluren's mechanism of action. In previous Phase 3 studies of ataluren, notable differences in treatment effect have been observed in ataluren-treated patients that had been concomitantly treated with chronic inhaled aminoglycosides (eg, tobramycin) vs patients that were not administered chronic inhaled aminoglycosides (eg, tobramycin), which have a ribosomal-binding mechanism of action. An in vitro experiment confirmed this ribosomal mechanistic interference theory [Study Report PTC124-12030]. For these reasons, chronic use of inhaled aminoglycoside use cannot occur during study participation. Short regimens (up to 3 months total) are permitted for eradication of newly acquired *Pseudomonas aeruginosa* infection but must be completed during the first 12 weeks of treatment. Prohibition of the use of inhaled aminoglycosides in the last 12 weeks of study treatment is intended to minimize the possible interference with ataluren at Week 48, the time point at which efficacy is primarily determined in this study. Eradication protocols that have been reported to have eradication success similar to 3 months of tobramycin inhalation solution (TIS) should be considered, including protocols requiring only 28 days of TIS therapy [Ratjen 2009] or use of alternative antibiotics such as inhaled sodium colistimethate plus oral ciprofloxacin for 3months [Proesmans 2013]. Furthermore, similar outcomes were seen in CF patients assigned to inhaled colistin/oral ciprofloxacin or to inhaled tobramycin/oral ciprofloxacin [Tacetti 2012]. Patients requiring *Pseudomonas aeruginosa* eradication protocols that require inhaled tobramycin in the last 12 weeks of the study must be withdrawn from study participation. Use of eradication using non-aminoglycoside antibiotics may occur at any time during the study. There is no prohibition of the use of inhaled vancomycin. Specific start and stop dates for all inhaled antibiotics used during the study must be captured in the eCRF.

In vitro studies have suggested that ataluren is potentially an inhibitor of cytochrome P450 (CYP) 2C8 and 2C9 at concentrations that may be achieved in the clinic. Because ataluren may slow the clearance of medications that are primarily metabolized by CYP2C8 or CYP2C9, investigators should pay specific attention to use of drugs that are known substrates of this enzyme, particularly when such drugs may have a low therapeutic index.

While no clinical evidence of drug-drug interactions has been demonstrated, the potential for ataluren interactions with other drugs has been assessed. Based on in vitro studies, ataluren is a substrate of UGT1A9 and 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, geftinib).

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.

14.3. Study Committees

Inclusion of an SSC comprising PTC Therapeutics clinical/biostatistical personnel and committed disease experts and a DMC of independent experts incorporates a high level of

collaborating skill in the design and conduct of the trial with a substantial degree of impartial oversight in analysis of trial results. Inclusion of a nephrologist on the DMC provides access to expert assistance in these disciplines that should enhance the review of any potential safety signals relating to the kidneys.

14.4. Efficacy measurements

14.4.1. Spirometry

Progressive pulmonary dysfunction is the major source of disability and shortened survival associated with CF, and reversing such dysfunction is an essential therapeutic goal. The principal means of assessing both the level of dysfunction and the effects of intervention has been spirometry [Ramsey 1994].

In order to maximize uniformity of testing, data collection, and analysis for this study, an experienced vendor has been engaged to provide a single spirometry system. This system ensures that all sites are provided with a study-specific spirometer for collection of pulmonary function data. In addition, the system establishes standard operating procedures for spirometry performance, requiring that spirometric effort is sufficient and that each test is valid consistent with American Thoracic Society/European Respiratory Society guidelines [Miller 2005a, Miller 2005b]. The system is preprogrammed to generate data normalized for gender, age, and height using well-established nomograms for children [Wang 1993], and adults [Hankinson 1999]. Flow-volume loops and derived data are transferred to a central site for expert over-reading and interpretation. Data capture, transmission, and storage are performed electronically using secure systems that are compliant with FDA 21 CFR Part 11.Advances in electronic spirometric evaluation and data capture permit a unified approach to pulmonary function testing in order to enhance the consistency and accuracy of test performance.

14.4.2. Pulmonary Exacerbations

Decreasing exacerbation frequency has been considered an important outcome of treatment in CF, and has been an endpoint documenting drug efficacy in prior randomized clinical trials [Fuchs 1994, McCoy 1996, Ramsey 1999, Quan 2001, Saiman 2003, Elkins 2006]. As in the previous double-blind study, the modified Fuchs definition (ie, presence of at least 4 of 12 Fuchs' signs and symptoms without the requirement for treatment with antibiotics) will be the primary definition used [Kerem 2014].

A respiratory event collection form has been developed to collect CF pulmonary exacerbation information from the physician perspective. These data will be collected by the investigator or other qualified medical personnel at clinic visits and any unscheduled visits as appropriate. Patients will also be instructed to contact their physician by telephone during or immediately after an exacerbation has occurred to describe any events that occur between on-site visits. This form is designed to systematically characterize health-care provider observations related to exacerbations, and to allow categorization and scoring consistent with Fuchs or Rosenfeld CF exacerbation definitions. The data generated from these forms will provide the basis for recording incidence and rate of pulmonary exacerbations, which will be assessed in this study

14.4.3. HRQL and the CFQ-R

The CFQ-R has been most extensively developed HRQL instrument in CF and is available in multiple languages. The CFQ-R comprises 44 items, including 7 generic scales of physical

functioning, role functioning, vitality, health perceptions, emotional functioning, and social functioning, and 5 CF specific scales of respiratory and digestive symptoms, body image, eating disturbances, and treatment burden. Variations of the CFQ-R can be employed in children from 6 to 13 years of age (CFQ child), parents with young children with CF (CFQ parent), and adolescents ≥14 years of age (CFQ teen/adult). The instrument has undergone large multicenter validation program within the centers of the CF TDN [Quittner 2005].

The focus of attention will be on changes in the respiratory scale as the most direct assessment of ataluren treatment effect. Changes in other HRQL domains (eg, emotional or social functioning) are likely to be less directly affected by drug therapy.

14.4.4. Weight/Body Mass Index

Patients with CF are almost universally underweight when compared to healthy individuals of the same gender and age. Contributing factors include malabsorption due to pancreatic insufficiency and high work of breathing [Zemel 1996]. There is an association between worsening lung function and malabsorption, and evidence that nutritional intervention may improve pulmonary function [Milla 2004].

Given this knowledge, assessment of body weight and BMI during the course of this Phase 3 extension study is planned. While changes in these parameters are quite nonspecific, they constitute simple-to-assess outcomes of general well-being that complement data obtained from other efficacy measures.

14.4.5. Hepatobiliary Markers

Patients with CF can experience hepatobiliary inflammation [Colombo 2007], manifest as abnormalities of liver-derived serum enzymes such as serum ALT or AST in ~15% of patients with the disease [Goss 2007]. Oral bile acid therapy is available, but is variably used, and its influence on CF-associated hepatic disease progression or serum transaminase values is unclear [Colombo 2007]. In the Phase 2a experience with ataluren, reductions in serum markers of hepatic injury (particularly ALT) were observed [Clancy 2006], although no significant changes were seen in Study 009. Assessing these markers as extrapulmonary manifestations of CF is planned in this study.

14.4.6. New *Pseudomonas Aeruginosa* Lung Infection

In addition to the treatment of persistent *Pseudomonas aeruginosa* lung infection with inhaled antibiotics recommend by both European and CF treatment guidelines [Mogaygel 2013, Heijerman 2009] a growing body of evidence suggests that treatment of early Pseudomonas aeruginosa infection may be warranted, leading to a recommendation for early eradication therapy by the European Cystic Fibrosis Society [Heijerman 2009]. To investigate the extent to which ataluren may influence the occurrence of new Pseudomonas aeruginosa lung infection, the incidence of the occurrence of new positive cultures will be calculated. These airway cultures will be collected using the procedures and at a frequency (eg, quarterly) consistent with local standard of care. To limit reporting bias, the presence of *Pseudomonas aeruginosa*-positive cultures will be specifically elicited from the investigator.

15. BENEFITS AND RISKS

15.1 Benefits and Risks: Nonclinical

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.

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 very weak potential for direct inhibition of CYP2C8 and CYP2C9. Enzyme induction evaluations in human hepatocytes showed that ataluren did not induce the activities of CYP450 enzymes. However, there were slight increases in the activities of CYP2C8 and CYP2C9 only with the highest incubated ataluren concentration of 400 μM. It was concluded that the increased activities of CYP2C8 and CYP2C9 were not clinically significant or relevant. Therefore, ataluren is not expected to decrease exposure to drugs that are eliminated via metabolism by these CYP enzymes.

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 nmCF.

15.2 Benefits and Risks: Clinical Efficacy

Multiple Phase 2 and Phase 3 trials have now shown the potential benefit and safety of ataluren in the treatment nmCF in adults and children. Ataluren activity was demonstrated with TEPD testing in 2 separate Phase 2 trials (further details are provided in the ataluren Investigator Brochure).

Clinical benefit was further explored in the multicenter Phase 3 double-blind study (Study 009). In this 48-week study positive trends favoring ataluren were seen in the primary endpoint, the relative change from baseline in %-predicted FEV_1 at 48 weeks, which demonstrated a 3% difference between ataluren and placebo (-2.5% change on ataluren vs -5.5% change on placebo; p=0.124). An analysis of the relative change from baseline in %-predicted FEV_1 across all post-baseline study visits demonstrated an average difference between ataluren and placebo of 2.5% (-1.8% average change on ataluren vs -4.3% average change on placebo; p= 0.0478). A larger effect was seen in the patients not receiving chronic inhaled antibiotics. The effect of inhaled antibiotics was largely attributable to the use of inhaled aminoglycosides (ie, tobramycin). In patients not receiving chronic inhaled tobramycin at baseline, the Week 48 difference between the ataluren and placebo arms in the relative change of %-predicted was 5.7% (-0.7% change on ataluren vs -6.4% change on placebo difference in FEV_1).

The secondary endpoint, the rate of pulmonary exacerbations (ie, the number of pulmonary exacerbations in 48 weeks) also showed a positive trend in favor of ataluren, with the rate in the ataluren group being 23% lower than the placebo group (p=0.0992). In the patients not receiving chronic inhaled tobramycin, the pulmonary exacerbation rate in the ataluren group was 40% lower than the rate in the placebo group. These results show a consistent treatment effect of ataluren on both pulmonary function and exacerbation rates.

Collectively, the FEV_1 and pulmonary exacerbation data demonstrate the beneficial effect of ataluren in patients with nmCF aged 6 years and older. The increased effect seen in patients not receiving chronic inhaled tobramycin makes benefit more likely in these patients, who constitute the study population of this trial.

15.3 Benefits and Risks: Clinical Safety

Safety results indicate that ataluren was generally well tolerated. Across all studies, the most common treatment-emergent adverse events were consistent with background CF-related sinus, pulmonary, or gastrointestinal symptoms. Notable in the Phase 2 and 3 trials was the occurrence of mild dysuria in several patients. Resolution was successfully achieved with increased hydration. No clearly dose-dependent increases in frequency or severity of adverse events were evident. There were no safety concerns identified in patients' physical examinations, vital sign measurements, or electrocardiograms (ECGs).

In Study 009, the overall incidence of adverse events through Week 48 was similar in the ataluren and placebo groups. The most common adverse events were typical for CF and included pulmonary exacerbation, cough, and upper respiratory tract infection, which occurred at similar frequencies in the ataluren and placebo arms. Most of the serious adverse events, those requiring hospitalization, were pulmonary exacerbations unrelated to study treatment and some patients experienced creatinine elevations that occurred at Grades 3 and 4 in connection with concomitant treatment with systemic aminoglycosides (further details are provided in Section 14.2.4). Therefore, the Study 009 protocol was amended to prohibit the concomitant use of these antibiotics with ataluren, and to encourage patients to maintain adequate hydration. Non-serious episodes of creatinine elevation occurred predominantly in the ataluren arm and were transient, generally mild, and resolved with or without interruption of study medication.

In addition, in clinical trials in nmDMD the adverse-event profile of ataluren was comparable to that of placebo. In the double-blind Phase 2b study of nmDMD, 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), although similar events were not seen in the nmCF studies. 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.

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

15.4 Benefit/Risk Conclusions

Cystic fibrosis (CF) is a disabling and life-threatening genetic disorder resulting from mutations in the gene encoding the cystic fibrosis transmembrane conductance regulator (CFTR). CFTR dysfunction leads to multiple organ dysfunction starting in early childhood. An urgent unmet medical need exists for a therapy that addresses the underlying cause of nmCF, 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.

The collective nonclinical and clinical data provide the basis for the continued development of ataluren treatment for nmCF. The clinical efficacy data, in addition to an overall generally favorable safety profile collected from Phase 2 and 3 clinical trials supports a positive benefit-risk profile for ataluren. Appropriate safety monitoring and laboratory evaluation, as detailed in Section 14, is incorporated in this protocol in order to minimize risk to study participants. The current trial (Study 021e) is feasible and will provide additional safety and efficacy data of ataluren in nmCF.

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