Relutrigine Demonstrates Disease-Modifying Impact in DEEs: Results from the EMBOLD Study

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Background

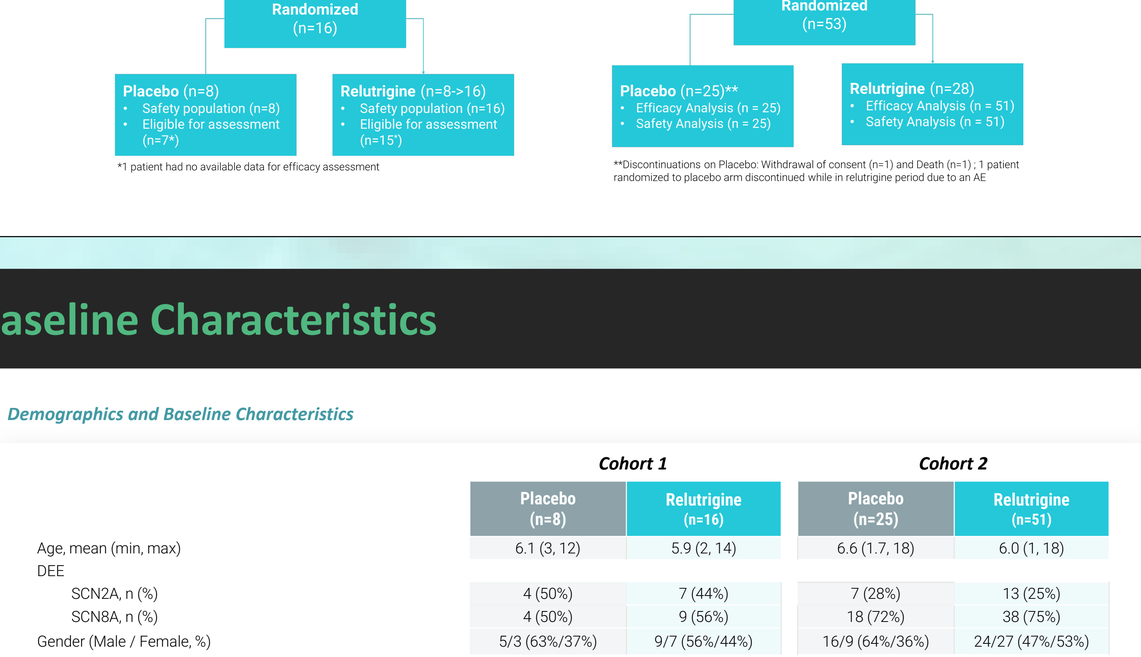
- Developmental and epileptic encephalopathies (DEEs) are severe childhood epilepsies marked by frequent, refractory seizures and high early mortality.
- Relutrigine is a next-generation sodium channel modulator designed to selectivity target the disease-driven hyperexcitability that causes seizures in DEEs.
- Emerging clinical data demonstrate a wide therapeutic window and the potential for superior safety and efficacy over current treatments.
- EMBOLD is a Phase 2/3 randomized clinical trial evaluating relutrigine's safety, tolerability, efficacy, and pharmacokinetics in children with *SCN2A*-DEE and *SCN8A*-DEE.

➢ ***Findings show relutrigine is well-tolerated and delivers strong, rapid, and sustained seizure reduction, supporting its potential as a first-line, best-in-class therapy for DEEs.***

Methods

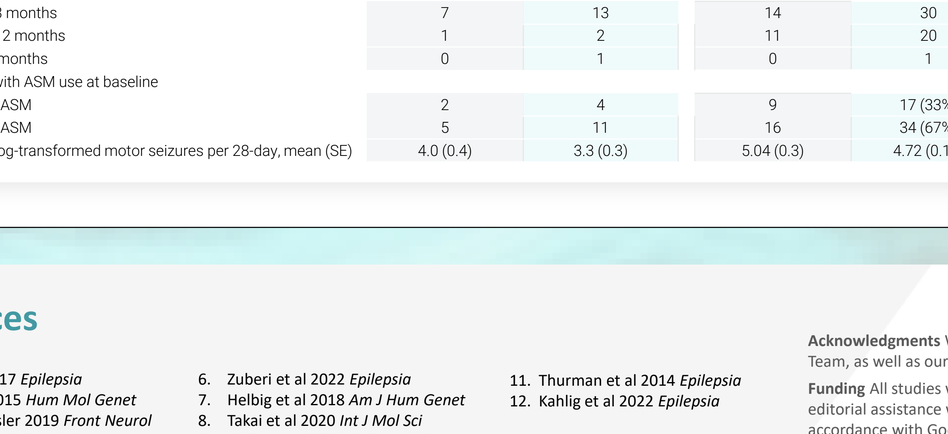
EMBOLD Study Design

- EMBOLD (NCT05818553) is a multicenter, randomized, double-blind, placebo-controlled study with an open-label extension, in children with *SCN2A*-DEE or *SCN8A*-DEE.
- Cohorts 1 and 2 were randomized (1:1) to relutrigine QD for 16 weeks, or relutrigine QD for 12 weeks + matching placebo QD for 4 weeks (placebo period timing blinded to families and investigators).
- Dosing:
  - Cohort 1: starting dose of 0.5 mg/kg/day with optional increase to 1.0 mg/kg/day; administered orally or via G/J tube.
  - Cohort 2: starting dose of 1.0 mg/kg/day and maintained through the double-blind period; administered orally or via G/J tube.



[†]Participants 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.

Disposition Per Cohort



*1 patient had no available data for efficacy assessment

**Discontinuations on Placebo: Withdrawal of consent (n=1) and Death (n=1) ; 1 patient randomized to placebo arm discontinued while in relutrigine period due to an AE

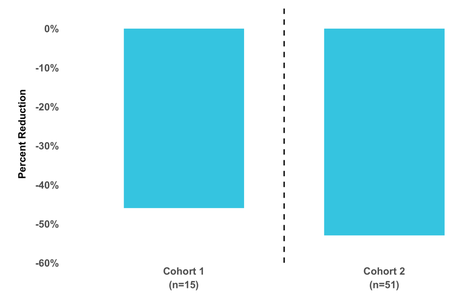
Baseline Characteristics

Demographics and Baseline Characteristics

	Cohort 1		Cohort 2	
	Placebo (n=8)	Relutrigine (n=16)	Placebo (n=25)	Relutrigine (n=51)
Age, mean (min, max)	6.1 (3, 12)	5.9 (2, 14)	6.6 (1.7, 18)	6.0 (1, 18)
DEE				
SCN2A, n (%)	4 (50%)	7 (44%)	7 (28%)	13 (25%)
SCN8A, n (%)	4 (50%)	9 (56%)	18 (72%)	38 (75%)
Gender (Male / Female, %)	5/3 (63%/37%)	9/7 (56%/44%)	16/9 (64%/36%)	24/27 (47%/53%)
Age at seizure onset (n)				
0 – 3 months	7	13	14	30
4 – 12 months	1	2	11	20
>12 months	0	1	0	1
Patients with ASM use at baseline				
1 - 2 ASM	2	4	9	17 (33%)
3 - 6 ASM	5	11	16	34 (67%)
Baseline log-transformed motor seizures per 28-day, mean (SE)	4.0 (0.4)	3.3 (0.3)	5.04 (0.3)	4.72 (0.19)

Consistent and Clinically Meaningful Effect

Placebo-adjusted seizure reduction – Cohort 1 and Cohort 2



Large, Consistent and Clinically Meaningful Effect in Seizure Reduction

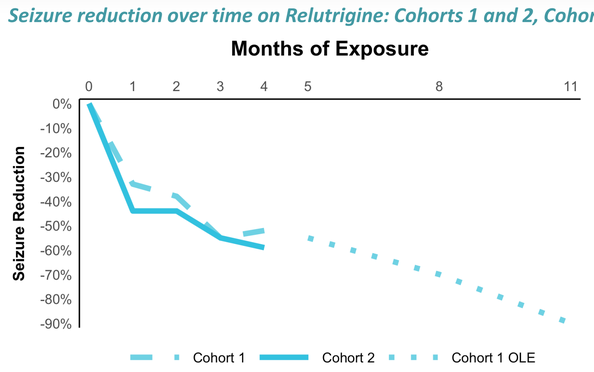
Relutrigine demonstrated placebo-adjusted seizure reduction in 16 weeks of 46% (p=0.0354) in the first cohort and 53% (p<0.0002) in the confirmatory, registration cohort

The effect was consistent in SCN2A and SCN8A patients

Overall Effect: Rapid, Durable Seizure Reduction with Strong Functional and Global Improvement

- Rapid and substantial early seizure reduction with sustained and progressively deepening effect over time
- Consistent treatment response across cohorts
- Meaningful functional improvement, reflected by a 66% increase in motor seizure-free days
- Robust clinician and caregiver reported global scores

Seizure reduction over time on Relutrigine: Cohorts 1 and 2, Cohort 1 OLE



Cohort 2 Key Secondary Endpoints

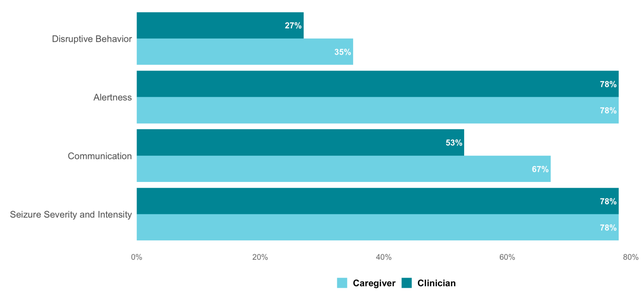
Key Secondary	Estimate	p-value
Motor seizure-free days	**+66.2%**	0.0340
CGI-I (Clinician)	**-2.62**	<0.0001
CgGI-I (Caregiver)	**-3.7**	0.002

Marked Improvement in Disease Modifying Domains

Broad, Clinically Meaningful Improvements Across Behavior, Function and Overall Status

- Global status improved substantially, with both clinician and caregiver scales showing large placebo-adjusted gains in a single 28-day period by > 25% in favor of relutrigine
- Marked behavioral benefit
- Strong enhancement in alertness
- Meaningful advances in communication
- Consistent reduction in seizure severity and intensity

Proportion of participants improving by domain – Last visit on relutrigine



Relutrigine Continues to be Well-Tolerated

Cohort 2 demonstrates a consistent safety and tolerability profile

- TEAEs mostly mild to moderate
- 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 and ECGs

Table 2. EMBOLD Tolerability Summary – Rate of Observed Occurrence (normalized to a per 100-patient-months of exposure)

	PLACEBO (n=25)	RELUTRIGINE (n=51)
TEAEs > 10% of Patients		
Pyrexia	13.35	11.74
Upper Respiratory Infection	4.45	9.79
Somnolence	13.35	9.13
Irritability	4.45	5.22
Diarrhea	8.90	4.57
Constipation	8.90	3.92
Cough	None	3.92
Vomiting	8.90	3.92

Conclusions

- **Relutrigine was well-tolerated with rapid, significant, and increasing seizure reduction over time with broad functional improvements across behavior, alertness, communication, and overall status. The pattern of early onset, sustained progression, and multi-domain benefit is consistent with disease modification and supports relutrigine's potential as best-in-class therapy for both SCN2A-DEE and SCN8A-DEE.**

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