Preclinical Data Supporting the Efficacy of OV329, A Next-Generation GABA Aminotransferase Inhibitor, Against Seizures

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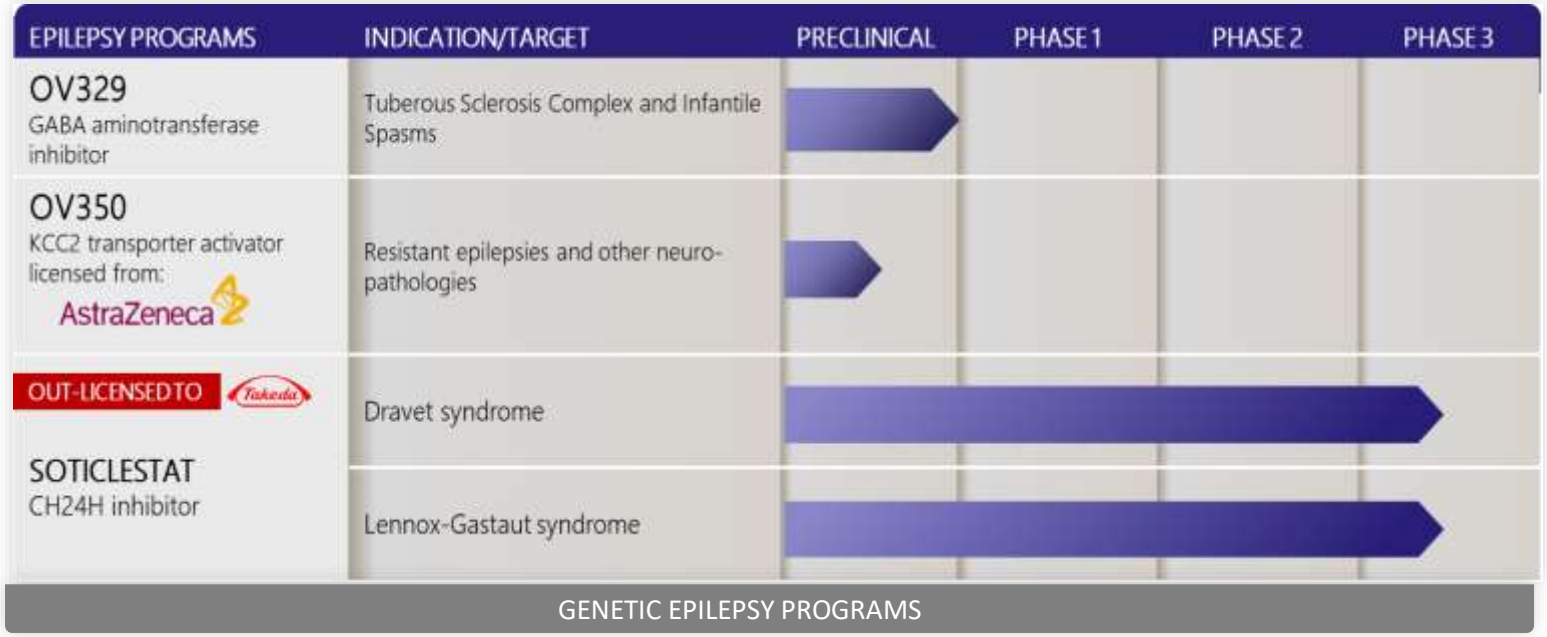
Ovid Therapeutics

Vision: Conquer epilepsies & brain disorders with courageous science

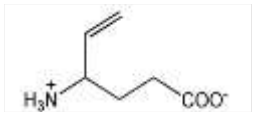
- 3 preclinical programs with potential 1st-in-class or best-in-class medicines
- Novel mechanisms of action for the potential treatment of epilepsy
- Out-licensed novel cholesterol 24-hydroxylase inhibitor to Takeda
- Preclinical pipeline targeting genetic epilepsies and seizures



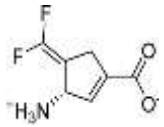
OV329 is a potent, next-generation GABA-AT inhibitor

- Potential candidate for treatment of drug-resistant epilepsy
- Well-characterized target
- Similar mechanism of action to vigabatrin
- More potent than vigabatrin
- Potentially improved safety profile

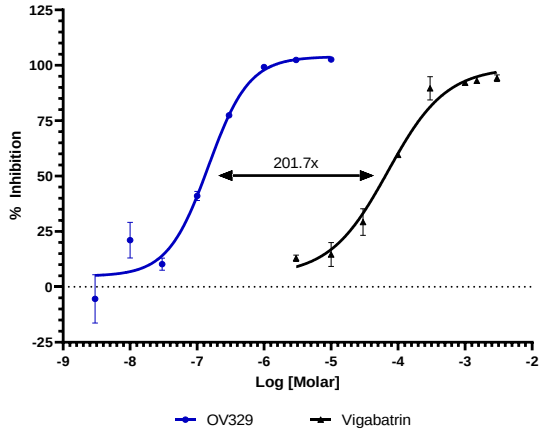
Vigabatrin



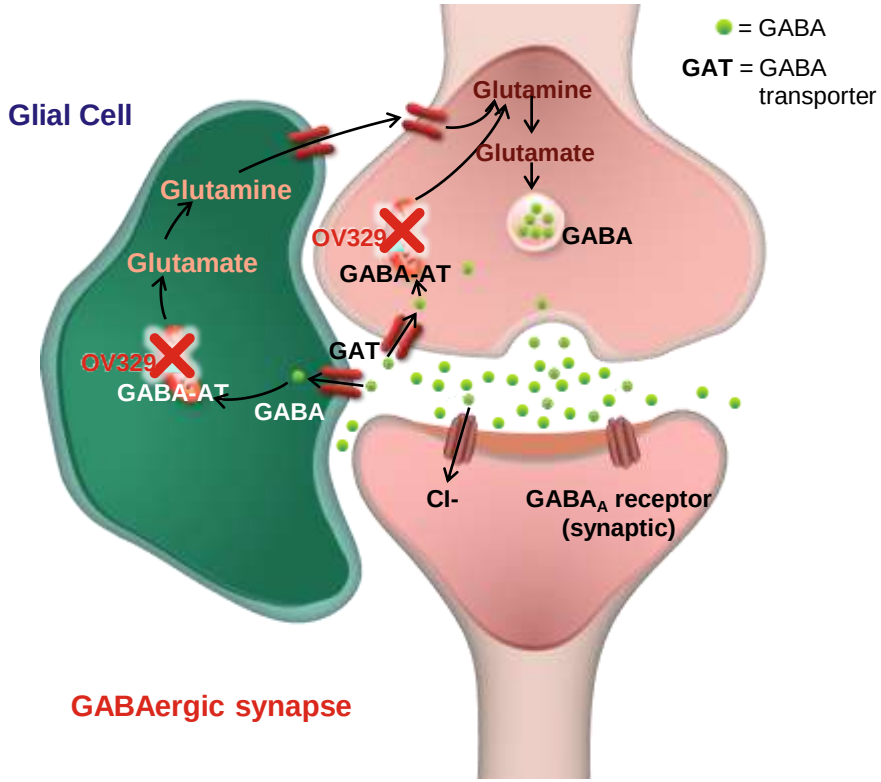
OV329



GABA Amino Transferase Assay (Rat Brain)



OV329 facilitates GABA transmission



OV329 is active in suppressing seizures in multiple animal models, including drug-resistant models

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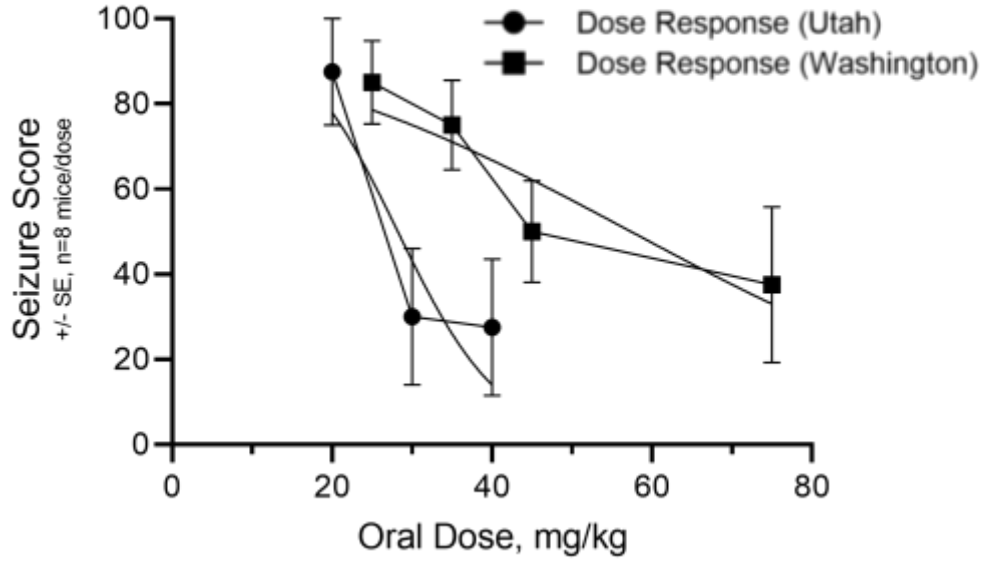
	6 Hz Electrical Stimulation	Maximal Electroshock (MES)	i.v. Pentylenetetrazol (ivPTZ)	NMDA-Induced Infantile Spasm model	Audiogenic Seizure	Amygdala Kindled	Corneal Kindled	Intrahippocampal Kainate Model of Mesial-Temporal Lobe Epilepsy (MTLE)
Injury Model	Acute/seizure	Acute/seizure	Acute/seizure	Acute/seizure	Acute	Chronic/epilepsy	**Chronic/epilepsy**	**Chronic/epilepsy**
Clinical Correlate	Acute focal to bilateral tonic-clonic seizure	Generalized tonic-clonic seizure	Nonconvulsive seizures (eg absence, myoclonic)	Infantile spasms	Generalized seizures	Chronic focal to bilateral tonic-clonic seizure/ Pharmacoresistant seizures	**Chronic focal to bilateral tonic-clonic seizure**	**Mesial temporal lobe epilepsy/ Pharmacoresistant seizures**
Species	Mouse	Mouse	Rat	Mouse	Mouse	Rat	**Mouse**	**Mouse**
Dosing	Acute (0.01, 0.1, 0.3, 1 mg/kg/day, p.o.)	Acute (1, 3, 10, 30 mg/kg, p.o.)	Acute (5, 20, 40 mg/kg i.p.)	Acute (0.0025, 0.01, 0.1, 1 mg/kg, p.o.)	Acute (0.01, 0.05, 0.1 mg/kg, p.o.)	Acute (30, 40 mg/kg, i.p.)	**Acute (1, 3, 10, 20, 30, 40, 60 mg/kg, p.o.)**	**Acute, single dose (0.01, 0.1, 1, 10 mg/kg, p.o.; 10 mg/kg, i.p.)** **Subacute (8 days q.d.) 0.3, 1.0 and 3.0 mg/kg/day (p.o.)**
Activity	—	—	+	+	+	+	+	+

OV329 significantly reduces seizures in the Corneal Kindled mouse

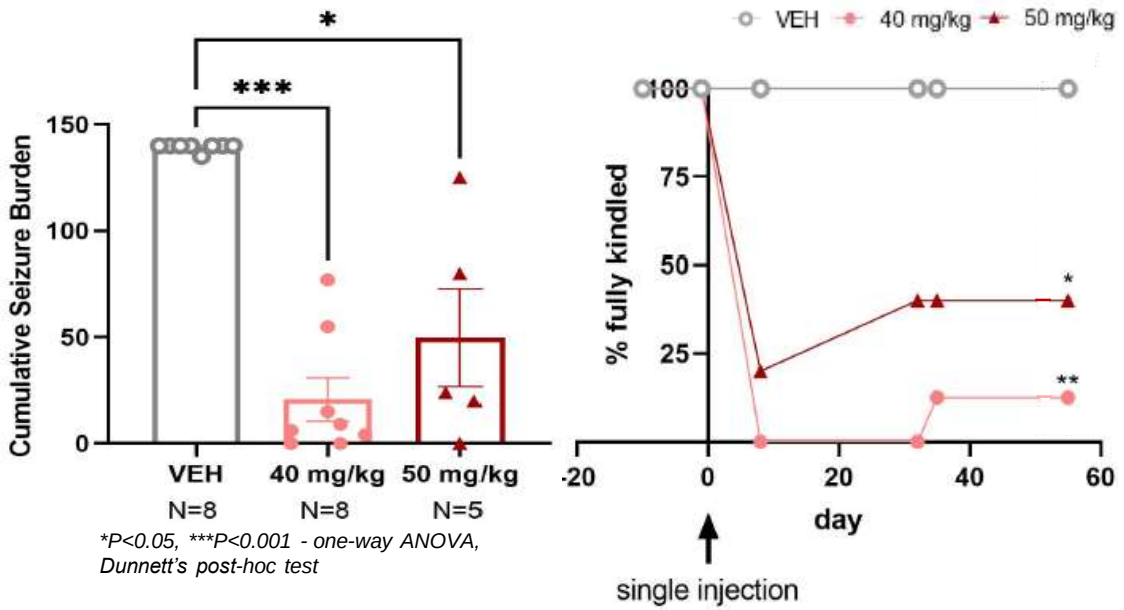
Dose response at 8 hours



		ED_{50}[a]	95% Confidence Interval	p[b]	z[c]
Corneal Kindling	UU	27.92	(19 – 36.7)	0.234	2.12
	UW	46.70*	(25 – 75)		

a median effective dose (ED_{50})
b proportion of the overlap
c test statistic z, reject the null hypothesis of the equality of the two means when z text is larger than 1.96 as long as p is less than 0.29

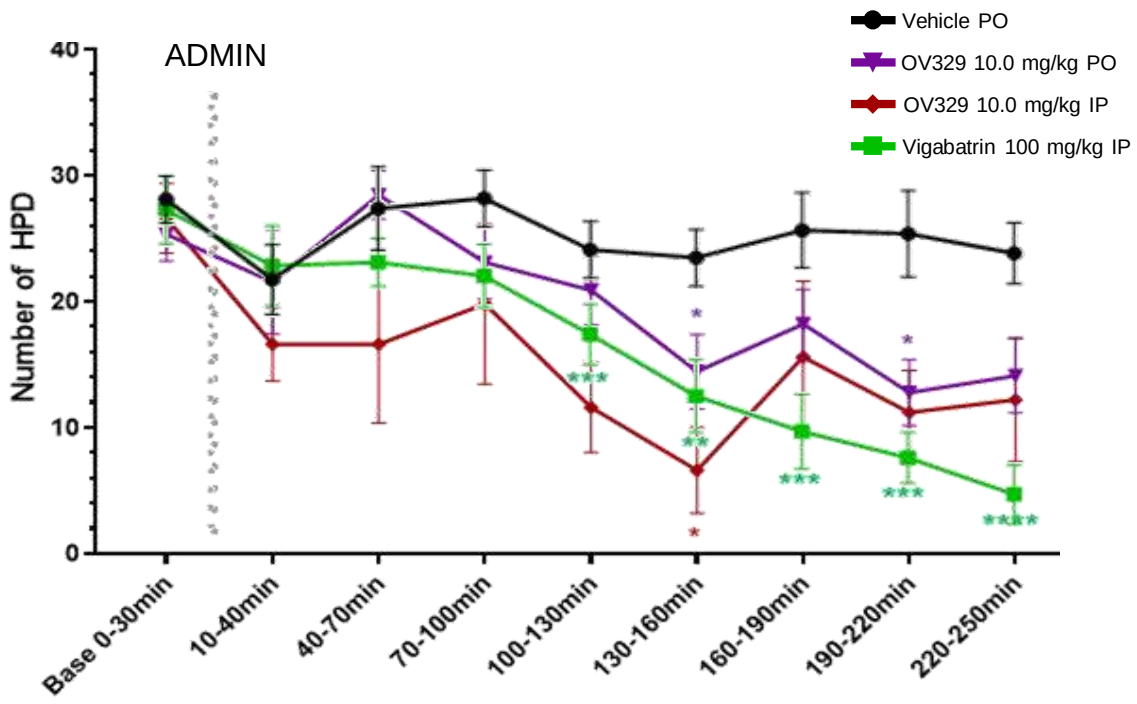
Seizure protection in fully kindled mice



- A single dose of 40 mg/kg OV329 prevented reestablishment of the kindled state for up to 55 days in 6/8 animals

OV329 significantly reduces seizures in the Mesial-Temporal Lobe Epilepsy (MTLE) mouse model

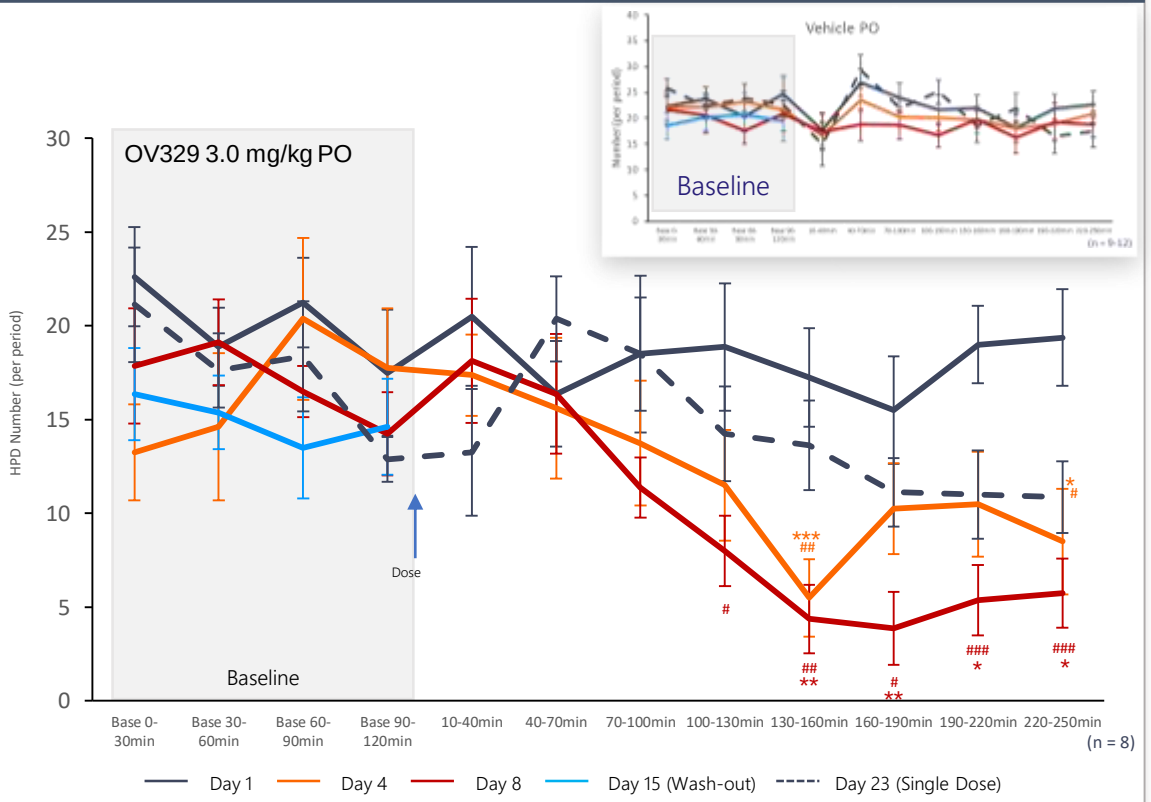
Single administration of OV329 reduced the number of hippocampal paroxysmal discharges (HPDs)[1]



- OV329 achieved a 55% reduction in seizure activity after IP administration
- OV329 achieved a 46% reduction after oral administration

Data are expressed as mean ± SEM. *,**, ***, ****: p < 0.05, 0.01, 0.001 or 0.0001, respectively

Repeat dosing of OV329 demonstrates activity in the MTLE mouse model of drug-resistant epilepsy at low doses



- 3.0 mg/kg in mice reduced seizures (HPD) by ~70% compared to baseline levels at Day 8

Data are expressed as mean ± SEM. *,**: p < 0.05, 0.01 vs Baseline; #, ##:p < 0.05, 0.01 vs Day 1

[1]Duveau, et al. *CNS Neurosci Ther.* 2016;22(6):497-506; [2]Sarmiere, PD et al. *American Epilepsy Society Meeting*, 2021.

OV329 preclinical efficacy & safety data support moving toward IND

OV329, a next-generation GABA-AT inhibitor, is in development as an anti-seizure medication for rare adult and pediatric epilepsy disorders

Non-clinical studies have demonstrated anti-seizure activity of OV329 in multiple seizure models, including drug-resistant animal models

Safety profiles established in mice, rat and canine models:

- At predicted therapeutic levels, no reported genotoxicity, no reported CV effect, no significant adverse CNS effect
- Efficacy seen with repeat administration at lower doses in animal models suggests potential for improved safety margin versus vigabatrin with respect to ocular toxicity.

Planning IND submission and Phase 1 initiation in 2H, 2022

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Thank you to the families who help make this work possible.