Lexeo Therapeutics Announces Progress in FDA Discussions for Accelerated Approval Pathway and Positive Interim Clinical Data for LX2006 in FA Cardiomyopathy

October 7, 2025

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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 structure of and timelines for completion of any current or additional clinical trials required by the FDA, the timing for receipt and announcement of data from any such clinical trials, and the timing and likelihood of potential regulatory developments, trial design changes and approval. 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 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 Quarterly Report on Form 10-Q for the quarterly period ended June 30, 2025, filed with the SEC on August 14, 2025, 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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FDA Open to Earlier Co-Primary Endpoint Analysis and Pooling Data from Ongoing Phase I/II Studies of LX2006 with Pivotal Data; Potential to Accelerate BLA Submission for Accelerated Approval

Progress in FDA Discussions for Accelerated Approval Pathway

- **FDA is open to a BLA submission that includes clinical data from the ongoing Phase I/II studies of LX2006 pooled with new clinical data to be generated in the planned pivotal study**
- **To enable pooling of these data, Lexeo will submit enhanced manufacturing comparability data to FDA and meet an additional nonclinical requirement prior to initiation of the planned pivotal**
- **FDA also previously agreed to evaluate co-primary endpoint of LVMI at a time point earlier than 12 months; Lexeo believes collective feedback may reduce size and length of pivotal study**

Clinically Meaningful Improvements in Cardiac and Neurologic Measures of FA

- **Interim clinical data show sustained or deepening improvements in the majority of participants across both cardiac and neurologic measures of Friedreich ataxia (FA)**
- **Participants with abnormal LVMI at baseline achieved mean reduction in LVMI of 18%(1) at 6 months and 23% at 12 months, exceeding FDA-aligned threshold of 10% reduction**
- **Clinically meaningful improvement observed in the modified Friedreich Ataxia Rating Scale (mFARS), indicative of slowed disease progression and improved neurological function**

Safety Profile

- **Generally well-tolerated across 17 participants dosed to date; no clinically significant complement activation and minimal, transient LFT elevations**

LVMI, Left Ventricular Mass Index; LFT, liver function tests.
(1) Participant 11 6-month visit not conducted due to hurricane; 3-month visit used for mean calculation.

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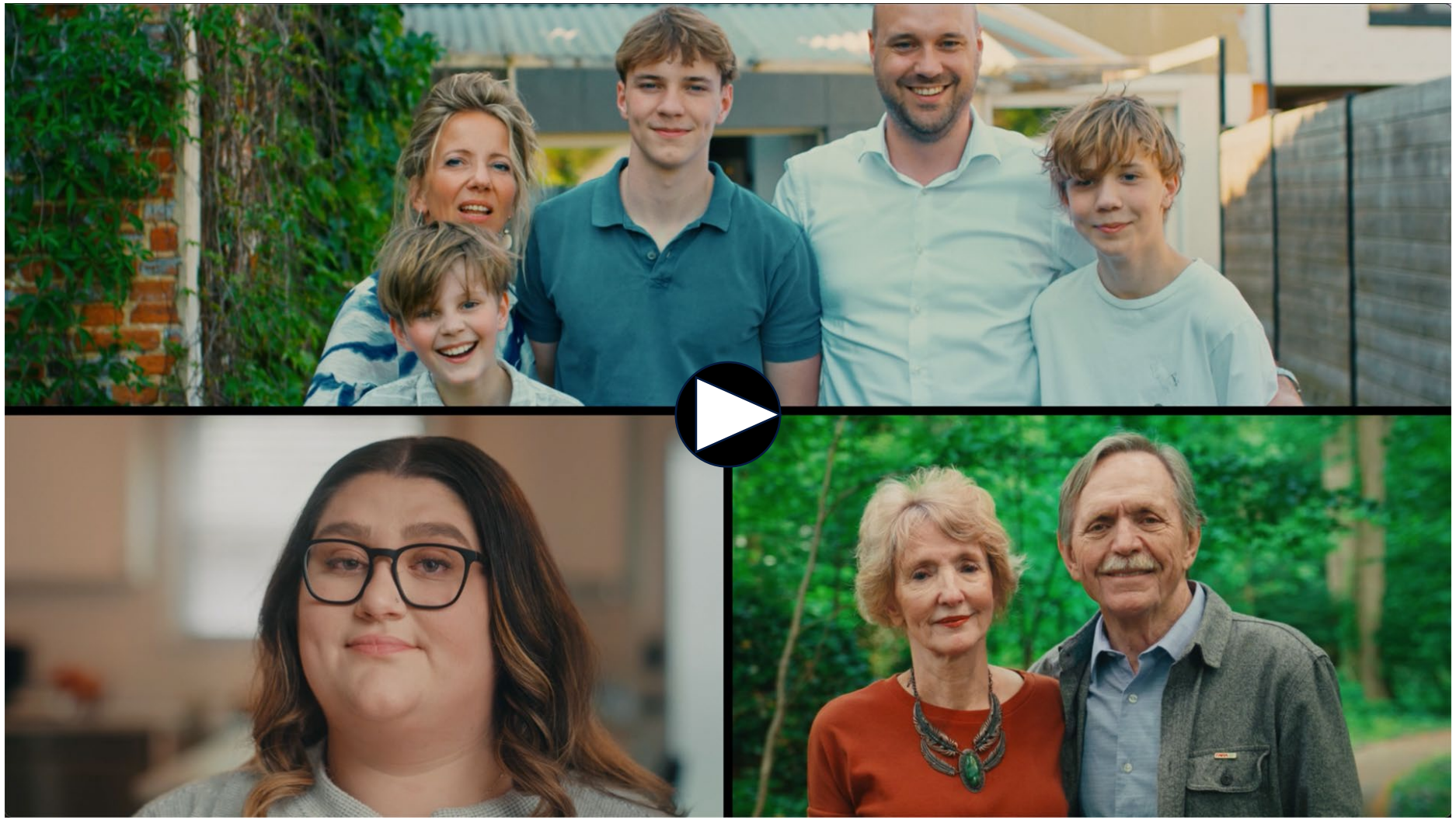
Treatment for FA Cardiomyopathy is Urgently Needed



Thank you sincerely to the participants, caregivers, investigators, health care professionals and to the FA community for supporting Lexeo research

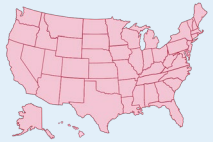
Cardiac Complications are the Leading Cause of Death in Friedreich Ataxia

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]

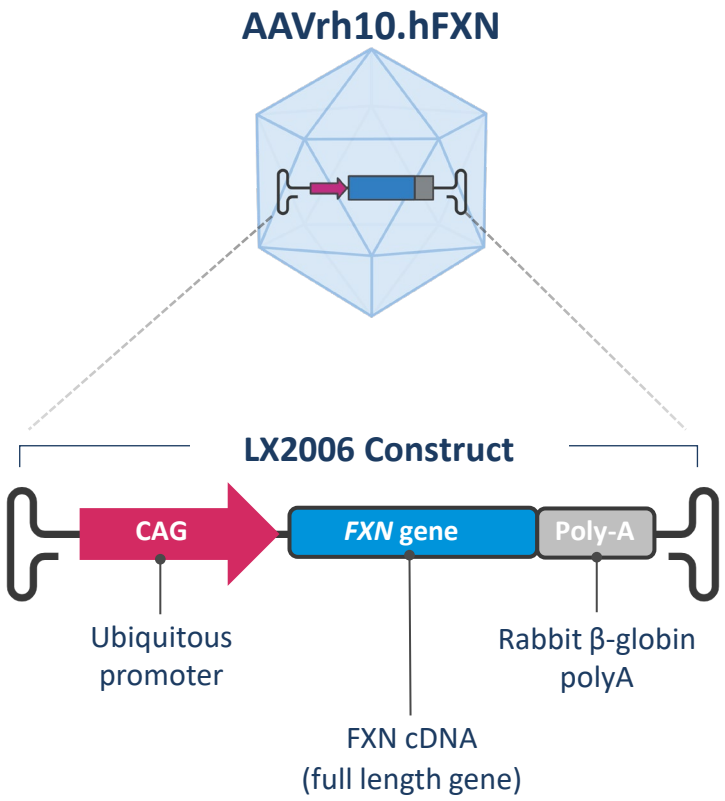
Cardiac complications account for **up to 80%** of deaths in those with FA, with an average life expectancy of 35–40 years[1][5]

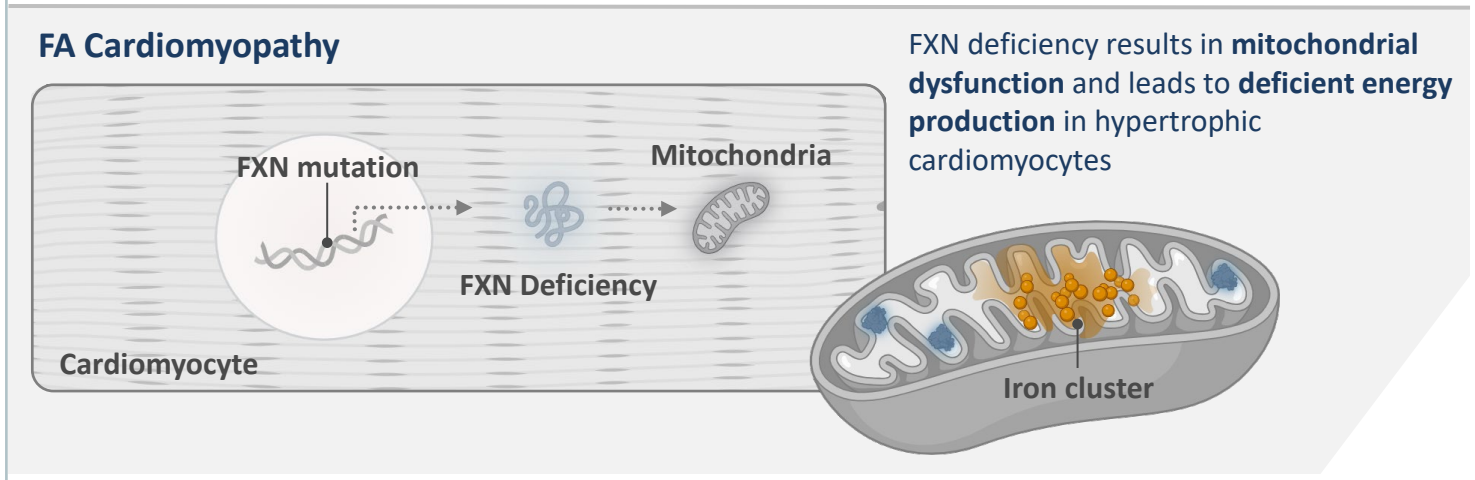
Up to 40% of adults with FA have left ventricular hypertrophy as defined by abnormal LVMI[6][7]

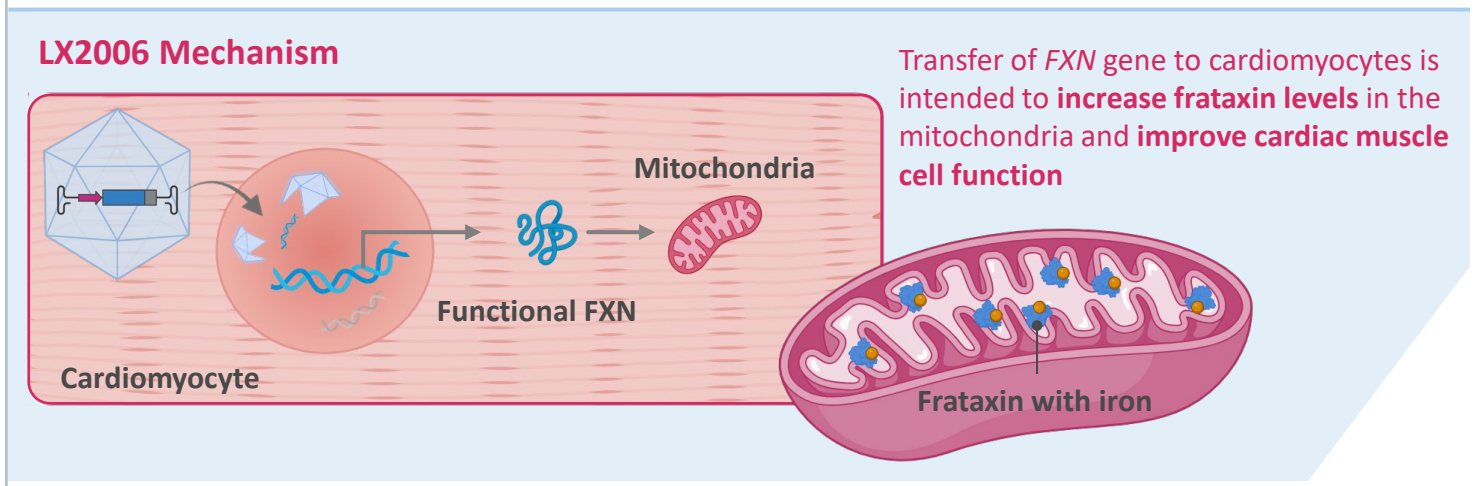
FA, Friedreich Ataxia; FXN, Frataxin; LVMI, Left Ventricular Mass Index.

(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.

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.

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

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

Cohort 1
$1.8x10^{11}$ vg/kg

Cohort 2
$5.6x10^{11}$ vg/kg

Cohort 3
$1.2x10^{12}$ vg/kg

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 / Reported Outcomes (mFARS, KCCQ)
- FXN Protein Expression Assessed Only in SUNRISE-FA

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

LVMI, Left Ventricular Mass Index; hsTnI, High Sensitivity Troponin I; mFARS, Modified Friedreich Ataxia Rating Scale; KCCQ, Kansas City Cardiomyopathy Questionnaire; FXN, Frataxin.
Note: LX2006 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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Lexeo Believes Collective Regulatory Feedback Could Reduce Size and Length of Planned Pivotal Study, Possibly Accelerating Overall Timeline to BLA Submission

FDA Feedback to Date

Co-primary Endpoints in Pivotal Study for Accelerated Approval

LVMI

- FDA open to BLA submission that includes **LVMI data from ongoing Phase I/II studies pooled with new clinical data** generated in planned pivotal, following enhanced manufacturing comparability data and an additional nonclinical requirement
- FDA also agreed to **evaluate LVMI co-primary endpoint at time point earlier than 12 months**
- >10% reduction remains target threshold; Phase I/II results exceeding threshold at 6 and 12 months

Frataxin Protein Expression

- Frataxin expression must be assessed with validated assay in the upcoming pivotal study; in Phase I/II studies, frataxin expression assessed with academic LCMS assay
- **Any increase from baseline expression remains target threshold** for planned pivotal study

Manufacturing Comparability

- Phase I/II studies used adherent HEK293 process, but future clinical and commercial supply will be produced using **optimized Sf9-baculovirus manufacturing platform**
- Lexeo will submit enhanced manufacturing comparability data to support pooling of LVMI data, including analytical comparability and nonclinical data to be shared prior to initiating the pivotal study from a murine bridging study using pre- and post-change drug product

LVMI, Left Ventricular Mass Index; LCMS, Liquid chromatography mass spectrometry.

In Phase I/II Studies, Baseline Characteristics Are Consistent with Cardiac Phenotype of FA

Participant Characteristic	Cohort 1 ($1.8x10^{11}$ vg/kg)						Cohort 2 ($5.6x10^{11}$ vg/kg)							Cohort 3 ($1.2x10^{12}$ vg/kg)			
	Participant #						Participant #							Participant #			
	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	#13	#17	#12	#14	#15	#16
Gender	F	M	F	F	M	M	F	M	F	F	F	F	F	M	F	M	F
LVMI, g/m^2	81	109	53	65	60	86	63	74	57	66	100	110	44	85	49	72	56
LWT, mm	12	11	8	11	9	9	9	10	7	10	9	13	8	8	6	7	7
Hs Troponin I, pg/ml	224	148	108	2023	5	22	38	376	820	650	115	2518	498	25	11	11	42
Cardiac Biopsy	✗	✗	✗	✗	✗	✓	✗	✗	✓	✓	✓	✗	✗	✓	✓	✓	✓
mFARS Score	72	73	69	91	63	52	79	68	42	73	53	55	68	27	60	70	56
SKYCLARYS® Use During Trial	✗	✓	✗	✓	✓	✗	✓	✗	✓	✗	✗	✗	✗	✓	✓	✓	✗
Follow-up, months	24	24	21	21	18	24	12	12	24	21	12	12	<6	12	9	9	9

Abnormal(1) | High-normal(1) | Normal(1)

- 6 of 17 participants dosed to date have abnormal LVMI at baseline; remains key inclusion criteria for future pivotal study
- Safety data summarized for all 17 participants dosed to date; efficacy data inclusive of 16 participants with ≥ 6 months of follow-up

(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 and for hs-troponin I abnormal defined as 99th percentile and high-normal defined as level above the threshold to detect individuals at risk of future CV events as referenced in Zeller at al. *European Heart Journal* (2014) 35, 271–281. Normal LVMI range for males: 39-85 g/m^2 and normal LVMI range for females: 30-68 g/m^2.

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Treatment with LX2006 Has Been Generally Well Tolerated to Date

Safety Summary

- No clinically significant complement activation
- Minimal, transient LFT elevations after dosing; no participants above 3X upper limit of normal
- No signs of frataxin over-expression observed in cardiac tissue
- No participants discontinued from either study
- One previously disclosed, possibly treatment-related Grade 2 event of asymptomatic myocarditis observed one year after dosing

LFT, liver function tests.

Participants with Abnormal LVMI at Baseline: Improvements Across Key Clinical Parameters at Latest Visit with Mean LVMI Reduction of 23% at 12 Months

Planned pivotal trial will only enroll people with abnormal(1) LVMI at baseline

Cohort	Participant # | LVMI(1) at Baseline	Latest Visit (months)	Δ LVMI (g/m²) Baseline → LV	Δ LWT (cm) Baseline → LV	Δ Hs-TNI (pg/ml) Baseline → LV
Cohort 1 (1.8E11 vg/kg)	Participant #1 (F)	**24**	**-17.3%** 81 → 67	**-16.7%** 1.2 → 1.0	**-26.8%** 224 → 164
	Participant #2 (M)	**24**	**-25.7%** 109 → 81	**-9.1%** 1.1 → 1.0	**-40.5%** 148 → 88
	Participant #6 (M)	**24** *NEW*	**-2.7%** 86 → 84	**-2.4%** 0.9 → 0.8	**-50.0%** 22 → 11
Cohort 2 (5.6E11 vg/kg)	Participant #11 (F)	**12**	**-35.6%** 100 → 64	**-44.4%** 0.9 → 0.5	**-85.2%** 115 → 17
	Participant #13 (F)	**12**	**-50.9%** 110 → 54	**-38.5%** 1.3 → 0.8	**-79.9%** 2518 → 505
Cohort 3 (1.2E12 vg/kg)	Participant #12 (M)	**12**	**-12.2%** 85 → 74	**-7.1%** 0.8 → 0.8	**-64.0%** 25 → 9

All participants reach the normal LVMI range at latest follow up

Improved Stabilized Worsened

Note: Normal LVMI range for males: 39-85 g/m² and normal LVMI range for females: 30-68 g/m².

(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.

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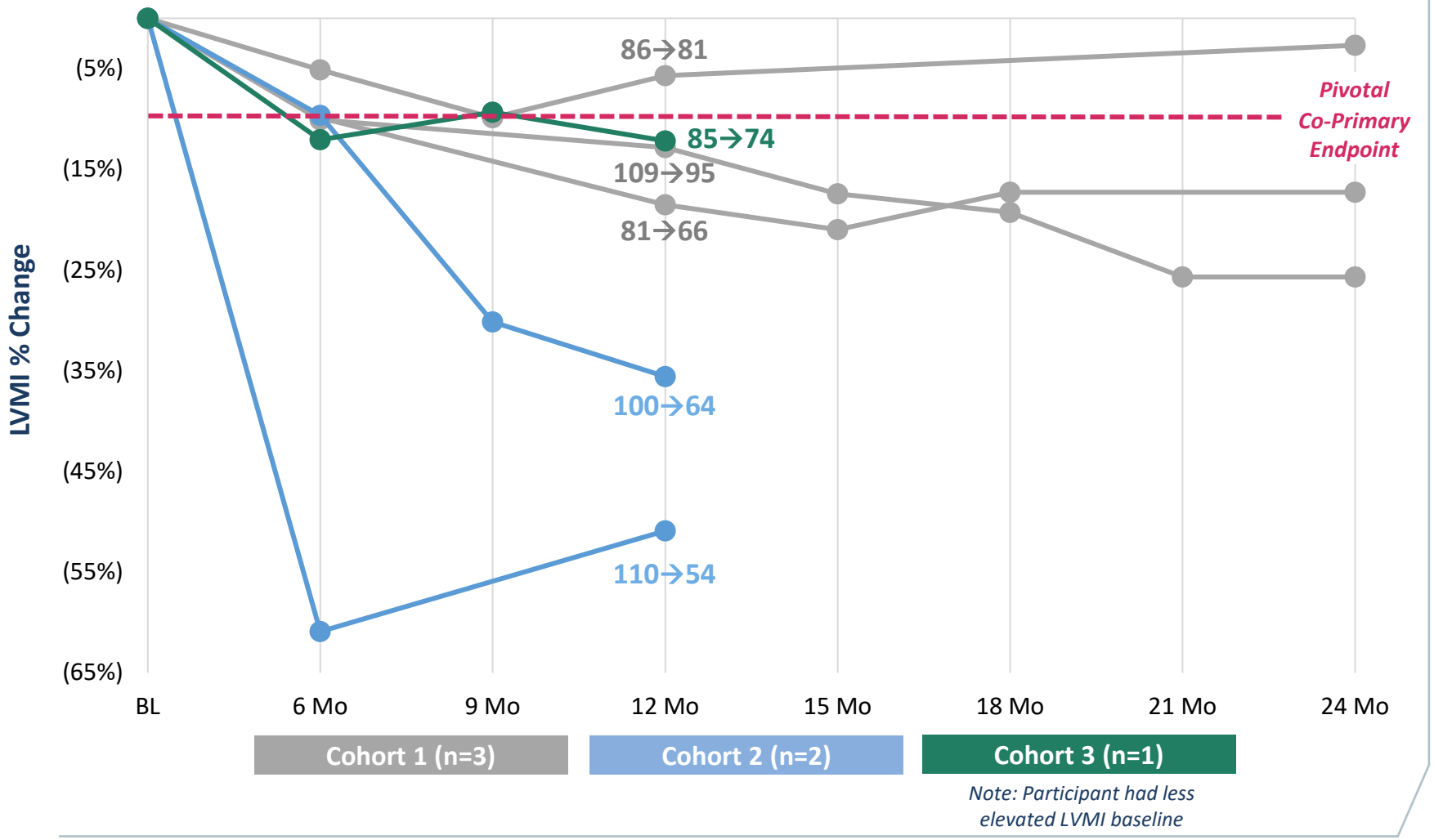
Participants with Abnormal LVMI at Baseline, LVMI: Sustained or Deepening Improvement in LVMI Over Time

Change in LVMI (%) for Participants with Abnormal LVMI at Baseline



Note: Participant had less elevated LVMI baseline

NEW

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

- ✓ **Mid- and high-dose participants maintain LVMI improvements at 12 months**
- ✓ 6 of 6 participants reach normal LVMI range at last follow up

(1) Participant 11 6-month visit not conducted due to hurricane; 3-month visit used for mean calculations.
9-month visits not conducted in Weill Cornell trial.

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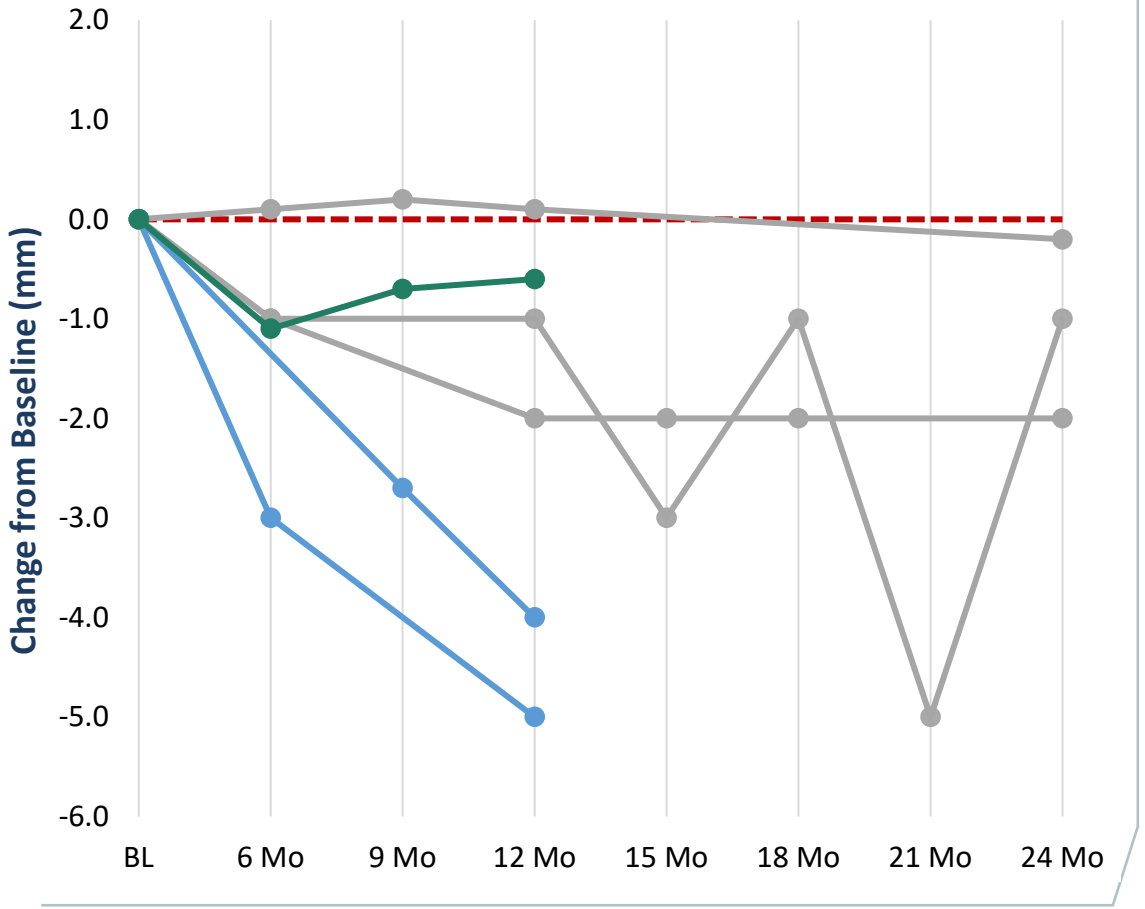
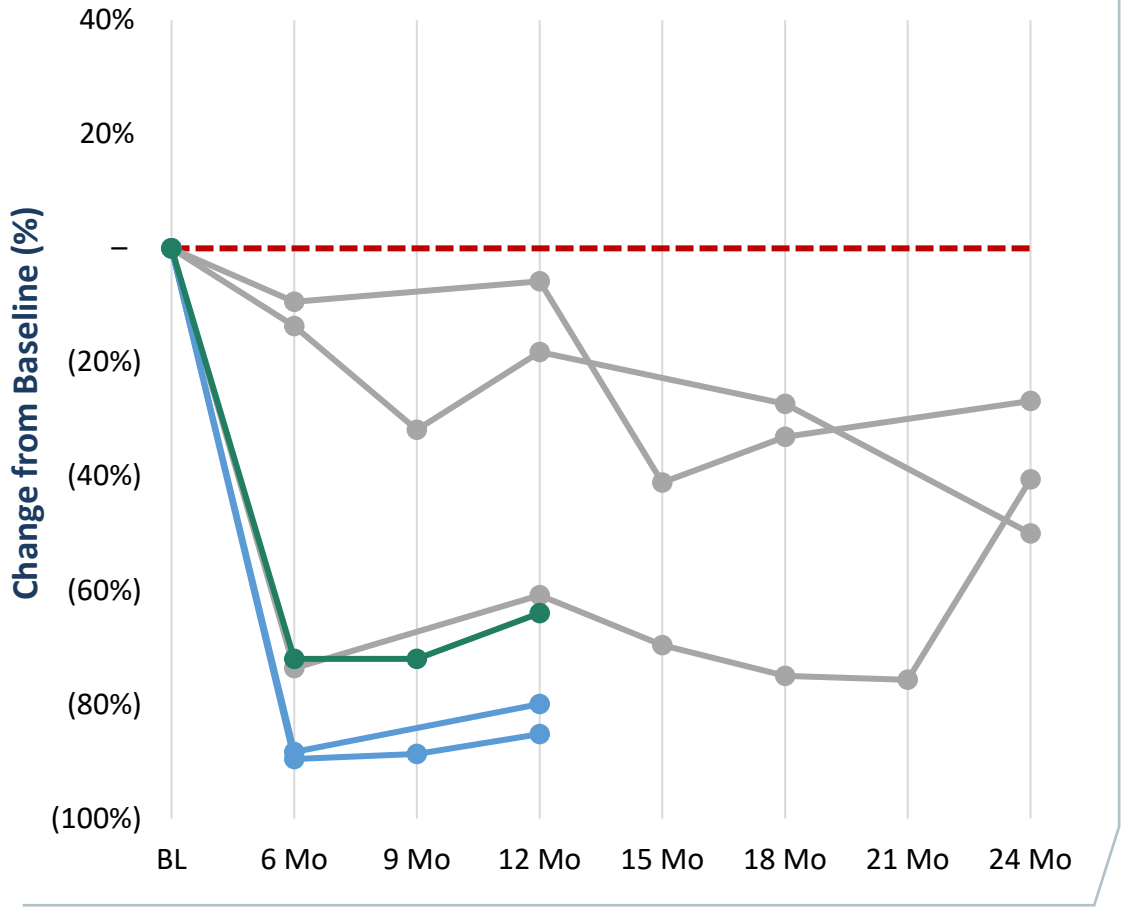
Participants with Abnormal LVMI at Baseline, Supportive Endpoints: LVMI Reductions Supported by Improvements in Lateral Wall Thickness and High-Sensitivity Troponin I

Change in LWT for Participants with Abnormal LVMI at Baseline



Change in Hs-TnI for Participants with Abnormal LVMI at Baseline



Cohort 1 (n=3) | Cohort 2 (n=2) | Cohort 3 (n=1)

Participant 11 6-month visit not conducted due to hurricane. 9-month visits not conducted in Weill Cornell trial.

Participants with Normal LVMI at Baseline: Improvement or Stabilization in Key Clinical Parameters at Latest Visit; All Participants Remained in Normal LVMI Range Excluding Participant #10

Cohort	Participant # | LVMI(1) at Baseline	Latest Visit (months)	Δ LVMI (g/m²) Baseline → LV	Δ LWT (cm) Baseline → LV	Δ Hs-TNI (pg/ml) Baseline → LV
Cohort 1 (1.8E11 vg/kg)	Participant #3 (F) *Normal*	**24**	**-17.0%** 53 → 44	**+25.0%** 0.8 → 1.0	**-50.9%** 108 → 53
	Participant #4 (F) *High normal*	**21**	**-3.1%** 65 → 63	**-9.1%** 1.1 → 1.0	**-50.8%** 2023 → 996
	Participant #5 (M) *Normal*	**21**	**0.0%** 60 → 60	**0.0%** 0.9 → 0.9	**-40.0%** 5 → 3
Cohort 2 (5.6E11 vg/kg)	Participant #7 (F) *High normal*	**12**	**-11.1%** 63 → 56	**+11.1%** 0.9 → 1.0	**-65.8%** 38 → 13
	Participant #8 (M) *High normal*	**12**	**-14.9%** 74 → 63	**-10.0%** 1.0 → 0.9	**-54.3%** 376 → 172
	Participant #9 (F) *Normal*	**24**	**+3.0%** 57 → 59	**-12.3%** 0.7 → 0.6	**-93.8%** 820 → 51
	Participant #10(1) (F) *High normal*	**21**	**+63.4%** 66 → 107	**+56.8%** 1.0 → 1.5	**+472.8%(1)** 650 → 3723
Cohort 3 (1.2E12 vg/kg)	Participant #14 (F) *Normal*	**9**	**-9.4%** 49 → 44	**-1.8%** 0.6 → 0.6	**+45.5%** 11 → 16
	Participant #15 (M) *High Normal*	**9**	**-12.1%** 72 → 63	**-1.4%** 0.7 → 0.7	**-27.3%** 11 → 8
	Participant #16 (F) *Normal*	**9**	**-15.7%** 56 → 47	**-11.3%** 0.7 → 0.6	**-52.4%** 42 → 20

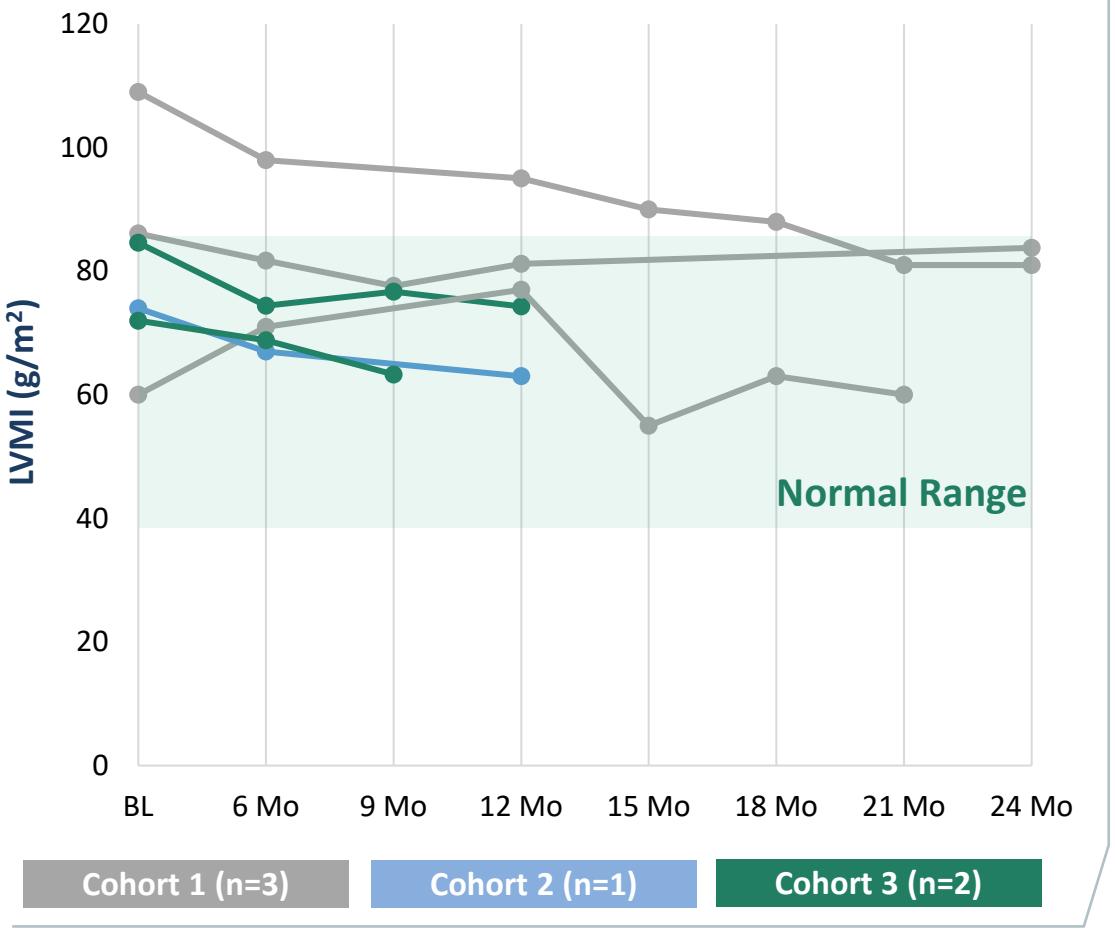
Improved Stabilized Worsened

Normal LVMI range for males: 39-85 g/m² and normal LVMI range for females: 30-68 g/m².

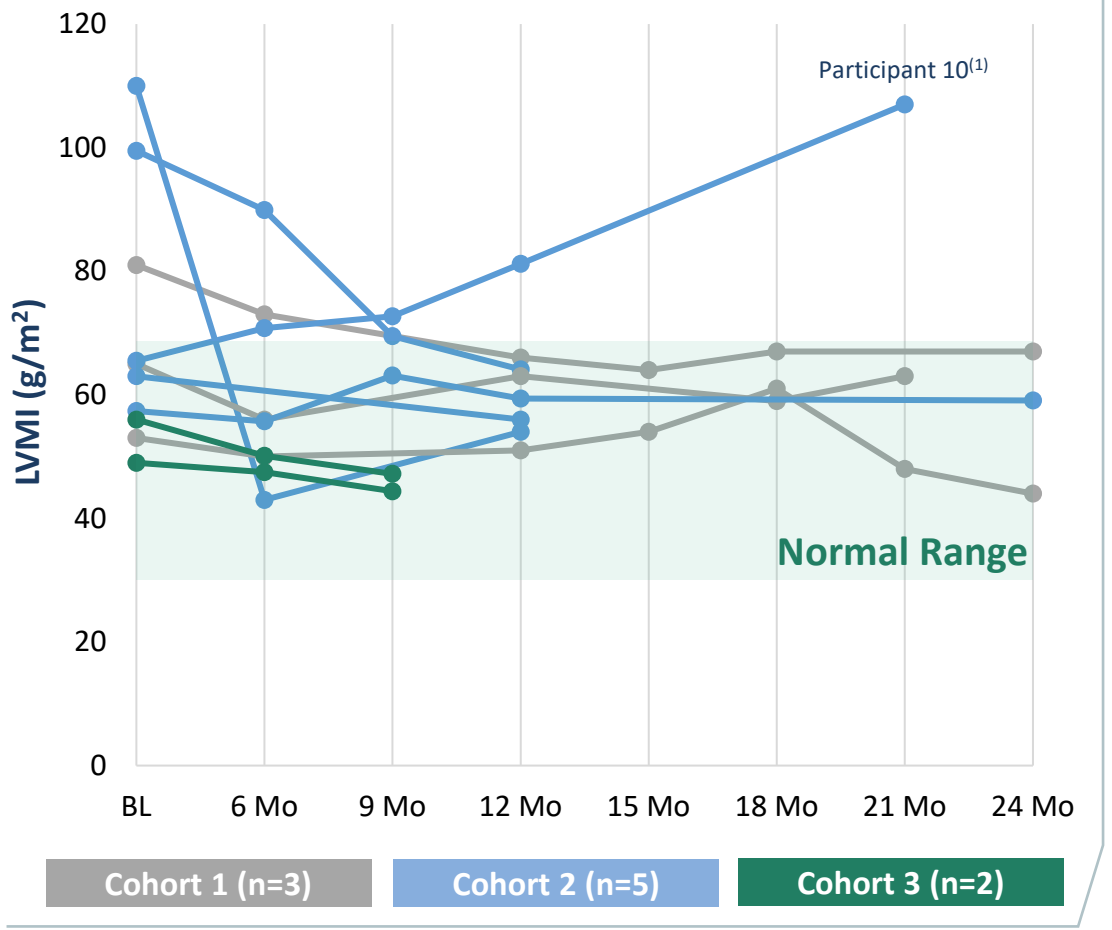
(1) Approximately 1 year post treatment Participant #10 experienced possible focal myocarditis. Participant #10 also experienced interruption of immunosuppression regimen in first three months following treatment due to multiple pneumonias. Biomarkers potentially confounded by myocarditis. Most recent troponin result included from safety monitoring, other values correspond to 21-month visit.

All Participants (n=16), LVMI: All Participants Excluding Participant #10 Reached or Remained in the Normal Range for LVMI at Latest Visit

LVMI (g/m²) for All Male Participants



LVMI (g/m²) for All Female Participants



Note: Normal LVMI range for males: 39-85 g/m² and normal LVMI range for females: 30-68 g/m². Participant 11 6-month visit not conducted due to hurricane. 9-month visits not conducted in Weill Cornell trial.

(1) Approximately 1 year post treatment Participant #10 experienced possible focal myocarditis. Participant #10 also experienced interruption of immunosuppression regimen in first three months following treatment due to multiple pneumonias. Biomarkers potentially confounded by myocarditis.

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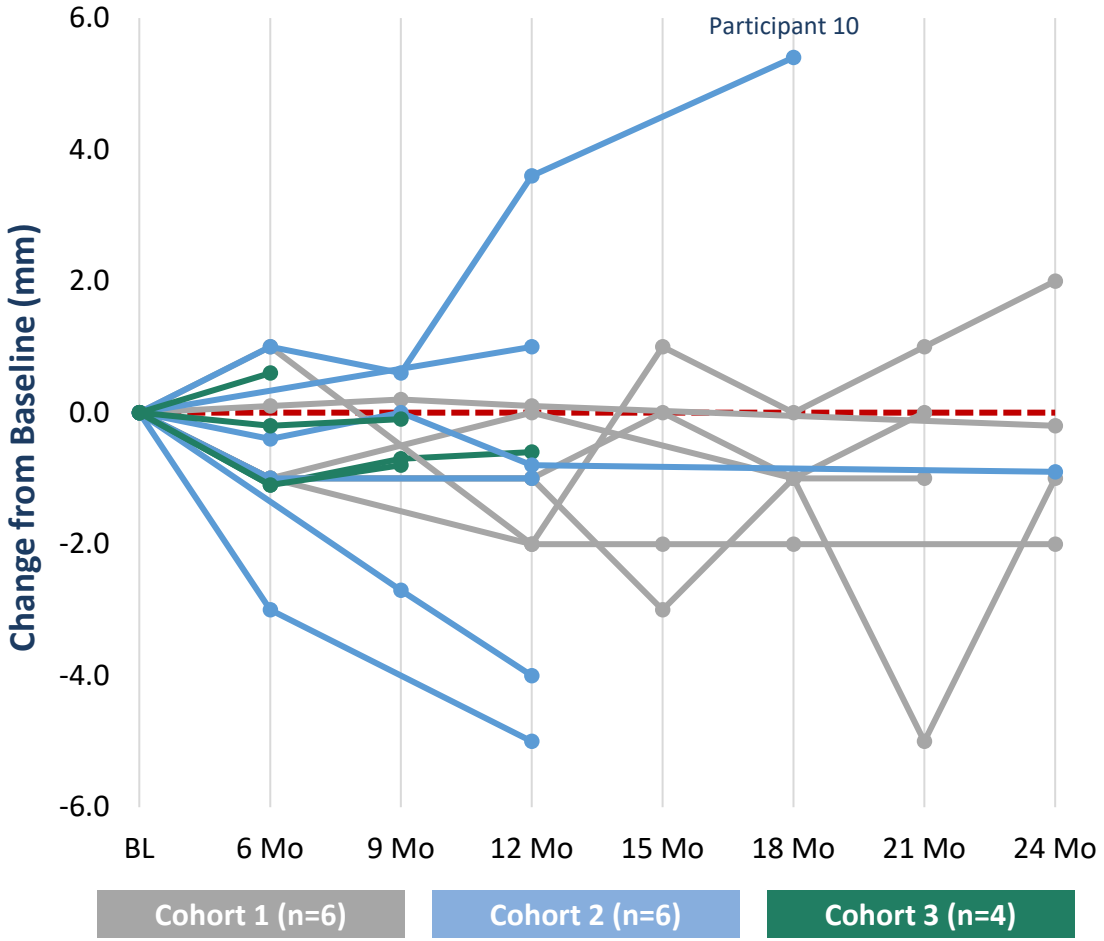
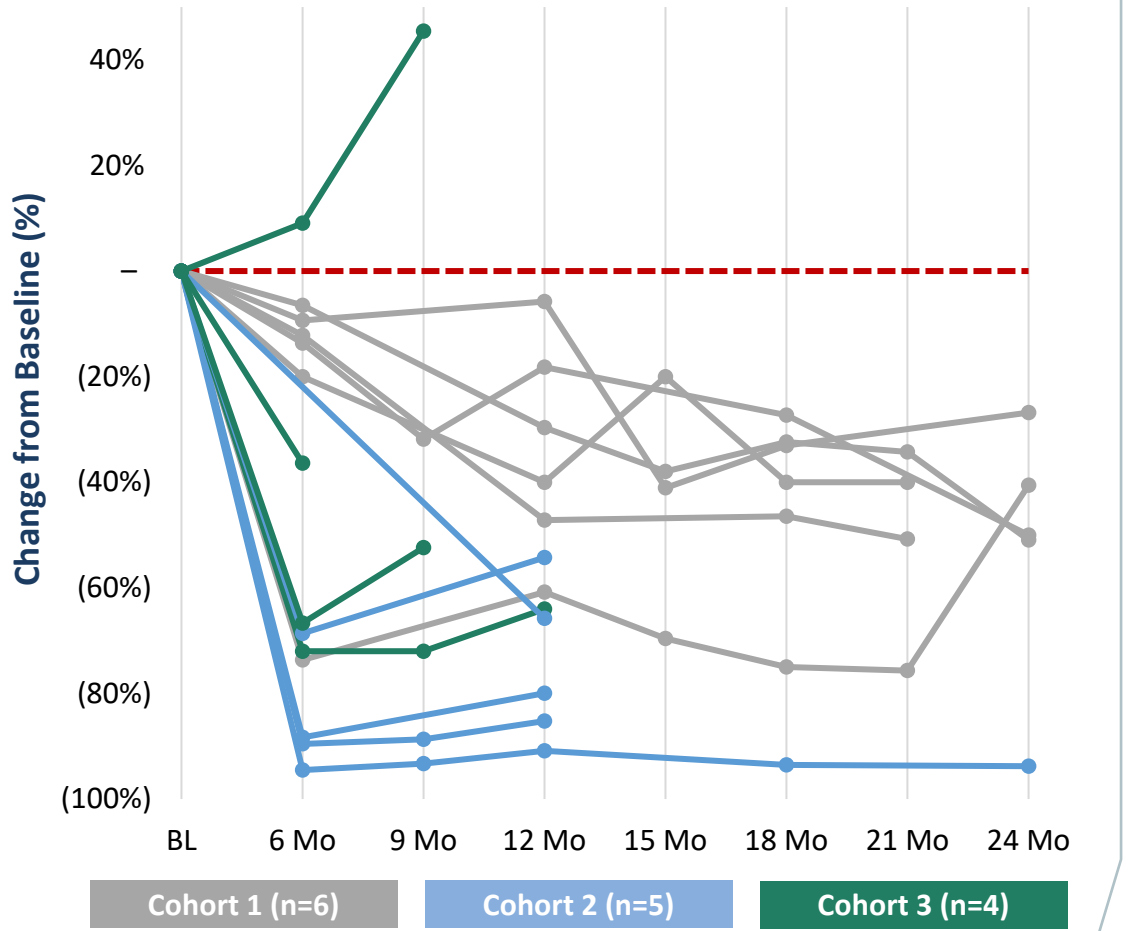
All Participants (n=16), Supportive Endpoints: Improvements in Lateral Wall Thickness and High-Sensitivity Troponin I Across Participants Regardless of Baseline LVMI

Change in Lateral Wall Thickness (2D Measurement)



Change in High-Sensitivity Troponin I*



*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 +473% as of most recent safety monitoring.
Participant 11 6-month visit not conducted due to hurricane. 9-month visits not conducted in Weill Cornell trial.

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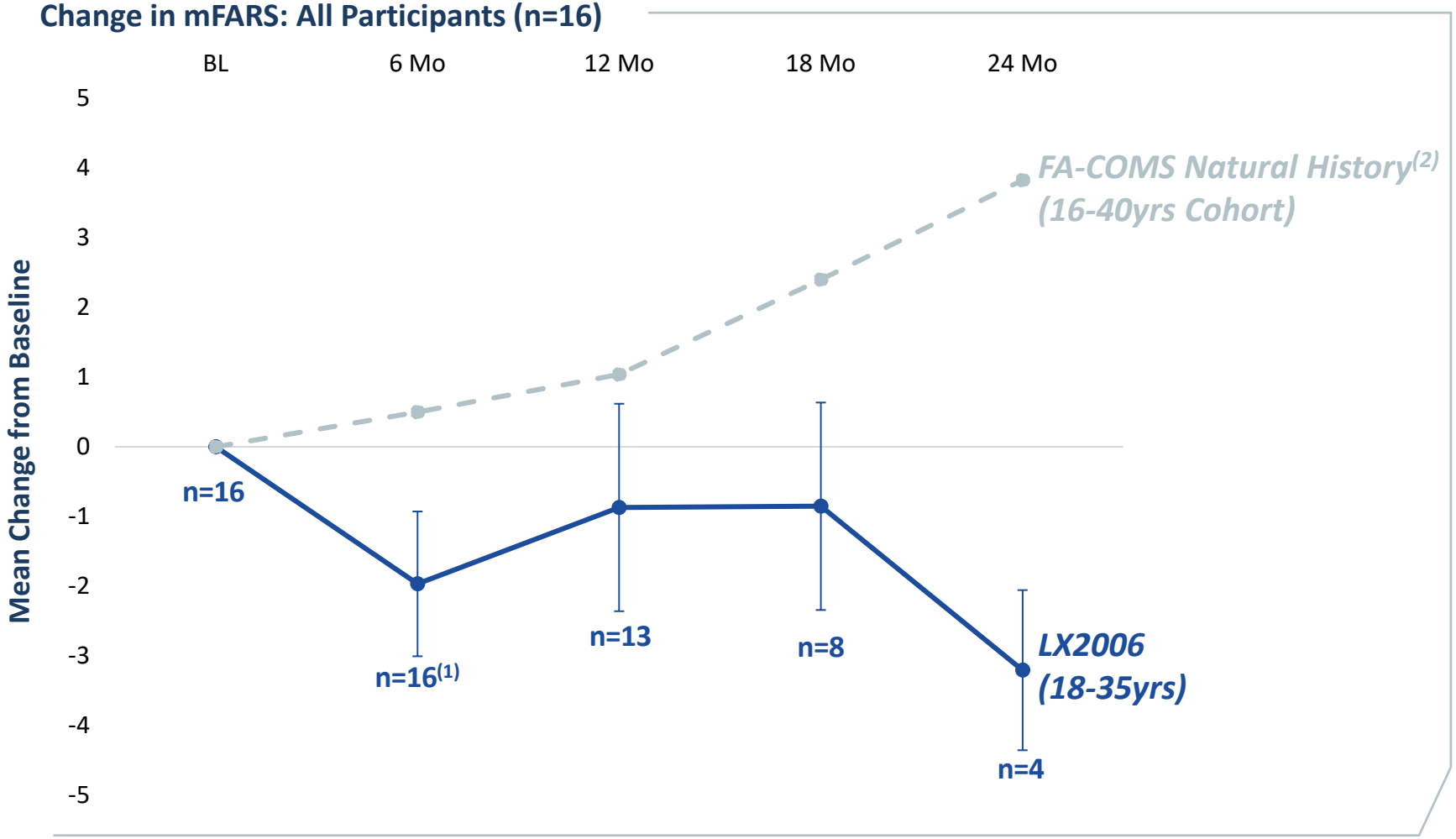
All Participants (n=16), mFARS: Functional Improvement Over Time Using the Modified Friedreich Ataxia Rating Scale (mFARS) Compared to Natural History



- ✓ mFARS clinical scale measures FA neurological progression across four sub-scales: upright stability, upper limb coordination, lower limb coordination and bulbar function
- ✓ **11 of 16 participants improved or stabilized relative to baseline at latest visit**
- ✓ Evidence of neurological functional improvement, compared to natural history progression of disease

Note: Natural history for illustrative purposes only. Differences exist between trial designs and participant characteristics, and caution should be exercised when comparing data across unrelated studies.
(1) Participant 11 6-month visit not conducted due to hurricane; 3-month visit used for mean calculations.
(2) Patel, M. et al. *Ann Clin Transl Neurol,* 2016. 3: 684-694. Progression of Friedreich ataxia: quantitative characterization over 5 years.https://doi.org/10.1002/acn3.332

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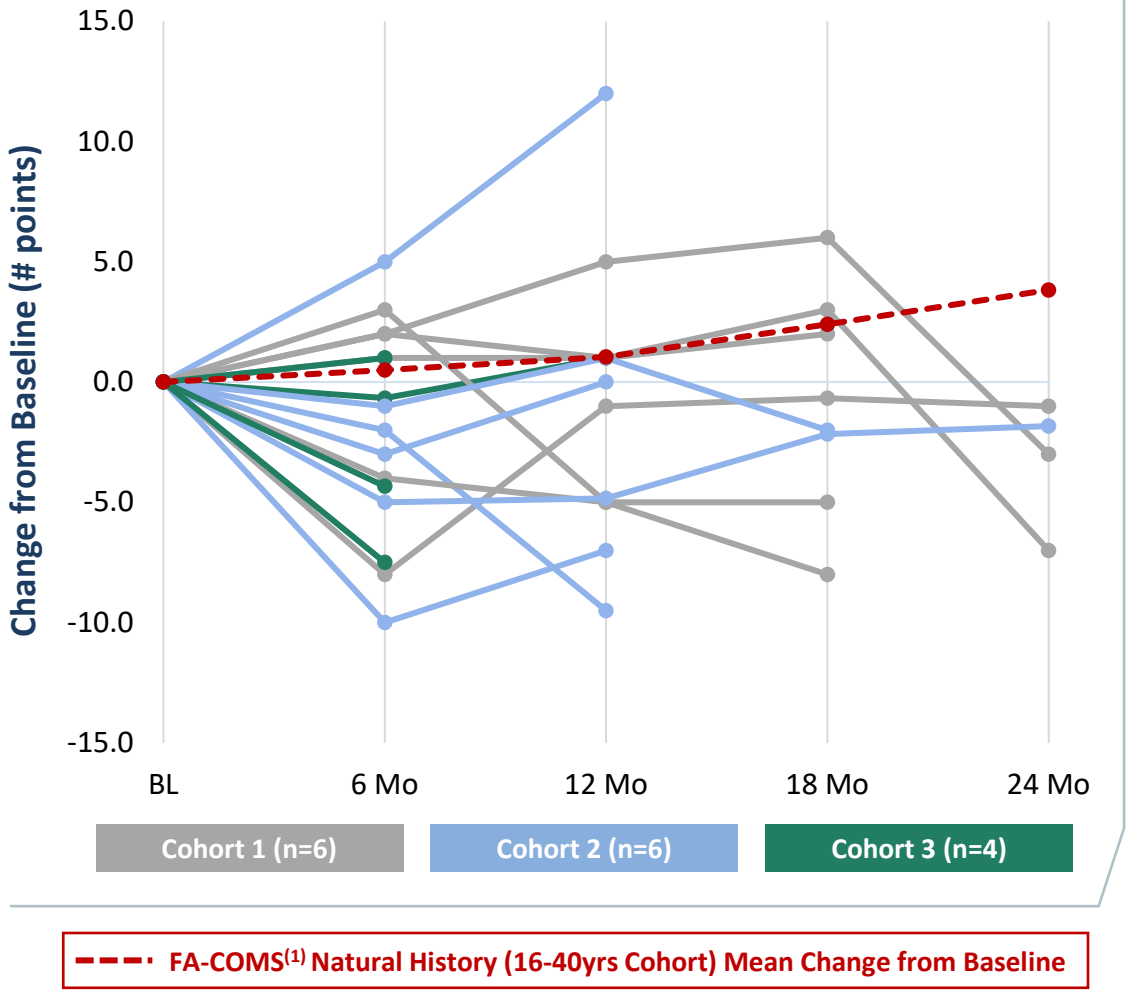
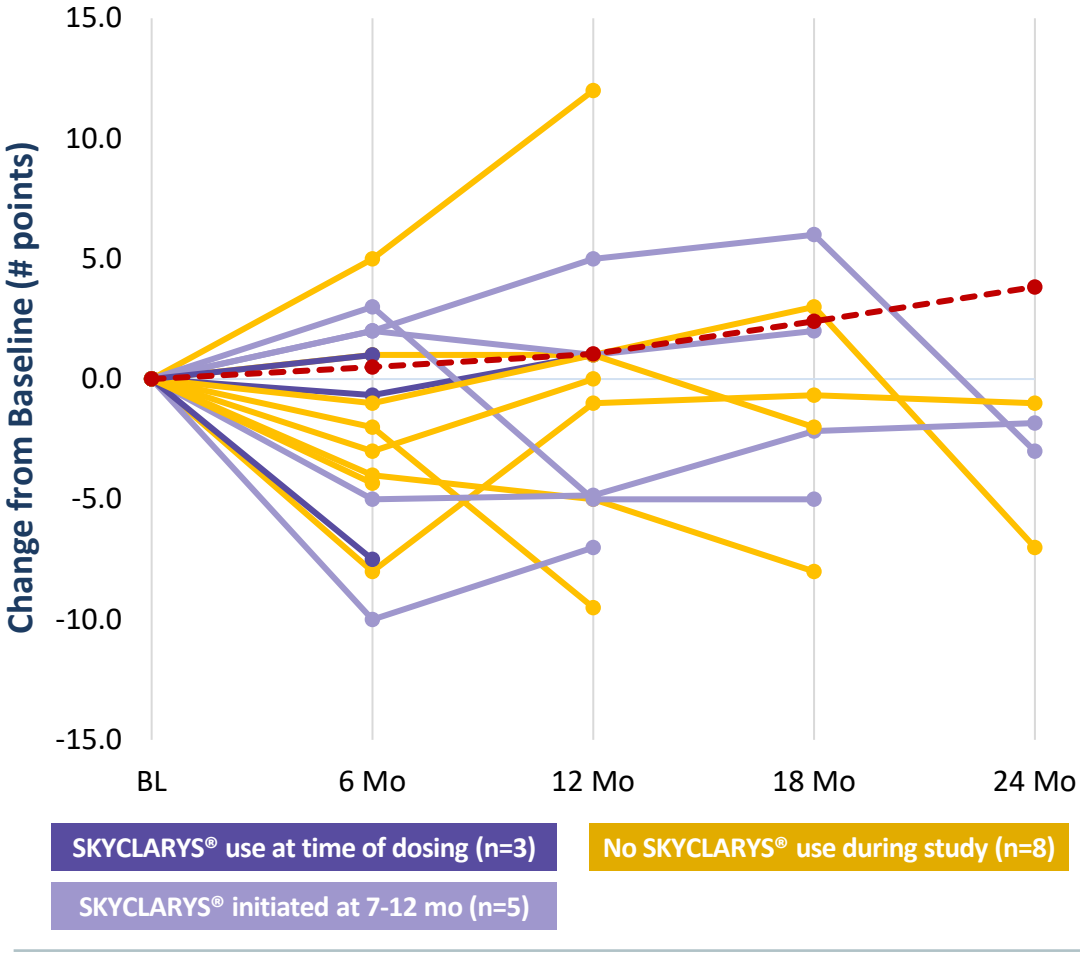
All Participants (n=16), mFARS: 11 of 16 Participants Improved or Stabilized Relative to Baseline at Latest Visit

Change in mFARS by Dose Cohort (n=16)



Change in mFARS by SKYCLARYS® Utilization (n=16)



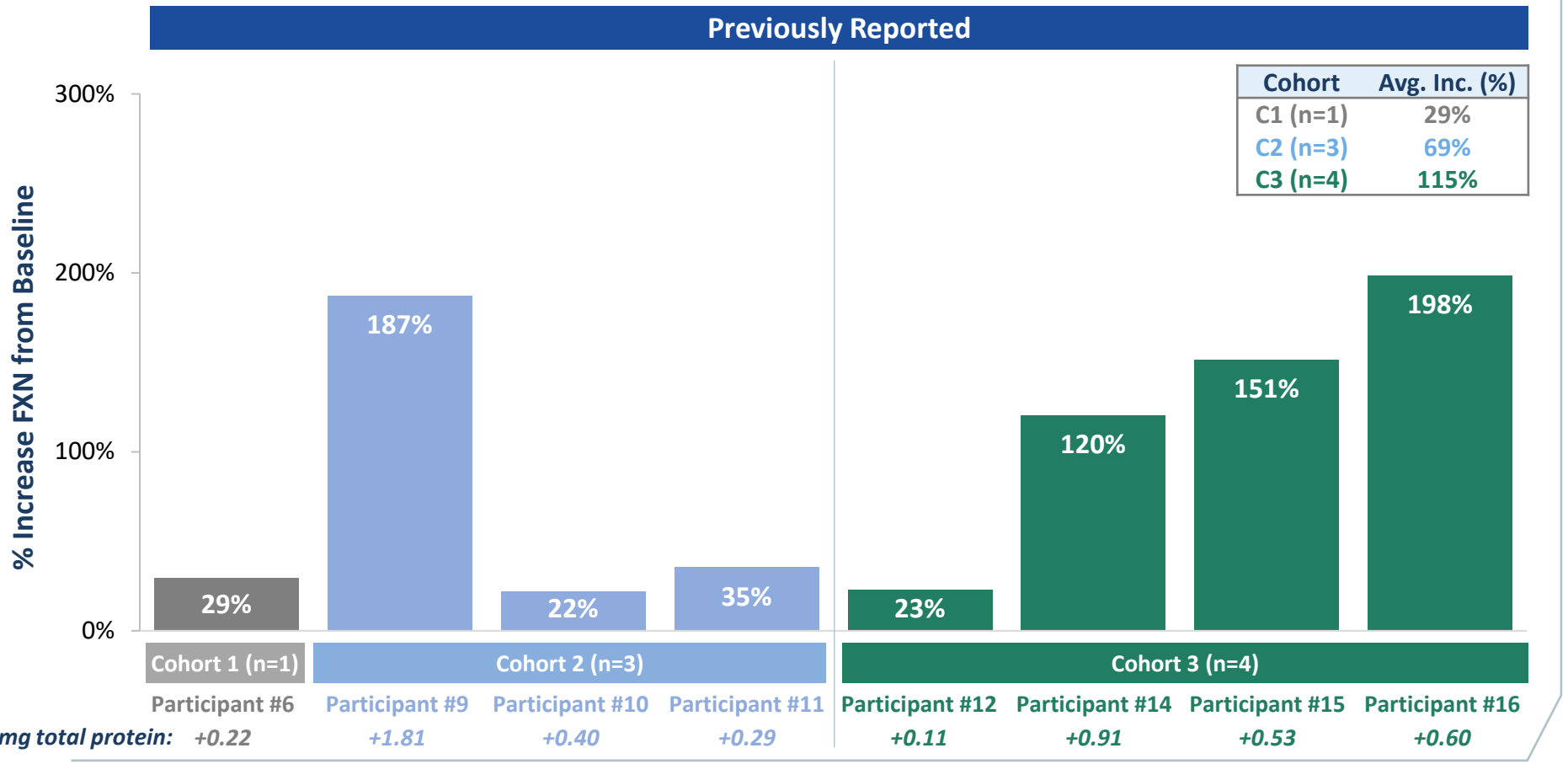
FA-COMS[1] Natural History (16-40yrs Cohort) Mean Change from Baseline

Note: Natural history for illustrative purposes only. Differences exist between trial designs and participant characteristics, and caution should be exercised when comparing data across unrelated studies.
Participant 11 6-month visit not conducted due to hurricane.

(1) Patel, M. et al. *Ann Clin Transl Neurol,* 2016. 3: 684-694. Progression of Friedreich ataxia: quantitative characterization over 5 years.https://doi.org/10.1002/acn3.332

Previously Reported: Increased Frataxin Expression Across All Participants Evaluated at 3-Months Post Treatment Utilizing LCMS

Post-Treatment FXN Levels Increased in All Participants – Measured by LCMS



- ✓ All participants showed increases in frataxin expression vs. baseline
- ✓ Data meet FDA threshold for detecting any increase in frataxin expression from baseline
- ✓ Four biopsies from high-dose Cohort 3 showed dose-responsive increases relative to Cohorts 1-2

FXN, Frataxin; LCMS, Liquid chromatography mass spectrometry.
FXN expression assessed with academic LCMS assay, assay validation in progress for pivotal study.

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Summary and Next Steps for LX2006

- LX2006 (AAVrh10.hFXN) has been generally well tolerated to date with no clinically significant complement activation and minimal, transient LFT elevations
- Sustained or deepening improvements in the majority of participants across both cardiac and neurologic measures of FA:
  - Participants with abnormal baseline LVMI achieved 18% mean reduction at 6 months and 23% mean reduction at 12 months
  - Reductions in LVMI supported by improvements in other markers of cardiac structure and health, including lateral wall thickness and high-sensitivity troponin I
  - Clinically meaningful improvement in mFARS, indicative of slowed disease progression and improved neurologic function
- FDA open to BLA submission for Accelerated Approval that includes clinical data from ongoing Phase I/II studies pooled with clinical data to be generated in planned pivotal study, with enhanced manufacturing comparability
  - Continued discussions on pivotal trial protocol and comparability, including analytical and nonclinical, expected into early 2026
- Lexeo plans to initiate pivotal study in first half of 2026

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Thank you