# The Impact of Disease Severity on Efficacy From a Phase 2b Study of XEN1101, a Novel Potassium Channel Opener, in Adults With Focal Epilepsy (X-TOLE)

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## BACKGROUND

### Introduction

- Despite the availability of several new antiseizure medications (ASMs), approximately 30% of patients still experience uncontrolled seizures. With each ASM failure, the likelihood of achieving seizure control with each subsequent ASM regimen decreases, 50.5% with the first ASM regimen, and if this fails, 11.6% with the second, and 4.1% with the third<sup>1</sup>
- XEN1101 is a novel, small molecule, selective KCNQ2/3 (K<sub>v</sub>7.2/7.3) potassium channel opener being developed for the treatment of epilepsy. In the recently completed X-TOLE Phase 2b clinical study, the clinical efficacy, safety, and tolerability of XEN1101 administered as adjunctive treatment was evaluated in adults with focal onset seizures (FOS)<sup>2</sup>
- Compared to other adult FOS clinical studies, X-TOLE included a "difficult-to-treat" patient population given the baseline seizure burden, number of prior failed ASMs, and number of concomitant ASMs during the study

### Background

- **Table 1** summarizes the combined median baseline monthly seizure frequencies and concomitant ASMs reported in select FOS clinical studies for cenobamate, brivaracetam, perampanel, lacosamide, and ezogabine. Of the studies not restricted to 1 to 2 concomitant ASMs, ~64.8% or more of subjects were on  $\leq$  2 ASMs at study start. Of the combined studies (N = 6176) with reported median baseline monthly seizure frequencies for each treatment arm, the mean and median were 10.1(±2.2) and 9.6 (min 5.5, max 16.5), respectively
- Of the reported ASMs taken prior to study start, 13.3 to 47.8% of subjects failed  $\ge 5$  ASMs that participated in brivaracetam studies,  $^{3,4,5,6,7}$  and 45.3 to 52.9% of subjects failed  $\geq$  7 ASMs in lacosamide studies<sup>8,9,10</sup>

### Table 1. Summary of Recent FOS Trials: Evaluation of Combined Baseline Seizure Frequencies and **Concomitant ASMs**

Drug	Phase (Study Years)	Total N (Population)	Baseline Monthly Seizure Frequency, Mean (SD)	Baseline Monthly Seizure Frequency, Median (Min, Max)	Allowed Concomitant ASMs	Concomitant ASMs ≤ 2, % of subjects	Concomitant ASMs = 3, % of subjects
Cenobamate <sup>11,12</sup>	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 <sup>3,4,5,6,7</sup>	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 <sup>13,14,15,16</sup>	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%
L	Phase 2 (2002-2004)	415 (Safety)	N/A	11-13***	1 to 2	100%	0%
Lacosamide <sup>8,9,10</sup>	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%
Ezogabine <sup>17,18,19</sup>	Phase 2 (<2007)	396 (ITT)	8.8 (1.1)	8.5 (7.9, 10.4)	1 to 2	99.2%***	1.0%***
	Phase 2 and 3 (2005-2008)	843 (Safety)	10.5 (1.2)	10.3 (9.3, 12.1)	1 to 3	69.8%	30.2%

\* Some additional patients received temporary treatment with a 4<sup>th</sup> antiepileptic drug.

\*\* Subset of patients used benzodiazepines as needed.

### \*\*\* As reported.

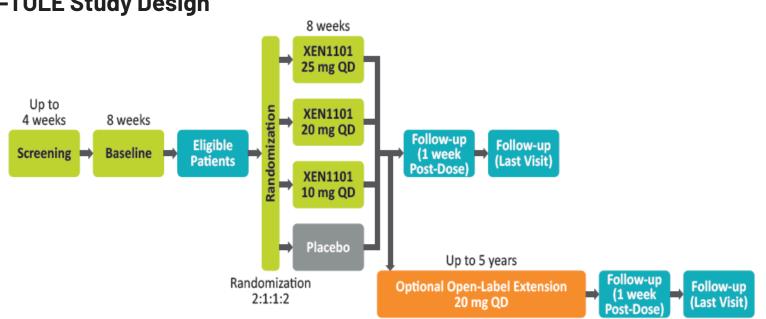
## METHODS

### **Key Inclusion Criteria**

- Patients aged 18-75 years (inclusive) with an International League Against Epilepsy [ILAE]<sup>20</sup> diagnosis of focal epilepsy ( $\geq 2$  years)
- Key eligibility criteria included  $\geq$ 4 countable focal seizures per month, recorded on an eDiary during a planned 8-week baseline period, while receiving stable treatment with 1-3 ASMs

**DISCLOSURES** Jacqueline French receives salary support from the Epilepsy Study Consortium for Aeonian/Aeovian; Alterity Therapeutics Ltd.; Baergic Bio; Beacon Biosignals, Inc.; Biogen; Biohaven Pharmaceuticals; BioMarin Pharmaceutical, Inc.; BioXcel Therapeutics; Jacqueline French receives salary support from the Epilepsy Study Consortium for Aeonian/Aeovian; Alterity Therapeutics, Inc.; BioXcel Therapeutics Ltd.; Baergic Bio; Beacon Biosignals, Inc.; BioAevian; Alterity Therapeutics, Inc.; BioXcel T Bloom Science, Inc.; BridgeBio Pharma, Inc.; Camp4 Therapeutics; Corp.; Cerebral Therapeutics; Engage Therapeutics; Corp.; Cerebral; Engage Therapeutics; Engage Therapeutics; Corp.; Cerebral; Engage Therapeutics; Corp.; Cerebral; Engage Therapeutics; Engage Therapeutics; Engage Therapeutics; Corp.; Cerebral; Engage Therapeutics; Engage Therapeutics; Engage Therapeutics; Corp.; Cerebral; Engage Therapeutics; Engage Therapeutics; Engage Therapeutics; Engage Therapeutics; Engage Therapeutics; Engage Therapeutics; Corp.; Cerebral; Engage Therapeutics; Engage Therapeuti Pharmaceuticals; Lundbeck; Marinus; Mend Neuroscience; Merck; NeuCyte, Inc.; Neuronetics, Therapeutics; Xenon Pharmaceuticals Inc.; Xeris; Zogenix; and Zynerba. 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Rogawski is a paid consultant to Xenon Pharmaceuticals Inc. Jennifer Leung, Cynthia Harden, Jenny Qian, Christopher Kenney, and Gregory N. Beatch are employees of and may own stock or stock options in Xenon Pharmaceuticals Inc.

### X-TOLE Study Design



- 25 mg treatment group

\* 8.5 was based on the average baseline seizure frequencies of cenobamate RCTs (Table 1).

## DEMOGRAPHICS

### Demographic and Baseline Characteristics (Safety Population)

- perampanel, and zonisamide

\* Valproic acid and valproate sodium combined.

### Table 2. Demographic and Baseline Characteristics

	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)
Baseline seizure frequency					
Mean (SD)	27.3 (38.5)	35.5(40.9)	29.0(42.0)	23.5(30.4)	27.4 (36.9)
Median	13.4	17.4	14.5	12.8	13.5
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					
≤3, n(%)	29(25.4)	11(23.9)	11(21.6)	31(27.2)	82(25.2)
> 3, n (%)	85(74.6)	35 (76.1)	40(78.4)	83(72.8)	243(74.8)
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]

**REFERENCES 1.** Chen Z, et al. JAMA Neurol. 2018;75(3):279-286. 2. French JA, et al. Epilepsia. 2014;55(1):57-66. 7. Klein P, et al. Epilepsia. 2015;56(12):1890-1898. 8. Ben-Menachem E, et al. Epilepsia. 2017;48(7):1308-1317. 9. Halász P, et al. Epilepsia. 2013;54(1):89-97. 4. French JA, et al. Epilepsia. 2017;48(7):1308-1317. 9. Halász P, et al. Epilepsia. 2007;48(7):1308-1317. 9. Halász P, et al. Epilepsia. 2017;56(12):1890-1898. 8. Ben-Menachem E, et al. Epilepsia. 2017;48(7):1308-1317. 9. Halász P, et al. Epilepsia. 2017;48(7):1308-1317. 9. Halász P, et al. Epilepsia. 2017;56(12):1890-1898. 8. Ben-Menachem E, et al. Epilepsia. 2017;55(12):1890-1898. 8. Ben-Menachem E, et al. Epilepsia. 2017;55(12):1890-1898. 8. Ben-Menachem E, et al. Epilepsia. 2017;55(12):1890-1898. 8. 11. Chung SS, et al. Neurology. 2020;94(22):e2311-e2322. 12. Krauss GL, et al. Lancet Neurology. 2012;78(18):1408-1415. 15. French JA, et al. Neurology. 2012;78(12):1408-1415. 15. French JA, et al. Neurology. 2012;78(12):117-125. 17. Porter RJ, et al. Neurol

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)

Sub-group analyses were performed to assess the role of disease severity in patients with differing baseline characteristics, namely baseline seizure burden, number of prior failed ASMs, and concomitant ASMs during the study. The following post hoc analyses pertain to the

• The post hoc analysis was categorized by  $\leq 8.5$  and  $> 8.5^*$  seizures per month for baseline seizure burden,  $\leq 6$  and > 6 prior failed ASMs (median), and = 3 or  $\leq 2$  concomitant ASMs (pre-specified)

• The median seizure frequency in X-TOLE was 13.5/month at baseline; 50.8% study subjects were taking 3 concomitant ASMs; and median number of ASMs failed prior to study entry was 6 (**Table 2**)

• **Table 3** summarizes the most common ASMs started and stopped prior to X-TOLE, with > 40% of subjects failing levetiracetam, carbamazepine, valproic acid\*, lacosamide, and perampanel

Most subjects were taking 2 to 3 ASMs at study entry, with 40.3% and 50.8% taking 2 and 3 ASMs respectively. The most common concomitant ASMs (**Table 4**) were lamotrigine, lacosamide, brivaracetam, clobazam, levetiracetam, eslicarbazepine, carbamazepine, oxcarbazepine,

### **Prior ASMs (Safety Population)**

Table 3. Antiseizure Medications Taken Prior to Study (Excluding Ongoing Medication)

Table 5. Antiseizure fredications Taken from to Study (Excluding ongoing fredication)						
ASM n (%)	Placebo (N = 114)	XEN1101 10mg (N = 46)	XEN1101 20mg (N = 51)	XEN1101 25mg (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)	

### Concomitant ASMs (Safety Population)

Table 4. Antiseizure Medications Taken at Time of Study Entry (Baseline ASMs) by  $\geq$  10% of Subjects

ASM n (%)	Placebo (N = 114)	XEN1101 10mg (N = 46)	XEN1101 20mg (N = 51)	XEN1101 25mg (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)

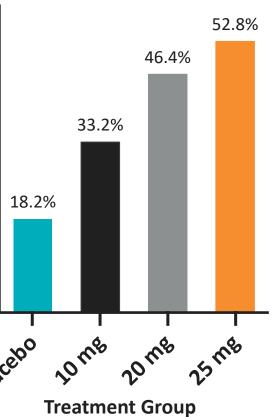
## RESULTS

### Efficacy Results: Median Percent Change (MPC) from Baseline<sup>2</sup>

 XEN1101 demonstrated a dose-dependent reduction from baseline in median monthly FOS frequency of 33.2% (P=0.035, n=46), 46.4% (P<0.001, n=51), and 52.8% (P<0.001, n=112) in the 10 mg, 20 mg, and 25 mg groups, respectively, compared to placebo (18.2%, n=114)

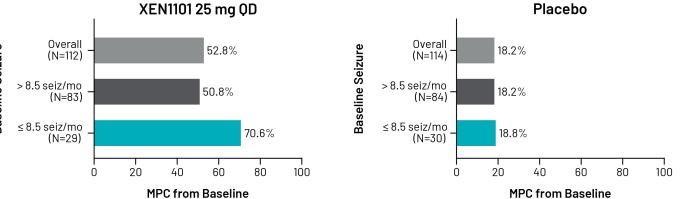
	Placebo (N=114)	XEN1101 10mg (N=46)	XEN1101 20mg (N=51)	XEN1101 25mg (N=112)	- 60 DC)
Monthly seizure frequency in baseline; n	114	46	51	112	Change (MPC) 5
Median[Q1,Q3]	13.4 [8.0, 30.1]	17.4 [8.0, 55.6]	14.5 [7.5, 36.4]	12.8 [8.4, 24.6]	98 ue 40 ·
Monthly seizure frequency in the DBP; n	114	46	51	112	
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
Percent change from baseline to the DBP; n	114	46	51	112	Ъ 20 ·
Median[01, 03]	-18.2 [-37.3, 7.0]	-33.2 [-61.8, 0.0]	-46.4 [-76.7, -14.0]	-52.8 [-80.4, -16.9]	Median
<i>P</i> -value from ranked ANCOVA model					Ě.
P-value for pairwise comparison vs. placebo (2-sided)		0.035	<0.001	<0.001	
<i>P</i> -value for primary dose response test (2-sided)	<0.001				21





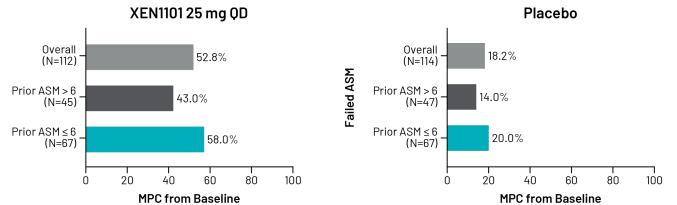
### **Baseline Seizure Sub-Group Analysis**

• Seizure reduction was 70.6% for subjects with  $\leq 8.5$  seizures/month at baseline compared to 50.8% for those with > 8.5 seizures/month



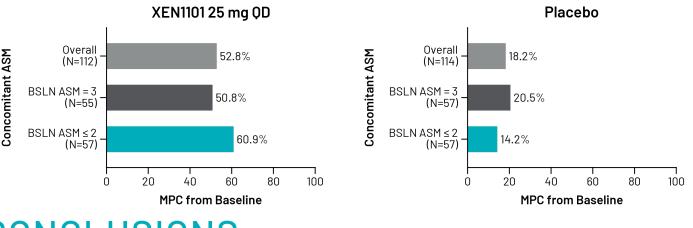
### **Prior Failed ASMs Sub-Group Analysis**

• Median monthly FOS reduction was 58.0% in subjects who failed  $\leq 6$  ASMs at baseline and 43.0% in subjects who failed > 6 ASMs



### **Concomitant ASMs Sub-Group Analysis**

Median monthly FOS reduction was 60.9% for subjects with 1-2 concomitant ASMs and 50.8% for subjects with 3 concomitant ASMs



## CONCLUSIONS

- X-TOLE met the primary and key secondary efficacy endpoints with XEN1101 demonstrating a statistically significant, dose-dependent reduction from baseline in monthly FOS frequency compared to placebo in a difficult-to-treat population
- Based on the number of concomitant ASMs, baseline seizure frequency, and number of failed ASMs, the X-TOLE study enrolled more difficult-to-treat patients than other FOS studies. In the 25 mg dose group, XEN1101 reduced seizure frequency in sub-groups of patients with  $\leq 8.5$  seizures/month, and in patients that failed  $\leq 6$ ASMs or were on 1-2 concomitant ASMs by 70.6%, 58.0% and 60.9%, respectively, compared with placebo (18.8%, 20.0% and 14.2%, respectively)
- These post hoc analyses suggest that efficacy may be more robust in patients with less severe disease, which mirrors likely use of XEN1101 if approved



