Azetukalner, a Novel, Potent Kv7 Potassium Channel Opener in Development for Major Depressive Disorder and Bipolar Depression: Updates From the Ongoing Clinical Programs

Noam N. Butterfield, Celene Grayson, Danny Lee, Erin MacKenzie, Joe McIntosh, Rostam Namdari, Anna Osmukhina, Jenny Qian, Christopher Kenney, Aleks Skuban

Xenon Pharmaceuticals Inc., Vancouver, BC, Canada

BACKGROUND

Unmet Medical Need in MDD and Bipolar Depression

- Effective treatments for major depressive disorder (MDD) and bipolar depression remain a major challenge[1,2]
- Therapies with a novel mechanism of action (MOA), improved efficacy and tolerability, and faster onset are needed[1]
- In addition, a recent Delphi consensus on MDD with anhedonia highlighted that effective antidepressants that specifically address anhedonia are lacking[3]

Kv7 Channels in Epilepsy, MDD, and Bipolar Depression

- Voltage-gated *KCNQ*-type potassium channels (Kv) regulate cell membrane excitability[4]
- Preclinical and clinical data suggest that certain Kv7 channel openers have the potential to reduce seizures[5] and improve symptoms of depression[6,7]
- Genetic research suggests an association between Kv7 and bipolar disorder, including altered gene expression of certain Kv7 subunits and potential Kv7 channel dysfunction[8-10]

Overview of Azetukalner

- Azetukalner is a novel, potent, Kv7.2/7.3 potassium channel opener currently under development for epilepsy and MDD, with a Phase 3 program in bipolar depression expected to begin by mid-year 2025
- In addition to its unique MOA, azetukalner has shown early-onset efficacy at week 1 in Phase 2 studies for focal epilepsy (X-TOLE™ [NCT03796962])[5] and MDD (X-NOVA™ [NCT05376150])[11,12]
  - X-TOLE was a Phase 2b study with an ongoing 7-year open-label extension (OLE) in patients with focal onset seizures (FOS)[5]
    - Over the 8-week double-blind period (DBP), azetukalner (10, 20, and 25 mg once daily [QD] with food with no titration period) demonstrated a dose dependent and statistically significant reduction in seizure frequency
  - X-NOVA was a multicenter, proof-of-concept, Phase 2, randomized, double-blind, parallel-arm, placebo-controlled clinical trial evaluating azetukalner in participants with MDD[11]
    - Participants were randomized 1:1:1 to receive placebo, azetukalner 10 mg, or azetukalner 20 mg taken orally QD with food with no titration period for 6 weeks, with a 4-week follow-up

ACKNOWLEDGMENTS The authors thank the patients and all members of the X-NOVA 2 study group. Medical writing support was provided by Matthew T. Rich, PhD, from Citrus Health Group, Inc. (Chicago, Illinois) and was funded by Xenon Pharmaceuticals Inc. (Vancouver, British Columbia, Canada).

FUNDING This study was funded by Xenon Pharmaceuticals Inc.

DISCLOSURES Noam N. Butterfield, Celene Grayson, Danny Lee, Erin MacKenzie, Joe McIntosh, Rostam Namdari, Anna Osmukhina, Jenny Qian, Christopher Kenney, and Aleks Skuban are employees of and own stock or stock options in Xenon Pharmaceuticals Inc.

REFERENCES **1.** Correll CU, et al. *World Psychiatry*. 2023;22(1):48-74. **2.** McIntyre RS, Calabrese JR. *Curr Med Res Opin*. 2019;35(11):1993-2005. **3.** Borsini A, et al. *Cogn Affect Behav Neurosci*. 2020;20(4):816-841. **4.** Zhang Y, et al. *J Neurosci*. 2022;42(16):3305-3315. **5.** French JA, et al. *JAMA Neurol*. 2023;80(11):1145-1154. **6.** Friedman AK, et al. *Nat Commun*. 2016;7:11671. **7.** Costi S, et al. *Am J Psychiatry*. 2021;178(5):437-446. **8.** Borsotto M, et al. *Pharmacogenomics J*. 2007;7(2):123-132. **9.** Smolin B, et al. *Int J Neuropsychopharmacol*. 2012;15(7):869-882. **10.** Judy JT, et al. *Front Genet*. 2013;4:87. **11.** Butterfield NN, et al. *JAMA Netw Open*. 2025; published online May 27th doi:10.10001/jamanetworkopen.2025.14278 **12.** ClinicalTrials.gov. A study to evaluate the safety, tolerability and efficacy of XEN1101 in major depressive disorder (X-NOVA). 2022. Accessed May 15, 2025. https://clinicaltrials.gov/study/NCT05376150 **13.** ClinicalTrials.gov. A randomized study of azetukalner versus placebo in major depressive disorder (X-NOVA2). 2024. Accessed May 1, 2025. https://clinicaltrials.gov/study/NCT06775379

X-NOVA STUDY RESULTS

- The totality of results from X-NOVA support the potential of azetukalner to improve depression and anhedonia in patients with MDD, with a safety profile potentially distinct from that of standard antidepressants, addressing a critical unmet medical need[11]

Building on the promising results of X-NOVA, we report on the design of X-NOVA2, the first of 3 planned Phase 3 trials to evaluate the efficacy and safety of azetukalner as monotherapy for MDD

X-NOVA™ Phase 2 proof-of-concept study of azetukalner in participants with MDD

Efficacy Profile[11]

Clinically Meaningful Reduction in Depression

MADRS score CFB at week 6[a], LS mean (SE):

-16.9 (1.5)	-13.9 (1.4)	*P*=0.135
20 mg azetukalner[b]	placebo	

Significant Reduction in Anhedonia

SHAPS score CFB at week 6[c], LS mean (SE):

-7.8 (0.9)	-5.3 (0.9)	*P*<0.05
20 mg azetukalner[b]	placebo	

Early Onset of Efficacy

MADRS score CFB at week 1[d], LS mean (SE):

-7.5 (0.9)	-4.9 (0.9)	*P*<0.05
20 mg azetukalner[b]	placebo	

Significant Reduction in Depression

HAMD-17 score CFB at week 6[d], LS mean (SE):

-13.3 (1.1)	-10.2 (1.0)	*P*<0.05
20 mg azetukalner[b]	placebo	

Safety Profile[11]

Most common TEAEs, 20 mg azetukalner[b]:

No notable weight gain

No participant reports of notable sexual dysfunction with azetukalner

CFB, change from baseline; FDA, US Food and Drug Administration; HAMD-17, Hamilton Depression Rating Scale, 17-item; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; SHAPS, Snaith-Hamilton Pleasure Score; TEAE, treatment-emergent adverse event.
[a]Primary endpoint.
[b]All doses administered as a once-daily capsule with food with no titration period. [c]Secondary endpoint. [d]Exploratory endpoint.
Note: Multiplicity adjustment was not applied and all *P* values are nominal. A mixed-effect model for repeated measures was used to perform analyses, with change from baseline as the outcome variable; the baseline MADRS, HAMD-17, or SHAPS score as the covariate; and treatment group, visit (up to week 6 visit), and treatment-by-visit interaction as fixed effects.
Assessments were performed in the mITT population per week 1 treatment. mITT population consists of all randomized participants who received ≥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.
Azetukalner is an investigational product and has not been approved by the FDA or other regulatory bodies.

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

- X-NOVA2 (NCT06775379)[13] is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of azetukalner as monotherapy in adults with MDD
- An estimated 450 participants with moderate to severe MDD will be randomized 1:1 to azetukalner 20 mg or placebo QD with food with no titration period for 6 weeks
- Upon completion of the DBP, eligible participants may enter an OLE for up to 12 months

X-NOVA2 Key Enrollment Criteria

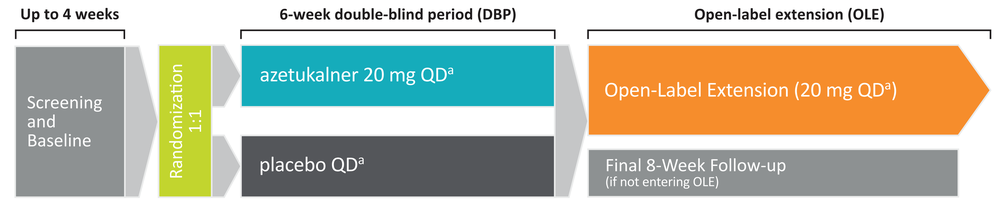
Key Inclusion Criteria
18–74 years (inclusive)
≤40 kg/m^2 BMI
First MDE before 50 years
DSM-5-TR criteria for MDD[a]
Currently experiencing MDE (via MINI)
MDE duration ≥6 weeks and ≤24 months

Key Exclusion Criteria
Primary diagnosis of a mood disorder other than MDD
History of • MDD with psychotic or catatonic features • MDD with mixed features • Bipolar I or II disorder, obsessive-compulsive disorder, or schizophrenia
Diagnosis of • MDD with seasonal pattern • Depression with peripartum onset • Antisocial or borderline personality disorder • Posttraumatic stress disorder • Panic disorder or agoraphobia • ADHD treated with a psychostimulant
Substance or alcohol use disorder or eating disorder within past year
Active suicidal plan/intent within past 6 months, presence of suicidal behavior within last 2 years, or ≥2 lifetime suicide attempts
Participant has a history of nonresponse to ≥2 antidepressant drugs of adequate dose and duration in the current MDE as determined by the ATRQ

ADHD, attention-deficit/hyperactivity disorder; ATRQ, Antidepressant Treatment Response Questionnaire; BMI, body mass index; DSM-5-TR, *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition, Text Revision; MDD, major depressive disorder; MDE, major depressive episode; MINI, Mini International Neuropsychiatric Interview.
[a]Comorbid generalized anxiety disorder and social anxiety disorder are permitted.

- Safety assessments will include severity and frequency of treatment-emergent adverse events, serious adverse events, and adverse events of special interest; clinical laboratory tests; electrocardiograms; and vital signs

X-NOVA 2™



FDA, US Food and Drug Administration; QD, once daily.
[a]Administered as a once-daily capsule with food with no titration period.
Azetukalner is an investigational product and has not been approved by the FDA or other regulatory bodies.

Primary Objective and Endpoint

OBJECTIVE	ENDPOINT
Assess efficacy of azetukalner for the treatment of MDD	**Change from baseline in HAMD-17 at week 6**

Key Secondary Objectives and Endpoints

OBJECTIVES	ENDPOINTS
Assess efficacy of azetukalner for the treatment of anhedonia	**Change from baseline in SHAPS at week 6**
Assess rapidity of efficacy onset of azetukalner for the treatment of MDD	**Change from baseline in HAMD-17 at week 1**
Assess clinician-perceived efficacy of azetukalner for the treatment of MDD	**Change from baseline in CGI-S at week 6**

CGI-S, Clinical Global Impression of Severity; HAMD-17, Hamilton Depression Rating Scale, 17 Item; MDD, major depressive disorder; SHAPS, Snaith-Hamilton Pleasure Scale.
Note: Azetukalner will be administered as a 20-mg dose taken QD with food with no titration.

CONCLUSIONS AND FUTURE DIRECTIONS

- Azetukalner has a novel MOA and has the potential to improve symptoms of depression in MDD with a potentially distinctive safety profile from currently marketed antidepressants
- The effects of azetukalner on anhedonia and its rapid onset of efficacy in depression may further distinguish it within the treatment landscape
- Additionally, a Phase 3 program, including two studies evaluating the efficacy and safety of azetukalner in both bipolar I and II depression, is expected to begin mid-2025
- Ongoing and planned azetukalner Phase 3 trials are expected to provide additional evidence of clinical benefit in MDD and bipolar depression