

Ovid® Therapeutics

Conquering seizures & rare brain disorders with courageous science

Corporate Presentation

August 2024

Forward looking statement

This presentation contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 including, without limitation, Ovid's expectations regarding the duration its cash runway, and the expectation that it will support the advancement of Ovid's pipeline and Ovid's potential future business development opportunities; the timing and development of Ovid's product candidate pipeline and achievement of expected near- and long-term milestones; the potential therapeutic benefits of Ovid's current or future product candidates and pipeline programs; the potential development and therapeutic opportunity of OV888/GV101; and the potential safety, selectivity and potency of OV888/GV101 and other ROCK2 inhibitors; the potential use of OV888/GV101 and other ROCK2 inhibitors to treat cavernous cerebral malformations and other rare central nervous system disorders; the potential timing of the pivotal formulation for OV888/GV101; the potential timing of clinical studies for OV888/GV101 and the resulting data; the reporting of data for the potential Phase 1 study in healthy volunteers for OV329; the potential use of OV329 to treat rare and treatment-resistant forms of epilepsy and seizures; the clinical and regulatory development of OV329, including the anticipated timing of clinical trials of OV329; the likelihood that data for OV329 will support future development and therapeutic potential; the potential development of OV350 and other KCC2 compounds in the Company's library; the potential timing of a potential IND filings OV350; the suitability of the Company's library of novel, direct KCC2 transporter activators for a range of formulations and administrations that would make it possible to pursue both chronic and acute epilepsies; statements regarding timing for the potential opportunity for soticlestat; the timing of potential regulatory filings and or regulatory decisions for soticlestat, and the potential for milestone and royalty payments from Takeda for soticlestat; discussions between Takeda and regulators related to the approval of soticlestat; the clinical and regulatory development and potential commercialization of OV888/GV101, OV329, OV350, or any of Ovid's other current or future product candidates and pipeline programs and market opportunities. You can identify forward-looking statements because they contain words such as "will," "may," "believes," "intends," "anticipates," "target," "expects," "demonstrates," and "potential," and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances).

Forward-looking statements are based on Ovid's current expectations and assumptions. Because forward-looking statements relate to the future, they are subject to inherent uncertainties, risks and changes in circumstances that may differ materially from those contemplated by the forward-looking statements, which are neither statements of historical factor guarantees or assurances of future performance. Important factors that could cause actual results to differ materially from those in the forward-looking statements include, without limitation, uncertainties inherent in the preclinical and clinical development and regulatory approval processes, risks related to Ovid's ability to achieve its financial objectives, the risk that Ovid may not be able to realize the intended benefits of its technology or its business strategy, risks related to Ovid's ability to identify business development targets or strategic partners, to enter into strategic transactions on favorable terms, or to consummate and realize the benefits of any business development transactions and risks to Ovid's or any of its partners' abilities to meet anticipated deadlines and milestones. Additional risks that could cause actual results to differ materially from those in the forward-looking statements are set forth under the caption "Risk Factors" in Ovid's Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on August 13, 2024, and in future filings Ovid makes with the SEC. Any forward-looking statements contained in this press release speak only as of the date hereof, and Ovid assumes no obligation to update any forward-looking statements contained herein, whether because of any new information, future events, changed circumstances or otherwise, except as otherwise required by law.

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EXCITING BIOLOGICAL TARGETS

Modulated by potential first-in-class or best-in-class mechanisms of action

SPECIFIC SMALL MOLECULES

Harnessing a scientific revolution in highly specific small molecules for the central nervous system



DIFFERENTIATED PIPELINE

Intended to treat rare epilepsies & brain conditions with few, or no treatment options

4 in 2024 CLINICAL & REGULATORY MILESTONES

Expected from Ovid's pipeline by the end of 2024

CASH BALANCE OF $77 MILLION EXPECTED TO SUPPORT PIPELINE TO LATE H1 2026[1]

[1] As of June 30, 2024

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Differentiated pipeline with cadence of value-driving events

Programs	Indication	Preclinic	Phase 1	Phase 2	Phase 3	Anticipated Milestones
OV888/GV101[1] Selective ROCK2 inhibitor Collaboration with: GRAVITON BIOSCIENCE CORPORATION	Cerebral cavernous malformations (CCM) and undisclosed neurovascular indications					Phase 2 in CCM initiating in H2 2024
OV329 (ORAL) GABA-aminotransferase inhibitor	Conditions with resistant seizures					Phase 1 readout in H2 2024 with biomarkers for target engagement and efficacy
KCC2 PLATFORM & OV350 KCC2 transporter activator	Psychoses Acute resistant epilepsies					Regulatory submission for OV350 human studies in H2 2024

Ovid maintains a financial interest in soticlestat. While soticlestat failed to meet its primary endpoint in a Phase 3 trial in Dravet syndrome (DS), Takeda Pharmaceuticals is exploring a potential path to marketing authorization in DS with the U.S. Food and Drug Administion (FDA). Takeda retains guidance that it may file soticlestat for approval in Dravet in its FY 2024 (i.e., by or before March 31, 2025). If soticlestat is approved and commercialized Ovid is eligible to receive milestones and royalty payments from Takeda.

1. Graviton is conducting development of OV888/GV101 through Phase 2, which will be directed by a Joint Development Committee that includes members from both Graviton and Ovid.

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Corporate updates & anticipated upcoming milestones

Corporate Updates

- ✓ **OV888/ GV101 – Phase 1 topline results demonstrated safety & target engagement**
- ✓ **Strengthened leadership team**
  - Dr. Amanda Banks appointed Chief Development Officer
- ✓ **Pipeline optimization (ongoing)**
  - Paused development of OV329 IV in status epilepticus and other undisclosed preclinical programs

Anticipated 2H 2024 Milestones

- **OV888 Phase 2 trial initiation in CCM**
- **OV329 Phase 1 SAD/ MAD trial results**
  - Inclusive of biomarker findings that are potential measures of target engagement and clinical effect
- **OV329 ocular accumulation rodent study**
  - Results may inform how OV329 differentiates from vigabatrin relative to ocular safety
- **OV350 submission for 1st-in-human studies**

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OV888 (GV101)

A highly selective ROCK2 inhibitor for potential treatment of cerebral cavernous malformations & other CNS disorders

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OVERVIEW OV888 (GV101)
A highly selective ROCK2 inhibitor for CCM

Potential Opportunity[1]

SYMPTOMATIC PATIENTS

7 major markets

~400K

CCM patients[2]

United States

~150-175K

CCM patients[2]

No approved pharmacologic treatments

Disease modifying therapies needed

Status

✓ **Completed Phase 1 safety study**

- Pivotal gel capsule formulation
- Healthy volunteer study
- No serious adverse events (SAEs) observed

✓ **Target engagement demonstrated in humans**

✓ **Moving into Phase 2**

- Intend to initiate patient signal finding trial in H2 2024

1. Addressable population is defined as symptomatic patients and patients with an incidental finding
2. Ovid 2022 global market research

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Indication overview: Cerebral cavernous malformations

Presentation

- Mulberry-shaped abnormal blood vessels in the brain and or spinal cord with thin, irregularly formed walls that can leak blood
- 1 in 500 people in the U.S. have at least one cavernous malformation in their brain[1,2]
- Symptoms include: seizures, headaches, hemorrhage, and functional neurological deficits[2]
- Diagnosis is typically classified as either sporadic or familial

Morbidity & mortality

- ~30% of patients who have a hemorrhage will suffer moderate to severe disability[3]
- One hemorrhage is a significant risk factor for future bleeds[4]
- Overall morbidity was 26% after a mean follow up of 1.9 years since the first hemorrhage[5]

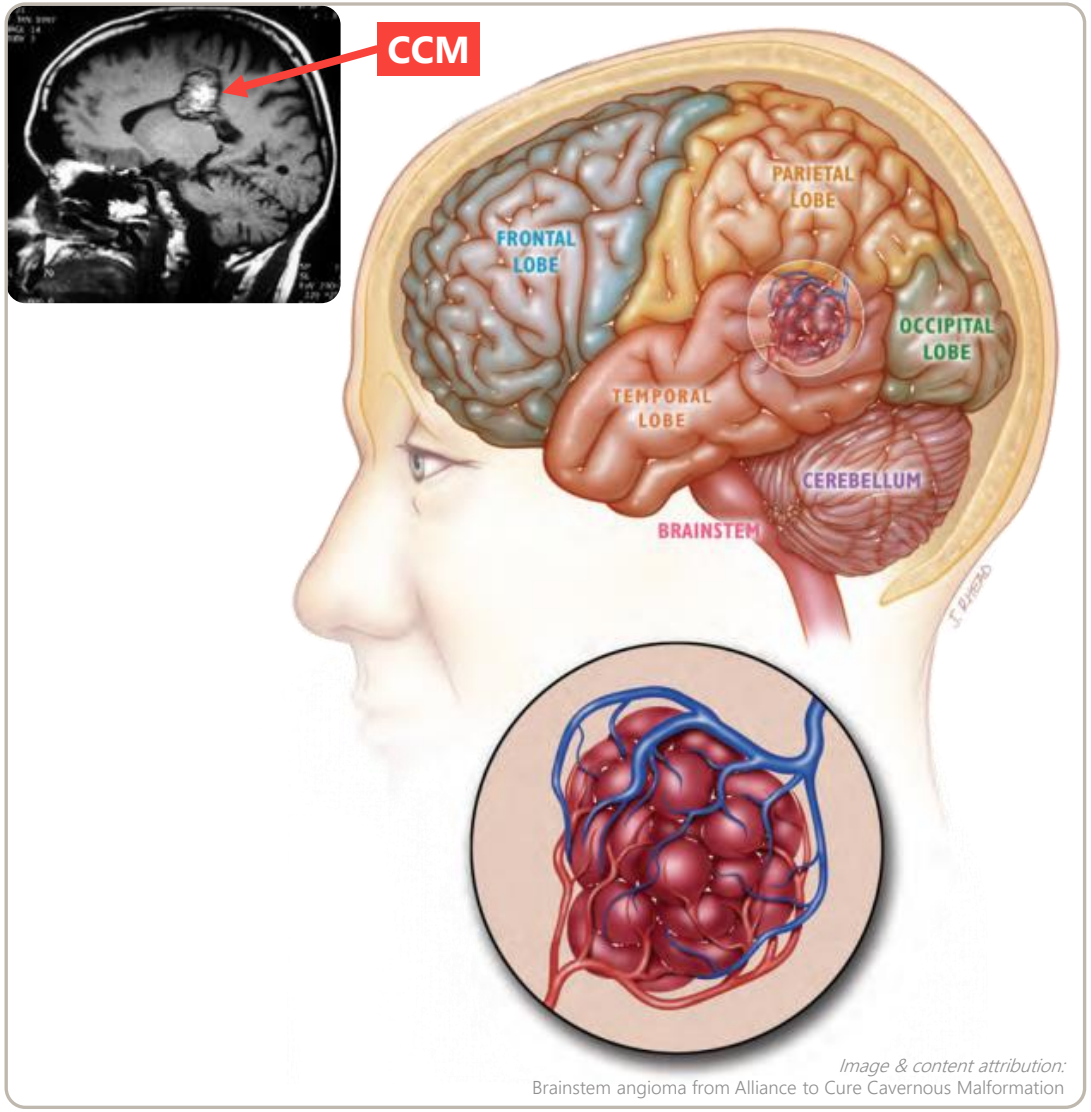


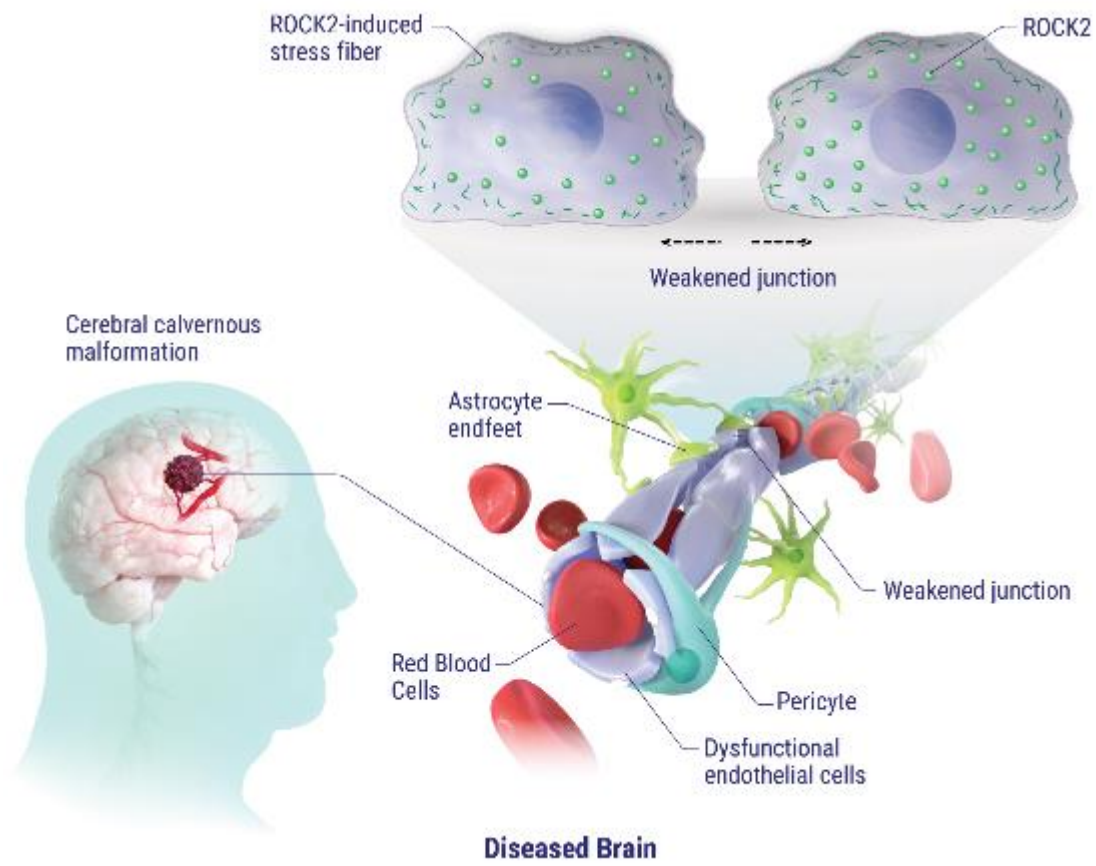
Image & content attribution:
Brainstem angioma from Alliance to Cure Cavernous Malformation

1. Zafar A, et al Stroke. 2019 May;50(5):1294-1301. doi: 10.1161/STROKEAHA.118.022314. PMID: 30909834; PMCID: PMC6924279
2. Caton MT, Stat Pearls Publishing; https://www.ncbi.nlm.nih.gov/books/NBK538144/.
3. Santos, A.N., et al. Sci Rep 13, 15490 (2023). https://doi.org/10.1038/s41598-023-42594-0
4. Dammann P, et al. World Neurosurg. 2016;91:73–80. doi: 10.1016/j.wneu.2016.03.080
5. Ma, Li Et al. Stroke, 2020 https://doi.org/10.1161/STROKEAHA.120.029942

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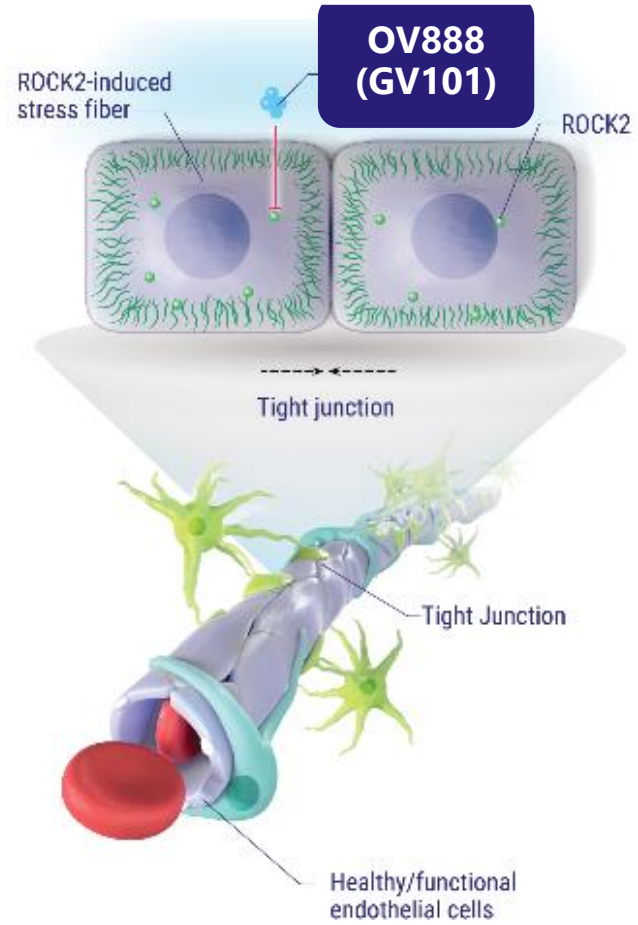
Proposed mechanism of action of OV888 (GV101)

Pathological State



Endothelial cytoskeleton abnormalities & weakened cell junctions can lead to lesions and bleeds

Proposed Mechanism of Action[1]



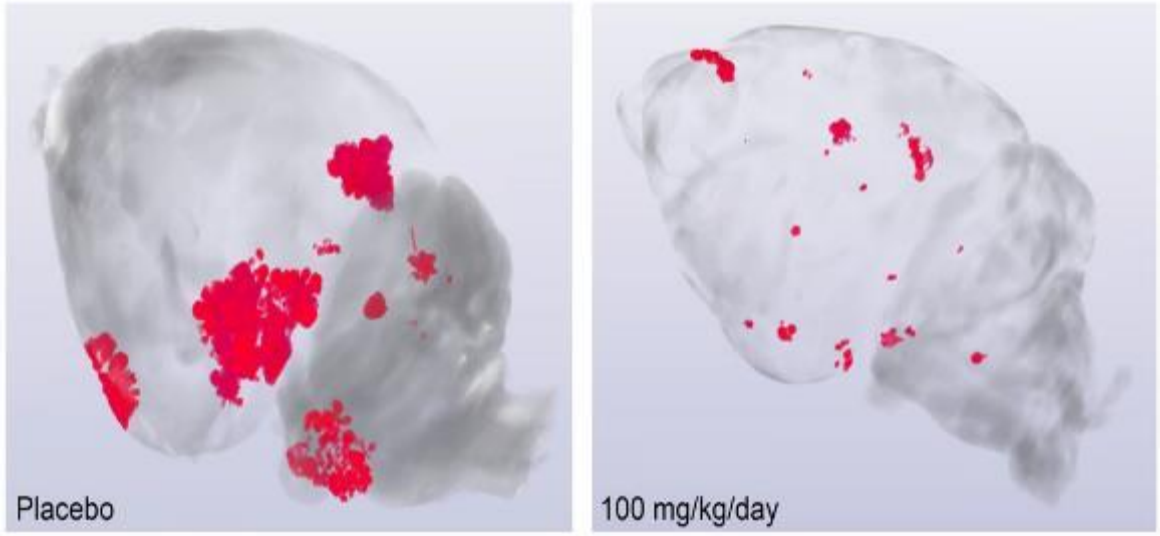
1. A. L. Borilkova, et. al (2010) Journal of Biological Chemistry, Vol 285. 11760 and O. Pertz, et al (2006) Nature, Vol 440:1069

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Preclinical validation for ROCK2 inhibition in cerebral cavernous malformations

- ROCK is hyperactive in brain capillary endothelial cells in patients with CCM[1]
- Inhibiting ROCK2 seeks to repair the endothelial cell defect to reduce the permeability of the blood–brain barrier[2]
- Preclinical studies have shown ROCK2 inhibitors[3]
  - Reduce lesion size and genesis
  - Restore the barrier function of endothelial cells
  - Reverse hyperactivation of ROCK

ROCK2 inhibition appeared to reduce the lesion volume and lesion sites



*Micro-CT imaging of the brain of ccm1$^{+/-}$ mice
Dosed with: ROCK2 inhibitor BA-1049

In CCM transgenic mice, ROCK2 inhibitor reduced the leakiness of lesions, prevented the growth and formation of lesions, and slowed disease progression[3]

1. Stockton RA et al. J Exp Med. 2010 Apr 12;207(4):881-96. doi: 10.1084/jem.20091258.
2. Niego B, et al. PLoS One. 2017 May 16;12(5):e0177332. doi: 10.1371/journal.pone.0177332. PMID: 28510599; PMCID: PMC5433693.
3. McKerracher L, et al. Stroke Res. 2020 Jun;11(3):365-376. doi: 10.1007/s12975-019-00725-8. Epub 2019 Aug 24. PMID: 31446620; PMCID: PMC7036327.

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OV888's potential as a potent, selective, best-in-class ROCK2 inhibitor

Pan-ROCK inhibition has shown off-target effects; OV888 believed to be ~70x more selective for ROCK2 than NRL-1049[1]

	ROCK2 IC_{50} (uM)	ROCK1 IC_{50} (uM)	Selectivity (ROCK1/ROCK2)	BBB Penetrant	Off-Target Effects	Indication
OV888 OVID/GRAVITON	**0.002-0.02**	**12.1**	**1071 fold**	✓		**CCM**
KD025[2] Kadmon Pharmaceuticals	0.105	24	~80 - 100 fold	×		Graft vs host disease
NRL-1049[3] (Neurellis)	0.24 – 0.73	3.9 – 10.2	13.9 – 16 fold	✓	✓	CCM

1 Based on analysis of OV888 and NRL-1049 biochemical assays
2. Ann Clin Transl Neurol. 2014 Jan; 1(1): 2–14. Published online 2013 Nov 19. doi: 10.1002/acn3.19
3 https://patents.google.com/patent/US10106525B2/ena
(Chart based on biochemical assays; not head-to-head studies)

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OV888 (GV101): Phase 1 topline results

Overview

- OV888 (GV101) capsule formulation
- Double-blinded, placebo controlled
- Male/female healthy adult volunteers
- 7-day consecutive dosing:
  - MAD: 100 mg, 200 mg, 400 mg, and 600 mg
- Objective to measure:
  - Safety
  - Tolerability
  - Pharmacokinetics

Results

- ✓ Objective met: Well-tolerated at all tested doses
- ✓ Target engagement achieved
- ✓ Exposure & half-life supportive of once daily dosing
- ✓ Results:
  - No SAEs; no participants met preset stopping criteria
  - All AEs were mild and resolved
  - Asymptomatic laboratory results rated grade 2 or higher in at least 5% of subjects:
    - Clinically insignificant increases in total bilirubin without direct hyperbilirubinemia, with no concurrent liver enzyme elevations, reported in 30% of participants
    - Creatine phosphokinase elevations without muscle pain or weakness were reported in 7% of participants
    - All participants normalized during the study period

NEXT STEPS: Expect to initiate Phase 2 PoC study for the potential treatment of CCM in H2 2024

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Source: Ovid & Graviton data on file



OV329

A next-generation GABA-aminotransferase inhibitor for the potential treatment of resistant seizures

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OVERVIEW: OV329 (oral)
Next-generation GABA-aminotransferase inhibitor

Potential Opportunity

Conditions with acute seizures

- Interdicts a validated target, GABA aminotransferase (GABA-AT)
- Desired profile: a safer vigabatrin (SABRIL)
- Deliver optimal levels of GABA to achieve:
  - Seizure suppression
  - Improved safety
  - Preferable (lower) dosing
- OV329 is believed to be >100x more potent than VGB in preclinical studies[1]

Status

Phase 1 SAD/MAD with biomarkers

- Primary endpoint: safety
- Secondary endpoints: exposure and GABA-AT levels as determined by MRS and TMS
- Anticipated results H2 2024

Ocular study findings

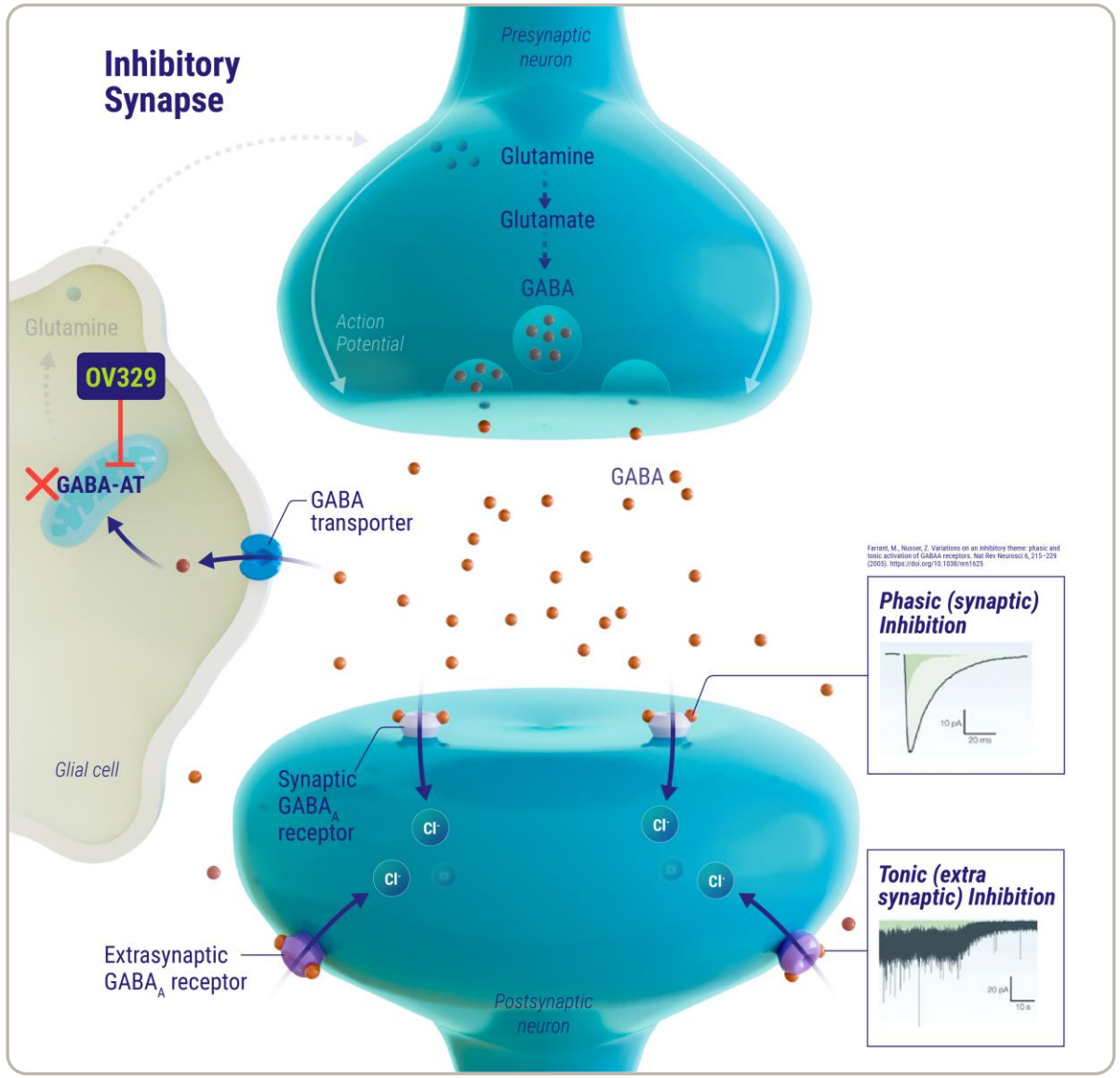
- A head-to-head animal study of the ocular accumulation tendencies of OV329 vs vigabatrin to be presented in September 2024

1. Ovid data on file, presented at Eilat conference in 2022

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OV329 mechanism of action

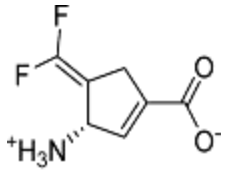
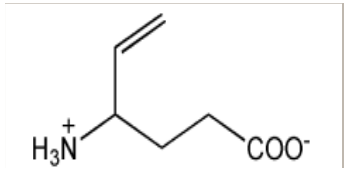
- GABA is the major inhibitory neurotransmitter
- OV329 reduces GABA aminotransferase activity, a key enzyme responsible for degrading GABA[1]
  - Leading to the elevation of GABA levels
  - Curbing excessive neuronal excitation and seizures
- OV329 shows increases in phasic and tonic inhibitory neurotransmission at GABAergic synapses in preclinical models[2]
- Repeated low doses of OV329 demonstrate sustained seizure reduction and profound changes in tonic (extra-synaptic) inhibition in preclinical and animal models[3]



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. Feja, Malte et al. "OV329, a novel highly potent γ-aminobutyric acid aminotransferase inactivator, induces pronounced anticonvulsant effects in the pentylenetetrazole seizure threshold test and in amygdala-kindled rats." Epilepsia vol. 62,12 (2021): 3091-3104. doi:10.1111/epi.17090
3. Ovid Data presented at AES 2023

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OV329 profile is differentiated from vigabatrin

	OV329	Vigabatrin
Molecule		
Potency	IC_{50}: ~0.1 - 0.3 mM	IC_{50}: ~60 – 100 mM
Exposure characteristics	Reduced exposure ($T_{1/2}$ ~1.0 Hour) coupled with prolonged PD duration	$T_{1/2}$ >5.0 Hours Both R (inactive) & S (active) enantiomers
Mechanism of enzyme inhibition	Electrostatic (more sophisticated chemistry, primarily enamine pathway) [2]	Covalent modification of GABA-AT (early generation chemistry, primarily Michael addition pathway) [1]
Purity	Only active, (S) enatiomer	Mixture of active (S) and inactive (R) enantiomers
Therapeutic window in Sprague Dawley rats (a proxy model used to assess ocular safety)	✓	✗ None – toxicity seen at therapeutic dose of 300 mg/kg

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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Repeated low doses of OV329 showed a reduction in seizure frequency & duration in animal models

Mesial temporal lobe epilepsy (MTLE) model reflects:

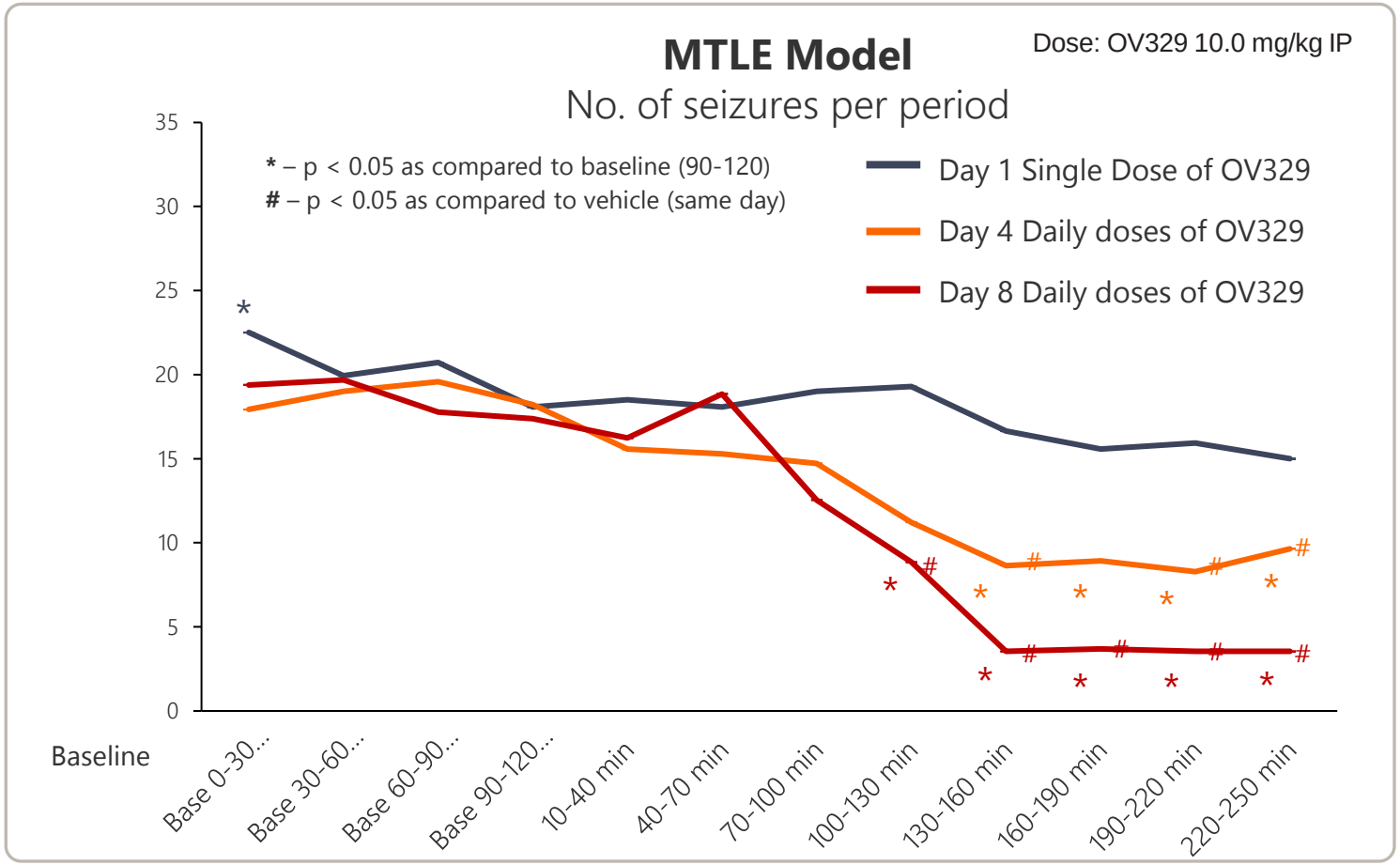
- The main pharmaco-resistant form of epilepsy[1]

Repeat dosing leads to improved efficacy of seizure reduction:

- Seizure numbers
- Cumulative duration of focal seizures

6 other seizure models demonstrate OV329 anti-convulsant activity

- NMDA-Induced Infantile Spasm Model
- Corneal kindled
- Audiogenic seizure
- Amygdala kindled
- i.v. Pentylenetetrazol
- Kainic acid model



Supports potential chronic dosing for refractory seizures

1. Venceslas D, Corinne R. A Mesiotemporal Lobe Epilepsy Mouse Model. Neurochem Res. 2017 Jul;42(7):1919-1925. doi: 10.1007/s11064-017-2239-3. Epub 2017 Mar 23. PMID: 28332054.

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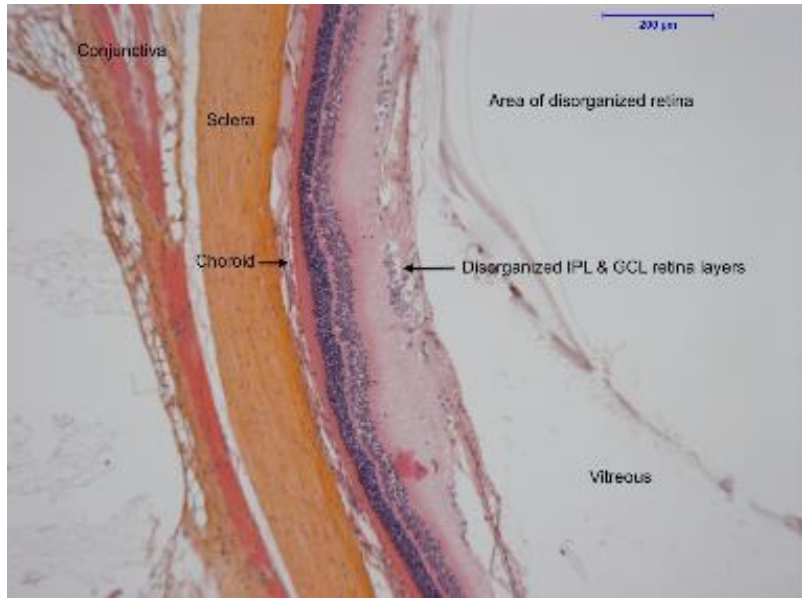
Multiple pre-clinical models in resistant seizures confirm OV329's anti-convulsant profile

	i.v. (ivPTZ)	NMDA-Induced Infantile Spasm model	Audiogenic Seizure	Amygdala Kindled	Corneal Kindled	Intrahippocampal Kainate Model of Mesial-Temporal Lobe Epilepsy (MTLE)	Intraamygdala Kainate Model of Mesial-Temporal Lobe Epilepsy (MTLE)	Lithium-Pilocarpine	Dravet *Scn1a* $^{A1783V/WT}$
Injury Model	Acute/ seizure	Acute/ seizure	Acute	Chronic/ epilepsy	Chronic/ epilepsy	Chronic/ epilepsy	Epilepsy prevention/ modification	Acute/ seizure	Chronic/ Genetic epilepsy
Clinical Correlate	Nonconvulsive Seizures (e.g., absence, myoclonic)	Infantile spasms	Generalized seizures	Chronic focal to bilateral tonic-clonic seizure/ Pharmacoresistant seizures	Chronic focal to bilateral tonic-clonic seizure	Focal Mesial temporal lobe epilepsy/ Pharmacoresistant seizures; Status Epilepticus	Focal Mesial temporal lobe epilepsy/ Pharmacoresistant seizures; Status Epilepticus	Like human, rodents exhibit EEG abnormalities, convulsions, and cognitive impairment	Spontaneous seizures, higher rate of SUDEP. Hyperthermia-induced Pharmcoresistant seizures.
Species	Rat	Mouse	Mouse	Rat	Mouse	Mouse	Mouse	Rat	Mouse
Dosing	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.)	Acute (40 mg/kg p.o.)	Acute (15mg/kg, IV)	Repeat (10mg/kg x 4d, IP)
Activity	+	+	+	+	+	+	+	+	+

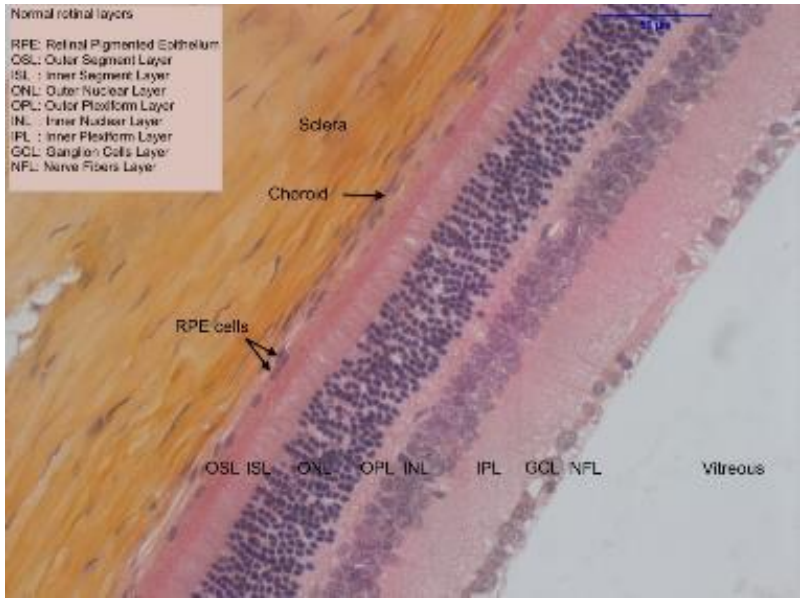
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No ocular effects seen following chronic exposure with OV329 (3 mg/kg)

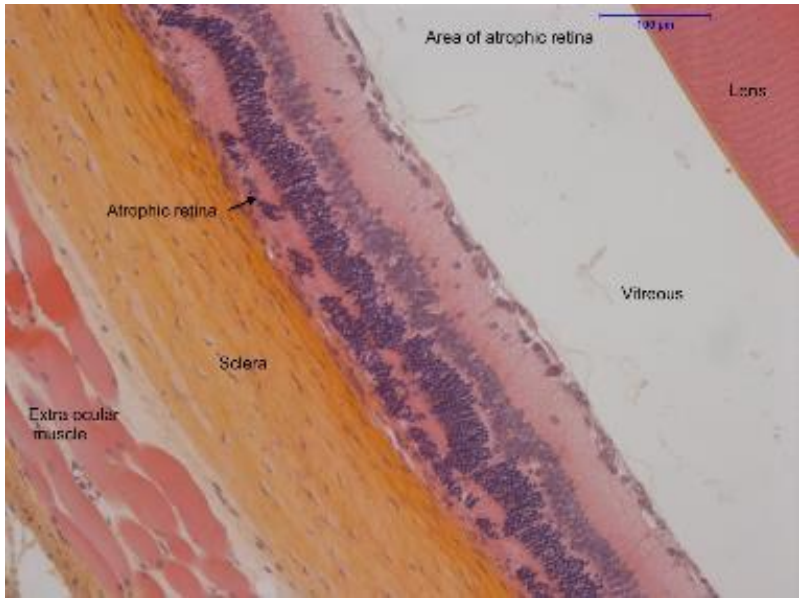
Vehicle



OV329 3.0 mg/kg



Vigabatrin 300 mg/kg



No ocular effects seen in 3 mg/kg OV329, q.d. and vehicle groups in rats at Day 45

Ocular effects seen in more than half of rats treated with Vigabatrin (300 mg/kg)

OVID, Data on file

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OV329 development program next steps

Upcoming clinical & non-clinical activities

Non-clinical

- Findings from head-to-head ocular accumulation study (OV329 vs vigabatrin) expected in September 2024

Clinical – Phase 1 (ongoing)

- 3 SAD cohorts completed in healthy volunteers
- MAD ongoing at 3 mg/kg dose
  - Two biomarkers for efficacy and target engagement being studied:
    - Transcranial magnetic stimulation
    - Magnetic resonance spectroscopy
  - Safety & other ophthalmic monitoring
- Expected completion late H2 2024

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KCC2 library & OV350

Potential first-in-class direct activators of the KCC2 co-transporter

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KCC2 direct activator portfolio & OV350 for seizure and psychosis indications

Potential Opportunity

Unique library of direct activators of potassium chloride co-transporter 2 (KCC2)

Activators directly modulate intrinsic hyperexcitability of neurons via chloride extrusion[1]

Animal disease models have suggested:

- Anti-convulsant properties
- Anti-psychotic and anti-schizophrenic properties
- No sedative effects at expected therapeutic windows

Represents a potential franchise of neurotherapeutics

Status

1st IND from franchise expected to be submitted in H2 2024 (OV350) in psychiatric indication

Characterizing & formulating broad library of ~100 compounds

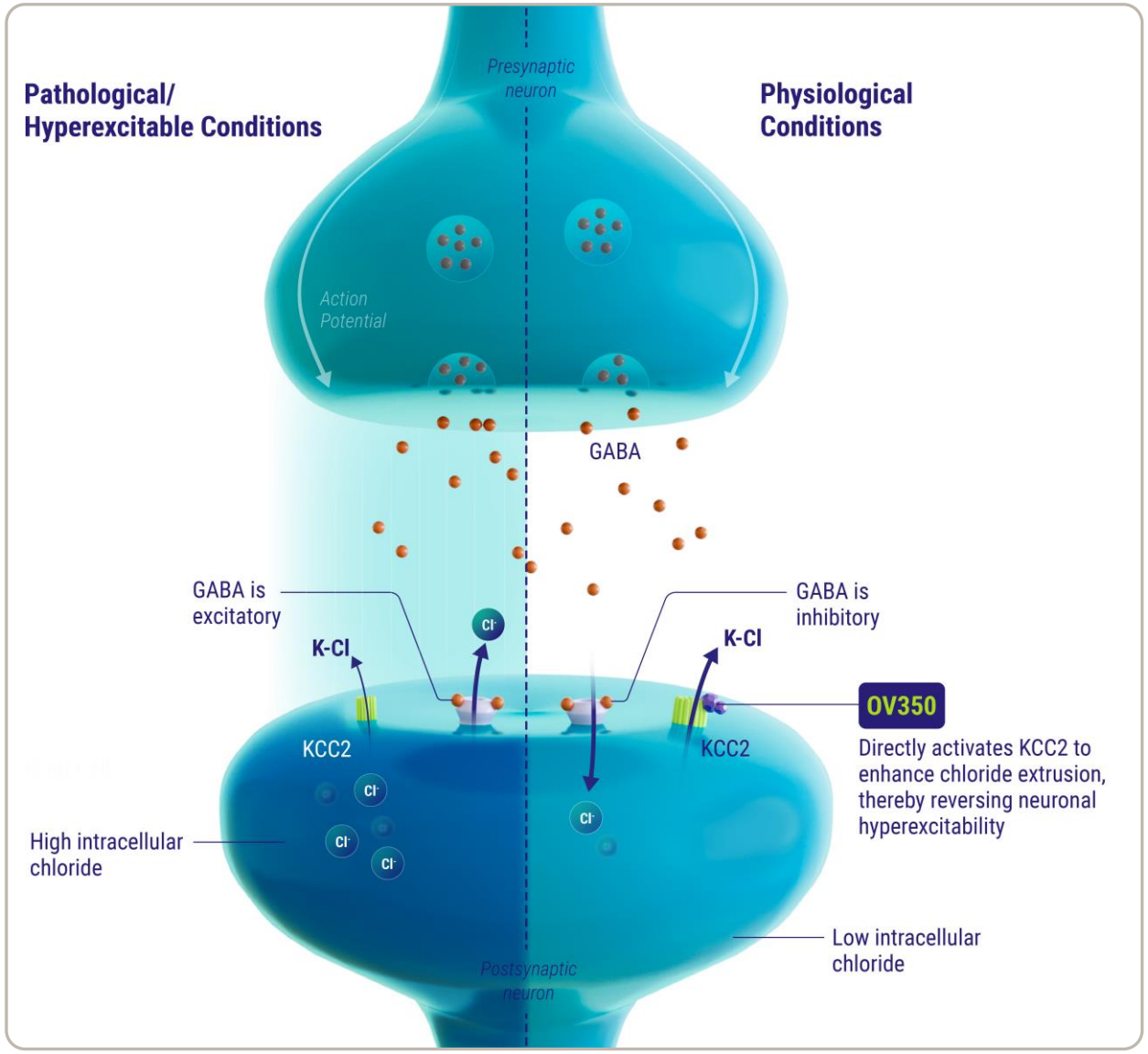
- Amenable to intravenous, oral and injectable formulations

1. Kahle KT, et al JAMA Neurol. 2014 May;71(5):640-5. doi: 10.1001/jamaneurol.2014.21. PMID: 24615367; PMCID: PMC4465580.

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KCC2 is the main regulator of GABA inhibition by maintaining neuronal chloride homeostasis[1]

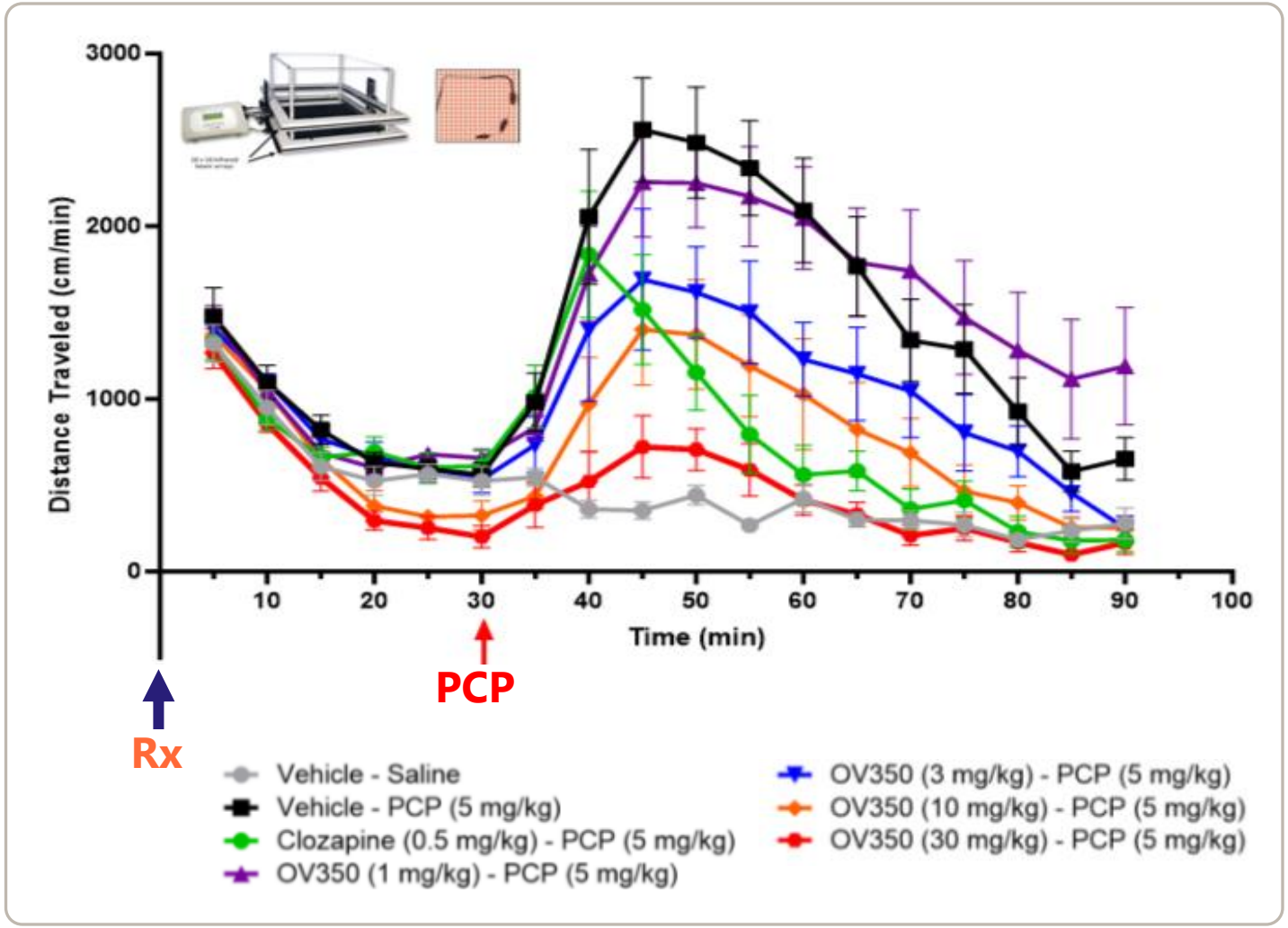
- Deficits in KCC2 activity have been linked to a variety of neurological disorders[2]
- OV350 shows direct activation of KCC2 transporter, improving:
  - Chloride extrusion
  - Neuronal inhibition in preclinical models



1. Mahadevan V, Woodin MA. J Physiol. 2016 May 15;594(10):2593-605. doi: 10.1113/JP271593. Epub 2016 Mar 31. PMID: 26876607; PMCID: PMC4865579.
2. Tomita K, et al. Jpn Dent Sci Rev. 2023 Dec;59:431-438. doi: 10.1016/j.jdsr.2023.11.001. Epub 2023 Nov 11. PMID: 38022385; PMCID: PMC10665825. 24:7, 629-637, DOI: 10.1080/14728222.2020.1762174

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OV350 demonstrates anti-psychotic effects in a schizophrenia model



- Phencyclidine-induced psychosis (PCP) is characterized by:
  - Confusion, excitation, aggression, paranoia, hallucinations, and can be experimentally measured by hyperlocomotion
- OV350 demonstrated dose dependent responses and inhibited PCP induced hyperlocomotion
- OV350 appears to have anxiolytic effects without causing sedation

OVID data on file

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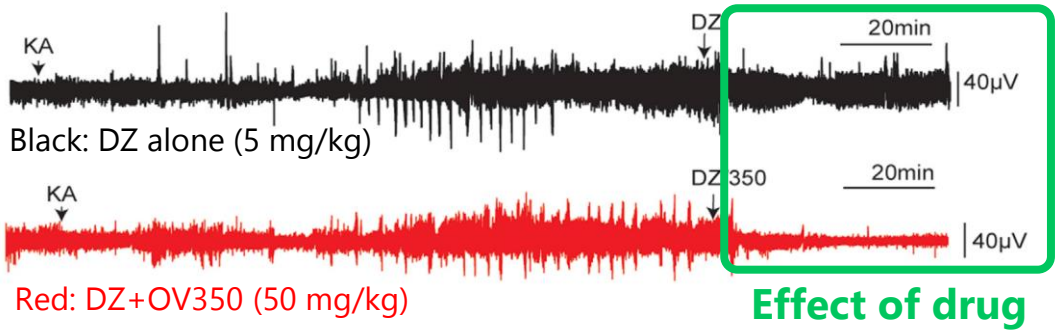
Preclinical POC for OV350 in epilepsy

OV350 potentially terminates ongoing and benzodiazepine refractory status epilepticus

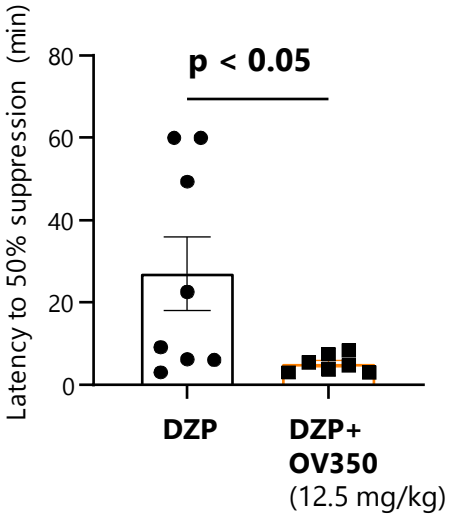
- OV350 demonstrated anti-seizure activities in kainate challenge model
- Mice implanted with electrodes to measure kainate induced seizures
- Demonstrated that OV350 at 50mg/kg and 12.5mg/kg
  - Restored diazepam activities in stopping seizures
- Supports development in status epilepticus using IV formulation of OV350/benzodiazepine combination

Induction of Status Epilepticus (SE)

EEG traces show SE cessation after OV350 intervention with DZ



Efficacy Confirmed at a Lower Dose



OV350 restores the activity of Diazepam in drug-refractory seizures

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Soticlestat

A cholesterol 24-hydroxylase inhibitor

Ovid retains financial interest following the sale of its rights back to Takeda Pharmaceuticals

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Status update: Soticlestat

Potential Financial Interest

Ovid sold its 50% rights in Soticlestat to Takeda Pharmaceuticals in March 2021

Ovid retains a financial interest

- If soticlestat is approved and commercialized, Ovid eligible for:
  - Regulatory and sales milestones[1]
  - Tiered, double-digit royalties on net sales (up to 20%) on all indications in all regions[1]

Status

Takeda announced topline results from two, pivotal Phase 3 trials in June 2024

SKYLINE (Dravet Syndrome):

- Soticlestat narrowly missed the primary endpoint, but showed statistically significant impact in key secondary endpoints and a pre-specified sub-population
- **NEXT STEPS:** Takeda moving forward to discuss totality of the data with regulatory authorities

SKYWAY (Lennox-Gastaut Syndrome)

- Soticelstat missed primary endpoint
- **NEXT STEPS:** Development discontinued in LGS

1. Ligand Pharmaceuticals has 13% interest in all milestones and royalties Ovid receives from Takeda.

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Topline SKYLINE & SKYWAY results

	skyline STUDY DRAVET SYNDROME	skyway STUDY LENNOX-GASTAUT SYNDROME
Primary endpoint	• Soticlestat narrowly missed primary endpoint of reduction from baseline in convulsive seizure frequency vs. placebo (p-value= 0.06) • Soticlestat showed, in a pre-specified subgroups of patients, significant treatment effects on the primary efficacy endpoint	• Soticlestat missed its primary endpoint in reduction in major motor drop seizure
Secondary endpoints	6 key secondary endpoints showed clinically meaningful and significant results (all p-values ≤ to 0.008) • Responder rate • Caregiver and clinician global impression of improvement scales • Seizure intensity and seizure duration scales	• Some secondary endpoints showed significant treatment effects
Safety	Favorable safety and tolerability profile consistent with prior trials	
Pooled analysis with Phase 2	• Soticlestat showed reduction from baseline in convulsive seizure frequency compared to placebo (p-value=0.001)	• N/A

NEXT STEPS: Takeda to discuss a potential path forward in Dravet syndrome with regulatory authorities based upon the totality of the data

1. Takeda data on file

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Thank you.

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