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

FORM 8-K

CURRENT REPORT

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

Date of Report (Date of earliest event reported): July 15, 2024

Lexeo Therapeutics, Inc.

(Exact name of Registrant as Specified in Its Charter)

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

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

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

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

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

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

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

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

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

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

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

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

Emerging growth company ☒

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

Item 8.01 Other Events.

On July 15, 2024, the Company issued a press release announcing positive interim Phase 1/2 clinical data of LX2006 for the treatment of Friedreich ataxia (FA) cardiomyopathy. As part of the press release, the Company announced that it would be hosting a conference call and webcast at 8:00 a.m. ET on July 15, 2024 to discuss the interim Phase 1/2 clinical data of LX2006 for the treatment of FA cardiomyopathy. The press release and the corporate presentation to be used in connection with the webcast are attached hereto as Exhibit 99.1 and 99.2, respectively, and are incorporated by reference herein.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit Number	Description
99.1	Press Release, dated July 15, 2024
99.2	Corporate Presentation, dated July 15, 2024
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

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

Lexeo Therapeutics, Inc.

Date: July 15, 2024

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

Lexeo Therapeutics Announces Positive Interim Phase 1/2 Clinical Data of LX2006 for the Treatment of Friedreich Ataxia Cardiomyopathy

Achieved mean reduction in left ventricular mass index (LVMI) of 11.4% at 12 months and 18.3% at 18 months in participants with elevated LVMI at baseline

>10% reduction in LVMI at 12 months in 75% of participants with elevated LVMI at baseline

Sustained and consistent improvements in other key measures of cardiac status, including left ventricular wall thickness and troponin I, in majority of participants at 12 months

Increased post-treatment frataxin expression above baseline in all participants evaluated via myocardial biopsy to date

LX2006 was well tolerated with no treatment-related serious adverse events to date; proceeding to Cohort 3 in SUNRISE-FA, with one participant dosed in this cohort to date

Company to host webcast today at 8:00 AM ET

NEW YORK – July 15, 2024 (GLOBE NEWSWIRE) – Lexeo Therapeutics, Inc. (Nasdaq: LXEO), a clinical stage genetic medicine company dedicated to pioneering treatments for genetically defined cardiovascular diseases and APOE4-associated Alzheimer's disease, today announced positive interim data of LX2006 for the treatment of Friedreich ataxia (FA) cardiomyopathy. Across both the Lexeo SUNRISE-FA Phase 1/2 clinical trial (NCT05445323) and the Weill Cornell Medicine investigator-initiated Phase 1A trial (NCT05302271), LX2006 was well tolerated with no treatment-related serious adverse events, and clinically meaningful improvements in cardiac biomarkers were observed with increasing improvement over time.

"We are very encouraged by these data and the potential of LX2006 to treat FA cardiomyopathy, a devastating and fatal condition with no currently approved therapies," said Dr. Eric Adler, Chief Medical Officer and Head of Research at Lexeo Therapeutics. "Based on the favorable safety profile and clinical benefits observed to date, we are excited to explore expedited clinical development of LX2006, including potential for accelerated approval of this possibly life-saving treatment."

"The interim data shared today demonstrate clinically meaningful improvements across multiple cardiac biomarkers of hypertrophy, a hallmark of FA cardiomyopathy," said Dr. Sandi See Tai, Chief Development Officer at Lexeo. "Together with the increases in frataxin protein expression observed in SUNRISE-FA cardiac biopsies to date, these results further highlight the potential of LX2006 to positively impact outcomes for people with FA cardiomyopathy. I would like to thank the participants, caregivers, and investigators participating in these trials who have helped to achieve this important milestone."

FA cardiomyopathy is a devastating, rare, and progressive disorder caused by loss of function mutations in the frataxin gene. Thus far in participants in the SUNRISE-FA trial with cardiac biopsies, low levels of frataxin have been found in the heart at baseline, estimated to be 2% or less of normal. In terms of clinical presentation, FA cardiomyopathy is typically characterized by left ventricular hypertrophy ultimately progressing to heart failure, and cardiac dysfunction is the cause of death in up to 80% of individuals with FA. A new natural history subset analysis conducted by Lexeo showed elevated left ventricular mass index (LVMI) in adults with FA cardiomyopathy, and LVMI remained stable or increased with age without spontaneous improvement. Elevated LVMI is an indicator of left ventricular hypertrophy and correlated with mortality in multiple cardiovascular conditions including FA cardiomyopathy.

Interim Safety Results

- LX2006 was well tolerated with no treatment-related serious adverse events to date in either study
- No signs of complement activation or other immunogenicity observed
- No cardiac or hepatic safety signals observed
- All adverse events were transient and resolved
- No participants discontinued from either study

Interim Clinical Results (from 8 participants with ≥ 6-months of follow-up)

- Left ventricular mass index (LVMI): Of participants with elevated LVMI at baseline, 75% achieved >10% reduction at 12 months (n=4). Of all participants, 50% achieved >10% reduction in LVMI at 12 months (n=6).
    - Among the participants with elevated LVMI at baseline, mean reduction in LVMI was 11.4% at 12 months (n=4) and 18.3% at 18 months (n=2).
- Left ventricular (LV) lateral wall thickness: wall thickening, an early indicator of left ventricular hypertrophy, was reduced by 13.6% on average in all participants at 12 months (n=6).
- High-sensitivity Troponin I (hsTnI): troponin I, a biomarker of myocardial injury, was reduced by 53.3% on average in all participants at 12 months (n=5).
- Frataxin protein expression evaluated via myocardial biopsy: observed increased frataxin levels compared to baseline following treatment with LX2006 in all participants evaluated to date utilizing two distinct measurements:
    - LCMS: frataxin increase observed in 3 of 3 evaluable participants.
    - IHC: frataxin increase observed in 2 of 2 evaluable participants.

Dosing Update and Next Steps

- As of July 15, 2024, 13 participants dosed to date across two trials:
    - Cohort 1 ($1.8x10^{11}$vg/kg): n=6
    - Cohort 2 ($5.6x10^{11}$ vg/kg): n=6
    - Cohort 3 ($1.2x10^{12}$ vg/kg): n=1
- SUNRISE-FA independent Data and Safety Monitoring Board endorsed proceeding to Cohort 3 dose level ($1.2x10^{12}$vg/kg). This cohort has started enrollment with 1 participant dosed to date and will include at least 3 participants.
- The Weill Cornell investigator-initiated trial is currently enrolling in Cohort 2.
- Lexeo expects to share further details of these interim results, including an additional cardiac biopsy from Cohort 2, at a scientific conference in Fall 2024.

Corporate Webcast Details

Lexeo Therapeutics will host a webcast at 8:00 AM ET today, July 15, 2024. Analysts and investors can participate by accessing the webcast live here or on the News & Events page in the Investors section of Lexeo's website, www.lexeotx.com. The webcast will be archived on the company's website following the completion of the call.

About the Clinical Studies

SUNRISE-FA is a Lexeo-sponsored, multicenter, 52-week, open-label trial evaluating the safety and preliminary efficacy of LX2006 in people who have FA cardiomyopathy, with three ascending dose cohorts. Investigators at Weill Cornell Medicine are conducting a Phase 1A study of AAVrh.10hFXN, known as LX2006 at Lexeo, in a single-site, 52-week, open-label trial evaluating the safety and preliminary efficacy in people who have FA cardiomyopathy, in two ascending-dose cohorts with five participants per cohort.

About LX2006

LX2006 is an AAV-based gene therapy candidate delivered intravenously for the treatment of FA cardiomyopathy, the most common cause of mortality in individuals with FA affecting approximately 5,000

people in the United States. LX2006 is designed to target the cardiac manifestations of FA by delivering a functional frataxin gene to promote the expression of the frataxin protein and restore mitochondrial function in myocardial cells. In preclinical studies, LX2006 reversed the cardiac abnormalities in FA disease models and showed improvement in cardiac function and survival while demonstrating a favorable safety profile. The FDA has granted Rare Pediatric Disease designation, Fast Track designation, and Orphan Drug designation to LX2006 for the treatment of FA cardiomyopathy.

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

Cautionary Note Regarding Forward-Looking Statements
Certain statements in this press release may constitute "forward-looking statements" within the meaning of the federal securities laws, including, but not limited to, our expectations and plans regarding our current product candidates and programs, including statements regarding the potential benefits of LX2006 for the treatment of Friedreich ataxia cardiomyopathy and the timing for receipt and announcement of data from its clinical trials, and the timing and likelihood of potential regulatory approval. Words such as "may," "might," "will," "objective," "intend," "should," "could," "can," "would," "expect," "believe," "design," "estimate," "predict," "potential," "develop," "plan" or the negative of these terms, and similar expressions, or statements regarding intent, belief, or current expectations, are forward-looking statements. While Lexeo believes these forward-looking statements are reasonable, undue reliance should not be placed on any such forward-looking statements. These forward-looking statements are based upon current information available to the company as well as certain estimates and assumptions and are subject to various risks and uncertainties (including, without limitation, those set forth in Lexeo's filings with the U.S. Securities and Exchange Commission (SEC)), many of which are beyond the company's control and subject to change. Actual results could be materially different from those indicated by such forward looking statements as a result of many factors, including but not limited to: risks and uncertainties related to global macroeconomic conditions and related volatility; expectations regarding the initiation, progress, and expected results of Lexeo's preclinical studies, clinical trials and research and development programs; the unpredictable relationship between preclinical study results and clinical study results; delays in submission of regulatory filings or failure to receive regulatory approval; liquidity and capital resources; and other risks and uncertainties identified in Lexeo's Quarterly Report on Form 10-Q for the quarterly period ended March 31, 2023, filed with the SEC on May 9, 2024, and subsequent future filings Lexeo may make with the SEC. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Lexeo claims the protection of the Safe Harbor contained in the Private Securities Litigation Reform Act of 1995 for forward-looking statements. Lexeo expressly disclaims any obligation to update or alter any statements whether as a result of new information, future events or otherwise, except as required by law.

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LEXEO therapeutics

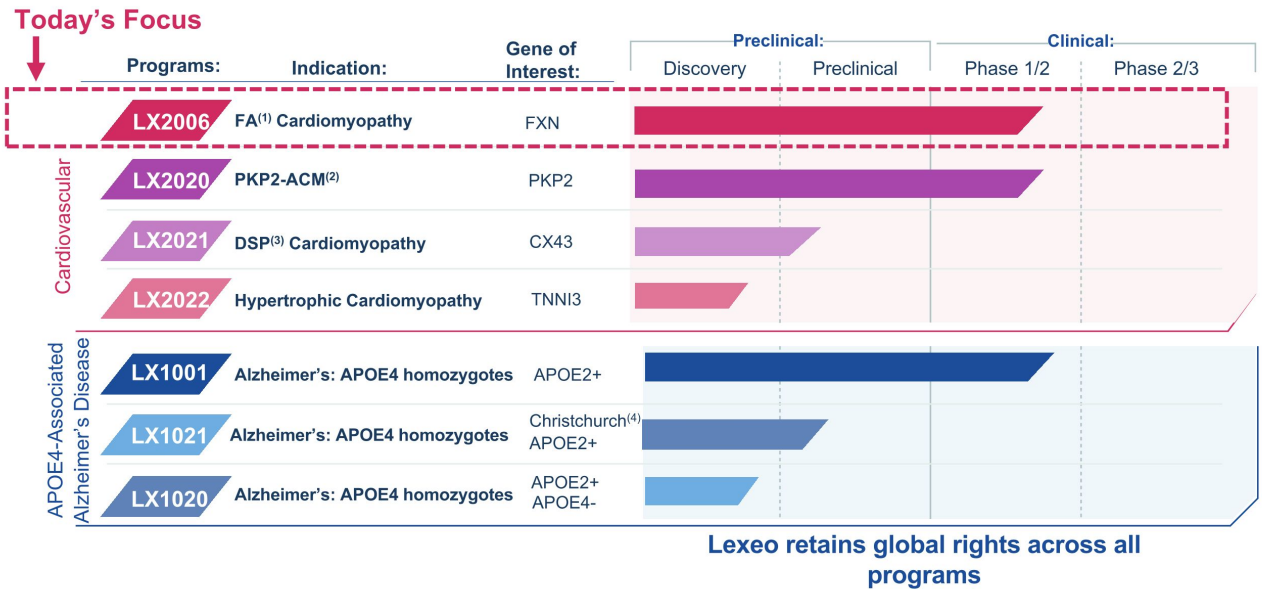
Interim Phase 1/2 Clinical Data of LX2006 for the Treatment of Friedreich Ataxia Cardiomyopathy

July 15, 2024

Forward-Looking Statements

This presentation contains “forward-looking statements” within the meaning of the federal securities laws, including, but not limited to, statements regarding Lexeo’s expectations and plans regarding its current product candidates and programs, including statements regarding the anticipated benefits of LX2006 for the treatment of Friedreich Ataxia Cardiomyopathy and the timing for receipt and announcement of data from its clinical trials. 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 Quarterly Report on Form 10-Q for the quarter ended March 31, 2024, filed with the SEC on May 9, 2024, and subsequent future filings Lexeo may make with the SEC. New risks and uncertainties may emerge from time to time, and it is not possible to predict all risks and uncertainties. Lexeo claims the protection of the Safe Harbor contained in the Private Securities Litigation Reform Act of 1995 for forward-looking statements. Lexeo expressly disclaims any obligation to update or alter any statements whether as a result of new information, future events or otherwise, except as required by law.

Advancing Genetic Medicines in Larger-Rare and Prevalent Patient Populations



Lexeo retains global rights across all programs

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

Lexeo Therapeutics: Revolutionizing Genetic Medicines for Cardiovascular Diseases

Pipeline of Clinical Stage Genetic Medicine Candidates	**Multiple cardiac programs in preclinically validated targets with high unmet need**
	Improvements in AAV delivery technology, with use of AAVrh10 allowing greater transduction of the heart
Favorable Clinical and Regulatory Environment	**Increased genetic screening with potential to expand awareness of genetic drivers of disease and increase familial screening**
	Regulatory precedents support smaller clinical trials with focus on protein expression and biomarker-based endpoints
Continued Validation of Cardiac Precision Therapies	**Vyndamax ($4.9B) and Camzyos ($2.5B) estimated peak sales(1) highlight potential impact of cardiac precision medicines**
	Recent cardiac data readouts, including gene therapies and small molecules, underscore significant market opportunity

(1) Peak sales estimate for Vyndamax and Camzyos per EvaluatePharma accessed July 2024.

LX2006 Begins with the Friedreich Ataxia Community in Mind

- Individuals with Friedreich Ataxia and their loved ones are at the center of everything we do
- Lexeo continues to collaborate with advocacy groups to support those impacted by FA, increase screening and diagnosis, and advance research
- We hear directly from the FA community to better incorporate their perspectives throughout our drug development process

FARA Friedreich's Ataxia Research Alliance

LEXEO therapeutics

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)

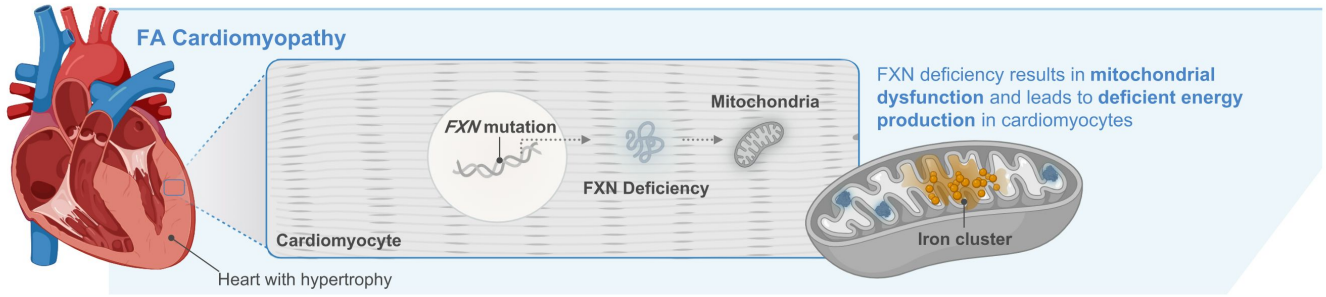
~15,000 individuals affected by FA worldwide(2)

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

FXN, Frataxin.

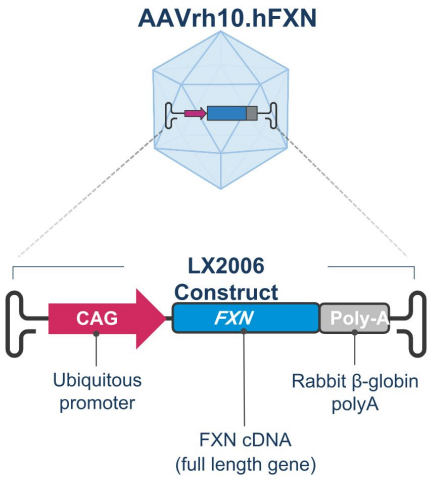
(1) Regner S, et al. *American Journal of Cardiology*, 2012. (2) Friedreich's Ataxia Research Alliance, 2024. (3) Subramoney S, et al. *MDA Clinical and Scientific Conference*, 2023. (4) Pousset, F. et al. *JAMA Neurol*, 2015;72(11):1334-1341.

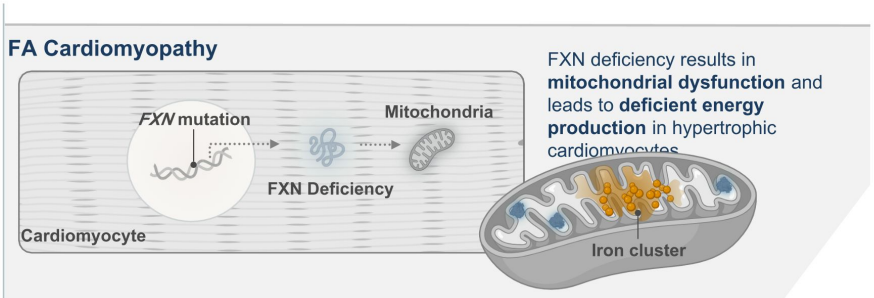
Friedreich Ataxia is a Result of Mutations in the Frataxin Gene, Leading to Impaired Mitochondrial Function in the Heart

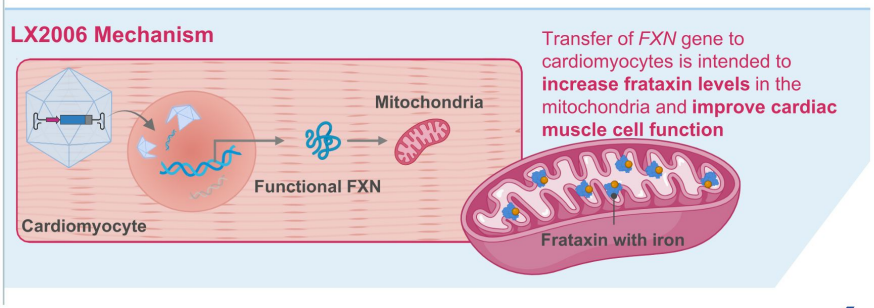


- FA is caused by mutations in the gene Frataxin (*FXN*), resulting in reduced FXN protein expression
- Reduced FXN protein expression decreases mitochondrial iron-sulfur cluster formation, causing mitochondrial dysfunction across multiple cells including cardiomyocytes
- Mitochondrial dysfunction leads 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







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

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

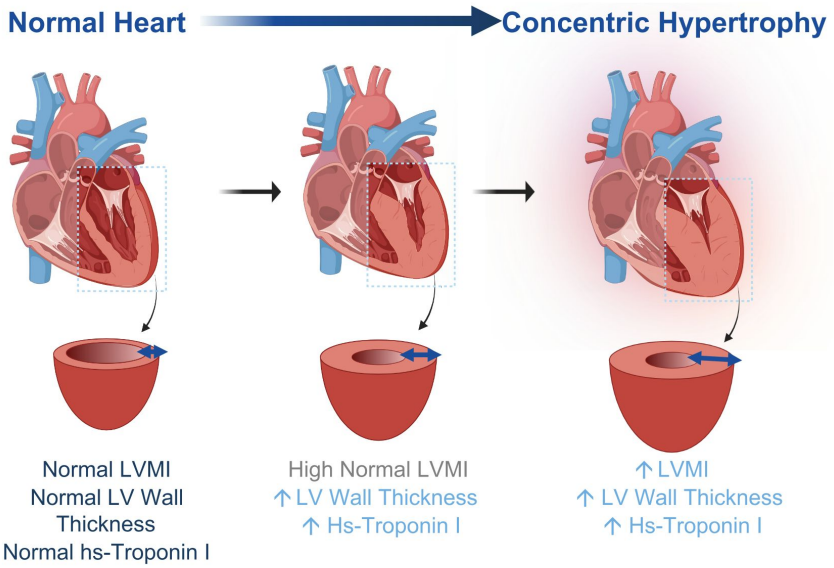
- In DMD **dystrophin is virtually absent**; whereas individuals with BMD have **10 – 40% of normal**, resulting in a milder disease with later onset and slower progression than DMD(4)
- Suggests **incremental dystrophin levels could result in improved clinical phenotype**(4)

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.

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

Disease Progression



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

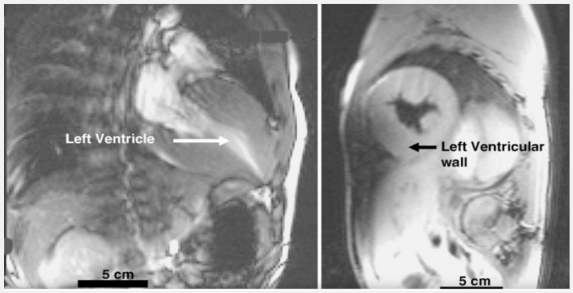
- Early indicator of left ventricular hypertrophy
- Associated with increase in cardiovascular events;(2) magnitude of LV wall thickness is directly related to risk of sudden cardiac death in HCM(6)

(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)



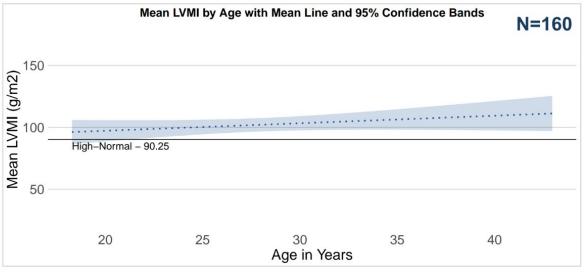
MRI of Individual With FA Cardiomyopathy Demonstrating Significant Hypertrophy

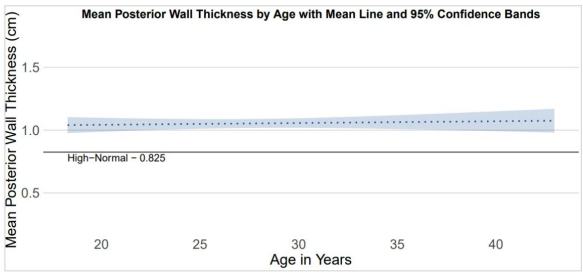
- Concentric hypertrophy is a hallmark of FA cardiomyopathy, including increased LVMI and abnormal left ventricular wall thickness(1)(2)
- Natural history suggests a 19% incremental risk of all cause mortality per ~10% increase in LVMI in individuals with FA; increased wall thickness was also associated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

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

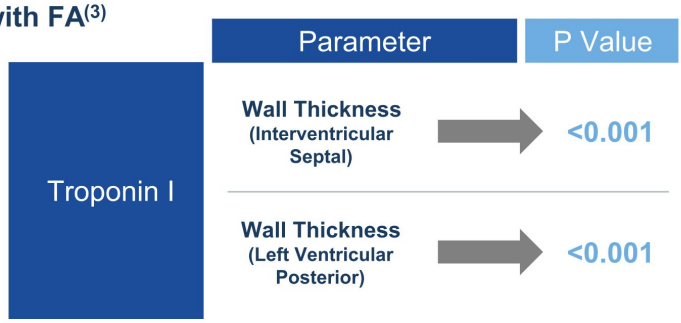
(1) Subset analysis performed by Lexeo Therapeutics including adults 18-50 years old with abnormal relative wall thickness, LV mass or LVMI (n=160; 830 echocardiographs) from a natural history cohort followed primarily at Children's Hospital of Philadelphia of FA patients including children and adults. (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.

High Sensitivity Troponin I (hsTnI): A Validated Biomarker Studied in Cardiomyopathy and Specifically Friedreich Ataxia

Utilization of Troponin I as Blood Biomarker[1][2]

- Cardiac troponin I is a component of the contractile apparatus of myocardial cells expressed almost exclusively in the heart
  - Circulating blood biomarker for the evaluation of myocardial injury
- hsTnI levels can predict hospitalizations, cardiovascular and all-cause mortality in chronic heart failure and hypertrophic cardiomyopathy
- Used as secondary endpoint in other clinical trials for cardiomyopathies

Recent Publication Highlights Relationship Between Troponin I and Left Ventricular Hypertrophy in People with FA[3]



Troponin I levels predict echocardiographic measures of hypertrophy, and are independently associated with worse outcomes in FA

(1) Ommen et al, *Circulation*, 2024. (2) Gohar et al, *European Journal of Heart Failure*, 2017. (3) Lynch et al, *Journal of Neurological Sciences*, 2024.

Recent LX2006 Program Updates

- 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
- In April, Lexeo provided a dosing update noting 11 participants dosed with 8 participants $\geq$ 6 months of follow-up
- As of July 15, 2024, 13 participants dosed; baseline data are not yet available for the two most recently dosed participants

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)(1)

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

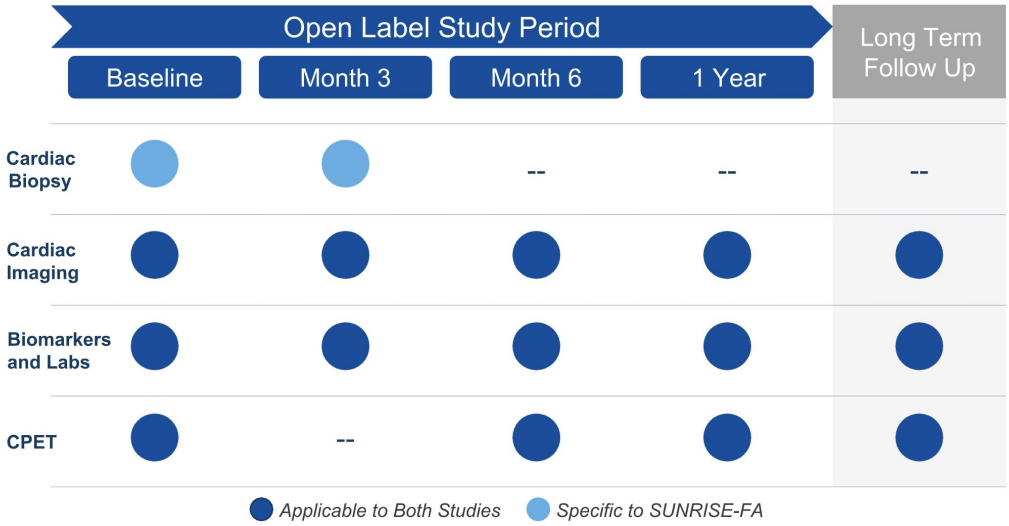
CPET, Cardiopulmonary Exercise Testing; hsTnI, High Sensitivity Troponin I; IHC, Immunohistochemistry; LCMS, Liquid Chromatography Mass Spectrometry; LVMI, Left Ventricular Mass Index.
(1) Cardiac biopsies are evaluated in SUNRISE-FA only.
Note: LX2006 is administered systemically; participants receive immune suppression with prednisone beginning on the day prior to treatment through 14 weeks following LX2006 administration.

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
Currently Enrolling

Weill Cornell
Investigator Initiated
– Cohort 1: $1.8x10^{11}$ vg/kg
– Cohort 2 : $5.6x10^{11}$ 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.

Baseline Characteristics and Follow-up Time by Dosing Cohort

Characteristic	Statistic	*Cohort 1 ($1.8x10^{11}$ vg/kg) N=6*	*Cohort 2 ($5.6x10^{11}$ vg/kg) N=5*
Age, years	Mean (SD) Min, Max	30.3 (5.0) 24.0, 35.0	23.4 (4.2) 19.0, 30.0
Female	N (%)	3 (50)	4 (80)
GAA Repeats	Mean (SD) Min, Max	731 (44.1) 695, 800	791 (156.9) 615, 1000
Left Ventricular Mass Index (LVMI), g/m^2	Mean (SD) Min, Max	75.7 (20.6) 53, 109	71.8 (16.6) 57.4, 99.5
Lateral Wall Thickness (LWT), cm	Mean (SD) Min, Max	1.0 (.16) 0.8, 1.2	0.9 (.12) 0.7, 1.0
High Sensitivity Troponin I (hsTnI), pg/ml	Mean (SD) Min, Max	428.2 (785.7) 5, 2023	409.5 (383.0) 53, 820
Peak VO2, mL/kg/min(1)	Mean (SD) Min, Max	15.0 (3.1) 11.7, 17.7	11.3 (2.8) 9.0, 14.4
Follow-up, months	Mean (SD) Min, Max	11 (5.9) 6, 18	4.2 (5.8) 0, 12

(1) Baseline inclusive only of participants who reached maximal exercise capacity (Respiratory Exchange Rate>1.1), N=3 in Cohort 1, N=3 in Cohort 2.

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
- 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 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.

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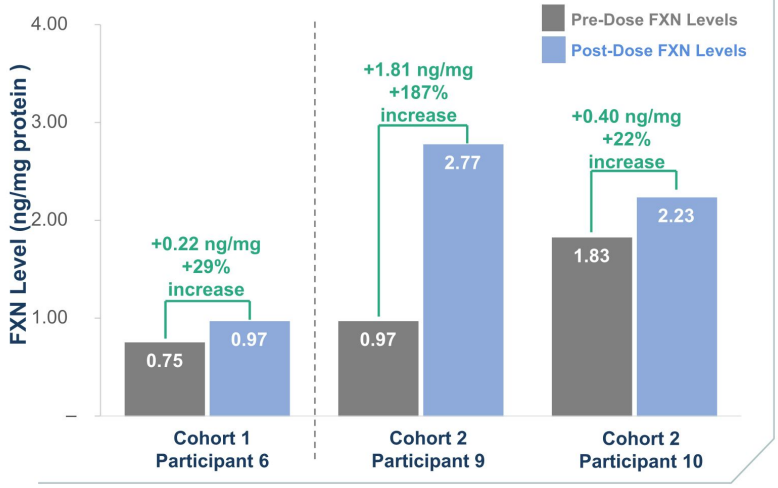
Treatment with LX2006 Has Been Well Tolerated to Date

- 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 ($1.2x10^{12}$vg/kg)

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

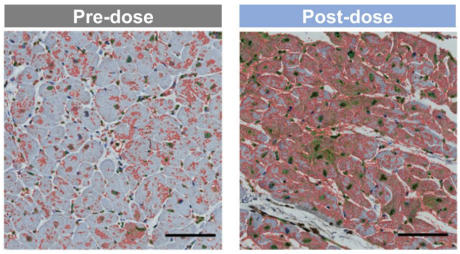
Pre- and Post-Treatment FXN Levels (LCMS)



Quantified IHC (FXN % Positive Area(1))

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

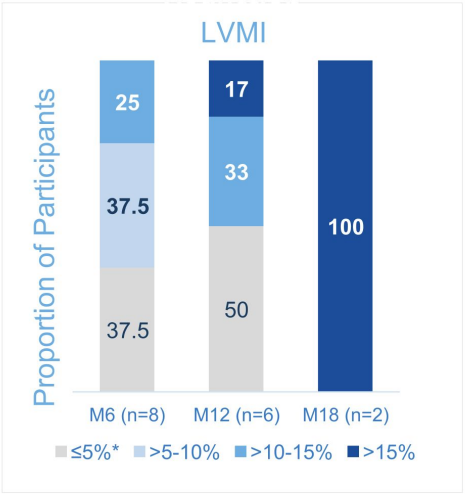
IHC images from Participant 10



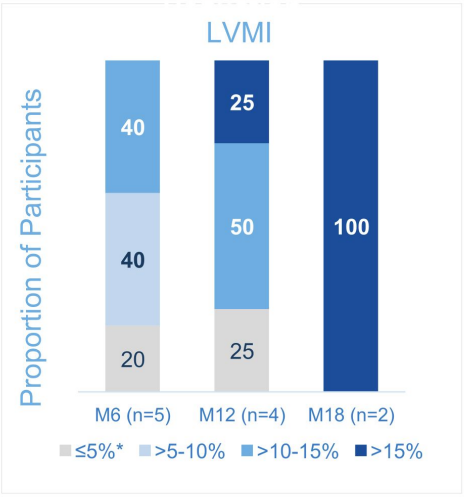
LCMS, Liquid chromatography mass spectrometry; FXN, Frataxin; IHC, Immunohistochemistry.
Note: Frataxin levels measured by ultrahigh performance liquid chromatography-multiple reaction monitoring/mass spectrometry (UHPLC-MRM/MS).
Note: Cohort 1 dose of $1.8x10^{11}$ vg/kg and Cohort 2 dose of $5.6x10^{11}$ 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 ≥ 6 Months of Follow-Up, Percentage of Participants with LVMI Reduction >10% Increased Over Time

All Participants: Responder Rate by LVMI



Elevated LVMI at Baseline: Responder Rate by LVMI

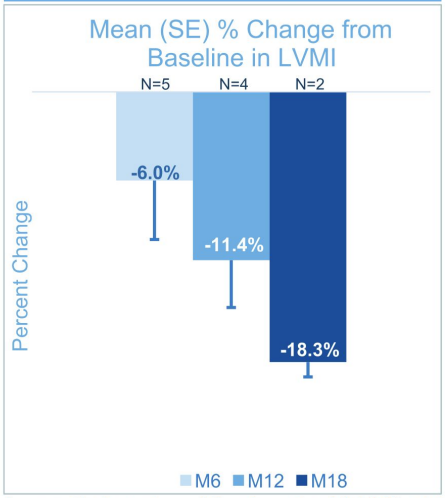


- Overall by month 12 (M12), 50% experienced a reduction in LVMI greater than 10%
- In participants with elevated LVMI at baseline, 75% experienced a reduction in LVMI greater than 10% by month 12

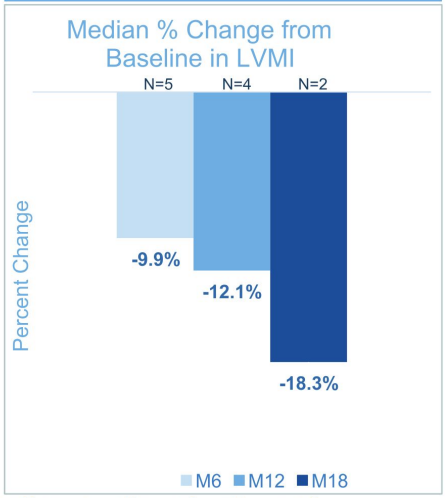
*Inclusive of participants with observed increases. LVMI, Left Ventricular Mass Index.
Note: Elevated defined as 1 or 2 standard deviations above mean for respective gender (from healthy volunteers) as referenced in Kawel-Boehm et al. *J Cardiovasc Magn Reson* (2020) 22:87.

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

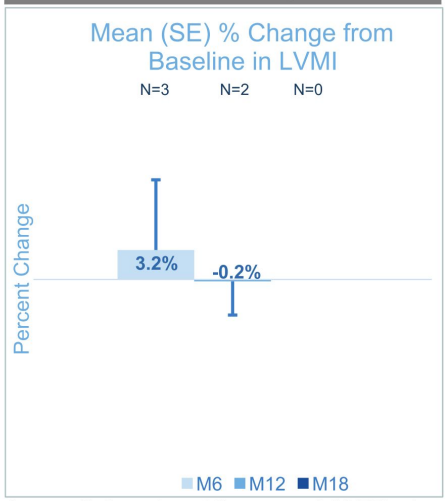
Elevated LVMI at Baseline: Mean Change



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

In participants with normal LVMI at baseline, minimal change 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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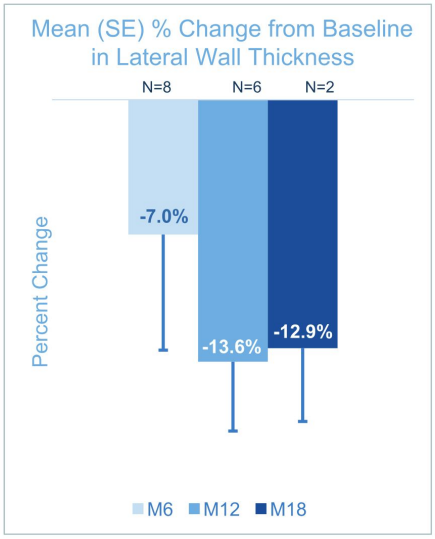
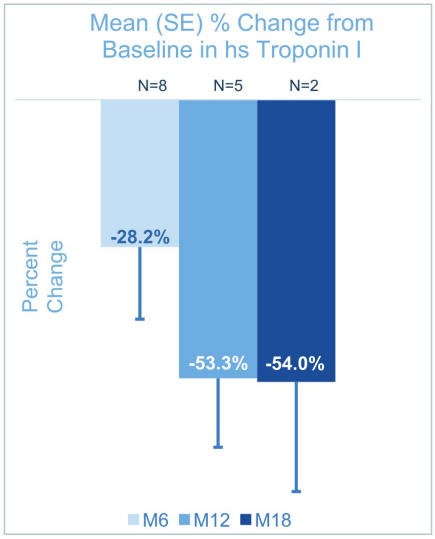
Average Change from Baseline in Other Key Cardiac Measures Demonstrates Pattern of Improvement with Increased Improvement Over

All Participants: Change in Lateral Wall Thickness



All Participants: Change in hs-Troponin I

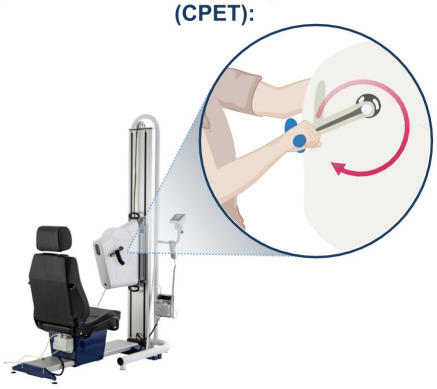


- Continued pattern of improvement with increased reduction from 6 to 12 months
  - Reduction of >10% in lateral wall thickness from baseline in 4 of 6 participants at 12 months
  - Reduction of >25% in hs-troponin I from baseline in 4 of 5 participants at 12 months

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.

Peak VO2 May Be Challenging to Assess in Friedreich Ataxia as Neurologic Disease Causes Interference

Upper Limb Cardiopulmonary Exercise Testing (CPET):



Enables assessment of functional capacity to determine severity of mitochondrial oxidative effect[1]

- Peak VO2 is defined as the highest amount of oxygen that an individual utilizes during maximal exercise in CPET[1]
  - This measure may **not represent the true functional capacity** in FA cardiomyopathy given **interference from neurologic symptoms**
  - 3 of 8 participants could not achieve maximal exercise capacity required for peak VO2 evaluation
  - Of those able to achieve maximal exercise, peak VO2 average change from baseline:
    - +1.1% (+0.3mL/kg/min) at 6-months (n=5)
    - +4.2% (+0.5mL/kg/min) at 12-months (n=3)
- Continuing evaluation of CPET measures, including alternative measures of functional capacity that could retain prognostic significance despite submaximal effort

(1) Pane C, et al. *Eur J Prev Cardiol.* 2022.
VO2, Volume Oxygen Maximum.

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*
Transgene Expression (LCMS and IHC) *Regulatory Precedent as Approvable Endpoint*	✓	Cardiac Biopsy	3 Month(1)
Left Ventricular Mass Index *Regulatory Precedent as Approvable Endpoint*	✓	Cardiac MRI	Months 6,12, Long-Term Follow Up
Lateral Wall Thickness *Clinically Meaningful Endpoint*	✓	Cardiac MRI	Months 6,12, Long-Term Follow Up
Circulating Blood Biomarkers (hs-Troponin I) *Clinically Meaningful Endpoint*	✓	Blood Sample	Months 6,12, Long-Term Follow Up

(1) Only evaluated in SUNRISE-FA.

Summary of Results and Next Steps for LX2006

- 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 ($1.2x10^{12}$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
- Lexeo expects to share further details of these interim results, including an additional cardiac biopsy from Cohort 2, at a scientific conference in Fall 2024

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Thank You and Q&A