ENCODE
IDEAS

Xenon Pharmaceuticals, Inc. (XENE)
INITIATION REPORT

October 16, 2019

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FINANCIAL SUMMARY TABLE

Symbol	XENE
Exchange	NASDAQ
52 week High	$13.70
52 week Low	$5.41
Fully diluted O/S	28.4mm
Market Cap	~$215mm*
Average Volume (30D)	45k
Cash	$102mm**
Debt	$13.2mm**

*as of 10/11/2019 **as of 6/30/2019

KEY CATALYST DATES

Q4 2019	Regulatory Agreement on Ph3 design for XEN496
Q4 2019	IND Submission for XEN496
1H 2020	Ph3 Initiation of XEN496 in KCNQ2-DEE
1H 2020	Ph2 Initiation of XEN 901 in SCN8A-DEE
Q4 2020	Ph2b top-line data release for XEN1101in adult focal epilepsy
1H 2021	Ph3 top-line data release for XEN496 in KCNQ2-DEE

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Valuation Summary

We are initiating coverage on Xenon as a high conviction investment idea. We believe through clinical success with their lead assets, XEN496 and XEN1101, Xenon can achieve a market cap of >$1 billion by 2021, reflecting a nearly 4.5x multiple from its recent share price of $8.35 (10/11/19).

XEN496 and XEN1101 are relatively de-risked assets in our opinion, given the history of ezogabine and the Kv7 target, and both should have important clinical readouts in the next 12 to 18 months.

XEN496 has potential to be the first drug approved in the U.S. for the rare paediatric epilepsy KCNQ2-DEE. KCNQ2-DEE's prevalence is estimated to be 50% of Dravet syndrome, where notable CNS companies GW Pharmaceuticals (Nasdaq: GWPH) and Zogenix (Nasdaq: ZGNX) traffic. We would highlight to investors that ZGNX added approximately $800mm in market cap in the days/weeks following their first successful Dravet syndrome Ph3 study. Though a rudimentary calculation, Xenon getting a $400mm (50% of $800mm) bump in valuation upon Ph3 success for XEN496 in KCNQ2-DEE seems appropriate, and arguably understated, given the lack of competition in the KCNQ2-DEE market relative to Dravet syndrome.

Xenon is currently enrolling a large Ph2b study with XEN1101 in adults with refractory partial onset epilepsy. We see upside potential in XEN1101 Ph2b success that parallels what Sage Therapeutics (Nasdaq: SAGE) received after brexanolone's successful Ph2a proof-of-concept study in postpartum depression (PDD). We believe the U.S. epilepsy market opportunity for XEN1101 to be a similar size to brexanolone's in PDD ($500mm–$1B). Sage added approximately $500mm in market cap immediately after announcing their Ph2a data, and we view this as highly achievable for Xenon assuming success in their Ph2b with XEN1101.

Xenon has been in a catalyst/clinical data drought throughout 2019, and not surprisingly, the stock has traded sideways for much of the year. The catalyst drought should come to an end in 2020, with the initiation of a pivotal program with XEN496 in KCNQ2-DEE and top-line data from XEN1101. Having spoken to a number of prospective investors on Xenon, the recurring theme seems to be, "good pipeline, good chance of clinical success, but data readouts are too far out." We see this theme changing in 2020 and believe Xenon should experience a nice speculative uptick throughout the year as the company draws closer to key catalysts. We see the potential for a substantial re-rating of Xenon in 2020/2021, with an achievable market cap of >$1b upon clinical success. As such, we believe there is a tremendous opportunity to accumulate Xenon at current levels.

Financial Considerations

At the end of June 30, 2019, Xenon reported a cash balance of $101.8mm. This, according to management, is sufficient runway to get the company into 2021, thereby through XEN1101 top-line data release. We recognize that Xenon management may look to strengthen their balance sheet in 2020. This most likely means an equity financing during the year, but we also don't rule out the possibility of partnering as a source of capital. Over its history, Xenon has demonstrated an aptitude for business development, having carried out deals with Genentech and Teva, most recently.

For a company of its size, Xenon has an enviable investor base, consisting of many well regarded deep-science funds such as Biotech Value Fund, Vivo Ventures, Avoro Capital (formerly known as venBio), Adage Capital, and Eventide to name but a few. We find having investors of this ilk validating; furthermore, we find it comforting to know all of these funds built their positions in 2018 (or earlier), fully realizing that patience would be required before any meaningful data catalysts.

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Pipeline Overview

DRUG	TARGET	INDICATION	FDA	POC DATA	STAGE	PROBABILITY OF SUCCESS	ADDRESSABLE MARKET
XEN1101	Kv7	Focal Seizures (Adults)	NCE	Ph1b Biomarker	Enrolling P2b	Above Average	>$500MM-$1B
XEN496	Kv7	KCNQ2-DEE (Paediatric)	505(b)2	Patient reported	Ph3 Initiation Imminent	Above Average	~$200MM
XEN901	Nav 1.6	SCN8A-DEE (Paediatric)	NCE	Ph1b Biomarker	Ph2/3 Initiation Immiinent	Average	~$100M
XEN007	Ca2.1	Childhood absence epilepsy (Paediatric)	NCE	Ex-US data	Ph2	Average	Unknown

Xenon Pharmaceuticals, Nasdaq: XENE

Encode Ideas is initiating coverage on Xenon Pharmaceuticals as a conviction investment idea. Xenon is at the forefront of a new wave of precision medicine in neurology, with arguably the deepest and most advanced pipeline of selective ion-channel drugs in development. The company's specific focus has been epilepsy, where it has four drugs in development. Xenon's epilepsy pipeline is uniquely diversified with drugs being developed for both adults and children, large markets and rare diseases, a variety of ion-channel targets (potassium, sodium, and calcium), and new chemical entities (NCEs) and reformulations (505(b)2). The next 12 to 18 months will be data rich for Xenon, with clinical readouts from a number of mid/late stage epilepsy studies. The risk profile of these clinical programs varies, but we believe there is a good likelihood the company reports positive data from one or more of their epilepsy assets. Given its modest tech value, we believe Ph2/Ph3 success from one or more of their epilepsy programs could have a dramatic impact on Xenon's valuation

The Kv7 Story

Kv7 is a well elucidated potassium channel in the central nervous system (CNS). Valeant developed ezogabine, a Kv7 opener (potentiator), for the treatment of adult partial onset epilepsy, and out-licensed it to GSK. Approved by the FDA in 2011, ezogabine (branded as Potiga), was the first and only potassium channel opener available in the United States. Of the three million American adults with epilepsy, it is estimated that 25%–33% are not well controlled on their current anti-epileptic drugs (AEDs). Therefore, when ezogabine was approved physicians were excited to have a new AED, with a unique mechanism of action (MOA), to treat their refractory epilepsy patients. GSK, however, ran into commercial and regulatory issues with ezogabine shortly after it was launched. Most notably, a small percentage of patients reported blue pigmentation occurring in their nail beds, gums and eyes, after prolonged use of ezogabine. FDA was particularly concerned over the ocular pigmentation and slapped a blackbox warning on ezogabine for potential visual acuity risk. Even though data would later demonstrate that the pigmentation was purely cosmetic, the brand never recovered, and in 2017 GSK removed ezogabine from the market.

Xenon's ion-channel expertise and epilepsy focus naturally led it to explore Kv7 as a target for new drug development. While working on new chemistries in-house, the company came across a unique external opportunity to accelerate its push into the clinic with a Kv7 opener. It was found that Valeant had follow-up compounds to ezogabine that hadn't been licensed to GSK. As Valeant pivoted out of R&D, they allowed the scientist working on the follow-up compounds to ezogabine to leave and take the compounds with him. In 2017, not long before GSK removed ezogabine from the U.S. market, Xenon acquired the company created by the former Valeant scientist, that included an IND-ready second generation of ezogabine. It is important to highlight that the drug was not a reformulation of ezogabine, rather a new chemical entity (NCE), with fresh composition of matter patents into 2031.

The rise of XEN1101

Now known as XEN1101, the next generation of ezogabine addresses many of the parent compound's known liabilities. XEN1101 has much greater affinity for the Kv7 target,

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allowing for once-daily dosing, whereas ezogabine was dosed three times a day. More importantly, XEN1101 is not expected to have the pigmentation issue that plagued ezogabine. Unlike ezogabine, XEN1101 cannot dimerize (bind to itself), which is now known to be the chemical culprit that caused the pigmentation issue.

Xenon completed a Ph1b study with XEN1101 in 2018. The study demonstrated a clean side effect profile, with the majority of the side effects typical of CNS drugs that cross the blood-brain barrier, such as drowsiness and dizziness. The drug's pharmacokinetic (PK) profile from the study supported once-daily dosing, such that patients can take XEN1101 before bed, minimizing the impact of the CNS-related side effects. Xenon also ran a pharmacodynamic test, known as transcranial magnetic stimulation (TMS), as part of the Ph1b. TMS is an emerging test that has been used to measure the ability of approved AEDs to dampen neuroexcitation. Xenon is believed to be the first company to use TMS to determine CNS activity in an experimental compound. The TMS data reported by Xenon demonstrated XEN1101 had a statistically significant impact on markers of neuroexcitation (TMS-EMG & TMS-EEG) versus placebo. When the XEN1101 TMS data are compared to historical TMS data from ezogabine, recognizing the limitations and risks of cross study comparisons, XEN1101 appears to dampen neuroexcitation more than ezogabine.

Xenon is currently enrolling a 300-patient international randomized placebo-controlled Ph2b study with XEN1101 in adults with focal epilepsy. Top-line data from this study are anticipated late in 2020. We believe XEN1101 is likely to be successful in the Ph2b study. XEN1101's parent, ezogabine,was successful in three Ph3 focal epilepsy studies, FDA approved, and used in thousands of patients as a commercial product. XEN1101 targets the same channel, Kv7, as ezogabine, and appears to have a superior PK and safety profile. XEN1101 appears to actively impact neuroexcitation in the CNS, as demonstrated by the statistically significant TMS data from the Ph1b study. All the factors above give us confidence in a positive outcome for XEN1101 in the ongoing Ph2b study.

We believe XEN1101 is being discounted due, in large part, to the lack of traditional Ph2a proof-of-concept data. Therefore, success in the ongoing Ph2b should lead to a substantial revaluation for Xenon, likely in the range of $500mm in added cap.

Longer-term, we see XEN1101 as an asset that Xenon likely partners. The next clinical step for XEN1101 would include a large, and rather expensive, Ph3 program, something we believe Xenon would prefer to risk-share with a partner.Furthermore, it is our belief that Xenon would prefer to focus on rare CNS clinical development, and maybe even commercialization in the future, and out-license assets that target larger markets after Ph2 development. We would therefore anticipate, upon a successful Ph2b outcome, that a partnering deal would likely be consummated in 2021.

The Rebirth of Ezogabine: XEN496

The ezogabine story didn't end with its removal from the U.S. market. In fact, the act of GSK removing the drug from the market was likely the galvanizing event that led to ezogabine's rebirth as XEN496.

Although ezogabine had been a commercial flop for its on-label indication in adult focal epilepsy, it was being prescribed with some success, by paediatric neurologists and epileptologists, for a rare form of infantile epilepsy known as KCNQ2 developmental and epileptic encephalopathy (KCNQ2-DEE). It is estimated there are 2,000–3,000 children in the United States with KCNQ2-DEE, and 200–250 KCNQ2-DEE live births per year. KCNQ2-DEE appears in children early in life, generally in the first weeks, and is characterized by a very heavy seizure burden, often daily. Due to their heavy seizure burden, children with KCNQ2-DEE experience developmental delays and challenges, have a high incidence of correlated disorders, like autism, and have high mortality rates (known as sudden unexplained death in epilepsy or SUDEP). Kv7 encodes for the KCNQ2 gene, and it was thought that an on-target treatment, like ezogabine, could curb or potentially completely alleviate seizure burden in these children. Thus, when GSK removed ezogabine from the market, parents of children benefiting from the treatment were apoplectic. GSK found itself in a precarious position: they no longer wanted to support the on-label commercial business in focal seizures, but were being pressured by parents, the patient advocacy group (KCNQ2 Cure Alliance) and the media (Washington Post Article, see link here) to keep the drug available for an off-label indication. That's when Xenon, with its knowledge of the Kv7 channel, stepped in.

In order to properly develop ezogabine for KCNQ2-DEE, Xenon needed several pieces to fall into place: (1) they needed to secure orphan drug designation (ODD) from FDA.

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Ezogabine's composition of matter patent was due to expire in 2019 and Xenon needed the 7.5-year ODD market exclusivity in lieu of patent protection (2) they needed FDA's guidance on whether ezogabine could be taken directly into a late-stage trial in infants (3) they needed GSK to allow them access (right of reference) to the ezogabine IND and NDA filings to avoid having to rerun preclinical toxicology. In 2018 Xenon was able to put all the pieces together, and announced they would develop a paediatric formulation of ezogabine, known as XEN496, for the treatment of KCNQ2-DEE.

Since the 2018 announcement, Xenon has been working on optimizing a paediatric formulation of ezogabine. Parents had been crushing ezogabine and adding it into breast milk, formula or cereal.

In order to develop XEN496 into a viable commercial product, Xenon had to optimize the delivery and formulation of ezogabine for infants and children. In its Q2 2019 earnings release, Xenon announced that XEN496 would be a granule formulation to be packaged as single-dose sachets. This new presentation of ezogabine should allow Xenon to secure new formulation patents, providing for greater protection beyond ODD. It is also important to highlight the historical pigmentation issue that derailed ezogabine's commercial utilization in adults, may be improved or completely addressed with Xenon's paediatric formulation. When discussing XEN496 on a recent conference call, the company noted "...we can limit the production of this pigmentation liability with the new drug product."

The company has disclosed that the FDA was supportive of a single Ph3 registrational study of XEN496 in approximately 20 KCNQ2-DEE children. Although we await final details on the study design, the company has disclosed that the FDA suggested a primary endpoint of seizure reduction versus baseline based on video EEG. Xenon has guided that it would file an IND with the FDA Q4 2019, and start dosing in the Ph3 study shortly thereafter. In the meantime, Xenon has opted to run a Ph1 PK study in healthy adults to confirm their new paediatric granule formulation achieves adequate drug exposure. That study is due to start imminently and be wrapped up by Q4 2019, and is not expected to impact timelines for the initiation of the Ph3 study. Xenon has not specifically guided to the timeline for top-line data in the Ph3 KCNQ2-DEE study, but we are budgeting for 1H2021.

We believe XEN496 will likely be successful in the Ph3 study. Our confidence derives from the precision medicine approach with XEN496 targeting the ion-channel that encodes for the mutated KCNQ2 gene, and the physician reported (both published and unpublished) treatment successes with ezogabine. Success in Ph3 should unlock substantial value for Xenon, that we conservatively estimate at $400mm in added market cap.

The Optionality of XEN901

Developed in Xenon's labs, XEN901, is a selective Nav1.6 antagonist. Sodium channel blockers are a mainstay of epilepsy treatment. However, approved sodium channel blockers are non-selective, and their utility is limited by off-target side effects. Xenon's preclinical work suggests that Nav1.6 is the predominant CNS sodium channel responsible for neuroexcitation leading to seizure activity. By selectively targeting this channel, Xenon believes XEN901 can have profound anti-seizure effect without the off-target side effects seen with existing approved non-selective sodium channel blockers. This MOA would suggest that XEN901 has potential to become a best-in-class, first-line treatment for adult focal epilepsy.

XEN901's MOA also lends itself to potentially benefiting another population of rare infant epilepsy patients, those with a mutation in the SCN8A gene. Similar to the XEN496 story, XEN901 hits the target that encodes for a gene mutation which gives rise to a devastating form of infantile epilepsy, in this case SCN8A-DEE, a population estimated to be half the size of KCNQ2-DEE. Children with SCN8A-DEE seize frequently, often multiple times a day, have muscle spasms, and often have development and cognitive disabilities similar to autism.

Xenon has completed Ph1 with XEN901 (as on oral tablet), that showed the drug was well tolerated. As part of the Ph1, they also completed a small TMS study, providing early evidence of CNS activity and dampening of neuroexcitation. The company has created a paediatric granule formulation, much like XEN496, and will be starting an adult healthy volunteer PK study imminently. Assuming the PK study goes as expected, it appears Xenon has opted to take XEN901 down the SCN8A-DEE path as opposed to adult focal seizures. According to the company, FDA appears open to XEN901 moving into a study in children with genetically defined SCN8A-DEE. The timing, size, and design of this study have yet to be disclosed, but we assume it would look similar to that of XEN496 in KCNQ2-DEE. Whether this study in SCN8A-DEE could be sufficient for approval, or

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subsequent studies will be required, is also yet to be determined.

The option to pursue SCN8A-DEE as opposed to focal seizures is likely due to a number of factors, including speed of development, cost, medical need, and probability of success. Pursuing SCN8A-DEE does not preclude Xenon from testing XEN901 in adult focal seizure, but we assume, given the number of trials (and associated costs) the company has ongoing, that it will focus its attention exclusively on SCN8A-DEE for the time being.

We believe targeting Nav1.6 could be a game changer in the treatment of epilepsy. Of all the assets in the Xenon pipeline, XEN901 arguably has the largest potential, when you consider the rare disease and broader adult epilepsy applications. Yet with all that potential comes risk, because selectively drugging Nav1.6 has not been tested in human efficacy studies. Fortunately for Xenon investors, we will likely get clinical readouts from the more de-risked, XEN1101 and XEN496 programs, before we see any data on XEN901. For that reason, we are treating XEN901 as a call option within the Xenon pipeline.

XEN007 Could Surprise in 2020

In 2018, Xenon announced its plans to develop flunarizine, a Ca2.1 modulator. Approved in many jurisdictions outside the U.S. for migraine, Xenon has secured access to key regulatory and manufacturing filings, allowing it to move flunarizine directly into human efficacy studies. There are numerous case reports and published papers of flunarizine's usage in off-label indications like vertigo, hemiplegic migraine, and certain epilepsy disorders. Originally, Xenon indicated it would be developing XEN007 for hemiplegic migraine or perhaps alternating hemiplegia of childhood. However, in the company's most recent quarterly call, they announced that flunarizine would be tested in a physician sponsored study in childhood absence epilepsy (CAE). CAE is a rare childhood epilepsy characterized by "petit mal" seizures that appear as staring spells, multiple times per day. Beyond the mechanistic rationale and medical need, it appears Xenon opted for this clinical path due to the speed and ease of recruitment. The study is expected to start imminently and will be open-label, so we may see incremental data disclosures throughout 2020.Investors are justifiably not paying attention to XEN007, but positive data, even from a single-center, open-label study, could be a pleasant surprise in 2020.

Summary

We recognize that "multiple shots on goal" is an overused investment cliché. Nonetheless, it seems appropriate when describing Xenon. The company has four unique ion-channel assets entering or in Phase II or later epilepsy studies, with data from most of these programs due in the next 12 to 18 months. We feel several of their assets have evidence of clinical benefit / activity, albeit from sources other than prospectively run proof-of-concept trials, that give us confidence in their likely future clinical success. We see the potential for a substantial re-rating of Xenon in 2020/2021, with an achievable market cap of >$1b upon clinical success. As such, we see a tremendous opportunity to accumulate Xenon at current levels.

Notable Risks

Notable risks to our investment thesis include; (1) regulatory issues developing around the IND submission for XEN496 and FDA's support of a single pivotal study in KCNQ2-DEE (2) Clinical setbacks in Xenon's later stage studies with XEN1101 and / or XEN496 (3) enrolment delays in either XEN1101 or XEN496 studies putting pressure on the balance sheet (4) capital market issues, whereby capital becomes challenging and / or excessively expensive to access.

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1 Introduction

1.1 Epilepsy

Epilepsies are chronic, noncommunicable, neurological disorders in which clusters of nerve cells, or neurons, in the brain sometimes signal abnormally and cause seizures. Neurons normally generate electrical and chemical signals that act on other neurons, glands, and muscles to produce human thoughts, feelings, and actions. During a seizure, many neurons fire at the same time, at rates much faster than normal. This surge of electrical activity causes involuntary movements, sensations, emotions, and behaviors. The temporary disturbance of normal neuronal activity may also cause a loss of awareness (National Institute of Neurological Diseases and Stroke).

Epilepsy is considered to be a spectrum disorder because of its different causes, different seizure types, its ability to vary in severity and its range of co-existing conditions (National Institute of Neurological Diseases and Stroke). Growing evidence suggests that the pathophysiological underpinnings of seizure generation may involve both aberrant structural integrity in certain brain regions as well as abnormal connections between these areas, resulting in large-scale network instability (Jiruska et al, 2013; Engel et al, 2013; Pittau et al, 2014). Epilepsy is among the most common neurological disorders, affecting over 1% of the population and leading to substantial morbidity and mortality (Choi et al, 2008). About 3.4 million people (3 million adults and 470,000 children) in the United States (Center for Disease Control and Prevention) and 50 million people worldwide (World Health Organization) currently live with epilepsy. Each year in the United States (US), an estimated 150,000 people are diagnosed with epilepsy. Epilepsy affects both males and females of all races, ethnic backgrounds and ages. In the US alone, the annual costs associated with epilepsy is estimated to be $15.5 billion in direct medical expenses and lost or reduced earnings and productivity (National Institute of Neurological Diseases and Stroke). In addition, the risk of premature death in people with epilepsy is up to three times higher than for the general population (World Health Organization).

Antiepileptic drug (AED) therapy is the mainstay of epilepsy management, which starts with accurate diagnosis of epilepsy, seizure types, and epilepsy syndromes (Park et al, 2019). AED therapy for epilepsy is complicated by unpredictable drug efficacy, adverse effects and the lack of information regarding optimal doses in individual patients. This necessitates systematic AED trials consisting of initial monotherapy with the first drug and subsequent trials of the second, third, and next drugs in either monotherapy or polytherapy, along with careful assessment of patient responses to each step of the drug trials. It is estimated that up to 70% of people living with epilepsy could live seizure- free if properly diagnosed and treated (World Health Organization).

A summary of epilepsy drug classes with their corresponding approved drugs and indications is provided in Table 1.

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Table 1 Major Classes of Epileptic Drugs

Drug Class	Approved Epilepsy Drugs	Indication
Nonselective voltage-gated ion channels	Phenytoin (Na+)	Indicated for the treatment of tonic-clonic (grand mal) and psychomotor (temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.
	Carbamazepine (Na+)	Indicated for use as an anticonvulsant drug. Evidence supporting efficacy of Carbamazepine as an anticonvulsant was derived from active drug-controlled studies that enrolled patients with the following seizure types: • Partial seizures with complex symptomatology (psychomotor, temporal lobe). Patients with these seizures appear to show greater improvement than those with other types. • Generalized tonic-clonic seizures (grand mal). • Mixed seizure patterns which include the above, or other partial or generalized seizures. Absence seizures (petit mal) do not appear to be controlled by Carbamazepine.
	Pregabalin (Ca2+)	• Management of neuropathic pain associated with diabetic peripheral neuropathy. • Management of postherpetic neuralgia. • Adjunctive therapy for the treatment of partial-onset seizures in patients 1 month of age and older. • Management of fibromyalgia. • Management of neuropathic pain associated with spinal cord injury.
	Lacosamide (Na+)	Indicated in patients 17 years and older with partial-onset seizures as adjunctive therapy.
GABA inhibitory neurotransmission	Clobazam	Indicated for the adjunctive treatment of seizures associated with LGS in patients 2 years of age or older.
	Diazepam	• Diazepam Tablets USP are indicated for the management of anxiety disorders or for the short-term relief of the symptoms of anxiety. Anxiety or tension associated with the stress of everyday life usually does not require treatment with an anxiolytic. • In acute alcohol withdrawal, Diazepam may be useful in the symptomatic relief of acute agitation, tremor, impending or acute delirium tremens and hallucinosis. • Diazepam is a useful adjunct for the relief of skeletal muscle spasm due to reflex spasm to local pathology (such as inflammation of the muscles or joints, or secondary to trauma); spasticity caused by upper motor neuron disorders (such as cerebral palsy and paraplegia); athetosis; and stiff-man syndrome. • Oral Diazepam may be used adjunctively in convulsive disorders, although it has not proved useful as the sole therapy.
	Vigabatrin	• Refractory Complex Partial Seizures - Vigabatrin for oral solution is indicated as adjunctive therapy for adults and pediatric patients 10 years of age and older with refractory complex partial seizures who have inadequately responded to several alternative treatments and for whom the potential benefits outweigh the risk of vision loss. Vigabatrin for oral solution is not indicated as a first line agent for complex partial seizures. • Infantile Spasms - Vigabatrin for oral solution is indicated as monotherapy for pediatric patients with infantile spasms 1 month to 2 years of age for whom the potential benefits outweigh the potential risk of vision loss.
	Tiagabine	Indicated as adjunctive therapy in adults and children 12 years and older in the treatment of partial seizures.

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Glutamate excitatory neurotransmission	Topiramate	• Monotherapy Epilepsy - Topiramate tablets are indicated as initial monotherapy for the treatment of partial-onset or primary generalized tonic-clonic seizures in patients 2 years of age and older • Adjunctive Therapy Epilepsy -Topiramate tablets are indicated as adjunctive therapy for the treatment of partial-onset seizures, primary generalized tonic-clonic seizures, and seizures associated with LGS in patients 2 years of age and older. • Migraine - Topiramate tablets are indicated for the preventive treatment of migraine in patients 12 years of age and older.
	Perampanel	• Partial-Onset Seizures - Perampanel is indicated for the treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy 4 years of age and older. • Primary Generalized Tonic-Clonic Seizures - Perampanel is indicated as adjunctive therapy for the treatment of primary generalized tonic-clonic seizures in patients with epilepsy 12 years of age and older.
Novel voltage-gated ion channels	Ezogabine	Indicated as adjunctive treatment of partial-onset seizures in patients aged 18 years and older who have responded inadequately to several alternative treatments and for whom the benefits outweigh the risk of retinal abnormalities and potential decline in visual acuity.
Other mechanisms	Levetiracetam	• Partial Onset Seizures - Levetiracetam tablets are indicated as adjunctive therapy in the treatment of partial onset seizures in adults and children 1 month of age and older with epilepsy. • Myoclonic Seizures in Patients with Juvenile Myoclonic Epilepsy - Levetiracetam tablets are indicated as adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents 12 years of age and older with juvenile myoclonic epilepsy. • Primary Generalized Tonic-Clonic Seizures - Levetiracetam tablets are indicated as adjunctive therapy in the treatment of primary generalized tonic-clonic seizures in adults and children 6 years of age and older with idiopathic generalized epilepsy.
	Brivaracetam	Indicated for the treatment of partial-onset seizures in patients 16 years of age and older with epilepsy.
	Epidiolex	Indicated for the treatment of seizures associated with LGS or DS in patients 2 years of age and older.
Ca2+ = Calcium; DS = Dravet Syndrome; GABA = Gamma-Aminobutyric acid; LGS = Lennox-Gastaut Syndrome; Na+ = Sodium; USP = United States Pharmacopeia		

In a hospital-based observational study, the first drug therapy was successful in 49.5% of patients and the second drug was successful in 36.7% of the patients (Brodie et al, 2012). The success rates of drug trials after failure of the first two drugs were significantly lower but was not different among subsequent drug regimens, ranging from 12.5% to 22.2% (Brodie et al, 2012). Therefore, the first and second drug trials are likely to be the major determinants of therapeutic outcomes of epilepsy and support the International League Against Epilepsy (ILAE) proposal of drug-resistant epilepsy (DRE), which is defined as the failure of seizure control by adequate trials of the first two AEDs (Kwan et al, 2010). Among adults taking epilepsy medication, those aged ≥65 years have better seizure control than among younger adults aged 35–54 years (Tian et al, 2018; Stefan et al, 2014). The apparent better response to epilepsy medication in older adults might be attributable to differences in seizure etiology, drug pharmacokinetics (PK), or better adherence to prescribed antiseizure medication regimens, possibly because of their experience with other chronic conditions or better access to care, including Medicare prescription drug coverage.

Gene defects underlying different forms of epilepsy have been identified and many of these genes code for ion channels, thus they appear to be important players in the pathogenesis of idiopathic epilepsy. Indeed, several epileptic phenotypes have been associated to dysfunctions of potassium channels (Brenner et al, 2012). These channels play a major role in neuronal excitability and their importance is related to the level of their expression in the subcellular domain, individual cell, or circuit (Cooper, 2012). Potassium channels are also involved in setting the inward-negative resting membrane potential. Based on their structures, biophysical characteristics, pharmacological sensitivities and physiology, these channels are classified as voltage-gated (Kv), inwardly rectifying (Kir), sodium (Na+)-activated or calcium (Ca2+)-activated channels (González et al, 2012).

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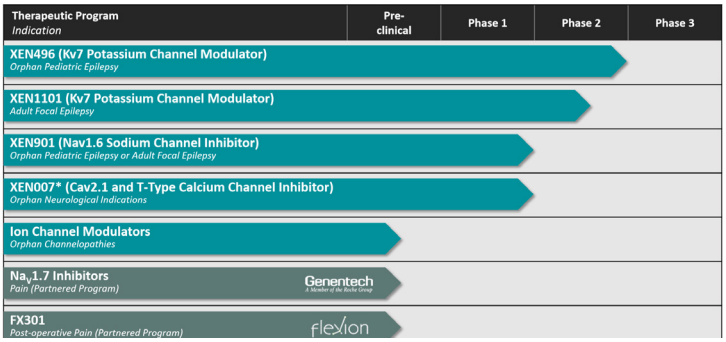
1.2 Xenon Pharmaceuticals

Xenon Pharmaceutical Inc. (Xenon) is a clinical stage biopharmaceutical company committed to developing innovative therapeutics to improve the lives of patients with neurological disorders. Xenon is advancing a novel product pipeline of neurology-focused therapies to address areas of high unmet medical need, with a focus on epilepsy.

Xenon's innovative therapeutics are based upon their expertise in the study of human rare disease genetics. Xenon's proprietary Extreme Genetics platform allows for the identification and rationale design of drug targets that are genetically validated to be of maximum therapeutic benefit in humans. The study of families with rare single gene defects that translate into severe phenotypes has enabled Xenon to gain critical insights into the genetic drivers associated with these rare traits and design promising pharmacologic candidates of human biological relevance. Xenon has also partnered with Genentech, a member of the Roche Group, and Flexion Therapeutics, Inc., on pain drug development.
Figure 1 provides an overview on Xenon's current product pipeline and their stage of development.

Figure 1 Xenon Pharmaceuticals Product Pipeline



Xenon's pipeline includes three distinct therapeutic candidates XEN496, XEN1101 and XEN901 that are aimed at treating epilepsy.

1.3 Report Objective

The objective of this report is to summarize the available information on three of Xenon's epilepsy candidates currently in clinical development.

- XEN496 (Kv7 potassium channel modulator)
- XEN1101 (Kv7 potassium channel modulator)
- XEN901 (Nav1.6 sodium channel inhibitor)

This information will then be used to determine the potential future commercial prospects for Xenon Pharmaceuticals Inc. and its products.

2 Literature Search

Pubmed searches (https://www.ncbi.nlm.nih.gov/pubmed) using the following keys words were performed by the author in mid-September of 2019:

- Xenon Pharmaceuticals
- Epilepsy, Focal Epilepsy
- Ion Channels, Voltage-gated Ion Channels
- Potassium Channels
- XEN496, Ezogabine, Potiga, Retigabine
- XEN1101
- Kv7, KCNQ2
- KCNQ2-related neonatal epileptic encephalopathy, KCNQ2-NEE, KCNQ2-DEE
- KCNQ2-related benign familial neonatal epilepsy, KCNQ2-BFNE
- Sodium Channels
- XEN901
- Nav1.6
- SCN8A Epileptic Encephalopathy, SCN8A-EE, SCN8A-DEE

Abstracts were reviewed for their relevance and if available free online, the full article was obtained. The pubmed searches were restricted to information available for humans. No time restrictions were imposed. Additional references, identified through article review, were also included if deemed relevant.

In addition to the pubmed searches, information from the following websites was also reviewed:

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- Xenon Pharmaceuticals - https://www.xenon-pharma.com
- International League Against Epilepsy - https://www.ilae.org/
- KCNQ2 Cure - https://www.kcnq2cure.org/kcnq2-epilepsy/
- Clinical Trials Government - https://clinicaltrials.gov
- Drug Information Portal - https://druginfo.nlm.nih.gov/drugportal
- U.S. Food and Drug Administration - https://www.fda.gov

A comprehensive list of references used for compiling this report can be found in Section 5.

3 Discussion

1.1 Potassium Channels

Ion channels are transmembrane proteins that form aqueous pores and drive the selective flow of ions, participating in the electrochemical gradient across the cell membrane. They are fundamental for excitable cells but are also involved in cell functions, such as proliferation, migration, cell volume and specific processes such as insulin release or muscular contractibility (Hille, 2001). Their participation in such highly diverse phenomena highlights a crucial biological relevance. Thus, mutations and alterations of the normal function of these proteins trigger alterations, called channelopathies, in the cardiovascular and nervous systems as well as autoimmune and metabolic diseases (Kass, 2005; Ashcroft, 2000).

The British Pharmacological Society (BPS) and the International Union of Basic and Clinical Pharmacology (IUPHAR) classify ion channels as the following:

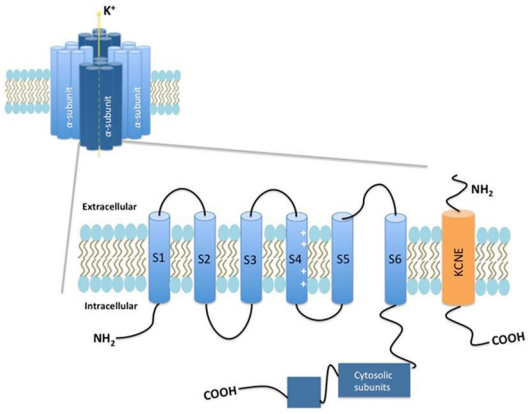
- Voltage-gated ion channels
- Ligand-gated ion channels
- Channels using other gating mechanisms

Voltage-gated ion channels form ion channels that are activated by changes in the electrical membrane potential near the channel. The membrane potential alters the conformation of the channel proteins, regulating their opening and closing.
Voltage-gated ion channels are usually ion-specific and include:

- potassium (K+),
- sodium (Na+),
- calcium (Ca2+), and
- chloride (Cl−) ions

The largest and most diverse class of voltage-gated ion channels are the potassium channels. Voltage-gated potassium (Kv) channels are key regulators of neuronal excitability (Serrano-Novillo et al, 2019). In humans, they are encoded by forty different genes and categorized into twelve sub-families, Kv1 through Kv12 (Gutman et al, 2005; Abbott, 2014). Mammalian Kv channels are tetramers, composed of four α-subunits that surround an ion conduction pore. Each α-subunit contains six α-helical transmembrane domains (S1–S6), a membrane-reentering P loop between S5 and S6, and cytosolic N- and C-termini. Four S5-P-S6 segments line the ion conduction pore, while the S1–S4 sequences are critical for channel voltage-sensing and gating (Figure 2) (Brenner et al, 2012).

Figure 2 Voltage-gated Potassium Channel Schematic



Potassium channels are ubiquitous in neuronal and glial cell membranes and are central to excitability. They are implicated in epilepsy because of their physiology, genetics, and pharmacology (Cooper, 2012).

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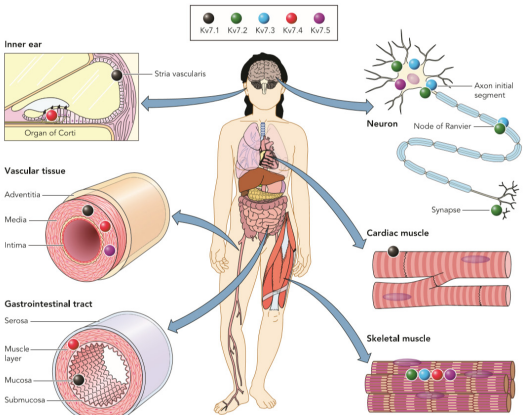
The following Kv subfamilies have been associated with either epilepsy or other disorders showing seizures (Villa et al, 2016):

- Kv1
- Kv4
- Kv7
- Kv8
- Kv11 – HERG

Kv7 channels are the molecular mediators of the M current and regulate membrane excitability in the central and peripheral neuronal systems (Wang et al, 1998; Copper et al, 2000). Neuronal Kv7 channels steady outwardly rectifying current and function as "brakes" for neurons receiving persistent excitatory input (Greene et al, 2017). Kv7 channels are distributed throughout the brain, making them a useful target for seizure prevention (Jespersen et al, 2005; Brown et al, 2009; Maljevic et al, 2010; Owen, 2010).

Kv7 channels are encoded by *KCNQ* genes that have a considerable physiological impact in many cell types. The Kv7 or KCNQ family include five members: KV7.1 to KV7.5 (KCNQ1 to KCNQ5) (Jentsch et al, 2000; Haick et al, 2016). The α-subunits are arranged as homomers or heteromers (Greene et al, 2017), each having a characteristic tissue distribution and function (Abbott, 2015). While Kv7.1 (KCNQ1) is predominantly found in peripheral tissues, Kv7.2 to 7.5 (KCNQ2 to 5) appear to be most widely expressed in the nervous system (Figure 3) (Jespersen et al, 2005; Brown et al, 2009; Maljevic et al, 2010; Owen, 2010).

Figure 3 Tissue Distribution of Kv7 Subunits



(Soldovieri et al, 2011)

KCNQ2-related disorders represent a continuum of overlapping neonatal epileptic phenotypes caused by a heterozygous pathogenic variant in KCNQ2. The clinical features of KCNQ2-related disorders range from KCNQ2-related benign familial neonatal epilepsy (KCNQ2-BFNE) at the mild end to KCNQ2-related neonatal epileptic encephalopathy (KCNQ2-DEE) at the severe end (Miceli et al, 2010).

- KCNQ2-BFNE is characterized by a wide spectrum of seizure types (tonic or apneic episodes, focal clonic activity, or autonomic changes) that start in otherwise healthy infants between the second and eighth day of life and spontaneously disappear between the first and the sixth to 12th month of life. Motor activity may be confined to one body part, migrate to other body regions, or generalize. Seizures are generally brief, lasting one to two minutes. Rarely, KCNQ2-BFNE may evolve into status epilepticus. About 10%-15% of individuals with KCNQ2-BFNE develop epileptic seizures later in life.
- KCNQ2-DEE is characterized by multiple daily seizures beginning in the first week of life that are mostly tonic, with associated focal motor and autonomic features. Seizures often cease around four years of age. At onset, electroencephalogram (EEG) shows a burst-suppression pattern or multifocal epileptiform activity; early brain magnetic resonance imaging (MRI) can show basal ganglia and thalamic hyper-intensities that later resolve. Moderate to severe developmental impairment is present.

KCNQ2-DEE affects both males and females and equally affects individuals across ethnic backgrounds. Cases often are undiagnosed or misdiagnosed, making it difficult to determine the disorder's true frequency in the general population. In addition, the relatively recent discovery of this disorder means that older patients exist in the community who have not been tested or have been given another, incorrect, diagnosis (KCNQ2 Cure).

Several researchers have attempted to determine the frequency of this disorder by testing groups of children with undiagnosed seizure disorders sharing some of the features of KCNQ2-DEE. In a group of 84 patients with neonatal or early infantile seizures and associated developmental impairment, mutations in *KCNQ2* were identified in 11 patients (13%) (KNCQ2 Cure). In another group of 239 patients with early infantile epileptic encephalopathy, 12 patients (5%) harbored mutations in the *KCNQ2* gene (Kato et al, 2013).

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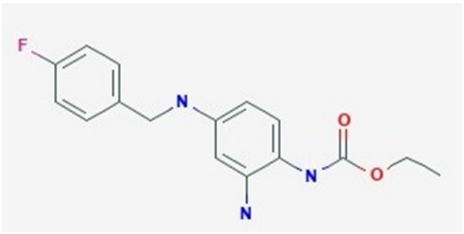
KCNQ2-DEE is rare, representing around 10% of patients with epileptic encephalopathy with onset in the first three months of life; however, the incidence of KCNQ2-DEE reported by KCNQ2 Cure is approximately 2.8/100,000 live births (or over 3,000 new cases annually worldwide). A recent report published by Symonds et al (2019) indicated that the prevalence of KCNQ2-DEE may be as high as 1 per 17 000 or 5.89/100 000 (95% confidence interval 2.24-9.56).

1.1.1 Ezogabine

Ezogabine (retigabine; potiga; (N-[2-amino-4(4-fluorobenzylamino)-phenyl] carbamic acid ethyl ester)) is a first-in-class antiepileptic drug (Figure 4) that was approved by the US Food and Drug Administration (FDA) in June 2011. It is indicated as adjunctive treatment of partial-onset seizures in patients aged 18 years and older who have responded inadequately to several alternative treatments.
Ezogabine stabilizes neuronal potassium channels (Kv7.2-7.5) in the open position, thereby causing hyperpolarization and reduced firing of high-frequency action potentials (Faught, 2011; Gunthorpe et al, 2012; Jankovic and Ilickovic, 2013; Verma et al, 2013).

Figure 4 Ezogabine Chemical Structure ((N- [2-amino-4-(4-fluorobenzyl amino) –phenyl] carbamic acid ethyl ester)



(Potiga Prescribing Information, 2016)

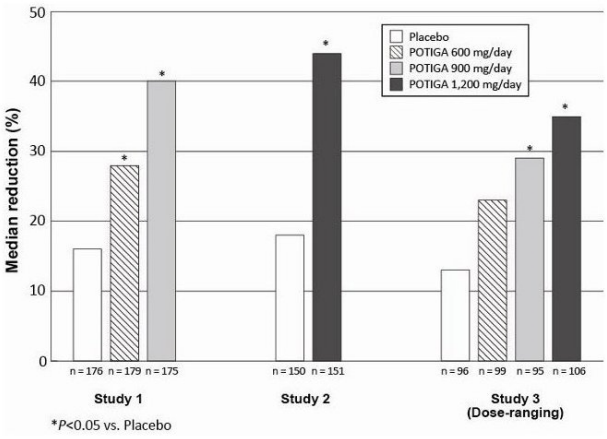
The efficacy of ezogabine 600, 900, and 1200 mg/day has been demonstrated in three pivotal clinical trials (PCTs):
- Study 205 (Porter et al, 2007),
- Study 301 - NCT00232596 (French et al, 2011), and
- Study 302 - NCT00235755 (Brodie et al, 2010).

Patients enrolled in these studies had partial onset seizures with or without secondary generalization and were not adequately controlled with 1 to 3 concomitant AEDs, with or without concomitant vagus nerve stimulation. More than 75% of patients were taking 2 or more concomitant AEDs. During an 8-week baseline period, patients experienced at least 4 partial onset seizures per 28 days on average with no seizure-free period exceeding 3 to 4 weeks. Patients had a mean duration of epilepsy of 22 years. Across the 3 studies, the median baseline seizure frequency ranged from 8 to 12 seizures per month.

Patients were randomized to the total daily maintenance dosages of 600 mg/day, 900 mg/day, or 1200 mg/day, each administered in 3 equally divided doses. During the titration phase of all 3 studies, treatment was initiated at 300 mg/day (100 mg 3 times/day) and increased in weekly increments of 150 mg/day to the target maintenance dosage.

Figure 5 shows the median percent reduction in 28-day seizure frequency (baseline to double-blind phase) as compared with placebo across all 3 studies. A statistically significant effect was observed with ezogabine at doses of 600 mg/day, 900 mg/day, and 1200 mg/day.

Figure 5 Median Percent Reduction from Baseline in Seizure Frequency per 28 Days by Ezogabine Dose



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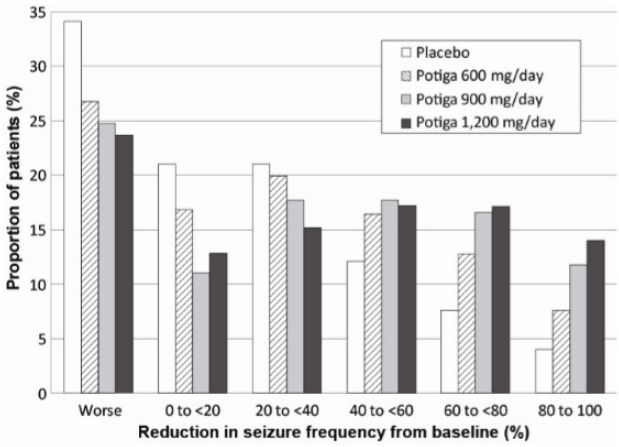
(Potiga Prescribing Information, 2016)

Figure 6 shows changes from baseline in the 28-day total partial seizure frequency by category for patients treated with ezogabine and placebo in an integrated analysis across the 3 clinical trials. Patients in whom the seizure frequency increased are shown at left as "worse." Patients in whom the seizure frequency decreased are shown in five categories.

Figure 6 Proportion of Patients by Category of Seizure Response for Ezogabine and Placebo across All Three Double-blind Trials



(Potiga Prescribing Information, 2016)

The PK profile of ezogabine is approximately linear in daily doses between 600 mg and 1200 mg in patients with epilepsy, with no unexpected accumulation following repeated administration. The PK of ezogabine are similar in healthy volunteers and patients with epilepsy. Ezogabine is rapidly absorbed, with a Tmax of 1.5-2 hours (Potiga Prescribing Information, 2016). Absorption is delayed but not reduced by food (Ferron et al, 2002). Ezogabine is rapidly absorbed and readily crosses the blood-brain barrier (BBB) at physiological concentrations with a half-life between 7 to 11 hours. The elimination half-life is prolonged in the elderly by up to 30%; thus a dose reduction is recommended in patients older than 65 years (Owen, 2010; Tompson and Crean, 2013).

Ezogabine is not metabolized via cytochrome P450 or P-glycoprotein pathways, allowing for a favorable drug interaction profile and predictable drug concentrations when used with most other antiepileptic medications (Tompson and Crean, 2014). Ezogabine is metabolized through N-glucuronidation and N-acetylation (Hempel et al, 1999; Mazarati et al 2008) and is excreted by the kidney (85%) and in feces (14%). The most frequently reported drug-related adverse reactions (ARs), reported by more than 10% of patients, in the regulatory PCTs (Porter et al, 2007; Brodie et al, 2010; French et al, 2011) were nonspecific dizziness, somnolence, and fatigue at 600 and 900 mg/day (Brodie et al, 2010), as well as confusion, dysarthria, ataxia, blurred vision, tremor and nausea at 1200 mg/day (French et al, 2011). Ezogabine also had relatively unique adverse effects, such as urinary retention, presumably related to an effect on potassium channels in bladder smooth muscle (Brickel et al 2012) and abnormal cutaneous pigmentation (Food and Drug Administration, 2013).

In April of 2013, the FDA issued a safety alert (Food and Drug Administration, 2013) which described unique adverse effects not documented in the three PCT's (Porter et al, 2007; Brodie et al, 2010; French et al, 2011; Garin Shkolnik et al, 2014; Potiga Prescribing Information, 2013). The alert warned ezogabine may cause blue-gray discoloration, most notably on or near the lips, nail beds, sclera and conjunctiva; however, more extensive involvement on the face and legs had also occurred. In October of 2013, the FDA revised the label for ezogabine to include a black boxed warning (Figure 7) emphasizing the serious risks of permanent skin and eye discoloration (Food and Drug Administration, 2013). In 2017, GlaxoSmithKline (GSK) removed ezogabine from the market not because of a lack of efficacy but because of reduced sales. It should be noted that it was subsequently demonstrated that the skin and eye pigmentation effects of ezogabine were reversible (Mathias et al, 2017; Garin Shkolnik et al, 2017).

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Figure 7 Ezogabine/Potiga Black Box Warning

> WARNING: RETINAL ABNORMALITIES AND POTENTIAL VISION LOSS
> Potiga can cause retinal abnormalities with funduscopic features similar to those seen in retinal pigment dystrophies, which are known to result in damage to the photoreceptors and vision loss. In addition, macular abnormalities characterized as vitelliform lesions have been observed. These lesions have been identified most consistently with optical coherence tomography imaging [see Warnings and Precautions (5.1), Adverse Reactions (6.2)].
> Some patients with retinal abnormalities have been found to have abnormal visual acuity. It is not possible to determine whether Potiga caused this decreased visual acuity, as baseline assessments are not available for these patients.
> Approximately one third of the patients who had eye examinations performed after approximately 4 years of treatment were found to have retinal pigmentary abnormalities. An earlier onset cannot be ruled out, and it is possible that retinal abnormalities were present earlier in the course of exposure to Potiga. The rate of progression of retinal abnormalities and their reversibility are unknown. Reversibility of retinal pigmentary abnormalities and partial resolution of vitelliform lesions has been reported after discontinuation of ezogabine in some patients.
> Potiga should only be used in patients who have responded inadequately to several alternative treatments and for whom the benefits outweigh the potential risk of vision loss. Patients who fail to show substantial clinical benefit after adequate titration should be discontinued from Potiga.
> All patients taking Potiga should have baseline and periodic (every 6 months) systematic visual monitoring by an ophthalmic professional. Testing should include visual acuity, dilated fundus photography, and optical coherence tomography. Additional testing may include fluorescein angiograms, perimetry, and electroretinograms.
> If retinal pigmentary abnormalities or vision changes are detected, Potiga should be discontinued unless no other suitable treatment options are available and the benefits of treatment outweigh the potential risk of vision loss.

(Potiga Prescribing Information, 2016)

1.1.2 XEN496

Xenon is currently developing XEN496 for the treatment of KCNQ2-DEE. The active ingredient in XEN496 is ezogabine. As stated above ezogabine acts directly on KCNQ2 channels, increasing their opening. Therefore, Xenon hypothesizes that by activating Kv7.2/7.3 channels, XEN496 should stabilize the resting membrane potential and reduce brain excitability in KCNQ2-DEE patients. Thus XEN496 could potentially improve brain function and cognitive development, in addition to decreasing seizures.

This hypothesis is supported by two studies published in the literature where ezogabine was used off label to treat KCNQ2-DEE patients. The first was a retrospective study (Millichap et al, 2016) of 23 KCNQ2-DEE patients, including 11 patients treated with ezogabine. The second was an observational study (Olson et al, 2017) which followed 8 KCNQ2-DEE patients treated with ezogabine.

1.1.2.1 Retrospective Study Results

In the Millichap et al (2016) retrospective study, ezogabine was given three times per day (TID), at milligrams-per-kilogram doses extrapolated from recommendations in adults. Patients were monitored for known side effects of chromaturia (red-brown urine) and urinary retention at baseline and during periodic urology visits, by renal/bladder ultrasound and parental diaper counting, as determined by each clinician.
A summary of the clinical responses and side effects of eleven KCNQ2-DEE patients treated with ezogabine can be found in Table 2.

Table 2 Treatment of KCNQ2-related Epilepsy Patients with Ezogabine

Patient Number	KCNQ2 Variant	Age Started	Initial; Highest Dose (mg/kg/day)	Side Effects	Clinical Response
3	p.Asn190Ser	15 months	2; 15	None reported	No change
5	p.Arg201Cys	2 months	10; 25	Somnolence	No change
6	p.Arg201Cys	4 years	2.8; 12.8	None reported	Parents report more discrete times of wakefulness and sleep, more alertness, more smiling, some improvement in EEG with less discontinuity in sleep, some sleep architecture, and less frequent epileptiform discharges[a]
9	p.Gly256 Trp	15 months	1; 19	Urinary retention	No change
11	p.Ala265 Thr	2 years	2; 8	Urinary retention	Improvement in development: alertness and interactions[a]
12	p.Trp269 Leu	4 months	3.1; 20	None reported	Improvement in seizures and development: seizures improved from 50–60/day to 1/week; can go up to 2 week without any seizures. Also, started to cry, started to hold head up, reach for objects, and play with toys[a]
14	p.Thr274Met	2 years	4.5; 17.7	Urinary retention	No change (discontinued)

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15	p.Thr274Met	5 months	9.5; 14	None reported	Improvement in seizures: on modest doses, seizure-free except with fevers; tried to lower dose and had breakthroughs; when dose increased had resolution of seizures and improved responsiveness[a]
16	p.Thr274Met	3 years	0.7; 40	Urinary retention	40 mg/kg/day, chromaturia (resolved with lower dose) Improvement in seizures and development: epileptic spasms in clusters; 2–3/day before and 0–1/day after, subsequent relapse to 1 cluster/day; parent report of increased alertness and tone[a]
18	p.Ala294 Val	6 years	2.3; 12	Urinary retention	No change; no developmental improvement noted (seizures in remission)
22	p.Ala337 Thr	5 months	8.5; 23	Urinary retention	Improvement in seizures and development: seizures began to decrease by the second week on 13 mg/kg/day; clearest EEG response: before ezogabine, hypsarrhythmia with occasional periods with organization for a few seconds; at 6 month on ezogabine 23 mg/kg/day, EEG had good organization, occasional slowing or spike wave[a]

[a] Indicates a positive response recorded by a parent or physician.

The eleven patients were treated with ezogabine, beginning between 2 months and 6 years of age. Dose-related side effects observed included urinary retention, chromaturia, and somnolence. These side effects had also previously been seen in adults (Brickel et al, 2012; Brodie et al, 2010). All of the side effects resolved with dose modification. Serious adverse side effects, including ophthalmologic and skin pigmentary changes included in the FDA black box warning (Figure 7), were not reported during the follow-up period (mean, 11.5 months; range, 2–24 months). However, these adverse effects were typically observed after 4 or more years of treatment (Food and Drug Administration, 2014), which exceeded the amount of follow-up time available in these patients.

Three of the four patients treated at less than 6 months of age were reported to exhibit improvement in seizures and development. These patients had failed multiple standard medication trials (at least 4) including several agents with activity on voltage-gated sodium channels (1 tried phenytoin and all 3 responders tried topiramate). In seven patients who started ezogabine at a later age, where seizures had remitted or were infrequent showed less clear evidence of drug effects. Patient 16, who started treatment when 3 years of age, had an improvement in seizures and development according to the pediatric neurologist and parents. One patient treated at 4 years of age was reported to have improved alertness and EEG background activity (Patient 6); one patient whose seizures had already remitted when treated at 2 years of age had improvement in development only (Patient 11). The association between age groups (<6 months and >6 months) and improved or not improved seizure control with ezogabine treatment was considered to be statistically significant (Fisher exact test; 2-tailed p value = 0.0242) (Millichap et al, 2016).

In conclusion, in this study ezogabine use was associated with improvement in seizures and/or development in 3/4 patients treated before 6 months of age, and 2/7 patients treated later. No serious side effects were observed (Millichap et al, 2016).

1.1.2.2 Observational Study

In the Olsen et al (2017) observational study 8 patients (6 males, 2 females) with KCNQ2-DEE were treated with ezogabine, starting at a median of 8 months (range 7 weeks and 2.5 years) and continuing for a median of 2.6 years (range 7 months to 4.5 years). Seven of eight patients had seizure onset in the first week of life and one patient had seizure onset at 5 months of age. Patients had multiple seizures types with tonic and tonic-clonic being the most commonly reported. Seizure frequency at onset was multiple daily in all patients, EEG patterns were variable. Developmental improvements were notably reported in all 8 patients. Specifically families reported improved alertness, vocalizations, and motor skills. The only AR reported was urinary retention in 3 patients. Upon weaning, 3/7 patients had increased seizure frequency, 2/7 had worsened agitation/irritability, 1/7 had poor sleep, 2/7 had developmental regression while 1/7 had improved alertness and muscle tone and 2/7 had no major changes (Olsen et al 2017).

In conclusion, data from this observational study suggested that ezogabine was effective and tolerable in patients with KCNQ2-DEE. Ezogabine may help not only seizure control but also developmental outcomes (Olsen et al 2017).

1.1.2.3 Other Ezogabine Experiences

Weckhuysen et al (2013) reported on another experience with ezogabine treatment of a child with KCNQ2-related epilepsy (pore variant p.Gly281Arg). They reported a marked reduction in seizure severity and frequency when the patient was given 40 mg/kg of ezogabine before 22 months of age.

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1.1.2.4 Clinical Development Plan

To simplify the regulatory pathway, Xenon has accessed GSK's ezogabine FDA files and will rely on them to support the XEN496 submission. XEN496 has been granted orphan drug designation (ODD) from FDA. Xenon will develop XEN496 as a novel paediatric-specific granulated formulation presented in single use sachets.

Xenon is currently testing the XEN496 paediatric formulation in a study of healthy adult volunteers. Xenon is also planning on filing an Investigational New Drug (IND) application in the fourth quarter of 2019 so they can initiate a Phase 3 clinical trial of XEN496 in KCNQ2-DEE. The FDA has indicated that it is acceptable to study XEN496 in infants and children up to 4 years old and have indicated that a single pivotal trial in approximately 20 patients may be considered adequate in order to demonstrate XEN496's efficacy in KCNQ2-DEE.

1.1.3 XEN1101

Xenon is developing XEN1101 as adjunctive treatment in adult patients with focal epilepsy. The treatment of an individual patient with focal seizures is currently based on reduction of seizure frequency, with seizure freedom as the ultimate goal.

XEN1101 is a novel chemical entity that enhances activation of neuronal Kv7.2-7.5 (KCNQ2-5) potassium channels. The Kv7 potassium channel mechanism has previously been clinically validated by ezogabine (see Section 3.1.1).

In work reported by Goldberg (2018a), XEN1101 appears to have greater potency than ezogabine and other AEDS in animal models of epilepsy, (Table 3).

Table 3 Potency of XEN1101, Ezogabine and Other AEDs in Epilepsy Animal Models

	Mice IP MES ED_{50} (mg/kg)	Mice IP Metrazol ED_{50} (mg/kg)	Mice IP Picrotoxin ED_{50} (mg/kg)	Mice IP Bicuculline ED_{50} (mg/kg)	Mice IP 6 Hz, 32 mA ED_{50} (mg/kg)	Mice IP 6 Hz, 44 mA ED_{50} (mg/kg)
Ezogabine	29.51	>50	33	>50	12.1	20.25
XEN1101	6.1 (2.2)	3.9	9.86	2.59	3.7	5.0
Carbamazepine	7.81	>50	>18.2	>50	75% @ 40 mg/kg	
Gabapentin	78.1	47.5	>500	>500	No activity	
Lamotrigine	7.47	>40	>40	>40	50% @ 20 mg/kg	
Levetiracetam	>500	>500	>500	4.7	19.4	
Topiramate	33	>800	>500	>500	>300	
AED = Antiepileptic Drugs; ED_{50} = Effective Dose 50%; GABA = Gamma-aminobutyric Acid; IP = Intraperitonea						

Electrically induced seizures: MES and 6 Hz;
$GABA_A$ antagonists: Bicuculline and Picrotoxin;
Chemical convulsant: Metrazol

In addition, XEN1101 is predicted to have a number of other benefits compared to ezogabine (Goldberg, 2018b). These benefits have been summarized in Table 4.

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Table 4 Predicted Benefits of XEN1101 over Ezogabine

Improvement	Key Difference to Ezogabine / Predicted Impact
Chemistry	• No dimerization or oxidative color changes • Predict no skin and retinal pigmentation
Potency	• 10-50X greater *in vitro* potency on Kv7.2/3
Pharmacokinetics	• Once daily dosing vs TID • Predict better CNS tolerability
Pre-clinical Efficacy and TMS Signal	• Broadly effective at lower doses in multiple preclinical epilepsy models • Superior TMS signal of cortical activity in humans at a significantly lower dose
CNS = Central Nervous System; TID = Three Times a Day; TMS = Transcranial magnetic stimulation	

Xenon has already completed Phase 1 (see Section 3.1.3.1) and Phase 1b (see Section 3.1.3.2) studies of XEN1101. They have also initiated a Phase 2b (see Section 3.1.3.3) clinical trial in adult patients with focal epilepsy.

1.1.3.1 Phase 1 - NCT03340220

Phase 1 clinical trial NCT03340220 was a randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability and PK of both single ascending doses (SAD) and multiple ascending doses (MAD) of XEN1101 in healthy subjects. In addition to safety and PK data, the clinical trial was designed to include a pharmacodynamic (PD) read-out by incorporating a pilot transcranial magnetic stimulation (TMS) sub-study. The TMS model sub-study was designed to demonstrate delivery of XEN1101 into the central nervous system (CNS) and to observe a change in cortical excitability as measured by EEG and/or EMG activity.

A brief overview of this Phase 1 study can be found in Table 5.

Table 5 Overview of Clinical Trial NCT03340220

Overview of Clinical Trial NCT03340220 (ClinicalTrials.gov)	
Title	Phase 1, First-in-human, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and PK of Single and Multiple Ascending Oral Doses of XEN1101 and Preliminary Open-label Pharmacodynamic Assessment in Healthy Subjects
Type	Interventional
Phase	Phase 1
Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Treatment
Intervention	• Drug: XPF-008 Capsule filled with XEN1101 • Drug: Microcrystalline Cellulose Placebo capsule

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Arms	• Experimental: XPF-008 Single ascending dose: Single oral dose for each cohort Multiple ascending dose: 7 days of single oral dose daily for each cohort Intervention: Drug: XPF-008 • Placebo Comparator: Placebo - Microcrystalline cellulose Single Ascending Dose: Single oral dose for each cohort Multiple Ascending Dose: 7 days of single oral dose daily for each cohort Intervention: Drug: Microcrystalline Cellulose
Primary Outcome	• Number of Participants with Adverse Events (AEs) as assessed by CTCAE v4.03 [Time Frame: From screening (28 days prior to Day 1) through to 30 days post-final dose] To assess AEs as a criteria of safety and tolerability • Resting electrocardiogram (ECG) [Time Frame: At screening (28 days prior to Day 1) through to 7 days post-final dose] To assess ECG as a criteria of safety and tolerability • Vital signs [Time Frame: At screening (28 days prior to Day 1) through to 7 days post-final dose] To assess vital signs as a criteria of safety and tolerability
Secondary Outcomes	• Maximum Observed Plasma Concentration (Cmax) [Time Frame: Day 1 pre-dose through to 7 days post-final dose] Cmax is the maximum observed plasma concentration in ng/mL • Time to the Maximum Observed Plasma Concentration (Tmax) [Time Frame: Day 1 predose through to 7 days post-final dose] Tmax is the time in hours to reach Cmax following dosing • Terminal elimination half-life (t1/2) [Time Frame: Day 1 predose through to 7 days post-final dose] The time in hours required for the plasma level of the study drug to decrease by one-half during the terminal elimination phase • Area Under the Plasma Concentration-Time Curve from Time Zero to the Time of the Last Quantifiable Plasma Concentration (AUC0-last) [Time Frame: Day 1 pre-dose through to 7 days post-final dose] The area under the plasma concentration-time curve [in ng.h/mL] from time zero to the time corresponding to the last quantifiable plasma concentration
Enrollment	64
Location	United Kingdom
Sponsor	Xenon Pharmaceuticals Inc.
Status	Active – not recruiting
AE = Adverse Event; AUC = Area Under Concentration Curve; Cmax = Maximum Concentration; CTCAE = Common Terminology Criteria for Adverse Events; ECG = Electrocardiogram; t1/2 = Half Life; Tmax = Time to Maximum Concentration	

In the SAD phase of this study, 32 healthy volunteers were randomized (3:1) to XEN1101 (5, 15, 20, 25 or 30 mg) or placebo. The study featured an adaptive design. A crossover food effect cohort (N=10) was also completed with single doses of 20 mg.

A summary of the PK results from the single dose portion of this clinical trial can be found in Table 6 (Aycardi et al, 2018).

HIGH CONVICTION IDEA

Table 6 XEN1101 Selected Pharmacokinetic Parameters in Plasma (Mean±SD) for Single Ascending Dose Cohorts

Parameter	XEN1101				
	5 mg (N=3)[a]	15 mg (N=3)[a]	20 mg (N=6)[a]	25 mg (N=6)[b]	30 mg (N=6)[a]
Tmax (hr)	3.17 ± 2.47	4.50 ± 2.60	3.69 ± 2.05	4.51 ± 1.22	3.17 ± 1.48
Cmax (ng/mL)	7.13 ± 6.12	27.3 ± 11.1	31.5 ± 21.1	45.8 ± 14.3	35.5 ± 33.5
T1/2 (hr)	49.2 ± 31.1	41.9 ± 31.1	48.9 ± 14.7	97.2 ± 18.0	63.4 ± 28.2
AUC-24 (ng*hr/mL)	74.6 ± 50.5	328 ± 141	376 ± 220	482 ± 130	369 ± 219
AUC0-t (ng*hr/mL)	91.3 ± 54.2	397 ± 166	709 ± 337	1470 ± 270	837 ± 280
AUC = Area Under Concentration Curve; Cmax = Maximum Concentration; hr = Hour; QD = Once Per Day; SD = Standard Deviation; t1/2 = Half Life; Tmax = Time to Maximum Concentration					

[a] *Fasted for 8 hours prior to dosing and 1 hour after dosing;*
[b] *Fed a standard breakfast 30 minutes prior to dosing followed by no food for 4 hours;*
[c] *tLast was 32 h for 5 and 15 mg Cohorts, 72 h for 20 and 30 mg Cohorts, 146 h for 25 mg Cohort*

Repeat doses of XEN1101 (15 mg/day) were evaluated in a fasted and fed state over 7 and 10 days, respectively. Repeat doses of XEN1101 (25 mg/day) were also evaluated in a fed state over 10 days. A summary of the PK results from the repeat dose portion of this clinical trial can be found in Table 7 (Aycardi et al, 2018).

Table 7 XEN1101 Selected Pharmacokinetic Parameters in Plasma (Mean±SD) for Multiple Ascending Dose Cohorts

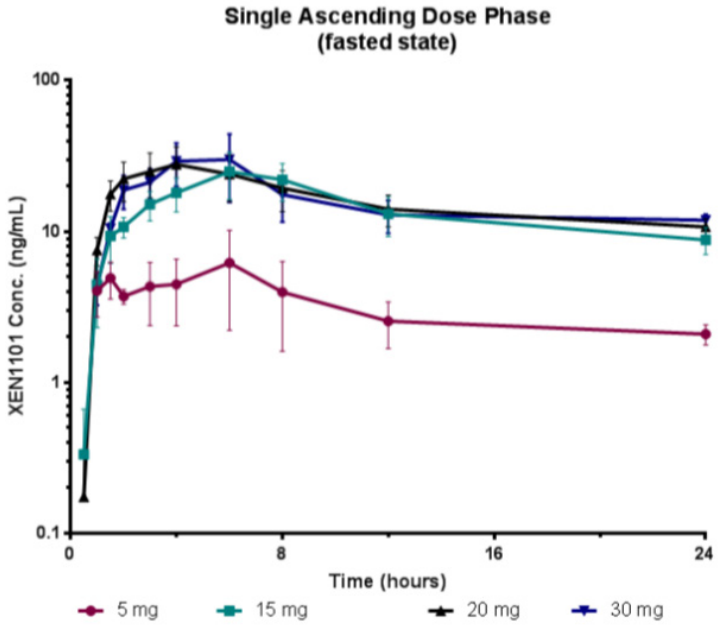
Parameter	XEN1101					
	15 mg QD Fasted[a] (N=6)		15 mg QD Fed[b] (N=6)		25 mg QD Fed[b] (N=6)	
	Day 1	Day 7	Day 1	Day 7	Day 1	Day 7
Tmax (hr)	2.68 ± 1.15	2.69 ± 1.19	4.37 ± 1.85	3.69 ± 0.56	4.38 ± 1.86	4.99 ± 1.69
Cmax (ng/mL)	10.5 ± 2.01	45.1 ± 11.4	35.9 ± 11.9	60.8 ± 11.2	49.6 ± 15.7	96.7 ± 8.6
T1/2 (hr)	--	167 ± 36.8	--	239 ± 179	--	218 ± 136
AUC-24 (ng*hr/mL)	125 ± 32.9	757 ± 200	353 ± 105	1020 ± 246	592 ± 133	1720 ± 198
AUC0-t (ng*hr/mL)	--	4260 ± 992	--	4950 ± 1250	--	8010 ± 1520
AUC = Area Under Concentration Curve; Cmax = Maximum Concentration; hr = Hour; QD = Once Per Day; SD = Standard Deviation; t1/2 = Half Life; Tmax = Time to Maximum Concentration						

[a] On Days 1 and 7, fasted for 8 hours prior to dosing and 4 hours after dosing. On Days 2-6, fasted for 8 hours prior to dosing and 1 hour after dosing;

[b] Fed a standard breakfast 30 minutes prior to dosing on each dosing day followed by no food for 4 hours
The PK profiles from the SAD portion of the trial under fasting conditions can be seen in Figure 8.

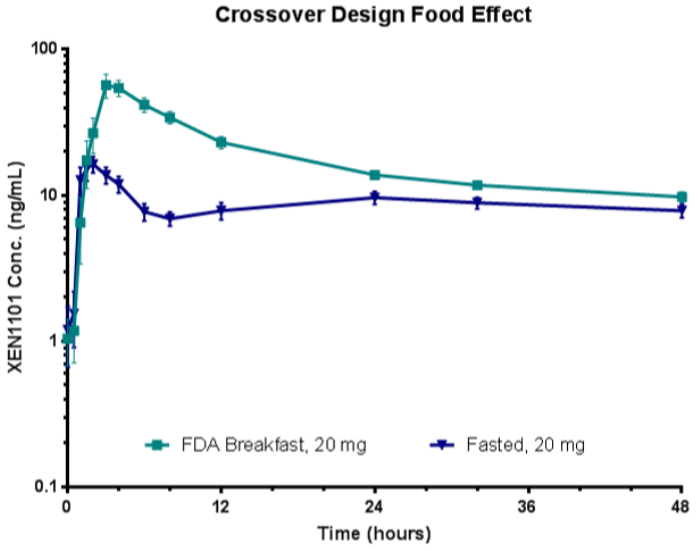
HIGH CONVICTION IDEA

Figure 8 PK Profile for Fasted XEN1101 Single Ascending Dose Cohort



XEN1101 had less than dose-proportional exposure in the fasted state (Figure 8), with absorption enhanced by food (~1.8 fold for AUCinf) (Figure 9).

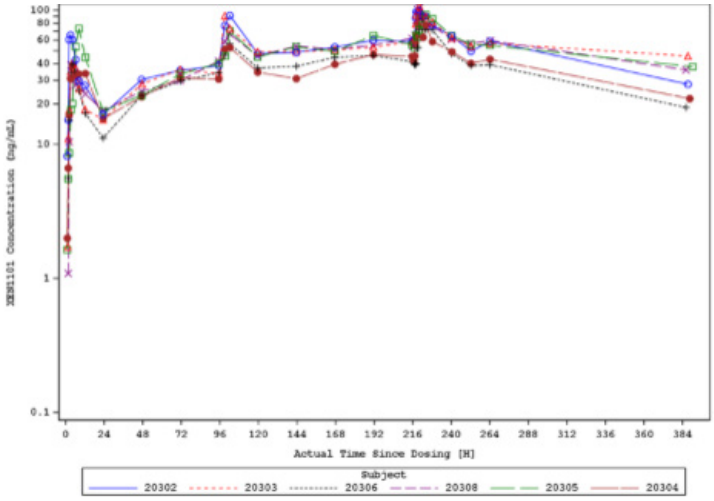
Figure 9 PK Profile of XEN1101 – Food Effect



With multiple doses in the fed state, exposure increased in proportion to dose (Figure 10 and Figure 11). Apparent steady state was achieved by Day 6-9, based on the 90% confidence interval (CI) for the successive day's exposure ratio within the range 0.8 - 1.25 (Aycardi et al, 2018)..

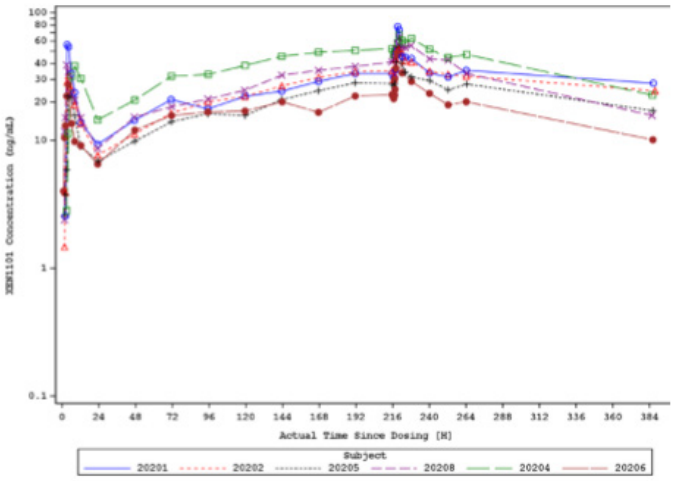
HIGH CONVICTION IDEA

Figure 10 PK Profiles for XEN1101 MAD Cohorts – 15 mg/day



Individual PK profiles or subjects dosed with 15 mg of XEN1101 once per day (administered 0.5 hr after a meal).

Figure 11 PK Profiles for XEN1101 MAD Cohorts – 25 mg/day



Individual PK profiles or subjects dosed with 25 mg of XEN1101 once per day (administered 0.5 hr after a meal).

Single and multiple doses of XEN1101 were well tolerated at individual Cmax levels up to 104 ng/mL and 107 ng/mL, respectively. The majority of adverse events (AEs) were mild or moderate, resolved spontaneously and were consistent with antiepileptic drugs of this class (e.g., dizziness, sedation). There have been no serious adverse events (SAEs), deaths, or clinically significant electrocardiogram (ECG) or laboratory findings (Table 8 and Table 9).

HIGH CONVICTION IDEA

Table 8 XEN1101 Adverse Events occurring in ≥2 subjects for Single Ascending Dose Cohorts

System Organ Class Preferred Term	XEN1101 Cohort 1 5 mg (N=3)	XEN1101 Cohort 2 15 mg (N=3)	XEN1101 Cohort 3 30 mg (N=6)	XEN1101 Cohort 4 20 mg (N=6)	XEN1101 Cohort 5[a] 20 mg (N=9)	XEN1101 Cohort 6 25 mg (N=6)	XEN1101 Overall (N=27)	Pooled Placebo (N=8)
	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E
Subjects with at least one TEAE	0 (0.0) 0	2 (66.7) 4	3 (50.0) 7	4 (66.7) 8	5 (55.6) 11	4 (66.7) 7	18 (54.5) 37	2 (25.0) 2
Eye Disorders	0	1 (33.3) 1	1 (16.7) 1	0	0	1 (16.7) 1	3 (9.1) 3	0
Vision blurred	0	0	1 (16.7) 1	0	0	1 (16.7) 1	2 (6.1) 2	0
Musculoskeletal and Connective Tissue Disorders	0	0	1 (16.7) 1	2 (33.3) 2	1 (11.1) 1	0	4 (12.1) 4	0
Myalgia	0	0	1 (16.7) 1	*1 (16.7) 1	1 (11.1) 1	0	3 (9.1) 3	0
Nervous System Disorders	0	1 (33.3) 1	2 (33.3) 3	2 (33.3) 3	2 (22.2) 4	3 (50.0) 5	10 (30.3) 17	0
Dizziness	0	0	0	2 (33.3) 2	1 (11.1) 1	3 (50.0) 3	6 (18.2) 6	0
Headache	0	1 (33.3) 1	1 (16.7) 1	1 (16.7) 1	1 (11.1) 2	0	4 (12.1) 5	0
Presyncope	0	0	*2 (33.3) 2	0	0	0	2 (6.1) 2	0
Somnolence	0	1 (33.3) 1	0	0	0	2 (33.3) 2	3 (9.1) 3	0

E = number of events; n = number of subjects having an adverse event; N = Number of subjects at risk.

[a] Note that cohort 5 was dosed under fed and fasted conditions according to a crossover design. For reasons of comparability frequencies presented in this table are based on the fasted condition.

* Denotes moderate AEs. All other AEs were mild, except for 1 severe AE of syncope (a vasovagal reaction following a PK blood draw during a standing BP assessment) in a single subject, 2 hours following a 30 mg dose in Cohort 3. A fed subject in the food effect cohort also had an unrelated moderate AE of varicella (chicken pox) which led to withdrawal.

Table 9 XEN1101 Adverse Events occurring in ≥2 subjects for Multiple Ascending Dose Cohorts

System Organ Class Preferred Term	XEN1101 Cohort 1 15 mg (fasted) (N=6)	XEN1101 Cohort 2 15 mg (fed) (N=6)	XEN1101 Cohort 3 25 mg (fed) (N=6)	XEN1101 Overall (N=18)	Placebo Pooled (N=6)
	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E
Subjects with at least one TEAE	4 (66.7) 11	4 (66.7) 18	6 (100.0) 39	14 (77.8) 68	2 (33.3) 5
Cardiac Disorders	0	2 (33.3) 2	0	2 (11.1) 2	0
Palpitations	0	2 (33.3) 2	0	2 (11.1) 2	0
Eye Disorders	1 (16.7) 1	0	5 (83.3) 5	6 (33.3) 6	0
Vision blurred	0	0	5 (83.3) 5	5 (27.8) 5	0
Musculoskeletal and Connective Tissue Disorders	0	0	2 (33.3) 3	2 (11.1) 3	1 (16.7) 1
Muscle twitching	0	0	2 (33.3) 2	2 (11.1) 2	1 (16.7) 1
Nervous System Disorders	3 (50.0) 6	3 (50.0) 13	6 (100.0) 23	12 (66.7) 42	2 (33.3) 4
Balance disorder	1 (16.7) 1	1 (16.7) 1	1 (16.7) 1	3 (16.7) 3	0
Dizziness	0	1 (16.7) 1	2 (33.3) 2	3 (16.7) 3	0
Headache	1 (16.7) 1	3 (50.0) 3	3 (50.0) 4	7 (38.9) 8	0
Memory impairment	2 (33.3) 2	1 (16.7) 1	2 (33.3) 2	5 (27.8) 5	0
Sensory disturbance	0	0	2 (33.3) 2	2 (11.1) 2	0
Somnolence	0	3 (50.0) 3	4 (66.7) 4	7 (38.9) 7	*1 (16.7) 1
Speech disorder	0	2 (33.3) 2	4 (66.7) 4	6 (33.3) 6	0
Vascular Disorders	0	1 (16.7) 1	4 (66.7) 4	5 (27.8) 5	0
Hot flush	0	1 (16.7) 1	2 (33.3) 2	3 (16.7) 3	0
Orthostatic hypotension	0	0	*2 (33.3) 2	2 (11.1) 2	0

E = number of events; n = number of subjects having an adverse event; N = Number of subjects at risk.

* Denotes moderate AEs. All other AEs were mild. There were no severe AEs, withdrawals due to AEs, or SAEs. Two active and 1 placebo were not reachable to complete the 30 day follow-up telephone call (lost to follow-up).

The current results suggest that XEN1101 is safe and well-tolerated up to the doses examined (single doses of up to 30 mg and multiple doses of 25 mg/day). The PK profile (including an effective half-life >24 hours), supports a once per day dosing schedule using an immediate release formulation, with attainment of steady state in 1 week without the need for titration.

HIGH CONVICTION IDEA

1.1.3.2 Phase 1b - NCT03468725

Transcranial magnetic stimulation (TMS), in combination with electromyography (EMG) and electroencephalography (EEG), allows measurement of resting and active motor threshold (RMT/AMT) and TMS-evoked EEG potentials (TEPs), which may indicate drug effects on corticospinal and cortical excitability, respectively. Several AEDs have been shown to significantly increase RMT values and modulate TEPs, indicating a shift towards corticospinal/cortical inhibition.

Phase 1b clinical trial NCT03468725 was a randomized, double-blind, placebo-controlled study that eventuated the safety, tolerability, PK and effects on TMS of oral doses of XEN1101 in healthy male subjects. The TMS procedure was designed to demonstrate delivery of XEN1101 into the CNS and to observe a change in cortical excitability as measured by EEG and/or EMG activity.

A brief overview of this phase 1b study can be found in Table 10.

Table 10 Overview of Clinical Trial NCT03468725

Overview of Clinical Trial NCT03468725 (ClinicalTrials.gov)	
Title	A Double-blind, Placebo-controlled Crossover Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Effects on Transcranial Magnetic Stimulation of Oral Administration of XEN1101 in Healthy Male Subjects
Type	Interventional
Phase	Phase 1
Design	Allocation: Randomized Intervention Model: Crossover Assignment Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Treatment
Intervention	Drug: XPF-008 • Capsule filled with XEN1101 Drug: Microcrystalline Cellulose • Placebo capsule
Arms	• Experimental: XPF-008 Single oral dose Intervention: Drug: XPF-008 • Active Comparator: Placebo Single oral dose Intervention: Drug: Microcrystalline Cellulose
Primary Outcome	• Number of participants with AEs as assessed by CTCAE v4.03 [Time Frame: From screening (28 days prior to Day 1) through to 30 days post-final dose] To assess AEs as a criteria of safety and tolerability • Resting 12-lead ECG [Time Frame: From screening (28 days prior to Day 1) through to Day 14] To assess ECG intervals (PR, QRS, QTcF, RR) as a criteria of safety and tolerability • Number of participants with vital sign abnormalities [Time Frame: From screening (28 days prior to Day 1) through to Day 14] To assess vital signs as a criteria of safety and tolerability • PD effects assessed by TMS biological markers of brain excitability [Time Frame: Day 1 pre-dose through to Day 7] To assess biological marker of brain excitability: amplitude (in uV) of TMS evoked potentials on the EEG • PD effects assessed by TMS biological markers of brain excitability [Time Frame: Day 1 pre-dose through to Day 7] To assess biological marker of brain excitability: resting motor threshold (in %) for elicitation of an EMG response

HIGH CONVICTION IDEA

Secondary Outcome	• Maximum Observed Plasma Concentration (Cmax) [Time Frame: Day 1 predose through to Day 8] Cmax is the maximum observed plasma concentration in ng/mL • Terminal elimination half-life (t1/2) [Time Frame: Day 1 pre-dose through to Day 8] The time in hours required for the plasma level of the study drug to decrease by one-half during the terminal elimination phase • Area Under the Plasma Concentration-Time Curve from Time Zero to the Time of the Last Quantifiable Plasma Concentration (AUC0-last) [Time Frame: Day 1 pre-dose through to Day 8] The area under the plasma concentration-time curve [in ng.hr/mL] from time zero to the time corresponding to the last quantifiable plasma concentration
Enrollment	20
Location	United Kingdom
Sponsor	Xenon Pharmaceuticals Inc.
Status	Completed
AE = Adverse Events; AUC = Area Under Concentration Curve; Cmax = Maximum Concentration; CTCAE = Common Terminology Criteria for Adverse Events; ECG = Electrocardiogram; EEG = Electroencephalogram; EMG = Electromyography; PD = Pharmacodynamics; t1/2 = Half Life; TMS = Transcranial Magnetic Stimulation	

XEN1101 plasma levels were 15.9 ± 21.4 ng/mL at 2 hr, 30.2 ± 21.1 ng/mL at 4 hr and 42.1 ± 19.1 ng/mL at 6 hr. Cmax was 59.2 ± 13.8 ng/mL and occurred at a median of 7.8 hr after dose. The mean ± SD half-life based on 16 subjects with PK samples collected up to 14 days was 127 ± 84.6 hr (Beatch et al, 2018).

XEN1101-related AEs included dizziness, fatigue, somnolence, headache, disturbance in attention, tension headache, ataxia, diplopia, vision blurred, nausea and sinus tachycardia. Somnolence was the only placebo-related AE that occurred in more than 1 subject. Moderate AEs during XEN1101 treatment included somnolence (3 subjects), nausea and vomiting (1 subject) and tension headache (1 subject). All other AEs were mild and generally transient. There were no deaths, SAEs or withdrawals. There were no clinically significant changes in laboratory evaluations, vital signs, or ECG (Beatch et al, 2018).

RMT increased in proportion to XEN1101 plasma concentration showing a mean ± SEM increase of 4.9 ± 0.7% at 6 hr. AMT also increased in proportion to plasma concentration with an increase of 2.0 ± 0.4% at 6 hr. Short Interval Cortical Inhibition (SICI), a measure of GABAergic effects, remained unchanged. XEN1101 significantly modulated TEPs in a pattern consistent with reductions in cortical excitability. Relative to time-matched placebo, at peak plasma levels, XEN1101 decreased the amplitude of TEPs vs placebo at 25, 45 and 180 ms after the TMS pulse. Additional measures of cortical excitability including global mean field power were similarly impacted. XEN1101 also shifted the power spectra of resting state EEGs toward lower frequencies (Beatch et al, 2018).

The results from this study suggest that TMS may be useful in identification of an active dose in healthy volunteers and support continued development of XEN1101 for treatment of patients with epilepsy.

1.1.3.3 Phase 2 - NCT03796962

Phase 2 clinical trial (NCT03796962) is a randomized, double-blind, placebo-controlled study that will evaluate the clinical efficacy, safety and tolerability of increasing doses of XEN1101 administered as adjunctive treatment in adult patients diagnosed with focal epilepsy.
A brief overview of this phase 2 study can be found in Table 11.

Table 11 Overview of Clinical Trial NCT03796962

Overview of Clinical Trial NCT03796962 (ClinicalTrials.gov)	
Title	A Randomized, Double Blind, Placebo Controlled, Multicenter Study to Evaluate the Safety, Tolerability and Efficacy of XEN1101 as Adjunctive Therapy in Focal Onset Epilepsy
Type	Interventional
Phase	Phase 2
Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor) Primary Purpose: Treatment

HIGH CONVICTION IDEA

Condition	Focal Epilepsy
Intervention	Drug: XEN1101 Oral dose
Arms	• Experimental: 25 mg XEN1101 Capsule filled with 25 mg XEN1101 Intervention: Drug: XEN1101 • Experimental: 20 mg XEN1101 Capsule filled with 20 mg XEN1101 Intervention: Drug: XEN1101 • Experimental: 10 mg XEN1101 Capsule filled with 10 mg XEN1101 Intervention: Drug: XEN1101 • Placebo Comparator: Placebo Placebo capsule Intervention: Drug: XEN1101
Primary Outcome	• To assess the efficacy of XEN1101 compared to placebo on focal seizure frequency (e.g., median percent change in focal seizure frequency) in adults with focal epilepsy taking 1-3 AEDs [Time Frame: From baseline (8 weeks prior to Day 0) through to the final dose (up to Day 56)] MPC in monthly (28 days) focal seizure frequency from baseline compared to double-blind treatment period versus placebo • To assess the safety and tolerability of XEN1101 (e.g., AEs) in adults with focal epilepsy taking 1-3 AEDs [Time Frame: From screening (up to 28 days prior to baseline) through to 30 days post-final dose] To assess AEs as a criteria of safety and tolerability
Secondary Outcome	• To evaluate the 50% XEN1101 response rates in comparison to placebo [Time Frame: From baseline (8 weeks prior to Day 0) through to the final dose (up to Day 56)] Responders are defined as patients experiencing ≥50% reduction in monthly (28 days) focal seizure frequency from baseline to treatment period • To evaluate trends in focal seizure frequency over time in the treatment period [Time Frame: From baseline (8 weeks prior to Day 0) through to the final dose (up to Day 56)] Median absolute, change and percent change from baseline in weekly focal seizure frequency for each week of the double-blind treatment period
Enrollment	300
Location	Canada Spain United Kingdom United States
Sponsor	Xenon Pharmaceuticals Inc.
Status	Recruiting
AE = Adverse Event; AED = Antiepileptic Drugs; MPC = Median Percent Change	

This clinical trial is in the recruitment phase and no results are currently available. The top-line results from the XEN1101 Phase 2 clinical trial are anticipated in the second half of 2020.

HIGH CONVICTION IDEA

1.2 Sodium Channels

Voltage-gated sodium channels are essential for the initiation and propagation of action potentials in neurons. The sodium channel α subunits are large, transmembrane proteins with approximately 2,000 amino acid residues, composed of 4 homologous domains containing well-characterized voltage sensor and pore regions. The transmembrane segments are highly conserved through evolution.

The sodium channel Nav1.6, encoded by the gene *SCN8A*, is one of the major voltage-gated channels in human brain. SCN8A is a member of the gene family comprised of nine evolutionarily related sodium channels with specific roles in neurons, skeletal muscle and cardiac muscle (Lopreato et al., 2001; Meisler and Kearney, 2005; Meisler et al., 2010; Zakon et al., 2011; Zakon, 2012).

Unique features of Nav1.6 include its contribution to persistent current, resurgent current, repetitive neuronal firing, and subcellular localization at the axon initial segment (AIS) and nodes of Ranvier. Loss of Nav1.6 activity results in reduced neuronal excitability, while gain-of-function mutations can increase neuronal excitability. *De novo* mutations of human *SCN8A* detected by exome sequencing have revealed a role for Nav1.6 in patients with epileptic encephalopathy and intellectual disability (O'Brien and Meisler, 2013).

SCN8A developmental and epileptic encephalopathy (SCN8A-DEE), also known as EIEE13, is a rare, extremely severe, single-gene epilepsy caused by mutations in the *SCN8A* gene that result in a gain-of-function in the Nav1.6 sodium channel. SCN8A-DEE typically presents with seizure onset between birth and 18 months of age. Most children diagnosed with SCN8A-DEE have seizures that can occur multiple times a day and are often difficult to treat. Other symptoms include learning difficulties, muscle spasms, low or high muscle tone, poor coordination, developmental delay, and features similar to autism. The extent of physical disability leaves some children able to make little or no voluntary movement. Most children will have trouble learning to speak, and some will need assistance from feeding tubes to get the nourishment they need to grow. It is also believed that children and teenagers with SCN8A-DEE are at risk for Sudden Unexpected Death in Epilepsy (SUDEP) (Wagon and Meisler, 2015).

1.2.1 XEN901

Xenon are developing XEN901, a potent, highly selective Nav1.6 sodium channel inhibitor, for the treatment of SCN8A-DEE. By selectively targeting Nav1.6, it is anticipated that XEN901 may achieve efficacy conferred by this well-validated epilepsy target, but with a potentially improved therapeutic index compared with currently available non-selective sodium channel inhibitors. Xenon has completed one phase 1 study of this Nav1.6 inhibitor.

1.2.1.1 Phase 1 - NCT03467100

Phase 1 clinical trial (NCT03467100) was a randomized, double-blind, placebo-controlled study that evaluated the safety, tolerability and PK of both single ascending doses and multiple ascending doses of XEN901 in healthy subjects.
A brief overview of this phase 1 study can be found in Table 12.

Table 12 Overview of Clinical Trial NCT03467100

Overview of Clinical Trial NCT03467100 (ClinicalTrials.gov)	
Title	Phase 1, Double-blind, Placebo-controlled Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Single and Multiple Ascending Oral Doses of XEN901 in Healthy Subjects
Type	Interventional
Phase	Phase 1
Design	Allocation: Randomized Intervention Model: Parallel Assignment Masking: Triple (Participant, Care Provider, Investigator) Primary Purpose: Treatment
Condition	Healthy Volunteers
Intervention	• Drug: XEN901 Capsule filled with XEN901 • Drug: Inert Ingredients Oral Product Placebo capsule

HIGH CONVICTION IDEA

Arms	• Experimental: XEN901 Single ascending dose: Single oral dose for each cohort; Multiple ascending dose: 7 days of single oral dose twice daily for each cohort Intervention: Drug: XEN901 • Placebo Comparator: Placebo Single Ascending Dose: Single oral dose for each cohort; Multiple Ascending Dose: 7 days of single oral dose twice daily for each cohort Intervention: Drug: Inert Ingredients Oral Product
Primary Outcome	• Number of Participants with Adverse Events (AEs) as assessed by CTCAE v4.03 [Time Frame: From screening (28 days prior to Day 1) through to 30 days post-final dose] To assess AEs as a criteria of safety and tolerability • Resting 12-lead electrocardiogram (ECG) [Time Frame: At screening (28 days prior to Day 1) through to 7 days post-final dose] To assess 12-lead ECG intervals (PR, QRS, QTcF, RR) as a criteria of safety and tolerability • Number of participants with vital sign abnormalities [Time Frame: At screening (28 days prior to Day 1) through to 7 days post-final dose] To assess vital signs as a criteria of safety and tolerability
Secondary Outcome	• Maximum Observed Plasma Concentration (Cmax) [Time Frame: Day 1 pre-dose through to 7 days post-final dose] Cmax is the maximum observed plasma concentration in ng/mL • Time to the Maximum Observed Plasma Concentration (Tmax) [Time Frame: Day 1 pre-dose through to 7 days post-final dose] Tmax is the time in hours to reach Cmax following dosing • Terminal elimination half-life (t1/2) [Time Frame: Day 1 pre-dose through to 7 days post-final dose] The time in hours required for the plasma level of the study drug to decrease by one-half during the terminal elimination phase • Area Under the Plasma Concentration-Time Curve from Time Zero to the Time of the Last Quantifiable Plasma Concentration (AUC0-last) [Time Frame: Day 1 pre-dose through to 7 days post-final dose] The area under the plasma concentration-time curve [in ng.hr/mL] from time zero to the time corresponding to the last quantifiable plasma concentration
Enrollment	70
Location	United Kingdom
Sponsor	Xenon Pharmaceuticals Inc.
Status	Completed
AE = Adverse Event; AUC = Area Under Concentration Curve; Cmax = Maximum Concentration; CTCAE = Common Terminology Criteria for Adverse Events; ECG = Electrocardiogram; t1/2 = Half Life; Tmax = Time to Maximum Concentration	

In this randomized, double blind study, 40 healthy subjects (3:1 active:placebo) received single ascending doses of XEN901 once daily and 30 subjects (3:1 active:placebo) received multiple ascending doses once or twice per day for 7 days. A food effect (FE) cohort received single doses of XEN901 in fed and fasted states in a crossover design. XEN901 was formulated as an immediate release capsule. Safety evaluations throughout the study included AE monitoring, laboratory tests, vital signs, ECGs, physical examinations, Columbia-Suicide Severity Rating Scale (CSSRS) and a brief cognitive assessment. Pilot TMS assessments were done in 50 and 75 mg/day cohorts (Namdari et al, 2018).

XEN901's PK profile displayed a reasonable dose proportional exposure (Figure 12) with a mild food effect (1.3-fold increase in Cmax and 1.6-fold in AUC). Typically, modest (≤40%) inter-individual variability was observed for the PK parameters. The median Tmax was similar among cohorts and typically ranged from 1-2 hr. The mean t1/2 was 8-11 hr across cohorts and did not change with increasing dose or upon repeated administration. No significant drug accumulation was observed upon 7 days of once/day (75 mg) or twice/day (23 mg x 2; i.e., 46 mg/day) dosing and steady state was achieved by day 2-3 (Figure 13). Significantly higher trough levels were maintained via twice/day dosing (Namdari et al, 2018).

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Figure 12 PK Profile of XEN901 Single Ascending Dose Cohorts

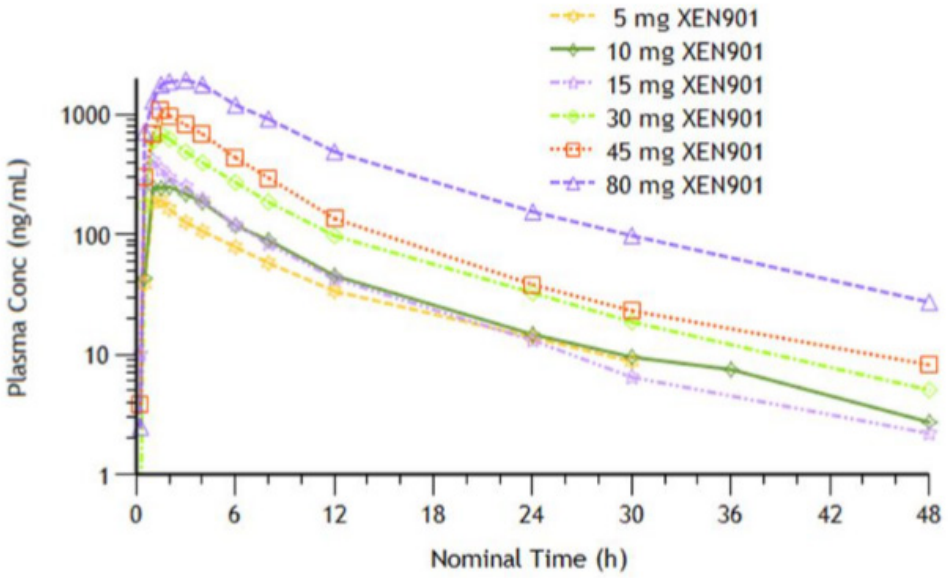
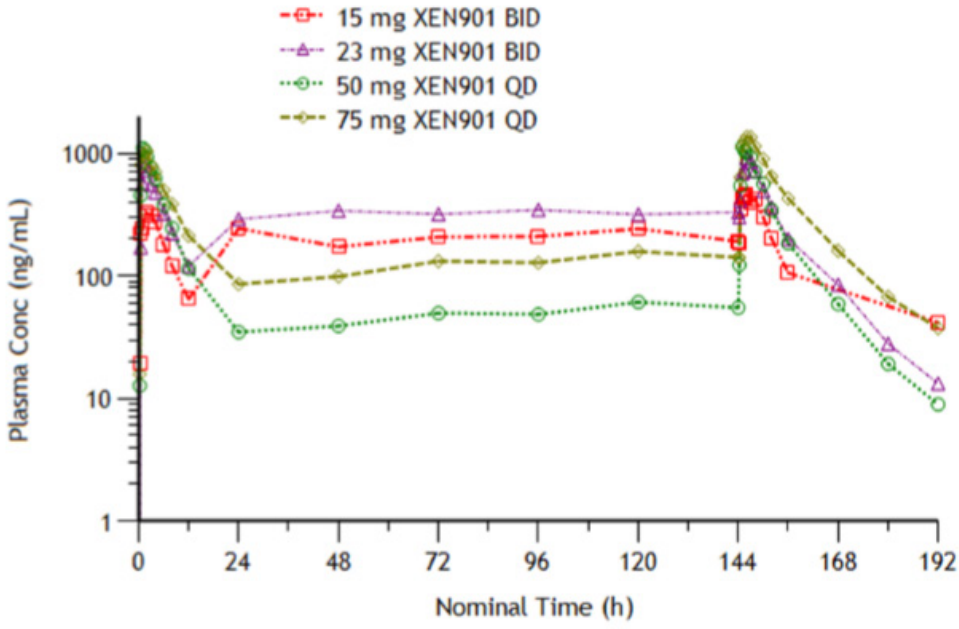


Figure 13 PK Profile of XEN901 Multiple Ascending Dose Cohorts



XEN901's effects on TMS measurements and EEG were assessed in 8 subjects with plasma levels >1000 ng/mL from the 50 and 75 mg/day cohorts and compared to 3 placebo subjects. TMS measures were recorded at baseline and on day 5/6. In this pilot study XEN901 showed trends for increases in RMT/AMT, decrease in amplitude of TEP at 180 ms (P180) and an increase in delta power in the resting state EEG (Namdari et al, 2018).

Single and multiple doses of XEN901 were well tolerated at plasma levels up to and including 2660 ng/mL and 2280 ng/mL, respectively. The majority of AEs for the SAD, MAD and FE cohorts were deemed unrelated to XEN901, were mild or moderate, transient and resolved spontaneously. There were no SAEs, deaths, or clinically significant ECG, vital signs or laboratory findings. The possibly related AEs in the SAD cohorts included dizziness, headache, nausea and restlessness. The AEs for the MAD cohorts are presented in Table 13 (Namdari et al, 2018).

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Table 13 XEN901 Adverse Events from Multiple Ascending Dose Cohort

System Organ Class Preferred Term	15 mg BID (N=7)	23 mg BID (N=6)	50 mg QD (N=6)	75 mg QD (N=4)	Overall (N=23)	Pooled Placebo (N=7)
	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E	n (%) E
Subjects with at least one TEAE	5 (71.4) 5	3 (50.0) 6	3 (50.0) 8	1 (25.0) 1	12 (52.2) 20	4 (57.1) 4
Eye Disorders	0	0	0	1 (25.0) 1	1 (4.3) 1	0
Eye pain*	0	0	0	1 (25.0) 1	1 (4.3) 1	0
Gastrointestinal Disorders	1 (14.3) 1	0	1 (16.7) 2	0	2 (8.7) 3	0
Flatulence	0	0	1 (16.7) 1	0	1 (4.3) 1	0
Nausea*	1 (14.3) 1	0	1 (16.7) 1	0	2 (8.7) 2	0
General Disorders and Administration Site Conditions	2 (28.6) 2	2 (33.3) 3	1 (16.7) 1	0	5 (21.7) 6	1 (14.3) 1
Fatigue*	0	1 (16.7) 1	0	0	1 (4.3) 1	0
Feeling cold*	1 (14.3) 1	0	0	0	1 (4.3) 1	0
Medical device site reaction	1 (14.3) 1	2 (33.3) 2	0	0	3 (13.0) 3	1 (14.3) 1
Vessel puncture site thrombosis	0	0	1 (16.7) 1	0	1 (4.3) 1	0
Infections and Infestations	1 (14.3) 1	0	0	0	1 (4.3) 1	1 (14.3) 1
Ear infection	0	0	0	0	0	1 (14.3) 1
Nasopharyngitis	1 (14.3) 1	0	0	0	1 (4.3) 1	0
Injury, Poisoning and Procedural Complications	0	1 (16.7) 1	0	0	1 (4.3) 1	0
Thermal burn	0	1 (16.7) 1	0	0	1 (4.3) 1	0
Musculoskeletal and Connective Tissue Disorders	0	1 (16.7) 1	0	0	1 (4.3) 1	0
Arthralgia	0	1 (16.7) 1	0	0	1 (4.3) 1	0
Nervous System Disorders	0	0	3 (50.0) 4	0	3 (13.0) 4	1 (14.3) 1
Dizziness*	0	0	1 (16.7) 1	0	1 (4.3) 1	0
Headache*	0	0	2 (33.3) 2	0	2 (8.7) 2	1 (14.3) 1
Nerve compression*	0	0	1 (16.7) 1	0	1 (4.3) 1	0
Respiratory, Thoracic and Mediastinal Disorders	0	1 (16.7) 1	1 (16.7) 1	0	2 (8.7) 2	0
Epistaxis	0	1 (16.7) 1	0	0	1 (4.3) 1	0
Nasal congestion	0	0	1 (16.7) 1	0	1 (4.3) 1	0
Skin and Subcutaneous Tissue Disorders	1 (14.3) 1	0	0	0	1 (4.3) 1	1 (14.3) 1
Rash	0	0	0	0	0	1 (14.3) 1
Rash papular	1 (14.3) 1	0	0	0	1 (4.3) 1	0

* Represents possibly related AEs; E = number of events; n = number of subjects having an AE; N = Number of subjects at risk

These results suggest that XEN901, a novel, first-in-class NaV1.6 inhibitor, is safe and well-tolerated at the doses examined (single doses of up to 80 mg/day and multiple doses of up to 75 mg/day for 7 days). In addition, XEN901 exhibited linear PK over the dose range studied. The t1/2 of 8 to 11 hr suggests that XEN901 could be compatible with a once or twice/day dosing regimen. No significant accumulation was observed upon repeated dosing and steady state was achieved in 2-3 days.

Changes in TMS/EMG and TMS/EEG parameters suggest XEN901 has effects on corticospinal and cortical excitability (Namdari et al, 2018). The favorable PK, tolerability, safety and pilot TMS data support the further clinical development of XEN901 in the treatment of epilepsy.

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4 Conclusions

Xenon is a clinical stage biopharmaceutical company committed to developing innovative therapeutics to improve the lives of patients with neurological disorders. They are advancing a novel product pipeline of neurology-focused therapies to address areas of high unmet medical need, with a focus on epilepsy.

Xenon's expertise in the study of human rare disease genetics has allowed them to gain critical insights into the genetic drivers associated with rare traits and design promising pharmacologic candidates of human biological relevance.
Xenon's three promising epilepsy candidates include:

- XEN496 (Kv7 potassium channel modulator) - KCNQ2-DEE
- XEN1101 (Kv7 potassium channel modulator) - Focal epilepsy
- XEN901 (Nav1.6 sodium channel inhibitor) - SCN8A-DEE

Each of these molecules has the potential to address areas of high unmet medical needs.

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