Darigabat: pronounced antiepileptic activity in the mesial temporal lobe mouse model of drug-resistant focal epilepsy

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- This presentation contains forward-looking statements that are based on management's beliefs and assumptions and on information currently available to management. In some cases, you can identify forward-looking statements by the following words: "may," "will," "could," "would," "should," "expect," "intend," "plan," "anticipate," "believe," "estimate," "predict," "project," "potential," "continue," "ongoing" or the negative of these terms or other comparable terminology, although not all forward-looking statements contain these words. These statements involve risks, uncertainties and other factors that may cause actual results, levels of activity, performance or achievements to be materially different from the information expressed or implied by these forward-looking statements. Although we believe that we have a reasonable basis for each forward-looking statement contained in this presentation, we caution you that these statements are based on a combination of facts and factors currently known by us and our projections of the future, about which we cannot be certain.
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Subtype selective $GABA_A$ receptor PAMs have therapeutic potential in epilepsy

Mechanistic Understanding of Pharmacology

	$GABA_A$ Receptor Subtype			
	α1	α2	α3	α5
Analgesia		✓✓	✓	✓✓
Anxiolysis		✓✓	✓✓	
Muscle Relaxation		✓✓	✓✓	
Anti-convulsant	✓✓	✓✓		
Sedation	✓✓			
Cognitive Impairment	✓✓	?	?	✓
Addiction	✓✓	✓		

Design α1-sparing $GABA_A$ PAM to enable clinically relevant high receptor occupancy

Program Goals:

- **Broad spectrum efficacy**
- **Improved AE profile vs classical BZDs, even at high receptor occupancy**
- **Chronic dosing**

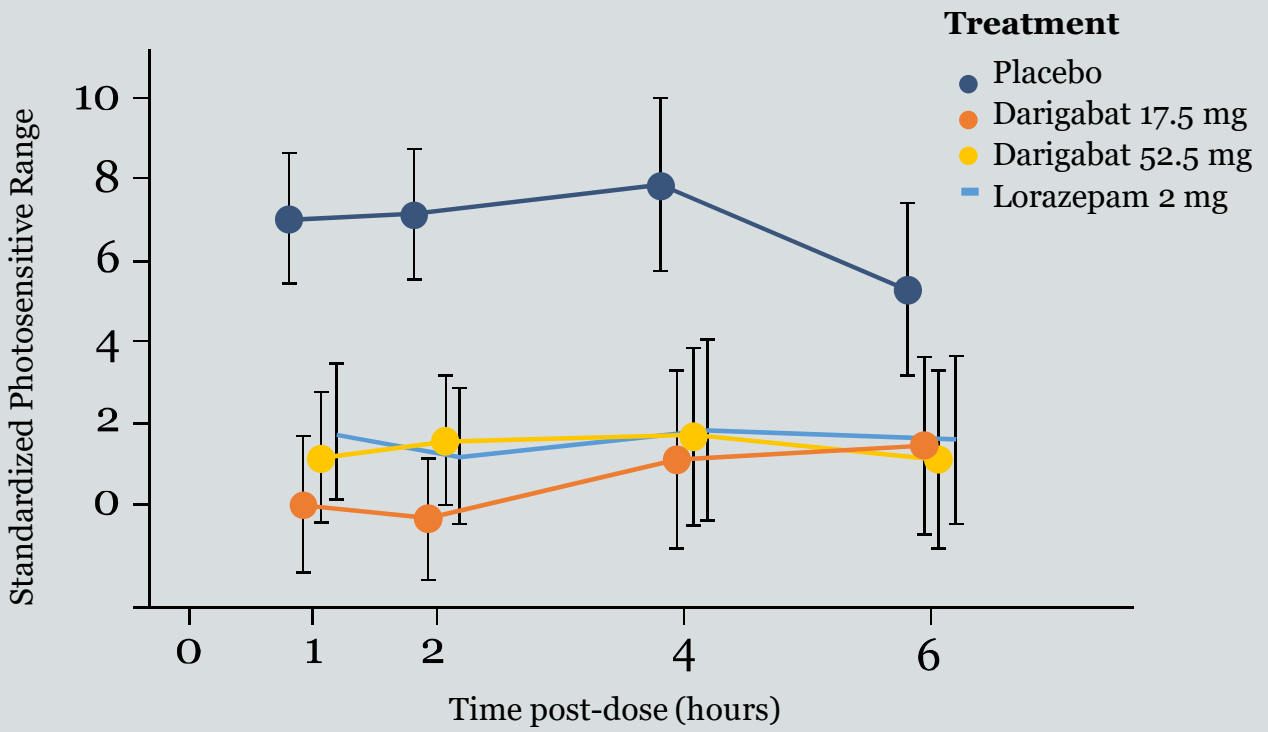
PAM = Positive Allosteric Modulator

Darigabat: compelling translational data package supports clinical development program

Darigabat Profile

- Novel mechanism: α2/3/5-selective $GABA_A$ receptor PAM
- Generally well-tolerated clinically, including at doses achieving ~80% receptor occupancy
- Antiepileptic activity in proof-of-principle photoepilepsy clinical trial – 6/7 subjects with complete suppression of response

Darigabat single dose photoepilepsy trial



Darigabat efficacy and safety profile warrants continued clinical development in epilepsy

Gurrell et al., Neurology 2019

An animal model of MTLE demonstrates key features of drug-resistant focal epilepsy

Pharmacoresistance in focal epilepsy

- Patients with drug-resistant focal epilepsy need innovative novel antiseizure medications (ASMs)
- Investigate darigabat in a translationally relevant nonclinical model of drug-resistant focal epilepsy
- Mesial temporal lobe epilepsy model:
  - Chronic spontaneous seizures
  - Morphological features
  - Pharmacoresistance

Intra-hippocampal kainate injection

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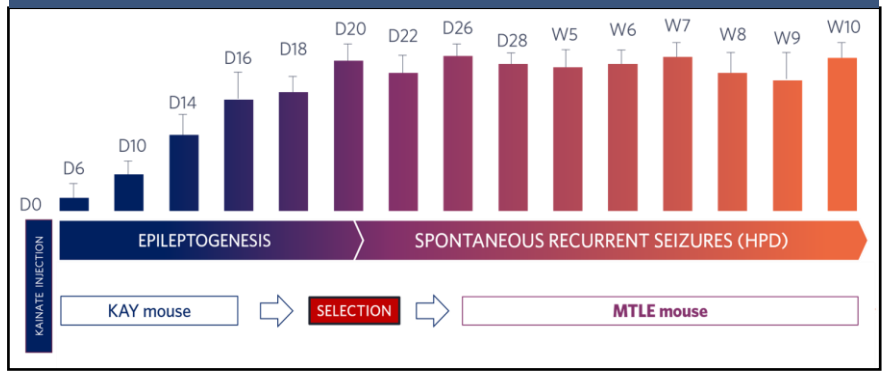
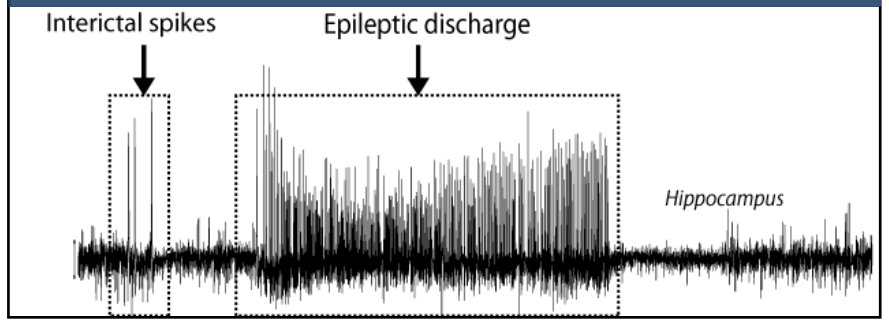
Implantation of bipolar electrode

Chronic spontaneous seizures



Hippocampal paroxysmal discharges

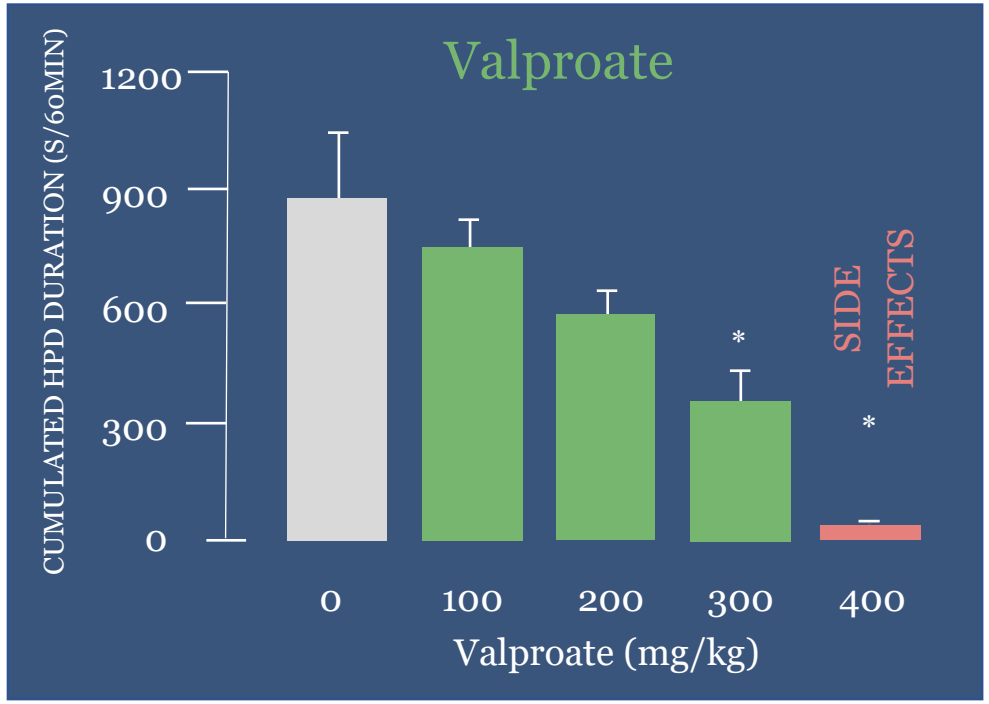


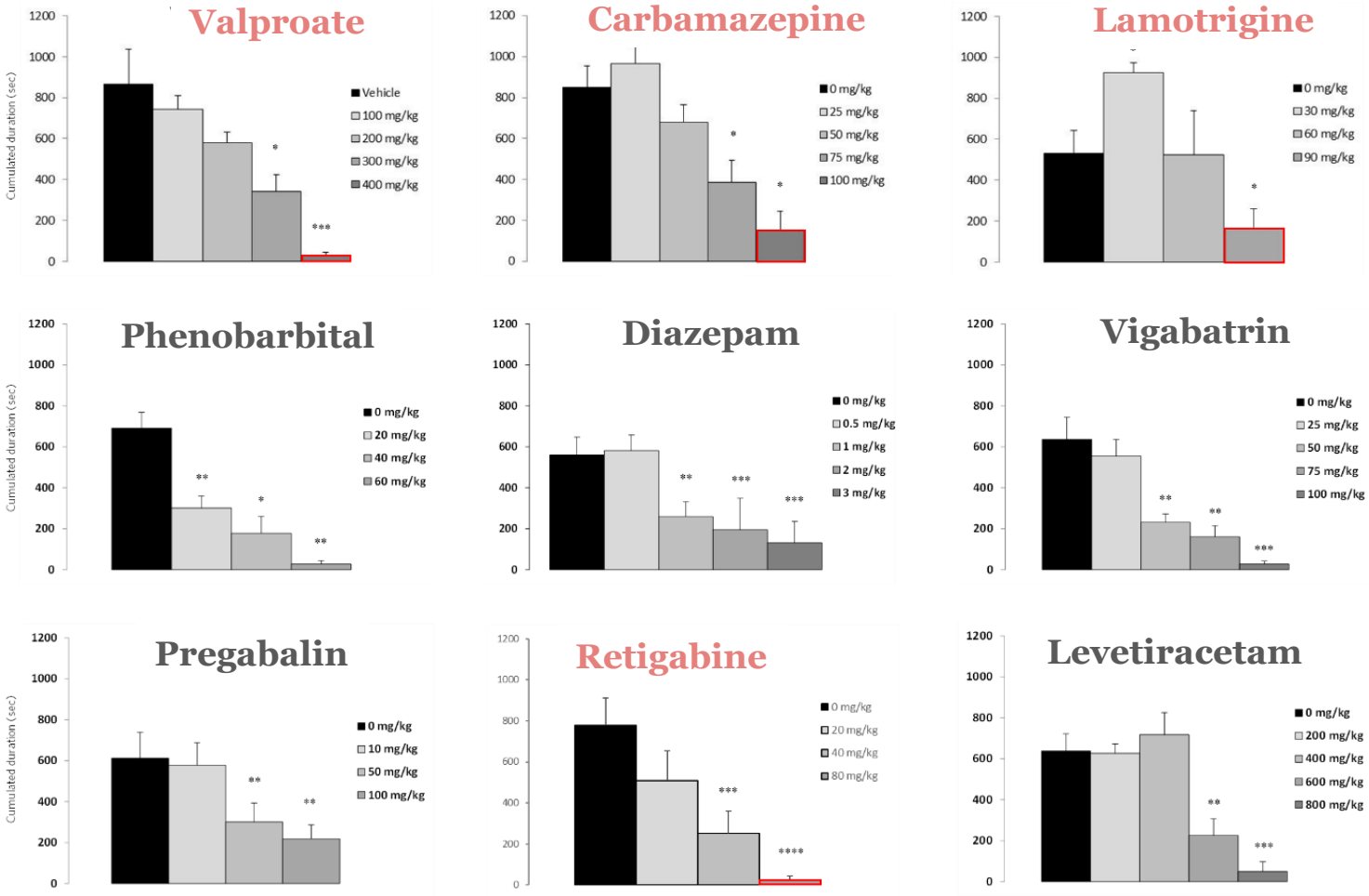
Hippocampal sclerosis

MTLE = mesial temporal lobe epilepsy

Pharmacoresistance in the animal model of MTLE

- MTLE mouse model exhibits differential sensitivity to ASMs
- Identify novel drugs with desired profile: no seizures, no side effects





HPD = hippocampal paroxysmal discharges; ASMs = antiseizure medications

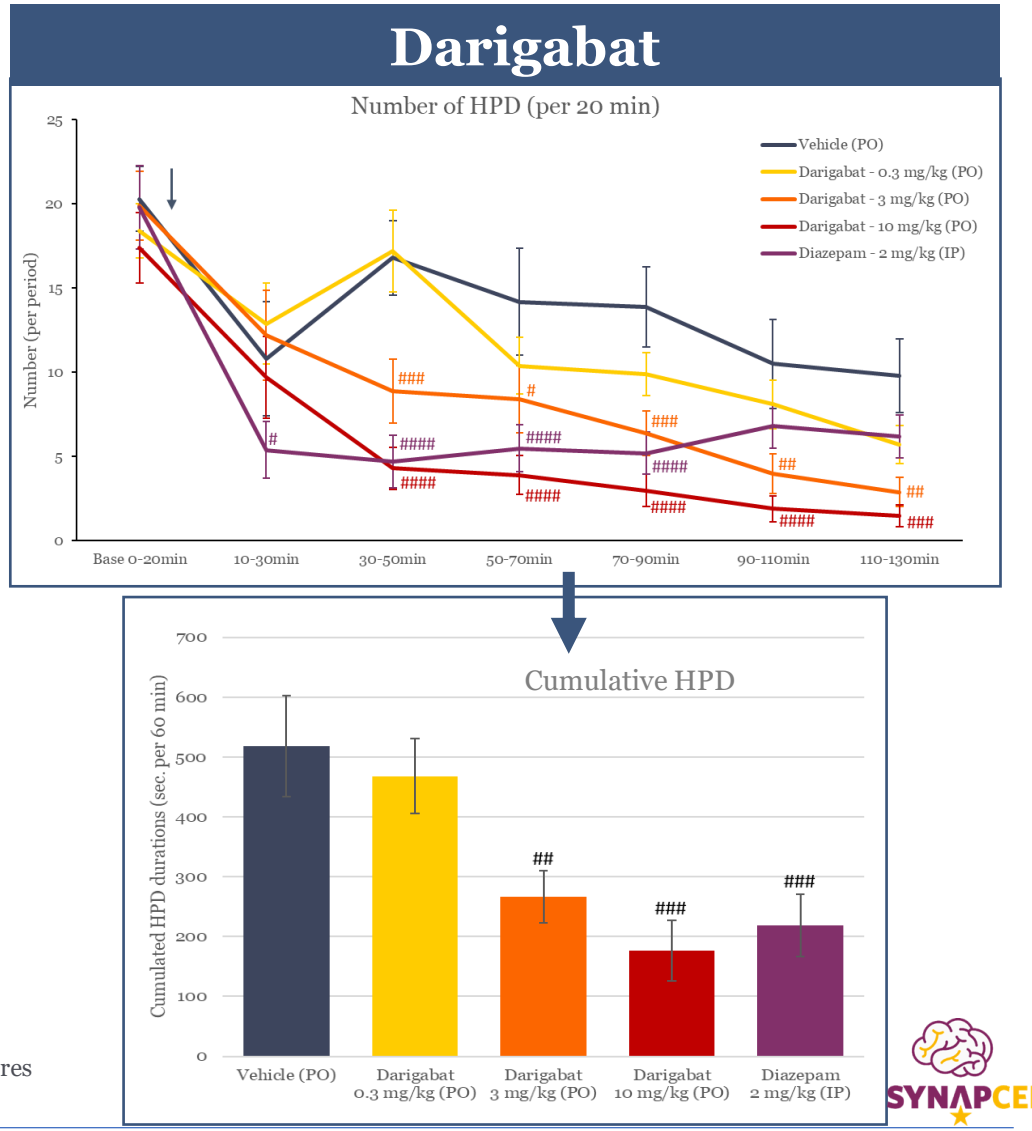
Duveau et al, CNS Neurosci Ther 2016

Darigabat demonstrates robust antiseizure activity in the MTLE mouse model, with no observable side effects

Darigabat Profile in MTLE mouse model

- Darigabat dose-dependently reduced the expression of focal seizures (HPDs)
- Comparable level of efficacy to diazepam at doses of 3 and 10 mg/kg
- No observable side effects, even at > 80% receptor occupancy

Darigabat warrants continued clinical development in drug-resistant focal epilepsy



HPD = hippocampal paroxysmal discharges

#, ##, ###, #### = p < 0.05, 0.01, 0.001, 0.001, respectively as compared to vehicle using two-way ANOVA for repeated measures

SYNAPCELL

REALIZE: Ph2 trial of darigabat in focal epilepsy

REALIZE: dRug rEsistAnt focaL onset seIZurEs

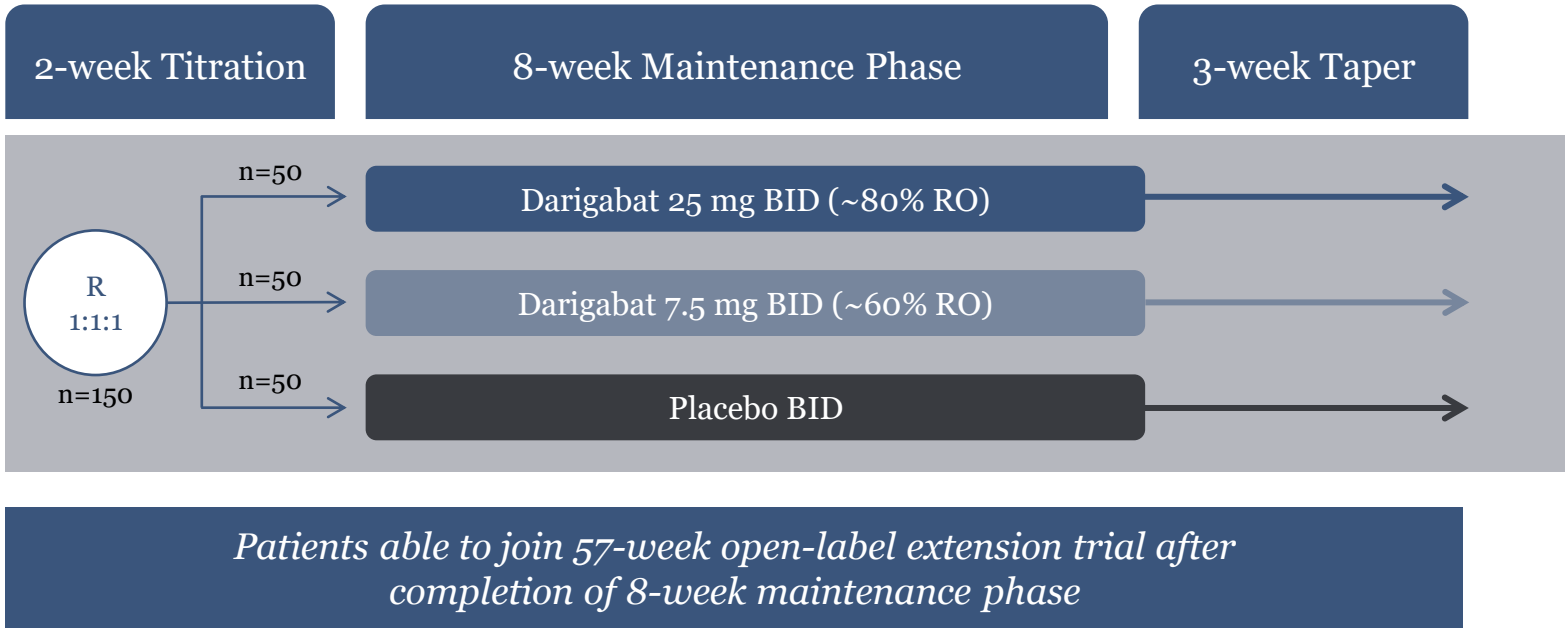
Focusing on the potential for patients to accomplish (realize) their goals

Inclusion criteria

- Adults (18-75) with drug-resistant focal onset seizures
- History of 4+ seizures per month for at least 3 months
- 1-3 stable background AEDs allowed

Primary endpoint

- Reduction in focal onset seizure frequency



Focal epilepsy intended to establish proof of concept and side effect profile to support development in broader epilepsy indications

CT.gov ID: NCT04244175

Thank You!

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