



Preclinical Findings of Relutrigine, a Precision Sodium Channel Modulator, Highlight Anticonvulsant Potential Across Broad DEEs

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BACKGROUND

- Developmental and epileptic encephalopathies (DEEs) are severe, early-onset epilepsies characterized by frequent seizures, severe neurodevelopmental delays and high early mortality.
- To date, no medications have been developed specifically for DEEs.
- Across DEEs, voltage-gated sodium (Na_v) channels directly drive hyperexcitability as the primary genetic mechanism, or serve as the downstream convergence point through which diverse upstream pathology leads to hyperexcitability.
- Relutrigine represents a differentiated sodium channel modulator class designed to precisely target the hyperexcitable state of sodium channels, and is currently in development for all DEEs.
- Relutrigine has shown efficacy in *Scn2a*- and *Scn8a* DEE mouse models, as well as clinical evidence of robust seizure reduction and broad functional improvements in *SCN2A*- and *SNC8A*-DEE.
- While use of sodium channel blockers in Dravet syndrome remains controversial, emerging preclinical and clinical data suggest that sodium channel modulation may be an appropriate therapeutic strategy in Dravet syndrome, highlighting relutrigine's therapeutic potential across DEEs.
- Consistent with this, relutrigine recently received Rare Pediatric Disease designation for Dravet syndrome, supported by clinical findings from the EMBOLD study demonstrating well-tolerated seizure reduction and freedom in *SCN2A*- and *SCN8A*-DEE.
- Here, we present preclinical evidence for relutrigine's anticonvulsant potential across diverse DEE models, extending evaluation to Dravet syndrome and non- Na_v DEEs (*Kcnc2*^{K556E/+}, *Kcnc1*^{R320H/+} and *Hcn1*^{M294L/+}).**

Relutrigine

- SMALL MOLECULE FUNCTIONAL STATE MODULATOR
- NO TITRATION REQUIRED
- ONCE DAILY DOSING
- LIQUID FORMULATION, ORAL OR G/J-TUBE ADMINISTRATION

- Demonstrated robust seizure reduction and marked seizure-free status over 28-day intervals in *SCN2A* and *SCN8A*-DEE
- Generally well-tolerated with mostly mild to moderate AEs, no drug-related SAEs and no relutrigine dose reduction required
- FDA: Orphan Drug, Rare Pediatric Disease Designations for *SCN2A*-DEE, *SCN8A*-DEE, and Dravet syndrome, plus Breakthrough Therapy
- EMA: Orphan Drug Designations for *SCN2A*-DEE and *SCN8A*-DEE
- NDA accepted by FDA, granted priority review, December 27, 2026 PDUFA target action date

METHODS

Acute Seizure Models

- Wild-type (WT) male CD-1 mice were used for MES and 6-Hz acute seizure experiments.
- Mice were administered either vehicle or relutrigine by oral gavage 30 min prior to electrical stimulus.
- Transauricular (50Hz, 0.8s, 10ms square pulse width, 50mA) and corneal electroshocks (6Hz, 3s, 0.2ms rectangular pulse width, 32mA) were delivered for MES and 6-Hz experiments, respectively.
- Mice were observed for the presence or absence of full tonic hindlimb extension (MES), or psychomotor seizures defined as stun/immobility, forelimb clonus, Straub tail and lateral head movement (6-Hz).

Na_v DEE Models

- Anticonvulsant activity of relutrigine was evaluated by comparing the number of spontaneous seizures during a 30 min pre-treatment period with the number occurring during a 30 min post-treatment period in *Scn2a*^{Q54} mice.
- Scn8a*^{N1768D/+} mice were treated with vehicle or relutrigine by oral gavage 60 min prior to acoustic stimulus (15Hz). Mice were observed for the presence or absence of seizure.

Non- Na_v DEE Models

- Mice (*Kcnc2*^{K556E/+}, *Kcnc1*^{R320H/+}) were pre-treated with vehicle or relutrigine by oral gavage 60 min prior to administration of PTZ (100mg/kg, s.c.).
- Mice were observed until the onset of first tonic-clonic seizure with hindlimb extension or a time of 40 min reached.
- Spontaneous electroencephalographic seizures were measured in *Hcn1*^{M294L/+} mice pre- and post-treatment with vehicle, relutrigine or lamotrigine.

Spontaneous Locomotor Activity (sLMA)

- Wild-type (WT) male CD-1 mice were used for sLMA experiments.
- Mice were pre-treated with vehicle or relutrigine for 30 min, then total distance travelled in a 30 min period was measured. Distance travelled following treatment with relutrigine was normalized to that of vehicle-treated mice.
- Carbamazepine and lamotrigine were also assessed using MES and sLMA. Protective index values were calculated by dividing the TC_{50} plasma concentrations from sLMA by the EC_{50} concentrations from MES.

Zebrafish Model of Dravet Syndrome

- The anticonvulsant potential of relutrigine was assessed in the *scn1Lab*^{s552/s552} zebrafish model of Dravet syndrome, which displays convulsive swim behaviors related to high-velocity movements.
- Wildtype and heterozygous zebrafish larvae as controls and *scn1Lab*^{s552/s552} larvae at 5 days post-fertilization were used.
- Following incubation with vehicle, relutrigine or fenfluramine for 1 hour, locomotor activity of individual larvae was tracked with the DanioVision/EthoVision automated tracking system to measure total distance travelled at high velocity (>20 mm/s) and maximum velocity.
- Values were normalized to those of *scn1Lab* and means from independent cohorts were combined. Standard error was calculated using the Satterthwaite approximation to combined standard deviations.
- Concentration-response curves were generated and fit with a four-parameter log function with constraints: top, 100; bottom constrained to control (40% relutrigine, 38% fenfluramine, 19% bexicaserin) and EC_{50} values calculated.

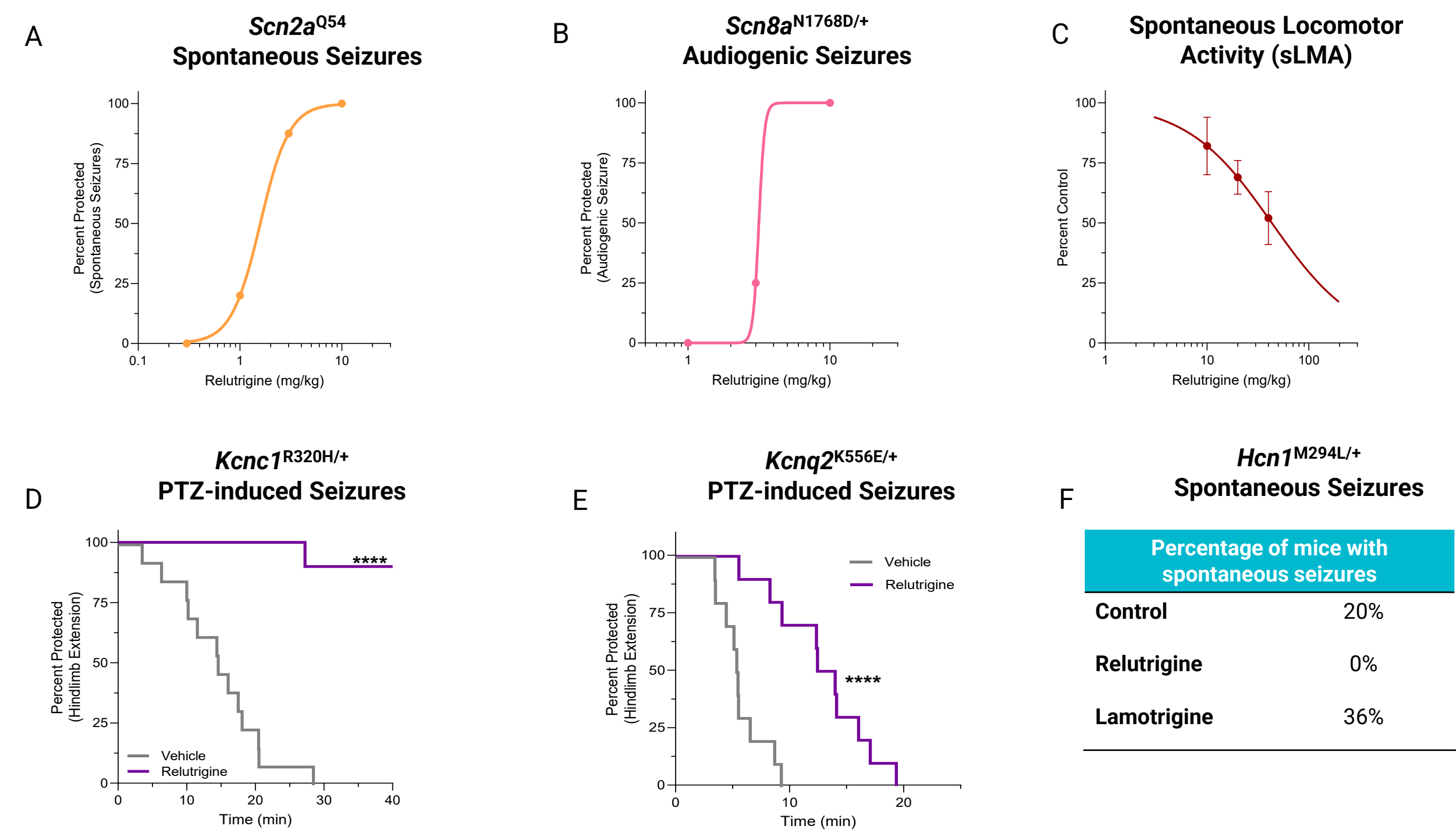
CONCLUSIONS

- Relutrigine shows robust anticonvulsant activity across mechanistically divergent genetic models of human epilepsy and markedly improved preclinical tolerability compared to standard-of-care Na_v blockers
- Anticonvulsant action in a zebrafish model of Dravet syndrome further points to its potential for superior efficacy over current standard-of-care.
- Together with clinical results from the EMBOLD study in *SCN2A* and *SCN8A*-DEE, relutrigine's profile to date highlights its potential to address significant unmet needs across the spectrum of DEEs, regardless of etiology.

RELUTRIGINE EXHIBITS ROBUST PRECLINICAL ANTICONVULSANT ACTIVITY ACROSS MULTIPLE GENETIC DEE MODELS

- Relutrigine protects from spontaneous seizures in *Scn2a*^{Q54} and audiogenic-induced seizures in *Scn8a*^{N1768D/+} mice.
- Relutrigine is anticonvulsant against PTZ-induced seizure in the *Kcnc1*^{R320H/+} DEE model and wildtype littermates, and PTZ-induced seizure in the *Kcnc2*^{K556E/+} DEE model.
- Relutrigine abolishes seizures in the *Hcn1*^{M294L/+} DEE model, while lamotrigine worsens them, mirroring clinical reports.

Anticonvulsant efficacy in DEE mouse models with both Na_v and non- Na_v channel mutations



Relutrigine is anticonvulsant in DEE mouse models with Na_v channel mutations and increases latency to PTZ-induced seizures in *Kcnc1*^{R320H/+} and *Kcnc2*^{K556E/+} mice. **A)** Dose-response curve for protection from spontaneous seizures in *Scn2a*^{Q54} mice. Curve represents fit to a four-parameter log function and ED_{50} value is presented in **Table below**. **B)** Dose-response curve for protection from audiogenic-induced seizures in *Scn8a*^{N1768D/+} mice, with n = 8 per treatment. Curve represents fit to a four-parameter log function and ED_{50} value is presented in **Table below**. **C)** Dose-response curve for relutrigine inhibition of spontaneous locomotor activity of wildtype CD-1 mice. Data are presented as mean $\pm$ SEM, with n = 10 per treatment. Curve represents fit to a four-parameter log function and TD_{50} value is presented in **Table below**. **D)** Curves of tonic hindlimb extension incidence induced by PTZ in *Kcnc1*^{R320H/+} (*Kcnc1*^{RH/+}) mice treated with vehicle or 10 mg/kg PRAX-562 administered orally 60 min before PTZ. The latency to tonic hindlimb extension significantly increases following treatment with relutrigine, with n = 8-13 per group, (**** p < 0.0001, logrank Mantel-Cox). **E)** Curves of tonic hindlimb extension incidence induced by PTZ in *Kcnc2*^{K556E/+} (*Kcnc2*^{KE/+}) mice treated with vehicle or 10 mg/kg relutrigine administered orally 60 min before PTZ. The latency to tonic hindlimb extension in *Kcnc2*^{KE/+} mice is significantly increased following treatment with relutrigine, with n = 8-10 per group (**** p < 0.0001, logrank Mantel-Cox). **F)** Relutrigine abolishes seizures in *Hcn1*^{M294L/+} mice and lamotrigine worsens seizures (n = 10-12 mice per group).

Relutrigine has a larger acute protective index compared with standard Na_v -targeting AEDs

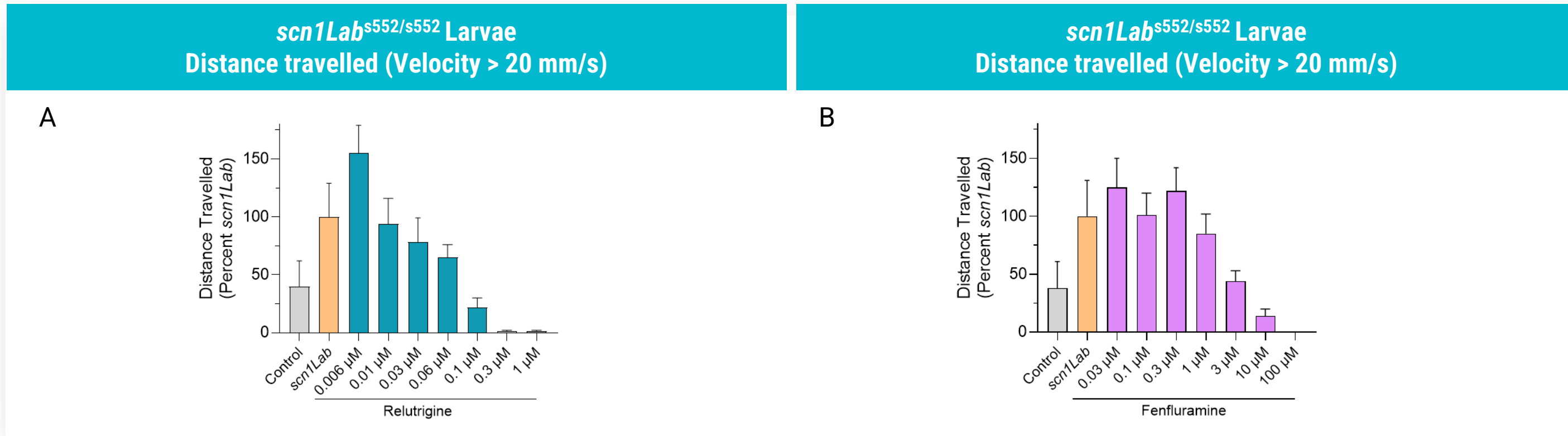
	Efficacy (MES)		6-Hz	Scn2a-Q54		Scn8a-N1768D		Tolerability (sLMA)		Protective Index	
	ED ₅₀ (mg/kg)	Plasma EC ₅₀ (ng/mL)	ED ₅₀ (mg/kg)	Plasma EC ₅₀ (ng/mL)	ED ₅₀ (mg/kg)	Plasma EC ₅₀ (ng/mL)	ED ₅₀ (mg/kg)	Plasma EC ₅₀ (ng/mL)	TD ₅₀ (mg/kg)	Plasma TC ₅₀ (ng/mL)	sLMA TC ₅₀ / MES EC ₅₀
Relutrigine	2.2	102	10.4	291	1.6	34	3.3	101	43.2	1388	13.6
Carbamazepine	5.4	5317			n.d.				37.5	16523	3.1
Lamotrigine	3.8	2353			n.d.				26.4	13980	5.9
n.d.=not determined											

n.d.=not determined

Relutrigine shows robust anticonvulsant activity across mechanistically divergent genetic models of human epilepsy and markedly improves preclinical tolerability compared with standard-of-care.

RELUTRIGINE POTENTLY REVERSES SEIZURE-LIKE BEHAVIOR IN THE ZEBRAFISH MODEL OF DRAVET SYNDROME

- Relutrigine significantly reversed seizure-like behavior in the *scn1Lab*^{s552/s552} zebrafish model of Dravet syndrome, demonstrating reductions in both total distance travelled at high velocity (>20 mm/s) and mean velocity.
- Relutrigine was more potent than fenfluramine in reversing seizure-like behavior.



Antiseizure Activity EC ₅₀ (μM)	
Relutrigine	0.04
Fenfluramine	1.4
Bexicaserin	15,789 ^a

^aDigitized data from AES 2023 poster

Relutrigine reverses seizure-like behavior (total distance travelled at velocity >20 mm/s) in a zebrafish model of Dravet syndrome. Concentration-response of relutrigine (**A**) and fenfluramine (**B**) on total distance travelled at high velocity (>20 mm/s) plotted as a percent of *scn1Lab*. Distance travelled for *scn1Lab* larvae were 35 $\pm$ 11 mm. Bars represent mean $\pm$ SEM, with n=22-24 per cohort, with 1-3 independent cohorts per group. **Table** shows corresponding EC_{50} values calculated from concentration-response curves fit with a four-parameter log function, along with digitized bexicaserin data as presented at AES 2023.

Relutrigine shows significant and superior reversal of seizure-like behaviors compared to standard ASMs in the *scn1Lab*^{s552/s552} zebrafish model of Dravet syndrome

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