2025 J.P. Morgan Healthcare Conference

Corporate Overview

PRESENTED BY: IAN MORTIMER, PRESIDENT & CEO, XENON PHARMACEUTICALS

JANUARY 13, 2025

Forward Looking Statement/Safe Harbor

This slide presentation and the accompanying oral commentary contain forward-looking statements 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 trials; 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 trial designs; our ability to successfully develop and achieve milestones in our azetukalner and other pipeline and development programs, including the anticipated filing of INDs; 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 trials 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 trials 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 trial results may not be replicated in later clinical trials; 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 of clinical trials; the impact of market, industry, and regulatory conditions on clinical trial 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.

About Xenon Pharmaceuticals

- Neuroscience-focused biopharma company and leader in small molecule, ion channel drug discovery and development
- Azetukalner, our **highly potent, selective Kv7 channel opener**, represents the most advanced, clinically validated potassium channel modulator in late-stage clinical development and the **only Kv7 molecule in development with efficacy and safety data** in epilepsy and MDD patients
  - Comprehensive intellectual property portfolio with patent coverage extending to at least 2040, absent any extensions of patent term
- Robust pipeline of therapeutic candidates targeting both potassium and sodium channels across various indications
- Strong financial position
  - $803.3 million in cash, cash equivalents and marketable securities as of September 30, 2024
  - Anticipated cash runway to fund operations into 2027

Xenon's Neuroscience-Focused Pipeline

	Clinical Trial/Partner	Pre-Clinical	Phase 1	Phase 2	Phase 3
Azetukalner (Potassium Channel Opener)					
Epilepsy: Focal Onset Seizures (FOS)	X-TOLE2				
Epilepsy: Focal Onset Seizures (FOS)	X-TOLE3				
Epilepsy: Primary Generalized Tonic-Clonic Seizures (PGTCS)	X-ACKT				
Major Depressive Disorder (MDD)	X-NOVA2				
Major Depressive Disorder (MDD)*	Mount Sinai				
Pre-clinical Ion Channel Modulators					
Kv7 Potassium Channel Openers (*Epilepsy, pain, and neuropsychiatric indications*)					
Nav 1.7 Sodium Channel Inhibitors (*Pain indications*)					
Nav 1.1 Sodium Channel Openers (*Dravet Syndrome*)					
Nav1.2/1.6 Sodium Channel Inhibitor (Partnered Program)					
Epilepsy	Neurocrine Biosciences				

*Investigator sponsored Phase 2 non-registrational proof-of-concept study

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.

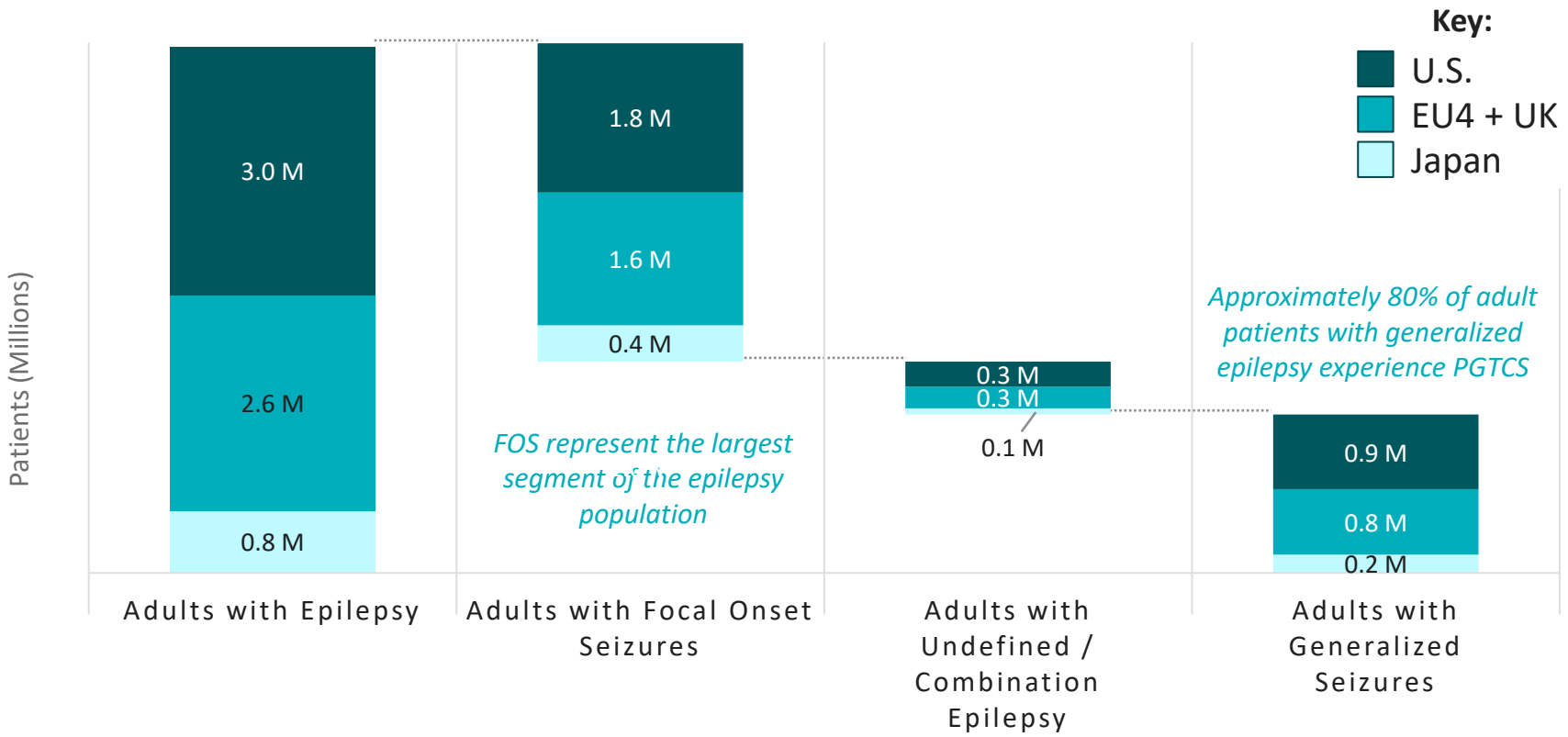
Overview of Azetukalner in Epilepsy

X-TOLE, X-TOLE2, X-TOLE3, AND X-ACKT CLINICAL TRIALS

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
- Rates of **comorbid depression** exist in up to 50% of epilepsy patients

Estimated Diagnosed Adult Epilepsy Patient Population (2020)



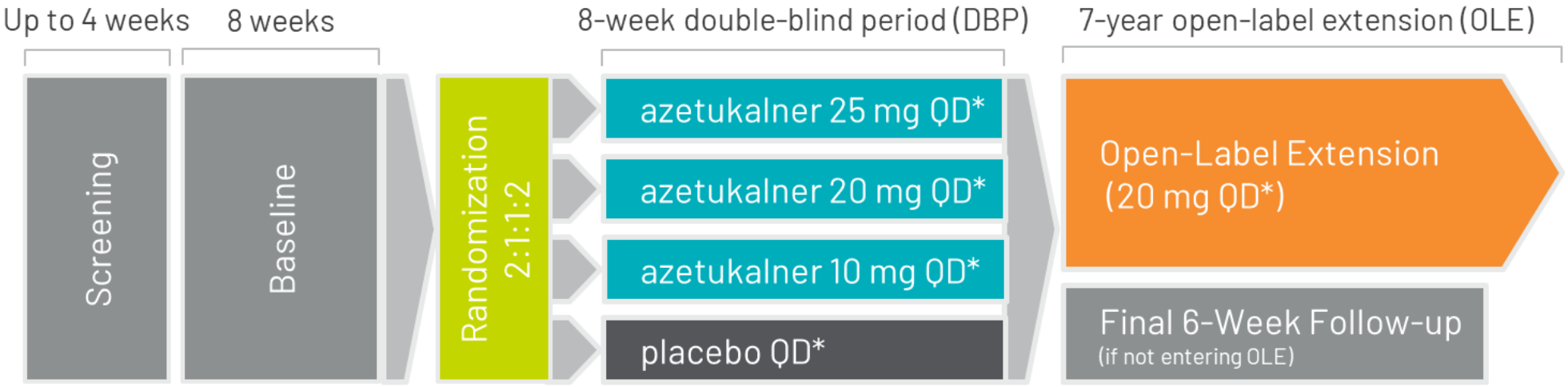
Despite the availability of multiple ASMs, a substantial unmet medical need exists

Sources: Company-sponsored market research; Mula, et al, *Effect of drug treatment changes and seizure outcomes on depression and suicidality in adults with drug-resistant focal epilepsy*, Epilepsia, December 11, 2023; Epilepsy Foundation; Epilepsy Currents, Englot (2018), National Association of Epilepsy Centers, National Institute of Neurological Disorders and Stroke

X-TOLE Phase 2b Clinical Trial in Focal Onset Seizures

X-TOLE™

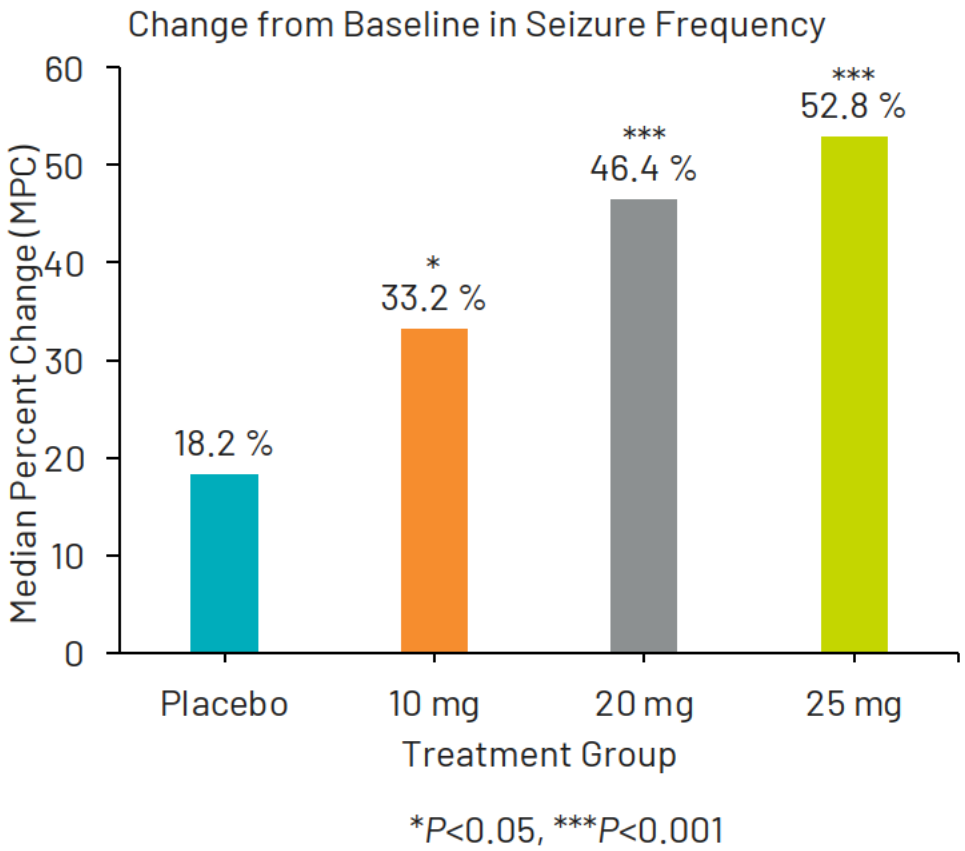
Phase 2b study and 7-year OLE

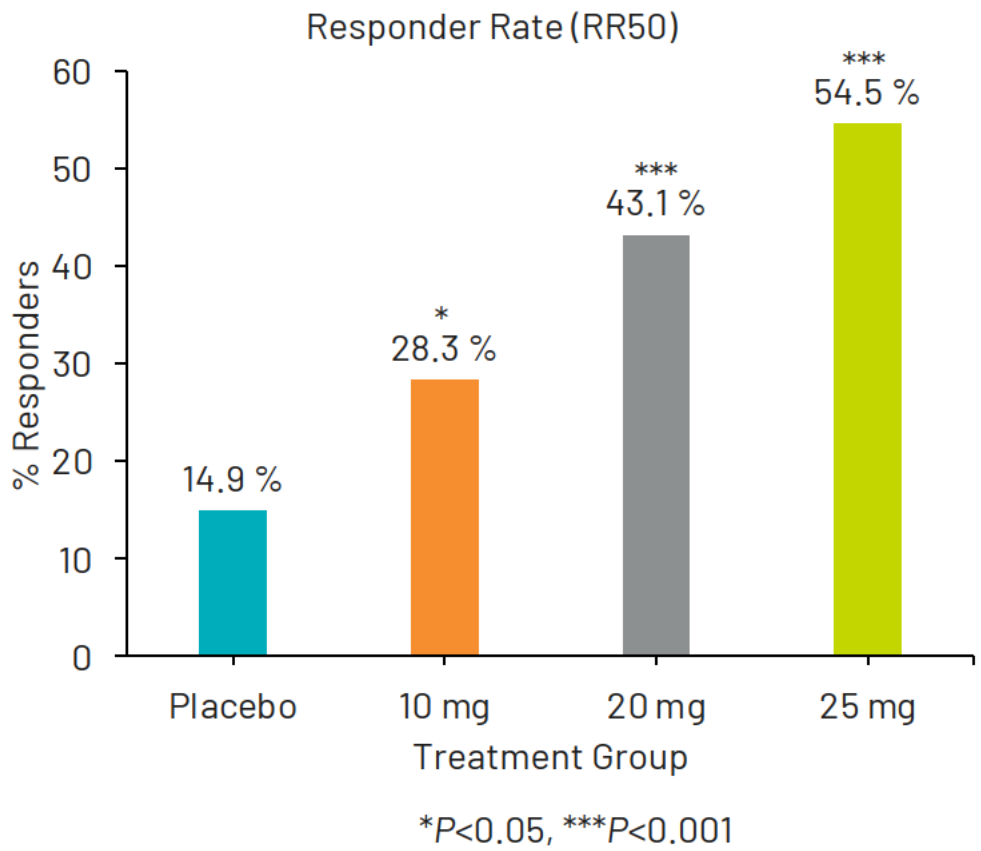


*Administered as a once-daily capsule with food with no titration period.

Topline results reported in October 2021 and subsequent *ad hoc* analyses and OLE data presented at AES meetings

Compelling Phase 2b Efficacy Results



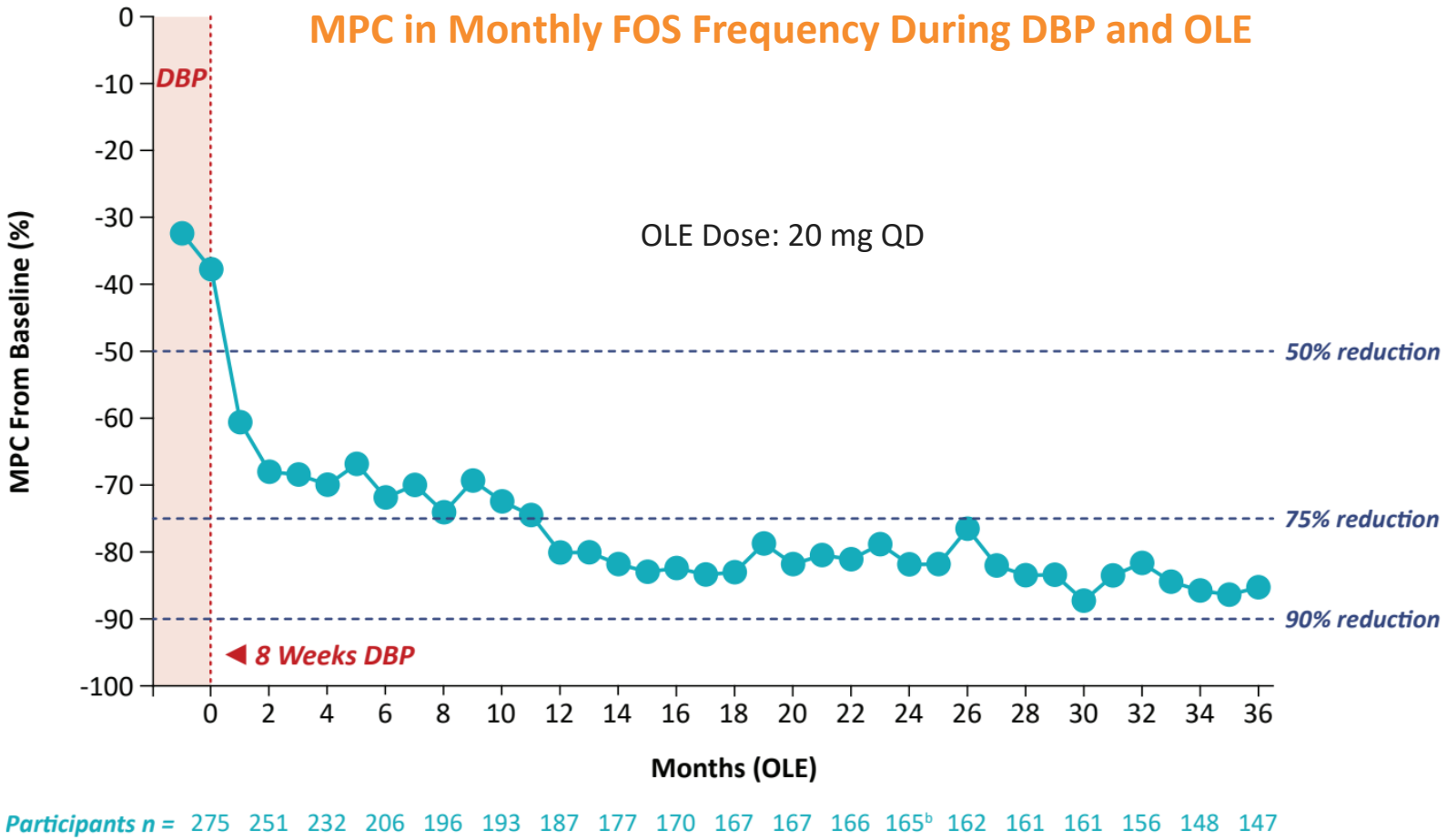


Azetukalner (XEN1101) was administered as a once-daily capsule with food with no titration period.

Statistically significant and dose dependent reduction in seizures

Source: "Phase 2b Efficacy and Safety of XEN1101, a Novel Potassium Channel Modulator, in Adults with Focal Epilepsy (X-TOLE)." 2022 Annual Meeting of the American Epilepsy Society (AES).

Robust Long-Term Efficacy Results in X-TOLE OLE



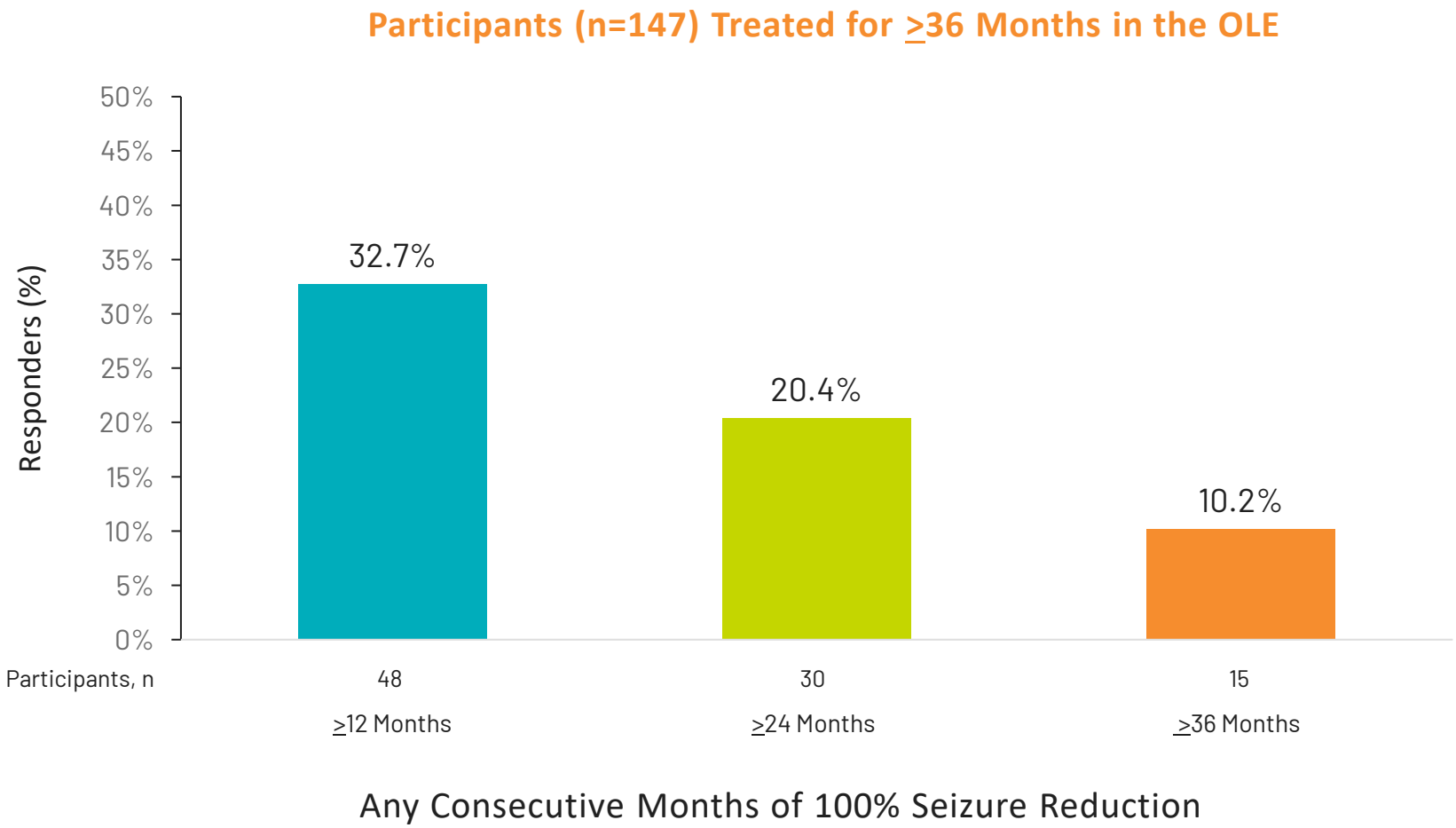
Azetukalner (XEN1101) was administered as a once-daily capsule with food with no titration period.

Patients receiving 1–2 ASMs at baseline experienced **higher monthly MPC reductions in FOS frequency from baseline at OLE study month 36** (100% seizure reduction, n=67), compared to those receiving 3 ASMs (80.6% seizure reduction, n=80)

Sustained monthly reduction in seizure frequency in OLE from DBP baseline with even greater improvements in patients on fewer baseline ASMs

Source: French J, Porter R, Perucca E, et al. Long-term safety and efficacy of azetukalner, a novel, potent Kv7 potassium channel opener in adults with focal epilepsy: Update from the ongoing 7-year open-label extension of X-TOLE. *American Epilepsy Society Annual Meeting,* December 6-10, 2024, Los Angeles, CA; Interim data cut October 7, 2024; OLE: open-label extension; MPC: median percent change; QD: once daily

Impressive Seizure Freedom in the X-TOLE OLE



Nearly 1 in 3 patients treated for ≥36 months in the OLE experienced ≥12 consecutive months of seizure freedom

Source: French J, Porter R, Perucca E, et al. Long-term safety and efficacy of azetukalner, a novel, potent Kv7 potassium channel opener in adults with focal epilepsy: Update from the ongoing 7-year open-label extension of X-TOLE. *American Epilepsy Society Annual Meeting,* December 6-10, 2024, Los Angeles, CA; Interim data cut October 7, 2024; All doses taken with food no titration; OLE: open-label extension

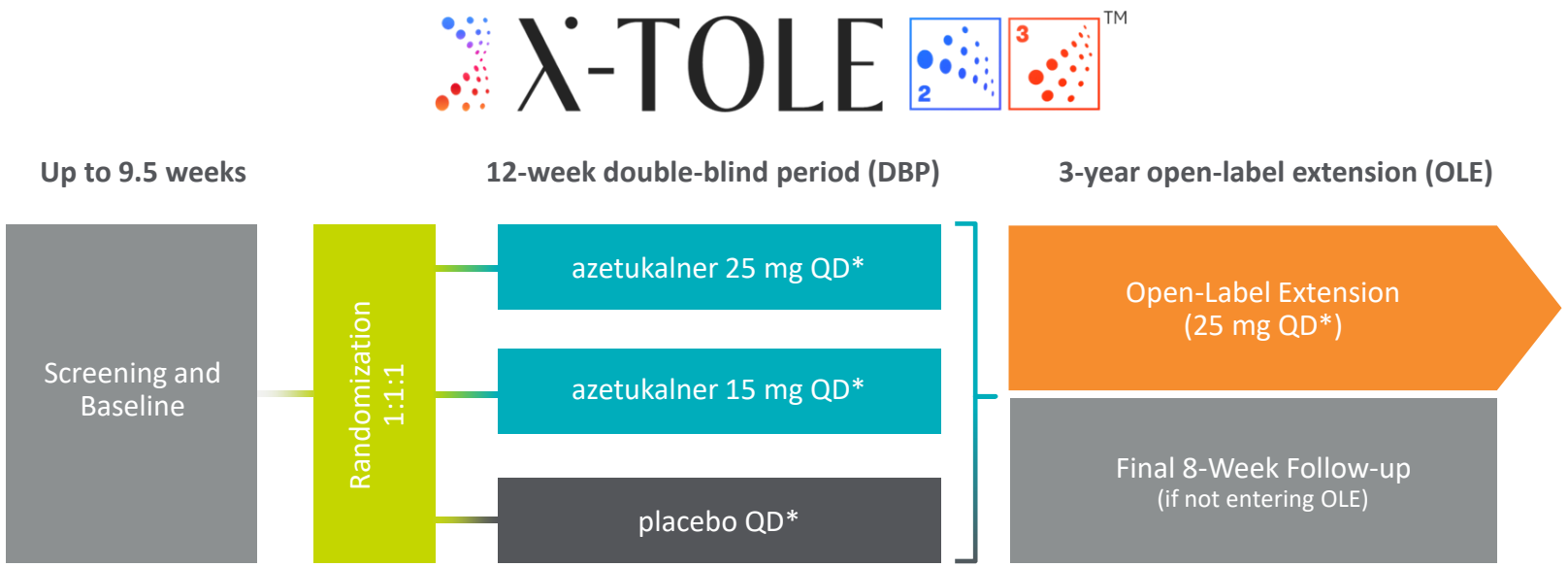
X-TOLE: Safety and Tolerability Data

- X-TOLE Double-Blind Period
  - Azetukalner was generally well-tolerated in this study with adverse events consistent with other 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 which 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 events (SAE) incidence was low and balanced across groups (3.3% across all azetukalner dose groups as compared to 2.6% in the placebo group)
- X-TOLE Open-Label Extension*
  - Azetukalner 20 mg QD was generally well tolerated in OLE, and the safety profile observed was similar to that of the DBP; no new safety signals were identified

* Results are from interim data from the open-label extension of X-TOLE (cutoff date October 7, 2024).

X-TOLE2 and X-TOLE3 Phase 3 Clinical Trials in FOS

- Plan to submit NDA supported by efficacy data from Phase 2b study (X-TOLE) and first Phase 3 study (X-TOLE2)
- Conducting two identical multi-center, placebo-controlled Phase 3 FOS trials (N = ~360 in each study)



*Administered as once-daily capsule with food with no titration period. There is no placebo dose in the OLE.

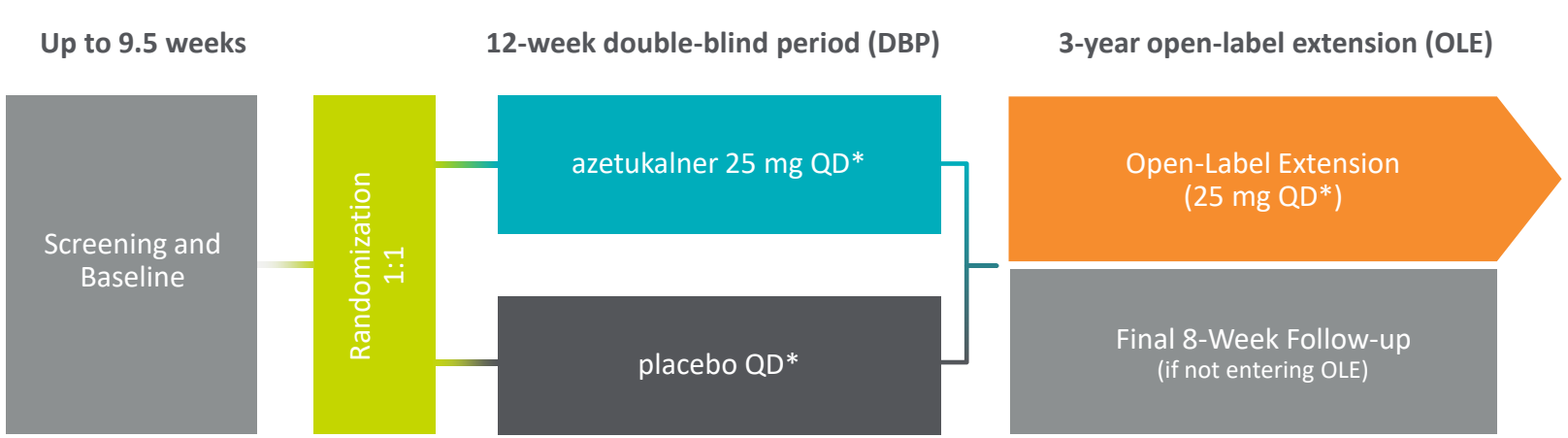
- **Primary Objective:** assess effect of azetukalner vs placebo on reducing focal onset seizure frequency
- **Secondary Objectives** include assessing the effect on azetukalner vs placebo on RR50, early treatment effect as measured at Week 1, and PGI-C

X-TOLE2 topline data anticipated in second half of 2025

X-ACKT Phase 3 Clinical Trial in PGTCS

- Significant unmet need remains in PGTCS despite available treatment options and an opportunity remains for a broad-spectrum agent with activity across seizure types
- Conducting a single, multi-center, placebo-controlled Phase 3 trial to support registration (N = ~160)

X-ACKT™



*Administered as once-daily capsule with food with no titration period. Subjects aged ≥12 years and <18 years will receive either azetukalner 15mg, azetukalner 25 mg, or placebo; subjects aged ≥18 years will receive either azetukalner 25 mg or placebo. There is no placebo dose in the OLE.

- **Primary Objective:** assess effect of azetukalner vs placebo on reducing frequency of primary generalized tonic clonic seizures
- **Secondary Objectives** include assessing the effect on azetukalner vs placebo on RR50, seizure freedom and PGI-C

Expanding Azetukalner in MDD

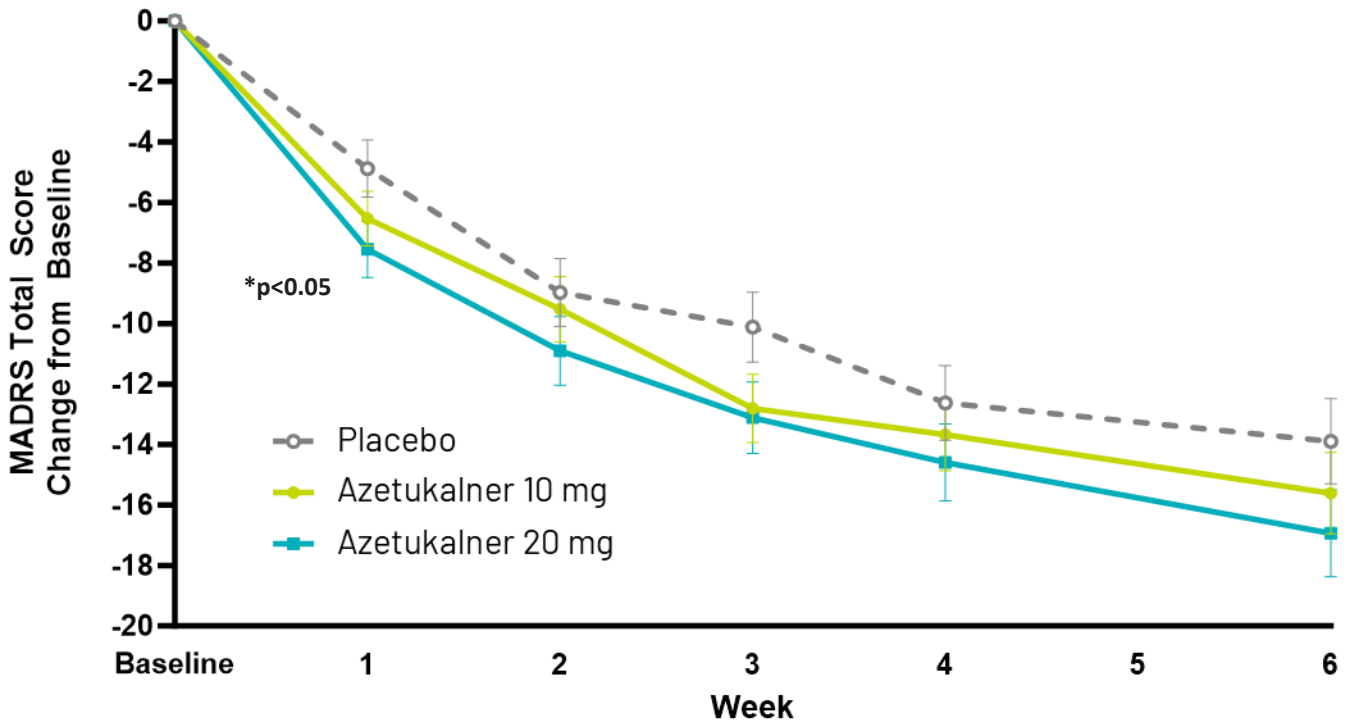
X-NOVA Phase 2 Proof-of-Concept Clinical Trial in MDD

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

- **Primary Objective:** Montgomery-Åsberg Depression Rating Scale (MADRS) score change through Week 6
- **Key Secondary Objective:** Snaith-Hamilton Pleasure Scale (SHAPS) score change through Week 6

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

Primary Efficacy Endpoint:
Change in MADRS Total Scores at Week 6 (mITT)



	Placebo (N=54)	Azetukalner 20 mg (N=53)
ΔMADRS from BL at **Wk 6** (LS mean)	-13.90	**-16.94**
Diff. vs Pbo		**-3.04**
p-value		0.135

A clear dose response and a clinically meaningful 3.04 difference in MADRS at Week 6 in the 20 mg group

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

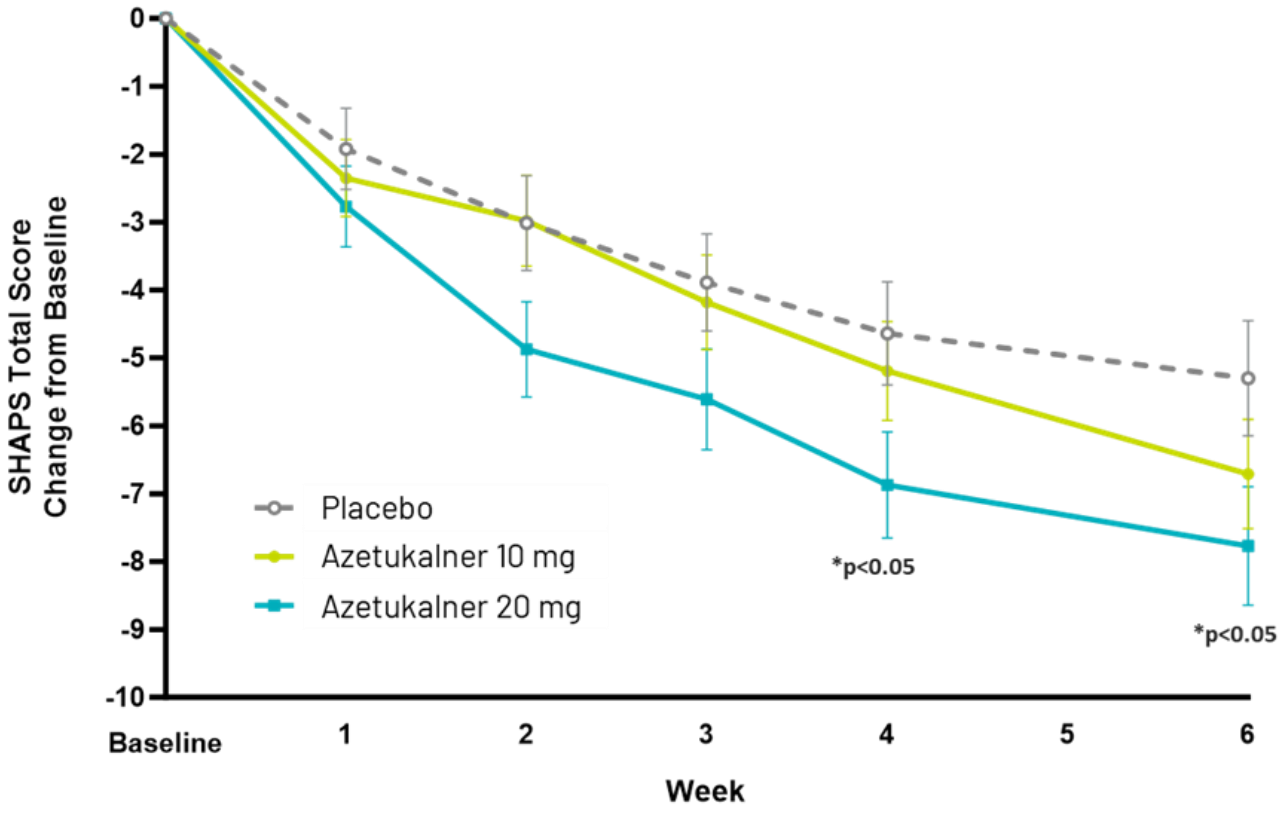
Pre-Specified Endpoint
Improvement in Depressive Symptoms:
Change in HAM-D17 Total Score at Week 6 (mITT)

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

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

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

Secondary Efficacy Endpoint:
Change in SHAPS Total Score at Week 6 (mITT)



	Placebo (N=54)	Azetukalner 20 mg (N=53)
SHAPS total score change from baseline at Week 6 (LSMean)	-5.30	-7.77
Difference vs. placebo		-2.46
p-value		**0.046**

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

SHAPS: Snaith-Hamilton Pleasure Scale; LSMean (SEM) shown

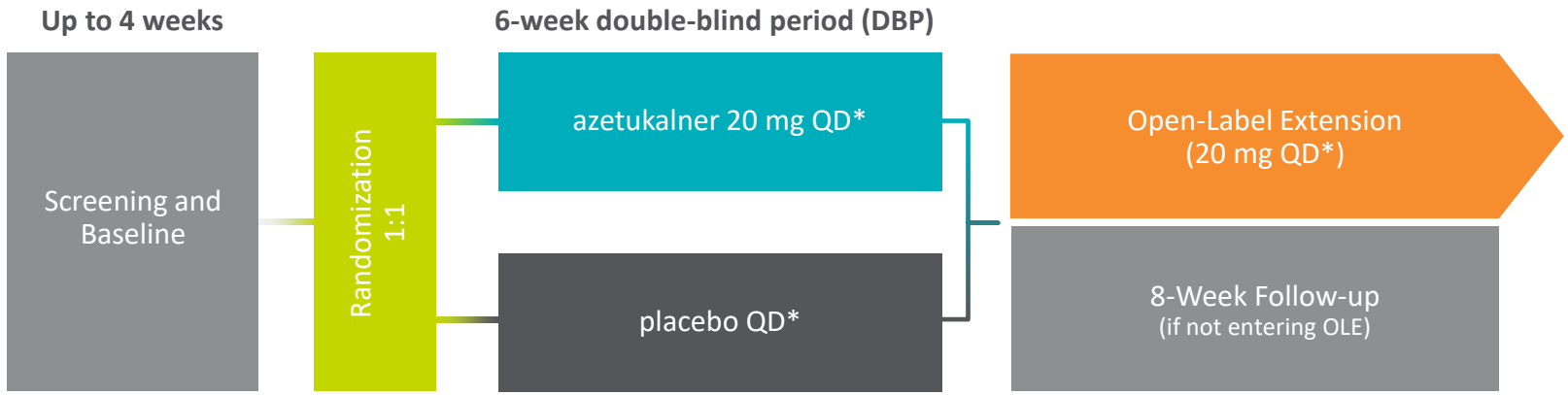
X-NOVA: Safety and Tolerability Data

- Azetukalner was generally well-tolerated with similar rates of overall adverse events reported across all treatment arms
  - 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%), as compared to 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 due to TEAEs were low with three patients in the azetukalner 20 mg group (5.4%), as compared to two patients in the placebo group (3.6%)
  - No SAEs were reported in the two azetukalner treatment groups, and there were two patients (3.6%) in the placebo group who experienced a treatment-emergent SAE
  - Azetukalner was not associated with notable weight gain; patients did not report notable sexual dysfunction

Phase 3 Clinical Studies in MDD

- Phase 3 MDD program consists of three multi-center, placebo-controlled clinical trials (N=~450 in each study)
- Plan to submit sNDA supported by efficacy data from two positive Phase 3 MDD trials

X-NOVA™ Phase 3 Studies



*Administered as once-daily capsule with food with no titration period. There is no placebo dose in the OLE.

- **Primary Objective:** change from baseline in HAM-D17 score at week 6
- **Key Secondary Objectives** include change from baseline in HAM-D17 score at week 1, change from baseline in SHAPS score at week 6, and change from baseline in CGI-S at week 6

X-NOVA2 has been initiated and is recruiting subjects

Azetukalner: Significant Potential Across Epilepsy and MDD

Robust Clinical Efficacy

- Highly compelling double-blind efficacy data in FOS patients, durable long-term seizure freedom data as demonstrated in the ongoing OLE
- Clinically meaningful activity in depression and significantly different reductions in anhedonia observed in MDD patients

Novel Mechanism

- Highly potent and selective Kv7.2/7.3 potassium channel opener with no activity on $GABA_A$

Rapid Onset of Effect

- Statistically significant efficacy demonstrated at Week 1 in patients with FOS, and significantly different efficacy seen at Week 1 in patients with MDD

Ease-of-Use Attributes

- Once-daily dosing and no required titration, enabling potential for rational polypharmacy

Well-Documented Safety Profile

- More than 600 patient years of data in FOS patients, with some patients dosed for more than 5 years
- Potentially differentiated profile in MDD patients, with no notable weight gain or sexual dysfunction observed

Sources: French, et al, AES 2021, poster 1.419; not approved for use; Butterfield, et al, ASCP 2024, poster W67; not approved for use; French J, Porter R, Perucca E, et al. Long-term safety and efficacy of azetukalner, a novel, potent Kv7 potassium channel opener in adults with focal epilepsy: Update from the ongoing 7-year open-label extension of X-TOLE. *American Epilepsy Society Annual Meeting,* December 6-10, 2024, Los Angeles, CA

Pipeline Programs

POTASSIUM & SODIUM CHANNEL SCIENCE

Xenon's Ongoing Pre-Clinical and Product Life Cycle Work

- Leveraging Xenon's deep ion channel expertise to develop promising drug candidates that target sodium and potassium channels
- Anticipate filing multiple INDs (or equivalent) across Kv7 and Nav1.7 programs in 2025
- Expect to nominate lead Nav1.1 candidate in 2025

Potassium Channel Program

- Strong conviction in broad applicability of Kv7 mechanism and strength of Xenon's discovery platform
- Next gen molecules to be explored in epilepsy and MDD
- Further potential pipeline expansion into other psychiatric indications beyond MDD, as well as pain and potentially other disorders

Sodium Channel Program

- Leveraging Xenon's extensive knowledge and prior work to advance Nav1.7 program in pain
  - Xenon scientists contributed to early work linking loss of function in SCN9A gene (Nav1.7) to pain, based on strong human genetic validation
- Nav1.1 channel work in epilepsy, based on genetic evidence of underlying pathophysiology of Dravet Syndrome

Potential Value-Creating Milestone Opportunities

Azetukalner Epilepsy Program

- Phase 3 clinical trials (X-TOLE2/X-TOLE3) in FOS underway; X-TOLE2 topline data expected in 2H:2025
- Phase 3 clinical trial (X-ACKT) in PGTCS underway to support registration in additional epilepsy indication
- NDA submission planned based on efficacy data from Phase 2b X-TOLE and first Phase 3 trial (X-TOLE2)

Azetukalner MDD Programs

- X-NOVA2, the first of three Phase 3 MDD studies, has been initiated and is recruiting subjects
- Mount Sinai investigator-sponsored Phase 2 POC in MDD underway, with enrollment complete and data anticipated in 1H:25
- Evaluating potential development in additional neuropsychiatric indications

Pre-clinical Programs

- Leveraging Xenon's extensive ion channel expertise to identify validated drug targets and develop new Kv7, Nav1.1, and Nav1.7 product candidates; anticipate filing multiple INDs, or equivalent, across Kv7 and Nav1.7 programs in 2025

Partnered Programs with Neurocrine Biosciences

- Nav1.2/1.6 inhibitor expected to enter clinical development in 2025 as potential treatment for epilepsy

For more information

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