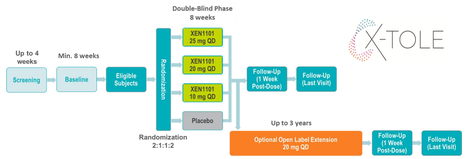
Phase 2b Efficacy and Safety of XEN1101, a Novel Potassium Channel Modulator, In Adults With Focal Epilepsy (X-TOLE)

Jacqueline French,[1] Roger Porter,[2] Emilio Perucca,[3] Martin Brodie,[4] Michael A. Rogawski,[5] Simon Pimstone,[6] Ernesto Aycardi,[6] Cynthia Harden,[6] Jenny Qian,[6] Constanza Luzon,[6] Christopher Kenney,[6] Gregory N Beatch[6]

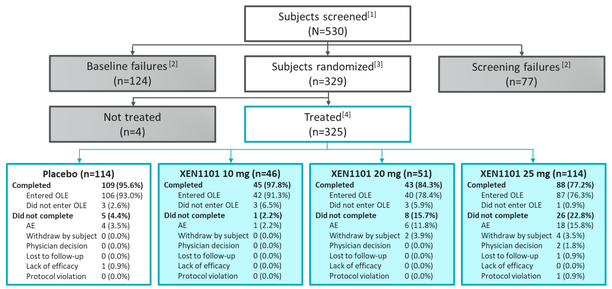
[1]New York University Comprehensive Epilepsy Center, New York, NY; [2]University of Pennsylvania, Philadelphia, PA; [3]University of Pavia, Pavia, IT; [4]University Department of Medicine and Therapeutics, Western Infirmary, Glasgow, Scotland, UK; [5] School of Medicine, University of California, Davis, Sacramento, CA; [6]Xenon Pharmaceuticals, Burnaby, BC, CA

- XEN1101 is a novel, small molecule, selective KCNQ2/3 (Kv7.2/7.3) potassium channel opener being developed for the treatment of focal onset seizures and major depressive disorder. Its pharmacokinetic properties support once daily oral dosing without the need for titration at initiation of dosing or tapering at termination of dosing. XEN1101 demonstrates higher in vitro and in vivo potency compared to the first generation Kv7.2-7.5 opener, ezogabine, and lacks the chemical properties that could form pigmented dimers.
- XEN1101 has been evaluated in Phase I clinical studies, including a companion pharmacodynamic crossover study using transcranial magnetic stimulation. These data demonstrated that dosing XEN1101 up to 25 mg QD was generally well tolerated and reduced cortical excitability, with a strong pharmacokinetic/pharmacodynamic relationship in healthy volunteers. These studies were used to inform dose selection for the recently completed Phase 2b X-TOLE study.
- X-TOLE is a Phase 2b randomized, double-blind, placebo-controlled, parallel group, dose-ranging, multicenter study with an optional 3-year open-label extension (OLE). X-TOLE evaluated clinical efficacy, safety, and tolerability of XEN1101 administered as adjunctive treatment in adults with focal onset seizures (FOS).
- Key eligibility criteria included ≥4 countable focal seizures per month, recorded on an eDiary during a planned 8-week baseline period, while receiving stable treatment with 1-3 antiseizure medications (ASMs).
- Subjects were randomized, for an 8- week double-blind phase, to one of three active treatment groups or placebo in a 2:1:1:2 ratio (XEN1101 25 mg: 20 mg: 10 mg: placebo).



PRIMARY OBJECTIVES	ENDPOINTS
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	• Severity and frequency of associated 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
SECONDAY OBJECTIVES	**ENDPOINTS**
To evaluate the 50% XEN1101 responder 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	• Clinician Global Impression of Change (CGI-C) and Patient Global Impression of Change (PGI-C) scores during the DBP

STUDY DISPOSITION: SAFETY POPULATION



Placebo (n=114)		XEN1101 10 mg (n=46)		XEN1101 20 mg (n=51)		XEN1101 25 mg (n=114)	
Completed	**109 (95.6%)**	**Completed**	**45 (97.8%)**	**Completed**	**43 (84.3%)**	**Completed**	**88 (77.2%)**
Entered OLE	106 (93.0%)	Entered OLE	42 (91.3%)	Entered OLE	40 (78.4%)	Entered OLE	87 (76.3%)
Did not enter OLE	3 (2.6%)	Did not enter OLE	3 (6.5%)	Did not enter OLE	3 (5.9%)	Did not enter OLE	1 (0.9%)
Did not complete	**5 (4.4%)**	**Did not complete**	**1 (2.2%)**	**Did not complete**	**8 (15.7%)**	**Did not complete**	**26 (22.8%)**
AE	4 (3.5%)	AE	1 (2.2%)	AE	6 (11.8%)	AE	18 (15.8%)
Withdraw by subject	0 (0.0%)	Withdraw by subject	0 (0.0%)	Withdraw by subject	2 (3.9%)	Withdraw by subject	4 (3.5%)
Physician decision	0 (0.0%)	Physician decision	0 (0.0%)	Physician decision	0 (0.0%)	Physician decision	2 (1.8%)
Lost to follow-up	0 (0.0%)	Lost to follow-up	0 (0.0%)	Lost to follow-up	0 (0.0%)	Lost to follow-up	1 (0.9%)
Lack of efficacy	1 (0.9%)	Lack of efficacy	0 (0.0%)	Lack of efficacy	0 (0.0%)	Lack of efficacy	0 (0.0%)
Protocol violation	0 (0.0%)	Protocol violation	0 (0.0%)	Protocol violation	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.

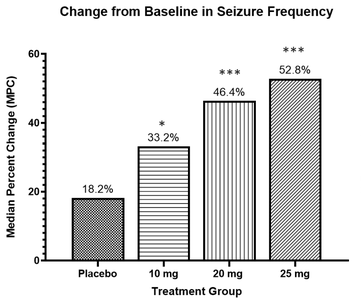
DEMOGRAPHICS AND BASELINE CHARACTERISTICS (SAFETY POPULATION)

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

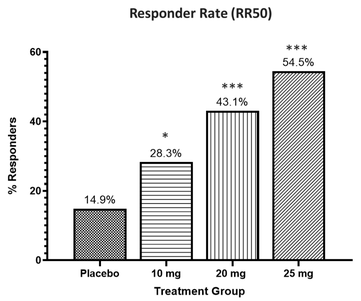
	Placebo (N=114)	XEN1101 10mg (N=46)	XEN1101 20mg (N=51)	XEN1101 25mg (N=114)	TOTAL (N=325)
Age in years, Mean (SD)	**42.9 (13.7)**	**40.0 (12.1)**	**41.7 (13.6)**	**38.7 (13.1)**	**40.8 (13.3)**
Age at study entry category					
≥ 65, n (%)	**5 (4.4)**	**2 (4.3)**	**4 (7.8)**	**1 (0.9)**	**12 (3.7)**
< 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)**
CYP3A4 Inducer Use					
No, n (%)	**45 (39.5)**	**21 (45.7)**	**22 (43.1)**	**49 (43.0)**	**137 (42.2)**
Yes, n (%)	**69 (60.5)**	**25 (54.3)**	**29 (56.9)**	**65 (57.0)**	**188 (57.8)**
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]**

Highly significant dose response for reduction in focal seizures, across primary & secondary FOS endpoints

Highly significant and dose-dependent reduction in seizures

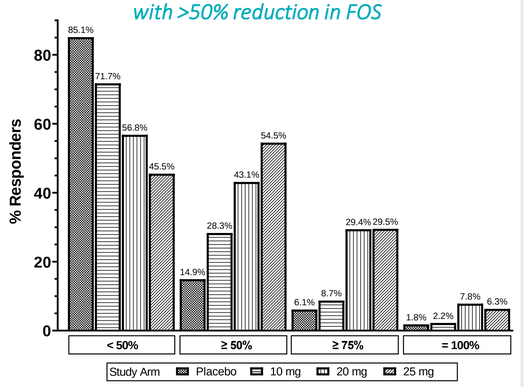


*p<0.05, ***p<0.001



*p<0.05, ***p<0.001

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

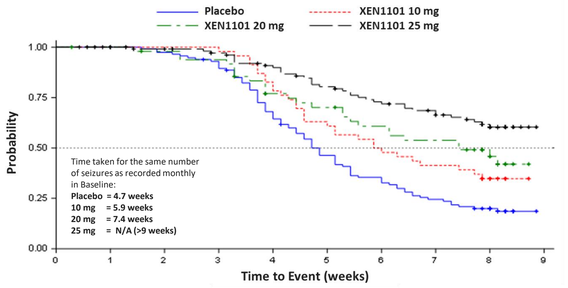


Marked reduction in FOS (MPC from baseline)

	Placebo (N=114)	XEN1101 10mg (N=46)	XEN1101 20mg (N=51)	XEN1101 25mg (N=112)
Monthly Seizure Frequency in Baseline; n	**114**	**46**	**51**	**112**
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; n	**114**	**46**	**51**	**112**
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; n	**114**	**46**	**51**	**112**
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 (2-sided)	**<.001**			

Exploratory endpoint: time to event analysis showed marked dose-dependent decrease in rate of seizure recurrence

TIME to Reach Baseline Monthly Focal Seizure Count during the DBP



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

Secondary endpoints - 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**

Safety and tolerability profile inline with commonly used ASMs

VITAL SIGNS AND OTHER SAFETY

- 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
- Mean ± SD body weight changes from baseline were 0.2±2.4 kg in placebo, 0.6 ± 2.3 kg at 10 mg, 1.6 ± 2.2 kg at 20 mg and 1.9 ± 2.9 kg at 25 mg.
  - Changes in body weight ≥7% were seen in 3 (2.6%) subjects in placebo, 2 (4.3%) at 10 mg, 2 (3.9%) at 20 mg and 15 (13.2%) at 25 mg.
- There were no signals of concern from electrocardiograms, safety labs or urinalysis
- There were no differences or signals between groups of urinary retention detected using the American Urological Association Symptoms Index

OVERALL ADVERSE EVENT PROFILE

- XEN1101 was generally well-tolerated in this study with adverse events (AEs) consistent with other commonly prescribed ASMs.
- The most common (>10%) treatment emergent adverse events across all XEN1101 dose groups were dizziness (24.6%), somnolence (15.6%) and fatigue (10.9%).
- 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%) subjects at 10 mg, 2 (3.9%) subjects at 20 mg and in 3 (2.6%) subjects at 25 mg.
- 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.
- SAE incidence was low and balanced across groups.

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

Summary of all treatment emergent adverse events (TEAEs) in the double-blind period 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)**

- 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%).

Most common treatment emergent adverse events (AEs) ≥5% in any arm:

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)

Low incidence of SAEs and balanced across treatment arms

Treatment emergent serious adverse events (SAEs) in double-blind period:

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)

CONCLUSIONS

- XEN1101 showed dose-dependent, consistent, highly statistically significant and clinically meaningful reduction in FOS across endpoints in a patient population who had failed a median of 6 ASMs and 50.8% were on 3 background ASMs.
- XEN1101 was generally well tolerated with a similar low SAE incidence (3.3%) as seen in placebo (2.6%) and no deaths in the study.
- 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%).
- There were no cardiovascular signals of concern in ECG or vitals signs.
- 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.

XENON