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

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SESSION: Neurologic diseases V

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- I am a full-time employee at Solid Biosciences

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Friedreich's Ataxia (FA): A Multisystem Progressive Disease

Estimated Population Affected by Friedreich's Ataxia

~5,000-7,000 patients in the US[1]

~6,500-9,000 patients in the EU[2]

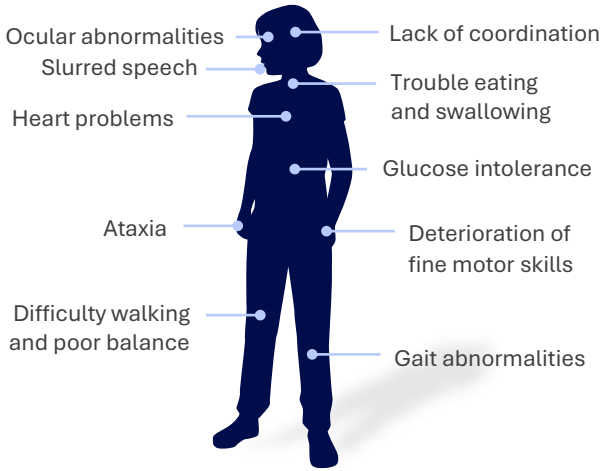
Disease Etiology & Pathophysiology

- FA is a multisystem disease caused by frataxin deficiency. 96% of patients have a GAA repeat expansion in both alleles of the *FXN* gene, while 4% are compound heterozygotes with a GAA expansion and point mutation.[3]
- Frataxin is a mitochondrial protein involved in Fe-S cluster biogenesis, which are critical for energy production and iron homeostasis.
- Highly metabolic cells such as neurons and cardiomyocytes are the most susceptible to damage resulting from frataxin deficiency.

Diagnosis & Prognosis

- Disease is progressive with an average age of onset between 10 to 15 years.
- Loss of ambulation on average 10 years after onset of symptoms.
- Mean life expectancy is ~38 years with cardiac dysfunction as the most common cause of death.[4]

Multisystem Manifestations of FA[4]



[1]National Organization for Rare Disorders. Accessed April 3, 2025. https://rarediseases.org/rare-diseases/friedreichs-ataxia;
[2]Koeppen AH, *J Neurol Sci* (2011); [3]Campuzano V et al, *Science* (1996); [4]Cook A and Giunti P, *Br Med Bull* (2017)

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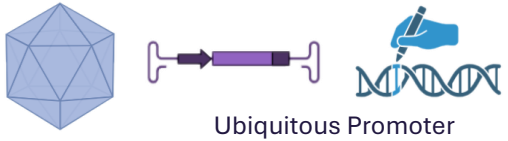
SGT-212 Leverages Precision Technology to Address Quality of Life and Cardiac Mortality

Solid Approach

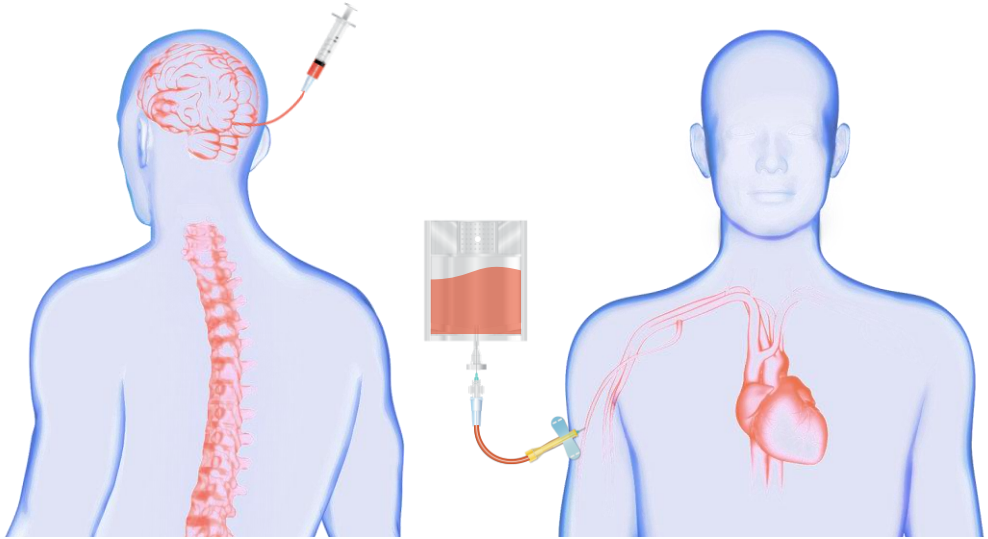
Dual route of administration – IV and IDN – to deliver AAV-based gene therapy directly to the heart and cerebellum to restore functional expression of FXN in the heart and central nervous system



AAVhu68

Ubiquitous Promoter
Codon Optimized cDNA

Dosing Cadence: IDN first, followed by IV



Intra Dentate Nucleus (IDN) Infusion

- Direct, bilateral administration to the most affected brain structure to treat ataxia and dysarthria
- Robotic placement of cannulas and real-time MR imaging ensures target perfusion of the dentate nucleus

IV Administration

- Treatment of the heart and the potential to treat muscle and DRG

DRG = dorsal root ganglion; IDN = intradentate nuclei; IV = intravenous

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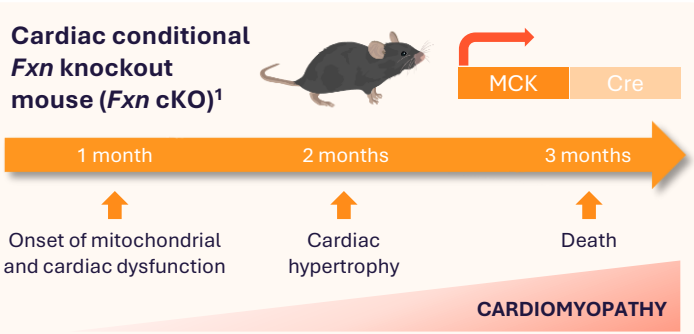
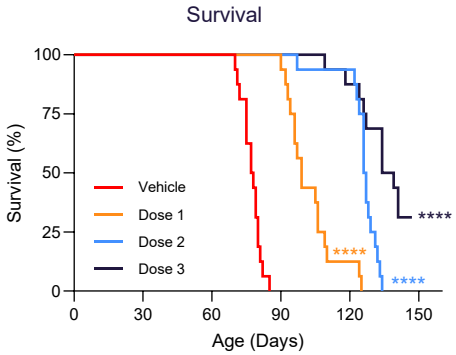
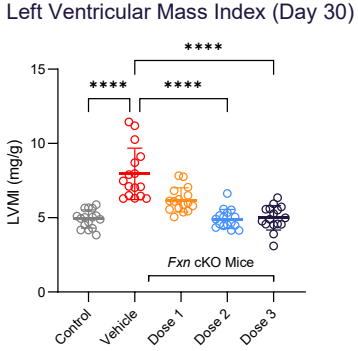
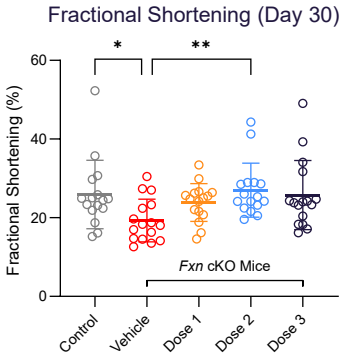
SGT-212 Improves Survival, Cardiac Outcomes, and Mitochondrial Function in a Mouse Model of FA-Associated Cardiomyopathy

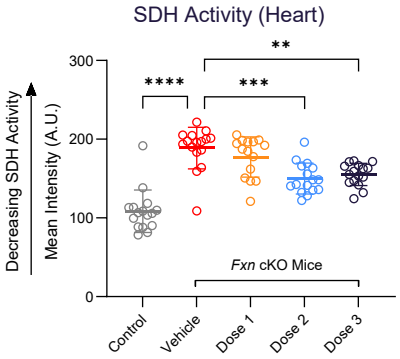


Juvenile *Fxn* cKO mice (28 days old) were administered SGT-212 at one of three dose levels by intravenous delivery.









- SGT-212 improved survival and expressed FXN transgene in the heart in *Fxn* cKO mice
- Reduced cardiac hypertrophy and improved contractile function
- Increased SDH activity in the heart and reduced serum GDF-15 levels, suggestive of improved mitochondrial function and reduced oxidative stress
- No test article adverse effects associated with SGT-212 were observed in hematology and serum clinical chemistry

[1]Cre-medicated deletion of *Fxn* in the heart & skeletal muscle

Asterisks indicate statistical significance (*p<0.05, **p<0.01, ****p<0.0001) between each groups to the vehicle-treated *Fxn* cKO group

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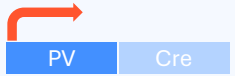
SGT-212 Improves Neurological Score and Neuromotor Function in a Neuronal Mouse Model of FA

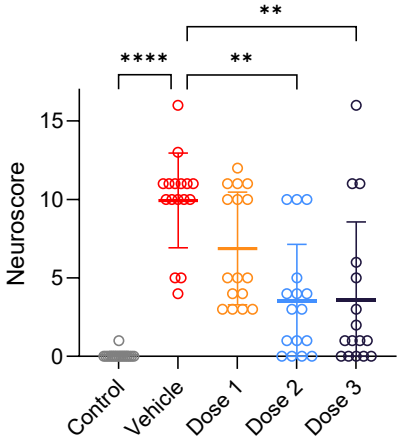
Neuronal conditional *Fxn* knockout mouse (*Fxn* nKO)[1]



Juvenile *Fxn* nKO mice (28 days old) were administered SGT-212 at one of three dose levels by intravenous delivery.

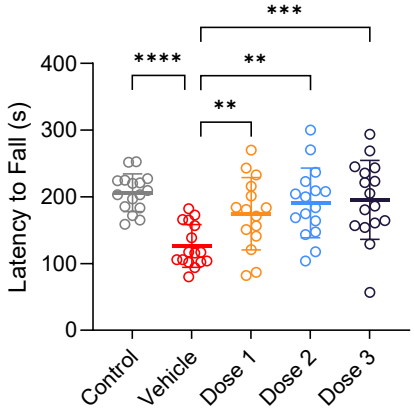
Neurological Assessment Score

Neuroscore (Day 56)



Neuromotor Function Assessment

Rotarod (Day 60)



- Delivery of SGT-212 **improved survival** in *Fxn* nKO mice
- Significantly **improved neuroscores, likely by delaying onset or progression of ataxia**
- Treatment increased latency to fall, indicative of **improved neuromotor function**
- No test article adverse effects associated with SGT-212 were observed in hematology and serum clinical chemistry

[1]Cre-mediated deletion of *Fxn* in parvalbumin-expressing neurons

Asterisks indicate statistical significance (*p<0.05, **p<0.01, ****p<0.0001) between each groups to the vehicle-treated *Fxn* nKO group

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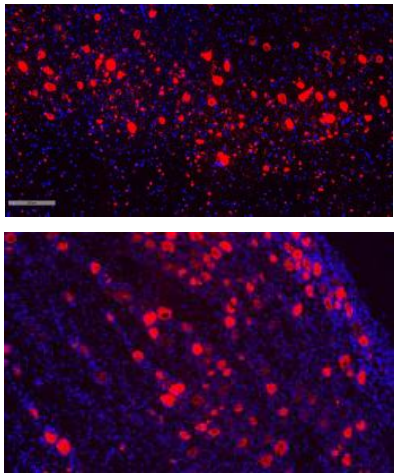
Dual Route of SGT-212 Administration is Safe and Well Tolerated in NHPs

SGT-212 GLP Tox Study Findings

- Biodistribution and safety explored, up to 365 days post-dosing, via dual delivery (IDN-IV)
- Dose-dependent & long-term biodistribution in NHP tissues was associated with corresponding transgene **expression in heart, dentate nucleus, and DRG**
- 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

Human *FXN* Transgene Expression in Disease Relevant Tissues



Dentate Nuclei (Cerebellum)

Dorsal Root Ganglion

● Human frataxin mRNA

SGT-212 Nonclinical Data Package Supports Safety and Potential Cardiac and Neurological Benefit for the Commencement of a FIH Phase 1b Trial

CNS = central nervous system; DRG = dorsal root ganglion; FIH = first in human; IDN = intradentate nuclei; IV = intravenous; MRI = magnetic resonance imaging; NHP = non-human primate

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FALCON Phase 1b Trial Design

A first-in-human, open-label, multi-center trial designed to evaluate the safety and tolerability of dual IDN and systemic IV infusion of SGT-212 gene therapy in participants with FA

Cohorts

Study to enroll approximately 10 participants aged 18-40 years with FA and documented cardiac hypertrophy

1. **Non-ambulatory Participants**
2. **Ambulatory Participants**
3. **Ambulatory & Non-Ambulatory**

Study Endpoints

Primary Endpoint

- Incidence and severity of TEAEs from baseline to month 12

Secondary & Exploratory Endpoints

- Change from baseline in serum biomarkers
- Change from baseline in cardiac frataxin expression at Day 90 and Month 18
- Change from baseline in assessments measuring key aspects of the disease such as neuromuscular function, fatigue and speech
- Change from baseline in cardiac structure and function

DSMB = data and safety monitoring board; IDN = intradentate nuclei; IV = intravenous

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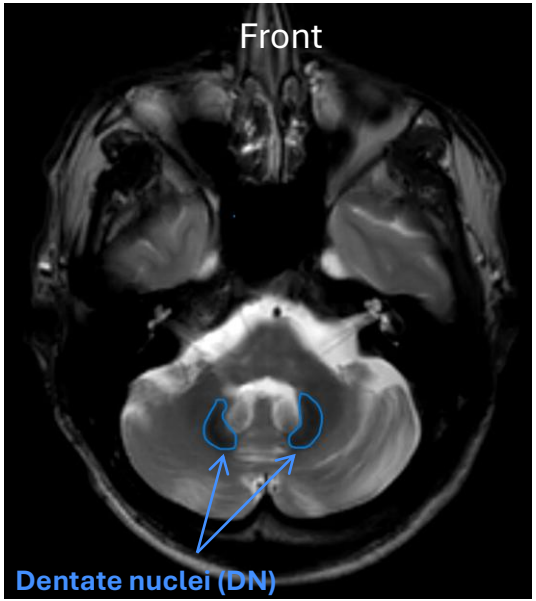
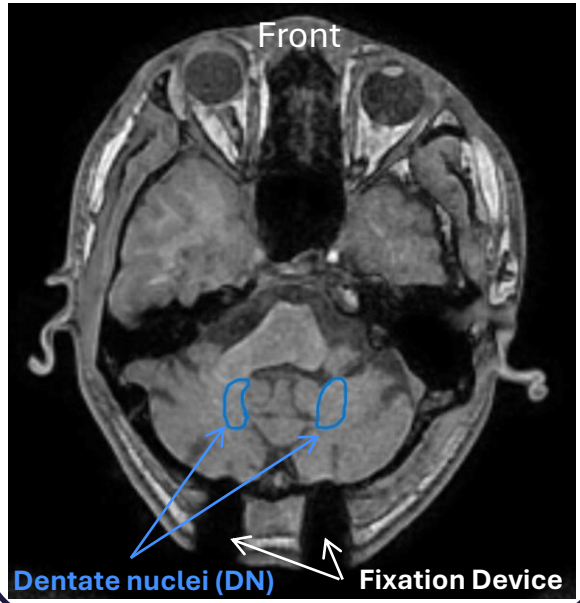
SGT-212: First Participant Dosed in Phase 1b FALCON Trial

Intra-procedural MR-imaging confirmed precise delivery of SGT-212 into the dentate nuclei

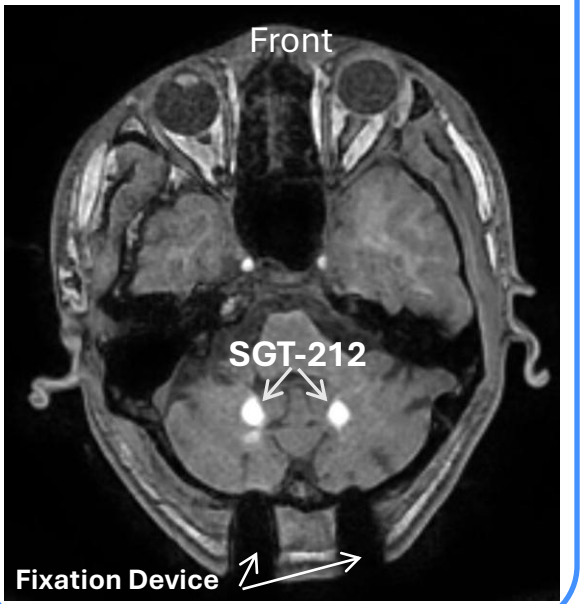
Baseline MRI



Pre-Treatment With SGT-212



Post-Treatment With SGT-212



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Summary

- SGT-212, a novel investigational AAV FXN gene therapy, demonstrates potential in treating neurological and cardiac manifestations of Friedreich's ataxia.
- SGT-212 improved survival, neurological, neuromotor, cardiac, and mitochondrial function in two conditional knockout mouse models of Friedreich's ataxia.
- SGT-212 has a favorable safety profile. Dual route of delivery was well tolerated in NHPs, with no treatment-related findings observed at the proposed clinical doses.
- Enrollment in the Phase 1b FALCON study (NCT07180355) is ongoing.
- Two participants have been dosed in the FALCON clinical trial, and SGT-212 has been well tolerated as of May 11, 2026, with no serious adverse events observed.

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Thank you!

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