Preclinical Findings of Relutrigine, a Precision Sodium Channel Modulator, Point to Anticonvulsant Potential in Dravet Syndrome

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Background

- Developmental epileptic encephalopathies (DEEs) are caused by diverse etiologies all of which converge on the same neurobiological mechanism of network hyperexcitability.
- Dravet syndrome is a severe, intractable DEE largely resulting from *SCN1A* haploinsufficiency and is characterized by frequent seizures, behavioral and developmental delays and increased mortality.
- While the 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.
- Relutrigine represents a differentiated sodium channel modulator class which exhibits selectivity for disease-state sodium channel hyperexcitability and is currently in development as a first- and best-in-class precision sodium channel modulator for all DEEs.
- Relutrigine has recently received Rare Pediatric Disease designation for Dravet syndrome, building on encouraging clinical findings from the EMBOLD study demonstrating well-tolerated seizure reduction and freedom in *SCN2A* and *SCN8A*-DEE.

➢ ***Here, we evaluate the effect of relutrigine in a zebrafish model of Dravet syndrome.***

Relutrigine demonstrates superior functional selectivity

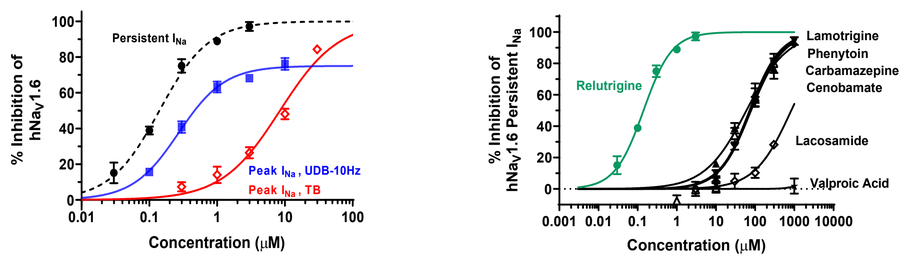
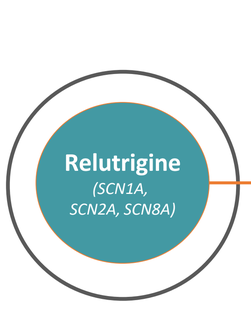


Figure 1. HEK-293 whole-cell patch clamp recordings with relutrigine and standards of care



- ❖ ORAL SOLUTION, NO TITRATION, ONCE DAILY ADMINISTRATION
- ❖ FORMULATED FOR PEDIATRIC USE
- ❖ SMALL MOLECULE
- ❖ FUNCTIONAL STATE MODULATOR

- Demonstrated robust seizure reduction and unprecedented seizure-free status per 28-day period in *SCN2A* and *SCN8A*-DEE
- Superior selectivity for hyperactive Na_V channels, a known cause of seizure manifestation in all DEEs regardless of etiology
- Generally well-tolerated with mostly mild to moderate AEs, no drug-related SAEs and no relutrigine dose reduction required
- Three Rare Pediatric Drug designations for Dravet syndrome (*SCN1A*), *SCN2A*-DEE and *SCN8A*-DEE

Methods

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). EC_{50} values were calculated from these fit curves.

Conclusions

- **Anticonvulsant action of relutrigine in a zebrafish model of Dravet syndrome points to its potential for superior efficacy over current standard-of-care.**
- **Combined with recent results from the EMBOLD study in *SCN2A* and S*CN8A*-DEE, these findings emphasize the promising potential of relutrigine to address significant unmet needs across the spectrum of DEEs.**
- **The EMERALD registrational study targeting phenotypic DEE regardless of etiology is currently enrolling, expanding the clinical profile of relutrigine to address the significant unmet meet across broad DEEs.**

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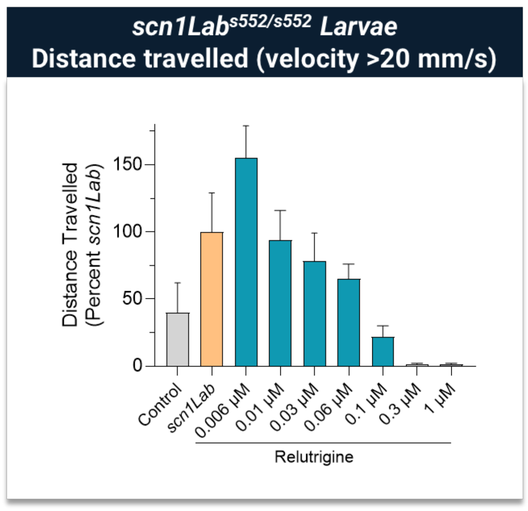
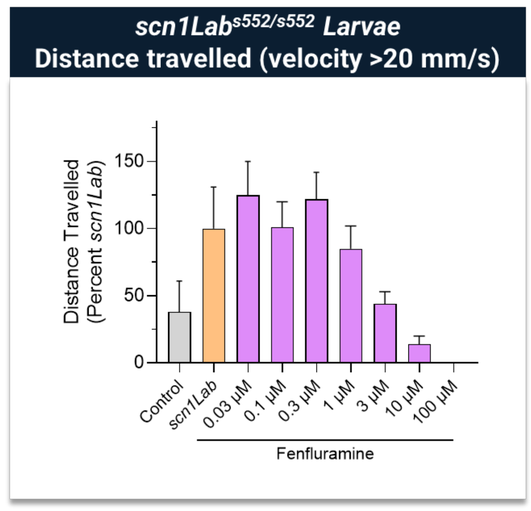
Relutrigine potently reverses seizure-like behavior in the zebrafish model of Dravet Syndrome

- 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.



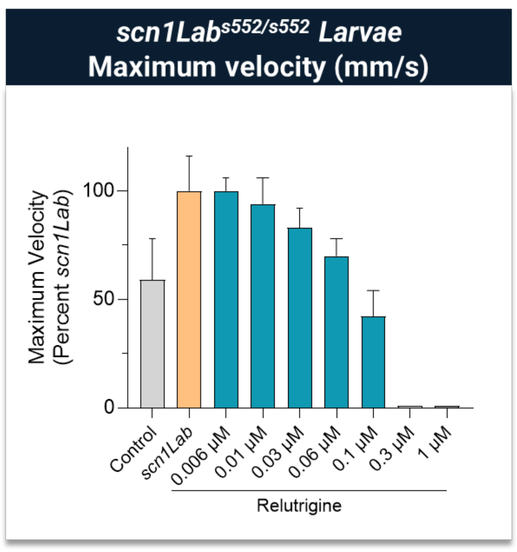


Antiseizure Activity EC_{50} (μM)

Relutrigine	**0.04**
Fenfluramine	1.4
Bexicaserin	15,789^

^Digitized data from AES 2023 poster.

Figure 2. Relutrigine reverses seizure-like behavior (total distance travelled at velocity >20 mm/s) in a zebrafish model of Dravet syndrome. *Concentration-response of relutrigine (left) and fenfluramine (right) on total distance travelled at high velocity (>20 mm/s) plotted as a percent of scn1Lab. Distance travelled for scn1Lab larvae were 35 ± 11 mm. Bars represent mean ± 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.*



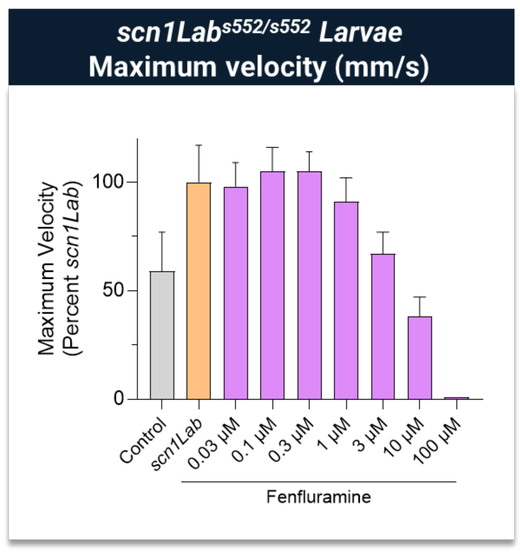


Figure 3. Relutrigine reverses seizure-like behavior (maximum velocity) in a zebrafish model of Dravet syndrome. *Concentration-response of relutrigine (left) and fenfluramine (right) on maximum velocity plotted as a percent of scn1Lab. Maximum velocity for scn1Lab larvae were 98 ± 15 mm/s. Bars represent mean ± SEM, with n = 22-24 per cohort, with 1-3 independent cohorts per group.*

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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