XENON

AES 2021 Symposium

The Unmet Need in Epilepsy: The Therapeutic Potential of Potassium Channel Modulators

FRIDAY, DECEMBER 3, 2021 | 6-8 PM (CT)

MCCORMICK PLACE WEST W196A/B, LEVEL1 | CHICAGO, IL

WELCOME!

"THE UNMET NEED IN EPILEPSY: THE THERAPEUTIC POTENTIAL OF POTASSIUM CHANNEL MODULATORS"

Please select a salad, dinner, drink, and dessert.

There is no assigned seating. Please find an open seat.

The symposium will begin shortly.

Agenda

	SPEAKER	TOPIC
6:00 pm	**Registration / Welcome**	
6:05 pm	Dr. Roger J. Porter	Introductions and session overview
6:10 pm	Dr. Roger J. Porter	Overview of focal onset seizures (FOS) and the unmet medical need
6:30 pm	Dr. Christopher Kenney	Summary of results from the “X-TOLE” study
7:00 pm	Dr. Cynthia Harden	Examples of innovations in FOS clinical trials: Use of TMS and eDiary
7:20 pm	Dr. Robin Sherrington	Overview of XEN1101’s K_V7 mechanism
7:40 pm	Dr. Roger J. Porter	Progress in epilepsy treatment avenues: The role of potassium channel modulators in the armamentarium
8:00 pm	**Q&A / Panel Discussion Moderated By Dr. Porter**	

An Overview of Focal Onset Seizures (FOS) and the Unmet Medical Need

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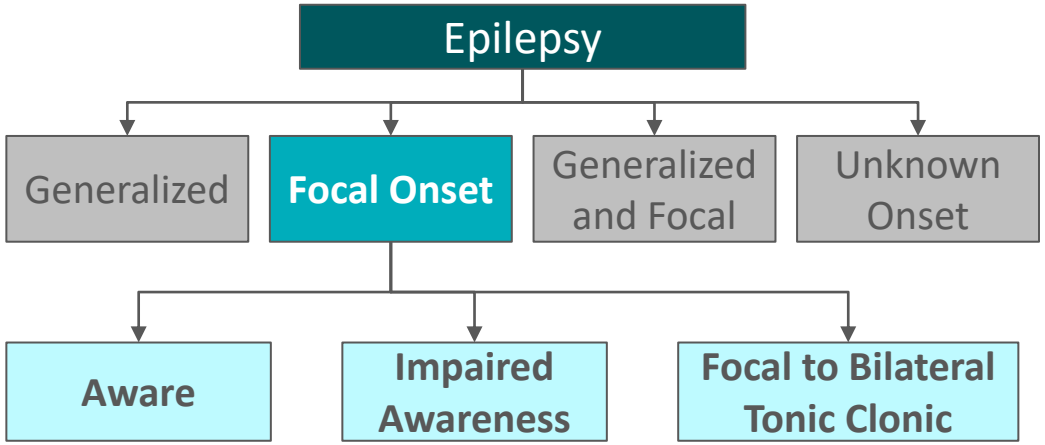
Focal-Onset Seizures (FOS) Overview



FOS Description

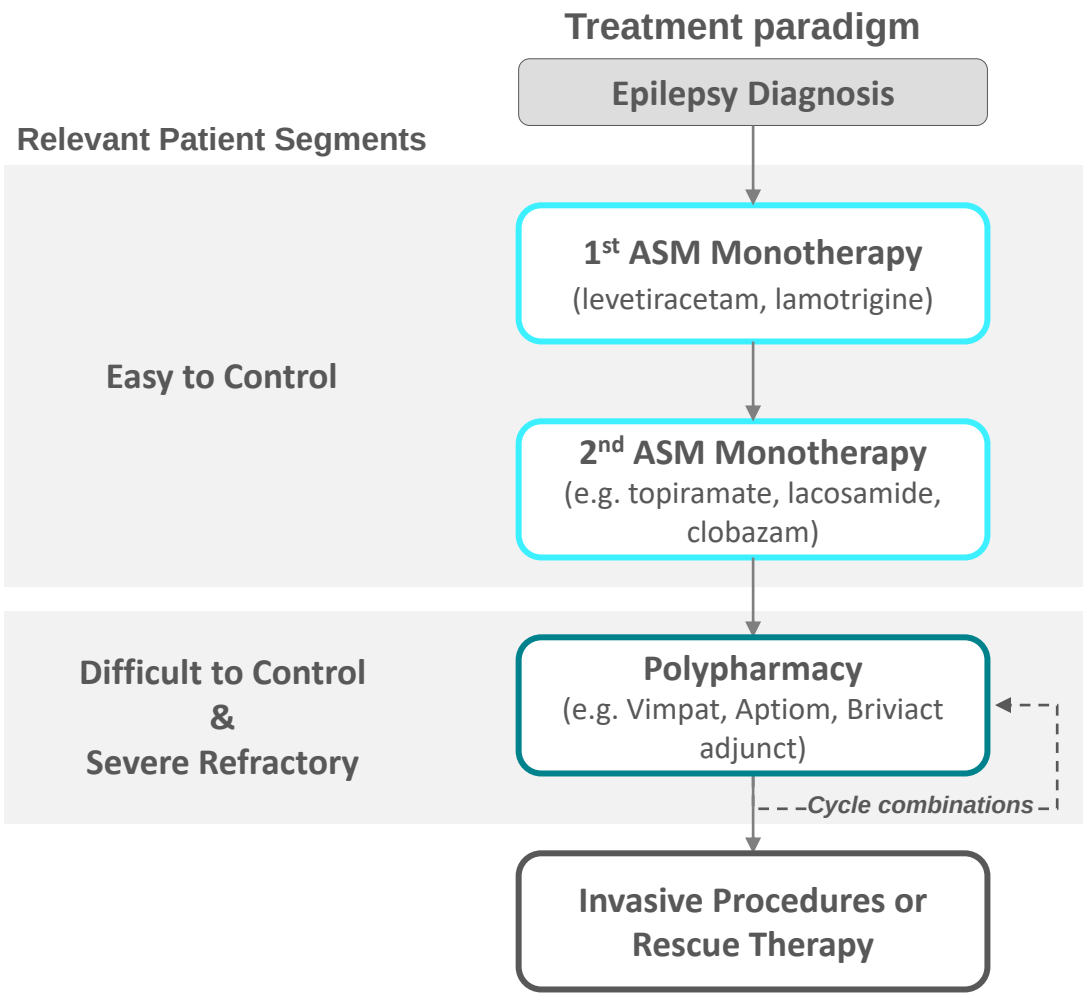
- Focal onset seizures (FOS) is one of the four major seizure groups, accounting for ~60% of epilepsy patients
- Seizures occur due to abnormal neural activity located in only one region of the cerebral hemisphere, and may or may not have associated impairment in consciousness
- FOS patients have a high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

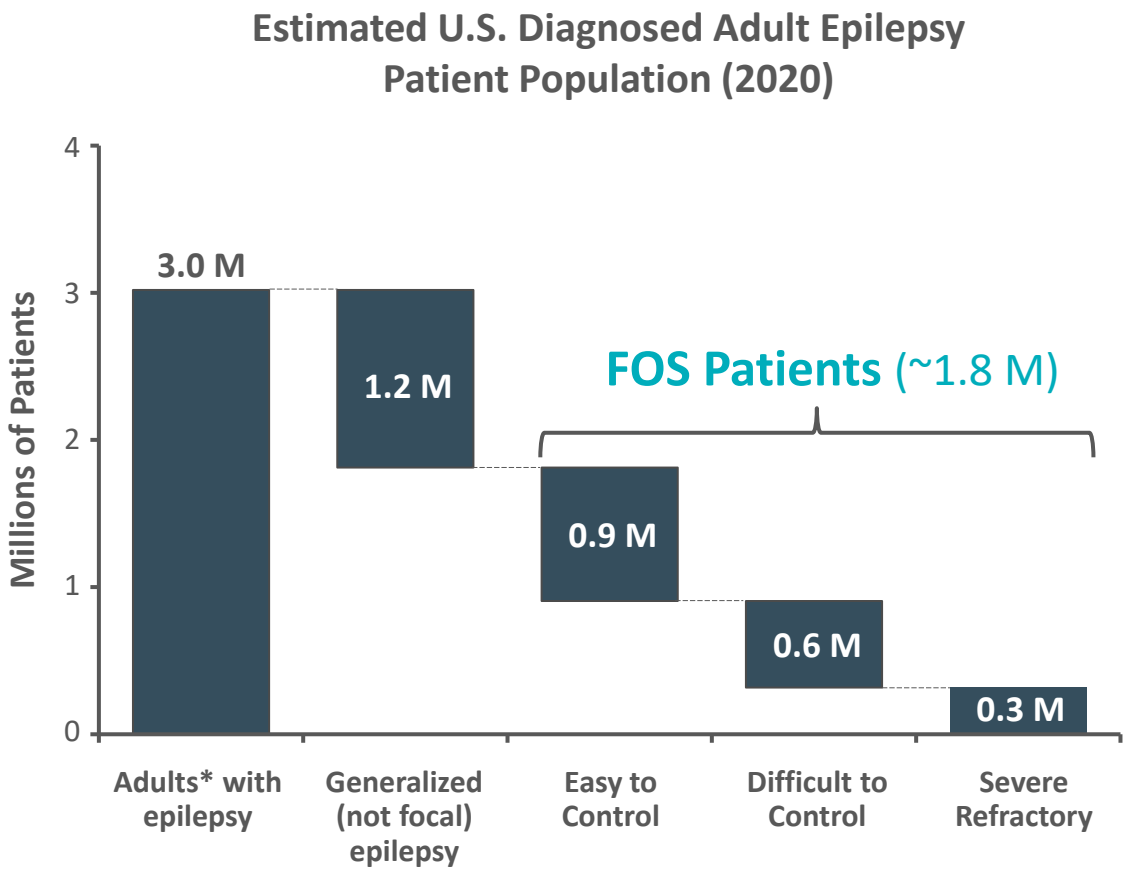
- Treatment goal aims to optimize efficacy while managing comorbidities and maximizing quality of life
- There are no standard first line therapies though levetiracetam or lamotrigine are commonly used early in the treatment paradigm
- Patients experiencing insufficient seizure efficacy or side effects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

Epilepsy Foundation; Epilepsy Currents, Englot (2018), National Association of Epilepsy Centers, National Institute of Neurological Disorders and Stroke

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%)	**Difficult to Control** (30 – 35%)	**Severe Refractory** (15 – 20%)
• **Typically monotherapy** and may involve switching to a second monotherapy • **Many patients are well-managed** with initial therapy	• 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**	• 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

Seizure Profile / Burden

Seizures vary in frequency, duration, and complexity, which may require different treatment MOAs to achieve seizure control

Side Effects and QoL

Safety and tolerability (e.g. adverse events and impact on mood) and ease of use (e.g. need for dosage titration, frequent dosing) significantly impact QoL and treatment decisions

Comorbid Conditions

Comorbidities (e.g. depression, anxiety, migraines) are assessed to select treatments that may benefit or not exacerbate them

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
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
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 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**
- **Novel MOAs for Rational Polypharmacy**
- **Efficacy for Comorbidities**

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.)
- ☐ Neutral impact on mood
- ☐ QD dosing
- ☐ Limited need for dose titration
- ☐ Limited drug-drug interactions
- ☐ MOA unique from existing ASMs

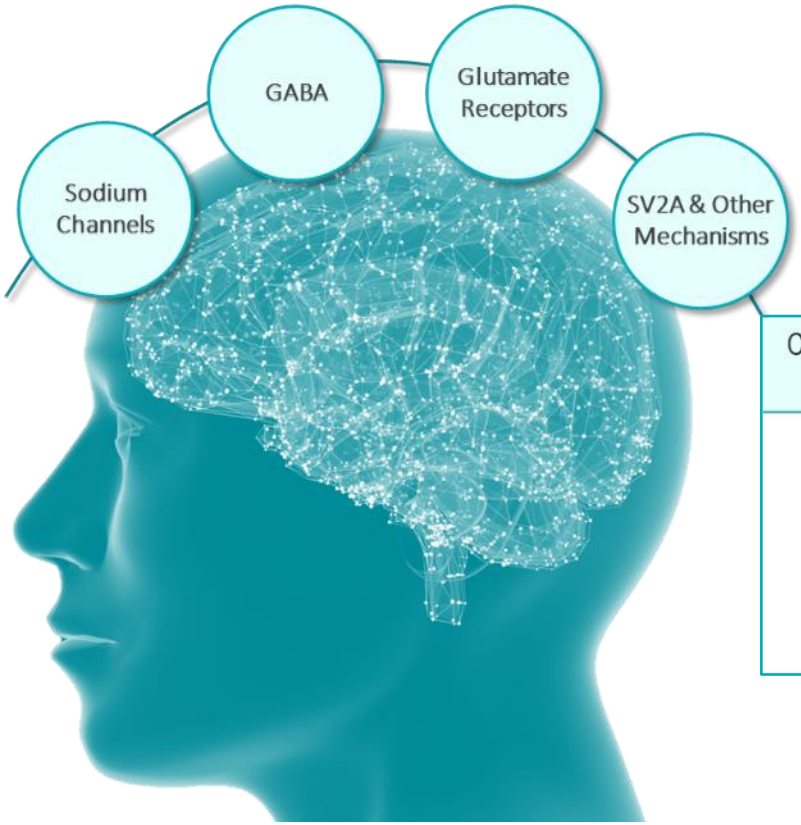
Summary of Results from the Phase 2b X-TOLE Study

DR. CHRISTOPHER KENNEY
CHIEF MEDICAL OFFICER, XENON PHARMACEUTICALS

XEN1101 Next-Gen K_V7 Channel Opener

- Only-in-class K_V7 potassium channel modulator to treat adult focal seizures
- Novel MOA for rational polypharmacy
- Designed to address limitations of first-gen K_V7 modulator, ezogabine
  - Higher in vitro and in vivo potency
  - PK TID → QD
  - Lacks the chemical properties that could form pigmented dimers
- Improved seizure reduction
- Potential to treat common comorbidities, such as depression

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

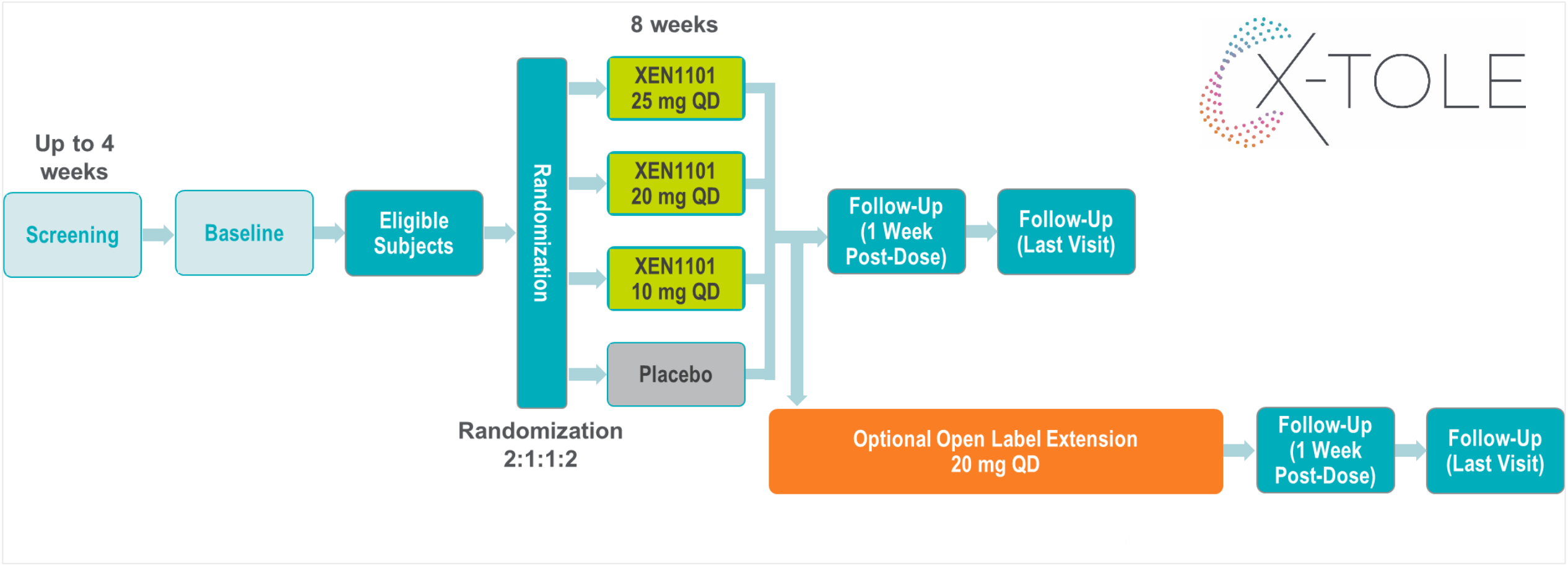


Commonly Prescribed ASMs for Adult Focal Epilepsy

- levetiracetam
- brivaracetam
- carbamazepine
- lamotrigine
- lacosamide

Addressing previous limitations, enhancing the K_V7 opportunity

X-TOLE Study Schema



Primary / Secondary Objectives of X-TOLE Study

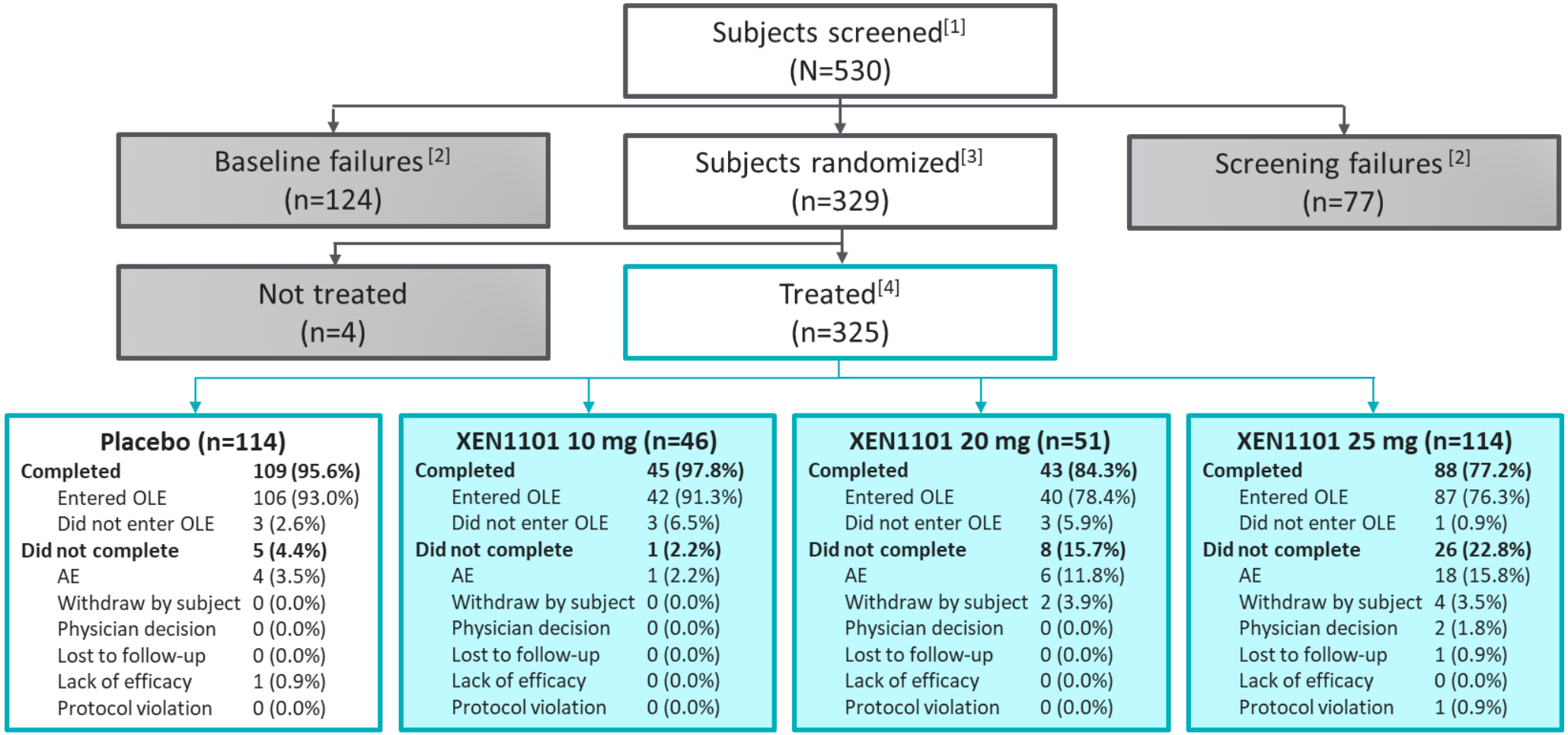
	OBJECTIVES	ENDPOINTS
Primary Objectives	To assess the efficacy of XEN1101 compared to placebo on focal seizure frequency in adults with focal epilepsy taking 1 to 3 ASMs in the double-blind period (DBP)	• Median percent change (MPC) in monthly (28 days) focal seizure frequency from baseline to DBP for XEN1101 versus placebo
	To assess the safety and tolerability of XEN1101 in adults with focal epilepsy taking 1 to 3 ASMs in the DBP	In the DBP: • Severity and frequency of associated adverse events (AEs)/serious adverse events (SAEs) • Clinically significant changes in clinical laboratory findings • Clinically significant changes in 12-lead ECG • Change in suicidality risk as assessed by the C-SSRS including increase in suicidal thoughts or an attempt • Clinically significant changes in vital signs including blood pressure, pulse, or weight • Clinically significant changes in urological symptoms including retention as measured by the American Urological Association (AUA) Symptom Index
Secondary Objectives	To evaluate the 50% XEN1101 response rates in comparison to placebo in the DBP	• Responders are defined as patients experiencing ≥50% reduction in monthly (28 days) focal seizure frequency from baseline compared to DBP
	To evaluate trends in focal seizure frequency over time in the DBP	• Percent change from baseline in weekly focal seizure frequency for each week of the DBP
	To assess the effect of XEN1101 vs placebo on seizure severity and impact in adults with focal epilepsy taking 1 to 3 ASMs in the DBP	• Clinical Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C) scores during the DBP

Demographics and Baseline Characteristics (Safety Population)

	Placebo (N=114)	XEN1101 10mg (N=46)	XEN1101 20mg (N=51)	XEN1101 25mg (N=114)	TOTAL (N=325)
Age in years, Mean (SD)	**42.9 (13.7)**	**40.0 (12.1)**	**41.7 (13.6)**	**38.7 (13.1)**	**40.8 (13.3)**
Age at study entry category					
≥ 65, n (%)	**5 (4.4)**	**2 (4.3)**	**4 (7.8)**	**1 (0.9)**	**12 (3.7)**
< 65, n (%)	**109 (95.6)**	**44 (95.7)**	**47 (92.2)**	**113 (99.1)**	**313 (96.3)**
Gender					
Female, n (%)	**61 (53.5)**	**27 (58.7)**	**26 (51.0)**	**54 (47.4)**	**168 (51.7)**
Male, n (%)	**53 (46.5)**	**19 (41.3)**	**25 (49.0)**	**60 (52.6)**	**157 (48.3)**
Region					
Europe, n (%)	**67 (58.8)**	**31 (67.4)**	**32 (62.7)**	**68 (59.6)**	**198 (60.9)**
North America, n (%)	**47 (41.2)**	**15 (32.6)**	**19 (37.3)**	**46 (40.4)**	**127 (39.1)**
Background ASM Use					
1, n (%)	**12 (10.5)**	**4 (8.7)**	**2 (3.9)**	**11 (9.6)**	**29 (8.9)**
2, n (%)	**46 (40.4)**	**18 (39.1)**	**20 (39.2)**	**47 (41.2)**	**131 (40.3)**
3, n (%)	**56 (49.1)**	**24 (52.2)**	**29 (56.9)**	**56 (49.1)**	**165 (50.8)**
Number of Pre-study ASMs failed					
Median [Q1, Q3]	**6.0 [3.0, 8.0]**	**5.0 [4.0, 9.0]**	**6.0 [4.0, 9.0]**	**5.5 [3.0, 9.0]**	**6.0 [4.0, 9.0]**

Arms well balanced and representative of a difficult to treat adult FOS patient population

Study Disposition (Safety Population)



Placebo (n=114)	
Completed	**109 (95.6%)**
Entered OLE	106 (93.0%)
Did not enter OLE	3 (2.6%)
Did not complete	**5 (4.4%)**
AE	4 (3.5%)
Withdraw by subject	0 (0.0%)
Physician decision	0 (0.0%)
Lost to follow-up	0 (0.0%)
Lack of efficacy	1 (0.9%)
Protocol violation	0 (0.0%)

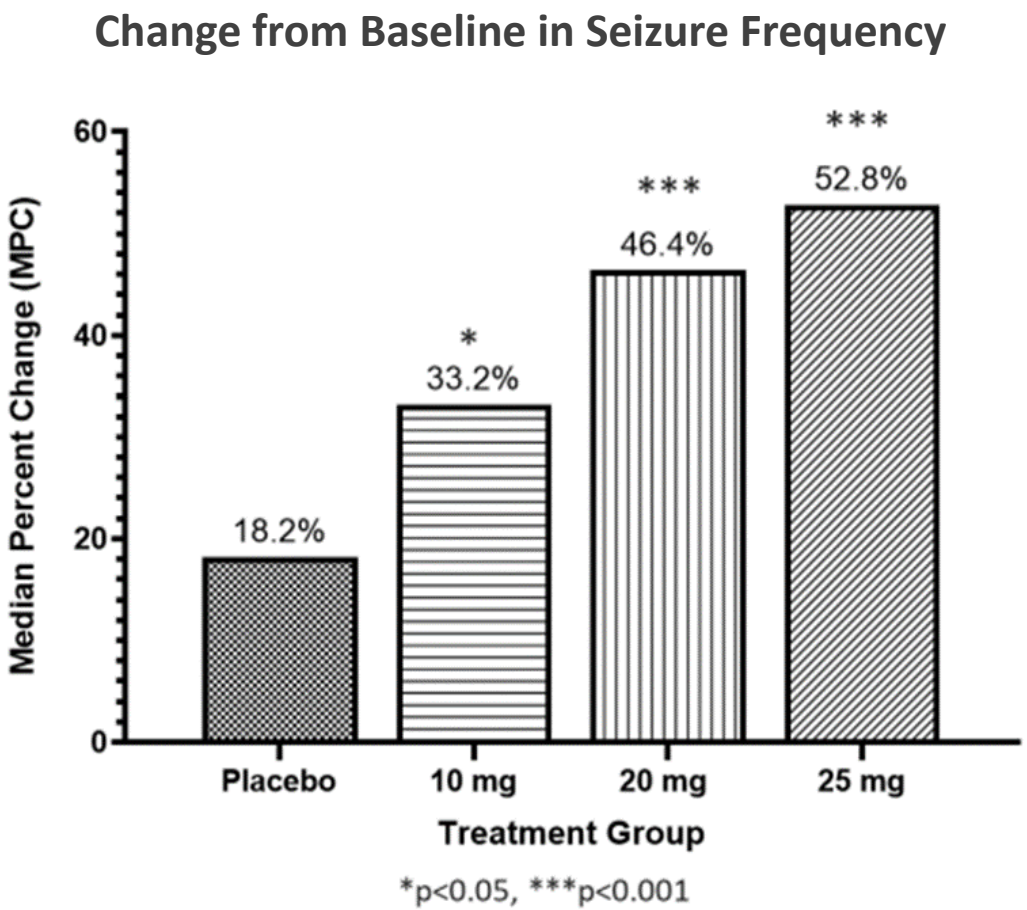
XEN1101 10 mg (n=46)	
Completed	**45 (97.8%)**
Entered OLE	42 (91.3%)
Did not enter OLE	3 (6.5%)
Did not complete	**1 (2.2%)**
AE	1 (2.2%)
Withdraw by subject	0 (0.0%)
Physician decision	0 (0.0%)
Lost to follow-up	0 (0.0%)
Lack of efficacy	0 (0.0%)
Protocol violation	0 (0.0%)

XEN1101 20 mg (n=51)	
Completed	**43 (84.3%)**
Entered OLE	40 (78.4%)
Did not enter OLE	3 (5.9%)
Did not complete	**8 (15.7%)**
AE	6 (11.8%)
Withdraw by subject	2 (3.9%)
Physician decision	0 (0.0%)
Lost to follow-up	0 (0.0%)
Lack of efficacy	0 (0.0%)
Protocol violation	0 (0.0%)

XEN1101 25 mg (n=114)	
Completed	**88 (77.2%)**
Entered OLE	87 (76.3%)
Did not enter OLE	1 (0.9%)
Did not complete	**26 (22.8%)**
AE	18 (15.8%)
Withdraw by subject	4 (3.5%)
Physician decision	2 (1.8%)
Lost to follow-up	1 (0.9%)
Lack of efficacy	0 (0.0%)
Protocol violation	1 (0.9%)

[1] Subjects screened are all subjects who signed informed consent and were entered into the clinical database.
[2] This category includes screening failures as well as subjects that did not enter baseline for any other reason.
[3] All subjects who were provided a treatment assignment and recorded in the interactive response technology database, regardless of whether the treatment kit was used.
[4] Subjects in the Safety Population.

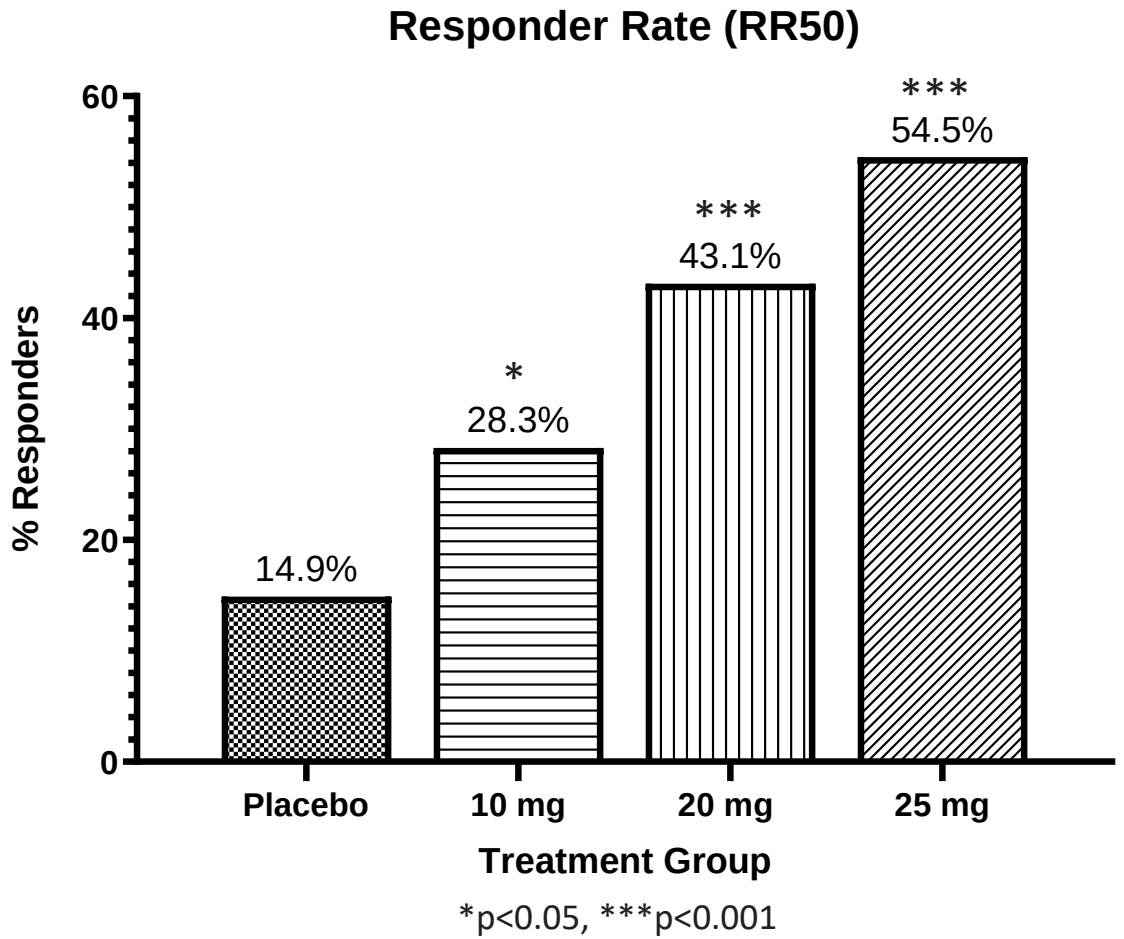
Efficacy Results: MPC from Baseline



	Placebo (N=114)	XEN1101 10mg (N=46)	XEN1101 20mg (N=51)	XEN1101 25mg (N=112)
Monthly Seizure Frequency in Baseline				
Median [Q1,Q3]	**13.4 [8.0, 30.1]**	**17.4 [8.0, 55.6]**	**14.5 [7.5, 36.4]**	**12.8 [8.4, 24.6]**
Monthly Seizure Frequency in the DBP				
Median [Q1, Q3]	**10.5 [5.4, 25.1]**	**10.9 [3.5, 41.2]**	**5.2 [3.0, 24.9]**	**5.3 [2.5, 13.6]**
Percent Change from Baseline to the DBP				
Median [Q1, Q3]	**-18.2 [-37.3, 7.0]**	**-33.2 [-61.8, 0.0]**	**-46.4 [-76.7, -14.0]**	**-52.8 [-80.4, -16.9]**
P-value from ranked ANCOVA model				
P-value for pairwise comparison vs. placebo (2-sided)		**0.035**	**<.001**	**<.001**
Primary Dose Response test p-value	**<.001**			

Highly significant and dose-dependent reduction in seizures

Secondary Endpoints: Response Rates and CGI-C/PGI-C



	XEN1101 25 mg (N=112)	Placebo (N=114)
CGI-C (Portion of Patients Much Improved or Very Much Improved)	46.4% (p<0.001)	22.8%
PGI-C (Portion of Patients Much Improved or Very Much Improved)	42.9% (p=0.001)	21.9%

Dose-dependent increase in the number of responders with >50% reduction in FOS

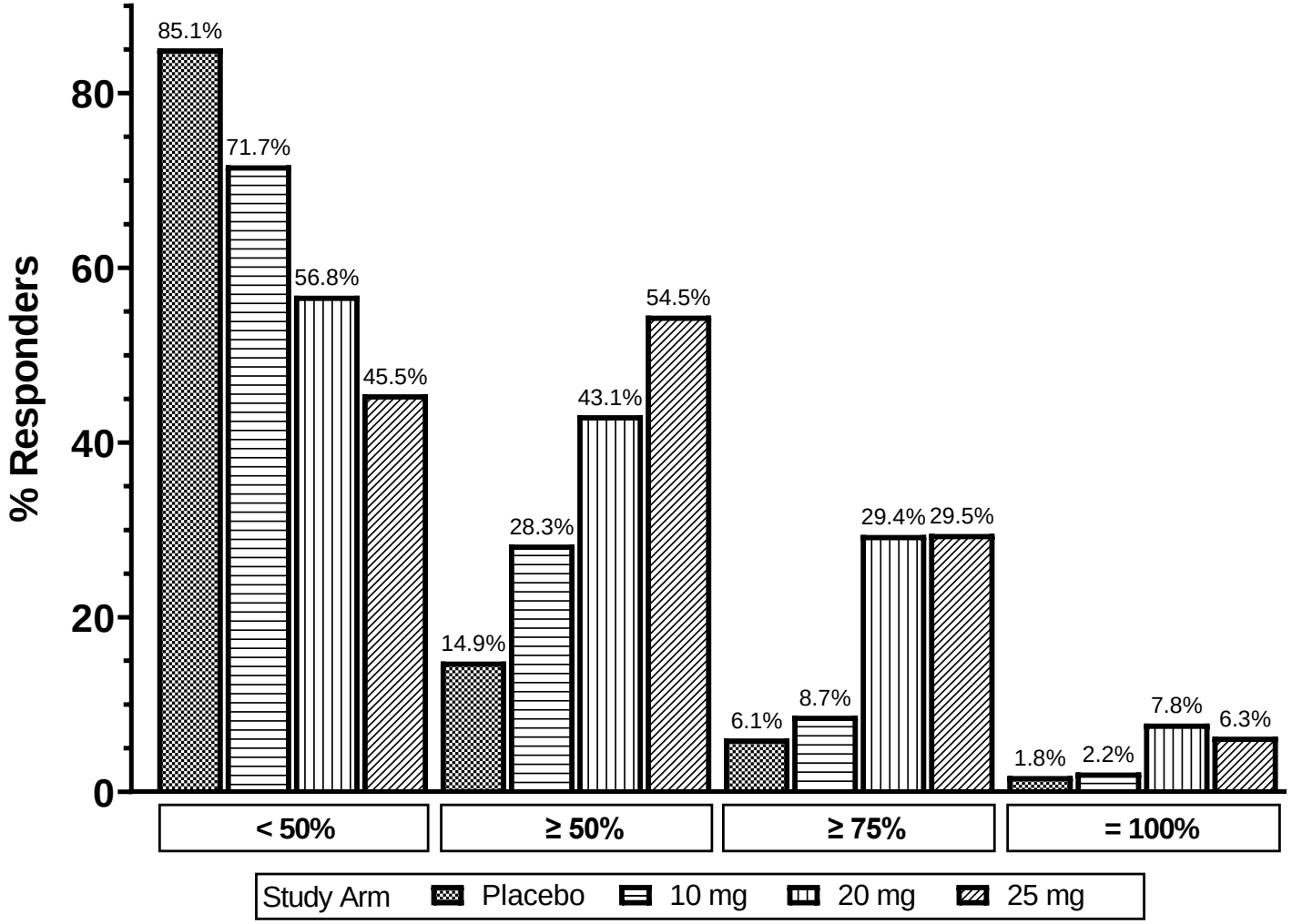
Secondary Endpoints: Response Rates and CGI-C/PGI-C (cont'd)

Clinician Global Impression of Change and Patient Global Impression of Change:

	Placebo (N=114)	XEN1101 10mg (N=46)	XEN1101 20mg (N= 51)	XEN1101 25mg (N=112)
Clinician - Global Impression of Change				
At least much improved, (% of subjects)	22.8%	23.9%	33.3%	**46.4%**
Difference (vs Placebo)		1.1	10.5	**23.6**
OR (vs Placebo)		1.02	1.67	**2.94**
95% CI for OR		(0.45, 2.30)	(0.80, 3.48)	(1.64, 5.24)
p-value (2-sided)		0.964	0.173	**<0.001**
Patient - Global Impression of Change				
At least much improved, (% of subjects)	21.9%	34.8%	**37.3%**	**42.9%**
Difference (vs Placebo)		12.9	**15.3**	**20.9**
OR (vs Placebo)		1.88	**2.10**	**2.66**
95% CI for OR		(0.88, 3.99)	(1.02, 4.33)	(1.48, 4.75)
p-value (2-sided)		0.103	**0.044**	**0.001**

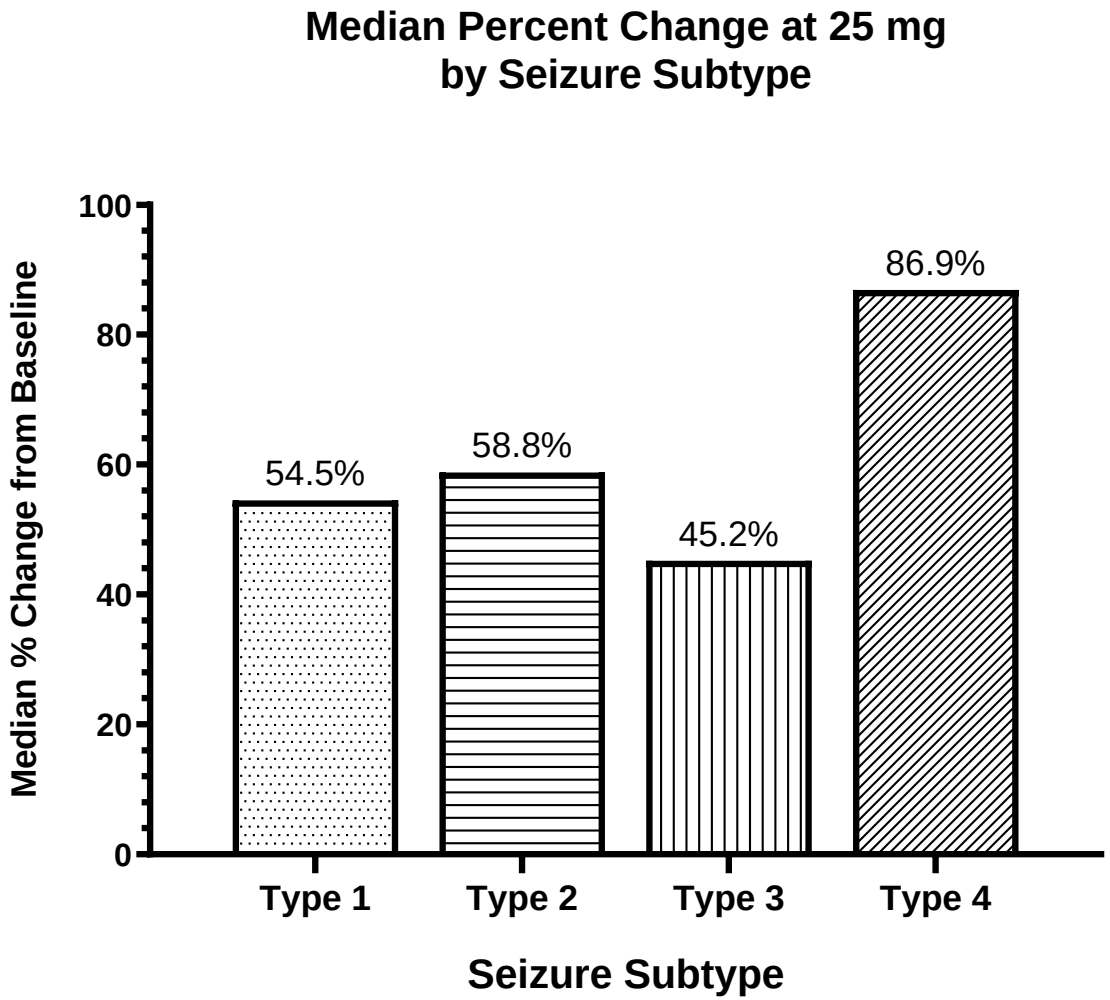
Clinically meaningful, dose-dependent improvements in CGI-C/PGI-C

Subgroup Analysis: Binned Responder Rate Analysis



Substantial number of responders with >75% seizure reduction in a patient population with significant baseline seizure burden

Subgroup Analysis of Seizure Reduction by Seizure Subtype (25 mg)



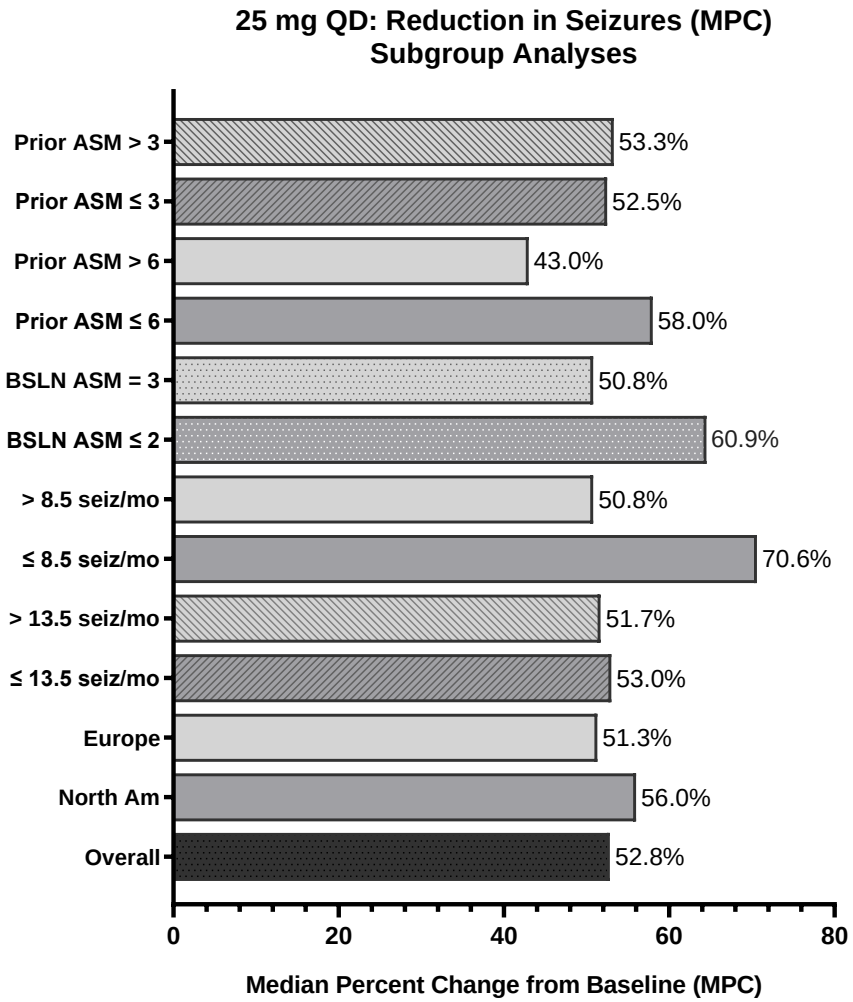
Focal Onset Seizure Types:

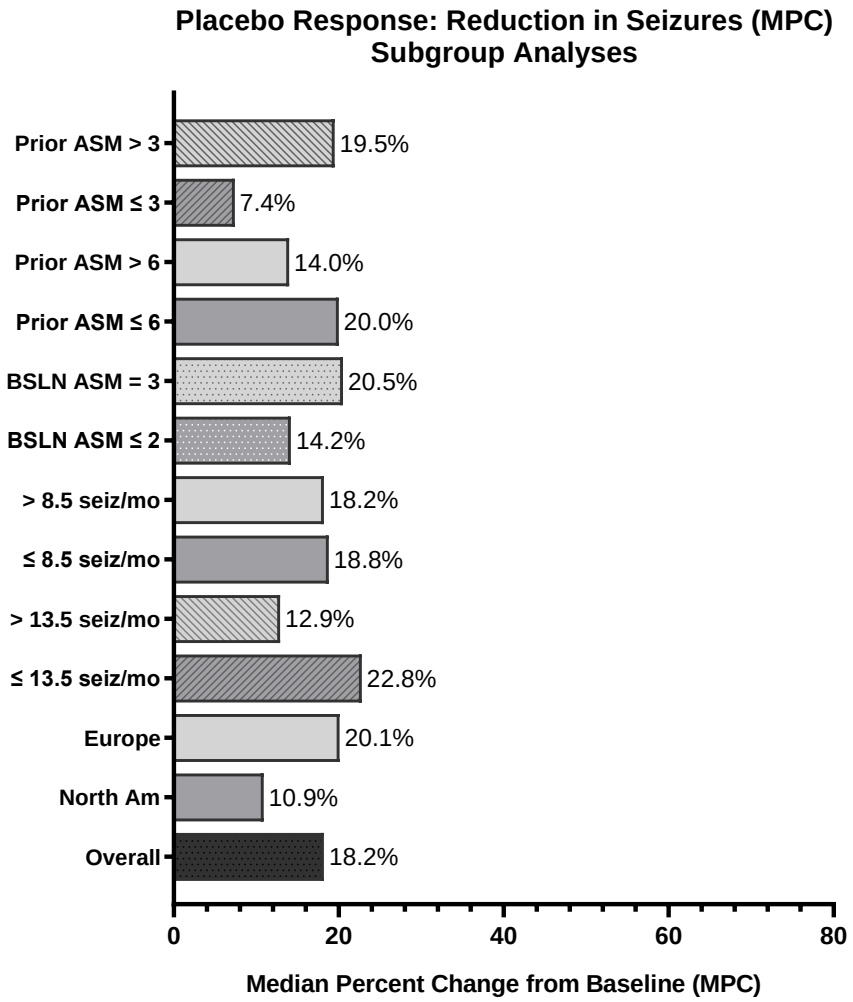
	Seizure Description
Type 1	Focal aware seizures with motor signs
Type 2	Focal seizures with impaired awareness with motor signs
Type 3	Focal seizures with impaired awareness with NO motor signs
Type 4	Focal seizures that lead to generalized tonic-clonic seizures
Type 5	Focal aware seizures with NO motor signs

Type 5 seizures not included in the primary and secondary efficacy endpoints

Significant seizure reduction at 25 mg across seizure subtypes

Subgroup Analyses of Seizure Reduction (25 mg QD vs Placebo)

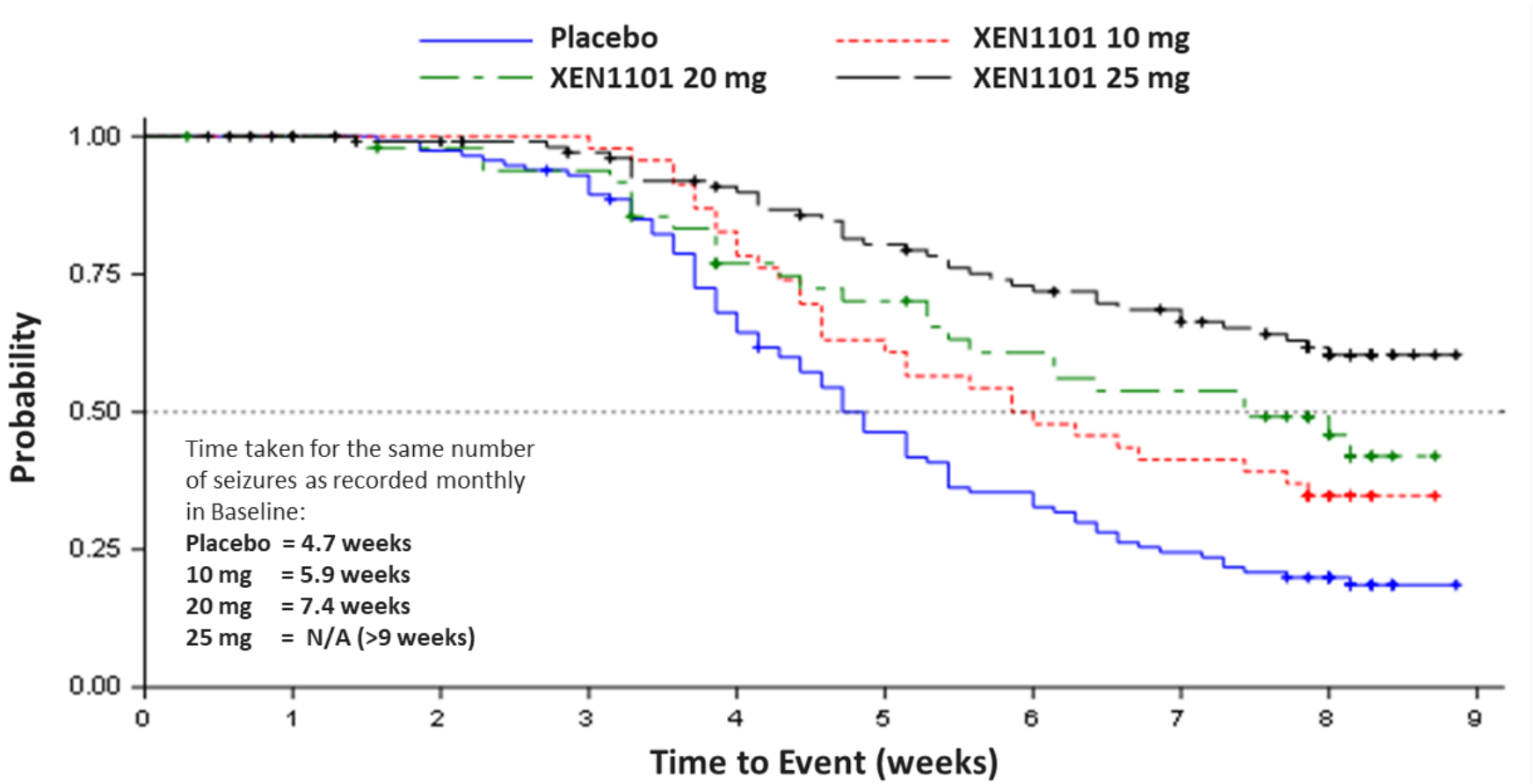




Increased seizure reduction in patients with less disease severity

Exploratory Endpoint: Time to Event Analysis

Time to reach baseline monthly focal seizure count during the double-blind period:



Time to event analysis showed marked dose-dependent decrease in rate of seizure recurrence

Summary of TEAEs* in the DBP (Safety Population)

Summary of all TEAEs in the DBP within the safety population:

Subjects with n(%)	Placebo (N=114)	XEN1101 10mg (N=46)	XEN1101 20mg (N=51)	XEN1101 25mg (N=114)	XEN1101 Any dose (N=211)
At least one TEAE	71 (62.3)	31 (67.4)	35 (68.6)	97 (85.1)	163 (77.3)
At least one serious TEAE	3 (2.6)	2 (4.3)	2 (3.9)	3 (2.6)	7 (3.3)
At least one TEAE leading to permanent treatment discontinuation	4 (3.5)	1 (2.2)	7 (13.7)	18 (15.8)	26 (12.3)
At least one serious TEAE leading to death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

*TEAE: Treatment Emergent Adverse Event, i.e. AEs started or worsened in Double Blind Phase including 6 weeks of follow-up

- The most common TEAEs leading to discontinuation across XEN1101 groups were dizziness (4.7%), balance disorder (2.4%), dysarthria (1.9%), gait disturbance (1.9%)

TEAE profile consistent with other ASMs, with majority of TEAEs within the CNS

Most Common TEAEs ≥5% in All Treatment Arms

System Organ Class/ Preferred Term	Placebo (N=114) n (%)	XEN1101 10mg (N=46) n (%)	XEN1101 20mg (N=51) n (%)	XEN1101 25mg (N=114) n (%)	XEN1101 Any dose (N=211) n (%)
Overall	**71 (62.3)**	**31 (67.4)**	**35 (68.6)**	**97 (85.1)**	**163 (77.3)**
Nervous System Disorders	**35 (30.7)**	**20 (43.5)**	**28 (54.9)**	**83 (72.8)**	**131 (62.1)**
Dizziness	8 (7.0)	3 (6.5)	13 (25.5)	36 (31.6)	52 (24.6)
Somnolence	8 (7.0)	5 (10.9)	11 (21.6)	17 (14.9)	33 (15.6)
Headache	9 (7.9)	6 (13.0)	6 (11.8)	9 (7.9)	21 (10.0)
Balance disorder	2 (1.8)	2 (4.3)	4 (7.8)	13 (11.4)	19 (9.0)
Tremor	2 (1.8)	3 (6.5)	3 (5.9)	12 (10.5)	18 (8.5)
Aphasia	1 (0.9)	1 (2.2)	1 (2.0)	8 (7.0)	10 (4.7)
Ataxia	1 (0.9)	3 (6.5)	1 (2.0)	5 (4.4)	9 (4.3)
Dysarthria	0 (0.0)	1 (2.2)	0 (0.0)	8 (7.0)	9 (4.3)
Memory impairment	1 (0.9)	1 (2.2)	2 (3.9)	6 (5.3)	9 (4.3)
Disturbance in attention	1 (0.9)	0 (0.0)	3 (5.9)	5 (4.4)	8 (3.8)
Psychiatric Disorders	**18 (15.8)**	**7 (15.2)**	**13 (25.5)**	**31 (27.2)**	**51 (24.2)**
Confusional state	1 (0.9)	1 (2.2)	3 (5.9)	6 (5.3)	10 (4.7)
Anxiety	6 (5.3)	0 (0.0)	5 (9.8)	2 (1.8)	7 (3.3)
Hallucination	0 (0.0)	0 (0.0)	3 (5.9)	0 (0.0)	3 (1.4)
General Disorders and Administration Site Conditions	**12 (10.5)**	**10 (21.7)**	**9 (17.6)**	**30 (26.3)**	**49 (23.2)**
Fatigue	6 (5.3)	5 (10.9)	4 (7.8)	14 (12.3)	23 (10.9)
Gait disturbance	1 (0.9)	2 (4.3)	2 (3.9)	8 (7.0)	12 (5.7)
Gastrointestinal Disorders	**10 (8.8)**	**10 (21.7)**	**5 (9.8)**	**19 (16.7)**	**34 (16.1)**
Nausea	3 (2.6)	1 (2.2)	1 (2.0)	7 (6.1)	9 (4.3)
Constipation	1 (0.9)	2 (4.3)	3 (5.9)	3 (2.6)	8 (3.8)
Eye Disorders	**6 (5.3)**	**3 (6.5)**	**5 (9.8)**	**18 (15.8)**	**26 (12.3)**
Vision blurred	1 (0.9)	0 (0.0)	1 (2.0)	7 (6.1)	8 (3.8)
Infections and Infestations	**13 (11.4)**	**6 (13.0)**	**6 (11.8)**	**6 (5.3)**	**18 (8.5)**
Urinary tract infection	4 (3.5)	4 (8.7)	3 (5.9)	2 (1.8)	9 (4.3)

TEAE profile consistent with other ASMs, with majority of TEAEs attributed to CNS

Summary of Treatment Emergent SAEs

Summary of all treatment emergent serious adverse events (SAEs) in the DBP:

System Organ Class / Preferred Term	Placebo (N=114) n (%)	XEN1101 10mg (N=46) n (%)	XEN1101 20mg (N=51) n (%)	XEN1101 25mg (N=114) n (%)	XEN1101 Any dose (N=211) n (%)
Overall	**3 (2.6)**	**2 (4.3)**	**2 (3.9)**	**3 (2.6)**	**7 (3.3)**
Psychiatric disorders	**0 (0.0)**	**1 (2.2)**	**2 (3.9)**	**1 (0.9)**	**4 (1.9)**
Confusional state	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.5)
Psychogenic seizure	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Psychotic disorder	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)
Somatic delusion	0 (0.0)	0 (0.0)	1 (2.0)	0 (0.0)	1 (0.5)
Nervous system disorders	**2 (1.8)**	**1 (2.2)**	**0 (0.0)**	**2 (1.8)**	**3 (1.4)**
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Muscle spasticity	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	1 (0.5)
Seizure	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.5)
Partial seizures	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Presyncope	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	**0 (0.0)**	**1 (2.2)**	**0 (0.0)**	**0 (0.0)**	**1 (0.5)**
Hyponatraemia	0 (0.0)	1 (2.2)	0 (0.0)	0 (0.0)	1 (0.5)
Infections and infestations	**1 (0.9)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Corona virus infection	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	**1 (0.9)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Pneumothorax traumatic	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Rib fracture	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Low incidence of SAEs and balanced across treatment arms

Vital Signs and Other Safety Outcomes

- There was no cardiovascular signal of concern based on vital signs from resting or orthostatic tests
- There were no safety signals of concern from physical or neurologic exams
- No signals of concern from ECGs, safety labs or urinalysis
- There was no evidence of urinary retention based upon mean differences across treatment groups in the total or individual items of the American Urological Associations Symptoms Index

- Weight changes were small and were different from placebo only at the highest dose:

Dose arm	Mean changes from baseline ± SD (in kg)	Number (%) of subjects with >7% change in body weight
Placebo	0.2 ± 2.4	3 (2.6%)
10 mg/day	0.6 ± 2.3	2 (4.3%)
20 mg/day	1.6 ± 2.2	2 (3.9%)
25 mg/day	1.9 ±2.9	15 (13.2%)*

*Based on change from mean of Screening (V1), Baseline (V2) and Randomization (V3) compared to end of DBP (V8/ET). If last record prior to treatment is used for Baseline, 7 (6.1%) subjects met threshold for increase. One subject had a decrease of >7%.

Summary of Safety and AE Profile

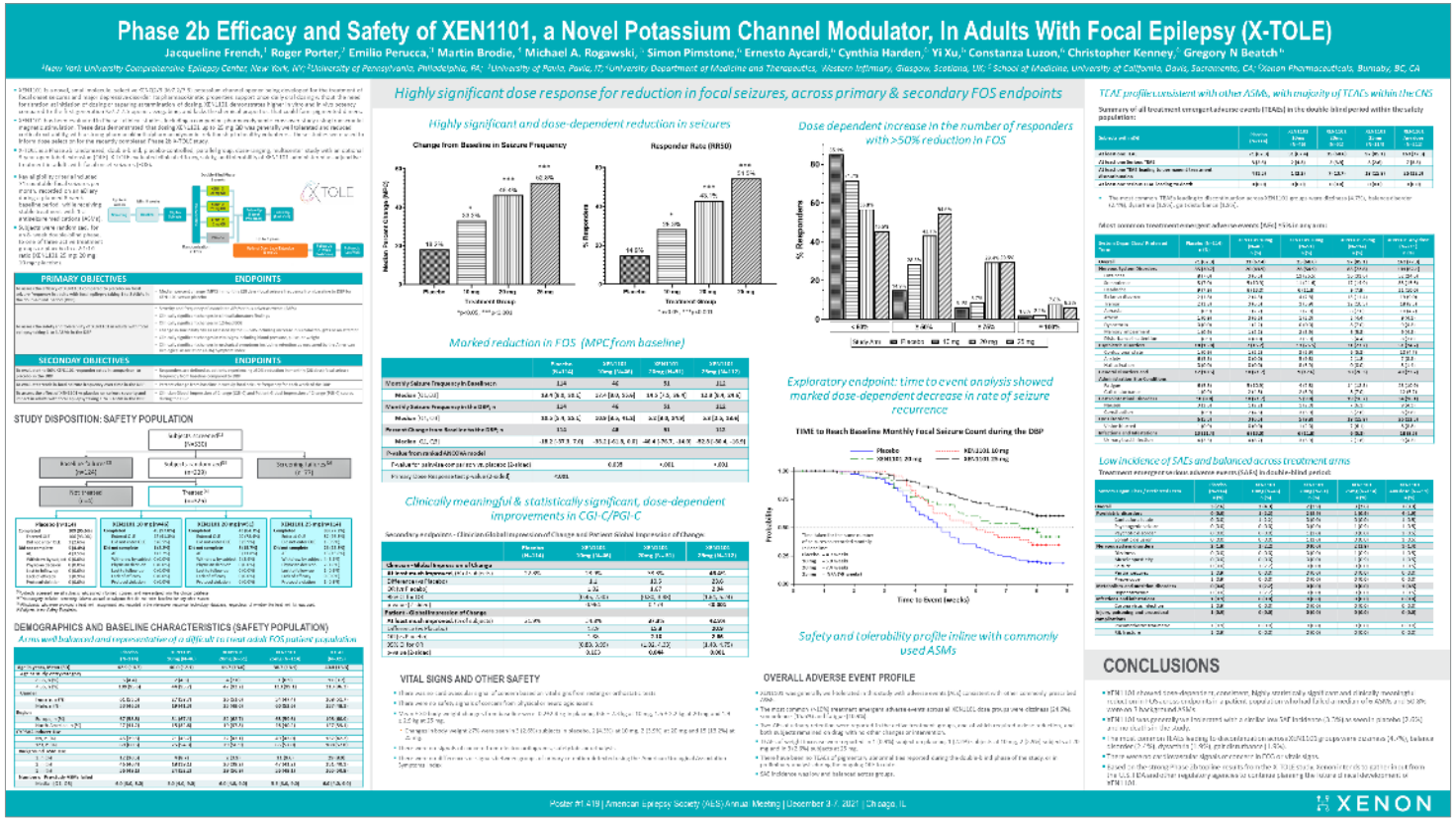
- XEN1101 was generally well-tolerated in this study with AEs consistent with other commonly prescribed ASMs
  - SAE incidence was low and balanced across groups; similar low SAE incidence (3.3%) as seen in placebo (2.6%) and no deaths in the study
  - The most common (>10%) TEAEs across all XEN1101 dose groups were dizziness (24.6%), somnolence (15.6%), and fatigue (10.9%)
  - The most common TEAEs leading to discontinuation across XEN1101 groups were dizziness (4.7%), balance disorder (2.4%), dysarthria (1.9%), gait disturbance (1.9%)
  - Two AEs of urinary retention were reported in the active treatment groups, one of which required a dose reduction, and both subjects remained on drug with no other changes or intervention
  - TEAEs of weight increase were reported in 1 (0.9%) subject on placebo, 1 (2.2%) subject at 10 mg, 2 (3.9%) subjects at 20 mg and in 3 (2.6%) subjects at 25 mg
    - More subjects experienced >7% change in body weight in the 25 mg treatment group compared to placebo
  - There were no cardiovascular signals of concern in ECG or vitals signs
  - There have been no TEAEs of pigmentary abnormalities reported during the double-blind phase of the study, or in preliminary analysis during the ongoing OLE to date

X-TOLE Study Conclusions

- XEN1101 showed dose-dependent, consistent, highly statistically significant and clinically meaningful seizure reduction in “difficult-to-treat” patient population
  - Heavily pre-treated patient population failed a median of 6 ASMs; 50.8% were on 3 background ASMs
- In addition, XEN1101 demonstrated increased efficacy in patients with less severe disease at baseline
- XEN1101 was generally well-tolerated in this study with AEs consistent with other commonly prescribed ASMs
- Based on the strong Phase 2b topline results from the X-TOLE study, Xenon intends to gather input from the U.S. FDA and other regulatory agencies to continue planning the future clinical development of XEN1101

Late-Breaking Poster 1.149 at AES 2021 – Saturday Dec 4th

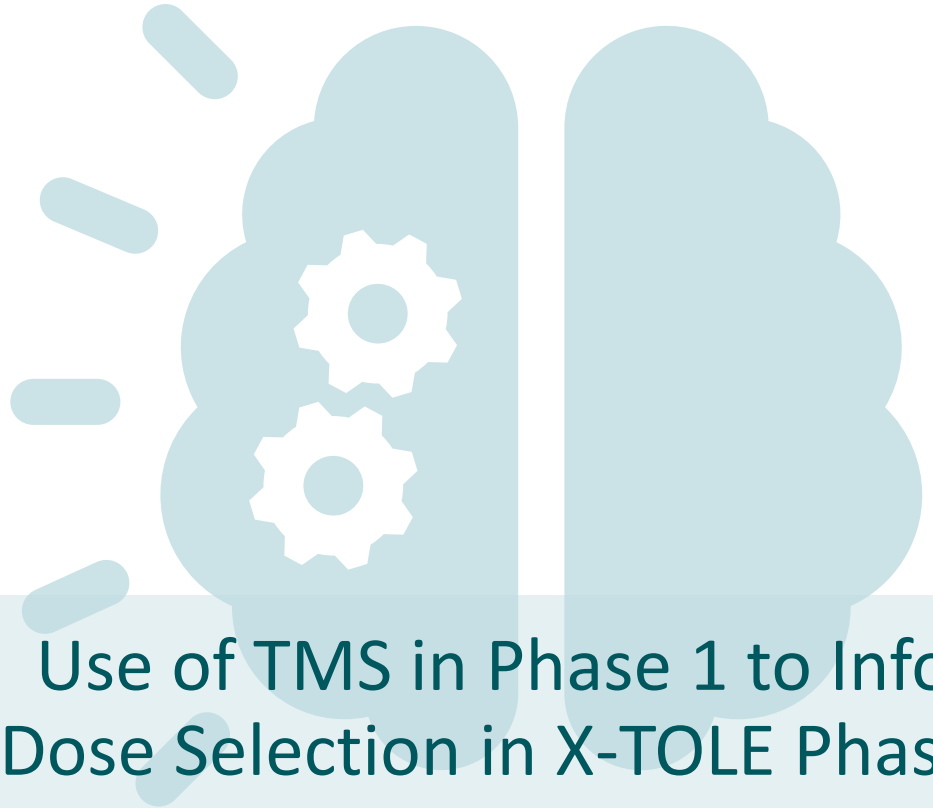
- "Phase 2b Efficacy and Safety of XEN1101, a Novel Potassium Channel Modulator, In Adults With Focal Epilepsy (X-TOLE)"
  - Jacqueline French, Roger Porter, Emilio Perucca, Martin Brodie, Michael A. Rogawski, Simon Pimstone, Ernesto Aycardi, Cynthia Harden, Yi Xu, Constanza Luzon, Christopher Kenney, Gregory N Beatch



Examples of Innovations in FOS Clinical Trials: Use of TMS and eDiary

DR. CYNTHIA HARDEN
THERAPEUTIC AREA HEAD, EPILEPSY, XENON PHARMACEUTICALS

Overview of Two Innovative Elements of the X-TOLE Clinical Trial



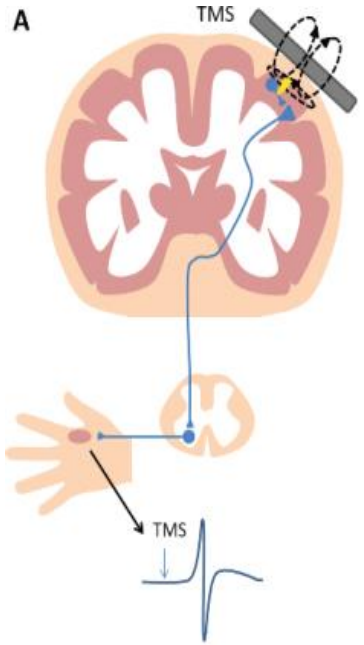
Use of TMS in Phase 1 to Inform Dose Selection in X-TOLE Phase 2b

Phase 2b Use of eDiary to Document Seizures

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

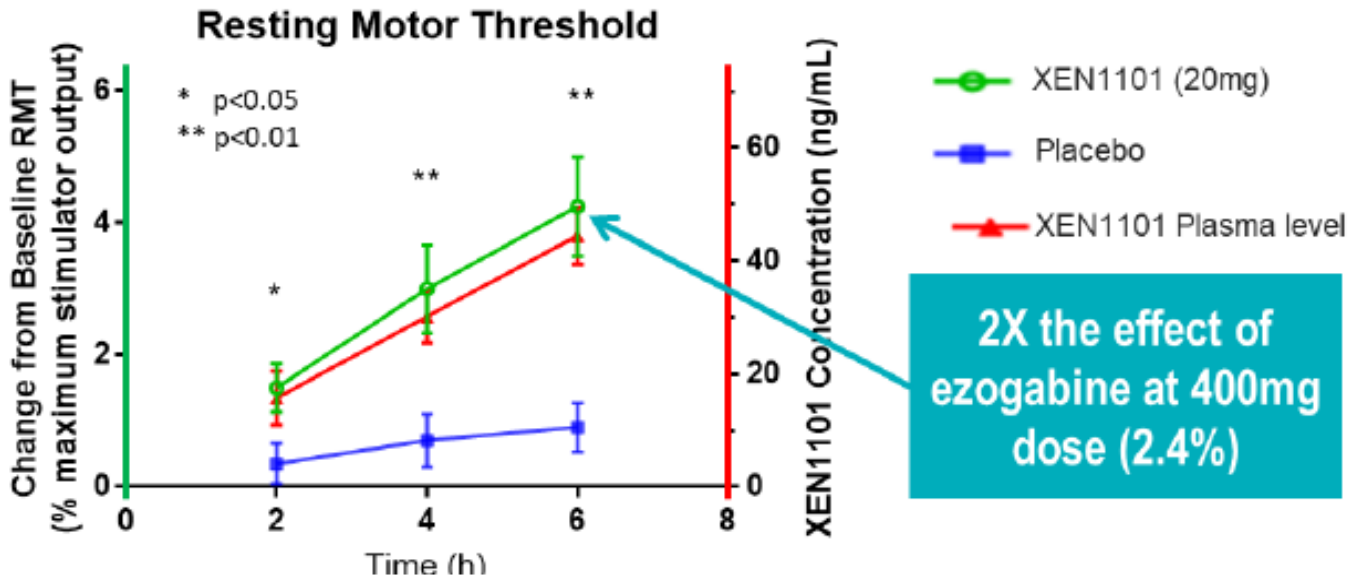
- TMS is a non-invasive tool to study human cortical excitability and target engagement of CNS acting drugs
  - XEN1101 clinical studies represented the first time TMS was used prospectively to determine target engagement and PD effect, and inform Phase 2 dosing

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



Multiple ASMs show effects on TMS at efficacious plasma levels, including ezogabine

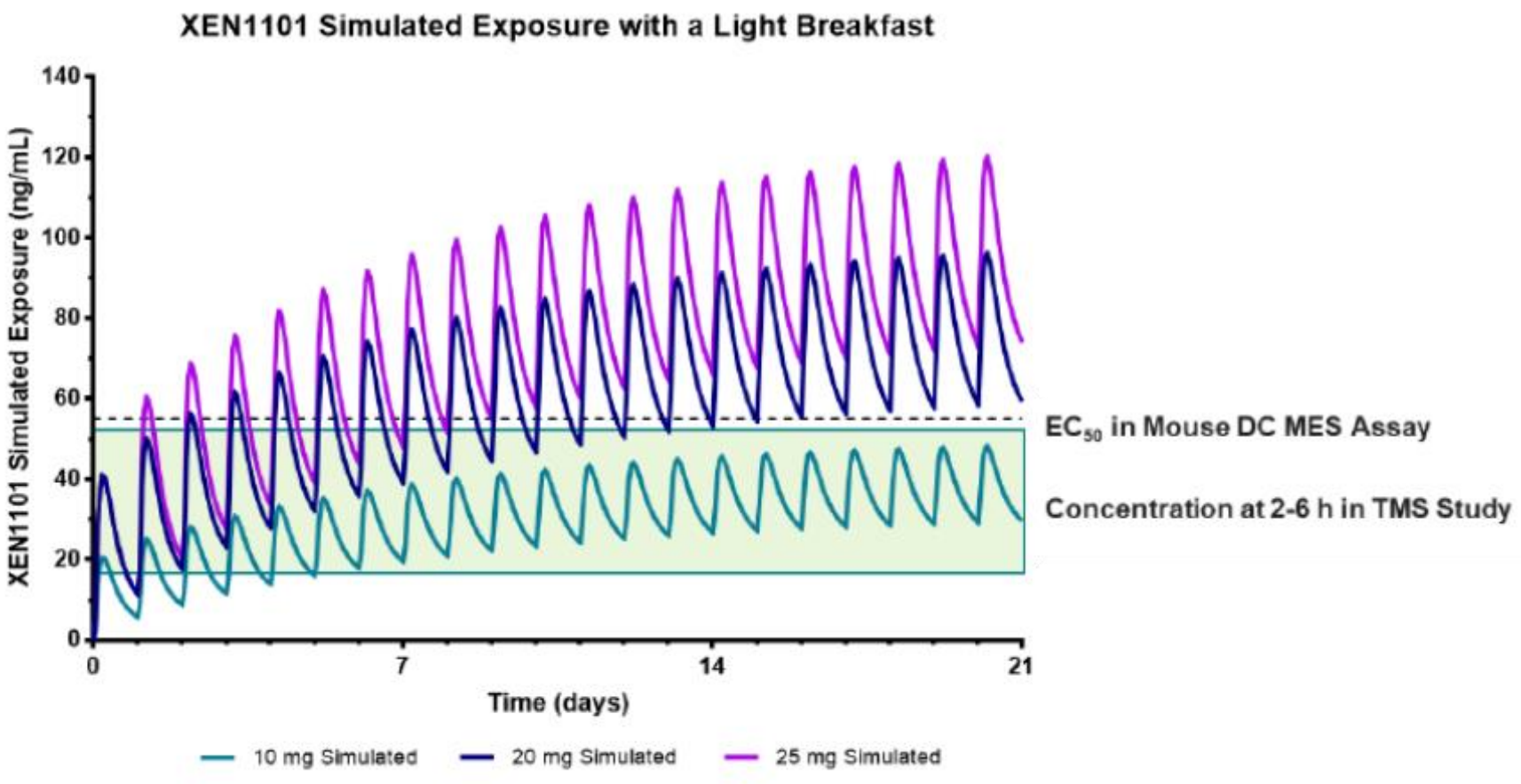
Relationship of XEN1101 Plasma Levels to CNS Activity



- RMT significantly increased compared to time-matched placebo subject in proportion to XEN1101 plasma level
- XEN1101 increased RMT by 4% at 6 hours post dose
- In a previously published study, ezogabine (400 mg) increased RMT by 2.4 ± 3.6% at 2 hours post dose (Osserman et al 2016)

XEN1101 induced changes in corticospinal excitability as assessed using TMS in Phase 1b cross-over study

Use of TMS to Inform Dose Selection in Phase 2



- Dose range chosen in Phase 2 includes two doses with trough levels above effective level in TMS and above mouse EC_{50}
- The TMS results also suggest the lowest potentially efficacious dose; effect in TMS but below mouse EC_{50}

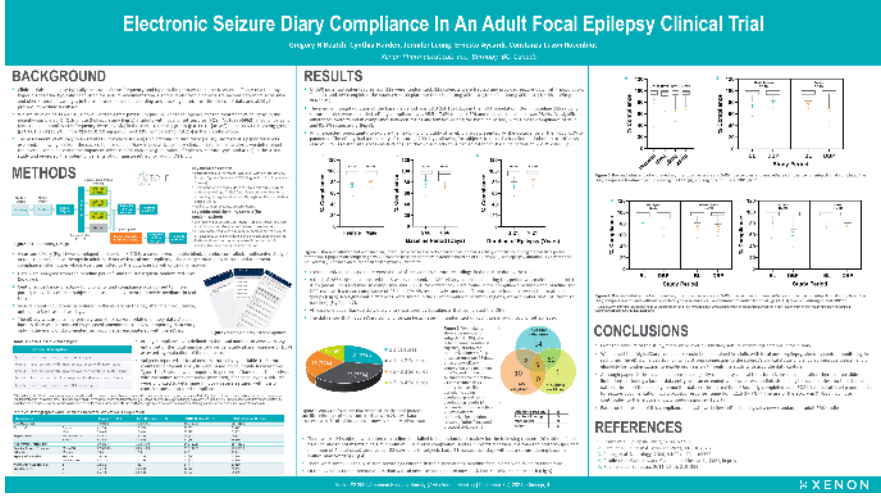
Summary of XEN1101 Phase 1 TMS Evaluation

- Significant effects on TMS measures present at 20 mg in a Phase 1b placebo-controlled trial were used to anchor the Phase 2b dose selection (Premoli et al 2019)
- The RMT signal observed with 20 mg XEN1101 in TMS is markedly greater than that observed following a 400 mg dose of ezogabine, providing confidence in the dose selection for the Phase 2b clinical trial
- Dose arms for the X-TOLE were selected based on XEN1101's side effect profile in Phase 1 studies and surrogate pharmacodynamic endpoints obtained from TMS studies conducted in healthy adult subjects

Premoli, I. *et al*. (2019), TMS as a pharmacodynamic indicator of cortical activity of a novel anti-epileptic drug, XEN1101. Ann Clin Transl Neurol, 6: 2164-2174. doi:10.1002/acn3.50896),

Incorporating TMS evidence of CNS activity in Phase 1 studies may be a useful biomarker for dose selection in Phase 2 development

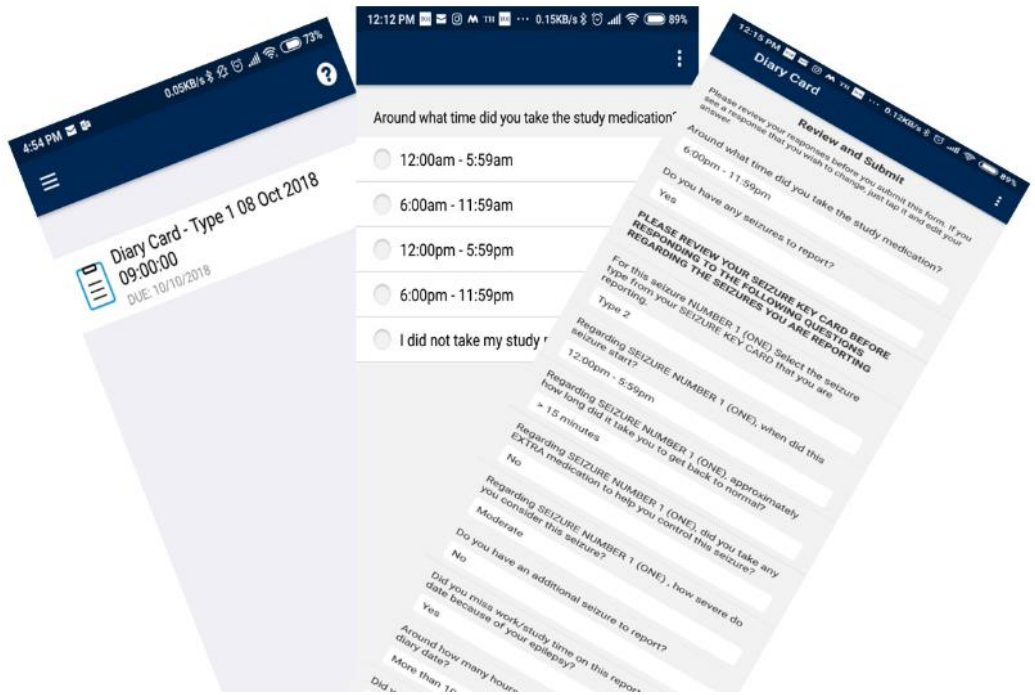
Use of eDiary in Epilepsy Trials



- "Electronic Seizure Diary Compliance In An Adult Focal Epilepsy Clinical Trial" – Poster 2.200; Sunday December 5, 2021
  - Gregory N Beatch, Cynthia Harden, Jennifer Leung, Ernesto Aycardi, Constanza Luzon Rosenblut
- Clinical trials in epilepsy typically measure seizure frequency and type as the primary outcome to assess efficacy of a therapy
- Although paper diaries have been used in a majority of epilepsy clinical trials for seizure documentation there are limitations, including a lack of data entry over an extended window between clinic visits, illegible data entries, no timestamps for data entries, and the inability to monitor data entries in real time (Patel et al 2021)
- The assessment of efficacy in an adult focal epilepsy clinical trial using an electronic seizure diary (eDiary) instead of a paper diary was explored
- Assessments were:
  - Overall compliance
  - Impact of select clinical factors (duration of epilepsy, seizure type, and AEDs)

1. Patel et al. Epilepsy & Behavior, 2021, 118, 107925; Chung et al. Neurology, 2020, 94(22), e2311-e2322; Brodie et al. Cannabis and Cannabinoid Research, 2021, in press;
2. Rheims et al. Epilepsia, 2011, 52(2), 219–233

X-TOLE eDiary



- The eDiary stored daily seizure and treatment compliance information which was transmitted to the database by wifi or cellular network
- Data were analyzed from the baseline period and the subsequent randomized DBP (56 days)
- Central surveillance of eDiary functionality and compliance was utilized to inform participating sites of their subjects' status, enabling them to provide feedback in real time
- Seizure counts could only be entered in the eDiary on the day after their occurrence, until up to 3 retrospective days
- The eDiary was used as the primary source for seizure related efficacy data
  - A paper backup diary was introduced by protocol amendment to allow temporary data entry only, in the event of documented technical issues encountered with the eDiary

eDiary Data Capture and Analysis

- eDiary compliance was defined as the total number of days with any entry out of the total number of days per study phase (baseline or DBP) assessed by evaluation of the database

Type 1 Focal aware seizures with motor sign
Type 2 Focal seizures with impaired awareness with motor signs
Type 3 Focal seizures with impaired awareness with NO motor sign
Type 4 Focal seizures that lead to generalized tonic-clonic seizure
Type 5 Focal aware seizures with NO motor signs

- Subjects reported all focal onset seizures by type
- Seizure counts for endpoint analysis were based on countable focal seizures Types 1 – 4
- Subjects were required to perform eDiary input themselves, with assistance for event recall permitted, if needed
- Type 4 seizures were analyzed to determine if having severe seizures with loss of consciousness impacted compliance

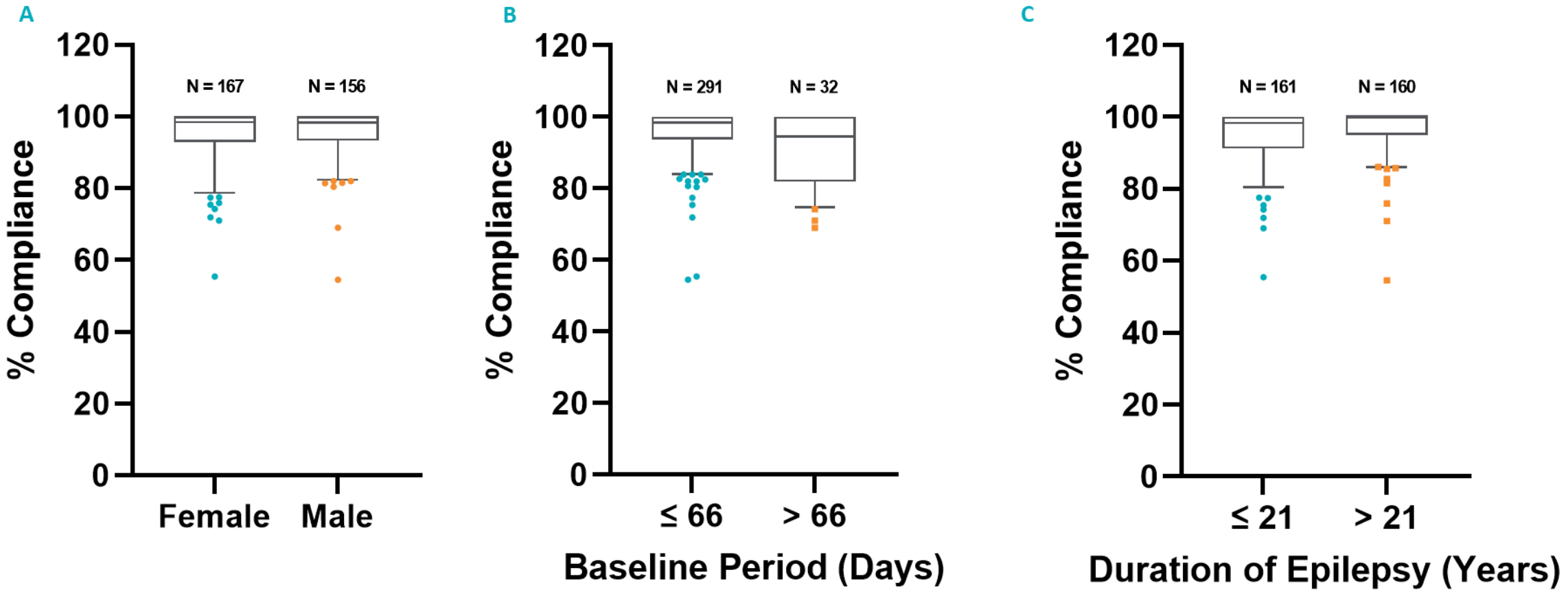
COVID Considerations During X-TOLE Trial

- Due to the global COVID pandemic, if in-person visits had to be delayed, subjects were permitted to continue in baseline up to a maximum of 140 days (per protocol amendment) until the required in-person randomization visit could take place

X-TOLE eDiary Results

- The median (range) duration of the baseline period was 58.0 (53 – 139) days in the mITT population
  - During baseline 18,997 daily seizure entries were recorded
- eDiary compliance was 95.5 ± 7.0% (mean ± SD) and median compliance was 98.4%
- Due to the COVID pandemic, thirty-two subjects had an extended baseline period of 67 – 139 days

X-TOLE eDiary Results cont'd

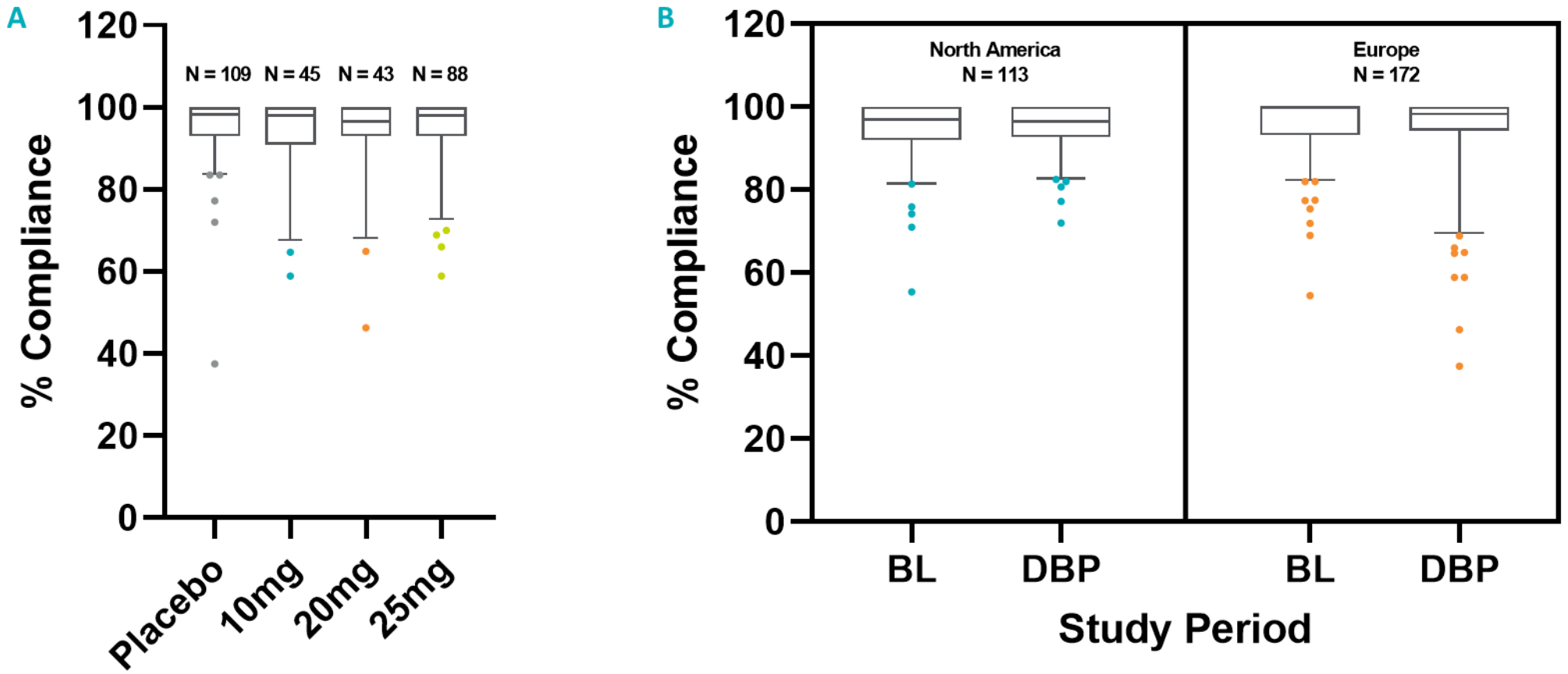


Box and whisker plot with median, interquartile range and 5 – 95th percentiles, showing eDiary compliance during the baseline period for the mITT population comparing sex (A); planned baseline period vs. extended baseline of > 66 days (B); and epilepsy duration, ≤ 21 years and >21 years (C). The median duration of epilepsy was 21 years.

X-TOLE eDiary Results cont'd

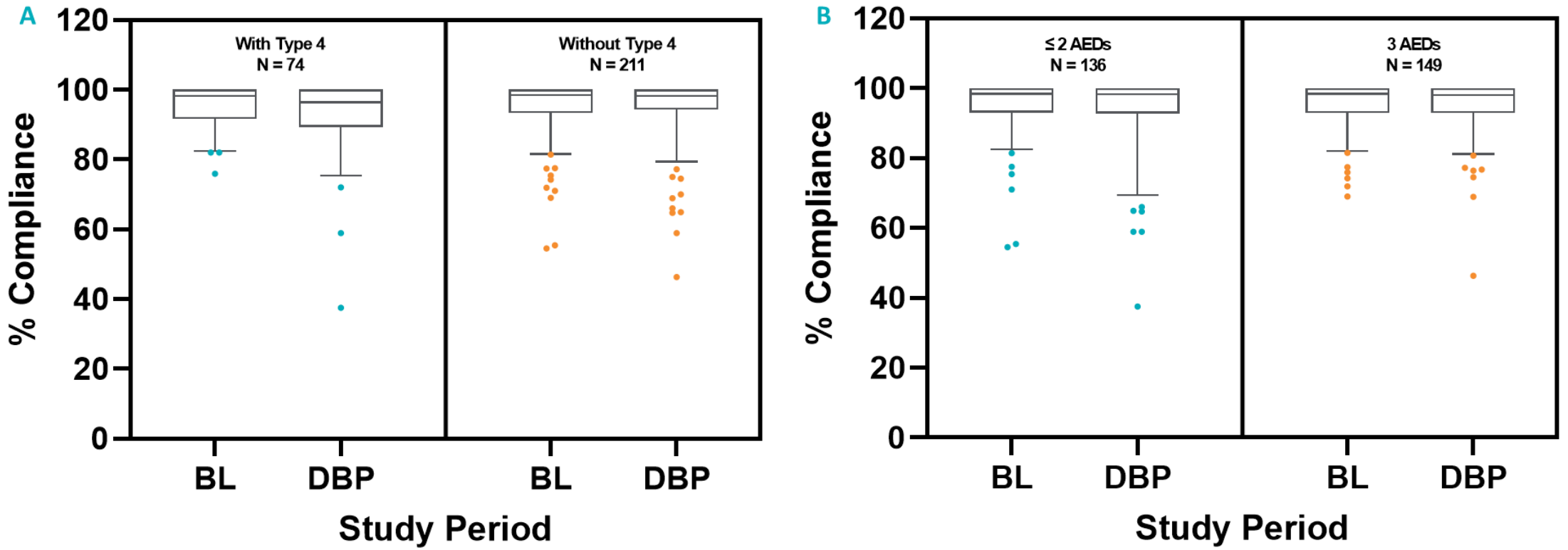
- For randomized subjects, there were a total of 15,941 daily seizure recordings in the eDiary during the DBP
- A total of 285 subjects completed the 8-weeks randomized DBP, eDiary compliance during this period was maintained at 94.4 ± 8.7% (mean ± SD) and median compliance was 98.2%
- No differences were found in the compliance between the baseline and DBP, each with a mean compliance of 95.4 and 94.4% respectively
- At least one paper backup daily diary entry was used by 26 subjects that completed the DBP

X-TOLE eDiary Results cont'd



Box and whisker plot with median, interquartile range and 5 – 95th percentiles, showing eDiary compliance for subjects that completed the DBP, comparing treatment groups during the DBP (A); and regions for BL and DBP (B)

X-TOLE eDiary Results cont'd



Box and whisker plot with median, interquartile range and 5 – 95th percentiles, showing eDiary compliance for subjects that completed the DBP, comparing with and without reported Type 4 seizures (A); and number of antiepileptic drugs (AEDs) taken (B) during BL and DBP

Conclusions from Use of eDiary in X-TOLE Trial

- We learned that high eDiary compliance could be maintained in adult focal epilepsy subjects, aided by central monitoring in real time
- The eDiary helped to maintain a strong connection to the subject's clinical status and enabled rigorous assessment of eligibility for randomization to enable progression through the study with accurate data capture
- eDiary use may have contributed to the relatively low placebo response (18.2%)
  - Recently completed adult FOS trials that utilized paper diaries for seizure documentation had a placebo response range from 21.5 – 37.7% (Chung et al, 200 Brodie et al 2021, Rheims et al 2011)

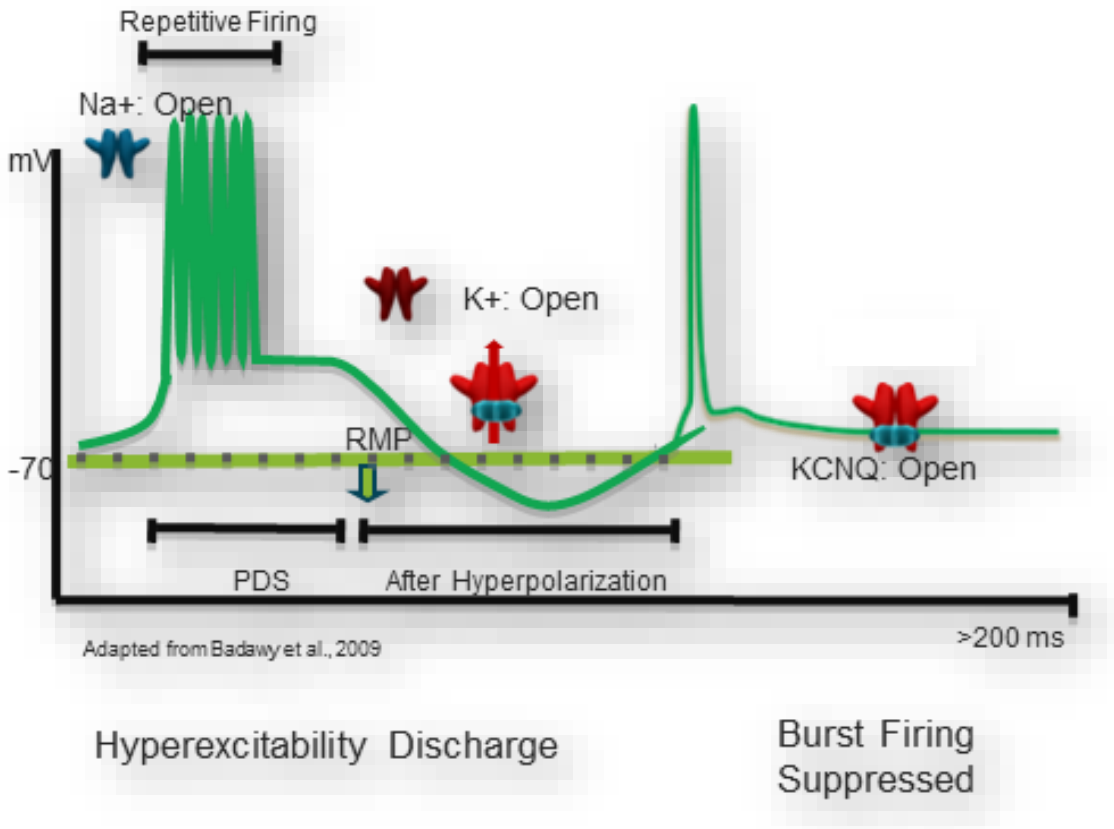
Based on the results of this compliance analysis, eDiaries may set a new standard for adult FOS studies

Overview of XEN1101's K_V7 Mechanism

DR. ROBIN SHERRINGTON
EVP, STRATEGY & INNOVATION, XENON PHARMACEUTICALS

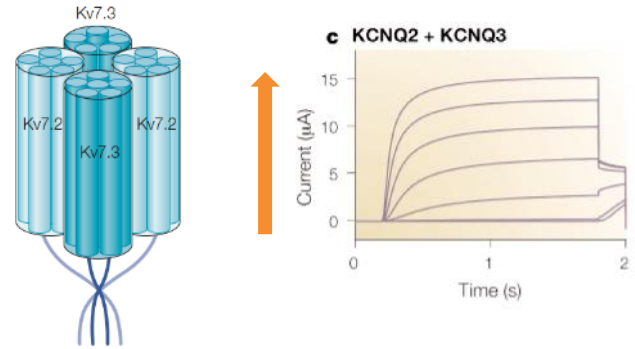
K_V7 Channels have a Critical Role in Neuronal Firing

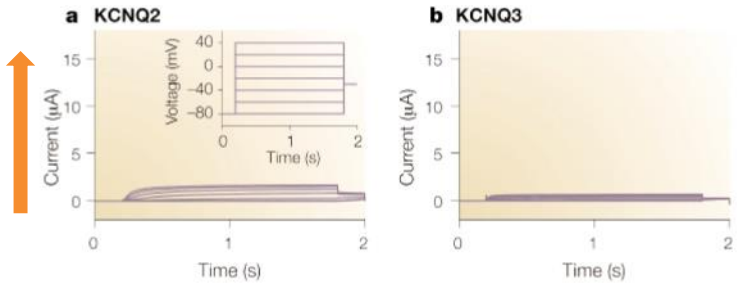
- K^+ channels repolarize membranes to end the action potential
- K_V7 channels are translated from the KCNQ gene family (Q1 – Q5)
- They exert important inhibitory control over neuronal firing
- Control unwanted burst and spontaneous firing that can lead to seizures

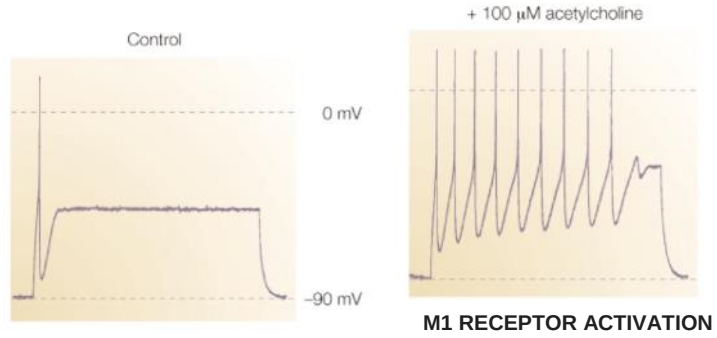


Loss of K_V7 Potassium Channel Currents Results in Hyperexcitability

- Four KV7 subunits required for a functional channel
- KV7.2/7.3 heterotetramers form the major current in the CNS
- Negatively modulated by muscarinic receptor activation via PLC and PIP2 hydrolysis
- Referred to as the M-current
- Depletion of the M-current leads to neuronal hyperexcitability and seizures
- Loss of function mutations in KCNQ2 or KCNQ3 lead to seizures in humans





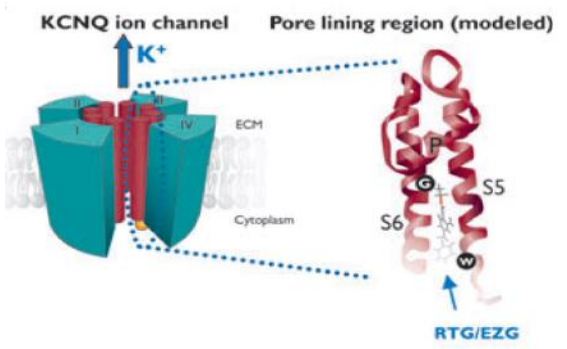


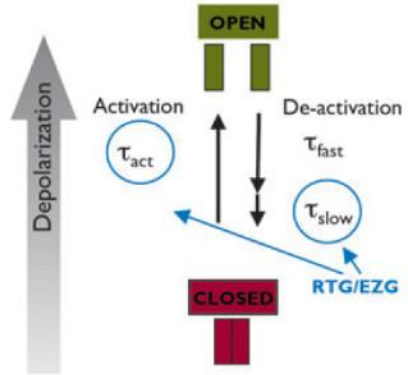
M1 RECEPTOR ACTIVATION

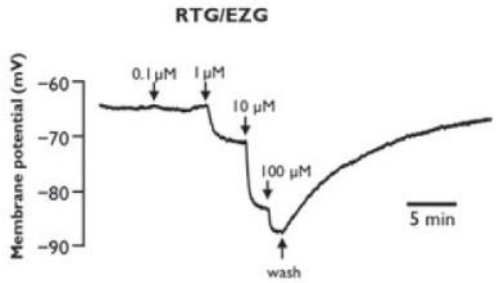
Jentsch, Nature Reviews Neuroscience 2000

MOA of K_V7 Potassium Channel Openers

- Ezogabine and XEN1101 bind to the pore of the tetramers
- Overall openers enhance the magnitude and duration of channel activation resisting depolarization
- They lower the K_V7 voltage dependency of activation and slow the rate deactivation
- This leads to an earlier and prolonged channel opening and more channels will be open at any given voltage
- Results in pronounced hyperpolarizing effect on neuron resting membrane potential and suppression of firing



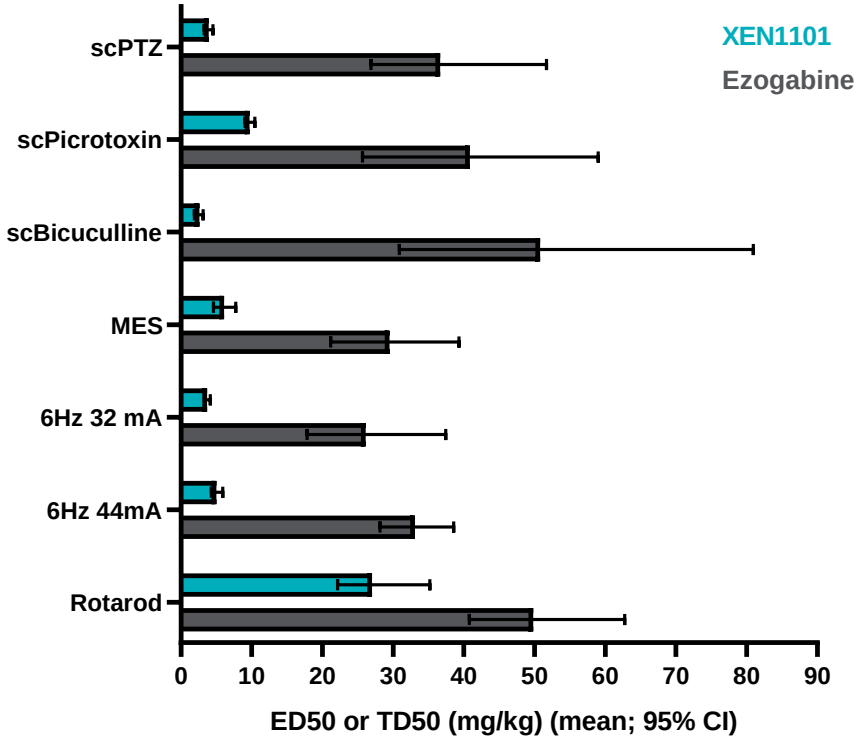


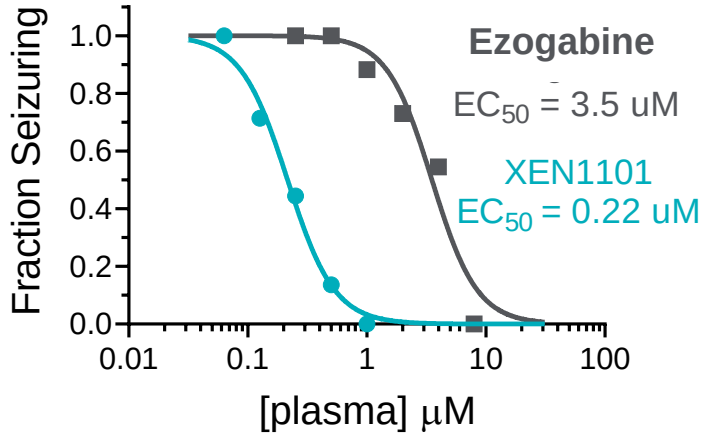


Gunthorpe et al, Epilepsia 2012

K_V7 Openers Work Across a Broad Range of Seizure Models

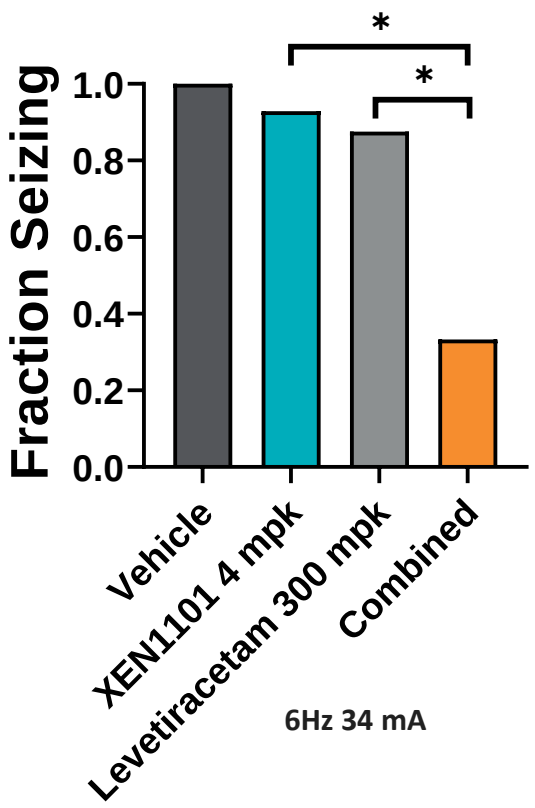
- Control seizures induced chemically or electrically, including models of treatment resistant seizures
- Seizure control most often occurs at doses lower than the TD_{50} for rotorod tolerability
- XEN1101 is ~16-fold more potent than ezogabine in Maximal Electroshock Stimulus (MES) model in CF-1 mice
- Highly consistent with the *in vitro* potency of the two compounds

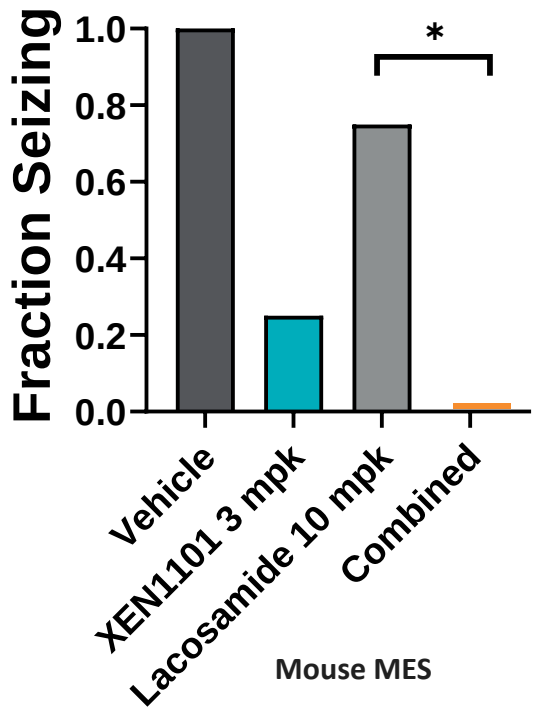


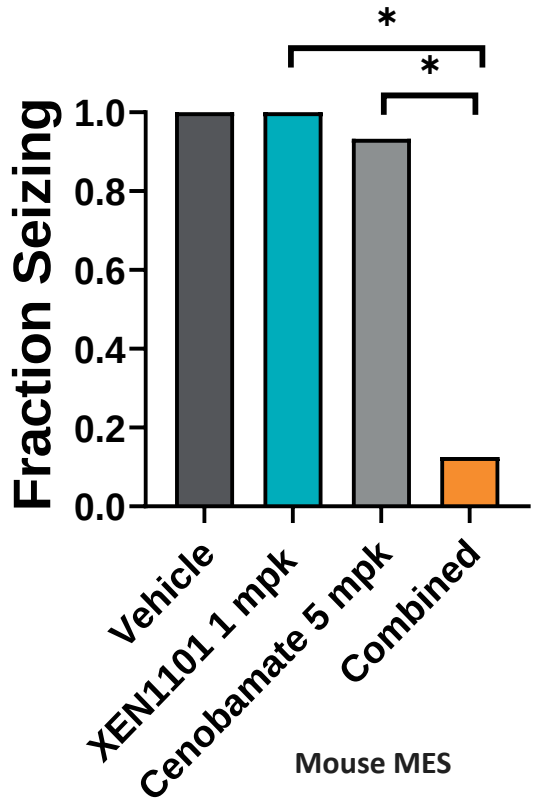


Combining K_V7 Opener XEN1101 with ASMs Promotes Seizure Protection in Pre-clinical Models

- Enhanced efficacy is not a drug-drug interaction phenomenon; not explained by changes in plasma levels
- Combination doses were well tolerated





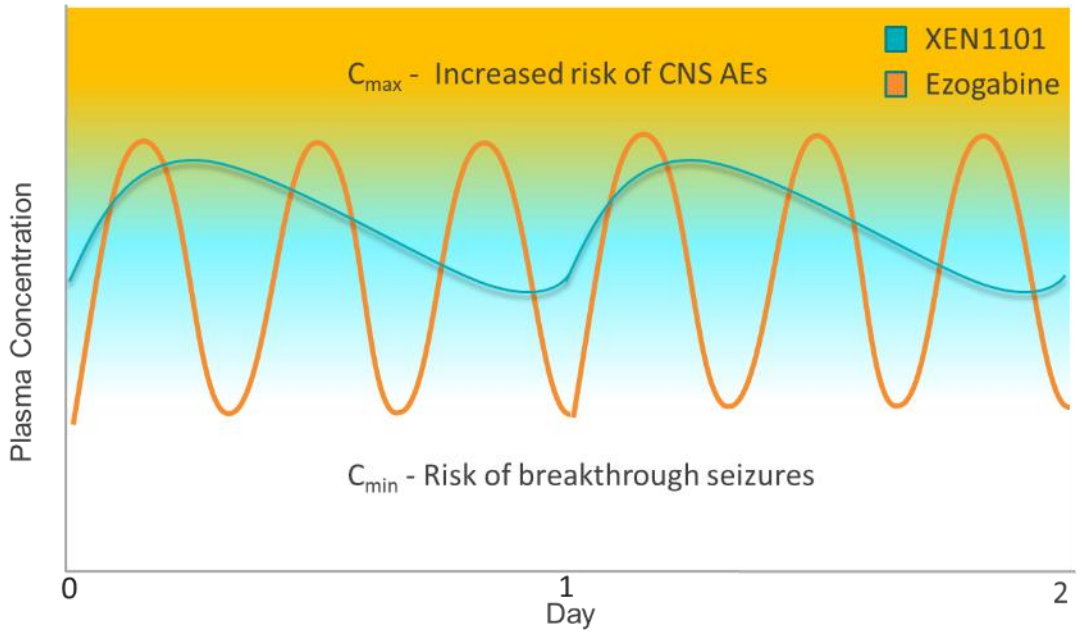


** Statistically significant*

Benefits of Improved PK Profile for K_V7 Openers

- Ezogabine was dosed TID due to relatively short $T_{1/2}$ coupled with C_{max} related CNS AEs to minimize peak to trough levels during the day
- XEN1101 relatively long $T_{1/2}$ allows QD dosing
- With QD dosing XEN1101 maintains a narrow ratio between C_{max} and C_{min}
- No necessity for titration as steady state plasma levels reached after ~14 days
- Profile likely consistent with maintenance of efficacy and tolerability
- Forgiving PK provides improved coverage for any missed doses

Aycardi et al, 72nd Annual Meeting AES 2018



K_V7 Openers and Skin Discoloration and Eye Pigmentation

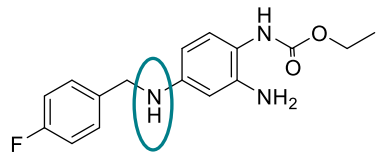
- Long term exposures (generally 900 mg or greater) of ezogabine resulted in skin discoloration and eye pigmentation, prominently associated with melanin containing tissues
- Median time to onset 4.4 yrs (0.04-7 yrs)
- 30% patients reported with discoloration (108/365) and 15% (53/365) with retinal pigmentation
- 36% of patients with retinal pigmentation had <20/20 visual acuity
- Resolution of the discoloration and eye pigmentation observed in many patients with discontinuation of treatment
- Safety reports do not indicate the pigment changes in the retina affect vision and the skin discoloration appears to be a cosmetic effect

Evans et al, 68th Annual Meeting AES 2014; FDA Drug Safety Communication 2013

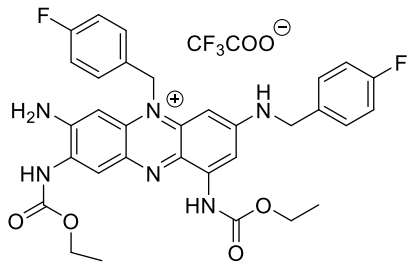
Pigmentation is Not Associated with K_V7 Opener MOA

- In the presence of oxygen ezogabine forms highly-colored phenazinium-type dimers
- The secondary aniline function is key to forming the dimers
- The dimers bind to melanin and have very slow off rates
- Clinical samples from patients demonstrated co-localization of dimers with pigmented areas
- No evidence of direct effect of ezogabine on melanogenesis or metal chelation
- XEN1101 does not have a secondary aniline preventing the formation of analogous dimers

Prescott and Evans, 68th Annual Meeting AES 2014



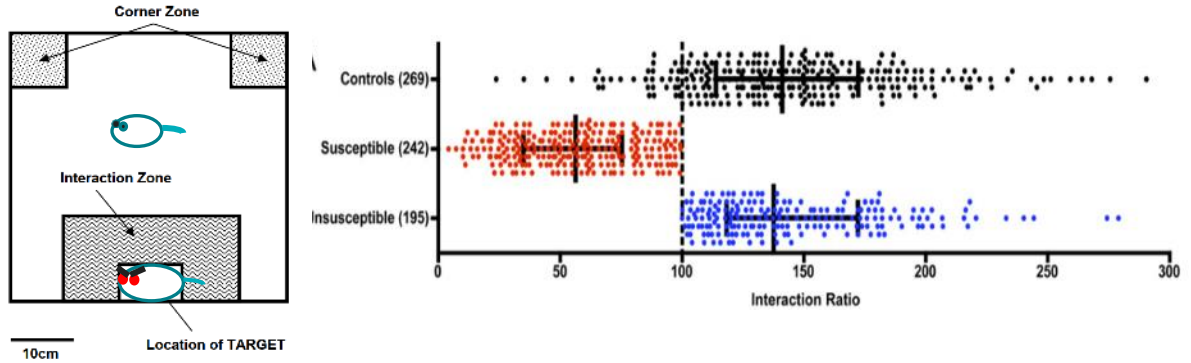
Ezogabine

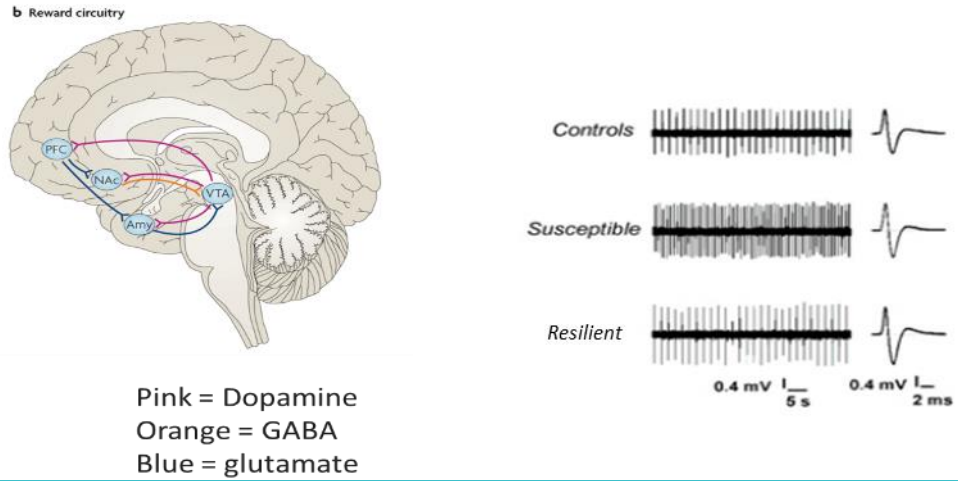


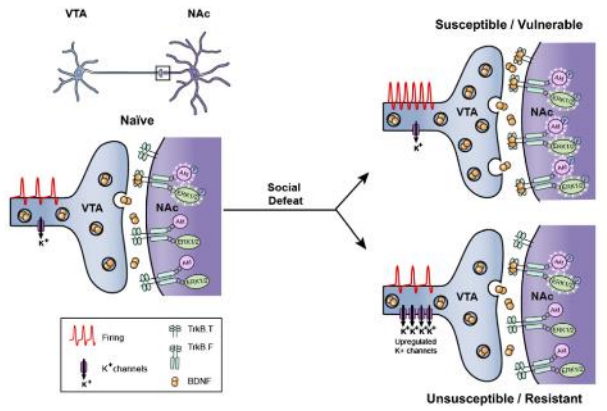
Ezogabine Phenazinium-Type Dimer

Chronic Social Defeat Stress Model of Depression

- Discordant behavioural outcomes to CSDS with both susceptible and resilient animals
- Hyperexcitability of the VTA DA neurons underpins susceptibility to CSDS
- Upregulation of voltage gated K+ channels were associated with resilient phenotype
- Resilience is proposed to be an active coping mechanism to stress induced depression





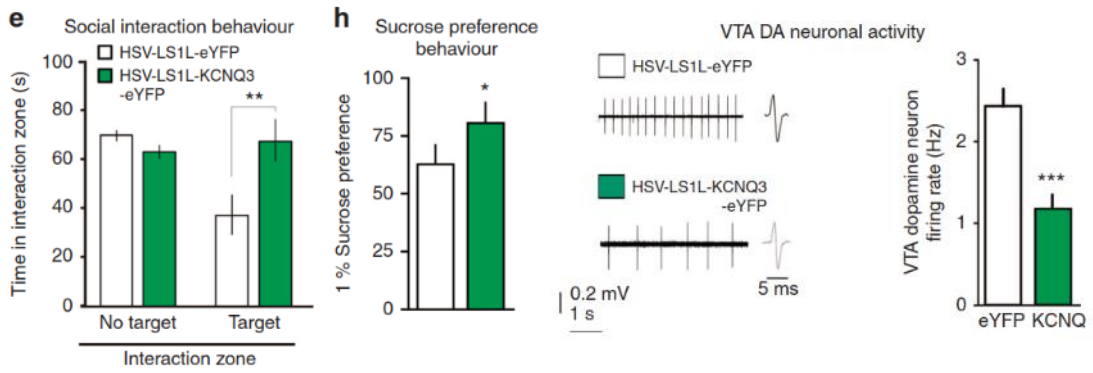


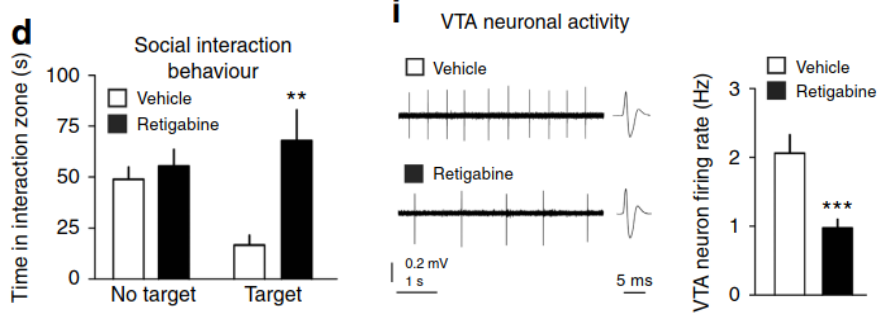
Krishman et al, Cell 2007; Cao et al, J Neuroscience 2010

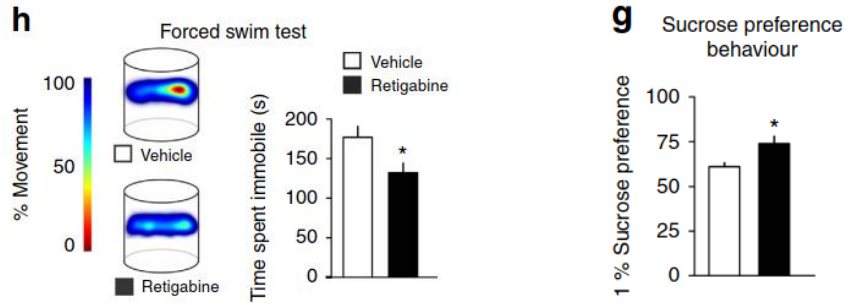
K_V7 Channels Alone can Mediate Active Resilience to Depression

- Viral expression of $K_V7.3$ in VTA reverses the CSDS susceptible phenotype and hyperexcitability and improved anhedonia
- Ezogabine dosed 8-days (1 mg/kg ip) reversed the susceptibility phenotype mimicking the resilient phenotype
- Blunted VTA hyperexcitability and normalized social interaction
- Demonstrated antidepressant activity and improved hedonic capacity
- A novel molecular mechanism to potentially treat depression and anhedonia through modulation of the reward system

Friedman et al, Nature Communications 2016





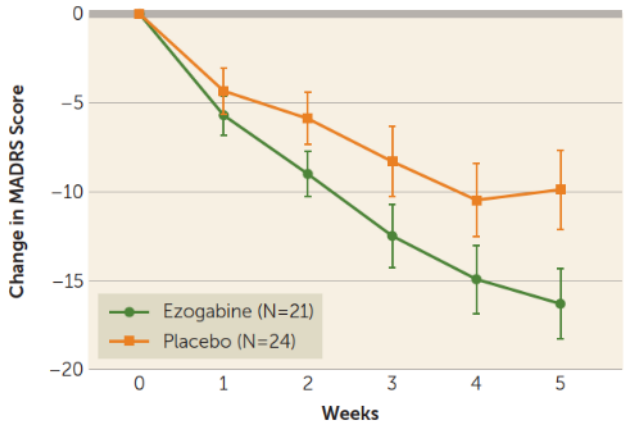


K_V7 Opener Phase 2 POC in Major Depressive Disorder

- Promising clinical results with ezogabine dosed 300 mg TID as a treatment for Major Depressive Disorder (MDD) and anhedonia
- Encouraging pre-clinical efficacy data with XEN1101
- Investigator-led (Mount Sinai) proof-of-concept clinical trial of XEN1101 for treatment of MDD and anhedonia to be initiated
- Initiating in 2022 a company-sponsored Phase 2 clinical study in MDD

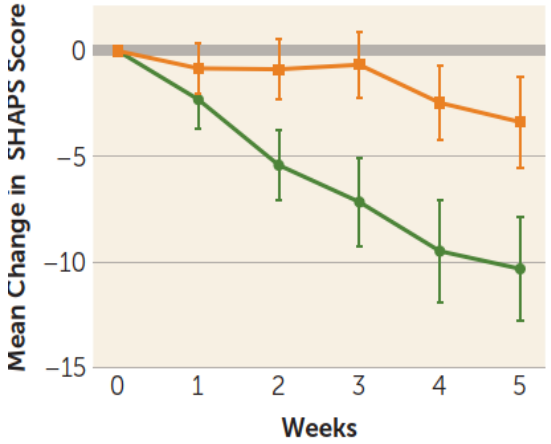
Costi et al, Am J Psychiatry 2021

Montgomery–Åsberg Depression Rating Scale



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

Snaith-Hamilton Pleasure Scale

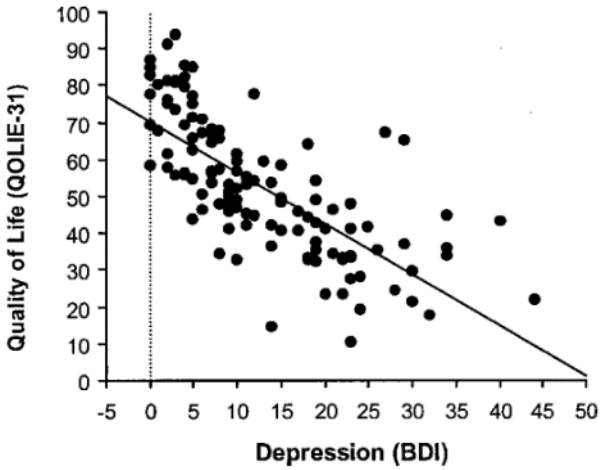


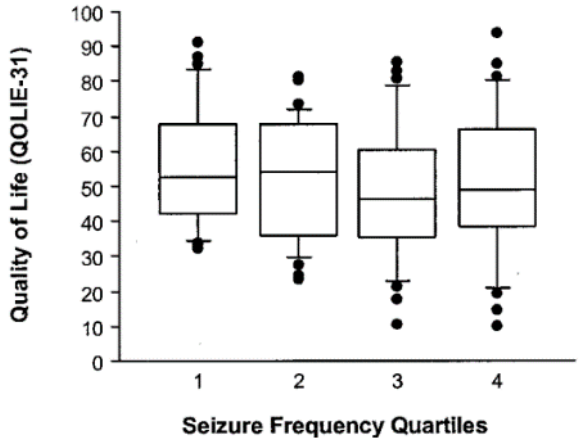
Compared with placebo, ezogabine was associated with a large improvement in hedonic capacity as measured by the Snaith-Hamilton Pleasure Scale (SHAPS score change from placebo: -6.9±3.2, p<.001)

Burden of Depression in Persons with Epilepsy

- A common co-morbidity of epilepsy, lifetime prevalence rate reported in the literature ~30 – 50%
- An independent predictor of reduced QOL
- Can be a significant cause of non-adherence to anti-seizure medications and predictor of pharmacoresistance
- Market research with 20 Epileptologists highlighted the need for ASMs offering a mood benefit
  - Majority of current ASMs do not adequately address depression
  - Some ASM side effect profiles can exacerbate mood-related co-morbidities
  - In later lines of treatment, physicians indicated the potential need to choose between improving seizure control at the expense of potentially worsening mood-related comorbidities

Hitiris et al, Epilepsy Research 2007; O'Rourke and O'Brien, Seizure 2017; Kanner et al, Epilepsy & Behavior 2012





Boylan et al, Neurology 2004

Summary of Learnings about K_V7 Mechanism

XEN1101 Potential Next-Gen K_V7 Opener	Greater efficacy than SOCs while maintaining tolerability Novel mechanism suitable for rational polypharmacy
Advantage of Improved PK	QD dosing, longer half-life and low C_{max} to C_{min} ratio likely promotes efficacy, minimizes breakthrough seizures No need for dosing titration, promoting ease of use
K_V7 Mechanism not the Cause of Pigmentation	Colored dimers of ezogabine caused the pigmentary abnormalities observed with long-term ezogabine exposure No evidence that XEN1101 forms analogous dimers
K_V7 Mechanism May Treat Depression, a Common Co-Morbidity of Epilepsy	K_V7 channels mediate resilience to chronic stress related depression in animal models through blunting of VTA excitability within the reward system Ezogabine significantly improved MDD and anhedonia in a Phase 2 study

Highlights from Today's Discussion: XEN1101 Summary

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
K_V7 Mechanistic Background	• K_V7 has a well validated role in decreasing neuronal excitability and is an important target for seizure control • XEN1101 targets K_V7 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 X-TOLE results show potential for XEN1101 as an efficacious ASM
XEN1101 Ongoing Development	• XEN1101 is perceived to meet significant unmet need with efficacy, strong safety/tolerability, and ease of use attributes for FOS and possibly in depression

Q&A | Panel Discussion

MODERATED BY DR. PORTER