Interim Phase 1/2 Clinical Data of LX1001 for the Treatment of APOE4-associated Alzheimer's Disease

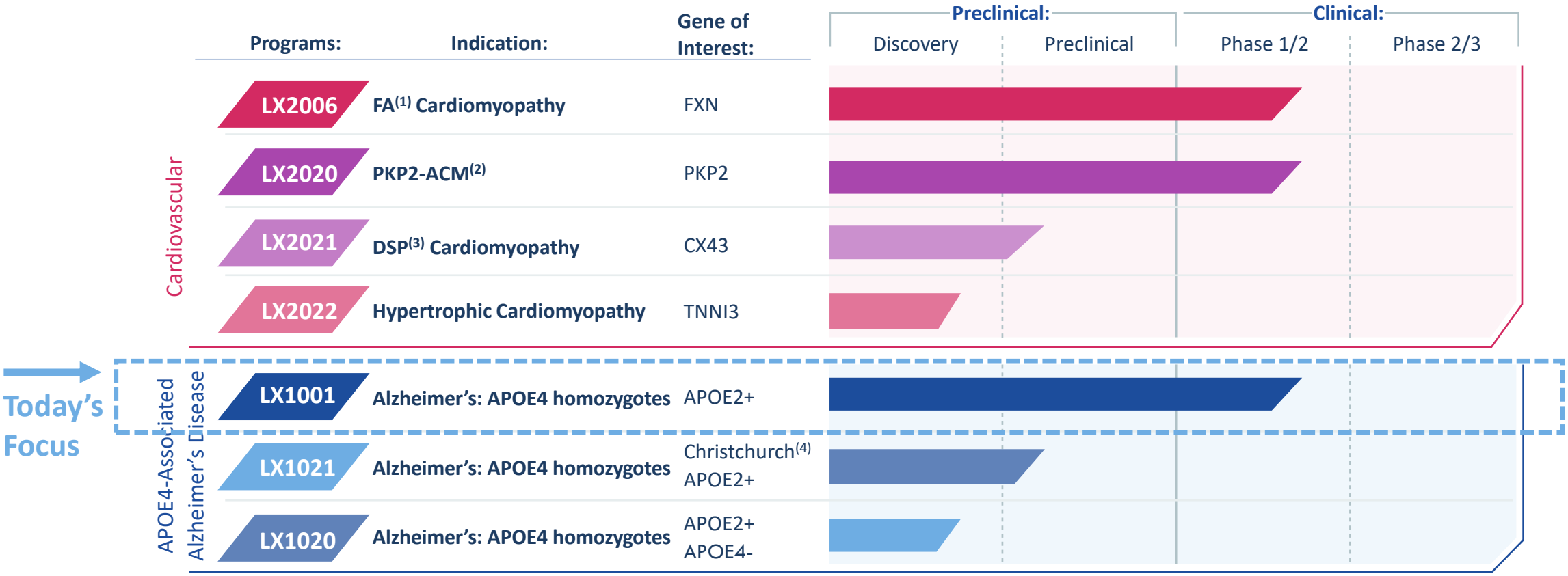
October 30, 2024

Forward-Looking Statements

This presentation contains “forward-looking statements” within the meaning of the federal securities laws, including, but not limited to, statements regarding Lexeo’s expectations and plans regarding its current product candidates and programs, including statements regarding the anticipated benefits of LX1001 for the treatment of APOE4-associated Alzheimer’s disease, the timing for receipt and announcement of data from its clinical trials and the likelihood of receiving regulatory approvals. Words such as “may,” “might,” “will,” “objective,” “intend,” “should,” “could,” “can,” “would,” “expect,” “believe,” “design,” “estimate,” “predict,” “potential,” “develop,” “plan” or the negative of these terms, and similar expressions, or statements regarding intent, belief, or current expectations, are forward-looking statements. While Lexeo believes these forward-looking statements are reasonable, undue reliance should not be placed on any such forward-looking statements. These forward-looking statements are based upon current information available to the company as well as certain estimates and assumptions and are subject to various risks and uncertainties (including, without limitation, those set forth in Lexeo’s filings with the U.S. Securities and Exchange Commission (SEC)), many of which are beyond the company’s control and subject to change. Actual results could be materially different from those indicated by such forward looking statements as a result of many factors, including but not limited to: risks and uncertainties related to expectations regarding the initiation, progress, and expected results of Lexeo’s preclinical studies, clinical trials and research and development programs; the unpredictable relationship between preclinical study results and clinical study results; delays in submission of regulatory filings or failure to receive regulatory approval; liquidity and capital resources; and other risks and uncertainties identified in Lexeo’s Annual Report on Form 10-K for the year ended December 31, 2023, filed with the SEC on March 11, 2024, Quarterly Report on Form 10-Q for the quarter ended June 30, 2024, filed with the SEC on August 12, 2024, and subsequent future filings Lexeo may make with the SEC. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Lexeo claims the protection of the Safe Harbor contained in the Private Securities Litigation Reform Act of 1995 for forward-looking statements. Lexeo expressly disclaims any obligation to update or alter any statements whether as a result of new information, future events or otherwise, except as required by law.

LEXEO therapeutics

Advancing Genetic Medicines in Larger-Rare and Prevalent Patient Populations



Wholly-owned pipeline with franchises in two core therapeutic areas of high unmet need

(1) Friedreich's ataxia. (2) Plakophilin 2 Arrhythmogenic Cardiomyopathy.
(3) Desmoplakin. (4) Christchurch Modified APOE2 gene.

LEXEO therapeutics

APOE 4/4 Homozygotes: A Distinct, Genetically Defined Alzheimer's Disease Population

Individuals with two copies of the APOE4 allele **carry a ~15x increased risk of developing Alzheimer's Disease**[1]

APOE4/4 homozygotes exhibit **earlier symptom onset**, a **distinct sequence of biomarker changes,** and a **faster rate of cognitive decline**[3,4]

Nearly all APOE4 homozygotes **will develop Alzheimer's symptoms within 49-81 years of age**[3]

No suitable treatment options for E4/E4s; anti-amyloid therapies carry increased ARIA risk & reduced efficacy for this population

~2% of population
are APOE4/4 homozygotes[2]

~15% of Alzheimer's cases
are APOE4/4 homozygotes

~900K

APOE4/4 AD patients in US[2]
population with high incidence rate, expected to increase with aging population

(1) Belloy, M. E., Napolioni, V. & Greicius, M. D. A quarter century of APOE and Alzheimer's disease: progress to date and the path forward. Neuron. 2019; 101, 820–838
(2) Alzheimer's Association: Alzheimer's Disease Facts & Figures, 2024 | Yamazaki Y, *et al*. Nature Neurology Review, 2019. Vol 15, p501
(3) Fortea, J. *et al*. APOE4 homozygozity represents a distinct genetic form of Alzheimer's disease. *Nature Med*icine. 2024; **30**, 1284–1291. doi: 10.1038/s41591-024-02931-w.
(4) Martins, C.A.R. *et al*. APOE alleles predict the rate of cognitive decline in Alzheimer disease: a nonlinear model. Neurology. 2005; 65(12):1888-93. doi: 10.1212/01.wnl.0000188871.74093.12. PMID: 16380608.

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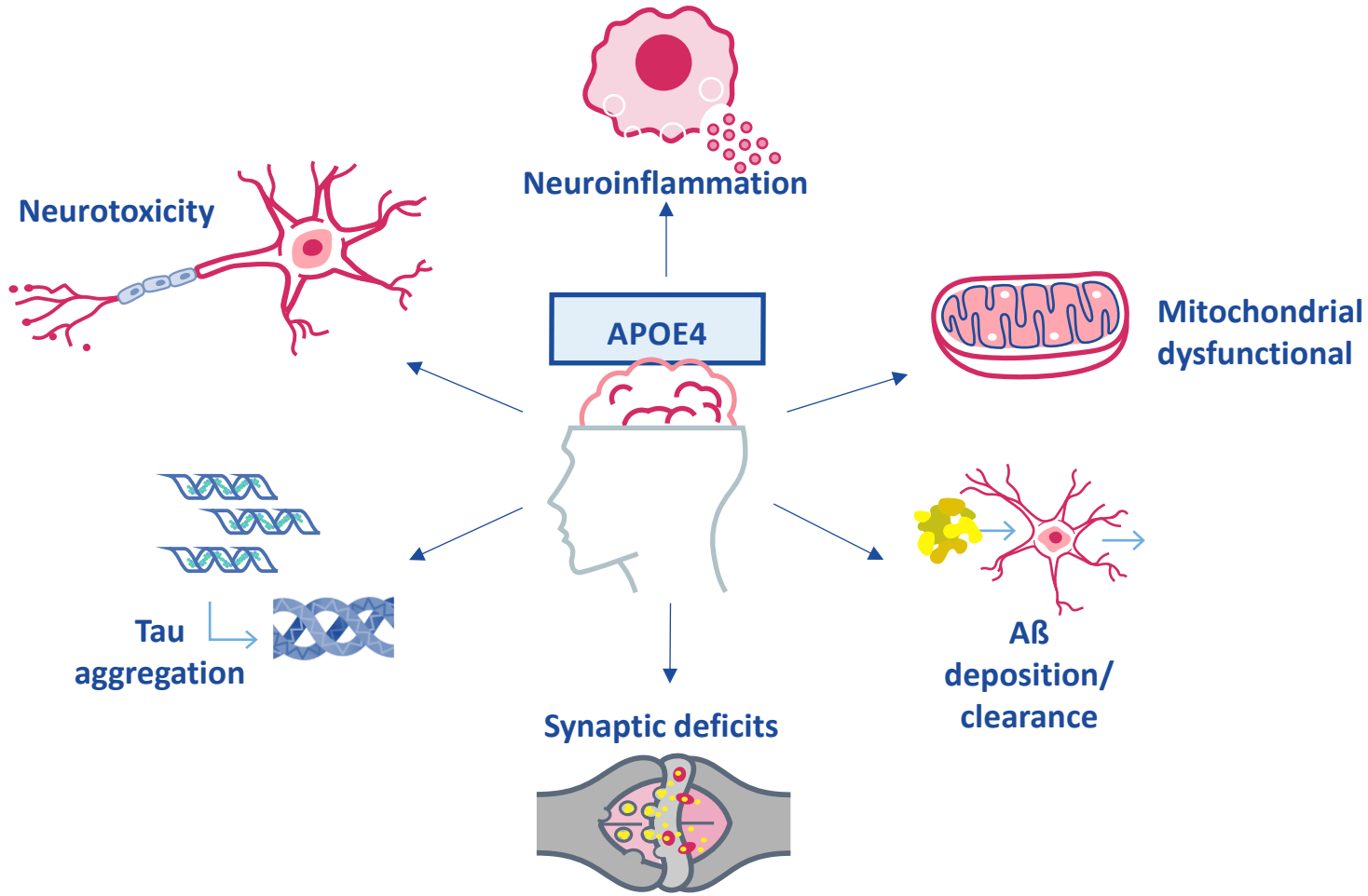
APOE4 Is A Known Driver of Alzheimer's Risk, Affecting Multiple Pathways

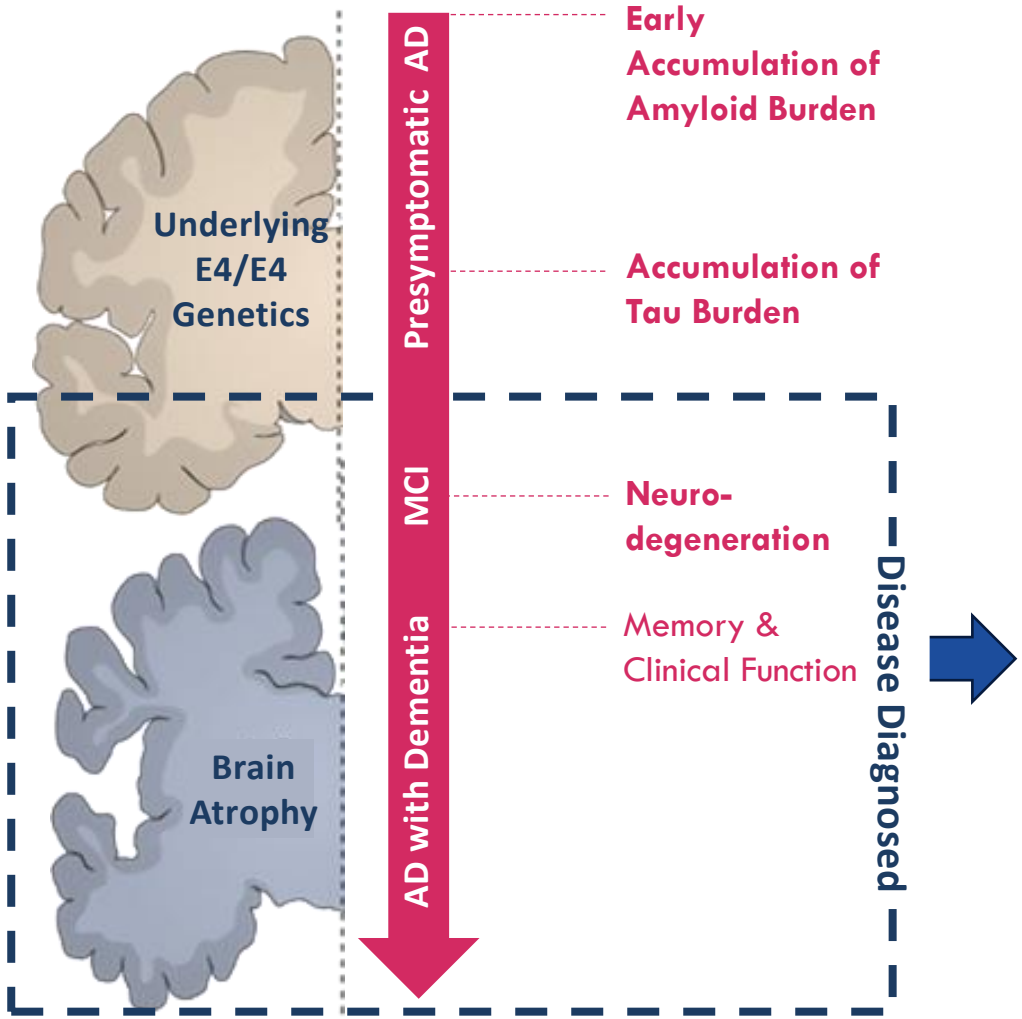
APOE4 drives Alzheimer's disease pathogenesis

- Associated with toxicity to neurons
- Accelerates amyloid deposition/slows clearance
- Accelerates propagation of tau tangles and tau-mediated neurodegeneration
- Linked to synaptic defects and mitochondrial dysfunction
- Activates microglia, adding to CNS inflammation
- Contributes to breakdown of BBB
- Associated with dysregulation and reduction of cerebral blood flow



Adapted from Yu J, et al. Annual Reviews of Neuroscience, 2014.

APOE2 is Protective Across Multiple Pathways; Increasing the Ratio of APOE2/4 Can Dilute APOE4 Toxicity and Express APOE2 Protectivity



APOE-Targeting Interventional Treatment

- **APOE2 can dilute APOE4:**
  - ✓ The dilutive effect in APOE2/4 vs. APOE4/4 AD genotypes demonstrates a strong case for therapeutic promise; APOE2/4 heterozygotes have lower risk of onset and slower disease progression[1]
  - ✓ Increasing evidence that APOE2 suppresses Aß toxicity and tau pathology later in disease course [2,3]
- **Introduction of APOE2 following AD diagnosis will address 'downstream' Tau pathology**[4]
  - ✓ Reduce Tau-mediated injury & degeneration for the most clinically meaningful impact on function & memory[5]

(1) Martins, C.A.R. *et al.* APOE alleles predict the rate of cognitive decline in Alzheimer disease: a nonlinear model. Neurology. 2005; 65(12):1888-93. doi: 10.1212/01.wnl.0000188871.74093.12. PMID: 16380608.
(2) Raulin, AC. *et al.* ApoE in Alzheimer's disease: pathophysiology and therapeutic strategies. *Mol Neurodegeneration* 17, 72 (2022). https://doi.org/10.1186/s13024-022-00574-4
(3) Shi, Y. *et al.* ApoE4 markedly exacerbates tau-mediated neurodegeneration in a mouse model of tauopathy. Nature. 2017;549(7673):523-527. doi: 10.1038/nature24016.
(4) Clifford, J.R. *et al.* Hypothetical Model of Dynamic Biomarkers of the Alzheimer's pathological cascade. The Lancet Neurology, 2010; Volume 9 Issue 1, 119-128.
(5) Rawat, P. et al. Phosphorylated Tau in Alzheimer's Disease and Other Tauopathies. *Int J Mol Sci.* 2022;23(21):12841. doi: 10.3390/ijms232112841. PMID: 36361631; PMCID: PMC9654278.

LEXEO therapeutics

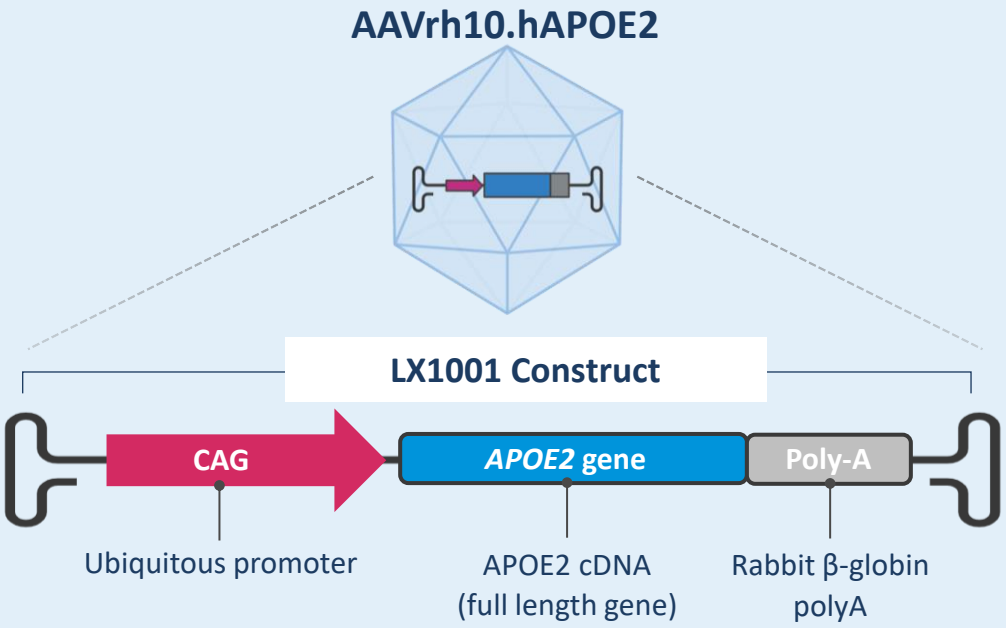
Unique Approach to Targeting Underlying Genetics of APOE4/E4 Alzheimer's Disease

LX1001

Phase 1/2

Mechanism of Action:

Gene therapy delivering protective APOE2 transgene to the CNS of APOE4 homozygotes



- ✓ **First & only clinical-stage gene therapy candidate** targeting genetics of APOE4/4 AD
- ✓ **Differentiated single-dose treatment**
- ✓ **Clinically validated AAVrh.10 capsid,** utilized in multiple human studies and large animal proof-of-concept studies

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LX1001 Phase 1/2 Trial in APOE4 Homozygotes

Study Summary

Key Features:

- 52-week, dose-ranging, open-label trial with 5-yr long-term follow-up
- **Vector:** AAVrh10
- **Route of Administration:** C1-C2 (between cervical vertebrae 1 and 2) or intracisternal injection
- **Immune Suppression:** corticosteroids prior to treatment & tapering post dosing

Key Inclusion Criteria:

- ≥50 yr APOE4 homozygotes
- Mild cognitive impairment (MCI) to moderate dementia with biomarkers (amyloid PET and CSF) consistent with Alzheimer's disease

Trial Design:

52-Week Follow-up

Cohort 1	Cohort 2	Cohort 3	Cohort 4
n=5	n=4	n=3	n=3
$1.4x10^{10}$ vg/ml CSF $5.7x10^{12}$ Total VGs	$4.4x10^{10}$ vg/ml CSF $1.8x10^{13}$ Total VGs	$1.4x10^{11}$ vg/ml CSF $5.7x10^{13}$ Total VGs	$1.4x10^{14}$ Total VGs

Vector genomes measured using ddPCR.
Assumes average CSF in patient of 408.7 ml.

Endpoints

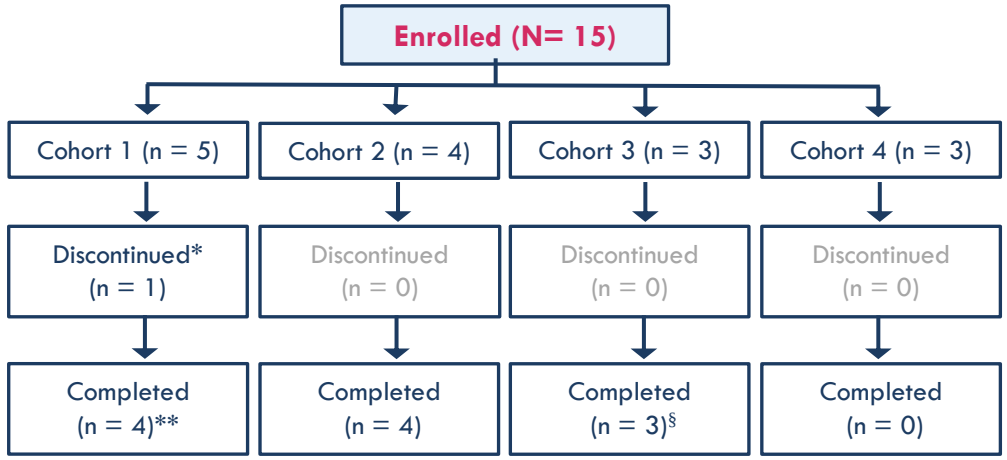
Primary Endpoint: Safety

Secondary Endpoint: APOE2 CSF protein expression

Other Secondary Endpoints:

- CSF biomarkers: Aß42/Aß40 ratio, T Tau and P Tau
- Amyloid and tau PET scans
- Cognitive testing

Study Status (as of July 26th data cut)



12-mo. data available for Cohorts 1-3; 6-mo. data for Cohort 4

*Withdrawal by Participant (no 6- and 12-month follow-up)
**One completed by remote visit; 12mo visit without CSF/imaging
§One completed M12 visit but lumbar puncture and PET scans not completed

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At Baseline, Cohorts 1 and 3 Include Patients with More Advanced Disease

Baseline Characteristics		Cohort 1 (n=5*)	Cohort 2 (n=4)	Cohort 3 (n=3)	Cohort 4 (n=3)	Total (n=15)
Demographics						
	Age, years, mean (SD)	63.8 (5.5)	64.3 (2.2)	63.7 (12.2)	70.7 (3.5)	**65.3 (6.4)**
	Sex – Female, n (%)	5 (100)	4 (100)	2 (66.7)	1 (33.3)	**12 (80)**
	Race – White, n (%)	5 (100)	4 (100)	3 (100)	3 (100)	**15 (100)**
	Ethnicity – Hispanic or Latino, n (%)	0	1 (25)	0	0	**1 (6.7)**
AD Diagnosis by Physician Assessment						
	MCI, n (%)	1 (20)	4 (100)	1 (33.3)	1 (33.3)	**7 (46.7)**
	Mild dementia, n (%)	0	0	0	2 (66.7)	**2 (13.3)**
	Moderate dementia, n (%)	4 (80)	0	2 (66.7)	0	**6 (40)**
Cognitive Scales						
MMSE	Mean (SD) Median (Min-Max)	14.8 (8.9) 13.0 (4-27)	27.0 (2.7) 28.0 (23-29)	15.3 (2.9) 17.0 (12-17)	25.3 (3.2) 24.0 (23-29)	**20.3 (7.8)** **23.0 (4-29)**
	MMSE Groups, n (%)					
	<20	**3 (60)**	0	**3 (100)**	0	**6 (40)**
	≥20 to ≤26	1 (20)	1 (25)	0	2 (66.7)	**4 (26.7)**
	≥27	1 (20)	3 (75)	0	1 (33.3)	**5 (33.0)**
CDR-SB	Mean Score (SD) Median Score (Min-Max)	8.10 (4.3) 10.0 (2.5-12.0)	2.00 (1.4) 2.0 (1.0-3.0)	5.17 (2.5) 4.0 (3.5-8)	2.50 (1.3) 3.00 (1.0-3.5)	**5.20 (3.8)** **3.50 (1.0-12.0)**
ADAS-Cog 13	Mean Score (SD) Median Score (Min-Max)	36.4 (16.1) 46.0 (16.0-50.0)	15.2 (14.7) 9.5 (5.0-37)	33.7 (5.6) 34.7 (27.7-38.7)	24.8 (12.2) 31.7 (10.7-32.0)	**27.9 (15.0)** **31.7 (5.0-50.0)**
PET Imaging						
	Amyloid PET SUVR, mean (SD) Centiloids, mean (SD)	1.5 (NA) 175.5 (120.9)	1.34 (0.39) 59.3 (55.4)	1.69 (0.19) 126.0 (37.6)	1.66 (0.12) 120.3 (21.1)	**1.54 (0.29)** **110.58 (65.7)**
	Tau PET SUVR, mean (SD)	NA	NA	2.09 (0.18)	1.62 (0.36)	**1.85 (0.36)**

MMSE 30-point scale
Lower score=
Greater impairment

CDR-SB 0-18 scale
ADAS-Cog 13 0-85 scale
Higher score=
Greater impairment

*Post-treatment data unavailable for two patients with moderate dementia in Cohort 1

LX1001 Was Well Tolerated Across All Four Dose Cohorts

Safety Findings

- Treatment with LX1001 was well-tolerated across all 4 dose cohorts
- No reports of ARIA[(1)]
- Transient CSF pleocytosis (>5cells/µL), predominantly lymphocytic, was observed in 12 participants, with no significant adverse events associated
- Four SAE's:
  - Three unrelated to treatment: diverticulitis, pneumothorax, skin ulcer
  - One event possibly related: mild-moderate sensorineural hearing loss
- Cognitive measures indicated no safety signal with no clear pattern of change observed in this study. Significant change not expected given sample size and measurement variability.
- Average change from baseline across all patients with 12-months of follow up:
  - MMSE -1.2 (n=9)
  - ADAS-Cog13 7.1 (n=8)
  - CDR-SB 1.8 (n=6)

(1) Amyloid-related imaging abnormalities (ARIA) refer to MRI findings observed in patients receiving anti-amyloid therapies for Alzheimer's disease. ARIA is most commonly observed as brain swelling, and/or microhemorrhages, and has a higher incidence in patients who are APOE4 allele carriers.

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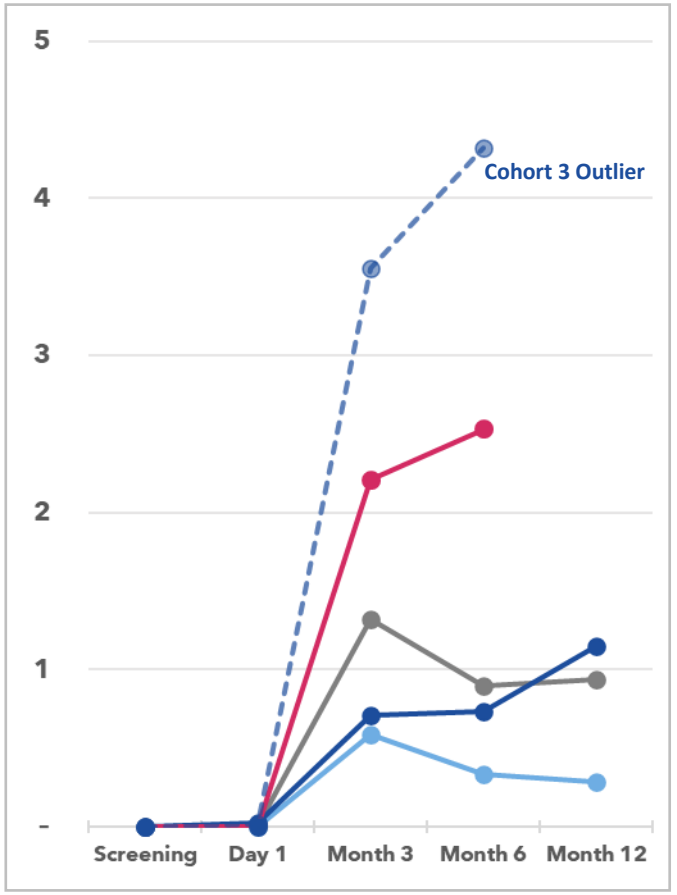
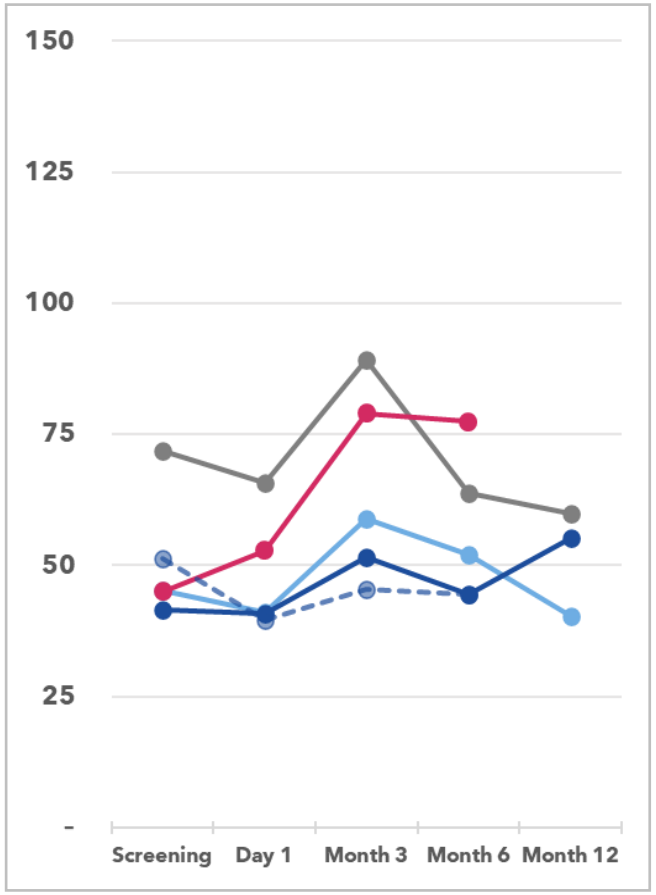
APOE2 Protein Expressed in CSF in All Participants, with Dose- and Time-Dependent Increase in Expression and Durability to 12 Months

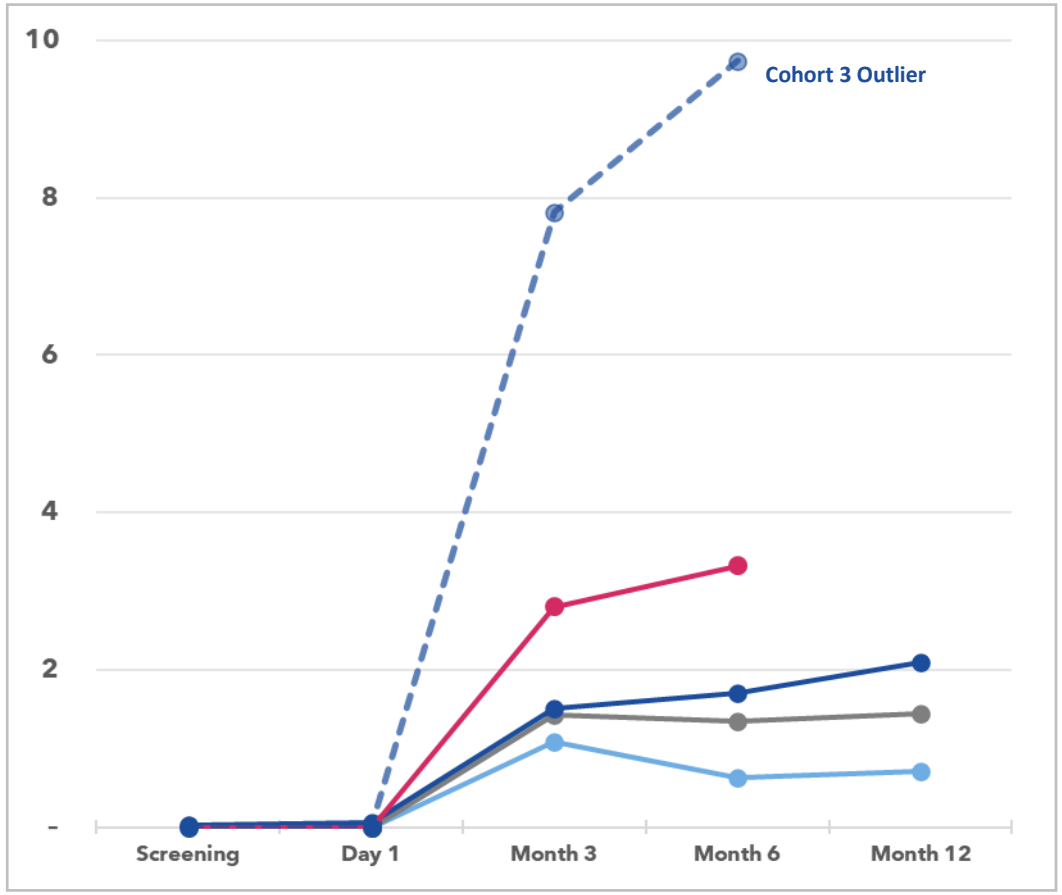
APOE2 (fmol/µl) – Mean



APOE4 (fmol/µl) – Mean



APOE 2:4 Ratio (%) – Mean



Cohort 1 Cohort 2 Cohort 3 Cohort 4

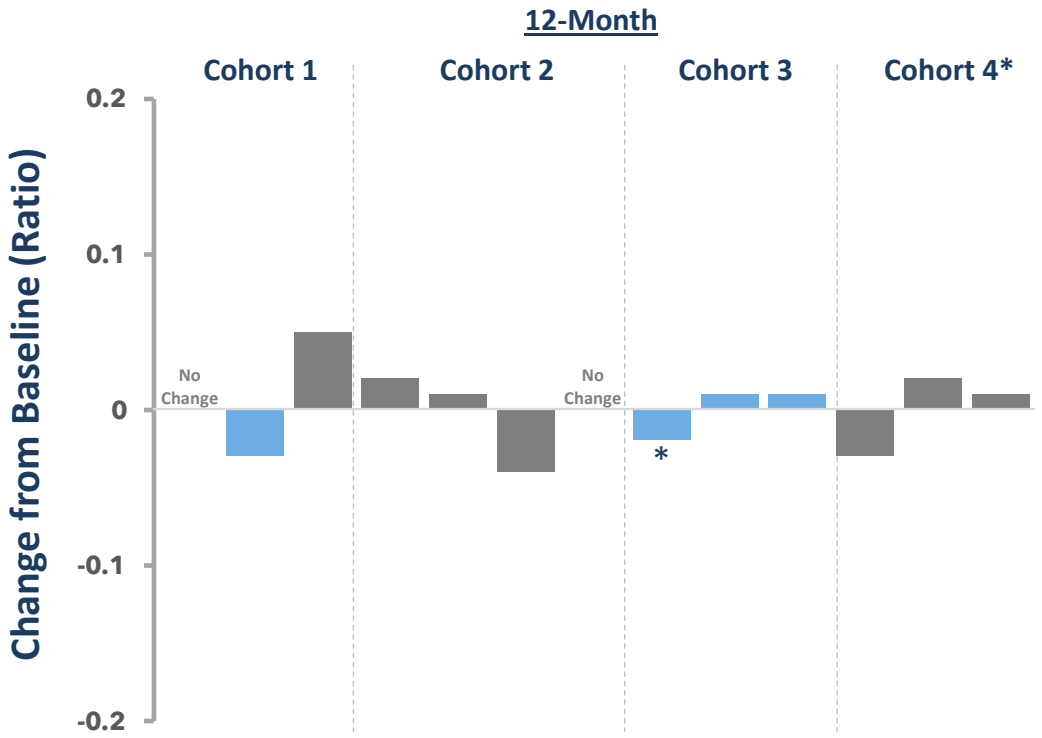
	Screening	Day 1	Month 3	Month 6	Month 12
Cohort 1	n=5	n=5	n=2	n=2	n=1
Cohort 2	n=4	n=3	n=4	n=4	n=4
Cohort 3*	n=2	n=2	n=2	n=2	n=2
Cohort 4	n=3	n=3	n=3	n=3	NA

*excludes Cohort 3 outlier

LX1001 Stabilized Amyloid Progression in Majority of Participants at Last Follow-Up

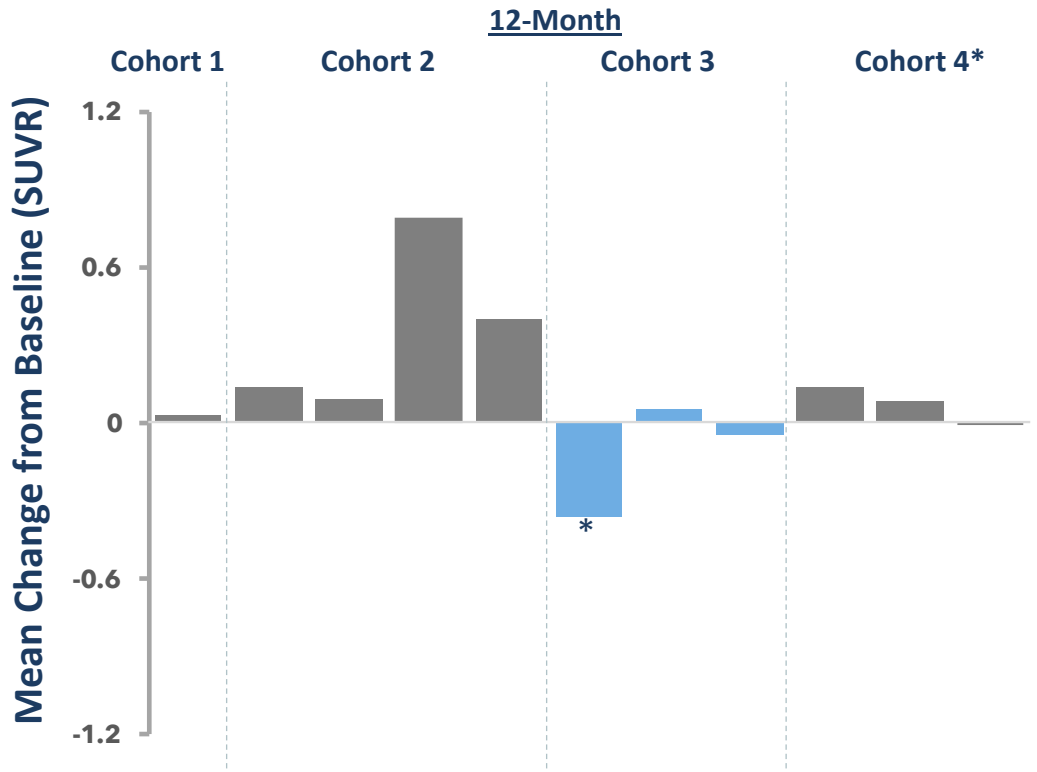
CSF Aß42/40

At 12 months or last follow up, patients remained similar to baseline, suggesting stabilization of Aß pathology



Amyloid PET – SUVR

Majority of patients with minimal change from baseline



Baseline Cognition by MMSE: MCI or MILD MOD

*Indicates results as of 6-month visit.
Each bar represents absolute change from baseline per participant at 12 months, or last follow up if 12-month follow-up unavailable.
Note: protocol deviation, amyloid PET not performed in two subjects in Cohort 1.

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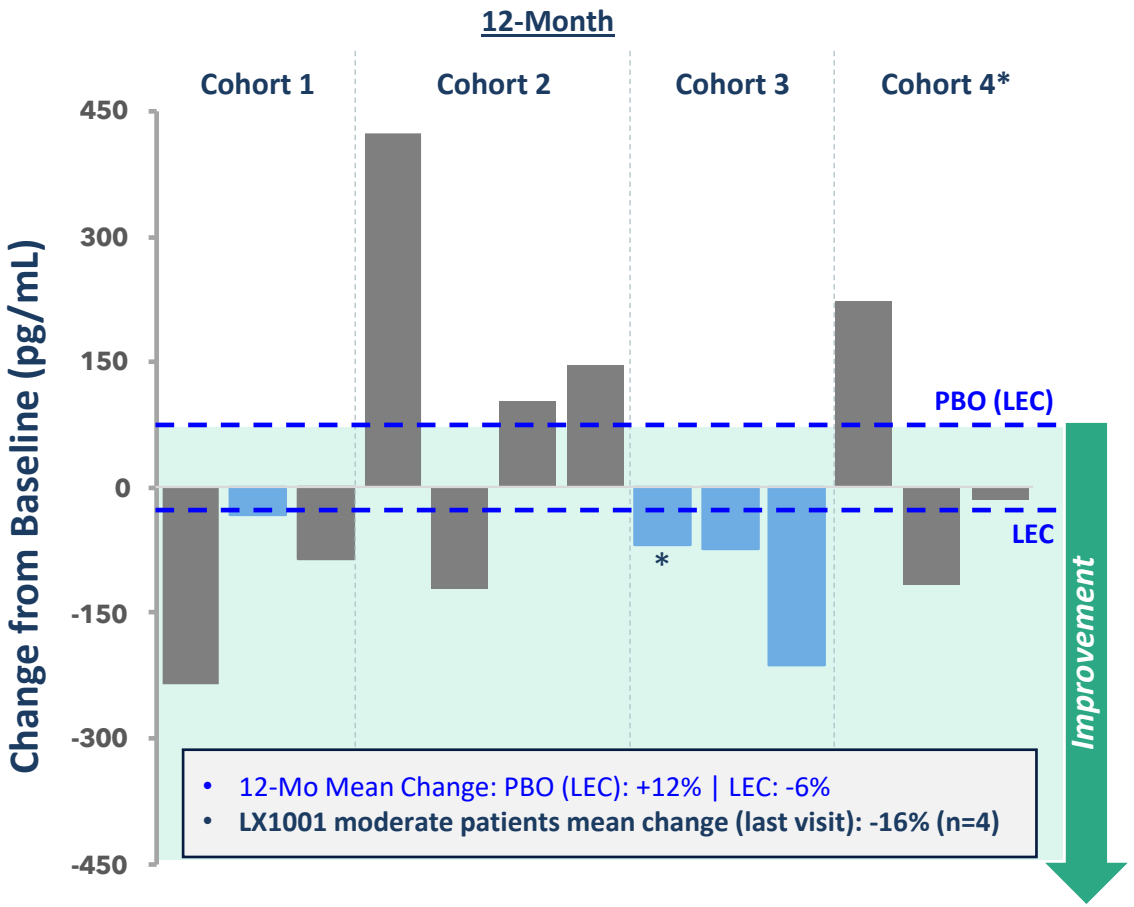
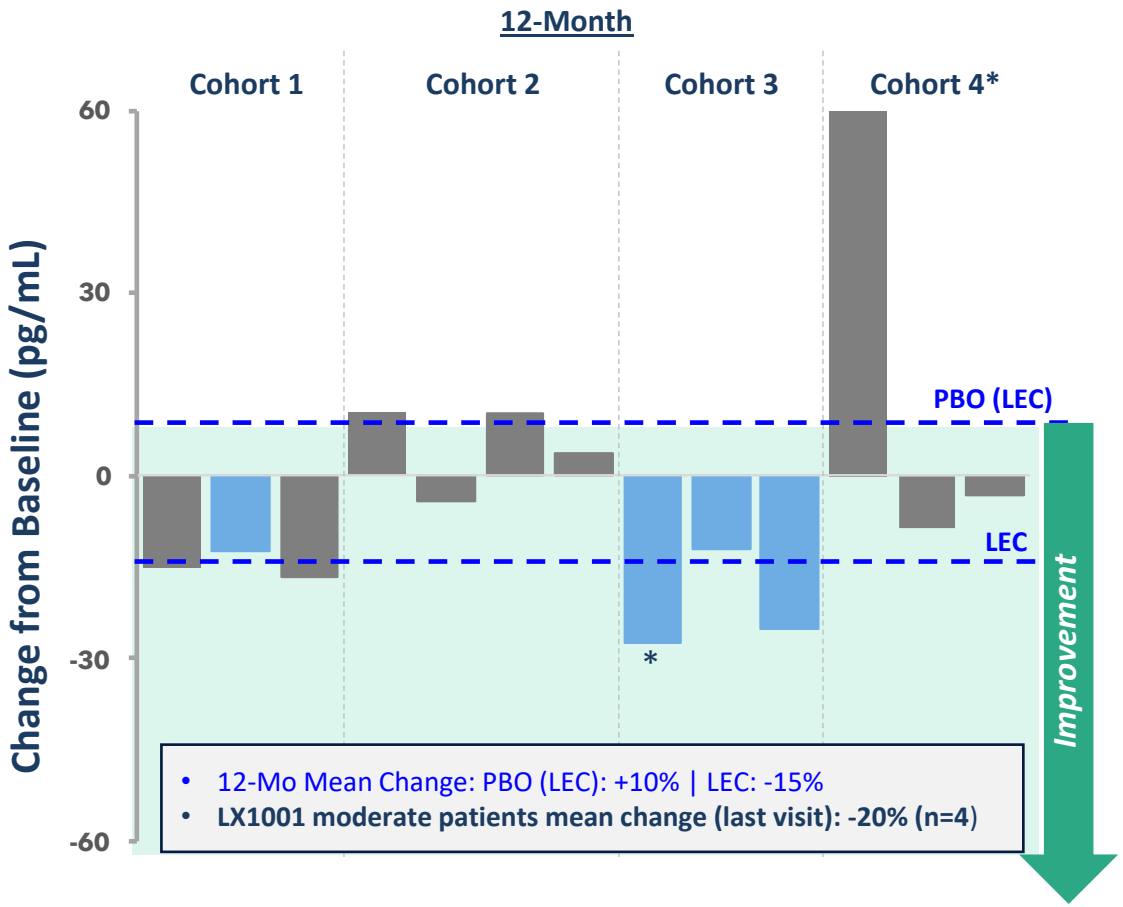
LX1001 Reduced CSF T-Tau & P-Tau181 in 9 of 13 Patients at Last Follow-Up

CSF T-Tau



CSF P-Tau181



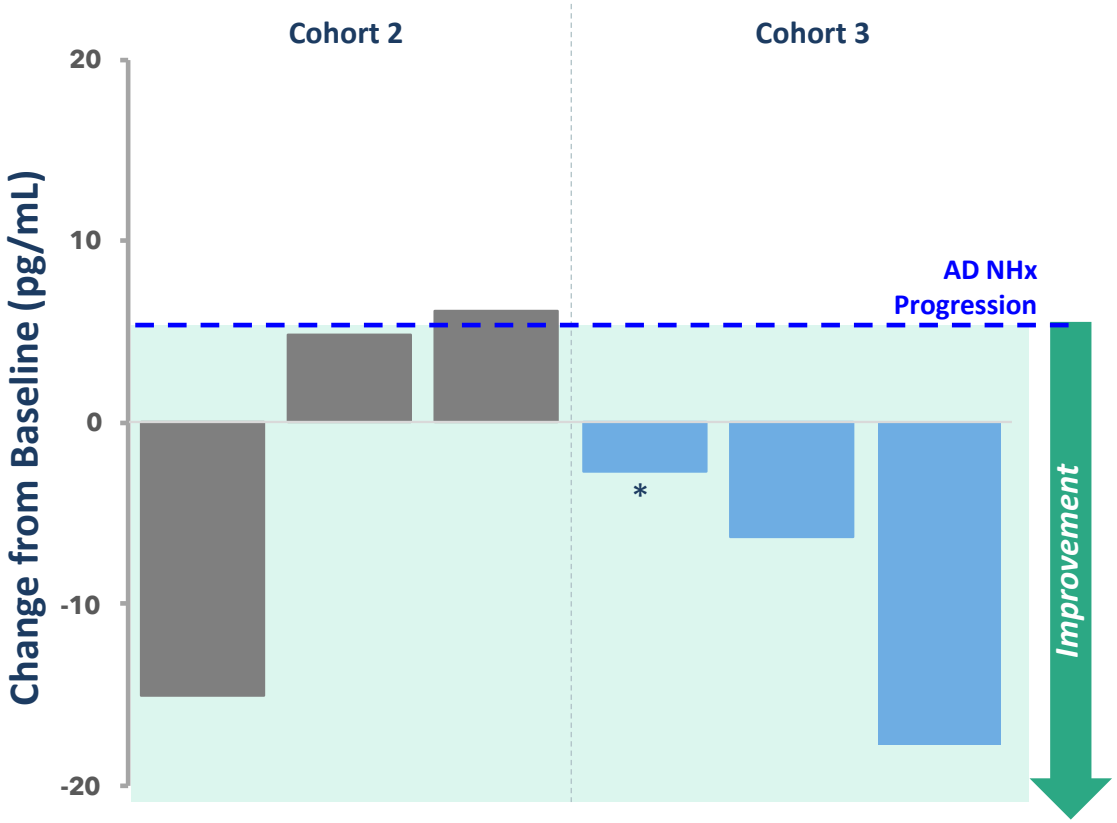
Baseline Cognition by MMSE: MCI or MILD | MOD

Note: Assay variability within +/- 6%
PBO = Placebo, LEC = Lecanemab.
*Indicates results as of 6-month visit. Each bar represents absolute change from baseline per participant at 12 months, or last follow up if 12-month follow-up unavailable.
Source: Iwatsubo, T., Irizarry, M., Van Dyck, C., Sabbagh, M., Bateman, R.J., Cohen, S. (2022) Clarity AD: A Phase 3 Placebo-Controlled, Double-Blind, Parallel-Group, 18-month Study Evaluating Lecanemab in Early Alzheimer's Disease. Powerpoint, Clinical Trials on Alzhiemer's Disease (CTAD). Dotted lines reflect mean results from separate study of lecanemab versus placebo, and are used to show mean change from baseline data for participants in that study, which included all APOE genotypes and only patients with MCI and mild AD. Lecanemab was not studied in the Phase 1/2 study of LX1001.

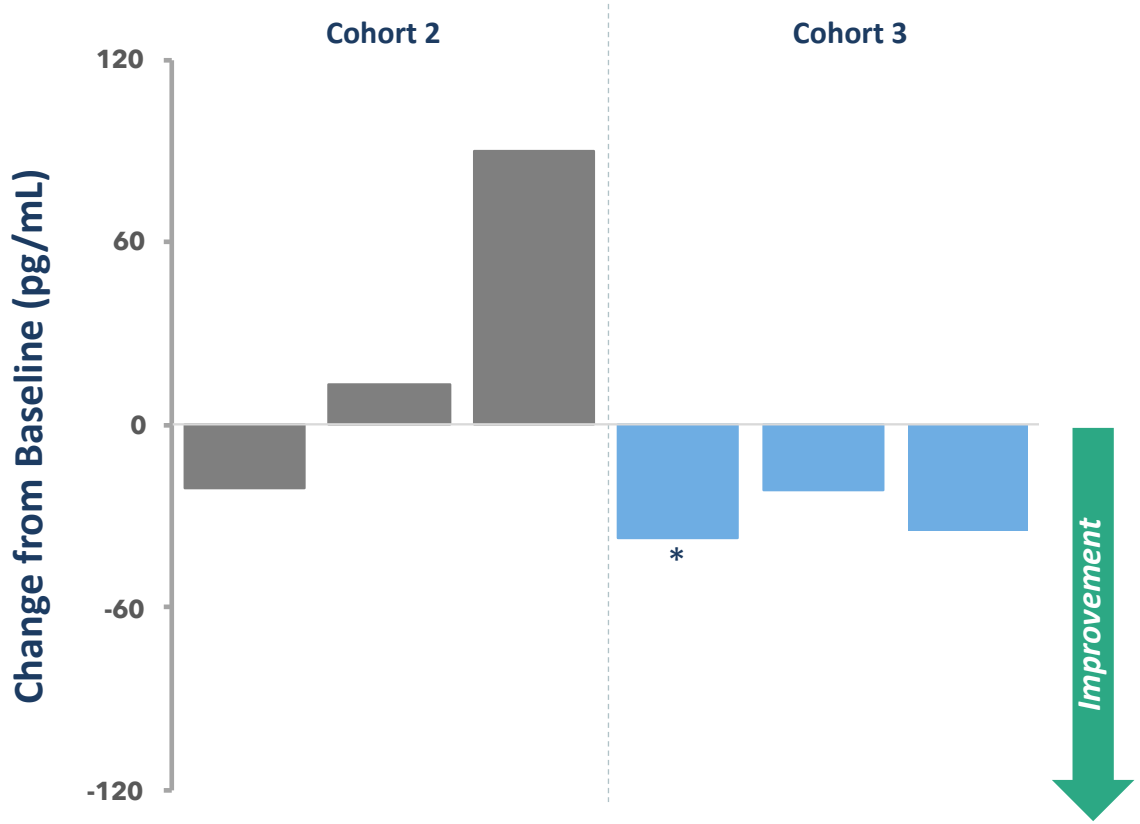
LEXEO therapeutics

LX1001 Reduced P-Tau217 & P-Tau231 In 4 of 6 Patients at Last Follow-Up

CSF P-Tau217 (12 month)



CSF P-Tau231 (12 month)



Baseline Cognition by MMSE: MCI or MILD MOD

Measure not collected in Cohort 1; Cohort 4 samples pending analysis

Note: Assay variability within +/- 6%
*Indicates results as of 6-month visit. Each bar represents absolute change from baseline per participant at 12 months, or last follow up if 12-month follow-up unavailable.
AD Natural History (NHx) progression represents natural history for CSF P-tau217 over 12 months per Ashton NJ, et al. Diagnostic Accuracy of a Plasma Phosphorylated Tau 217 Immunoassay for Alzheimer Disease Pathology. JAMA Neurol. 2024 Mar 1;81(3):255-263. Sample includes 70% E4 carriers with MCI/mild dementia.

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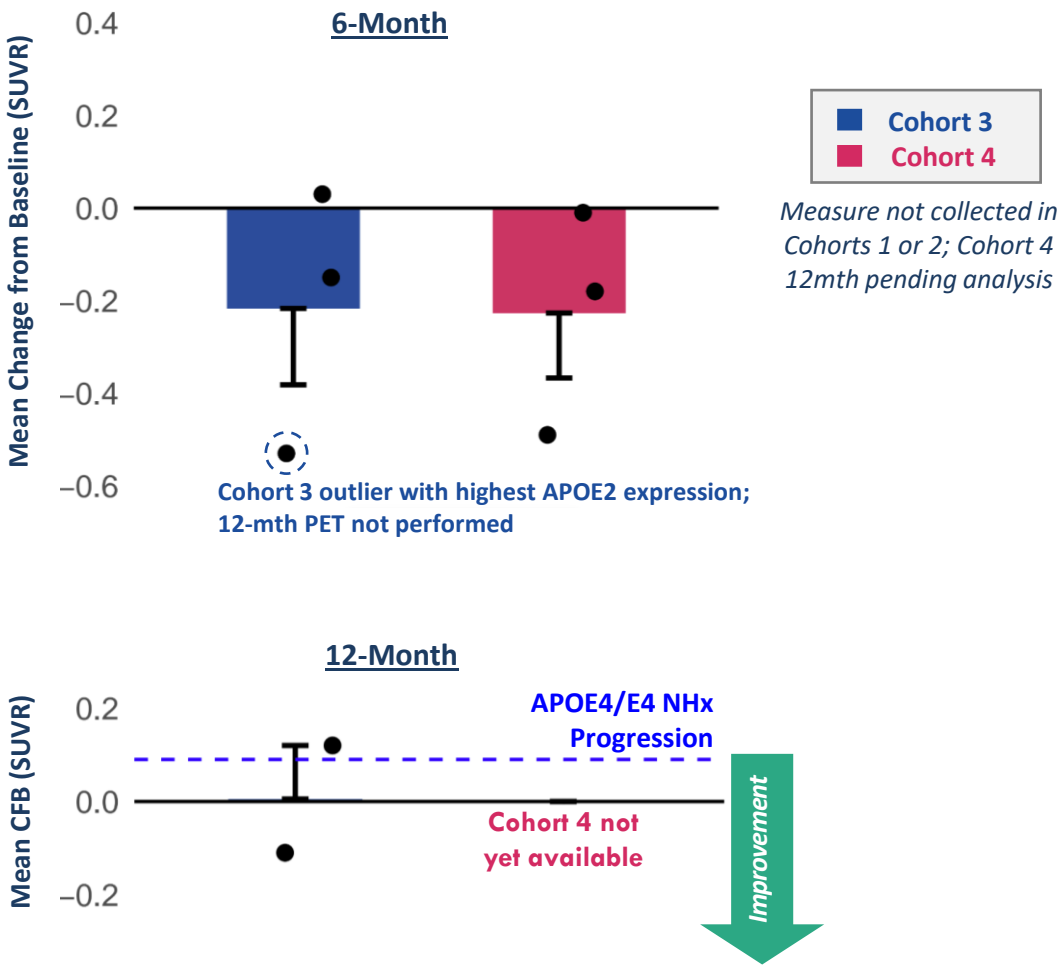
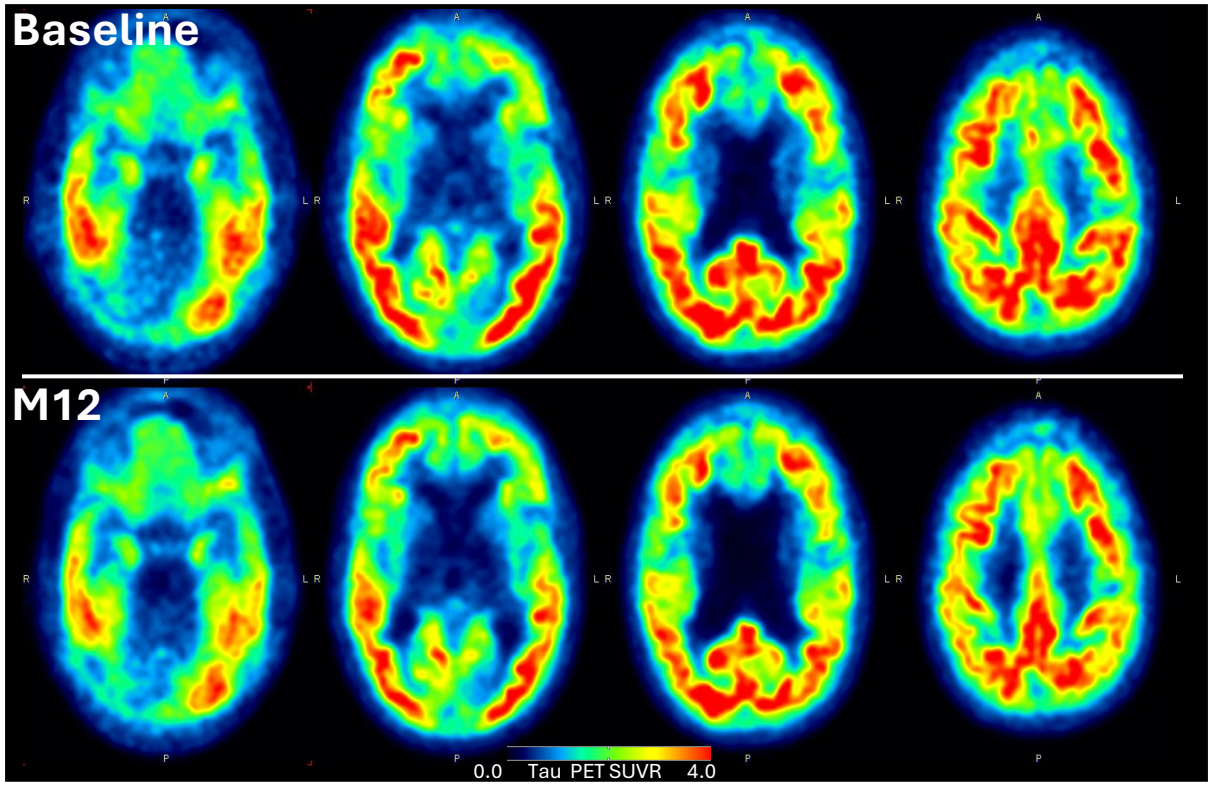
LX1001 Reduced Tau Burden via Global SUVR (PET); Highly Correlated Predictor of Cognitive Outcomes Driven by Alzheimer's Disease[1]

Tau PET – Global SUVR



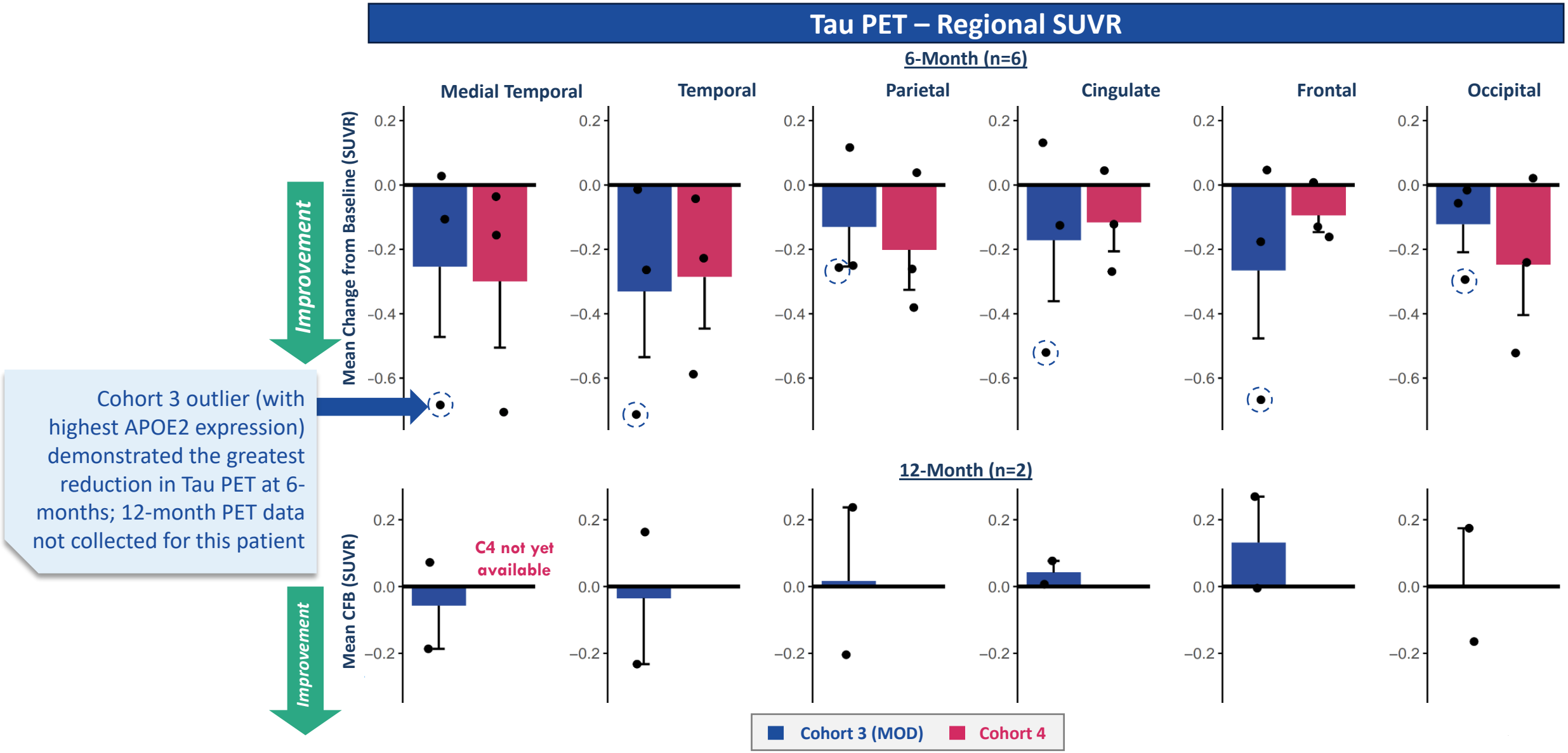
Reduced intensity in Tau PET SUVR from a single patient in Cohort 3 over 12 months



Note: APOE4/4 NHx progression represents natural history for tau PET in E4 homozygotes over 12 months per ADNI database, converted from centiloids;

(1) Malpetti. M. *et al*. Tau Beats Amyloid in Predicting Brain Atrophy in Alzheimer Disease: Implications for Prognosis and Clinical Trials. J Nucl Med. (2022)

LX1001 Reduced Tau Burden via Regional SUVR (PET), Indicating Reduction of Tau Propagation and Slowing of Disease Progression



LX1001 Phase 1/2 Key Takeaways

1 Safety

- ✓ **Well-tolerated across all cohorts**
- ✓ **No reports of ARIA**
- ✓ **Four SAEs, one possibly treatment related**

2 Efficacy

- ✓ **APOE2 expressed in CSF of all participants,** with dose- and time-dependent increase in E2:E4 expression
- ✓ **Stabilization of amyloid pathology**
- ✓ **Consistent reduction in key tau biomarkers**
- ✓ **Greatest effect observed in patients with moderate dementia**

Ph. 1/2 results confirm therapeutic potential of APOE2 for APOE4 homozygotes

Regulatory Precedent for Biomarker-Based Approvals in Alzheimer's and Gene Therapy

- ✓ Regulatory precedent: accelerated approval of two Alzheimer's therapies to date

LEQEMBI® (lecanemab-irmb) 100 mg/mL
INJECTION FOR INTRAVENOUS USE

Aduhelm (aducanumab avwa)

Accelerated approval based on reduction in amyloid plaques as seen in amyloid-PET scans

- ✓ Significant unmet need in APOE4/4 Alzheimer's, and particularly in moderate AD patients
- ✓ Stated interest from CBER to leverage accelerated approval in neurologic diseases where traditional endpoints could take more time to measure

Growing acceptance of tau as a predictor of cognitive decline

- ✓ Scientific literature confirms tau pathology is closely correlated with Alzheimer's disease progression and cognitive decline(1)
- ✓ Studies suggest tau PET is a more sensitive marker than amyloid-beta for Alzheimer's disease and is a clear predictor of cognitive decline(2)

(1) Ioannou, K. *et al.* Tau PET positivity predicts clinically relevant cognitive decline driven by Alzheimer's disease compared to comorbid cases; proof of concept in the ADNI study. Mol Psychiatry. 2024; doi: 10.1038/s41380-024-02672-9.
(2) Malpetti M. *et al.* Tau Beats Amyloid in Predicting Brain Atrophy in Alzheimer Disease: Implications for Prognosis and Clinical Trials. J Nucl Med. 2022;63(6):830-832. doi: 10.2967/jnumed.121.263694. PMID: 35649659; PMCID: PMC9157718.

LEXEO therapeutics

LX1001 Offers Encouraging Clinical Data with Potential Path to Accelerated Approval

1 Meaningful impact across hallmark Alzheimer's biomarkers

Consistent reduction in Tau biomarkers that are highly correlative to progression & cognition

Stabilization of amyloid pathology; indicative of disease slowing

Meaningful improvement vs. APOE/AD progression based on natural history

2 Effect on biomarkers comparable to approved therapies, without ARIA

Comparable or better effect vs. anti-amyloid therapies in key tau biomarkers, particularly in patients with moderate disease

No ARIA events demonstrating favorable safety profile for APOE4 homozygotes

3 Patient population with worse prognosis and no suitable alternatives

Significant Unmet Need for safe and effective treatment for APOE4 homozygotes despite approved therapies

Increased Flexibility for biomarker-based accelerated approvals from FDA (Alzheimer's) and CBER (neurodegenerative conditions)

Q&A