Ovid Therapeutics

Biomarkers in epilepsy and OV329 program updates

June 12, 2025

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Welcome

Dr. Jeremy Levin
Chairman & Chief Executive Officer

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Forward-looking statements

This presentation contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 including, without limitation, the potential therapeutic benefits of Ovid's current or future product candidates and pipeline programs; statements regarding the expected timing of the initiation, completion, and results and data of Ovid's clinical studies; expected timing of IND submission for OV4041 oral; the potential use, development and therapeutic opportunity of OV329, OV350 IV, OV4071 oral and OV4041 oral; expectations regarding the size of the market for OV329; the likelihood that data, including safety and tolerability data, for OV329 will support future development and therapeutic potential; and the suitability of OV329 for a range of indication opportunities. You can identify forward-looking statements because they contain words such as "will," "may," "plan," "believe," "intend," "anticipate," "design," "advance," "target," "seek," "expect," "demonstrate," and "potential," and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances).

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Our brain trust

Ovid approach

Jeremy Levin, DPhil, MB BChir
Chairman & Chief Executive Officer

Opportunity & strategy

Meg Alexander
President & Chief Operating Officer

Clinical development

Amanda Banks, MD
Chief Development Officer

From biomarkers to bedside

Alex Rotenberg, MD, PhD
Epileptologist
Professor of Neurology,
Harvard Medical School
Director, Neuromodulation Program,
Boston Children's Hospital

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Our purpose

- **Review the paradigm shift** in antiseizure medication (ASM) development with biomarkers

- **Share updates on OV329** clinical development and opportunity

- **Discuss de-risking biomarkers** applied to the OV329 development program in advance of expected Phase 1 topline readout in Q3 2025

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Ovid's focus

Foundational biological targets

underlying excess neural excitation with broad potential therapeutic utility

Highly selective small molecule medicines

with the opportunity for multiple clinical-stage programs and commercial medicines

Differentiated mechanisms of action

that stand out in a field of me-too medicines

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Neuronal **hyperexcitability** is at the biological root of many brain diseases that have no effective treatment today

The unmet need: Quelling excess neural excitation

Meg Alexander

President & Chief Operating Officer

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Differentiated pipeline, with multiple near-term milestones

Programs	Indication opportunities	Preclinical	Phase 1	Phase 2	Anticipated milestones*
OV329					
GABA-aminotransferase inhibitor	Drug resistant adult epilepsies (DREs) & developmental epileptic encephalopathies (DEEs)				Phase 1 topline Q3 2025 (includes biomarkers of target engagement and potential clinical effect) Phase 2a initiation Q1 2026; topline Q1 2027
KCC2 direct activator portfolio					
OV350 IV	First-in-human potential proof of mechanism				Phase 1 initiated Q1 2025 Safety, tolerability and PK Q4 2025
OV4071 oral	Psychosis assoc. with Parkinson's disease and Lewy body dementia				IND-enabling studies in progress Phase 1 initiation expected in Q2 2026 Patient Phase 1b initiation in Q3 2026; topline results in Q1 2027
OV4041 oral	Generalized anxiety disorder or Rett syndrome				Initiating IND-enabling late 2025 IND submission late H2 2026

* Subject to Ovid capital runway or partnerships.

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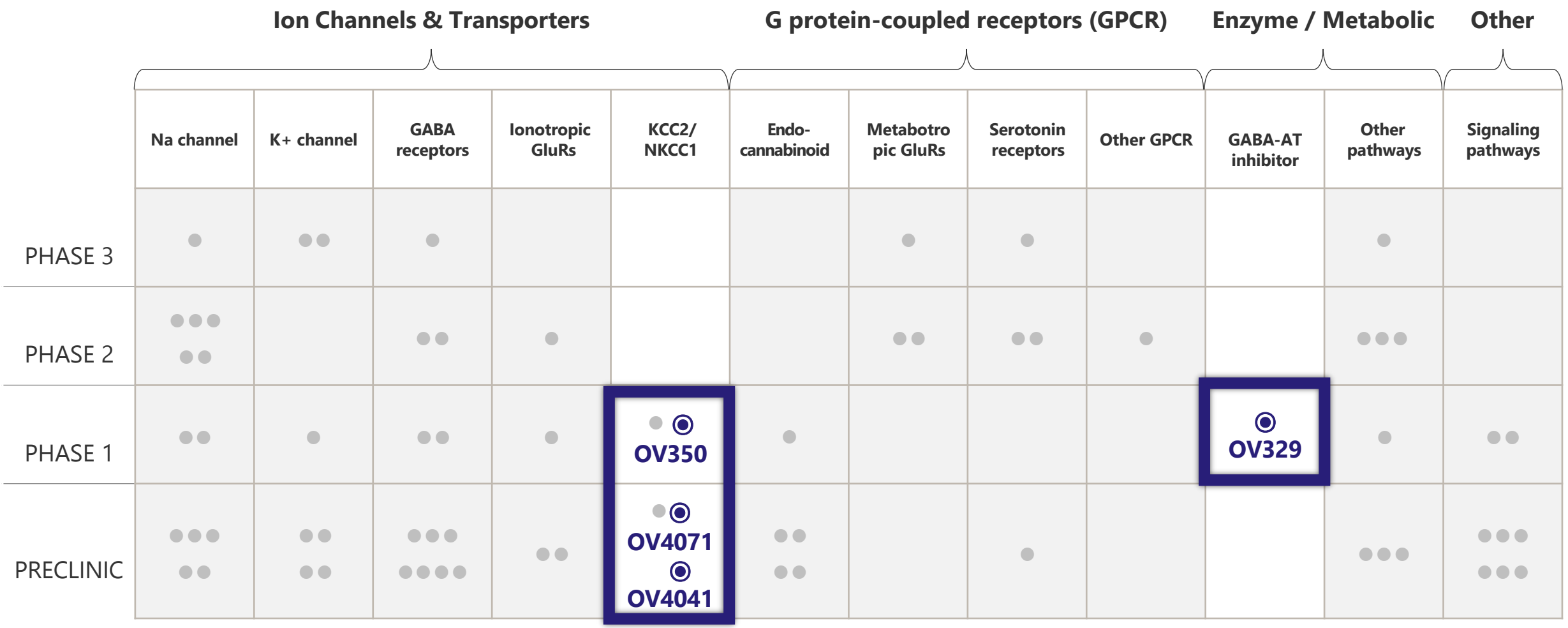
Anti-seizure drug
development has
been a sea of sameness

Ovid pipeline:
Differentiated mechanisms fundamental to achieving excitatory:inhibitory balance

Illustrative map of programs in development



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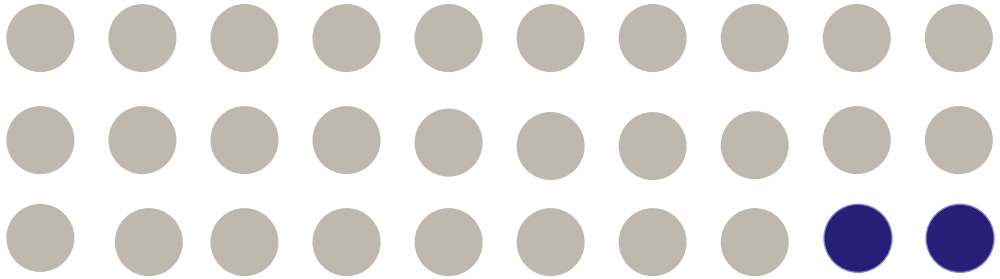
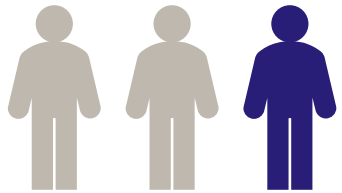
Drug-resistant epilepsy (DRE): The unmet need hiding in plain sight

30 anti-seizure medications approved in 15 years, but only 2 with novel mechanisms



A crowded treatment landscape and yet—
>1 in 3 patients live with uncontrolled seizures



Each dot = 1 FDA-approved ASM; Purple dot= Fycompa and Cenobamate

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OV329

A next-generation, best-in-class GABA-aminotransferase inhibitor for the potential treatment of conditions of neuronal hyperexcitability & seizures

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Unmet need in drug-resistant epilepsies & OV329 opportunity

Challenges of existing GABA-enhancing medicines

- **Short-acting**
  - Inhibition not sustained with many medicines
- **Sedating**
- **Safety challenges of 1st generation**
  - Vigabatrin causes irreversible visual toxicity
  - Black Box and REMS
  - Routine ocular monitoring required
- **High dose burden** of 1st generation medicine
  - Sabril (vigabatrin) starting dose is 3 grams, OV329 is ~1000-fold LESS drug

Intended OV329 target product profile*

Optimally tuned inhibition at low doses

- Durable inhibition and anti-convulsant activity

Sustained seizure reduction

- Strong reduction effect across focal & other seizure types

Improved safety profile

- No evidence of ocular changes in humans
- No monitoring expected on label
- No expected titration
- Not sedating in humans
- No anticipated drug-drug interactions

*Intended label reflected; profile will need to be demonstrated through future clinical development and patient studies

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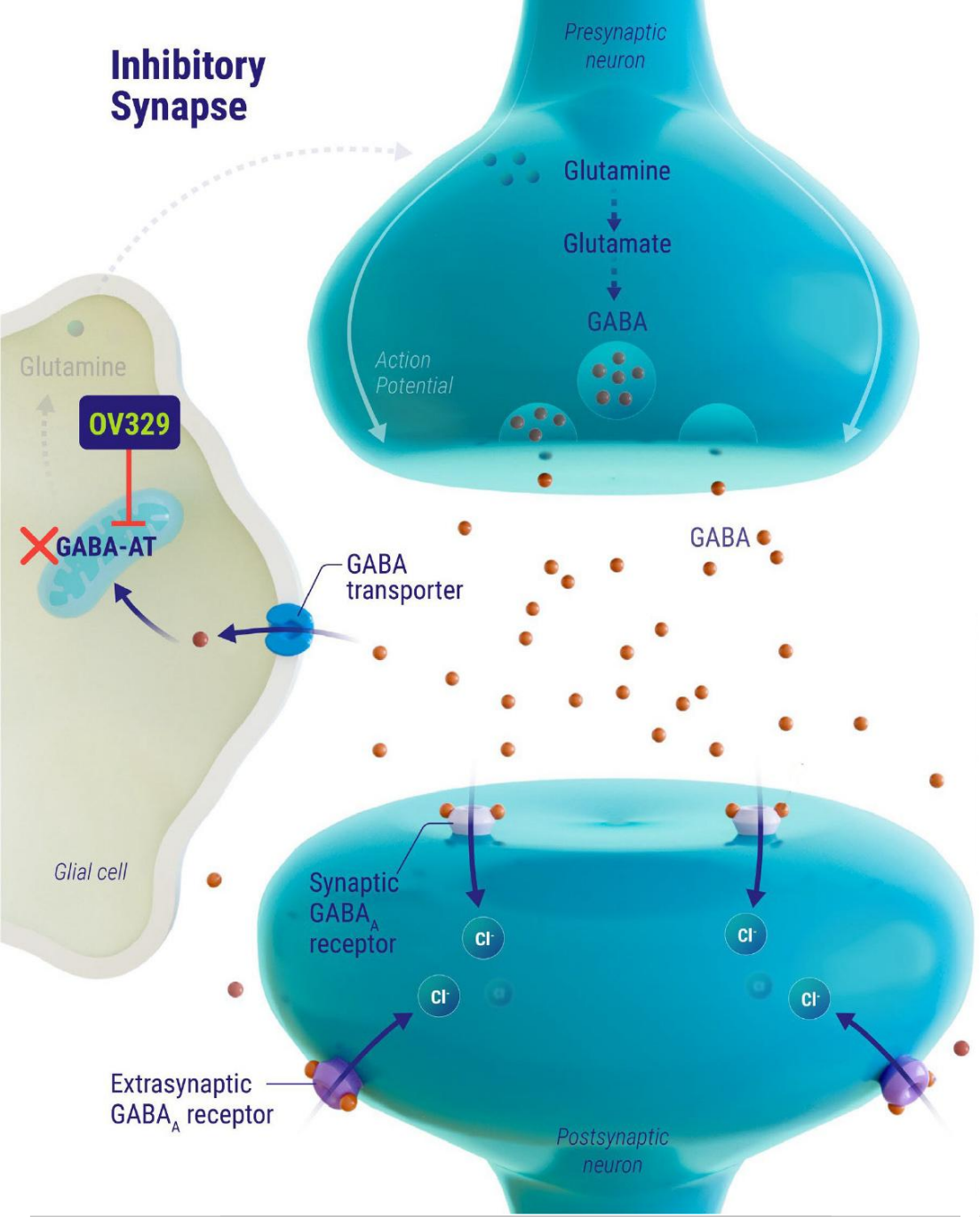

Mechanism of action

- Validated mechanism of action
- Inhibits GABA-AT, the enzyme that catabolizes the inhibitory neurotransmitter, GABA
- Increases GABA in the synapse & extrasynaptic regions
- Believed to optimally tune GABA to create an inhibitory neural milieu

1. Silverman RB. Chem Rev. 2018 Apr 11;118(7):4037-4070. doi: 10.1021/acs.chemrev.8b00009. Epub 2018 Mar 23. PMID: 29569907; PMCID: PMC8459698
2. Colmers P et al. eNeuro 27 June 2024, 11 (7) ENEURO.0137-24.2024; https://doi.org/10.1523/ENEURO.0137-24.2024

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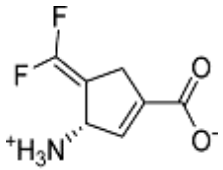
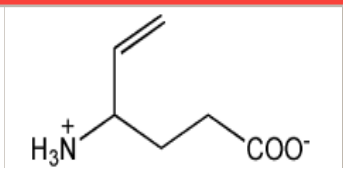
OV329 rationally designed to deliver potential best-in-class profile

	OV329	Vigabatrin
Molecule		
Potency (IC_{50})[1]	~0.1 - 0.3 mM	~60 – 100 mM
Exposure	$T_{1/2}$ ~1.0 Hour with prolonged PD duration	$T_{1/2}$ >5.0 Hours
Mechanism of enzyme inhibition	Electrostatic (irreversible) (more sophisticated chemistry, primarily enamine pathway) [2]	Covalent modification of GABA-AT (irreversible)
Therapeutic index[3,4]	No ocular changes in humans	Visual toxicity at therapeutic dose
Inhibition delivered	Phasic & tonic inhibition (synaptic & extrasynaptic)	Toxicity limits ability to achieve phasic & tonic inhibition

1. J Med Chem. 2012 Jan 26; 55(2): 567–575; 2. J Am Chem Soc. 2018 Feb 14; 140(6): 2151–2164
2. Feja et al. OV329, a novel highly potent γ-aminobutyric acid aminotransferase inactivator, induces pronounced anticonvulsant effects in the pentylenetetrazol seizure threshold test and in amygdala-kindled rats. Epilepsia. 2021 Dec;62(12):3091-3104. doi: 10.1111/epi.17090. Epub 2021 Oct 7.
3. As seen in clinical trials to date.
4. Ovid data on file. Therapeutic index measured in Sprague Dawley rats, a proxy model used to assess ocular safety.

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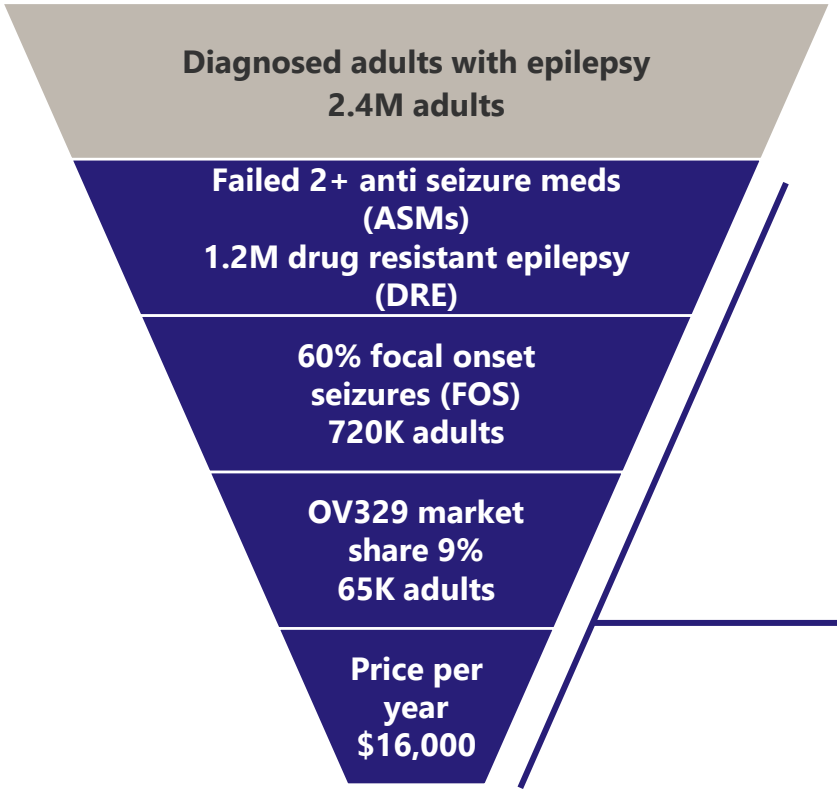
Unique, well-tolerated MoAs are rewarded in epilepsy, even in a competitive DRE market

Substantial opportunity within the DRE segment



>$1 Billion

Key: Voltage-gated Ion Channel Target | GABAergic | Synaptic Target | Other / Mixed / Unknown

Focal / Partial seizures

1L	Carbamazepine	Levetiracetam	Oxcarbazepine
	Phenytoin	Eslicarbazepine	Lacosamide
2L	Clobazam	Lamotrigine	Topiramate
	Rufinamide	Zonisamide	
Refractory + polypharmacy (~40%)	OV329 *In Phase 1*	XEN1101	XCOPRI
		Fycompa perampanel	BRIVIACT (brivaracetam)

Reimbursement & coverage dynamics remain favorable. Polypharmacy well covered

1. J Med Chem. 2012 Jan 26; 55(2): 567–575; 2. J Am Chem Soc. 2018 Feb 14; 140(6): 2151–2164

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Broader life-cycle opportunity for a safe GABA-AT inhibitor is significant

Initial intended indication

Focal seizures in adults with drug resistant epilepsy

Potential follow-on indications

Focal seizures in developmental epileptic encephalopathies

Post-surgical & perioperative pain

Substance abuse and alcohol withdrawal

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Imaging and electrophysiology improvements are enabling:

use of predictive biomarkers in ASM development

assessment of CNS drug effects prior to lengthy and costly proof-of-concept trials

comparability across ASMs (in some parameters)

Validate MOA

- **Demonstrate target engagement**
- **Measure pharmacodynamic response**
- **Provide early efficacy signals**
- **Quantify dose-dependent response**

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Evolving application of imaging & electroencephalogram technologies to measure ASM biomarkers

Company	Approved/investigational product	Technology applied		
		MRS	TMS	EEG
Ovid Therapeutics	**OV329**	✓	✓	✓
Lundbeck	Sabril	✓	✓	✓
SK Life Science	XCOPRI			✓
Lundbeck	BRIVIACT (brivaracetam)		✓	✓
Xenon	XEN-1101		✓	✓
Biohaven	BHV-7000			✓
Praxis	PRAX-628			✓
Longboard	LB-352			✓
Bright Minds Bio	BMB-101			✓

Pierantozzi et al. Effect of vigabatrin on TMS motor responses shows utility in probing in vivo GABAergic inhibition. *Brain Res.* 2004;1028(1):1–8
Selatu et al. Vigabatrin increases beta activity in human EEG. *Electroencephalogr Clin Neurophysiol.* 1986;63(2):152–155.

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Biomarker strategy applied in OV329 Phase 1

- Healthy volunteers measured pre- and post-treatment with OV329, includes placebo comparators
- Multiple parameters being assessed via:
  - Magnetic resonance spectroscopy
  - Transcranial magnetic stimulation
  - Electroencephalogram
- Leverage biomarker parameters that have measured vigabatrin & other GABAergic ASMs
- Assess drug effect after 7 days of treatment, relative to participant baselines and placebo
- Designed to detect directional signal
- Good safety and tolerability profile with no drug-related ocular changes

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Comprehensive biomarker strategy evaluating OV329

Tool	Magnetic resonance spectroscopy (MRS)	Transcranial magnetic stimulation (TMS)	Electroencephalogram (EEG)
Measures	**Neurotransmitter concentrations**	**Cortical excitability and brain circuit function**	**Brain waves linked to inhibitory (GABAergic) activity**
Metrics* (positive & negative controls)	• GABA concentrations in the medial parietal lobe	• Cortical silent period (CSP) • Paired-pulse long-interval intracortical inhibition (LICI) • Paired-pulse short-interval intracortical inhibition (SICI) • Resting motor threshold (rMT) • Intracortical facilitation (ICF)	High and low frequencies
What it suggests	✓ **Target engagement** as measured by increased in GABA concentrations using modern MRI "fitting" technology	✓ **Pharmacodynamic activity** on $GABA_A$, $GABA_B$ receptors and overall enhancing brain inhibition ✗ No excitatory (glutamatergic) activity	✓ **GABAergic pharmacodynamic** effect as shown by changes in high frequency brain activity

* All metrics compare post-OV329 values with baseline

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From biomarkers to bedside

Dr. Alex Rotenberg

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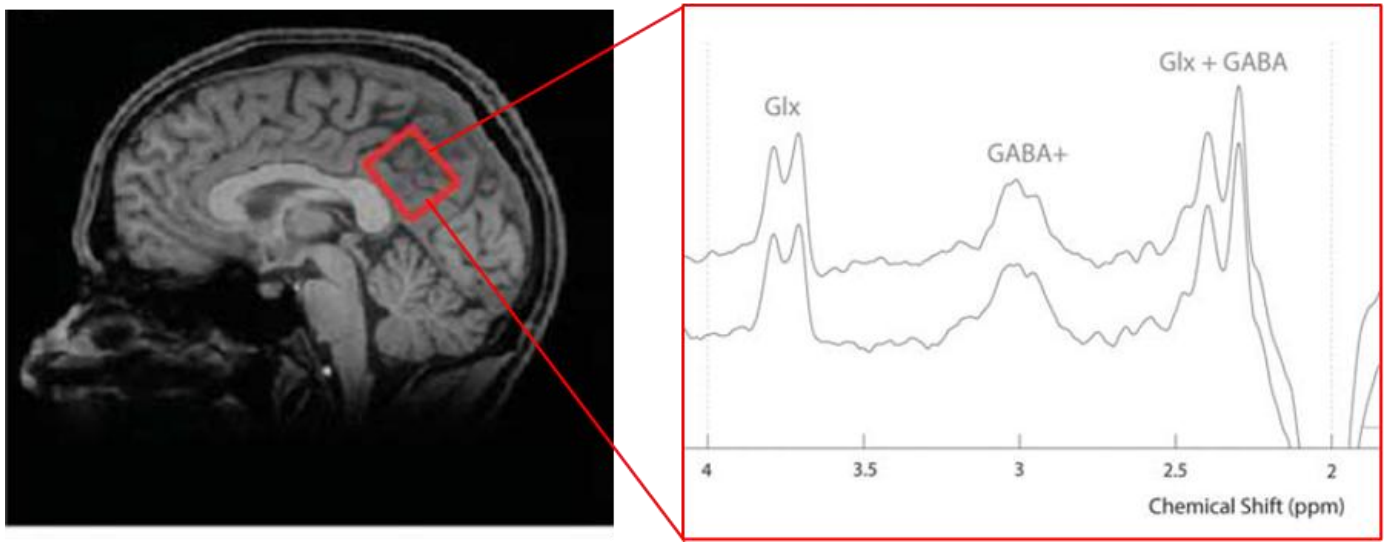
MRS may validate the OV329 approach

- Specialized MRI scan that provides a noninvasive way to measure chemicals in the brain
- Evaluates changing GABA concentrations in response to antiseizure medications



Prescot et al. 2018 Neuropsychopharmacology

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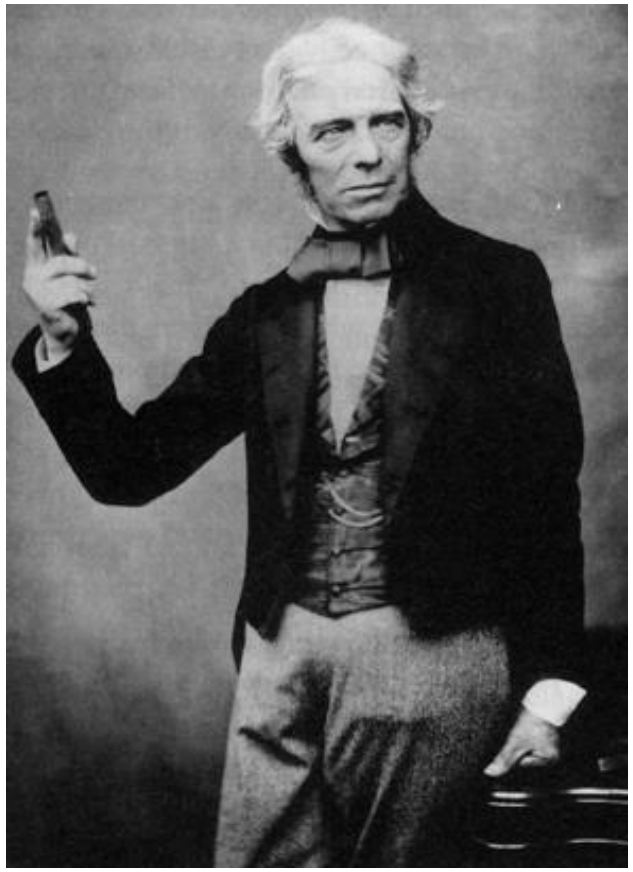
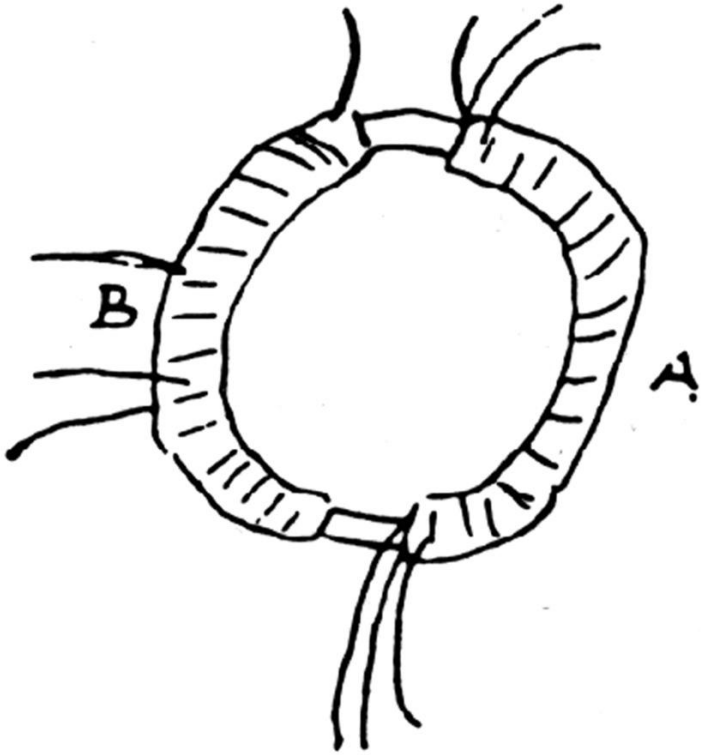
TMS is based on Faraday's Principle



Michael Faraday (1791 - 1867)



Electromagnetic induction: 1831

Induction stove

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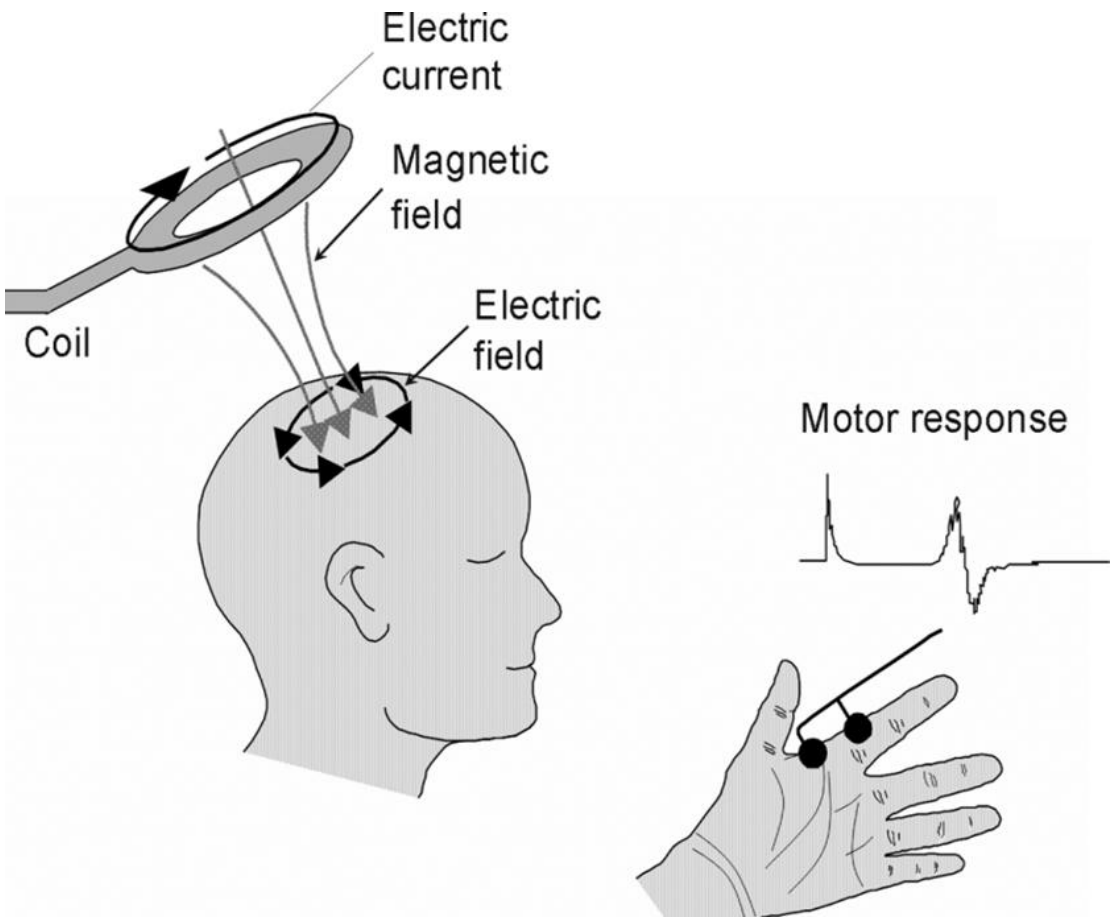
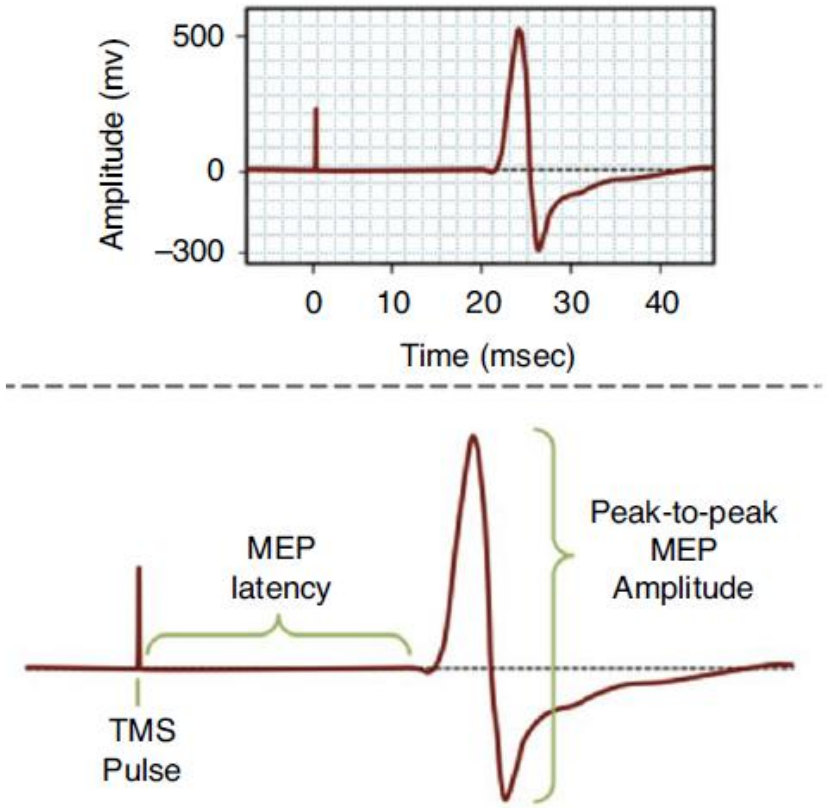
TMS: a method for focal noninvasive electrical brain stimulation





Frye, Rotenberg et al., J child Neurol 2007

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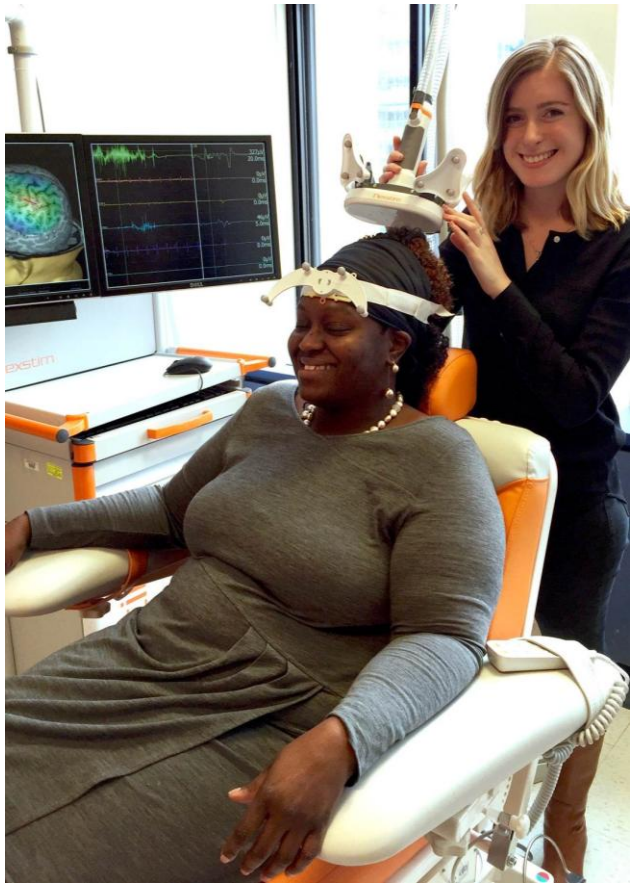
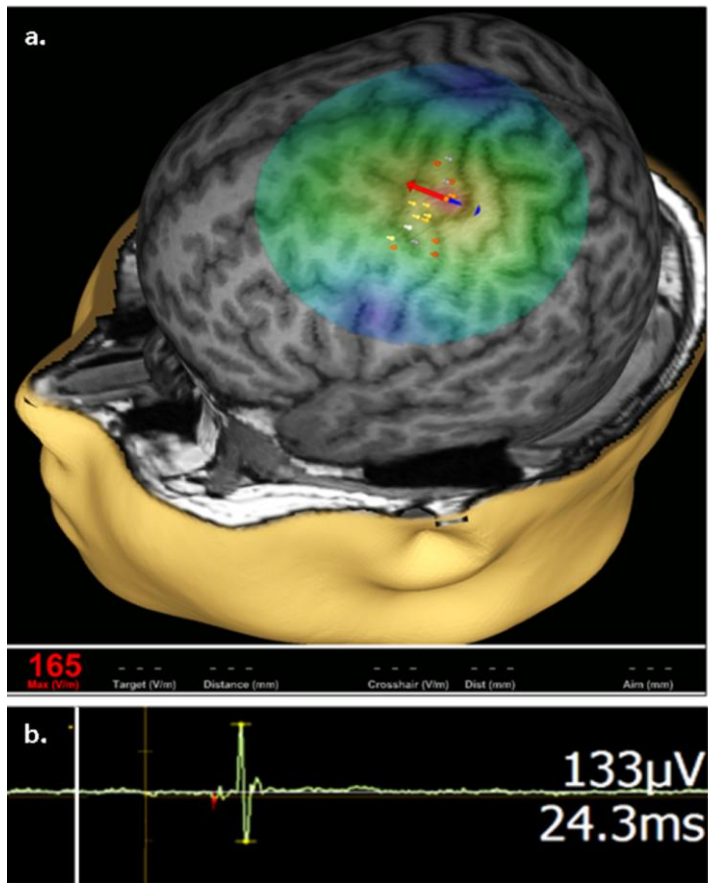
TMS is feasible across ages





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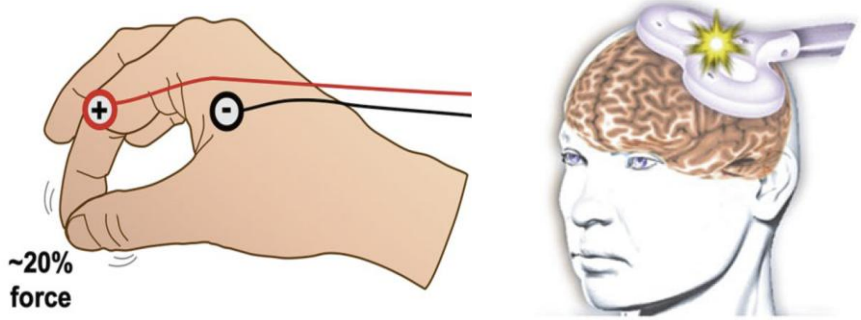
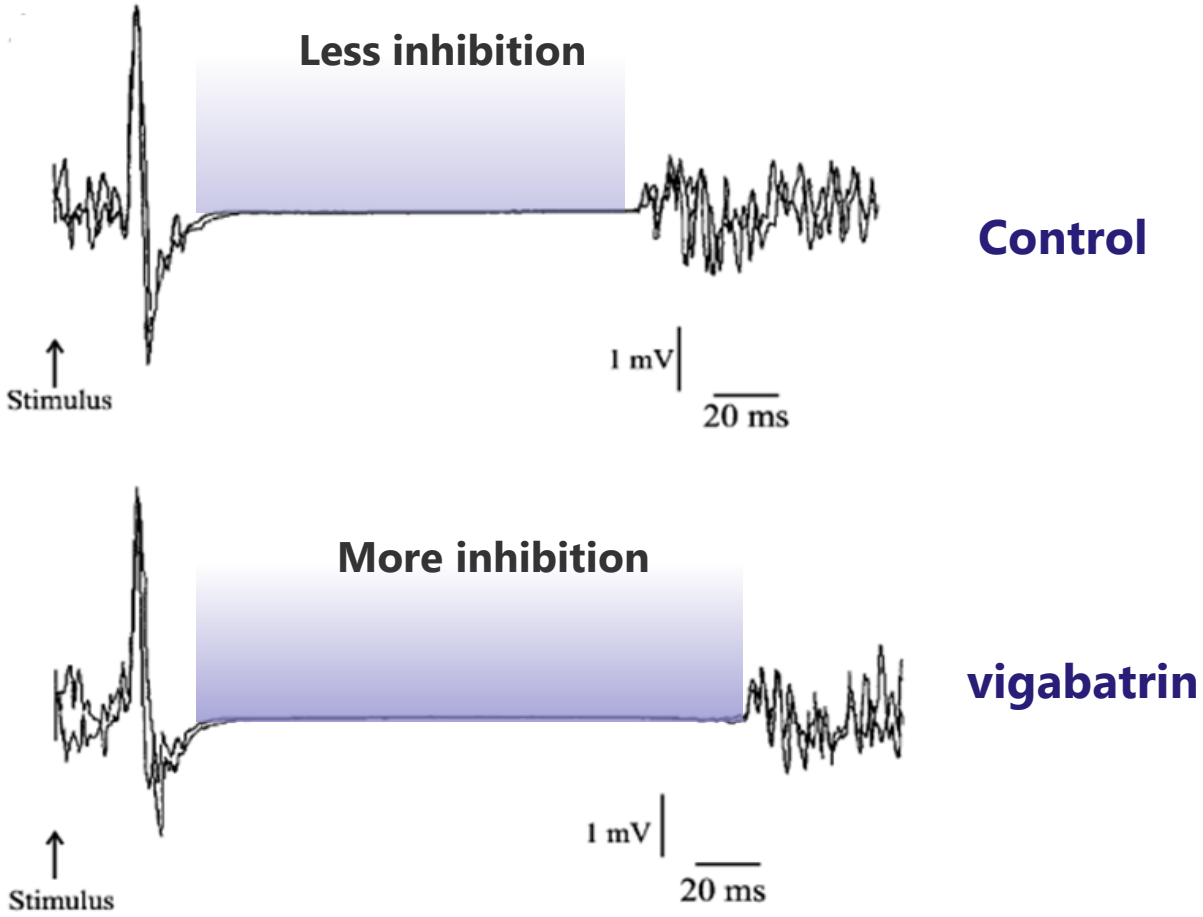
Why measure CSP? It increases with enhanced cortical inhibition





Edwards D, Davila Perez P, Horvath J, Rotenberg A, Pascual-Leone A. *A Practical Manual for Transcranial Magnetic Stimulation.* Springer; 2024. doi:10.1007/978-3-031-62304-2.
Pierantozzi et al. (2004), Brain Res; 1028(1):1–8.

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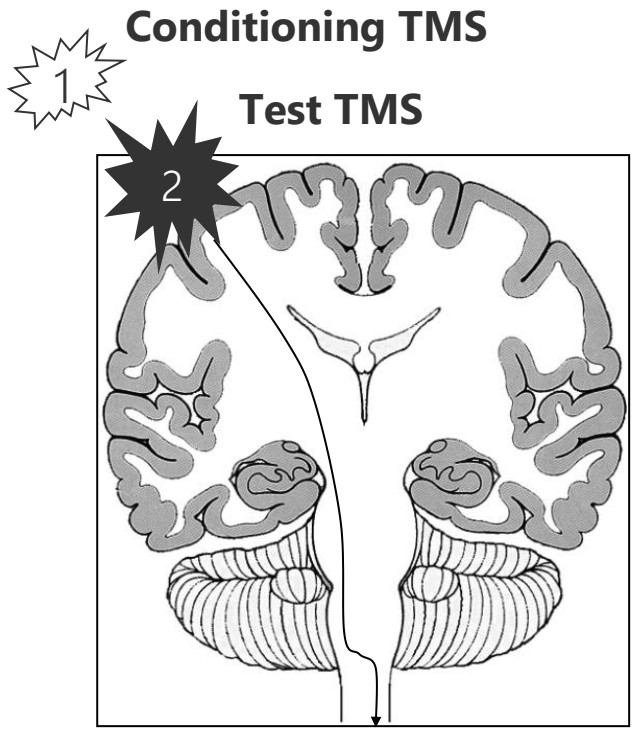
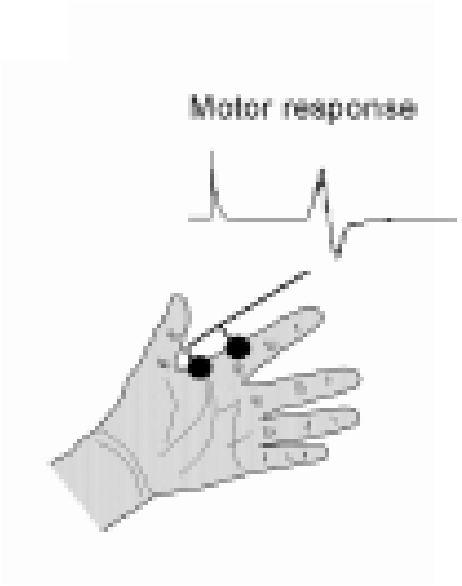
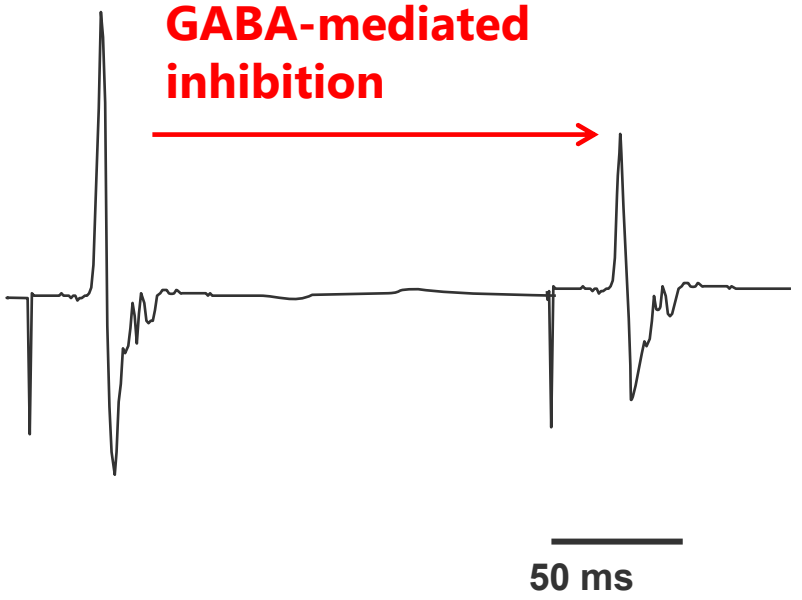
GABAergic cortical inhibition measures by paired-pulse TMS (ppTMS) LICI



Rotenberg and Pascual-Leone, 2010



Paired-pulse MEP inhibition



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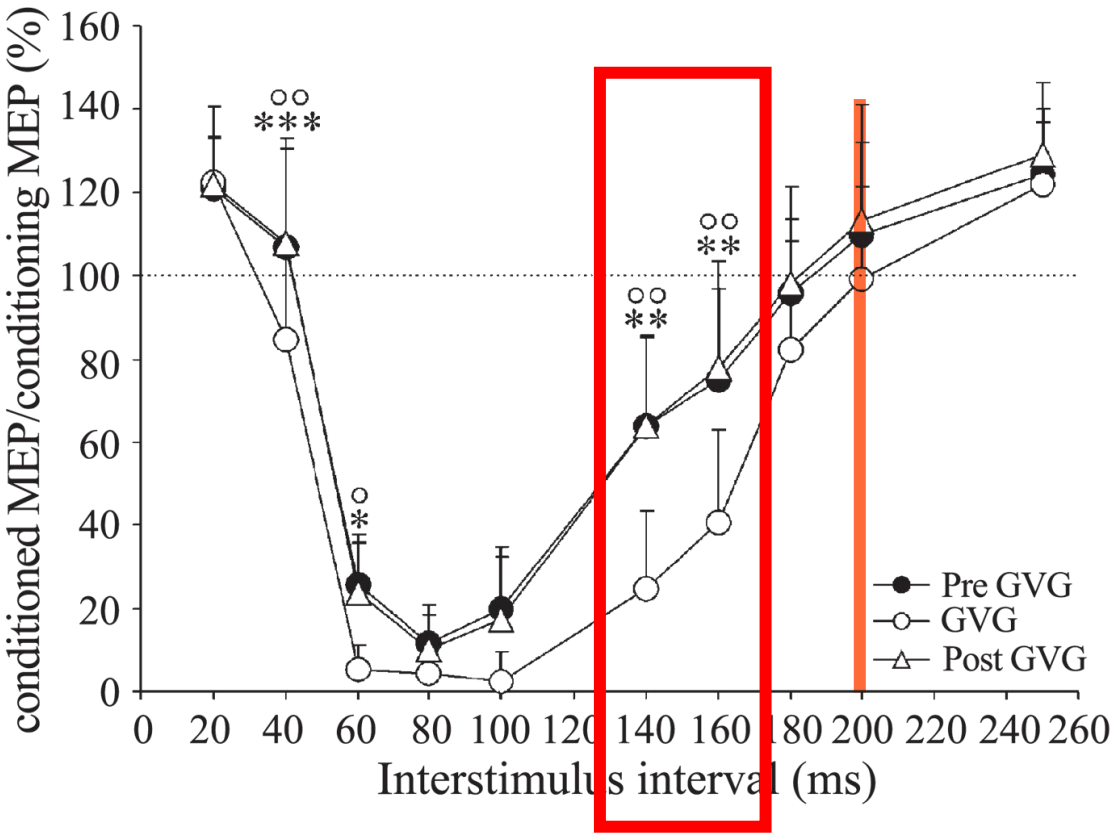
Why measure LICI? Inhibition increases with vigabatrin

VGB showed greatest impact & statistical significance on the LICI between 140 ms – 160 ms

More inhibition

Less inhibition



Pierantozzi M et al. Effect of Vigabatrin on motor responses to transcranial magnetic stimulation: an effective tool to investigate in vivo GABAergic cortical inhibition in humans. Brain Research, Nov. 26, 2004.

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Targeted directional change in TMS biomarkers

Metric	Published with therapeutic vigabatrin	OV329 anticipated change
Cortical silent period (CSP)	↑ Increased 19%	↑
Paired-pulse long-interval intracortical inhibition (LICI)	↑ Increased 35%	↑
Paired-pulse short-interval intracortical inhibition (SICI)	✕ No change	✕
Resting motor threshold (rMT)	✕ No change	✕
Intracortical facilitation (ICF)	✕ No change	✕

1.. In this study, vigabatrin was dosed at 50 mg/kg. in keeping with the recommended therapeutic dose of 2,500 – 3000 mg in patients daily.
2. Pierantozzi M et al. Effect of Vigabatrin on motor responses to transcranial magnetic stimulation: an effective tool to investigate in vivo GABAergic cortical inhibition in humans. Brain Research, Nov. 26, 2004.

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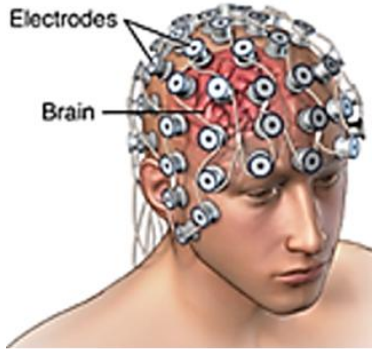
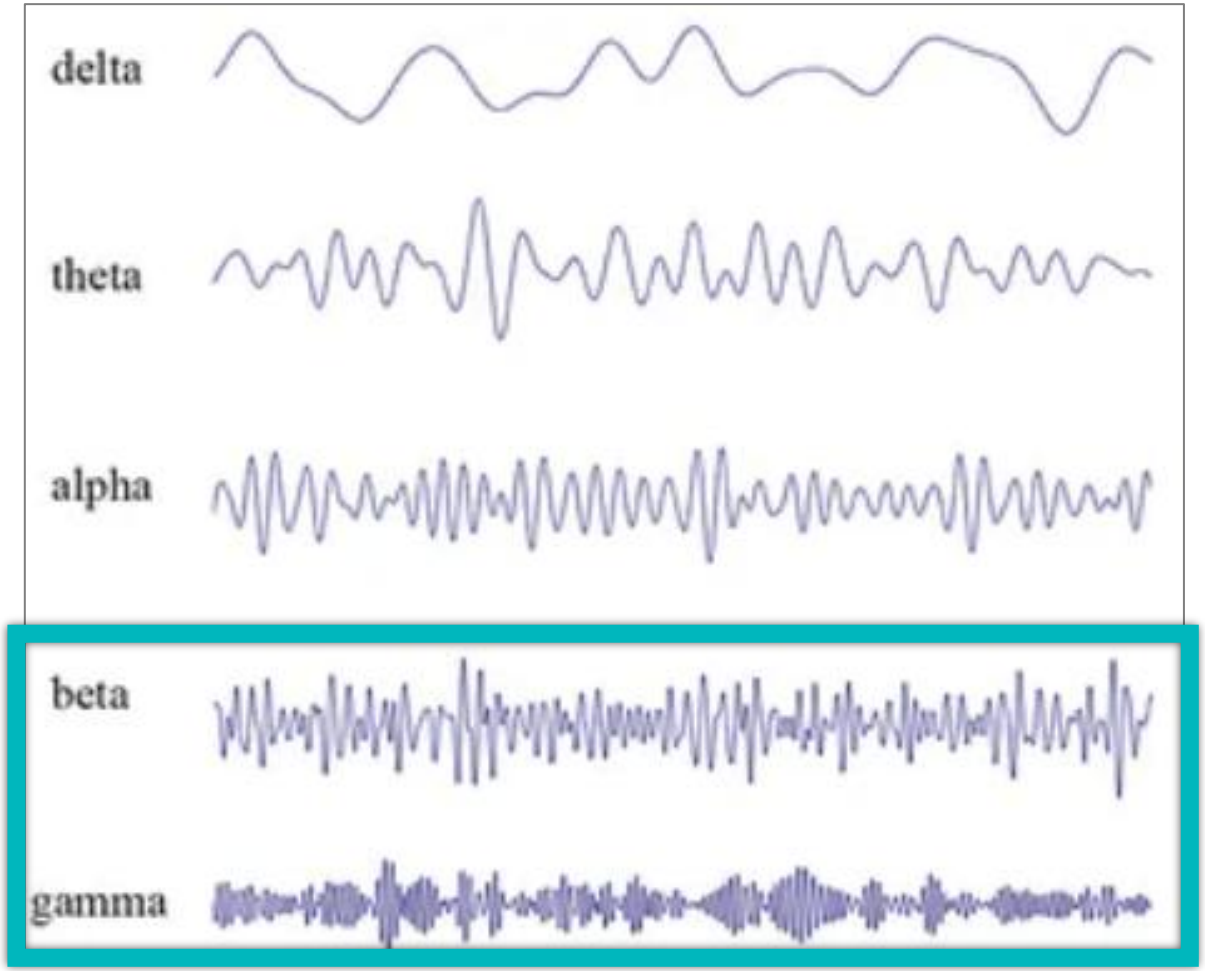
EEG may further demonstrate OV329's ability to modulate inhibition

- Noninvasive tool that uses sensors placed on the scalp to measure brain electrical activity
- Detects abnormal brain activity associated with seizures
- GABAergic drugs can increase faster frequencies
  - Beta and gamma power





Adapted from Sun et al. 2020 Front Med.

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Combination of biomarkers as powerful indicator of target engagement and biological effect

Increase in GABA by MRS + **Increase in EEG beta** + **Increase in key TMS measures (e.g., LICI 150 ms and CSP)**

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There is significant unmet need for a safe and well-tolerated GABA-AT inhibitor

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Clinical development

Dr. Amanda Banks

Chief Development Officer

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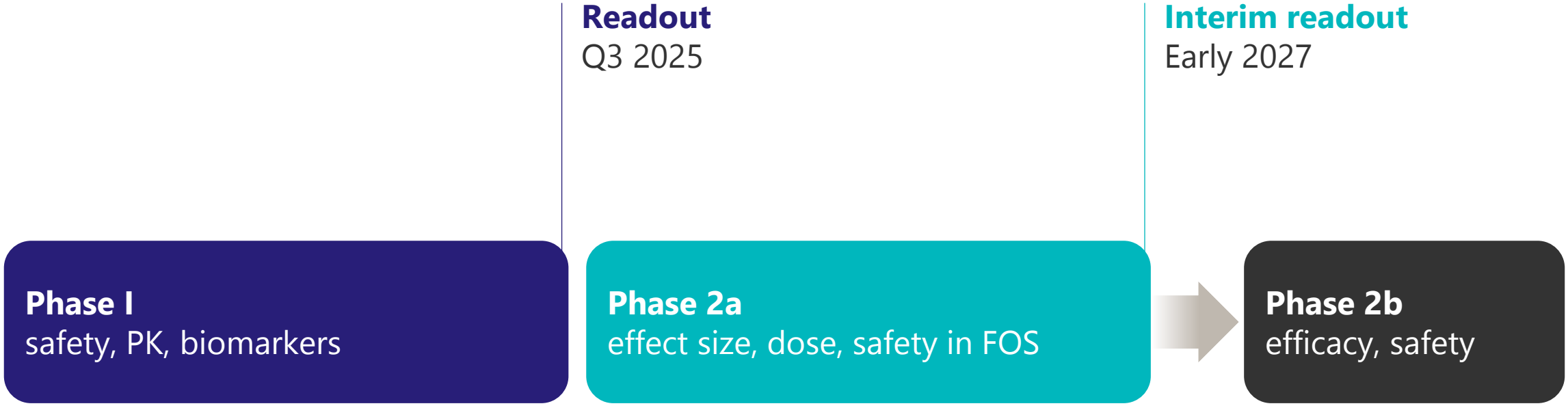
Status and key anticipated upcoming readouts for OV329 next 24 months



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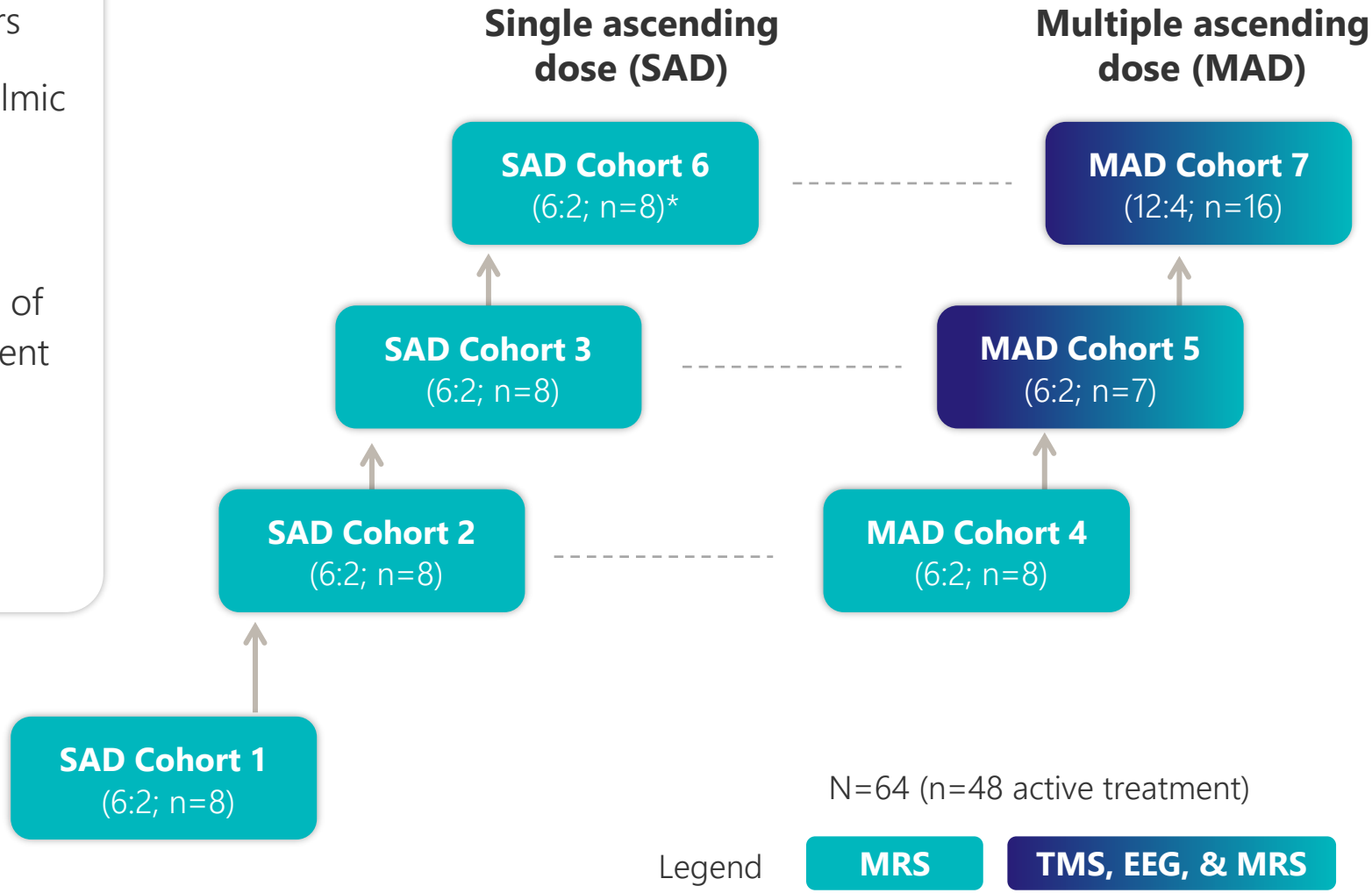
OV329 Phase 1 trial design

- Ph 1 SAD/MAD in healthy volunteers
- Safety/tolerability including ophthalmic safety & metrics
- Pharmacokinetics
- Exploratory biomarker assessments of biological effect & target engagement
  - MRS
  - TMS
  - EEG



*no imaging

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Targeted outcomes of biomarker metrics

Measurement/Endpoint	Precedent	What we expect	Why it matters
MRS GABA concentration	VGB showed increase	Increase	Direct measure of GABA increase validates target engagement
TMS Long-interval intracortical inhibition (LICI 150)	VGB showed 35% increase	Increase	Pharmacodynamic response consistent with increase in GABA
TMS CSP Duration	VGB 25 – 30 millisecond prolongation	Increase	Pharmacodynamic response consistent with increase in GABA
EEG Brain wave frequency	GABAergic ASMs increase beta & gamma power	Increase	Pharmacodynamic response consistent with increase in GABA

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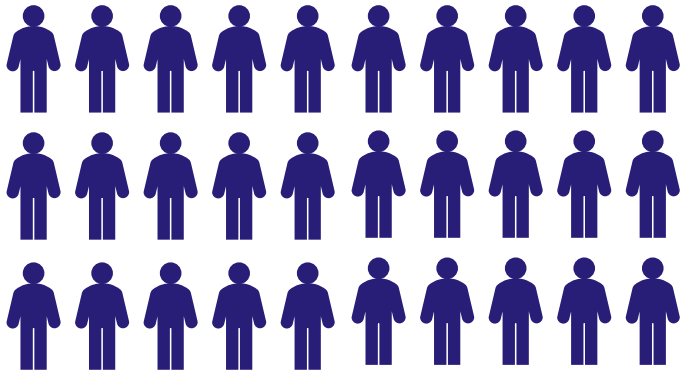
A differentiated safety profile



30 treated participants

No treatment-related AEs or SAEs

- Most common AE was headache

No vision or ocular findings associated with treatment

Comprehensive ocular safety metrics

- Best corrected visual acuity
- Indirect dilated ophthalmoscopy
- Automated threshold visual field perimetry
- Fundus photography
- Optical coherence tomography (OCT)

SOURCE: OVID data on file as of March 9, 2025

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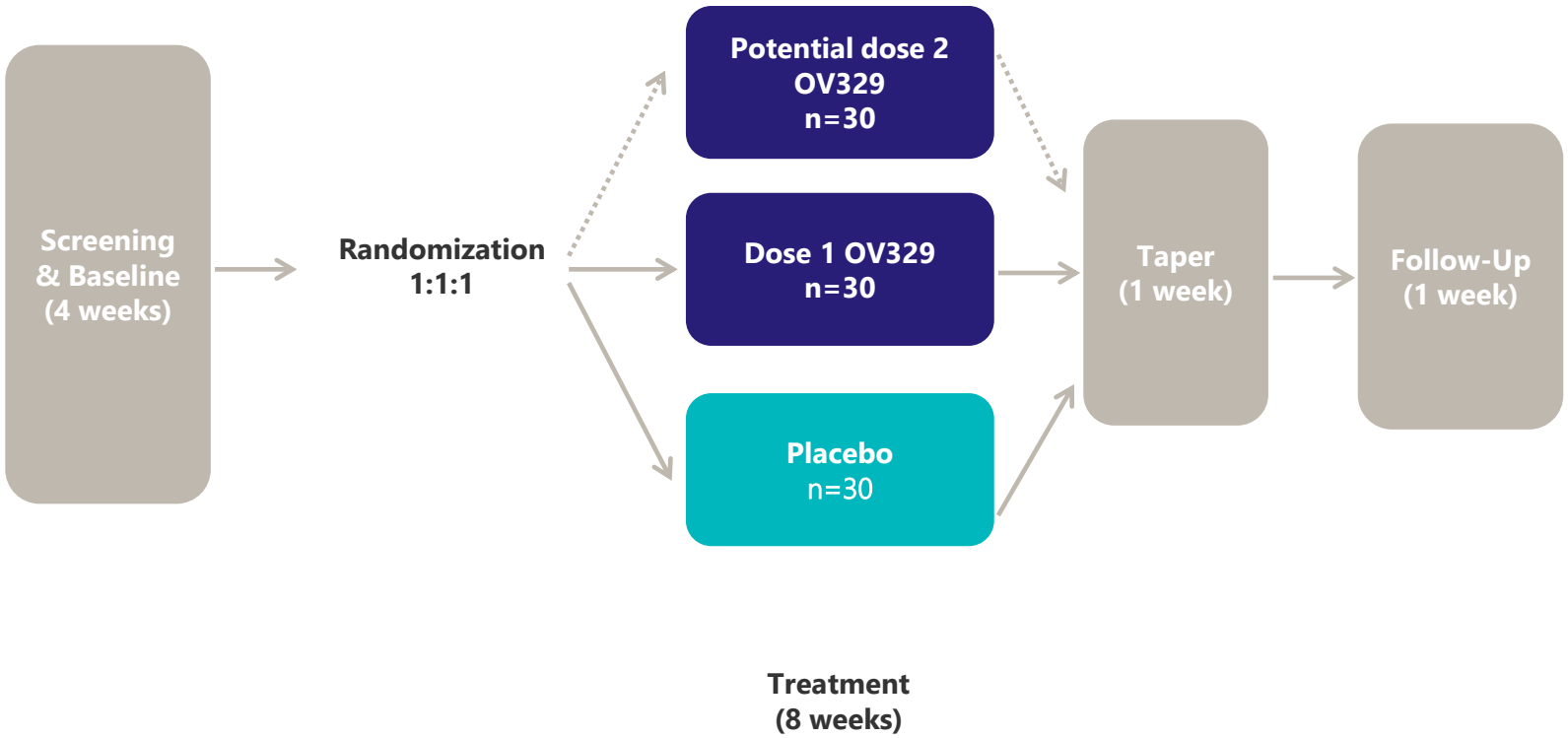
A fast path to patients: Phase 2a trial design in patients with focal-onset seizures

Evaluating the safety, tolerability, and antiseizure effect of OV329



- Seizure reduction effect size
- Building comprehensive safety package
- Phase 2b dose & design guidance
- Preliminary readout in early 2027

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IN MEMORIAM

Savannah Salazar

1993-2025

What comes next?

Topline OV329 readout expected Q3 2025. Designed to demonstrate potential:

- Proof of target engagement
- Delivering GABAergic (inhibitory) activity
- Comparable results relative to first-generation GABA-AT
- Good tolerability and safety

Results should deliver insights, further conviction and de-risk Phase 2

Patient trials in drug-resistant epilepsies (DRE) to begin in Q1 2026

On track to bring an effective differentiated mechanism of action with preferred safety and tolerability

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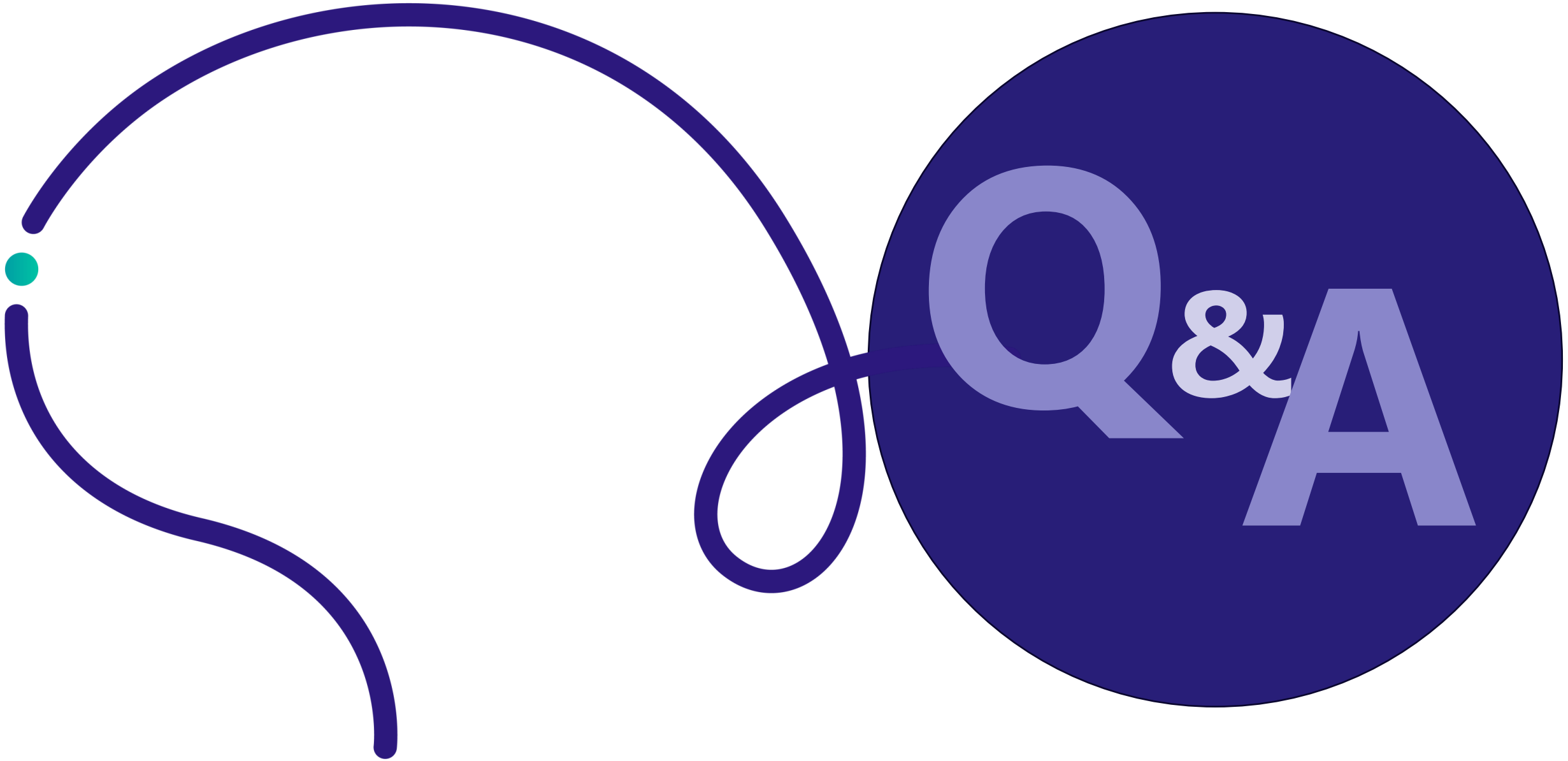

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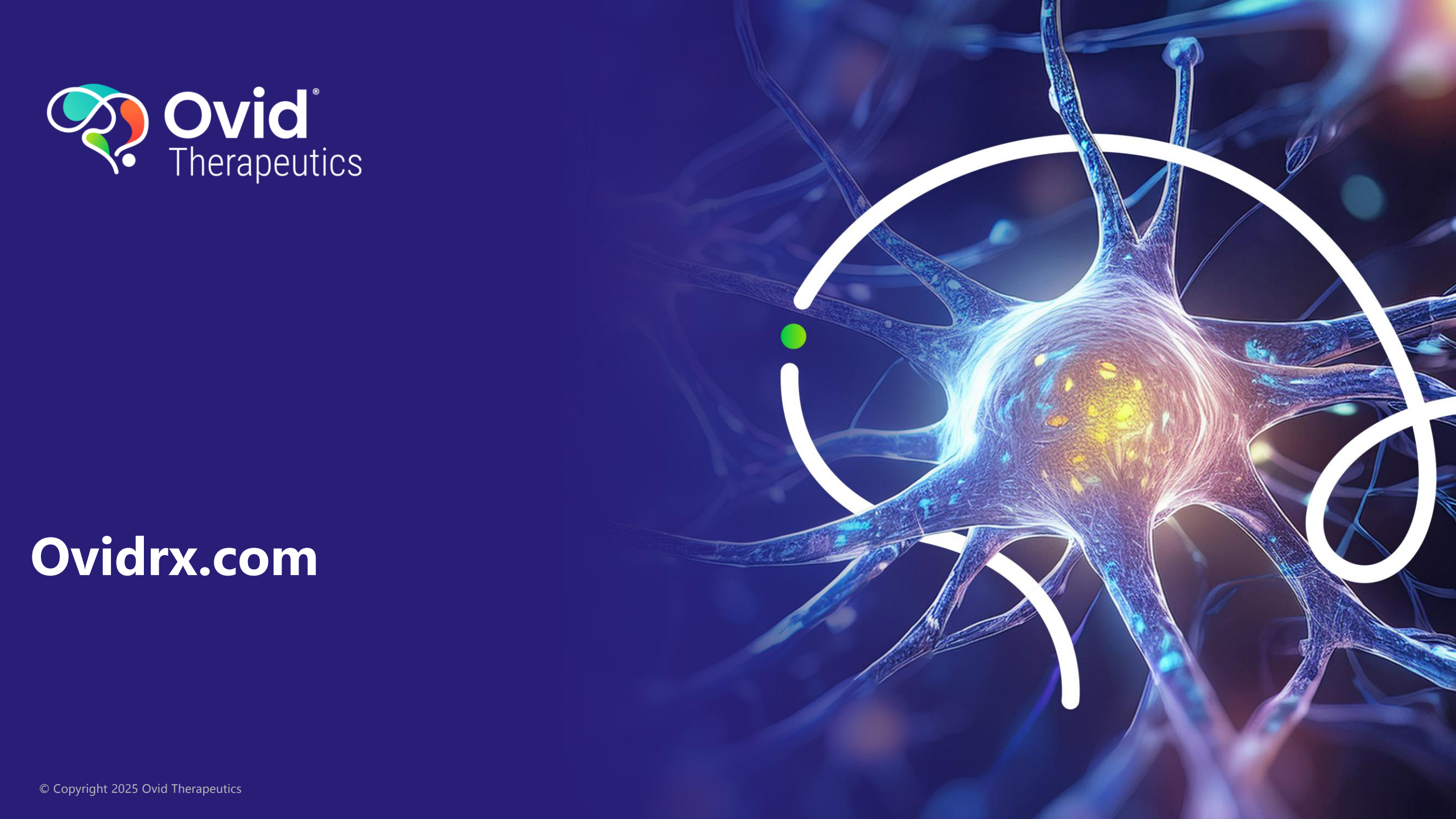

Ovidrx.com

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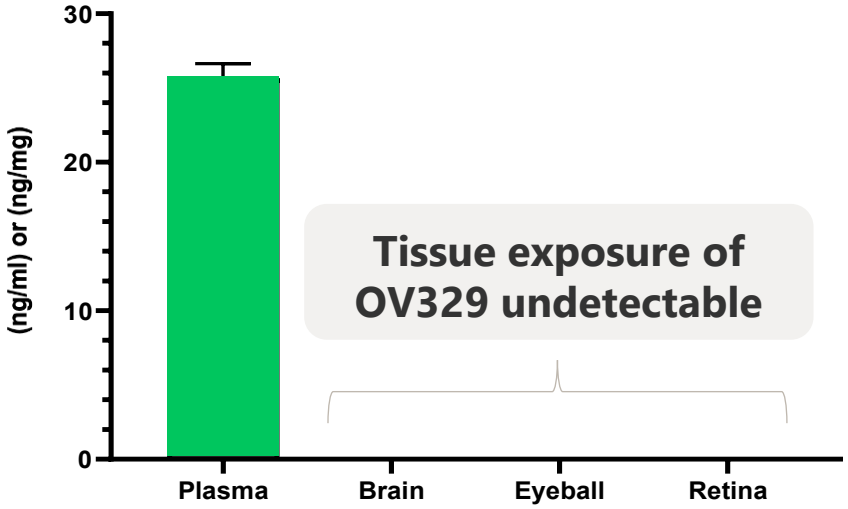
Head-to-head ocular accumulation study of OV329 versus vigabatrin

Lack of retinal accumulation of OV329 supports differentiated profile vs. vigabatrin[1]

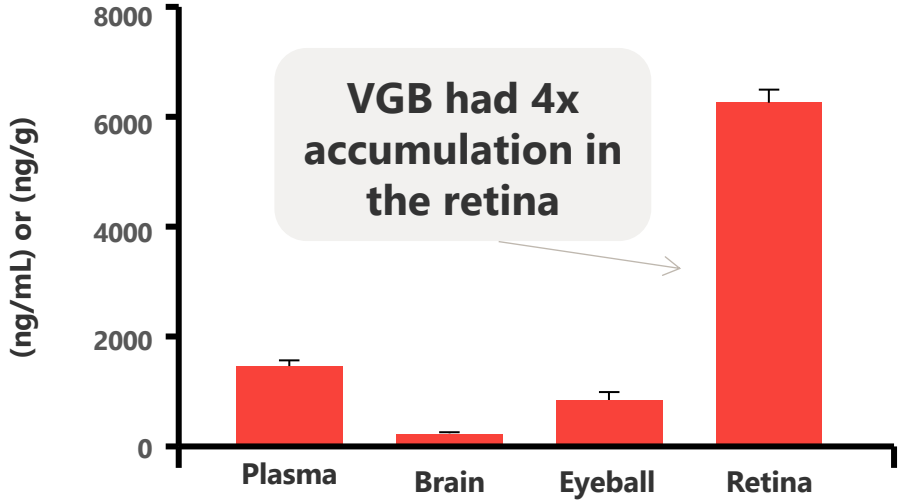
OV329

Mean Plasma and Tissue Concentration 5.0 mg/kg/day



VIGABATRIN

Mean Plasma and Tissue Concentration at 80.0 mg/kg/day



OV329 penetrated the brain, was present in the plasma and then cleared the tissue

- No accumulation detected of OV329 in the eye or retina
- 4-fold greater exposure of vigabatrin in retina as compared to plasma
- Suggests vigabatrin, but not OV329, preferentially partitions into the retina when plasma exposure is kept at a relatively constant level

1. Tsai, J., et al. (2024). *Evaluation of the Potential Accumulation of OV329 in the Brain, Retina, and Eye Following Continuous Infusion*. Poster presented at the 2024 Epilepsy Pipeline Conference.

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Differentiated safety in retinal model required by regulators

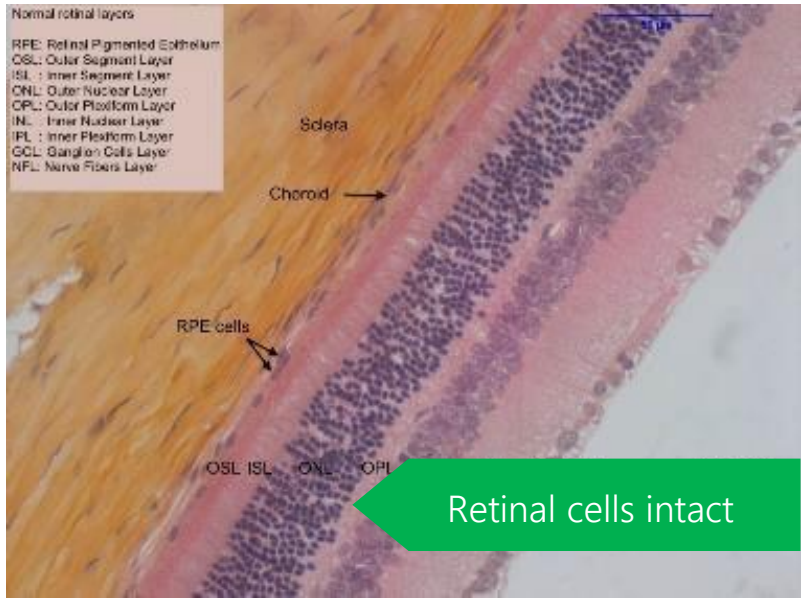
Anti-convulsant activity in 9 animal seizure models

- Represent a wide range of seizures
- Clinically active at low doses

Ocular safety profile differentiation

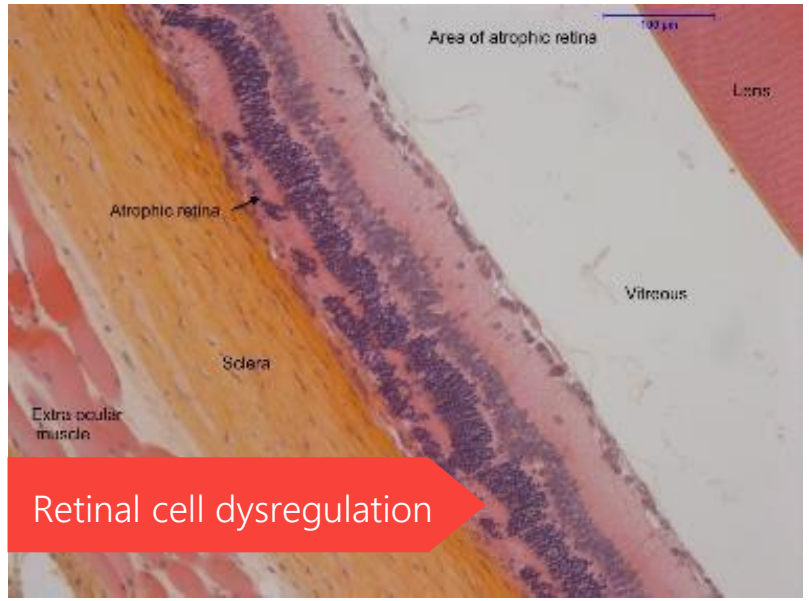
- Demonstrated in 2 models & toxicology
- Unique potency, binding & clearance profile likely related to lack of accumulation in eye

OV329 3.0 mg/kg
(Therapeutic dose)



No ocular effects seen in 3 mg/kg q.d. in rats

vigabatrin 300 mg/kg
(Therapeutic dose)



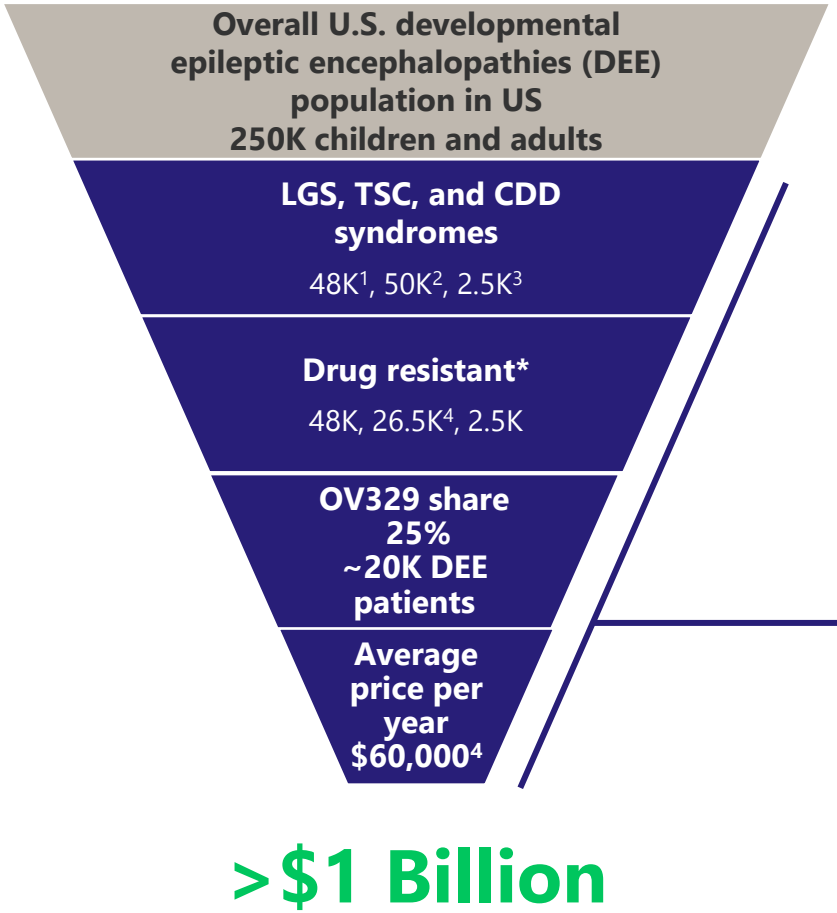
Ocular changes in more than half of rats treated (300 mg/kg)

45-day study

OVID, Data on file

Continued unmet need across a range of rare epilepsies; limited treatment options indicated for LGS, TSC, CDD with drug resistant seizures

Substantial opportunity within the DEE segment



>$1 Billion

	TSC	LGS	CDD
1L	Vigabatrin Valproate	Valproate Clobazam	Valproate Clobazam
2L	Clobazam Levetiracetam Lamotrigine Carbamazepine	Felbamate Lamotrigine Topiramate Rufinamide	Levetiracetam Topiramate Vigabatrin
3L (Failed 2 ASMs- prior authorization criteria)	Epidiolex® (cannabidiol)	Epidiolex® (cannabidiol) Fintepla® (fenfluramine)	Ztalmy® (ganaxolone) oral suspension 50 mg/mL Epidiolex® (cannabidiol)
DEE options in development	OV329 *In phase 1* Bexicaserin *Phase 2 completed*		
Non-pharm. Options	Surgical Resection Vagus Nerve Stimulation Ketogenic Diet		

Key: Voltage-gated Ion Channel Target; GABAergic; Synaptic Target; Other / Mixed / Unknown

1. https://www.tscalliance.org/understanding-tsc/what-is-tsc/
2. https://www.lgsfoundation.org/about-lgs-2/how-many-people-have-lgs/https://pmc.ncbi.nlm.nih.gov/articles/PMC3065368/
3. https://www.epilepsy.com/causes/genetic/cdkl5-disorder
4. Assuming weight based dosing 50% 25kg and 50% 55kg. Analgoue pricing Fintepla ranges from 60-130K and epidiolex 35k-70K

* assuming all patients will become resistant at some point during treatment; TSC 80% with seizure and 65% resistant

Effects of GABAergic drugs on GABA concentrations based on MRS studies

No.	Drugs	Dose (mg)	Study Population	Single voxel placement	Magnet strength (Tesla)	Magnitude of change	Year
1	Gabapentin	900	11/Healthy	Visual cortex	7	>50% compared to baseline	2012
		1200-3600 mg/day	14/Complex partial seizures	Occipital cortex	2.1	~28-50% increase treated vs. untreated	1996
2	Topiramate	100	15/Complex partial seizures	Occipital cortex	2.1	Increase 0.8 mM by 4h vs. baseline	2001
		2.8 mg/kg	17/Healthy	Occipital lobe	4.1	~70% increase over 3 hrs; stable at 6 hrs	2002
		75-500 mg/day	9/Healthy + 12/Complex partial	Occipital cortex	2.1	~80% compared to baseline	1999
		3 mg/kg	6/Healthy	Occipital lobe	4.1	72% over 3 hrs; 64% at 6 hrs	1998
3	Lamotrigine	3.5 mg/kg	6/Healthy	Occipital lobe	4.1	25% after 4 weeks	2002
4	Levetiracetam	1000-2000 (avg. 1322)	16/Focal epilepsy	Occipital lobe	3	~20%	2010
5	Valproate	1250-3000 mg/day	10/Healthy + 14 complex partial	Occipital cortex	2.1	No sig difference	1999
6	CPP-115	80	6/Healthy	Parietal-Occipital cortex + motor area	2.89	52-141%	2018
7	Vigabatrin	3000 mg	6/Partial seizures	Occipital cortex	2.1	Near 3-fold increase	1999
		1000-3000 mg/day	17/Partial complex	Occipital cortex	2.1	2 to 5-fold increase	2001

OV329 Phase 1 trial design

Establish safety & tolerability of GABA-AT inhibitor OV329

Exploratory biomarkers measuring biological effect and target engagement

- Magnetic resonance spectroscopy (MRS)
- Transcranial magnetic stimulation (TMS)
- Electroencephalography (EEG)

Endpoints

- Pharmacokinetics
- Safety and tolerability
- Ophthalmic safety metrics & monitoring
  - Best corrected visual acuity
  - Fundus photography
  - Indirect dilated ophthalmoscopy
  - Automated threshold visual field perimetry
  - Optical coherence tomography (OCT)

Excellent safety observed to date

- No serious adverse events
- Adverse events mild and transient (e.g., headache)

Current cohort

- Higher dose cohort added to optimize Phase 2 dosing opportunities
- Larger patient enrollment to support ability to show biomarker signal