

## 6,974,248 Shares of Common Stock



This prospectus supplement is being filed to update and supplement the information contained in the prospectus dated April 12, 2024 (as supplemented from time to time, the "Prospectus"), which forms a part of our registration statement on Form S-1 (No. 333-278566), with the information contained in our Current Report on Form 8-K filed with the Securities and Exchange Commission on October 9, 2024 (the "Current Report"). Accordingly, we have attached the Current Report to this prospectus supplement. This prospectus relates to the offer and resale from time to time of up to 6,974,248 shares (the "Shares") of common stock, par value \$0.0001 per share ("Common Stock"), of Lexeo Therapeutics, Inc., a Delaware corporation (the "Company"), by the selling stockholders identified in this prospectus, including their transferees, pledgees or donees or their respective successors (the "Selling Stockholders"). The Shares consist of (i) 6,278,905 shares which were issued and sold to the Selling Stockholders on March 13, 2024 (the "Closing Date") in a private placement (the "Private Placement") pursuant to a common stock purchase agreement among us and such Selling Stockholders dated March 11, 2024 (the "Purchase Agreement") and (ii) 695,343 shares of Common Stock held by the Selling Stockholders as of March 11, 2024. Concurrently with the Purchase Agreement, we entered into a registration rights agreement (the "Registration Rights Agreement") with the Selling Stockholders, and we are registering the Shares being offered hereunder pursuant to such registration rights agreement on behalf of the Selling Stockholders, to be offered and sold by them from time to time.

This prospectus supplement updates and supplements the information in the Prospectus and is not complete without, and may not be delivered or utilized except in combination with, the Prospectus, including any amendments or supplements thereto. This prospectus supplement should be read in conjunction with the Prospectus and if there is any inconsistency between the information in the Prospectus and this prospectus supplement, you should rely on the information in this prospectus supplement.

Our Common Stock is listed on The Nasdaq Global Market ("Nasdaq") under the symbol "LXEO". On October 8, 2024, the last quoted sale price for our Common Stock as reported on Nasdaq was \$8.75 per share.

We are an "emerging growth company" and a "smaller reporting company" as defined under the federal securities laws, and, as such, may elect to comply with certain reduced public company reporting requirements for this prospectus and for future filings.

**Investing in our securities involves a high degree of risk. Before buying any securities, you should carefully read the discussion of the risks of investing in our securities in "Risk Factors" beginning on page 13 of the Prospectus.**

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

Prospectus supplement dated October 9, 2024

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

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**FORM 8-K**

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**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 09, 2024**

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**Lexeo Therapeutics, Inc.**

(Exact name of Registrant as Specified in Its Charter)

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**Delaware**  
(State or Other Jurisdiction  
of Incorporation)

**001-41855**  
(Commission File Number)

**85-4012572**  
(IRS Employer  
Identification No.)

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

**10010**  
(Zip Code)

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

N/A

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

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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 9, 2024, Lexeo Therapeutics, Inc. (the “**Company**”) posted on its website an updated corporate presentation (the “**Corporate Presentation**”), noting the Company expects to share Cohort 1 data from LX2020 for the treatment of PKP2-ACM in the late first quarter or the early second quarter of 2025 and that the Company plans to present data from LX1001 for the treatment of APOE4-associated Alzheimer’s disease at the Clinical Trials on Alzheimer’s Disease conference in October 2024. The Corporate Presentation will be used from time to time in meetings with investors and analysts. A copy of the Corporate Presentation is attached hereto as Exhibit 99.1 and is incorporated by reference herein.

### Cautionary Note Regarding Forward-Looking Statements

This report contains certain forward-looking statements regarding the business of the Company that are not a description of historical facts within the meaning of the Private Securities Litigation Reform Act of 1995. Forward-looking statements include statements regarding the Company’s expected plans with respect to clinical trials of the Company’s gene therapy candidates and the timing for announcement of data from such trials. Actual results could differ materially from those anticipated in such forward-looking statements as a result of various risks and uncertainties, which include, without limitation, expectations regarding the initiation, progress, and expected results of the Company’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 and liquidity and capital resources. Additional risks and uncertainties that could cause actual results to differ materially from those contemplated by the forward-looking statements are included in the Company’s Annual Report on Form 10-K for the fiscal year ended December 31, 2023, Quarterly Report on Form 10-Q for the quarter ended June 30, 2024 and subsequent future filings the Company may make with the Securities and Exchange Commission from time to time that are available at [www.sec.gov](http://www.sec.gov).

You are cautioned not to place undue reliance on forward-looking statements which are current only as of the date hereof. Except as required by applicable law, the Company undertakes no obligation to revise or update any forward-looking statement, or to make any other forward-looking statements, whether as a result of new information, future events or otherwise.

### Item 9.01 Financial Statements and Exhibits.

(d) Exhibits.

Exhibit Number	Description
99.1	<a href="#">Corporate Presentation, dated October 9, 2024</a>
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 9, 2024

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



# Lexeo Therapeutics Corporate Overview

October 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 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 Team

## Management Team & Key Advisors



**R. Nolan Townsend**  
Chief Executive Officer



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



**Sandi See Tai, M.D.**  
Chief Development Officer



**Jenny R. Robertson**  
Chief Business and Legal Officer



**José Manuel Otero, Ph.D.**  
Chief Technical Officer



**Rajiv Patni, M.D.**  
Senior Advisor to the CEO  
and Board of Directors



## Chair and Scientific Founder



**Steven Altschuler, M.D.**  
Chairman



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



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

Former Chief,  
Pulmonary Branch



Founder / Co-founder of **DVERUM**, **GENVEC**, **XyloCor Therapeutics**

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



# Revolutionizing Genetic Medicines for Cardiovascular Diseases and APOE4-

## Attractive Disease Area Strategy

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

Genetic Variant or Disease Phenotype



### 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<sup>(1)</sup>

APOE4 homozygotes demonstrated lower efficacy results compared to heterozygotes and noncarriers



### Higher Risk of ARIA-E<sup>(1)</sup>

APOE4 homozygotes were associated with a higher incidence of ARIA-E compared to heterozygotes and noncarriers

Focused on genetically-defined cardiovascular diseases with data from Alzheimer's disease driving business development

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 Investment Highlights

Clinical-stage genetic medicine company addressing larger-rare and prevalent patient populations



### Cardiac Portfolio

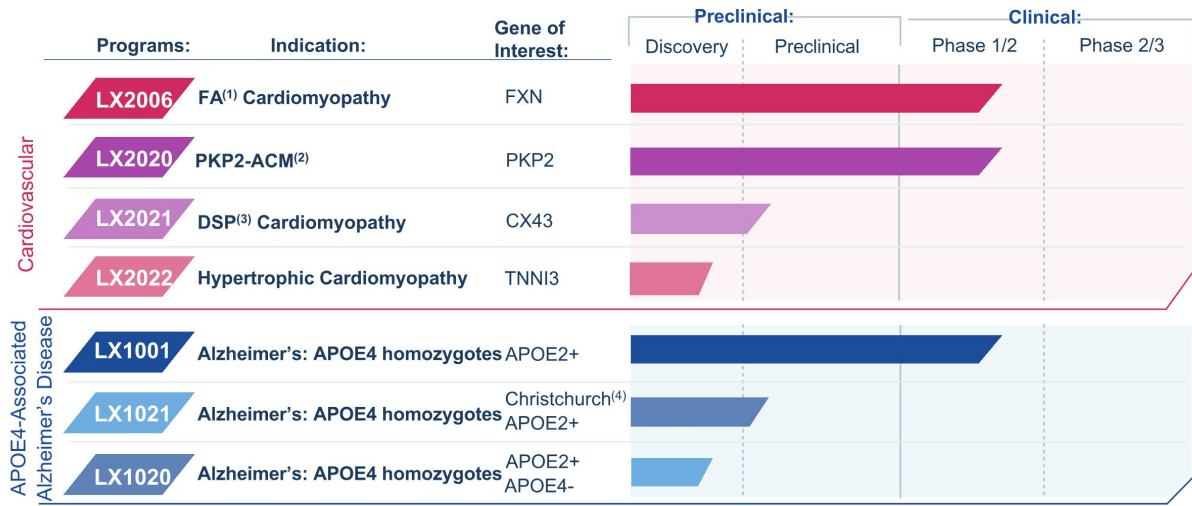
- Ongoing Phase 1/2 trial for **Friedreich ataxia cardiomyopathy** with interim clinical results shared in July 2024
  - **Mean reduction in LVMI of 11.4%** at 12 months in participants with elevated LVMI at baseline (n=4)
  - Clinically meaningful **reductions in LV wall thickness and hs-troponin I**
  - Increased **post-treatment frataxin expression above baseline** in all participants evaluated via myocardial biopsy
- Ongoing Phase 1/2 trial for the treatment of **arrhythmogenic cardiomyopathy caused by mutations in the PKP2 gene (PKP2-ACM)**



### APOE4 Alzheimer's Portfolio

- **Significant optionality on portfolio of approaches to treat the genetics underlying APOE4-associated Alzheimer's disease;** estimated 900,000 E4 homozygotes in the US
- **Observed a decline in CSF biomarkers** in initial clinical data from Cohort 1 of ongoing Phase 1/2 clinical study of LX1001
- Phase 1/2 data readout to be shared at the CTAD conference in October 2024 **potentially driving business development**

# Advancing Genetic Medicines in Larger-Rare and Prevalent Patient Populations

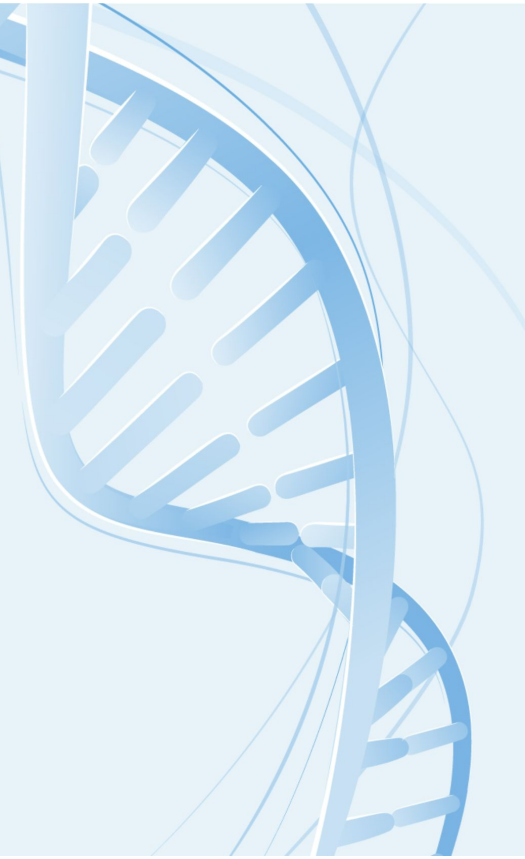
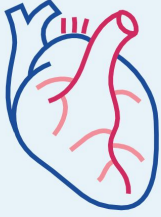


**Lexeo retains global rights across all programs**



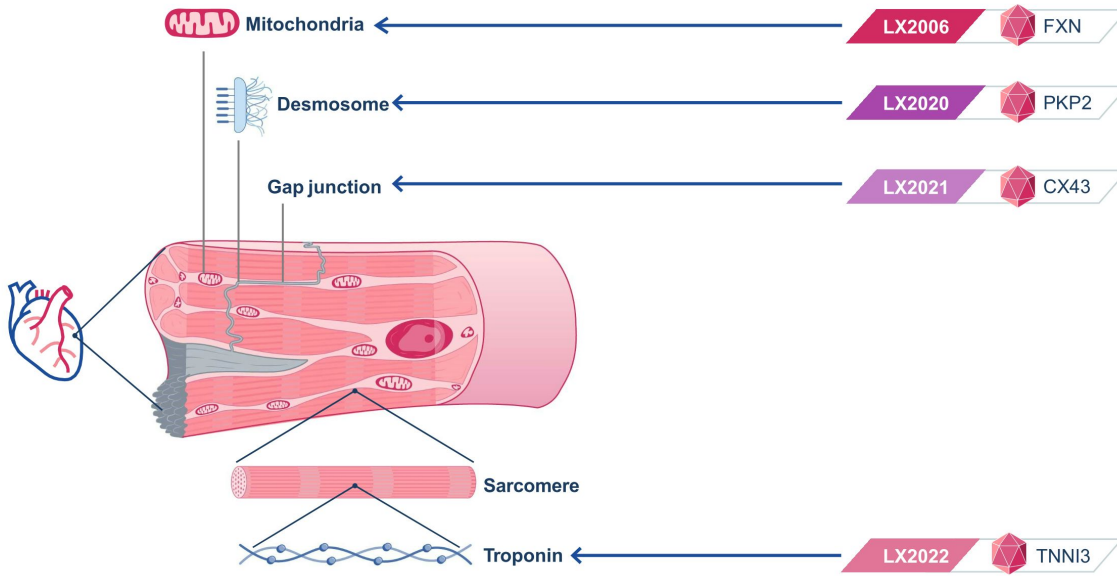
(1) Friedreich Ataxia. (2) Plakophilin 2 Arrhythmogenic Cardiomyopathy. (3) Desmoplakin. (4) Christchurch Modified APOE2 gene.

# Cardiovascular diseases





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





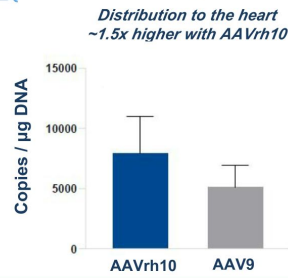
# Utilizing AAVrh10 for Initial Genetic Cardiac Indications

- ✓ 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

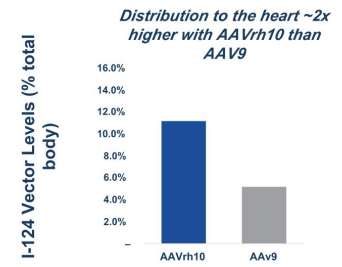
## Compelling Cardiac Tropism



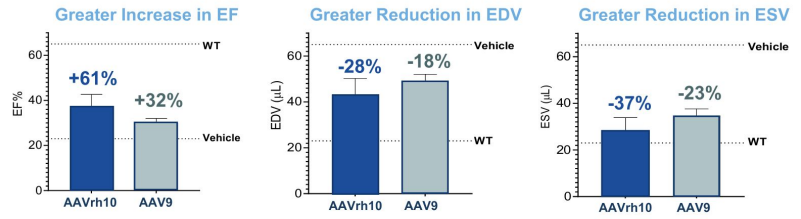
### Yucatan Minipig Biodistribution<sup>(1)</sup>



### NHP Biodistribution<sup>(2)</sup>



## Greater Trends of Functional Improvement Versus AAV9 in PKP2-ACM Model<sup>(1)</sup>

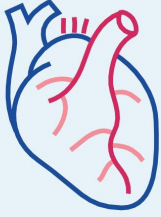


Note: PKP2 homozygous mouse model administered with human PKP2 (N = 5 mice / group).

(1) Data presented at ASGCT 2023.

(2) Ballon DJ et al, Human Gene Therapy, 2020.

# LX2006 (FA Cardiomyopathy)



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

LX2006

FA Cardiomyopathy



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<sup>(1)</sup>



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.<sup>(2)</sup>



**~15,000**  
individuals  
affected by FA  
worldwide<sup>(2)</sup>

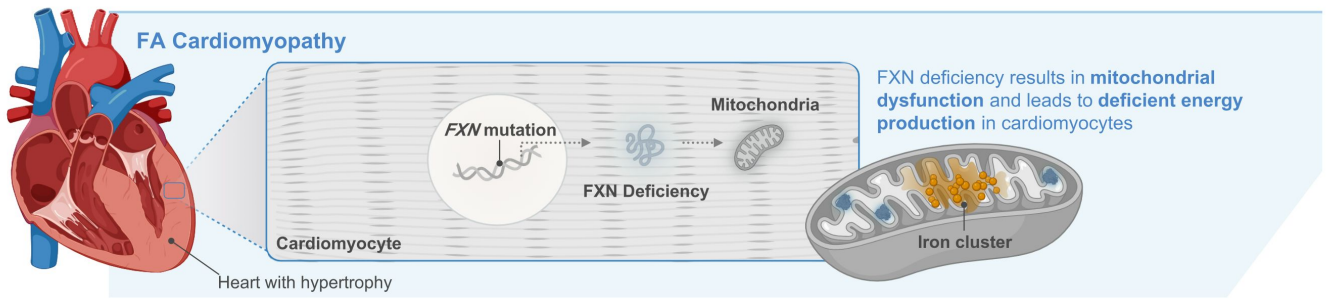
Cardiac dysfunction is the cause of  
death in **60-80%** of those with  
FA<sup>(3)(4)</sup>

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.

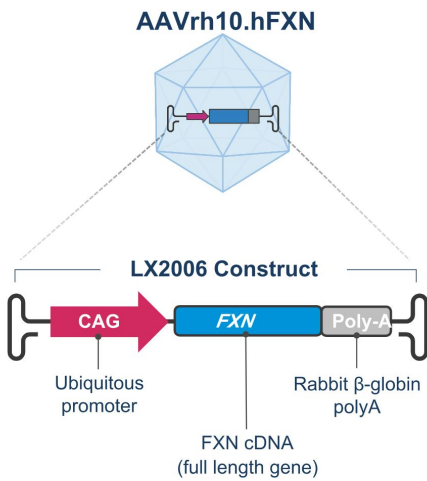
**LEXEO**  
therapeutics

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

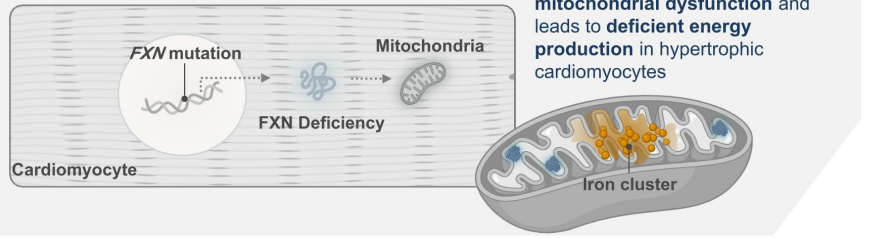


- FA is caused by mutations in the gene Frataxin (*FXN*), resulting in reduced *FXN* protein expression
- Reduced *FXN* protein expression decreases mitochondrial iron-sulfur cluster formation, causing mitochondrial dysfunction across multiple cells including cardiomyocytes
- Mitochondrial dysfunction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

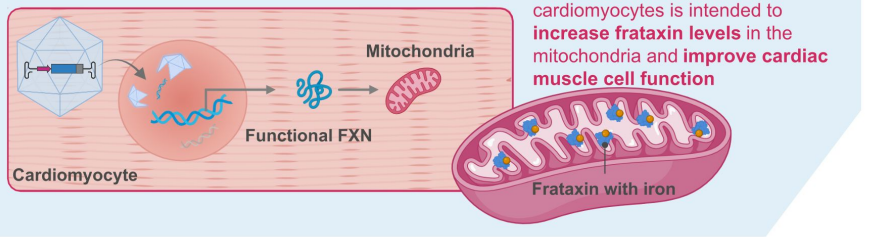
# LX2006 Has the Potential to Treat the Root Cause of FA Cardiomyopathy: The Significant Decrease in Frataxin in the Heart



## FA Cardiomyopathy



## LX2006 Mechanism



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

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

**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<sup>(1)</sup>
- 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%<sup>(2)</sup>
- Individuals with > 40% usually have normal coagulation *in vivo*<sup>(2)</sup>
- Clinical data indicates even a **small increase to 5% of normal factor IX levels significantly reduces bleeding**<sup>(3)</sup>

**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<sup>(4)</sup>
- Suggests **incremental dystrophin levels could result in improved clinical phenotype**<sup>(4)</sup>

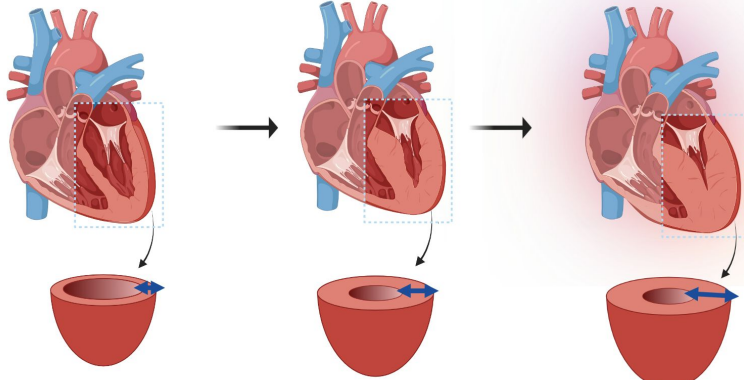
Existing literature suggests small increases in frataxin may be sufficient to produce physiological improvement

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.



## Disease Progression

Normal Heart → Concentric Hypertrophy



Normal LVMI  
Normal LV Wall  
Thickness  
Normal hs-Troponin I

High Normal LVMI  
↑LV Wall Thickness  
↑ Hs-Troponin I

↑LVMI  
↑ LV Wall Thickness  
↑ 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<sup>(1)</sup>
  - Hypertensive cardiomyopathy<sup>(2)</sup>
  - Fabry disease<sup>(3,4)</sup>
  - Obstructive hypertrophic cardiomyopathy (HCM)<sup>(5)</sup>

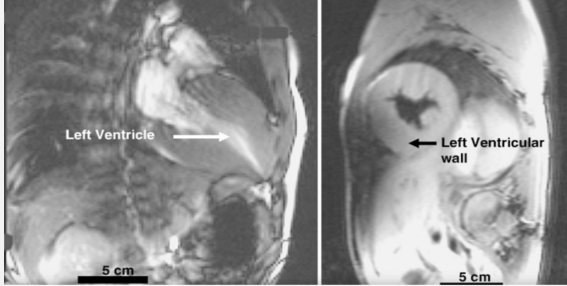
### ✓ Left Ventricular (LV) Wall Thickness

- Early indicator of left ventricular hypertrophy
- Associated with increase in cardiovascular events;<sup>(2)</sup> magnitude of LV wall thickness is directly related to risk of sudden cardiac death in HCM<sup>(6)</sup>

(1) Shah et al, *Journal of American College of Cardiology*, 2019. (2) Muiresan 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.

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

Natural history study showed a 19% higher risk of death per  $10\text{g}/\text{m}^2$  (HR 1.19; 95% CI)<sup>(1)</sup>



**MRI of Individual With FA Cardiomyopathy Demonstrating Significant Hypertrophy**

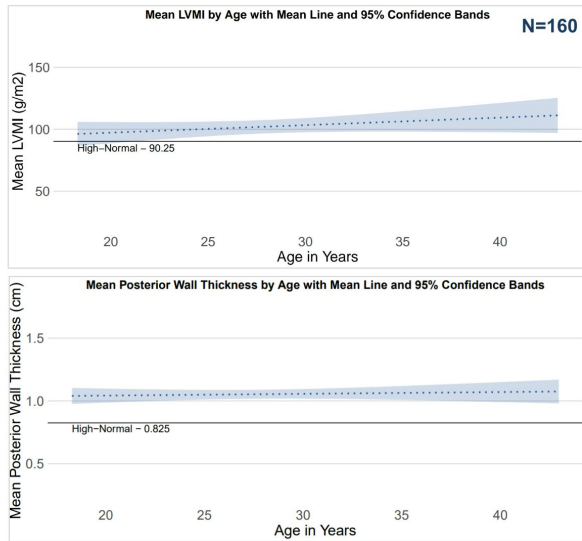
- Concentric hypertrophy is a hallmark of FA cardiomyopathy, including increased LVMI and abnormal left ventricular wall thickness<sup>(1)(2)</sup>
- Natural history suggests a 19% incremental risk of all cause mortality per ~10% increase in LVMI in individuals with FA; increased wall thickness was also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

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



# 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)<sup>(1)</sup>



## 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 <sup>(2)</sup>	-2 g/m <sup>2</sup> (-2.2%)
Amyloidosis (ATTR)	LVM at 18 Months <sup>(3)</sup>	+0.6g (0.3%)
HCM	LVMI at 30 Weeks <sup>(4)</sup>	-1.6 g/m <sup>2</sup> (-1.7%)

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.

- 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
- Both studies share similar inclusion and exclusion criteria, however the Weill Cornell trial does not conduct cardiac biopsies

# Interim Data Update Supports LX2006 as Potential Treatment for FA Cardiomyopathy

Data from Lexeo Sponsored SUNRISE-FA and Weil Cornell Medicine Investigator-Initiated Phase 1/2 Trials

<b>Safety and Tolerability</b>	<ul style="list-style-type: none"> <li>LX2006 well tolerated with no treatment-related serious adverse events to date</li> <li>No signs of complement activation or other immunogenicity</li> <li>No cardiac or hepatic safety signals observed</li> <li>All adverse events were transient and resolved</li> <li>No participants discontinued from either study</li> </ul>				
<b>Cardiac Biomarkers</b>	<table border="1"> <tr> <td data-bbox="341 430 804 568"> <b>LVMi:</b> <ul style="list-style-type: none"> <li>Among participants with elevated LVMi at baseline, 75% achieved &gt;10% improvement at 12 months with mean reduction of 11% at 12 months (n=4) and 18% at 18 months (n=2)</li> <li>Natural history analysis shows elevated LVMi in adults with FA cardiomyopathy, stable to increasing with age</li> </ul> </td> <td data-bbox="804 430 1150 568"> <b>LV Lateral Wall Thickness:</b> <ul style="list-style-type: none"> <li>Early indicator of LV hypertrophy</li> <li>14% mean improvement at 12-months (n=6)</li> </ul> </td> </tr> <tr> <td colspan="2" data-bbox="341 568 1150 692"> <b>Hs-Troponin I:</b> <ul style="list-style-type: none"> <li>Biomarker of myocardial injury</li> <li>53% mean improvement at 12-months (n=5)</li> </ul> </td> </tr> </table>	<b>LVMi:</b> <ul style="list-style-type: none"> <li>Among participants with elevated LVMi at baseline, 75% achieved &gt;10% improvement at 12 months with mean reduction of 11% at 12 months (n=4) and 18% at 18 months (n=2)</li> <li>Natural history analysis shows elevated LVMi in adults with FA cardiomyopathy, stable to increasing with age</li> </ul>	<b>LV Lateral Wall Thickness:</b> <ul style="list-style-type: none"> <li>Early indicator of LV hypertrophy</li> <li>14% mean improvement at 12-months (n=6)</li> </ul>	<b>Hs-Troponin I:</b> <ul style="list-style-type: none"> <li>Biomarker of myocardial injury</li> <li>53% mean improvement at 12-months (n=5)</li> </ul>	
<b>LVMi:</b> <ul style="list-style-type: none"> <li>Among participants with elevated LVMi at baseline, 75% achieved &gt;10% improvement at 12 months with mean reduction of 11% at 12 months (n=4) and 18% at 18 months (n=2)</li> <li>Natural history analysis shows elevated LVMi in adults with FA cardiomyopathy, stable to increasing with age</li> </ul>	<b>LV Lateral Wall Thickness:</b> <ul style="list-style-type: none"> <li>Early indicator of LV hypertrophy</li> <li>14% mean improvement at 12-months (n=6)</li> </ul>				
<b>Hs-Troponin I:</b> <ul style="list-style-type: none"> <li>Biomarker of myocardial injury</li> <li>53% mean improvement at 12-months (n=5)</li> </ul>					
<b>Cardiac Biopsy Analyses</b>	<ul style="list-style-type: none"> <li><b>LCMS:</b> increase in post-treatment FXN levels observed in 3 of 3 participants</li> <li><b>IHC:</b> increase in post-treatment FXN levels observed in 2 of 2 participants</li> </ul>				

## Program Status

- As of July 15, 2024, 13 participants dosed, including 1 participant in Cohort 3
- SUNRISE-FA currently enrolling Cohort 3 (1.2x10<sup>12</sup>vg/kg) and will include at least 3 participants
- The Weill Cornell investigator-initiated trial is currently enrolling in Cohort 2
- Previously disclosed data, and one additional cardiac biopsy from Cohort 2 will be shared at a scientific conference in Fall 2024



Note: Data as of interim clinical update shared July 15, 2024.

# The SUNRISE-FA and Weill Cornell Trials Are Similarly Designed to Assess the Effect of LX2006 in Adults with FA Cardiomyopathy

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 (LCMS and IHC)<sup>(1)</sup>

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.  
(1) Cardiac biopsies are evaluated in SUNRISE-FA only.  
Note: LX2006 is administered systemically; participants receive immune suppression with prednisone beginning on the day prior to treatment through 14 weeks following LX2006 administration.

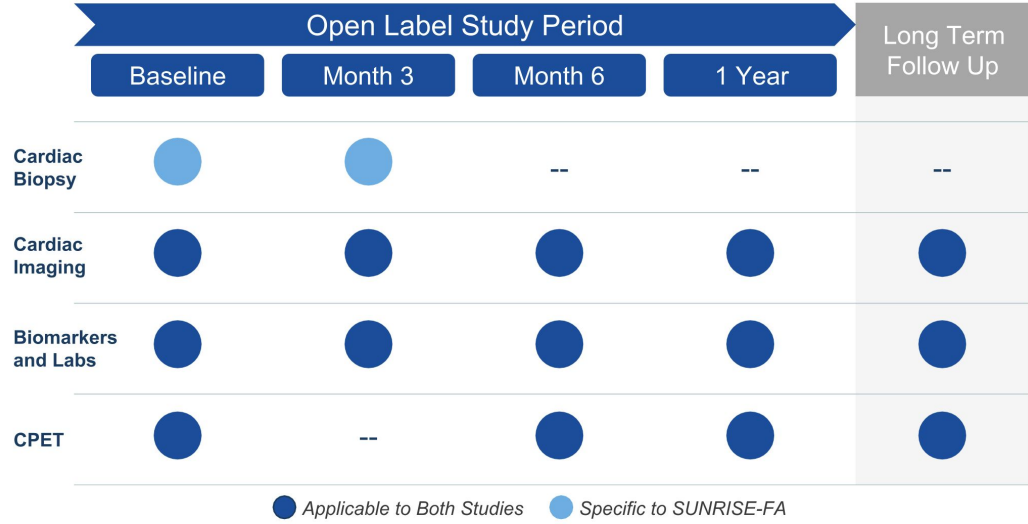
# Both Studies Utilize Similar Metrics to Evaluate Safety and Efficacy

## SUNRISE-FA Lexeo Sponsored

- Cohort 1:  $1.8 \times 10^{11}$  vg/kg
- Cohort 2:  $5.6 \times 10^{11}$  vg/kg
- Cohort 3:  $1.2 \times 10^{12}$  vg/kg  
*Currently Enrolling*

## Weill Cornell Investigator Initiated

- Cohort 1:  $1.8 \times 10^{11}$  vg/kg
- Cohort 2:  $5.6 \times 10^{11}$  vg/kg  
*Currently Enrolling*



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.

Characteristic	Cohort 1 (1.8x10 <sup>11</sup> vg/kg)						Cohort 2 (5.6x10 <sup>11</sup> 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 <sup>2</sup>	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<sup>(1)</sup>    High-normal<sup>(1)</sup>    Normal<sup>(1)</sup>

- 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
- Safety data summarized for all 11 participants; 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 99<sup>th</sup> percentile and high-normal defined as level above the threshold to detect individuals at risk of future CV events as referenced in Zeller et al. *European Heart Journal* (2014) 35, 271–281.

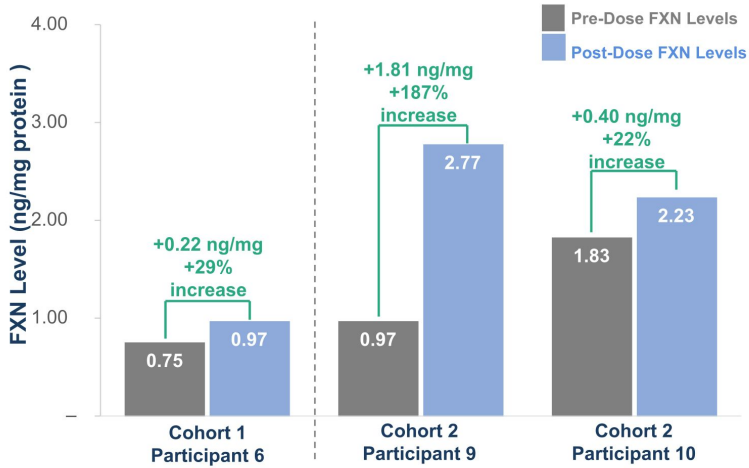
- LX2006 has been well tolerated with no treatment-related serious adverse events
- No signs of complement activation or other immunogenicity
- No cardiac or hepatic safety signals
- All AEs were transient and resolved
- No participants discontinued from either study
- SUNRISE-FA independent Data and Safety Monitoring Board endorsed proceeding to Cohort 3 dose level ( $1.2 \times 10^{12}$ vg/kg)

Note: Data as of interim clinical update shared July 15, 2024.



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

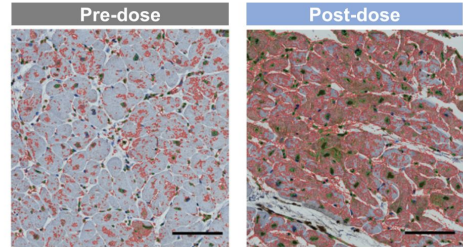
## Pre- and Post-Treatment FXN Levels (LCMS)



## Quantified IHC (FXN % Positive Area<sup>(1)</sup>)

	Pre-Dose	Post-Dose
Participant 6	31%	51%
Participant 10	18%	54%

IHC images from Participant 10



LCMS, Liquid chromatography mass spectrometry; FXN, Frataxin; IHC, Immunohistochemistry.

Note: Frataxin levels measured by ultrahigh performance liquid chromatography-multiple reaction monitoring/mass spectrometry (UHPLC-MRM/MS).

Note: Cohort 1 dose of  $1.8 \times 10^{11}$  vg/kg and Cohort 2 dose of  $5.6 \times 10^{11}$  vg/kg.

Note: Lexeo data on file from healthy cadaver samples (n=29 tissue samples from 16 patients) with mean and median FXN levels of 56.97 ng/mg and 50.84 ng/mg, respectively.

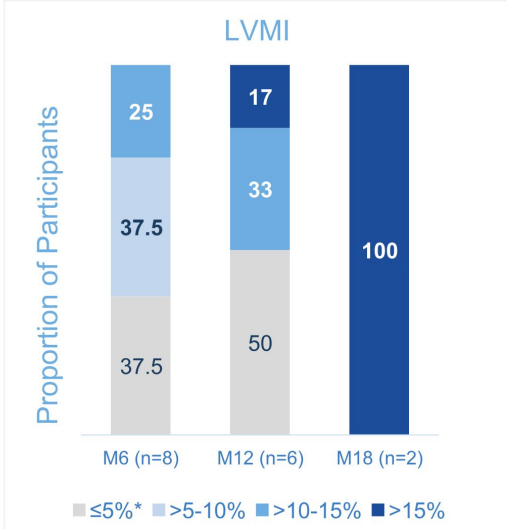
Note: Participant 9 IHC data could not be interpreted reliably due to technical issues due to sample quality.

(1) Area measurement in square microns, FXN area as a percentage of total tissue showing FXN expression.

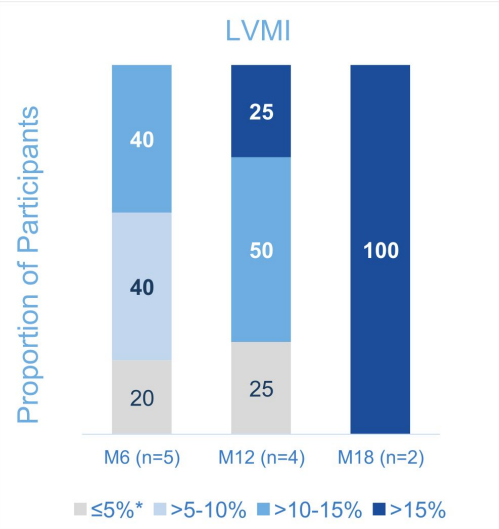


## Across Participants With $\geq 6$ Months of Follow-Up, Percentage of Participants with LVMI Reduction $>10\%$ Increased Over Time

**All Participants:  
Responder Rate by LVMI Reduction**



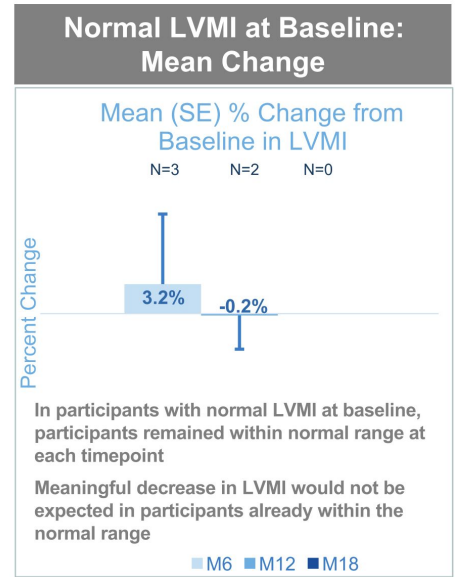
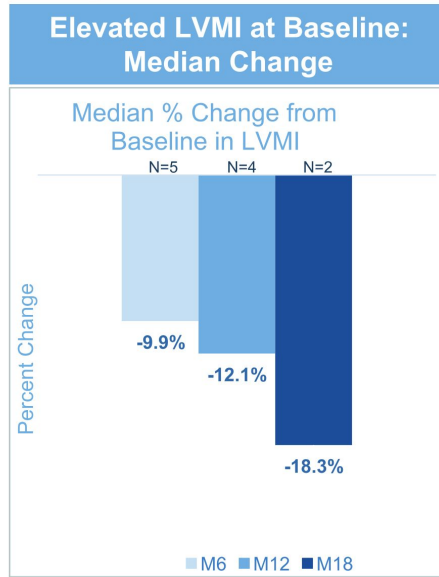
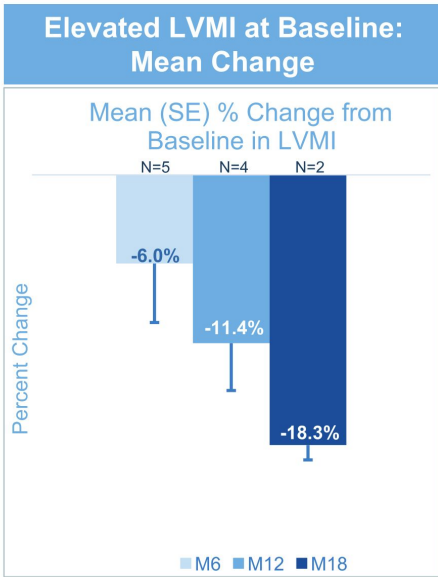
**Elevated LVMI at Baseline:  
Responder Rate by LVMI Reduction**



- Overall by month 12 (M12), 50% experienced a reduction in LVMI greater than 10%
- In participants with elevated LVMI at baseline, 75% experienced a reduction in LVMI greater than 10% by month 12

\*Inclusive of participants with observed increases. LVMI, Left Ventricular Mass Index.  
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.

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

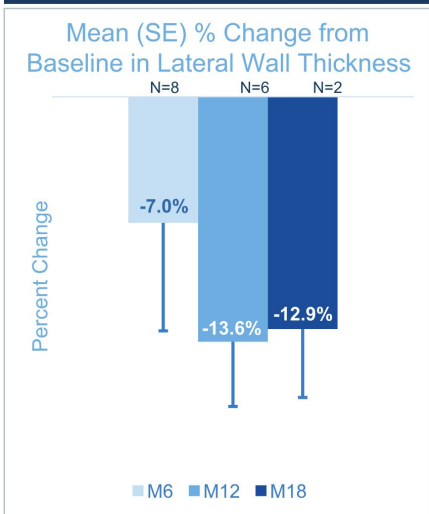


**In participants with elevated LVMI at baseline, continued pattern of improvement with increased reduction over time with >10% reduction on average at 12 months**

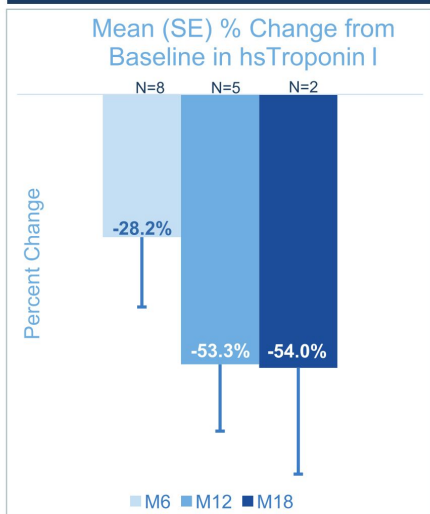
Note: Elevated defined as 1 or 2 standard deviations above mean for respective gender (from healthy volunteers) as referenced in Kawel-Boehm et al. *J Cardiovasc Magn Reson* (2020) 22:87.  
 Note: Standard Error of the Mean for Elevated LVMI at Baseline M6=4.0, M12=3.2, M18=1.0; For Normal LVMI at Baseline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

# 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.

# Multiple Cardiac Assessments in Ongoing Studies of LX2006 Have Regulatory Precedent as Potentially Approvable or Supportive Endpoints

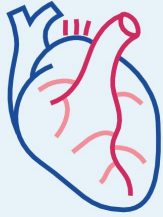
Key Assessment	Ability to Impact	Assessment Method	Timepoints
<b>Transgene Expression (LCMS and IHC)</b> <i>Regulatory Precedent as Approvable Endpoint</i>	✓	Cardiac Biopsy	3 Month <sup>(1)</sup>
<b>Left Ventricular Mass Index</b> <i>Regulatory Precedent as Approvable Endpoint</i>	✓	Cardiac MRI	Months 6,12, Long-Term Follow Up
<b>Lateral Wall Thickness</b> <i>Clinically Meaningful Endpoint</i>	✓	Cardiac MRI	Months 6,12, Long-Term Follow Up
<b>Circulating Blood Biomarkers (hs-Troponin I)</b> <i>Clinically Meaningful Endpoint</i>	✓	Blood Sample	Months 6,12, Long-Term Follow Up

(1) Only evaluated in SUNRISE-FA.

- LX2006 (AAVrh10.hFXN) has been well tolerated with no treatment-related serious adverse events to date
- Improvements in key clinical parameters observed at 12-months:
  - 75% of participants with elevated LVMI at baseline experienced >10% reduction in LVMI (n=4)
  - 14% mean reduction from baseline in lateral left ventricular wall thickness (n=6)
  - 53% mean reduction from baseline in hs-troponin I (n=5)
- As of July 15, 2024, 13 participants dosed, including 1 participant in Cohort 3
  - SUNRISE-FA Data and Safety Monitoring Board endorsed proceeding to Cohort 3 dose level ( $1.2 \times 10^{12}$ vg/kg); this cohort has started enrollment with 1 participant dosed, and will include at least 3 participants
  - The Weill Cornell investigator-initiated trial is currently enrolling in Cohort 2
- Previously disclosed data, and one additional cardiac biopsy from Cohort 2 will be shared at a scientific conference in Fall 2024

Note: Data as of interim clinical update shared July 15, 2024.

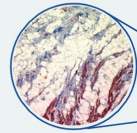
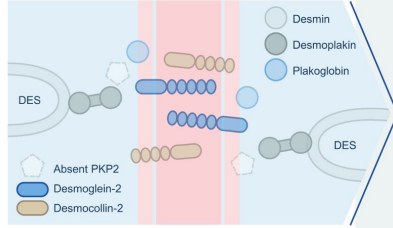
# LX2020 (PKP2-ACM)



**Disease mechanism**



**Desmosomal Complex**

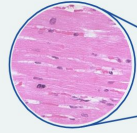
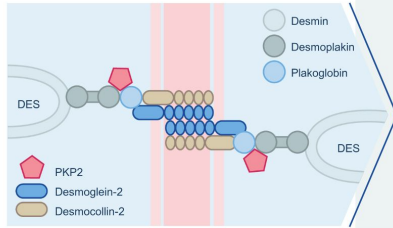


Absence of PKP2 results in impairment of cardiac desmosomes, leading to abnormal cardiac rhythms (arrhythmias) and onset of cardiac dysfunction

**LX2020 mechanism**



**Desmosomal Complex**



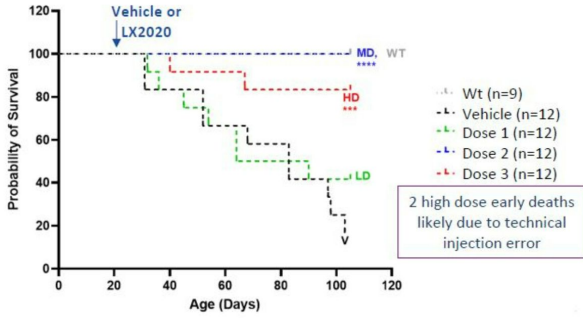
Delivering a functional PKP2 gene to cardiac muscle to increase desmosomal PKP2 protein levels, reassemble desmosomes and restore myocardial cell function



## Robust Preclinical Package

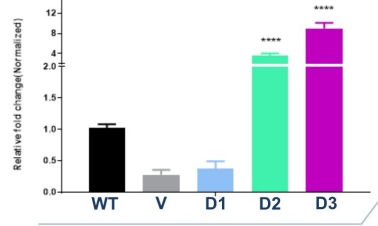
- Murine studies utilizing CRISPR-Cas 9 edited model recapitulating PKP2-ACM disease features
- NHP safety study showed no toxicity at highest evaluated dose levels (low  $\times 10^{14}$  vg/kg)

## LX2020 Significantly Extended Survival in Severe Mouse Model

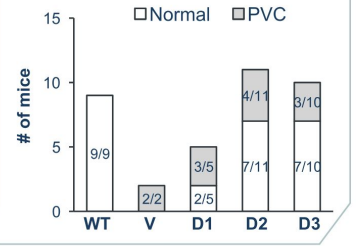


Note: PVC = premature ventricular contractions; VCN = vector copy number.

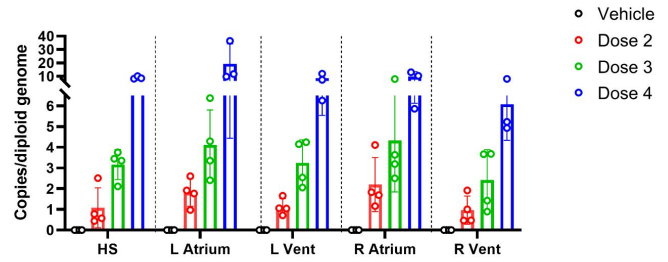
## Quantification of PKP2 Expression in Severe Mouse Model



## PVC Analysis in Severe Mouse Model



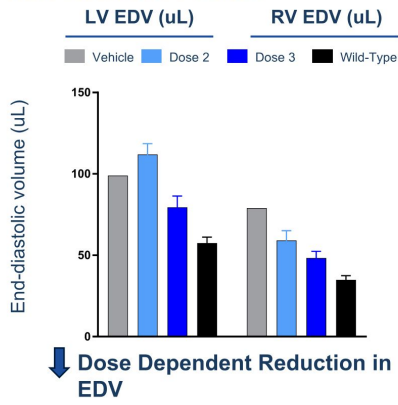
## IND-Enabling NHP: VCN in Various Heart Regions



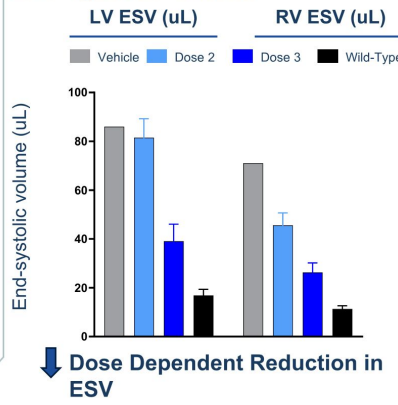


# Quantitative MRI Analysis Showed Improvement in Cardiac Function in Homozygous Mouse Model

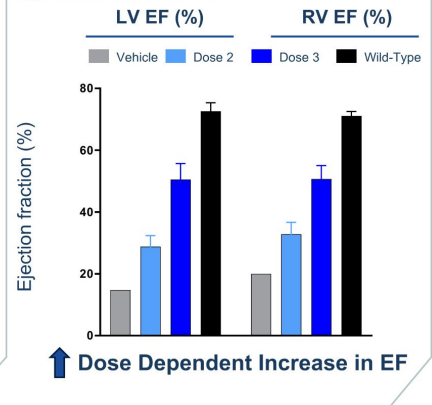
## End-Diastolic Volume



## 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

Arrhythmogenic  
cardiomyopathy

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

**LEXEO**  
therapeutics

### 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

### Endpoints

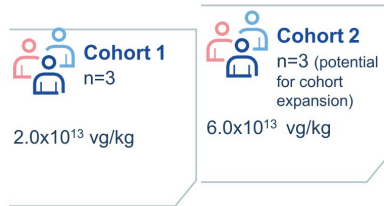
**Primary Endpoint:** Safety

#### 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)

### Trial Design

52-Week



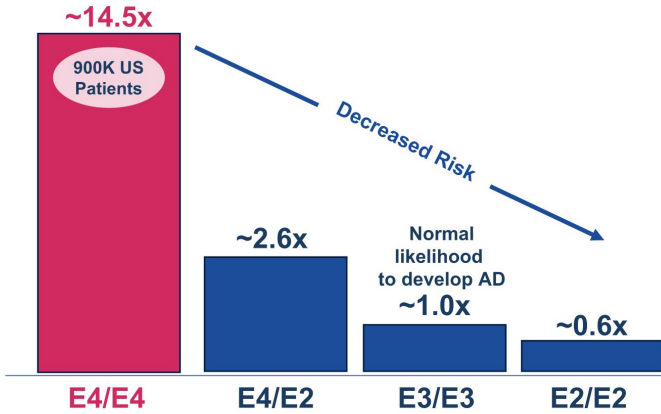
# APOE4-Associated Alzheimer's Disease



# APOE4 Homozygotes Represent a Patient Subgroup with Continued Unmet Need

## Alzheimer's Disease Risk by APOE Genotype<sup>(1)</sup>

~15x more likely to develop AD than APOE3/E3



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

(1) Yamazaki Y, et al. Nature Neurology Review, 2019.

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

(3) Reduction in CDR-SB is improvement.

## Unmet Need Persists Despite Recent Approvals

APOE4 homozygotes demonstrated lower efficacy results compared to heterozygotes and noncarriers and were associated with a higher incidence of ARIA-E

### ↓ Reduced Efficacy<sup>(2)</sup>

CDR-SB <sup>(3)</sup>	APOE4 Noncarrier	APOE4 Heterozygote	APOE4 Homozygotes
Lecanemab	-0.75	-0.50	0.28
Donanemab	-0.76	-0.73	-0.41

### ↑ Increased Incidence of Adverse Events<sup>(2)</sup>

ARIA-E	APOE4 Noncarrier	APOE4 Heterozygote	APOE4 Homozygotes
Lecanemab	5.4%	10.9%	32.6%
Donanemab	15.7%	22.8%	40.6%

### Key Features:

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

### Key Inclusion Criteria:

- ≥50 yr APOE4 homozygotes
- Mild cognitive impairment to moderate dementia with biomarkers consistent with Alzheimer's disease

### Endpoints

**Primary Endpoint:** Safety

**Secondary Endpoint:** Conversion of CSF APOE4 to APOE2/APOE4

#### Other Secondary Endpoints:

- CSF biomarkers: Aβ42, T Tau and P Tau
- Amyloid and tau PET scans
- Quantitative MRI
- Cognitive testing

### Trial Design

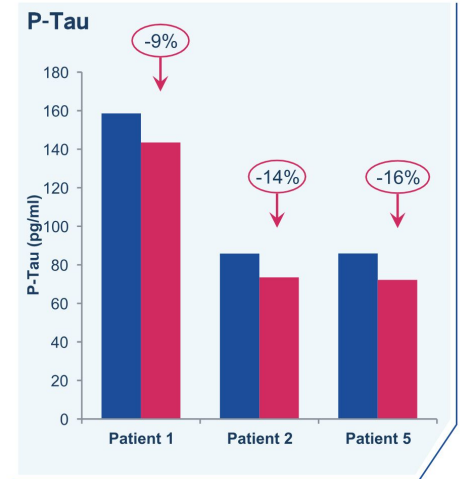
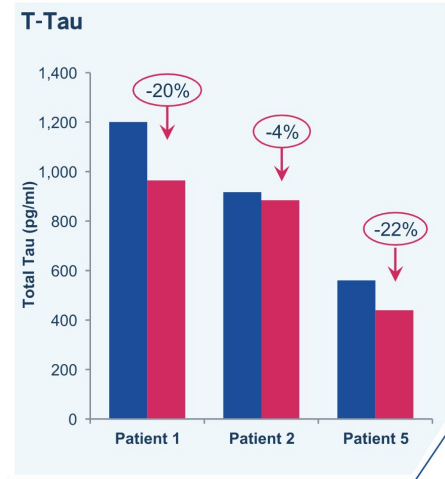
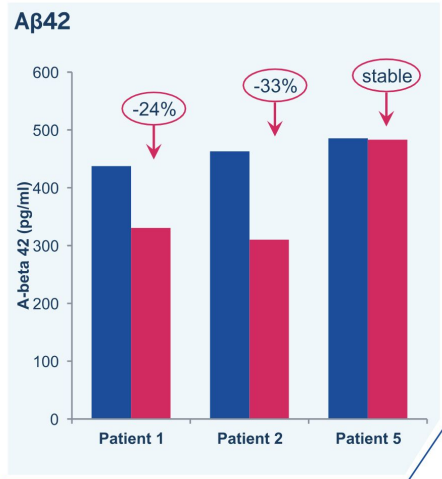
52-Week Follow-up



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

Initial CSF core biomarker data for patients with 12-month follow-up<sup>(1)</sup>

■ Baseline ■ Month 12



Reduction in CSF total tau and phospho-tau were observed in all 3 patients, reduction in CSF Aβ42 was observed in 2 of the 3 patients

Note: Patient 3 transitioned to a long-term care-facility prior to Month 3 and unlikely to have follow-up efficacy data. Patient 4 was unable to travel to the study site for the month 6 and 12 visits.  
 (1) If a screening and baseline value was obtained the mean was used as the baseline.



## Significant Catalysts Across Lead Programs Supported by Strong Balance Sheet

Program	Upcoming Milestones	US Prevalence
<b>LX2006</b> FA Cardiomyopathy	<ul style="list-style-type: none"> <li>Mid 2024: Interim Data Readout ✓</li> <li>Year End 2024: Update on ongoing regulatory engagements</li> </ul>	~5K
<b>LX2020</b> PKP2-ACM	<ul style="list-style-type: none"> <li>Late Q1/Early Q2 2025: Interim Data Readout (Cohort 1)</li> </ul>	~60K
<b>LX1001</b> Alzheimer's: APOE4	<ul style="list-style-type: none"> <li>October 2024: Interim Phase 1/2 Data Readout (CTAD Conference)</li> </ul>	~900K
<b>LX2021</b> DSP Cardiomyopathy	<ul style="list-style-type: none"> <li>2024: Initiate IND-enabling Studies</li> </ul>	~35K

Cash and marketable securities<sup>(1)</sup>  
~\$175M

Balance sheet as of June 30, 2024

Projected runway into  
2027

More than 2 years of runway  
following key catalysts

Shares of common stock outstanding<sup>(2)</sup>  
33.1M

Shares outstanding as of August 8, 2024

(1) Cash, cash equivalents and investments in marketable securities as of June 30, 2024.

(2) Shares outstanding as of August 8, 2024.

Thank you

