Results From the Phase 3 X-TOLE2 Study Evaluating Azetukalner, a Novel, Potent K_V7 Channel Opener, in Adults With Focal Onset Seizures (FOS)

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INTRODUCTION

- Azetukalner (AZK) is a novel, potent K_V7 channel opener being developed for the treatment of focal onset seizures (FOS), primary generalized tonic-clonic seizures, major depressive disorder, and bipolar depression[1-7]
- In the completed phase 2b X-TOLE study (NCT03796962), AZK demonstrated dose-dependent, statistically significant seizure frequency reductions and was generally well tolerated[8]
- Long-term efficacy and safety of AZK is being evaluated in the ongoing 7-year X-TOLE open-label extension (OLE) study[9]
- X-TOLE2 (NCT05614063) was a phase 3, multicenter, randomized, double-blind, placebo-controlled study evaluating the clinical efficacy, safety, and tolerability of AZK as adjunctive treatment in adults with FOS
- Here we report initial findings from the X-TOLE2 study (data cutoff: February 26, 2026), which, alongside the results from X-TOLE, will support the planned New Drug Application for AZK in FOS

METHODS

- Eligible adults taking 1 to 3 antiseizure medications (ASMs) were randomized 1:1:1 to receive AZK (15 or 25 mg) or placebo (PBO) with food once daily (QD) for 12 weeks with no titration period (**Figure 1; Table 1**)
  - After the double-blind period (DBP), eligible participants were offered the option of entering a 6-year OLE

Figure 1. X-TOLE2 Study Design

[a]Administered as a once-daily capsule with food with no titration period. [b]NCT05718817; patients who successfully completed the DBP with ≥80% compliance with study medication were eligible to enter the OLE.
Azetukalner is an investigational product and has not been approved by the FDA or other regulatory bodies.
AZK, azetukalner; DBP, double-blind period; FDA, US Food and Drug Administration; OLE, open-label extension; PBO, placebo; QD, once daily.

Table 1. X-TOLE2 DBP Eligibility Criteria

Select Inclusion Criteria
• Age ≥18 years
• Diagnosis (≥2 years) of focal epilepsy according to the International League Against Epilepsy 2017 classification criteria
• Receiving stable treatment with 1 to 3 ASMs for ≥1 month prior to screening and during baseline/DBP
• Countable seizure frequency (over 8-week baseline period) of ≥4 focal seizures/month on average, recorded in an eDiary

ASM, antiseizure medication; DBP, double-blind period.

Select Efficacy Endpoints (AZK vs PBO)

- *Primary endpoint:*
  - Median percent change (MPC) in monthly (28 days) FOS frequency from baseline through the DBP
- *Key secondary endpoints*:
  - Proportion of participants with ≥50% reduction in monthly (28 days) FOS frequency from baseline through the DBP
  - MPC in weekly (7 days) FOS frequency from baseline through week 1
  - Proportion of participants scoring "much improved" or better on the Patient Global Impression of Change (PGI-C) at week 12
- *Other endpoints*:
  - MPC in weekly (7 days) FOS frequency for each week of the DBP
  - Proportion of participants with ≥75%, ≥90%, and 100% reduction in 28-day FOS frequency from baseline through DBP
  - Proportion of participants scoring "much improved" or better on the Clinical Global Impression of Change (CGI-C) at week 12

Safety Endpoints

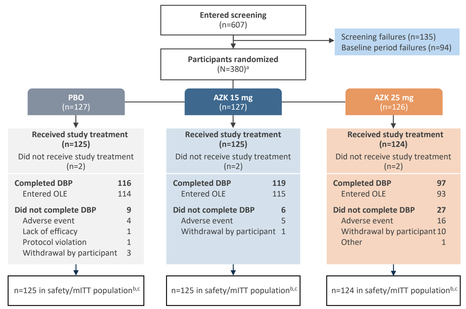
- Severity and frequency of treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs)

RESULTS

Participants

- A total of 380 participants were randomized; 374 participants received PBO or treatment (PBO [n=125], AZK 15 mg [n=125], AZK 25 mg [n=124]), and 97% of participants completing the DBP entered the OLE (**Figure 2**)
- Baseline demographic and clinical characteristics were generally comparable across groups (**Table 2**)
  - Participants had highly treatment-resistant epilepsy, with a median of 5 prior ASMs, a median baseline seizure frequency of 12.75 per month, and 51.3% using 3 concomitant ASMs

Figure 2. X-TOLE2 Study Disposition



[a]Two participants did not meet randomization eligibility criteria but were randomized. [b]Safety population defined as all randomized participants who received ≥1 dose of study treatment. [c]mITT population defined as all randomized participants who received ≥1 dose of study treatment during the DBP.
AZK, azetukalner; DBP, double-blind period; mITT, modified intent-to-treat; OLE, open-label extension; PBO, placebo.

Table 2. Baseline Demographic and Clinical Characteristics

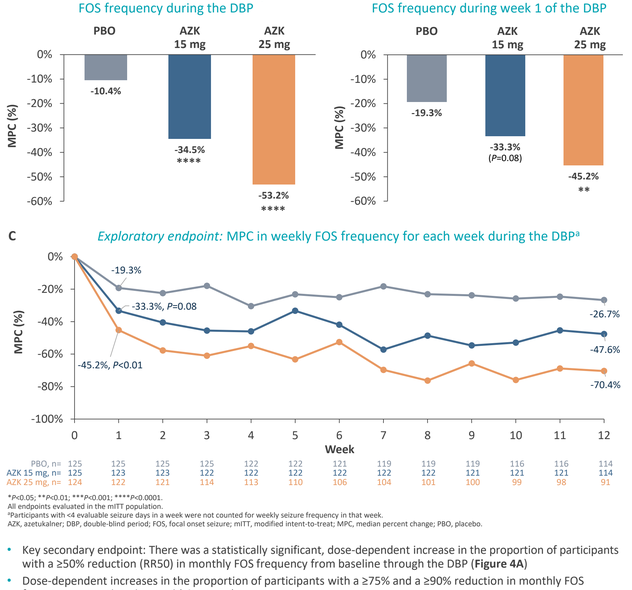
Characteristics	PBO (n=125)	AZK 15 mg (n=125)	AZK 25 mg (n=124)	Overall (n=374)
Age, mean (SD), years	39.9 (12.4)	38.3 (11.9)	41.8 (14.3)	40.0 (12.9)
Age at study entry category, n (%)				
<65 years	122 (97.6)	121 (96.8)	117 (94.4)	360 (96.3)
≥65 years	3 (2.4)	4 (3.2)	7 (5.6)	14 (3.7)
Sex, n (%)				
Female	69 (55.2)	62 (49.6)	59 (47.6)	190 (50.8)
Male	56 (44.8)	63 (50.4)	65 (52.4)	184 (49.2)
Region, n (%)				
North America	54 (43.2)	52 (41.6)	52 (41.9)	158 (42.2)
Ex-North America	71 (56.8)	73 (58.4)	72 (58.1)	216 (57.8)
BMI, mean (SD), kg/m²	26.1 (5.5)	27.0 (6.0)	27.3 (5.5)	26.8 (5.7)
Age at epilepsy onset, mean (SD), years	14.9 (13.1)	16.2 (12.4)	16.6 (14.0)	15.9 (13.2)
Duration of epilepsy (years)				
Mean (SD)	25.96 (13.66)	23.12 (13.19)	26.18 (14.30)	25.09 (13.75)
Baseline seizure frequency (28-day FOS)				
Median (IQR)	12.50 (7.21, 39.50)	12.50 (7.11, 28.47)	14.34 (8.13, 36.44)	12.75 (7.56, 32.97)
Participants taking concomitant ASM, n (%)				
1	13 (10.4)	15 (12.0)	10 (8.1)	38 (10.2)
2	43 (34.4)	49 (39.2)	52 (41.9)	144 (38.5)
3	69 (55.2)	61 (48.8)	62 (50.0)	192 (51.3)
ASMs tried and discontinued before study entry, n				
Median (IQR)	5.0 (3.0, 9.0)	5.0 (3.0, 8.0)	6.0 (3.0, 8.0)	5.0 (3.0, 8.0)
CYP3A4 inducer ASM use, n (%)				
No	38 (30.4)	35 (28.0)	44 (35.5)	117 (31.3)
Yes	87 (69.6)	90 (72.0)	80 (64.5)	257 (68.7)

Evaluated in the safety population.
ASM, antiseizure medication; AZK, azetukalner; BMI, body mass index; CYP3A4, cytochrome P450 3A4; FOS, focal onset seizure; IQR, interquartile range; PBO, placebo; SD, standard deviation.

Efficacy

- Statistically significant, dose-dependent reductions in MPC in monthly FOS frequency from baseline were seen over the 12-week DBP, AZK versus PBO (**Figure 3A**)
- Dose-dependent reductions in MPC in weekly FOS frequency were observed from baseline to week 1, AZK versus PBO (**Figure 3B**)
- Early dose-dependent reductions in weekly FOS frequency increased over time during the 12-week DBP with AZK 15 mg and 25 mg (**Figure 3C**)

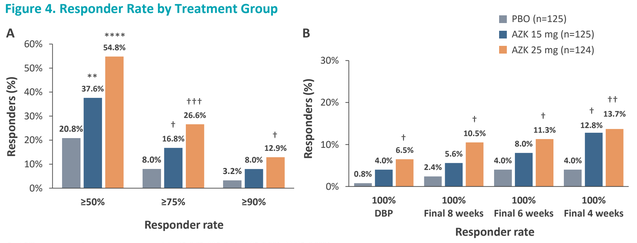
Figure 3. FOS Frequency During the DBP



*P<0.05; **P<0.01; ***P<0.001; ****P<0.0001.
All endpoints evaluated in the mITT population.
[a]Participants with ≤4 evaluable seizure days in a week were not counted for weekly seizure frequency in that week.
AZK, azetukalner; DBP, double-blind period; FOS, focal onset seizure; mITT, modified intent-to-treat; MPC, median percent change; PBO, placebo.

- Key secondary endpoint: There was a statistically significant, dose-dependent increase in the proportion of participants with a ≥50% reduction (RR50) in monthly FOS frequency from baseline through the DBP (**Figure 4A**)
- Dose-dependent increases in the proportion of participants with a ≥75% and a ≥90% reduction in monthly FOS frequency were also observed (**Figure 4A**)
- A 100% reduction in monthly FOS frequency was attained by a greater proportion of participants with AZK 25 mg than with PBO (nominal *P*<0.05; **Figure 4B**)
  - Post hoc analysis of the modified intent-to-treat (mITT) population showed that a greater proportion of participants achieved seizure freedom over time with AZK in the final 8, 6, and 4 weeks of the DBP (nominal *P*<0.05 vs PBO)

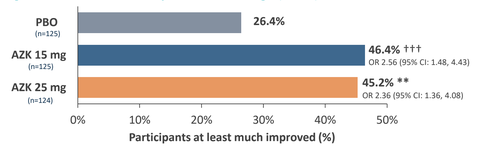
Figure 4. Responder Rate by Treatment Group



For ≥50% responder rate (key secondary endpoint): *P<0.05; **P<0.01; ***P<0.001; ****P<0.0001.
For ≥75%/≥90%/100% responder rates (exploratory endpoints), *P* values are nominal: †*P*<0.05; ††*P*<0.01 †††*P*<0.001.
Proportion of participants experiencing ≥50%/≥75%/≥90%/100% reduction in monthly FOS frequency in the mITT population.
AZK, azetukalner; DBP, double-blind period; FOS, focal onset seizure; mITT, modified intent-to-treat; PBO, placebo.

- Statistically significant improvement in PGI-C was seen with AZK 25 mg versus PBO; improvement was also seen with AZK 15 mg (**Figure 5**)
  - Improvements with AZK were also seen in CGI-C (PBO, 23.1%; AZK 15 mg, 37.7%; AZK 25 mg, 38.5%; both nominal *P*<0.05 vs PBO)

Figure 5. Patient Global Impression of Change (PGI-C) at Week 12



**P<0.01; †††P<0.001 (nominal)[a]
PGI-C is a key secondary endpoint. PGI-C change is defined as participants experiencing at least much improved (ie, "much improved" and "very much improved") at week 12. PGI-C response at week 12 evaluated in the mITT population.
[a]*P* value associated with PGI-C AZK 15 mg dose is nominal due to statistical hierarchy.
AZK, azetukalner; CI, confidence interval; mITT, modified intent-to-treat; OR, odds ratio; PBO, placebo.

Safety

- AZK was generally well tolerated with a dose-dependent incidence of TEAEs consistent with the safety profile observed in X-TOLE DBP[8] (**Table 3**)
  - The most common TEAEs across all AZK groups included dizziness, somnolence, headache, and fatigue
- The most common TEAEs leading to permanent treatment discontinuation across AZK groups were dizziness (3.2%), headache (1.6%), fatigue (1.6%), gait disturbance (1.2%), coordination abnormal (1.2%), and speech disorder (1.2%)
  - No single TEAE led to permanent treatment discontinuation in >5% of participants
- Four nonserious TEAEs of urinary retention events were reported: 1 participant in the PBO group, 1 in the AZK 15 mg group, and 2 in the AZK 25 mg group (no dose reduction required)
  - The 1 AZK 15 mg participant was hospitalized for acute psychosis, which included catheterization and discontinuation of AZK; both the event of psychosis and urinary retention resolved thereafter
- No notable weight gain, severe allergic rashes, retinal pigment epithelium or macular abnormalities, or notable cardiovascular adverse events occurred during the DBP
- The incidence of TESAEs was low and similar across groups (**Table 3**)
  - TESAEs reported in >1 participant were dysarthria (n=2), tremor (n=2), confusional state (n=2), and fall (n=2); all occurred in the AZK 25 mg group

Table 3. TEAEs During the X-TOLE2 DBP

Summary of TEAEs, n (%)	PBO (n=125)	AZK 15 mg (n=125)	AZK 25 mg (n=124)	AZK any dose (n=249)
At least 1 TEAE	78 (62.4)	84 (67.2)	102 (82.3)	186 (74.7)
At least 1 TESAE	3 (2.4)	4 (3.2)	7 (5.6)	11 (4.4)
At least 1 TEAE leading to permanent treatment discontinuation	4 (3.2)	6 (4.8)	18 (14.5)	24 (9.6)
Any TEAE leading to death	0	0	0	0
Most common TEAEs (≥5% in any treatment group), n (%)				
Nervous system disorders	**32 (25.6)**	**37 (29.6)**	**73 (58.9)**	**110 (44.2)**
Dizziness	4 (3.2)	12 (9.6)	39 (31.5)	51 (20.5)
Headache	8 (6.4)	8 (6.4)	14 (11.3)	22 (8.8)
Somnolence	9 (7.2)	10 (8.0)	12 (9.7)	22 (8.8)
Tremor	2 (1.6)	2 (1.6)	15 (12.1)	17 (6.8)
Aphasia	0	3 (2.4)	12 (9.7)	15 (6.0)
Balance disorder	2 (1.6)	1 (0.8)	8 (6.5)	9 (3.6)
Dysarthria	0	0	8 (6.5)	8 (3.2)
Psychiatric disorders	**15 (12.0)**	**16 (12.8)**	**31 (25.0)**	**47 (18.9)**
Confusional state	1 (0.8)	0	13 (10.5)	13 (5.2)
General disorders and administration site conditions	**13 (10.4)**	**11 (8.8)**	**27 (21.8)**	**38 (15.3)**
Fatigue	8 (6.4)	5 (4.0)	14 (11.3)	19 (7.6)
Gait disturbance	0	2 (1.6)	12 (9.7)	14 (5.6)
Gastrointestinal disorders	**19 (15.2)**	**14 (11.2)**	**22 (17.7)**	**36 (14.5)**
Constipation	1 (0.8)	4 (3.2)	8 (6.5)	12 (4.8)
Eye disorders	**9 (7.2)**	**6 (4.8)**	**24 (19.4)**	**30 (12.0)**
Vision blurred	4 (3.2)	2 (1.6)	10 (8.1)	12 (4.8)
Diplopia	1 (0.8)	0	8 (6.5)	8 (3.2)
Injury, poisoning and procedural complications	**18 (14.4)**	**13 (10.4)**	**11 (8.9)**	**24 (9.6)**
Fall	5 (4.0)	6 (4.8)	9 (7.3)	15 (6.0)
Renal and urinary disorders	**4 (3.2)**	**6 (4.8)**	**18 (14.5)**	**24 (9.6)**
Pollakiuria	1 (0.8)	0	7 (5.6)	7 (2.8)

AZK, azetukalner; DBP, double-blind period; PBO, placebo; TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

CONCLUSIONS

- AZK treatment resulted in a statistically significant, dose-dependent reduction from baseline in median monthly FOS frequency over the 12-week treatment period versus PBO
- AZK treatment showed a statistically significant, dose-dependent increase in number of responders, with ≥50% reduction in monthly FOS frequency for AZK versus PBO
- Rapid onset of efficacy was seen with both AZK 15 and 25 mg, with statistically significant reduction in weekly FOS frequency during week 1 for AZK 25 mg versus PBO
- Statistically significant improvement in PGI-C was seen with AZK 25 mg versus PBO; improvements were also seen in PGI-C with AZK 15 mg, and in CGI-C with both AZK doses (nominal *P* values)
- AZK safety findings were consistent with the phase 2b X-TOLE study[8]; no new safety signals were identified, and the benefit-risk profile remains favorable
- X-TOLE2 results will support the regulatory submission of AZK in FOS and could mark the next generation of ASMs available to people living with epilepsy

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DISCLOSURES:

Jacqueline A. French, W. Curt LaFrance, Jr, Philippe Ryvlin, Eugen Trinka, Vicente Villanueva, and Robert Wechsler are members of the X-TOLE2 Steering Committee**. Jacqueline A. French** has numerous relationships on behalf of the Epilepsy Study Consortium with various commercial and academic entities (consulting, salary support, research support, travel reimbursement, or served on the editorial board), including Xenon Pharmaceuticals Inc. She receives salary support from the Epilepsy Study Consortium and no other income from these relationships. **W. Curt LaFrance, Jr** has received personal compensation for serving as an expert witness for medicolegal work, and has received author and editor publishing royalties from a publication relating to healthcare. His institution has received research support from the US Department of Defense. **Philippe Ryvlin** has served on an advisory board for UCB. **Eugen Trinka** received personal fees from EVER Pharma, Marinus, Arvelle, Angelini, Argenx, Medtronic, Biocodex, Bial-Portela & Ca, NewBridge, GL Pharma, GlaxoSmithKline, Boehringer Ingelheim, LivaNova, Eisai, Epilog, UCB, Biogen, Sanofi, Jazz Pharmaceuticals, and Actavis, and his institution received grants from Biogen, UCB, Eisai, Red Bull, Merck, Bayer, the European Union and FWF Österreichischer Fond zur Wissenschaftsforderung, Bundesministerium für Wissenschaft und Forschung, and Jubiläumsfond der Österreichischen Nationalbank. **Vicente Villanueva** has participated in advisory boards and symposia organized by Angelini, Bial, Biocodex, Eisai, Jazz Pharmaceuticals, Novartis, Paladin, Takeda, MD, and Xenon. **Robert Wechsler** has been a clinical trial investigator for Aquestive, Cerevel, Eisai, Eliem, Engage Pharmaceuticals, Epalex, Equilibre, Greenwich Biosciences, Jazz Pharmaceuticals, Otsuka, Receptor Neuroscience, SK Life Science, Third Rock, UCB, Xenon, and Zogenix; has served on advisory boards and/or carried out consulting work for Aquestive, Cerevel, Eisai, Engage Pharmaceuticals, Engrail, Greenwich Biosciences, Jazz Pharmaceuticals, Novella, Otsuka, SK Life Science, and UCB Pharmaceuticals; has received speaker bureau honoraria for Aquestive, Eisai, Jazz Pharmaceuticals, Neurelis, SK Life Science, and UCB; has pay-for-call arrangements with St. Luke's Health System in Boise, ID; has served as the medical director of the Epilepsy Center at St. Luke's Health System in Boise, ID, and as the president of the Epilepsy Foundation of Idaho; and is a member of the Epilepsy Study Consortium and the Executive Committee of the Consortium of Private Epilepsy Centers. **Gregory N. Beatch, Monica B. Dhakar, Peter B. Forgacs, Constanza Luzon Rosenblut, Joseph W. McIntosh, Rostam Namdari, Jenny Qian, and Christopher Kenney** are employees of and own stock or stock options in Xenon Pharmaceuticals Inc.

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