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

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Background

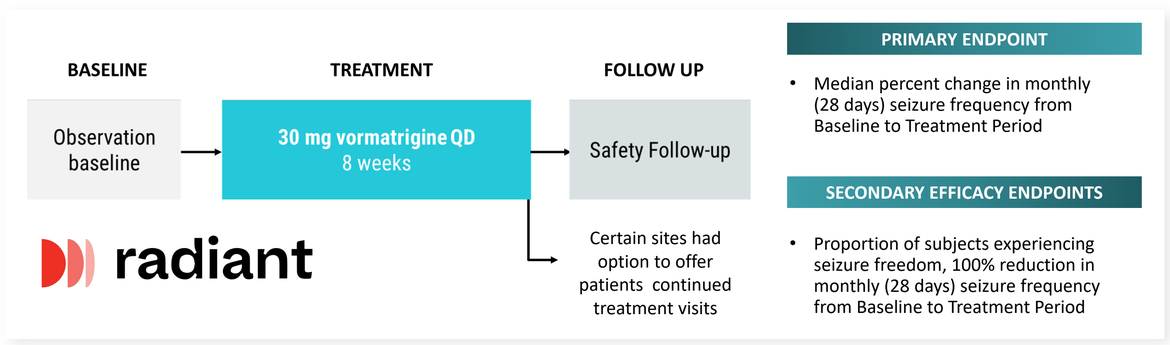
- Despite the availability of numerous antiseizure medications (ASMs), a large subset of the ~50 million people living with epilepsy worldwide still experience uncontrolled seizures
- Sodium channel blockers are central to current antiseizure treatment, yet tolerability issues and side effects restrict the extent to which patients can achieve optimal seizure control
- Vormatrigine selectively targets hyperexcitable sodium channels and is in development for adult FOS and generalized epilepsy with the potential to improve efficacy without compromising tolerability
- Recent data indicate superior preclinical and early clinical performance, favorable safety up to 45 mg, and no significant food effect
- Emerging data show that vormatrigine can exceed therapeutic target concentrations while remaining well tolerated without the need for titration
- The RADIANT study was designed to evaluate vormatrigine's efficacy, safety, and pharmacokinetics in adults with focal onset seizures (FOS) or primary generalized tonic–clonic seizures (PGTCS)

➢ ***Here we present the latest results from all subjects dosed to date and highlight seizure-efficacy outcomes beyond the initial 56-day treatment period.***

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 PGTCS
- Participants received vormatrigine 30 mg daily for 8 weeks, with the study consisting of Screening/Observation (Baseline), Treatment and Follow-up periods
- Based on local regulations and site availability, some patients were eligible to continue receiving vormatrigine beyond 8 weeks

Figure 1. RADIANT Study Design.



Participant Eligibility and Baseline Characteristics

Key Inclusion Criteria

- FOS or idiopathic PGTCS, with progressive causes excluded by CT/MRI
- Aged 18-75 years
- ≥2 countable seizures in screening for FOS or ≥ 1 countable in screening for PGTCS patients
- On 1–3 ASMs for ≥4 weeks prior to screening

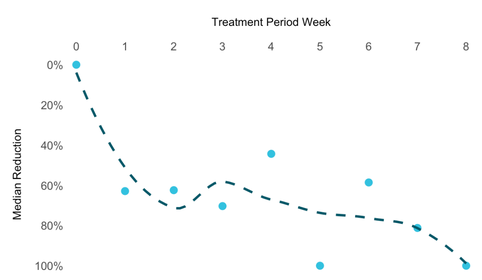
Demographics and Baseline Characteristics

	N = 65
Age (Years), mean (SD)	43.0 (14.45)
Sex (Male, Female)	29, 36
# Background ASMs, mean (SD)	2.1 (0.85)
Concomitant ASM	
Sodium Channel Blocker*	77%
SV2A	59%
GABA modulators	29%
Others	12%
Baseline seizures, median (IQR)	9.0 (4, 21)

* 35% of FOS patients were on cenobomate at baseline

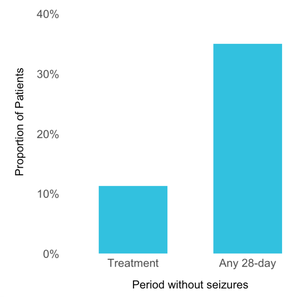
RADIANT - Vormatrigine as a Potential Best-in-Disease Therapy

MEDIAN % FOCAL SEIZURE REDUCTION OVER THE FIRST 8 WEEKS OF TREATMENT (N=62)



Dashed line shows a LOESS smooth, illustrating the underlying trend across weekly median reductions.

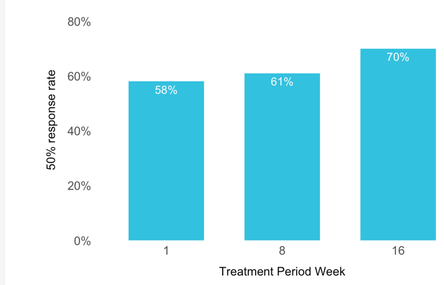
PATIENTS WITH 100% FOCAL SEIZURE REDUCTION (N=62)



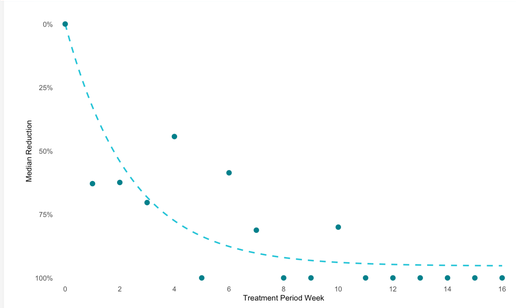
Rapid and Sustained Seizure-Reduction Profile

- Median seizure reduction improves steadily, reaching ~100% by Week 8 and maintained through Week 16.
- Seizure-free intervals emerge early, with over one-third of patients achieving ≥28 days without seizures
- Seizure-freedom in over 11% of patients within the treatment period.

RESPONDER RATES BY WEEK FOR 50% FOCAL SEIZURE REDUCTION

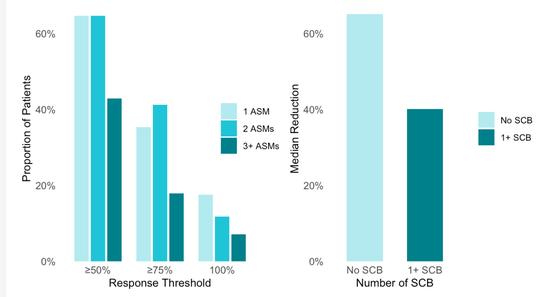


MEDIAN % FOCAL SEIZURE REDUCTION THROUGH WEEK 16



Dashed line shows an exponential fit, capturing the continuous decline and plateau in median seizure reduction.
N for weeks 9 to 16 (35,29,29,30,28,27,28 and 26, respectively)

RESPONDER PROPORTIONS ON BACKGROUND ASMs AND SCBs (8 WEEKS)

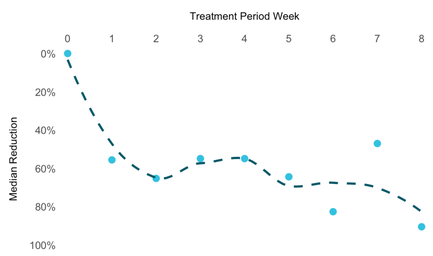


Efficacy Profiles On Background Therapy Support Vormatrigine's Intrinsic Activity and Monotherapy Potential

- Highest responder rates were observed with fewer background ASMs, indicating clearer expression of the drug's intrinsic effect.
- Greater median reductions with no SCB compared to 1+ SCB, revealing the drug's full pharmacologic impact.
- Strong response in combination with 1+ SCB supports both flexibility in combination use and independence from polytherapy.
- Maintained efficacy under heavier ASM or SCB loads reflects a robust stand-alone effect, consistent with monotherapy potential.

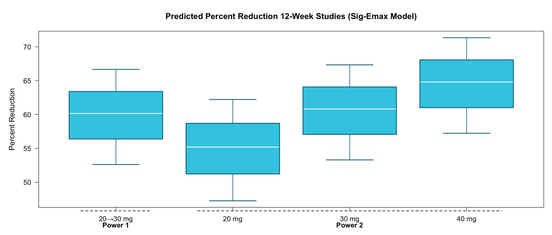
Rapid, Sustained Seizure Reduction in PGTCS Patients

GENERALIZED SEIZURE REDUCTION BY TREATMENT PERIOD WEEK (N=3)



Model-based Simulation Supports Power 1 and 2 Designs

VORMATRIGINE EXPOSURE RESPONSE PREDICTIONS



Conclusion

- **RADIANT results position vormatrigine as a best-in-disease therapy: fast-acting efficacy without titration, sustained reduction over longer treatment duration, seizure-freedom potential, favorable DDI, tolerability and safety profiles with once-daily dosing.**
- **Increasing and sustained effect in FOS patients was observed, reaching 100% median weekly seizure reduction after 8 weeks and maintained through 16 weeks.**
- **Seizure-freedom emerged early, with roughly one-third of patients achieving ≥28 consecutive seizure-free days during the treatment-period assessments, and ~11% attaining complete seizure freedom.**
- **Greater response rates and efficacy under minimal background therapy demonstrate vormatrigine's intrinsic activity and monotherapy potential, which will be studied in the Power3 study that is expected to initiate in the first half of 2026.**
- **Patients with generalized epilepsy also demonstrated rapid and sustained seizure reduction, reinforcing the broad potential of vormatrigine across seizure types**
- **Exposure response modeling predicts significant seizure reduction across a range of doses, validating the Power1 and Power2 study designs.**

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

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

	Vormatrigine 30 mg (N = 65)	Cenobamate 400 mg (N = 111)	XEN1101 25 mg (N = 114)
Study	RADIANT	Study C017[1]	X-TOLE[2]
Discontinuation	16 (25%)	30 (27%)	26 (23%)
Patients with ≥1 TEAE	44 (68%)	100 (90%)	97 (85%)
Patients with severe AEs	4 (6.2 %)	18 (16%)	Not reported
Serious AEs (SAEs)	4 (6.2%)	8 (7%)	3 (2.6%)
Related SAE	1 (1.5%) [3]	–	Not reported
CNS-related AEs	39 (60%)	80 (72.1%)	83 (72.8%)
Dizziness	21 (32 %)	37 (33%)	36 (31.6%)
Somnolence	8 (12%)	41 (37%)	17 (14.9%)
Headache	9 (14%)	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	None[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]Refer to Poster 3.36
*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

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