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Preliminary Results from SUNRISE-FA: A Phase 1/2 Study of Investigational Gene Therapy, LX2006, for Cardiomyopathy of Friedreich Ataxia

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Friedreich Ataxia (FA) is a Devastating Rare Disease Impacting Both the Nervous System and the Heart

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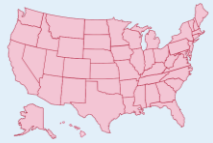
FA is a **rare, devastating and progressive disorder** caused by loss of function mutations in the *FXN* gene (GAA repeat expansion)

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)

Cardiac dysfunction is the **leading cause of death in FA**

The only approved disease-specific treatment for FA demonstrated efficacy on neurological measures but was not evaluated for the treatment of cardiac dysfunction, **leaving a 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.

Small Increases in Frataxin Following Treatment May Produce Clinical Benefits

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Modest FXN Levels Resulted in Near Normal Cardiac Function in FA Murine Model

YG8-800 FA Murine Model

- YG8-800 mice have **5% of normal frataxin levels** in the heart, with approximately 800 GAA repeats, but display **near normal** cardiac output and stroke volume(1)
- Suggests **potential to improve cardiac phenotype with restoration to modest frataxin levels**

Moderate Restoration of Protein Function Correlates with Better Disease Prognosis and Physiological Improvement in Other Diseases

Hemophilia B

- In humans, factor IX clotting activity is typically 50 – 150%(2)
- Individuals with > 40% usually have normal coagulation *in vivo*(2)
- Clinical data indicates even a **small increase to 5% of normal factor IX levels significantly reduces bleeding**(3)

Muscular Dystrophies

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

Existing literature suggests small increases in frataxin may be sufficient to produce physiological improvement

BMD, Becker Muscular Dystrophy; DMD, Duchenne Muscular Dystrophy; FXN, Frataxin; GAA, Guanine-adenine-adenine.

(1) Gérard C, et al. *Behav Brain Res,* 2023. (2) Konkle BA, Fletcher SN. *Gene Reviews,* 2000 [Updated 2023]. (3) Nathwani AC. *Hematology Am Soc Hematol Educ Program,* 2022.
(4) Bellayou et al. *Journal Biomedicine Biotechnology,* 2009.

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Investigational Gene Therapy LX2006 Has the Potential to Address the Underlying Cause of Friedreich Ataxia (FA) Cardiomyopathy

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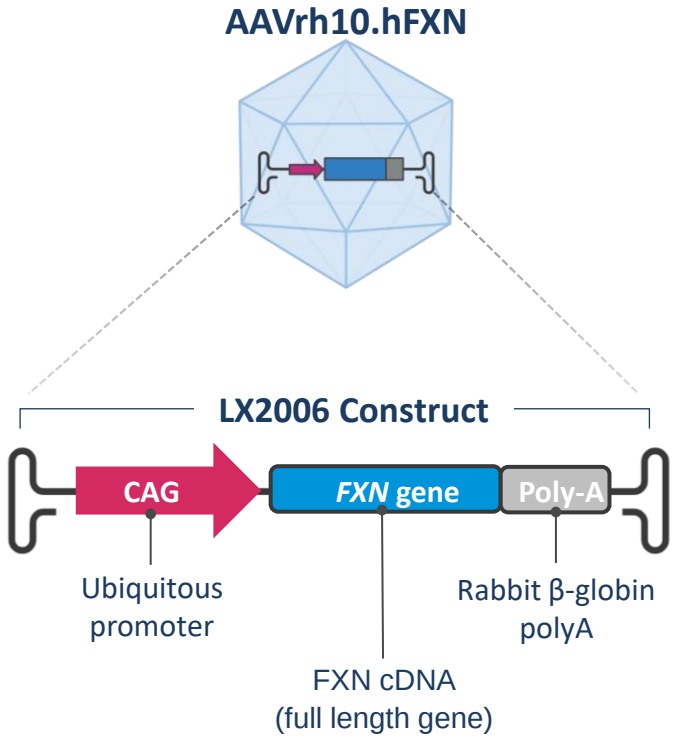

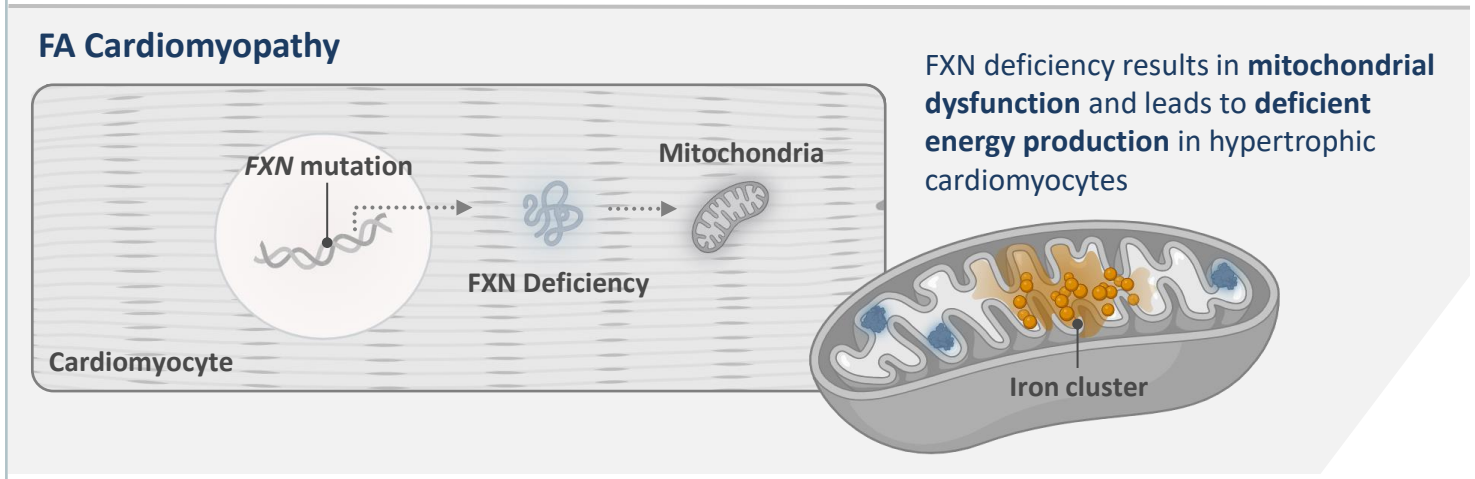

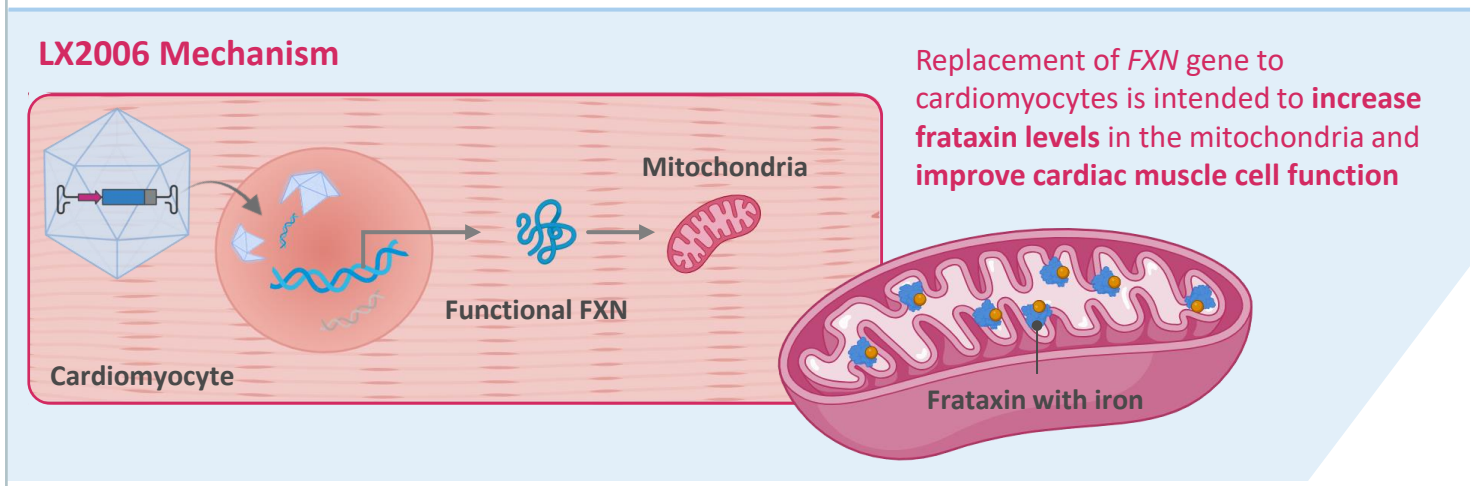

AAV, Adeno-Associated Virus; CAG, Chicken Beta-Actin; cDNA, Copy DNA; FA, Friedreich Ataxia; FXN, Frataxin; Poly-A, Poly Adenosine.

LX2006 is Being Evaluated in the Ongoing SUNRISE-FA Trial

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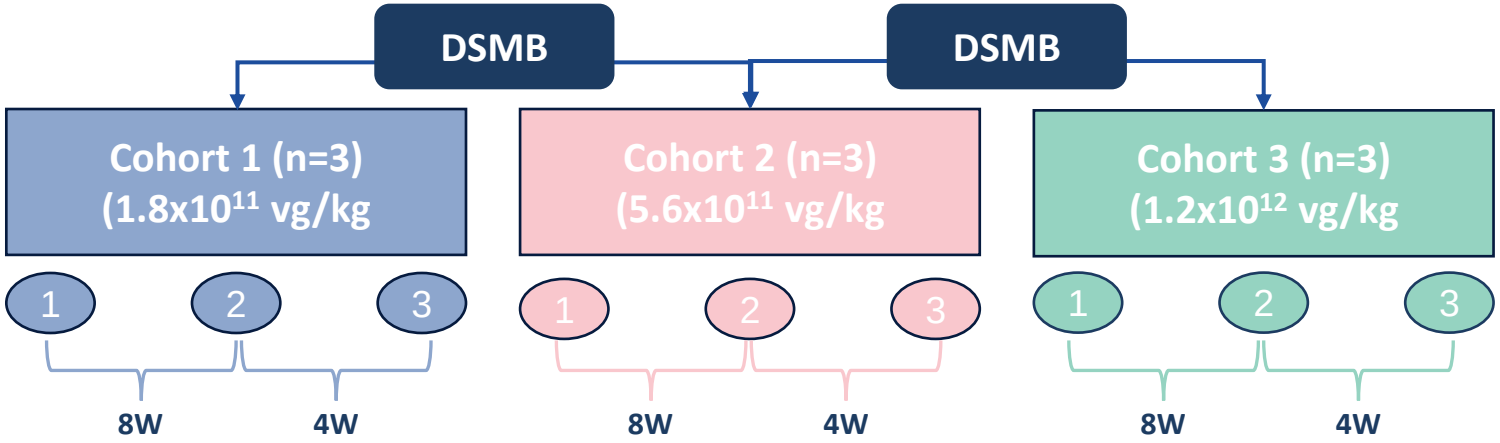
Phase 1/2, open-label, dose-ascending, multicenter study of the safety and efficacy of AAVrh10.hFXN (LX2006) in FA-CM



- DSMB approved moving to Cohort 2 after 1 participant treated in Cohort 1 of SUNRISE-FA
- DSMB approved including 1 additional participant to Cohort 3

At the time of this analysis (30 June 2024): 4 participants were treated with LX2006 and 3 participants have at least 6 months of follow-up data.

- Cohort 1: n = 1
- Cohort 2: n = 3

Patient Population and Key Inclusion and Exclusion Criteria

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Key Inclusion/Exclusion criteria

- Male or female, age ≥ 18 to 50 years old
- Diagnosis of FA, based on clinical phenotype and genotype (GAA expansion on both alleles), with onset of FA being before 25 years of age
- Evidence of cardiomyopathy as measured by any 2 of the parameters below:
  - Elevated posterior wall thickness or Elevated septal wall thickness by echocardiogram (echo) or elevated relative wall thickness by echo
  - Either elevated left ventricular mass (LVM) or left ventricular mass index (LVMi) by echo
  - Characteristic T-wave inversions of FA (defined as abnormal if it occurred in any of leads II, III, aVF, V2 through V6 in ECG
- LVEF ≥40% (left ventricular ejection fraction)
- Willingness to comply with study procedures and no contra-indication to perform cMRI and cardiac biopsy
- Standard safety and consent I/E criteria including negative antibodies to viral capsid

FA, Friedreich ataxia; GAA, guanine adenine adenine; LVMi, left ventricular mass index; LVEF, left ventricular ejection fraction.

Key Outcomes Evaluated in SUNRISE-FA

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Outcome	Open Label Study Period				Long Term Follow Up 4 Year
	Baseline	Week 12	Week 24	Week 52	
Cardiac Biopsy	●	●	--	--	--
Cardiac Imaging	●	●	●	●	●
Biomarkers and Labs	●	●	●	●	●
CPET	●	--	●	●	●
PROs ClinROs	●	●	●	●	●
Safety	→	→	→	→	→

Cardiac Biomarker Data from SUNRISE-FA Previously Presented in July 2024

Note: Participants receive immune suppression with prednisone beginning on the day prior to treatment through 14 weeks following LX2006 administration.

Baseline Demographics, mFARS and KCCQ-12 Levels by Dosing Cohort

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Characteristics	Statistic	Cohort 1 ($1.8x10^{11}$ vg/kg) N=1	Cohort 2 ($5.6x10^{11}$ vg/kg) N=3
Age, years	Mean (SD) Min, Max	24	25.7 (3.8) 23, 30
GAA Repeats, shortest	Mean (SD) Min, Max	750	768 (204) 615, 1000
mFARS	Mean (SD) Min, Max	52	55.4 (15.8) 41.8, 73
KCCQ-12 **(Kansas City Cardiomyopathy Questionnaire)**	Mean (SD) Min, Max	NA	73.78 (17.98) 53.1, 85.9

At the time of this analysis, 3 participants had at least 6 months of follow-up data.

- Cohort 1: n = 1 (12-month follow-up data)
- Cohort 2: n = 3 (one with 12-month, one with 6-month, and one with <6-month follow-up data)

mFARS, modified Friedreich ataxia rating scale; KCCQ-12, Kansas City Cardiomyopathy Questionnaire.

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

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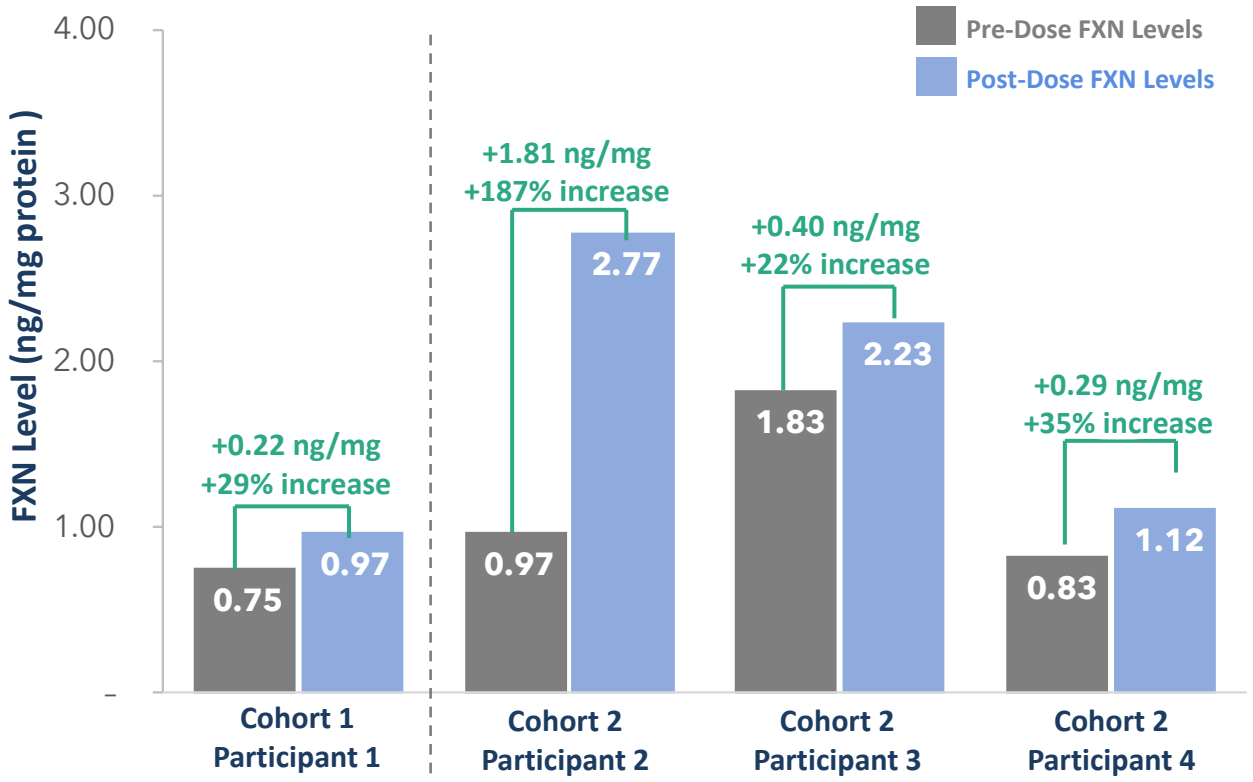
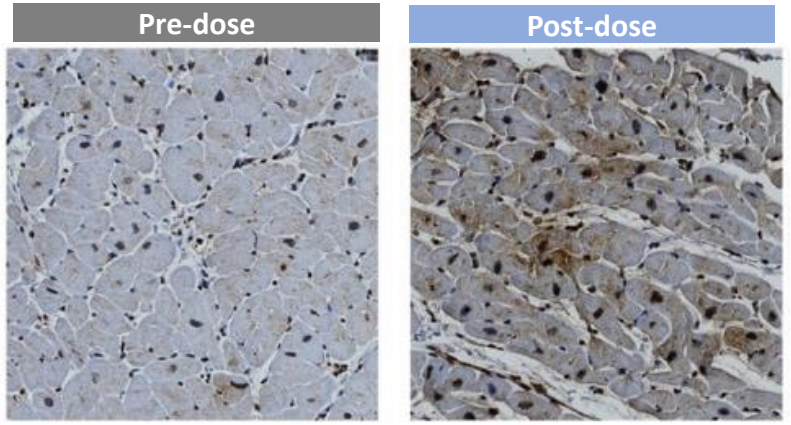
Pre- and Post-Treatment FXN Levels (LCMS)



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

	Pre-Dose	Post-Dose	% Increase
Participant 1	31%	51%	+65%
Participant 3	18%	54%	+209%
Participant 4	7%	26%	+279%

IHC images from Participant 3



Increased dose resulted in higher cardiac FXN level

LCMS, Liquid chromatography mass spectrometry; FXN, Frataxin; IHC, Immunohistochemistry. Note: Participant 2 IHC data could not be interpreted reliably due to technical issues due to sample quality.
Note: If comparing to July 2024 interim data update, Participant 6 has been relabeled Participant 1; Participant 9 has been relabeled Participant 2; Participant 10 has been relabeled Participant 3; Participant 11 has been relabeled Participant 4 for this presentation.
(1) Area measurement in square microns, FXN area as a percentage of total tissue showing FXN expression.

Preliminary Results Suggest Clinically Meaningful Improvements in Health Status Measured by Kansas City Cardiomyopathy Questionnaire (KCCQ)

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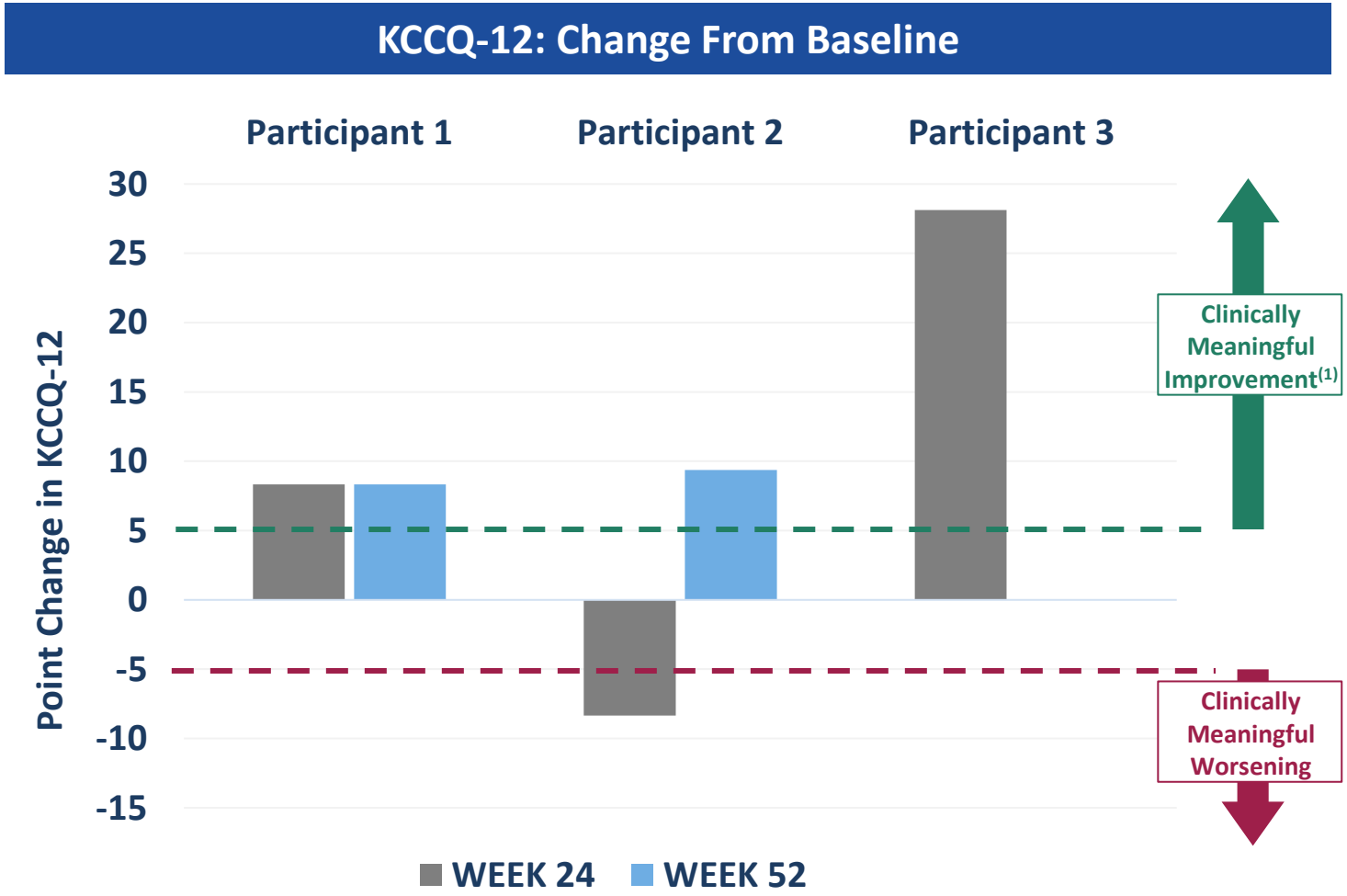

- KCCQ measures several aspects of health status including physical limitation, symptom frequency, quality-of-life (QoL) and social limitations in patients with cardiomyopathy
- Both participants with 52 weeks data, had more than 5 points improvement as measured by KCCQ
- Additional data is required to define the potential benefit of LX2006 in QoL in participants with FA-CM

(1) Spertus, J, Jones, P, Sandhu, A. et al. Interpreting the Kansas City Cardiomyopathy Questionnaire in Clinical Trials and Clinical Care: *JACC* State-of-the-Art Review. *JACC.* 2020 Nov, 76 (20) 2379–2390.

Participant 1 KCCQ-12 was not collected at baseline – 12-week collection was used as baseline for this analysis.

Participant 3 12-month data not available at time of analysis, Participant 4 did not reach 6-months of follow-up at time of analysis.

Preliminary Results Point Towards Numerical Improvements in mFARS

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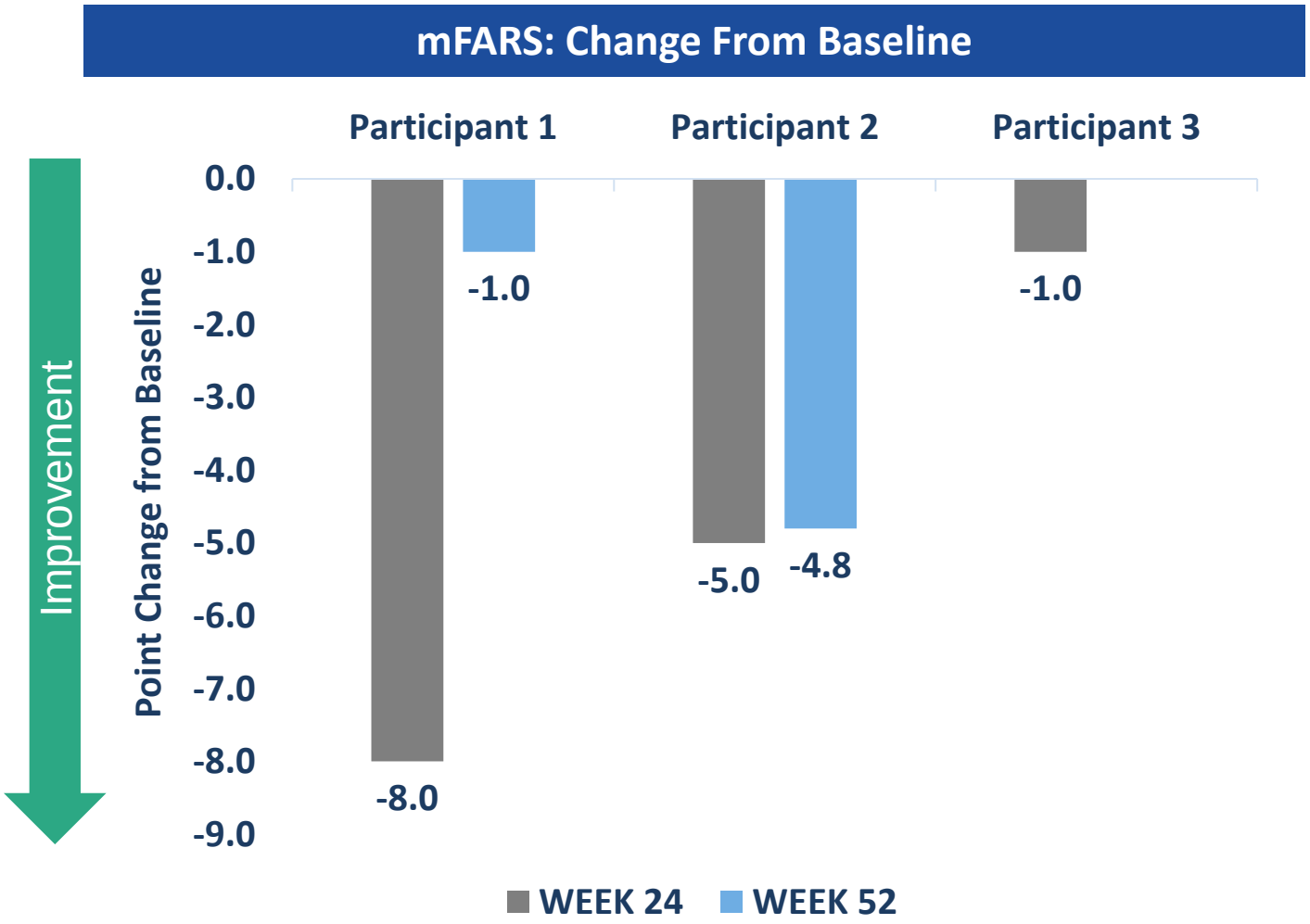

- At 24 weeks, all 3 participants with available data had at least 1-point improvement in mFARS
- Both participants with 52 week data available had at least 1-point improvement in mFARS
- Additional data is required to define the potential benefit of LX2006 in mFARS in participants with FA-CM

mFARS, modified Friedreich ataxia rating scale.
Participant 3 12-month data not available at time of analysis, Participant 4 did not reach 6-months of follow-up at time of analysis.

Numerical Changes in mFARS were Driven by Upright Stability, Lower and Upper Limb Domains

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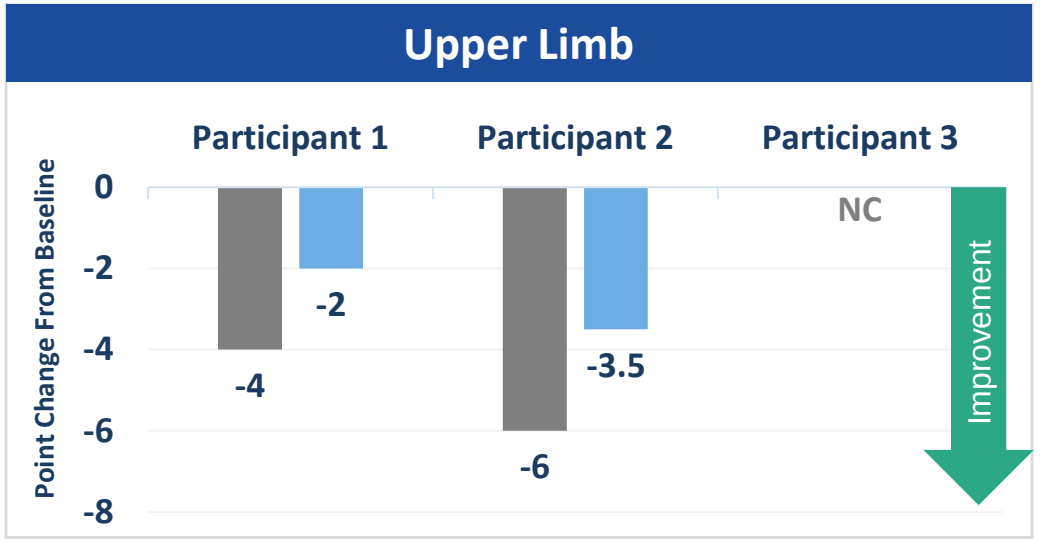

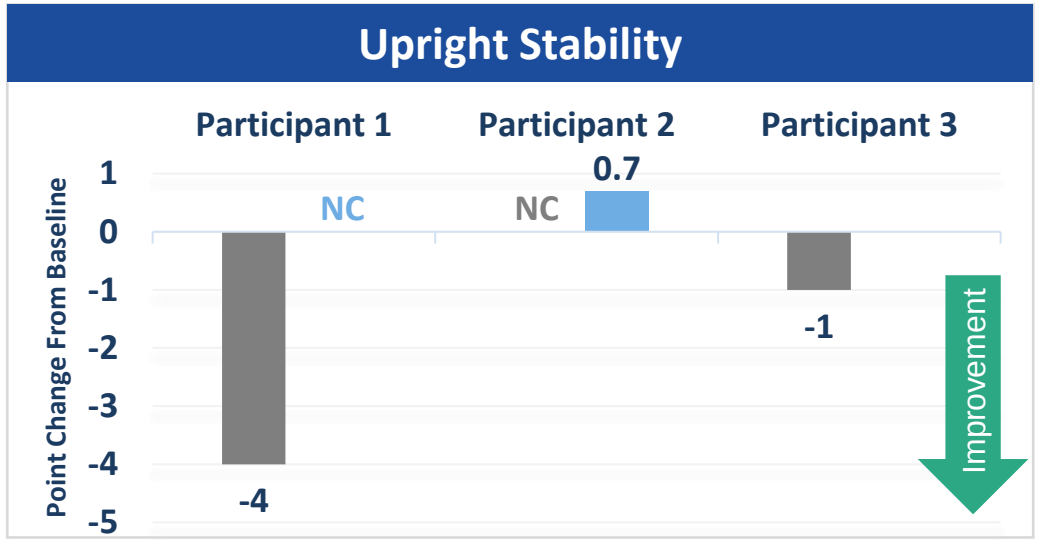

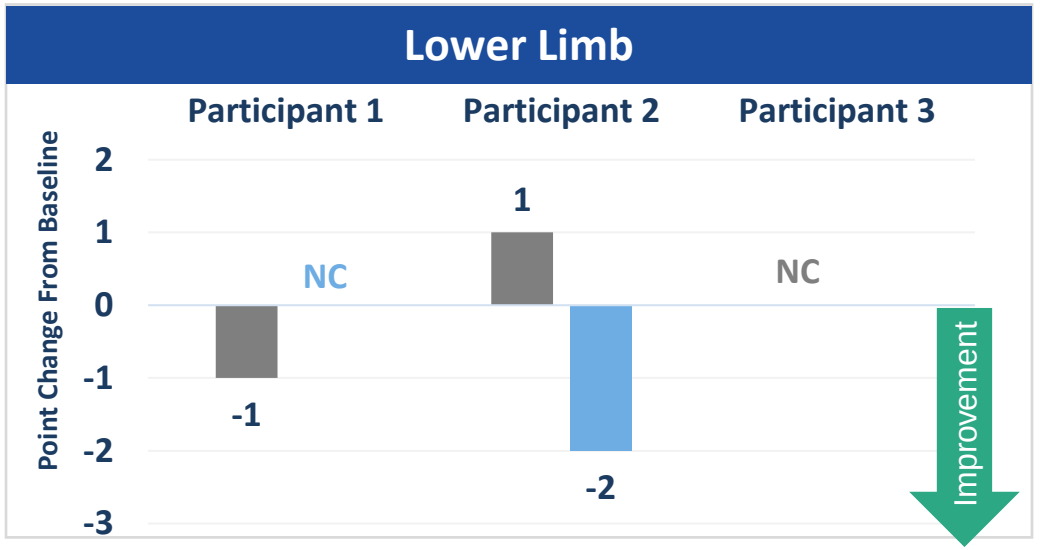

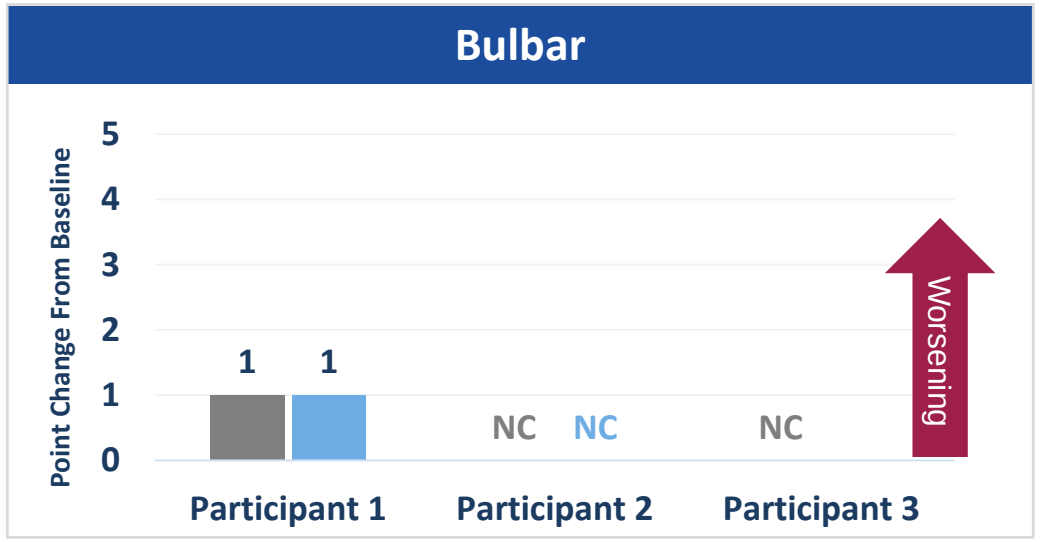

Week 24 Week 52

NC, no change from baseline.
Participant 3 12-month data not available at time of analysis, Participant 4 did not reach 6-months of follow-up at time of analysis.

Treatment with LX2006 Has Been Generally Well Tolerated to Date

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- No signs of complement activation or other immunogenicity were reported
- No safety signals were identified on arrhythmia burden as monitored by cardiac rhythm monitoring
- No participants discontinued from the study
- 1 possibly treatment-related Grade 2 event of asymptomatic myocarditis observed one year after dosing
  - Participant with multiple comorbidities; history of flu-like symptoms prior to diagnosis
  - Biopsy performed 6 weeks after diagnosis and results negative for myocarditis and participant remains asymptomatic
- Most common non-treatment related SAEs were chest pain, unspecified, occurring in 2 participants
- One AE of mild and transient increase in alanine and aspartate aminotransferases has been reported
- DSMB meeting in October 2024 recommended continuing study as designed and dosing an additional participant in Cohort 3

SAE, serious adverse event. AE, adverse event.

Summary of Preliminary Results

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- LX2006 (AAVrh10.hFXN) has been generally well tolerated
- Cardiac biopsies from SUNRISE-FA demonstrated increased frataxin expression in target organ in all participants across multiple measurement techniques
- Preliminary data suggest trends towards improvement in QoL (KCCQ-12) and mFARS
- As of October 30, 2024, 8 participants were dosed and enrollment is complete
  - Cohort 1 (n=1)
  - Cohort 2 (n=3)
  - Cohort 3 (n=4)

Thank you to all participants involved in this trial!

Thank you