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POWER1 – A Double-Blind, Randomized, Multicenter Registrational Study Evaluating the Efficacy and Safety of Vormatrigine in Adults with Focal Onset Seizures

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Disclosure: Orrin Devinsky is a current employee of Praxis Precision Medicines and is a Praxis stockholder.

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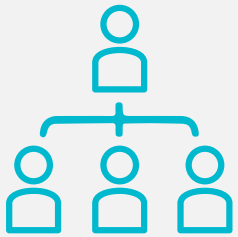
Innovative Epilepsy Treatments Needed Faster and More Than Ever

~50 MILLION PEOPLE
worldwide are affected by epilepsy

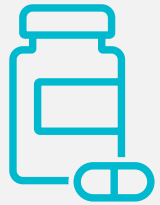
FOS accounts for the majority of epilepsy cases in adults

Seizures and their frequency are directly related to QoL and outcomes in epilepsy patients



A significant number of patients remain refractory, rapidly cycling through treatment lines; 48% reach 3rd-line and 25% reach 5th-line ASM therapy

~35% of patients change medications annually



63% require two or more medications

ASM=antiseizure medication; FOS=focal onset seizures; QoL=quality of life

GBD 2021 Global Prevalence Data Lancet Public Health; WHO 2023 Epilepsy Fact Sheet; Moshe et al. *Lancet.* 2015 Mar 7;385(9971):884-98; Gupta et al *Epilepsia Open*. 2017 Mar 27;2(2):199-213; Who can get epilepsy? Epilepsy Foundation. Updated February 4, 2022. Accessed August 7, 2026. https://www.epilepsy.com/what-is-epilepsy/understanding-seizures/who-gets-epilepsy; Hauser et al. *Epilepsia*. 1991;32(4):429-45; Vikin et al. *Epilepsia*. 2025 Jan 11;66(3):776-89; Gazdag et al. EEC 2026 Poster P0024

Vormatrigine: Functionally Selective Sodium Channel Modulator in Development for Focal Onset Seizures and Generalized Epilepsy

Vormatrigine

Focal and generalized epilepsies

No titration

Small molecule

Functional state modulator

Significantly more potent than competitive molecules in highly translatable pre-clinical models

Rapidly achieves therapeutic concentrations after once-daily dose with no food effect – ***see also Poster P0022***

Ability to significantly exceed therapeutic concentrations while well tolerated – ***see also Poster P0022***

Favorable tolerability profile and minimal drug-drug interaction risk with common ASMs – ***see also Poster P0023***

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

Kahlig et al. AAN 2023; Patel et al. AAN 2024; Hansen et al. IEC 2025; Hansen et al. AES 2025; Bialer et al. *Epilepsia.* 2026;00:1-51

PHASE 2/3 CLINICAL FINDINGS
POWER1 STUDY

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

POWER1 Phase 2/3 Study Design

Primary Endpoint

- Percent change in monthly (28 days) focal seizure frequency from Baseline to Treatment Period

Key Secondary Efficacy Endpoint

- Proportion of subjects experiencing a ≥50% reduction in monthly (28 days) focal seizure frequency from Baseline Period to Treatment Period

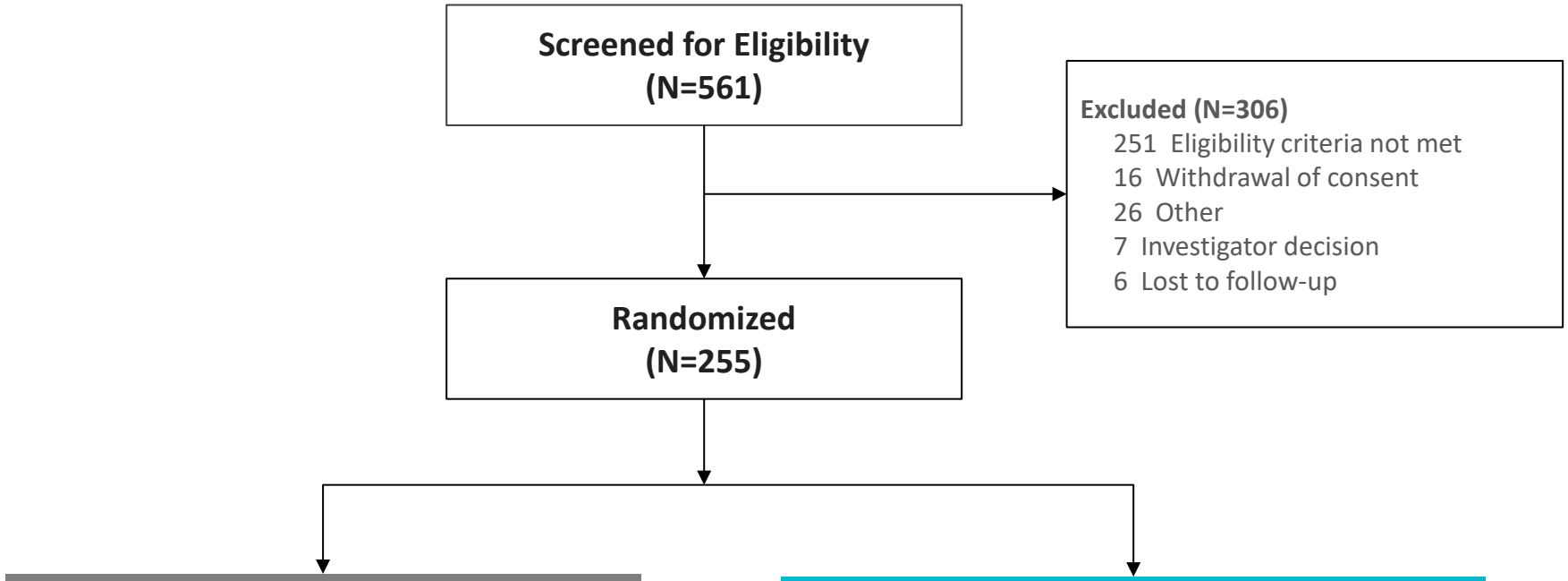
Key Inclusion Criteria

- A diagnosis of focal onset epilepsy according to International League Against Epilepsy (ILAE) Classification (2017), and progressive epilepsy cause ruled out on CT or MRI
- Male or female aged 18-75 years inclusive
- On 1–3 stable doses of ASMs for at least 4 weeks prior to screening

Key Exclusion Criteria

- Planned or recent epilepsy surgery or recent neurostimulator placement
- Pseudo- or psychogenic seizures, uncountable cluster seizures only or episode of convulsive status requiring hospitalization/intubation in the past 12 months
- History of schizophrenia, obsessive-compulsive disorder, or other serious mental health disorders
- Significant cardiac conduction abnormalities or family history of sudden death
- Use of prohibited drugs
- Pregnant or breastfeeding at the time of Screening, positive serum pregnancy test at Screening or planning to become pregnant within 14 days of the last study drug dose

Participant Disposition



6 withdrawal by patient; 1 AE; 1 death (not related)

12 AE; 5 withdrawal by patient; 1 other; 1 death (not related)

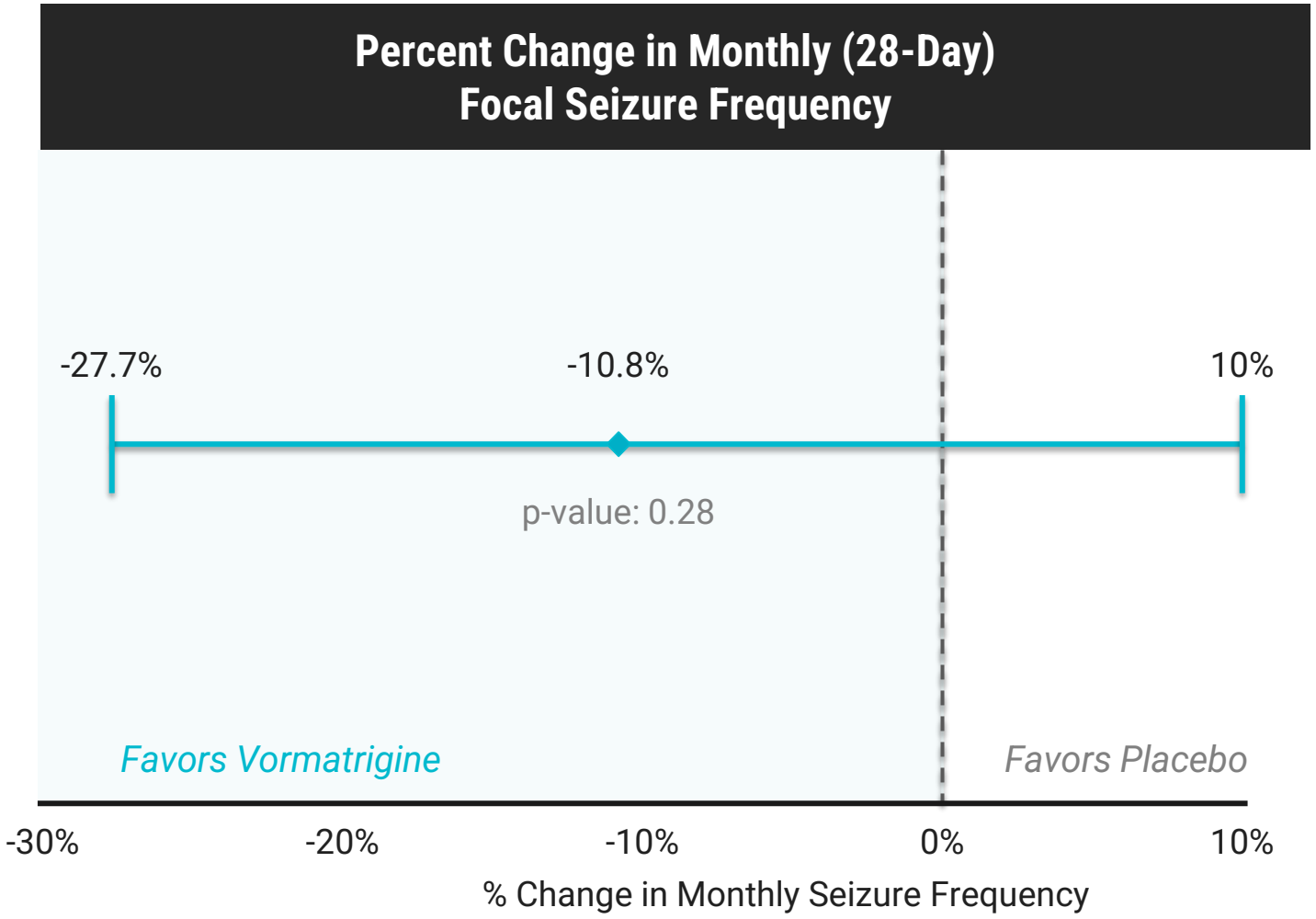
AE=adverse event

Participant Demographics and Baseline Characteristics

		Placebo (N=128)	Vormatrigine (N=127)
Age, years	Mean (SD)	40.5 (13.3)	40.7 (13.0)
Sex	M, F	63, 65	54, 73
# Background ASMs	Mean (SD)	2.3 (0.7)	2.4 (0.7)
Concomitant ASM*	Sodium Channel Blocker	111 (86.7%)	114 (89.8%)
	SV2A	51 (39.8%)	53 (41.7%)
	GABA modulators	53 (41.4%)	43 (33.9%)
	Others	38 (29.7%)	50 (39.4%)
Baseline seizures	Median	15.1	13.0

ASM=antiseizure medication; SD=standard deviation
*Unique-patient counts; % of patients on at least one baseline ASM within the class, Safety Population (N=255)
Classes are not mutually exclusive — a patient on both a sodium-channel blocker and a GABA modulator is counted in both rows.

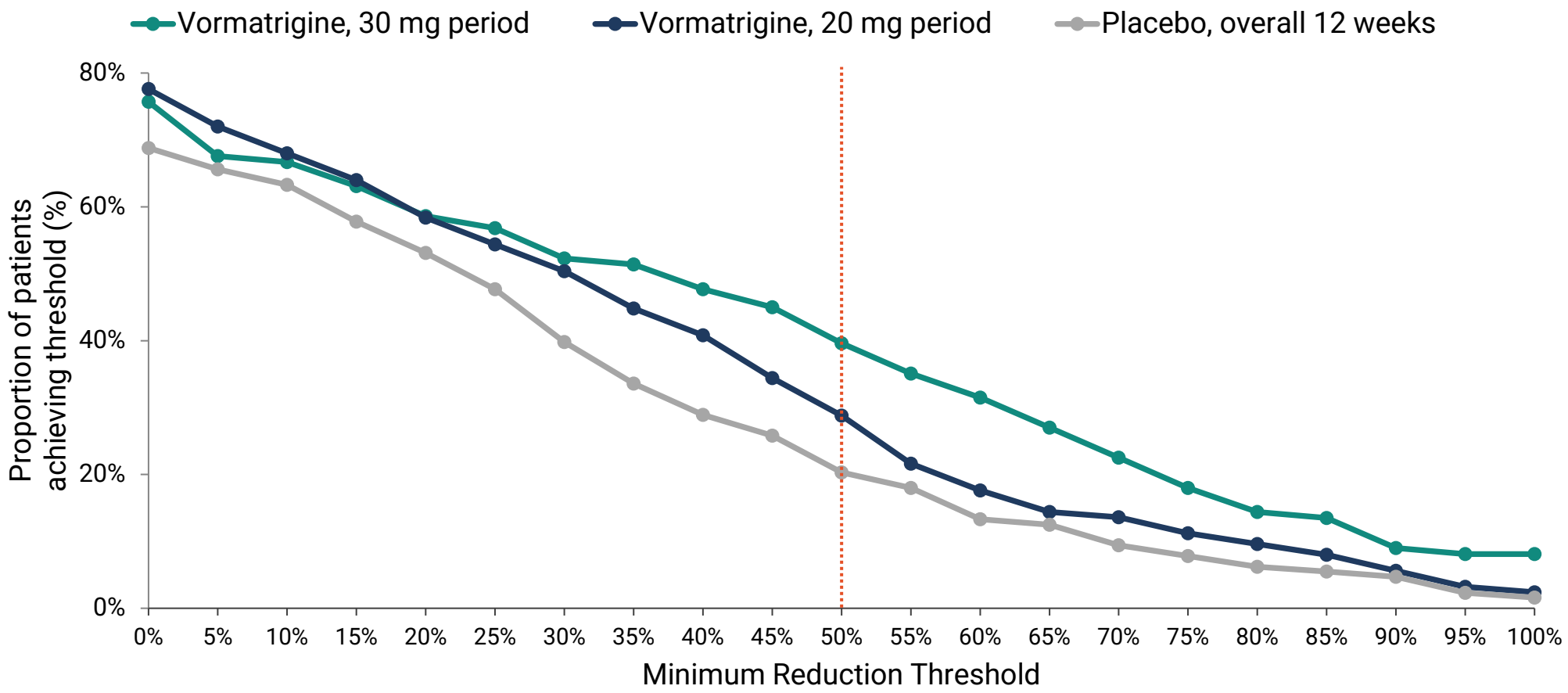
Primary Endpoint Not Met



- Primary endpoint % change from baseline in 28-day seizure frequency not met (p=0.28)
- Seizure reduction was more pronounced during the second half of the study on the higher 30 mg dose

Intention-to-Treat (N=255: Placebo N=128; Vormatrigine N=127); placebo median change, 22.8%

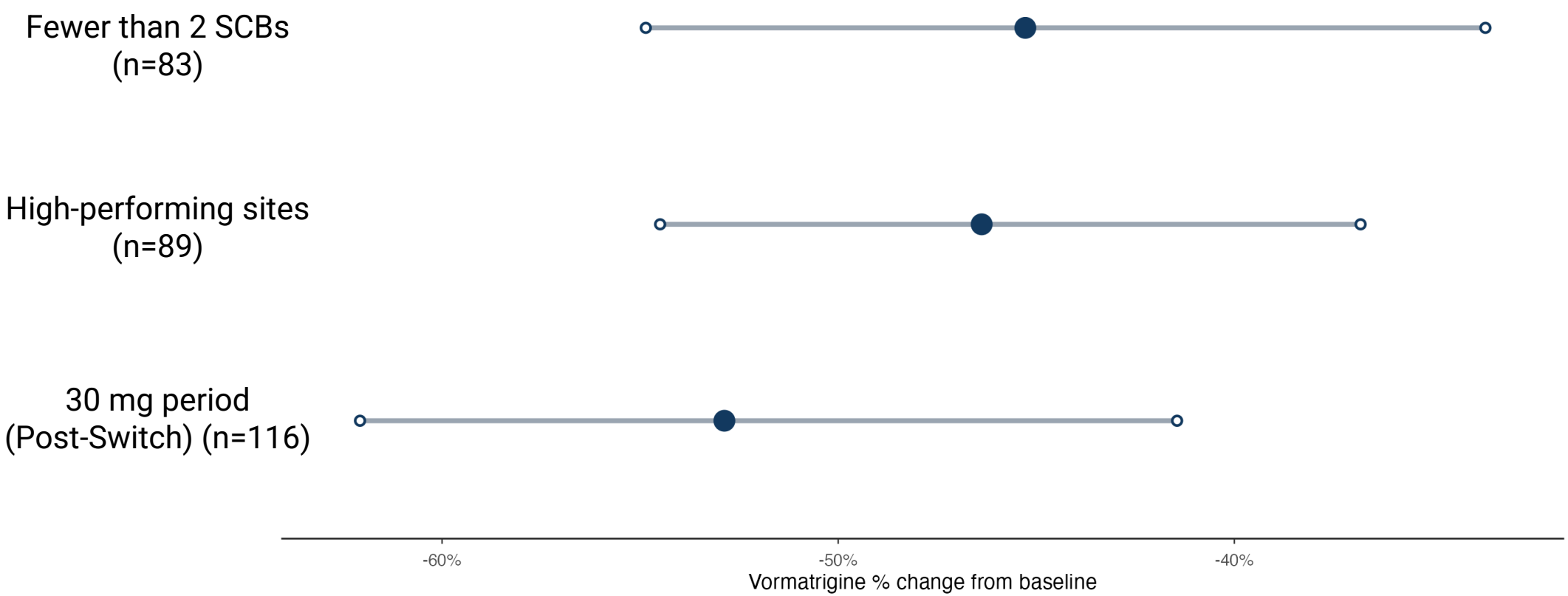
Key Secondary Endpoint Nominally Met Significance
RR 50%, Odds Ratio = 1.85 (p=0.0355)



Intention-to-Treat (N=255)

RR50=proportion of participants achieving ≥50% reduction in seizure frequency; odds ratio > 1 favors vormatrigine

Key Learnings from POWER1: Drivers of Vormatrigine Treatment Effect



% change +/- 95 CI

Drivers of Vormatrigine Treatment Effect: Site Performance

High performing sites – more participants, fewer discontinuations

Group	Patients (N)	Per Site (N)	Disc. (%)
High-performing	175	5.3	7%
Other	78	2.7	18%
Overall			10%

Safety Summary

	Placebo (N=128)	VORMATRIGINE (N=127)
Discontinuation due to TEAE	**1 (0.8)**	**12 (9.4)**
Participants with ≥1 TEAE	**69 (53.9)**	**104 (81.9)**
Serious AEs (SAEs)	2 (1.6)	5 (3.9)
Drug-related TEAE	36 (28.1%)	86 (67.7%)
CNS-Related AEs	**39 (30.5)**	**80 (63.0)**
Dizziness	16 (12.5)	49 (38.6)
Headache	14 (10.9)	24 (18.9)
Somnolence	7 (5.5)	23 (18.1)

- Vormatrigine was generally well-tolerated; AE-related discontinuations were <10%
- Most common TEAEs consistent with class effects
- Approximately 90% of patients from the vormatrigine arm transitioned to and remain in the OLE study

- All but 2 SAEs (Diplopia) were not related to drug
- 1 death in each arm, not related to treatment

POWER1 Study Summary

- The study did not meet its primary endpoint of reduction in monthly focal seizure frequency from baseline at Week 12.
- The study nominally met the secondary endpoint, with a significant number of patients achieving ≥50% reduction in seizure frequency.
- Seizure reduction during the second half of the study on the higher 30 mg dose was more pronounced compared to the initial 20 mg dose phase.
- Vormatrigine demonstrated general tolerability, with adverse event-related discontinuations in less than 10% of patients and approximately 90% of the vormatrigine arm transitioning into and remaining in the open-label extension study.
- Expectation of larger effect in POWER2 study with longer period at 30 mg (and addition of 40 mg) dose, restricting participation to high performing sites, and reducing concomitant SCBs.

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Questions?

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