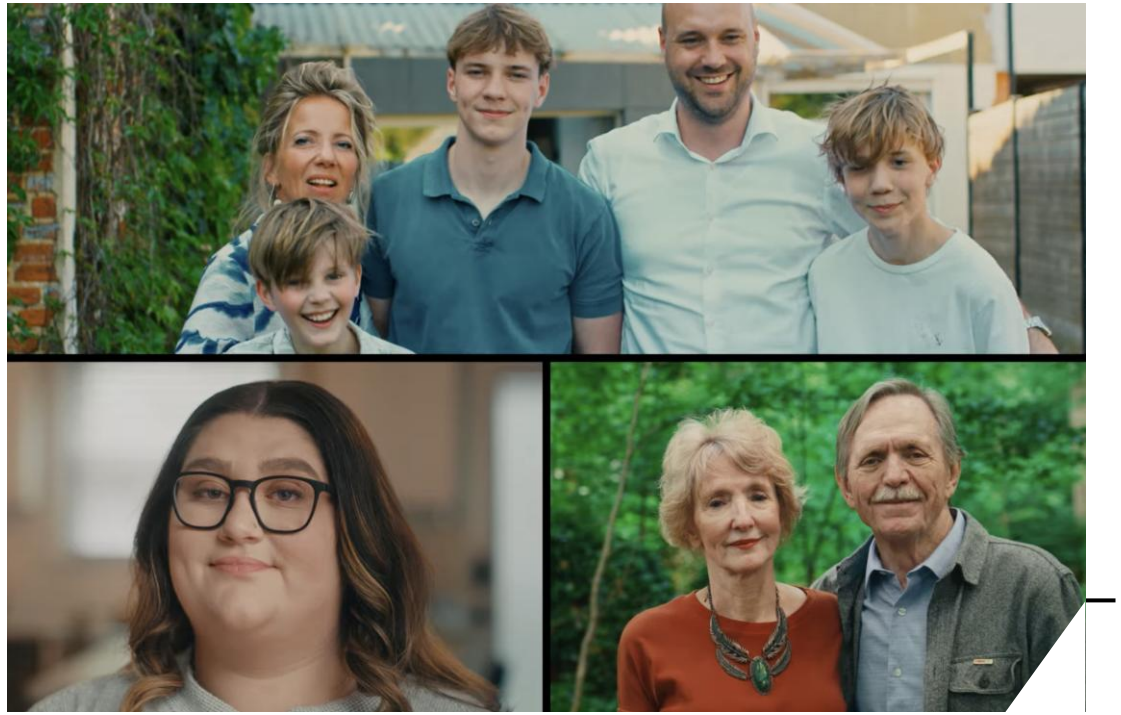
Lexeo Therapeutics
Corporate Overview

June 2026

Forward-looking statements

This presentation contains “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 and 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: the outcome of ongoing discussions with the U.S. Food and Drug Administration (FDA) regarding the design of our pivotal trial for accelerated approval pathway and the design of our confirmatory study for obtaining full approval; 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; topline data and final results from our pivotal trial; delays in submission of regulatory filings or failure to receive regulatory approval; risks and uncertainties related to global macroeconomic conditions and related volatility; 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, 2026, filed with the SEC on May 11, 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



Dedicated to **reshaping heart health** by applying pioneering science to fundamentally change how cardiovascular disease is treated

Individuals and families impacted by Friedreich ataxia

LEXEO therapeutics

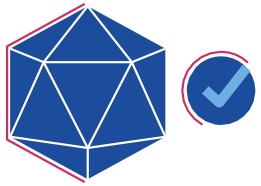
- **Genetic medicine leader with rare cardiac disease focus**
- **Proven experience in the clinic**
- **Platform designed for safety and scalability**

LEXEO therapeutics

Building a leading cardiac gene therapy platform

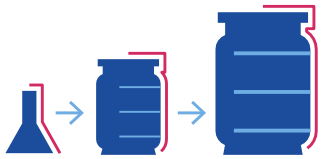
Genetic cardiac disease expertise

Leader in genetic medicine for inherited cardiac diseases



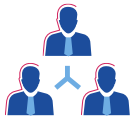
Differentiated AAVrh10 capsid

Proven cardiac tropism allows for lower doses and improved therapeutic index



Innovative AAV manufacturing

Optimized Sf9 baculovirus manufacturing platform designed to support future commercial scale-up



Operating experience

Deep cardiac genetic medicine know-how, anchored by two clinical and two preclinical programs

Strong financial position

Cash runway into 2028, supporting multiple value creating milestones

LEXEO therapeutics

Advancing cardiac genetic medicines in diseases with high unmet need

Market opportunity:

High unmet need
Cardiomyopathies have few disease-modifying therapies and high morbidity/mortality

White space
Cardiac gene therapy is less competitive, offering opportunity to establish leadership

Transformative potential
Lexeo's vision is to fundamentally change the course of inherited cardiac disease with a single infusion

Lexeo cardiac programs and expertise:

Clinical:

- **LX2006** — Friedreich Ataxia Cardiomyopathy
- **LX2020** — PKP2 Arrhythmogenic Cardiomyopathy

Proven clinical experience with 27 patients treated using AAVrh10

Pre-Clinical:

- **LX2021** — Desmoplakin Cardiomyopathy
- **LX2022** — Hypertrophic Cardiomyopathy

Deep expertise in genetic cardiac disease models and IND enabling studies

LEXEO therapeutics

Lexeo's AAVrh10 is a highly differentiated capsid

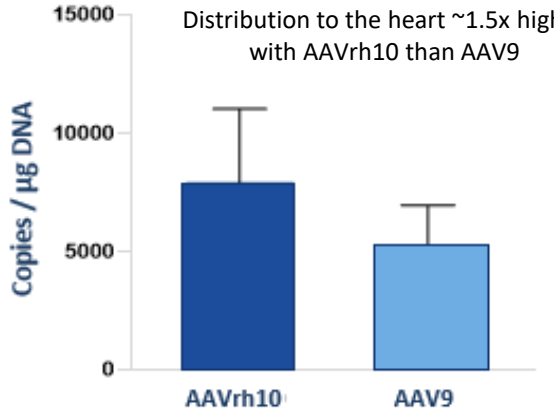
Cardiac tropism of AAVrh10 may allow lower doses for cardiac gene therapy

- **AAVrh10 cardiac tropism may allow for lower doses** compared to other vector serotypes while achieving targeted transgene biodistribution
- 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 has been utilized systemically across multiple Lexeo clinical programs with **no clinically significant complement activation**; both LX2006 and LX2020 have been generally well-tolerated to date

Compelling Cardiac Tropism

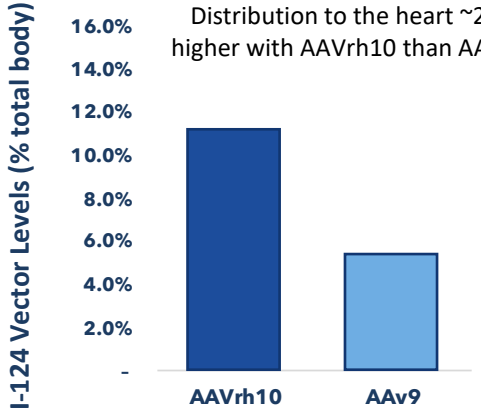
Yucatan Minipig Biodistribution(1)

Distribution to the heart ~1.5x higher with AAVrh10 than AAV9

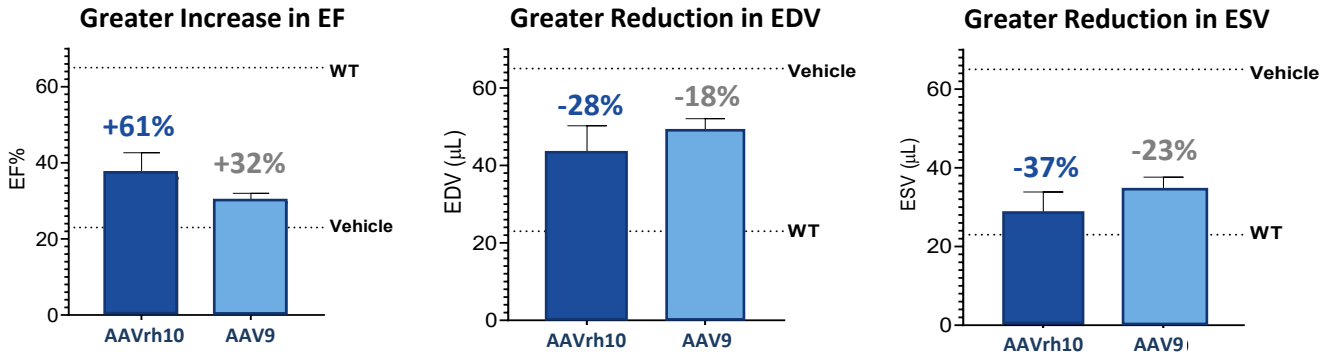


NHP Biodistribution(2)

Distribution to the heart ~2x higher with AAVrh10 than AAV9



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



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

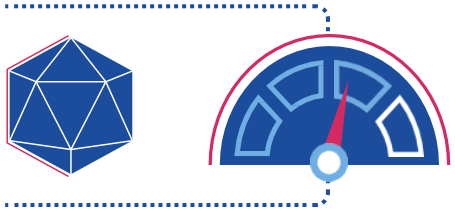
1 - Data presented at ASGCT 2023.
2 - Ballon DJ et al, Human Gene Therapy, 2020.

Lexeo manufactures AAVrh10 utilizing an optimized Sf9 baculovirus process

Innovative approach

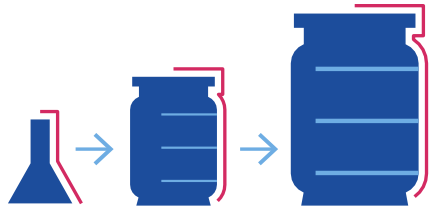
- High yield, high quality Sf9 baculovirus manufacturing platform compared to conventional manufacturing (e.g. HEK based)

- LX2006 selected for **FDA CDRP program,** created to facilitate CMC registrational readiness and support faster patient access



Optimal potency

- Higher yields (1.0E15 vg/L)
- Greater downstream recovery (>55%)
- Fewer empty AAV capsids (<25%)
- Improved genomic purity owing to lack of plasmid transfections



Scalable manufacturing

- Sustainable and defined starting materials, similar to therapeutic protein process (e.g. cell banks, virus banks)
- Low overall complexity
- Enables robust commercialization
- Poised to deliver an industry-leading and potentially transformational COGS profile

LEXEO therapeutics

Lexeo's two clinical stage programs address devastating cardiac diseases

Focus:

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

LX2006

Friedreich Ataxia Cardiomyopathy

- Only program with clinical-stage data in FA cardiomyopathy, 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 & SAP for accelerated approval; Study on track to initiate in Q2 2026; Expect topline data in 2H 2027 and potential BLA filing in 1H 2028

LX2020

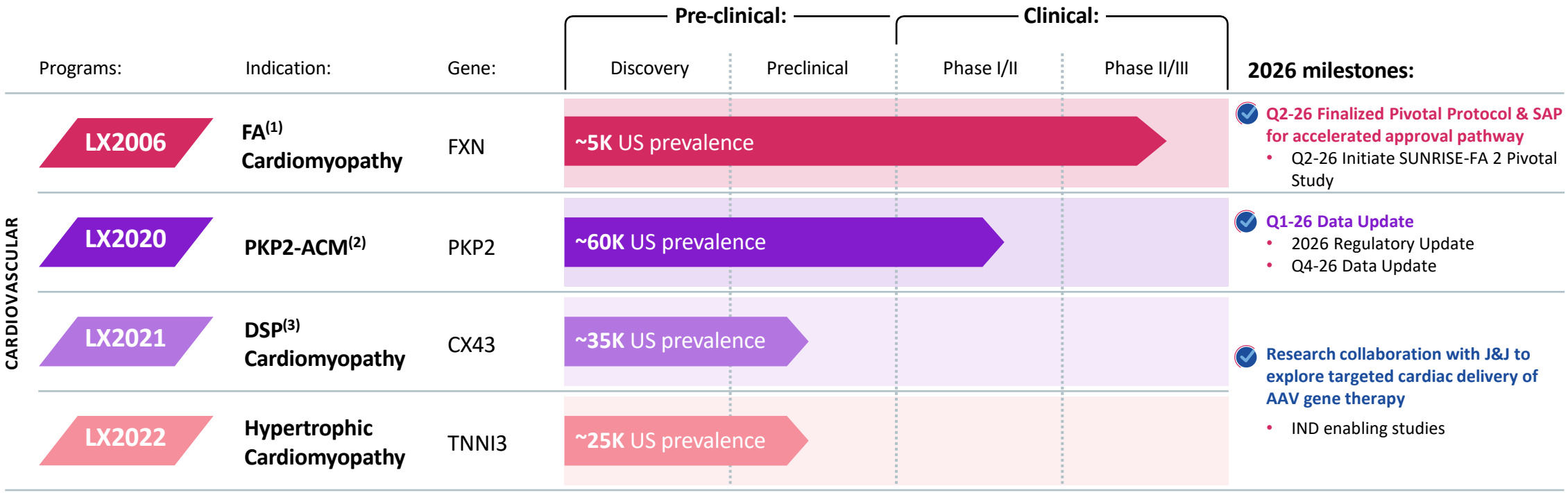
PKP2 Arrhythmogenic Cardiomyopathy

- Potential best-in-class treatment for PKP2-ACM; ~60K people in US with no disease-modifying treatment available
- Interim clinical data show encouraging early signals on efficacy and safety measures across patients dosed in the low and high dose cohorts
- 12-month data update for all high dose participants expected in Q4 2026; regulatory engagement expected in 2026.

FA - Friedreich Ataxia; FXN - Frataxin; LVMI - Left Ventricular Mass Index; ACM - arrhythmogenic cardiomyopathy; SAP – Statistical analysis plan.

LEXEO therapeutics

Our pipeline



Lexeo retains global rights across all programs.

1 - Friedreich ataxia.
2 - Plakophilin 2 Arrhythmogenic Cardiomyopathy.
3 - Desmoplakin.

LX2006

Friedreich Ataxia Cardiomyopathy (FA-CM)

Cardiac complications are the leading cause of death in Friedreich Ataxia

FA is a **rare, progressive and devastating multisystem disease** caused by a loss of function mutation in the FXN gene[1].

With a typical age of onset between 5 and 15 years[2], individuals with FA experience a combination of cardiac and neurological manifestations, with **cardiac complications accounting for up to 80% of deaths**[1]

Cardiac dysfunction in FA is associated with a multitude of symptoms but ultimately presents as **cardiac hypertrophy and subsequent heart failure**[1]; **hypertrophy in childhood** is potentially associated with a **more severe phenotype**, with earlier progression to end-stage disease[3]

The only approved disease-specific treatment for FA demonstrated efficacy on neurological measures but was not evaluated for the treatment of cardiac dysfunction in clinical trials, **leaving significant unmet need within FA cardiomyopathy**[4]

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

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

Cardiac complications account for **up to 80%** of deaths in those with FA, with an average life expectancy of 35–40 years[1,5]

Up to 40% of adults with FA have left ventricular hypertrophy as defined by abnormal LVMI[6,7]

FA - Friedreich Ataxia;
FXN - Frataxin;
LVMI - Left Ventricular Mass Index.

1 - Payne R.M. JACC Basic Transl Sci, 2022;13;7(12):1267-1283.
2 - Friedreich's Ataxia Research Alliance, 2024.
3 - Norrish G., et al. Arch Dis Child, 2022;107(5), 450–455.
4 - Reetz, K., et al. Lancet Neurol, 2025;24(7):614-624.
5 - Indelicato, E., et al. Mov Disord, 2024;39(3), 510–518.
6 - Clinical Management Guidelines for Friedreich Ataxia. Chapter 4. The heart and cardiovascular system in Friedreich ataxia. 2022.
7 - Lexeo Therapeutics, Data on File, 2025.

LEXEO therapeutics

Timely, multidisciplinary care is critical to diagnose and manage FA-CM

Individuals with FA typically present with cardiac symptoms in adolescence, and face an average life expectancy of 35-40 years

Symptom onset

Early signs often associated with the onset of ataxia

~5% of young children present with cardiac symptoms years before ataxia[2]

Journey to diagnosis

Journey to diagnosis with genetic test can take years

Guidelines recommend an EKG and ECHO at diagnosis and annually[5]

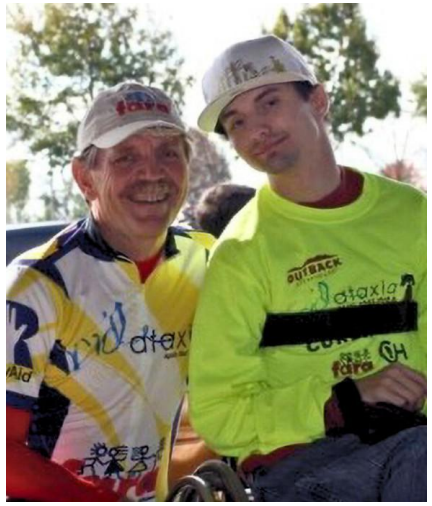
Cardiac dysfunction

Almost all individuals with FA will develop cardiomyopathy or cardiac dysfunction during their lifetime[1]

Life expectancy

Cardiac dysfunction is the cause of death in 60-80% of those with FA, often occurring by mid-30s[3,4]

Ron Bartek and his son, Keith, who passed from FA cardiomyopathy at age 24



"There are no approved treatments for the cardiomyopathy of FA. Time is of the essence.

Ron Bartek, Co-founder of FARA

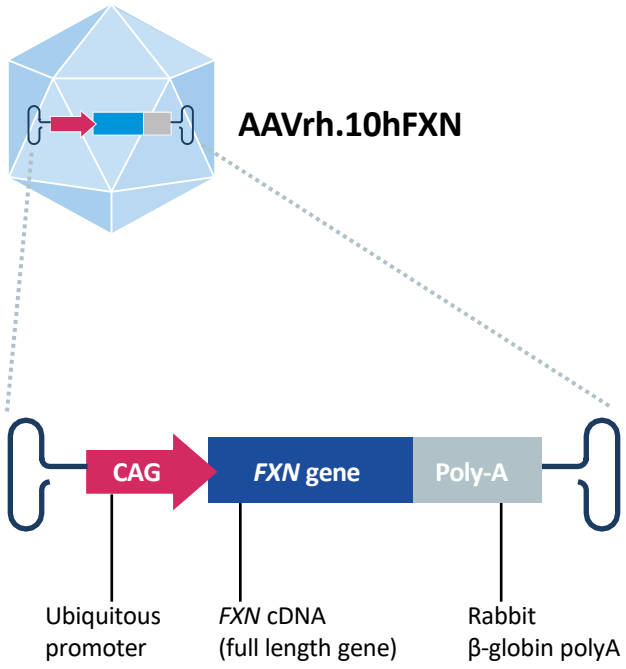
FARA Friedreich's Ataxia Research Alliance

1 - Regner S, et al. American Journal of Cardiology, 2012.
2 - Norrish G., et al. Friedreich's ataxia-associated childhood hypertrophic cardiomyopathy: a national cohort study. Archives of disease in childhood, 107(5), 450–455, 2022.
3 - Subramoney S, et al. MDA Clinical and Scientific Conference, 2023.
4 - Pousset, F. et al. JAMA Neurol, 2015;72(11):1334-1341.
5 - Clinical Management Guidelines for Friedreich Ataxia. Chapter 4. The heart and cardiovascular system in Friedreich ataxia. 2022.

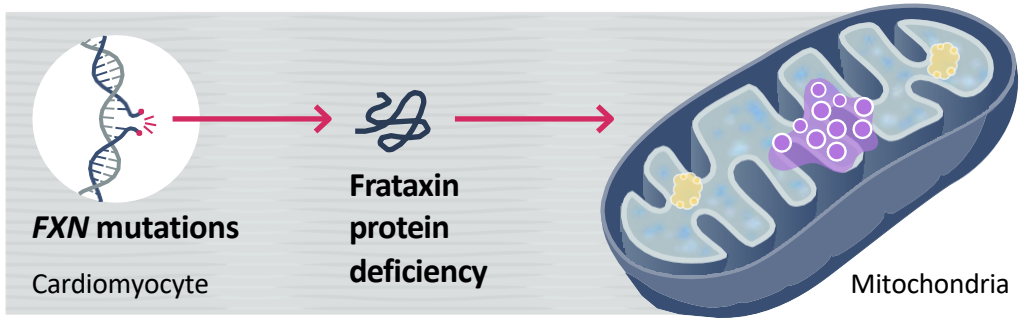
LEXEO therapeutics

LX2006 has the potential to treat the root cause of FA cardiomyopathy: significant decrease in frataxin in the heart

LX2006 construct:

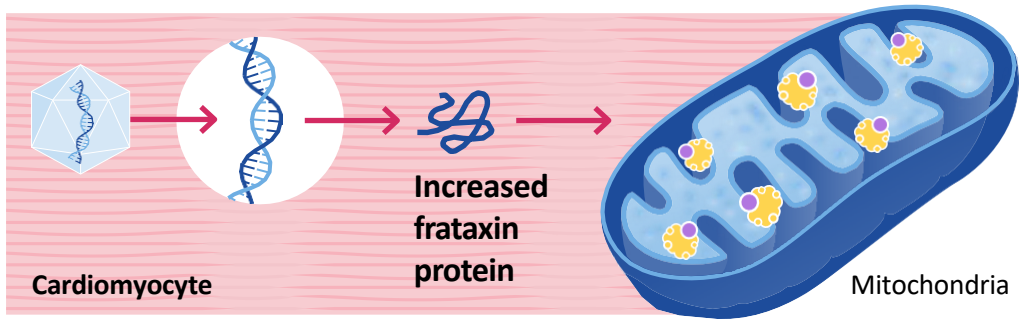


FA cardiomyopathy:



Frataxin deficiency results in **mitochondrial dysfunction** and leads to **deficient energy production** in hypertrophic cardiomyocytes

LX2006 mechanism:



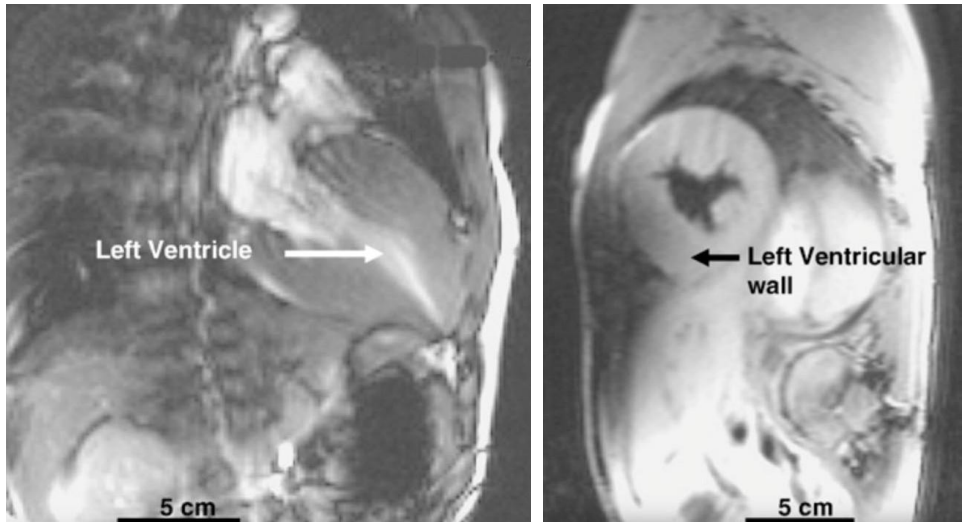
Transfer of *FXN* gene to cardiomyocytes is intended to **increase frataxin levels** in the mitochondria and **improve cardiac muscle cell function**

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)

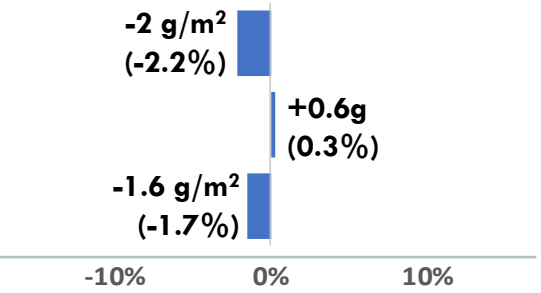
Natural history study showed a **19%** higher risk of death per 10g/m^2 (HR 1.19; 95% CI)[1]



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; FDA alignment on endpoint for pivotal trial in FA cardiomyopathy

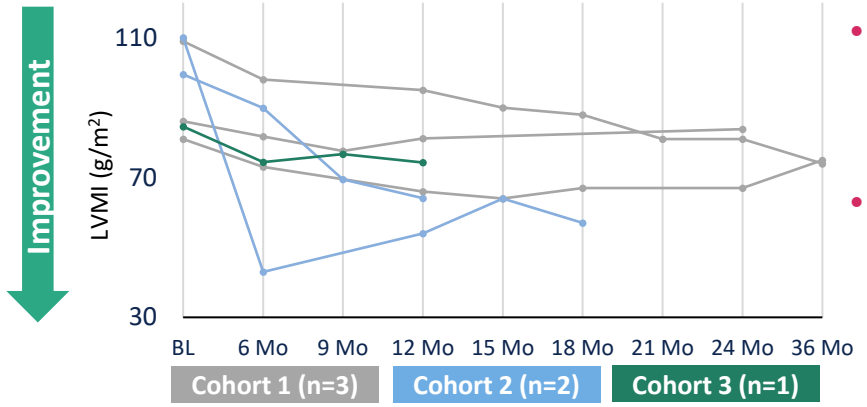
HR - Hazard Ratio; CI - Confidence Internal;
LVMI - Left Ventricular Mass Index.
Note: 10g/m^2 represents approximately 10% change in LVMI based on echocardiography measurements of upper bound of normal (105 g/m^2).

1 - Pousset, F. et al. JAMA Neurol, 2015;72(11):1334-1341.
2 - 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.

LEXEO therapeutics

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)



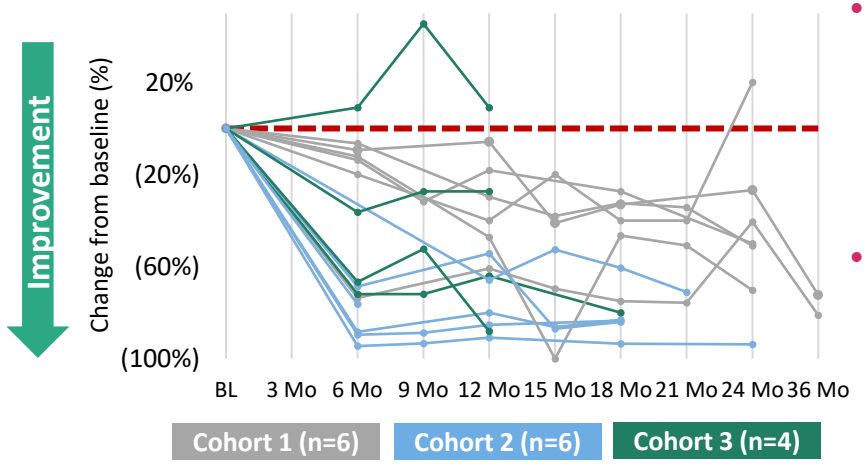
- Majority of participants reach or remain in normal LVMI range at latest visit
- **Durable LVMI improvement maintained out to three years following treatment**

Cardiac MRI: LVMI

Mean LVMI Change	
Participants at 12-mo visit *(n=6)*	**-23%**
Participants at 6-mo visit[1] *(n=6)*	**-18%**
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 December 2025.

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

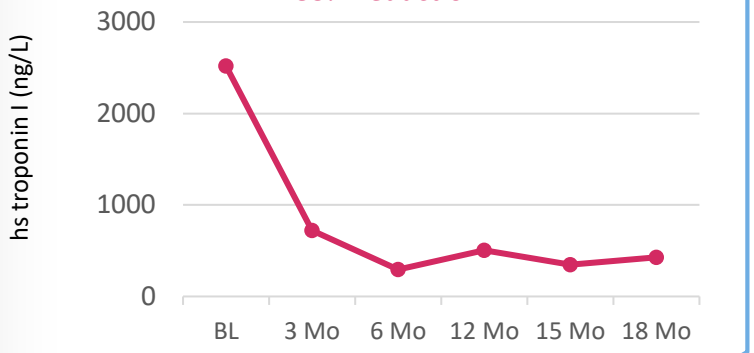
One Participant (#13) with later stage cardiomyopathy

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

Cardiac Improvements 18 months Post LX2006 Treatment in Participant with Low Baseline LVEF

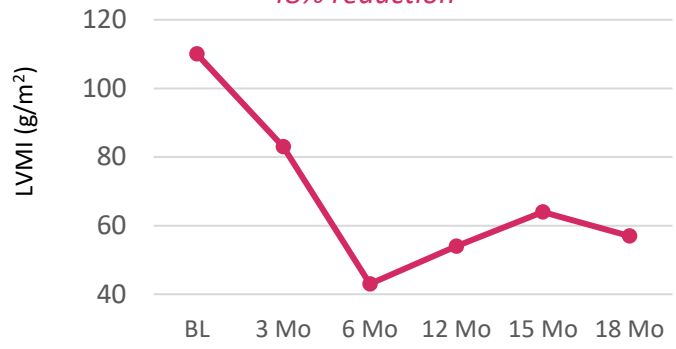
Biomarkers: High-Sensitivity Troponin I

83% reduction

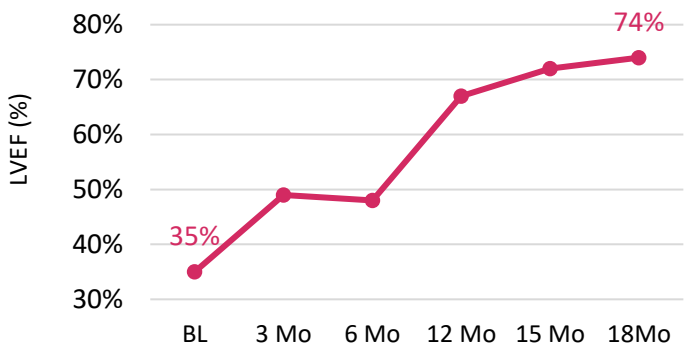


Cardiac MRI: LVMI

48% reduction



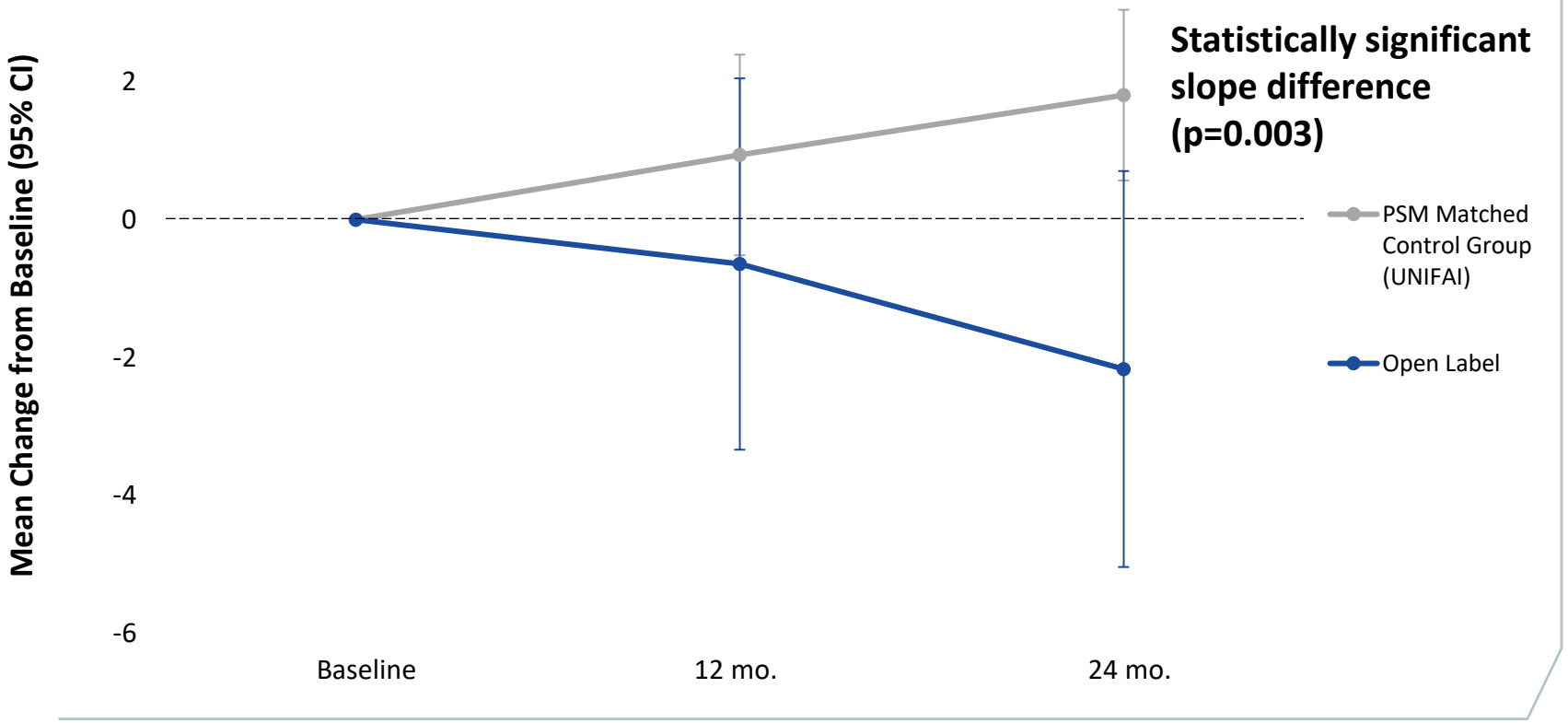
Cardiac MRI: LVEF



LVMI = left ventricular mass index, LVEF = left ventricular ejection fraction.
Note: Data as of December 2025.

Statistically significant improvement in mean mFARS scores for LX2006-treated participants compared to propensity-matched control cohort

Change in mFARS: Open Label Cohort (n=16) vs. UNIFAI Matched Control (n=45)



- ✓ mFARS validated clinical scale measures FA neurological progression; higher scores represent disease worsening
- ✓ Majority of LX2006-treated participants demonstrate mFARS improvement or stabilization at latest visit relative to baseline
- ✓ **New evidence of neurological functional improvement compared to propensity matched control, with annualized difference in progression of 2.3 points per year** (95% CI: 0.82-3.84)

PSM, propensity score matched.
Note: Data as of December 2025. 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.

LEXEO therapeutics

Finalized SUNRISE-FA 2 pivotal protocol and SAP for LX2006

Study on track to initiate in Q2 2026; Expect topline data in 2H 2027 and potential BLA filing in 1H 2028

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:** Adults (16yrs+): Abnormal baseline LVMI, ≥2SD above normal mean
  - Pediatric (6-15yrs): 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
  - SAP 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

Phase I/II results **exceed the 15% effect size in LVMI** used to power the SUNRISE-FA 2 pivotal study

28% mean LVMI reduction at 6-mo in higher dose participants with abnormal baseline LVMI (n=3)

18% mean LVMI reduction at 6-mo in participants with abnormal baseline LVMI (n=6)

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.

LX2020

Plakophilin 2 Arrhythmogenic Cardiomyopathy (PKP2-ACM)

Arrhythmogenic cardiomyopathy caused by mutations in the *PKP2* gene: devastating genetic heart disease with clearly defined mechanism

PKP2-ACM is a **rare, genetic cardiac disease** caused by loss of function mutations in the *PKP2* gene

Progressive replacement of cardiac muscle with fatty fibrotic tissue, with an **increased risk of ventricular arrhythmias and sudden cardiac death (SCD) due to disrupted cardiac electrical signals**[1][2]

Approximately 23% of individuals experience **SCD as the presenting symptom** and individuals often suffer from **anxiety and reduced quality of life**[3][4]

ICDs are commonly utilized but **do not halt disease progression**. Individuals experience ongoing arrhythmias, along with both appropriate and inappropriate shocks necessitating escalating treatments, **underscoring severe unmet need**[2][3]

Prevalence:

US **~60,000**

Mortality:

23%

of individuals experience SCD as presenting symptom

Standard of care:

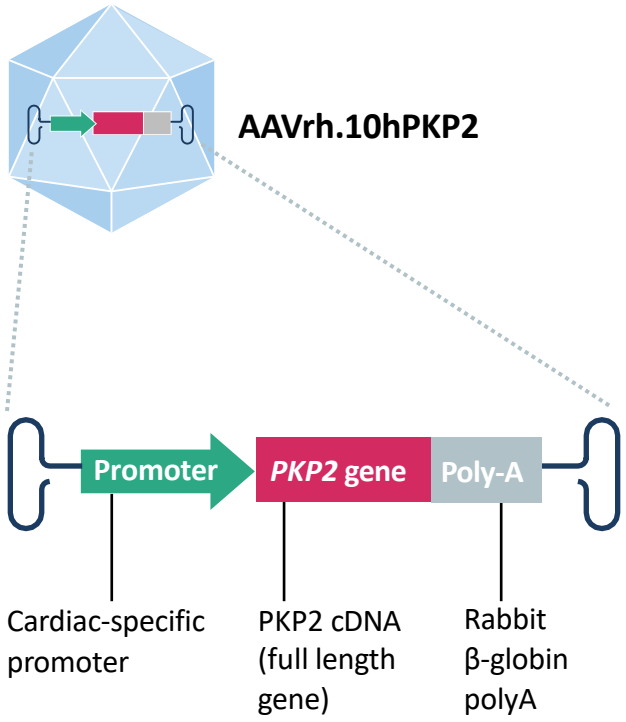
Current management methods are focused on relieving symptoms and preventing SCD, **and do not address the underlying cause of ACM.**

ACM, arrhythmogenic cardiomyopathy; ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; ICD implantable cardioverter defibrillator; SDC sudden cardiac death.
(1) Cedars-Sinai ARVC overview. (2023). (2) Corrado et al. (2017). (3) Dalal et al. (2005). (4) Day, Circulation: Cardiovascular Genetics (2012).

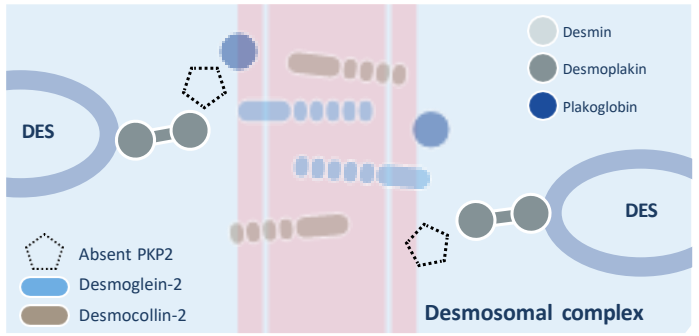
LEXEO therapeutics

Mutations in the *PKP2* gene are the most common genetic cause of ACM; LX2020 delivers a full-length *PKP2* gene to cardiomyocytes, restoring the desmosome

LX2020 construct:

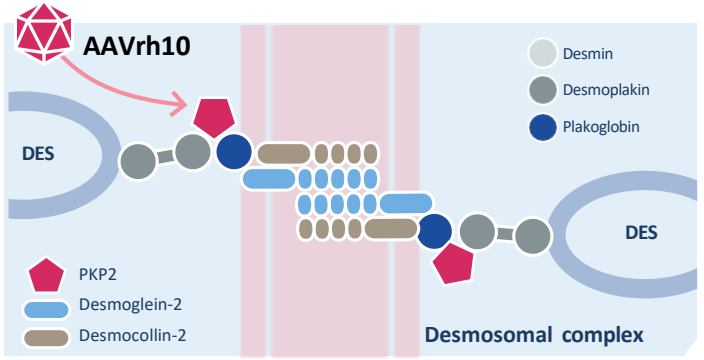


PKP2-ACM:



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**

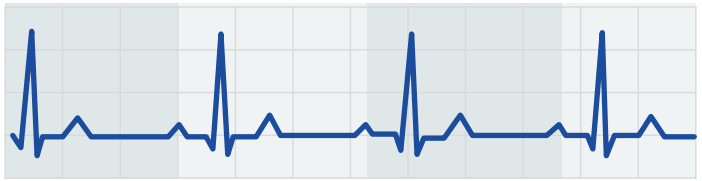
ACM, arrhythmogenic cardiomyopathy.

Individuals with ACM experience high arrhythmia burden with a spectrum of severity

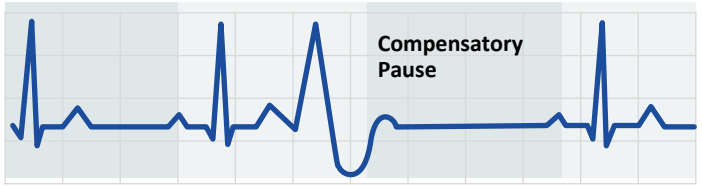
Severity of Arrhythmias

Premature Ventricular Contractions (PVCs)

Normal Sinus Rhythm

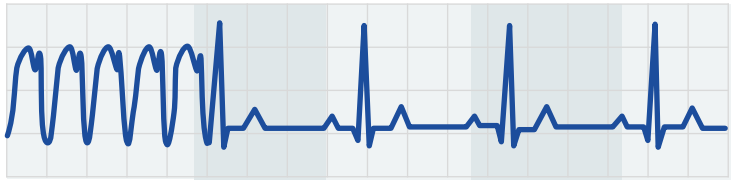


Premature Ventricular Contraction (PVC)



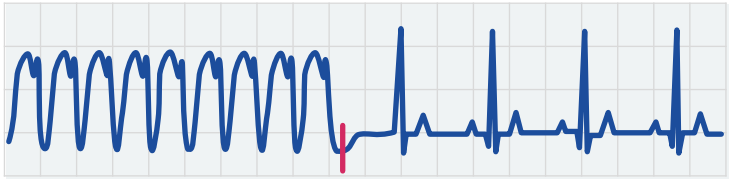
- Early indicator of electrical instability that **can trigger more severe/sustained arrhythmia**

Non-Sustained Ventricular Tachycardia (NSVT)



- **≥3 ventricular beats in a row, lasting under 30 seconds**; self-terminating
- Closely associated with **increased risk of sustained VT, ICD shock and SCD[1]**; impacts patient anxiety and quality of life

Sustained VT / ICD Shock



Ventricular Tachycardia | **Cardioversion Shock** | **Sinus Rhythm**

- ≥3 ventricular beats in a row **lasting over 30 seconds**
- **Can cause collapse, cardiac arrest or SCD**; sustained VT may be terminated by ICD shock to restore normal rhythm

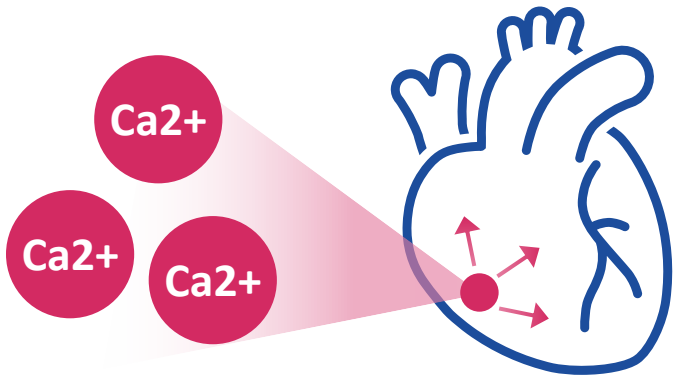
SCD, sudden cardiac death; ICD, implantable cardioverter defibrillator; VT, ventricular tachycardia.

(1) Gasperetti A, et al. *JAMA Cardiology*, 2022; 7

LEXEO therapeutics

Premature ventricular contractions (PVCs) may trigger ventricular tachycardia (VT); measures are related but driven by potentially different mechanisms

PVCs Are a Trigger That Can Precipitate More Severe Arrhythmias

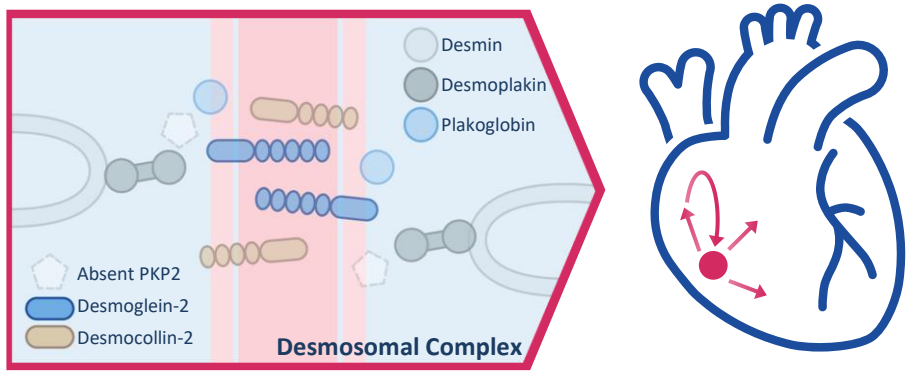


Ventricular Depolarization

- **PKP2 deficient myocytes demonstrate calcium instability**; Ca^{2+} leak can disrupt refractory period and depolarization[1,2]
- PVCs are not reentry loops but can trigger them
- Calcium instability due to PKP2 deficiency **likely driven by downstream proteins**, which may take more time to repair versus the desmosome with direct PKP2 function

VT is Caused When a Trigger (PVC) Meets an Electrical or Structural Vulnerability

PKP2 Deficiency Reduces Cell-to-Cell Adhesion, Slowing Electrical Conduction and Causing Reentry Loops:



- **VT occurs when a PVC meets a vulnerability like slow electrical conduction**, enabling the premature beat to propagate as a reentry loop[3,4]
- Reentry loops are self-sustaining electrical circuits that override normal rhythm, consistently re-exciting the heart
- PKP2 deficiency causes electrical and structural vulnerabilities like slow conduction and scarring; hypothesis that **VT could be reduced if vulnerabilities are improved even if PVCs persist**

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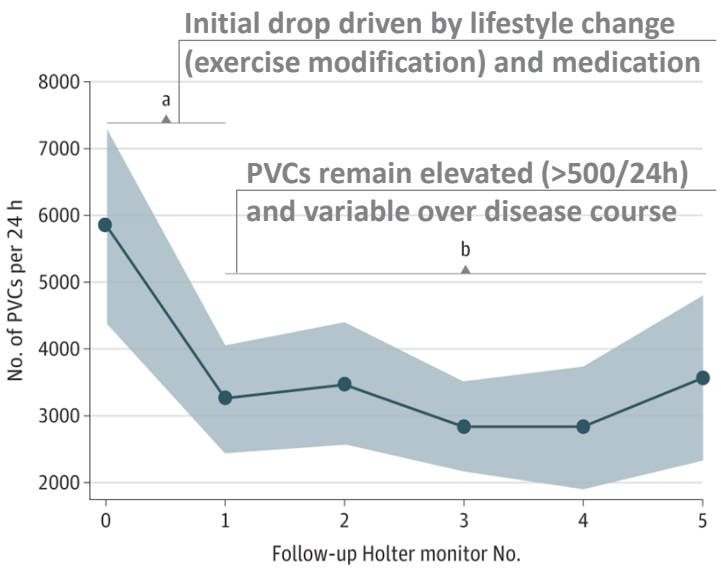
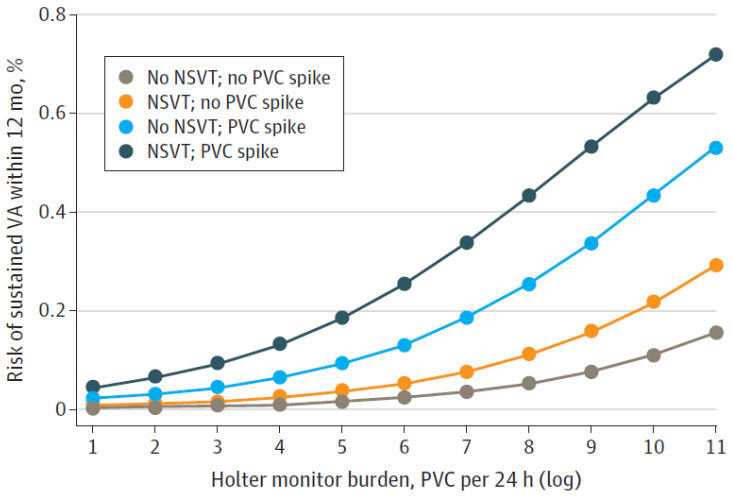
(1) Cerrone et al. *Nature Comm,* 2017. (2) Kim et al. *Circulation,* 2019. (3) Sato P. et al. *Circulation Research,* 2009. (4) Oxford E.M et al. *Circulation Research,* 2007.

In people with ACM, sustained VT risk is predicted by increased PVC burden and by non-sustained VT events

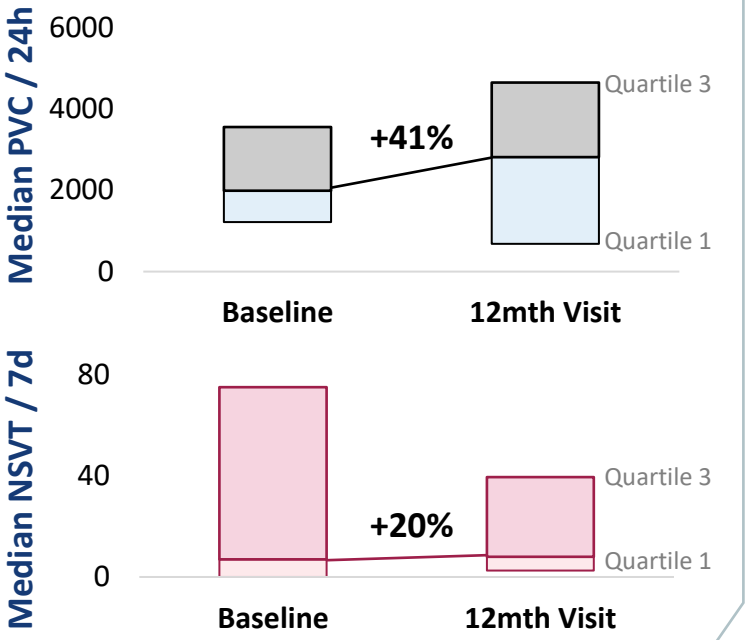
PVC burden in ACM decreases initially after diagnosis but persists long term[1]



VT risk increases with PVCs and NSVT[1]



Prospective natural history SNAPSHOT (n=15)



Participants mean 8 years after diagnosis

While lifestyle modification may reduce PVCs immediately following diagnosis, Lexeo-sponsored SNAPSHOT natural history data suggests that PVCs and NSVT may increase later in disease progression, both of which are associated with greater VT risk

LEXEO therapeutics

1. Gasperetti A, et al. JAMA Cardiol. 2022;7(4):378–385

Lexeo's role in advancing PKP2-ACM research

Phase I/II Trial

Objective: Assess the safety and efficacy of LX2020 in individuals with PKP2-ACM

Dose: 2.0E13 vg/kg (Cohort 1), 6.0E13 vg/kg (Cohorts 2, 3)

Key Endpoints: PKP2 expression, VT, PVC, QRS, T-wave inversion, cardiac function, PROs

Status: Ongoing (fully enrolled, n=10)

Retrospective EMR Review and Prospective Observational Natural History Study

Objective: Evaluate the clinical burden of illness for patients with PKP2-ACM, and prospectively evaluate changes in key cardiac parameters and patient-reported outcome measures (PROs) associated with PKP2-ACM progression

Dose: N/A

Key Assessments: VT, PVC, QRS, T-wave inversion, cardiac function, PROs

Status: Ongoing (actively recruiting)

LEXEO therapeutics

LX2020 is being evaluated in an ongoing phase 1/2 study (HEROIC-PKP2); enrollment completed in Q4 2025

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

52-Week

Cohort 1
n=3
$2.0x10^{13}$ vg/kg
Fully Enrolled

Cohort 2
n=3
$6.0x10^{13}$ vg/kg
Fully Enrolled

Cohort 3
n=4
$6.0x10^{13}$ vg/kg
Fully Enrolled

2 Key Inclusion Criteria

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

3 Key Measurements

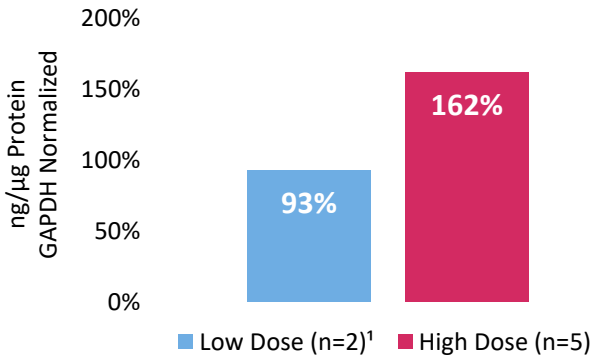
- Ventricular arrhythmias and associated measures (PVC, VT, QRS, T-wave inversion)
- Cardiac Structure & Function (EF, EDV, ESV)
- Change in Symptoms (NYHA Class and PROs)
- PKP2 Protein Expression (quantitative WB)

PVC, Premature Ventricular Contraction; hsTnI, High Sensitivity Troponin I; WB, Western Blot; ECG, Electrocardiogram; NYHA, New York Heart Association; PROs, Patient Reported Outcomes.
Note: LX2020 is administered systemically; participants receive immune suppression with prednisone and sirolimus beginning on the day prior to treatment through 12 weeks following LX2020 administration.

LEXEO therapeutics

Interim results demonstrate increased PKP2 expression and potential for LX2020 to reduce severe arrhythmia burden

Mean change in PKP2 expression from baseline (western blot)

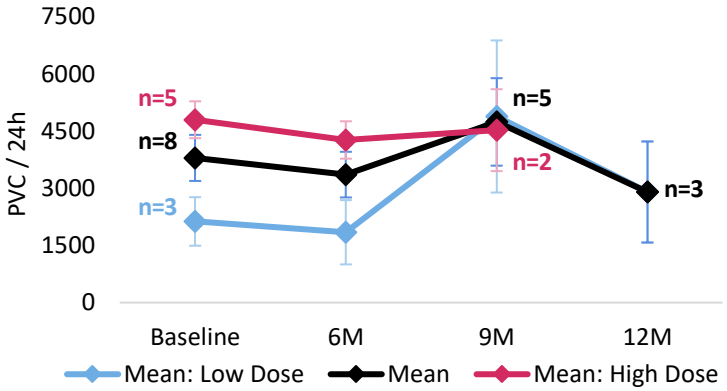


Patient reported outcomes

4 of 5

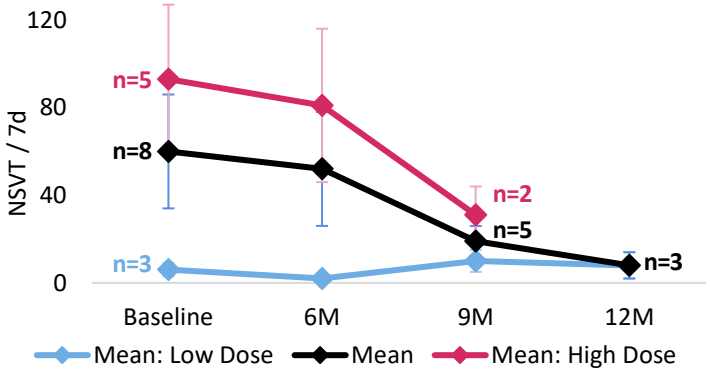
participants at high dose report improvement relative to baseline on the Patient Global Impression of Change (PGIC) scale

Mean PVC change



- **PVCs reduced or stabilized in majority of participants** with >6 months of follow up
- **-14% improvement** in mean PVCs at latest visit in high-dose cohort

Mean NSVT change



- **NSVT reduced or stabilized in majority of participants** with >6 months of follow up
- **-22% improvement** in mean NSVT at latest visit in high-dose cohort

LX2020 generally well tolerated

- LX2020 generally well tolerated across ten participants dosed
- No clinically significant complement activation
- Elevations in liver function tests (LFT) observed in seven participants at the high-dose, treated successfully per trial protocol with no complications or hospitalization[(2)]
- No participants discontinued from study
- One previously disclosed Grade 3 serious adverse event of sustained ventricular tachycardia (VT) was observed three months after dosing. This event is consistent with the natural course of PKP2-ACM and its known clinical manifestations. The participant was successfully treated with anti-arrhythmic medication and discharged with no additional intervention required.

Note: Data as of January 2026.
(1) Participant 3 elected not to undergo a post-treatment biopsy (2) Five participants' elevations occurred following steroid tapering and resolved with re-introduction of low-dose prednisone; two participants' elevations occurred prior to steroid tapering and resolved with increased prednisone and sirolimus treatment; all elevations have since resolved without other complications or hospitalization, and no other medications were required for resolution

LEXEO therapeutics

Preclinical Programs

Lexeo is also advancing two preclinical cardiac gene therapy programs

LX2021

Desmoplakin Cardiomyopathy

- High unmet need characterized by extensive fibrosis, high arrhythmic risk, and high heart failure burden
- 30-50% mortality within 5 years of diagnosis for dilated phenotype
- ~35K patients in U.S.
- IND-enabling studies and potential regulatory engagement in 2026

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 EF; myosin inhibitors not effective
- ~25K patients in U.S.

+2026 research collaboration with Johnson & Johnson exploring novel routes of administration for cardiac AAV gene therapy to maximize safety and efficacy

LEXEO therapeutics

Lexeo – a leader in cardiac gene therapy

1. Leader in cardiac genetic medicine addressing **high unmet need** and **clear market opportunity**
2. **Catalyst rich 2026** with multiple key milestones expected across **two clinical stage programs**
3. Differentiated **AAVrh10 capsid** and innovative **Sf9 baculovirus manufacturing** platform
4. **Advancing toward late-stage development**; SUNRISE-FA 2 pivotal study on track to initiate in Q2 2026 with BLA filing expected 1H 2028 under accelerated approval pathway
5. Strong financial position with **cash runway into 2028**

LEXEO therapeutics

Thank You