Supplemental Online Content

Butterfield NN, Luzon Rosenblut C, Fava M, et al. Azetukalner, a novel K_V7 postassium channel opener, in adults with major depressive disorder: a randomized clinical trial. *JAMA Netw. Open*. 2025;8(5):e2514278. doi:10.1001jamanetworkopen.2025.14278

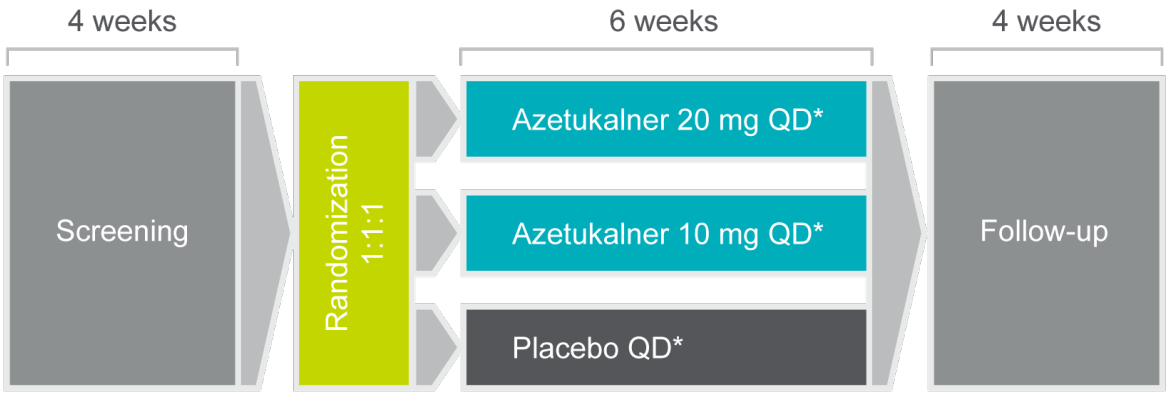
This supplemental material has been provided by the authors to give readers additional information about their work.

eTable 1. Allowed and Prohibited Medications in the Trial

Prohibited Medications and Procedures	• Antidepressants, antipsychotics, ASMs, mood stabilizers, benzodiazepines, lithium, stimulants, and opioids, within the 2 weeks (4 weeks for fluoxetine) or within a period less than 5-times the drug's half-life, whichever is longer, prior to randomization through the end of the treatment period. • ECT, DBS, TMS, and VNS. • Recreational or medicinal use of marijuana, cannabinoids, and/or derivatives, including cannabidiol (CBD). • Drugs of abuse or any prescribed or over-the-counter medication used in a manner that the investigator considers indicative of abuse, dependence, or habitual use. • Any other investigational drug or device within 5 half-lives of its pharmacological/therapeutic effect or 30 days prior to screening, whichever is longer.
Permitted Medications and Interventions	• Limited use of as needed (PRN) nonbenzodiazepine hypnotic agents (including zolpidem, zaleplon, eszopliclone, diphenhydramine, suvorexant, lemborexant, and ramelteon) • Subjects receiving psychotherapy may continue treatment provided the therapy has been ongoing and stable for at least 3 months prior to screening and is expected to remain unchanged during the study treatment period. • Subjects who need to start psychotherapy during the study will be discontinued

Abbreviations: ASM, antiseizure medication, DBS, deep brain stimulation; ECT, electroconvulsive therapy; TMS, transcranial magnetic stimulation; VNS, vagus nerve stimulation.

eFigure. X-NOVA Phase 2 Clinical Trial Design



Abbreviation: QD, once a day.
*Administered as a once-daily capsule with food with no titration period.

eTable 2. Change in BAI Total Score From Baseline at Week 6 in Participants With Moderate to Severe BAI Score at Baseline (Post hoc Analysis)

Participants with moderate to severe BAI scores (≥16) at baseline (post hoc analysis)	Placebo (n=14)	Azetukalner 10 mg (n=18)	Azetukalner 20 mg (n=16)
BAI total score change from baseline at week 6, LS mean (SE)	–9.64 (2.27)	–11.76 (2.14)	–13.83 (2.26)
Difference vs placebo (95% CI)		–2.12 (–8.25 to 4.02)	–4.19 (–10.66 to 2.27)
P value[a]		0.49	0.20

Abbreviations: BAI, Beck Anxiety Inventory; HAM-D17, Hamilton Depression Rating Scale; LS, least-squares.
[a]All *P* values are nominal. BAI was assessed at screening, baseline, and week 6. An analysis of covariance model was used to perform analysis, with change from baseline as the outcome variable, treatment group as the factors, and the baseline HAM-D17 score as the covariate.

eTable 3. Summary of TEAEs Leading to Drug Discontinuation (Safety Population)

System organ class/ preferred term, n (%)	Placebo (n=55)	Azetukalner 10 mg (n=56)	Azetukalner 20 mg (n=56)	Azetukalner any dose (n=112)
Overall	2 (3.6)	5 (8.9)	3 (5.4)	8 (7.1)
Nervous system disorders	0 (0)	1 (1.8)	3 (5.4)	4 (3.6)
Disturbance in attention	0 (0)	0 (0)	1 (1.8)	1 (0.9)
Dizziness	0 (0)	0 (0)	1 (1.8)	1 (0.9)
Headache	0 (0)	1 (1.8)	0 (0)	1 (0.9)
Syncope	0 (0)	0 (0)	1 (1.8)	1 (0.9)
Psychiatric disorders	1 (1.8)	2 (3.6)	0 (0)	2 (1.8)
Depression	0 (0)	1 (1.8)	0 (0)	1 (0.9)
Dissociation	0 (0)	1 (1.8)	0 (0)	1 (0.9)
Homicidal ideation	1 (1.8)	0 (0)	0 (0)	0 (0)
Eye disorders	0 (0)	1 (1.8)	0 (0)	1 (0.9)
Ocular hyperemia	0 (0)	1 (1.8)	0 (0)	1 (0.9)
Gastrointestinal disorders	0 (0)	1 (1.8)	0 (0)	1 (0.9)
Nausea	0 (0)	1 (1.8)	0 (0)	1 (0.9)
Vomiting	0 (0)	1 (1.8)	0 (0)	1 (0.9)
Investigations	1 (1.8)	0 (0)	0 (0)	0 (0)
Blood chloride decreased	1 (1.8)	0 (0)	0 (0)	0 (0)
Blood potassium decreased	1 (1.8)	0 (0)	0 (0)	0 (0)
Blood sodium decreased	1 (1.8)	0 (0)	0 (0)	0 (0)

Abbreviation: TEAEs, treatment-emergent adverse events.