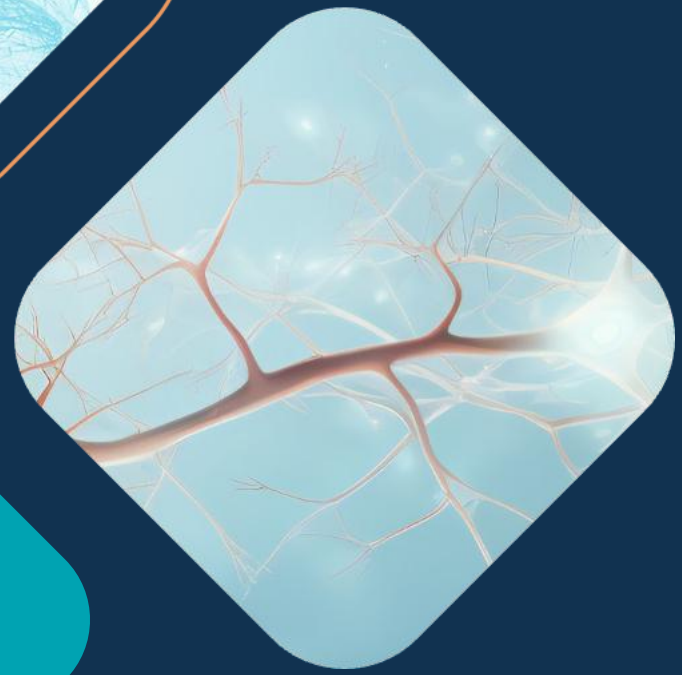
Investor Presentation

CORPORATE OVERVIEW
SEPTEMBER 2026





NASDAQ: XENE
xenon-pharma.com

Xenon™

Forward Looking Statement/Safe Harbor

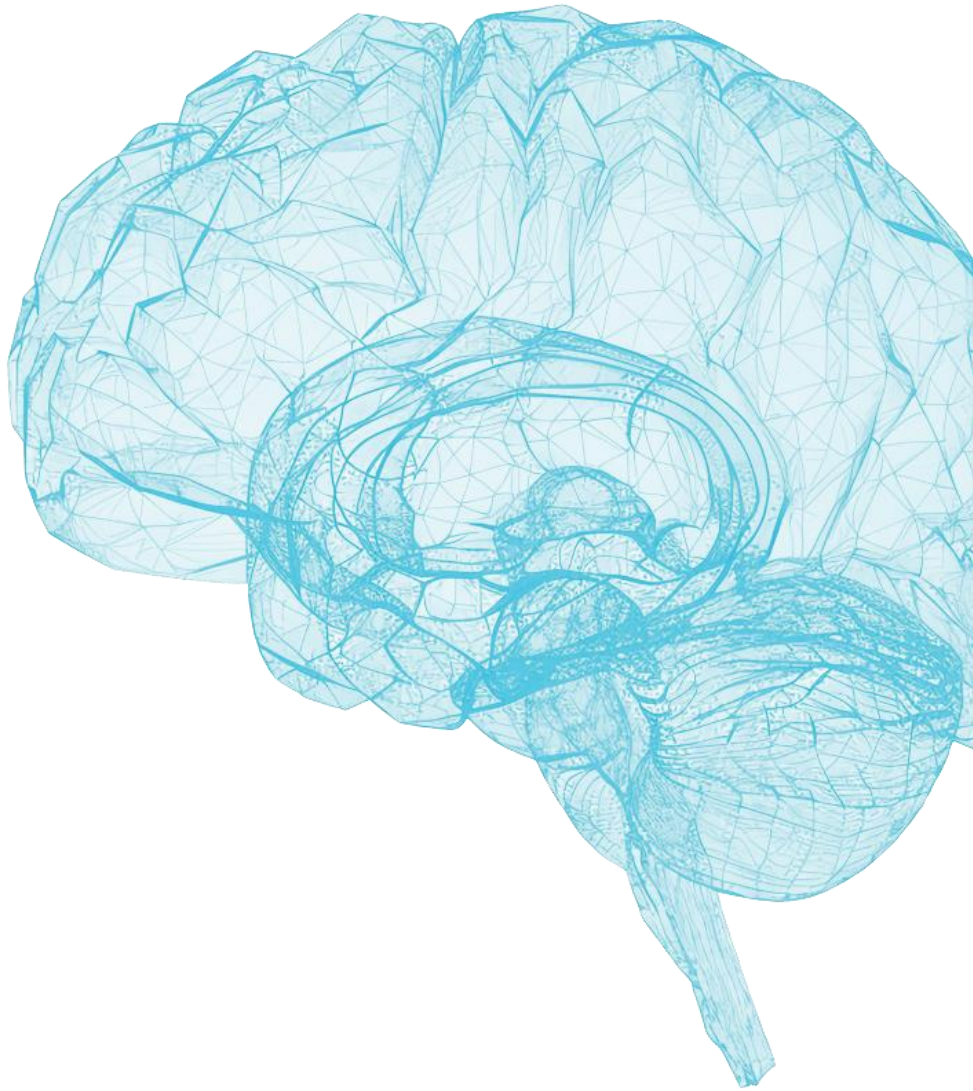
This slide presentation contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, and the Private Securities Litigation Reform Act of 1995 and Canadian securities laws. These forward-looking statements are not based on historical fact, and include statements regarding the status of, and potential results from, clinical studies; the potential efficacy, safety profile, future development plans in current and anticipated indications, addressable market, regulatory success and commercial potential of our and our partners' product candidates; the efficacy of our clinical study designs; our ability to achieve milestones in our pipeline and development programs, including the anticipated filing of INDs (or equivalent), initiation of clinical studies, completion of trial enrollment and timing of topline data readout from any studies; the timing and results of our interactions with regulators; and our ability to successfully develop, obtain regulatory approval for, and commercialize azetukalner and our other product candidates.

These forward-looking statements are based on current assumptions that involve risks, uncertainties and other factors that may cause the actual results, events, or developments to be materially different from those expressed or implied by such forward-looking statements. These risks and uncertainties, many of which are beyond our control, include, but are not limited to: clinical studies may not demonstrate safety and efficacy of any of our or our collaborators' product candidates; promising results from pre-clinical development activities or early clinical study results may not be replicated in later clinical studies; our assumptions regarding our planned expenditures and sufficiency of our cash to fund operations may be incorrect; our ongoing discovery and pre-clinical efforts may not yield additional product candidates; any of our or our collaborators' product candidates, including azetukalner, may fail in development, may not receive required regulatory approvals, or may be delayed to a point where they are not commercially viable; we may not achieve additional milestones in our proprietary or partnered programs; regulatory agencies may delay the initiation or completion of clinical studies or impose additional requirements prior to approval; the impact of market, industry, and regulatory conditions on clinical study enrollment; the impact of competition; the impact of expanded product development and clinical activities on operating expenses; the impact of new or changing laws and regulations; the impact of unstable economic conditions in the general domestic and global economic markets; adverse conditions from geopolitical events; as well as the other risks identified in our filings with the U.S. Securities and Exchange Commission and the securities commissions in British Columbia, Alberta, and Ontario. These forward-looking statements speak only as of the date hereof and we assume no obligation to update these forward-looking statements, and readers are cautioned not to place undue reliance on such forward-looking statements.

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About Xenon Pharmaceuticals

- Neuroscience-focused biopharmaceutical company and leader in small molecule, ion channel drug discovery and development
- Robust pipeline of therapeutic candidates targeting potassium and sodium channels across various indications
- Lead molecule, azetukalner (AZK), is a highly potent K_V7 channel opener in late-stage development for epilepsy and neuropsychiatric disorders
- Strong financial position
  - Cash, cash equivalents and marketable securities of $1.2 billion with cash runway into 2029



Azetukalner is an investigational drug that has yet to be approved by the FDA.

Xenon's Strategy

Building a fully-integrated neuroscience company committed to discovery, development and commercialization of life-changing medicines for patients in need

Approval and Launch of AZK in Epilepsy

- NDA submitted Q3 2026 in epilepsy, based on two positive RCTs
- Phase 3 X-ACKT study ongoing to support potential label expansion in PGTCS
- Phase 3 X-TOLE3 study ongoing to support ex-U.S. filings, including Japan

Broaden AZK Opportunity to Neuropsychiatry

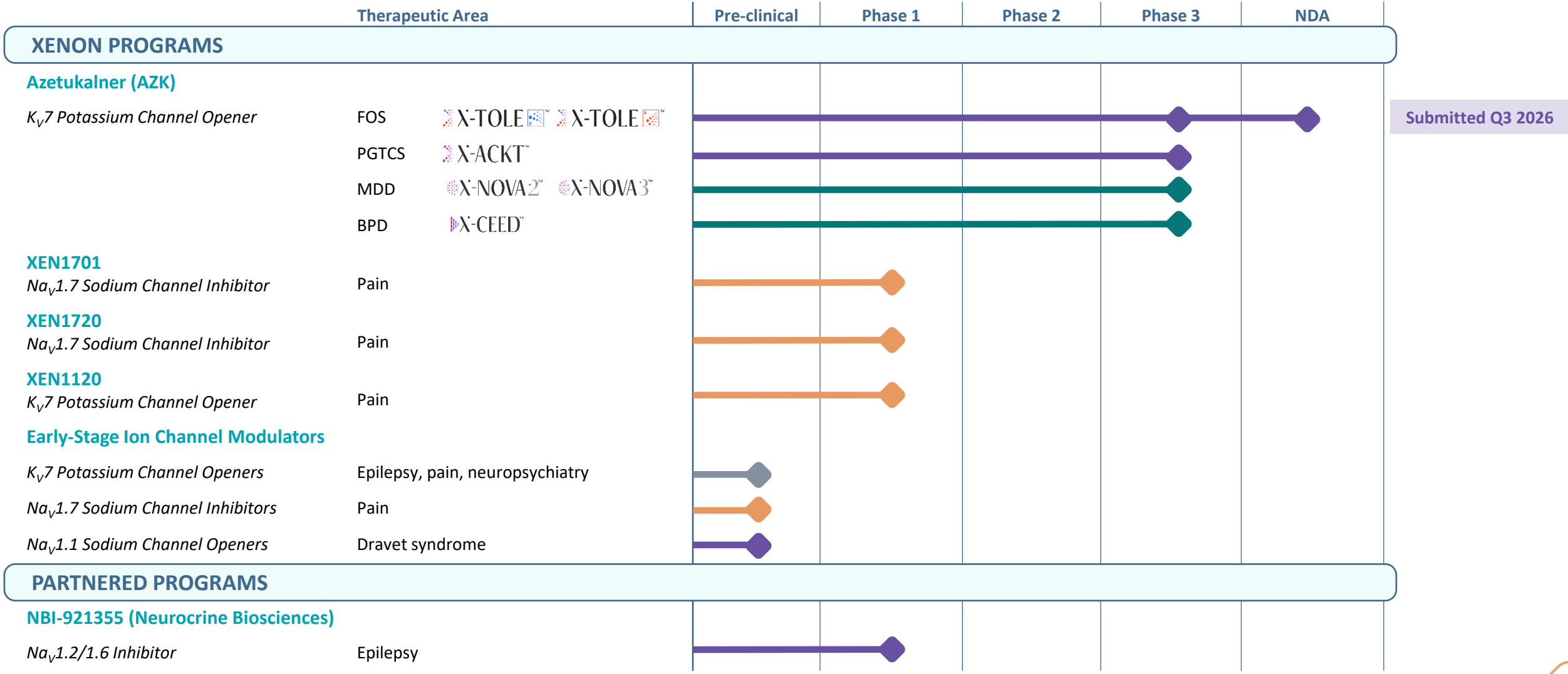
- Clinical, pre-clinical and genetic data supportive of K_V7 mechanism in MDD and BPD
- X-NOVA2 enrollment completed, topline data anticipated Q1 2027
- Phase 3 X-NOVA3, X-CEED and OLE ongoing*

Advance Early-Stage Pipeline

- Three $Na_V1.7$ and K_V7 molecules in Phase 1 development for pain
- Early-stage pipeline targeting multiple potassium and sodium channels

**New enrollment temporarily paused to evaluate adjustments to protocol; AZK: azetukalner; RCT: randomized controlled trials; NDA: New Drug Application; FOS: focal onset seizures; PGTCS: primary generalized tonic-clonic seizures; MDD: major depressive disorder; BPD: bipolar depression; OLE: open-label extension.*

Neuroscience-Focused Pipeline



This chart displays pipeline drug candidates currently undergoing clinical and pre-clinical testing in a variety of therapeutic areas. 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 seizures; PGTCS: primary generalized tonic-clonic seizures; MDD: major depressive disorder; BPD: bipolar depression; NDA: New Drug Application.
Purple: epilepsy; Green: depression; Orange: pain; Grey: multiple.

Azetukalner in Epilepsy

AZK's Potential for a Differentiated Profile in Epilepsy



Robust Clinical Data

- Compelling double-blind efficacy data in FOS patients from two PBO-controlled studies
- Durable long-term seizure reduction and seizure freedom data in ongoing X-TOLE OLE



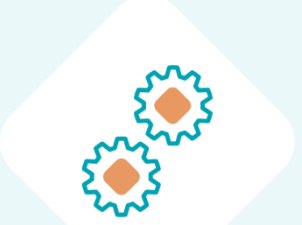
Well-Documented Safety Profile

- 1,500+ patient years of data in FOS patients, with some dosed for more than 5 years
- Consistent safety profile between X-TOLE and X-TOLE2 studies



Ease-of-Use

- Once-daily dosing
- No titration needed
- No meaningful DDIs with other ASMs or anticipated monitoring requirements



Novel Mechanism

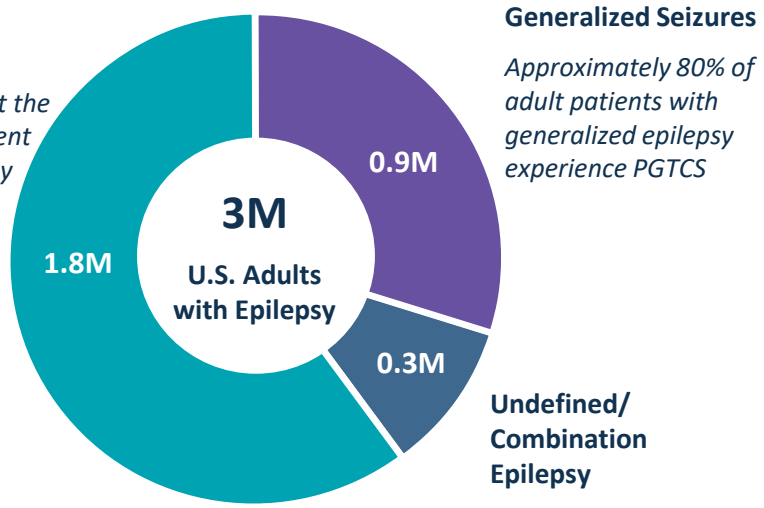
- Highly potent $K_V7.2/7.3$ potassium channel opener
- Differentiated mechanism of action may support rational polytherapy for epilepsy

FOS: focal onset seizures; DDIs: drug-drug interactions; ASMs: antiseizure medications; PBO: placebo; OLE: open label extension; MDD: major depressive disorder.

Significant Epilepsy Burden in U.S.

Fourth most common neurological condition with substantial unmet medical needs and limited innovation

Estimated Diagnosed Adult Epilepsy Patient Population in the U.S.



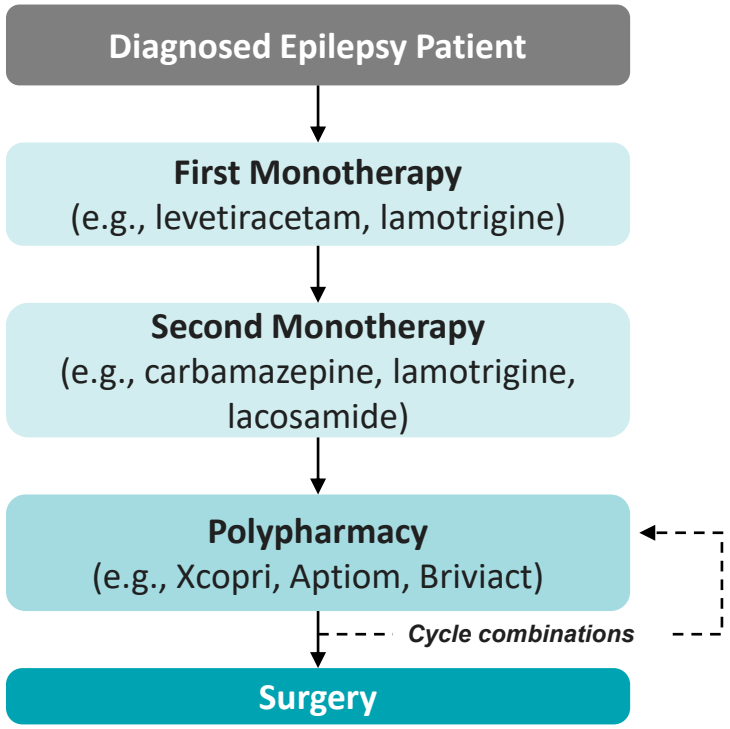
Ongoing Treatment Challenges in Epilepsy

Inadequate Seizure Control	Complicated Treatment Regimens	Limited Opportunities for Rational Polytherapy
Despite availability of 30+ ASMs, **up to 50% of patients** do not achieve seizure freedom with 1st line ASMs, and **about 1/3** have drug-resistant epilepsy	Many ASMs require **burdensome management of DDIs and lengthy or complex titration periods** to avoid serious AEs, complicating treatment for patients	**Most ASMs fall into four main mechanisms of action**, which may limit use of rational polytherapy for patients with uncontrolled seizures

FOS: focal onset seizures; PGTCS: primary generalized tonic-clonic seizures; AEs: adverse events; ASMs: antiseizure medications

Milligan TA. Am J Med. 2021; Kobau R et al. Epilepsy Behav. 2023; Gupta S et al. Epilepsia Open. 2017; Keränen T et al. Epilepsia. 1988; ScienceDirect. 2026; Landmark CJ et al. Epileptic Disord. 2023; Chen Z et al. JAMA. 2018; Kwan P. Epilepsia. 2010; Barnard SN et al. JAMA Neurol. 2025; Löscher W and Klein P. CNS Drugs. 2021; Stern JM et al. 2025 AES Annual Meeting; Stern JM et al. 2026 AAN Annual Meeting; Drugs@FDA: FDA-Approved.

Treatment Decisions Are Highly Individualized and Complex



Focal and general epilepsy have similar treatment considerations, with select ASMs (e.g. valproate) used more frequently in FOS than in generalized

Treatment goal aims to optimize efficacy while managing tolerability

- Levetiracetam and lamotrigine are commonly used in early lines of treatment
- Monotherapy switching in second line driven by desire for better seizure control or tolerability/AE issues
- Comorbid conditions influence prescribing decisions

Patients continuing to experience sub-optimal response (poor efficacy, tolerability) frequently receive polypharmacy

- Branded therapies can potentially be accessed if a patient has tried and failed 1-2 generic ASMs
- Combinations typically involve mechanistic differentiation from early lines of therapy
- Effectiveness of polytherapy can be limited by the number of available MOAs:
  - Patients who do not respond to or tolerate one ASM with a specific MOA may be less likely to benefit from others with overlapping MOAs
  - Combining ASMs with overlapping MOAs may limit the potential benefit

FOS: focal onset seizures; MOAs: mechanisms of action; ASMs: antiseizure medications; AE: adverse event.
Company sponsored market research; Polychronidis K et al. Epilepsy Behav. 2024; D'Onofrio G et al. Neurotherapeutics. 2024; Lee JW and Dworetzky B. Pharmaceuticals. 2010.

Phase 3 X-TOLE2 Study: Results Summary

Results included in NDA submitted in Q3 2026

PRIMARY ENDPOINT WAS MET: Highly statistically significant, dose-dependent reduction from baseline in median monthly FOS frequency (MPC) over the 12-week treatment period vs. placebo



Responder rate 50:
Statistically significant, dose-dependent (15 and 25 mg) increase in number of responders with >50% reduction in monthly FOS frequency



Onset of efficacy:
Rapid onset of response as assessed by statistically significant MPC achieved within one week for AZK 25 mg vs. placebo



Overall health status:
Significant improvements in PGI-C/CGI-C for both 15 and 25 mg treatment groups vs. placebo

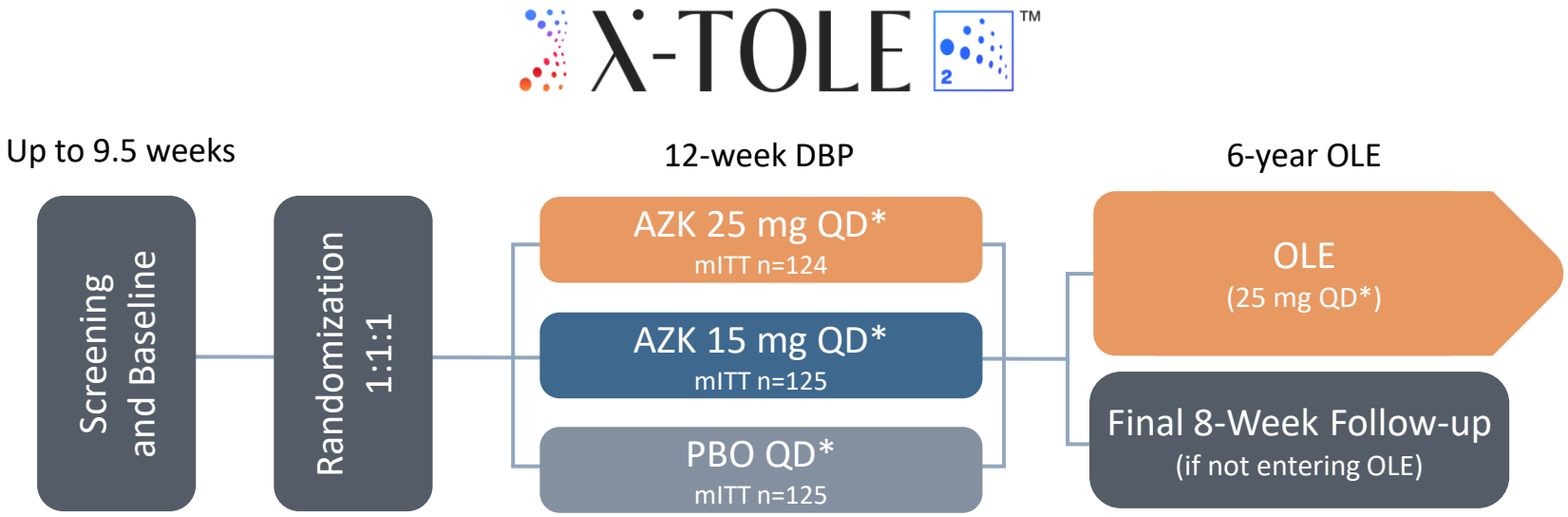


Safety and tolerability:
AZK profile consistent with Phase 2b X-TOLE study

AZK: azetukalner; PGI-C: Patient Global Impression of Change; CGI-C: Clinical Global Impression of Change; MPC: median percent change; FOS: focal onset seizures.

Phase 3 X-TOLE2 Clinical Study in FOS

Multicenter, randomized, double-blind, placebo-controlled clinical study to evaluate the clinical efficacy, safety, and tolerability of AZK as adjunctive treatment in adults diagnosed with FOS



Primary objective:

- Evaluate effect of AZK vs. PBO on MPC from baseline in monthly FOS frequency during the DBP

Secondary objectives include:

- Assess the effect of AZK vs. PBO on RR50, treatment effect as measured at Week 1, and PGI-C score

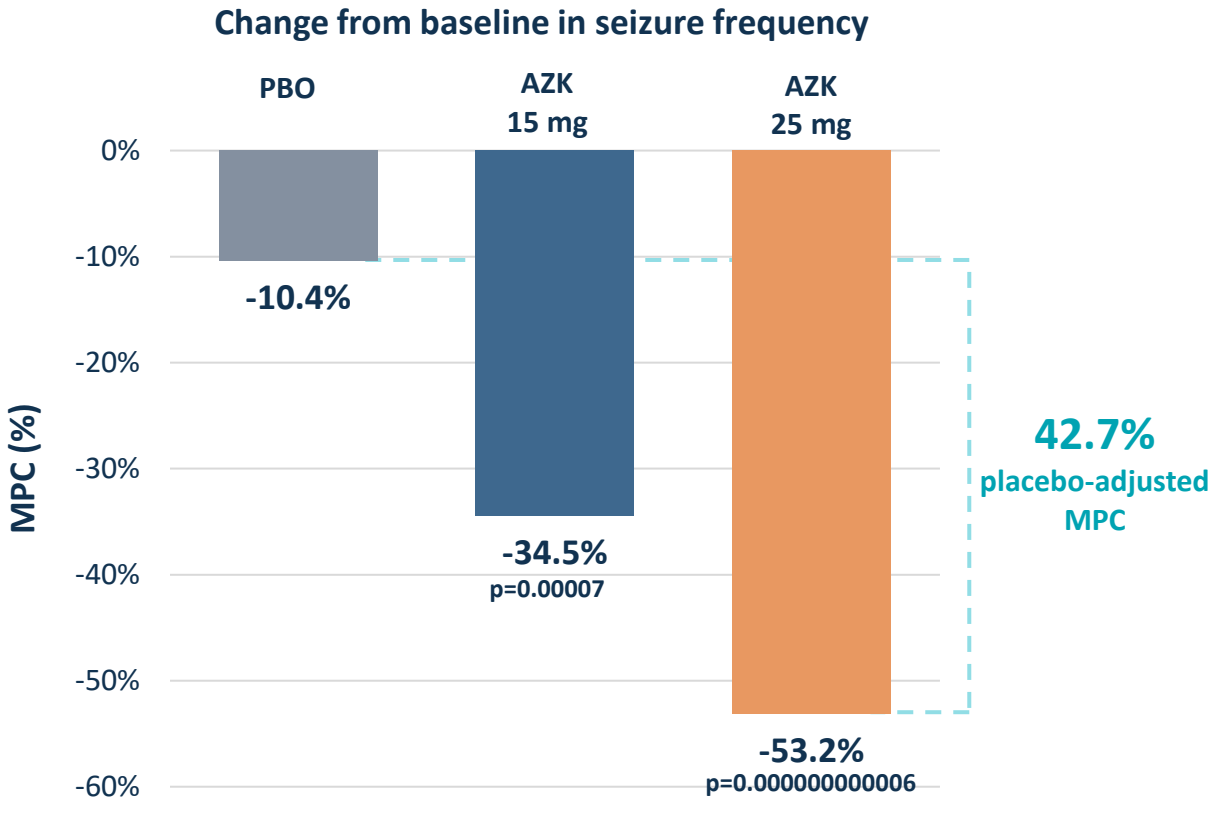
Safety and tolerability of AZK

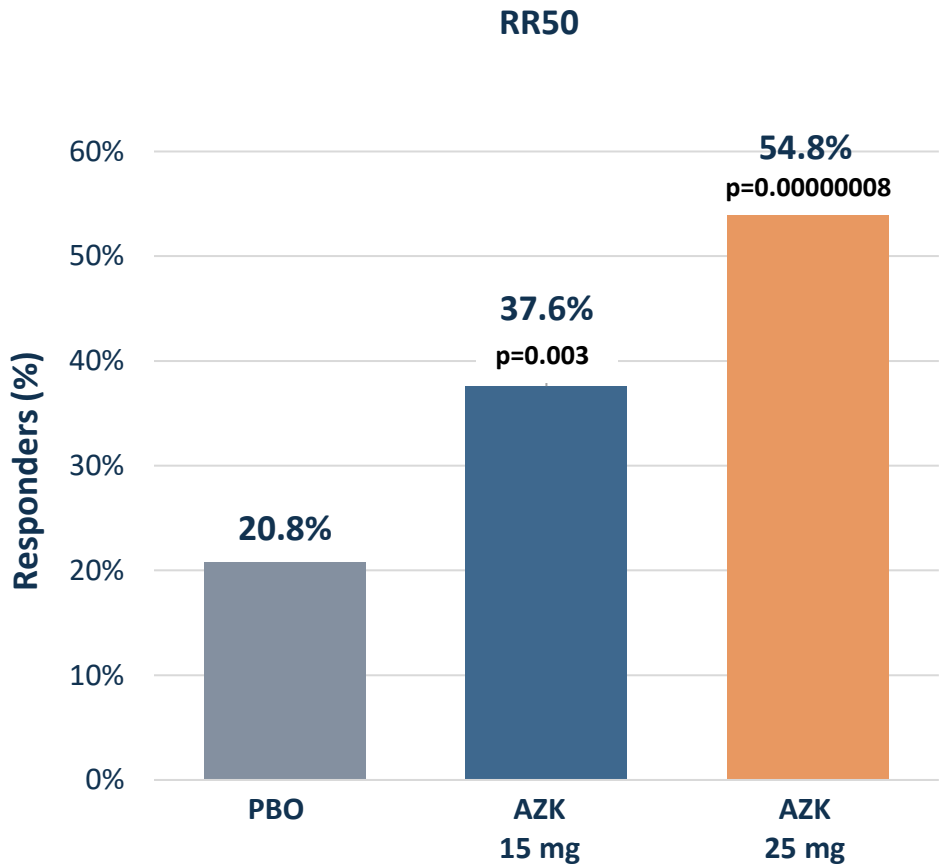
*Administered as a once-daily capsule with food with no titration period. Participants had highly treatment-resistant epilepsy, with a median of 5 prior ASMs, a baseline seizure frequency of 12.75 per month, and 51.3% using 3 concomitant ASMs.

Positive Phase 3 topline results from the X-TOLE2 study announced March 2026

AZK: azetukalner; DBP: double-blind period; FOS: focal onset seizures; MPC: median percent change; OLE: open-label extension; PBO: placebo; PGI-C: Patient Global Impression of Change; QD: once-daily; RR50: 50% responder rate; mITT: modified intent-to-treat.
X-TOLE2: NCT05614063; Open-Label Extension: NCT05718817.

X-TOLE2: Statistically Significant, Dose-Dependent Reduction in Seizures

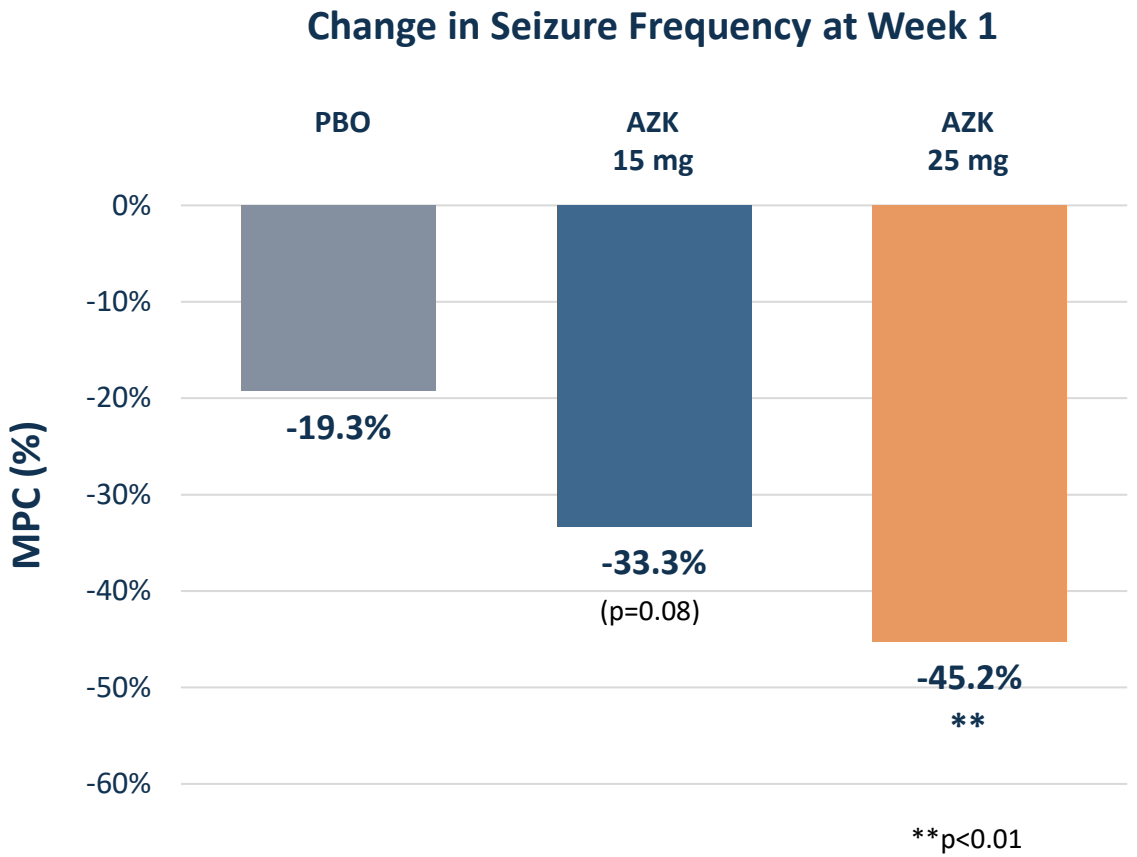




Highly statistically significant reduction in monthly FOS frequency with placebo-adjusted MPC for 25 mg cohort outperforming Phase 2b X-TOLE study

AZK: azetukalner; FOS: focal onset seizures; MPC: median percent change; PBO: placebo; RR50: 50% Responder Rate.
Phase 2b X-TOLE results: -34.6% placebo-adjusted MPC over 8 weeks in the 25 mg group (-52.8% from baseline in 25 mg group and -18.2% from baseline in placebo group)
"Results From the Phase 3 X-TOLE2 Study Evaluating Azetukalner, a Novel, Potent K_V7 Channel Opener, in Adults With Focal Onset Seizures (FOS)." 2026 AAN Annual Meeting.

X-TOLE2: Dose-Dependent Reductions in Weekly FOS Frequency Observed as Early as Week 1



Reductions in weekly FOS frequency sustained through DBP

AZK: azetukalner; DBP: double-blind period; FOS: focal onset seizures; MPC: median percent change; PBO: placebo.

"Results From the Phase 3 X-TOLE2 Study Evaluating Azetukalner, a Novel, Potent K_V7 Channel Opener, in Adults With Focal Onset Seizures (FOS)." 2026 AAN Annual Meeting.

X-TOLE2: Summary of TEAEs

Treatment-Emergent Adverse Events

Any TEAE occurred in:

- 62.4% in PBO
- 67.2% in AZK 15 mg
- 82.3% in AZK 25 mg

Most common TEAEs across all AZK groups included:

- Dizziness (20.5%)
- Somnolence (8.8%)
- Headache (8.8%)
- Fatigue (7.6%)

TEAEs resulted in discontinuation in:

- 3.2% in PBO
- 4.8% in AZK 15 mg
- 14.5% in AZK 25 mg

Most common TEAEs leading to discontinuation across all AZK groups:

- Dizziness (3.2%)
- Headache (1.6%)
- Fatigue (1.6%)
- Gait disturbance (1.2%)
- Coordination abnormal (1.2%)
- Speech disorder (1.2%)

Serious Adverse Events

Incidence of SAEs was low and similar across AZK groups:

- PBO (2.4%)
- AZK 15 mg (3.2%)
- AZK 25 mg (5.6%)

SAEs reported in >1 participant:

- Dysarthria (2)
- Tremor (2)
- Confusional state (2)
- Fall (2)

All reported from the AZK 25 mg group

AZK: azetukalner; PBO: placebo; TEAEs: treatment-emergent adverse events; SAEs: serious adverse events.

"Results From the Phase 3 X-TOLE2 Study Evaluating Azetukalner, a Novel, Potent K_V7 Channel Opener, in Adults With Focal Onset Seizures (FOS)." 2026 AAN Annual Meeting.

X-TOLE2: Additional Safety Findings & Safety Summary

Additional Safety Findings

- No severe allergic rashes (SJS, DRESS) occurred
- No signals of retinal pigment epithelium or macular abnormalities
- No signals of cardiovascular events
- No notable weight gain
- No deaths occurred
- Four non-serious TEAEs of urinary retention were reported
  - One participant in PBO and two in 25 mg with no dose reduction
  - One participant in 15 mg was hospitalized for a psychiatric event, which included catheterization and discontinuation

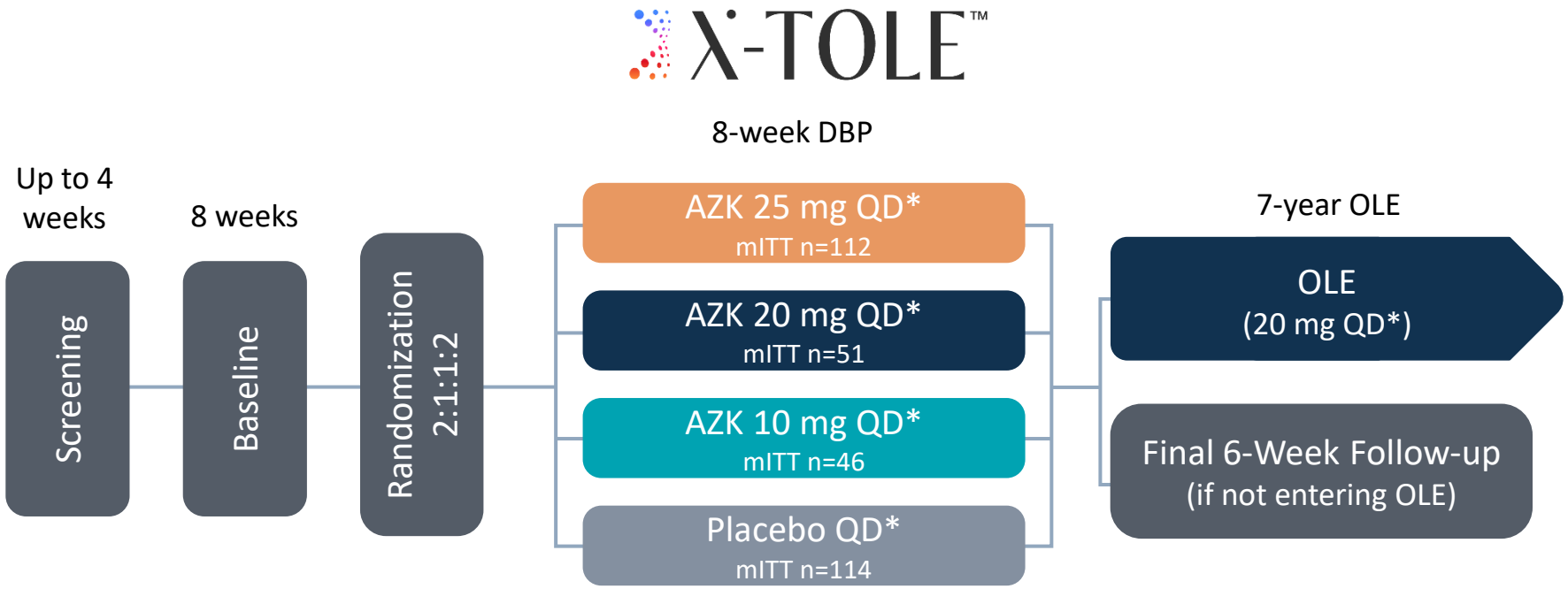
Summary of Safety and Tolerability

- AZK was generally well-tolerated with a dose-dependent incidence of TEAEs consistent with X-TOLE
- Incidence of TEAEs for AZK 15 mg was similar to PBO
- Most common TEAEs across all AZK groups were consistent with those reported for X-TOLE
- No individual TEAE led to discontinuation in >5% of participants
- Incidence of SAEs was low and similar across AZK groups

AZK: azetukalner; PBO: placebo; TEAE: treatment-emergent adverse event; SJS: Stevens-Johnson Syndrome; DRESS: Drug Reaction with Eosinophilia and Systemic Symptoms.
"Results From the Phase 3 X-TOLE2 Study Evaluating Azetukalner, a Novel, Potent K_V7 Channel Opener, in Adults With Focal Onset Seizures (FOS)." 2026 AAN Annual Meeting.

Phase 2b X-TOLE Clinical Study in FOS

Multicenter, randomized, double-blind, placebo-controlled clinical study to evaluate the clinical efficacy, safety, and tolerability of AZK as adjunctive treatment in adults diagnosed with FOS



Primary objective:

- Evaluate effect of AZK vs. PBO on MPC from baseline in monthly FOS frequency during the DBP

Secondary objectives include:

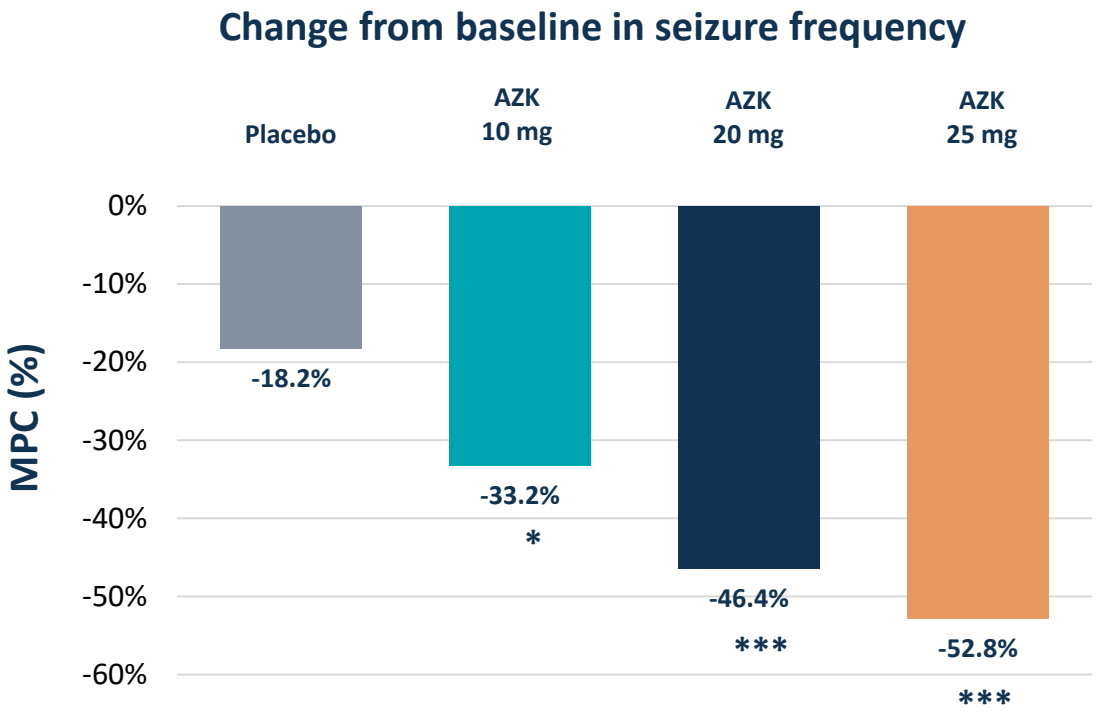
- Assess the effect of AZK vs. PBO on RR50, treatment effect over time

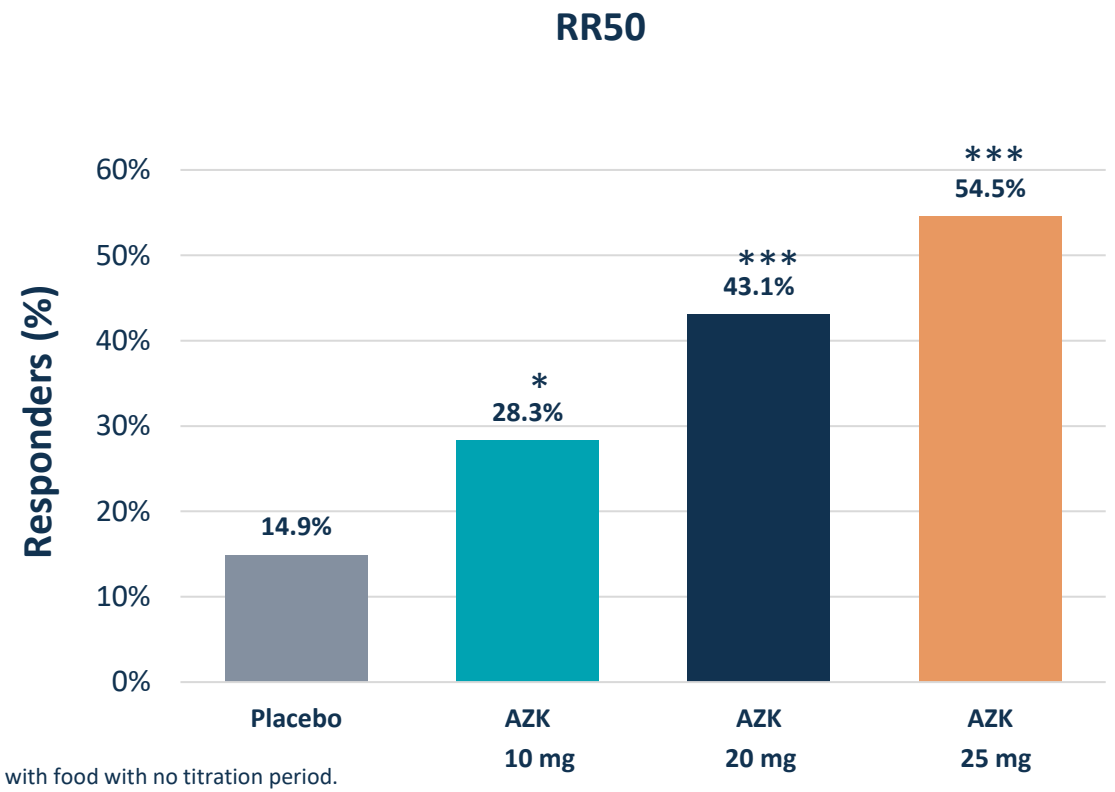
Safety and tolerability of AZK

*Administered as a once-daily capsule with food with no titration period.

AZK: azetukalner; DBP: double-blind period; FOS: focal onset seizures; MPC: median percent change; OLE: open-label extension; PBO: placebo; QD: once-daily; RR50: 50% responder rate; mITT: modified intent-to-treat.
NCT03796962.

Phase 2b X-TOLE: Statistically Significant, Dose-Dependent Reduction in Seizures





AZK was administered as a once-daily capsule with food with no titration period.

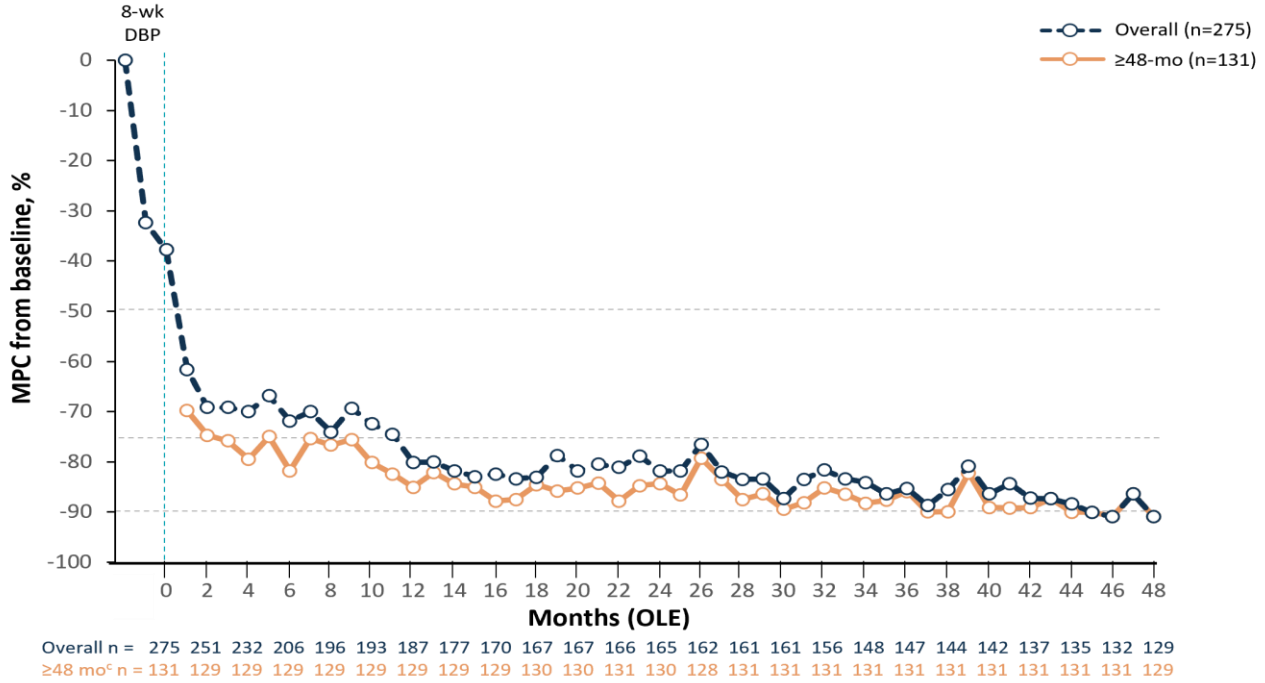
*p<0.05, ***p<0.001

*p<0.05, ***p<0.001

AZK: azetukalner; MPC: median percent change; RR50: 50% responder rate.
French et al., JAMA Neurol. 2023;80(11):1145-1154.

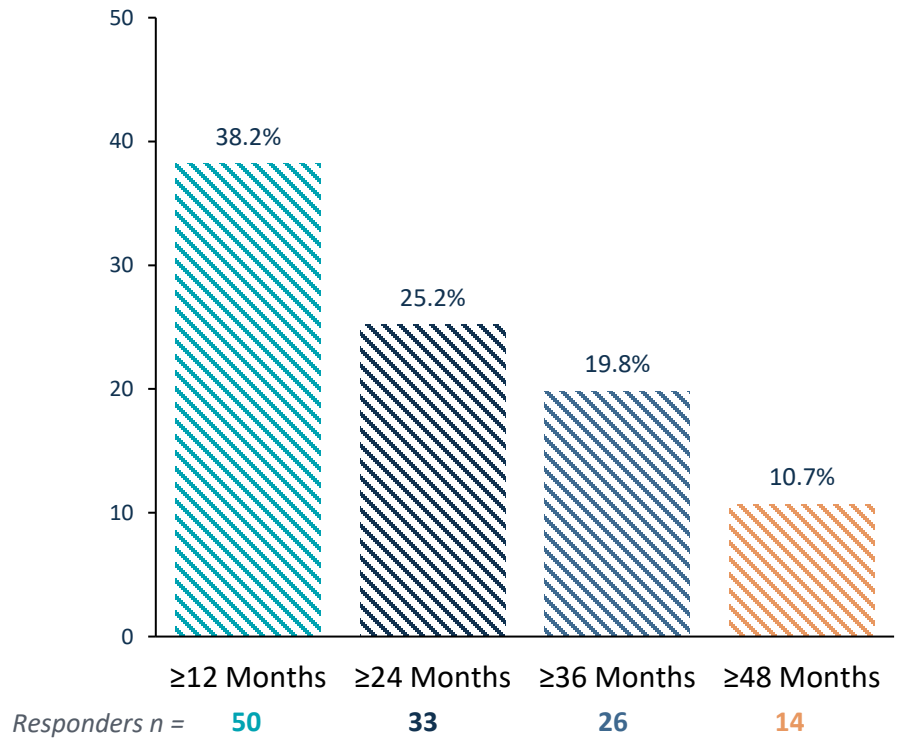
X-TOLE OLE: Robust Long-Term Efficacy and Seizure Freedom

MPC in monthly FOS frequency for overall population and those treated for ≥48 months in OLE



- **90.9% reduction** in monthly FOS frequency from DBP baseline at OLE month 48
- Higher reductions in FOS frequency in participants receiving **1-2 ASMs at DBP baseline (n=60, 100%)** vs. those receiving 3 ASMs (n=69, 81.8%) (data not shown)

Seizure freedom rates (100% seizure reduction) for participants treated for ≥48 months



After the DBP, all participants received 20 mg azetukalner at start of OLE as a once-daily capsule with food and no titration period. Data cutoff: October 6, 2025.
DBP: double-blind period; FOS: focal onset seizures; mo: month; MPC: median percent change; OLE: open-label extension; ASMs: antiseizure medications.
"Long-Term Safety and Efficacy of Azetukalner, a Novel, Potent K_V7 Potassium Channel Opener, in Adults With Focal Epilepsy: ≥48-Month Interim Analysis of the Ongoing 7-Year X-TOLE Open-Label Extension," 2025 Annual Meeting of the American Epilepsy Society (AES).

X-TOLE and X-TOLE OLE: Safety and Tolerability Data

X-TOLE Double-blind Period

- AZK was generally well-tolerated in this study with adverse events consistent with commonly prescribed ASMs

Most common TEAEs across all AZK groups included:

- Dizziness (24.6%)
- Somnolence (15.6%)
- Fatigue (10.9%)

Incidence of SAEs was low and balanced across AZK groups:

- All AZK (3.3%)
- PBO (2.6%)

Most common TEAEs leading to discontinuation across all AZK groups:

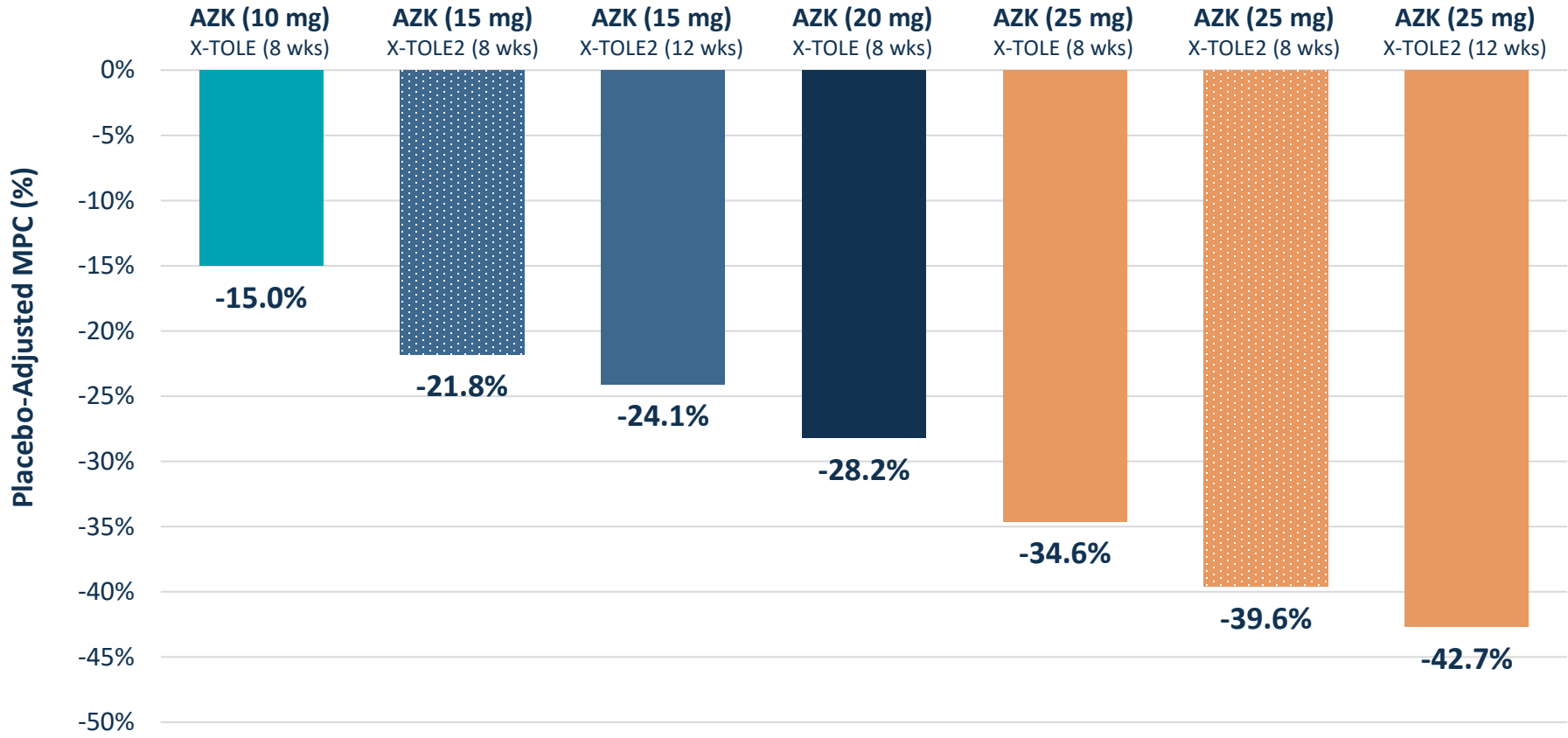
- Dizziness (4.7%)
- Balance disorder (2.4%)
- Dysarthria (1.9%)
- Gait disturbance (1.9%)

X-TOLE OLE

- AZK was generally well-tolerated in the OLE
- Long-term safety in the OLE is comparable with the safety observed in the DBP
- As of October 6, 2025, the OLE has generated >775 patient-years of safety data exposure

ASMs: antiseizure medications; AZK: azetukalner; OLE: open-label extension; SAEs: serious adverse events; TEAEs: treatment-emergent adverse events.
French et al., JAMA Neurol. 2023;80(11):1145-1154; "Long-Term Safety and Efficacy of Azetukalner, a Novel, Potent K_V7 Potassium Channel Opener, in Adults With Focal Epilepsy: ≥48-Month Interim Analysis of the Ongoing 7-Year X-TOLE Open-Label Extension," 2025 Annual Meeting of the American Epilepsy Society (AES).

Placebo-Adjusted MPCs for All AZK Doses in X-TOLE and X-TOLE2



Placebo-adjusted MPC in monthly FOS frequency shows consistent dose-dependent efficacy for AZK at all doses tested

AZK: azetukalner; MPC: median percent change; FOS: focal onset seizures.
All doses administered once daily with food and no titration. Post-hoc week 8 values for X-TOLE2 AZK 25 mg: Focal Seizure Frequency During the first 8 weeks in the Modified Intent-to-Treat Population. French et al., JAMA Neurol. 2023;80(11):1145-1154; Phase 2b X-TOLE results: -34.6% placebo-adjusted MPC over 8 weeks in the 25 mg group (-52.8% from baseline in 25 mg group and -18.2% from baseline in placebo group).

Next Steps for AZK in Epilepsy

Path to Commercialization

- NDA submitted to FDA in Q3 2026
- NDA submission includes data from two RCTs: X-TOLE, X-TOLE2
- Pending FDA review and approval, product availability to follow commercial launch
- AZK would be the only K_V7 opener available to treat FOS

Opportunities for Growth

- Phase 3 X-TOLE3 study ongoing to support regulatory submissions outside the U.S., including Japan
- Phase 3 X-ACKT study ongoing to support potential label expansion to PGTCS

Ongoing launch preparation and transition to a commercial company

NDA: New Drug Application; FOS: focal onset seizures; FDA: U.S. Food and Drug Administration; PGTCS: primary generalized tonic-clonic seizures; RCTs: randomized controlled trials.

A Focused HCP Strategy to Drive Branded ASM Adoption at Launch

Prescriber Universe

All Epileptologists (~2,400)

All General Neurologists (~18,000)

Epilepsy-Focused APPs (~16,000)

2L+ Disease Managers

7,000 – 9,000 HCPs

Epileptologists

General Neurologists

APPs

Write >90% of cenobamate and other branded ASM new patient starts and total scripts

Priorities at Launch

~4,500 HCPs prioritized at launch

Own >80% of all branded new patient starts and scripts

Dedicated field force, with virtual and non-personal efforts to access more restrictive locations

2L: second line; APP: advanced practice provider; ASM: antiseizure medication; HCP: healthcare professional.
IQVIA LAAD.

Market Research Supports Potential for Broad Physician Appeal

	Epilepsy Specialists[1]	General Neurologists[1]
Perceptions of "Product X"	*Unfavorable* — *Favorable*	*Unfavorable* — *Favorable*
"Product X" Value Drivers	✓ **Novel Mechanism of Action** ✓ **Dosing Flexibility to Balance Efficacy and Safety** ✓ **Branded ASM-like Efficacy**	✓ **Ease of Use[2]** ✓ **Manageable Safety Profile** ✓ **Fast Onset of Action**

> The MOA is interesting to me. I like to choose something that is different than what my patients have received. This product gives me more flexibility.
>
> *–Epilepsy Specialist*

> The side effect profile of Product X is tolerable. I also don't have to wait to get my patients to an effective dose, but have some flexibility in the dose I choose.
>
> *–Epilepsy Specialist*

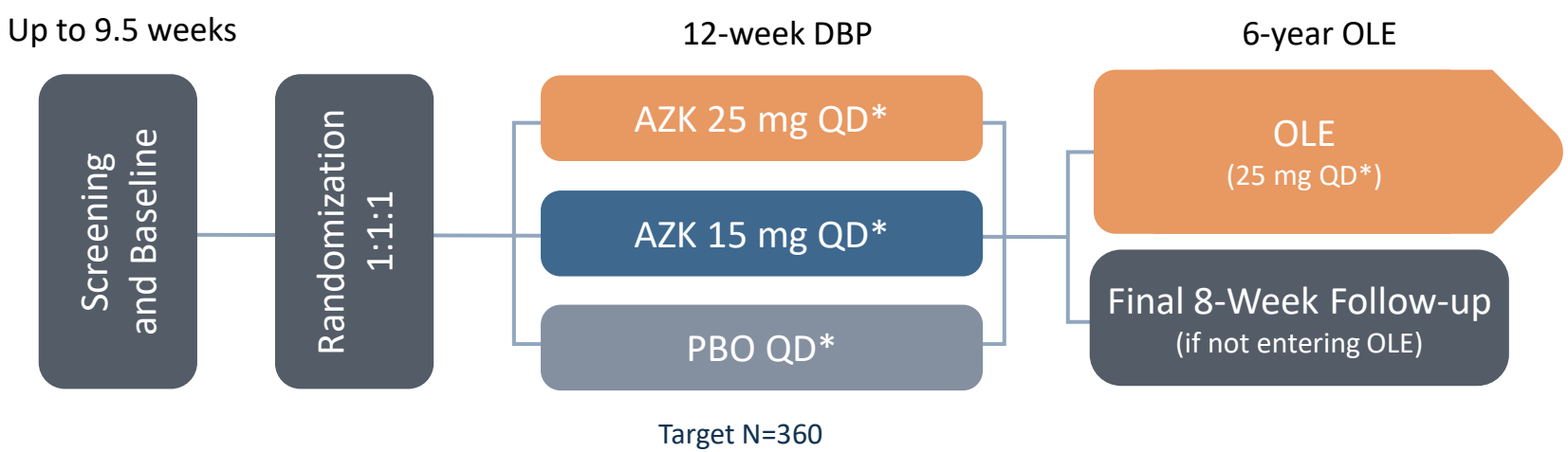
> Product X is distinguished from other brands from a safety perspective, along with the lack of titration and rapid onset.
>
> *– General Neurologist*

> Product X has strong efficacy, great onset and [manageable] side effects, it would be a 2/3L agent.
>
> *– General Neurologist*

2/3L: second/third line; ASM: antiseizure medication; MOA: mechanism of action.
1. Research sample includes 14 general neurologists and 4 epileptologists. 2. Lack of titration schedule and limited DDIs drove physician perceptions of Product X as an "easy to use" treatment option with simple onboarding. Physician Interviews; ClearView Analysis. Market research referenced herein is preliminary and qualitative in nature.

Phase 3 X-TOLE3 Clinical Trial in FOS

X-TOLE3 is ongoing with study design identical to X-TOLE2; intended to support regulatory submissions outside the U.S., with enrollment outside Japan expected to complete in 2026



Primary objective:

- Evaluate effect of AZK vs. PBO on MPC from baseline in monthly FOS frequency during the DBP

Secondary objectives include:

- Assess the effect of AZK vs. PBO on RR50, treatment effect as measured at Week 1, and PGI-C score

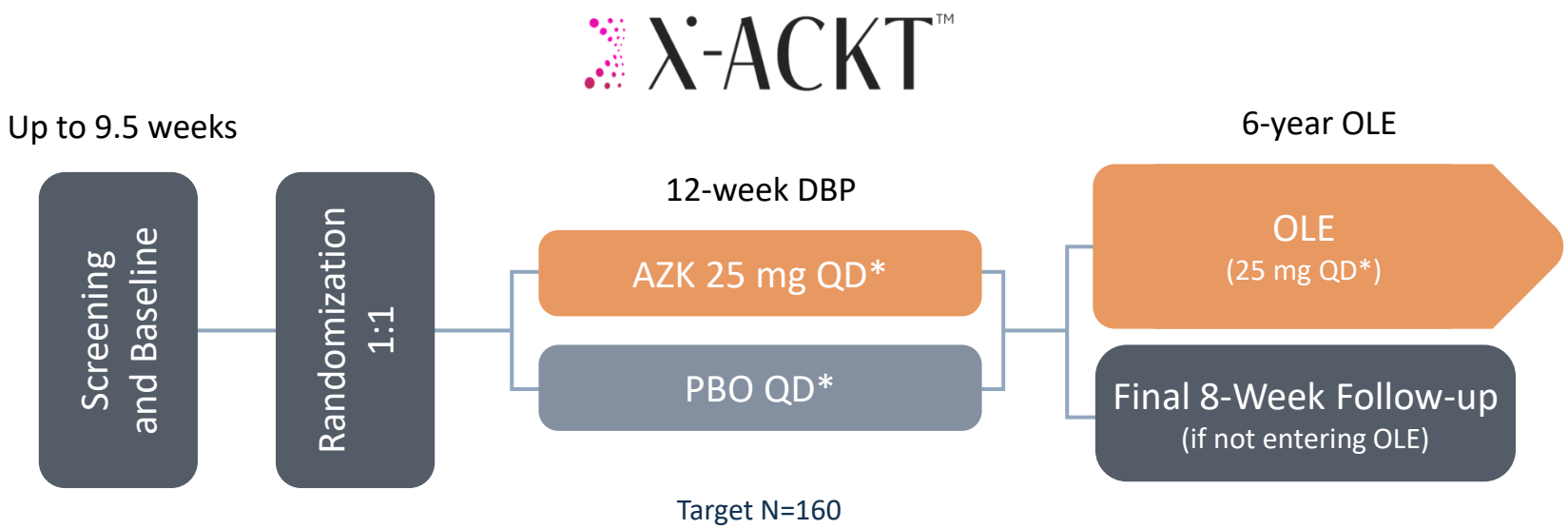
Safety and tolerability of AZK

*Administered as once-daily capsule with food with no titration period.

AZK: azetukalner; FOS; focal onset seizures; MPC: median percent change; OLE: open-label extension; PBO: placebo; PGI-C: Patient Global Impression of Change; RR50: 50% responder rate; QD: once-daily.
NCT05716100.

Phase 3 X-ACKT Clinical Trial in PGTCS

PGTCS opportunity for a broad-spectrum agent with activity across seizure types; enrollment is ongoing in single, multicenter, placebo-controlled Phase 3 trial to support registration



Primary objective:

- Assess effect of AZK vs. PBO on reducing frequency of PGTCS

Secondary objectives include:

- Assess the effect of AZK vs. PBO on RR50, PGTCS freedom and PGI-C

Safety and tolerability of AZK

*Administered as once-daily capsule with food with no titration period. Participants aged ≥12 years and <18 years will receive either AZK 15mg, azetukalner 25 mg, or placebo; participants aged ≥18 years will receive either AZK 25 mg or placebo.

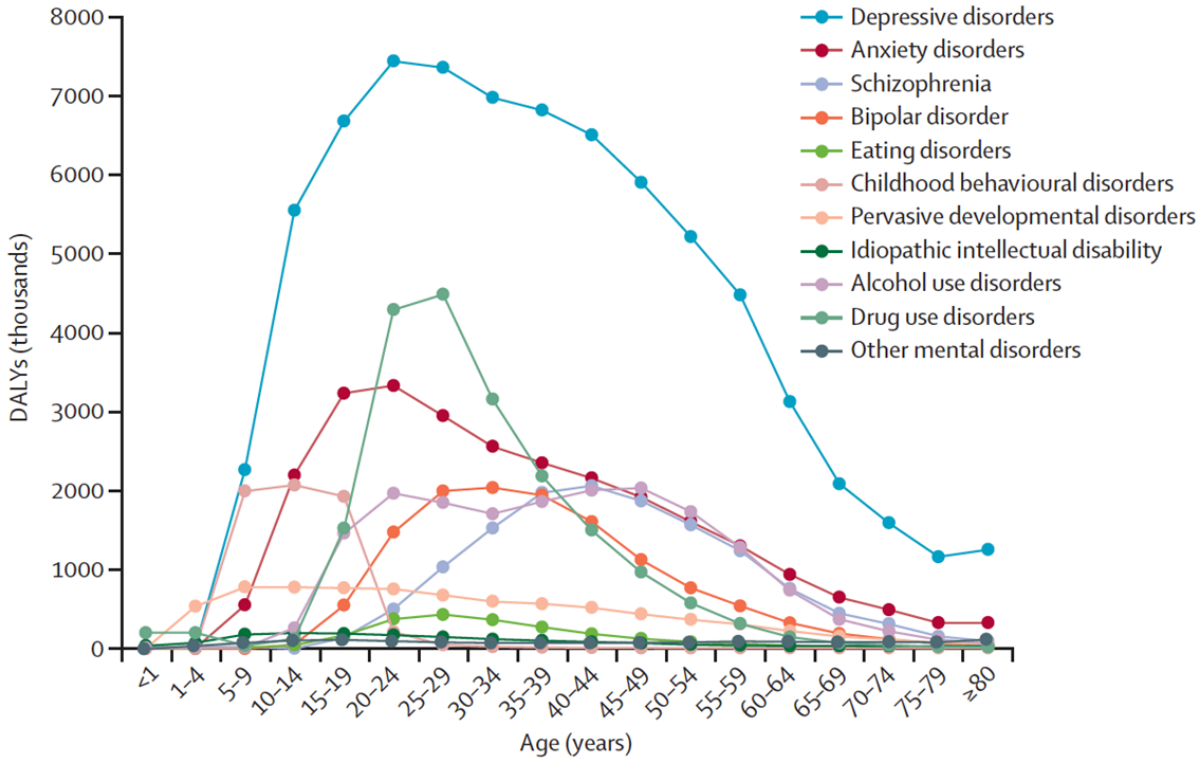
AZK: azetukalner; DBP: double-blind period; OLE: open-label extension; PBO: placebo; PGTCS: primary generalized tonic-clonic seizures; QD: once-daily; RR50: 50% responder rate; PGI-C: Patient Global Impression of Change.
NCT05667142.

Azetukalner in Neuropsychiatry

MDD Is a Highly Prevalent Mental Health Disorder

- In 2022, the MDD diagnosed prevalent population in the U.S. was approximately 21 million adults
  - ~55% treated with pharmacotherapy
  - 1 in 3 patients are inadequately managed on pharmacotherapy
- Anhedonia is a common comorbidity of MDD
  - Associated with poorer treatment outcomes

Depression Accounts for Greatest Disability Among All Central Nervous System Disorders



Disability-adjusted life years (DALYs) for each mental and substance use disorder in 2010 by age

MDD: major depressive disorder

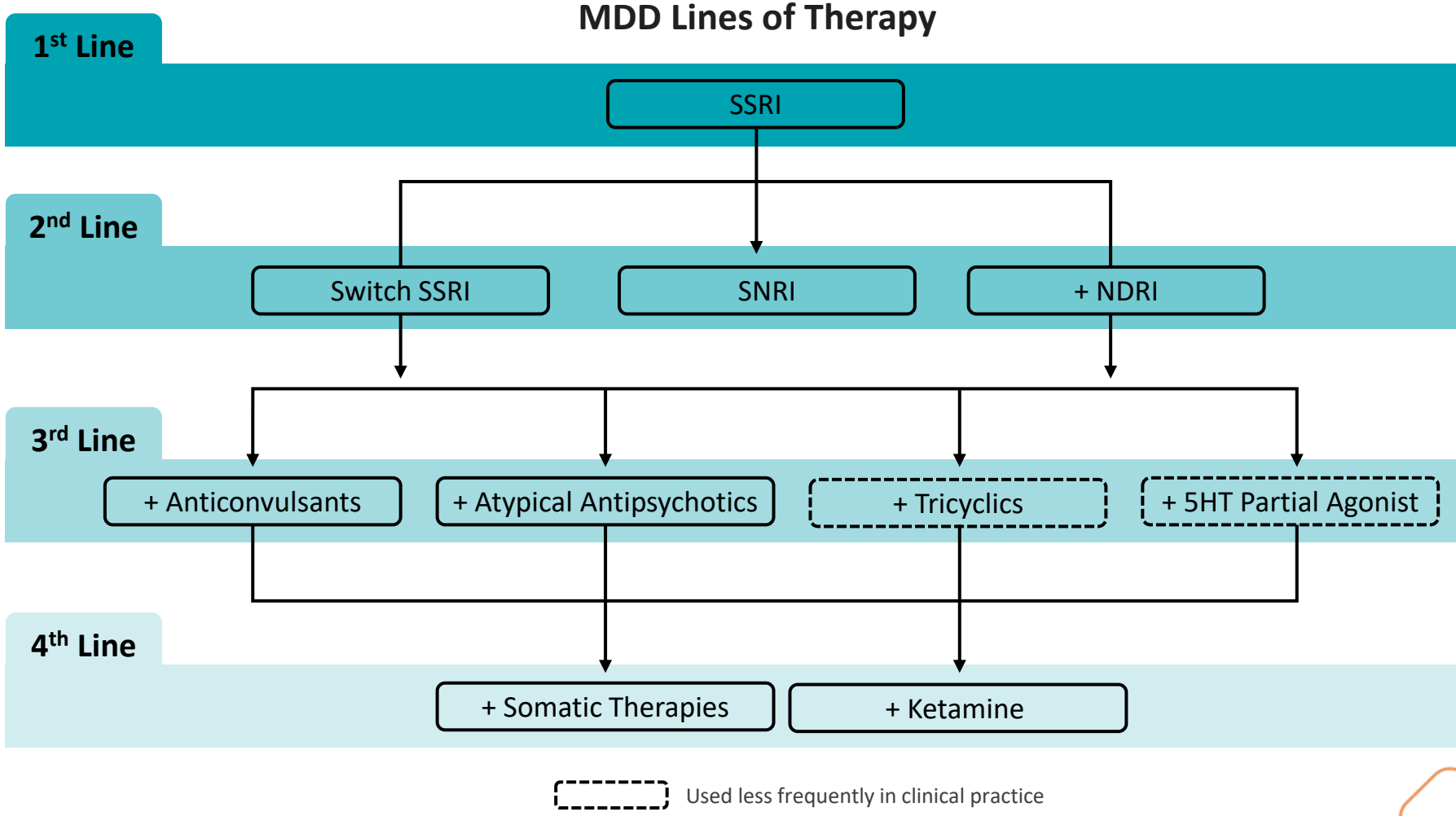
Whiteford et al. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet. 2013; Kern et al. Treatment patterns and sequences of pharmacotherapy for patients diagnosed with depression in the United States: 2014 through 2019. BMC Psychiatry. 2020; Fava, M. Definition and epidemiology of treatment-resistant depression. Psychiatry Clin North Am. 1996.

Opportunity to Improve MDD Treatment Paradigm

Treatment Considerations

- Physicians typically use multiple SSRIs/SNRIs, prior to progressing to branded therapy
- Poorly managed patients may seek alternative MOAs in 3L+
- Opportunity exists for novel mechanisms that offer efficacy in anhedonia with a differentiated safety profile

MDD Lines of Therapy

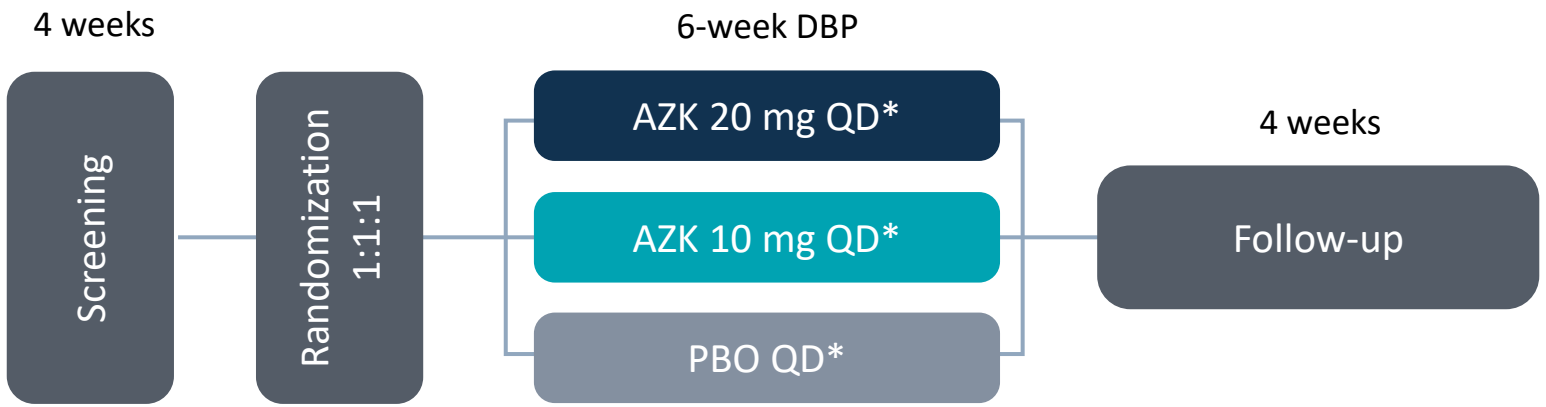


MDD: major depressive disorder; MOAs: mechanisms of action; NDRI: Norepinephrine-Dopamine Reuptake Inhibitor; SNRI: Serotonin-Norepinephrine Reuptake Inhibitor; SSRI: Selective Serotonin Reuptake Inhibitor
Xenon-sponsored market research.

X-NOVA Phase 2 Proof-of-Concept Clinical Study in MDD

Conducted a Phase 2 proof-of-concept, randomized, double-blind, placebo-controlled, multicenter study to evaluate the safety, tolerability, and efficacy of AZK in major depressive disorder (MDD)

X-NOVA™



*Administered as once-daily capsule with food with no titration period.

Primary objective:

- Montgomery-Åsberg Depression Rating Scale (MADRS) score change through week 6

Secondary objectives include:

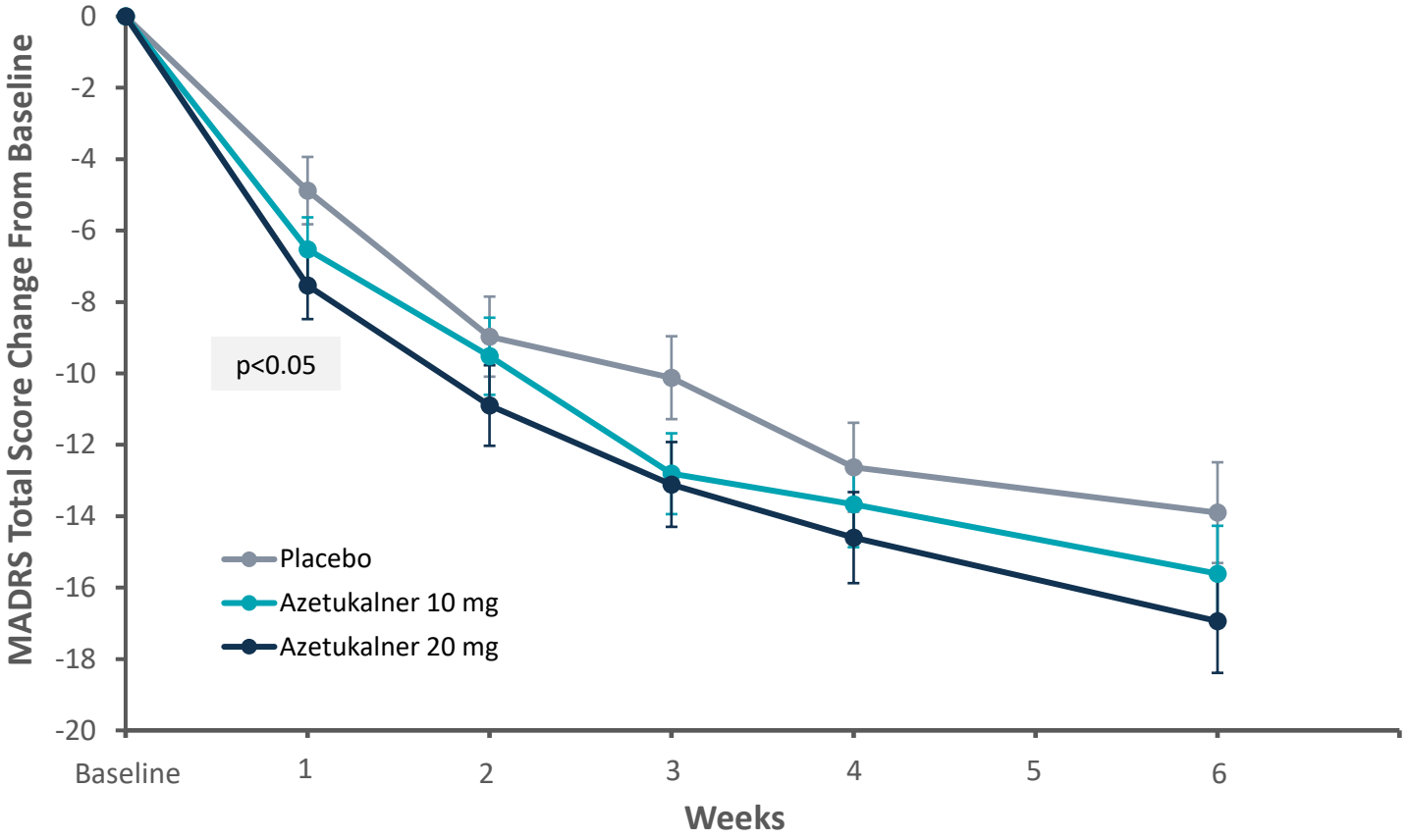
- Snaith-Hamilton Pleasure Scale (SHAPS) score change through week 6

Phase 2 topline data from X-NOVA study announced in November 2023

AZK: azetukalner; DBP: double-blind period; PBO: placebo; QD: once-daily.
NCT05376150.

X-NOVA: Primary Efficacy Endpoint (MADRS)

Change in MADRS Total Scores at Week 6 (mITT)



	PBO (n=54)	AZK 20 mg (n=53)
MADRS total score change from baseline at Week 6, LS mean	-13.90	-16.94
Difference vs. PBO		-3.04
p-value		0.135

AZK was administered as a once-daily capsule with food with no titration period.

A clear dose response and a clinically meaningful, but not statistically significant, 3.04 difference in MADRS at week 6 in the 20 mg group

PBO: placebo; AZK: azetukalner.
MADRS: Montgomery-Åsberg Depression Rating Scale; LSMean (SEM) shown; mITT: modified intent-to-treat; population included all randomized participants who received at least 1 dose of study treatment and at least 1 post randomization MADRS score.

X-NOVA: Pre-Specified Endpoint Improvement in Depressive Symptoms

Change in HAM-D17 Total Score at Week 6 (mITT)

	placebo (n=54)	AZK 20 mg (n=53)
HAM-D17 total score change from baseline at Week 6 (LS mean)	-10.18	-13.26
Difference vs PBO		-3.08
p-value		0.042*

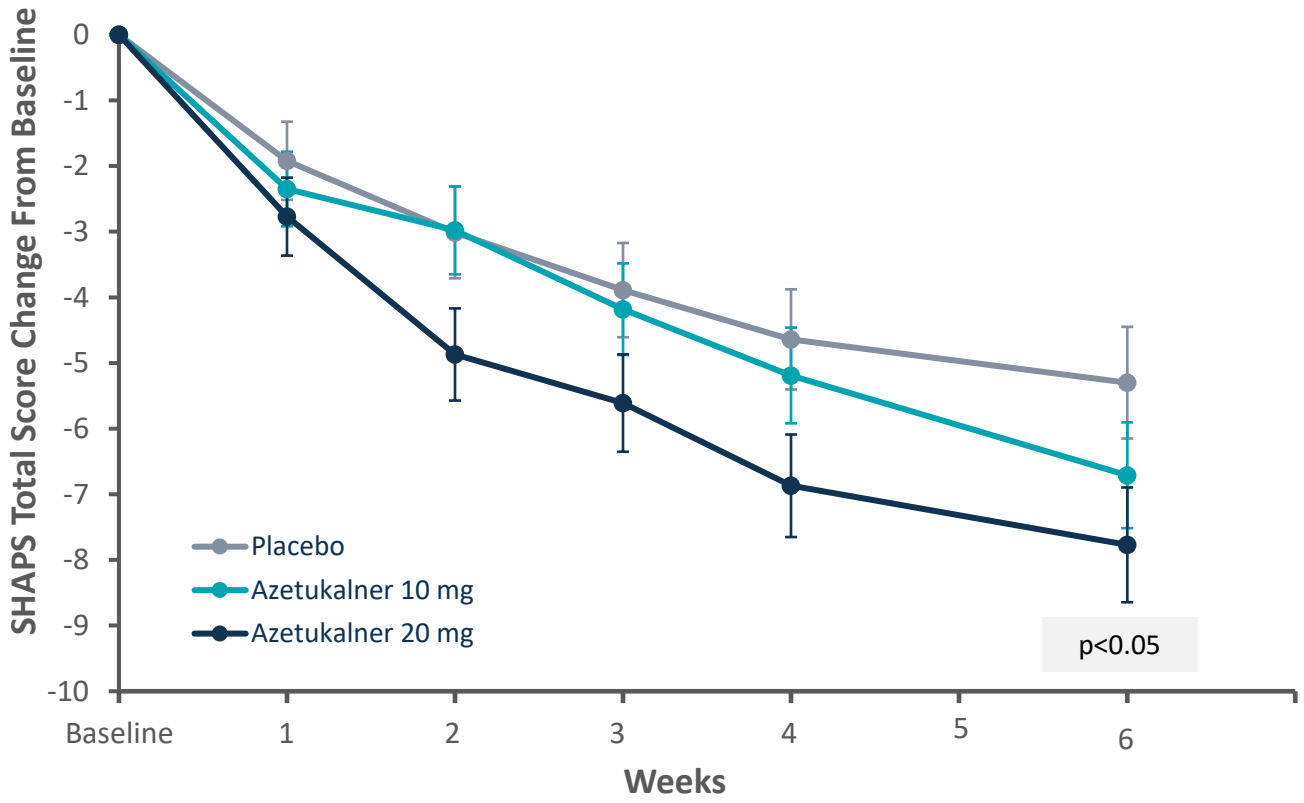
AZK was administered as a once-daily capsule with food with no titration period; *p value nominal.

Improvement in depressive symptoms assessed by HAM-D17 total scores was significantly different at week 6

PBO: placebo; AZK: azetukalner.
HAM-D17: Hamilton Depression Rating Scale was assessed at screening, baseline, and week 6; mITT: modified intent-to-treat; population included all randomized participants who received at least 1 dose of study treatment and at least 1 post randomization MADRS score

X-NOVA: Secondary Efficacy Endpoint

Change in SHAPS Total Score at Week 6 (mITT)



	PBO (n=54)	AZK 20 mg (n=53)
SHAPS total score change from baseline at Week 6 (LS mean)	-5.30	-7.77
Difference vs placebo		-2.46
p-value		0.046

AZK was administered as a once-daily capsule with food with no titration period.

Anhedonia symptom improvement: significantly different change in SHAPS at week 6 in 20 mg group

PBO: placebo; AZK: azetukalner; SHAPS: Snaith-Hamilton Pleasure Scale.
LSMean (SEM) shown; p-value nominal.

X-NOVA: Safety and Tolerability Data

AZK was generally well-tolerated with similar rates of overall adverse events reported across all treatment arms

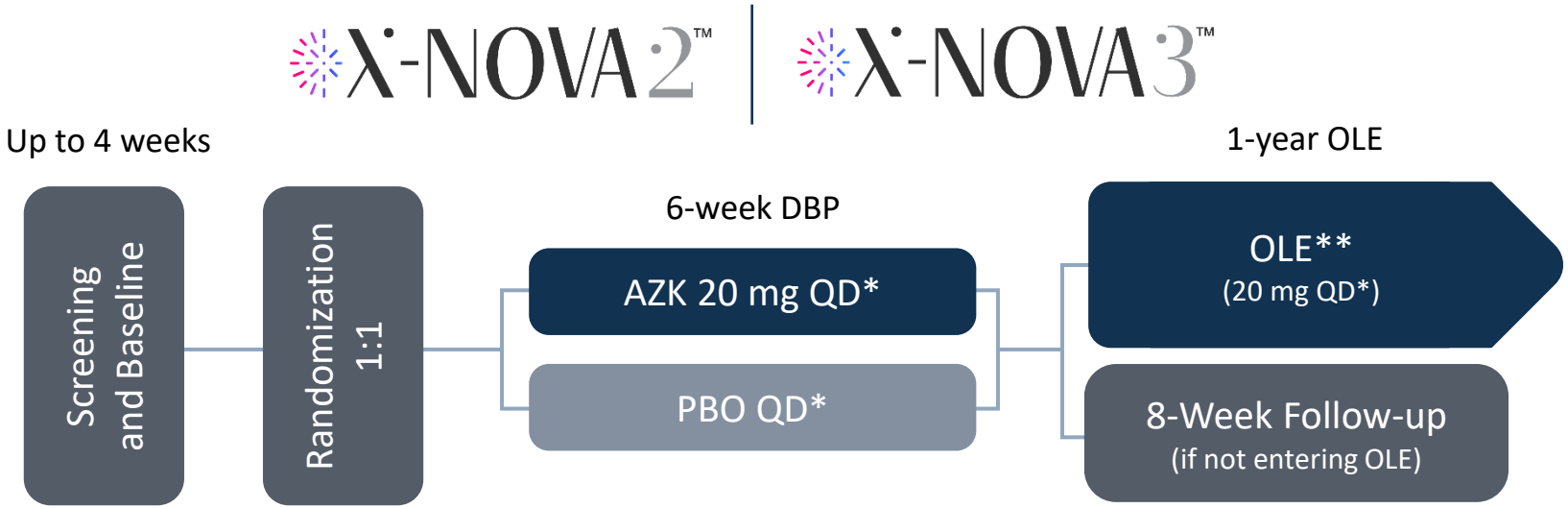
Treatment-Emergent Adverse Events

- The most commonly reported TEAEs in the AZK 20 mg group included dizziness (17.9%), somnolence (10.7%), headache (8.9%), and disturbance in attention (8.9%), as compared to the PBO 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 due to TEAEs were low with three patients in the AZK 20 mg group (5.4%), as compared to two patients in the PBO group (3.6%)
- No SAEs were reported in the two AZK treatment groups, and there were two patients (3.6%) in the PBO group who experienced a treatment-emergent SAE
- AZK was not associated with notable weight gain; patients did not report notable sexual dysfunction

AZK: azetukalner; TEAEs: treatment-emergent adverse events; PBO: placebo; SAEs: serious adverse events.

Phase 3 Clinical Studies in Major Depressive Disorder

Phase 3 MDD program consists of three multi-center, placebo-controlled clinical trials with plan to submit sNDA supported by efficacy data from two positive Phase 3 MDD trials



Primary objective:

- Change from baseline in HAM-D17 score at week 6

Secondary objectives include:

- Change from baseline in HAM-D17 score at week 1; change from baseline in SHAPS score at week 6; change from baseline in CGI-S at week 6

Safety and tolerability of AZK

X-NOVA2 enrollment completed at N=~360; X-NOVA3 target N=450

*Administered as once-daily capsule with food with no titration period.

**New enrollments in X-NOVA3 and the MDD OLE study are temporarily paused

X-NOVA2 enrollment completed with topline data expected in Q1 2027

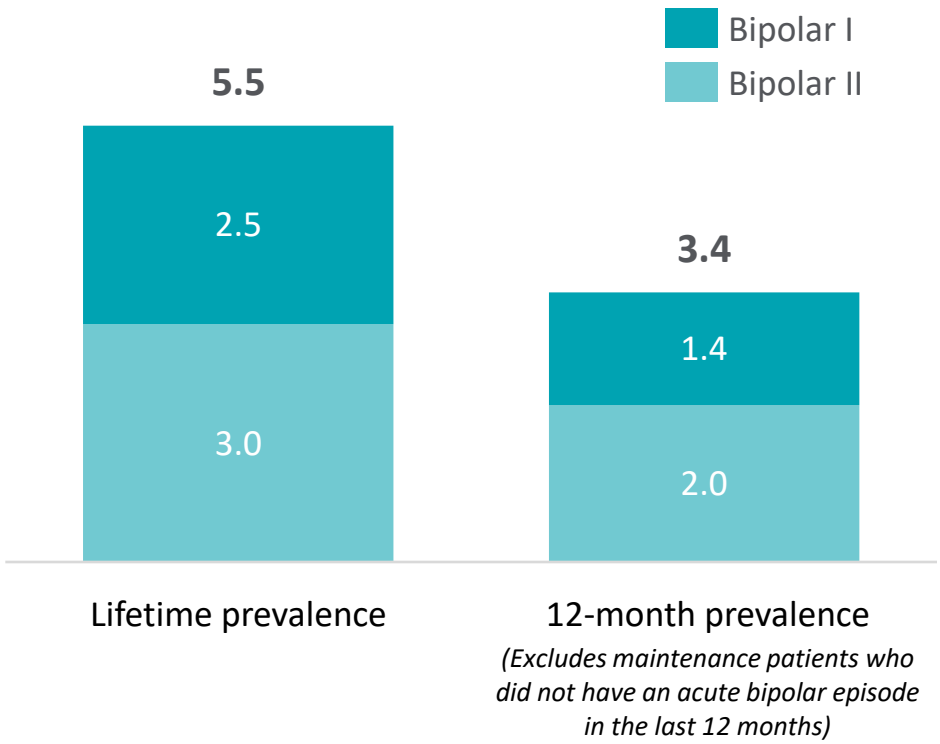
AZK: azetukalner; PBO: placebo; DBP: double-blind period; sNDA: supplemental New Drug Application; MDD: major depressive disorder; OLE: open-label extension; QD: once-daily; CGI-S: Clinical Global Impression of Severity; HAM-D17: Hamilton Depression Rating Scale; SHAPS: Snaith-Hamilton Pleasure Scale.
X-NOVA2: NCT06775379; X-NOVA3: NCT07076407; X-NOVA-OLE: NCT06922110.

Limited Options to Address Lifelong Nature of Bipolar Depression

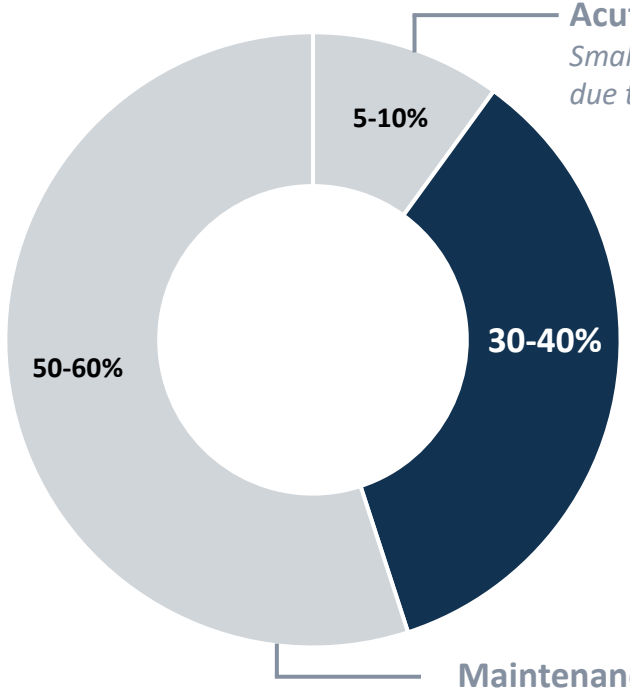
Hallmark of bipolar disorder is its cyclical pattern, where individuals alternate between mania/hypomania and depression, often with periods of normal in between

Estimated U.S. bipolar disorder prevalence

Millions of adults



Percent of patients by disease phase



Acute Mania

Small portion of the overall patient population due to the infrequent nature of manic episodes

Acute Depression

Significant population as depressive episodes are more common in bipolar disorder

Maintenance

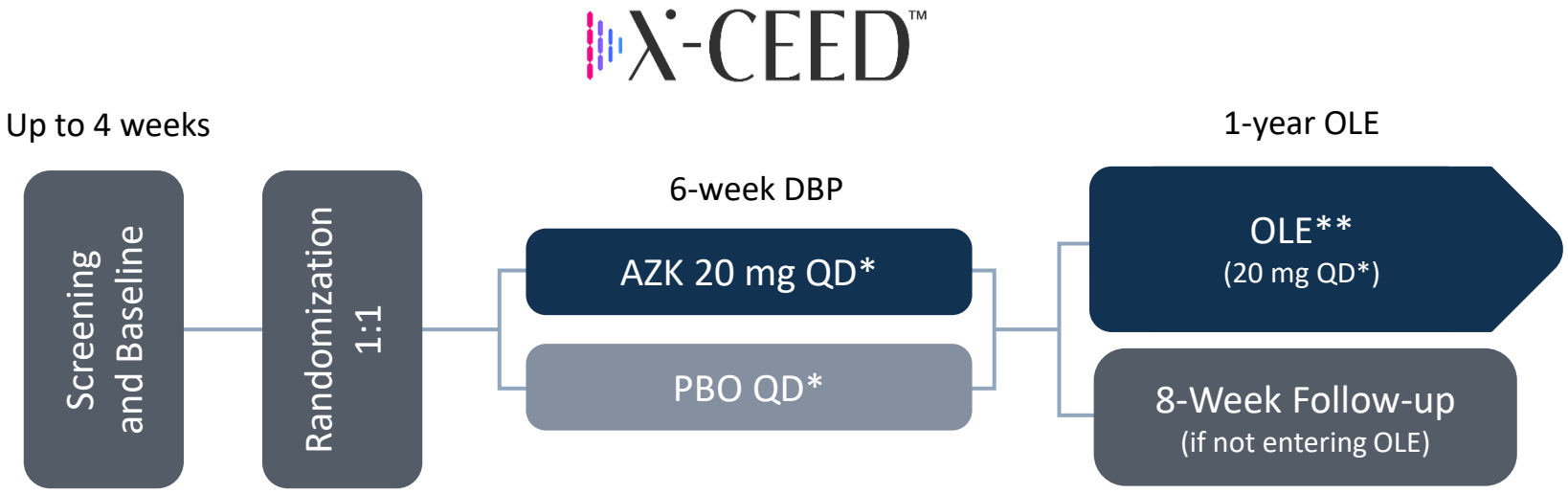
Stabilized patients who are not experiencing an active manic or depressed state are on maintenance therapy

12-month prevalence is defined as patients who had bipolar disorder episodes in the 12 months before the clinical interview.

Hoertel et al., J. Affect Disord. (2013); Merikangas et al., Arch. Gen. Psychiatry (2007); Merikangas et al., Arch. Gen. Psychiatry (2011); Angst et al., Am. J. Psychiatry (2010); Kessler et al., Int. J. Methods Psychiatr. Res. (2012); and corporate presentations; company-sponsored market research.

Phase 3 Clinical Studies in Bipolar Depression

Phase 3 BPD program consists of two multi-center, placebo-controlled clinical trials in patients with bipolar I or II depression (BPD)



Target N=~400 in each study

*Administered as once-daily capsule with food with no titration period.

**New enrollments in X-CEED and the BPD OLE study are temporarily paused

Primary objective:

- Change from baseline in MADRS score at week 6

Secondary objectives include:

- Change from baseline in MADRS score at week 1; change from baseline in SHAPS score at week 6; change from baseline in CGI-S at week 6

Safety and tolerability of AZK

AZK: azetukalner; PBO: placebo; DBP: double-blind period; OLE: open-label extension; QD: once-daily; MADRS: Montgomery-Åsberg Depression Rating Scale; CGI-S: Clinical Global Impression of Severity.
X-CEED: NCT07172516; X-CEED OLE: NCT07217860.

Clinical Programs for Pain

Prevalence and Treatment Paradigms Across Pain Types

Acute Pain

1L

NSAIDs, acetaminophen
(e.g., diclofenac, Tylenol)

1L/2L

Opioid analgesics
(tramadol, hydrocodone)

~1 in 4 Americans experience acute pain annually, with ~50% being prescribed opioids at some point during their management

~80M
Annual U.S. Treated Patients
(Treated incidence)

Chronic Nociceptive Pain*

1L

NSAIDs; Neuromodulators
(e.g., diclofenac, diazepam, Cymbalta)

Add-on *– patients stay on 1L*

2&3L

Opioids
(Weak & strong opioid analgesics: tramadol, tapentadol, morphine, oxycodone)

4L+

Interventional procedures

~35-40M
Annual U.S. Diagnosed Patients
(Prevalence)

Neuropathic Pain

1L

Neuromodulators
(e.g., TCAs, anticonvulsants, Cymbalta)

Add-on *– patients stay on 1L*

2&3L

Opioids
(Weak & strong opioid analgesics: tramadol, tapentadol, morphine, oxycodone)

4L+

Interventional procedures

~10M
Annual U.S. Diagnosed Patients
(Prevalence)

Current pain treatments rely on NSAIDs, neuromodulators and opioids, which pose risks of addiction and poor tolerability

NSAIDs: Nonsteroidal Anti-Inflammatory Drugs.
**Patients cycle through opioid treatment in chronic pain; patients often cycle between medications and therapeutic lines in all three pain categories and occasionally use medicines together.*
External expert interviews; Mayo Clinic; Johns Hopkins; Cleveland Clinic

Maturing Pipeline of Novel Phase 1 Programs in Pain

Leveraging Xenon's deep ion channel expertise to develop promising drug candidates that target sodium and potassium channels

$Na_V1.7$ Programs

- Phase 1 SAD/MAD studies underway for two $Na_V1.7$ candidates: XEN1701 and XEN1720
- Preliminary Phase 1 SAD/MAD data suggest XEN1701 reached drug concentrations predicted to achieve receptor occupancies required for therapeutic activity based on human genetic data
- Advancing multiple clinical and preclinical $Na_V1.7$ molecules with differentiated profiles:
  - CNS penetrant to globally inhibit $Na_V1.7$, better mimicking patient genetics
  - Demonstrate good free fraction and tissue distribution, achieving high levels of target engagement
  - Excellent potency and selectivity to safely achieve target therapeutic levels of $Na_V1.7$ inhibition

K_V7 Program

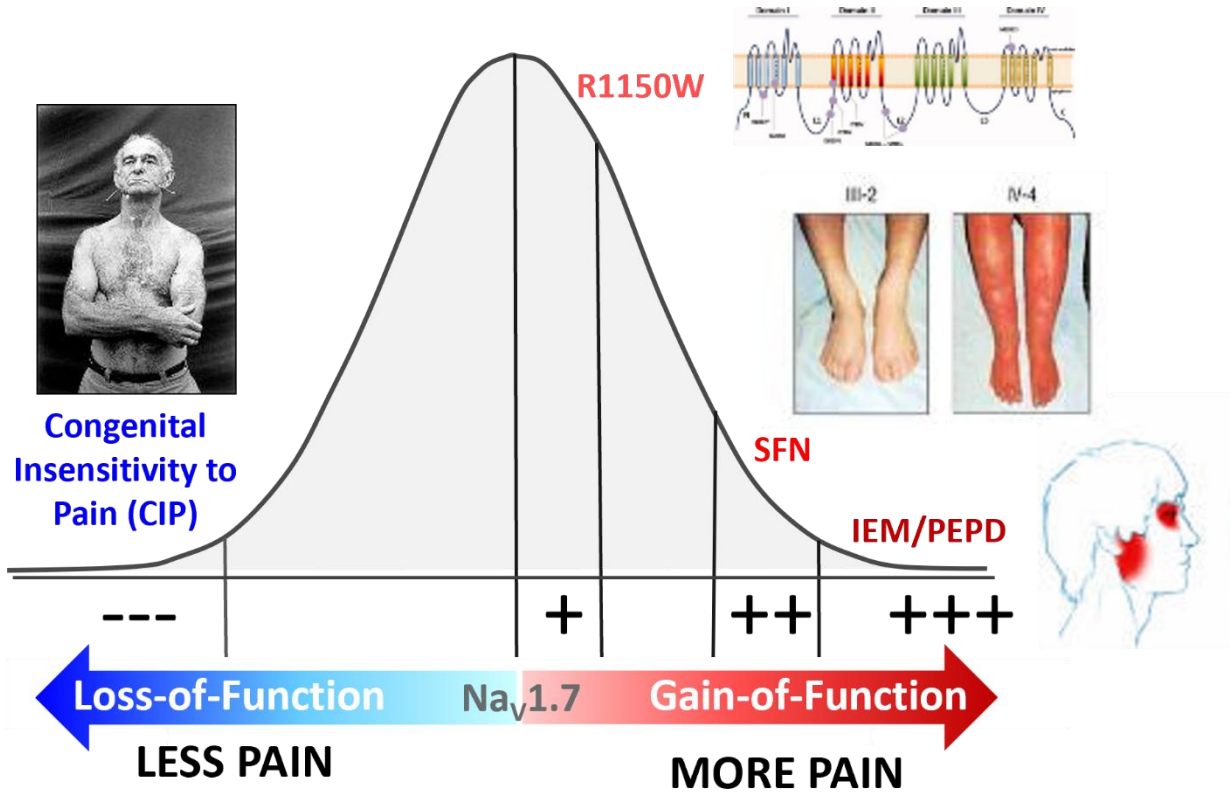
- Phase 1 SAD/MAD study underway for XEN1120
- Preliminary Phase 1 SAD/MAD data suggest XEN1120 has reached drug concentrations that are consistent with pain reductions in pre-clinical models
- Advancing additional K_V7-targeted compounds through IND-enabling studies – distinct molecules targeting unique:
  - Binding sites/mechanisms
  - Tissue distribution profiles

Phase 1 study completion for XEN1701 and XEN1120 expected in H2 2026 to support initiating Phase 2 PoC studies in acute pain

CNS: central nervous system; IND: Investigational New Drug; SAD: single ascending dose; MAD: multiple ascending dose; PoC: proof-of-concept.

The Human Genetics of $Na_V1.7$ in Pain

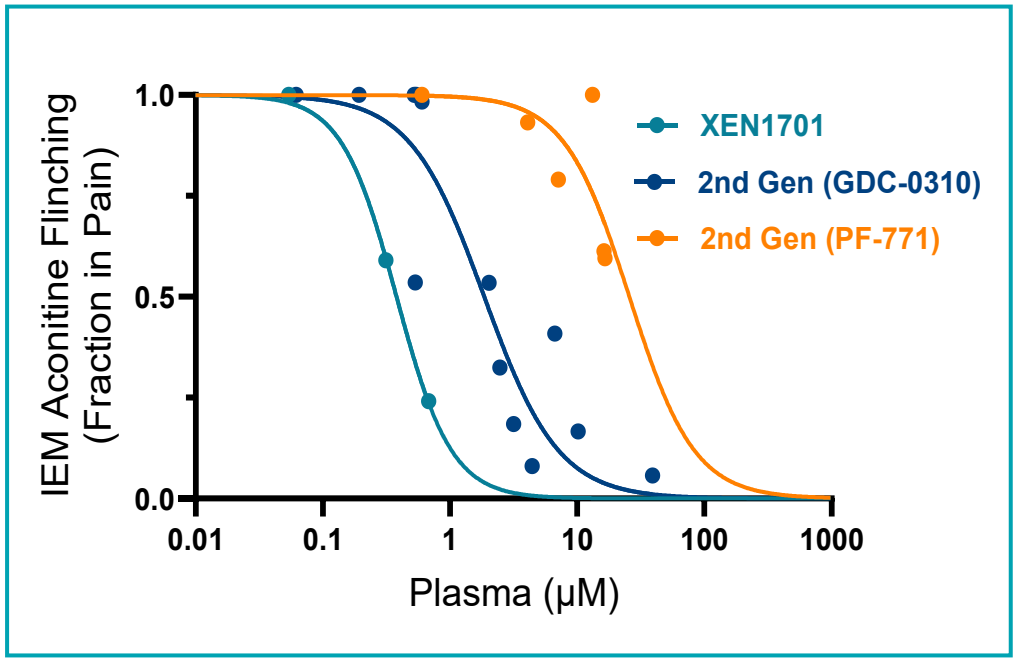
- **Loss-of-function mutations in SCN9A** (the gene encoding $Na_V1.7$) can cause congenital indifference to pain (CIP) – individuals who are otherwise healthy but cannot feel pain
- **Gain-of-function mutations in SCN9A** can lead to extreme pain disorders, such as inherited erythromelalgia (IEM) or paroxysmal extreme pain disorder (PEPD), demonstrating that excessive $Na_V1.7$ activity can drive pain



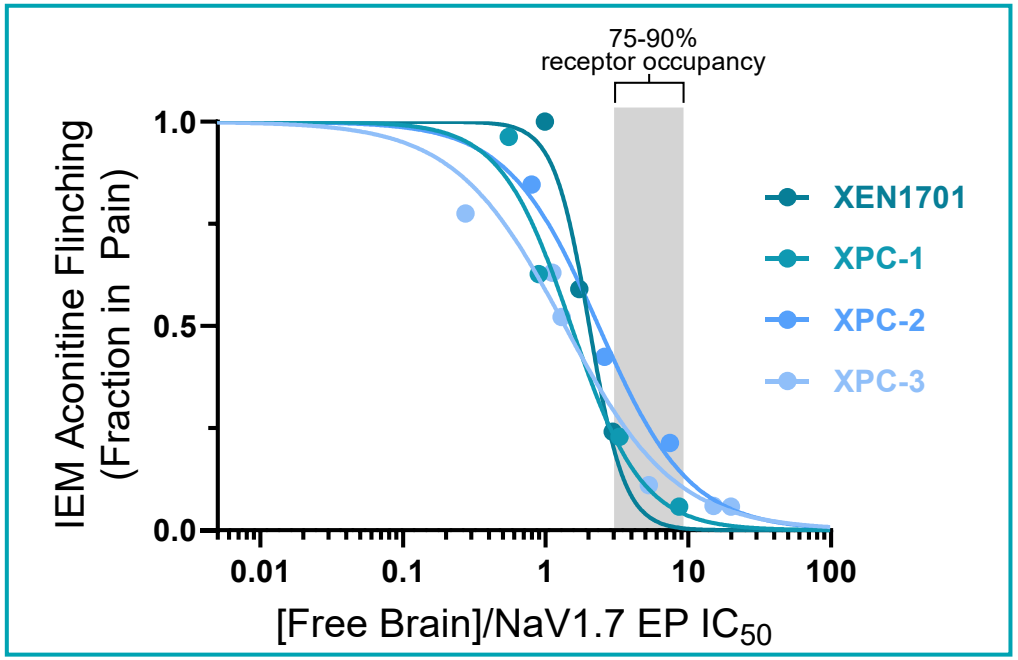
There is strong human genetic evidence to support $Na_V1.7$ as a compelling target for pain drug development

XEN1701 Performance in IEM Mouse Model

XEN1701 demonstrates target engagement at low total plasma concentrations



In vivo activity correlates to free brain concentrations across Xenon's lead compounds

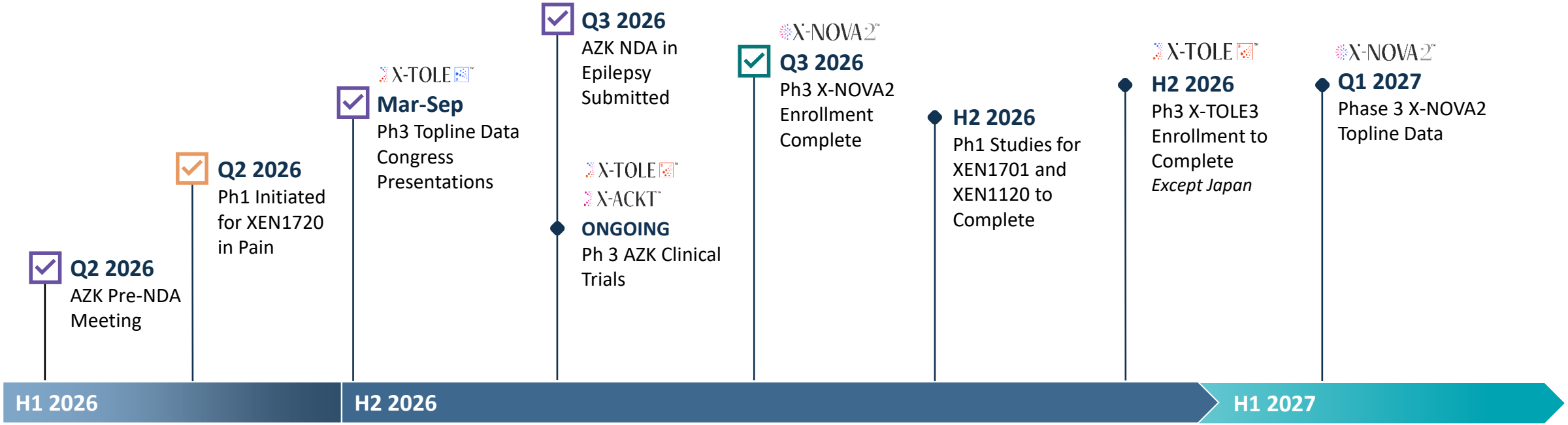


CNS penetrance, improved free fraction and good potency and selectivity demonstrate target engagement at low plasma exposures

IEM: inherited erythromelalgia; CNS: central nervous system.

Upcoming Milestones

Catalyst-rich period as AZK progresses toward U.S. approval and broader pipeline delivers key clinical data



AZK: azetukalner; FOS: focal onset seizures; NDA: New Drug Application.



For more information

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