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SPECIAL REPORT

# Progress report on new epilepsy treatments: A summary of the Eighteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XVIII). I. Treatments in preclinical and early clinical development

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## Abstract

Over the last 34 years, the Eilat Conference on New Antiepileptic Drugs and Devices has provided an interactive forum for stakeholders to discuss investigational and recently licensed treatments for seizures and epilepsy. The Eighteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XVIII) took place in Madrid, Spain, on May 3–6, 2026. This article provides summaries of eight treatments in preclinical and early clinical development that were presented at EILAT XVIII. These include AUT00206, a positive allosteric modulator of Kv3.1 and Kv3.2 voltage-gated potassium channels in development for the treatment of rare epilepsy syndromes as well as neurodevelopmental and neuropsychiatric disorders; ION283, an antisense oligonucleotide designed to suppress the expression of glycogen synthase 1, under investigation for the

treatment of Lafora disease; MSCA-7136, a selective allosteric RAS/mitogen-activated protein kinase—extracellular signal regulated kinase (MEK) inhibitor being developed for the treatment of focal seizures associated with mesial temporal lobe epilepsy and seizures associated with tuberous sclerosis complex; OV329, a selective inhibitor of γ-aminobutyric acid (GABA) aminotransferase, in development for the treatment of drug-resistant focal seizures; PTI5803 (probenecid), an uricosuric agent and a blocker of pannexin 1 channels, repurposed as a treatment for seizures associated with focal cortical dysplasia; simufilam, a filamin A modulator under investigation for the treatment of tuberous sclerosis complex-related epilepsy; SN-2000, a selective allosteric phosphodiesterase 4B inhibitor, in development for the treatment of focal seizures; and sodium selenate, a promoter of the dephosphorylation of pathological hyperphosphorylated tau in the brain, under investigation as a disease-modifying agent in mesial temporal lobe epilepsy. Treatments in more advanced clinical development are discussed in an accompanying article.

**KEYWORDS**

anti-seizure medications, AUT-00206, drug development, epilepsy, ION283, MSCA-7136, OV329, PTI5803 (probenecid), simufilam, SN-2000, sodium selenate

## 1 | INTRODUCTION

The Eighteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XVIII) took place in Madrid, Spain, on May 3–6, 2026, and was attended by 160 delegates from 24 countries. According to the highly interactive format that has been in place for the last 34 years, the Conference provided healthcare professionals, researchers, and consumer representatives, including participants from industry, academia, and advocacy groups, the opportunity to present and discuss updates on the latest developments in epilepsy therapeutics. The event, which started with a symposium hosted by the Dravet Foundation of Spain, included sessions on preclinical models of developmental and epileptic encephalopathies (DEEs), state-of-the-art strategies for the clinical development of novel therapies for DEEs, updates on recently marketed anti-seizure medications (ASMs) and therapeutic devices, and presentations of investigational therapies in preclinical and clinical development. As per tradition, summaries of the latter have been incorporated in the present progress report. Investigational treatments are defined here as novel treatments that have not yet received regulatory approval for an epilepsy-related indication, including both novel chemical entities as well as molecules that have been approved previously for other indications and are being evaluated for potential repurposing for the treatment of seizures or epilepsy.

**Key points**

- The Eighteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XVIII), which took place in Madrid, Spain, on May 3–6, 2026, provided scientists from industry and academia with the opportunity to present updates on investigational treatments under development for the treatment of seizures and epilepsy.
- This report summarizes information presented on eight compounds currently in preclinical and early clinical development (AUT00206, ION283, MSCA-7136, OV329, PTI5803, simufilam, SN-2000, and sodium selenate).
- The compounds reviewed differ widely in chemical structure, mechanisms of action, and targeted indications, reflecting the diversity of approaches being applied to discovery and development of novel epilepsy treatments.

Details of the methodology used to identify epilepsy treatments in development, and the procedure applied to prepare EILAT progress reports have been described previously.[1] In short, industries and academic researchers willing to present an update on investigational epilepsy treatments in active development are invited by the

Organizing Committee to submit an extended summary of their presentation, using a structured standardized format, several months prior to the Conference. Members of the EILAT Organizing Committee review and edit each of the summaries, a process that typically involves returning the manuscripts to the authors with suggestions, queries, and comments in a multistep revision process over a period of 4 to 12 weeks. The objective is to ensure that manuscripts are as informative as possible, while respecting the sponsors' right to protect proprietary information that they consider commercially sensitive at the applicable stage of development. Upon completion of this process, accepted abstracts are incorporated into the progress report, which is then submitted to *Epilepsia* where it undergoes further external peer review. Of the 37 industries/investigators invited to present their data at EILAT XVIII, 25 (involved in the development of a total of 27 compounds) agreed to participate. Four sponsors declined to submit a manuscript for the progress report, and three withdrew their participation prior to the Conference. Hence, the EILAT XVIII progress report (Part 1 and Part 2) includes structured information on 21 different investigational treatments, an unprecedented high number compared with the previous 17 conferences. The present manuscript (Part I) provides information on investigational treatments in preclinical or early clinical development, where early clinical development refers to treatments that have undergone or are undergoing clinical evaluation, but for which seizure outcome data in people with epilepsy have not yet been reported. Treatments in more advanced clinical development are described in an accompanying article.[2]

## 2 | AUT00206

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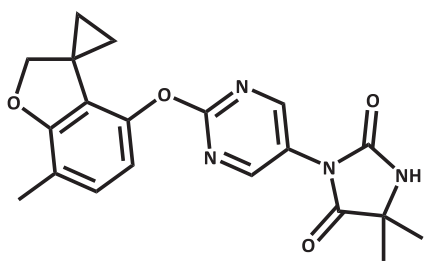


AUT00206

### 2.1 | Introduction and rationale for development

Kv3.1 (*KCNC1*) and Kv3.2 (*KCNC2*) are high-voltage-activated potassium channels that are preferentially expressed by parvalbumin-positive (PV+) γ-aminobutyric acid (GABA) interneurons in corticolimbic circuits. These channels enable neurons to fire precisely timed action potentials at high frequency to regulate the firing and synchronization of excitatory pyramidal neurons.[3] Consequently, Kv3.1 and Kv3.2 channels play a critical role in the control of cortical excitability and information processing. Genetic variants of *KCNC1* and *KCNC2* are associated with a range of hyperexcitability disorders, including neurodevelopmental epilepsy syndromes and autism.[4] Furthermore, reduced function/activity of PV+ interneurons has been identified as a pathological feature across a wide range of disorders, ranging from genetic epilepsy syndromes such as Dravet syndrome (DS),[5] acquired epilepsies arising from brain trauma,[6] disorders affecting information processing such as schizophrenia or fragile X syndrome,[7] and the early phases of neurodegenerative disorders such as Alzheimer's disease.[8]

AUT00206 is a positive allosteric modulator of Kv3.1 and Kv3.2 voltage-gated potassium channels that is being developed for the treatment of epilepsy as well as neurodevelopmental and neuropsychiatric disorders such as fragile X syndrome and schizophrenia. A Phase 1b study in patients with schizophrenia has been completed, providing initial positive results on biomarkers relevant across these disorders. Although not yet explored in patients with epilepsy, AUT00206 has the potential to reduce seizures and improve cognitive and behavioral symptoms in individuals with a range of epilepsy syndromes, including DS.

### 2.2 | Pharmacology

#### 2.2.1 | Activity profile in animal models of seizures and epilepsy

AUT00206 is effective at reducing spontaneous seizures and protecting against pentylenetetrazol (PTZ)–induced kindling in a genetic mouse model of Progressive Myoclonus Epilepsy Type 7 (EPM7)/Myoclonus Epilepsy and Ataxia due to Potassium Channel Mutation (MEAK) at doses consistent with Kv3 channel modulation.[9]

Kv3 channel positive modulators also protect against hyperthermia-induced seizures on postnatal Days 19–20 mice from a genetic *Scn1a*+/− line that models DS.[10] In this model, adult (postnatal Days >90) mice show an emergence of spontaneous tonic–clonic seizures. The Kv3

channel modulators AUT1 and AUT00063 significantly reduced spontaneous seizures in these mice. Specifically, weekly seizure frequency was reduced from 9.32 ± 4.61 (mean ± standard deviation [SD]) at baseline to 4.22 ± 3.24 after treatment with AUT1 ($p = .0061$), and from 6.72 ± 2.53 at baseline to 2.41 ± 1.94 after treatment with AUT00063 ($p = .196$) (Figure 1). Notably, seizing *Scn1a*+/− mice had reduced brain levels of Kv3.1 protein (78 ± 4% of control wild-type [WT] *Scn1a*+/+ mice, $p = .013$, $n = 7–8$ per group), whereas non-seizing *Scn1a*+/− mice had normal Kv3.1 levels (95 ± 11%, $p = .734$ vs WT mice). A relationship between seizures and Kv3.1 protein levels is supported by the finding that in a PTZ kindling model in WT mice, Kv3.1 protein levels were decreased after repeated seizures (79 ± 3% of saline-treated mice, $p = .0017$, $n = 8$ per group).

AUT00206 was effective at rescuing the behavioral phenotype of *Fmr1*−/*y* mice, a genetic model of fragile X syndrome. Of note, these mice, similar to the human condition, show susceptibility to seizures. In two independent studies conducted by the fragile X syndrome charity, FRAXA, AUT00206 (30 mg/kg, i.p.) reduced the incidence of audiogenic seizures and death in male *Fmr1* −/*y* mice by 50%, providing further evidence that Kv3 channel modulation can reduce brain hyperexcitability (P. Cogram, FRAXA, unpublished data).

Finally, in rats where acute electroencephalography (EEG) epileptiform activity occurs after traumatic brain injury (TBI), the effect of a close analogue of AUT00206, AUT00201 was explored on the ictal-interictal continuum (IIC) and background EEG activity. Adult male Sprague–Dawley rats were exposed to severe lateral fluid percussion-induced TBI,[11] implanted with four epidural electrodes, and connected to continuous video-EEG monitoring immediately after the impact. Vehicle or AUT00201 (6 mg/kg i.p.) treatment was started after online electrographic diagnosis of status epilepticus, which developed in 77% of rats exposed to the TBI. Fragmentation of the IIC was assessed after treatment using a modification of the Leitinger clinical criteria.[12] In animals with continuous IIC, responder status was defined as an IIC break of 1 min after treatment. In animals with non-continuous IIC, responder status was defined as an IIC break with a duration exceeding three times the longest spontaneously occurring break prior to treatment. Overall, in the AUT00201-treated group ($n = 18$), the responder rate was 83% (15/18 rats), which was greater than that in the vehicle group (36%, 4/11) ($p = .017$, Fisher's exact test). This effect was comparable to that observed with levetiracetam (responder rate: 5/7 or 71%) in a previous study (Pitkanen A., personal communication).

### 2.2.2 | Mechanism of action

AUT00206 is a highly selective positive modulator of Kv3.1 and Kv3.2 potassium channels. Using patch-clamp electrophysiology methods, AUT00206 increased whole cell currents in a concentration-dependent manner with mean median effective concentrations ($EC_{50}$) of 5 μM and 2 μM, for Kv3.1 and Kv3.2, respectively. The compound causes a leftward shift in the voltage dependence of activation of the channels, leading to greater Kv3 current at more hyperpolarized membrane potentials. AUT00206 has no notable effect on a wide range of other channels, including key cardiac channels, and no effects on an

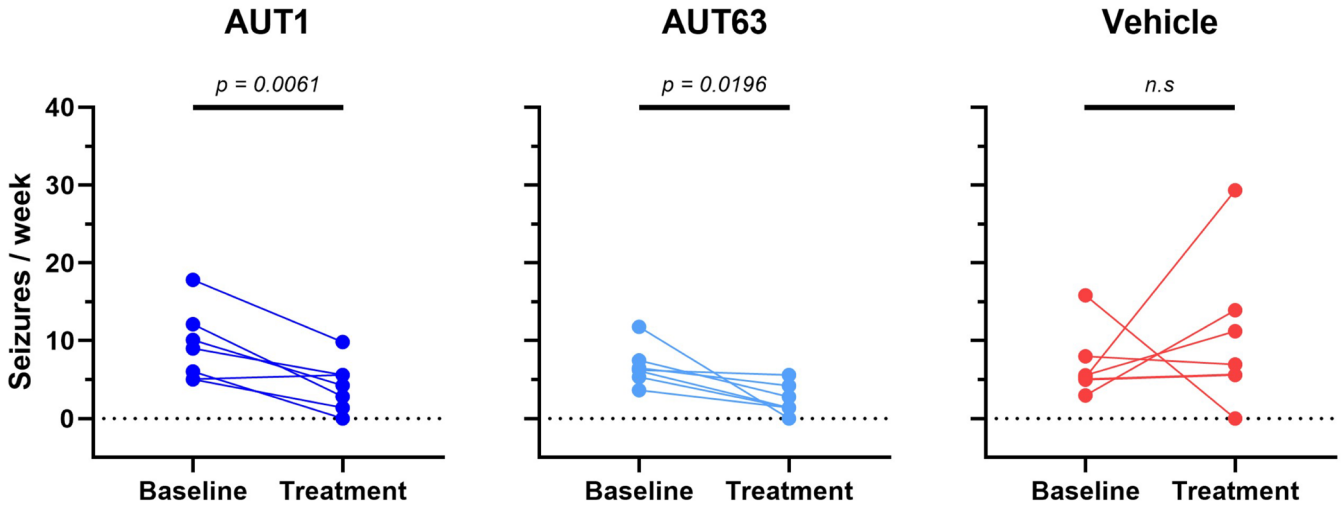


**FIGURE 1** A population of Scn1a+/− mice at >P90 display frequent spontaneous electrographic seizures measured using an implanted EEG electrode over 5 days (baseline). Subsequent treatment with AUT1 (30 mg/kg/day, i.p.) or AUT00063 (labeled as AUT63 in the figure) (60 mg/kg/day, i.p.) over 5 days produced a significant reduction in seizure count. Vehicle treatment had no effect on seizure count. Statistical comparisons (treatment vs baseline) were done by *t* test (data from Choe et al.[5]).

**TABLE 1** In patients with a diagnosis of schizophrenia, performance of a word-in-noise task improved significantly following daily dosing with AUT00206 (800 mg, b.i.d., for 4 weeks), whereas patients receiving placebo did not improve.

| Treatment | Baseline | Day 1 | Day 5 | Day 21 | Change from baseline to Day 21 |
|---|---|---|---|---|---|
| AUT00206 ($n=10$) | 9.76 | 8.16 | 7.76 | 7.20 | −2.56 dB |
| Placebo ($n=4$) | 9.60 | 9.60 | 10.8 | 10.4 | +.8 dB |
| Change from Placebo (AUT00206—Placebo) | | | −3.10 ($p=.097$) | −3.21 ($p=.016$) | |

*Note*: The task was performed with words presented at 40 dB HL (decibel Hearing Level) against a background of multi-talker babble. The signal-to-noise ratio at which subjects could correctly identify 50% of the words was calculated and is shown in the table. The task was conducted at baseline and at different intervals over the course of the trial.

extensive range of receptors, kinases, and transporters. Identification of the binding site for compounds similar to AUT00206 on Kv3.1 channels shows that the compounds interact with the unique turret domain on Kv3 channel proteins, which also explains the high selectivity of these compounds. Interaction with this domain stabilizes the activated state of the channels.[13]

### 2.2.3 | Target engagement and biomarker studies in humans

Human central target engagement by AUT00206 has been confirmed in a single-center ketamine-challenge study in healthy volunteers.[14] Ketamine challenge is considered a model for increased cortical excitability.[15,16] The study investigated whether pre-treatment with AUT00206 can attenuate the effects of ketamine on blood oxygen–level dependent (BOLD) signals using pharmacological magnetic resonance imaging (phMRI). According to a double-blind, placebo-controlled four-way crossover design, subjects ($n=16$ completers) received single oral doses of AUT00206 (800 mg or 2000 mg) or placebo, followed 4 h later by intravenous (i.v.) ketamine (.26 mg/kg bolus dose administered over 1 min, followed by a 30-min infusion at .25 mg/kg/h) or saline. The initial dry-blend capsule formulation of AUT00206 was used. Participants were assessed in four separate phMRI sessions, during which they received in random order placebo + saline, placebo + ketamine, 2000 mg AUT00206 + ketamine, and 800 mg AUT00206 + ketamine. Ketamine administered after pre-treatment with placebo evoked robust increases in BOLD-phMRI signal in the dorsal anterior cingulate cortex. Pre-treatment with both doses of AUT00206 significantly attenuated the effect of ketamine on the BOLD signal compared to placebo, with pairwise effects of treatment estimated at $\beta=-.72$ (95% confidence interval [CI] −1.19 to −.25, $p=.003$) for the 800 mg dose and $\beta=-.49$ (95% CI −.97 to −.02, $p=.04$) for the 2000 mg dose. Pharmacokinetic analysis showed that plasma concentrations of AUT00206 of ~1500–2500 ng/mL were associated with significant effects in this model. These findings suggest that AUT00206 could have beneficial effects in multiple disorders such as epilepsy, schizophrenia, and fragile X syndrome, in which cortical hyperexcitability is considered a key driver of symptoms.

Patients with schizophrenia have well-documented abnormalities in sensory processing,[17] including a reduced response to auditory stimuli in the gamma frequency band (30–100 Hz) of the EEG.[18] This reduced response has been linked to a dysfunction of PV+ interneurons involved in generating neural activity within the gamma band.[19] Thus, rescue of these abnormalities by AUT00206 would confirm target engagement and provide evidence that a Kv3-positive allosteric modulator could have beneficial effects in these patients. In a biomarker study in patients with a diagnosis of schizophrenia ($n=16$), AUT00206 at a dose of 800 mg twice daily (b.i.d.) for 4 weeks increased auditory stimulus-evoked gamma frequency EEG power compared to placebo treatment ($n=8$) with a Cohen's $d$ effect size of .43. In a test of auditory information processing (Word-in-Noise task), AUT00206 also significantly improved performance by Week 3, with a clinically relevant improvement of 2.5 dB ($n=10$); four patients receiving placebo did not improve, and the difference between groups was statistically significant ($p=.016$) (Table 1). Mean plasma concentrations of AUT00206 at Week 4 were ~3000 ng/mL.

## 2.3 | Toxicology

AUT00206 has been assessed for safety and toxicology for up to 13 weeks in Good Laboratory Practice (GLP)–compliant rat and dog studies. The compound was very well tolerated at plasma concentrations up to 60 000 ng/mL. In each study, the No-Observed-Adverse-Effect-Level (NOAEL) was established at the highest dose tested and was limited by exposure. In comparison, human clinical studies confirm a target engagement at plasma concentrations in the range from 1500 to 3000 ng/mL. In discussions

with the U.S. Food and Drug Administration (FDA), doses achieving peak plasma concentrations ($C_{max}$) of AUT00206 up to 14 500 ng/mL are likely to be acceptable in future clinical trials.

## 2.4 | Pharmacokinetics

A tablet formulation of AUT00206 was developed in order to reduce a food effect observed with the original capsule dry-blend formulation and to increase gastrointestinal absorption, thereby reducing the oral dose requirement. A pharmacokinetic study was conducted using this tablet formulation in healthy male and female volunteers (UK Clinical Study Registry identifier: ISRCTN80267019). During the single ascending dose portion of the study, single doses up to 1000 mg in the fasted state and 800 mg in the fed state were evaluated. The food effect was significantly reduced compared with the original capsule formulation, with a modest increase in exposure of AUT00206 being observed when the tablets were taken after a meal. Analysis of variance (ANOVA) confirmed that prior feeding with a standard breakfast increased the bioavailability of 400 mg AUT00206: geometric least squares (LS) mean ratios (fed/fasted) were 1.46, 1.25, and 1.26 for $C_{max}$, area under the plasma drug concentration–time curve ($AUC_{0-\infty}$), and $AUC_{last}$, respectively, with all >90% CIs outside the range .8–1.25. The highest dose in the multiple ascending dose portion of the study was 600 mg once daily (q.d.) (fed) for 7 days ($n = 6$).

After oral administration of a single dose, time to peak plasma concentration ($t_{max}$) was about 5 h on average. During multiple dosing, steady state was achieved around Day 3, with $C_{max}$ values up to 7420 ng/mL and AUC values during a dosing interval up to 97 652 ng*h/mL. The half-life of AUT00206 after 7 days of treatment at a dose of 600 mg q.d. was 11 h on average. AUT00206 is primarily eliminated by metabolism, with preliminary in vitro studies in human liver microsomes suggesting involvement of cytochrome P450 (CYP) isozymes CYP2C9, CYP2C19, and CYP3A4.

## 2.5 | Drug interactions

No formal drug–drug interaction studies have been performed.

## 2.6 | Efficacy data

Studies of AUT00206 in patients with epilepsy have not been conducted to date.

## 2.7 | Adverse effects

AUT00206 has been administered to over 100 healthy male and female subjects and patients with schizophrenia across four clinical studies. In the first three studies using the capsule formulation, single doses up to 2000 mg and repeat doses up to 800 mg, b.i.d., for 28 days ($n = 16$) were evaluated. In the latest study of the tablet formulation, where we achieved the highest plasma exposures to date, the highest dose tested during multiple dosing was 600 mg, q.d., for 7 days ($n = 6$). AUT00206 was very well tolerated with few treatment-emergent adverse events (TEAEs) across all four studies in both healthy subjects and patients with schizophrenia, the latter taking a range of medications for their condition. The most common TEAEs were sedation and headache, which were mild to moderate and resolved. There have been no deaths, no serious TEAEs, and no TEAEs leading to subject withdrawal from treatment in clinical studies of AUT00206.

## 2.8 | Planned studies

AUT00206 has now completed Phase 2–enabling nonclinical studies and clinical assessment of the novel tablet formulation. In the next phase, AUT00206 will be assessed for safety and efficacy in adolescent and adult patients with rare neurodevelopmental epilepsy syndromes, such as DS. A study in patients with fragile X syndrome is also under consideration. AUT00206 received Orphan Drug Designation from the FDA and from the European Medicines Agency (EMA) for fragile X syndrome, supported by sound preclinical evidence and target rationale.

# 3 | ION283

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## 3.1 | Introduction and rationale for development

ION283 is an antisense oligonucleotide (ASO) therapy for Lafora Progressive Myoclonus Epilepsy (PME). Lafora disease is caused by loss-of-function pathogenic variants in the *EPM2A* or *EPM2B* gene, encoding laforin and malin, respectively.[20] Laforin and malin form a functional complex that ensures that glycogen molecules remain water soluble by preventing abnormal glycogen structure. In

the absence of either laforin or malin, glycogen molecules with overlong branches are produced, which become insoluble and gradually accumulate and aggregate into Lafora bodies.[20] In patients with Lafora disease, Lafora bodies are formed throughout the whole body, but in the brain they are particularly detrimental, causing the intractable and fatal epilepsy.

Glycogen synthase 1 (GYS1), encoded by the *GYS1* gene, is the rate-limiting enzyme of glycogen synthesis. Slowing glycogen synthesis by reducing GYS1 amount and/or activity prevents Lafora body formation as well as neuroinflammation, myoclonus, increased seizure susceptibility, and epileptiform discharges in mice.[21–24] Accordingly, a promising therapeutic strategy for Lafora disease is to employ *GYS1*-targeting ASOs to suppress glycogen synthesis via *GYS1* silencing.

## 3.2 | Pharmacology

### 3.2.1 | Mechanism of action

ION283 belongs to the class of chimeric 2′-*O*-(2-methoxyethyl) (2′-MOE)/DNA modified ASOs designed to enable RNase H1 recruitment upon specific complementary binding to *GYS1* messenger RNA (mRNA) via Watson–Crick base pairing. RNase H1 action in turn selectively degrades *GYS1* mRNA, thereby decreasing GYS1 protein levels and therefore the rate of glycogen synthesis. Slowing of glycogen synthesis prevents the formation of Lafora bodies, the key drivers of Lafora disease (Figure 2). ION283 was developed through a collaboration with Ionis Pharmaceuticals.

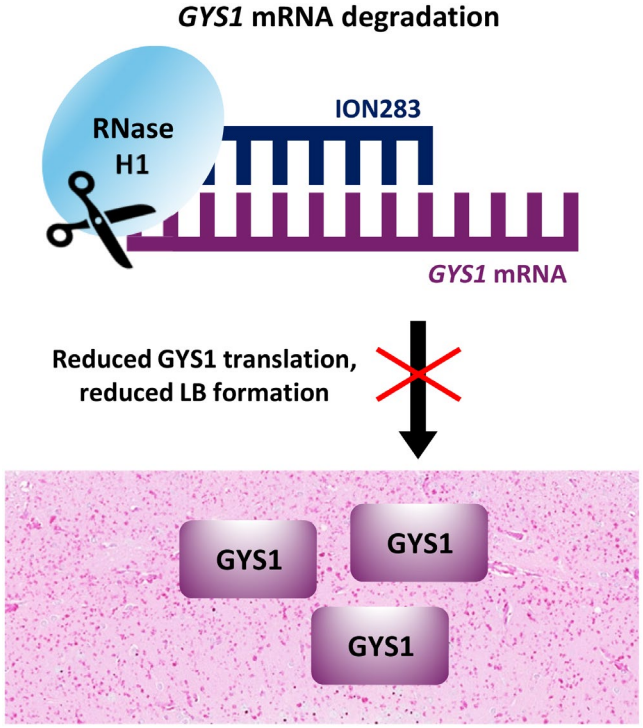


**FIGURE 2** Schematic illustration of ION283's mode of action. Binding of ASO ION283 to *GYS1* mRNA leads to recruitment of RNase H1, which degrades the targeted mRNA. In turn, this *GYS1* silencing results in reduced GYS1 protein levels and prevents Lafora body (LB) formation.

### 3.2.2 | Activity profile in animal models of Lafora disease

Proof-of-concept experiments in Lafora disease mouse models were performed using a mouse *Gys1*-targeting ASO.[24,25] Intracerebroventricular (i.c.v.) ASO administration successfully reduced *Gys1* mRNA and protein levels in the brain and prevented further disease progression, that is, halting glycogen accumulation, Lafora body formation, and neuroinflammation. ASO-dependent *Gys1* silencing also reduced epileptiform discharges in Lafora disease mice (Figure 3).

A humanized mouse model (hGYS1) was used to screen human *GYS1*-targeting ASOs. ION283 was selected and showed potent concentration-dependent reduction of *GYS1* mRNA. hGYS1 Lafora disease mice treated with ION283 show a strong reduction in accumulation of insoluble glycogen and Lafora body formation.

## 3.3 | Toxicology

GLP toxicology studies with ION283 were conducted in rodents first. The rodent screening studies included a single-dose i.c.v. study in mice, a single-dose intrathecal study in rats, and a repeated-dose i.c.v. study in mice. Primary endpoints for the assessment of tolerability included the evaluation of both acute and delayed effects on gross motor function. In addition, brain and spinal cord sections underwent standard histopathology and were examined for microgliosis and astrogliosis. Standard assays such as the bacterial reverse mutation assay, the in vitro chromosomal aberration assay, and the in vivo mouse micronucleus test were performed to rule out genotoxicity of ION283. Non-human primates (cynomolgus monkeys) were used for non-rodent toxicology screenings. These included a single-intrathecal dose maximum tolerated dose study and a 9-month repeat-dose intrathecal bolus toxicity study with a 29-week recovery phase. The NOAEL was determined to be 15 mg.

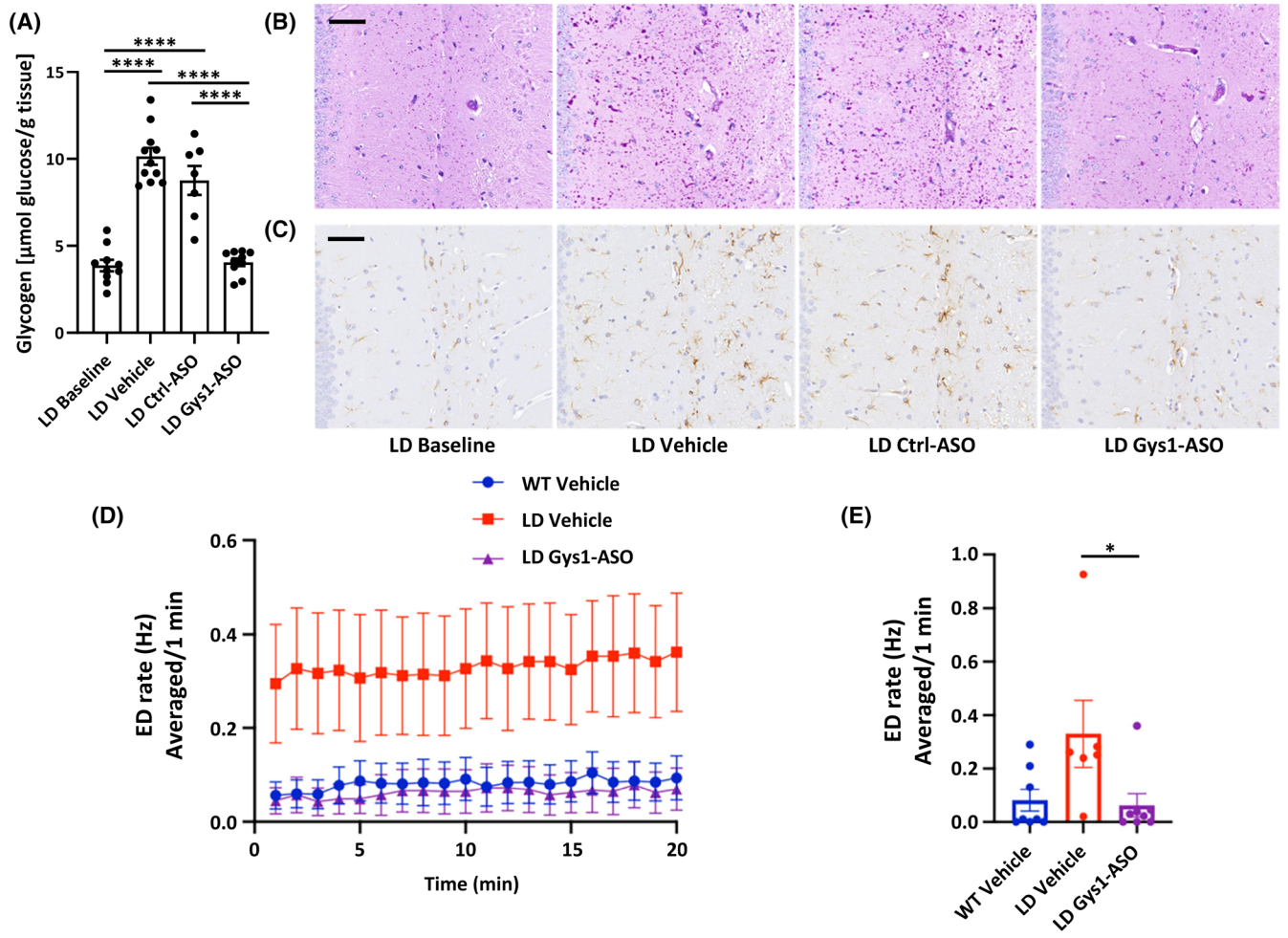


**FIGURE 3** Proof-of-concept experiments using the mouse *Gys1*-targeting ASO to treat Lafora disease (LD) mice. The Gys1-ASO prevents (A) glycogen accumulation, (B) Lafora body (LB) formation, (C) astrogliosis, and (D) to (E) epileptiform discharges (EDs) in the brains of LD mice. Scale bar, 50 µm. Intracerebroventricular injections were started at 3–4 months and tissues were collected at 12–13 months. Re-dosing was done every 3 months. Baseline, untreated at age 3–4 months. Ctrl-ASO, control no-target ASO; WT, wild-type. Data shown are means ± SEM. *$p < .05$ and ****$p < .0001$. Data shown in this figure were adapted from Donohue et al.[24] and Ahonen et al.[25] with permission from Elsevier and Oxford University Press, respectively.

## 3.4 | Pharmacokinetics and drug interactions

Pharmacokinetic studies were part of the 9-month repeat-dose intrathecal bolus toxicity study in monkeys and helped determine the dose levels and dose interval for the first-in-human study. Drug interaction studies with ION283 have not been conducted to date.

## 3.5 | Efficacy data and adverse effects

A 2-year Phase 1/2 human safety study (NCT06609889) was initiated in late 2024 and is ongoing. The study aims to enroll 10 patients with a genetically confirmed diagnosis of Lafora disease, documented by pathogenic variants in known causative genes (*EPM2A*/laforin, *EPM2B*/*NHLRC1*/malin). To be eligible for enrollment, patients must be 10 to 18 years of age and have a score ≥9 on the Lafora Disease Progression Scale (LDPS), with a LDPS motor subscore ≥2 (independent ambulation, walking 10 steps independently). In this study, ION283 is administered intrathecally at a dose of 15 mg (recently increased to 30 mg) every 12 weeks. Efficacy endpoints relate to determination of slowing in worsening scores of the comprehensive LPDS previously established through a natural history study, as well as biomarker analyses including EEG, MRI volumetry, and MR spectroscopic brain glycogen measurement. All 10 patients have already been enrolled. No efficacy data are available at this time. No trial impacting TEAEs have been reported to date.

## 3.6 | Planned studies

If the current study confirms safety and provides positive efficacy signals, further trials will be conducted pending availability of funding.

# 4 | MSCA-7136

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## 4.1 | Introduction and rationale for development

MSCA-7136 is a novel non-ion channel ASM being developed for the treatment of focal seizures associated with mesial temporal lobe epilepsy (MTLE) and seizures associated with tuberous sclerosis complex (TSC). Numerous studies in animal models and humans have demonstrated the importance of Rat Sarcoma (RAS)/mitogen-activated protein kinase—extracellular signal regulated kinases (MAPK–ERK) signaling in the development and maintenance of drug-resistant epilepsy.[26] The RAS/MAPK–ERK pathway is an intracellular master regulator of neuronal hyperexcitability through its direct and indirect regulation of gene expression, membrane trafficking, and phosphorylation of ion channels and various other proteins involved in neuronal hyperexcitability.[26] Furthermore, pathologic somatic RAS/MAPK–ERK variants have recently been found in surgically resected hippocampi from patients with drug-resistant MTLE.[27] Of note, several case series and case reports from patients with refractory epilepsy caused by germline RASopathies show successful control of seizures after treatment with FDA-approved MAPK–ERK (MEK) inhibitors that only achieve concentrations around the inhibitory concentration 10% ($IC_{10}$) on-target activity in the brain, but were poorly tolerated systemically due to low brain penetration and had to be discontinued because of systemic toxicity.[28–31] In TSC, that is caused by *TSC1/2* loss-of-function variants activating mechanistic target of rapamycin (mTOR) signaling, the RAS/MAPK–ERK pathway is also activated via increased ERK phosphorylation and upregulation of RAS/MAPK–ERK pathway genes, as shown in both animal models of TSC and human brain tissue from patients with TSC.[32,33] There is significant crosstalk between mTOR and RAS/MAPK–ERK pathways, and recent studies have reported that although mTOR signaling mediates abnormal cellular metabolism and growth in TSC, RAS/MAPK–ERK is an important contributor to seizures.[34] MSCA-7136 is a novel next-generation allosteric MEK inhibitor (arylamino pyridine structure) with differentiating features, including significantly improved brain penetration and a highly selective profile. MSCA-7136 has been evaluated at 10 μM in the CEREP panel of up to 169 common pharmacological targets with no hits. In addition, MSCA-7136 was tested in a kinome panel with no relevant hits, showing selectively for MEK. MSCA-7136 has excellent pharmacokinetic characteristics, being brain penetrant with a measured $K_{p,uu}$ (unbound brain/unbound plasma concentration ratio) of .9. Because of its unique characteristics relative to existing MEK inhibitors and effective plasma concentrations seen in epilepsy animal models, MSCA-7136 is projected to require low brain and systemic exposures to achieve clinically meaningful seizure reduction while being well tolerated.

## 4.2 | Pharmacology

### 4.2.1 | Activity profile in animal models of seizures and epilepsy

MSCA-7136 demonstrated dose-dependent anti-seizure activity in the kainic acid mouse model of MTLE. In this model, acute (Day 1) and chronic (Day 20, b.i.d. dosing) oral administration of MSCA-7136 induced a durable effect on hippocampal paroxysmal discharges (HPDs) without any signs of tachyphylaxis or central nervous system (CNS) adverse effects (Figure 4). The reduction in HPDs lasted at least 5 h after each dose even though the drug half-life in mice is only ~1.5 h. This suggests that MSCA-7361 regulates ERK-mediated transcriptional programs to produce a long-lasting reduction in neuronal hyperexcitability, allowing for sustained activity that outlasts the drug pharmacokinetics. No behavioral abnormalities were observed. These data are consistent with significant anti-seizure activity occurring at trough brain concentrations associated with about 10% MEK inhibition.

MSCA-7136 has also been tested in two mouse knockout (KO) models of TSC, the *GFAP-cre TSC1* KO and *TSC2* KO mice. In both models, MSCA-7136 demonstrated significant reductions in seizure count and duration at doses estimated to achieve 10% MEK inhibition at trough brain concentrations, without any signs of CNS toxicity (Figure 5). In addition, treatment with MSCA-7136 produced statistically significant improvements in body weight in both TSC models—not previously reported even with rapamycin treatment—and prolonged survival in the TSC1 model compared to treatment with vehicle. No behavioral abnormalities were observed. The data also

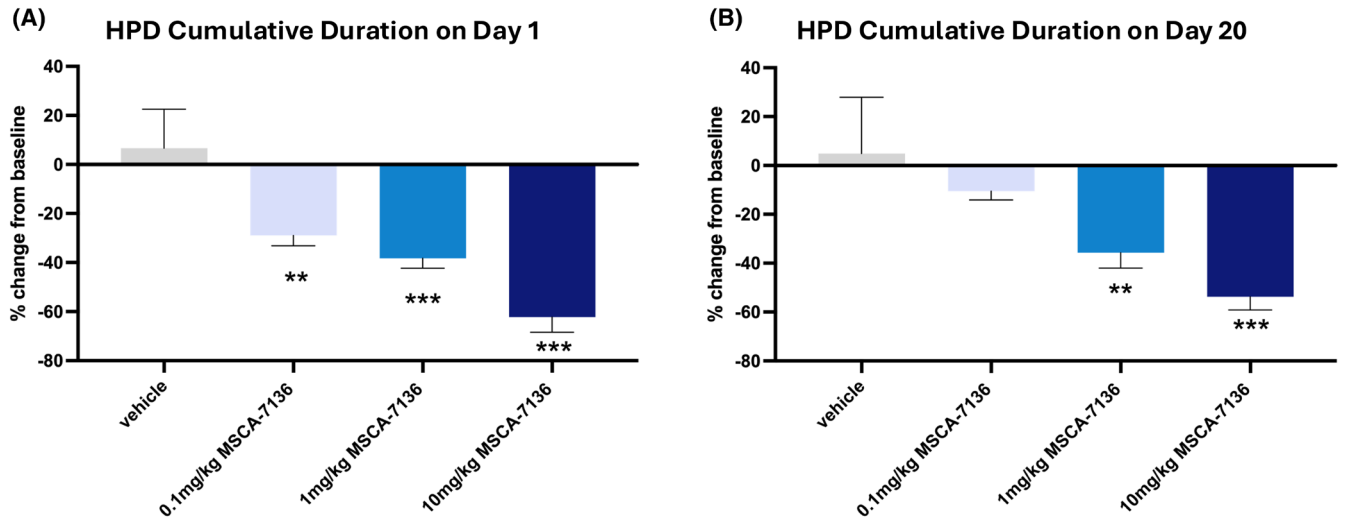


**FIGURE 4** Effect of acute (Day 1; A) and chronic (Day 20; B) oral administration of MSCA-7136 on cumulative duration of hippocampal paroxysmal discharges (HPDs) in the intrahippocampal kainate mouse model of mesial temporal lobe epilepsy (MTLE). Treatments were administered on a b.i.d. schedule; doses are expressed as mg/kg/day. $n = 16$ mice per dose group; except for 1 mg/kg dose group, $n = 24$. Error bars represent standard error of the mean (SEM). $^{**}p < .01$ vs baseline, $^{***}p < .001$ vs baseline. HPDs at baseline are measured for each treatment day, 2 h prior to compound administration.

confirm that anti-seizure activity is present at MSCA-7136 trough brain concentrations associated with MEK inhibition levels as low as 10%, that is, the $IC_{10}$.

### 4.2.2 | Other pharmacological properties

MSCA-7136 has been found to suppress ERK phosphorylation in a dose-dependent manner in the periphery (liver and lung) and in the brains of WT mice, and in brain tissue obtained from the mouse intrahippocampal kainate model of MTLE and from both TSC1 and TSC2 mouse models. This finding provides direct evidence of brain penetration and direct target engagement in different animal epilepsy models of MTLE and TSC. The pharmacokinetic profiles of MSCA-7136 in plasma and brain demonstrate a brain-to-plasma ratio very close to 1 throughout the period the drug is detectable in plasma, confirming efficient brain penetration.

### 4.2.3 | Mechanism of action

MSCA-7136 is a MEK inhibitor. Inhibition of ERK activity triggers a wide range of transcriptional and translational events that result in reduction of neuronal hyperexcitability and protection against seizures.[35,36] As detailed in the previous sections, both animal studies and clinical case reports indicate that only trough concentrations close to $IC_{10}$ for ERK inhibition are likely needed for anti-seizure activity.

## 4.3 | Toxicology

MSCA-7136 has been studied in standard GLP-compliant toxicology studies, including 28-day and 13-week repeat dosing in both rats and dogs. The NOAEL was 20 mg/kg/day in dogs (highest dose tested), 2 mg/kg/day in male rats (stomach mineralization rat-specific finding not relevant to humans), and 6 mg/kg/day in female rats, which is indicative of wide therapeutic margins (>30x) for the active dose in humans (2.5 mg, b.i.d.) as projected from the animal model data. The human active dose was determined as the dose projected to achieve a plasma AUC (340 ng*h/mL) demonstrated to drive pharmacological effects in the MTLE and TSC models. MSCA-7136 is not genotoxic based on findings in in vivo micronucleus (2, 6, and 20 mg/kg), in vivo Comet (from 12.5 mg/kg, 25 mg/kg, and 50 mg/kg), and in vitro Ames (200–5000 µg/well) studies.

In the rotarod assay in WT mice, MSCA-7136 doses up to 30 mg/kg, which achieve high target engagement (>99% MEK inhibition) for an extended period (>4 h), were not associated with coordination disturbances or any other detectable CNS abnormalities.

## 4.4 | Pharmacokinetic and metabolic profile

A first-in-human Phase 1 study is planned for 2026. The Phase 1 program will consist of single ascending dose/

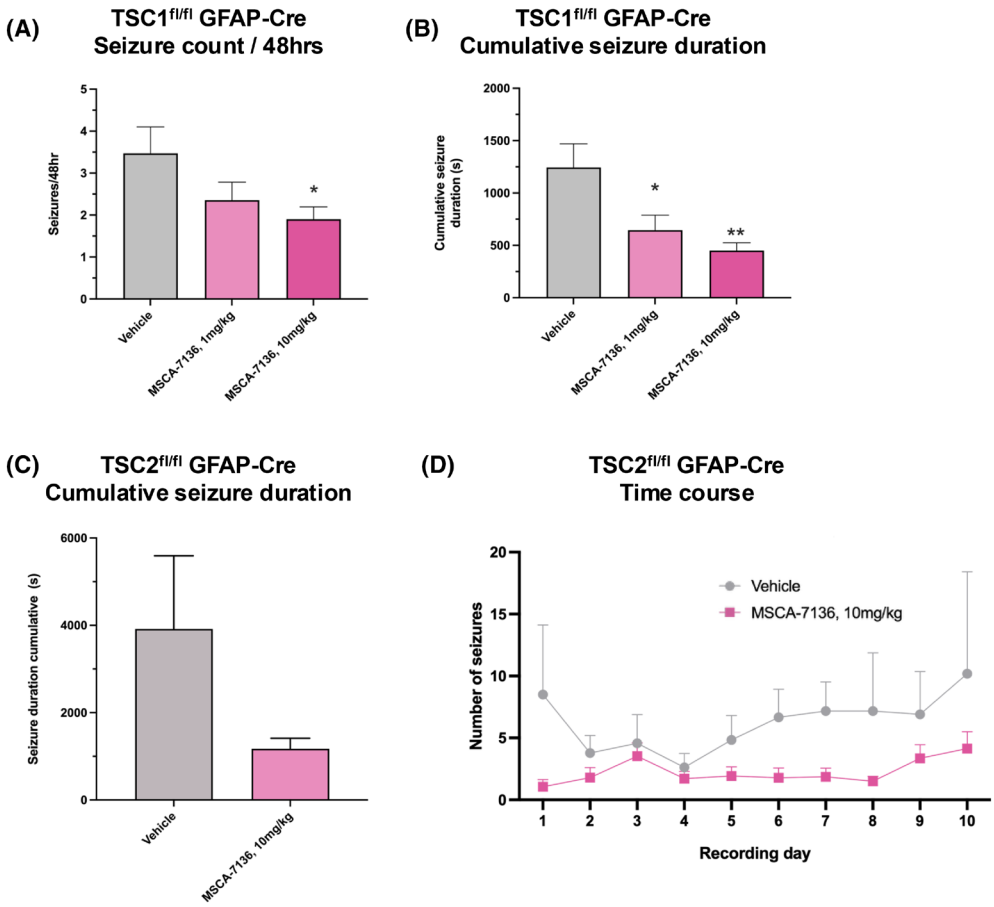


**FIGURE 5** MSCA-7136 demonstrated dose-dependent decreases in seizure numbers (A) and seizure cumulative duration (B) in the TSC1$^{fl/fl}$ GFAP-Cre KO mouse model. Furthermore, MSCA-7136 showed robust seizure reductions in both numbers (not shown), and cumulative duration (C), as well as seizure decreases throughout the 10 days of the study (D) in the TSC2$^{fl/fl}$ GFAP-Cre KO mouse model at doses projected to achieve 10% MEK inhibition in the brain. Treatments were administered orally on a b.i.d. schedule; doses are expressed as mg/kg/day. $n = 15$ animals per dose group in both TSC1 and TSC2 studies. Error bars represent standard error of the mean (SEM). A and B, $^{*}p < .05$; $^{**}p < .01$ vs vehicle. D, $^{***}p < .0001$ vs vehicle, two-way ANOVA, Multiple comparisons.

multiple ascending doses/preliminary food effect studies in healthy adult volunteers.

## 4.5 | Drug interactions

Application of the basic kinetic model and the mechanistic model per FDA 2025 guidance using the predicted human pharmacokinetic parameters of our projected therapeutic dose did not demonstrate a risk for MSCA-7136 to act as a CYP inhibitor, and suggested only a very limited potential for MSCA-7136 to act as an inducer, especially when considering the expected low systemic levels needed for efficacy. A formal drug–drug interaction risk assessment will be conducted once sufficient human pharmacokinetic data are available.

## 4.6 | Efficacy data and adverse effects

To date, there have been no clinical trials performed with MSCA-7136.

## 4.7 | Planned studies

Upon completion of the Phase 1 pharmacokinetic studies, two Phase 2 proof-of-concept studies are planned: (1) a 12-week open-label study of 40 TSC patients with drug-resistant epilepsy (70% pediatric/adolescents and 30% adults) and (2) a 12-week open-label study utilizing the responsive neurostimulation (RNS) paradigm[37] in 30 patients, including 20 patients with drug-resistant MTLE and electrodes in the temporal lobe and up to 10 patients

with electrodes in the neocortex, using the biomarker Long Episodes as the primary outcome variable and clinical seizures assessed via seizure diaries as a secondary endpoint.

## 5 | OV329

Julia Tsai,[1] Jatinder Singh,[1] Petra Kaufmann,[1] Andrea Vecchione,[1] Alexander Rotenberg,[2] Zhong Zhong[1]

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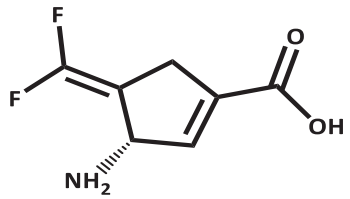



OV329

### 5.1 | Introduction and rationale for development

GABA is the main inhibitory transmitter in the brain and enhancement of GABA-mediated signaling represents a validated strategy to inhibit seizure activity. One approach to enhance GABAergic transmission is to inhibit GABA-aminotransferase (GABA-AT), which is the primary enzyme involved in GABA catabolism. OV329 is a potent GABA-AT inhibitor that increases GABA levels in the brain and has been found to be effective in multiple rodent models of drug-resistant seizures.[38–40] Its safety, tolerability, and pharmacokinetics have been evaluated in a Phase 1 study. The data provided in this section provide further support for the development of OV329 for the treatment of drug-resistant seizures.

### 5.2 | Pharmacology

Results of non-clinical pharmacology studies have been summarized in the EILAT XVII report.[1]

### 5.3 | Toxicology

The results of standard GLP toxicology studies of OV329 have been described in the EILAT XVI progress report.[41] In light of the reported retinal accumulation and toxicity of the first-generation GABA-AT inhibitor vigabatrin in rodents[42,43] and visual field deficits in humans,[44,45] we compared the accumulation of OV329 and vigabatrin in the retinal tissue in mouse studies, as described here. To evaluate the tissue distribution of OV329 in the eye, male C57BL/6J mice received a two-day subcutaneous (s.c.) infusion of OV329 5 mg/kg/day via osmotic pump. At 48 h post-dose, the concentration of OV329 (mean ± SD) was 25.7 ± 1.7 ng/mL in plasma, and below the lower limit of quantitation of the assay (3 ng/mL) in brain, eyeball, and retina. In contrast, following 2 days of s.c. infusion of vigabatrin 80 mg/kg/day, the concentrations of vigabatrin in plasma, brain, eyeball, and retina at 48 h post-dose were 1462 ± 104 ng/mL, 239 ± 19.4 ng/g, 846 ± 144 ng/g, and 6256 ± 238 ng/g, respectively. The brain, eyeball, and retina to plasma vigabatrin concentration ratios were .165 ± .0248, .583 ± .127, and 4.30 ± 0 .411, respectively. These results indicate that OV329 does not accumulate in the eye as compared to vigabatrin, and thus potentially avoids similar safety issues related to ocular accumulation of vigabatrin.

### 5.4 | Pharmacokinetic profile

The pharmacokinetics of OV329 in healthy adults was assessed in a Phase 1, double-blind, randomized, placebo-controlled study. Participants were enrolled into single ascending dose (OV329 1, 2, 3, 5 mg, or placebo) or multiple ascending dose (OV329 2, 3, 5 mg, or placebo q.d. for 7 days) cohorts. For the single-dose studies, there were six active treatment and two placebo treatment subjects per cohort. For the multiple-dose studies, there were six active treatment and two placebo treatment subjects for the 2 and 3 mg cohort, and 15 active treatment and five placebo treatment subjects for the 5 mg cohort. Subjects were followed up for 7 or 30 days for the single- and the multiple-dose cohorts, respectively. Both $C_{max}$ and AUC increased with increasing dose; $C_{max}$ was achieved at 1 h after dosing at all dose levels after single and multiple doses. The half-life ranged from .7 to 1.2 h and steady state was reached in fewer than 3 days. Plasma exposure increased with repeat dosing in humans. Additional experiments are in progress to characterize the increase; however, exposure levels remain predictable as confirmed by actual exposure data.

In in vitro studies, the unbound fraction of OV329 in human plasma was .81 to .84. Following single dose administration of 1, 2, 3, and 5 mg OV329 to healthy subjects, the fraction of OV329 excreted unchanged in urine ranged from 4.3% to 11.9% over the first 12 h period after dosing and similar values were observed over a 24 h period. Of note, previous preclinical work showed that although OV329 is rapidly eliminated, it causes a prolonged

inhibition of brain GABA-AT due to its high potency, its irreversible binding to GABA-AT, and the slow regeneration of GABA-AT in the brain.[46]

## 5.5 | Drug interactions

OV329 did not inhibit CYP isoforms (CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, or CYP3A4) in a direct, time-, or metabolism-dependent manner ($IC_{50}$ values >100 μM). No induction of CYP1A2, CYP2B6, or CYP3A4 was observed with OV329 in human hepatocytes. Furthermore, OV329 was not metabolized by human recombinant CYP enzymes. Therefore, no drug–drug interactions are expected between OV329 and drugs that are sensitive CYP substrates or that are CYP inhibitors or inducers.

OV329 did not inhibit P-glycoprotein (P-gp)-, breast-cancer resistant protein (BCRP)-, multidrug and toxin extrusion protein (MATE) 1-, MATE2-K-, organic acid transporting polypeptide (OATP) 1B1-, OATP1B3-, organic acid transporter (OAT) 1-, OAT3-, or OCT2-mediated transport. Thus, no drug–drug interactions are anticipated with drugs that are substrates of these transporters. OV329 was not a substrate of P-gp, BCRP, MATE1, MATE2-K, OATP1B1, OATP1B3, or OCT2; therefore, drug–drug interactions with drugs that are inhibitors of these transporters are not expected. However, OV329 is a substrate of OAT1 and OAT3 transporters; therefore, co-administration of OV329 with drugs that are OAT inhibitors may increase OV329 plasma concentrations. Common ASMs do not inhibit OAT and, therefore, these potential interactions should not limit the use of OV329 in patients with epilepsy.

## 5.6 | Cortical inhibition data in healthy subjects

In the Phase 1 study, transcranial magnetic stimulation (TMS) was performed to assess cortical inhibition as evidence of target engagement, comparing pre-OV329 baseline to post-treatment results on Day 7. Changes in paired-pulse long-interval intracortical inhibition at a 150 ms interpulse interval ($LICI_{150}$) were evaluated in cohorts receiving OV329 doses of 3 mg/day or 5 mg/day for 7 days. Testing was conducted within 24 h of Day 7 dosing. On average, OV329 5 mg/day increased the $LICI_{150}$ from baseline by 53% ($p = .0001$) and 44.3% ($p = .0001$) on the abductor pollicis brevis and first dorsal interosseous muscles, respectively (Figure 6). In contrast, decreases of 24.9% ($p = .744$) and 59.5% ($p = .135$) were seen with placebo. The 3 mg/day dose was also associated with statistically significant increases from baseline in the $LICI_{150}$ on the abductor pollicis brevis and first dorsal interosseous muscles, when accommodating for random effects ($p < .05$). A positive relationship between serum OV329 exposure and response was observed for first dorsal interosseous muscle $LICI_{150}$ change (Figure 7), which was particularly strong for the 5 mg/day dose ($R^2 = .4553$; $p = .011$). These results showing cortical inhibition, as measured by a biomarker, are consistent with OV329's GABAergic mechanism of action.

## 5.7 | Adverse effects

In the Phase 1 study, 68 participants (62% male; age 19–52 years; 53% White) were enrolled; 51 received OV329 and were included in the analysis. Safety assessments included TEAEs, vital signs, physical/neurological exams, electrocardiography (ECG), laboratory tests, ophthalmologic assessments (including visual acuity, visual field perimetry, optical coherence tomography, and fundus photography), and the Columbia Suicide Severity Rating Scale (CSSRS). OV329 was well tolerated, with potentially treatment-related TEAEs of headache (2 mg/day), drowsiness (2 mg/day), and metallic taste (5 mg/day) reported by three participants in the multiple ascending dose study; all were of mild severity and transient. No treatment-related serious TEAEs were reported, and no ophthalmic safety findings or retinal changes were associated with OV329. A follow-up single-/multiple-ascending dose study testing higher doses is in progress, and interim blinded results for the 7 mg single dose cohort (six active, two placebo) and 7 mg multiple dose cohort (six active, two placebo) were generally safe and well tolerated with no TEAEs related to study drug. There have been no serious TEAEs, treatment interruptions, treatment withdrawals or deaths due to TEAEs. There were no clinically significant changes from baseline in vital parameters, ECG, hematology, chemistry, urinalysis, physical, neurological, ophthalmic examinations, or CSSRS deemed related to study drug.

## 5.8 | Planned studies

Ovid Therapeutics is engaging sites and regulators and intends to initiate a Phase 2, randomized, placebo-controlled study evaluating OV329 in adults with drug-resistant focal epilepsy. In addition, Ovid Therapeutics intends to characterize OV329's anti-seizure profile in an open-label study.

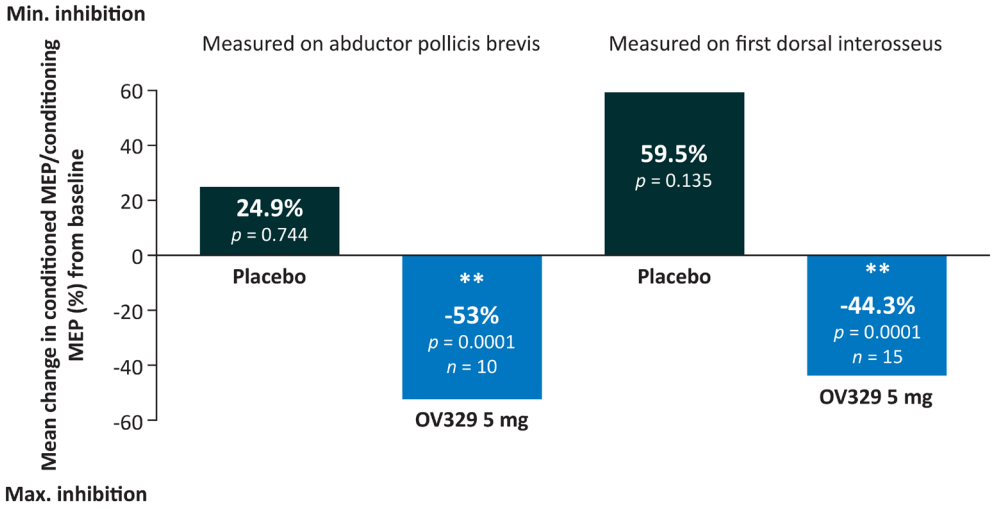



**FIGURE 6** OV329 enhanced cortical inhibition as measured by transcranial magnetic stimulation (TMS). Motor evoked potentials (MEPs) were measured on the abductor pollicis brevis (APB) and the first dorsal interosseous (FDI). Results are shown as % change in TMS-paired pulse long-interval intracortical inhibition at a 150 ms interpulse interval ($LICI_{150}$) after 7-day treatment with OV329 (5 mg/day) or placebo compared with baseline (Day 1 prior to treatment). OV329, 5 mg/day, increased inhibition by 53% ($p = .0001$; $n = 10$) on the APB muscle, whereas placebo showed a 24.9% decrease ($p = .744$; $n = 4$). On the FDI muscle, OV329 5 mg increased inhibition by 44.3% ($p = .0001$; $n = 15$) vs a 59.5% decrease with placebo ($p = .135$; $n = 5$). All values were $log_{10}$ transformed before averaging. Six subjects were missing APB data due to lack of electrode capture. **Statistically significant.

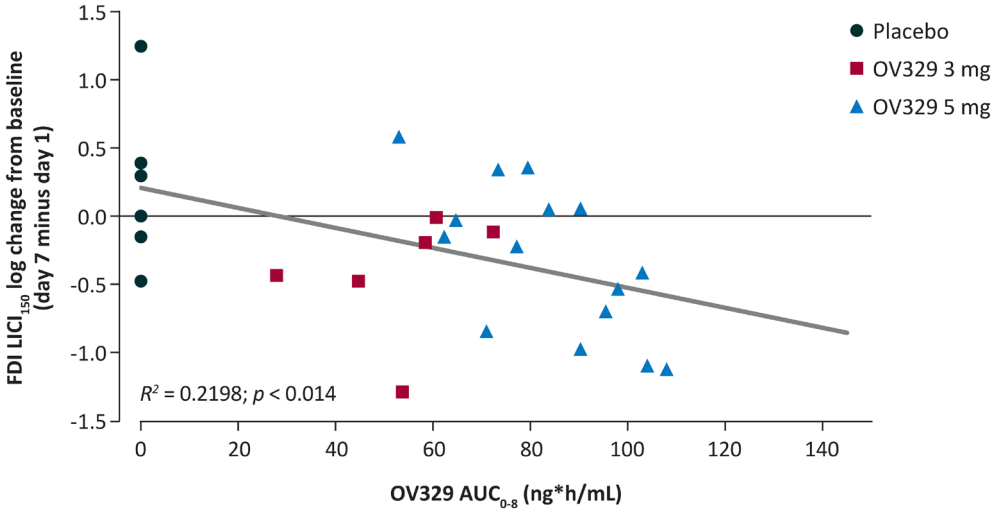
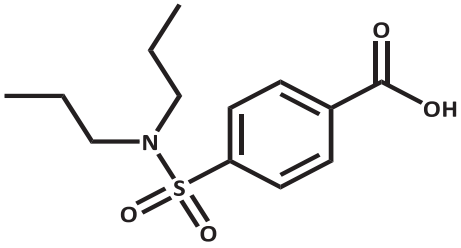



**FIGURE 7** OV329 serum concentration–response relationships in cortical inhibition studies in healthy subjects who underwent transcranial magnetic stimulation (TMS). Recordings we made on the first dorsal interosseous (FDI) muscle. The figure shows the correlation between area under the serum OV329 concentration–time curve from 0 (pre-dose) to 8 h ($AUC_{0\text{-}8}$) and the change in TMS-paired pulse long-interval intracortical inhibition at a 150 ms interpulse interval ($LICI_{150}$, calculated as the ratio of mean motor evoked potential amplitude from a conditioned stimulus to the amplitude of an unconditioned [test] stimulus, specifically using an interstimulus interval of 150 ms) after 7-day treatment with OV329 (3 or 5 mg/day) or placebo (PBO) compared with baseline (Day 1 prior to treatment) in all participants. Linear regression analysis demonstrated a statistically significant ($p < .014$) negative association between OV329 on Day 7 $AUC_{0\text{-}8}$ values and FDI $LICI_{150}$ in the combined groups. A subset analysis of the OV329 5 mg cohort indicated a particularly strong dose effect ($R^2 = .4553$; $p < .001$).

# 6 | PTI5803

Gilles Huberfeld, Elsa Brillaud, Nathalie Rouach, Luc-André Granier

Panntherapi Pharmaceutics, Nimes, France




**PTI5803 (probenecid)**

## 6.1 | Introduction and rationale for development

Pannexin 1 (PANX1) channels, discovered over 20 years ago,[47] are expressed in the brain and upregulated in epileptic tissues.[48] Ictogenic factors such as extracellular potassium, glutamate, and ATP contribute to elicit PANX1 opening in a high conductance state, resulting in release of ATP, which plays a key role in seizure initiation.[49] PANX1 is upregulated in focal cortical dysplasia (FCD) postoperative tissue, and a correlation has been reported between seizure frequency and PANX1 expression in FCD types I and II.[48] The uricosuric anti-gout compound probenecid, in addition to acting on kidney transporters, is a blocker of PANX1 channels.[50] PTI5803 is a novel microgranular sustained-release formulation of probenecid in development for the treatment of epilepsy related to FCD in children by targeting ictogenesis.

## 6.2 | Pharmacology

### 6.2.1 | Activity profile in animal models of seizures and epilepsy

PANX1 1 blockade by probenecid (250 mg/kg, i.p.) has been shown to protect against seizures induced by systemic injection of PTZ and electrical kindling of the hippocampus in mice.[51] Probenecid, at a 500 µM concentration, also inhibits seizure activity in neocortical slices exposed to 4-aminopyridine.[51] In electrophysiological studies performed on human postoperative FCD tissue, PANX1 blockade induced by using either a selective blocker or probenecid resulted in suppression of seizure-like events without interfering with neuronal background activity.[52] After i.p. administration, probenecid also has been shown to be effective in protecting against temporal lobe seizures in the hippocampal kainate mouse model, with a mean seizure frequency reduction of 87% ± 13% at a dose of 200 mg/kg (Panntherapi Pharmaceutics, data on file).

### 6.2.2 | Other pharmacological properties

In addition to its effect on PANX1, probenecid is a blocker of organic anion transporters OAT1 and OAT3, of the urate transporter URAT1, and of other transporters in the kidney and other organs.[53,54] Probenecid is currently used as an uricosuric agent for the treatment of gout, and has been used to reduce the renal excretion of some antibiotics in order to enhance their effects. Probenecid has also been considered for the treatment of PANX1-related neurological conditions such as pain, multiple sclerosis, Parkinson's disease, and cerebral ischemia.[54]

### 6.2.3 | Mechanism of action

The anti-seizure activity of probenecid is considered to be mediated primarily by blockade of PANX1 channels. The contribution of additional mechanisms of action, including modulation of transporter systems at the blood–brain barrier, cannot be excluded.

## 6.3 | Toxicology

After single-dose oral administration of probenecid, the highest dose not causing any adverse effect, converted into a human equivalent dose (HED), was 73.4 mg/kg in rats and 48.8 mg/kg in mice (Panntherapi Pharmaceutics, data on file). Following chronic administration (13 weeks), the highest dose devoid of adverse effects, expressed as HED, was 64.5 mg/kg in rats and 32.5 mg/kg in mice. Following a 2-year treatment period (oral route) at the same doses, no carcinogenicity was observed in male rats and mice, whereas an increased incidence of hepatocellular adenoma with no increase of carcinoma incidence was observed in female mice. No evidence of genotoxicity and teratogenicity was found.

Probenecid has been marketed for more than 70 years and is approved in adults and children older than the age of 2 years. The recommended maintenance dose varies by indication but generally does not exceed 2 g per day (in divided daily doses) in adults and children 2–14 years of age weighing >50 kg and 40 mg/kg/day for children 2–14 years of age weighing ≤50 kg.[55] The safety profile of the drug in humans is well documented with safe doses up to 4 g/

day.[56] Probenecid is classified by the FDA as Pregnancy Category B, although the limited clinical data available show no evidence of teratogenic effects when the drug was used in pregnancy.[57]

## 6.4 | Pharmacokinetic and metabolic profile

In early studies conducted with the marketed formulation, orally administered probenecid has been found to be completely absorbed, achieving systemic exposure (AUC) comparable to that observed with i.v. dosing.[58] At doses of .5 to 2 g, $t_{max}$ ranges between 1–5 h for .5–2 g doses, with inter-individual variability but minimal dose dependence ($t_{max}$ 3.1–3.9 h). Probenecid is about 95% bound to plasma proteins. The volume of distribution (V/F) reported in the literature is on average 11 L, with confirmed CNS penetration.[58] The CSF/unbound plasma concentration ratio is .2–.6 (mean .36)[58] and CSF/total plasma concentration ratio is .071 after 100 mg/kg/day dosing in healthy subjects.[59] Probenecid crosses the intestinal barrier via monocarboxylate transporters (MCTs)/sodium coupled monocarboxylate (uptake) transporters (SMCTs) and MCT-mediated efflux.[58] Probenecid undergoes extensive metabolism, primarily through oxidation of alkyl side chains (~70%) and glucuronidation (20%–30% via UGT1A9). Oxidized non-active metabolites contribute ~10% of circulating parent drug exposure and exhibit lower protein binding and faster clearance. The half-life of probenecid is dose dependent, increasing from 4.2 ± 1.1 h after a .5 g dose to 4.9 ± .8 h after a 1 g dose and 8.5 ± .4 h after a 2 g dose.[60] In studies with radiolabeled drug, 75% to 88% of the dose was recovered in urine as acyl-glucuronide, unchanged probenecid, and four minor metabolites within 24 h.[58] Across oral doses of .5–2 g, cumulative urinary excretion over 4 days ranged from 75%–88%, comprising 5%–11% unchanged drug, 16%–47% acyl-glucuronide, and the remainder distributed across oxidized metabolites. In a study conducted in children with severe TBI ($n = 7$, mean age 8.6 ± 4.9 years) receiving probenecid (25 mg/kg loading dose, followed by 10 mg/kg every 6 h for 4 days) as an adjunct to *N*-acetylcysteine, the pharmacokinetic profile of probenecid was similar to that observed in adults.[61] Steady-state was achieved by 24 h. The drug penetrated the CNS efficiently, with an unbound CSF/unbound plasma concentration ratio of 7.3%–10.2%.

A Phase 1 study to investigate the pharmacokinetics of probenecid after single oral doses of PTI5803 in comparison with the marketed reference formulation (Biokanol) has been completed. Following administration of PTI5803 (1000 mg), the absorption of probenecid was slower, with a median $t_{max}$ of 4.03 h. Compared with the reference formulation, $C_{max}$ was slightly reduced, with a geometric mean ratio (GMR) of .79 (90% CI: .69–.89). In terms of AUC, PTI5803 was equivalent to the reference. CL/F (.90 L/h) and V/F (6.6 L) were also similar to those observed with the reference formulation. After administration of 1 and 2 g doses, PTI5803 demonstrated dose-proportional increases in $C_{max}$, whereas AUC increased slightly above dose proportionality, consistent with saturable elimination. No food effect was detected, with AUC and $t_{max}$ being comparable when PTI5803 was administered in the fasting and the fed states. PTI5803 showed an extended elimination phase, consistent with its sustained release properties and a b.i.d. dosing schedule. Over the period between 0 and 48 h after a PTI5803 dose, the decline in plasma probenecid concentration was characterized by apparent half-lives of 15.4 ± 4.3 h and 17.4 ± 1.7 h (1 g fasted/fed), and 21.3 ± 3.8 h (2 g, fasted). Total plasma hydroxy-probenecid concentrations after administration of PTI5803 were 0%–1% of parent drug plasma levels, with urinary excretion of this metabolite accounting for 8%–10% of the administered dose. For total probenecid glucuronide, the slower absorption of PTI5803 resulted in a delayed rising phase in plasma, but the plasma AUC of this metabolite was comparable to that observed with the reference formulation.

## 6.5 | Drug interactions

Probenecid inhibits OAT1, OAT3, and other transporters and can reduce by this mechanism the renal clearance of drugs that are substrates of these transporters.[55] Examples of major identified interactions include those with baricitinib, glycerol phenylbutyrate, ketorolac, methotrexate, pegloticase, pexidartinib, and sodium phenylbutyrate.[62] Probenecid is also an inhibitor of uridine 5′-diphospho-glucuronosyltransferase (UGT) and decreases by this mechanism the clearance of UGT substrates such as paracetamol, naproxen and lorazepam.[55,63]

Potential interactions between probenecid and ASMs have been little investigated. In animal models of epilepsy, probenecid has been reported to reverse the decrease in cortical extracellular fluid concentration of carbamazepine and phenytoin caused by upregulations of transporters,[64] but the clinical relevance of this observation is unclear. A study in healthy subjects evaluated the effect of probenecid (500 mg, b.i.d., for 10 days) on the pharmacokinetics of a single dose of carbamazepine (200 mg).[65] Probenecid was associated with a small (19%) decrease in carbamazepine AUC and a 33% increase in the AUC of carbamazepine-10,11 epoxide. Panntherapi has conducted a dedicated in vitro assessment of probenecid interactions with ASM transport, using Human Embryonic Kidney (HEK) cells

expressing OAT1 and OAT3 and testing the effect of probenecid on the uptake of carbamazepine, lacosamide, lamotrigine, levetiracetam, perampanel, phenobarbital, phenytoin, primidone, topiramate, valproate, and zonisamide (Panntherapi Pharmaceutics, data on file). No effect was detected at clinically relevant plasma concentrations of these compounds. PTI5803 interactions with current ASMs will be investigated in Panntherapi's Phase 2a trial.

### 6.6 | Efficacy data

Clinical studies of PTI5803 in patients with epilepsy have not been conducted to date.

### 6.7 | Adverse effects

Probenecid has been in clinical use for over 70 years, although it is rarely used today. A retrospective study in 2502 patients taking probenecid doses from 1 to 4 g/day with treatment duration from 1 day to up to 4 years reported TEAEs in 201 cases (7.9% incidence). The most common were gastrointestinal symptoms such as gastrointestinal upset, nausea, and vomiting, which were reported in 78 patients (3.1%) but required discontinuation of treatment in only 8 cases (.3%). Hypersensitivity reactions have also been reported. In some studies, most patients took penicillin in addition to probenecid, which could confound attribution of adverse reactions. Nausea and vomiting are usually associated with plasma probenecid concentration above .3 mg/mL.[56]

### 6.8 | Planned studies

An open-label uncontrolled adjunctive-therapy Phase 2a exploratory study is planned in 15 patients ≥14 years of age with FCD and drug-resistant epilepsy. The design includes a 1-month baseline followed by three consecutive 1-month treatment periods with dose escalation up to 4 g/day. Primary objectives are safety and tolerability, including TEAEs, quality-of-life assessments, and monitoring of plasma levels of concomitant ASMs. Secondary objectives include assessment of probenecid pharmacokinetics based on sparse blood sampling, seizure frequency, and potential biomarkers in blood.

A planned Phase 2b/Phase 3 multicenter (Europe, United States) randomized, double-blind, placebo-controlled adjunctive-therapy trial will enroll children (>2 years of age) with FCD (type I, II, III)–associated drug-resistant epilepsy who are not eligible for surgery or failed to achieve seizure freedom after surgery. After a prospective baseline, patients will be randomized to receive placebo or two doses of PTI5803 for 12 weeks. The primary endpoints will be seizure frequency reduction from baseline and responder rate.

## 7 | SIMUFILAM

Joseph Hulihan and Angelique Bordey
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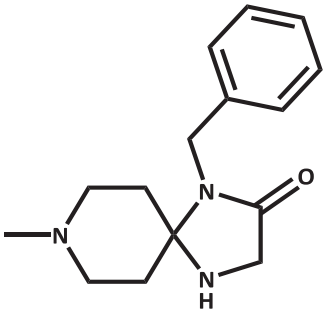


**Simufilam**

### 7.1 | Introduction and rationale for development

Simufilam (formerly PTI-125) is a small molecule that is being developed for the treatment of seizures associated with TSC. A clinical trial is in development to assess safety, pharmacokinetics, and exploratory measures of effectiveness.

Simufilam is believed to act by modulating the activity of filamin A, an actin cross-linking protein present in various tissues including muscle, connective tissue, vascular endothelium, and brain.[66] Abnormalities involving filamin A gene expression have been implicated in several CNS disorders characterized by focal cortical malformations and tumorigenesis in which intractable epilepsy is a frequent manifestation, including TSC and FCD type II.[67,68] An agent that modulates the activity of filamin A, such as simufilam, therefore has therapeutic potential in TSC-associated seizures and possibly other disorders.

### 7.2 | Pharmacology

#### 7.2.1 | Activity profile in animal models of seizures and epilepsy

Simufilam has not been tested to date in standard animal models of seizures, but it has been evaluated in animal models specific to FCD type II and TSC.

In a mouse model of FCD type II, filamin A knockdown partially prevented cytoarchitectural abnormalities and attenuated seizure activity.[67] Simufilam has demonstrated effects similar to filamin A knockdown in this model. When administered i.p. at doses of 6 or 12 mg/kg, b.i.d., from postnatal Days 8 to 28 (corresponding to the neonatal age of humans and completion of dendritic development, respectively), simufilam reduced structural abnormalities in neuronal soma and dendrites. Simufilam 12 mg/kg, b.i.d., also significantly reduced the frequency of seizures when it was initiated either before or after seizure onset.

Subsequent experimental work assessed the impact of simufilam in a *Tsc1* conditional *GFAP* knockout mouse model.[69] Phenotypic features of affected mice include cortical cell enlargement and progressive seizures, with a fatality rate of ~50% by postnatal Day 60. In this experiment, mice were treated b.i.d. with either vehicle or simufilam 5, 10, or 20 mg/kg (free base) i.p. for 33 days beginning at postnatal Day 22, with EEG monitoring performed for the last 20 days (Figure 8A). A heatmap of seizure number per day shows that vehicle- and 5 mg/kg-treated mice displayed a clear increase in seizure frequency over time—with a marked rise during the last 5 days—in contrast to less-marked seizure worsening in mice administered 10 or 20 mg/kg (Figure 8B). Seizure frequency decreased proportionally with both simufilam dose (Figure 8C) and plasma concentration (Figure 8D).

### 7.2.2 | Other pharmacological properties

Based on potential involvement of filamin A in the pathogenesis of Alzheimer's disease, two double-blind Phase 3 trials were conducted to assess the safety and efficacy of simufilam in patients with mild to moderate Alzheimer's disease.[70] The studies failed to reach statistical significance on prespecified efficacy endpoints.

### 7.2.3 | Mechanism of action

Simufilam is believed to act as a filamin A modulator, and the precise molecular basis of target engagement and downstream signaling effects remains under active investigation. Filamin A is a cytoskeletal anchoring protein involved in cell structure and processes.[66] In the CNS, filamin A guides neuronal migration and the resultant functional differentiation of brain regions and, through cross-linking of actin filaments, mediates formation of a three-dimensional scaffold to support the structure of cells and neuronal networks. Filamin A also regulates signaling pathways and receptor trafficking through interactions with its binding partners.

The relevance of simufilam as a potential treatment for seizures associated with TSC and FCD type II stems from the pathophysiology of these conditions. Both TSC and FCD type II are caused by gene mutations affecting the PI3K–AKT–mTOR pathway.[67] TSC is an autosomal dominant disorder caused by mutations in the *TSC1* or *TSC2* genes, which code for the proteins hamartin and tuberin, respectively.[71] These proteins form a heterodimer that, when functioning normally, inhibits the activity of the GTPase, Rheb (ras homolog enriched in brain), a canonical activator of mTOR. Therefore, loss of Rheb inhibition due to *TSC1/TSC2* mutations causes mTOR hyperactivation and the downstream structural and functional CNS manifestations of TSC. In contrast to TSC, FCD type II is a sporadic disorder caused by a range of somatic mutations in the TSC-Rheb-mTOR pathway genes, including mutations affecting mTOR itself.[72]

Filamin A expression is increased in experimental models and resected human cortical tissue in both TSC and FCD type II.[67,73] However, the upregulation of filamin A is not seen in the subset of FCD type II cells that carry mTOR mutations. This finding indicates that the increase in filamin A expression from gain-of-function Rheb is not dependent on an intermediate step involving mTOR activation, that is, the processes of mTOR activation and increased filamin A activity proceed in parallel (Figure 9).[73] Although these observations support a biologically plausible connection between filamin A dysregulation and mTOR pathway–driven cortical malformations, further preclinical studies are required to establish precisely how the modulation of filamin A by simufilam translates into functional effects on neuronal signaling and seizure phenotypes in TSC.

## 7.3 | Toxicology

Simufilam has been evaluated in a robust safety pharmacology and nonclinical toxicology program, including in vitro testing, single-dose toxicity studies and repeat-dose toxicity studies of 26-week duration in rats and 9-month duration in dogs, and carcinogenicity studies in rats and transgenic mice. The data from this battery of studies will be reported pending completion of several ongoing experiments, including a juvenile toxicity study in rats. Genotoxicity studies have also been conducted, including an in vitro bacterial reverse mutation (Ames) assay, an in vitro chromosomal aberration assay, and an in vivo rat micronucleus test. These studies showed no evidence of mutagenic or clastogenic effects.

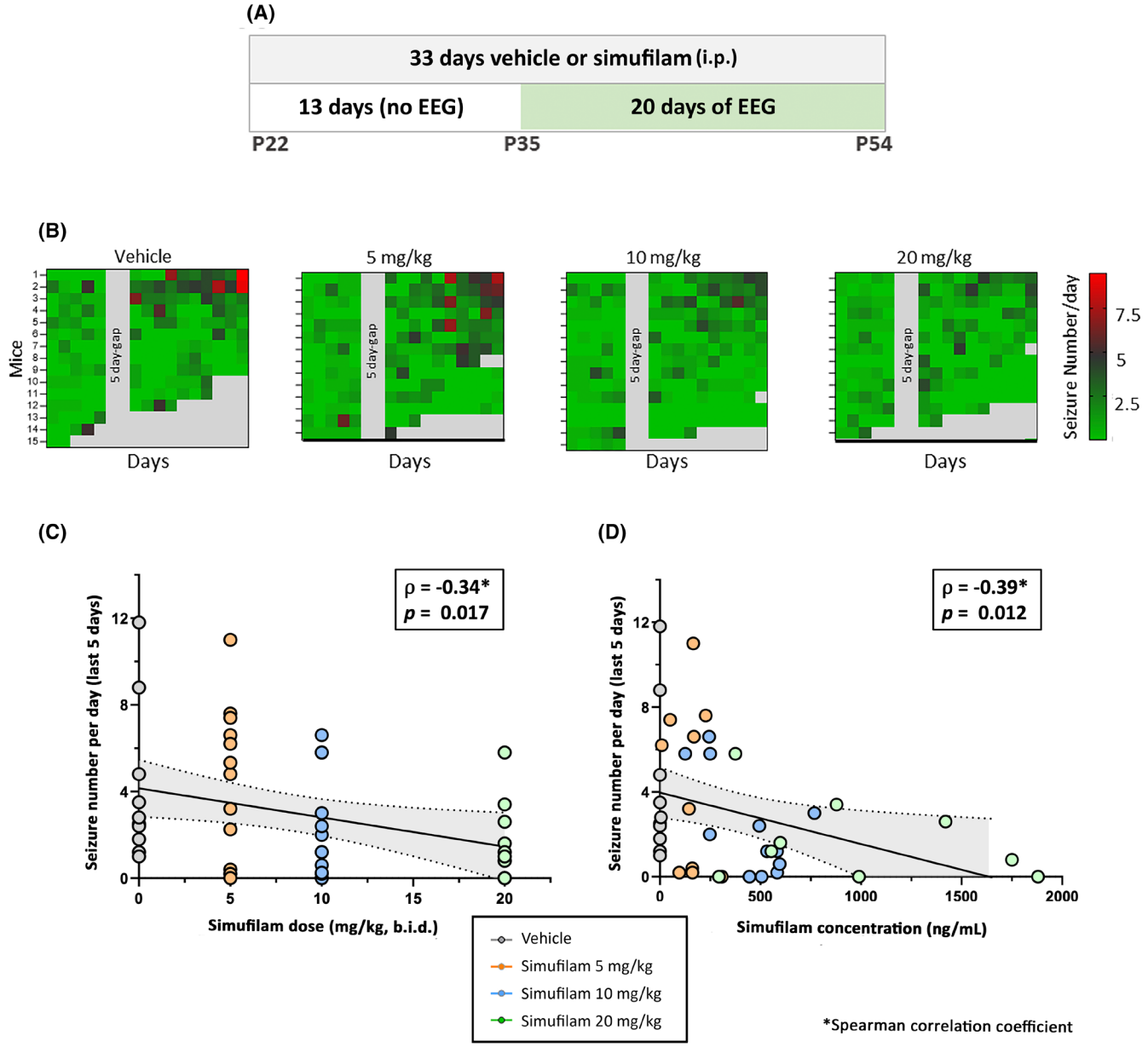


**FIGURE 8** Treatment with simufilam prevents progression of seizure activity in a dose-dependent manner in a Tsc1 conditional knockout mouse model. (A) Experimental design in Tsc1 conditional GFAP knockout mouse model. Simufilam or vehicle was administered b.i.d. beginning on postnatal Day 22 with monitoring of EEG and seizure frequency (seizures/day) for 20 days, beginning on postnatal Day 35. (B) Heatmap of daily seizure number per mouse. (C and D) Plot of the mean number of seizures per day on the last 5 days of monitoring (P50–P54) as a function of simufilam doses (C) and plasma concentrations (D).

## 7.4 | Pharmacokinetic and metabolic profile

The clinical pharmacology profile of simufilam has been characterized in several studies, including a first in human single ascending dose study and biopharmaceutical studies evaluating bioavailability and food effects.

The single ascending dose study was conducted in 24 healthy subjects aged 18–45 years, with three cohorts of eight subjects each, two receiving placebo and six receiving simufilam. Active doses were 50, 100, and 200 mg administered as an oral solution. Simufilam was rapidly absorbed, with a $t_{max}$ of 2.0 h following a 50 mg dose and 1.0 h following 100 or 200 mg doses. Exposure was approximately dose proportional. Following 50, 100, or 200 mg doses, $C_{max}$ was 315, 550, and 1240 ng/mL; $AUC_{last}$ was 2040, 3130, and 8130 h*ng/mL; and half-life was 6.0, 4.4, and 5.9 h, respectively.

A Phase 1 study evaluated the absorption, metabolism, and excretion of [$^{14}$C] simufilam. In addition to the parent compound, seven metabolites were detected with corresponding radioactive peaks after a

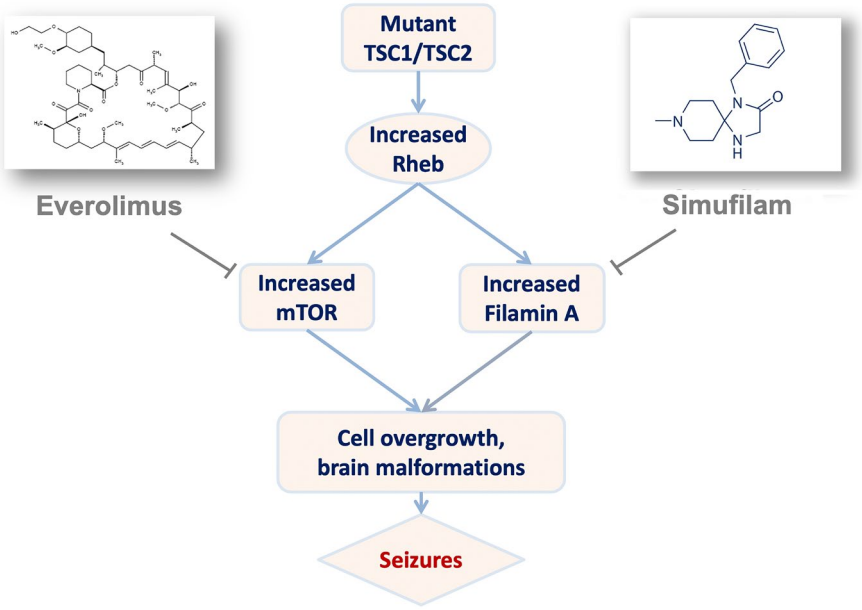


**FIGURE 9** Rheb-dependent pathways involved in the development of brain malformations and seizures in tuberous sclerosis complex (TSC). Disinhibition of Rheb due to mutations in *TSC1* or *TSC2* leads to both mTOR hyperactivation and increased expression of filamin A. The illustration also shows the inhibitory actions of simufilam and everolimus on these pathways.

single oral administration. Unchanged simufilam was the major circulating entity, accounting for a mean 61.8% of $AUC_{0\text{-}12}$ in plasma and was a major radioactive component in urine, accounting for 55.8% of the dose, and a minor drug-related entity in feces. M245/1, an *N*-demethylation product of simufilam, was the most abundant circulating metabolite, accounting for a mean of 9.02% of $AUC_{0\text{-}12}$ in plasma. Other tentatively identified metabolites each accounted for ≤4.89% of $AUC_{0\text{-}12}$. M245/1 was also the most abundant metabolite in urine, accounting for 27.0% of the dose. Other metabolites in urine each accounted for ≤1.64% of the dose. No single metabolite in feces accounted for ≥.8% of the dose. Subsequent in vitro studies showed that CYP2C19 is the primary hepatic microsomal enzyme responsible for the metabolism of simufilam, with CYP2D6 contributing to a lesser extent.

A crossover study was conducted in healthy subjects aged 18–45 years to determine the effect of food on the pharmacokinetics of simufilam. Compared with the fasting state, administration of simufilam with either a low- or high-fat meal resulted in an ~.5–1 h delay in the median $t_{max}$ and a small increase in $C_{max}$. $AUC_{last}$ values fell within bioequivalence limits, indicating a lack of clinically significant effect of food, including a high-fat meal, on simufilam absorption.

Absolute oral bioavailability has been evaluated in preclinical studies and found to be 75% in rats and near 100% in dogs. In rats, the CSF to plasma concentration ratio was .54.

## 7.5 | Drug interactions

In vitro testing has demonstrated no or limited inhibition of simufilam on CYP1A2, CY2B6, CYP2C8, CYP2C9, CYP2C19, and CYP3A4. Simufilam inhibited CYP2D6 in a reversible manner with apparent median inhibitory concentration ($IC_{50}$) values of 451 μM, which is 50 to 100 times the anticipated plasma level at clinically relevant doses. Simufilam showed no induction of CYP1A2, CYP2B6, or CYP3A4.

As mentioned in Section 7.4, CYP2C19 is the primary CYP enzyme involved in simufilam metabolism, with a lesser contribution from CYP2D6. Simufilam does not undergo appreciable UGT-dependent glucuronidation and is a P-gp substrate.

Because of the potential for CYP2C19-mediated interactions with simufilam, subjects taking potent CYP2C19 inhibitors, including fluoxetine and fluconazole, would be excluded from a planned Phase 2 proof-of-concept study. Because of the clinical relevance of several moderate or weak CYP2C19 inhibitors, including cannabidiol, cenobamate, felbamate, and topiramate in the treatment of TSC, concomitant administration with these ASMs would be permitted, with close monitoring for potential adverse effects and dosage adjustments, if necessary.

## 7.6 | Efficacy data

Simufilam has not yet undergone clinical trials in epilepsy.

## 7.7 | Adverse effects

In the Phase 1 single ascending dose study conducted in 24 healthy volunteers at doses of 50, 100, and 200 mg vs placebo, there were no serious TEAEs, and no TEAEs considered related to study drug. Three TEAEs were recorded, two of which occurred in a subject receiving placebo. The third, in a subject who received 100 mg, was lightheadedness upon standing 1 h post-dose; mild orthostatic hypotension had been noted at screening.

In two double-blind Phase 3 trials in Alzheimer's disease, simufilam showed a favorable safety and tolerability profile.[70] In these studies, 773 participants were randomized to simufilam 100 mg, b.i.d., 376 to 50 mg, b.i.d., and 771 to placebo. Double-blind treatment duration was 52 weeks (Study PTI-125-07) or 76 weeks (Study PTI-125-06). No serious drug-related TEAEs were observed. In pooled data from the two trials, TEAEs that occurred in more than 5% of study participants in the simufilam 100 mg, b.i.d, simufilam 50 mg, b.i.d., and placebo groups were coronavirus disease 2019 (COVID-19) infection (9.6%, 13.0%, and 9.9%, respectively), fall (8.0%, 11.4%, and 10.5%, respectively), urinary tract infection (8.2%, 10.9%, and 8.2%, respectively), dizziness (6.1%, 2.9%, and 3.1%, respectively), and diarrhea (3.9%, 5.1%, and 4.0%, respectively). No clinically significant changes in hepatic, hematologic, or metabolic laboratory tests were observed.

## 7.8 | Planned studies

Filana Therapeutics is developing a proof-of-concept study of simufilam in TSC-related seizures. The proposed primary objectives of the study are the assessment of safety, tolerability, and pharmacokinetics. A secondary objective would be assessment of effectiveness in reducing seizure frequency. Additional outcomes being considered are changes in seizure intensity and duration and monitoring of nighttime seizures and sleep parameters. Study details will be finalized pending the outcome of regulatory discussions. The planned study is anticipated to inform pharmacokinetic modeling for dosing of younger patients in future studies, to yield an initial signal of effectiveness to guide design of a Phase 3 trial, and to further the understanding of nocturnal seizures and sleep disturbances in patients with TSC.

# 8 | SN-2000

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## 8.1 | Introduction and rationale for development

SN-2000 is a selective allosteric phosphodiesterase 4B (PDE4B) inhibitor in preclinical development for the treatment of focal seizures in adults. Phosphodiesterase 4 (PDE4) was initially identified as an epilepsy-relevant target using a patented drug-screening platform designed to uncover novel, druggable mechanisms for seizure control.[74] Subsequent studies have corroborated the role of non-selective PDE4 inhibition in reducing seizures and associated neuropathology in acquired epilepsy models.[75] To overcome the dose-limiting tolerability effects associated with non-selective PDE4 inhibitors, SN-2000 was rationally designed to selectively target the PDE4B isoform,[76] since genetic knockdown of this isoform showed the greatest anticonvulsant activity in our preclinical screening and validation pipeline. The chemical scaffold of SN-2000 is structurally distinct from first-generation catalytic-site PDE4 inhibitors (e.g., roflumilast), supporting isoform selectivity and a differentiated pharmacologic profile. With a molecular weight of ~380 g/mol, SN-2000 exhibits physicochemical properties consistent with other CNS-active agents, including moderate lipophilicity and blood–brain barrier penetration.[77,78]

## 8.2 | Pharmacology

### 8.2.1 | Activity profile in animal models of seizures and epilepsy

SN-2000 was evaluated in the rat intra-amygdala kindling model of focal epilepsy. Oral q.d. administration (40 mg/kg) significantly reduced afterdischarge duration and attenuated the kindling-associated reduction in seizure threshold by ~38%, compared to vehicle controls. Reductions in behavioral seizure duration were observed during late-stage kindling, consistent with anti-seizure activity in an established focal epilepsy network.[79] SN-2000 is also active in the *Scn1a*$^{+/-}$ hyperthermia-induced seizure

model. In this model, oral doses protected 75% of animals from febrile seizures, comparable to protection observed with standard doses of valproic acid and clobazam.[78] In the same model, continuous video-EEG monitoring demonstrated a reduction in spontaneous seizure frequency over the 10-day observation period. In zebrafish models of genetic generalized epilepsy (*kcna1a*$^{-/-}$ and *gabra1*$^{-/-}$) and the PTZ model of generalized seizures, SN-2000 reduced seizure-associated hyperlocomotion with efficacy comparable to the established ASMs valproic acid, carbamazepine, lamotrigine, levetiracetam, and clobazam.[79] Single oral doses of SN-2000 (40–80 mg/kg) also conferred 50%–75% protection against generalized tonic–clonic seizures at doses between 40 and 80 mg/kg in the auricular maximal electroshock seizure (MES) test in mice.[79] Together, these findings suggest anti-seizure activity in focal and generalized preclinical seizure and epilepsy models.

### 8.2.2 | Other pharmacological properties

Beyond anti-seizure activity, SN-2000 (40 mg/kg, p.o.) has shown signals of improved cognition in epileptic and WT mouse models and reduced anxiety-like behavior in WT mice; if translatable, these findings suggest potential benefit for patients impacted by cognitive and neuropsychiatric side effects of existing ASMs. In post-ictal aggression assays following auricular MES-induced seizures, SN-2000 (80 mg/kg, p.o.) significantly increased latency to aggressive behaviors compared to valproic acid (250 mg/kg, p.o.), without delaying recovery to baseline mobility, suggesting a potential reduction of post-ictal irritability.[78] In the open-field test, SN-2000 increased time spent in the center zone, consistent with anxiolytic behavior. Cognitive effects were assessed using the Barnes maze, where SN-2000 increased time spent near the target location during probe trials in both WT and *Scn1a*$^{+/-}$ mice. These effects were observed at the lowest dose showing anti-seizure properties (40 mg/kg, p.o.) and are consistent with positive outcomes reported in early-phase clinical trials of non-selective PDE4 inhibitors for depression and cognitive enhancement.[80]

### 8.2.3 | Mechanism of action

SN-2000 is a selective allosteric inhibitor of PDE4B, an intracellular enzyme that regulates cyclic adenosine monophosphate (cAMP) signaling. Ongoing studies are focused on the role of hyperpolarization cation channels (HCNs) in SN-2000's anti-seizure effects. HCNs are enriched in excitatory neurons and can be directly activated by cAMP, leading to excitatory neuronal activation when super-stimulated,[81] as occurs during a seizure event. Accordingly, our mesoscale imaging analyses reveal that SN-2000 reshapes large-cluster cortical activity, particularly within the retrosplenial cortex, in a manner consistent with reduced excitatory tone and enhanced network stabilization across trans-thalamic circuits implicated in both seizure and mood regulation (Figure 10A–D). Moreover, a substantial body of literature shows that increased cAMP acts upstream of core signaling cascades mediating neuronal plasticity and survival,[82] thereby providing a secondary mechanism contributing to pro-cognitive properties. Overall, the results obtained in seizure models coupled with a novel mechanism of action suggest that SN-2000 may provide a promising new treatment for patients in need of seizure control.

The lack of isozyme selectivity of older generation non-selective PDE4 inhibitors is thought to underlie the dose-limiting emesis observed in neurological clinical trials, rendering the development of drugs that target a single PDE4 isoform critical.[82] Allosteric modulation is an emerging strategy to achieve PDE4 isoform selectivity, as demonstrated by the PDE4D allosteric modulator zatolmilast, currently in registrational trials for the treatment of fragile X syndrome and showing improved tolerability in clinical settings.[83] SN-2000 has been rationally designed as an allosteric PDE4B inhibitor and demonstrates >500-fold selectivity for PDE4B over PDE4D.[78]

## 8.3 | Toxicology

Sprague–Dawley rats receiving oral q.d. administration of SN-2000 at 40 mg/kg for 14 days during intra-amygdala kindling showed no overt clinical signs, including weight loss, distress, or sedation. Similarly, in WT C57BL/6 mice dosed up to 60 mg/kg and *Scn1a*$^{+/-}$ mice dosed at 40 mg/kg for 14 days, no treatment-related clinical signs were observed. At 80 mg/kg, WT mice exhibited behavioral changes consistent with mild CNS slowing, suggesting an upper exposure range to inform subsequent formal toxicology studies. Non-GLP genotoxicity, cardiac safety, and additional in vivo studies are currently ongoing.

## 8.4 | Pharmacokinetic and metabolic profile

Preliminary in vitro profiling indicates favorable drug-like properties, including appropriate permeability and brain penetration. An exploratory pharmacokinetic study in mice demonstrated dose-proportional plasma exposure

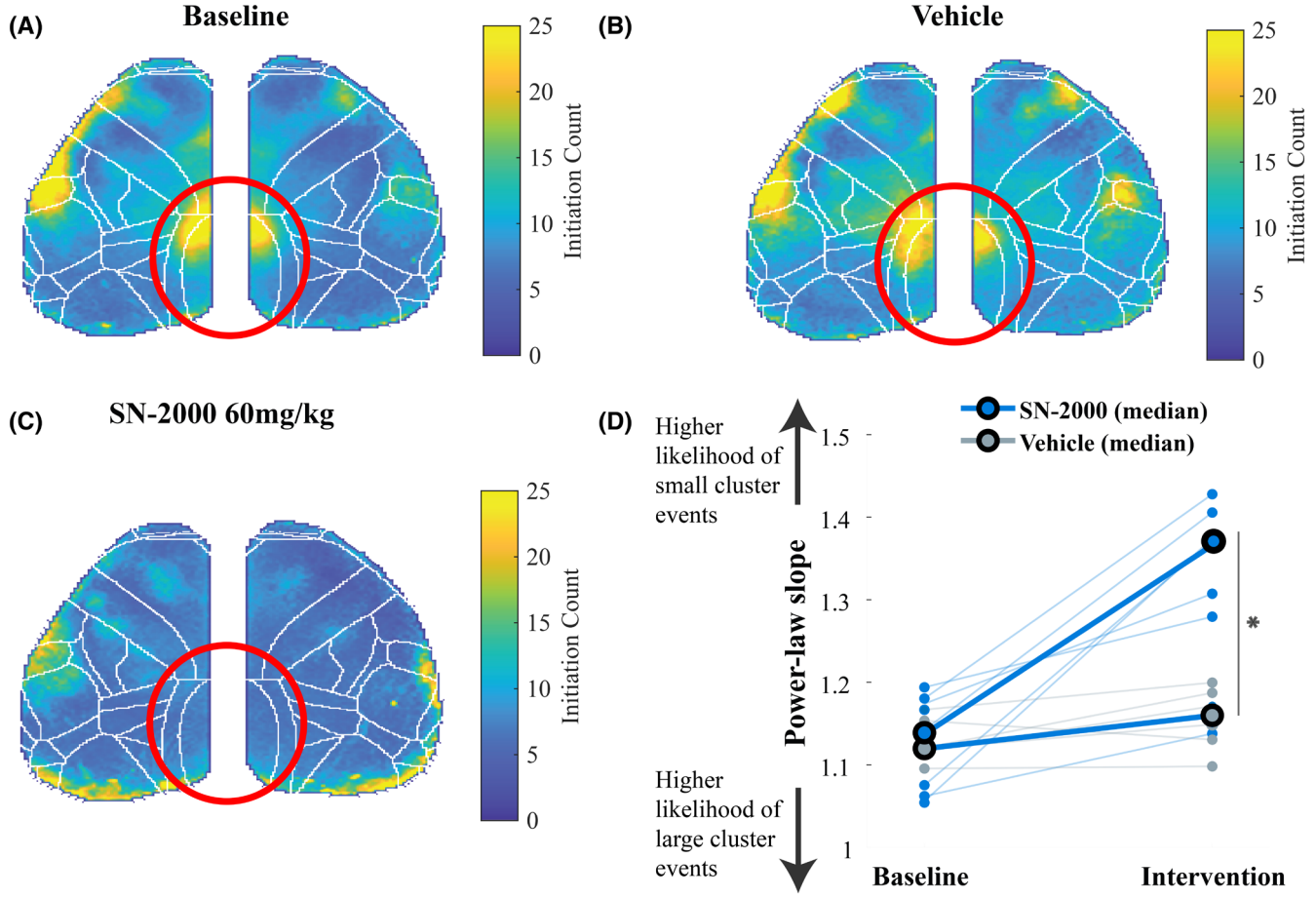


**FIGURE 10** SN-2000 modulates mesoscale network activity across the dorsal cortical surface, including the retrosplenial cortex. (A–C) Mesoscale maps of event incidences across the dorsal surface of the live mouse cortex at baseline, with vehicle, and following a single oral dose of SN-2000 (60 mg/kg). The red box denotes the retrosplenial cortex, a regional relay station between the thalamus and cortex. Baseline and vehicle conditions show a higher prevalence of large-cluster events, whereas SN-2000 reduces event incidence and spatial spread within the retrosplenial cortex and surrounding dorsal cortical regions. (D) Power-law slope analysis shows a treatment-associated steepening from baseline to intervention with SN-2000, consistent with reduced large-cluster dominance and normalization of cortical network excitability, compared with vehicle controls. In this analysis, a predominance of large cluster events increases the likelihood of hyperexcitable network activity.

after oral administration, consistent with potential for q.d. dosing.[79]

### 8.5 | Drug interactions

Drug interaction studies have not been conducted to date.

### 8.6 | Efficacy and adverse effects

Clinical studies with SN-2000 have not been initiated.

### 8.7 | Planned studies

The program will advance through Investigational New Drug (IND)–enabling nonclinical development, including toxicology, safety pharmacology, and Chemical Manufacturing and Control (CMC) activities, conducted in accordance with applicable FDA regulations and guidance to support initiation of first-in-human clinical studies. The initial target indication is adjunctive therapy of focal seizures in adults. Mechanistically, ongoing experiments continue to explore local and broad-spectrum network dynamics of SN-2000 in WT and epileptic models.

## 9 | SODIUM SELENATE

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## 9.1 | Introduction and rationale for development

A key challenge for translational epilepsy research is to develop effective medical or cellular disease-modifying therapies for drug-resistant epilepsy. We have pursued a preclinical development program, and have now commenced a Phase 2 clinical trial, of sodium selenate ($Na_2SeO_4$), an oxidized form of selenium with favorable toxicity characteristics compared with other selenium species.[84] Sodium selenate is being developed as a potential medical disease-modifying therapy for drug-resistant MTLE, the most common form of drug-resistant epilepsy in adults, and more broadly for hyperphosphorylated tau–associated neurodegenerative disorders (e.g., frontotemporal dementia, progressive supranuclear palsy, and TBI).[85] Sodium selenate promotes dephosphorylation of pathological hyperphosphorylated tau in the brain,[84,86,87] for which there is a growing body of evidence supporting a pathogenic role in MTLE.[87–90]

## 9.2 | Pharmacology

### 9.2.1 | Activity profile in animal models of seizures and epilepsy

Our group has generated substantial preclinical evidence that sodium selenate has: (i) anti-seizure effects in acute seizure models (e.g., PTZ-induced seizures and 6 Hz stimulation in mice)[91] and (ii) anti-epileptogenic (disease-modifying) effects in established rodent epilepsy models, including electrical amygdala kindling and acquired epileptogenesis following kainic acid–induced status epilepticus and fluid percussion injury.[86] More recently, we provided proof-of-concept that chronic sodium selenate treatment at 1 mg/kg/day, producing blood levels comparable to those achieved in human trials using 30–45 mg/day,[92] exerts disease-modifying effects in established chronic epilepsy. In the well-validated post–kainic acid status epilepticus rat model of MTLE, treatment produced a sustained reduction in spontaneous seizure frequency, improvements in behavioral and cognitive comorbidities, and favorable changes in molecular biomarkers of tau hyperphosphorylation and cellular senescence (Figure 11).[88]

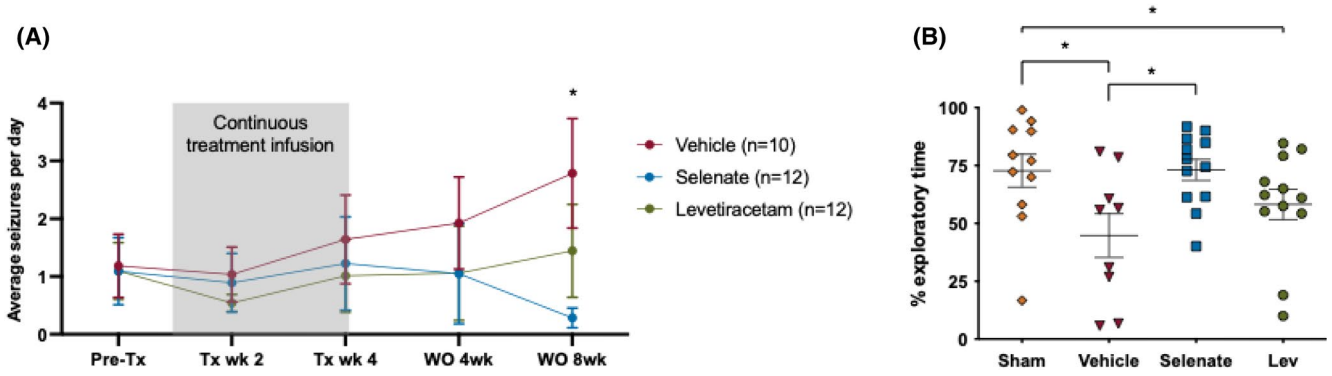


**FIGURE 11** Sodium selenate has disease-modifying effects in chronic epileptic animals. The figure illustrates its effects on established temporal lobe epilepsy using the kainic acid post-status epilepticus model in rats. Ten weeks after status epilepticus, chronically epileptic rats were randomly assigned to receive either sodium selenate (1 mg/kg/day, $n = 12$), levetiracetam (200 mg/kg/day, $n = 12$) or vehicle ($n = 10$) treatments continuously i.p. for 4 weeks via osmotic pumps. To evaluate the effects of the treatments on seizures, continuous video-EEG was acquired for 7 days before, during, and 8 weeks post-treatment. To assess the effect of treatments on cognitive deficits, behavioral tests were also performed at 8 weeks post-treatment. (A) Comparison of average seizures per day before, during, and post-treatment. Following the cessation of treatment, one-way ANOVA showed a treatment effect reducing the number of seizures that the animal experienced [$F(31) = 3.956$, $p < .0001$]. Tukey's post hoc analysis showed that sodium selenate treatment significantly reduced the number of seizures 8 weeks post-treatment in contrast to vehicle-treated animals ($p < .05$). Levetiracetam did not significantly reduce the number of seizures during treatment, indicating drug-resistant temporal lobe epilepsy (*$p < .01$). Data are shown as means and SEM. Tx, treatment; WO, washout; wk, week. (B) Sodium selenate ($n = 12$) reduced memory deficits on the novel object placement (NOP) test compared with both levetiracetam (Lev, $n = 12$) and vehicle ($n = 10$) (*$p < .01$, Kruskal–Wallis tests). Sham animals ($n = 11$) received saline injections instead of kainic acid. Behavioral tests were performed 1 week after the last period of EEG. Data are expressed as % of the total exploratory time that the animals prefer to inspect the novel object. Bars indicate means and SEM. Based on data from Casillas-Espinosa et al.[88]

### 9.2.2 | Mechanism of action

Hyperphosphorylated tau is implicated as a key pathological driver across multiple neurodegenerative diseases, including Alzheimer's disease, frontotemporal dementia, progressive supranuclear palsy, and chronic traumatic encephalopathy. Increasing clinical and preclinical evidence also supports a role for hyperphosphorylated tau in the pathogenesis of chronic MTLE.[87–90] In experimental models, reducing hyperphosphorylated tau can modify epileptogenesis and improve associated neuropsychiatric comorbidities.[86,88,91] A leading strategy to reduce pathological hyperphosphorylated tau is the upregulation of protein phosphatase 2A (PP2A), the principal tau serine/threonine phosphatase in the brain, accounting for >70% of phosphatase activity.

Sodium selenate stimulates the activity of the PP2A/PR55 heterotrimer that consists of the PR55 regulatory B-subunit.[84] This is the PP2A form most directly implicated in tau dephosphorylation in the human brain. Notably, PR55-containing PP2A has been shown to be reduced in brain tissue from people with drug-resistant MTLE[93] and in animal models.[86] Beneficial effects of sodium selenate have also been demonstrated in rodent models of a variety hyperphosphorylated tau–associated neurological conditions, including TBI and MTLE.[84,86,87,91] Of note, sodium selenate appears to be unique among selenium salts in producing these PP2A- and tau-related effects, which are observed in therapeutic contexts only at supranutritional doses (i.e., 15–45 mg/day).[84,87]

## 9.3 | Toxicology

Sodium selenate has shown no toxicity in preparations in vitro (i.e., cultured rat hippocampal slices), even at high concentrations (100 μM).[84] A 13-week GLP toxicity study of sodium selenate and sodium selenite conducted in two species (rats and mice),[94] complemented by multiple non-GLP toxicology studies of sodium selenate and related selenium compounds, demonstrated dose-related toxicity, which in the case of sodium selenate is likely due to accumulation of its major metabolite, selenite.[92] In the GLP study, sodium selenate (0, 3.75, 7.5, 15, 30, or 60 mg/L/day) was administered in drinking water for 13 weeks to groups of 10 male and 10 female F344/N rats and B6C3F1 mice. Estimated daily selenium cation ($Se^{++}$) doses were ~0, .3, .5, .9, 1.6, and 1.2 mg $Se^{++}$/kg in rats, and ~0, .7, 1.2, 2.0, 3.6, and 6.3 mg $Se^{++}$/kg in mice when delivered as sodium selenate. Sodium selenite was also administered via drinking water (0, 2, 4, 8, 16, and 32 mg/L/day). Estimated $Se^{++}$ doses were ~0, .2, .3, .5, .9, and 1.6 mg $Se^{++}$/kg in rats, and ~0, .3, .7, 1.1, 1.9, and 3.5 mg $Se^{++}$/kg in mice. Hematology, clinical chemistry, urinalysis (rats), histopathology, and reproductive outcomes were assessed. All rats in the 60 mg/L/day sodium selenate group died before the end of the experiment. Rats exposed to 15–30 mg/L/day sodium selenate and 16–32 mg/L/day sodium selenite, and mice exposed to 15–60 mg/L/day sodium selenate and 16–32 mg/L/day sodium selenite showed 13%–29% lower final mean body weight compared with controls. Water intake decreased at ≥15 mg/L/day sodium selenate and ≥16 mg/L/day sodium selenite, with additional findings including reduced urine volume and increased erythrocyte counts. Based on mortality, body weight effects, reduced water consumption, and renal papillary lesions, the estimated NOAEL was .4 mg $Se^{++}$/kg/day in rats and .8 mg $Se^{++}$/kg/day in mice.[94]

In epilepsy and TBI chronic rat models, subcutaneous delivery of sodium selenate 1 mg/kg/day (equivalent to .4 mg $Se^{++}$/kg/day) did not produce overt adverse effects or evidence of neurotoxicity.[86,88]

The maximum tolerated dose of sodium selenate determined from a Phase 1 study in humans with prostate cancer treated up to 19 weeks was 20 mg three times daily (t.i.d.).[92]

There is no evidence that sodium selenate is carcinogenic in rats or mice. However, another selenium salt, selenium sulfide, is carcinogenic in both species.[95] Reproductive toxicology data showed that sodium selenate administered at .42 mg $Se^{++}$/kg/day in drinking water did not adversely affect reproduction in mice, whereas sodium selenite at the same dose reduced fertility. In hamsters, oral gavage dosing of sodium selenate (0–20.8 mg/kg) on gestational Day 8 was associated with reduced crown–rump length and an increased proportion of abnormal livers.[96]

## 9.4 | Pharmacokinetic and metabolic profile

Human pharmacokinetics was characterized in a Phase 1 trial in patients with prostate cancer.[92] After oral doses of 5 to 30 mg, sodium selenate was absorbed rapidly from the gastrointestinal tract, with $t_{max}$ values of .7 to 2.2 h, and was eliminated with a half-life of 1.2 to 2.9 h. With multiple administration at doses of 10, 15, 20, and 30 mg, t.i.d., for 3 weeks, plasma exposure did not clearly deviate from linearity, and mean half-life values ranged from 1.7 to 3.1 h. The major selenium metabolite in plasma was selenite, which showed evidence of accumulation in plasma and reached steady-state by 3 weeks. Seleno-methionine, seleno-cyanate, and methyl selenium species were other minor metabolites identified in plasma. During multiple dosing, 16.4% to 37.2% of the daily selenium dose was

recovered in urine during a 24-h period. Selenate ($SeO_4^{++}$) was the major urinary selenium species (9.7%–23.5% of the daily dose). Selenomethionine and methyl selenium derivatives were also prominent metabolites in urine, but their excretion varied substantially between participants.

## 9.5 | Drug interactions

No clinically relevant drug interactions are currently known; however, interactions have not been systematically evaluated, and there are no immediate plans to undertake drug–drug interaction studies.

## 9.6 | Efficacy data

In 2024, the Phase 2 SELECT Trial (Australian New Zealand Clinical Trial Registry Identifier ACTRN12623000446662) was commenced to test the hypothesis that 6 months of sodium selenate produces a sustained disease-modifying effect persisting 6 months after treatment cessation in adults with chronic drug-resistant MTLE.[97] The trial design builds on the standard paradigm for double-blind add-on randomized trials in drug-resistant epilepsy, with an additional 6-month post-treatment follow-up to assess the persistence of effect consistent with disease modification (seizure frequency, drug resistance, and comorbidities) (Figure 12).

The study plans to recruit 124 adults with drug-resistant MTLE, no potentially epileptogenic lesion other than mesial temporal/hippocampal sclerosis on MRI, and ≥2 countable seizures per month during a prospective 2-month baseline period. Outcomes are assessed at baseline, Week 26, and Week 52, including an 8-week seizure diary, 24-h EEG, and cognitive, neuropsychiatric, and quality-of-life measures. Participants are randomized to a proprietary sustained-release sodium selenate formulation (10 mg, t.i.d., increasing to 15 mg, t.i.d., at Week 4 if tolerated) or matching placebo for 26 weeks. The primary outcome is a consumer co-designed Epilepsy–Desirability of Outcome Ranking (Epilepsy-DOOR), integrating changes in seizure frequency, adverse events, quality of life, and ASM burden into a single endpoint compared between arms across the full 52-week period.[98] Secondary analyses compare baseline to Week 26 (anti-seizure effect) and baseline to Week 52 (durable disease modification). Exploratory outcomes include biomarkers of treatment response. The trial is being conducted through the Australian Epilepsy Clinical Trials Network[99] encompassing all 16 major academic adult epilepsy centers in Australia. Epilepsy consumer organizations (Epilepsy Action Australia, the Epilepsy Foundation, and Australian Women with Epilepsy) have contributed to trial design, implementation, and planned translation of outcomes. To our knowledge, this is the first randomized controlled trial of a putative disease-modifying therapy in people with drug-resistant temporal lobe epilepsy. To date, 18 participants have been screened (5 screen failures) and 13 randomized. Of those randomized, four have completed the study, two have completed the treatment phase, two withdrew early due to TEAEs (i.e., exacerbation of depression/suicidal ideation), one withdrew because of unwillingness to continue to travel for study visits, and four remain on treatment. No serious TEAEs have been reported.

## 9.7 | Adverse effects

Our group has completed four Phase 1/1b/2a clinical studies of sodium selenate in non-epilepsy populations (prostate cancer, Alzheimer's disease, and frontotemporal dementia) with chronic oral dosing at 15–60 mg/day.[92,100–103] Across the three Phase 1b/2a trials, sodium selenate has demonstrated safety and tolerability with chronic treatment for up to 2.5 years at doses of 15–45 mg/day in Alzheimer's disease and frontotemporal dementia.[100–103] Furthermore, three ongoing Phase 2 placebo-controlled double-blind randomized controlled trials in frontotemporal dementia,[104] progressive supranuclear

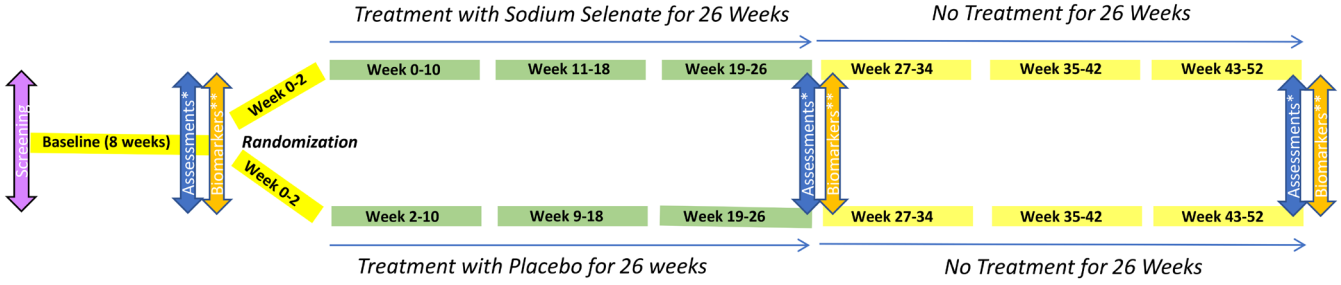


**FIGURE 12** Outline of the trial design for the SELECT Trial (ACTRN12623000446662). Baseline and subsequent assessments include seizure diary; medication burden and adverse effects; neuropsychiatry questionnaires; quality of life questionnaires; neurocognitive measures; and 24-h EEG recordings. Serum biomarkers include serum tau, total tau, and neurofilament light (NfL). Based on Vivash et al.[97]

palsy,[105] and MTLE[97] have not identified significant safety or tolerability concerns to date at the above doses.

In the Phase 1 study in patients with prostate cancer (treatment up to 19 weeks, 19 patients), dose-limiting toxicities (fatigue, diarrhea, intermittent muscle cramps) occurred at 30 mg, t.i.d., and 20 mg, t.i.d., was defined as the maximum tolerated dose.[92] Across doses, the most frequently reported TEAEs at least possibly related to study drug were fatigue, muscle spasms, and alopecia, each occurring in eight patients (42%). Nausea, diarrhea, decreased appetite, and nail disorder were each reported by five patients (27%), followed by dizziness and diarrhea, vomiting, and constipation, each reported by four patients (21%).

Our Phase 2a double-blind placebo-controlled trial in mild–moderate Alzheimer's disease (10 mg, t.i.d., for 6 months, $n = 20$), and an open-label extension study (up to 23 months), demonstrated that sodium selenate was safe and generally well tolerated in chronic dosing.[100,102] In the double-blind trial, treatment-related TEAEs occurred in 16 (80%) of participants assigned to receive sodium selenate 10 mg, t.i.d., vs 11 (55%) of 20 participants assigned to receive placebo or sodium selenate at a nutritional dose (.32 mg, t.i.d.). Common TEAEs in the sodium selenate 10 mg, t.i.d., arm included fatigue (35%), headache (35%), lethargy (30%), nausea (30%), muscle spasms (20%), dizziness (20%), nail disorder (10%), and myalgia (10%), vs 30%, 20%, 20%, 0%, 10%, 15%, 5%, and 0%, respectively, in the placebo/nutritional control group. Most TEAEs were mild; two participants discontinued due to TEAEs—both in the active supra-nutritional group—and no significant laboratory abnormalities were observed.

In an open-label Phase 1b study in patients with frontotemporal dementia (15 mg, t.i.d., for 52 weeks), 12 participants were enrolled and all completed the study with no withdrawals; treatment was well tolerated and 7 participants showed reduced brain atrophy with no cognitive decline.[103] All participants experienced at least one TEAE. The most common were nail changes (58%), alopecia (42%), fatigue (25%), and myalgia (25%). Most events were mild. Five participants down-titrated to 10 mg, t.i.d., due to nail changes and/or alopecia; one further down-titrated to 5 mg, t.i.d. TEAEs resolved following dose reduction.

### 9.8 | Ongoing/planned studies

The SeLECT Trial is designed to provide high-level evidence for the first medical disease-modifying treatment in chronic drug-resistant MTLE.[97] Recruitment is anticipated to complete in December 2029, with last patient last visit in December 2030. If results support a sustained disease-modifying effect, we will plan a larger Phase 3 multicenter multinational trial. In parallel, we are planning a trial of sodium selenate as an anti-epileptogenic and disease-modifying therapy following moderate–severe TBI; funding applications are currently under review.

## 10 | CONCLUSIONS

The data reviewed in this report confirm the continuing interest of industry and academia in developing novel treatments for epilepsy, aimed at ensuring greater safety as well as improved effectiveness for patients with seizures that are resistant to existing medications. The information presented demonstrates a wide variety of development strategies, including a broad array of novel targets as well as a considerable diversity of indications. Some treatments, such as ION283, MSCA-7136, PTI5803, and simufilam, target epilepsies associated with specific etiologies, whereas the other four (AUT00206, OV329, SN-2000, and sodium selenate) aim at improving control of seizures irrespective of the underlying etiology. Of note, some of the treatments reviewed possess mechanisms of action that have the potential to improve not only seizure control but also associated comorbidities and, possibly, affect the trajectory of the disease.[106] Although disease modification has been the Holy Grail of epileptology for a long time, advances in understanding the pathophysiological mechanisms of the epilepsies, coupled with the development of improved animal models, have made achievement of this goal a realistic target for the near future.[107–110] Of interest, one of the treatments discussed in this report, sodium selenate, is being developed specifically as a disease-modifying agent for patients with drug-resistant temporal lobe epilepsy, and is undergoing clinical testing in this indication.[97] When the data reviewed in this report are considered together with those summarized in an accompanying article dedicated to treatments in more advanced development,[2] it is reasonable to predict that these therapeutic advances will lead over the next few years to significantly improved outcomes for many people with severe epilepsies not responding satisfactorily to currently available treatments.

### AUTHOR CONTRIBUTIONS

M.B. was responsible for the conceptualization of the Conference program and progress report structure, in consultation with all other primary authors, and contributed to the review and revision of the manuscript. E.P. drafted the introduction, conclusions, and was primarily responsible for the reviewing/editing of most sections of the manuscript, in consultation with other primary authors, and for liaising with authors of individual summaries. H.S.W.

was primarily responsible for reviewing/editing the pharmacology section of each summary in consultation with other primary authors, and contributed to the review and revision of the manuscript. C.J.L., M.J.K., P.P., T.T., and E.W. contributed to the review, revision, and editing of the entire manuscript. Summary authors were responsible for preparing the initial draft of each summary and for its revision, based on the feedback received from primary authors.

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## CONFLICT OF INTEREST STATEMENT

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*Summary Authors*: *AUT00206:* A.S., M.G., and C.L. are employees and shareholders in Autifony Therapeutics Ltd. E.M. is a consultant and shareholder in Autifony Therapeutics Ltd. A.R. is co-founder of Galibra Neuroscience, PrevEp, and Neuromotion, and has served in advisory boards or received recent research support or consulting fees from A-Synaptic, Autifony, Bionaut Labs, CRE Medical, Modulight, Neuroelectrics, Oak Hill, Ovid, Roche, Takeda, and Travena. None of the other authors has any conflict of interest to disclose. *ION283*: S.N. and B.A.M. have no conflicts of interest to disclose. *MSCA-7136:* All authors have stock options in Mosaica Medicines. B.G., J.S., H.M.B., and D.S. are employees of Mosaica Medicines. *PTI5803:* G.H., E.B., N.R., and L-A.G. are co-founders of Panntherapi Pharma. *OV329*: J.T., J.S., P.K., A.V., and Z.Z. are employees of and may hold stock options in Ovid Therapeutics Inc. A.R. is a co-founder of Galibra Neuroscience, Neuromotion, and PrevEp and has served in advisory boards or received recent research support or consulting fees from A-Synaptic, Autifony, Bionaut Labs, CRE Medical, Modulight, Neuroelectrics, Oak Hill, Ovid, Roche, Takeda, and Tavena. *Simufilam:* J.H. and A.B. are employees of Filana Therapeutics, Inc. *SN-2000*: C.D.K. is an employee and shareholder of Stream Neuroscience, Inc. M.K. is an employee of Stream Neuroscience, Inc. D.M.K.

is a co-founder and shareholder of Stream Neuroscience, Inc. D.M.K. and T.J.H. are the inventors of intellectual property related to SN-2000 and have licensed such intellectual property to Stream Neuroscience, Inc. A.McG., S.R., and G.C.T. declare no competing financial interests. *Sodium selenate:* T.O.B. declares research funding and consultancies from Industry including UCB Pharma, Eisai Pharma, Kinoxis Pharmaceuticals, Jazz Pharma, LivaNova, ES Therapeutics, and Supernus, outside the submitted work. Outside the submitted work, P.M.C.E. has received research funding to his institution from the Commonwealth Scientific and Industrial Research Organisation (CSIRO), Data61, Supernus Pharmaceuticals, Praxis, Eisai, Bright Minds, and Kaoskey. The other authors have no disclosures.

## DATA AVAILABILITY STATEMENT

Information concerning availability of source data may be obtained from the respective authors of each summary.

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