Efficacy and Safety of Azetukalner, a Novel, Potent K_V7 Potassium Channel Opener in Adults With Moderate to Severe Major Depressive Disorder: Results From the Proof-of-Concept Phase 2 X-NOVA Study

Noam N. Butterfield, PhD[1]; Constanza Luzon Rosenblut, MD[1]; Maurizio Fava, MD[2]; Christoph U. Correll, MD[3]; Anthony J. Rothschild, MD[4]; James W. Murrough, MD, PhD[5]; Sanjay J. Mathew, MD[6]; Gregory N. Beatch, PhD[1]; Celene Grayson, PhD[1]; Cynthia Harden, MD[1]; Jenny Qian, MS[1]; Joe McIntosh, MD[1]; Christopher Kenney, MD[1]

[1]Xenon Pharmaceuticals Inc., Vancouver, BC, Canada; [2]Massachusetts General Hospital, Boston, MA; [3]The Donald and Barbara Zucker School of Medicine at Hofstra/Northwell, Hempstead, NY; [4]UMass Chan Medical School and UMass Memorial Health Care, Worcester, MA; [5]Icahn School of Medicine at Mount Sinai, New York, NY; [6]Baylor College of Medicine, Houston, TX

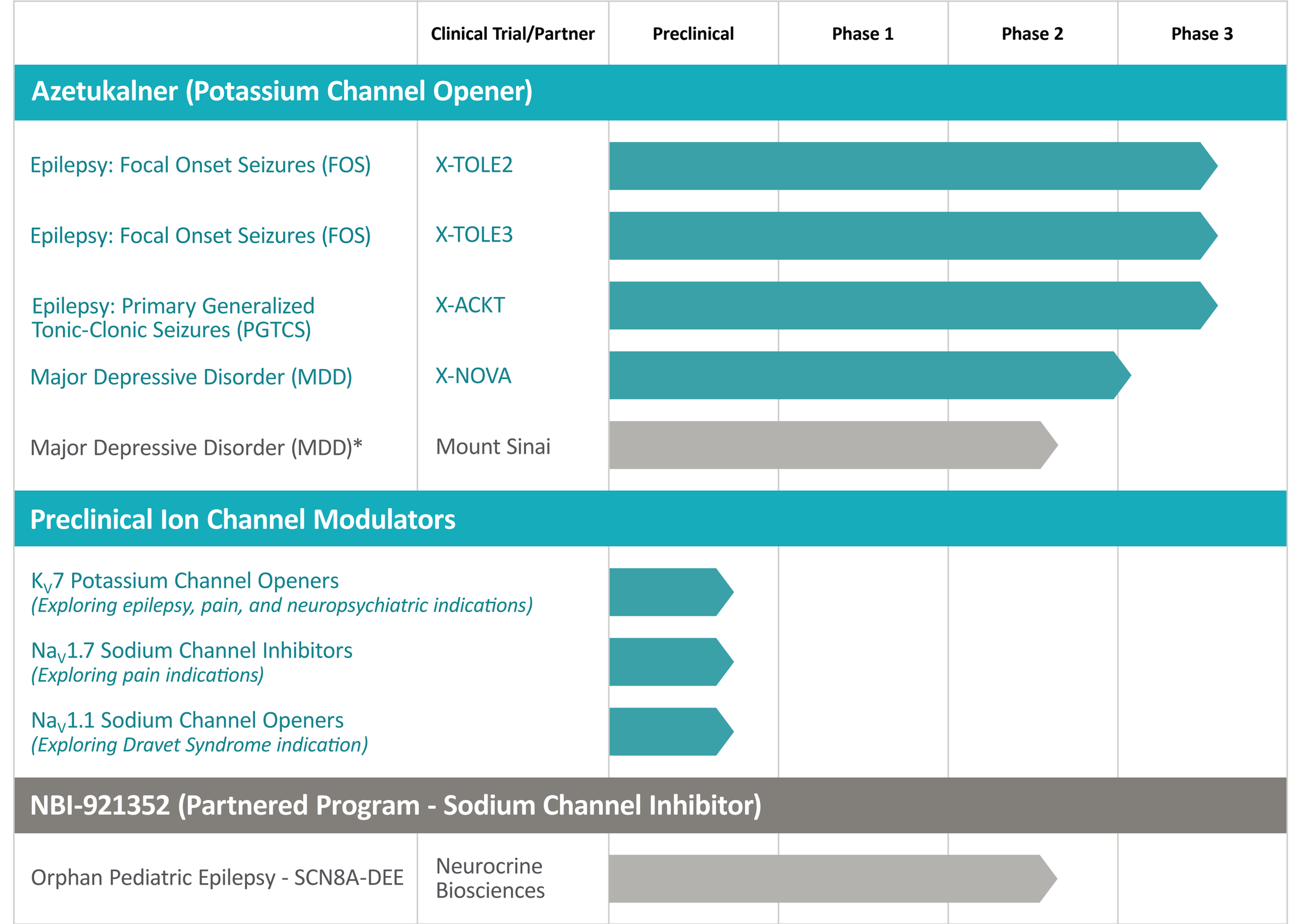
ABOUT XENON

- Xenon Pharmaceuticals is a neuroscience-focused biopharmaceutical company committed to discovering, developing, and commercializing innovative therapeutics to improve the lives of people living with neurological and psychiatric disorders
- As a leader in small molecule, ion channel drug development, Xenon is advancing a novel product pipeline to address areas of high unmet medical need, including epilepsy and depression

XENON'S PIPELINE

- Xenon is focused on advancing our ion channel pipeline with candidates targeting K_V7, $Na_V1.1$, and $Na_V1.7$ ion channels (**Figure 1**). Our clinical stage candidate azetukalner (XEN1101) is being developed for the treatment of focal onset seizures (FOS), primary generalized tonic-clonic seizures (PGTCS), and moderate to severe major depressive disorder (MDD)

Figure 1. Xenon's Neuroscience-Focused Pipeline



*Investigator sponsored Phase 2 proof-of-concept study.
This chart displays pipeline drug candidates currently undergoing clinical testing in a variety of disease indications. The safety and efficacy of these investigational drug candidates have not been fully evaluated, and they have not yet been approved for use by any regulatory authorities. FOS, focal onset seizure; MDD, major depressive disorder; PGTCS, primary generalized tonic-clonic seizures; SCN8A-DEE, *SCN8A*-related developmental and epileptic encephalopathy.

OVERVIEW OF AZETUKALNER

- Azetukalner is a novel, potent K_V7 potassium channel opener being studied for the treatment of FOS, PGTCS, and MDD[1]

Epilepsy

- The efficacy and safety of azetukalner in focal epilepsy was investigated in a Phase 2b randomized clinical trial (X-TOLE)[2]
- X-TOLE (NCT03796962) met the primary and key secondary efficacy endpoints with azetukalner (10 mg [P<0.05], 20 and 25 mg doses [P<0.001]), demonstrating a statistically significant reduction from baseline in monthly FOS frequency compared with placebo in the completed 8-week, randomized, double-blind phase[2]
- Azetukalner was generally well tolerated in X-TOLE and treatment-emergent adverse events (TEAEs) were similar to those of commonly prescribed antiseizure medications (ASMs)[2]
- Safety and efficacy are being further investigated in the ongoing, 7-year, open-label extension (OLE) phase of X-TOLE
- As of September 2023, azetukalner 20 mg taken once daily (QD) with food was generally well tolerated in the OLE, and the safety profile observed was similar to that of the double-blind period[3]

More than 500 participant-years of safety data have been generated to date through the X-TOLE OLE study as of September 2023

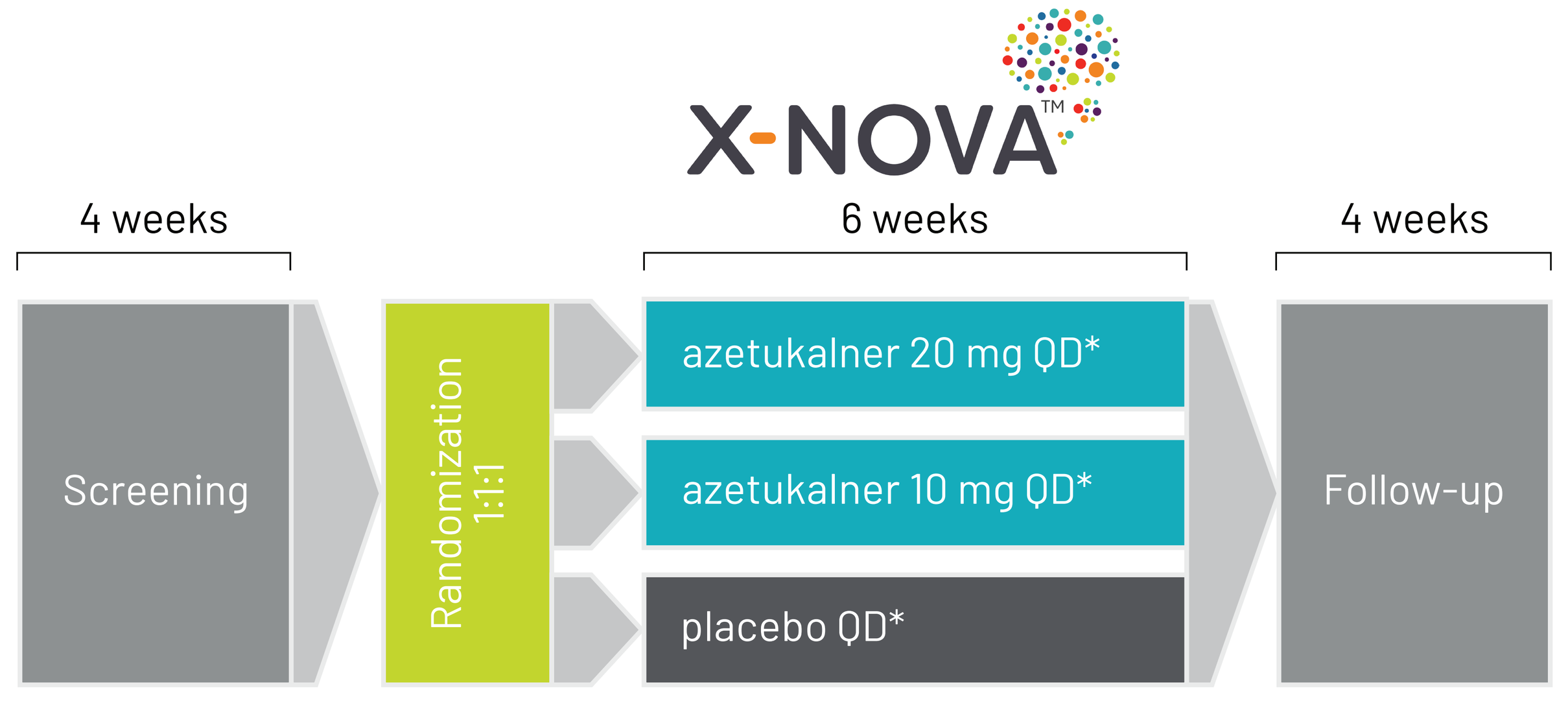
MDD

- MDD is a significant public health concern globally,[4] with 1 in 3 patients experiencing inadequate responses to initial antidepressant therapy[5]
- Although the pathophysiology of MDD is partially elucidated, the complete spectrum of biologic pathways contributing to MDD is yet to be fully understood[6]
- Novel treatment approaches targeting distinct pathways are warranted to address this unmet need
- Certain K_V7 potassium channel openers were shown to have antidepressant efficacy in a rodent model[7] and improvements in clinical measures of depression and anhedonia in participants with MDD[8]
- Here, we highlight the results from a proof-of-concept, Phase 2, clinical trial of azetukalner in adults with moderate to severe MDD

METHODS

- X-NOVA (NCT05376150)[9] was a proof-of-concept, randomized, double-blind, placebo-controlled, Phase 2 study conducted across 20 sites in the US to evaluate the safety, tolerability, and efficacy of azetukalner in MDD (**Figure 2**)
- Key eligibility criteria are provided in **Table 1**

Figure 2. X-NOVA Phase 2, Proof-of-Concept, Clinical Trial Design



*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.
FDA, US Food and Drug Administration; QD, once daily.

Table 1. Key Eligibility Criteria

Inclusion Criteria

1. Male or female aged 18–65 years (inclusive) with a BMI ≤35 kg/m²
2. Participant must meet the DSM-5 criteria for MDD and currently experiencing a moderate to severe MDE, confirmed using MINI
3. Current MDE duration ≥2 months and <24 months at the time of screening
4. Current illness severity that is at least moderate, defined as a score of ≥20 on the HAM-D17 at screening and on day 1
5. Score ≥20 on the SHAPS at screening and on day 1

Exclusion Criteria

1. A primary psychiatric diagnosis other than MDD as defined by DSM-5 (comorbid anxiety disorders are allowed)
2. Concomitant use of antidepressants and/or other disallowed pharmacotherapy (including benzodiazepines)
3. History of schizophrenia or other psychotic disorder, MDD with psychotic features, bipolar I or II disorder, or MDD with mixed features
4. History of nonresponse to >1 antidepressant drug owing to lack of efficacy in the current MDE
5. Failing >3 antidepressant drug trials for any reason in the current MDE
6. Active suicidal plan/intent in the past 6 months or >1 lifetime suicide attempt
7. Meets criteria for a substance use disorder within the past 12 months, with the exception of tobacco use, and/or has a positive urine toxicology screen for drugs of abuse

BMI, body mass index; DSM-5, *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition[10]; HAM-D17, Hamilton Depression Rating Scale, 17-Item[11]; MDD, major depressive disorder; MDE, major depressive episode; MINI, Mini International Neuropsychiatric Interview; SHAPS, Snaith–Hamilton Pleasure Scale.[12]

- Evaluations were taken at screening and randomization (week 0); weeks 1, 2, 3, 4, and 6 (primary outcome, end of treatment); and at weeks 7 and 10 for posttreatment follow-up
- Participants were randomized (1:1:1) to receive placebo, azetukalner 10 mg, or azetukalner 20 mg taken once daily with food with no titration period
- Key efficacy objectives and endpoints are summarized in **Table 2**

Table 2. Key Efficacy Objectives and Endpoints

Objectives	Endpoints
Primary	
• To assess the efficacy of 10 mg and 20 mg doses of azetukalner compared with placebo on improvement of depressive symptoms	• Change in MADRS score at week 6
Secondary	
• To assess the efficacy of azetukalner compared with placebo on improvement of anhedonia symptoms • To assess the efficacy of azetukalner compared with placebo on improvement of anxiety symptoms	• Change in SHAPS score at week 6 • Change in BAI score at week 6
Exploratory	
• To evaluate the effect of azetukalner compared with placebo on depressive symptoms • To assess the effect of azetukalner compared with placebo on overall health status	• Change in HAM-D17 score at week 6 • CGI-I score at week 6

BAI, Beck Anxiety Inventory[13]; CGI-I, Clinical Global Impression of Improvement; HAM-D17, Hamilton Depression Rating Scale, 17-Item[11]; MADRS, Montgomery–Åsberg Depression Rating Scale[14]; SHAPS, Snaith–Hamilton Pleasure Scale.[12]

Safety Assessments

- Safety assessments include TEAEs, serious AEs, clinical laboratory tests, electrocardiograms, and vital signs

RESULTS

Study Population

- 168 participants were randomized, and 167 participants received ≥1 dose of study treatment (safety population)
- 164 participants received ≥1 dose of study treatment and had ≥1 postrandomization Montgomery–Åsberg Depression Rating Scale (MADRS) score (modified intent-to-treat [mITT] population)
- Baseline demographic characteristics were similar across treatment arms (**Table 3**)

Table 3. Participant Demographics and Baseline Characteristics (Safety Population)

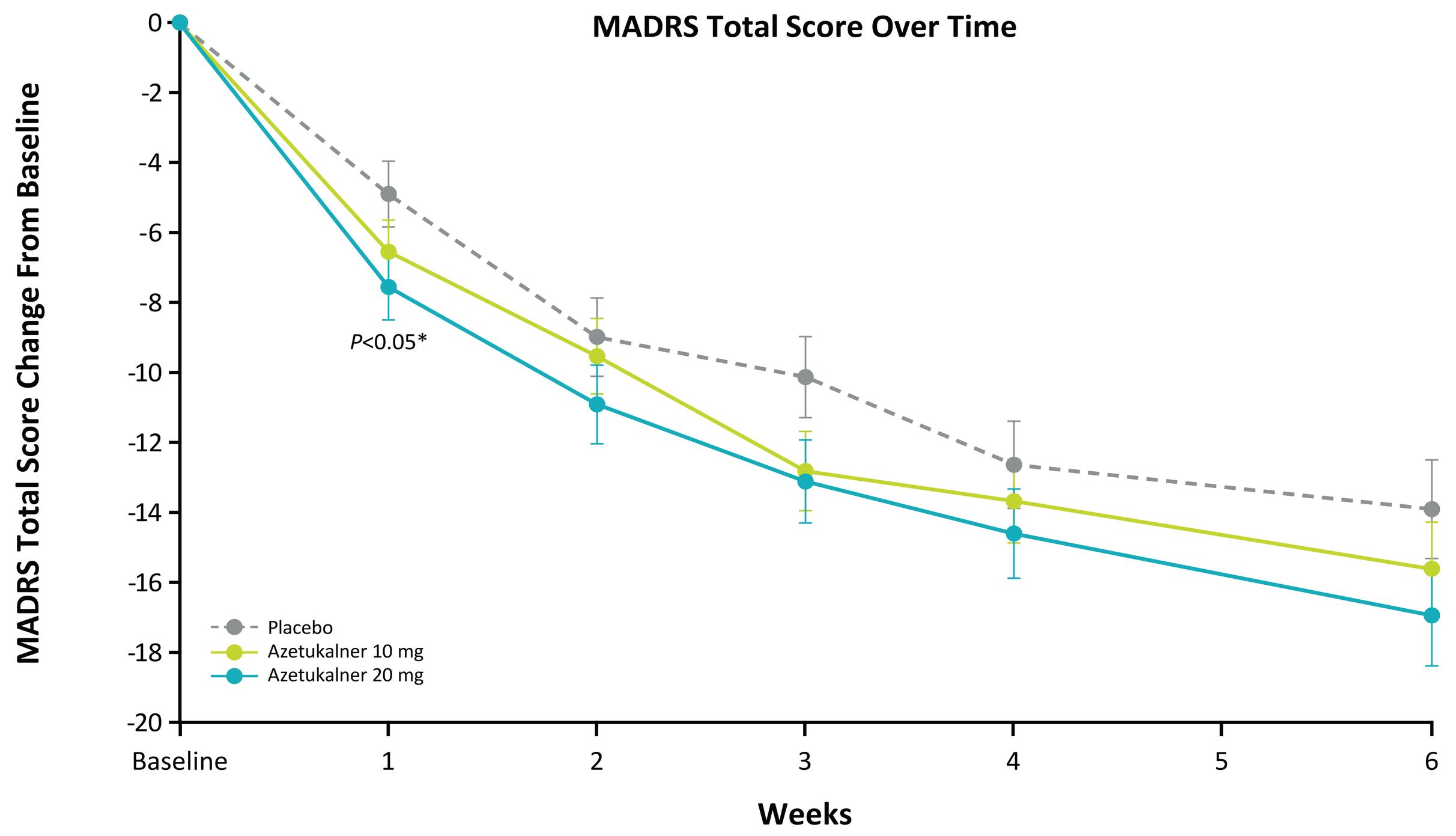
Characteristic	Placebo (n=55)	Azetukalner 10 mg (n=56)	Azetukalner 20 mg (n=56)
Age, mean (SD), y	47.5 (12.7)	47.4 (14.6)	46.6 (13.8)
Female sex, n (%)	37 (67.3)	44 (78.6)	30 (53.6)
Race, n (%)			
White	37 (67.3)	32 (57.1)	32 (57.1)
Black or African American	16 (29.1)	22 (39.3)	20 (35.7)
Asian	1 (1.8)	2 (3.6)	2 (3.6)
Multiple	1 (1.8)	0 (0)	2 (3.6)
Ethnicity, Hispanic or Latino, n (%)	20 (36.4)	30 (53.6)	22 (39.3)
BMI, mean (SD), mg/kg²	28.2 (4.1)	29.2 (4.2)	28.0 (4.4)
MADRS total score, mean (SD)	34.5 (4.6)	34.2 (4.8)	33.1 (5.8)
SHAPS total score, mean (SD)	35.3 (5.6)	36.8 (5.4)	37.5 (6.3)
BAI score, mean (SD)	13.5 (8.3)	12.5 (9.1)	14.9 (13.6)
HAM-D17 total score, mean (SD)	25.5 (3.2)	24.7 (2.9)	24.0 (2.9)
Duration of current MDE, mean (SD), y	0.79 (0.51)	0.80 (0.47)	0.91 (0.52)
Number of previous depressive episodes, mean (SD)	4.9 (6.5)	4.6 (5.2)	4.0 (3.4)

Safety population: all participants who received ≥1 dose of study treatment. BAI, Beck Anxiety Inventory; BMI, body mass index; HAM-D17, Hamilton Depression Rating Scale, 17-Item; MADRS, Montgomery–Åsberg Depression Rating Scale; MDE, major depressive episode; SHAPS, Snaith–Hamilton Pleasure Scale.

Efficacy

- At week 6, the mean reduction in MADRS score from baseline (primary endpoint) was 13.90 in the placebo group, 15.61 in the azetukalner 10 mg group, and 16.94 in the azetukalner 20 mg group
- The dose-dependent mean reduction from baseline in MADRS was clinically meaningful,[15] but not statistically significant, showing a –3.04-point difference between placebo and the azetukalner 20 mg group (nominal P=0.135) (**Figure 3**)
  - At week 1, the mean reduction in MADRS score from baseline (exploratory endpoint) was significantly different between placebo and azetukalner 20 mg groups (4.88 vs 7.54; nominal P=0.047)

Figure 3. Change in MADRS Total Score From Baseline (mITT Population per Week 1 Treatment)



Primary Endpoint — Week 6	Placebo (n=54)	Azetukalner 10 mg (n=57)	Azetukalner 20 mg (n=53)
MADRS total score change from baseline at **week 6**, LS mean (SE)	–13.90 (1.41)	–15.61 (1.34)	–16.94 (1.45)
Difference vs placebo (95% CI)		–1.71 (–5.56, 2.14)	–3.04 (–7.04, 0.96)
P value†		0.381	0.135

Exploratory Endpoint — Week 1	Placebo (n=54)	Azetukalner 10 mg (n=57)	Azetukalner 20 mg (n=53)
MADRS total score change from baseline at **week 1**, LS mean (SE)	–4.88 (0.94)	–6.53 (0.90)	–7.54 (0.94)
Difference vs placebo (95% CI)		–1.66 (–4.23, 0.92)	–2.66 (–5.30, –0.03)
P value†		0.206	0.047*

*Azetukalner 20 mg vs placebo, nominal P<0.05.
†All P values are nominal. A mixed-effect model for repeated measures was used to perform the analysis, with change from baseline as the outcome variable; the baseline MADRS score as a covariate; and treatment group, visit (up to week 6 visit), and treatment-by-visit interaction as fixed effects. Graph shows LS mean (SE). All doses taken once daily with food with no titration period. mITT population consists of all randomized participants who received ≥1 dose of study treatment and had ≥1 postrandomization MADRS.
LS, least squares; MADRS, Montgomery–Åsberg Depression Rating Scale; mITT, modified intent to treat.

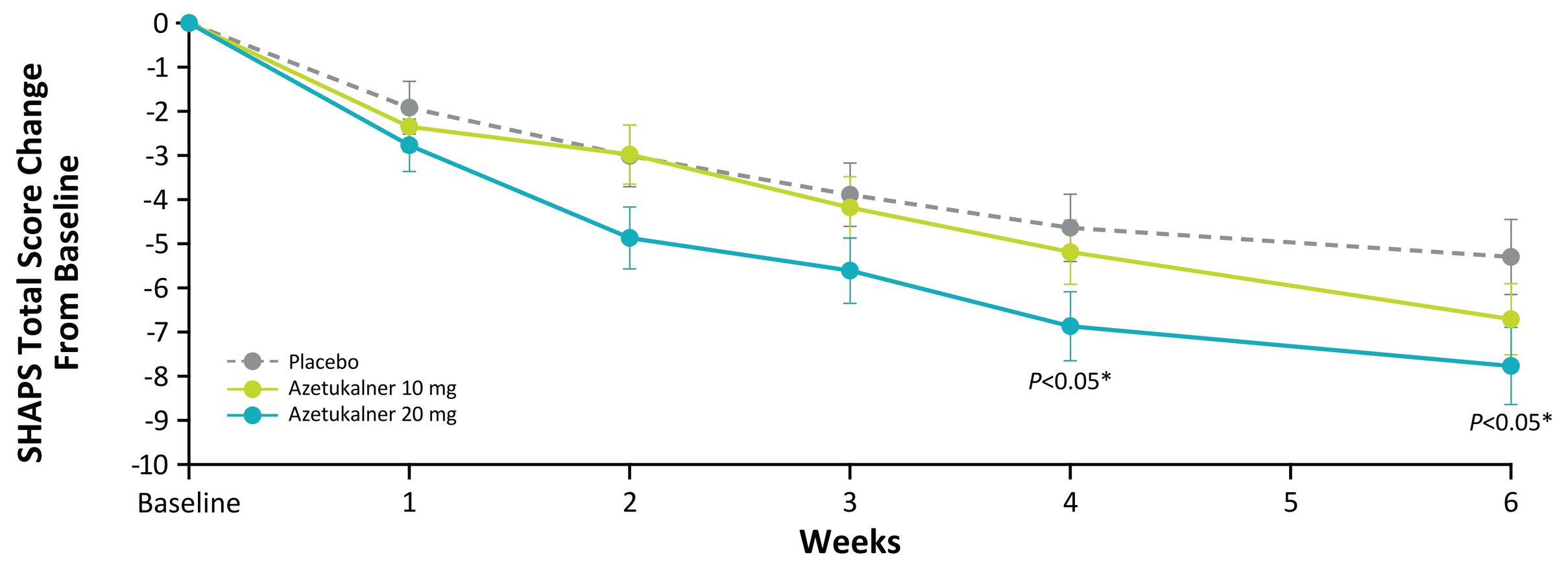
Table 4. Change in HAM-D17 Total Score From Baseline at Week 6 (Exploratory Endpoint) (mITT Population per Week 1 Treatment)

Exploratory Endpoint – Week 6	Placebo (n=54)	Azetukalner 10 mg (n=57)	Azetukalner 20 mg (n=53)
HAM-D17 total score change from baseline at **week 6,** LS mean (SE)	–10.2 (1.04)	–12.2 (0.95)	–13.3 (1.07)
Difference vs placebo (95% CI)		–2.1 (–4.8, 0.7)	–3.1 (–6.0, –0.1)
P value†		0.146	0.042*

*Azetukalner 20 mg vs placebo, nominal P<0.05.
†All P values are nominal. 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. HAM-D17 was assessed at screening, baseline, and week 6. All doses taken once daily with food with no titration period. mITT population consists of all randomized participants who received ≥1 dose of study treatment and had ≥1 postrandomization MADRS. HAM-D17, Hamilton Depression Rating Scale, 17-Item; LS, least squares; MADRS, Montgomery–Åsberg Depression Rating Scale; mITT, modified intent to treat.

- The mean reduction in HAM-D17 score from baseline to week 6 was significantly different between placebo and azetukalner 20 mg groups (10.2 vs 13.3; difference –3.1, nominal P=0.042) (**Table 4**)

Figure 4. Change in SHAPS Total Score From Baseline at Week 6 (Secondary Endpoint) (mITT Population per Week 1 Treatment)



Secondary Endpoint – Week 6	Placebo (n=54)	Azetukalner 10 mg (n=57)	Azetukalner 20 mg (n=53)
SHAPS total score change from baseline at **week 6**, LS mean (SE)	–5.30 (0.85)	–6.71 (0.81)	–7.77 (0.87)
Difference vs placebo (95% CI)		–1.41 (–3.72, 0.91)	–2.46 (–4.88, –0.04)
P value†		0.232	0.046*

*Azetukalner 20 mg vs placebo, nominal P<0.05.
†All P values are nominal. A mixed-effect model for repeated measures was used was used to perform the analysis, with change from baseline as the outcome variable; the baseline SHAPS score as a covariate; and treatment group, visit (up to week 6 visit), and treatment-by-visit interaction as fixed effects. Graph shows LS mean (SE). All doses taken once daily with food with no titration period. mITT population consists of all randomized participants who received ≥1 dose of study treatment and had ≥1 postrandomization MADRS. LS, least squares; MADRS, Montgomery–Åsberg Depression Rating Scale; mITT, modified intent to treat; SHAPS, Snaith–Hamilton Pleasure Scale.

- The mean reduction in SHAPS score from baseline to week 6 was significantly different between placebo and azetukalner 20 mg groups (5.30 vs 7.77; difference –2.46, nominal P=0.046) (**Figure 4**)
- There were no statistically significant differences in change from baseline BAI total scores to week 6 between the placebo and the azetukalner groups in the mITT population. At baseline, the X-NOVA population demonstrated minimal to mild symptoms of anxiety[16] (baseline mean BAI total score ≤15; **Table 3**)
- In a post hoc analysis, amongst those participants with moderate to severe BAI scores (≥16) at baseline, numerical improvements were noted in the change from baseline BAI total scores to week 6 in the 20 mg azetukalner group compared with the placebo group
  - The mean reduction in BAI total score from baseline at week 6 was –9.36 in the placebo group (n=14), –10.83 in the azetukalner 10 mg (n=18) group, and –15.38 in the azetukalner 20 mg group (n=16)
- Statistical significance was achieved in reporting of at least minimally improved symptoms of depression as assessed by physicians using the Clinical Global Impression of Improvement (nominal P=0.004) in the azetukalner 20 mg group compared with placebo

Safety

- Azetukalner was generally well tolerated, with low incidence of TEAEs reported across all treatment arms (**Table 5**)

Table 5. Most Common TEAEs ≥5% (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	33 (60.0)	29 (51.8)	37 (66.1)	66 (58.9)
Nervous system disorders	15 (27.3)	14 (25.0)	24 (42.9)	38 (33.9)
Dizziness	4 (7.3)	4 (7.1)	10 (17.9)	14 (12.5)
Somnolence	1 (1.8)	6 (10.7)	6 (10.7)	12 (10.7)
Headache	7 (12.7)	5 (8.9)	5 (8.9)	10 (8.9)
Disturbance in attention	0 (0)	0 (0)	5 (8.9)	5 (4.5)
Paresthesia	1 (1.8)	0 (0)	3 (5.4)	3 (2.7)
Psychiatric disorders	8 (14.5)	7 (12.5)	7 (12.5)	14 (12.5)
Depression	2 (3.6)	3 (5.4)	2 (3.6)	5 (4.5)
Insomnia	3 (5.5)	1 (1.8)	1 (1.8)	2 (1.8)
Gastrointestinal disorders	6 (10.9)	5 (8.9)	7 (12.5)	12 (10.7)
Nausea	3 (5.5)	2 (3.6)	2 (3.6)	4 (3.6)
Eye disorders	2 (3.6)	1 (1.8)	6 (10.7)	7 (6.3)
Vision blurred	1 (1.8)	0 (0)	3 (5.4)	3 (2.7)

All doses taken once daily with food with no titration period. Safety population: all participants who received ≥1 dose of study treatment. TEAE, treatment-emergent adverse event.

- The most commonly reported TEAEs in the azetukalner 20 mg group included dizziness (17.9%), somnolence (10.7%), headache (8.9%), and disturbance in attention (8.9%), compared with the placebo group, which reported dizziness (7.3%), somnolence (1.8%), headache (12.7%), and disturbance in attention (0%)
- Rates of discontinuation were similar across all treatment arms, and rates of discontinuation owing to TEAEs were low, with 3 participants in the azetukalner 20 mg group (5.4%) compared with 2 participants in the placebo group (3.6%) (**Table 6**)

Table 6. 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)

All doses taken once daily with food with no titration period. Safety population: all participants who received ≥1 dose of study treatment. TEAE, treatment-emergent adverse event.

- No serious TEAEs were reported in the 2 azetukalner treatment groups, and there were 2 participants (3.6%) in the placebo group who experienced a serious TEAE (idiopathic intracranial hypertension [n=1] and homicidal ideation [n=1])
- Azetukalner was not associated with notable weight gain, with a mean (SD) gain of 0.84 kg (2.3) from baseline reported overall in azetukalner-treated participants
- There were no patient reports of notable sexual dysfunction; only 1 participant (0.9%) of all azetukalner-treated participants reported a TEAE of mild decreased libido

CONCLUSIONS

- Azetukalner demonstrated a clinically meaningful reduction of depression measured by the MADRS, a statistically significant reduction in HAM-D17 (depression), an early onset of action, a significant reduction in anhedonia, and a potentially differentiated safety profile compared with other antidepressants
- The X-NOVA results are particularly meaningful given that there was a 2 in 3 chance of receiving active treatment, which has been previously shown to increase the placebo response[17]
- Based on the promising results of X-NOVA, 3 Phase 3 clinical trials are being planned to explore azetukalner in MDD, with the first Phase 3 study expected to initiate in the second half of 2024

References

1. Bialer M, et al. *Epilepsia*. 2022;63(11):2883-2910.
2. French JA, et al. *JAMA Neurol*. 2023;80(11):1145-1154.
3. French J, et al. Interim long-term safety and efficacy of XEN1101, a potent, selective potassium channel opener: update from an ongoing, open-label extension of a phase 2b study (X-TOLE) in adults with focal epilepsy (Poster 1.277). 2023. Presented at American Epilepsy Society Annual Meeting, December, 1-5 2023 https://aesnet.org/abstractslisting/interim-long-term-safety-and-efficacy-of-xen1101-a-potent-selective-potassium-channel-opener-update-from-an-ongoing-open-label-extension-of-a-phase-2b-study-(x-tole)-in-adults-with-focal-epilepsy
4. World Health Organization. Depressive disorder (depression). World Health Organization. Accessed November 15, 2023. https://www.who.int/news-room/fact-sheets/detail/depression
5. Rush AJ, et al. *Am J Psychiatry*. 2006;163(11):1905-1917.
6. Marx W, et al. *Nat Rev Dis Primers*. 2023;9(1):44.
7. Friedman AK, et al. *Nat Commun*. 2016;7(1):11671.
8. Costi S, et al. *Am J Psychiatry*. 2021;178(5):437-446.
9. ClinicalTrials.gov. A study to evaluate the safety, tolerability and efficacy of XEN1101 in major depressive disorder (X-NOVA). 2022. Accessed October 26, 2023. https://clinicaltrials.gov/study/NCT05376150
10. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Text Revision Dsm-5-tr* 5th ed. American Psychiatric Association; 2022.
11. Hamilton M. *J Neurol Neurosurg Psychiatry*. 1960;23(1):56-62.
12. Snaith RP, et al. *Br J Psychiatry*. 1995;167(1):99-103.
13. Beck AT, et al. *J Consult Clin Psychol*. 1988;56(6):893-897.
14. Montgomery SA and Asberg M. *Br J Psychiatry*. 1979;134:382-389.
15. Duru G and Fantino B. *Curr Med Res Opin*. 2008;24(5):1329-1335.
16. Brenner LA. Beck Anxiety Inventory. In: Kreutzer JS, et al, eds. *Encyclopedia of Clinical Neuropsychology*. Springer New York; 2011:359-361.
17. Papakostas GI and Fava M. *Eur Neuropsychopharmacol*. 2009;19(1):34-40.

ACKNOWLEDGMENTS Medical writing and editorial support was provided by Kirk W. Evanson, PhD, from The Curry Rockefeller Group, LLC, a Citrus Health Group, Inc., company (Chicago, Illinois), and was funded by Xenon Pharmaceuticals Inc.

DISCLOSURES Noam N. Butterfield, Constanza Luzon Rosenblut, Gregory N. Beatch, Celene Grayson, Cynthia Harden, Jenny Qian, Joe McIntosh, and Christopher Kenney are employees of and own stock or stock options in Xenon Pharmaceuticals Inc. Maurizio Fava has numerous relationships with various commercial and academic entities (served as an ad board member, research support, speaking engagements, etc), including Xenon. He also had equity holdings with Neuromity, Psy Therapeutics, and Sensorium. He has received royalty/patent and other income from patents for Sequential Parallel Comparison Design (SPCD), licensed by mgH to Pharmaceutical Product Development, LLC (PPD); patent application for a combination of ketamine plus scopolamine in MDD, licensed by mgH to Biohaven; and patents for pharmacogenomics of depression treatment with folate and for a compound for improving l-arginine bioavailability. He holds the copyright for the mgH Cognitive & Physical Functioning Questionnaire (CPFQ), Sexual Functioning Inventory (SFI), Antidepressant Treatment Response Questionnaire (ATRQ), Discontinuation-Emergent Signs & Symptoms (DESS), Symptoms of Depression Questionnaire (SDQ), Anxiety Symptoms Questionnaire (ASQ), and SAFER. Christoph U. Correll has been a consultant and/or advisor to or has received honoraria from many companies including AbbVie, Allergan, Biogen, Boehringer Ingelheim, Bristol Meyers Squibb, Cerevel, Denovo, Gedeon Richter, Hikma, IntraCellular Therapies, Lundbeck, MedInCell, Neurelis, Novo Nordisk, Sunovion, Teva, and Xenon. He has served on a numerous data safety monitoring boards. He has received grant support from Janssen and Takeda. He received royalties from UpToDate and is also a stock option holder of Cardio Diagnostics, Kuleon Biosciences, LB Pharma, Mindpax, and Quantic. Anthony J. Rothschild has received grant or research support from Compass Pathways, Janssen, Otsuka, and the Irving S. and Betty Brudnick Endowed Chair in Psychiatry; is a consultant to Daiichi Sankyo, Sage, Xenon, Neumora, Zydus (USA), Sandoz, and Lupin; and has received royalties for various publications published by the American Psychiatric Press and from UpToDate. James W. Murrough has provided consultation services to Xenon, LivaNova, KetaMed, Merk, Cliniclabs, Biohaven Pharmaceuticals, and Compass Pathfinder and is named on a patent pending for KCNQ channel openers to treat depression. Sanjay J. Mathew has received consultant fees from numerous companies including Abbott, Boehringer Ingelheim, Brii Biosciences, Clexio Biosciences, Delix Therapeutics, Merck, Sage, Sunovion, and Xenon. He has received research support from Boehringer Ingelheim, Engrail, Merck, Neurocrine, and Sage.

FUNDING This study is funded by Xenon Pharmaceuticals Inc.

XENON