Ovid Therapeutics

March 2024

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Forward looking statement

This presentation contains "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995 including, without limitation, statements regarding the timing for the completion of Takeda's two pivotal Phase 3 trials evaluating soticlestat for Lennox-Gastaut and Dravet syndromes; the potential timing of regulatory decisions on soticlestat; the success of Takeda's trials in soticlestat; the duration of the Company's cash runway, and the expectation that it will support the advancement of the Company's pipeline; 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 and other Rho/Rho associated coiled-coil containing protein kinase 2 inhibitors; and the potential safety, selectivity and potency of OV888 and other ROCK2 inhibitors; the potential use of OV888 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; the potential timing of clinical studies for OV888 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 for OV329 and 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; Ovid's business development intentions; the success of any licensing or partnering opportunities; the success, timing, ability to attract and maintain strategic collaborations; the clinical and regulatory development and potential commercialization of soticlestat, OV329, OV350, OV888 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," "plan," "believes," intends," "anticipates," "design," "advance," "target," "seek," "expects," "demonstrates," "observe," 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 fact nor 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 Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) on March 8, 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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FOCUSED PIPELINE

To treat epilepsy and conditions with seizure symptoms

HARNESSING A SCIENTIFIC REVOLUTION

Targeted small molecules for the central nervous system

NOVEL BIOLOGICAL TARGETS

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

Well positioned to be a leading pipeline in seizures

Multiple milestones expected in next 15 months

5X 2025

- **Clinical and regulatory milestones** expected from Ovid's pipeline by early 2025
- **Two Phase 3 pivotal trials for soticlestat fully enrolled;** data expected by or before September 2024 from Takeda

Differentiated pipeline & veteran team

- 3 potential first-in-class or best-in-class mechanisms of action
- Collective track record of developing and commercializing more than 25 medicines
- Proven dealmakers

Expected cash runway into 1H 2026

$105.8M in capital to fund company[1]

Eligible for additional non-dilutive capital[3]

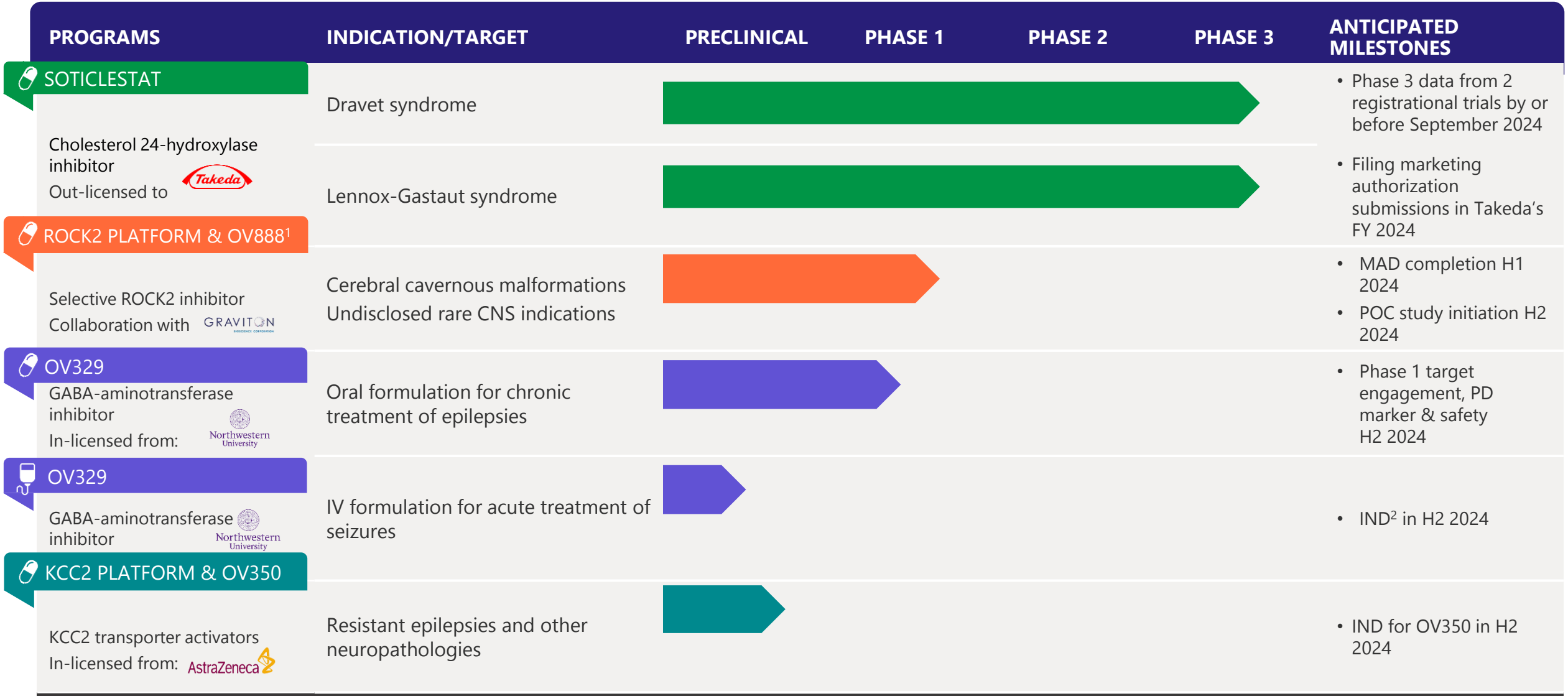
Eligible to receive from Takeda:

- **Up to $660 million** in regulatory and commercial milestones
- **Tiered double-digit royalties up to 20%** on all global sales for any indications
- Ligand Pharmaceuticals receives 13% of all milestones and royalties Ovid receives from Takeda

1. As of 12/31/23
2. Received for 13% interest of potential milestones and royalties Ovid is eligible to receive from Takeda if soticlestat is approved and commercialized
3. If soticlestat is successfully approved and commercialized

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Differentiated pipeline of potential first-in-class or best-in-class mechanisms of action



1. Graviton is conducting development of OV888 (formerly GV101) through Phase 2, which will be directed by a Joint Development Committee that includes members of both Graviton and Ovid.
2. Or equivalent regulatory application

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Robust clinical & regulatory milestones expected in next 15 months

5X[1] 2025

Expected from Takeda

PROGRAM	MILESTONE	ANTICIPATED TIMING
OV888 (GV101)	Complete Phase 1 MAD study	H1 2024
	Initiate signal-finding trial in CCM	H2 2024
OV329	Phase 1: SAD/MAD with MRS biomarker and TMS (chronic)	H2 2024
	IND[2] for IV formulation (acute)	H2 2024
KCC2 & OV350	IND submission (IV formulation)	H2 2024
Soticlestat	Phase 3 data for Lennox-Gastaut syndrome Phase 3 data for Dravet syndrome	Trials are fully enrolled; data expected by or before September 2024
	Regulatory submissions for Lennox-Gastaut syndrome and Dravet syndrome	Takeda's FY 2024 (April 2024 – March 2025)

Expected cash runway supports programs to and through milestones

1. Milestones expected from Ovid 's pipeline by early 2025
2. Or equivalent regulatory application

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Significant medical need persists in epilepsy & seizures

Up to 1 in 10

humans will experience a seizure in their lifetime[1]

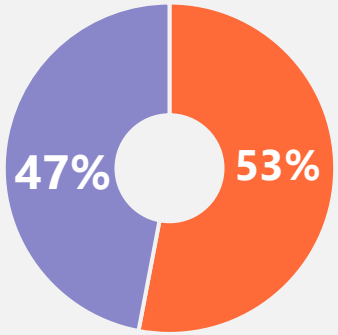


50 million

Living with epilepsy across the globe[4]

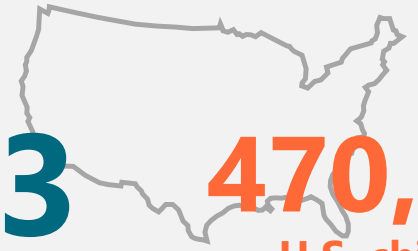
Pharmaco-resistant epilepsy common[2]

Seizures controlled by 1 ASM



Pharmaco-resistant epilepsy

Seizures not controlled with ≥ 2 ASMs



3 million

adults living with epilepsy in the US[5]

470,000 U.S. children

≤17 years
1 have epilepsy[6]

~47%

of epilepsy patients report **polypharmacy** – taking on average 5 medications[3]



Reimbursement & coverage dynamics remain favorable

Polypharmacy generally well covered

1. Epilepsy. World Health Organization. Updated February 9, 2022. Accessed July 12, 2022. https://www.who.int/news-room/fact-sheets/detail/epilepsy.
2. Based upon UK Study of 525 individuals (9-93 years) with newly diagnosed epilepsy, followed for 5 years
3.Terman SW, Aubert CE, Hill CE, et al. Polypharmacy in patients with epilepsy: a nationally representative cross-sectional study. Epilepsy Behav. 2020;111:107261.
4. World Health Organization epilepsy fact sheet updated in February 2023. https://www.who.int/news-room/fact-sheets/detail/epilepsy
5. Epilepsy fast facts. Centers for Disease Contr Easl and Prevention. Updated September 30, 2020. Accessed July 12, 2022. https://www.cdc.gov/epilepsy/about/fast-facts.htm.
6. Who can get epilepsy. Epilepsy Foundation. Updated February 4, 2022. Accessed February 9, 2023. https://www.epilepsy.com/what-is-epilepsy/understanding-seizures/who-gets-epilepsy.

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Soticlestat

A potential first-in-class cholesterol 24 hydroxylase inhibitor for the potential treatment of Lennox-Gastaut syndrome & Dravet syndrome

Soticlestat Overview

- Potential first-in-class, selective inhibitor of cholesterol 24-hydroxylase
- Shows decreases in glutamatergic signaling to reduce seizure susceptibility and improve seizure control
- Completing one of the more robust development programs for developmental and epileptic encephalopathies (DEE)
- Demonstrated sustained seizure reduction efficacy, safety & tolerability with no anticipated monitoring in clinical trials to-date

STATUS

Phase 3 studies are fully enrolled; data expected by or before September 2024

Anticipated global regulatory filings in Takeda's FY2024 (April 2024 – March 2025)

Initial indications being studied by Takeda in Phase 3 global studies:

- Lennox-Gastaut syndrome (SKYWAY trial)
- Dravet syndrome (SKYLINE trial)

Evidence of clinical findings included on subsequent slides.

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Potential milestones & royalties from Takeda can provide significant additional non-dilutive capital

2021	2024 -2025*	Est. 2025 and later*
Upfront payment • All Ovid financial obligations for soticlestat are terminated	**Phase 3 data & expected regulatory decisions** • Takeda funding comprehensive LGS and Dravet trials • Soticlestat is leading neuroscience Phase 3 program for Takeda[1]	**Commercial milestones & royalties** • Tiered double-digit royalties on ALL indications • Up to 20% on GLOBAL soticlestat sales
$196M (Q1'21)	**Up to $660M in additional milestones⁺ + royalties (up to 20%)** ⁺Potential for combined regulatory and commercial milestone payments	

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

FUNDS PIPELINE & BUSINESS DEVELOPMENT

*Estimated timing based upon Takeda's guidance that it anticipates regulatory filings in its fiscal year 2024.

1. Takeda Consolidated Development Pipeline by Phase Presentation. Accessed November 2022.

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The soticlestat opportunity

- Market research supports potential use as an early line option for patients not well-controlled on other antiseizure medications:

- Anticipated profile:[1]
  - Efficacy on top of standard of care therapies
  - Fewer side effects
  - No clinically relevant drug-to-drug interactions
  - No expected monitoring requirements
  - Promising safety profile

LARGE MARKET OPPORTUNITY

7 major markets	U.S. market
~110-135K Lennox-Gastaut syndrome[2]	**~45-65K** Lennox-Gastaut syndrome[2]
~30-45K Dravet syndrome[3]	**~15-20K** Dravet syndrome[3]

Potential for diagnoses to grow as modern ASMs become more accessible globally

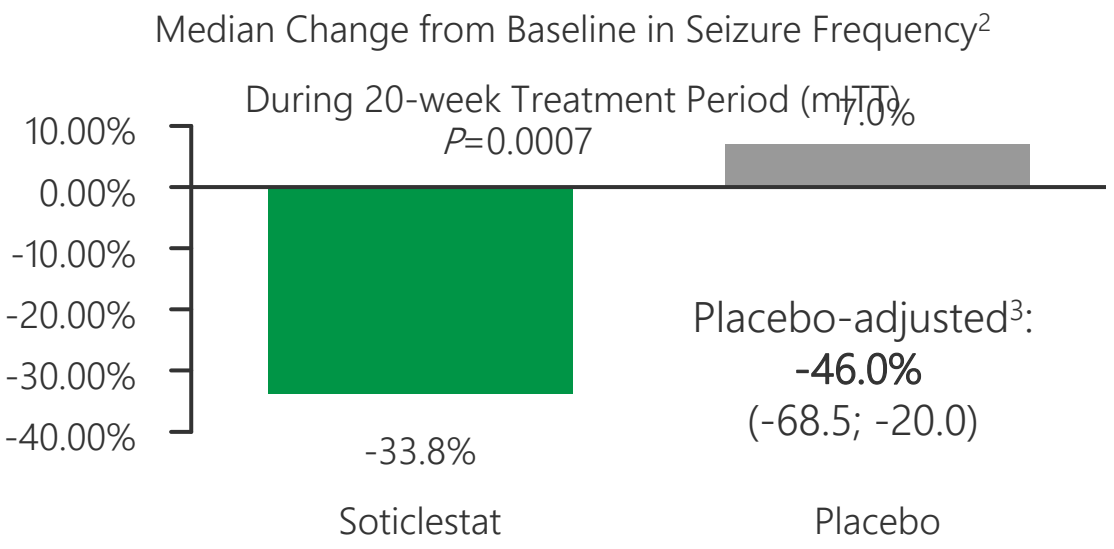
1) Hahn et al. A phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of soticlestat as adjunctive therapy in pediatric patients with Dravet syndrome or Lennox–Gastaut syndrome (ELEKTRA). Epilepsia. 2022; 00: 1–13. https://doi.org/10.1111/epi.17367
2) LGS Foundation
3) Wu et al 2015

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Phase 2 (ELEKTRA): Soticlestat demonstrated statistically significant seizure reduction in Dravet; numeric reduction in Lennox-Gastaut[1]

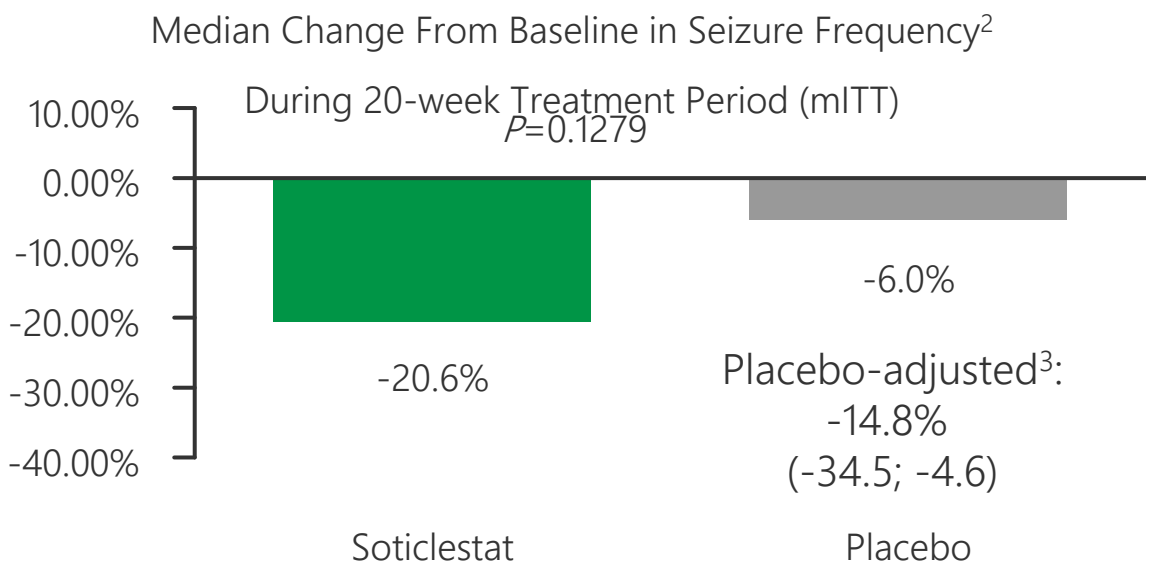
Soticlestat

Dravet Syndrome (Convulsive Seizures)



- Statistically significant placebo-adjusted median seizure reduction of 46%
- DS cohort was <u>not</u> powered for efficacy

Lennox-Gastaut Syndrome (Drop Seizures)



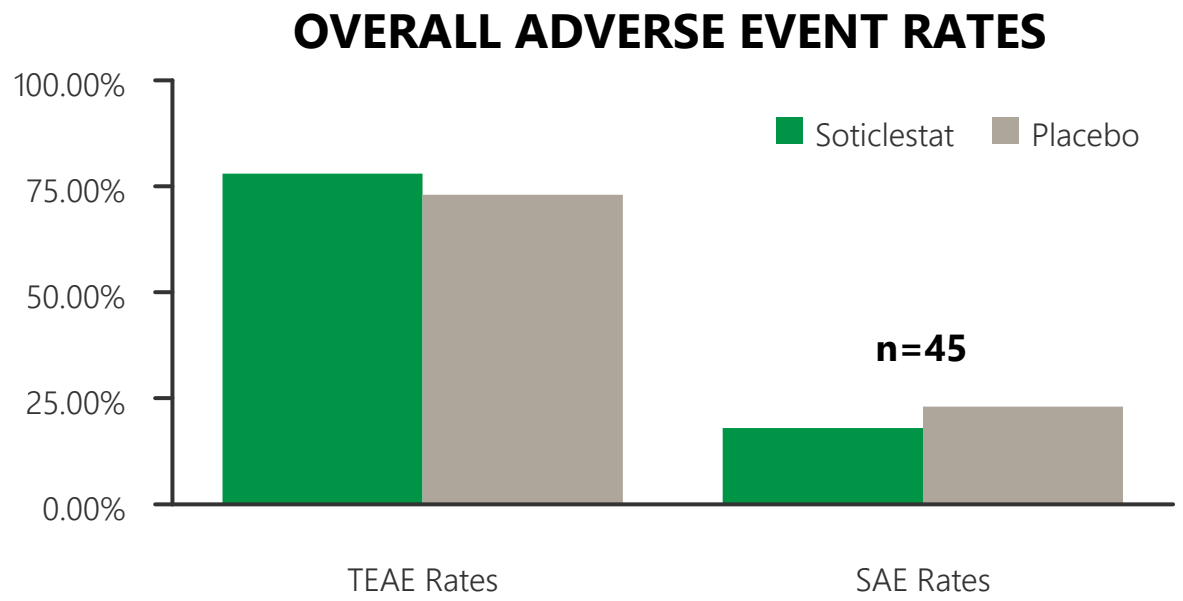
- Placebo-adjusted median seizure reduction of 14.8% did not reach statistical significance; this was impacted by the LGS cohort using a broad definition of drop seizure frequency at baseline of 4 to >5,000 drop seizures/28 days
- A subsequent sensitivity analysis supportive of more stringent, countable drop seizure definition

1 Hahn et al. A phase 2, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of soticlestat as adjunctive therapy in pediatric patients with Dravet syndrome or Lennox–Gastaut syndrome (ELEKTRA). Epilepsia. 2022; 00: 1–13. https://doi.org/10.1111/epi.17367 2Asymptotic 95% confidence interval and Hodges-Lehmann estimation of the median of differences in % change between the two arms from un-adjusted rank statistics. The modified intent-to-treat (mITT) = All randomized subjects who received at ≥ 1 dose of study drug and were assessed for ≥1 day during treatment

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Phase 2 (ELEKTRA): Safety & tolerability profile

TEAEs >5% in soticlestat & >3% difference from placebo	Soticlestat (n=71)	Placebo (n=70)
Pyrexia	11 (15.5%)	8 (11.4%)
Somnolence	6 (8.5%)	3 (4.3%)
Lethargy	5 (7%)	0 (0%)
Constipation	4 (5.6%)	0 (0%)



- Safety profile consistent with previous findings; no new safety findings
- TEAEs and SAEs similar in frequency across soticlestat vs. placebo
- Main TEAEs for soticlestat over placebo are lethargy/somnolence and constipation
- No anticipated monitoring needs

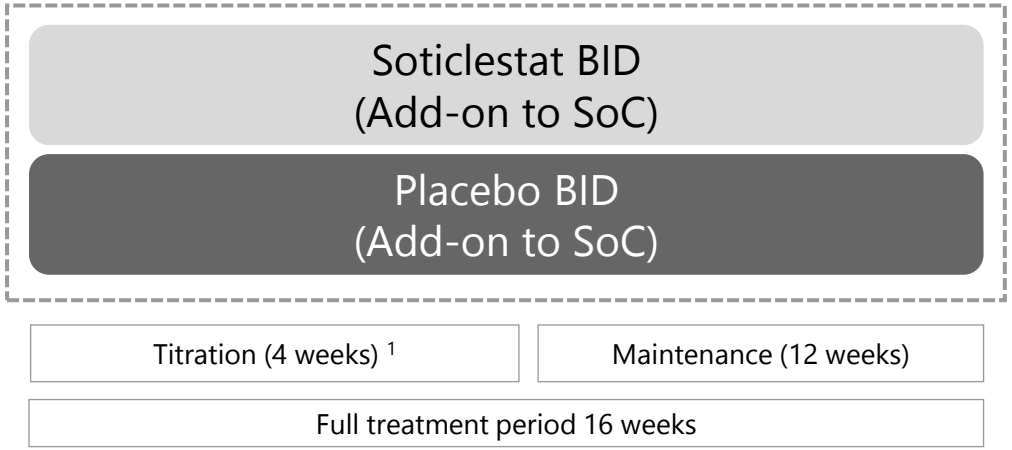
TAEA = Treatment emergent adverse event; SAE = Serious adverse event
Source: Takeda Wave 1 Market Opportunity Presentation. April 6, 2021

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Phase 3 pivotal trials (Conducted by Takeda)

skyline STUDY DS N = 142

skyway STUDY LGS N = 234



TRIAL DESIGN

- Trial design based on feedback from FDA, EMA & PMDA
- Ages ≥ 2 years
- Adjunctive to ASMs
- Active seizures at baseline[2]

OUTCOME MEASURES

Primary

- Frequency change in convulsive seizures (DS study) during full treatment period
  - DS: ≥4 convulsive seizures at baseline
- LGS study uses **Major Motor Drop seizure endpoint** (frequency change in major motor drop seizures) during full treatment period
  - LGS: ≥8 Major Motor Drop (MMD) seizures at baseline.
  - For LGS, countable drop seizures reliably recognized by the caregivers and consistently implemented by the investigators

Trials are fully enrolled, data expected by or before September 2024, Takeda anticipates global regulatory filing in its FY 2024 (April 1, 2024- March 31,2025)

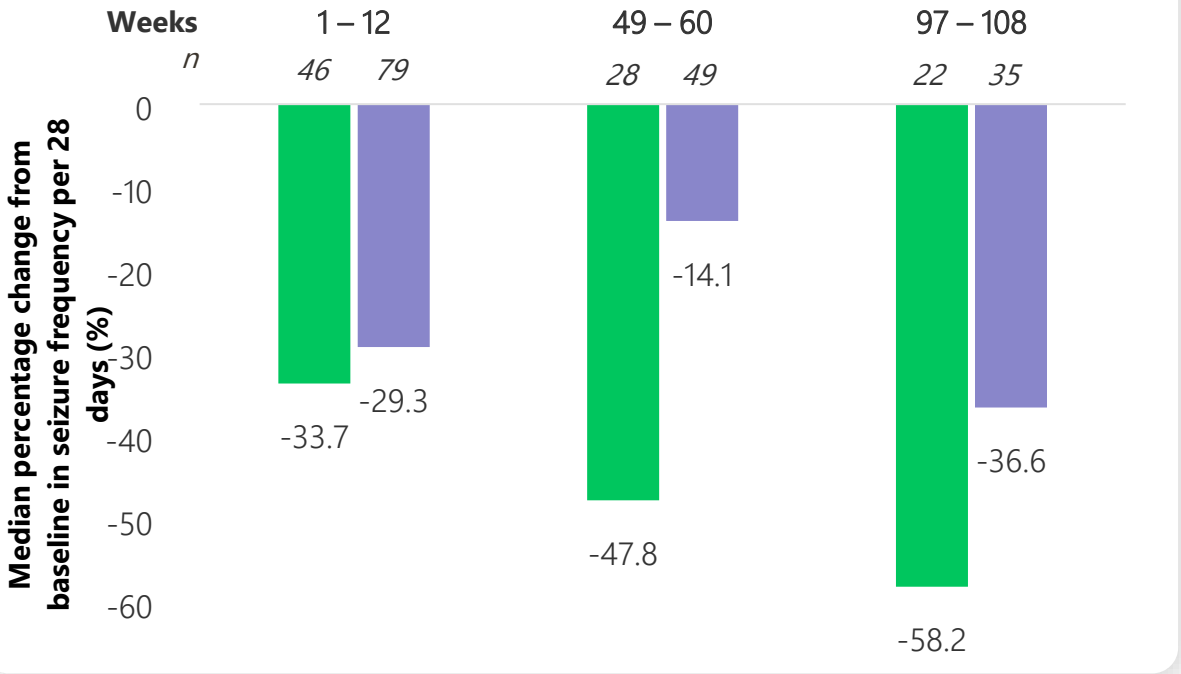
[1]100 mg BID, 200 mg BID, 300 mg BID (mg/kg dosing)
[2]Clinical Trials.gov Accessed October 26, 2021.

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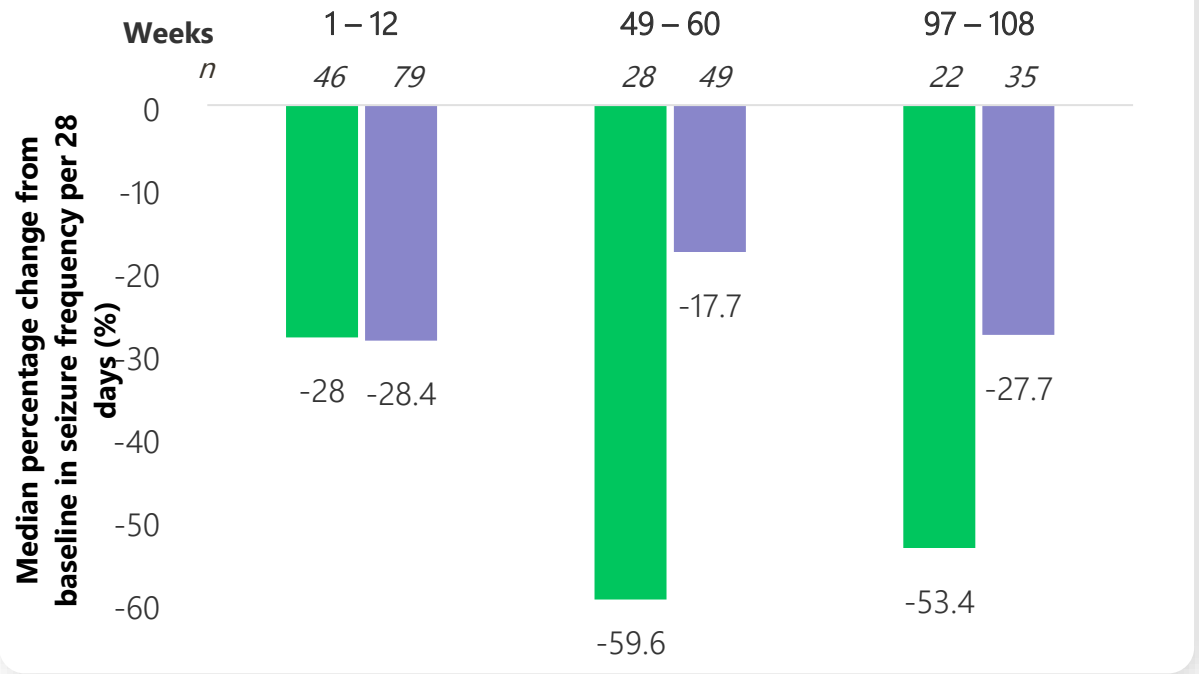
OLE (ENDYMION1): Sustained seizure reduction shown in DS & LGS patients up to 2 years[1]

Dravet syndrome Lennox-Gastaut syndrome

Reduction in frequency of convulsive seizures for DS & drop seizures for LGS



Reduction in all seizure frequency



Soticlestat demonstrated up to 2 years of treatment and:

- Contributed to a sustained reduction in convulsive seizures in DS patients and drop seizures in LGS patients, which are similar endpoints being used in two pivotal Phase 3 trials ongoing in the same epilepsies
- Was associated with a reduced seizure frequency up to 2 years of treatment

1.: Long-Term Treatment Effects of Soticlestat in Patients with Dravet Syndrome or Lennox–Gastaut Syndrome: Interim Data from the ENDYMION 1 Trial as presented at AAN: https://www.aan.com/MSA/Public/Events/AbstractDetails/52787

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OV888 (GV101)

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

OV888 (GV101): Highly selective ROCK2 inhibitor for rare neurological conditions

- OV888 (GV101) has potential as a best-in-class and disease modifying treatment for CCM
  - We believe ROCK2 (not ROCK1) to be the most highly selective inhibitor for that is known[1,2]
  - Blood-brain barrier penetrant in preclinical studies
- Novel mechanism for multiple CNS indications
  - ROCK2 is a signaling pathway that acts on actin cytoskeletal processes, cellular to extracellular matrix adhesion, fibrosis, autoimmunity
  - Endothelial dysfunction & autoimmune MoAs
- Well characterized safety profile in humans
  - Compound studied in two Phase 1 studies
- Regulatory precedent
  - Prior ROCK2 FDA approval (Rezurock® in GVHD)
  - Potential to leverage orphan and/or accelerated approval programs
- Significant commercial opportunity

STATUS

Dose escalating in multiple ascending dose study (ongoing)

- Studying pivotal gel capsule formulation
- Healthy volunteer study
- No SAEs observed

Intend to initiate signal- finding trial in H2 2024

1. Based upon animal models
2. Ann Clin Transl Neurol. 2014 Jan; 1(1): 2–14. Published online 2013 Nov 19.

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OV888 (GV101)

Cerebral cavernous malformations

Presentation & prevalence

- Mulberry-shaped abnormal blood vessels with thin, leaky walls located in the brain and or spinal cord, which increase over age
- 2nd most common intracranial vascular malformation in humans[1,2]

CCMs located in the brainstem pose unique challenges

- Brainstem CCMs are a key risk factor for brain bleeds, can cause significant morbidity due to repeated hemorrhaging[3]
- 82% of patients with brainstem lesions involve major fiber tracts, making surgery extremely difficult[3]
- Guidelines indicate that surgical resection of brainstem CCM could be considered only after a second symptomatic bleed given risks associated with the surgery[4]
    - Post operative mortality and morbidity are high among patients who undergo surgery to remove brainstem lesions[4]
    - 53% of the cases experience post operative neurologic deficits[2]

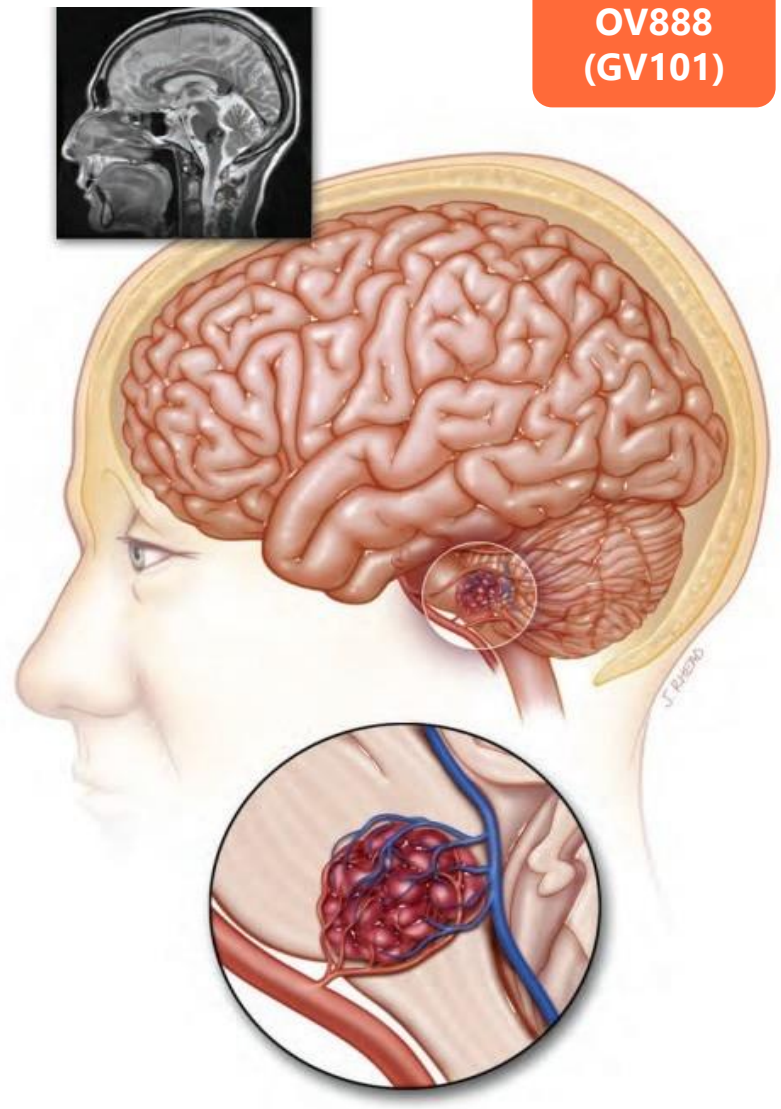


Image attribution: Brainstem angioma from Alliance to Cure Cavernous Malformation

1. Zafar A, Quadri SA, Farooqui M, Ikram A, Robinson M, Hart BL, Mabray MC, Vigil C, Tang AT, Kahn ML, Yonas H, Lawton MT, Kim H, Morrison L. Familial Cerebral Cavernous Malformations. Stroke. 2019 May;50(5):1294-1301. doi: 10.1161/STROKEAHA.118.022314. PMID: 30909834; PMCID: PMC6924279 | 2. Caton MT, Shenoy VS. Cerebral Cavernous Malformations. [Updated 2022 Oct 3]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK538144/. | 3. Ma L, Zhang S, Li Z, Wu CX, Wang Z, Zhan L, Hao Q, Wang H, Ye X, Chen X, Liu YO, Wang S, Zhao YL. Morbidity After Symptomatic Hemorrhage of Cerebral Cavernous Malformation: A Nomogram Approach to Risk Assessment. Stroke. 2020 Oct;51(10):2997-3006. doi: 10.1161/STROKEAHA.120.029942. Epub 2020 Sep 21. PMID: 32951540. | 4. Akers A, Al-Shahi Salman R, A Awad I, Dahlem K, Flemming K, Hart B, Kim H, Jusue-Torres I, Kondziolka D, Lee C, Morrison L, Rigamonti D, Rebeiz T, Tournier-Lasserve E, Waggoner D, Whitehead K. Synopsis of Guidelines for the Clinical Management of Cerebral Cavernous Malformations: Consensus Recommendations Based on Systematic Literature Review by the Angioma Alliance Scientific Advisory Board Clinical Experts Panel. Neurosurgery. 2017 May 1;80(5):665-680. doi: 10.1093/neuros/nyx091. PMID: 28387823; PMCID: PMC5808153.

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Unmet need is substantial, and no pharmacological therapies exist

LARGE MARKET OPPORTUNITY[1]

~400K

Addressable CCM patients (7 major markets)

1 in 500 people in the U.S. have at least one cavernous malformation in their brain

SIGNIFICANT NEED FOR DISEASE MODIFYING THERAPIES

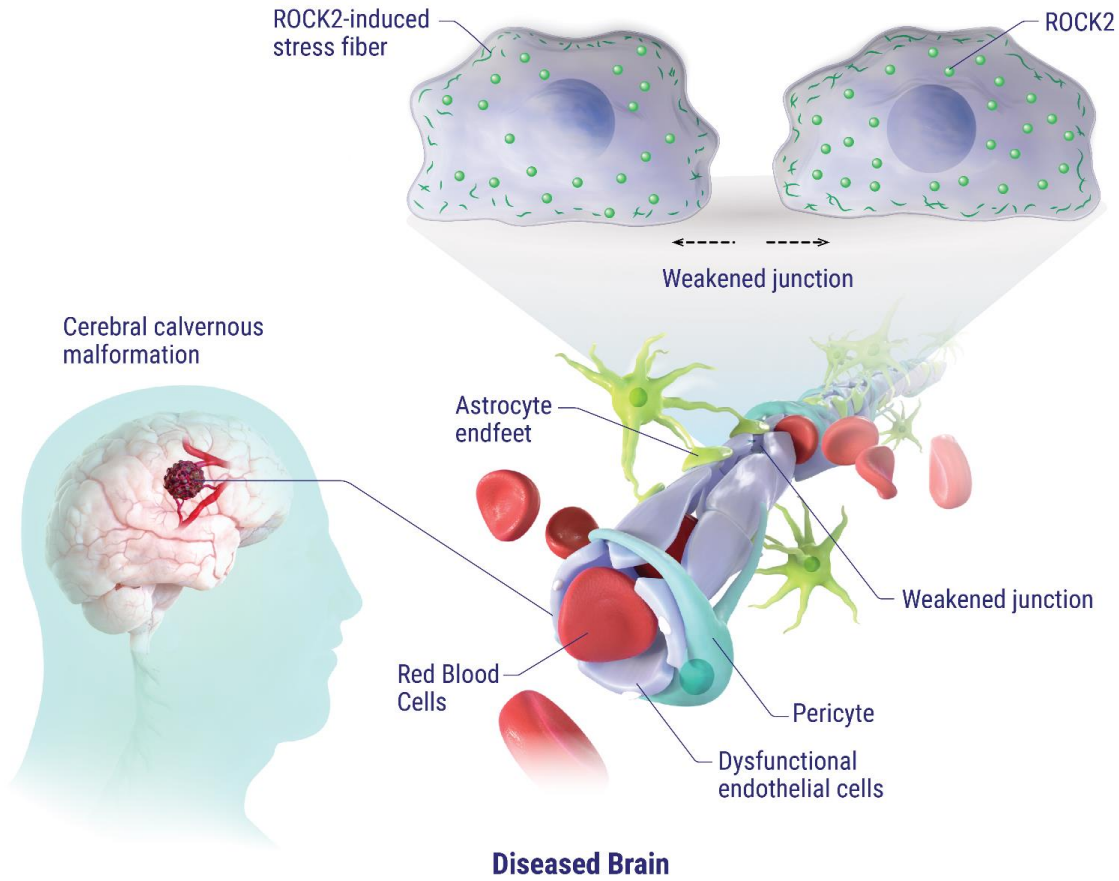
- Lesions can result in intracranial hemorrhage, epileptic seizures, or focal neurological deficits, and potentially lead to severe disability
- No drugs available to prevent or reduce the clinical symptoms
- Only available therapy is surgical resection of the CCM (when possible)
- Risk/benefit balance of surgical resection remains conflicting; some studies report worsening of symptoms after surgery approximately in 15% of cases and mortality in 1.5% of cases
- Prior CCM hemorrhage carries significant risk of additional hemorrhage

1. Ovid 2022 Global market research.

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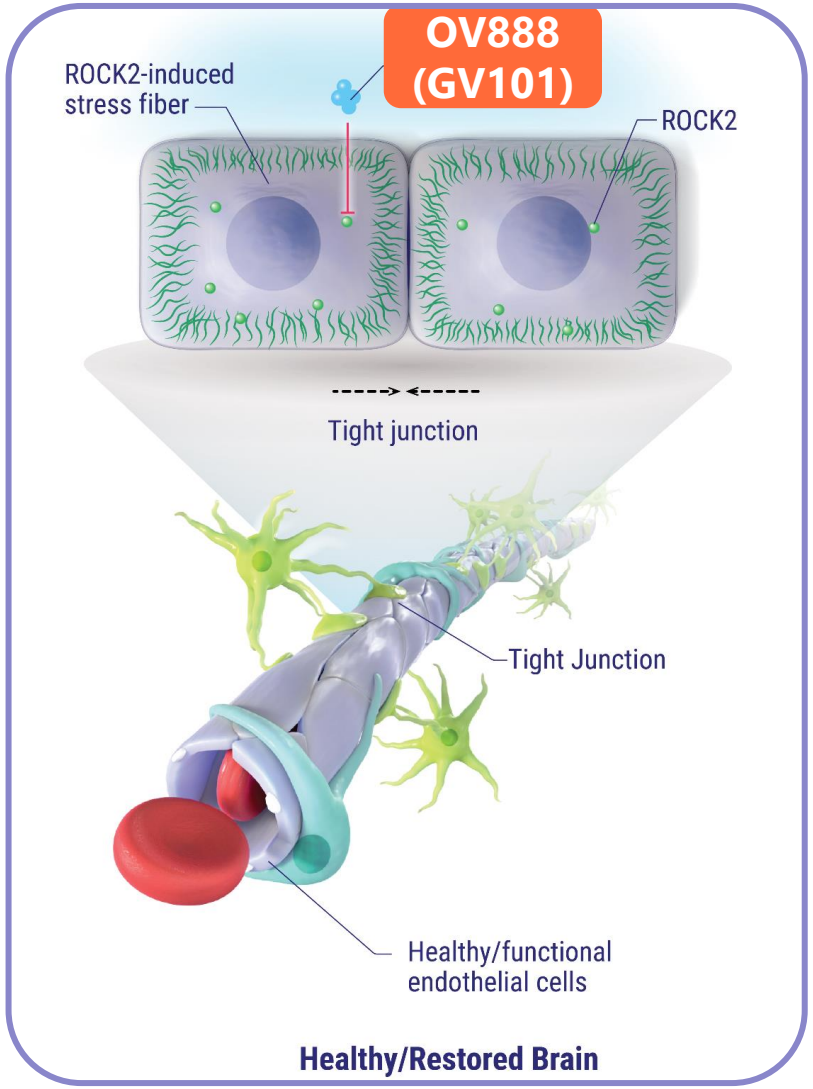
Believed mechanism of action of OV888 (GV101)

PATHOLOGICAL STATE



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

BELIEVED MECHANISM OF ACTION



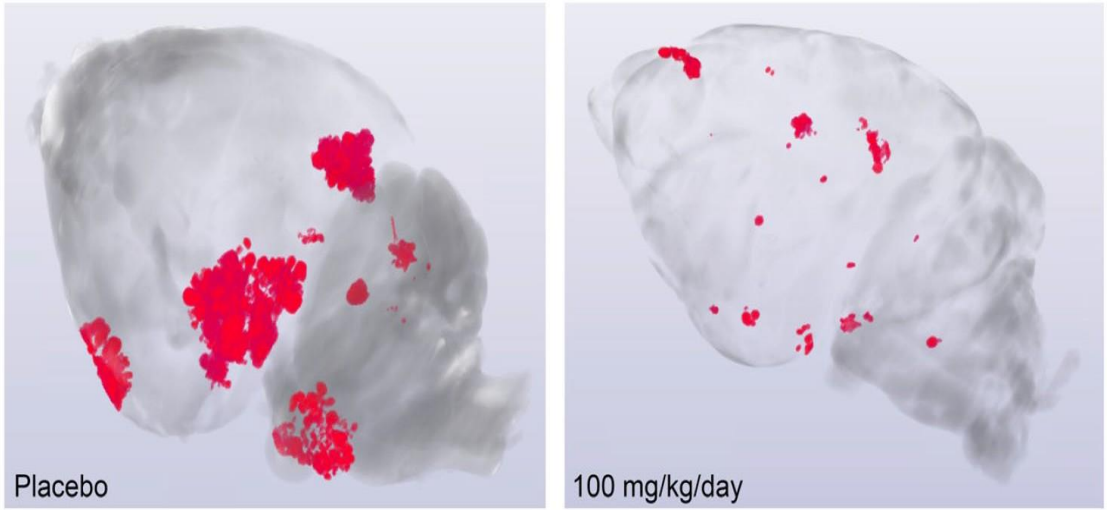
A. L. Borilkova, et. al (2010) Journal of Biological Chemistry, Vol 285. 11760 and O. Pertz, et al (2006) Nature, Vol 440:1069

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Preclinical validation for ROCK2 inhibition in cavernous malformations

- ROCK is hyperactive in brain capillary endothelial cells in patients with CCM[1]
- A potent, selective ROCK2 inhibitor seeks to repair the endothelial cell defect to reduce the permeability of the blood–brain barrier[2]
- Preclinical studies have shown that ROCK2 inhibitors[3]
  - Reduce lesion size and genesis
  - Restore the barrier function of endothelial cells
  - Reverse hyperactivation of ROCK
- In CCM transgenic mice, ROCK2 inhibitors show reduction in the leakiness of lesions, prevents the growth and formation of lesions, and slows disease progression[3]

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

SOURCE: McKerracher L.; et. al. Translational Stroke Research (2020) 11:365-376

1. Stockton RA, Shenkar R, Awad IA, Ginsberg MH. Cerebral cavernous malformations proteins inhibit Rho kinase to stabilize vascular integrity. J Exp Med. 2010 Apr 12;207(4):881-96. doi: 10.1084/jem.20091258. Epub 2010 Mar 22. PMID: 20308363; PMCID: PMC2856024. 2. Niego B, Lee N, Larsson P, De Silva TM, Au AE, McCutcheon F, Medcalf RL. Selective inhibition of brain endothelial Rho-kinase-2 provides optimal protection of an in vitro blood-brain barrier from tissue-type plasminogen activator and plasmin. PLoS One. 2017 May 16;12(5):e0177332. doi: 10.1371/journal.pone.0177332. PMID: 28510599; PMCID: PMC5433693. 3. McKerracher L, Shenkar R, Abbinanti M, Cao Y, Peiper A, Liao JK, Lightle R, Moore T, Hobson N, Gallione C, Ruschel J, Koskimäki J, Girard R, Rosen K, Marchuk DA, Awad IA. A Brain-Targeted Orally Available ROCK2 Inhibitor Benefits Mild and Aggressive Cavernous Angioma Disease. Transl 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 (GV101) clinical development update

PRIOR PHASE 1: NANO-SUSPENSION

- Double-blinded, placebo controlled
- 50 male/female healthy adult volunteers
- 7-day consecutive dosing:
  - SAD: 400 mg, 800 mg, and 1200 mg
  - MAD: 200 mg and 400 mg
- Endpoints: Safety & tolerability; PK
- Findings as of Q3, 2023:
  - 0 SAEs
  - AE of interest (headache (21%), diarrhea (11%), CPK elevations (6%) nausea/vomiting (2%))
- Similar Area Under the Curve (AUC) to U.S. study (AUC 11,600 in 1,200 mg group

PROGRESS UPDATE: OV888 (GV101) CLINICAL FORMULATION

Timing:
- Multiple ascending dose trial ongoing

Objective:
- Confirm safety and establish maximum dose tolerated

Approach:
- Randomized, placebo-controlled, double-blind, single-center MAD
- 8 per dose group; 3:1 randomization
- 7-day dosing, 72-hour trailing PK data collection

Status:
- No serious adverse events; no voluntary discontinuations

Next steps:
- Complete multiple ascending dose program
- Requesting FDA pre-IND meeting

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OV329

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

OV329: Potential best-in-class GABA-AT inhibitor for acute & chronic seizures

- Unique molecule for a validated target, GABA aminotransferase (GABA-AT)
- Promotes inhibitory neurotransmitter (GABA) to reduce seizures
- Designed to supplant a prior GABA-AT inhibitor, vigabatrin (VGB)
  - Prior GABA-AT inhibitor, vigabatrin, had no therapeutic window in animal models
  - OV329 established a potential therapeutic window in animals relative to VGB
  - OV329 demonstrated to be >200x more potent than VGB in preclinical studies
- 6 preclinical models demonstrate OV329 anti-convulsant activity
- Actively studying safety & surrogate biomarkers for efficacy
- Potential utility in acute and chronic seizures

STATUS

Phase 1 SAD / MAD

- 3 cohorts SAD complete
- No safety signals
- Dose escalating
- Expected to initiate MAD

Expanding formulations

- Oral
- Intravenous

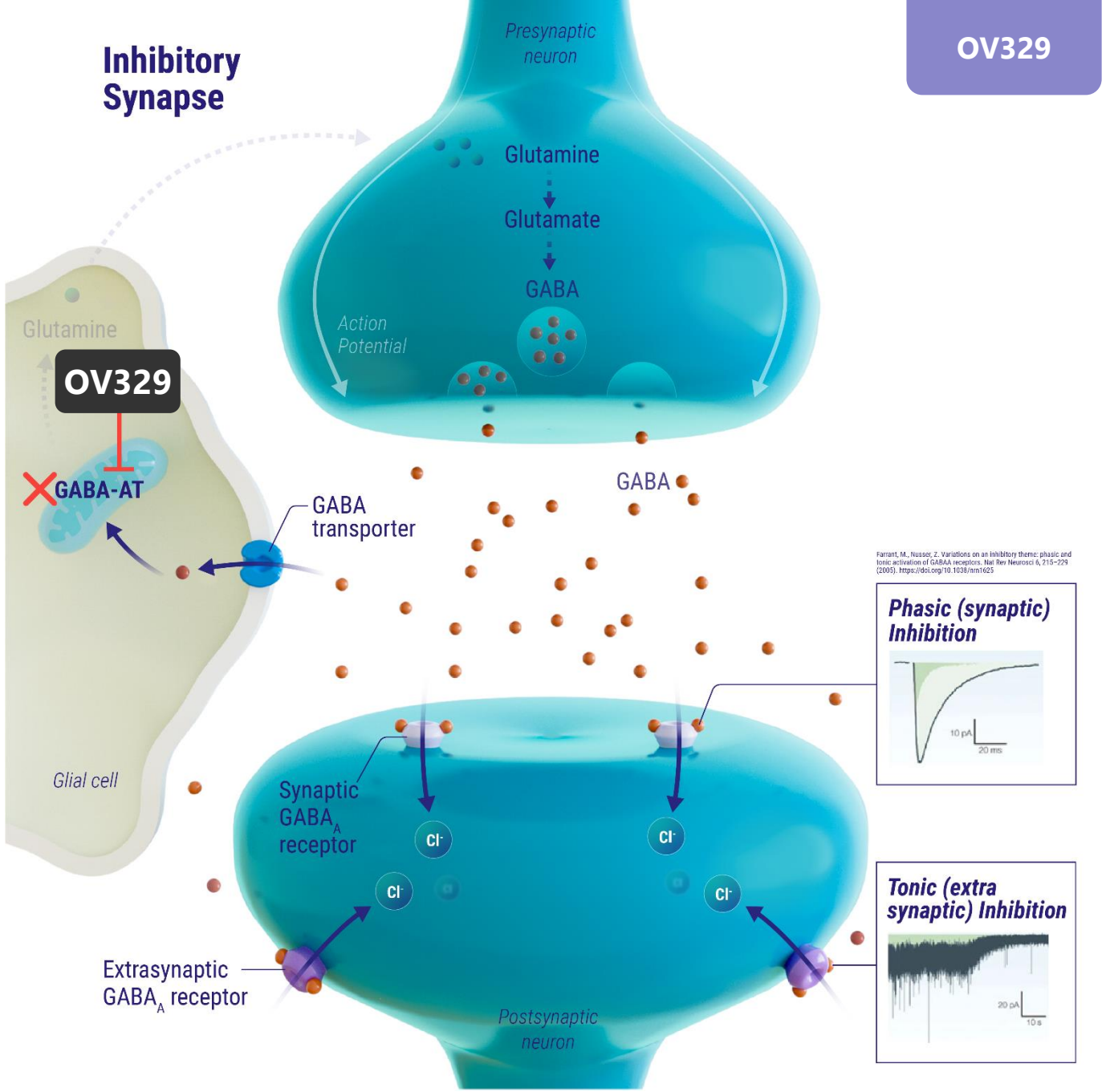
Expanding development program for multiple potential indications

- Chronic
- Acute

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OV329 mechanism of action

- GABA is the major inhibitory neurotransmitter in brain
- OV329 demonstrates substantial reduction of GABA-AT activity, a key enzyme responsible for degrading GABA, thus elevating GABA levels
- OV329 increases phasic and tonic inhibitory neurotransmission at GABAergic synapses
- Curbs excessive neuronal excitation and reduces seizures in animal models



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Preclinical findings support human development program

OV329 ANTICIPATED PROFILE

Significant potency expected to allow for:

- ✓ Efficacy
- ✓ Safety
- ✓ Lower dosing

OPTIMAL LEVELS OF GABA FOR SUSTAINED SEIZURE SUPPRESSION

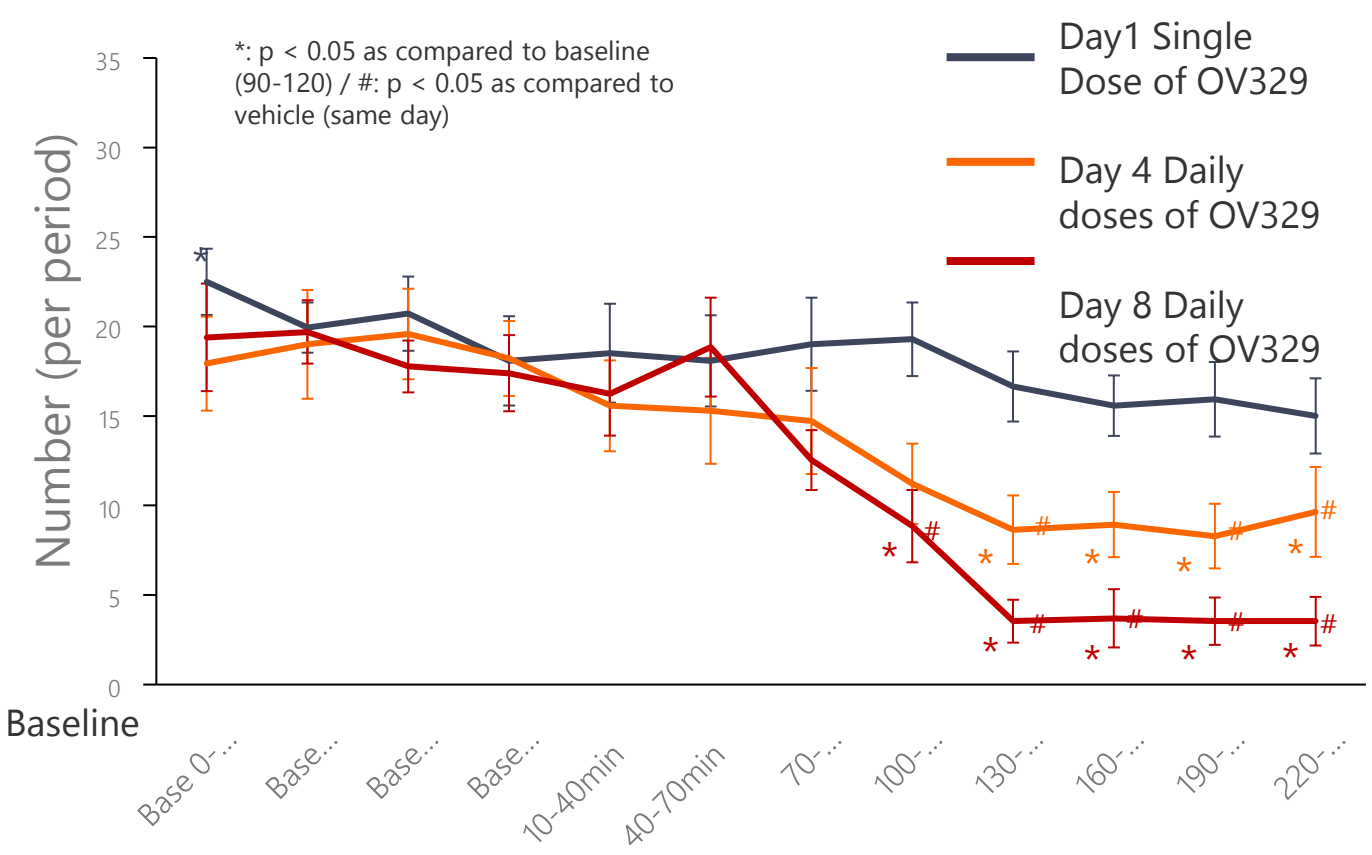
- Delivers anti-convulsant effects at very low doses
- Repeated (chronic) low doses deliver sustained seizure reduction and profound changes in tonic (extra-synaptic) inhibition
- Anti-convulsant properties in chronic and acute seizures (efficacy in 6 pharmaco-resistant animal models)
- Electrophysiology data has established pharmacodynamic effects at low doses & support signal detection efforts in humans
- Tissue accumulation of OV329 is expected to be less than vigabatrin

Ovid 2022 Global market research.

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Repeated, low doses of OV329 reduce seizure frequency & duration in animal models

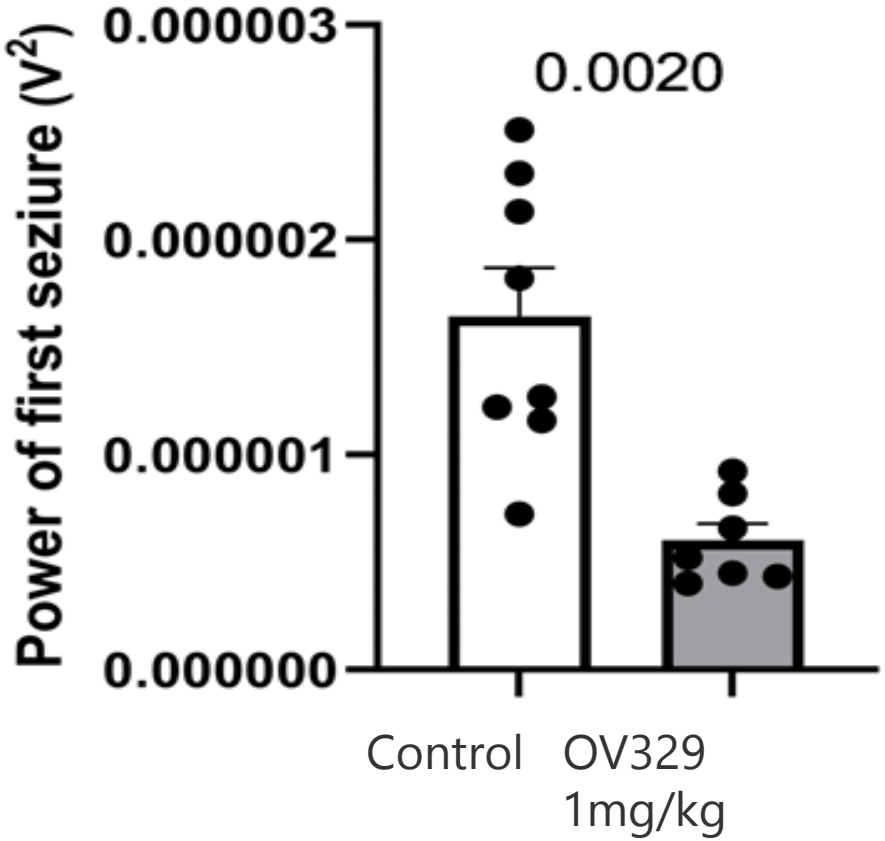
MTLE DISEASE MODEL



- Mesial temporal lobe epilepsy (MTLE) mouse model reflects:
  - Common epilepsy
  - The main pharmaco-resistant form of epilepsy
- Repeat dosing leads to improved efficacy of seizure reduction:
  - Seizure numbers
  - Cumulative duration of focal seizures
- OV329 shows prolonged GABA-AT inhibition and enhanced effects by repeat low doses

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EEG studies indicate OV329 reduces seizures at low doses



- Modulation of neuronal hyperexcitability is reflected in EEG measurements in animal models
- 0.5-1mg/kg of OV329 leads to detectable EEG changes in mice
- OV329 at 1mg/kg significantly reduced the intensity of kainate induced seizure in mice

EEG response serves as an additional pharmacodynamic marker for human trials

OVID data on file

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OV329 development program status

Potential for chronic and acute treatments (via oral & IV formulations)

ORAL – CHRONIC DOSING

- 3 SAD cohorts completed in healthy volunteers
  - No safety signals found
  - Moving to MAD
  - Adding site for the Phase 1 SAD/MAD
- Pursuing simultaneous demonstration of anti-convulsant utility via simultaneous transcranial magnetic stimulation (TMS) study
- Conducting animal studies to further differentiate PK/PD and safety from vigabatrin
- Target readout H2 2024

IV – ACUTE DOSING

- Formulating OV329 in IV
- Initiated toxicology for acute dosing
- Intent to initiate a status epileptic signal finding trial in 2025

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KCC2 library & OV350

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

KCC2 library & OV350 (1st program from library) overview

- Library of ~100 compounds that are direct activators of potassium chloride co-transporter 2 (KCC2)
  - Unique compounds offer discrete properties
  - Amenable to intravenous, oral and injectable formulations
- Activators directly modulate intrinsic hyperexcitability of neurons via chloride extrusion
- Animal disease models have confirmed:
  - Anti-convulsant properties as monotherapy and as a potentiator
  - Anti-psychotic and anti-schizophrenic properties
  - No sedative effects at expected therapeutic windows
- Represents a potential franchise of neurotherapeutics

STATUS

IND anticipated for OV350 in H2 2024

- IV formulation initially
- Intend to pursue an oral formulation

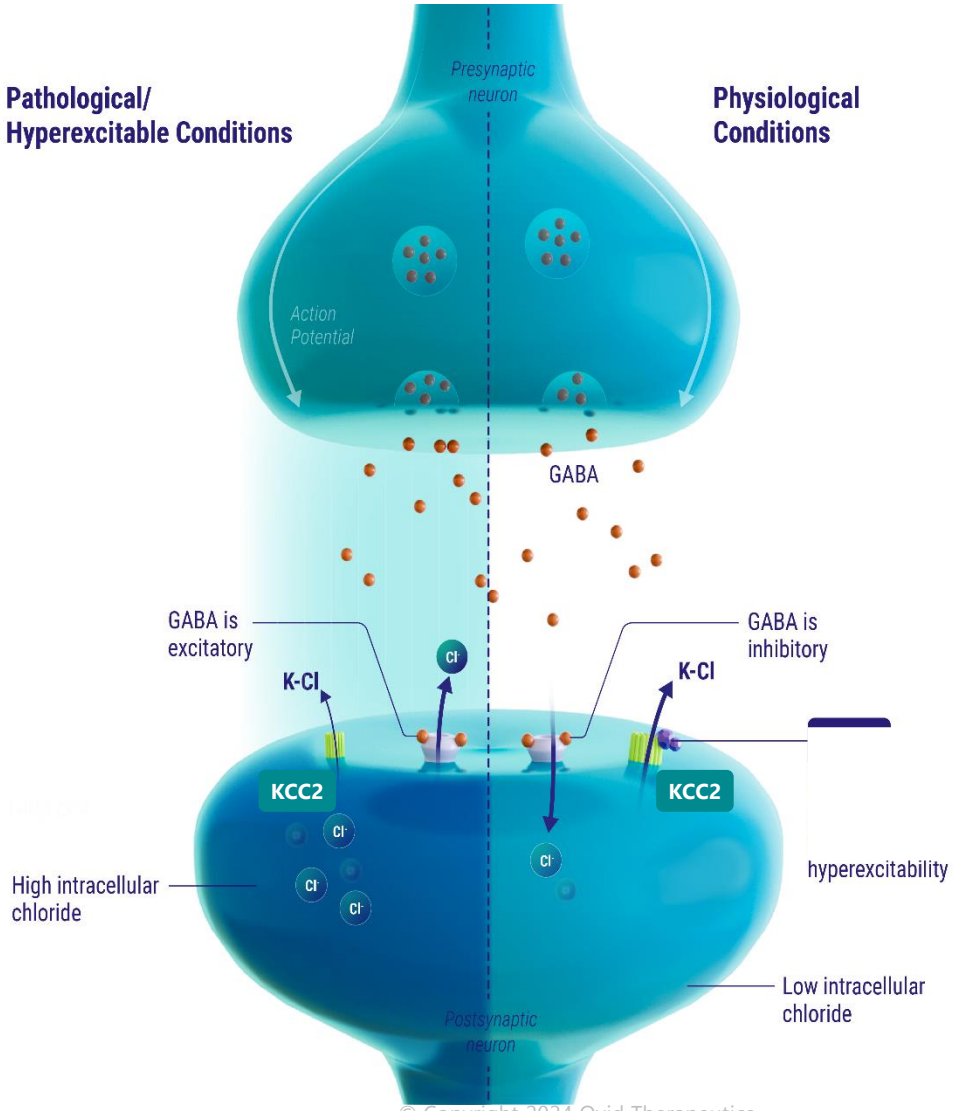
Therapeutic potential in multiple CNS conditions

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OV350 mechanism of action

Impaired KCC2 activity

- Causes high intra-neuronal chloride concentrations leading to abnormal depolarizing of the GABA receptor
- Causes neuronal hyperexcitability leading to epilepsy, seizures & other pathologies



In normal KCC2 activity

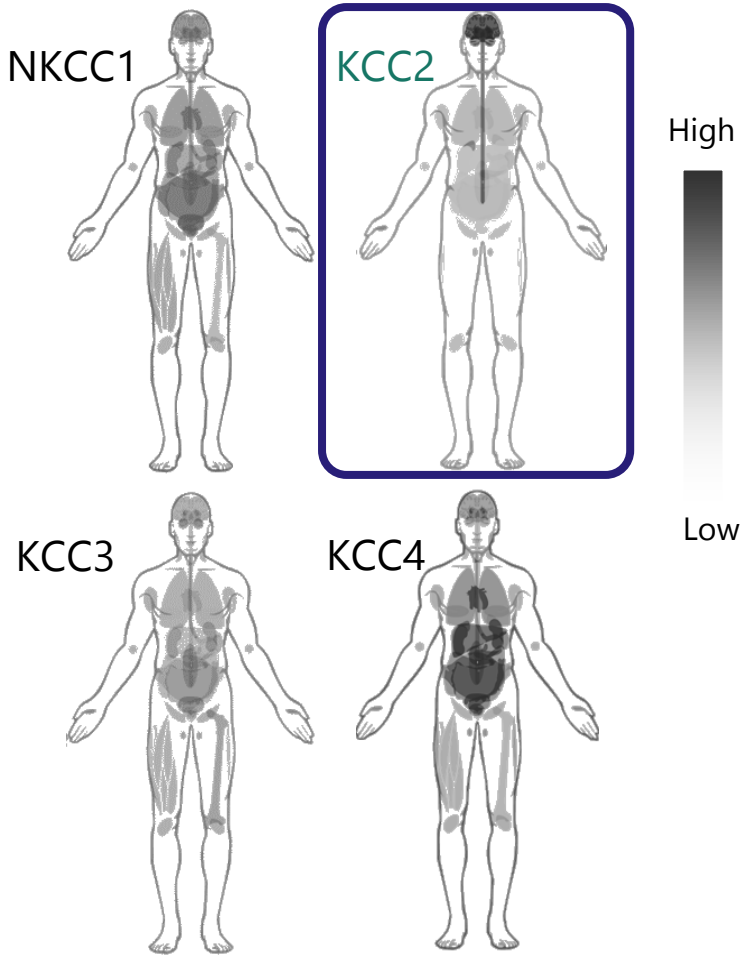
- NKCC1 activity is low while KCC2 activity is high leading to low intra-neuronal Cl− concentration
- Enables a GABA-driven influx of Cl−, causing an inhibitory effect (hyperpolarizing) to the GABAA current

OV350 shows direct activation of KCC2 transporter, improving chloride extrusion and improving neuronal inhibition in preclinical models

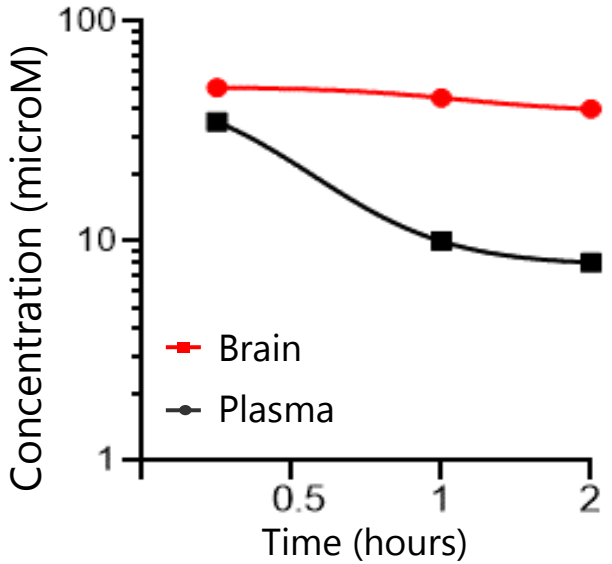
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In animal models OV350 shows rapid, stable accumulation in the brain with a translatable pharmacodynamic biomarker[1]

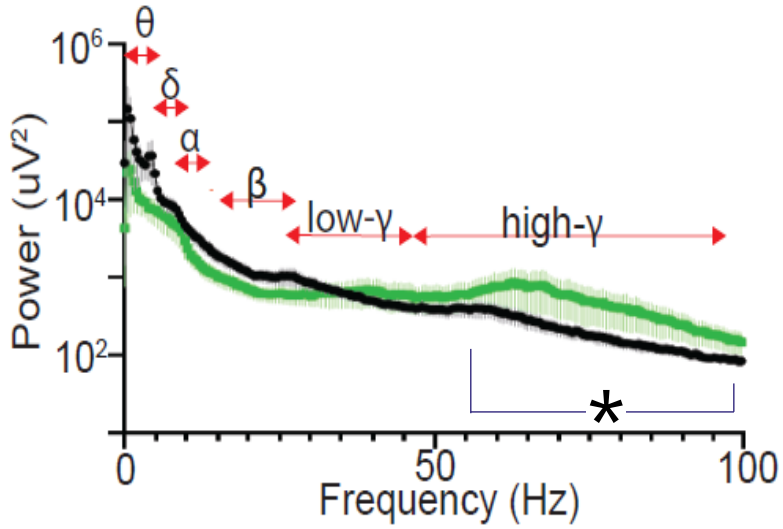
KCC2 is expressed exclusively in neurons



OV350 rapidly accumulates in rodent brain via IV/IP dosing



OV350 induces a shift in EEG high gamma power spectrum (biomarker)



- OV350 in-vivo pharmacokinetics shows high micromolar accumulation in the brain within minutes
- Highly translatable EEG pharmacodynamic biomarker confirmed in healthy animals[1]

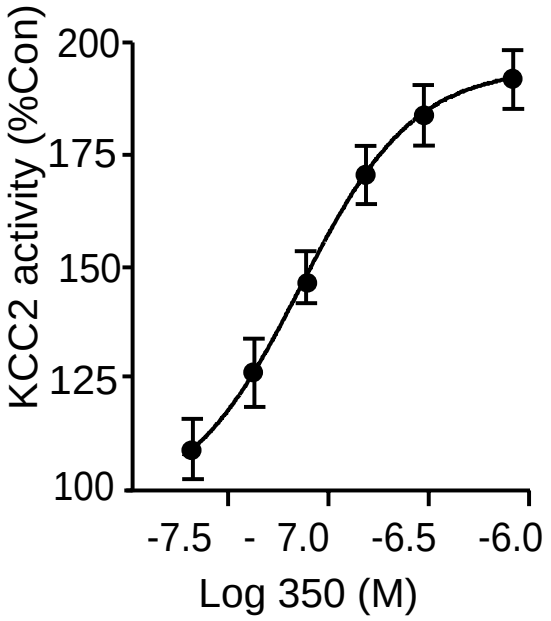
1. Ovid data on file

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Why does direct activation matter?

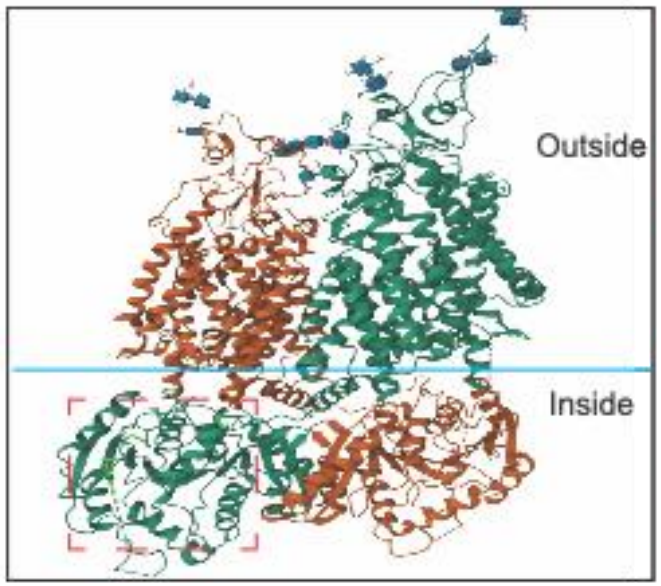
OV350 increases KCC2 activity via binding to amino acids in its cytoplasmic domain

A.

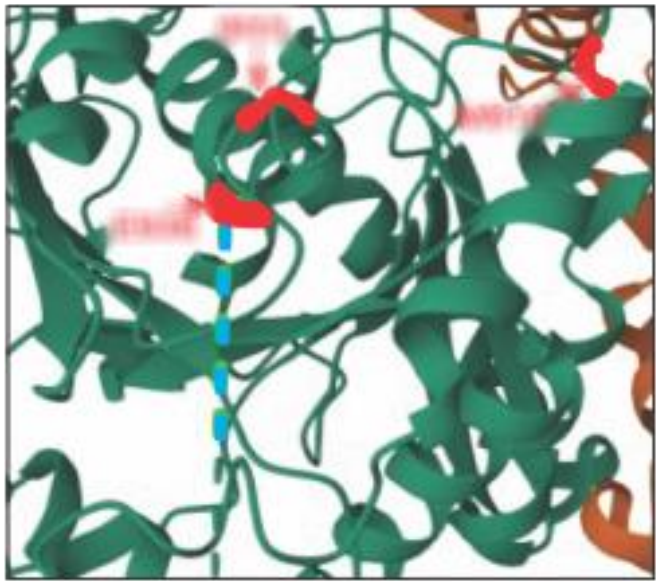


	OV350
MW	<500
LogD	4.4
KCC2 EC_{50} (nM)	261.2 ± 60.2
KCC3 EC_{50} (nM)	>100,000
KCC4 EC_{50} (nM)	>100,000
NKCC1 EC_{50} (nM)	>100,000

B. KCC2 Cryo-EM



C. OV350 binding site



OV350 exhibits 100-1,000 fold higher potency for KCC2 compared to other peripheral K/Cs and NKCC1, limiting peripheral side effects seen with other NKCC1 inhibitors

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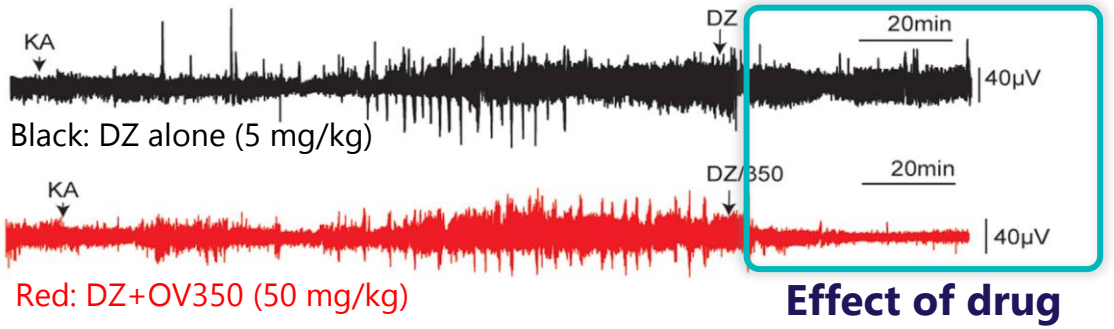
In-vivo preclinical POC data for OV350 in epilepsy

OV350 terminates ongoing and benzodiazepine refractory status epilepticus

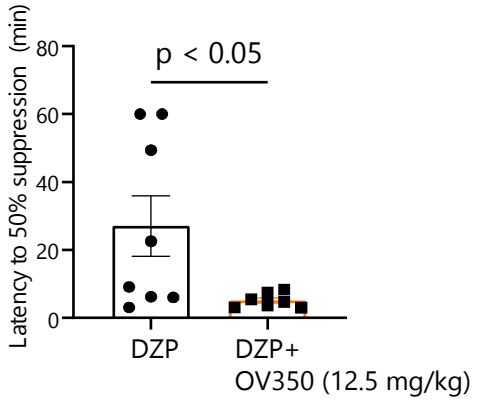
- OV350 demonstrated anti-seizure activities in kainate challenge model
- Mice implanted with electrodes to measure kainate induced seizures and demonstrated that OV350 at 50mg/kg and 12.5mg/kg
  - Restored diazepam activities in stopping seizures
- Supports development in Status Epilepticus using IV 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

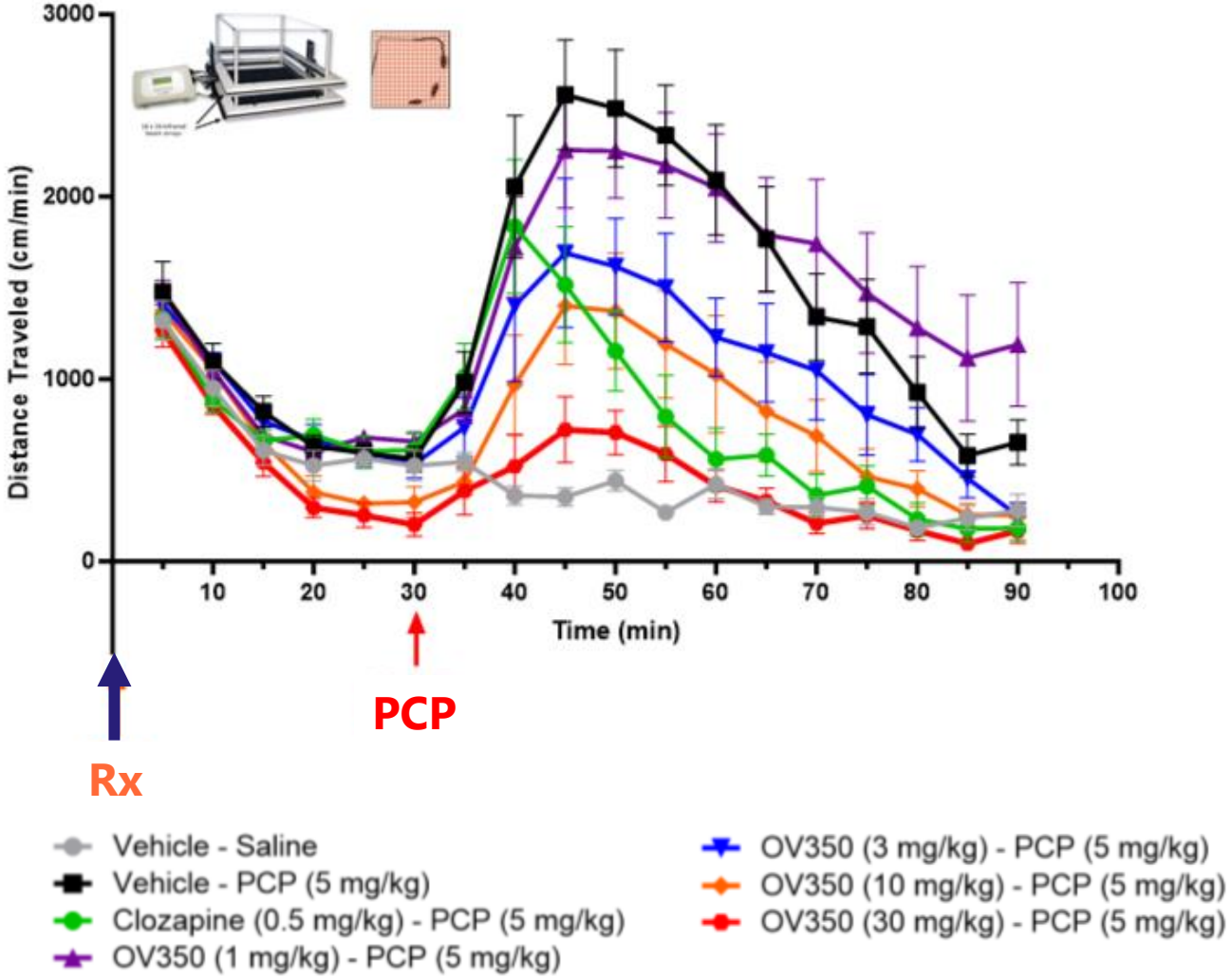


OV350 restores the activity of Diazepam in drug-refractory seizures

Jarvis et al., 2023, Cell Reports Medicine 4, 100957; PNAS, 2015;112:3523; Unpublished data

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OV350 anti-psychotic effects demonstrates in a schizophrenia model

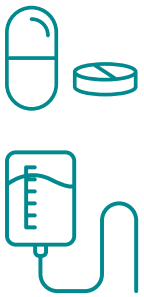


- Phencyclidine-induced psychosis (PCP) is characterized by:
  - Confusion, excitation, aggression, paranoia, hallucinations, and can be experimentally measured by hyperlocomotion
- OV350 inhibited PCP induced hyperlocomotion with clear dose dependent responses
- OV350 appears to have anxiolytic effects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

OVID data on file

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Development plans

	DEVELOPMENT	POTENTIAL INDICATIONS
 **OV350 anti-convulsant applications**	• Conducting IND-enabling animal toxicology for current IV formulation • Formulating additional oral and injectable formulations • **Expected IND filing for IV: H2 2024**	• Status epilepticus (IV) • Oral (multiple acute and chronic resistant seizure conditions)
 **OV350 anti-psychotic applications**	• Conducting further animal disease models • Oral formulation and toxicology ongoing • Characterizing additional KCC2 activator compounds	• Psychosis • Schizophrenia • Depression

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Why Ovid?

- ✓ 7 clinical and regulatory milestones expected within the next 12-15 months[1]
- ✓ Differentiated pipeline
- ✓ Programs with multiple value creating opportunities
- ✓ Eligible for stream of non-dilutive capital if soticlestat is approved and commercialized
- ✓ Potential to partner non-seizure applications for current programs
- ✓ Strong capital base and financial strategy to fund anticipated milestones

1. Includes two soticlestat milestones from Takeda

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