Vormatrigine Rapidly Reduces Seizures in Adults with Treatment-Resistant Epilepsy: Results from the RADIANT Open Label Phase 2 Study

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Background

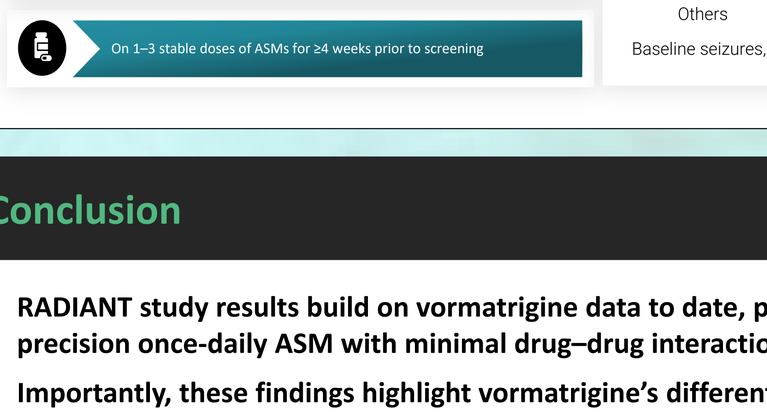
- Epilepsy affects ~50 million individuals worldwide with a significant number experiencing uncontrolled seizures despite antiseizure medications (ASMs).
- While sodium channel blockers remain a cornerstone of antiseizure therapy, approved medications have limited efficacy or dose-limiting side effects.
- Vormatrigine is a functional state modulator precisely targeting the hyperexcitable state of sodium channels in the brain, and is in development for adult focal onset seizures (FOS) and generalized epilepsy.
- Recent data highlight a superior preclinical and early clinical profile compared to approved ASMs, demonstrate a favorable safety and tolerability profile in doses up to 45 mg, with no clinically significant food effect.
- Notably, emerging data demonstrate vormatrigine's ability to significantly exceed therapeutic concentrations while being well tolerated, without the need for titration.
- The RADIANT study was designed to evaluate vormatrigine's efficacy, safety, and pharmacokinetics in adult patients with FOS or idiopathic primary generalized tonic-clonic seizures (PGTS).

➢ ***Here we present results from the initial cohort of subjects with FOS.***

Methods

RADIANT Study Design

- RADIANT (NCT06908356) is a Phase 2, open-label, single-arm, multicenter clinical trial enrolling participants aged 18-75 years diagnosed with FOS or ideopathic PGTS based on the ILAE classification.
- Participants received vormatrigine 30mg daily for 8 weeks, with the study consisting of Screening/Observation (Baseline), Treatment and Follow-up periods.
- As of July 25, 2025, a total of 61 participants have been dosed, with efficacy data presented for the initial cohort of 37 participants with FOS.



PRIMARY ENDPOINT

- Median percent change in monthly (28 days) seizure frequency from Baseline to Treatment Period

SECONDARY EFFICACY ENDPOINTS

- Proportion of subjects experiencing seizure freedom, 100% reduction in monthly (28 days) seizure frequency from Baseline to Treatment Period

Figure 1. RADIANT Study Design.

Participant Eligibility and Baseline Characteristics

Key Inclusion Criteria

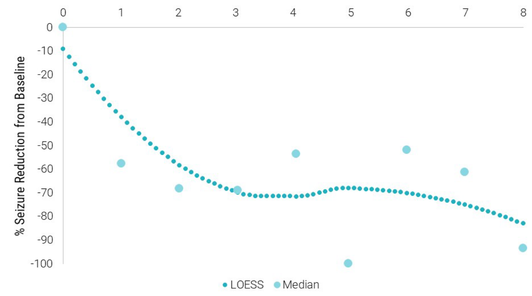
- A diagnosis of FOS or idiopathic PGTS according to ILAE Classification (2017), and progressive epilepsy cause ruled out on CT or MRI
- Male or female aged 18-75 years inclusive
- ≥2 countable seizures per month for FOS patients, or 1 countable generalized tonic-clonic seizure per month in the 3 months prior to screening for PGTS patients
- On 1–3 stable doses of ASMs for ≥4 weeks prior to screening

Table 1. Demographics and Baseline Characteristics

	N = 37
Age (Years), mean (SD)	43.1 (12.78)
Sex (Male, Female)	14, 23
# Background ASMs, mean (SD)	2.2 (0.81)
Concomitant ASM	
Sodium Channel Blocker	81%
SV2A	65%
GABA modulators	30%
Others	5%
Baseline seizures, median (IQR)	12 (5, 25)

RADIANT Results Point to Vormatrigine Best-in-disease Efficacy

MEDIAN % SEIZURE REDUCTION BY WEEK



56%

Rapid, sustained overall seizure reduction

- 56.3% median seizure reduction across the treatment period (n=37)
- 54% achieving ≥ 50% response in 1st week (n=37)

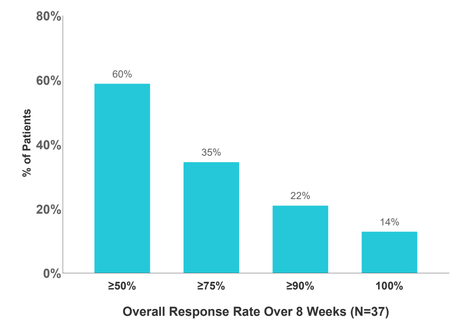
Wilcoxon sign test p<0.05 in all weeks and overall; LOESS: Locally weighted plot smoothing

Robust Response Rate

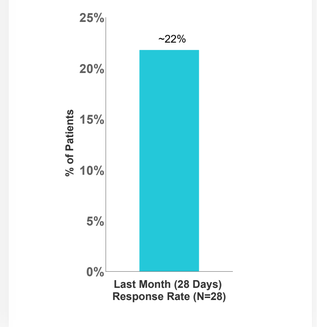
Meaningful seizure reduction

- Majority experienced meaningful seizure reduction across the treatment period
- 14% achieving seizure freedom overall (n=37) and >20% seizure free during last month of treatment (n=28)

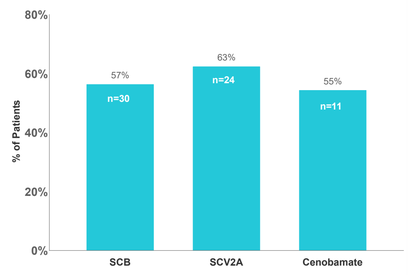
RESPONDER RATES BY SEIZURE REDUCTION THRESHOLD



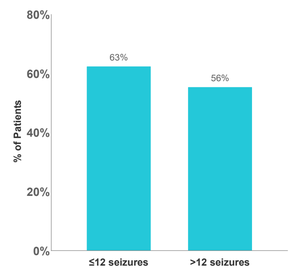
PATIENTS WITH 100% REDUCTION



PROPORTION OF PATIENTS ACHIEVING ≥50% REDUCTION ON TOP OF BACKGROUND ASMs



PROPORTION OF PATIENTS ACHIEVING ≥ 50% REDUCTION BY BASELINE SEIZURE BURDEN



Consistent efficacy

Across background ASMs and baseline seizure burden

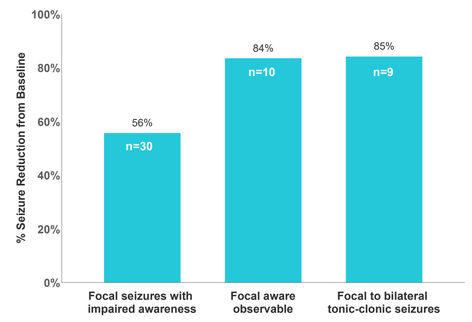
- Over 55% of patients achieved ≥50% response when added to background ASMs including SCBs, SV2A agents, and cenobamate (used by ~30% of participants)
- Robust response independent of baseline seizure burden

Consistent efficacy

Across seizure types

- Marked seizure reduction across seizure subtypes
  - Focal aware observable
  - Focal seizures with impaired awareness
  - Focal to bilateral tonic-clonic seizures

MEDIAN % SEIZURE REDUCTION BY SEIZURE TYPE



Overlaid n values denote number of unique participants reporting respective seizure type

Conclusion

- **RADIANT study results build on vormatrigine data to date, positioning it as a fast-acting, precision once-daily ASM with minimal drug–drug interactions and a favorable safety profile.**
- **Importantly, these findings highlight vormatrigine's differentiation from conventional SCBs, approved or in development for FOS, many of which show modest efficacy and substantial tolerability concerns.**
- **Notably, the observed ~60% responder rate exceeds placebo response rates typically seen in recent FOS trials, and was achieved consistently within the setting of a modern ASM background across seizure subtypes and independent of baseline seizure burden.**
- **Further, vormatrigine response in the RADIANT study was observed without the CNS burden seen with XEN1101 or the complex titration required for cenobamate.**
- **Full dataset for FOS and PGTS expected by Q4 and will be presented at a meeting later in 2025.**
- **Collectively, these findings strongly support the accelerated advancement of Phase 3 studies in the vormatrigine ENERGY program.**

Vormatrigine Safety Profile Positioned to be Best-in-disease ASM

*Table 2. RADIANT Tolerability Summary – Topline Results (with Comparator Reference Data)**

	Vormatrigine 30 mg (N = 61)	Cenobamate 400 mg (N = 111)	XEN1101 25 mg (N = 114)
Study	RADIANT	Study C017[1]	X-TOLE[2]
Discontinuation	14 (23%)	30 (27%)	26 (23%)
Patients with ≥ 1 TEAE	36 (59%)	100 (90%)	97 (85%)
Patients with severe AEs	3 (4.9%)	18 (16%)	Not reported
Serious AEs (SAEs)	3 (4.9%)	8 (7%)	3 (2.6%)
Related SAE	1 (1.6%)[3]	–	Not reported
CNS-related AEs (≥ 10%)	32 (52.5%)	80 (72.1%)	83 (72.8%)
Dizziness	18 (29.5%)	37 (33%)	36 (31.6%)
Somnolence	10 (16.4%)	41 (37%)	17 (14.9%)
Headache	8 (13.1%)	12 (11%)	9 (7.9%)
Titration	None	12-weeks	None
Food Effect	None; Any time of day, with or without food	None; Any time of day, with or without food	Yes; Evening dosing with food
Significant DDIs	N/A[4]	Multiple	CYP3A

[1]Cenobamate: Krauss et al. *Lancet Neurol*. 2020;19(1), 38–48; https://www.ema.europa.eu/en/documents/assessment-report/ontozry-epar-public-assessment-report_en.pdf
[2]XEN1101: French et al *JAMA Neurol*. 2023;80(11):1145–1154
[3]Episode of diplopia, resolved after reduction of lamotrigine dose
[4]Based on PRAX data available to-date
*Not a head-to-head comparison

- Lowest rate of TEAEs and CNS AEs with modern ASMs
- Most AEs were mild to moderate and transient
- All severe and serious AEs recovered and resolved
- 23% of patients discontinued the study
- Investigators had the option to reduce the dose of background medications to manage AEs; when done (6 patients) no discontinuation was observed

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