



XENON

Investor Webinar

A Discussion with KOLs: XEN1101 and the Focal Epilepsy Landscape

JULY 12, 2021

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NOTE: Comparisons of XEN1101 and ezogabine are based on results in published literature, not based on data resulting from head-to-head trials, and are not direct comparisons of safety or efficacy. Different protocol designs, trial designs, patient selection and populations, number of patients, trial endpoints, trial objectives and other parameters that are not the same between the relevant trials may cause any comparisons of results from different trials to be unreliable.

Welcome and Introductions



Dr. Jacqueline French

Professor of Neurology in the Comprehensive Epilepsy Center at NYU Langone School of Medicine and
Founder/Director of the Epilepsy Study Consortium



Dr. Michael Rogawski

Professor in the Department of Neurology with joint appointment in the Department of Pharmacology, and
an affiliate member of the Center for Neuroscience at the University of California, Davis

Joined by Ian Mortimer, CEO, of Xenon Pharmaceuticals (moderator) with:

- Dr. Simon Pimstone, Executive Chair of the Board
- Dr. Chris Von Seggern, Chief Commercial Officer

Summary of Today's Discussion



**FOS Unmet Medical
Need**

Dr. Jacqueline French



**Kv7 Mechanistic
Background**

Dr. Michael Rogawski



**XEN1101 Clinical
Experience**

Dr. Simon Pimstone



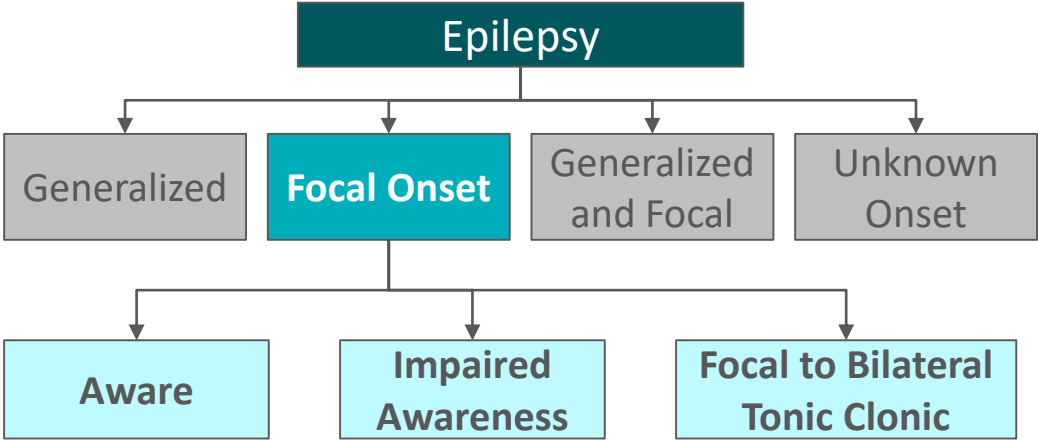
**XEN1101 Commercial
Opportunity**

Dr. Chris Von Seggern

Dr. Jacqueline French

AN OVERVIEW OF FOCAL ONSET SEIZURES (FOS)
AND THE UNMET MEDICAL NEED

Focal-Onset Seizures (FOS) Overview



FOS Description

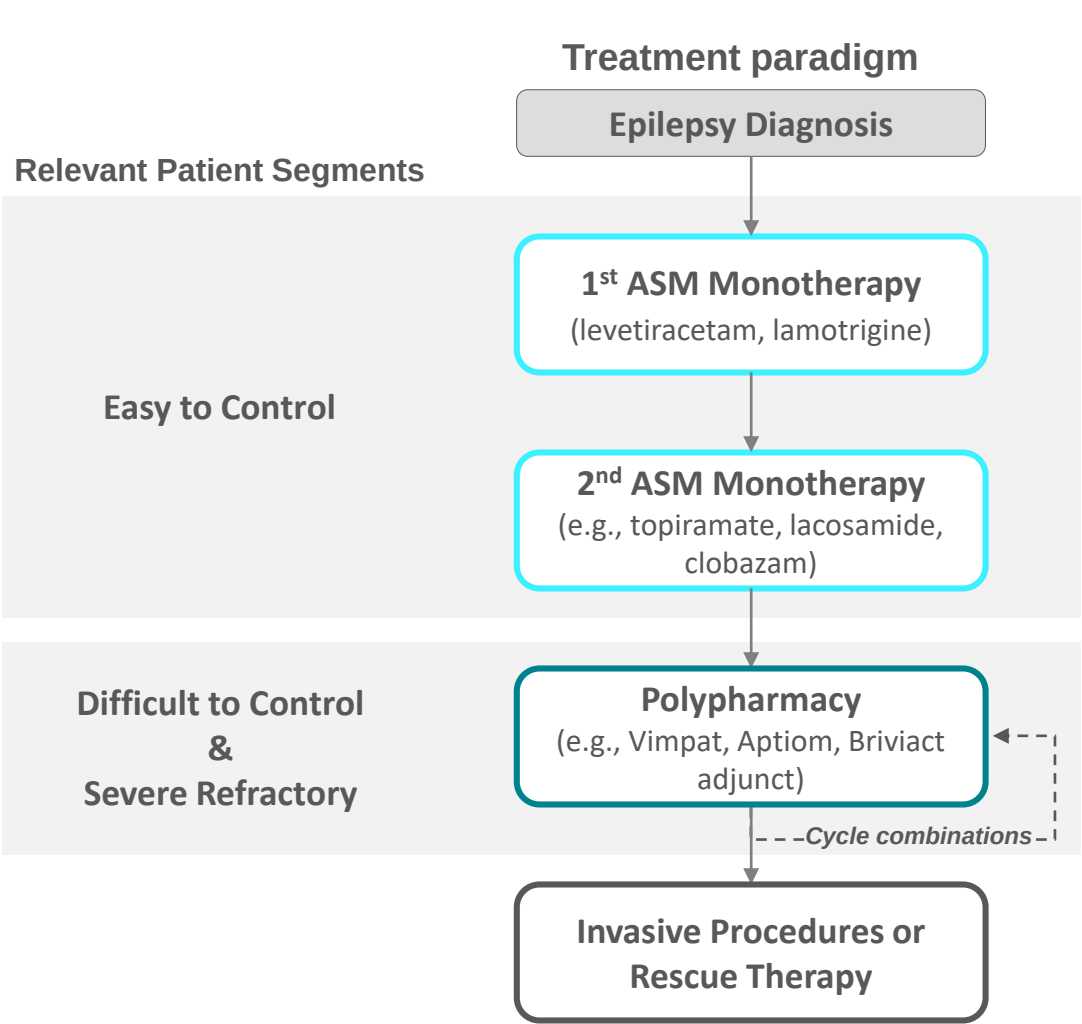
- Focal onset seizures (FOS) is one of the four major seizure groups, accounting for ~60% of epilepsy patients
- Seizures occur due to abnormal neural activity located in only one region of the cerebral hemisphere, and may or may not have associated impairment in consciousness
- FOS patients have a high risk of seizure recurrence which can result in falls and trauma

FOS Subtypes

Aware	• Patients are awake or aware during seizure event, select patients may be able to communicate during the event • Also known as simple partial seizure
Impaired Awareness	• Patients are confused or have impaired awareness during seizure event • Also known as complex partial seizure
Focal to Bilateral Tonic Clonic	• Seizures that start on one side of the brain and spread to both sides, can cause serious injuries and sudden unexpected death in epilepsy • Also known as secondarily generalized seizure

Across FOS subtypes, patients may experience motor (e.g. jerking, limp/weak or tense/rigid muscles, twitching) or non-motor symptoms (e.g. sensation, emotions, autonomic impairment)

FOS Treatment Paradigm



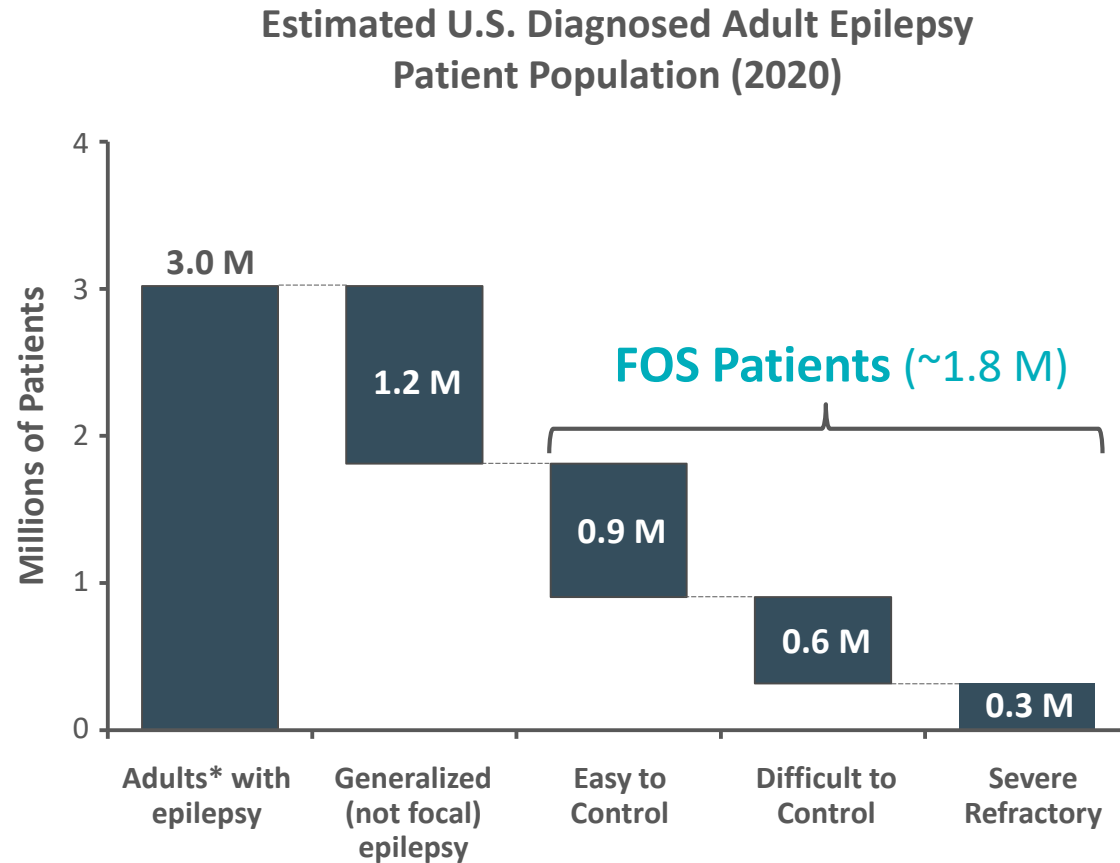
1st/2nd ASM Treatment

- Treatment goal aims to optimize efficacy while managing comorbidities and maximizing quality of life
- There are no standard first line therapies though levetiracetam or lamotrigine are commonly used early in the treatment paradigm
- Patients experiencing insufficient seizure efficacy or side effects will switch to another monotherapy ideally with a different MOA and therapy may be selected from a slightly broader set of ASMs

Polypharmacy

- Patients continuing to experience sub-optimal response (poor efficacy, tolerability) receive polypharmacy
 - Combination typically involve adding a branded agent (e.g. Vimpat, Briviact) to the initial treatment and preference for a different MOA from the initial monotherapy
- Safety/tolerability challenges may arise during either monotherapy or polypharmacy, leading to reduced quality of life and potentially adherence issues which hinders effective seizure control
- Select patients may require 3+ concurrent ASMs at the further cost of quality of life

Adult FOS Epidemiology



- FOS patients accounts for ~60% of all adults with epilepsy
- Patients can be segmented into multiple groups based on treatment required for seizure control, though many patients require multiple lines of therapy
- Patients may become refractory at any point in their life
- Drug resistance may remit and reappear; active epilepsy may be impacted by periods of remission

1. CDC.gov

2. Chen Z et al. Treatment outcomes in patients with newly diagnosed epilepsy treated with established and new antiepileptic drugs in JAMA Neurology 2018. 75(3):279-286.

FOS Patient Segmentation

Increasing Exposure to Multiple ASMs

Easy to Control (~50%)

- **Typically monotherapy** and may involve switching to a second monotherapy
- **Many patients are well-managed** with initial therapy

Difficult to Control (30 – 35%)

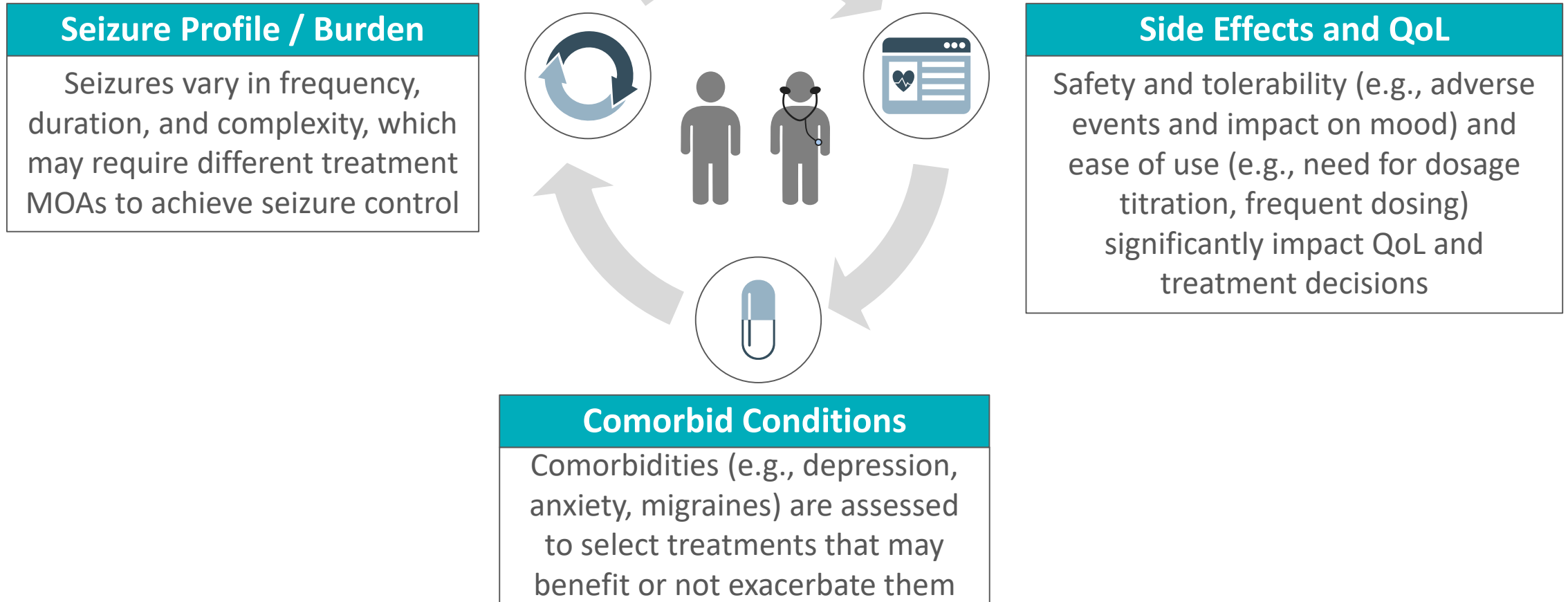
- Difficult to treat patients will **cycle through multiple adjunctive therapies** with the goal of reducing seizure burden
- **Patients may be exposed to a multitude of therapies**

Severe Refractory (15 – 20%)

- These patients are **frequently referred to academic centers for management**
- **Severe refractory patients typically remain uncontrolled**, despite exhausting pharma/non-pharma interventions

As patients progress, increasing need arises for adjuvant therapy and polypharmacy

Factors Influencing Clinical Decision-Making



Key Unmet Needs for FOS Patients

Key Unmet Needs	Key Insights
More Effective Treatments for Difficult to Treat Patients	• Significant portion of patients who progress on initial therapy are not well managed on polypharmacy and could benefit from improved efficacy • Select patients may have cycled through 10+ ASMs and still experience difficult to control seizures
Efficacy for Comorbidities	• Current ASMs do not adequately address depression, anxiety, or migraine • ASM side effect profiles often exacerbate comorbidities, therefore forcing seizure control at the expense of potentially worsening comorbidities
Novel MOAs for Rational Polypharmacy	• Rational polypharmacy preference towards combinations of distinct MOAs to avoid exacerbating side effect profiles and to achieve potentially greater efficacy • As majority of commonly used ASMs target the Na⁺ channel, need for additional MOAs exist
Improved Safety/Tolerability For Rational Polypharmacy	• Patients on multiple ASMs experience compounding adverse events such as fatigue, somnolence, irritability, and cognitive impairment • The issues contribute to poor quality of life and compliance which lead to lower efficacy from the intended treatment

Novel ASM Characteristics

Despite the plethora of ASMs available today, unmet need for an improved ASM exists and it should aim to address the following gaps in treatment

More Effective Treatments for Difficult to Treat Patients

Efficacy for Comorbidities

Novel MOAs for Rational Polypharmacy

Key Characteristics of a Novel ASM for Focal Onset Seizures

- ☐ Comparable or better efficacy compared to existing ASMs
- ☐ Mild AE profile (limited fatigue, somnolence, irritability, etc.)
- ☐ Limited need for dose titration
- ☐ Neutral impact on mood
- ☐ QD dosing
- ☐ Ability to address comorbidities (e.g., depression, anxiety, migraines)
- ☐ Limited drug-drug interactions
- ☐ MOA unique from existing ASMs

XEN1101 Profile

- 1 **K_v7 novel MoA** for use in polypharmacy
- 2 Anticipated strong **tolerability/efficacy** profile
- 3 Novel **broad spectrum ASM** regarded as **unmet need in FOS treatment**
- 4 **QD dosing** and **no titration** supporting ease of use
- 5 **Mood neutral or positive profile** offers potential ancillary efficacy benefit

XEN1101 has the potential to meet key novel ASM characteristics in order to address remaining unmet need in FOS

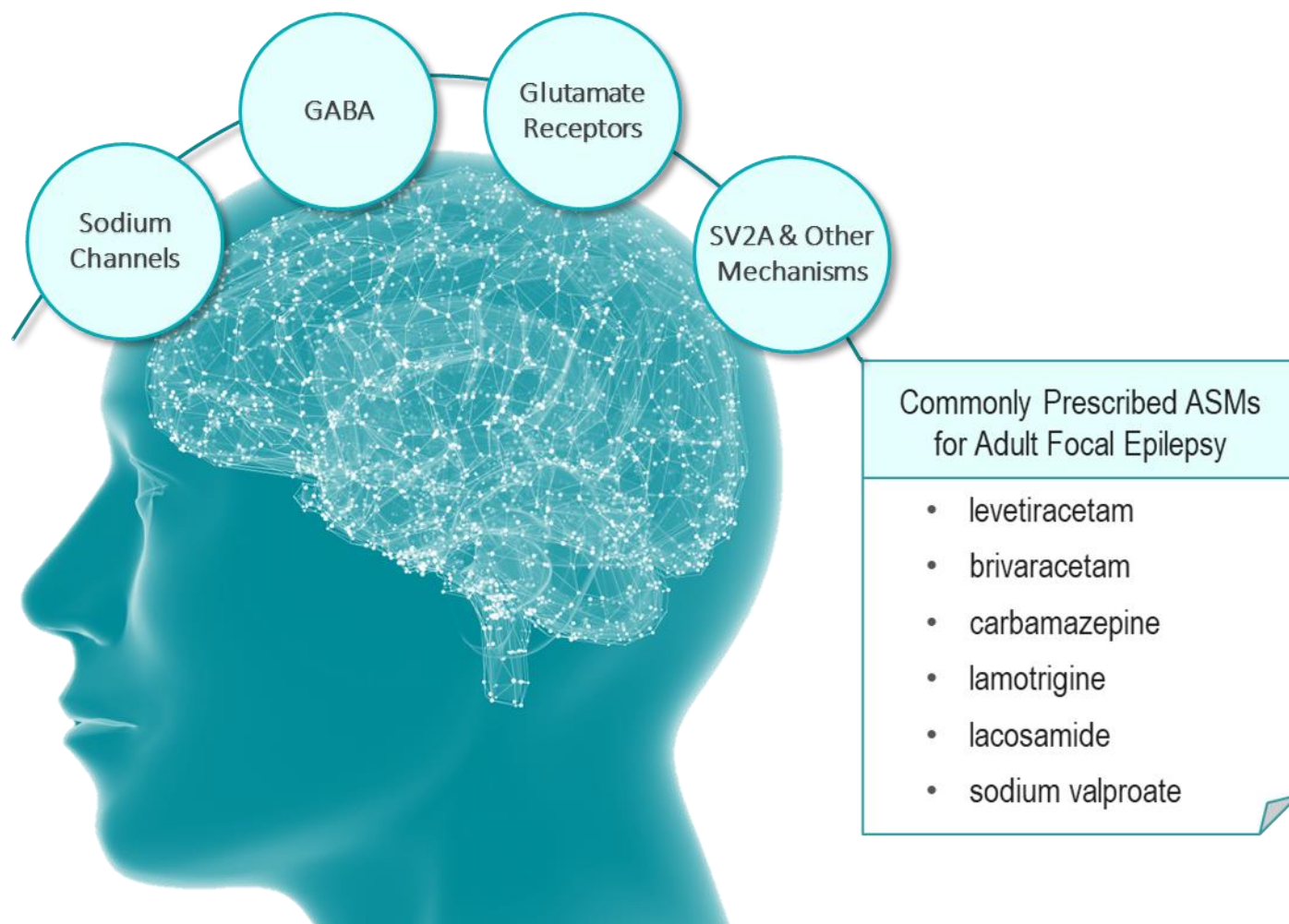
Dr. Michael Rogawski

AN OVERVIEW OF THE K_v7 MECHANISM

XEN1101 is a Novel, “Next-Gen” K_v7 Channel Modulator

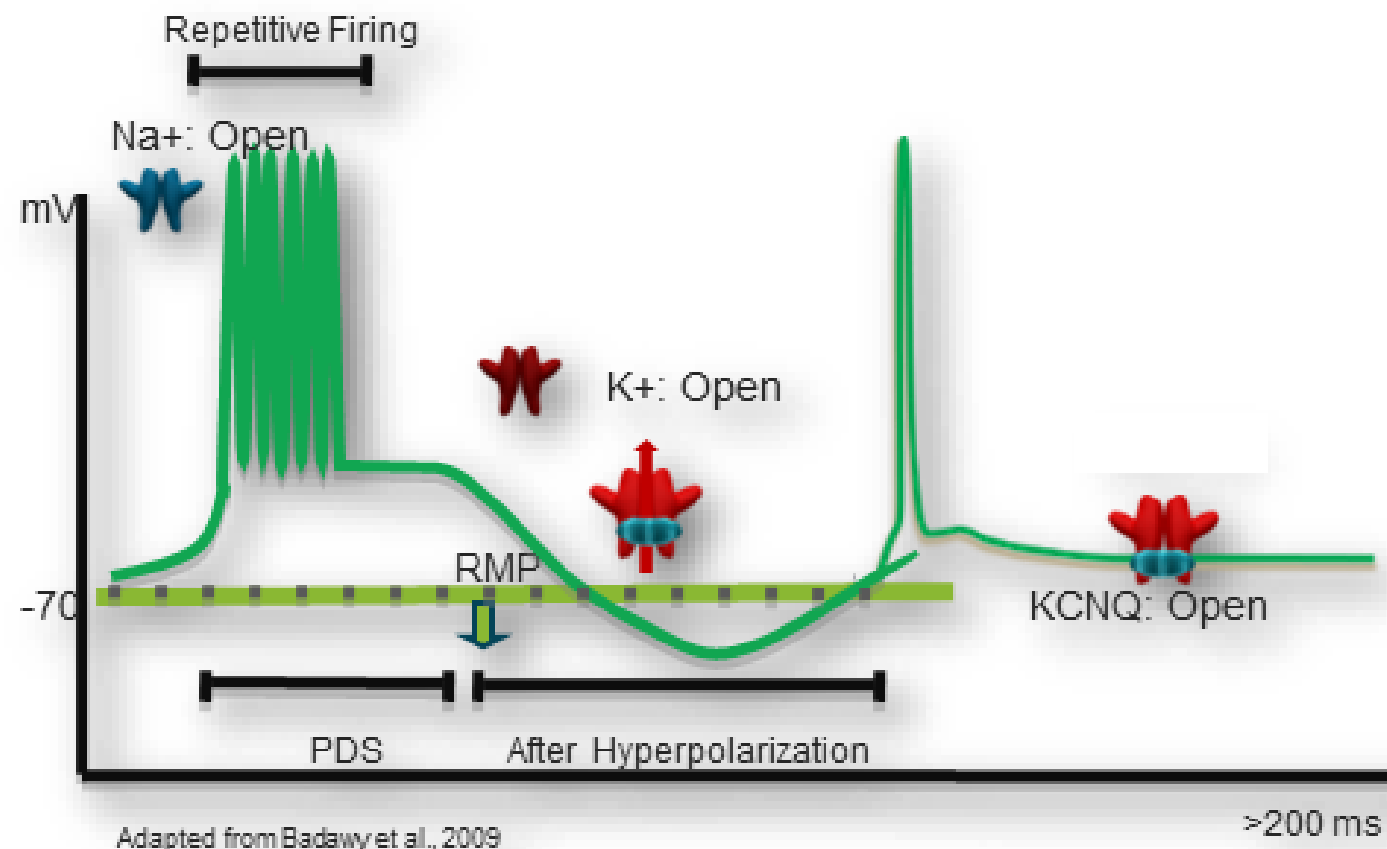
- Potential “only-in-class” K_v7 potassium channel modulator to treat adult focal seizures
- Designed to address limitations of first-gen K_v7 modulator, ezogabine
 - No pigmentation or urinary symptoms observed
 - PK addressed (TID → QD)
- Novel MOAs needed for rational polypharmacy approach
- Potential efficacy for common comorbidities, such as depression

Common Pharmacological Actions of Approved Anti-Seizure Medications (ASMs)



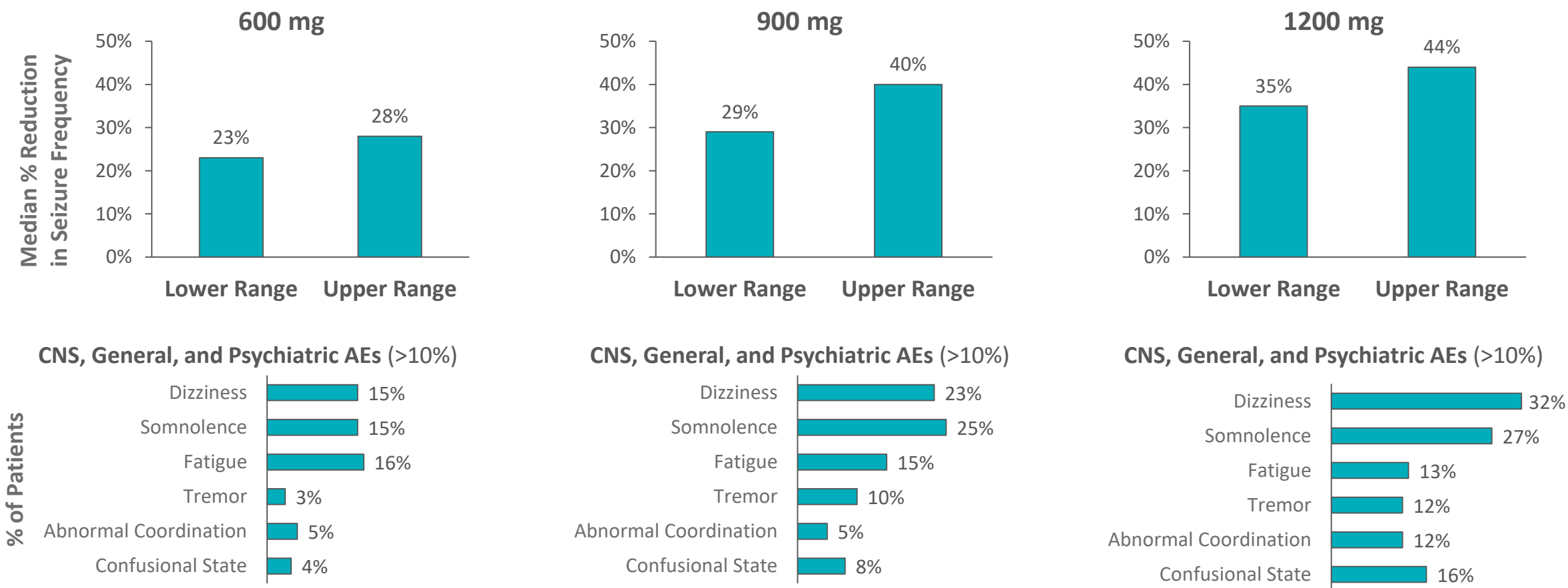
K_v7 Channels are Highly Validated Epilepsy Targets

- K_v7 (KCNQ) activity dampens neuronal hyper-excitability
- K⁺ channels have important inhibitory control over neuronal firing in the CNS
- K⁺ channels repolarize membranes to end the action potential
- K⁺ channel opener (potentiator) decreases hyper-excitability in the brain
- Mechanism validated clinically with first-generation K_v potentiator, ezogabine



Burst Firing
Suppressed

Ezogabine Clinical Data: Narrow Therapeutic Utility

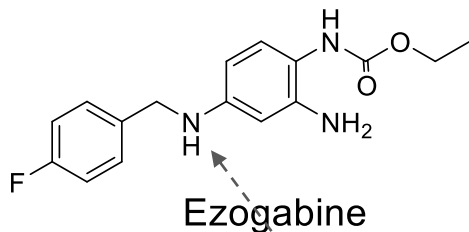


- Ezogabine was efficacious in adult focal epilepsy in a dose dependent manner
- TID dosing resulted in significant CNS AEs and 25% of patients in RCTs discontinued (vs 11% in placebo) treatment and an overall narrow TI
- Additionally, ~10% of patients in long term clinical trial developed skin discoloration, generally after 2 or more years of treatment and higher doses (900 mg or greater)

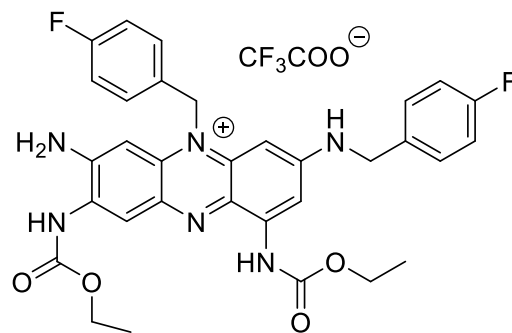
Source: FDA Prescribing Information

XEN1101 Designed to Address Ezogabine's Dimerization Liability

- Ezogabine can form a number of dimeric species, including highly-colored phenazinium-type dimers which have been implicated in the pigmentary abnormalities observed with long-term ezogabine exposure¹



Ezogabine



Ezogabine Phenazinium-Type Dimer



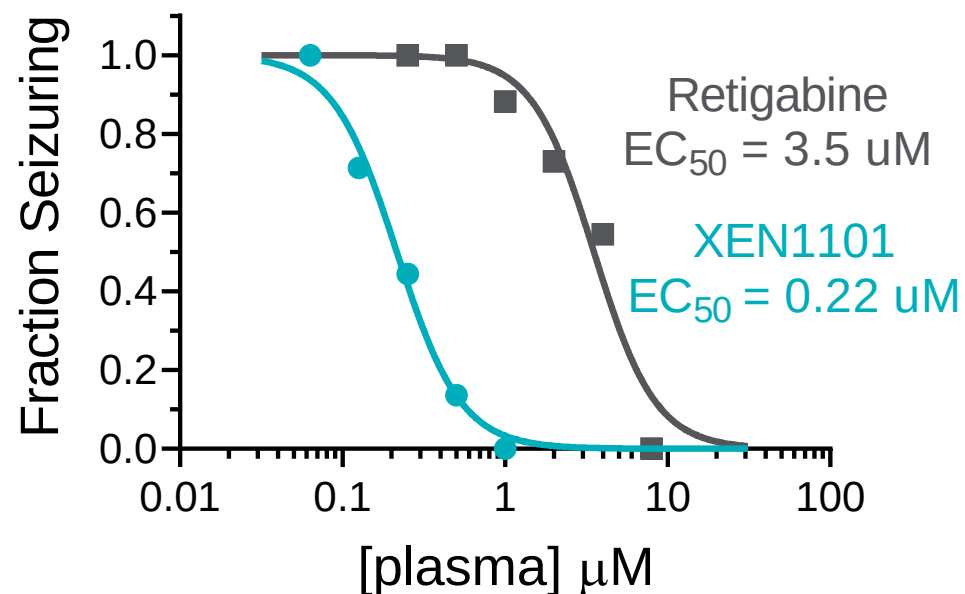
Sample of purified phenazinium-type dimer

- Ezogabine has a secondary aniline function, which is key to forming phenazinium-type dimers
- XEN1101 instead has a tertiary aniline at the corresponding position
- This key structural difference prevents XEN1101 from forming analogous dimers**

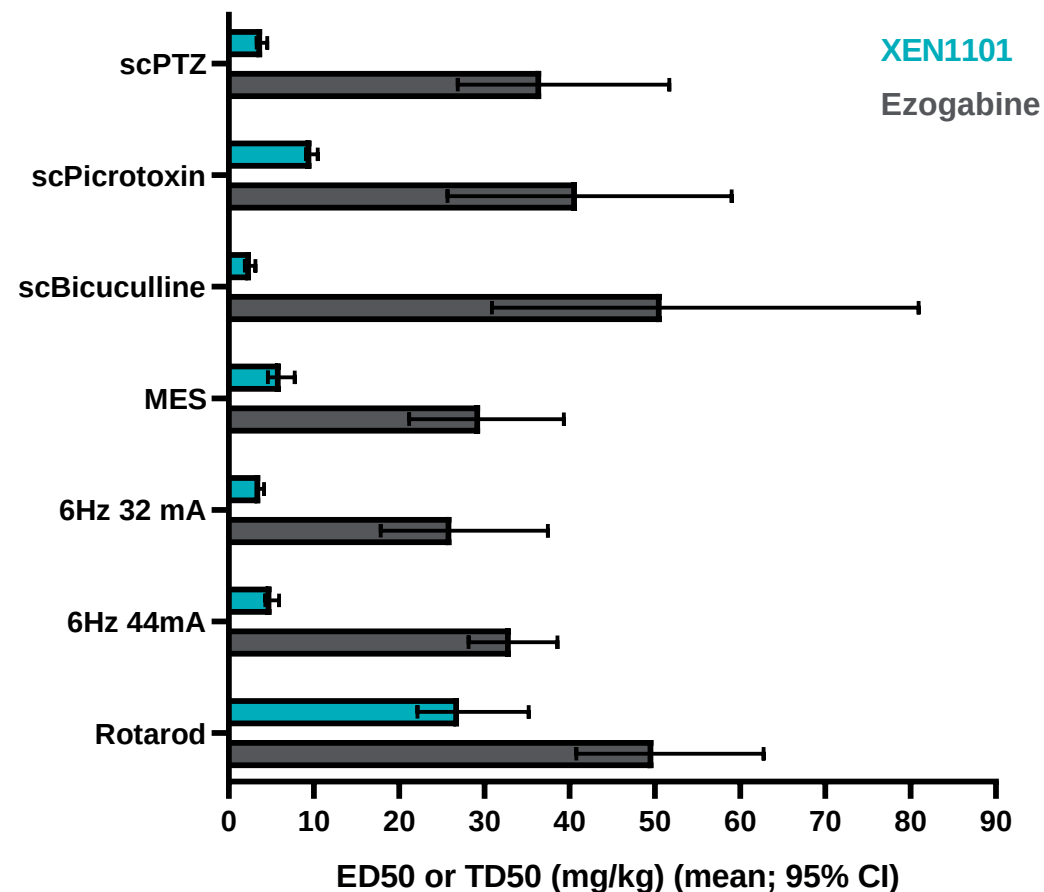
1. Groseclose et al. Chem. Res. Toxicol. 2019, 32:294-303

XEN1101: Potency and TI Advantages vs Ezogabine

- XEN1101 is ~16-fold more potent than ezogabine in Maximal Electroshock Stimulus (MES) model in CF-1 mice

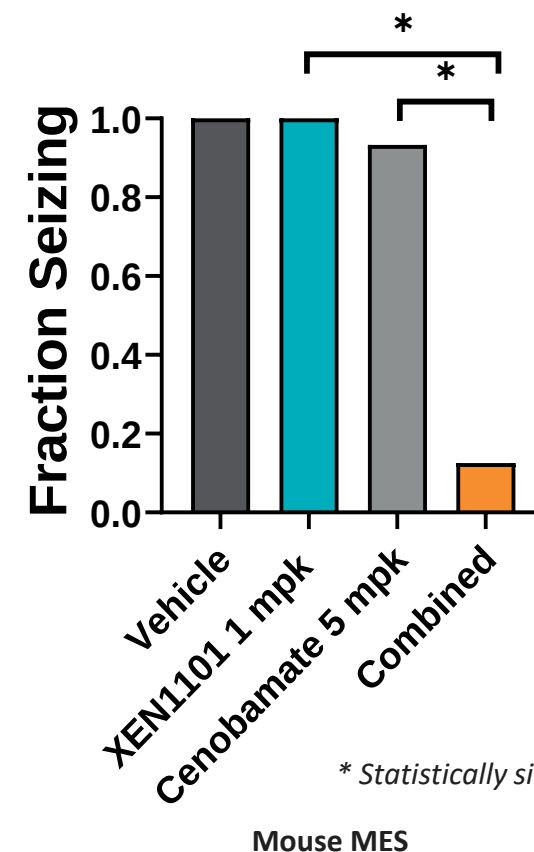
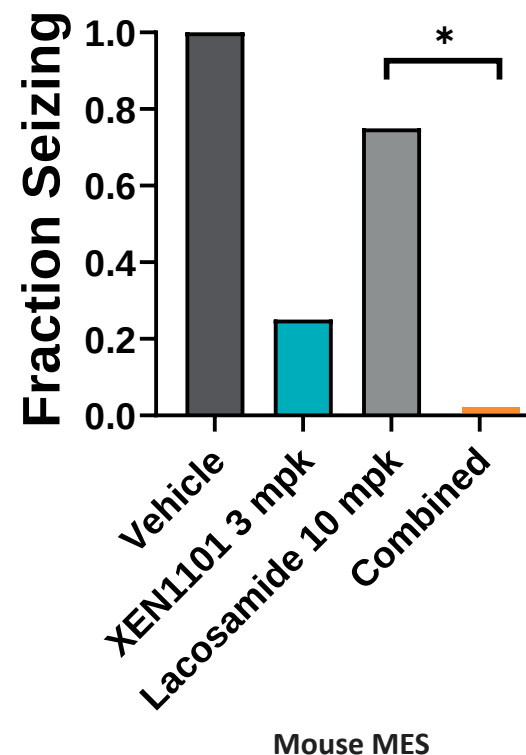
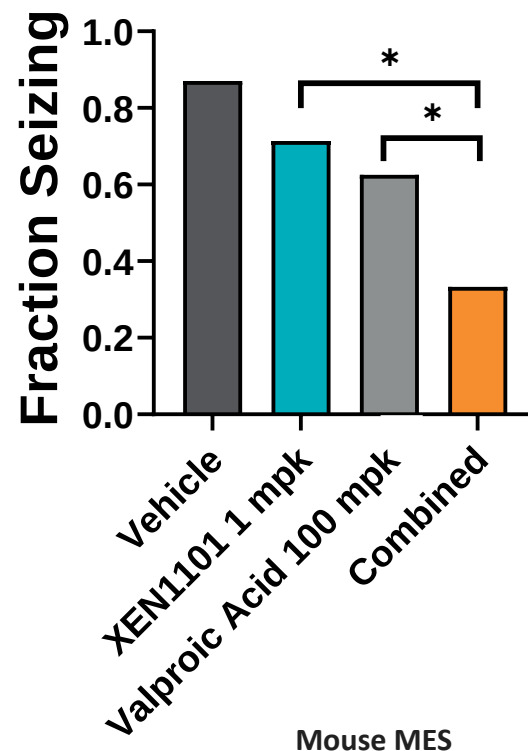
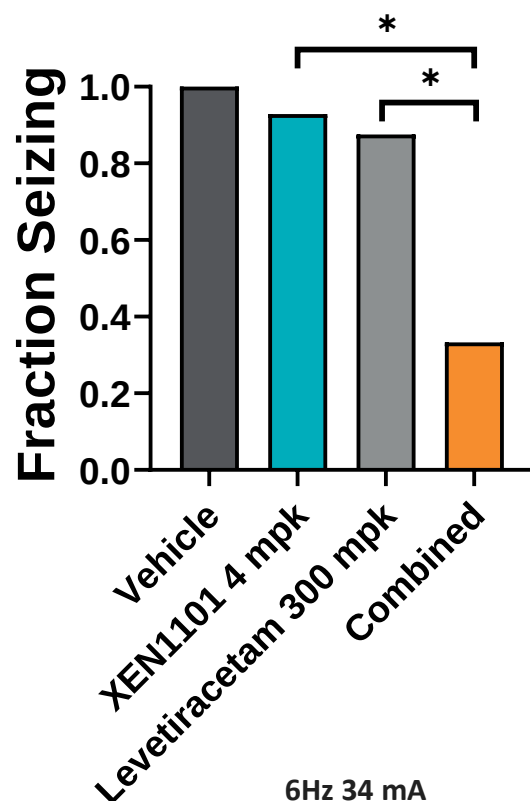


- XEN1101 has an improved therapeutic index versus Ezogabine



Combining XEN1101 with Common ASMs Provides Robust Seizure Protection in Pre-clinical Models

- Combining ineffective or weakly active doses of XEN1101 and common ASMs with distinct mechanisms enhances robust seizure protection
- Enhanced efficacy is not a drug-drug interaction phenomenon; not explained by changes in plasma levels
- Combination doses were well tolerated



* Statistically significant

XEN1101 is a Differentiated K_v7 Channel Modulator

Kv7 is a Validated Mechanism

- K_v7 plays an important role in dampening neuronal hyper-excitability and potentiators help provide anti-seizure effects
- Ezogabine is a first-generation potentiator with strong clinical validation

XEN1101 Lacks Dimerization-related Issues

- No XEN1101 dimerization due to tertiary aniline
- Lack of dimerization prevents pigmentary abnormalities experienced by long-term ezogabine exposure

XEN1101 has Higher Potency and Improved PK

- XEN1101 has significantly higher potency than ezogabine *in vitro* and *in vivo*
- Plasma levels corresponding to the pre-clinical models EC_{50s} have been achieved in Phase 1 clinical trials

XEN1101 has an Effective and Tolerable Combination Potential

- Combining XEN1101 and common ASMs boosts seizure protection pre-clinically and not caused by drug-drug interactions or plasma level changes
- XEN1101 combinations are well tolerated pre-clinically

Dr. Simon Pimstone

OVERVIEW OF XEN1101'S CLINICAL DEVELOPMENT

Phase 1: Summary of Single & Multiple Dose Findings

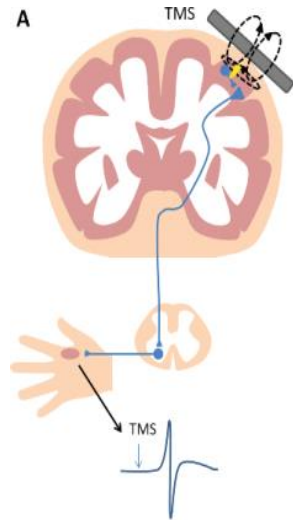
- XEN1101 Phase 1 used an adaptive integrated design, and included a Phase 1b TMS study
- XEN1101 has a PK profile consistent with QD
 - Long terminal elimination half-life
- Near steady-state within 1 week, full steady-state within 3 weeks
- Absorption is enhanced by food
- Exposure increased dose proportionally (15-25 mg QD) in fed state
- Low inter-individual PK variability with repeat dose
- AE profile consistent with CNS MOA (e.g., dizziness, sedation, blurred vision)
 - No signal of urinary retention
 - Post-void residual volume normal (bladder ultrasound)
 - Minimal renal excretion of drug
 - No safety signals in ECG or safety labs; no SAEs

Phase 1b: Transcranial Magnetic Stimulation (TMS) PD Study

- TMS is a non-invasive tool to study human cortical excitability and target engagement of CNS acting drugs
- Multiple ASMs show effects on TMS at efficacious plasma levels, including ezogabine

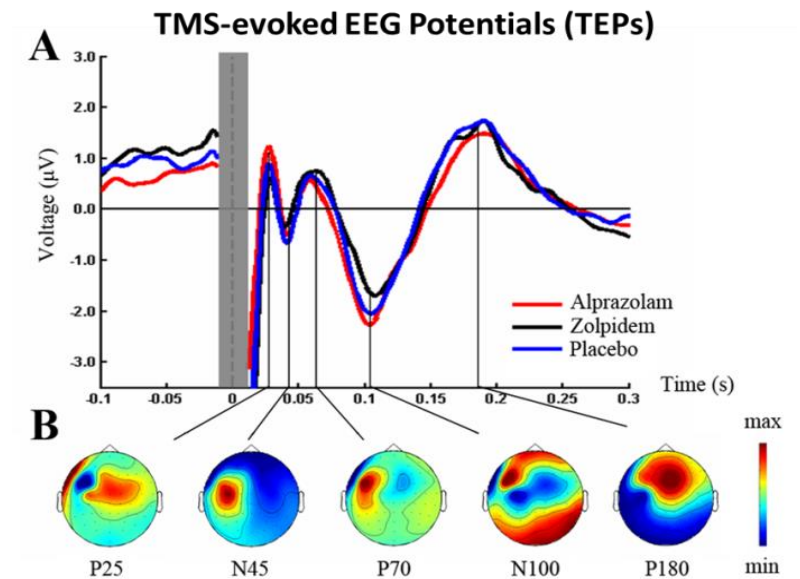
EMG:

Resting Motor Threshold (RMT%)
reflects cortico-spinal excitability



EEG:

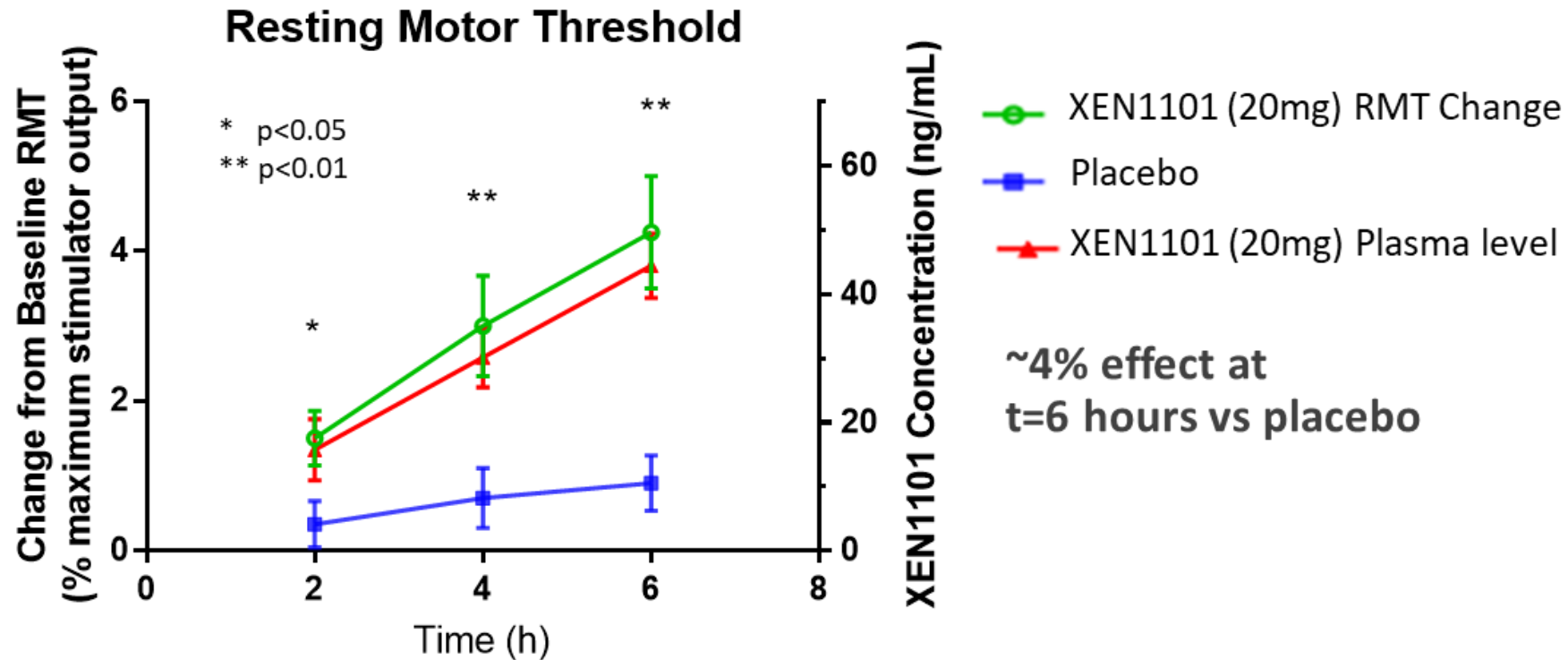
TMS-evoked EEG potentials (TEPs) allow direct evaluation
of cortical excitability in a time-resolved fashion manner



Premoli et al., 2014 *Journal of Neuroscience*

Summary of XEN1101 Phase 1b TMS Results

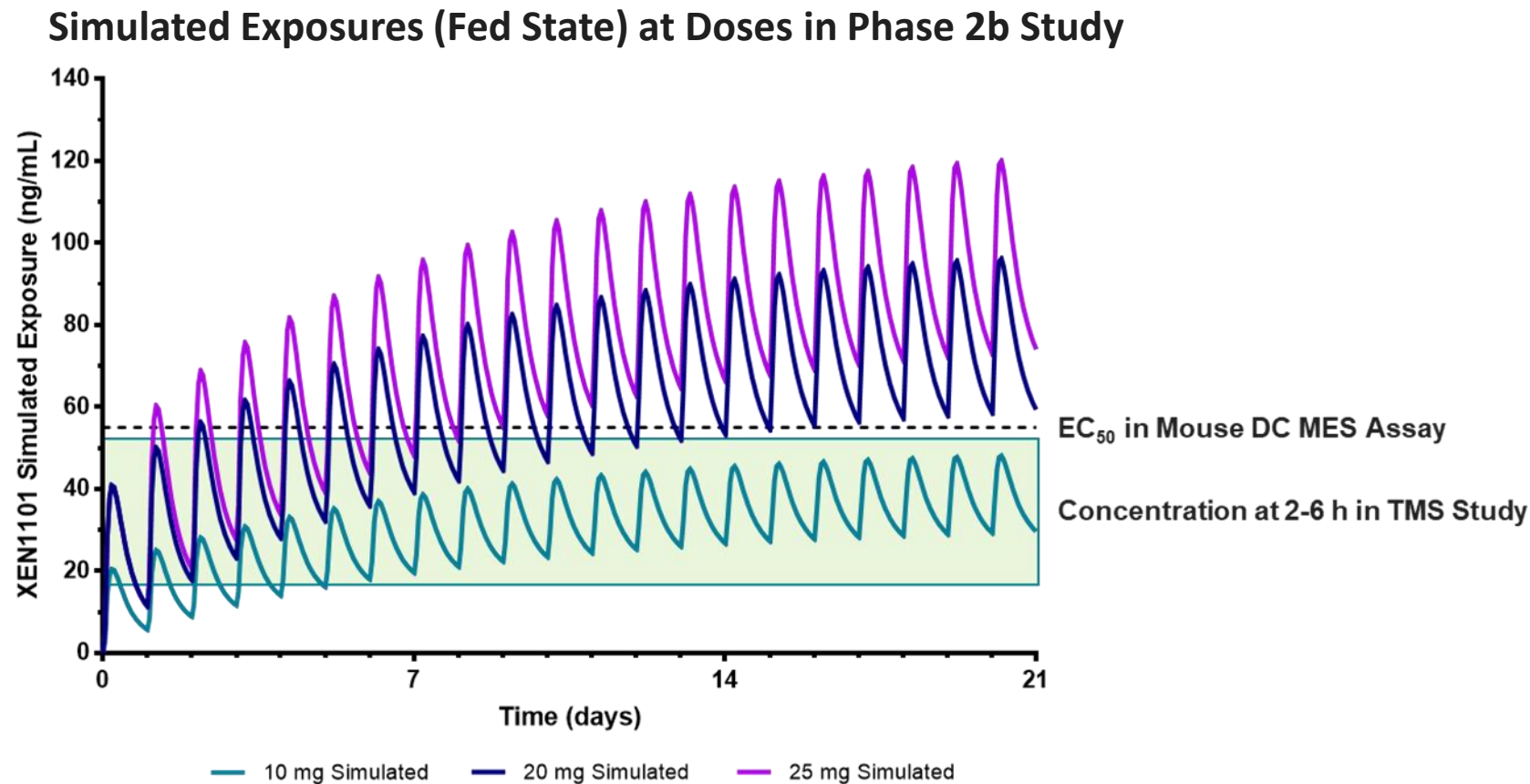
- TMS was used to evaluate the corticospinal and cortical activity profile of XEN1101 compared to placebo in healthy male volunteers



Significant plasma concentration dependent reduction of corticospinal (RMT) and cortical (TEP) excitability

Use of Phase 1 and TMS to Inform Dose Selection in Phase 2b

- Simulations based upon PK parameters in Phase 1
- Dose range chosen in Phase 2b will provide two doses with trough levels above effective level in TMS and pre-clinical efficacy models



X-TOLE Phase 2b Clinical Trial Underway

- **X-TOLE Study:**
Randomized, placebo-controlled Phase 2b clinical trial in 300 subjects with focal epilepsy

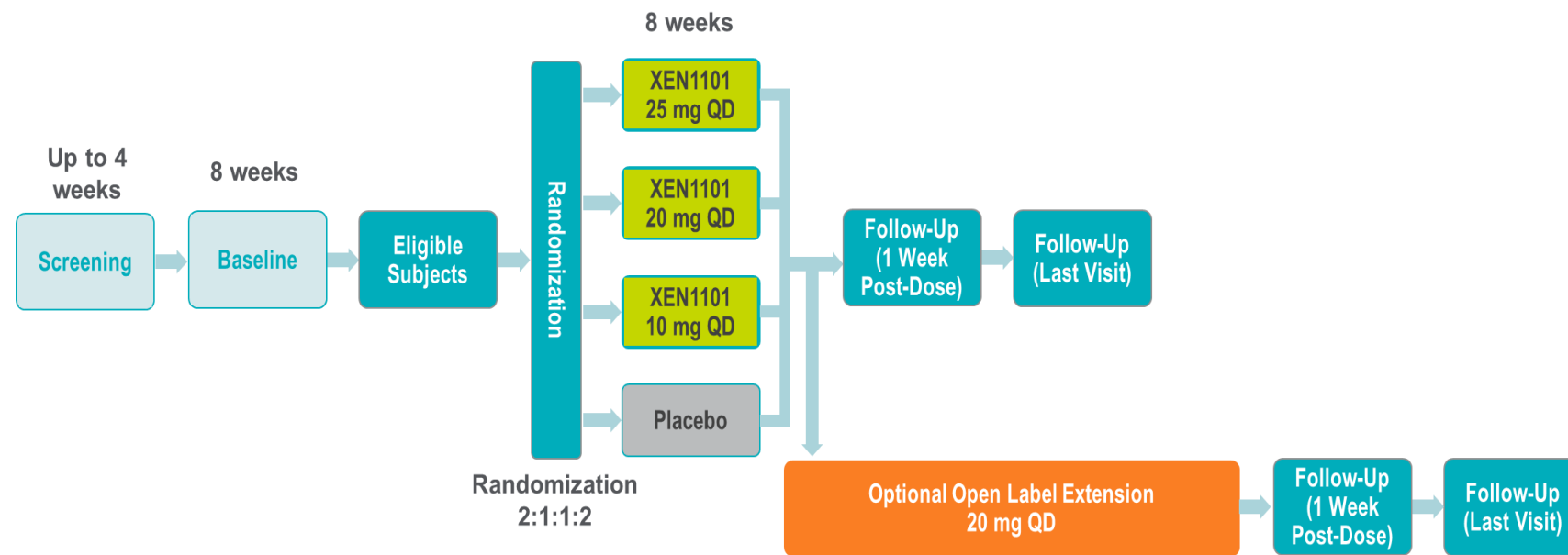
- **Endpoints:**

- The primary endpoint is median percent change (MPC) from baseline in monthly (28 days) focal seizure frequency in the 8-week double-blind treatment period compared to placebo

- The study is well powered (around 90% power)

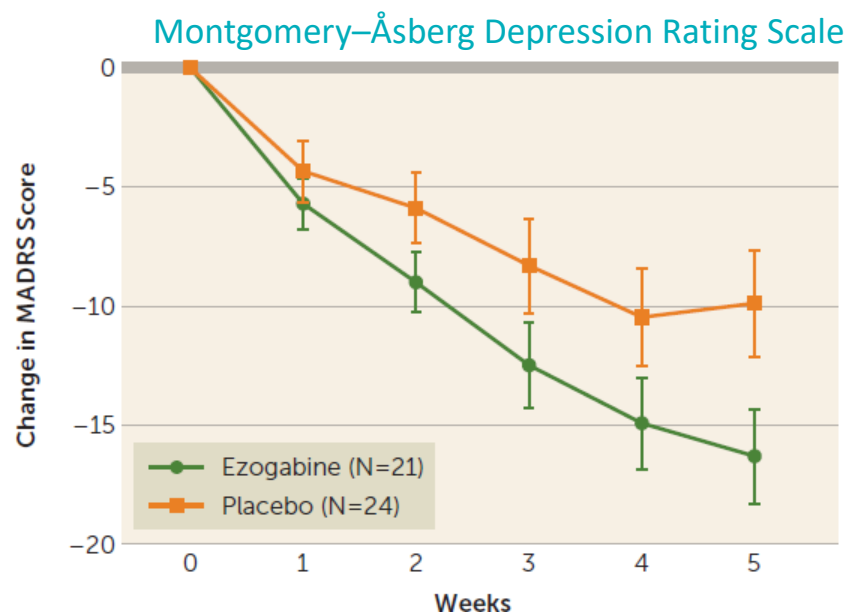
- Designed to detect a monotonic dose response assuming a -20% MPC in placebo and -25%, -30% and -35% MPC at 10, 20 and 25 mg QD XEN1101, respectively

- Electronic diary to capture seizures, allowing subjects to be closely monitored for events and compliance

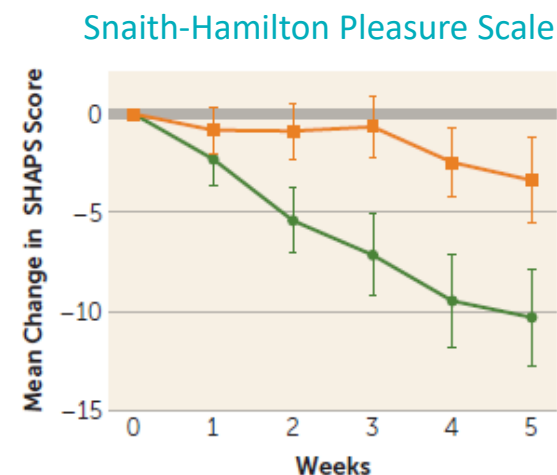


XEN1101 Phase 2 POC Studies in Major Depressive Disorder

- Promising clinical results with ezogabine when targeting KCNQ channels as a treatment for Major Depressive Disorder (MDD)



Ezogabine, compared with placebo, was associated with a large improvement in depression as measured by the Montgomery-Åsberg Depression Rating Scale (MADRS score change: -7.9 ± 3 , $p < .001$)



Compared with placebo, ezogabine was associated with a large improvement in hedonic capacity as measured by the Snaith-Hamilton Pleasure Scale (SHAPS score change: -6.9 ± 3.2 , $p < .001$)

- Anticipate initiation of investigator-led (Mount Sinai) Phase 2 proof-of-concept clinical trial of XEN1101 for treatment of MDD and anhedonia in the coming months
- In parallel, Xenon is planning a company-sponsored clinical study in MDD based on encouraging pre-clinical data with XEN1101

Costi et al., "Impact of the KCNQ2/3 Channel Opener Ezogabine on Reward Circuit Activity and Clinical Symptoms in Depression: Results from a Randomized Controlled Trial." *Am J Psychiatry*. 2021.

Clinical Experience Summary

Phase 1 Studies Show Promising Drug Profile and Tolerability

- Phase 1 SAD and MAD studies demonstrate favorable PK supporting QD dosing
- XEN1101 is well tolerated at up to 30mg, with majority of AEs mild and CNS related

TMS Demonstrates strong PK-PD Relationship

- Phase 1b TMS study shows that XEN1101 reduces corticospinal excitability, suggesting strong PK-PD relationship
- Additionally, the effect was greater than that of ezogabine

Phase 2b Readout Late Sept to mid Oct

- SAD/MAD and TMS studies informed Phase 2b dose selection
- Phase 2b study includes 300 patients with >4 focal seizures/month receiving 10mg, 20mg, or 25mg QD doses, with topline readout in late September to mid October

Additional XEN1101 Development in MDD

- Promising efficacy by ezogabine in MDD supports XEN1101 trial in MDD
- Phase 2 proof-of-concept study in MDD to be initiated by Mount Sinai in the near future and Xenon-sponsored trial to follow

Dr. Chris Von Seggern

OVERVIEW OF XEN1101'S COMMERCIAL OPPORTUNITY

XEN1101 Commercial Overview

1

Physician Presentation of FOS Landscape and XEN1101 Background



FOS Landscape Overview and Unmet Needs

Novel ASM XEN1101 Mechanistic Overview



2

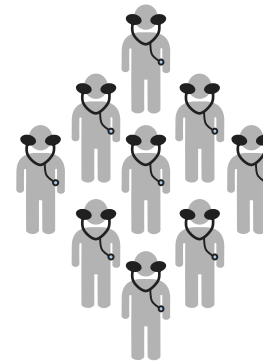
Market Research to Further Understand Landscape and XEN1101 Opportunity

Market Research Goals

Pinpoint Drivers of Clinical Decision Making

Understand Remaining Unmet Needs in FOS

Identify Key Attributes Desired in Future ASMs



N= 50 Physicians
(Including academic epileptologists and high volume prescribing neurologists/epileptologists)

Focus of Commercial Overview

Market Research Key Takeaways

Unmet Needs Remain Despite Numerous ASMs Available

- Physicians emphasized that **high clinical unmet needs exist, particularly among rational polypharmacy patients**, despite the availability of >25 ASMs today
- **Better safety/tolerability, unique MOA, and potential to address comorbidities were all cited as key unmet needs** physicians hope novel ASMs will address

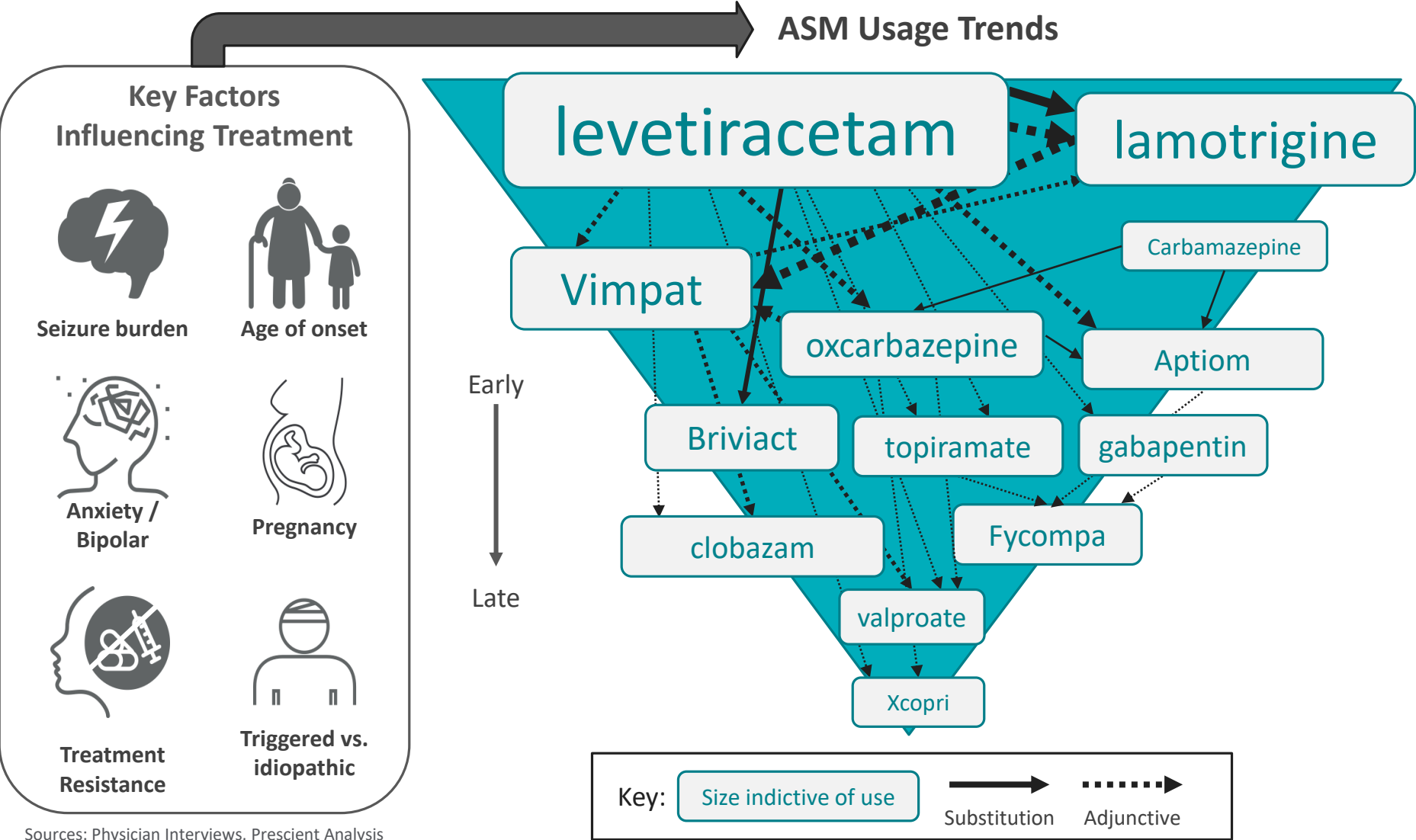
Tolerability and Impact on Comorbidities Significantly Influence Treatment Decisions

- Efficacy is the main treatment goal, but given little perceived difference across ASMs, **physicians focus on tolerability and impact on comorbidities** to determine treatment approach
- AEs such as fatigue, somnolence, irritability, and cognitive disruption are common drivers of non-compliance
- Comorbidities (i.e., psychiatric, migraines, pain) are strong determinants of treatment selection such as use of broad vs. narrow spectrum ASMs

XEN1101 Meets Key Characteristics Desired by Physicians

- **Strong physician enthusiasm around XEN1101 use in rational polypharmacy patients**
- In particular, the **Kv7 novel MOA and anticipated strong tolerability profile were regarded as highly attractive**
- Additionally, long half-life viewed as flexible for missed and delayed doses and once daily dosing and lack of titration is perceived as convenient for patients and clinicians

Physician Reported Treatment Paradigm



Sources: Physician Interviews, Prescient Analysis

Key Takeaways

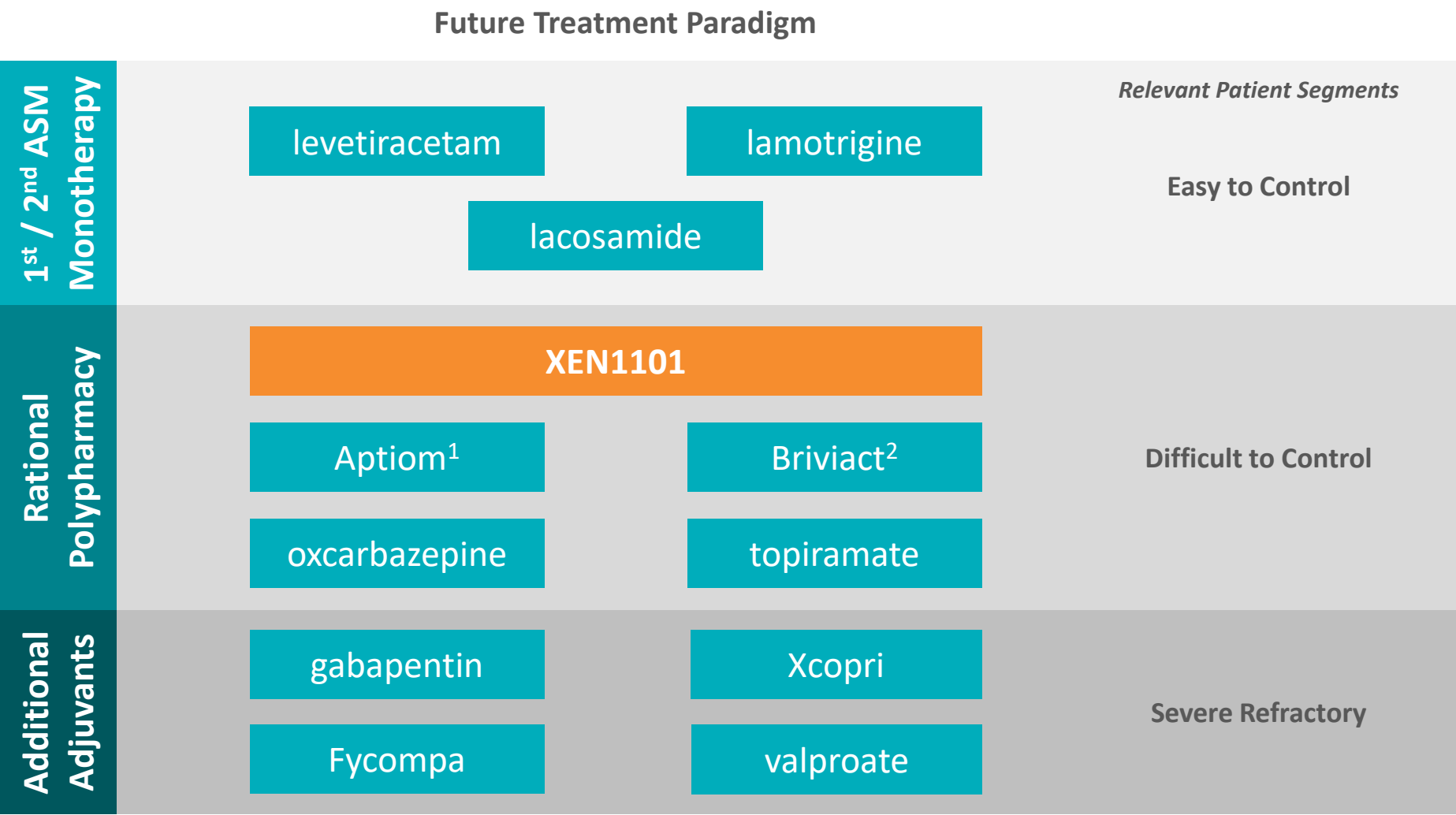
- **Physician** stress the **subtle ‘art’ of treatment selection**, admitting the central role of **trial and error**

“Universally, cannot point to such and such a drug and say that it works better and is clearly the one to use...it’s still trial and error” – KOL

- Treatment selection requires **experimentation on a per-individual basis**

“Each medication is unique for each patient” – KOL

XEN1101 Clinical Positioning



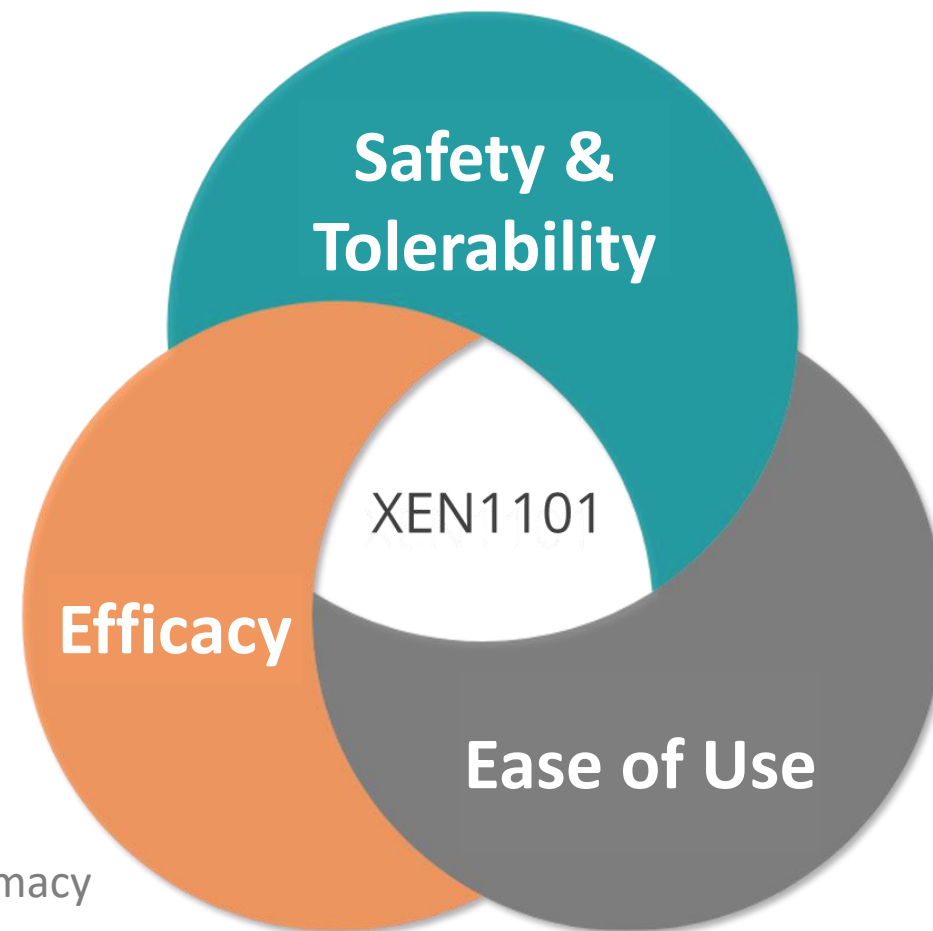
Note: ¹Aptiom use higher among HVPs, including as early monotherapy, dictated by market access; ²Briviact use driven by psych. comorbidities or psych. AEs with levetiracetam
Sources: Physician Interviews, Prescient Analysis

XEN1101 Profile Opportunity

Well-tolerated with low drop-out rates in Phase 2b
Not expected to exacerbate psych comorbidities
Evening dose = $C_{\max}$ during sleep
No drug allergic reactions observed

Proven anti-seizure MOA
Broad efficacy in multiple pre-clinical seizure models
May provide mood benefit beyond seizure control
Strong TMS engagement

One pill, once-daily
No titration required
Unique MOA and low DDI risk can be leveraged in rational polypharmacy
Forgiving PK provides coverage for missed doses



Summary of Today's Discussion



FOS Unmet Medical Need

- FOS accounts for a majority of epilepsy patients and is a high unmet need disease despite the plethora of ASMs available today
- Unmet needs exist for improved efficacy, treating comorbidities, and novel MOAs



Kv7 Mechanistic Background

- Kv7 has a well validated role in decreasing neuronal excitability and is an important target for seizure control
- XEN1101 targets Kv7 and has shown promising potency, therapeutic index, lack of dimerization, and combination potential



XEN1101 Clinical Experience

- Phase 1 studies have shown PK supporting convenient QD dosing and strong PK-PD relationship
- Phase 2b readout anticipated in late September to mid October, with future Phase 2 POC in MDD



XEN1101 Commercial Opportunity

- Market research (N=50 physicians) supports attractive XEN1101 commercial positioning as a top adjunctive choice
- XEN1101 is perceived to meet significant unmet need with efficacy, strong safety/tolerability, and ease of use attributes