UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): October 30, 2024

Lexeo Therapeutics, Inc.

(Exact name of Registrant as Specified in Its Charter)

Delaware	**001-41855**	**85-4012572**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

345 Park Avenue South, Floor 6 **New York, New York**	**10010**
(Address of Principal Executive Offices)	**(Zip Code)**

Registrant's Telephone Number, Including Area Code: 212 547-9879

N/A
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	Trading Symbol(s)	Name of each exchange on which registered
Common Stock, $0.0001 par value per share	LXEO	Nasdaq Global Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☐

Item 8.01 Other Events.

On October 30, 2024, Lexeo Therapeutics, Inc. (the "**Company**") issued a press release announcing positive interim Phase 1/2 clinical data of LX1001 for the treatment of APOE4-associated Alzheimer's disease (the "**Press Release**") and posted on its website a corresponding corporate presentation (the "**Corporate Presentation**"). As part of the Press Release, the Company announced that it would be hosting a conference call and webcast at 7:00 a.m. ET on October 30, 2024 to discuss the interim Phase 1/2 clinical data of LX1001 for the treatment of APOE4-associated Alzheimer's disease. The Press Release and the Corporate Presentation to be used in connection with the webcast are attached hereto as Exhibit 99.1 and 99.2, respectively, and are incorporated by reference herein.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit Number	Description
99.1	Press Release, dated October 30, 2024
99.2	Corporate Presentation, dated October 30, 2024
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

Lexeo Therapeutics, Inc.

Date: October 30, 2024

By: /s/ R. Nolan Townsend
R. Nolan Townsend, Chief Executive Officer

Exhibit 99.1

Lexeo Therapeutics Announces Positive Interim Data for LX1001, First-Ever Gene Therapy to Impact the Underlying Genetic Cause of APOE4-Associated Alzheimer's Disease, at the Clinical Trials on Alzheimer's Disease (CTAD) Conference

Dose-dependent increase in neuroprotective APOE2 expression in all participants with ongoing durability at 12 months

Consistent reductions across CSF tau biomarkers and tau PET in majority of participants

LX1001 well tolerated across all dose cohorts with no reports of amyloid-related imaging abnormalities (ARIA)

Company to host webcast today at 7:00 AM ET

NEW YORK – October 30, 2024 (GLOBE NEWSWIRE) – Lexeo Therapeutics, Inc. (Nasdaq: LXEO), a clinical stage genetic medicine company dedicated to pioneering treatments for genetically defined cardiovascular diseases and APOE4-associated Alzheimer's disease, today announced positive interim results from the Phase 1/2 study of LX1001 (NCT03634007) for the treatment of APOE4-associated Alzheimer's disease (AD). Treatment with LX1001 led to dose-dependent increases in APOE2 protein expression and improvements in AD-associated tau biomarkers, measures which have been closely correlated with cognitive outcomes. LX1001 also demonstrated a favorable safety profile with no reports of ARIA[1]. The data were presented today in a late-breaking oral presentation at the Clinical Trials on Alzheimer's Disease (CTAD) conference in Madrid, Spain and expand the body of evidence on LX1001 as a potential therapy for the more progressive course of Alzheimer's seen in APOE4 homozygotes.

"APOE4 homozygotes are approximately 15 times more likely to develop Alzheimer's disease than the general population, have faster disease progression, and have an increased risk of ARIA with currently available therapies that can cause serious complications," said Dr. Kim Johnson, Division Chief, Memory Disorders at the Department of Neurology of Duke University School of Medicine and a principal investigator in the Phase 1/2 study. "Today's results suggest the potential of LX1001, which based on available data is well tolerated without reports of ARIA. The study also resulted in notable reductions in tau biomarkers, which suggests a possible effect on Alzheimer's disease pathology."

LX1001 is an AAVrh10-based gene therapy candidate designed to deliver the protective APOE2 allele into the central nervous system of APOE4 homozygous patients, who have two copies of the toxic APOE4 allele. APOE2 is associated with a significantly lower risk of Alzheimer's onset and slower disease progression. In the Phase 1/2 study, which completed enrollment in Q4 2023, fifteen patients with mild cognitive impairment (MCI) or mild or moderate AD were dosed with LX1001 in four dose-ascending cohorts. The study's primary objective was to assess safety and tolerability, with secondary outcomes including cerebrospinal fluid (CSF) APOE2 protein expression and change in tau and amyloid biomarkers.

"In light of the rapid progression of Alzheimer's disease in this population, these data highlight the therapeutic potential of delivering APOE2, which can impact multiple mechanisms of Alzheimer's disease upstream of any specific pathway and thereby meaningfully alter the devastating course of this complex disease," said Dr. Sandi See Tai, Chief Development Officer of Lexeo Therapeutics. "These data are highly encouraging and provide clinical evidence of the unique and targeted mechanism of LX1001 to potentially treat Alzheimer's disease."

[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.

The interim Phase 1/2 data include follow-up through 12-months for dose Cohorts 1 through 3 and follow-up through 6-months for dose Cohort 4, demonstrating:

- CSF APOE2 protein expression in all participants, with dose- and time-dependent increases in expression and durability out to 12 months
- Stabilization of amyloid pathology in the majority of participants, with minimal change from baseline in Aß42/40 ratio and amyloid PET
- Consistent reductions across CSF tau biomarkers including CSF T-tau, P-tau181, P-tau217[2] and P-tau231[2], in over two thirds of participants relative to baseline and natural history
- Reductions at 6 months in global tau PET[3] SUVR in 5 of 6 participants and in regional SUVR in a majority of participants across all brain regions
- Participants with moderate AD (n=4) generally demonstrated the most improvement across various biomarker endpoints
- Four SAEs were reported, with three deemed unrelated to treatment and one event of mild-moderate sensorineural hearing loss assessed as possibly related to treatment with repeat audiometry pending.

The Company has initiated engagement with FDA on these data and expects to provide an update on regulatory interactions and further LX1001 development plans in 2025.

Conference Call Information
Lexeo will host a webcast today at 7:00 AM ET to review these data and next steps for the program. To register for and access the conference call and webcast presentation, please visit https://ir.lexeotx.com/news-events/events. The webcast presentation includes slides with further analysis of the LX1001 interim data. The on-demand webcast presentation may be accessed under the News & Events tab in the Investors section of the Company's website, and a replay will be available following the presentation.

About LX1001
LX1001 is an AAVrh10-based gene therapy candidate for the treatment of APOE4-homozygous Alzheimer's disease. Individuals homozygous for APOE4, an allele of the gene APOE, are approximately 15 times more likely to develop Alzheimer's disease than the general population, and it is estimated that there are approximately 900,000 APOE4 homozygous patients with Alzheimer's disease in the United States. Conversely, individuals homozygous for the APOE allele APOE2 are 40% less likely to develop Alzheimer's disease than the general population. LX1001 is designed to express the protective APOE2 gene in the central nervous system of APOE4 homozygous patients, potentially slowing or halting the progression of Alzheimer's disease. LX1001 has been granted Fast Track designation by the FDA.

About Lexeo Therapeutics
Lexeo Therapeutics is a New York City-based, clinical stage genetic medicine company dedicated to transforming healthcare by applying pioneering science to fundamentally change how genetically defined cardiovascular diseases and APOE4-associated Alzheimer's disease are treated. Using a stepwise development approach, Lexeo is leveraging early proof-of-concept functional and biomarker data to advance a pipeline of cardiovascular and APOE4-associated Alzheimer's disease programs.

[2]CSF P-tau217 and P-tau231 collected only in Cohorts 2, 3 and 4; all Cohort 4 samples, including 6 month and 12 month, pending analysis
[3]Tau PET performed only in Cohorts 3 and 4; Cohort 4 12-mth visits pending analysis

Cautionary Note Regarding Forward-Looking Statements
Certain statements in this press release may constitute "forward-looking statements" within the meaning of the federal securities laws, including, but not limited to, our expectations and plans regarding our current product candidates and programs, including statements regarding the potential benefits and safety of LX1001 for the treatment of Alzheimer's disease and the timing for receipt and announcement of data from its clinical trials, and the timing and likelihood of potential regulatory approval. 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 global macroeconomic conditions and related volatility; 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 Quarterly Report on Form 10-Q for the quarterly period 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.

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Investors:
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Exhibit 99.2

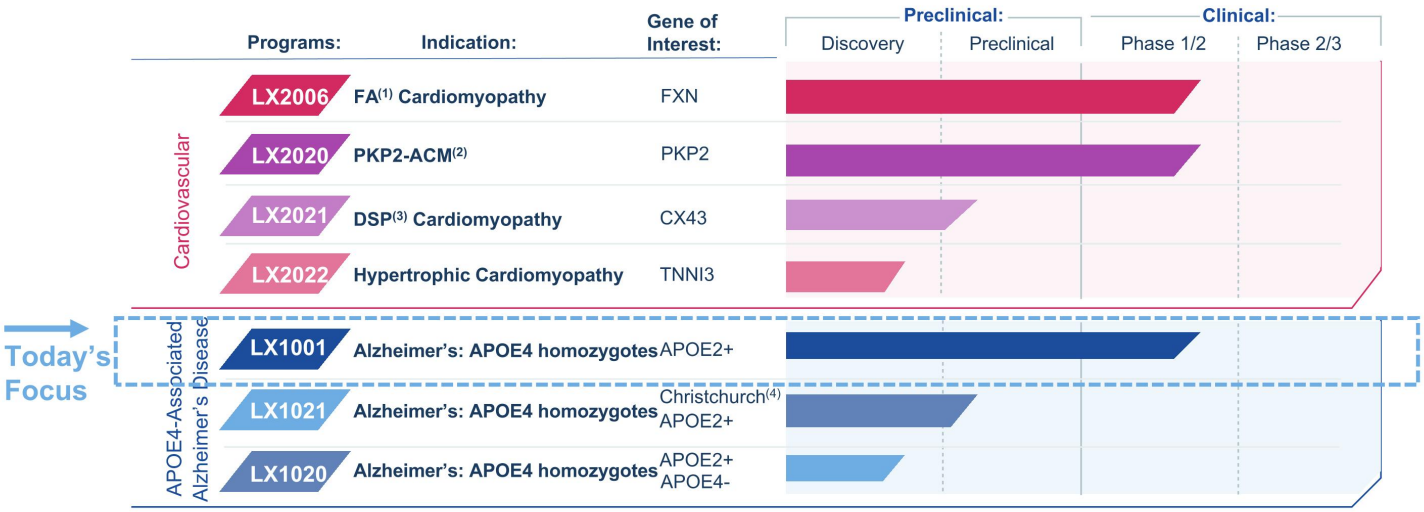
Interim Phase 1/2 Clinical Data of LX1001 for the Treatment of APOE4-associated Alzheimer's Disease

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.

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.

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]

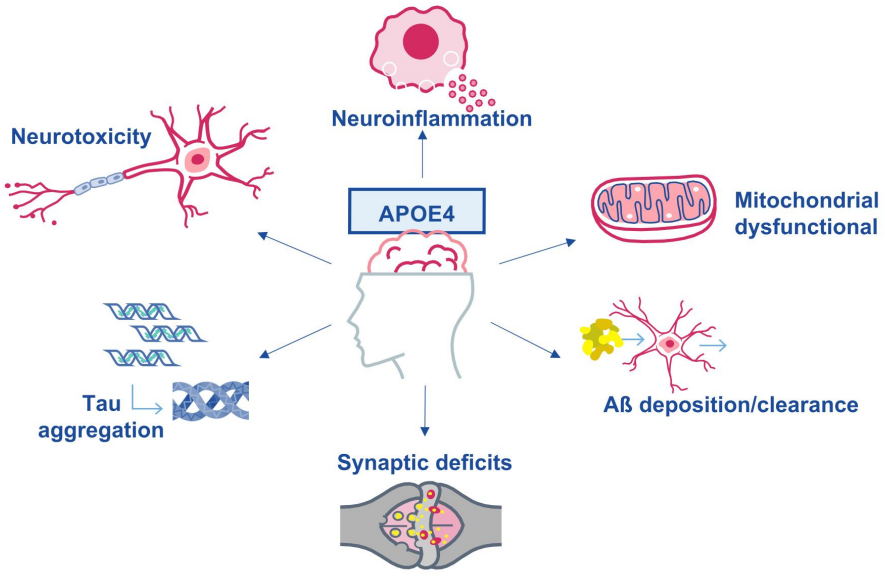
population with high incidence rate, expected to increase with aging population

(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 Medicine*. 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.

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

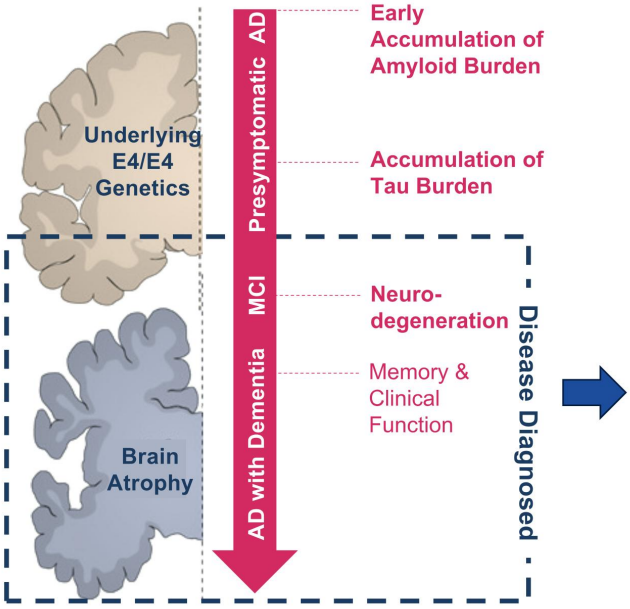
APOE4 drives Alzheimer's disease pathogenesis

- 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

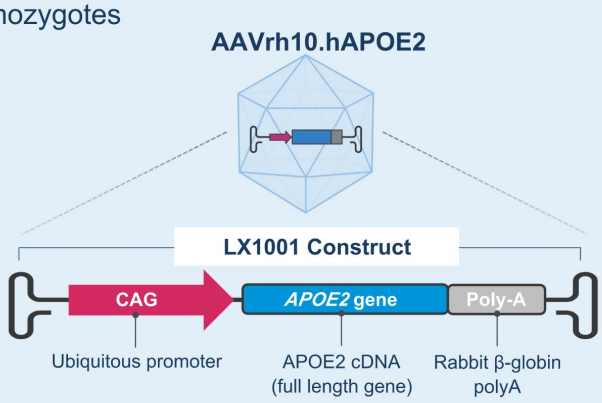
Unique Approach to Targeting Underlying Genetics of APOE4/E4 Alzheimer's Disease

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

LEXEO therapeutics

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

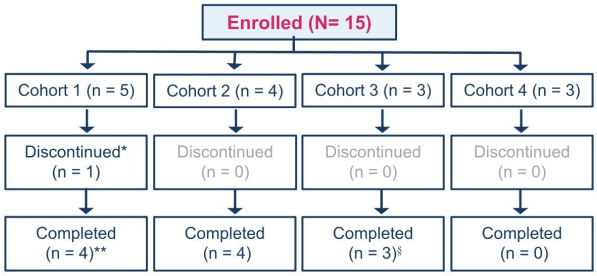
Primary Endpoint: Safety

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

LEXEO therapeutics

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

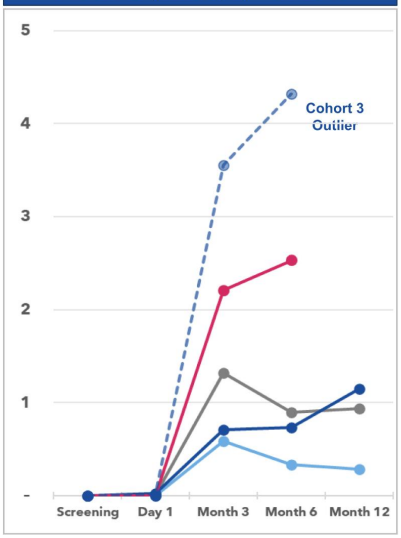
- Treatment with LX1001 was well-tolerated across all 4 dose cohorts
- No reports of ARIA[1]
- Transient CSF pleocytosis (>5cells/μL), predominantly lymphocytic, was observed in 12 participants, with no significant adverse events associated
- Four SAE's:
  - Three unrelated to treatment: diverticulitis, 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.

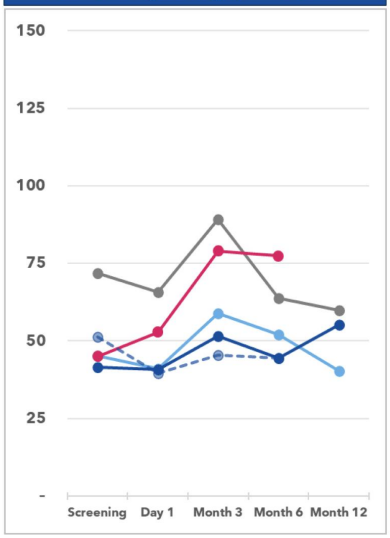
LEXEO therapeutics

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

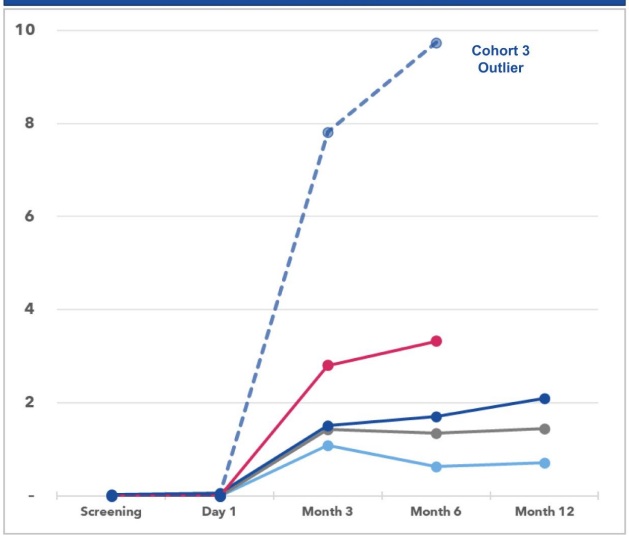
APOE2 (fmol/µl) – Mean



APOE4 (fmol/µl) – Mean



APOE 2:4 Ratio (%) – Mean



Cohort 1 — Cohort 2 — Cohort 3 — Cohort 4

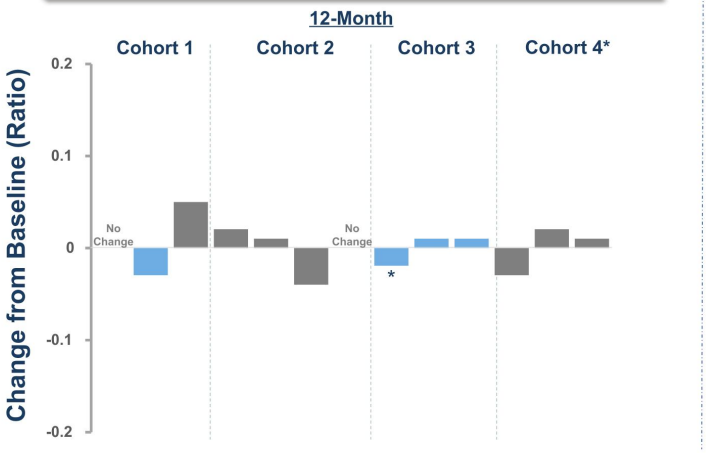
	Screening	Day 1	Month 3	Month 6	Month 12
Cohort 1	n=5	n=5	n=2	n=2	n=1
Cohort 2	n=4	n=3	n=4	n=4	n=4
Cohort 3*	n=2	n=2	n=2	n=2	n=2
Cohort 4	n=3	n=3	n=3	n=3	NA

*excludes Cohort 3 outlier

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

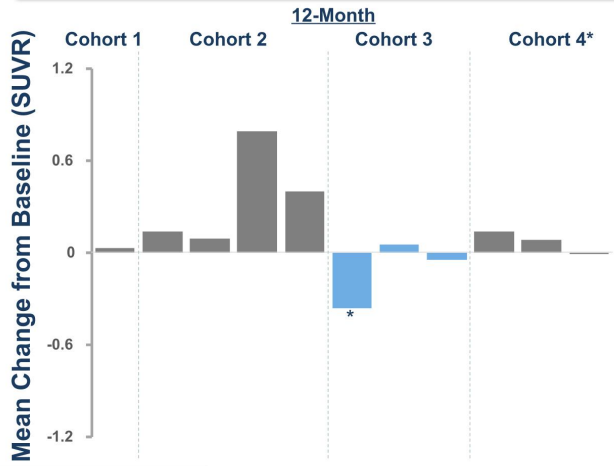
CSF Aß42/40

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



Amyloid PET – SUVR

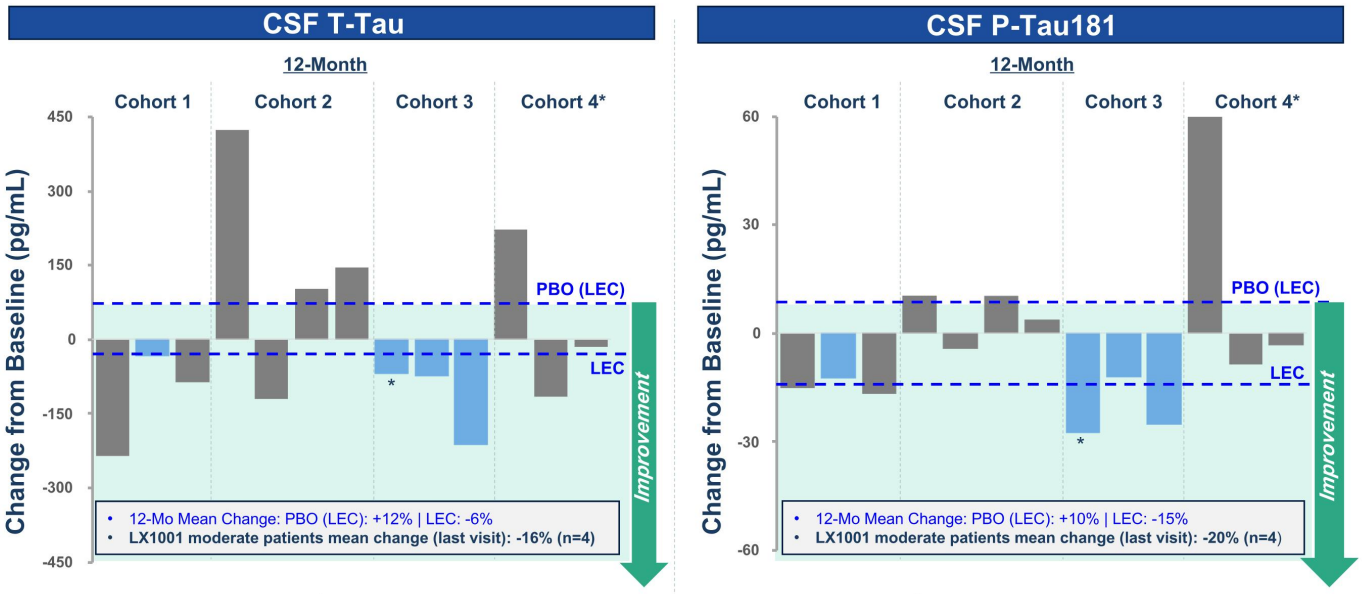
Majority of patients with minimal change from baseline



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.

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



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.

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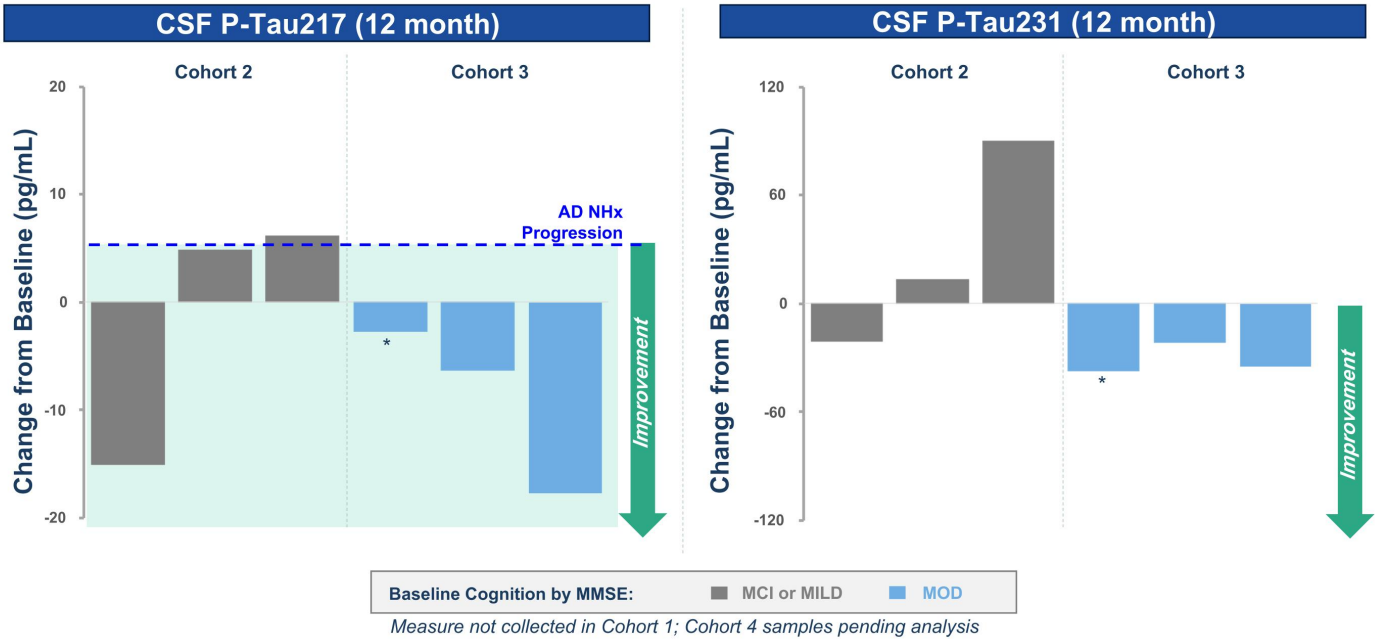
LX1001 Reduced P-Tau217 & P-Tau231 In 4 of 6 Patients at Last Follow-Up



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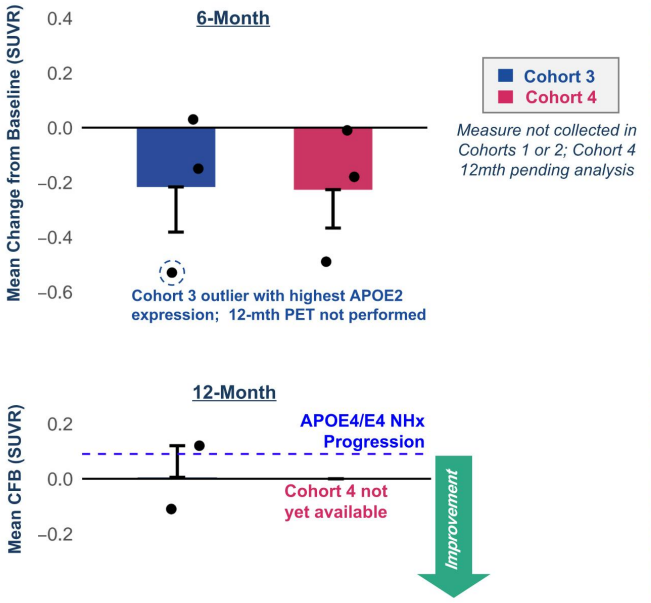
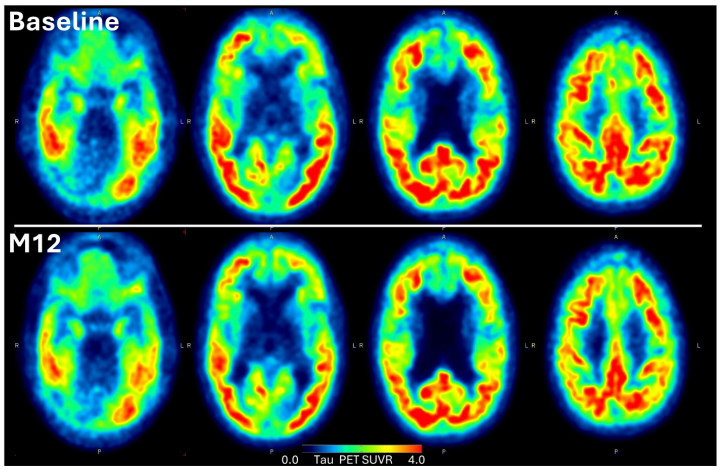
LX1001 Reduced Tau Burden via Global SUVR (PET); Highly Correlated Predictor of Cognitive Outcomes Driven by Alzheimer's Disease[1)]

Tau PET – Global SUVR

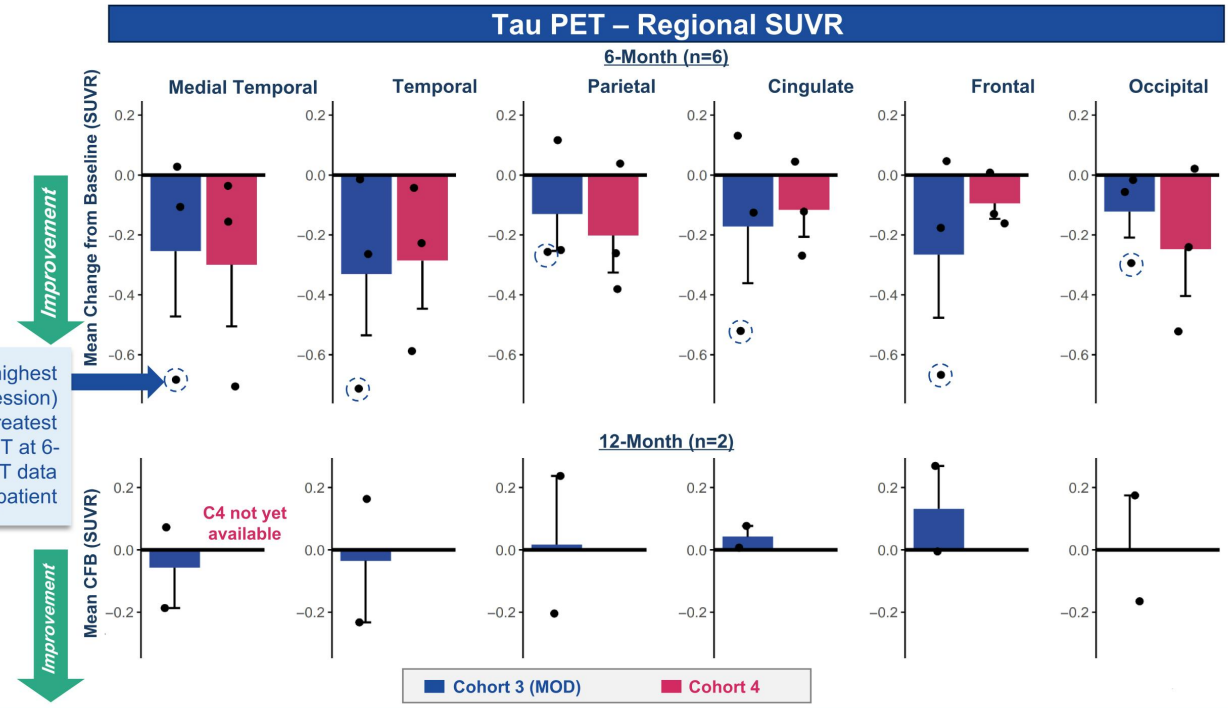


Reduced intensity in Tau PET SUVR from a single patient in Cohort 3 over 12 months



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



Cohort 3 outlier (with highest APOE2 expression) demonstrated the greatest reduction in Tau PET at 6-months; 12-month PET data not collected for this patient

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.

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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