



NCT02107859

**CLINICAL PROTOCOL**

**An Open-Label Safety and Efficacy Study for Patients with Nonsense Mutation Cystic Fibrosis Previously Treated with Ataluren (PTC124)**

**Protocol Number PTC124-GD-023-CF**

**08 February 2016**

**Version 3.0**

**PTC Therapeutics, Inc.  
100 Corporate Court  
South Plainfield, NJ 07080 USA**

Notice of Proprietary Information: This document contains confidential information belonging to PTC Therapeutics, Inc. Except as may otherwise be permitted in writing, by accepting or reviewing these materials, you agree that this information should not be disclosed to others (except where required by applicable law) and should not be used for unauthorized purposes. In the event of an actual or suspected breach of this obligation, PTC Therapeutics, Inc. should be notified promptly.

## PROTOCOL IDENTIFIERS AND STUDY PERSONNEL

<b>Project Code</b>	PTC124-GD
<b>Therapeutic Area</b>	Genetic Disorders – Cystic Fibrosis
<b>PTC Therapeutics Substance Identifier</b>	Ataluren (PTC124)
<b>IND Number</b>	48,648
<b>EudraCT Number</b>	2013-005449-35
<b>Included in clinical trials.gov Database</b>	NCT02107859
<b>Protocol Number</b>	PTC124-GD-023-CF
<b>Protocol Version</b>	Version 3.0
<b>Protocol Version Date</b>	08 February 2016
<b>Protocol Phase</b>	Phase 3
<b>Protocol Title</b>	An Open-Label Safety and Efficacy Study for Patients with Nonsense Mutation Cystic Fibrosis Previously Treated with Ataluren (PTC124®)
<b>PTC Clinical Program Scientist</b>	[REDACTED] PTC Therapeutics, Inc. 100 Corporate Court South Plainfield, NJ 07080 USA Phone: [REDACTED] E-mail: [REDACTED]
<b>PTC Medical Monitor</b>	[REDACTED] PTC Therapeutics, Inc. 100 Corporate Court South Plainfield, NJ 07080 USA Phone: [REDACTED] Facsimile: [REDACTED] E-mail: [REDACTED]
<b>PTC Biostatistician</b>	[REDACTED] PTC Therapeutics, Inc. 100 Corporate Court South Plainfield, NJ 07080 USA Phone: [REDACTED] Facsimile: [REDACTED] E-mail: [REDACTED]

## PTC THERAPEUTICS PROTOCOL APPROVAL SIGNATURES

---

[Redacted Signature]

PTC Therapeutics, Inc.

---

Date

---

[Redacted Signature]

PTC Therapeutics, Inc.

---

Date

---

[Redacted Signature]

PTC Therapeutics, Inc.

---

Date

---

[Redacted Signature]

PTC Therapeutics, Inc.

---

Date

## PRINCIPAL INVESTIGATOR AGREEMENT AND SIGNATURE

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

---

**Principal Investigator**

Institution:  
Address:  
City:  
State/Province:  
Country:  
Phone:  
Fax:  
E-mail:

---

**Date**

## TABLE OF CONTENTS

<b>1. OVERVIEW .....</b>	<b>11</b>
<b>2. BACKGROUND .....</b>	<b>12</b>
2.1. DISEASE INDICATION.....	12
2.2. ATALUREN (PTC124®).....	13
2.2.1. <i>Therapeutic Concept</i> .....	13
2.2.2. <i>Chemical Description</i> .....	14
2.2.3. <i>Clinical Studies</i> .....	14
2.2.3.1. <i>Phase 1 Studies</i> .....	14
2.2.3.2. <i>Phase 2a Studies</i> .....	15
2.2.3.3. <i>Phase 3 Study</i> .....	17
2.2.3.3.1. <i>Phase 3 Extension Study</i> .....	18
<b>3. STUDY OBJECTIVE AND ENDPOINTS .....</b>	<b>19</b>
3.1. OBJECTIVES.....	19
3.2. ENDPOINTS.....	19
<b>4. SUBJECT SELECTION CRITERIA.....</b>	<b>19</b>
4.1. OVERVIEW .....	19
4.2. INCLUSION CRITERIA.....	20
4.3. EXCLUSION CRITERIA .....	20
<b>5. ENROLLMENT PROCEDURES .....</b>	<b>22</b>
5.1. SOURCE AND NUMBER OF SUBJECTS.....	22
5.2. SCREENING AND STUDY DRUG DISPENSATION.....	22
<b>6. INVESTIGATIONAL MEDICINAL PRODUCT .....</b>	<b>22</b>
6.1. STUDY DRUG SUPPLY .....	22
6.1.1. <i>Study Drug Packaging and Labeling</i> .....	22
6.1.2. <i>Study Drug Storage</i> .....	22
6.1.3. <i>Study Drug Dispensation</i> .....	23
6.1.4. <i>Study Drug Preparation</i> .....	23
6.1.5. <i>Study Drug Accountability</i> .....	23
6.1.6. <i>Overdose Precautions</i> .....	24
6.1.7. <i>Inadvertent Exposure and Spill Precautions</i> .....	24
6.2. STUDY DRUG TREATMENT .....	24
6.2.1. <i>Study Drug Dosing</i> .....	24
6.2.2. <i>Duration of Treatment</i> .....	24
6.2.3. <i>Schedule of Administration</i> .....	24
<sup>a</sup> <i>Dosing times are examples and may be varied to suit each subject's schedule. However, the time between morning and midday doses and between midday and evening doses should be maintained at ~6 hour intervals, while the time between the evening and next morning dose should be maintained at an ~12 hour interval.</i> .....	25
6.2.4. <i>Instructions for Delays in Dosing</i> .....	26
6.3. SAFETY MONITORING AND STUDY DRUG DOSE INTERRUPTION/MODIFICATION.....	26
6.3.1. <i>Laboratory Abnormalities and Adverse Events Requiring Evaluation and Potential Drug Interruption/Modification</i> .....	26
6.3.2. <i>Evaluation of Adverse Events or Laboratory Abnormalities</i> .....	27
6.3.3. <i>Instructions for Resuming Ataluren Administration after an Interruption for Safety Concerns</i> .....	29
6.3.4. <i>Instructions for Discontinuation of Study Drug Administration for Safety Concerns</i> .....	30
<b>7. CONCOMITANT AND SUPPORTIVE THERAPY.....</b>	<b>30</b>
7.1. CONCOMITANT MEDICATIONS.....	30
7.1.1. <i>Therapy/Prophylaxis for CF-Related Conditions</i> .....	30
7.1.2. <i>Therapy for CF Pulmonary Exacerbations or Other CF Complications</i> .....	31

7.1.3.	<i>Drugs Metabolized by CYP2C8 or CYP2C9</i> .....	31
7.1.4.	<i>Other Potential Interactions</i> .....	32
7.1.5.	<i>Other Concomitant Medications</i> .....	32
7.2.	NON-DRUG THERAPY.....	33
7.2.1.	<i>Physical and Respiratory Therapy</i> .....	33
7.2.2.	<i>Dietary Restrictions</i> .....	33
7.2.3.	<i>Hydration</i> .....	33
<b>8.</b>	<b>SCHEDULE OF EVENTS AND STUDY PARAMETERS</b> .....	<b>33</b>
8.1.	SCHEDULE OF EVENTS.....	33
8.2.	EXPLANATION OF STUDY PROCEDURES .....	37
8.2.1.	<i>Screening and Week 1 Visits</i> .....	37
8.2.2.	<i>Treatment Visits / Calls During Study</i> .....	37
8.2.2.1.	End of Treatment .....	37
8.2.2.2.	Post-Treatment Visits.....	37
8.2.3.	<i>Informed Consent</i> .....	37
8.2.4.	<i>Clinical/Medication History</i> .....	37
8.2.5.	<i>Vital Signs</i> .....	38
8.2.6.	<i>Height, Weight, and Physical Examination</i> .....	38
8.2.7.	<i>Central Laboratory Assessments</i> .....	38
8.2.7.1.	Viral Screen and Pregnancy Laboratory Assessments .....	38
8.2.7.2.	Adrenal Laboratory Assessment .....	38
8.2.7.3.	Hematology Laboratory Assessment .....	38
8.2.7.4.	Serum Biochemistry Laboratory Assessment .....	39
8.2.7.5.	Urinalysis.....	39
8.2.7.6.	Pharmacokinetic Analysis (PK) .....	39
8.2.8.	<i>Renal Ultrasound</i> .....	39
8.2.9.	<i>12-Lead ECG</i> .....	39
8.2.10.	<i>Ataluren Administration and Dispensation</i> .....	40
8.2.11.	<i>Ataluren Compliance</i> .....	40
8.2.12.	<i>Adverse Events</i> .....	40
8.2.13.	<i>Concomitant Medications</i> .....	40
8.2.14.	<i>Spirometry</i> .....	41
8.2.15.	<i>Pulmonary Exacerbation Rate</i> .....	41
8.2.16.	<i>Presence of Pseudomonas aeruginosa in Sputum</i> .....	42
8.3.	BLOOD COLLECTION SUMMARY.....	42
<b>9.</b>	<b>ADVERSE EVENT ASSESSMENTS</b> .....	<b>42</b>
9.1.	ADVERSE EVENT DEFINITIONS .....	42
9.1.1.	<i>Adverse Events</i> .....	42
9.1.2.	<i>Serious Adverse Events (SAEs)</i> .....	43
9.1.3.	<i>Unexpected Adverse Events</i> .....	45
9.2.	ELICITING ADVERSE EVENT INFORMATION .....	45
9.3.	ADVERSE EVENT RECORDING .....	45
9.4.	DESCRIBING ADVERSE EVENT RELATIONSHIP TO STUDY DRUG .....	46
9.5.	GRADING OF ADVERSE EVENT SEVERITY.....	46
9.6.	PREGNANCY .....	47
9.7.	FOLLOW-UP OF UNRESOLVED ADVERSE EVENTS .....	47
9.8.	ADVERSE EVENT REPORTING PERIOD .....	48
9.9.	INVESTIGATOR SITE ADVERSE EVENT REPORTING REQUIREMENTS.....	48
9.10.	PTC THERAPEUTICS ADVERSE EVENT REPORTING REQUIREMENTS .....	49
<b>10.</b>	<b>WITHDRAWAL OF SUBJECTS</b> .....	<b>50</b>
<b>11.</b>	<b>STATISTICS AND DATA MANAGEMENT</b> .....	<b>50</b>
11.1.	SAMPLE SIZE CALCULATION FOR THE PRIMARY ENDPOINT .....	50
11.2.	POPULATION DEFINITION .....	51

11.2.1.	<i>As-Treated Population</i> .....	51
11.2.2.	<i>Intent-to-Treat Population</i> .....	51
11.3.	GENERAL STATISTICAL CONSIDERATIONS .....	51
11.4.	SPECIFIC STATISTICAL ANALYSES.....	51
11.4.1.	<i>Study Conduct and Subject Disposition</i> .....	51
11.4.2.	<i>Baseline Characteristics</i> .....	51
11.4.3.	<i>Study Treatment Administration</i> .....	51
11.4.4.	<i>Use of Concomitant Medication and Supportive Therapy</i> .....	51
11.4.5.	<i>Primary Variables</i> .....	51
11.4.5.1.	Adverse Events .....	51
11.4.5.2.	Laboratory Data .....	52
11.4.6.	<i>Secondary Variables</i> .....	52
11.4.6.1.	<i>12-Lead ECG and Other Safety Parameters</i> .....	52
11.4.6.2.	<i>Spirometry</i> .....	52
11.4.6.2.1.	Change from Baseline in %-predicted FEV <sub>1</sub> .....	52
11.4.6.3.	Pulmonary Exacerbation Rates .....	52
11.4.7.	<i>Tertiary Variables</i> .....	53
11.4.7.1.	<i>Spirometry</i> .....	53
11.4.7.2.	<i>Weight and BMI</i> .....	53
11.4.8.	<i>Exploration of Correlations</i> .....	53
<b>12.</b>	<b>STUDY COMMITTEES</b> .....	<b>53</b>
12.1.	DATA MONITORING COMMITTEE .....	53
<b>13.</b>	<b>OBLIGATIONS OF THE INVESTIGATOR AND THE SPONSOR</b> .....	<b>54</b>
13.1.	COMPLIANCE WITH ETHICAL AND REGULATORY GUIDELINES .....	54
13.2.	INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE .....	54
13.3.	INFORMED CONSENT/ASSENT .....	55
13.4.	CASE REPORT FORMS.....	55
13.5.	STUDY RECORDS.....	56
13.6.	CONFIDENTIALITY .....	56
13.7.	RETENTION OF RECORDS.....	57
13.8.	MONITORING AND AUDITING .....	57
13.9.	TERMINATION OF THE STUDY .....	58
13.10.	PUBLIC NOTIFICATION OF STUDY CONDUCT .....	58
13.11.	DISSEMINATION OF RESULTS.....	58
13.12.	COMMUNICATION WITH REGULATORY AUTHORITIES.....	59
<b>14.</b>	<b>RATIONALE FOR STUDY DESIGN FEATURES</b> .....	<b>59</b>
14.1.	PATIENT SELECTION.....	59
14.1.1.	<i>General</i> .....	59
14.1.2.	<i>Inclusion of Minors</i> .....	59
14.1.3.	<i>Safety Measurements</i> .....	61
14.1.3.1.	Safety Profiling .....	61
14.1.3.2.	Study Drug Compliance.....	61
14.1.4.	<i>Required Laboratory Values</i> .....	61
14.1.5.	<i>Reproductive Considerations</i> .....	62
14.1.6.	<i>Prior and Concomitant Therapies</i> .....	62
14.2.	TREATMENT RATIONALE.....	63
14.2.1.	<i>Schedule and Ataluren Dose Selection</i> .....	63
14.2.2.	<i>Duration of Therapy</i> .....	63
14.2.3.	<i>Safety Monitoring</i> .....	63
14.2.3.1.	Renal Abnormalities .....	64
14.2.3.1.1.	Overview.....	64
14.2.3.1.2.	Renal Monitoring Plan .....	65
14.2.4.	<i>Hepatic Monitoring Plan</i> .....	67
14.2.5.	<i>Blood Pressure Assessment</i> .....	67

14.2.6.	<i>Other Nonclinical Findings</i> .....	67
14.2.7.	<i>Other Abnormalities</i> .....	68
14.2.8.	<i>Actions to be Taken in Response to Safety Signals</i> .....	68
14.2.9.	<i>Efficacy Measurements</i> .....	68
14.2.9.1.	Spirometry .....	68
14.2.9.2.	Pulmonary Exacerbations .....	69
14.2.9.3.	Weight/Body Mass Index.....	70
14.2.10.	<i>Exposure Outcome Measures</i> .....	70
14.2.10.1.	Trough Ataluren Plasma Concentrations .....	70
14.2.11.	<i>Timing of Assessments</i> .....	70
14.3.	STUDY COMMITTEES.....	70
<b>15.</b>	<b>BENEFITS AND RISKS</b> .....	<b>71</b>
15.1.	BENEFITS AND RISKS: NONCLINICAL .....	71
15.2.	BENEFITS AND RISKS: CLINICAL .....	72
15.3.	BENEFITS AND RISKS: SAFETY .....	73
15.4.	BENEFIT/RISK CONCLUSIONS .....	73
<b>16.</b>	<b>BIBLIOGRAPHY</b> .....	<b>75</b>

## LIST OF TABLES

<b>TABLE 1:</b>	<b>SUGGESTED DAILY DOSING SCHEDULE</b> .....	<b>25</b>
<b>TABLE 2:</b>	<b>SAFETY MONITORING PARAMETERS AND ACTIONS TO BE TAKEN</b> .....	<b>27</b>
<b>TABLE 3:</b>	<b>SCHEDULE OF EVENTS</b> .....	<b>34</b>
<b>TABLE 4:</b>	<b>RELATIONSHIP OF ATALUREN TO ADVERSE EVENT</b> .....	<b>46</b>
<b>TABLE 5:</b>	<b>GRADING OF ADVERSE EVENT SEVERITY</b> .....	<b>47</b>
<b>TABLE 6:</b>	<b>INVESTIGATOR SITE REPORTING REQUIREMENTS FOR ADVERSE EVENTS</b> .....	<b>48</b>



## ABBREVIATIONS

Abbreviation	Definition
ACTH	Adrenocorticotrophic hormone
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical-Therapeutic-Chemical
AUC	Area under the concentration-time curve
BCRP	Breast Cancer Resistant Protein
β-HCG	Beta human chorionic gonadotropin
BID	Bis in die (2 times per day)
BMI	Body mass index
BUN	Blood urea nitrogen
cAMP	Cyclic adenosine monophosphate
CD-ROM	Compact disc read-only memory
CF	Cystic fibrosis
CFR	Code of Federal Regulations
CFTR	Cystic fibrosis transmembrane conductance regulator
cGMP	Current Good Manufacturing Practices
CI	Confidence interval
CK	Creatine kinase
C <sub>max</sub>	Maximum plasma concentration
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 <sub>25-75</sub>	Forced expiratory flow between 25% and 75% of expiration
FEV <sub>1</sub>	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
HIV	Human immunodeficiency virus
HRQL	Health-related quality of life
ICH	International Conference on Harmonization
ICJME	International Committee of Medical Journal Editors
ICTRP	WHO International Clinical Trials Registry Platform
IL-8	Interleukin 8

<b>Abbreviation</b>	<b>Definition</b>
IND	Investigational New Drug (Application)
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	Intention-to-treat
IVR/IWR	Interactive Voice Response/Interactive Web Response
IV	Intravenous
LDH	Lactate dehydrogenase
LABA	Long-acting beta agonist
LDL	Low-density lipoprotein
LOAEL	Lowest-observed-adverse-effect level
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MTD	Maximum tolerated dose
NEL	No-effect-level
nmCF	Nonsense mutation cystic fibrosis
nmDBMD	Nonsense mutation Duchenne/Becker muscular dystrophy
nmDMD	Nonsense mutation Duchenne muscular dystrophy
NOAEL	No-observed-adverse-effect level
OAT1	Organic anion transporter 1
OAT3	Organic anion transporter 3
OATP1B3	Organic anion transporting polypeptide 1B3
PK	Pharmacokinetic(s)
PTCAD	PTC Therapeutics Awareness Date
PTC124®	Ataluren
SABA	Short-acting beta agonist
SSC	Study Steering Committee
TID	3 times per day
TEPD	Transepithelial Potential Difference
T $\frac{1}{2}$	Plasma half-life
ULN	Upper limit of Normal
WIRB	Western Institutional Review Board

## 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. Ivacaftor (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, double-blind, placebo-controlled study (PTC124-GD-009-CF; Study 009) of patients  $\geq 6$  years of age with nmCF receiving ataluren 10, 10, and 20 mg/kg for 48 weeks favored positive trends in the primary (relative change in %-predicted forced expiratory volume in 1 second [FEV<sub>1</sub>]) and secondary endpoint (pulmonary exacerbation rate over 48 weeks) of the trial compared to placebo [Rowe 2012]. Interim analysis of a subsequent Phase 3, open-label, extension study (PTC124-GD-009e-CF; Study 009e) lasting ~96 weeks supported the positive trends favoring ataluren vs placebo that were demonstrated in Study 009 [Kerem 2013].

The primary objective of this study is to determine the long-term safety and tolerability of 10-, 10-, 20-mg/kg ataluren in patients with nmCF that have completed participation in the double-blind study (Study 009) as assessed by adverse events and laboratory abnormalities.

The secondary objectives are to determine the efficacy and safety of ataluren as assessed by spirometry (forced expiratory volume in 1 second [FEV<sub>1</sub>]), pulmonary exacerbation rate, and other safety parameters (eg, 12-lead ECG measurements, vital signs).

The tertiary objectives are to determine the efficacy of ataluren as assessed by other parameters of pulmonary function (FVC and FEF<sub>25-75</sub>), and changes in body weight and body mass index (BMI).

It is planned that approximately 70 patients that completed participation in Study 009 will be enrolled into the study. All participating sites must therefore have had at least 1 patient that completed participation in Study 009. It is anticipated that most eligible patients would have also

been enrolled in Study 009e, the 96-week open-label study that immediately proceeded Study 009.

Compliance with study medication will be assessed and use of concomitant therapies will be described.

Planned interim safety analyses will be conducted by an independent data monitoring committee (DMC). The first safety review will occur when ~35 patients have completed  $\geq 32$  weeks of treatment. The second safety review will occur when ~35 patients have completed  $\geq 64$  weeks of treatment.

## 2. BACKGROUND

### 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<sub>1</sub> is reduced; it is estimated that FEV<sub>1</sub> 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 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/Becker muscular dystrophy (nmDBMD) 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. This study aims to further evaluate the safety profile of ataluren in nmCF patients.

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 readthrough 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 readthrough of nonsense mutations and production of full-length, functional proteins [Welch 2007, Du 2008]. In the subset of subjects 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  $\mu\text{g/mL}$ ) 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. Clinical Studies**

#### **2.2.3.1. Phase 1 Studies**

Two Phase 1 safety and pharmacokinetic (PK) studies of ataluren were conducted in 62 healthy adult male and female volunteers ranging in age from 18 to 30 years (PTC124-GD-001-HV) [Hirawat 2007]. Single doses of ataluren administered orally at dose levels ranging from 3 mg/kg to 100 mg/kg were palatable and generally well tolerated. Mild adverse events of

headache, dizziness, nausea, vomiting, diarrhea, and stomach discomfort at dose levels of 150 and 200 mg/kg appeared to be coincident with achieving the maximum concentration ( $C_{max}$ ). Elevations of serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) were observed in 1 subject receiving a single dose of 200 mg/kg. With repeated doses through 50 mg/kg/dose 2 times per day (BID), reversible, low-grade (<2 times the upper limit of normal) transaminase elevations were observed in some patients (PTC124-GD-002-HV). No bilirubin increases were observed. In addition, no notable BUN, creatinine, or urinalysis abnormalities were observed. PK analyses indicated rapid oral absorption, generally dose-proportional PK, an effective plasma half-life ( $t_{1/2}$ ) in the range of 2 to 6 hours, and no relevant drug accumulation with repeated dosing. The data also demonstrated that ataluren can be given with or without food and that trough plasma concentrations exceeding the  $\sim 2$   $\mu\text{g/mL}$  to  $\sim 10$   $\mu\text{g/mL}$  target values active in the *mdx* mouse model of nmDBMD might best be achieved with TID dosing after meals.

In addition, a Phase 1 single-dose study of the absorption, metabolism, and excretion of radiolabeled ataluren was conducted in 7 healthy male subjects (PTC124-GD-010-HV). This study documented that ataluren bioavailability is  $\geq 50\%$  following oral administration of a single 20 mg/kg dose under fasting conditions. An inactive acyl glucuronide of ataluren represented the sole plasma metabolite in humans. Relative to unchanged ataluren, the ataluren acyl glucuronide plasma exposures were 6.2% for  $C_{max}$  and 7.6% for area under the concentration versus time curve (AUC). Based on available data, relative exposures to ataluren acyl glucuronide in the toxicology species were as high as or higher than in humans. Excretion data indicated that 47.3% of the administered radioactive dose is recovered in the feces and 55.1% was recovered in the urine. In feces, parent drug accounted for  $\sim 0.4\%$  and various minor metabolites were present due to metabolism by fecal microorganisms. In the urine, unchanged ataluren and ataluren acyl glucuronide accounted for <1% and 49%, respectively, of the administered dose.

#### 2.2.3.2. Phase 2a Studies

Phase 2a studies in adult patients with nmCF were conducted in the United States and in Israel (PTC124-GD-003-CF, PTC124-GD-005-CF), and in children with nmCF in Europe (PTC124-GD-006-CF) [Clancy 2006, Kerem 2008a, Sermet-Gaudelus 2008]. These studies were similar in design and were performed as open-label, dose-ranging, challenge-dechallenge-rechallenge evaluations of the activity, safety, and PK of ataluren in patients with nmCF. Participants with analyzed data from these studies totaled 47 adult patients (18 through 57 years of age) and 30 pediatric patients (6 through 18 years of age). All patients received ataluren in 2 repeated 28-day cycles, each comprising 14 days on therapy and 14 days off therapy. In one cycle, participants received ataluren TID at morning, midday, and evening doses of 4-, 4-, 8-mg/kg and in the other cycle, they received ataluren TID at doses of 10-, 10-, 20-mg/kg.

TEPD testing was used to assess total transepithelial chloride transport as the primary outcome measure. This parameter constitutes an integrated evaluation of the presence and surface localization of full-length, functional, membrane-associated CFTR. The results in the studies in Israel and Europe indicated statistically significant improvements in TEPD chloride transport, the percentage of patients with a chloride transport response (improvements of  $\geq 5$  mV relative to baseline), and the proportion of patients with a chloride transport value in the normal range (equal to or more electrically negative than -5.0 mV). Responses were observed in multiple stop types (including Q493X, G542X, R553X, W846X, W882X, E1104X, R1162X, W1282X, and

3849+10kB C→T). Changes in pharmacodynamic parameters were not clearly dose-dependent although persistence of effects may have been greater at the 10-, 10-, 20-mg/kg dose level. In contrast, a Phase 2 study (PTC124-GD-003-CF) conducted in adults in 5 centers in the United States did not show significant improvements in total chloride response in nmCF patients [Clancy 2006]. Positive trends in pulmonary function changes were observed during ataluren administration. Sweat chloride concentration, measured over 2 weeks in the trial conducted in Israel, showed no improvement with ataluren administration.

Across all studies and both dose levels, treatment-emergent adverse events were consistent with background CF-related sinus, pulmonary, or gastrointestinal symptoms. No drug-related serious adverse events were reported. The only notable event was the occurrence of mild dysuria in several patients with the morning void; no drug, uric acid, or calcium oxalate crystals; hematuria; pyuria; or other abnormalities were detected in urine from these subjects. 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 subjects' physical examinations, vital sign measurements, or electrocardiograms (ECGs). Treatment-emergent laboratory abnormalities showed no obvious dose dependency and none of these events was considered clinically relevant. Compliance was very good; on average, patients received >95% of the planned ataluren doses and no patient discontinued ataluren due to an adverse event.

Ataluren has also been tested in Israel in an open-label, extension study in patients with nmCF (PTC124-GD-005e-CF) [Kerem 2008b]. The study was designed to evaluate the activity, safety, and ataluren plasma concentrations associated with 3 months of continuous treatment in the same patients who were enrolled in the previous Phase 2a study performed in Israel. In this extension study, 19 patients were assigned to respective morning, midday, and evening doses of either 4-, 4-, 8-mg/kg (n=11) or 10-, 10-, 20-mg/kg (n= 8) based on the investigator interpretation of the best chloride transport response previously observed in the Phase 2a study. Patients who had not experienced a chloride transport response in the previous Phase 2a study were allocated to the 10-, 10-, 20-mg/kg dose level. Patients were to receive 84 consecutive days (12 weeks) of treatment with ataluren followed by 28 days of post-treatment follow-up.

The results indicated statistically significant, time-dependent improvements in TEPD chloride transport, the percentage of patients with a chloride transport response (improvements of  $\geq -5$  mV relative to baseline), and the proportion of patients with a chloride transport value in the normal range (equal to or more electrically negative than  $-5.0$  mV). Changes in pharmacodynamic parameters were not clearly dose-dependent. However, 2 patients who had not experienced a chloride transport normalization at either dose level in the previous Phase 2a study showed normalization over 3 months in this extension study. In addition, 2 patients who had not experienced a chloride transport response at either dose level in the previous Phase 2a study showed a response in this extension study. Statistically significant, time-dependent improvements in CF-related cough were also evident, particularly at the higher dose level of 10-, 10-, 20-mg/kg. Positive trends over time in pulmonary function were also observed.

Across both dose levels, treatment-emergent adverse events were primarily consistent with CF-related sinus, pulmonary, or gastrointestinal symptoms and no clearly dose-dependent increases in frequency or severity of adverse events were evident. Three patients (2 at the lower dose level and 1 at the higher dose level) noted mild dysuria. One patient receiving the higher dose level with a history of CF-related distal intestinal obstruction syndrome (DIOS) developed



constipation and dehydration on Day 80 of ataluren dosing; the event was considered possibly related to ataluren and was deemed serious because the patient was hospitalized for rehydration. There were no safety concerns identified in subjects' physical examinations, vital sign measurements, or ECGs. Repeated measurements of basal serum ACTH and cortisol concentrations during the 84 days of dosing showed no evidence of insufficiency of corticosteroid production. There was no evidence of hyperkalemia that would suggest hypoaldosteronism. One patient receiving the 10-, 10-, 20-mg/kg dose level of ataluren had unexplained treatment-emergent Grade 1 serum creatinine concentrations throughout the study; there were no urine abnormalities and the finding resolved upon cessation of treatment. Two patients discontinued ataluren early. One patient withdrew consent on Day 52 due to a transient Grade 1 increase in liver transaminase levels. The other patient, who had almost completed the 84-day course of dosing, developed DIOS on Day 80 (described above) and did not resume ataluren administration after resolution of her DIOS-related symptoms.

Hour 0 (trough) and Hour 3 plasma concentrations relative to the first daily dose were evaluated at monthly intervals. Ataluren showed generally stable concentrations over time, achieving mean trough concentrations of  $\geq 2$   $\mu\text{g/mL}$  at the 4-, 4-, 8-mg/kg dose level, and of  $\geq 5$   $\mu\text{g/mL}$  at the 10-, 10-, 20-mg/kg dose level.

### 2.2.3.3. Phase 3 Study

Ataluren was tested in a 48-week, double-blind, placebo-controlled study PTC124-GD-009-CF (Study 009) comparing ataluren to placebo in nmCF patients [Rowe 2012]. Eligible patients  $\geq 6$  years of age with nmCF and %-predicted FEV<sub>1</sub> between 40-90% were randomized to receive ataluren 10-, 10-, 20-mg/kg orally TID or placebo for 48 weeks. Primary and secondary endpoints were %-predicted FEV<sub>1</sub> change from baseline at 48 weeks and pulmonary exacerbations, respectively. Tertiary endpoints included nasal TEPD, sweat chloride, and chest CT scan. The trial enrolled 238 patients, ages six years and older, at multiple sites in North America, Europe, and Israel. Patients were randomly assigned to one of two treatment arms: ataluren (10 mg/kg morning, 10 mg/kg midday, 20 mg/kg evening) or placebo (morning, midday, evening).

The primary endpoint, the relative change from baseline in %-predicted FEV<sub>1</sub> at 48 weeks showed a positive trend favoring ataluren versus placebo, and a larger effect in the patients not receiving chronic inhaled antibiotics. The effect of inhaled antibiotics was largely attributable to the use of inhaled aminoglycosides. In the intent-to-treat population, there was a 3% difference in the relative change from baseline in %-predicted FEV<sub>1</sub> between the ataluren and placebo groups at Week 48 (-2.5% change on ataluren vs -5.5% change on placebo;  $p=0.124$ ). The relative decline in FEV<sub>1</sub> of -5.5% in the placebo arm over 48 weeks is indicative of the severity of nmCF patients. An analysis of the relative change from baseline in %-predicted FEV<sub>1</sub> 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;  $p=0.0478$ ).

The study was stratified by age, baseline FEV<sub>1</sub>, and the use of chronic inhaled antibiotics. A statistically significant effect (nominal  $p=0.0072$ ) was seen between treatment and use of inhaled antibiotics at baseline, indicating that inhaled antibiotics was a significant confounder of the overall results. A substantial treatment effect was seen in the patients not receiving chronic inhaled antibiotics at baseline; the Week 48 difference between the ataluren and placebo arms in FEV<sub>1</sub> was 6.7% (-0.2% change on ataluren vs -6.9% change on placebo). This difference in

treatment effect was driven by the use of inhaled 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<sub>1</sub>).

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 antibiotics, the pulmonary exacerbation rate in the ataluren group was 43% lower than the rate in the placebo group; 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.

The endpoints of nasal TEPD and sweat chloride, which were included in the study as biomarkers, failed to discriminate active treatment from placebo.

The CT scan score, which was included in Study 009 as an exploratory endpoint, failed to discriminate active treatment from placebo over the 48-week study duration. Specifically, there was no appreciable change in CT scan scores in the placebo group, despite significant decrease in %-predicted FEV<sub>1</sub>, suggesting that this outcome measure may not have been sufficiently sensitive to detect clinical changes over 48 weeks in this trial.

Safety results indicate that ataluren was generally well tolerated. 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 14.2.3.1](#)). 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.

#### **2.2.3.3.1. Phase 3 Extension Study**

Ataluren was also further tested in an international open-label, extension study in patients with nmCF (PTC124-GD-009e-CF). Subjects that completed the Phase 3 study (Study 009) were eligible for enrollment. The primary objective of this 96-week study (n=191) was to evaluate the long-term safety of ataluren in nmCF patients, at the planned daily dose level of 10-, 10-, 20-mg/kg of ataluren. Secondary objectives were to determine the long-term effect of ataluren on pulmonary function; pulmonary exacerbations, medical interventions; health-related quality of life (HRQL); general well-being; compliance with ataluren therapy; and ataluren plasma exposure. During the first 48 weeks of the trial, study assessments were performed at clinic visits every 4 to 8 weeks, depending upon the type of outcome measure. During the final 48 weeks of the trial, study assessments were performed at clinic visits every 8 to 16 weeks, depending upon the type of outcome measure. The results of this study are pending.

### **3. STUDY OBJECTIVE AND ENDPOINTS**

#### **3.1. Objectives**

The primary objective of this study is to determine the long-term safety and tolerability of 10-, 10-, 20- mg/kg ataluren in patients with nmCF who completed participation in the double-blind study (Study 009) as assessed by adverse events and laboratory abnormalities.

The secondary objectives are to determine the efficacy and safety of ataluren as assessed by spirometry (FEV<sub>1</sub>), pulmonary exacerbation rate, and other safety parameters (eg, 12-lead ECG measurements, vital signs).

The tertiary objectives are to determine the efficacy of ataluren as assessed by other parameters of pulmonary function (FVC and FEF<sub>25-75</sub>), and changes in body weight BMI.

#### **3.2. Endpoints**

##### *Primary*

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

##### *Secondary*

- Change from baseline to end of treatment in spirometric performance as measured by FEV<sub>1</sub>
- Rate of pulmonary exacerbations, as assessed by modified Fuchs (primary definition), and Fuchs and expanded Fuchs criteria
- Change from baseline in other safety parameters (eg, 12-lead ECG measurements, vital signs)

##### *Tertiary*

- Change from baseline to end of treatment in spirometric performance as measured by FVC and FEF<sub>25-75</sub>
- Change from baseline to end of treatment in body weight and BMI

### **4. SUBJECT SELECTION CRITERIA**

#### **4.1. Overview**

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

## 4.2. Inclusion Criteria

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

1. Evidence of signed and dated informed consent/assent document(s) indicating that the subject (and/or parent/legal guardian) has been informed of all pertinent aspects of the trial. **Note: If the study candidate is considered a child under local regulation, a parent or legal guardian must provide written consent prior to initiation of study screening procedures and the study candidate may be required to provide written assent. The rules of the responsible Institutional Review Board/Independent Ethic Committee (IRB/IEC) regarding whether one or both parents must provide consent and the appropriate ages for obtaining consent and assent from the subject should be followed.**
2. Evidence of completed participation in the double-blind study, PTC124-GD-009-CF (Study 009).
3. Body weight  $\geq 16$  kg.
4. Performance of a valid, reproducible spirometry test using the study-specific spirometer during the screening period. **Note: An FEV<sub>1</sub> value within a pre-specified range is not required for eligibility.**
5. Confirmed screening laboratory values within the central laboratory ranges. **Note: Confirmation should be performed for out-of-range values during the screening period to determine if the abnormality is real or artifactual. Values used to establish eligibility should be obtained during the screening period, and should generally be the most recent measurement obtained. All screening laboratory results must be received, reviewed and deemed acceptable for study participation before a subject is enrolled into the study.**
6. In male and female subjects who are sexually active, willingness to abstain from sexual intercourse or employ a barrier or medical method of contraception during the study drug administration and 60-day follow-up period.
7. Willingness and ability to comply with all study procedures and assessments, including scheduled visits, drug administration plan, laboratory tests, and study restrictions. **Note: The Investigator should consider any psychological, social, familial, or geographical factors that might preclude adequate study participation.**

## 4.3. Exclusion Criteria

The presence of any of the following conditions will exclude a subject from study enrollment:

1. Known hypersensitivity to any of the ingredients or excipients of ataluren (polydextrose, polyethylene glycol 3350, poloxamer 407, mannitol 25C, crospovidone XL10, hydroxyethyl cellulose, vanilla, colloidal silica, or magnesium stearate).
2. Any change (initiation, change in type of drug, dose modification, schedule modification, interruption, discontinuation, or re-initiation) in a chronic treatment/prophylaxis regimen for CF or for CF-related conditions within 4 weeks prior to screening or between screening and randomization. **Note: A subject can be enrolled who is using inhaled medications such as aztreonam, colistin, dornase-alfa, hypertonic saline, corticosteroids, or  $\beta_2$  agonists; or systemic drugs such as azithromycin or ibuprofen.**

***Expected cycling of inhaled aztreonam or inhaled colistin is permitted. Other than for treatment of CF pulmonary exacerbations, subjects should remain on a stable medical regimen of treatment/prophylaxis for CF-related conditions to avoid confounding interpretation of study results.***

3. Chronic use of systemic, tobramycin within 4 weeks prior to screening.
4. Exposure to another investigational drug within 4 weeks prior to screening. ***Note: Subjects receiving another investigational drug as part of a pre-approval expanded access program for that drug may participate with the prior consent of the PTC Therapeutics medical monitor.***
5. Ongoing participation in any other therapeutic clinical trial. ***Note: Subjects receiving another investigational drug as part of a pre-approval expanded access program for that drug may participate with the prior consent of the PTC Therapeutics medical monitor.***
6. Evidence of pulmonary exacerbation or acute upper or lower respiratory tract infection (including viral illnesses) within 3 weeks prior to screening or between screening and randomization. Treatment with intravenous antibiotics within 3 weeks prior to screening.
7. Treatment with intravenous antibiotics within 3 weeks prior to screening.
8. Ongoing immunosuppressive therapy (other than corticosteroids).
9. Ongoing warfarin, phenytoin, or tolbutamide therapy.
10. History of solid organ or hematological transplantation.
11. Major complications of lung disease (including massive hemoptysis, pneumothorax, or pleural effusion) within 8 weeks prior to screening.
12. Known portal hypertension.
13. Positive hepatitis B surface antigen, hepatitis C antibody test, or human immunodeficiency virus (HIV) test. ***Note: Subjects who are hepatitis C antibody positive but do not have active hepatitis C as documented by normal serum bilirubin; ALT and AST; and negative hepatitis C RNA test during the screening period may be eligible for inclusion. Subjects with hepatitis C with elevated serum bilirubin, ALT, or AST and negative hepatitis C RNA test may be eligible if the abnormalities are attributed to other causes by a gastroenterologist or hepatologist.***
14. Pregnancy or breast-feeding.
15. Current smoker or a smoking history of  $\geq 10$  pack-years (number of cigarette packs/day  $\times$  number of years smoked).
16. Prior or ongoing medical condition (eg, concomitant illness, alcoholism, drug abuse, psychiatric condition), medical history, physical findings, ECG findings, or laboratory abnormality that, in the investigator's opinion, could adversely affect the safety of the subject, makes it unlikely that the course of treatment or follow-up would be completed, or could impair the assessment of study results.

## **5. ENROLLMENT PROCEDURES**

### **5.1. Source and Number of Subjects**

Approximately 70 subjects will be enrolled following completion of participation in the double-blind study PTC124-GD-009-CF (Study 009).

### **5.2. Screening and Study Drug Dispensation**

The investigator must inform each 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 subject number used in the PTC124-GD-009-CF study shall be retained for use in this study. This subject number must be used for subject identification on all study related documents (case report forms [CRFs], laboratory samples, etc.).

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

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

## **6. INVESTIGATIONAL MEDICINAL PRODUCT**

### **6.1. Study Drug Supply**

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 is packaged in aluminium-foil, child-resistant sachets (packets), and supplied in dose strengths containing 125-, 250-, or 1000-mg of the active drug substance.

Ataluren will be supplied free of charge to the investigator site by PTC Therapeutics for appropriate distribution to the subjects/caregivers. It is intended that ataluren will be provided in sufficient supply for a 16-week study period. However, in the event of pending commercial availability of ataluren, drug may be supplied for a treatment period of less than 16 weeks. Resupply may be obtained via the IVR/IWR system.

#### **6.1.1. 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.

#### **6.1.2. Study Drug Storage**

Sachets of ataluren will be shipped to the investigational sites, and stored and monitored 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.

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

### **6.1.3. Study Drug Dispensation**

Dosing of ataluren will be based on milligrams of drug per kilogram of subject body weight at Screening (Visit 1) and will be calculated to allow for dosing with 1 or 2 of the 3 available sachet dose strengths (125- or 250- or 1000-mg of ataluren).

The clinic staff (eg, pharmacist or other qualified person) will be responsible for dispensing ataluren in 16-week increments according to the dosing schedule and IVR/IWR directions.

Because of potential changes in subject body weight over time, at Week 32 (Visit 4), Week 64 (Visit 6), Week 96 (Visit 8), Week 128 (Visit 10) and Week 160 (Visit 12) a dose adjustment may be made based on the subject's body weight at that visit. Depending upon the magnitude of change in subject body weight since baseline, the number and strengths of sachets to be used by the subject may remain the same or may be adjusted.

### **6.1.4. Study Drug Preparation**

Once at the investigational site and/or with the subject/caregiver, ataluren sachets should be stored at room temperature, away from the reach of children until time of reconstitution. One (1) or 2 of the 3 available sachet dose strengths (125-, 250-, or 1000-mg of ataluren) will be used to prepare each dose. 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, or 3 tablespoons of semi-solid food. The prepared dose should be mixed well before administration. The amount of the liquid or semi-solid food can be increased based on subject preference.

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 (if kept at room temperature).

Detailed written drug mixing and dosing instructions will be provided to the subject/caregiver when ataluren supplies are dispensed. A copy of these instructions will be maintained in the investigator site study file.

### **6.1.5. Study Drug Accountability**

The investigator and/or the responsible site personnel must maintain accurate records of the receipt of all ataluren shipped by PTC Therapeutics or its designee, including, but not limited to, the date received, lot number, amount received, and the disposition of all ataluren. Current reconciliation and dispensing records must also be maintained that include the date and amount of ataluren dispensed, relevant batch numbers, and subject's assigned study number. Subjects should return all unused sachets of ataluren to the investigational site at the end of each 16-week treatment period for inventory. The CRF will serve as the source document for drug supply to the subjects and will document the return of any unused drug for compliance assessments.

Depending upon the decision of PTC Therapeutics, unused clinical supplies must be destroyed or returned to PTC Therapeutics (or its designee) after the study is completed and drug accountability has been verified by the monitor. Records documenting the date of study drug destruction or shipping, relevant batch numbers, and amount destroyed or shipped should be kept in the investigator site study file.

#### **6.1.6. Overdose Precautions**

For any subject experiencing an overdose (administration of an ataluren dose >4.0 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](#)).

#### **6.1.7. Inadvertent Exposure and Spill Precautions**

Based on available data from nonclinical studies, ataluren does not appear to be acutely toxic or genotoxic at levels that are likely to result from inadvertent exposure to the contents of the packet, if opened. Based on general experience with the drug during manufacturing, it does not appear that exposure to formulated ataluren is likely to be irritating to skin or eyes. However, personnel handling the drug should use reasonable precautions to avoid eye contact, skin contact, inhalation, or ingestion of the material in the packets. 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. Study Drug Dosing**

Dosing of ataluren will be based on milligrams of drug per kilogram of subject body weight at Screening (Visit 1). All subjects will receive approximately 10-, 10-, 20-mg/kg ataluren TID for ~192 weeks. At Week 32 (Visit 4), Week 64 (Visit 6), Week 96 (Visit 8), Week 128 (Visit 10) and Week 160 (Visit 12) dose adjustment may be made based on the subject's body weight at that visit.

#### **6.2.2. Duration of Treatment**

Study duration will be 192 weeks. If ataluren becomes commercially available or the clinical development of ataluren in nmCF is discontinued prior to the 192 weeks, subjects will be discontinued from the study. The actual duration of ataluren treatment under this protocol will be subject to the provisions in [Section 10](#).

#### **6.2.3. Schedule of Administration**

As noted in [Table 1](#), 3 doses should be taken per day – the 1<sup>st</sup> dose in the morning, the 2<sup>nd</sup> dose during the middle of the day (mid-day), and the 3<sup>rd</sup> dose in the evening. 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 ( $\pm 1$  hour) between



morning and mid-day doses, ~6 hours ( $\pm 1$  hour) between mid-day and evening doses, and ~12 hours ( $\pm 1$  hour) between the evening dose and the morning dose on the next day.

**Table 1: Suggested Daily Dosing Schedule**

Dose Designation	Preceding Meal	Example Dosing Times <sup>a</sup>
Morning	Breakfast	~7:00 AM – 0700 hours ( $\pm 1$ hour)
		↑ ~6 hours ↓
Mid-day	Lunch	~1:00 PM – 1300 hours ( $\pm 1$ hour)
		↑ ~6 hours ↓
Evening	Dinner	~7:00 PM – 1900 hours ( $\pm 1$ hour)
		↑ ~12 hours ↓
Next Day Morning	Breakfast	7:00 AM – 0700 hours ( $\pm 1$ hour)

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

#### **6.2.4. Instructions for Delays in Dosing**

Dosing delays should be handled as follows:

- If dosing of ataluren is delayed by  $\leq 1$  hour, the planned dose should be taken with no changes to the subsequent dose schedules.
- If ataluren dosing is delayed by  $> 1$  hour but  $\leq 4$  hours, the planned dose should be taken; however, all future doses for that day should be shifted later by an approximately corresponding amount.
- If ataluren dosing is delayed by  $> 4$  hours, the dose should not be taken. Ataluren administration may continue but the missed dose should not be taken and the planned timing of subsequent study drug dosing should not be altered.

### **6.3. Safety Monitoring and Study Drug Dose Interruption/Modification**

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

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

Renal abnormalities will be followed closely in this study given findings that have occurred in an international, multicenter, double-blind, placebo-controlled Phase 3 trial evaluating ataluren in patients  $\geq 6$  years of age with nonsense mutation cystic fibrosis (PTC124-GD-009-CF; as described in [Section 14.2.3.1](#) and in the Ataluren Investigator Brochure).

For adverse events or laboratory abnormalities, the investigator will use judgment in determining whether the event or abnormality is clinically significant, whether diagnostic evaluation is warranted, and whether potential interruption of ataluren treatment is appropriate. In general, life-threatening (Grade 4) or severe (Grade 3) adverse events or laboratory abnormalities should be considered clinically significant, although recurrent or persistent moderate events (Grade 2) may also be considered clinically significant in certain circumstances. Reference should be made to the Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0 (see [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/ctcae3.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.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 ataluren immediately, for interrupting ataluren after confirmation of a value beyond the threshold, or for continuing ataluren while evaluating for potential drug-related toxicity. For adverse events or laboratory abnormalities not listed in [Table 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 ataluren is appropriate.

**Table 2: Safety Monitoring Parameters and Actions To Be Taken**

Organ System and Laboratory Parameter	Stop Study Drug Immediately, Confirm <sup>a</sup> Abnormal Value, and Then Start Work-Up	Stop Study Drug After Confirming <sup>a</sup> Abnormal Value, and Then Start Work-Up	Continue Study Drug, Confirm <sup>a</sup> Abnormal Value, and then Start Work-Up
<b>Hepatic</b>			
Serum total bilirubin <sup>b</sup>	≥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)	---
<b>Renal</b>			
Serum cystatin C	>2.00 mg/L	>1.33 – 2.00 mg/L	---
Serum creatinine	≥ Grade 2 (≥1.5 x ULN for age)	Grade 1 (>ULN – 1.5 x ULN for age)	---
Serum BUN	≥3.0 x ULN	≥1.5 – 3.0 x ULN	---
Urine protein: urine creatinine (spot)	---	>0.40 mg:mg	---
Urine blood (by dipstick)	4+ (in absence of menstruation)	3+ (in absence of menstruation)	2+ (in absence of menstruation)

<sup>a</sup> Laboratory abnormalities may be confirmed immediately or based on investigator judgment.

<sup>b</sup> 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, Ca<sup>2+</sup> = calcium, GGT = gamma glutamyl transferase, HCO<sub>3</sub><sup>-</sup> = bicarbonate, K<sup>+</sup> = potassium, Mg<sup>2+</sup> = magnesium, Na<sup>+</sup> = sodium, ULN = upper limit of normal

It should be noted that blood samples for cortisol, renin and aldosterone determinations will be obtained as necessary during the study, for patients with 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 study baseline 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 subjects 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 [Table 6](#)). Once it has been documented that a subject 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. Subjects 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 subjects 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 subjects with multiple stones at first presentation, in subjects 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 subject 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 subject 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 Ataluren Administration after an Interruption for Safety Concerns**

In deciding whether to re-institute ataluren 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 ataluren
- The subject'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 ataluren treatment. If the investigator considers the hepatic or renal event that led to ataluren interruption to be probably related to ataluren, restarting ataluren is not advised. In this case, the subject should be discontinued from the study (see [Sections 6.3.4](#) and [10](#)). If the investigator considers the hepatic or renal event that prompted ataluren interruption to be possibly related or unlikely related to ataluren, the investigator should use best judgment in determining whether to restart ataluren. If the hepatic or renal event is considered unrelated to ataluren, re-institution of ataluren is recommended.

If the investigator believes it is appropriate to do so and the PTC Therapeutics medical monitor has been consulted, ataluren may be re-initiated. If the event was determined to be unrelated to ataluren, the treatment may be resumed at full dose. Otherwise, if the drug is resumed, it should be initially re-initiated at half of the original dose. The appropriate clinic staff should instruct the subject/caregiver about the revised number of study drug sachets to be used per dose according to the new schedule. Re-challenge at half dose should be initiated only as a bridge to full dosing. If a subject cannot tolerate the full dose, they should be discontinued from study participation.

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

If after dose reduction, the subject experiences a recurrence of a previous abnormality that led to ataluren dose interruption or experiences the new occurrence of an unacceptable adverse event or laboratory abnormality, the investigator should interrupt ataluren and confer with the

PTC Therapeutics medical monitor regarding the potential need to discontinue ataluren permanently.

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

If after appropriate consideration of ataluren interruption/modification and consultation with the PTC Therapeutics medical monitor, it is not appropriate for a subject to continue with study treatment, then ataluren should be permanently discontinued. If permanent discontinuation of ataluren is the result of an SAE, then a follow-up SAE report form should be completed (see [Section 9.7](#)). In the case of a treatment discontinuation due to an adverse event that is not an SAE, the PTC Therapeutics medical monitor should be notified (see [Section 10](#)). 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 case report form (CRF). The End of Treatment Visit CRF should be completed and appropriate follow-up (at ~4 weeks as per protocol or until recovery from or stabilization of the adverse event, whichever comes last) should be instituted.

## **7. CONCOMITANT AND SUPPORTIVE THERAPY**

### **7.1. Concomitant Medications**

Other than ataluren, any treatments (including prescription and non-prescription drugs, health foods, herbal remedies, self-prescribed drugs, street drug, tobacco products, or alcohol) taken by a subject from the screening period through the 4-Week Post-Treatment Follow-Up Visit 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 subjects 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. If considered necessary for the subject's wellbeing, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator. The decision to authorize the use of any drug other than ataluren should take into account subject safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more relevant underlying event, and whether use of a concomitant medication will compromise the outcome or integrity of the study.

For subjects 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 subjects who are on CF-specific therapy/prophylaxis at baseline, a stable regimen should be maintained during ataluren treatment while participating in this clinical trial. 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, subjects 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**

Subjects 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 subjects 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 subjects 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. Subjects requiring IV therapy with a glycopeptide antibiotic (eg, vancomycin), should be closely monitored in an appropriate setting, such as a hospital. 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 subjects receiving any type of potentially nephrotoxic agents, antibiotic drug levels, and renal function should be closely monitored. Creatinine and BUN should be measured prior to initiating aminoglycosides or other potentially nephrotoxic therapy, and at least twice a week during the course of such antibiotic treatment, where possible. 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, where possible. Additionally, subjects 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 subjects experiencing nausea, vomiting, diarrhea, fever, or laboratory evidence of dehydration. Treatment with ataluren may be resumed no earlier than 2 days after administration of nephrotoxic antibiotics has ceased.

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

It should be emphasized to subjects/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.

### **7.1.3. Drugs Metabolized by CYP2C8 or CYP2C9**

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.

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 subjects 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 subjects who require anticoagulation during the study, use of an alternative form of anticoagulation (eg, fractionated heparin) should be considered. Phenytoin is metabolized by CYP2C9 and concomitant use with ataluren may be of potential concern. For subjects who require anticonvulsant therapy during the study, use of alternative anticonvulsant drugs should be considered.

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

#### **7.1.4. Other Potential Interactions**

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

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.

#### **7.1.5. Other Concomitant Medications**

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

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

Subjects/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 subject during the course of the study and the reason for use will be recorded in the source documents and in the concomitant medication CRF.



## **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 subjects participating in the study. Respiratory care guidelines as suggested by the American Thoracic Society/European Thoracic Society should be followed [[ATS 2004](#)].

### **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 subjects receiving ataluren, it is important to encourage study subjects to maintain adequate hydration throughout the study. Subjects should be adequately hydrated prior to receiving 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 subjects 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 types and timing of data to be recorded are summarized in [Table 3](#). Please see [Section 8.2](#) for cross-referenced explanations of the study procedures outlined.

**Table 3: Schedule of Events**

Study Period	Screening	Ataluren Treatment							
Study Week	Week -4 to -1	Week 1	Week 8 (Phone Call)	Week 16	Week 24 (Phone Call)	Week 32	Week 40 (Phone Call)	Week 48	Week 56 (Phone Call)
Study Day	-28 to -1	1 (+7 days)	56 (±7 days)	112 (±7 days)	168 (±7 days)	224 (±7 days)	280 (±7 days)	336 (±7 days)	392 (±7 days)
Visit / Call	1	2	2a	3	3a	4	4a	5	5a
Informed Consent	X								
IVR/IWR System Screening	X								
Clinical and Medication History	X								
Vital Signs (including pulse oximetry)	X	X		X		X		X	
Height	X	X		X		X		X	
Weight	X	X		X		X		X	
Physical Examination	X	As clinically indicated						X	As clinically indicated
Serum Viral Screen	X								
β-HCG <sup>a</sup>	X	X		X		X		X	
Cortisol, Renin, and Aldosterone	X	As clinically indicated							
Biochemistry <sup>b</sup>	X	X		X		X		X	
Hematology	X	X		X		X		X	
Urinalysis	X	X		X		X		X	
Ataluren PK (trough)				X		X		X	
Renal Ultrasound	X	As clinically indicated							
12-Lead ECG	X			X		X		X	
Ataluren Administration in Clinic		X <sup>c</sup>							
Ataluren Dispensation		X		X		X		X	
Review Ataluren Compliance				X		X		X	
Adverse Events	X <sup>d</sup>	X		X		X		X	
Concomitant Medication / Non-Drug Therapy	X	X		X		X		X	
Spirometry	X	X		X		X		X	
Respiratory Event Evaluation <sup>e</sup>	X	X	X	X	X	X	X	X	X
Presence of <i>P. aeruginosa</i> in Sputum	X	X		X		X		X	

**Table 3: Schedule of Events - Continued**

Study Period	Ataluren Treatment									
	Week 64	Week 72 (Phone Call)	Week 80	Week 88 (Phone Call)	Week 96	Week 104 (Phone Call)	Week 112	Week 120 (Phone Call)	Week 128	Week 136 (Phone Call)
Study Day	448 (+7 days)	504 (±7 days)	560 (±7 days)	616 (±7 days)	672 (±7 days)	728 (±7 days)	784 (±7 days)	840 (±7 days)	896 (±7 days)	952 (±7 days)
Visit / Call	6	6a	7	7a	8	8a	9	9a	10	10a
Vital Signs (including pulse oximetry)	X		X		X		X		X	
Height	X		X		X		X		X	
Weight	X		X		X		X		X	
Physical Examination	As clinically indicated				X	As clinically indicated				
Serum Viral Screen										
β-HCG <sup>a</sup>	X		X		X		X		X	
Cortisol, Renin, and Aldosterone	As clinically indicated									
Biochemistry <sup>b</sup>	X		X		X		X		X	
Hematology	X		X		X		X		X	
Urinalysis	X		X		X		X		X	
Ataluren PK (trough)	X		X		X		X		X	
Renal Ultrasound	As clinically indicated									
12-Lead ECG	X		X		X		X		X	
Ataluren Administration in Clinic										
Ataluren Dispensation	X		X		X		X		X	
Review Ataluren Compliance	X		X		X		X		X	
Adverse Events	X		X		X		X		X	
Concomitant Medication / Non-Drug Therapy	X		X		X		X		X	
Spirometry	X		X		X		X		X	
Respiratory Event Evaluation <sup>c</sup>	X	X	X	X	X	X	X	X	X	X
Presence of <i>P. aeruginosa</i> in Sputum	X		X		X		X		X	

**Table 3: Schedule of Events - Continued**

Study Period	Ataluren Treatment							4-Week Post-Treatment Follow-Up (End of Study)
	Week 144	Week 152 (Phone Call)	Week 160	Week 168 (Phone Call)	Week 176	Week 184 (Phone Call)	Week 192 EOT/ Early D/C <sup>f</sup>	
Study Week	1008 (±7 days)	1064 (±7 days)	1120 (±7 days)	1176 (±7 days)	1232 (±7 days)	1288 (±7 days)	1344 (±7 days)	1372 (±7 days)
Study Day								
Visit / Call	11	11a	12	12a	13	13a	14	15
Vital Signs (including pulse oximetry)	X		X		X		X	X
Height	X		X		X		X	X
Weight	X		X		X		X	X
Physical Examination	X	As clinically indicated					X	X
Serum Viral Screen								
β-HCG <sup>a</sup>	X		X		X		X	X
Cortisol, Renin, and Aldosterone	As clinically indicated							
Biochemistry <sup>b</sup>	X		X		X		X	X
Hematology	X		X		X		X	X
Urinalysis	X		X		X		X	X
Ataluren PK (trough)	X		X		X		X	
Renal Ultrasound	As clinically indicated							
12-Lead ECG	X		X		X		X	X
Ataluren Administration in Clinic								
Ataluren Dispensation	X		X		X			
Review Ataluren Compliance	X		X		X		X	
Adverse Events	X		X		X		X	X
Concomitant Medication / Non-Drug Therapy	X		X		X		X	X
Spirometry	X		X		X		X	X
Respiratory Event Evaluation <sup>c</sup>	X	X	X	X	X	X	X	
Presence of <i>P. aeruginosa</i> in Sputum	X		X		X		X	

<sup>a</sup> Testing for female subjects only.

<sup>b</sup> Ideally, subjects should have fasted for at least 8 hours prior to blood collection.

<sup>c</sup> Clinic staff will administer the first dose of study drug at Study Day 1 (Visit 2).

<sup>d</sup> Adverse events (AEs) should be elicited from subjects at all study visits; however, any untoward medical occurrences collected at Screening will be used to assess study eligibility only and will not be reported as AEs in the CRF.

<sup>e</sup> Includes completion of the Respiratory Event Form (REF).

<sup>f</sup> Patients that do not complete ≥192 Weeks of treatment will be considered prematurely discontinued.

**Abbreviations:** β-HCG = human chorionic gonadotropin, D/C = discontinuation, ECG = electrocardiogram, EOT = end of treatment, IVR/IWR = Interactive Voice Response/Interactive Web Response, PK = pharmacokinetics

## **8.2. Explanation of Study Procedures**

### **8.2.1. Screening and Week 1 Visits**

No study-related procedures should be performed prior to the signature of the informed consent/assent document(s). Thereafter, subjects should undergo the initial set of screening procedures as noted in [Table 3](#), including registration in the IVR/IWR system. If a subject has successfully completed the necessary screening assessments and has been confirmed as eligible by the investigator, the Week 1 visit for the subject can be conducted and ataluren treatment may be initiated immediately. The subject/caregiver will receive a 16-week supply of study drug before leaving the clinic. Instructions regarding appropriate study drug storage, compliance, preparation, and administration will also be provided.

### **8.2.2. Treatment Visits / Calls During Study**

Each subject will subsequently return to the clinical research facility for on-site visits every 16 weeks ( $112 \pm 7$  days) over 192 weeks of treatment. In addition, phone calls will be conducted between on-site visits approximately 8 weeks ( $56 \pm 7$  days) after the previous on-site visit.

#### **8.2.2.1. End of Treatment**

Each subject will return to the clinical research facility at Week 192 (Visit 14) for the End of Treatment (EOT) Visit. However, study duration may be altered (either extended or terminated), if clinically appropriate according to interim study results. In this case, the timing of the EOT Visit will be adjusted appropriately. If the subject discontinues prematurely (ie, before Week 192 (Visit 14)) and the last visit to the investigational site occurred  $>4$  weeks previously, the procedures that would normally be performed at Week 192 (Visit 14) should be performed before the subject leaves the study as a Premature Discontinuation Visit. However, if the subject discontinues prematurely and the date of the last dose of ataluren was  $\geq 4$  weeks prior to discontinuation, the subject should return for the 4-Week Post-Treatment Follow-up Visit only.

#### **8.2.2.2. Post-Treatment Visits**

All subjects, including those who discontinue study drug prematurely, will return to the investigational site 4 weeks ( $\pm 7$  days) after the last dose of ataluren for a 4-Week Post-Treatment Follow-up Visit. Please refer to [Section 10](#) for further details regarding subject withdrawal procedures. The end of trial will be defined as the date the last subject completes the last study visit, which is expected to be the 4-Week Post-Treatment Follow-up Visit.

### **8.2.3. Informed Consent**

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

### **8.2.4. Clinical/Medication History**

The investigator or a qualified designee should review the patient's clinical history, including details relating to CF and any other medical conditions. Information regarding clinical history and current medications must be captured on the medical history and prior/concomitant medication CRFs, respectively. In particular, details regarding any inhaled aminoglycoside use

within 6 months prior to study entry should be documented. In addition, history of *Pseudomonas aeruginosa* infection, history of renal insufficiency, and history of exocrine pancreatic insufficiency should also be collected.

#### **8.2.5. Vital Signs**

Vital signs (including systolic and diastolic blood pressure, pulse rate, pulse oximetry, and body temperature) will be monitored at Screening (Visit 1) through Week 196 (Visit 15 - Post-Treatment Visit; 4 weeks post discontinuation of study drug). Pulse rate, pulse oximetry and blood pressure determinations will be performed with the subject in a sitting position after a 5-minute rest.

#### **8.2.6. Height, Weight, and Physical Examination**

Height (in cm) and weight (in kg) will be measured at Screening (Visit 1) through Week 196 (Visit 15- Post-Treatment Visit; 4 weeks post discontinuation of study drug) at each clinic visit as outlined in Table 3.

A full physical examination (including evaluation of the cardiovascular system, chest and lungs, thyroid, abdomen, nervous system, skin and mucosae, musculoskeletal system, eyes, ears, nose, mouth, throat, spine, lymph nodes, and extremities) will be conducted at Screening (Visit 1), Week 48 (Visit 5), Week 96 (Visit 8), Week 144 (Visit 11), Week 192 (Visit 14/End of Treatment), and Week 196 (Visit 15 - Post-Treatment Visit; 4 weeks post discontinuation of study drug).

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

#### **8.2.7. Central Laboratory Assessments**

All laboratory samples will be analyzed by a central laboratory. Please refer to the Central Laboratory Manual for instructions regarding collection, processing, and shipment of all laboratory samples.

Please refer to [Section 8.3](#) for a summary of blood draw volume requirements for this study.

##### **8.2.7.1. Viral Screen and Pregnancy Laboratory Assessments**

The following serum laboratory parameters will be measured at Screening (Visit 1): hepatitis B surface antigen, hepatitis C antibody, human immunodeficiency virus (HIV).

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

##### **8.2.7.2. Adrenal Laboratory Assessment**

Plasma adrenal laboratory assessments will include cortisol, renin, and aldosterone. These parameters will be measured at Screening (Visit 1) and as clinically indicated during the study in subjects who develop evidence of adrenal dysfunction.

##### **8.2.7.3. 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 all study visits.

#### **8.2.7.4. Serum Biochemistry Laboratory Assessment**

Serum 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 all study visits. Ideally, subjects should have fasted for at least 8 hours prior to blood collection.

#### **8.2.7.5. Urinalysis**

Urinalysis assessments will include pH, specific gravity, glucose, ketones, blood, protein, creatinine urobilinogen, bilirubin, nitrite, and leukocyte esterase. These parameters will be measured at all study visits.

#### **8.2.7.6. Pharmacokinetic Analysis (PK)**

A plasma PK trough sample will be collected prior to the morning ataluren administration at Week 16 (Visit 3), Week 32 (Visit 4), Week 48 (Visit 5), Week 64 (Visit 6), Week 80 (Visit 7), Week 96 (Visit 8), Week 112 (Visit 9), Week 128 (Visit 10), Week 144 (Visit 11), Week 160 (Visit 12), Week 176 (Visit 13), and Week 192 (Visit 14/End of Treatment). These samples will be sent to a central bioanalytical laboratory for analysis of ataluren trough levels. Please refer to the Lab Manual for instructions regarding the collection, processing and shipment of all PK samples to the bioanalytical laboratory

#### **8.2.8. Renal Ultrasound**

An ultrasound to examine the kidneys and collecting system will be performed at Screening (Visit 1) in order to obtain a baseline assessment for each subject. 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 results of such ultrasounds must also be included in the CRF. 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.

#### **8.2.9. 12-Lead ECG**

A 12-lead electrocardiogram (ECG) will be obtained at Screening (Visit 1), Week 16 (Visit 3), Week 32 (Visit 4), Week 48 (Visit 5), Week 64 (Visit 6), Week 80 (Visit 7), Week 96 (Visit 8), Week 112 (Visit 9), Week 128 (Visit 10), Week 144 (Visit 11), Week 160 (Visit 12), Week 176 (Visit 13), Week 192 (Visit 14/End of Treatment), and Week 196 (Visit 15 - Post-Treatment Visit; 4 weeks post discontinuation of study drug). The central reading provided by a certified vendor will serve as the official study result. Starting in the second year of the study, after Week 56, ECGs will be read locally at investigational sites and interpreted for clinical significance. The findings will be captured in source documents and within the CRF.

Additional ECGs may be performed at any time during the study as clinically indicated at the discretion of the investigator. However, the PTC medical monitor must be informed via e-mail that an additional ECG was obtained.

#### **8.2.10. Ataluren Administration and Dispensation**

Subjects should take ataluren TID as described in [Section 6.2.3](#). Study drug supply sufficient for each 16-week treatment period will be supplied to the subject/caregiver at Study Day 1 (Visit 2) and each subsequent on-site visit through Week 176 (Visit 13). Sufficient drug for 120 days (16 weeks + 8 days) will be provided at each of these visits to lessen the likelihood that subjects will experience drug shortages due to inadvertent loss of study drug or scheduling delays for return visits.

Clinic staff will administer the first dose of the study drug at Study Day 1 (Visit 2). Subjects should remain in the study center for at least 30 minutes to determine that no immediate untoward reactions occurred after ataluren administration.

#### **8.2.11. Ataluren Compliance**

Subjects/caregivers will return all unused sachets of ataluren to the study site. A Study Drug Administration Record (to be completed by the investigational site pharmacist or designated personnel) will document the return of unused sachets for compliance assessments at Week 16 (Visit 3), Week 32 (Visit 4), Week 48 (Visit 5), Week 64 (Visit 6), Week 80 (Visit 7), Week 96 (Visit 8), Week 112 (Visit 9), Week 128 (Visit 10), Week 144 (Visit 11), Week 160 (Visit 12), Week 176 (Visit 13), and Week 192 (Visit 14/End of Treatment). Clinic staff will record the ataluren dosing information including the actual clock time of the first dose administered in the clinic.

#### **8.2.12. Adverse Events**

Adverse events must be assessed and documented at each clinic visit. This information will be collected at Week 1 (Visit 2) through Week 196 (Visit 15 - Post-Treatment Visit; 4 weeks post discontinuation of study drug). In addition, subjects/caregivers will be encouraged to report adverse events of concern at any time in the intervals between visits. Refer to [Section 9](#) for additional information regarding adverse event collection and reporting.

#### **8.2.13. Concomitant Medications**

Information regarding any concomitant medications administered, as well as information regarding all non-drug therapies, will be collected throughout the study. Specifically, start and stop dates for all inhaled antibiotics used during the study must be captured in the CRF. This information will be collected at Screening (Visit 1), Week 1 (Visit 2), Week 16 (Visit 3), Week 32 (Visit 4), Week 48 (Visit 5), Week 64 (Visit 6), Week 80 (Visit 7), Week 96 (Visit 8), Week 112 (Visit 9), Week 128 (Visit 10), Week 144 (Visit 11), Week 160 (Visit 12), Week 176 (Visit 13), Week 192 (Visit 14/End of Treatment) and Week 196 (Visit 15 - Post-Treatment Visit; 4 weeks post discontinuation of study drug). In addition, subjects/caregivers will be encouraged to report any change in concomitant medications at any time in the intervals between visits. Please refer to [Section 7](#) for additional information regarding concomitant medications and other supportive (ie, non-drug) therapies.



#### **8.2.14. Spirometry**

Lung function will be assessed by spirometry using standardized equipment and procedures. Spirometry will be performed at Screening (Visit 1), Week 1 (Visit 2), Week 16 (Visit 3), Week 32 (Visit 4), Week 48 (Visit 5), Week 64 (Visit 6), Week 80 (Visit 7), Week 96 (Visit 8), Week 112 (Visit 9), Week 128 (Visit 10), Week 144 (Visit 11), Week 160 (Visit 12), Week 176 (Visit 13), Week 192 (Visit 14/End of Treatment) and Week 196 (Visit 15 - Post-Treatment Visit; 4 weeks post discontinuation of study drug). 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 obtain 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).

#### **8.2.15. 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 at Screening (Visit 1), Week 1 (Visit 2), Week 16 (Visit 3), Week 32 (Visit 4) and Week 48 (Visit 5), Week 64 (Visit 6), Week 80 (Visit 7), Week 96 (Visit 8), Week 112 (Visit 9), Week 128 (Visit 10), Week 144 (Visit 11), Week 160 (Visit 12), Week 176 (Visit 13), and Week 192 (Visit 14/End of Treatment). Information regarding pulmonary exacerbations will also be collected via phone call in between on-site visits (ie, Week 8, Week 24, Week 40, Week 56, Week 72, Week 88, Week 104, Week 120, Week 136, Week 152, Week 168 and Week 184), and at the time of any unscheduled contact between the subject and the clinic.

In addition to subject/caregiver and investigator discussion at scheduled study visits and phone calls, subjects/caregivers are encouraged to contact their investigator by telephone with all pulmonary exacerbation details for any events that occur between scheduled visits or phone calls.

### **8.2.16. 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 Screening (Visit 1), Week 1 (Visit 2), Week 16 (Visit 3), Week 32 (Visit 4), and Week 48 (Visit 5), Week 64 (Visit 6), Week 80 (Visit 7), Week 96 (Visit 8), Week 112 (Visit 9), Week 128 (Visit 10), Week 144 (Visit 11), Week 160 (Visit 12), Week 176 (Visit 13), and Week 192 (Visit 14/End of Treatment).

### **8.3. Blood Collection Summary**

Assuming a 192-week treatment period and all visits completed as noted in [Table 3](#), the maximum amount of blood to be drawn at a single visit is approximately 18.0 mL, which occurs at the Screening visit only. The maximum blood to be drawn at subsequent visits (Visits 2-15) is approximately 9.0 mL or less. The total amount of blood to be drawn over the entire study period (including the Screening visit, the 192-week treatment period, and the 4-week follow-up period) is approximately 144.0 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 subject who is administered ataluren in this study.

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

- All adverse events that are suspected or are not suspected to be due to ataluren.
- Overdose (administration of an ataluren dose >4.0 times the highest intended total daily dose level for this protocol [ $>160$  mg/kg/day]).
- All reactions from medication misuse, abuse, withdrawal, sensitivity, or toxicity
- All reactions that result from medication errors or uses of ataluren outside what is described in the protocol.
- Apparently unrelated illnesses, including the worsening of a pre-existing illness.
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate adverse events. The outcome of the accident (hip fracture secondary to the fall) should be recorded in source documents.

- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Laboratory or ECG abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (eg, elevated liver enzymes in a subject with jaundice) should be captured in the source documents. Laboratory abnormalities not requiring clinical intervention or further investigation will be captured as part of overall laboratory monitoring, and should not be reported as adverse events.
- A 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 ataluren administration), including deaths due to disease progression. Any death occurring later than 4 weeks following the last dose need not be reported as a serious adverse event unless it is a result of an event that started within the period covered by the on-study definition. The reported adverse event should be the event that caused the death. In addition, any adverse event resulting in death that occurs subsequent to the adverse event-reporting period and that the investigator assesses as possibly related to ataluren should also be reported as serious.
- Life-threatening adverse event. This is an event that, in the view of either the investigator or the sponsor, places the subject at immediate risk of death. It does not include an event that, had it occurred in a more severe form, hypothetically might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (excluding hospitalizations for administration of ataluren, procedures required by the study protocol,

or 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 subject to the hospital and observational durations in the emergency room for less than 24 hours are not considered serious.

- Persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions.
- Any other medically important event that the investigator or the sponsor judges to be serious or which is defined as serious by the regulatory agency in the local country. Medical judgment should be exercised in deciding whether a reaction is serious in other situations. Important medical events that do not result in death, are not immediately life-threatening, and do not require hospitalization may be considered serious when, based on appropriate medical judgment, they may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment administration in an emergency room or at home, newly diagnosed malignancy, or blood dyscrasias, or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- 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 unless hospitalization is required. 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  $>1.33 \times \text{ULN}$
- Serum creatinine  $> \text{ULN}$  for age
- Serum BUN  $>1.5 \times \text{ULN}$
- Urine dipstick with  $\geq 2+$  blood
- Urine dipstick with  $\geq 2+$  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 ataluren as referenced in the most current investigator brochure, or that are symptomatically and pathophysiologically related to a known toxicity but differ because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. “Unexpected,” as used in this definition, also refers to an adverse event that is mentioned in the most current investigator brochure as occurring with the class of drugs or as anticipated from the pharmacological properties of ataluren, 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 subject will be questioned about adverse events at each study visit or during any telephone contact with the subject or parent/guardian caregiver. The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the subject/caregiver at each scheduled clinic visit after ataluren administration or during any telephone contact with the subject/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 subjects 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 CRF using concise medical terminology; whenever possible terms contained in Medical Dictionary for Regulatory Activities (MedDRA) should be employed. In addition, the following information should be recorded:

- Indication of whether the event is serious or non-serious (see [Section 9.1](#))
- Relationship to ataluren (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 non-serious determines the reporting procedures to be followed.

#### 9.4. Describing Adverse Event Relationship to Study Drug

Based on the considerations outlined in [Table 4](#), 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 Ataluren to Adverse Event**

Relationship	Description
Probable	A clinical event in which a relationship to ataluren 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 ataluren 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 ataluren exposure that does not preclude causality but for which there is a clear alternate cause that is more likely to have caused the adverse event than study drug. Such alternatives include a concomitantly administered drug, the subject's disease state, other medical conditions, or environmental factors.
Unrelated	A clinical event, for which a relationship to ataluren seems improbable because of factors such as inconsistency with known effects of the ataluren, lack of a temporal association with ataluren administration, lack of association of the event with ataluren withdrawal or rechallenge, and/or presence of alternative explanations for the event. Alternative explanations might include a known relationship of the adverse event to a concomitant drug, medical history of a similar event, the subject's disease state, other medical conditions, or environmental factors.

#### 9.5. Grading of Adverse Event Severity

The severity of adverse events will be graded using the CTCAE, Version 3.0 (refer to [http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/ctcae3.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.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 5](#).

**Table 5: Grading of Adverse Event Severity**

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

Note the distinction between the seriousness and the severity of an adverse event. Severity is a measure of intensity; thus, a severe reaction is not necessarily a serious reaction. For example, a headache may be severe in intensity, but would not be classified as serious unless it met one of the criteria for serious events listed in [Section 9.1.2](#).

## 9.6. Pregnancy

PTC Therapeutics should be notified in the event that a female subject in the study becomes pregnant at any time after the subject's first dose of ataluren. Any such pregnancy occurring on-study or within 60 days of the last administration of ataluren must be reported on a Pregnancy Notification Form). 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 subject until completion of the pregnancy and notify the PTC Therapeutics medical monitor of the outcome within 5 days or as specified below. The investigator will provide this information as a follow up to the initial Pregnancy Notification Form via the Pregnancy Outcome Form

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

## 9.8. Adverse Event Reporting Period

The first day of adverse event reporting will coincide with the day the first dose of ataluren is administered. The adverse event reporting period for this study ends with the 4-Week ( $\pm$  7 days) Post-Treatment Follow-up visit, except as described in [Section 9.7](#). In addition, SAEs occurring in a subject after the study period should be reported to the sponsor if the investigator becomes aware of them.

## 9.9. Investigator Site Adverse Event Reporting Requirements

Classification of an event as serious or non-serious (see [Section 9.1](#)) 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
SAE	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 <sup>a</sup> (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 of relevant source documents <sup>a</sup> (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)

<sup>a</sup> Subject name, address, and other personal identifiers should be redacted from all study documents prior to submission.

**Abbreviations:** AESI = adverse events of special interest; 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 PTC Therapeutics Safety Department or assigned designee (such as a 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.

**PTC Therapeutics, Inc.**

**Safety Lead:** [REDACTED]

**Phone:** [REDACTED]

**SAE Fax number:** [REDACTED]

**E-mail:** [REDACTED]

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

## **9.10. PTC Therapeutics Adverse Event Reporting Requirements**

As the sponsor of the study, PTC Therapeutics is responsible for reporting certain safety information, particularly SAEs and subject deaths related to participation in the study, to each investigator in an expedited manner. If notification of an adverse event requiring expedited reporting to investigators is received, PTC Therapeutics or its designated representative will contact each investigator site participating in this study by e-mail, fax, and/or overnight mail such that the investigator can promptly notify the site IRB/IEC, 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 SUBJECTS**

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

- The subject has the right to withdraw consent and discontinue ataluren at any time.
- If the subject's condition substantially worsens after initiating ataluren, the subject will be carefully evaluated by the investigator in consultation with the PTC Therapeutics medical monitor. The subject will be withdrawn from treatment if continuing would place them at risk.
- Upon consultation with the PTC Therapeutics medical monitor, the investigator may withdraw the subject from ataluren treatment, if, in the investigator's clinical judgment, it is not in the subject's best interest to continue.
- If the subject becomes significantly noncompliant with ataluren administration, study procedures, or study requirements, the subject should be withdrawn, particularly when the circumstances surrounding noncompliance increase risk to the subject or are anticipated to substantially compromise the interpretation of study results.
- The subject will be withdrawn from treatment if he/she is unable to tolerate ataluren.
- If the subject becomes eligible to participate in another ataluren nmCF clinical trial program initiated by PTC Therapeutics, and elects to enroll in said study, they will be withdrawn from this study.
- This study may be discontinued by the relevant regulatory authority and/or PTC Therapeutics at any time.

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

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

A subject who completes the study through Week 192 (Visit 14-End-of-Treatment/Premature-Discontinuation) and is then lost to follow-up during the follow-up period will not be considered to have prematurely withdrawn.

## **11. STATISTICS AND DATA MANAGEMENT**

### **11.1. Sample Size Calculation for the Primary Endpoint**

The pool of patients potentially eligible for this study is described by the inclusion criteria. The sample size is determined by how many patients satisfy all inclusion/exclusion criteria upon applying for study participation, not by any formal statistical analysis.

## **11.2. Population Definition**

### **11.2.1. As-Treated Population**

The as treated population consists of all subjects who received at least 1 dose of ataluren. This population will be evaluated in the analyses of safety and treatment administration.

### **11.2.2. Intent-to-Treat Population**

The intent-to-treat (ITT) population consists of all subjects who have at least 1 post-baseline efficacy assessment. This population will be evaluated in the analysis of efficacy.

## **11.3. General Statistical Considerations**

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

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

## **11.4. Specific Statistical Analyses**

### **11.4.1. Study Conduct and Subject Disposition**

Subjects who prematurely discontinue from the study will be reported. Reasons for screening failures and early discontinuations, reasons for study discontinuation, and time of withdrawal from the study will be described.

### **11.4.2. Baseline Characteristics**

Subject characteristics at entry and in each phase of the study 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. Type and timing of specific concomitant medications (and non-drug therapies) will be listed and summarized.

### **11.4.5. Primary Variables**

#### **11.4.5.1. Adverse Events**

Adverse events will be classified using the MedDRA classification system. The severity of adverse events will be graded by the investigator according to the CTCAE, Version 3.0 whenever possible. A treatment-emergent adverse event is defined as an adverse event that occurs or worsens in the period extending from the day of a subject's first ataluren dose in this study to 4 weeks after the last ataluren dose in this study.

The frequency of subjects experiencing a specific adverse event will be tabulated by treatment group, body system, and MedDRA term. In the by-subject analysis, a subject having the same event more than once will be counted only once. Adverse events will be summarized by worst CTCAE grade.

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

#### **11.4.5.2. Laboratory Data**

Hematological, serum biochemistry, adrenal assessments, and urine data and their changes (only for continuous laboratory parameters) from baseline will be summarized by visit.

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

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

Separate listings and tables will be created for assessment of adrenal, hepatic, and renal parameters based on the conditions listed in [Section 6.3.1](#).

#### **11.4.6. Secondary Variables**

##### **11.4.6.1. 12-Lead ECG and Other Safety Parameters**

ECG and vital sign data will be listed and summarized by visit. Physical examination findings will be listed. Where appropriate, changes from baseline at each visit will be presented.

##### **11.4.6.2. Spirometry**

###### **11.4.6.2.1. Change from Baseline in %-predicted FEV<sub>1</sub>**

A secondary variable analysis will evaluate relative change in %-predicted FEV<sub>1</sub> from Baseline to Week 192. Pediatric equations for calculating %-predicted FEV<sub>1</sub> [[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<sub>1</sub> [[Hankinson 1999](#)] will be used. Each %-predicted FEV<sub>1</sub> will be based on the height value obtained at the same study visit. The changes in the variable from baseline to each post-baseline visit will be summarized descriptively. The changes from baseline to each post-baseline visit will be analyzed using paired t-tests.

###### **11.4.6.3. Pulmonary Exacerbation Rates**

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  $>38^{\circ}\text{C}$ ; 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 rates 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. Spirometry**

FVC and FEF<sub>25-75</sub> will be analyzed with the same methods used in the analysis of FEV<sub>1</sub>.

##### **11.4.7.2. Weight and BMI**

Weight and BMI will be summarized by visit. Change from baseline to post-baseline measurements will also be summarized.

#### **11.4.8. Exploration of Correlations**

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

## **12. STUDY COMMITTEES**

### **12.1. Data Monitoring Committee**

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

In general, the DMC will be responsible for:

- Examining accumulated 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 subject accrual, study conduct, and protocol violations
- Providing expert advice to PTC Therapeutics on an ad hoc basis regarding matters such as safety concerns or diagnostic evaluations in individual subjects

Interim safety analyses are planned when ~35 subjects have completed  $\geq 32$  weeks of treatment and when ~35 subjects have completed  $\geq 64$  weeks of treatment. Additional interim safety analyses may be performed based on the discretion of the DMC and will be described in the DMC charter. 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 Declaration of Helsinki and 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 subjects 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 subjects evaluated, the number of subjects who discontinued (and the reasons for discontinuation), the number of subjects who completed the study, and the results of the study,

including a description of any 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 the CRF). At all times, the principal investigator has final responsibility for the accuracy and authenticity of all clinical data entered onto the eCRFs and/or reported to PTC Therapeutics from the investigator site.

### **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 subject
- Laboratory reports
- A CD-ROM or paper copies of the data that have been captured in the EDC for each subject
- 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 subject discontinuation and completion of the study

Current regulations require PTC Therapeutics (or an authorized designee) to inspect all documents and records required to be maintained by the investigator, including but not limited to medical records (office, clinic, or hospital) for the subjects enrolled in this study. These regulations also allow the same records to be inspected by 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 subject information. The names and identities of all research subjects will be kept in strict confidence and will not appear on eCRFs, paper CRFs, or other records provided to or retained by PTC Therapeutics (or its authorized designee). The names and identities of the subjects need not be divulged; however, the records must nevertheless be inspected. This will be accomplished by redacting the subject's name and replacing the name with the subject's study 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 but not limited to the documents listed in [Section 13.5](#), as well as the identity of all participating subjects (sufficient information to link CRFs and clinic records). 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. These records will be maintained by the investigator until notified by PTC Therapeutics that record retention is no longer required.

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

### **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 CRFs (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 CRFs; ensure that all protocol requirements, applicable FDA and other relevant regulations, and investigator's obligations are being fulfilled; and resolve any inconsistencies in the study records. This includes inspection of all documents and records required to be maintained by the investigator, including but not limited to medical records (office, clinic, or hospital) for the subjects in this study. The names and identities of all research subjects will be kept in strict confidence and will not appear on CRFs or other records provided to or retained by PTC Therapeutics. The investigator/institution guarantees direct access to source documents by PTC Therapeutics or its designee 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 subjects. The investigator, after consultation with the PTC Therapeutics medical monitor, reserves the right to discontinue the study at the investigator site for safety reasons at any time.

After a decision to terminate the study, investigators must contact all subjects who are currently participating 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 the PTC Therapeutics Publications Committee.

### **13.12. Communication with Regulatory Authorities**

PTC Therapeutics will be responsible for regulatory interactions with the FDA, the European Medicines Agency (EMA), and/or other regulatory authorities, as required. 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 for notification or for approval, as applicable (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. General**

This study is an open-label safety and tolerability study in previously treated ataluren patients with nmCF, that have successfully completed their participation in the Phase 3 double-blind study, PTC124-GD-009-CF. Consistent with GCP guidelines, patients and/or parents/guardians 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.

The assessment and evaluation of the overall safety profile of ataluren in nmCF patients is developed with safety endpoints considered as having a logical possible connection to the disease, testing that can be performed on the study population, are unlikely to have limitations due to floor or ceiling effects or confounding factors, can be accurately and reproducibly assessed, offer standardized simplicity in performance and analysis, can be interpreted relative to normative data, and provide data in a useful timeframe. The efficacy and safety results of Study 009 and the open-label extension Study 009e have also been considered in the selection of the secondary endpoints of this study.

#### **14.1.2. Inclusion of Minors**

Inclusion of both children and adults in this protocol is appropriate and necessary. Based on past experience in multiple randomized clinical trials [[Fuchs 1994](#), [Ramsey 1999](#), [Saiman 2003](#), [Elkins 2006](#)], including the double-blind study of ataluren in nmCF [[Rowe 2012](#)], there is strong precedence for this approach. The benefit-risk ratio is enhanced by inclusion of only children with FEV<sub>1</sub> values ≤ 90% of predicted, weighting enrollment toward those who are already experiencing CF-related pulmonary compromise. In addition, this ratio is enhanced by the known severity of the disease phenotype in patients with CF caused by nonsense mutations [[Shoshani 1992](#), [Cystic Fibrosis Genotype-Phenotype Consortium 1993](#), [Kerem 1996](#), [de Gracia 2005](#), [McKone 2006](#)], the generally favorable safety profile of ataluren, and the limited

population of patients with nonsense-mutation-mediated disease (10% of the total CF population).

Inclusion of children as well as adults will allow an understanding of how age-dependent disease characteristics may affect treatment outcomes. A total of 65 (86.7%) patients <18 years of age completed Study 009 and are eligible for this open-label extension study. Participation of these younger patients in this extension study will allow further exploration of the influence of age on safety and efficacy outcomes. Study participants will now be at least 9 years of age, enhancing the ability of participants to reliably perform protocol procedures [Loeb 2008] and will have nomogram data describing %-predicted FEV<sub>1</sub> values [Wang 1993].

Participants in this trial have the potential for direct benefit from treatment with ataluren, which justifies the known and potential risks. Substantial nonclinical and clinical safety experience provides appropriate risk-benefit information that supports the conduct of this study. This information is detailed in the Investigator Brochure and is summarized in Section 9.8 of the Investigator Brochure. The potential risks (real and theoretical) have been weighed against the expected benefits for the children enrolled in the clinical trial. It is believed that the balance of risks versus expected benefits will be positive for the clinical trial. In Phase 2 clinical studies, including those conducted in nmDMD, a population almost entirely comprised of children, ataluren has demonstrated comparable pharmacodynamic activity, safety, and PK profiles in children and adults with CF [Clancy 2006, Kerem 2008, Sermet-Gaudelus 2008]. The drug has also shown pharmacodynamic activity and was generally well tolerated at even higher dose levels in children with DMD [Bönnemann 2007].

This study includes a comprehensive safety monitoring plan. The safety monitoring plan builds on the safety observations from previous nonclinical and clinical studies in order to protect study participants and more fully define the potential risk profile of ataluren. During study conduct, patients will be monitored closely for adverse clinical and laboratory events. This protocol clearly defines the actions to be taken if adverse events occur. Procedures have been established for defining adverse events, eliciting adverse event information, recording adverse events, evaluating the relationship of adverse events to the study drug, grading the severity of adverse events, following up on unresolved adverse events, and reporting adverse events. These procedures are fully detailed in Section 9. Additional risk/benefit information that becomes available during the conduct of the study will be provided to each investigative site as a “letter to the investigator” or safety alert. In addition, pain and discomfort will be prevented as much as possible, and investigations will be limited to a minimum necessary to provide meaningful data and performed using size/age appropriate material and devices.

Because the level of risk may evolve over time, during the trial and with evolving knowledge, safety will be monitored by a data monitoring committee (DMC) (refer to Section 12.1). The oversight of an independent DMC provides an added measure of risk mitigation for study participants. The DMC will provide recommendations to PTC Therapeutics about the evolving risks and benefits observed in the course of the study and any modifications required during the course of the study. DMC members will be responsible for reviewing study conduct, protecting subject well-being, and reviewing the quality and integrity of the data in the study. The investigative sites will be informed of all DMC recommendations that relate to subject safety and any modifications to the study that may affect the willingness of study subjects to continue with study participation.

### **14.1.3. Safety Measurements**

#### **14.1.3.1. 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, and other safety assessments. For consistency of interpretation, adverse events will be coded using the MedDRA and the severity of these events and laboratory abnormalities will be graded using the well-defined CTCAE, Version 3.0. Version 3.0 will remain the reference for this study to facilitate comparison with safety data from previously conducted ataluren trials. Concomitant medications will be coded with the WHODRUG dictionary. ECG data will be evaluated in accordance with the relevant ICH ECG guidance.

#### **14.1.3.2. 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 subject acceptance of therapy, integrating factors of tolerability, palatability, and convenience. The compliance of the subject will be verified by counting used ataluren sachets.

#### **14.1.4. Required Laboratory Values**

The required laboratory values for eligibility are necessary in order to implement the safety monitoring plan described in [Section 6.3](#).

Minimal reversible serum transaminase elevations (ALT, AST) have been observed in healthy volunteers receiving ataluren ([Section 2.2.3.1](#)) [[Hirawat 2007](#)]. However, because such findings have not been prominent in prior nmCF clinical trials testing ([Section 2.2.3](#)), and because many patients with CF may have chronic elevations in serum ALT, AST, and GGT, it is not practical to exclude all patients with such abnormalities. Therefore, candidates with Grade 1 elevations in serum ALT, AST, or GGT values at screening may be enrolled. Patients with more severe elevations in these parameters or with chronic active hepatitis infections will be excluded. The requirement that subjects have a screening serum albumin  $\geq 3.0$  g/dL (in conjunction with exclusion for those with known portal hypertension) avoids accrual of those who have profoundly unstable hepatic or nutritional status.

Mild nephrosis in mice has been observed in toxicology studies. Renal findings in Study 009 included episodes of creatinine elevations and nephrolithiasis. Overall, treatment-emergent renal adverse events were seen more frequently in the ataluren arm; cases of reversible Grade 3-4 creatinine elevations were observed in the ataluren arm, which were associated with the treatment of exacerbations with nephrotoxic systemic antibiotics and, in some cases, dehydration. 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. 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 new onset nephrolithiasis was similar in both arms (5 patients [4.2%] on ataluren vs 4 patients [3.4%] on placebo).

Thus, ultrasound will be performed in each subject during screening to establish an anatomic baseline against which to compare any future renal findings and subjects must have adequate baseline renal function as established by serum markers (cystatin C, creatinine, BUN), urine

markers (protein and blood), and serum electrolytes (Na<sup>+</sup>, K<sup>+</sup>, HCO<sub>3</sub><sup>-</sup>, Mg<sup>2+</sup>, Ca<sup>2+</sup>, and phosphate).

During the Phase 2b double-blind study of ataluren in nmDMD (PTC124-GD-007-DMD), mean total cholesterol and triglycerides were in the upper range of normal at baseline and increased on study, reaching borderline high or high values. Baseline mean cholesterol and triglycerides values were higher in patients receiving systemic corticosteroid therapy. During the treatment period, increases in mean cholesterol levels were observed in patients receiving systemic corticosteroid therapy, more prominently in ataluren-treated patients than in the placebo arm. In patients not receiving systemic corticosteroid therapy, mean cholesterol levels increased similarly across all 3 treatment arms (placebo, 10-, 10-, 20-mg/kg TID, and 20-, 20-, 40-mg/kg TID), and mean triglyceride levels increased minimally in ataluren-treated patients. Similar changes were not seen in the double-blind study for nmCF (Study 009). In that study, low cholesterol levels were observed prior to treatment in >40% of patients across both treatment arms. No ataluren-treated patients shifted from normal cholesterol at baseline to high cholesterol at Week 48. Shifts from normal triglycerides at baseline to high triglycerides at Week 48 were observed in both treatment arms, and were somewhat higher in placebo. Despite the lack of effect of ataluren on total cholesterol and triglycerides in nmCF, total cholesterol and triglycerides will continue to be monitored throughout this study.

#### **14.1.5. 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.

#### **14.1.6. Prior and Concomitant Therapies**

Conventional supportive therapies will be permitted; however, efforts will be made to avoid use of concomitant medications that might confound interpretation of study results 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. Concomitant use of potentially nephrotoxic 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, inhaled aminoglycoside use cannot occur within four months prior to the Screening Visit, and it is strongly recommended that alternative agents be utilized for CF treatment/prophylaxis.

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, gefitinib).

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

Physicians and subjects are encouraged to avoid the use of extraneous drugs or alternative therapies in order to minimize the possibility that drug-drug interactions might occur. In particular, physicians are advised to closely monitor subjects when drugs of low therapeutic index that are cleared by CYP2C9 (eg, phenytoin or warfarin) are administered concomitantly with ataluren.

## **14.2. Treatment Rationale**

### **14.2.1. Schedule and Ataluren Dose Selection**

Dosing based on body weight will continue to be employed. Such dosing reduces variability in exposure by accommodating differences in subject size across the span of ages in subjects 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 subjects, thus enhancing compliance.

### **14.2.2. Duration of Therapy**

Duration of therapy in this study is intended to provide approximately 4 years of additional safety data for nmCF patients that have completed Study 009, and as a secondary outcome, to provide additional long-term efficacy data in this population. Study duration may be expanded to include multiple years, if so determined by PTC Therapeutics.

### **14.2.3. Safety Monitoring**

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 subjects, obtain a thorough assessment of any clinically relevant adverse events or laboratory

abnormalities, and to offer recommendations for interruption and dose modification of ataluren in response to potential safety signals. The nature of these risks and the measures to monitor for them will be reflected in the informed consent form.

As noted in [Section 6.3](#), subjects must be monitored closely for adverse events or laboratory abnormalities during the course of the study. [Section 6.3](#) provides information on actions to be taken in the event that abnormalities are noted on specified monitoring studies. Thresholds are provided for interrupting ataluren immediately, for interrupting ataluren after confirmation of a value beyond the threshold, or for continuing ataluren while evaluating for potential drug-related toxicity.

#### **14.2.3.1. Renal Abnormalities**

##### **14.2.3.1.1. Overview**

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 Phase 1 studies in healthy volunteers and Phase 2 studies in patients with DMD and cystic fibrosis, renal laboratory abnormalities have been infrequent.

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.



The renal monitoring program included in this protocol considers nonclinical and clinical findings with ataluren, and past experience with known nephrotoxins. Concomitant use of potentially nephrotoxic antibiotics with ataluren is prohibited. A focus is placed on well-established clinical indicators 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.

#### 14.2.3.1.2. Renal Monitoring Plan

- **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 was observed, BUN was elevated in some of the affected animals, confirming that this marker should also be measured in clinical studies of ataluren. Monitoring serum BUN, like monitoring creatinine, provides an additional frame of reference relative to other markers assessed within this study and in other studies of known nephrotoxins. 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  $\geq 1.5 \times$  ULN should prompt a review of potential pre-renal, renal, and post-renal causes for the abnormality as well as consideration of potential interruption/modification of ataluren dosing.
- **Urine Protein:Creatinine:** Proteinuria can be an early marker for renal injury in experimental models [Amin 2004] and is commonly observed with even modest clinical decreases in renal function [National Kidney Foundation 2002]. Glomerular disease (eg, diabetic nephropathy) is often associated with albuminuria due to defects in exclusion of plasma proteins in the glomerular filtrate. Tubular injury (eg, as observed in mice

receiving ataluren) more often leads to increases in low-molecular-weight proteins (eg, beta-2 microglobulin,  $\beta$ 2-microglobulin,  $\alpha$ 1-microglobulin retinol-binding protein, lysozyme) as tubular protein catabolism is compromised or proteins of injury are produced [Guignard 2004, Stevens 2007]. Because mice that developed nephrosis while receiving ataluren had proteinaceous material in the renal tubules on histological examination, monitoring of urine protein in humans receiving ataluren is additionally warranted.

Traditional methods of urine protein screening are only semiquantitative, are relatively insensitive, and are confounded by exogenous substances and subjective interpretation [Kim 2007]. The presence of urinary protein may be masked in dilute urine or exaggerated in concentrated urine. For these reasons, a quantitative method of accessing proteinuria is planned in this study, specifically urinary protein concentration relative to urinary creatinine concentration [Ginsberg 1983, Schwab 1987]. These methods of screening, using spot urine samples, have been found to be as accurate as and more practical than quantification of urine protein during a 24-hour collection. Values for protein:creatinine of  $\geq 0.2$  mg/dL:mg/dL have been established as abnormal [Morgenstern 2003]. Follow-up methods such as urine electrophoresis may be useful in discriminating among the types of proteins present and may suggest a site of injury (eg, an albumin-specific pattern with glomerular damage versus a diffuse multiple low-molecular-weight protein pattern with tubular damage) [Stevens 2007]. Confirmed proteinuria should prompt consideration of interruption/modification of study drug dosing.

- **Urine Blood:** Blood in the urine may indicate pathology of the renal parenchyma or of the urinary collecting system (eg, ureters, bladder, and urethra). Like proteinuria, hematuria is commonly found in patients with minimal changes in GFR due to renal (particularly glomerular) dysfunction [National Kidney Foundation 2002]. Confirmed, persistent evidence of urinary blood by dipstick and/or microscopic examination will prompt further evaluation. Ultrasound or other imaging can evaluate for a potential renal cause for bleeding. Urology consultation can be obtained to assess for post-renal sources of hematuria. Clotting function and use of drugs that may impair platelet function will be reviewed. Confirmed, persistent hematuria in the absence of a post-renal source of bleeding or a bleeding diathesis will prompt potential interruption/modification of ataluren dosing.
- **Serum Electrolytes:** Assessments of serum electrolytes (sodium, chloride, potassium, bicarbonate, magnesium, calcium, and phosphorus) provide information regarding renal function that may supplement more primary assessments. Derangements in serum concentrations may reflect altered tubular handling of these ions. With worsening renal function, hyperphosphatemia and hypocalcemia may develop and reductions in serum bicarbonate or elevations in potassium may suggest an impaired ability of proximal tubules or collecting ducts to maintain acid-base balance [National Kidney Foundation 2002]. Given the cardiovascular and neurological consequences of severe derangements of serum potassium, calcium, or magnesium, evaluation of these ions is important to avoid potential secondary complications. Because transient Grade 1 alterations in the concentrations of electrolytes are very unlikely to be associated with significant

secondary side effects, alterations to  $\geq$ Grade 2 are considered appropriate to prompt potential interruption/modification of ataluren 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.

#### 14.2.4. Hepatic Monitoring Plan

CF-related hepatobiliary obstruction and inflammation can 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 hepatotoxicity monitoring should focus special attention on any increases in bilirubin [Abboud 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 much larger-scale Phase 3 studies of ataluren. Since no significant changes in hepatic serum markers were observed in the Phase 3 studies, these markers are not included in this protocol as efficacy assessments. Therefore, the hepatic monitoring of this study is for monitoring of general safety thresholds specific to the nmCF population.

#### 14.2.5. Blood Pressure Assessment

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

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

#### **14.2.7. Other Abnormalities**

Recommendations for interruption of dosing are provided in [Section 6.3](#), 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.

#### **14.2.8. 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 subject safety with the potential for observing efficacy in circumstances under which a subject experiencing an adverse event may still be able to continue on ataluren therapy at a lower dose. Interruption of therapy is advocated as the primary response in order to determine reversibility of the adverse finding.

#### **14.2.9. Efficacy Measurements**

##### **14.2.9.1. 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]. Because the initial pulmonary defect in CF is obstructive, FEV<sub>1</sub> has commonly been evaluated. Rates of decline in FEV<sub>1</sub> are correlated with survival [Corey 1997] and have prognostic significance for mortality [Kerem 1992]; the relative risk of death is doubled with each 10% decrement in the %-predicted FEV<sub>1</sub>. The more rapid declines in FEV<sub>1</sub> in patients with pancreatic-insufficient disease and in women are correlated with shorter survival in these subgroups [Corey 1997, Kerem 1992], providing internal corroboration of the predictive import of FEV<sub>1</sub> within the available data. The statistical relationship between FEV<sub>1</sub> values and survival appears to strengthen as patients grow older [Schlucter 2002], reaching a zenith at ages  $\geq 15$  years.

A clinically meaningful FEV<sub>1</sub> treatment effect has been established. Data from patients with chronic obstructive pulmonary disease suggest that a >4% change in %-predicted FEV<sub>1</sub> can be detected symptomatically [Redelmeier 1996]. In CF, the experience with dornase-alfa, inhaled tobramycin, azithromycin, and hypertonic saline demonstrate respective relative improvements in %-predicted FEV<sub>1</sub> over 6 to 12 months of 5.7%, 10%, 6.2%, and 3.2%, respectively, compared to patients receiving placebo [Fuchs 1994, Ramsey 1999, Saiman 2003, Elkins 2006]. In the previous double-blind study of ataluren (Study 009), the subgroup of patients not receiving chronic inhaled tobramycin showed a 5.7% difference in the relative change of %-predicted FEV<sub>1</sub> the ataluren arm when compared to placebo. Hence, FEV<sub>1</sub> was selected as a secondary endpoint of this study, to further assess the effect of ataluren on pulmonary performance.

In order to maximize uniformity of testing, data collection, and analysis for this study, an experienced CRO 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 and 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.

#### **14.2.9.2. Pulmonary Exacerbations**

The approach to CF pulmonary exacerbations to be taken in this study evolves from that used in the study of hypertonic saline [Elkins 2006], ie, by characterizing exacerbations as those presenting symptomatically (whether or not antibiotics are given) and those requiring intervention (with oral or parenteral antibiotics). As in the previous open-label Phase 3 extension 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 [Rowe 2012].

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 scheduled phone calls as appropriate.

Subjects 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 or scheduled phone calls. 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.

#### **14.2.9.3. Weight/Body Mass Index**

Patients with CF are generally underweight compared to healthy individuals of the same gender and age [Rabin 2004]. Assessment of body weight and BMI during the course of this Phase 3 study is planned. While changes in these parameters are quite nonspecific, they constitute simple-to-assess outcomes of general well-being.

#### **14.2.10. Exposure Outcome Measures**

##### **14.2.10.1. 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 subjects with CF, plasma sampling will be limited to before dosing. 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.

##### **14.2.11. Timing of Assessments**

The timing of study assessments are considered adequate for safety and efficacy monitoring and the design builds upon the results of previous ataluren Phase 3 studies. The 16-week interval takes into account time for full cycling of concomitant medications, ie, inhaled non-aminoglycoside antibiotics.

Study activities have been mapped across the study (as outlined in [Sections 8.1](#)) and within each study visit (as described in [Section 8.2](#)). The intent is to minimize variability by maintaining a timely, clear and consistent approach to evaluations for each subject, across subjects at a site, and across sites. At the beginning of each visit, discussion of subject health status and adverse events, concomitant medication usage, and compliance permits investigators and clinic staff to determine early in the visit if medical events or other problems have developed that require additional diagnostic testing or subject counseling. The clustering and sequencing of study procedures considers practical, subject convenience, and staff convenience factors while seeking to minimize subject time in the clinic.

### **14.3. Study Committees**

Inclusion of the SSC 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.

## **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  $t_{1/2}$ , 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  $\mu$ M. 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<sub>1</sub> reproduction or F<sub>2</sub> 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

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 [Section 2.2](#)).

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<sub>1</sub> at 48 weeks (-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<sub>1</sub> 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<sub>1</sub>).

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<sub>1</sub> and pulmonary exacerbation data, supported by TEPD results in the previous Phase 2 clinical trials, demonstrate the beneficial effect of ataluren in patients with



nmCF. Ataluren thus offers an important advance in the genetic-based treatment of nmCF in patients aged 6 years and older. The increased effect seen in patients not receiving chronic inhaled tobramycin makes benefit more likely in this subgroup, who will be enrolled in this study, further supports the potential for the benefit of ataluren therapy.

### **15.3. Benefits and Risks: 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 subjects' 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 14.2.3.1](#)). 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, clinical trials in nmDMD have demonstrated that the adverse-event profile of ataluren was comparable to that of placebo. In the double-blind 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 to ataluren. Appropriate monitoring and laboratory evaluation, as detailed in [Section 14](#), is incorporated in this protocol in order to mitigate any risks to study participants. The current trial (Study 023) is feasible and will provide additional safety and efficacy data of ataluren in nmCF.

## 16. BIBLIOGRAPHY

- Abboud G, Kaplowitz N. Drug-induced liver injury. *Drug Saf.* 2007;30(4):277-94.
- Ambry Genetics. Ambry test: CF. [www.ambrygen.com/cysticfibrosistest.htm](http://www.ambrygen.com/cysticfibrosistest.htm). 2001.
- American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med.* 1995 Sep;152(3):1107-36.
- Amin RP, Vickers AE, Sistare F, Thompson KL, Roman RJ, Lawton M, Kramer J, Hamadeh HK, Collins J, Grissom S, Bennett L, Tucker CJ, Wild S, Kind C, Oreffo V, Davis JW 2nd, Curtiss S, Naciff JM, Cunningham M, Tennant R, Stevens J, Car B, Bertram TA, Afshari CA. Identification of putative gene based markers of renal toxicity. *Environ Health Perspect.* 2004 Mar;112(4):465-79.
- Amrani N, Ganesan R, Kervestin S, Mangus DA, Ghosh S, Jacobson A. A faux 3'-UTR promotes aberrant termination and triggers nonsense-mediated mRNA decay. *Nature* 2004 Nov;432:112.
- Avni FE, Hall M. Diagnostic imaging. In: Avner ED, Harmon WE, Niaudet P, ed. *Pediatric nephrology*, 5th ed. Philadelphia, Lippincott Williams & Wilkins 2004; 286-298.
- Barratt TM, Niaudet P. Clinical evaluation. In: Avner ED, Harmon WE, Niaudet P, ed. *Pediatric nephrology*, 5th ed. Philadelphia, Lippincott Williams & Wilkins 2004; 286-298.
- Barton-Davis ER, Cordier L, Shoturma DI, Leland SE, Sweeney HL. Aminoglycoside antibiotics restore dystrophin function to skeletal muscles of mdx mice. *J Clin Invest.* 1999 Aug;104(4):375-81.
- Bell SC, Robinson PJ. Exacerbations in cystic fibrosis: 2. prevention. *Thorax.* 2007 Aug;62(8):723-32.
- Bellis G, Cazes MH, Le Roux E, Parant A, Rault G, Ravilly S. Observatoire national de la mucoviscidose: Bilan des données 2004. 2006. [http://www.vaincrelamuco.org/publications/bilan\\_donnees\\_ONM2004.pdf](http://www.vaincrelamuco.org/publications/bilan_donnees_ONM2004.pdf).
- Bobadilla JL, Macek M Jr, Fine JP, Farrell PM. Cystic fibrosis: a worldwide analysis of CFTR mutations – correlation with incidence data and application to screening. *Hum Mutat.* 2002 Jun;19(6):575-606.
- Bönnemann C, Finkel R, Wong B, Flanigan K, Samson J, Sweeney L, Reha A, Elfring G, Miller L, Hirawat S. Phase 2 study of PTC124 for nonsense mutation suppression therapy of Duchenne muscular dystrophy (DMD). *Neuromuscul Disord.* 2007 Oct 1;17(9-10):783 (abst# G.P.3.05).
- Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. *Physiol Rev.* 2004;84:277-359.
- Cheng SH, Rich DP, Marshall J, Gregory RJ, Welsh MJ, Smith AE. Phosphorylation of the R domain by cAMP-dependent protein kinase regulates the CFTR chloride channel. *Cell.* 1991 Sep 6;66(5):1027-36.
- Clancy JP, Bebok Z, Ruiz F, King C, Jones J, Walker L, Greer H, Hong J, Wing L, Macaluso M, Lyrene R, Sorscher EJ, Bedwell DM. Evidence that systemic gentamicin suppresses premature stop mutations in patients with cystic fibrosis. *Am J Respir Crit Care Med.* 2001 Jun;163(7):1683-92.

Clancy JP, Konstan MW, Rowe SM, Accurso F, Zeitlin P, Moss R, Bebok Z, Northcutt V, Elfring G, Miller L, Hirawat S. A Phase 2 study of PTC124 in cystic fibrosis patients harboring premature stop mutations. *Pediatr Pulmonol* 2006;40 Suppl29:301 (abst #269).

Curhan GC, Willett WC, Speizer FE, Spiegelman D, Stampfer MJ. Comparison of dietary calcium with supplemental calcium and other nutrients as factors affecting the risk for kidney stones in women. *Ann Intern Med*. 1997 Apr 1;126(7):497-504.

Corey M, Edwards L, Levison H, Knowles M. Longitudinal analysis of pulmonary function decline in patients with cystic fibrosis. *J Pediatr*. 1997 Dec;131(6):809-14.

Cystic Fibrosis Foundation. Patient registry annual data report 2002. Bethesda: Cystic Fibrosis Foundation, 2003: 1-13.

Cystic Fibrosis Genetic Analysis Consortium (CFGAC). 2004 [www.genet.sickkids.on.ca/cftr](http://www.genet.sickkids.on.ca/cftr).

Cystic Fibrosis Genotype-Phenotype Consortium. Correlation between genotype and phenotype in patients with cystic fibrosis. *N Engl J Med*. 1993 Oct 28; 329(18): 1308-13.

Danziger KL, Black LD, Keiles SB, Kammesheidt A, Turek PJ. Improved detection of cystic fibrosis mutations in infertility patients with DNA sequence analysis. *Hum Reprod*. 2004 Mar;19(3):540-6.

de Gracia J., Mata F, Alvarez A, Casals T, Gatner S, Vendrell M, de la RD, Guarner L, Hermosilla E. Genotype-phenotype correlation for pulmonary function in cystic fibrosis. *Thorax* 2005 Jul;60(7):558-63.

Dharnidharka VR, Kwon C, Stevens G. Serum cystatin C is superior to serum creatinine as a marker of kidney function: a meta-analysis. *Am J Kidney Dis*. 2002 Aug;40(2):221-6.

Du M, Jones JR, Lanier J, Keeling KM, Lindsey JR, Tousson A, Bebok Z, Whitsett JA, Dey CR, Colledge WH, Evans MJ, Sorscher EJ, Bedwell DM. Aminoglycoside suppression of a premature stop mutation in a Cfr<sup>-/-</sup> mouse carrying a human CFTR-G542X transgene. *J Mol Med*. 2002 Sep;80(9):595-604.

Du M, Liu X, Welch EM, Hirawat S, Peltz SW, Bedwell DM. PTC124 is an orally bioavailable compound that promotes suppression of the human CFTR-G542X nonsense allele in a CF mouse model. *Proc Natl Acad Sci U S A*. 2008 Feb 12;105(6):2064-9.

Elkins MR, Robinson M, Rose BR, Harbour C, Moriarty CP, Marks GB, Belousova EG, Xuan W, Bye PT; National Hypertonic Saline in Cystic Fibrosis (NHSCF) Study Group. A controlled trial of long-term inhaled hypertonic saline in patients with cystic fibrosis. *N Engl J Med*. 2006 Jan 19;354(3):229-40.

Farrell PM. The prevalence of cystic fibrosis in the European Union. *J Cyst Fibros*. 2008 Sep;7(5):450-3.

FDA. 62nd Anti-Infective Drugs Advisory Committee. Discussion of NDA for tobramycin solution for inhalation (Tobi®) for the management of cystic fibrosis patients. 1997 Nov; [www.fda.gov/ohrms/dockets/ac/97/transcpt/3349t3.pdf](http://www.fda.gov/ohrms/dockets/ac/97/transcpt/3349t3.pdf).

Ferrone M, Raimondo M, Scolapio JS. Pancreatic enzyme pharmacotherapy. *Pharmacotherapy*. 2007 Jun;27(6):910-20.

Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, Rosenstein BJ, Smith AL, Wohl ME. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. *N Engl J Med.* 1994 Sep;331(10):637-42 [comment in *N Engl J Med.* 1994 Sep;331(10):672-3].

Furlong M, Fanburg-Smith J, Miettinen M. The morphologic spectrum of hibernoma - a clinicopathologic study of 170 cases. *Am J Surg Pathol* 2001;25(6):809-14.

Gilead. Adefovir dipivoxil (Hepsera®) product labeling. 2006.

Gilead. Amphotericin B liposome (AmBisome®) product labeling. 2002.

Ginsberg JM, Chang BS, Matarese RA, Garella S. Use of single voided urine samples to estimate quantitative proteinuria. *N Engl J Med.* 1983 Dec 22;309(25):1543-6.

Grubb A, Nyman U, Bjork J, Lindstrom V, Rippe B, Sterner G, Christensson A. Simple cystatin C-based prediction equations for glomerular filtration rate compared with the modification of diet in renal disease prediction equation for adults and the Schwartz and the Counahan-Barratt prediction equations for children. *Clin Chem.* 2005 Aug;51(8):1420-31.

Guignard JP, Santos F. Laboratory investigations. In: Avner ED, Harmon WE, Niaudet P, ed. *Pediatric nephrology*, 5th ed. Philadelphia, Lippincott Williams & Wilkins 2004; 286-298.

Hankinson JL, Odencrantz JR, Fedan KB. Spirometric reference values from a sample of the general U.S. population. *Am J Respir Crit Care Med.* 1999 Jan;159(1):179-87.

Herget-Rosenthal S, Bokenkamp A, Hofmann W. How to estimate GFR-serum creatinine, serum cystatin C or equations? *Clin Biochem.* 2007 Feb;40(3-4):153-61.

Hirawat S, Welch EM, Elfring GL, Northcutt VJ, Paushkin S, Hwang S, Leonard EM, Almstead NG, Ju W, Peltz SW, Miller LL. Safety, tolerability, and pharmacokinetics of PTC124, a non-aminoglycoside, nonsense mutation suppressor, following single- and multiple-dose administration to healthy male and female adult volunteers. *J Clin Pharmacol* 2007 Apr;47(4):430-14.

Iatropoulos M, Williams G. The function and pathology of brown adipose tissue in animals and humans. *J Toxicol Pathol* 2004;17:147-53.

Kerem E, Reisman J, Corey M, Canny GJ, Levison H. Prediction of mortality in patients with cystic fibrosis. *N Engl J Med.* 1992 Apr 30;326(18):1187-91.

Kerem E, Kalman YM, Yahav Y, Shoshani T, Abeliovich D, Szeinberg A, Rivlin J, Blau H, Tal A, Ben-Tur L, Springer C, Augarten A, Godfrey S, Lerer I, Branski D, Friedman M, Kerem B. Highly variable incidence of cystic fibrosis and different mutation distribution among different Jewish ethnic groups in Israel. *Hum Genet.* 1995 Aug; 96(2): 193-7.

Kerem E, Kerem B. Genotype-phenotype correlations in cystic fibrosis. *Pediatr Pulmonol* 1996 Dec; 22(6): 387-95.

Kerem B, Chiba-Falek O, Kerem E. Cystic fibrosis in Jews: frequency and mutation distribution. *Genet Test.* 1997; 1(1): 35-9.

- Kerem E, Hirawat S, Armoni S, Yaakov Y, Shoseyov D, Cohen M, Nissim-Rafinia M, Blau H, Rivlin J, Aviram M, Elfring GL, Northcutt VJ, Miller LL, Kerem B, Wilschanski M. Effectiveness of PTC124 treatment of cystic fibrosis caused by nonsense mutations: a prospective phase II trial. *Lancet*. 2008a Aug 30;372(9640):719-27.
- Kerem E, Yaakov Y, Armoni S, Pugatsch T, Shoseyov D, Cohen M, Blau H, Hirawat S, Reha A, Elfring G, Miller L, Wilschanski M. PTC124 induces time-dependent improvements in chloride conductance and clinical parameters in patients with nonsense-mutation-mediated cystic fibrosis. *Pediatric Pulmonol*. 2008b Oct;43 Suppl S31:294 (abst #266).
- Kerem E, Wilschanski M, Sermet-Gaudelus I, DeBoeck K, Accurso F, Konstan M, Rowe SM, Miller NL, Elfring GL, Spiegel R, Peltz S, Barth J, Ajayi T for the Ataluren CF Steering Committee and Study Group. Interim results of the Phase 3 open-label study of ataluren in nonsense mutation cystic fibrosis (nmCF). *J Cyst Fibros*. 2013;12(Suppl 1):S15.
- Khan TZ, Wagener JS, Bost T, Martinez J, Accurso FJ, Riches DW. Early pulmonary inflammation in infants with cystic fibrosis. *Am J Respir Crit Care Med*. 1995 Apr;151(4):1075-82.
- Kim MS, Corwin HL. Urinalysis. In: Schreir RW, ed. *Diseases of the kidney and urinary tract*, 8th ed. Philadelphia, Lippincott Williams & Wilkins 2007; 286-298.
- Konstan MW, Byard PJ, Hoppel C, Davis PB. Effect of high-dose ibuprofen in patients with cystic fibrosis. *N Engl J Med* 1995;332:848-54.
- LeGrys VA, Rosenstein BJ, Dumas BT, Miller WG, D'Orazio P, Eckfeldt JH, Evans SA, Graham GA, Myers GL, Parsons PJ, Stanton NV. Sweat testing: Sample collection and quantitative analysis: Approved guidelines – Second edition. National Committee for Clinical Laboratory Standards 2000; Vol 20:14; <http://subservice.nccls.org/edds/free/c34-a2.pdf>.
- Loeb JS, Blower WC, Feldstein JF, Koch BA, Munlin AL, Hardie WD. Acceptability and repeatability of spirometry in children using updated ATS/ERS criteria. *Pediatr Pulmonol*. 2008 Oct;43(10):1020-4.
- McCoy KS, Quittner AL, Oermann CM, Gibson RL, Retsch-Bogart GZ, Montgomery AB. Inhaled aztreonam lysine for chronic airway Pseudomonas aeruginosa in cystic fibrosis. *Am J Respir Crit Care Med*. 2008 Nov 1;178(9):921-8.
- McKone EF, Goss CH, Aitken ML. CFTR genotype as a predictor of prognosis in cystic fibrosis. *Chest* 2006 Nov;130(5):1441-7.
- Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J; ATS/ERS Task Force. Standardisation of spirometry. *Eur Respir J*. 2005a Aug;26(2):319-38.
- Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J; ATS/ERS Task Force. General considerations for lung function testing. *Eur Respir J*. 2005b Jul;26(1):153-61.

Morgenstern BZ, Butani L, Wollan P, Wilson DM, Larson TS. Validity of protein-osmolality versus protein-creatinine ratios in the estimation of quantitative proteinuria from random samples of urine in children. *Am. J. Kidney Dis.* 2003 Apr;41(4):760-6.

Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS.

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/docs/ctcae3.pdf](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcae3.pdf). Updated August 9, 2006. Accessed January 22, 2014.

National Kidney Foundation. Kidney Disease Outcomes Quality Initiative: Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification, Part 5. Evaluation of Laboratory Measurements for Clinical Assessment of Kidney Disease, Guideline 6. Markers of Chronic Kidney Disease Other than Proteinuria. 2002; [http://www.kidney.org/professionals/KDOQI/guidelines\\_ckd/p5\\_lab\\_g6.htm](http://www.kidney.org/professionals/KDOQI/guidelines_ckd/p5_lab_g6.htm).

Novartis. Cyclosporine (Neoral®) product labeling. 2005.

Oermann C, McCoy K, Retsch-Bogart G, Gibson R, Quittner A, Montgomery AB. Effect of multiple aztreonam lysine for inhalation (AZLI) cycles on disease-related endpoints and safety in patients with cystic fibrosis (CF) and *Pseudomonas aeruginosa* (PA): Interim analysis of 12-month data. *J Cyst Fibros* 2008;7(6) Suppl 2:S25 (abst #100).

O'Sullivan BP, Freedman SD. Cystic fibrosis. *Lancet.* 2009 May;373(9678):1891-904.

Politano L, Nigro G, Nigro V, Piluso G, Papparella S, Paciello O, Comi LI. Gentamicin administration in Duchenne patients with premature stop codon. Preliminary results. *Acta Myol.* 2003 May;22(1):15-21.

Rabin HR, Butler SM, Wohl ME, Geller DE, Colin AA, Schidlow DV, Johnson CA, Konstan MW, Regelmann WE; Epidemiologic Study of Cystic Fibrosis. Pulmonary exacerbations in cystic fibrosis. *Pediatr Pulmonol.* 2004 May;37(5):400-6.

Ramsey BW, Dorkin HL, Eisenberg JD, Gibson RL, Harwood IR, Kravitz RM, Schidlow DV, Wilmott RW, Astley SJ, McBurnie MA, Wentz K, Smith AL. Efficacy of aerosolized tobramycin in patients with cystic fibrosis. *N Engl J Med.* 1993 Jun;328(24):1740-6 [comment in *N Engl J Med.* 1993 Nov;329(22):1659-60].

Ramsey BW, Boat TF. Outcome measures for clinical trials in cystic fibrosis. Summary of a Cystic Fibrosis Foundation consensus conference. *J Pediatr.* 1994 Feb;124(2):177-92.

Ramsey BW. Management of pulmonary disease in patients with cystic fibrosis. *N Engl J Med* 1996 Jul; 335(3): 179-88.

Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, Vasiljev-K M, Borowitz D, Bowman CM, Marshall BC, Marshall S, Smith AL. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. *N Engl J Med.* 1999 Jan 7;340(1):23-30.

Redelmeier DA, Goldstein RS, Min ST, Hyland RH. Spirometry and dyspnea in patients with COPD. When small differences mean little. *Chest.* 1996 May;109(5):1163-8.

Retsch-Bogart GZ, Burns JL, Otto KL, Liou TG, McCoy K, Oermann C, Gibson RL; AZLI Phase II Study Group. A phase 2 study of aztreonam lysine for inhalation to treat patients with cystic fibrosis and *Pseudomonas aeruginosa* infection. *Pediatr Pulmonol.* 2008 Jan;43(1):47-58.

Retsch-Bogart GZ, Montgomery B, Gibson R, McCoy K, Oermann CM, Cooper P. Phase 3 trial (AIR-CF 1) measuring improvement in respiratory symptoms in patients with cystic fibrosis (CF) following treatment with aztreonam lysine for inhalation (AZLI). *Pediatr Pulmonol* 2007;41 Suppl 30:310 (abst #308).

Rosenfeld M, Gibson RL, McNamara S, Emerson J, Burns JL, Castile R, Hiatt P, McCoy K, Wilson CB, Inglis A, Smith A, Martin TR, Ramsey BW. Early pulmonary infection, inflammation, and clinical outcomes in infants with cystic fibrosis. *Pediatr Pulmonol*. 2001 Nov;32(5):356-66.

Rowe SM, Sermet-Gaudelus I, Konstan M, Kerem E, Wilschanski M, DeBoeck K, Accurso F, Miller NL, Elfring GL, Barth J, Ajayi T. Results of the Phase 3 Study of Ataluren in Nonsense Mutation Cystic Fibrosis (nmCF). *Pediatric Pulmonology* 2012 Sep; 47(S35): 290 (abst #193)

Sachs AB, Varani G. Eukaryotic translation initiation: there are (at least) two sides to every story. *Nat Struct Biol*. 2000 May;7(5):356-61.

Sagel SD, Chmiel JF, Konstan MW. Sputum biomarkers of inflammation in cystic fibrosis lung disease. *Proc Am Thorac Soc*. 2007 Aug 1;4(4):406-17.

Saiman L, Marshall BC, Mayer-Hamblett N, Burns JL, Quittner AL, Cibene DA, Coquillette S, Fieberg AY, Accurso FJ, Campbell PW 3rd; Macrolide Study Group. Azithromycin in patients with cystic fibrosis chronically infected with *Pseudomonas aeruginosa*: a randomized controlled trial. *JAMA*. 2003 Oct 1;290(13):1749-56.

Schluchter MD, Konstan MW, Davis PB. Jointly modelling the relationship between survival and pulmonary function in cystic fibrosis patients. *Stat Med*. 2002 May 15;21(9):1271-87.

Schwab SJ, Christensen RL, Dougherty K, Klahr S. Quantitation of proteinuria by the use of protein-to-creatinine ratios in single urine samples. *Arch Intern Med*. 1987 May 147(5): 943-4.

Sermet-Gaudelus I, De Boeck K, Casimir G, Leal T, Vermeulen F, Mogenet A, Roussel D, Hage P, Hanssens L, Constantine S, Hirawat S, Elfring G, Miller L. Children with nonsense-mutation-mediated cystic fibrosis respond to investigational treatment with PTC124. *Pediatric Pulmonol*. 2008 Oct;43 Suppl S31:313 (abst #316).

Shoshani T, Augarten A, Gazit E, Bashan N, Yahav Y, Rivlin Y, Tal A, Seret H, Yaar L, Kerem E, Kerem B. Association of a nonsense mutation (W1282X), the most common mutation in the Ashkenazi Jewish cystic fibrosis patients in Israel, with presentation of severe disease. *Am J Hum Genet*. 1992 Jan;50(1):222-8.

Smyth A, Elborn JS. Exacerbations in cystic fibrosis: 3--Management. *Thorax*. 2008 Feb;63(2):180-4.

Stern RC. The diagnosis of cystic fibrosis. *N Engl J Med*. 1997 Feb;336(7): 487-91.

Stevens LA, Lafayette RA, Perrone RD, Levey AS. Laboratory evaluation of kidney function. In: Schreir RW, ed. *Diseases of the kidney and urinary tract*, 8th ed. Philadelphia, Lippincott Williams & Wilkins 2007; 299-336.

Tiddens HA. Detecting early structural lung damage in cystic fibrosis. *Pediatr Pulmonol*. 2002 Sep; 34(3): 228-31.



US Food and Drug Administration. Drug Approval Package. Kalydeco (ivacaftor 150 mg Tablets). FDA Web site. Accessed February 06, 2013. Updated January 31, 2012. [http://www.accessdata.fda.gov/drugsatfda\\_docs/nda/2012/203188s000TOC.cfm](http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203188s000TOC.cfm)

Vonderscher J. Biomarker of drug-induced kidney injury: qualification for regulatory decision-making. Institute of Medicine of the National Academies: Forum on Drug Discovery, Development, and Translation Workshop – Emerging Safety Science. 2007 Apr. <http://www.iom.edu/Object.File/Master/42/665/Vonderscher.pdf>.

von Unruh GE, Voss S, Sauerbruch T, Hesse A. Dependence of oxalate absorption on the daily calcium intake. *J Am Soc Nephrol*. 2004 Jun;15(6):1567-73.

Wang X, Dockery DW, Wypij D, Fay ME, Ferris BG Jr. Pulmonary function between 6 and 18 years of age. *Pediatr Pulmonol*. 1993 Feb;15(2):75-88.

Welch EM, Wong W, Peltz, SP. Translation termination: It's not the end of the story. In Sonenberg N, Hershey JWB, and Matthews M, eds. *Translational control of gene expression*. 2000 Cold Spring Harbor Press, New York: 467-485.

Welch EM, Barton ER, Zhuo J, Tomizawa Y, Friesen WJ, Trifillis P, Paushkin S, Patel M, Trotta CR, Hwang S, Wilde RG, Karp G, Takasugi J, Chen G, Jones S, Ren H, Moon YC, Corson D, Turpoff AA, Campbell JA, Conn MM, Khan A, Almstead NG, Hedrick J, Mollin A, Risher N, Weetall M, Yeh S, Branstrom AA, Colacino JM, Babiak J, Ju WD, Hirawat S, Northcutt VJ, Miller LL, Spatrack P, He F, Kawana M, Feng H, Jacobson A, Peltz SW, Sweeney HL. PTC124 targets genetic disorders caused by nonsense mutations. *Nature*. 2007 May 3;447(7140):87-91.

Welsh MJ, Ramsey BW, Accurso F, Cutting GR. Cystic fibrosis. In: Scriver CR, Beaudet AL, Sly WS, Valle D, eds. *The metabolic basis of inherited disease*. 8th ed. Vol. 3. New York: McGraw-Hill, 2001:5121-5188.

Wilschanski M, Yahav Y, Yaacov Y, Blau H, Bentur L, Rivlin J, Aviram M, Bdolah-Abram T, Bebok Z, Shushi L, Kerem B, Kerem E. Gentamicin-induced correction of CFTR function in patients with cystic fibrosis and CFTR stop mutations. *N Engl J Med*. 2003 Oct 9;349(15):1433-41.

Zappitelli M, Joseph L, Gupta IR, Bell L, Paradis G. Validation of child serum creatinine-based prediction equations for glomerular filtration rate. *Pediatr Nephrol*. 2007 Feb;22(2):272-81.