Mechanistic Characterization of Azetukalner (AZK): K_V7 Binding, Enhanced Channel Opening, and Rational Polytherapy Potential in Epilepsy

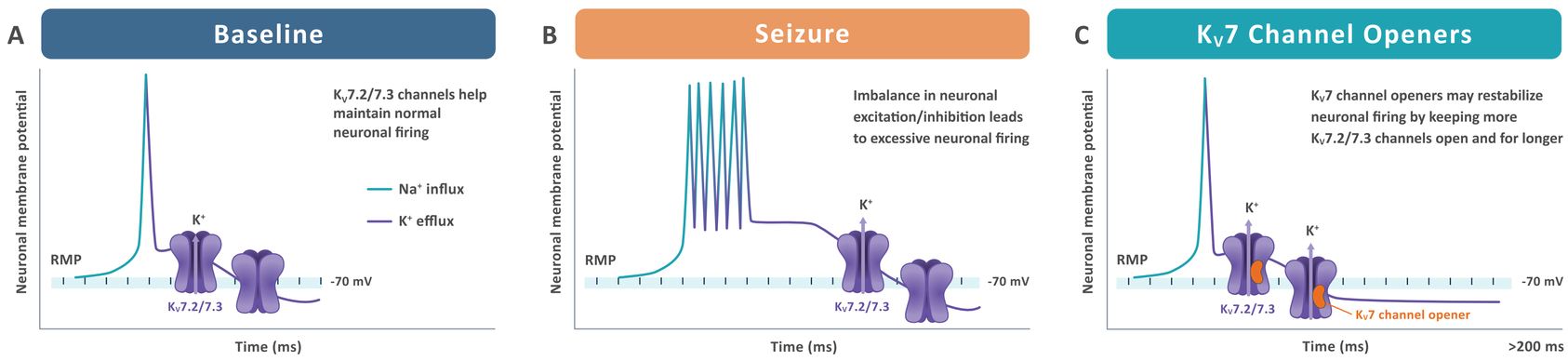
Raman Sankar[1]; J.P. Johnson, Jr[2]; Korie Handwerger[2]; Richard Dean[2]

[1]David Geffen School of Medicine at UCLA, Los Angeles, CA, USA; [2]Xenon Pharmaceuticals Inc., Vancouver, BC, Canada

INTRODUCTION

- The underlying cause of epileptic seizures is abnormal, excessive, and synchronous activity in the brain arising from an imbalance between excitatory and inhibitory neuronal activity[1]
- About 1/3 of patients with epilepsy have difficult-to-treat epilepsy and do not achieve seizure freedom after 2 antiseizure medication (ASM) trials[2-4]
- The voltage-gated potassium channel subtypes $K_V7.2$ and 7.3 are predominantly expressed in the nervous system at the axon initial segment (AIS), nodes of Ranvier (NoR), and both pre- and postsynaptic terminals[5-11]
- $K_V7.2/7.3$ heterotetramers play a role in the neuronal K_V7 current (also known as the M-current), which controls neuronal excitability and firing threshold (**Figure 1A**)[5-14]
- Targeting voltage-gated potassium channels (including $K_V7.2/7.3$) has demonstrated clinical efficacy in epilepsy treatment,[7,15] and offers a mechanistically attractive approach in epilepsy management (**Figure 1B,C**)[16]
- Here we use a range of preclinical methods to investigate the binding site, electrophysiological effects, and potential in vivo additive effects of azetukalner (AZK), a novel K_V7 channel opener

Figure 1. Role of $K_V7.2/7.3$ Channels in Modulating Neuronal Membrane Potential[1,16-19]



Information has been simplified to convey general concepts and principles.
K_V7, voltage-gated potassium channel subtype 7; RMP, resting membrane potential.

Methods

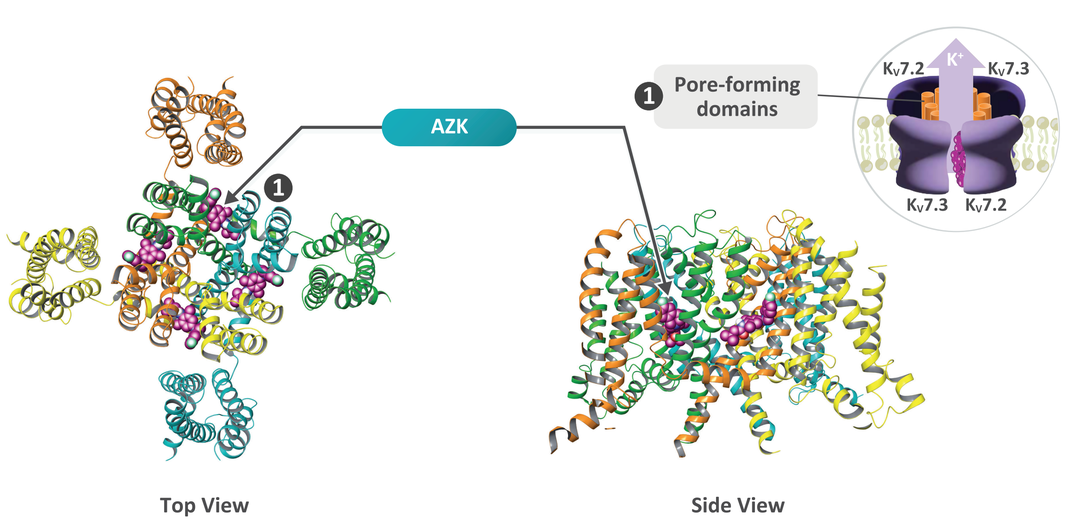
- The binding mode of AZK to $K_V7.2$ channels was generated using Schrödinger 2025-2 for induced-fit docking into a cryogenic electron microscopy human KCNQ2 structure (PDB: 7CR2)
- Effects of AZK on $K_V7.2/7.3$ channel opening were explored electrophysiologically in HEK cells
- A 34-mA, 6-Hz mouse model, a direct-current maximal electroshock seizure (DC-MES) mouse model, and an alternating-current maximal electroshock seizure (AC-MES) mouse model were employed to investigate the potential additive effects of AZK in combination with common ASMs

RESULTS

AZK Binding Site

- Based on modeling with the $K_V7.2$ homotetramer, AZK is believed to dock within the pore-forming domains of $K_V7.2$ (**Figure 2**), a binding site expected to be conserved in $K_V7.2/7.3$ heterotetramers; this interaction is thought to enhance neuronal K_V7 current and sustain K^+ efflux from neurons

Figure 2. AZK Docked Into $K_V7.2$ Homotetramer Protein Model

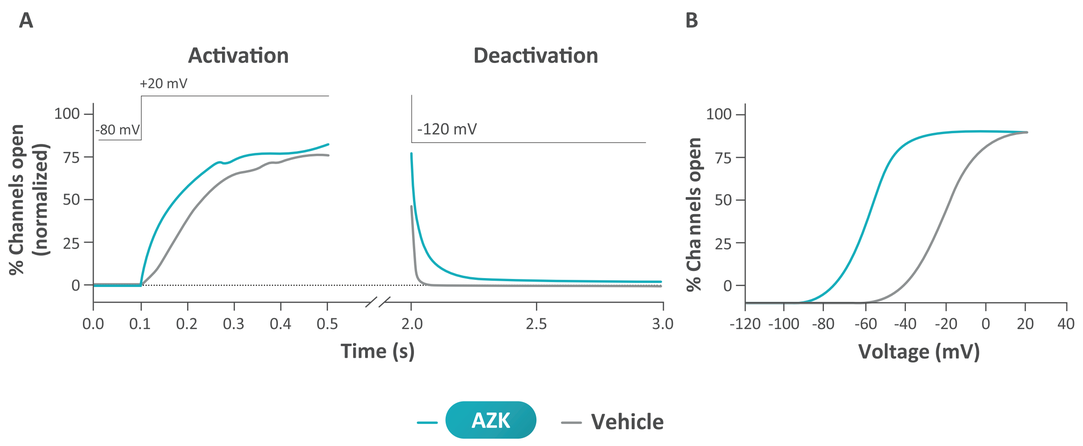


Ribbon diagrams are based on $K_V7.2$ homotetramer; $K_V7.2/7.3$ heterotetramer structure expected to be similar (Xenon, data on file).
AZK is an investigational drug that has not been approved by any health authority and its safety and effectiveness have not been established.
AZK, azetukalner.

Electrophysiology of AZK

- AZK accelerates $K_V7.2/7.3$ channel activation and slows channel deactivation relative to vehicle (**Figure 3A**)
- With AZK, $K_V7.2/7.3$ channels open at lower membrane voltages, and a greater fraction of channels are open at a given voltage (**Figure 3B**)

Figure 3. AZK Enables $K_V7.2/7.3$ Channels to Open Earlier at Lower Membrane Voltages and Remain Open Longer

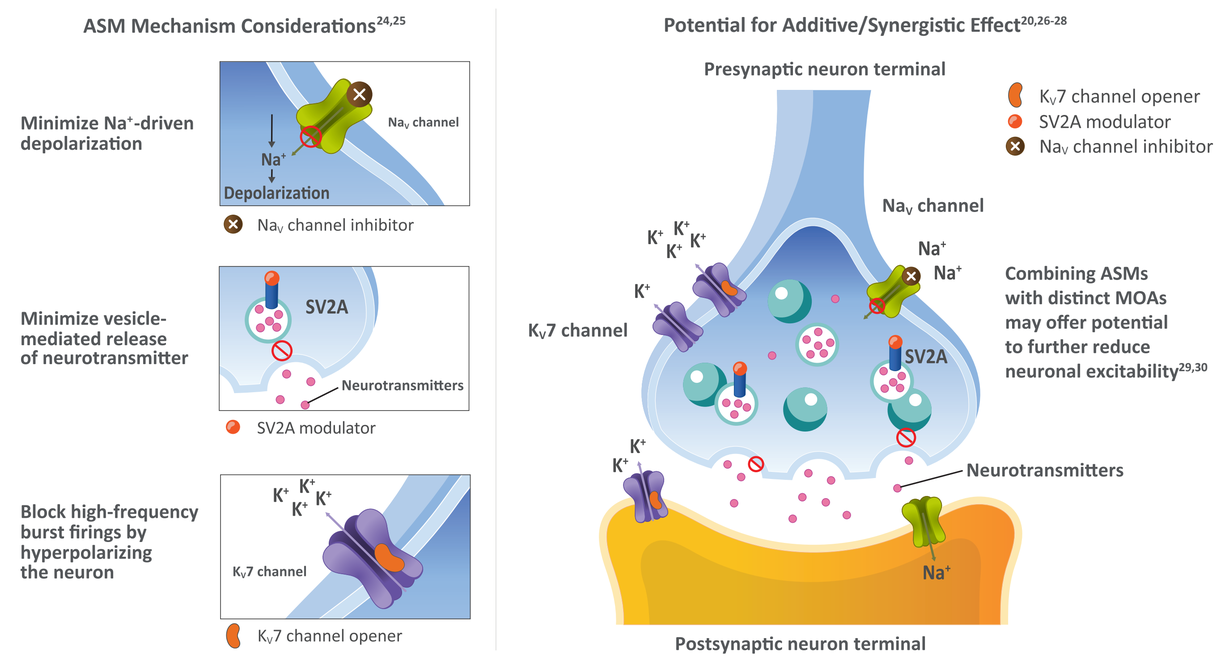


AZK, azetukalner.

Rationale for Polytherapy in Epilepsy

- Rational polytherapy involves combining ASMs with distinct mechanisms of action (MOAs) (**Figure 4**) to potentially (1) improve seizure control, (2) help reduce risk of compounded adverse effects, and (3) improve tolerability and promote long-term adherence[20-23]

Figure 4. Model of the Potential Role of $K_V7.2/7.3$ Channel Openers in Polytherapy

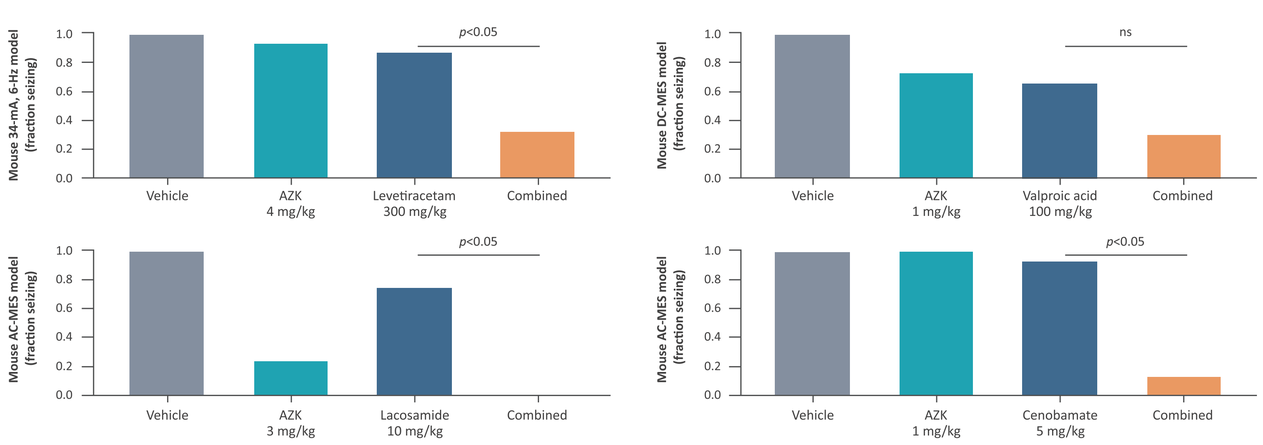


ASM, antiseizure medication; K_V7, voltage-gated potassium channel subtype 7; Na_V, voltage-gated sodium channel; MOA, mechanism of action; SV2A, synaptic vesicle glycoprotein 2A.

Potential of AZK as Polytherapy

- Preclinical studies combining AZK with levetiracetam (SV2A modulator), lacosamide (sodium channel blocker), valproic acid (multiple MOAs), or cenobamate (potentiates GABA-A tonic current and inhibits persistent Na_V currents) provided robust seizure protection with enhanced efficacy (**Figure 5**)

Figure 5. AZK in Combination With Commonly Used ASMs



AC-MES, alternating-current maximal electroshock seizure; ASM, antiseizure medication; AZK, azetukalner; DC-MES, direct-current maximal electroshock seizure; ns, not significant.

CONCLUSIONS

- AZK is a novel, potent $K_V7.2/7.3$ channel opener that:
  - Binds within the pore-forming domains of $K_V7.2/7.3$ heterotetramers
  - Allows $K_V7.2/7.3$ channels to open earlier at lower membrane voltages and remain open longer
- AZK is thought to enhance the neuronal K_V7 current, thereby limiting neuronal hyperexcitability and secondarily, reducing hypersynchrony that underlies epileptic seizures
- AZK has the potential to yield additive or synergistic effects when combined with other classes of ASMs

References: **1.** Sumadewi KT, et al. *Acta Epileptol*. 2023;5(1):28. **2.** Chen Z, et al. *JAMA Neurol*. 2018;75(3):279-286. **3.** Kwan P, et al. *Epilepsia*. 2010;51(6):1069-1077. **4.** Kwan P, et al. *N Engl J Med*. 2000;342(5):314-319. **5.** Shah NH, et al. *Transl Stroke Res*. 2014;5(1):38-58. **6.** Barrese V, et al. *Annu Rev Pharmacol Toxicol*. 2018;58:625-648. **7.** Meldrum BS, et al. *Neurotherapeutics*. 2007;4(1):18-61. **8.** Dirkx N, et al. *Front Physiol*. 2020;11:1-12. **9.** Battefeld A, et al. *J Neurosci*. 2014;34(10):3719-3732. **10.** Martinello K, et al. *Commun Biol*. 2019;2:1-12. **11.** Hansen HH, et al. *J Physiol*. 2008;586(7):1823-1832. **12.** Ranjan R, et al. *Front Cell Neurosci*. 2019;13. **13.** Li L, et al. *Br J Pharmacol*. 2017;174(23):4277-4294. **14.** Borgini M, et al. *RSC Med Chem*. 2021;12(4):483-537. **15.** Potiga. Prescribing Information. GlaxoSmithKline; 2016. **16.** Perucca E, et al. *CNS Drugs*. 2025;39(3):263-288. **17.** Badawy RA, et al. *J Clin Neurosci*. 2009;16(3):355-365. **18.** Brown DA, et al. *Br J Pharmacol*. 2009;156(8):1185-1195. **19.** Soldovieri MV, et al. *Physiology (Bethesda)*. 2011;26(5):365-376. **20.** Verrotti A, et al. *Epilepsy Behav*. 2020;104(pt A):106939. **21.** St Louis, EK. *Curr Neuropharmacol*. 2009;7(2):115-119. **22.** Chang C-W, et al. *Ther Adv Neurol Disord*. 2023;16:17562864231207161. **23.** Li C, et al. *Int J Mol Sci*. 2025;26:4035. **24.** Landmark CJ, et al. *Epileptic Disord*. 2023;25(4):454-471. **25.** Löscher W, et al. *CNS Drugs*. 2021;35(9):935-963. **26.** Rana ZS, et al. *Int J Drug Discov Pharmacol*. 2023;2(2):2504000154. **27.** Gidal BE. *Epilepsy Curr*. 2015;15(5):260-262. **28.** Margolis JM, et al. *JAMA Neurol*. 2014;71(8):985-993. **29.** Luszczki JJ, et al. *Epilepsia*. 2006;47(1):10-20. **30.** Luszczki JJ, et al. *Pharmacology*. 2015;96(1-2):11-15.

ACKNOWLEDGMENTS: Medical writing and editorial support were provided by Danielle Frodyma, PhD, CMPP and Heidi Reinholdt, MS, MA, CMPP, of Helios Global Group. Previous medical writing assistance was provided by Oishika Panda, PhD, CMPP, from Citrus Health Group, Inc. (Chicago, Illinois). Medical writing and editorial support were funded by Xenon Pharmaceuticals Inc. (Vancouver, BC, Canada).

DISCLOSURES: **Raman Sankar** has served as a consultant and/or speaker for which he has received honoraria from Biocodex, Eisai, BioMarin, Jazz Pharmaceuticals, Neurelis, Ovid, SK Life Science, UCB, Xenon Pharmaceuticals Inc., and Zogenix. **Richard Dean**, **J.P. Johnson**, **Jr**, and **Korie Handwerger** are employees of and own stock or stock options in Xenon Pharmaceuticals Inc.

FUNDING: This study was funded by Xenon Pharmaceuticals Inc.

Portions of these data were previously presented at the Xenon Pharmaceuticals Inc. Scientific Exhibit at American Epilepsy Society Annual Meeting, December 5-9, 2025, Atlanta, GA, USA.