NCT #NCT02647359

CLINICAL PROTOCOL

STAR: A Phase 2, Multicenter, Randomized, Double-Masked, Placebo-Controlled Study of the Safety and Efficacy of Ataluren (PTC124) for the Treatment of Nonsense Mutation Aniridia

PTC124-GD-028-ANI

17 DECEMBER 2019

VERSION 7.0

PTC THERAPEUTICS, INC.
100 CORPORATE COURT
SOUTH PLAINFIELD, NJ 07080 USA

SYNOPSIS

Name of Sponsor/Company:	PTC Therapeutics, Inc.
Name of Investigational Product:	Ataluren
Title of Study:	STAR: A Phase 2, Multicenter, Randomized, Double-Masked, Placebo Controlled Study of the Safety and Efficacy of Ataluren (PTC124) for the Treatment of Nonsense Mutation Aniridia
Study Centers:	[redacted] Canada [redacted]
Phase of Development:	Phase 2
Objectives:	***Primary Objective:*** The primary objective of this study is to evaluate the effect of ataluren on Maximum Reading Speed as measured using the Minnesota Low Vision Reading Test (MNREAD) Acuity Charts in subjects with nonsense mutation aniridia. ***Secondary Objectives:*** The secondary objectives of this study are to: • Evaluate the effect of ataluren on the following: o Reading Accessibility Index o Best corrected visual acuity (BCVA) o Critical Print Size o Reading Acuity o Severity of corneal keratopathy o Iris area • Characterize the systemic and ocular safety profile of ataluren in subjects with nonsense mutation aniridia. [redacted]

Endpoints:	***Primary Endpoint:*** The primary endpoint of this study is the change from baseline (Visit 2/Day 1) to Week 48 in Maximum Reading Speed of OU as measured using the MNREAD Acuity Charts. ***Secondary Endpoints:*** The key secondary efficacy endpoints of this study are: • Change from baseline (Visit 2/Day 1) to Week 48 in Reading Accessibility Index of OU • Change from baseline (Visit 2/Day 1) to Week 48 in BCVA Additional secondary efficacy endpoints of this study are as follows: • Change from baseline (Visit 2/Day 1) to Week 48 in Maximum Reading Speed of OD and OS • Change from baseline (Visit 2/Day 1) to Week 48 in Reading Accessibility Index of OD and OS • Change from baseline (Visit 2/Day 1) to Week 48 in Critical Print Size of OU, OD and OS • Change from baseline (Visit 2/Day 1) to Week 48 in Reading Acuity of OU, OD and OS • Change from baseline (Visit 2/Day 1) to Week 48 in severity of corneal keratopathy • Change from baseline (Visit 2/Day 1) to Week 48 in iris area • Change from baseline (Visit 2/Day 1, Stage 1) to Week 240 (End of Study Visit) in BCVA. Note: This endpoint will be assessed only for the cohort of subjects who enroll into the sub-study. The secondary safety endpoint of this study is the overall systemic and ocular safety profile of ataluren as determined by: • incidences of treatment-emergent adverse events • abnormal findings on laboratory assessments • vital signs • physical examinations • ophthalmoscopy • slit-lamp examination • visual field testing [redacted]

	[redacted]
Study Description and Methodology	This is a multicenter, stratified, randomized, double-masked, placebo-controlled study with a 4-week screening period, a 144-week treatment period, an optional 96-week open label sub-study, and a 4-week post-treatment follow-up period (either study completion or early termination).
Study Population:	A minimum of 36 subjects with nonsense mutation aniridia who are ≥2 years of age
Main inclusion and exclusion criteria	***Inclusion criteria*:** Subjects who will be selected for this study must meet the following criteria: 1. Evidence of signed and dated informed consent document(s) indicating that the study candidate (and/or a parent/legal guardian) has been informed of all pertinent aspects of the study. *Note: If the study candidate is considered a child under local regulation, a parent or legal guardian must provide written consent prior to initiation of study screening procedures and the study candidate may be required to provide written assent. The rules of the responsible institutional review board/independent ethics committee 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. Age ≥2 years and of either gender. 3. Body weight ≥12 kg.

	4. Documentation of the presence of a nonsense mutation in 1 allele of the PAX6 gene as determined by genotyping performed at a laboratory certified by the College of American Pathologists, or under the Clinical Laboratory Improvement Act/Amendment, or by an equivalent organization. *Note: Sponsor review of the genotyping documentation is required.* 5. Clinical diagnosis of aniridia. 6. Willingness and ability to comply with scheduled visits, drug administration plan, study procedures, and study restrictions. 7. Good general health, as determined at Visit 1 (Screening) by medical history and physical examination (including vital sign measurements). 8. No clinically significant abnormality based upon laboratory assessments at Visit 1 (Screening), in the opinion of the investigator. 9. Female subjects of childbearing potential are eligible for the study but must be willing to use adequate (at least 1 form of) contraceptive methods as described below during the study treatment period (starting from the day of first dose of study drug and ending 60 days after the last dose of study drug). Childbearing potential is defined as subjects who have experienced menarche and who are neither postmenopausal nor have been permanently sterilized. • Hormonal methods of contraception (including oral and transdermal contraceptives, injectable progesterone, progestin subdermal implants, progesterone-releasing intrauterine device [IUDs]) initiated at least 14 days prior to the first dose of study drug • Abstinence • Placement of a copper-containing IUD • Condom with spermicidal foam/gel/film/cream/suppository • Postmenopausal at least 12 months prior to first dose of study drug or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy) • Male partner who has had a vasectomy for at least 3 months prior to the first dose of study drug 10. Male subjects with partners of childbearing potential must agree to use adequate (at least 1 form of) contraception as described below during the study treatment period (starting from the day of first dose of study drug and ending 60 days after the last dose of study drug). • Abstinence • Vasectomy for at least 3 months prior to first dose of study drug or surgically sterile • Without a vasectomy, must use a condom with spermicidal foam/gel/film/cream suppository

	Exclusion Criteria: The presence of any of the following conditions will exclude a subject from study enrollment: **General exclusion criteria** 1. Subjects participating in any drug or device clinical investigation within 90 days prior to Visit 1 (Screening) or who anticipate participating in any other drug or device clinical investigation within the duration of this study. 2. Exposure to ataluren within 90 days prior to Visit 1 (Screening). 3. Surgery within 30 days prior to enrollment. 4. Female subjects who are pregnant or breastfeeding. Female subjects of childbearing potential must have a negative pregnancy test (beta-human chorionic gonadotropin) at screening and must use adequate (at least 1 form of) contraceptive methods. 5. Active ocular infection or inflammation. 6. Prior or ongoing medical condition (e.g., concomitant illness, alcoholism, drug abuse, psychiatric condition), medical history, physical 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 study drug administration or follow-up would be completed, or could impair the assessment of study results. 7. Subjects with a positive result for hepatitis B, hepatitis C, or human immunodeficiency virus at Visit 1 (Screening). **Drug therapies** 8. Ongoing warfarin, phenytoin, or tolbutamide therapy. 9. Ongoing intravenous (IV) aminoglycoside or IV vancomycin use. 10. Ongoing systemic cyclosporine therapy. *Note: Topical cyclosporine therapy is permitted.* 11. Known hypersensitivity to any of the ingredients or excipients of the study drug (polydextrose, polyethylene glycol 3350, poloxamer 407, mannitol 25C, crospovidone XL10, hydroxyethyl cellulose, vanilla, colloidal silica, or magnesium stearate). **Ocular exclusion criteria** 12. 20/200 or worse visual acuity in the better eye with best correction. 13. Subjects who are monocular. 14. Subjects with a history of complications due to ocular surgery that could interfere with the study procedures or assessment of study endpoints. 15. Subjects with any other significant ocular or systemic disease that the Investigator determines could interfere with the study.

Statistical analyses:	Two separate analyses will be conducted, one for the double-masked phase (Day 1 through Week 48), and the second for the entire study (Day 1 through Week 240). For patients randomized to placebo, two baselines will be used, one at randomization (Visit 2, Day 1) and the other at first dose of open-label ataluren (Visit 4, 48 weeks) for the analyses outlined below. a) Analyses on the double-masked phase (Day 1 through Week 48). Both placebo and ataluren will be presented and comparison will be made through 48 weeks between these two treatment groups. For the analyses of the double-masked phase, assessments at randomization (Visit 2 [Day 1]) will serve as baseline. b) Analyses of the entire study (Visit 2, Day 1 through Week 240). Efficacy will be presented based on two different baselines for placebo, one baseline at randomization (Visit 2) and the other baseline at Week 48 when placebo subjects first take open-label ataluren. Three analysis groups will be presented: 1) ataluren (all visits), 2) placebo (all visits) with Visit 2 assessments serving as baseline, and 3) combined groups with baseline at the first dose of ataluren (i.e., randomization -Visit 2 for ataluren patients and at the first dose of open-label ataluren (Visit 4, 48 weeks) for placebo patients). Safety data for the entire study will be presented for the combined group for patients receiving ataluren. By-subject listings will be created for each eCRF module. Summary tables for continuous variables will contain the following statistics: N, mean, median, standard deviation, standard error, minimum, maximum, and 95% confidence interval (CIs), as appropriate. Summary tables for categorical variables will include N, percentage, and 95% CIs on the percentage. Any CIs for proportions will be computed using normal approximation, if the number of the events is at least five. Otherwise, CIs using an exact method will be provided. Graphical techniques will be used when such methods are appropriate and informative. For safety summaries, CIs will not be presented, unless specified otherwise. Transformations of the data may be explored if warranted by the distribution of the data. Unless otherwise specified, all analyses will be two-sided at the 0.05 level of significance. All analyses will be performed using SAS® (Version 9.0 or higher).

PROTOCOL IDENTIFIERS AND STUDY PERSONNEL

Project Code	PTC124-GD
Therapeutic Area	Genetic Disorders - Aniridia
PTC Therapeutics Substance Identifier	Ataluren (PTC124®)
IND Number	126792
Included in clinical trials.gov Database	NCT02647359
Protocol Number	PTC124-GD-028-ANI
Protocol Version	Version 7.0
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Protocol Phase	Phase 2
Protocol Title	STAR: A Phase 2, Multicenter, Randomized, Double-Masked, Placebo Controlled Study of the Safety and Efficacy of Ataluren (PTC124) for the Treatment of Nonsense Mutation Aniridia
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PTC THERAPEUTICS
PROTOCOL APPROVAL SIGNATURES

[redacted] 18 Dec 2019
PTC Therapeutics, Inc. **Date**

[redacted] Dec 18, 2019
PTC Therapeutics, Inc. **Date**

[redacted] 18 Dec 2019
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	**Date**

Institution: _____

Address: _____

City: _____

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Country: _____

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Fax: _____

Email: _____

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Term	Definition
β-HCG	Beta-human chorionic gonadotropin
AE	Adverse event
ALT	Alanine aminotransferase
ANCOVA	Analysis of Covariance
ANOVA	Analysis of Variance
AST	Aspartate aminotransferase
BCRP	Breast cancer resistant protein
BCVA	Best corrected visual acuity
BMI	Body mass index
BUN	Blood urea nitrogen
CAP	College of American Pathologists
CD-ROM	Compact disc read-only memory
CFTR	Cystic fibrosis transmembrane conductance regulator
cGMP	Current Good Manufacturing Practices
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Act/Amendment
C_{max}	Maximum concentration
CTCAE	Common Terminology Criteria for Adverse Events
CYP	Cytochrome P450
DNA	Deoxyribonucleic acid
eCRF	Electronic case report form
EDC	Electronic data capture
EMA	European Medicines Agency
EOS/ET	End of study/ early termination
ETDRS	Early Treatment Diabetic Retinopathy Study
FDA	Food and Drug Administration
GCL	Ganglion cell layer
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
Hz	Hertz
ICH	International Council for Harmonisation
INL	Inner nuclear layer
IPL	Inner plexicon layer
IRB/IEC	Institutional review board/independent ethics committee
IS	Inner segments
ITT	Intent-to-treat
IUD	Intrauterine device
IV	Intravenous
IVR	Interactive Voice Response
IWR	Interactive Web Response
L	Lens
LEA	LEA Symbols Visual Acuity Test System
MedDRA	Medical Dictionary for Regulatory Activities
MMA	Methylmelonic acidemia
MNREAD	Minnesota Low Vision Reading Test (MNREAD) Acuity Charts
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MT	Mutant
nmCF	Nonsense mutation cystic fibrosis
nmDMD	Nonsense mutation Duchenne muscular dystrophy
nmPAX6	Nonsense mutation PAX6

Term	Definition
OAT1	Organic anion transporter 1
OAT3	Organic anion transporter 3
OATP1B3	Organic anion transporting polypeptide 1B3
OCT	Optical coherence tomography
OD	Oculus dexter (right eye)
ONL	Outer nuclear layers
OS	Oculus sinister (left eye)
OS	Outer segments
OTC	Over-the-counter
OU	Oculus unitas (both eyes)
P	Postnatal day
P-gp	P-glycoprotein
PAX6	Paired box 6
Pax6Sey+/–	Semidominant small eye mouse model of aniridia
PI	Principal Investigator
PK	Pharmacokinetic(s)
PTC124	Ataluren
qd	One a day
R	Retina
SAE	Serious adverse event
SC	Subcutaneous
SYS	Systemic ataluren (30 mg/kg qd)
TID	Three times a day
UGT1A9	UDP-glucuronosyltransferase 1-9
WT	Wild type

1 OVERVIEW

1.1 Introduction

Congenital aniridia, a familial condition with autosomal dominant inheritance, is a bilateral, panocular disorder affecting the cornea, iris, intraocular pressure, lens, fovea, and optic nerve (Valenzuela 2004, Netland 2011, Hingorani 2012, Chang 2014). The vast majority of cases of aniridia are associated with mutations in the paired box 6 (PAX6) gene, which is located on chromosome 11p13 and regulates ocular development. The phenotype is variable between and within families; however, affected individuals usually show little variability between the two eyes. Individuals with aniridia characteristically show absence of iris, nystagmus, impaired visual acuity (usually 20/100 to 20/200), and foveal hypoplasia.

Aniridia mainly manifests in the eye, but there are additional characteristics of aniridia, including obesity (Netland 2011) and impaired glucose tolerance and/or diabetes (Wen 2009) as PAX6 regulates not only eye development but also islet cell development (Yasuda 2002). PAX6 continues to be expressed through adulthood, contributing to maintenance of function in the eye and other tissues. Individuals with isolated aniridia may show reduced olfaction and cognition, behavioral problems, or developmental delay.

Many of the treatment methods used today for aniridia are ineffective. Tinted or photochromic lenses may be used to reduce light sensitivity. Surgical management of some of the visually disabling manifestations, such as cataract surgery or glaucoma shunt surgery, has provided improvement in eyesight visual acuity. However, due to the structural defects, patients with aniridia often experience post-operative complications, including aniridic fibrosis syndrome, which together with limbal stem cell deficiency leads to decompensation of the cornea or aniridia-related keratopathy. The eyesight vision of most aniridia patients progressively declines to the point of legal blindness. Corneal disease may be treated with lubricants, mucolytics, or punctual occlusion. Corneal transplants, or keratoplasty, can be performed on patients with aniridia, but often produce only temporary vision improvements. The treatment of keratopathy associated with aniridia via amniotic membrane transplant has proven to be only a temporary solution for aniridia patients suffering from moderate keratopathy. In patients with severe keratopathy who exhibit limbal insufficiency, treatment involves limbus transplant of lumbar cells. Self-transplants are excluded since aniridia usually affects both eyes, therefore patients must receive allografts from compatible healthy relatives or cadavers and be treated with oral immunosuppression treatment post-transplant to alleviate the risk of rejection.

Currently, there are no pharmacological approaches to the treatment of aniridia. There is a high unmet medical need for a safe, convenient treatment targeting the underlying cause of this orphan genetic disorder.

Nonsense mutations are the cause of congenital aniridia in ~40% of patients (Tzoulaki 2005). Nonsense mutations in deoxyribonucleic acid (DNA) correspond to premature stop codons in messenger ribonucleic acid (mRNA). PTC Therapeutics, Inc., South Plainfield, NJ, USA, has discovered and developed ataluren, a novel, orally available, 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 those patients for whom a nonsense mutation causes aniridia.

Ataluren has demonstrated readthrough activity in a wide range of preclinical models of nonsense mutation diseases, including nonsense mutation aniridia. In $PAX6^{Sey+/-}$ mice with a nonsense mutation in the mouse PAX6 gene, ataluren treatment during the postnatal period not only inhibited disease progression but also stably reversed corneal, lens, and retinal malformation defects and restored electrical and behavioral responses of the retina (Gregory Evans 2014). Pharmacological activity of ataluren also has been documented in nonsense mutation choroideremia (Tracey-White 2014), nonsense mutation retinitis pigmentosa (Schwarz 2015), nonsense mutation Duchenne muscular dystrophy (nmDMD) (Welch 2007), nonsense mutation cystic fibrosis (nmCF) (Du 2008), and various other nonsense mutation genetic disorders. In nonclinical neurological, respiratory, and cardiovascular safety pharmacology studies, ataluren has shown no adverse effects. Secondary pharmacodynamic assessments performed in vitro and in vivo have documented selective readthrough of premature stop codons without readthrough of normal stop codons. Toxicology studies in mice through 1 month, in rats through 6 months, and in dogs through 1 year have indicated acceptable tolerability and support dosing in subjects ≥2 years old.

Phase 1 clinical trials in which 62 healthy volunteers (ages 18 to 30 years) were administered ataluren at doses ranging from a single dose of 3 mg/kg to 50 mg/kg twice a day for 14 days demonstrated that oral ataluren can achieve target plasma concentrations associated with activity in preclinical testing. Phase 2a studies in 77 subjects (ages 6 to 57 years) with nmCF receiving oral ataluren for periods of 14 days through 12 weeks demonstrated that oral ataluren is generally well tolerated and can generate production of apically localized epithelial cystic fibrosis transmembrane conductance regulator (CFTR) protein. Phase 2a studies in 38 subjects (ages 5 to 17 years) with nmDMD administered oral ataluren through 28 days confirm the ataluren safety profile and demonstrated evidence of pharmacodynamic activity, with improvements in muscle expression of dystrophin. Phase 2b/3, placebo-controlled, 48 week studies in nmCF and nmDMD support the long-term safety of chronic ataluren administration and indicate that ataluren treatment is associated with clinical benefit (Bushby 2014, Kerem 2014). In July 2014, the European Medicines Agency (EMA) conditionally approved ataluren for the treatment of nmDMD and it has been subsequently renewed five times.

1.2 Study Design

This is a Phase 2, multicenter, stratified, randomized, double-masked, placebo-controlled study with a 4-week screening period, a 144-week treatment period, an optional 96-week open label sub-study, and a 4-week post-treatment follow-up period (either study completion or early termination). A minimum of 36 subjects with nonsense mutation aniridia who are ≥2 years of age are planned for enrollment into this study at investigator sites in US and Canada.

During the 4-week screening period, subjects will be assessed for eligibility.

Eligible subjects will enter the 144-week treatment period consisting of two stages:

- Stage 1 (Weeks 1 to 48) during which subjects will receive either ataluren or placebo in a masked fashion;
- Stage 2 (Weeks 49 to 144) during which subjects will receive open-label ataluren.

Eligible subjects will be randomized in a masked 2:1 fashion to either ataluren or placebo. Randomization will be stratified by age: ≤10 years versus >10 years. Masked study drug will be dosed three times a day (TID): 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening for 48 weeks. Subjects (or parent/legal guardian) will record each dose on a diary card provided by PTC Therapeutics.

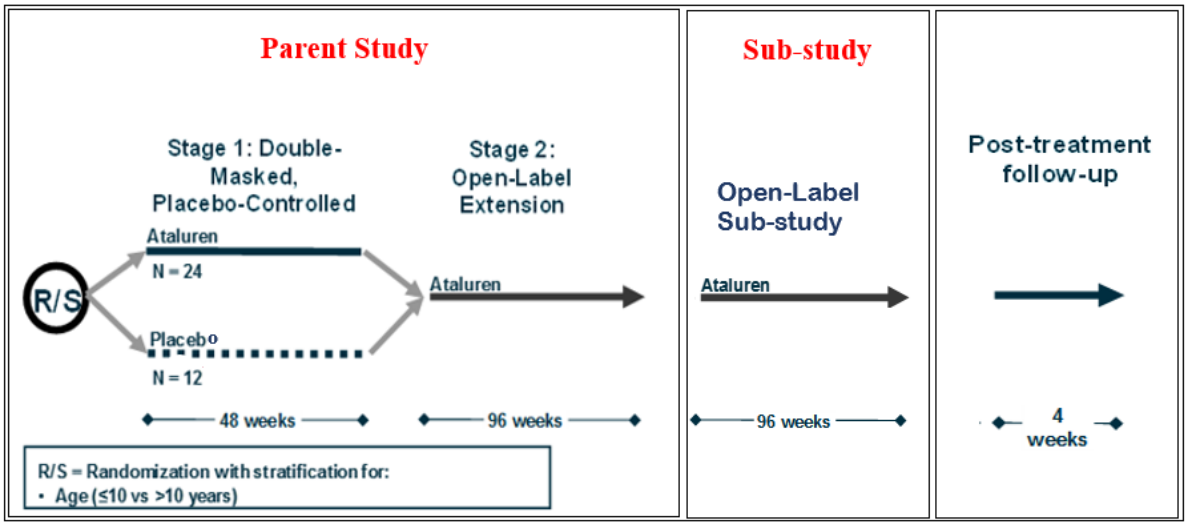
After completion of the Stage 1 (Week 48), subjects will be eligible for an additional 96 weeks of open-label ataluren treatment. Subjects who received ataluren during Stage 1 will continue to receive ataluren; subjects who had been randomized to placebo will receive ataluren during Stage 2.

There will be an optional sub-study at the end of the Stage 2 Open-Label Extension. Subjects will be able to consent to receive an additional 96 weeks of ataluren treatment, returning to the clinic every 24 weeks. The assessments to be conducted are outlined in the schedule of events. Subjects that choose not to participate in the sub-study will be required to complete the Post-treatment follow-up visit at the end of the Stage 2 Open-Label Extension. The start of the sub-study will require prior approval of a protocol amendment from applicable IRBs and will continue for 96 weeks or until commercial availability of ataluren for this indication, whichever is first, or until a positive risk-benefit assessment in this indication is not demonstrated.

After the subject's last dose of ataluren, there will be a 4-week post-treatment follow-up period. Analyses of the double-masked phase will be conducted after the last subject has completed Week 96.

A schematic of the study design is provided in Figure 1.

Figure 1. STAR Aniridia Study Schematic



2 BACKGROUND

2.1 Disease Indication

Aniridia, a familial condition with autosomal dominant inheritance, is a bilateral panocular disorder affecting the cornea, iris, intraocular pressure, lens, fovea, and optic nerve. Aniridia is caused by mutations in the PAX6 gene, which is located on chromosome 11p13 and regulates ocular development. The phenotype is variable between and within families; however, affected individuals usually show little variability between the two eyes. Individuals with aniridia characteristically show absence of iris, nystagmus, impaired visual acuity (usually 20/100 to 20/200), and foveal hypoplasia. Milder forms of aniridia with subtle iris architecture changes, good vision, and normal foveal structure do occur. Other abnormalities include corneal changes, glaucoma, cataract, lens subluxation, strabismus, optic nerve coloboma and hypoplasia, and occasionally microphthalmia.

Aniridia is inherited as an autosomal dominant trait caused by mutations including nonsense mutations (premature stop codons), frameshift insertions and deletions, and splice mutations in the PAX6 gene located on chromosome 11p13. The PAX6 gene is a transcriptional regulator that is expressed in the iris tissue and other ocular tissues derived from neural crest cells.

Reduction in visual acuity (usually 20/100–20/200), a universal abnormality associated with aniridia, usually starts at birth and is caused by foveal hypoplasia or optic nerve hypoplasia. As the patient reaches adulthood visual acuity progressively declines due to the occurrence of cataracts, nystagmus, amblyopia, glaucoma, and corneal keratopathy. Most children with aniridia present at birth with an obvious iris or pupillary abnormality or in infancy with nystagmus (usually apparent by six weeks of age). Congenital glaucoma rarely occurs in aniridia; in such cases, a large corneal diameter and corneal edema may be the presenting findings. Cataracts develop at a young age in 50 to 85% of aniridia patients usually prior to 20 years of age.

Ocular manifestations of aniridia are described below:

- **Iris**. The most obvious ocular abnormality is iris hypoplasia. The severity varies from a nearly normal iris to almost complete iris absence in which a small stump of residual iris tissue is visible on gonioscopy, anterior segment optical coherence tomography (OCT), or ultrasound biomicroscopy. In less extreme cases, the pupil size may be normal, but there may be loss of the iris surface architecture or presence of iris transillumination. Other iris changes include partial iris defects (resembling a coloboma) or eccentric or misshapen pupils and iris ectropion.
- **Lens**. Congenital lens opacities are common. Often there is persistent vascularization of the anterior lens capsule (tunica vasculosa lentis) or remnants of the pupillary membrane. The lens opacities are rarely dense enough to require lens extraction in infancy, but visually significant lens opacities eventually develop in 50% to 85% of affected individuals, often in the teens or early adulthood.

- [redacted]

- **Cornea**. Keratopathy (corneal degeneration) is a relatively late manifestation with multifactorial causes including limbal stem cell abnormalities and abnormal wound healing occurring in approximately 80% of the eyes of aniridia patients and causes visual disturbances in 26% of eyes. Changes vary from mild peripheral vascularization to pan-corneal vascularization, opacification, and keratinization.
- **Fovea**. Foveal hypoplasia is usually (but not always) present. Findings include reduced foveal reflex, macular hypopigmentation, and crossing of the usual foveal avascular zone by retinal vessels. OCT images can clearly delineate the absence of normal foveal architecture.
- **Optic nerve**. Optic nerve hypoplasia (i.e., the optic nerve head appears abnormally small) may occur in aniridia patients, as well as optic nerve coloboma.
- **Retina**. Retinal detachment may occur, probably as a consequence of a high myopia or previous intraocular surgery. Very rarely, primary retinal manifestations such as an exudative vascular retinopathy or chorioretinal degeneration may occur.
- **Other ocular manifestations**. Affected individuals may have significant refractive errors and may develop a secondary strabismus (squint, eye misalignment).

  Aniridia mainly manifests in the eye, but there are additional characteristics of aniridia, including effects on hearing and the central nervous system as well as obesity and glucose intolerance. Systemic manifestations associated with aniridia are described below:

- **Central nervous system**. Individuals with isolated aniridia may show reduced olfaction and cognition, behavioral problems, or developmental delay.
- **Hearing**. Central auditory processing difficulties (from abnormal interhemispheric transfer) present in some individuals may cause hearing difficulties. This finding is particularly important in the context of associated visual impairment.
- **Obesity**. Patients with aniridia are significantly more likely to be classified as overweight or obese compared with siblings without aniridia. The high prevalence of obesity in aniridic patients may be related to endocrine pancreatic function, which is influenced by PAX6 gene expression.
- **Glucose Intolerance**. PAX6 regulates not only eye development but also islet cell development. In patients with aniridia, PAX6 mutations are associated with impaired glucose tolerance and/or diabetes.

Aniridia is diagnosed via a clinical examination entailing slit lamp examination, fundoscopy, iris fluorescein angiography, OCT, and high-frequency ultrasound biomicroscopy. Gene sequencing is performed to identify the disease-causing mutation.

Many of the treatment methods used today for aniridia are ineffective. Surgical management of some of the visually disabling manifestations, such as cataract surgery or glaucoma shunt surgery, has provided improvement in eyesight. However, due to the structural defects, aniridia patients often experience post-operative complications, including aniridic fibrosis syndrome, which leads to decompensation of the cornea or aniridia-related keratopathy. The eyesight of most aniridia patients progressively declines to the point of legal blindness. Corneal transplants, or keratoplasty, can be performed on patients with aniridia, but often produce only temporary vision improvements. The treatment of keratopathy associated with aniridia via amniotic membrane transplant has proven to be only a temporary solution for aniridia patients suffering from moderate keratopathy. In patients with severe keratopathy who exhibit limbal insufficiency, treatment involves limbus transplant of lumbar cells. Self-transplants are excluded since aniridia usually affects both eyes, therefore patients must receive allografts from compatible healthy relatives or cadavers and be treated with oral immunosuppression treatment post-transplant to alleviate the risk of rejection.

2.2 Ataluren

2.2.1 Therapeutic Rationale

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 PAX6 tells the ribosomes to halt production of the protein before the full-length protein is completed. The resulting truncated PAX6 is too short to serve its necessary function and causes disease.

Drugs with translation-modifying mechanisms of action, such as the aminoglycoside antibiotics (e.g., gentamicin), can modulate 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 nmDMD have demonstrated gentamicin-induced restoration of dystrophin, the structural protein that is defective in that disease (Barton-Davis 1999, Politano 2003). Nonsense suppression also has been documented in a number of ocular disorders (Wang 2015). Current data suggest that the geometry of mRNA and associated initiation-termination proteins is critically different at a premature stop codon than at a normal stop codon. This may explain why a drug can permit the ribosomes to selectively read through the premature stop codon, but will not allow the ribosomes to read through the normal stop codon at the end of the mRNA protein-coding region (Sachs 2000, Welch 2000, Amrani 2004). Because serious renal and otic toxicities, and the need for parenteral administration, preclude the long-term clinical use of gentamicin, there has been considerable interest in the identification

of safer and more conveniently administered, low-molecular-weight, synthetic compounds with the ability to promote readthrough of disease-causing nonsense mutations.

PTC Therapeutics, Inc. is a biopharmaceutical company involved in the discovery and development of new therapies for genetic diseases. PTC Therapeutics has conducted a drug discovery program with the objective of finding and developing new agents that overcome the effects of nonsense mutations. A high-throughput screening program identified sets of novel, non-aminoglycoside chemical structures that selectively induce ribosomal read-through of premature stop codons in mRNA. Chemical optimization, pharmacologic characterization, and toxicological evaluation led to identification of ataluren as an orally bioavailable, small molecule with potential clinical utility in treating genetic disorders through induction of read-through of nonsense mutations and production of full-length, functional proteins (Welch 2007, Du 2008, Gregory-Evans 2014). In the subset of patients whose disease is mediated by a nonsense mutation, ataluren may offer an effective therapy by restoring critical protein production for aniridia and other disabling and life-threatening genetic disorders.

In July 2014, the EMA conditionally approved ataluren for the treatment of nmDMD and it has been subsequently renewed five times.

2.2.1.1 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 Class 2 compound, possessing low aqueous solubility (<31 μg/mL) but high permeability across gastrointestinal epithelium, consistent with its high oral bioavailability. The drug is manufactured and formulated under current Good Manufacturing Practices (cGMP) and is provided as a vanilla-flavored, white to off-white granules for oral suspension.

2.2.1.2 Nonclinical Studies

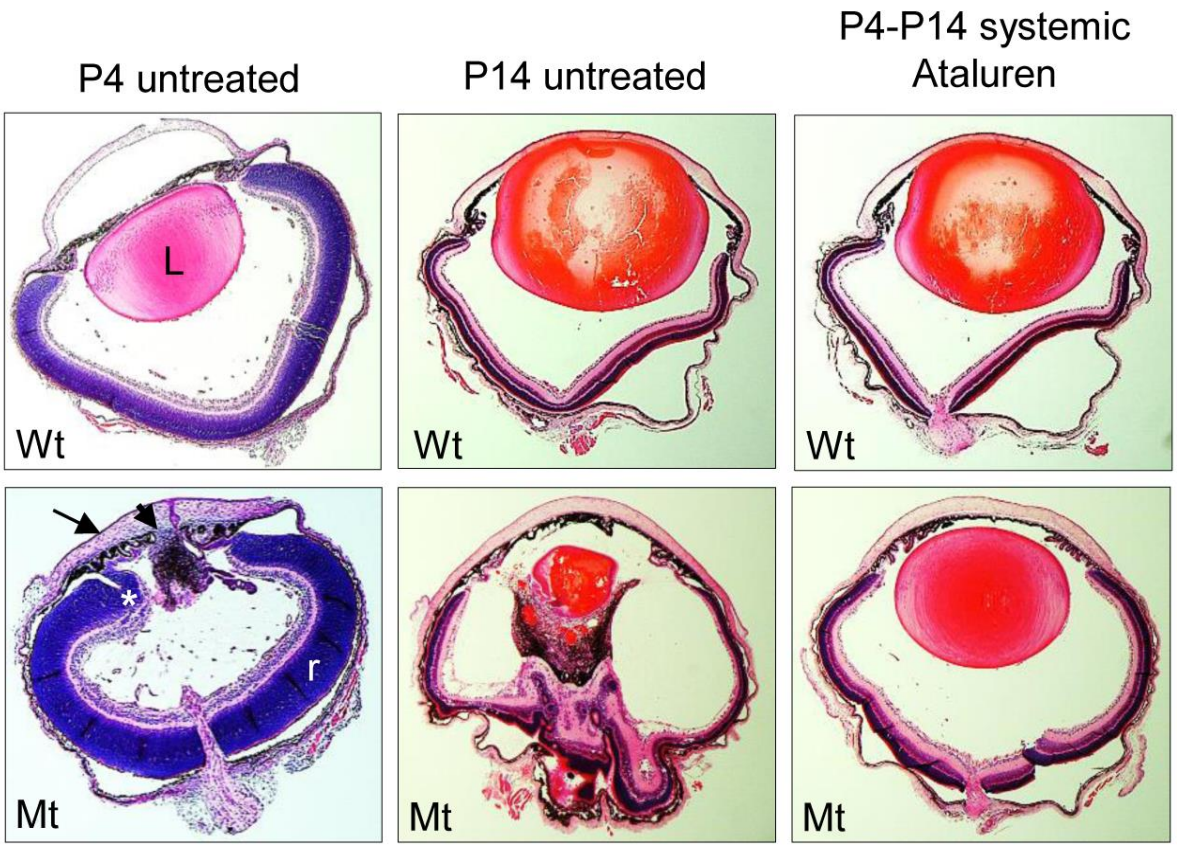
Refer to the Ataluren Investigator Brochure for a detailed presentation of efficacy pharmacology, safety pharmacology, toxicology, and pharmacokinetic (PK) data from ataluren nonclinical studies. A study of ataluren in a nonclinical model of aniridia is described below.

Ataluren was evaluated in the small-eye mouse model of nonsense mutation aniridia ($PAX6^{Sey+/-}$) (Gregory-Evans 2014). Aniridia in the small eye mouse model is caused by a naturally occurring nonsense mutation in the mouse PAX6 gene.

Treatment with ataluren caused an increase in the PAX6 protein by 90% in the corneal and retinal epithelium protein lysates compared to wild-type mice (Figure 2) as measured by enzyme-linked immunosorbent assay. A mouse model containing a splice-site mutation in PAX6 ($PAX6^{Sey\text{-}1Neu}$) did not show a response to ataluren therapy, demonstrating that ataluren is specific to nonsense mutation-mediated disease.

Dramatic improvements in the eye morphology were observed in mice treated for 10 days by subcutaneous injection (30 mg/kg qd) compared to untreated mice. Untreated nmPAX6 mutant eyes at postnatal day 4 (P4) (Figure 2, lower left panel) showed thickening of the cornea, the appearance of a lenticular stalk in which the underdeveloped lens was attached to the cornea, and thickening of the retina with abnormal in-folding at the ciliary margin and by P14 (Figure 2, lower middle panel) there is progressive in-folding of the retina and an abnormally small lens is observed. In contrast, when ataluren was administered by subcutaneous injection at 30 mg/kg qd for 10 days (P4 to P14) retinal in-folding was prevented and the size of the lens increased by 70% (Figure 2, lower right panel).

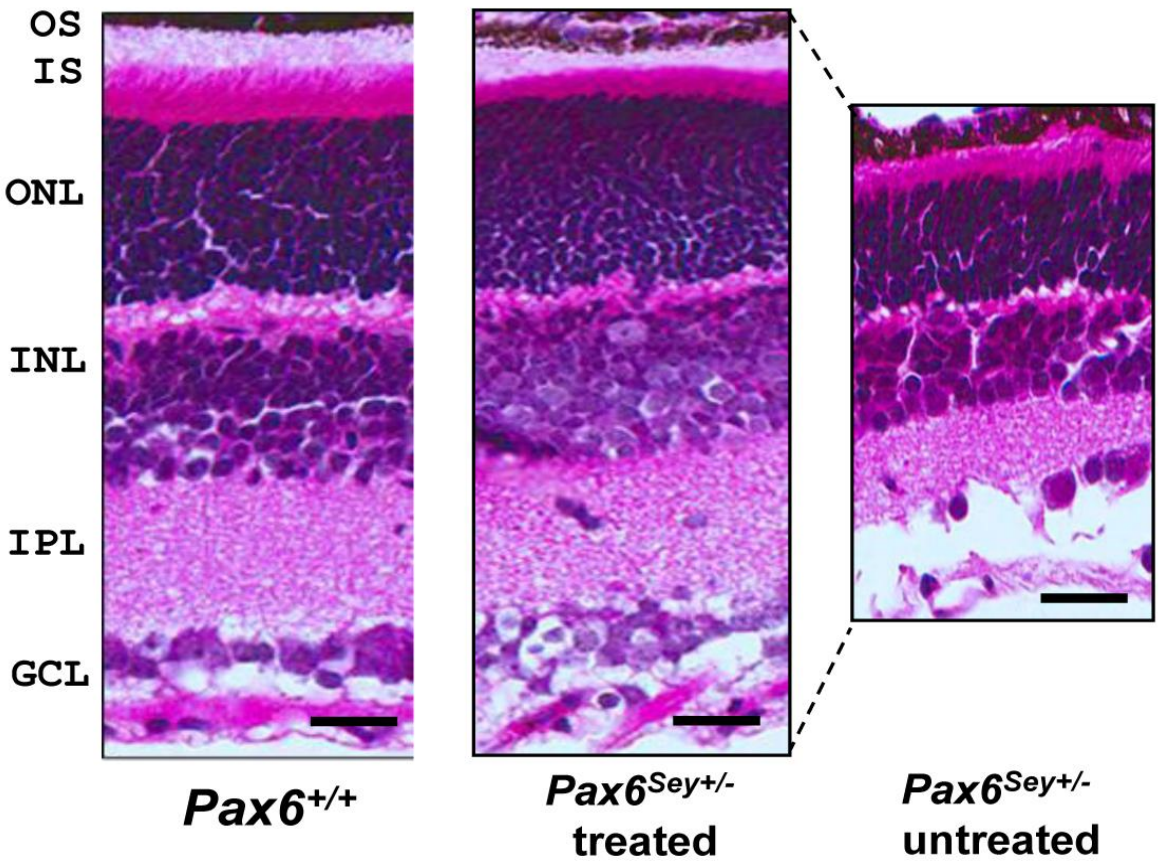
Figure 2. Ataluren Treatment Improves Eye Morphology in nmPAX6 Mutant Mice



Abbreviations: L, lens; Mt, mutant; nmPAX6, P, Postnatal day; r, retina; Wt, wild type
Effect of ataluren treatment on eye morphology in nmPAX6 mice (1) administered once daily subcutaneously (30 mg/kg) for 10 days. The black arrow-head indicates the lenticular stalk; the black arrow indicates the cornea; and the asterisk indicates the ciliary margin.

In addition to the morphological improvements, mice treated with ataluren showed improvements in the thickness of the retinal layers (Figure 3) and higher packing density of photoreceptor nuclei.

Figure 3. Ataluren Treatment Improves Retinal Histology in nmPAX6 Mutant Mice

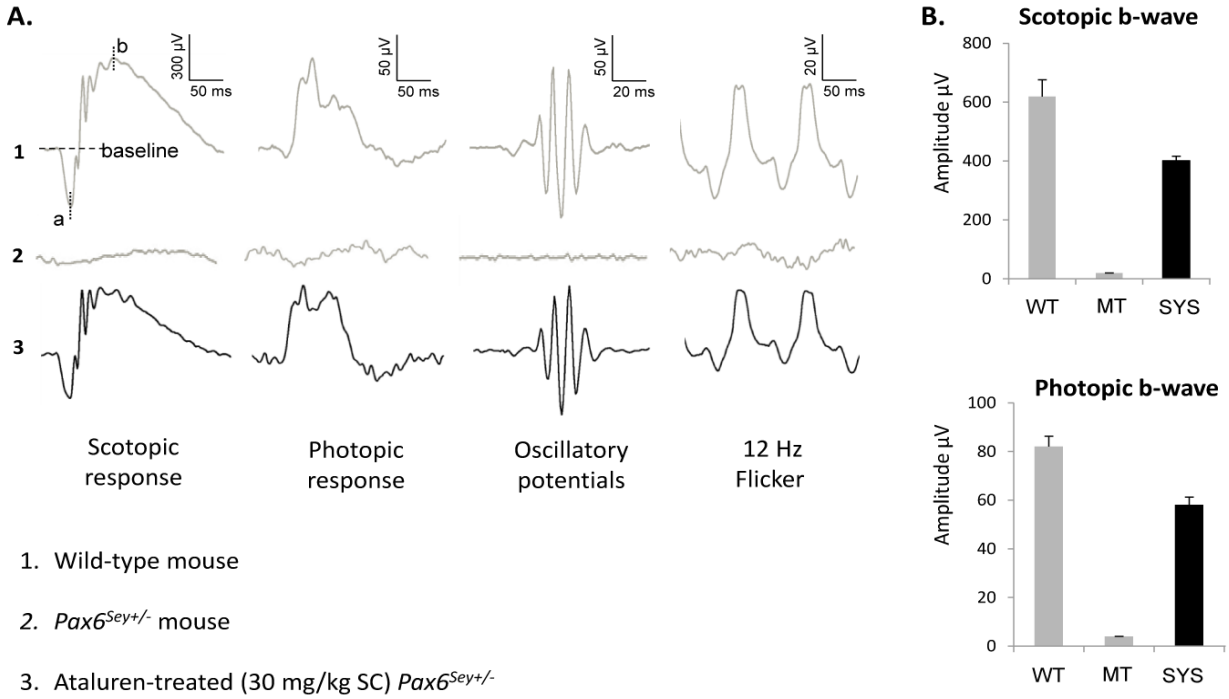


Abbreviations: GCL, ganglion cell layer; INL, inner nuclear layer; IPL, inner plexiform layer; IS, inner segments; nmPAX6, nonsense mutation PAX6; ONL, outer nuclear layers; OS, outer segments, $PAX6^{Sey+/-}$, semidominant small eye mouse model of aniridia

Retinal sections from wild-type systemically-treated PAX6 mutant mice (30 mg/kg subcutaneous injection from P4-14) and untreated nmPAX6 mice, showing the photoreceptor inner segments (IS) and outer segments (OS) are shorter in treated mice (n=6). The outer nuclear layers (ONL) are more densely packed in the treated mice compared with those in the wild-type mice. All the retinal layers in the untreated mice are thinner than normal.

Dramatic improvements in the response to light as measured by electroretinograms were observed in mice treated for 46 days by subcutaneous injection (30 mg/kg qd) compared to untreated mice (Figure 4: compare Trace 2 [mutant untreated] to Trace 3 [subcutaneous administration 30 mg/kg daily P14-P60]). Dramatic improvements were also observed in mice administered the topical formulations for 46 days (Figure 4: compare Trace 4 [1% ataluren twice a day P14-P60] to Trace 2).

Figure 4. Ataluren Treatment Improves Response to Light Stimulation (Electroretinographic) in nmPax6 Mutant Mice



Abbreviations: ANOVA, analysis of variance; Hz, hertz; MT, mutant; nmPAX6, nonsense mutation PAX6; P, postnatal day; PAX6$^{Sey+/-}$, semidominant small eye mouse model of aniridia; qd, one a day; SC, subcutaneous; SYS, systemic ataluren (30 mg/kg qd); WT, wild type
Electroretinographic analyses in response to light stimulation. (A) Restoration of light sensitivity in Pax6Sey+/– eyes measured at P60. Trace 1 shows wild-type mice with systemic ataluren. Trace 2 shows untreated Pax6Sey+/– mouse responses. Trace 3 shows Pax6Sey+/– mice with systemic ataluren. a,a-wave maximum from baseline; b, b-wave maximum from baseline. (B) Quantification of scotopic and photopic b-wave responses (n = 6). Significance determined by 1-way ANOVA with Tukey post-hoc tests *P<0.05; **P<0.01.).

As shown above (Figure 4), treatment with ataluren resulted in increased response of the retina to light stimulation, demonstrating that the PAX6 protein produced was functional. The optokinetic tracking response was measured to determine changes in behavioral response mediated through the retina-brain circuitry as an approximation for visual acuity. These results support the previous observations that ataluren treatment improves the morphology of the eye and the response of the retina to light by demonstrating that PAX6 protein is produced and is functional as measured by optokinetic tracking.

Taken together, these results demonstrate that ataluren treatment of the nonsense mutation small eye enables readthrough of the nonsense codon in the PAX6 mRNA producing full-length functional PAX6 protein. The increased PAX6 protein results in the reversal of the congenital ocular malformation associated with the disease. These results demonstrate that ataluren has the potential to be a promising treatment for the underlying cause of aniridia.

2.2.1.3 Clinical Studies

In total, >1036 subjects, including healthy volunteers as well as subjects with several nonsense mutation genetic disorders, have been exposed to ataluren in Phase 1 (Hirawat 2007), Phase 2 (Kerem 2008, Sermet-Gaudelus 2010, Wilschanski 2011, Finkel 2013) and Phase 3 (Bushby 2014, Kerem 2014) clinical studies. Refer to the Ataluren Investigator Brochure for a detailed presentation of safety, efficacy, and PK data from these clinical studies.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objectives

3.1.1 Primary Objective

The primary objective of this study is to evaluate the effect of ataluren on Maximum Reading Speed as measured using the Minnesota Low Vision Reading Test (MNREAD) Acuity Charts in subjects with nonsense mutation aniridia.

3.1.2 Secondary Objectives

The secondary objectives of this study are to:

- Evaluate the effect of ataluren on the following:
  - Reading Accessibility Index
  - Best corrected visual acuity (BCVA)
  - Critical Print Size
  - Reading Acuity
  - Severity of corneal keratopathy
  - Iris area
- Characterize the systemic and ocular safety profile of ataluren in subjects with nonsense mutation aniridia.

3.1.3 [redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

3.2 Endpoints

3.2.1 Primary Endpoint

The primary endpoint of this study is the change from baseline (Visit 2/Day 1) to Week 48 in Maximum Reading Speed of OU as measured using the MNREAD Acuity Charts.

3.2.2 Secondary Endpoints

The key secondary efficacy endpoints of this study are:

- Change from baseline (Visit 2/Day 1) to Week 48 in Reading Accessibility Index of OU
- Change from baseline (Visit 2/Day 1) to Week 48 in BCVA

Additional secondary efficacy endpoints of this study are as follows:

- Change from baseline (Visit 2/Day 1) to Week 48 in Maximum Reading Speed of OD and OS
- Change from baseline (Visit 2/Day 1) to Week 48 in Reading Accessibility Index of OD and OS
- Change from baseline (Visit 2/Day 1) to Week 48 in Critical Print Size of OU, OD and OS
- Change from baseline (Visit 2/Day 1) to Week 48 in Reading Acuity of OU, OD and OS
- Change from baseline (Visit 2/Day 1) to Week 48 in severity of corneal keratopathy
- Change from baseline (Visit 2/Day 1) to Week 48 in iris area
- Change from baseline (Visit 2/Day 1, Stage 1) to Week 240 (End of Study Visit) in BCVA. Note: This endpoint will be assessed only for the cohort of subjects who enroll into the sub-study.

The secondary safety endpoint of this study is the overall systemic and ocular safety profile of ataluren as determined by:

- incidences of treatment-emergent adverse events
- abnormal findings on laboratory assessments
- vital signs
- physical examinations
- ophthalmoscopy

- slit-lamp examination
- visual field testing

3.2.3 [redacted]

[redacted]

4 SUBJECT SELECTION CRITERIA

4.1 Overview

The following eligibility criteria are designed to select subjects for whom study participation is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether this protocol is suitable for a particular subject. Eligibility criteria 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 or designee prior to enrollment.

Subjects that complete the parent study will be eligible to participate in the sub-study. The principal investigator (PI) or sub-investigator will discuss the possibility of participation directly with study subjects and/or parent/legal guardian in the clinic.

4.2 Inclusion Criteria

Subjects who will be selected for this study must meet the following criteria:

1. Evidence of signed and dated informed consent document(s) indicating that the study candidate (and/or a parent/legal guardian) has been informed of all pertinent aspects of the study. *Note: If the study candidate is considered a child under local regulation, a parent or legal guardian must provide written consent prior to initiation of study screening procedures and the study candidate may be required to provide written assent. The rules of the responsible institutional review board/independent ethics committee (IRB/IEC) regarding whether one or both parents must provide consent and the appropriate ages for obtaining consent and assent from the subject should be followed.*
2. Age ≥2 years and of either gender.
3. Body weight ≥12 kg.
4. Documentation of the presence of a nonsense mutation in 1 allele of the PAX6 gene as determined by genotyping performed at a laboratory certified by the College of American Pathologists (CAP), or under the Clinical Laboratory Improvement Act/Amendment (CLIA), or by an equivalent organization. *Note: Sponsor review of the genotyping documentation is required.*
5. Clinical diagnosis of aniridia.
6. Willingness and ability to comply with scheduled visits, drug administration plan, study procedures, and study restrictions.
7. Good general health, as determined at Visit 1 (Screening) by medical history and physical examination (including vital sign measurements).
8. No clinically significant abnormality based upon laboratory assessments at Visit 1 (Screening), in the opinion of the investigator.

9. Female subjects of childbearing potential are eligible for the study but must be willing to use adequate (at least 1 form of) contraceptive methods as described below during the study treatment period (starting from the day of first dose of study drug and ending 60 days after the last dose of study drug). Childbearing potential is defined as subjects who have experienced menarche and who are neither postmenopausal nor have been permanently sterilized.
    - Hormonal methods of contraception (including oral and transdermal contraceptives, injectable progesterone, progestin subdermal implants, progesterone-releasing intrauterine devices [IUDs]) initiated at least 14 days prior to the first dose of study drug
    - Abstinence
    - Placement of a copper-containing IUD
    - Condom with spermicidal foam/gel/film/cream/suppository
    - Postmenopausal at least 12 months prior to first dose of study drug or permanently sterilized (e.g., tubal occlusion, hysterectomy, bilateral salpingectomy)
    - Male partner who has had a vasectomy for at least 3 months prior to the first dose of study drug
10. Male subjects with partners of childbearing potential must agree to use adequate (at least 1 form of) contraception as described below during the study treatment period (starting from the day of first dose of study drug and ending 60 days after the last dose of study drug).
    - Abstinence
    - Vasectomy for at least 3 months prior to first dose of study drug or surgically sterile
    - Without a vasectomy, must use a condom with spermicidal foam/gel/film/cream suppository

4.3 Exclusion Criteria

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

General exclusion criteria

1. Subjects participating in any drug or device clinical investigation within 90 days prior to Visit 1 (Screening) or who anticipate participating in any other drug or device clinical investigation within the duration of this study.
2. Exposure to ataluren within 90 days prior to Visit 1 (Screening).
3. Surgery within 30 days prior to enrollment.

4. Female subjects who are pregnant or breastfeeding. Female subjects of childbearing potential must have a negative pregnancy test (beta-human chorionic gonadotropin [β-HCG]) at screening and must use adequate (at least 1 form of) contraceptive methods.
5. Active ocular infection or inflammation.
6. Prior or ongoing medical condition (e.g., concomitant illness, alcoholism, drug abuse, psychiatric condition), medical history, physical 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 study drug administration or follow-up would be completed, or could impair the assessment of study results.
7. Subjects with a positive result for hepatitis B, hepatitis C, or human immunodeficiency virus at Visit 1 (Screening).

Drug therapies

8. Ongoing warfarin, phenytoin, or tolbutamide therapy.
9. Ongoing intravenous (IV) aminoglycoside or IV vancomycin use.
10. Ongoing systemic cyclosporine therapy. *Note: Topical cyclosporine therapy is permitted.*
11. Known hypersensitivity to any of the ingredients or excipients of the study drug (polydextrose, polyethylene glycol 3350, poloxamer 407, mannitol 25C, crospovidone XL10, hydroxyethyl cellulose, vanilla, colloidal silica, or magnesium stearate).

Ocular exclusion criteria

12. 20/200 or worse visual acuity in the better eye with best correction.
13. Subjects who are monocular.
14. Subjects with a history of complications due to ocular surgery that could interfere with the study procedures or assessment of study endpoints.
15. Subjects with any other significant ocular or systemic disease that the Investigator determines could interfere with the study.

5 ENROLLMENT PROCEDURES

5.1 Number of Subjects

A minimum of 36 subjects with nonsense mutation aniridia who are ≥2 years of age will be enrolled into this study at investigative sites in the US and Canada.

5.2 Subject Recruitment

Subjects will be recruited from aniridia populations who receive care at or are referred to the investigational site for evaluation. The PI or sub-investigator will discuss the possibility of participation directly with study candidates and/or parent/legal guardian in the clinic and who may be appropriate subjects for the study.

Subjects will be recruited for the sub-study from the parent study.

5.3 Screening

The investigator must inform each study candidate and/or parent/legal guardian of the nature of the study, explain the potential risks, and obtain written informed consent/assent from the study candidate and/or the parent(s)/legal guardian (as required by local regulations) prior to performing any study related screening procedures. Once written informed consent/assent has been obtained, screening procedures for determination of eligibility can be initiated.

At the time the study candidate signs the informed consent a site representative should access the Interactive Voice Response/Interactive Web Response (IVR/IWR) system to indicate that a candidate is being screened. The caller will need to supply the IVR/IWR system with information, including the following:

- Site number as previously assigned by PTC Therapeutics
- Subject initials (as allowed by local regulations)
- Subject date of birth (as allowed by local regulations)
- Age
- Date of Screening (Visit 1)
- Documentation of the presence of a nonsense mutation in of the PAX6 gene
- Subject body weight (in kilograms)

The IVR/IWR will use this information to maintain a central screening log documenting that screening occurred. The screening subject number must be used for subject identification on all study related documents (electronic case report forms [eCRFs], clinic notes, laboratory samples, etc.). Upon successful completion of the call and confirmation of all subject eligibility requirements, the subject may proceed to Baseline procedures.

5.4 Randomization and Stratification

The IVR/IWR system will register each subject with a unique subject identification number (a 3-digit site number followed by a 3-digit subject number [3-digit stratum number + 3-digit randomization number]). The subject may be enrolled and begin ataluren or placebo administration after confirmation of eligibility has been received from the IVR/IWR system.

6 STUDY DRUG ADMINISTRATION

6.1 Investigational Product

6.1.1 Ataluren

Masked ataluren (treatment through Week 48) as well as open-label ataluren (treatment from Week 49 to Week 144 and during the sub-study) will be provided as granules for oral suspension with a white to off-white powder appearance. The drug substance and drug product are manufactured under cGMP conditions. The formulation includes matrix and suspending agents, surfactants, and various excipients that aid in the manufacturing process. The granules for oral suspension are packaged in aluminum-foil, child-resistant sachets (packets) and supplied in dose strengths containing 125, 250, or 1000 mg of the active drug substance. For administration, the powder in the sachet may be mixed with water, fruit juice, fruit punch, or milk (skim, 1% fat, 2% fat, whole milk, chocolate milk, soy milk, or lactose-free milk), or semi-solid food (yogurt, pudding, or applesauce).

6.1.2 Placebo

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

6.1.3 Packaging and Labeling

Drug kits will be provided, each of which contains 90 sachets of one of the dose strengths (125, 250, or 1000 mg or matching placebo). Sachets and cartons will be color coded to indicate dosage strength (125 mg – yellow, 250 mg – pink, 1000 mg – blue).

Each kit will have a unique kit ID number. During Stage 1, labeling for active drug and placebo will be identical. 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.

Open-label ataluren will be provided during Stage 2 and during the sub-study.

6.1.4 Study Drug Dispensing

During the parent study (masked Stage 1 and open-label Stage 2) and the sub-study, dosing of ataluren will be based on milligrams of drug per kilogram of subject body weight and will be adjusted to allow for dosing with up to 2 of the available sachet dose strengths (125 mg, 250 mg, and/or 1000 mg). The sachet dose strengths and number of sachets to be taken per dose will be calculated and provided by the IVR/IWR system.

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

The clinic staff (e.g., pharmacist or other qualified person) will write the subject number on each kit that is dispensed. A 180-day supply (2 kits each containing 90 sachets; 24 weeks + 6 days) of study drug will be provided for each two 24-week study periods of Stage 1, the four 24-week study periods of Stage 2, and the four 24-week study periods during the sub-study.

Because of potential changes in subject body weight over time, at Week 24 (Visit 3) and every 24 weeks thereafter, a dose adjustment will 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.

6.1.5 Return of Study Drug

Subjects and/or parents/caregivers should return all remaining ataluren (all unused sachets) to the study site at each onsite study visit. The Study Drug Administration Record will serve as the source document for drug supply to the subjects and will document the return of any unused drug for compliance assessments.

6.1.6 Storage and Stability

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

6.1.7 Study Drug Accountability

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

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

Unused clinical supplies must be destroyed or returned to PTC Therapeutics or its designee. Records documenting the date of study drug destruction or shipping, relevant sachet numbers, and amount shipped should be kept in the investigator site study file.

6.1.8 Overdose Precautions

For any subject experiencing an overdose (administration of an ataluren dose >4 times the intended total daily dose level for this protocol [>160 mg/kg/day]), observation for any symptomatic side effects should be instituted, and vital signs and biochemical and hematological parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. 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 or designee must be contacted if an overdose occurs, and the overdose must be reported as an adverse event (AE) according to Section 9.1.1 (or as a serious adverse event [SAE] if it meets the applicable criteria for an SAE in Section 9.1.2).

6.1.9 Inadvertent Exposure and Spill Precautions

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

6.2 Study Drug Treatment

6.2.1 Stratification and Randomization

After a subject has completed the necessary screening assessments and has been confirmed to be eligible by the investigator, the subject can be randomized into the study.

During Stage 1, a minimum of 36 eligible subjects will be stratified by age group (≤10 years old versus >10 years old) and then be randomized in a 2:1 ratio to 1 of 2 possible treatment assignments:

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

The first dose of study drug will be administered in the clinic and the date and time of administration will be recorded. At the end of each Stage, the last dose of study drug will be taken on the evening before the clinic visit (i.e., the night before the Visit 4/Week 48 [end of Stage 1], the night before Visit 8 (EOS/ET)/Week 144 [end of Stage 2], and the night before Visit 12 (end of Sub-study)/Week 240).

6.2.1.1 Masked Dosing

During Stage 1, the identity of the treatments will be concealed by the use of a placebo that is matched to the active drug in appearance, taste, odor, packaging, labeling, and schedule of administration. Unmasking will only occur in the case of subject emergencies before study completion and at the conclusion of the study. Except for emergency unmasking, individual subjects, subjects/caregivers, and site personnel will not be informed of the randomized treatment assignments until the implications of revealing such data for the overall ataluren clinical development program have been determined by PTC Therapeutics.

Emergency unmasking should only occur after the PI deems the subject's emergency warrants the unmasking of the treatment. Unmasking of the treatment can only be performed by the PI in the IVR/IWR system. Unmasking instructions are provided in the IVR/IWR system instruction manual.

6.2.1.2 Open-Label Dosing

After completion of the Stage 1 (Week 48), subjects will be eligible for an additional 96 weeks of open-label ataluren treatment. Subjects who received ataluren during Stage 1 will continue to receive ataluren; subjects who had been randomized to placebo will receive ataluren during Stage 2. Upon completion of the parent study, subjects will be eligible to continue receiving open-label ataluren for an additional 96 weeks in the sub-study.

6.2.2 Drug Administration Plan

Study drug (masked ataluren or placebo [during Stage 1] as well as open-label ataluren [during Stage 2 and the sub-study]) will be administered TID. The dose level to be administered is: 10 mg/kg in the morning, 10 mg/kg at midday, and 20 mg/kg in the evening.

6.2.3 Schedule of Administration

Throughout the study (i.e., during the parent study and the sub-study), study drug should be taken TID – the 1st dose (10 mg/kg) in the morning, the 2nd dose (10 mg/kg) at mid-day, and the 3rd dose (20 mg/kg) in the evening. Intervals for dosing should be ~6 hours (±1 hour) between morning and mid-day doses, ~6 hours (±1 hour) between mid-day and evening doses, and ~12 hours (±1 hour) between evening doses and the morning dose on the next day.

6.2.4 Instructions for Delays in Dosing

Dosing delays should be handled as follows:

- If dosing of ataluren is delayed by **≤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 ≤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.

6.2.5 Study Drug Preparation and Storage

Once at the investigational site and/or with the subject/caregiver, study drug sachets should be stored at room temperature, away from the reach of children until time of reconstitution and should only be opened at the time of dose preparation. The full contents of the sachets should be mixed with at least 30 mL (1 ounce) of liquid (water, milk, fruit juice, fruit punch), or 3 tablespoons of semi-solid food (yogurt, pudding, or applesauce). The prepared dose should be mixed well before administration. The amount of the liquid can be increased based on subject preference.

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

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

6.3 Safety Monitoring and Ataluren Treatment Modification

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

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

For adverse events or laboratory abnormalities, the investigator will use judgment in determining whether the event or abnormality is clinically significant, whether diagnostic evaluation is warranted, and whether potential interruption of study drug treatment is appropriate. In general, life-threatening (Grade 4) or severe (Grade 3) adverse events or laboratory abnormalities should be considered clinically significant, although recurrent or persistent moderate events (Grade 2) may also be considered clinically significant in certain circumstances. Reference should be made to the Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 for grading the severity of adverse events and laboratory abnormalities.

6.3.2 Evaluation of Adverse Events or Laboratory Abnormalities

The PTC Therapeutics medical monitor or designee 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.

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

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

filtration rate, concentrating ability, or other renal functions; computed tomography, MRI, or other imaging methods; and/or renal biopsy.

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

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

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

If further evaluation reveals that the adverse event that led to dose interruption was not related to the study drug, study drug may be restarted.

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

6.3.4 Instructions for Discontinuation of Study Drug Administration for Safety Concerns

If after appropriate consideration of study drug interruption/modification and consultation with the PTC Therapeutics medical monitor or designee, it is not appropriate for a subject to continue with study treatment, then study drug should be permanently discontinued. If permanent discontinuation of study drug 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 or designee 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 eCRF. The End of Treatment Visit eCRF should be completed and appropriate follow-up (at ~4 weeks as per protocol or until recovery from or stabilization of the adverse event, whichever comes last) should be instituted

7 CONCOMITANT AND SUPPORTIVE THERAPY

7.1 Concomitant Medications

Other than the study drug, any treatments (including prescription and non-prescription drugs, health foods, herbal remedies, self-prescribed drugs, street drug, tobacco products, or alcohol) taken by a subject from the screening period through the 4-Week End of Treatment Follow-Up are considered concomitant medications. Information regarding all concomitant medications will be collected and documented in the concomitant medication page of the eCRF.

7.1.1 Treatment for Aniridia-Related Conditions

Surgery for aniridia-related conditions (e.g., glaucoma, cataract) during this study is permitted.

Study subjects may receive supportive care medications (e.g., drops, lubricants) consistent with local best practices and guidelines. The use of topical cyclosporine is permitted.

7.1.2 Nephrotoxic Medications

Renal abnormalities were observed in a Phase 3 trial evaluating ataluren in subjects ≥6 years of age with nmCF who were receiving concomitant IV aminoglycosides (as described in the Ataluren Investigator Brochure). Caution should therefore be exercised during concomitant use of study drug and potentially nephrotoxic agents.

In subjects who require treatment for serious infections, investigators should substitute other antibiotics for systemic aminoglycosides when clinically appropriate. If IV aminoglycosides or other nephrotoxic antibiotics (e.g., vancomycin) are administered, study drug must be interrupted during the course of antibiotic therapy. Subjects requiring IV aminoglycoside or vancomycin therapy should be closely monitored in an appropriate setting, such as a hospital. In subjects receiving such agents, antibiotic drug levels and serum creatinine and blood urea nitrogen (BUN) should be monitored closely as follows:

- Creatinine and BUN should be measured:
  - Prior to initiating IV aminoglycoside or vancomycin therapy
  - Within 24 to 48 hours of the first antibiotic administration (and further antibiotic dosing should be based on these results)
  - At least twice a week during the course of antibiotic treatment
- Antibiotic trough levels should be measured:
  - Within 24 to 48 hours of the first antibiotic administration (and further antibiotic dosing should be based on these results)
  - At intervals during the course of antibiotic treatment.

7.1.3 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.

7.1.4 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" (e.g., 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 eCRF.

7.1.5 Drugs Metabolized by Cytochrome P450 Enzymes

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

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

Drugs that are metabolized by CYP2C8 or CYP2C9 that have low therapeutics indices (in particular, paclitaxel for CYP2C8 and coumarin anticoagulants [e.g., 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 (e.g., 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.

7.1.6 Other Potential Drug Interactions

Based on in vitro studies, ataluren is a substrate of UGT1A9 and of breast cancer resistant protein (BCRP). Coadministration with rifampin, a strong inducer of metabolic enzymes, including UGT1A9 and CYP3A4, did not affect exposure of ataluren in healthy subjects. No dose adjustment is required when ataluren is co-administered with UGT1A9-inducing medications. Caution should be exercised when ataluren is co-administered with drugs that are inhibitors of BCRP (e.g., cyclosporine, eltrombopag, gefitinib), as these drugs may affect ataluren plasma concentrations, e.g. *Note: Topical cyclosporine therapy is permitted.*

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

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

7.2 Dietary Restrictions

There are no specific dietary restrictions in the study.

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 1 (Stage 1, double-masked period), Table 2 (Stage 2, open-label period), and Table 3 (open-label sub-study).

Table 1. Schedule of Events (Stage 1)

Protocol Activities	**Screening**		**Double-Masked Treatment**					
Day±Window **Week**	**-28**	**-4**	**1[a]**	**1**	**169±28**	**24**	**337±28**	**48/End of Stage 1[b]**
Visit	**1**		**2**		**3**			**4**
Informed consent	X							
Medical and ophthalmic history[c]	X							
Serum viral screen	X							
Physical exam	X		X					X
Height and weight	X		X		X			X
Vital signs	X		X		X			X
Ophthalmoscopy	X		X		X			X
Hematology, biochemistry, urinalysis	X				X			X
Serum β-HCG[d]	X		X		X			X
Study drug and diary dispensing			X		X			X
Study drug administration			X		X			X
Study drug compliance and return					X			X
Collect diary					X			X
Adverse events			X		X			X
Concomitant meds	X		X		X			X
MNREAD			X					X
[redacted]			X		X			X
Slit-lamp examination[e]			X		X			X
Slit-lamp photography			X		X			X
OCT			X		X			X
Fundus photography			X		X			X
Humphrey visual fields			X					X
BCVA and refraction[f]	X		X		X			X
[redacted]			X		X			X
[redacted]			X		X			X
[redacted]			X		X			X
[redacted] blood sample for plasma PK[g]			If feasible (i.e., during surgery for glaucoma, cataracts, etc.)					

Abbreviations: β-HCG, beta-human chorionic gonadotropin, BCVA, best corrected visual acuity, ETDRS, early treatment diabetic retinopathy study; LEA, LEA Symbols Visual Acuity Test System, MNREAD, Minnesota Low Vision Reading Acuity Charts, OCT, optical coherence tomography, PK, pharmacokinetic(s)

[a] All study and laboratory assessments on the first day of treatment must be done prior to in-clinic administration of the first dose.

[b] Open-label study drug administration will start at the end of Stage 1 (Visit 4/Week 48).

[c] Should include capture of available historical values for ocular assessments included in this study, such as visual acuity, [redacted], etc.

[d] Sample taken only for female subjects of childbearing potential.

[e] Slit-lamp examination should precede [redacted] measurement.

[f] BCVA and refraction will be assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) or an age-appropriate alternative (e.g., LEA).

[g] [redacted]

Table 2. Schedule of Events (Stage 2)

Protocol Activities	Open-Label Treatment						End of Treatment[a]		Follow-Up[b]	
Day± Window	**Week**	**505±28**	**72**	**673±28**	**96**	**841±28**	**120**	**1009±28**	**144**	**28 Days Post End of Treatment ±7**	**148**
Visit		**5**		**6**		**7**		**8**		**9**	
Physical exam				X				X		X	
Height and weight		X		X		X		X		X	
Vital signs		X		X		X		X		X	
Ophthalmoscopy		X		X		X		X		X	
Hematology, biochemistry, urinalysis		X		X		X		X		X	
β-HCG[c]		X		X		X		X			
Study drug and diary dispensing		X		X		X					
Study drug administration		X		X		X					
Study drug compliance and return		X		X		X		X			
Collect diary		X		X		X		X			
Adverse events		X		X		X		X		X	
Concomitant meds		X		X		X		X		X	
[redacted]		X		X		X		X			
MNREAD				X				X			
Slit-lamp examination[d]		X		X		X		X			
Slit-lamp photography		X		X		X		X			
OCT		X		X		X		X			
Fundus photography		X		X		X		X			
Humphrey visual field				X				X			
BCVA and refraction[e]		X		X		X		X			
[redacted]		X		X		X		X			
[redacted]		X		X		X		X			
[redacted]		X		X		X		X			
[redacted] blood sample for plasma PK[f]		If feasible (e.g., during surgery for glaucoma, cataracts, etc.)									

Abbreviations: β-HCG, beta-human chorionic gonadotropin; BCVA, best corrected visual acuity; LEA, LEA Symbols Visual Acuity Test System; MNREAD, Minnesota Low Vision Reading Acuity Charts; OCT, optical coherence tomography; PK, pharmacokinetic(s)

[a] Refer to Table 3 for the schedule of events for subjects participating in the sub-study for Visits 8-13.

[b] This visit is only required for subjects not participating in the sub-study.

[c] Sample taken only for female subjects of childbearing potential.

[d] Slit-lamp examination should precede [redacted] measurement.

[e] BCVA and refraction will be assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) or an age-appropriate alternative (e.g., LEA).

[f] [redacted]

Table 3. Schedule of Events (Open-label Sub-study)

Protocol Activities	Open-Label Treatment				End of Study/ Early Termination	Follow-Up
Week	144 ±28 days	168±28 days	192±28 days	216±28 days	240 ±28 days	28 Days (4 weeks) Post EOS/ET (Week 244±7days)
Visit	8	9	10	11	12	13
Informed consent	X					
Physical exam	X					X
Height and weight	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X
Ophthalmoscopy	X	X	X	X	X	X
Hematology, biochemistry, urinalysis	X	X	X	X	X	X
β-HCG[a]	X	X	X	X	X	
Study drug and diary dispensing	X	X	X	X		
Study drug administration	X	X	X	X		
Study drug compliance and return	X	X	X	X	X	
Collect diary	X	X	X	X	X	
Adverse events	X	X	X	X	X	X
Concomitant meds	X	X	X	X	X	X
[redacted]	X					
MNREAD	X	X	X	X	X	
Slit-lamp examination[b]	X					
Slit-lamp photography	X					
OCT	X					
Fundus photography	X					
Humphrey visual field	X				X	
BCVA and refraction[c]	X	X	X	X	X	
[redacted]	X					
[redacted]	X	X	X	X	X	
[redacted]	X					
Schedule next visit	X	X	X	X	X	

Abbreviations: β-HCG, beta-human chorionic gonadotropin; BCVA, best corrected visual acuity; EOS/ET, end of study/early termination; ETDRS, early treatment diabetic retinopathy study; LEA, LEA Symbols Visual Acuity Test System; MNREAD, Minnesota Low Vision Reading Acuity Charts; OCT, optical coherence tomography

[a] Sample taken only for female subjects of childbearing potential.

[b] Slit-lamp examination should precede [redacted] measurement.

[c] BCVA and refraction will be assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS) or an age-appropriate alternative (e.g., LEA).

8.1.1 Screening, Treatment and Follow-up Periods

No study-related procedures should be performed prior to the signing of the informed consent/assent document(s). Screening evaluations for the study will be performed at the clinical research facility as needed.

Study participants will report to the clinic on the morning of each on-site visit and will remain in the clinic until released by the investigator after all the study-related procedures have been completed and the subject has been instructed regarding drug storage, reconstitution, and administration.

Subjects must return to the clinic for follow-up assessment at 4 weeks after the last dose of study drug.

8.1.1.1 Stage 1: Visit 1 (Screening, 4 Weeks Prior to Baseline Visit 2)

The Screening Visit (Visit 1) will occur 4 weeks prior to Baseline Visit 2. Screening procedures will proceed as follows:

- Obtain written informed consent/assent
- Determine if the subject meets the preliminary eligibility criteria:
    - Documentation of the presence of a nonsense mutation in 1 allele of the PAX6 gene as determined by genotyping performed at a laboratory certified by the CAP, or under the CLIA, or by an equivalent organization. *Note: Sponsor review of genotyping documentation is required prior to randomization.*
    - Collect demographic information
    - Collect current and relevant medical history and ophthalmic history
    - Identify concomitant medications used
    - BCVA and refraction

If the subject meets the preliminary eligibility criteria, the following assessments will be performed:

- Ophthalmoscopy
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the subject has been in a sitting position for 3 - 5 minutes
- Physical examination
- Height (in centimeters) and weight (in kilograms) will be measured at each clinic visit
- Blood draw for clinical laboratory evaluations:
    - Serum β-HCG, as applicable (sample taken only for female subjects of childbearing potential)
    - Hematology and biochemistry

- Serum viral screen
- Urinalysis
- Schedule Visit 2

8.1.1.2 Visit 2 (Baseline, Week 1 ±1 Day)

After the 4-week Screening period, subjects who continue to meet all eligibility criteria will complete the Baseline Visit (Visit 2/Week 1) as follows:

- Record any adverse events occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Physical examination
- Height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the subject has been in a sitting position for 3 - 5 minutes
- Complete the following ophthalmological assessments:
  - [redacted]
  - Ophthalmoscopy examination
  - BCVA and refraction
  - Slit-lamp examination - Slit-lamp examination should precede [redacted] measurement
  - Slit-lamp photography. The Reading Center manual should be referenced for detailed instructions regarding macro photography
  - OCT/Fundus photography - Anterior and posterior segment OCT and fundus photography will be performed. The Reading Center manual should be referenced for detailed instructions
  - Humphrey visual fields
  - [redacted]
  - [redacted]
  - MNREAD
- Blood draw for clinical laboratory evaluations
  - [redacted]
  - Serum β-HCG, as applicable (sample taken only for female subjects of childbearing potential)

- [redacted]
  - [redacted]
- Dispense masked study drug and Study Drug Dosing Diary, and review administration instructions
  - TID dosing 10 mg/kg, 10 mg/kg, 20 mg/kg (morning, midday, evening)
  - The first dose of study drug should be administered in the clinic *after* completion of all other assessments and procedures required at this visit
- Schedule Visit 3

8.1.1.3 Visit 3 (Week 24 ±28 Days)

The subject will return to the site for visit 3. Visit 3 will proceed as follows:

- Record any adverse events occurring since administration of first dose at last visit, and any that occur during this visit
- Record any changes in concomitant medications
- Collect any unused study drug
- Study Drug Dosing Diary review and collection: The diary will be collected and reviewed
- Height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the subject has been in a sitting position for 3 - 5 minutes
- Complete the following ophthalmological assessments:
  - [redacted]
  - Ophthalmoscopy examination
  - BCVA and refraction
  - Slit-lamp examination - Slit-lamp examination should precede [redacted] measurement.
  - Slit-lamp photography. The Reading Center manual should be referenced for detailed instructions regarding macro photography.
  - OCT/Fundus photography - Anterior and posterior segment OCT and fundus photography will be performed. The Reading Center manual should be referenced for detailed instructions.
  - [redacted]

- [redacted]
- Blood draw for clinical laboratory evaluations
  - [redacted]
  - Serum β-HCG, as applicable (sample taken only for female subject of childbearing potential)
  - Hematology and biochemistry
- Urinalysis
- [redacted]
  - [redacted]
- Dispense masked study drug and Study Drug Dosing Diary
  - TID dosing 10 mg/kg, 10 mg/kg, 20 mg/kg (morning, midday, evening)
- Schedule Visit 4

8.1.1.4 Visit 4 (Week 48 ±28 Days [End of Stage 1/Start of Stage 2])

The subject will return to the site for visit 4. Visit 4 will proceed as follows:

- Record any adverse events occurring since last visit, and any that occur during this visit
- Record any changes in concomitant medications
- Physical examination
- Collect any unused study drug
- Study Drug Dosing Diary review and collection: The diary will be collected and reviewed
- Height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the subject has been in a sitting position for 3 - 5 minutes
- Complete the following ophthalmological assessments:
  - [redacted]
  - Ophthalmoscopy examination
  - BCVA and refraction
  - Slit-lamp examination - Slit-lamp examination should precede [redacted] measurement

- Slit-lamp photography. The Reading Center manual should be referenced for detailed instructions regarding macro photography
- OCT/Fundus photography - Anterior and posterior segment OCT and fundus photography will be performed. The Reading Center manual should be referenced for detailed instructions
- Humphrey visual fields
- [redacted]
- [redacted]
- MNREAD

- Blood draw for clinical laboratory evaluations
  - [redacted]
  - Serum β-HCG, as applicable (sample taken only for female subject of childbearing potential)
  - Hematology and biochemistry
- Urinalysis
- [redacted]
  - [redacted]
- Dispense open-label ataluren and Study Drug Dosing Diary
  - TID dosing 10 mg/kg, 10 mg/kg, 20 mg/kg (morning, midday, evening)
- Schedule the Visit 5

8.1.1.5 Visit 5 (Week 72 ±28 Days)

Procedures at Visit 5, will proceed as follows:

- Record any adverse events occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Collect any unused study drug
- Study Drug Dosing Diary review and collection: The diary will be collected and reviewed
- Height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the subject has been in a sitting position for 3 - 5 minutes
- Complete the following ophthalmological assessments:

- [redacted]
- Ophthalmoscopy examination
- BCVA and refraction
- Slit-lamp examination - Slit-lamp examination should precede [redacted] measurement.
- Slit-lamp photography. The Reading Center manual should be referenced for detailed instructions regarding macro photography
- OCT/Fundus photography - Anterior and posterior segment OCT and fundus photography will be performed. The Reading Center manual should be referenced for detailed instructions
- [redacted]
- [redacted]
- Blood draw for clinical laboratory evaluations
- [redacted]
- Serum β-HCG, as applicable (sample taken only for female subject of childbearing potential)
- Hematology and biochemistry
- Urinalysis
- [redacted]
- [redacted]
- Dispense open-label ataluren and Study Drug Dosing Diary
- TID dosing 10 mg/kg, 10 mg/kg, 20 mg/kg (morning, midday, evening)
- Schedule Visit 6

8.1.1.6 Visit 6 (Week 96 ±28 Days)

The subject will return to the site for visit 6. Visit 6 will proceed as follows:

- Record any adverse events occurring since last visit, and any that occur during this visit
- Record any changes in concomitant medications
- Physical examination
- Collect any unused study drug
- Study Drug Dosing Diary review and collection: The diary will be collected and reviewed

- Height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the subject has been in a sitting position for 3 - 5 minutes
- Complete the following ophthalmological assessments:
  - [redacted]
  - Ophthalmoscopy examination
  - BCVA and refraction
  - Slit-lamp examination - Slit-lamp examination should precede [redacted] measurement.
  - Slit-lamp photography. The Reading Center manual should be referenced for detailed instructions regarding macro photography
  - OCT/Fundus photography - Anterior and posterior segment OCT and fundus photography will be performed. The Reading Center manual should be referenced for detailed instructions
  - Humphrey visual fields
  - [redacted]
  - [redacted]
  - MNREAD
- Blood draw for clinical laboratory evaluations
  - [redacted]
  - Serum β-HCG, as applicable (sample taken only for female subject of childbearing potential)
  - Hematology and biochemistry
- Urinalysis
- [redacted]
  - [redacted]
- Dispense open-label ataluren and Study Drug Dosing Diary, and review administration instructions
  - TID dosing 10 mg/kg, 10 mg/kg, 20 mg/kg (morning, midday, evening)
- Schedule Visit 7

8.1.1.7 Visit 7 (Week 120 ±28 Days)

The subject will return to the site for visit 7. Visit 7 will proceed as follows:

- Record any adverse events occurring since last visit, and any that occur during this visit
- Record any changes in concomitant medications
- Collect any unused study drug
- Study Drug Dosing Diary review and collection: The diary will be collected and reviewed
- Height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the subject has been in a sitting position for 3 - 5 minutes
    - Complete the following ophthalmological assessments:
    - [redacted]
    - Ophthalmoscopy examination
    - BCVA and refraction
    - Slit-lamp examination - slit-lamp examination should precede [redacted] measurement
    - Slit-lamp photography. The Reading Center manual should be referenced for detailed instructions regarding macro photography
    - OCT/Fundus photography - anterior and posterior segment OCT and fundus photography will be performed. The Reading Center manual should be referenced for detailed instructions
    - [redacted]
    - [redacted]
- Blood draw for clinical laboratory evaluations
    - [redacted]
    - Serum β-HCG, as applicable (sample taken only for female subject of childbearing potential)
    - Hematology and biochemistry
- Urinalysis
- [redacted]
    - [redacted]

- Dispense open-label ataluren and Study Drug Dosing Diary
  - TID dosing 10 mg/kg, 10 mg/kg, 20 mg/kg (morning, midday, evening)
- Schedule Visit 8 (EOS/ET)

8.2 Visit 8 (Week 144±28 Days – End of Treatment/Start of Sub-study

The subject will return to the site for Visit 8 (Week 144). Additionally, any subject who discontinues early from the parent study should complete the Visit 8 assessments and return in 4 weeks for follow-up assessments.

This visit will be considered the end of the parent study and the beginning of the sub-study. Subjects should have taken their final dose of study drug for the parent study the night before the clinic visit.

Visit 8 will proceed as follows:

- Record any adverse events occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Collect any unused study drug
- Study Drug Dosing Diary review and collection: The diary will be collected and reviewed
- Physical examination
- Height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the subject has been in a sitting position for 3 - 5 minutes
- Complete the following ophthalmological assessments:
  - [redacted]
  - Ophthalmoscopy examination
  - BCVA and refraction
  - Slit-lamp examination - Slit-lamp examination should precede [redacted] measurement.
  - Slit-lamp photography. The Reading Center manual should be referenced for detailed instructions regarding macro photography.
  - OCT/Fundus photography - Anterior and posterior segment OCT and fundus photography will be performed. The Reading Center manual should be referenced for detailed instructions.
  - Humphrey visual fields
  - [redacted]

- [redacted]
- MNREAD

- Blood draw for clinical laboratory evaluations:
  - Hematology and biochemistry
  - Serum β-HCG, as applicable (sample taken only for female subjects of childbearing potential)
  - [redacted]
- Urinalysis
- No study drug will be dispensed at this visit for subjects that do not consent to the sub-study. Subjects not continuing into the sub-study should return to the clinic in 4-weeks (±7 days) for their Follow-up visit.

For all subjects that choose to participate in the open-label sub-study, in addition to the Visit 8 assessments listed above, the following will need to be completed:

- Obtain written informed consent/assent
- Dispense open-label ataluren and Study Drug Dosing Diary, and review administration instructions
  - TID dosing 10 mg/kg, 10 mg/kg, 20 mg/kg (morning, midday, evening)
- Schedule Visit 9 in 24 weeks ±28 days

8.2.1.1 Sub-study Visits 9, 10, and 11 (Weeks 168, 192, and 216 ±28 Days)

During the sub-study, subjects will return to the site every 24 weeks (±28 days). The following will be performed at Visits 9, 10, and 11:

- Record any adverse events occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Collect any unused study drug
- Study Drug Dosing Diary review and collection: The diary will be collected and reviewed
- Height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the subject has been in a sitting position for 3 – 5 minutes
- Complete the following ophthalmological assessments:
  - Ophthalmoscopy examination
  - BCVA and refraction

- [redacted]
- MNREAD

- Blood draw for clinical laboratory evaluations:
  - Hematology and biochemistry
  - Serum β-HCG, as applicable (sample taken only for female subjects of childbearing potential)
- Urinalysis
- Dispense open-label ataluren and Study Drug Dosing Diary, and review administration instructions
  - TID dosing 10 mg/kg, 10 mg/kg, 20 mg/kg (morning, midday, evening)
- Schedule next visit in 24 weeks ±28 days

8.2.1.2 Visit 12 (Week 240 ±28 Days – End of Study/Early Termination Visit)

This visit will be considered the end of sub-study and should be completed for all subjects. Subjects participating in the sub-study who terminate the study before Visit 12 should complete the Visit 12 assessments at the time of early termination. Subjects should take their final dose of study drug the night before the clinic visit.

Visit 12, End of Study/Early Termination Visit will proceed as follows:

- Record any adverse events occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Collect any unused study drug
- Study Drug Dosing Diary review and collection: The diary will be collected and reviewed
- Height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the subject has been in a sitting position for 3 - 5 minutes
- Complete the following ophthalmological assessments:
  - Ophthalmoscopy examination
  - BCVA and refraction
  - [redacted]
  - MNREAD
  - Humphrey visual fields
- Blood draw for clinical laboratory evaluations:

- Hematology and biochemistry
- Serum β-HCG, as applicable (sample taken only for female subjects of childbearing potential)

- Urinalysis
- No study drug will be dispensed at this visit
- Schedule Follow-up Visit in 4 weeks ±7 days

8.2.1.3 Follow-up Visit (4 Weeks Post End of Study/Early Termination Visit ±7 Days)

Follow-up should occur 4 weeks (±7 days) after the End of Study/Early Termination visit. Additionally, any subject who discontinues early from the parent study or the sub-study should complete this visit. The Follow-up visit will proceed as follows:

- Record any adverse events occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Physical examination
- Height and weight
- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): performed after the subject has been in a sitting position for 3 – 5 minutes
- Complete the following ophthalmological assessments:
  - Ophthalmoscopy examination
- Blood draw for clinical laboratory evaluations
  - Hematology and biochemistry
- Urinalysis

8.3 Assessments

All assessment should be completed as per the Schedules of Events:

Table 1 (Stage 1, double-masked period), Table 2 (Stage 2, open-label period), and Table 3 (open-label sub-study).

8.3.1 Informed Consent

The investigator/study staff member must inform each study candidate of the nature of the study, explain the potential risks, and obtain written informed consent at Visit 1 (Screening) and Visit 8 (if participating in the sub-study) from the study candidate and/or parent(s)/legal guardian (as required by local regulations) prior to performing any study-related activities.

8.3.2 Medical and Ophthalmic History

The investigator or a qualified designee will review the subject's clinical and ophthalmic history at Visit 1 (Screening), including details relating to aniridia and any other medical conditions. Information regarding clinical history and current medications must be captured on the medical history and prior/concomitant medication eCRFs, respectively. Ophthalmic history may include capture of available historical values for ocular assessments included in this study, such as visual acuity or [redacted]. Any historical ocular assessments to be collected will only come from three most recent examinations that have occurred within the last two (2) years. Ocular assessments would include the date of the exam, [redacted], cup/disc ratios, visual acuities, as well as if previous fundus photos were captured and any associated PI comments/notes on the photos.

8.3.3 Serum Viral Screen

Tests to be conducted at Visit 1 (Screening) include hepatitis B surface antigen, hepatitis C antibody, and human immunodeficiency virus. The study manual should be referenced for collection, processing, and shipping information.

8.3.4 Physical Examination

The physical examination (including general appearance, head, eyes, ears, nose, mouth, throat, heart, thyroid, chest and lungs, abdomen, extremities, neuromuscular system, skin, and lymph nodes) will be conducted.

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

8.3.5 Vital Signs

Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature) will be monitored at each clinic visit and should be performed after the subject has been in a sitting position for 3 - 5 minutes.

8.3.6 Height and Weight

Height (in cm) and weight (in kg) will be measured at each clinic visit.

8.3.7 Hematology Laboratory Assessment

Hematology laboratory assessments will include white blood cell count with differential, hemoglobin, hematocrit, other red cell parameters, and platelet count. Your institute's local laboratory's manual should be referenced for specimen collection, processing, storing, and/or shipping information.

8.3.8 Biochemistry Laboratory Assessment

Biochemistry laboratory assessments will include sodium, potassium, chloride, bicarbonate, BUN, creatinine, magnesium, calcium, phosphorus, uric acid, glucose, total protein, albumin, bilirubin (total, direct, and indirect), AST, ALT, GGT, creatine kinase, lactate dehydrogenase, alkaline phosphatase, total cholesterol, high-density lipoprotein, low-density lipoprotein, triglycerides, and cystatin C. Your institute's local laboratory's manual should be referenced for specimen collection, processing, storing, and/or shipping information.

8.3.9 Pregnancy

Serum β-HCG will be measured only in females of childbearing potential. Childbearing potential is defined as subjects who have experienced menarche and who are neither postmenopausal nor have been permanently sterilized.

8.3.10 Urinalysis

Urinalysis will include analysis for pH, specific gravity, glucose, ketones, blood, protein, bilirubin, nitrite, and leukocyte esterase. A test for urobilinogen should be performed if the bilirubin test is abnormal. Your institute's local laboratory's manual should be referenced for specimen collection, processing, storing, and/or shipping information.

8.3.11 Study Drug Administration

Refer to Section 6.2.

8.3.12 Adverse Events

Systemic and ocular adverse events must be assessed and documented at each scheduled clinic visit, beginning at Visit 2. If the subject does not visit the clinic on the scheduled day, a telephone call to the subject by qualified site personnel is required to assess adverse events. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result, or to monitor the course of an adverse event should be obtained when clinically indicated. Subjects must be followed for adverse events for at least 28 days after the last dose of ataluren administration, or until any drug-related adverse events and/or ongoing SAEs have resolved or become stable, whichever is later.

8.3.13 Concomitant Medications

Concomitant medication information will be collected and documented at each scheduled clinic visit. Any concomitant drugs (prescribed or over-the-counter, which include vitamin and herbal supplements) used during the course of the study and the reason for their use will be recorded. Information regarding the timing, type, and amount will be recorded in an eCRF. Excluded drug therapies to consider during screening are listed in the exclusion criteria in Section 4.3.

8.3.14 [redacted]

[redacted]

8.3.15 MNREAD

Standard MNREAD Acuity Charts will be used to assess Reading Acuity, Critical Print Size, Maximum Reading Speed, and Reading Accessibility Index.

Reading speed is a strong predictor of visual ability and vision-related quality of life for patients with vision loss (Hazel 2000). For this reason, reading performance has been used as an outcome measure in clinical trials for judging the effectiveness of treatments (Mahmood 2015).

The Reading Accessibility Index summarizes an individual's access to text over the range of print sizes found in everyday life. The Reading Accessibility Index relies on a simple calculation: averaging the reading speed measured over the 10 largest print sizes on the MNREAD and normalizing it by the mean value for a group of normally sighted young adults (Calabrese 2016). The Reading Accessibility Index is a single-valued measure that depends on both the range of accessible print sizes for a subject, and the subject's speed of reading within this range. Because the Reading Accessibility Index is normalized by the value for a group of normally sighted young adults (aged 18–39 years), a Reading Accessibility Index of 1.0 represents normal performance for this age group. Values less than 1.0 mean reduced accessibility to printed text within the range of print size encountered in daily life (Calabrese 2016).

The MNREAD Acuity Charts are continuous-text reading-acuity charts suitable for measuring reading acuity and reading speed of normal and low-vision patients. The study manual should be referenced for detailed instructions.

The reading level of the MNREAD Acuity Charts is approximately 2nd to 3rd grade level. It is estimated that subjects around the age of 8 years or older will be able to complete this assessment. Any subject less than the age of 8 years old will not be required to have this study assessment administered.

Three charts will be utilized for the MNREAD testing; one chart will be used for OD, one chart for OS, and the third chart for OU. It is imperative that the charts used for the monocular and binocular testing be changed out to decrease the likelihood of memorization of the text sentences by the subject.

8.3.16 Slit-Lamp Examination and Macro Photography

Slit lamp examination and macro photography will be performed on the lids, conjunctiva, limbus, cornea, anterior chamber, vitreous, and lens without pupil dilation. The Reading Center manual should be referenced for detailed instructions regarding macro photography.

Slit lamp examination (without pupil dilation) will be done for both eyes of the subjects for this study. Both the Haag-Streit and Zeiss slit lamp biomicroscopes are acceptable for study use and it is at the Investigator's discretion which manufacturer's brand will be used during the study; however, the same slit lamp biomicroscope must be used for assessing the anterior segment for all subjects enrolled and for all study visits throughout the trial.

It is recommended that the slit lamp examinations for an individual subject be performed by the same personnel using the same slit lamp for each study visit.

8.3.17 Fundus Examination and Photography

Fundus examination and photography should be performed after testing visual acuity, slit lamp examination and macro photography.

A fundus exam will be performed of the retina, macula, and choroid. The largest cup-to-disc ratio measured should be entered on to the electronic case report form (eCRF). The Reading Center manual should be referenced for detailed instructions regarding fundus photography.

8.3.18 Optical Coherence Tomography

Optical Coherence Tomography will be performed. The Reading Center manual should be referenced for detailed instructions.

8.3.19 Humphrey Visual Field

Vision field testing will be performed by a Duke certified study technician. Humphrey visual field will be assessed. The Reading Center manual should be referenced for detailed instructions.

8.3.20 Ophthalmoscopy

Ophthalmoscopic examination of the fundus will be performed using an indirect binocular ophthalmoscope. The largest cup to disc ratio measured should be entered on to the eCRF for each eye. Any abnormalities of the macula, vessels, periphery and disc are to be recorded. The study manual should be referenced for detailed instructions.

8.3.21 Best Corrected Visual Acuity (BCVA) and Refraction

BCVA and refraction will be assessed using the Early Treatment Diabetic Retinopathy Study (ETDRS).

Refraction and testing of BCVA must be performed before the subject's eyes are dilated and prior to fundus photography and OCT imaging. Manifest refraction must precede the BCVA testing. For this study, it is estimated that children at the age of 6 or older will be able to be tested with a subjective refraction and ETDRS charts.

Age-appropriate alternative visual acuity chart (e.g., LEA symbols) will be used for any subject under the age of 6; however, the same chart should be used throughout the duration of the study.

The study manual should be referenced for detailed instructions.

[redacted]

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 study drug in this study.

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

- All adverse events that are suspected or are not suspected to be due to study drug.
- Overdose (administration of a study drug dose >4 times the intended total daily dose level for this protocol [>160 mg/kg/day]) of study drug.
- All reactions from medication misuse, abuse, withdrawal, sensitivity, or toxicity.
- All reactions that result from medication errors or uses of the study drug outside what is described in the protocol.
- Apparently unrelated illnesses, including the worsening of a preexisting illness.
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as two 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 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 (e.g., 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 (e.g., allergic rhinitis) must be noted on the appropriate eCRF for Visit 1 but should not be reported as an adverse event unless the condition worsens, or episodes increase in frequency during the adverse event reporting period. Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as adverse events. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an adverse event. For example, an acute appendicitis that begins during the adverse event reporting period should be reported as the adverse

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

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

- Death (i.e., all deaths on treatment or within 4 weeks after last study drug administration), including deaths due to disease progression. Any death occurring later than 4 weeks following the last dose need not be reported as an SAE unless it is a result of an event that started within the period covered by the on-study definition. The reported adverse event should be the event that caused the death. In addition, any adverse event resulting in death that occurs subsequent to the adverse event-reporting period and that the investigator assesses as possibly related to the study drug should also be reported as serious.
- Life-threatening adverse event. This is an event that, in the view of either the investigator or the sponsor, places the 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 (e.g., excluding hospitalizations for administration of the study drug, procedures required by the study protocol, or aniridia-related diagnostic procedures; other planned hospitalizations; or hospitalizations related only to progression of disease). Treatments in the emergency room for procedures such as hydration that do not require admitting the subject to the hospital and observational durations in the emergency room for less than 24 hours are not considered serious.
- Persistent or significant disability or incapacity or substantial disruption of the ability to conduct normal life functions, not related to aniridia.
- 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]).

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

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

9.1.3 Unexpected Adverse Events

Unexpected adverse events are defined as those events that were not previously reported with study drug as referenced in the most current investigator's 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's 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's brochure as occurring with the class of drugs or as anticipated from the pharmacological properties of the study drug but is not specifically mentioned as occurring with the medicinal product.

For the purposes of considering expectedness, the ataluren investigator's 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

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the study subject or parent/guardian in case of a child. In addition, each study subject will be questioned about adverse events at each scheduled clinic visit after study drug administration or during any telephone contact with the subject or parent/guardian in case of a child. The type of question asked should be open-ended, e.g., *"How has 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 known untoward event that occurs subsequent to the adverse event reporting period that the investigator assesses as possibly related to the investigational drug/product should also be recorded as an adverse event.

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

- Indication of whether the event is serious or non-serious (see Section 9.1.2)
- Relationship to study drug (see Section 9.4)
- Severity of the event (see Section 9.5)
- Onset date
- Resolution date, or date of death
- Action taken
- Outcome of the event

Classification of the event as serious or 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, i.e., whether there is a reasonable possibility that the study drug caused the adverse event.

Table 4. Relationship of Study Drug to Adverse Event

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

The severity of adverse events will be graded using the CTCAE Version 4.0 (refer to the Study Manual*)*. For each episode, the highest severity grade attained should be reported.

If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate), Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the 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 9.2.

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 study drug. Any such pregnancy occurring on-study or within 60 days of the last administration of study drug must be reported on a Pregnancy Notification Form (see Study Manual for details). This must be done whether or not an adverse event has occurred and within 24 hours of awareness of the pregnancy. The information submitted should include the anticipated date of birth or pregnancy termination.

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

If the outcome of the pregnancy meets the criteria for immediate classification as an SAE (i.e., spontaneous abortion, stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator should follow the procedures for reporting SAEs, i.e., report the event to the PTC Therapeutics Safety Department or designee and follow up by submission of appropriate adverse event eCRFs (see Section 9.8).

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 PTC Therapeutics Safety Department or designee 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 study drug is administered. The adverse event reporting period for this study ends with the 4-week post-treatment follow-up visit (±7 days) after the end of study or end of treatment, 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 9.1.2) determines the reporting procedures to be followed. Investigator site reporting requirements for adverse events are summarized in Table 6.

Table 6. Investigator Site Requirements for Reporting Adverse Events

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

Abbreviations: eCRF, electronic case report form; IRB/IEC, Institutional Review Board/Independent Ethics Committee; SAE, Serious Adverse Event

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

For SAEs, in addition to completing the adverse event eCRF, the SAE report form must also be completed. The SAE report form should be signed by the investigator; however, if the investigator is unable to sign at the time of the event or within 24 hours, the form should be signed by the clinical staff member reporting the SAE (e.g., the study coordinator). The SAE report form must be faxed or emailed to the PTC Therapeutics Safety Department or designee and to the site IRB/IEC (if required by local regulations) within 24 hours. Follow-up information to the SAE should be clearly documented as "follow up" in the SAE report form and must also be faxed or emailed to the same parties. All follow up SAE report forms for the event must be signed by the investigator. Any source documents (e.g., progress notes, nurses' notes, laboratory and diagnostic test results, discharge summaries) provided to the sponsor must 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 eCRF and the SAE report form(s) must match or be reconciled. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same 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 (e.g., if a subject initially seeks treatment elsewhere or if not brought to the attention of the investigator), 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 / designee contact information for reporting SAEs is provided below. This information is also provided in the Study Manual and in the SAE report form.

PTC Therapeutics Safety Department

E-mail: [redacted]

SAE Fax Line: [redacted]

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

10 WITHDRAWAL OF SUBJECTS

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

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

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

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

11 STATISTICS

11.1 Sample Size

The study is planned to enroll a minimum of 36 subjects with nonsense mutation aniridia who are ≥2 years of age. This number of subjects should provide adequate information to evaluate the safety of ataluren in this population. For a statistical hypothesis test for any efficacy endpoint, the study will have 60% power to detect an effect size (i.e., standardized mean difference) of 0.85, or 80% power to detect an effect size of 1.06, at the 0.05 significance level (two-sided).

11.2 Analysis Populations

Intent-to-Treat (ITT) Population / Safety Population: This population will include all randomized subjects who receive at least 1 dose of study drug.

Efficacy Analysis Populations: For each efficacy outcome measure, this population will include all subjects who have a baseline value and at least 1 post-baseline value.

11.3 General Statistical Considerations

Two separate analyses will be conducted, one for the double-masked phase (Day 1 through Week 48), and the second for the entire study (Day 1 through Week 240). For patients randomized to placebo, two baselines will be used, one at randomization (Visit 2, Day 1) and the other at first dose of open-label ataluren (Visit 4, 48 weeks) for the analyses outlined below.

a) Analyses on the double-masked phase (Day 1 through Week 48).

Both placebo and ataluren will be presented and comparison will be made through 48 weeks between these two treatment groups. For the analyses of the double-masked phase, assessments at randomization (Visit 2 [Day 1]) will serve as baseline.

b) Analyses of the entire study (Visit 2, Day 1 through Week 240).

Efficacy will be presented based on two different baselines for placebo, one baseline at randomization (Visit 2) and the other baseline at Week 48 when placebo subjects first take open-label ataluren. Three analysis groups will be presented:

1. ataluren (all visits),
2. placebo (all visits) with Visit 2 assessments serving as baseline, and
3. combined groups with baseline at the first dose of ataluren (i.e., randomization -Visit 2 for ataluren patients and at the first dose of open-label ataluren (Visit 4, 48 weeks) for placebo patients).

Safety data for the entire study will be presented for the combined group for patients receiving ataluren.

By-subject listings will be created for each eCRF module. Summary tables for continuous variables will contain the following statistics: N, mean, median, standard deviation, standard error, minimum, maximum, and 95% confidence interval (CIs), as appropriate. Summary tables for categorical variables will include N, percentage, and 95% CIs on the percentage. Any CIs for proportions will be computed using normal approximation, if the number of the events is at least five. Otherwise, CIs using an exact method will be provided. Graphical techniques will be used when such methods are appropriate and informative. For safety summaries, CIs will not be presented, unless specified otherwise.

Transformations of the data may be explored if warranted by the distribution of the data.

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

All analyses will be performed using SAS® (Version 9.0 or higher).

11.4 Study Conduct

All protocol deviations will be listed and summarized.

11.5 Study Population

Frequency distributions or summary statistics of data pertaining to subject disposition, demographics, baseline characteristics, and medical history will be tabulated.

11.5.1 Subject Disposition

The disposition of subjects, including the number of subjects screened, the number of subjects enrolled, the number of subjects who received at least one dose of study drug, and the number of subjects who discontinued study drug during each of the two stages, as well as the reasons for premature termination of study drug, will be tabulated. Screening failure might also be summarized.

11.5.2 Demography and Baseline Characteristics

Demographic and baseline characteristics of subjects will be summarized descriptively by means and standard deviations for continuous variables, and by frequency distributions for categorical variables. Summaries will be presented for the ITT population only.

11.5.3 Medical History and Prior Medication

Medical history and prior medication information will be summarized.

11.6 Extent of Exposure

The extent of exposure to ataluren treatment is defined as the last dose date minus the first dose date + 1 day. The frequency will be presented according to the duration ranges in each Stage (i.e., Stage 1 [double-masked dosing] or Stage 2 [open-label dosing]): <24 weeks, >24 to <48 weeks, ≥48 to <72 weeks, ≥72 to <96 weeks, ≥96 to <120 weeks, ≥120 to <144 weeks, ≥144 to <168 weeks, ≥168 to <192 weeks, ≥192 to <216 weeks, and ≥216 to ≥240 weeks. The number r of subjects in each category as well as the mean duration (in days) will also be presented.

11.6.1 Treatment Compliance

Study drug compliance will be assessed by analysis of unused study drug reported. This information will be used to describe and summarize compliance by treatment arm. Compliance will be assessed in terms of the percentage of drug actually taken relative to the amount that should have been taken during the study.

11.7 Efficacy

All efficacy analyses will be performed in the ITT population.

11.7.1 Primary Efficacy Endpoint

The primary endpoint is change from baseline (Visit 2/Day 1) to Week 48 in Maximum Reading Speed of OU as measured using the MNREAD Acuity Charts.

To assess the treatment effect on the Maximum Reading Speed (OU) at Week 48, change from baseline will be analyzed using Analysis of Covariance (ANCOVA) with age and baseline Maximum Reading Speed (OU) as covariates, and treatment as a factor. The p-value of testing treatment difference will be provided. Significance level is 0.05 two-sided.

11.7.2 Secondary Efficacy Endpoints

The key secondary efficacy endpoints of this study are:

- Change from baseline (Visit 2/Day 1) to Week 48 in Reading Accessibility Index of OU
- Change from baseline (Visit 2/Day 1) to Week 48 in BCVA

Additional secondary efficacy endpoints of this study are as follows:

- Change from baseline (Visit 2/Day 1) to Week 48 in Maximum Reading Speed of OD and OS
- Change from baseline (Visit 2/Day 1) to Week 48 in Reading Accessibility Index of OD and OS
- Change from baseline (Visit 2/Day 1) to Week 48 in Critical Print Size of OU, OD and OS
- Change from baseline (Visit 2/Day 1) to Week 48 in Reading Acuity of OU, OD and OS
- Change from baseline (Visit 2/Day 1) to Week 48 in severity of corneal keratopathy
- Change from baseline (Visit 2/Day 1) to Week 48 in iris area
- Change from baseline (Visit 2/Day 1, Stage 1) to Week 240 (End of Study Visit) in BCVA. Note: This endpoint will be assessed only for the cohort of subjects who enroll into the sub-study.

All secondary efficacy endpoints will be analyzed similarly as the primary endpoint.

A summary of the efficacy endpoints listed above will also be provided by visit to assess the trend.

11.7.3 [redacted]

[redacted]

11.8 Safety

All safety presentations will be based on the safety population and will be based only on data included in the analysis period of interest

Adverse event and SAE summaries will also be presented for the following periods:

- Through Week 48 (double-masked phase)
- Through End of Treatment (entire study, including the sub-study)

Additional frequency tables summarizing the occurrence of adverse events and SAEs after the end of the analysis period of interest will also be provided. All AEs and SAEs will be summarized by treatment arm, as defined in Section 11.2. Marked laboratory abnormalities will also be descriptively summarized. No statistical tests will be performed for AEs or laboratory marked abnormalities.

11.8.1 Adverse Events

Adverse events are recorded by the investigators on the Serious and Non-Serious Adverse Event page(s) of the eCRF. All investigators are required to report the nature, the onset and resolution date, intensity, action taken, treatment required for event, and to express their opinion regarding the relationship between the AE and the study medication.

Summary information (the number and percent of subjects by treatment) will be tabulated for:

- Treatment-emergent adverse events, including clinical and laboratory adverse events
- Treatment-emergent and treatment-related adverse events
- Treatment-emergent adverse events by severity
- SAEs
- Adverse events leading to discontinuation
- Ocular adverse events

Summaries will be presented by System Organ Classes and Preferred Terms. The frequencies of adverse events displayed will be the crude rates that represent the number of subjects experiencing adverse events divided by the total number of subjects.

11.8.2 Laboratory Parameters

Changes in clinical laboratory tests from baseline (last measurement prior to entering the study at Visit 2, and, in addition, for placebo subjects last measurement prior to receiving open-label ataluren at Visit 4) and laboratory marked abnormalities (laboratory adverse events) using pre-defined abnormality criteria will be descriptively summarized. For laboratory adverse events, the severity will be graded by CTCAE, when possible. 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. In the by-subject analysis, a subject having the same abnormality more than once will be counted only once based on the worst severity grade observed.

11.8.3 Other Parameters

Height, weight, vital signs, physical examination, ophthalmoscopy, slit-lamp examination, and visual fields will be summarized descriptively.

11.9 [redacted]

[redacted]

11.10 Concomitant Medication Use

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

The frequency, timing (between each visit), type, and amount of any other therapies for aniridia will be considered with special interest.

11.11 Exploration of Correlations

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

11.12 Subgroup Analyses

Data will be summarized within subject subgroups of interest based on potentially relevant demographic, genetic, and clinical factors, such as age, nonsense mutation stop codon type (UGA, UAG, UAA), nonsense mutation exon location, and/or baseline efficacy parameters.

11.13 Multiplicity

The key secondary endpoints will be tested sequentially in the order of Reading Accessibility Index and then BCVA at the two-sided significance level 0.05. For example, if the hypothesis for the primary endpoint, Maximum Reading Speed of OU, is rejected at 0.05 level, then Reading Accessibility Index will be tested at 0.05 level. Further, if the hypothesis for Reading Accessibility Index is rejected at 0.05 level, then BCVA will be tested at 0.05 level. If the hypothesis for the primary endpoint is not rejected at 0.05 level, then no hypothesis testing will be performed for the key secondary endpoints.

12 OBLIGATIONS OF THE INVESTIGATOR AND THE SPONSOR

12.1 Compliance with Ethical and Regulatory Guidelines

The investigator is responsible for ensuring that the clinical study is performed in accordance with the Declaration of Helsinki (The World Medical Association 2008) and the International Council for Harmonisation (ICH) GCP guideline (International Council for Harmonisation 1996).

12.2 Institutional Review Board/Independent Ethics Committee

Prior to enrollment of subjects into the study, as required by regulatory authorities, the protocol and informed consent document will be reviewed and approved by an appropriate IRB/IEC. By signing the protocol, the investigator assures that approval of the 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.

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

The investigator shall submit a progress report, at least once yearly, to the IRB/IEC, and must provide a copy to PTC Therapeutics. As soon as possible after completion or termination of the study, the investigator will submit a final report to the IRB/IEC and to PTC Therapeutics. This report should include the dates of initiation and completion of the study, a description of any changes in study procedures or amendments to the protocol, any deviations from the protocol, the number and type of 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.

12.3 Informed Consent/Assent

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

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

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

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

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

12.4 Electronic Case Report Forms

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

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

12.5 Study Records

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

12.6 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.

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

12.7 Retention of Records

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

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

12.8 Monitoring and Auditing

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

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

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

12.9 Termination of the Study

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

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

12.10 Public Notification of Study Conduct

Consistent with requirements of the International Committee of Medical Journal Editors as a condition of consideration for publication of study results, PTC Therapeutics will be responsible for ensuring that this protocol is listed at the World Health Organization International Clinical Trials Registry Platform, European Union Clinical Trials Registry, and at ClinicalTrials.gov. PTC Therapeutics will also be responsible for ensuring that information at these 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.

12.11 Dissemination of Results

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

To allow for the use of the information derived from this clinical study and to 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, Health Canada, or other regulatory authorities. Such information may be disclosed as deemed necessary by PTC Therapeutics.

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

12.12 Communication with Regulatory Authorities

PTC Therapeutics (or designee) will assume responsibility for regulatory interactions with the FDA, Health Canada, and/or other regulatory authorities. In fulfilling this responsibility, PTC Therapeutics (or a designee) will collect, assemble, and communicate all required regulatory documents (e.g., investigator financial disclosure forms, protocol and protocol amendments, investigator's brochure, 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.

13 RATIONALE FOR STUDY DESIGN FEATURES

13.1 Subject Selection

13.1.1 General

This study is a randomized, double-masked, placebo-controlled safety and efficacy study of ataluren in subjects with nonsense mutation aniridia. Consistent with GCP guidelines, parents/guardians and subjects must provide informed consent/assent before initiation of any study procedures. To minimize missing data and premature discontinuations, subjects must have the personal and family resources to comply with study procedures and restrictions. In addition, subjects must not have serious concomitant conditions that would compromise safety, compliance, or evaluation.

13.1.2 Reproductive Considerations

Ataluren is not genotoxic, did not affect fertility in male and female rats, and was not teratogenic in rats and rabbits. In addition, lack of sexual maturity in many of the subjects likely to be enrolled in this study limits reproductive risks. However, restriction on eligibility relating to willingness to avoid unprotected sexual intercourse in any subjects known to be sexually active is included as a general precaution. Because it is unknown if ataluren is excreted in breast milk, lactating female subjects who are breast-feeding are excluded from participation.

13.1.3 Prior and Concomitant Therapies

Surgery for aniridia-related conditions is permitted during the study.

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

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

In vitro, ataluren is a weak inhibitor of CYP2C8 and CYP2C9, but in vivo drug-drug interactions mediated by these enzymes are not expected according to the criteria described in the EMA guideline on the investigation of drug interactions (EMA 2012).

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

Based on in vitro studies, ataluren is also not expected to be an inhibitor or a substrate of P-glycoprotein (P-gp)-mediated transport.

Note: Topical cyclosporine therapy is permitted.

In vitro data indicate that ataluren is an inhibitor of UGT1A9, OAT1, OAT3 and OATP1B3. Caution should be exercised when ataluren is co-administered with drugs that are substrates of OAT1, OAT3, or OATP1B3 (e.g., oseltamivir, acyclovir, ciprofloxacin, captopril, furosemide, bumetanide, valsartan, pravastatin, rosuvastatin, atorvastatin, pitavastatin) because of the risk of increased concentration of these drugs.

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

Please refer to the IB for the latest information on prohibited medications.

13.2 Treatment Rationale

13.2.1 Ataluren Schedule and Dose Selection

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

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

In clinical studies of ataluren in other nonsense mutation genetic disorders, particularly nmDMD and nmCF, ataluren has been studied most extensively at the 10, 10, 20 mg/kg dose level. In the Phase 2b, randomized, double-masked, placebo-controlled study of ataluren in nmDMD (Study 007), a total of 57 subjects received ataluren 10, 10, 20 mg/kg for 48 weeks. In addition, all subjects in the ongoing open-label safety studies of ataluren in nmDMD (Studies 016 and 019) are receiving the 10, 10, 20 mg/kg dose level. As of 31 January 2015, the estimated median duration of exposure was 196.6 weeks for Study 016 (N=108) and 102.4 weeks for Study 019 (N=93). Across the Phase 3, randomized, double-masked, placebo-controlled study of ataluren in nmCF (Study 009) and its open-label extension (009e), a total of 170 nmCF subjects have received ataluren 10, 10, 20 mg/kg for ≥48 weeks, including 132 subjects who have received ataluren 10, 10, 20 mg/kg for ≥96 weeks. The controlled studies in nmDMD (Study 007) and nmCF (Study 009) have documented a favorable risk-benefit at the 10, 10, 20 mg/kg dose level in these indications (Bushby 2014, Kerem 2014). In nmDMD, ataluren has been conditionally approved at a dose of 10, 10, 20 mg/kg for the treatment of nmDMD. Based on the collective clinical experience with ataluren 10, 10, 20 mg/kg in other indications, this dose level will be evaluated in subjects with nonsense mutation aniridia.

13.2.2 Duration of Therapy

The primary objective of this Phase 2 study is to evaluate the effect of ataluren on Maximum Reading Speed as measured using the MNREAD Acuity Charts in subjects with nonsense mutation aniridia. Secondarily, this study also aims to evaluate other efficacy outcome measures in this patient population. Given that there have been very few clinical trials in aniridia, it is important to gather information regarding long-term changes and variability of outcome measures.

This study also aims to determine whether ataluren can be safely administered as a chronic treatment for subjects with nonsense mutation aniridia. In subjects with other nonsense mutation genetic disorders, ataluren has been generally well tolerated when administered chronically for >4 years. Therefore, exposure to ataluren for up to 240 weeks in this study is not expected to pose undue safety risk.

13.2.3 Selection of Outcome Measures

The proposed efficacy, safety, and exposure evaluations are chosen based on relevance to the pathophysiology and clinical manifestations of the disease and past experience that these assessments can be performed with acceptable accuracy.

13.2.3.1 Slit-Lamp Examination and Macro Photography

Slit-lamp examination and macro photography are standard ophthalmological techniques to inspect the anterior segment of the eye. In the diagnosis of aniridia, slit-lamp examination and macro photography are critical to identify and document iris and pupillary abnormalities (Hingorani 2012). Corneal opacification and vascularization and cataract or glaucoma can also be detected, if present. The procedure is non-invasive and can be performed in children and adults. Images will be analyzed by an independent central reader masked to subject identity.

13.2.3.2 Fundus Photography

Fundus examination including posterior segment photography will be used to assess for abnormalities in the retina, macula, and choroid as well as the optic disc. Abnormalities of posterior ocular structures, namely foveal and optic nerve hypoplasia, often occur in patients with aniridia and cause or contribute to visual impairment (McCulley 2005). Images will be analyzed by an independent central reader masked to subject identity.

13.2.3.3 MNREAD

An MNREAD Acuity Chart curve of reading speed vs print size is characterized by 3 summary values. At large print sizes, reading speed remains constant, forming a plateau that represents the Maximum Reading Speed. As the print size decreases, a Critical Print Size is reached at which reading speed begins to decline rapidly. Finally, the smallest print size that can be read is defined as the Reading Acuity. These 3 parameters of the MNREAD Acuity Chart curve are used to summarize visual reading function.

Maximum Reading Speed is a person's reading speed when reading is not limited by print size. Maximum Reading Speed is known to be reduced when foveal vision is degraded, such as is seen in patients with aniridia. Reading speed, in words per minute, has been widely used in psychophysical studies because it can be measured objectively, is reproducible, and is sensitive to variations in visual parameters (Legge 1985). Maximum Reading Speed is a measure that reflects the dynamic nature of reading.

The Reading Accessibility Index is defined as an individual's mean reading speed measured across the 10 largest print sizes on the MNREAD Acuity Chart (0.4–1.3 logarithm of the minimum angle of resolution at 40 cm), normalized by 200 words per minute (the mean value for a group of 365 normally sighted young adults). The Reading Accessibility Index is a single-value measure that captures an individual's range of accessible print sizes and reading fluency within this range (Calabrese 2016). These charts were developed at the Minnesota Laboratory for Low-Vision Research, University of Minnesota, Minneapolis, Minnesota, USA.

The reading level of the MNREAD Acuity Charts is approximately 2nd to 3rd grade level. It is estimated that subjects around the age of 8 years or older will be able to complete this assessment. Any subject less than the age of 8 years old will not be required to have this study assessment administered.

13.2.3.4 Optical Coherence Tomography

High-resolution OCT enables the measurement and visualization of microscopic structures of the anterior and posterior segments. Anterior segment OCT imaging will be performed to detect potential changes in the anterior angle structures. Posterior segment OCT will be attempted to detect potential changes in foveal and optic disc structures, although corneal opacities may preclude clear imaging in some patients (Gregory-Evans 2011). Images will be analyzed by an independent central reader masked to subject identity.

13.2.3.5 Best Corrected Visual Acuity (BCVA) and Refraction

Poor visual acuity resulting from iris hypoplasia and foveal hypoplasia is a hallmark symptom of aniridia (Netland 2011, Hingorani 2012). BCVA and refraction will be evaluated using the well-established ETDRS method. If needed, an age-appropriate alternative visual acuity chart (e.g., LEA symbols) may be used; however, the same chart should be used throughout the duration of the study.

[redacted]

[redacted]

[redacted]

[redacted]

13.2.3.9 Body Mass Index

Systemic abnormalities associated with aniridia include increased body mass index (BMI) and obesity (Netland 2011). Accordingly, BMI will be calculated.

[redacted]

13.2.3.11 Safety

In defining therapeutic activity in a particular clinical setting, it is imperative that the drug's safety profile be fully characterized. As is conventional in all clinical studies, proper description of each adverse event or laboratory abnormality requires an understanding of the type, incidence, timing, severity, and relatedness to study drug. In this study, particular focus will be placed on monitoring for ocular adverse findings. For consistency of interpretation, adverse events will be coded using the standard MedDRA, and the severity of these events will be graded using the well-defined CTCAE Version 4.0. Standard definitions for seriousness will be applied. Particular attention will be paid to any adverse events causing discontinuation of ataluren and to SAEs requiring rapid regulatory reporting.

Ocular safety will be monitored via slit lamp, ophthalmoscopy, and visual field assessments.

14 BENEFITS AND RISKS

14.1 Benefits and Risks: Non-Clinical

In addition to the non-clinical studies of $PAX6^{Sey+/-}$ mice described in Section 2.2.1.2 in cellular assays and animal models of genetic disease, ataluren demonstrated the ability to specifically and selectively enable readthrough of mRNA containing a premature stop codon, inducing production of full-length protein that localizes to the appropriate cellular location and is functionally active. Ataluren consistently enabled mRNA readthrough and functional full-length protein production from mRNAs that contain a premature stop codon without promoting readthrough of normal stop codons.

Ataluren was shown to be selective for translation. Ataluren did not alter levels of mRNA with premature stop codons or wild type mRNA demonstrating that ataluren does not modify transcription or mRNA stability. In cell-free translation assays, ataluren functions at the level of translation and not transcription. Ataluren does not produce a functional protein by promoting readthrough of premature stop codons due to frameshift mutations (insertions or deletions) or of mRNAs harboring multiple sequential premature stop codons. Ataluren is selective for premature stop codons and does not promote readthrough of normal stop codons.

Toxicokinetic data were obtained in toxicity studies conducted in mice, rats, rabbits and dogs. Consistent with the short t½, there was no accumulation of drug in plasma upon repeated daily dosing. In all species, ataluren exposure increased with increasing dose, but the increase was generally less than dose proportional. There were no sex-related differences in ataluren exposure in dogs, but in rats and mice, exposure was slightly higher in females than in males. The major metabolite seen in mice, rats and dogs was ataluren acyl glucuronide; exposure to this metabolite in the toxicology species at lowest-observed-adverse-effect levels, no-observed-adverse-effect levels, and no-effect levels in the toxicology program was greater than the exposure observed in humans administered the clinical dose of 10, 10 and 20 mg/kg 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-gp. Enzyme inhibition studies with human liver microsomes showed that ataluren has a weak potential for direct inhibition of CYP2C8 and CYP2C9. As an added measure of safety, investigators should pay specific attention to use of drugs that are known substrates of these enzymes, particularly

when such drugs may have a narrow therapeutic index. Enzyme induction evaluations in human hepatocytes showed that ataluren did not induce the activities of CYP450 enzymes. Induction of metabolism by ataluren is not expected since slight increases in CYP2B6 and CYP2C9 activity are observed only at an ataluren concentration that is 3- to 5-fold higher than the average peak concentration after a 20 mg/kg dose.

Based on in vitro studies, ataluren is a substrate of UGT1A9 and BCRP. Coadministration with rifampin, a strong inducer of metabolic enzymes, including UGT1A9 and CYP3A4, did not affect exposure of ataluren in healthy subjects. No dose adjustment is required when ataluren is co-administered with UGT1A9-inducing medications. Caution should be exercised when ataluren is co-administered with drugs that are inhibitors of BCRP (e.g., cyclosporine, eltrombopag, gefitinib), as these drugs may affect ataluren plasma concentrations.

Note: Topical cyclosporine therapy is permitted.

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

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, i.e., observed in one toxicology species only. These findings included kidney findings in mice (nephrosis, predominantly in the distal nephron, reversible following cessation of dosing) and adrenal gland cortical findings in dogs (lymphohistiocytic infiltrates with focal parenchymal cell degeneration in regions responsible for synthesis of glucocorticoids). Chronic studies were conducted in weanling rats and dogs to support dosing in children as young as 2 years of age. Ataluren was not genotoxic and was not teratogenic in rats and rabbits. In rats and rabbits, fetal toxicity was observed only at materno-toxic doses. Ataluren had no effect on the fertility of male and female rats. In rats, postnatal developmental effects were observed only at materno-toxic doses. Maternal administration of ataluren in rats had no effect on F_1 reproduction or F_2 embryo/fetal development. Ataluren did not increase the incidence of tumors in a 26-week carcinogenicity study in Tg.rasH2 mice. Tumors observed in rats in the toxicology program occurred at exposures that exceeded clinical exposure and/or 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, 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 subjects as young as 2 years of age.

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

14.2 Benefits and Risks: Clinical

The ability of ataluren to enable readthrough of nonsense mutations has been clinically demonstrated in other indications of nonsense mutation-mediated disease (Kerem 2008, Sermet-Gaudelus 2010, Wilschanski 2011, Finkel 2013). Ataluren's effect in treatment of nmDMD has been demonstrated (Bushby 2014), and in July 2014 ataluren was approved by the EMA for treatment of nmDMD. In addition, in a Phase 3 study of nmCF subjects, ataluren-treated subjects had less lung function decline and fewer pulmonary exacerbations than placebo-dosed subjects (Kerem 2014).

Totaling all ataluren clinical studies, including healthy volunteers as well as subjects with several nonsense mutation genetic disorders, >750 subjects have been exposed to ataluren in Phase 1 (Hirawat 2007), Phase 2 (Kerem 2008, Sermet-Gaudelus 2010, Wilschanski 2011, Finkel 2013) and Phase 3 (Bushby 2014, Kerem 2014) clinical studies. Ataluren has shown a favorable safety profile in clinical studies.

Approximately 40% of patients with aniridia have a nonsense mutation in one allele of the PAX6 gene (Tzoulaki 2005). Because ataluren-induced readthrough of nonsense mutations has been demonstrated in Phase 2 and Phase 3 clinical studies of other nonsense mutation genetic diseases, while showing a favorable clinical safety profile, it can be expected that ataluren treatment of nonsense mutation aniridia will exhibit acceptable benefit vs risk.

14.2.1 Justification for Inclusion of Minors

In standard toxicology studies, dosing is initiated in young adult rats (6 to 8 weeks old) and in 4-to 6-month old dogs. However, the chronic toxicology studies conducted with ataluren initiated dosing in weanling animals (approximately 4- to 5-week-old rats, and dogs <3 months of age) to support dosing of pediatric subjects as young as two years of age. A detailed summary of methods and results of these chronic toxicity studies is provided in Section 7 of the ataluren investigator's brochure.

In the clinic, ataluren has already been administered to subjects as young as three years old. A Phase 2 study of ataluren in subjects with methylmelonic acidemia (MMA) enrolled 11 subjects, including two subjects who were three years old and one subject who was 4 years old. All three of these subjects completed the study as planned, receiving ataluren 5, 5, 10 mg/kg for 28 days in Cycle 1 and ataluren 10, 10, 20 mg/kg for 28 days in Cycle 2; there was a washout period of 21 days between the cycles.

Ataluren was well tolerated by the three subjects <6 years old in the MMA study. Treatment-emergent adverse events in these subjects were vomiting, pyrexia, nasopharyngitis, cough, flatulence, and rash. All treatment-emergent adverse events were mild or moderate in severity, and none were serious or led to discontinuation of treatment. Overall, the ataluren safety profile was similar in <6 years old and ≥6 years old.

Twenty-four-hour blood sampling for ataluren PK assessments was performed on Day 28 of each cycle; the data from Cycle 2, in which a dose of 10, 10, 20 mg/kg was administered, are of particular relevance to the proposed study in nonsense mutation aniridia. Ataluren plasma concentrations in the 3 subjects <6 years old were comparable to ataluren plasma concentrations in the 8 subjects ≥6 years old who participated in this study. Mean area under the curve $(AUC)_{0\text{-}24h}$ was 279.3 h•µg/mL and 358.4 h•µg/mL for subjects <6 and ≥6 years old, respectively, on Day 28 of Cycle 2. Mean maximum concentration (C_{max}) was 28.2 µg/mL and 29.9 µg/mL for subjects <6 and ≥6 years old, respectively, on Day 28 of Cycle 2 (10, 10, 20 mg/kg). These data suggest similar ataluren PK profiles in subjects <6 and ≥6 years old.

Based on the above considerations, inclusion of young children in this protocol is appropriate. Furthermore, there has been careful consideration of the study design, wherein measures have been taken to minimize the number of subject visits and blood draws while maximizing the amount and quality of data required to effectively achieve the study objectives.

Study of young children is important given the onset of disease in early childhood, the importance of intervention when the disorder is still in its early phases, the limited treatment options that are currently available for this condition, and ataluren's favorable benefit/risk profile.

14.3 Benefit/Risk Conclusions

Aniridia is a devastating disease wherein patients have multiple ocular pathologies and become progressively visually handicapped. Current therapeutic approaches to treat aniridia are limited in efficacy, such as surgical management of cataracts and glaucoma treatments to relieve intraocular pressure. These treatments do not correct the anatomical defects associated with aniridia nor halt the progressive decline in visual acuity. There is a high unmet medical need for an effective treatment for aniridia.

Evaluation of ataluren as a treatment for nonsense mutation aniridia has sound scientific rationale founded on activity data from nonclinical disease models and clinical data from subjects with other genetic diseases, including efficacy and safety data from Phase 2b/3, placebo-controlled trials in nmDMD and nmCF. The safety profile of ataluren is supported by safety pharmacology and toxicology studies of appropriate type and duration, and by Phase 1, Phase 2, and Phase 3 safety data obtained in children and adults; the development program has identified potential clinical safety risks and appropriate monitoring strategies are included in the clinical studies.

Given the seriousness of aniridia and the limitations of available therapies, the aggregate potential benefits relative to the potential risks support further development of ataluren in this disease.

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16 APPENDICES

16.1 Protocol Amendment History

Changes in Version 6.0 (08 Nov 2018) to Version 7.0 (17 DEC 2019)

Justification for the amendment: Due to the continuing unavailability of any treatment options targeting the underlying cause of nonsense mutation aniridia, a very small disease population, and the enrollment challenges that were encountered during the study, PTC Therapeutics amended the protocol, changing the primary endpoint from safety to efficacy in order to investigate the clinical utility of intervention with ataluren in the current study. The revised primary endpoint is the change from baseline (Visit 2/Day 1) to Week 48 in Maximum Reading Speed of OU as measured using the MNREAD Acuity Charts, [redacted] Maximum Reading Speed is a person's reading speed when reading is not limited by print size and is a measure that reflects the dynamic nature of reading. Maximum Reading Speed is known to be reduced when foveal vision is degraded, such as is seen in patients with aniridia. The primary objective was amended accordingly to reflect this change in primary endpoint. Additionally, the characterization of the systemic and ocular safety profile of ataluren in subjects with nonsense mutation aniridia was moved from being the primary objective to one of the secondary objectives. A corresponding secondary safety endpoint was added to reflect this change.

Summary of Protocol Changes

Item No.	Protocol Section(s)	Update	Rationale
1	Protocol	Text modified	Document date and protocol version number were updated where they occurred; visual acuity was specified to be best corrected visual acuity (BCVA) where applicable; abbreviations and references were updated as needed; minor editorial revisions were incorporated throughout to provide clarity.
2	Synopsis	Text added	A protocol synopsis was included in this version (7.0) of the protocol.
3	Section 1.1 Introduction and Section 2.2.1 Therapeutic Rationale	Text modified	The number of times ataluren was renewed by the EMA was updated.
4	Section 3.1.1 Primary Objective	Text modified	Text was modified to reflect the change in primary objective from "to characterize the systemic and ocular safety profile of ataluren when administered chronically in subjects with nonsense mutation aniridia" to "to evaluate the effect of ataluren on Maximum Reading Speed as measured using the Minnesota Low Vision Reading Test (MNREAD) Acuity Charts in subjects with nonsense mutation aniridia".
5	Section 3.1.2 Secondary Objectives	Text added	Text added to reflect the modification of the secondary objectives to include the effect of ataluren on the Reading Accessibility Index, Critical Print Size and Reading Acuity and the systemic and ocular safety profile of ataluren in subjects with nonsense mutation aniridia.

Summary of Protocol Changes			
Item No.	**Protocol Section(s)**	**Update**	**Rationale**
6	Section 3.1.3 [redacted]	Text deleted	Text deleted to reflect the removal of MNREAD as one of the [redacted].
7	Section 3.2.1 Primary Endpoint	Text modified	Text modified to reflect the change in primary endpoint to "change from baseline (Visit 2/Day 1) to Week 48 in Maximum Reading Speed of OU as measured using the MNREAD Acuity Charts".
8	Section 3.2.2 Secondary Endpoints	Text added/moved	Text added/moved to reflect the addition of key secondary endpoints: "change from baseline (Visit 2/Day 1) to Week 48 in Reading Accessibility Index of OU" and "change from baseline (Visit 2/Day 1) to Week 48 in BCVA". Text added to reflect the addition of secondary efficacy endpoints related to Reading Accessibility Index, Maximum Reading Speed, Critical Print Size and Reading Acuity associated with the change in primary endpoint. Text added to reflect the addition of a secondary safety endpoint of assessments related to the systemic and ocular safety profile of ataluren in subjects with nonsense mutation aniridia.
9	Section 3.2.3 [redacted]	Text added/deleted	[redacted]
10	Section 8.3.15 MNREAD	Text added	Text added to further elaborate on the endpoints Maximum Reading Speed and Reading Accessibility Index.
11	Section 11.7 Efficacy	Text modified	Text modified to reflect change in primary endpoint and secondary efficacy endpoints and associated analysis shown in Sections 3.2.1 and 3.2.2.
12	Sections 11.7 Efficacy, 11.8 Safety and 11.9 [redacted]	Text moved	Sections were re-arranged to reflect changes to the primary endpoint from being a safety endpoint to an efficacy endpoint.
13	Section 11.13 Multiplicity	Text added	Text added describing multiplicity.
14	Section 13.2.2 Duration of Therapy	Text modified	Text modified to reflect changes to the primary and secondary objectives.
15	Section 13.2.3.3 MNREAD	Text modified	Text modified to include more detail about the new primary endpoint "change from baseline (Visit 2/Day 1) to Week 48 in Maximum Reading Speed of OU as measured using the MNREAD Acuity Charts".

Appendix A [redacted]

[redacted]

[redacted]