Editorial

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XEN1101, a novel potassium channel opener: hope or hype for adults with focal seizure

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Dear Editor,

Epilepsy is one of the most common neurological illnesses in the world affecting ~65 million individuals worldwide[1,2]. Its chronicity incurs a severe cost on individual and communal levels[1]. The disease classification of epilepsy is currently under revision, with literature suggesting its disease trajectory to be dependent on the underlying aetiology. The fortune spent on treating this condition was estimated to be $119.27 billion, calculated by applying individual costs to the estimated 52.51 million individuals worldwide while accounting for the treatment gap[3]. We evaluated the burden and unmet needs of the diseased individuals and their caregivers by concentrating on focal seizures, which are the most prevalent type of seizure in both adults and children[1].

Up to 61% of people with epilepsy have focal seizures. Compared to the general population, they are associated with a higher risk of injury and early mortality. Persistent seizures are associated with a 20–40% chance of physical injuries (such as fractures, burns, and concussions) over a 12-month follow-up[1,2]. Treatment involves seizure elimination while minimizing the associated side effects of antiseizure drugs (ASDs).

Recent studies have highlighted the auspicious potential of XEN1101, a potassium channel opener. XEN1101, a small molecule specifically designed to activate potassium channels Kv7.2/Kv7.3, is currently undergoing development. This compound aims to address FOSs, the most prevalent seizures in individuals with epilepsy. The Kv7.2/Kv7.3 voltage-gated potassium channels are strategically positioned in the perisomatic and axonal regions of brain neurons, making them an attractive target for intervention. These channels are vital in counteracting neuronal membrane depolarization near the spike threshold, thus limiting epileptic hyperexcitability. Mutations in the KCNQ2 and KCNQ3 genes, responsible for encoding these channels, can result in conditions such as benign familial neonatal seizures and early-onset epileptic encephalopathy[4,5]. Conversely, medications like XEN1101 that enhance the opening of Kv7.2/Kv7.3 channels have shown efficacy in reducing seizures, offering a promising therapeutic option for patients experiencing seizures.

A Phase 2b Randomized Clinical Trial (X-TOLE Trial) conducted by French and colleagues strongly suggest that XEN1101 holds significant promise in filling the unmet therapeutic gap for patients with FOSs by offering a novel mechanism of action. This study encompassed 325 randomized and treated patients, with 285 completing the 8-week double-blinded phase. It demonstrated a dose-dependent decrease in seizures, with a substantial median percentage reduction compared to placebo. In comparison to placebo (18.2%), a significant median percentage reduction was observed in monthly focal-onset seizure frequency for 25 mg (52.8%, $P < 0.001$), 20 mg (46.4%, $P < 0.001$), and 10 mg (33.2%, $P = 0.04$). There were no recorded deaths and good tolerability, with side effects similar to those of prescription antiseizure drugs. The most frequent treatment-emergent adverse events (TEAEs), observed in over 10% of participants across all XEN1101 dosage groups, included dizziness (24.6%), somnolence (15.6%), and fatigue (10.9%). In terms of weight increase as a TEAE, one patient (2.2%) at the 10 mg dosage, two patients (3.9%) at the 20 mg dosage, and three patients (2.6%) at the 25 mg dosage reported this side effect. No TEAEs related to tissue discoloration were documented. The adverse event of confusional state was noted in 4.7% of the treated groups, with percentages of 2.2% for the 10 mg group, 5.9% for the 20 mg group, and 5.3% for the 25 mg group. Additionally, clinical development for the management of focal-onset seizures is supported by positive efficacy and safety outcomes[6].

Further investigations into the potential of XEN1101 include its use in patients experiencing developmental and epileptic encephalopathy (DEE), specifically those with mutations in the Potassium Voltage-Gated Channel Subfamily Q Member 2 (KCNQ2) gene. Compared to known KCNQ openers like retigabine and pynegabine, XEN1101 has a competitive standing. Clinical trials are ongoing to evaluate its safety and efficacy in real-world scenarios, indicating its potential for personalized therapy in DEE patients with specific mutations in the KCNQ2 gene[7].

In addition to clinical outcomes, studies on healthy volunteers explored the effects of XEN1101, Lamotrigine, and Levetiracetam on electroencephalographic (EEG) activity. The results provide valuable insights into the diverse impacts of these drugs on brain function, emphasizing the importance of understanding their effects

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for effective seizure and epilepsy management. The study analyzed the effects of lamotrigine, levetiracetam, and XEN1101 on healthy volunteers' EEG activity. Results showed that levetiracetam reduced TMS-related spectral perturbation (TRSP) power, lamotrigine increased alpha power and reduced theta band power, while XEN1101 lowered the TRSP power. EEG analysis provides valuable insight into anti-epileptic drug effects[8].

The relevance of XEN1101 extends beyond its direct effects on seizures, as evidenced by studies involving transcranial magnetic stimulation (TMS). The suppression of TMS-evoked potentials and changes in resting motor threshold suggest broader implications for cortical and corticospinal excitability, aligning with other anti-epileptic drugs. A study on anti-epileptic drugs (AEDs) targeting ion channels found that a 20 mg dose of XEN1101 significantly suppressed TMS-evoked potentials and increased resting motor threshold (RMT) compared to baseline. The study also found that 20 mg of XEN1101 reduced cortical and corticospinal excitability, similar to other AEDs. These findings suggest that TMS can be a valuable tool for informing early-stage clinical trials[9].

'Investigational Compounds Overview,' a report published in October 2018, outlines the list of investigational compounds analyzed from preclinical or early-stage clinical studies. XEN1101 is one of the compounds discussed. Of the listed designer compounds discussed, some act as enzyme inhibitors, while others target specific epilepsy syndromes through precision medicine[10].

Lastly, this letter highlights the discussions at the Sixteenth Eilat Conference on New Antiepileptic Drugs and Devices, which aimed at bringing field experts together to discuss the latest therapeutic advancements against seizures and epilepsy. A day was dedicated to discussing 'investigational compounds', conferring their role in treating seizures and epilepsy. XEN1101 was among the compounds discussed[11].

The article highlights the worldwide impact of epilepsy, with focal seizures posing elevated risks of injury and mortality. Shifting attention to XEN1101, a potassium channel opener, the Phase 2b X-TOLE trial illustrates its effectiveness in diminishing focal-onset seizures, introducing a distinctive therapeutic approach. The drug's scope extends to DEE, targeting individuals with KCNQ2 gene mutations. Insights from studies involving healthy volunteers reveal varied effects on EEG activity. The impact of XEN1101 on cortical excitability, as observed through TMS, indicates broader potential applications. Discussions at the Sixteenth Eilat Conference and its recognition in the Investigational Compounds Overview highlight its importance in precision medicine for diverse epilepsy syndromes. Having the potential to enhance patients' quality of life by improving seizure control, this approach requires further studies to comprehend its effectiveness and long-term implications. Future research on XEN1101 should prioritize long-term efficacy and safety studies to understand its sustained impact. Diversifying patient populations is crucial for evaluating its effectiveness across demographics and epilepsy types. Comparative studies with existing antiseizure drugs will provide insights into XEN1101's efficacy and safety. Exploring its application in various epilepsy syndromes beyond focal-onset seizures is essential. In-depth studies on its mechanism of action, particularly its effects on Kv7.2/Kv7.3 channels, will guide targeted interventions. Collaborative efforts in real-world scenarios, supported by ongoing clinical trials, are crucial for evaluating XEN1101's safety and efficacy in diverse populations, positioning it as a cornerstone in personalized epilepsy therapy.

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