Efficacy and safety of a novel AAV FXN gene therapy (SGT-212) for the treatment of Friedreich's ataxia

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Financial Disclosure

LIST ALL DISCLOSURES FROM PAST 12 MONTHS

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Friedreich's Ataxia: A Multisystem Disease With High Unmet Need

Estimated Population Affected by Friedreich's Ataxia

~5,000-7,000 patients in the US[3]

~25,000 patients in the EU[4]

Progressive[1]

- Disease progresses over time with worsening disability and symptoms

Debilitating

- Loss of ambulation on average 10 years after onset of symptoms

Life-Shortening[1,2]

- Mean life expectancy is ~38 years, with cardiac dysfunction as the most common cause of death

Clinical Presentation[3]

- Average onset between ages 10 to 15 years
- Difficulty with motor control and coordination
- Loss of vision and hearing, slurred speech, and muscle weakness
- Cardiac complications, most commonly presenting as FA-cardiomyopathy and arrhythmia, are the primary cause of death

Multisystem Disease[1]

- Neurologic
  - Brain
  - Spinal Cord
  - Peripheral Nervous System
- Cardiac
- Ocular
- Muscle
- Endocrine

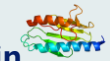
1. Cook A, Giunti P. Br Med Bull. 2017;124(1):19-30 | 2. Rare Disease Advisor. Accessed April 3, 2025 | 3. National Organization for Rare Disorders. Accessed April 3, 2025 | 4. Koeppen AH. J Neurol Sci. 2011;303(1-2):1-12. 3.

Gene Therapy to Address the Underlying Molecular Etiology of FA

Exon 1 — Exon 2 — Exon 3 — Exon 4 — Exon 5

GAA●TTC$_{(n>60)}$ repeat region

↓ FXN mRNA → ↓ FXN Protein



➢ FA is caused by deficiency in FXN protein, which leads to reduced energy production and buildup of toxic byproducts, ultimately resulting in oxidative stress that damages cells in the central nervous system & heart

Fe^{2+} Iron deposits accumulation

Fe-S enzyme deficiency

↓ ATP Energy Production

↑ ROS Oxidative Stress

Hypertrophic Cardiomyopathy progresses to Dilated and HF

Dentate Nucleus degeneration

DRG, spinal cord, peripheral nerves degeneration

SGT-212: The Only Dual-Administration Approach to Treat FA

AAVhu68

Ubiquitous Promoter Codon Optimized cDNA

Intra Dentate Nucleus Infusions

- Precision dosing of target tissue
- Direct administration to affected brain structure

Intravenous Administration

- Treatment focused on the heart
- Potential to treat other disease-relevant organ systems

Administration simplified for illustrative purposes. Actual SGT-212 IDN administration will use FDA-approved, MRI-guided delivery system. FA: Friedreich's Ataxia | FXN: Frataxin | ATP: Adenosine triphosphate | ROS: Reactive Oxygen Species | HF: Heart Failure | cDNA: complementary DNA | GAA=guanine-adenine-adenine | DRG=dorsal root ganglia

Methods and Materials

The therapeutic effect of SGT-212 was evaluated in dose response efficacy studies pursued in mouse models of disease

Cardiomyopathy characteristic for late-stage FA

***Fxn* cKO**
MCK-Cre

Model Phenotype
- 4-5 weeks: Onset of mitochondrial and cardiac dysfunction
- ~9 weeks: Cardiac hypertrophy
- ~11-12 weeks: Death

Ataxia mainly driven by DRG neuronal degeneration characteristic for early-stage FA

***Fxn* nKO**
PV-Cre

Model Phenotype
- 3-4 weeks: Coordination deficits
- 9-10 weeks: Onset of ataxia
- ~17 weeks: Severe ataxia / Death

Early symptomatic mice in both models were dosed IV with SGT-212

The safety of SGT-212 was evaluated in a dose response study pursued in NHPs

SGT-212 GLP Tox: Biodistribution and Safety explored, up to 365 days post-dosing, via dual ROA (IV/IDN)

- 4 IV doses and 5 IDN doses

cKO=cardiac conditional knockout; Cre-medicated deletion of Fxn in the heart & skeletal muscle
nKO=neuronal conditional knockout; Cre-mediated deletion of Fxn 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.

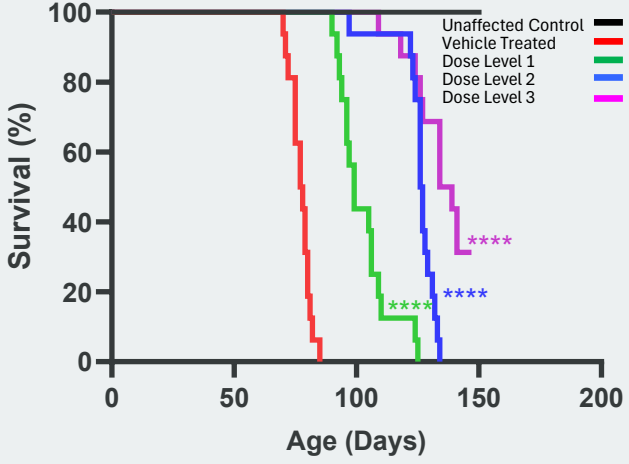
One day prior to dosing, NHPs started on a tapering dexamethasone regimen at 2 mg/kg twice a day, with tapering beginning on study Day 3 and stopping on study Day 10.

NHP: Non-Human Primate | FA: Friedreich's Ataxia | MCK: Muscle Creatine Kinase | IV: Intra Venus | IDN: Intra Dentate | ROA: Route of Administration | GLP: Good Lab Practices | DRG: Dorsal Root Ganglia

SGT-212 IMPROVES SURVIVAL & CARDIAC OUTCOMES IN THE FA CARDIAC MODEL

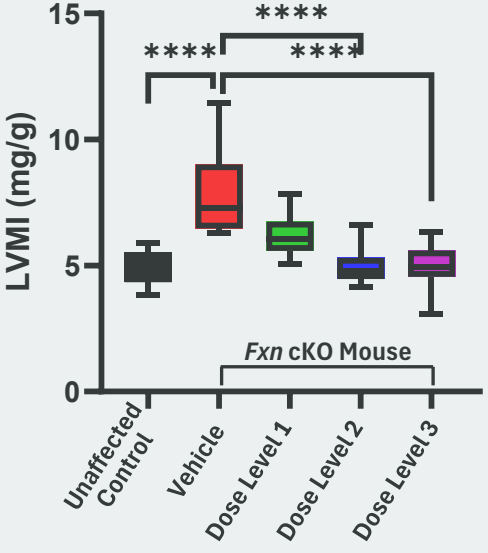
Dose-dependent expression and activity achieved in disease-relevant tissue of knockout mouse model (cKO)

Survival



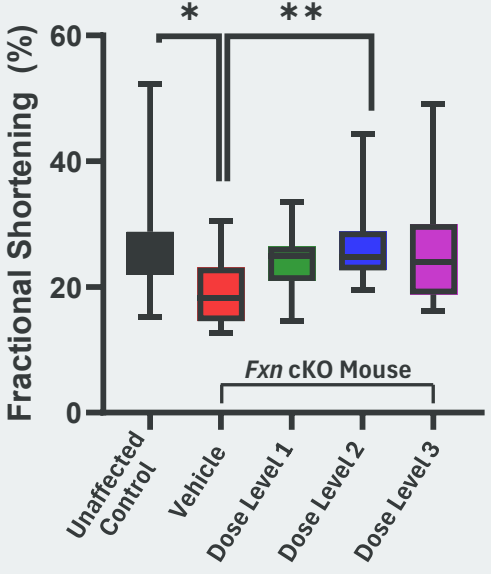
Indicator of Cardiac Structure

Left Ventricular Mass Index (Day 30)



Indicator of Cardiac Function

Fractional Shortening (Day 30)



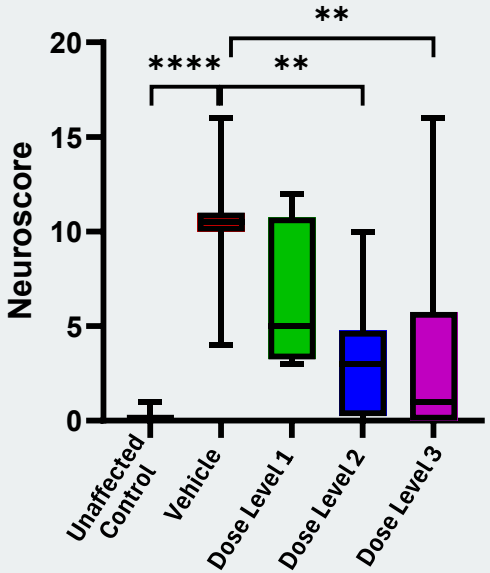
- Hematology and serum chemistry: No toxicity associated with SGT-212 was observed in all three dose levels
- Improvement in biomarkers of mitochondrial function/activity (SDH, GDF15)

n: 16 per group | Asterisks indicate statistical significance between groups (*p<0.05, **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 cKO group

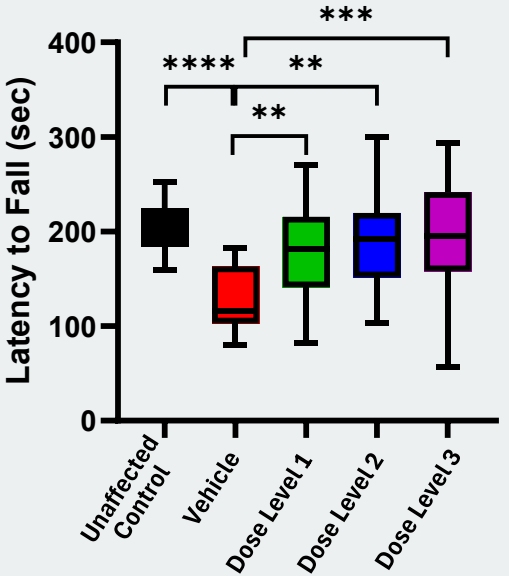
SGT-212 Improves Function in the Neurologic Mouse Model

Neuronal proof-of-concept achieved in disease-relevant knockout mouse model (nKO)

Neurological Assessment Score
Neuroscore (Day 56)



Neuromotor Function Assessment
Rotarod (Day 60)



n: 16 per group | 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.
The neurologic score assessment was used to assess the severity of ataxia. | The RotaRod test evaluates coordination and balance by measuring the time to fall for mice running on a spinning rod that progressively accelerates – a decreased latency to fall indicates neuromotor impairment.

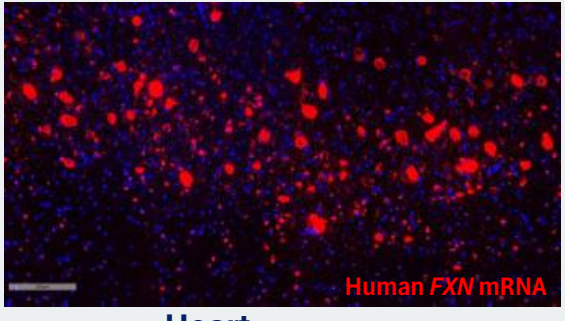
SGT-212 WAS WELL TOLERATED IN NON-HUMAN PRIMATES

Confidence in Dual Route of Administration, Informed by Exhaustive Exploration of Possible Routes

SGT-212 NHP Tox Study Findings

- SGT-212 GLP Tox: Biodistribution and Safety explored, up to 365 days post-dosing, via dual ROA (IV/IDN)
- 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

Dentate Nucleus (Cerebellum)



Heart

Human FXN Transgene Expressed in Disease-Relevant Tissues

Representative Images | Data on file

NHP: Non-Human Primate | FA: Friedreich's Ataxia | MCK: Muscle Creatine Kinase | IV: Intra Venus | IDN: Intra Dentate | ROA: Route of Administration | GLP: Good Lab Practices | DRG: Dorsal Root Ganglia

CONCLUSIONS

Robust Nonclinical Package Supports Potential Efficacy in Cardiac and Neuro Manifestations of Disease and the Commencement of a FIH Phase 1b Trial

- The novel AAV FXN gene therapy (SGT-212) for Friedreich's ataxia demonstrates 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.
- Improved mitochondrial function observed in mouse model of cardiomyopathy.
- SGT-212's showed a favorable safety profile. Dual route dosing regimen was well tolerated in non-human primates, with no treatment-related findings observed at the proposed clinical doses
- FALCON clinical trial evaluating SGT-212 is active (ClinicalTrials.gov ID: NCT07180355)

FIH: First-in-Human | AAV: Adeno Associated Virus | FXN: Frataxin | KO: Knock Out