Darigabat: A Potential Treatment Option for Epilepsy

Targeted GABA α 2/3/5 Receptor Selectivity

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Disclosures

- Employee of Cerevel Therapeutics Holdings, Inc.
- Previous employee of Pfizer Inc. and owns shares

Forward-Looking Statements

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.

Forward-looking statements in this presentation include, but are not limited to: statements about the potential attributes and benefits of our product candidates, including with respect to receptor subtype selectivity, activity, side effect and tolerability profile and relevant indications; the format and timing of our product development activities and clinical trials, including the design of clinical trials and the timing of initiation, completion and data readouts for clinical trials; the timing and outcome of IND submissions and other regulatory interactions; the ability to compete with other companies currently marketing or engaged in the development of treatments for relevant indications; the size and growth potential of the markets for product candidates and ability to serve those markets; and the rate and degree of market acceptance of product candidates, if approved.

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Introduction to Cerevel

Cerevel: A Differentiated Approach to Treating Neurologic Diseases

cerevel

cere = cerebrum

revel = revelation/reveal

Our responsibility is to serve our patients and our people

Targeted Neurocircuitry

Cerevel unlocks new treatment opportunities by precisely identifying and targeting the neurocircuitry that underlies a given neurological disease

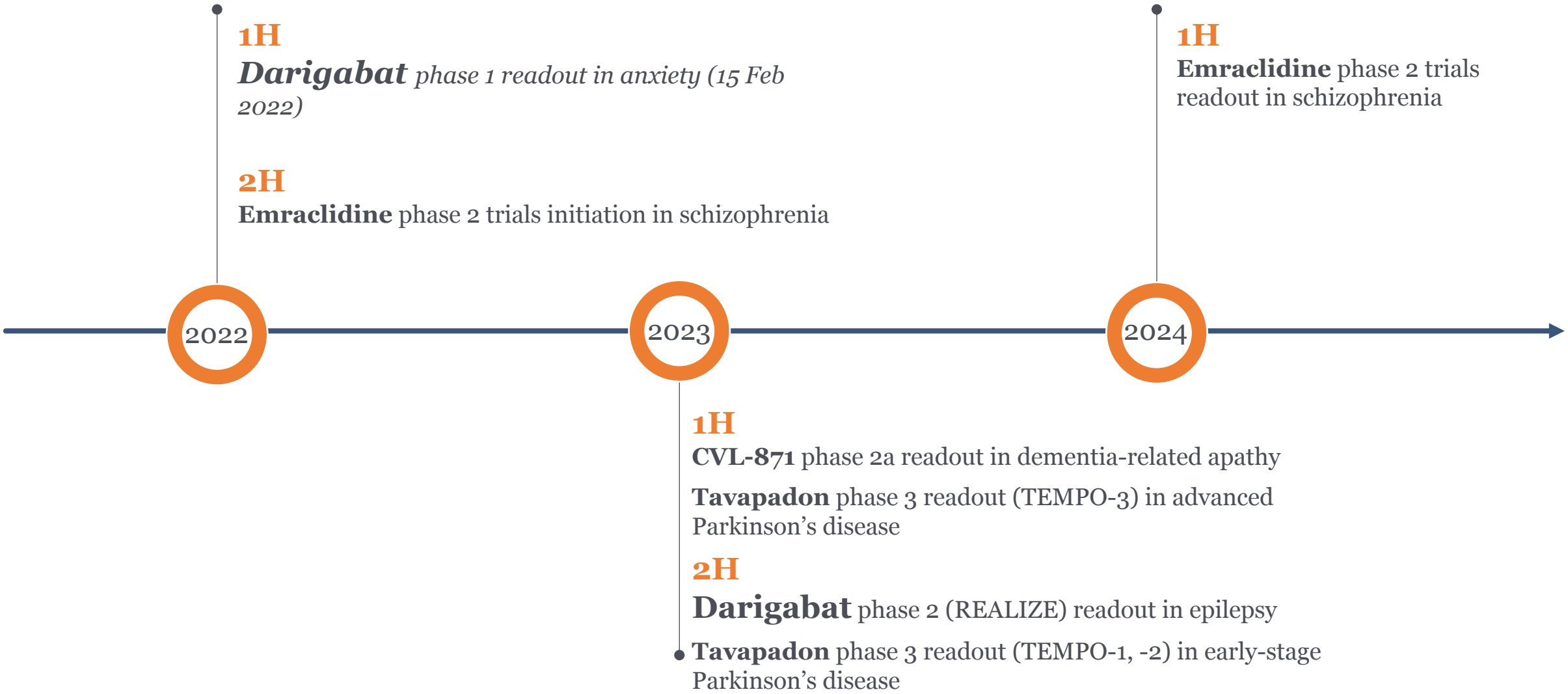
Receptor Subtype Selectivity

Cerevel is selectively targeting only the receptor subtype(s) related to the disease physiology, to minimize undesirable off-target effects while maximizing activity to provide effective treatment options with long-term tolerability

Differentiated Pharmacology

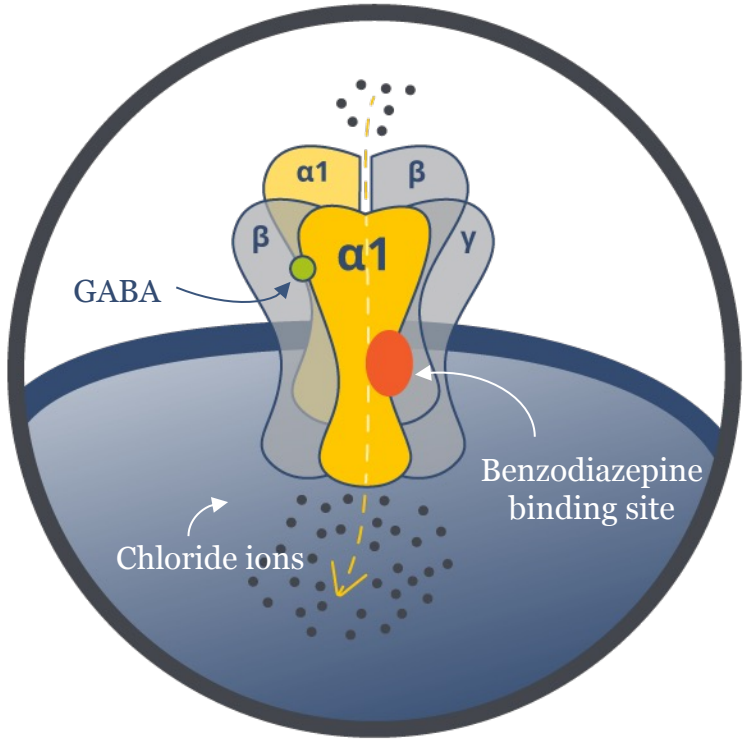
Cerevel designs full and partial agonists, antagonists, and allosteric modulators that can precisely fine-tune the receptor pharmacology and neurocircuit activity without overactivation or oversuppression of the endogenous physiologic range

Cerevel's Pipeline Has Multiple Upcoming Clinical Milestones



Darigabat: α1-sparing $GABA_A$ PAM

$GABA_A$ Receptor Pharmacology



GABA-induced chloride influx hyperpolarizes neurons, preventing action potentials and dampening excitability[1]

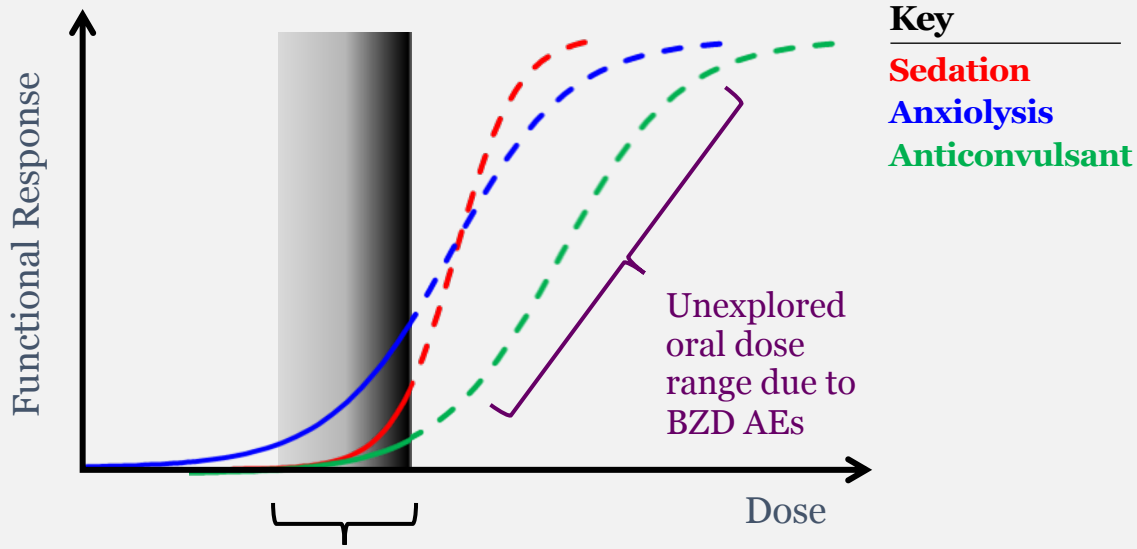
- $GABA_A$ receptors are ligand-gated ion channels controlling chloride flux[1]
- Benzodiazepine-sensitive $GABA_A$ receptors are pentameric and frequently contain[1]
  - Two α subunits – one of 4 subtypes (1, 2, 3, and 5)
  - Two β subunits
  - One γ subunit
- Benzodiazepines have no intrinsic effect of their own but are positive allosteric modulators (PAMs), potentiating the effects of GABA nonselectively at $GABA_A$ receptors containing α1/2/3/5 subunits[1]
  - Used widely for anxiety, mood disorders, epilepsy, sleep, and anesthesia[1]

1. Rudolph and Knoflach. *Nat Rev Drug Discov*. 2011;10:685-697.

The Problem With Benzodiazepines

- BZDs are efficacious in a range of indications, but their usage and dosage are limited by adverse events, even at low receptor occupancy[1]
  - Sedation, somnolence, cognitive impairment, falls, overuse, misuse and addiction[1]
- In general, BZDs are used acutely in epilepsy, but are not indicated for chronic use due to tolerance or loss of efficacy[2]

Clinical experience with BZDs

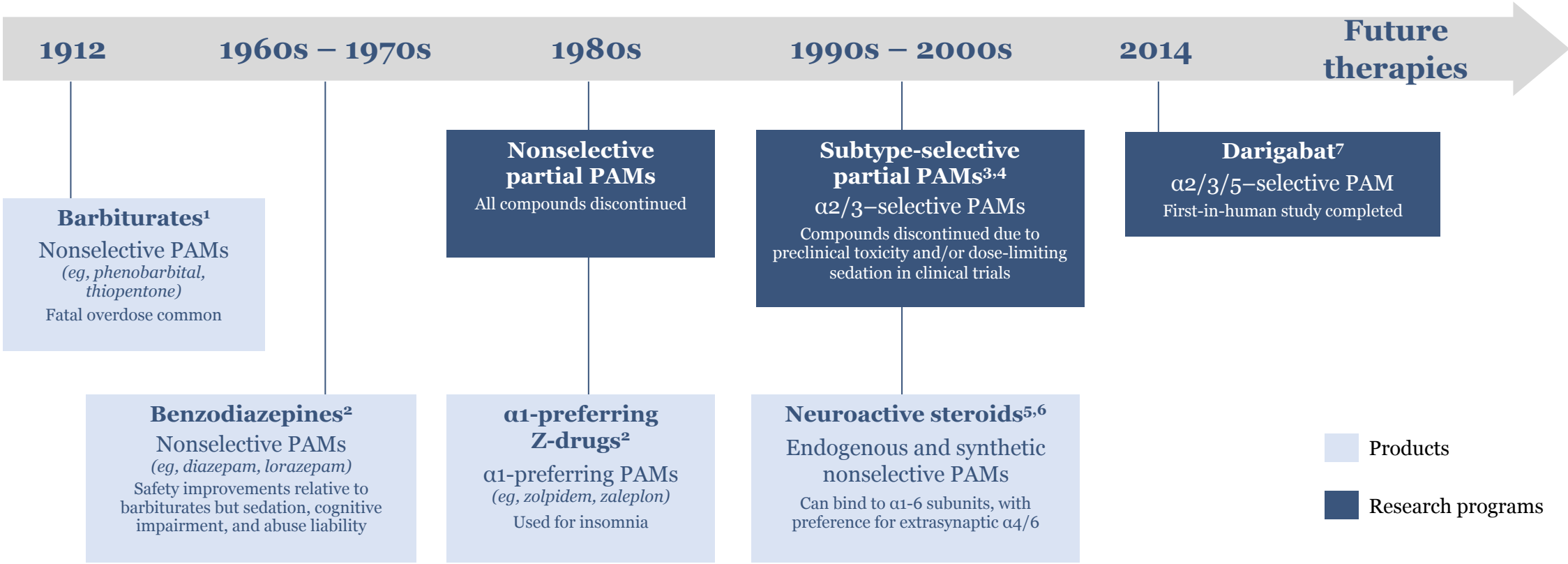


The dose range for oral classical BZDs is limited by sedative AEs **(<20% receptor occupancy)**

AE, adverse event; BZD, benzodiazepine.
1. Rudolph and Knoflach. *Nat Rev Drug Discov*. 2011;10:685-697. **2.** Ochoa and Kilgo. *Curr Treat Options Neurol*.2016;18:18.

$GABA_A$ Receptor PAMs – Class Innovation

Timeline of GABA Research and Drug Development



PAM, positive allosteric modulator.

1. Lopez-Munoz et al. *Neuropsychiatr Dis Treat*. 2005;1:329-343. **2.** Rudolph and Knoflach. *Nat Rev Drug Discov*. 2011;10:685-697. **3.** Atack. *Adv Pharmacol*. 2009;57:137-185. **4.** Atack et al. *J Psychopharmacol*. 2011;25:314-328. **5.** Belelli et al. *Neurobiol Stress*. 2019;12:100207. **6.** Wang M. *Front Endocrinol*. 2011;2:44. **7.** Nickolls et al. *Br J Pharmacol*. 2018175:708-725.

Subtype-Selective $GABA_A$ Receptor PAMs Have Therapeutic Potential in Epilepsy

Mechanistic Understanding of Pharmacology[1-8]

	$GABA_A$ receptor subtype			
	α1	α2	α3	α5
Analgesia		✓✓	✓	✓✓
Anxiolysis		✓✓	✓✓	
Muscle relaxation		✓✓	✓✓	
Anticonvulsant	✓✓	✓✓		
Sedation	✓✓			
Cognitive impairment	✓✓	?	?	✓
Addiction	✓✓	✓		

Design α1-sparing $GABA_A$ PAM to enable clinically relevant high receptor occupancy:
Darigabat (formerly CVL-865; PF-06372865)

Program goals

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

AE, adverse event; BZD, benzodiazepine; PAM, positive allosteric modulator.

1. Ralvenius et al. *Nat Commun*. 2015;6:6803; **2.** Knabl et al. *Pain*. 2009;141:233-238. **3.** Löw et al. *Science*. 2000;290:131-134. **4.** Dias et al. *J Neurosci*. 2005;25:10682-10688. **5.** Fradley et al. *J Psychopharmacol*. 2007;21:384-391. **6.** Rowlett et al. *Proc Natl Acad Sci USA*. 2005;102:915-920. **7.** McKernan et al. *Nat Neurosci*. 2000;3:587-592. **8.** Makaron et al. *Pharmacol Biochem Behav*. 2013;104:62-68.

Modeling Mesiotemporal Lobe Epilepsy (MTLE)

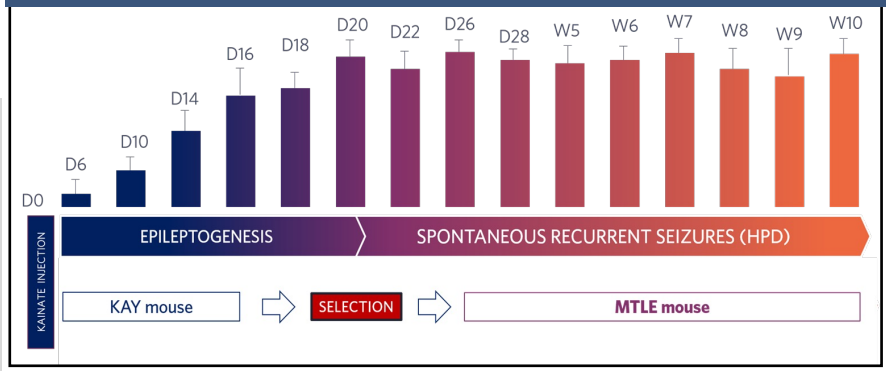
- Novel antiseizure medications are needed for patients with drug-resistant focal epilepsy[1]
- A clinically relevant translational model of drug-resistant focal epilepsy provides the opportunity to investigate novel therapies[1]
- The animal MTLE model demonstrates key features of drug-resistant focal epilepsy, including[1]
  - Chronic spontaneous seizures
  - Morphological features
  - Pharmacoresistance with differential sensitivity to antiseizure medications

Intrahippocampal kainate injection

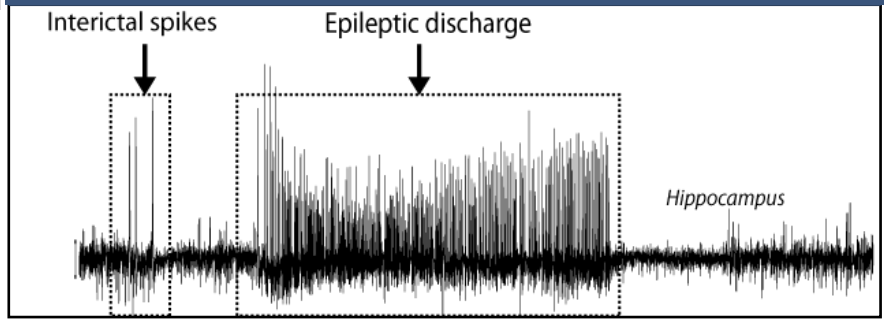
↓

Implantation of bipolar electrode

Chronic spontaneous seizures



Hippocampal paroxysmal discharges



Hippocampal sclerosis

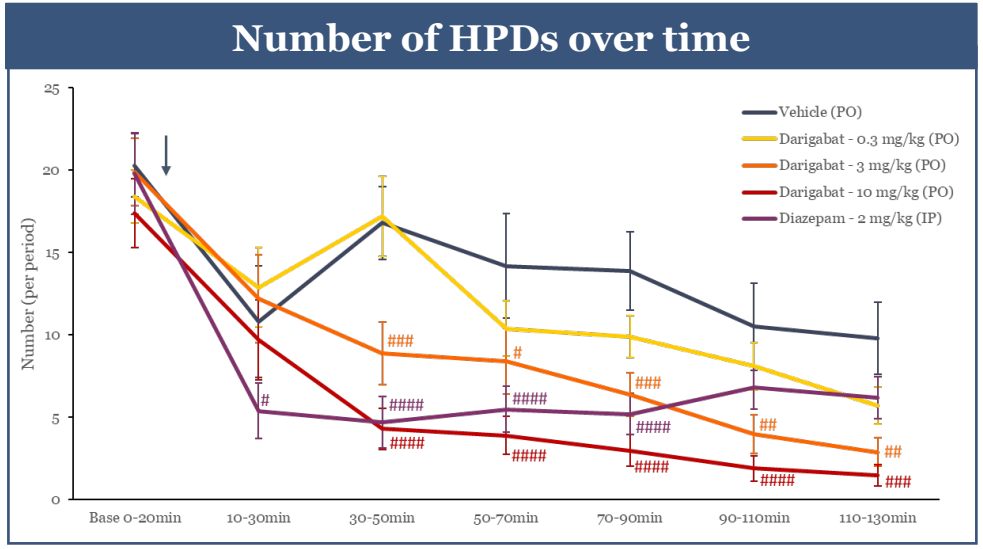
Images used with permission of SynapCell, SynapCell SAS, Saint Ismier, France.

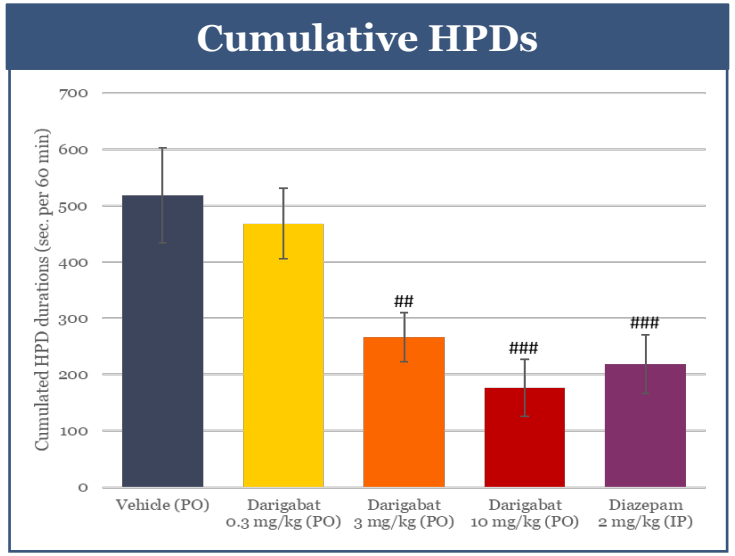
HPD, hippocampal paroxysmal discharge; MTLE, mesiotemporal lobe epilepsy.

1. Duveau et al. *CNS Neurosci Ther*. 2016;22:497-506.

Darigabat Demonstrated Robust Antiseizure Activity in the MTLE Mouse Model, With No Observable Side Effects

- Darigabat has been investigated in the MTLE model in partnership with SynapCell
- Darigabat dose-dependently reduced the expression of focal seizures (HPDs), with a comparable efficacy profile to diazepam at doses of 3 and 10 mg/kg
- There were no observable side effects, even at >80% receptor occupancy





Darigabat warrants continued clinical development in drug-resistant focal epilepsy

#, ##, ###, #### = P< 0.05, 0.01, 0.001, 0.001, respectively, as compared with vehicle using two-way ANOVA for repeated measures.
HPD, hippocampal paroxysmal discharges; MTLE, mesiotemporal lobe epilepsy.

Darigabat: Clinical Profile

Mechanism and Clinical Safety Profile of Darigabat

Novel mechanism

α2/3/5-selective
$GABA_A$ receptor PAM[1]

Clinical trials

300+ participants | **10** completed **2** ongoing

The **majority** of side effects **were mild or moderate**, even at doses achieving **~80% receptor occupancy**[1-4]

The **most common** side effects were **dizziness**, **drowsiness**, and **fatigue**[1,3,4]

No sedation was observed at any dose to date[1,3,4]

- Pharmacodynamic changes in markers of α2/3 pharmacology combined with previous clinical trial data suggest that doses achieving >50% receptor occupancy may be required for maximal pharmacodynamic effects[3]
- Side effects were **mitigated by titration** in multidose studies, with no dose-dependent increases in AE severity[3]
- No evidence of withdrawal in multidose, phase 2 studies using the Physician's Withdrawal Checklist or on self-reported AEs in all clinical trials to date[3]

AE, adverse event; PAM, positive allosteric modifier.

1. Nickolls et al. *Br J Pharmacol*. 2018175:708-725. **2.** Gurrell et al. *Pain*. 2018;159:1742-1751. **3.** Gurrell et al. *Clin Pharm Drug Dev*. 2021;10:756-764. **4.** Gurrell et al. *Neurology*. 2019; 92:e1786-1795.

Darigabat in a Proof-of-Principle Photoepilepsy Clinical Trial

- Darigabat completely suppressed response in 6/7 participants in a clinical trial of the epilepsy photosensitivity model[1]
- The epilepsy photosensitivity model is a translationally relevant model that predicts efficacy and dose in wider epilepsy populations[2]

Darigabat single-dose photoepilepsy trial

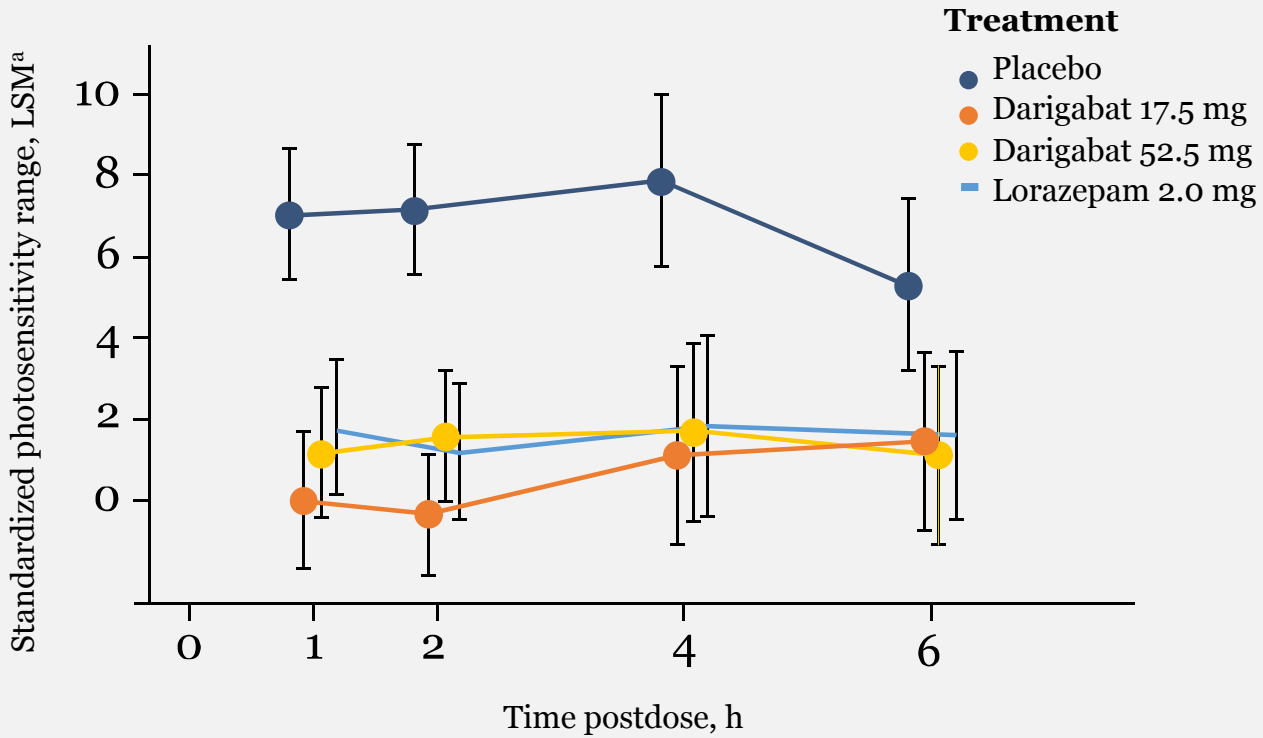


Figure adapted from Gurrell R, Gorman D, Whitlock M, et al. Photosensitive epilepsy. *Neurology*. 2019;92:e1786-1795. With permission from American Academy of Neurology. Copyright © 2022 Wolters Kluwer Health.

Darigabat profile warrants continued clinical development in epilepsy

[a]90% confidence interval.
LSM, least-squares mean.
1. Gurrell et al. *Neurology*. 2019; 92:e1786-1795. **2.** Yuen and Sims. *Seizure*. 2014; 23:490-493.

REALIZE: Phase 2 Trial of Darigabat in Focal Epilepsy

REALIZE: dRug rEsistAnt focaL onset seIZurEs

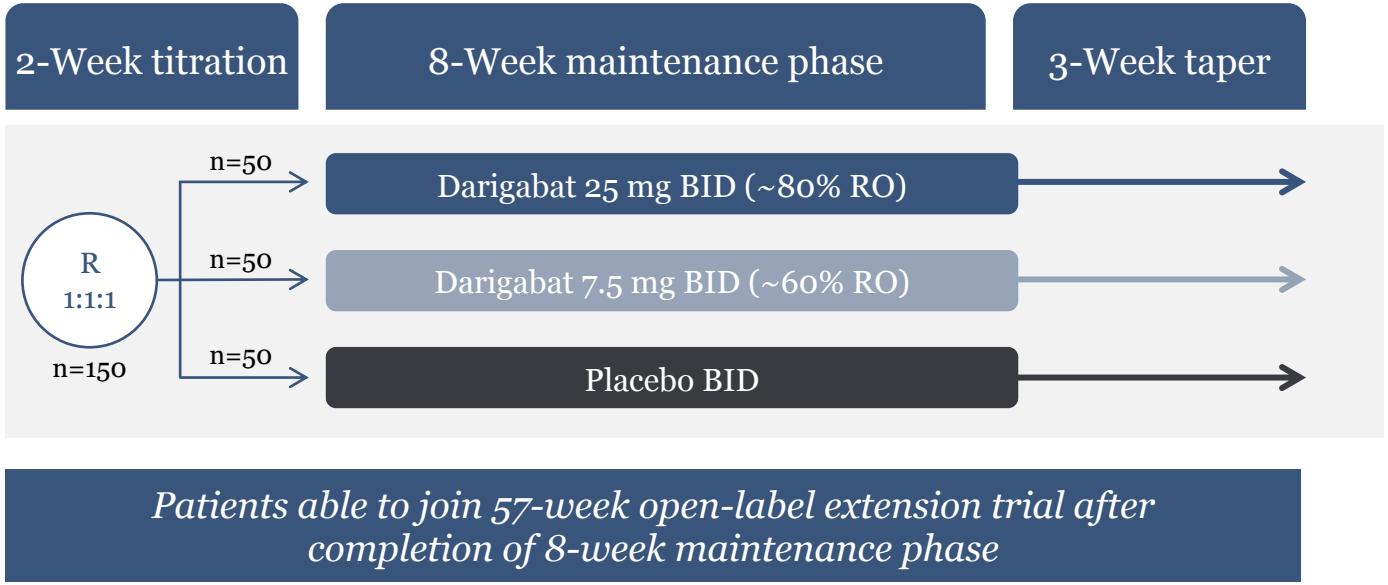
Focusing on the potential for patients to accomplish (realize) their goals

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 ASMs allowed

Primary endpoint

- Reduction in seizure frequency



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

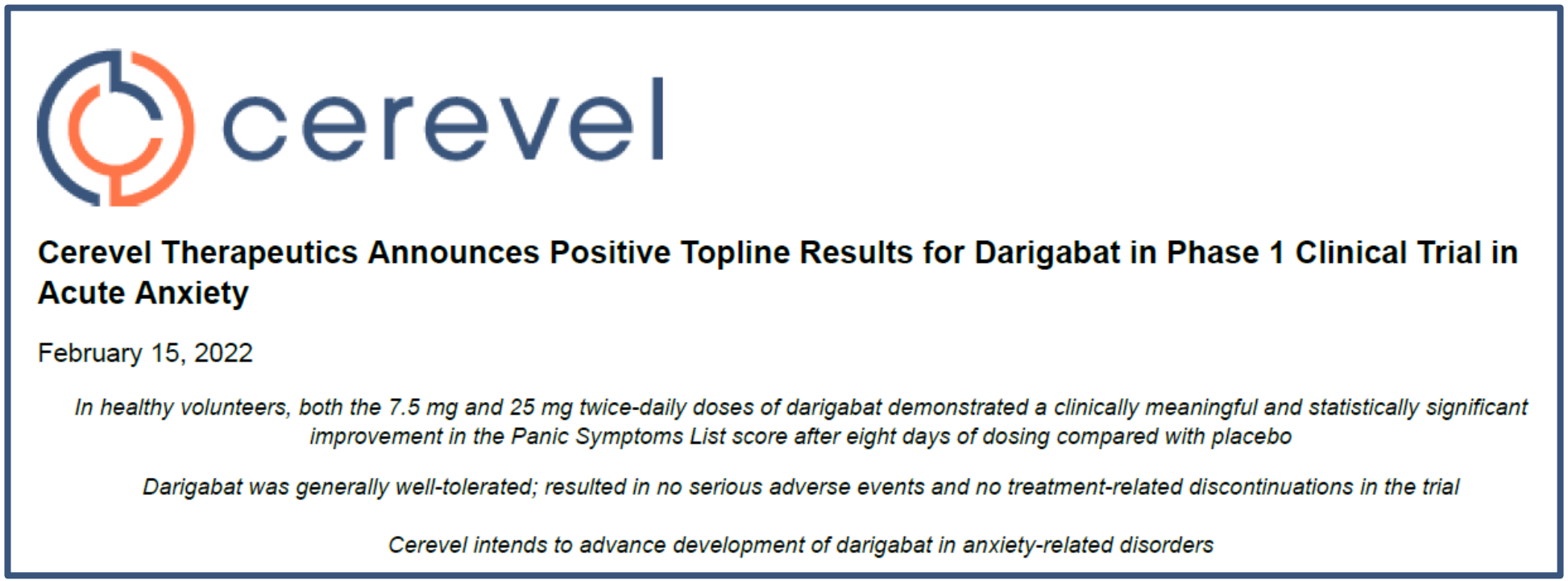
ASM, antiseizure medication; BID, twice daily; R, randomize; RO, receptor occupancy.
CT.gov ID: NCT04244175

Ensuring the Continuity of Data Collection in the REALIZE Clinical Trial During the COVID-19 Pandemic

- In response to the COVID-19 pandemic, the Phase 2 REALIZE clinical trial protocol and trial processes were updated to include the following:
  - Remote participant visits permitted at certain prespecified time points due to COVID-19–related issues
    - Home nursing, IMP delivery, and remote ECG collection
  - Allowance in the protocol to over-enroll if there are higher than anticipated early terminations due to COVID-19 or other reasons
  - Addition of COVID-19 consent addendum

ECG, electrocardiogram; IMP, investigational medicinal product.

Recent Positive Data Readout in Hypercapnia Study of Darigabat



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Cerevel Therapeutics Announces Positive Topline Results for Darigabat in Phase 1 Clinical Trial in Acute Anxiety

February 15, 2022

In healthy volunteers, both the 7.5 mg and 25 mg twice-daily doses of darigabat demonstrated a clinically meaningful and statistically significant improvement in the Panic Symptoms List score after eight days of dosing compared with placebo

Darigabat was generally well-tolerated; resulted in no serious adverse events and no treatment-related discontinuations in the trial

Cerevel intends to advance development of darigabat in anxiety-related disorders

Summary of Darigabat in the Treatment of Epilepsy

- Selective targeting of the $GABA_A$ receptor α2/3/5 subunits while sparing α1 has the **potential for anticonvulsant activity while avoiding the dose-limiting side effects of benzodiazepines**[1]
- The **MTLE mouse model approximates key features of drug-resistant focal epilepsy**, including chronic spontaneous seizures, morphological features, and pharmacoresistance to antiseizure medications**, providing a model for preclinical evaluation of novel antiseizure medications**[2]
- Darigabat has **shown robust antiseizure activity** in the MTLE model with **no observable side effects**, **supporting continued development** of darigabat for the treatment of drug-resistant focal epilepsy
- Darigabat has been **generally well tolerated in clinical trials**, with the **majority of AEs being mild to moderate**, even at doses achieving ~80% receptor occupancy[3-6]
- A **phase 2 clinical trial of darigabat in focal epilepsy (REALIZE) is currently ongoing**, aided by strategies to support continued data collection through the COVID-19 pandemic

AE, adverse event; MTLE, mesiotemporal lobe epilepsy.

1. Bialer et al. *Epilepsia*. 2020;61:2365-2385. **2.** Duveau et al. CNS *Neurosci Ther*. 2016;22:497-506. **3.** Nickolls et al. *Br J Pharmacol*. 2018175:708-725. **4.** Gurrell et al. *Pain*. 2018;159:1742-1751. **5.** Gurrell et al. *Clin Pharm Drug Dev*. 2021;10:756-764. **6.** Gurrell et al. *Neurology*. 2019; 92:e1786-1795.

Thank You!

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