

XEN1101: A Novel Potassium Channel Modulator for the Potential Treatment of Focal Epilepsy in Adults

Tian Wang and Gregory L Krauss

Department of Neurology, The Johns Hopkins University School of Medicine, Baltimore, MD, USA

DOI: <https://doi.org/10.17925/USN.2022.18.1.2>

Antiseizure medications that reduce seizures via new mechanisms are needed. XEN1101 is an agonist of voltage-gated potassium ion channels (Kv) that was recently shown to reduce focal-onset seizures in a placebo-controlled phase II study. The molecular structure of this potassium channel “opener” is different from ezogabine/retigabine, preventing dimer formation and the pigmentary deposition associated with ezogabine/retigabine treatment. This article reviews the pharmacology and early clinical results for XEN1101.

Keywords

Antiseizure medication, clinical trials, drug development, epilepsy, potassium channels, XEN1101

Disclosure: Tian Wang and Gregory L Krauss have no financial or non-financial relationships or activities to declare in relation to this article.

Review process: Double-blind peer review

Compliance with ethics: This study involves a review of the literature and did not involve any studies with human or animal subjects performed by any of the authors.

Data availability: Data sharing is not applicable to this article as no datasets were generated or analysed during the writing of this study.

Authorship: The named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship of this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval for the version to be published.

Access: This article is freely accessible at touchNEUROLOGY.com. © Touch Medical Media 2022

Received: 29 March 2022

Accepted: 18 May 2022

Published online: 21 June 2022

Citation: *touchREVIEWS in Neurology*, 2022;18(1):2–4

Corresponding author: Gregory L Krauss, Department of Neurology, The Johns Hopkins University School of Medicine, Baltimore, MD 21287, USA. E: gkrauss1@jhmi.edu

Support: No funding was received in the publication of this article.

Despite the use of various concurrent antiseizure medications (ASMs), over 30% of patients with focal onset seizures have persistent, uncontrolled seizures.¹ Hence, the search for new ASMs with better efficacy and tolerability is continuing. Voltage-gated potassium ion channels (Kv) repolarize neuronal action potentials, thus making potassium channel “openers” potentially attractive targets for the development of a new class of ASMs. In 2011, ezogabine/retigabine (Trobal[®] [EU] or Potiga[®] [USA]) (GlaxoSmithKline, Brentford, London, England and Bausch Health, Laval, Canada respectively) was the first neuronal potassium channel (KCNQ/Kv7) opener approved by the US Food and Drug Administration and the European Medicines Agency.^{2,3} It had a narrow therapeutic window and was discontinued in 2017, when patients developed lavender skin discolouration and retinal pigment clumping after several years of exposure.^{4–6} Recently, a positive allosteric modulator of neuronal Kv7.2/7.3 channels, XEN1101, has shown promise in treating focal onset epilepsy.⁷ XEN1101 is structurally distinct from ezogabine: it has a tertiary rather than a secondary aniline compound, which prevents the formation of chromophoric phenazinium-type dimers, which are associated with ezogabine’s pigmentary clumping. Preclinical studies, the pharmacological profile and a recent phase IIa study of XEN1101 (A study to evaluate XEN1101 as adjunctive therapy in focal epilepsy; ClinicalTrials.gov identifier: NCT03796962) support its development as a potential therapy for focal onset seizures.^{7–9}

XEN1101 pharmacology: Mechanism of action, toxicology, pharmacodynamics and pharmacokinetics

Mechanism of action

XEN1101 is a neuronal Kv7.2–7.5 potassium channel (KCNQ2-5) agonist that is more selective than ezogabine in modulating Kv7 channel subtypes in *in vitro* cell line studies.^{7,8} Compared with ezogabine, XEN1101 has a high affinity for the receptor, so it interacts more selectively with Kv7.2/7.3 channels than Kv7.3/7.5 and Kv7.4 channels.^{8,10} It was not found to affect Kv7.1, hERG and GABA channels in preclinical studies.^{8,10} XEN1101 was found to be 16 times more potent than ezogabine in the maximal electroshock stimulus screening seizure model.^{8,10} It was also found to be much more potent than ezogabine in modulating potassium ion channel conductance in patch-clamp studies in human embryonic kidney cells expressing Kv7.2/7.3 channels.^{8,10}

Pharmacokinetics and pharmacodynamics

In single-ascending-dose studies, the effective half-life of XEN1101 is greater than 24 hours, which allows once-a-day dosing.¹¹ Both the absorption and elimination phases of XEN1101 are long.¹¹ The peak serum concentration (C_{max}) for 20 mg single doses is 31.5 ng/mL (at time to peak drug concentration [T_{max}] 3.69 hours) and a half-life (t_{1/2}) of 41 hours; the C_{max} for 30 mg doses is 35.5 ng/mL (at T_{max} 3.17 hours) and t_{1/2} is 63.4 hours (all were mean values from the data of preclinical studies in human subjects). The bioavailability of XEN1101 increases approximately 1.5-times by food intake: in the fed state, a 25 mg dose produces a mean C_{max} of 45.8 ng/L and a t_{1/2} of 97 hours. The terminal elimination profile is long, with a t_{1/2} of approximately 4–10 days, likely due to its slow release from tissue compartments.¹¹ Near steady-state trough plasma levels were reached about 1 week after dosing.^{8,11}

Drug interactions, safety and toxicology

Based on microsome and transporter screening laboratory assays, drug interactions are not expected for XEN1101.^{8,10,11} XEN1101 did not inhibit or significantly induce CYP450 enzymes. The compound was not metabolized by most Cytochrome P450 inducers. *In vitro* studies show that CYP4A4 plays a minor role in the metabolism of XEN1101.⁸ The major hepatic oxidative metabolite of XEN1101 did not appear to alter the function of KCNQ channels in preliminary studies. However, human drug interaction studies are still needed.

Long-term animal studies have demonstrated a relatively safe, long-term preclinical profile of XEN1101.^{7,8,10} Dose-limiting sedation and ataxia were observed in monkeys during the initiation of treatment.⁸ Teratogenic studies in rats and rabbits did not show any embryo-foetal developmental abnormalities at 6 and 10 mg/kg/d dosages.⁸ The results of carcinogenicity and detailed non-human safety studies have not been reported. In recently completed 6-month and 9-month studies with rats and monkeys, respectively, the daily administration of XEN1101 at maintenance doses of 1, 2.5 or 4 mg/kg/day did not result in major adverse events.⁸

Ezogabine has a secondary aniline structure that can form chromophoric phenazinium-type dimers causing skin and retinal pigmentation changes.¹² Due to its tertiary aniline structure, XEN1101 does not form dimers as ezogabine did, and pigmentary deposits are unlikely to occur.¹⁰

XEN1101 clinical trials: Preliminary results

The effects of XEN1101 on a transcranial magnetic stimulation model of cortical excitability in humans

Transcranial magnetic stimulation motor thresholds have been used to define cortical excitability and to probe the effects of ASMs on cortical excitability. In a phase I study of 20 healthy volunteers, XEN1101 increased the participants' motor thresholds compared with placebo, thus suggesting that it decreases cortical excitability.¹³⁻¹⁵

The adverse events in the study were mild and included dizziness, fatigue, headache and attention disturbances; there were no serious adverse events in the 20 healthy volunteers.¹³⁻¹⁵

A phase IIb study of the efficacy and safety of XEN1101 in adults with focal epilepsy

The safety and efficacy of XEN1101 for treating focal onset epilepsy were studied in a multicentre, phase IIb, randomized, double-blind, placebo-controlled study (X-TOLE) with a 3-year open-label extension (OLE) option (ClinicalTrials.gov Identifier: NCT03796962).^{9,16,17} Adult subjects were randomized to receive placebo or adjunctive XEN1101 therapy at 10 mg, 20 mg and 25 mg doses.^{9,16,17}

The study had baseline and treatment periods of 8 weeks. A total of 530 individuals were screened, with 325 randomly assigned and treated.^{16,17} The subjects had an average age of 39.8 ± 13 years, and 50.5% of them were women. The study subjects had focal onset

epilepsy that was highly resistant to drugs: 91% of them were taking two or three background ASMs. During the study, eight treatment-emergent serious adverse events were reported: severe dizziness (n=1), muscle spasticity (n=1), seizure (n=1), hyponatremia (n=1), confusional state (n=1), psychogenic seizure (n=1), unspecified psychotic disorder (n=1) and somatic delusion (n=1).¹⁷ A blinded evaluation of safety labs, vital signs and electrocardiograms showed no safety signals. A total of 12.3% of patients discontinued the study treatment; this discontinuation appeared to be dose dependent: participants receiving placebo had a discontinuation rate of 4.4%, participants receiving 10 mg of XEN1101 had a discontinuation rate of 2.2%, participants receiving a 20 mg dose had a discontinuation rate of 15.7% and participants receiving a 25 mg dose had a discontinuation rate of 22.8%. The most common (>10%) treatment-emergent adverse events were dizziness (24.6%), somnolence (15.6%) and fatigue (10.9%). Six subjects (10 mg: n=1; 20 mg: n=2; 25 mg: n=3) reported treatment-emergent adverse events of weight increase of ≥7% from baseline. Two subjects developed urinary retention requiring dose reductions. This possible adverse event should be monitored in future studies: voltage-gated K⁺ channels regulate the bladder detrusor smooth muscle function and ezogabine-produced urinary retention in rodents but had minimal effects in humans.¹⁸

At baseline, the subject's median seizure frequency was ~13 per month (28 days).^{16,17} During the study treatment, participants in the 25 mg, 20 mg, 10 mg and placebo groups had a median percentage change in monthly seizure frequency of 52.8%, 46.4%, 33.3% and 18.2%, respectively.¹⁷ The 50% responder rates (a secondary endpoint) were 54.5%, 43.1%, 28.3% and 14.9% in the 25 mg, 20 mg, 10 mg and placebo groups, respectively.¹⁷ There were statistically significant differences between the treatment groups and the placebo group (p<0.05). The >75% seizure responder rates for both the 20 mg and 25 mg doses were 29% (compared with 6.1% for placebo), while 7.8% of participants taking a 20 mg dose of XEN1101 were 100% responders (compared with 1.7% for placebo).¹⁷

To date, no pigmentary abnormalities have been recorded during the study's double-blind phase or early analysis of the continuing OLE.

Conclusion

XEN1101 is a novel ASM that functions as a positive allosteric modulator of neuronal Kv7.2/7.3 channels and shows promise in treating focal onset seizures.^{7,8} It has higher potency in animal seizure models and *in vitro* studies than ezogabine. XEN1101 has a tertiary aniline structure that prevents the formation of chromophoric dimers, thus making ezogabine-like pigmentation changes unlikely.^{10,11} A transcranial magnetic stimulation study was used to identify the optimal tolerated doses that decrease cortical excitability.¹³ The data from the pharmacokinetics studies support once-a-day dosing. The phase IIb X-TOLE study (ClinicalTrials.gov Identifier: NCT03796962) demonstrated the preliminary safety and a favourable dose-dependent efficacy and tolerability profile.¹⁶ The OLE phase of the trial to monitor the safety of XEN1101 is still ongoing. □

1. Sultana B, Panzini M, Carpentier AV, et al. Incidence and prevalence of drug-resistant epilepsy: A systematic review and meta-analysis. *Neurology*. 2021;96:805-17.
2. GlaxoSmithKline. GlaxoSmithKline and Valeant announce US FDA approval of Potiga™ (ezogabine). 2011. [Press release]. Available at: [www.gsk.com/en-gb/media/press-releases/glaxosmithkline-and-valeant-announce-us-fda-approval-of-potiga-ezogabine/#:~:text=\(NYSE%2F\)TSX%3A%20VRX,aged%2018%20years%20and%20older.&text=GlaxoSmithKline%20\(NYSE%3A%20GSK\)%20and%20Valeant%20Pharmaceuticals%20International%2C%20Inc.,\(NYSE%2F\)TSX%3A](http://www.gsk.com/en-gb/media/press-releases/glaxosmithkline-and-valeant-announce-us-fda-approval-of-potiga-ezogabine/#:~:text=(NYSE%2F)TSX%3A%20VRX,aged%2018%20years%20and%20older.&text=GlaxoSmithKline%20(NYSE%3A%20GSK)%20and%20Valeant%20Pharmaceuticals%20International%2C%20Inc.,(NYSE%2F)TSX%3A) (accessed 15 June 2022).
3. GlaxoSmithKline. Regulatory update - GSK and Valeant

4. receive positive opinion in Europe from the CHMP for Trobalt (retigabine). 2011. [Press release]. Available at: www.gsk.com/en-gb/media/press-releases/regulatory-update-gsk-and-valeant-receive-positive-opinion-in-europe-from-the-chmp-for-trobalt-retigabine/ (accessed 15 June 2022).
4. GlaxoSmithKline. GlaxoSmithKline: Advance notification of Trobalt® discontinuation, 2016. Available at: https://assets.publishing.service.gov.uk/media/57fe4b6640f0b6713800000c/Trobalt_letter.pdf (accessed 15 June 2022).
5. Stafstrom CE, Grippon S, Kirkpatrick P. Ezogabine (retigabine). *Nat Rev Drug Discov*. 2011;10:729-30.
6. Ezogabine (Potiga) toxicity. *Med Lett Drugs Ther*. 2013;55:96.
7. Bialer M, Johannessen SI, Koepf MJ, et al. Progress report

- on new antiepileptic drugs: A summary of the Fourteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XIV). I. Drugs in preclinical and early clinical development. *Epilepsia*. 2018;59:1811-41.
8. Bialer M, Johannessen SI, Koepf MJ, et al. Progress report on new antiepileptic drugs: A summary of the Fifteenth Eilat Conference on New Antiepileptic Drugs and Devices (EILAT XV). I. Drugs in preclinical and early clinical development. *Epilepsia*. 2020;61:2340-64.
9. ClinicalTrials.gov. A Study to Evaluate XEN1101 as Adjunctive Therapy in Focal Epilepsy. ClinicalTrials.gov Identifier: NCT03796962. Available at: <https://clinicaltrials.gov/ct2/show/NCT03796962> (accessed 15 June 2022).

10. Dean R, Lin S, Bankar G, et al. Preclinical in vitro and in vivo comparison of the Kv7 activator XEN1101 with ezogabine. Presented at: American Epilepsy Society Annual Meeting, virtual, 7 December 2020. Abstr 654.
11. Aycardi E, Namdari R, Cadieux J, et al. A first in human study to assess the safety, tolerability, pharmacokinetics and preliminary pharmacodynamics of a novel small molecule KV7.2/7.3 positive allosteric modulator (XEN1101) in healthy subjects. Presented at: American Epilepsy Society Annual Meeting, New Orleans, LA, USA, 3 December 2018. Abstr 3282.
12. Groseclose MR, Castellino S. An investigation into retigabine (ezogabine) associated dyspigmentation in rat eyes by MALDI imaging mass spectrometry. *Chem Res Toxicol*. 2019;32:294–303.
13. Premoli I, Rossini PG, Goldberg PY, et al. TMS as a pharmacodynamic indicator of cortical activity of a novel anti-epileptic drug, XEN1101. *Ann Clin Transl Neurol*. 2019;6:2164–74.
14. Beatch GN, Rossini PG, Abela E, et al. A phase I sub-study utilizing transcranial magnetic stimulation to assess the pharmacodynamic effects of a novel potassium channel opener (XEN1101) on human cortical excitability. Presented at: American Epilepsy Society Annual Meeting, New Orleans, LA, USA, 30 November – 4 December 2018. Poster 3292.
15. Beatch GN, Harden C, Namdari R, et al. Use of transcranial magnetic stimulation data in the design of a dose range finding efficacy, safety, tolerability, and pharmacokinetics study of XEN1101 in patients with focal epilepsy. Presented at: American Epilepsy Society Annual Meeting, Baltimore, MD, USA, 9 December 2019. Abstr 331.
16. French J, Porter R, Perucca E, et al. Phase 2b efficacy and safety of XEN1101, a novel potassium channel modulator, in adults with focal epilepsy (X-TOLE). Presented at: American Epilepsy Society Annual Meeting, Chicago, IL, USA, 4 December 2021. Abstr 1419.
17. Xenon Pharmaceuticals. Phase 2b efficacy and safety of XEN1101, a novel potassium channel modulator, in adults with focal epilepsy (X-TOLE). [Poster presentation]. Available at: www.xenon-pharma.com/wp-content/uploads/2021/12/French_Poster_AES2021_FINAL4.pdf (accessed 15 June 2022).
18. Malysz J, Petkov GV. Detrusor smooth muscle KV7 channels: Emerging new regulators of urinary bladder function. *Front Physiol*. 2020;11:1004.