Lexeo Therapeutics Corporate Overview

January 13, 2025

Forward-Looking Statements

This presentation contains “forward-looking statements” within the meaning of the federal securities laws, including, but not limited to, statements regarding Lexeo’s expectations and plans regarding its current product candidates and programs, including statements regarding the timing, progress and results of preclinical and clinical trials of Lexeo’s gene therapy product candidates, the anticipated benefits of its current product candidates, the timing and likelihood of regulatory approval, and expected cash runway. Words such as “may,” “might,” “will,” “objective,” “intend,” “should,” “could,” “can,” “would,” “expect,” “believe,” “design,” “estimate,” “predict,” “potential,” “develop,” “plan” or the negative of these terms, and similar expressions, or statements regarding intent, belief, or current expectations, are forward-looking statements. While Lexeo believes these forward-looking statements are reasonable, undue reliance should not be placed on any such forward-looking statements. These forward-looking statements are based upon current information available to the company as well as certain estimates and assumptions and are subject to various risks and uncertainties (including, without limitation, those set forth in Lexeo’s filings with the U.S. Securities and Exchange Commission (SEC)), many of which are beyond the company’s control and subject to change. Actual results could be materially different from those indicated by such forward looking statements as a result of many factors, including but not limited to: risks and uncertainties related to expectations regarding the initiation, progress, and expected results of Lexeo’s preclinical studies, clinical trials and research and development programs; the unpredictable relationship between preclinical study results and clinical study results; delays in submission of regulatory filings or failure to receive regulatory approval; liquidity and capital resources; and other risks and uncertainties identified in Lexeo’s Annual Report on Form 10-K for the year ended December 31, 2023, filed with the SEC on March 11, 2024, Quarterly Report on Form 10-Q for the quarter ended September 30, 2024, filed with the SEC on November 13, 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: Advancing Cardiac Genetic Medicines In Diseases with High Unmet Need

Focus	**Leveraging gene therapy to address devastating cardiac diseases with no existing disease-modifying treatments**
LX2006: Friedreich Ataxia Cardiomyopathy	**Only program in the clinic for the treatment of FA cardiomyopathy; the cause of death in 60-80% of individuals** **Initial clinical data show robust cardiac FXN expression and clinically meaningful reductions in multiple cardiomyopathy markers** **FDA alignment on key elements of accelerated approval pathway based on LVMI reduction and protein expression** **High-dose data expected mid-2025; potential to initiate registrational study by end of 2025 / early 2026**
LX2020: PKP2-ACM	**Potential best-in-class treatment of PKP2-ACM; ~60K patients in US with no disease-modifying treatment available** **Initial clinical data, focused on protein expression and safety expected late Q1 / early Q2 of 2025**

FA, Friedreich Ataxia; FXN, Frataxin; LVMI, Left Ventricular Mass Index; ACM, arrhythmogenic cardiomyopathy.

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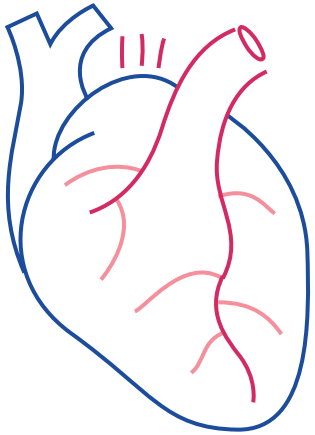
Favorable Landscape for Cardiac Genetic Medicines Continues to Mature



- **Evolving Regulatory Environment:** Continued shift towards surrogate endpoints may circumvent need for larger cardiovascular outcome trials to achieve accelerated approval
- **Improved Delivery Platforms:** Improvements in modern AAV delivery technology, including AAVrh10, allow for greater targeting of the heart with lower doses
- **Well-Established Biomarkers:** Growing acceptance of cardiac biomarkers potentially allow for earlier signs of clinical activity
- **Maturing Safety Profile:** Multiple AAV-based cardiac gene therapies currently being evaluated in clinical trials, expanding the field's safety understanding
- **Increased Genetic Screening:** Increased screening has potential to expand awareness and increase opportunity across genetic cardiac diseases

Favorable tailwinds supporting multi-billion $ commercial potential for cardiac genetic medicines

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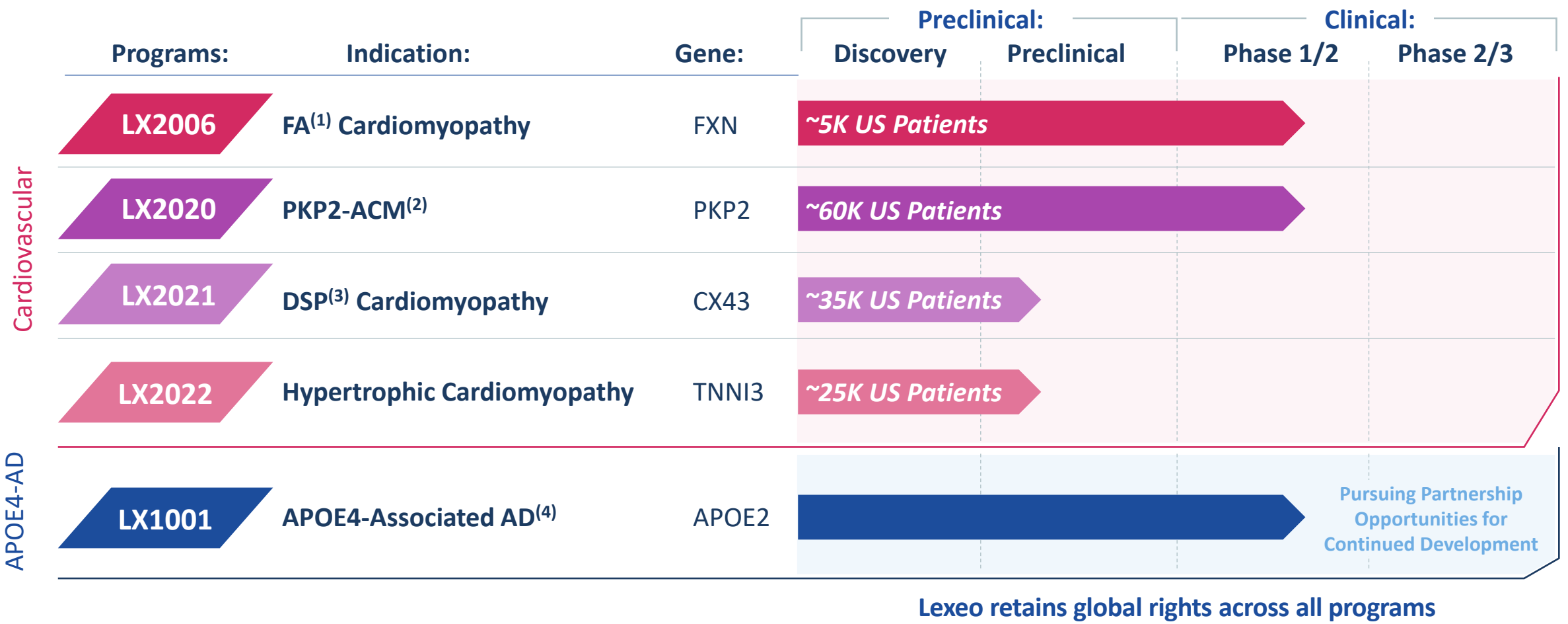
Our Pipeline: Focused on Diseases with Significant Unmet Need and Clear Mechanisms



Lexeo retains global rights across all programs

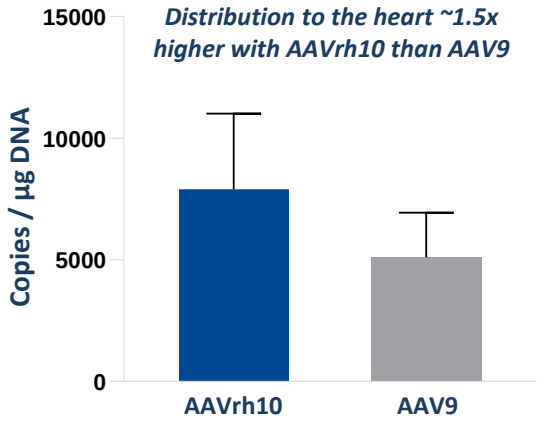
(1) Friedreich ataxia. (2) Plakophilin 2 Arrhythmogenic Cardiomyopathy. (3) Desmoplakin. (4) Alzheimer's disease; LXEO has two additional preclinical second-generation programs.

Cardiac Tropism of AAVrh10 May Allow Lower Dosing for Cardiac Gene Therapy

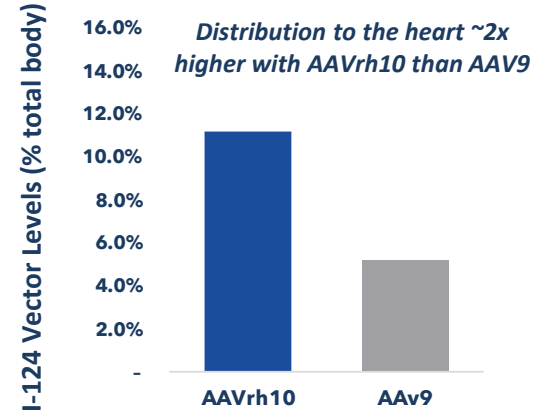
- ✓ AAVrh10 cardiac tropism may allow for lower doses compared to other vector serotypes while achieving targeted transgene biodistribution
- ✓ Observed ~1.5x to 2.0x greater biodistribution in the heart compared to AAV9 in multiple large animal models
- ✓ Observed greater trends of functional improvements in PKP2-murine model compared to AAV9
- ✓ AAVrh10 has been utilized systemically across multiple Lexeo clinical programs with no signs of complement-mediated toxicity

Compelling Cardiac Tropism

Yucatan Minipig Biodistribution(1)

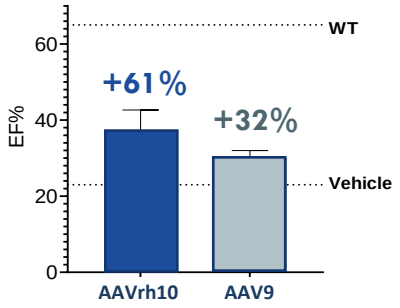


NHP Biodistribution(2)

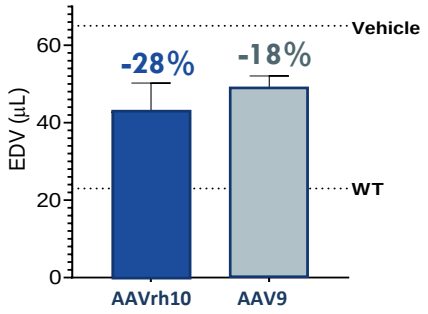


Greater Trends of Functional Improvement Versus AAV9 in PKP2-ACM Model(1)

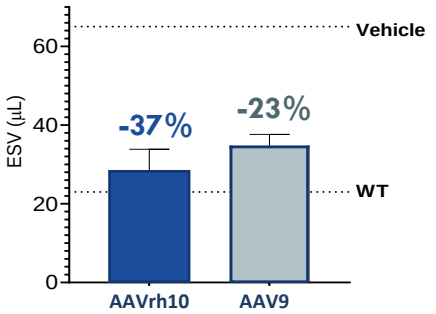
Greater Increase in EF



Greater Reduction in EDV



Greater Reduction in ESV



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

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

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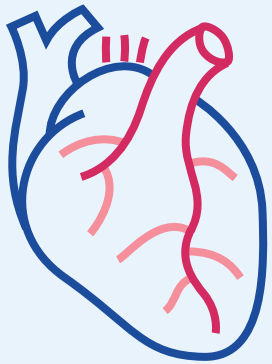
LX2006 (FA Cardiomyopathy)



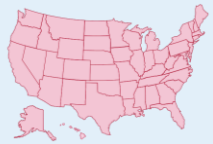
Cardiac Dysfunction is the Leading Cause of Death in Friedreich Ataxia (FA)

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,** often occurring by mid-30 years of age

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



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

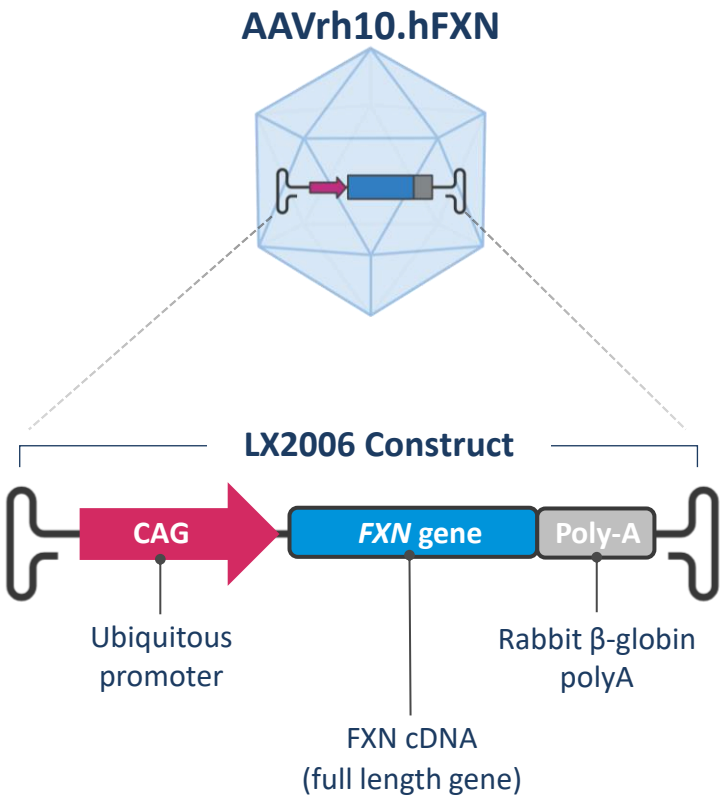
~15,000
individuals affected by FA worldwide(2)

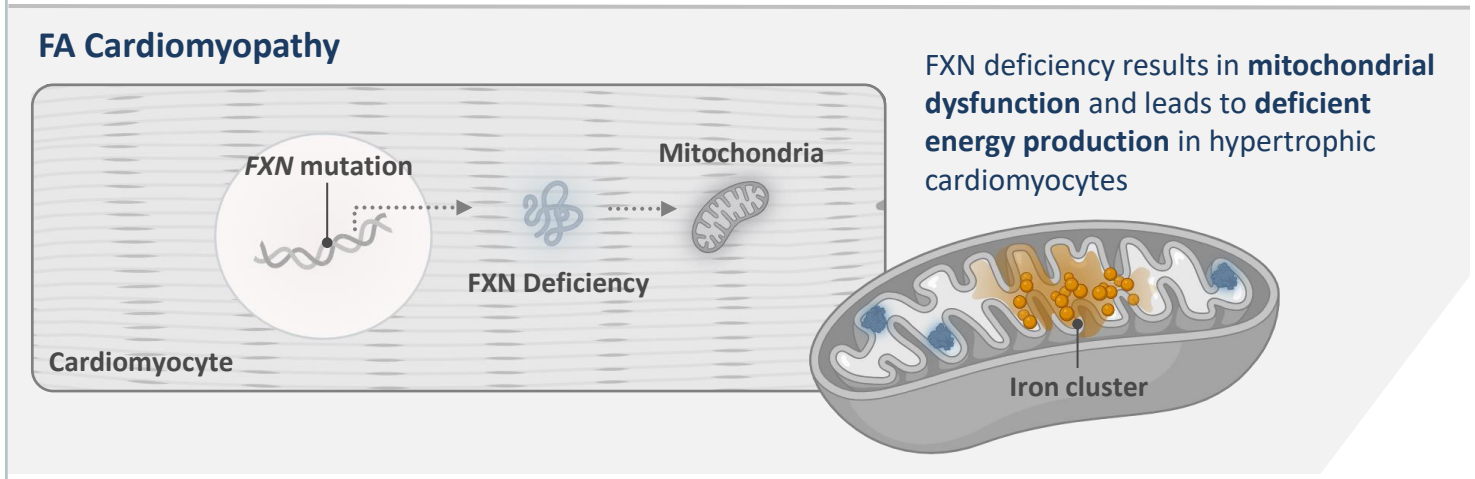
Cardiac dysfunction is the cause of death in **60-80%** of those with FA(3)(4)

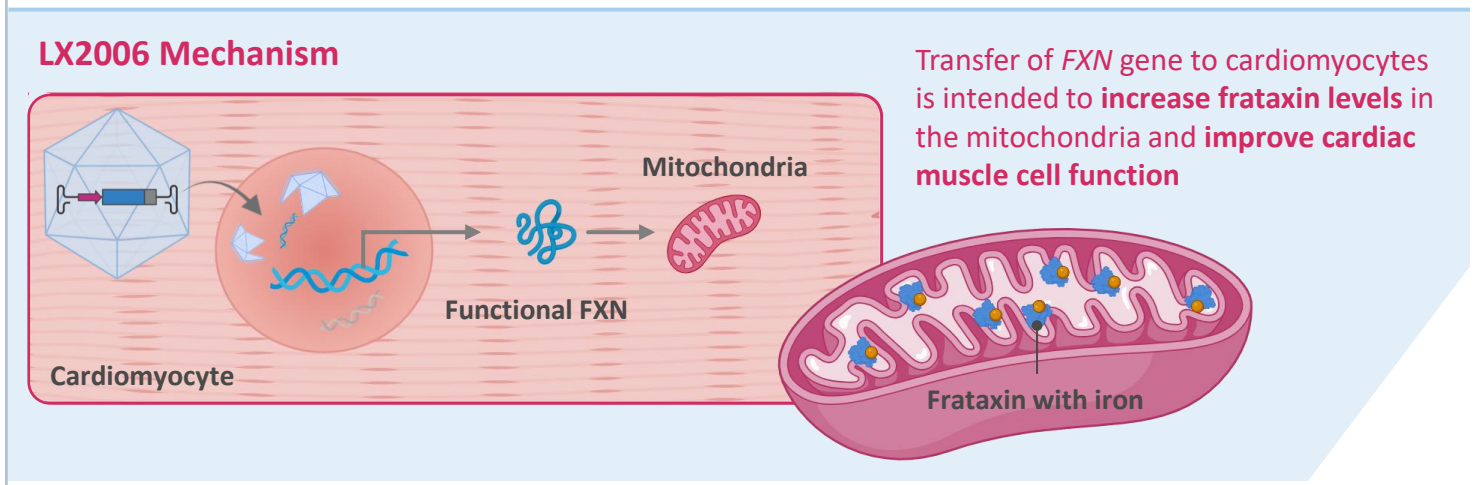
FXN, Frataxin.

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

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





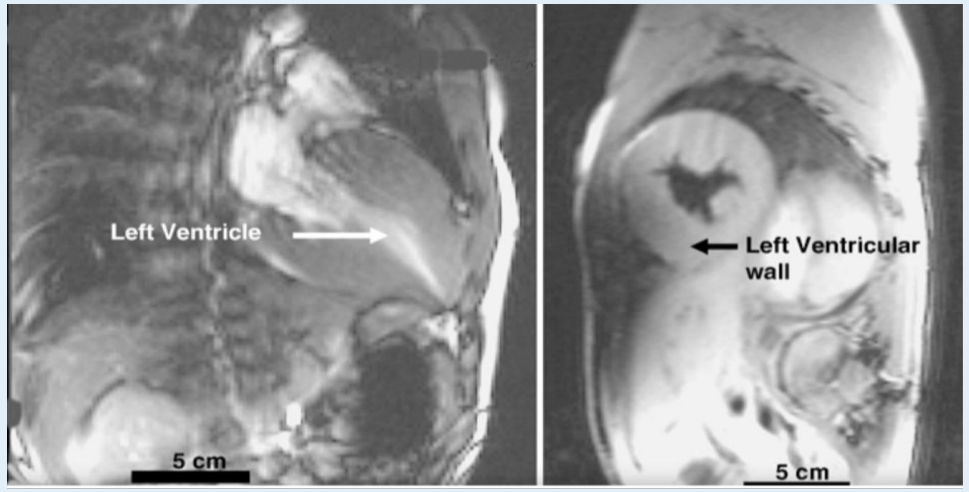


AAV, Adeno-Associated Virus; CAG, Chicken Beta-Actin; cDNA, Copy DNA; FA, Friedreich Ataxia; FXN, Frataxin; Poly-A, Poly Adenosine.

Elevated LVMI Predicts Mortality in FA and is Not Expected to Significantly Decrease 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

60-80% of FA Patients Will Die from Cardiac Dysfunction

- Concentric hypertrophy is a hallmark of FA cardiomyopathy(1)
  - Literature shows a 19% incremental risk of all cause mortality per ~10% increase in LVMI(1)
  - Natural history data suggests that LVMI is expected to slightly increase with age(2)
- In FA and other cardiac diseases, LVMI is not expected significantly decrease without intervention
- Reduction in LVMI may improve cardiac outcomes; FDA alignment as co-primary endpoint for potential 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) Data on file.

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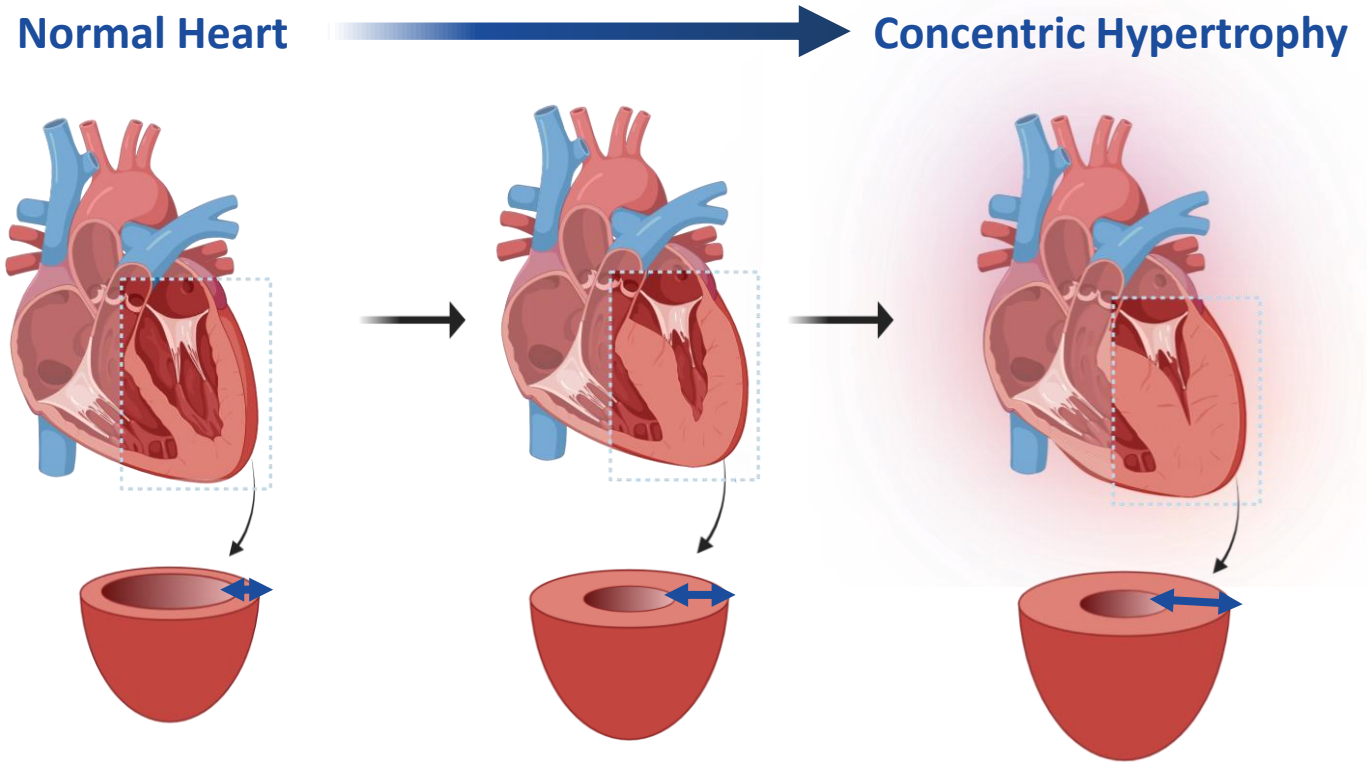
Dysfunction in Heart Muscle Cells Can Lead to Concentric Hypertrophy and Poorer Outcomes in Multiple Cardiomyopathies

Disease Progression



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

Measurements of Hypertrophy

✓ Left Ventricular Mass Index (LVMI)

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

✓ Left Ventricular (LV) Wall Thickness

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

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

LX2006 is Being Evaluated in Parallel Lexeo-Sponsored SUNRISE-FA and Weill Cornell Investigator Initiated Trial

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

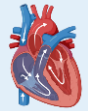
Adults
(18-50 years)

Evidence of FA cardiomyopathy

Neutralizing anti-AAVrh.10 titer cutoff

3 Key Measurements

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



Functional Capacity / Reported Outcomes
(KCCQ, mFARS, and CPET)

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

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

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

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Q3’24 Enrollment Update Across Ongoing Clinical Trials

Lexeo Sponsored SUNRISE-FA

Dose Cohort	Participant #	Cardiac Biopsy	Months of Follow-up in Prior Data Update
Cohort 1 ($1.8x10^{11}$ vg/kg)	Participant 6	✓	12 months
Cohort 2 ($5.6x10^{11}$ vg/kg)	Participant 9	✓	12 months
	Participant 10	✓	6 months
	Participant 11	✓	Not included
Cohort 3 ($1.2x10^{12}$ vg/kg)	Participant 12	✓	Not included
	Participant 14	✓	Not included
	Participant 15	✓	Not included
	Participant 16	✓	Not included

Weill Cornell Investigator Initiated

Dose Cohort	Participant #	Cardiac Biopsy	Months of Follow-up in Prior Data Update
Cohort 1 ($1.8x10^{11}$ vg/kg)	Participant 1	✗	18 months
	Participant 2	✗	18 months
	Participant 3	✗	12 months
	Participant 4	✗	12 months
	Participant 5	✗	6 months
Cohort 2 ($5.6x10^{11}$ vg/kg)	Participant 7	✗	Not included
	Participant 8	✗	Not included
	Participant 13	✗	Not included
	Participant 17 and 18: Not yet enrolled		

Treatment with LX2006 has been generally well-tolerated to date

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

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Recent FDA Alignment Guides Future Pivotal Study Inclusion Criteria and Co-Primary Endpoints to Support Accelerated Approval

FDA Alignment		Pivotal Trial Design Elements and Interim Phase 1/2 Results
Proposed Pivotal Trial Inclusion Criteria		• Enrollment of patients with **abnormal LVMI at baseline**
Co-primary Registrational Endpoints	**Target Reduction in LVMI**	• Threshold of **10% reduction in LVMI** as measured by cMRI – Interim Phase 1/2 Results: All patients with abnormal LVMI at baseline achieved > 10% reduction in LVMI at 12-month timepoint (n=3, **average reduction of 14%**)
	Target Increase in Frataxin Expression	• Threshold of **40% frataxin positive area** as measured by IHC – Interim Phase 1/2 Results: Average **post-treatment IHC of 44%** across Cohorts 1 and 2 (n=3)

Note: Abnormal LVMI defined as values 2 standard deviations (SD) above mean for respective gender (from healthy volunteers) as referenced in Kawel-Boehm et al. *J Cardiovasc Magn Reson* (2020) 22:87.

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Participants with Abnormal LVMI at Baseline from July 2024 Data Update Showed Improvements in Key Clinical Parameters

- All patients with abnormal LVMI at baseline achieved > 10% reduction in LVMI at 12-months
- Future pivotal trial will enroll patients with abnormal LVMI at baseline

Participant (sex)	LVMI at Baseline(1)	Δ LVMI (g/m²) Baseline → 12-mo	Δ LWT (cm) Baseline → 12-mo	Δ Hs-TNI (pg/ml) Baseline → 12-mo
Participant 1 (F)	Abnormal	81 → 66 *-18.5%*	1.2 → 1.0 *-16.7%*	224 → 211 *-5.8%*
Participant 2 (M)	Abnormal	109 → 95 *-12.8%*	1.1 → 1.0 *-9.1%*	148 → 58 *-60.8%*
Participant 6 (M)	Abnormal	86 → 76 *-11.6%*	0.9 → 0.7 *-22.0%*	22 → 19(2) *-13.6%*
		Average Reduction: -14.3%		

Improved Stabilized Worsened

(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.

(2) Value shown is 6-month timepoint for Participant 6 Hs-TNI as 12-month timepoint was not collected.

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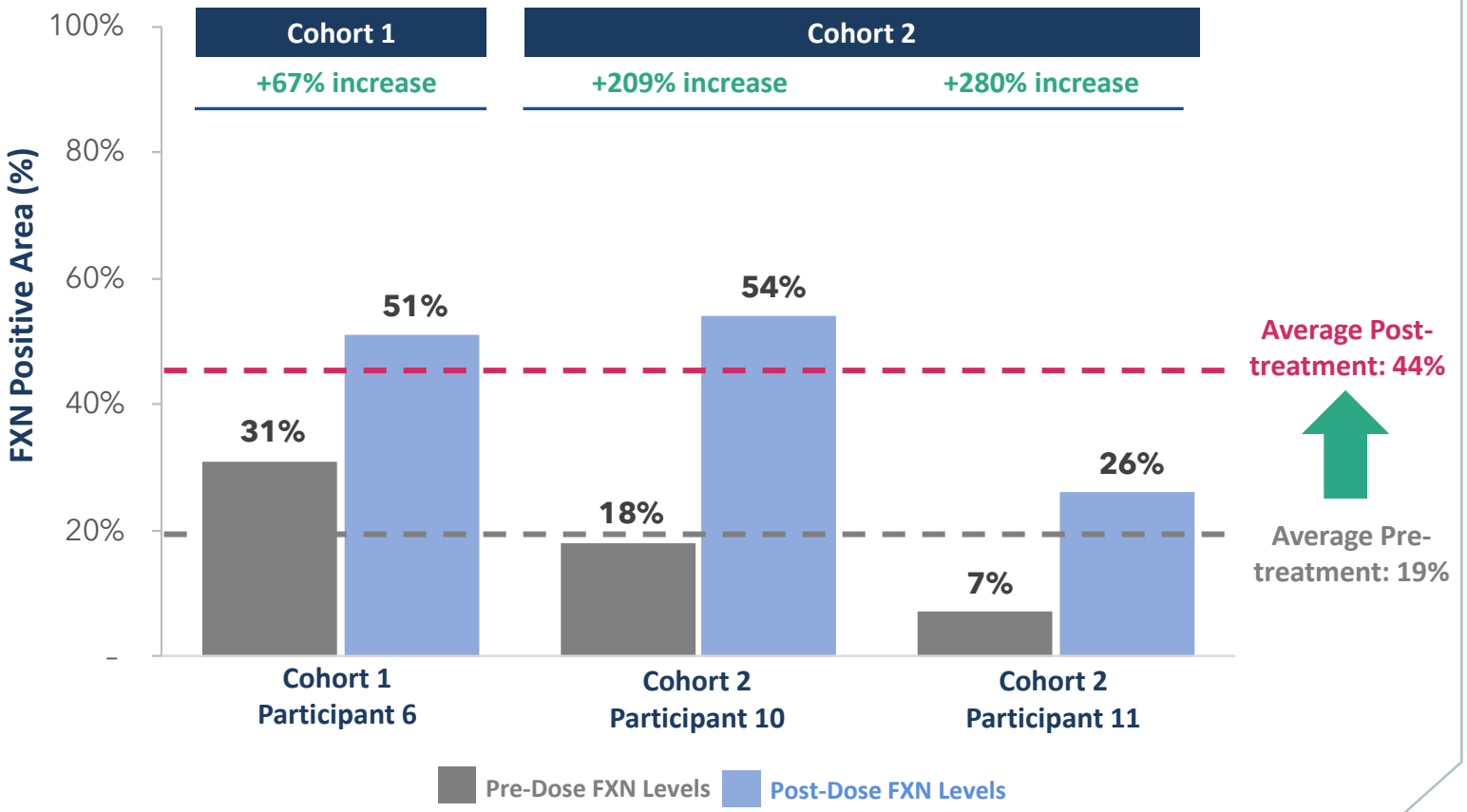
Increased Frataxin Expression Across All Participants Evaluated to Date Utilizing FDA Aligned Immunohistochemistry

Quantified IHC (FXN % Positive Area[(1)])



- ✓ Average IHC results **exceed 40% threshold** with **average post-treatment FXN positive area of 44%**
- ✓ Supportive LCMS assay showed frataxin increase in post-dose tissue in all samples evaluated
- ✓ Four additional cardiac biopsies from higher dose Cohort 3 expected in mid-2025
- ✓ Preclinical studies demonstrated higher dose led to greater frataxin expression; providing comfort on ability of Cohort 3 biopsies to achieve 40% frataxin positive area

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

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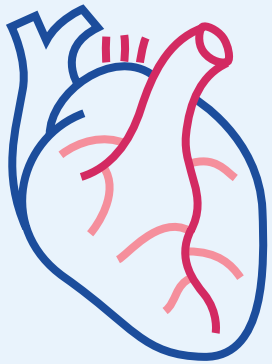
LX2020 (PKP2-ACM)



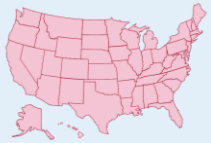
Arrhythmogenic Cardiomyopathy Caused by Mutations in the PKP2 Gene: Devastating Genetic Heart Disease With Clearly Defined Mechanism of Disease

PKP2-ACM is a **rare, genetic, cardiac disorder** 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]

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



~60,000
individuals affected by PKP2-ACM in the U.S.

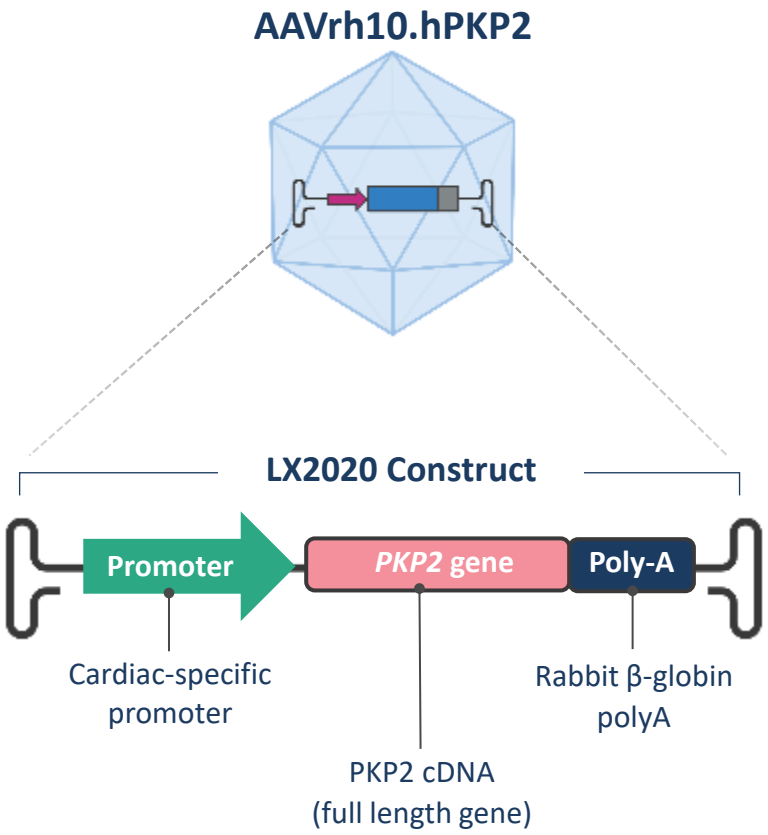
23%
individuals experience SCD as presenting symptom

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

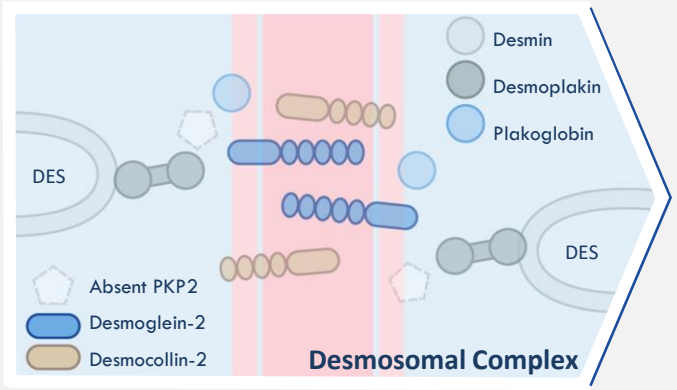
ACM, arrhythmogenic cardiomyopathy; ARVD/C, arrhythmogenic right ventricular dysplasia/cardiomyopathy; ICD implantable cardioverter defibrillator; SDC sudden cardiac death.

(1) Cedars-Sinai ARVC overview. (2023). (2) Corrado et al. (2017). (3) Dalal et al. (2005). (4) Day, Circulation: Cardiovascular Genetics (2012).

LX2020 Has Potential to Treat PKP2-ACM by Delivering a Full-Length PKP2 Gene to Cardiomyocytes, Restoring the Desmosomal Complex

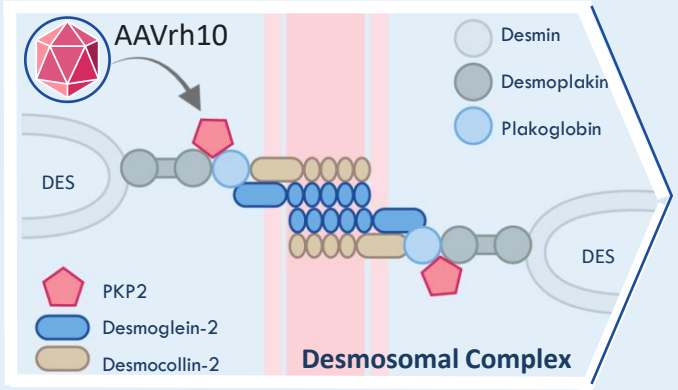


PKP2-ACM



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**

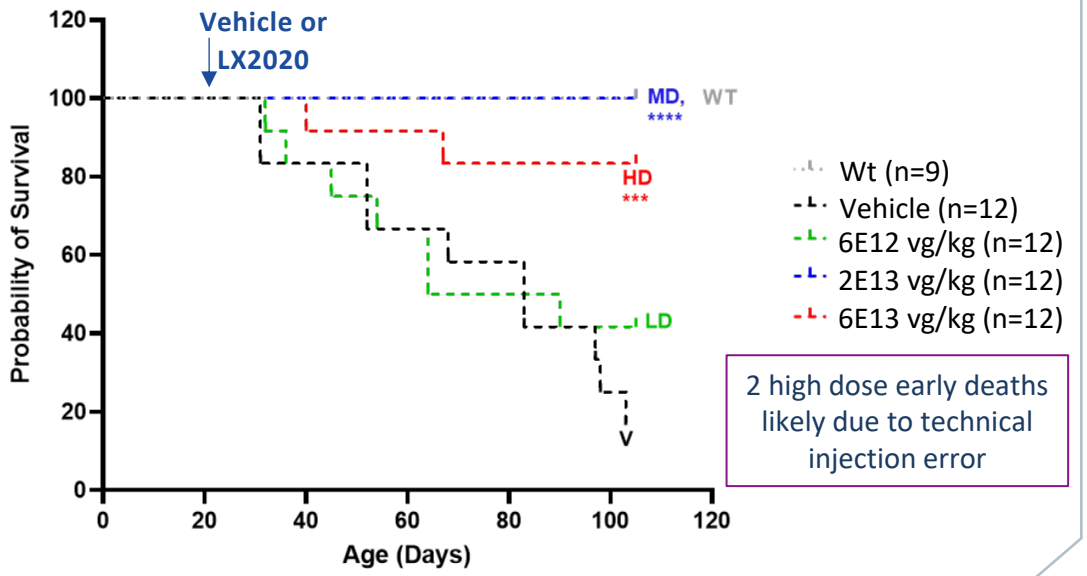
ACM, arrhythmogenic cardiomyopathy.

Robust Preclinical Package Supporting Ongoing Phase 1/2 Trial

Robust Preclinical Package

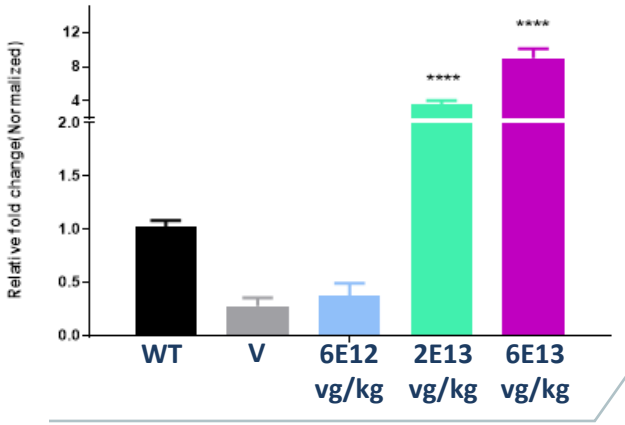
- Murine studies utilizing CRISPR-Cas 9 edited model recapitulating PKP2-ACM disease features
- NHP safety study showed no toxicity at highest evaluated dose level ($1x10^{14}$ vg/kg)

LX2020 Significantly Extended Survival in Severe Mouse Model

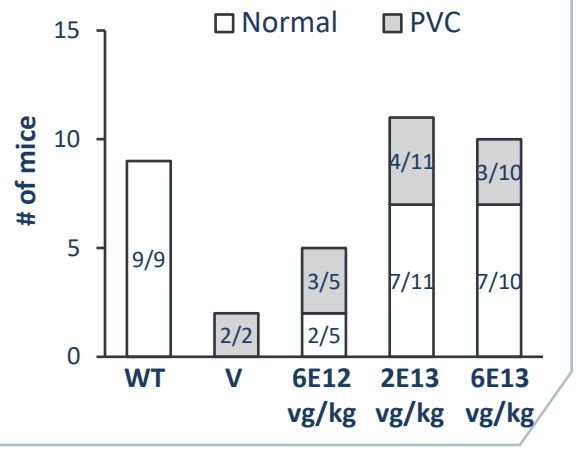


2 high dose early deaths likely due to technical injection error

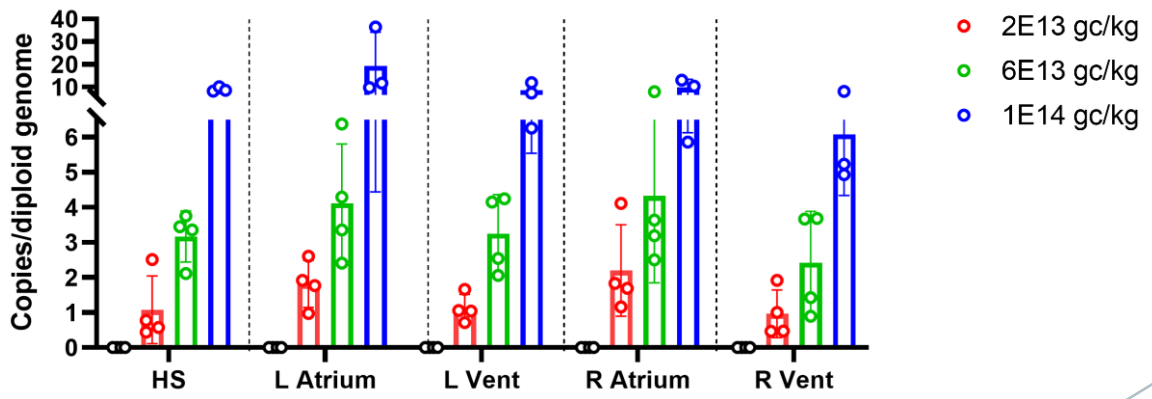
Quantification of PKP2 Expression in Severe Mouse Model



PVC Analysis in Severe Mouse Model



IND-Enabling NHP: VCN in Various Heart Regions



PVC, Premature Ventricular Contractions; VCN, Vector Copy Number.

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

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

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

PVC, Premature Ventricular Contractions.

LX2020 is Being Evaluated in an Ongoing Phase 1/2 Study (HEROIC-PKP2); Cohort 1 Fully Enrolled

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
2.0×10^{13} vg/kg
Fully Enrolled

Cohort 2
n=3 (potential for cohort expansion)
6.0×10^{13} vg/kg

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 clinical outcomes (PVCs and events)
- Cardiac Structure & Function (ECG, cMRI, hsTNI and others)
- Change in Patient 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 rapamycin beginning on the day prior to treatment through 12 weeks following LX2020 administration.
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Multiple Program Updates in 2025 Across Two Clinical Stage Cardiac Programs

Clinical Stage Program	Upcoming 2025 Milestones
LX2006 FA Cardiomyopathy	• Mid 2025: LX2006 program update (Cohort 3 biopsies and longer duration cardiac biomarker data across all cohorts)
LX2020 PKP2-ACM	• Late Q1/Early Q2 2025: Interim Data Readout (Cohort 1 protein expression and safety) • 2H 2025: LX2020 program update (Cohort 1 and Cohort 2)
LX1001 APOE4-Associated AD	• Pursuing partnership opportunities for continued development

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

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

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Thank you