A Phase 2 Randomized, Double-Masked Placebo-Controlled Crossover Safety and Tolerability Study of Ataluren for Drug-Resistant Epilepsy in Patients with Nonsense Mutation CDKL5 or Dravet Syndrome

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PRINCIPAL INVESTIGATOR AGREEMENT AND SIGNATURE

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

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	adverse event
AED	antiepileptic drug
BCRP	breast cancer resistance protein
BUN	blood urea nitrogen
CBC	complete blood count
CDKL5	cyclin-dependent kinase-like 5
cGMP	current Good Manufacturing Practices
CI	confidence interval
CMP	comprehensive metabolic panel
CRF	case report form
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP	cytochrome P450
EMA	European Medicines Agency
EOS	End of Study
EOT	End of Treatment
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HCG	human chorionic gonadotropin
HIPAA	Health Insurance Portability and Accountability Act
IB	Investigator's Brochure
ILAE	International League Against Epilepsy
IRB	institutional review board
ITT	Intent-to-Treat
LFT	liver function test
MECP2	methyl CpG binding protein-2
MMA	methylmelonic acidemia
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NORD	National Organization for Rare Disorders
nm	nonsense mutation
nmCF	nonsense mutation cystic fibrosis
nmDMD	nonsense mutation Duchenne muscular dystrophy
NYU CEC	New York University Comprehensive Epilepsy Center
NYULMC	New York University Langone Medical Center
OAT	organic anion transporter
PHI	protected health information

Abbreviation	Definition
PK	pharmacokinetic(s)
PTC124	ataluren
QOL	quality of life
QOLCE	Quality of Life in Childhood Epilepsy
SAE	serious adverse event
SCN1A	sodium channel, voltage-gated type 1 alpha
SUDEP	sudden unexpected death in epilepsy
$t_{½}$	half-life
TEAE	treatment-emergent adverse event
TID	three (3) times per day
UGT	uridine 5'-diphospho-glucuronosyltransferase
US	United States
VABS-II	Vineland Adaptive Behavior Scales, Second Edition
VNS	vagus nerve stimulator

CLINICAL PROTOCOL SYNOPSIS

Title:	A Phase 2 Randomized, Double-Masked Placebo-Controlled Crossover Safety and Tolerability Study of Ataluren for Drug-Resistant Epilepsy in Patients with Nonsense Mutation CDKL5 or Dravet Syndrome
Short Title:	Ataluren for nonsense mutation CDKL5 or Dravet syndrome
Protocol Number:	s15-00426
Other Study ID Number:	PTC124-GD-035-EP
Phase:	Phase 2
Methodology:	Interventional study
Study Duration:	32 weeks with extension available
Study Center(s):	Single-center at New York University Comprehensive Epilepsy Center
Objectives:	The primary objective of this study is to: • Evaluate changes in convulsive and/or drop seizure frequency from Baseline following ataluren treatment in subjects with CDKL5 or Dravet syndrome resulting from a nonsense mutation The secondary objectives of this study are to: • To determine changes in minor seizure types following ataluren treatment in subjects with CDKL5 or Dravet syndrome resulting from a nonsense mutation. (Seizure types as defined by the International League Against Epilepsy criteria.) • Characterize the safety profile of ataluren in subjects with CDKL5 or Dravet syndrome resulting from a nonsense mutation The exploratory objectives of this study are to: • Evaluate changes from Baseline in cognitive, motor, and behavioral function as well as quality of life following ataluren treatment in subjects with CDKL5 or Dravet syndrome resulting from a nonsense mutation.
Number of Subjects:	18 evaluable (10 nonsense mutation CDKL5, 8 nonsense mutation Dravet syndrome)

Diagnosis and Main Inclusion Criteria:	• Age ≥ 2 years old and ≤ 12 years old, male or female, at Week 0 (at time informed consent/assent is signed) • Documentation of a diagnosis of nonsense mutation in 1 allele for Dravet syndrome or CDKL5 deficiency as evidenced by medical records, genetic testing, and the following clinical feature: ○ Failure to control seizures despite appropriate trial of 2 or more antiepileptic drug (AEDs) at therapeutic doses • Current regimen of 1 to 3 baseline AEDs at stable doses for a minimum of 4 weeks prior to enrollment (i.e., Screening Visit). (Vagus nerve stimulator, ketogenic diet, and modified Atkins diet do not count towards this limit but must be unchanged for 3 months prior to enrollment [Screening].) • Minimum of 6 convulsive or drop seizures with duration > 3 seconds over the 4 weeks of diary screening prior to randomization and ≥ 6 convulsive or drop seizures with duration > 3 seconds during the 4 weeks from Screening to Baseline.
Study Product, Dose, Route, Regimen:	Ataluren (powder for oral suspension) Dose: 3 times per day (TID; 10 mg/kg, 10 mg/kg, and 20 mg/kg morning, midday, and evening, respectively) Titration: None Maximum dose: TID (10 mg/kg, 10 mg/kg, 20 mg/kg morning, midday, and evening respectively)
Duration of Administration:	Each subject will receive a total of 12 weeks of active drug (ataluren) and 12 weeks of placebo, in a masked fashion
Reference Therapy:	None

1 INTRODUCTION

This document is a clinical research protocol for a human research study. This study will be conducted in accordance with the protocol, United States (US) government research regulations, applicable international standards of Good Clinical Practice (GCP), and institutional research policies and procedures.

1.1 Background

Drug-resistant epilepsy is a serious condition that negatively impacts patients' quality of life (QOL). Those with drug-resistant epilepsy are at a higher risk for sudden unexpected death in epilepsy (SUDEP). The risk factors associated with SUDEP, including frequent generalized tonic-clonic seizures, antiepileptic drug (AED) polytherapy, and common nocturnal seizures, are also factors present in those with drug-resistant epilepsy (Pack 2012). The risk of SUDEP in those with drug-resistant epilepsy can exceed 5% per decade (Devinsky 2011). Most patients with drug-resistant epilepsy, despite trials of multiple combinations of AEDs, have no US Food and Drug Administration (FDA)-approved treatment options left. CDKL5 and Dravet syndrome are rare epilepsies commonly associated with drug-resistant epilepsy.

1.1.1 CDKL5

Cyclin-dependent kinase-like 5 (*CDKL5*) is a gene that produces the CDKL5 protein, which is primarily expressed in the brain, thymus, and testes. The gene is composed of 24 exons; exons 2–11 code for the catalytic domain whereas exons 12–18 code for the carboxy-terminus. In mice, the gene expression profile suggests that the CDKL5 protein is involved in neuronal maturation (Rusconi 2008). CDKL5 phosphorylates the protein product of the methyl CpG binding protein-2 (*MECP2*) gene in the nucleus MECP2 regulates genes associated with synapse function and maintenance. Loss of CDKL5 function drives phenotype and likely accounts for the similarity between Rett syndrome and CDKL5 (Mari 2005). CDKL5 also phosphorylates DNA methyltransferase 1 and amphiphysin, and interacts with Rac1 to influence actin remodeling and neuronal morphogenesis.

CDKL5 is an X-linked genetic epileptic encephalopathy most often present in females. Males, however, are more severely affected than females (Melani 2011). The incidence of CDKL5 is ~1 in 45,000 live births. Patients with CDKL5 exhibit early signs of poor developmental skills (eg, poor sucking, poor eye contact) in the first several months of life. Later, impairment of hand motor skills, lack of speech acquisition, and severe and global developmental delays become apparent (Fehr 2013, Melani 2011). Eye contact and social interactions are often reduced. Many patients are never able to walk independently. However, CDKL5 is not associated with cortical atrophy or degeneration.

CDKL5 causes an epileptic encephalopathy in which epileptiform abnormalities contribute to progressive functional impairment. Epilepsy often presents with infantile spasms within the first four months of age (Mei 2010). The average age of seizure onset is 6 weeks, with more than 90% of patients experiencing seizures in the first 3 months of life. Later, tonic–clonic seizures, consisting of a vibratory tonic phase followed by a clonic phase, occur and often last 2 to 4 minutes (Melani 2011). After age 3 years, seizures remit in many children while others continue to have drug-resistant epilepsy, with tonic spasms and myoclonic seizures (Mei 2010).

The electroencephalogram findings often include slowing of the background with interictal generalized, focal, or multifocal discharges. A burst-suppression pattern may be seen in younger children (Melani 2011).

1.1.2 Dravet Syndrome

Sodium channel, voltage-gated type 1 alpha (*SCN1A* or Nav1.1) is the sodium channel α1 subunit gene and is expressed almost exclusively in the brain. Mutations in *SCN1A* can cause a variety of epilepsies that range from benign febrile seizures to severe epileptic encephalopathy and Dravet syndrome (Severe Myoclonic Epilepsy of Infancy; Mulley 2005, Catterall 2010). The major mechanism underlying epilepsy appears to be impairment of gamma-aminobutyric acid interneuron inhibitory function (Catterall 2005, Yu 2006).

Dravet syndrome was initially described in 1978 as Severe Myoclonic Epilepsy of Infancy by Charlotte Dravet (Dravet 2011). The incidence of Dravet syndrome is ~1 in 15,700 live births, comprising approximately 6% of epilepsies starting before the age of 3 years (Hurst 1990, Yakoub 1992, Wu 2015). It causes febrile and afebrile, generalized and unilateral, clonic or tonic-clonic seizures; it can also cause absence, absence-myoclonic, and complex partial seizures. Seizures typically begin in the first year of life in an otherwise normal infant. Initial seizures are often febrile status epilepticus (Dravet 2005). Later, myoclonic, atypical absence, and partial seizures often develop. Seizures are usually drug-resistant but the severity of the epilepsy tends to diminish around puberty. Developmental delays in the second year of life and intellectual disability are present in more than 95% of patients (Chieffo 2011). Autism spectrum disorder is diagnosed in approximately 25% of patients (Genton 2011). Most patients develop cerebellar dysfunction in later childhood, manifesting as an ataxic gait disorder, dysarthria, and intention tremor (Genton 2011). The mortality rate is high; approximately 15% of patients die by adolescence and 20% die by early adulthood (Genton 2011). SUDEP and status epilepticus are the most common causes of death.

1.2 Study Drug History

PTC Therapeutics 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. Nonsense mutations are single-point alterations in the DNA that, when transcribed, result in conversion of a messenger ribonucleic acid (mRNA) triplet (eg, CAG) that codes for an amino acid to a triplet (eg, UAG) that is interpreted as a stop codon. The presence of the premature stop codon within the mRNA leads to a premature cessation of translation, with a protein truncation and consequent disease due to loss of enzymatic function or a structural deficit. Nonsense mutations are the basis for approximately 13% to 40% of the individual cases of most inherited disease, including CDKL5 and Dravet syndrome amongst many others (Frame 2013).

PTC Therapeutics conducted a high-throughput screening program that 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 the identification of ataluren as an orally bioavailable small molecule with potential clinical utility in treating genetic disorders through induction of

read-through of nonsense mutations and production of full-length, functional proteins (Welch 2007, Du 2008). In the subset of patients whose disease is mediated by a nonsense mutation, ataluren may offer an effective therapy by restoring critical protein production for CDKL5, Dravet syndrome, and other disabling and life-threatening genetic disorders.

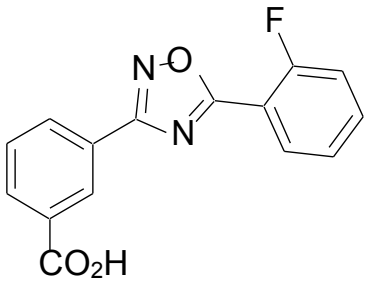
Phase 1 clinical testing in 62 healthy volunteers (ages 18–30 years) who were administered ataluren at relevant doses through 14 days of dosing has documented that oral ataluren can achieve target plasma concentrations associated with activity in preclinical testing. Phase 2a studies in 77 patients (ages 6–57 years) with nonsense mutation cystic fibrosis (nmCF) receiving oral ataluren for periods of 14 days to 12 weeks demonstrated that oral ataluren is generally well-tolerated and can generate production of apically localized epithelial cystic fibrosis transmembrane conductance regulator protein. Phase 2a studies in 38 patients (ages 5–17 years) with nonsense mutation Duchenne muscular dystrophy (nmDMD) administered oral ataluren through 28 days confirmed 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 authorized ataluren for the treatment of nmDMD.

This study will specifically enroll patients with nonsense mutation CDKL5 and Dravet syndrome, which are both major forms of drug-resistant epilepsy.

1.2.1 Ataluren

Ataluren (PTC124) is a novel 1,2,4-oxadiazole linked to 2 ring structures: fluorobenzene and benzoic acid. The molecule has no chiral centers. Its chemical name is 3-[5-(2-fluorophenyl)-1,2,4 oxadiazol-3-yl]-benzoic acid and its chemical formula is $C_{15}H_9FN_2O_3$. The compound has no structural similarity to other currently used drugs. The drug substance is a white to off-white, crystalline powder. The ataluren chemical structure is shown in Figure 1.

Figure 1 Ataluren Chemical Structure



Ataluren to be used in this study will be in the form of a white to off-white granules for suspension packaged in child-resistant aluminum foil packets. Each packet contains 125, 250, or 1000 mg of drug substance, which is 25% of the total formulation weight.

Ataluren is practically insoluble in water and has high permeability across layers of Caco-2 gastrointestinal epithelial cells. Ataluren, as well as its primary metabolite, an acyl glucuronide,

are excreted by both hepatic and renal routes. The plasma level peaks 1 to 2 hours after oral administration. The half-life ($t_{½}$) in healthy volunteers ranges from 2 to 6 hours. The side effects of ataluren that have been indicated in trials include vomiting, nausea, abdominal pain, headache, pyrexia, rhinitis, and sinusitis (PTC Therapeutics; ataluren Investigator's Brochure [IB]).

1.2.2 Placebo

The placebo for placebo-controlled clinical studies will be provided as a white to off-white powder for suspension. The placebo powder will be supplied in packets matching the fill weights of the active drug product that contain 125, 250, or 1000 mg of the drug substance. The placebo is similar to the active product except that ataluren is replaced by the addition of a filler (microcrystalline cellulose) and an increased amount of mannitol, which together comprise approximately 50% of the powder.

1.3 Preclinical Data

In cellular assays and animal models of genetic disease, ataluren has demonstrated the ability to specifically and selectively enable read-through of mRNA containing a premature stop codon, resulting in production of full-length protein that localizes to the appropriate cellular location and is functionally active (Welch 2007, Du 2008). Ataluren is selective for premature stop codons and does not promote read-through of normal stop codons, consistent with evidence that normal translation termination and premature translation termination appear to have significant mechanistic differences (Amrani 2004, Amrani 2006, Ghosh 2010). Studies demonstrated that the ataluren dose-response relationship is bell-shaped (ie, the response initially increases with increasing drug concentrations, but at higher concentrations the response is reduced despite increasing drug concentrations).

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 read-through of premature stop codons due to frameshift mutations (insertions or deletions) or of mRNAs harboring multiple sequential premature stop codons.

Toxicokinetic data were obtained in toxicity studies conducted in mice, rats, rabbits and dogs. Consistent with the short $t_{½}$, 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/day at morning, midday, and evening, respectively. Ataluren is highly bound (> 97%) to plasma proteins in all species, including humans. Ataluren is neither a substrate for nor an inhibitor of P-glycoprotein.

Preclinical studies have suggested that the target ataluren plasma concentrations are similar across multiple diseases. Concentration response studies were performed in various systems including an in vitro translation system. In cell model systems, an ataluren concentration of 10 µg/mL is the most active concentration in a range of cell culture models, including: (1) human and mouse myotube cultures that were used to measure dystrophin protein production and (2) mouse embryonic fibroblasts from the Idua-W392X mouse model of nmHurler syndrome that were used to measure changes in glycosaminoglycan levels. These data show that different cell types demonstrate similar sensitivity to ataluren. In addition, efficacy pharmacology data following oral administration of ataluren in animal models of nmDMD (*mdx* mouse), nmCF (*Cftr-/-FABP-hCFTR-G542X* mouse), and nmHurler syndrome (*Idua-W392X* mouse) support the in vitro data demonstrating that achieving ataluren concentrations that range from ~1 to 20 µg/mL were associated with pharmacodynamic activity. Therefore, across different mouse models and assessing different tissues (brain, intestine, muscle, lung, liver, spleen), activity was seen within the target dose range. Concentrations outside the target range of 1 to 20 µg/mL result in reduced activity (bell-shaped concentration response).

Enzyme inhibition studies with human liver microsomes showed that ataluren has a weak potential for direct inhibition of cytochrome P450 (CYP) 2C8 and CYP2C9. As an added measure of safety, investigators should pay specific attention to the 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 uridine 5'-diphospho-glucuronosyltransferase (UGT) 1A9 and breast cancer resistance protein (BCRP). Caution should be exercised when ataluren is co-administered with drugs that are inducers of UGT1A9, or inhibitors of BCRP (eg, systemic cyclosporine, eltrombopag, gefitinib). Note: Topical cyclosporine therapy is permitted.

In vitro data indicate that ataluren is an inhibitor of UGT1A9, organic anion transporter (OAT)-1, OAT3, and OATP1B3. Caution should be exercised when ataluren is co-administered with drugs that are substrates of UGT1A9 (eg, propofol, mycophenolate mofetil), OAT1, OAT3, or OATP1B3 (eg, oseltamivir, acyclovir, ciprofloxacin, captopril, furosemide, bumetanide, valsartan, pravastatin, rosuvastatin, atorvastatin, pitavastatin) because of the risk of increased concentration of these drugs. The investigator is encouraged to consult the PTC Therapeutics medical monitor or designee with questions relating to specific drugs and their potential for interactions with ataluren.

Ataluren was evaluated in safety pharmacology studies and was found to have no effects on the cardiovascular system, respiratory system, or central nervous system. In the toxicology program, the major findings observed were species-specific (ie, observed only in one species). 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/day, respectively. Ataluren is a small molecular weight compound, and therefore, is not expected to produce anti-drug antibodies. Ataluren had no effect on the immune system in the toxicology program and in clinical trials; therefore, immunotoxicity studies were not performed with ataluren.

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

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

Refer to the IB for a detailed presentation of efficacy pharmacology, safety pharmacology, toxicology, and pharmacokinetic (PK) data from ataluren nonclinical studies.

1.4 Clinical Data to Date

Ataluren has shown a favorable safety profile in clinical studies. In total, more than 750 subjects, including healthy volunteers as well as patients with several nonsense mutation genetic disorders, have been exposed to ataluren in Phase 1 (Hirawat 2007), Phase 2 (Kerem 2008, Sermet-Gaudelus 2010, Wilschanski 2011, Finkel 2013), and Phase 3 (Bushby2014, Kerem 2014) clinical studies. The effect of ataluren in the treatment of nmDMD has been demonstrated (Bushby 2014), and in July 2014 ataluren was conditionally approved by the EMA for treatment of nmDMD. In addition, in a Phase 3 study of nmCF patients, ataluren-treated patients had fewer pulmonary exacerbations than placebo-dosed patients (Kerem 2014).

In clinical studies of ataluren in other nonsense mutation genetic disorders, particularly nmDMD and nmCF, dose-ranging studies were performed to identify the active dose of ataluren. Three dose levels were evaluated in patients with nmDMD, a disease that predominantly affects skeletal muscle due to mutations in the structural protein dystrophin, and 2 doses were evaluated in patients with nmCF, a channelopathy that primarily affects lung tissue due to mutations in a chloride channel. In both studies, 10, 10, 20 mg/kg was identified as the active dose of ataluren. The first dosing regimen studied in both disease settings was 4, 4, 8 mg/kg, the second dose studied was the 10, 10, 20 mg/kg dose, and, in DMD, a third dose was studied, 20, 20, 40 mg/kg. In both nmDMD and nmCF patients, the 10, 10, 20 mg/kg dose-maintained plasma levels in the predicted efficacious range based on preclinical work in a cell and animal models of disease. Confirmatory studies in both nmCF and nmDMD evaluating the 10, 10, 20 mg/kg dose are either ongoing (CF Study 021) or recently completed (DMD Study 020). Open-label extension studies are ongoing at the 10, 10, 20 mg/kg dose for each of these trials.

Approximately 20% of people suffering from CDKL5 and 20% of people suffering from Dravet syndrome have a nonsense mutation. Because ataluren-induced read-through 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 Dravet syndrome/CDKL5 will exhibit acceptable benefit versus risk.

Refer to the IB for a detailed presentation of safety, efficacy, and PK data from these clinical studies.)

1.5 Study Design

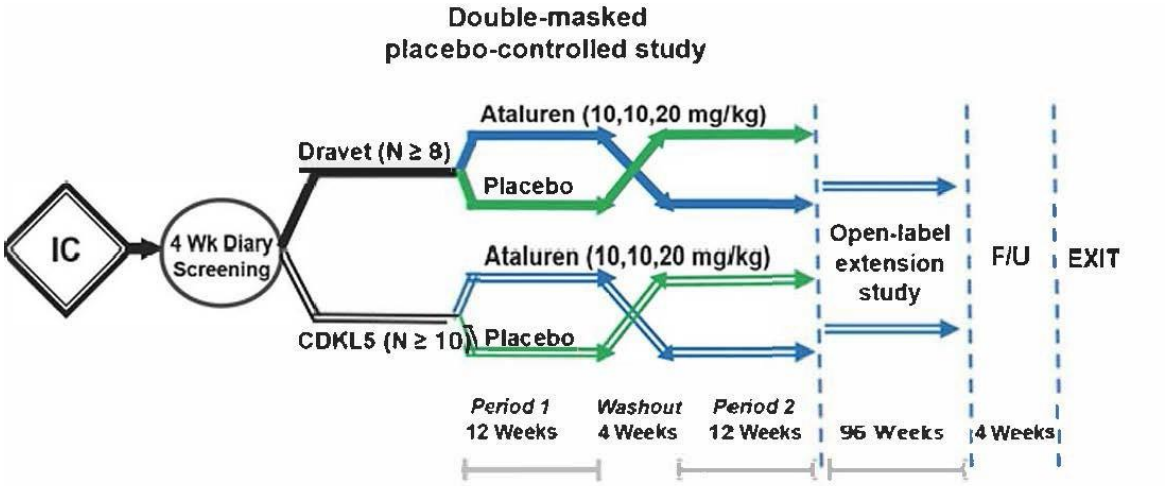
Crossover designs are usually statistically efficient and thus require fewer subjects. Additionally, the influence of confounding covariates is reduced because each crossover subject serves as his or her own control. A 12-week treatment period with ataluren provides sufficient time to assess changes in the subject's seizure activity and QOL while still allowing appropriate monitoring of the subject. Due to the lack of effective alternative treatment, subjects and their parents/legal guardians will be motivated to participate in this study. Therefore, we expect a low dropout rate.

The study to be conducted is a Phase 2 interventional study which includes the following: Screening (Week -4 to Week 0/Day 1), Treatment Period 1 (Week 0/Day 1 to Week 12), Washout Period (Week 12 to Week 16), crossover to Treatment Period 2 (Week 16 to Week 28), and a Follow-up visit after 4 weeks. Subjects who complete this study may be eligible to enroll in a 96-week open-label extension study (Week 28 to Week 124). A Follow-up visit is to occur 4 weeks after the last dose of study drug for all subjects, regardless of whether a subject discontinues prematurely or completes the End-of-Study (EOS) visit and/or the open-label extension. For subjects who enroll in the extension study, Follow-up is scheduled to occur at Week 128. The opportunity to enroll in the extension study will be explained to subjects during the initial study informed consent by the site investigator; subjects enrolling in the extension study do not need to re-consent.

The treatment period in this study ends at Week 124 (Visit 11). However, for subjects that want to continue on study medication beyond Week 124, PTC Therapeutics will continue to supply drug. All subsequent visits will be standard of care and any blood work will be at the discretion of the investigator. A follow up visit for subjects who do not want to continue will be scheduled 4 weeks following the last dose. Access to study drug will continue until commercial availability of ataluren for this indication or until a positive risk-benefit assessment in this indication is not demonstrated whichever is first.

The study design is shown in Figure 2. The Schedule of Events is provided in Table1.

Figure 2: Study Design



Note: Subjects have the option to continue receiving open-label drug upon completion of the 96-week open-label extension. The Follow-up visit is to occur 4 weeks after the last dose of study drug, regardless of whether the subject discontinues prematurely or completes the EOS visit and/or the open-label extension.
Abbreviations: EOS = end of study; F/U = follow-up; IC = informed consent; Wk = week

1.5.1 Drug Administration Plan

Subjects will receive 12 weeks of ataluren or placebo during each treatment period. Treatment Period 1 will be followed by a 4-week Washout Period. Based on ataluren PK and pharmacodynamic data, the 4-week washout period is deemed an appropriate length of time to eliminate any ataluren drug effects. Following the Washout Period, subjects will crossover to receive the opposite treatment during Treatment Period 2 as follows:

- Subjects receiving ataluren during Treatment Period 1 will receive placebo during Treatment Period 2.
- Subjects receiving placebo during Treatment Period 1 will receive ataluren during Treatment Period 2.

Study drug will be administered 3 times per day (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.

Dosing will be based on the subject's body weight at Baseline. Weight will be assessed at every clinic visit. If the subject's body weight changes by ≥ 10% from Baseline, the actual dose may be re-calculated.

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 Treatment Period, the last dose of study drug will be taken on the evening before the clinic visit (ie, the night before the Visit 4/Week 12 [end of Treatment Period 1] and the night before Visit 7/Week 28 [end of Treatment Period 2]).

1.5.2 Research Risks & Benefits

1.5.2.1 Risk of Study Drug

Ataluren has been studied in previously completed as well as ongoing clinical trials for other diseases. The side effects of ataluren indicated in trials include vomiting, nausea, abdominal pain, headache, pyrexia, rhinitis, and sinusitis. All subjects will be closely monitored for adverse events (AEs) throughout the study.

CYP Inhibition

Ataluren is a weak inhibitor of CYP2C9 and CYP2C8. Clinical drug interaction studies between ataluren and CYP2C8 and CYP2C9 substrates have not been conducted. Ataluren has the potential to increase the plasma concentration of drugs that are primarily metabolized by CYP2C8 or CYP2C9, which includes drugs with a narrow therapeutic index that are substrates of CYP2C8 or CYP2C9. The effects of other concomitant AEDs and other drug levels metabolized by these enzyme systems are not known, but it may increase their levels leading to potential toxicities. Therefore, AED plasma levels will be measured at Baseline (pre-dose of AED) and 6 weeks following the first ataluren dose in each Treatment Period (ie, Visit 3/Week 6 and Visit 6/Week 22), Visit 5/Week 16, , Visit 7/Week 28 [EOS], and Visit 8/Week 52, and Visit 11/Week 124 [EOT]. Antiepileptic drugs may be adjusted as needed based on signs and symptoms of toxicity and/or changes in drug levels.

1.5.2.2 Potential Benefits

Both the CDKL5 and the Dravet syndromes are conditions that lead to devastating neurological, developmental, and physical conditions that significantly impair the QOL of the affected patients. Current therapeutic approaches to treat these conditions are limited in efficacy. There is a high unmet medical need for an effective treatment for CDKL5 and Dravet syndromes.

Evaluation of ataluren as a treatment for nonsense mutation CDKL5 or Dravet syndromes has sound scientific rationale founded on activity data from nonclinical disease models and clinical data from patients with other nonsense mutation 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.

The potential benefits of this study include the possibility of reduced seizure frequency due to the addition of ataluren to the patient's current AED regimen. We hope that knowledge gained about the efficacy and tolerability of ataluren during this study will benefit all study participants' QOL by reducing their seizure frequency.

Given the seriousness of these conditions and the limitations of available therapies, the aggregate potential benefits relative to the potential risks support further development of ataluren for these diseases.

1.5.3 Justification for Inclusion of Minors

In the clinic, ataluren has already been administered to patients as young as 3 years old. A Phase 2 study of ataluren in patients with methylmelonic acidemia (MMA) enrolled 11 patients, including 2 patients who were 3 years old and 1 patient who was 4 years old. All 3 of these patients 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.

In the MMA study, 24-hour blood sampling for ataluren PK assessments was performed on Day 28 of each cycle (ie, the data from Cycle 2, in which a dose of 10, 10, 20 mg/kg was administered). Ataluren plasma concentrations in the 3 patients < 6 years old were comparable to ataluren plasma concentrations in the 8 patients ≥ 6 years old who participated in this study. Mean area under the curve from 0 to 24 hours was 279.3 h•µg/mL and 358.4 h•µg/mL for patients < 6 and ≥ 6 years old, respectively, on Day 28 of Cycle 2. Mean maximum plasma concentration was 28.2 µg/mL and 29.9 µg/mL for patients < 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 patients < 6 and ≥ 6 years old.

Ataluren was well-tolerated by the 3 patients < 6 years old in the MMA study. Treatment-emergent adverse events (TEAEs) in these patients were vomiting, pyrexia, nasopharyngitis, cough, flatulence, and rash. All TEAEs were mild or moderate in severity, and none were serious or led to discontinuation of treatment. Overall, the ataluren safety profile was similar in those < 6 years old and those ≥ 6 years of age.

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 patient visits and blood draws while maximizing the amount and quality of data required to effectively achieve the study objectives.

Study of children including the age group from > 2 to 6 years 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 the favorable benefit/risk profile of ataluren.

2 STUDY OBJECTIVES AND ENDPOINTS

2.1 Objectives

The primary objective of this study is to:

- Evaluate changes in convulsive and/or drop seizure frequency from Baseline following ataluren treatment in subjects with CDKL5 or Dravet syndrome resulting from a nonsense mutation.

The secondary objectives of this study are to:

- To determine changes in minor seizure types (absence, myoclonic, complex partial/focal dyscognitive) following ataluren treatment in subjects with CDKL5 or Dravet syndrome resulting from a nonsense mutation. (Seizure types as defined by the International League Against Epilepsy [ILAE] criteria [Appendix A].)
- Characterize the safety profile of ataluren in subjects with CDKL5 or Dravet syndrome resulting from a nonsense mutation

The exploratory objectives of this study are to:

- Evaluate changes from Baseline in cognitive, motor, and behavioral function as well as QOL following ataluren treatment in subjects with CDKL5 or Dravet syndrome resulting from a nonsense mutation.

2.2 Endpoints

2.2.1 Primary Endpoint

The primary study endpoints of this study include:

- Change in convulsive and/or drop seizure frequency from baseline. Convulsive/Motor seizures to be counted are tonic-clonic seizures, hemiconvulsive seizures, atonic/drop attacks, tonic seizures, and focal motor seizures.
- The effect on myoclonic seizures (ie, persistence or disappearance) will also be evaluated.
- Data will be collected at Baseline and at each 6-week post-Baseline visit to identify changes in:
    - Number of episodes of status epilepticus, defined as a convulsion lasting > 10 minutes
    - Number of uses of rescue medications
    - Number of emergency room visits/hospitalizations

2.2.2 Secondary Endpoints

The secondary endpoints of this study are as follows:

- Changes in minor seizure types:
  - Number of myoclonic seizures
  - Number of staring (absence or complex partial) seizures
  - Number of other seizure types (atypical; absence, pure sensory seizure, etc)

2.2.3 Exploratory Endpoints

Exploratory endpoints will include the severity of epilepsy, cognitive and motor scales, QOL, and safety and tolerability will be assessed using the following instruments:

- Clinical and adaptive measures of personality and behavior using the Behavior Assessment System for Children: Third Edition (Sabaz 2003)
- Adaptive level of behavioral function as measured by the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) (Sparrow 2005)
- QOL as assessed by the Quality of Life in Childhood Epilepsy (QOLCE) (Sabaz 2003)

3 SUBJECT SELECTION AND WITHDRAWAL

All subjects and/or their parent/legal guardian must sign the appropriate informed consent prior to beginning any study-related activities, including Screening procedures. Additionally, an assent form should be signed by subjects age 7 to 12 years old, unless lacking capacity.

3.1 Inclusion Criteria

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

1. Age ≥ 2 years old and ≤ 12 years old, male or female, at Week 0 (at time informed consent/assent is signed)
2. Documentation of a diagnosis of Dravet syndrome or CDKL5 deficiency resulting from a nonsense mutation in 1 allele, as evidenced by medical records, genetic testing, and the following clinical feature:
    a. Failure to control seizures despite appropriate trial of 2 or more AEDs at therapeutic doses
3. Between 1 to 3 baseline AEDs at stable doses for a minimum of 4 weeks prior to enrollment (ie, Screening visit)
    a. Vagus nerve stimulator (VNS), ketogenic diet, and modified Atkins diet do not count towards this limit but must be unchanged for 3 months prior to enrollment (Screening).
4. VNS must be on stable settings for a minimum of 3 months prior to the Baseline visit
5. If on ketogenic or modified Atkins diet, must be on stable ratio for a minimum of 3 months prior to the Baseline visit
6. Written consent obtained from the subject or subject's legal representative must be obtained prior to performing any study procedures
7. Minimum of 6 convulsive or drop seizures with duration > 3 seconds over the 4 weeks of diary screening prior to randomization and ≥ 6 convulsive or drop seizures with duration > 3 seconds during the 4 weeks from Screening to Baseline.

3.2 Exclusion Criteria

Subjects cannot be included in the study if any of the following exclusion criteria are met:

1. Subject is < 2 years old or >12 years old
2. Epilepsies associated with genetic disorders other than Dravet syndrome or CDKL5 deficiency
3. Subject has Dravet or CDKL5 genetic mutations that are NOT nonsense mutations
4. Felbamate has been initiated within the past 12 months prior to the Screening Visit
5. Subjects who are currently or have participated in clinical trials in the 30 days prior to enrollment (Screening Visit)

6. Prior or ongoing medical condition (eg, concomitant illness, 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 thecourse of study drug administration or follow-up would be completed, or could impair the assessment of study results
7. Ongoing intravenous administration of aminoglycosides or vancomycin.

3.3 Subject Recruitment and Screening

Approximately eight nonsense mutation Dravet syndrome subjects and 10 nonsense mutation CDKL5 subjects will be recruited for the study from the Principal Investigator or sub-investigator's clinical practice at New York University Comprehensive Epilepsy Center (NYU CEC). All subjects will have had diagnoses confirmed by a geneticist. If this has not been done, then they will be referred to a neurogeneticist at New York University Langone Medical Center (NYULMC). During a routine visit, subjects who meet criteria for the study (or their parents/legal guardians) will be asked if they would like to participate in the study. Male and female subjects of any ethnicity between ages of 2 and 12 (inclusive) will be assessed for inclusion. During the routine visit, the investigator will inform each prospective subject/parent/legal guardian of the nature of the study, and explain the potential risks and study-related procedures. If the subject/parent/legal guardian agrees, they will be given the informed consent documents to read and sign prior to starting any study procedures. Only the Principal Investigator, sub-investigators, and other research personnel listed on the study will have access to subject information. Once the study subject/parent/legal guardian has signed the informed consent, the investigator will explain the study during the routine visit and inform the subject and surrogate that a capacity assessment will be performed to determine whether the subject is capable of providing an informed decision to participate in the study. At this time, a capacity assessment will be conducted if the subject does not refuse the assessment. Capacity will be assessed through neurological examinations and neuropsychology reports conducted by the physician as well as learning and/or development delays that have been documented. If there is already documentation of lack of capacity, no assessment will be needed. If it has been determined by the investigator that the subject has capacity, they will be given the assent formto review. The investigator will go over the study as described in the assent form including study visits and procedures. The subject will be allowed time to ask questions. If the subject is comfortable, then they can sign the assent. All documentation will be placed in the study binder and documented in the study visit note. A copy of the informed assent and consent documents will be given to the subject and the subject's parent/legal guardian. Screening procedures may begin. The Screening Period is 4 weeks, during which study candidates must complete a diary documenting the frequency and duration of convulsive or drop seizures.

Refer to Section 6 for the Schedule of Events and specific requirements for each study visit.

3.4 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.

Eighteen subjects (8 with CDKL5 syndrome and 10 with Dravet syndrome) will be enrolled. Within each disorder group, subjects will be randomized in a 1:1 ratio to 1 of 2 possible treatment assignments during Treatment Period 1:

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

3.5 Masking

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 before study completion will only occur in the case of subject emergencies. Except for emergency unmasking, individual subjects and their parents/legal guardians 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 the investigator.

3.6 Early Withdrawal of Subjects

3.6.1 When and How to Withdraw Subjects

A subject may be discontinued from study drug at any time if the subject, subject's legal guardian, or the investigator feels that it is not in the subject's best interest to continue (see also Section 7). The following is a list of possible reasons for study drug discontinuation:

1. Parental/legal guardian withdrawal of consent.
2. Subject is not compliant with study procedures.
3. Protocol violation requiring discontinuation of study drug.
4. Severe adverse events, including significant toxicity such as severe cognitive or behavioral toxicity, impaired liver and renal function, or impaired hematopoiesis.
5. Seizure exacerbation not attributable to other known provocative factors.
6. Interaction with concomitant AED regimen that leads to unacceptable toxicity. Medication adjustments will be avoided, if possible, and may require the subject to exit the study, at the discretion of the Investigator.

Specific drug-related toxicities will be assessed and managed by the Principal Investigator.

Depending on the nature of the signs (eg, changes in serum chemistries, liver function tests) or symptoms (eg, rash), the subject will be assessed to determine the severity and likelihood of relation to study medication. Based on this assessment, the medication may be discontinued, the dose may be reduced, or the drug may be continued with ongoing assessment. If the study drug is discontinued due to a suspected toxicity, it will only be restarted if there is strong evidence that the toxicity was likely not related to the study medication (eg, liver tests were elevated due to a cytomegalovirus infection).

If a subject must discontinue study drug, the method for discontinuation from study drug will be determined based on the type of reaction and/or reason for withdrawal. For example, if the subject experiences a rapidly progressive rash, it would lead to abrupt cessation of study drug,

but if subject experiences excess tiredness, study drug may be tapered off. A discussion of the method of cessation will occur between the subject and/or subject's parent/legal guardian and the physician.

3.6.2 Data Collection and Follow-up for Withdrawn Subjects

For all subjects who withdraw from the study, there will be 1 final visit 4 weeks after the last dose of study drug (Follow-up Visit). If the subject/parent/legal guardian cannot be contacted after 4 phone calls to subject/parent/legal guardian, a certified letter will be sent to the subject/parent/legal guardian.

Refer to Section 6 for the Schedule of Events and specific requirements for each study visit.

4 STUDY DRUG

4.1 Description

4.1.1 Ataluren

Ataluren will be provided as a white to off-white granules for oral suspension. The drug substance and drug product are manufactured under current Good Manufacturing Practices (cGMP) conditions. The formulation includes matrix and suspending agents, surfactants, and various excipients that aid in the manufacturing process. The powder for oral suspension is packaged in aluminum foil, child-resistant sachets (packets) and supplied in dose strengths containing 125, 250, or 1000 mg of the active drug substance. All of the excipients have been tested to pharmaceutical or food grade and are generally recognized as safe. (See also Section 1.2.1 for additional details.)

4.1.2 Placebo

A white to off-white powder placebo formulation will be provided for oral suspension. The placebo formulation has been manufactured under cGMP conditions. The dry powder 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 (packets) matching each of the 125-, 250-, and 1000-mg dose strengths of active drug sachets.

4.1.3 Drug Kits

Drug kits will be provided, each of which contains 90 sachets of 1 of the dose strengths (125, 250, or 1000 mg or matching placebo).

4.2 Treatment Regimen

Subjects will receive 90 days (12 weeks + 6 days) of masked ataluren or placebo during each treatment period. Each subject will start at a dose based on their weight in kilograms. The study drug is to be administered in a TID fashion of 10 mg/kg, 10 mg/kg and 20 mg/kg (morning, midday, and evening, respectively). The dose will be administered from 125, 250, and 1000 mg foil packets.

Dosing will be based on the subject's body weight at Baseline. Weight will be assessed at every clinic visit. If the subject's body weight changes by ≥10% from Baseline, the actual dose maybe re-calculated.

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 Treatment Period, the last dose of study drug will be taken on the evening before the clinic visit (ie, the night before the Visit 4/Week 12 [end of Treatment Period 1] and the night before Visit 7/Week 28 [end of Treatment Period 2).

Intervals for dosing should be ~6 hours (D1 hour) between morning and mid-day doses, ~6 hours (D1 hour) between mid-day and evening doses, and ~12 hours (D1 hour) between evening doses and the morning dose on the next day.

4.2.1 Instructions for Delays in Dosing

Dosing delays in study drug (masked ataluren or placebo) administration should adhere to the following guidelines:

- If dosing of study drug is delayed by ≤ 1 hour, the planned dose should be taken with no changes to the subsequent dose schedules;
- If study drug 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 study drug dosing is delayed by D 4 hours, the dose should not be taken. Study drug administration may continue but the missed dose should not be taken and the planned timing of subsequent study drug dosing should not be altered.

4.2.2 Study Drug Preparation and Storage

Study drug sachets should be stored at room temperature, away from the reach of children until time of reconstitution and should only be opened at the time of dose preparation. The full contents of each sachet should be mixed with at least 30 mL (1 ounce) of liquid (water, milk, fruit punch), or 3 tablespoons of semi-solid food (yogurt or applesauce). The prepared dose should be mixed well before administration. The amount of the liquid or semi-solid food can be increased based on 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 (2°C–8°C), or within 3 hours at room temperature (15°C–30°C).

The clinic staff will instruct each subject or 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 caregiver when drug supplies are dispensed.

4.3 Method for Assigning Subjects to Treatment Groups

This interventional study contains a placebo portion where subjects will not receive active drug therapy beyond the existing background AED regimen. The allocation of ataluren and placebo to treatment number will be completed according to a masked randomization schedule.

Randomization is an accepted means to reduce bias and allows for the highest standard of evidence in documenting a treatment effect. The permuted block randomization technique will be used. Such a method allows the treatment groups to be balanced with respect to the predefined stratification factors as well as for the number of subjects in each arm. The process will be established and performed by experienced clinical research organizations to maximize the integrity and security of the randomization and ensure appropriate access and convenience-of- use by the investigational sites. The method should be sufficient to preclude site personnel from making inferences regarding treatment assignments based on known block sizes. A 1:1 randomization of ataluren to placebo is planned in order to avoid the loss of statistical power associated with an unbalanced randomization.

To minimize the potential compromise of study drug masking and to reduce the chance of inadvertent dosing errors or intentional attempts to mix active drug and placebo within families, if the case occurs, the randomization system will allocate subsequently enrolled family members (eg, siblings) to the same treatment group as the first family member enrolled. There is past precedence for this approach.

When a subject is randomized in the study and is ready to begin study drug, the Principal Investigator or qualified designee will dispense the appropriate quantity of masked study medication and distribute it to the subject and/or subject's caregiver. Extensive instructions on the correct dosage administration and schedule will be discussed and fully understood prior to leaving the appointment.

4.4 Subject Compliance Monitoring

The study team will assess and track subject compliance with the study drug regimen via clinical evaluations and follow-up email or phone calls. The subjects will be seen for clinical evaluations every month for up to the next 10 months on study drug regimen.

Any subject who is significantly non-compliant with the study drug regimen (< 80% or > 120%) will be withdrawn from the study as per the Principal Investigator.

4.5 Prior and Concomitant Therapy

Throughout the study, including during the Treatment Periods with study drug administration, subjects will continue their current AED regimen consisting of 1 to 3 drugs at stable doses for at least 4 weeks prior to the Screening Visit. Concomitant AED concentrations will be collected at the Baseline Visit and during the study to assess for the potential interactions. If the subject has a VNS, the settings must be on stable settings for a minimum of 3 months prior to the Screening Visit. In addition, if the subject is on a ketogenic diet, a stable ratio must be present for at least3 months prior to the Screening Visit. All concomitant AEDs are permitted during the randomized portion of the study; felbamate is allowed if the subject has been on a stable dose for ≥ 12 months prior to the Screening Visit. Epidiolex will be allowed as a concomitant AED as it has received FDA approval. Medication adjustments will be avoided, if possible, and may require the subject to exit the study at the discretion of the investigator. Medication adjustments and changes will be allowed in the open label portion of the study.

4.6 Receiving, Storage, Dispensing, and Return

4.6.1 Receipt of Drug Supplies

Study drug (ie, masked ataluren and masked placebo) will be shipped to the site of the Principal Investigator at NYU from PTC Therapeutics, via FedEx.

Upon receipt of the study drug supplies, an inventory will be performed and a drug receipt log filled out and signed by the person accepting the shipment. The designated study staff will count and verify that the shipment contains all the items noted in the shipment inventory. Any damaged or unusable study drug in a given shipment (active drug or comparator) will be documented in the study files. The investigator will notify PTC Therapeutics of any damaged or unusable study drugs that were supplied to the investigator's site.

4.6.2 Storage

Sachets containing study drug will be stored at controlled room temperature (15°C–30 °C) in a locked room accessible only to study personnel. 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.

4.6.3 Dispensing of Study Drug

Dosing of ataluren will be based on mg/kg of subject body weight and will be adjusted to allow for dosing with up to 3 of the available sachet dose strengths (125 mg, 250 mg, and/or 1000 mg). The entire contents of the sachet will be constituted with the constitution medium and will be administered. Supply of study drug will be calculated based on subject weight and will be provided by the Principal Investigator or qualified designee. Quantity of study drug sachets distributed to each study subject will be noted in a study log upon dispensation. Regular study drug reconciliation will be performed to document drug assigned and drug remaining. This reconciliation will be logged on the drug reconciliation form, and signed and dated by the study team.

4.6.4 Study Drug Accountability, Return and Destruction of Study Drug

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

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

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

A final reconciliation of drug shipped, drug consumed, and drug remaining will be completed at the completion of the study. Any discrepancies noted will be investigated, resolved, and/or documented prior to destruction of unused study drug.

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

4.6.5 Overdose Precautions

For any subject experiencing an overdose (administration of an ataluren dose > 4 times the intended total daily dose level for this protocol [ie, > 160 mg/kg/day]), observation for any symptomatic side effects should be instituted, and vital signs and biochemical and hematological parameters should be followed closely (consistent with the protocol or more frequently, as needed). Appropriate supportive management to mitigate adverse effects should be initiated. Pending the acquisition of sufficient human experience with the drug, use of gastric lavage or induction of emesis is not specifically recommended nor contraindicated. The Principal Investigator must be contacted if an overdose occurs and the overdose must be reported as an AE according to Section 8.5 (or as an SAE if the overdose meets the applicable criteria for an SAE). The Principal Investigator is responsible for reporting the information to PTC Therapeutics.

4.6.6 Inadvertent Exposure and Spill Precautions

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

5 SAFETY MONITORING AND STUDY DRUG TREATMENT MODIFICATION

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

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

For AEs 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) AEs 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 4.1 (see *http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf*) for grading the severity of AEs and laboratory abnormalities.

5.1.1 Evaluation of Adverse Events or Laboratory Abnormalities

The Principal Investigator (Dr. Devinsky) or designee should be notified of any AE or laboratory abnormality that leads to dose interruption and should be apprised of ancillary laboratory or other diagnostic findings and the evolving data from any work-up of the initial abnormality.

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, aspartate aminotransferase, and alanine aminotransferase values), and all concomitant medications should be reviewed. Depending upon changes observed, the recommended diagnostic workup may include more frequent monitoring or further evaluations for viral hepatitis and immune disorders; tests for cholelithiasis; or abdominal ultrasound, computed tomography (CT), magnetic resonance imaging (MRI), or other imaging methods.
- **Renal:** The medical history, 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; CT, MRI, or other imaging methods; and/or renal biopsy.
- Elevation of aspartate aminotransferase or alanine aminotransferase to > 3× baseline will lead to repeat laboratory studies and if these remain elevated, to a reduction in study medication and repeat laboratory studies. No other significant toxicities have been reported with ataluren, and elevated liver function studies are rare.

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

In deciding whether to re-institute study drug after a dose interruption due to any clinically significant safety concern, the investigator should consider factors such as the following (and may confer with the appropriate personnel at PTC Therapeutics if needed):

- Type and severity of the AE or laboratory abnormality
- The potential causal relationship of study drug
- The subject's status in terms of epileptic seizures (frequency and types) and other health conditions
- The ability to monitor for recurrence of the event

If further evaluation reveals that the AE 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 AE or laboratory abnormality, the investigator will interrupt study drug and may confer with the appropriate personnel at PTC Therapeutics if needed regarding the potential need to discontinue study drug permanently.

5.2 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 drug, 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 will be completed (see Section 8.5). In addition, details regarding the reasons for discontinuation and the AEs leading to the discontinuation should be recorded in the source documents and in the appropriate case report form (CRF). The EOS Visit CRF should be completed and appropriate follow-up (at ~4 weeks as per protocol or until recovery from or stabilization of the AE, whichever comes last) should be instituted.

Study drug may be permanently discontinued as a result of an SAE. If study drug is discontinued for lack of efficacy or other side effects, it will be reduced by 50% for 5 days and then discontinued.

6 SCHEDULE OF EVENTS AND STUDY PARAMETERS

6.1 Schedule of Events

The types and timing of data to be recorded are summarized in Table 1.

Table 1 Schedule of Events

Protocol Activities	Screening[a]	Treatment Period 1			4-Week Washout/ Crossover	Treatment Period 2[b]		EOS Visit[c] or Begin Open-Label	Open-Label Extension[d]			End of Treatment	Follow Up[e]
Week (±6 days)	**-4 (Wk -4 to Wk 0; Day -28 to Day 1)**	**0**	**6**	**12**		**16**	**22**	**28**	**52**	**76**	**100**	**124**	**128**
Visit	**1**	**2[f]**	**3**	**4**		**5**	**6**	**7**	**8[g]**	**9**	**10**	**11**	**12**
Informed consent/assent	X												
Medical history	X												
Serum viral screen	X												
Physical examination	X	X		X		X		X	X	X	X	X	X
Height and weight	X	X	X	X		X	X	X	X	X	X	X	X
Vital signs	X	X	X	X		X	X	X	X	X	X	X	X
Seizure data diary provided	X	X	X	X		X	X	X	X	X	X	X	
Seizure data diary collected		X	X	X		X	X	X	X	X	X	X	X
Study drug dispensed		X[h]	X			X[h]	X	X[h]	X[h]	X[h]	X[h]		
Study drug administration		X[i]				X[i]		X[i]					
Study drug compliance and return			X	X			X	X	X	X	X	X	
Adverse events	X	X	X	X		X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X		X	X	X	X	X	X	X	X

Protocol Activities	Screening[a]	Treatment Period 1			4-Week Washout/ Crossover	Treatment Period 2[b]		EOS Visit[c] or Begin Open-Label	Open-Label Extension[d]			End of Treatment	Follow Up[e]
Week (±6 days)	**-4 (Wk -4 to Wk 0; Day -28 to Day 1)**	**0**	**6**	**12**		**16**	**22**	**28**	**52**	**76**	**100**	**124**	**128**
Visit	**1**	**2[f]**	**3**	**4**		**5**	**6**	**7**	**8[g]**	**9**	**10**	**11**	**12**
Blood for CBC, CMP, LFTs, BUN, creatinine levels, serum HCG[j]	X	X		X		X		X	X	X	X	X	
Blood for plasma PK for ataluren[k]			X			X	X						
Blood for plasma PK for AED assessment[l]		X	X			X	X	X	X			X	
Urinalysis	X	X		X		X		X	X	X	X	X	
Behavior Assessment System for Children		X		X		X		X				X	
Vineland Adaptive Behavior Scales		X		X		X		X				X	
Quality of Life in Childhood Epilepsy		X		X		X		X				X	

Abbreviations: AED = antiepileptic drug; BUN = blood urea nitrogen; CBC = complete blood count; CMP = comprehensive metabolic panel; EOS = end of study; EOT = End of treatment; F/U = follow-up; HCG= human chorionic gonadotropin; LFTs = liver function tests; PK = pharmacokinetics; wk = week

a. Screening will occur from Week -4 to Week 0 (ie, 28 days). The ±6 day visit window is not applicable to the Screening Period.

b. During Treatment Period 2, subjects will crossover and begin receiving masked study drug opposite of what they received during Treatment Period 1 (ie, subjects previously receiving masked ataluren will now receive placebo and subjects previously receiving placebo will now receive ataluren).

c. The EOS visit (Week 28) will be completed for all subjects who complete or discontinue early from Treatment Period 1 and 2. Subjects who complete the EOS visit may continue in the open-label portion of the study at Week 28, otherwise a follow-up visit should be scheduled after 4 weeks.
d. All subjects enrolling in the open-label extension study will receive ataluren 10, 10, 20 mg/kg 3 times per day for 96 weeks.
e. The Follow-up visit is to occur 4 weeks after the last dose of study drug, regardless of whether the subject discontinues prematurely or completes the EOS visit and/or the open-label extension.
f. Visit 2 is considered the Baseline Visit. Visit 2 must occur no sooner than 28 days and up to 42 days after Visit 1. All study and laboratory assessments must be completed prior to the first dose of study drug administration.
g. If the subject begins but does not complete the open-label extension, complete EOT (Week 124).
h. The first dose of study drug should be given in the clinic at Visit 2 (Baseline), Visit 5 (Week 16), and, if applicable, in the open-label extension at Visit 7 (Week 28).
i. The last dose of study drug prior to Visit 4/Week 12 (Treatment Period 1) and Visit 7/Week 28 (EOS Visit) should be taken the night before, at home. No morning dose should be taken prior to the clinic visit.
j. Serum HCG samples taken only for female subjects of childbearing potential
k. Ataluren plasma PK will be assessed at 0 hr (pre-dose) at Visit 5/Week 16 and at 0 hr (pre-dose) and 2 hr post-dose at Visit 3/Week 6 and Visit 6/Week 22.
l. AED plasma PK will be assessed at 0 hr (pre-dose of AED, including but not limited to valproate, clonazepam, lamotrigine, topiramate, and levetiracetam).

6.1.1 Screening, Treatment, and Follow-up Periods

The investigator/study staff member must inform each study candidate 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 parent(s)/legal guardian (as required by local regulations) prior to performing any study-related Screening procedures. Screening evaluations for the study will be performed at the clinical research facility. Study participants will report to the clinic on the morning of each scheduled on-site visit and will remain in the clinic until released by the investigator after all study-related procedures have been completed and the subject has been instructed regarding drug storage, reconstitution, and administration.

Adverse events will be assessed beginning at the time of informed consent through the end of the follow-up period.

Subjects must return to the clinic for a follow-up assessment at 4 weeks after the last dose. If subjects enroll in the open-label extension, follow-up assessment will occur 4 weeks after the last dose of the extension period.

6.1.1.1 Visit 1 (Screening, 4 Weeks Prior to Baseline Visit 2)

The Screening Visit (Visit 1) will occur 4 weeks prior to the Baseline Visit during a routine visit at NYU CEC. Screening procedures will proceed as follows:

- Obtain written informed consent/assent.
- Determine if the subject meets the preliminary eligibility criteria:
    - Collect demographic information
    - Collect current and relevant medical history
    - Identify concomitant medications used
    - Identify and confirm stable use AED medications

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

- Vital signs (including systolic and diastolic blood pressure, radial pulse rate, and body temperature): perform in sitting position
- Physical examination
- Height and weight
- Blood draw for clinical laboratory evaluations:
    - Blood urea nitrogen (BUN), complete blood count (CBC), comprehensive metabolic panel (CMP), liver function tests (LFTs) and creatinine levels
    - Serum human chorionic gonadotropin (HCG), as applicable (sample taken only for female subjects of childbearing potential)
    - Serum viral screen
- Urinalysis
- Record any AEs occurring since signing the ICF and any that occur during this visit

- Instruct subject or subject's caregiver to keep a seizure diary for the next 4 weeks, including the following information:
    - Seizure type, duration, intensity
    - Presence or absence of cyanosis
    - Use of rescue medications

6.1.1.2 Visit 2 (Baseline, Week 0)

After the 4-week Screening period, the diary card provided at the Screening Visit will be reviewed and all inclusion/exclusion criteria will be confirmed. Eligible subjects complete the Baseline Visit (Visit 2/Week 0) as follows:

- 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
- Collect seizure diary and review entries
- Record any AEs occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Complete the following QOL assessments:
    - Behavior Assessment System for Children
    - VABS-II
    - QOLCE
- Blood draw for clinical laboratory evaluations
    - CBC, CMP, LFTs, BUN, creatinine, serum HCG
    - Plasma PK for AED level assessment (0 hr, pre-dose)
- Urinalysis
- Dispense new seizure diary and review instructions for completion
- Dispense masked study drug 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.
- Instruct subject to return in 6 weeks for Visit 3

6.1.1.3 Visit 3 (Week 6)

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

- 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

- Collect seizure diary and review entries
- Record any AEs occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Blood draw for plasma PK of ataluren (0 hr, pre-dose, and 2 hr post-dose)
- Blood draw for plasma PK AED level assessment (0 hr, pre-dose)
- Dispense new seizure diary and review instructions for completion
- Review returned study drug and compliance
- Dispense masked study drug and review administration instructions
    - TID dosing 10 mg/kg, 10 mg/kg, 20 mg/kg (morning, midday, evening)
- Instruct subject to return in 6 weeks for Visit 4

6.1.1.4 Visit 4 (Week 12 [Beginning of 4-Week Washout])

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

- 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
- Collect seizure diary and review entries
- Record any AEs occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Blood draw for clinical laboratory evaluations
    - CBC, CMP, LFTs, BUN, creatinine, serum HCG
- Urinalysis
- Complete the following QOL assessments:
    - Behavior Assessment System for Children
    - VABS-II
    - QOLCE
- Review returned study drug and compliance
- Dispense new seizure diary and review instructions for completion
- No study drug will be dispensed at this visit
- Instruct subject to return in 4 weeks for Visit 5.

6.1.1.5 Treatment Period 2 - Visit 5 (Week 16 [Crossover Visit])

The subject will return to the site for Visit 5. Subjects will crossover and begin receiving masked study drug opposite of what they received during Treatment Period 1 (ie, subjects

previously receiving masked ataluren will now receive placebo and subjects previously receiving placebo will now receive ataluren). Visit 5 will proceed as follows:

- 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
- Collect seizure diary and review entries
- Record any AEs occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Blood draw for plasma PK of ataluren (0 hr, pre-dose)
- Blood draw for plasma PK AED level assessment (0 hr, pre-dose)
- Blood draw for clinical laboratory evaluations
    - CBC, CMP, LFTs, BUN, creatinine, serum HCG
- Urinalysis
- Complete the following QOL assessments:
    - Behavior Assessment System for Children
    - VABS-II
    - QOLCE
- Dispense new seizure diary and review instructions for completion
- Dispense masked study drug 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.
- Instruct subject to return in 6 weeks for Visit 6

6.1.1.6 Visit 6 (Week 22)

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

- 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
- Collect seizure diary and review entries
- Record any AEs occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Blood draw for plasma PK of ataluren (0 hr, pre-dose and 2 hr post-dose)
- Blood draw for plasma PK AED level assessment (0 hr, pre-dose)

- Dispense new seizure diary and review instructions for completion
- Review returned study drug and compliance
- Dispense masked study drug and review administration instructions
    - TID dosing 10 mg/kg, 10 mg/kg, 20 mg/kg (morning, midday, evening)
- Instruct subject to return in 6 weeks for Visit 7

6.1.1.7 Visit 7 (Week 28 – EOS Visit [or Early Termination Visit])/Start ofOpen-Label Extension Study

The subject will return to the site for Visit 7. This visit will be considered the EOS visit and should be completed for all subjects. Subjects should have taken their final dose of study drug the night before the clinic visit.

Additionally, any subject who discontinues early from the study should complete this visit.

Visit 7 will proceed as follows:

- 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
- Collect seizure diary and review entries
- Record any AEs occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Blood draw plasma PK for AED level assessment (0 hr, pre-dose)
- Complete the following QOL assessments:
    - Behavior Assessment System for Children
    - VABS-II
    - QOLCE
- Blood draw for clinical laboratory evaluations
    - CBC, CMP, LFTs, BUN, creatinine, serum HCG
- Urinalysis
- Review returned study drug and compliance
- If subject is enrolling in the open-label extension study, dispense new seizure diary and review instructions for completion
- No study drug will be dispensed at this visit if the subject is not enrolling in the open-label extension study.
- If the subject is enrolling in the open-label extension study, open-label study drug willbe dispensed to the subject.

6.1.2 Open-Label Extension Study

6.1.2.1 Visit 8 (Week 52)

The subject will return to the site for Visit 8 (Week 52), of the open-label extension study.
Visit 8 (Week 52) will proceed as follows:

- 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
- Collect seizure diary and review entries
- Review returned study drug and compliance
- Record any AEs occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Blood draw plasma PK for AED level assessment
- Blood draw for clinical laboratory evaluations
    - CBC, CMP, LFTs, BUN, creatinine, serum HCG
- Urinalysis
- Complete the following QOL assessments:
    - Behavior Assessment System for Children
    - VABS-II
    - QOLCE
- Open-label study drug will be dispensed at this visit.
- Dispense new seizure diary and review instructions for completion.

6.1.2.2 Visit 9 (Week 76)

The subject will return to the site for Visit 9 (Week 76).
Visit 9 (Week 76) will proceed as follows:

- 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
- Collect seizure diary and review entries
- Review returned study drug and compliance
- Record any AEs occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Blood draw for clinical laboratory evaluations

- CBC, CMP, LFTs, BUN, creatinine, serum HCG

- Urinalysis
- Open-label study drug will be dispensed at this visit.
- Dispense new seizure diary and review instructions for completion.

6.1.2.3 Visit 10 (Week 100)

The subject will return to the site for Visit 10 (Week 100).

Visit 10 (Week 100) will proceed as follows:

- 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
- Collect seizure diary and review entries
- Review returned study drug and compliance
- Record any AEs occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Blood draw for clinical laboratory evaluations
  - CBC, CMP, LFTs, BUN, creatinine, serum HCG
- Urinalysis
- Open-label study drug will be dispensed at this visit.
- Dispense new seizure diary and review instructions for completion.

6.1.2.4 Visit 11 (Week 124)

The subject will return to the site for Visit 11 (Week 124)

Visit 11 (Week 124) will proceed as follows:

- 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
- Collect seizure diary and review entries
- Review returned study drug and compliance
- Record any AEs occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications
- Blood draw plasma PK for AED level assessment
- Blood draw for clinical laboratory evaluations
  - CBC, CMP, LFTs, BUN, creatinine, serum HCG

- Urinalysis
- Complete the following QOL assessments:
    - Behavior Assessment System for Children
    - VABS-II
    - QOLCE
- For subjects that want to continue on study medication, open-label study drug will be dispensed at this visit.
- For subjects that do not want to continue, study drug will not be dispensed at this visit and subjects will return in 4 weeks for the final follow up.
- Dispense new seizure diary if subject continues to visit 12 and review instructions for completion.

6.1.2.5 Visit 12 (Week 128 [Follow-up Visit])

The Follow-up visit is to occur 4 weeks after the last dose of study drug, regardless of whether the subject discontinues prematurely or completes the EOS visit and/or the open-label extension.

Visit 12 will proceed as follows:

- 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
- Collect seizure diary and review entries
- Record any AEs occurring since last visit and any that occur during this visit
- Record any changes in concomitant medications.

6.2 PK for AED and Ataluren

Antiepileptic drug plasma PK will be assessed at 0 hr (pre-dose of AED). The AED levels will be done prior to the subject taking the medication (trough level). Antiepileptic drug levels will be analyzed by NYU outpatient labs and/or MedTox laboratories.

Ataluren plasma PK will be assessed at 0 hr (pre-dose) at Week 16 and at 0 hr (pre-dose) and 2 hr post-dose at Weeks 6 and 22. Ataluren plasma samples will be shipped to InVentiv Bioanalytical Facility, 301D College Road East, Princeton, NJ 08540, for analysis and levels.

6.3 Blood Collection Summary

Assuming a subject completes the study, the maximum amount of blood to be drawn at a visit is approximately 8 to 20 mL (depending on the number of AEDs the subject is taking and blood withdrawn for the ataluren PK assessment). The total amount of blood to be drawn over the entire study period (including the Screening Visit, Treatment Period 1, Treatment Period 2, and EOS) is approximately 70 mL (depending on the number of AEDs the subject is taking as well as blood samples collected for the ataluren PK assessment).

6.4 Blood for Analysis of Pharmacokinetics

6.4.1 Ataluren Plasma Concentration

Blood for trough ataluren concentrations will be collected at 0 hr (pre-dose) at Visit 5/Week 16 and at 0 hr (pre-dose) and 2 hr post-dose at Visit 3/Week 6 and Visit 6/Week 22. Reference the Instruction Manual for handling ataluren in human PK samples for collection, processing, and shipping details. Samples will be stored at the bioanalytical laboratory for analysis of ataluren parent drug using a validated high-performance liquid chromatography with tandem mass spectrometry method. Thereafter, samples may be retained for potential follow-up analyses of ataluren metabolites.

7 STATISTICS

7.1 Sample Size Determination

The original study was not powered for statistical testing since the primary objective is to characterize the safety profile of ataluren in subjects with CDKL5 or Dravet syndrome resulting from a nonsense mutation. Eighteen subjects (10 with CDKL5 syndrome and 8 with Dravet syndrome) was planned to be included in this study. At the time of protocol amendment, 7 subjects Dravet syndrome have been randomized and 8 subjects with Dravet syndrome have been randomized. Enrolment has been stopped. The number of subjects randomized will provide an initial assessment on the efficacy for subjects with CDKL5 syndrome and with Dravet syndrome.

The number of subjects enrolled in the open-label extension study will be determined by the number of subjects who complete the initial study and remain eligible to participate in the extension study.

7.2 Randomization

Eighteen subjects (10 with CDKL5 syndrome and 8 with Dravet syndrome) will be enrolled. Within each disorder group, subjects will be randomized in a 1:1 ratio to 1 of 2 possible treatment assignments during Treatment Period 1:

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

After the completion of Treatment Period 1 and a 4-week Washout Period, subjects will crossover and begin receiving masked study drug opposite of what they received during Treatment Period 1 (ie, subjects previously receiving masked ataluren will now receive placebo and subjects previously receiving placebo will now receive ataluren).

7.3 Populations for Analyses

Intent-to-Treat (ITT) Population - The ITT Population will contain all randomized subjects.

7.4 Efficacy Endpoint Definitions

7.4.1 Seizures

Based on observational studies of subjects with CDKL5 and Dravet syndrome in other drug studies, mean seizure frequency of 70 with a standard deviation of 65 has been estimated. From the epilepsy literature (Cramer 1999), a clinically meaningful difference will be a ≥ 20% reduction in seizure frequency over placebo.

Seizure activity will be assessed based on ILAE criteria for the following:

- Motor seizure including tonic-clonic seizures, hemiconvulsive seizures, drop attacks, tonic seizures, focal motor seizures.
- Staring seizure is an absence seizure or a complex partial seizure.
- Myoclonic seizure is the persistence or disappearance seizure.
- Episode of status epilepticus: a convulsive state lasting longer than 10 minutes.

Baseline total number of seizures/emergency room visits/hospitalizations is defined as the total number of seizures/emergency room visits/hospitalizations during the 4-week Screening Period (Week -4 to Week 0 [Day 1]).

7.4.2 Clinical and Adaptive Measures of Personality and Behavior

Assessment of clinical and adaptive measures of personality and behavior will be made using the Behavior Assessment System for Children (Third Edition). This is a screening system for measuring behavioral and emotional strengths and weaknesses. It will be conducted by the Principal Investigator or Clinical Research Nurse/Coordinator.

7.4.2.1 Adaptive Level of Behavioral Function

Adaptive level of behavioral function will be measured by the VABS-II (Sparrow 2005). The assessment is used to evaluate the child's ability to adapt to practical, everyday skills that are required to function and meet environmental demands. The assessment will be conducted by the Principal Investigator or Clinical Research Nurse/Coordinator.

7.4.2.2 Quality of Life

Quality of life will be assessed by the QOLCE (Sabaz 2003). This questionnaire is used to evaluate the QOL of these children living with epilepsy. It will be distributed to the caregivers to complete.

7.5 Statistical Analyses

The confidence interval (CI) for the proportion, if presented, will be computed using normal approximation, if the number of the events is at least 5. Otherwise, CI using an exact method will be provided. For safety summaries, CI will not be presented, unless specified otherwise. Summary statistics will be analyzed within each disorder group.

All analyses will be performed using Statistical Analysis System (SAS®), Version 9.0 or higher.

7.5.1 Study Conduct

All protocol deviations will be listed and summarized.

7.5.2 Study Population

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

7.5.2.1 Subject Disposition

The disposition of subjects, including the number of subjects screened, the number of subjects randomized, the number of randomized subjects who received at least 1 dose of study drug, and the number of subjects who prematurely discontinue study drug will be tabulated. The number of subjects enrolled in the open-label extension study will also betabulated.

7.5.2.2 Demographics and Baseline Characteristics

Demographic and baseline characteristics of subjects will be summarized descriptively by means and standard deviations for continuous variables, and frequency distribution for categorical variables. Summaries will be performed based on all randomized subjects (ie, ITT Population).

7.5.2.3 Medical History and Prior Medication

Medical history and prior medication information will be summarized.

7.5.3 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 days): ≤ 28 (≤ 4 weeks), 29 to 42 (4–6 weeks), 43 to 84 (6–12 weeks), 85 to 112 (12–16 weeks), 113 to 154 (16–22 weeks), 155 to 196 (22–28 weeks), 197 to 364 (28-52 weeks), 365 to 532 (52-76 weeks), 533 to 700 (76-100 weeks), 701 to 868 (100-124 weeks), and 869 to 896 (124-128 weeks). The number of subjects in each category as well as the mean duration will also be displayed.

7.5.3.1 Discontinuation of Study Therapy

The ITT Population will be used to summarize discontinuation from study drug as indicated in Section 7 as well as the reason for the premature termination of study drug. The proportion of subjects who discontinue study drug will be summarized using point estimates and 95% CI.

7.5.3.2 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 disorder group and treatment group. 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.

7.6 Safety Analyses

All safety presentations will be based on the ITT Population and will be based only on data included in the analysis period of interest. Listings of all AEs will also be based on all available data at the scheduled analysis time point. Adverse event and SAE summaries will also be presented for the following periods:

- Up to the end of Visit 4 (Week 12)
- Up to the end of Visit 7 (Week 28, EOS Visit)
- Between the start of Week 17 and the end of Week 28.
- Up to the end of the open-label extension (Week 124, if applicable)
- Between the start of Week 29 and the end of Week 124 (if applicable).

Additional frequency tables summarizing the occurrence of AEs and SAEs after the end of the analysis period of interest will also be provided. All AEs and SAEs will be summarized by treatment group. Marked laboratory abnormalities will also be descriptively summarized. No statistical tests will be performed for AEs or laboratory marked abnormalities.

7.6.1 Adverse Events

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

- TEAEs, including clinical and laboratory AEs

- Treatment-related AEs
- TEAEs by severity
- Treatment-related AEs by severity
- SAEs
- AEs leading to discontinuation

Summaries will be presented by treatment groups and categorized by System Organ Class and Preferred Term. The frequencies of AEs displayed will be the crude rates that represent the number of subjects experiencing AEs divided by the total number of subjects.

It should be noted that all laboratory data sent to and analyzed by the NYU laboratory will be reported to the investigator. However, only those laboratory abnormalities meeting the protocol-defined criteria of an AE (ie, those that require clinical intervention or further investigation beyond ordering a repeat [confirmatory] test) should be reported as AEs in the appropriate CRF, whether they were analyzed by the NYU laboratory or another laboratory.

7.6.2 Laboratory Parameters

Changes in clinical laboratory tests from Baseline (last measurement prior to randomization) and laboratory marked abnormalities (laboratory AEs) using pre-defined abnormality criteria will be descriptively 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.

7.6.3 Other Parameters

Height, weight, vital signs, and physical examination data will be descriptively summarized. Concomitant medications will be summarized.

7.7 Efficacy Analyses

All efficacy endpoints will be summarized within each disorder group (Dravet syndrome or CDKL5) and by treatment group.

Summary statistics for the total numbers of the following measurements per 28 days along with percent changes from Baseline per 28 days will be tabulated for the following:

- Convulsive/motor seizures
  - Tonic-Clonic Seizures
  - Hemiconvulsive Seizures
  - Drop Attacks
  - Tonic Seizures
  - Focal Motor Seizures
  - Staring seizures
  - Myoclonic seizures
- Use of rescue medications

- Emergency room visits/hospitalizations

For the primary endpoint, the percent change from baseline in 28 day convulsive seizure frequency in each treatment period, the method from Mary E. Putt and Vernon M. Chinchilli[1] will be used. In short, differences d_{ij} between two treatment periods in percent change in total seizure frequency per 28 days will be calculated for each patient, where i is the sequence and j is the patient. Wilcoxon rank sum test and Hodges–Lehmann confidence interval will be applied to the two sequences dij, as in [1].

As a supportive analysis rank mixed models will also be used. The rank of percent change from baseline in 28 day total seizure frequency in each treatment period are used as dependent variables, with the rank of baseline 28 day total seizure frequency, treatment group, treatment sequence and treatment period as fixed factors, subjects within treatment sequence as random factors. The rank mixed model will be applied in each disorder group separately.

Summary statistics at each measurement time point, along with changes from Baseline will be tabulated for:

- Behavior Assessment System for Children
- VABS-II
- QOLCE

The same methods described above to assess efficacy outcome measures will be continued for subjects that enroll in the extension study up to Week 124 or final dose, if prematurely discontinued.

8 SAFETY AND ADVERSE EVENTS

8.1 Definitions

8.1.1 Unanticipated Problems Involving Risk to Subjects or Others

Any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in nature, severity, or frequency (ie, not described in study-related documents such as the Institutional Review Board (IRB)-approved protocol or consent form, the IB, etc)
- Related or possibly related to participation in the research (ie, possibly related means there is a reasonable possibility that the incident experience, or outcome may have been caused by the procedures involved in the research)
- Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm).

8.1.2 Adverse Event

An AE is any symptom, sign, illness, or experience that develops or worsens in severity during the course of the study. Intercurrent illnesses or injuries should be regarded as AEs. Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:

- results in study withdrawal
- is associated with an SAE
- is associated with clinical signs or symptoms
- leads to additional treatment or to further diagnostic tests
- is considered by the investigator to be of clinical significance

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

- All AEs that are suspected or are not suspected to be due to study drug.
- Overdose (administration of a study drug dose > 4 times the highest intended total daily dose level for this protocol [> 160 mg/kg/day]) of study drug.
- All reactions from medication misuse, abuse, withdrawal, sensitivity, or toxicity.
- All reactions that result from medication errors or uses of the study drug outside what is described in the protocol.
- Apparently unrelated illnesses, including the worsening of a preexisting illness.
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate AEs. The outcome of the accident (hip fracture secondary to the fall) should be recorded in source documents.

- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- A pre-existing condition (eg, allergic rhinitis) must be noted on the appropriate CRF for Visit 1, but should not be reported as an AE unless the condition worsens or episodes increase in frequency during the AE reporting period. Diagnostic and therapeutic non-invasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE 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 AE. Note that, as described in the SAE paragraph below, any inpatient hospitalization occurring as the consequence of an AE during the study period should be reported as an SAE.

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

8.1.3 Serious Adverse Event

Adverse events are classified as serious or non-serious. A ***serious adverse event*** is any AE that is:

- fatal
- life-threatening
- requires or prolongs hospital stay
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event

Important medical events are those that may not be immediately life threatening, but are clearly of major clinical significance. They may jeopardize the subject, and may require intervention to prevent one of the other serious outcomes noted above. For example, study drug or other drug overdose or abuse, a seizure that did not result in inpatient hospitalization, or intensive treatment of bronchospasm in an emergency department would typically be considered serious.

Overdose of study drug is considered to be administration of a study drug dose > 4 times the intended total daily dose level for this protocol (> 160 mg/kg/day).

All AEs that do not meet any of the criteria for serious should be regarded as non-serious AEs.

Note that any SAEs occurring within 4 weeks of the date of last dose should be reported to the investigator who will notify PTC Therapeutics.

8.2 Adverse Event Reporting Period

The study period during which AEs must be reported is defined as the period from the initiation of any study procedures (ie, after informed consent is given) to the end of the study drug follow-up. For this study, the study drug follow-up is defined as 4 weeks following the final administration of study drug.

8.2.1 Preexisting Condition

A preexisting condition is one that is present at the start of the study. A preexisting condition should be recorded as an AE if the frequency, intensity, or the character of the condition worsens during the study period.

8.2.1.1 General Physical Examination Findings

At screening, any clinically significant abnormality should be recorded as a preexisting condition. At the EOS Visit, any new clinically significant findings/abnormalities that meet the definition of an AE will also be recorded and documented as an AE.

8.2.2 Post-study Adverse Event

All unresolved AEs will be followed by the Investigator until the events are resolved, the patient is lost to follow-up, or the AE is otherwise explained. At the last scheduled visit, the investigator will instruct each subject to report any subsequent event(s) that the subject, or the subject's personal physician, believes might reasonably be related to participation in this study. The investigator will notify PTC Therapeutics of any death or AE occurring at any time after a subject has discontinued or terminated study participation that may reasonably be related to this study. The investigator will notify PTC Therapeutics if he becomes aware of the development of cancer or of a congenital anomaly in a subsequently conceived offspring of a subject that has participated in this study.

8.2.3 Abnormal Laboratory Values

A clinical laboratory abnormality will be documented as an AE if any one of the following conditions is met:

- The laboratory abnormality is not otherwise refuted by a repeat test to confirm the abnormality.
- The abnormality suggests a disease and/or organ toxicity.
- The abnormality is of a degree that requires active management: change of dose, study drug discontinuation, more frequent follow-up assessments, further diagnostic investigation, etc.

8.3 Hospitalization, Prolonged Hospitalization or Surgery

Any AE that results in hospitalization or prolonged hospitalization will be documented and reported as an SAE unless specifically instructed otherwise in this protocol. Any condition

responsible for surgery will be documented as an AE if the condition meets the criteria for an AE.

Neither the condition, hospitalization, prolonged hospitalization, nor surgery are reported as an AE in the following circumstances:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for a preexisting condition. Surgery should ***not*** be reported as an outcome of an AE if the purpose of the surgery was elective or diagnostic and the outcome was uneventful.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.
- Hospitalization or prolonged hospitalization for therapy of the target disease of the study, unless it is a worsening or increase in frequency of hospital admissions as judged by the clinical investigator.

8.4 Recording of Adverse Events

At each contact with the subject, the investigator will seek information on AEs by specific questioning and, as appropriate, by examination. Information on all AEs will be recorded immediately in the source document, and also in the appropriate AE module of the CRF. All clearly related signs, symptoms, and abnormal diagnostic procedures results will be recorded in the source document, but should be grouped under one diagnosis whenever possible.

All AEs occurring during the study period will be recorded. The clinical course of each event will be followed until resolution, stabilization, or until it has been determined that the study drug or participation is not the cause. Serious adverse events that are still ongoing at the end of the study period will be followed up to determine the final outcome. Any SAE that occurs after the study period and is considered to be possibly related to the study drug or study participation will be recorded and reported immediately.

8.5 Reporting of Serious Adverse Events and Unanticipated Problems

The investigator will conform to the AE reporting timelines, formats, and requirements of the various entities to which they are responsible, but at a minimum those events that will be reported are those that meet any of the following criteria (see also Section 8.1):

- Related to study participation
- Unexpected
- Serious or involve risks to subjects or others (see Section 8.1).

8.5.1 Narrative Reports of Safety Events

If the report is supplied as a narrative, the minimum necessary information to be provided at the time of the initial report includes the following:

- Study identifier
- Study Center
- Subject number
- A description of the event
- Date of onset
- Current status
- Whether study drug was discontinued
- The reason why the event is classified as serious
- Investigator assessment of the association between the event and study drug

8.5.2 Investigator Reporting: Notifying the Supplier of the Study Drug (PTC Therapeutics)

This study is a physician-sponsored intermediate-sized study.

The following describes events that will be reported to the supplier of the study drug in an expedited fashion.

8.5.2.1 Initial Report: Within 24 Hours

The following events will be reported to PTC Therapeutics within 24 hours of awareness of the event:

- Unanticipated problems related to study participation
- Serious adverse events, regardless of whether they are unexpected.

Additionally, an SAE report form will be completed and emailed to the following mailbox within 24 hours. The investigator will maintain a copy of the form on file at the study site.

E-mail: Pharmacovigilance@ptcbio.com

8.5.2.2 Follow-up Report: Within 48 Hours

As a follow-up to the initial report, within the following 48 hours of awareness of the event, the investigator will provide further information, as applicable, on the unanticipated adverse event or the unanticipated problem in the form of a written narrative. This will include a copy of the completed Unanticipated Problem form, and any other diagnostic information that will assist the understanding of the event. Significant new information on ongoing unanticipated adverse effects will be provided promptly to the supplier of the study drug.

8.5.2.3 Other Reportable Events

Deviations from the protocol will receive the investigator's IRB approval before they are initiated. Any protocol deviations initiated without the investigator's IRB approval that may affect the scientific soundness of the study, or affect the rights, safety, or welfare of study

subjects, will be reported to the investigator's IRB as soon as a possible, but ***no later than 5 working days*** of the protocol deviation.

8.5.3 Investigator Reporting: Notifying the IRB

Federal regulations require timely reporting by investigators to their local IRB of unanticipated problems posing risks to subjects or others. The following describes the NYULMC IRB reporting requirements, though investigators at participating sites are responsible for meeting the specific requirements of their IRB of record.

8.5.4 Report Promptly, but No Later Than 5 Working Days:

Researchers are required to submit reports of the following problems promptly but no later than 5 working days from the time the investigator becomes aware of the event:

- Unanticipated problems including AEs that are unexpected and related
    - Unexpected: An event is "unexpected" when its specificity and severity are not accurately reflected in the protocol-related documents, such as the IRB-approved research protocol, any applicable IB, and the current IRB-approved informed consent document and other relevant sources of information, such as product labeling and package inserts.
    - Related to the research procedures: An event is related to the research procedures if in the opinion of the Principal Investigator, the event was more likely than not to be caused by the research procedures.
- Harmful: either caused harm to subjects or others, or placed them at increased risk

8.5.4.1 Other Reportable Events:

The following events also require prompt reporting to the IRB, though ***no later than 5 working days***:

- ***Complaint of a research subject*** when the complaint indicates unexpected risks or the complaint cannot be resolved by the research team.
- ***Protocol deviations or violations*** (includes intentional and accidental/unintentional deviations from the IRB approved protocol) for any of the following situations:
    - One or more participants were placed at increased risk of harm
    - The event has the potential to occur again
    - The deviation was necessary to protect a subject from immediate harm
- ***Breach of confidentiality***
- ***Incarceration of a participant*** when the research was not previously approved under Subpart C and the investigator believes it is in the best interest of the subject to remain on the study.
- ***New information indicating a change to the risks or potential benefits*** of the research, in terms of severity or frequency (eg, analysis indicates lower-than-expected response

rate or a more severe or frequent side effect; other research finds arm of study has no therapeutic value; FDA labeling change or withdrawal from market).

8.5.4.2 Reporting Process

The reportable events noted above will be reported to the IRB using the form "Reportable Event Form" or as a written report of the event (including a description of the event with information regarding its fulfillment of the above criteria, follow-up/resolution, and need for revision to consent form and/or other study documentation).

Copies of each report and documentation of IRB notification and receipt will be kept in the clinical investigator's study file.

8.5.5 Sponsor Reporting: Notifying the FDA

The Principal Investigator at NYU, in collaboration with PTC Therapeutics, is required to report certain study events in an expedited fashion to the FDA. These written notifications of AEs are referred to as IND safety reports. In order for the study sponsor to notify the FDA within the required timelines, after notification that an event meeting serious criteria has occurred, the following information will be obtained within the timelines noted:

- ***Within 4 calendar days*** *(via telephone or facsimile report)*

  Any study event that is:

  - Associated with the use of the study drug
  - Unexpected
  - Fatal or life-threatening

- *Within 10 calendar days (via written report)*

  Any study event that is:

  - Associated with the use of the study drug,
  - Unexpected
  - Serious, but not fatal or life-threatening

    -or-

  - A previous AE that was not initially deemed reportable but is later found to fit the criteria for reporting (reporting within 15 calendar days from when event was deemed reportable).

  Any finding from tests in laboratory animals that:

  - Suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

Additional reporting requirements

The Principal Investigator at NYU, in collaboration with PTC Therapeutics, is also required to identify in IND safety reports all previous reports concerning similar AEs and to analyze the significance of the current event in light of the previous reports.

Reporting Process

Adverse events may be submitted on FDA Form 3500A (MEDWATCH Form) or in a narrative format. If supplied as in a narrative format, the minimum information to be supplied is noted in Section 8.5. The contact information for submitting IND safety reports is noted below:

Jack Dan, RPh

Regulatory Project Manager

Food and Drug Administration

Center for Drug Evaluation and Research

Division of Neurology Products

5901-B Ammendale Road

Beltsville, MD 20705-1266

Office:(240)-402-6940

Fax:(301)796-9842
Email: Jack.Dan@fda.hhs.gov

8.6 Unmasking Procedures

All subjects will receive a pack (depending on the visit) of study drug according to the randomization code. The identity of study drug (placebo vs ataluren) assigned to subjects will be contained in individually sealed randomization code-break mailers, held by the investigator. The Principal Investigator is responsible for ensuring that information on how to access the treatment allocation for an individual subject is available to the relevant staff in case of an emergency and unmasking is required. A subject's treatment assignment should only be unmasked when knowledge of the treatment is essential to make a decision on the medical management of the subject. Unmasking for any other reason will be considered a protocol deviation. Subjects whose treatment is unmasked will be withdrawn from the study (Section 7).

8.7 Medical Monitoring

It is the responsibility of the Principal Investigator to oversee the safety of the study at his/her site. This safety monitoring will include careful assessment and appropriate reporting of AEs as noted above, as well as the construction and implementation of a site data and safety-monitoring plan (see Section 10 Data Safety Monitoring Plan). Medical monitoring will include a regular assessment of the number and type of SAEs.

9 DATA HANDLING AND RECORD KEEPING

9.1 Confidentiality

Research records will be collected and stored in a manner that protects the confidentiality of subject information. Research records such as laboratory test results, study notes, questionnaires, and CRFs will be collected at the time of the visit from the study subjects. This information will be stored in subject study binders that will be located at the Epilepsy Center in a locked room. Only the research team will have access to the key and the information. The names and identities of all research subjects will be kept in strict confidence and will not appear on the CRFs or other records provided to or retained by the investigator or 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 the investigator or PTC Therapeutics. The informed consent form must include appropriate statements explaining these requirements.

9.2 Confidentiality and HIPAA

Information about study subjects will be kept confidential and managed according to the requirements of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Those regulations require a signed subject authorization informing the subject of the following:

- What protected health information (PHI) will be collected from subjects in this study
- Who will have access to that information and why
- Who will use or disclose that information
- The rights of a research subject to revoke their authorization for use of their PHI.

In the event that a subject/parent/legal guardian revokes authorization to collect or use PHI, the investigator, by regulation, retains the ability to use all information collected prior to the revocation of subject authorization. For subjects that have revoked authorization to collect or use PHI, attempts should be made to obtain permission to collect at least vital status (ie, that the subject is alive) at the end of their scheduled study period.

9.3 Source Documents

Source data are all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include: hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, X-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial.

9.4 Case Report Forms

The study CRF is the primary data collection instrument for the study. All data requested on the CRF must be recorded. All missing data must be explained. If a space on the CRF is left blank because the procedure was not done or the question was not asked, write "N/D". If the item is not applicable to the individual case, write "N/A". All entries should be printed legibly in black ink. If any entry error has been made, to correct such an error, draw a single straight line through the incorrect entry and enter the correct data above it. All such changes must be initialed and dated. DO NOT ERASE OR WHITE OUT ERRORS. For clarification of illegible or uncertain entries, print the clarification above the item, then initial and date it.

9.5 Records Retention

It is the investigator's responsibility to retain essential study documents for at least 2 years after the last approval of a marketing application in their country and until there are no pending or contemplated marketing applications in their country or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product.

10 Data Safety Monitoring Plan

A Safety Project Plan will be provided by PTC Therapeutics Pharmacovigilance outlining safety activities, processes, and study responsibilities. The PTC Therapeutics Pharmacovigilance Safety Lead-Pharmacist and Pharmacovigilance Safety Physician will be responsible for monitoring all SAEs, requesting follow-up information, and performing reconciliation.

The overall safety and conduct of the study will be monitored by the Principal Investigator, Orrin Devinsky, MD, the PTC Pharmacovigilance Safety Lead, and the PTC Pharmacovigilance Safety Physician. Under the safety monitoring plan, all SAEs will be reviewed. Data monitoring reviews will take place quarterly. Summary reports of the data monitoring review will also be taken quarterly.

10.1 Study Monitoring Plan

The investigator will allocate adequate time for such monitoring activities. The investigator will also ensure that the monitor or other compliance or quality assurance reviewer is given access to all the above noted study-related documents and study-related facilities (e.g., pharmacy, diagnostic laboratory), and has adequate space to conduct the monitoring visit.

10.2 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the IRB/EC, PTC Therapeutics, government regulatory bodies, and New York University compliance and quality assurance groups of all study-related documents (e.g., source documents, regulatory documents, data collection instruments, study data). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory).

Participation as an investigator in this study implies acceptance of potential inspection by government regulatory authorities and applicable New York University compliance and quality assurance offices.

11 ETHICAL CONSIDERATIONS

This study is to be conducted accordance with applicable US government regulations and international standards of GCP, and applicable institutional research policies and procedures.

This protocol and any amendments will be submitted to a properly constituted IRB in agreement with local legal prescriptions, for formal approval of the study conduct. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be filed in the investigator study file before commencement of this study. The investigator should also file a list of IRB members and their affiliate.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. See Attachment for a copy of the Subject Informed Consent Form. This consent form will be submitted with the protocol for review and approval by the IRB for the study. The formal consent of a subject, using the IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed by the subject or a legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

In addition, describe who will obtain consent and how the process of informed consent will be structured to be conducive to rational and thoughtful decision making by the subject/subject's parent/guardian. If children will be subjects, include a specific plan to assess comprehension during assent or the subject's agreement Individuals who are authorized to obtain consent must be listed on the protocol (or FDA form 1572) and consent form document. If necessary to use 'Auditor/Witness' and/or translator, these roles would be described in this section.

The investigator will explain the study during the routine visit and inform the subject and surrogate that a capacity assessment will be performed to determine whether the subject is capable of providing an informed decision to participate in the study. At this time, capacity assessment will be conducted if the subject does not refuse the assessment. If there is already documentation of lack of capacity, no assessment will be needed.

Capacity will be assessed through neurological examinations and neuropsychology reports conducted by the physician as well as learning and/or development delays that have been documented. Capacity will be monitored through the documentation in the subject's diary, the questionnaires administered, study visits and AEs. We do not expect the capacity of subject to change throughout the study. However, if at any time, the subject appears to have a change in their capacity (capacity is lost or gained), the independent assessor will perform a capacity assessment again. If capacity is lost, a parent/legal guardian must be consented in order for the subject to continue in the study. If capacity is gained, the subject must sign a consent form him/herself in order to continue participation in the study.

Once capacity has been determined, the subject will review and sign an assent form.

Subjects and/or their parent/legal guardian/or surrogate who does not wish to participate in the capacity assessment (adults) or decline consent (and assent for minors) will not participate in this study. Any individuals who appear to be distressed during participation will be withdrawn based on a decision by the physician.

12 STUDY FINANCES

12.1 Funding Source

This study is financed through a grant from the Epilepsy and Dravet Foundation as well as PTC Therapeutics.

12.2 Costs to Subjects

PTC Therapeutics will provide the study medicine free of charge to participating research subjects for the duration of this study. The subjects will be receiving medical care as a part of this research study. Subjects or their insurance company will not be charged or held responsible for the costs of that care.

All costs related to procedures and assessments associated with participating in this study will be free of charge.

Procedures that are part of routine care or to assess the subject's health but are not mandatory for the study will not be covered. The subject's individual insurance or government health insurance program may not cover certain services, items, or procedures. This may be discussed with the subject's insurance carrier in advance. The subject/parent/legal guardian will be responsible for any co-payments and/or deductibles for services rendered.

The subject and/or the subject's health insurance may be billed for the costs of medical care during this study if these expenses would have happened even if the subject was not in the study, or if the subject's insurance agrees in advance to pay. If the subject has health insurance, the cost of these services will be billed to the subject's insurance company. If the subject's insurance does not cover these costs or the subject does not have insurance, these costs will be the subject's responsibility.

12.3 Payments to Subjects

Reasonable reimbursement will be made for travel expenses required for subjects in this study.

Subjects will receive compensation at each visit for their participation as follows:

Screening Visit - $75

All Other Visits up to Week 128 - $50 for each

If compensation is greater than the minimum reporting requirements as set by the Internal Revenue Service (>$600), the sponsor must report this income to the IRS and will issue subjects a 1099 form as compensation will be considered taxable income. The sponsor will ask that subjects provide social security number for this purpose. Subjects will be responsible for reporting this compensation when they file tax returns. If subjects withdraw from the study prior to its completion, subjects will be compensated for the time actually spent in proportion to the fraction of the study completed.

The National Organization for Rare Disorders (NORD) can provide assistance with travel and lodging arrangements for subjects who go to study research centers in the United States. If subjects participate in this optional program, they will need to provide personal information such

as name, address, and telephone numbers to a member of NORD. The research center will provide a separate brochure from NORD, which explains the details and rules of the program.

12.4 Conflict of Interest

Any investigator who has a conflict of interest with this study (patent ownership, royalties, or financial gain greater than the minimum allowable by their institution, etc) must have the conflict reviewed by a properly constituted Conflict of Interest Committee with a Committee-sanctioned conflict management plan that has been reviewed and approved by NYU prior to participation in this study. All NYULMC investigators will follow the applicable New York University conflict of interest policies.

13 PUBLICATION PLAN

The publication plan will be to publish the entire series of subjects, inclusive of efficacy and tolerability findings. Depending on what other groups are involved in similar studies, we may elect to publish in collaboration with other groups.

Neither the complete nor any part of the results of the study carried out under this protocol, nor any of the information provided by PTC Therapeutics for the purposes of performing the study, will be published or passed on to any third party without the consent of PTC Therapeutics. Any investigator involved with this study is obligated to provide PTC Therapeutics with complete test results and all data derived from the study.

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15 APPENDICES

Appendix A

Seizure definition

Absence: A generalized seizure with abrupt onset and offset of altered awareness, which can vary in severity. Memory for events during the seizures is usually impaired although there may be some retained awareness, particularly for adolescents. Clonic movements of eyelids, head, eyebrows, chin, perioral, or other facial parts may occur, most typically at 3 Hz (International League Against Epilepsy).

Myoclonic: A single or series of jerks (brief muscle contractions). Each jerk is typically milliseconds in duration (International League Against Epilepsy).

Complex partial/focal dyscognitive: Focal seizures are conceptualized as originating within networks limited to one hemisphere. They may be discretely localized or more widely distributed. Focal seizures may originate in subcortical structures. Dyscognitive refers to altered awareness or responsiveness. Degree of loss of awareness or responsiveness may vary (International League Against Epilepsy).