Efficacy and Safety of a Novel AAV FXN Gene Therapy (SGT-212) for the Treatment of Friedreich's Ataxia

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INTRODUCTION

- Friedreich's ataxia (FA) is an autosomal recessive neurodegenerative disorder caused by variants in the frataxin (FXN) gene, leading to mitochondrial dysfunction and impaired energy metabolism. Cardiomyopathy is the leading cause of death in FA and represents a critical therapeutic target alongside progressive neurological decline.[1,2]
- A promising approach to address these challenges is through AAV-mediated gene replacement therapy, which aims to safely restore FXN expression in disease-relevant tissues and modify the course of FA.[3,4]

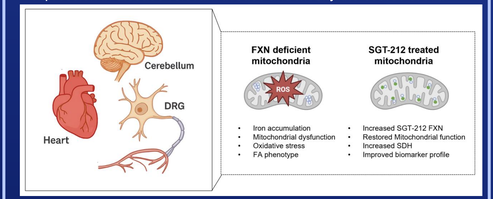


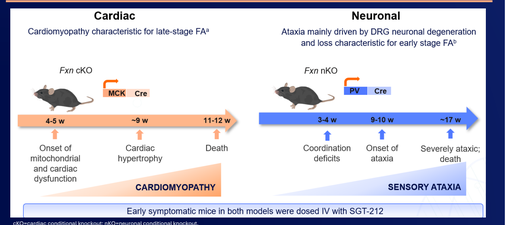
Figure 1. The goal of SGT-212 is to increase levels of FXN in the mitochondria of key target tissues (heart, dorsal root ganglion (DRG), and dentate nuclei of the cerebellum) using AAV-mediated gene delivery. Image made with Biorender.

- In this study, we developed a gene therapy candidate (SGT-212) utilizing an AAVhu68 capsid and a ubiquitous promoter to express human FXN. SGT-212 was administered using a dual route of administration via intravenous (IV) and intraparenchymal dentate nucleus (IDN) infusions in non-human primates (NHPs).
- The efficacy of this approach was evaluated by IV infusions in conditional Fxn knockout mouse models, while long-term safety and SGT-212 expression were assessed in NHPs.

1. Koeppen AH. J Neurol Sci. 2011;303(1-2):1-12. 2. Lynch DR et al. Arch Neurol. 2002;59(5):743-747. 3. Perdomini M et al. Nat Med. 2014;20(5):542-547. 4. Martier R et al. Mol Ther Methods Clin Dev. 2022;24:1-13.

SGT-212: APPROACH TO FA TREATMENT

MODEL SYSTEMS FOR THERAPEUTIC EVALUATION



cKO=cardiac conditional knockout; nKO=neuronal conditional knockout.
[a]Cre-mediated deletion of Fxn in heart and skeletal muscle. [b]Cre-mediated deletion of Fxn in parvalbumin-expressing neurons of the dorsal root ganglia, cerebellar Purkinje cells and deep nuclei, interneurons in the brain. Model does not recapitulate human-relevant dentate nuclei neuronal loss found in later stages of FA.

SGT-212 IMPROVES SURVIVAL AND NEUROLOGICAL OUTCOMES IN THE NEURONAL KNOCKOUT MOUSE MODEL (nKO)

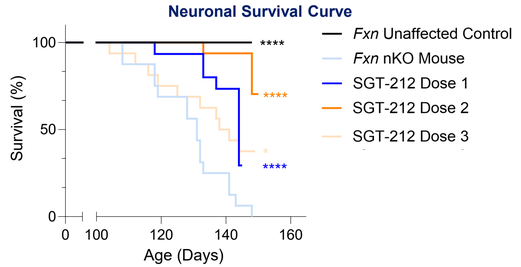


Figure 1. SGT-212 Improved Survival in the Affected Mouse Model *Fxn* nKO mice (N=64) were enrolled in this study and given a single IV administration of SGT-212 at three ascending doses on Day 28 of age (± 3 days). Age-matched *Fxn* nKO mice (N=16) and *Fxn* unaffected (healthy control) mice (N=16) were administered vehicle (ITFFB) as controls. Mice were monitored for survival and euthanized at humane endpoints or at the terminal study endpoint (120 days post-dose). Administration of SGT-212 at all doses resulted in a significant increase in survival of *Fxn* nKO mice compared to that of vehicle-treated *Fxn* nKO mice. Asterisks indicate statistical significance between groups (*p<0.05, ****p<0.0001) using a simple survival analysis (Kaplan-Meier).

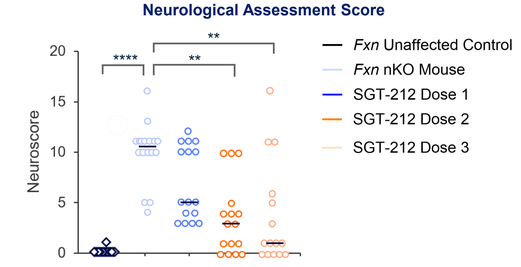


Figure 2. SGT-212 Reduced Ataxia Phenotype Weekly neurological exams were performed to assess the severity of ataxia. Dose 2 and 3 resulted in a significant decrease in neuroscores at Day 56 following treatment, likely due to the delayed onset or slower progression of the ataxia phenotype. Asterisks indicate statistical significance between groups (**p<0.01, ****p<0.0001) based on the Kruskal-Wallis with Dunn's multiple comparison test to compare each group to the vehicle-treated *Fxn* nKO group.

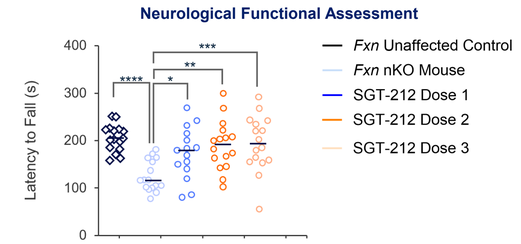


Figure 3. SGT-212 Improved Neuromotor Function RotaRod testing was performed to assess neuromotor function. Administration of SGT-212 at all doses resulted in a significant increase in latency to fall compared to that of vehicle-treated *Fxn* nKO mice. Asterisks indicate statistical significance between groups (*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001) based on the Kruskal-Wallis with Dunn's multiple comparison test to compare each group to the vehicle-treated *Fxn* nKO group.

SGT-212 IMPROVES SURVIVAL AND CARDIAC OUTCOMES IN THE CARDIAC KNOCKOUT MOUSE MODEL (cKO)

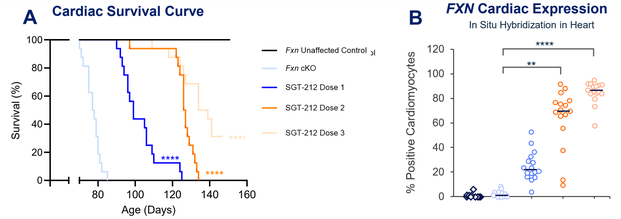


Figure 4. (A) SGT-212 Improved Survival in the Affected Mouse Model *Fxn* cKO mice (N=64) were enrolled in this study and given a single IV administration of STG-212 at three ascending doses on Day 28 of age (± 3 days). Age-matched *Fxn* cKO mice (N=16) and *Fxn* unaffected (healthy control) mice (N=16) were administered vehicle (ITFFB) as controls. SGT-212 at all doses resulted in a significant increase in survival when compared to vehicle-treated *Fxn* mice. Asterisks indicate statistical significance between groups (****p<0.0001) using a simple survival analysis (Kaplan-Meier). **(B) SGT-212 Showed Dose Response in Cardiac Tissue *FXN* Expression** in heart which was significantly increased in Dose 2 and 3 based on the Kruskal-Wallis with Dunn's multiple comparison test to compare each group to the vehicle-treated *Fxn* cKO group. Asterisks indicate statistical significance between groups (**p<0.01, ****p<0.0001).

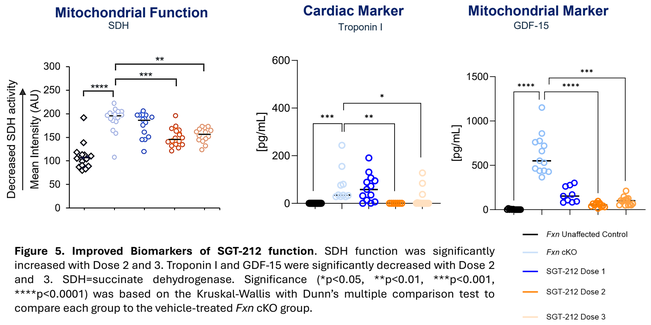


Figure 5. Improved Biomarkers of SGT-212 function. SDH function was significantly increased with Dose 2 and 3. Troponin I and GDF-15 were significantly decreased with Dose 2 and 3. SDH=succinate dehydrogenase. Significance (*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001) was based on the Kruskal-Wallis with Dunn's multiple comparison test to compare each group to the vehicle-treated *Fxn* cKO group.

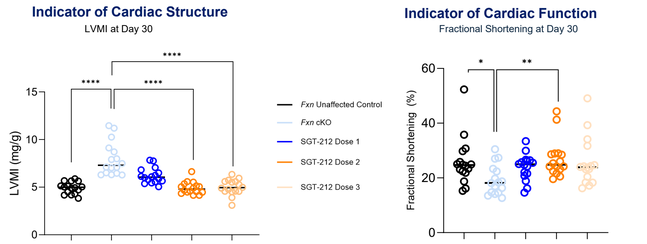


Figure 6. Cardiac Structure and Function Improved with SGT-212. Echocardiograms show that the LVMI is statistically improved from vehicle dosed cKO mice in cKO mice dosed with Dose 2 and 3. Fractional shortening is significantly increased at Dose 2 compared to *Fxn* cKO vehicle control,. LVMI = Left Ventricular Mass Index. Asterisks indicate statistical significance between groups (*p<0.05, **p<0.01, ***p<0.001) based on the Kruskal-Wallis with Dunn's multiple comparison test to compare each group to the vehicle-treated *Fxn* cKO group. Research has indicated LVMI is correlated with increased risk of all-cause mortality (Pousset et al., 2015).

SGT-212 WELL TOLERATED IN NHP WITH EXTENSIVE EVALUATION OF SAFETY AND DOSING STRATEGY

BOTH IDN AND IV DOSE LEVELS DEMONSTRATED NO TREATMENT-RELATED FINDINGS (BOTH IN CNS AND NON-CNS)

Overall NHP Studies Performed

- **9 NHP studies** conducted in total, across 4 different development candidates
- n = 120+ NHPs tested
- Range of dose levels tested across 4 routes of administration (**IV**, **IT**, **IV & IT**, **IV & IDN**)
- Follow-up time as long as **365 days postdosing** (including SGT-212)

SGT-212 NHP Tox Study Findings

- **Dose-dependent** & **long-term biodistribution** in tissues was associated with corresponding transgene expression in heart, dentate nucleus, and DRG
- The **precision** MRI-guided IDN injection procedure was **safe and well tolerated** by NHPs
- The proposed clinical IDN and IV dose levels demonstrated **no treatment-related findings** (both in CNS and non-CNS)
- The proposed clinical IDN and IV dose levels elicited **therapeutically relevant levels** of FXN expression

IDN Administration of SGT-212 Resulted in Safe and Robust *FXN* Expression in the Cerebellum in NHPs at Clinically Relevant Dose

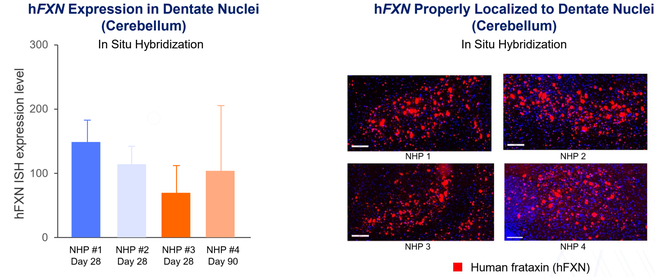


Figure 7. SGT-212 IDN administration resulted in robust *FXN* expression across multiple animals and timepoints. Injections were performed using a MRI-compatible stereotactic injection system targeting the dentate nuclei in the cerebellum. The procedure utilized a flexible microcatheter coupled with real-time MRI guidance to ensure accurate placement and minimize off-target delivery. The device enabled precise administration of AAV vector encoding *FXN*, with injection volumes and rates optimized for tissue tolerance and transduction efficiency. The precision MRI-guided IDN injection procedure was safe and well tolerated by NHPs and elicited therapeutically relevant levels of *FXN* expression.

CONCLUSIONS

- The novel AAV FXN gene therapy (SGT-212) intended for Friedreich's ataxia demonstrates significant potential in treating the disease.
- SGT-212 has shown improved survival and functional outcomes in both neuronal and cardiac KO mouse models, indicating its potential as an effective treatment for Friedreich's ataxia.
- SGT-212's safety profile and dosing regimen were well tolerated in non-human primates, with no treatment-related findings observed at the proposed clinical IDN and IV dose levels.
- FALCON clinical trial evaluating SGT-212 is active (ClinicalTrials.gov ID: NCT07180355).

Presented at The Society for Neuroscience, November 2025, San Diego, California