RESEARCH ARTICLE

Ataluren for drug-resistant epilepsy in nonsense variant-mediated Dravet syndrome and CDKL5 deficiency disorder

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Abstract

Objective: Ataluren is a compound that reads through premature stop codons and increases protein expression by increasing translation without modifying transcription or mRNA stability. We investigated the safety and efficacy of ataluren in children with nonsense variants causing Dravet Syndrome (DS) and CDKL5 Deficiency Syndrome (CDD).

Methods: This single-center double-blind, placebo-controlled crossover trial randomized subjects to receive ataluren or placebo for 12 weeks (period 1), a 4-week washout, then another 12-week treatment (period 2). The primary outcome was ataluren’s safety profile. The secondary outcome measures were (1) changes in convulsive and/or drop seizure frequency and (2) changes in minor seizure types during ataluren treatment compared to placebo. Exploratory objectives assessed changes in cognitive, motor, and behavioral function as well as quality of life during ataluren therapy.

Results: We enrolled seven subjects with DS and eight subjects with CDD. Three treatment-related adverse events (AE) occurred during the blinded phases. Two subjects withdrew due to AE. Ataluren was not effective in reducing seizure frequency or improving cognitive, motor, or behavioral function or quality of life in subjects with either DS or CDD due to nonsense variants. Limitations included a small sample size and 12-week treatment phase, possibly too short to identify a disease-modifying effect.

Significance: There was no difference between ataluren and placebo; ataluren is not an effective therapy for seizures or other disorders in children with DS or CDD due to nonsense variants. There were no drug-related serious AE during the double-blind period, consistent with ataluren’s favorable safety profile in larger studies. (Funded by Epilepsy Foundation, Dravet Syndrome Foundation, Finding A Cure for Seizures and Epilepsy and PTC Therapeutics, Inc.; ClinicalTrials.gov number, NCT02758626).

Key points

• Ataluren was used to treat children with CDKL5 Deficiency Disorder (CDD) and Dravet Syndrome due to premature stop codons.
• This was a single site double-blind placebo-controlled randomized study.
• Ataluren was not associated with a reduction in seizures in positive impact on nonseizure outcomes.

Introduction

Patients with epileptic encephalopathies such as Dravet syndrome (DS) and CDKL5 deficiency disorder (CDD) suffer from global developmental delays and treatment-resistant epilepsy, leading to severe morbidity and elevated mortality. CDKL5 is an X-linked genetic epileptic encephalopathy most frequent in females. CDD patients exhibit signs of poor developmental skills (e.g., poor
sucking, poor eye contact) in the first months of life. Later, impaired fine and gross motor skills, lack of speech, and reduced eye contact and social interactions are evident. Many patients never walk independently. DS often presents in the first year of life in an otherwise normal infant with fever-related generalized tonic-clonic seizures and/or alternating unilateral hemiconvulsions. Later, myoclonic, atypical absence, and partial seizures often develop. Developmental delays develop in the second year of life and intellectual disability affects nearly all patients. Seizures are usually drug-resistant, but epilepsy severity often diminishes by adolescence. Ataxic gait disorder, dystonia, and intention tremor often develop in later childhood. The mortality rate due to seizures and status is high; 15% of patients die by adolescence and 20% die by early adulthood.

Ataluren is a novel 1,2,4-oxadiazole linked to two ring structures: fluorobenzene and benzoic acid (C15H9FN2O3) that promotes read-through of premature stop codons and increases protein expression in animal and human studies. In cellular assays and animal models of genetic disease, ataluren selectively enables read-through of mRNA containing a premature stop codon, producing full-length functionally active proteins localized to the appropriate cellular location. Ataluren does not read-through normal stop codons. Ataluren is selective for translation and does not alter levels of mRNA with premature stop codons or wild-type mRNA; that is, it does not modify transcription or mRNA stability. Ataluren has a favorable safety profile and is approved to treat nonsense-mediated Duchenne's muscular dystrophy in more than 30 countries. In this randomized blinded cross-over pilot study, we examined the effect of ataluren on seizure control and cognitive function in patients with DS and CDD due to nonsense variants which account for ~15–20% of cases.

Methods

We screened children with DS and CDD due to a nonsense variant in one allele documented by a CLIA-certified laboratory report at the NYU Langone Comprehensive Epilepsy Center. Additional inclusion criteria included: (1) Age ≥2 years old and ≤12 years old, (2) male or female, (3) failure to control seizures despite appropriate trial of 2 or more antiseizure drug (ASDs) at therapeutic doses, (4) current regimen of 1–3 baseline ASDs at stable doses for a minimum of 4 weeks before enrollment (i.e., Screening Visit). For children with a vagus nerve stimulator or on the ketogenic or modified Atkins diets, these therapies were not considered an ASD but had to be unchanged for 3 months before enrollment, (5) ≥6 convulsive or drop seizures with duration ≥3 sec over the 4 weeks of diary screening before randomization and ≥6 convulsive or drop seizures with duration >3 sec during the 4 weeks from Screening to Baseline.

This was a single-center randomized, double-blind, placebo-controlled crossover trial. Subjects received either placebo or ataluren, 10 mg/kg in morning and midday and 20 mg/kg in the evening, for 12 weeks in period one and then after a 4-week washout, received the other treatment for 12 weeks (Fig. 1). A dose increase was allowed for subjects who increased ≥10% of body weight. Ataluren is a powder for oral suspension. There was no titration.

Partway through the study, the Sponsor (PTC

Figure 1. Study trial design. EOS, end of study; F/U, follow-up; IC, informed consent; Wk, week.
Pharmaceuticals) changed dosage based on weight for subjects who were 14 ± 2 kg. They originally took 125 mg/375 mg/375 mg daily and were changed to 125 mg/250 mg/250 mg. This affected three subjects.

The main outcome was percent change in motor seizure frequency. Other outcomes included safety and tolerability of ataluren; changes in cognitive, motor, and behavioral function; and quality of life. These outcomes were assessed by the following neuropsychological scales: Behavior Assessment System for Children (BASC), Veland Adaptive Behavior Scales (VABS), and Quality of Life in Childhood Epilepsy (QOLCE).

Results

We enrolled seven children with DS and eight children with CDD (Table 1). The Dravet subjects included five girls and two boys; mean age 6.4 years (median 7; range, 2–11). The Dravet subjects had a mean weight of 24 kg (median 23.6; range 13.6–48.1) and mean body mass index of 16.8 (range, 13.6–23.8). The eight CDD subjects were all girls; mean age 4.0 years (median 3.5; range, 2–11). The CDD subjects had a mean weight of 14.5 kg (range 10.0–19.1) and body mass index of 14.6 (range 12.5–18.1).

All subjects with DS completed the double-blind phase. One subject in the ataluren/placebo group completed the open-label extension phase. Four subjects, two each in the ataluren/placebo and the placebo/ataluren group were still in the open-label extension phase at the time of the data cut; and two subjects, one each in the ataluren/placebo (due to AE) and placebo/ataluren group (consent) discontinued during open-label extension phase.

Safety during the blinded phase

Dravet Syndrome

Six of seven subjects had adverse events (AEs) while on ataluren. Among them, three subjects had serious adverse events (SAEs) considered unlikely related to the study medicine. One subject had two mild SAEs (decreased valproic acid level and increased seizure frequency) and two subjects had a moderate SAE (each with influenza). Three of seven subjects had AEs while on placebo. There were no study withdrawals due to an AE.

CDKL5 deficiency disorder

Seven of eight subjects had AEs while on ataluren. One subject had a mild SAE (decreased valproic acid level; considered unrelated to study medicine). Two subjects had AEs leading to study withdrawal. One had GI symptoms (burping, flatulence, vomiting) of moderate severity, possibly related to study medicine. The other had increased seizures of mild severity, unlikely related to study medicine. Two of seven subjects had AEs while on placebo; one had a mild SAE (Croup; unrelated to study medicine). There were no study withdrawals on placebo.

Safety during the open-label period

Dravet syndrome

Six of seven subjects had AEs during the open-label period. One subject had two mild SAEs (ear infection and tooth infection) that were unrelated to study medicine. One subject withdrew from the study due to an AE (increased seizure frequency).

CDKL5 deficiency disorder

Six of seven subjects had AEs during the open-label period. Two subjects had mild SAEs: one subject had elevated liver function enzymes twice (mild and severe), both possibly related to study medicine and both resolved. The other subject had Mycoplasma pneumoniae, moderate severity, unrelated to study medicine. One subject withdrew from the study due to an AE (elevated hepatic enzymes).

Protocol variances

Of 15 randomized subjects, 12 subjects missed an average of three doses, usually midday and less often evening due to school, therapy, or sleep. Some parents reported that their child spit out some of the

Table 1. Subject demographics.

|                         | DRAVET syndrome          | CDKL5 deficiency disorder |
|-------------------------|--------------------------|---------------------------|
| Sex                     | 5 male                   | 2 female                  |
| Age                     | Mean 6.4 years           | Mean 4.0 years            |
|                         | Median 7 years           | Median 3.5 years          |
| Weight                  | Mean 24 kg               | Mean 14.5 kg              |
|                         | Median 23.6 kg           | Median 14.1               |
|                         | Range 13.6–48.1 kg       | Range 10.0–19.1 kg        |
medication and others reported that they had to split
the dose to have their child take it all. Ten parents did
not return all medication sachets at all study visits,
which limited our ability to assess adherence. The fol-
lowing inconsistencies with diary data included: (1) for-
going to document: time, duration or severity or
seizure type, (2), caregiver recall is uncertain of exact
data, and provided an average or “guessimate,” or (3)
forgetting to return diary. Questionnaire-related in-
consistencies included (1) missed questions and (2) excess
“Not applicable” choices that limited scoring.

Efficacy

There was no change in motor seizure frequency or cog-
nitive, motor, or behavioral functions or quality of life in
the ataluren group compared to placebo among these
patients with nonsense variant CDKL5 or Dravet Syn-
drome.

For DS, the median percent change from baseline in
motor seizure, total seizure, and myoclonic seizure fre-
quency is summarized in Table 2.

For the primary endpoint of percent change from base-
line in motor seizures, the median difference between the
two treatment groups along with 95% Hodges–Lehmann
confidence interval is 54.9% (6.95, 1648.8).

For CDD, the median percent change from baseline in
motor seizure, total seizure, and myoclonic seizure fre-
quency is summarized in Table 3.

For the primary endpoint of percent change from base-
line in motor seizures, the median difference between the
two treatment groups along with 95% Hodges–Lehmann
confidence interval is 11.2 (−32.7, 40.5).

Table 2. Median percent change from baseline in different types of
seizures in DS by treatment.

| Ataluren (n, median [IQR]) | Placebo (n, median [IQR]) |
|-----------------------------|---------------------------|
| Motor seizure n = 7, 28.6 (163)% | n = 7, −22.7 (54.2)% |
| Total seizure n = 7, 12.5 (42.1)% | n = 7, −19.0 (82.2)% |
| Myoclonic seizure n = 4, −46.7 (78.3)% | n = 4, 28.0 (299)% |

Table 3. Median percent change from baseline in different types of
seizures in CDD by treatment.

| Ataluren (n, median [IQR]) | Placebo (n, median [IQR]) |
|-----------------------------|---------------------------|
| Motor seizure n = 7, 16.0% | n = 7, −9.10 (59.6)% |
| Total seizure n = 7, 42.9 (51.9)% | n = 7, 18.6 (105.4)% |
| Myoclonic seizure n = 2, 1251 (2098)% | n = 2, 630 (1021)% |

Discussion

In this pilot randomized placebo-controlled cross-over
trial, ataluren did not reduce seizure frequency or
improving cognitive, motor, or behavioral function or
quality of life in subjects with DS and CDD due to non-
sense variants. Our trial was limited by small sample size
and a treatment-phase of 12 weeks, which may be too
short to identify a disease-modifying effect. Ataluren had
a good safety profile in these children with severe devel-
opmental delays and treatment-resistant epilepsy. The
reduced levels of valproic acid seen in two patients likely
reflect the known variability in serum valproic acid
levels. Ataluren is metabolized primarily by glu-
curonidation by UGT1A9,12 which is one of eight UGT
enzymes that collectively metabolize ~50% of valproic
acid (40% by beta-oxidation in mitochondria, 10% by
hepatic cytochromes).13 However, any interaction at
UGT1A9 is predicted to insignificantly raise valproic acid
levels.14

This is the first assessment of a read-through com-
pound in patients with primary brain disorders. Most
prior human studies with ataluren were performed on
patients with Duchenne’s muscular dystrophy (DMD).
The efficacy of ataluren in DMD led to approval by the
European Medical Agency and multiple other coun-
tries.15,16

There are many potential reasons why ataluren may
not have reduced seizures or functional measures in these
subjects. First, ataluren may not be effective in treating
these disorders. However, the numerous preclinical mod-
elses showing efficacy in other disorders17,18 make this unli-
likely if the drug reached affected neurons at therapeutic
levels. The drug may not be effective in central nervous
system disorders due to limited or erratic crossing of the
blood–brain barrier. Evidence that ataluren crosses the
blood–brain barrier comes from studies in single oral
dose administration of radiolabeled ataluren to Sprague–
Dawley and Long Evans rats as well as the Hurler mouse
model.19 However, it is possible that for some drugs, such
as ataluren, there may be large species or inter-individual
differences in blood–brain barrier penetration. Other pos-
sibilities for failure include (1) insufficient treatment
duration for an effect, (2) selection of insensitive outcome
measures, or (3) challenges related to protocol variances
including adherence, accurate completion of seizure dia-
aries, and missing data from questionnaires.

This study has implications for future trials of com-
pounds that promote read-through compounds in treat-
ing CNS disorders. In addition to variability in lipid
solubility, genetic, and other individual factors may affect
this. CNS pharmacokinetic studies with brain levels in
large mammals may help refine dosing in humans. Small
animal models may help predict likelihood of success in human studies. We did not assess ataluren in a rodent model of nonsense-mediated DS or CDD, nor did we measure changes in SCN1A or CLDK1 expression levels, which if possible, should be considered in future CNS trials. However, compounds that rescue the phenotype in rodent models of CNS disorders may fail to show efficacy in human studies (Fragile X trials with mGlur5 antagonists, GABA receptor agonist and glutamate agonists).20 Future trials should carefully consider patient age ranges (i.e., there may be different temporal windows to alleviate neuronal dysfunction in different CNS disorders), consideration of periods of disease progression or regression based on natural history studies, refined clinical trial design and duration, outcome measures that are sensitive and specific for relevant phenotypic changes, and biomarkers that reflect CNS penetration and molecular efficacy.

We confirm that we have read the Journal’s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Conflict of interest

Orrin Devinsky has equity interests in Qstate Biosciences, Tevarid Biosciences, Regel Therapeutics, and Script Biosciences, Privateer Holdings, Tilray, Receptor Life Sciences, Empatica, Engage, Egg Rock/Papa & Barkley, Retcco, SilverSpike, and California Cannabis Enterprises (CCE). Orrin Devinsky receives grant support from NINDS, NIMH, MURI, CDC, and NSF. He is an investigator for PTC Therapeutics, Inc., Stoke Therapeutics, Marinus, Ovid and GW Pharmaceuticals. Daniel Friedman receives salary support for consulting and clinical trial-related activities performed on behalf of The Epilepsy Study Consortium, a nonprofit organization. Dr. Friedman receives no personal income for these activities. NYU receives a fixed amount from the Epilepsy Study Consortium toward Dr. Friedman’s salary. Within the past 2 years, The Epilepsy Study Consortium received payments for research services performed by Dr. Friedman from: Axcella, Biogen, Cerevel, Crossject, Engage Pharmaceuticals, Eisai, Pfizer, SK Life Science, Xenon, and Zynreba. He has also served as a paid consultant for Eisai and Neurelis Pharmaceuticals. He has received travel support from Medtronic, Eisai and the Epilepsy Foundation. He receives research support from the CDC, NINDS, Epilepsy Foundation, Empatica, Epitel, UCB, Inc and Neuropace unrelated to this study. He serves on the scientific advisory board for Receptor Life Sciences. He holds equity interests in Neuroview Technology and Receptor Life Sciences.

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