EMBOLD: A Clinical Trial of PRAX-562 in Subjects with Developmental and Epileptic Encephalopathies

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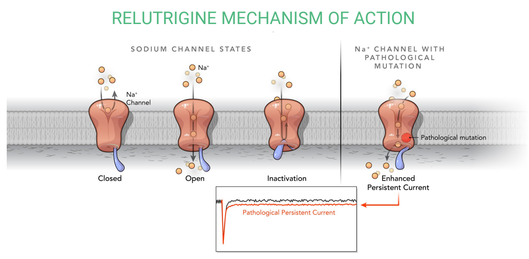
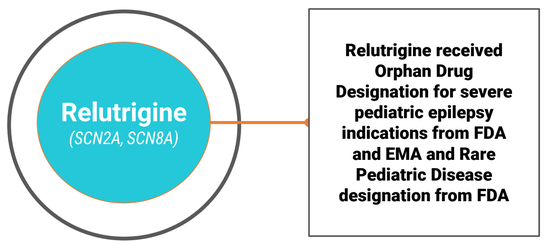
Background

- Developmental and epileptic encephalopathies (DEEs) are devastating neurological disorders presenting in infancy and early childhood characterized by severe, frequent seizures that are often refractory to current treatment regimens.
- Gain-of-function pathogenic variants in voltage-gated sodium channel (Na_V) genes can increase Na_V activity leading to the neuronal hyperexcitability observed in severe DEEs.
- In addition to the associated seizure burden, surviving children suffer developmental delay, intellectual disability, and other comorbidities, and are at continuous risk of status epilepticus and sudden unexpected death from epilepsy (SUDEP).
- Relutrigine (PRAX-562) is a next-generation, functionally selective, precision sodium channel modulator, tailored for pediatric needs, with demonstrated superior selectivity for disease-state Na_V hyperexcitability, and has been generally well tolerated in over 130 healthy volunteers to date.
- This profile suggests a wide therapeutic window and potential for superior safety and efficacy over standard-of-care.
- The EMBOLD study was a Phase 2 randomized clinical trial designed to explore the safety, tolerability, efficacy, and pharmacokinetics of relutrigine in pediatric participants with seizures associated with early onset *SCN2A*-DEE and *SCN8A*-DEE.



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

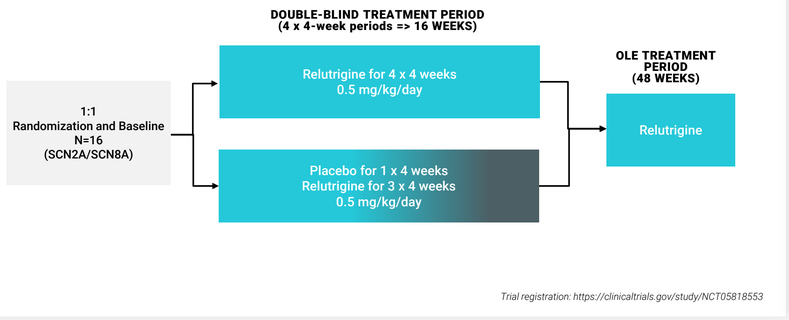


Methods

EMBOLD Study Design

- EMBOLD (NCT05818553) is a multicenter, double-blind, placebo-controlled, randomized study, followed by open-label extension (OLE), which enrolled 16 eligible male and female participants aged 2-18 years, inclusive, with a diagnosis of early onset *SCN2A*-DEE or *SCN8A*-DEE.
- Participants were randomized (1:1) to receive relutrigine QD for 16 weeks, or relutrigine QD for 12 weeks and matching placebo QD for 4 weeks, with timing of placebo administration blinded for both participants and investigator.
- Dose was administered orally or via gastrostomy/jejunostomy tube (G/J-tube), with dose adjustment permitted from initial dose of 0.5mg/kg/day to a maximum of 1.0 mg/kg/day and a minimum of 0.25 mg/kg/day.
- The randomized, double-blind portion consisted of the following periods: Screening, Double-Blind Treatment, and Safety Follow-up.
- The open-label extension is ongoing.
- Participants had the option to be enrolled to undergo the study assessments in a hybrid fashion (with in-clinic and at-home visits) or with at-home visits only (fully decentralized).

Figure 1. EMBOLD Design



Trial registration: https://clinicaltrials.gov/study/NCT05818553

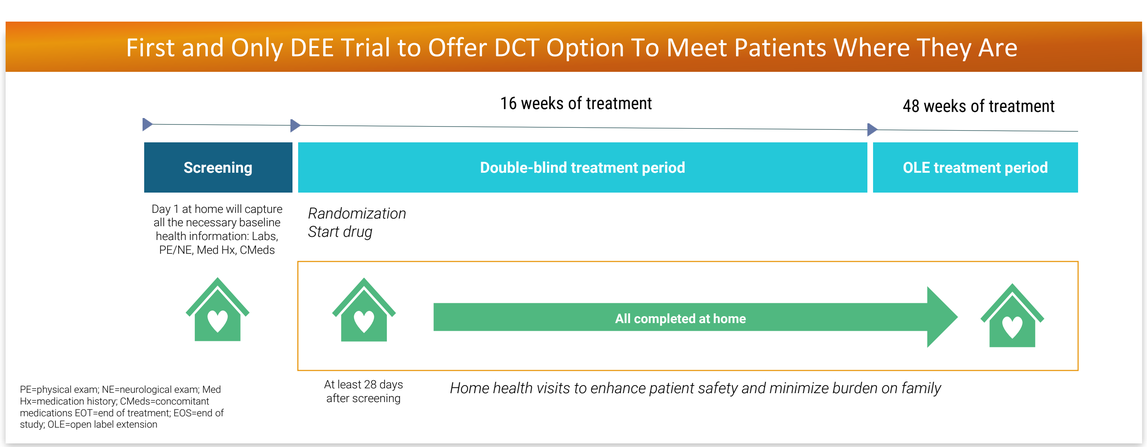
EMBOLD

KEY ENDPOINTS

- Incidence and severity of treatment-emergent adverse events (TEAEs)
- Change from baseline in monthly (28 day) motor seizure frequency
- Seizure freedom achieved for a 4-week period
- Clinical and Caregiver Global Impression of Improvement and Severity

Decentralized Clinical Trial Design: Patient-Centric, Clinical Rigor

First and Only DEE Trial to Offer DCT Option To Meet Patients Where They Are



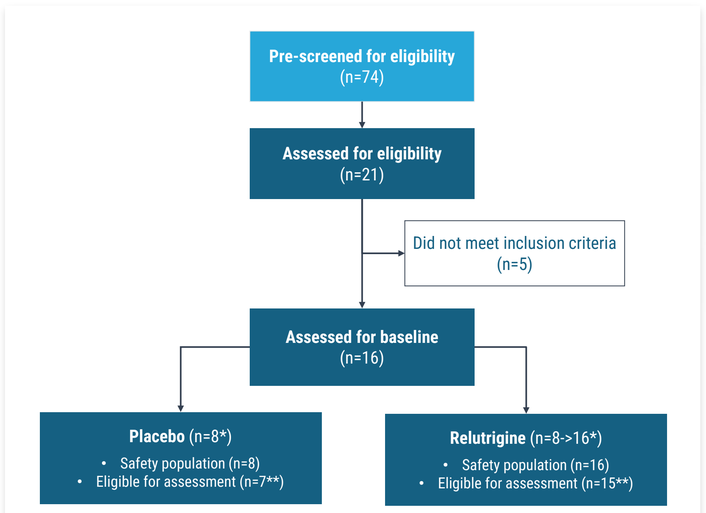
- ❖ User-friendly seizure diaries
- ❖ Streamlined at-home nurse services for collection of labs
- ❖ State-of-the-art seizure detection and measurement at home
- ❖ Reduced in-clinic visits to minimize travel burden for patients and caregivers
- ❖ Open-label extension to continue benefiting from treatment

- ❖ Designed with families' needs in mind
- ❖ Balancing scientific rigor and safety
- ❖ Increased inclusion for potential patients normally excluded
- ❖ Families also have the option of a hybrid model with some visits at home and some in the clinic if they choose

Figure 2. EMBOLD Study – DCT At Home. Families could participate in the EMBOLD trial from their homes, with the clinic coming to them. The DCT nature of the trial allowed all study-related procedures to be done at home, with doctors and nurse visits ensuring the trial is conducted in a convenient manner for families.

EMBOLD Study Disposition and Baseline Characteristics

Figure 3. EMBOLD Participant Disposition



*Patients assigned to placebo received placebo for one (4 week) period and relutrigine for 3 periods
**1 patient had no available data for efficacy assessment

Key Inclusion Criteria

- Documented severe DEE with mutations in SCN2A or SCN8A genes
- Age 2-18 years inclusive; weight ≥10 kg
- ≥8 countable motor seizures in 4 weeks preceding AND during 28-day baseline observation period screening
- On stable ASM doses for ≥1 month prior to screening

Table 1. Demographics and Baseline Characteristics

	PLACEBO (n = 8)	RELUTRIGINE (n = 16)
Age, mean (min, max)	6.1 (3, 12)	5.9 (2, 14)
DEE		
SCN2A, n (%)	4 (50)	7 (44)
SCN8A, n (%)	4 (50)	9 (56)
Gender (Male / Female, %)	5/3 (63/37)	9/7 (56/44)
Age at seizure onset (n)		
0 – 3 months	7	13
4 – 12 months	1	2
>12 months	0	1
Patients with ASM use at baseline		
1 or 2 ASM	2	4
3 or 4 ASM	5	11
Baseline motor seizures per 28-day, median (min, max)	58.7 (15, 844)	53.5 (13, 844)
Baseline log-transformed motor seizures per 28-day, mean (SE)	4 (0.4)	3.3 (0.3)
Baseline CGI-S, mean (min, max)	5.5 (4, 6)	5.6 (4, 6)

Relutrigine was Generally Well Tolerated

- AEs were mostly mild to moderate.
- No dose reduction of relutrigine was required.
- All SAEs that occurred in the study were determined to be not drug related and were consistent with disease background, including infections, crying, and seizure-related events
- No clinically significant safety findings in vital signs, clinical laboratory results, physical exams, ECGs.

Table 2. EMBOLD Tolerability Summary

	PLACEBO (n = 8)	RELUTRIGINE (n = 16)
ANY TEAE	*4 (50%)*	*14 (88%)*
TEAEs > 2 Patients		
Infections*	3 (38%)	8 (50%)
Vomiting	1 (13%)	5 (31%)
Pyrexia	0	5 (31%)
Somnolence	0	4 (25%)
Constipation	0	3 (19%)
Nasopharyngitis	2 (25%)	1 (6%)

AEs were mostly mild to moderate

No drug-related SAE

No dose reduction of relutrigine required

One severe TEAE of status epilepticus related to an infection

*Infections include bronchiolitis, conjunctivitis, gastroenteritis, influenza, metapneumovirus infection, nasopharyngitis, otitis media, pneumonia, respiratory tract infection, rhinovirus infection scarlet fever, tonsillitis, upper respiratory tract infection

Conclusions

- **Relutrigine poised to be a first-line, best-in-class treatment for all DEEs.**
- **Building on Phase 1 findings, the EMBOLD trial results demonstrate relutrigine is well tolerated across SCN2A and SCN8A groups.**
- **Registration enabling cohort extension initiated; Praxis seeking regulatory advice on advancing development in other DEEs.**

RELUTRIGINE

FORMULATED FOR PEDIATRIC USE

FUNCTIONAL STATE MODULATOR

Superior selectivity for disease-state Na_V hyperexcitability

Well-tolerated in pediatric patients with DEEs

Convenient auto-titration regimen with stable PK

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