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Efficacy and Safety of Relutrigine in Pediatric Participants with *SCN2A*- and *SCN8A*-Related Developmental and Epileptic Encephalopathies: Results from the EMBOLD Study

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Disclosure: Antonio Gil-Nagel is a Study Investigator

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DEEs Are Demanding and Devastating with Early Mortality

Epilepsy and other morbidities, arising from diverse pathologies that cause Nav dependent neuronal hyperexcitability

Multiple etiologies: genetic, structural, metabolic, … including *SCN2A* and *SCN8A*-DEE, where mutations directly alter Na_V channel function

Characterized by frequent seizures, and developmental disabilities, typically beginning in infancy

Treatment is sub-optimal, often associated with safety and tolerability issues

Significantly impact quality of life for both patients and their caregivers

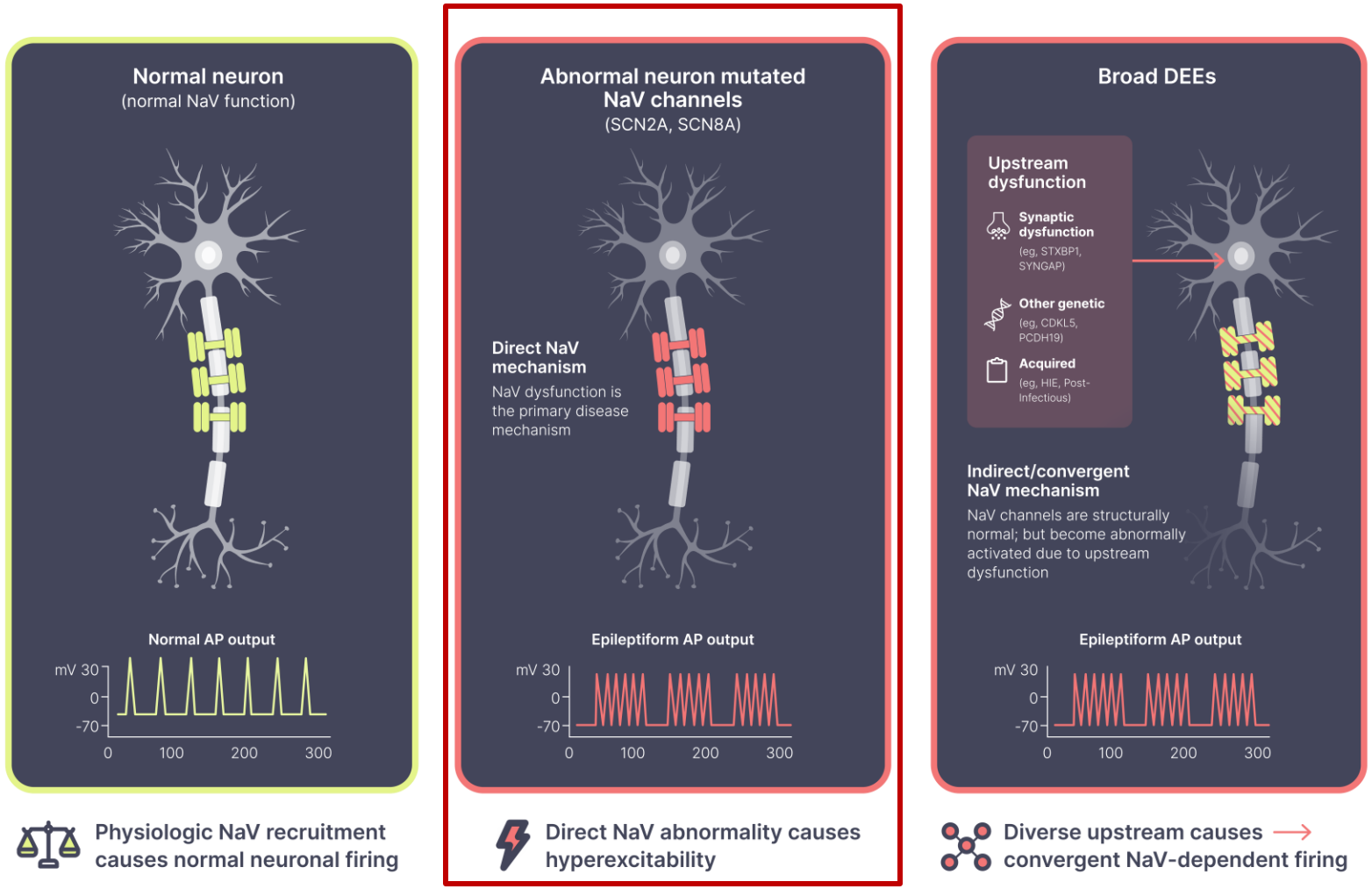
Life-expectancy significantly shortened, with SUDEP and aspiration pneumonia amongst common causes of early mortality

DEE=developmental and epileptic encephalopathy; Na_V=voltage-gated sodium channel; SUDEP=Sudden Unexpected Death in Epilepsy

Scheffer et al. *Nat Rev Dis Primers*. 2024;10(1):61; Wolff et al. *Brain*. 2017;140:1316-36; Wagnon & Meisler. *Front Neurol*. 2015;6:104; Zuberi et al. *Epilepsia*. 2022;63(6):1349-97; Gallop et al. *Epilepsy Behav*. 2021;124:108324; Johannessen Landmark et al. *Epilepsia*. 2021;62(4):857-73; Donnan et al. *Neurology*. 2023;100:e1712-22; Radaelli et al. *Epilepsy & Behavior*. 2018;85:32-6

Direct vs Indirect Voltage-Gated Sodium Channel (Na_V) Involvement in DEEs

- Across DEEs, Na_V channels either directly drive hyperexcitability as the primary genetic mechanism (eg in *SCN2A*- or *SCN8A*-DEE) or serve as the downstream convergence point through which diverse upstream pathology indirectly produces hyperexcitability (broad DEEs)
- The development of Na_V channel modulators with selective affinity for sodium channels involved in pathological firing holds significant promise



AP=action potential; DEE=developmental and epileptic encephalopathy; Na_V=voltage-gated sodium channel

Scheffer et al. *Nat Rev Dis Primers*. 2024;10(1):61; Wengert et al. *J Neurosci*. 2021;41(44):9257-73; Guerrini et al. *Physiol Rev*. 2023;103(1):433-513; Berecki et al. *Proc Natl Acad Sci U S A*. 2018;115(24):E5516-25; Mao et al. *J Neurosci*. 2024;44(8):e0692232023; Kaplan et al. *Cold Spring Harb Perspect Med*. 2016;6(6):a022814

Relutrigine: Small Molecule Functional State Modulator

Relutrigine

No titration required

Once daily dosing

Liquid formulation

Oral or G/J tube administration

Precision Mechanism:

- Na_V channel modulator that preferentially blocks the persistent, voltage-dependent, and use-dependent Na current, while sparing the transient/peak current, essential for normal physiologic signaling

Clinical Profile

- In EMBOLD study, demonstrated robust seizure reduction and marked seizure-free periods in SCN2A- and SCN8A-DEE over 28-day intervals
- Generally well tolerated with mostly mild to moderate AEs, no drug-related SAEs and no dose reductions required

Regulatory Designations

- FDA: Orphan Drug, Rare Pediatric Disease Designations for SCN2A-DEE, SCN8A-DEE, and Dravet syndrome, plus Breakthrough Therapy Designation
- EMA: Orphan Drug Designations for SCN2A-DEE and SCN8A-DEE
- NDA accepted, granted priority review, December 2026 PDUFA target action date

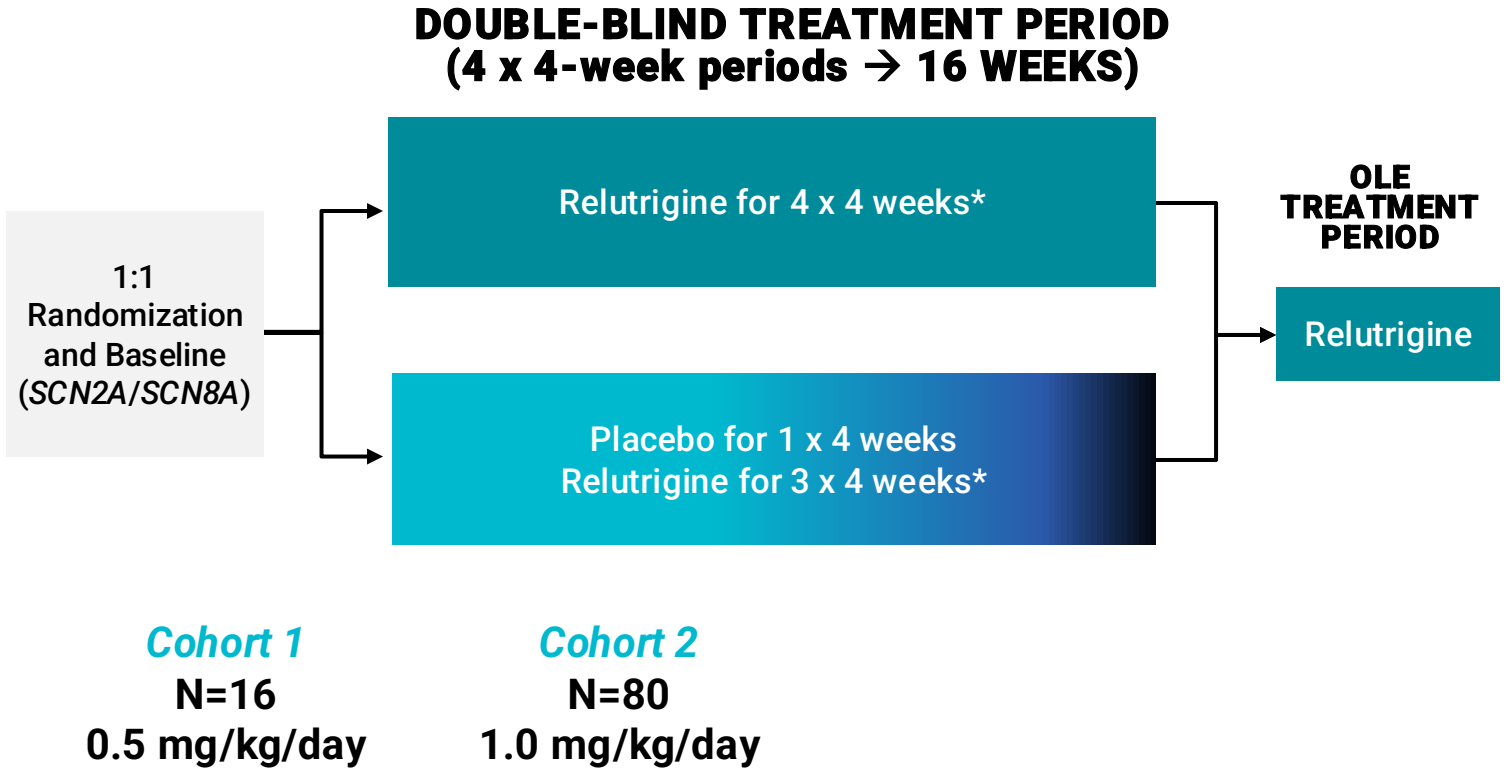
AE=adverse event; DEE=developmental and epileptic encephalopathy; Na_V=voltage-gated sodium channel; SAE=serious adverse event
Relutrigine is an investigational drug and has not been approved by any regulatory body for use.
Kahlig et al. *Epilepsia.* 2022;63:697-708; Kamireddy et al. AES 2025; Bialer et al. *Epilepsia*. 2026;00:1-51

PHASE 2/3 CLINICAL TRIAL
EMBOLD STUDY

Relutrigine showed well-tolerated efficacy in patients with SCN2A- and SCN8A-DEEs, along with marked improvements across multiple functional domains

Relutrigine is an investigational drug and has not been approved by any regulatory body for use.

EMBOLD Pivotal Relutrigine Study in Children with *SCN2A*-DEE or *SCN8A*-DEE



KEY ENDPOINTS:

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

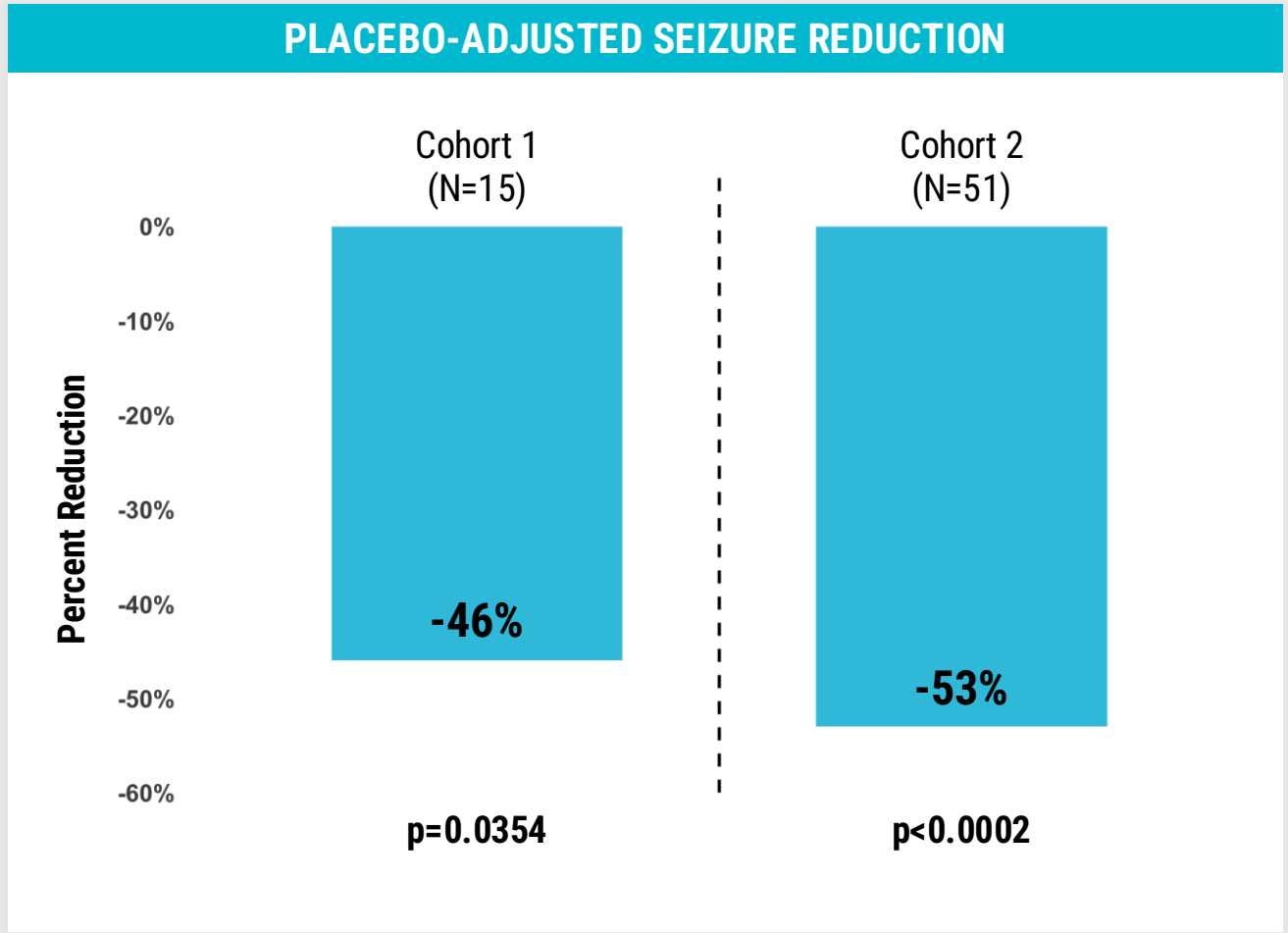
DEE=developmental and epileptic encephalopathy; OLE=open-label extension; QD=once daily dosing; Cohort 1 Starting dose of 0.5 mg/kg/day with optional increase to 1.0 mg/kg/day; ClinicalTrials.gov Identifier: NCT05818553 *Participants randomized (1:1) to receive relutrigine QD for 16 weeks, or relutrigne QD for 12 weeks and matching placebo QD for 4 weeks, with timing of placebo administration blinded for both participants and investigator. Frizzo et al. IEC 2025; Kamireddy et al. AES 2025

Participant Demographics (N=67 patients)

	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=20 (30%)	4 (50%)	7 (44%)	7 (28%)	13 (25%)
SCN8A, n=47 (70%)	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, n=21 (31%)	2	4	9	17 (33%)
3 - 6 ASM, n=45 (67%)	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)

ASM=antiseizure medication; DEE=developmental and epileptic encephalopathy; SE=standard error; >80% of patients were on stable doses of sodium channel blockers (SCBs) at baseline
*1 patient in Cohort 1 had previously failed ASMs and was on 0 ASM at the start of the clinical trial
Kamireddy et al. AES 2025

Consistent and Clinically Meaningful Effect in Seizure Reduction

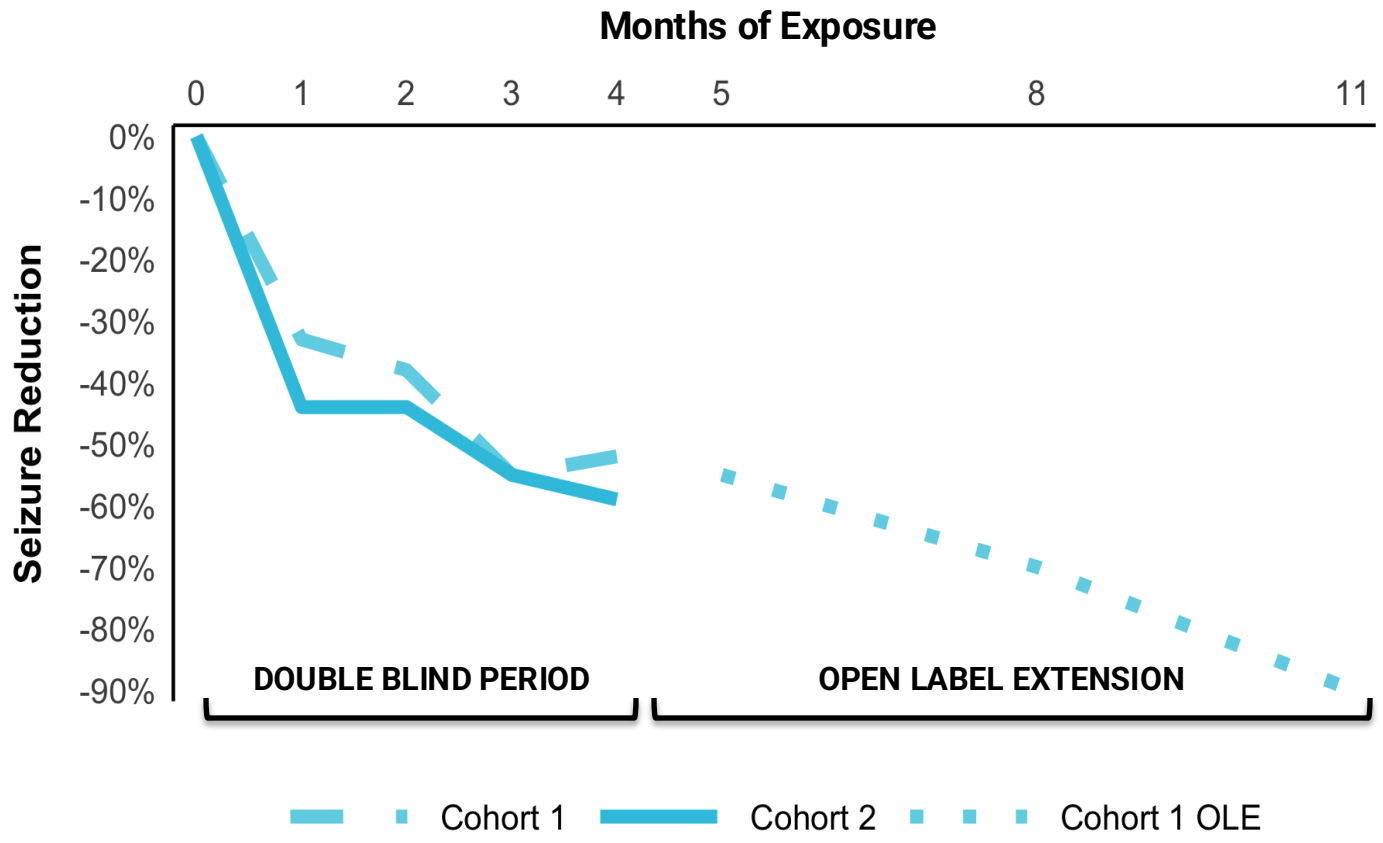


- Placebo-adjusted seizure reduction in 16 weeks of:
  - 1st cohort: 46% (p=0.0354)
  - 2nd cohort: 53% (p<0.0002)
- Effect was similar in participants with *SCN2A*- and *SCN8A*-DEE

DEE=developmental and epileptic encephalopathy
Kamireddy et al. AES 2025; Bialer et al. *Epilepsia*. 2026;00:1-51

Overall Effect: Rapid, Sustained Seizure Reduction on Top of Standard of Care

Seizure Reduction over Time on Relutrigine – Cohorts 1 and 2, Cohort 1 OLE



- Rapid and substantial early seizure reduction with sustained and progressively deepening effect over time
- Robust short- and long-term improvements; 90% seizure reduction at 11 months in Cohort 1 OLE
- Consistent treatment response across cohorts

OLE=open-label extension
Cohort 1 (N=15); Cohort 2 (N=51); Inclusive of OLE period as of April 24, 2025; data available at Month 11 for 13 participants
Kamireddy et al. AES 2025; Bialer et al. *Epilepsia*. 2026;00:1-51

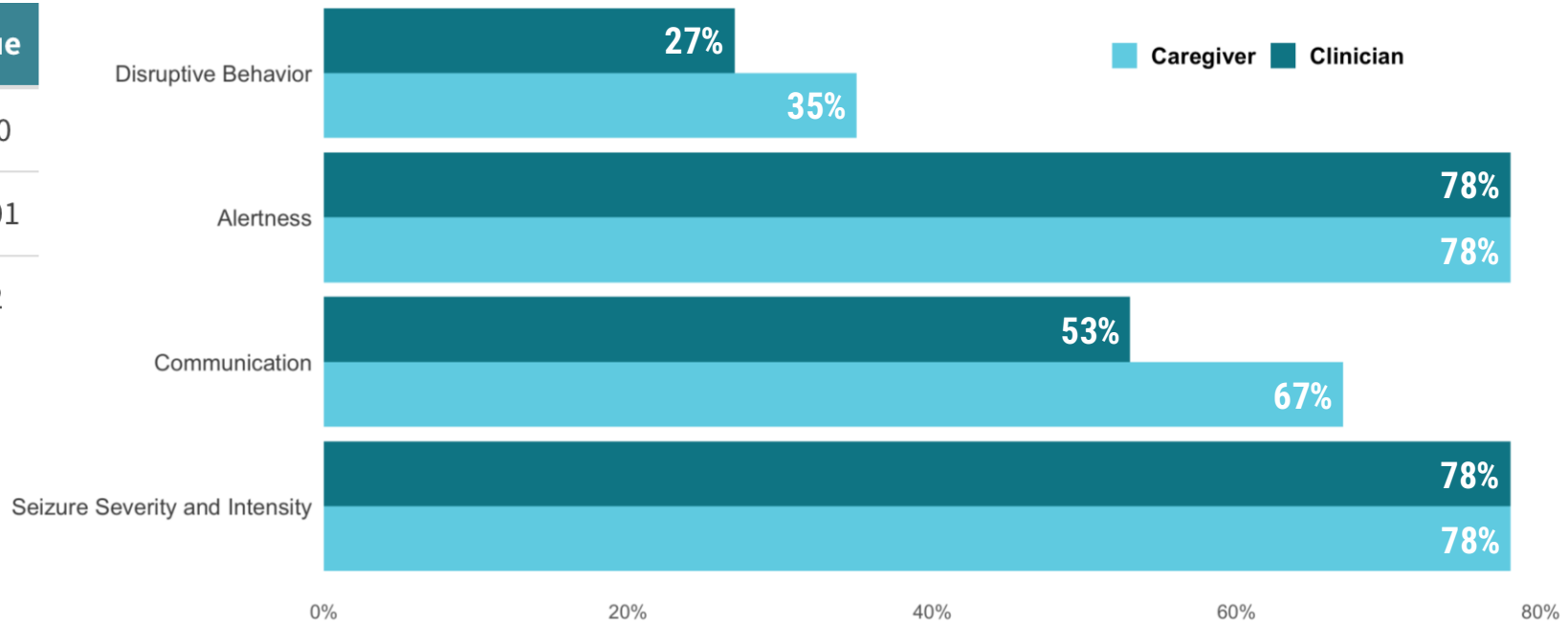
EMBOLD Cohort 2: All Key Secondary Endpoints Met

Seizure Freedom and Clinician- and Caregiver-Rated Functional Improvements

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

Proportion of Participants Improving by Domain – Last Visit on Relutrigine



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

CgG-I=Caregiver Global Impression of Improvement; CGI-I=Clinical Global Impression of Improvement; CGI-I and CgGI-I assessed at Week-16 visit

Kamireddy et al. AES 2025; Bialer et al. *Epilepsia*. 2026;00:1-51

Relutrigine Was Generally Well Tolerated

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

- TEAEs mostly mild to moderate
- No drug-related SAEs
- No dose reductions of relutrigine required
- 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

ECG=electrocardiogram; SAE=serious adverse event; TEAE=treatment-emergent adverse event

Kamireddy et al. AES 2025; Bialer et al. *Epilepsia*. 2026;00:1-51

Summary

- **Marked Seizure Reduction with Broad Functional Benefits.** Rapid and sustained improvements in seizure control and functional outcomes, with marked seizure-free periods over 28-day intervals, in patients with *SCN2A*- and *SCN8A*-DEE.
- **Strong Safety and Tolerability.** Generally well tolerated with mostly mild to moderate AEs, no drug-related SAEs and no dose reductions required.
- **Potential Across Broad DEEs.** Recruitment for the EMERALD study in broad DEEs is complete, with topline results expected in the fourth quarter of 2026.

Positive EMBOLD results triggered early stop for efficacy, and the FDA has accepted with priority review the relutrigine NDA for the treatment of *SCN2A*- and *SCN8A*-DEEs, with a PDUFA target action date of December 2026

AE=adverse event; DEE=developmental and epileptic encephalopathy; SAE=serious adverse event

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Questions?

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