Gene Therapy for Friedreich Ataxia Cardiomyopathy: Safety and Preliminary Assessment of Efficacy

American Society of Gene and Cell Therapy

R. Crystal
Department of Genetic Medicine
Weill Cornell Medicine

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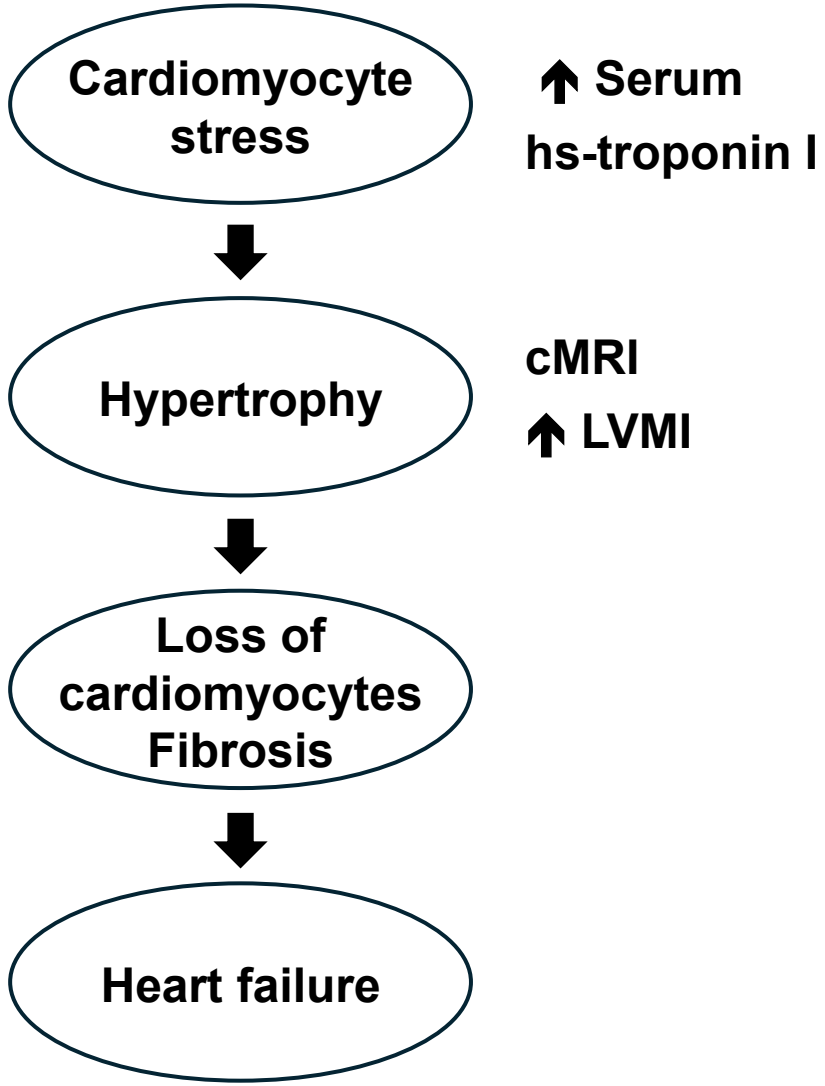
- R Crystal is a consultant with equity in Lexeo Therapeutics

Friedreich Ataxia

- Autosomal recessive, fatal disorder characterized by neurologic and cardiac dysfunction
- Caused by expansion of GAA repeats in intron 1 of the frataxin (FXN) gene, causing frataxin deficiency
- FXN functions in mitochondria to generate energy
- Neurologic - bulbar, upper and lower limb dysfunction
- Cardiac - major cause of death (60-65%), hypertrophy, fibrosis, heart failure
- Omaveloxolone (Skyclarys) is approved for the neurologic disease
- No specific therapy for the cardiac disease

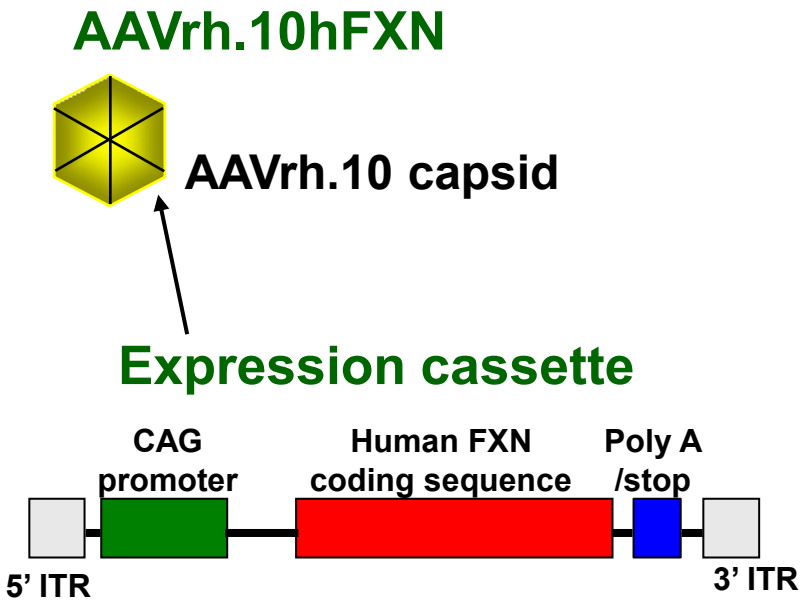
Pathogenesis and Assessment of the Cardiac Disease in Friedreich Ataxia

- Frataxin deficiency induces cardiomyocyte stress, assessed by serum levels of high sensitivity troponin I
- In response, the heart hypertrophies, assessed by cardiac MRI quantification of left ventricular mass index (LVMI)
- As the disease progresses, there is loss of cardiomyocytes, cardiac fibrosis and eventual heart failure



Trial Design - AAVrh.10hFXN Gene Therapy for the Cardiac Manifestations of Friedreich Ataxia

- Therapy – intravenous administration of AAVRh.10hFXN, an AAVrh.10 serotype AAV vector coding for human frataxin
- Combined data from 2 independent trials with similar protocols and identical gene therapy
  - Weill Cornell, funded by NHLBI, n=9 patients
  - Lexeo Therapeutics, n=8 patients
- Open-label trial doses $1.8x10^{11}$, $5.6x10^{11}$ and $1.2x10^{12}$ vg/kg
- Combined study population, n=17
  - 6 male, 11 female; ages 25 ± 6 years
  - FXN gene: 670–1176 GAA repeats in intron 1
  - n=11 patients with early disease, elevated serum troponin I, normal LVMI
  - n=6 patients with advanced disease, elevated LVMI
- Periodic assessments pre- and post-therapy cMRI LVMI, serum hs-troponin I and mFARS neurologic scale

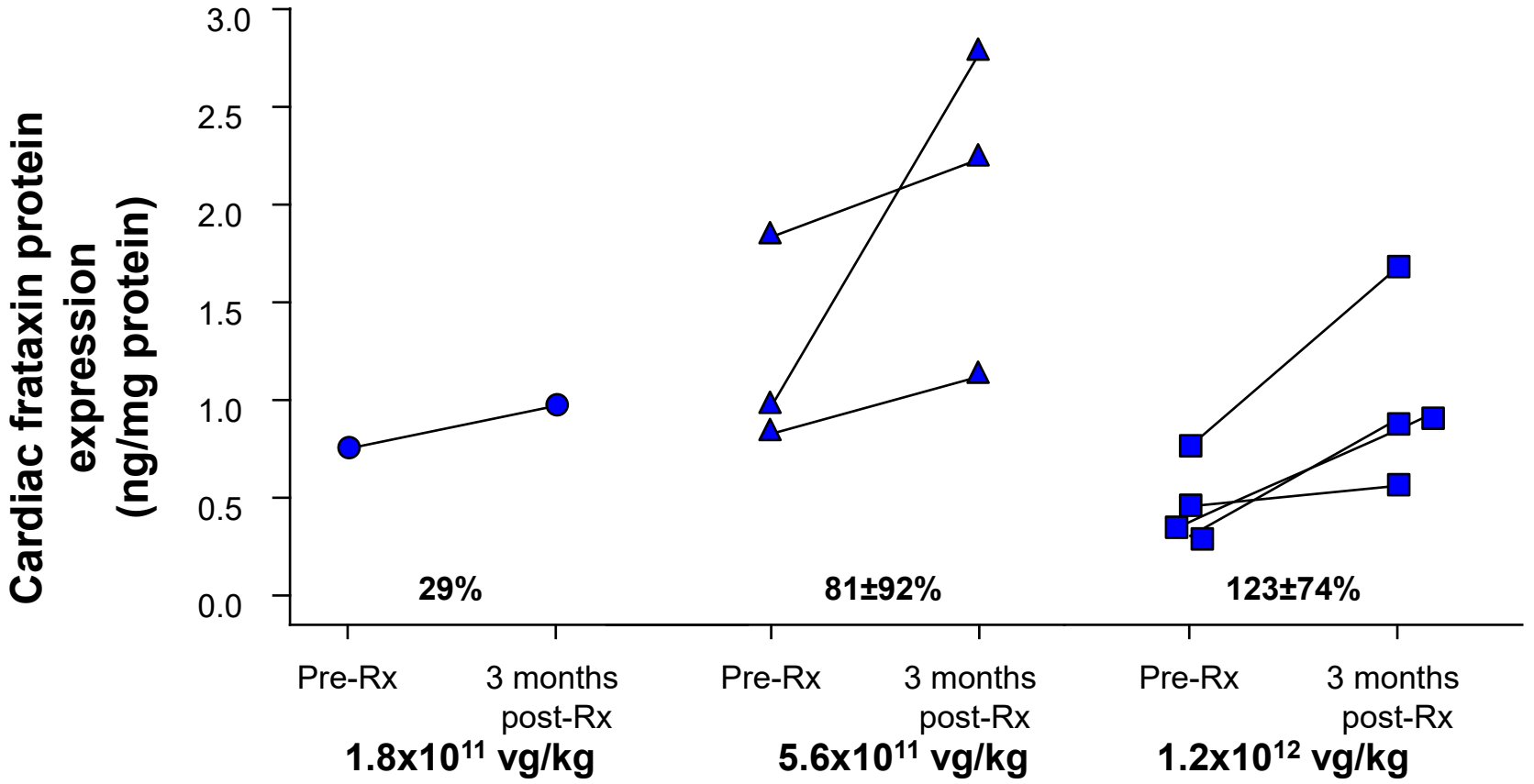


Safety

- Intravenous administration of AAVrh.10hFXN to patients with Friedreich ataxia is well tolerated
- No significant liver toxicity or complement activation
- 4 serious adverse events
  - 1 possibly linked to the gene therapy vector, myocarditis that developed 1-year post-therapy, resolved with corticosteroid therapy[1]
  - 3 possibly linked to prednisone immunosuppression, all resolved
- All other adverse events were transient, non-serious or not treatment related

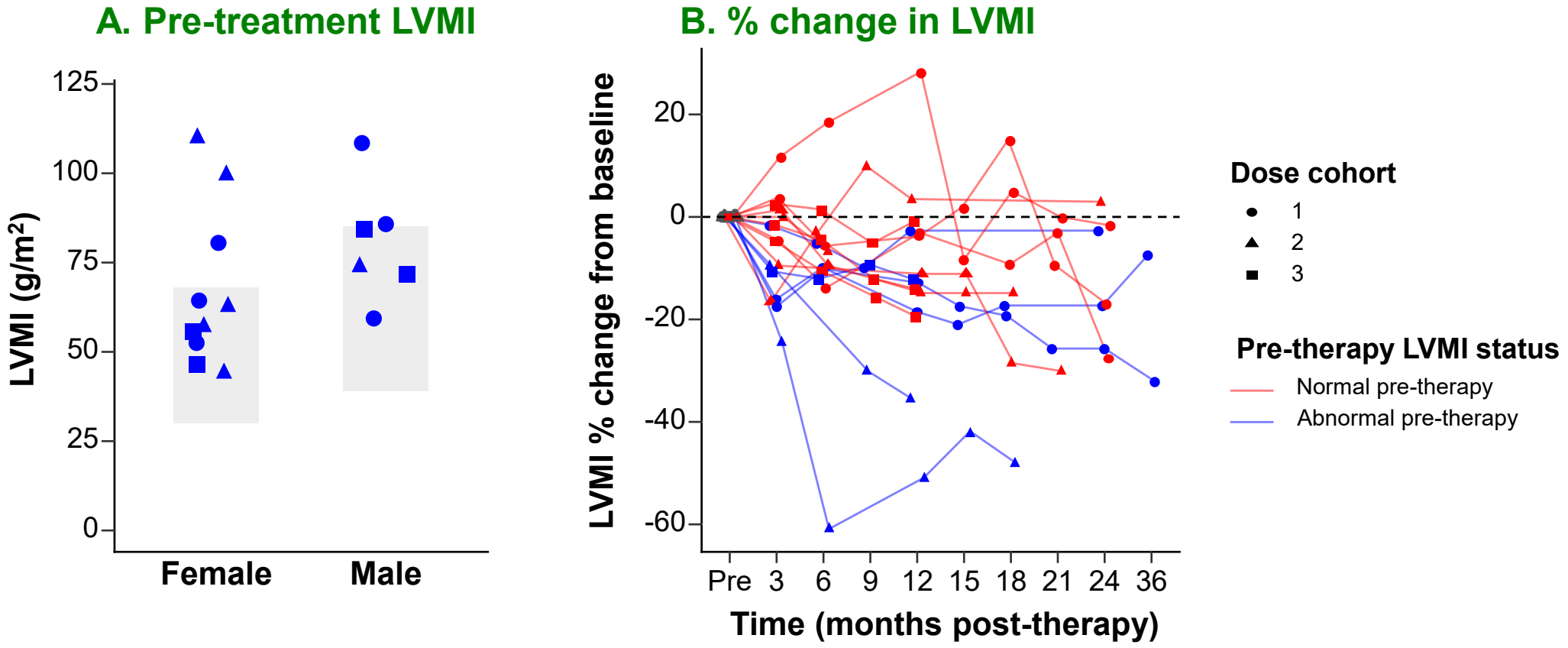
[1] Not included in the analysis of the efficacy data

Cardiac Biopsy FXN Levels Pre-therapy and 3 Months Following AAVrh.10hFXN Therapy



- All patients with cardiac biopsy 3 months post-AAVrh.10hFXN therapy had increased cardiac frataxin levels compared to baseline

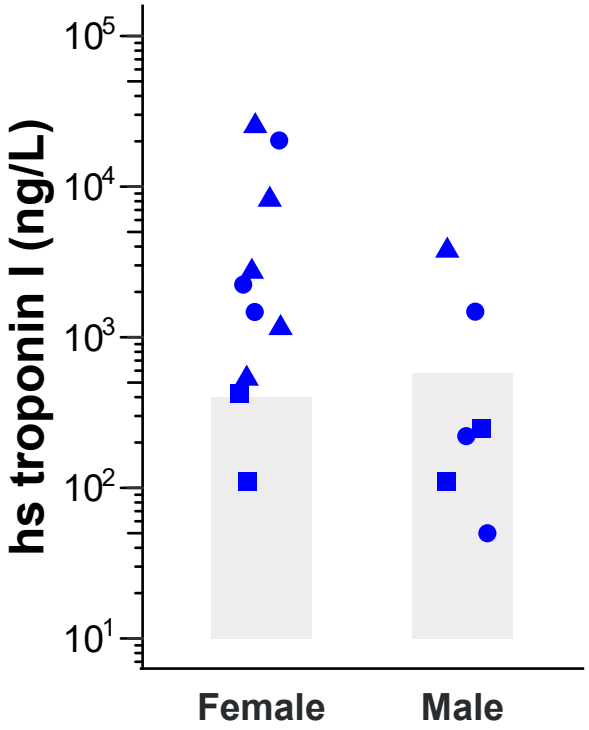
Change in Left Ventricular Mass Index (LVMI) Post-therapy



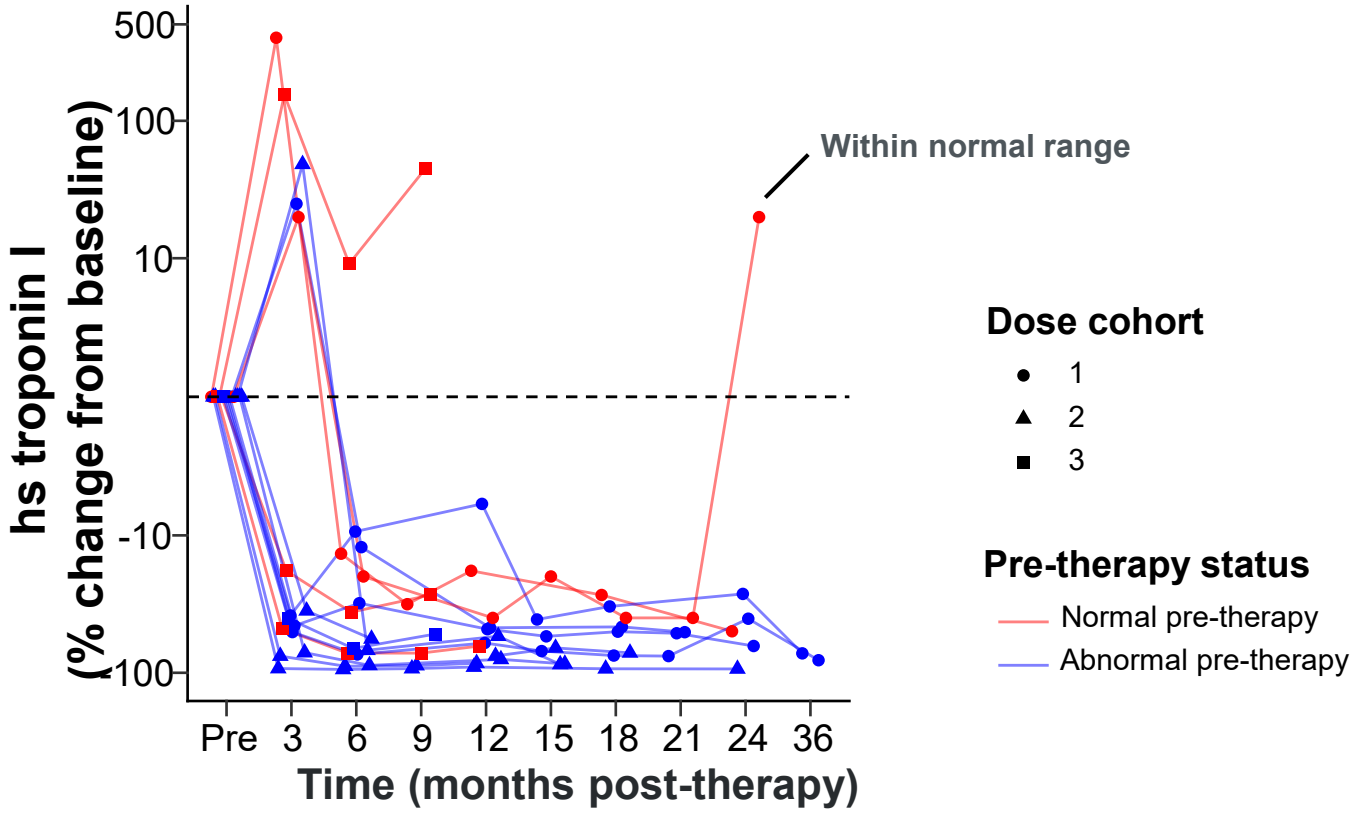
- At the last assessment compared to pre-therapy, 56% had decreased LVMI, 44% stabilized and 0% increased

Change in High Sensitivity Troponin I Post-therapy

A. Pre-treatment hs troponin I

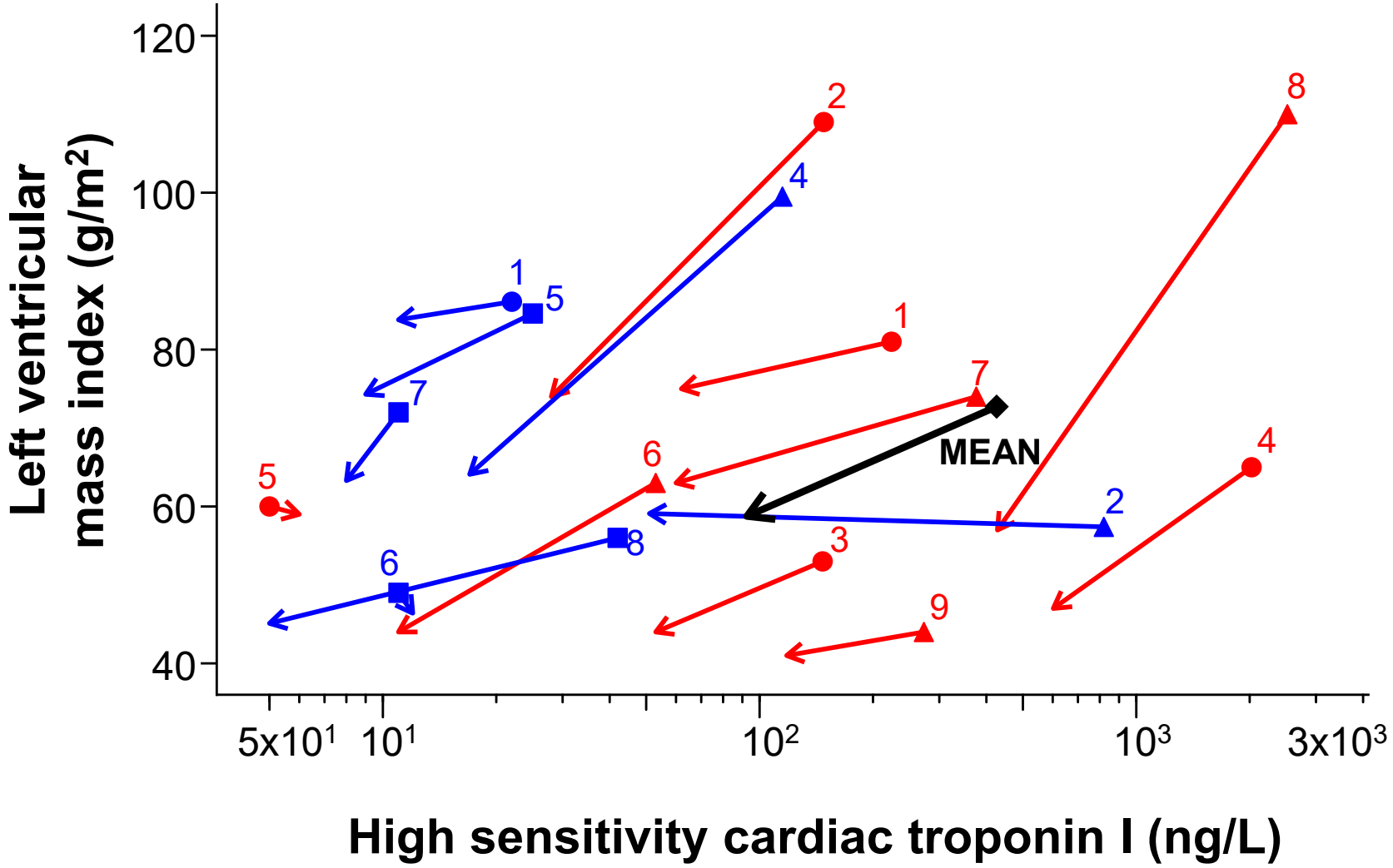


B. % change in hs troponin I



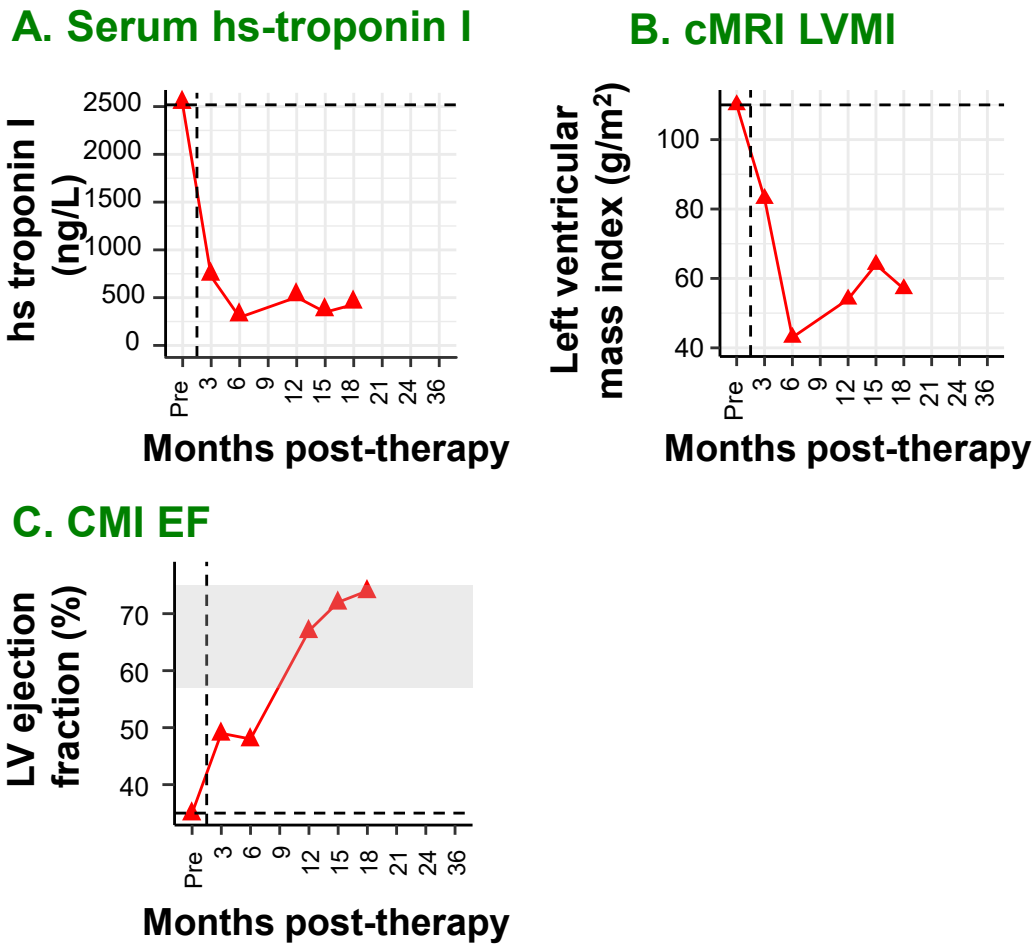
- At the last assessment compared to pre-therapy 94% had decreased serum hs troponin I

Comparison of LVMI and Serum hs-Troponin I Pre- and Post-therapy



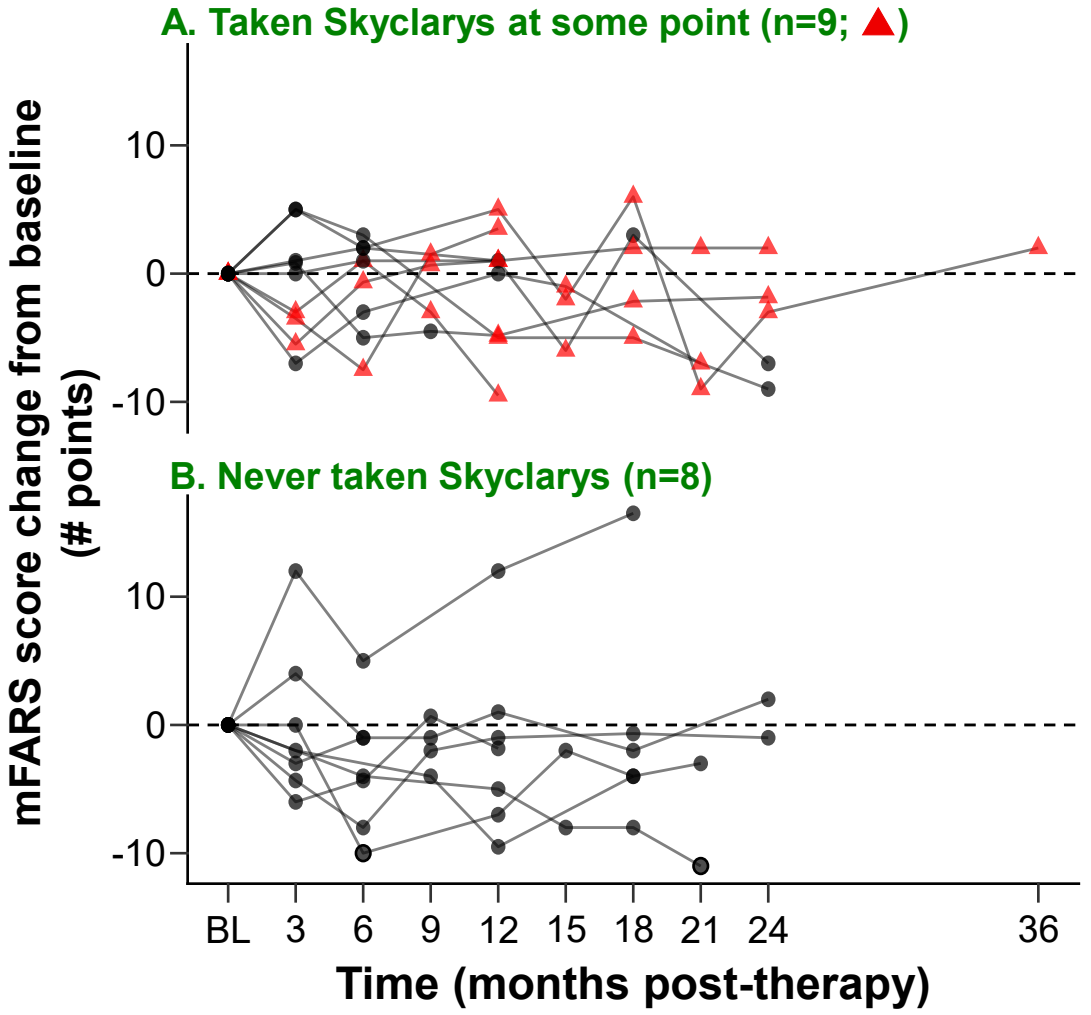
Effect of AAVrh.10hFXN Gene Therapy on Left Ventricular Ejection Fraction (EF)

- 16/17 patients had normal EF at baseline, with no change with therapy
- 1/17 had a low EF at baseline; 18 months post-therapy
  - serum hs-troponin I decreased 83%
  - cMRI LVMI decreased 48%
  - cMRI EF 35% → 74%



Effect of AAVrh.10hFXN Therapy on the Modified Friedreich Ataxia Rating Scale (mFARS)

- mFARS is a neurologic rating scale for FA
- Total score 93; increase indicates worsening, decrease indicates improvement
- Measures bulbar function, limb coordination and stability
- Natural history of untreated FA patients shows gradual worsening of mFARS over time
- AAVrh.10hFXN therapy of FA patients never treated with Skyclarys had stabilization of the mFARS neurologic scale, similar to that with Skyclarys



Summary

Gene therapy of Friedreich ataxia with AAVrh.10hFXN

- Intravenous doses of $1.8x10^{11}$–$1.2x10^{12}$ vg/kg are well tolerated
- Reduces left ventricular mass index
- Reduces serum levels of hs-troponin I
- Preliminary data suggests improvement in mFARS neurologic scale
- May be efficacious for treatment of Friedreich ataxia