FARA Webinar: Gene Therapy for the Cardiac Manifestations of Friedreich's Ataxia

Jay Barth, MD
Chief Medical Officer
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Department of Genetic Medicine, Weill Cornell Medicine

June 27, 2022

Disclosure

Ronald Crystal is the founder and has equity and is a consultant to LEXEO Therapeutics

Jay Barth is an employee of LEXEO Therapeutics

The LEXEO Therapeutics and NHLBI-funded Department of Genetic Medicine, Weill Cornell clinical studies are independent and have differences that will be discussed

Agenda

Topic	Presenter
Cardiac Disease of Friedreich's Ataxia	Jay Barth
Preclinical Efficacy and Toxicology Studies	Ronald Crystal
LEXEO Therapeutics Clinical Study	Jay Barth
Department of Genetic Medicine, Weill Cornell Clinical Study	Ronald Crystal
Q&A	Jay Barth & Ronald Crystal

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Cardiac Disease of Friedreich's Ataxia

Jay Barth, MD
Chief Medical Officer
LEXEO Therapeutics

Cardiac Disease in Friedreich's Ataxia (FA)

FA has various clinical manifestations, including cardiomyopathy, which is due to frataxin deficiency in the cells of the heart

The cardiomyopathy is progressive and is characterized by cardiac hypertrophy, which can lead to cardiac dysfunction and fibrosis as well as arrythmias, and affects most individuals with FA

FA-associated cardiomyopathy can substantially compromise the health status and quality of life of those living with the disease and is the main cause of shortened lifespan

Improving prognosis of the cardiomyopathy in FA is clearly a significant unmet medical need

To date, there have been limited prospective studies to determine the effects of drugs typically used to treat cardiomyopathy, and no therapy to date addresses the underlying cause of the disease (ie, frataxin deficiency)

AAVrh.10hFXN (LX2006) holds the potential to stabilize or improve cardiomyopathy in patients with FA based on the proof-of-concept studies completed in mouse models of FA cardiac disease

The gene therapy studies that will be discussed today were developed based on knowledge and evidence from the preclinical studies to potentially treat cardiomyopathy in FA

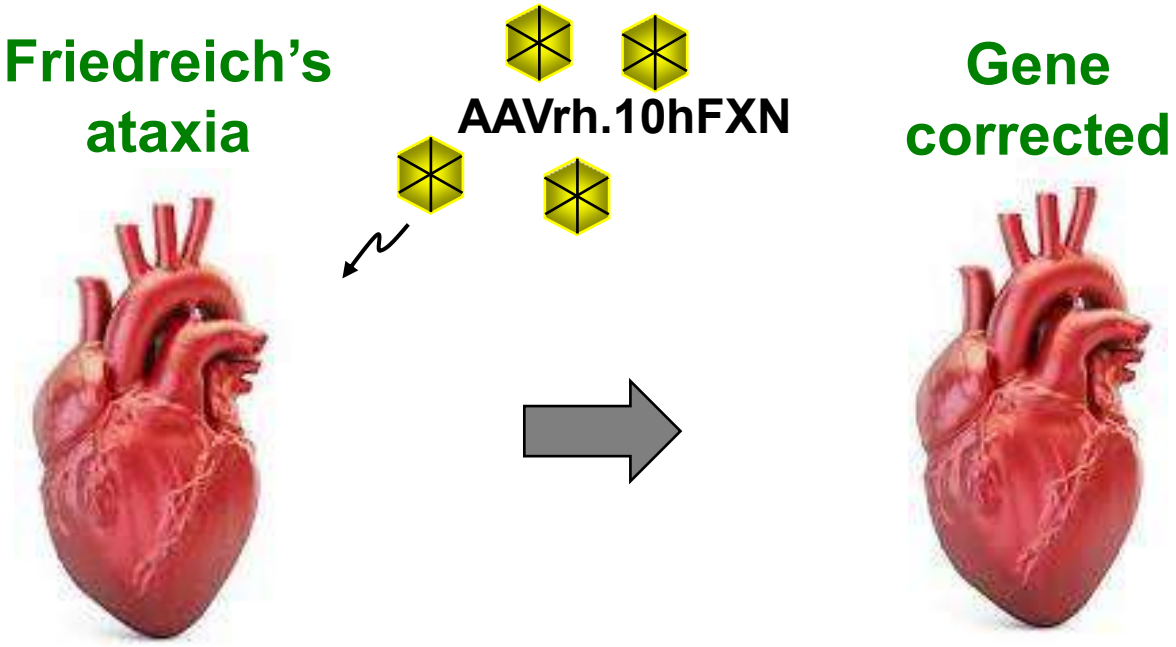
Tsou, A.Y et al, J Neurol Sci 2011, 307: 46-9.

FARA Webinar: Gene Therapy for the Cardiac Manifestations of Friedreich's Ataxia

Preclinical Efficacy and Toxicology Studies

Ronald Crystal, MD
Professor and Chairman
Department of Genetic Medicine, Weill Cornell Medicine

Gene Therapy with AAVrh.10hFXN (LX2006) to Treat the Cardiac Frataxin Deficiency in Friedreich's Ataxia

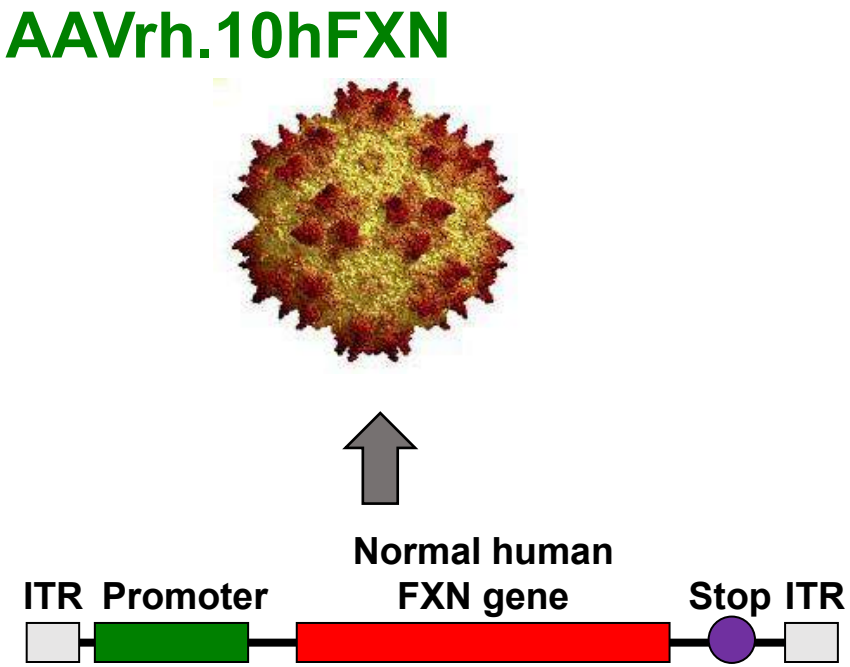


- Cardiac dysfunction

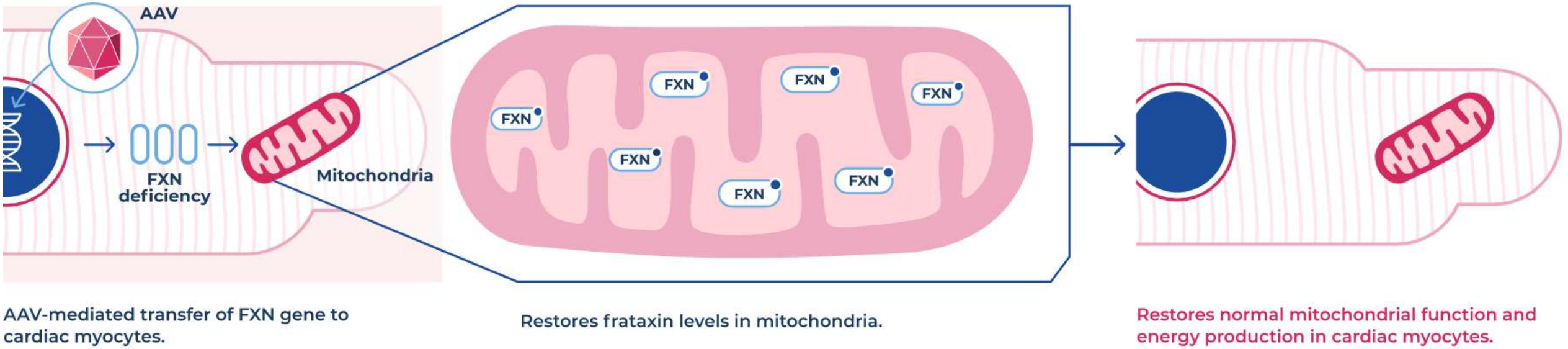
- Improved function

AAVrh.10hFXN (LX2006) Modified Adeno-associated Virus Used to Deliver the Normal Frataxin Gene to the Heart

- Serotype rh.10 nonhuman primate adenoassociated virus
- Not associated with any human disease
- Modified to deliver the normal human frataxin (FXN) gene
- Excellent gene delivery (tropism) for the heart
- Administered intravenously

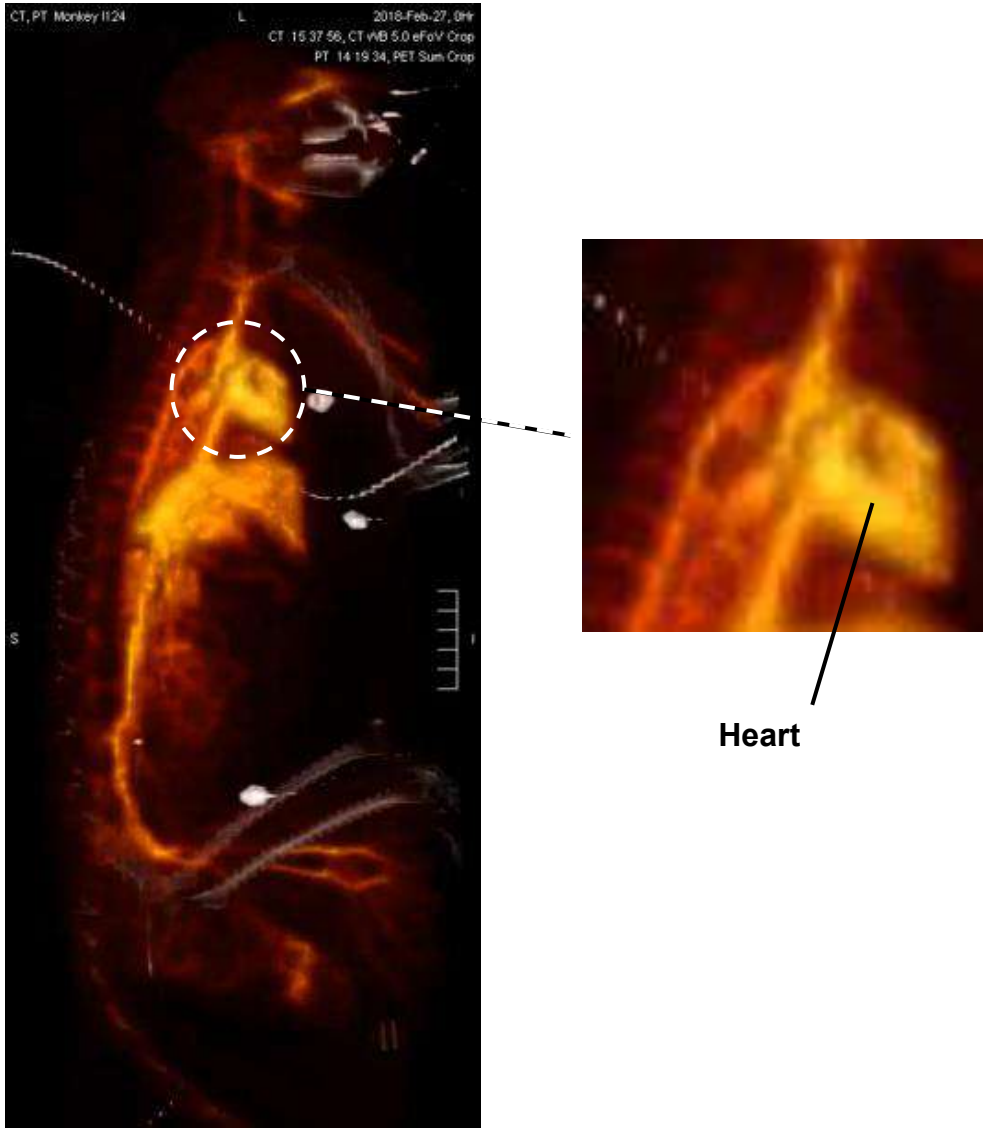


AAVrh.10hFXN (LX2006): Mechanism of Action



- AAVrh.10hFXN is an AAVrh10-based gene therapy candidate designed to intravenously deliver a functional frataxin (*FXN*) gene for the treatment of FA cardiomyopathy
- AAVrh.10hFXN is designed to increase the level of frataxin protein to restore normal mitochondrial function and energy production in cardiac cells

Positron Emission Tomography (PET) Scan Imaging of the Distribution of an AAVrh.10 Vector to the Nonhuman Primate Heart 1 Hour Following Intravenous Administration



Heart

Murine FXN-related Cardiac Preclinical Efficacy Studies

- Mck mouse[1], severe cardiac and skeletal muscle complete FXN knockout model – IV administration of AAVrh.10hFXN reversed increased cardiac mass, improved cardiac function, corrected cardiac FXN-related biochemical defects, improved survival
- αMyhc mouse[2], cardiac-specific mild knockout model - IV administration of AAVrh.10hFXN reversed stress-induced cardiac dysfunction

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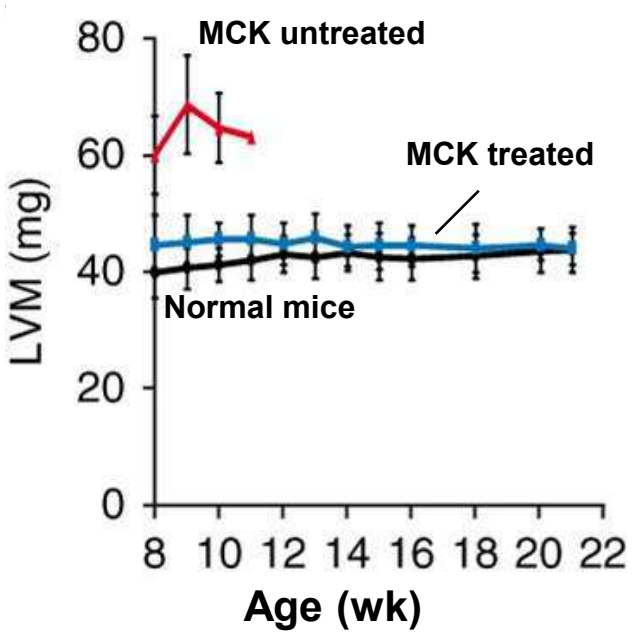
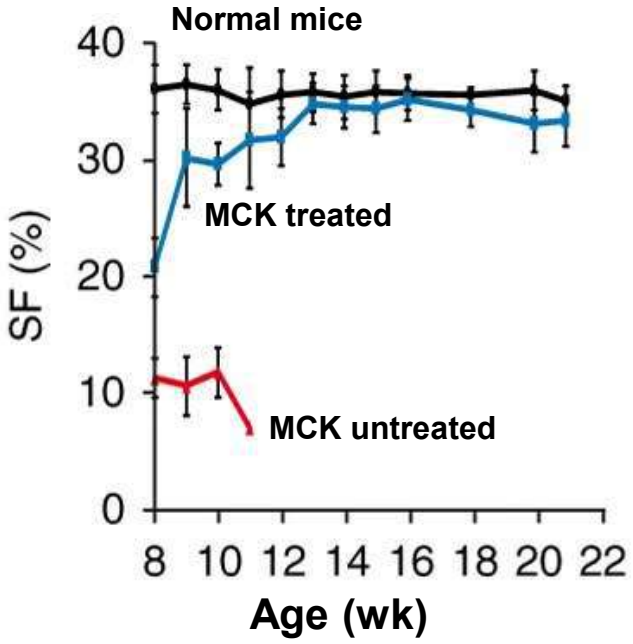
[1] Perdomini M et al, Nat Med 2014; 20:542
[2] Salami CO et al, Hum Gene Ther 2020; 31: 819

Intravenous AAVrh.10hFXN (LX2006) Correction of the Cardiac Disease in the MCK Model[1]

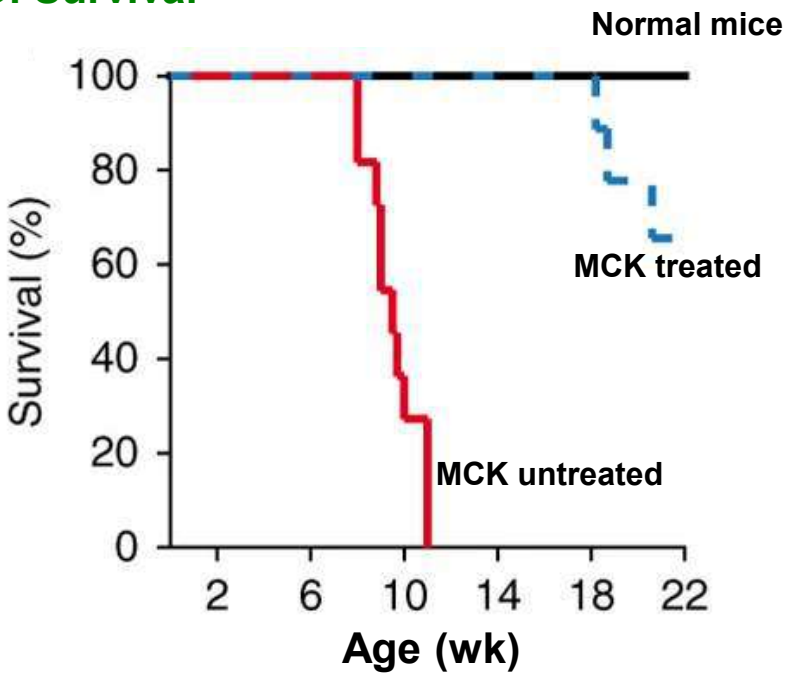
A. Left ventricular mass



B. Shortening fraction

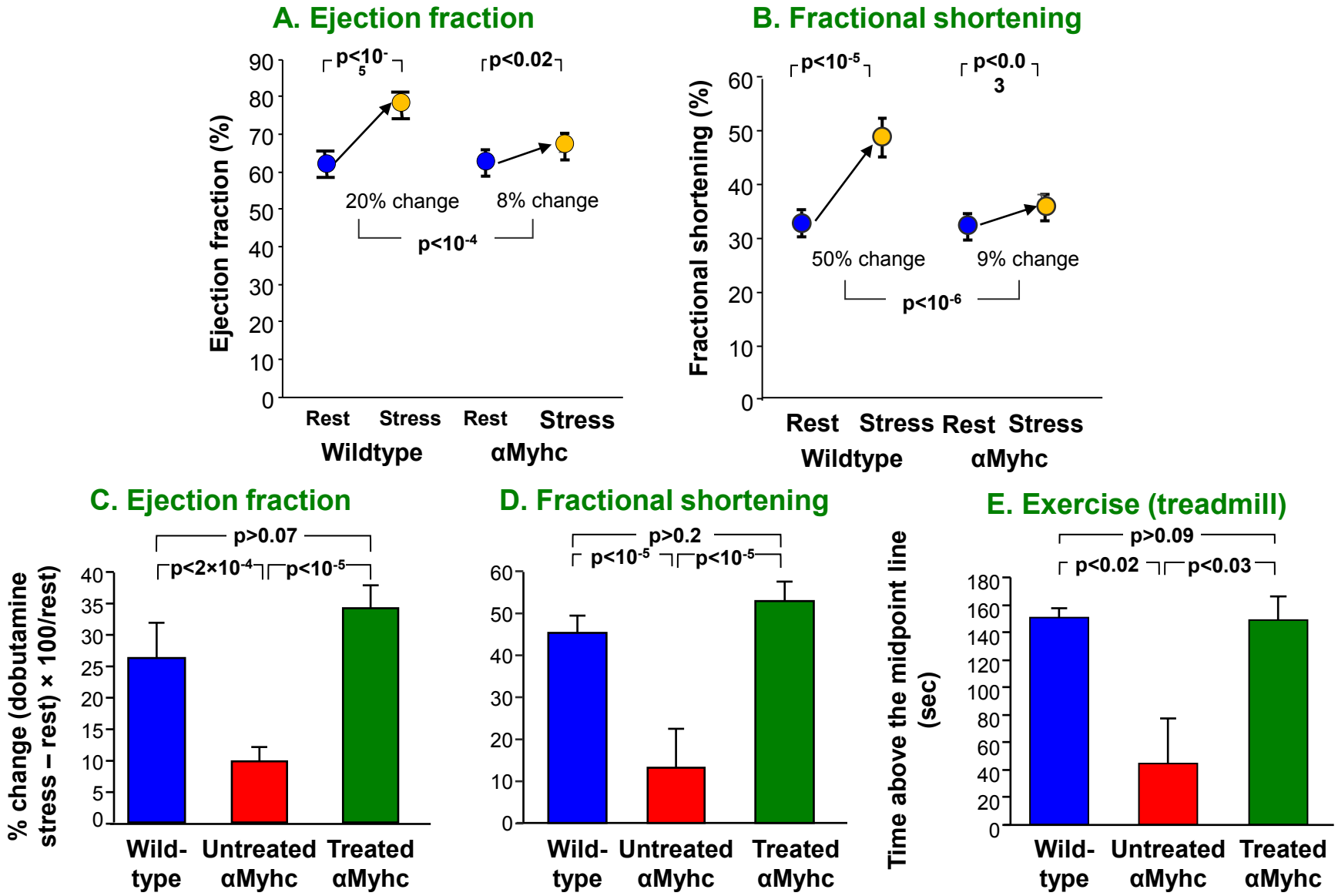


C. Survival



[1] Perdomini M et al. Nat Med 2014; 20:542

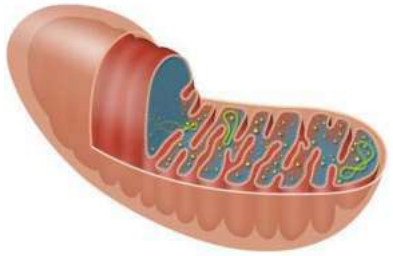
Intravenous Administration of AAVrh.10hFXN (LX2006) to αMyhc Mice Corrects Echocardiography Quantification of Ejection Fraction and Fractional Shortening Under Stress and Improves Exercise Ability



Effects of FXN Overexpression

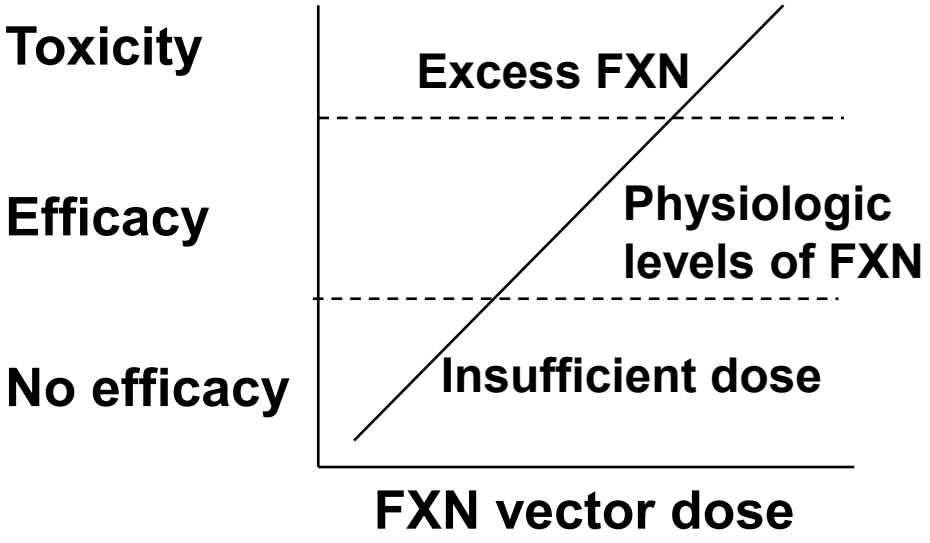
Observation	References
***In vitro* studies** • Increase in FXN levels above normal levels adversely affects cellular metabolism, increases oxidative stress/damage and iron pool levels, leading to eventual cell death	Li et al Hum Gene Ther 2020; Vannocci et al Sci Rep 2019; Vannocci et al Dis Model Mech 2018; Llorens et al FASEB J 2007; Navarro et al PLoS One 2011; Seguin et al Mitochondrion 2009
Gene therapy animal studies	
• Cardiac toxicity, MCK mice at ≥2.5x10^{13} gc/kg (AAVrh.10)	Belbellaa et al Mol Ther Methods Clin Dev 2018
• Cardiac and liver toxicity, MCK mice at ≥1x10^{13} gc/kg (AAV9)	Huichalaf et al Mol Ther Methods Clin Dev 2022
• Cardiac toxicity nonhuman primates at ≥3x10^{13} gc/kg and liver toxicity at 1x10^{14} gc/kg (AAVhu68)	Hinderer et al Mol Ther 2022

Challenge for Effective and Safe Gene Therapy of the Cardiac Manifestation of Friedreich's Ataxia



Cardiomyocyte mitochondria

Frataxin levels



Challenge

- FXN levels are deficient in heart cells, resulting in insufficient energy production
- High levels of FXN from gene therapy may provide efficacy but may also be associated with adverse effects

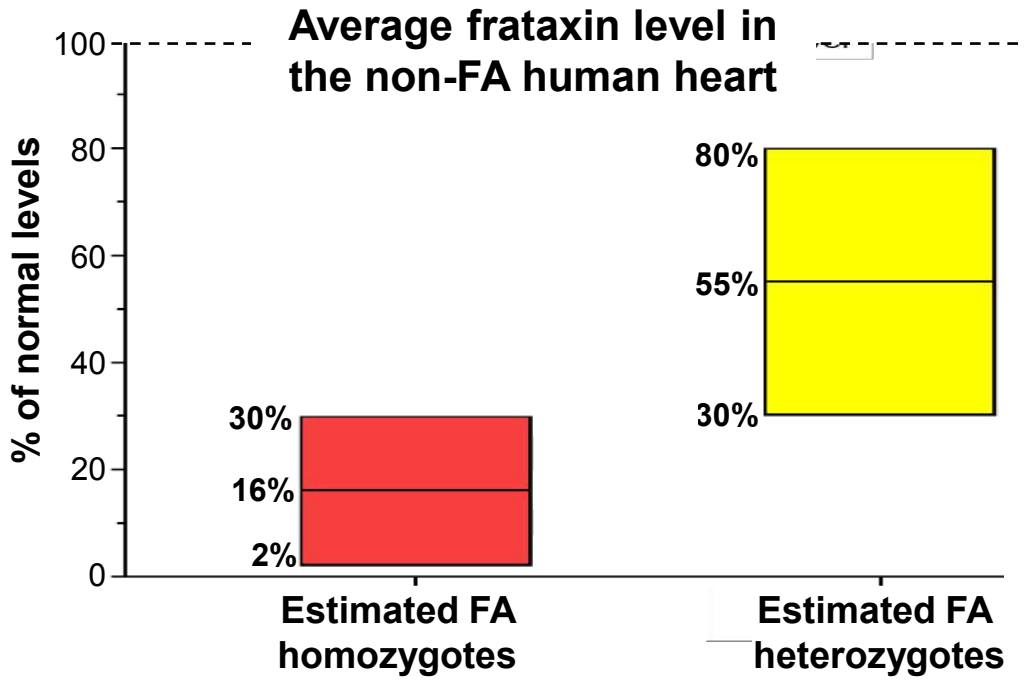
Solution

- Since FA heterozygotes have normal cardiac function, determine the minimal amount of FXN that gene therapy needs to provide to convert the homozygote FA heart to a heterozygote FA heart

Goal of Effective, Safe Gene Therapy for the Cardiac Manifestations of Friedreich's Ataxia

Estimated cardiac FXN levels in FA homozygotes and heterozygotes compared to normals[1]

Goal: convert the homozygote heart to a heterozygote heart



[1] Lazaropoulos M et al. Ann Clin Transl Neurol 2015; 2:831 [studies in blood and buccal mucosal cells]

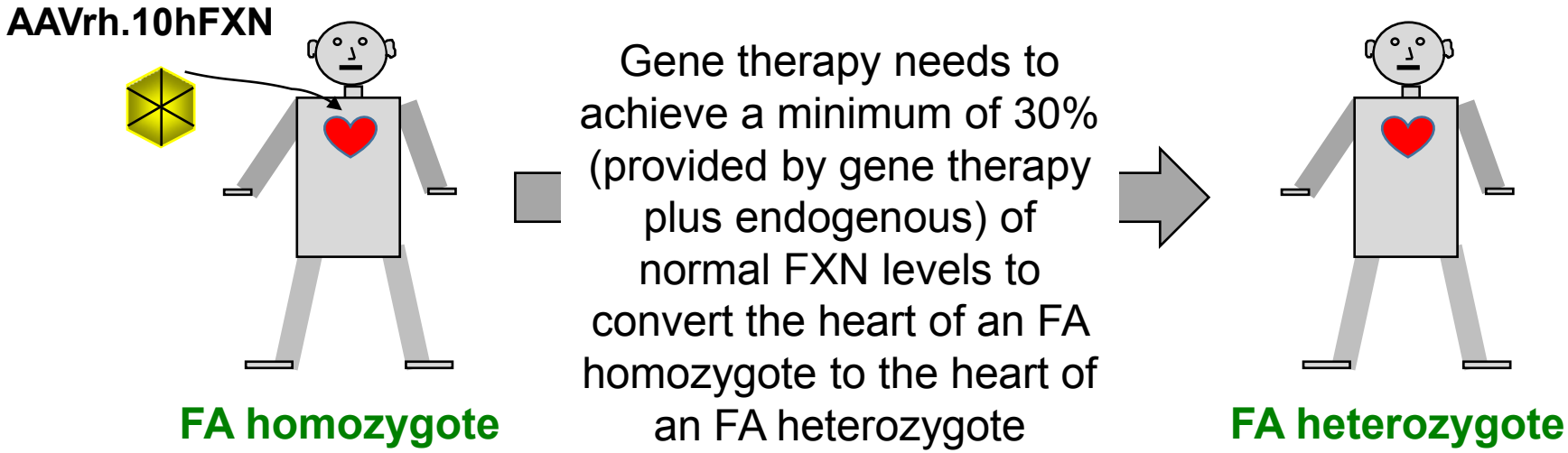
AAVrh.10hFXN (LX2006) Gene Therapy

Goal

- To determine the minimal intravenous dose of AAVrh.10hFXN required to treat the cardiac manifestation of FA

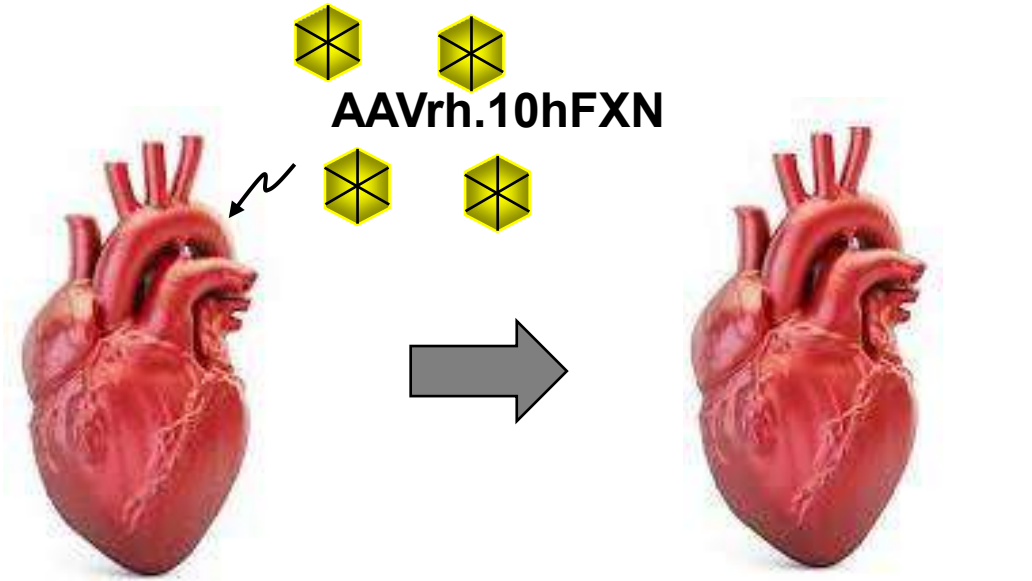
Background

- FA heterozygotes are normal; minimal heterozygote levels are 30% of homozygotes[1]
- Cells of FA homozygotes have some endogenous FXN levels[1]



[1] Lazaropoulos M et al. Ann Clin Transl Neurol. 2015;2:831

Minimum Dose of AAVrh.10hFXN (LX2006) Required to Safely Convert the FA Homozygote Heart to an FA Heterozygote Heart

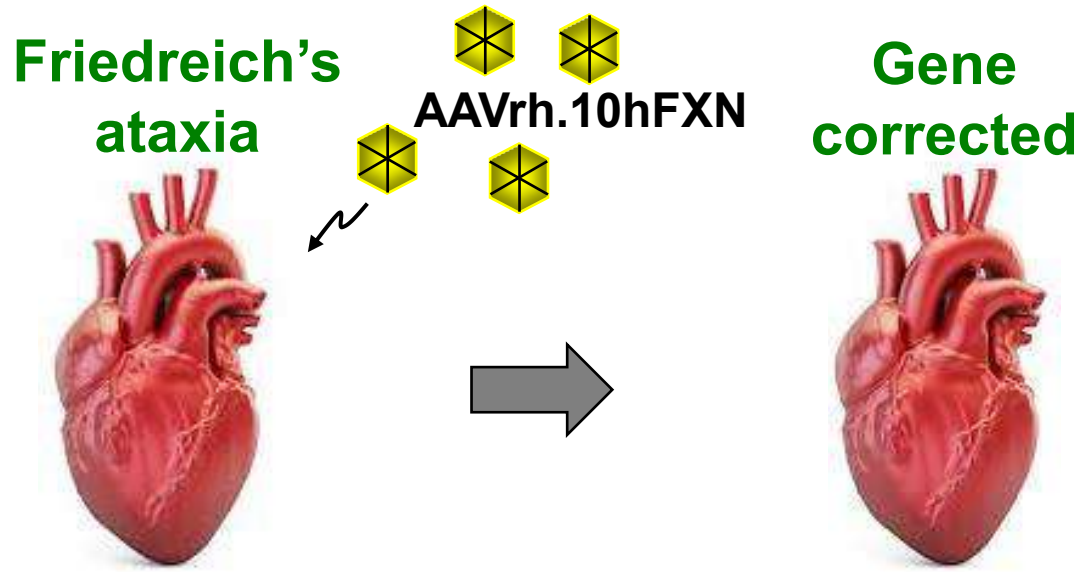


- Efficacy studies in experimental animals demonstrate that to safely convert the average FA homozygote heart to an FA heterozygote heart requires doses of 10^{11}-10^{12} gc/kg, well below the doses of 10^{13}-10^{14} gc/kg, which have been associated with toxicity

Toxicology Studies: Safety of Intravenous AAVrh.10hFXN (LX2006) in Non-human Primates

- Formal toxicology studies in non-human primates testing doses in the 10^{11}-10^{12} gc/kg range demonstrated normal results for weight, mortality, blood hematology, blood chemistry, serum troponin, organ histology and cardiac echocardiography

FDA approved the INDs to Conduct Clinical Trials of Gene Therapy with AAVrh.10hFN (LX2006) to Treat the Cardiomyopathy of Friedreich's Ataxia



- Cardiac dysfunction
- Improved function

- Based on the preclinical efficacy and safety data, vector production and characterization and proposed clinical studies, the FDA has approved both the Weill Cornell and LEXEO Investigational New Drug applications to initiate two independent trials

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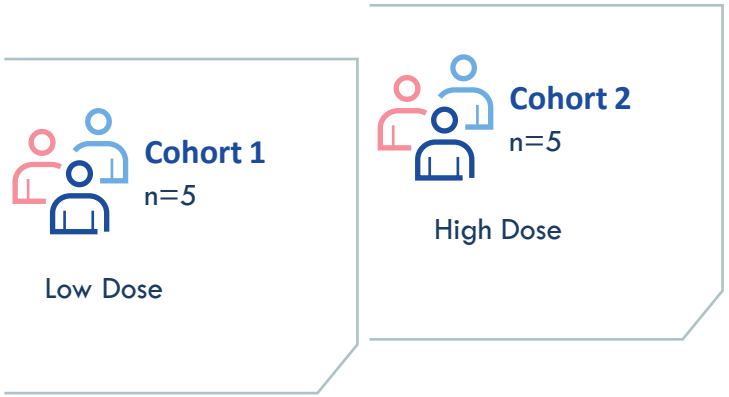
LEXEO Therapeutics Clinical Study

Jay Barth, MD
Chief Medical Officer
LEXEO Therapeutics

LX2006 Friedreich's Ataxia Phase 1/2 Overview (Study LX2006-01)

Trial Design

52-Week Follow-up



Key Features:

- 52-week, dose-ascending, open-label trial with long-term follow-up (5-years post dose)
- Vector: AAVrh10
- Route of Administration: Intravenous (IV) administration

Study Endpoints

Primary endpoint: Safety

Key Secondary endpoint: CPET peak VO2

Secondary endpoints:

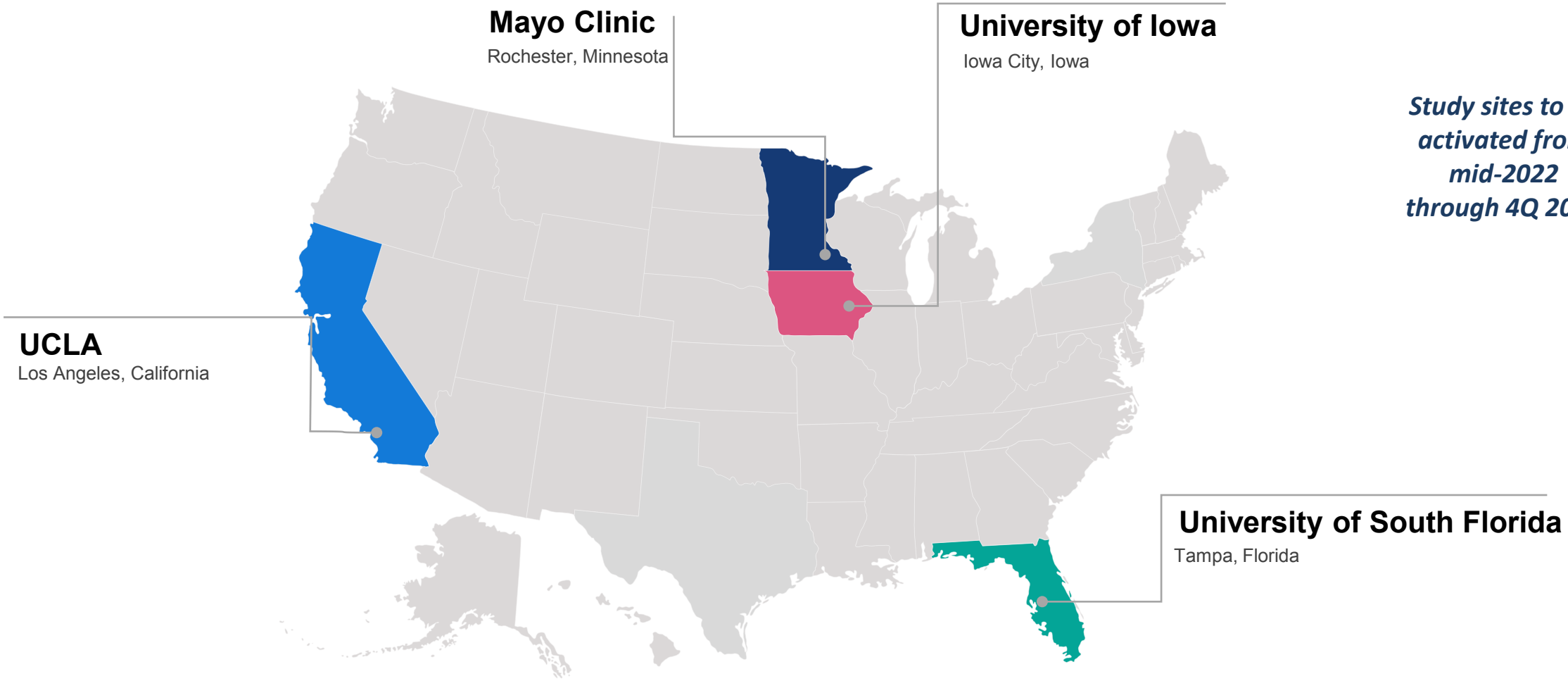
- Cardiac biopsy, FXN expression
- Cardiac symptoms, including fatigue, chest pain, dyspnea
- Symptoms during CPET
- LV hypertrophy
- Cardiac strain
- Ejection fraction
- Cardiac arrythmias
- Cardiac serum biomarkers
- FA neurologic scales

Timing

- Initiation of trial in mid-2022

LEXEO therapeutics

Study Sites



Study sites to be activated from mid-2022 through 4Q 2022

Site in Montreal, Canada in early start-up (pending discussions with Canada Regulatory Authority)

LEXEO therapeutics

Key Inclusion Criteria (1 of 2)

- Age ≥18 to ≤40 years at time of signing the informed consent
- Willing and able to provide informed consent
- Definitive diagnosis of FA, based on clinical phenotype and genotype (GAA expansion on both alleles), with onset of FA before age 25 years
- No contraindications to undergoing cardiac biopsies
- Able to perform cardiopulmonary exercise test (arm crank test) consistent with early cardiac dysfunction (within protocol-specified ranges)
- Left ventricle ejection fraction measured by cardiac MRI of ≥45%
- Left ventricular hypertrophy (LVH), and stroke volume and/or global longitudinal left ventricular strain consistent with early cardiac dysfunction (within protocol-specified ranges) on cardiac MRI
- Fibrosis ≤5% in the left ventricular wall

LEXEO therapeutics

Key Inclusion Criteria (2 of 2)

- Minimal antibodies against AAVrh.10
- Acceptable parameters relating to blood, liver, kidney function
- No active infection
- Barrier birth control
- No contraindications to receiving corticosteroid immunosuppression (prednisone)
- Must be fully vaccinated against COVID-19 including all recommended boosters by age prior to dosing

LEXEO therapeutics

Key Exclusion Criteria (1 of 2)

- Coronary artery disease or any structural heart or vascular disease
- Hemodynamically unstable arrhythmias requiring physician intervention
- Thromboembolic phenomenon or increased risk of thromboembolic phenomenon (blood clots)
- Clinically significant lung function abnormality such as chronic obstructive pulmonary disease (COPD) and emphysema
- Hypersensitivity or contraindications to corticosteroids
- Uncontrolled psychiatric disease
- Uncontrolled diabetes
- Alcoholism or drug addiction

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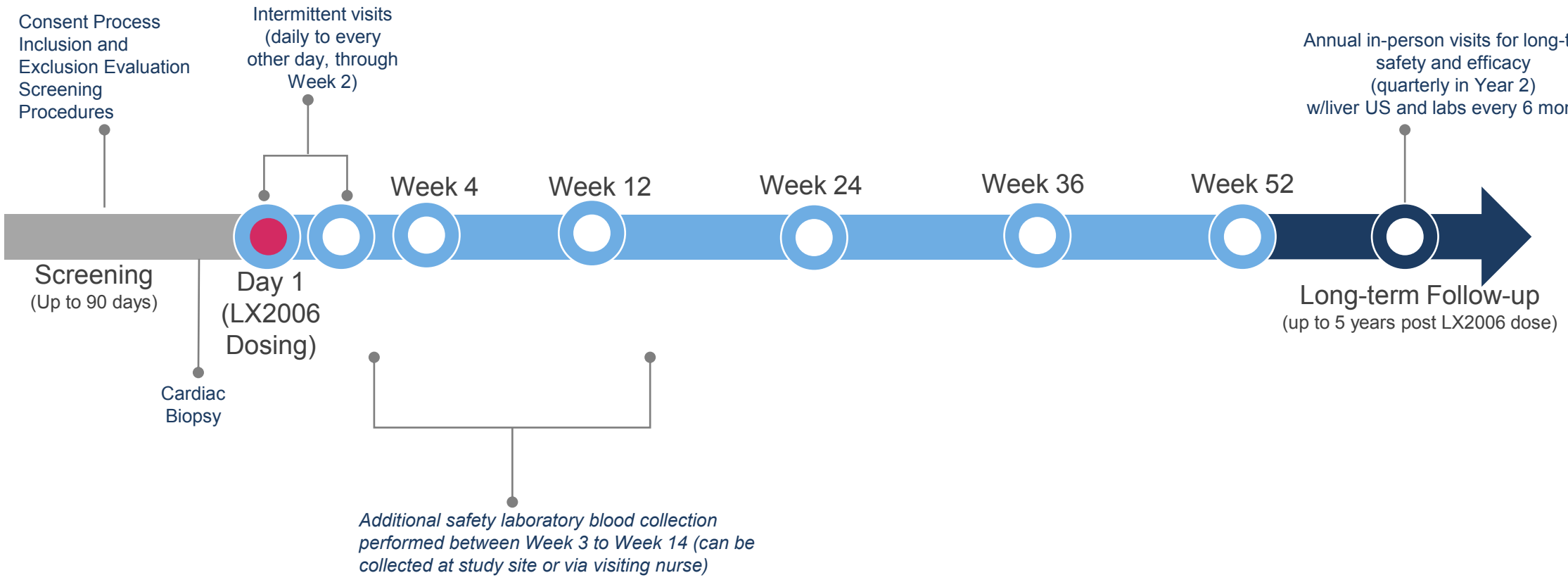
Key Exclusion Criteria (2 of 2)

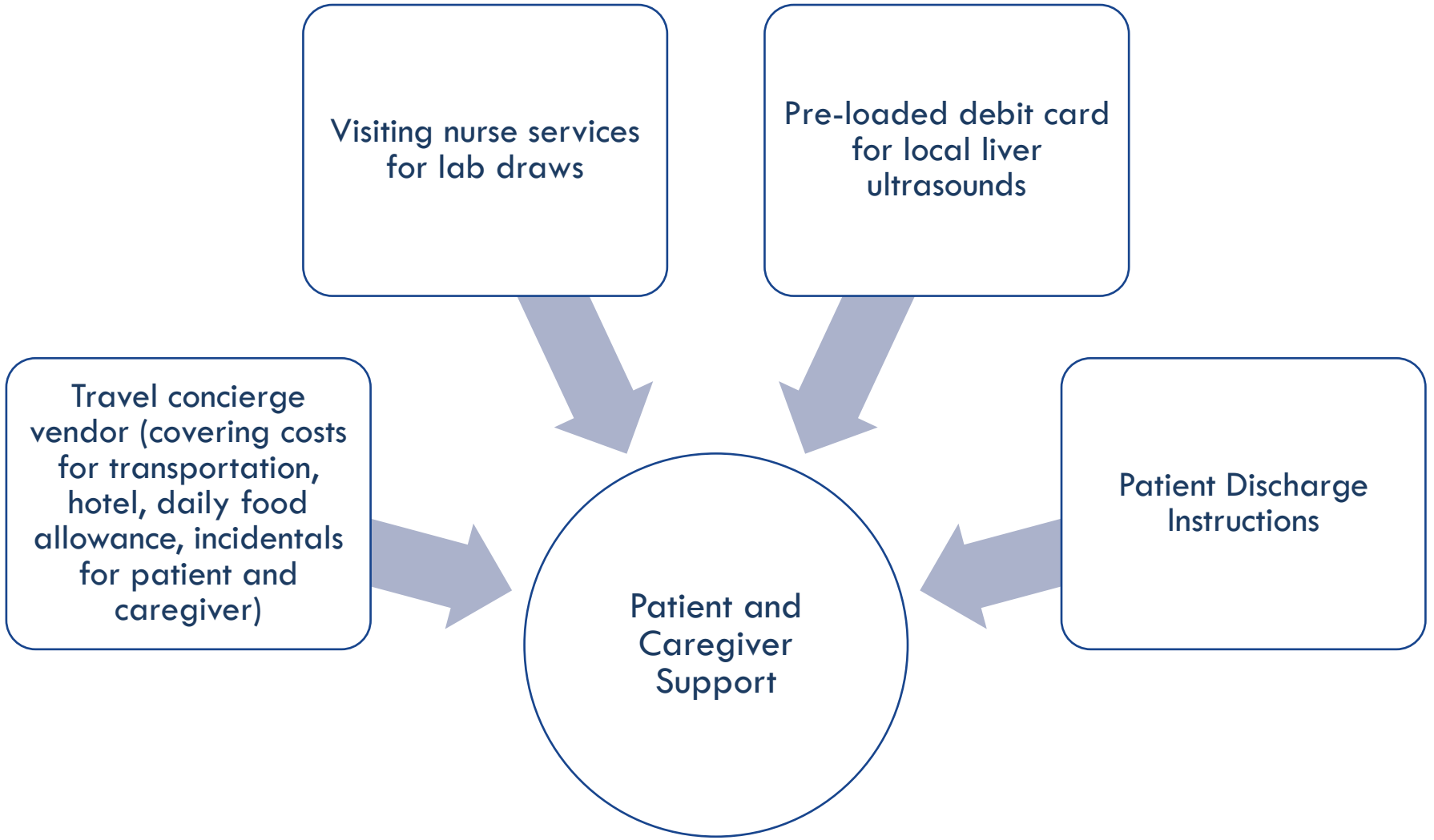
- Any malignancy during the last five years, except basal cell skin cancer
- Current infection
- Receiving corticosteroids or other immunosuppressive medications
- Participation in an investigational drug or device study within 12 weeks prior to Screening or any previous gene therapy or cell therapy at any time prior to Screening
- Contraindication to cardiac MRI (e.g., non-MRI compatible pacemaker/defibrillator) or gadolinium (known or suspected hypersensitivity, glomerular filtration rate <30 mL/min/1.73m^2)
- Pregnant or breastfeeding

LEXEO therapeutics

Study Procedures and Visits



Patient and Caregiver Support in Study Participation



Next Steps for Study

- Information regarding Study LX2006-01 to be posted on clinicaltrials.gov as we near the time of activation of the first study site
- Contact details for each study site will be posted on clinicaltrials.gov once a site is able to start screening patients for potential participation in the study
- Updates regarding the study will be provided to the FA Community by LEXEO, in collaboration with FARA

LEXEO therapeutics

FARA Webinar:
Gene Therapy for the Cardiac Manifestations of Friedreich's Ataxia

Department of Genetic Medicine, Weill Cornell Clinical Study

Ronald Crystal, MD
Professor and Chairman
Department of Genetic Medicine, Weill Cornell Medicine

Department of Genetic Medicine, Weill Cornell Medical College, NHLBI-funded Clinical Trial Phase IA Study of AAVrh.10hFXN Gene Therapy for the Cardiomyopathy of Friedreich's ataxia

- **Purpose:** to test the safety and preliminary efficacy of AAVrh.10hFXN to treat the cardiomyopathy associated with Friedreich's ataxia
- The drug is administered intravenously
- Phase 1, open label, dose escalation study with a total of 10 participants
- Participants are assessed frequently in year 1, with follow up assessments in years 2-5
- To protect against liver inflammation secondary to an immune reaction to AAVrh.10hFXN, all participants will be treated with once daily oral prednisone (an anti-inflammatory medication) for 12 weeks

Primary and Secondary Outcome Measures

Primary

- To determine the safety of AAVrh.10hFXN

Secondary

- Change in cardiopulmonary exercise testing
- Change in cardiac-relevant parameters in cardiac-magnetic resonance scans and echocardiograms
- Change in arrhythmias with 24 hr monitoring

Inclusion Criteria

- Males and females, age 18 to 40
- Willing and able to provide informed consent
- Definitive diagnosis of Friedreich’s ataxia, based on clinical phenotype and genotype (GAA expansion on both alleles)
- >600 GAA repeats in intron 1 in at least one allele
- FARS and SARA neurologic scores consistent with diagnosis of Friedreich's ataxia

Cardiac-related Inclusion Criteria

- Left ventricle ejection fraction measured by cardiac MRI of ≥45% to 75%
- Evidence of FA-related cardiac disease: must be abnormal in ≥2 of the following parameters, at least one of which is an abnormal cardiac MRI left ventricular mass index or abnormal cardiopulmonary exercise test
  - In the absence of other factors known to cause left ventricular hypertrophy, cardiac MRI left ventricular mass above the normal range
  - Cardiopulmonary exercise test (arm crank testing) consistent with early cardiac dysfunction
  - Cardiac MRI stroke volume index consistent with early cardiac dysfunction
  - Cardiac MRI global longitudinal left ventricular strain consistent with early cardiac dysfunction
  - Serum high-sensitivity cardiac troponin above the normal range
- Fibrosis ≤5% in the left ventricular wall

Additional Inclusion Criteria

- Minimal antibodies against AAVrh.10
- Acceptable parameters relating to blood, liver, kidney function
- No active infection
- No experimental medication
- No contraindications to receiving prednisone
- Must be fully vaccinated against SARS-CoV2

Exclusion Criteria

- Receiving immunosuppressive medications
- Uncontrolled diabetes
- Current infection
- Decompensated heart failure
- Hemodynamically unstable atrial or ventricular arrhythmias which require medical intervention
- Contraindication to cardiac MRI
- Malignancy
- Conditions other than FA known to produce left ventricular hypertrophy
- Use of oxygen supplementation
- Risk for thromboembolic disease (blood clots)
- Uncontrolled psychiatric disease
- Pregnant or breastfeeding
- Prior participation in gene and/or cell therapy
- Coronary artery disease
- Alcoholism or drug addiction

Overview of the Department of Genetic Medicine, Weill Cornell Clinical Study

Screening

- Assessment to ensure eligibility

Administration of the gene therapy and followup

- Repeat assessment to establish baseline
- Start prednisone immunosuppression therapy before gene therapy and continue for 3 months
- Gene therapy – intravenous administration over 1 hour
- Overnight stay in the hospital for monitoring
- Two week stay at a hotel on the Weill Cornell campus, with frequent outpatient visits for monitoring
- Followup assessment at frequent intervals over 1 year
- Assessment 4x year 2, 1x years 3-5

Cost

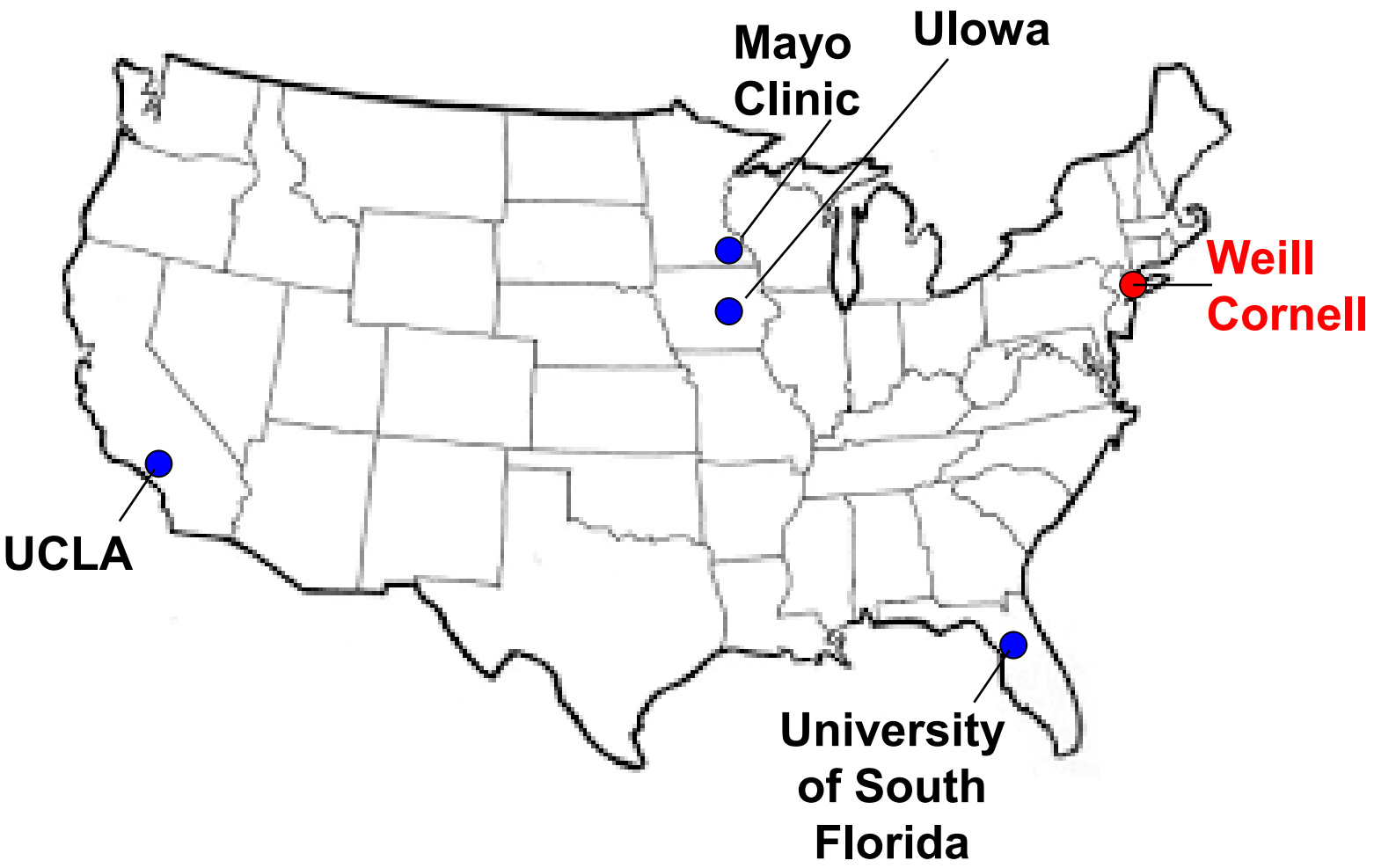
- The study, including travel and stay in NYC, is of no cost to the patient and caregiver

Important differences from the LEXEO study

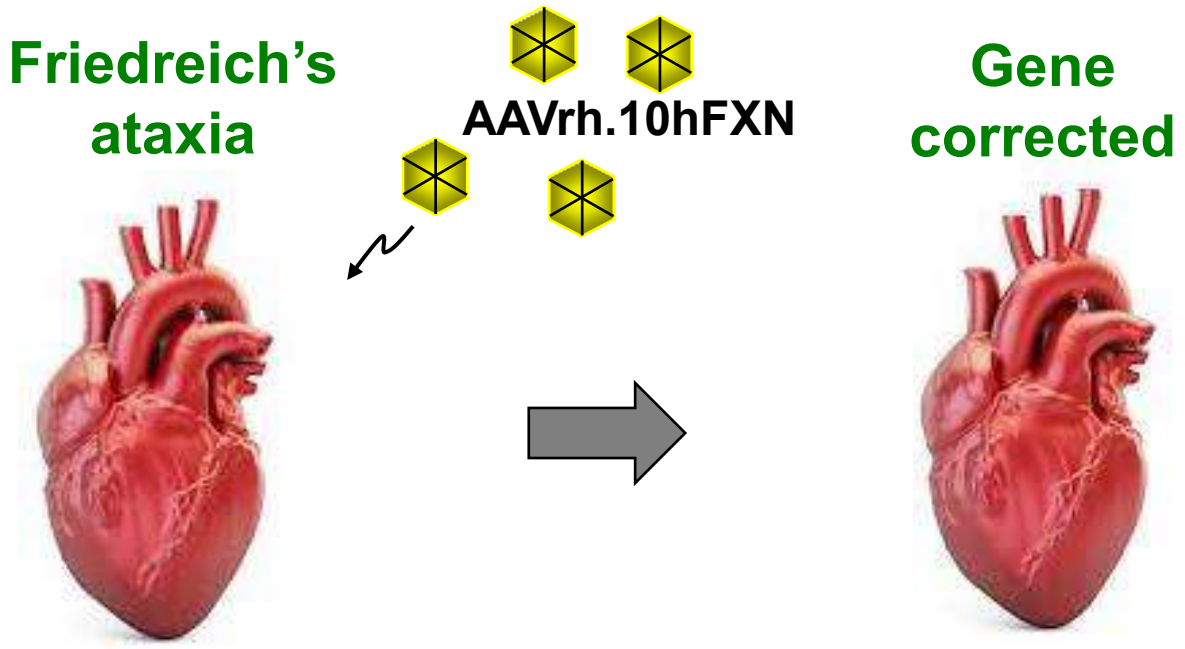
- Criteria allow for patients who are unable to perform cardiopulmonary exercise testing
- No cardiac biopsy

LEXEO and Weill Cornell Sites

- LEXEO Sites
- Cornell Site



Gene Therapy with AAVrh.10hFN (LX2006) to Treat the Cardiac Frataxin Deficiency in Friedreich's Ataxia



- Cardiac dysfunction
- Improved function

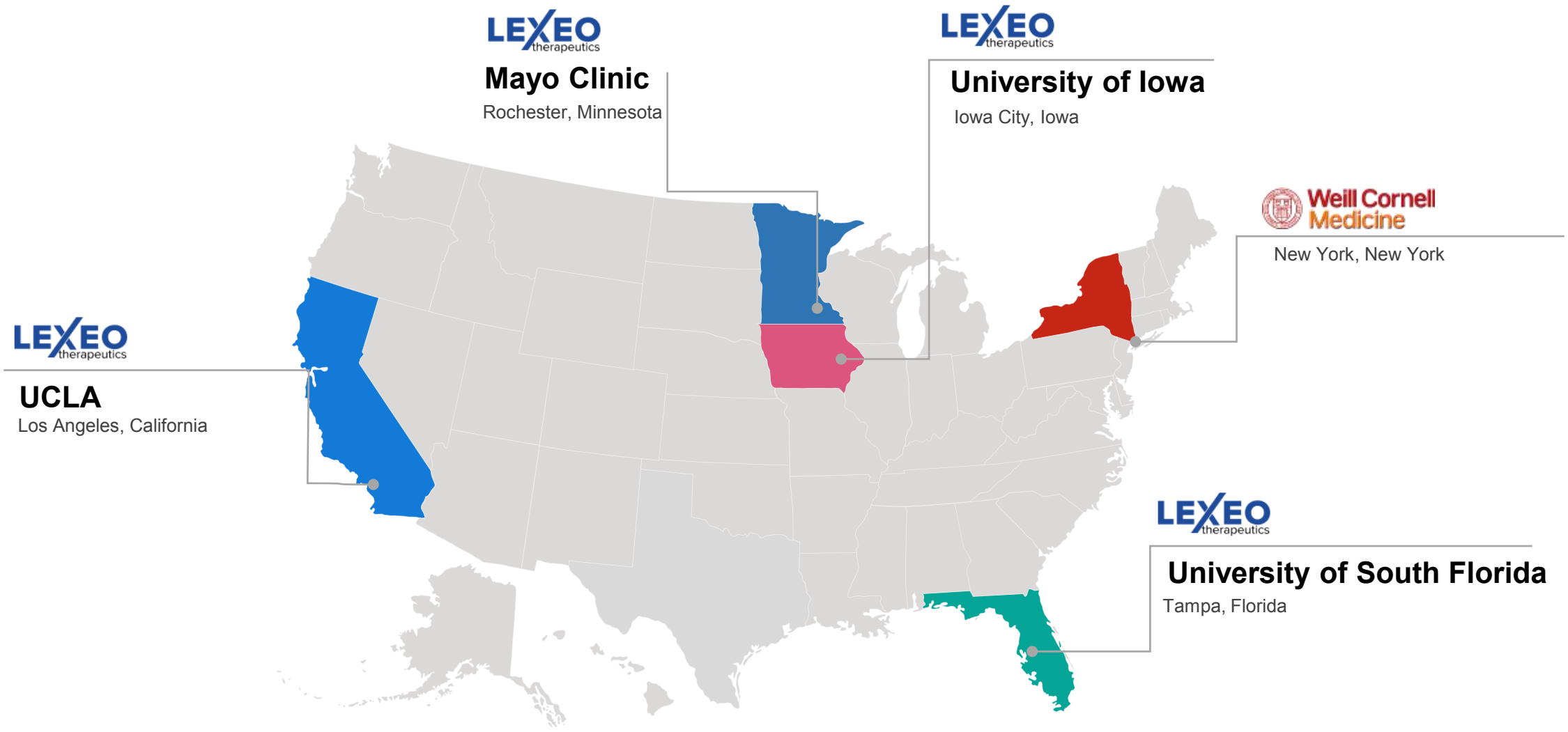
Further Information Regarding the Weill Cornell Study

- See clinicaltrials.gov/ct/show/NCT05302271
- Updates will be provided to the FA Community in collaboration with FARA
- Contacts at Weill Cornell regarding the study:
  - Hallie Bowe: 646-962-4580, hab4007@med.cornell.edu
  - Noor Hassan: 646-962-5583, noh404@med.cornell.edu

Summary: Weill Cornell and LEXEO First-in-Human Studies

	Weill Cornell Study	LEXEO Study
Intent	• Academic institution as sponsor • National Heart, Lung, and Blood Institute (NHLBI) as funder	• Industry-sponsored • Data supports dose selection for future pivotal study • Supportive study for potential future Regulatory filings for marketing authorization
Patient Population	✓ Mild-to-moderate cardiomyopathy • Abnormal cardiopulmonary exercise test not required – may include more neurologically progressed patients	✓ Mild-to-moderate cardiomyopathy • Abnormal cardiopulmonary exercise test (within defined limits) required for study entry – To assess effect of LX2006 on cardiac function
Planned Centers	• Single-center (Cornell)	• Multicenter (4 centers in US, potentially 1 center in Canada)
Design	✓ 2-dose levels (n=10 subjects total) ✓ 52-week study (followed by 4-year long-term follow-up)	✓ 2-dose levels (n=10 subjects total) ✓ 52-week study (followed by 4-year long-term follow-up)
Endpoints	✓ Safety ✓ CPET ✓ Cardiac MRI ✓ ECHO ✓ Monitoring for arrythmias ✓ QOL/symptoms • No cardiac biopsy	✓ Safety ✓ CPET ✓ Cardiac MRI ✓ ECHO ✓ Monitoring for arrythmias ✓ QOL/symptoms • Cardiac biopsy for assessment of safety and FXN expression (baseline and Month 3)

LEXEO and Weill Cornell Sites



LEXEO therapeutics *Site in Montreal, Canada in early start-up (pending discussions with Canada Regulatory Authority)*

Acknowledgements

We would like to thank the individuals living with FA, their family, and caregivers

We would like to thank FARA for their support and opportunity to present at this webinar

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Q&A