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Article type : Special Report

Progress Report on New Antiepileptic Drugs: A Summary of the Fifteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XV). II. Drugs in More Advanced Clinical Development

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Running title: EILAT XV - Part 2

Key words: Antiepileptic drugs, epilepsy, drug development, anakinra, cenobamate, CVL-865, fenfluramine, ganaxolone

Number of text pages: 27 **(excluding summary, key points, disclosures and references)**

Number of words: **10,196 (excluding summary, key points, disclosures and references)**

Number of words (summary): 98

Number of references: 60

Number of Tables: 2

Number of Figures: 4

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Summary

The Fifteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XV) was held as a fully virtual conference from July 27 to July 30, 2020 for the sessions on drugs, and on August 3, 2020 for the sessions on devices. A total of 534 delegates from 63 countries attended lectures and interactive discussions, representing a broad range of disciplines from basic science, clinical research, and clinical care. This Progress Report provides summaries of recent findings on investigational compounds for which preclinical data as well as data from patient studies were presented. The report includes the following five compounds: anakinra, cenobamate, CVL-865, fenfluramine, and ganaxolone, all with novel modes of action compared to more established antiepileptic drugs. Some of these compounds demonstrated promising results in placebo-controlled Phase III trials, and indeed two have recently received approval from the U.S. Food and Drug Administration (FDA). These include cenobamate, which was approved by the FDA on November 21, 2019 for the treatment of partial-onset (focal) seizures in adults, and fenfluramine oral solution, which was approved by the FDA on June 25, 2020, for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older.

Key Points

- This article summarizes key preclinical and clinical data for five novel medications, including findings obtained in patients with epilepsy.
- The medications discussed (anakinra, cenobamate, CVL-865, fenfluramine and ganaxolone) differ in mechanisms of actions and targeted indications.
- The FDA recently granted approval to cenobamate for the treatment of focal seizures in adults, and to fenfluramine for the treatment of seizures associated with Dravet syndrome in patients aged 2 years and older.

1. INTRODUCTION

The Fifteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XV) was held as a virtual conference from July 27 to July 30, 2020 for sessions on drugs and on August 3, 2020 for sessions on devices. The conference attracted a record number of registered delegates with 534 people from 63 countries attending lectures and interactive discussions, representing stakeholders from a broad range of disciplines from basic science, clinical research, and clinical care.

The core of the conference was the presentation of data on compounds that are under development for the treatment of seizures and epilepsy. The identification and selection of these compounds is explained in an accompanying article, which presents summaries of data on eight compounds in preclinical or early (Phase I) clinical development.[1] The current article provides summary updates on compounds in more advanced clinical development, for which at least preliminary efficacy and safety data from relevant epilepsy patient groups are available. The five compounds include anakinra, cenobamate, CVL-865, fenfluramine, and ganaxolone. On November 21, 2019, the U.S. Food and Drug Administration (FDA) granted approval to cenobamate for the treatment of partial-onset (focal) seizures in adults, and on June 25, 2020, FDA approved fenfluramine oral solution for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older.

2. ANAKINRA

Elaine Wirrell

Child and Adolescent Neurology, Mayo Clinic, Rochester, MN, USA

Molecular structure of anakinra here

2.1 Introduction and rationale for development

Anakinra is a recombinant human interleukin-1 (IL-1) receptor antagonist currently approved for the treatment of rheumatoid arthritis and other inflammatory conditions.[2] As explained in the previous EILAT Progress Report,[3] the rationale for investigating its potential usefulness in the treatment of epilepsy stems from the evidence that neurogenic inflammation can play a pathogenic role in certain syndromes such as febrile-infection-related epilepsy syndrome (FIRES), and that blockade of interleukin-1β (IL-1β) receptors can be of value in inhibiting the inflammatory process in those conditions. In agreement with this hypothesis, findings from a recent study in seven patients suggest that FIRES can be associated with reduced expression of endogenous intracellular

IL-1 receptor antagonist isoforms and with a functional deficiency in IL-1 receptor antagonist activity.[4]

2.2 Pharmacology, pharmacokinetics and drug interactions

An overview of the pharmacologic properties of anakinra relevant to its use as a potential treatment for some forms of epilepsy is provided in the EILAT XIV Progress Report.[3] Pharmacokinetics and drug interactions are also summarized in the same report.[3]

2.3 Update on efficacy and safety

Studies of anakinra in human epilepsy have predominantly focused on FIRES. Case series have documented that between 10-11.7% of cases with FIRES treated with conventional therapies, not including anakinra, die during the acute phase of the illness, either due to intractable status epilepticus (SE) or complications of treatment.[5,6] The majority of survivors are left with varying but often severe degrees of cognitive impairment and medically intractable, multifocal epilepsy. The first case of FIRES treated with anakinra and published in 2016,[7] described a 32-month-old girl with FIRES whose seizures and psychomotor development improved markedly following treatment with anakinra. Since then, 11 additional case reports of the use of anakinra in FIRES have been published either as abstracts or case reports. [8-13] Anakinra was started after variable latency since initial onset of SE (ranging from day 12 to initiation in the chronic phase 1.5 years after initial presentation) at doses of 3-10 mg/kg/day. Five cases became seizure free, five more had a >50% reduction but were not seizure free, and one did not respond. Three cases developed Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) syndrome [8,12], which in one case did not recur during a subsequent cycle of anakinra treatment [8] and presumably was unrelated to the drug. The other two DRESS cases were included in a retrospective international case series described below, and also considered to be unrelated to anakinra even though the presumed causative agents were not mentioned. Careful neuropsychological assessments were not done. Among seven of the reported cases, three showed improvement in neurocognitive function after FIRES [7,11,13], and four were left with deficits of variable degree. [8-11] Few details were provided for the remaining five cases, but neurocognitive outcomes at discharge were reported to 'appear favorable compared to published cohorts' managed without use of anakinra [12].

An international retrospective cohort of 25 children with FIRES treated with anakinra has been submitted for publication (personal communication from Dr. Eyal Muscal). Anakinra was initiated

at a median of 20 days after seizure onset and continued for a median duration of 83 days. The median dose was 5 mg/kg/day. Eighteen children (73%) exhibited a greater than 50% reduction in seizures by one week of anakinra treatment. Anakinra was generally well tolerated. Three children developed DRESS (including the two cases mentioned above), which was considered to be due to other medications, and they all recovered while continuing on anakinra treatment. Two of the 25 children had reversible cytopenias. As for ultimate outcome, three children died (12%) and of the survivors, 35% had no/mild cognitive disability, 35% moderate cognitive disability and 29% severe cognitive disability.

Information on the use of anakinra in other epilepsy syndromes is scarce. In a retrospective report of four children with intractable epilepsy and comorbid specific polysaccharide antibody deficiency, treatment with anakinra was associated with seizure reduction (marked in two children), with subsequent exacerbation after dose reduction or discontinuation.[14] Anakinra was well-tolerated in this small cohort. In one other case report of a 14-year-old girl with intractable generalized epilepsy, increasing school difficulties, and mildly elevated erythrocyte sedimentation rate (ESR) and C-reactive protein with elevated alarmin proteins, anakinra treatment led to an 80% reduction in seizure burden and decreased expression of previously upregulated genes involved in systemic immune activation.[15] She also had profound improvements in her fatigue, general malaise, quality of life, and academic performance, and no documented adverse effects.

3. CENOBAMATE (YKP3089)

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Molecular structure of cenobamate here

3.1 Introduction and rationale for development

Cenobamate is a novel tetrazole alkyl carbamate derivative [(1R)-1-(2-chlorophenyl)-2-(tetrazol-2-yl) ethyl] carbamate] recently approved by the FDA for the treatment of partial-onset (focal) seizures in adults. Cenobamate [(R)-enantiomer)] as well as the (S)-enantiomer and the racemate were studied in preclinical models but only cenobamate was selected for further development as it demonstrated a broader spectrum of anticonvulsant activity.[16]

3.2 Pharmacology

3.2.1 Activity profile in experimental models of seizures and epilepsy

An extensive series of *in vivo* studies were conducted to evaluate cenobamate's antiseizure activity profile. Cenobamate was found to prevent maximal electroshock (MES)-induced seizures in both mice and rats, with ED_{50} values of 9.8 mg/kg, intraperitoneally (i.p.) and 1.9 mg/kg, per os (p.o.), respectively. In mice, clonic seizures induced by subcutaneous (s.c.) administration of pentylenetetrazole (PTZ) and picrotoxin were prevented by cenobamate, with ED_{50} values of 28.5 and 34.5 mg/kg, i.p., respectively. In rats, cenobamate was effective against PTZ-induced clonic seizures and lithium/pilocarpine-induced SE with ED_{50} values of 14 and 7 mg/kg, i.p., respectively. Cenobamate was also effective in two models of focal seizures, i.e., the hippocampal kindled rat (ED_{50} of 16.4 mg/kg, i.p.) and the mouse 6 Hz 22 mA psychomotor seizure model (ED_{50} of 11 mg/kg, i.p.), with little change in potency being observed when the current was increased to 32 or 44 mA (ED_{50} values of 18 and 17 mg/kg, i.p. respectively).[16] Furthermore, cenobamate dose-dependently reduced the number and cumulative duration of spike-and-wave discharges characteristic of absence seizures in the genetic absence epilepsy rat from Strasbourg (GAERS) model.[17]

In rat central nervous system (CNS) safety pharmacology studies, signs of motor impairment, including ataxia, abnormal gait and stance, were only observed at oral doses ≥50 mg/kg (SK Life Science Inc., data on file).

3.2.2 Mechanism of action

Cenobamate is a novel AED with a unique, dual, complementary mechanism of action which integrates enhancement of gamma-aminobutyric acid (GABA)ergic inhibition with sodium channel-mediated excitatory neurotransmission. Cenobamate combines positive allosteric modulation of the $GABA_A$ receptor at a non-benzodiazepine binding site with significant and preferential block of the persistent sodium current and enhancement of the inactivated state of voltage-gated sodium channels.[18,19] Binding to a non-benzodiazepine site of the $GABA_A$ receptor may mediate reduced tolerance, physical dependence and withdrawal effects. This complementary mechanism of action might be a key contributor to the efficacy shown during the placebo-controlled clinical trials. [17]

3.3 Toxicology

Cenobamate administered at doses of 0, 11, 22, or 44 mg/kg/day p.o. to male and female rats prior to and throughout mating and continuing in females to Gestation Day 6 did not result in any adverse effects on fertility, general reproductive performance, or early embryonic development. Administration of cenobamate (0, 5, 15, or 35 mg/kg/day p.o) to Tg.rasH2 mice for ≤ 26 weeks did not result in tumor increase. Doses of 0, 4, 8, or 20 mg/kg/day p.o. to male and female rats for ≤ 87 or 90 weeks, respectively, did not result in an increase in tumors. Cenobamate was negative for genotoxicity in *in vitro* (Ames, mouse lymphoma) and *in vivo* (rat bone marrow micronucleus) assays. In summary, cenobamate did not show a negative effect on fertility, reproduction or embryonic development, nor did cenobamate result in tumor increases.

3.4 Pharmacokinetics and metabolic profile

Cenobamate is absorbed almost completely and is widely distributed in multiple compartments with low intra- and inter-subject variability. Cenobamate area under the plasma concentration-time curve (AUC) increases in a greater-than-proportional manner after single doses ranging from 5 mg to 750 mg, but at steady-state, both AUC and peak plasma concentration (C_{max}) increase proportionally with doses within the therapeutic range (100-400 mg/day)(Arvelle Therapeutics GmbH., data on file). [20] Steady-state plasma concentrations are attained after about two weeks of once daily dosing. Cenobamate is highly soluble in aqueous solutions and is estimated to have a high oral bioavailability, with at least 88% of an oral dose being absorbed. Median time to peak concentration (t_{max}) ranges from 1 to 4 h. The volume of distribution (V/F) after oral administration is ~40-50 L. Plasma protein binding is 60% and independent of plasma concentration *in vitro*.

Cenobamate is extensively metabolized primarily by glucuronidation via uridine 5'-diphospho-glucuronosyltransferase (UGT) UGT2B7 and to a lesser extent by UGT2B4, and by oxidation via cytochrome P450 (CYP) enzymes CYP2E1, CYP2A6, CYP2B6, and to a lesser extent CYP2C19 and CYP3A4/5. [20] Following oral administration of radiolabeled cenobamate, unchanged cenobamate accounted for >98% of the total AUC of radioactivity in plasma. Cenobamate is eliminated extensively in urine (88%), primarily as metabolites; urinary excretion of unchanged cenobamate account for 6.8% of the dose. The terminal half-life of cenobamate is 50-60 h, allowing for once daily dosing.

No clinically relevant differences in cenobamate pharmacokinetics have been observed in relation to age (based on data from individuals aged 18 to 77 years), sex, race/ethnicity, weight/body surface area, or following a high-fat meal. Hepatic impairment increases exposures in mild and moderately

impaired subjects by 1.9 to 2.3-fold, respectively. Renal impairment increases exposures in mild and moderately impaired subjects by 1.4 to 1.5-fold.

3.5 Drug interactions

3.5.1 Effect of concomitant drugs on the pharmacokinetics of cenobamate

Based on results from dedicated drug interaction studies and population pharmacokinetic analyses, changes observed in cenobamate exposures and simulated steady-state plasma concentrations when co-administered with other AEDs were generally below 20%. Cenobamate AUC was reduced 28% by phenytoin and based on population pharmacokinetic analysis, cenobamate AUC was estimated to be increased 24% by clobazam. These findings should not impact cenobamate's initial dosing because cenobamate is titrated slowly to an effective dose. However, when clobazam or phenytoin are added to a regimen containing cenobamate, their impact on cenobamate AUC may be considered (SK Life Science Inc., data on file).[20]

3.5.2 Effect of cenobamate on the pharmacokinetics of concomitant medications

Based on results from dedicated studies and population pharmacokinetics analyses, cenobamate increases the serum concentrations of phenobarbital (AUC +37% for cenobamate 200 mg/day) and phenytoin (AUC +84% for cenobamate 200 mg/day), reduces the serum concentrations of lamotrigine (steady-state concentrations -21 to -52% for cenobamate 100 to 400 mg/day) and carbamazepine (steady-state concentrations -11 to -34% for cenobamate 100 to 400 mg/day), and has no relevant effect on the serum concentrations of levetiracetam, valproic acid, lacosamide or licarbazepine (the active monohydroxy-metabolite of oxcarbazepine). Cenobamate is predicted to increase the plasma exposure to the active metabolite of clobazam, desmethylclobazam, based on cenobamate's ability to induce CYP3A4 and inhibit CYP2C19, enzymes that are involved in the formation and inhibition, respectively, of desmethylclobazam.[20] Serum phenobarbital or phenytoin concentrations should be monitored during titration of cenobamate. Phenytoin dose may need to be reduced by up to 50% and phenobarbital and clobazam doses may also need to be reduced to limit the occurrence of side effects.

Multiple doses of concomitant cenobamate 200 mg once daily decreased the AUC of the CYP2B6 substrate bupropion by 39% and decreased the AUC of the CYP3A substrate midazolam by 72%. Multiple doses of concomitant cenobamate 200 mg once daily increased the AUC of the CYP2C19 substrate omeprazole by 107%.[20] Co-administration of low-dose cenobamate (100 mg/day for 14

days) with an oral contraceptive did not affect the pharmacokinetics of ethinylestradiol; however, exposure to norethindrone was increased (37% for $AUC_{0-\tau}$). The effectiveness of oral contraceptives is reduced by CYP3A4 inducers, and because cenobamate is an inducer of CYP3A4, women of reproductive potential taking oral contraceptives should use additional or alternative non-hormonal birth control if treated with on cenobamate. [20,21]

3.6 Efficacy data

3.6.1 Randomized double-blind trials

Two double-blind, placebo-controlled trials (C013; NCT01397968 and C017; NCT01866111) evaluated the efficacy of adjunctive cenobamate given once daily in adults with uncontrolled focal seizures. [22,23] During an 8-week baseline period, patients were required to have at least 3 or 4 focal seizures per 28 days and be stable on 1-3 AEDs. Patients had a mean duration of epilepsy of approximately 22 years and median baseline seizure frequency of 8.5 seizures per 28 days. Both studies had an 8-week baseline period, and a 6-week titration period. Study C017 had a fixed-dose maintenance period of 12 weeks, while study C013 had a fixed-dose maintenance period of 6 weeks.

The C017 study randomly assigned 437 patients to placebo (n =108) or cenobamate 100 mg/day (n = 108), 200 mg/day (n = 110), or 400 mg/day (n =111).[23] Responder rates (percentage of patients with ≥ 50% reduction in seizure frequency from baseline) during the maintenance phase were significantly higher for cenobamate 100 mg/day (40%, P = 0.0365), 200 mg/day (56%, P < 0.0001) and 400 mg/day (64%, P < 0.0001) than placebo (25%). Utilizing more stringent responder definitions (≥ 75%, ≥ 90%, and 100% reduction in seizure frequency), patients treated with cenobamate consistently showed greater responder rates compared to those on placebo, with patients on higher doses showing the greatest response (Figure 1). Seizure freedom rates (100% seizure reduction) were 4% (NS), 11% (P = 0.002) and 21% (P < 0.0001) for the 100, 200, and 400 mg/day dose groups, respectively, compared to 1.0% for placebo. Median percentage reduction in seizure frequency during the maintenance phase was 25% for the placebo group, 40% for cenobamate 100 mg/day (P = 0.0365), 56% for cenobamate 200 mg/day (P < 0.0001), and 64% for cenobamate 400 mg/day (P < 0.0001).[23] Cenobamate showed statistically significant reductions in seizure frequency across all types of seizures (focal aware motor, focal impaired awareness, focal to bilateral tonic-clonic) at doses of 200 and 400 mg/day, achieving statistical significance for seizure freedom rates (versus placebo) for focal impaired awareness at the dose of 400 mg/day and for focal to bilateral tonic-clonic seizures at doses of 200 and 400 mg/day.

Additionally, a post-hoc analysis of study C017 in which patients were stratified by disease severity, showed that responder rates (patients with ≥ 50% or 100% seizure reductions) for cenobamate in each dose group were higher compared with placebo, regardless of baseline seizure frequency or disease duration. Similar trends were observed for responder rates in patients taking one, two or more than two concomitant AEDs at baseline. [24]

In study C013, patients were randomly assigned to placebo (n = 109) or cenobamate 200 mg/day (n = 113). [22] The responder rate in the maintenance phase was significantly higher for cenobamate versus placebo (62% vs 33%; P < 0.0001). The seizure freedom rate was also significantly higher for cenobamate 200 mg/day compared with placebo (28% versus 9%; P = 0.0003). Patients receiving cenobamate in study C013 also experienced a greater median percent reduction in seizure frequency than those receiving placebo (56% versus 22%; P < 0.0001). Median percent reductions in seizure frequency by seizure type, during the maintenance phase, were significantly higher for cenobamate compared with placebo across all types of seizures (92% versus 47%, P = 0.0086, for focal aware motor; 62% versus 28%, P = 0.0012, for focal impaired awareness; 100% versus 53%, P = 0.0227, for focal to bilateral tonic-clonic) (Arvelle Therapeutics GmbH., data on file).

Figure 1 here

3.7 Open label extension studies

Of the 360 patients who completed the maintenance period of the double-blind phase of study C017, 98.3% entered an open-label extension study. The target dose was 300 mg/day and investigators were able to adjust the dose as needed (up to a maximum of 400 mg/day) to achieve optimal efficacy and limit tolerability issues. The protocol allowed investigators to adjust comedication as needed. As of April 2018, 63.9% of patients (227/355) were continuing in the open label extension (Figure 2). The primary reasons for discontinuation were lack of efficacy (15.5%), followed by treatment emergent adverse events (TEAEs) (6.8%) and withdrawal by patient's decision (6.5%). The most frequently reported TEAEs (occurring at a frequency ≥0.5%) leading to discontinuation were dizziness (0.8%) and somnolence (0.6%). The median duration of cenobamate exposure was 40.1 months (1.1-54.4 months), with 80% of patients remaining in the study after 1 year, and 70% remaining after 2 years.[26] 149 patients entered the open-label extension phase of study C013. As of April 2018, 86 patients (57.7%) remained in the open-label extension with a median duration of exposure of 60.6 months (0.3-79.4 months). [27]

Seizure outcome data was collected in the open-label extension of study C017. Median percent reduction in seizure frequency (from initial baseline) during the first 6 months of the open-label

extension for all patients treated with cenobamate was 65.4% and was similar among patients originally treated with cenobamate during the double-blind study. Seizure outcomes have been analyzed in 6-month intervals for the first 3 years of study participation, and showed 63.6%, 68.3%, 71.2%, 73.1% and 74.9% seizure reduction for each of the intervals. Seizure freedom rate during the last interval (25-30 month) was 20.2%. These data are consistent with the results of the double-blind placebo-controlled trials. [26]

Figure 2 here

3.8 Tolerability and adverse effect profile

Cenobamate is generally well tolerated with a consistent safety profile. Most frequent treatment-emergent adverse events (TEAEs) reported during the two placebo-controlled clinical trials (C013, C017) were mild to moderate in intensity, CNS-related and increased in a dose-dependent manner. The most frequently occurring TEAEs across both trials (≥ 10%) were dizziness, somnolence, headache, fatigue and diplopia. Among the most common TEAEs in the double-blind phase of study C017, somnolence occurred in 37% of patients in the 400 mg/day group versus 21% in the 200 mg/day group, 19% in the 100 mg/day group and 8% in the placebo group, whereas dizziness was reported in 33% of patients in the 400 mg/day group versus 20% in the 200 mg/day group, 18% in the 100 mg/day group and 14% in the placebo group.[23] In both trials, there were no clinically meaningful changes from baseline in hematology, clinical chemistry or laboratory values. [22,23]

During early clinical development, among the first 953 adults exposed to cenobamate, three confirmed cases of DRESS (two in healthy volunteers and one in a patient with epilepsy) occurred when cenobamate was initiated at a high starting dose and/or titrated weekly or faster.[28] In one of the healthy volunteers affected, cenobamate was started at 200 mg/day and titrated by 100 mg/day every 5-7 days, while in the other volunteer the compound was initiated at 50 mg/day and titrated by 50 mg/day weekly. In the patient with epilepsy who developed DRESS, cenobamate was initiated at 100 mg/day and titrated by 100 mg/day weekly. After these findings,, a slower titration rate was used in an ongoing multicenter, open-label study (C021) which enrolled adult epilepsy patients with uncontrolled focal seizures taking stable doses of 1-3 AEDs.[28] Increasing daily doses of cenobamate were administered (12.5, 25, 50, 100, 150, and 200 mg/day) at 2-week intervals. Further increases to a maximum dose of 400 mg/day, by 50-mg/day increments every other week, were allowed. All hypersensitivity reactions were reviewed monthly to screen for DRESS. As of April, 2018, 1339 patients received at least one dose of cenobamate, 82.9% of patients (n = 1110) were exposed to cenobamate for ≥ 6 months and 80% of patients (n = 1078) were still ongoing. No

new cases of DRESS were reported. Reducing the starting dose and slowing the titration rate of cenobamate to 2-week intervals might mitigate the risk of DRESS in patients with epilepsy receiving cenobamate. Of note, the above titration plan is approved by the FDA and is included in the US prescribing information.[20] The most frequent TEAEs (incidence ≥ 10%) were somnolence (28.1%), dizziness (23.6%), fatigue (16.6%) and headache (11.4%).

In addition to the C021 study, an open label extension of the double-blinded trials C013 and C017 is ongoing, as detailed in the section above. The most frequent TEAEs (≥ 10%) in the C017 open label extension were dizziness (32.7%), somnolence (23.9%), fatigue (14.9%), diplopia (13.8%), headache (11.8%) and gait disturbances (11%).[26] Most frequent TEAEs (≥ 10%) during the C013 open label extension were dizziness (32.2%), headache (26.2%), somnolence (20.8%), viral upper respiratory tract infection (17.4%), upper respiratory tract infection (13.4%), nausea (10.7%), fatigue (10.7%) and urinary tract infection (10.1%).[27] In both extension studies, most TEAEs were mild or moderate.

3.9 Planned studies

Cenobamate is being further studied in an ongoing randomized, double-blind, placebo-controlled trial evaluating its safety and efficacy as adjunctive therapy in patients with idiopathic generalized epilepsy and generalized tonic-clonic seizures (NCT03678753).

4. CVL-865

Rachel Gurrell

Cerevel Therapeutics, LLC, Boston, MA, USA

. *Molecular structure of CVL-865 here*

4.1 Introduction and rationale for development

Benzodiazepines (BZDs), non-selective positive allosteric modulators (PAMs) of $GABA_A$ receptors, are highly efficacious across a range of therapeutic indications, including epilepsy. However, even at low receptor occupancy, they are associated with significant side effects such as somnolence, and they are liable to abuse and to the development of efficacy tolerance, all of which often limit their clinical utility. As many of these undesirable properties are mediated by the α1 subunit-containing $GABA_A$ receptors,[29] there has been a concerted effort to develop α2/3/5 subtype selective PAMs for epilepsy and other CNS disorders.

CVL-865 (formerly PF-06372865), which is structurally unrelated to benzodiazepines, was designed to selectively enhance the inhibitory effect of GABA at α2/3/5 subunit-containing $GABA_A$ receptors and is expected to suppress aberrant overexcitation that underlies epileptic activity. As there is minimal impact via the α1 subunit, high receptor occupancy may be achieved with CVL-865, potentially without the emergence of dose-limiting side effects. To our knowledge, CVL-865 is the first α2/3/5-subtype selective $GABA_A$ PAM to be examined in a clinical trial in patients with drug-resistant focal seizures.

4.2 Pharmacology

4.2.1 Activity profile in experimental models of seizures and epilepsy

CVL-865 has demonstrated activity in widely used and translationally relevant preclinical models of epilepsy. For example, amygdala kindling is a well-characterized model which has been shown to be predictive of efficacy in focal and focal to bilateral tonic-clonic seizures in the clinical setting.[30] When tested at 3 mg/kg and 10 mg/kg p.o., CVL-865 displayed potent activity in fully kindled rats, providing protection against convulsive seizures and significantly reducing seizure severity.[31]

In the GAERS model, CVL-865 (0.3, 1, 3, 10 mg/kg p.o.) demonstrated robust dose-dependent efficacy, reducing the expression of spike and wave discharges, including full suppression at the highest doses by 30 minutes after administration.

To date, CVL-865 has not been assessed in the MES seizure model. However, doses of 0.3, 3, and 10 mg/kg (p.o.) were effective in increasing seizure latency in the s.c. PTZ test in mice.[31]

Overall, these data suggest that CVL-865 may have broad-spectrum utility across different types of epilepsy.

4.2.2 Other pharmacological properties

Mechanistic studies using α1-preferring ligands such as zolpidem in humans, primates and rodents, and genetic studies in mice all indicate that α1-containing receptors mediate motor coordination, balance and sedation.[32] Models such as rotarod or beam walking have been used to estimate these effects, although humans appear to be particularly sensitive to α1-mediated effects, which are apparent at low levels of receptor occupancy (< 10%). In a drug discrimination study, rats were trained using an operant food-maintained task to discriminate between the presence and absence of

zolpidem (a $GABA_A$ α1-selective PAM). Drugs eliciting 80% or greater responding on the drug-trained lever are classified as producing full generalization to the training compound.[33] CVL-865 (10 mg/kg p.o.) did not cause generalization to the sedative zolpidem, even at full (~100%) receptor occupancy, confirming the minimal α1 activity observed *in vitro*.

In the rotarod test in mice, CVL-865 did not impair motor performance at doses (10 mg/kg, p.o.) that exert antiseizure activity in preclinical models of epilepsy.[34]

In addition to the demonstration of efficacy in preclinical models of epilepsy, CVL-865 was also profiled in preclinical models of pain and anxiety.[3] In a chronic constriction injury model of neuropathic pain in rats, CVL-865 demonstrated analgesic efficacy at doses of 3 and 10 mg/kg p.o. In a mouse elevated plus maze mouse model of anxiety, anxiolytic activity was observed at doses of 3.2 and 10 mg/kg p.o.

4.2.3 Mechanism of action

The majority of $GABA_A$ receptors present in the CNS contain two α, two β and a single γ subunit, and those that contain an α1, α2, α3 or α5 subunit in conjunction with a γ2 subunit are sensitive to BZDs.[29] Sophisticated molecular studies in which $GABA_A$ receptors containing specific α subunits have been rendered unresponsive to diazepam have elucidated the contribution of those subunits to different aspects of the *in vivo* pharmacology of BZDs. These studies, together with the use of subtype-selective tool compounds have attributed the sedative effects of BZD to α1 subunits, anticonvulsant activity to α1/2 subunits, anxiolysis to α2/3 subunits and analgesia to α2/3/5 subunits.[31,32] As such, there has been a rigorous effort to develop subtype-selective PAMs for epilepsy and other CNS disorders.

The affinity of CVL-865 for the BZD site of $GABA_A$ receptors was determined in competition-binding experiments, versus [3H]-flumazenil (receptors containing α1/2/3/5 subunits) or [3H] Ro15-4513 (receptors containing α4/6 subunits), in membranes from recombinant cell lines expressing $GABA_A$ receptors containing specific α subunits. CVL-865 was determined to be a high-affinity ligand at $GABA_A$ receptors containing an α1, α2, α3 or α5 subunit but had no affinity for $GABA_A$ receptors containing α4 or 6 subunits, which is typical of BZD site ligands. The functional activity of CVL-865 was determined in electrophysiological experiments in the same recombinant cell lines. CVL-865 exhibits functional selectivity for those receptors containing α2/3/5 subunits, with significant positive allosteric modulation (90-140%) but negligible activity (≤ 20%) at $GABA_A$ receptors containing α1 subunits.[32]

The ability to achieve high receptor occupancy with a subtype-selective PAM such as CVL-865 is believed to be an important component of attaining efficacy. Non-selective BZDs are not full

agonists at the BZD site of $GABA_A$ receptors but are highly effective PAMs with high intrinsic activity, which presumably enables efficacy to be observed in epilepsy with low (< 20%) receptor occupancy.[35] There is preclinical evidence in models of anxiety and epilepsy that PAMs with lower intrinsic activity at the BZD binding site such as CVL-865 need to occupy a greater proportion of the receptors to produce the same magnitude of pharmacological activity as a BZD.[35] In addition, agents like CVL-865 with lower intrinsic activity could be associated with a reduced potential for tolerance induction, as previously demonstrated for other subtype-selective PAMs in animal models.[36] Efficacy in preclinical epilepsy models and in the clinical photosensitive epilepsy model supports the hypothesis that antiseizure activity can be attained with CVL-865, presumably by achieving high receptor occupancy at α2-containing subunits.

4.3 Toxicology

CVL-865 has been evaluated in several safety pharmacology studies, genotoxicity studies, embryofetal developmental toxicity studies in rats and rabbits, and an *in vivo* phototoxicity study. Multiple-dose toxicology studies have been conducted in rats and dogs up to 13 weeks. The results of these studies enabled the clinical development program. Chronic toxicology studies in rats and dogs as well as male and female fertility studies in rats are ongoing. The preclinical package is designed to support long term clinical studies at a dose of 25 mg b.i.d.

4.4 Pharmacokinetics and pharmacokinetic/pharmacodynamic (PK/PD) correlations

A total of 45 healthy subjects completed a single ascending dose pharmacokinetic/pharmacodynamic (PK/PD) study which included 4 cohorts.[32] There were 10 subjects in each of the first 3 cohorts (8 on treatment) and 15 subjects in cohort 4. CVL-865 was absorbed rapidly following single doses of 0.04 to 100 mg administered orally as a suspension with median t_{max} of 1 to 4 h. The mean CL/F ranged from 17.35 to 26.86 L/h, and the mean V/F ranged from 194.7 to 260 L across all doses.

The early clinical program was designed to characterize the pharmacology of CVL-865 and utilized a battery of pharmacodynamic endpoints (NeuroCart) in order to understand the contributions of the different $GABA_A$ receptor subtypes.[32] For example, saccadic peak velocity (SPV) was included as a measure of desired α2/3 pharmacology, and postural instability (as measured by body sway) as a marker of undesired α1 pharmacology, with the hypothesis being that CVL-865 effects on SPV would be greater than those observed with lorazepam, and the effects on body sway would be less

with CVL-865 than with lorazepam. As such, NeuroCart was employed in each cohort of the single ascending dose study, with the fourth cohort being a crossover explicitly designed to make comparisons between single doses of 15 mg and 65 mg CVL-865 with placebo and 2 mg lorazepam. In summary, the reduction in SPV caused by 15 mg CVL-865 was approximately twice that caused by 2 mg lorazepam, probably due to high levels of α2 receptor occupancy achieved by CVL-865 compared to lorazepam. In the body sway endpoint (assessing postural instability) there were small, but significant, increases at sub-milligram doses of CVL-865, which plateaued at 10 mg and did not significantly increase up to 100 mg despite marked increases in receptor occupancy across this dose range. The overall effect size was less than that caused by a 2 mg dose of lorazepam (which is predicted to result in approximately 11% receptor occupancy), indicating that CVL-865 has considerably less impairing effect on balance than a non-selective BZD.

In a multiple 21-day ascending dose study, two cohorts of up to 10 subjects (7-8 CVL-865 tablets, 2 placebo) were titrated up in the first 7 days and then the dose was maintained for the following 14 days.[37] In cohort 1, subjects received 5 mg b.id. for 3 days, 12.5 mg b.i.d. for 4 days and 25 mg b.i.d. for 14 days. In cohort 2, subjects received 5 mg b.i.d. for 2 days, 12.5 mg b.i.d. for 2 days, 25 mg b.i.d for 3 days and 42.5 mg b.i.d. for 14 days. Of the 19 subjects enrolled, 18 completed treatment and one subject was withdrawn due to a lack of compliance with the study protocol. CVL-865 was rapidly absorbed with a median t_{max} of 1 to 2 h following both single-and multiple-dose administration. Mean half-life values on Day 21 were 11.2 h (25 mg b.i.d.) and 11.5 h (42.5 mg b.i.d.).

4.5 Receptor occupancy

A positron emission tomography (PET) study was conducted in humans using a [^{11}C]-flumazenil ligand to evaluate occupancy at $GABA_A$ receptors after single oral doses of 10 and 65 mg CVL-865.[32] Modeling of the PET data confirmed high levels of total receptor occupancy in the whole brain at the time of the first post-dose PET scan (nominal time post-dose 1.5 h), of 68.6% and 88.9% at 10 mg and 65 mg, respectively.

4.6 Drug interactions

CVL-865 is primarily metabolized by CYP3A4 based on human *in vitro* studies and no active metabolites have been identified. The potential for drug interactions with co-administered enzyme inducers and inhibitors will be evaluated.

4.7 Efficacy data

The potential antiseizure activity of CVL-865 was evaluated clinically in the photosensitive epilepsy model.[38] A total of seven patients with photosensitive epilepsy received single oral doses of 17.5 mg and 52.5 mg CVL-865, 2 mg lorazepam as an active control and placebo, with each patient receiving all treatments in a random order with a one to three week washout between doses. The 52.5 mg dose of CVL-865 was selected based on the expectation that it would achieve maximal receptor occupancy of approximately 80%, with the lower 17.5 mg dose of CVL-865 being expected to achieve approximately 60% receptor occupancy.

Both doses of CVL-865 produced a marked and statistically significant reduction in the standardized photosensitivity range compared to placebo, which was similar in degree to lorazepam (Figure 3). There was complete suppression of standardized photosensitivity range in 6/7 participants following CVL-865 or lorazepam administration. This is the first demonstration of antiseizure activity of a α2/3/5-subtype selective $GABA_A$ PAM in humans.

Figure 3 here

4.8 Tolerability and adverse effect profile

Across 6 Phase I trials, a total of 81 healthy subjects received single doses and 55 healthy subjects received multiple doses of CVL-865 for up to 21 days. CVL-865 was assessed to be safe and well tolerated with no clinically significant safety observations in this population. The most common TEAEs following CVL-865 were dizziness, somnolence, fatigue, and bradyphrenia. All TEAEs were mild or moderate in severity. There were no drug-related study withdrawals and no treatment-related serious TEAEs reported across the Phase I trials.

In 2 Phase II trials, a total of 146 subjects (74 with chronic low back pain and 72 with generalized anxiety disorder) received multiple doses of up to 7.5 mg b.i.d. of CVL-865 for up to 4 weeks. Additionally, 7 patients with photosensitive epilepsy were enrolled in the single dose Phase II trial reported above. No clinically significant safety findings emerged across the Phase II trials. The most frequently reported TEAEs following CVL-865 treatment were dizziness and somnolence and most were mild or moderate. Use of titration in the multiple dose studies appeared to decrease the

incidence of CNS TEAEs. Four subjects, all in the CVL-865 groups, discontinued treatment due to TEAEs, three of which were assessed not to be treatment-related. One subject experienced a serious TEAE (transient ischemic attack) that was determined by the investigator to be related to CVL-865; this subject had a history of multiple cardiovascular risk factors and was subsequently diagnosed with Type 2 diabetes mellitus.

4.9 Planned studies

The robust efficacy observed in the photosensitivity model with CVL-865 justify further clinical development. A Phase II proof-of-concept placebo-controlled, adjunctive-therapy trial (CVL-865-SZ-001, NCT04244175) has initiated screening and is evaluating the efficacy and safety of CVL-865 (maintenance doses of 7.5 mg b.i.d. and 25 mg b.i.d.) in patients with drug-resistant focal seizures. An open-label extension study (CVL-865-SZ-002, NCT# to be confirmed) will evaluate efficacy and long-term safety as an extension to the proof-of-concept trial.

5. FENFLURAMINE HYDROCHLORIDE (ZX008)

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Molecular structure of fenfluramine here

5.1 Introduction and rationale for development

The initial rationale for the development of fenfluramine (Fintepla®) was based on observational studies of patients with refractory epilepsy and on anticonvulsive effectiveness seen in two cohorts of patients with Dravet syndrome who have now been treated for up to 30 years.[3,39] Continuing development has been supported by the positive results of the first Phase III, double-blind, placebo-controlled clinical trial which showed that patients with Dravet syndrome treated with fenfluramine experienced significant and in some cases profound reductions in convulsive seizure frequency and significantly longer periods of seizure freedom.[3,40] On June 25, 2020, fenfluramine received approval from the FDA for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older. [41]

5.2 Pharmacology

The pharmacological profile of fenfluramine has been presented previously. [3,39] A recent study of fenfluramine and its active metabolite norfenfluramine examined their binding to receptors that have been implicated in seizure activity, *in vitro* functional responses due to binding at these receptors, and *in vivo* physiologic effects due to specific interactions with these receptors.[42] In addition to serotonin receptors, fenfluramine and norfenfluramine have been shown to non-selectively bind to sigma receptors with sub-micromolar K_i values. The functional and *in vivo* assays suggested that fenfluramine positively modulated sigma-1 receptors. The mechanism by which serotoninergic and sigma-1 receptors exert control over seizures related to loss of function of the sodium channel has not been elucidated. However, the authors hypothesized that fenfluramine modulation of sigma-1 receptors may increase the release of neuroactive steroids.[42] Supporting this hypothesis is the observation that the synthetic neuroactive steroid, SGE-516, reduced the incidence of thermally-induced seizures and prolonged survival of Scn1a+/- Dravet mice.[43]

5.3 Toxicology

Preclinical toxicology studies of fenfluramine have been summarized previously.[39]

5.4 Pharmacokinetics

As reported previously,[3,39,44] studies conducted in healthy subjects have shown that fenfluramine is absorbed rapidly from the gastrointestinal tract, with C_{max} being observed after about 3 h of dosing. Fenfluramine is extensively metabolized by CYP enzymes, including CYP1A2, CYP2B6, CYP2D6, with additional contributions by CYP2C9, CYP2C19, and CYP3A4, and is eliminated with a terminal half-life of about 20 h. Its major demethylated metabolite, norfenfluramine, does not appear to be a strong substrate for any CYP450 enzyme, and is considered to contribute to fenfluramine's pharmacological effects.[3]

5.5 Drug interactions

In a clinical study in healthy subjects that evaluated the pharmacokinetics of a single dose of fenfluramine (0.7 mg/kg) administered alone and together with single doses of stiripentol, clobazam, and valproate in combination, fenfluramine AUC was significantly increased after co-administration with the three other drugs, and norfenfluramine AUC was significantly decreased.

The effect was mediated by inhibition of fenfluramine metabolism. As a result of the drug-drug interaction, a dose adjustment will be required.[3,44]

The interaction between fenfluramine and cannabidiol (CanniMed® Oil; CanniMed Ltd, Saskatchewan, Canada) was studied in healthy adult subjects. [45] On Day 1, fenfluramine was dosed with food (0.4 mg/kg). Starting on Day 14, cannabidiol was administered orally with food starting at 100 mg b.i.d. and titrated through Day 18 to 400 mg b.i.d., and continued at that dose through Day 31. A single oral dose of fenfluramine (0.4 mg/kg) was administered with food on Day 22. Pharmacokinetic blood sampling was conducted following dosing on Day 1 (fenfluramine alone), Day 21 (cannabidiol alone), and Day 22 (fenfluramine and cannabidiol). Blood sampling following fenfluramine dosing was continued for 144 h. Co-administration of fenfluramine and cannabidiol resulted in increases in fenfluramine C_{max} (10%) and AUC_{0-t} (60%) and decreases in norfenfluramine C_{max} (33%) and AUC_{0-t} (22%). The mean steady-state $AUCss_{0-12h}$) of cannabidiol was not affected by co-administration of fenfluramine.

Study 1504 studied the safety and efficacy of fenfluramine in children with Dravet syndrome who were treated with an AED regimen including stiripentol combined with clobazam and/or valproate. The fenfluramine dose in combination with stiripentol was selected for this Phase III clinical trial to account for the anticipated drug interaction between fenfluramine and stiripentol. The dose was identified using a preliminary physiology-based pharmacokinetic model based on single-dose pharmacokinetic data from healthy adults [44] and from 18 pediatric subjects with Dravet syndrome. This modeling exercise informed the selection of the fenfluramine dose for Study 1504, 0.4 mg/kg/day (maximum dose, 17 mg/day), which was predicted to result in similar exposure to fenfluramine 0.7 mg/kg/day (maximum dose, 26 mg/day) when dosed in the absence of stiripentol. [46]

5.6 Efficacy data

The efficacy results of the first Phase III double-blind, placebo-controlled trial of fenfluramine in Dravet syndrome have been reported previously. [3,40] The second Phase III, double-blind, placebo-controlled trial in Dravet syndrome (Study 1504) enrolled 87 patients with Dravet syndrome aged 2 to 18 years. [46] Unlike the first Phase III clinical trial in which concomitant use of stiripentol was prohibited, [40] all enrolled patients in Study 1504 were required to be receiving a stiripentol-inclusive antiseizure drug regimen. Baseline seizure frequency was established during a 6-week run-in period after which patients were randomized (1:1) to placebo or fenfluramine 0.4 mg/kg/day (maximum dose 17 mg/day). Daily doses were given in two equal administrations approximately 12 h apart and blindly titrated over a 3-week period. Fixed doses were maintained for 12 weeks. The study met its

primary efficacy endpoint: analysis of covariance showed that patients treated with fenfluramine had a 54.0% greater decrease in monthly convulsive seizure frequency over the 15-week titration-maintenance period than patients treated with placebo ($P < 0.001$). The median percent reduction from baseline in monthly convulsive seizure frequency was 63.1% in the fenfluramine group, compared with 1.1% in the placebo group ($P < 0.001$). An analysis of responders (defined as percentage of patients exhibiting ≥ 25%, ≥ 50%, ≥ 75% or 100% reduction in convulsive seizure frequency) is presented in Figure 4. A ≥ 50% reduction in monthly convulsive seizure frequency was recorded in 23 of 43 patients (54%) in the fenfluramine group and 2 of 44 patients (5%) in the placebo group ($P < 0.001$). Similarly, a 75% reduction in monthly convulsive seizure frequency was experienced by significantly more patients treated with fenfluramine than with placebo (35% vs 2%, $P = 0.003$). The longest seizure-free interval for patients treated with fenfluramine was significantly longer (median 22 days; range, 3-105 days) than that seen in the placebo-treated group (median 13; range, 1-40 days; $P = 0.004$), further supporting the efficacy of fenfluramine in this study.

Patients who completed a Phase III clinical trial of fenfluramine for the treatment of Dravet syndrome were invited to participate in a long-term, open-label extension study (Study 1503).[47] A total of 330 patients have enrolled in Study 1503 as of February 15, 2019 and had received at least 1 dose of fenfluramine and comprised the safety population. Of these patients, 314 had baseline data to enable evaluation of seizure outcomes. All patients initiated treatment in the open-label extension at a fenfluramine dose of 0.2 mg/kg/day regardless of their treatment group in the fixed-dose, double-blind Phase III study. After 4 weeks of treatment, the fenfluramine dose could be titrated based on efficacy and tolerability up to 0.7 mg/kg/day (maximum dose, 26 mg/day) in patients not receiving stiripentol, or up to 0.4 mg/kg/day (maximum dose, 17 mg/day) in patients concomitantly treated with stiripentol. Effectiveness was assessed as the change in monthly convulsive seizure frequency throughout the duration of treatment in the extension phase compared to baseline in the core Phase III trial. The median duration of treatment at the time of this analysis was 445 days (range, 7-899 days). After 1 month of treatment in the open-label extension study, monthly convulsive seizure frequency was reduced by a median of 55.2%, and at the end of month 2 (when flexible dosing had been in place for 1 month) monthly convulsive seizure frequency was reduced by a median of 66.0%. This level of effectiveness was sustained through at least the first 24 months of the analysis period. During the median 445 day fenfluramine treatment duration 75.1%, 61.7%, and 37.1% of patients demonstrated ≥ 25%, ≥ 50%, and ≥ 75% reduction in convulsive seizure frequency, respectively (n = 314, Figure 4).

Figure 4 here

Results of a Phase III, double-blind, placebo-controlled clinical trial of fenfluramine for the treatment of Lennox-Gastaut syndrome have been reported in a press release (Study 1601).[48] The study randomized 263 patients between 2 and 35 years of age to one of three treatments (1:1:1): placebo, fenfluramine 0.2 mg/kg/day, and fenfluramine 0.7 mg/kg/day (maximum dose, 26 mg/day). Doses were titrated over 2 weeks and maintained for an additional 12 weeks. The study met its primary endpoint demonstrating that at the 0.7 mg/kg/day dose fenfluramine provided an approximately 3.4-fold greater median percent reduction in monthly drop seizures versus placebo (P = 0.0012). The median percent reductions in monthly drop seizures in the fenfluramine 0.7 mg/kg/day, fenfluramine 0.2 mg/kg/day, and placebo groups were 26.5% (P = 0.0012), 13.2% (P = 0.09), and 7.8%, respectively.

5.7 Tolerability and adverse effect profile

In Study 1504 early withdrawals occurred in 3 of 44 (7%) placebo-treated patients and in 7 of 43 (16%) fenfluramine-treated patients. [46] The most common TEAEs (occurring in ≥ 15% of patients) in the fenfluramine group were decreased appetite (44%), pyrexia (26%), fatigue (26%), diarrhea (23%), and nasopharyngitis (16%). In the placebo group, nasopharyngitis (34%) and seizures (16%) were the most common TEAEs.

In the open-label extension study (Study 1503), 56 of 330 patients (17%) discontinued fenfluramine during the 24-month follow-up.[47] Thirty-five early withdrawals were due to lack of efficacy, and TEAEs were cited as reason for discontinuation for 4 patients (1.2%). Two deaths (0.6%) due to sudden unexpected death in epilepsy (SUDEP) occurred. The most common TEAEs recorded in this study were nasopharyngitis (23.3%), pyrexia (23.0%), decreased appetite (21.2%), and diarrhea (15.2%).

In Study 1601, fenfluramine was well-tolerated and TEAEs were consistent with those observed in Study 1 and Study 1504. Those most common (≥ 10% of patients) were decreased appetite, somnolence, fatigue, vomiting, diarrhea, and pyrexia. One death due to SUDEP occurred in the fenfluramine group.

Use of fenfluramine as a treatment for obesity has been associated with an increased prevalence of cardiac valvulopathy and pulmonary artery hypertension,[49] and therefore cardiac function has been monitored closely during the development program in patients with epilepsy. In the Phase III double-blind trials of fenfluramine in Dravet syndrome[40,46] and Lennox-Gastaut syndrome, no cases of cardiac valvulopathy or pulmonary artery hypertension have been observed. Lagae and colleagues[40] reported that five (13%), seven (18%), and nine (23%) patients with Dravet syndrome

in the placebo, fenfluramine 0.2 mg/kg/day, and fenfluramine 0.7 mg/kg/day groups, respectively, had at least one echocardiogram examination with trace mitral or trace aortic valve regurgitation. Nabbout et al.[46] in their study of patients also receiving stiripentol, reported that 12 children (9 [21%] treated with fenfluramine and 3 [7%] treated with placebo) demonstrated trace mitral valve regurgitation at one or more echocardiographic examinations. In the open-label extension study (Study 1503) all patients are receiving echocardiograms at study entry, after 4-6 weeks of treatment, and every 3 months thereafter.[50-52] No aortic or mitral valvulopathy has been observed in any patient at any time during the analysis period. A single patient (0.4%) had a transient finding of trace aortic valve regurgitation and 23% of patients had one or more findings of trace mitral valve regurgitation.[52] In most patients, this finding was transient and often fluctuated between trace and absent regurgitation. Trace regurgitation is considered to represent normal physiology and is not considered to be a risk factor for future valve disease.[53]

In the U.S., fenfluramine is currently available only through a restricted program under a risk evaluation and mitigation strategy (REMS) that requires echocardiogram assessments before, during, and after treatment.[41]

5.8 Planned studies

Study 1503 is ongoing and will continue to enroll patients with Dravet syndrome who have completed a Phase III clinical trial of fenfluramine. An open-label extension phase of Study 1601 for patients with Lennox-Gastaut syndrome who have completed the double-blind phase of the study is ongoing.

Open-label investigations of the effect of fenfluramine in CDKL5 developmental disorder, Doose syndrome, and Sunflower syndrome are ongoing.

6. GANAXOLONE

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Molecular structure of ganaxolone here

6.1 Introduction and rationale for development

Ganaxolone (3α-hydroxy-3β-methyl-5α-pregnan-20-one) is an analogue of the endogenous neurosteroid, allopregnanolone.[54] It has demonstrated preliminary evidence of efficacy in several rare pediatric epilepsies, including cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder and protocadherin 19 (PCDH19)-related epilepsy, as well as in refractory SE.

Levels of endogenous neurosteroids may be altered in genetic epileptic encephalopathies, and these alterations may have relevance to the potential utility of ganaxolone. For example, in tuberous sclerosis complex (TSC), levels of inhibitory 3α,5α-tetrahydroprogesterone (3α,5α-THP, allopregnanolone) and 3α-5β-THP are decreased relative to the excitatory enantiomers, 3β,5α- and 3β,5β-THP, which may result in decreased GABAergic tone and contribute to the genesis of seizures in TSC.[55]

6.2 Pharmacology

Ganaxolone is a positive allosteric modulator of $GABA_A$ receptors at both synaptic and extrasynaptic sites. In contrast to ganaxolone, benzodiazepines only bind to synaptic GABA receptors, which, when activated by a brief exposure to a high concentration of GABA modulate phasic responses to GABA. Presynaptically controlled phasic responses or inhibitory postsynaptic potentials (IPSPs) are responsible for rapid communication between neurons. In contrast, extrasynaptic $GABA_A$ receptors, localized away from the synapses, are persistently exposed to a low concentration of GABA, that diffuses away from the synapse, modulate the persistent (tonic) inhibitory conductance and play an important role in regulating the membrane potential and network excitability.

Synaptic $GABA_A$ receptors are internalized during prolonged seizures, becoming functionally inactive and resistant to benzodiazepine actions as seizure duration increases.[56] Ganaxolone-responsive extrasynaptic $GABA_A$ receptors (containing α and δ subunits) mediate tonic inhibition, do not internalize nor become functionally inactive with prolonged seizure activity. Therefore, these characteristics make modulation of extrasynaptic receptors an attractive mechanism for the treatment of SE.[57]

The antiseizure activities of ganaxolone were defined in an array of *in vivo* models (Table 1). Ganaxolone was effective at behaviorally non-toxic doses against clonic convulsions induced by subcutaneous PTZ in mice and rats. It exhibited potent anticonvulsant activity against bicuculline-, aminophylline-, strychnine-, and t-butylbicyclophosphorothionate (TBPS)-induced seizures and antagonized 4-amino-pyridine lethality in mice. Ganaxolone was also active against corneal-kindled

seizures in rats and seizures due to 6-Hz electrical stimulation in mice (Marinus Pharmaceuticals, Inc., data on file).

Insert Table 1 here

Although ganaxolone effectively blocked tonic seizures induced by MES in mice and rats, seizure control occurred only at doses that produced ataxia on the rotarod test (TD_{50} = 33.4 mg/kg in mice and 14.2 mg/kg in rats). Conversely, at doses well below those that resulted in ataxia and ethanol potentiation, ganaxolone was a potent anticonvulsant against fully kindled Stage 5 seizures induced by corneal kindling in the rat. Seizure threshold, as determined by the dose of intravenously infused PTZ required to induce clonus, was also significantly elevated by non-toxic doses of ganaxolone in the mouse. The results obtained from these seizure models suggest that ganaxolone acts as an anticonvulsant to a greater extent by elevation of seizure threshold than by blocking seizure propagation. For example, by elevating the threshold at the seizure focus, ganaxolone may decrease focal firing and the clinical expression of a focal seizure; however, an elevation in seizure threshold may not be sufficient to decrease the spread of seizure activity under conditions which maximally activate a population of neurons in the seizure focus. The protective index of ganaxolone is 3- to 5-fold versus that for ataxia in most animal seizure models and is comparable or superior to that of valproic acid, phenobarbital and benzodiazepines. Given i.v., ganaxolone was also effective in lithium-pilocarpine models of SE, producing a sustained reduction in behavioral and EEG seizures and in seizure-related mortality.[56]

Additional information on the pharmacology of ganaxolone and a summary of toxicology data have been provided in the EILAT XIII and EILAT XIV Progress Reports.[3,39]

6.3 Pharmacokinetics

After administration of single 200, 400 or 600 mg oral doses of ganaxolone capsules to healthy subjects, absorption was rapid, with mean C_{max} values of 27.9, 35.7 and 41 ng/mL, respectively, occurring at 1.5-2.0 h after dosing. This was followed by a rapid re-distribution phase (less than 10 h) characterized by a half-life of 6.9-10.6 h, which in turn was followed by a longer elimination phase (Marinus Pharmaceuticals, Inc., data on file). After acute administration, the late-phase half-life was related to the extent of deposition into extravascular compartments and varied across studies and different formulations from approximately 3.5 to 50 h. When ganaxolone suspension was administered to healthy subjects at doses of 200 mg in the fasting state and 400 mg in either the fasting state or with a high-fat meal, intake with food resulted in a 2- and 3-fold increase in $AUC_{0-\infty}$ and C_{max}, respectively. C_{max} observed after single 200 and 400 mg doses in the fasted state was

dose-proportional. After multiple dosing (600, 800 or 1,000 mg capsules b.i.d.), steady-state plasma ganaxolone levels were reached by Day 3. Mean C_{max} was obtained within 2 h for all doses and was dose-proportional at 600 to 800 mg b.i.d. and did not increase further at 1,000 mg b.i.d.

The pharmacokinetics and pharmacodynamics of ganaxolone have also been studied after i.v. administration with bolus doses of 10 or 30 mg over 5 min or 20 mg over 2 min; infusions of 10 or 30 mg over 1 h; and with a bolus dose of 6 mg over 5 min with concurrent initiation of a continuous infusion of 20 mg/h for 4 h. With bolus dosing, C_{max} values were 73.8, 441 and 1240 ng/mL with 10, 20 and 30 mg, respectively. With infusion over 1 h, C_{max} was 80.2 ng/mL with 10 mg and 257 ng/mL with 30 mg. t_{max} was 0.08 h (time of first post-dose sampling) with bolus administration and 0.98 h with 1-h infusion. With concurrent initiation of 6 mg bolus and 20 mg/h infusion for 4 h, C_{max} was 215 ng/mL and t_{max} was 3.00 h. Plasma concentration declined in a multi-phasic manner following cessation of i.v. ganaxolone.

The bispectral index score, a surrogate EEG measure for sedation,[58] was utilized as a pharmacodynamic marker of brain ganaxolone activity. Bispectral index scores correlated with estimated plasma ganaxolone concentration, with changes evident within 5 to 15 min of ganaxolone initiation. There was little or no delay between the appearance of drug in plasma and a change in the bispectral index score.

6.4 Drug interactions

Ganaxolone is metabolized by CYP3A4/5, and *in vitro* data and human pharmacokinetic data from subjects taking strong CYP inducers such as carbamazepine and phenytoin have shown increased ganaxolone clearance. However, there has been no observed difference in response to ganaxolone between patients with epilepsy receiving these drugs compared with patients not receiving enzyme inducers (Marinus Pharmaceuticals, Inc., data on file). Likewise, strong inhibitors of CYP3A4 may reduce ganaxolone clearance. Additional studies are planned to better characterize the potential for interactions with potent inducers of CYP3A4.

6.5 Efficacy in refractory status epilepticus

Data have been recently reported for a Phase II study of ganaxolone in refractory SE.[59] Seventeen patients who presented with convulsive or nonconvulsive SE and had failed at least one i.v. AED other than a benzodiazepine received one of three dose regimens of i.v. ganaxolone, each of which included a bolus followed by continuous infusion. The dose regimens are described in Table 2.

Insert Table 2 here

All dose regimens were initiated with an i.v. bolus of ganaxolone delivered over 3 min with simultaneous initiation of a continuous infusion of up to 96 h duration. In the low- and high-dose regimens, the i.v. infusion was maintained for 2 h at a rate to provide a plasma ganaxolone level of 800-1,000 ng/mL, after which the infusion rate was decreased to provide a plasma level of 500 ng/mL for an additional 2 h (low-dose cohort) or 6 h (high-dose cohort). The medium dose cohort received an infusion that maintained a plasma level of 400-450 ng/mL, not attaining a level above 500 ng/mL beyond the immediate post-bolus interval. Dosing with i.v. ganaxolone was tapered over 18 h.

Etiologies of SE included stroke/hemorrhage (n = 7), tumor (n = 4), autoimmune encephalitis (n = 2) or drug overdose/withdrawal (n = 2). Two participants had a history of epilepsy with no other identified cause for SE; five subjects with other etiologies for SE also had a history of epilepsy. Median number of failed second-line AEDs for SE treatment was 2.1, most commonly levetiracetam (n = 16) or lacosamide (n = 12).

The primary efficacy outcome was lack of progression to i.v. anesthesia for 24 h following ganaxolone initiation. Secondary efficacy assessments included time to SE cessation, lack of SE recurrence within 24 h, lack of additional intervention to treat SE recurrence including progression to i.v. anesthesia for 24 h following ganaxolone discontinuation (72 h from initiation) and lack of SE recurrence at 4-week follow up.

None of the 17 subjects required i.v. anesthesia within 24 h of ganaxolone initiation. The median time to SE cessation was 5 minutes. Investigators reported recurrence of SE in none of the subjects, although an investigator determined on post-hoc review of continuous EEG monitoring that SE had recurred in one subject and had stopped without additional intervention. There was no additional intervention to treat SE recurrence for 72 h following ganaxolone initiation in 8/8 subjects in the high-dose, 4/5 in the medium-dose and 3/5 in the low-dose cohort. Of the 14 subjects without additional treatment for SE recurrence at 72 h, 11 were evaluable at 4-week follow up (two patients died for reasons unrelated to study treatment and two terminated study participation). There was no recurrence of SE at 4-week follow up in 6/6 (100%), 2/3 (66%) and 3/5 (60%) in the high-, medium- and low-dose cohorts, respectively.

Post-hoc review of continuous EEG by a central reader determined that seizure burden was most substantially decreased in the high-dose cohort, followed by the low-dose and medium-dose cohorts (Marinus Pharmaceuticals, Inc., data on file). The lesser decrease in seizure burden in the medium- compared to the low-dose cohort may be due the absence of an infusion rate to maintain the target

plasma concentration of ≥ 500 ng/mL following ganaxolone bolus. This suggests that the more important factor in SE control is duration at or above the target concentration rather than total daily dose.

Preliminary efficacy data in patients with CDKL5 or PCDH19-related epilepsy have been described in the EILAT XIV Progress Report.[3] The relationship between baseline allopregnanolone-sulfate (Allo-S) levels and seizure reductions in 11 patients with PCDH19-related epilepsy has been subsequently reported.[60] The median percent seizure reduction in subjects with baseline Allo-S < 2,500 pg/mL was 50% (n = 7), compared to a median increase in seizure frequency of 84% in subjects with baseline Allo-S ≥ 2,500 pg/mL. These findings suggest that reduced Allo-S may be a response biomarker for ganaxolone in PCDH19-related epilepsy and possibly other genetic epilepsies.

6.6 Tolerability and adverse effect profile

Based on preliminary analysis of data from the Phase II study of i.v. ganaxolone in refractory SE, there were 63 TEAEs in 15 subjects. Most were mild to moderate in severity and unrelated to ganaxolone treatment. Ten TEAEs (6 subjects) were considered serious, with two instances of severe sedation considered related to ganaxolone (Marinus Pharmaceuticals, Inc., data on file).

In completed and ongoing studies of oral ganaxolone in CDKL5 deficiency disorder or PCDH19-related epilepsy, the most common TEAE is sedation. Adjustment of ganaxolone dosage or titration schedule is often effective in reducing sedation, permitting treatment to be continued.

6.7 Planned studies

A multicenter, double-blind, placebo-controlled study of 124 subjects with refractory SE is planned for the latter half of 2020. Adolescents and adults with refractory SE who have failed initial treatment with benzodiazepines and two second-line i.v. AEDs will be randomized in a 1:1 ratio to ganaxolone or placebo given as a bolus followed by continuous infusion. Study treatment will be added to standard of care, and investigators will be permitted to escalate treatment, whether with another second-line i.v. AEDs or i.v. anesthesia, as soon as indicated if no response is observed following study drug initiation. The total daily dose of ganaxolone on Day 1 will be 830 mg, with an infusion rate that will maintain the target plasma concentration at or above 500 ng/mL for 12 h, compared to the maximum duration at the target level in Phase II of 8 h.

The primary outcome measures assess onset and durability of effect, with a co-primary endpoint: 1) proportion of patients with SE cessation within 30 minutes of study drug initiation, and 2) the proportion of patients who do not progress to i.v. anesthesia within 36 h.

Additionally, a 30-subject, open-label study of ganaxolone in seizures due to TSC has been initiated, which will assess effectiveness, tolerability and safety of oral ganaxolone and whether reduced Allo-S levels are predictive of response.

7. CONCLUSIONS

This report provides information on the preclinical and clinical profile of five novel compounds evaluated in experimental seizure and epilepsy models, and in patients with epilepsy. Anakinra and fenfluramine were first introduced into the market for other indications, and therefore their novelty is associated with their repurposing as treatments for epilepsy. The medications discussed in this article provide examples of the variety of development strategies, mechanisms of actions, and targeted indications of innovative treatments being considered in the ongoing search for more effective drugs for epilepsy. In addition to the repurposing of medications approved for other indications, there is an increasing trend to direct drug discovery and initial development to orphan conditions where unmet needs are high, rather than for treatment of common epilepsies, which are still associated with a significant burden of drug resistance. Despite the introduction of more than 20 AEDs since the first Eilat Conference in 1992, the need for improved treatments for patients with epilepsy persists. It is gratifying to see that newer medications continue to be developed, and that some of these have been successful in fulfilling regulatory requirements and have now become available for use in routine clinical practice.

ACKNOWLEDGMENTS

We wish to thank the authors of the summary sections for their patience in addressing the queries raised during the review process, and for their collaboration with the final editing of this manuscript.

For the section on cenobamate, medical writing support to the summary authors was provided by Leonard Lionnet (Lev Medical Communications). Edward Weselcouch, funded by Zogenix Inc, Inc provided professional medical writing assistance to the summary authors in the preparation of the section on fenfluramine.

DISCLOSURES ON CONFLICT OF INTEREST

Article authors

Meir Bialer received speaker's or consultancy fees from Alkaloid, Boehringer Ingelheim, Medison and US WorldMeds. He is also co-inventor of *sec*-butylpropylacetamide and its individual stereoisomers, the patents of which are owned by The Hebrew University and its Tech transfer company Yissum.

Matthias Koepp received speaker's or consultancy fees Bial, Eisai, GW Pharma, Novartis, Sanofi, UCB Pharma and currently receives research support from Medical Research Council UK, Wellcome Trust, Epilepsy Research UK, Henry Smith Foundation, Newton Foundation and the Epilepsy Society.

Rene Levy received consultancy fees from Biocodex.

Emilio Perucca received speaker's or consultancy fees from Amicus Therapeutics, Arvelle, Biogen, Eisai, GW Pharma, Intas Pharmaceuticals, Laboratorios Bagò, Sanofi, Sun Pharma, UCB Pharma and Xenon Pharma.

Piero Perucca is supported by the National Health and Medical Research Council (APP1163708), the Epilepsy Foundation, the Royal Australasian College of Physicians, and Melbourne Health. His institution has received speaker honoraria or consultancy fees from Eisai, UCB Pharma, Sun Pharma, Novartis, and Supernus.

Torbjörn Tomson received speaker's honoraria or consultancy fees to his institution from Arvelle, Eisai, Sanofi, Sun Pharma, UCB, and Sandoz, and received research support from Stockholm County Council, EU, CURE, GSK, UCB, Eisai, and Bial.

Svein I. Johannessen has received honoraria for his participation in a consultant board for GW Pharma.

H. Steve White has received grant funding from Eisai and UCB, served on the Scientific Advisory Board of Otsuka Pharmaceuticals, has served as an advisor to Biogen Pharmaceuticals, is a member of the UCB Speakers Bureau and is a scientific co-founder of NeuroAdjuvants, Inc., Salt Lake City, UT, USA.

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Anakinra: Elaine Wirrell received consulting fees from Biocodex and Biomarin.

Cenobamate (YKP3089): Ilise Lombardo and Elena Alvarez-Baron are employees of Arvelle Therapeutics International, GmbH. MK and LF are employees of SK Life Science Inc.

CVL-865: Rachel Gurrell is a paid consultant for Cerevel Therapeutics, LLC and a previous employee of Pfizer Inc. and owns Pfizer stock.

Fenfluramine hydrochloride (ZX008): Gail Farfel, Glenn Morrison, and Brooks Boyd are employees of Zogenix, Inc. and report stock ownership in the company.

Ganaxolone: Joe Hulihan, Alex Aimetti and Maciej Gasior are employees of Marinus Pharmaceuticals. Michael Saporito is a paid consultant for Marinus Pharmaceuticals.

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Table 1. Summary of ganaxolone activity in animal models of seizures and epilepsy.

Model	Species/Strain	ED_{50}/ Route of Administration
Pentylenetetrazole	Mouse/NSA	4.3 mg/kg i.p.
Pentylenetetrazole	Rat/Sprague-Dawley	7.8 mg/kg i.p; 21 mg/kg p.o.
Maximal electroshock	Mouse/NSA	29.7 mg/kg i.p.
Maximal electroshock	Rat/Sprague-Dawley	58.4 mg/kg i.p.
Corneal-kindled seizures	Rat /Sprague-Dawley	4.5 mg/kg i.p.
6-Hz stimulation	Mouse/NIH Swiss	6.3 mg/kg i.p.
Bicuculline	Mouse/NSA	4.6 mg/kg i.p.
Aminophylline	Mouse/NSA	11.5 mg/kg i.p.
Strychnine	Mouse/NSA	40 mg/kg i.p.
TBPS	Mouse/NSA	11.7 mg/kg i.p.
4-aminopyridine lethality	Mouse/NSA	20-30 mg/kg i.p.

Abbreviations: NSA, non-Swiss albino; TBPS, tert-butylbicyclophosphorothionate

Table 2. Ganaxolone i.v. dose regimens in the Phase II study in patients with refractory status epilepticus.

Regimen	**N**	**Total daily dose (mg)**	**Duration of exposure at target plasma level ≥ 500 ng/mL (h)**
Low dose	5	500	4
Medium dose	4	650	0
High dose	8	713	8

LEGENDS OF FIGURES

Figure 1. Responder rates (percentage of patients achieving ≥ 50%, ≥ 75%, ≥ 90%, and 100% reduction in seizure frequency from baseline) during the 12-week maintenance phase of study C017. P values refer to comparison of cenobamate groups with placebo.

Figure 2. Kaplan-Meier plot illustrating retention on cenobamate treatment during the open label extension of study C017. Patients who completed the study and patients ongoing at the time of data cut-off are considered as censored.

Figure 3. Time course of treatment effects for the standardized photosensitivity range (least square means and 90% confidence intervals) after administration of single oral doses of CVL-865, lorazepam and placebo in 7 patients with photosensitive epilepsy.

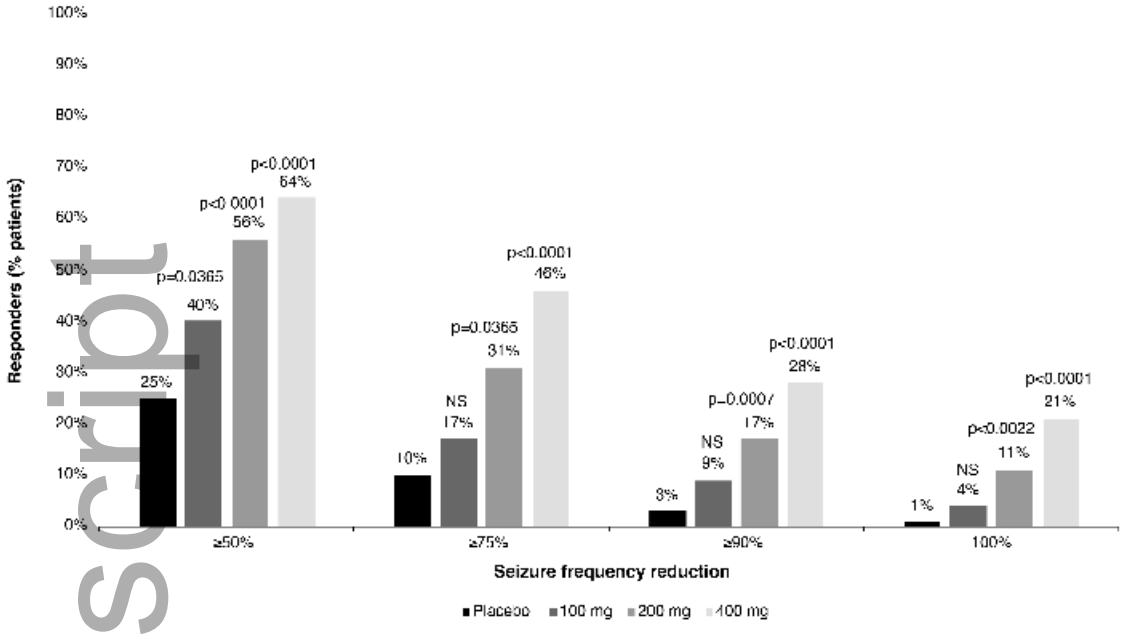
Figure 4. Responder rates for patients treated in fenfluramine (FFA) Study 1 (Panel A), Study 1504 (Panel B), and Study 1503 (Panel C). In Study 1503 (open label extension), all patients started fenfluramine at 0.2 mg/kg/day and after 1 month doses could be titrated based on effectiveness and tolerability. * $P < 0.05$, ** $P < 0.001$, *** $P < 0.001$ compared with placebo.

Table 1. Summary of ganaxolone activity in animal models of seizures and epilepsy.

Model	Species/Strain	ED_{50}/ Route of Administration
Pentylenetetrazole	Mouse/NSA	4.3 mg/kg i.p.
Pentylenetetrazole	Rat/Sprague-Dawley	7.8 mg/kg i.p; 21 mg/kg p.o.
Maximal electroshock	Mouse/NSA	29.7 mg/kg i.p.
Maximal electroshock	Rat/Sprague-Dawley	58.4 mg/kg i.p.
Corneal-kindled seizures	Rat /Sprague-Dawley	4.5 mg/kg i.p.
6-Hz stimulation	Mouse/NIH Swiss	6.3 mg/kg i.p.
Bicuculline	Mouse/NSA	4.6 mg/kg i.p.
Aminophylline	Mouse/NSA	11.5 mg/kg i.p.
Strychnine	Mouse/NSA	40 mg/kg i.p.
TBPS	Mouse/NSA	11.7 mg/kg i.p.
4-aminopyridine lethality	Mouse/NSA	20-30 mg/kg i.p.

Table 2. Ganaxolone i.v. dose regimens in the Phase II study in patients with refractory status epilepticus.

Regimen	**N**	**Total daily dose (mg)**	**Duration of exposure at target plasma level ≥ 500 ng/mL (h)**
Low dose	5	500	4
Medium dose	4	650	0
High dose	8	713	8



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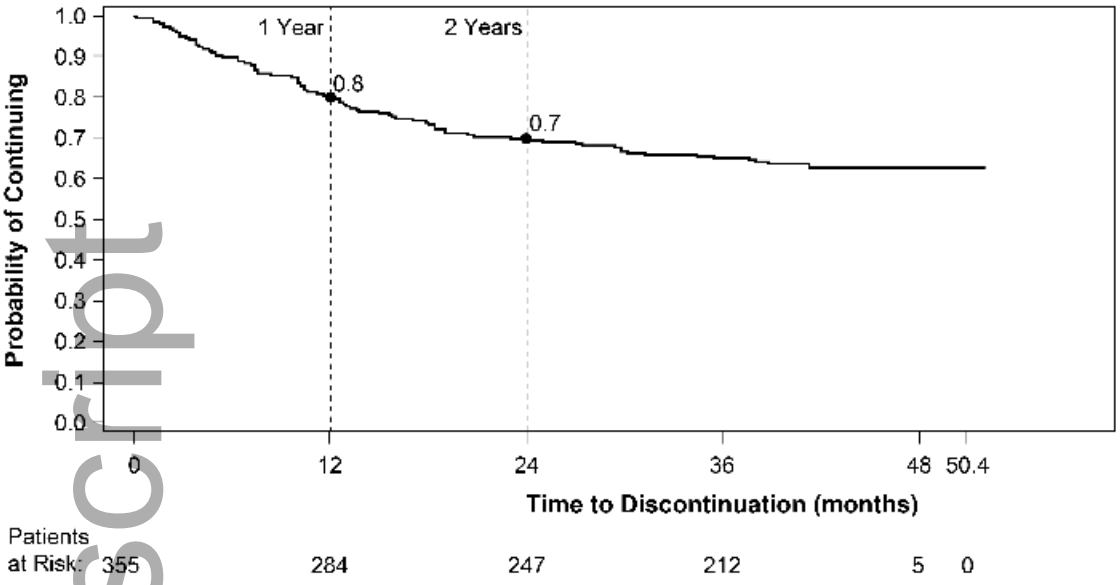

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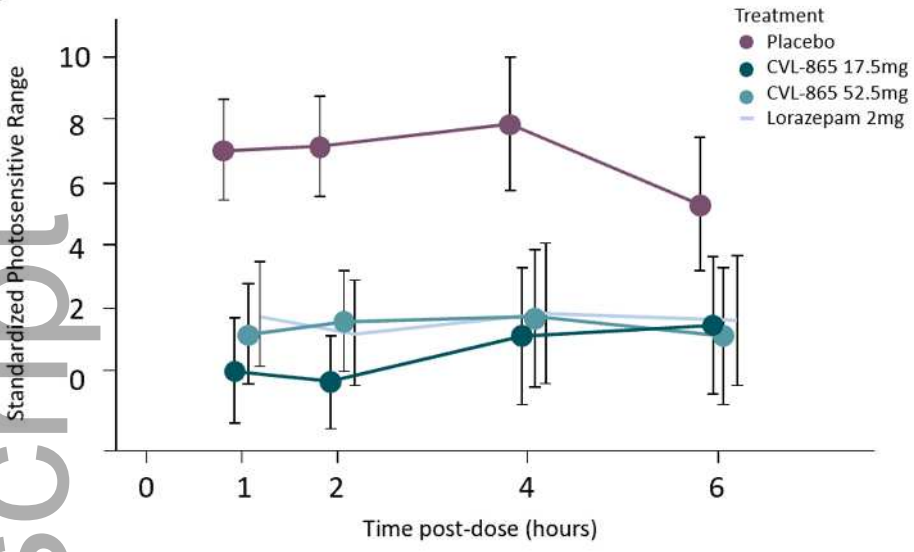

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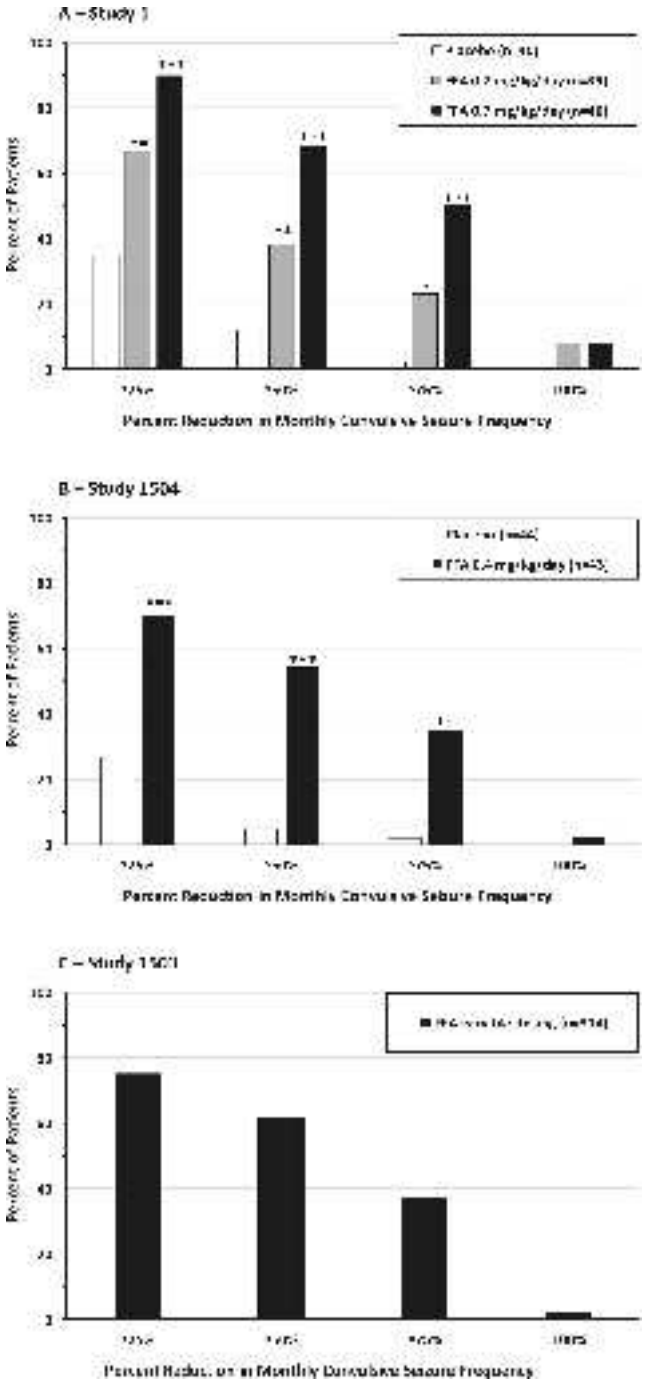

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Title:
Progress report on new antiepileptic drugs: A summary of the Fifteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XV). II. Drugs in more advanced clinical development

Date:
2020-11-09

Citation:
Bialer, M., Johannessen, S. I., Koepp, M. J., Levy, R. H., Perucca, E., Perucca, P., Tomson, T. & White, H. S. (2020). Progress report on new antiepileptic drugs: A summary of the Fifteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XV). II. Drugs in more advanced clinical development. EPILEPSIA, 61 (11), pp.2365-2385. https://doi.org/10.1111/epi.16726.