# Azetukalner, a Novel, Potent Kv7 Channel Opener: Updates From the Ongoing Clinical Development Program in Major Depressive Disorder

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## 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*-encoded 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, MDD, and bipolar depression
- 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

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## 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 designs of two ongoing Phase 3 studies, X-NOVA2 and X-NOVA3, evaluating 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[c], LS mean (SE):

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

**Significant Reduction in Anhedonia**
SHAPS score CFB at week 6[c], LS mean (SE):

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

**Early Onset of Efficacy**
MADRS score CFB at week 1[d], LS mean (SE):

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

**Significant Reduction in Depression**
HAMD-17 score CFB at week 6[d], LS mean (SE):

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

### 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 AND X-NOVA3: PHASE 3 STUDIES OF AZETUKALNER IN PARTICIPANTS WITH MDD

- X-NOVA2 (NCT06775379)[13] and X-NOVA3 (NCT07076407)[14] are identical Phase 3, multicenter, randomized, double-blind, placebo-controlled studies to evaluate the efficacy, safety, and tolerability of azetukalner as monotherapy in adults with MDD
- Each study will enroll approximately 450 participants with moderate to severe MDD who 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

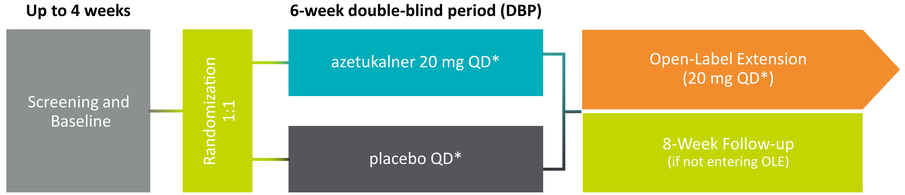
### X-NOVA2 and X-NOVA3 Key Enrollment Criteria

| 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<br>• MDD with psychotic or catatonic features<br>• MDD with mixed features<br>• Bipolar I or II disorder, obsessive-compulsive disorder, or schizophrenia |
| Diagnosis of<br>• MDD with seasonal pattern<br>• Depression with peripartum onset<br>• Antisocial or borderline personality disorder<br>• Posttraumatic stress disorder<br>• Panic disorder or agoraphobia<br>• 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-NOVA2™ | X-NOVA3™




QD, once daily.
*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, X-CEED, which is the first of two planned Phase 3 clinical studies evaluating the efficacy and safety of azetukalner in bipolar I and II depression, has been initiated
- Ongoing and planned azetukalner Phase 3 trials are expected to provide additional evidence of clinical benefit in MDD and bipolar depression