

Azetukalner & Epilepsy Data Update: AES 2025

INVESTOR WEBINAR
DECEMBER 10, 2025

NASDAQ: XENE
xenon-pharma.com



Forward-Looking Statement/Safe Harbor

This slide presentation and the accompanying oral commentary contain 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) that involve risks, uncertainties and assumptions. If the risks or uncertainties ever materialize or the assumptions prove incorrect, our results may differ materially from those expressed or implied by such forward-looking statements. All statements other than statements of historical fact could be deemed forward-looking and include statements regarding the timing 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 successfully develop and achieve milestones in our azetukalner and other pipeline and development programs, including the anticipated filing of INDs and NDAs; the timing and results of our interactions with regulators; our ability to successfully develop and obtain regulatory approval of azetukalner and our other product candidates; anticipated timing of topline data readout from our clinical studies of azetukalner; and our expectation that we will have sufficient cash to fund operations into 2027.

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 impose additional requirements or delay the initiation or completion of clinical studies; 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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On Today's Call



Ian Mortimer
President &
Chief Executive Officer



Chris Kenney, MD
Chief Medical Officer



Darren Cline
Chief Commercial Officer



Tucker Kelly
Chief Financial Officer

Today's Agenda

- ◆ Opening Remarks
- ◆ AES Data Update
- ◆ Progress Toward Commercialization
- ◆ Q&A

About Xenon Pharmaceuticals

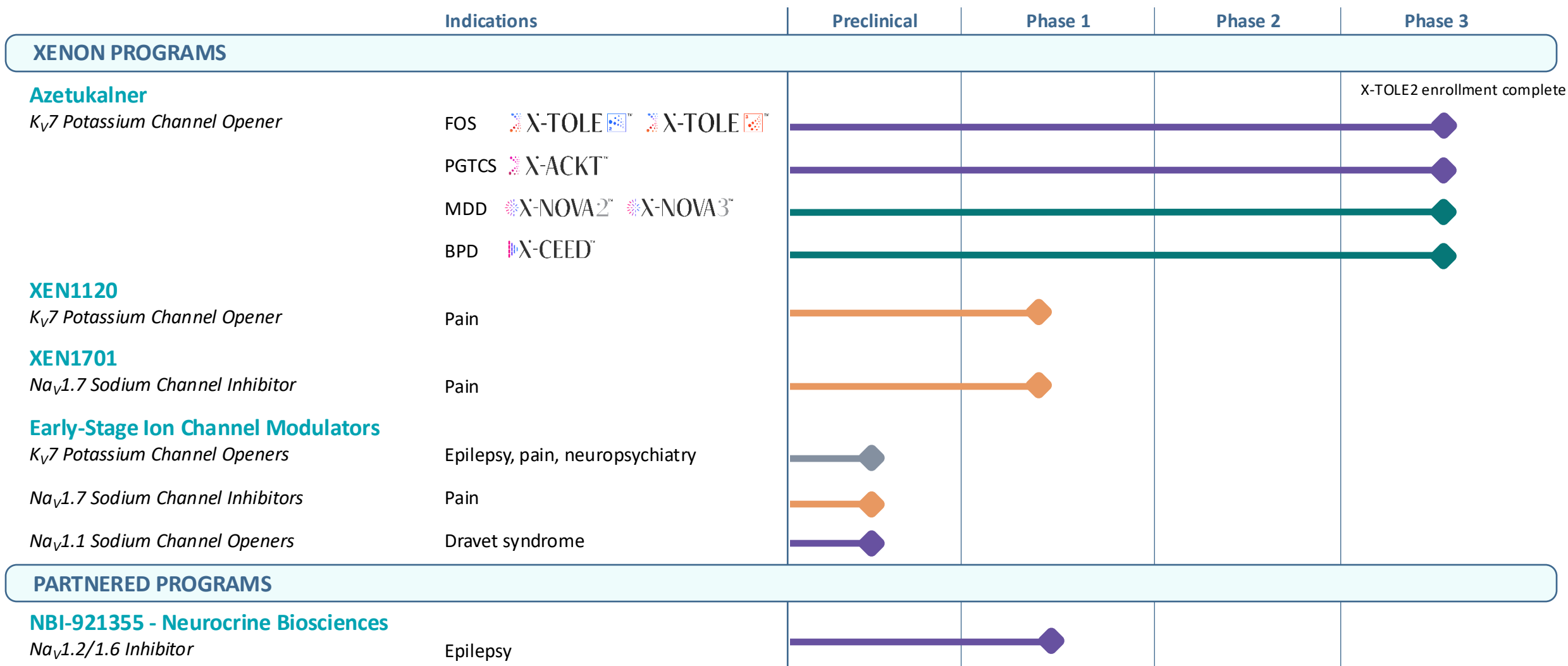
- Neuroscience-focused biopharmaceutical company and leader in small molecule, ion channel drug discovery and development
- Robust pipeline of therapeutic candidates targeting potassium and sodium channels across various indications
- Lead molecule, azetukalner, is a highly potent K_v7 channel opener in Phase 3 development in epilepsy and depression*
- Strong financial position
 - \$555.3 million in cash, cash equivalents and marketable securities (as of September 30, 2025) and anticipated cash runway to fund operations into 2027

*Comprehensive intellectual property portfolio with patent coverage extending to at least 2040, absent any extensions of patent term



AZETUKALNER (AZK) is the **most advanced** potassium channel modulator in late-stage clinical development across multiple indications and the **only K_v7 program with 800+ patient-years of efficacy & safety data**

Xenon's Neuroscience-Focused Pipeline



This chart displays pipeline drug candidates currently undergoing clinical and pre-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.

Xenon Presence at AES Underscored Growing Visibility in Epilepsy



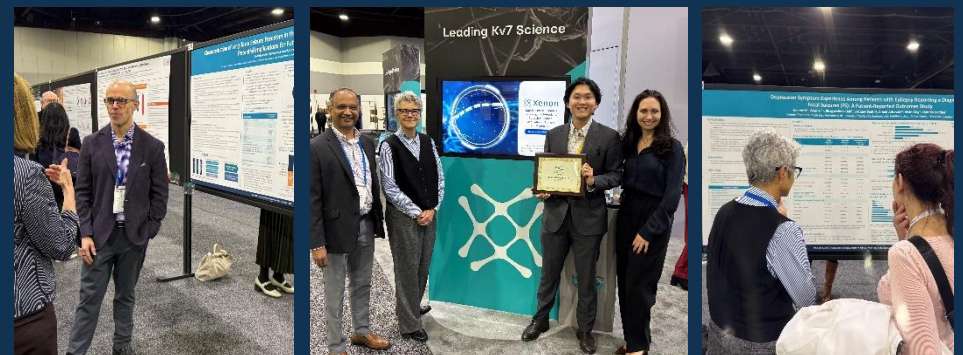
7 posters highlighting 48-month azetukalner OLE data, real-world epilepsy studies, and early-stage Na_v1.1 program; **1 poster** selected for AES press program



~1,500 total engagements through onsite meetings, presentations and scientific exhibit highlighting azetukalner and other epilepsy programs



Symposium held with **Epilepsy Foundation of America** and **three leading epileptologists** regarding depression and anxiety in epilepsy



Differentiating Attributes Based on X-TOLE Phase 2b and OLE Data



Robust Clinical Efficacy

- Highly compelling double-blind efficacy data in FOS patients, durable long-term seizure freedom data as demonstrated in the ongoing OLE
- Potentially mood-neutral or mood-positive



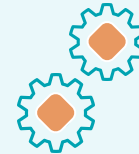
Ease-of-Use

- Once-daily dosing and no required titration, enabling potential for rational polypharmacy
- No meaningful DDIs or anticipated monitoring requirements



Rapid Onset of Effect

- Statistically significant efficacy demonstrated at Week 1 in patients with FOS



Novel Mechanism

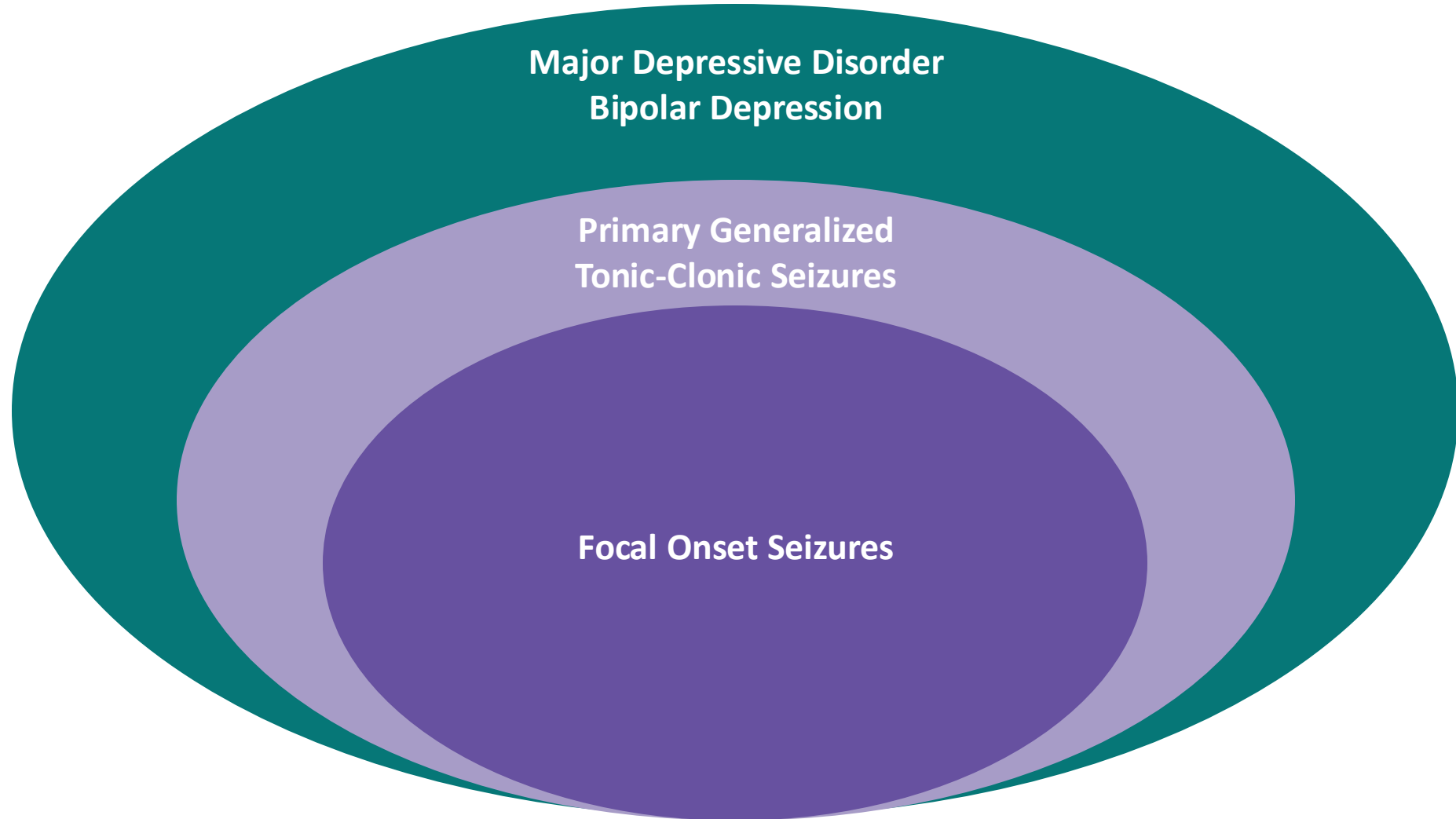
- Highly potent $K_v7.2/7.3$ potassium channel opener with no activity on $GABA_A$



Well-Documented Safety Profile

- More than 800 patient years of data in FOS patients, with some patients dosed for more than 5 years

Significant Commercial Opportunity

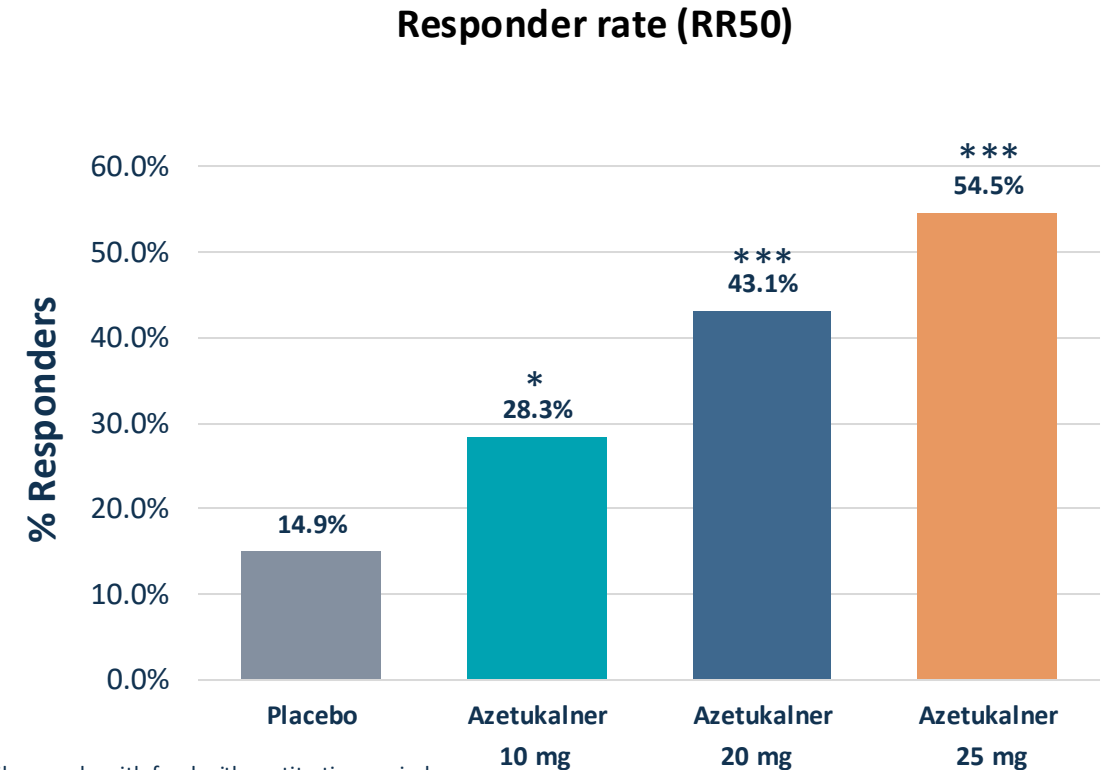
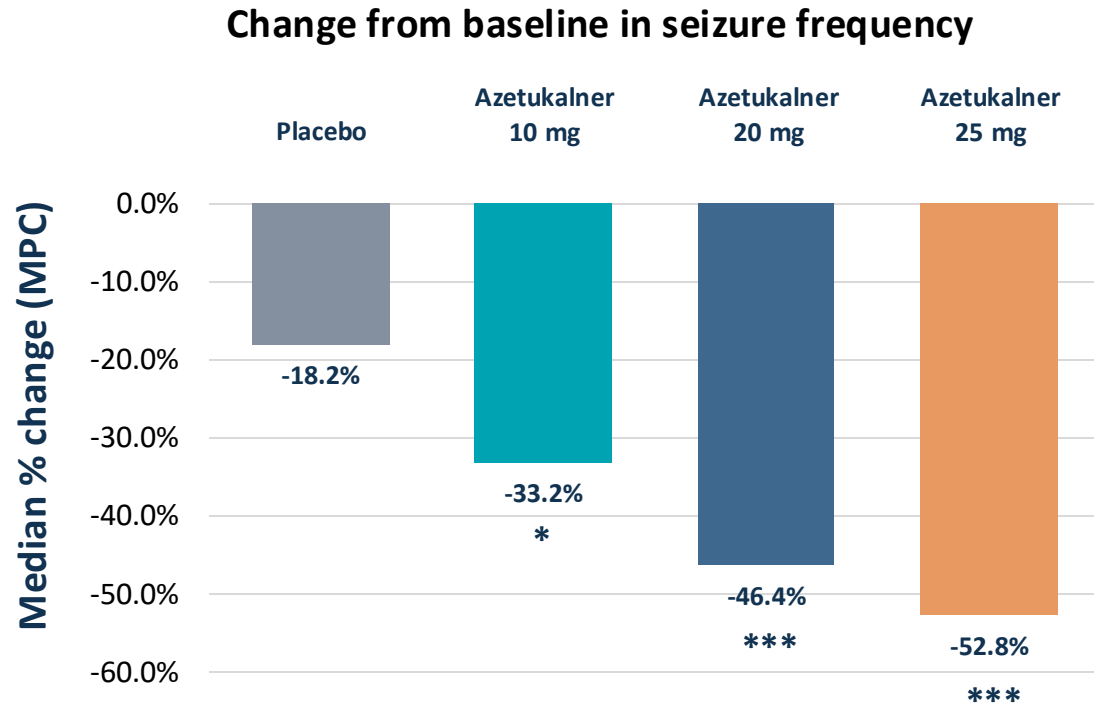


AES Data Update

Chris Kenney, MD
Chief Medical Officer



Statistically Significant and Dose Dependent Reduction in Seizures Observed in Phase 2b X-TOLE Study



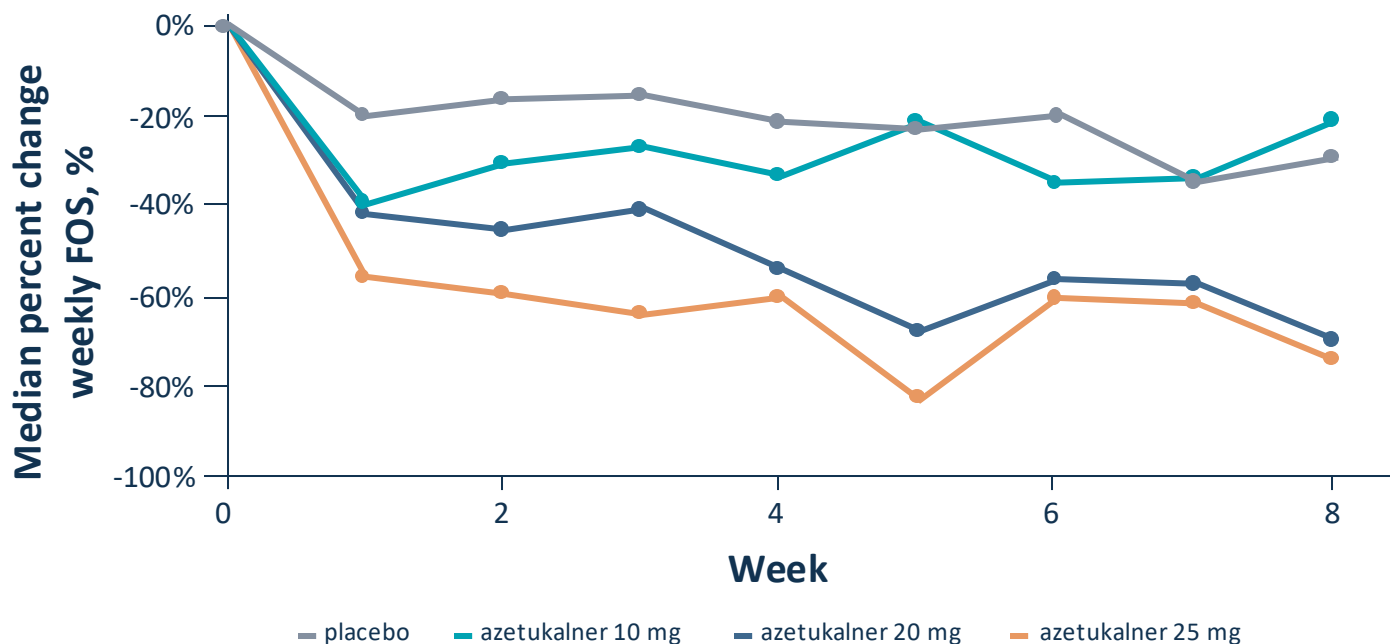
Azetukalner (XEN1101) was administered as a once-daily capsule with food with no titration period.

*p<0.05, ***p<0.001

*p<0.05, ***p<0.001

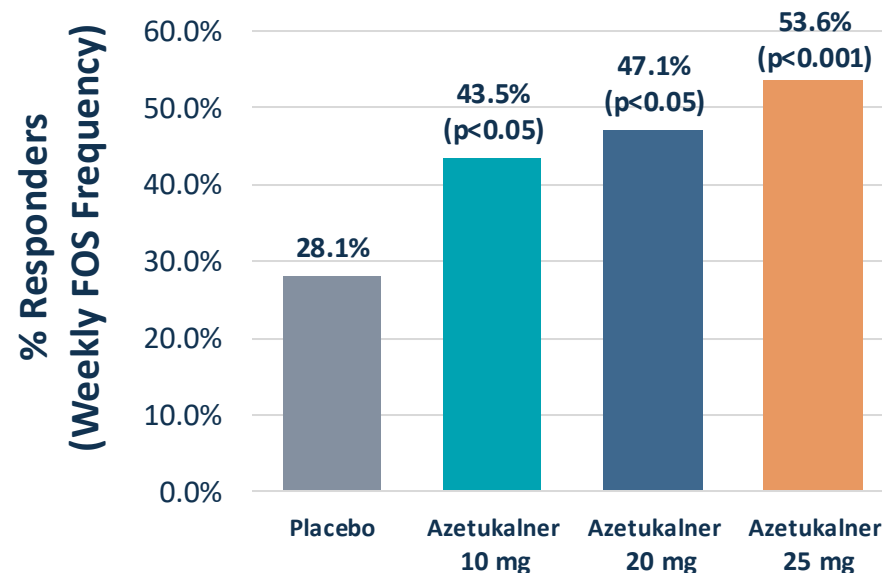
Rapid Onset of Efficacy in Double-Blind Period (DBP)

Change from baseline in FOS frequency in DBP



Responders (RR50) based on percent change from baseline for Week 1 in weekly FOS frequency in DBP

Responder Rate (RR50)- Week 1



*Azetukalner (XEN1101) was administered as a once-daily capsule with food with no titration period.

Marked reduction in median FOS frequency at Week 1 for all doses compared with placebo

X-TOLE: Safety and Tolerability Data from DBP

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

- The most common reported treatment emergent adverse events (TEAEs) across all azetukalner dose groups were dizziness (24.6%), somnolence (15.6%), and fatigue (10.9%), as compared to the placebo group that reported dizziness (7.0%), somnolence (7.0%), and fatigue (5.3%)
- The most common TEAEs leading to discontinuation across all azetukalner dose groups were dizziness (4.7%), balance disorder (2.4%), dysarthria (1.9%), and gait disturbance (1.9%)
- Serious adverse event (SAE) incidence was low and balanced across groups (3.3% across all azetukalner dose groups as compared to 2.6% in the placebo group)

AES 2025: Seven Posters on Azetukalner, Real-World Studies and Na_v1.1 Program

Long-Term Data for Azetukalner in Epilepsy

- ≥48-Month Interim Analysis of the Ongoing 7-Year X-TOLE Open-Label Extension
- Characterization of Long-Term Seizure Freedom in the Ongoing Open-Label Extension of X-TOLE

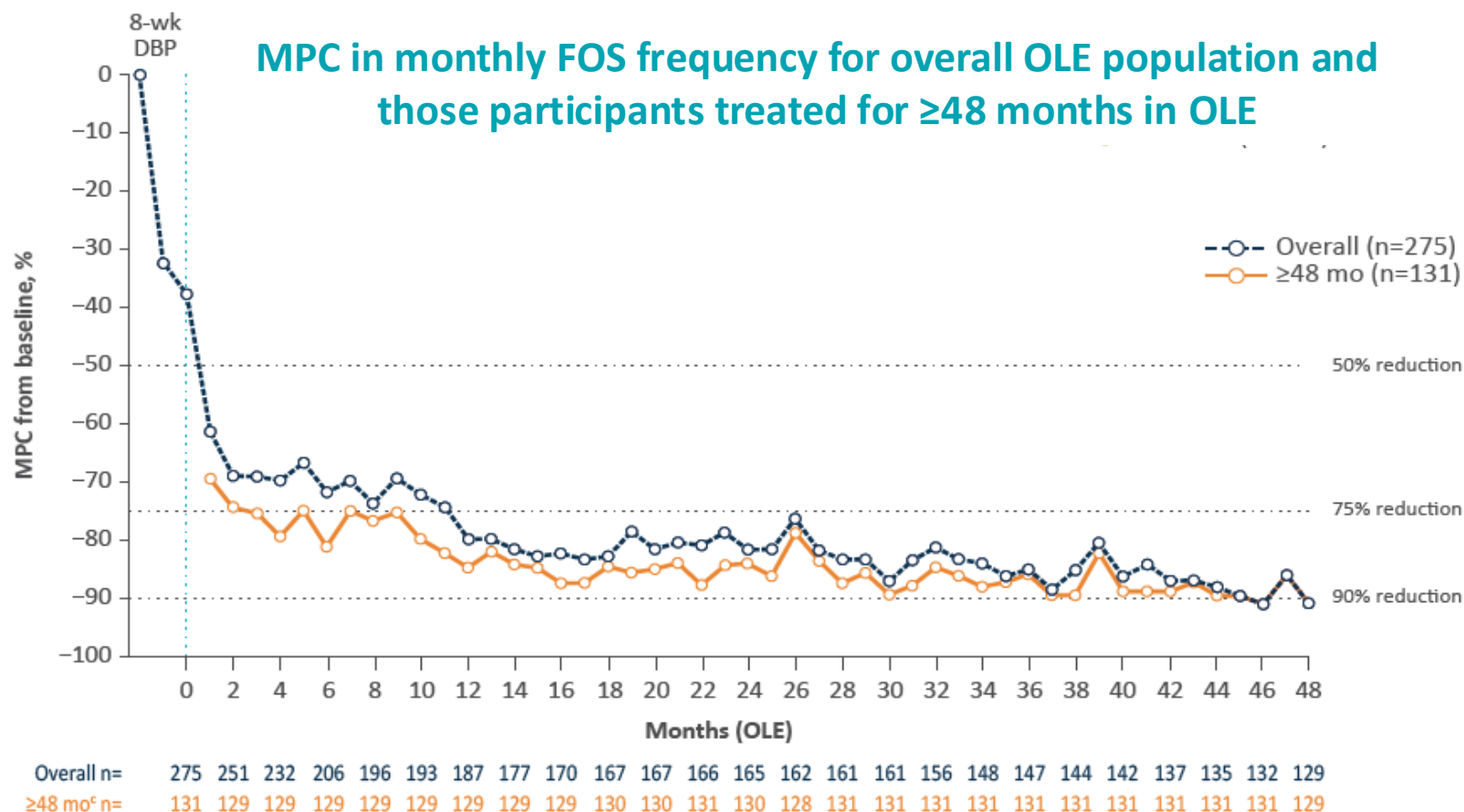
Impact of Depression and Burden of Titration in Epilepsy Care

- Depression Symptom Experience Among Patients with Focal Seizures
- Impact of Depression on Outcomes and Treatment Patterns in Patients with Newly Diagnosed Epilepsy
- Multivariable Models Reporting Increased Economic and Humanistic Burden Among Patients with Focal Seizures Experiencing Moderate to Severe Depression Symptoms
- Clinical Practice and Patient Burden Associated with ASM Titration

Pre-clinical Na_v1.1 Program in Dravet Syndrome

- Selective Potentiation of Na_v1.1 Channels in Dravet Mice Suppresses Spontaneous Seizures, Prevents SUDEP and Increases Long-Term Potentiation

X-TOLE OLE: 48-Month Efficacy of Azetukalner

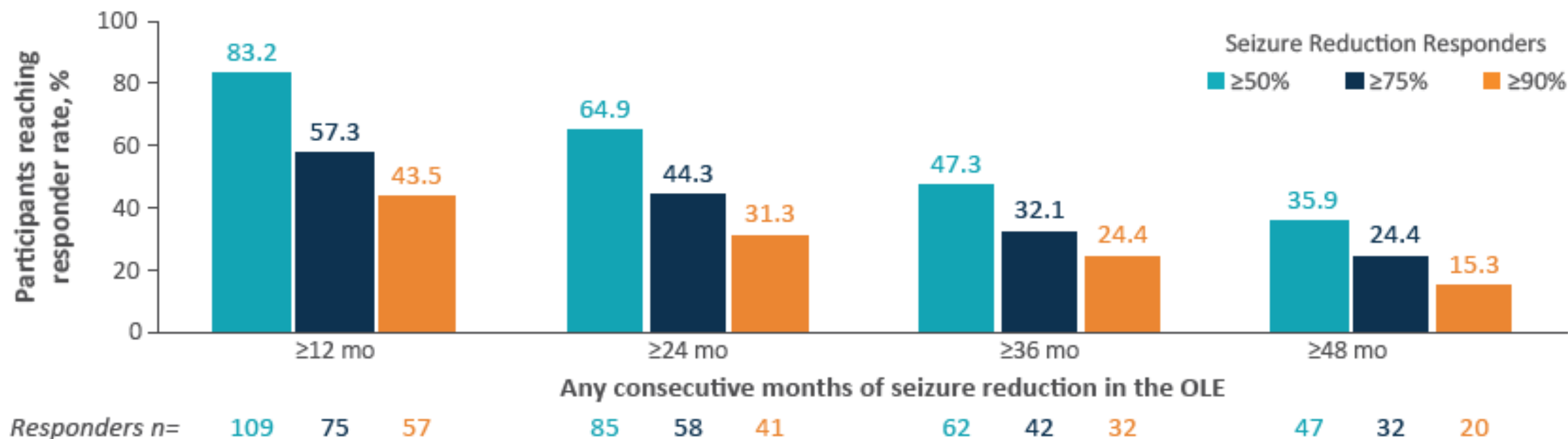


- MPC reductions in monthly FOS frequency from DBP baseline increased to a **90.9% reduction** at OLE month 48
- Higher monthly MPC reductions in participants receiving **1-2 ASMs at DBP baseline (n=60, 100%)** vs. those receiving 3 ASMs (n=69, 81.8%) (data not shown)

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. Monthly seizure rate was calculated for 28 days per month. Sample sizes for each month varied for the 131 participants treated for ≥48 months in the OLE due to non-compliance with daily seizure diary entries. DBP: double-blind period; FOS: focal onset seizures; mo: month; MPC, median percent change; OLE, open-label extension. Source: “Long-Term Safety and Efficacy of Azetukalner, a Novel, Potent KV7 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).

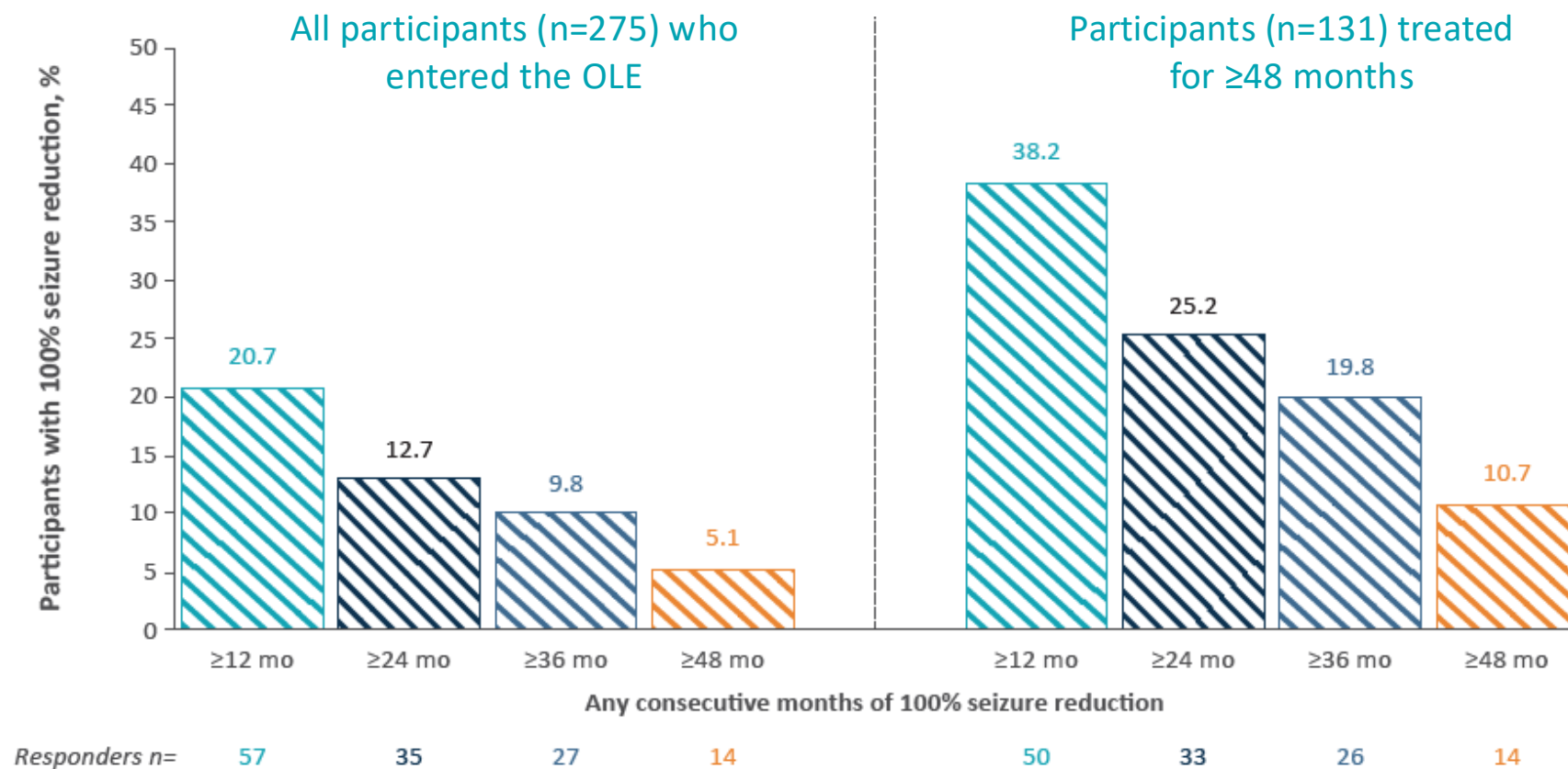
X-TOLE OLE: 48-Month Efficacy of Azetukalner

Responder rates for any consecutive ≥ 12 , ≥ 24 , ≥ 36 , and ≥ 48 months in OLE among participants (n=131) treated for ≥ 48 months



X-TOLE OLE: 48-Month Efficacy of Azetukalner

Seizure freedom rates for any consecutive ≥ 12 , ≥ 24 , ≥ 36 , and ≥ 48 months in OLE

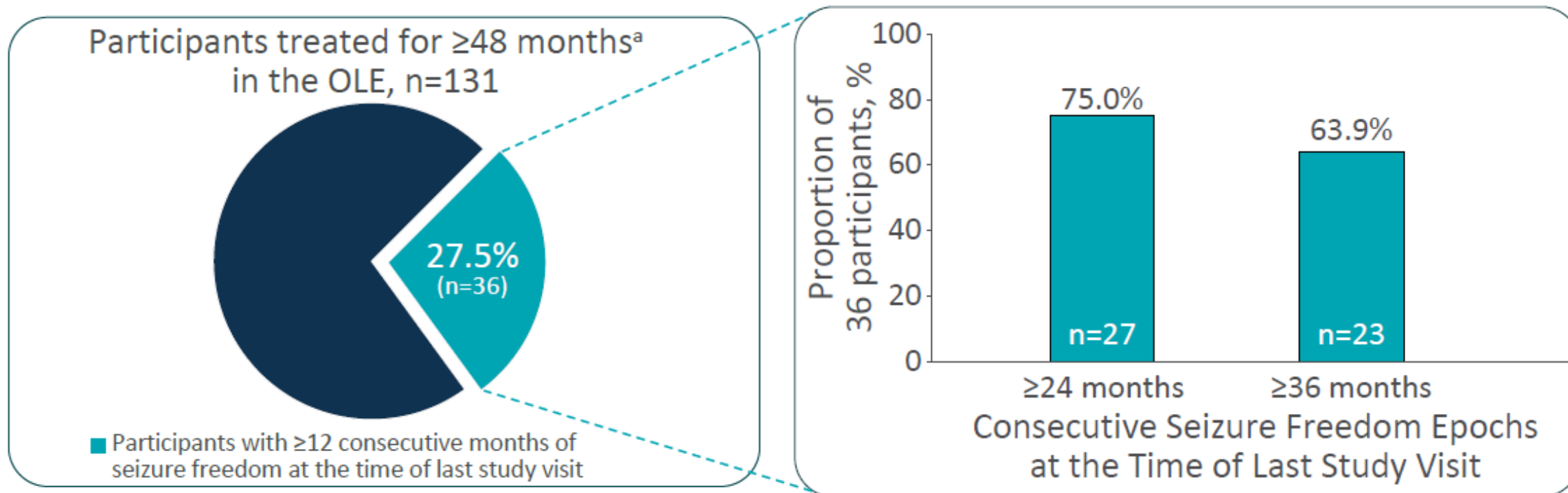


New Long-Term Seizure Freedom Analysis

- Seizure freedom is a primary goal of epilepsy management, but patients may define expectations of seizure freedom differently based on their individual circumstances and treatment goals¹⁻⁵
- Most patients with epilepsy experience a fluctuating clinical course of attaining and regaining variable periods of seizure control, due to either provoked (e.g. missed medication) or unprovoked breakthrough seizures^{2,6}
- Understanding patterns of seizure freedom following a breakthrough seizure is clinically relevant for guiding patient expectations and treatment planning
- Long-term OLE studies investigating ASMs allow continuous observation of seizure patterns, enabling the calculation of various seizure-free “epochs” to better characterize the dynamic patterns of treatment response

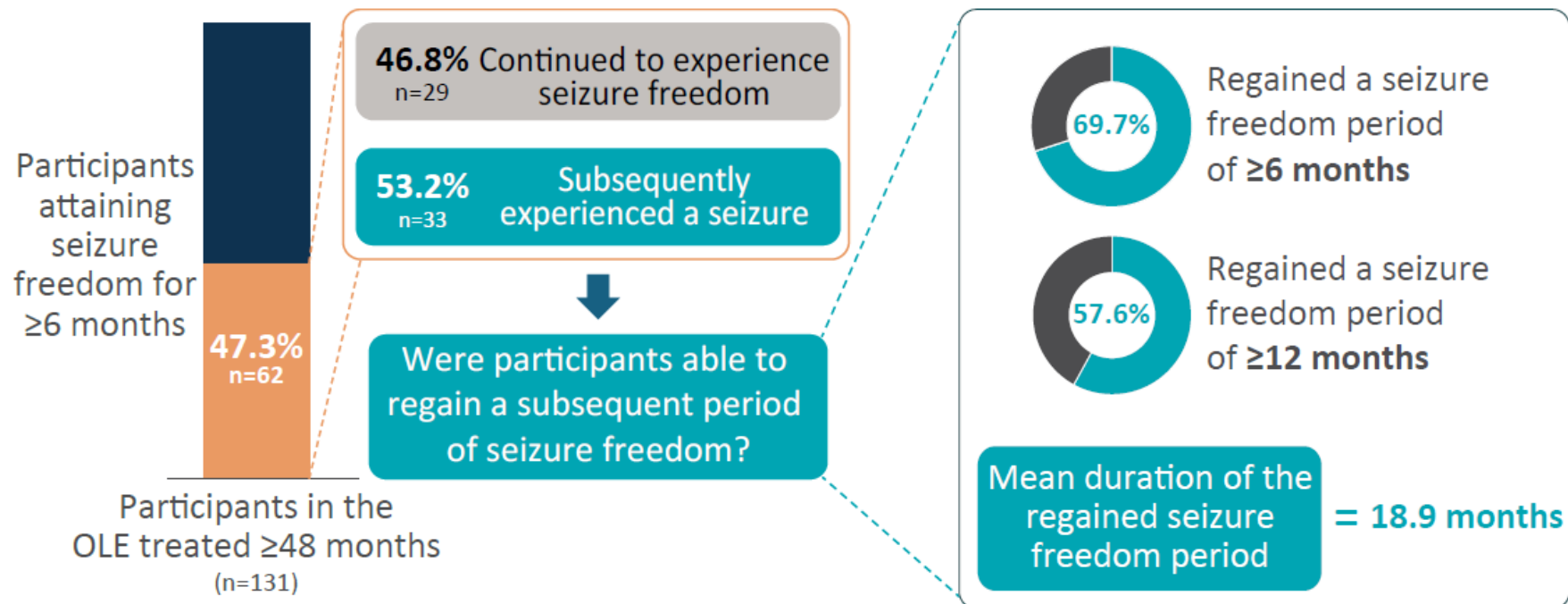
X-TOLE OLE: Long-Term Seizure Freedom Analysis

Sustained seizure freedom in participants treated for ≥ 48 months in the OLE at the time of last study visit



X-TOLE OLE: Long-Term Seizure Freedom Analysis

Participants treated for ≥ 48 months in the OLE who attained any ≥ 6 consecutive months of seizure freedom, had a subsequent breakthrough seizure, and regained seizure freedom



Following a breakthrough seizure, long-term seizure freedom can be regained with ongoing azetukalner treatment, even in patients with difficult-to-treat disease

X-TOLE OLE: 48-Month Safety of Azetukalner

Long-term safety and tolerability of azetukalner in the OLE remains comparable with that observed in the DBP

- As of October 6, 2025, the OLE has generated >775 patient-years of safety data
- TEAEs and treatment-related TEAEs occurred in 89.5% and 65.8% of the safety population, respectively
- Most common AEs (>10% of overall population) included: dizziness (25.1%), headache (18.9%), COVID-19 (17.1%), somnolence (17.1%), fall (14.5%), weight increased (11.3%), memory impairment (10.9%), and gait disturbance (10.2%)
- Four participants reported urinary retention, 1 reported as mild and the other 3 as moderate; no dose changes were made in any case
- Serious TEAEs were reported in 45 (16.4%) participants, and those occurring in >1 participant included seizure (n=12, 4.4%); deep vein thrombosis (n=3, 1.1%); and paresthesia, seizure cluster, influenza, pneumonia aspiration, rhabdomyolysis, and fall (n=2, 0.7% each)
- Two deaths considered unrelated to azetukalner treatment were reported (SUDEP and viral pneumonia, n=1 each)

Impact of Depression in Epilepsy Care

◆ Three posters highlighted significant burden of depression on patients with FOS:

- Patients with FOS experienced considerable mental health burden, including depressed mood and anhedonia¹
- Patients with FOS with depression symptoms experienced lower QoL and higher HCRU²
- Depression was associated with shorter duration of initial therapy and an increased risk of treatment failure³

◆ Studies underscore importance of:

- Considering the “whole patient” when making treatment decisions
- Developing treatment options that do not exacerbate or cause depression, anxiety or other mood disorders

“ People with epilepsy are known to be at higher risk for mood disorders, but our study uncovers new information that those with depression are more likely to fail their first treatment.

Depression could affect epilepsy treatment in various ways, such as influencing a person’s motivation to continue medication, making their complex drug regimen too challenging or magnifying side effects. ”

Samuel W. Terman, M.D., M.S.

Assistant professor of neurology at the University of Michigan, Ann Arbor (AES Press Release)

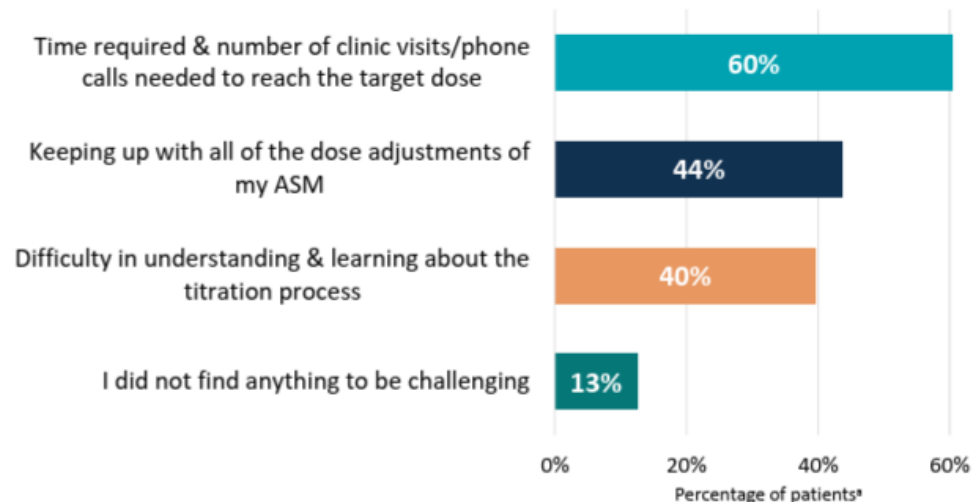
Source: 1. “Depression Symptom Experience Among Patients with Epilepsy Reporting a Diagnosis of Focal Seizures (FS): A Patient-Reported Outcomes Study.” 2025 Annual Meeting of the American Epilepsy Society (AES). 2. “Multivariable Models Reporting Increased Economic and Humanistic Burden Among Patients With Epilepsy Reporting Focal Seizures (FS) Experiencing Moderate to Severe Depression Symptoms.” 2025 Annual Meeting of the American Epilepsy Society (AES). 3. “Impact of Depression on Outcomes and Treatment Patterns in Patients with Newly Diagnosed Epilepsy: A Retrospective Claims Analysis.” 2025 Annual Meeting of the American Epilepsy Society (AES).

Clinical Practice and Patient Burden Associated with ASM Titration

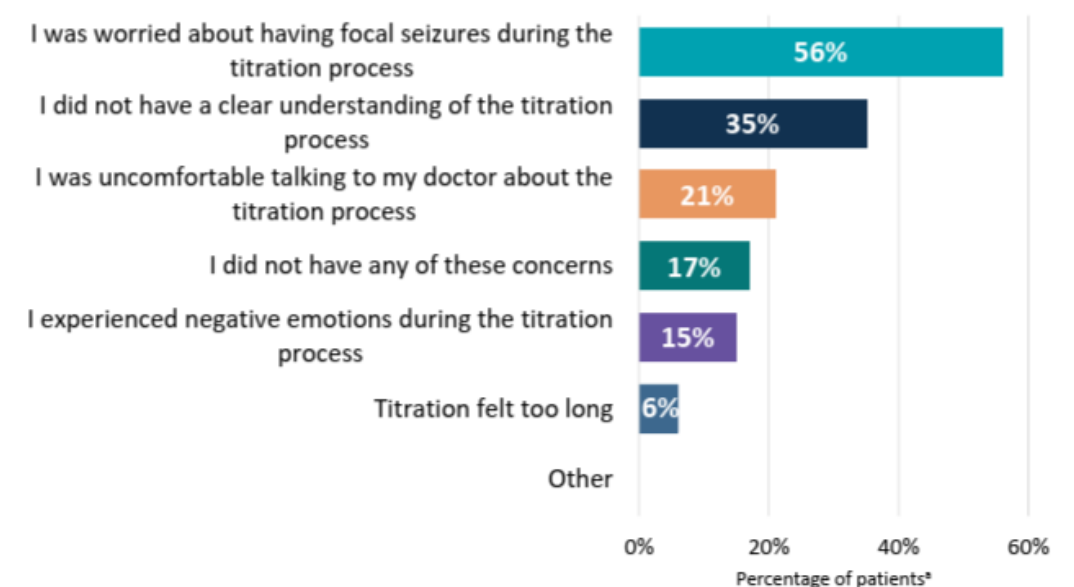
- Most ASMs include a manufacturer-recommended initial drug titration phase to improve tolerability, ranging from weeks to months¹
- Lengthy titration schedules can delay therapeutic dosing and optimal seizure control
- There is a need for ASMs with simplified or no titration

Results from patient survey reveal substantial burden associated with ASM titration²

Patient-Reported Challenges Encountered During Titration (N=48)



Patient-Reported Concerns Experienced During Titration (N=48)



Respondents were able to select all response options that applied; therefore, the responses are not mutually exclusive. ASM: anti-seizure medications.

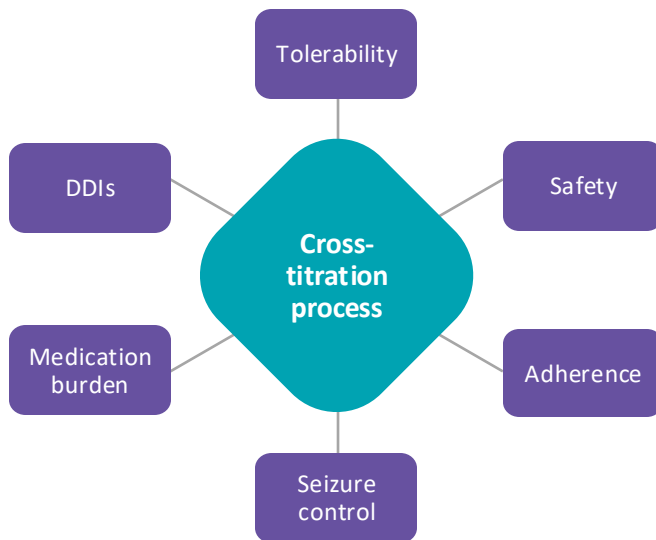
Source: 1. Seiden LG, Connor GS. *Epilepsy Behav.* 2022; 128. 2. "Clinical Practice and Patient Burden Associated with Anti-Seizure Medication Titration: A Thematic Analysis." 2025 Annual Meeting of the American Epilepsy Society (AES).

Clinical Practice and Patient Burden Associated with ASM Titration

Themes from HCP roundtable reinforced findings from patient survey and burden on HCPs and health resources

Greater complexity of clinical management

During cross-titration, physicians balance multiple, often competing considerations



Increased strain on healthcare resources

- ✔ Need for additional staff
- ✔ Additional visit time dedicated to titration education for patients
- ✔ Frequent follow-up visits
- ✔ Increased coordination with and between pharmacy and patients
- ✔ Increased communication workload to check in with patients

Underrecognized burden of titration with both patients and HCPs

“ What is a straightforward titration to me is straightforward because I have done it over and over again, and to the patient, they have never done it before... to the patient, everything is [unfamiliar]. ”

“ We are adding [ASMs] to get better efficacy because of this concept of polytherapy and rational polypharmacy... even if that medication had some efficacy, you have got to lower [its dose] because of [its pharmacodynamic and pharmacokinetic interactions]. You have to take that risk, which comes back to the stress of all of this. ”

Key Insights from 2025 AES Data

- 48 months into OLE, azetukalner continues to demonstrate strong efficacy:
 - 90.9% MPC reduction in monthly FOS frequency
 - 100% monthly reduction observed among patients receiving 1-2 ASMs at DBP baseline
- 38% of patients on treatment with azetukalner for at least 48 months achieved seizure freedom for a period of one year or longer
- Following a breakthrough seizure, seizure freedom can be regained with ongoing azetukalner treatment, even in patients with difficult-to-treat disease
- Azetukalner safety and tolerability profile in the OLE remains comparable with the DBP
- Depression is a significant burden for patients in FOS, underscoring need to consider the “whole patient” and offer therapeutics that do not exacerbate or cause depression or other mood disorders
- Titration is a significant burden for patients and HCPs, underscoring need for improved patient/provider communication and ASMs with simplified or no titration

OLE: open-label extension; DBP: double-blind period

Sources: 1. “Long-Term Safety and Efficacy of Azetukalner, a Novel, Potent KV7 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. 2. “Characterization of Long-Term Seizure Freedom in the Ongoing Open-Label Extension of X-TOLE: Potential Implications for Future Clinical Practice.” 2025 Annual Meeting of the American Epilepsy Society. 3. “Depression Symptom Experience Among Patients with Epilepsy Reporting a Diagnosis of Focal Seizures (FS): A Patient-Reported Outcomes Study.” 2025 Annual Meeting of the American Epilepsy Society. 4. “Multivariable Models Reporting Increased Economic and Humanistic Burden Among Patients With Epilepsy Reporting Focal Seizures (FS) Experiencing Moderate to Severe Depression Symptoms.” 2025 Annual Meeting of the American Epilepsy Society. 5. “Impact of Depression on Outcomes and Treatment Patterns in Patients with Newly Diagnosed Epilepsy: A Retrospective Claims Analysis.” 2025 Annual Meeting of the American Epilepsy Society. 6. “Clinical Practice and Patient Burden Associated with Anti-Seizure Medication Titration: A Thematic Analysis.” 2025 Annual Meeting of the American Epilepsy Society.

Progress Toward Commercialization

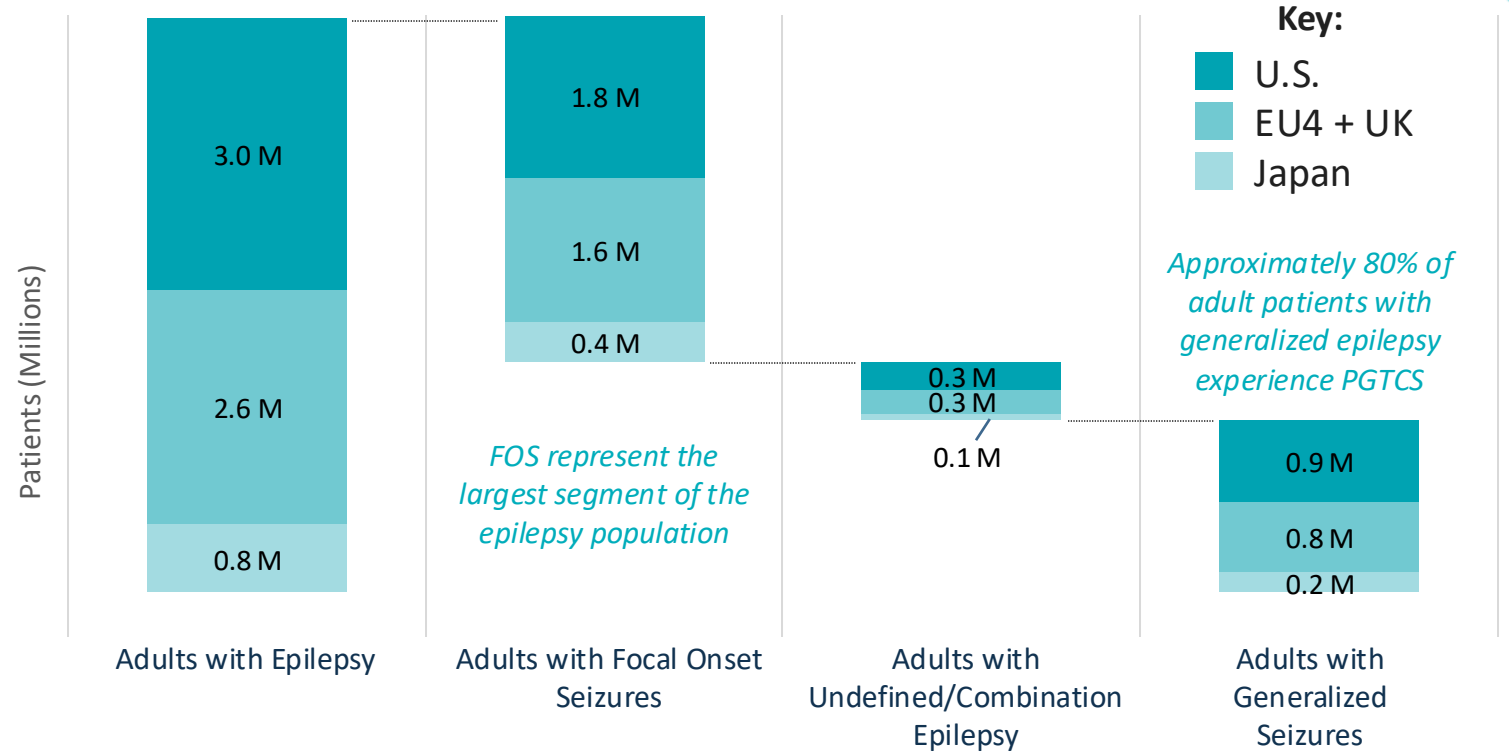
Darren Cline
Chief Commercial Officer



Significant Global Epilepsy Burden

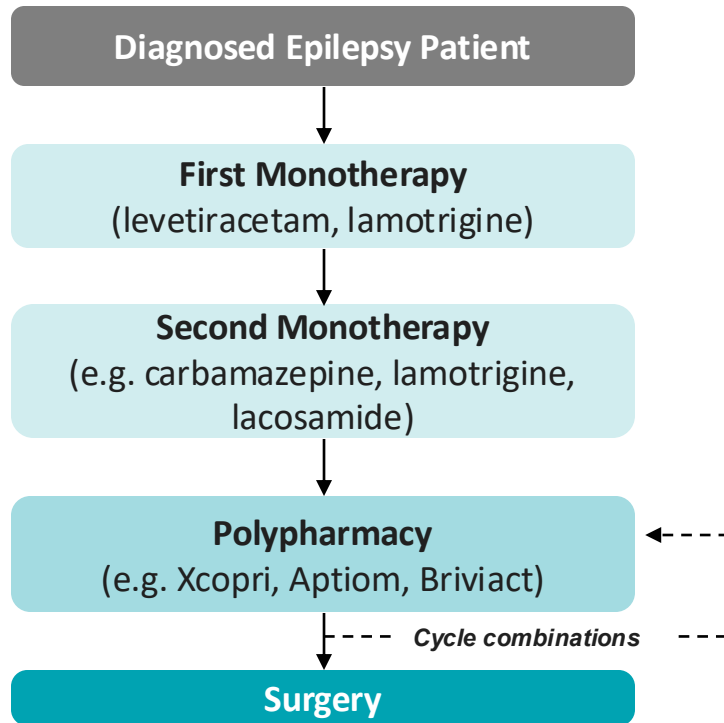
- Epilepsy is the **fourth most common neurological condition**
- Hallmark symptoms include:
 - **focal seizures** that start in one brain hemisphere (either aware or unaware)
 - **generalized seizures** the most common of which are tonic-clonic/convulsive seizures
- Despite the availability of multiple ASMs, a **substantial unmet medical need exists**
- Rates of **comorbid depression** exist in up to 50% of epilepsy patients

Estimated Diagnosed Adult Epilepsy Patient Population (2020)



Approximately 1 million children under the age of 18 have epilepsy across the three geographic regions

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, including mood issues
- Comorbid conditions influence prescribing decisions

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

- Combinations typically involve mechanistic differentiation from early lines of therapy
- Branded therapies can potentially be accessed if a patient has tried and failed 1-2 generic ASMs

Significant opportunity remains with up to 50% of epilepsy patients requiring additional treatment options

Understanding Target Prescribers

Target HCPs

- Subset of epileptologists, neurologists and APPs
- High volume prescribers with high likelihood of early azetukalner adoption based on branded prescribing behavior

All Epileptologists (~2,400)

- Most productive prescribers
- ~80% prescribe branded ASMs

All General Neurologists (~18,000)

- Largest Rx volume
- ~33% prescribe branded ASMs

Epilepsy-Focused APPs (~16,000)

- More limited brand use – but appears to be growing

Azetukalner attributes may enable faster uptake with neurologists and APPs compared with other brand launches

Market Research Suggests Epileptologists and Neurologists May Both Find Value in Potential Azetukalner Attributes



Epileptologists¹

Perceptions of
“Product X”

Unfavorable ● ———— ◆ Favorable

Novel Mechanism of Action

Dosing Flexibility to Balance Efficacy and Safety

Branded ASM-like Efficacy

“Product X”
Value Drivers

“The MoA is interesting to me. I like to choose something that is different than what my pts have received. This product gives me more flexibility.” – Epileptologist

“The side effect profile of Product X is tolerable. I also don’t have to wait to get my pts to an effective dose, but have some flexibility in the dose I choose.” – Epileptologist



General Neurologists¹

Unfavorable ● ———— ◆ Favorable

Ease of Use²

Manageable Safety Profile

Fast Onset of Action

“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

Preparing for a Successful Launch with Early Investment



**Enabling
Technology**

Leveraging AI applications to enhance marketing tactics with high-precision targeting

Planning for Strong Channel and Patient Services to Drive Adoption and Retention

1

Enable a simple, easy, and positive provider experience

2

Ensure broad payer access

3

Optimize and simplify the patient experience

4

Maximize success rate at time of first fill and beyond

5

Build the infrastructure and resources to ensure compliance and retention

Investing in a Commercial and Medical Team with a Proven Track Record in Epilepsy

Recent team additions and upcoming priorities to enable a strong launch trajectory



Commercial Leadership

Expanding leadership team – new SVP of Sales & Marketing hired in 2025 with history of success in epilepsy launches and innovative commercial strategy



Customer Engagement

Has already been in the field for the past 1.5 years, focused on building and deepening relationships with CoEs and KOLs



Market Access

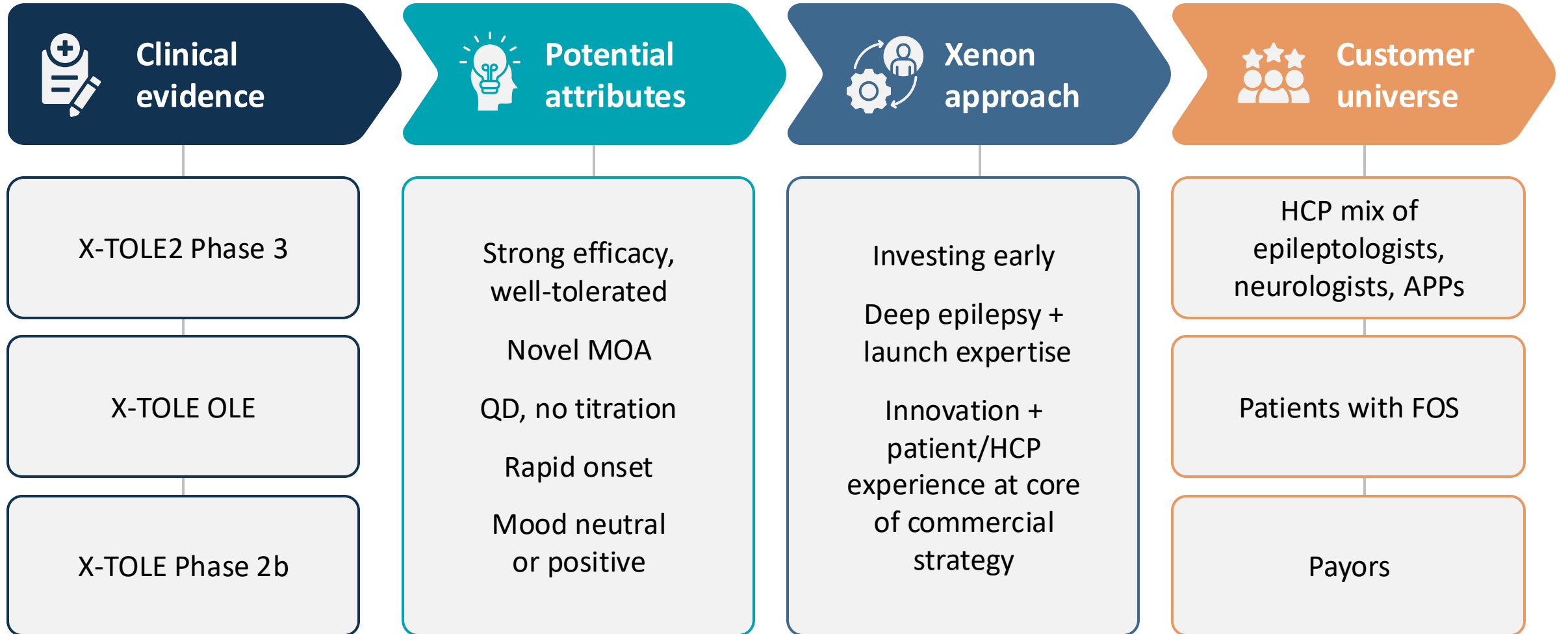
Growing team and initiating discussions with payors in 2026



Medical Affairs

Expanding leadership team focused on HCP education and engagement + evidence generation; MSLs already in the field with more being added in 2026

Path to Launch in FOS



Closing Remarks

Ian Mortimer

President & Chief Executive Officer



Advancing Azetukalner Toward Phase 3 Data and Launch in FOS

AES data reinforced key differentiating attributes for azetukalner and opportunities to disrupt the epilepsy treatment landscape

Azetukalner has significant commercial opportunity with potential for rapid adoption by epileptologists, neurologists, and APPs

We are investing early in insights, innovation, infrastructure, and integration of top commercial/medical leaders for a highly successful FOS launch

Topline Phase 3 X-TOLE2 data in FOS are anticipated early 2026



Q&A

 Xenon™



Thank you

INVESTORS@XENON-PHARMA.COM