Ovid Therapeutics

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Ovid® Therapeutics

OVID R&D DAY

OCTOBER 2, 2023



Dawn of the neurotherapeutics era

Dr. Jeremy Levin
CEO & Chairman

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 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 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 OV888 (GV101) and other Rho/Rho associated coiled-coil containing protein kinase 2 inhibitors; and the potential safety, selectivity and potency of OV888 (GV101) and other ROCK2 inhibitors; the potential use of OV888 (GV101) and other ROCK2 inhibitors to treat cavernous cerebral malformations and other rare central nervous system disorders; the potential timing of the pivotal formulation for OV888 (GV101); the potential timing of Phase 1 and 2 clinical studies for OV888 (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 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, OV329, OV350, OV888 (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," "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 of 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 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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Epilepsy will be a key to **unlocking a revolution** of targeted small molecules for neurological conditions

Ovid is part of this revolution.

Today's news

- ✓ Pipeline programs offer anti-convulsant & broader CNS opportunities
- ✓ New preclinical research offers confidence to accelerate & expand programs
- ✓ 5 clinical milestones expected within the next 12-15 months
- ✓ Strong capital base and financial strategy to propel pipeline to milestones
- ✓ Potential for substantial non-dilutive capital from Takeda* to support pipeline

*If soticlestat is approved and commercialized

FOCUSED PIPELINE

To treat epilepsy and conditions with seizure symptoms

HARNESSING A SCIENTIFIC REVOLUTION

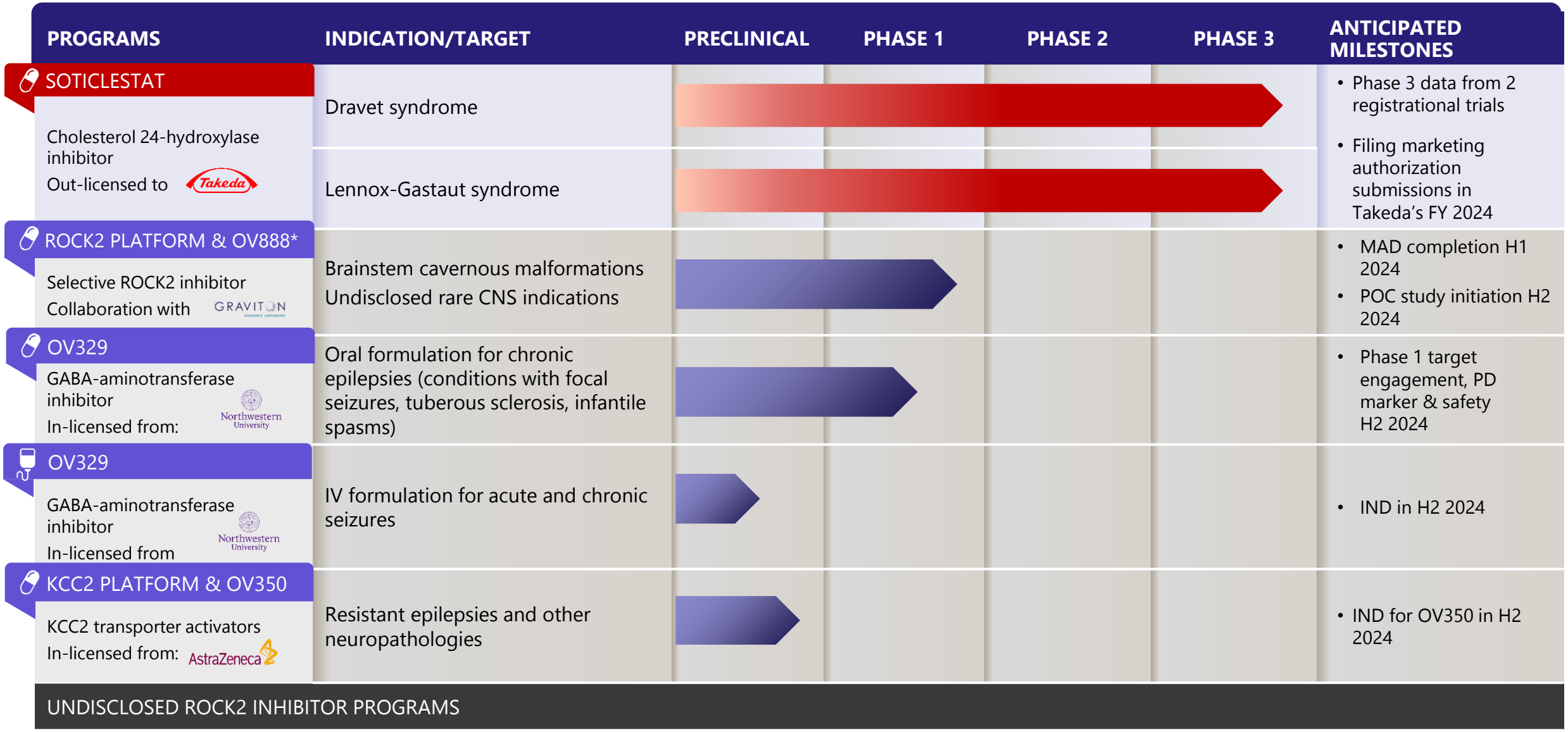
Targeted small molecules for the central nervous system

NOVEL BIOLOGICAL TARGETS

Modulated by unique first-in-class or potential best-in-class mechanisms of action to deliver preferable:

- Efficacy
- Safety
- Tolerability

Expected to be first-in-class or best-in-class mechanisms of action



*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.

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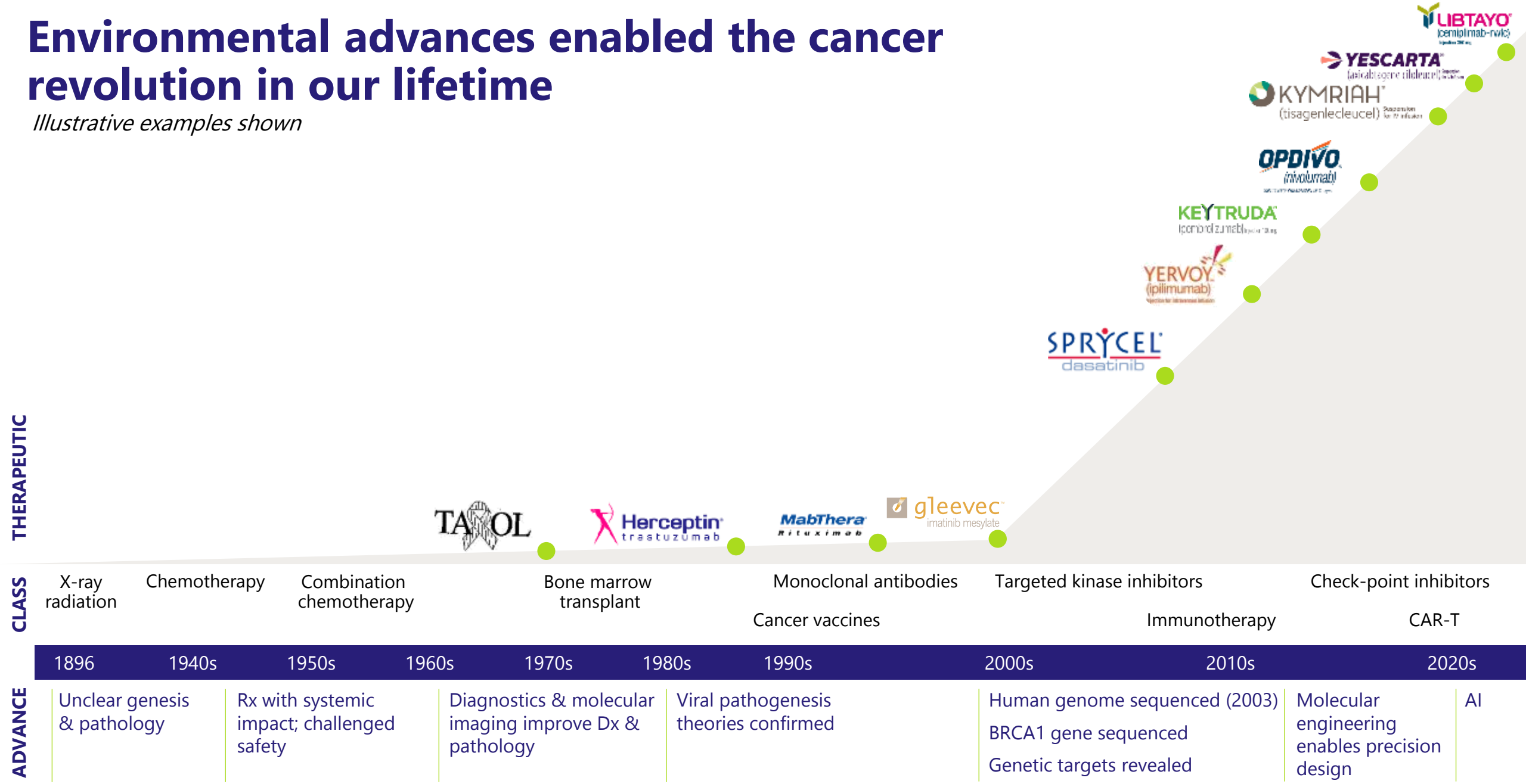
Environmental advances enabled the cancer revolution in our lifetime

Illustrative examples shown



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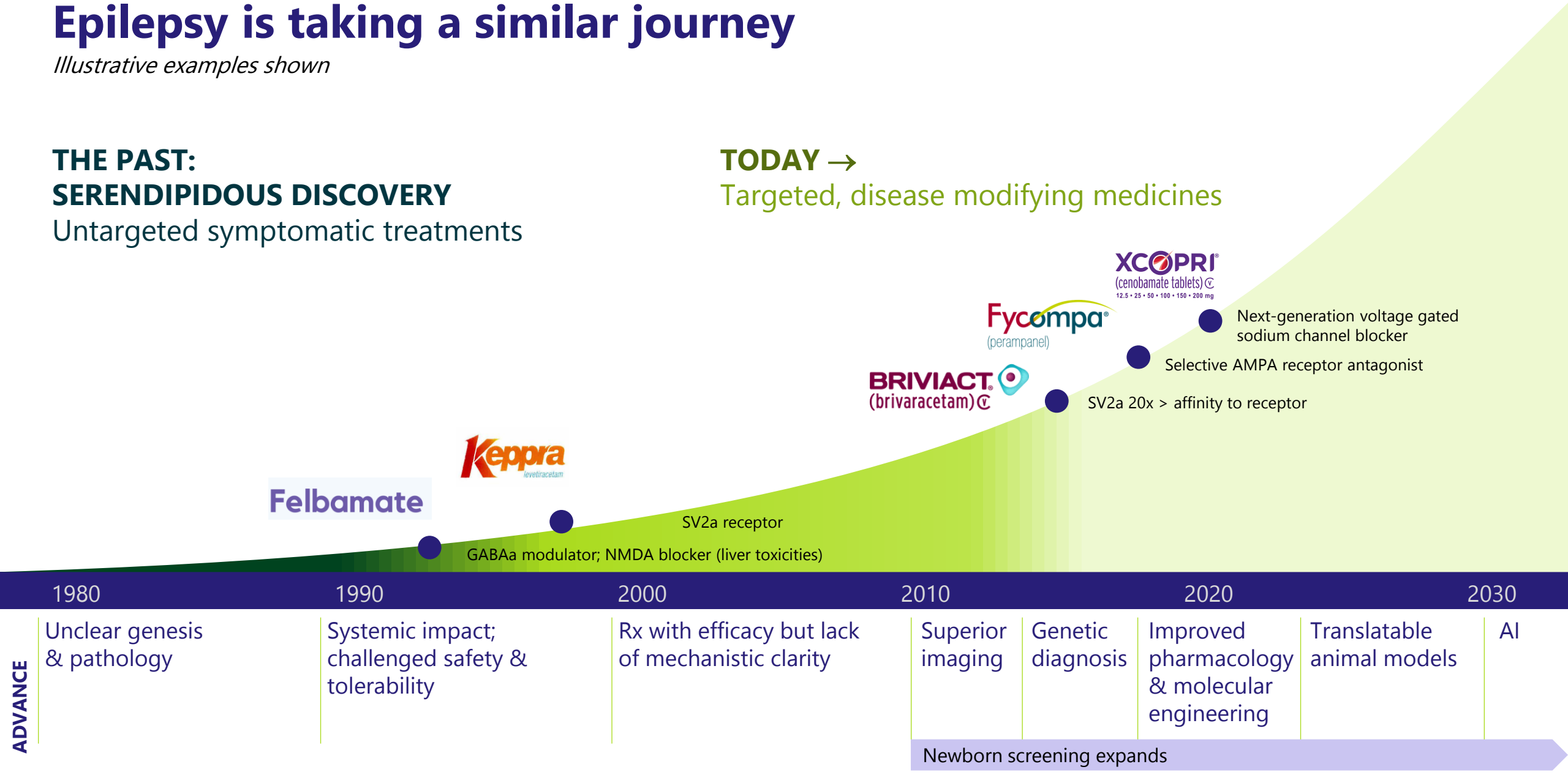
Epilepsy is taking a similar journey

Illustrative examples shown

THE PAST:
SERENDIPIDOUS DISCOVERY
Untargeted symptomatic treatments

TODAY →
Targeted, disease modifying medicines



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Our trust



01 Epilepsy burden: The need for new mechanisms & medicines

- Dr. Imad Najm, Director, Epilepsy Center, Cleveland Clinic, Vice Chair for Strategy & Development, Neurological Inst.



02 Scientific & pipeline strategy

- Meg Alexander, Chief Strategy Officer





03 ROCK2 inhibition for cerebral cavernous malformations & CNS conditions

- Dr. Zhong Zhong, Chief Scientific Officer
- Dr. Connie Lee, Founder & CEO, Alliance To Cure Cavernous Malformations



04 A next-generation GABA aminotransferase inhibitor



- Dr. Manoj Malhotra, Chief Medical Officer
- Dr. Zhong Zhong, Chief Scientific Officer

Q&A FOLLOWED BY COFFEE BREAK



05 Unlocking a new CNS target: KCC2 direct activation



- Dr. Stephen Moss, Director, Moss Lab For Neuropharmacology at Tufts University & Professor of Molecular Pharmacology At University College London
- Dr. Zhong Zhong, Chief Scientific Officer



06 Soticlestat: Anticipated profile

- Jason Tardio, Chief Operating Officer



07 Milestones & financial strategy

- Jeff Rona, Chief Business & Financial Officer



Q&A & CONCLUDE

- Jeremy Levin, Chief Executive Officer & Chairman

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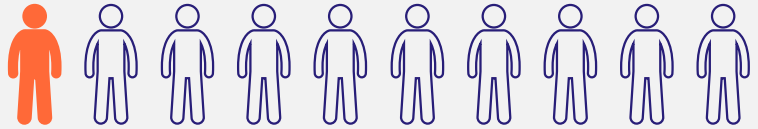
The need for new mechanisms & medicines in epilepsy

Dr. Imad Najm
Director of Epilepsy Center
Vice Chair for Strategy & Development,
Cleveland Clinic Neurological Institute

Epilepsy has been known for 3,000 years; yet remains a major unmet need



Up to 1 in 10

humans will experience a seizure in their lifetime[1]

~47%

of epilepsy patients report polypharmacy – taking on average 5 medications[2]



Reimbursement & coverage dynamics remain favorable

Polypharmacy generally well covered



50

million

living with epilepsy across the globe[3]



3

million

adults living with epilepsy in the US[4]



470,000

US children

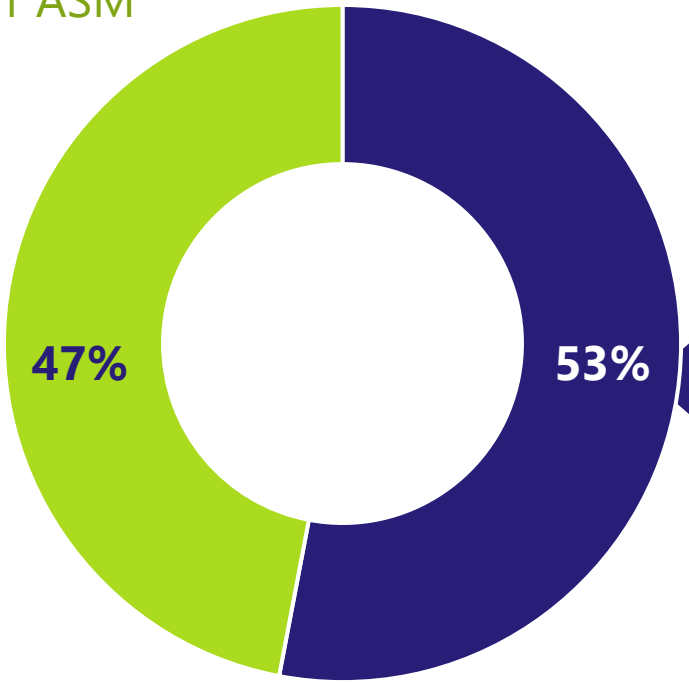
≤17 years have epilepsy[4]

1. Epilepsy. World Health Organization. Updated February 9, 2022. Accessed July 12, 2022. https://www.who.int/news-room/fact-sheets/detail/epilepsy.
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. World Health Organization epilepsy fact sheet updated in February 2023. https://www.who.int/news-room/fact-sheets/detail/epilepsy
4. 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.

Huge unmet need

Polypharmacy is common & refractory rates are high among pediatric DEEs

Seizures controlled by 1 ASM



Pharmaco-resistant epilepsy

Seizures are not controlled with ≥ 2 ASMs

Based upon UK Study of 525 individuals (9-93 years) with newly diagnosed epilepsy, followed for 5 years[1]

REFRACTORY SEIZURE RATES

~90%

of Dravet and LGS patients are not adequately controlled[2,3]

>50%

of Tuberous sclerosis patients do not respond to medicines[4]

64%

of infantile spasm patients experience refractory seizures[5]

1) Kwan, Patrick and Brodie, Martin J.Early Identification of Refractory Epilepsy, 2000/02/03, New England Journal of Medicine, p 314-319; V 342 2) Lagae, L., Brambilla, I., Mingorance, A., Gibson, E. and Battersby, A. (2018), Quality of life and comorbidities associated with Dravet syndrome severity: a multinational cohort survey. Dev Med Child Neurol, 60: 63-72 3) Douglass LM. Conclusions: long-term management of Lennox-Gastaut syndrome: future directions. Epilepsia 2011; 52(Suppl 5): 28. 4) TSC Alliance website as accessed in September 2023 5) Long-term developmental outcome in patients with West syndrome after epilepsy surgery, Iwatani, Yoshiko et al. Brain and Development, Volume 34, Issue 9, 731 - 738

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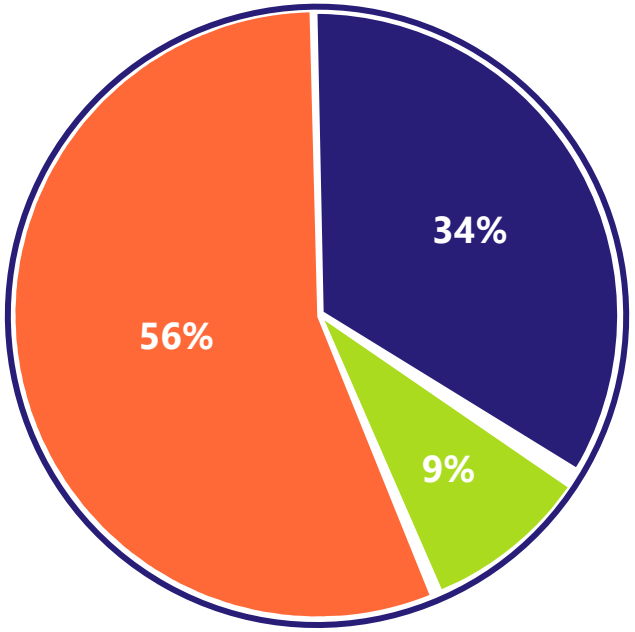
Why is this happening?

Historically, anti-seizure medicines have failed to

- Adequately target the root cause(s) underlying excitability
- Achieve a maximal effective dose due to side effects or tolerability
- Avoid “off target” effects causing safety issues

Next generation medicines are arriving

ASM MARKET SHARE 2020 (G7)[1]



1. Source: Clarivate Epilepsy Landscape Report 2022

New targeted small molecule & genetic medicines

Next generation technologies that have the potential to be preventative or disease modifying

Selective & specific for targets & tolerability

Increasingly selective targets, mechanistically designed for specific targets to improve efficacy, tolerability and off-target effects

Narrowed, more targeted ASMs

Potent therapeutics that were more targeted, but also with improved side-effect & safety profiles

1st Generation: Broad spectrum

Early CNS suppressants that dampen excitability; but carry heavy side-effect & safety profiles

1850 1870 1910 1930 1950 1970 1990 2010 - 2022



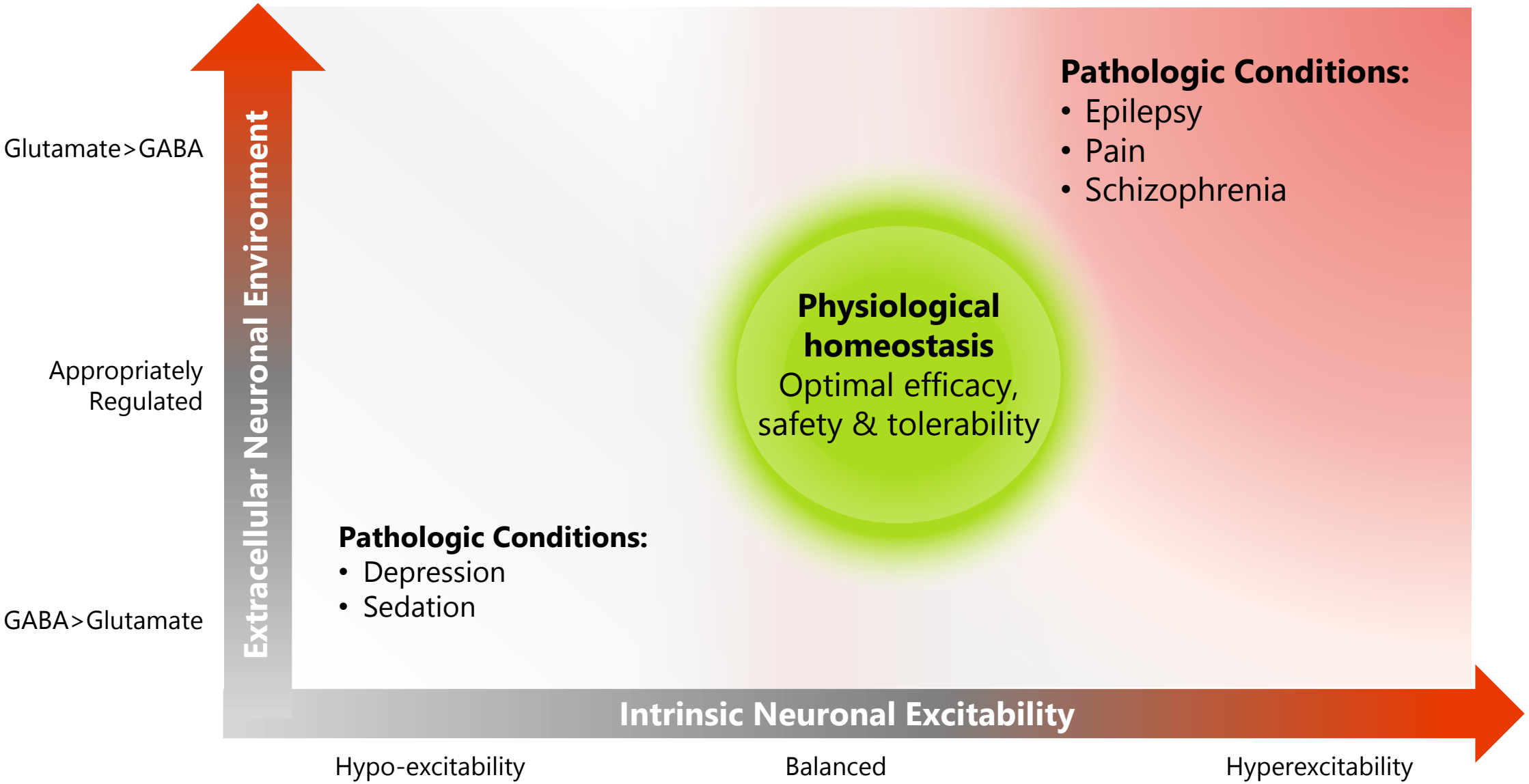
Scientific & pipeline strategy

Meg Alexander
Chief Strategy Officer

Ovid scientific & pipeline strategy

- ✓ Exclusively targeted small molecules
- ✓ Expected to be first-in-class or best-in-class mechanisms of action
- ✓ Under-addressed biological targets expressed in CNS
- ✓ Mechanisms to modulate metabolic, enzymatic, intracellular & structural causes of hyperexcitability
- ✓ Potential application in multiple indications for which hyperexcitability is the cause for the pathology

The goal of many CNS medicines: Neuronal homeostasis (balance)



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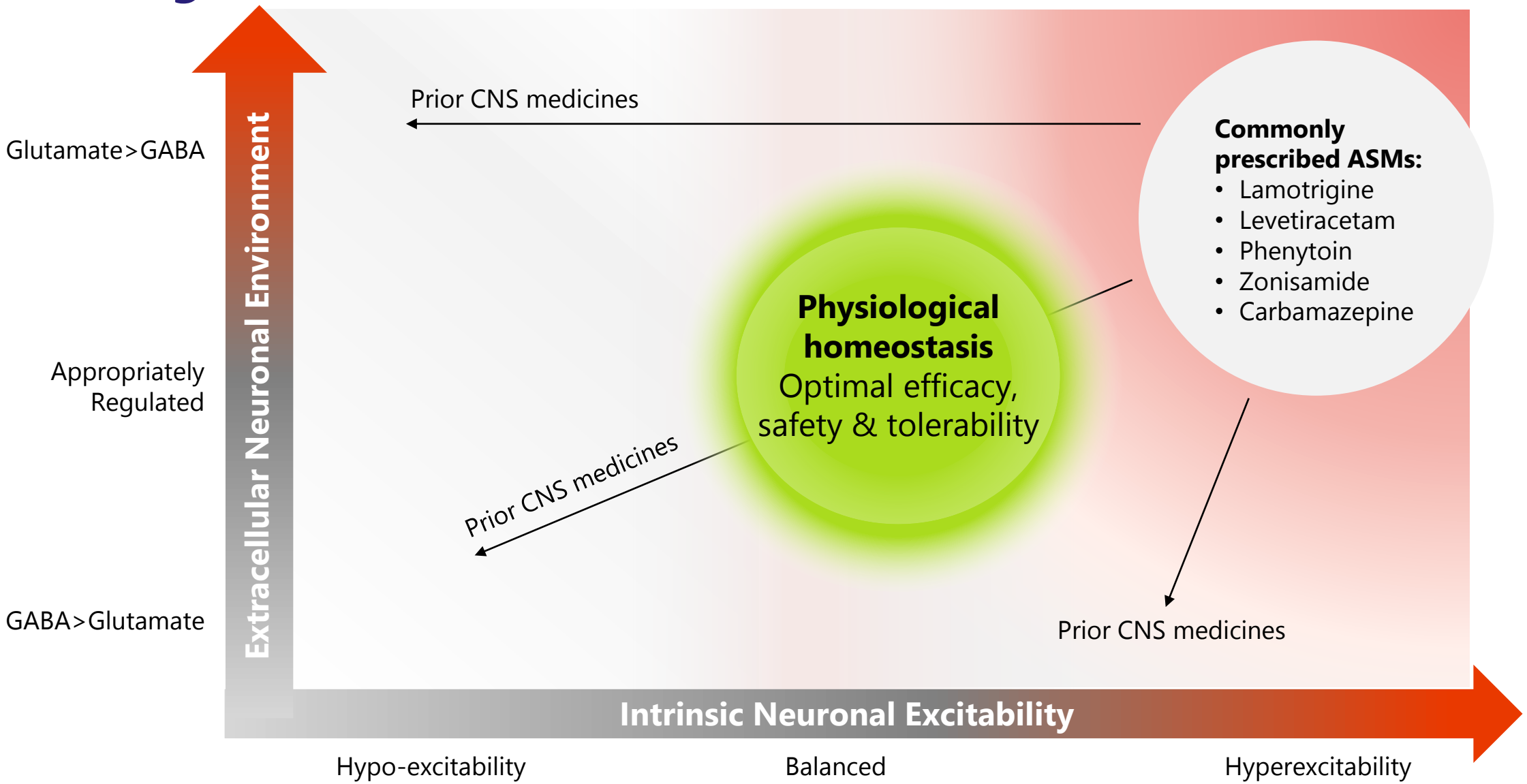
Prior CNS medicines used blunt overmodulation; leading to side effects



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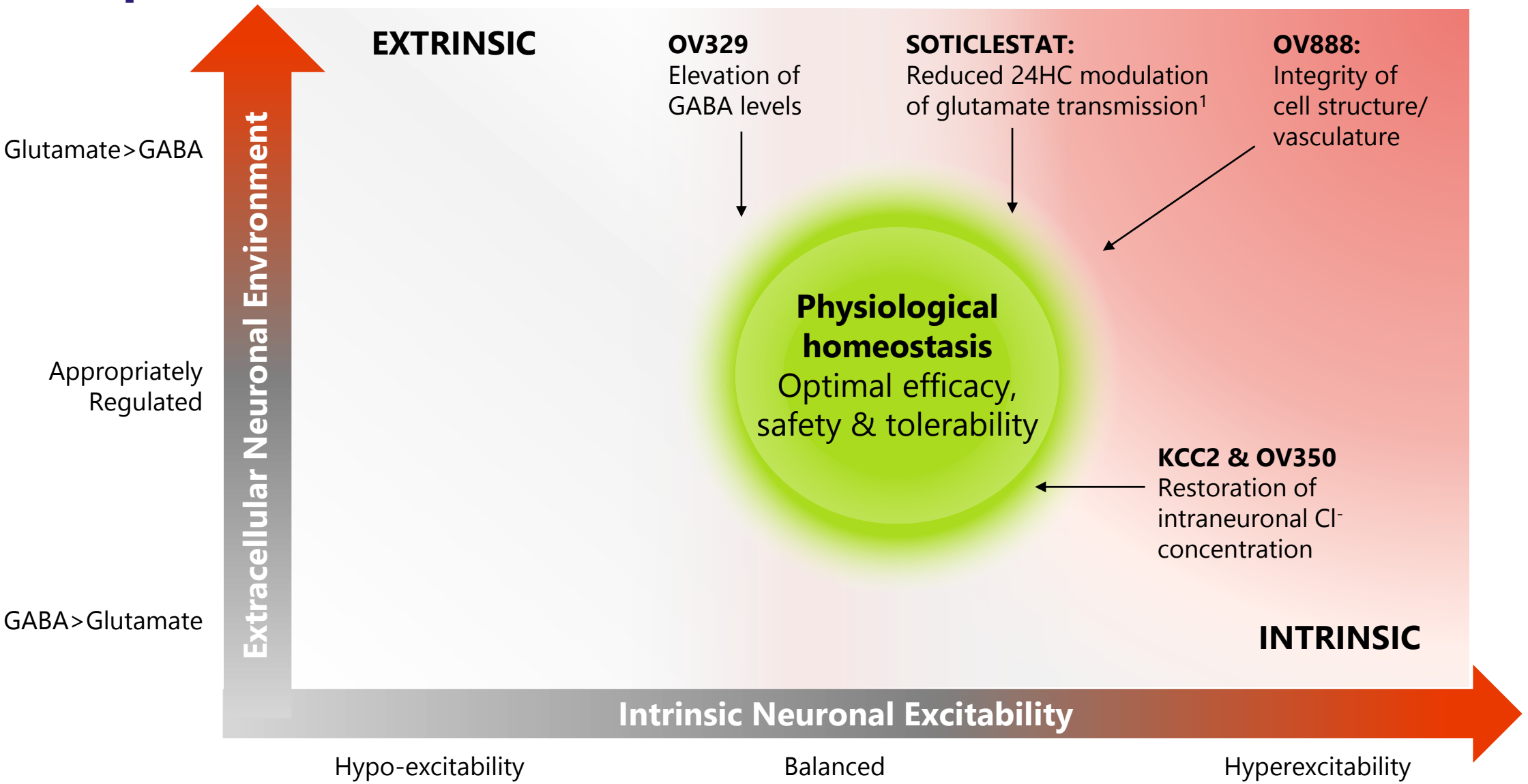
Ovid strategy:
Unique mechanisms to achieve neuronal balance (homeostasis)



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1) Out-licensed rights to Takeda

Ovid mechanisms of action

Mitigating extrinsic & intrinsic causes of neuronal hyperexcitability

Metabolic & enzymatic:
Modulate extracellular neurotransmitter balance

Cholesterol 24 hydroxylase inhibition (soticlestat): Reduces glutamatergic signaling and glial cell inflammation

GABA-AT inhibition (OV329): Chronic and persistent elevation of GABA leads to profound tonic inhibitory activities in neurons

Structural & cellular integrity:
Restore endothelial cell junction integrity (ROCK2 inhibition)

ROCK2 inhibition (OV888, previously GV101): Improving endothelial integrity to reduce leakage

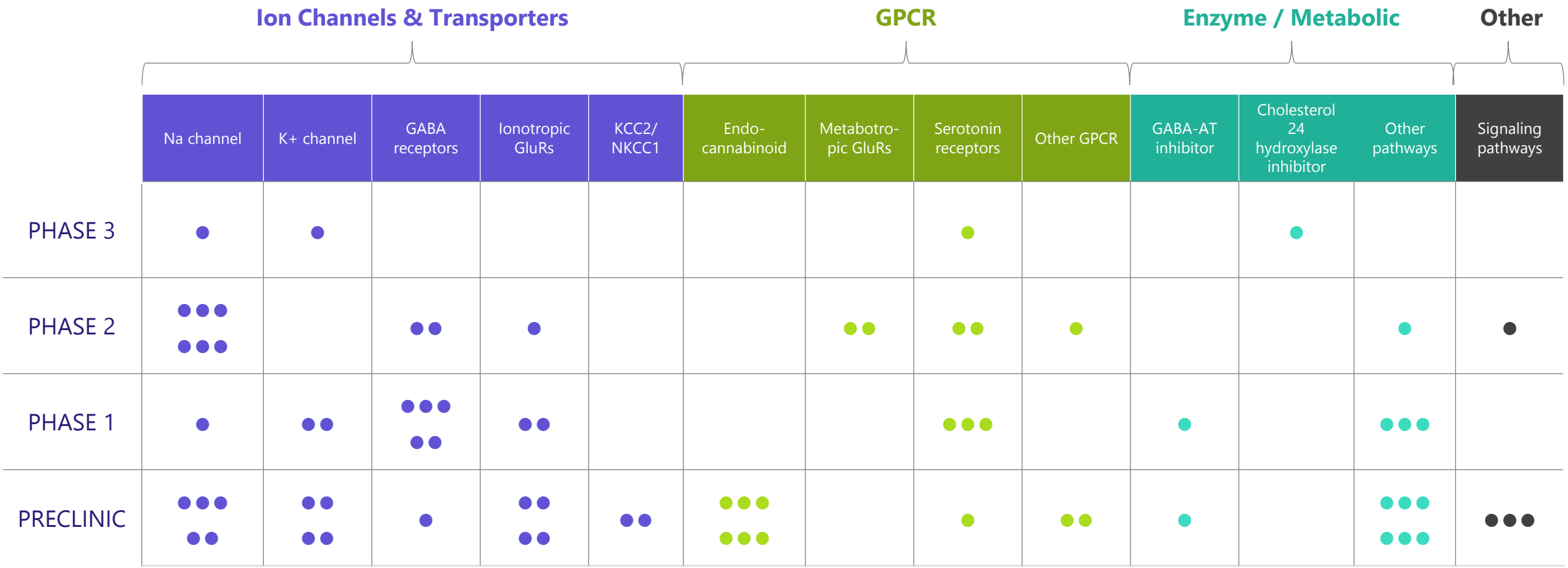
Cellular intrinsic properties:
Restore chloride homeostasis in neurons

KCC2 direct activation (OV350): Restoring proper chloride homeostasis by activating the K+/Cl- co-transporter leads to rebalance of excitatory/inhibitory response of neurons

Specific mechanism references on page 35, 58, 76 and 90

Specific targets will be increasingly competitive & non-differentiating

Illustrative map of disclosed epilepsy programs in development



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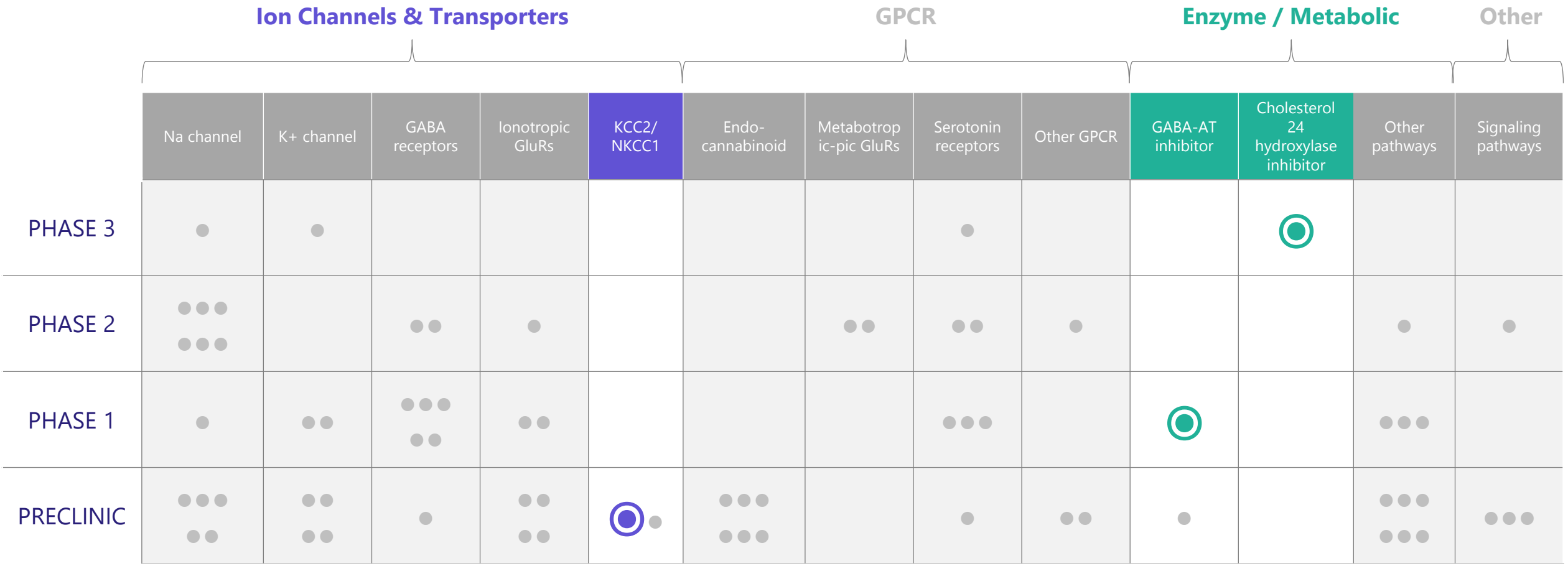
Ovid pursuing unique mechanisms with great potential

Illustrative map of disclosed epilepsy programs in development



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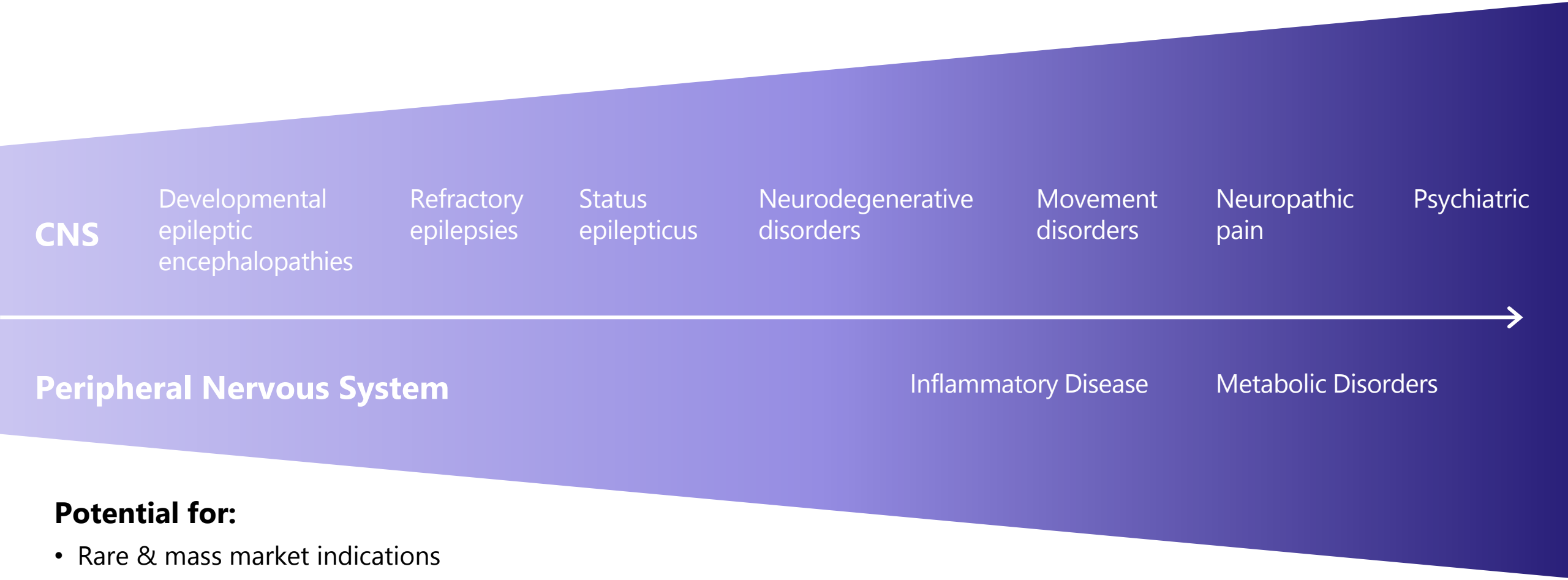
Significant opportunity for growth



Potential for:

- Rare & mass market indications
- Chronic & acute indications
- Efficient proof-of-concept in rare, sentinel populations

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Anti-seizure medicines are commonly used for other CNS conditions[1]

ASM	Bipolar disorder	Neuropathic pain	Migraine	Schizophrenia	Anxiety	Essential tremor
Carbamazepine	✓	✓		●		
Gabapentin		✓	✓		●	●
Lamotrigine	✓	✓	●	●		
Levetiracetam		✓	●			●
Oxcarbazepine	●	✓		●		
Phenytoin	●	✓				
Pregabalin		✓			✓	
Tiagabine	●	●	●		●	
Topiramate	●	●	✓	●	●	✓
Valproate	✓	●	✓	●		
Zonisamide	●	●	●			

✓ = approved for use in this indication or general acceptance of utility; ● = investigational/preliminary use in this indication;

1) Johannessen Landmark C. Antiepileptic drugs in non-epilepsy disorders: relations between mechanisms of action and clinical efficacy. CNS Drugs. 2008;22(1):27-47.

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ROCK2 inhibition & OV888

Dr. Zhong Zhong
Chief Scientific Officer



OV888

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

Hemorrhage, symptom exacerbation, and seizure can happen at any time.

The disease is **mercilessly unpredictable**.

-**Dr. Connie Lee**, mother of daughter with cavernous malformations & founder of Alliance to Cure Cavernous Malformations

ROCK2 inhibition: OV888 (lead program, formerly GV101)

UPDATE

Initiated multiple ascending dose study

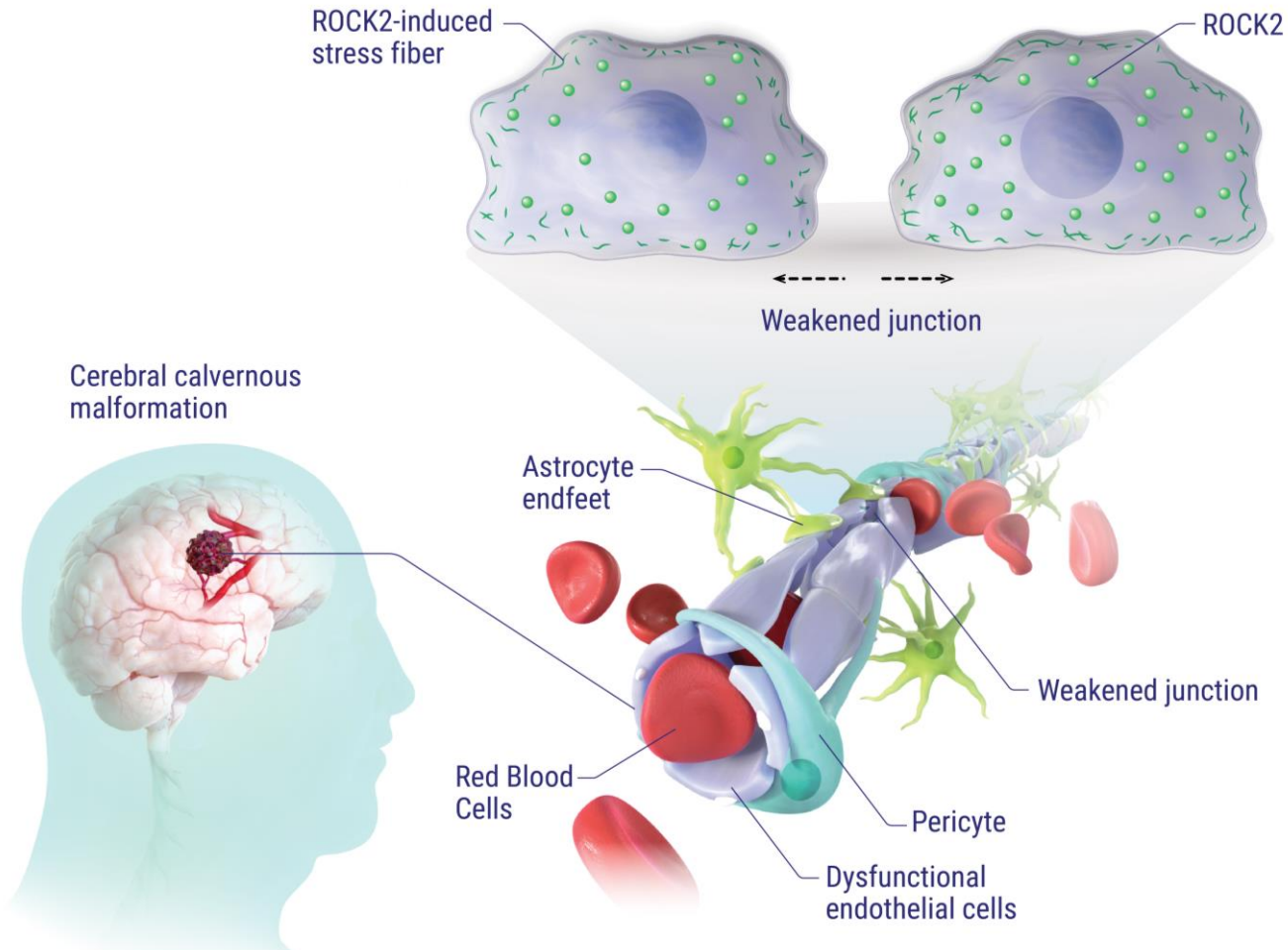
- Studying pivotal gel capsule formulation
- No SAEs observed

Intend to initiate signal-finding trial in H2 2024

- Strong mechanistic rationale for ROCK2 signaling pathway in multiple CNS indications
- Blood-brain barrier penetrant in preclinical studies
- Well characterized safety profile in humans
- Most highly selective inhibitor for ROCK2 (not ROCK1) that is known[1,2]
- **Potential to be 1st disease modifying treatment for cerebral cavernous malformations (CCM)**

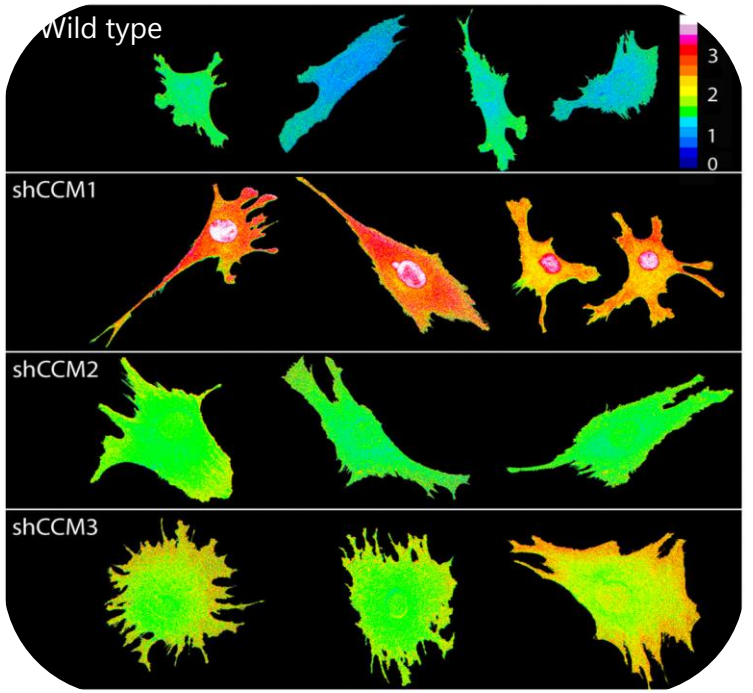
1) Based upon animal models
2) Ann Clin Transl Neurol. 2014 Jan; 1(1): 2–14. Published online 2013 Nov 19.

Illustrative cerebral cavernous malformation (CCM) brain



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

EXAMPLE AT CELLULAR LEVEL



Relative to wild type (healthy) cells CCM exhibits cellular mis-formation due to stress fibers

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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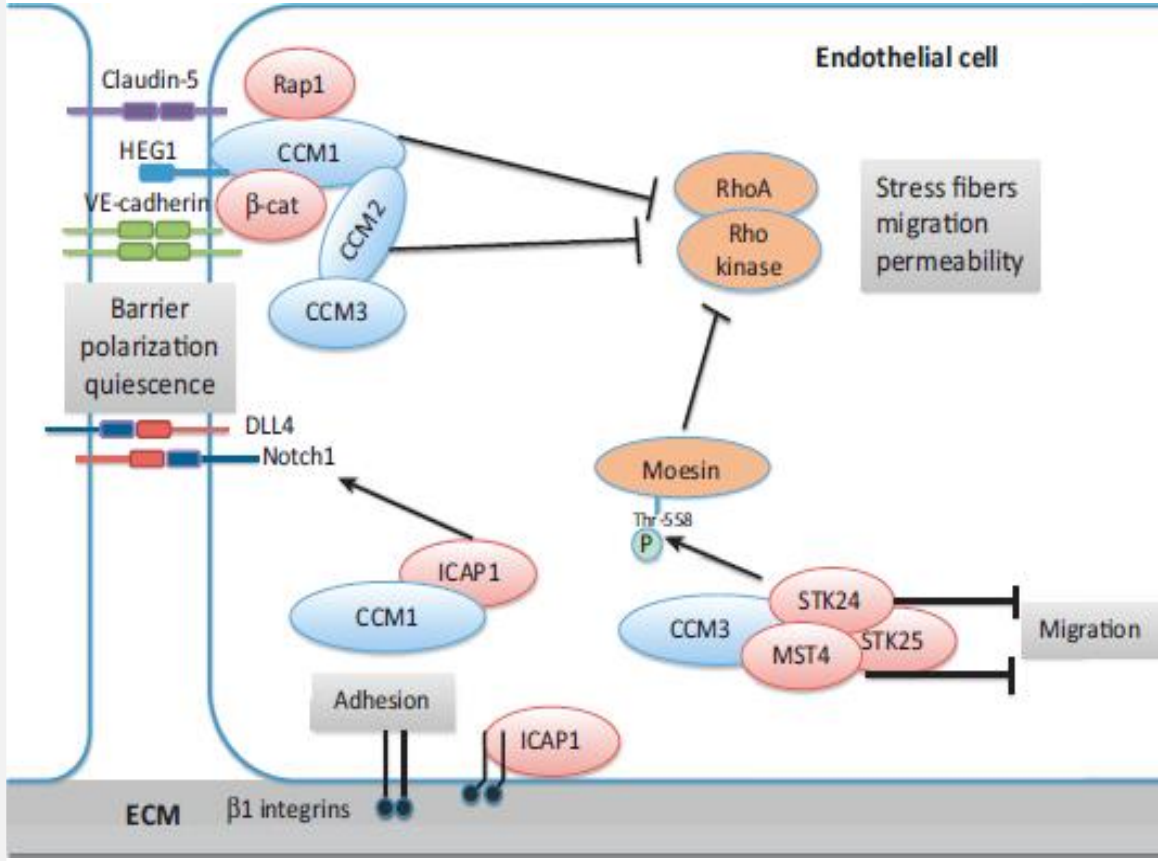
Role of RhoA kinases in cellular formation & adhesion

- Underlying endothelial cell culture knockdown of CCM1, CCM2, or CCM3
  - Causes stress fiber formation
  - Loses of junctional integrity due to an increase RhoA activity
- Rho-associated protein kinase (ROCK) is an effector kinase of RhoA
  - RhoA is hyperactive in brain capillary endothelial cells in people with CCM
  - Dysregulates endothelial cell function
- Targeting ROCK rescues CCM endothelial dysfunction phenotypes[1,2,3]



Source: Fischer et al, 2013.

1) Whitehead KJ, Chan AC, Navankasattusas S, Koh W, London NR, Ling J, Mayo AH, Drakos SG, Jones CA, Zhu W, Marchuk DA, Davis GE, Li DY. The cerebral cavernous malformation signaling pathway promotes vascular integrity via Rho GTPases. Nat Med. 2009 Feb;15(2):177-84. 2) A. L. Borilkova, et. al (2010) Journal of Biological Chemistry, Vol 285. 11760 and O. Pertz, et al (2006) Nature, Vol 440:1069 3) 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.

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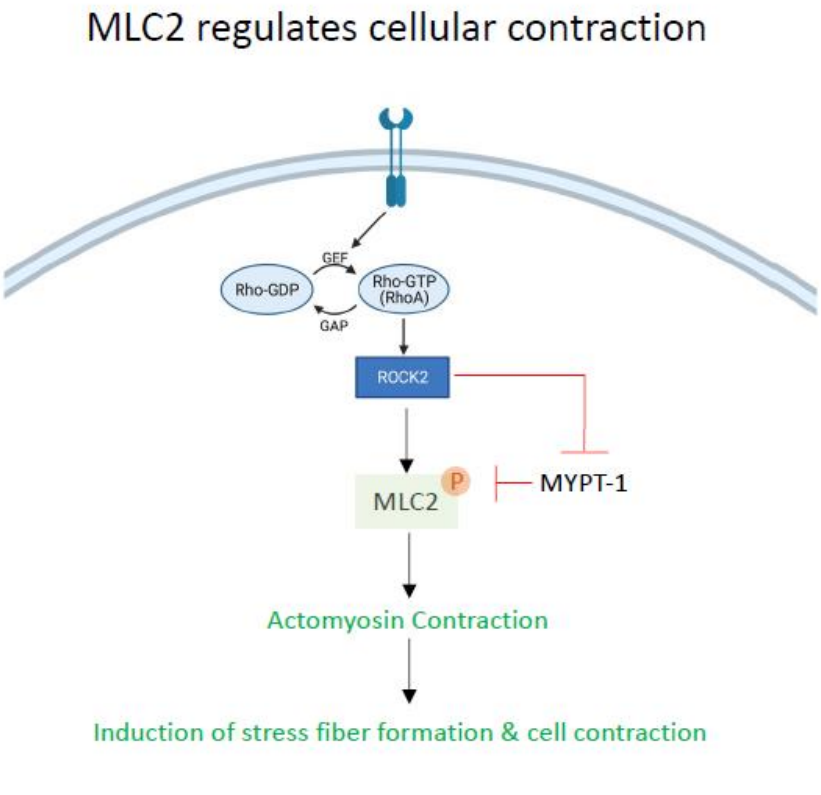
Mechanistic rationale for ROCK2 in CCM: MLC2 phosphorylation upregulated with CCM mutations

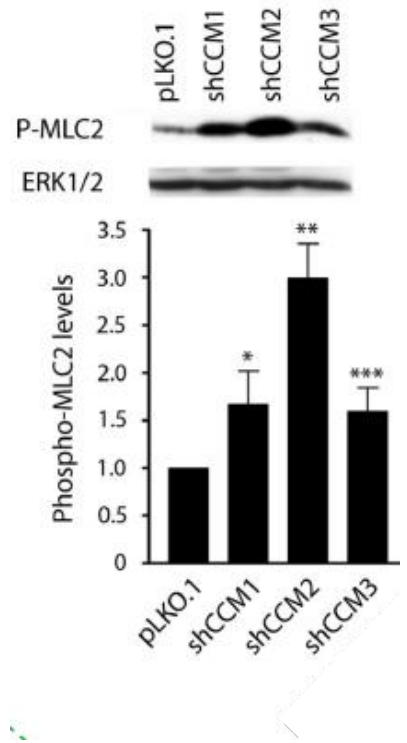
ROCK is activated by RhoA

Phosphorylates substrates for the regulation of actin cytoskeletal dynamics:

- Myosin light chain (MLC)
- Myosin light chain phosphatase
- LIM kinase

ROCK has also been shown to regulate vascular permeability





RhoA and ROCK2 connect CCM protein complex to cytoskeletal dynamics

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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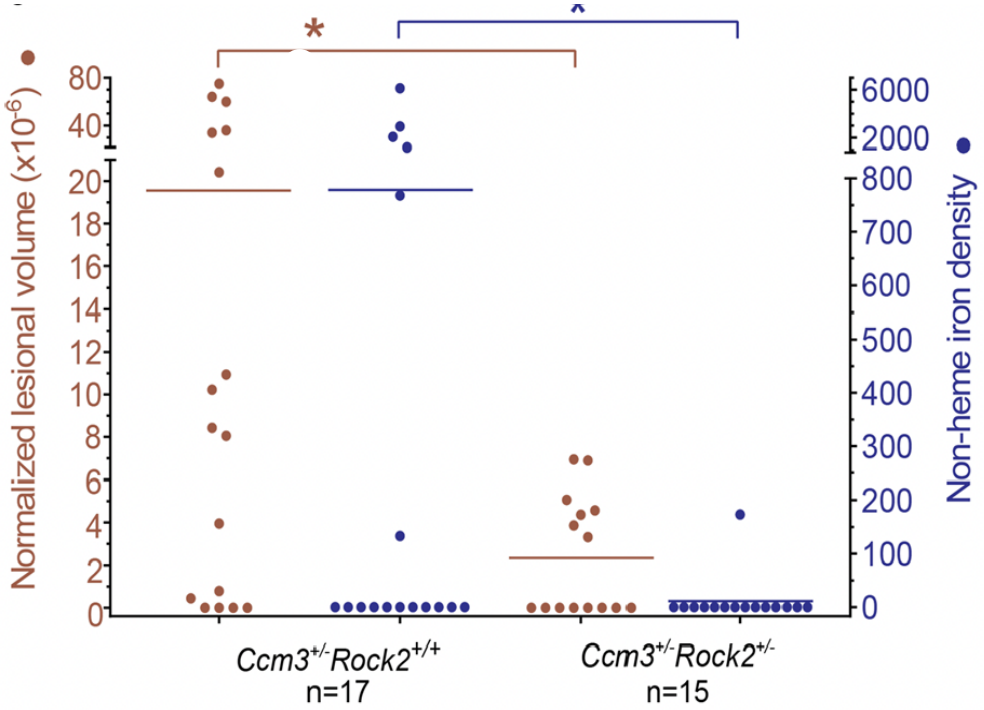
Validation of ROCK2 vs. ROCK1 as Targets for CCM

ROCK2$^{+/-}$, not *ROCK1*$^{+/-}$ mice have lower cavernous angiomatosis

Transgenic mouse model of CCM3

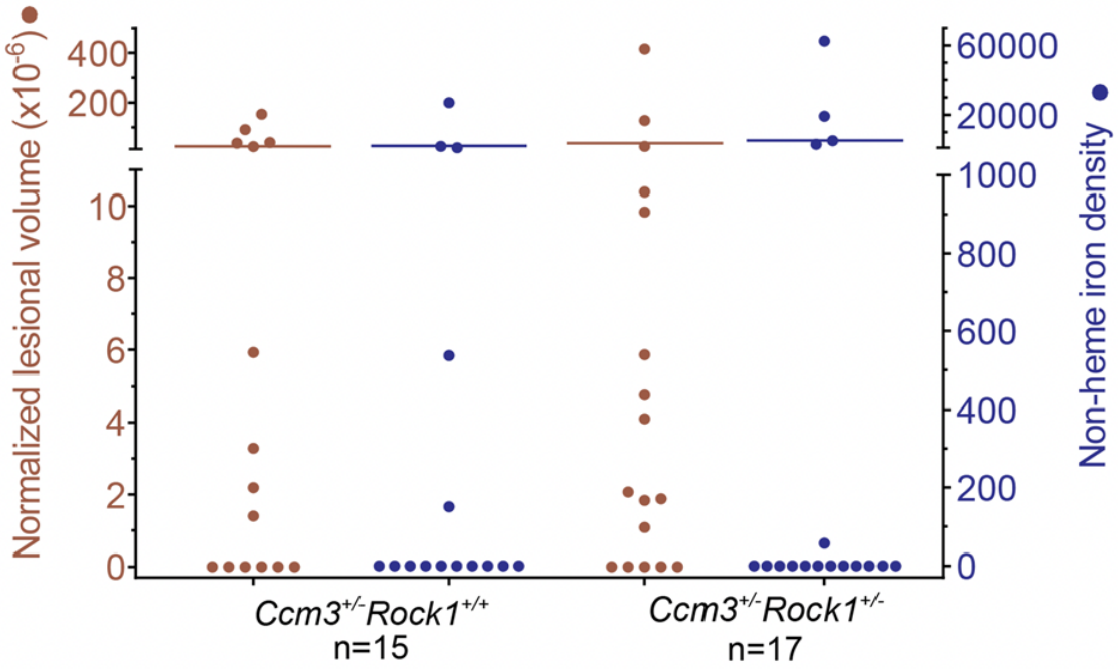
ROCK2:

Rescue effect & reduced a marker of hemorrhage



ROCK1:

No rescue effect



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

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

	ROCK2 IC_{50} (uM)	ROCK1 IC_{50} (uM)	Selectivity (ROCK1/ROCK2)	BBB Penetrant	Off-Target Effects	Indication
OV888 OVID/GRAVITON	**0.002-0.02**	**12.1**	**1071 fold**	✓		**CCM**
KD025[1] Kadmon Pharmaceuticals	0.105	24	~80 - 100 fold	×		Graft vs host disease
NRL-1049[2] (Neurellis)	0.24 – 0.73	3.9 – 10.2	13.9 – 16 fold	✓	✓	CCM

Molecules with pan-ROCK inhibition have shown off-target effects

1 Ann Clin Transl Neurol. 2014 Jan; 1(1): 2–14. Published online 2013 Nov 19. doi: 10.1002/acn3.19

2 https://patents.google.com/patent/US10106525B2/en

Chart based on biochemical assays

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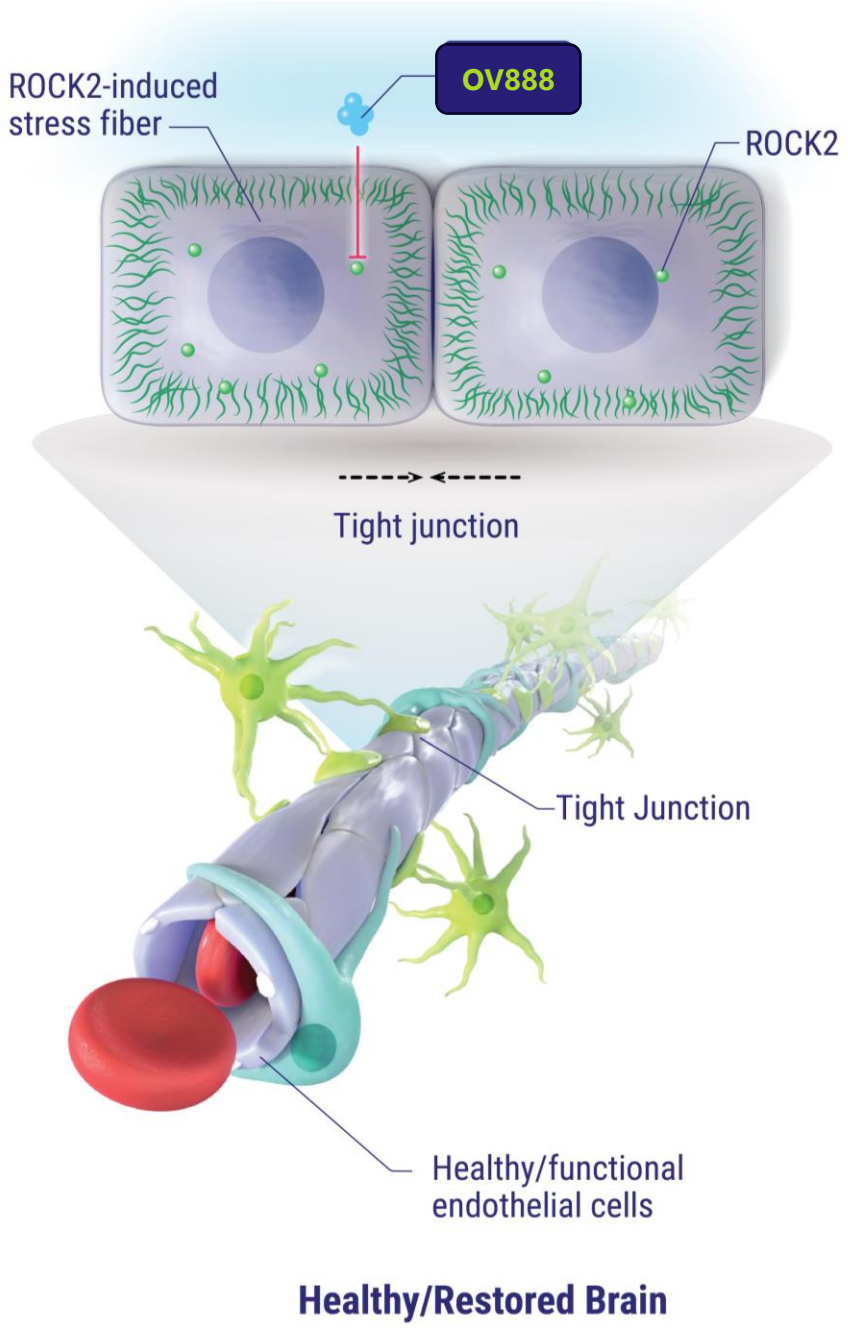
Believed mechanism of action for OV888

- Inhibits ROCK2
- Returns extracellular matrix and tube formation to more normalized state
- **Thereby, anticipated to help stabilize and shrink cavernoma lesions**



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Unmet need in cavernous malformations

Dr. Connie Lee, President & Founder of the Alliance to Cure Cavernous Malformations

ALLIANCE TO CURE

CAVERNOUS MALFORMATION



Cerebral Cavernous Malformation (CCM)

Connie Lee, CEO

October 2023

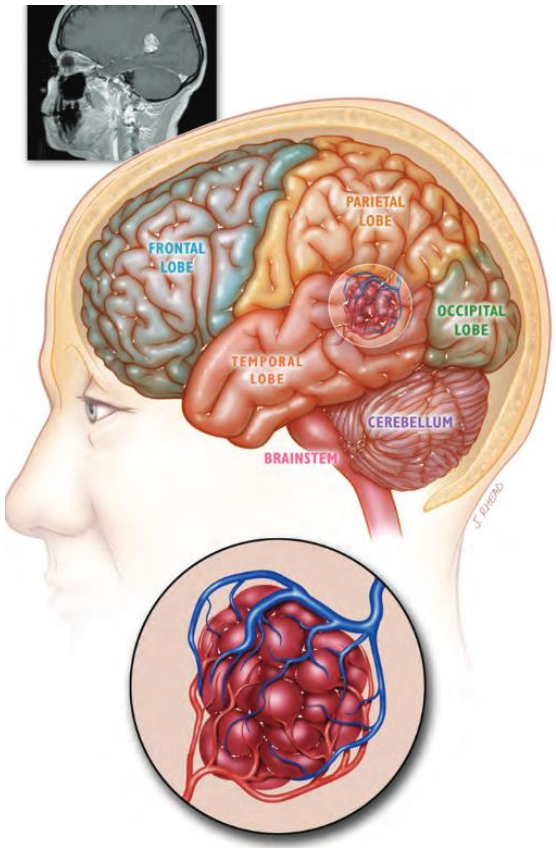
What is a Cavernous Malformation?

A **cavernous malformation** is a blood vessel abnormality characterized by large, adjacent capillaries with little or no intervening brain.

- Cavernous malformations can occur anywhere in the central nervous system
- The blood flow through these vessels is slow and can leak into the surrounding brain or spinal cord tissue, causing seizures (50%), hemorrhage (25%), and functional neurological deficits (25%).

These malformations can also be classified as either **sporadic** or **familial**.

- Sporadic CCMs typically present as **solitary lesions** in otherwise healthy individuals.
- Familial CCMs present with **multiple lesions** and follow an **autosomal dominant** inheritance pattern.
  - Familial CCMs are associated with heterozygous loss of function (LOF) mutations in **CCM1 (KRIT), CCM2, or CCM3 (PDCD10).**
- Aggressive sporadic and familial lesions may also harbor **PIK3CA** or **MAP3K3** mutations.



Diagnostic Radiography

- On MRI, lesions appear popcorn-like with an outer dark ring of residual blood product called hemosiderin.

- The number of lesions in familial CCM can become extreme – often too many to count.



ALLIANCE TO CURE
CAVERNOUS MALFORMATION

Cavernous Malformation Has a High Unmet Need

1 in 500

people have at least one cavernous malformation in their brain, making it the 3rd **most common CNS vascular abnormality.**



Age 25-45

is the most common time for symptom onset, often leading to lifelong disease burden.

Prior CCM hemorrhage is a **significant risk factor** for another hemorrhage.

Within **5 years** of an original hemorrahage, up to **1 in 3** lesions will undergo a second bleed.

8000+

are diagnosed in the US each year. At this time, 50% will eventually undergo brain surgery.

The US economic burden of symptomatic CCM patients equates to an estimated lifetime healthcare cost of

~$2+ billion

ALLIANCE TO CURE CAVERNOUS MALFORMATION

What Challenges Do Patients Face?

- Hemorrhage, symptom exacerbation, and seizure can happen at any time. The disease is mercilessly unpredictable.
- 15-20% of patients in our registry experience serious, lifelong disability. Long-term deterioration from these disabilities can cause premature death. CCM-related seizures can also be fatal.
- All patients are traumatized.
- Brain surgery or symptom management remain the only treatment options. Surgery is not an option available to everyone.
- Because the illness most often strikes young adults who may already be parents, the disease affects the entire family unit.







ALLIANCE TO CURE
CAVERNOUS MALFORMATION

Thank You!

Our families are hopeful for a day when they no longer live in fear of their next hemorrhage, a new onset seizure, or their next life-changing neurological event.

Ovid® Therapeutics







ALLIANCE TO CURE
CAVERNOUS MALFORMATION



OV888 clinical development update

Dr. Manoj Malhotra
Chief Medical Officer

OV888 clinical development update

PRIOR PHASE 1: NANO-SUSPENSION

Single & multiple ascending dose study in healthy adult volunteers in 2022

- 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%)
- Similar AUC to U.S. study (AUC 11,600 in 1,200 mg group)

PROGRESS UPDATE: OV888 CLINICAL FORMULATION

Timing:
- Initiated multiple ascending dose trial in Q3

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

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

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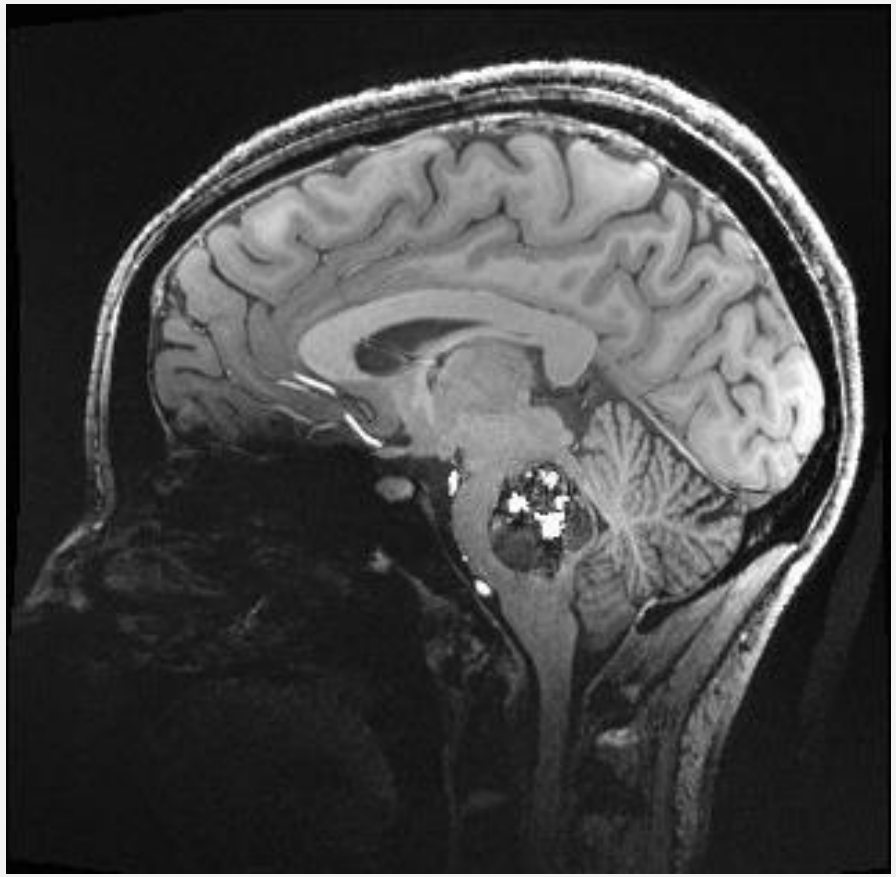
What comes next?

- Establish proof of concept to “tie” the radiological endpoints to functional & quality of life endpoints

- Anticipated enrichment strategy
  - Prioritize brainstem and symptomatic patients for whom surgery is not preferred
  - Radiological endpoints to stabilize and shrink the malformation lesion
  - Clinical endpoints to correlate with treatment
  - Open label “signal finding” portion to measure changes at time intervals
  - Targeting “hard” secondary endpoints

Radiological scan of a brainstem cavernoma



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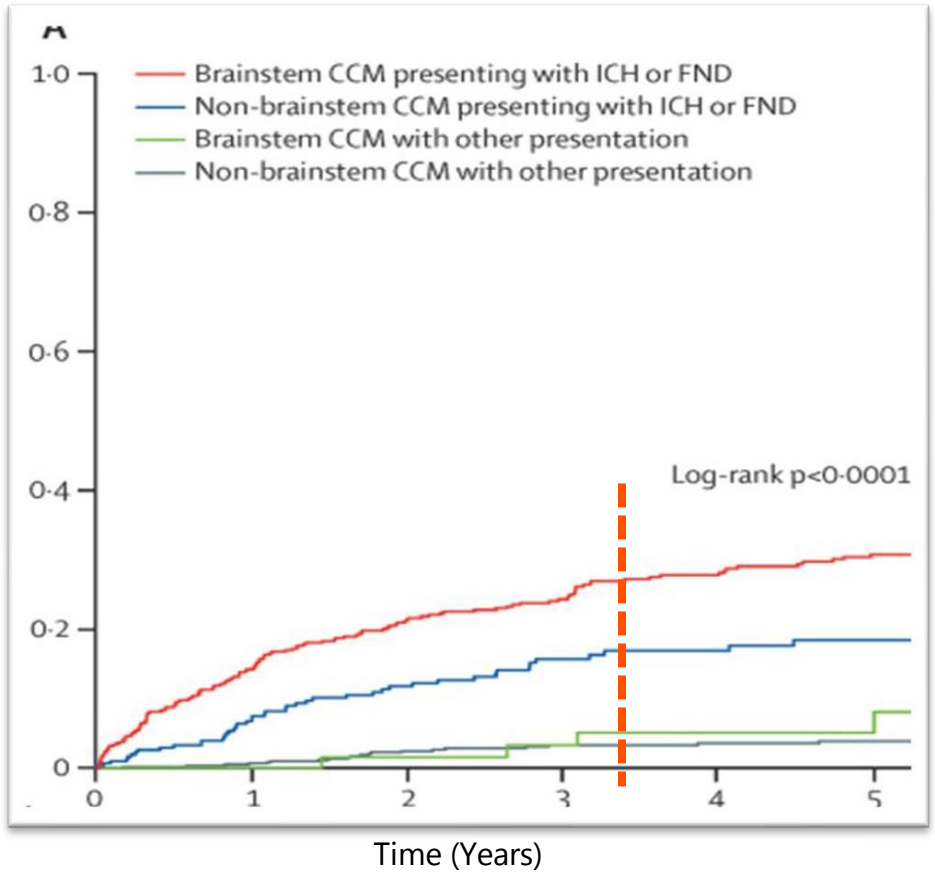
Rates of intracranial hemorrhage among brainstem & symptomatic patients

NATURAL HISTORY



N=1620 from Toronto, Seoul, UK-Scottish Cohort, Mayo-Rochester, Beijing, Paris
Median Follow-up: 3.5 years

Presentation	5-year Risk
Brainstem present with ICH (red line)	30.8%
Non brainstem present with ICH (blue line)	18.4%
Brainstem other presentation (green line)	8.0%
Non-brainstem other presentation (gray line)	3.8%

Courtesy of Dr. Kelly Flemming, Mayo Clinic

SOURCE: Horne, Lancet Neurol, 2015
Dammann WNS, 2016

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OV888: An opportunity to bring hope to the CCM community

Huge unmet need for an effective pharmacological therapy to address the underlying disease

Large market opportunity

~400K

Addressable CCM patients (7 major markets)

Common intracranial vascular malformation in humans

Significant need for a pharmacological therapy

- Lesions can result in intracranial hemorrhage, epileptic seizures, or focal neurological deficits, and potentially lead to severe disability
- No drugs available to prevent and/or reduce the clinical symptoms of CCM
- Only available curative 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

Ovid 2022 Global market research.

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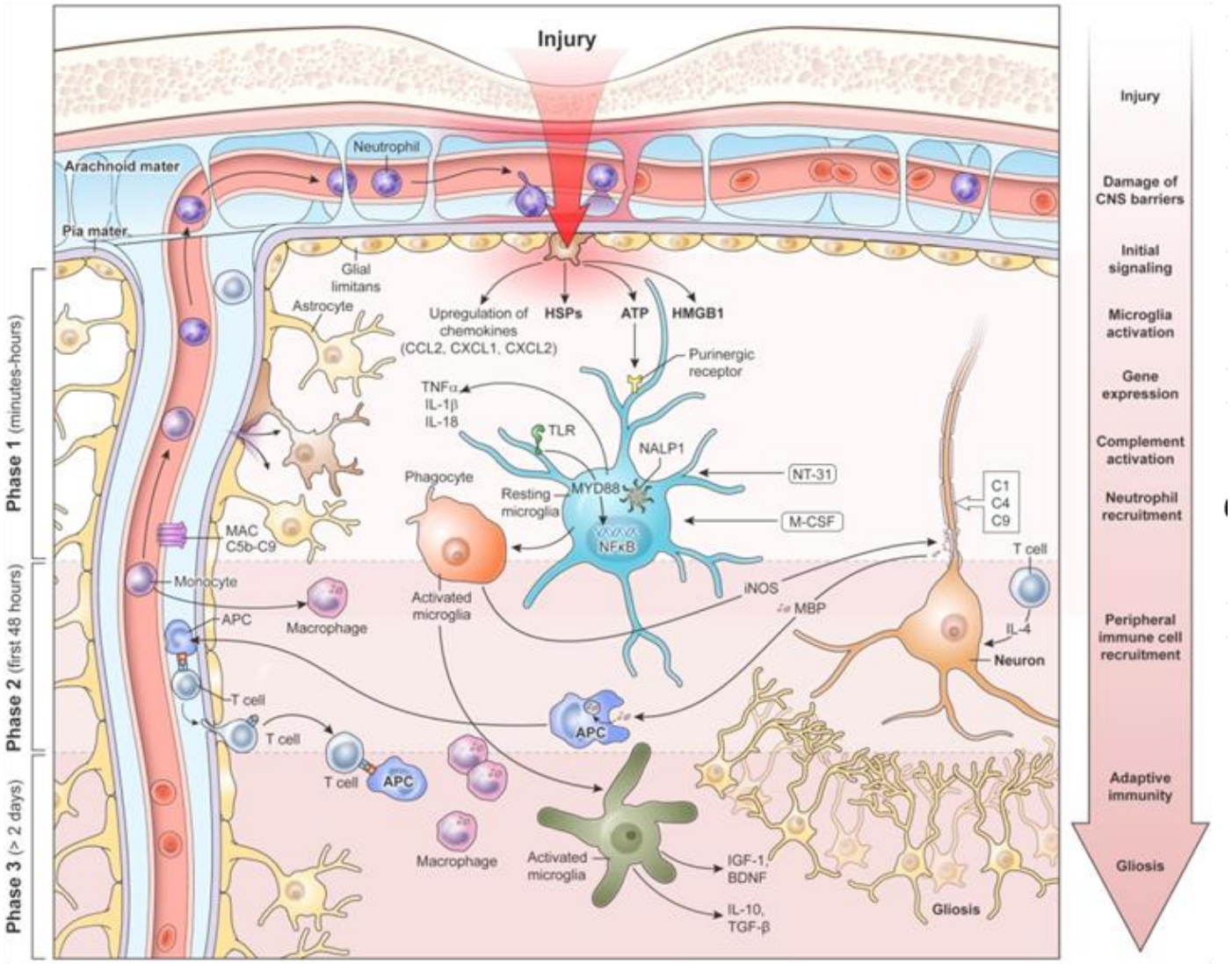
Potential for ROCK2 inhibition in other CNS disorders

Dr. Zhong Zhong
Chief Scientific Officer

Potential of ROCK2 inhibition mechanism for additional indications

Traumatic brain injury (TBI) pathophysiology in pediatrics

- Causes neural damage, cell death and disruption of neural circuits
- Long term consequences:
  - Motor and cognitive deficits
  - Memory impairment
  - Emotional disturbance



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Potential mechanisms for ROCK2 Inhibition in TBI

Endothelial Leakage

- Reestablishment of tight junctions and endothelial barrier formation following trauma
- BBB repair/reduction of brain bleeds, effects on neuroinflammation

Neuroinflammation

- Lessening of leukocyte infiltration into CNS
- Reduced inflammatory cytokine responses and activation of CNS microglia

Axon/Spine Function

- Overcome inhibitory growth environment of lesion – axon and dendrite elongation
- Maintain proper synaptic connections within dendritic spines – learning/cognitive function/synaptic plasticity

Source: 1) Hahmeyer, M.L.d.S.; da Silva-Santos, J.E. Rho-Proteins and Downstream Pathways as Potential Targets in Sepsis and Septic Shock: What Have We Learned from Basic Research. Cells 2021, 10, 1844. 2) https://www.mechanobio.info/cytoskeleton-dynamics/what-is-axon-guidance-and-the-growth-cone/ 3) Ben Zablah Y, Zhang H, Gugustea R, Jia Z. LIM-Kinases in Synaptic Plasticity, Memory, and Brain Diseases. Cells. 2021; 10(8):2079.

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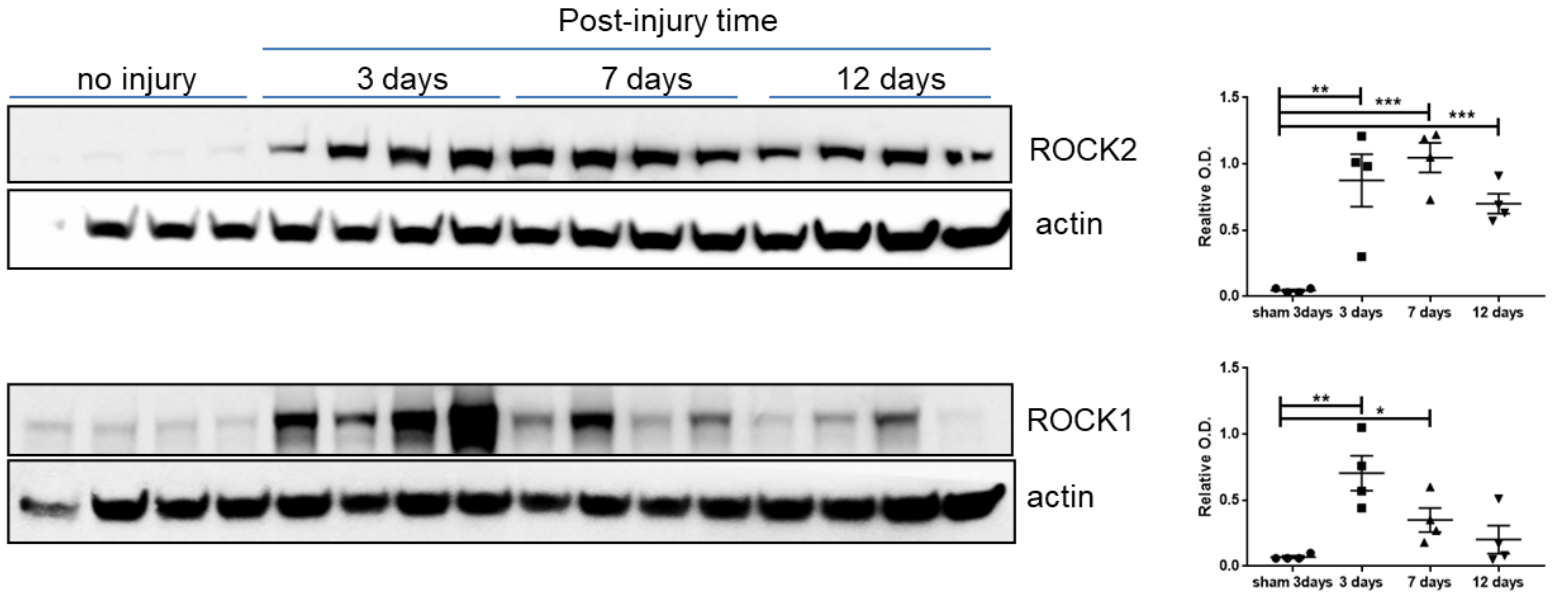
Role of ROCK2 in traumatic brain injury

ROCKs converge & mediate pathogenesis of CNS injury

- Regulators of cytoskeletal and cell adhesion dynamics to affect endothelial integrity
- Promote axonal outgrowth and regeneration post injury
- Inhibition of neuroinflammation

ROCK1 & ROCK2 are differently expressed in brain post TBI



Lysates were generated from brain tissue from mice subjected to CCI model of TBI, each lane represents a different mouse (4 per group)

Data Graviton Biosciences 2023

ROCK2 is uniquely implicated in mouse model of traumatic brain injury

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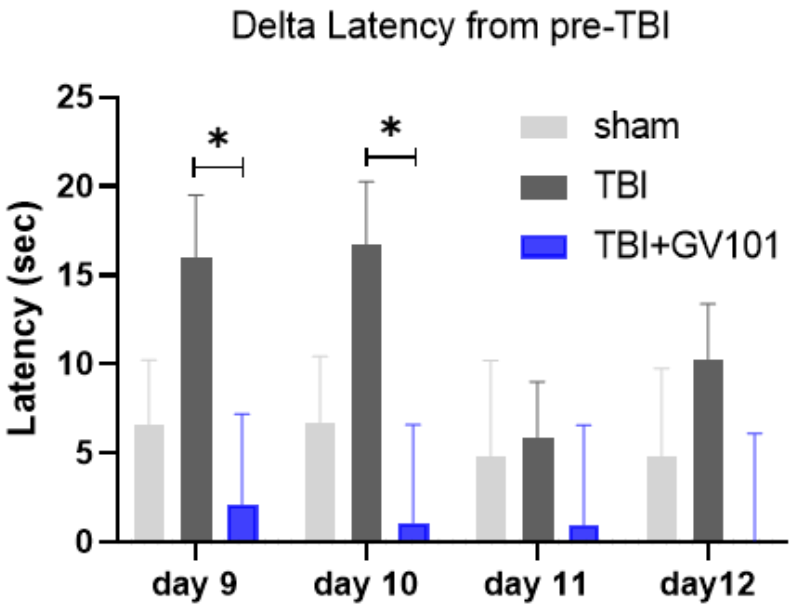
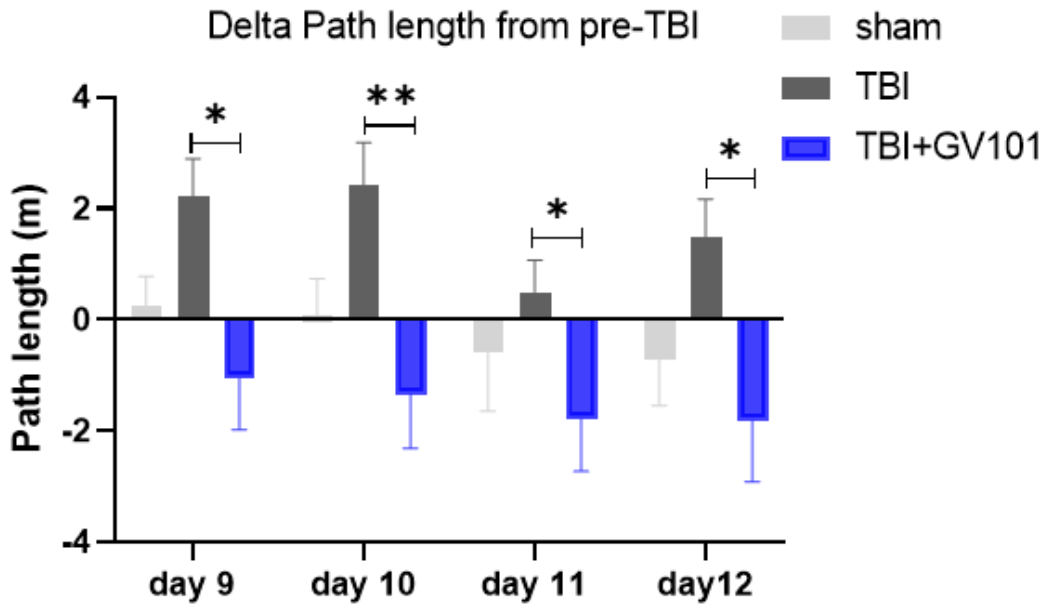
OV888 significantly preserves memory and learning after TBI

Morris Water Maze test : latency to find platform and path length to platform





Individual change as compared to the performance level at day -4 (last day of pre-testing).
Data are presented as mean + SEM, n = 11-15 per group. Statistical significance: treatment effect * p<0.05, ** p<0.01
Group 2 vs Group 3 (Two-way RM ANOVA, Uncorrected Fisher's LSD)

Data Graviton Biosciences 2023

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OV329: Large opportunities

Dr. Manoj Malhotra
Chief Medical Officer



OV329

A next-generation GABA-aminotransferase inhibitor for treatment resistant seizures

…Pediatricians tell you that you never recover from this disease.

- Father of a 10-year-old girl with TSC

Beyond the first line benzodiazepine therapy, we do not have one ASM that is clearly best in stopping status epilepticus…

…among those tested in randomized clinical trials, ASMs stopped the status in less than half of the patients.

- Neurologist, Cleveland Clinic

Graffigna G, Bosio C, Cecchini I. Assisting a child with tuberous sclerosis complex (TSC): a qualitative deep analysis of parents' experience and caring needs. BMJ Open. 2013 Dec 6;3(12):e003707.

OV329: Large opportunities

UPDATE

Phase 1 SAD (3 cohorts complete)

- No safety signals
- Dose escalating

Expanding formulations

- Oral
- Intravenous

Expanding development program

Multiple potential indications

- Chronic
- Acute

- Unique molecule for a validated target, GABA aminotransferase (GABA-AT)
- Promotes inhibitory neurotransmitter (GABA) to reduce seizures
- Established therapeutic window[1]
  - Prior GABA-AT inhibitor, vigabatrin, had no window
- Phase 1 study - exploring safety & surrogate biomarker for efficacy
- New findings support low, repeat dosing:[1]
  - Prolonged effects in seizure reduction
  - Ability to maintain optimal levels of GABA
  - Sustained shifts of tonic and phasic current
  - Established a PD marker for human studies
- OV329 may have utility in acute seizures in addition to chronic

1) In animal models

OV329 development program update

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

ORAL – CHRONIC DOSING

- Three 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 models to further differentiate PK/PD and safety from vigabatrin

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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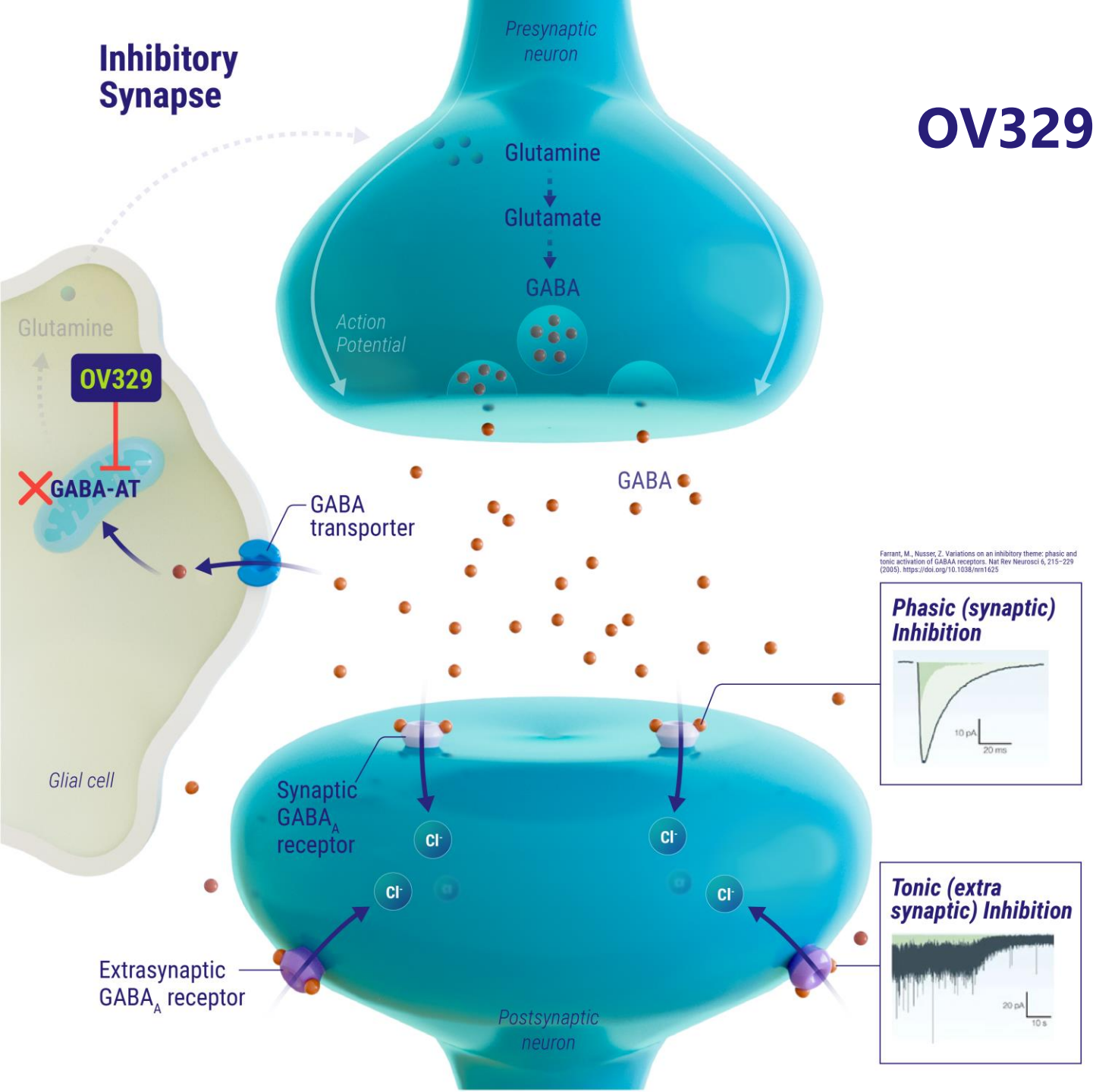
OV329 mechanism of action



- GABA is the major inhibitory neurotransmitter in brain
- OV329 substantially reduces 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

NEW: Preclinical findings



Low, multiple day doses of OV329 have a prolonged effect in seizure reduction



Animal models demonstrate anti-convulsant properties in chronic and acute seizures



OV329 induces profound inhibitory tonic currents in postsynaptic neurons at very low doses



Electrophysiology data shows pharmacodynamic effects at low doses & support signal detection efforts in humans

Supports repeated low dosing of oral OV329 in humans

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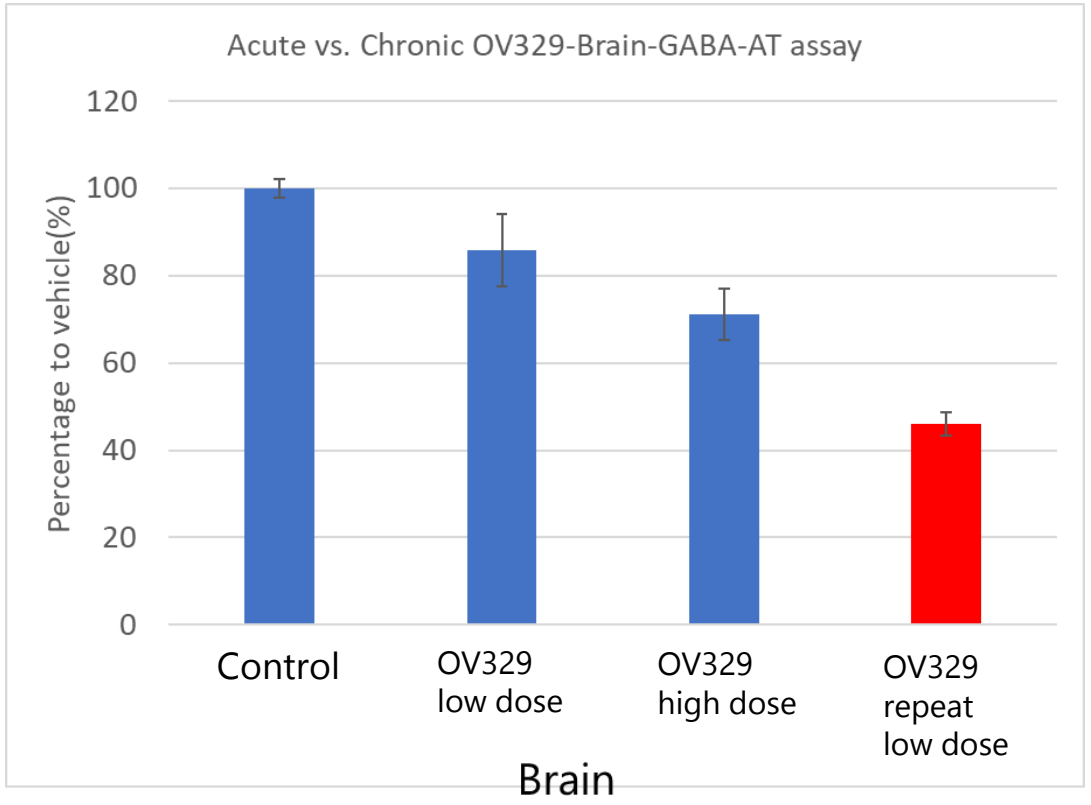
Repeat dosing of OV329 leads to enhanced GABA-AT inhibition



- A single dose of OV329 leads to long-lasting (>24 hours) inhibition of GABA-AT enzymatic activity
- Cumulative effect of repeated, low dosing of OV329 was expected and observed
  - Enhancing GABA-AT inhibition as compared to a single dose of OV329

Persistent and chronic elevation of GABA is expected to modulate neuronal excitability and thereby reduce seizures

OVID data on file

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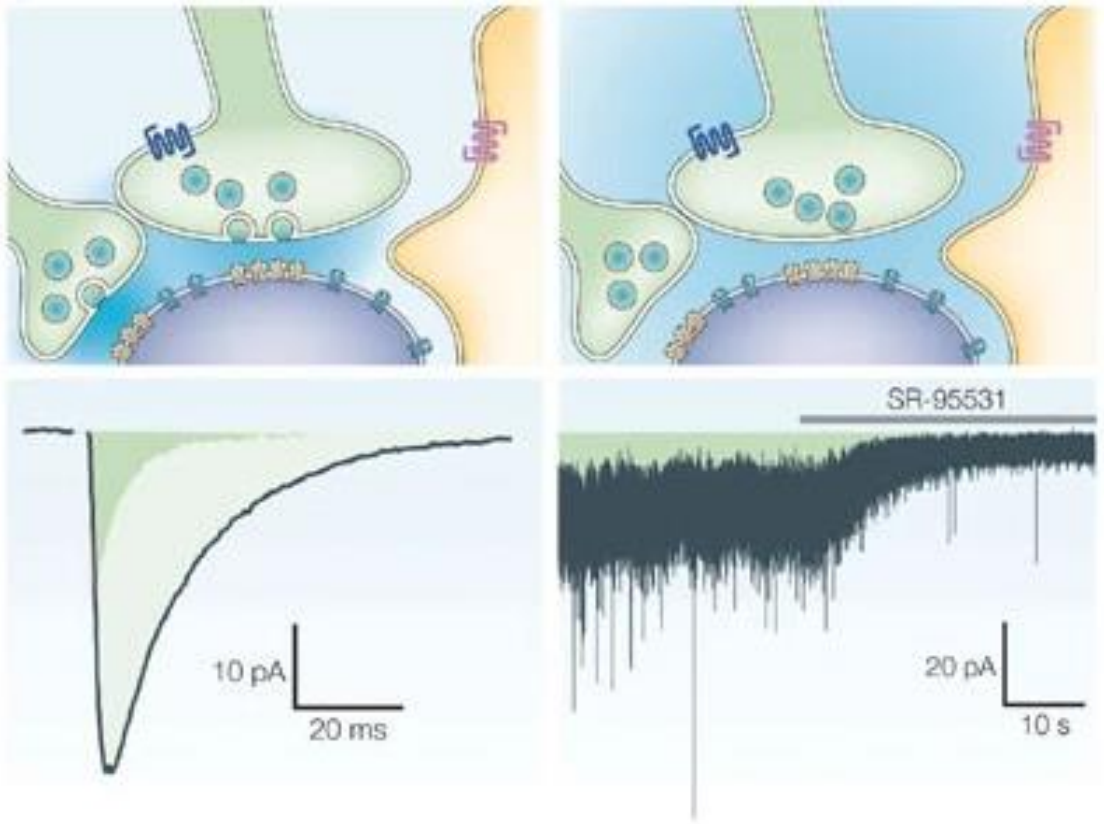
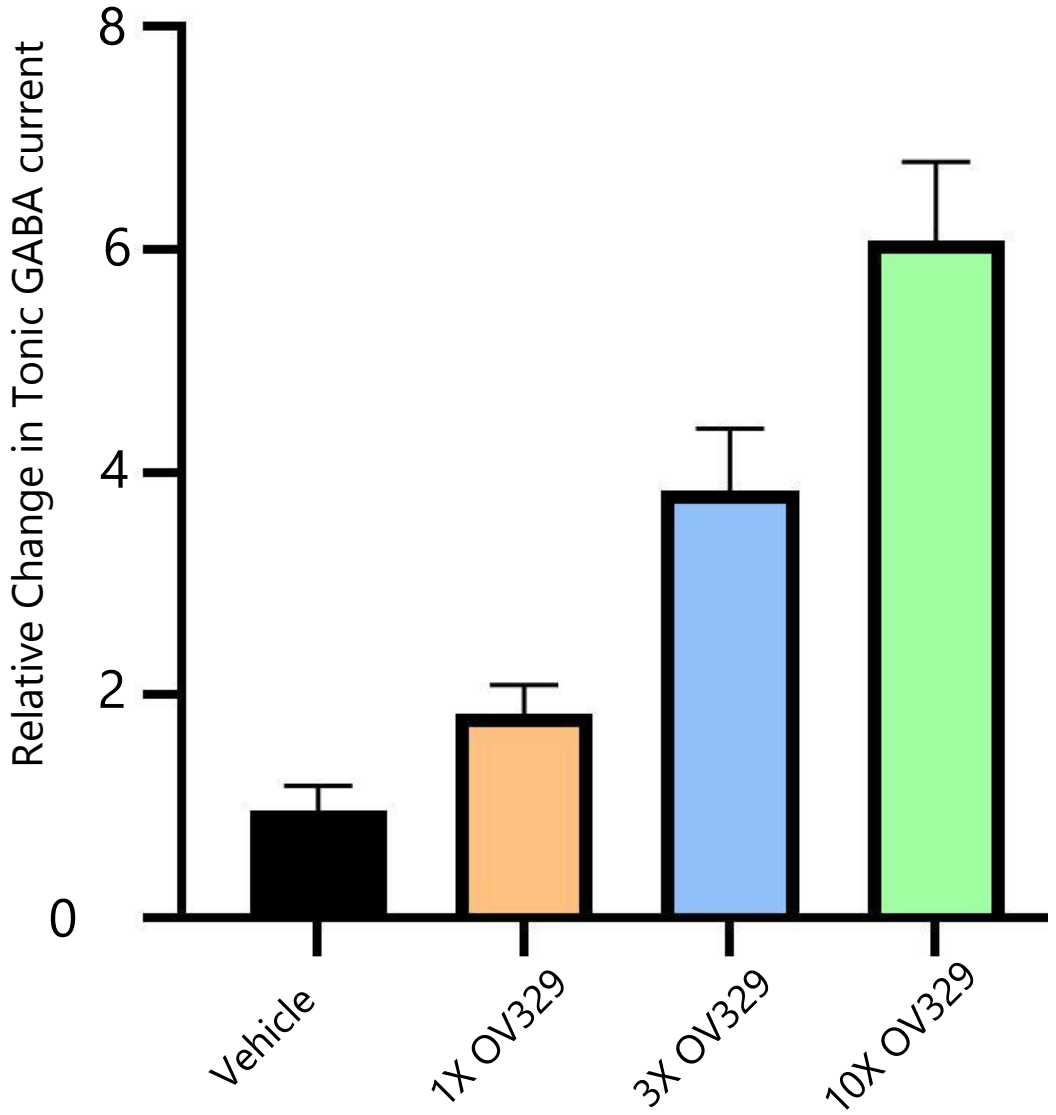
Repeat dosing of OV329 enhances tonic GABA inhibition



Phasic (Synaptic) Inhibition

Tonic (Extra-synaptic) Inhibition



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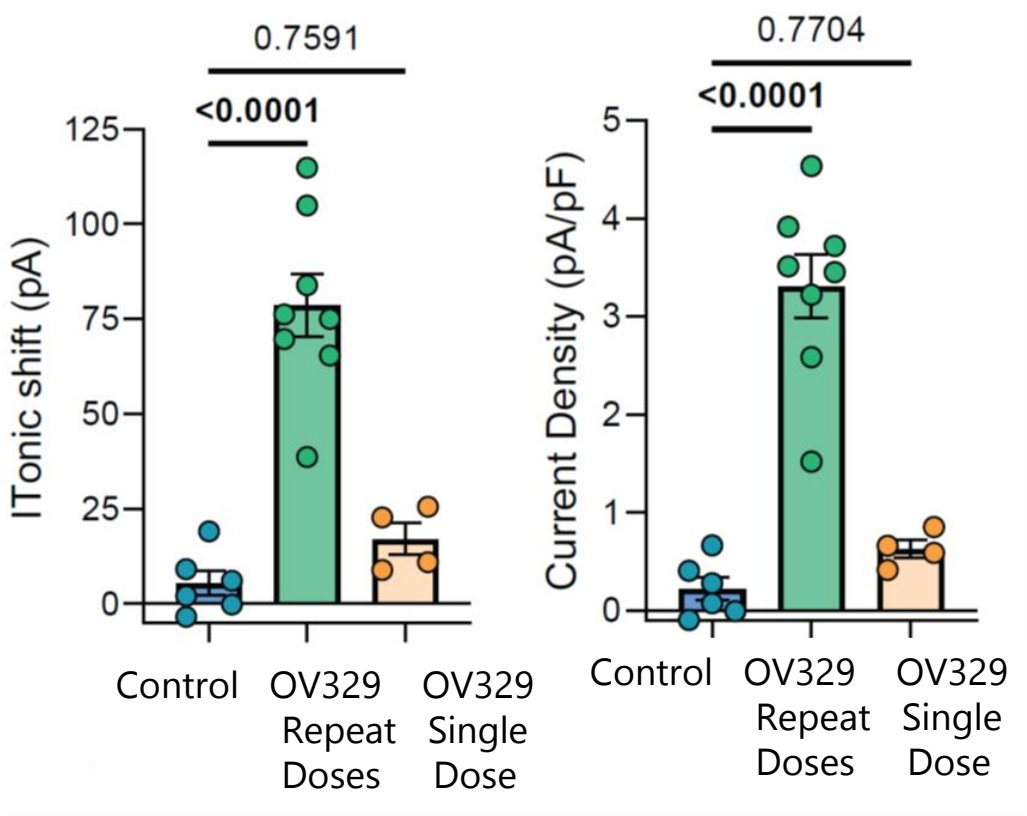
OV329 repeat dosing induced GABA tonic current

CHANGE IN TONIC CURRENT (Mice)



- Acute treatment of OV329 promotes GABA-AT inhibition like vigabatrin
- Modulation of GABAergic inhibition by both phasic (synaptic) and tonic current (extra-synaptic)
- Chronic dosing of OV329 leads to sustained GABA increase and enhanced tonic current (extra-synaptic)
- The tonic GABA inhibitory response is likely to modulate neuronal hyperexcitability more effectively
- Suggests repeated, low dosing of OV329 in humans should suppress seizures

Inhibiting tonic and phasic GABA currents may enable profound & prolonged seizure reduction in humans via repeated, low dosing of OV329

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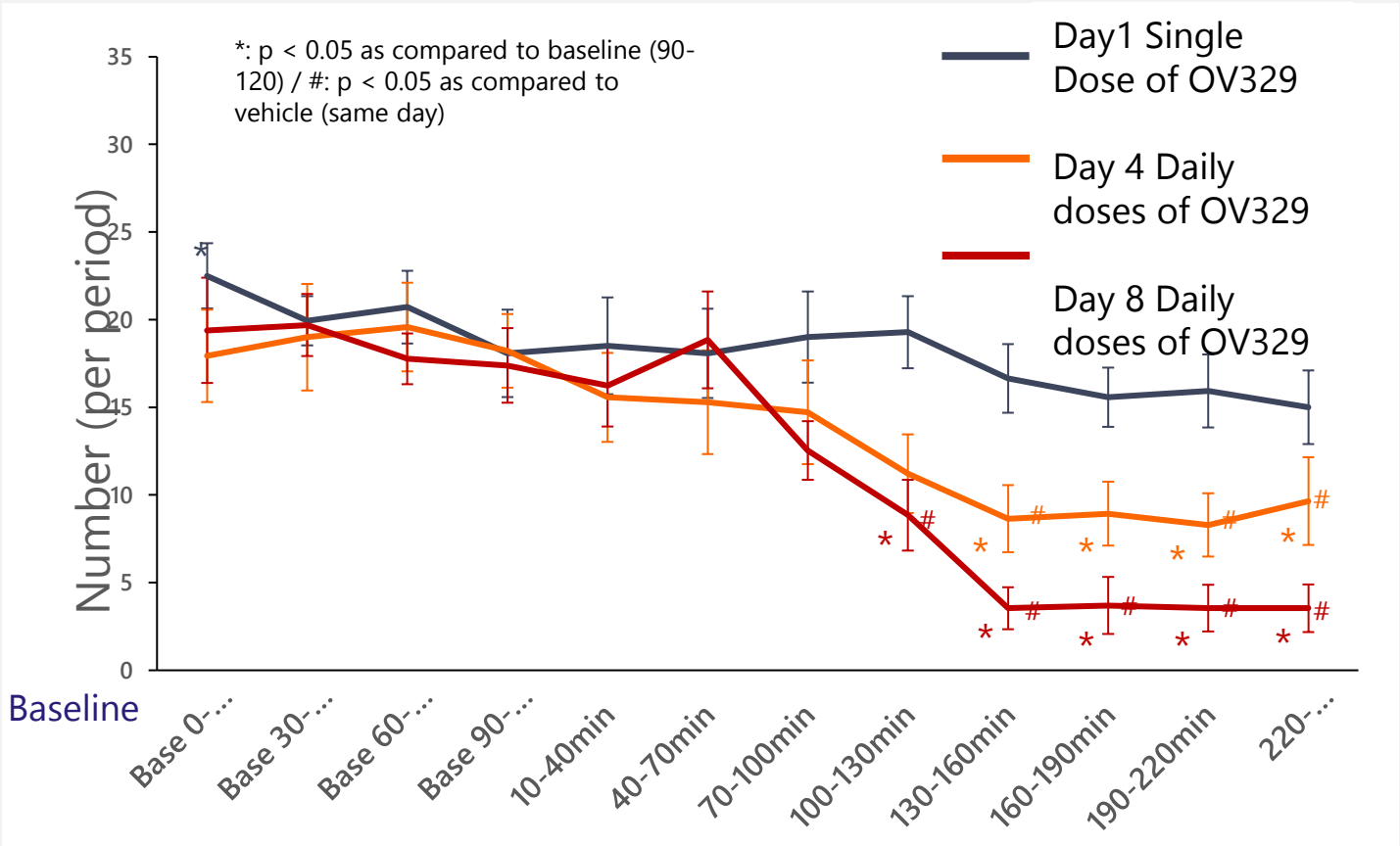
Repeated, low doses of OV329 reduce seizure frequency & duration

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
  - More to be presented at AES 2023

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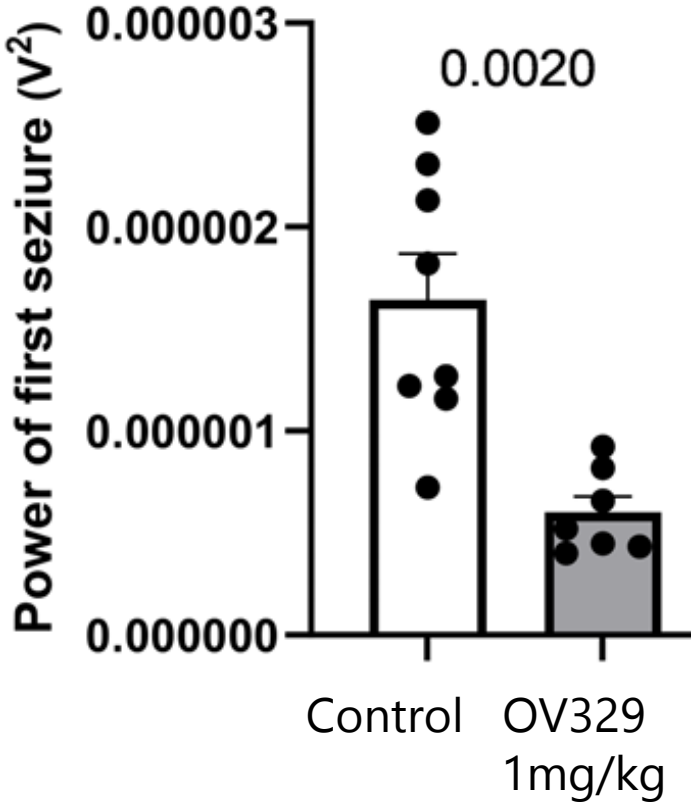
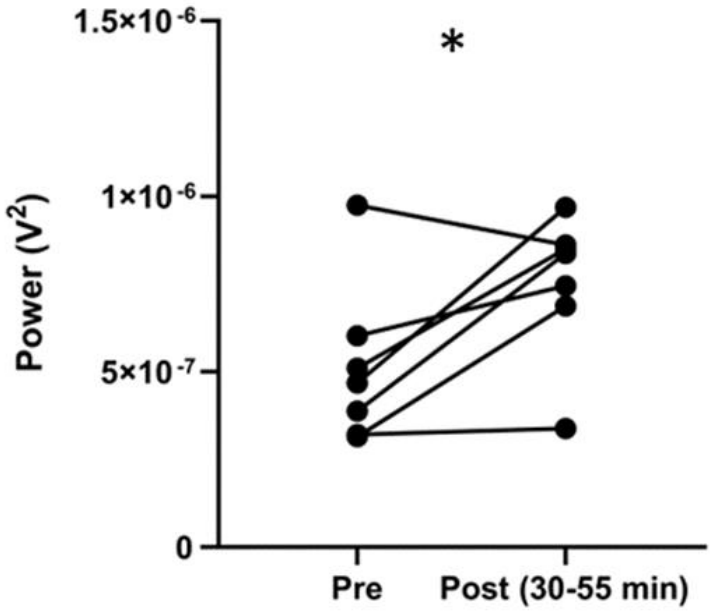
EEG studies indicate OV329 reduces seizures at low doses



EEG power induced by 1mg/kg OV329



- 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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Preclinical findings support human development program

OV329 PROFILE

Significant potency expected to deliver enhanced

- ✓ 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
- ✓ EEG measurements confirm anti-convulsant properties at very low doses
- ✓ Tissue accumulation of OV329 is expected to be less than vigabatrin

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OV329 potential for acute seizures

- Mounting evidence that GABA-AT inhibition may be effective to treat Status Epilepticus (SE)
- More epileptologists are using Vigabatrin to treat SE
- OV329 in a kainic acid induced mouse SE model demonstrate that it can significantly reduce:
  - EEG power of seizures
  - Power of status epilepticus[1]
- Electrophysiology data in acute brain slices show enhancement of both phasic and tonic currents within hours after OV329 treatment, a highly relevant mechanism in status epilepticus[1]

"…results suggest that vigabatrin has beneficial role in the management of patients with super-refractory status epilepticus (SRSE).

Resolution of SE was achieved in 70% (38/54) of patients on VGB."

- Dr. R. E. Ramsay[2]

"…two cases where Vigabatrin (VGB), an irreversible binder of GABA transaminase, was successfully used for SRSE after exhausting the use of all the recommended treatment modalities… within 24 hours of the first dose. "

- Dr. J McCormick et al.[3]

OV329 may be a promising potential intravenous (IV) treatment for acute seizures & in-hospital dosing for chronic epilepsy patients

Source: 1) Ovid data on file 2) Ramsay, Clinical Neurophysiology, Volume 129, Supplement 1, May 2018, Pages e206-e207 3) Jason McCormick, Nicholas Jonas, R. Ramsay, Vivek Sabharwal; Neurology, April 23, 2012; 78 (1 Supplement) First published February 8, 2016

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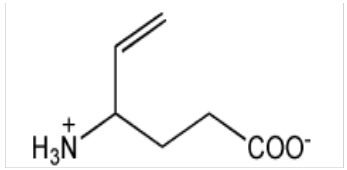
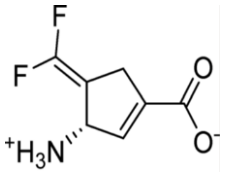
OV329 profile differentiates from vigabatrin

	Vigabatrin	OV329
Molecule		
Potency	IC_{50}: ~60 – 100 µM	IC_{50}:~0.1 - 0.3 µM
Exposure characteristics	$T_{1/2}$ >5.0 Hours Both R (inactive) & S (active) enantiomers	Reduced exposure ($T_{1/2}$ ~1.0 Hour) coupled with prolonged PD duration
Mechanism of enzyme inhibition	Covalent modification of GABA-AT (early generation chemistry, primarily Michael addition pathway) [1]	Electrostatic (more sophisticated chemistry, primarily enamine pathway) [2]
Purity	Racemase (mixture of active (S) and inactive (R) enantiomers)	Only active, S form
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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Next steps

	DEVELOPMENT	POTENTIAL INDICATIONS
OV329 Oral formulation	• Initiating multiple ascending dose cohorts • Expect higher dose escalation in humans • Concurrent TMS study to demonstrate PD • Measuring target engagement surrogate biomarker via MRS (vs VGB) • Concurrently assessing back of eye accumulation vs VGB in animals • **Timing**: Full readout H2 2024	• Tuberous sclerosis seizures • Infantile spasms • Conditions with focal seizures
OV329 IV formulation	• Formulating OV329 for IV • Conducting supportive animal toxicology & disease models	• Status epilepticus • Refractory status epilepticus

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Open Q&A

- Ovid strategy
- ROCK2 inhibition & OV888
- OV329, a next-generation GABA-AT inhibitor



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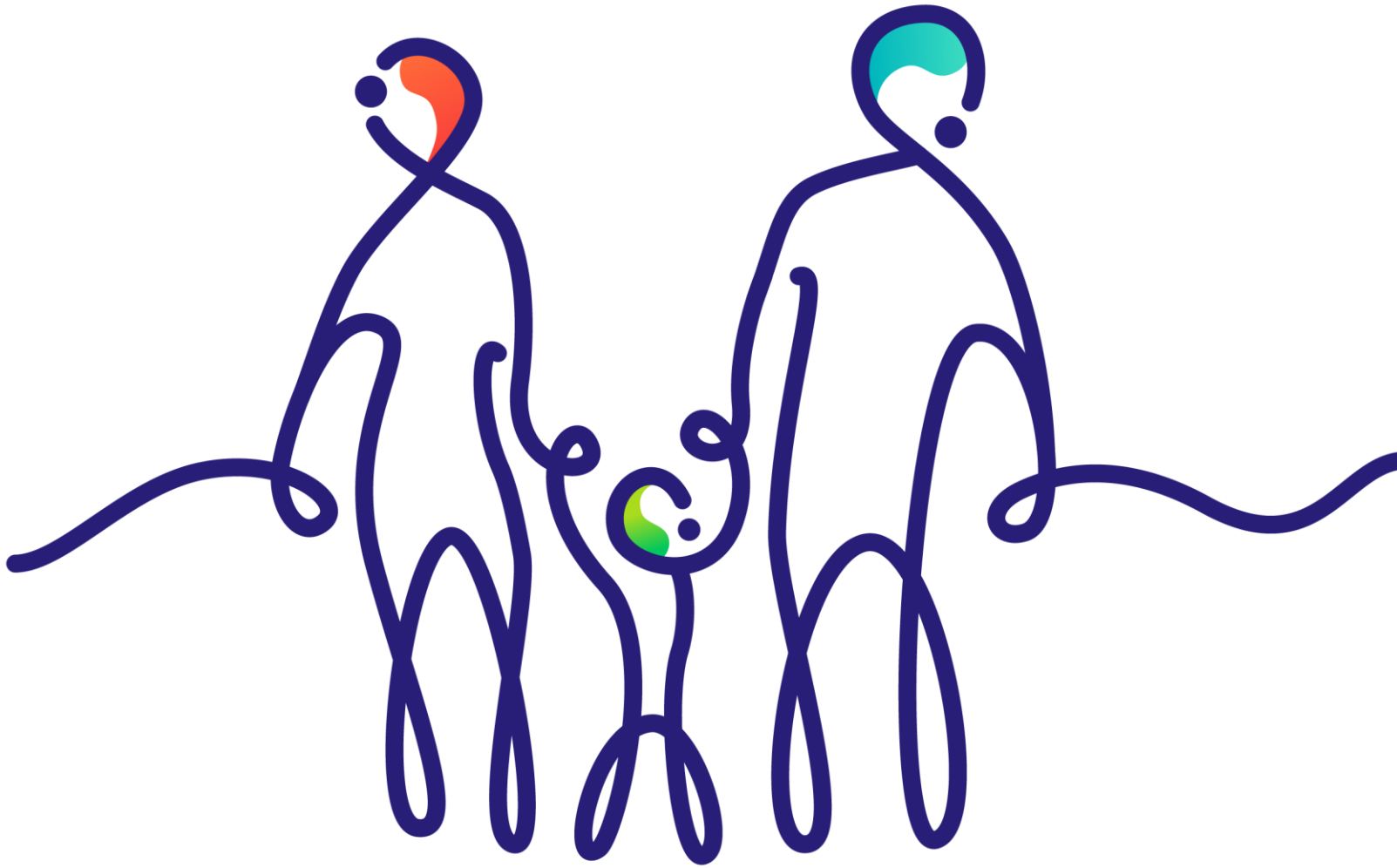
Break
(10 minutes)



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KCC2 direct activator portfolio & OV350

Dr. Zhong Zhong
Chief Scientific Officer

KCC2 direct activation: OV350 (lead program)

UPDATE

1st IND for OV350 in resistant epilepsy anticipated for H2 2024

- Planning for intravenous formulation initially
- Intend to pursue an oral formulation

New animal findings

Broad therapeutic potential in CNS conditions

- 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
- Represent a potential franchise of neurotherapeutics
- Activators directly modulate intrinsic hyperexcitability of neurons via chloride extrusion
- Animal models of disease have confirmed
  - Anti-convulsant properties as monotherapy and as a potentiator
  - Anti-psychotic and anti-schizophrenic properties
  - No sedative effects at expected therapeutic windows

Animal findings suggest broader therapeutic potential

NEW ANIMAL FINDINGS

- ✓ Two animal models demonstrate independent anti-convulsant activity, improving survival and neuroprotection in acute models
- ✓ Rodent kainite model for status epilepticus also suggests potentiating properties of benzodiazepines

Potential anti-convulsant therapies

- ✓ Two separate models suggest strong anti-psychotic and anti-schizophrenic effect
- ✓ Appears to be well-tolerated in animals and non-sedating

Potential psychiatric therapies

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Unlocking a new CNS target: KCC2 direct activation

Dr. Stephen Moss
Director, Moss Lab for Neuropharmacology at Tufts University

Professor of Molecular Pharmacology at University College London

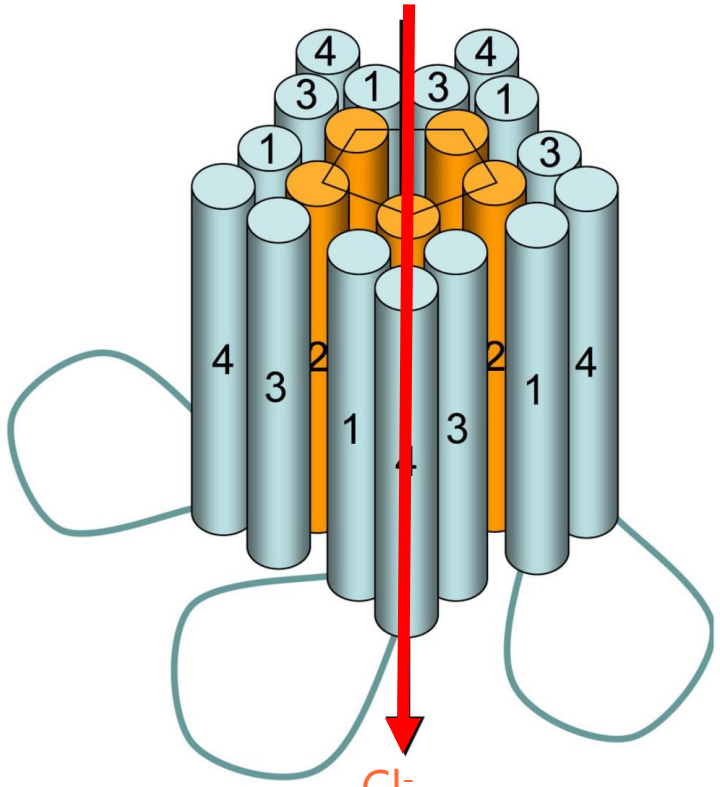
KCC2 is critical for chloride dependent neuronal hyperpolarization

A. KCC2



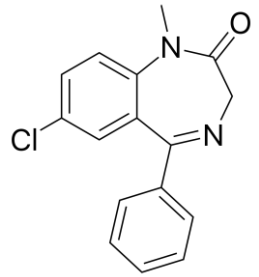
Cl^-

B. $GABA_AR$

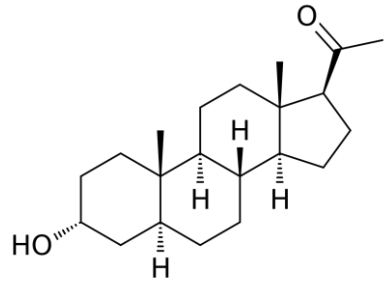


Cl^-

C. Benzodiazepines



D. Neurosteriods



KCC2 is a CNS specific electroneutral K^+/Cl^- co-transporter that is critical for $GABA_AR$ Cl- dependent neuronal hyperpolarization

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

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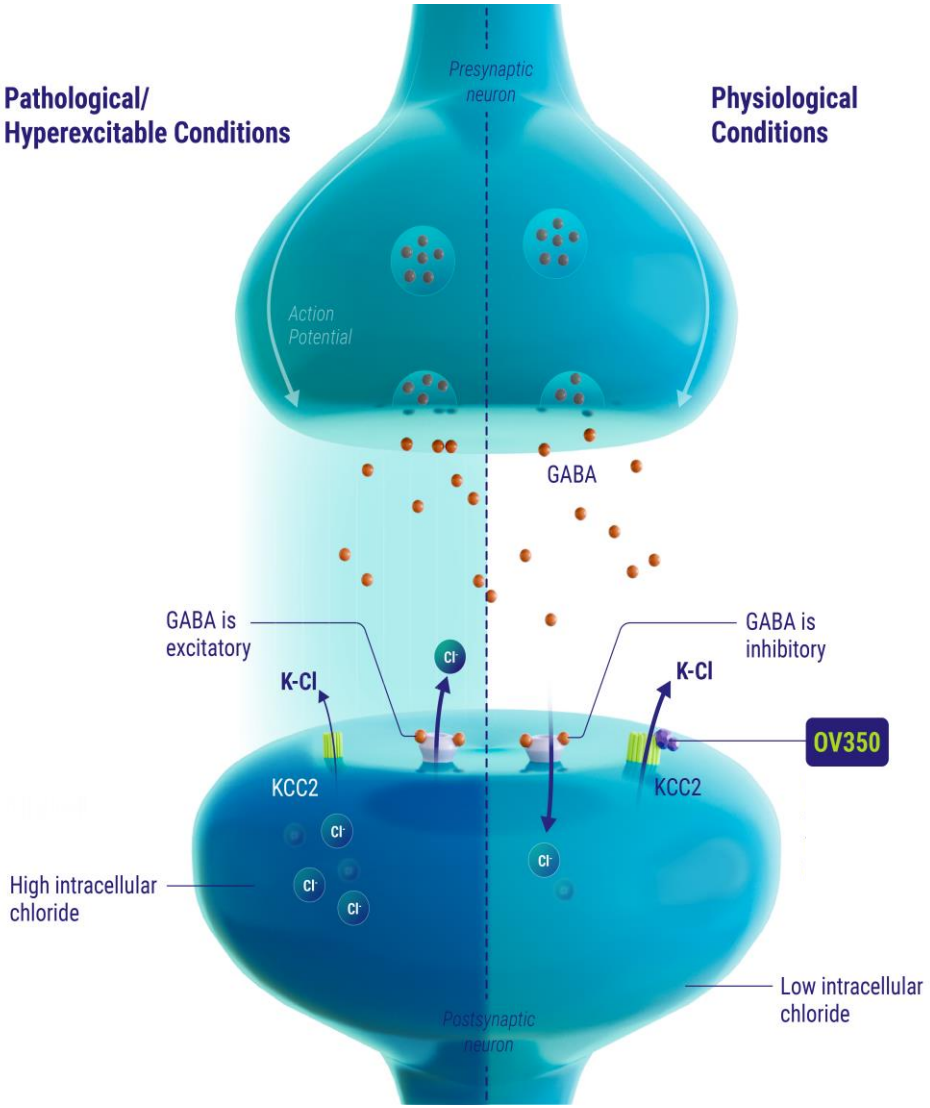
OV350 mechanism of action

Impaired KCC2 activity

- Causes high intra-neuronal chloride concentrations leading to abnormal depolarizing of the GABA receptor
- Causes neuronal hyperexcitability leading to epilepsy seizures and 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 directly activates KCC2 transporter, improving chloride extrusion and improving neuronal inhibition in preclinical models

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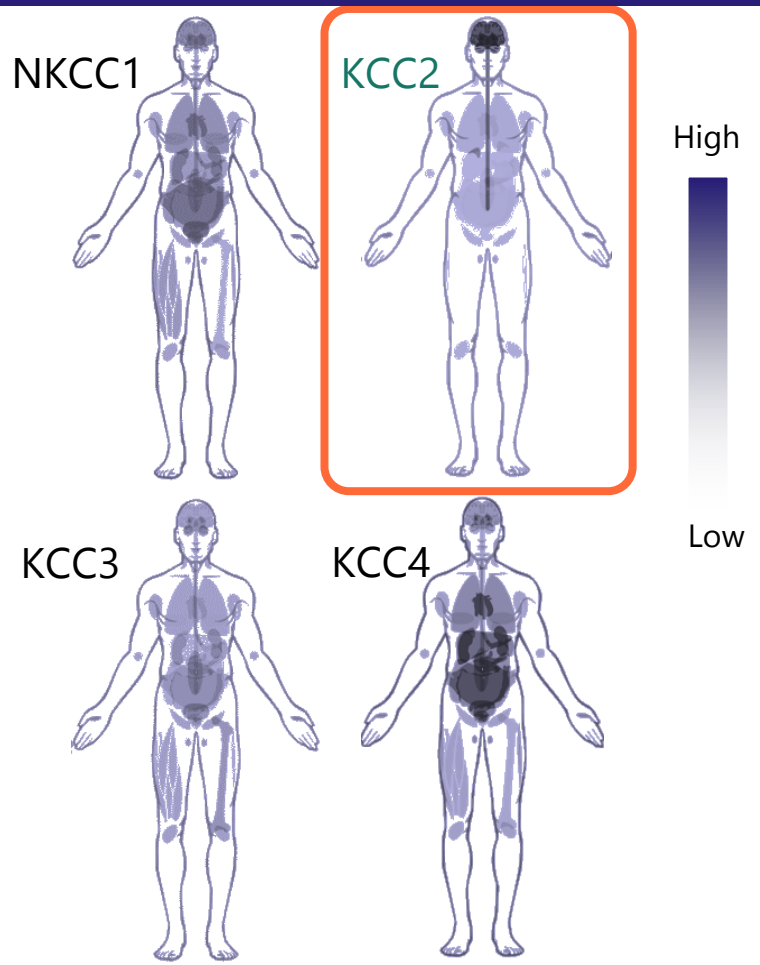
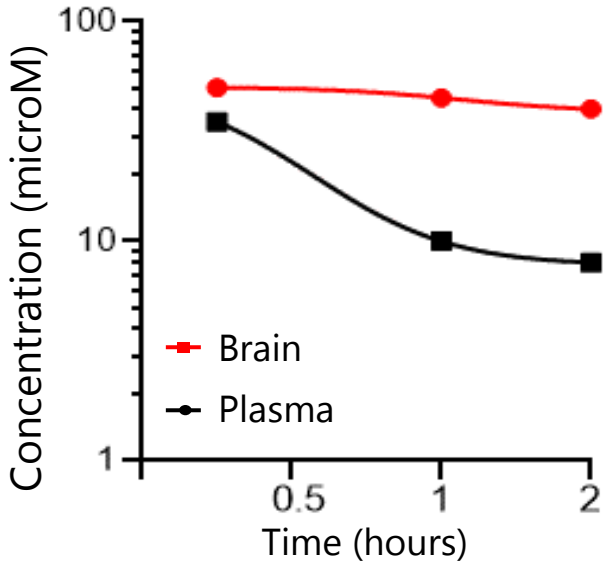
OV350 shows rapid, stable accumulation in the brain with a translatable pharmacodynamic biomarker[1]

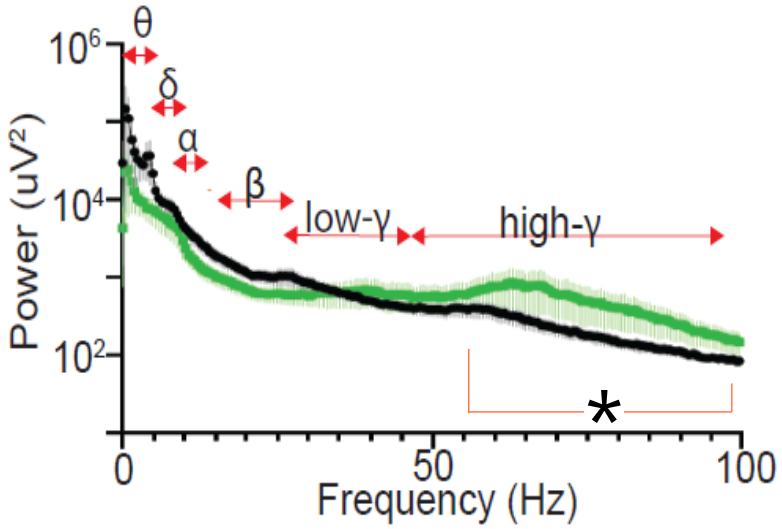
A. KCC2 is expressed exclusively in neurons



B. OV350 rapidly accumulates in rodent brain via IV/IP dosing



C. 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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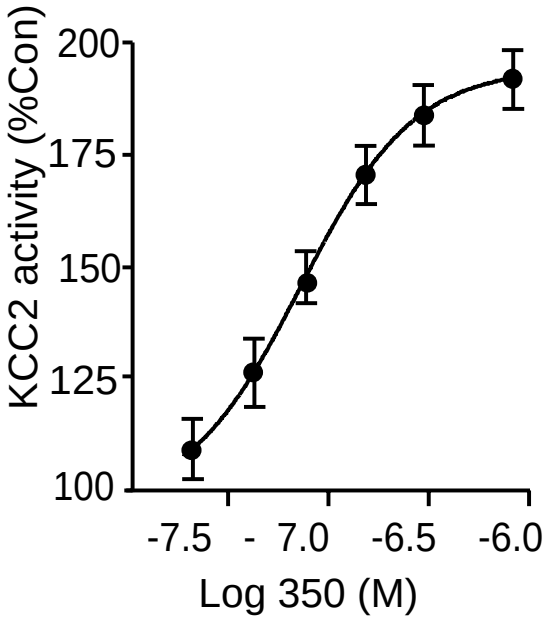
Why does direct activation matter?

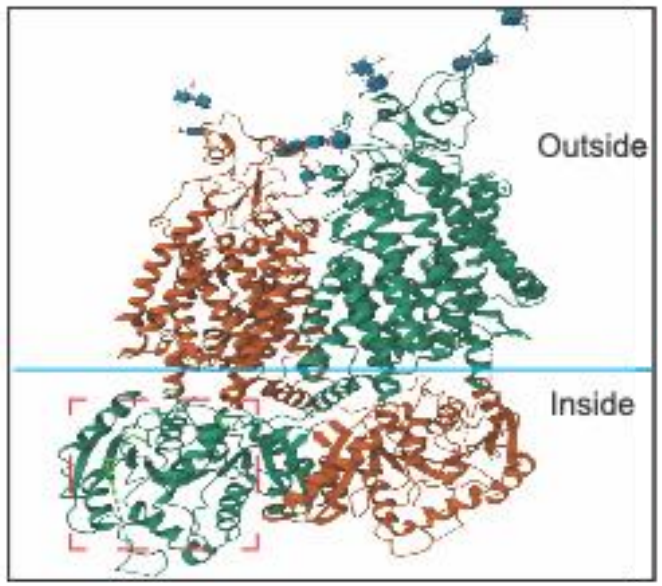
OV350 increases KCC2 activity via binding to amino acids in its cytoplasmic domain

A.

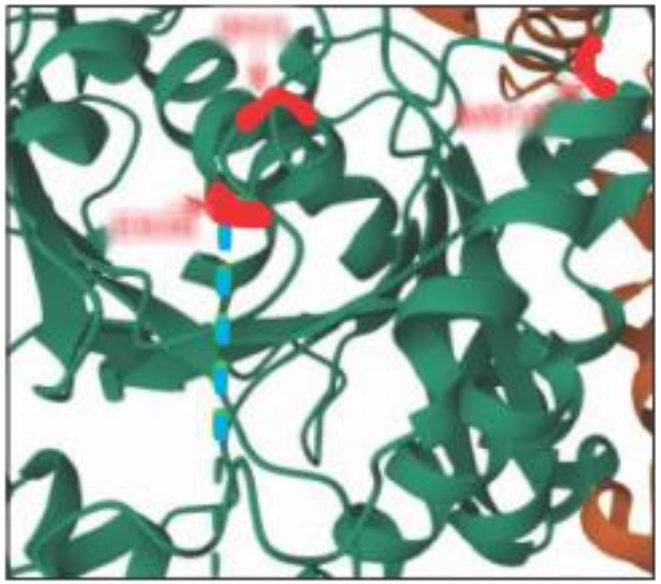


	OV350
MW	395g
LogD	4.4
KCC2 EC_{50} (nM)	261.2±60.2
KCC3 EC_{50} (nM)	>100,000
KCC4 EC_{50} (nM)	>100,000
NKCC1 EC_{50} (nM)	>100,000

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

OVID data on file

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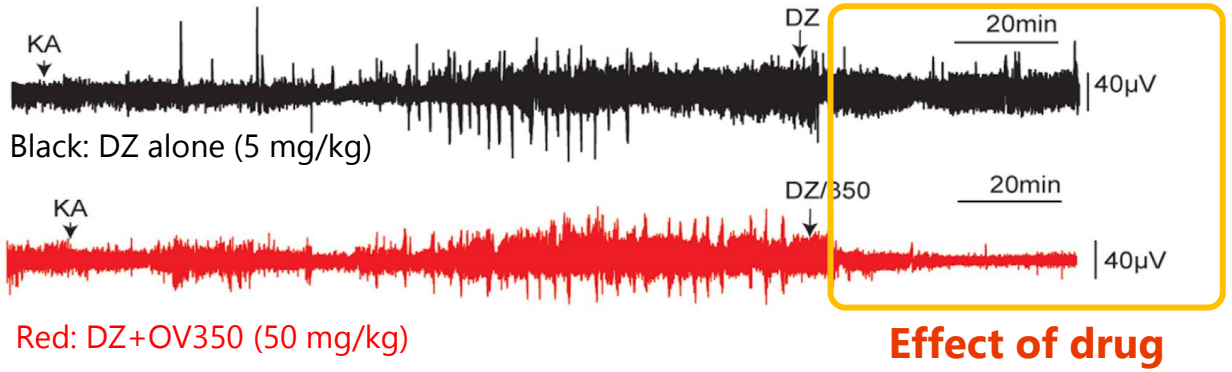
In-vivo preclinical POC data for OV350 in epilepsy

OV350 terminates ongoing and benzodiazepine refractory status epilepticus

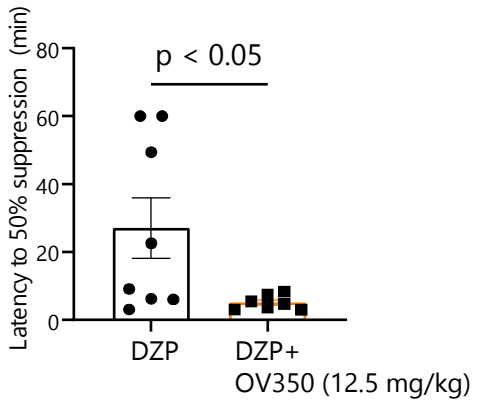
- OV350 demonstrated anti-seizure activities in kainate challenge model
- Mice implanted with electrodes to measure kainate induced seizures and demonstrated that OV350 at 50mg/kg and 12.5mg/kg
  - Restored diazepam activities in stopping seizures
- Supports development in Status Epilepticus using IV 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; [2]PNAS, 2015;112:3523; [3]Unpublished data

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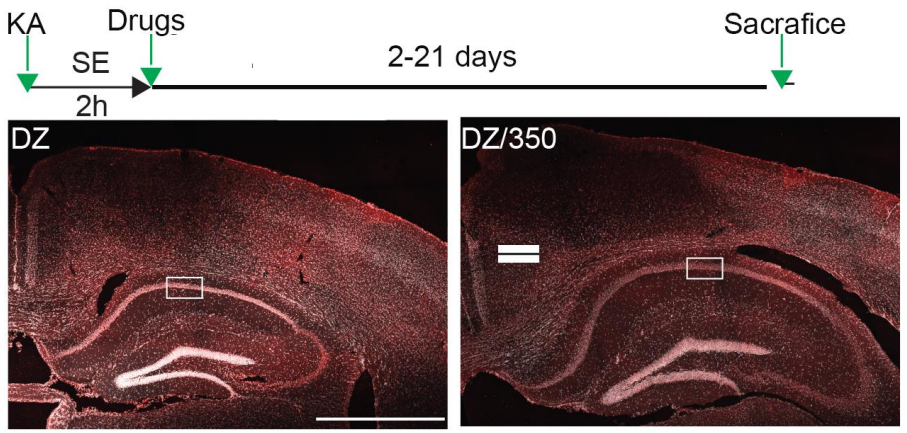
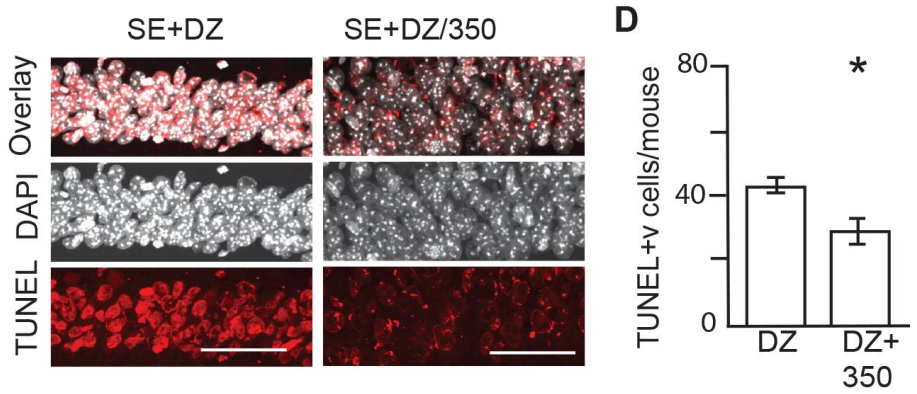
OV350 reduces neuronal death, neurodegeneration and neuroinflammation by altering neuronal hyperexcitation

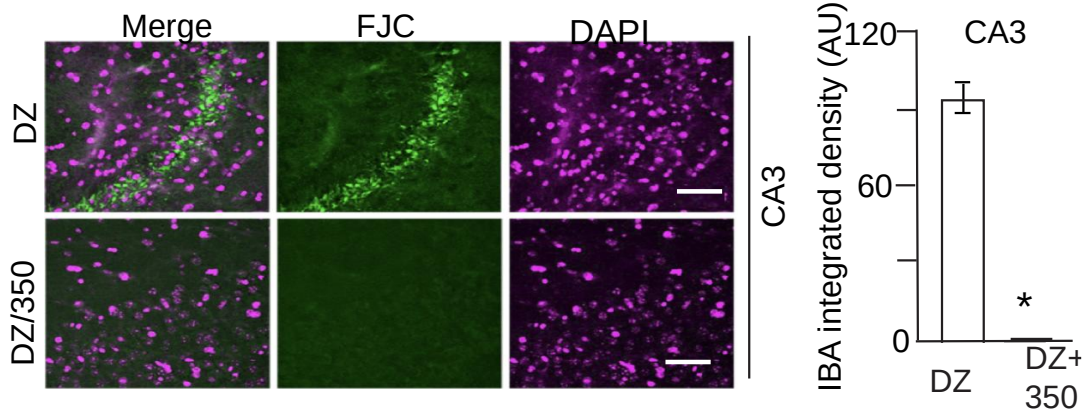
A. Reduces neuronal death
Independent experiment #1



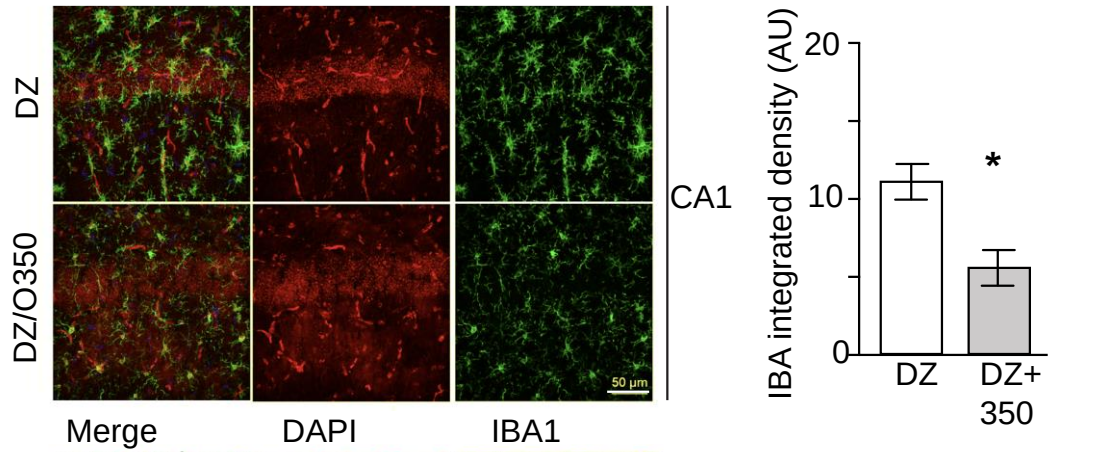


Shows TUNEL positive neurons by confocal microscopy were significantly elevated in DZ but not DZ + OV350 group

B. Reduces ongoing neurodegeneration
Independent experiment #2



C. Reduces neuroinflammation
Independent experiment #3



OVID data on file

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KCC2 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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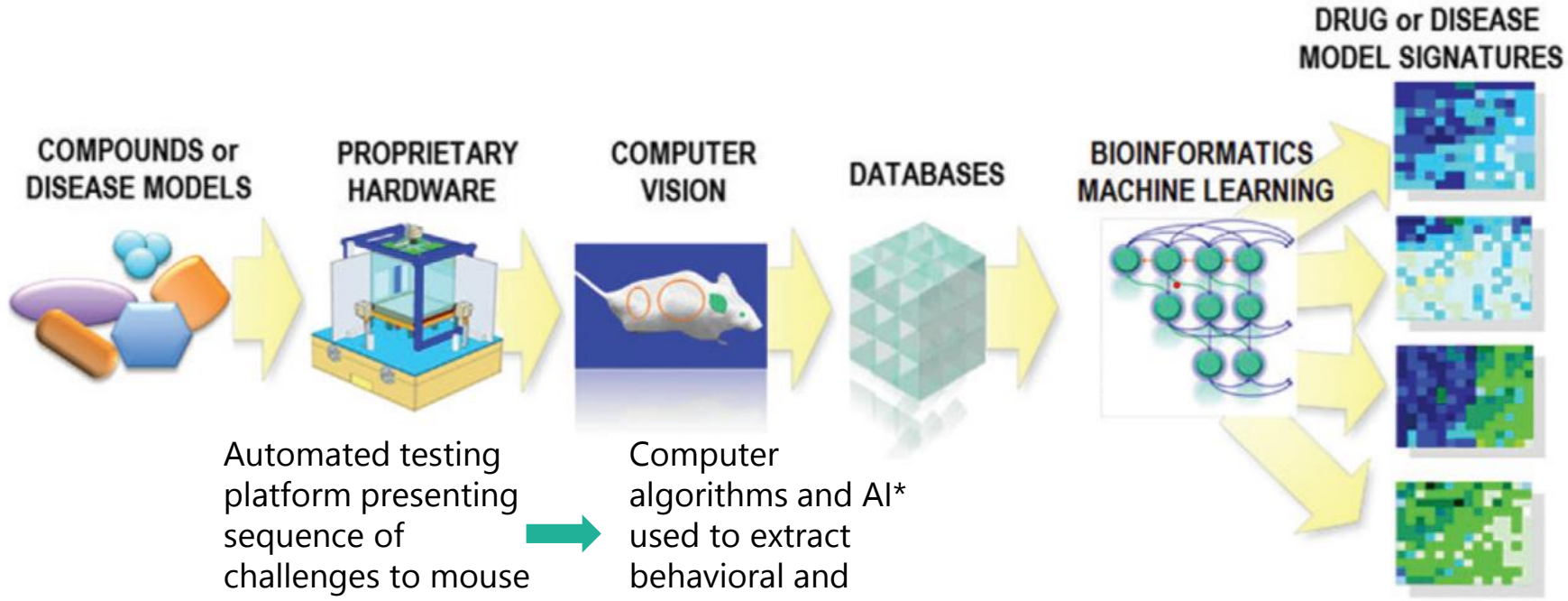
New non-clinical findings: SmartCube® is a phenotypic, high throughput screen that is unbiased to mechanism



SmartCube methodology is validated for clinical translatability as a behavioral phenotyping platform

Leahy, E. Drug Discovery, 2019, 19:2

*Artificial intelligence/machine learning,

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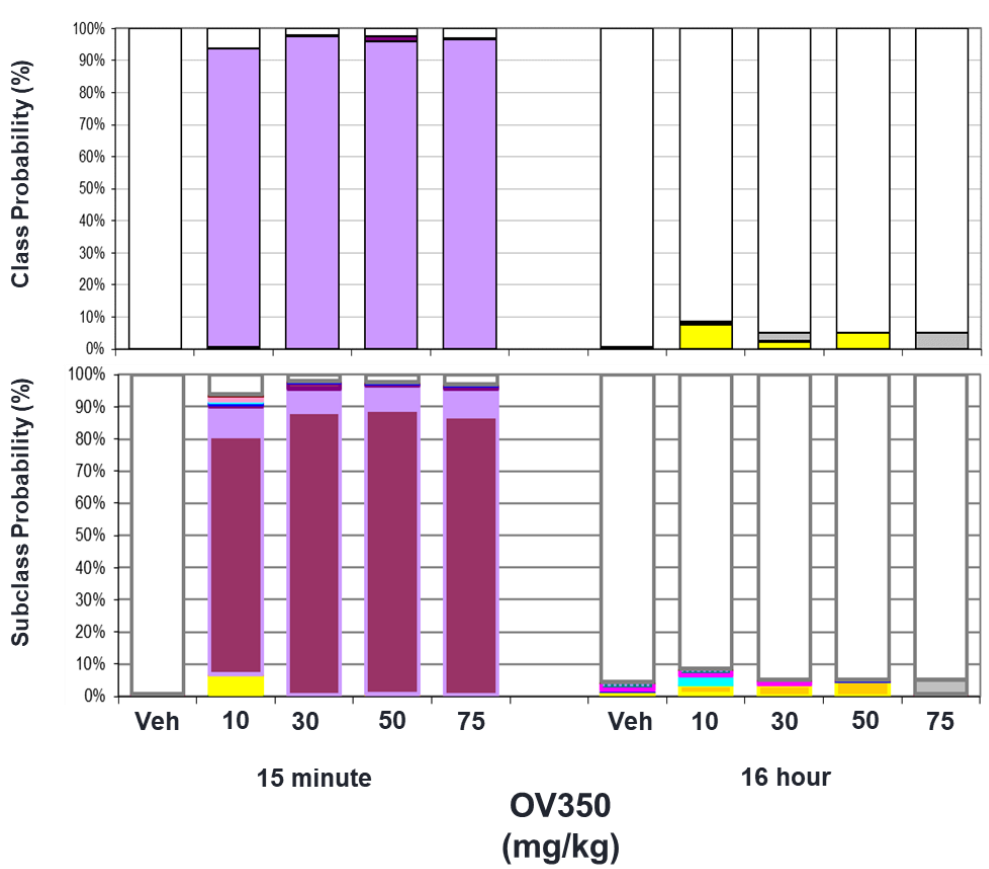
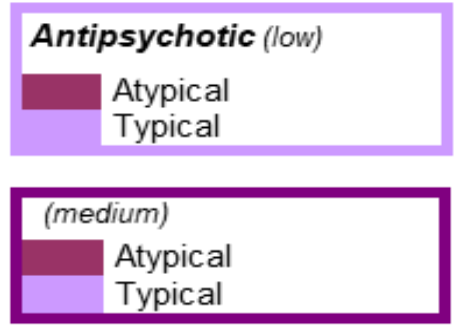
OV350 acutely elicits “antipsychotics-like” effects

- Behaves as atypical antipsychotics with a clean profile
- Elicits in vivo effects within 15 minutes of administration and dissipates in 16 hours
- Effects are robust at 10mg/kg dose and increase with higher dosing
- No sedation or other adverse behavior effects observed up to 75mg/kg



LEGEND



Potent, robust, rapid and reversable antipsychotic activities observed for OV350 in preclinical studies

1. Ovid data on file

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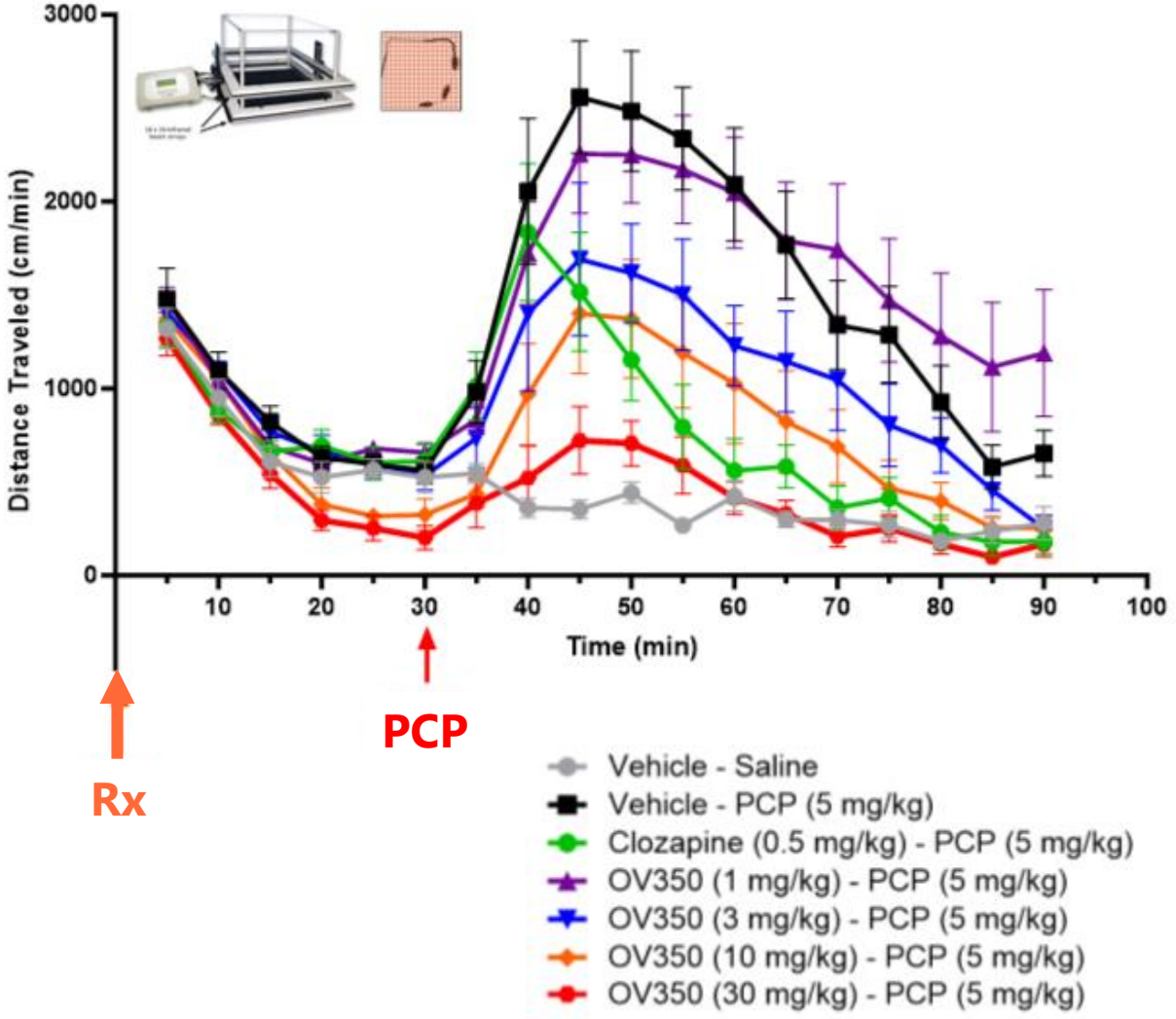
OV350 anti-psychotic effects demonstrated in a schizophrenia model



- Phencyclidine-induced psychosis is characterized by:
  - Confusion, excitation, aggression, paranoia, hallucinations, and can be experimentally measured by hyperlocomotion
- Phencyclidine challenge is a widely used as model for schizophrenia
- 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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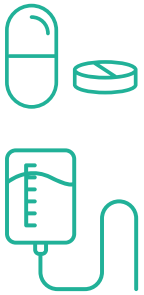
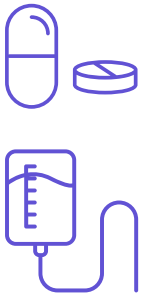
Development plans

	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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Soticlestat anticipated profile

Mr. Jason Tardio
Chief Operating Officer



Soticlestat

Making a difference in Dravet & Lennox-Gastaut syndromes

… The most distinctive feature of this drug is that it has a **new mechanism of action**. There has never been such a drug before.

This product has a **good efficacy** rates compared to others, but it seems to have a **better safety profile,** which is a strong suit. It also **doesn't interact** with other medications, so it's probably going to be something I'd want to include as an adjunct treatment …**My likelihood to prescribe is high**"

-Epileptologist, Children's Hospital

Overview

UPDATE

Phase 3 global studies (ongoing)

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

Anticipated global regulatory filings in Takeda's FY2024

Trial completion estimates and site updates available on **www.ClinicalTrials.gov**

- First-in-class, selective inhibitor of cholesterol 24-hydroxylase
- Believed to decrease glutamatergic signaling with the potential to reduce seizure susceptibility and improve seizure control
- Studied in one of the most robust development programs for developmental and epileptic encephalopathies (DEE)
- To-date, has demonstrated sustained seizure reduction efficacy, safety & tolerability with no anticipated monitoring in clinical trials
- Initial indications:
  - Lennox-Gastaut syndrome
  - Dravet syndrome

Evidence of clinical findings included on subsequent slides.

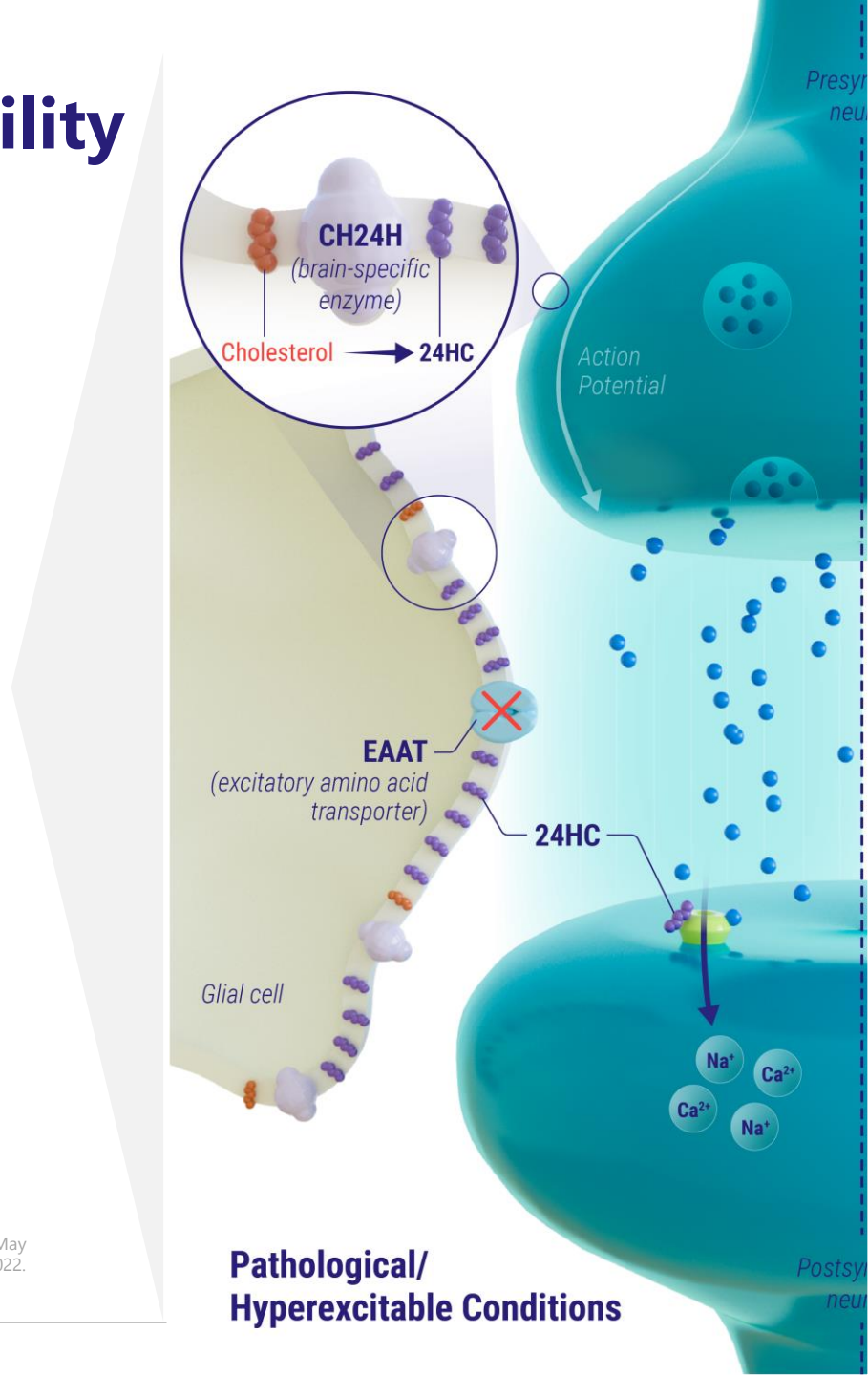
Role of cholesterol 24 hydroxylase in excitability

- To maintain the steady-state level, excess brain cholesterol is converted into the metabolite 24-S-hydroxycholesterol (24HC) by the enzyme cholesterol 24-hydroxylase (CH24H)

- 24HC is a positive allosteric modulator of the NMDA receptor and modulates glutamatergic signaling

- CH24H is involved in over-activation of the glutamatergic pathway
  - Modulation of the NMDA channel
  - Increases expression of CH24H
  - Disrupts the reuptake of glutamate by astrocytes, resulting in hyperexcitability

- **It is believed inhibition of CH24H lowers levels of 24HC and thus reduces glutamate hyperexcitability**



1) Gamba P, Giannelli S, Staurenghi E, Testa G, Sottero B, Biasi F, Poli G, Leonarduzzi G. The Controversial Role of 24-S-Hydroxycholesterol in Alzheimer's Disease. Antioxidants (Basel). 2021 May 7;10(5):740. 2)Salamone A, et al. Cholesterol 24-hydroxylase is a novel pharmacological target for antiictogenic and disease modification effects in epilepsy. Neurobiology of Disease. 173, 2022.

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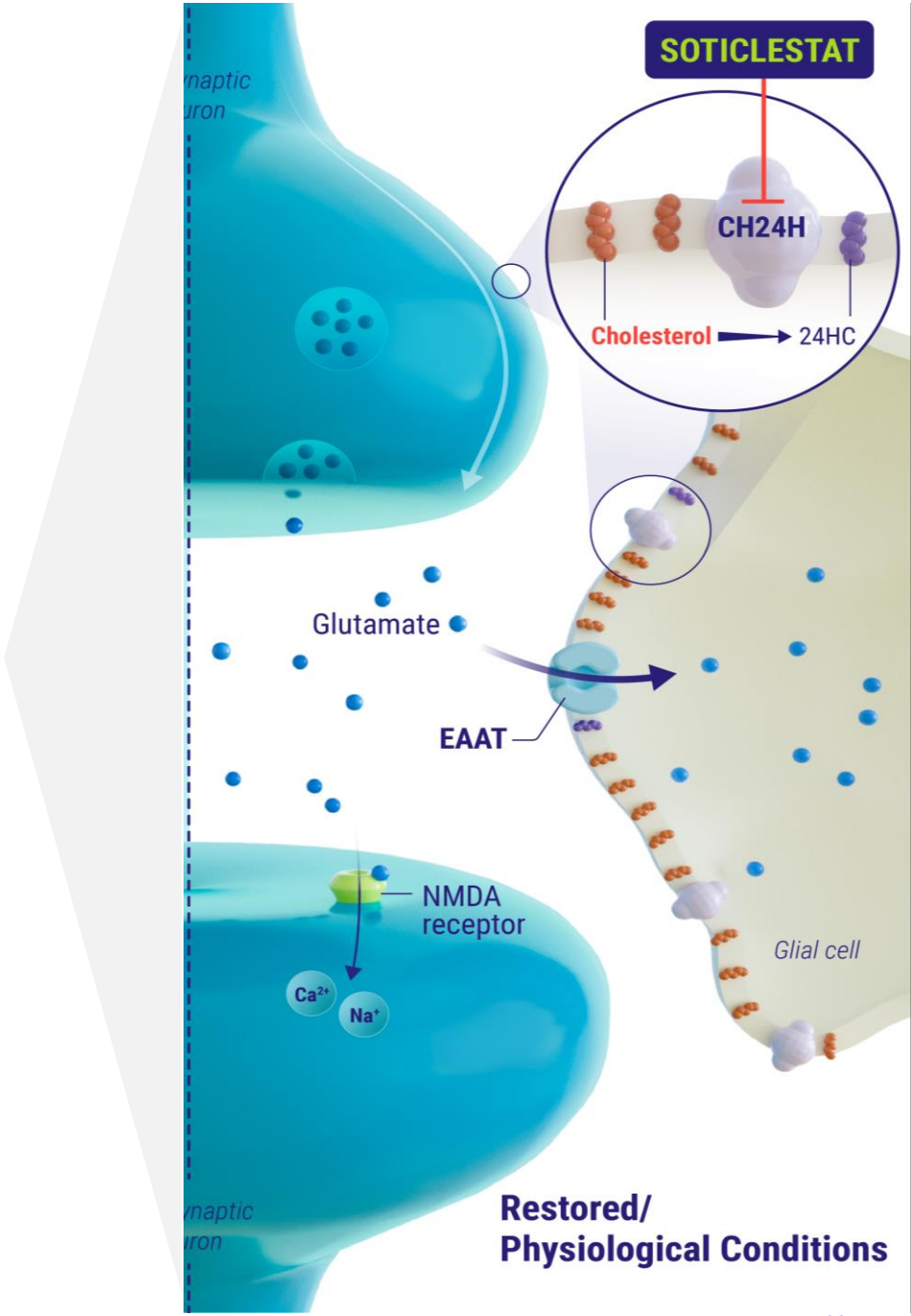
Novel mechanism of action

- Preclinical findings showed:
  - Soticlestat selectively binds to CH24H
  - Dose-dependently reduced brain 24HC levels in mice

- Clinical studies in both healthy volunteers and DEE patients confirmed a dose-dependent reduction of circulating levels of 24HC in humans

- 24HC reduction is multi-modal & ameliorates:
  - Over-activated glutamatergic signaling
  - Inflammation

- Thus, reducing seizure susceptibility and improving seizure control



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

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Highly consistent profile across robust development program

Preclinical	Phase 1	Phase 1b/2a	Phase 2	Open Label Extension	Phase 3

FINDINGS

Demonstrated efficacy & reduced 24HC levels in several animal models of epilepsy

Reduced total seizure burden

- Delayed acquisition of kindling seizures
- Prevented progression of spontaneous recurrent seizures
- Increased seizure threshold against environmental stimuli

Improved survival

- Protection from seizure-related mortality

Demonstrated Neuroprotection

- Protection against glutamate excitotoxicity
- Preserved cognitive functions

Selectively binds to CH24H and dose-dependently reduced brain 24HC levels

SOURCE: 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

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Highly consistent profile across robust development program

Preclinical | Phase 1 | Phase 1b/2a | Phase 2 | Open Label Extension | Phase 3

FINDINGS

In four Phase 1 studies in healthy adults (n=108), soticlestat appeared to be safe, well-tolerated and dose-dependently reduced plasma 24HC concentrations

Well-tolerated

- Soticlestat appeared to be well tolerated up to a single dose of 1350 mg

Adverse events (AEs) were mild in intensity

- Dose-dependent increase in AE prevalence was not apparent

Soticlestat can be administered via oral solution or tablet

- Soticlestat oral solution was rapidly absorbed
- Tablet formulation and food do not significantly affect the bioavailability of soticlestat or overall drug exposure

Plasma 24HC concentrations decreased with increasing dose

- Mean plasma concentrations increased with increasing soticlestat dose with a Cmax at approximately 0.5–1 hours after soticlestat administration, followed by a relatively fast decline

SOURCE: in 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

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Highly consistent profile across robust development program

Preclinical	Phase 1	Phase 1b/2a	Phase 2	Open Label Extension	Phase 3

FINDINGS

In DEE patients (n=18), soticlestat was well tolerated at doses of up to 300 mg BID

- **Associated with a reduction in median seizure frequency over the study duration**
- **Reduced plasma 24HC levels**

Well-tolerated

- Soticlestat was generally well tolerated in this study at dosages up to 300 mg BID for up to 90 days, as measured by the incidence of primarily mild TEAEs in adults with DEE

A reduction in seizure frequency over time in the open-label period of the study

- -36% median change from baseline in total seizures per 28 days

Consistent PK profile

- PK profile of soticlestat is generally comparable between healthy adults and adult patients with DEE

Reduced plasma 24HC levels

- Decreased plasma 24HC concentrations were found in the soticlestat versus placebo group

SOURCE: 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.

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Highly consistent profile across robust development program

Preclinical	Phase 1	Phase 1b/2a	Phase 2 LGS/DS	Open Label Extension	Phase 3

FINDINGS

In DS or LGS participants (DS, n=51; LGS, n=88), soticlestat treatment resulted in:

- **Statistically significant reductions from baseline in median seizure frequency (combined patient population)**
- **A safety profile consistent with previous studies**

Efficacy

- Soticlestat treatment in ELEKTRA significantly reduced the placebo-adjusted median seizure frequency in the combined patient population (LGS & Dravet)
- Statistically significant reduction in median convulsive seizure in Dravet
- Numeric reduction in seizure frequency in LGS

Safety & Tolerability

- TEAE incidences were similar between the soticlestat (80.3%) and placebo (74.3%) groups and were mostly mild or moderate in severity
- Serious TEAEs were reported by 15.5% and 18.6% of participants receiving soticlestat and placebo, respectively. TEAEs reported in soticlestat-treated patients with ≥5% difference from placebo were lethargy and constipation. No deaths were reported.

Reduced plasma 24HC levels

- Soticlestat treatment reduced plasma 24HC levels compared with placebo

SOURCE: 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

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Highly consistent profile across robust development program

Preclinical	Phase 1	Phase 1b/2a	Phase 2 CDD/Dup15q	Open Label Extension	Phase 3

FINDINGS

In 20 participants with CDD or Dup15q (CDD, n=12; Dup15q, n=8) soticlestat treatment was associated with:

- **Decrease in motor seizure frequency from baseline in patients with CDD**
- **Decrease in all seizure frequency in both patient groups**
- **Safety findings consistent with findings from previous studies**

Efficacy

- Soticlestat in the maintenance period was associated with a median change from baseline in motor seizure frequency of +11.7% in the Dup15q syndrome group and −23.6% in the CDD group
  - Increase from baseline in motor seizure frequency was observed in patients with Dup15q syndrome, likely due to the older age of this cohort
- Reductions in all seizure frequency of −23.4% and −30.5% were also observed during the maintenance period in the Dup15q syndrome group and CDD group, respectively
- Improvements in CGI-C and Care GI-C scores were observed in both groups of patients, and all patients in this open-label study elected to enroll in the open-label extension study, suggesting a perceived benefit of treatment

Safety & Tolerability

- Most TEAEs were of mild or moderate severity. Serious TEAEs were reported by three patients (15.0%); none were considered drug related. The most common TEAEs were constipation, rash, and seizure. No deaths were reported

Reduced plasma 24HC levels

- Treatment with soticlestat resulted in a reduction of plasma 24HC levels, which was maintained throughout the full treatment period

SOURCE: 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.

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Highly consistent profile across robust development program

Preclinical | Phase 1 | Phase 1b/2a | Phase 2 | Open Label Extension | Phase 3

FINDINGS

Interim analysis of ENDYMION 1 (DS, n=47; LGS, n=83) soticlestat demonstrated:

- **Sustained reduction in frequency of convulsive (DS) and drop (LGS) seizures from baseline for up to 2 years**
- **Sustained reduction in "all seizure" frequency from baseline up to 2 years**
- **Generally well-tolerated**

Well-tolerated

- Majority of TEAEs were mild or moderate in severity.
- Drug-related TEAEs occurring in > 5% of patients were decreased appetite (10.0%), seizure (7.7%), and somnolence (7.7%)

Efficacy

- At weeks 1–12, 49–60, and 97–108 median changes in Dravet patients' convulsive seizures was respectively: -33.7% (n = 46); -47.8 (n = 28), -58.2 (n = 22).
- In LGS patients, the median change in drop seizures at weeks 1-12, 49–60, and 97–108 was respectively: -29.3% (79), -14.1% (n = 49), -36.6% (n=35).
- Reduction in "all seizure" frequency:
  - At weeks 1–12, 49–60, and 97–108 median changes in all seizure frequency from baseline were –28.0% (n=46), –59.6% (n=28), and –53.4% (n=22) in DS patients
  - At weeks 1–12, 49–60, and 97–108 median changes in all seizure frequency from baseline were –28.4% (n=79), –17.7% (n=49), and –27.7% (n=35) in LGS patients

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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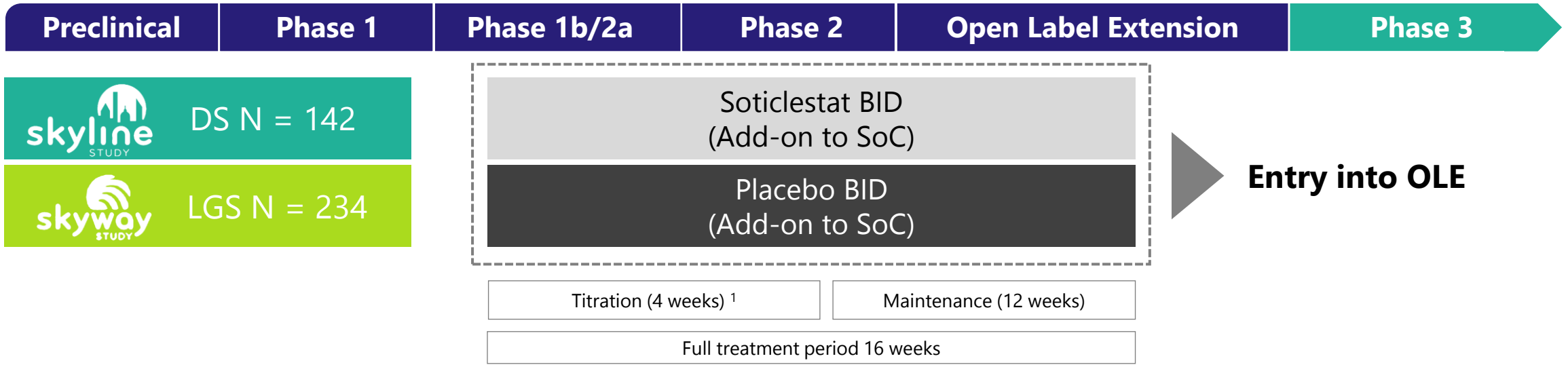
Phase 3 pivotal trials

(Conducted by Takeda)



TRIAL DESIGN

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

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

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

Takeda anticipates global regulatory filing during its FY 2024 (April 1, 2024 – March 31, 2025)

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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 GLOBAL MARKET OPPORTUNITY[2]

~110-135K

Lennox-Gastaut syndrome
(7 major markets)

~30-45K

Dravet syndrome
(7 major markets)

If soticlestat is approved and commercialized, subsequent milestones (up to $660M) and royalties (tiered up to 20%) create a stream of non-dilutive capital to Ovid to fuel our pipeline

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) Ovid Global Market Reseach 2022

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Milestones & financial strategy

Mr. Jeff Rona
Chief Business & Financial Officer

Robust near-term news flow of clinical & regulatory milestones

Cash runway supports programs to and through de-risking milestones

PROGRAM	MILESTONE	ANTICIPATED TIMING
Soticlestat	Phase 3 data for Lennox-Gastaut syndrome Phase 3 data for Dravet syndrome	Prior to regulatory filings in Takeda FY 2024 Estimated trial completion dates on www.clinicaltrials.gov
	Regulatory submissions for Lennox-Gastaut syndrome and Dravet syndrome	Takeda's FY 2024 (April 2024 – March 2025)
OV888	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 for IV formulation (acute)	H2 2024
KCC2 & OV350	IND submission (IV formulation)	H2 2024

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Capital to propel our pipeline

$96.5M cash balance end H1 2023

- Runway to complete signal-finding and/or proof of concept milestones or all programs

Potential for non-dilutive capital

- Up to $660 million in milestones (regulatory & commercial);
- Royalties in double digits up to 20%

If soticlestat is approved & commercialized

Business development

- Collaborating to accelerate & expand development of existing pipeline, specifically:
  - Expand geographies
  - Expand into non-core indications
  - Expand modalities
- Bring value by monetizing IP that we are not developing

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Why Ovid?

- ✓ Differentiated and risk mitigated pipeline
- ✓ Programs with multiple value creating opportunities
- ✓ Financial interest in two imminent Phase 3 pivotal study readouts & regulatory filings
- ✓ 5 additional clinical milestones expected within the next 12-15 months
- ✓ Potential to partner non-seizure applications
- ✓ Strong capital base and financial strategy to fund anticipated milestones

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Ovid is part of a revolution in targeted small molecules that can unlock epilepsy and an era of neurotherapeutics.

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Open Q&A

- KCC2 direct activation and OV350
- Soticlestat, a cholesterol 24 hydroxylase inhibitor
- Financial strategy



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FOCUSED PIPELINE
to treat epilepsy &
conditions with seizure symptoms

HARNESSING A REVOLUTION
in targeted small molecules for
the central nervous system

NOVEL BIOLOGICAL TARGETS
implicated in the balance of neuronal
excitation/inhibition or underlying
structural conditions

UNIQUE MECHANISMS OF ACTION
To deliver potential anti-seizure medicines
with preferable efficacy,
safety & tolerability

POTENTIAL TO PARTNER
non-epilepsy indications and ex-U.S. rights

CAPITAL ANTICIPATED TO FUND
programs through major de-risking events

Appendix

Soticlestat: Agreement with Takeda holds value of up to $856M1, 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 Dravet 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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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 US 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 US 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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