

# Vormatrigine Demonstrates Potent Antiseizure Activity Across Three Acute Models with Highest Predictive Validity for Focal Onset Seizures

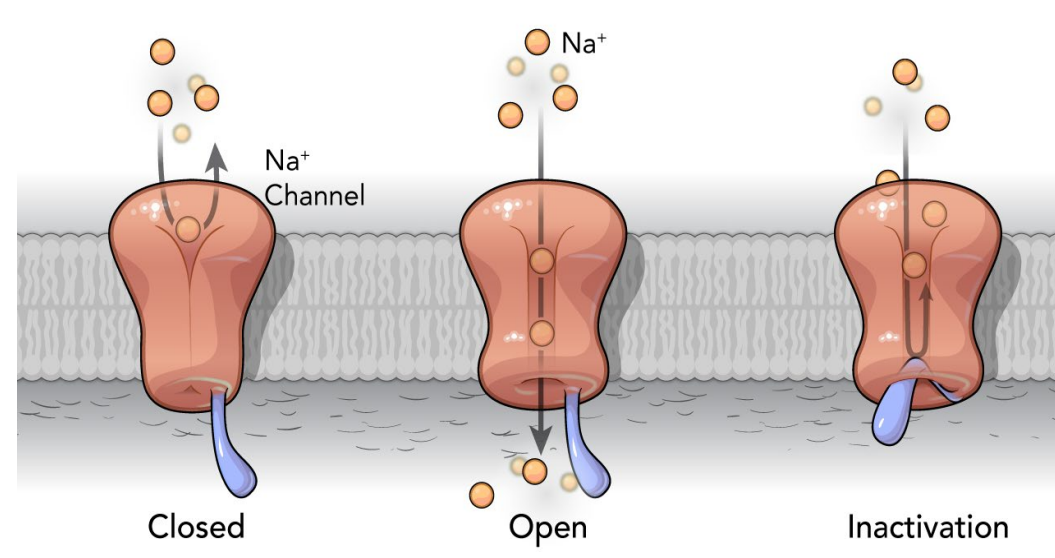
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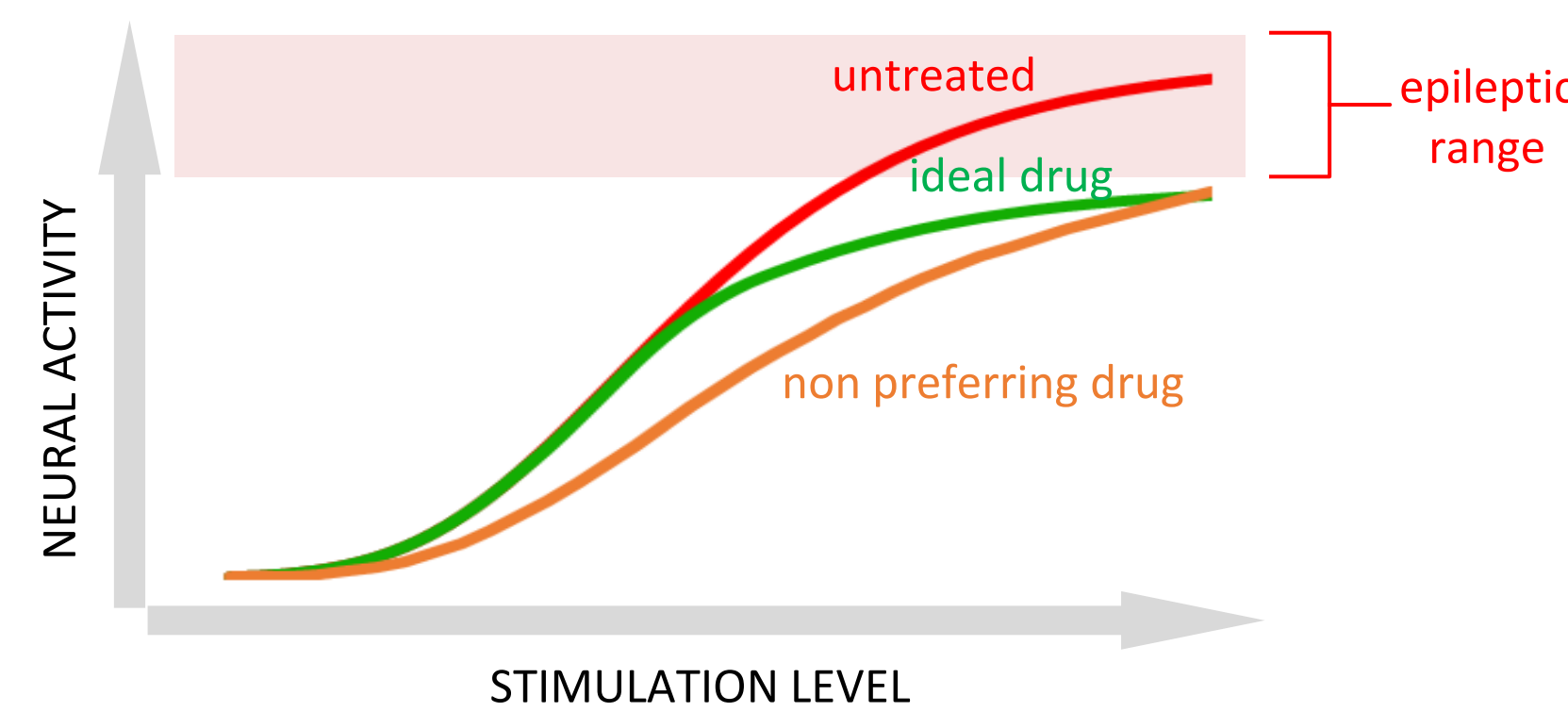
## Background

- Approximately 50 million people worldwide have epilepsy, most of whom are classified as focal onset seizures (FOS).
  - Despite the availability of over 30 antiseizure medications (ASMs), a significant proportion of patients remain refractory to current treatments, with current standard-of-care limited by tolerability issues and a need to titrate up to an effective dose to minimize side effects.
  - Vormatrigine (PRAX-628) is a functional state modulator targeting the hyperexcitable states of sodium channels in the brain that is currently in development for adult FOS and generalized epilepsy, with emerging data pointing to an ideal precision ASM profile.
  - Preclinical and clinical data highlight a differentiated profile over current standard-of-care, with ability to significantly exceed therapeutic concentrations while well tolerated.
  - We recently implemented the Praxis Analysis of Concordance (PAC) framework to assess the translational concordance of common preclinical seizure models for FOS. Using this framework, we deployed a decision tree for accelerated FOS drug discovery that includes three acute seizure models with high predictive validity: audiogenic, maximal electroshock (MES) and 6-Hz (32mA).
- *In this study we assess the antiseizure efficacy of vormatrigine across these models, providing robust support for its accelerated development as a treatment for FOS.*

### SODIUM CHANNEL STATES



### PREFERENTIAL ACTION AGAINST DISEASE STATE HYPEREXCITABILITY



IC <sub>50</sub> , nM (Slope)	Persistent I <sub>Na</sub>	Peak I <sub>Na</sub> TB	Ratio to Pers. I <sub>Na</sub>	Peak I <sub>Na</sub> UDB-10Hz	Ratio to Pers. I <sub>Na</sub>	Peak I <sub>Na</sub> VDB	Ratio to Pers. I <sub>Na</sub>
<b>Vormatrigine</b>	<b>128</b> (1.4)	<b>8,707</b> (1.0)	<b>68</b>	<b>200</b> (0.7) Max 100%	<b>1.6</b>	<b>72</b> (1.0)	<b>0.56</b>

Data are IC<sub>50</sub> (nM) with the hill slope in parenthesis. I<sub>Na</sub>=sodium current; Pers.=persistent; TB=tonic block; UDB=use-dependent block; VDB=voltage-dependent block

**Figure 1. Vormatrigine, a next-generation precision medicine with an ideal ASM profile.** Vormatrigine's unique profile including its high potency and activity dependence for peak sodium current (I<sub>Na</sub>) has the potential to address limitations of current treatments through preferential action against disease-related hyperexcitability.

## Methods

### Acute Seizure Models

- Male and female juvenile DBA/2J mice were used to assess the antiseizure activity of vormatrigine in the audiogenic seizure model. MES and 6-Hz experiments were conducted in adult male CD-1 mice.
- Mice were pre-treated with either vehicle or vormatrigine by oral gavage 30 min prior to audio or electrical stimulus.
- For audiogenic seizure experiments, mice were exposed to 110dB of white noise for 60s. Electroshocks for MES experiments were 50Hz, 0.8s, 10ms square pulse width, 50mA, and for 6-Hz experiments were 6Hz, 3s, 0.2ms rectangular pulse width, 32mA.
- Mice were observed for the presence or absence of full tonic hindlimb extension (MES and audiogenic) or psychomotor seizures defined as stun/immobility, forelimb clonus, Straub tail and lateral head movement (6-Hz).

### Rotarod

- Male CD-1 mice were pre-treated with vehicle or vormatrigine by oral gavage 30 min prior to the rotarod assay. The rotarod was operated under constant speed at 15 rpm. Latency to fall during each test session was recorded with a cutoff time of 180 s.

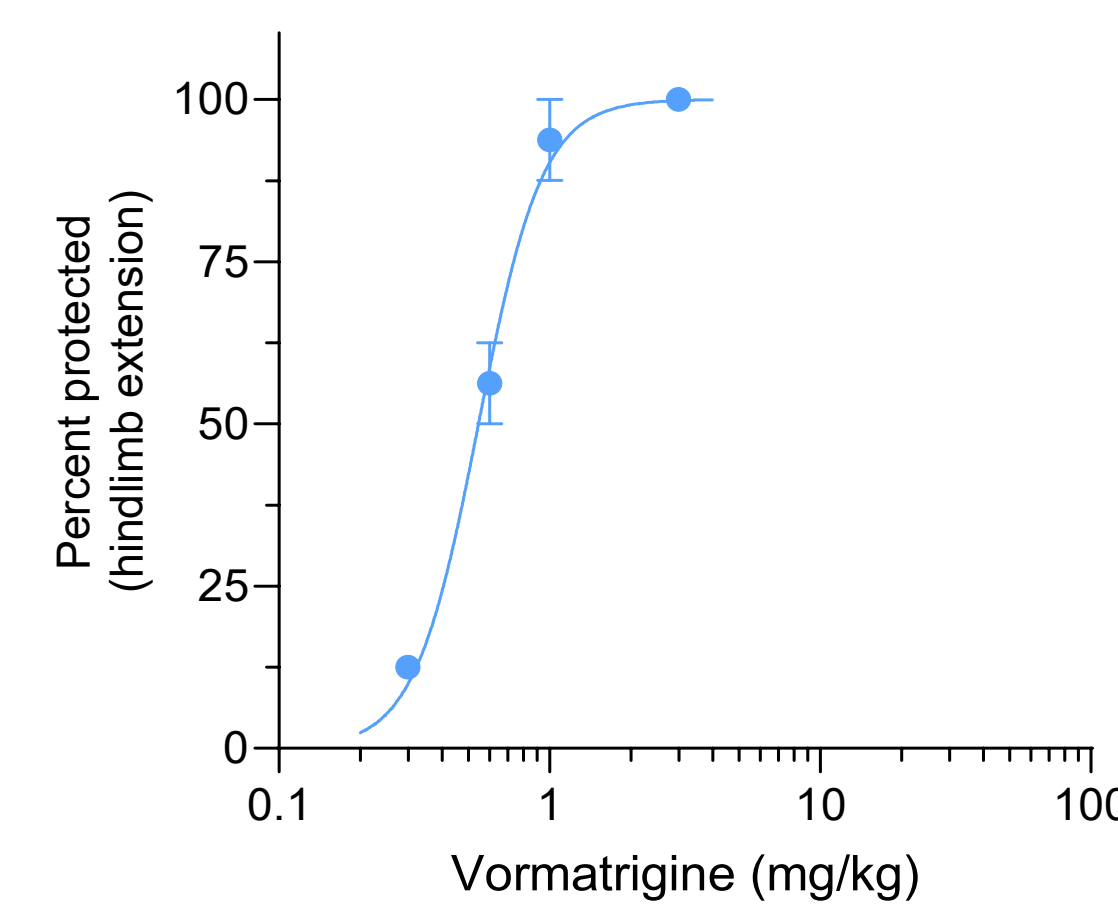
## Conclusion

- Vormatrigine exhibits potent antiseizure activity across three acute seizure models shown to have the highest predictive validity for FOS within our PAC framework.**
- Vormatrigine demonstrates a large preclinical protective index; consistent with Phase 1 studies demonstrating its ability to significantly exceed therapeutic concentrations while well tolerated.**
- Vormatrigine surpasses thresholds needed to progress development, with FOS efficacy studies rapidly advancing as part of the ENERGY Program.**

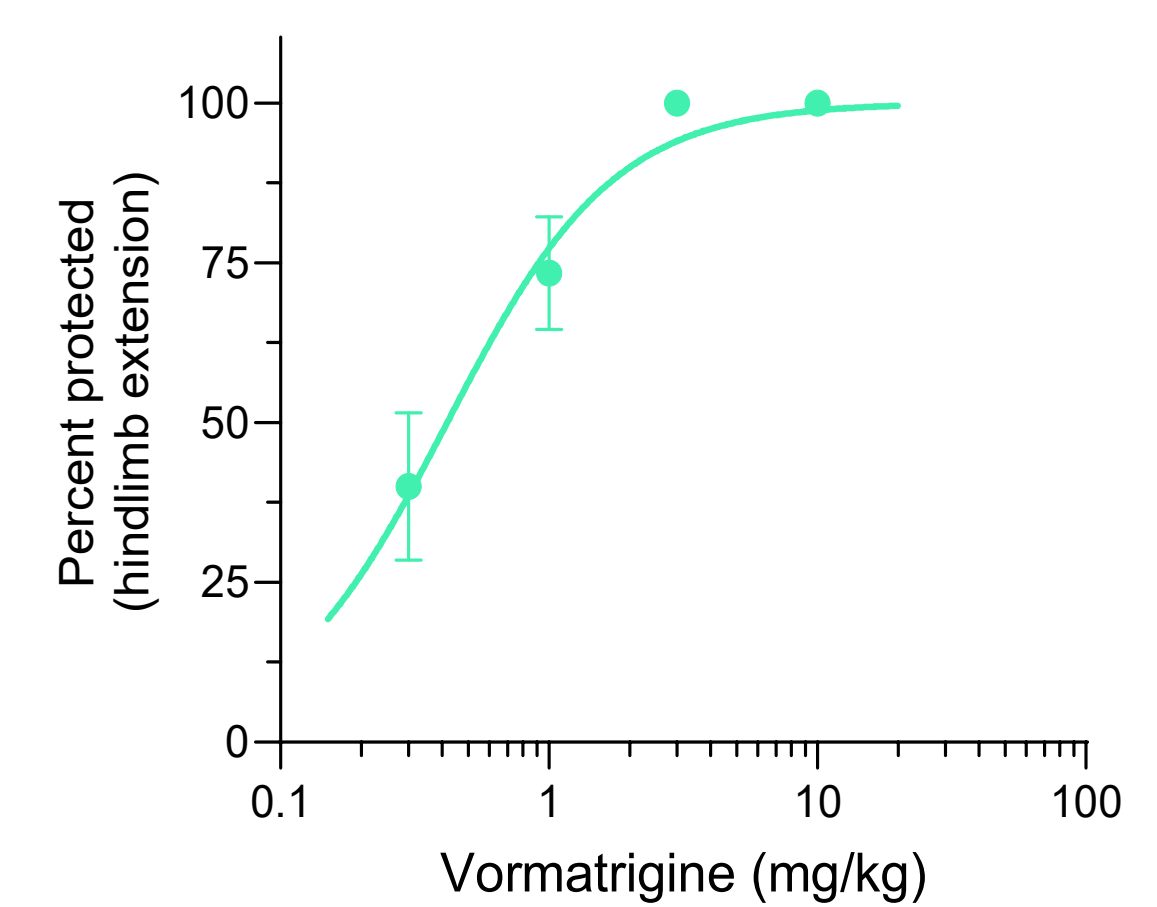


## Vormatrigine Demonstrates Broad, Potent Anticonvulsant Activity with a Large Preclinical Protective Index

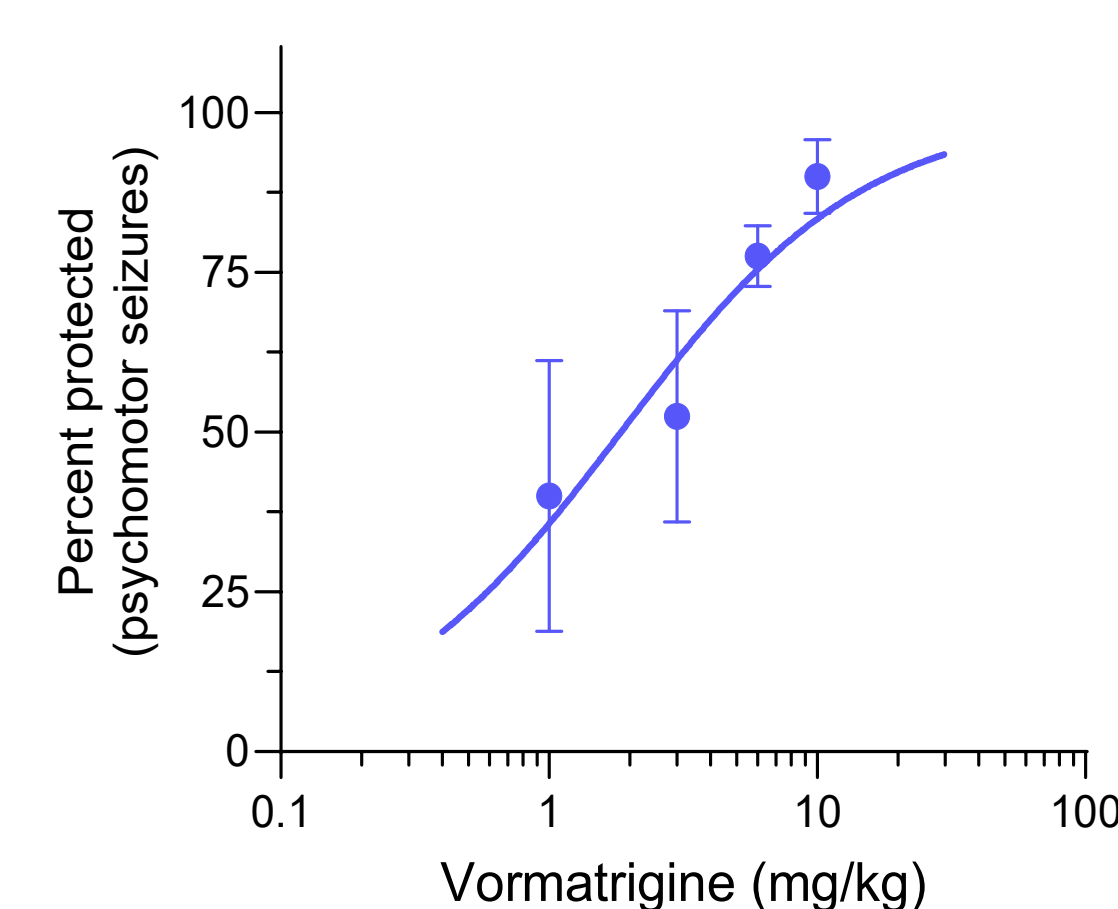
- Mice were completely protected from audiogenic-induced tonic hindlimb extension, with an ED<sub>50</sub> value of 0.55mg/kg.
- In the MES acute seizure model, vormatrigine (3 and 10mg/kg) completely protected mice from tonic hindlimb extension, with an ED<sub>50</sub> value of 0.42mg/kg.
- Vormatrigine also significantly reduced incidence of psychomotor seizures induced by 6-Hz (32mA), with an ED<sub>50</sub> value of 1.9mg/kg.
- Reduction in rotarod function was observed at vormatrigine doses higher than those demonstrating potent anticonvulsant activity.



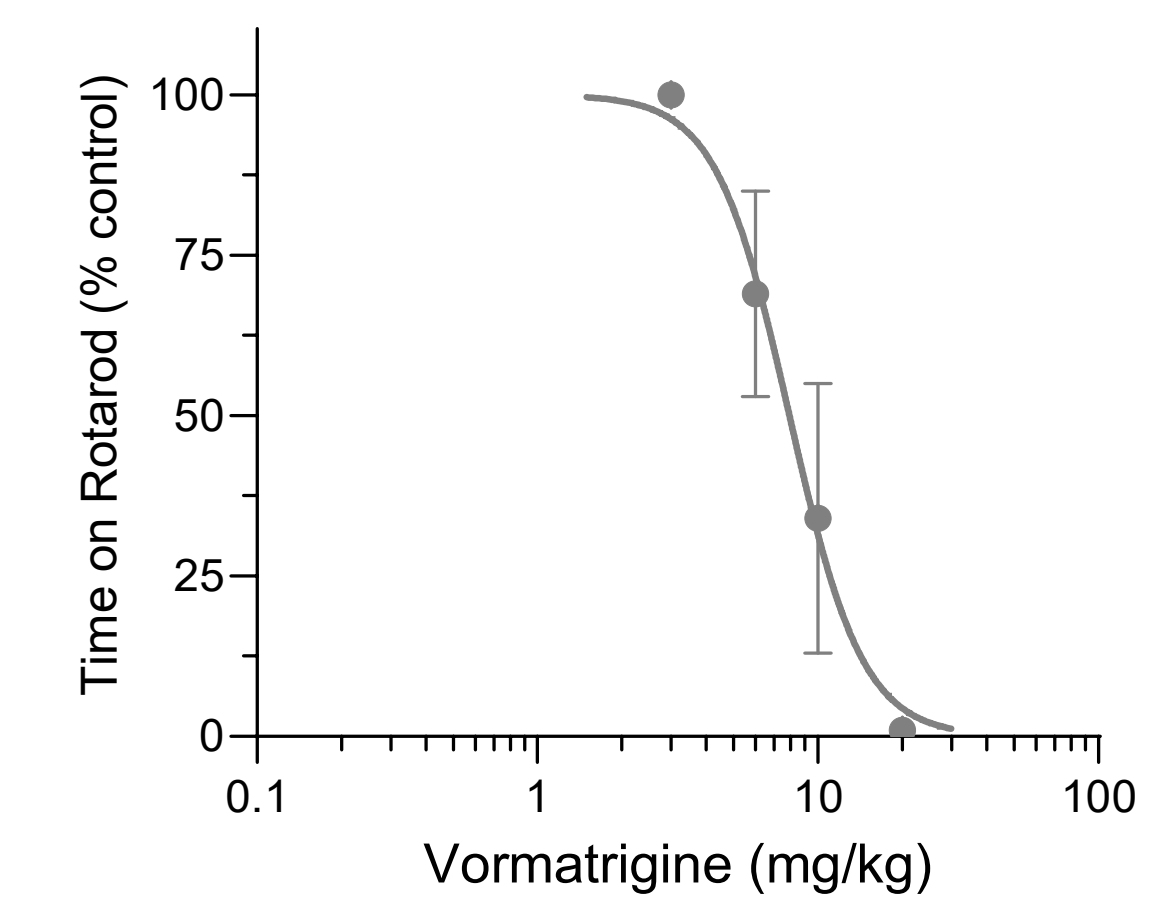
**Figure 2. Vormatrigine is anticonvulsant in the audiogenic acute seizure model.** Dose-response curves for protection from audiogenic-induced tonic hindlimb extension. Vormatrigine (0.3-3 mg/kg) was administered by oral gavage 30 min prior to audio stimulus. Data are presented as mean  $\pm$  SEM for two cohorts, with n = 10 per treatment for each cohort. Curve represents fit to a four-parameter log function.



**Figure 3. Vormatrigine is anticonvulsant against MES-induced seizures.** Dose-response curves for protection from MES-induced tonic hindlimb extension. Vormatrigine (0.3-10 mg/kg) was administered by oral gavage 30 min prior to electrical stimulation. Complete protection was achieved following treatment with 3 and 10 mg/kg vormatrigine. Data are presented as mean  $\pm$  SEM for three cohorts, with n = 10 per treatment for each cohort. Curve represents fit to a four-parameter log function.



**Figure 4. Vormatrigine is anticonvulsant in the 6-Hz acute seizure model.** Dose-response curves for protection from psychomotor seizures induced by 6-Hz. Vormatrigine (1-10 mg/kg) was administered by oral gavage 30 min prior to electrical stimulation. Data are presented as mean  $\pm$  SEM for three to four cohorts, with n = 10 per treatment for each cohort. Curve represents fit to a four-parameter log function.

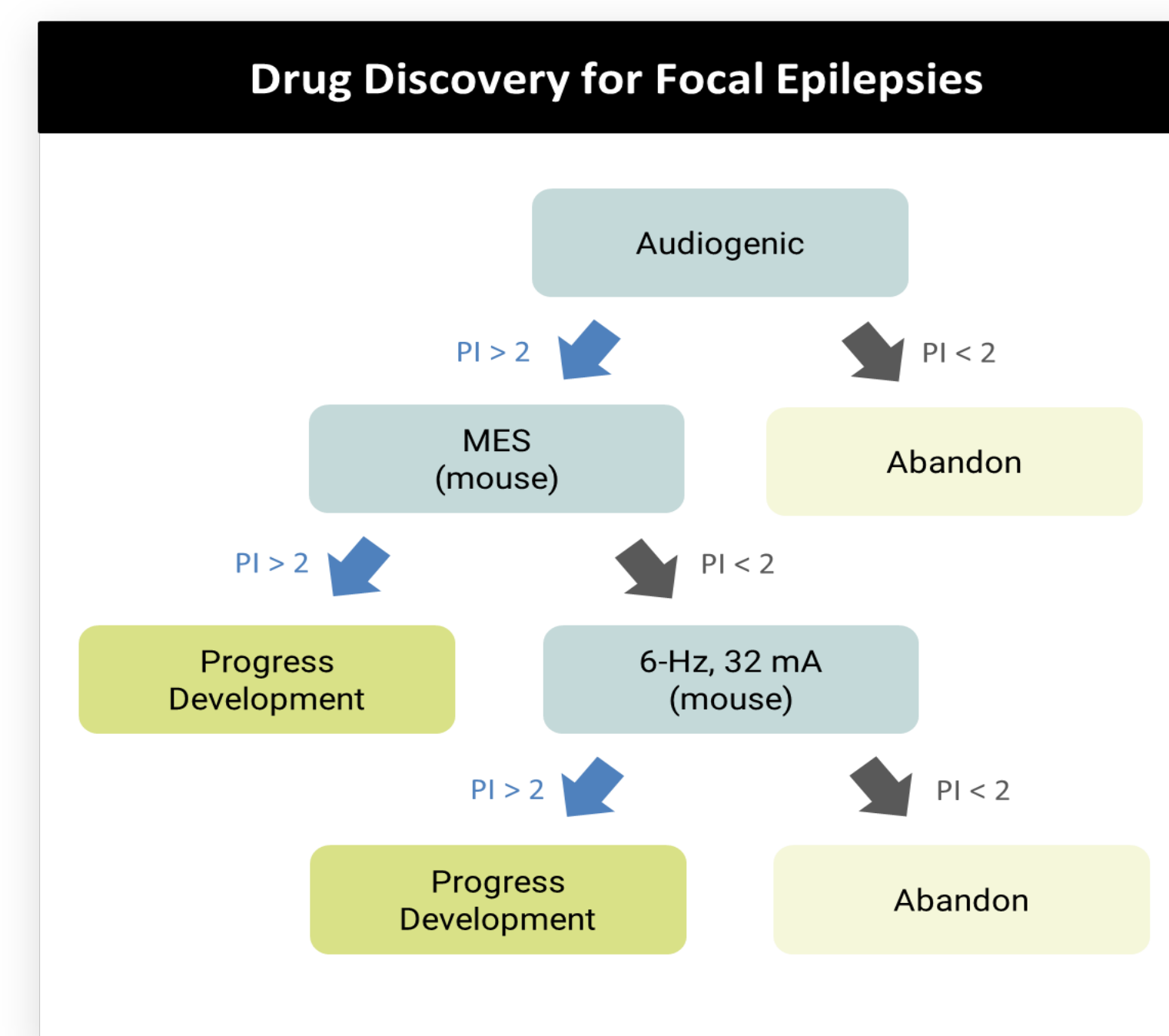


**Figure 5. High doses of vormatrigine impair rotarod function.** Dose-response curve for vormatrigine inhibition of rotarod function. Vormatrigine (3-20 mg/kg) was administered by oral gavage 30 min prior to the rotarod assay. Data are presented as mean  $\pm$  SEM, with n = 10 per treatment for each cohort. Curve represents fit to a four-parameter log function.

## Vormatrigine Surpasses Preclinical Benchmarks, Advancing to the Next Phase of Development

### Vormatrigine PI Values Surpass Thresholds

- Based on the PAC framework and associated decision tree, vormatrigine surpasses PI thresholds preclinical models with highest predictive validity: audiogenic, maximal electroshock (MES) and 6-Hz (32mA).
- PI calculated by dividing rotarod TD<sub>50</sub> by ED<sub>50</sub> values calculated in acute seizure models.



### Vormatrigine Protective Index (PI) values

✓	<b>Audiogenic</b>	✓✓✓ (14)
✓	<b>MES (mouse)</b>	✓✓✓ (19)
✓	<b>6 Hz, 32 mA (mouse)</b>	✓ (4.2)

Praxis data on file

## References

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- WHO 2023 Epilepsy Fact Sheet
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**Ethical Statement** All *in vivo* studies were performed in accordance with local and institutional animal care and use guidelines.

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**Disclosures** All authors are current or former employees/consultants of Praxis Precision Medicines and may be Praxis stockholders.

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