Epilepsy Currents
2020, Vol. 20(2) 85-87

DOI: 10.1177/1535759720903032
journals.sagepub.com/home/epi
SAGE

Remarkably High Efficacy of Cenobamate in Adults With Focal-Onset Seizures: A Double-Blind, Randomized, Placebo-Controlled Trial

Safety and Efficacy of Adjunctive Cenobamate (YKP3089) in Patients With Uncontrolled Focal Seizures: A Multicentre, Double-Blind, Randomized, Placebo-Controlled, Dose-Responsive Trial

Krauss GL, Klein P, Brandt C, et al. *Lancet Neurol*. 2020;19(1):38-48. https://doi.org/10.1016/S1474-4422(19)30399-0.

BACKGROUND: More than a third of patients with epilepsy are treatment resistant, and thus new, more effective therapies to achieve seizure freedom are needed. Cenobamate (YKP3089), an investigational antiepileptic drug, has shown broad-spectrum anticonvulsant activity in preclinical studies and seizure models. We aimed to evaluate the safety, efficacy, and tolerability of adjunctive cenobamate in patients with uncontrolled focal (partial)-onset epilepsy. METHODS: We did a multicenter, double-blind, randomized, placebo-controlled, dose–response study at 107 epilepsy and neurology centers in 16 countries. Adult patients (aged 18-70 years) with focal seizures despite treatment with 1 to 3 antiepileptic drugs were randomly assigned (1:1:1:1) via an interactive web response system, by block sizes of 4 within each country, to adjuvant once daily oral cenobamate at dose groups of 100 mg, 200 mg, or 400 mg, or placebo following an 8-week baseline assessment. Patients, investigators, and study personnel were masked to treatment assignment. The study included a 6-week titration phase and 12-week maintenance phase. The primary efficacy outcomes were percentage change in 28-day focal seizure frequency (focal aware motor, focal impaired awareness, or focal to bilateral tonic–clonic seizures) from baseline analyzed in the modified intention-to-treat population ($\geq$1 dose and any postbaseline seizure data) and responder rates ($\geq$50% reduction) analyzed in the maintenance phase population ($\geq$1 dose in the maintenance phase and any maintenance phase seizure data). The primary efficacy outcomes were analyzed using a hierarchal step-down procedure comparing 200 mg versus placebo, 400 mg versus placebo, then 100 mg versus placebo. Safety and tolerability were compared descriptively across treatment groups for all randomized patients. This study is registered with ClinicalTrials.gov, number NCT01866111. FINDINGS: Between July 31, 2013, and June 22, 2015, 437 patients were randomly assigned to either placebo (n = 108) or cenobamate 100 mg (n = 108), 200 mg (n = 110), or 400 mg (n = 111). Of these patients, 434 (106 [98%] in placebo group, 108 [100%] in 100 mg group, 109 [99%] in 200 mg group, and 111 [100%] in 400 mg group) were included in the modified intention-to-treat population, and 397 (102 [94%] in placebo group, 102 [94%] in 100 mg group, 98 [89%] in 200 mg group, and 95 [86%] in 400 mg group) were included in the modified intention-to-treat maintenance phase population. Median percentage changes in seizure frequency were −24.0% (interquartile range: −45.0 to −7.0%) for the placebo group compared to −35.5% (−62.5 to −15.0%; $P = .0071$) for the 100 mg dose group, −55.0% (−73.0 to −23.0%; $P < .0001$) for the 200 mg dose group, and −55.0% (−85.0 to −28.0%; $P < .0001$) for the 400 mg dose group. Responder rates during the maintenance phase were 25% (26 of 102 patients) for the placebo group compared to 40% (41 of 102; odds ratio: 1.97, 95% confidence interval: 1.08-3.56; $P = .0365$) for the 100 mg dose group, 56% (55 of 98; 3.74, 2.06-6.80; $P < .0001$) for the 200 mg dose group, and 64% (61 of 95; 5.24, 2.84-9.67; $P < .0001$) for the 400 mg dose group. Treatment-emergent adverse events occurred in 76 (70%) of 108 patients in the placebo group, 70 (65%) of 108 in the 100 mg group, 84 (76%) of 110 in the 200 mg group, and 100 (90%) of 111 in the 400 mg group. Treatment-emergent adverse events led to discontinuation in 5 (5%) patients in the placebo group, 11 (10%) in the 100 mg dose group, 15 (14%) in the 200 mg dose group, and 22 (20%) in the 400 mg dose group. One serious case of drug reaction with eosinophilia and systemic symptoms occurred in the 200 mg cenobamate group. No deaths were reported. INTERPRETATION: Adjunctive cenobamate reduced focal (partial)-onset seizure frequency, in a dose-related fashion. Treatment-emergent adverse events were most frequent in the highest dose group. Cenobamate appears to be an effective treatment option in patients with uncontrolled focal seizures.

Commentary

Cenobamate (YKP3089) is a new antiseizure medication (ASM) approved by the US Food and Drug Administration on November 21, 2019, for the treatment of partial- (focal-) onset seizures in adults.[1] It is a novel tetrazole alkyl carbamate derivative,[1] structurally different from carisbamate. It was effective in animal models of epilepsy, including the maximal electroshock seizure test, seizures produced by picrotoxin and pentylenetatrazol, the hippocampal kindled rat model, and the mouse 6 Hz psychomotor seizure model.[2] Cenobamate suppressed the photoparoxysmal response in photosensitive epilepsy at 250 mg and 400 mg single doses in one small human epilepsy study.[3]

Cenobamate (CNB) reduces repetitive neuronal firing by inhibiting voltage-gated sodium currents.[1] Specifically, it enhances the fast and slow inactivation of sodium channels and potently inhibits the noninactivating persistent component of the sodium channel current (I_{NaP}) by which many ASMs, notably lacosamide, are believed to work.[2-4] Also, CNB is a positive allosteric modulator of the γ-aminobutyric acid ($GABA_A$) ion channel.[1]

At least 88% of CNB is absorbed following oral administration, with a T_{max} of 1 to 4 hours, and terminal half-life of 50 to 60 hours.[1] The drug is extensively metabolized via glucuronidation and oxidation, so drug–drug interactions exist. Cenobamate inhibits CYP2C19, so it increases phenytoin C_{max} 70% and phenobarbital 34%. By contrast, CNB induces CYP3A4, so lamotrigine serum concentrations are expected to fall 21% to 52%. Administration of phenytoin causes CNB serum concentrations to fall 27% to 28%.

In the above clinical trial (YKP3089-C017), adults were given adjunctive placebo or 1 of 3 doses of CNB.[4] An inclusion criterion was ≥8 focal-onset seizures with an objective, observable component during an 8-week baseline. After a 6-week titration to full dose, patients were maintained on their assigned dose of CNB during the 12-week maintenance phase. If the assigned dose of CNB was not tolerated due to adverse effects, one blinded decrease in CNB dose was permitted. A longer titration period would have been optimal for an ASM with such a long half-life, because steady state concentrations are not reached for 4 to 5 half-lives (in this case approximately 10 days) after each dose increase.

For the modified intent-to-treat (MITT) entire-treatment phase, the median percent seizure reductions were 24%, 36%, 55%, and 55% for the placebo and CNB 100, 200, and 400 mg cohorts, respectively. It should be noted that the median modal dose in the 400 mg group was actually 300 mg, presumably due to poorer tolerability of the 400 mg dose. The 400 mg group did not reach that assigned dose until the start of the maintenance phase, and steady-state serum concentration would not be reached for about 10 days later, so it is very reasonable to look at the results of just the MITT maintenance-phase cohorts. In doing so, one sees robust dose–response median percent seizure reductions of 25%, 40%, 56%, and 65% for the placebo and CNB 100, 200, and 400 mg cohorts, respectively. The 65% reduction at the maximum dose is greater than that seen in any of the pivotal studies on all the second- and third-generation ASMs. C017[4] represents "study 2" in the US prescribing information.[1] For replication, "Study 1" (YKP3089-C013) compared placebo to CNB at 200 mg/d, but used an unusually short maintenance phase of only 6 weeks. The median percent decrease in seizure frequency in the C013 "study 1" was 21.5% for placebo and 55.6% for CNB 200 mg/d.[1] The C013 study manuscript is in press at the time of this writing.

In both trials, the most common adverse effects in CNB-treated patients were somnolence, dizziness, fatigue, and headache (although headache was reported in 10% of patients on CNB and 9% on placebo).[1] As is typical, adverse effects occurred in the greatest number of subjects at the highest dose. Adverse reactions leading to discontinuation were ataxia, dizziness, somnolence, diplopia, nystagmus, and vertigo. Hyperkalemia (greater than 5 meq/L) was seen, and followed a dose–response relationship. Shortening of the electrocardiogram QT interval occurred in a greater percentage of CNB than placebo patients. The incidence of psychiatric adverse effects was low.

Three cases of drug reaction with eosinophilia and systemic symptoms (DRESS, formerly "multiorgan hypersensitivity") occurred in the C13 and C17 studies in which CNB was titrated quickly, but no cases of DRESS were reported in a much larger, open-label safety study (YKP3089-C021) of 1339 adults with focal-onset seizures when CNB was started at just 12.5 mg/d and titrated every 2 weeks.[1] Hence, a "start low and go slow" titration schedule of 12.5 mg/d for weeks 1 and 2, 25 mg/d for weeks 3 and 4, 50 mg/d for weeks 5 and 6, 100 mg per day for weeks 7 and 8, and then 200 mg/d is recommended.[1] If needed, the dose may be slowly titrated up to a maximum of 400 mg given once daily.[1]

In clinical trials, it appears that CNB may be one of the most effective ASMs, but we don't yet know if this will be borne out in clinical practice. In addition to the high median percent reductions in the 12-week maintenance phase, the seizure-free rate is very high compared to ASMs approved since 1994. In a meta-analysis[5] of the results of 62 pivotal placebo-controlled randomized trials of lamotrigine, gabapentin, topiramate, tiagabine, levetiracetam, zonisamide, pregabalin, lacosamide, and eslicarbazepine, and in pooled analyses of the 3 pivotal trials conducted both for perampanel[6] and for brivaracetam,[7] seizure-free rates ranged from 0% to 6.5%.[5] By comparison, the seizure-free rate was 1% in the placebo group and 21% in the CNB 400 mg group.[1] Although no accurate comparisons can be made between the results of these various studies done with different protocols, and at different times and locations around the world, the high seizure-free rate in the C017 study is unique.

In an analysis of the seizure-free rate of newly diagnosed patients treated at the Western Infirmary in Glasgow, Scotland between 1982 and 2012, Chen et al reported in 2018 that the seizure-free rates for 1+ year with the first ASM, second ASM regimen, and third ASM regimen were 45.7%, 11.6%, and 4.4%, respectively.[8] These results were nearly identical to those published in 2000 using older ASMs at the same

institution by Kwan and Brodie.[9] These data suggest that despite the introduction of numerous new ASMs, some with novel mechanisms of action, in the 18 years between their first report and their most recent one, little has changed in the percentage of persons with epilepsy achieving the ultimate goal of seizure-freedom (with its attendant major benefits in quality of life). If CNB maintains its high seizure-free rate in long-term use, then it may represent an important new ASM.

By David G. Vossler

ORCID iD

David G. Vossler http://orcid.org/0000-0003-4823-0537

References

1. Xcopri Prescribing Information. 21 November 2019. Accessed 28 November 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212839s000lbl.pdf.
2. Nakamura M, Sho JH, Shin H, Jang IS. Effects of cenobamate (YKP3089), a newly developed anti-epileptic drug, on voltage-gated sodium channels in rat hippocampal CA3 neurons. *European J Pharm*. 2019;855(1):175-182. doi:10.1016/j.ejphar.2019.05.007.
3. Kasteleijn-Nolst DGAT, DiVentura BD, Pollard JR, et al. Suppression of the photoparoxysmal response in photosensitive epilepsy with cenobamate (YKP3089). *Neurology*. 2019;93(2):e559-e567. doi:10.1212/WNL.0000000000007894.
4. Krauss GL, Klein P, Brandt C, et al. Safety and efficacy of adjunctive cenobamate (YKP3089) in patients with uncontrolled focal seizures: a multicentre, double-blind, randomised, placebo-controlled, dose-responsive trial. *Lancet Neurology*. 2020;19(1):38-48. doi:10.1016/S1474-4422(19)30399-0.
5. Costa J, Fareleira F, Ascencao R, Borges M, Sampaio C, Vaz-Carneiro A. Clinical comparability of the new antiepileptic drugs in refractory partial epilepsy: a systematic review and meta-analysis. *Epilepsia*. 2011;52(3):1280-1291.
6. Steinhoff BJ, Ben-Menachem E, Ryvlin P, et al. Efficacy and safety of adjunctive perampanel for the treatment of refractory partial seizures: a pooled analysis of three phase III studies. *Epilepsia*. 2013:54(8):1418-1419.
7. Ben-Menachem E, Mameniskiene R, Quarato PP, et al. Efficacy and safety of brivaracetam for partial-onset seizures in 3 pooled clinical trials. *Neurology*. 2016;87(1):314-323.
8. Chen Z, Brodie MJ, Liew D, Kwan P. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs: a 30-year longitudinal cohort study. *JAMA Neurology*. 2018;75(3):279-286. doi:10.1001/jamaneurol.2017.3949.
9. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *New Engl J Med*. 2000;342(5):314-319.