X-NOVA Topline Results in Major Depressive Disorder

NOVEMBER 27, 2023

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, including, but not limited to, statements regarding the potential efficacy, safety profile, future development plans, addressable market, regulatory success and commercial potential of XEN1101 and our product candidates; the anticipated timing of the initiation of future clinical trials for XEN1101 and other proprietary products, the efficacy of our clinical trial designs; the timing and results of our planned interactions with regulators regarding XEN1101; our ability to successfully develop and obtain regulatory approval of XEN1101; our intent to explore future development of XEN1101 in MDD and potentially other indications; the timing and results of our interactions with regulators; anticipated enrollment in our clinical trials and the timing thereof; the progress and potential of our other ongoing development programs; and the timing of potential publication or presentation of future clinical data.

These statements are based on estimates and information available to us at the time of this presentation and are not guarantees of future performance. Actual results could differ materially from our current expectations as a result of many factors, including but not limited to: research and clinical development plans and timelines and results of operations, including impact on our clinical trial sites, collaborators, and contractors who act for or on our behalf, may be more severe and more prolonged than currently anticipated; clinical trials may not demonstrate safety and efficacy of any of our or our collaborators' product candidates; 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 XEN1101, 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 competition; the impact of expanded product development and clinical activities on operating expenses; impact of new or changing laws and regulations; adverse conditions in the general domestic and global economic markets; as well as the other risks identified in our filings with the Securities and Exchange Commission and the securities commissions in British Columbia, Alberta and Ontario. Except as required by law, we assume no obligation and do not intend to update these forward-looking statements or to conform these statements to actual results or to changes in our expectations.

Executive Summary: X-NOVA Study

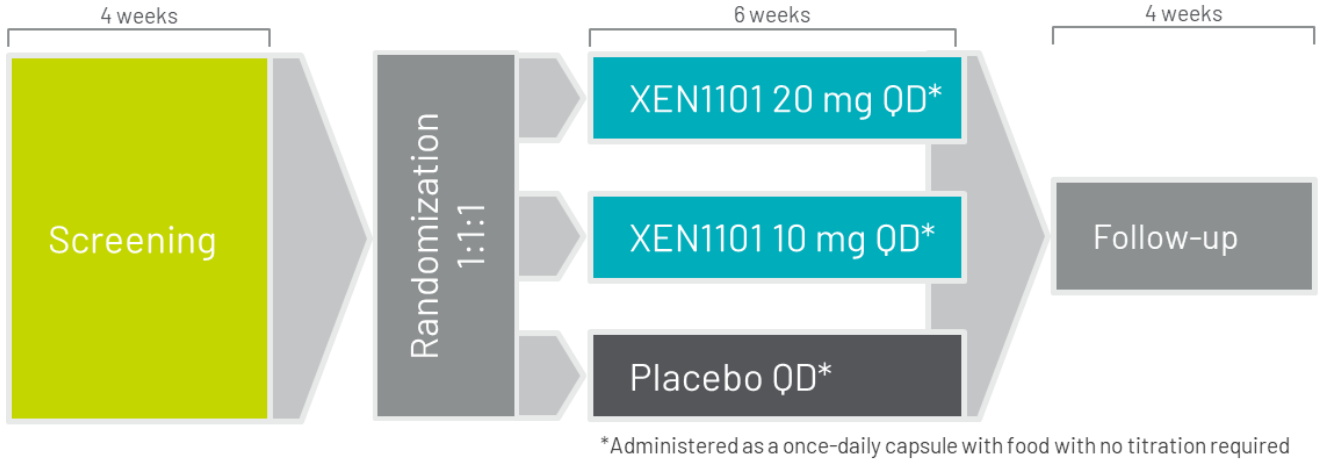
X-NOVA

Summary of Key Findings	• Clinically meaningful, dose-dependent drug activity in depression and anhedonia • XEN1101 was generally well tolerated with a low incidence of treatment-emergent adverse events, and no serious adverse events in either dose group
Efficacy	• A clear dose response and a clinically meaningful, but not statistically significant, 3.04 difference in MADRS at week 6 in the XEN1101 20 mg group vs placebo (p=0.135) • Statistical significance in MADRS at week 1 in the XEN1101 20 mg group vs placebo (p<0.05) demonstrating rapid onset • Statistical significance in SHAPS measuring anhedonia at week 6 in the XEN1101 20 mg group (p<0.05) • Statistical significance in HAM-D17 at week 6 in the XEN1101 20 mg group vs placebo (p<0.05)
Safety / Tolerability	• XEN1101 was generally well tolerated with similar rates of adverse events reported across all treatment arms • The most common treatment-emergent adverse events (TEAEs) across all XEN1101 dose groups were dizziness, somnolence, headache and disturbance in attention • Rates of discontinuation due to TEAEs were similar across all treatment arms • XEN1101 was not associated with notable weight gain; patients did not report notable sexual dysfunction
Overall Profile / Opportunity	• XEN1101 demonstrated clinically meaningful drug activity in depression and anhedonia, a rapid onset of action and a differentiated safety profile in patients with MDD, potentially offering a compelling clinical profile in MDD • X-NOVA data support that XEN1101 may have an impact on mood, and a potential attribute that could provide an important element of differentiation in epilepsy, given the significant co-morbidity of depression

Study Overview

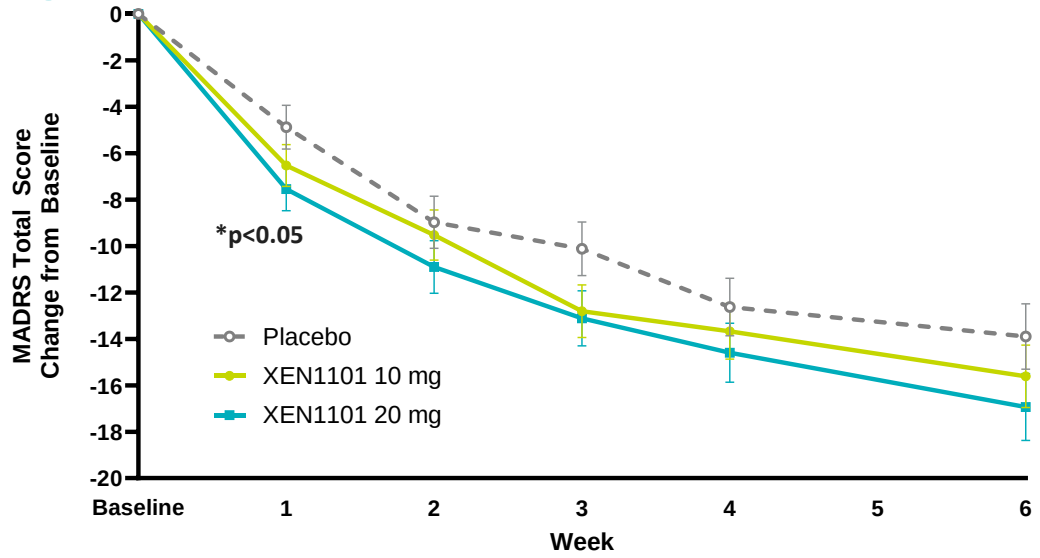
X-NOVA

A Proof-of-Concept, Randomized, Double-blind, Placebo-Controlled, Multicenter Study to Evaluate the Safety, Tolerability, and Efficacy of XEN1101 in Major Depressive Disorder

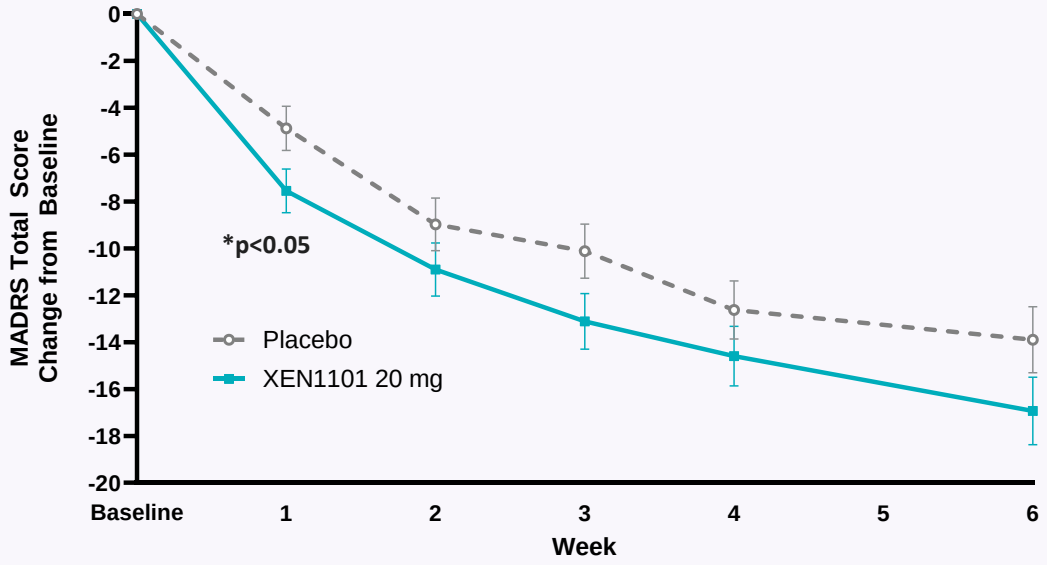


- **Primary Endpoint**
  - Montgomery-Åsberg Depression Rating Scale (MADRS) score change through Week 6
- **Key Secondary Endpoints**
  - Snaith-Hamilton Pleasure Scale (SHAPS) score change through Week 6

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



	Placebo (N=54)	XEN1101 20 mg (N=53)
ΔMADRS from BL at **Wk 6** (LSMean)	-13.90	**-16.94**
Diff. vs Pbo		**-3.04**
p-value		0.135



	Placebo (N=54)	XEN1101 20 mg (N=53)
ΔMADRS from BL at **Wk 1** (LSMean)	-4.88	**-7.54**
Diff. vs Pbo		**-2.66**
p-value		**0.047***

MADRS = Montgomery Åsberg Depression Rating Scale; LSMean (SEM) shown
mITT Population: All randomized subjects who receive at least 1 dose of study treatment and at least 1 postrandomization MADRS

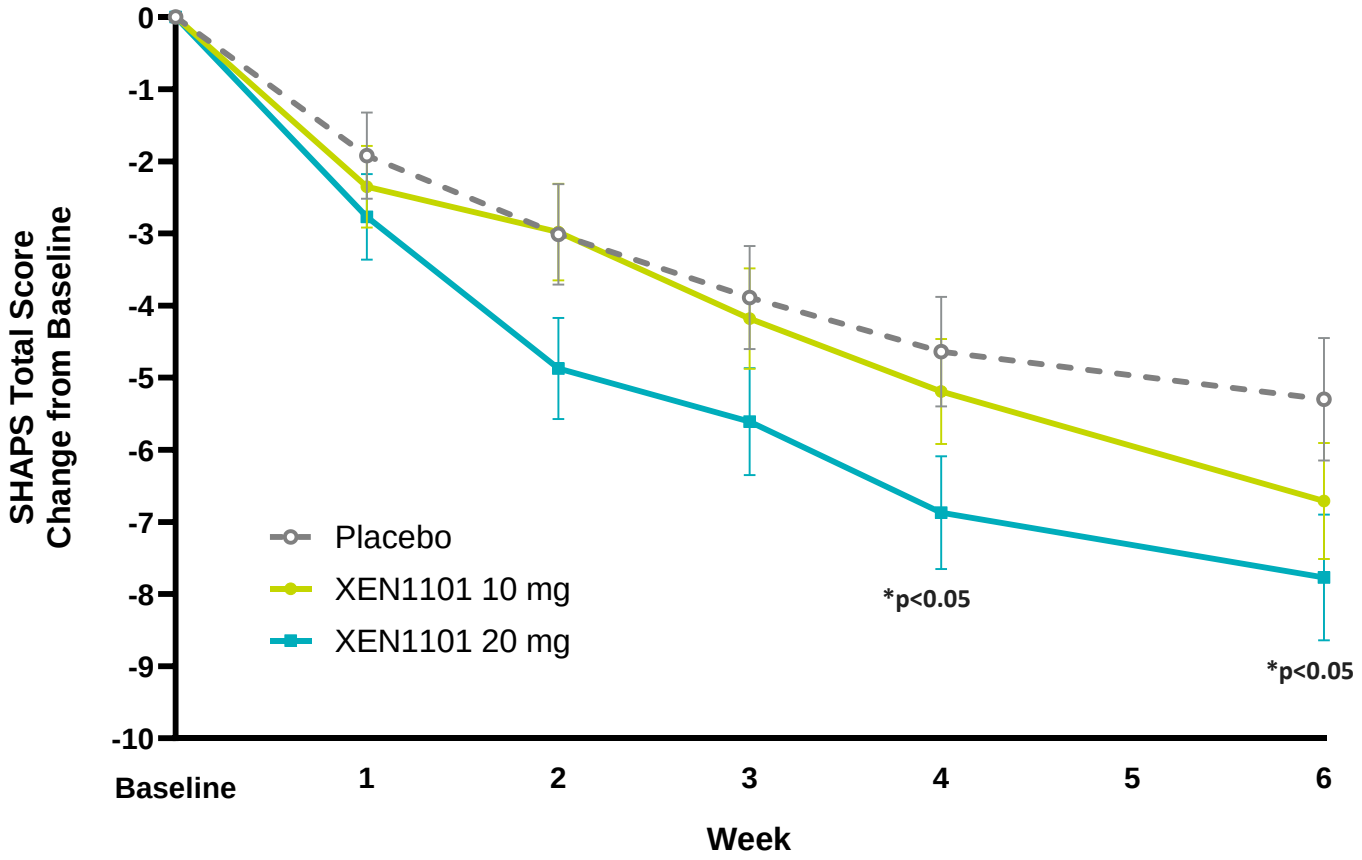
Improvement in Depressive Symptoms:
Change in HAM-D17 Total Score (mITT)

	Placebo (N=54)	XEN1101 20 mg (N=53)
HAM-D17 total score change from baseline at Week 6 (LSMean)	-10.18	-13.26
Difference vs. placebo		-3.08
p-value		**0.042***

HAM-D17: Hamilton Depression Rating Scale was assessed at screening, baseline, and Week 6

Improvement in depressive symptoms assessed by HAM-D17 total scores was statistically significant at Week 6

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



Change from baseline in SHAPS scores at week 6

	Placebo (N=54)	XEN1101 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***

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

Anhedonia symptom improvement: Statistically significant change in SHAPS at Week 6 with XEN1101 20 mg

Most Common TEAEs ≥5%
(Safety Population)

System Organ Class/ Preferred Term	Placebo (N=55) n (%)	XEN1101 10 mg (N=56) n (%)	XEN1101 20 mg (N=56) n (%)	XEN1101 Any Dose (N=112) n (%)
Overall	**33 (60.0)**	**29 (51.8)**	**37 (66.1)**	**66 (58.9)**
Nervous System Disorders	**15 (27.3)**	**14 (25.0)**	**24 (42.9)**	**38 (33.9)**
Dizziness	4 (7.3)	4 (7.1)	10 (17.9)	14 (12.5)
Somnolence	1 (1.8)	6 (10.7)	6 (10.7)	12 (10.7)
Headache	7 (12.7)	5 (8.9)	5 (8.9)	10 (8.9)
Disturbance in attention	0 (0.0)	0 (0.0)	5 (8.9)	5 (4.5)
Paraesthesia	1 (1.8)	0 (0.0)	3 (5.4)	3 (2.7)
Psychiatric Disorders	**8 (14.5)**	**7 (12.5)**	**7 (12.5)**	**14 (12.5)**
Depression	2 (3.6)	3 (5.4)	2 (3.6)	5 (4.5)
Insomnia	3 (5.5)	1 (1.8)	1 (1.8)	2 (1.8)
Gastrointestinal Disorders	**6 (10.9)**	**5 (8.9)**	**7 (12.5)**	**12 (10.7)**
Nausea	3 (5.5)	2 (3.6)	2 (3.6)	4 (3.6)
Eye Disorders	**2 (3.6)**	**1 (1.8)**	**6 (10.7)**	**7 (6.3)**
Vision blurred	1 (1.8)	0 (0.0)	3 (5.4)	3 (2.7)

TEAE: Treatment Emergent Adverse Event, i.e. AEs started or worsened during treatment and follow-up periods
Safety Population: All subjects who received at least one dose of study treatment

XEN1101 was safe and generally well tolerated with similar rates of overall adverse events reported across all treatment arms

Summary of TEAEs Leading to Drug Discontinuation (Safety Population)

System Organ Class/ Preferred Term	Placebo (N=55) n (%)	XEN1101 10 mg (N=56) n (%)	XEN1101 20 mg (N=56) n (%)	XEN1101 Any Dose (N=112) n (%)
Overall	**2 (3.6)**	**5 (8.9)**	**3 (5.4)**	**8 (7.1)**
Nervous System Disorders	**0 (0.0)**	**1 (1.8)**	**3 (5.4)**	**4 (3.6)**
Disturbance in attention	0 (0.0)	0 (0.0)	1 (1.8)	1 (0.9)
Dizziness	0 (0.0)	0 (0.0)	1 (1.8)	1 (0.9)
Headache	0 (0.0)	1 (1.8)	0 (0.0)	1 (0.9)
Syncope	0 (0.0)	0 (0.0)	1 (1.8)	1 (0.9)
Psychiatric Disorders	**1 (1.8)**	**2 (3.6)**	**0 (0.0)**	**2 (1.8)**
Depression	0 (0.0)	1 (1.8)	0 (0.0)	1 (0.9)
Dissociation	0 (0.0)	1 (1.8)	0 (0.0)	1 (0.9)
Homicidal ideation	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Eye Disorders	**0 (0.0)**	**1 (1.8)**	**0 (0.0)**	**1 (0.9)**
Ocular hyperaemia	0 (0.0)	1 (1.8)	0 (0.0)	1 (0.9)
Gastrointestinal Disorders	**0 (0.0)**	**1 (1.8)**	**0 (0.0)**	**1 (0.9)**
Nausea	0 (0.0)	1 (1.8)	0 (0.0)	1 (0.9)
Vomiting	0 (0.0)	1 (1.8)	0 (0.0)	1 (0.9)
Investigations	**1 (1.8)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Blood chloride decreased	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Blood potassium decreased	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Blood sodium decreased	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)

TEAE: Treatment Emergent Adverse Event, i.e. AEs started or worsened during treatment and follow-up periods
Safety Population: All subjects who received at least one dose of study treatment

Rates of discontinuation were similar across all treatment arms

Summary of Treatment-Emergent SAEs
(Safety Population)

System Organ Class/ Preferred Term	Placebo (N=55) n (%)	XEN1101 10 mg (N=56) n (%)	XEN1101 20 mg (N=56) n (%)	XEN1101 Any Dose (N=112) n (%)
Overall	**2 (3.6)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Nervous System Disorders	**1 (1.8)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Idiopathic intracranial hypertension	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	**1 (1.8)**	**0 (0.0)**	**0 (0.0)**	**0 (0.0)**
Homicidal ideation	1 (1.8)	0 (0.0)	0 (0.0)	0 (0.0)

SAE: Serious Adverse Event
Safety Population: All subjects who received at least one dose of study treatment

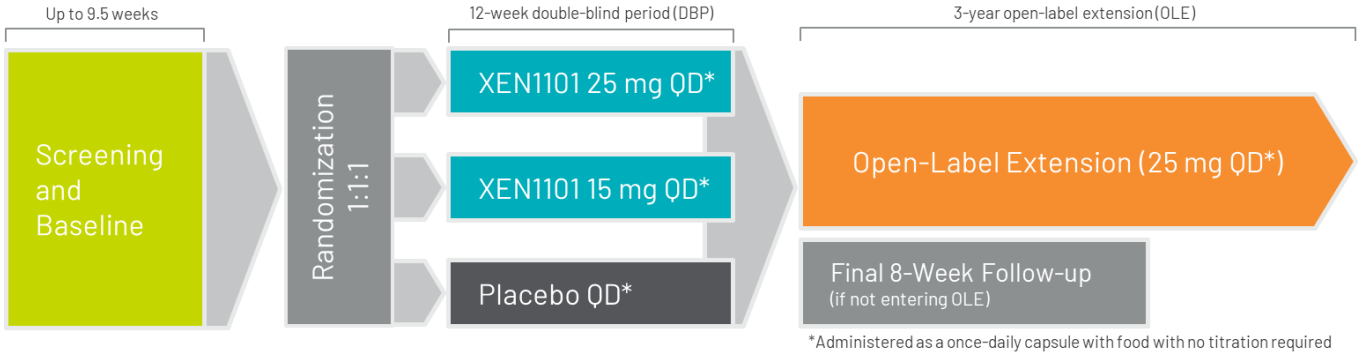
Both SAEs occurred in patients treated with placebo

X-NOVA Phase 2 Topline Data Summary

- XEN1101 demonstrated clinically meaningful drug activity
  - Failed to meet statistical significance on the primary endpoint; ΔMADRS vs placebo of -3.04 at week 6
  - Significant reduction in anhedonia at week 6 (SHAPS); $p<0.05$
  - Significant reduction in depression at week 6 (HAM-D17); $p<0.05$
  - Significant reduction in MADRS at week 1; $p<0.05$
- XEN1101 was generally well tolerated with similar rates of overall TEAEs across all treatment arms
  - No SAEs on XEN1101
  - The most commonly reported TEAEs were nervous system disorders: dizziness, somnolence, headache, disturbance in attention
  - Similar rates of discontinuation across all treatment arms
  - XEN1101 was not associated with notable weight gain; patients did not report notable sexual dysfunction

XEN1101 Phase 3 Epilepsy Program Underway

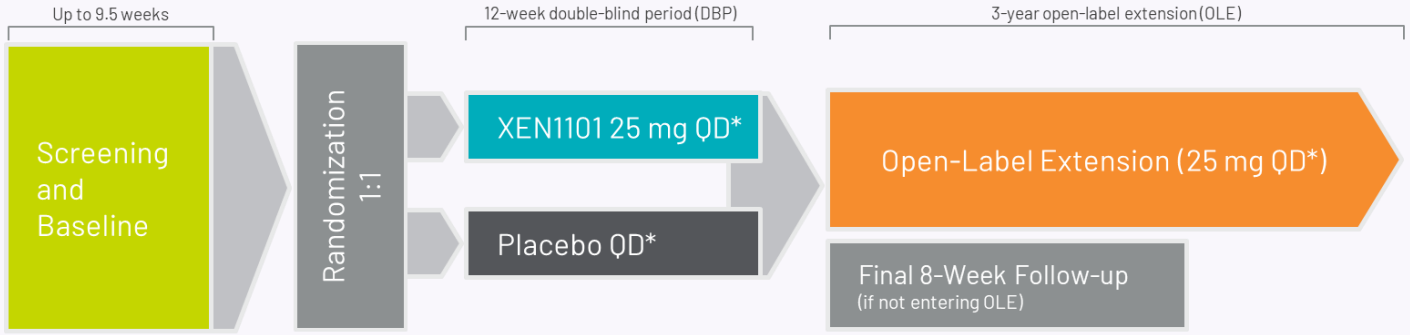
X-TOLE 2 3



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

- **X-TOLE2** and **X-TOLE3** are assessing effect of XEN1101 vs placebo on reducing focal onset seizure (**FOS**) frequency
- Conducting two identical multi-center, placebo-controlled Phase 3 trials (N=~360 in each study)
- Patient enrollment in X-TOLE2 anticipated to be complete in second half of 2024

X-ACKT

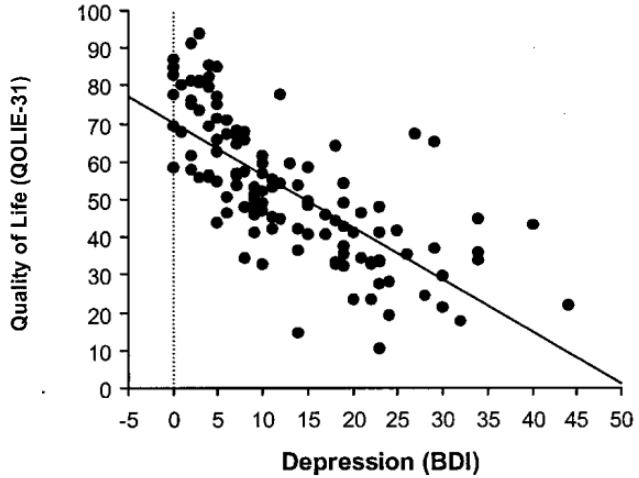


*Administered as a once-daily capsule with food with no titration required

- **X-ACKT** is assessing effect of XEN1101 vs placebo on reducing primary generalized tonic-clonic seizure (**PGTCS**) frequency
- Conducting a single, multi-center, placebo-controlled Phase 3 trial to support registration (N=~160)

Depression is a Common Comorbidity in Persons with Epilepsy

- The prevalence of depression in people with epilepsy reported in the literature ~15-50%
- Greater severity of depression associated with higher seizure frequency
- Depression is an independent and strong predictor of reduced QOL
- Lifetime history of depression may predict resistance to treatment
- Depression is a significant cause of non-adherence to anti-seizure medications (ASMs)



Source of figure Boylan et al. 2004.

Sources: Elger et al. Diagnosing and treating depression in epilepsy. *Seizure*. 2017. D'Alessio et al. Reduced expression of the glucocorticoid receptor in the hippocampus of patients with drug-resistant temporal lobe epilepsy and comorbid depression. *Epilepsia*. 2020. Kanner et al. Depression and epilepsy: epidemiologic and neurobiologic perspectives that may explain their high comorbid occurrence. *Epilepsy Behav*. 2014. Boylan et al. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. *Neurology*. 2004.

A Survey of the Burden of Illness in Focal Onset Seizures

- Anxiety and depression are common comorbidities in epilepsy that further exacerbate the burden of epilepsy and may require additional care or support[1]
- Of the patients reporting mood symptoms as a non-seizure symptom, 74.0% experienced mood symptoms at least once a week and 53.0% considered their mood symptoms highly severe (Figure 1)
- 40.0% of patients in the survey indicated a physician-reported diagnosis of depression yet 63.6% exhibited moderate-to-severe depression symptoms based on the PHQ-9 scores (Figure 2)

PHQ-9 assesses and monitors depression symptom severity; scores range from 0 to 27 and higher scores indicate more severe depression or depressive symptoms

Figure 1: Self-Reported Experience with Mood Symptoms in Patients Reporting FOS

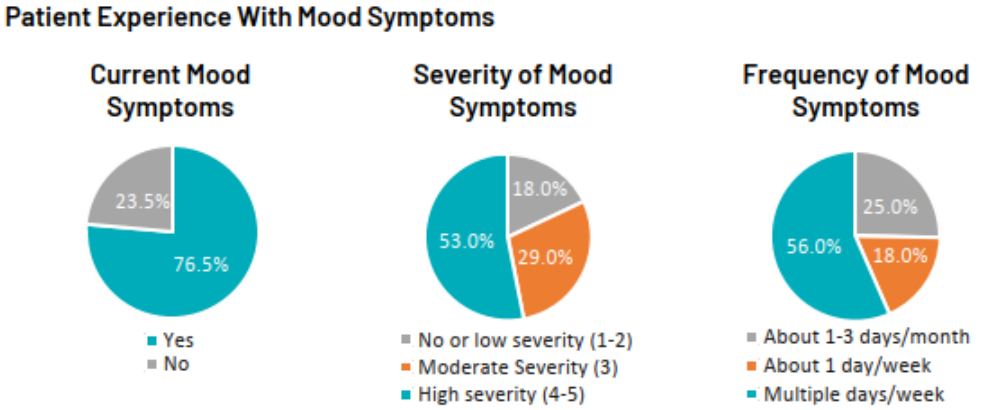
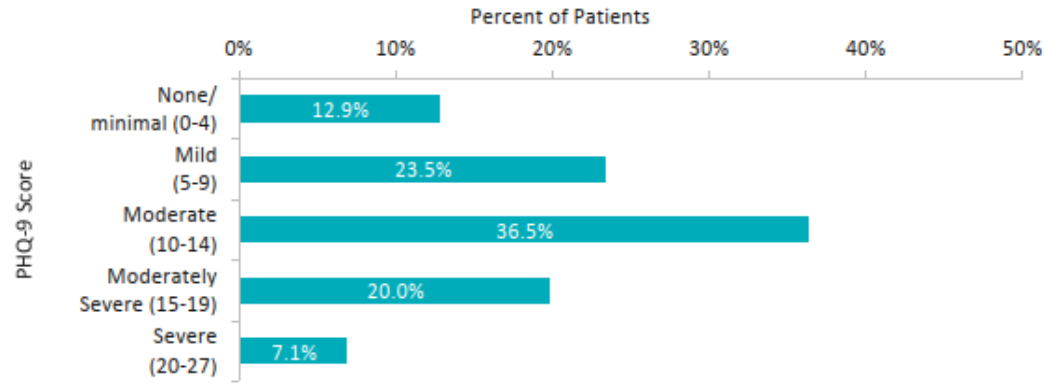


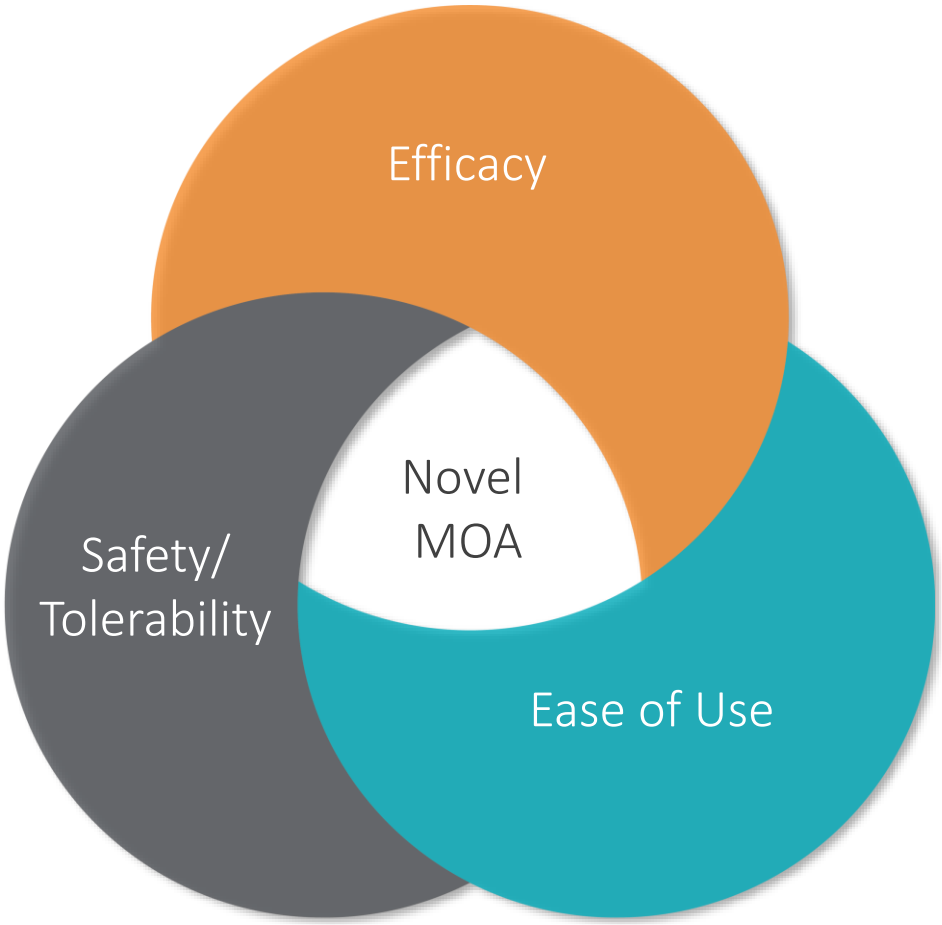
Figure 2: PHQ-9 Score Distribution for Patients Reporting FOS



This survey supports the ongoing body of information that depression and anxiety disorders are frequent and may be severe problems for patients with epilepsy

Sources: (1) Scott AJ, et al. Epilepsia. 2017;58(6):973-982; Xenon sponsored patient survey

Value Proposition of XEN1101 in Epilepsy



- Unique and novel Kv7 mechanism can be leveraged in rational polypharmacy

- Compelling efficacy data in difficult to treat adult FOS patient population
- Rapid efficacy as demonstrated by statistical significance at Week 1
- Durable efficacy observed in open label extension

- Well-tolerated with AE profile in line with other ASMs
- Evening dose with food = C_{max} during sleep
- No drug allergic reactions observed
- Long-term safety data with more than 500 hundred patient years

- One pill, once-daily with food
- No titration required
- Low DDI risk

Thank you for joining us today!

FOR MORE INFO, PLEASE EMAIL: INVESTORS@XENON-PHARMA.COM