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The Impact of Disease Severity on Responder Rates in a Phase 2b Study of XEN1101, a Potent, Selective Potassium Channel Opener, in Adults With Focal Epilepsy (X-TOLE)

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Burden of Focal Onset Seizures

- An estimated 3.4 million individuals in the US have epilepsy in 2015[1]
- Focal onset seizures (FOS) affect up to ~60% of people with epilepsy[2,3]
- Despite the availability of many new antiseizure medications (ASMs), >30% of patients continue to have uncontrolled seizures[4]

Probabilities of seizure freedom with increasing exposure to multiple ASMs[4]

Monotherapy	2nd regimen	3rd regimen
50.5%	**11.6%**	**4.1 %**
seizure-free[a]	seizure-free[a]	seizure-free[a]

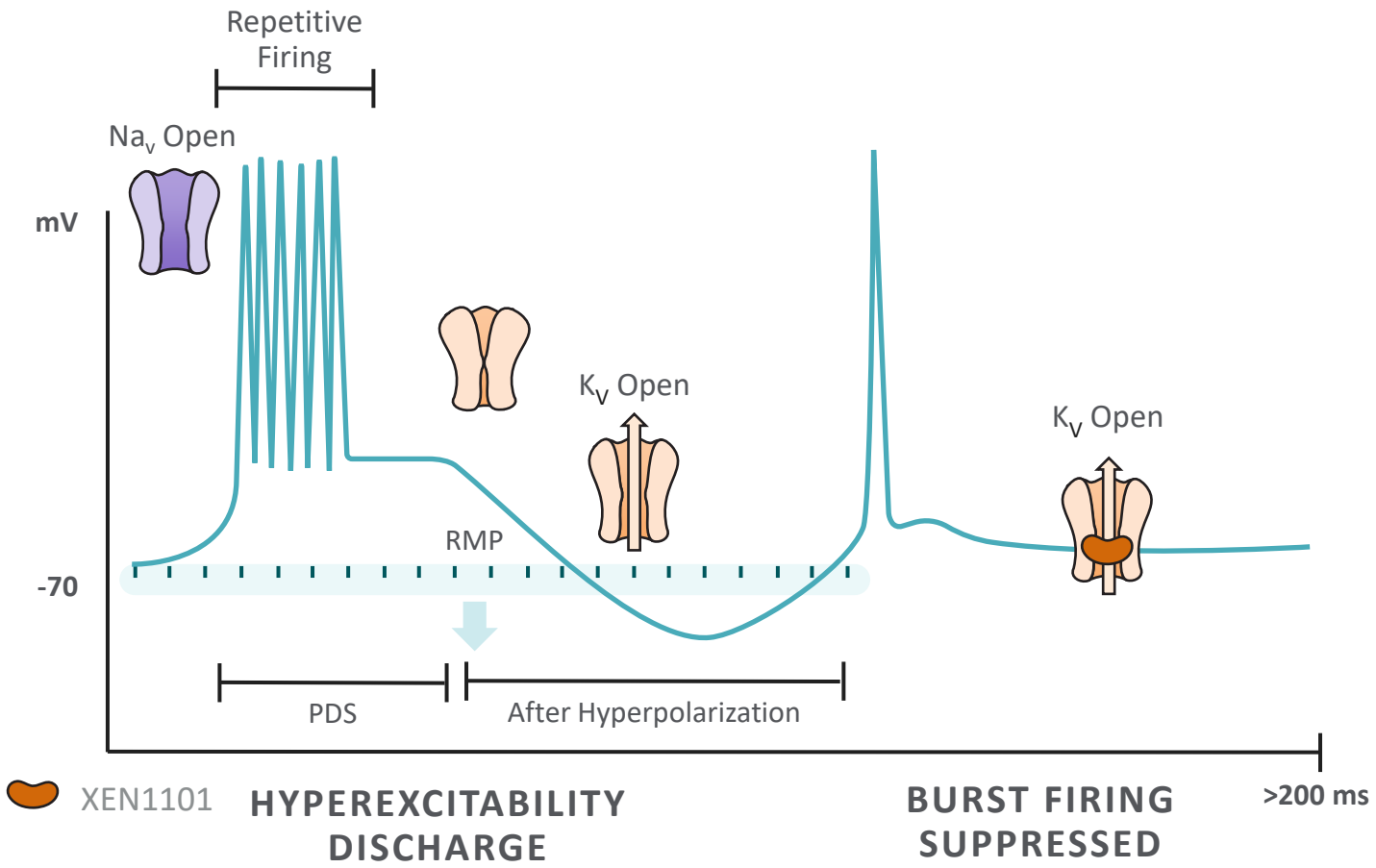
- Substantial unmet need exists for novel, well-tolerated therapies that provide seizure reduction or seizure freedom in patients with FOS

- A successful outcome for any treatment depends on both the tolerability and efficacy of the treatment[5]
- Potential for adverse events (AEs) may increase when administering concomitant ASMs with similar mechanisms of action[6]

[a]*Seizure freedom was defined as a patient experiencing no seizures from treatment initiation for the previous ≥12 months.*

1. Zack MM and Kobau R. *MMWR Morb Mortal Wkly Rep*. 2017;66(31):821-825. 2. Gupta S, et al. *Epilepsia Open*. 2017;2(2):199-213. 3. Picot MC, et al. *Epilepsia*. 2008;49(7):1230-1238. 4. Chen Z, et al. *JAMA Neurol*. 2018;75(3):279-286. 5. Hogan RE. *Epilepsy Curr.* 2018;18(5):304-306. 6. Smith MC, et al. *Neurol Ther*. 2022;11(4):1705-1720.

K_V7 Channels Have a Critical Role in Neuronal Firing



Adapted from Badawy et al.[2]

- Voltage-gated *KCNQ*-type potassium channels (K_V7) family comprises 5 subunit channels, $K_V7.1$ to $K_V7.5$[1]
- K_V7 channel openers induce a hyperpolarized resting membrane potential that reduces action potential spiking and cortical/corticospinal excitability[1,2]

PDS, paroxysmal depolarizing shift; PK, pharmacokinetics; RMP, resting membrane potential; Na_v, voltage-gated sodium channel.

1. Khan R, et al. *CNS Neurol Disord Drug Targets*. 2024;23(1):67-87. 2. Badawy RAB, et al. *J Clin Neurosci.* 2009;16(3):355-365.

XEN1101: A Novel, Potent K_V7 Potassium Channel Opener

XEN1101 Neurology Pipeline	Clinical Trial/Partner	Pre-Clinical	Phase 1	Phase 2	Phase 3
XEN1101 (Potassium Channel Opener)					
Focal Onset Seizures (FOS)	X-TOLE2				
Focal Onset Seizures (FOS)	X-TOLE3				
Primary Generalized Tonic-Clonic Seizures (PGTCS)	X-ACKT				
Major Depressive Disorder (MDD)	X-NOVA				
Major Depressive Disorder (MDD)*	Mount Sinai				

*Investigator Sponsored Phase 2 Proof-of-Concept Study

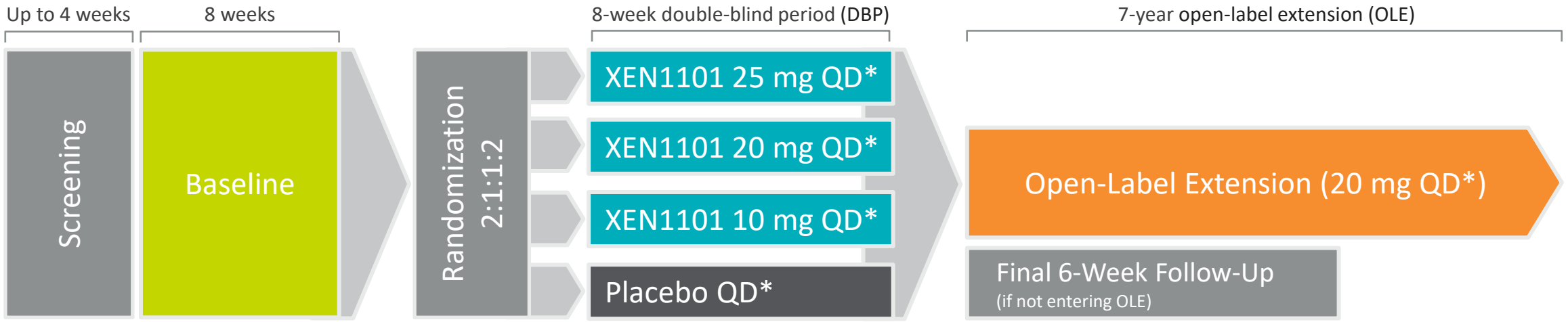
- XEN1101 is a novel, potent, K_V7 potassium channel opener in development for epilepsy and major depressive disorder[1-5]
- XEN1101 was more selective for $K_V7.2/7.3$ relative to $K_V7.4$ and $K_V7.5$ in in vitro assays[6]
- The pharmacokinetic properties support once-daily dosing with food, with no titration required[6]

XEN1101 is in Phase 3 clinical investigation and has not been approved by the US Food and Drug Administration or other regulatory bodies.

1. https://www.clinicaltrials.gov/study/NCT03796962. 2. https://clinicaltrials.gov/study/NCT05667142. 3. https://clinicaltrials.gov/study/NCT05614063.
4. https://clinicaltrials.gov/study/NCT05716100. 5. https://clinicaltrials.gov/study/NCT05376150. 6. Bialer M, et al. *Epilepsia*. 2022;63(11):2883-2910.

Study Design

X-TOLE™
Phase 2b study and 7-year OLE



*Administered as a once-daily capsule with food with no titration required

- X-TOLE evaluated the efficacy, safety, and tolerability of XEN1101 administered with food in adults with FOS (n=325)

Primary endpoint

- Median percentage change (MPC) in monthly (28 days) focal seizure frequency from baseline to DBP for XEN1101 vs placebo

Secondary endpoints

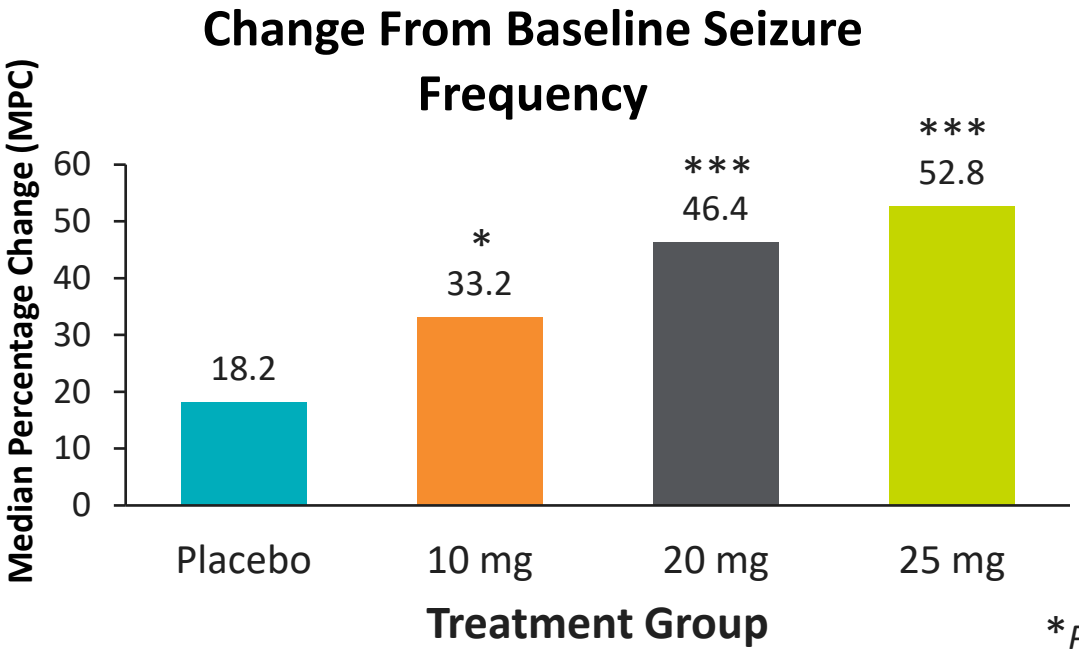
- **Response rate**, defined as patients experiencing ≥50% reduction in monthly (28 days) focal seizure frequency from baseline compared to DBP
- Percentage change from baseline and weekly focal seizure frequency for each week of the DBP
- Clinical Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C) scores during the DBP
- Treatment-emergent adverse events (TEAEs) and serious adverse events (SAEs), and other measures

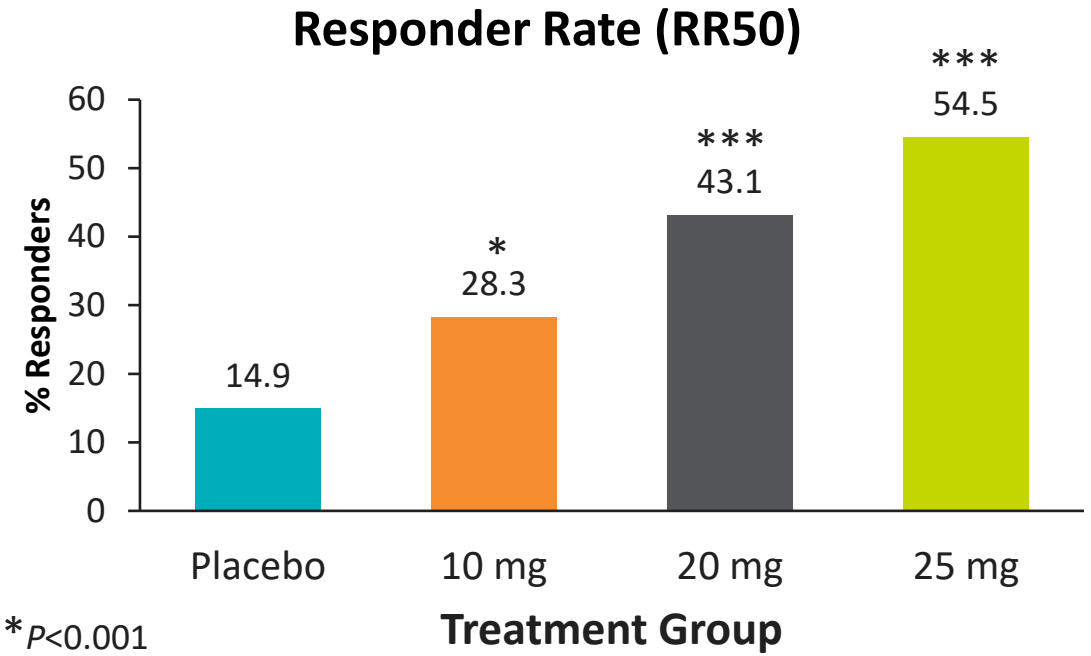
ASM, antiseizure medication; DBP, double-blind period; FOS, focal onset seizure; QD, once daily.

French JA, et al. *JAMA Neurol*. 2023;80(11):1145-1154.

X-TOLE: Results of Completed DBP Phase 2b Trial for FOS

- XEN1101 demonstrated a statistically significant, dose-dependent reduction from baseline in monthly FOS frequency compared to placebo in a difficult-to-treat population[1]





*P<0.05 ***P<0.001

- XEN1101 was generally well tolerated. The most common TEAEs (>10% of patients) across all doses of XEN1101 (n=211) were dizziness (24.6%), somnolence (15.6%), and fatigue (10.9%)
- The rate of serious TEAEs was the same for the highest dose of XEN1101 and placebo (2.6%)
- No cardiovascular signals of concern in ECGs or vital signs, or deaths were reported
- The discontinuation rate across all doses of XEN1101 due to TEAEs was 12.3%

DBP, double-blind period; ECG, electrocardiogram; FOS, focal onset seizure; TEAE, treatment-emergent adverse event.

1. French JA, et al. *JAMA Neurol*. 2023;80(11):1145-1154.

X-TOLE: Demographic and Baseline Characteristics (Safety Population)

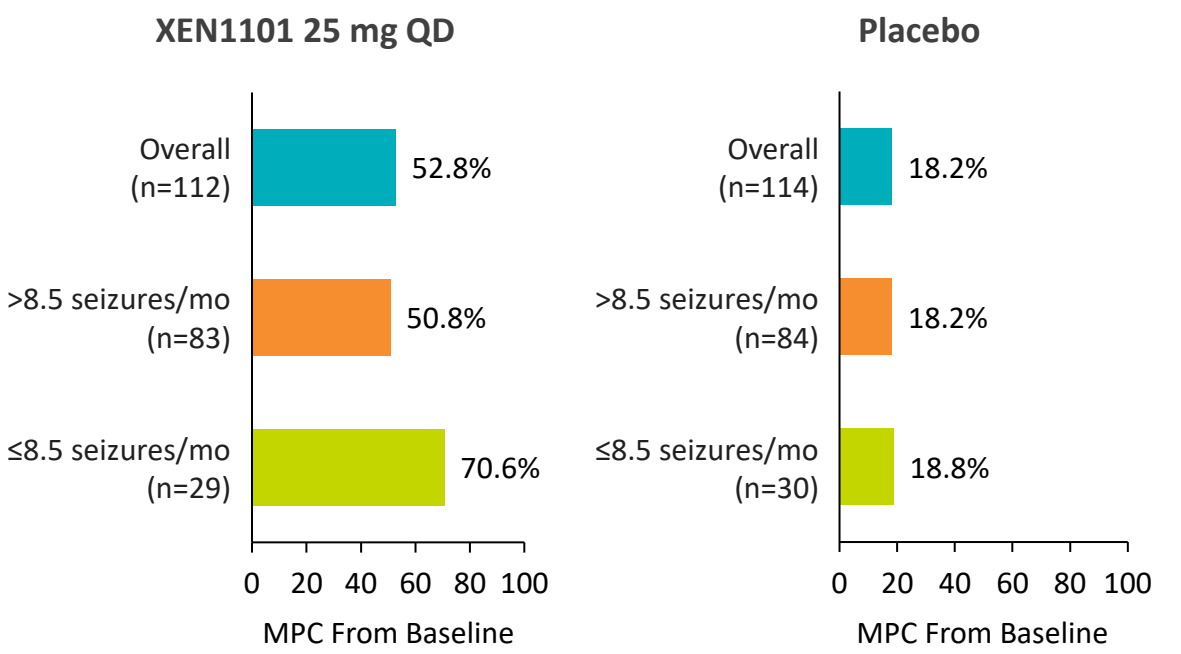
Characteristic	Placebo (n=114)	XEN1101 25 mg (n=114)
Age in years, mean (SD)	42.9 (13.7)	38.7 (13.1)
Age at study entry category, n (%)		
≥65	5 (4.4)	1 (0.9)
<65	109 (95.6)	113 (99.1)
Sex, n (%)		
Female	61 (53.5)	54 (47.4)
Male	53 (46.5)	60 (52.6)
Region, n (%)		
Europe	67 (58.8)	68 (59.6)
North America	47 (41.2)	46 (40.4)
Baseline seizure frequency		
Mean (SD)	27.3 (38.5)	23.5 (30.4)
Median	13.4	12.8
Background ASM use, n (%)		
1	12 (10.5)	11 (9.6)
2	46 (40.4)	48 (42.1)
3	56 (49.1)	55 (48.2)
Number of pre-study ASMs failed, n (%)		
≤ 3, n (%)	29 (25.4)	31 (27.2)
> 3, n (%)	85 (74.6)	83 (72.8)
Median [Q1, Q3]	6.0 [4.0, 8.0]	6.0 [3.0, 9.0]

ASM, antiseizure medication.

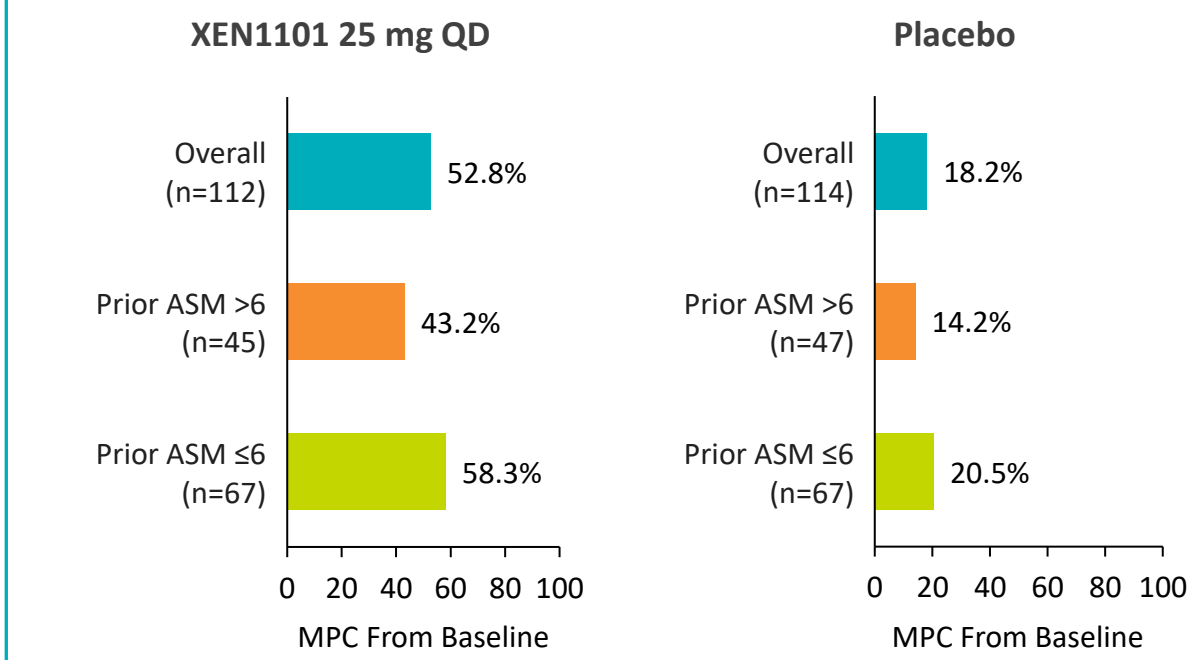
- The X-TOLE study enrolled difficult-to-treat patients
- Patients in the 25 mg group had a median of 12.8 monthly seizures
- Patients in the placebo group had a median of 13.4 monthly seizures

X-TOLE Post Hoc Analysis: Impact of Baseline Disease Severity on Median Percentage Change in Monthly FOS Frequency

Baseline Seizure Subgroup Analysis



Prior Failed ASMs Subgroup Analysis

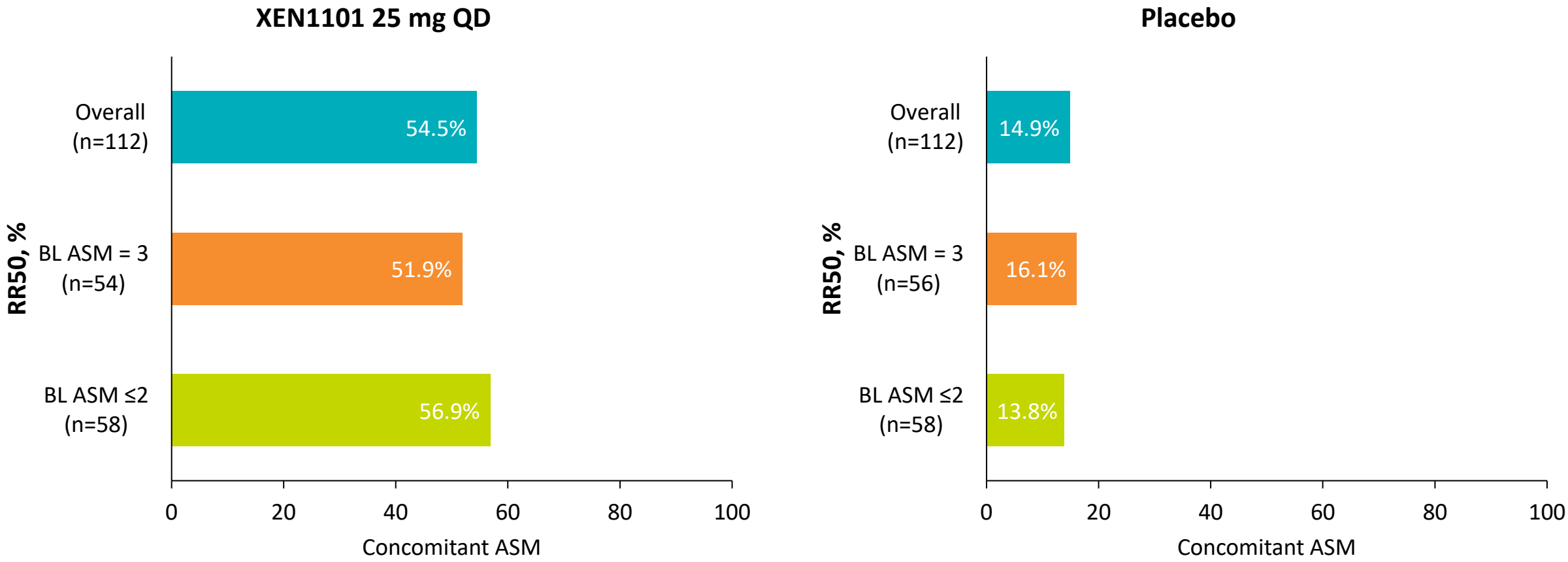


ASM, antiseizure medication; FOS, focal onset seizure; QD, once daily.

Leung J, et al. Poster No. 2.233. Presented at American Epilepsy Society Annual Meeting, Nashville, TN, December 2–6, 2022.

X-TOLE Post Hoc Analysis: Impact of Number of Concomitant ASMs on Responder Rate (RR50)

- RR50 was achieved by 56.9% of patients treated with 1–2 concomitant ASMs throughout and 51.9% treated with 3 concomitant ASMs throughout the study

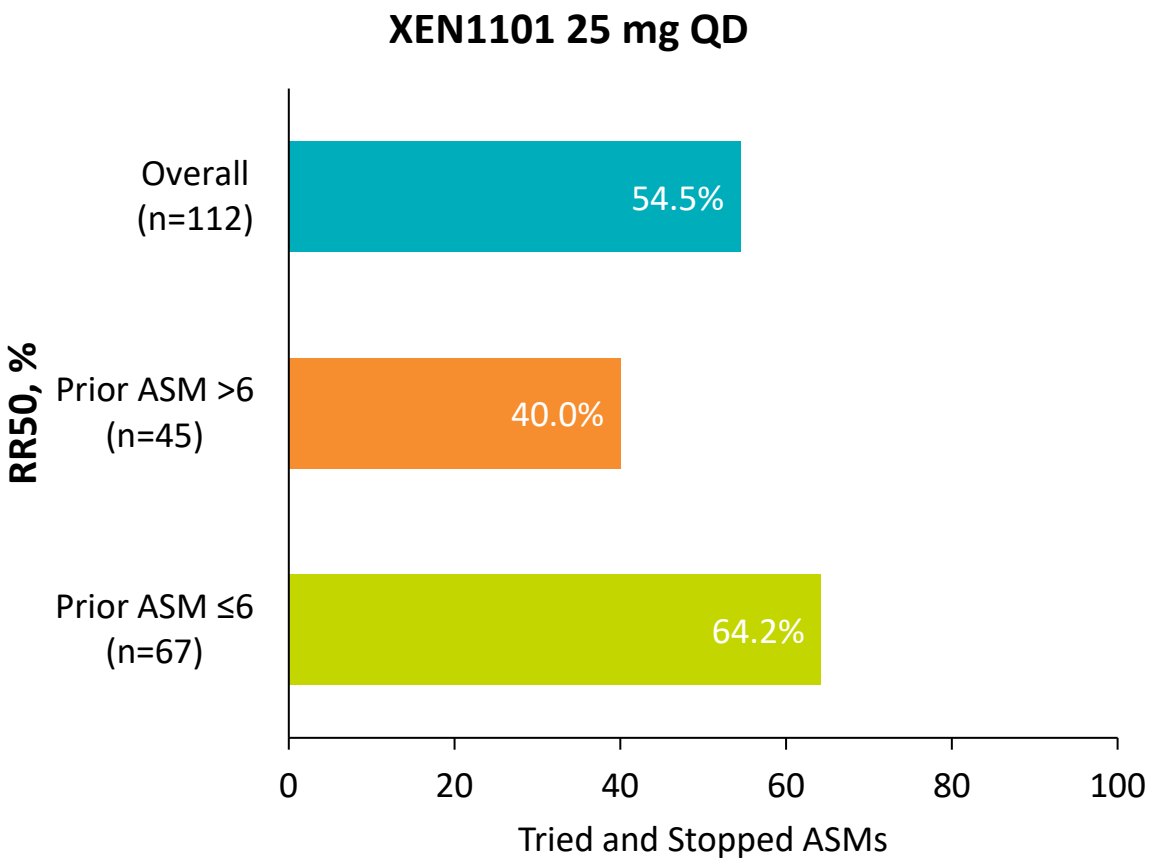


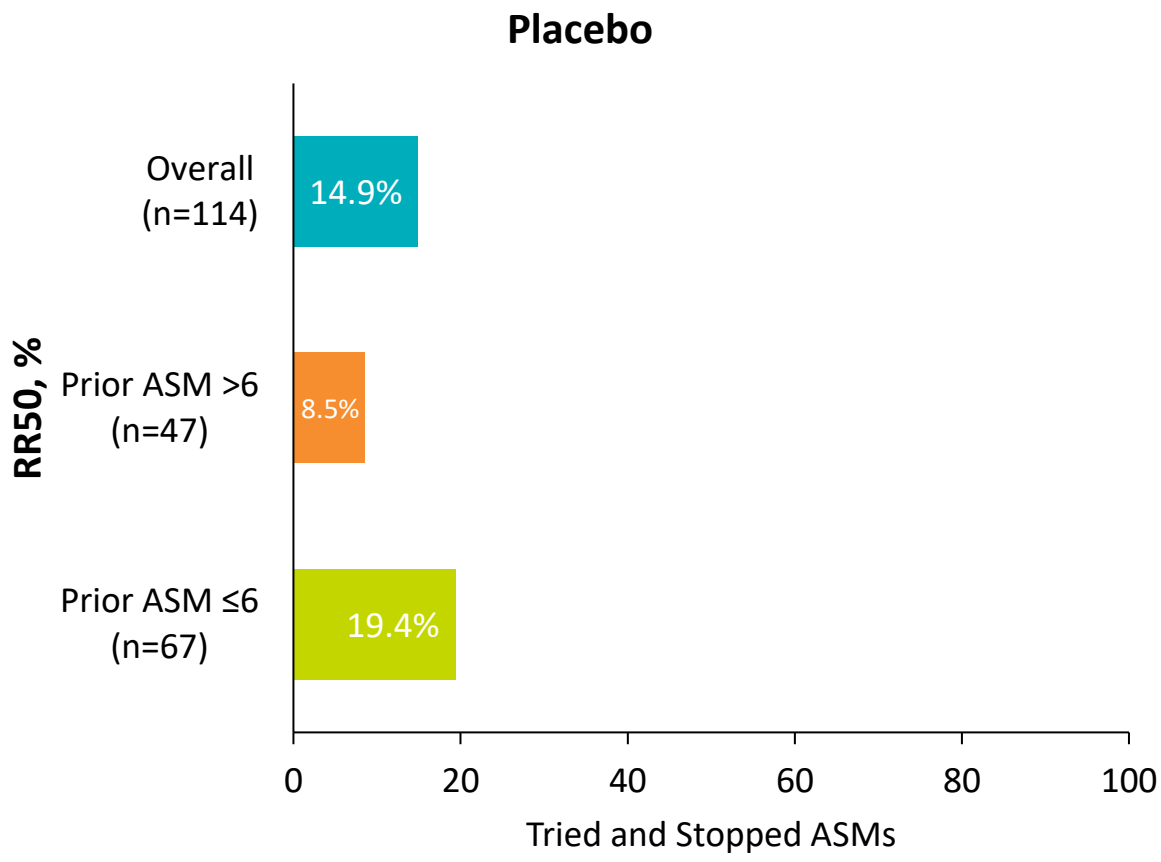
Note: All doses taken with food.

ASM, antiseizure medication; BL, baseline; RR50, percentage of patients with a ≥50% reduction in seizure frequency; QD, once daily.

X-TOLE Post Hoc Analysis: Impact of Number of Prior ASMs on Responder Rate (RR50)

- RR50 was achieved by 64.2% of patients with ≤6 tried and stopped ASMs and 40.0% with >6 ASMs

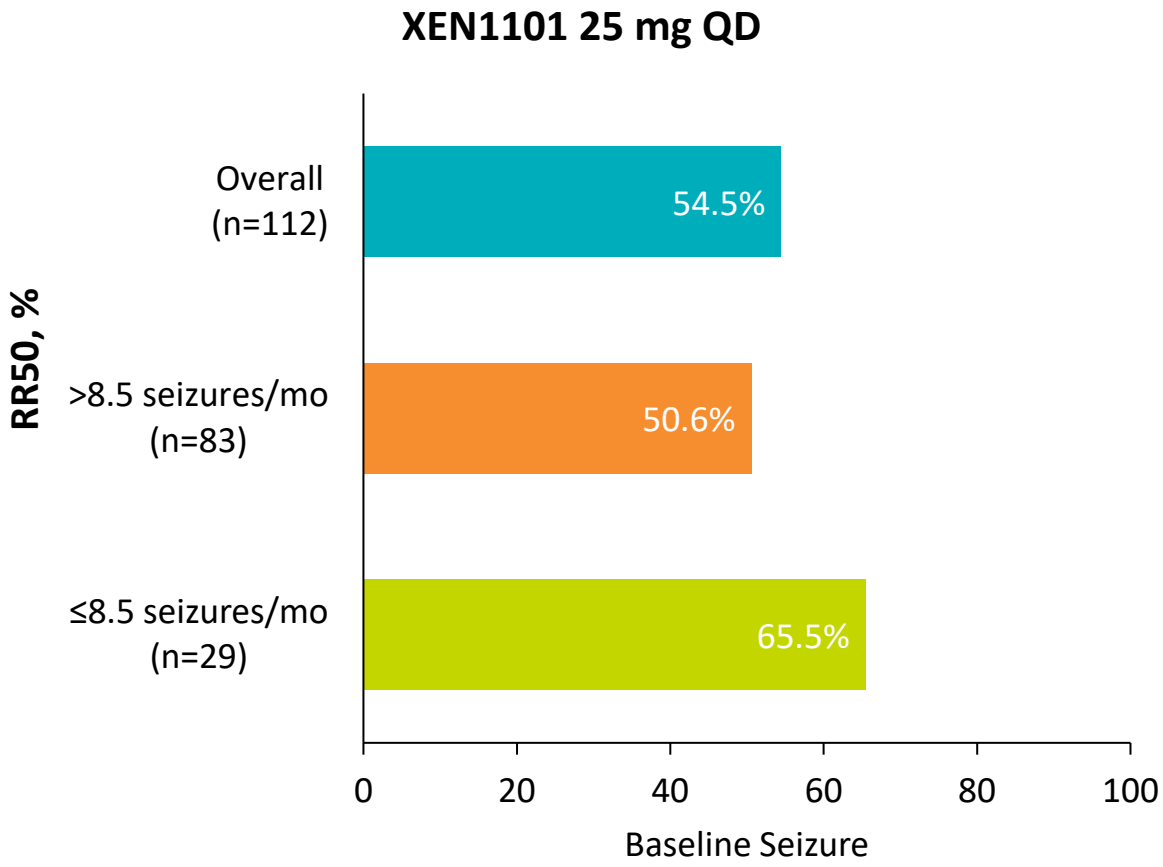


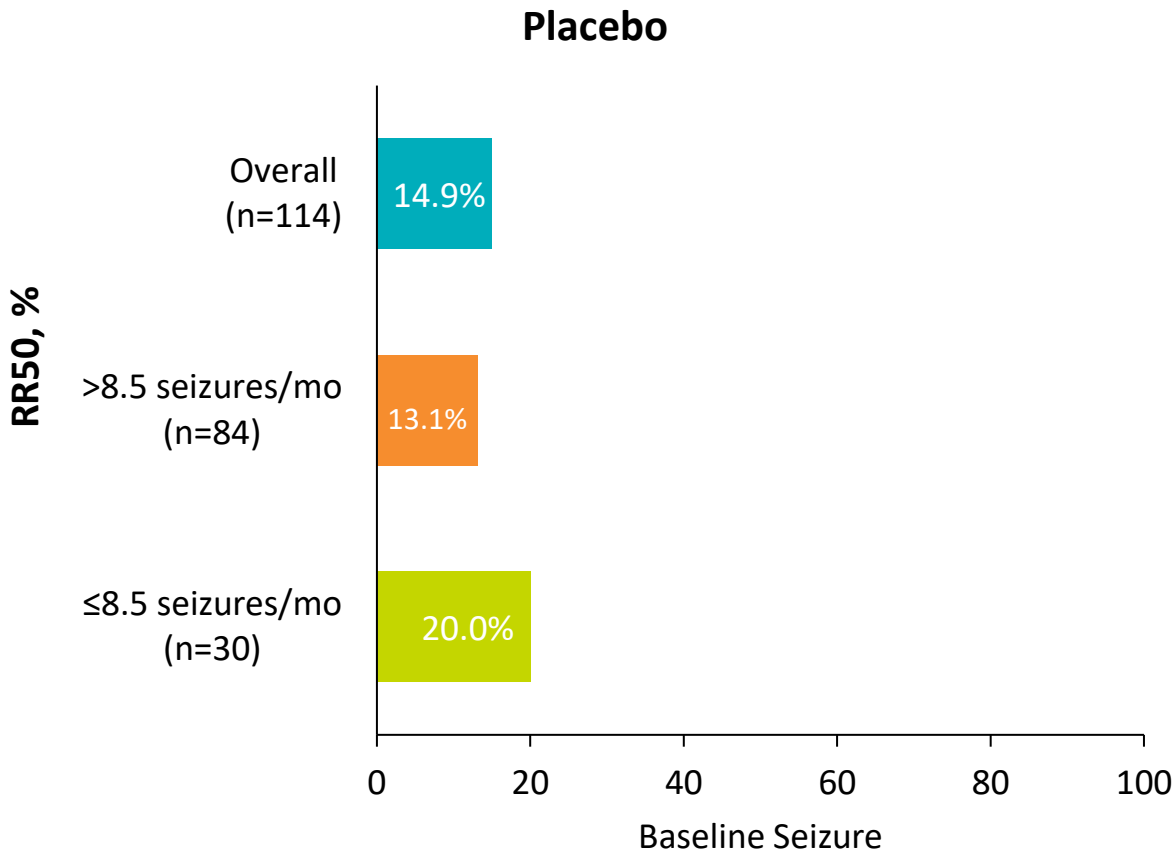


Note: All doses taken with food.
ASM, antiseizure medication; RR50, percentage of patients with a ≥50% reduction in seizure frequency; QD, once daily.

X-TOLE Post Hoc Analysis: Impact of Baseline Seizure Frequency on Responder Rate (RR50)

- RR50 was achieved by 65.5% of patients with ≤8.5 seizures per month at baseline and 50.6% with >8.5 seizures per month





Note: All doses taken with food. RR50, percentage of patients with a ≥50% reduction in seizure frequency; QD, once daily.

Conclusions

X-TOLE™
Phase 2b study and 7-year OLE

- Based on the number of concomitant ASMs, baseline seizure frequency, and number of failed ASMs, the X-TOLE study enrolled difficult-to-treat patients
- Consistent with the significant MPC reduction in X-TOLE, 54.5% of the patients in the 25 mg group achieved the benchmark of RR50
- XEN1101 was relatively more effective in patients with indicators of less-severe disease in the trial population
- These findings suggest that XEN1101 may be appropriate for use in patients with focal epilepsy across the spectrum of disease severity

ASM, antiseizure medication; MPC, median percentage change; RR50, percentage of patients with a ≥50% reduction in seizure frequency.

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APPENDIX

Summary of Recent FOS Trials: Baseline Seizure Frequencies and Concomitant ASMs

Drug	Phase (Study Years)	Total N (Population)	BL Median Monthly Seizure Frequency, Mean (SD)*	BL Median Monthly Seizure Frequency, Median (Min, Max)†	Allowed Concomitant ASMs	Concomitant ASMs ≤2, % of Patients	Concomitant ASMs = 3, % of Patients
XEN1101[5]	Phase 2b (2019–2021)	325 (Safety)	N/A‡	13.5 (13.5,13.5)	1 to 3	49.5%	50.5%
Cenobamate[8,9]	Phase 2 and 3 (2011–2015)	659 (Safety)	8.5 (1.9)	8.7 (5.5, 11)	1 to 3	70.1%	29.6%§
Brivaracetam[10-14]	Phase 2 and 3 (2005–2014)	1919 (ITT)	9.1 (1.3)	9.0 (7.0, 11.8)	1 to 2	96.1%	3.8%¶
Perampanel[15-18]	Phase 2 (2005–2007)	153 (Safety)	N/A#	N/A#	1 to 2	99.3%‖	0%
	Phase 2 and 3 (2007–2010)	1526 (Safety)	11.9 (1.8)	11.9 (9.3, 14.3)	1 to 3	64.8%	35.2%
Lacosamide[19-21]	Phase 2 (2002–2004)	415 (Safety)	N/A**	11-13‖	1 to 2	100%	0%
	Phase 2 and 3 (2004–2006)	879 (Safety)	12.5 (2.7)	11.5 (9.9, 16.5)	1 to 3	67.6%	32.4%

*ASM, antiseizure medication; BL, baseline; FOS, focal onset seizure. *Calculated as the mean (SD) of median monthly seizure frequency reported in each referenced study. †Calculated as the median (min, max) of median monthly seizure frequency reported in each referenced study. ‡Requires multiple studies for analysis. §Some additional patients received temporary treatment with a fourth ASM. ¶Subset of patients used benzodiazepines as needed. #Not reported. ||As reported. **Not calculated due to method used to report baseline median monthly seizures.*

Prior ASMs for Patients Enrolled in X-TOLE (Safety Population)

ASMs Taken Prior to Study (Excluding Ongoing Medication)

ASM, n (%)	Placebo (n = 114)	XEN1101 10 mg (n = 46)	XEN1101 20 mg (n = 51)	XEN1101 25 mg (n = 114)	Total (n = 325)
Levetiracetam	78 (68.4)	27 (58.7)	33 (64.7)	76 (66.7)	214 (65.8)
Carbamazepine	66 (57.9)	20 (43.5)	26 (51.0)	54 (47.4)	166 (51.1)
Lacosamide	48 (42.1)	18 (39.1)	25 (49.0)	50 (43.9)	141 (43.4)
Perampanel	48 (42.1)	25 (54.3)	20 (39.2)	46 (40.4)	139 (42.8)
Lamotrigine	47 (41.2)	19 (41.3)	19 (37.3)	43 (37.7)	128 (39.4)
Topiramate	40 (35.1)	20 (43.5)	21 (41.2)	46 (40.4)	127 (39.1)
Zonisamide	37 (32.5)	17 (37.0)	22 (43.1)	40 (35.1)	116 (35.7)
Oxcarbazepine	43 (37.7)	14 (30.4)	16 (31.4)	38 (33.3)	111 (34.2)
Phenytoin	38 (33.3)	11 (23.9)	20 (39.2)	33 (28.9)	102 (31.4)
Valproic acid	27 (23.7)	14 (30.4)	18 (35.3)	31 (27.2)	90 (27.7)
Clobazam	35 (30.7)	9 (19.6)	15 (29.4)	28 (24.6)	87 (26.8)
Brivaracetam	30 (26.3)	9 (19.6)	11 (21.6)	28 (24.6)	78 (24.0)
Eslicarbazepine	23 (20.2)	11 (23.9)	11 (21.6)	24 (21.1)	69 (21.2)
Phenobarbital	23 (20.2)	8 (17.4)	14 (27.5)	22 (19.3)	67 (20.6)
Valproate sodium	20 (17.5)	7 (15.2)	9 (17.6)	19 (16.7)	55 (16.9)
Gabapentin	20 (17.5)	7 (15.2)	6 (11.8)	13 (11.4)	46 (14.2)
Pregabalin	18 (15.8)	8 (17.4)	3 (5.9)	15 (13.2)	44 (13.5)
Clonazepam	14 (12.3)	8 (17.4)	7 (13.7)	14 (12.3)	43 (13.2)
Retigabine	8 (7.0)	5 (10.9)	6 (11.8)	8 (7.0)	27 (8.3)

ASM, antiseizure medication.

Concomitant ASMs for Patients Enrolled in X-TOLE (Safety Population)

ASMs Taken at Time of Study Entry (Baseline ASMs) by ≥10% of Patients

ASM, n (%)	Placebo (n = 114)	XEN1101 10 mg (n = 46)	XEN1101 20 mg (n = 51)	XEN1101 25 mg (n = 114)	Total (n = 325)
Lamotrigine	33 (28.9)	14 (30.4)	16 (31.4)	39 (34.2)	102 (31.4)
Lacosamide	35 (30.7)	14 (30.4)	17 (33.3)	28 (24.6)	94 (28.9)
Brivaracetam	25 (21.9)	11 (23.9)	13 (25.5)	30 (26.3)	79 (24.3)
Clobazam	20 (17.5)	11 (23.9)	13 (25.5)	31 (27.2)	75 (23.1)
Levetiracetam	24 (21.1)	13 (28.3)	10 (19.6)	18 (15.8)	65 (20.0)
Eslicarbazepine	21 (18.4)	7 (15.2)	11 (21.6)	18 (15.8)	57 (17.5)
Carbamazepine	17 (14.9)	7 (15.2)	7 (13.7)	18 (15.8)	49 (15.1)
Oxcarbazepine	12 (10.5)	5 (10.9)	5 (9.8)	15 (13.2)	37 (11.4)
Perampanel	14 (12.3)	2 (4.3)	7 (13.7)	13 (11.4)	36 (11.1)
Zonisamide	14 (12.3)	4 (8.7)	7 (13.7)	8 (7.0)	33 (10.2)

ASM, antiseizure medication.