Azetukalner, a Novel, Potent K_V7 Potassium Channel Opener in Development for the Treatment of Focal Onset Seizures, Primary Generalized Tonic-Clonic Seizures, and Major Depressive Disorder

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ABOUT XENON

- Xenon Pharmaceuticals is a neuroscience-focused biopharmaceutical company committed to discovering, developing, and commercializing innovative therapeutics to improve the lives of people living with neurological and psychiatric disorders
- As a leader in small molecule, ion channel drug development, Xenon is advancing a novel product pipeline to address areas of high unmet medical need, including epilepsy and depression

XENON'S PIPELINE

- Xenon is focused on advancing our ion channel pipeline with candidates targeting K_V7, $Na_V1.1$, and $Na_V1.7$ ion channels. Our clinical stage candidate azetukalner is being developed for the treatment of focal onset seizures (FOS), primary generalized tonic-clonic seizures (PGTCS), moderate to severe major depressive disorder (MDD), and potentially other neurological disorders[1]

Figure 1. Product Pipeline

	Clinical Trial/Partner	Preclinical	Phase 1	Phase 2	Phase 3
Azetukalner (Potassium Channel Opener)					
Epilepsy: Focal Onset Seizures (FOS)	X-TOLE2				
Epilepsy: Focal Onset Seizures (FOS)	X-TOLE3				
Epilepsy: Primary Generalized Tonic-Clonic Seizures (PGTCS)	X-ACKT				
Major Depressive Disorder (MDD)	X-NOVA2				
Major Depressive Disorder (MDD)[a]	Mount Sinai				
Preclinical Ion Channel Modulators					
K_V7 Potassium Channel Openers *(Epilepsy, pain, and neuropsychiatric indications)*					
$Na_V1.7$ Sodium Channel Inhibitors *(Pain indications)*					
$Na_V1.1$ Sodium Channel Openers *(Dravet Syndrome)*					
NBI-[a]355 (Partnered Program)					
$Na_V1.2/1.6$ Inhibitor (Epilepsy)	Neurocrine Biosciences				

[a]Investigator-sponsored Phase 2 non-registrational proof-of-concept study.
This chart displays pipeline drug candidates currently undergoing clinical testing in a variety of disease indications. The safety and efficacy of these investigational drug candidates have not been fully evaluated, and they have not yet been approved for use by any regulatory authorities.
FOS, focal onset seizure; MDD, major depressive disorder; PGTCS, primary generalized tonic-clonic seizures.

OVERVIEW OF AZETUKALNER

- Azetukalner is a novel, potent K_V7 potassium channel opener
- Voltage-gated, KCNQ-type potassium channels modulate cell membrane excitability, and K_V7 channel openers induce a hyperpolarized resting membrane potential that reduces action potential spiking and cortical/corticospinal excitability[2]

SUMMARY

- As of the last safety data cut (October 7, 2024), >600 participant-years of safety have been generated through the ongoing OLE study in FOS
- Current and future studies are designed to further evaluate the therapeutic potential and safety of azetukalner for the treatment of FOS (X-TOLE2/X-TOLE3), PGTCS (X-ACKT), and MDD (X-NOVA2)
- Azetukalner has a novel mechanism of action, and it represents the most advanced K_V7 potassium channel opener in clinical development for multiple indications

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DISCLOSURE Aleks Skuban is an employee of and owns stock in Xenon Pharmaceuticals Inc.

REFERENCES **1.** Bialer M, et al. *Epilepsia*. 2022;63(11):2883-2910. **2.** Khan R, et al. *CNS Neurol Disord Drug Targets*. 2024;23(1):67-87. **3.** French JA, et al. *JAMA Neurol*. 2023;80(11):1145-1154. **4.** French J, et al. Long-term safety and efficacy of azetukiner, a novel. potent K_V7 potassium channel opener in adults with focal epilepsy: update from the ongoing 7-year open-label extension of X-TOLE. Presented at: American Epilepsy Society Annual Meeting: December 6-10, 2024; Los Angeles, CA. **5.** ClinicalTrials.gov. A randomized study of XEN1101 versus placebo in focal-onset seizures(X-TOLE2). https://clinicaltrials.gov/study/NCT05614063. **6.** ClinicalTrials.gov. A randomized study of XEN1101 versus placebo in focal-onset seizures(X-TOLE3). https://clinicaltrials.gov/study/NCT05716100. **7.** ClinicalTrials.gov. A study to evaluate XEN1101 as adjunctive therapy in primary generalized tonic-clonic seizures(X-ACKT). https://clinicaltrials.gov/study/NCT05667142. **8.** Butterfield NM, et al. Efficacy and safety of azetukalner(XEN1101), a novel, K_V7 potassium channel opener in adults with moderate to severe major depressive disorder: results from the phase 2, proof-of-concept X-NOVA study [poster W67]. Presented at: American Society of Clinical Psychopharmacology Annual Meeting; May 28–31, 2024; Miami, FL. **9.** Montgomery SA and Asberg M. *Br J Psychiatry*. 1979;134:382-389. **10.** Duru G and Fantino B. *Curr Med Res Opin*. 2008;24(5):1329-1335. **11.** Hamilton M. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56-62. **12.** Snaith RP, et al. *Br J Psychiatry*. 1995;167(1):99-103. **13.** ClinicalTrials.gov. A randomized study of azetukalner versus placebo in major depressive disorder (X-NOVA2). https://clinicaltrials.gov/study/NCT06775379.

X-TOLE: COMPLETED PHASE 2B TRIAL OF AZETUKALNER IN PARTICIPANTS WITH FOS

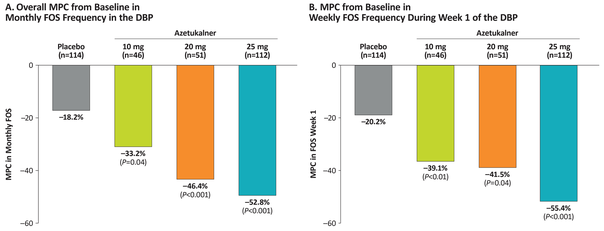
X-TOLE Study Design[3]

- X-TOLE (NCT03796962) evaluated the clinical efficacy, safety, and tolerability of azetukalner, administered as a once-daily (QD) capsule with food with no titration period as adjunctive treatment in adults with FOS who experienced ≥4 countable focal seizures per month (recorded in an eDiary during a planned, 8-week baseline period) while receiving stable treatment with 1–3 antiseizure medications (ASMs)
- After completion of the double-blind period (DBP), participants were offered the option of entering a 7-year open-label extension (OLE) in which participants received open-label azetukalner at a dose of 20 mg QD with food with no titration period

Results of the X-TOLE Study for FOS[3]

- X-TOLE met the primary and key secondary efficacy endpoints with azetukalner, with a statistically significant reduction from baseline in monthly and week 1 FOS frequency compared with placebo (**Figure 2**)

Figure 2. Reduction in FOS Frequency



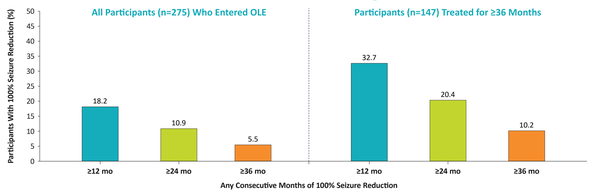
DBP, double-blind period; FOS, focal onset seizure; MPC, median percentage change. *P* value vs placebo from a post hoc pairwise comparison. Azetukalner was administered as a once-daily capsule with food with no titration.

- The most common (>10%) treatment-emergent adverse events (TEAEs) across all the azetukalner dose groups during the DBP were dizziness (24.6%), somnolence (15.6%), and fatigue (10.9%)

ONGOING 7-YEAR OLE[4]

- At the last safety data cut (October 7, 2024), 182 participants were treated in the OLE for ≥12 months, 165 participants were treated for ≥24 months, and 143 participants were treated for ≥36 months
- During OLE study months 24–36, there was a sustained monthly reduction in seizure frequency (77%–87% median percentage change [MPC]) from DBP baseline
- For all participants who entered the OLE, 18.2% (50/275) achieved 100% seizure reduction for any consecutive ≥12-month period; 32.7% (48/147) of participants who were treated for ≥36 months in the OLE achieved 100% seizure reduction for any consecutive ≥12-month period (**Figure 3**)

Figure 3. Percentage of Participants Who Achieved Any Consecutive ≥12, ≥24, and ≥36 Months of 100% Seizure Reduction During the OLE



DBP, double-blind period; OLE, open-label extension. Following the DBP, all participants received azetukalner 20 mg at the start of the OLE as a once-daily capsule with food with no titration.

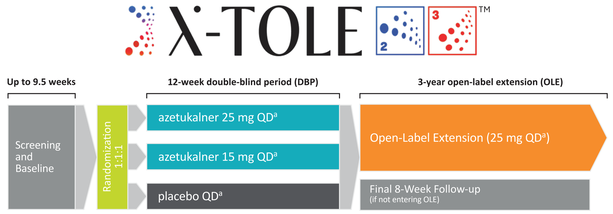
- At the last safety data cut (October 7, 2024), azetukalner 20 mg QD was generally well tolerated, and the safety profile observed was similar to that of the DBP. The most common (>10%) TEAEs during the OLE period were dizziness (23.3%), headache (17.5%), coronavirus infection (17.1%), somnolence (16.0%), fall (13.5%), weight increased (10.9%), and memory impairment (10.2%)

X-TOLE2 AND X-TOLE3: PHASE 3 TRIALS OF AZETUKALNER IN PARTICIPANTS WITH FOS

X-TOLE2 and X-TOLE3 Study Design[5,6]

- X-TOLE2 (NCT05614063) and X-TOLE3 (NCT05716100) are identical Phase 3, multicenter, randomized, double-blind, placebo-controlled trials designed to evaluate the clinical efficacy, safety, and tolerability of azetukalner as adjunctive treatment in adults aged ≥18 years diagnosed with FOS and taking 1–3 ASMs
- Approximately 360 eligible participants will be randomized per trial (**Figure 4**)
- Upon completion of the DBP, eligible participants may enter an OLE study for up to 3 years
- X-TOLE2 and X-TOLE3 are currently enrolling participants

Figure 4. X-TOLE2 and X-TOLE3 Study Design



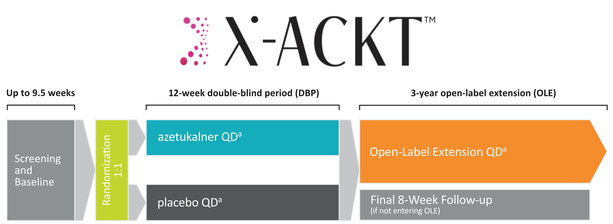
[a]Administered as a once-daily capsule with food with no titration period.
QD, once daily.

X-ACKT: PHASE 3 TRIAL OF AZETUKALNER IN PARTICIPANTS WITH PGTCS

X-ACKT Study Design[7]

- X-ACKT (NCT05667142) is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the pharmacokinetics, safety, and efficacy of azetukalner as adjunctive treatment in participants aged ≥12 years with a seizure frequency of ≥3 PGTCS during the last 8 weeks of the baseline period and taking 1–3 ASMs
- Approximately 160 eligible participants will be randomized (**Figure 5**)
- On completion of the DBP, eligible participants may enter an OLE study for up to 3 years

Figure 5. X-ACKT Study Design



[a]Administered as a once-daily capsule with food with no titration period. Participants aged ≥12 years and <18 years will receive either azetukalner 15 mg, azetukalner 25 mg, or placebo; participants aged ≥18 years will receive either azetukalner 25 mg or placebo. There is no placebo dose in the OLE.
QD, once daily.

- X-ACKT is currently enrolling participants
- The primary efficacy endpoints for XTOLE 2/3 and X-ACKT include MPC in monthly seizure frequency from baseline through the DBP (US Food and Drug Administration) or proportion of participants experiencing ≥50% reduction in monthly seizure frequency from baseline through the DBP (European Medicines Agency)

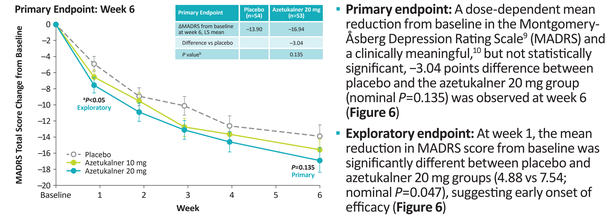
X-NOVA: COMPLETED PHASE 2 PROOF-OF-CONCEPT TRIAL OF AZETUKALNER IN PARTICIPANTS WITH MDD

X-NOVA Study Design[8]

- X-NOVA (NCT05376150) evaluated the efficacy and safety of azetukalner 10 and 20 mg taken QD with food with no titration period in adults aged 18–65 years with moderate to severe MDD and anhedonia

Results of the X-NOVA Study for MDD[8]

Figure 6. Change in MADRS Total Score From Baseline (mITT Population per Week 1)



Primary Endpoint	Placebo (n=54)	Azetukalner 20 mg (n=53)
ΔMADRS from baseline at week 6, LS mean	−13.90	−16.94
Difference vs placebo		−3.04
P value[a]		0.135

[a]Azetukalner 20 mg vs placebo, nominal *P*<0.05. [b]All *P* values are nominal.
The mITT population consists of all randomized participants who receive ≥1 dose of study treatment and had ≥1 postrandomization MADRS. mITT population per week 1 treatment represents 2 participants in 20 mg group dose reduced to the 10 mg group during week 1.
Graph shows LS mean (SEM).
LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; mITT, modified intent-to-treat.

- **Primary endpoint:** A dose-dependent mean reduction from baseline in the Montgomery-Åsberg Depression Rating Scale[9] (MADRS) and a clinically meaningful,[10] but not statistically significant, –3.04 points difference between placebo and the azetukalner 20 mg group (nominal *P*=0.135) was observed at week 6 (**Figure 6**)
- **Exploratory endpoint:** At week 1, the mean reduction in MADRS score from baseline was significantly different between placebo and azetukalner 20 mg groups (4.88 vs 7.54; nominal *P*=0.047), suggesting early onset of efficacy (**Figure 6**)

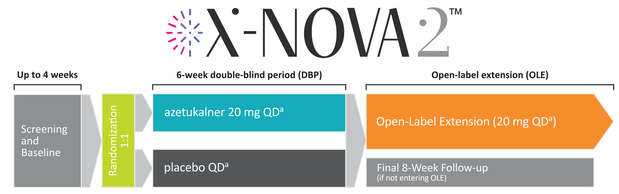
- The LS mean reductions in the Hamilton Depression Rating Scale, 17-Item[11] (HAMD-17) score from baseline to week 6 was significantly different between placebo and azetukalner 20 mg groups (10.2 vs 13.3; difference –3.1, nominal *P*=0.042 [exploratory endpoint])
- The mean reduction from baseline to week 6 in Snaith-Hamilton Pleasure Scale[12] score measuring anhedonia, a key secondary endpoint, was significantly different between placebo and azetukalner 20 mg groups (5.30 vs 7.77; difference –2.46, nominal *P*=0.046)
- Azetukalner was generally well tolerated, with no serious AEs reported in the treatment groups. The incidence of TEAEs was 52% and 66% in the 10 mg and 20 mg groups, respectively, compared with placebo (60%)
  - The most commonly reported TEAEs (>10%) in the azetukalner 20 mg group were dizziness (17.9%) and somnolence (10.7%)
- Azetukalner was not associated with notable weight gain, a mean (SD) gain of 0.84 kg (2.3) from baseline reported overall in azetukalner-treated participants
- There were no participant reports of notable sexual dysfunction; 1 participant (0.9%) of all azetukalner-treated participants reported a TEAE of mild decreased libido

X-NOVA2: PHASE 3 TRIAL OF AZETUKALNER IN PARTICIPANTS WITH MDD

X-NOVA2 Study Design[13]

- X-NOVA2 (NCT06775379) is the first of the 3 MDD Phase 3 clinical trials to evaluate the clinical efficacy, safety, and tolerability of 20 mg azetukalner as a monotherapy in adult participants diagnosed with MDD
- Approximately 450 eligible participants will be randomized (**Figure 7**), and the trial is currently enrolling participants
- The primary efficacy endpoint for X-NOVA2 is the change from baseline in the HAM-D17 score at week 6

Figure 7. X-NOVA2 Study Design



[a]Administered as a once-daily capsule with food with no titration period.
QD, once daily.

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