Emergency Use Case of Relutrigine, a Next-Generation Sodium Channel Functional State Modulator, in an Infant with SCN2A-DEE and Refractory Seizures and Recurrent Status Epilepticus

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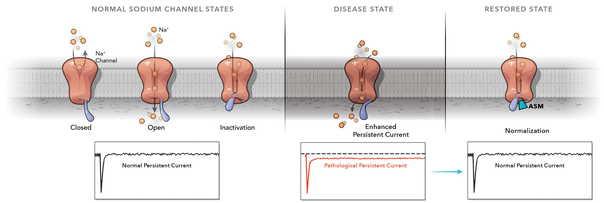
Background

- Developmental and epileptic encephalopathies (DEEs) are devastating neurological disorders presenting in infancy and early childhood, characterized by severe, frequent seizures and increased mortality, as well as developmental delay, intellectual disability, and other comorbidities.
- Certain pathogenic variants in voltage-gated sodium channel (Na_V) genes can increase Na_V activity leading to the neuronal hyperexcitability observed in severe DEEs.
- Relutrigine (PRAX-562) is a next-generation, functionally selective, precision Na_V modulator, in development for the treatment of DEEs, with demonstrated superior selectivity for disease-state Na_V hyperexcitability.
- Preclinical and clinical data have demonstrated potential for relutrigine to be a first- and best-in-class treatment for DEEs (**P1.528**).
- *Here we describe the first emergency use case of relutrigine in an infant with SCN2A-DEE and refractory seizures and recurrent status epilepticus (SE).*

RELUTRIGINE MECHANISM OF ACTION



Persistent sodium current (I_{NaP}) is a critical driver of pathological hyperexcitability in CNS disorders

Relutrigine First Emergency Use Case: New Zealand

Case presentation: SCN2A-DEE and refractory seizures and recurrent status epilepticus

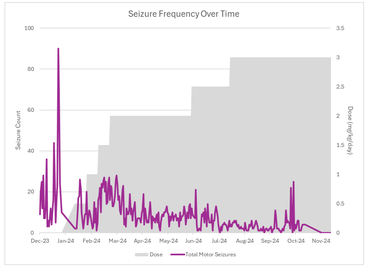
- An infant with SCN2A-DEE began receiving relutrigine in February 2024 at age 4 months, on a named patient, emergency-use basis following a medical history of refractory seizures with multiple episodes of SE requiring ICU hospital admissions and IV medications to resolve the clinical status.
- In the 7 days preceding relutrigine treatment initiation, the patient had been in SE on three separate occasions and was receiving clobazam (2 mg/kg/day), lacosamide (12.4 mg/kg/day) and phenytoin (3.7 mg/kg/d) without any impact on seizure frequency and severity.
- Other ASMs tried in the first months of life without response included: levetiracetam 80 mg/kg/day, carbamazepine 25 mg/kg/day, vigabatrin up to 100 mg/kg/day, topiramate 10 mg/kg/day, and sodium valproate 40 mg/kg/day.

Demonstrated Tolerability and Seizure Reduction

Marked reduction in seizures alongside a well-tolerated profile

- Following weaning off phenytoin, treatment with relutrigine commenced at a starting dose of 0.5 mg/kg/day, with increasing increments of 0.5 mg/kg every two to four weeks, up to a dose of 3 mg/kg/day as of November 2024.
- Thus far, the patient has been receiving relutrigine once a day over a period of 10 months.
- Since relutrigine treatment initiation, there has been a marked reduction in episodes of SE and hospital admissions, with demonstrated durable reduction in seizure frequency (***Fig. 1***), as well as a decrease in emergency medications administered.
- 24-hour EEG showed a further interval reduction in seizure frequency, with an overall >50% reduction in seizures following the increase from 2 to 3mg/kg/day, with incremental improvement observed at 2.5 mg/kg/day.
- In addition, the patient has been more alert and awake, responding to, and looking towards, familiar voices.
- Over the course of treatment, relutrigine has been well-tolerated and there have been no clinically significant findings on biweekly blood draws, urine or ECG analysis, and no drug-related or severe adverse events.

A



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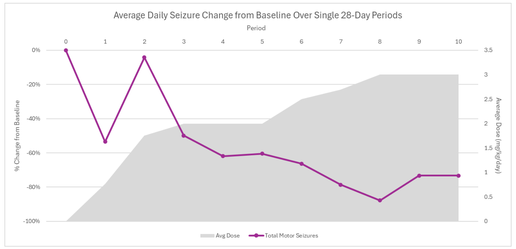

Figure 1. Patient clinical course following introduction of relutrigine dosing regimen and effects on motor seizures. **(A)** Change in total motor seizure frequency over time following relutrigine dosing regimen. **(B)** Percentage change in average daily seizures over single 28-day periods following relutrigine dosing regimen demonstrating durable seizure reduction. Period 2 included hospitalization and seizures following immunization. Period 9 included hospitalization for elective gastronomy insertion, with prolonged seizures in the context of aspiration pneumonia as a procedural complication.

Pharmacokinetic Summary

- Blood samples were collected for sparse measurement of relutrigine plasma concentrations.
- PK data demonstrated generally dose-dependent exposure.
- Plasma concentrations were quantifiable following multiple doses of 0.5 to 3 mg/kg/day relutrigine.
- Concentrations exceeding therapeutic levels were achieved and well tolerated.

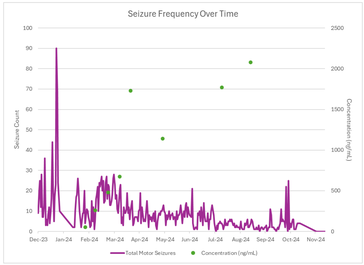

Figure 2. Patient clinical course in relation to relutrigine plasma concentration. Change in total motor seizure frequency following relutrigine dosing regimen over time, with PK timepoints overlaid.

Conclusions

- **Relutrigine is poised to be a first- and best-in-class treatment for DEEs, with early clinical experience in the first emergency use case indicating a well-tolerated profile and marked seizure reduction, including cessation of previous SE.**
- **Ongoing follow up will determine long-term effects on seizure frequency and intensity, and associated comorbidities.**

RELUTRIGINE DEEs SMALL MOLECULE FUNCTIONAL STATE MODULATOR	Superior selectivity for disease-state Na_V channel hyperexcitability
	Unprecedented therapeutic window with potential for superior safety and efficacy
	Generally well-tolerated with mostly mild to moderate AEs, no drug-related SAEs and no relutrigine dose reduction required (see also **P1.528**)
	Demonstrated robust seizure reduction and unprecedented motor seizure-free status per 28-day period (see also **P1.528**)

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