Ovid Therapeutics

# Corporate presentation

May 12, 2026




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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; 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; 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

## Fundamental biological targets

implicated in many conditions driven by neural hyperexcitability

## Differentiated, universal mechanisms of action

that may hold broad therapeutic utility and stand out in a growing field of me-too medicines

## Pipeline of highly specific small molecules

intended to culminate in a fully integrated neurotherapeutics company

## Multiple, sequential clinical & regulatory milestones throughout 2026 - 2027

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# High-value, differentiated pipeline

| 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:<br>• Competitive efficacy<br>• Superior tolerability & safety profile<br>• No expected titration or drug:drug interactions | **Phase 2 RCT**<br>**Open label photo paroxysmal response PoC** | • Phase 2 initiation (Q2 2026)<br>• Open-label photo paroxysmal response (PPR) initiation and results H2 2026<br>• Phase 2a topline results (mid-2027) |
| **Tuberous sclerosis complex seizures (TSC)** | 1st approved GABA-AT inhibitor<br>• Preferable safety profile, tolerability<br>• Increased treatment duration | **PoC & safety** | • PoC safety and signal finding study to initiate in Q4 2026 |
| **Infantile spasms (IS)** | Disease modifying 1st line agent<br>• Preferable safety profile, tolerability<br>• Increased treatment duration | **PoC & safety** | • Infant formulation and enabling studies ongoing |
| **OV4071, potassium-chloride cotransporter 2 (KCC2) direct activator (oral)** | | | |
| **Broad spectrum psychosis, initially psychosis associated with Parkinson's disease (PD) and Lewy body dementia (LBD), and acute schizophrenia** | • Psychosis associated with Parkinson's disease and Lewy body dementia<br>• Acute schizophrenia<br>**Additional indications:**<br>• Neurodegenerative psychoses<br>• Other undisclosed indications | **Phase 1**<br>**Ketamine study** | • Phase 1 initiation (Q2 2026)<br>• Proof-of-mechanism ketamine study (initiation H2 2026)<br>• Phase 1b PoC studies & results (H2 2027) |

**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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# OV329:
# A next-generation, potential best-in-class GABA-aminotransferase (AT) inhibitor

**Precision inhibition**
for conditions of neuronal hyperexcitability, including drug-resistant epilepsies (DREs) and developmental epileptic encephalopathies (DEEs)

**Validated mechanism**
for focal seizures and infantile spasms

Differentiated safety profile & potential therapeutic index relative to 1st generation GABA-AT inhibitor Sabril (vigabatrin)

**Clinical results**
favorable safety profile, tolerability and cortical inhibition from Phase 1 studies

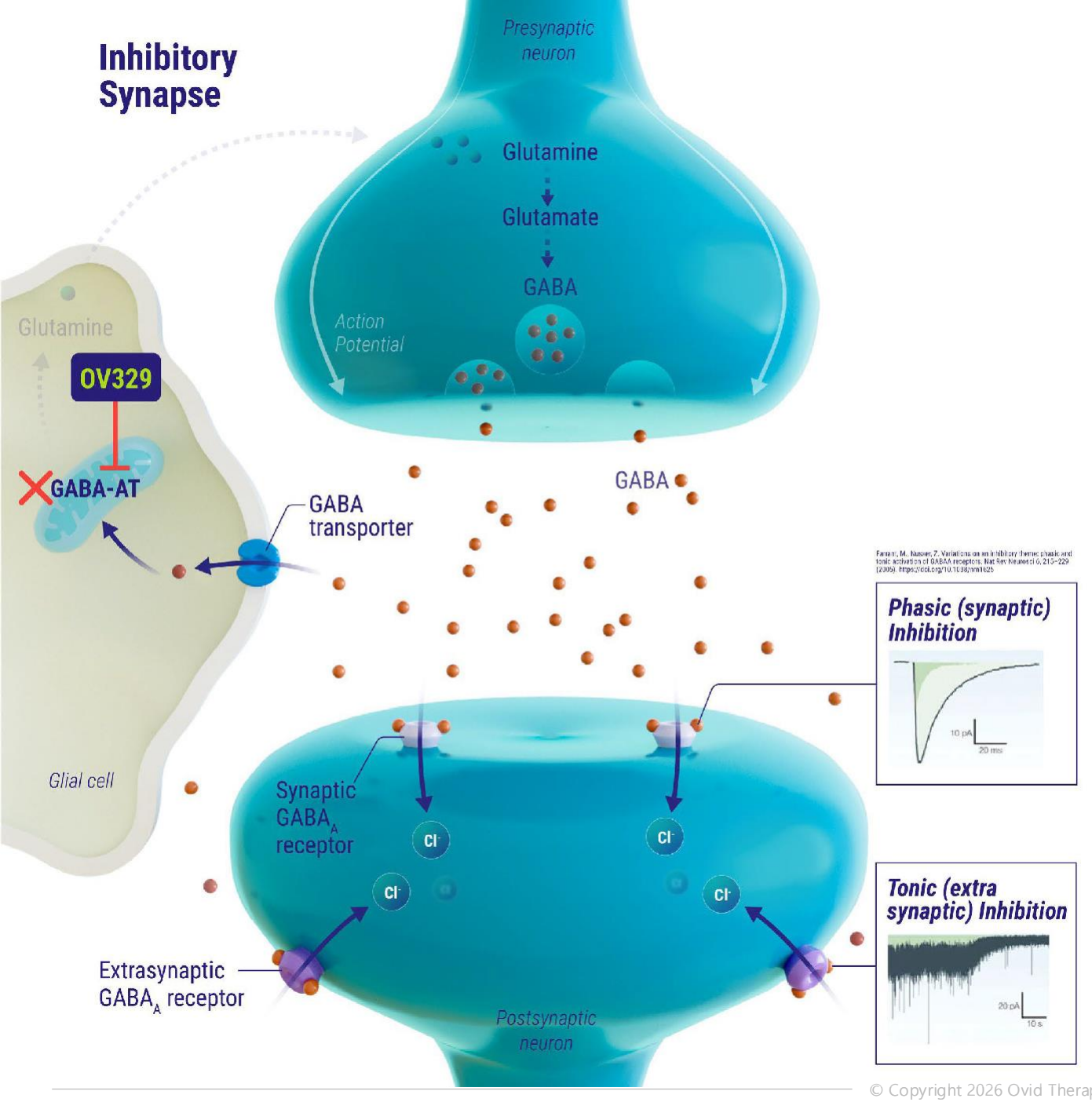
Now advancing into 4 PoC studies in 2026 - 2027

**IP through 2041***
10 additional patent families

**A universal mechanism for restoring GABAergic inhibition & quelling neural hyperexcitability**

*Assumes five-year patent term extension

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# OV329: believed to 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

**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

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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# The broad OV329 opportunity: Treatment resistant focal seizures

**ONGOING**

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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

**Quell hyper-excited neurons by optimally tuning synaptic and extra-synaptic GABAergic inhibition**

**Potent, lower dosing**
(est. OV329 human doses:
5-7 mg vs 2,000-3,000 mg for VGB)

**Oral, once daily dosing with no titration anticipated**

**Best-in-category tolerability**
(no treatment-related or treatment emergent adverse events associated with OV329 higher doses in Phase 1 participants)

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

**Validated mechanism for focal seizures and infantile spasms**

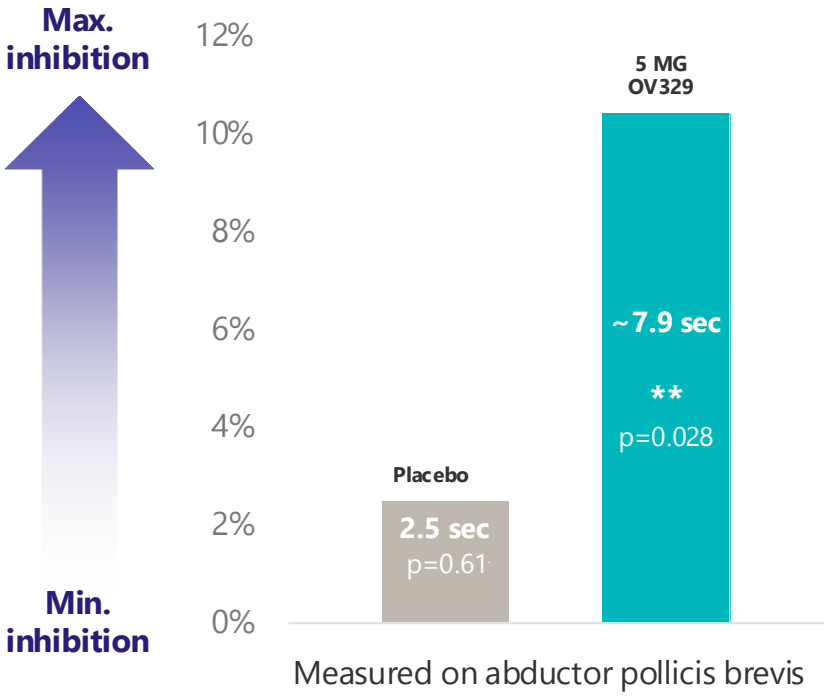
**Advancing 4 PoC studies in 2026 - 2027**

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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**

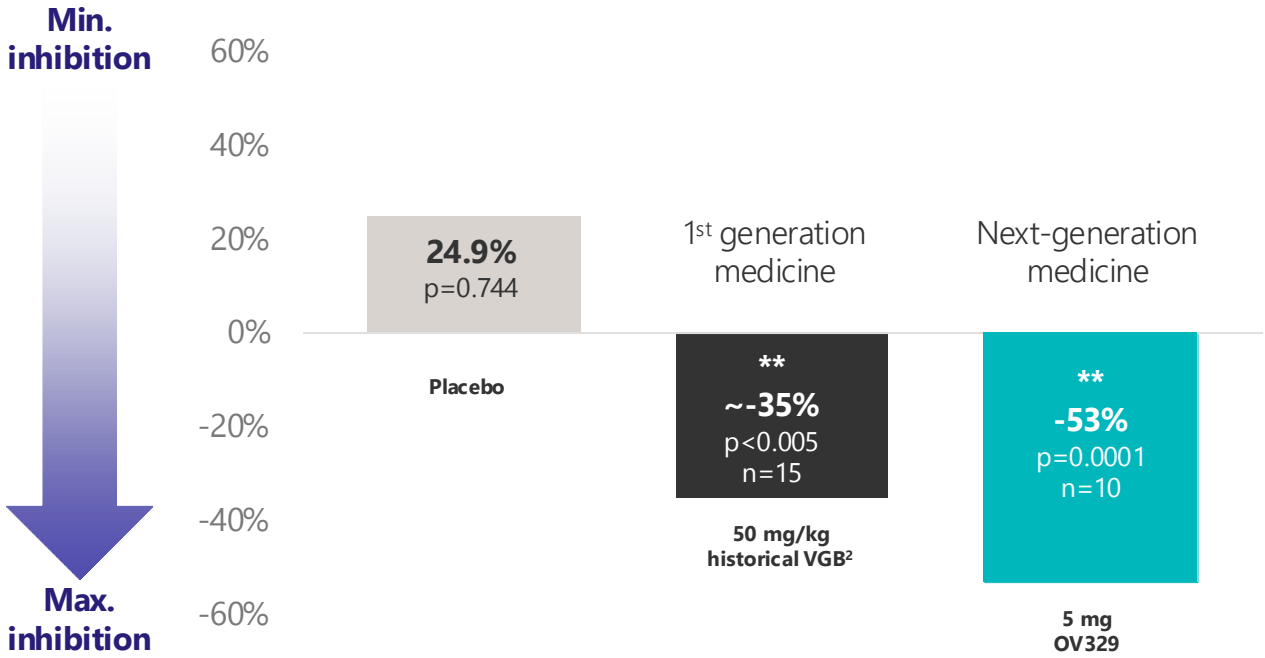



Measured on abductor pollicis brevis

## 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

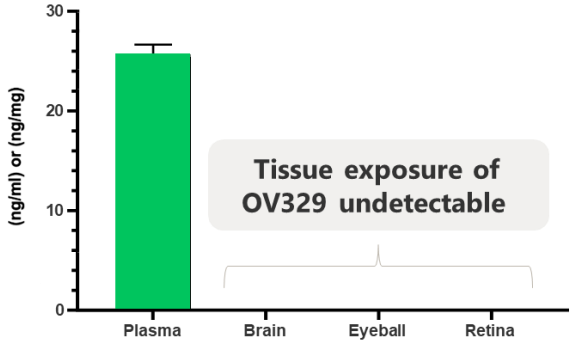
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# OV329 does not accumulate in the retina like vigabatrin (VGB)

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

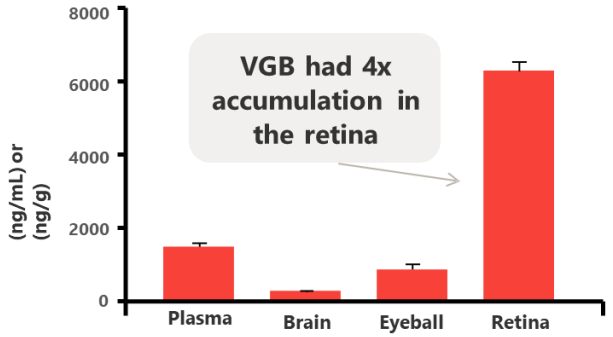
**OV329**

Mean Plasma and Tissue Concentration 5.0 mg/kg/day

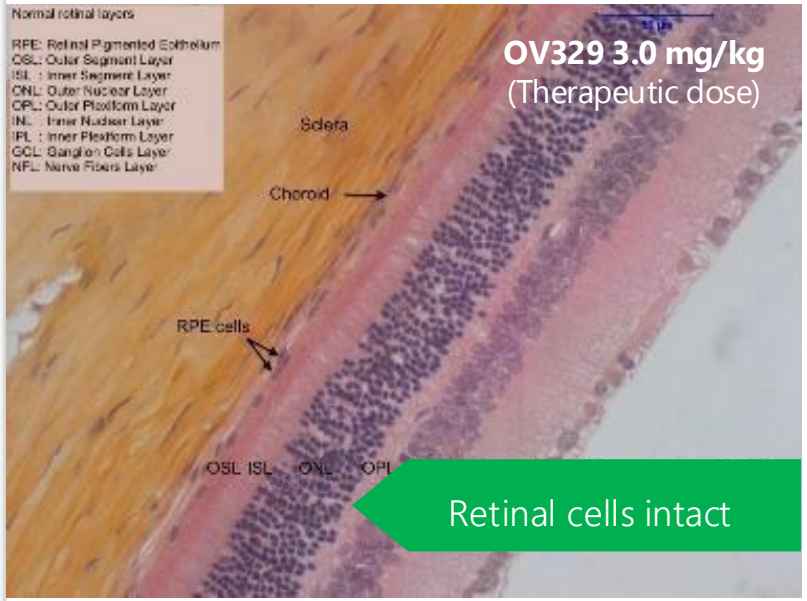



**VIGABATRIN**

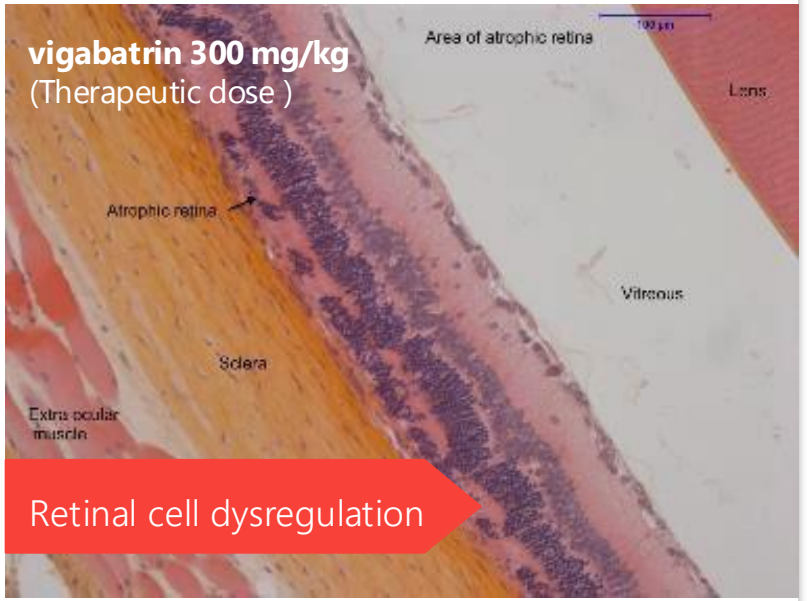
Mean Plasma and Tissue Concentration at 80.0 mg/kg/day




## 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 |

1. N= number of participants
2. (x "number") = number of events

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# No ophthalmic or retinal changes at all doses

| 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 profile 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 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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# Next steps in FOS: 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

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## Pediatric weight-based

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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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# An urgent unmet need

## 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, <5% have a good developmental prognosis
- Seizures evolve to Lennox-Gastaut syndrome (LGS) or other drug-resistant seizures

**Current standard of care**

- Acthar gel (or high dose steroids)
- Vigabatrin, includes risk of blindness

## 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

**Current standard of care**

- Afinitor
- Sabril

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# Potential for OV329

## Profile

### Safety

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

### Tolerability

- No anticipated sedation
- Clean profile at higher doses in adults

**OV329**

### Proven mechanism*

- >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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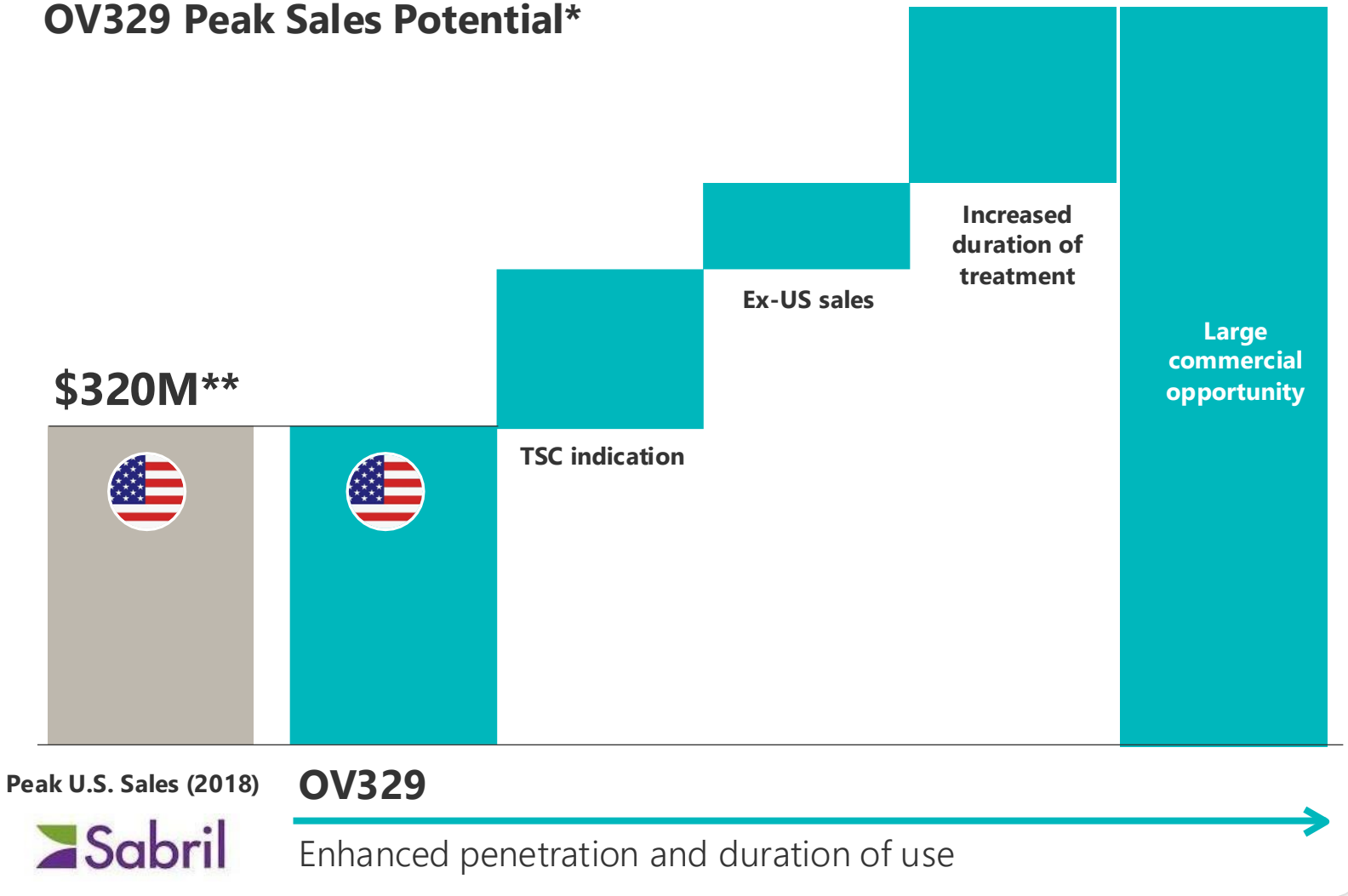
# OV329 holds significant potential in TSC & IS

**Anticipate earlier-line use, longer treatment duration**

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

**Differentiated pediatric formulation**
**& weight-based pricing**

**Potential for disease modification**




* Projected estimates
**IQVIA

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# KCC2: A common "master switch" to restore excitatory/inhibitory balance

**Transformational target** that is a fulcrum rebalance inhibitory/excitatory signaling in many diseases of the brain

**Potential first-in-class** direct activators

**Demonstrated safety profile, central activity with tool program** (OV350)

**CLEARED & initiating Phase 1 for oral direct activator** (OV4071) in Q2 2026

**Composition of matter IP through 2046***

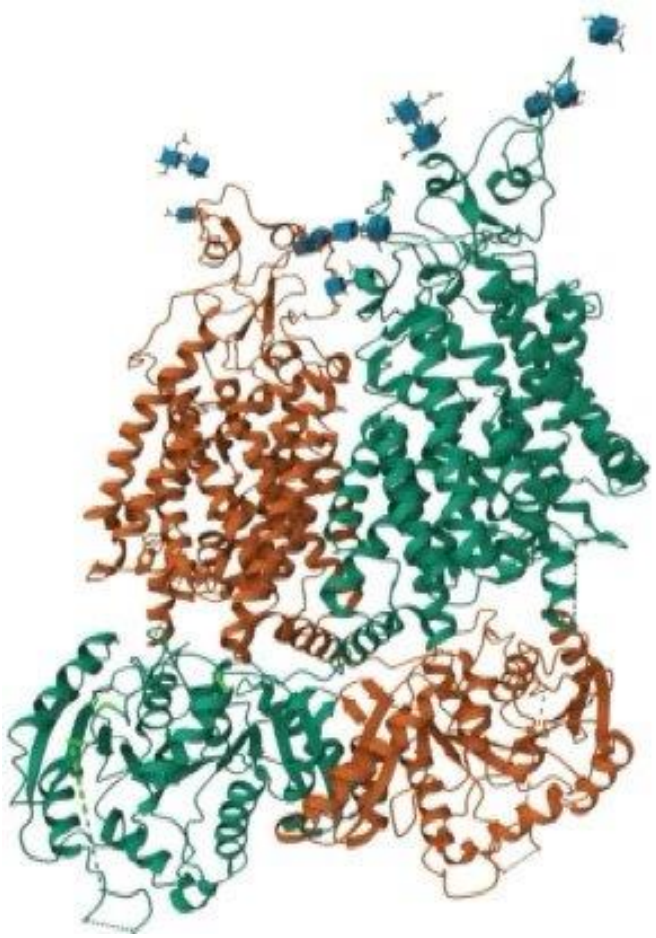
12 method-of-use patents filed

**One mechanism: MANY medicines**

*Assumes five-year patent term extension

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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 suboptimally extruding chloride

Converges on a broad spectrum of disorders with hyperexcitability

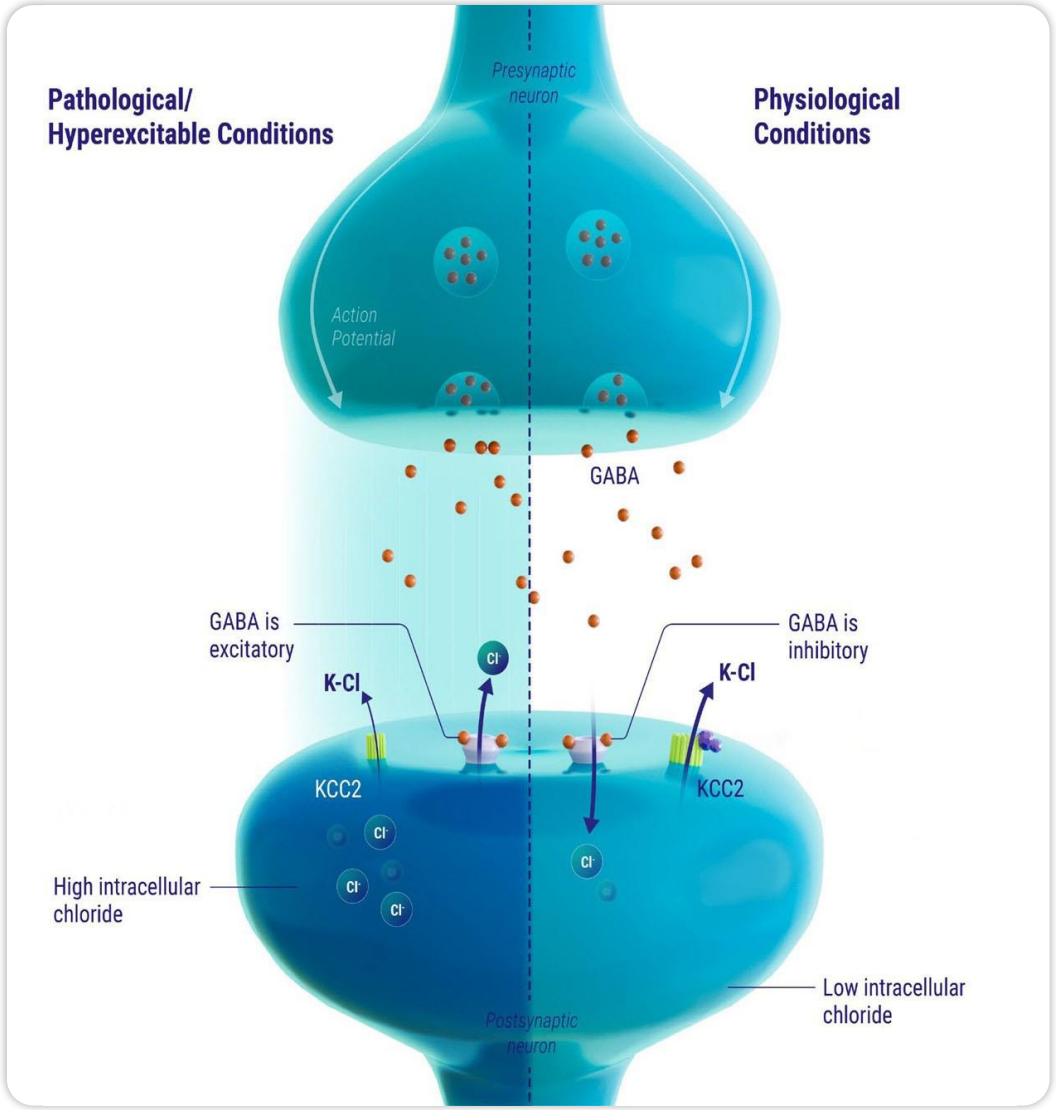
Self-limiting chemical gradient makes it nearly impossible to overmodulate

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# KCC2 direct activation: Mechanism of action

## Impaired KCC2 activity

- Causes high intra-neuronal chloride concentrations
- Leads to abnormal depolarizing of the GABA receptor
- Causes neuronal hyperexcitability




## Normal KCC2 activity

- KCC2 activity is high
- Leads to low intra-neuronal $Cl^-$ concentration
- Enables a GABA-driven influx of $Cl^-$, causing an inhibitory effect (hyperpolarizing) to the $GABA_A$ current

**KCC2 direct activation improves chloride extrusion and thereby, GABAergic inhibition**

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# Therapeutic opportunity: KCC2 direct activation

### Neurodegenerative psychoses & cognition

- Schizophrenia
- Alzheimer's agitation
- Alzheimer's hallucinations & delusions
- Parkinson's disease psychosis
- Lewy body dementia
- 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

### Pain & trauma

- Neuropathic pain
- Centralized pain
- Audiogenic trauma
- Spinal cord injury

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# OV4071 fundamentals

## Highly potent & selective

**20-fold potency**
in psychosis models vs OV350

**0.64 µM** KCC2 selectivity

## 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

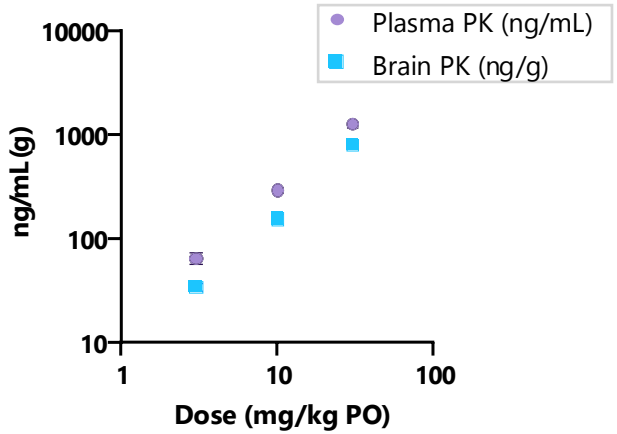
## Potential tolerability

**No sedation**

**No significant drug:drug**
interactions anticipated

**No catalepsy**

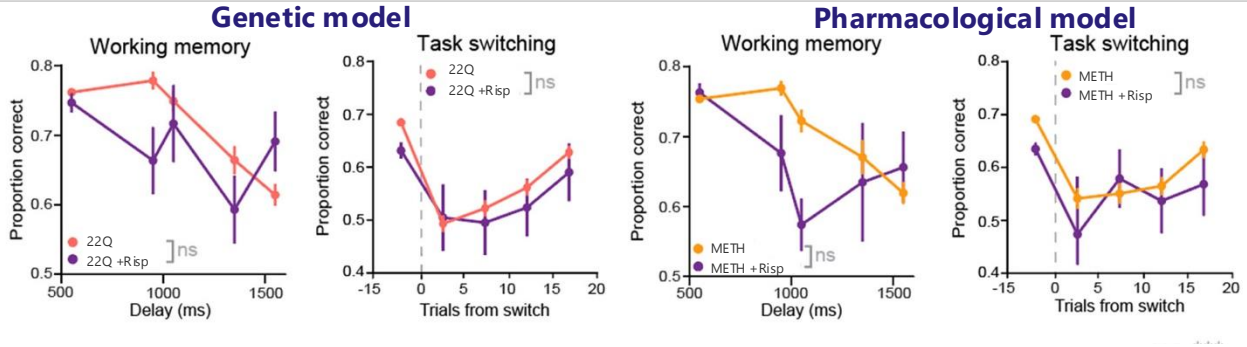
## 1:1 brain-to-plasma ratio



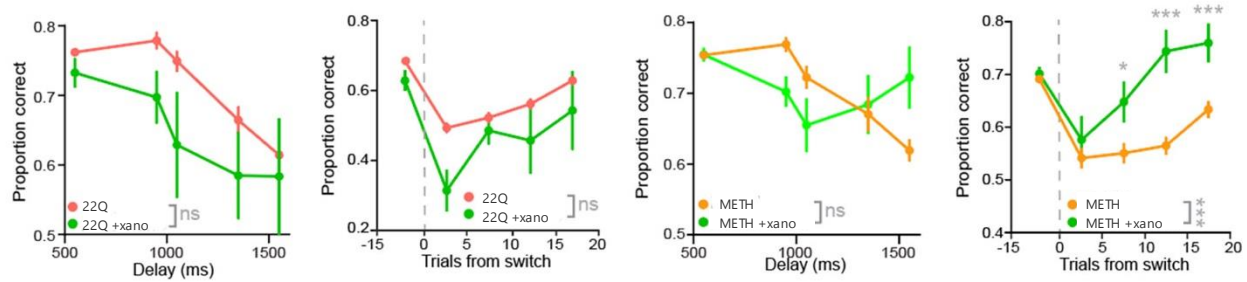

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# KCC2 direct activation consistently restores working memory and task switching across numerous models

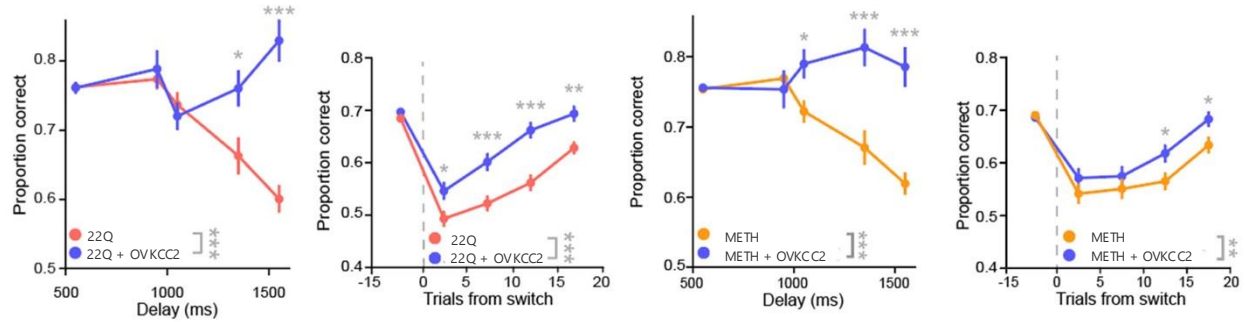
**Traditional antipsychotic D2 Receptor antagonist, (risperidone)**




**First-in-class antipsychotic M1/M4 receptor agonist, (xanomeline/trospium)**




**Ovid KCC2 direct activator**




Data source: Mukherjee et al., in preparation

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# Robust armamentarium of pharmacodynamic evidence

**Findings reinforce restoration of E/I balance**

**Consistent with KCC2 mechanism of action**

## Ovid KCC2 direct activators

| Model | Relevance | Rescue Activity |
|---|---|---|
| **Psychosis & locomotion** | | |
| **MK801 induced hyperlocomotion (repeat dose)** | Psychosis, schizophrenia | ✓ |
| **MK801 induced hyperlocomotion** | Psychosis, schizophrenia | ✓ |
| **Methamphetamine induced psychosis** | Psychosis & cognition | ✓ |
| **22Q deletion model (schizophrenia)** | Schizophrenia | ✓ |
| **Huntington's disease motor symptoms (R6/2)** | Motor function deficits | ✓ |
| **Amphetamine model** | Psychosis | ✓ |
| **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) | ✓ |
| **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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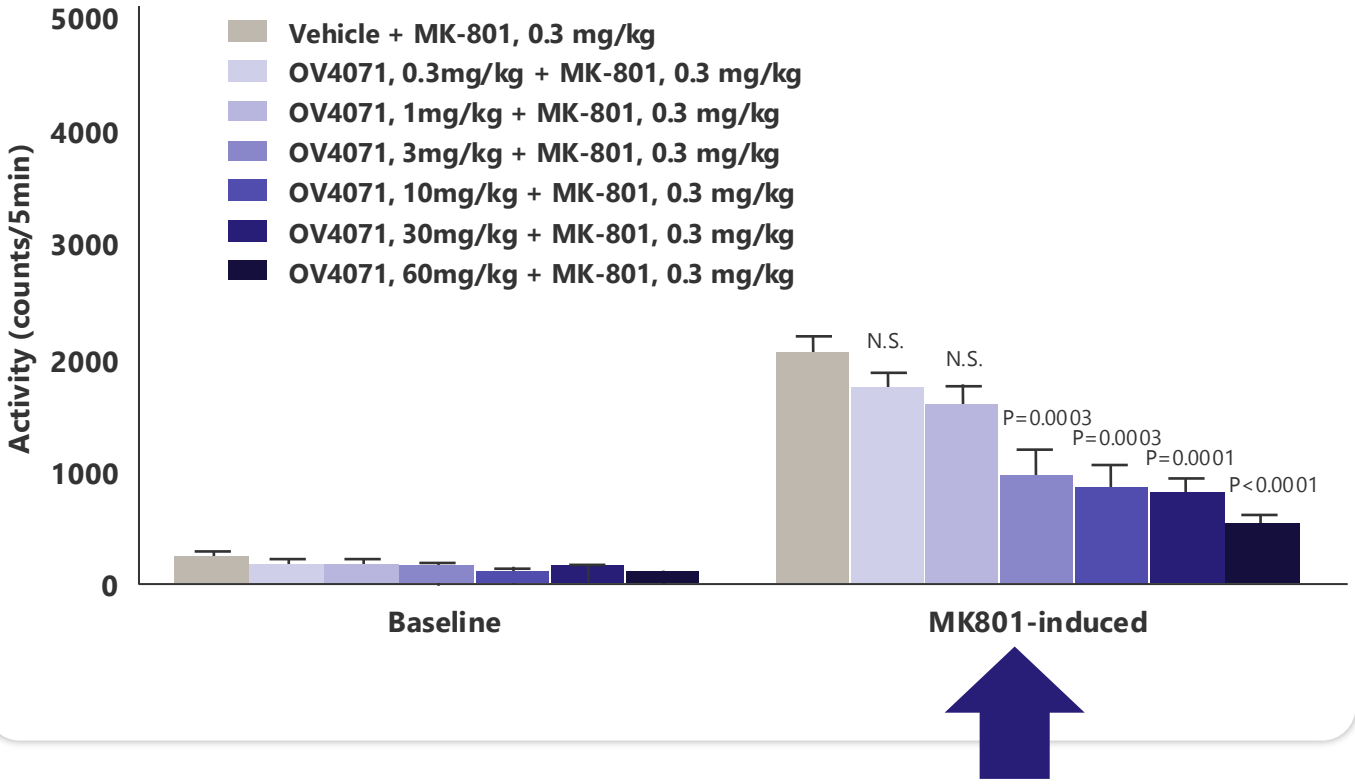
# Pharmacodynamic results suggest OV4071 has broad antipsychotic effects

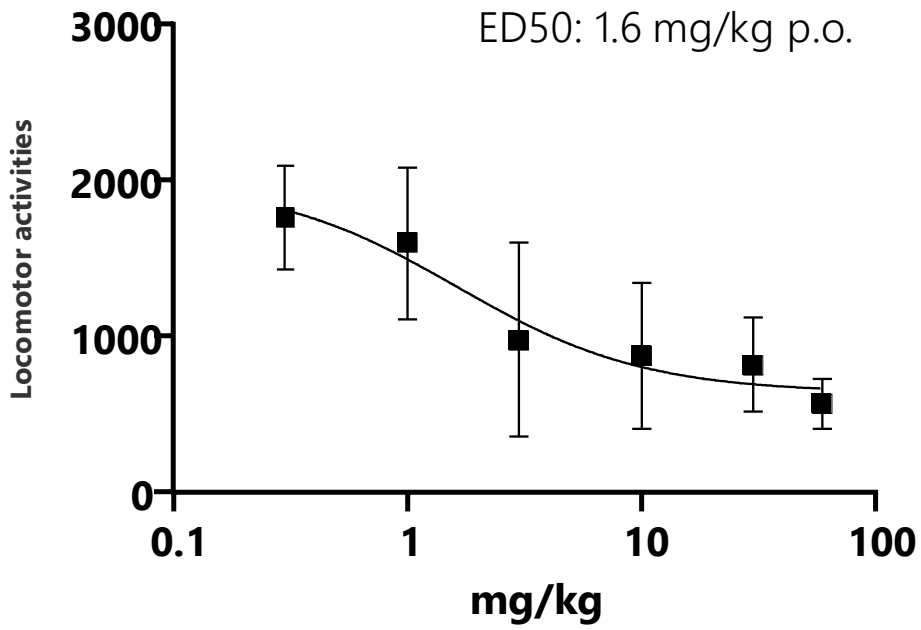
| Model | **MK801** (NMDA antagonist) | **Amphetamine** | **Phencyclidine behavior** (NMDA glutamate receptor antagonist) | **MECP2 deletion** |
|---|---|---|---|---|
| | **Acute** | | **Chronic** | |
| **Relevance** | • Induces hyperlocomotion<br>• Surges glutamate & dopamine in the striatum | • Acute model<br>• Induces hyperlocomotion<br>• Surges striatal dopamine | • Chronic model of negative symptoms<br>• Suppresses social interaction<br>• Reflects insufficient dopaminergic input in cortex | • Deletes a protein abundant in mature neurons central to maintaining normal synaptic communication |
| **Results** | • Rapidly (< 1 h) restored normal locomotion in dose-dependent fashion<br>• Single dose effect maintained in repeat dosing<br>• Reduced striatal dopamine | • Single dose reduced excitation induced hyperlocomotion<br>• Not sedating like Haldol | • Single dose rescued social (interaction time) behavior<br>• Results commensurate with clozapine | Demonstrated EEG effects on:<br>• Gamma power<br>• Delta power |
| **OV4071 profile implications** | Rapid, sustained effect to rescue physiological behavior and an on-mechanism reduction in dopamine | • Rescues psychosis behaviors without sedation<br>• Shows activity in models where pimavanserin had no activity | Restores animal sociability as effectively as clozapine | • EEG biomarker activity consistent with the MoA<br>• Shift EEG power frequencies relevant to 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**



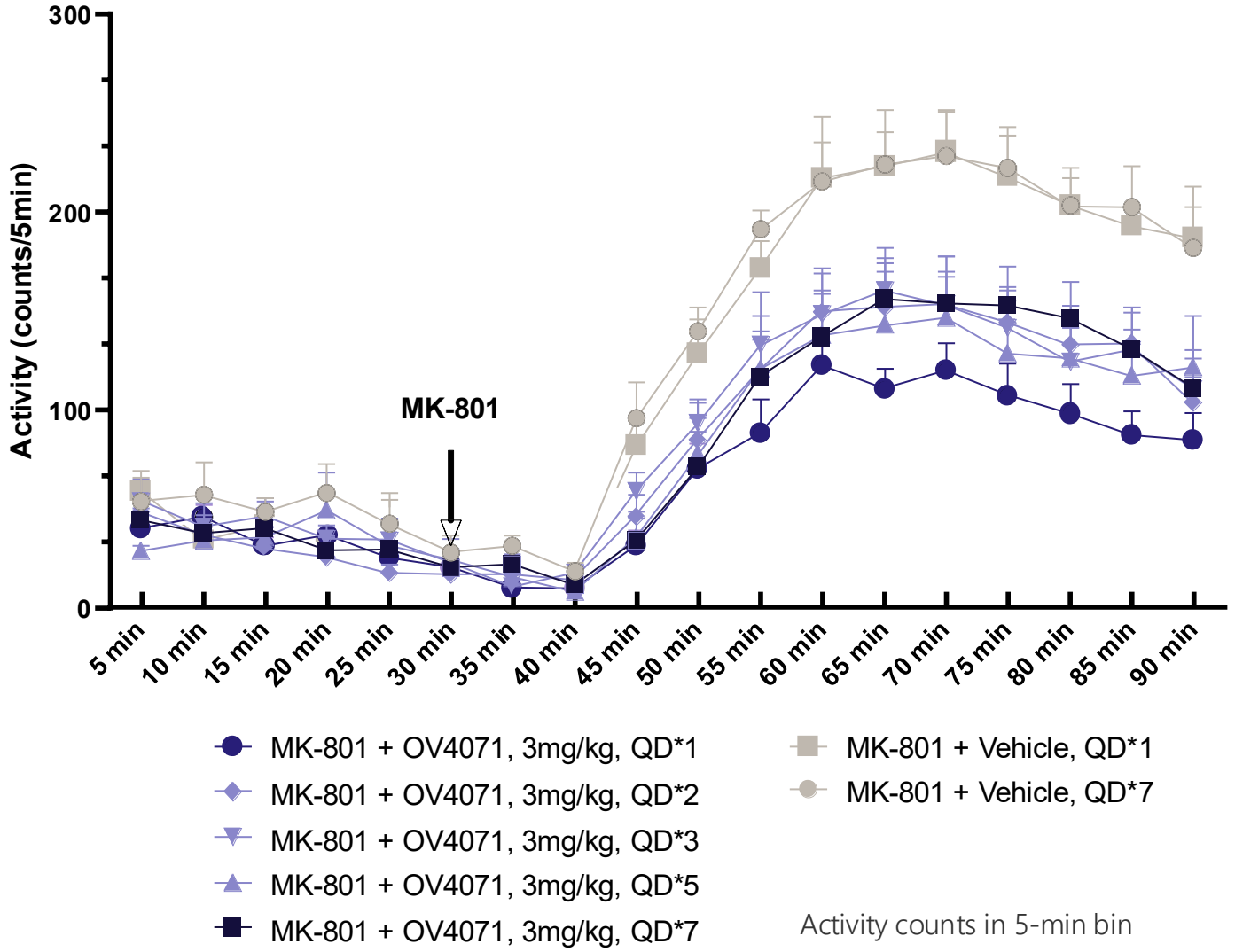



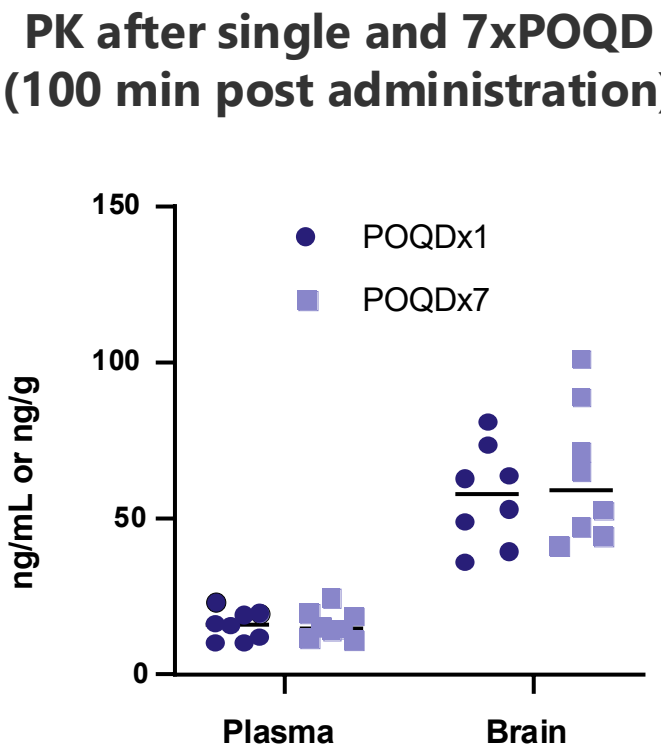

**OV4071 returned locomotion to natural levels (1,500 – 2,000 counts) in a dose-dependent fashion and reduced striatal dopamine**

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# Rapid single dose effect: maintained upon repeated administration

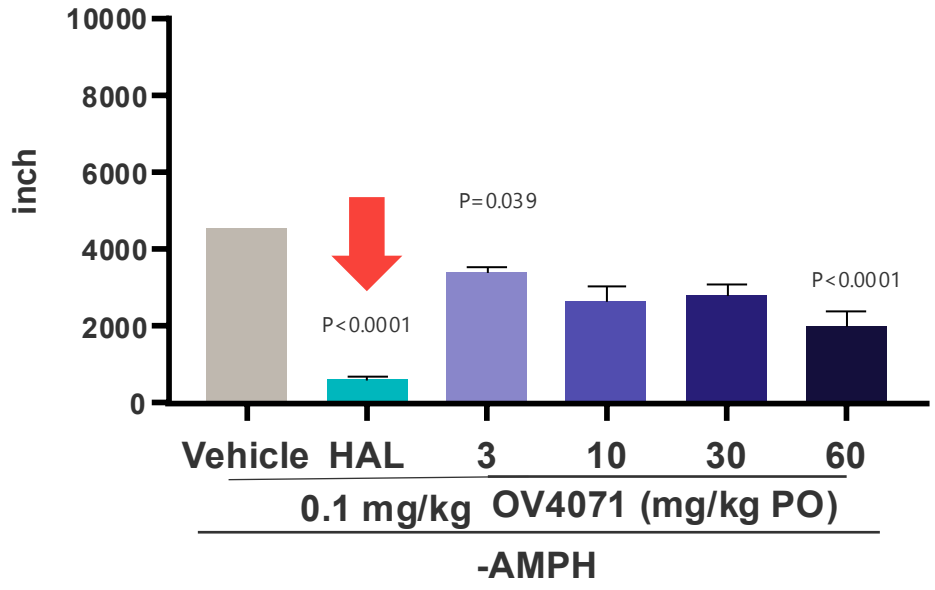


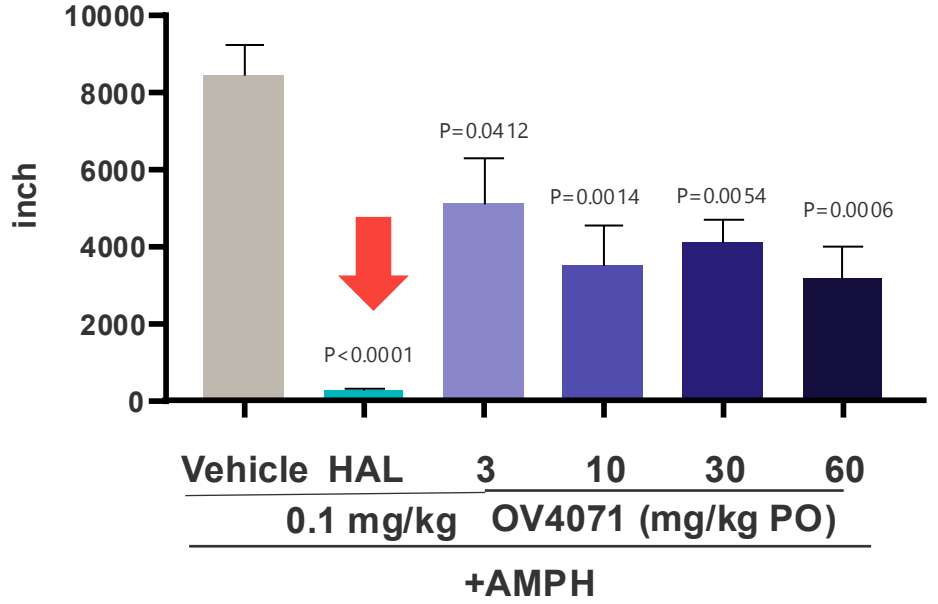




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# OV4071 single administration in the mouse AMPH hyperlocomotion model




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**

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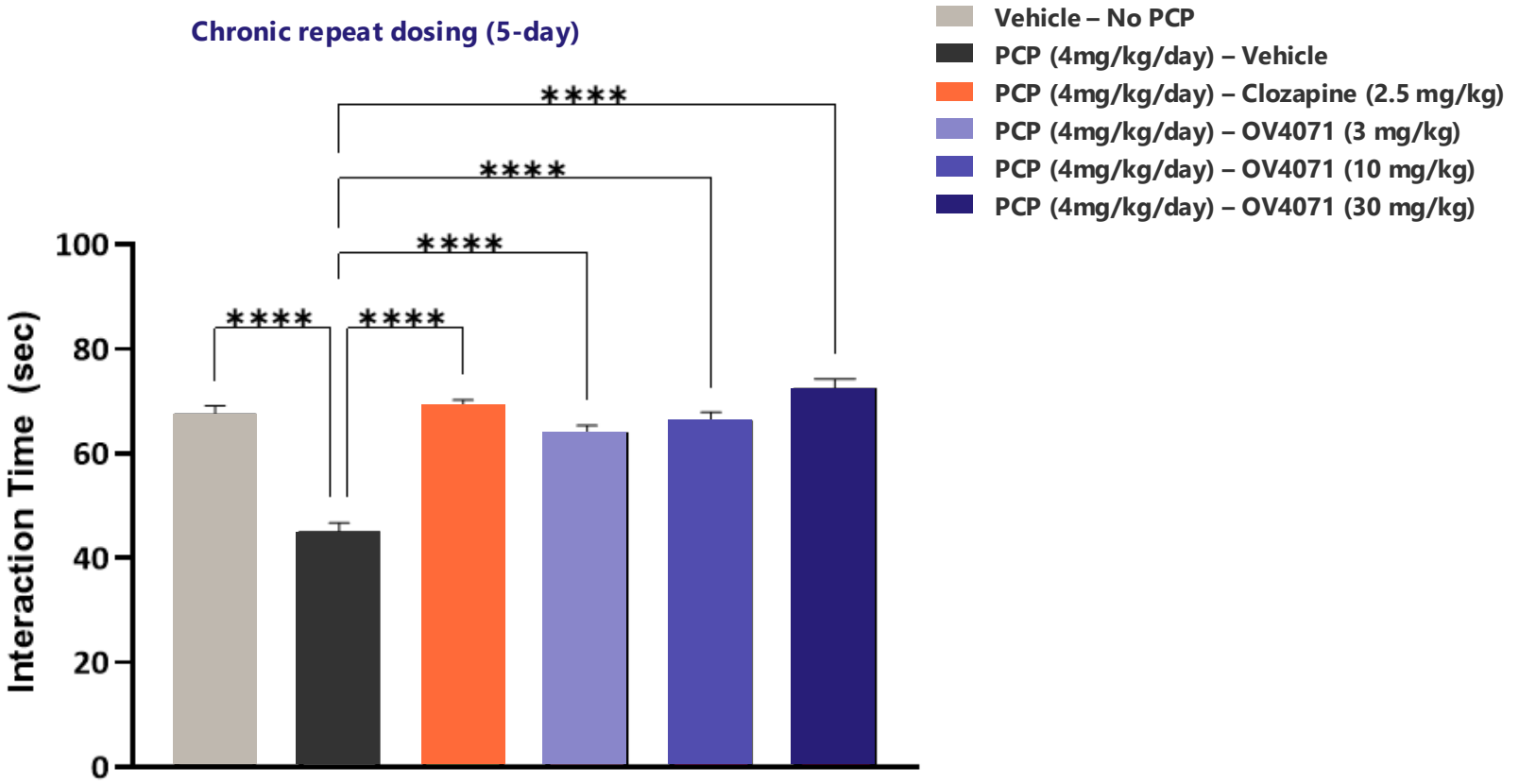
# OV4071 restores social interaction in chronic PCP-induced animal behavior model

## 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

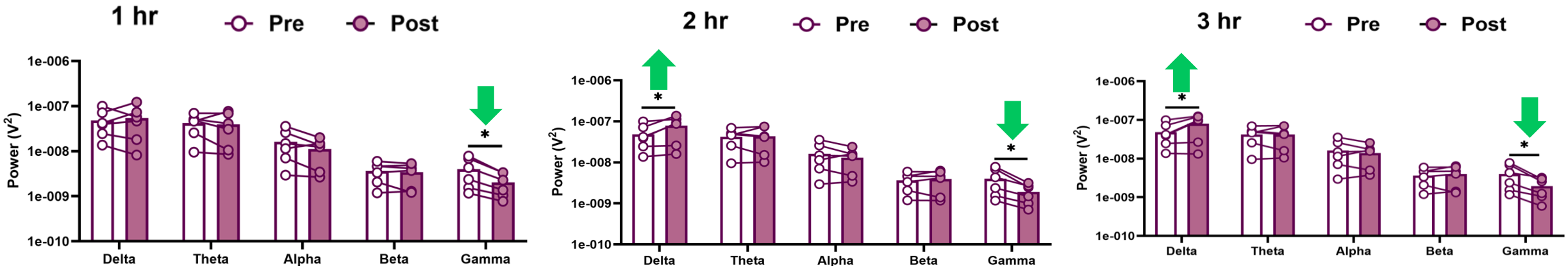



*Effects of clozapine and OV4071 on interaction time in rats chronically treated with PCP. Data are presented as mean ± SEM. ***p<0.0001 compared to PCP-Vehicle group.*

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# OV4071 demonstrated translationally relevant biomarkers




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

## Methods

| Recovery | Baseline | OV 4071 7.5mg/kg (i.p.) |
|---|---|---|
| 1-week | 2-hours | 3.5 hours |

- Low dose of KCC2 (7.5 mg/kg) on baseline EEG power in Rett (MeCP2) mice
- Comparisons were made with the pre-treatment period

## Results

- Rapid reduction in Gamma observed 1-hour post-dose
- Delta power increases

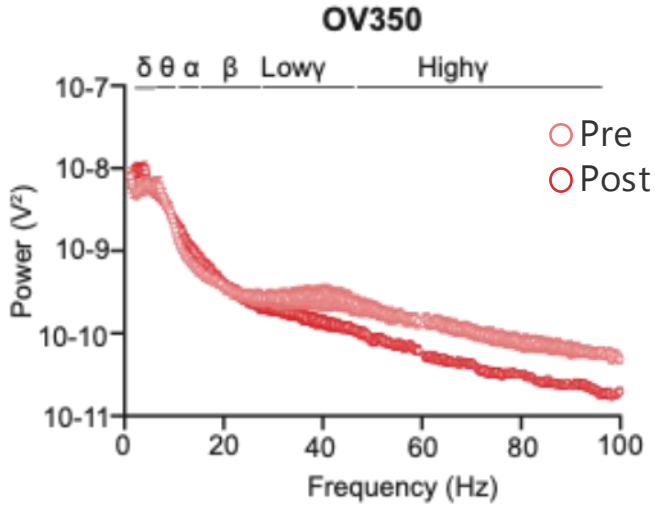
## Implications

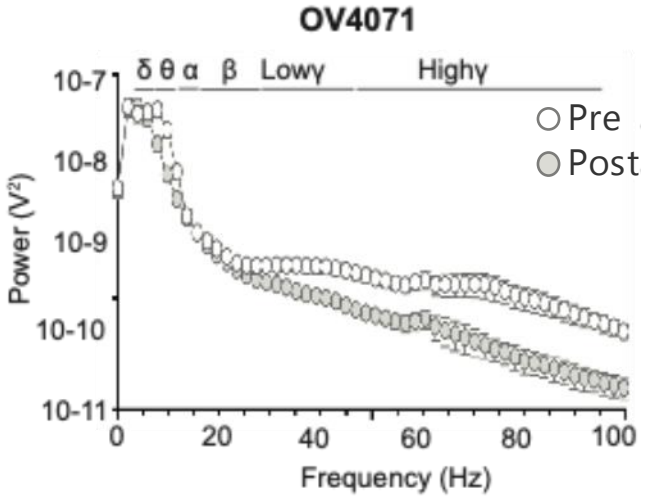
- Gamma increased is schizophrenia at rest, so reductions are suggestive of activity
- Delta power increases suggesting synaptic signaling restoration

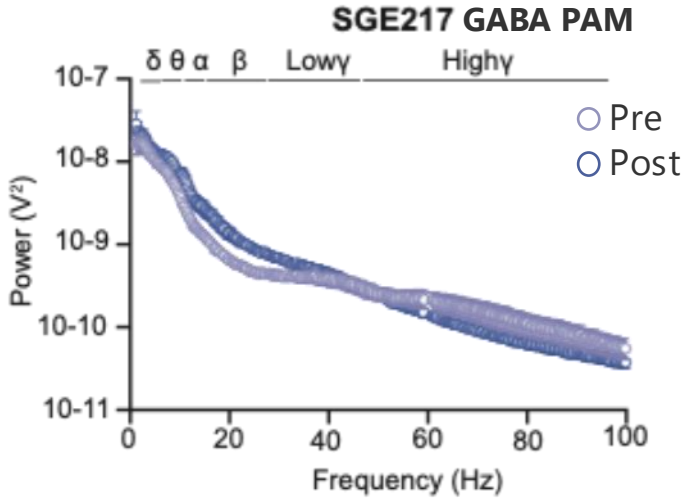
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# KCC2 activators share a pharmacodynamic profile that is clearly distinguished from drugs that directly enhance GABAergic activity




- SGE217 (Zuranolone) a positive allosteric modulator of $GABA_A$ receptors induces a robust increase in beta power (13-30 Hz)
- Ovid KCC2 direct activators increase low frequencies and decrease gamma at rest

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

- Parkinson's disease psychosis
- Alzheimer's psychosis & agitation
- Lewy body dementia
- Huntington's hallucinations & delusions
- Schizophrenia
- Rett syndrome
- Generalized anxiety

**Psychoses** — **Cognition & executive function** — **Anxiolytic**

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# Translational strategy

Pharmacodynamic activity characterization in phenotypic and in vivo models

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

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Broad electrophysiology biomarkers in healthy volunteers

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

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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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# OV4071 phase 1 SAD/MAD/FE study design

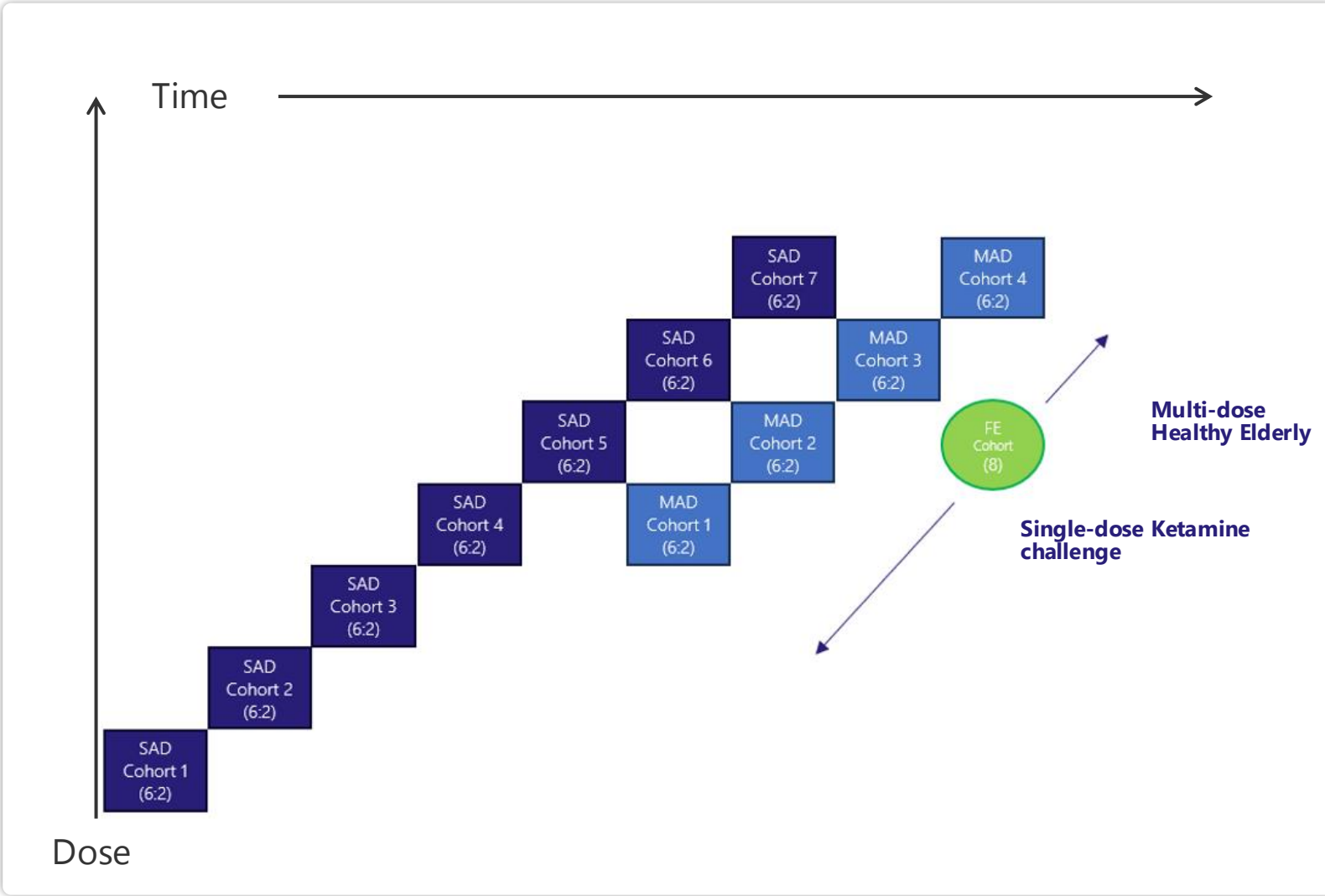
Healthy volunteer SAD/MAD/FE

**Endpoints:**

- Safety and tolerability
- Pharmacokinetic profile
- Pharmacodynamic biomarkers
  - Quantitative EEG
  - Event-related potentials (ERPs)
- Food effect cohort in parallel

Ketamine challenge target engagement study in parallel to SAD

Healthy elderly safety cohort




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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<br>• Slope of aperiodic (non-oscillatory) component |
| **Active Auditory Oddball** | Cognitive processing speed and resource allocation | • Amplitude of early sensory-evoked (N100, P200)<br>• 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<br>• P3a amplitude evoked by deviant stimuli |
| **Auditory Steady State Response** | Neural synchrony | • Evoked spectral power (uV) in gamma (30-50 Hz)<br>• 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)<br>• Reduced alpha power, primarily in the frontal lobes<br>• Δ to gamma power |
| **Active Auditory Oddball** | Impaired attentional allocation and working memory updating<br><br>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<br><br>Associated with higher symptom severity and functional impairment<br><br>Predictive of conversion to psychotic disorder in clinically high-risk patients | • Lower MMN amplitude in difference wave<br>• Low P3a amplitude in response to deviant stimuli |
| **Auditory Steady State Response** | Associated with clinical symptom severity (hallucinations, psychotic severity, and cognitive decline)<br><br>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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# ELECTROPHYSIOLOGY STRATEGY:
# Parkinson's disease psychosis (PDP)

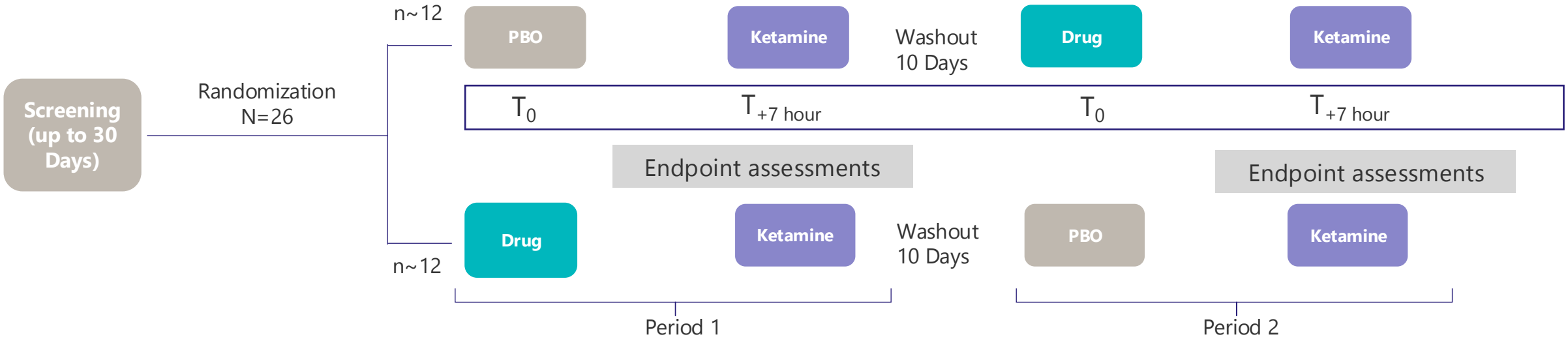
## Electroencephalography (EEG) and event-related potential (ERP) biomarkers

| Biomarker | Relevance in PDP | Changes |
|---|---|---|
| **Quantitative EEG (qEEG)** | In PD characterized by increased slow wave (delta – theta) activity, coupled with reduced alpha - beta reactivity<br><br>Progresses with disease, associated with cognitive dysfunction, hallucinations, and dementia<br><br>PDP found to have higher intra-hemispheric coherence in beta and gamma bands than PD non-psychosis | • Δ progressive "slowing pattern" |
| **Active Auditory Oddball** | Associated with longer reaction time in response to targets and smaller P300 amplitude compared to PD non-psychosis<br>correlates with attention and working memory test performance | • Δ latency and decreased amplitude of P300 response |
| **Mismatch Negativity** | Visual MMN is significantly reduced or absent in PD patients experiencing visual hallucinations compared to those without | • Δ to amplitude of P2a response to deviance |
| **Auditory Steady State Response** | Data on ASSR in PDP is limited; though 40 Hz is increasingly used as a biomarker of dementia | • Δ in ASSR (40 Hz) |
| **Prepulse Inhibition** | PPI is reduced in PD and pre-clinical models of PDP<br><br>PD patients exhibit reduced PPI of the N1/P2 component in auditory cortex tests | • Δ in PPI |

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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# Translational study: ketamine challenge in healthy volunteers




## Trial design

- Single site study in the US
- Healthy volunteers 18 - 55 years of age
- Cross-over design with single dose of OV4071 vs PBO

## Key Endpoints

- Resting quantitative EEG
  - Power spectral analysis of waking EEG (1-70 Hz)
- Event-related potentials (ERPs)
  - ASSR (40 Hz entrainment), P300 (active oddball), MMN (passive oddball)
- Cognitive testing, psychotomimetic effects (CADSS, BPRS)
- Plasma biomarkers (GABA, Glu, BDNF, cytokines, ketamine metabolites)

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# Patient studies with OV4071

**Phase 2 proof of concept in schizophrenia**

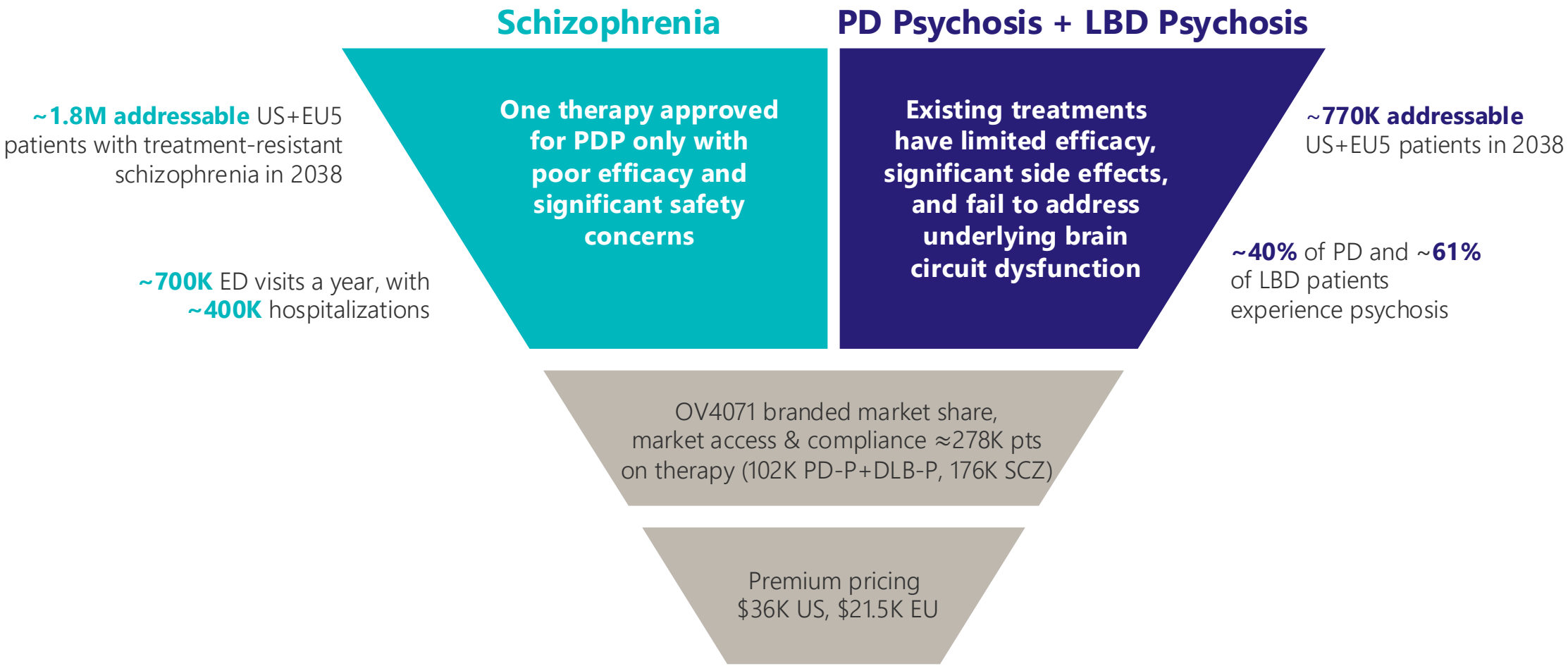
- Randomized, double-blind, placebo-controlled study in patients with acute schizophrenia
- Evaluate safety, tolerability, and efficacy
- Multi-site study in US

**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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# A meaningful market for OV4071




## ~$6.8 Billion Peak US + EU5 Revenue in 2038

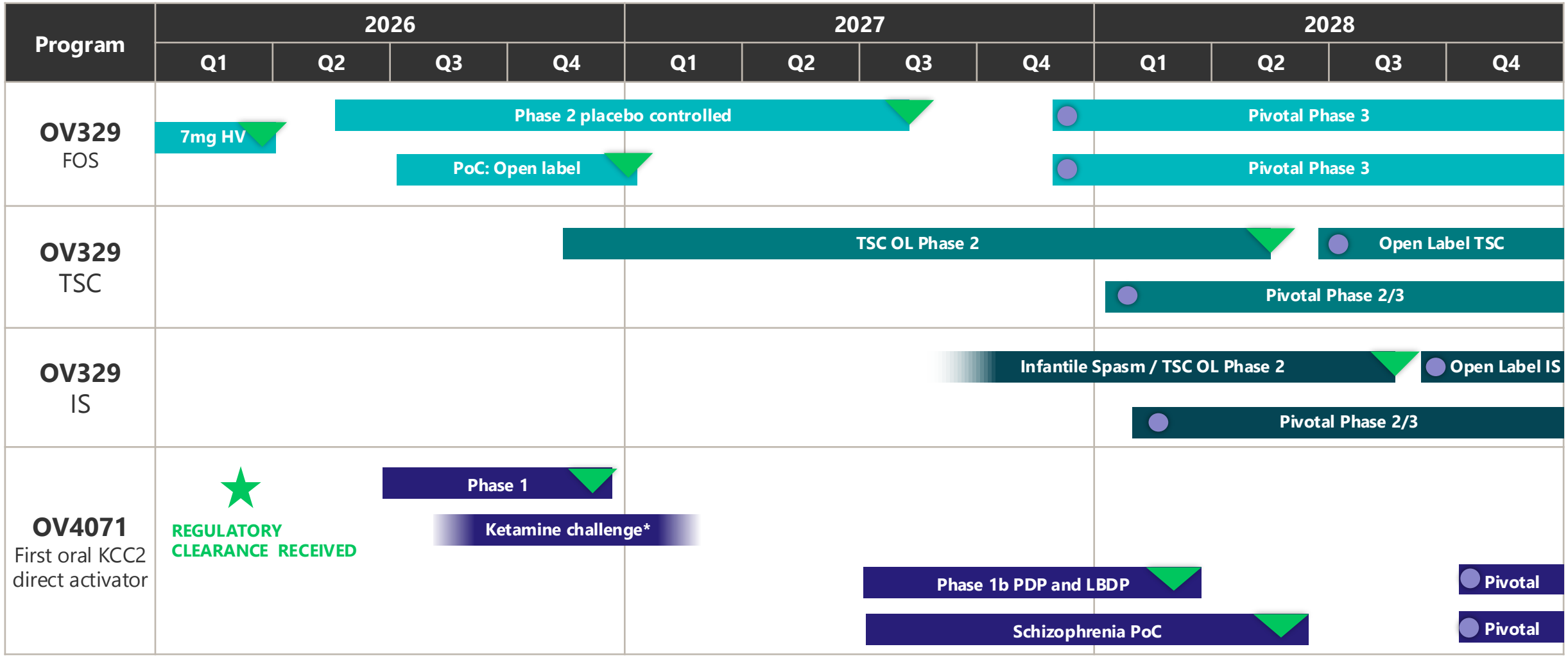
Estimates for peak OV4071 revenue in 2038; LifeSci Consulting

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# A milestone rich runway

Pivotal and OLE trials that would require funding post PoC

Data availability




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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