Lexeo Therapeutics

Corporate Overview

November 2026



Forward-looking statements

Certain statements in this presentation may constitute “forward-looking statements” within the meaning of the federal securities laws, including, but not limited to, Lexeo’s expectations and plans regarding its current product candidates and programs, the anticipated benefits of its current product candidates, the timing for receipt and announcement of data from its clinical trials, the timing and likelihood of potential regulatory developments, trial design changes and approval, and expectations regarding the time period over which Lexeo's capital resources will be sufficient to fund its anticipated operations and estimates regarding Lexeo's financial condition. 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: expectations regarding the initiation, progress, and expected results of Lexeo’s preclinical studies, clinical trials and research and development programs, including the outcome of ongoing discussions with the U.S. Food and Drug Administration (FDA) regarding the design of our pivotal trials for accelerated approval pathway and the confirmatory strategy; the unpredictable relationship between preclinical study results and clinical study results; delays in submission of regulatory filings or failure to receive regulatory approval; liquidity and capital resources; and other risks and uncertainties identified in Lexeo’s Quarterly Report on Form 10-Q for the quarterly period ended June 30, 2026, filed with the SEC on August 12, 2026, 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

Reshaping the path of genetic disease

Our vision: To set a new standard in the treatment of genetic diseases with high unmet need, charting the path to patient outcomes once thought out of reach

- Genetic disease expertise with cardiovascular and neurological focus
- Proven experience in the clinic
- Platform designed for safety and scalability



Individuals and families impacted by Friedreich ataxia



LEXEO therapeutics

Pioneering science that fundamentally changes how genetic diseases are treated



Genetic disease expertise

Leader in developing disease-modifying therapies for inherited diseases with high morbidity and mortality



Innovative AAV manufacturing

Optimized Sf9 baculovirus manufacturing platform designed to support future commercial scale-up for lead gene therapy assets



Multimodal therapeutic portfolio

Robust pipeline of complementary approaches to address the full complexity of genetic disease



Strong cardiac foundation

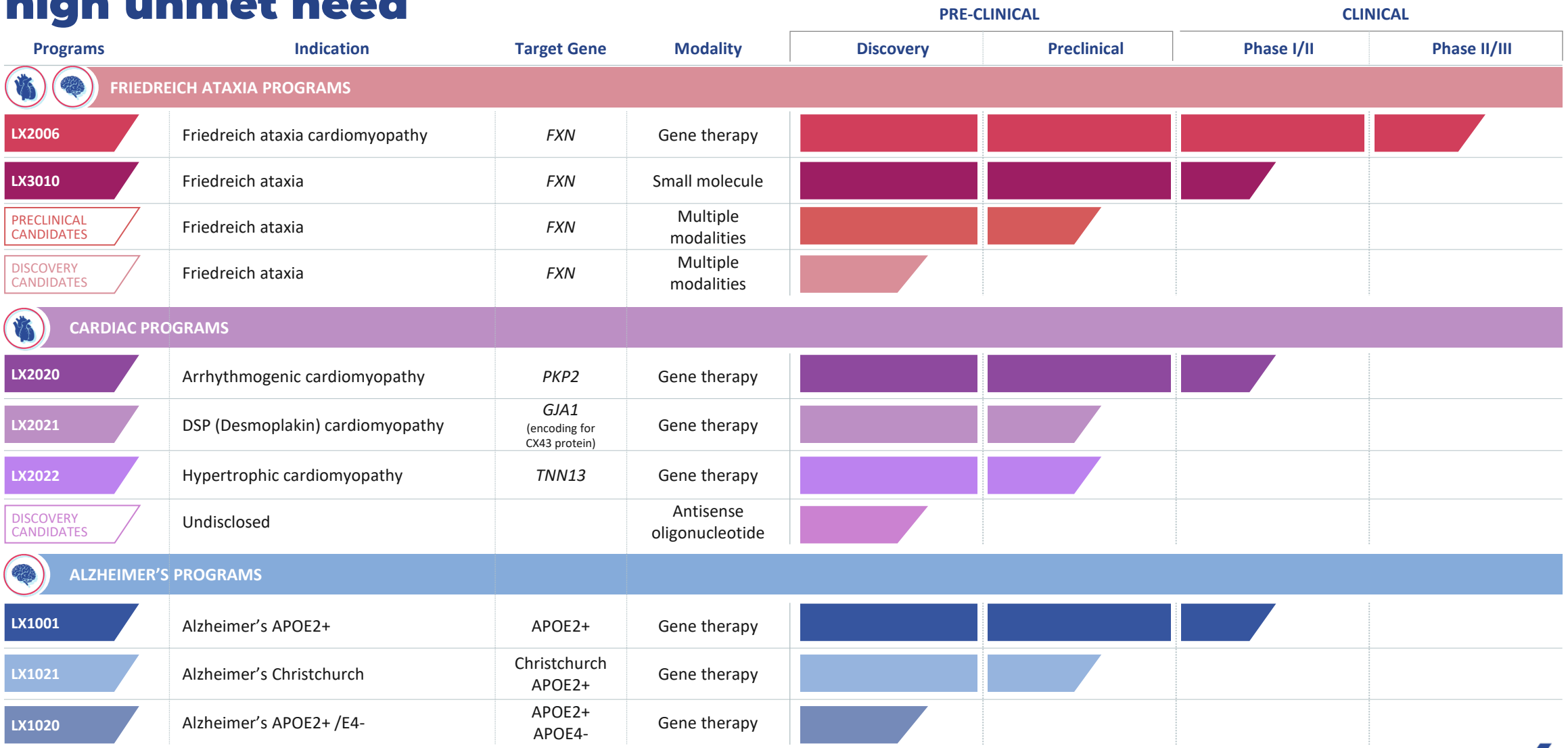
Genetic medicine know-how rooted in cardiac science, with proven clinical experience and preclinical disease model expertise



Strong financial position

Cash runway into 2028, supporting multiple value creating milestones

Advancing cardiac and neurological therapies in diseases with high unmet need

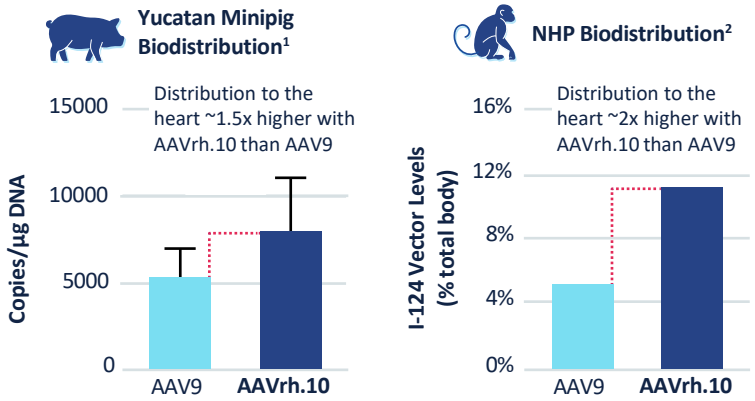


Lexeo retains global rights across all programs

Gene therapy backbone: Highly differentiated capsid supports Lexeo's lead cardiac programs

Cardiac tropism of AAVrh.10 may allow lower doses for cardiac gene therapy

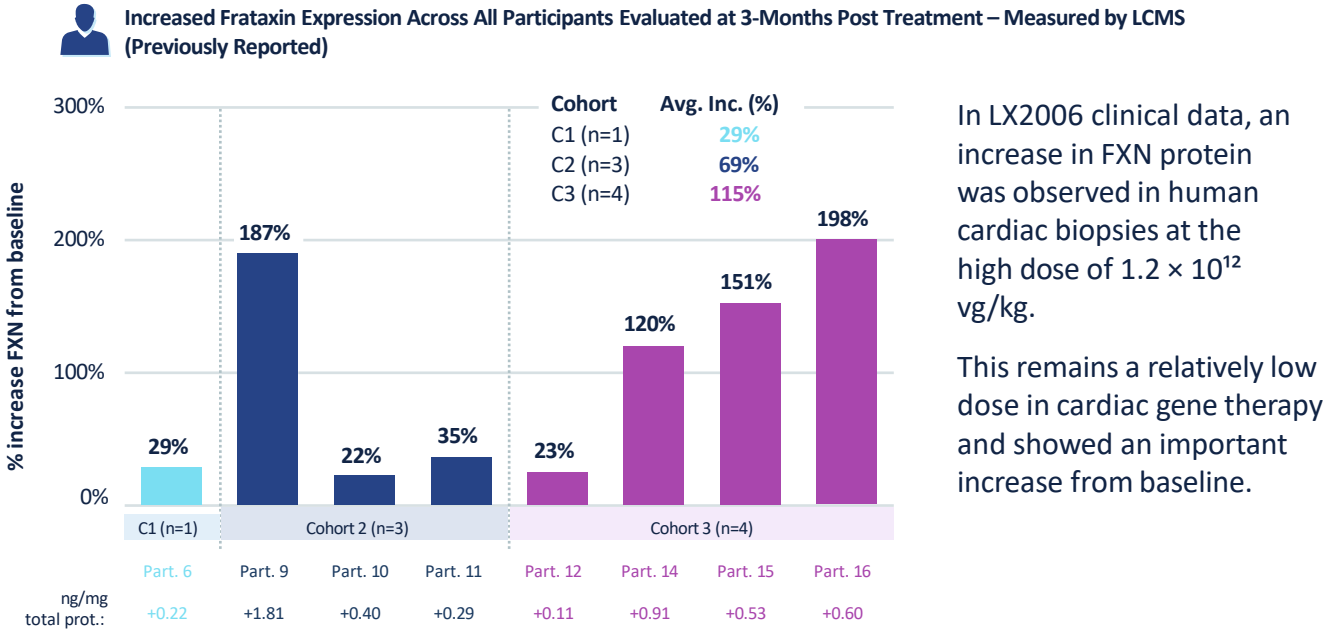
Compelling cardiac tropism in preclinical data



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

Significant evidence of protein expression in clinical data with AAVrh.10 capsid



In LX2006 clinical data, an increase in FXN protein was observed in human cardiac biopsies at the high dose of 1.2×10^{12} vg/kg.

This remains a relatively low dose in cardiac gene therapy and showed an important increase from baseline.

AAVrh.10 has been utilized systemically across LX2006 and LX2020 with no clinically significant complement activation. Both LX2006 and LX2020 have been generally well-tolerated to date.

1 - Selvan, N. et al. Poster presented at: ASGCT Annual Meeting; May 16-20, 2023; Los Angeles, CA. 2 - Ballon DJ et al, Human Gene Therapy, 2020.
Note: FXN, Frataxin; LCMS, Liquid chromatography mass spectrometry. FXN expression assessed with academic LCMS assay, assay validation in progress for pivotal study. LX2006 FXN data previously reported in April 2025.

Gene therapy backbone: Lexeo's optimized Sf9 baculovirus platform combines differentiated manufacturing, attractive economics and demonstrated commercial readiness

Differentiated Manufacturing

Fewer empty AAV capsids
<25%

Higher yields
1.0E15 vg/L

Greater downstream recovery
>55%

- Optimized Sf9 baculovirus platform
- Improved genomic purity
- High-quality vector production
- Higher yield and quality compared to HEK model

Potentially Transformational COGS Profile

- Higher Yield + Well Defined Starting Materials
- Higher Recovery
- Fewer Empty Capsids
- Fewer Production Runs
- **Lower Cost Per Dose**

Launch Readiness

- LX2006 selected for FDA CDRP program



- FDA confirmed no additional nonclinical bridging studies required
- Final commercial manufacturing process cleared for SUNRISE-FA 2
- Commercial-scale drug product available immediately for patient dosing

High yield, strong product quality, and an FDA-endorsed commercial manufacturing process position Lexeo for attractive economics and execution readiness across our pipeline

Lexeo's two clinical stage gene therapy programs address devastating cardiac diseases

Goal:

Leveraging gene therapy to address devastating cardiac diseases with no existing disease-modifying treatments

LX2006

Friedreich Ataxia Cardiomyopathy

- Potential first disease-modifying gene therapy for FA cardiomyopathy (FA-CM)
- Only program with clinical trial data in FA-CM, which accounts for death in up to 80% of people with FA
- Clinical data to date demonstrate an encouraging safety profile and sustained and deepening improvements across both cardiac and neurologic measures of FA
- Finalized SUNRISE-FA 2 pivotal protocol and SAP for accelerated approval; Study initiated in June 2026

Milestones:

- Topline data readout expected in 2H 2027
- Potential BLA submission under accelerated approval pathway in 1H 2028

LX2020

PKP2 Arrhythmogenic Cardiomyopathy

- Potential best-in-class treatment for PKP2-ACM; ~60K people in US with no disease-modifying treatment available
- Clinical data to date demonstrate a well tolerated safety profile and clinically meaningful reductions in severe arrhythmia burden
- FDA open to guideline-defined NSVT as a primary surrogate endpoint to support potential accelerated approval of LX2020

Milestones:

- Finalization of pivotal protocol, SAP and confirmatory evidence strategy expected in 1H 2027
- Initiation of pivotal study anticipated in 2H 2027

FA - Friedreich ataxia; FA-CM - Friedreich ataxia cardiomyopathy; FXN - Frataxin; LVMi - Left ventricular mass index; ACM - arrhythmogenic cardiomyopathy; NSVT - non-sustained ventricular tachycardia; SAP – statistical analysis plan.

CONFIDENTIAL

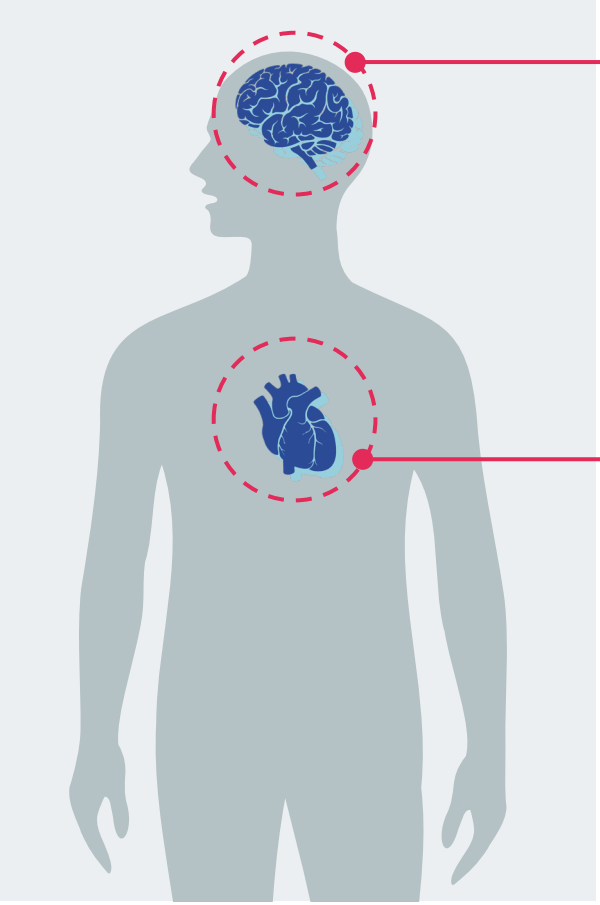
FRIEDREICH ATAXIA PLATFORM

Lead Asset:
Gene Therapy LX2006

LEXEO therapeutics

Friedreich ataxia is a rare, progressive multisystem disease with significant unmet need

FA is caused by a loss of function mutation in the *FXN* gene



Neurological Burden

Progressive ataxia, impaired coordination and peripheral nervous system involvement can materially reduce independence and quality of life

Cardiac Burden

Cardiac dysfunction in FA associated with a multitude of symptoms but ultimately presents as cardiac hypertrophy and subsequent heart failure[1]

Cardiac complications account for up to 80% of deaths in those with FA, with an average life expectancy of 35–40 years[1,2]

There is no approved treatment specifically for FA cardiomyopathy

~5,000
individuals affected by FA in the U.S.[2]

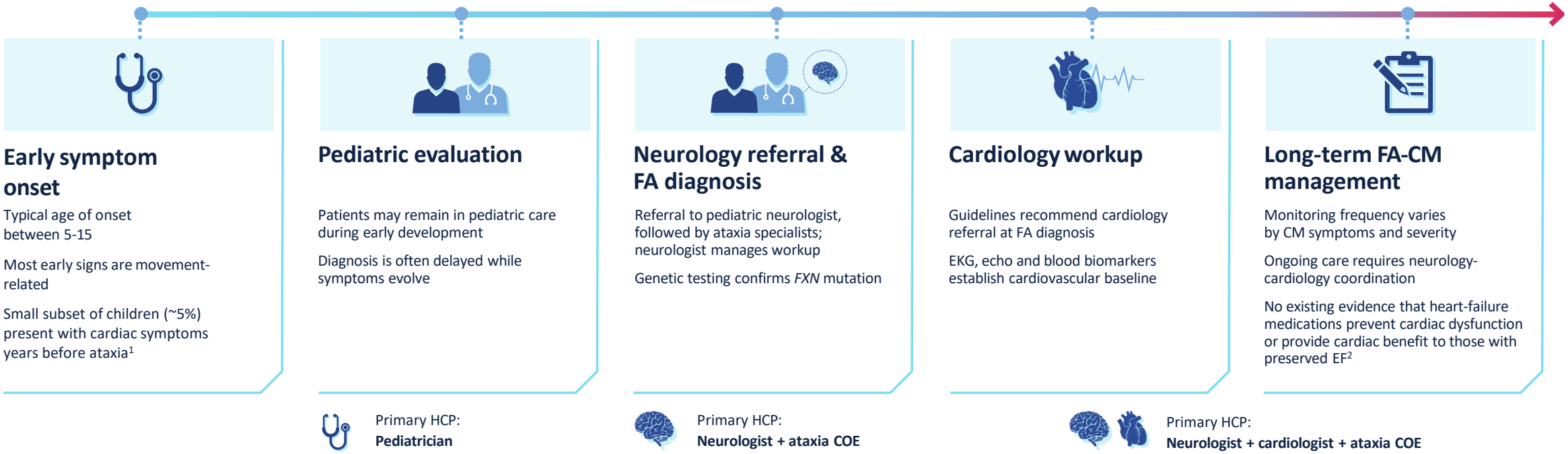
~15,000
individuals affected by FA worldwide[2]

Cardiac complications are the leading driver of mortality, while neurological decline drives substantial lifelong disability; a leading FA platform must address both.

1 - Payne R.M. JACC Basic Transl Sci, 2022;13;7(12):1267-1283.
2 - Indelicato, E., et al. Mov Disord, 2024;39(3), 510–518.

Timely, multidisciplinary care is critical to identifying and managing Friedreich ataxia cardiomyopathy (FA-CM)

Cardiac symptoms may be absent or under-recognized even as cardiomyopathy evolves, supporting the need for earlier evaluation and coordinated neurology-cardiology care



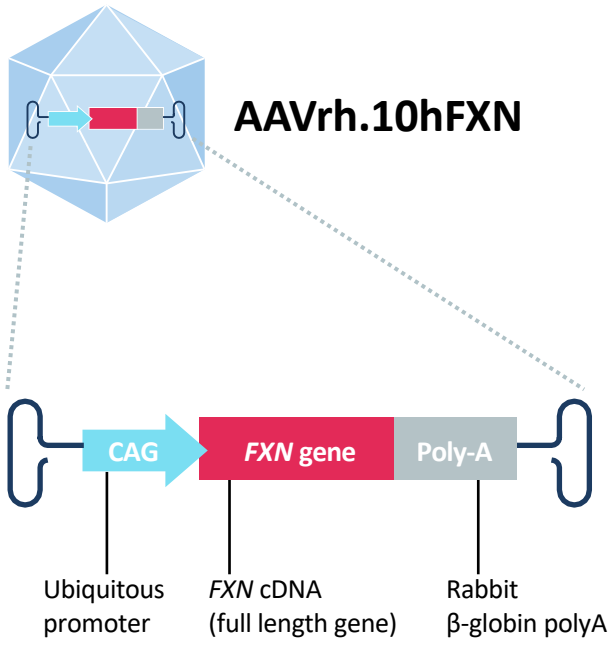
Cardiac complications drive up to 80% of FA deaths, often by the mid-30s, reinforcing the need for early cardiac evaluation, coordinated follow-up and disease-modifying treatments[3,4]

Source: HCP and patient market research. COE, center of excellence.

1 - Norrish G., et al. Friedreich's ataxia-associated childhood hypertrophic cardiomyopathy: a national cohort study. 2 - Clinical Management Guidelines for Friedreich Ataxia. Chapter 4. The heart and cardiovascular system in Friedreich ataxia. 2022. 3 - Tsou AY, Paulsen EK, Lagedrost SJ, et al. Mortality in Friedreich ataxia. J Neurol Sci. 2011;307(1-2):46-49. doi:10.1016/j.jns.2011.05.023. PMID:21652007. 4 - Pousset F, Legrand L, Monin ML, et al. A 22-Year Follow-up Study of Long-term Cardiac Outcome and Predictors of Survival in Friedreich Ataxia. JAMA Neurol. 2015;72(11):1334-1341. doi:10.1001/jamaneurol.2015.1855. PMID:26414159.

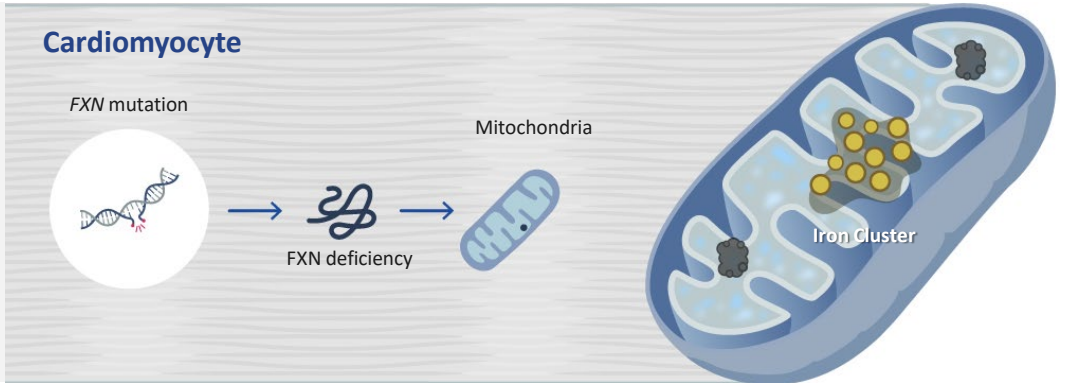
Gene therapy LX2006 has the potential to treat the root cause of FA-CM: significant decrease in frataxin in the heart

LX2006 construct:



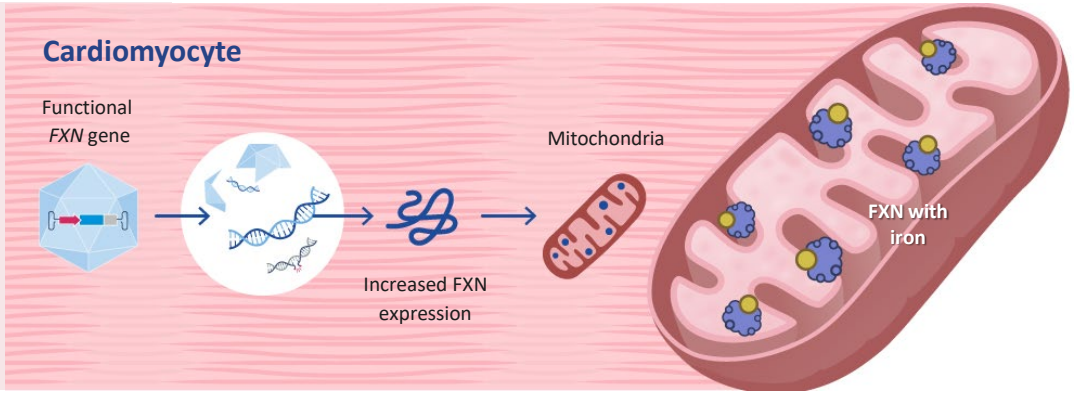
FA Cardiomyopathy

FXN deficiency results in **mitochondrial dysfunction** and leads to **deficient energy production** in thickened cardiomyocytes



LX2006 Mechanism

Delivery of *FXN* gene in cardiomyocytes by LX2006 is intended to **increase frataxin protein levels** in the mitochondria and **improve heart muscle function**

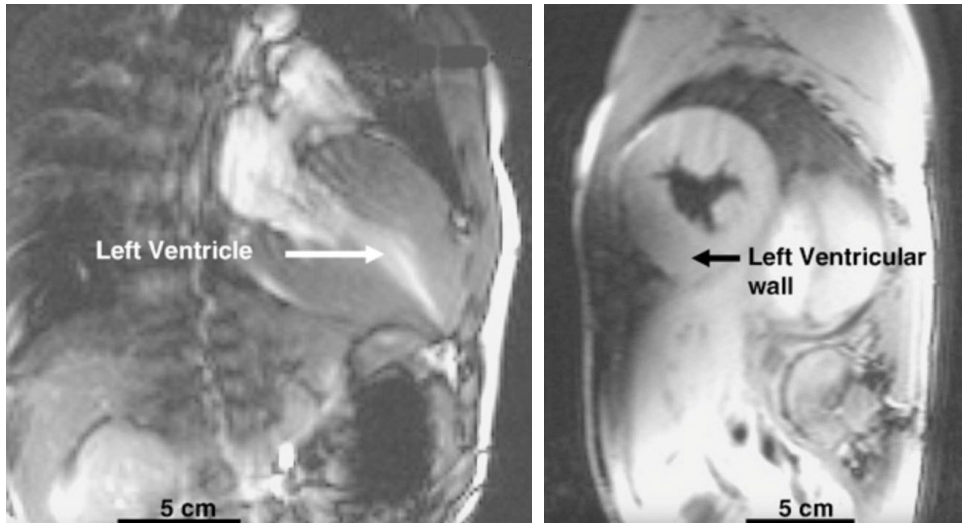


AAV, Adeno-Associated Virus; CAG, Chicken Beta-Actin; cDNA, Copy DNA; FA, Friedreich Ataxia; FXN, Frataxin; Poly-A, Poly Adenosine.

Elevated LVMi predicts mortality in FA and is not expected to decrease significantly without intervention

Increases in LVMi independently predict mortality in Friedreich Ataxia (FA)

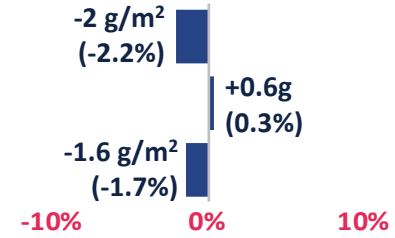
Natural history study showed a **19%** higher risk of death per 10g/m^2 (HR 1.19; 95% CI)[1]



MRI of individual with FA cardiomyopathy demonstrating significant hypertrophy.

No Significant Change in LVMi or LV Mass (LVM) Control Across Multiple Randomized Controlled Trials

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



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

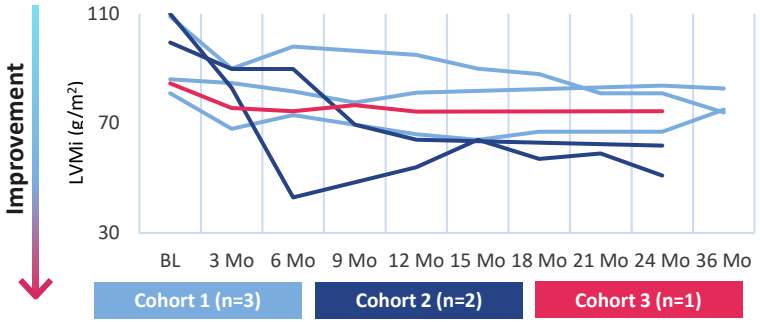
- Concentric hypertrophy, with increased left ventricular mass and wall thickness, is a hallmark of FA cardiomyopathy[1]
- In FA and many other cardiac diseases, elevated LVMi is not expected to significantly decrease without intervention,[1,3] and abnormal LVMi is closely correlated with poor outcomes[2]
- Reduction in LVMi may improve cardiac outcomes; key primary endpoint for pivotal trial in FA cardiomyopathy

HR, Hazard Ratio; CI, Confidence Internal; LVMi, Left Ventricular Mass Index.
Note: 10g/m2 represents approximately 10% change in LVMi based on echocardiography measurements of upper bound of normal (105 g/m2).

1 - Pousset, F. et al. JAMA Neurol, 2015;72(11):1334-1341.
2 - Includes heart failure with preserved ejection fraction, Shah et al, Journal of American College of Cardiology, 2019; hypertensive cardiomyopathy, Muiesan et al, Hypertension, 2004; Fabry disease, Orsborne et al, Journal of American College of Cardiology, 2022; and obstructive hypertrophic cardiomyopathy, Hegde et al, Journal of American College of Cardiology, 2021.
3 - Hughes DA, et al. J Med Genet, 2017;54:288–296; Migalastat; Solomon S, et al. Circulation, 2018. Patisiran; Saberi S, et al. Circulation, 2021;143:606–608. Mavacamten; Data on file.

LX2006 clinical data show sustained or deepening improvements across cardiac measures of FA; LX2006 generally well tolerated

Cardiac MRI: LVMi (n=6; abnormal at baseline)



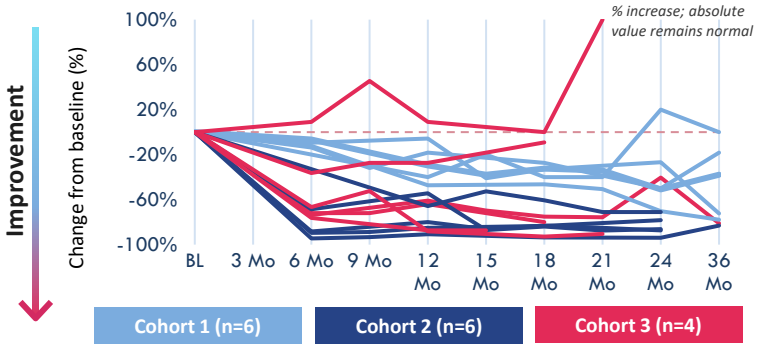
- Majority of participants reach or remain in normal LVMi range at latest visit
- **Durable LVMi improvement maintained out to three years following treatment**

Mean LVMi Change

Participants at 24-mo visit *(n=6)*	**-25%**
Participants at 12-mo visit *(n=6)*	**-23%**
Participants at 6-mo visit[1] *(n=6)*	**-18%**
Cohorts 2 and 3 at 24-mo visit *(n=3)*	**-35%**
Cohorts 2 and 3 at 12-mo visit *(n=3)*	**-33%**
Cohorts 2 and 3 at 6-mo visit[1] *(n=3)*	**-28%**

Among participants with abnormal baseline LVMi (key inclusion criteria for pivotal study; n=6):

Biomarkers: High-Sensitivity Troponin I (n=17)



- **16 of 17 participants have significantly reduced or stable troponin I,** excluding participant with myocarditis[2]
- Highly specific, blood-based marker of myocardial injury

LX2006 generally well tolerated

- LX2006 generally well tolerated across 17 participants dosed with no Grade 3 treatment-related SAEs to date
- No clinically significant complement activation
- Minimal, transient LFT elevations
- No signs of frataxin over-expression observed in cardiac tissue
- One previously disclosed, possibly treatment-related Grade 2 event of asymptomatic myocarditis observed one year after dosing

1- Participant 11 6-month visit not conducted due to hurricane; 3-month visit used for mean calculations. (2) Participant 10 not included in Hs-TNI chart due to scale. Values are +29% at 6M, +45% at 9M, +2,702% at 12M, +1,857% at 18M, +1,620% at 21M, and +1,458% at 24M as of most recent safety monitoring.
Note: Data as of September 2026.

Cardiac function improvement observed in individual with later stage cardiomyopathy

Effect of LX2006 on Cardiac Function

Majority of Participants (16/17)

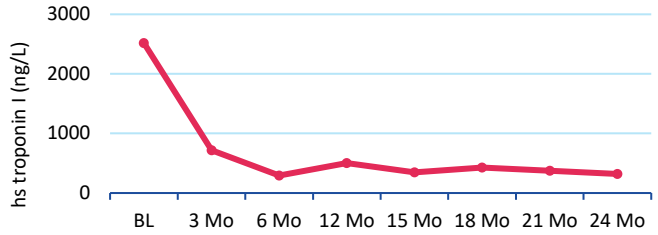
- **Baseline LVEF:** Normal
- **Post therapy:** No change

One Participant (#13) with later stage cardiomyopathy

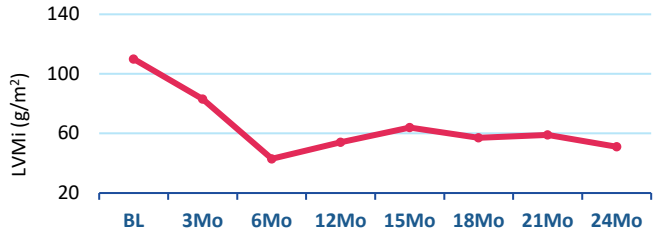
- **Baseline LVEF:** Low (35%)
- **Post Therapy:** Significant improvements across all cardiac biomarkers

Cardiac Improvements 24 months Post LX2006 Treatment in Participant with Low Baseline LVEF

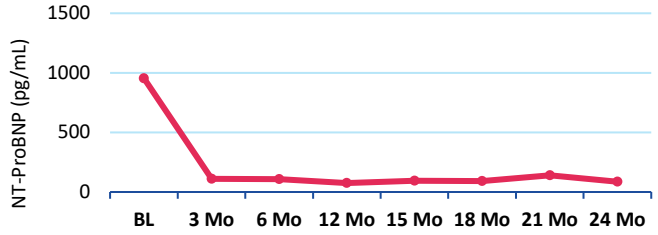
Biomarker: High-Sensitivity Troponin I
86% reduction



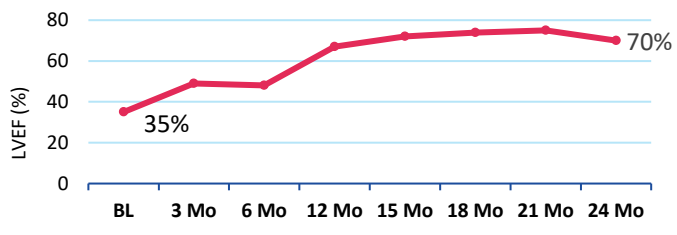
Cardiac MRI: LVMi
54% reduction



Biomarker: NT-Pro-BNP
91% reduction



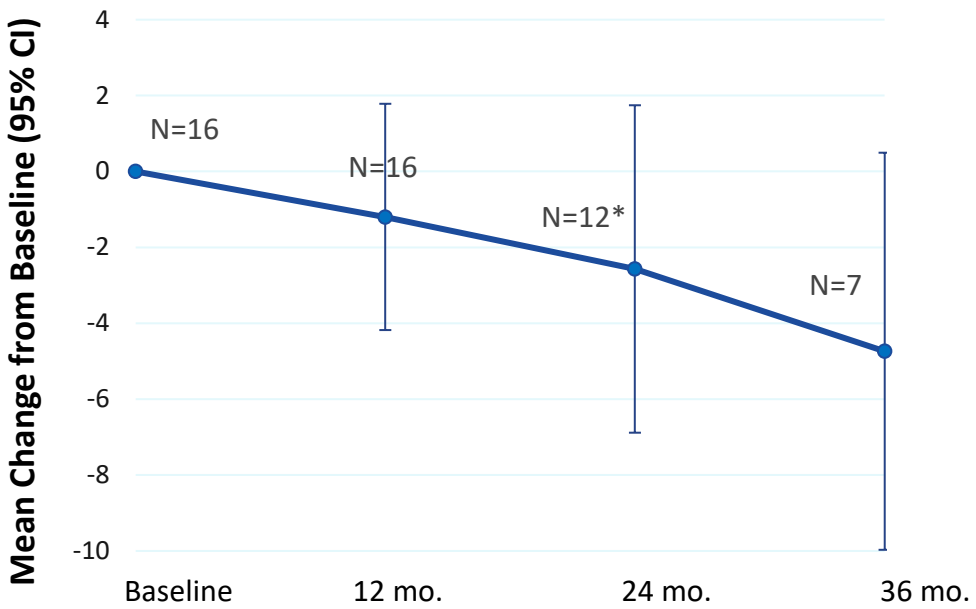
Cardiac MRI: LVEF



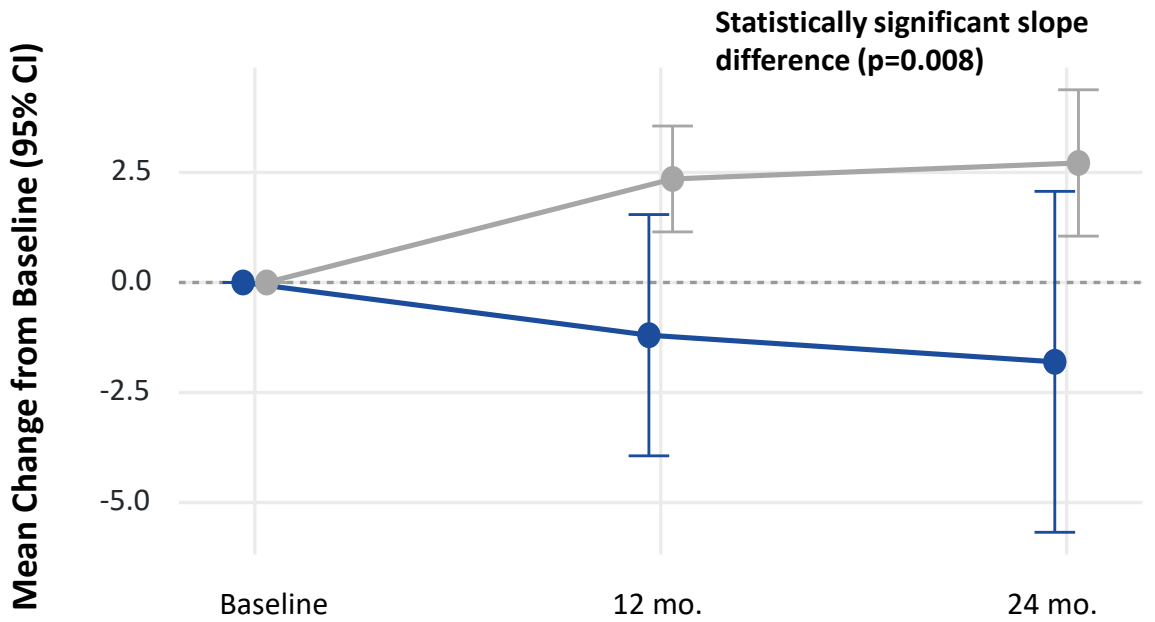
BL, Baseline; LVMi, Left ventricular mass index; LVEF, Left ventricular ejection fraction; MRI, Magnetic resonance imaging; NT-Pro-BNP, N-terminal pro-B-type natriuretic peptide.
Note: Data as of September 2026.

Sustained and deepening neurological improvement observed with LX2006 at 36 months

Mean change in mFARS:



Change in mFARS (Total): Open Label Cohort (n=16) vs. UNIFAI Matched Control (n=44)[1]



- mFARS validated clinical scale measures FA neurological progression; higher scores represent disease worsening
- Among all participants with 24 months of follow-up (n=11), treatment with LX2006 resulted in a **mean improvement of 2.13 points per year, or 4.26 points over two years, on the mFARS scale compared to propensity-matched control**
- Among a subset of participants with **36 months of follow-up (n=7), treatment with LX2006 resulted in further improvement, with a mean change of over 4 points relative to baseline**

mFARS, Modified Friedreich Ataxia Rating Scale; PSM, propensity score matched.
Note: Data as of September 2026; *Participant #3 missed the Month 24 visit; Month 21 data were used instead.
1. 16 patients treated with LX2006 in the Open Label study were matched to a control group of individuals in the Friedrich Ataxia Global Clinical Consortium UNIFIED Natural History Study of Friedrich's Ataxia (UNIFAI) in a 3:1 ratio. While some patients did not have 2 years of follow up, this model is using every patient's earlier visits to inform the rate-of-change estimate for mFARS (an annualized slope). Analysis performed by Christian Rumney in partnership with FARA.

Finalized SUNRISE-FA 2 pivotal protocol and SAP for LX2006

SUNRISE FA2

- **Study design:** Open-label pivotal study with untreated control arm (no placebo or sham)
- **Dose:** $1.2x10^{12}$ vg/kg, one-time IV infusion
- **Sample Size:** 26 participants, 13 participants treated with LX2006
- **Key Eligibility Criteria:**
  - 16 years and older: Abnormal baseline LVMi, ≥2SD above normal mean
  - 6 to <16 years: Abnormal baseline LV wall thickness, assessed via echocardiography. Pediatric cohorts assessed primarily for safety
- **Primary Endpoint:** LVMi, via cMRI at 6 months
- **Statistical Analysis Plan:** Pivotal arms stratified to balance baseline LVMi
  - Study powered for 15% or greater LVMi change at 6 months
- **Key Secondary Endpoints:** mFARS, KCCQ, Hs-Troponin I, lateral wall thickness
- **Confirmatory Evidence Strategy:** Lexeo remains in ongoing discussions with the FDA regarding potential use of certain secondary endpoints at the 12-month time point in SUNRISE-FA 2 to support full approval

Expect topline data in the second half of 2027 and a potential BLA filing in the first half of 2028

Vg/kg, vector genomes per kilogram; LVMi, left ventricular mass index; cMRI, cardiac magnetic resonance imaging; mFARS, modified Friedreich Ataxia Rating Scale; KCCQ, Kansas City Cardiomyopathy Questionnaire; Hs, high sensitivity.

LEXEO therapeutics

SUNRISE-FA 2 is supported by clinical evidence, robust study design and execution readiness

Phase I/II LVMi Reductions Exceeded the Threshold Used to Power SUNRISE-FA 2

- ~18% LVMi reduction observed at 6 months, with ~28% reduction in higher dose cohorts (2 & 3) in patients with abnormal baseline LVMi[1]
- Effect exceeds both the 10% clinically meaningful benchmark and the 15% powering threshold for SUNRISE-FA 2
- LVMi has not been shown to improve without intervention

Observed Phase I/II efficacy exceeds assumptions incorporated into the pivotal study design

Study Design Maximizes Ability to Detect a Clinically Meaningful Treatment Effect

- Stratification ensures balanced distribution of disease severity and aligns study population
- Monte Carlo simulations support study assumptions

>99% of simulated trials met or exceeded the 15% powering threshold, with most outcomes exceeding by a wide margin

Execution Readiness With Clear Catalyst Path

- First SUNRISE-FA 2 participant enrolled in June 2026
- CLARITY-FA enrollment continues to advance and supports identification of eligible participants into pivotal study; 19 active sites across 8 countries
- Topline data expected in 2H 2027; potential BLA submission in 1H 2028

Operational infrastructure is in place to support key milestones through topline data and potential registration

Phase I/II data exceeded pivotal-study assumptions, statistical simulations demonstrate a high likelihood of achieving the primary endpoint, and operational execution is already underway, providing multiple independent sources of confidence in SUNRISE-FA 2

1 -Participant 11 6-month visit not conducted due to hurricane; 3-month visit used for 6 month mean calculation.

FA patients are highly concentrated and readily identifiable

FA Patient Populations



Patient Identification

- Majority of FA patients are managed at a limited number of specialized treatment centers
- Most target patients are genetically confirmed and actively followed at academic institutions
- Established partnerships with leading FA patient advocacy organizations facilitate patient identification and community outreach
- Existing relationships with multidisciplinary FA care teams, including cardiologists managing FA-CM, support efficient patient identification, evaluation and treatment activation

Addressable FA patients are concentrated within a small network of specialty centers, creating a clear and efficient path to patient identification, referral and treatment for LX2006 if approved

Sources: Data on file. Katharina Buesch & Rongrong Zhang (2022) A systematic review of disease prevalence, health-related quality of life, and economic outcomes associated with Friedreich's Ataxia, Current Medical Research and Opinion, 38:10, 1739-1749, DOI: 10.1080/03007995.2022.2112870.

Strong path forward for LX2006



Clinical Development

SUNRISE-FA 2 Initiated with First Patient Enrolled in June 2026



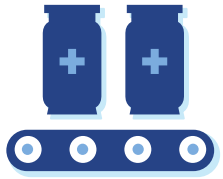
Clinical Results

Phase I/II Results Exceed the Effect Size in LVMi Used to Power the Pivotal Study



Commercial Preparation

Building Internal Commercial Capabilities to Support Successful Launch



Manufacturing & Supply

Differentiated AAVrh.10 Capsid and Commercial-Ready CMC Supply Chain

Next Steps

- Continued FDA engagement on confirmatory evidence strategy; update expected once finalized
- Topline data readout expected in **second half of 2027**
- Potential BLA submission under accelerated approval pathway in **first half of 2028**

EARLIER STAGE FRIEDREICH ATAXIA PROGRAMS



Lexeo's FA platform also includes four differentiated approaches to increasing or replacing frataxin for the treatment of FA

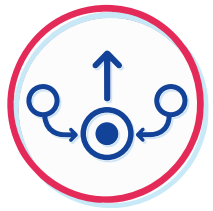
Program	Therapeutic approach	Stage	Route	Role in FA platform
LX3010 (MTL-104)	Oral combination designed to increase frataxin through complementary mechanisms	Clinical	Oral	Potential complementary oral approach
LX3030 (MTL-707)	Third-generation benzamide HDAC inhibitor designed to increase production of endogenous frataxin	Preclinical	Oral	Potential differentiated oral approach
LX3050 (MTL-501)	TfR1-targeted frataxin-replacement fusion protein	Preclinical	IV	Potential tissue-directed protein replacement
LX3070 (MTL-801)	TfR1-targeted antisense oligonucleotide for FXN mRNA stabilization	Discovery	IV	Potential CNS-directed RNA approach

Plan to prioritize investment on the opportunities with the strongest potential for clinical patient impact, regulatory success and shareholder value creation

HDAC, histone deacetylase; FXN, frataxin; TfR1, transferrin receptor 1; mFARS, modified Friedreich Ataxia Rating Scale.

LEXEO therapeutics

Program highlights: Differentiated oral approaches to increase frataxin

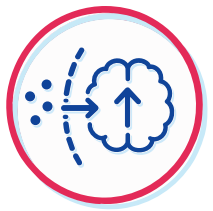


LX3010

Clinical-stage, oral combination designed to increase frataxin through complementary mechanisms

- Approximately six-point improvement in mFARS scores at 16 weeks
- Mean nine-fold increase in frataxin protein levels from baseline in muscle biopsies across 11 FA patients
- Convenient oral formulation designed with the needs of individuals with FA in mind
- Potential differentiated approach supported by both an early functional signal and evidence of increased FXN protein levels

Early functional and biological signals support the potential for a differentiated oral approach



LX3030

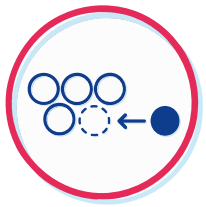
Third-generation oral small molecule (sub-500Da) designed to increase production of endogenous frataxin in the CNS

- Builds on prior scientific validation of the HDAC target class
- Designed to enhance frataxin upregulation and central nervous system exposure
- Preclinical studies demonstrated robust increases in frataxin
- Potential differentiated oral approach to addressing the neurological manifestations of FA

Differentiated oral profile combining robust frataxin upregulation with CNS exposure

mFARS, modified Friedreich Ataxia Rating Scale; FA, Friedreich ataxia; CNS, central nervous system; HDAC, histone deacetylase.

Program highlights: Complementary approaches to restore frataxin

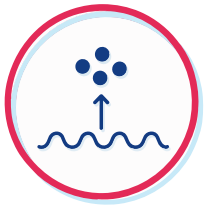


LX3050

Preclinical recombinant human frataxin fused to a proprietary anti-TfR1 Fab, designed to directly replace deficient frataxin and increase delivery to the brain

- Directly replaces deficient frataxin rather than depending on increased endogenous production
- TfR1 brain shuttle supports delivery across the blood-brain barrier and into multiple disease-relevant tissues
- In vitro studies demonstrated dose-responsive improvements in measures of mitochondrial function

Direct protein replacement diversifies the platform beyond approaches that rely on endogenous frataxin production



LX3070

Discovery-stage ASO Fab conjugate program designed to stabilize FXN mRNA and increase translation of endogenous frataxin protein

- Differentiated RNA mechanism designed to increase the body's own production of frataxin
- Combines an RNA-targeted mechanism with a proprietary anti-TfR1 Fab
- In vitro studies demonstrated dose-responsive increases in frataxin
- Potential CNS-directed RNA approach that further diversifies Lexeo's multimodal FA platform

CNS-directed RNA stabilization creates an additional path to increasing endogenous frataxin

TfR1, transferrin receptor 1; ASO, antisense oligonucleotide; FXN, frataxin; CNS, central nervous system.

Lexeo's research collaborations also support sequential dosing of CNS-targeted gene therapy

Weill Cornell Medicine

Sequential dosing

Sponsored research agreement evaluating intra-cisternal administration of LX2006 following systemic dosing in large animal models.

Apertura GENE THERAPY

Blood Brain Barrier-Crossing Capsid

Option agreement providing the opportunity to secure a license to a novel IV, BBB-crossing capsid.

Vivet THERAPEUTICS

Novel immune suppression strategies

Option agreement providing the opportunity to secure an exclusive license to VTX-PID, an IgG-degrading enzyme.

CNS, central nervous system; IgG, immunoglobulin G.

LEXEO therapeutics

Unlocking the full spectrum of FA

Neurological burden can span the full continuum

Cardiomyopathy Spectrum

No cardiomyopathy	Mild CM	Moderate CM	Advanced CM
Neuro-predominant disease	Diagnosed cardiac involvement	Moderate cardiac disease	Greater cardiac disease burden

Potential label-broadening opportunity for LX2006 pending additional mFARS data

LX2006 FA-CM Opportunity
Potential disease-modifying gene therapy for FA cardiomyopathy

Future Multimodal Platform Potential

Complementary modalities with potential standalone, sequential or combined use with LX2006

Potential reach regardless of cardiomyopathy status or stage

Gene therapy | **Small molecules** | **Protein replacement** | **RNA-based** | **Neuro-targeted collaborations**

LX2006 has the potential to serve as the cardiac foundation of a broader multimodal FA platform addressing both cardiac and neurological disease

FA, Friedreich ataxia; FA-CM, Friedreich ataxia cardiomyopathy; CM, cardiomyopathy; mFARS, modified Friedreich Ataxia Rating Scale.

CARDIAC PROGRAMS

PLAKOPHILIN 2 ARRHYTHMOGENIC CARDIOMYOPATHY

Gene Therapy LX2020

LEXEO therapeutics

PKP2 arrhythmogenic cardiomyopathy is a progressive genetic heart disease with significant unmet need



Disease overview

- Rare, genetic cardiac disease
- Caused by loss of function mutations in the *PKP2* gene
- Progressive replacement of cardiac muscle with fatty fibrotic tissue[1,2]
- **~60,000** affected in the U.S.



Cardiac impact

- Disrupted electrical signaling → **ventricular arrhythmias and sudden cardiac death (SCD)**[1,2]
- **~23% of individuals present with SCD**[3,4]
- Progressive disease associated with **reduced quality of life**[3,4]



The unmet need

- **No therapies address the underlying genetic cause of ACM**
- Current management focuses on symptom control and SCD prevention (e.g., ICDs)[2,3]
- Disease progression continues despite intervention

PKP2-ACM has a clearly defined genetic cause alongside progressive, potentially life-threatening cardiac consequences, with no disease-modifying therapy today

ACM, arrhythmogenic cardiomyopathy; ICD, implantable cardioverter defibrillator; PKP2, Plakophilin-2; SCD, sudden cardiac death.

Sources: (1) Cedars-Sinai, 2023, Accessed from: https://www.cedars-sinai.org/health-library/diseases-and-conditions/a/arrhythmogenic-right-ventricular-dysplasia.html. (2) Corrado, D., et al. Cir Res, 2017;121:784-802; (3) Dalal, D. et al. Circulation, 2005;112:3823-3832. (4) Day, S.M., Circ: Cardiovasc Genet, 2012;5(1):2-4.

LEXEO therapeutics

Significant commercial potential for LX2020 given unmet need and global patient population

60K

Patients in the U.S.

Larger-rare, diagnosed population

>$4-6B

Total addressable market opportunity

Significant commercial upside at peak



Global prevalence

Pivotal study feasible across US, EU, Asia and other geographies



Trial ready

Broad patient pool expected to support rapid recruitment

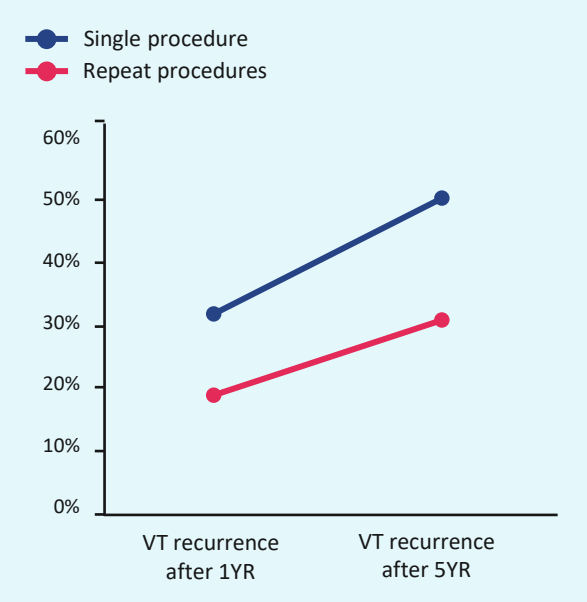


Manufacturing scale

Differentiated Lexeo process will enable rapid and cost-efficient supply

Current therapies may help manage arrhythmias, but limitations in durability, efficacy & tolerability leave a significant unmet need

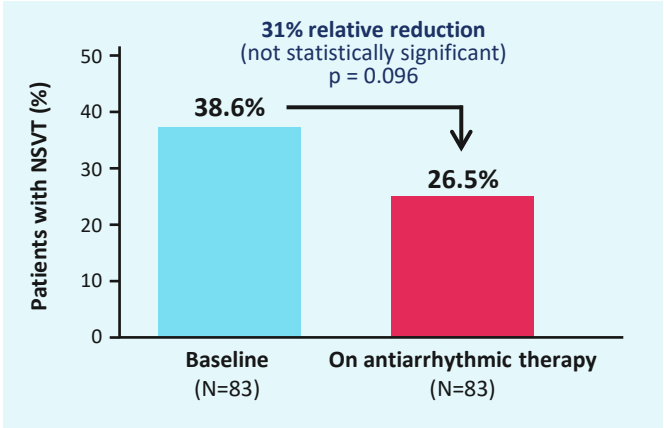
Severe arrhythmia recurrence common after ablation



50% VT recurrence reported within 5 years after a single procedure[1]

Limited reduction in NSVT burden with available drugs

Effect of antiarrhythmic therapy flecainide on NSVT in PKP2-ACM population
Largest available dataset[2]



~39% of those with PKP2-ACM experienced NSVT prior to treatment, and ~27% continued to experience NSVT after treatment (31% relative reduction)

Safety and tolerability may limit long-term use of AADs*

- Flecainide may increase the risk of **proarrhythmia and conduction abnormalities**
- Amiodarone is associated with **pulmonary, thyroid, hepatic, ocular, and dermatologic toxicities**, particularly with long-term use
- Chronic use may require **ongoing safety monitoring and treatment modification**
- **Existing therapies are not approved for ACM and are used off label**

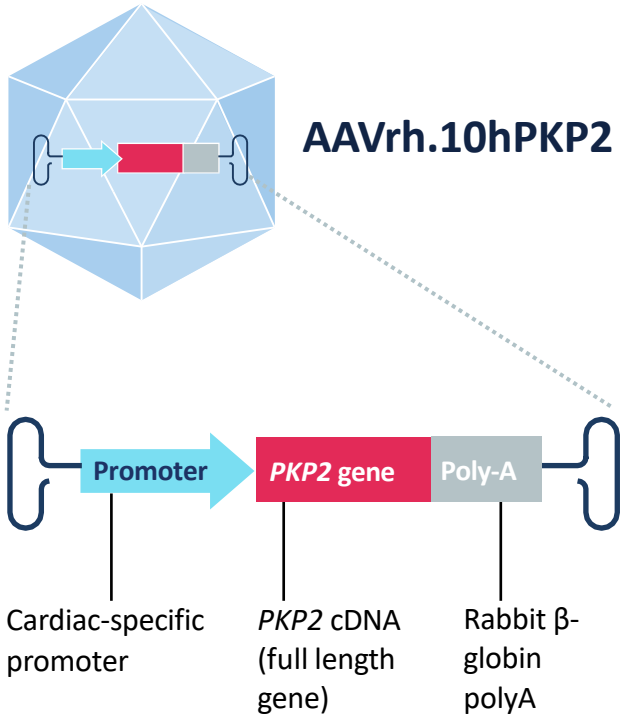
Existing therapies may reduce arrhythmia burden but overall efficacy in PKP2-ACM may be limited and certain AADs present tolerability concerns

Importantly, no existing therapies address the underlying genetic cause of ACM; Disease progression continues despite intervention

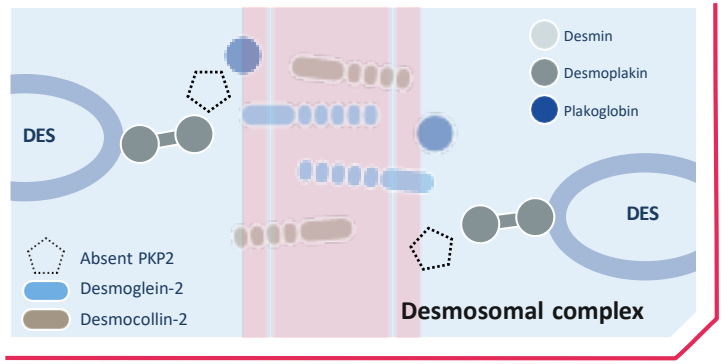
*AADs, aanti-arrhythmia drugs; ACM, arrhythmogenic cardiomyopathy.
Sources: (1) Daimee et al 2021 n=166. (2) Gaine et al. 2025, N=83.

LX2020 delivers a full-length PKP2 gene to cardiomyocytes, restoring the desmosome

LX2020 construct:

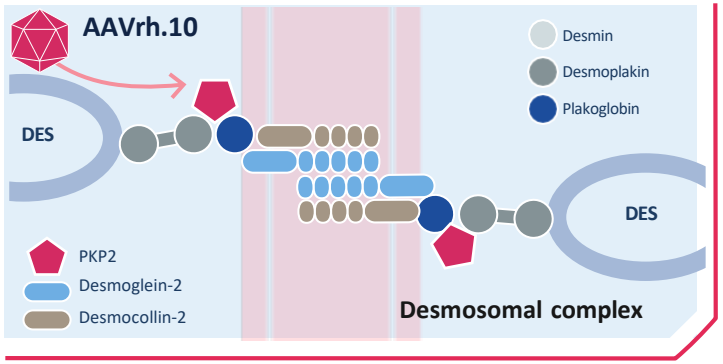


PKP2-ACM:



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

LX2020 mechanism:



PKP2 expression **is expected to restore the balance of desmosomal proteins** by scaffolding adjacent cell-cell junctional proteins

The restoration of PKP2 may lead to **improvement in cardiac electrical and mechanical function** as well as **inhibit further structural damage**

AAV, Adeno-Associated Virus; PKP2, Plakophilin-2; cDNA, Copy DNA; Poly-A, Poly Adenosine, ACM; arrhythmogenic cardiomyopathy.

LX2020 is being evaluated in an ongoing Phase I/II study: HEROIC-PKP2

1

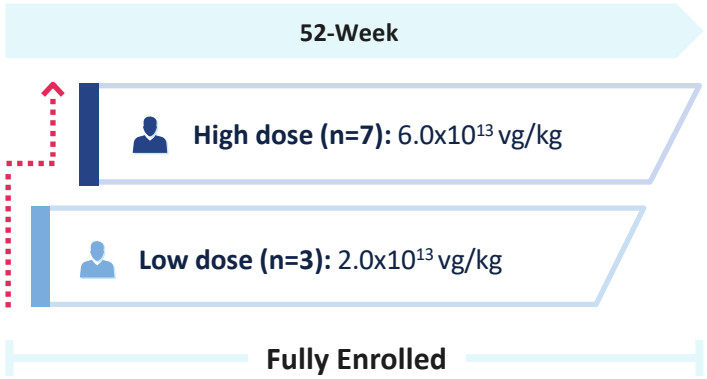
Study Design & Objective

Design:

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

Objective:

To assess the **safety** and **efficacy** of LX2020 in individuals with PKP2-ACM



2

Key Inclusion Criteria

- Adults (18-65 years)
- Diagnosis of ACM with documented *PKP2* mutation
- Existing ICD that is MRI compatible
- Minimum threshold of PVCs/24-hr
- Neutralizing anti-AAVrh.10 titer cutoff

3

Key Measurements

- Ventricular arrhythmias and associated measures (PVC, NSVT, VT, QRS)
- Cardiac structure & function (EF, EDV, ESV, RV strain)
- Change in symptoms (NYHA Class and PROs)
- Vector Transduction & Expression

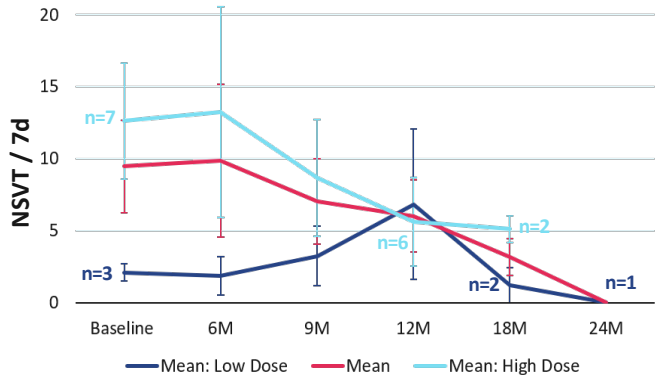
ACM, arrhythmogenic cardiomyopathy; ICD, implantable cardioverter defibrillator; PVC, premature ventricular contraction; NSVT, non-sustained ventricular tachycardia; VT, ventricular tachycardia; EF, ejection fraction; EDV, end-diastolic volume; ESV, end-systolic volume; RV, right ventricular; NYHA, New York Heart Association; PROs, patient reported outcomes.

Note: LX2020 is administered systemically; participants receive immune suppression with prednisone and sirolimus on the day prior to treatment through ~14 weeks following LX2020 dosing. Lexeo has also sponsored SNAPSHOT, a retrospective EMR review and prospective observational natural history study (n=15).

Interim LX2020 data demonstrate clinically meaningful reductions in severe arrhythmia burden

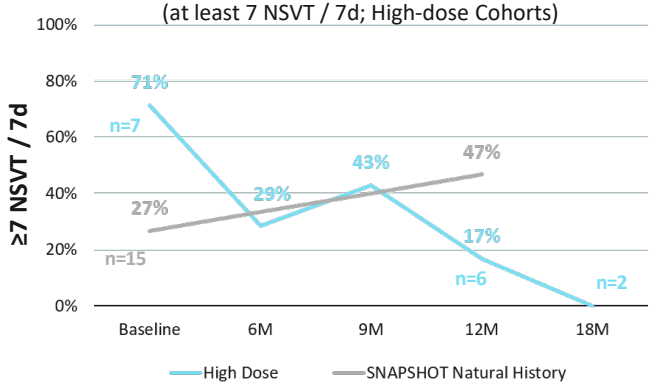
NSVT:

Mean NSVT Change



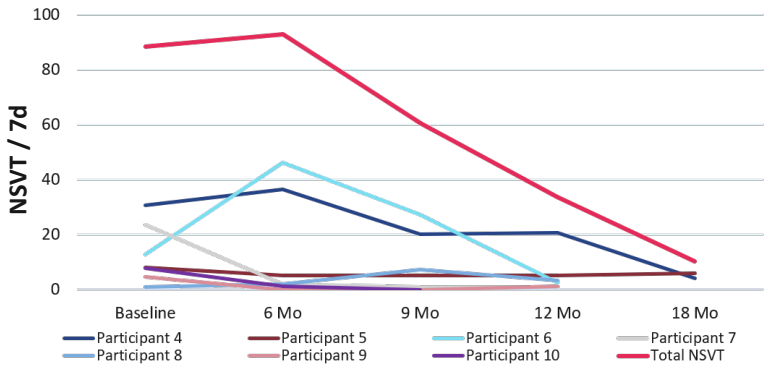
- **Deepening NSVT reduction over time with 80% mean reduction** at latest visit in high-dose cohorts (n=7); 53% increase in NSVT at 12 months in SNAPSHOT natural history study (n=15)

% Participants with Significant NSVT Burden
(at least 7 NSVT / 7d; High-dose Cohorts)



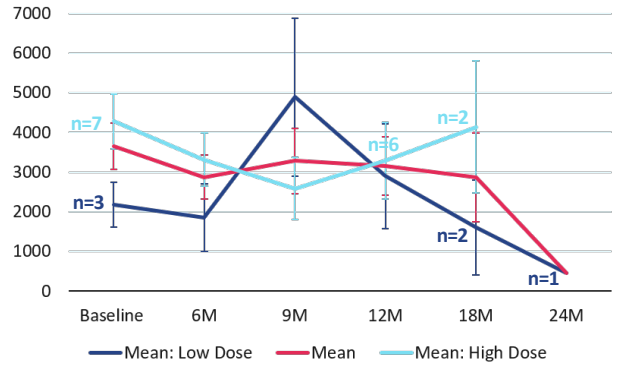
- **5 of 6 participants experienced <1 NSVT per day at 12 months**, a clinically relevant threshold to predict risk of future sustained and life-threatening arrhythmias

NSVT Change Per Participant



- **NSVT improved in 6/7 participants** at latest visit relative to baseline; **in most participants, NSVT reductions were substantial**

Mean PVC Change:



LX2020 generally well tolerated

- LX2020 generally well tolerated across 10 participants dosed
- No clinically significant complement activation
- No study discontinuations
- Previously disclosed LFT elevations observed in high-dose cohorts were successfully managed per protocol with no hospitalizations or complications
- One previously disclosed Grade 3 SAE of sustained ventricular tachycardia (VT), consistent with the natural course of PKP2-ACM

Sources: (1) Gasperetti A, et al. JAMA Cardiol. 2022;7(4):378-385.
Note: Data as of October 15, 2026. Participant 3 (low dose) declined 18-month follow up visit but is expected for 24-month follow up.
NSVT, non-sustained ventricular tachycardia; PVC, premature ventricular contraction; LFT, liver function tests; SAE, serious adverse event; ACM, arrhythmogenic cardiomyopathy.

Strong path forward for LX2020

1



Meaningful Clinical Activity

LX2020 continues to demonstrate improvements across multiple measures of disease burden and patient experience

2



Increasing Confidence in Dataset

Additional follow-up strengthens the durability, consistency, and overall benefit-risk profile of LX2020

3



Clear Path Forward

FDA open to guideline-defined NSVT[1] as a primary surrogate endpoint to support potential accelerated approval of LX2020

Interim HEROIC-PKP2 data continue to support LX2020's potential as the first disease-modifying therapy for PKP2-ACM

Sources: Al-Khatib SM, et al. Circulation. 2018;138:e272–e391. Carrick RT, et al. Circ Arrhythm Electrophysiol. 2022;15:e011207.

(1) NSVT defined in guidelines as hemodynamically stable ventricular tachycardia at a rate of >100 beats per minute, lasting three or more beats and less than 30 seconds.

LEXEO therapeutics

PRECLINICAL CARDIAC PROGRAMS

LEXEO therapeutics

Lexeo is also advancing two preclinical cardiac gene therapy programs

LX2021

DSP (Desmoplakin) Cardiomyopathy

- Significant unmet need characterized by extensive fibrosis, high arrhythmic risk and substantial heart failure burden
- 30-50% mortality within 5 years of diagnosis for dilated phenotype
- ~35K patients in the U.S.
- IND-enabling studies ongoing

LX2022

Hypertrophic Cardiomyopathy

- TNNI3 variants compose 3-5% of all HCM cases, causing cardiomyopathy, clinical heart failure and shortened lifespan
- Non-obstructive phenotype, often with preserved ejection fraction; myosin inhibitors not effective
- ~25K patients in the U.S.

+Research collaboration with Johnson & Johnson exploring novel routes of administration for cardiac AAV gene therapy to maximize safety and efficacy

THANK YOU