XENON

AES 2021 Symposium

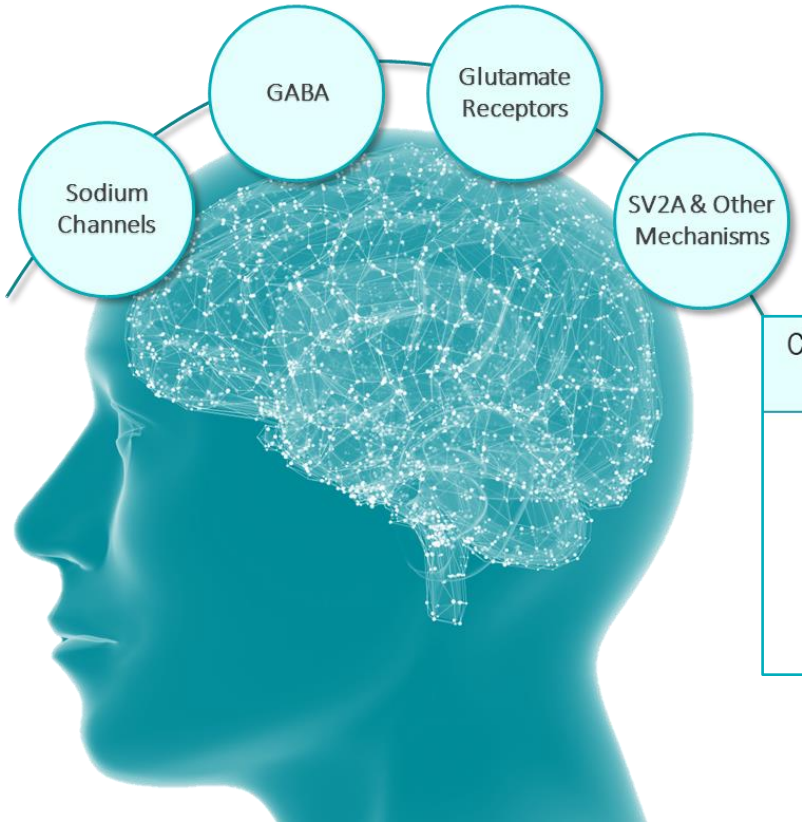
Summary of Results from the “X-TOLE” Study

FRIDAY, DECEMBER 3, 2021

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)

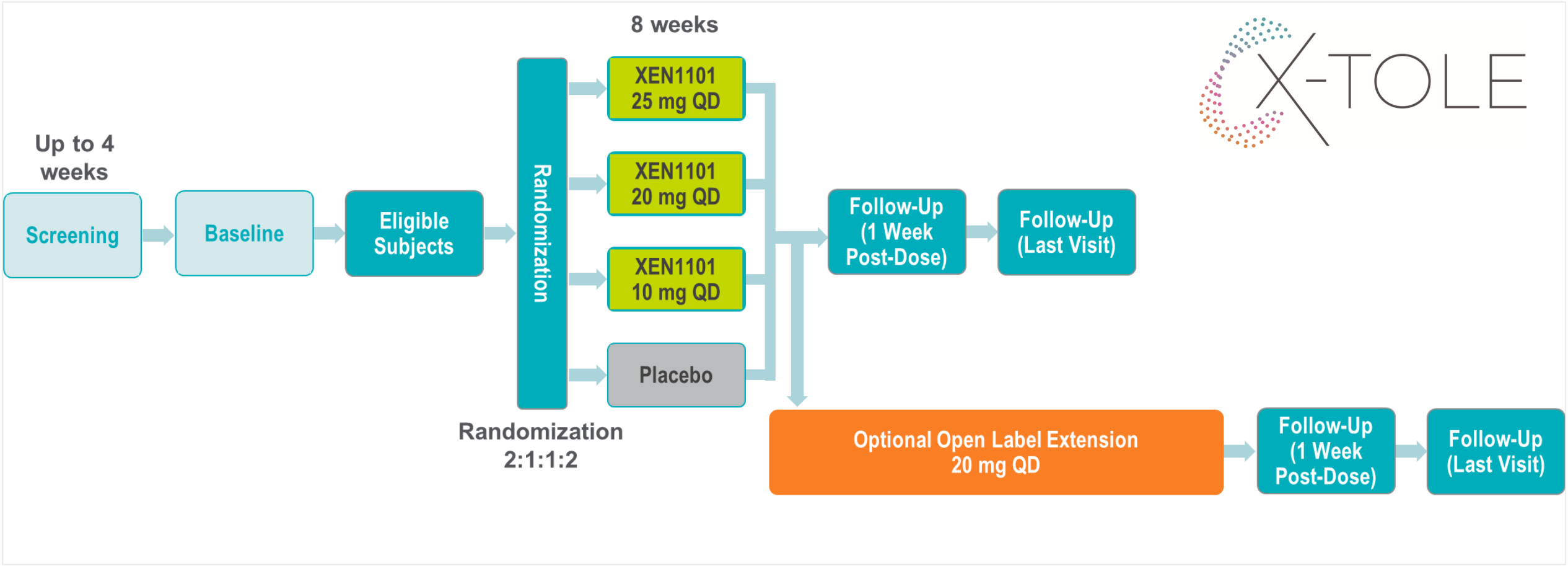


Commonly Prescribed ASMs for Adult Focal Epilepsy

- levetiracetam
- brivaracetam
- carbamazepine
- lamotrigine
- lacosamide

Addressing previous limitations, enhancing the K_V7 opportunity

X-TOLE Study Schema



Primary / Secondary Objectives of X-TOLE Study

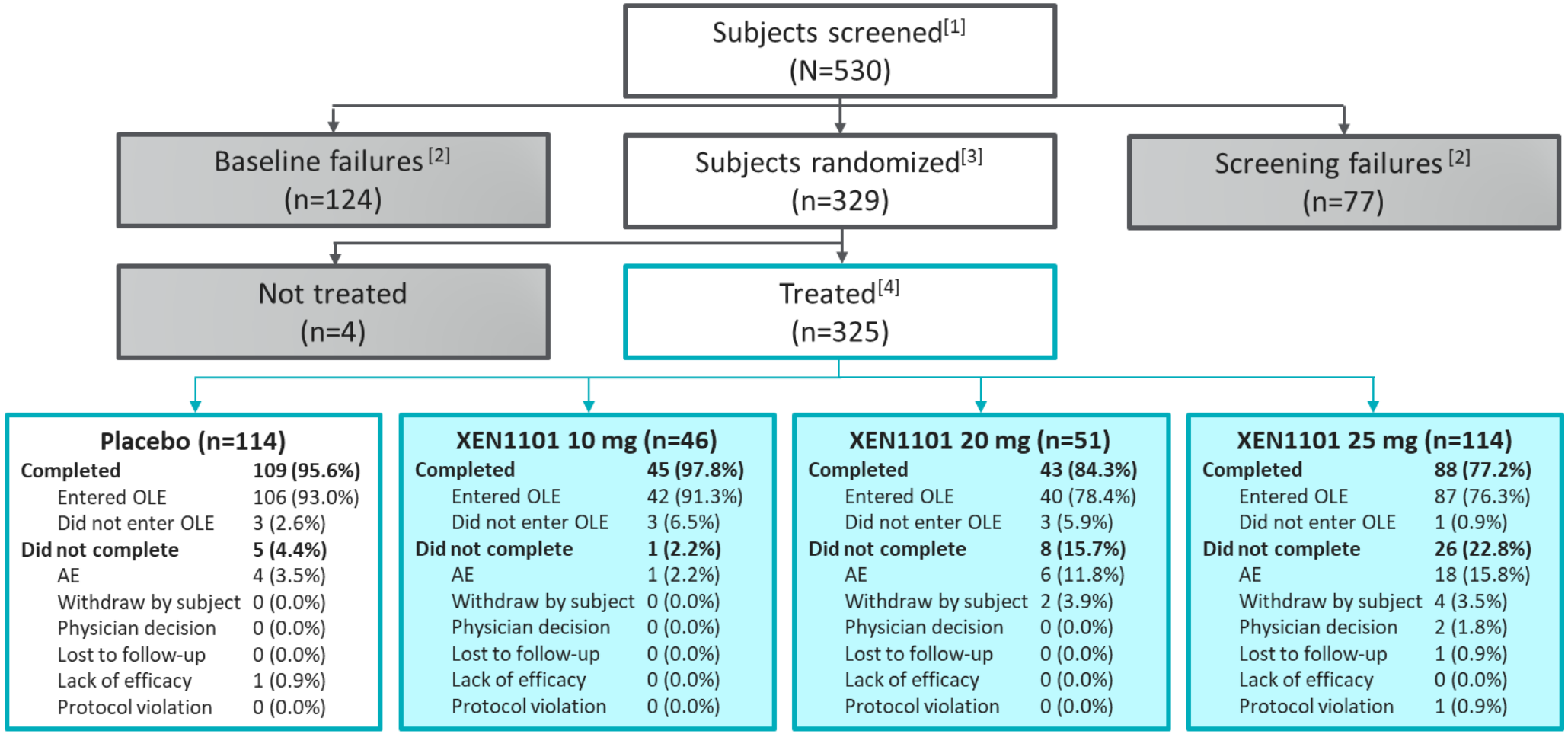
	OBJECTIVES	ENDPOINTS
Primary Objectives	To assess the efficacy of XEN1101 compared to placebo on focal seizure frequency in adults with focal epilepsy taking 1 to 3 ASMs in the double-blind period (DBP)	• Median percent change (MPC) in monthly (28 days) focal seizure frequency from baseline to DBP for 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%)

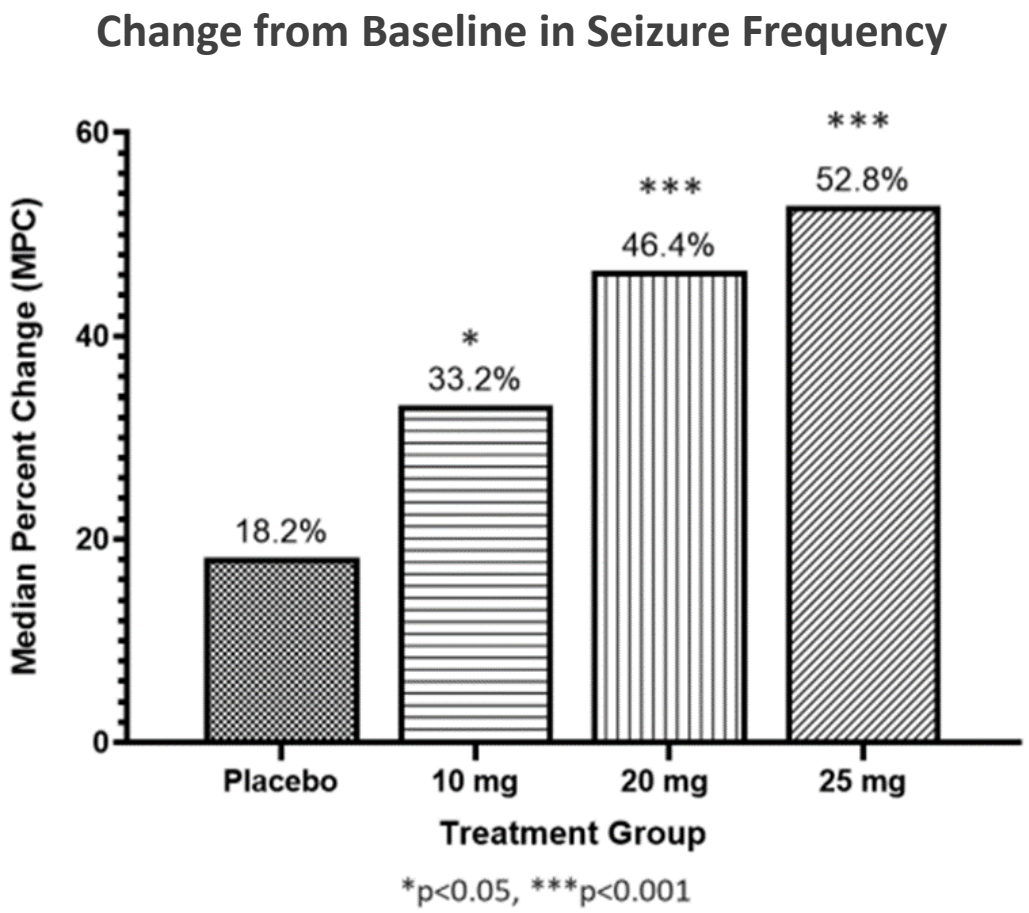
XEN1101 10 mg (n=46)	
Completed	**45 (97.8%)**
Entered OLE	42 (91.3%)
Did not enter OLE	3 (6.5%)
Did not complete	**1 (2.2%)**
AE	1 (2.2%)
Withdraw by subject	0 (0.0%)
Physician decision	0 (0.0%)
Lost to follow-up	0 (0.0%)
Lack of efficacy	0 (0.0%)
Protocol violation	0 (0.0%)

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.

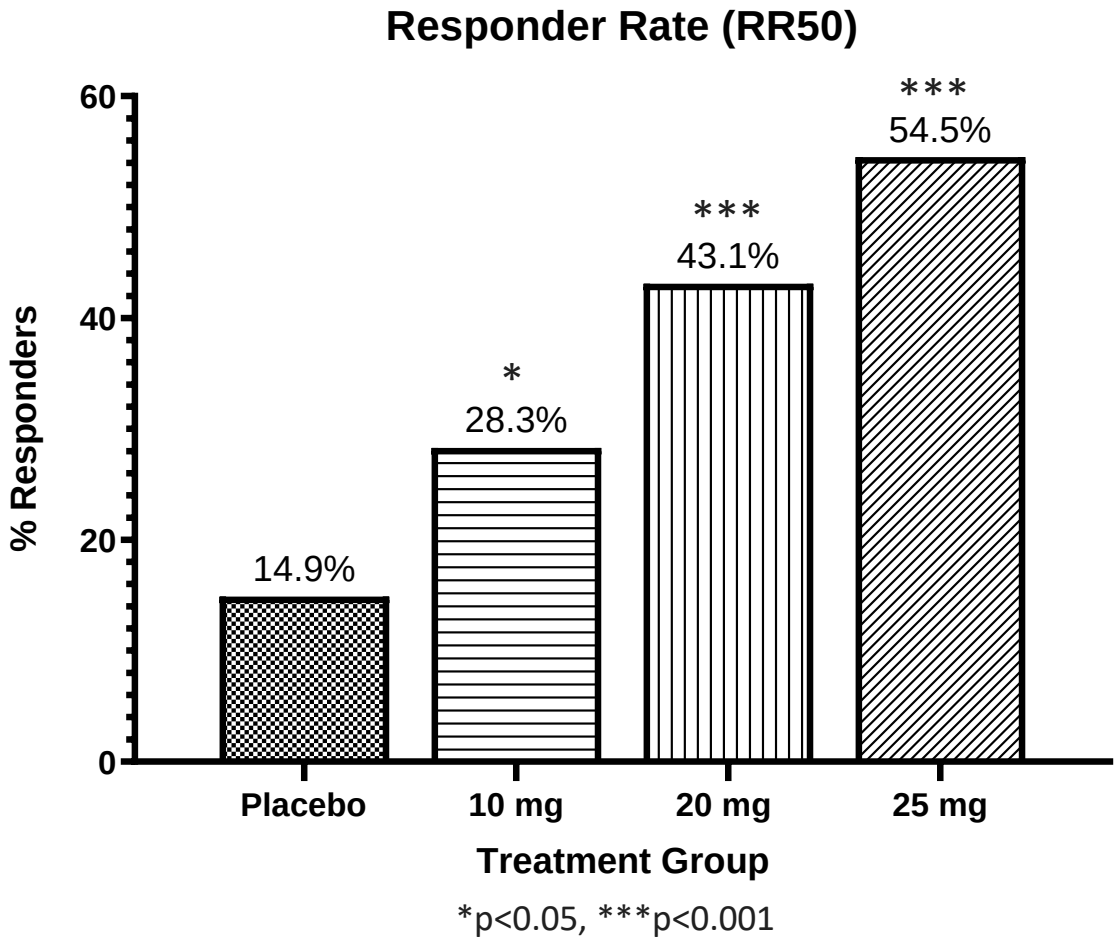
Efficacy Results: MPC from Baseline



	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

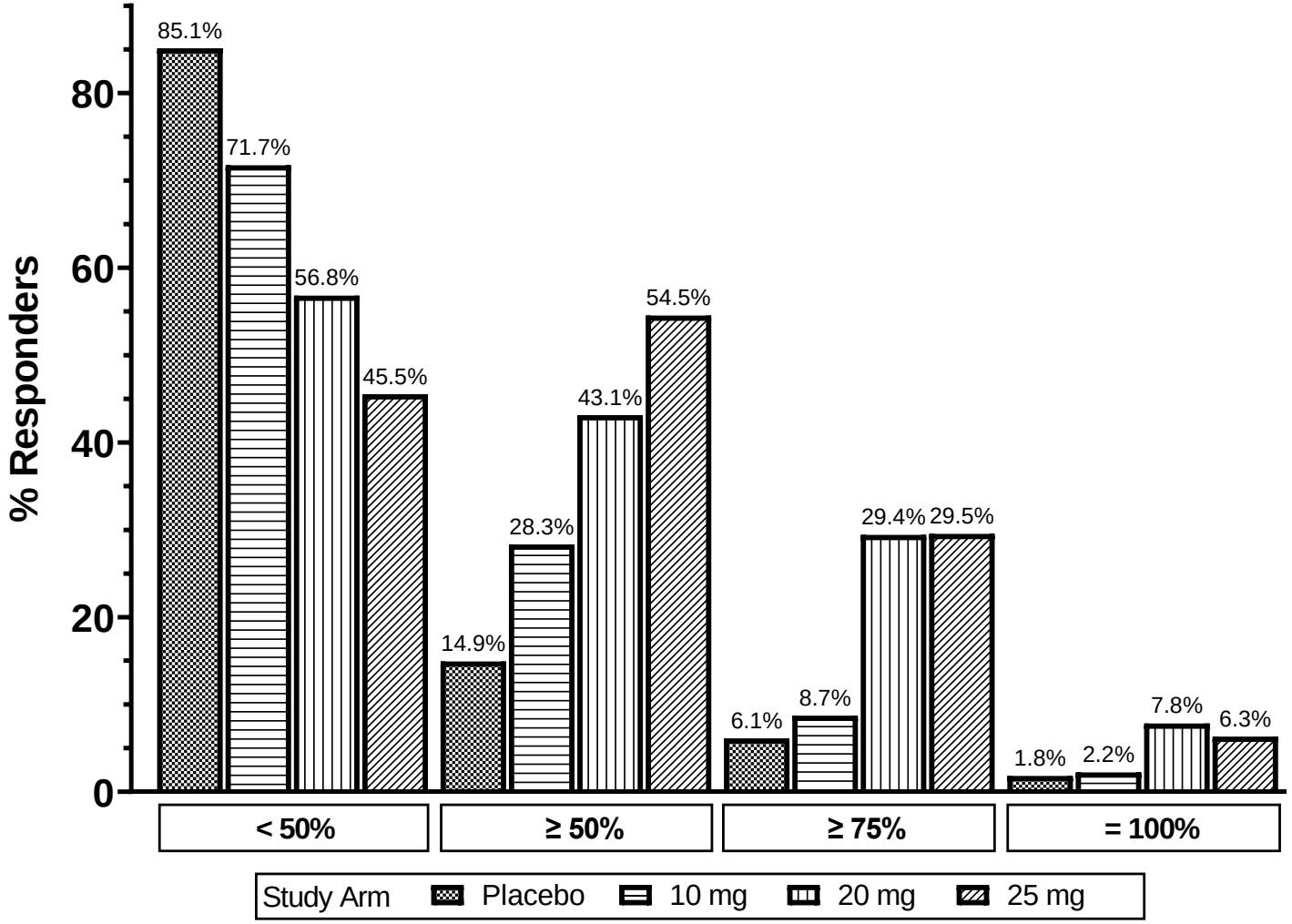
Secondary Endpoints: Response Rates and CGI-C/PGI-C (cont'd)

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**

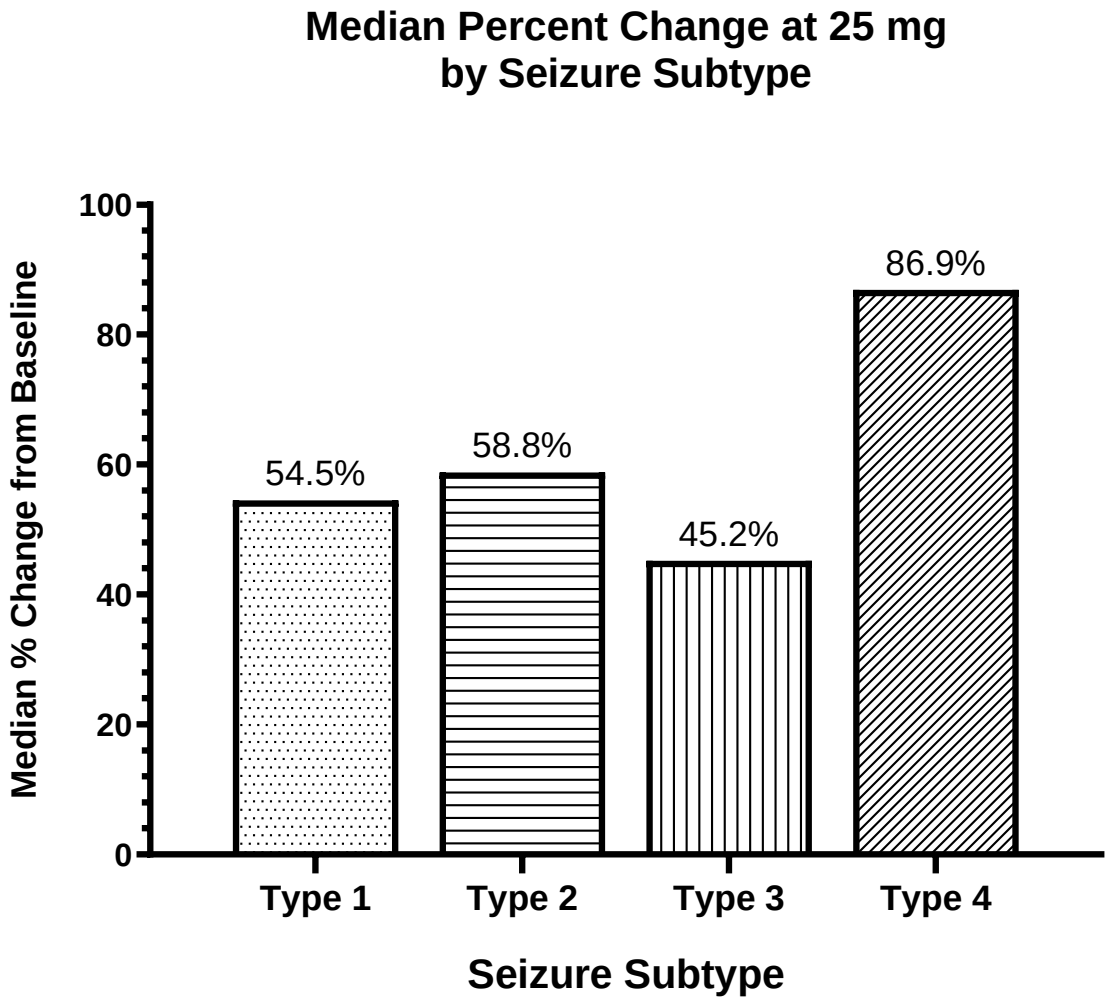
Clinically meaningful, dose-dependent improvements in CGI-C/PGI-C

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)



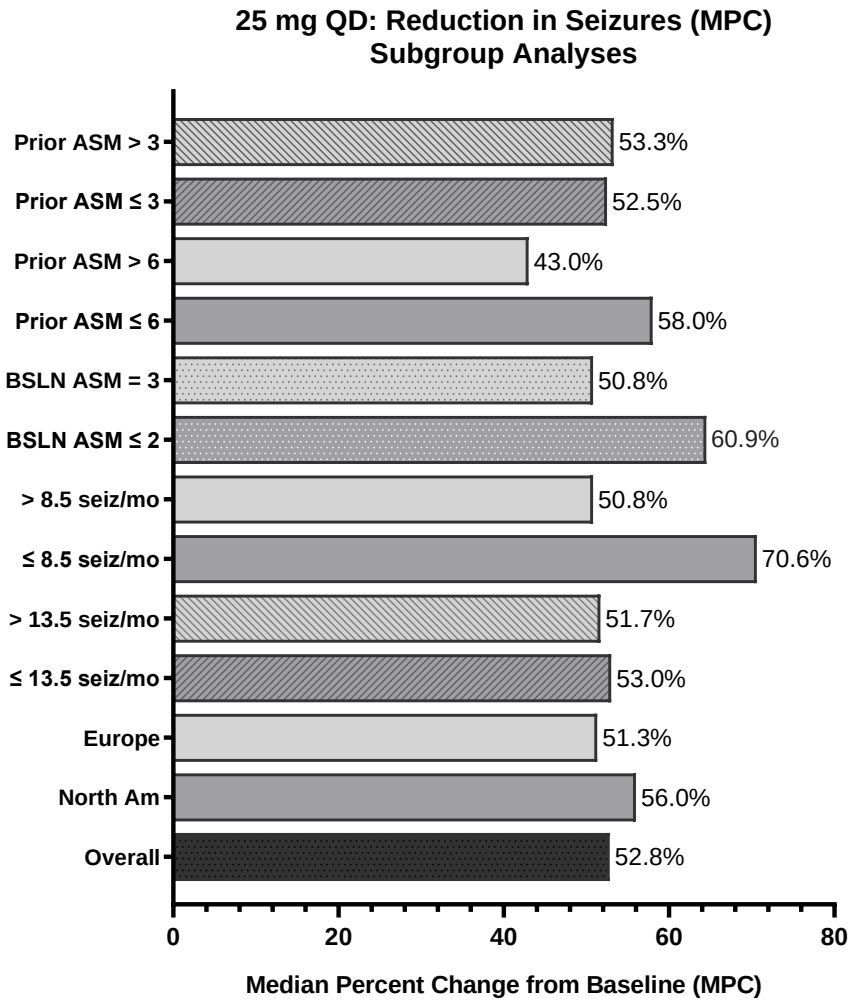
Focal Onset Seizure Types:

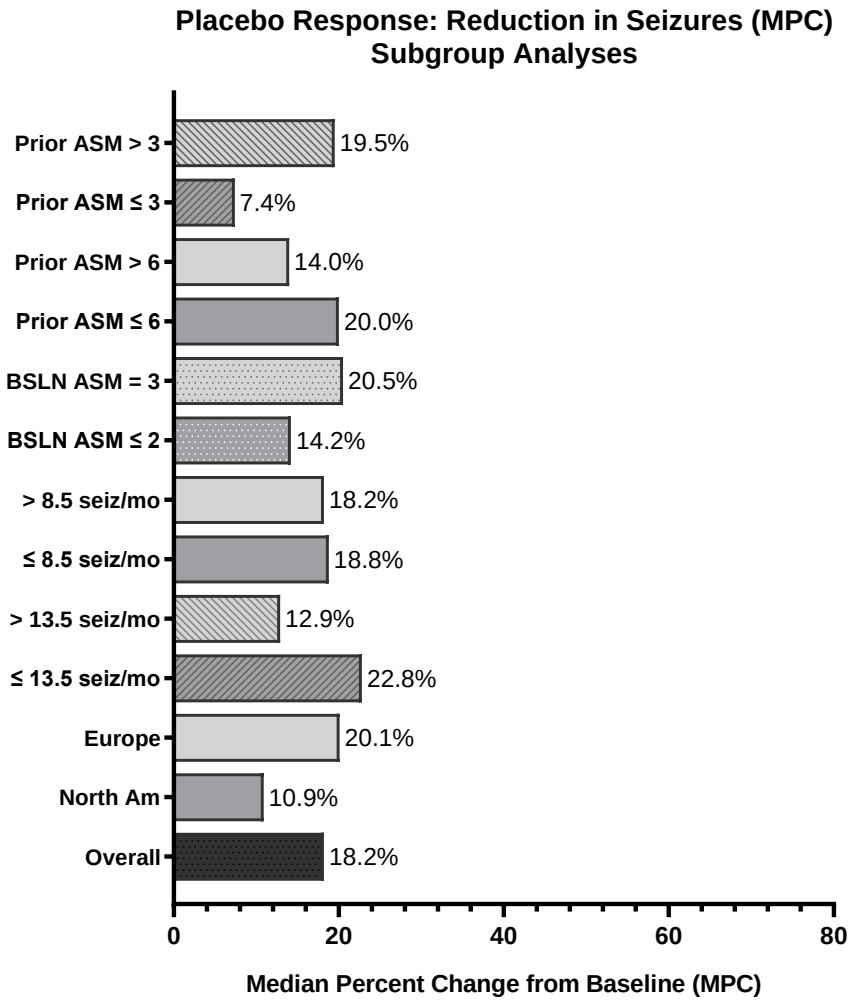
	Seizure Description
Type 1	Focal aware seizures with motor signs
Type 2	Focal seizures with impaired awareness with motor signs
Type 3	Focal seizures with impaired awareness with NO motor signs
Type 4	Focal seizures that lead to generalized tonic-clonic seizures
Type 5	Focal aware seizures with NO motor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

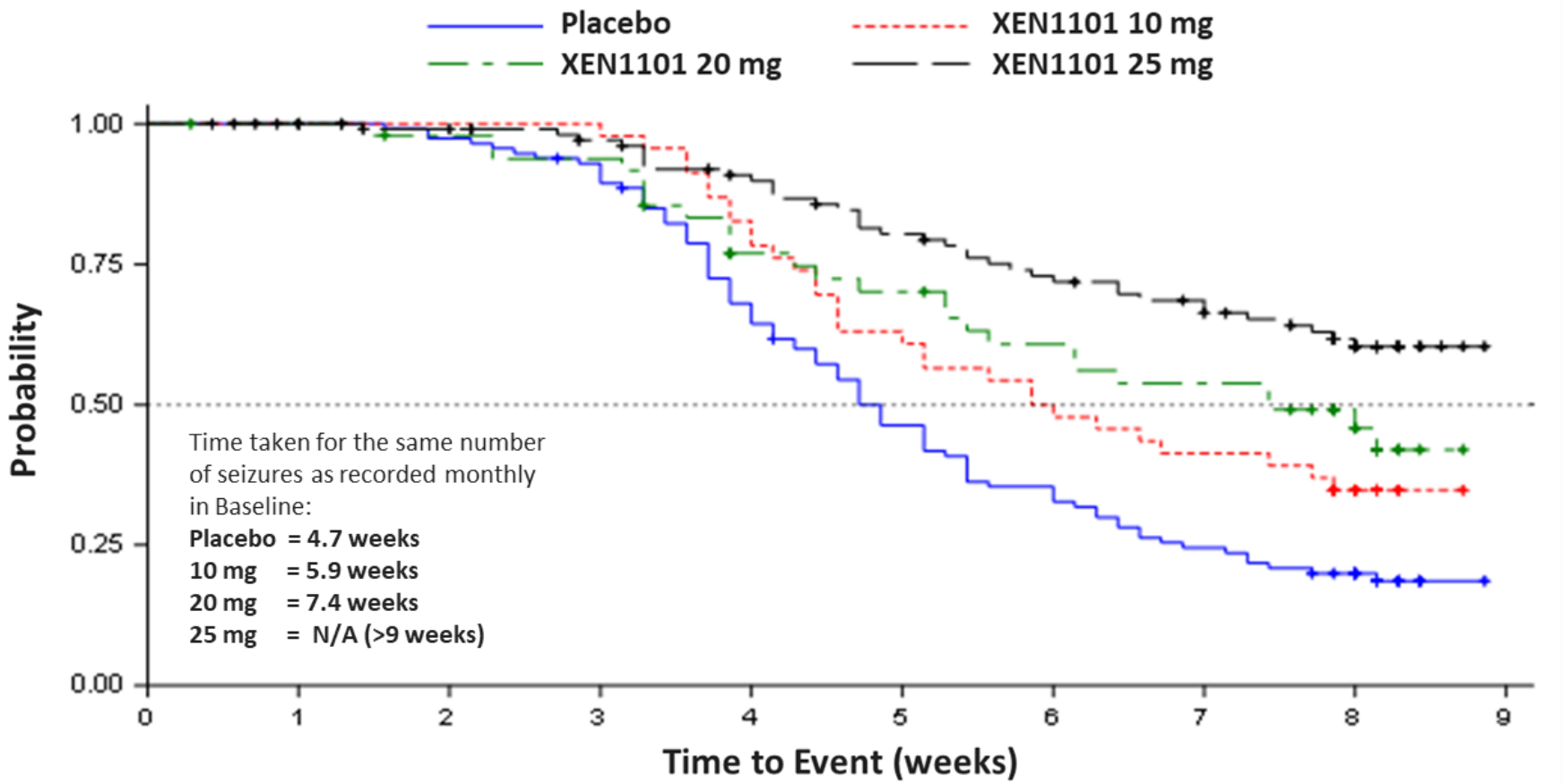




Increased seizure reduction in patients with less disease severity

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