Ovid Therapeutics

Corporate presentation

August 2026

PIONEERING BETTER, GENTLER MEDICINES FOR THE BRAIN.



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Forward-looking statements

This presentation includes certain disclosures by Ovid that contain "forward-looking statements" including, without limitation: statements regarding the reproducibility and durability of any favorable results initially seen to date in clinical trials; the potential therapeutic and market opportunity of OV329, OV4071 and other compounds from Ovid's library of direct activators of KCC2; the expected timing of initiation, completion, and results and data of Ovid's ongoing and planned clinical studies; Ovid's expectations regarding the duration of its cash runway and the expectation that it will support Ovid's operations and development programs; the potential use and development of OV329, OV4071, OV4041 and other compounds from Ovid's library of direct activators of KCC2; Ovid's clinical pipeline strategy and plans for future clinical studies; the potential future indications for OV4071 and other compounds from Ovid's library of direct activators of KCC2; and other statements that are not historical fact. You can identify forward-looking statements because they contain words such as "anticipates," "believes," "expects," "intends," "may," "plan," "potentially," and "will," and similar expressions (as well as other words or expressions referencing future events, conditions or circumstances).

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Focus:
Medicines to quell conditions caused by neural hyperexcitability

1 IDENTIFY

Targets empirically implicated in disease

Fundamental biological nodes, GABA-AT and KCC2, with human genetic, post-mortem and pharmacologic evidence tying them to conditions driven by neural hyperexcitability

2 EXPLOIT

Differentiated mechanisms

Universal mechanisms of action that may hold broad therapeutic utility and stand apart in a field crowded with me-too medicines

3 ENGINEER

Preeminent medicinal chemistry

Rationally designed, highly specific small molecules purpose-built for best-in-class or first-in-class profiles

Culminating in a fully integrated neurotherapeutics company

with multiple, sequential clinical & regulatory milestones throughout 2026 – 2027

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Clinical pipeline of differentiated small molecule medicines

Programs	Potential Opportunity	Preclinical / Phase 1 / Phase 2	Anticipated milestones*
OV329, a next-generation GABA-aminotransferase inhibitor			
Drug-resistant adult focal onset seizures (FOS)	Novel mechanism of action in FOS with: • Competitive efficacy • Superior tolerability & safety • No expected titration or drug:drug interactions	**Phase 2 RCT** **Open label photo paroxysmal response PoC initiated**	• Phase 2 initiated (topline results in mid-2027) • Open-label photo paroxysmal response (PPR) initiated
Tuberous sclerosis complex seizures (TSC)	1st approved GABA-AT inhibitor • Preferable safety, tolerability • Increased treatment duration	**PoC & safety**	• PoC safety and signal finding study to initiate in Q4 2026
Infantile spasms (IS)	Potentially disease modifying 1st line agent • Preferable safety, tolerability • Increased treatment duration	**PoC & safety**	• Infant formulation and enabling studies ongoing
OV4071, potassium-chloride cotransporter 2 (KCC2) direct activator (oral)			
Broad spectrum psychosis	• Psychosis associated with Parkinson's disease and Lewy body dementia • Acute schizophrenia **Additional indications:** • Neurodegenerative psychoses • Other undisclosed indications	**Phase 1** **Ketamine study**	• Phase 1 proof-of-mechanism ongoing • Ketamine study (initiation H2 2026)

Additional undisclosed KCC2 development candidates from unique direct activator portfolio

*Timelines pending feedback from regulatory discussions Ketamine challenge to initiate pending PK characterization in Phase 1 study

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The OV329 opportunity: A universal mechanism for quelling conditions driven by excess neural excitation

Ovid planned indications

Neurodevelopmental conditions

Fragile X

Autism spectrum disorders

Seizures & developmental epileptic encephalopathies

Focal onset seizures

Infantile spasms

Tuberous sclerosis complex seizures

Other developmental epileptic encephalopathies (DEEs)

Pain

Neuropathic pain

Pain disorders

Anxiolytic | **Anti-psychosis** | **Anti-convulsant** | **Pain modulation**

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OV329: A next-generation, potential best-in-class GABA-aminotransferase inhibitor

Precision inhibition
for conditions of neuronal hyperexcitability, including drug-resistant epilepsies (DREs) and developmental epileptic encephalopathies (DEEs), pain, and select neurodevelopmental disorder symptoms

Validated mechanism
for focal seizures and infantile spasms
Differentiated safety & potential therapeutic index relative to 1st generation GABA-AT inhibitor Sabril (vigabatrin)

Clinical data - established safety, tolerability & cortical inhibition
from Phase 1 studies and advancing into 4 PoC studies in 2026 – 2027

Multiple formulations
Non-interchangeable adult capsule, intravenous; pediatric (weight-based) formulations

Pharmacodynamic data established
13 models establish PD effect consistent with GABAergic mechanism (MTLE, iPTZ, corneal kindle, Dravet, IS, paclitaxel induced pain, FMR1 among others)

IP through 2041 and expanding
10 additional patent families

*Assumes five-year patent term extension

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Significant unmet need & sizeable opportunity

Only U.S. opportunity reflected

	Fixed-dose capsule	Pediatric formulation Weight-based dose	
Indication	**Treatment resistant Focal onset seizures** **1.2M**	**Tuberous sclerosis complex** **21,000**	**Infantile spasms** **4,500**
Validated mechanism	✓	✓	✓
Addressable population with seizure type	720,000 (62% of treatment resistant epilepsies have FOS)	16,800 (~80% of people with TSC have seizures)	3,500 - 4,000
Assumed market penetration	10%	High	High
Duration	Ongoing	Potential 1st line use for long duration	Potential 1st line use with Acthar Gel
List pricing assumptions	>$16,000	Orphan	Orphan
Opportunity	>$1 billion	>$700M - $1 billion	

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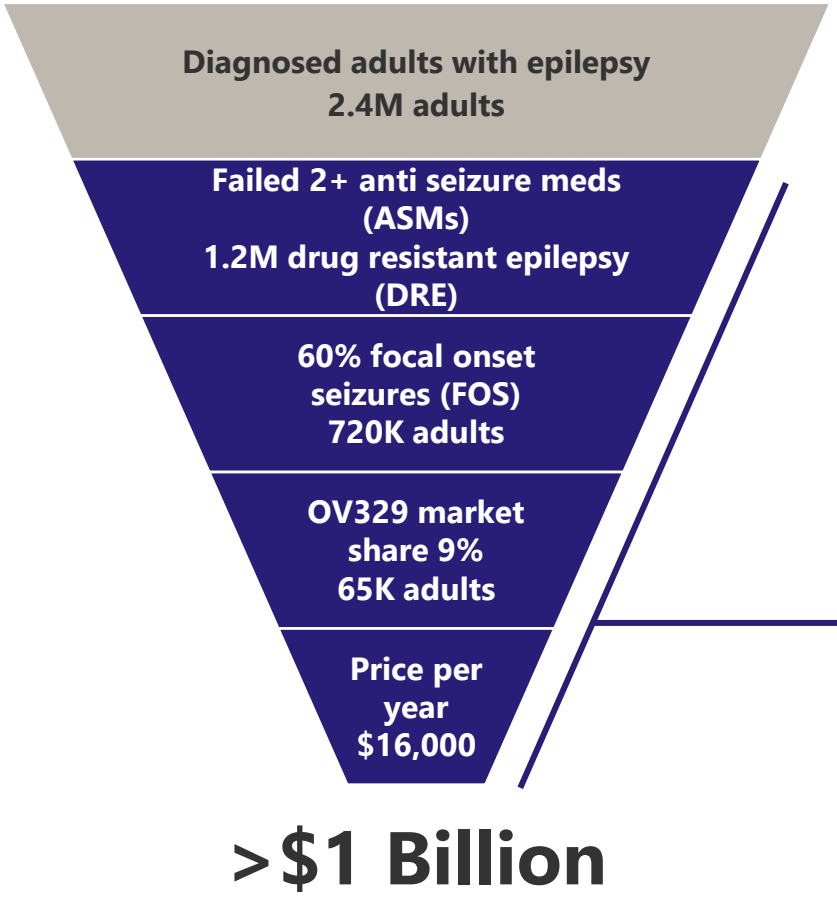
Unique, well-tolerated MoAs are rewarded in epilepsy, even in a competitive DRE market

Substantial opportunity within the DRE segment



>$1 Billion

Refractory + polypharmacy (~40%)

Key: Voltage-gated Ion Channel Target | GABAergic | Synaptic Target | Other / Mixed / Unknown

Focal / Partial seizures

1L	Carbamazepine	Levetiracetam	Oxcarbazepine
	Phenytoin	Eslicarbazepine	Lacosamide
2L	Clobazam	Lamotrigine	Topiramate
	Rufinamide	Zonisamide	
Refractory + polypharmacy (~40%)	OV329 *In Phase 1*	XEN1101	XCOPRI
		Fycompa perampanel	BRIVIACT (brivaracetam)

Reimbursement & coverage dynamics remain favorable. Polypharmacy well covered

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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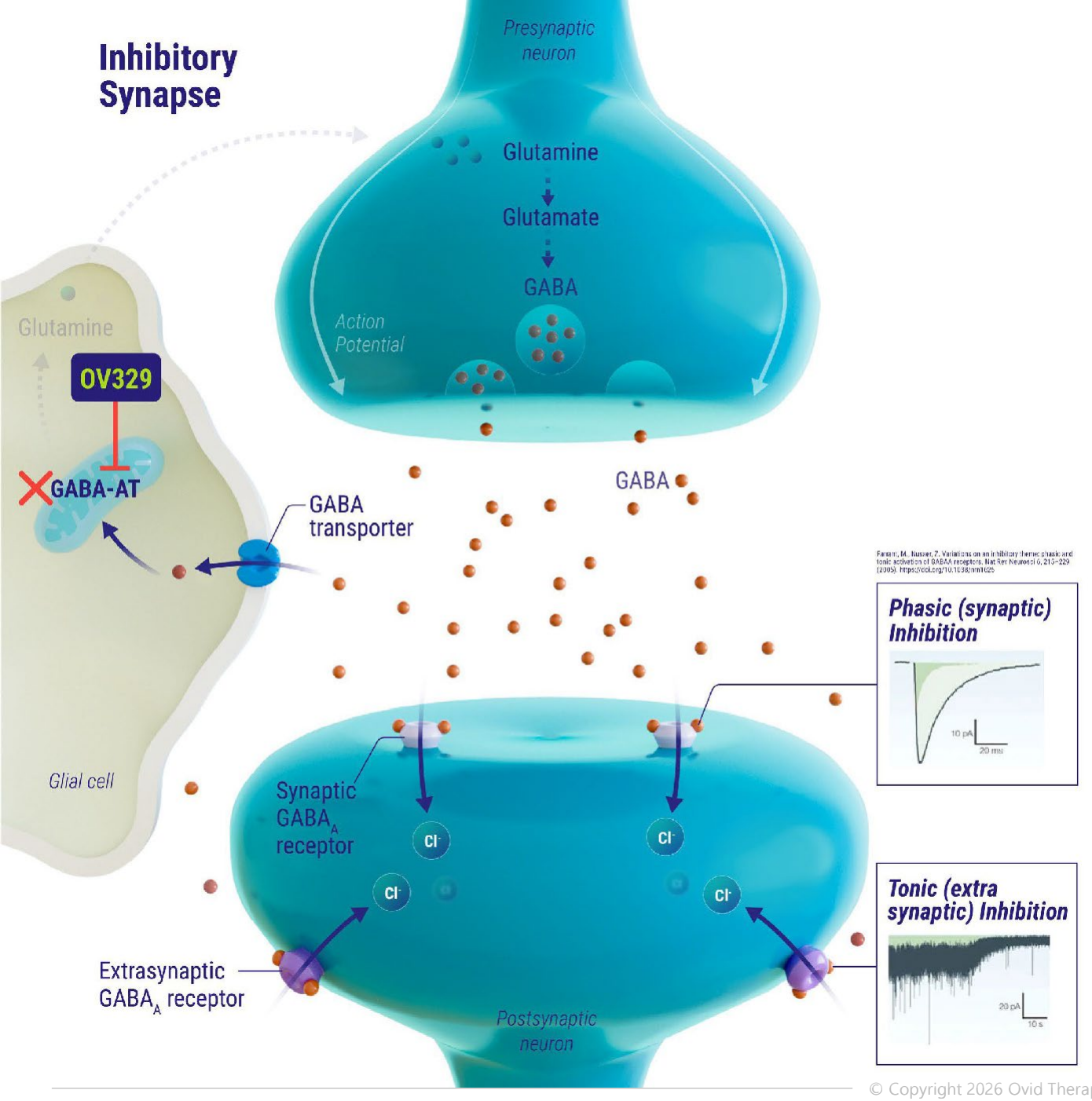

OV329 mechanism of action: optimally tune GABA to enhance tolerability & efficacy

Inhibits GABA-AT, the enzyme that degrades the inhibitory neurotransmitter, GABA[1]

Increases GABA in the synapse & extra-synaptic regions delivering phasic & tonic inhibition[2]

Creates an inhibitory neural environment that averts the tolerability issues associated with surging GABA in the synapse

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. Colmers P et al. eNeuro 27 June 2024, 11 (7) ENEURO.0137-24.2024; https://doi.org/10.1523/ENEURO.0137-24.2024

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The broad OV329 opportunity: Treatment resistant seizures and DEEs

ADULT FOS



Capsule formulation (adult)

Indication

Adjunctive therapy for focal onset seizures (FOS)

Prevalence*

15 million adults with uncontrolled FOS worldwide

Validated mechanism in FOS

1st generation drug, vigabtrin (SABRIL) used last line due to compound specific ophthalmic safety

DEEs



Pediatric weight-based formulation

Indications

Tuberous sclerosis complex associated seizures (TSC)

Infantile spasms (IS) with clinical spasms and hypsarrhythmia

Prevalence*

TSC: 41,000 in the U.S. and EU5

IS: 14,000 in the U.S. and EU5

Validated mechanism in IS & TSC

IS: 1st generation drug, vigabatrin (SABRIL) used 2nd line & for short duration due to ophthalmic safety

TSC: Vigabatrin (SABRIL) used in limited treatment duration due to ophthalmic safety concerns

*CDC https://www.cdc.gov/epilepsy/data-research/facts-stats/index.html; Kobau et al., 2024 https://pubmed.ncbi.nlm.nih.gov/38820685/; Ioannou et al., 2022 https://pmc.ncbi.nlm.nih.gov/articles/PMC9480957/; WHO https://www.who.int/news-room/fact-sheets/detail/epilepsy

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First indication: OV329 treatment resistant focal seizures

ADULT FOS

Capsule formulation (adult)



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Adjunctive therapy for focal onset seizures (FOS)

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NEW EXPANSION

Pediatric weight-based

Indications

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*CDC https://www.cdc.gov/epilepsy/data-research/facts-stats/index.html; Kobau et al., 2024 https://pubmed.ncbi.nlm.nih.gov/38820685/; Ioannou et al., 2022 https://pmc.ncbi.nlm.nih.gov/articles/PMC9480957/; WHO https://www.who.int/news-room/fact-sheets/detail/epilepsy

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A potential best-in-category anti-seizure medicine profile

Validated anti-convulsant mechanism enhancing GABAergic inhibition

Competitive seizure reduction efficacy and potential best-in-category safety profile
(predicted)

Oral, once daily dosing

Best-in-condition tolerability
No treatment-related or treatment emergent adverse events associated with OV329 7 mg in Phase 1 participants

Potent, low doses
Est. OV329 human doses:
5-7 mg vs 2,000-3,000 mg for VGB

No titration anticipated

Advancing to multiple proof-of-concept studies

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Phase 2 RCT & photo-paroxysmal studies (Now initiatiated)

- Strong safety profile with few treatment-related adverse events; no ophthalmic safety findings
- Demonstrated, competitive cortical inhibition as measured by multiple well recognized biomarkers
- Inhibitory effects match or exceed therapeutic doses of vigabatrin
  - Historically, VGB has shown 50% or greater reduction in FOS frequency and potential for seizure freedom[1]
- Favorable tolerability profile with no adverse events associated as drug related at 7 mg dose
- 5 mg and 7 mg doses achieve drug exposure in plasma predicted to be anti-convulsant
- Current doses anticipated to optimize responder rate

1. FDA Medical Review(s) for Sabril (vigabatrin). (2009). U.S. Food and Drug Administration. [accessdata.fda.gov]

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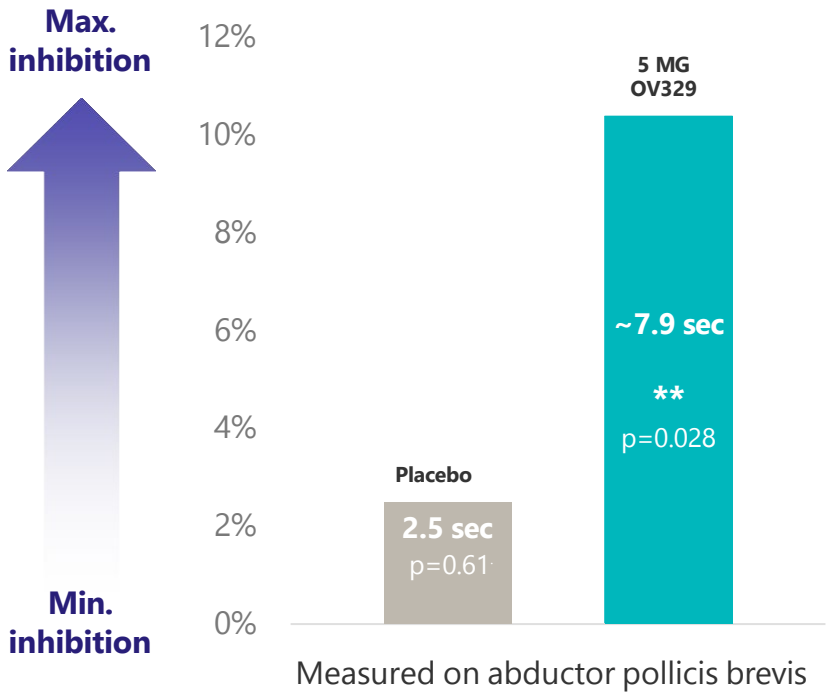
OV329 demonstrated dose dependent GABA elevation & cortical inhibition

OV329 increases inhibition as measured by the cortical silent period (CSP)

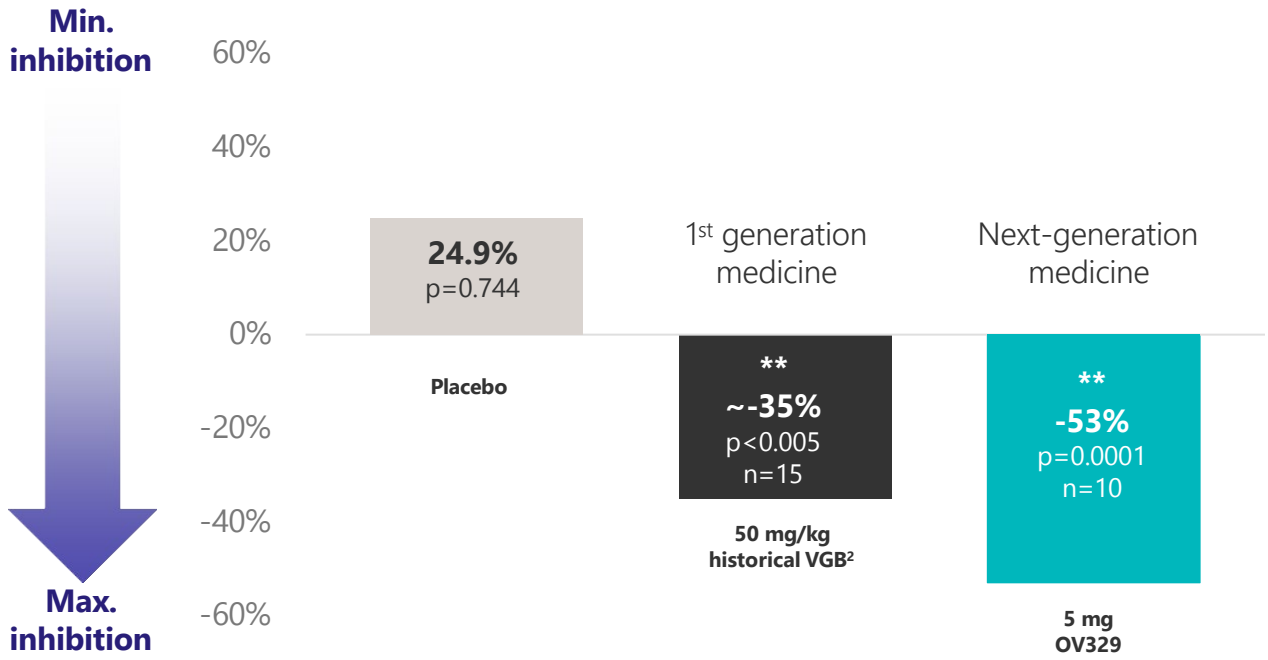
Untreated baseline vs post-treatment on day 7



Significantly increased cortical inhibition exceeding vigabatrin's inhibition

LICI 150 ms change: Undrugged baseline vs post-treatment on day 7[1,2]

Measured on abductor pollicis brevis



Note: Information compares similar studies and methodologies; a head-to-head trial was not conducted

1. Baseline is at Day 1 prior to any treatment
2. Pierantozzi et al., Brain Res. 2004 Nov 26; 1028(1):1-8

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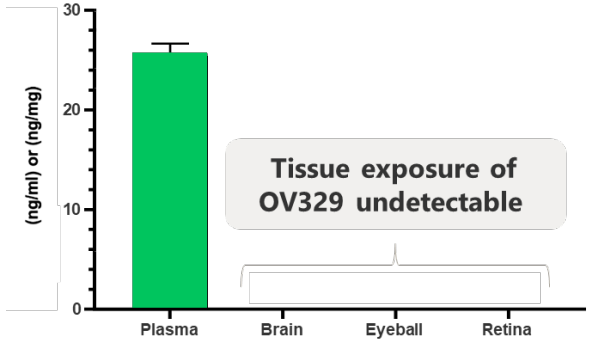
OV329 does not accumulate in the retina like vigabatrin (VGB)

No accumulation of OV329 detected in the eye or retina, vigabatrin accumulates[1,2]

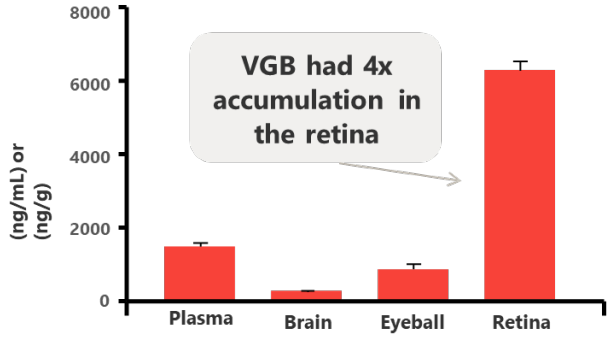
OV329

Mean Plasma and Tissue Concentration 5.0 mg/kg/day

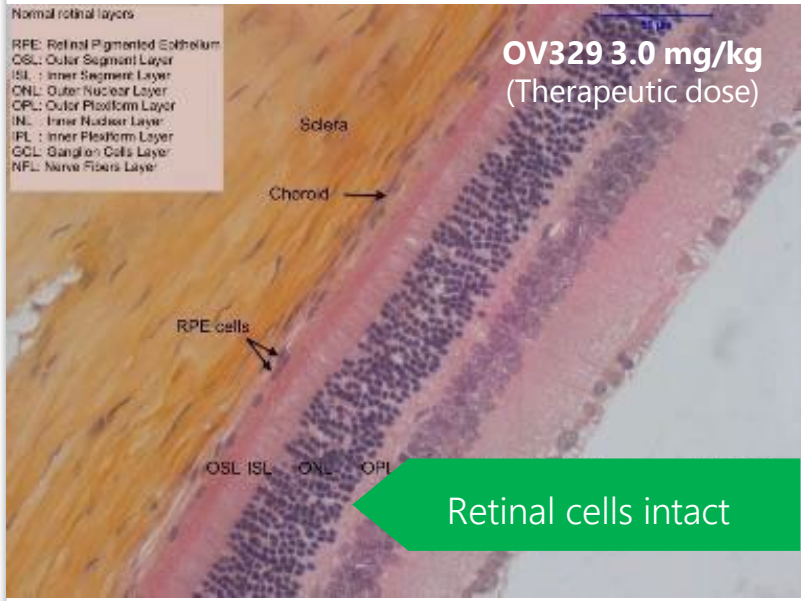


VIGABATRIN

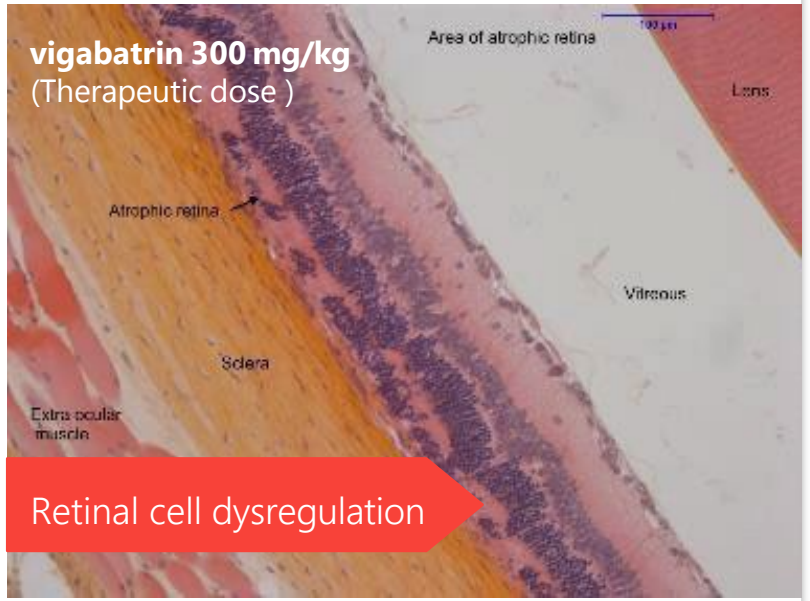
Mean Plasma and Tissue Concentration at 80.0 mg/kg/day



VGB shown to cause retinal cell dysregulation in < 45 days, OV329 shows no ocular effects[1]



No ocular effects seen in 3 mg/kg q.d. in rats



Ocular changes in more than half of rats treated (300 mg/kg)

Dedicated ophthalmic safety studies of OV329 conducted in mice, rats, humans

1. Zhong, et al. (2024). OV329 A potent GABA-AT inhibitor Does Not Accumulate in Mouse Retina A Pharmacokinetic Study to Differentiate Eye Accumulation between Vigabatrin Poster presented at the 2024 American Epilepsy Society
2. Walters et al. Pharmacol Res Perspect. 2019 Jan 7:7(1)
Ovid data on file

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OV329 was well-tolerated at all doses, with no treatment-related SAEs

Summary of potentially treatment-related and treatment-emergent AEs reported

Dosage	Adverse Event	OV329	PBO	Severity	Drug Related	Outcome
2 mg MAD	Headache	n=1	n=0	Mild (grade 1)	Possibly related (x2)	Recovered or resolved (x2)
	Drowsiness	n=1	n=0	Mild (grade 1)	Possibly related	Recovered or resolved
5 mg MAD	Metallic taste	n=1	n=0	Mild (grade 1)	Related	Recovered or resolved
7 mg MAD	None	None	None	N/A	N/A	N/A
9 mg MAD	None	None	None	N/A	N/A	N/A

N= number of participants
(x "number") = number of events

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No ophthalmic or retinal changes at all doses, including 7 mg

Ophthalmic metric*	Result
Best corrected visual acuity	No treatment-related effects
Fundus photography	No treatment-related effects
Indirect dilated ophthalmoscopy	No treatment-related effects
Automated threshold visual field perimetry	No treatment-related effects
Optical coherence tomography	No treatment-related effects

- Results consistent with prior clinical and preclinical ophthalmic safety characterization evidence demonstrating OV329 does not accumulate in the eye or change human visual health or structure
- Vigabatrin was shown to preferentially partition and accumulate in the retina, thus new 7 mg safety data supports differentiation of OV329 and potential best-in-class profile

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OV329 achieves target exposures for pharmacology strategy & potential anti-convulsant activity

Dose modeling: Leveraged multiple streams of evidence

- OV329 human cortical inhibition & plasma exposure data (healthy volunteers)
- Mesial temporal lobe epilepsy repeat dosing models (mice)
- GABA-AT enzyme inhibition studies (mice)
- Vigabatrin pharmacology from therapeutic doses*

Strategy

Target enzyme inhibition for adults with focal onset seizures: ~ 50 – 60%

Modeled drug exposure in plasma to achieve anti-convulsant effect:

- ~60 ng* hr/mL – 120 ng* hr/mL

Human drug plasma exposure by dose

Dose	Demonstrated mean exposure
3 mg	52.1 ng* hr/mL
5 mg	81.7 ng* hr/mL
7 mg	154 ng* hr/mL

* Adjusted for molecular weight and potency

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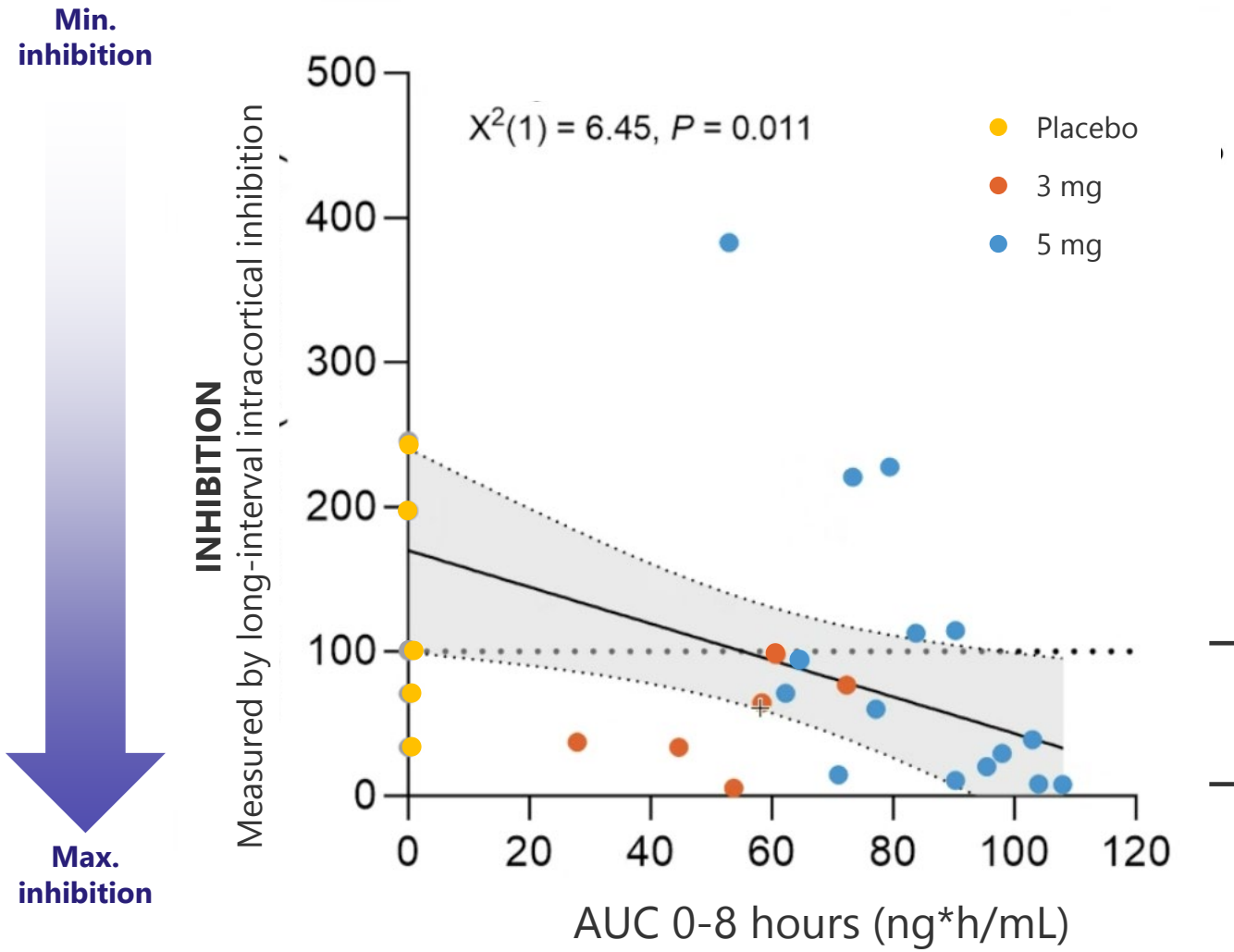
7 mg delivers targeted brain exposure



Clear relationships between:

- Dose and brain exposure
- Brain exposure and cortical inhibition as measured by LICI 150 ms
- Results confirm Ovid internal Tx models
- Support advancement of 7 mg as maximal dose

Target brain exposure threshold of >80 ng*hr/mL highly correlated with inhibition

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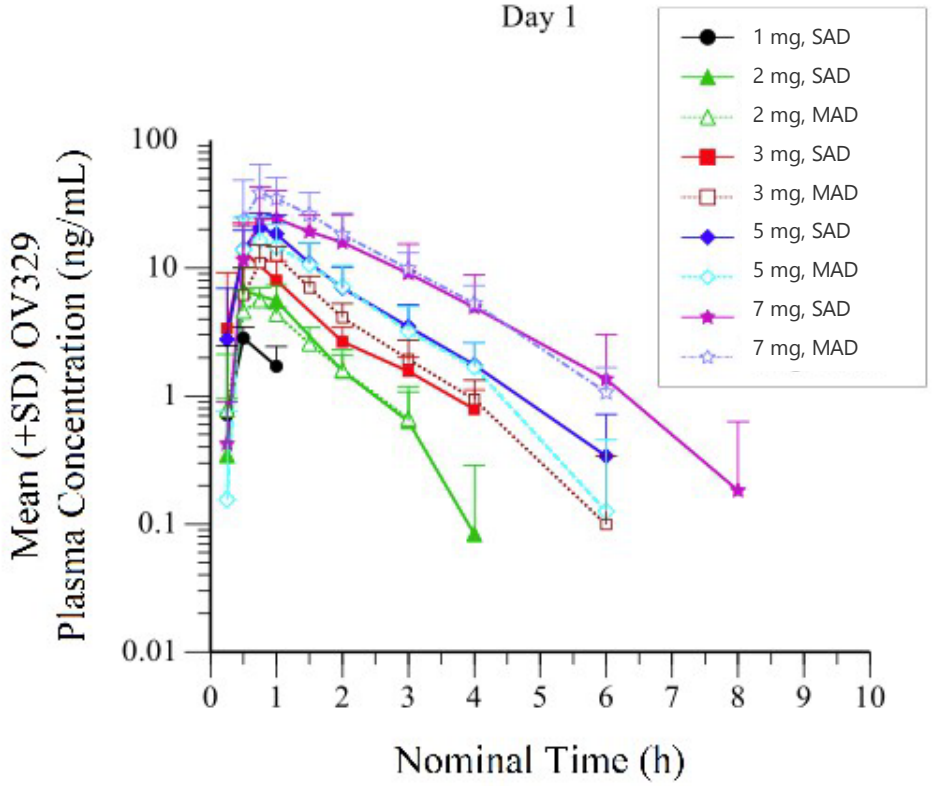
7 mg results reaffirmed predictable pharmacokinetic profile aligned with pharmacology strategy

- Dose dependent linear increases in AUC and Cmax demonstrated in repeat dosing
- Consistent renal clearance after single and repeated dosing
- Steady state achieved by Day 3
- Time to peak drug concentration (Tmax) is 1 hour
- OV329's potency and irreversible binding exploit the slow turnover of GABA-AT enzyme in the brain
    - Effect: Enduring enzyme inhibition and rapid half-life



Ovid data on file

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Next steps in FOS: Conducting Phase 2 PoC studies

Two, parallel PoC studies to confirm anti-convulsant activity and effect size

Open label seizure PoC study

Objective

Characterize suppression of photo-paroxysmal EEG response (PPR), which is correlated with ASM seizure reduction efficacy

Population

Patients with photosensitive epilepsy

Utility

- Demonstrates PoC in a seizure population; and potentially dose responsiveness
- Potential to deliver a milestone with possible readout results in Q4 2026

Phase 2 – Randomized placebo controlled

Objective

Characterize seizure reduction efficacy, responder rate, safety, tolerability, pharmacokinetics and clinical global impression (CGI)

Population

Adults with treatment-resistant epilepsy

Utility

- Understand anti-convulsant profile
- Reinforce indication sequencing
- Builds controlled safety database
- Informs powering and effect size insights for pivotal trials

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The OV329 opportunity:
A universal mechanism for treatment resistant seizures

ONGOING

Capsule formulation (adult)

Indication

Adjunctive therapy for focal onset seizures (FOS)

Prevalence*

15 million adults with uncontrolled FOS worldwide

Validated mechanism in FOS

1st generation drug, vigabtrin (SABRIL) used last line due to compound specific ophthalmic safety

NEW EXPANSION

Pediatric weight-based



Indications

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Infantile spasms (IS) with clinical spasms and hypsarrhythmia

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TSC: Vigabatrin (SABRIL) used in limited treatment duration due to ophthalmic safety concerns

*CDC https://www.cdc.gov/epilepsy/data-research/facts-stats/index.html; Kobau et al., 2024 https://pubmed.ncbi.nlm.nih.gov/38820685/; Ioannou et al., 2022 https://pmc.ncbi.nlm.nih.gov/articles/PMC9480957/; WHO https://www.who.int/news-room/fact-sheets/detail/epilepsy

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Substantial unmet need
Few medicines marketed or in development



Infantile spasms

Rare, seizure manifestation in the infantile brain

- Hallmark jackknife seizures typically occur between 4-7 months of age
- Moderate-to-severe developmental disability
- Increased mortality
- Seizures evolve to Lennox-Gastaut syndrome (LGS) or other drug-resistant seizures
- <5% have a good developmental prognosis

Treatment goal

- Early seizure control, improved developmental outcomes
- Mitigate development of LGS

Current standard of care

- Acthar hormone
- Vigabatrin (Sabril)



Tuberous sclerosis complex

A rare autosomal-dominant disorder of TSC1 and/or TSC2 genes

- Upregulation of the rapamycin (mTOR) pathway with subsequent excessive cell growth and proliferation
- Benign hamartomas in multiple organ systems, most frequently in brain, skin, kidneys, lungs, heart, and eyes
- Epilepsies, including focal seizures, and intellectual disability, and autism

Treatment goal

- Approximately 80% of TSC community experiences seizures
- Mitigate the developmental and neurodevelopmental outcomes

Current standard of care

- Afinitor
- Vigabatrin (Sabril)

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GABA-AT is a proven mechanism in TSC & IS

Sabril



Proven efficacy

Infantile spasms

- Freedom from spasms ~47%
- Freedom from treatment failure ~37%

TSC seizures

- Responders >90% seizure reduction
- 46% seizure freedom

Short treatment duration

- 2nd or 3rd line
- Short duration due to safety

Copious dosing

- Starting dose: 2,000 mg – 3,000 mg

Onerous monitoring

- On label - risk of irreversible blindness
- REMS with visual perimetry & ERG every 3 months

Priced for a broad population

- $14K per/mo list price
- Priced prior to post-market safety findings which limited use to acute populations

Vigabatrin historical data

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Potential for OV329

Profile

Safety

- Therapeutic index
- Positive ophthalmic safety record
- No intramyelinic edema

Tolerability

- No anticipated sedation
- Clean profile at high dose (7mg) in adults

OV329

Potential efficacy*

- >40% freedom from infantile spasms (after 25 weeks)
- Responders >90% improvement; 46% seizure freedom

Flexibility of use

- No anticipated titration
- No DDIs

Potential to increase use, if approved

Infantile spasms

- 1st line use with Acthar Gel
- Prolonged use to mitigate LGS

Tuberous sclerosis complex

- 1st line for seizure reduction
- Prevention of epilepsy from TSC (later expansion indication)

*Extrapolated from vigabatrin historical data

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SABRIL (vigabatrin) sales under-reflect the sizeable market opportunity

Tuberous sclerosis complex (Addressable population 2026: U.S. = ~21K and EU5 = 20K)

	Acthar GEL (repository corticotropin injection) 80 U/mL	AFINITOR (everolimus) Tablets	Epidiolex (cannabidiol)	Sabril
Pricing	$90K[1] avg treatment course	$5 - $20K / year	~$20K/year[2]	**~$130K / year**
Average treatment duration	Two courses	Annually	Annually	**9 mos.**
Use	2nd line	2nd line	2nd line	**Limited due to visual safety**

Infantile spasms (Addressable population 2026: U.S.=4.5K and EU5=9.4K)

	Acthar GEL (repository corticotropin injection) 80 U/mL	Synthetic steroids	Sabril
Pricing	$90K[1] avg treatment course	$90 - $450/course	**$84 – 126** ($14K / mo) [2]
Average treatment duration	Two courses	A few courses	**6 – 9 mos.**
Use	1st line w/steroids	1st line	**2nd line**

Sabril

- $320M peak U.S. sales (2018)[3]
- Limited use
- Approved for infantile spasms in U.S.

1. As priced in U.S., assumes two courses of treatment at $45K per vial
2. Estimate; actual pricing is based on weight-based dosing
3. IQVIA

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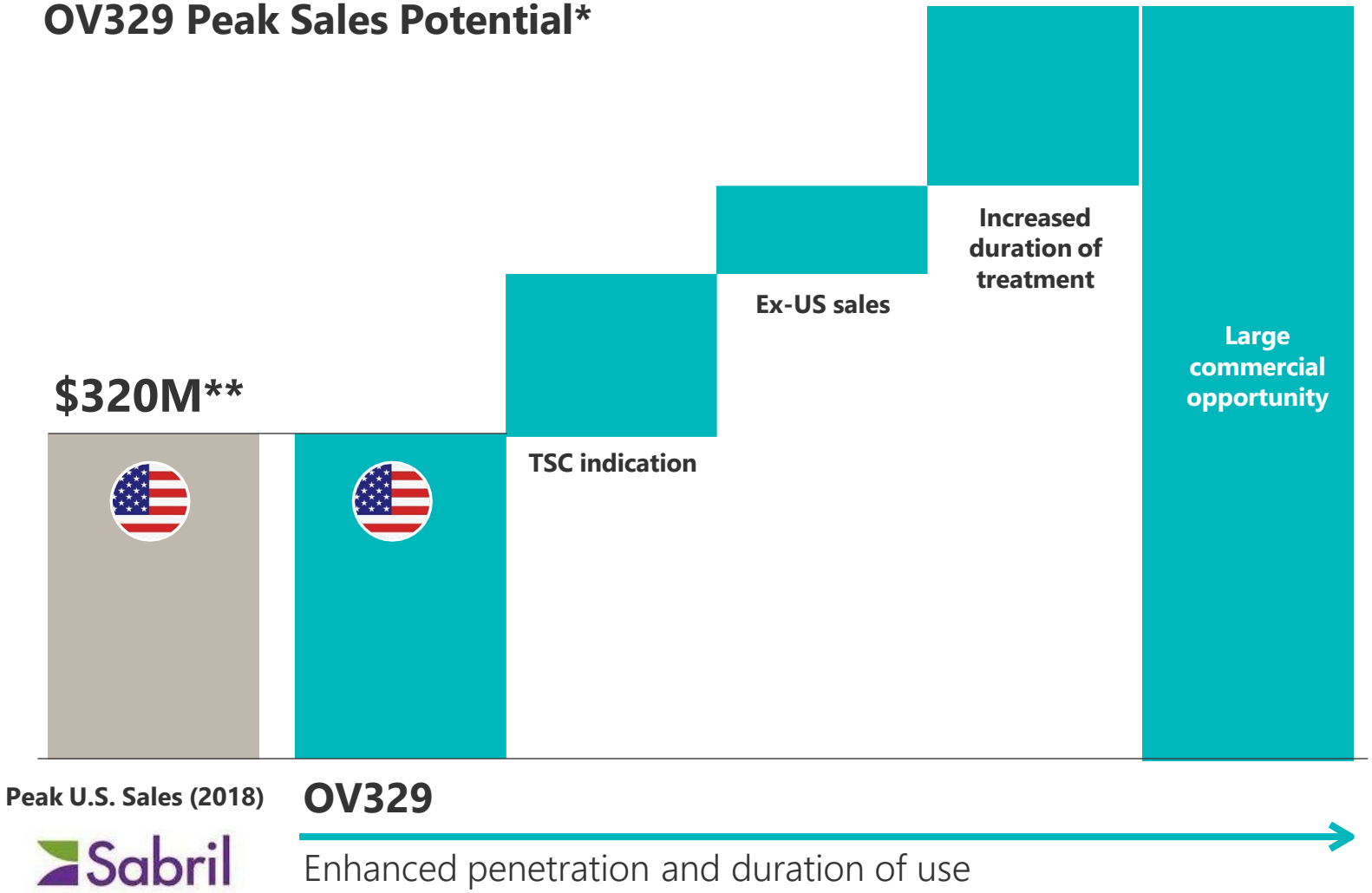
OV329 holds significant potential in TSC & IS

Anticipate earlier-line use, longer treatment duration

Validated MoA with an improved profile:
Enhanced safety, efficacy and tolerability

Differentiated pediatric formulation & weight-based pricing

Potential for disease modification



* Projected estimates
**IQVIA

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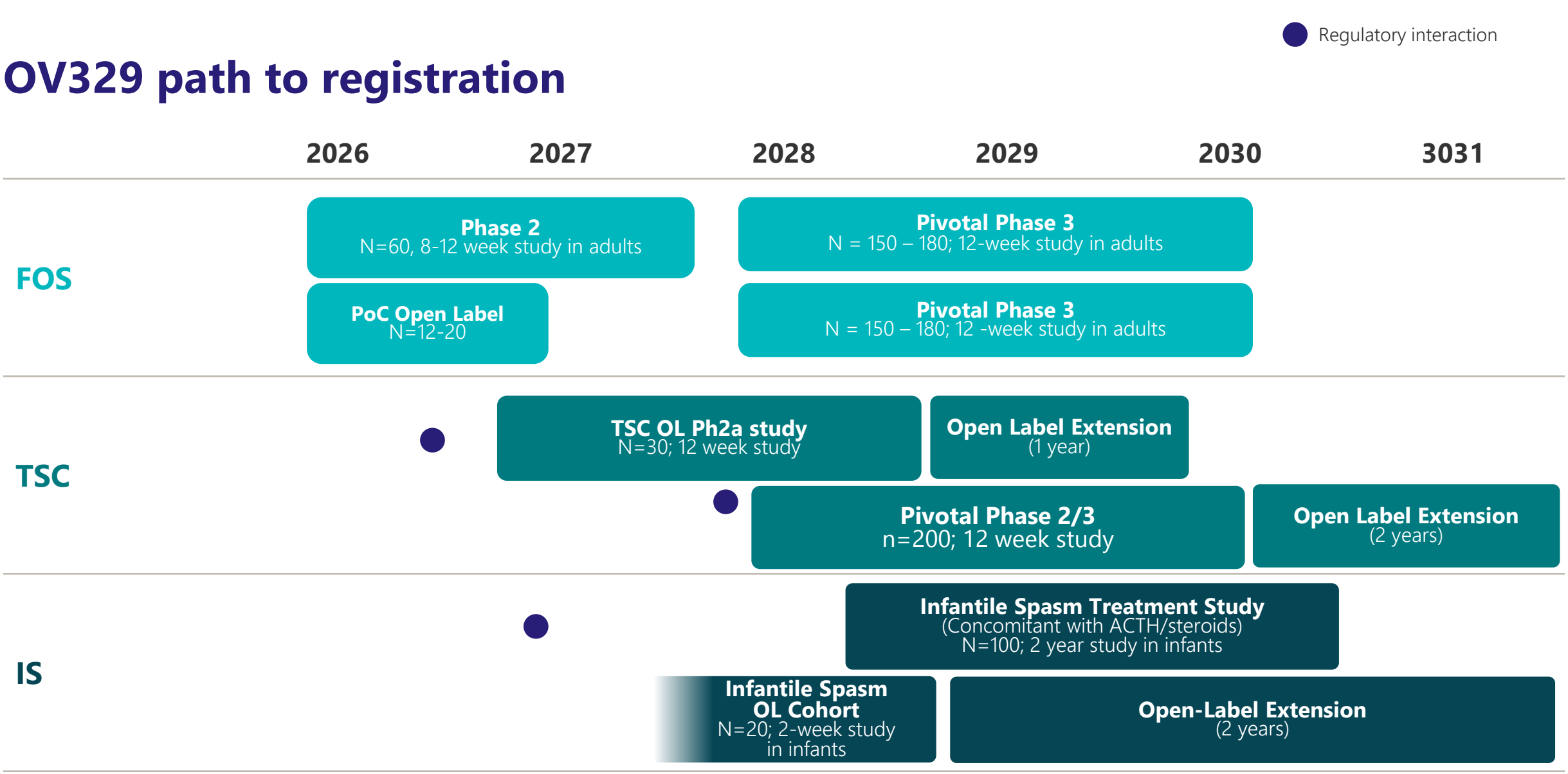
OV329 path to registration



TSC and IS efforts are additive and non-competitive with existing activities

Development paths are not mutually exclusive and are dependent on global regulatory feedback

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KCC2 Portfolio

29

Pioneers of KCC2 direct activation

- One mechanism: multiple medicines
- Safely drugged KCC2 with signal of GABAergic activity (OV350 tool program)
- Dosed humans with oral KCC2 direct activator (OV4071)
- Translational biomarkers to inform profile & indications
- Discovery engine of novel, next-generation activators
- Potential for robust franchise of mono- and combination therapies

Opportunity: Large therapeutic areas with great unmet need

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Therapeutic opportunity: KCC2 direct activation

Neurodegenerative psychoses & cognition

Schizophrenia

Alzheimer’s agitation

Alzheimer’s cognition

Alzheimer's hallucinations & delusions

Parkinson’s disease psychosis

Lewy body dementia psychosis

Huntington’s disease delusions

Bipolar mania

Conditions of anxiety & behavioral dysregulation

Generalized anxiety disorder

Obsessive compulsive disorder



Neurodevelopmental conditions

Rett syndrome

Developmental and epileptic encephalopathies

Autism spectrum disorders

Seizure disorders

Pain & trauma

Neuropathic pain

Centralized pain

Audiogenic trauma

Spinal cord injury

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KCC2: a common “master switch” regulating neural excitatory/inhibitory balance

Exclusively expressed in the CNS

Precision mechanism of action to rebalance neural network hyperexcitability

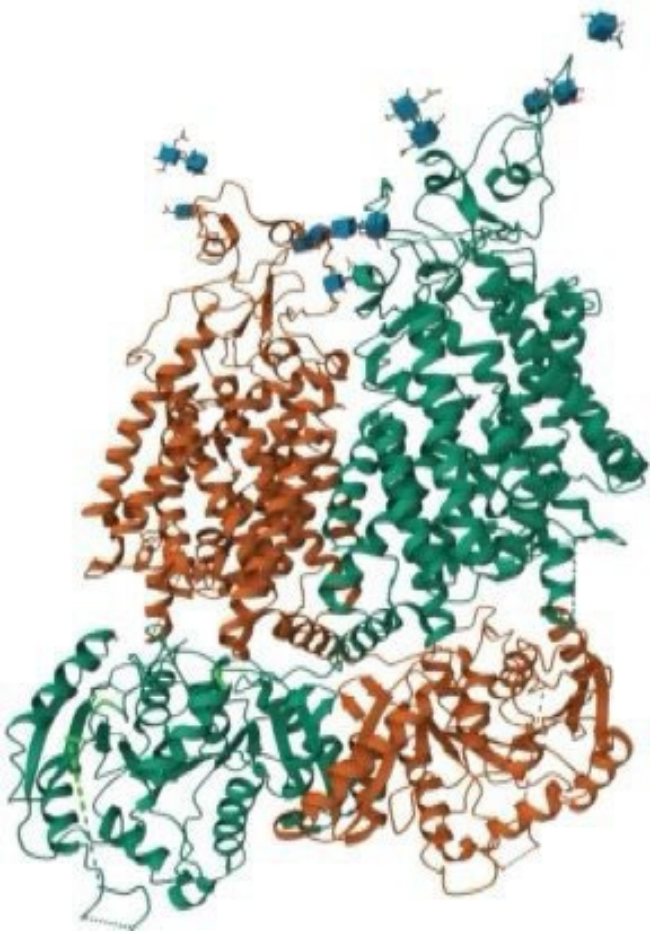
Restores neural sensitivity to GABA and thereby regulates synaptic inhibition

- Upstream of neurotransmitter blockers (e.g., D2 antagonists)
- Downstream of many acquired and genetic causes of hyperexcitability

Function occurs only when the transporter is sub-optimally extruding chloride

Converges on a broad spectrum of disorders with hyperexcitability

Self-limiting chemical gradient makes it nearly impossible to overmodulate



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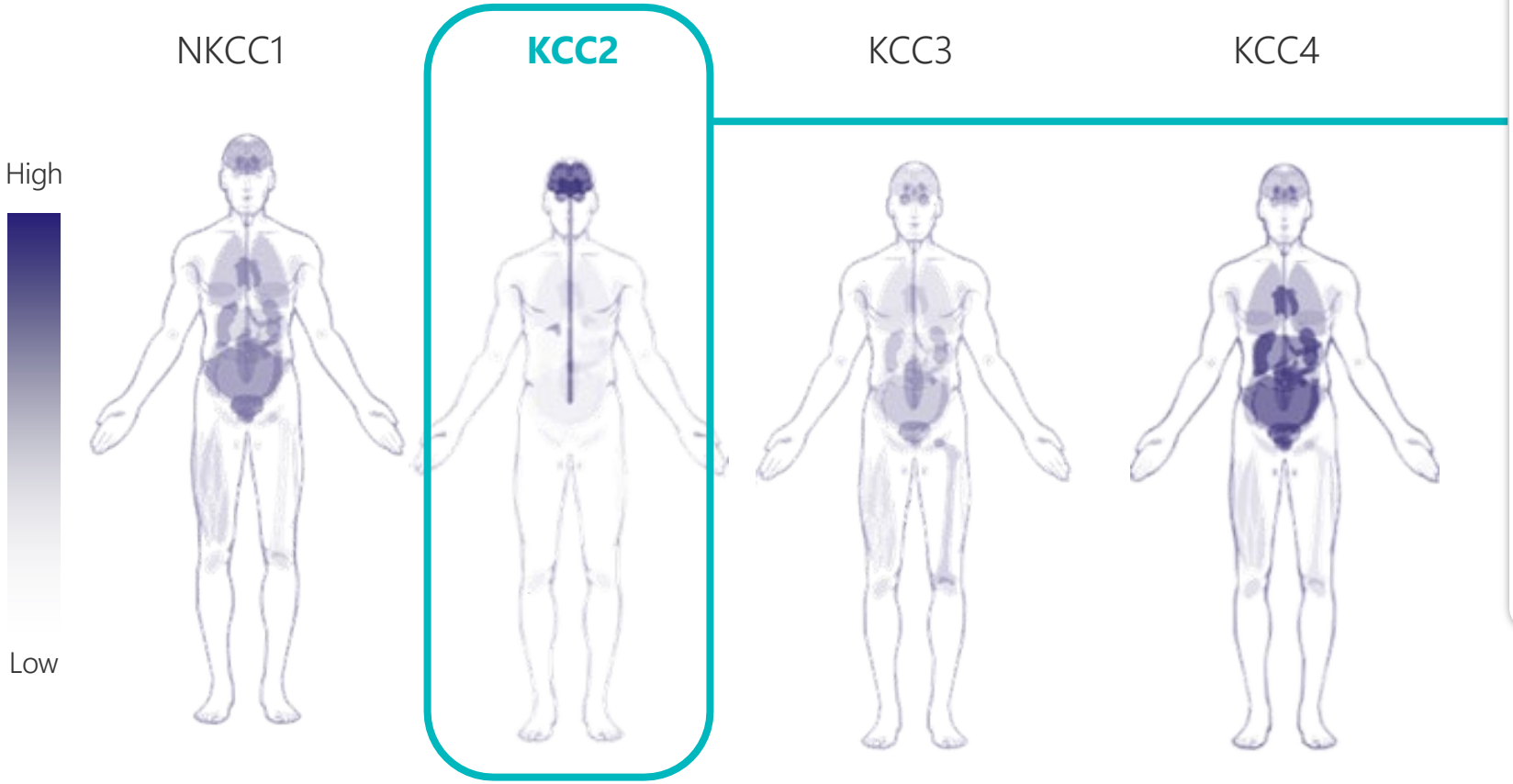
KCC2 is exclusively expressed in the CNS

KCC2 expression vs. other transporters modulating chloride homeostasis



Isoform of the potassium chloride co-transporter family

KCC2 expression only in neurons

Not systemically expressed in other organs

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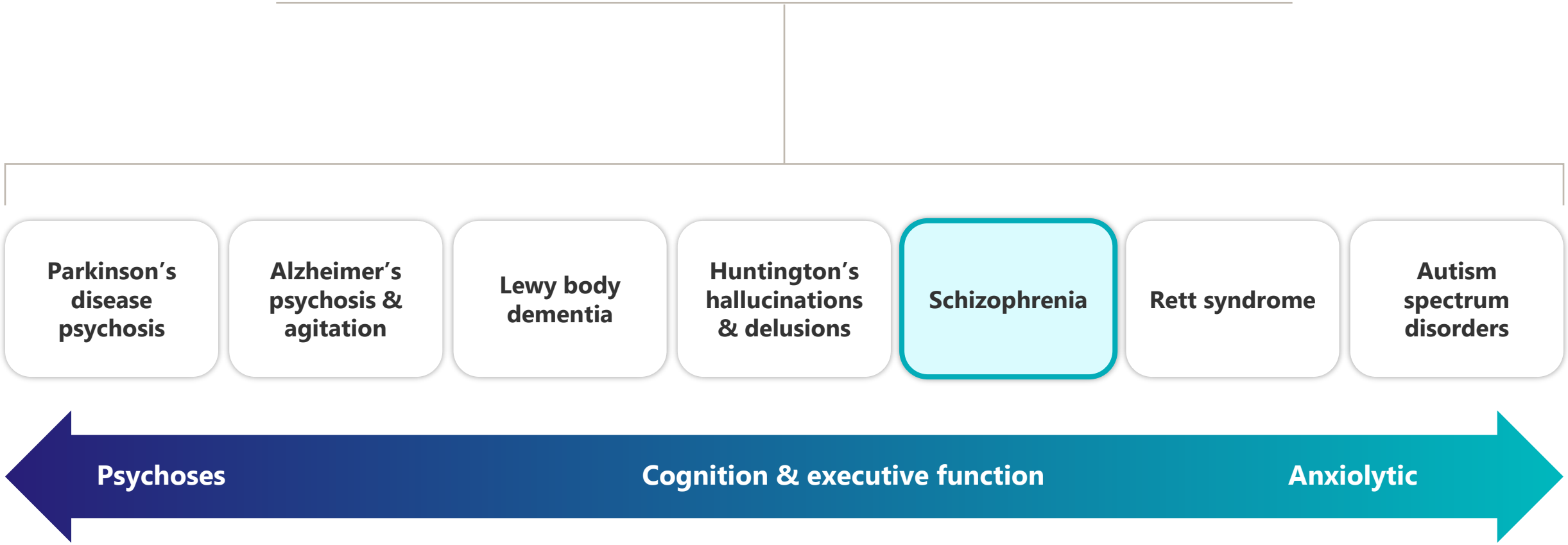
The OV4071 opportunity:
Broad applications in syndromic psychosis & psychiatric disorders



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Robust armamentarium of pharmacodynamic evidence supporting OV4071

Findings reinforce restoration of E/I balance

Consistent with KCC2 mechanism of action

Sample: PD studies evaluating Ovid KCC2 direct activators

Model	Relevance	Rescue Activity
Psychosis & locomotion		
MK801 induced hyperlocomotion (repeat dose)	Psychosis, schizophrenia	✓
MK801 induced hyperlocomotion	Psychosis, schizophrenia	✓
Amphetamine-induced hyper-locomotion model	Psychosis	✓
Methamphetamine induced psychosis	Psychosis & cognition	✓
22Q deletion model (schizophrenia)	Schizophrenia	✓
Huntington's disease motor symptoms (R6/2)	Motor function deficits	✓
Resident intruder model	Negative symptoms of schizophrenia	✓
PCP social interaction model	Sociability & physiological interactions	✓
Anxiety & behavior		
Rett syndrome (MecP2-KO)	Behavior; sociability	✓
Elevated plus maze	Agitation vs. anxiolytic properties	✓
SmartCube (phenotypic screen)	Wide range of attributes	✓
Pain		
Paclitaxel induced pain	Neuropathic pain (Grip strength)	✓
Spinal nerve ligation	Signal in chronic pain	✓
Paw withdrawal threshold	Sensitivity to pain stimuli	✓
Epilepsies & seizures		
Kainate diazepam resistant model	Cessation of status epilepticus	✓
iPTZ model	Anticonvulsant	✓
Soman model	Anticonvulsant	✓

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OV4071 attributes

STATUS

Phase 1 healthy volunteer study ongoing

~100 pharmacology studies

- in vivo PD models
- Phenotypic screens
- IND enabling studies & toxicology

Potent, rapid (< 1 hour), durable activity observed in vivo animal models

Broad pharmacodynamic activity and outperformance relative to therapeutic reference drugs

- Resolution of positive symptoms
- Restoration of sociability
- Rescue of cognition, working memory and task switching
- No sedation; maintenance of typical physiological activity
- Enhancement of grip strength and prophylaxis in chronic pain models
- Comparable to superior activity vs. clozapine, risperidone, xenomaline, haloperidol

Precise GABA tuning and activation

- Wild type animals unaltered in typical physiological activity
- Amelioration of phenotype symptoms in genetic, stimulant models

Bioavailable in humans and half life consistent with chronic, daily dosing

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OV4071 drug properties

Highly potent & selective

20-fold potency
in psychosis models vs OV350

0.64 µM KCC2 activity

Suitable for chronic dosing

13 hours
predicted half-life (T½)

Orally active

Direct binding & activation

Confirmed activation
of potassium/chloride ion flux

Therapeutic index

17-fold safety margins

No relevant off-target activity in other receptors relevant to psychosis

No activity for other potassium/chloride transporters

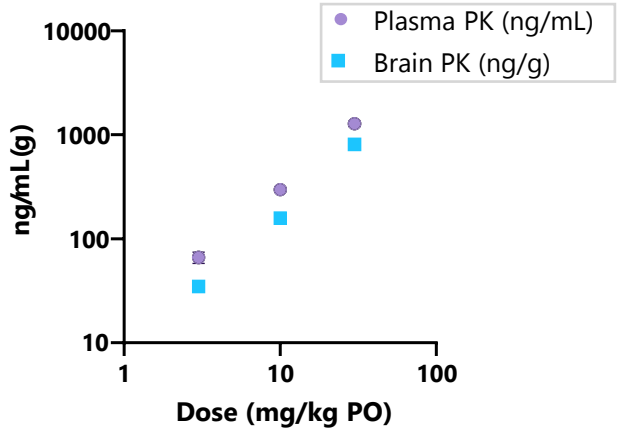
Potential tolerability

No sedation

No significant drug:drug interactions anticipated

No catalepsy

1:1 brain-to-plasma ratio



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KCC2 relevance in schizophrenia neurobiology

Post-mortem

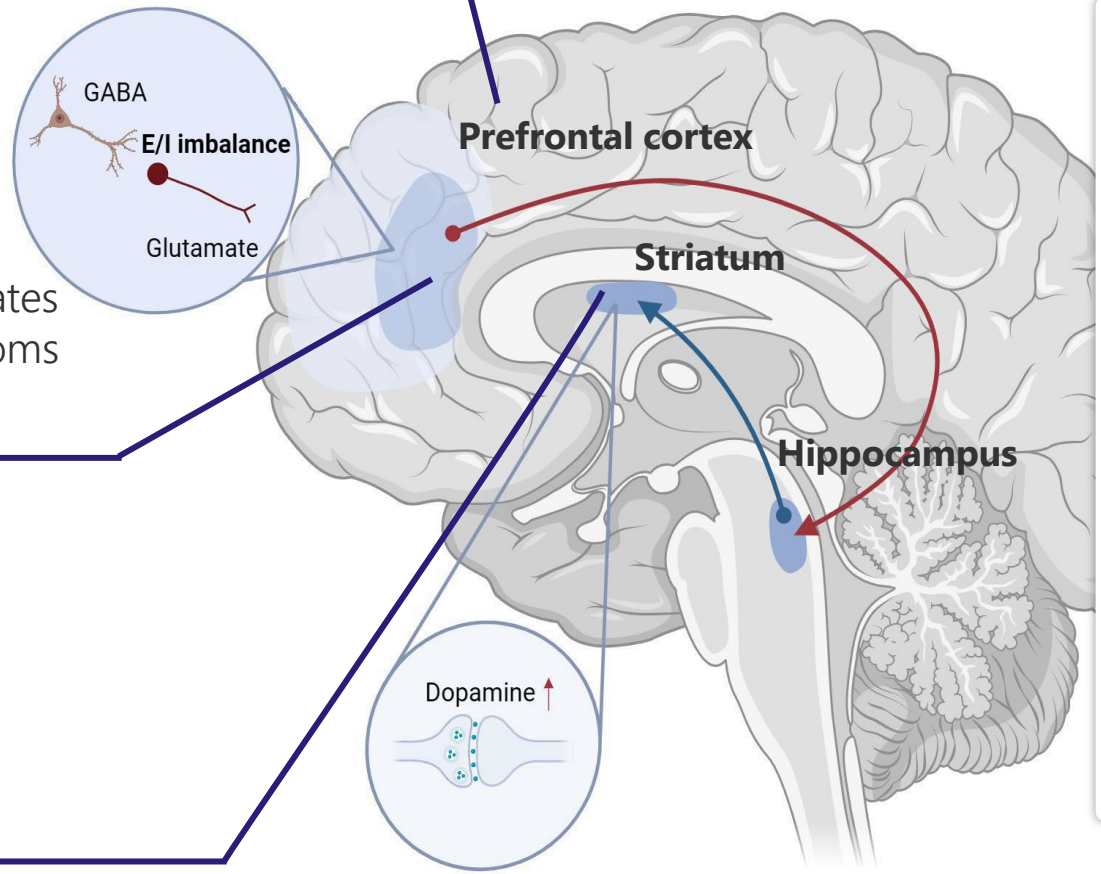
KCC2 expression reduced in the pre-frontal cortex of human & animals with schizophrenia

Negative symptoms & cognition

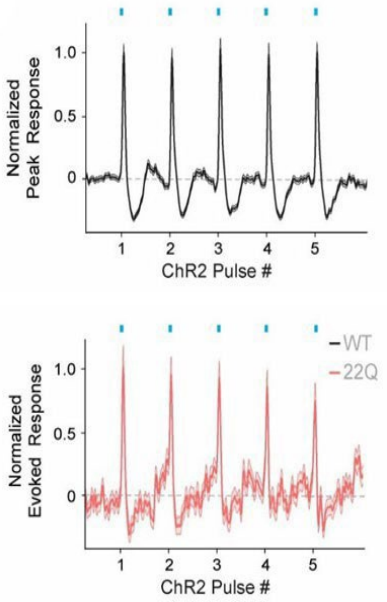
KCC2 function in prefrontal cortex mediates brain circuits regulating negative symptoms and cognition

Positive symptoms

Glutamatergic-driven excitation in the prefrontal cortex drives excess dopamine in mesolimbic pathways and striatum, leading to positive psychosis and cognitive symptoms



PFC E/I balance is perturbed in animals with 22q deletion



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Pharmacodynamic characterization to-date

OV4071 is modulating E/I balance

Psychosis & behavioral models

- **MK801** (NMDA antagonist)
- **Amphetamine**
- **Phencyclidine induced social deficits**
- **Resident intruder**
- *In progress* **Methamphetamine**
- *In progress* **22Q11 deletion**

- Consistent PD activity beginning at 3 mg/kg
- Normalized physiological locomotion in hyperlocomotion models
- Restored typical social interaction
- Rapid effect (<1 hr); no tachyphylaxis with repeat dosing
- Reduced striatal dopamine
- Reduced aggressivity
- No catalepsy or sedation

Electrophysiological biomarkers

- **MECP2 deletion**

- Translational biomarker established in wild type and genetic schizophrenia mice (22q11)
- EEG signal & rapid activity (1 – 3 hrs)
- EEG changes relevant for intended indications (schizophrenia and psychosis)

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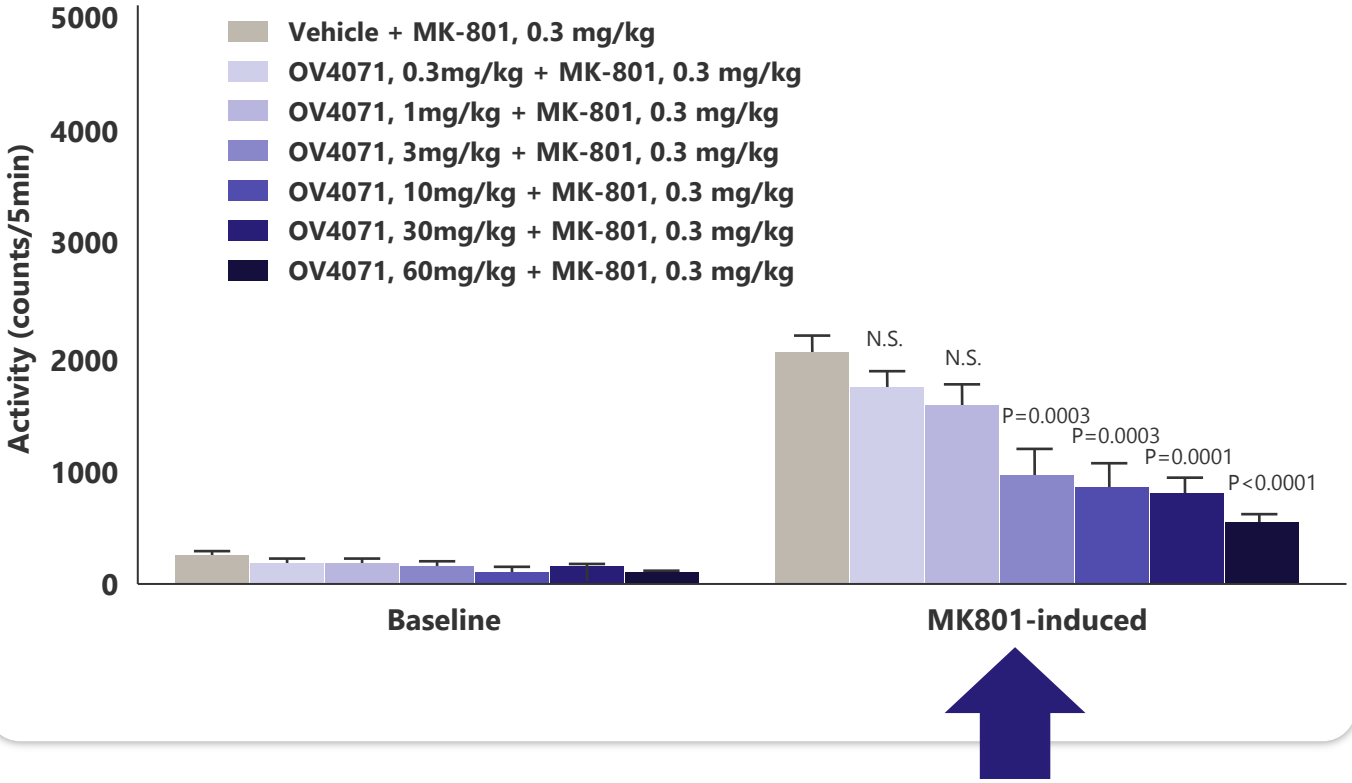
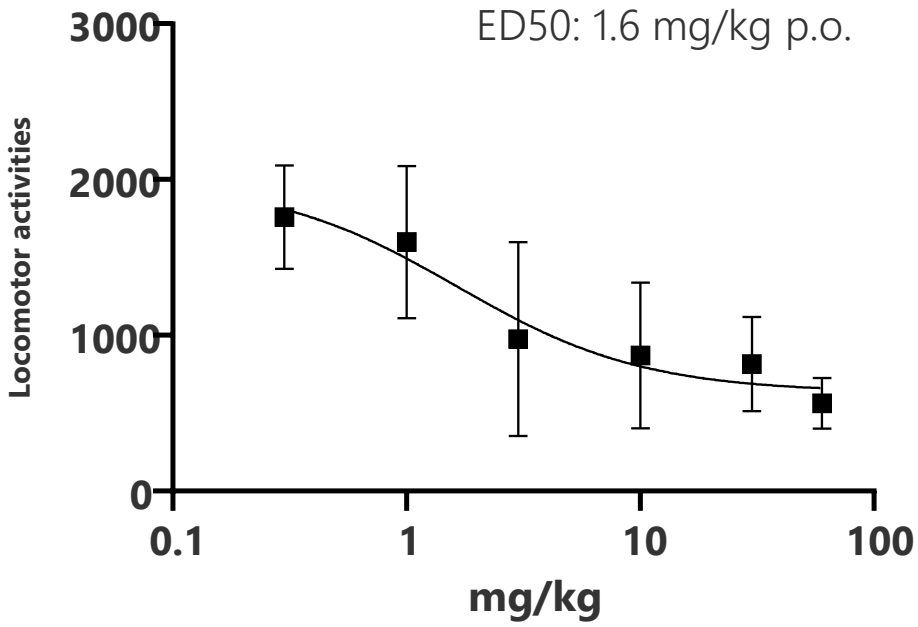
OV4071 delivers robust, dose-dependent signal in MK801 schizophrenia model

MK801 (NMDA antagonist) hyperlocomotion model comparing effect of vehicle to escalating doses of OV4071





OV4071 returned locomotion to natural levels (1,500 – 2,000 counts) in a dose-dependent fashion

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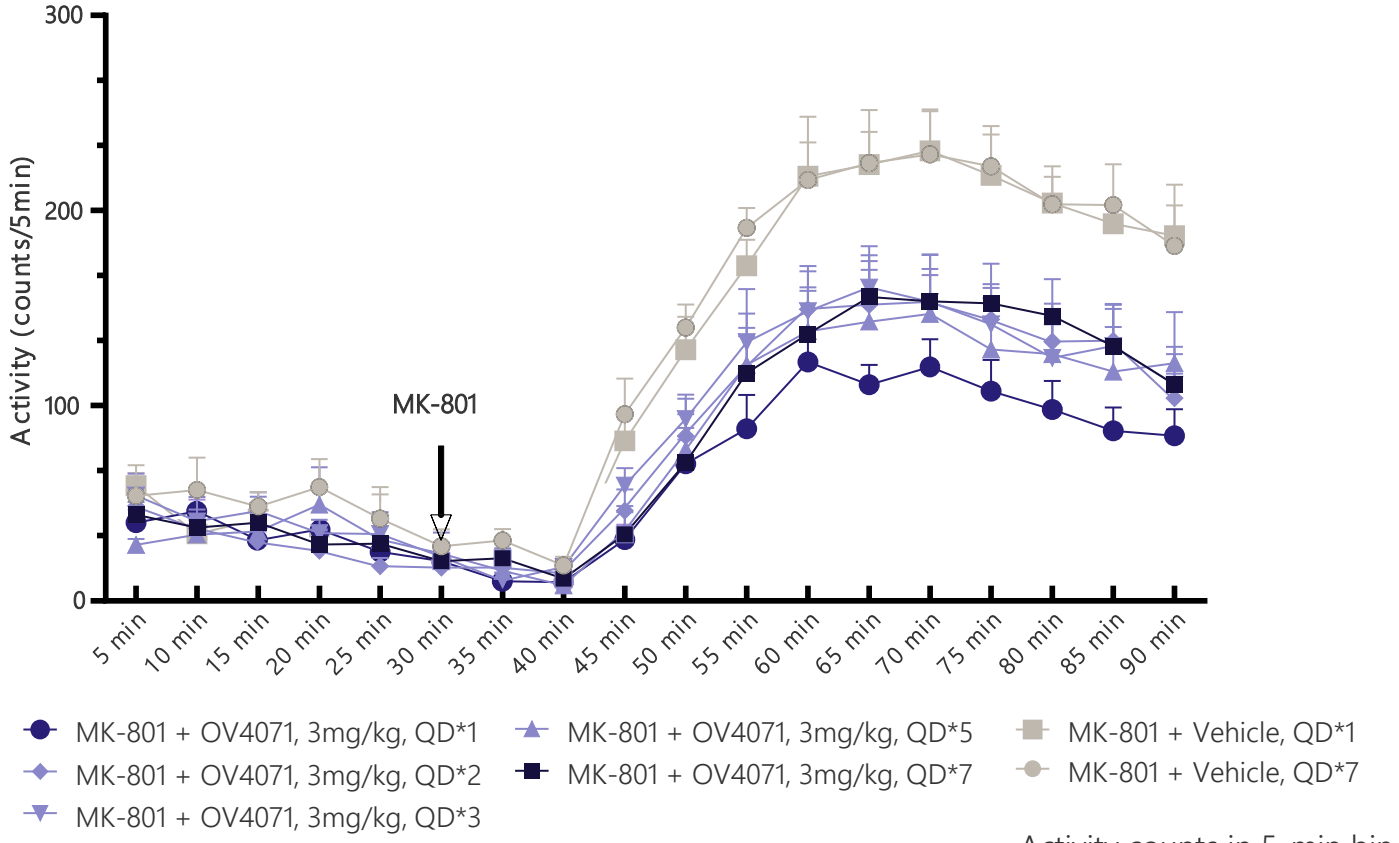
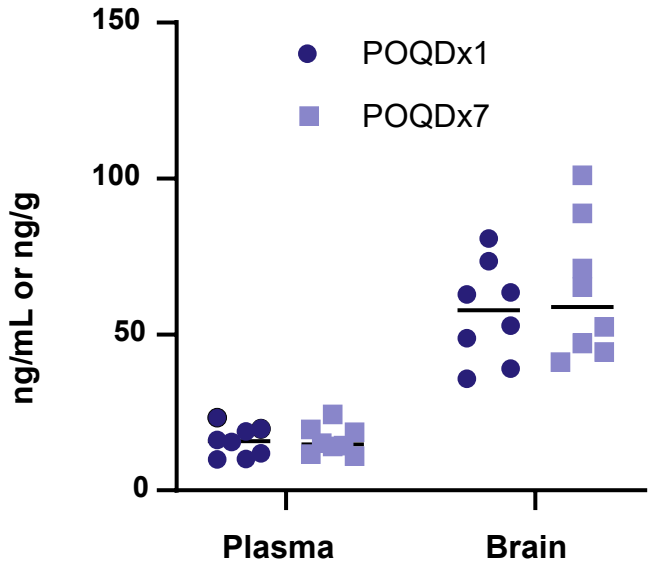
Rapid single dose effect: maintained upon repeated administration



PK after single and 7xPOQD (100 min post administration)



OV4071 maintained consistent rescue of hyperlocomotion in repeat dosing models
No tachyphylaxis observed

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OV4071 reduced levels of striatal dopamine in MK801 model

MK-801 (an NMDA antagonist that increases striatal dopamine)

- Increases extracellular concentration and firing rate of dopamine neurons

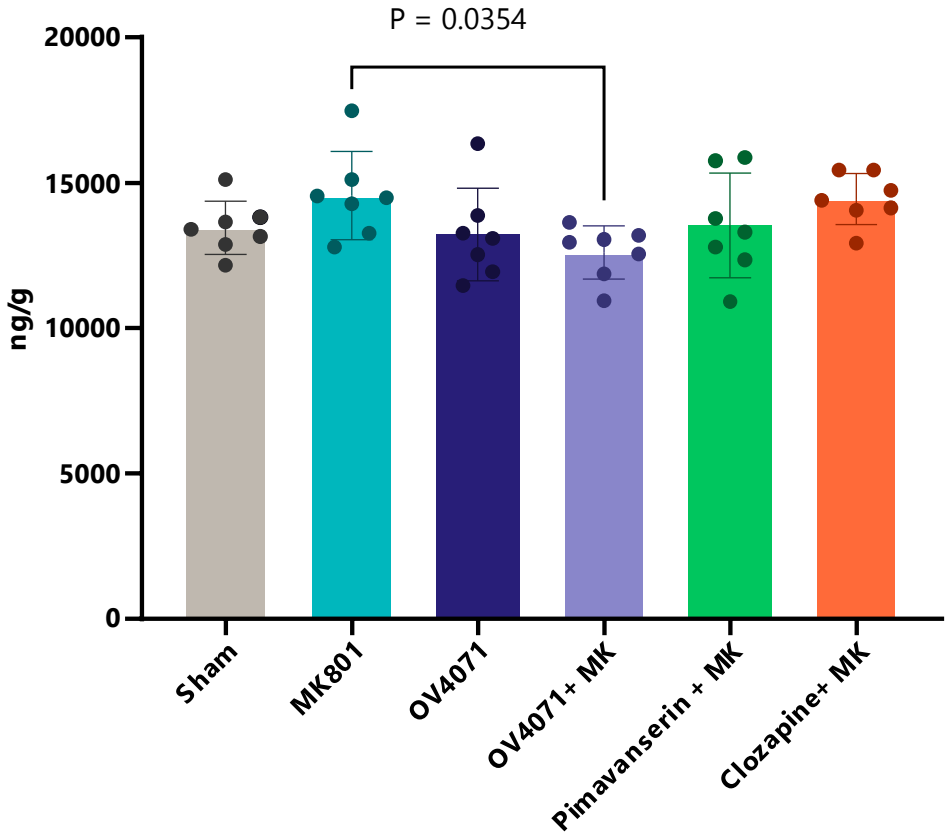
OV4071 decreased striatal dopamine levels

Results similar to pimavanserin and clozapine, which have a different mechanism of action

Results suggest

- A novel MOA for antipsychotic activities by KCC2 activation

Modulation of dopaminergic turnover in the striatum due to enhancement of GABAergic activity



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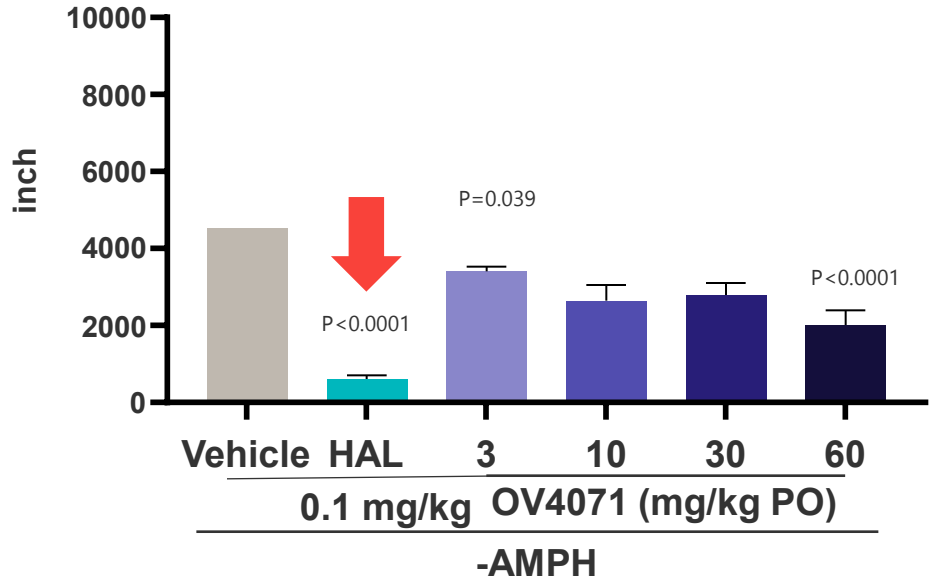
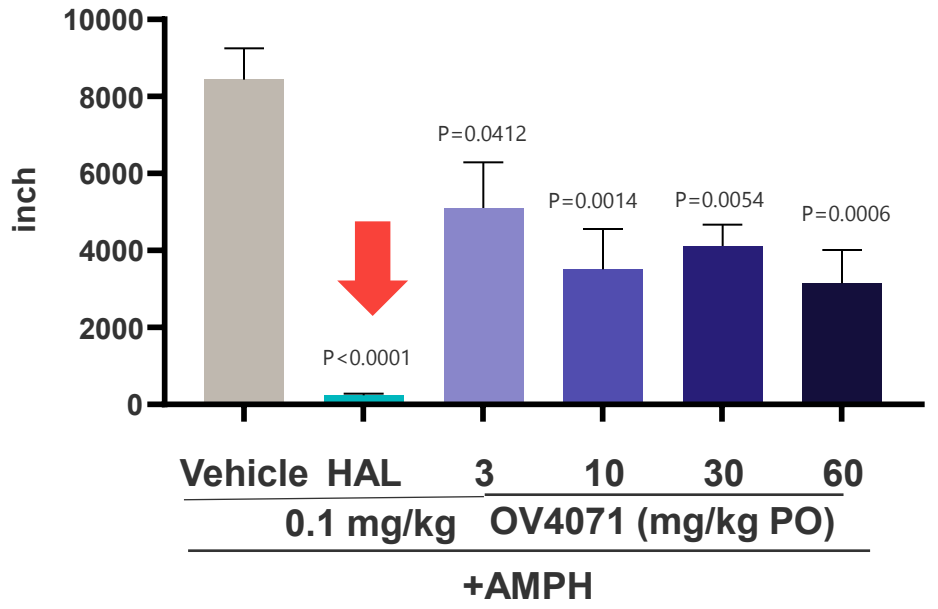
OV4071 single administration in the mouse AMPH hyperlocomotion model





OV4071 was orally dosed in 0.5%HPMC/0.1%Tween80 suspension 30 min before AMPH injection (N=5-7).
Haloperidol (HAL) was injected intraperitoneally (0.1 mg/kg)

Post-amphetamine stimulant, OV4071 reduces hyperlocomotion, while maintaining normal physiological movement at consistent dose with MK801 model

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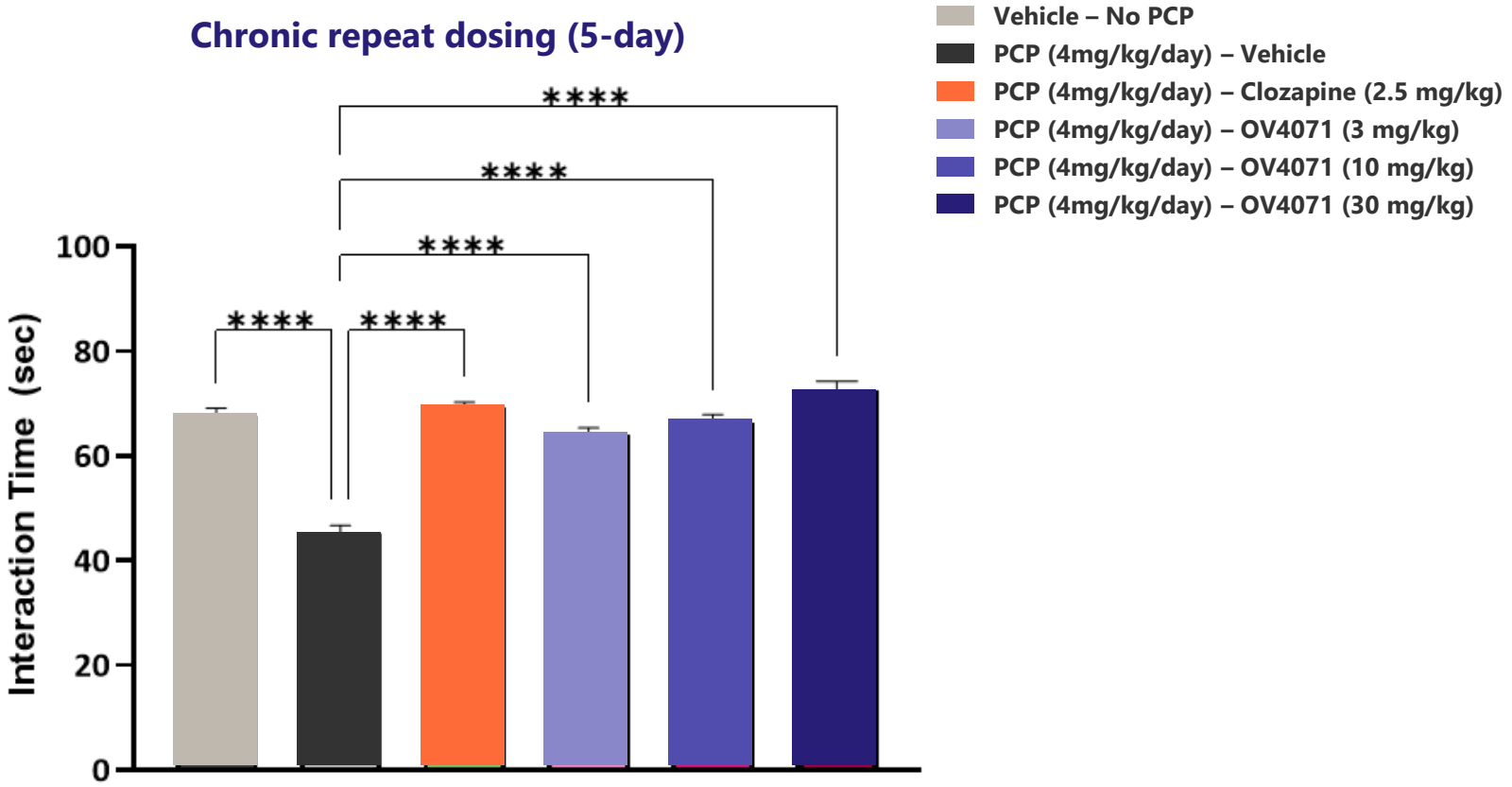
OV4071 restores social interaction in chronic PCP-induced animal behavior model

Methods

Induce asociality and reduced interactions with phencyclidine

Results

- OV4071 restored typical animal physiological interactions consistent with:
  - Natural control
  - Clozapine
- E/I is restored, suggesting a complementary mechanism of action



*Effects of clozapine and OV4071 on interaction time in rats chronically treated with PCP. Data are presented as mean ± SEM. ***p<0.0001 compared to PCP-Vehicle group.*

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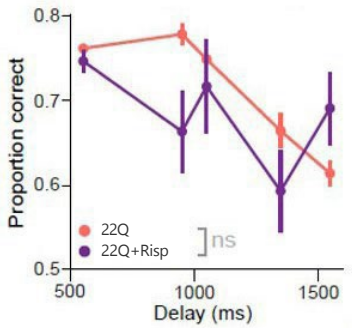
KCC2 direct activation vs. marketed antipsychotics in a genetic model of psychotic disorders

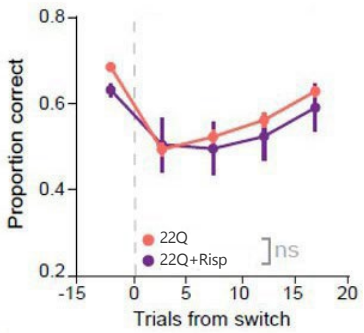
22Q11 deletion model

Antipsychotics (risperidone)

Working memory

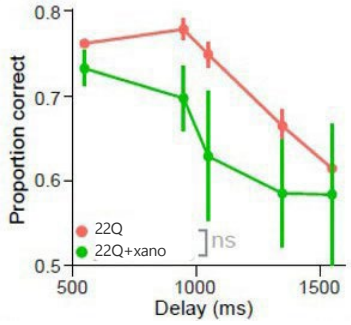


Task switching



Xanomeline/trospium (Cobenfy)

Working memory



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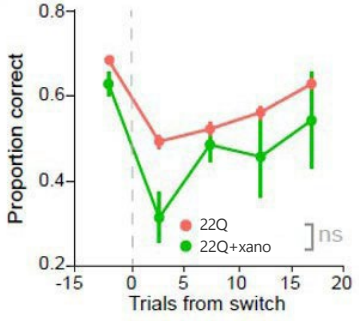
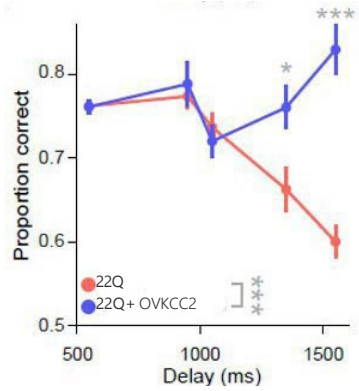


Ovid KCC2 direct activator

Working memory



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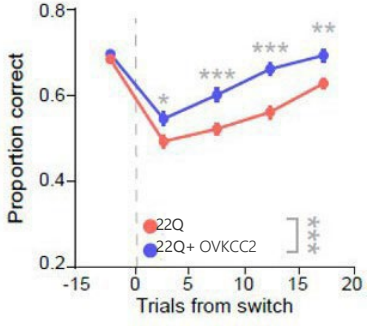

Ovid KCC2 direct activator provides benefits across working memory and task switching

Data source: Mukherjee et al., in preparation

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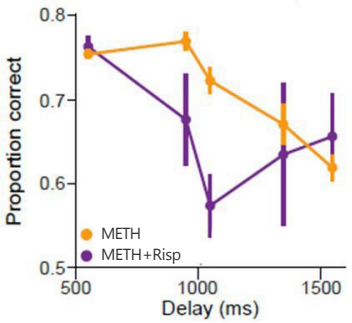
KCC2 direct activation vs. marketed antipsychotics in a pharmacological model of psychotic disorders

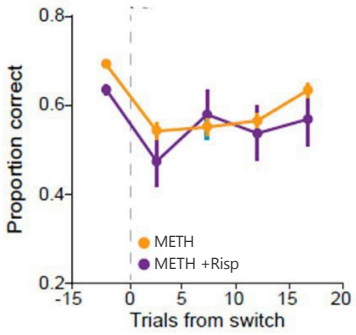
Methamphetamine model

Antipsychotics (risperidone)

Working memory

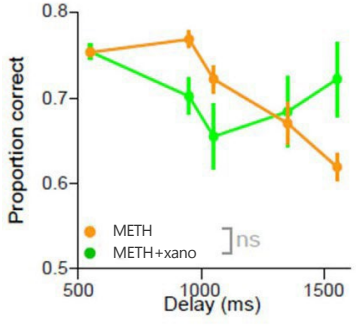


Task switching

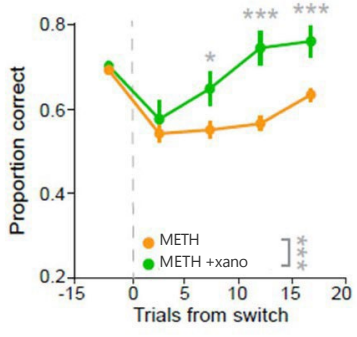


Xanomeline/trospium (Cobenfy)

Working memory

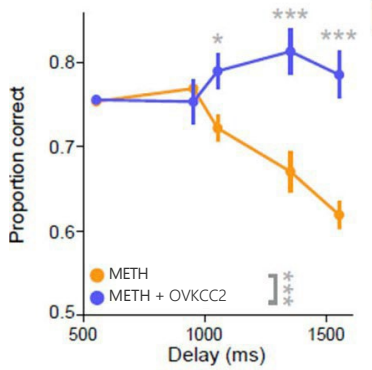


Task switching

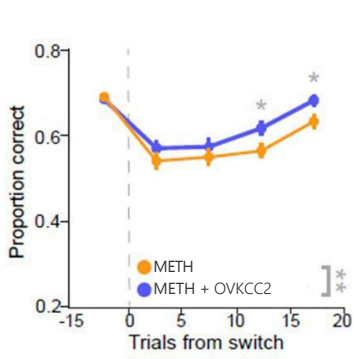


Ovid KCC2 direct activator

Working memory



Task switching



Ovid KCC2 direct activator outperformed in working memory relative to risperidone and xanomeline and provided task switching benefit compared to risperidone

1. Data source: Mukherjee et al., in preparation

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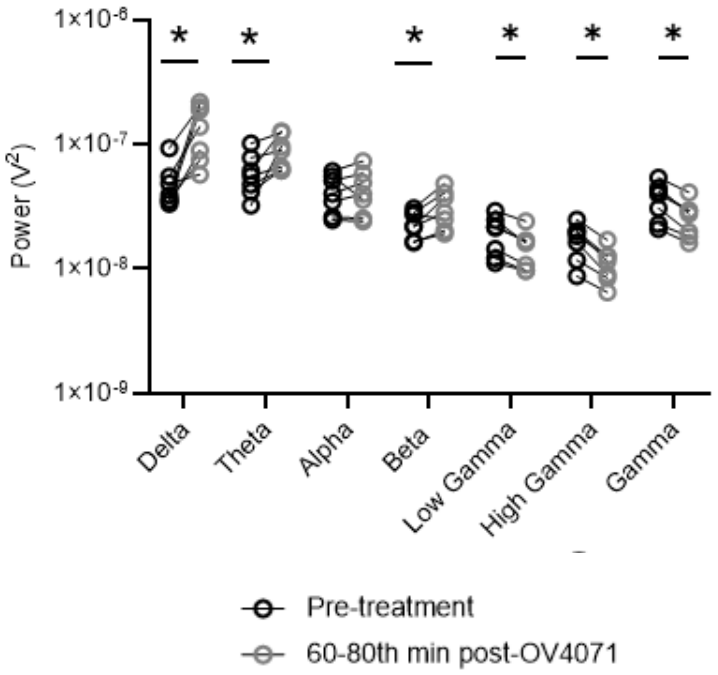
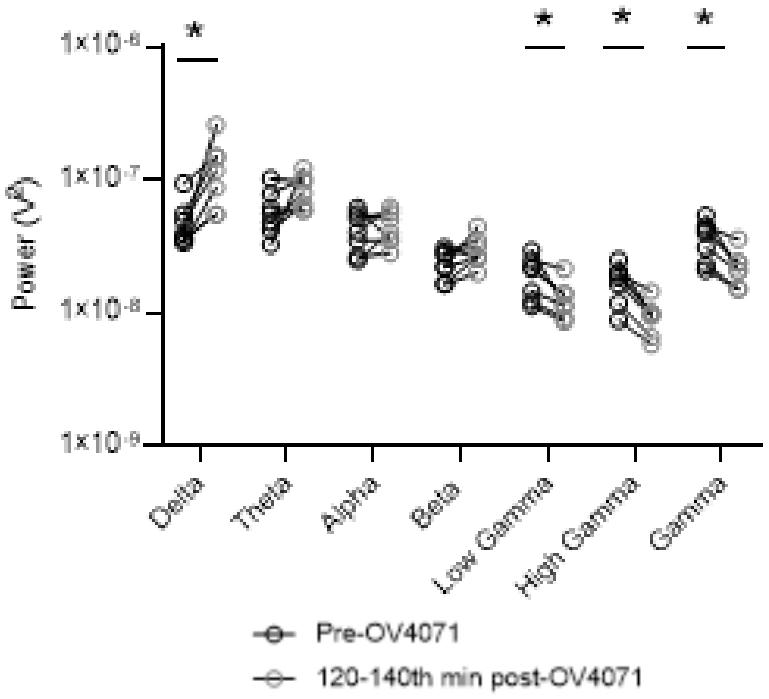
OV4071 demonstrates potentially translatable EEG biomarkers

Wild type Mice
(OV4071 3.75 mg/kg)

60 – 80 mins post dose

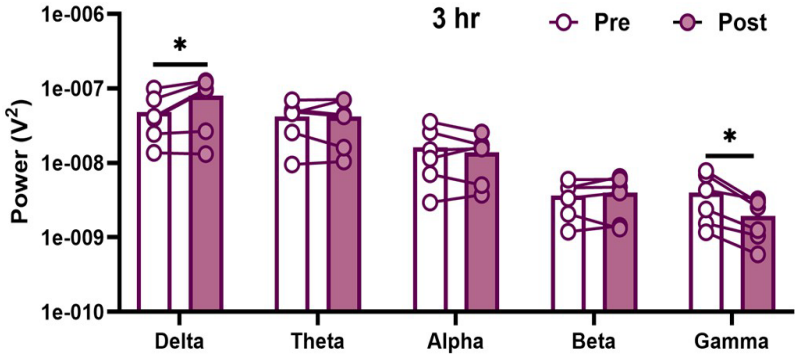


120 – 140 mins post dose



MECP2 (Rett) Mice
(OV4071 7.5 mg/kg)

3 hours post dose



N= 6 animals; pairwise t-test, *p<0.05

A consistent translational biomarker established in animal pharmacology and human studies

1. Tufts Lab of Neuropharmacology

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Translational biomarker (EEG)

Approach

Exploratory electrophysiology using electroencephalography (EEG) in animal PD models and humans, including:

- Tool program (OV350) in MECP2 mice
- Tool program (OV350) in healthy human volunteers
- Tool program (OV350) ketamine challenge in mice
- OV4071 in MECP2 mice
- OV4071 in wild type mice
- OV4071 in healthy human volunteers

Results

Similar biomarker (frequency) activity observed for both KCC2 direct activators (OV350 and OV4071)

- Gamma decrease, delta increases

Frequencies consistent with KCC2 activation MoA and GABAergic activity (gamma band modulation)

Activity seen rapidly; similar time-to-effect in pharmacodynamic models

Modulation of EEG frequencies supportive of planned indications

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Translational & clinical strategy

Translational strategy

Pharmacodynamic activity characterization in phenotypic and in vivo models

- Genetic models
- Stimulant induced models
- Reference drug comparators
- Suggestive/predictive electrophysiology

Broad electrophysiology biomarkers in healthy volunteers

Broad and indication-relevant electrophysiology biomarkers in stimulant induced humans (ketamine, an NMDA antagonist)

Electrophysiology and clinical symptom evaluation in patient signal finding and proof of concept studies

Establish a consistent “red thread” through animal pharmacology, human and patient studies

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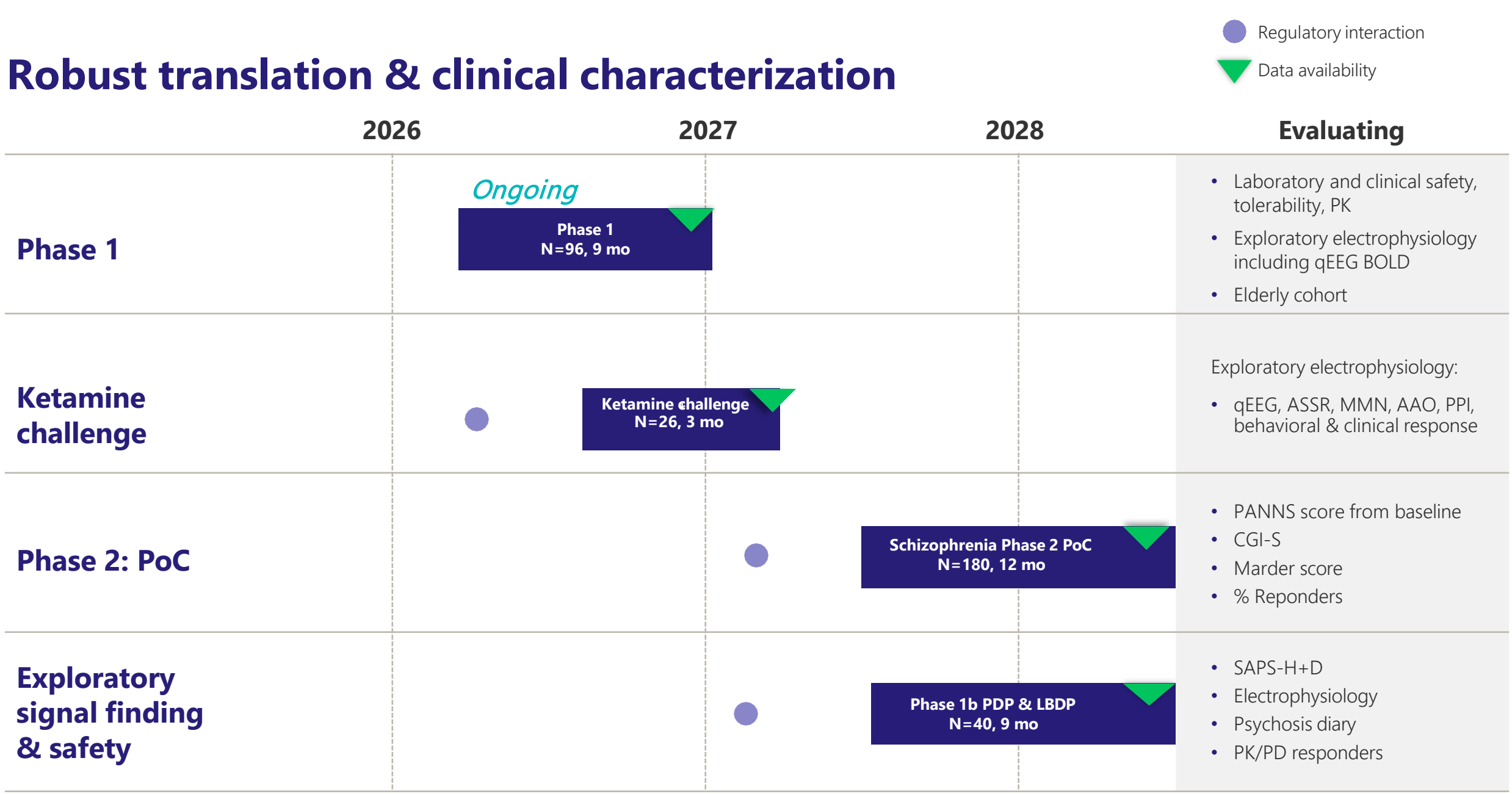
Robust translation & clinical characterization



Development paths are not mutually exclusive and are dependent on global regulatory feedback
*Ketamine challenge to initiate pending PK characterization in Phase 1 study

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Patient studies with OV4071

Phase 2 proof of concept in schizophrenia

- Randomized, double-blind, placebo-controlled study in patients with acute schizophrenia
- Evaluate safety, tolerability, and efficacy
- Multi-site study in US

Phase 1b exploratory signal finding & safety in PDP & LBDP

- Single arm, open-label study with titration up to two doses in patients with Parkinson's disease psychosis and Lewy body dementia psychosis
- Evaluate safety, tolerability, and exploratory clinical effect in psychosis
- Multi-site study in US

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Electrophysiology biomarkers leveraged in Phase 1

Electroencephalography (EEG) and event-related potential (ERP) biomarkers

Biomarker	Relevance	Measure
Quantitative EEG (qEEG)	Arousal and activation	• Absolute and relative spectral power (uV) in traditional frequency bands • Slope of aperiodic (non-oscillatory) component
Active Auditory Oddball	Cognitive processing speed and resource allocation	• Amplitude of early sensory-evoked (N100, P200) • Amplitude and latency of P300b
Mismatch Negativity	Automatic encoding and detection of change in sensory scene	• MMN amplitude measured in difference wave of standard-deviant conditions • P3a amplitude evoked by deviant stimuli
Auditory Steady State Response	Neural synchrony	• Evoked spectral power (uV) in gamma (30-50 Hz) • Phase consistency measured by intertrial coherence
Prepulse Inhibition	Auditory sensory gating	• % change in amplitude of auditory-evoked response to “pulse” stimuli

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ELECTROPHYSIOLOGY STRATEGY:
Relevance in schizophrenia

Electroencephalography (EEG) and event-related potential (ERP) biomarkers

Biomarker	Relevance in schizophrenia	Biomarker changes
Quantitative EEG (qEEG)	Hypo-frontality pattern associated with negative symptoms and cognitive dysfunction	• Δ low-frequency power (delta and theta) • Reduced alpha power, primarily in the frontal lobes • Δ to gamma power
Active Auditory Oddball	Impaired attentional allocation and working memory updating Deficits present in clinical high-risk and first-episode patients, and continue to progress with disease chronicity	• Δ latency and decreased amplitude of P300 response
Mismatch Negativity	Implicates NMDA hypofunction Associated with higher symptom severity and functional impairment Predictive of conversion to psychotic disorder in clinically high-risk patients	• Lower MMN amplitude in difference wave • Low P3a amplitude in response to deviant stimuli
Auditory Steady State Response	Associated with clinical symptom severity (hallucinations, psychotic severity, and cognitive decline) Predictive of conversion to psychotic disorder in CHR samples	• Lower evoked spectral power and phase-locking / coherence
Prepulse Inhibition	Reduced sensory gating capacity is a trait-marker of sensory input dysfunction	• Lower PPI ration (less suppression)

qEEG: Gattaz et al. *Eur Arch Psychiatry* 1992; AOD: Hamilton et al. *Schizophr Bull.* 2019; MMN: Nagai et al. *Front. Psychiatry* 2013; ASSR: Sugiyama et al. *Front. Psychiatry* 2021; PPI: Swerdlow et al. *Schizophr Res.* 2018

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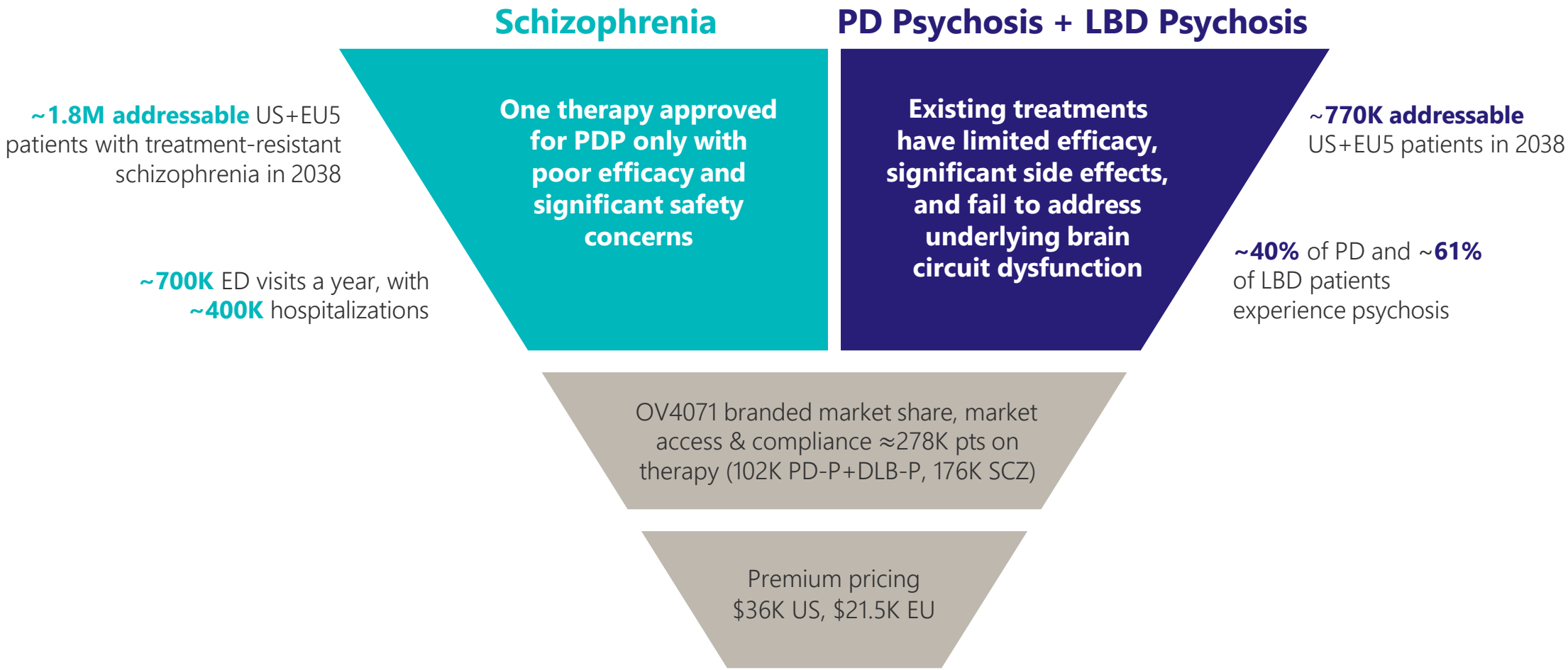
A meaningful psychosis market for OV4071



~$6.8 Billion Peak US + EU5 Revenue in 2038

1. Estimates for peak OV4071 revenue in 2038; LifeSci Consulting

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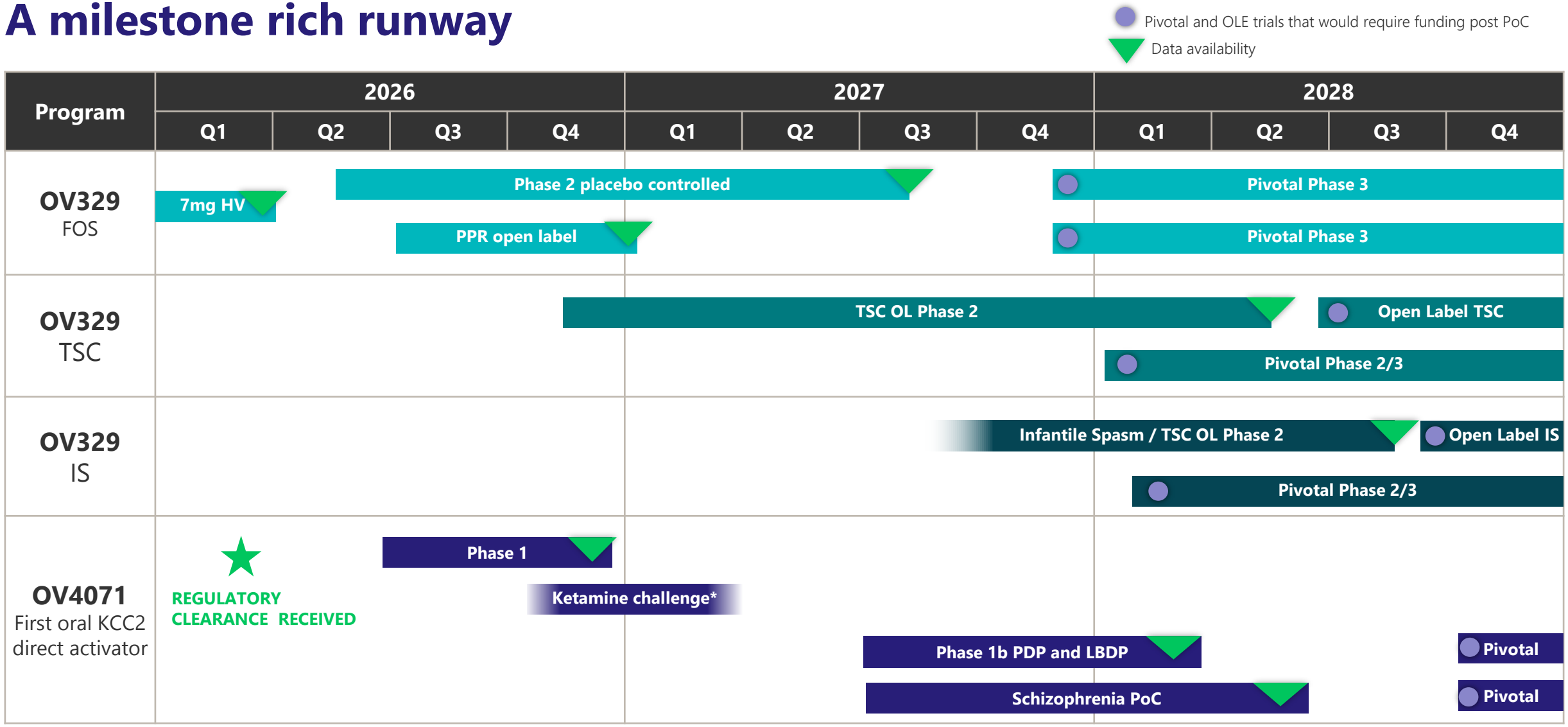
A milestone rich runway



Timelines pending feedback from regulatory discussions
*Ketamine challenge to initiate pending PK characterization in Phase 1 study
**Assumes exercise of all current outstanding warrants

Cash runway into 2029 fueling multiple catalysts**

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