Relutrigine Demonstrates Robust Seizure Reduction and Seizure Freedom in DEEs: Results from the EMBOLD Study

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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 early mortality.
- 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 emerging clinical data suggest a wide therapeutic window and potential for superior safety and efficacy over current standard-of-care for DEEs.
- The EMBOLD study is 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.

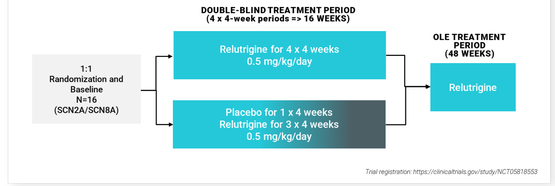
➢ *Findings demonstrate relutrigine is poised to be a first-line, best-in-class treatment for DEEs, with topline data in SCN2A-DEE and SCN8A-DEE showing well-tolerated, robust, short- and long-term improvement in motor seizures alongside marked seizure freedom.*

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



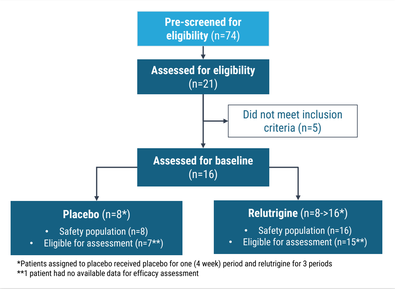
EMBOLD

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

EMBOLD Study Disposition and Baseline Characteristics

Figure 2. 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 required, and >50% of participants increased dosing to 1 mg/kg/day.
- All SAEs determined to be not drug-related and were consistent with disease background.
- 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%)

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
Active treatment duration was at least 7 times longer than placebo duration with respect to total period of observation.

AEs were mostly mild to moderate

No drug-related SAE

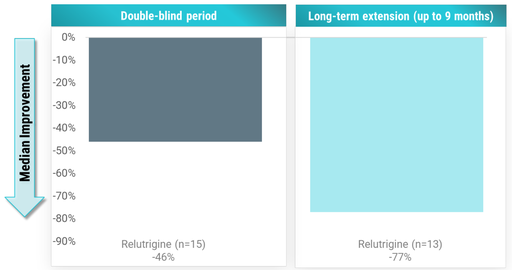
No dose reduction of relutrigine required

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 all DEEs (EMERALD trial).**

https://www.emboldstudy.com/

Robust Reduction in Motor Seizures and Unprecedented Seizure-free Status



Long-term extension data for 13 patients with data available for a median of 4, 28-day periods as of November 22, 2024

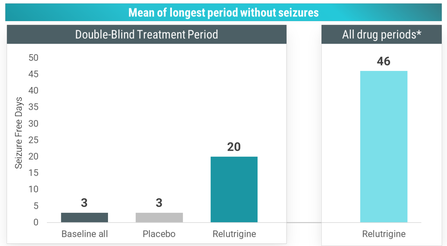
Significant improvement over the short and long-term in motor seizures

- Significant reductions in motor seizures observed over single 28-day and OLE periods
- 7 patients increased the dose of relutrigine to 1 mg/kg during the double-blind period
- 2 additional patients during the long-term extension
- Seizure freedom associated with exposures achievable by 1 mg/kg

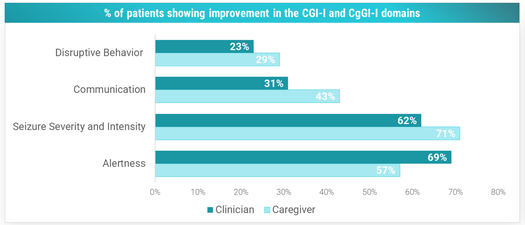
Meaningful and consistent impact in days without motor seizures for relutrigine treated patients

- 33% of patients seizure-free after initiating on relutrigine*
- Longest follow-up >200 days seizure-free

*Assessment of motor seizures over the controlled plus open-label periods through August 21, 2024



* Inclusive of OLE period



Clinical Global Impression of Improvement and Caregiver Global Impression of Improvement assessed at Week-16 visit

Meaningful gains in overall well-being of patients, despite severity and historical lack of improvement with available treatments

- Disease modifying impact for patients assessed by clinicians and caregivers
- ~30-70% improvements reported by clinicians and caregivers across multiple domains on CGI-I and CgGI-I, respectively

References

1. Schefferet al 2017 *Epilepsia*
2. Wagnon et al 2015 *Hum Mol Genet*
3. Wagnon & Meisler 2019 *Front Neurol*
4. Ware et al 2019 *Epilepsia Open*
5. Wolff et al 2017 *Brain*
6. Zuberi et al 2022 *Epilepsia*
7. Helbig et al 2018 *Am J Hum Genet*
8. Takai et al 2020 *Int J Mol Sci*
9. Gallop et al 2021 *Epilepsy Behav*
10. Johannessen et al 2021 *Epilepsia*
11. Thurman et al 2014 *Epilepsia*

Acknowledgments We thank the participants and their families, the EMBOLD Study Team, as well as our collaborators for their contributions to this work.

Funding All studies were funded by Praxis Precision Medicines. Medical writing and editorial assistance were provided by Lillian G. Matthews in accordance with Good Publication Practice (GPP3).

Disclosures SF, BS, KD, DP, HJ, SP and MS are current or former employees/consultants of Praxis Precision Medicines and may be Praxis shareholders

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Presented at:
2024 AES Annual Meeting
December 6-10
Los Angeles, CA

AES AMERICAN EPILEPSY SOCIETY