Ovid Therapeutics

Corporate Overview

AUGUST 2023

Disclaimers and forward-looking statements

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 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 including OV329, OV350 and GV101; 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 filing for 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; the potential development and therapeutic opportunity of GV101 and other Rho/Rho associated coiled-coil containing protein kinase 2 inhibitors; and the potential safety, selectivity and potency of GV101 and other ROCK2 inhibitors; the potential use of 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 GV101; the potential timing of Phase 1 and 2 clinical studies for GV101 and the resulting data; 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 potential use of soticlestat or potential commercial success of soticlestat; the duration of the Company's cash runway, and the expectation that it will support the advancement of the Company's pipeline; 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, OV350, GV101 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," "demonstrates," 'observes," "design," "advance," "target," "seek," "expects," 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 Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on August 4, 2023, and in future filings Ovid makes with the SEC. Any forward-looking statements contained in this corporate deck 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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Epilepsy & seizure-related pipeline

of potential 1st –in-class or best-in-class candidates to serve significant unmet need & large addressable markets



Harnessing an emerging scientific revolution in novel small molecules for the central nervous system

pursuing differentiated mechanisms of action (MoAs) and targets implicated in excitability & structural neurological conditions



Eligible for significant financial milestones

due from Takeda surrounding the potential regulatory approval & commercial sales of soticlestat



Cash runway expected into first half of 2025

multiple Phase 1 and preclinical programs with significant opportunity & upside

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Epilepsy market is a significant and growing market

Significant patient need

30 – 40%
of individuals have seizures not controlled with anti-seizure medicines[1]

47%
of patients take 5 medicines on average, demonstrating need for unique, well tolerated anti-seizure mechanisms[2]

Supportive of predictive development

Validated & emerging targets cause neuronal hyperexcitability

Small molecules that can cross the blood-brain barrier

Predictive, clinically-translatable seizure models

Hard endpoints (seizures) and biomarkers

Addressable patient population

50 million
people living with epilepsy worldwide[3]

3 million
adults and 470,000 children living with epilepsy in US[4]

>$8B
global market[5]

1. Huron Primary Research (11/2019-12/2019)
2. Terman SW, Aubert CE, Hill CE, et al. Polypharmacy in patients with epilepsy: a nationally representative cross-sectional study. *Epilepsy Behav.* 2020;111:107261.
3. WHO Fact Sheet. Accessed March 12, 2023: https://www.who.int/news-room/fact-sheets/detail/epilepsy#:~:text=Globally%2C%20an%20estimated%205%20million,as%20139%20per%20100%20000.
4. CDC Epilepsy data: https://www.cdc.gov/epilepsy/data/index.html
5. Global Data Report, Epilepsy: Global Drug Forecast and Market Analysis to 2030 – Forecast Update

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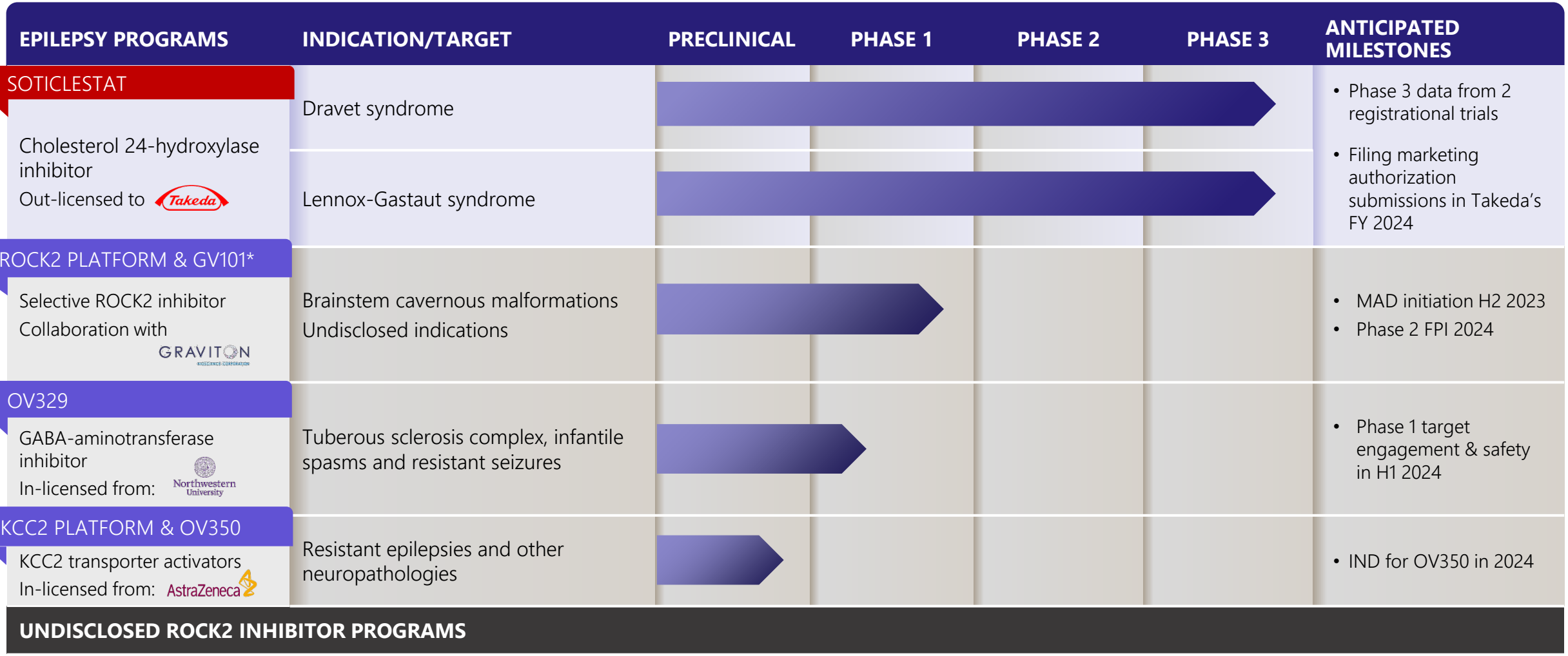
Differentiated epilepsy & seizure pipeline

First-in-class or best-in-class mechanisms of action



*Graviton is conducting development of GV101 through Phase 2 and such development will be directed by a Joint Development Committee that includes members of both Graviton and Ovid.

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Potential near-term milestones

+ Strong balance sheet

$96.5M — in cash, cash equivalents and marketable securities[1]

70.6M — shares of common stock outstanding[2]

Current cash runway expected into first half of 2025

Potential for a non-dilutive capital stream from Takeda

+ Veteran team

with a track record of developing and commercializing blockbuster medicines

+ Differentiated epilepsy franchise

- 3 small molecule programs (4th program sold to Takeda and we retain significant financial interest)
- Potential 1st-in-class or potential best-in-class medicines
- Novel, complementary mechanisms of action for the potential treatment of epilepsy & seizures
- Significant unmet need

+ Potential upcoming events

- Initiate multiple ascending dose study to evaluate a pivotal formulation for GV101
- Data from a Phase 3 pivotal study of soticlestat in Lennox-Gastaut syndrome (SKYWAY); conducted by Takeda
- Data from a Phase 3 pivotal study of soticlestat in Dravet syndrome (SKYLINEY); conducted by Takeda
- Phase 1 results for OV329 assessing target engagement, safety profile & pharmacokinetics
- Anticipated submission of IND for OV350
- Series of potential country regulatory filings for soticlestat (conducted by Takeda) - Following regulatory submissions in Takeda's FY 2024

1 As of 6/30/23
2 As of 6/30/23, on an as if converted basis
3 Clinical Trials.gov as of 6/15/23

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Team of disciplined operators & value creators



Jeremy Levin D. Phil, MB BChir
Chairman, CEO



Manoj Malholtra, M.D.
Chief Medical Officer



Zhong Zhong, Ph.D.
Chief Scientific Officer



Meg Alexander
Chief Strategy Officer



Jeffrey Rona
Chief Business & Financial Officer



Jason Tardio, MBA
Chief Operating Officer



Tom Perone, MBA, J.D.
General Counsel, Corporate Secretary, Chief Compliance Officer

- **Transformative transactions**
  Invested ~$83M in soticlestat, which secured $196M in upfront payment & potential milestones of up to $660M and tiered royalties of up to 20%
- **Track record of expedited development**
  Completed soticlestat Phase 2 six months ahead of schedule and under budget
- **Experience from 25+ launches, including 4 CNS blockbusters**
- **Deep knowledge from development & launch of multiple epilepsy medicines**

Management team contributed to development & launch:

TYSABRI (natalizumab)
Ztalmy (ganaxolone) oral suspension 50 mg/mL
GILENYA (fingolimod) capsules 0.5mg
Acthar GEL (repository corticotropin injection) 80 U/mL
Revlimid (lenalidomide) capsules
SPRYCEL dasatinib 100 mg tablets
Fintepla (fenfluramine) CV 2.2 mg/mL oral solution
Brineura (cerliponase alfa)
SPINRAZA (nusinersen) injection 12 mg/5 mL
Tecfidera (dimethyl fumarate) delayed-release capsules 240mg
Fycompa (perampanel)

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REPURCHASED BY TAKEDA

OVERVIEW: soticlestat

Potential first-in-class cholesterol 24-hydroxylase inhibitor for treatment resistant epilepsies[1]

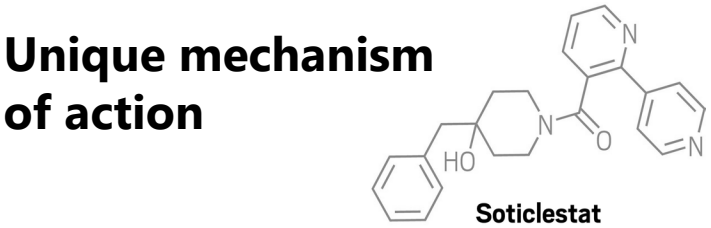
Being studied in two pivotal, Phase 3 trials

(conducted by Takeda):

- Dravet syndrome (DS)
- Lennox-Gastaut syndrome (LGS)

Designed to reduce seizure susceptibility & improve seizure control[2]

Unique mechanism of action



Soticlestat

- Reduces glutamatergic signaling & reduced inflammation[1,3]
- Dose dependent response[1,3]

Encouraging safety, tolerability & seizure reduction in Phase 2 trials[2]

- Main adverse events for soticlestat over placebo are lethargy/somnolence and constipation
- No anticipated monitoring needs

Potential to be used in early treatment lines[2]

- Based upon promise of seizure control efficacy and tolerability profile observed in clinical trials
- No monitoring anticipated for soticlestat as is required for other new anti-seizure medicines[4]

Takeda targets filing for regulatory approvals in its fiscal year 2024[4]

1. Nishi T, et al. AAN 2018.
2. 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
3. Salamone A, et al. ECE 2018 [4] FINTEPLA prescribing information label, pages 5-8.
4. Takeda's FY2022 Q2 Earnings Announcement dated October 27th, 2022.

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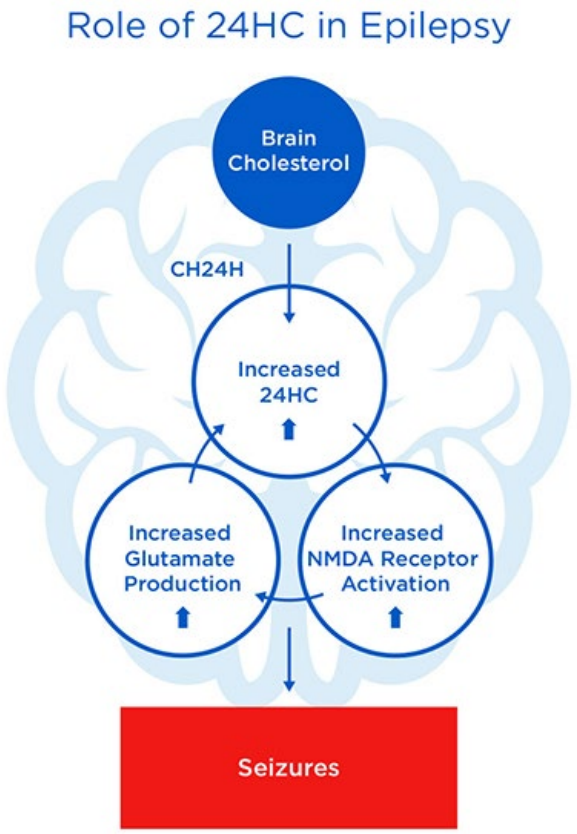
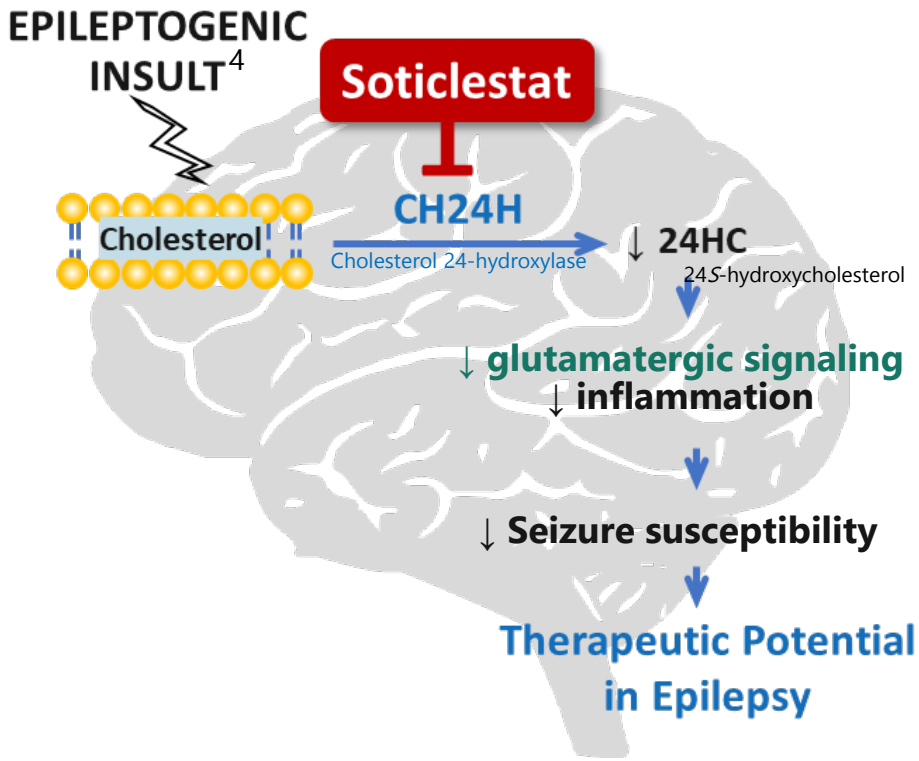
Cholesterol 24-hydroxylase inhibition



Soticlestat inhibits CH24H, resulting in a dose-dependent reduction in 24HC levels[1]

24HC reduction ameliorates over-activated glutamatergic signaling and inflammation[1,2]

Thus, soticlestat has the potential to reduce seizure susceptibility and improve seizure control[2,3]



Soticlestat may provide benefit through mechanisms that are not targets of conventional ASMs [1,2]

1. Nishi T, et al. Sci Rep (2020) 10: 17081
2. Salamone A, et al. Poster presented at: ECE 2018.
3. Nishi T, et al. Neurology (2018) 15 Suppl: P5.264 (Poster at: AAN 2018)
4. Sodero. A.O et al. EMBO (2012) 31: 1764-73. Illustration source: Takeda

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Soticlestat profile:
May support use as potential 1st choice for adjunctive therapy

Potential for:

- Competitive seizure reduction efficacy with approved anti-seizure medicines (ASMs)
  - Utility demonstrated in multiple seizure types[1]
- Preferable safety and tolerability profile comparable to placebo[2]
  - No anticipated monitoring
  - No anticipated black box warning such as other ASMs
- Ease of adding in polypharmacy regimen
  - No known drug-drug interactions[2]
- Benefit in non-seizure symptoms as measured by caregiver impression[2]
- Life cycle management opportunity other refractory seizure types

SUGGESTED PREVALENT POPULATION[3]



Lennox-Gastaut*	**69,000**	**50,500**	**18,300**
Dravet	**19,100**	**17,600**	**6,400**

1. Efficacy of Soticlestat Treatment by Seizure Type in Patients with Dravet Syndrome or Lennox–Gastaut Syndrome in a Phase 2, Randomized, Placebo-Controlled Study (ELEKTRA), Presented at AAN 2023
2. 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
3. Research conducted by LEK on behalf of Ovid Therapeutics

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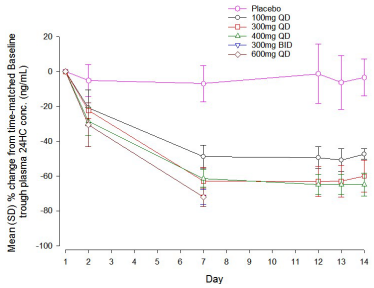
Soticlestat profile appears highly consistent across development program

	1 Preclinical	2 Phase 1	3 Phase 1b/2a	4 Phase 2	5 OLE	6 Phase 3
FINDINGS	**Demonstrated Neuroprotection** • Protection against glutamate excitotoxicity[1] • Preserved cognitive functions[1] **Reduced total seizure burden** • Delayed acquisition of kindling seizures[1] • Prevented progression of spontaneous recurrent seizures[1] • Increased seizure threshold against environmental stimuli[1] **Biomarker for optimal target engagement** **Improved survival** • Protection from seizure-related mortality[1]	**4 studies in healthy volunteers** • Target engagement confirmed & correlated to human dosing regimen[2] • Dose-dependent decrease of plasma 24HC concentrations 	**DEE basket trial** • Favorable safety profile & generally well tolerated • -36% median change from baseline in total seizures per 28 days[3] • Reduced mean 24HC levels and correlated with a decrease in seizure frequency[3] • Mean 24HC levels decreased 81% from baseline to Day 85[3]	**2 studies in 4 indications** *(CDD, DUP15Q, DS, LGS)* • Statistically significant reduction in median convulsive seizure in DS[4] • Numeric reduction in seizure frequency in LGS[4] • Generally safe and well tolerated, consistent with previous studies[4] • Encouraging signal in CDKL5[5]	**Open Label Extension** *(DS, LGS, CDD)* • Reduced seizure frequency up to 2 years[6] • Showed sustained reduction in convulsive seizures in DS[6] • Sustained reduction drop seizures in LGS[6]	**Pivotal Phase 3 trials** *(LGS, DS)* • Trial completion estimated for 1H 2024 for LGS • Trial completion estimated for 1H 2024 for DS
N =		N = 108	N = 18	N = 148		N = 376

1 Anticonvulsive properties of soticlestat, a novel cholesterol 24-hydroxylase inhibitor. Nishi T, Metcalf CS, Fujimoto S, Hasegawa S, Miyamoto M, Sunahara E, Watanabe S, Kondo S, White HS. Epilepsia. 2022 Mar 22. doi: 10.1111/epi.17232 **2**. Yin W, Facius A, Wagner T, et al. Population pharmacokinetics, enzyme occupancy, and 24S-hydroxycholesterol modeling of soticlestat, a novel cholesterol 24-hydroxylase inhibitor, in healthy adults. Clin Transl Sci. 2023;00:1-14. doi:10.1111/cts.13517 **3.** A phase 1b/2a study of soticlestat as adjunctive therapy in participants with developmental and/or epileptic encephalopathies. Halford JJ, Sperling MR, Arkilo D, Asgharnejad M, Zinger C, Xu R, During M, French JA. Epilepsy Res. 2021 Aug;174:106646. doi: 10.1016/j.eplepsyres.2021.106646. **4.** Hahn CD, Jiang Y, Villanueva V, Zolnowska M, Arkilo D, Hsiao S, Asgharnejad M, Dlugos D. 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 Oct;63(10):2671-2683. doi: 10.1111/epi.17367. Epub 2022 Aug 4. PMID: 35841234; PMCID: PMC9804149 **5.** Demarest S, Jeste S, Agarwal N, et al. Efficacy, safety, and tolerability of soticlestat as adjunctive therapy for the treatment of seizures in patients with Dup15q syndrome or CDKL5 deficiency disorder in an open-label signal-finding phase 2 study (ARCADE). Epilep & Behav. 2023;142:109173. **6.**. 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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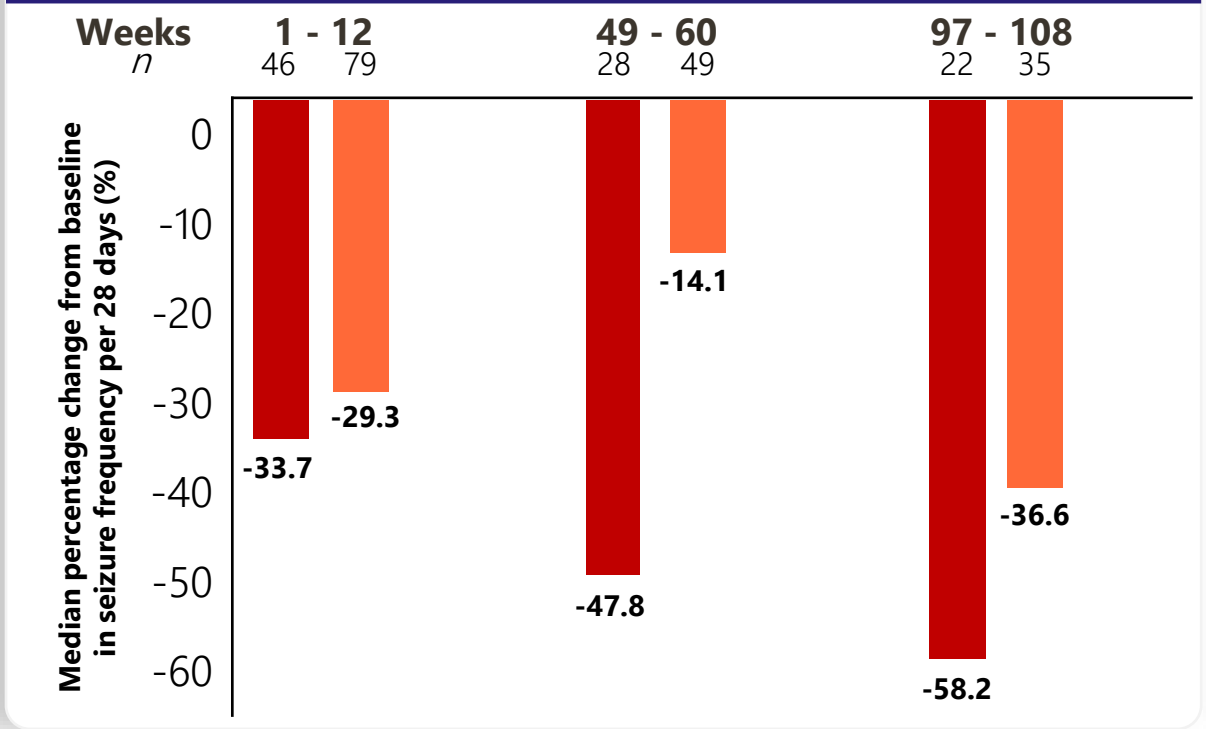
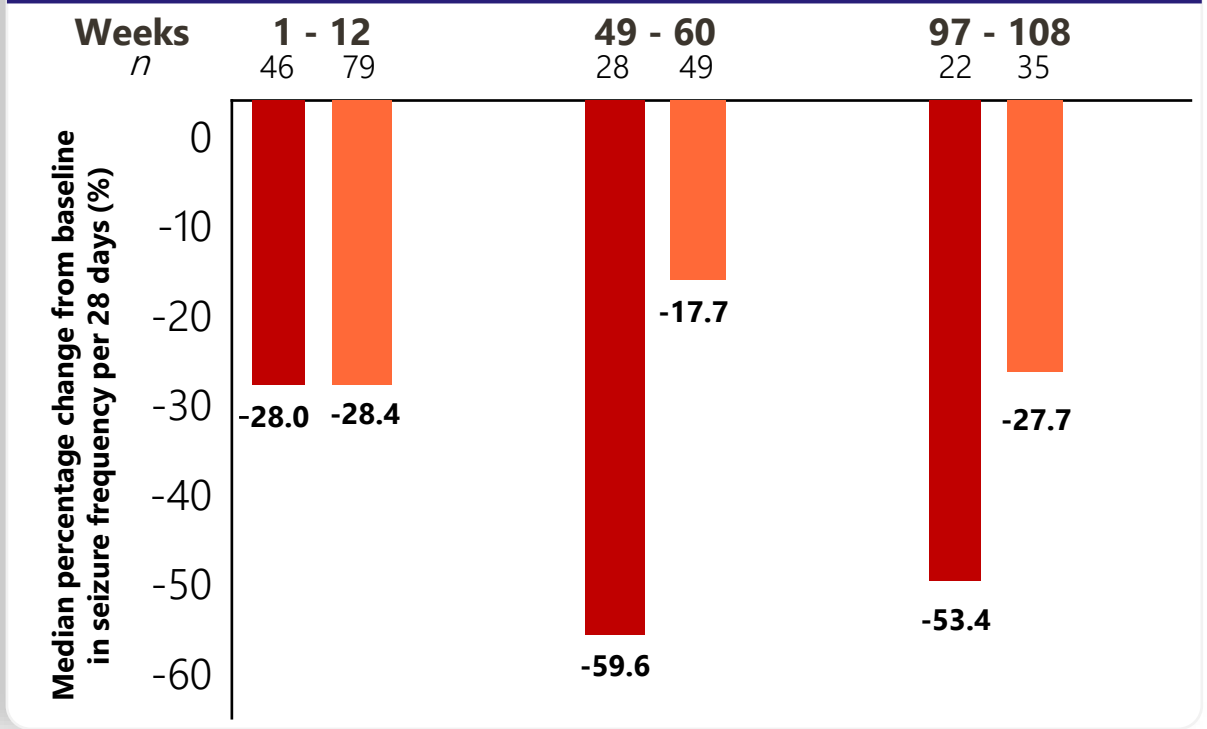
OLE (ENDYMION1): Sustained seizure reduction shown in DS & LGS patients up to 2 years

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

SOURCE: 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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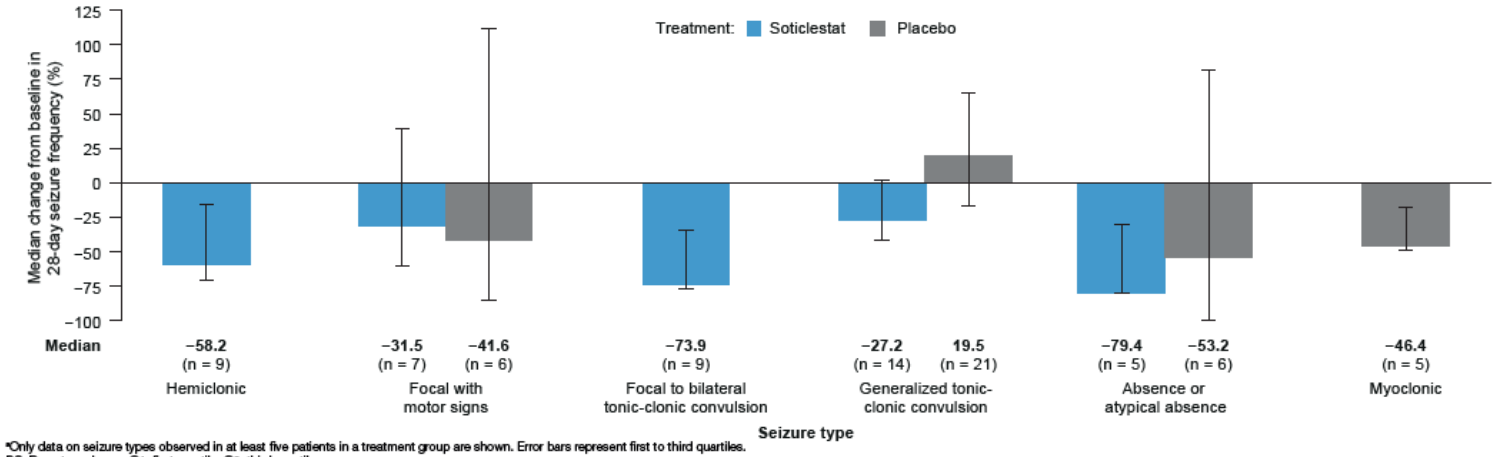
Phase 2 (ELEKTRA): Post hoc analysis indicates soticlestat potential in reducing frequency of multiple seizure types

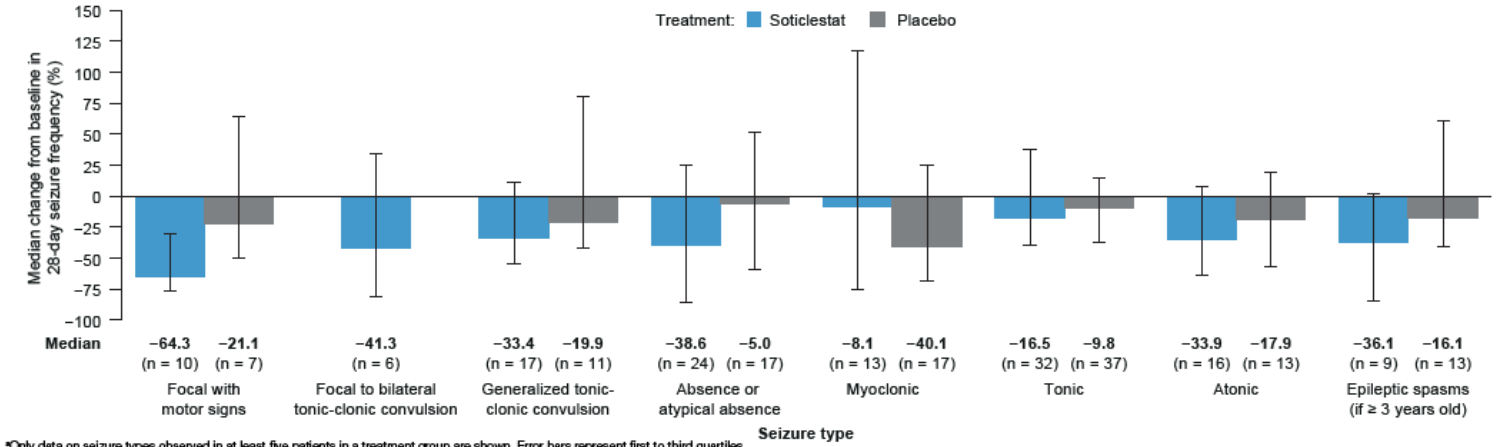
- Post hoc analysis conducted of DS & LGS patients in Phase 2, ELEKTRA study
- Soticlestat was numerically superior to placebo in all but two seizure types over the full 20-week treatment period
- DS patients experienced % change in seizure frequency across:
  - Hemiclonic seizures
  - Focal to bilateral tonic-clonic seizures
  - Generalized tonic-clonic seizures
  - Absence or atypical absence seizures
- LGS patients experienced % change in seizure frequency across:
  - Focal seizures with motor signs
  - Focal to bilateral tonic-clonic seizures
  - Generalized tonic-clonic seizures
  - Absence seizures
  - Atonic seizures
  - Epileptic spasms

Figure 1. Median (Q1, Q3) percentage change in seizure frequency from baseline over the full 20-week treatment period in patients with DS.[a]



[a]Only data on seizure types observed in at least five patients in a treatment group are shown. Error bars represent first to third quartiles.
DS, Dravet syndrome; Q1, first quartile; Q3, third quartile.

Figure 2. Median (Q1, Q3) percentage change in seizure frequency from baseline over the full 20-week treatment period in patients with LGS.[a]



[a]Only data on seizure types observed in at least five patients in a treatment group are shown. Error bars represent first to third quartiles.
LGS, Lennox–Gastaut syndrome; Q1, first quartile; Q3, third quartile.

SOURCE: Efficacy of Soticlestat Treatment by Seizure Type in Patients with Dravet Syndrome or Lennox–Gastaut Syndrome in a Phase 2, Randomized, Placebo-controlled Study (ELEKTRA), Presented at AAN 2023: https://www.aan.com/MSA/Public/Events/AbstractDetails/53067

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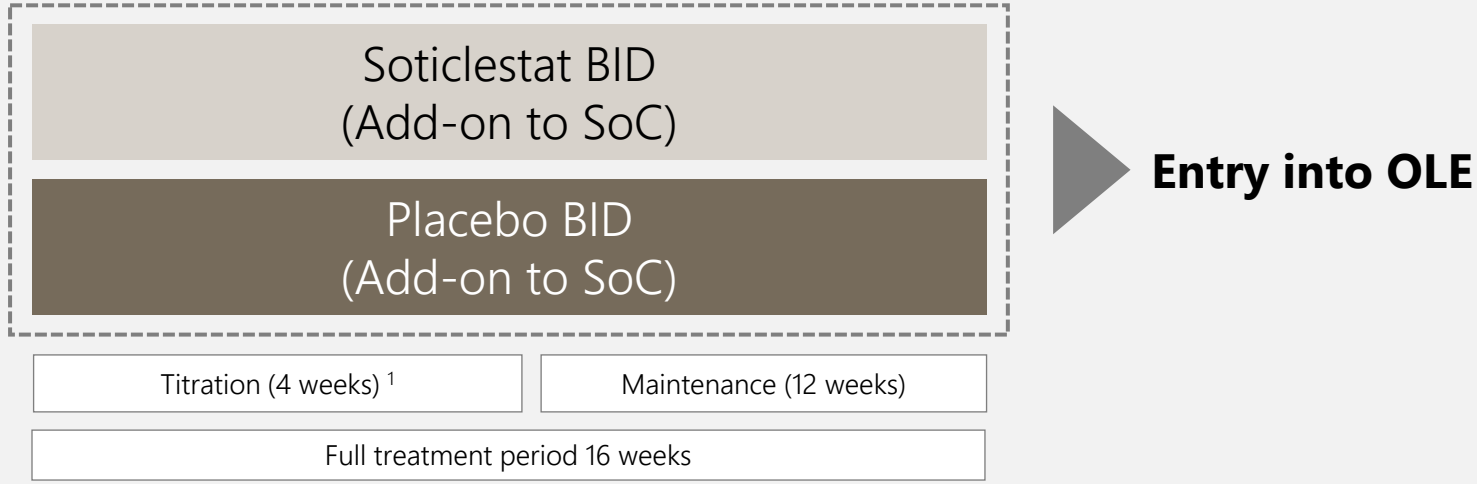
Ongoing Phase 3 placebo-controlled studies in Dravet & Lennox-Gastaut syndromes

soticlestat

Trials currently being conducted by Takeda

SKYLINE: DS N = 142

SKYWAY: 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

[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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Soticlestat agreement with Takeda holds value of up to $856M[1], creating a potential non-dilutive cash stream

Invested ~$26M upfront & $57M in clinical development

2021	2025*	Est. 2025 and later
Upfront payment • All Ovid financial obligations for soticlestat are terminated	**Expected regulatory decision milestone(s)** • Takeda funding comprehensive LGS and DS trials • Soticlestat is leading neuroscience Phase 3 program for Takeda[2]	**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	

ROYALTY & MILESTONES TO FUND PIPELINE & BUSINESS DEVELOPMENT

Estimated timing based on Takeda disclosure that it anticipates regulatory filings in its fiscal year 2024.

[1] $856M includes the $196M already received as an upfront payment in 1H 2021
[2] Takeda Consolidated Development Pipeline by Phase Presentation. Accessed November 2022.

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IN COLLABORATION WITH GRAVITON

OVERVIEW: GV101 & ROCK2 inhibitor library

Potent, highly selective inhibitors of Rho/Rho associated coiled-coil containing protein kinase 2 (ROCK2) for cerebral cavernous malformations (CCM)[1]

GV101, best-in-class potential

- More selective for ROCK2 than Rezurock,® REDX10843, NRL-1049[1,2]
- Well characterized safety profile (2 Phase 1 studies)
- Blood-brain barrier penetrant[3]

Completed Phase 1 study (in nano-suspension formulation)

- Supportive preclinical safety profile & toxicology
- Completed dosing of Phase 1 SAD/MAD in China (nano-suspension)
- Modeled therapeutic plasma levels have been shown to be generally well tolerated
- Cmax values up to 2 µ/ML

Novel mechanism; rationale in multiple CNS indications

- ROCK2 is a signaling pathway that acts on actin cytoskeletal processes, cellular to extracellular matrix adhesion, fibrosis, autoimmunity
- Fit for CNS conditions with endothelial dysfunction & autoimmune MoAs

Regulatory precedent

- Prior ROCK2 regulatory approvals (Rezurock® in GVHD)
- Potential to leverage orphan and/or accelerated approval programs

Seek to evaluate desired pivotal formulation (gel capsule) in a Phase 1 MAD study in H2 2023

1 Based upon animal models | 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/en | Graviton data on file

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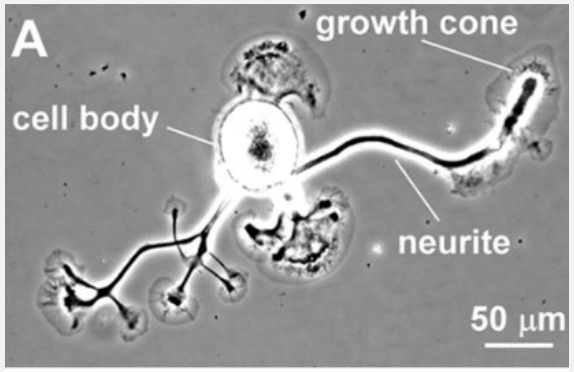
ROCK2 inhibition in the CNS

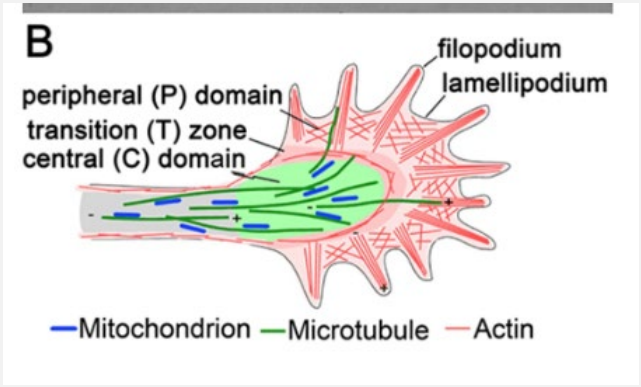
ROCK1 and ROCK2 are highly homologous isoforms of the ROCK protein kinase that function differently

- ROCK inhibitors to-date have relatively equipotent inhibition against ROCK1 and ROCK2 isoforms
- Toxicity is associated with pan-ROCK inhibition, notably hypotension

In the CNS, ROCK2 inhibition has the potential to:

- Promote growth and the cell-to-cell junction formation that is critical to endothelial function[1,2]
- In neurons, is associated with increased neurite growth and decreased cell death







A – B. Miller KE, Suter DM. An Integrated Cytoskeletal Model of Neurite Outgrowth. Front Cell Neurosci. 2018 Nov 26;12:447. Adapted from O'Toole et al. (2015) with permission from Elsevier
C. Gibieža P, Petrikaitė V. The regulation of actin dynamics during cell division and malignancy. Am J Cancer Res. 2021 Sep 15;11(9):4050-4069.
1. McKerracher L.; et. al. Translational Stroke Research (2020) 11:365-376
2. Borikova AL, Dibble CF, Sciaky N, Welch CM, Abell AN, Bencharit S, Johnson GL. Rho kinase inhibition rescues the endothelial cell cerebral cavernous malformation phenotype. J Biol Chem. 2010 Apr 16;285(16):11760-4. doi: 10.1074/jbc.C109.097220.

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GV101 1st intended indication:

Brainstem cavernous malformations

GV101 — **A potent and highly selective inhibitor of ROCK2 for potential treatment of lesions located in the brainstem of people with cavernous malformations**[1]

Why CCM?

- Mechanistic rationale for reversing hyperactivity of ROCK; restoring barrier function and endothelial cell junctions[2]
- Animal model proof-of-concept in ROCK2 inhibitors[3]
- Unmet need; rare, acute disease with no approved therapy
- Potential to gain POC with subset prior to a larger registrational trial
- Will pursue measurable endpoints (radiographic)
- Possibility of accelerated path to market

Large population with great need

Total patients (prevalence)
1.6M[4]

CCM patients with symptoms
960K[5]

Brainstem Involvement
~190K[6]

1. Ovid data on file | 2. 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: | 3 McKerracher L.; et. al. Translational Stroke Research (2020) 11:365-376 | 4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6924279/pdf/nihms-1059977.pdf | 5. https://www.ncbi.nlm.nih.gov/books/NBK1293/ | 6. Otten P, Pizzolato GP, Rilliet B, Berney J. [131 cases of cavernous angioma (cavernomas) of the CNS, discovered by retrospective analysis of 24,535 autopsies]. Neurochirurgie. 1989;35(2):82-3, 128-31.

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Brainstem 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]

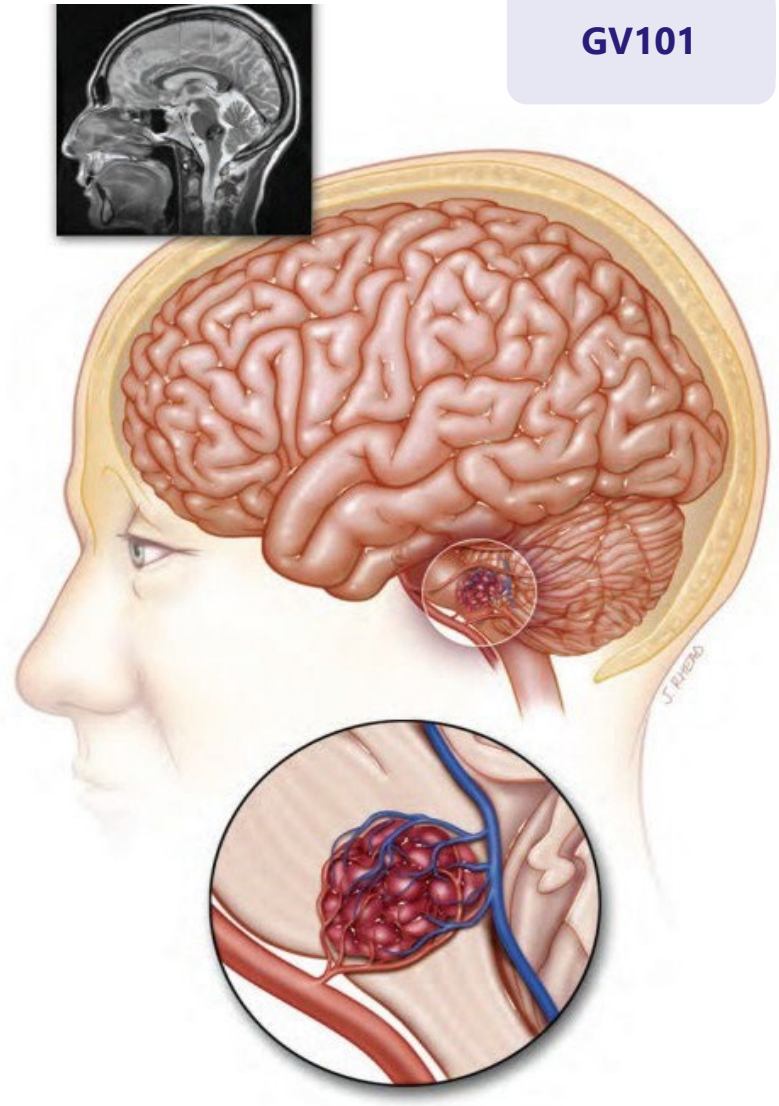

Image attribution: Brainstem angioma from Alliance to Cure Cavernous Malformation

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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ROCK2 inhibitor initial development strategy

1. **Demonstrate CNS penetration and characterize safety**
2. **MAD study to confirm pivotal formulation**
3. **Proof-of-concept demonstration in high-need subset**
4. **Pivotal study (Brainstem or symptomatic patients)**

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OVERVIEW:

OV329

A potential best-in-class GABA-aminotransferase inhibitor for treatment of rare adult & pediatric epilepsy disorders

OV329's enhanced potency may deliver:

- Potential increased seizure reduction efficacy
- Potential improved safety profile (better ocular safety profile)
- Potential preferred dosing

Demonstrated anti-seizure activity in 6 separate animal models

Multiple possible applications:

- Seizures associated with tuberous sclerosis complex (TSC)
- Infantile spasms
- Conditions with refractory seizures

Phase 1 study ongoing

- Findings including potential indicator of efficacy & safety expected H1 2024

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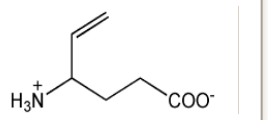
A potent, next-generation GABA-AT inhibitor

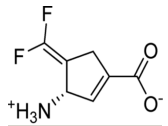
OV329 — **Believed to act upon a validated anti-seizure target to increase GABA and reduce neuronal hyperexcitability**

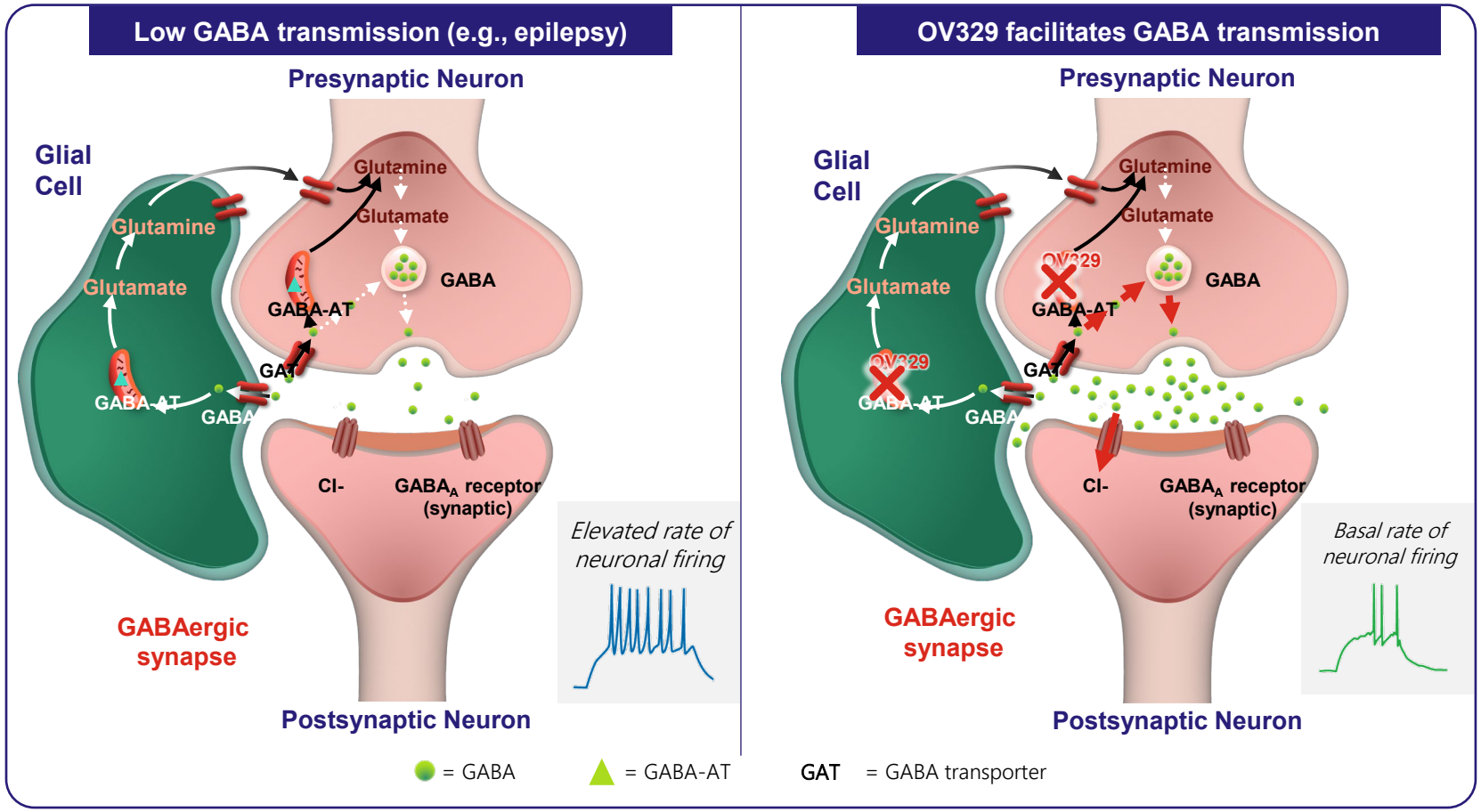
- More potent than vigabatrin in preclinical testing
- Potentially improved safety profile
- Anticipated lower dosing than vigabatrin will be needed

Vigabatrin



OV329





SOURCE:
[1]Juncosa, JI et al. *J. Am Chem. Soc.* 2018;140(6):2151-2164;
J Med Chem. 2012 Jan 26; 55(2): 567–575
J Am Chem Soc. 2018 Feb 14; 140(6): 2151–2164
J. Tsai, EILAT 2023 presentation

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Need for next-generation GABA-AT inhibitors

Sabril (vigabatrin) is only approved GABA-AT inhibitor

- Approved in 2009
- 1st line treatment for certain forms of infantile spasms, including seizures associated with tuberous sclerosis complex[1]
- Effective seizure reduction, but no therapeutic window[2]
- Post-approval, use of vigabatrin was associated with progressive visual field loss from retinal toxicity[3]
  - Deterred use
  - REMS

Significant market opportunity



Sabril peak sales in U.S.
(Not representative of global sales)[4]

Underserved patient populations

Prevalence: Tuberous sclerosis complex

~1 in 6,000 live births[5,6]



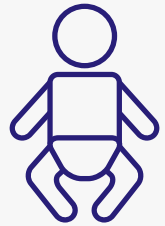
As many as 2 million people worldwide are believed to have disorder

~40,000 to 80,000 people in the U.S. have TSC

Seizures are the most common neurological features of TSC (occur in ~85%)[7]

Prevalence: Infantile spasms
1.6-4.5 cases per 10,000 live births in the U.S.

~2,000 to 2,500 new cases in U.S. per year[8]



[1] Pesaturo KA, Spooner LM, Belliveau P. Vigabatrin for infantile spasms. Pharmacotherapy. 2011 Mar;31(3):298-311. doi: 10.1592/phco.31.3.298. PMID: 21361740.
[2] Maguire et al., 2010; Epilepsia, 51(12):2423–2431, 2010
[3] BMJ 1997;314:180–181
[4] IMS sales of oral solution vigabatrin 2017

[5] Osborne, JP et al. *Lancet.* 2000;355(9216):1698 P;615:125
[6] Hong, CH et al. *Br J Dermatol.* 2016;174(6):1282-1289
[7] Kingswood, JC et al. *Orphanet J Rare Dis.* 2017;12(1):2
[8] Wheless, JW et al. *BMC Pediatr.* 2012;12:108;

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Six preclinical models reaffirm OV329 seizure reduction activity, including resistant seizure models[1]

	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 (e.g. 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	—	—	+	+	+	+	+	+

1. Ovid data on file

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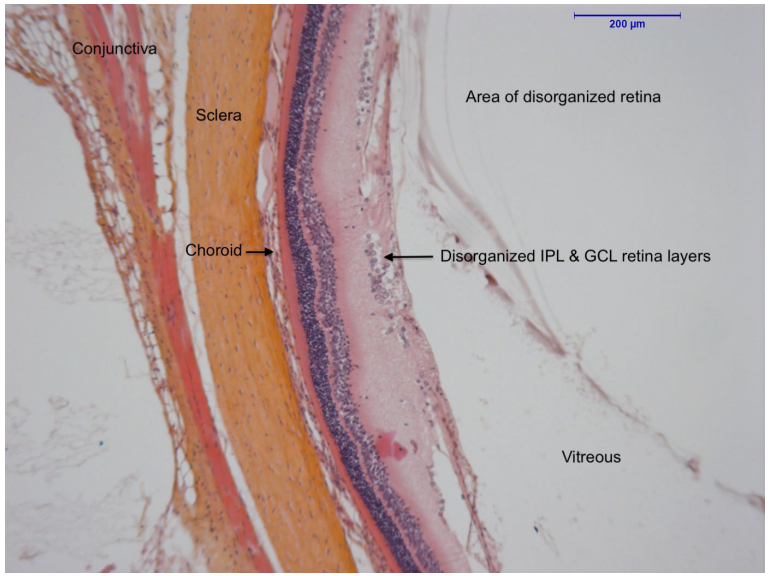
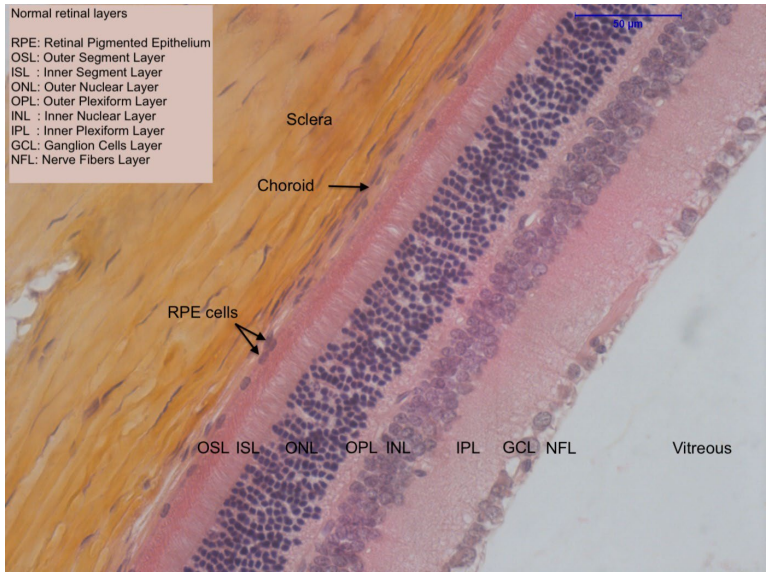
No ocular effects seen following chronic exposure with OV329 (3 mg/kg)

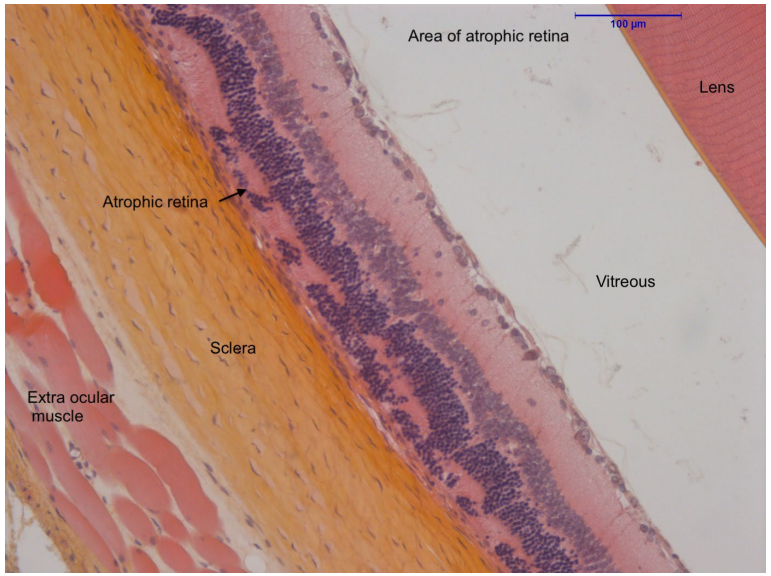
Vehicle



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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Ongoing Phase 1 study

Design
Single (Part 1) and multiple (Part 2) ascending dose studies gated by cohort

Conducted at Duke University School of Medicine

Healthy volunteers (6 active; 2 placebo)
8 volunteers per cohort

Target engagement measured by magnetic resonance spectrometry (MRS)
Levels of target engagement, as measured by MRS, have been correlated to therapeutic effect in prior GABA-AT inhibitors.[1, 2, 3]

Safety, tolerability and pharmacokinetic characterization of single (completed) and multiple doses of OV329

1. Petroff OA, Rothman DL, Behar KL, Collins TL, Mattson RH. Human brain GABA levels rise rapidly after initiation of vigabatrin therapy. Neurology. 1996 Dec;47(6):1567-71. doi: 10.1212/wnl.47.6.1567. PMID: 8960747.
2. Petroff OA, Rothman DL, Behar KL, Mattson RH. Human brain GABA levels rise after initiation of vigabatrin therapy but fail to rise further with increasing dose. Neurology. 1996 May;46(5):1459-63. doi: 10.1212/wnl.46.5.1459. PMID: 8628502.
3. Prescot AP, Miller SR, Ingenito G, Huber RS, Kondo DG, Renshaw PF. In Vivo Detection of CPP-115 Target Engagement in Human Brain. Neuropsychopharmacology. 2018 Feb;43(3):646-654. doi: 10.1038/npp.2017.156. Epub 2017 Jul 25. PMID: 28741622; PMCID: PMC5770752.

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OVERVIEW:

KCC2 portfolio & OV350

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

Innovative KCC2 program

- Consulting support by neuropharmacologist, Prof. Steve Moss
- Chemistry & lead identification conducted by AstraZeneca

Franchise in a program

- OV350 & compound library
- Individual compounds potentially suitable for:
  - IV – acute indications
  - Oral – chronic needs

Novel mechanism of action

- Only known direct KCC2 activator
- Measurable with biomarker (EEG high gamma power spectrum)[1]

Does not induce sedation[1]

in preclinical models

Broad therapeutic potential in rare & common populations including:

- Genetic epilepsies
- Acute epilepsies
- Neuropathic pain
- Behavioral & cognitive conditions

Preclinical proof of concept demonstrated in-vivo & in-vitro in resistant seizures and other CNS indications[1]

[1] Jarvis et al., 2023, Cell Reports Medicine 4, 100957, March 21, 2023

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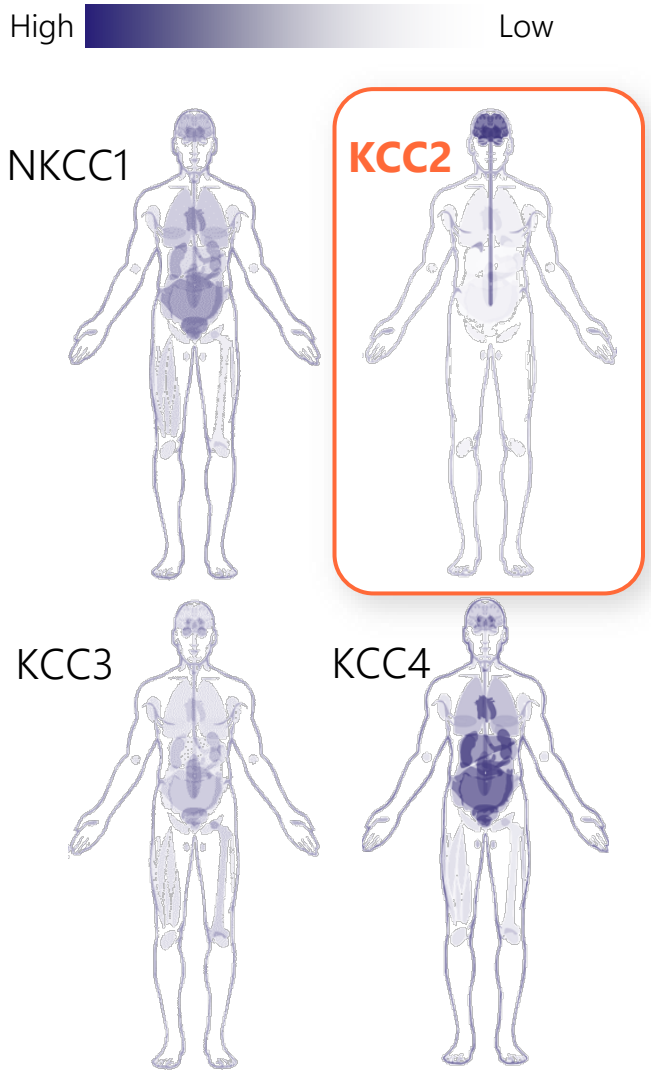
Validated target: KCC2 regulates chloride homeostasis exclusively in the CNS



Regulation of chloride homeostasis in neurons appears to be a validated target for controlling neuronal hyperexcitability

NKCC1 and KCC2 work in opposing fashion to regulate intracellular chloride

KCC2 activation represents a valid target to regulate Cl- levels and presents with several advantages over NCKK1 inhibitors

- NKCC1 transporters are chloride intruders, but expression is systemic, with potential for off-target/non-CNS effects[1]
- Bumetanide is a potent and widely used NKCC1 inhibitor; however, **it is NOT highly brain permeant**
- Human data with bumetanide suggests efficacy in some temporal lobe epilepsies
- Bumetanide can cause extreme fluid loss because of its action on the kidneys and diuretic effect

1. Loscher, W. and Kaila, K, CNS pharmacology of NKCC1 Inhibitors, 2022; Neuropharm:205, 108910

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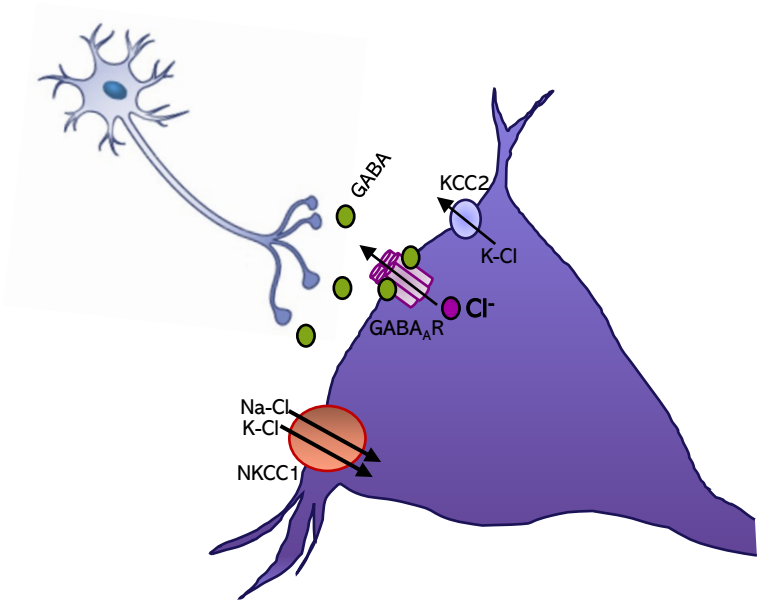
KCC2 activator shown to normalize neuronal excitatory/inhibitory balance

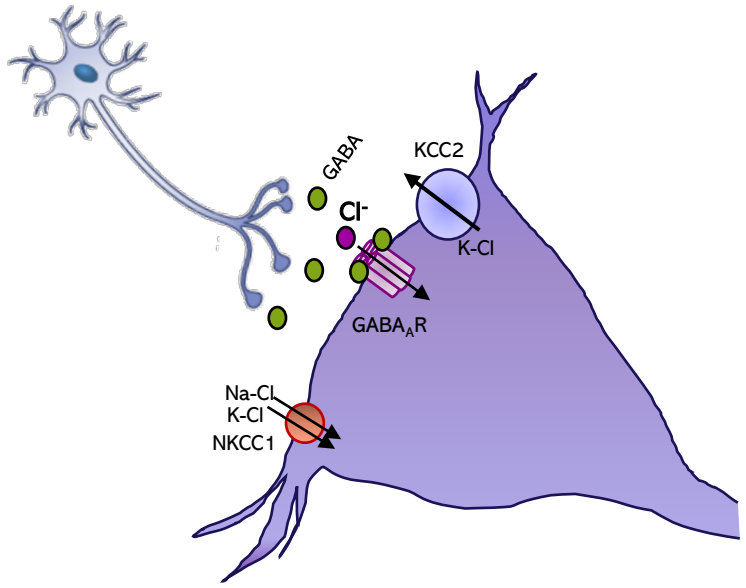
Immature Neuron



High intracellular chloride

GABA → **excitatory**

Mature Neuron

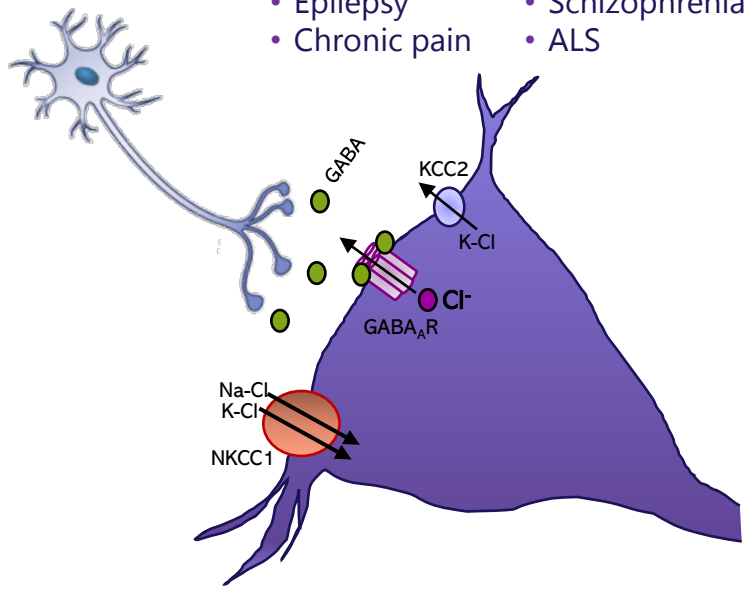


Low intracellular chloride

GABA → **inhibitory**

Pathological conditions

- Epilepsy
- Chronic pain
- Schizophrenia
- ALS



High intracellular chloride

GABA → **excitatory**

Deficits in KCC2 activity have been linked to a variety of neurological disorders

[1] Illustrations adapted from publication by Phan Q. Duy, Miao He, Zhigang He & Kristopher T. Kahle (2020) Preclinical insights into therapeutic targeting of KCC2 for disorders of neuronal hyperexcitability, Expert Opinion on Therapeutic Targets, 24:7, 629-637, DOI: 10.1080/14728222.2020.1762174

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KCC2 is down-regulated & may have applications in several neuro-pathologic indications

Indication	Mechanism of Action	Reference
Epilepsy/seizures	Downregulation and reduced activity of KCC2	Jarvis et al. 2023
Neuropathic pain	Decreased KCC2 surface expression	Hasbargan et al. 2010
Schizophrenia	Downregulation of KCC2 mRNA, mutation	Mohaghghegh et al. 2022
Cognition and sleep	Loss of function and phosphorylation	Andrews et al. 2020
Autism, behavior, neuropsychiatry	Loss of KCC2 function and phosphorylation deficit	Anacker et al. 2020 Moore et al. 2018
Neuronal death after insult, spinal cord injury	Downregulation of KCC2	Boulenguez et al., 2010
ALS and spasticity	Decreased activity and expression of KCC2	Modol et al. 2014
Hyperalgesia	Downregulation of KCC2	Braz et al. 2014 Coull et al. 2003
Pathologic itch	Downregulation of KCC2	Braz et al. 2014
Rett Syndrome	Decreased KCC2 protein expression	Andho-Noda et al. 2016 Hinz et al. 2019
Huntington's disease	Downregulation of KCC2 mRNA	Andrews et al. 2020

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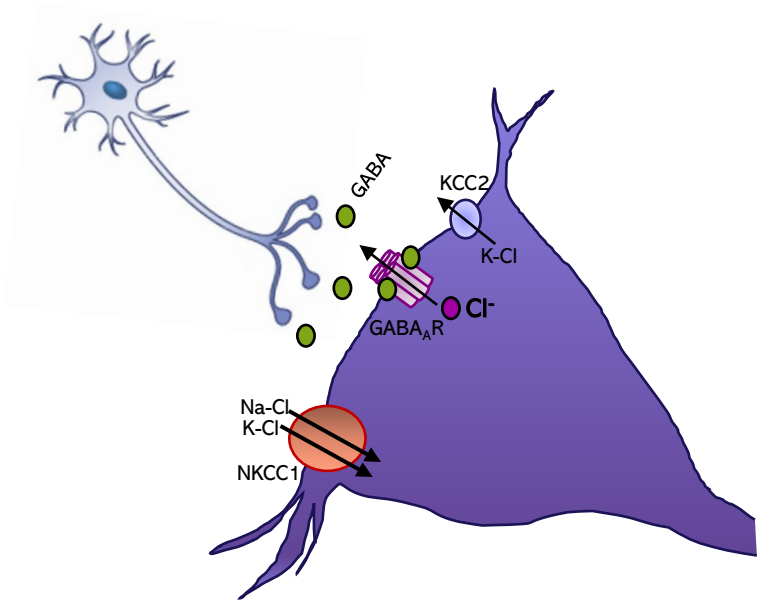
OV350 appears to normalize neuronal excitatory/inhibitory balance

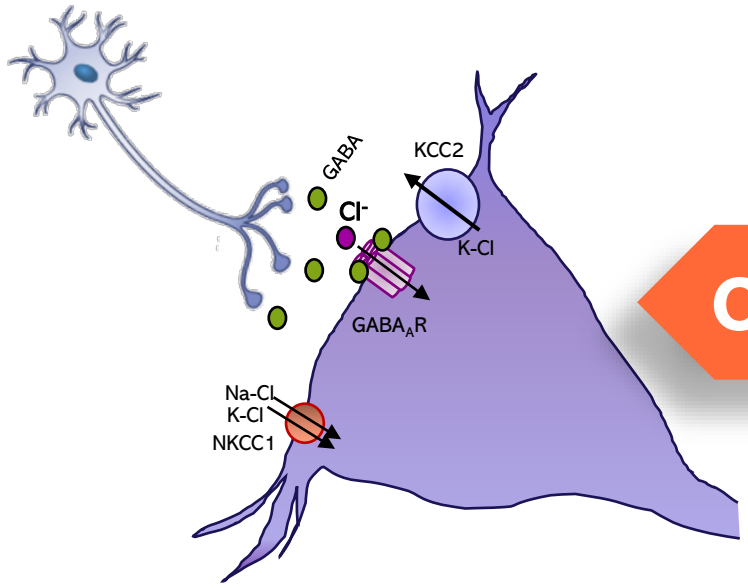
Immature Neuron



High intracellular chloride

GABA → **excitatory**

Mature Neuron



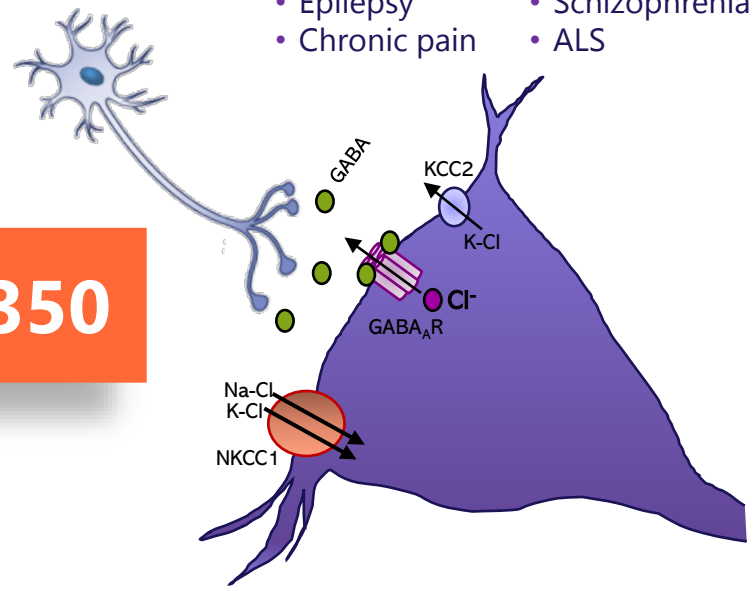
Low intracellular chloride

GABA → **inhibitory**

OV350

Pathological conditions

- Epilepsy
- Chronic pain
- Schizophrenia
- ALS



High intracellular chloride

GABA → **excitatory**

Deficits in KCC2 activity have been linked to a variety of neurological disorders

[1] Illustrations adapted from publication by Phan Q. Duy, Miao He, Zhigang He & Kristopher T. Kahle (2020) Preclinical insights into therapeutic targeting of KCC2 for disorders of neuronal hyperexcitability, Expert Opinion on Therapeutic Targets, 24:7, 629-637, DOI: 10.1080/14728222.2020.1762174

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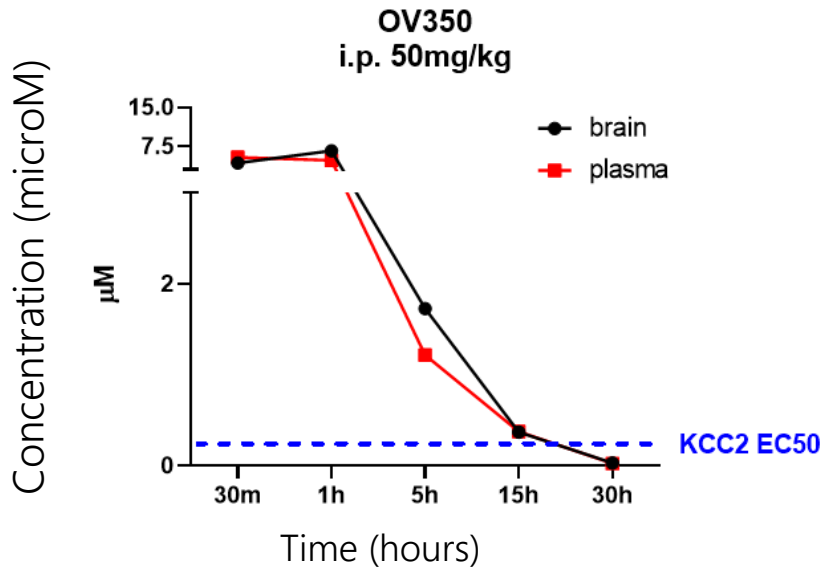
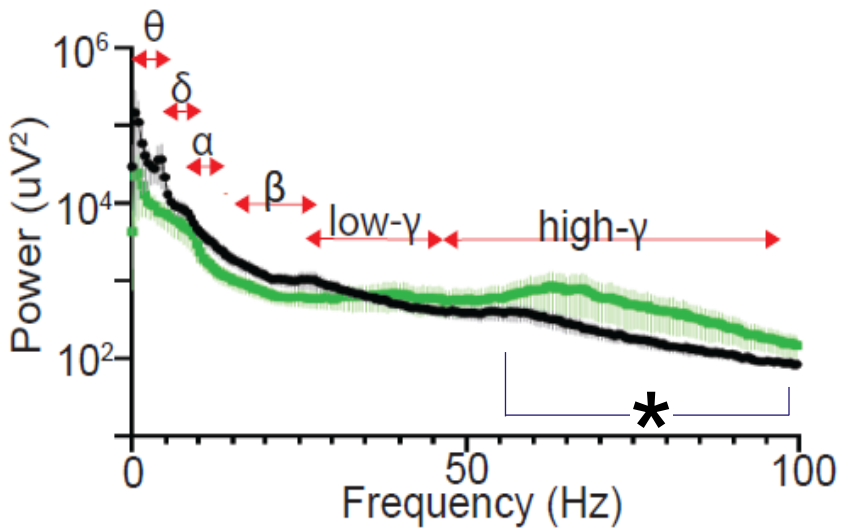
OV350 preclinical models show rapid, stable accumulation in the brain with a translatable pharmacodynamic biomarker

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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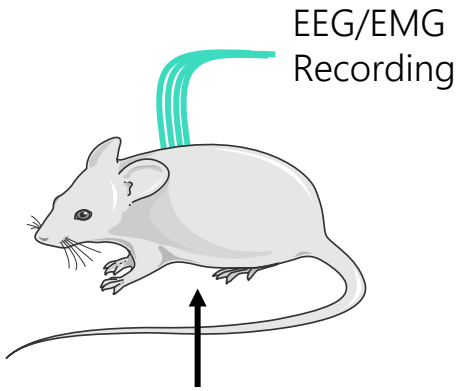
In-vivo studies demonstrate mechanistic proof of concept

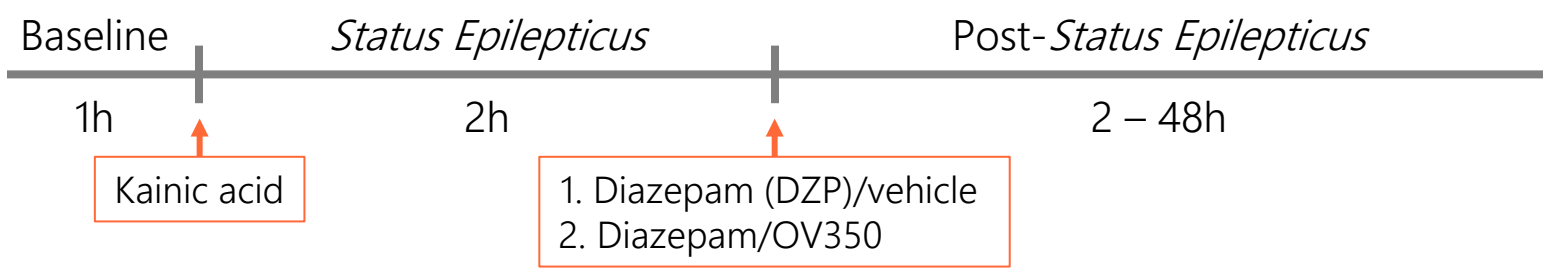
OV350 restores the efficacy of diazepam to terminate "refractory" *Status Epilepticus* in preclinical study

Adult Mouse

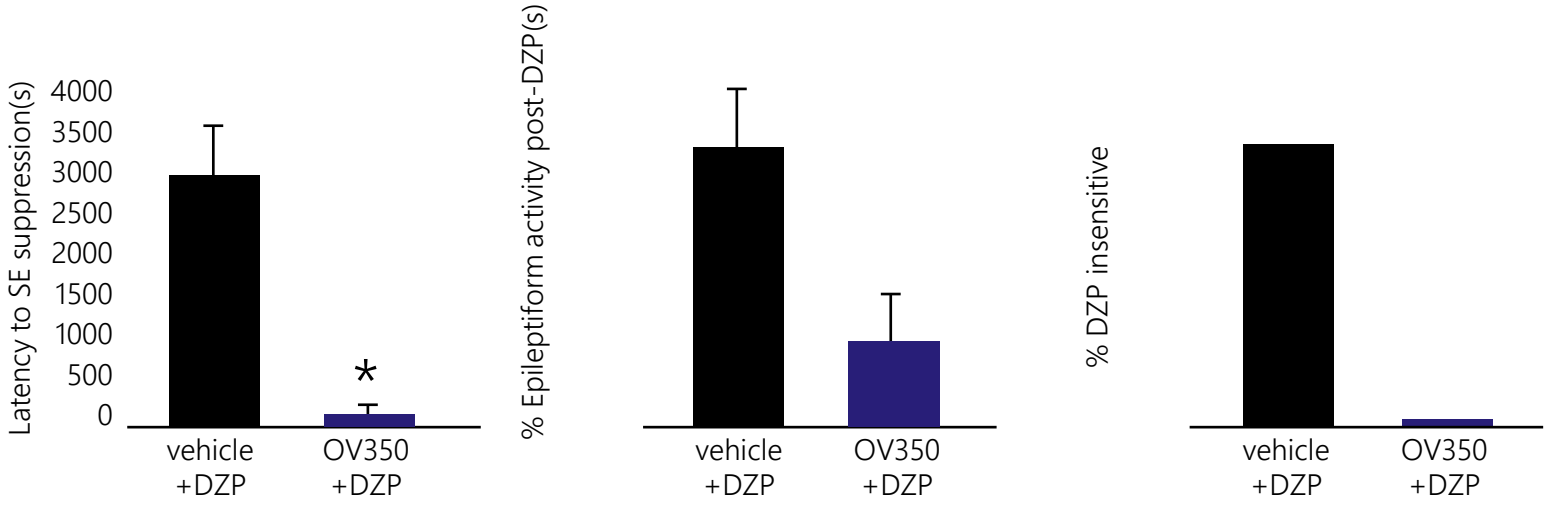


- Potentiating KCC2 activity observed to be well tolerated in-vivo
- Unlike other anticonvulsants, OV350 appears to not induce sedation

Experimental design



Post-treatment EEG analysis



*p<0.05 by academic lab t-test

Source: Jarvis et al., 2023, Cell Reports Medicine 4, 100957, March 21, 2023

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Development focus

Clinically suitable formulation
IV formulation candidate suitable for clinical trials achieved for OV350

Demonstrated anti-seizure activity in iPTZ and kainite status epilepticus models
Publication of findings in *Cell Reports Medicine* March 2023[1]

Characterization efforts of OV350 ongoing in seizure and non-seizure neurological disease models

Further formulation and characterization of additional compounds in KCC2 portfolio ongoing
Efforts seek to achieve oral and IV formulations

KCC2 library represents potential future partnership opportunities
in non-seizure indications

[1] Jarvis et al., 2023, Cell Reports Medicine 4, 100957, March 21, 2023

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Conquering epilepsies & brain disorders with courageous science









