Lexeo Therapeutics Corporate Overview

November 13, 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 timing, progress and results of preclinical and clinical trials of Lexeo’s gene therapy product candidates, the anticipated benefits of its current product candidates, the timing and likelihood of regulatory approval, and expected cash runway. 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

Lexeo Therapeutics Team

Management Team & Key Advisors

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Chief Executive Officer

Pfizer · Lehman Brothers

Eric Adler, M.D.
Chief Medical Officer and
Head of Research

UC San Diego School of Medicine Division of Cardiology · Boston University

Sandi See Tai, M.D.
Chief Development Officer

Pfizer · Wyeth

Jenny R. Robertson
Chief Business and Legal Officer

Pfizer · Hogan Lovells

José Manuel Otero, Ph.D.
Chief Technical Officer

Auregen BioTherapeutics · Turnstone Biologics · Merck

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Senior Advisor to the CEO
and Board of Directors

judobio · Reata Pharmaceuticals · GBT · Portola

Chair and Scientific Founder

Steven Altschuler, M.D.
Chairman

The Children's Hospital of Philadelphia · Spark Therapeutics

Ronald Crystal, M.D.
Founder & Chief Scientific Adviser

Weill Cornell Medicine Genetic Medicine

Professor and Chairman, Weill Cornell Medicine
Director, Belfer Gene Therapy Core Facility

Former Chief,
Pulmonary Branch — NIH National Heart, Lung, and Blood Institute

Founder / Co-founder — Adverum Biotechnologies · GenVec · XyloCor Therapeutics

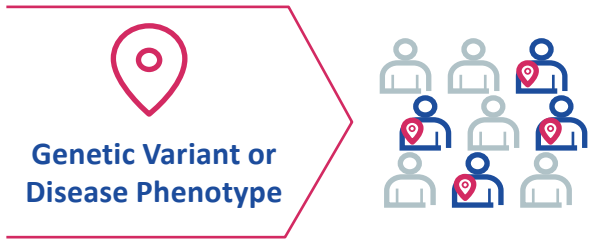
Management team with broad leadership experience in gene therapy and rare disease

LEXEO therapeutics

Revolutionizing Genetic Medicines for Cardiovascular Diseases and APOE4-Alzheimer's

Attractive Disease Area Strategy

- Genetically-defined cardiovascular and APOE4-associated Alzheimer's disease
- Well established biomarkers potentially allowing for early signs of clinical activity



Evolving Regulatory Environment	Shift towards surrogate endpoints could circumvent need for large cardiovascular outcome trials
Targeted Delivery Platform	Improvements in modern AAV delivery technology, including AAVrh10 allows for greater targeting of the heart
Increased Genetic Screening	Increased screening has potential to expand awareness and increase opportunity
Lower Efficacy for APOE4 Patients[1]	Approved amyloid directed antibodies demonstrated lower efficacy results for APOE4 homozygotes compared to heterozygotes and noncarriers
Higher Risk of ARIA-E[1]	APOE4 homozygotes were associated with a higher incidence of ARIA-E compared to heterozygotes and noncarriers with approved therapies

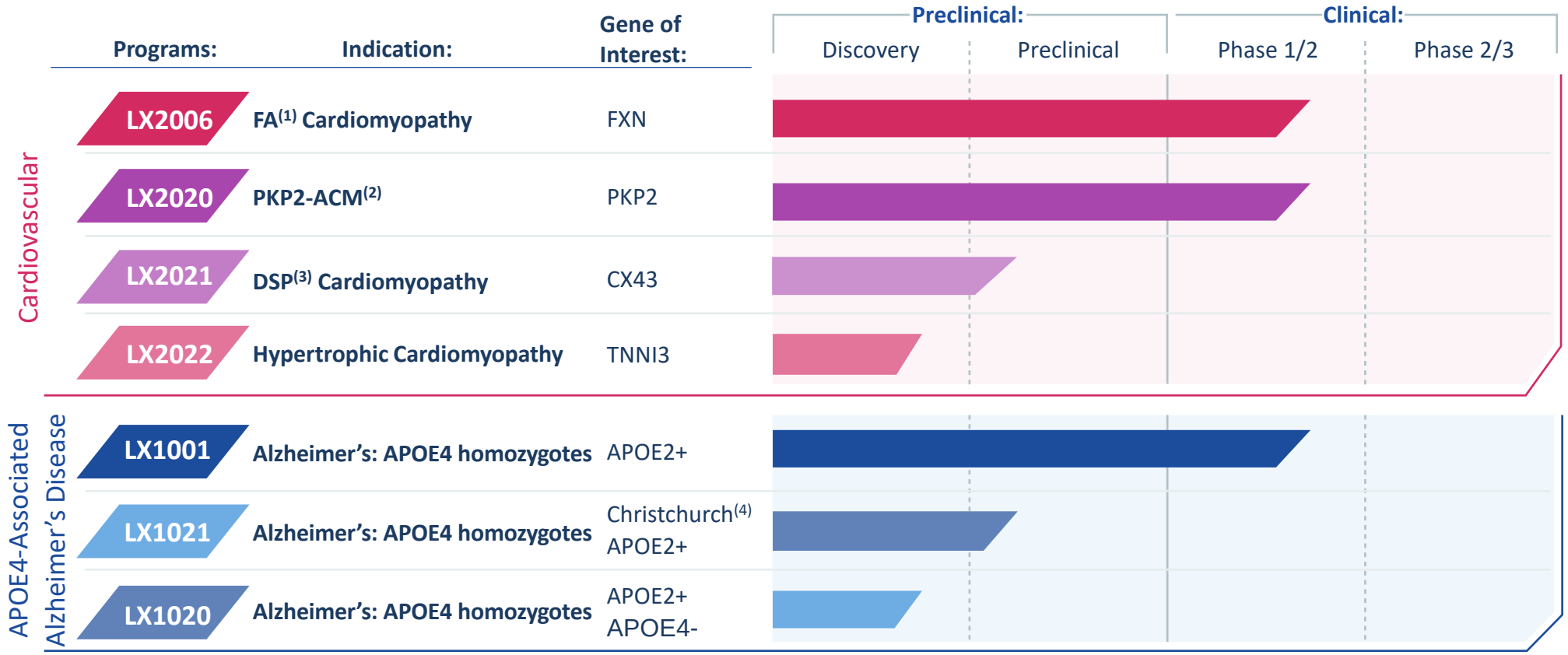
Focused on areas of high-unmet need with potential for gene therapy to drive meaningful outcomes

Note: ARIA-E = amyloid-related imaging abnormalities characterized by edema and effusion.

(1) Van Dyck, et al. New England Journal of Medicine, 2022. Sims, et al. JAMA, 2023.

LEXEO therapeutics

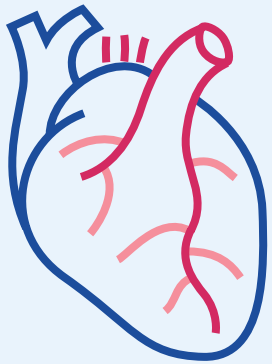
Advancing Genetic Medicines in Larger-Rare and Prevalent Patient Populations



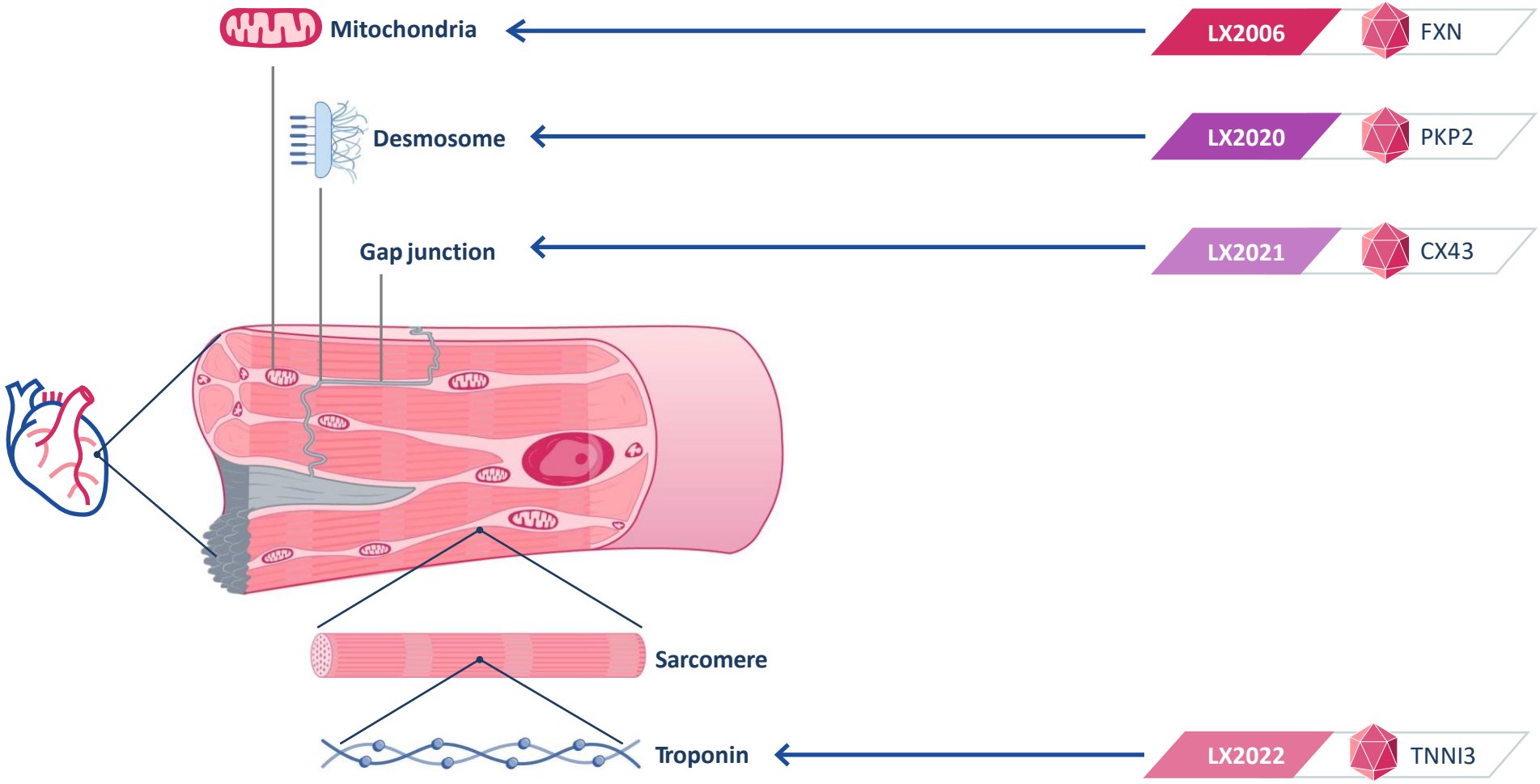
Wholly-owned pipeline with programs in two core therapeutic areas of high unmet need

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

Cardiovascular diseases



Several Targets in Cardiac Organelles that are Dysregulated in Cardiomyopathy; Potential Readthrough to Other Therapeutic Indications

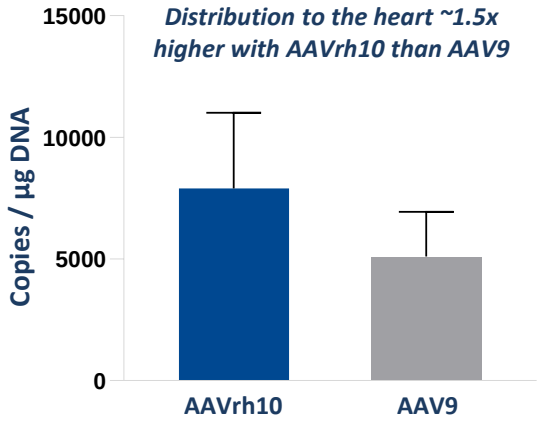


Utilizing AAVrh10 for Initial Genetic Cardiac Indications

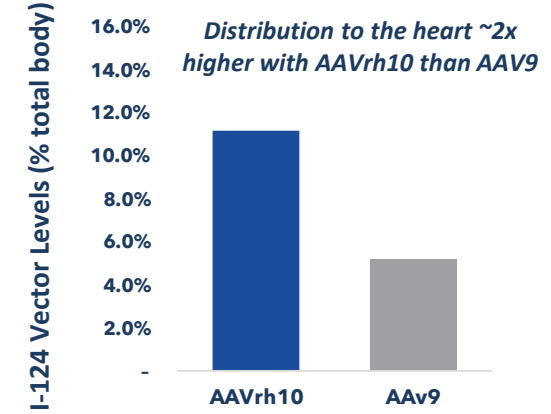
- ✓ Observed ~1.5x to 2.0x greater biodistribution in the heart compared to AAV9 in multiple large animal models
- ✓ Observed greater trends of functional improvements in PKP2-murine model compared to AAV9
- ✓ AAVrh10 cardiac tropism may allow for lower doses compared to other vector serotypes while achieving targeted transgene biodistribution

Compelling Cardiac Tropism

Yucatan Minipig Biodistribution(1)

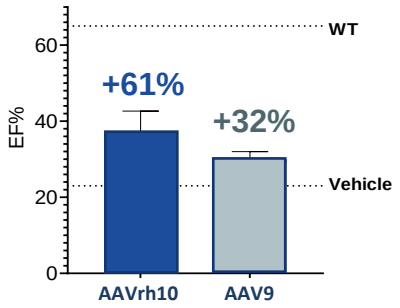


NHP Biodistribution(2)

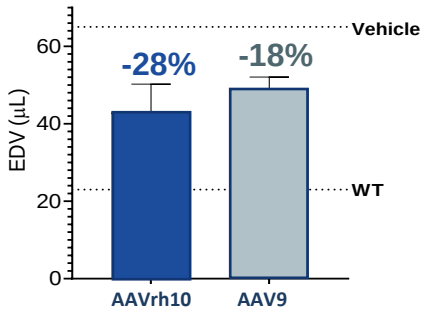


Greater Trends of Functional Improvement Versus AAV9 in PKP2-ACM Model(1)

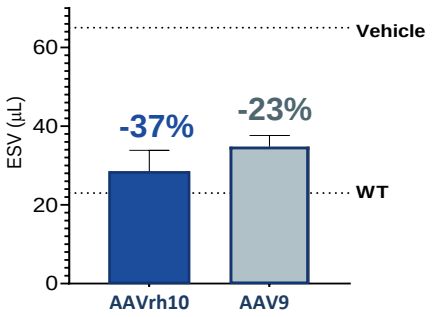
Greater Increase in EF



Greater Reduction in EDV



Greater Reduction in ESV

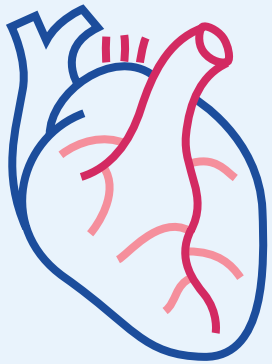


Note: PKP2 homozygous mouse model administered with human PKP2 (N = 5 mice / group).

(1) Data presented at ASGCT 2023.
(2) Ballon DJ et al, Human Gene Therapy, 2020.

LEXEO therapeutics

LX2006 (FA Cardiomyopathy)



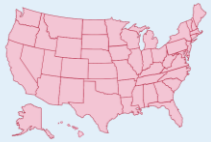
Friedreich Ataxia (FA) is a Devastating Rare Disease Impacting Both the Nervous System and the Heart

FA is a **rare, devastating and progressive disorder** caused by loss of function mutations in the *FXN* gene (GAA repeat expansion)

With a typical age of onset between 10 and 15 years, people with FA experience a **combination of neurological and cardiac manifestations**, with ~80% developing cardiomyopathy(1)

Complications from **cardiac dysfunction** are the **leading cause of death in FA**

The only approved disease-specific treatment for FA demonstrated efficacy on neurological measures but was not evaluated for the treatment of cardiac dysfunction, **leaving significant unmet need within FA cardiomyopathy**



~5,000
individuals affected by FA in the U.S.(2)

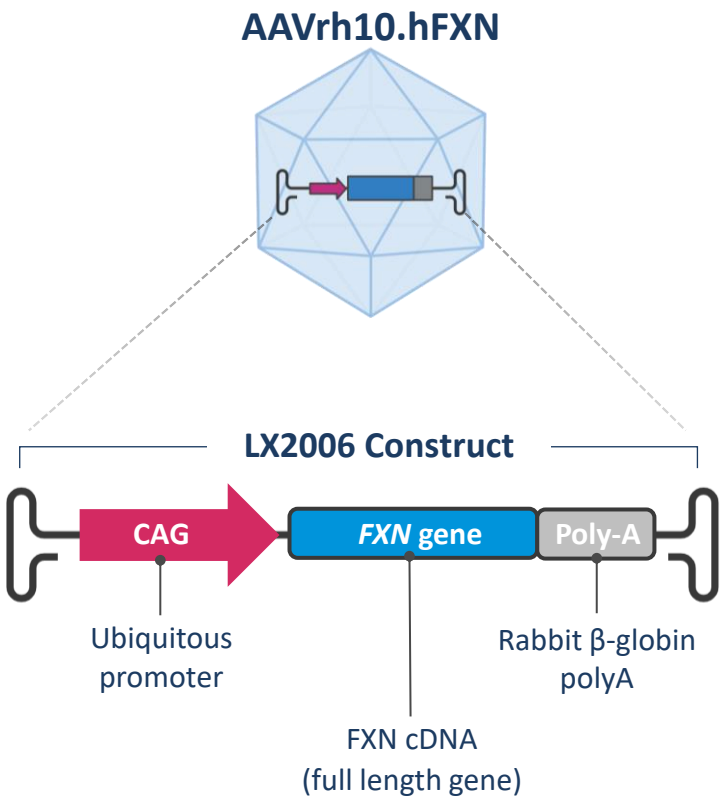
~15,000
individuals affected by FA worldwide(2)

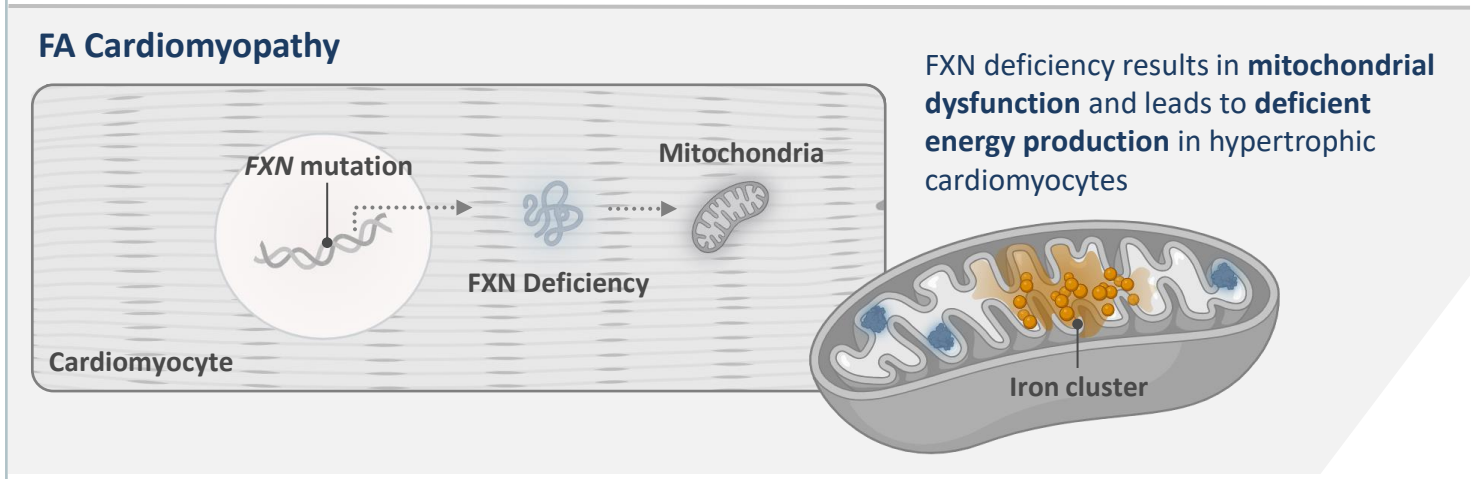
Cardiac dysfunction is the cause of death in **60-80%** of those with FA(3)(4)

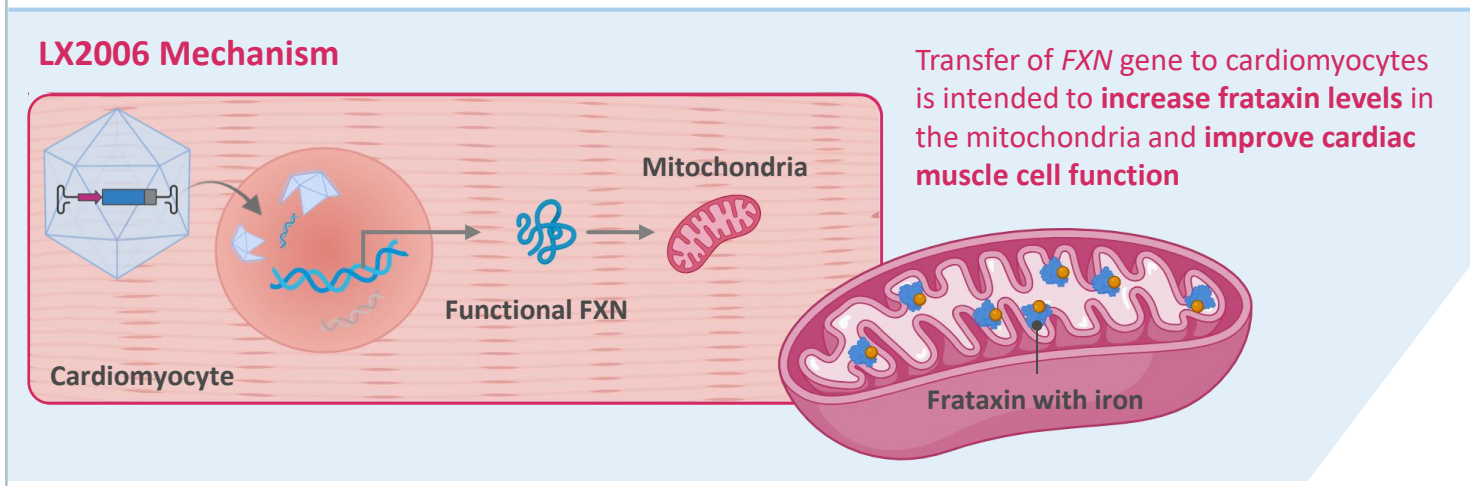
FXN, Frataxin.

(1) Regner S, et al. *American Journal of Cardiology*, 2012. (2) Friedreich's Ataxia Research Alliance, 2024. (3) Subramoney S, et al. *MDA Clinical and Scientific Conference*, 2023.
(4) Pousset, F. et al. *JAMA Neurol,* 2015;72(11):1334-1341.

LX2006 Has the Potential to Treat the Root Cause of FA Cardiomyopathy: The Significant Decrease in Frataxin in the Heart



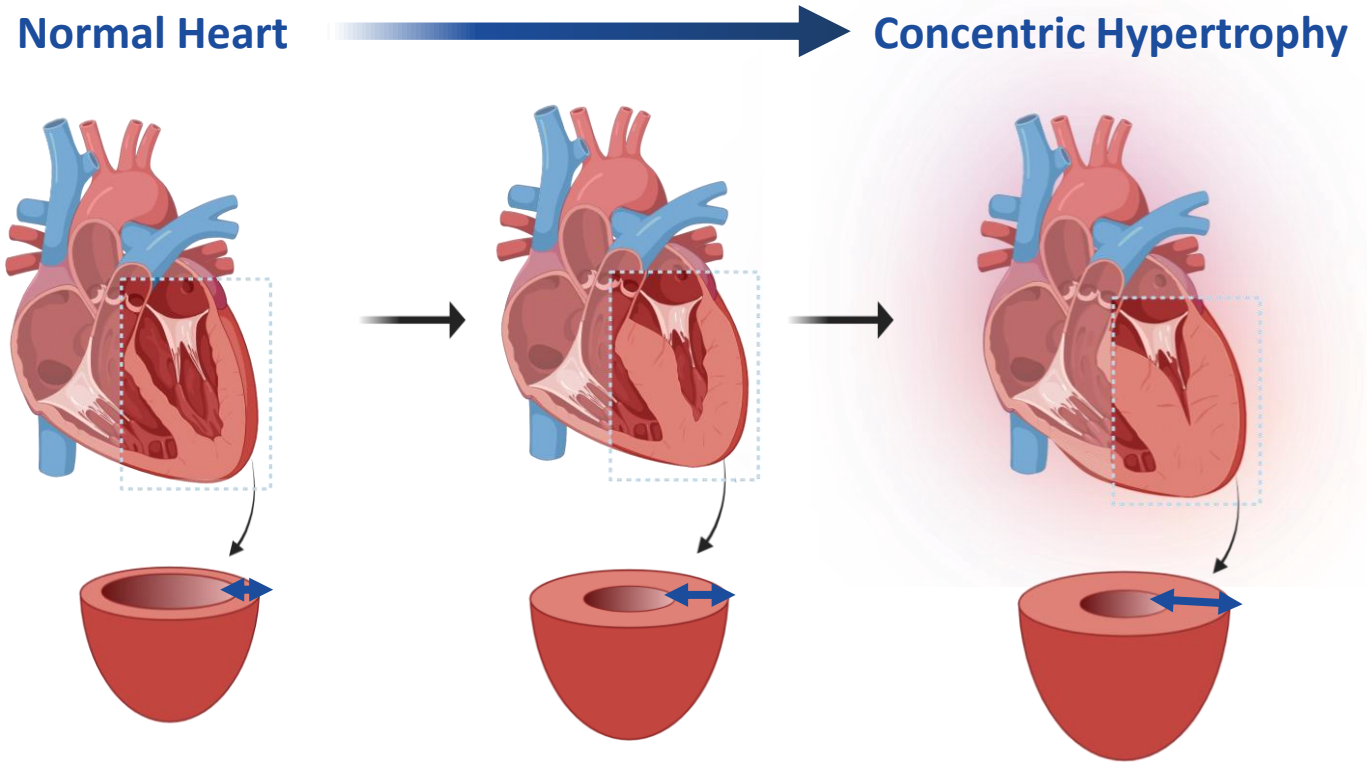




AAV, Adeno-Associated Virus; CAG, Chicken Beta-Actin; cDNA, Copy DNA; FA, Friedreich Ataxia; FXN, Frataxin; Poly-A, Poly Adenosine.

Dysfunction in Heart Muscle Cells Can Lead to Concentric Hypertrophy and Poorer Outcomes in Multiple Cardiomyopathies

Disease Progression



Normal Heart		Concentric Hypertrophy
Normal LVMI	High Normal LVMI	↑ LVMI
Normal LV Wall Thickness	↑ LV Wall Thickness	↑ LV Wall Thickness
Normal hs-Troponin I	↑ Hs-Troponin I	↑ Hs-Troponin I

Measurements of Hypertrophy

✓ Left Ventricular Mass Index (LVMI)

- Indicator of left ventricular hypertrophy
- Closely correlated with outcomes such as death or hospitalization in multiple conditions:
  - Heart failure with preserved ejection fraction[1]
  - Hypertensive cardiomyopathy[2]
  - Fabry disease[3,4]
  - Obstructive hypertrophic cardiomyopathy (HCM)[5]

✓ Left Ventricular (LV) Wall Thickness

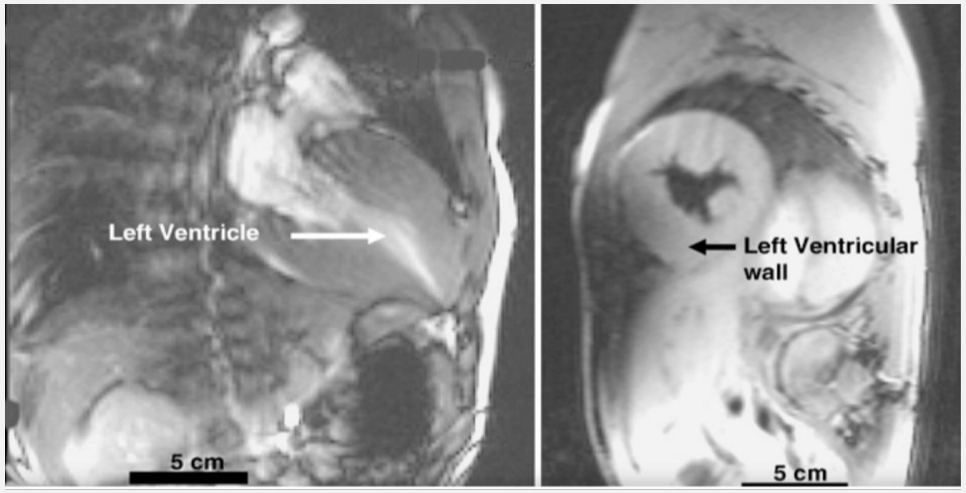
- Early indicator of left ventricular hypertrophy
- Associated with increase in cardiovascular events;[2] magnitude of LV wall thickness is directly related to risk of sudden cardiac death in HCM[6]

(1) Shah et al, *Journal of American College of Cardiology,* 2019. (2) Muiesan et al, *Hypertension,* 2004. (3) Orsborne et al, *Journal of American College of Cardiology,* 2022. (4) Hanneman et al, *Radiology,* 2020. (5) Hegde et al, *Journal of American College of Cardiology,* 2021. (6) Spirito et al, *NEJM,* 2000.

Individuals with FA Demonstrate Concentric Hypertrophy Including Increased Wall Thickness and Elevated LVMI, Which Predicts Mortality

Increases in LVMI Independently Predict Mortality in Friedreich Ataxia (FA)

Natural history study showed a 19% higher risk of death per 10g/m^2 (HR 1.19; 95% CI)(1)



MRI of Individual With FA Cardiomyopathy Demonstrating Significant Hypertrophy

- Concentric hypertrophy is a hallmark of FA cardiomyopathy, including increased LVMI and abnormal left ventricular wall thickness(1)(2)
- Natural history suggests a 19% incremental risk of all cause mortality per ~10% increase in LVMI in individuals with FA; increased wall thickness was also associated with mortality(1)
- **Improvement in LVMI and left ventricular wall thickness may improve cardiac outcomes in those with FA**

HR, Hazard Ratio; CI, Confidence Internal; LVMI, Left Ventricular Mass Index.
Note: 10g/m^2 represents approximately 10% change in LVMI based on echocardiography measurements of upper bound of normal (105 g/m^2).
(1) Pousset, F. et al. *JAMA Neurol,* 2015;72(11):1334-1341. (2) Peverill et al, *PLOS ONE,* 2019.

LEXEO therapeutics

LX2006 is Being Evaluated in Lexeo-Sponsored SUNRISE-FA and Weill Cornell Investigator Initiated Trial: Similar Trial Designs Enable Joint Evaluation

1 Study Design & Objective

Design:
52-week open-label study with a **4-year** long term follow up

Objective:
To assess the **safety** and **efficacy** of LX2006 in individuals with cardiomyopathy associated with Friedreich Ataxia

2 Key Inclusion Criteria

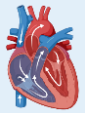
Adults
(18-50 years)

Evidence of FA cardiomyopathy

Neutralizing anti-AAVrh.10 titer cutoff

3 Key Measurements

Cardiac Structure & Function
(LVMI, hsTnI, other measures)



Functional Capacity
(CPET)

FXN Protein Expression Assessed Only in SUNRISE-FA
(LCMS and IHC)

SUNRISE-FA and Weill Cornell trials share a similar study design, enabling data from the two studies to be evaluated together

CPET, Cardiopulmonary Exercise Testing; hsTnI, High Sensitivity Troponin I; IHC, Immunohistochemistry; LCMS, Liquid Chromatography Mass Spectrometry; LVMI, Left Ventricular Mass Index.
Note: LX2006 is administered systemically; participants receive immune suppression with prednisone beginning on the day prior to treatment through 14 weeks following LX2006 administration.
Note: In April 2024, Lexeo announced a license agreement with Cornell University for intellectual property rights including current and future clinical data from the ongoing Weill Cornell Medicine investigator-initiated trial of AAVrh10.hFXN (LX2006). Lexeo-sponsored SUNRISE-FA trial and Weill Cornell Medicine investigator-initiated trial utilize identical drug product manufactured at Weill Cornell for these ongoing studies.

LEXEO therapeutics

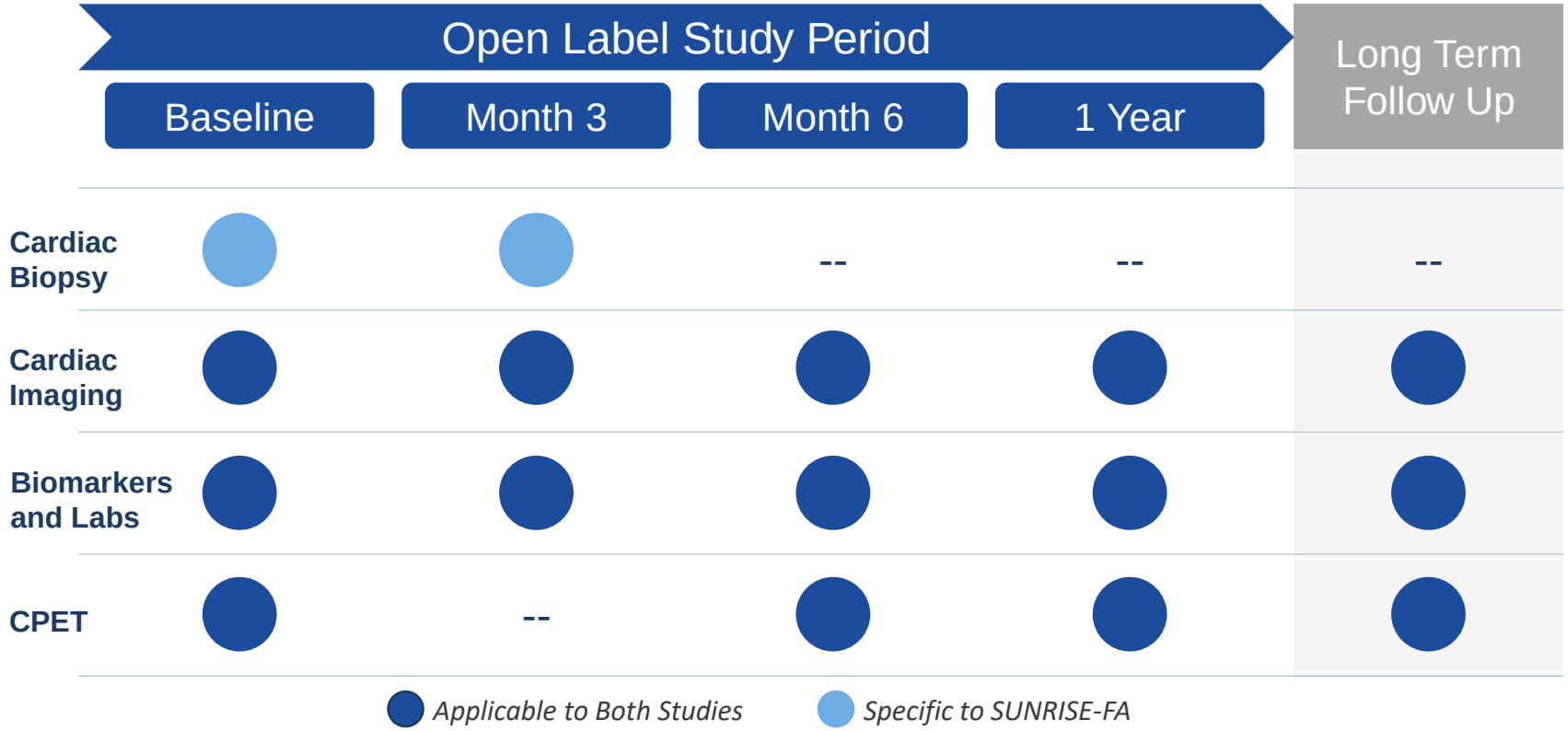
Both Studies Utilize Similar Metrics to Evaluate Safety and Efficacy

SUNRISE-FA *Lexeo Sponsored*

- Cohort 1: $1.8x10^{11}$ vg/kg
- Cohort 2: $5.6x10^{11}$ vg/kg
- Cohort 3: $1.2x10^{12}$ vg/kg

Weill Cornell *Investigator Initiated*

- Cohort 1: $1.8x10^{11}$ vg/kg
- Cohort 2 : $5.6x10^{11}$ vg/kg



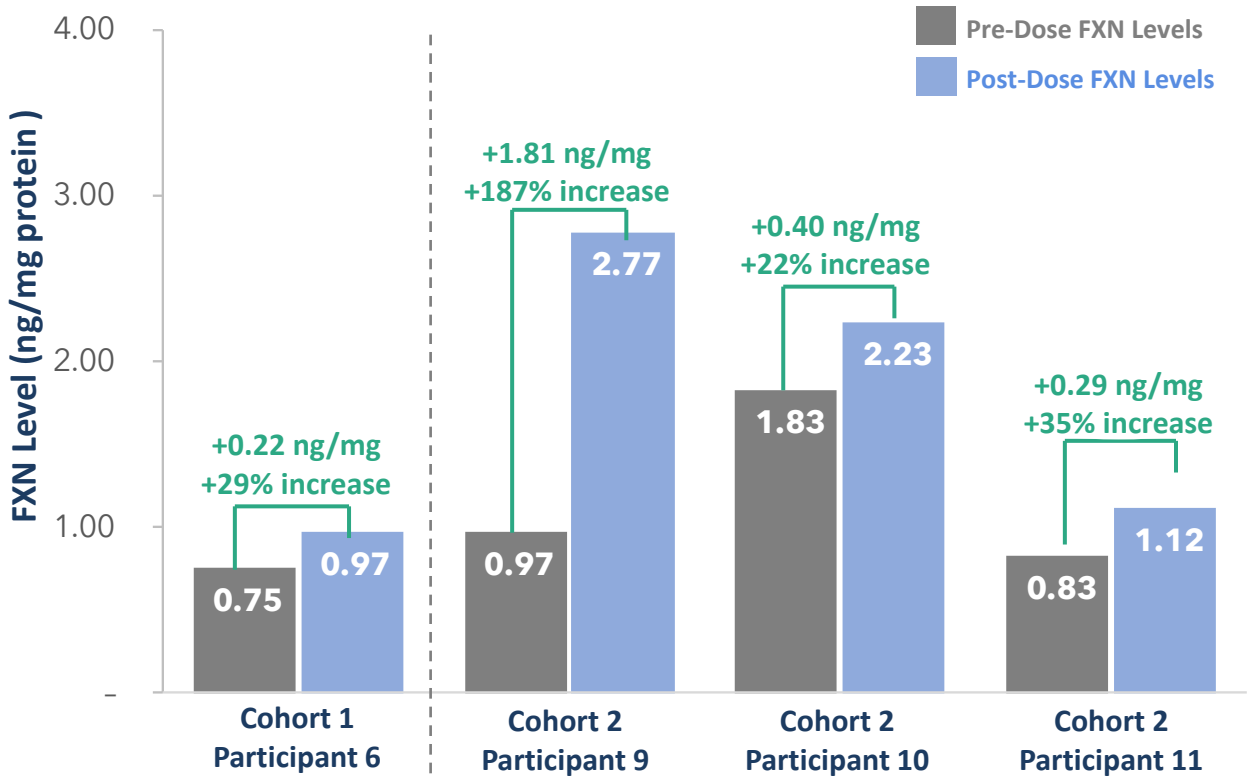
Treatment with LX2006 has been generally well-tolerated to date

- No signs of complement activation or other immunogenicity have been reported
- 1 possibly treatment-related Grade 2 event of asymptomatic myocarditis observed one year after dosing
  - Patient with multiple comorbidities; history of flu-like symptoms prior to diagnosis which may have been a contributing factor
  - Biopsy performed 6 weeks after diagnosis and results negative for myocarditis and patient remains asymptomatic

Note: Participants receive immune suppression with prednisone beginning on the day prior to treatment through 14 weeks following LX2006 administration, as such cardiac imaging and biomarkers post-treatment are shown beginning with the 6-month timepoint.

Cardiac Biopsies Have Demonstrated Increased Frataxin Expression in Heart in All Participants Evaluated to Date Utilizing Two Measurement Techniques

Pre- and Post-Treatment FXN Levels (LCMS)

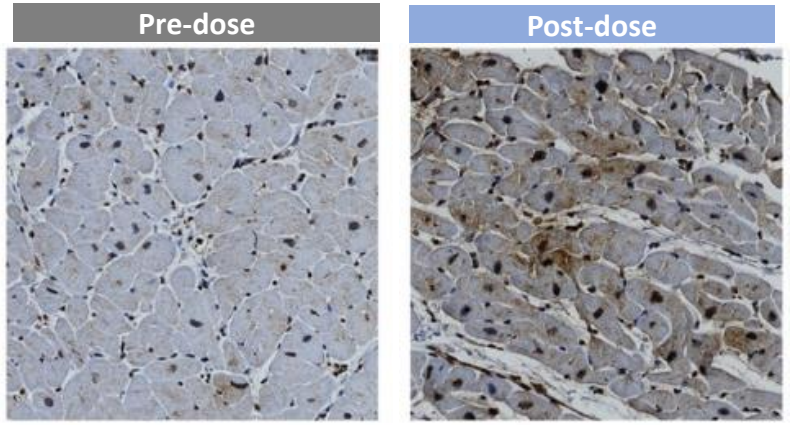


Quantified IHC (FXN % Positive Area[1])

	Pre-Dose	Post-Dose	% Increase
(C1) Participant 6	31%	51%	+65%
(C2) Participant 10	18%	54%	+209%
(C2) Participant 11	7%	26%	+279%

Average Post-Dose IHC of 44%

IHC images from Participant 10



LCMS, Liquid chromatography mass spectrometry; FXN, Frataxin; IHC, Immunohistochemistry. Note: Participant 9 IHC data could not be interpreted reliably due to technical issues due to sample quality.
(1) Area measurement in square microns, FXN area as a percentage of total tissue showing FXN expression.

Baseline Characteristics Consistent with Cardiac Phenotype of FA

Characteristic	Cohort 1 ($1.8x10^{11}$ vg/kg)						Cohort 2 ($5.6x10^{11}$ vg/kg)				
	Participant 1	Participant 2	Participant 3	Participant 4	Participant 5	Participant 6	Participant 7	Participant 8	Participant 9	Participant 10	Participant 11
Gender	F	M	F	F	M	M	F	M	F	F	F
LVMI, g/m^2	81.0	109.0	53.0	65.0	60.0	86.1	63.0	74.0	57.4	65.0	99.5
LWT, cm	1.2	1.1	0.8	1.1	0.9	0.9	0.9	1.0	0.7	1.0	1.0
Hs Troponin I, pg/ml	224	148	147	2023	5	22	53	376	820	650	115
Follow-up, months	18	18	12	12	6	12	<6	<6	12	9	<6

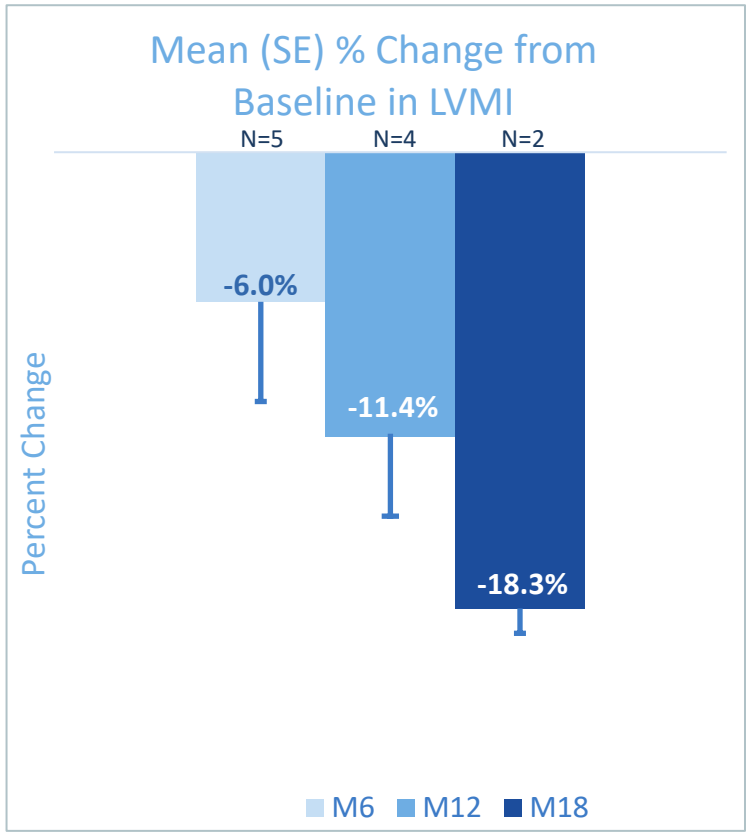
Abnormal(1) High-normal(1) Normal(1)

- 8 of 11 participants have high-normal or abnormal LVMI
- 10 of 11 participants have high-normal or abnormal lateral wall thickness and high-sensitivity Troponin I
- Efficacy data inclusive of 8 participants with ≥ 6 months of follow-up

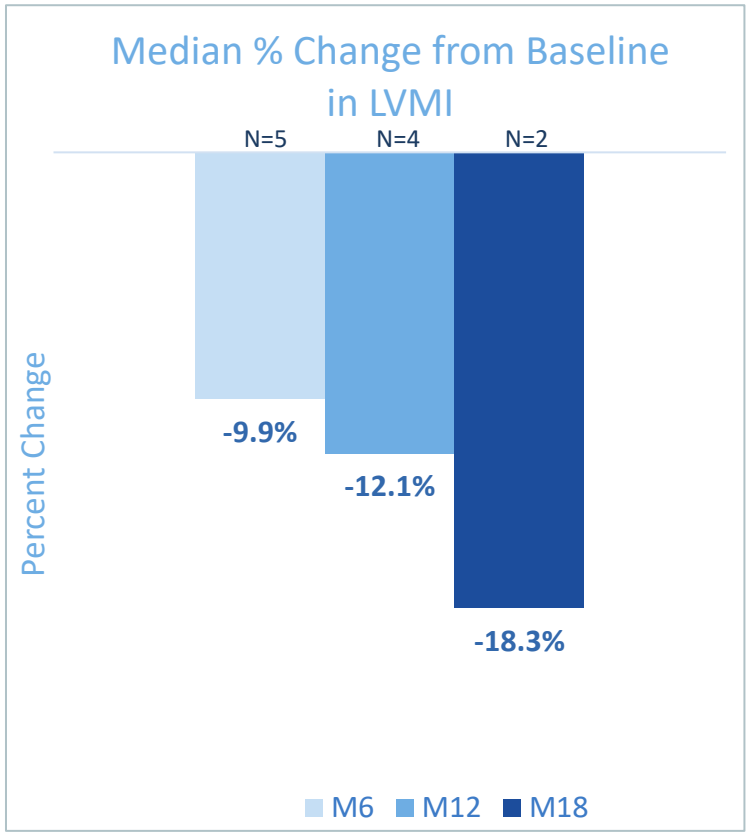
(1) For cardiac imaging, abnormal defined as values 2 standard deviations (SD) above mean and high-normal defined as values 1SD above mean for respective gender (from healthy volunteers) as referenced in Kawel-Boehm et al. *J Cardiovasc Magn Reson* (2020) 22:87 and for hs-troponin I abnormal defined as 99th percentile and high-normal defined as level above the threshold to detect individuals at risk of future CV events as referenced in Zeller at al. *European Heart Journal* (2014) 35, 271–281.

Meaningful LVMI Change from Baseline With Pattern of Increased Improvement Over Time in Participants with Elevated LVMI

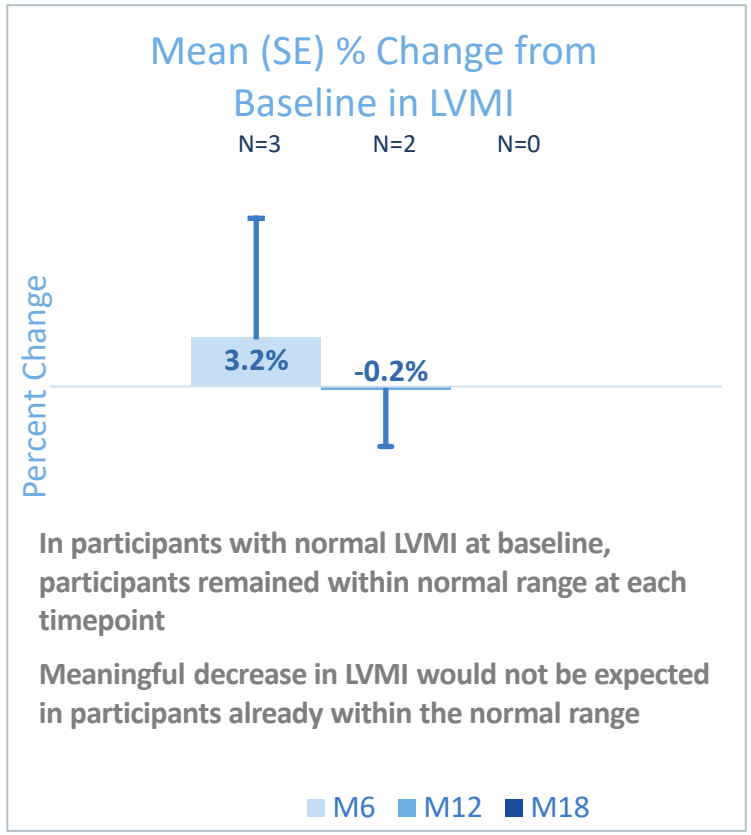
Elevated LVMI at Baseline: Mean Change



Elevated LVMI at Baseline: Median Change



Normal LVMI at Baseline: Mean Change



In participants with elevated LVMI at baseline, continued pattern of improvement with increased reduction over time with >10% reduction on average at 12 months

Note: Elevated defined as 1 or 2 standard deviations above mean for respective gender (from healthy volunteers) as referenced in Kawel-Boehm et al. *J Cardiovasc Magn Reson* (2020) 22:87.
Note: Standard Error of the Mean for Elevated LVMI at Baseline M6=4.0, M12=3.2, M18=1.0; For Normal LVMI at Baseline M6=7.6, M12=3.7

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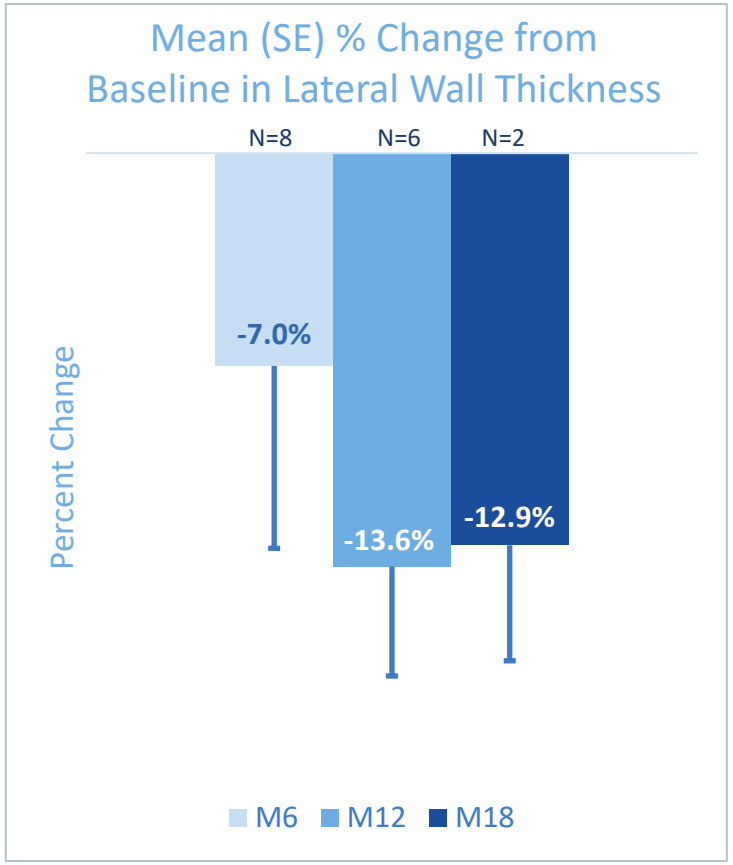
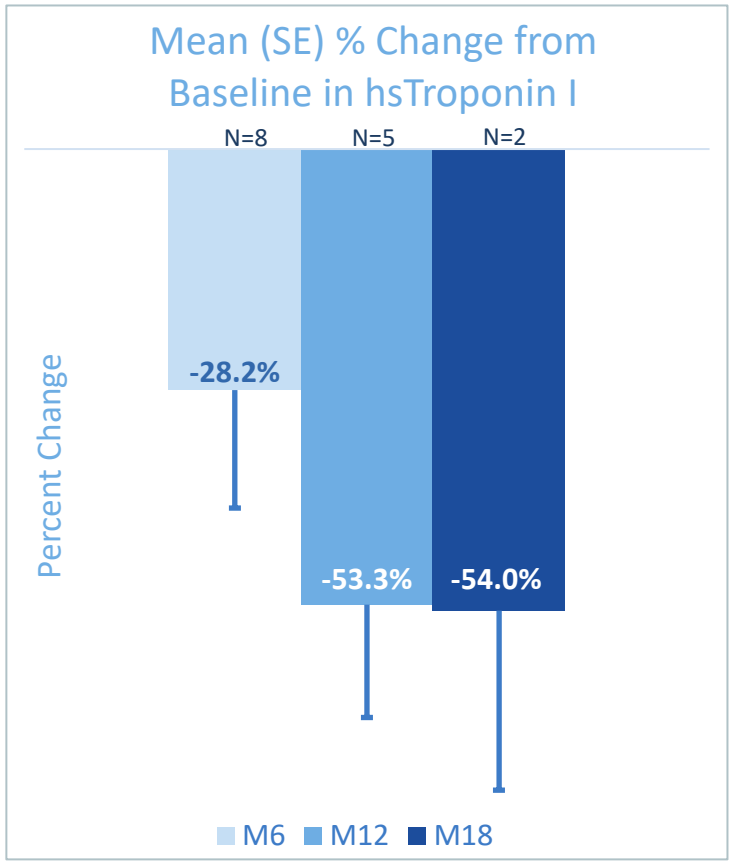
Average Change from Baseline in Other Key Cardiac Measures Demonstrates Pattern of Improvement with Increased Improvement Over Time

All Participants: Change in Lateral Wall Thickness



All Participants: Change in hs-Troponin I



- Continued pattern of improvement with increased reduction from 6 to 12 months
  - Reduction of >10% in lateral wall thickness from baseline in 4 of 6 participants at 12 months
  - Reduction of >25% in hs-troponin I from baseline in 4 of 5 participants at 12 months

Note: Standard Error of the Mean for Lateral Wall Thickness at Baseline M6=6.0, M12=3.6, M18=3.8; For Troponin at Baseline M6=13.7, M12=13.2, M18=21.0
Note: Troponin sample not available for one participant at 12 months.

Regulatory Update Following Type C Meeting Focused on Surrogate Endpoints

Key Registrational Trial Design Element	FDA Alignment
• Increase in frataxin expression and reduction in LVMI as co-primary registrational endpoints to support accelerated approval	✓ Alignment
• Agreed upon target levels, including 10% reduction in LVMI and 40% frataxin positive area as measured by immunohistochemistry	✓ Alignment
• Histology-based measurement of frataxin and cardiac MRI as acceptable measurement tools	✓ Alignment
• Use of secondary endpoints including left ventricular wall thickness and troponin as supportive measures of efficacy	✓ Alignment
• Enrollment of patients with elevated LVMI at baseline in registrational trial	✓ Alignment
• Final dose selection and size of registrational trial guided by cohort 3 biopsy results	Alignment Expected in 2025

LVMI, Left Ventricular Mass Index; MRI magnetic resonance imaging.

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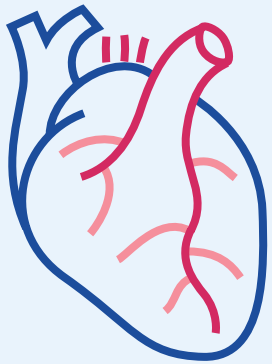
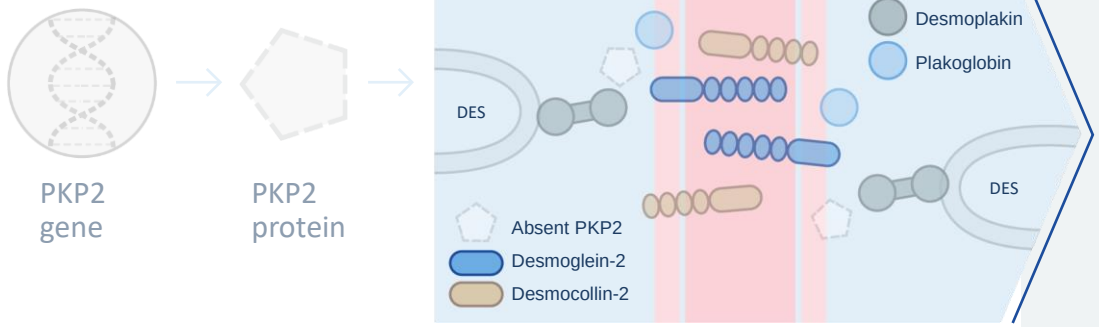
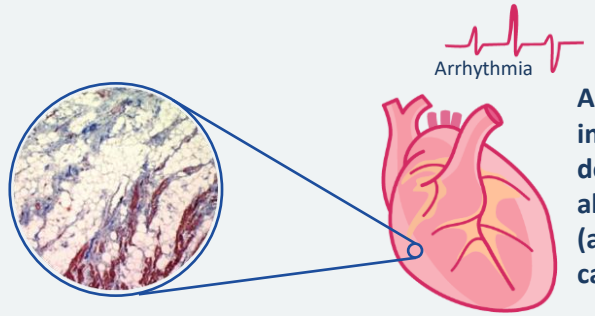
LX2020 (PKP2-ACM)



ACM Caused by Mutations in PKP2 and How LX2020 is Designed to Treat It

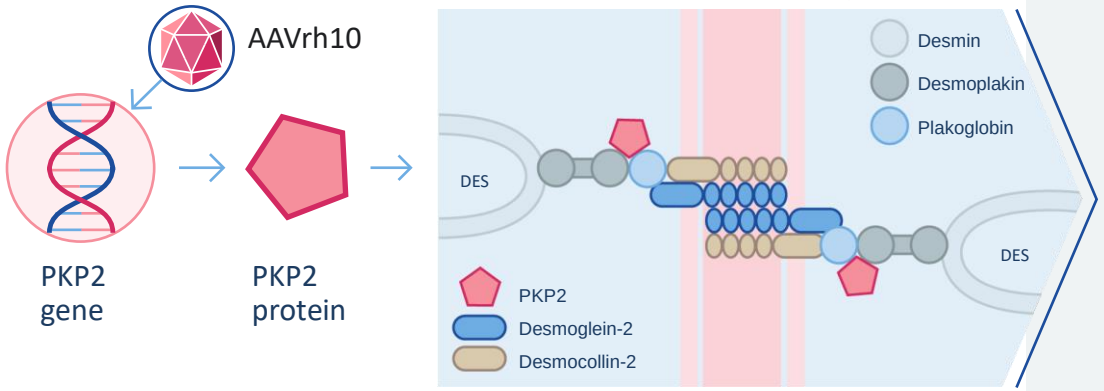
Disease mechanism

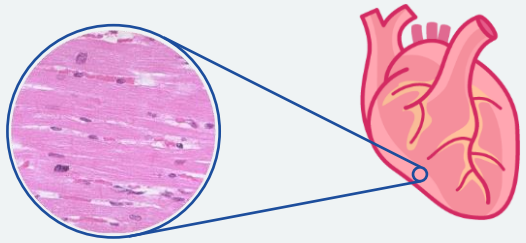




Absence of PKP2 results in impairment of cardiac desmosomes, leading to abnormal cardiac rhythms (arrhythmias) and onset of cardiac dysfunction

LX2020 mechanism





Delivering a functional PKP2 gene to cardiac muscle to increase desmosomal PKP2 protein levels, reassemble desmosomes and restore myocardial cell function

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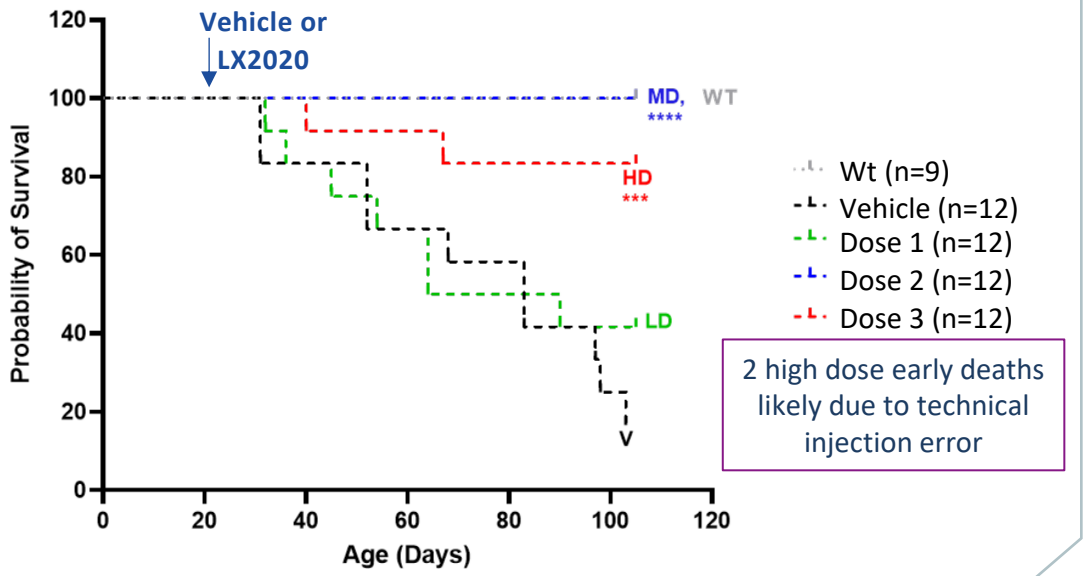
Robust Preclinical Package Supporting Ongoing Phase 1/2 Trial

Robust Preclinical Package

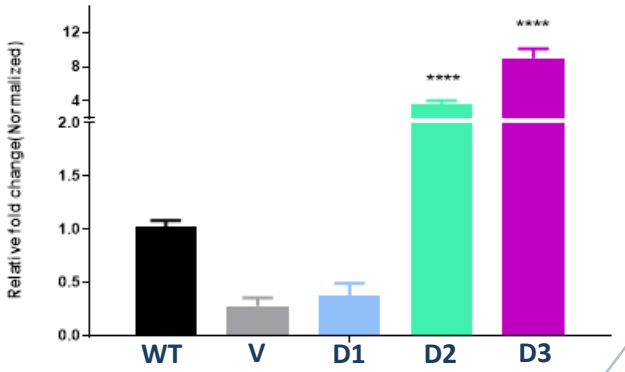
- Murine studies utilizing CRISPR-Cas 9 edited model recapitulating PKP2-ACM disease features
- NHP safety study showed no toxicity at highest evaluated dose levels (low x10^{14} vg/kg)

LX2020 Significantly Extended Survival in Severe Mouse Model

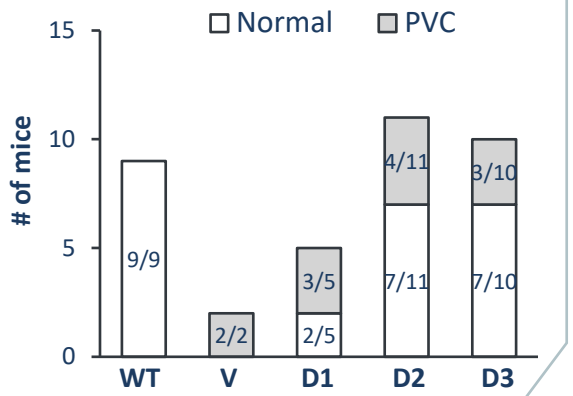


2 high dose early deaths likely due to technical injection error

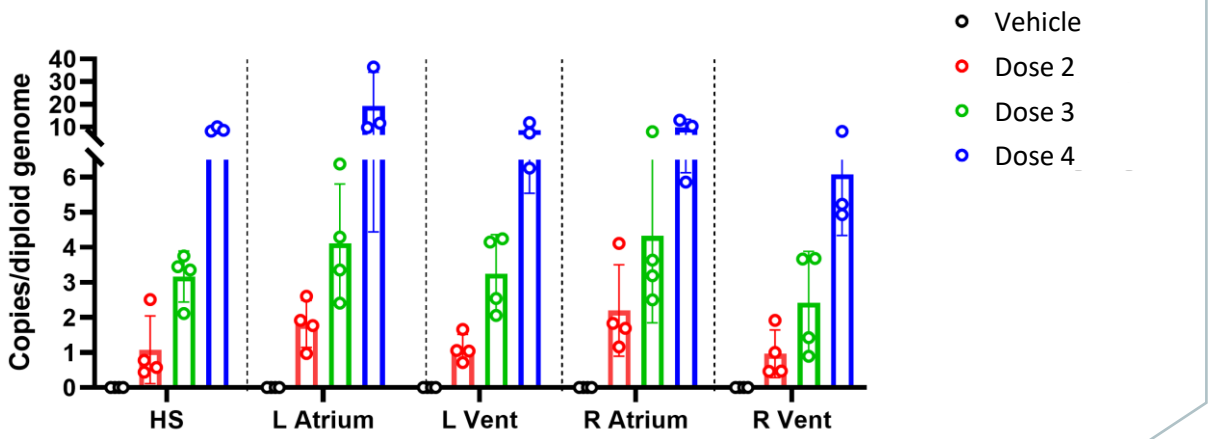
Quantification of PKP2 Expression in Severe Mouse Model



PVC Analysis in Severe Mouse Model



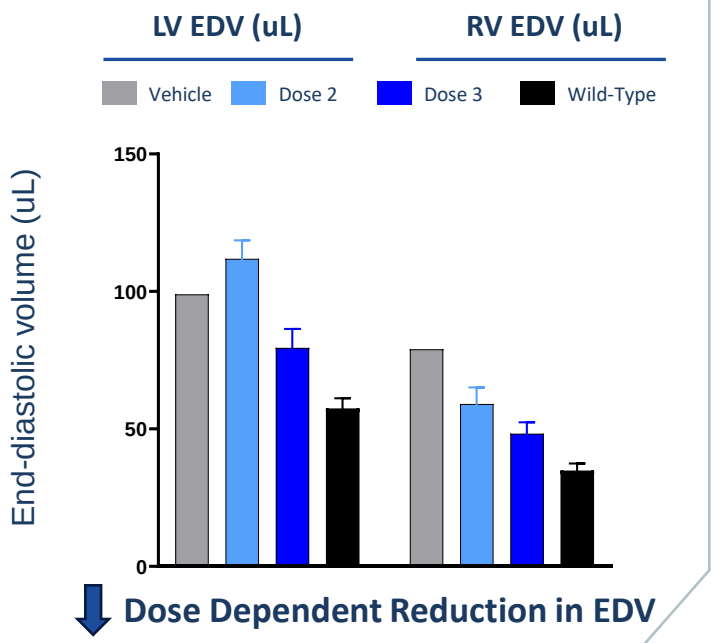
IND-Enabling NHP: VCN in Various Heart Regions



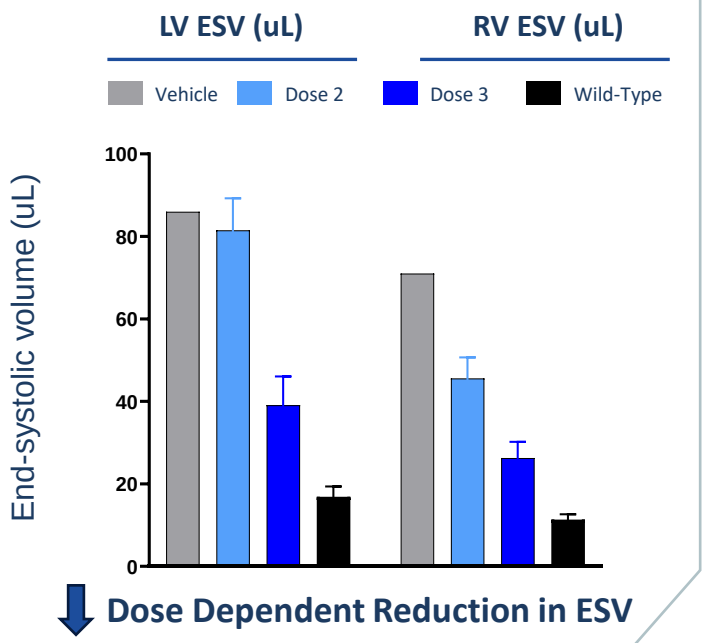
Note: PVC = premature ventricular contractions; VCN = vector copy number.

Quantitative MRI Analysis Showed Improvement in Cardiac Function in Homozygous Mouse Model

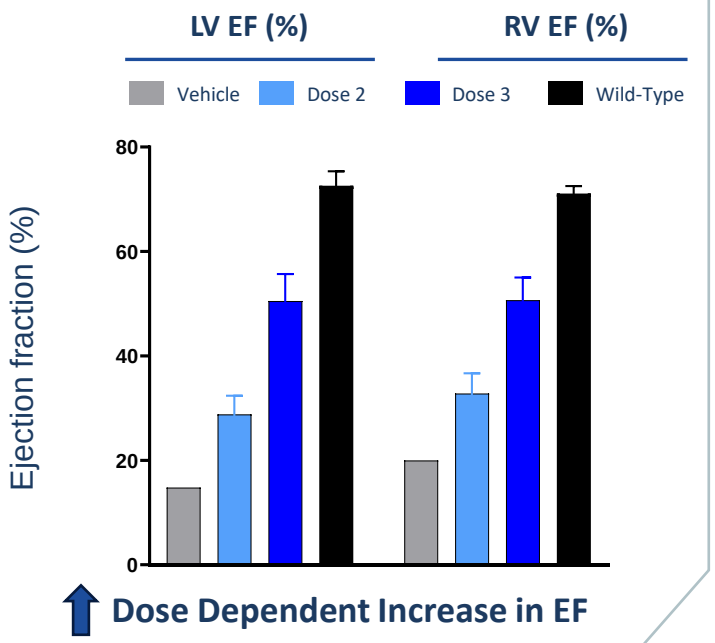
End-Diastolic Volume



End-Systolic Volume



Ejection Fraction



Quantitative MRI showed improved LV and RV ejection fraction and cardiac function in mid and high dose groups. RV improvements are most relevant as it is the primary ventricle impacted in PKP2-ACM

Note: LV = left ventricle; RV = right ventricle.

In Preclinical Studies LX2020 Successfully Impacted All Modifiable Elements of ACM Diagnosis and Risk Calculator

		LX2020 Preclinical Evidence
Arrhythmias	**Arrhythmia Burden** Daily Premature Ventricular Contraction (PVC) Count	↓ **Ectopic Beats** (7/10 without PVC)
	Life-threatening Arrhythmia Events SCD, ICD Shocks, VT/VF Events	↑ **Survival** (100%)
Repolarization & Depolarization	**Depolarization/Repolarization Abnormalities** T-wave Inversions/ QRS Complex	↓ **QRS Interval** (18% reduction)
Cardiac Structure & Function	**Cardiac Contractility** RV Dysfunction and Enlargement	↑ **Cardiac Fxn/EF** ↓ **Cardiac Dilation**
	Cardiac Structure/Function Myocardial Tissue Integrity (Fibrosis, Calcifications, Fragility)	↓ **Fibrosis, Calcifications, & Tissue Tearing**

LX2020 preclinical data demonstrated improvement across key areas for determining ACM diagnosis and risk profile

Note: PVC = premature ventricular contractions; VCN = vector copy number.

LX2020 PKP2-ACM Phase 1/2 (HEROIC-PKP2) Overview

Key Features:

- 52-week, dose-ascending, open-label trial with long-term follow-up (5-years post dose)
- Vector: AAVrh10
- Route of Administration: systemic administration
- Immune Suppression: prednisone + rapamycin

Key Inclusion Criteria:

- Male or female 18-65 years of age
- Confirmed diagnosis of ACM with either 2010 Task Force Criteria or 2020 International Criteria for ACM as affected
- Documented PKP2 mutation
- Existing implantable cardioverter defibrillator (ICD) that is MRI compatible
- Minimum threshold of PVCs/24-hr

Trial Design

52-Week

Cohort 1
n=3

$2.0x10^{13}$ vg/kg

Cohort 2
n=3 (potential for cohort expansion)

$6.0x10^{13}$ vg/kg

Cohort 1 fully enrolled

Endpoints

Primary Endpoint: Safety

Additional Endpoints:

- Change in ventricular arrhythmias and associated clinical events
- Change in 12-lead ECG
- Change in cardiac MRI and ECHO
- Change in cardiac biomarkers (including troponin and BNP)
- Change in Patient Symptoms (NYHA Functional Class and PROs)
- Change in PKP2 cardiac transduction & protein expression (cardiac biopsy)

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APOE4-Associated Alzheimer's Disease

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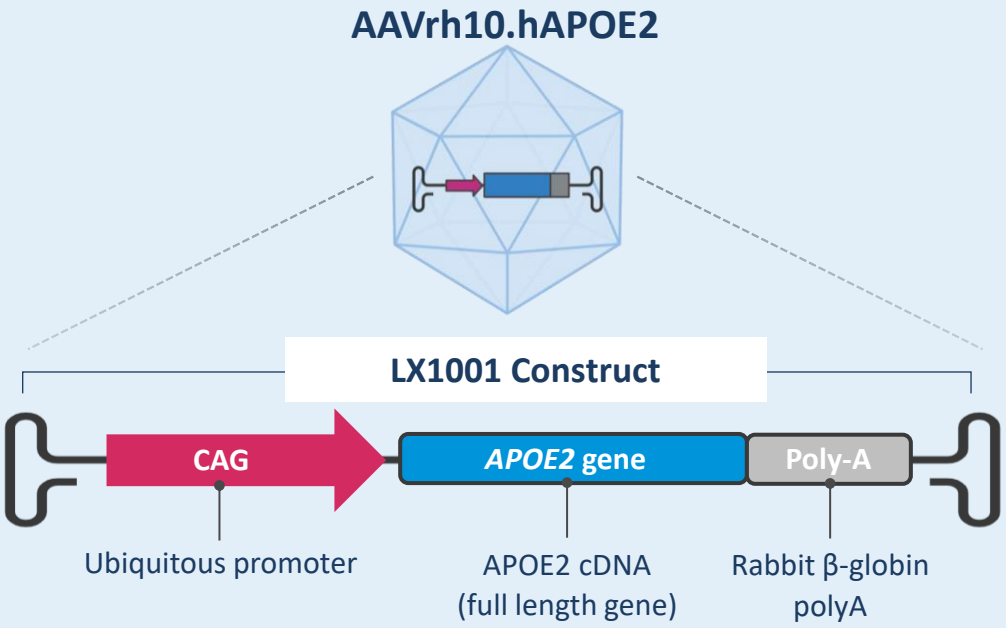
Unique Approach to Targeting Underlying Genetics of APOE4/E4 Alzheimer's Disease

LX1001

Phase 1/2

Mechanism of Action:

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



- ✓ **APOE2 is protective** across multiple pathways, suppressing Aß and tau toxicity
- ✓ **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 – Results Presented at 2024 CTAD

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

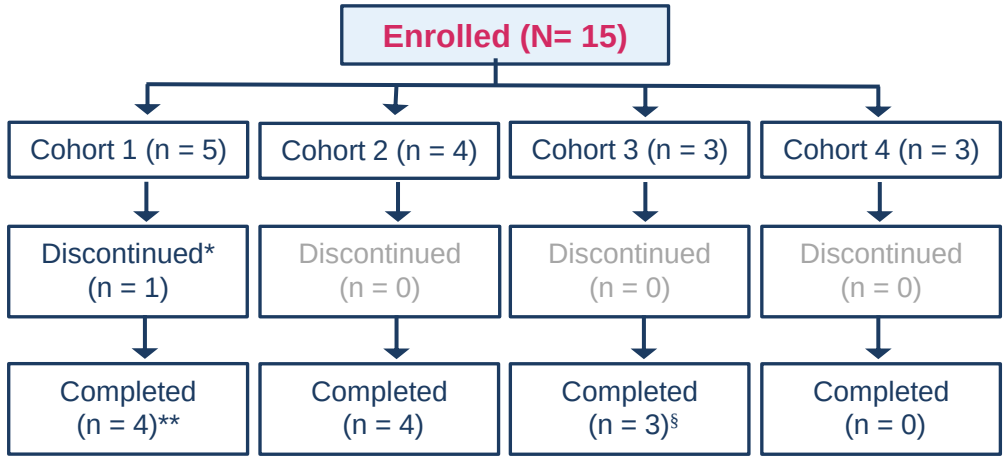
Primary Endpoint: Safety

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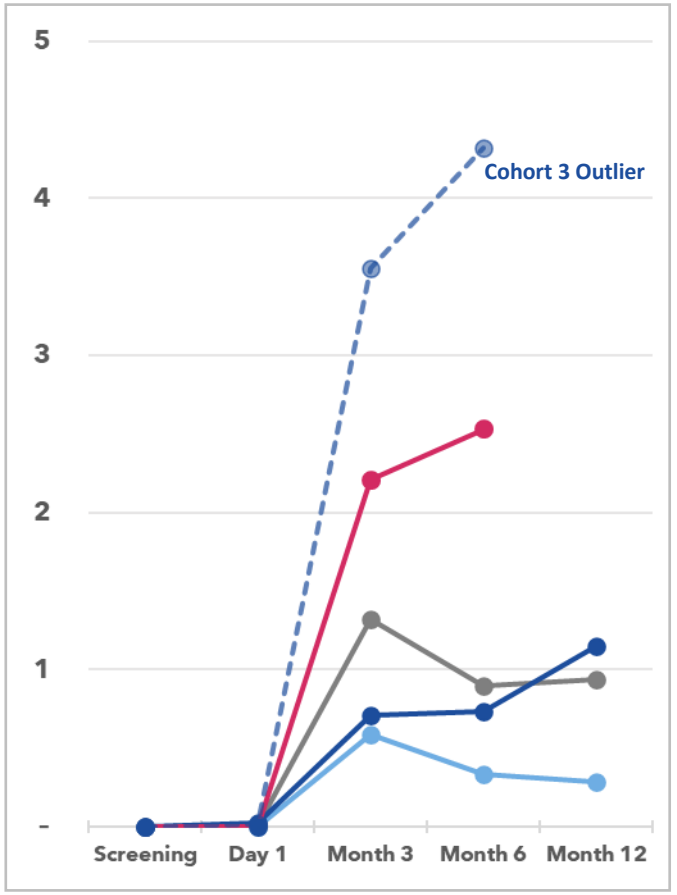
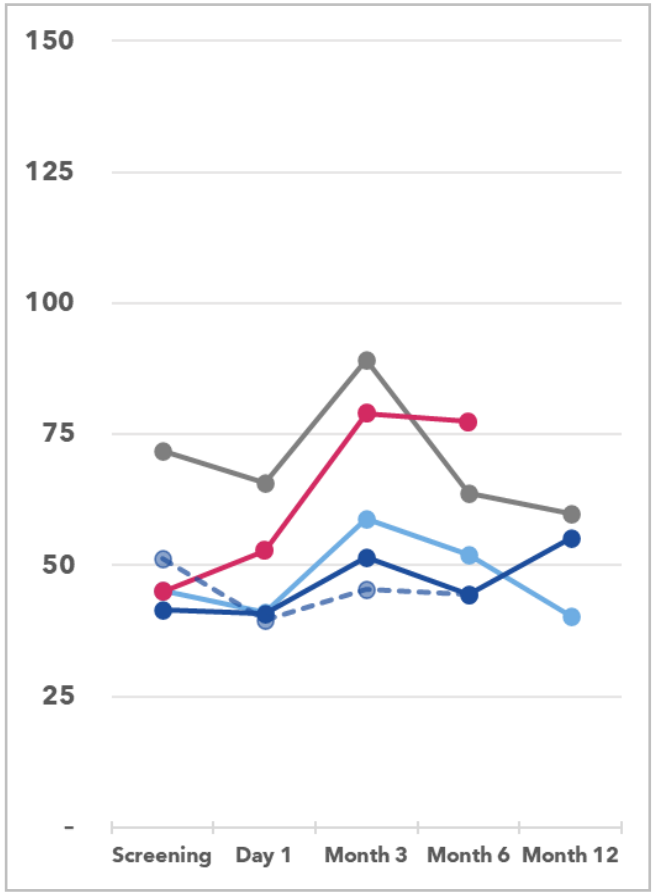
APOE2 Protein Expressed in CSF in All Participants, with Dose- and Time-Dependent Increase in Expression and Durability to 12 Months

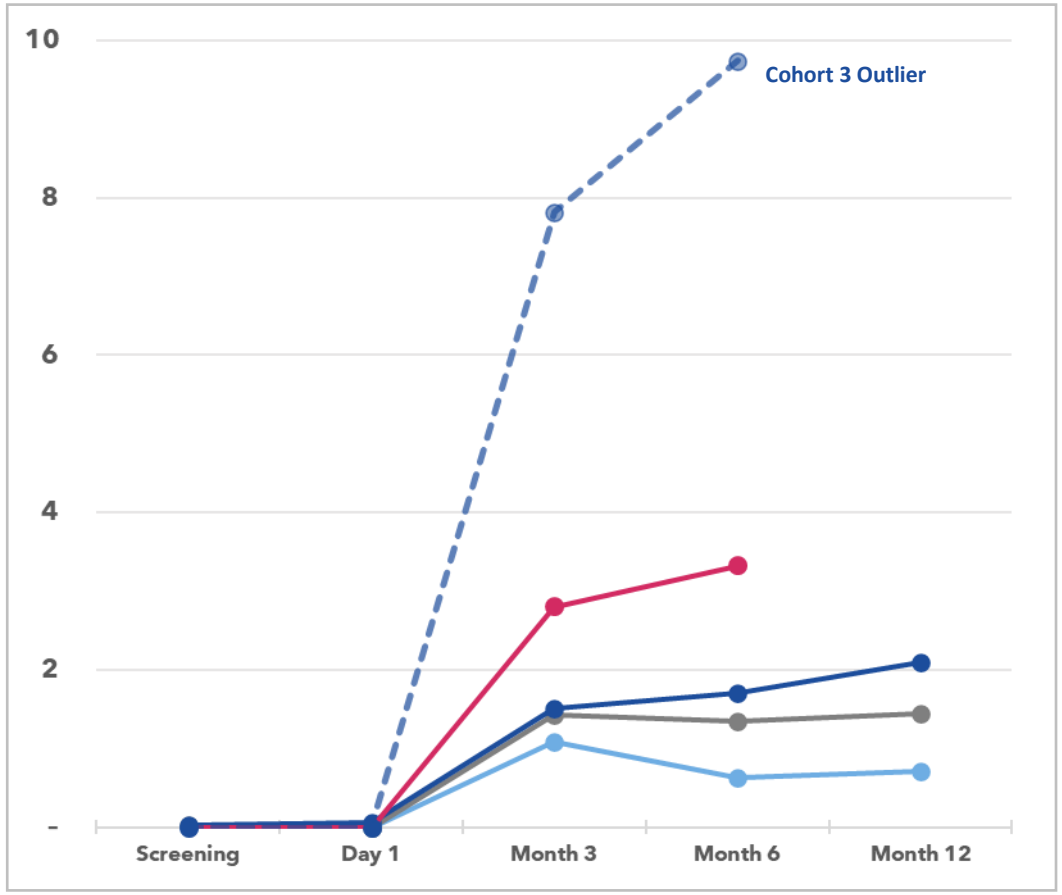
APOE2 (fmol/µl) – Mean



APOE4 (fmol/µl) – Mean



APOE 2:4 Ratio (%) – Mean



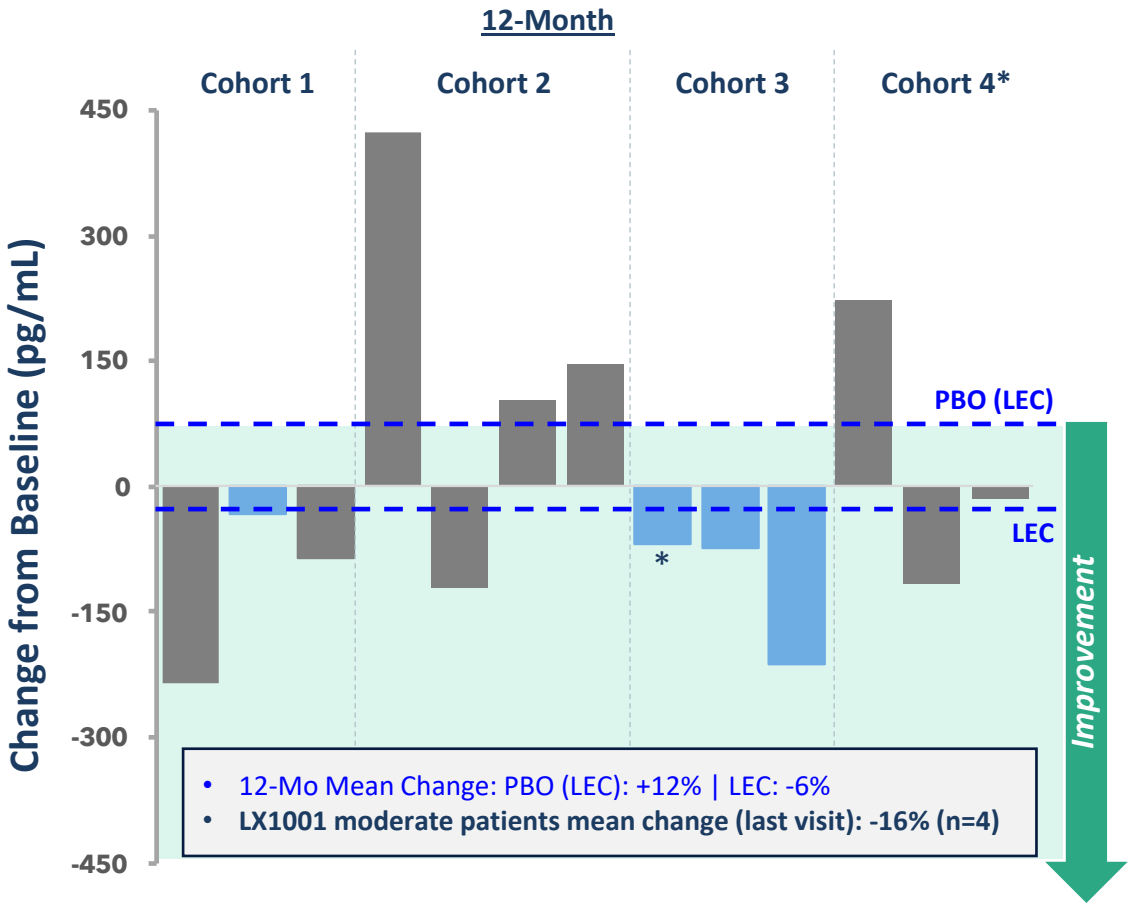
Cohort 1 Cohort 2 Cohort 3 Cohort 4

	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

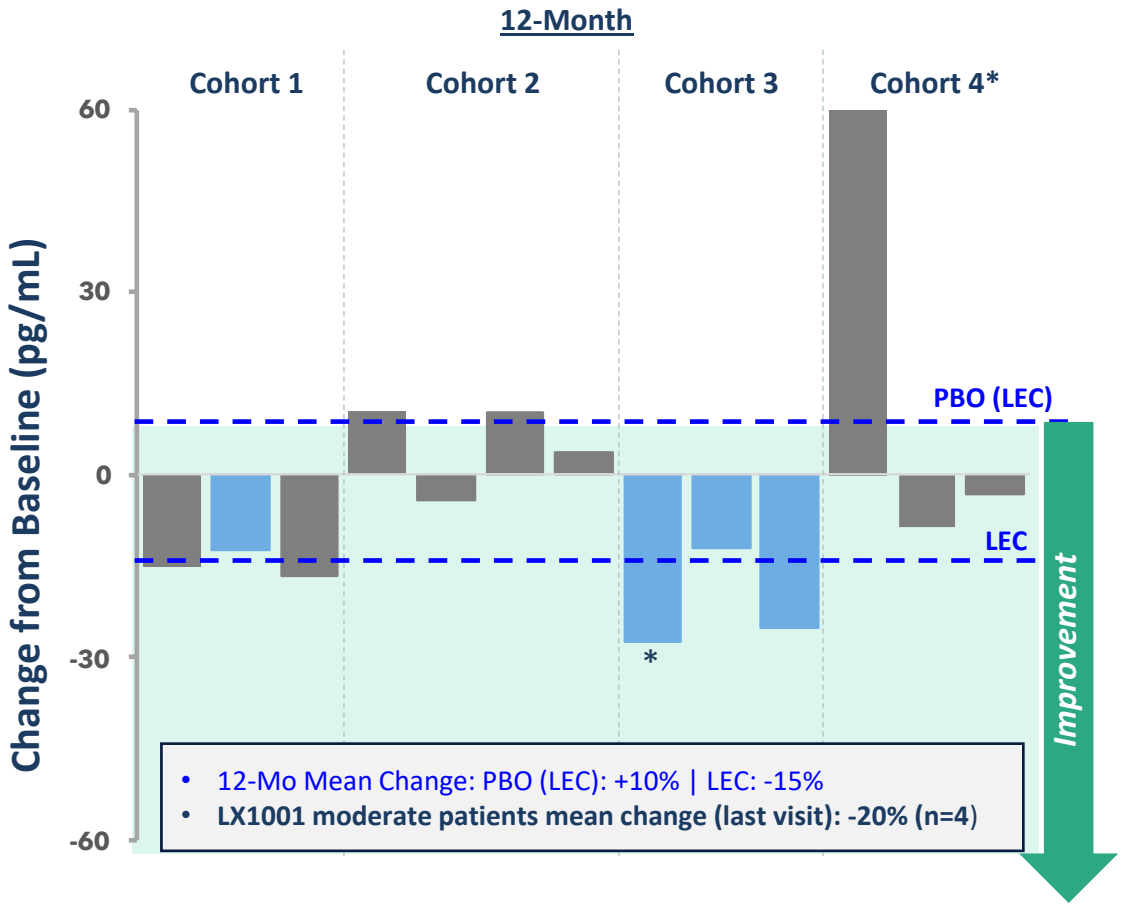
*excludes Cohort 3 outlier

LX1001 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.

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LX1001 Interim Phase 1/2 Key Takeaways

1 Safety

- ✓ **Well-tolerated across all cohorts**
- ✓ **No reports of ARIA**
- ✓ **Four SAEs, one possibly treatment related event of mild-moderate sensorineural hearing loss with repeat audiometry pending**

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**

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

Significant Progress in 2024 Across Lead Programs Supported by Strong Balance Sheet

Program	Upcoming Milestones	US Prevalence
LX2006 FA Cardiomyopathy	• Mid 2024: Interim Data Readout ✓ • Year End 2024: Update on ongoing regulatory engagements ✓	~5K
LX2020 PKP2-ACM	• Late Q1/Early Q2 2025: Interim Data Readout (Cohort 1)	~60K
LX1001 Alzheimer's: APOE4	• October 2024: Interim Phase 1/2 Data Readout ✓	~900K
LX2021 DSP Cardiomyopathy	• 2024: Initiate IND-enabling Studies	~35K

Upcoming Program Milestones to be Announced at 2025 JPMorgan Healthcare Conference

Cash and marketable securities[1]	Projected runway into	Shares of common stock outstanding[2]
~$157M	2027	33.1M
Balance sheet as of September 30, 2024	Significant runway following key catalysts	Shares outstanding as of November 11, 2024

(1) Cash, cash equivalents and investments in marketable securities as of September 30, 2024.
(2) Shares outstanding as of November 11, 2024.

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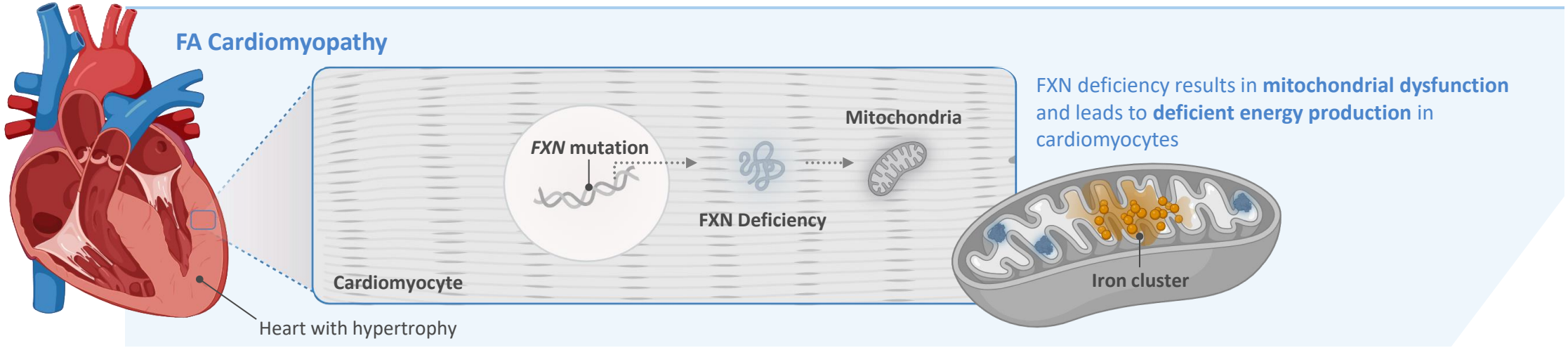
Thank you

Appendix

Friedreich Ataxia is a Result of Mutations in the Frataxin Gene, Leading to Impaired Mitochondrial Function in the Heart



- FA is caused by mutations in the gene Frataxin (*FXN*), resulting in reduced FXN protein expression
- Reduced FXN protein expression decreases mitochondrial iron-sulfur cluster formation, causing mitochondrial dysfunction across multiple cells including cardiomyocytes
- Mitochondrial dysfunction leads to impaired cellular energy production and mitochondrial proliferation
- Impaired energetics and mitochondrial proliferation speculated to lead to cardiac hypertrophy and cell death

Small Increases in Frataxin Following Treatment May Produce Clinical Benefits

Modest FXN Levels Resulted in Near Normal Cardiac Function in FA Murine Model

YG8-800 FA Murine Model

- YG8-800 mice have **5% of normal frataxin levels** in the heart, with approximately 800 GAA repeats, but display **near normal** cardiac output and stroke volume(1)
- Suggests **potential to improve cardiac phenotype with restoration to modest frataxin levels**

Moderate Restoration of Protein Function Correlates with Better Disease Prognosis and Physiological Improvement in Other Diseases

Hemophilia B

- In humans, factor IX clotting activity is typically 50 – 150%(2)
- Individuals with > 40% usually have normal coagulation *in vivo*(2)
- Clinical data indicates even a **small increase to 5% of normal factor IX levels significantly reduces bleeding**(3)

Muscular Dystrophies

- In DMD **dystrophin is virtually absent**; whereas individuals with BMD have **10 – 40% of normal**, resulting in a milder disease with later onset and slower progression than DMD(4)
- Suggests **incremental dystrophin levels could result in improved clinical phenotype**(4)

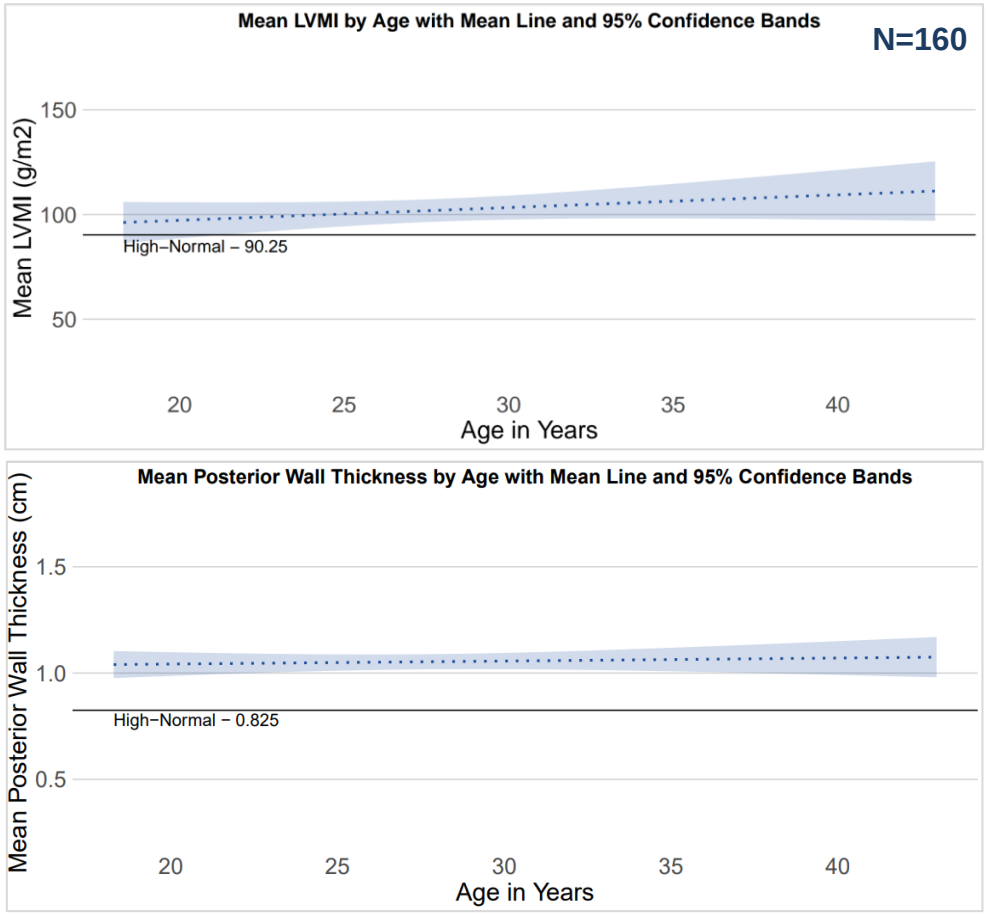
Existing literature suggests small increases in frataxin may be sufficient to produce physiological improvement

BMD, Becker Muscular Dystrophy; DMD, Duchenne Muscular Dystrophy; FXN, Frataxin; GAA, Guanine-adenine-adenine.

(1) Gérard C, et al. *Behav Brain Res,* 2023. (2) Konkle BA, Fletcher SN. *Gene Reviews,* 2000 [Updated 2023]. (3) Nathwani AC. *Hematology Am Soc Hematol Educ Program,* 2022.
(4) Bellayou et al. *Journal Biomedicine Biotechnology,* 2009.

LVMI is Elevated in Individuals with FA Cardiomyopathy, and Not Expected to Decrease Without Intervention

Natural History Data of Adults with FA Cardiomyopathy Show Elevated LVMI and Posterior Wall Thickness (PWT)[1]



Across Multiple Randomized Controlled Trials, No Significant Change Observed in LVMI or LV Mass (LVM) in Control Arms

Disease	Measure	LVMI / LVM Percent Change from Baseline in Placebo/Control Arm
Fabry Disease	LVMI at 18 months on ERT[2]	**-2 g/m² (-2.2%)**
Amyloidosis (ATTR)	LVM at 18 Months[3]	**+0.6g (0.3%)**
HCM	LVMI at 30 Weeks[4]	**-1.6 g/m² (-1.7%)**

-10% 0% 10%

Note: Percent change in LVM / LVMI calculated based on change applied to baseline levels.

In other cardiac diseases, LVMI does not significantly decrease without intervention

(1) Subset analysis performed by Lexeo Therapeutics including adults 18-50 years old with abnormal relative wall thickness, LV mass or LVMI (n=160; 830 echocardiographs) from a natural history cohort followed primarily at Children's Hospital of Philadelphia of FA patients including children and adults. (2) Hughes DA, et al. *J Med Genet,* 2017;54:288–296. Migalastat. (3) Solomon S, et al. *Circulation,* 2018. Patisiran. (4) Saberi S, et al. *Circulation,* 2021;143:606–608. Mavacamten.