Ovid Therapeutics

CORPORATE PRESENTATION

MAY 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 data readouts 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 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, OV888, 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," "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 Quarterly Report on Form 10-Q filed with the Securities and Exchange Commission (SEC) on May 14, 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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NOVEL BIOLOGICAL TARGETS

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

HARNESSING A SCIENTIFIC REVOLUTION

Applying highly specific small molecules for the central nervous system (CNS)

DIFFERENTIATED PIPELINE

Intended to treat epilepsy & conditions with seizure symptoms

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Strong fundamentals to drive multiple pipeline programs

- 5X 2025 clinical and regulatory milestones from Ovid's pipeline expected by 2025
- Two pivotal Phase 3 readouts for soticlestat expected by or before Sept. 2024
- Eligible for up to $660M of milestones payments and tiered double-digit royalties up to 20% if soticlestat is approved and commercialized[1]
- Non-seizure applications for current programs provide partnering opportunities
- $90.3M cash balance as of March 31, 2024, with anticipated runway into H1 2026

1. Ovid owes Ligand Pharmaceuticals 13% of potential milestone and royalties received from Takeda if soticlestat is approved and commercialized

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Cadence of value-driving events expected over next 12-15 months

PROGRAMS	INDICATION/TARGET	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	ANTICIPATED MILESTONES
ROCK2 PLATFORM & OV888[1] Selective ROCK2 inhibitor Collaboration with: GRAVITON	Cerebral cavernous malformations Undisclosed rare CNS indications					• MAD completion in H1 2024 • Initiating Phase 2 in H2 2024
OV329 GABA-aminotransferase inhibitor	Oral formulation for chronic treatment of epilepsies					• Phase 1 readout in H2 2024
OV329 GABA-aminotransferase inhibitor	IV formulation for acute treatment of seizures					• IND in H2 2024[2]
KCC2 PLATFORM & OV350 KCC2 transporter activator	Resistant epilepsies and other neurological conditions					• IND for OV350 in H2 2024[2]
SOTICLESTAT Cholesterol 24-hydroxylase inhibitor Out-licensed to: Takeda	Dravet syndrome					• Phase 3 data from 2 registrational trials by or before September 2024
	Lennox-Gastaut syndrome					• Filing marketing authorization submissions in Takeda's FY 2024
UNDISCLOSED INDICATIONS OUTSIDE SEIZURES THAT MAY PROVIDE BUSINESS DEVELOPMENT OPPORTUNITY						

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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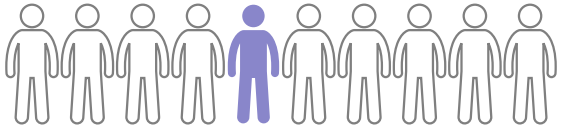
Epilepsy & seizure landscape

Significant populations

Up to 1 in 10

humans will experience a seizure in their lifetime[1]



50 million

living with epilepsy across the globe[1]

3 million

adults living with epilepsy in the US[2]

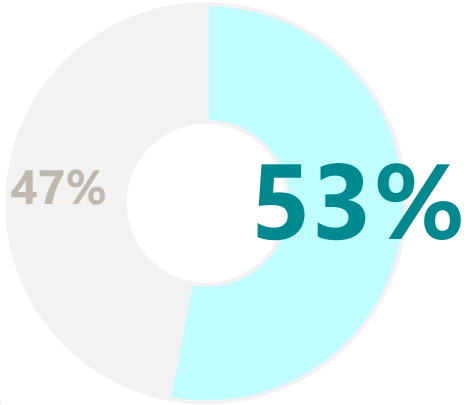
470,000 U.S. children

≤17 years have epilepsy[2]

Deep unmet need & polypharmacy use

Pharmaco-resistant epilepsy common

Seizures controlled by 1 ASM



Pharmaco-resistant epilepsy

seizures not controlled with ≥ 1 ASMs[4]



~Half of patients take 5+ medicines

as part of polypharmacy regimens[3]

Favorable reimbursement

& coverage dynamics
Polypharmacy generally well covered

1. World Health Organization. https://www.who.int/news-room/fact-sheets/detail/epilepsy.
2. Epilepsy fast facts. Centers for Disease Contr Easl and Preventionhttps://www.cdc.gov/epilepsy/about/fast-facts.htm.
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. Zhong J, Tan G, Wang H and Chen Y (2023) Front. Neurol. 14:1153563. doi: 10.3389/fneur.2023.1153563

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Soticlestat

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

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Soticlestat opportunity

POTENTIAL PROFILE

Early line option for patients not well-controlled with 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

STATUS

2 pivotal Phase 3 studies have been completed by Takeda

Indications:

- Lennox-Gastaut syndrome
- Dravet syndrome

Takeda planning for global launch

1. Hahn et al. Epilepsia. 2022; 00: 1– 13. https://doi.org/10.1111/epi.17367

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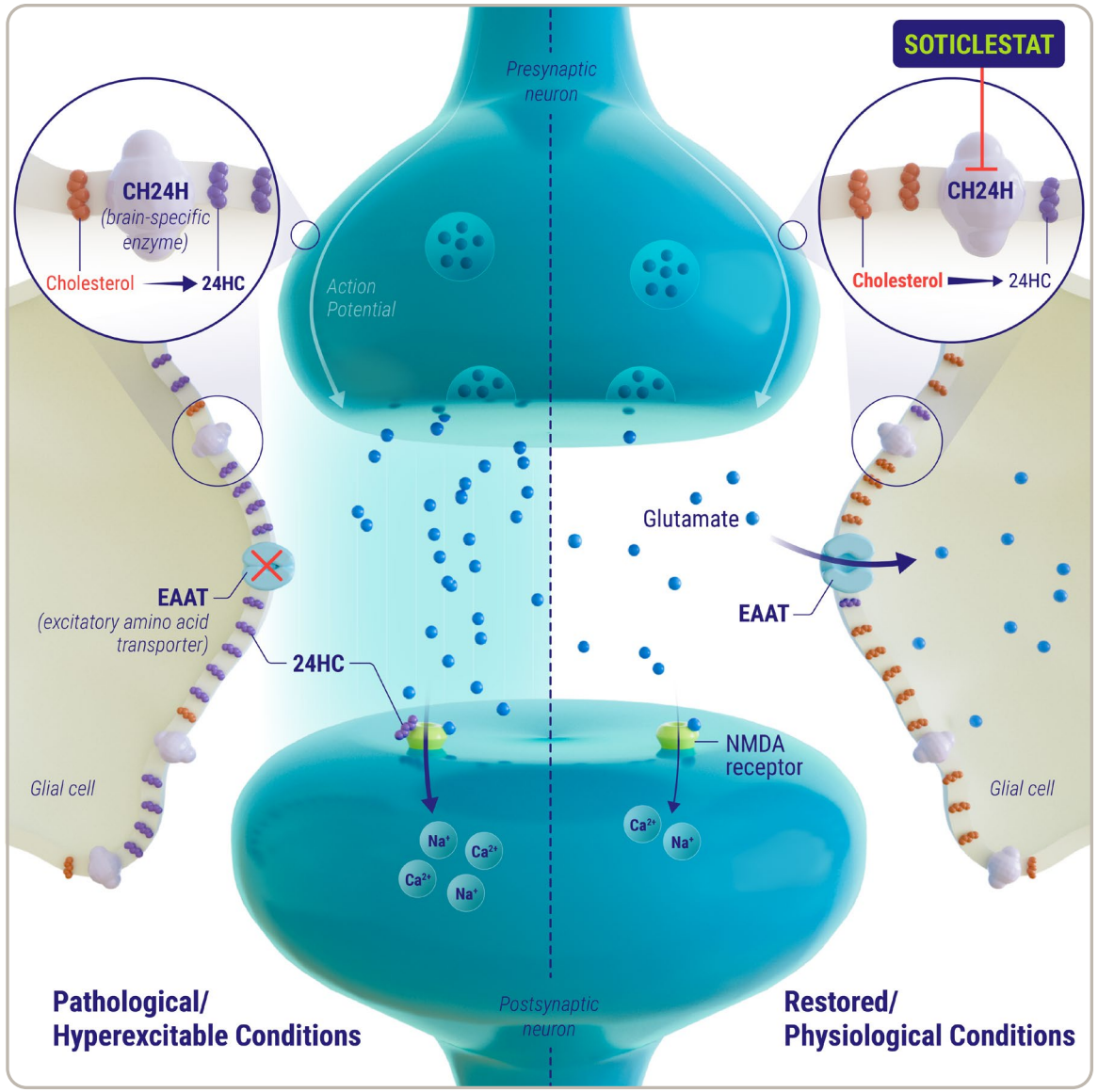
Novel mechanism of action

- Cholesterol 24 hydroxylase (CH24H) is a potent neurosteroid that can contribute to hyperexcitability and seizures[1]
- Soticlestat selectively inhibits cholesterol 24 hydroxylase[2,3,4,5]
  - → Creating dose-dependent reduction of circulating levels of CH24H in humans[6]
- CH24H reduction is multi-modal & ameliorates:
  - → Over-activated glutamatergic signaling
  - → Inflammation
- Soticlestat MoA represents a novel target for chronic seizure inhibition and disease modification[7]



1. Alessia Salamone, et al. Neurobiology of Disease, Volume 173, 2022, 105835, ISSN 0969-9961, https://doi.org/10.1016/j.nbd.2022.105835.
2. Nishi T, et al. Sci Rep (2020) 10:17081
3. Salamone A, et al. Poster Presented at ECE 2018.
4. Nishi T, et al. Neurology (2018) 15 Suppl: P5264 (Poster at AAN: 2018)
5. Sodero. A O et a. EMBO (2012) 31: 1764-74
6. J. Halford et al. A phase 1b/2a study of soticlestat as adjunctive therapy in participants with developmental and/or epileptic encephalopathies, Epilepsy Research, Volume 174, 2021, 106646,
7. Salamone, A. et al Neurobiology of Disease (Oct. 2022) https://doi.org/10.1016/j.nbd.2022.105835

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Eligible for significant milestones & royalties from Takeda

If soticlestat is approved and commercialized by Takeda:

Up to $660M in regulatory and sales milestones[1]

+

Tiered, double-digit royalties (up to 20%)[1]

Royalties applicable to all indications & all regions

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

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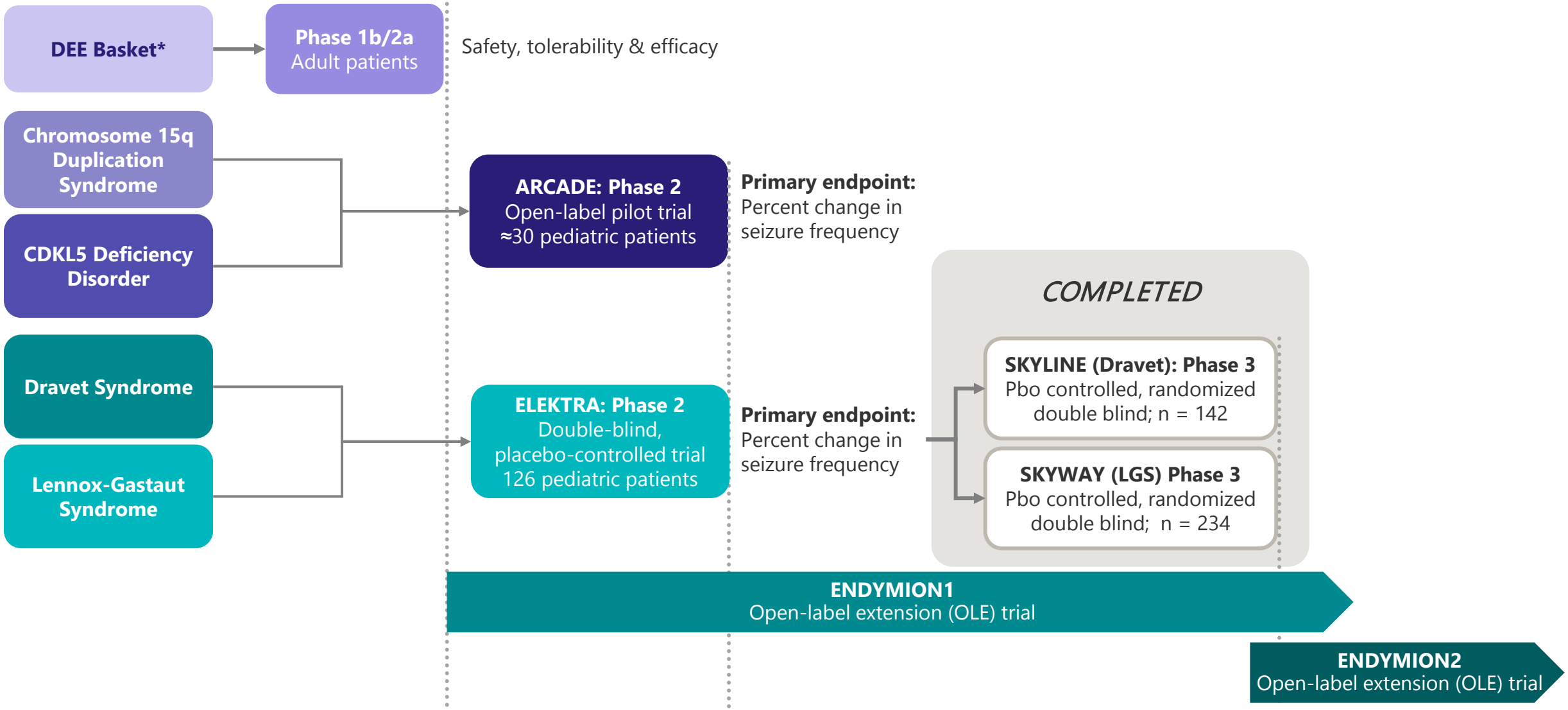
Soticlestat clinical development:
One of the most rigorous development programs in LGS & DS



*DEE Basket includes LGS, DS, Tuberous Sclerosis Complex, Cerebral dysgenesis, Hypothalamic Hamartoma, Epileptic Encephalopathy

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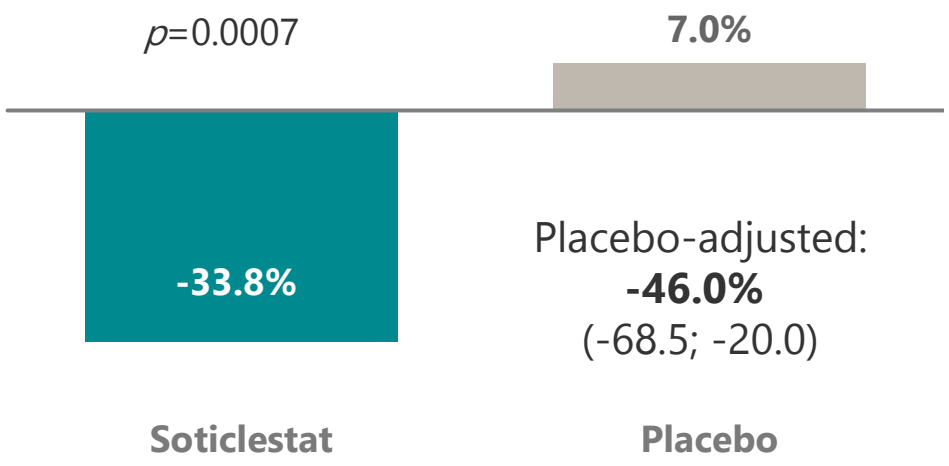
Phase 2 (ELEKTRA): Soticlestat demonstrated statistically significant seizure reduction in combined DS and LGS study population

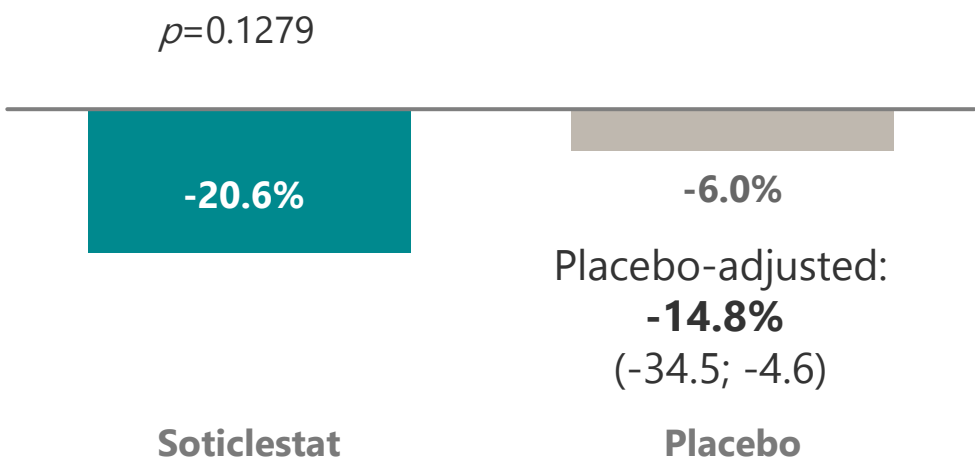
Median Change from Baseline in Seizure Frequency
During 20-week Treatment Period (mITT)[2]

Dravet Syndrome (Convulsive Seizures)



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

Lennox-Gastaut Syndrome (Drop Seizures)



- Placebo-adjusted median seizure reduction of 14.8% was numerically indicative, but not statistically significant
- A post-hoc sensitivity analysis of the LGS cohort determined other seizures were incorrectly recorded as "drop seizures"
- Analysis supportive of more stringent, countable drop seizure definition for the Phase 3 protocol

1. Hahn et al. Epilepsia. 2022; 00: 1– 13. https://doi.org/10.1111/epi.17367
2. Asymptotic 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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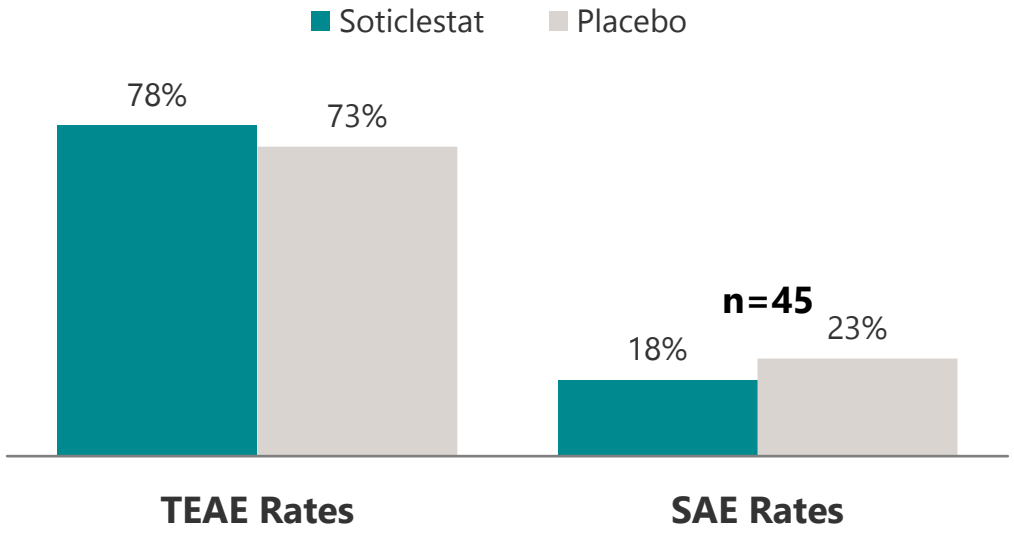
Phase 2 (ELEKTRA): Safety & tolerability profile

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%)

Overall Adverse Event Rates



- 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

1. TEAE = Treatment emergent adverse event; SAE = Serious adverse event

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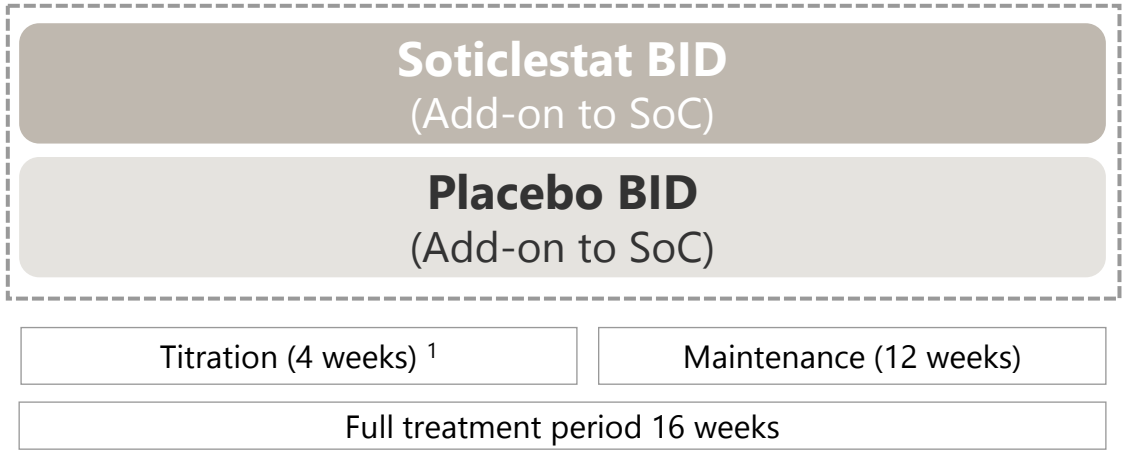
Overview: Phase 3 pivotal trials & modifications from the Phase 2

Being conducted by Takeda

skyline STUDY DS N = 142

skyway STUDY LGS N = 234



Entry into ENDYMION 2 OLE

TRIAL DESIGN

- Ages ≥ 2 years
- Adjunctive to ASMs
- Active seizures at baseline[2]

PRIMARY OUTCOME MEASURES

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

TRIALS ARE COMPLETE; DATA EXPECTED BY OR BEFORE SEPTEMBER 2024

1. 100 mg BID, 200 mg BID, 300 mg BID (mg/kg dosing)

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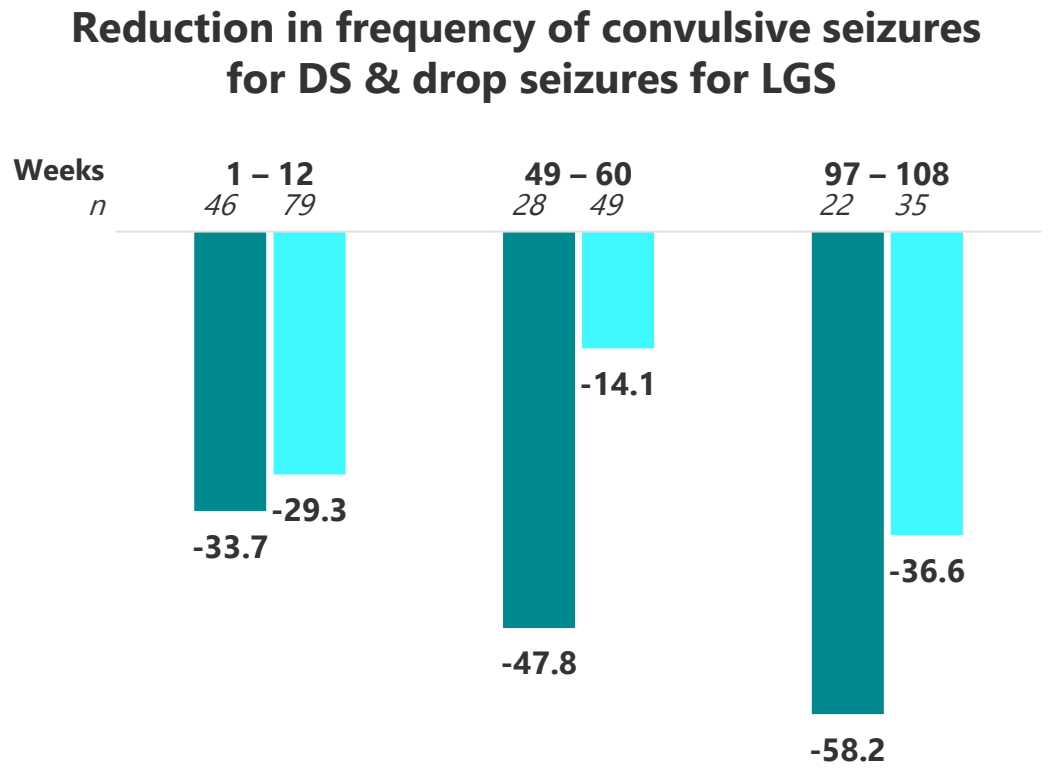
Soticlestat demonstrated sustained seizure reduction up to 2 years for DS & LGS patients in ENDYMION1[1]

Sustained reduction in:

- Convulsive seizures in DS patients
- Drop seizures in LGS patients



Median percentage change from baseline in seizure frequency per 28 days (5)

1. Long-Term Treatment Effects of Soticlestat in Patients with Dravet Syndrome or Lennox–Gastaut Syndrome: https://www.aan.com/MSA/Public/Events/AbstractDetails/52787

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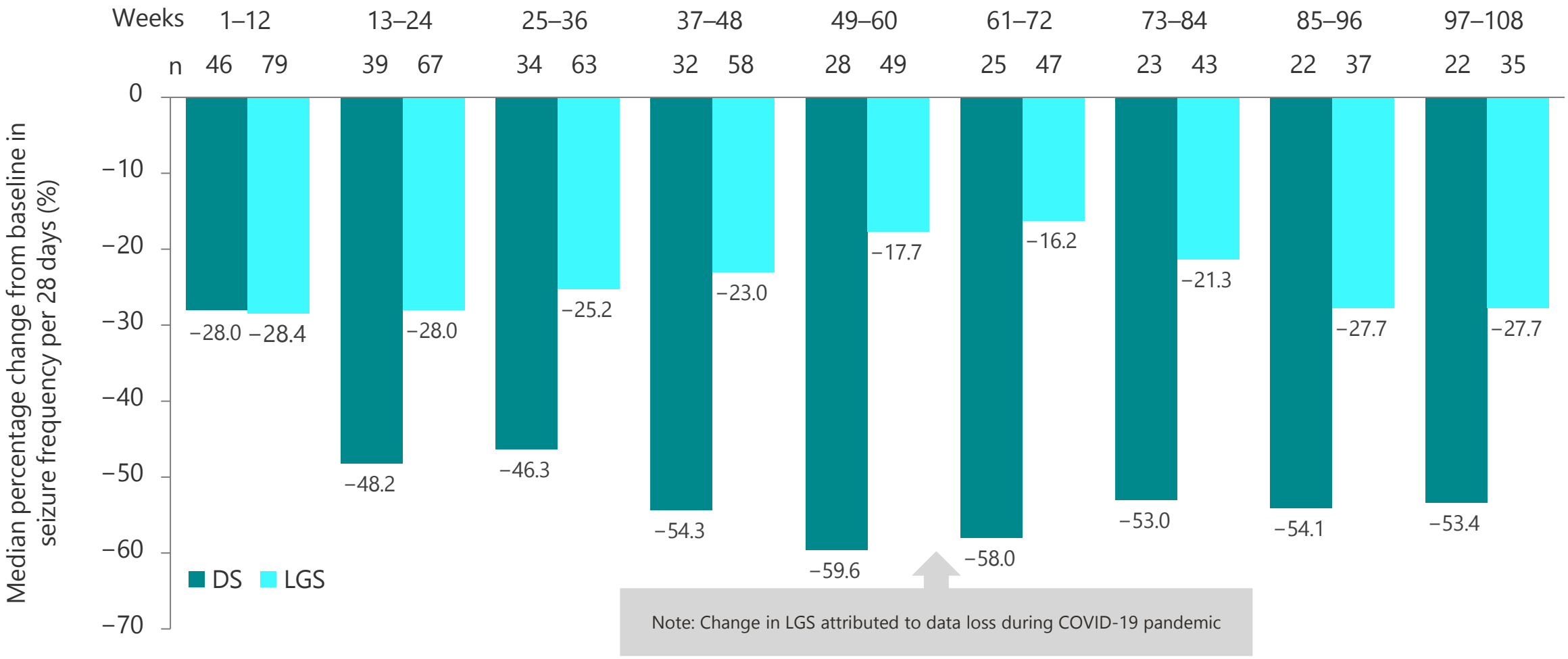
Sustained reduction in all-seizure frequency from baseline up to 2 years for patients with DS or LGS



'Baseline' refers to the 4-week ELEKTRA baseline period. Includes time points with at least five observations based on all enrolled individuals who have received at least one dose of study drug and have been assessed for at least 1 day in the treatment period
DS, Dravet syndrome; LGS, Lennox–Gastaut syndrome

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Comparison randomized, placebo-controlled trials in Dravet syndrome

Soticlestat and approved ASMs*

Information from the product labels of marketed medicines & ELEKTRA Phase 2 results for Soticlestat.
Epidiolex and Fintepla did not conduct randomized placebo-controlled Phase 2 trials.

Endpoints	Soticlestat (Phase 2, n=51)			Fintepla (Phase 3, n=40)			Epidiolex (Phase 3, n=128)		
	20- week full treatment period (full dose)			14-week full treatment period (0.7 mg/kg/day)			14-week full treatment period (20 mg/kg/day)		
% change of frequency in convulsive seizures	Treatment -33.8%	Placebo 7.0%	Placebo-adjusted **46.0%**[1]	Treatment -73.7%	Placebo -7.6%	Placebo-adjusted **64.8%**[2]	Treatment -39%	Placebo -13%	Placebo-adjusted **26%**[3]
Patient Reported Outcome	**Caregiver** Global Impression of Change			Endpoint not available			**Caregiver** Global Impression of Change[4]		
	Treatment Any improvement: 57.7%	**Placebo** Any improvement: 32.0%	Placebo-adjusted **25.7%**[3]				**Treatment** Any improvement: 62%	**Placebo** Any improvement: 34%	Placebo-adjusted **28%**[3]
Discontinuation rate due to AEs from placebo controlled trial	**1.4%**			**13%**			**11.8%** (5.9% due to Transaminase elevation)		

***Information reflected do not represent head-to-head studies. Differences exist between trial designs and subject characteristics, and caution should be exercised when comparing data across studies**

1. Hodges-Lehmann Estimation of the median in treatment difference; 2. Only the placebo-adjusted figure cited in label; 3. Placebo-adjustments taken as difference between treatment arm and placebo arm; 4. FDA label doesn't provide the CGI values for DS – values as reported by EMA

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Randomized, placebo-controlled trials in Lennox-Gastaut syndrome

Soticlestat and approved ASMs*

Information from the product labels of marketed medicines & ELEKTRA Phase 2 results for Soticlestat.
Epidiolex and Fintepla did not conduct randomized placebo-controlled Phase 2 trials

Endpoints	Soticlestat (Phase 2, n=88)			Fintepla (Phase 3, n=87)			Epidiolex (Phase 3, n=162)		
	20 week full treatment period (full dose)			14-week full treatment period (0.7 mg/kg/day)			14-week full treatment period (20 mg/kg/day)		
% change of frequency in drop seizures	Treatment -20.6%	Placebo -6.0%	Placebo-adjusted **14.8%**[1]	Treatment -26.5%	Placebo -7.8%	Placebo-adjusted **18.7%**[2]	Treatment -41.9 to -43.9%	Placebo -21.9 to -17.2%	Placebo-adjusted **22-24.7%**[3]
	Caregiver Global Impression of Change			Clinical Global Impression of Improvement			Caregiver Global Impression of Change[4]		
Patient Reported Outcome	Treatment Any improvement: 51.1%	Placebo Any improvement: 28.9%	Placebo-adjusted **22.2%**	Treatment Any improvement: 48.8% Very much improved: 26.3%	Placebo Any improvement: 33.8% Very much improved: 6.3%	Placebo-adjusted **15%**	Treatment Any improvement: 58-57%	Placebo Any improvement: 34-44%	Placebo-adjusted **13-24%**
Discontinuation rate due to AEs from placebo controlled trial	**3.5%**			**6.9%**			**11.8%** (5.9% due to Transaminase elevation)		

***Information reflected do not represent head-to-head studies. Differences exist between trial designs and subject characteristics, and caution should be exercised when comparing data across studies**

1. Hodges-Lehmann Estimation of the median in treatment difference; 2. Only the placebo-adjusted figure cited in label; 3. Placebo-adjustments taken as difference between treatment arm and placebo arm; 4. FDA label doesn't provide the CGI values for DS – values as reported by EMA

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Safety & tolerability indicators

Soticlestat and approved ASMs

Information from the product labels of marketed medicines & ELEKTRA Phase 2 results for Soticlestat.
Epidiolex and Fintepla did not conduct randomized placebo-controlled Phase 2 trials

Endpoints	Soticlestat (Phase 2)		Fintepla+ (Phase 3)		Epidiolex (Phase 3)	
	Dravet Syndrome and LGS (n=141)		Dravet Syndrome only (n=40)		Dravet Syndrome and LGS (n=238)	
	Soticlestat	Placebo	Fintepla	Placebo	Epidiolex	Placebo
Common TEAEs	• Upper resp. tract infection 18.3% 17.1% • Pyrexia 15.5% 11.4% • Somnolence 8.5% 4.3% • Vomiting 8.5% 5.7% • Decreased appetite 8.5% 7.1% • Lethargy 7.0% 0% • Diarrhea 7.0% 5.7% • Fatigue 5.6% 4.3% • Irritability 5.6% 2.9% • Pneumonia 5.6% 2.9% • Constipation 5.6% 0%		• Decrease appetite 36% 6% • Somnolence 21% 10% • Pyrexia 19% 8% • Blood glucose decrease 24% 12% • Diarrhea 15% 8% • Fatigue, malaise, asthenia 10% 2% • Tremor 12% 2%		• Somnolence 25% 8% • Decreased appetite 22% 5% • Diarrhea 20% 9% • Transaminase elevated 16% 3% • Rash 13% 3% • Fatigue, malaise, asthenia 12% 4% • Lethargy 8% 2% • Sedation 6% 1% • Aggression, anger 5% 0%	
Warnings / Monitoring	None		**Black Box warning** - **Valvular Heart Disease** - **Pulmonary Artery Hypertension** - **Echo assessments required** • Decreased Appetite and decreased weight • Somnolence, Sedation and Lethargy • Withdrawal of Antiepileptic Drugs • Serotonin Syndrome • Increase in Blood Pressure • Glaucoma **REMS – Elements to Assure Safe Use (ETASU) restricting providers access** **Schedule IV**		• Hepatocellular injury, LFT monitoring required - Somnolence and Sedation - Suicidal Behavior and Ideation - Hypersensitivity Reactions - Withdrawal of Antiepileptic Drugs	
Drug-drug interactions	No known drug-drug interactions		Adjust dose with stiripentol plus clobazam, caution with serotonergic drugs (i.e., serotonin syndrome)		Significant with multiple AEDs and other medication	

***Information reflected do not represent head-to-head studies. Differences exist between trial designs and subject characteristics, and caution should be exercised when comparing data across studies**

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+FINTEPLA only reflects Dravet syndrome



OV888
(GV101)

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

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

POTENTIAL OPPORTUNITY

- Potential 1st- and best-in-class disease modifying treatment for CCM
- Well characterized safety profile in humans
- Large addressable population with no pharmacological treatment
- Mechanism applicable for other CNS conditions

STATUS

Completed Phase 1 safety study

- Pivotal gel capsule formulation
- Healthy volunteer study
- No SAEs observed

Potential 1st indication: CCM

Intend to initiate patient signal finding trial in H2 2024

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Cerebral cavernous malformations

Presentation

- Mulberry-shaped abnormal blood vessels in the brain and or spinal cord
- Vessels have thin, irregularly formed walls that can leak blood over time
- 2nd most common intracranial vascular malformation in humans[1,2]
  - 1 in 500 people in the U.S. have at least one cavernous malformation in their brain
- 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[4]
- Overall morbidity was 26% after a mean follow up of 1.9 years since the first hemorrhage[5]
- One hemorrhage is a significant risk factor for future bleeds[4]

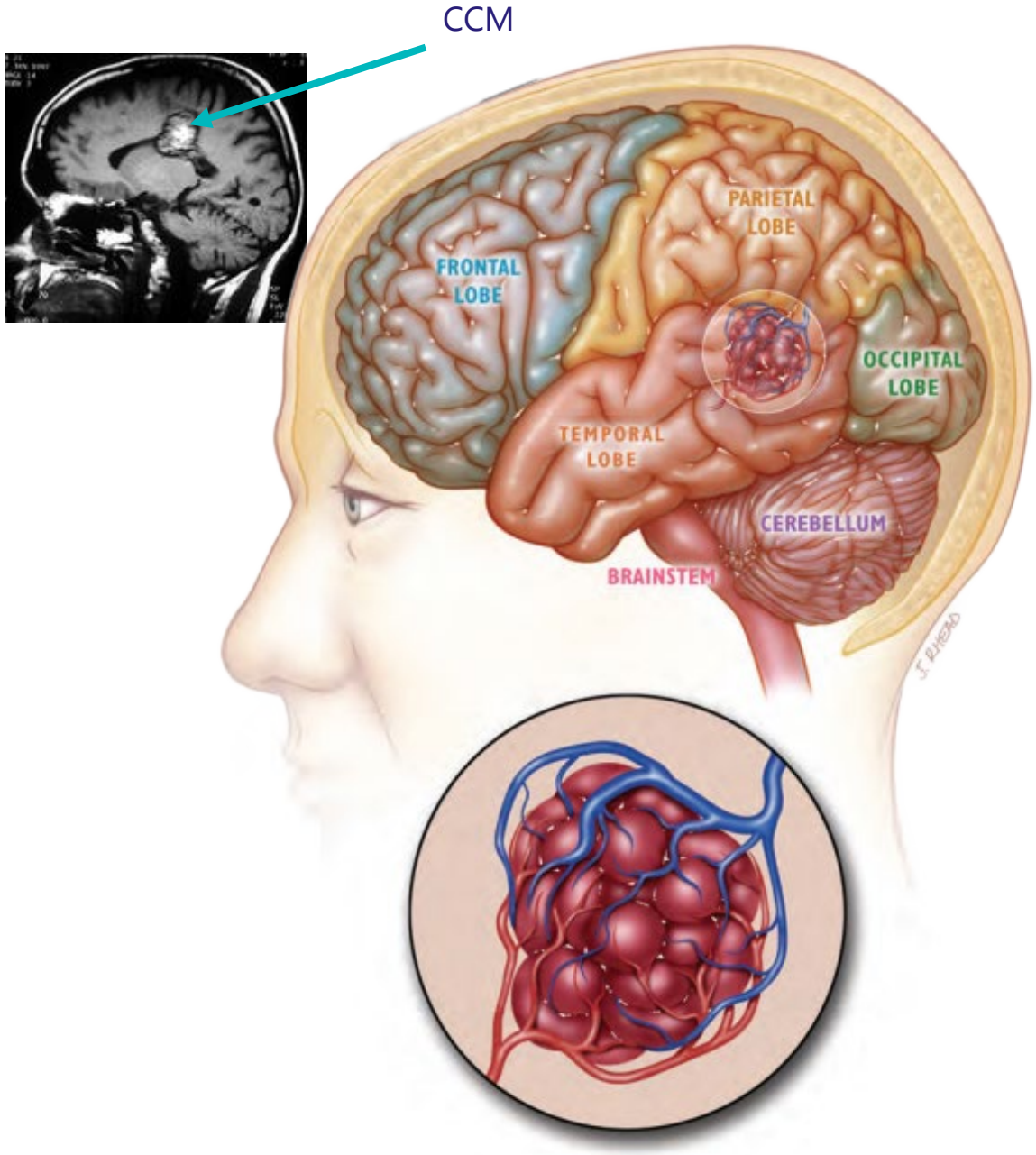

Image & content attribution:
Brainstem angioma from Alliance to Cure Cavernous Malformation

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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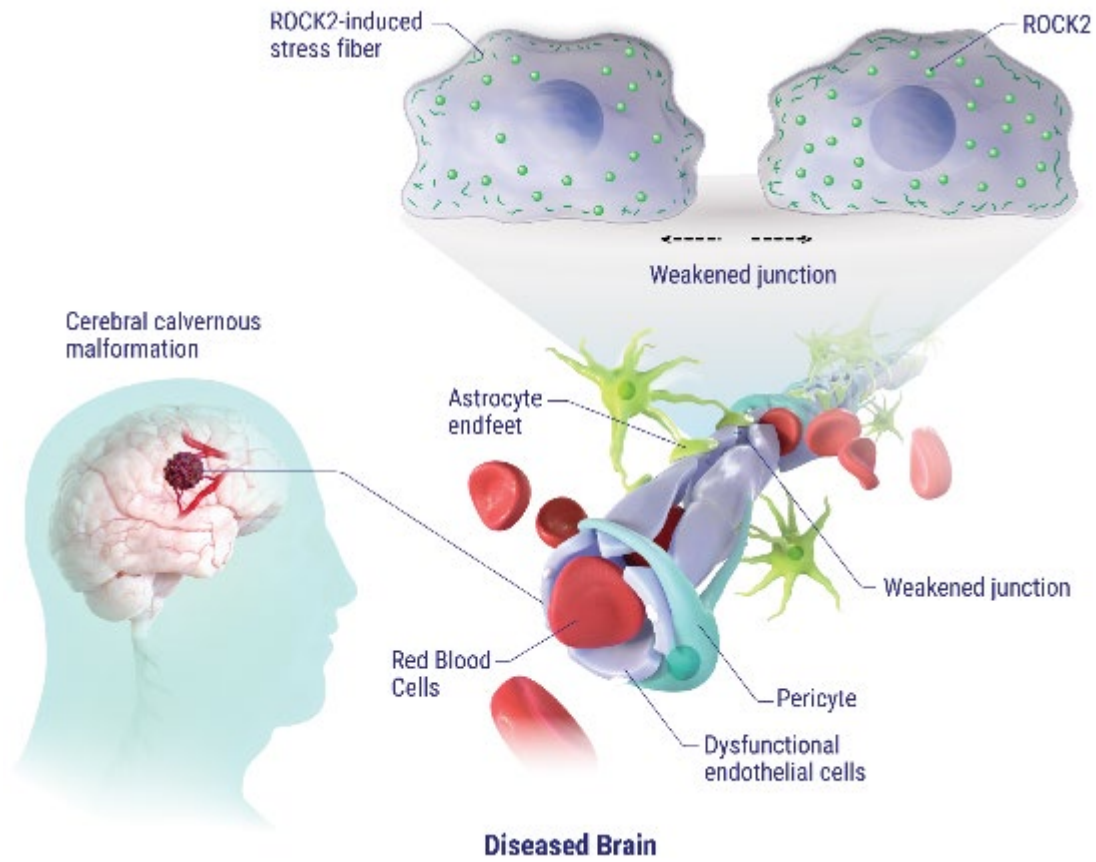
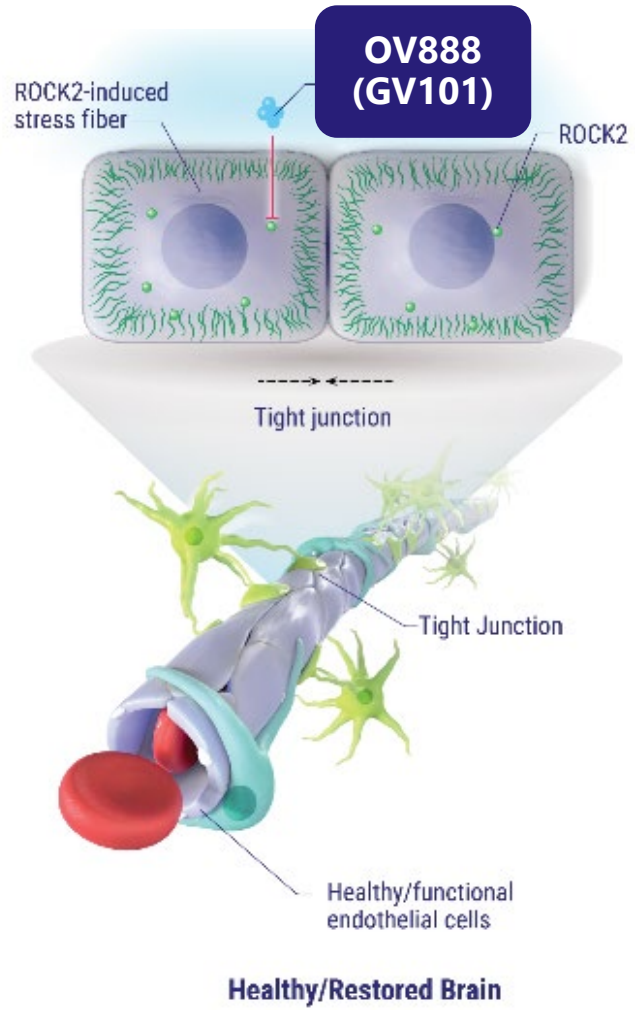
Proposed mechanism of action of OV888 (GV101)

Pathological State



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

Proposed Mechanism of Action



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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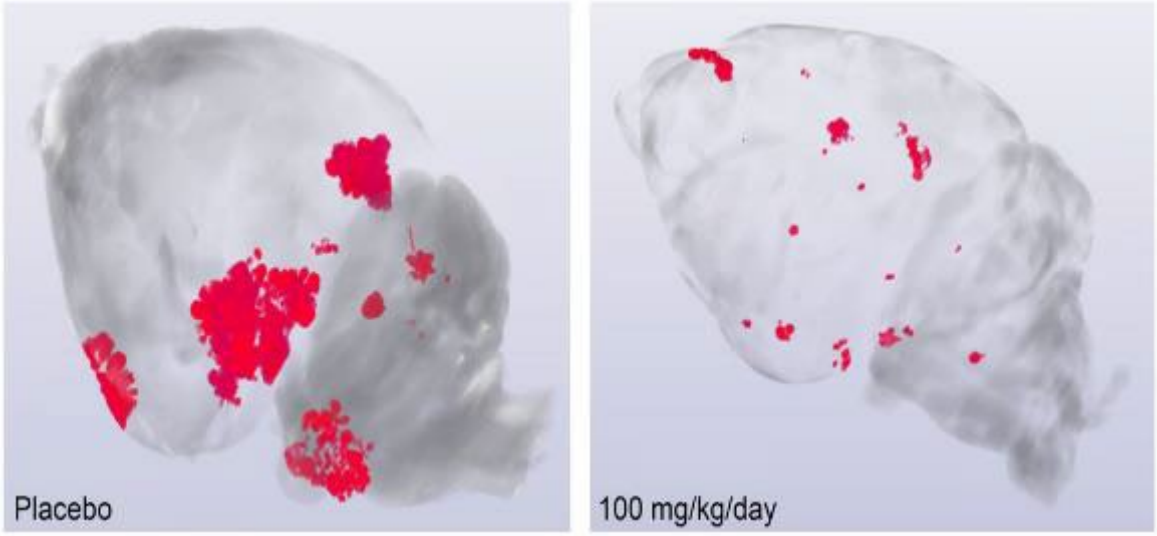
Preclinical validation for ROCK2 inhibition in cerebral cavernous malformations

- 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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Unmet need is substantial and no pharmacological therapies exist

Addressable symptomatic population[1]

7 major markets

~400K

CCM patients[2]

United States

~150K-175K

CCM patients[2]

Disease modifying therapies are needed

- Symptoms from lesions can result in neurological deficits & potentially lead to severe disability
- Only available therapy is surgical resection of the CCM (when possible)
- Prior CCM hemorrhage carries significant risk of additional hemorrhage[3]

1. Addressable population is defined as symptomatic patients and patients with an incidental finding
2. Ovid 2022 global market research
3. Ma L et al. Stroke. 2020 Oct;51(10):2997-3006. doi: 10.1161/STROKEAHA.120.029942. Epub 2020 Sep 21. PMID: 32951540.

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Clinical development & regulatory status

✓ Complete: Phase 1 in China

- GV101 nano-suspension formulation (same API as OV888)
- 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:
  - 0 SAEs
  - AE of interest (headache (21%), diarrhea (11%), CPK elevations (6%), nausea/vomiting (2%)

Ongoing: Phase 1 in U.S.

- Multiple ascending dose trial ongoing to test capsule formulation
- Objective: confirm safety & establish maximum tolerated dose tolerated
- Randomized, placebo-controlled, double-blind, single-center MAD
- No serious adverse events; one voluntary discontinuation

NEXT STEPS

- Complete multiple ascending dose program
- Initiate Phase 2 signal finding

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OV329

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

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GABA-aminotransferase inhibitor programs for potential treatment of chronic and acute refractory seizures

POTENTIAL OPPORTUNITY

- Unique molecule for a validated target, GABA aminotransferase (GABA-AT)
- Intended to deliver optimal levels of GABA to achieve:
  - Sustained seizure suppression
  - Improved safety
  - Preferable (lower) dosing
- 7 preclinical models demonstrate OV329's anti-convulsant activity
- Designed to supplant vigabatrin (VGB) which had a safety issue at the therapeutic index
- OV329 is believed to be >100x more potent than VGB in preclinical studies[1]

STATUS

2 formulations
- Oral – chronic refractory seizures
- Intravenous (IV) – acute seizures

Multiple indication opportunities

Phase 1 SAD/MAD with biomarkers
- Anticipated results H2 2024

IV formulation
- Investigational new drug authorization anticipated to be submitted H2 2024

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

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Significant unmet need & mortality in status epilepticus (SE)

SE defined as a seizure of 5+ minutes or more than 1 seizure in a 5-minute period, without a return to normal level of consciousness between episodes

Current treatment paradigm: Status epilepticus

1st line: IV benzodiazepines

Established SE:

If SE persists after treatment with benzos:

2nd line: IV antiseizure medications (ASMs)

Refractory SE:

If SE persists after treatment with IV ASMs

3rd line: IV anesthetics

Super refractory SE:

If SE persists > 24 hours after anesthetics have been given or SE returns when a wean of the anesthetics is attempted

EFFECTIVENESS OF THERAPY		
LINE	**SUCCESS RATES**	**REFERENCE**
1st line	~60%	n = 384 Treiman et al. 1998
2nd line	~50%	n = 384 Kapur et al. 2019
3rd line	~35% recovery to baseline	n = 596 Shorvon and Firlisi, 2012

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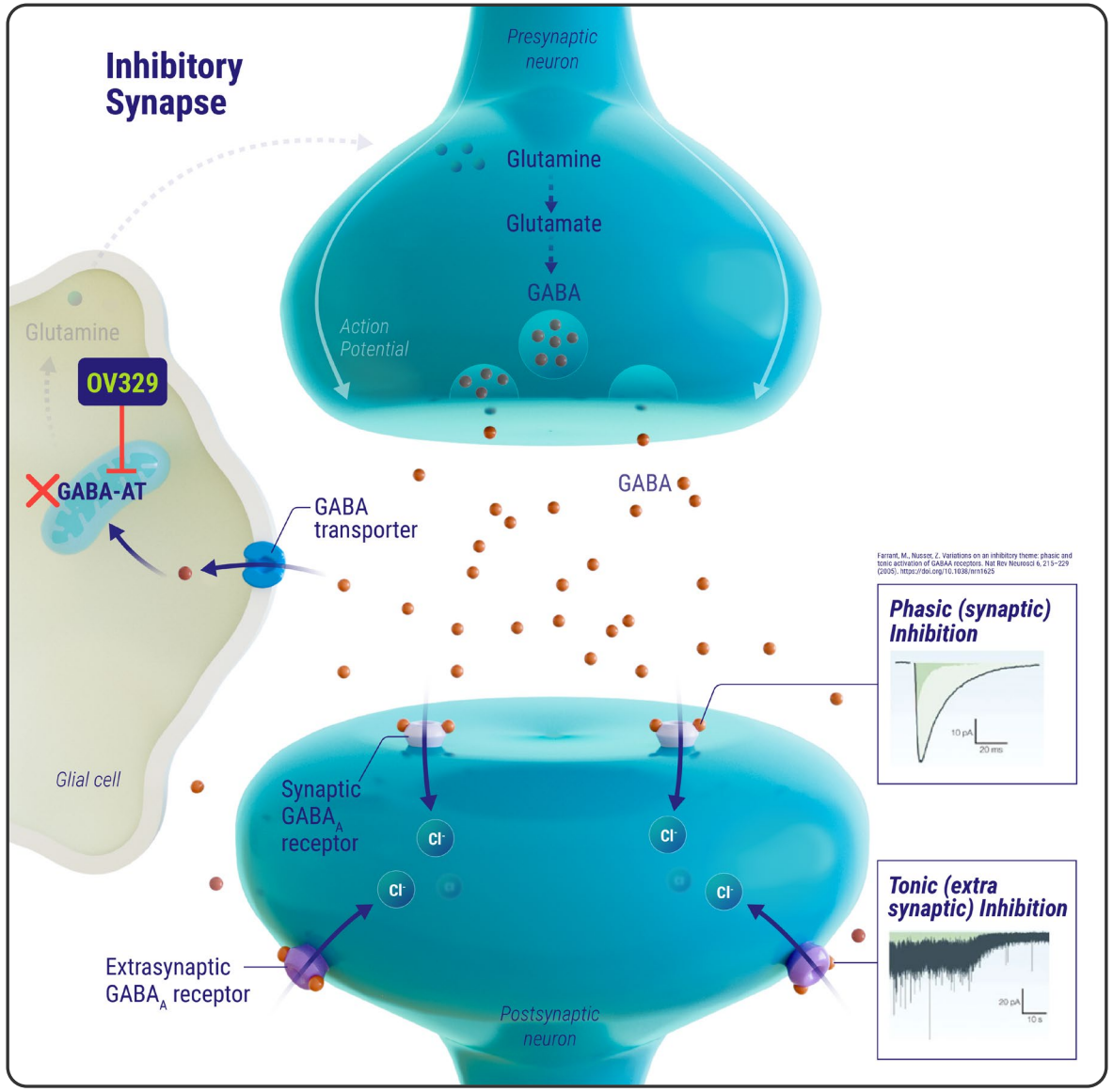
OV329 mechanism of action

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

Mesial temporal lobe epilepsy (MTLE) model reflects:

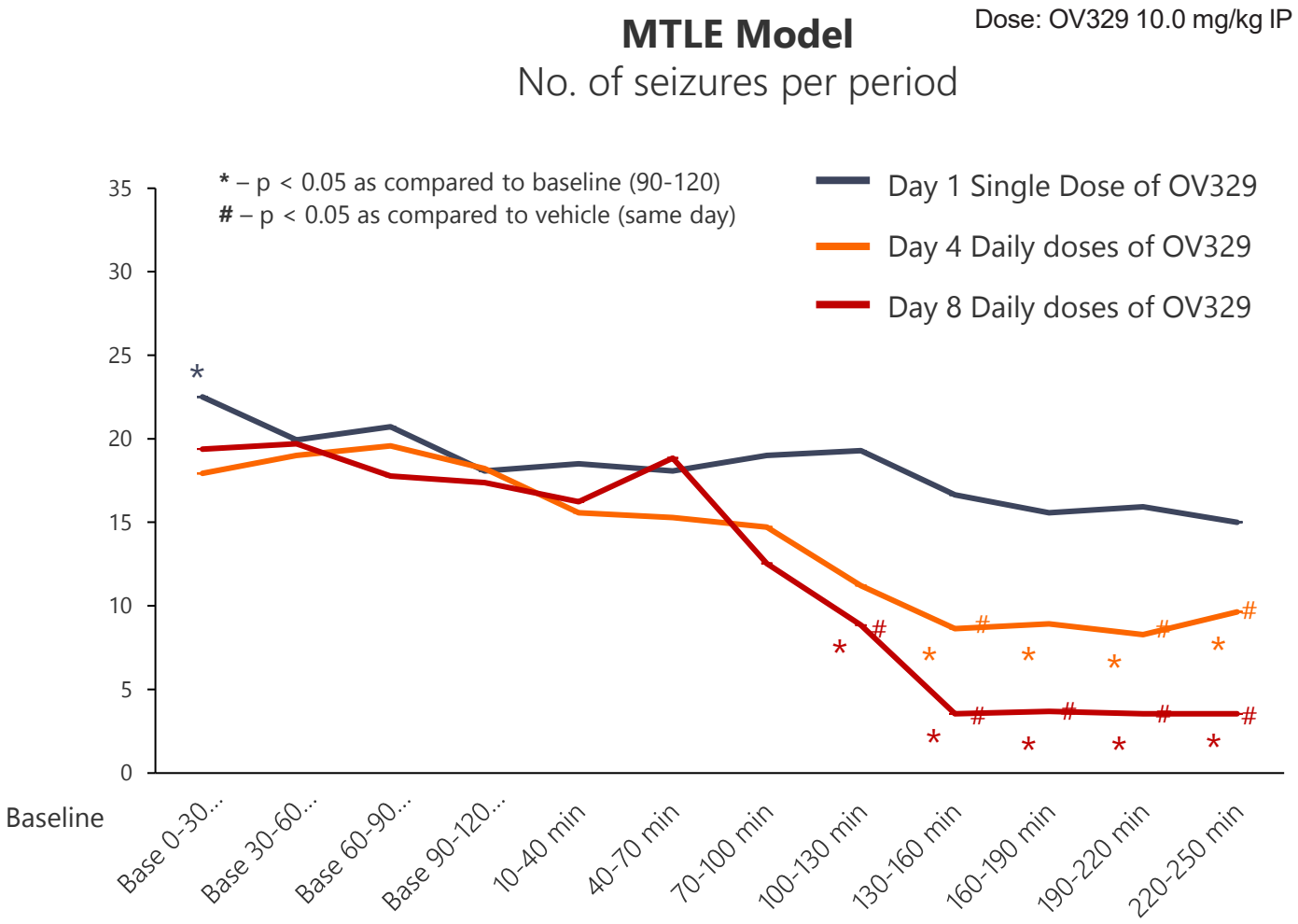
- The main pharmaco-resistant form of epilepsy[1]

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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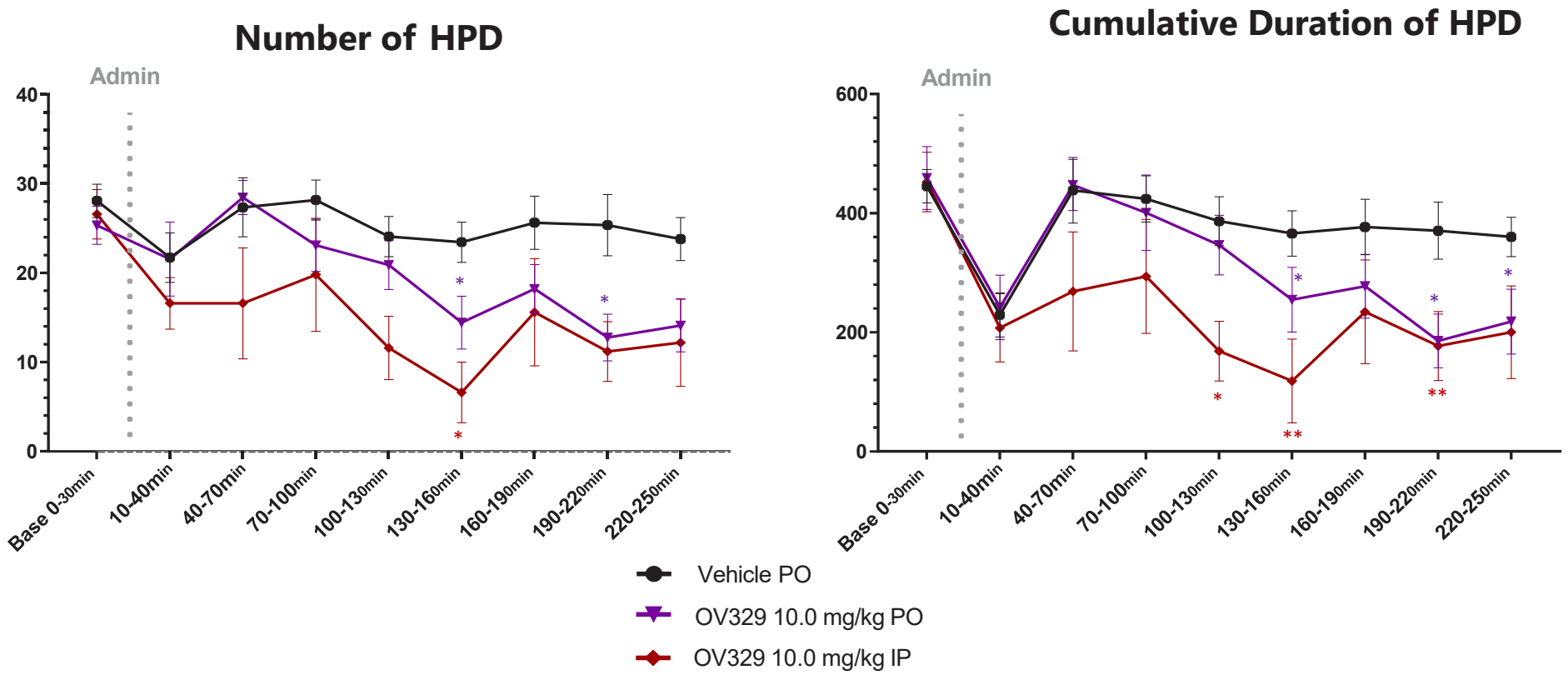
Single dose of OV329 reduced number & duration of hippocampal paroxysmal discharges in animal models



Single dose preclinical studies & investigator led studies with vigabatrin support acute dosing in refractory seizures & status epilepticus[1,2]

1. Ramsay, Clinical Neurophysiology, Volume 129, Supplement 1, May 2018, Pages e206-e207
2. Jason McCormick, Nicholas Jonas, R. Ramsay, Vivek Sabharwal; Neurology, April 23, 2012; 78 (1 Supplement) First published February 8, 2016

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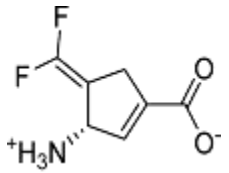
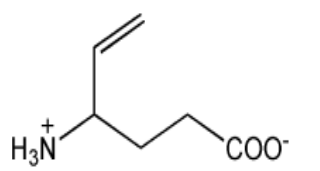
OV329 profile is differentiated from vigabatrin

	OV329	Vigabatrin
Molecule		
Potency	IC_{50}: ~0.1 - 0.3 μM	IC_{50}: ~60 – 100 μM
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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Development program

Oral – Chronic Dosing

- 3 SAD cohorts completed in healthy volunteers
  - MAD ongoing
- Two biomarkers included:
  - Transcranial magnetic stimulation (TMS)
  - Magnetic resonance spectrometry
- Conducting animal back-of-eye accumulation study to differentiate OV329 safety from vigabatrin
- Target readout late H2 2024

IV – Acute Dosing

- IV formulation achieved
- Anticipated IND submission in H2 2024
- Intent to initiate a Phase 1 trial in 2025

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KCC2 library & OV350

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

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KCC2 direct activator portfolio & OV350 for anti-convulsant and anti-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 confirmed:

- 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)

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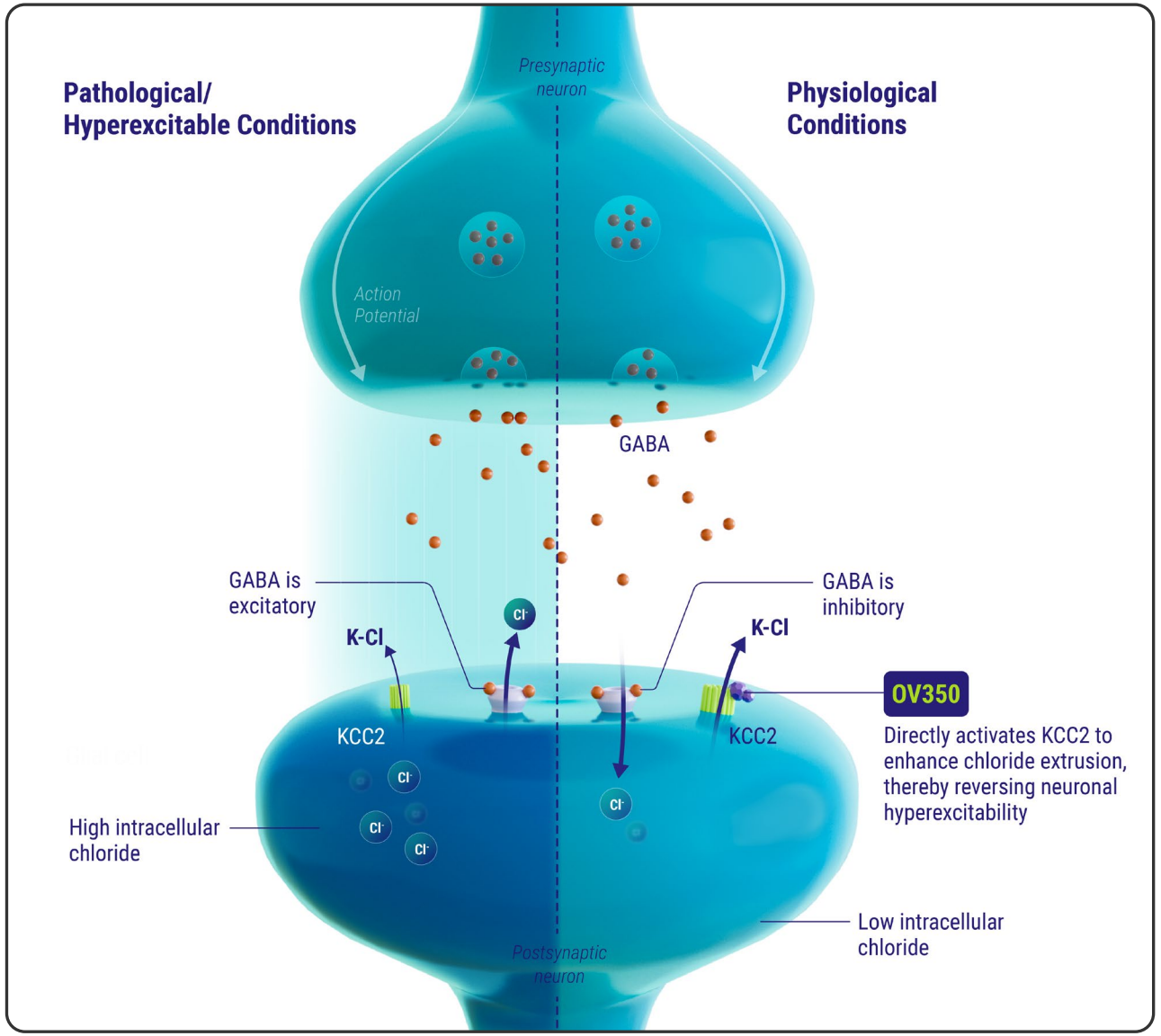
KCC2 is the main regulator of GABA inhibition by maintaining neuronal chloride homeostasis[1]

- 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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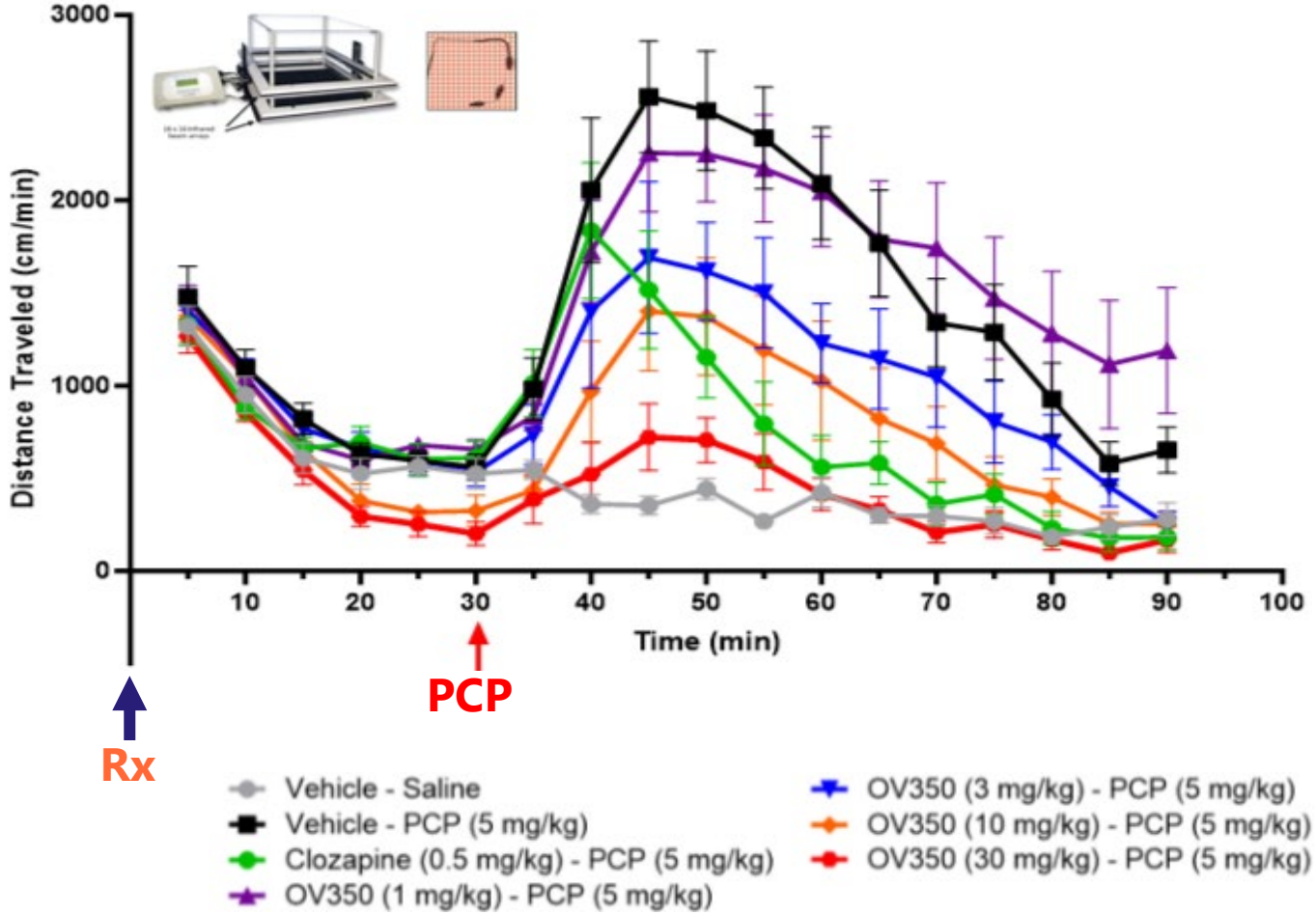
OV350 demonstrates anti-psychotic effects in a schizophrenia model



- 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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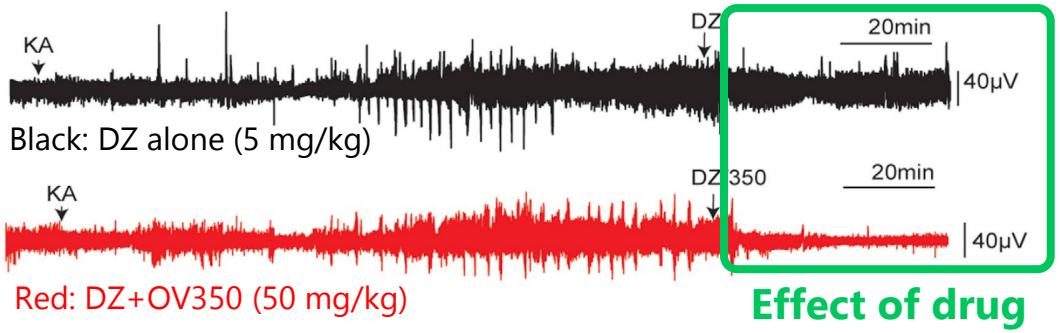
Preclinical POC for OV350 in epilepsy

OV350 potentially terminates ongoing and benzodiazepine refractory status epilepticus

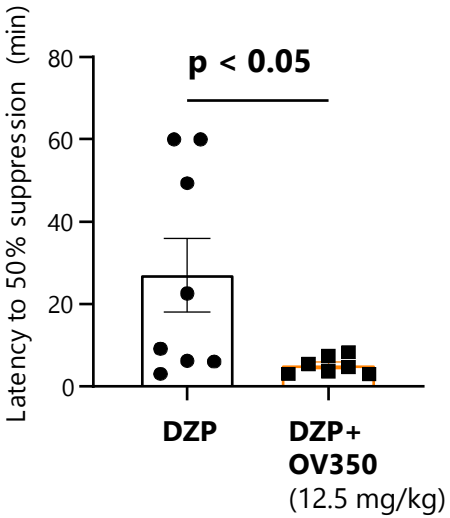
- OV350 demonstrated anti-seizure activities in kainate challenge model
- Mice implanted with electrodes to measure kainate induced seizures
- Demonstrated that OV350 at 50mg/kg and 12.5mg/kg
  - Restored diazepam activities in stopping seizures
- Supports development in Status Epilepticus using IV formulation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

- 5X 2025 clinical and regulatory milestones from Ovid's pipeline expected by 2025
- Two pivotal Phase 3 readouts for soticlestat expected by or before Sept. 2024
- Eligible for up to $660M of milestones payments and tiered double-digit royalties up to 20% if soticlestat is approved and commercialized[1]
- Non-seizure applications for current programs provide partnering opportunities
- $90.3M cash balance as of March 31, 2024, with anticipated runway into H1 2026

1. Ovid owes Ligand Pharmaceuticals 13% of potential milestone and royalties received from Takeda if soticlestat is approved and commercialized

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Thank you

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