OV329, a Potent Next Generation GABA-AT Inhibitor, is Well-Tolerated and Produces GABAergic Cortical Inhibition in a Phase 1 SAD/MAD Study in Healthy Volunteers

Julia Tsai[1], Alexander Rotenberg[2], Nigel C. Rogasch[3,4], Wei-Yeh Liao [3,4], Shruti Raja[5], Matthew Jung[1], Amanda Yaari[1], Amanda Banks[1], Zhong Zhong[1]

Poster: 2.451

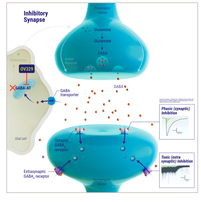
[1]Ovid Therapeutics, 441 9th Avenue, 14th floor New York, NY 10001, [2]F.M. Kirby Neurobiology Center and Department of Neurology, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA, [3]School of Biomedicine, Faculty of Health and Medical Sciences, University of Adelaide, Adelaide, SA, Australia, [4]Hopwood Centre for Neurobiology, Lifelong Health Theme, South Australian Health & Medical Research Institute (SAHMRI), Adelaide, SA, Australia, [5]Duke Early Phase Research Unit, Duke University School of Medicine, Durham, North Carolina USA

Background and Rationale

γ-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the central nervous system (CNS) and is primarily catabolized by GABA amino transferase (GABA-AT).

In patients with epilepsy, reduced CNS GABA levels are associated with poor seizure control. Increasing GABA levels through GABA-AT inhibition is a validated mechanism of action for seizure control. Currently, vigabatrin (VGB) is the only FDA-approved drug that blocks GABA-AT activity as a primary mechanism of action with proven efficacy in seizure reduction in up to 40% of chronically treated patients. However, clinical use of VGB in epilepsy is associated with retinal damage, limiting its use[1,2].

OV329 is a next-generation highly potent, GABA-AT inhibitor with the potential to be a best-in-class antiseizure medicine[3,4]. OV329 increases synaptic and extrasynaptic GABA to deliver both phasic and tonic inhibition, and effectively suppresses treatment-resistant seizures in multiple animal epilepsy models[5,6]. A Phase 1 ascending, single and multiple dose(s), double-blind, randomized, placebo-controlled study was conducted to assess the safety, tolerability, pharmacokinetics (PK) and exploratory pharmacodynamic (PD) activity of OV329 in healthy adults. Dosing was based on pharmacology studies suggesting OV329 pharmacodynamic activity between 59 ng*hr/mL - 140 ng*hr/mL exposure range, corresponding to a human dose range of 3 mg to 7 mg.



Phase 1 SAD/MAD Study Design With Expansive Exploratory Biomarker

Objective

Establish safety, tolerability, pharmacokinetic, and pharmacodynamic activity of OV329 in healthy volunteers to inform Phase 2 dosing

Vitals, labs & clinical safety & tolerability

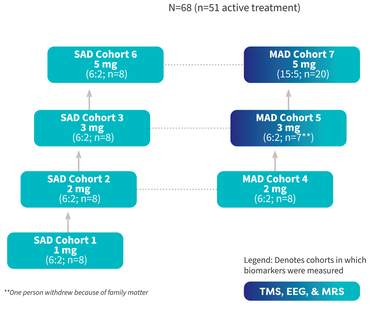
Ophthalmic safety metrics (measured for 30 days post-dose initiation)

- Best corrected visual acuity
- Fundus photography
- Indirect dilated ophthalmoscopy
- Automated threshold visual field perimetry
- Optical coherence tomography

Pharmacokinetics

Biomarker assessments explore pharmacodynamic activity, inhibition, & target engagement

- Transcranial magnetic stimulation (TMS)
- Magnetic resonance spectroscopy (MRS)
- Electroencephalography (EEG)



Methods: 68 healthy participants (42 male, 26 female) were enrolled at 3 sites in the U.S. and Australia into one of 4 single ascending dose (SAD) cohorts or 3 multiple ascending dose (MAD) cohorts. Participants in SAD cohorts received one dose of oral OV329 or placebo and were followed for 3 days in-patient and returned on Day 7 for follow up. Participants in the MAD cohorts received one dose of OV329 or placebo daily for 7 days, remained in-patient until Day 9, and returned for follow up on Days 14 and 30.

Safety assessments included adverse events (AEs), vital signs, physical/neurological exams, electrocardiograms (ECGs), laboratory tests, ophthalmologic assessments (including visual acuity, visual field perimetry, optical coherence tomography, and fundus photography), and the Columbia Suicide Severity Rating Scale (CSSRS). Blood and urine PK samples were obtained. Exploratory biomarkers assessed potential PD effects, including transcranial magnetic stimulation (TMS) metrics (i.e., paired-pulse motor evoked potential inhibition and cortical silent period) that were previously used to study a 1st-generation GABA-AT inhibitor, vigabatrin (VGB)[7], magnetic resonance spectroscopy (MRS), and electroencephalograms (EEG). A number of positive and negative control biomarkers were used to assess potential excitatory/inhibitory activity.

References

1. Wild JM, et al. CNS Drugs. 2009; 23(11):965-82
2. Maguire MJ, et al., Epilepsia, 2010. 51(12): 2423-31
3. Juncosa JI, et al. J Am Chem Soc. 2018;140(6): 2151-64
4. Silverman R, Chem Rev 2018 Apr 11;118(7):4037-4070
5. Colmers P et al. eNeuro 27 June 2024, 11 (7) ENEURO.0137-24.2024
6. Tsai J, et al. 17th Eilat Conference on New Antiepileptic Drugs and Devices. May 5-8 2024; Madrid, Spain
7. Pierantozzi et al., Brain Res. 2004 Nov 26; 1028(1):1-8
8. Lin et al. 77th Annual meeting of American Epilepsy Society. December 1-5, 2023; Orlando, FL
9. Ziemann U et al. Ann Neurol 1996; 40(3):367–373

OV329 Was Well Tolerated With a Favorable Safety Profile, No Ocular Changes and Predictable PK

Study Demographics

- Mostly white (53%) or black or African American (25%), not hispanic or Latino (86.8%)
- Ages: 19–52 years (mean 32 yrs SAD, 29.8 yrs MAD)
- Mean BMI 27.3 kg/m^2 SAD, 26.0 kg/m^2 MAD
- Gender distribution was mixed across cohorts
  - SAD: 1 mg (3 M/3 F), 2 mg (2 M/4 F), 3 mg (5 M/1 F), 5 mg (4 M/2 F), placebo (4 M/4 F)
  - MAD: 2 mg (4 M/2 F), 3 mg (4 M/2 F), 5 mg (10 M/5 F), placebo (6 M/3 F)

Pharmacokinetics

- C_{max} and AUC increases with increasing dose
- C_{max} rapidly achieved at all dose levels after single and multiple doses (T_{max} 1 hour)
- $T_{1/2}$ 0.7-1.2 hours
  - Previous preclinical work showed that while OV329 is rapidly eliminated, it exhibits a prolonged inhibition of GABA-AT in the brain due to its potency and irreversible binding[8]
- Repeat doses OV329 demonstrated predictable, linear PK
- Steady state achieved by Day 3

Safety

- No treatment-related SAEs; One SAE of anxiety, which was unrelated to study drug
- Potentially treatment-related AEs: headache (n=1), drowsiness (n=1), metallic tase (n=1); all mild in severity, all resolved
- Most frequently reported AE was cannula site reactions at the site of blood draw (n=13), all of which were mild to moderate and not related to treatment
- No treatment related changes in vitals, electrocardiograms, physical/neurological exams, chemistry, hematology, urinalysis, and Columbia Suicide Severity Rating Scale

Overall Summary of Adverse Events

No participants with related serious or severe TEAE, drug interruptions, withdrawals, or deaths due to TEAEs

	OV329							Placebo	
Category	Cohort 1 1 mg SAD (N=6) n (%)	Cohort 2 2 mg SAD (N=6) n (%)	Cohort 3 3 mg SAD (N=6) n (%)	Cohort 4 2 mg MAD (N=6) n (%)	Cohort 5 3 mg MAD (N=6) n (%)	Cohort 6 5 mg SAD (N=6) n (%)	Cohort 7 5 mg MAD (N=15) n (%)	Placebo (SAD) (N=8) n (%)	Placebo (MAD) (N=9) n (%)
Number of Adverse Events (AE)	1	1	3	7	6	1	28	6	17
Participants with Any AE	1 (16.7)	1 (16.7)	2 (33.3)	3 (50.0)	3 (50.0)	1 (16.7)	11 (73.3)	4 (50.0)	8 (88.9)
Number of Treatment Emergent Adverse Events (TEAE)	1	1	3	6	5	1	28	6	17
Participants with Any TEAE	1 (16.7)	1 (16.7)	2 (33.3)	3 (50.0)	3 (50.0)	1 (16.7)	11 (73.3)	4 (50.0)	8 (88.9)
Participants with Related TEAE	0	0	0	2 (33.3)	0	0	1 (6.7)	0	0
Participants with Severe TEAE	0	0	0	0	0	0	0	0	0
Participants with Serious TEAE	0	0	1 (16.7)	0	0	0	0	0	0

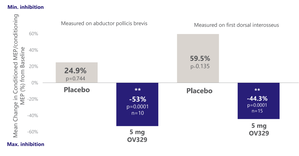
n (%) = number and percent of participants in the specified group; N = number of participants in the specified study population under each treatment group; TEAE = Treatment Emergent Adverse Event.

No ophthalmic safety findings or retinal changes associated with OV329

- Ophthalmic measures were assessed from baseline through 30 days post-dose initiation
- No treatment related effects on:
  - Best corrected visual acuity
  - Fundus photography (macula, disc, and periphery using 5 standard fields)
  - Indirect dilated ophthalmoscopy
  - Automated threshold visual field perimetry (Humphrey 30-2 SITA)
  - Optical coherence tomography

Multiple Biomarkers Results Show OV329 Produces GABAergic Inhibition

FIGURE 1: OV329 enhanced cortical inhibition as measured by TMS paired pulse long-interval intracortical inhibition, 150 ms interpulse interval ($LICI_{150}$)



Baseline is at day 1 prior to treatment
Note: 6 subjects were missing APB data due to lack of electrode capture.

Figure 1. Average change $LICI_{150}$ metric for OV329 5 mg and placebo as measured on APB and FDI. OV329 5 mg increased inhibition by 53% (p=0.0001; n=10) on the APB muscle, while placebo showed a 24.9% decrease (p=0.744; n=4). On the FDI muscle, OV329 5 mg increased inhibition by 44.3% (p=0.0001; n=15) compared with a 59.5% change with placebo (p=0.135; n=5). All values were log_{10} transformed before averaging.

FIGURE 2: Clear OV329 dose exposure response relationship

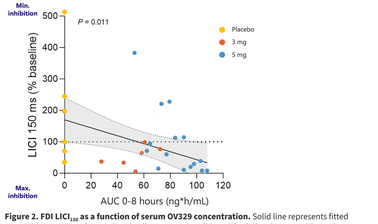


Figure 2. FDI $LICI_{150}$ as a function of serum OV329 concentration. Solid line represents fitted regression across 27 observations in all treatment conditions (shaded region: 95% CI). A subset analysis of the 5 mg OV329 cohort indicates a particularly strong dose effect (R^2 = 0.4553; p<0.001).

Additional analysis using a two-tailed paired t-test showed statistically significant decrease in FDI $LICI_{150}$ in participants treated with 5 mg OV329 treated compared to placebo post treatment p<0.05.

Other Biomarker Results

- OV329 3 mg and 5 mg doses showed increases of 6-19% in the TMS cortical silent period, when analyzed using a random effects model
- Negative control, $LICI_{200}$ does not show enhancement with OV329
- Target engagement biomarker, Magnetic Resonance Spectroscopy, showed numerically increased GABA levels relative to placebo, though it was not statistically significant due to large standard deviations
- EEG readings had significant noise, significant increase in beta + gamma power was noted in 3 mg MAD cohort, post-hoc analysis showed increased relative delta and theta power during an eyes open condition parietal electrodes in 5 mg MAD cohort

Discussion

TMS metric	Vigabatrin therapeutic dose (50 mg/kg) Measured in healthy volunteers[1,2]	OV329 3 mg and 5 mg doses Measured in healthy volunteers
Paired-pulse long-interval intracortical inhibition (LICI) 150 ms	Improved ~35%	Improved inhibition by 44-53%
Paired-pulse long-interval intracortical inhibition (LICI) 200 ms	No change as expected for GABAergic drugs	No change as expected for GABAergic drugs
Cortical silent period (CSP) as measured in two separate studies	Increased 19% in one study No change in another study	Increased 6-19%

OV329 showed similar or better pharmacodynamic effects as first-generation GABA-AT inhibitor vigabatrin in confirmatory biomarkers[7,9]

Results reaffirmed dose models that projected 3 mg and 5 mg doses would be pharmacodynamically active. Human data, in vivo and in vitro modeling suggests that 7 mg should maximize PD activity with good tolerability.

Note: Information compares similar studies and methodologies; a head-to-head trial was not conducted
6 subjects were unavailable for APB findings because of inconsistent capture, of which 5 were active, one was placebo

Conclusions

- Single and repeated doses of OV329 from 1 mg to 5 mg were well tolerated with favorable safety profile
- Demonstration of cortical inhibition at 3 mg and 5 mg doses, as measured by TMS biomarkers, consistent with the mechanism of action
- Clear exposure response relationship with predictable PK guides clinical dose selection
- Favorable safety profile and promising GABAergic inhibition supports advancement to Phase 2 study evaluation of OV329 in patients with focal epilepsy