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

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SOLID BIOSCIENCES

INTRODUCTION

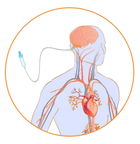
- Friedreich's ataxia (FA) is an autosomal recessive neurodegenerative disorder caused by an abnormal GAA repeat expansion within the frataxin (FXN) gene[1]
- FXN is a mitochondrial protein that regulates iron homeostasis and supports the formation of iron–sulfur (Fe-S) clusters essential for cellular energy production and protection against oxidative stress.
- FXN deficiency results in a multi-system disorder marked by progressive ataxia, sensory neuropathy, and cardiomyopathy[2,3]
- There remains a need for on-target disease-modifying therapies that address both the cardiomyopathy and the neurologic manifestations which are the main determinants of morbidity and disability
- AAV-mediated gene replacement therapy aims to safely increase FXN expression in disease-relevant tissues and modify the course of FA
- In this study, we developed a novel investigational gene therapy (SGT-212) for FA that uses a dual route of administration via intravenous (IV) and intraparenchymal dentate nucleus (IDN) infusions that is currently being investigated in humans

SGT-212 TECHNOLOGY OVERVIEW

AAVhu68
- Clade F AAV vector related to AAV9
- High transduction efficiency, particularly in heart and central nervous system (CNS) tissues

CB7 promoter and enhancer elements
- Hybrid of the human cytomegalovirus immediate-early enhancer and the chicken beta-actin (CBA) promoter to enhance transcriptional strength for robust gene expression across multiple tissues in mammalian systems

Codon-optimized complementary DNA encoding human frataxin protein (FXN)
- Encodes the 210-amino acid FXN protein, which undergoes proteolytic processing to form mature FXN, crucial for mitochondrial function



Intra Dentate Nucleus Infusions[a]
- Precision dosing of target tissue
  - Mitigating undesirable off-target effects
- Direct administration to most affected brain structure:
  - Intended to treat ataxia and dysarthria
- Peri-infusion imaging will provide confirmation of delivery

Intravenous Administration
- Treatment focused on cardiomyopathy, which is the leading cause of mortality
- Potential to treat other disease-relevant organ systems (eg, muscle, DRG)

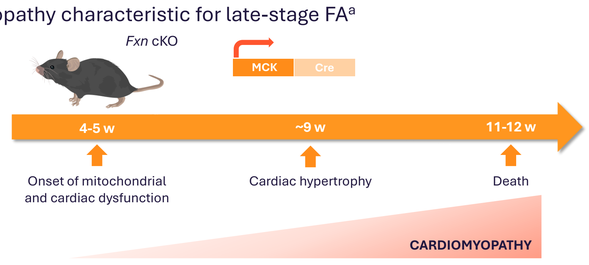
DRG=dorsal root ganglia; MRI=magnetic resonance imaging.
[a]Administration simplified for illustrative purposes. Actual SGT-212 IDN administration will use FDA-approved, MRI-guided delivery system[4].

METHODS

Nonclinical Models of FA

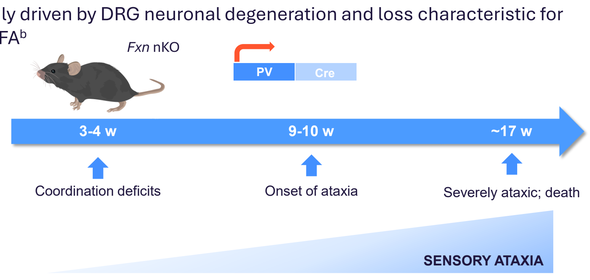
Cardiac

Cardiomyopathy characteristic for late-stage FA[a]



Neuronal

Ataxia mainly driven by DRG neuronal degeneration and loss characteristic for early stage FA[b]



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

cKO: cardiac conditional knockout; nKO: neuronal conditional knockout
[a]Cre-medicated deletion of *Fxn* in the heart & skeletal muscle. [b]Cre-mediated deletion of Fxn in parvalbumin-expressing neurons. Model does not recapitulate human-relevant dentate nuclei neuronal loss found in later stages of FA.

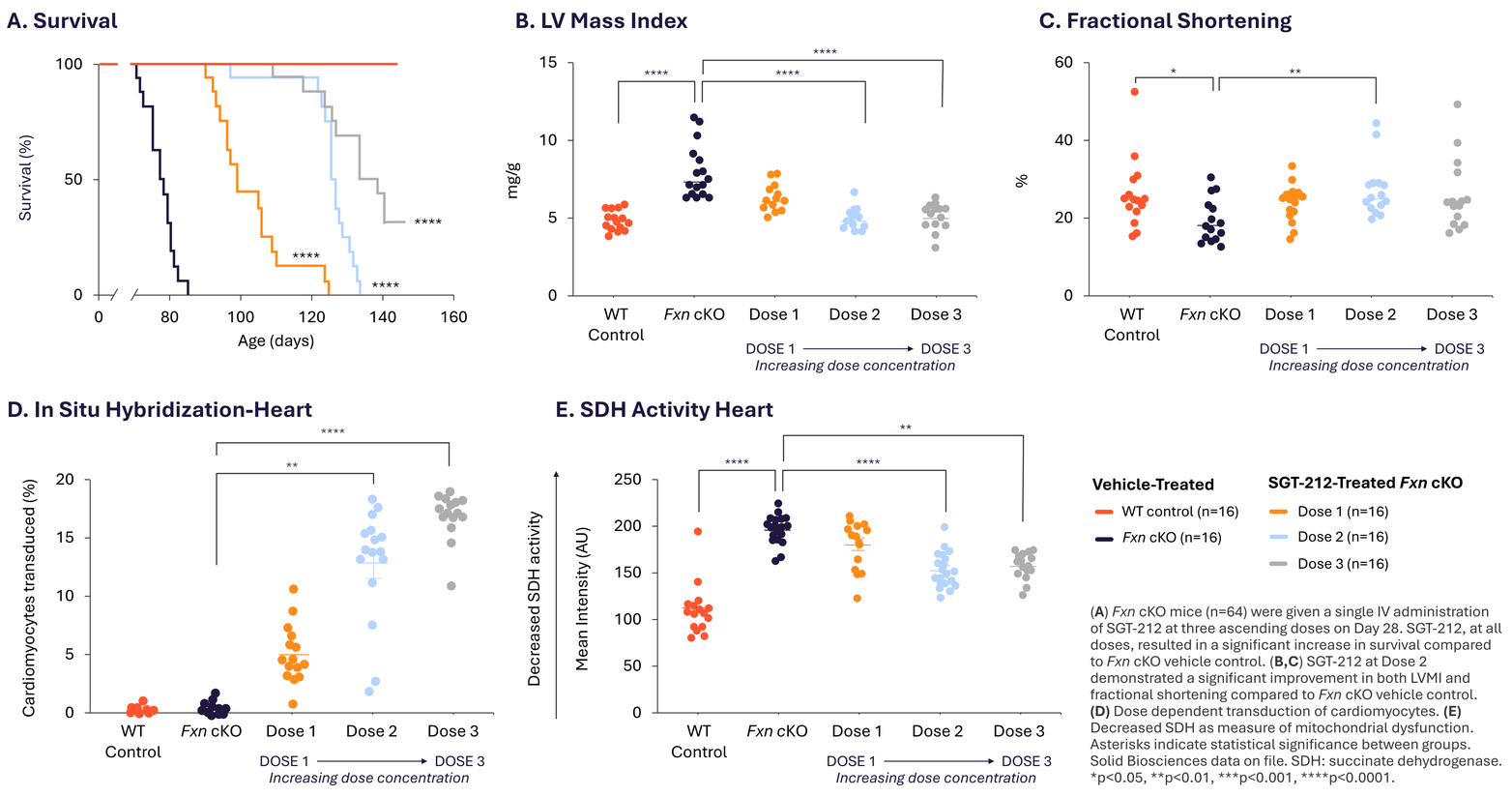
NHP GLP Tox

- Biodistribution and safety explored, up to 365 days post-dosing, via dual ROA (IV-IDN)
- 4 IV doses and 5 IDN doses
- 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

RESULTS

Survival and cardiac outcomes in the cardiac knockout mouse model (cKO)

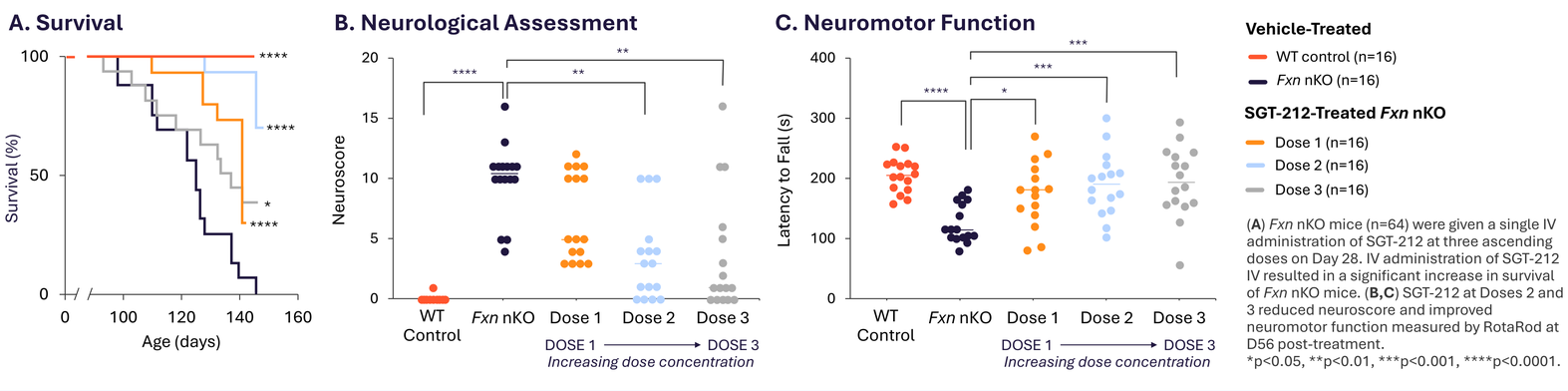
Figure 1. SGT-212 improved survival and cardiac structure and function in Fxn cKO mice



(**A**) *Fxn* cKO mice (n=64) were given a single IV administration of SGT-212 at three ascending doses on Day 28. SGT-212, at all doses, resulted in a significant increase in survival compared to *Fxn* cKO vehicle control. (**B,C**) SGT-212 at Dose 2 demonstrated a significant improvement in both LVMI and fractional shortening compared to *Fxn* cKO vehicle control. **(D)** Dose dependent transduction of cardiomyocytes. **(E)** Decreased SDH as measure of mitochondrial dysfunction. Asterisks indicate statistical significance between groups. Solid Biosciences data on file. SDH: succinate dehydrogenase. *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

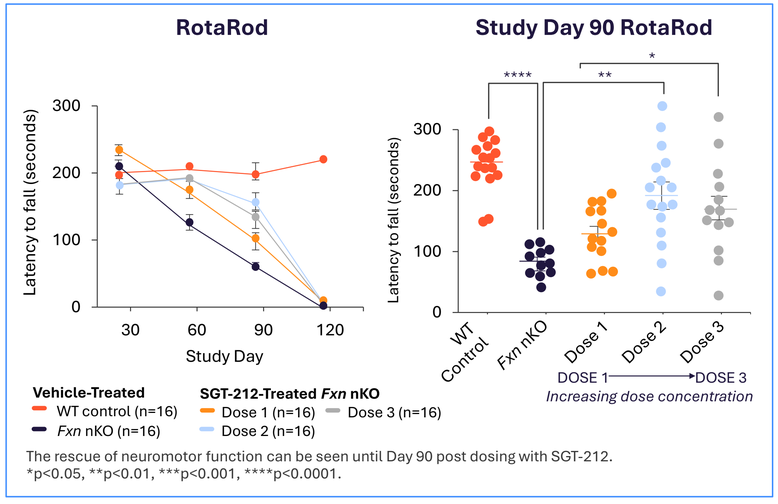
Survival and neurological outcomes in the neuronal mouse knockout model (nKO)

Figure 2. SGT-212 improved survival and neurological function in Fxn nKO mice



(**A**) *Fxn* nKO mice (n=64) were given a single IV administration of SGT-212 at three ascending doses on Day 28. IV administration of SGT-212 IV resulted in a significant increase in survival of *Fxn* nKO mice. (**B,C**) SGT-212 at Doses 2 and 3 reduced neuroscore and improved neuromotor function measured by RotaRod at D56 post-treatment.
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

Figure 3. SGT-212 led to improvement in Rotarod performance in Fxn nKO mice



The rescue of neuromotor function can be seen until Day 90 post dosing with SGT-212.
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

Dual route of SGT-212 administration was well tolerated in NHPs

Figure 4. Overview of SGT-212 NHP studies and toxicology findings

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 NHP tissues was associated with corresponding transgene expression in the 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

CNS: central nervous system; DRG: dorsal root ganglia; IDN: intraparenchymal dentate nucleus; IT: Intrathecal; IV: intraveneous; NHP: nonhuman primate.

Transgene expression in dentate nucleus of NHPs

Figure 5. SGT-212 IDN administration resulted in h*FXN* expression in the dentate nucleus in multiple animals

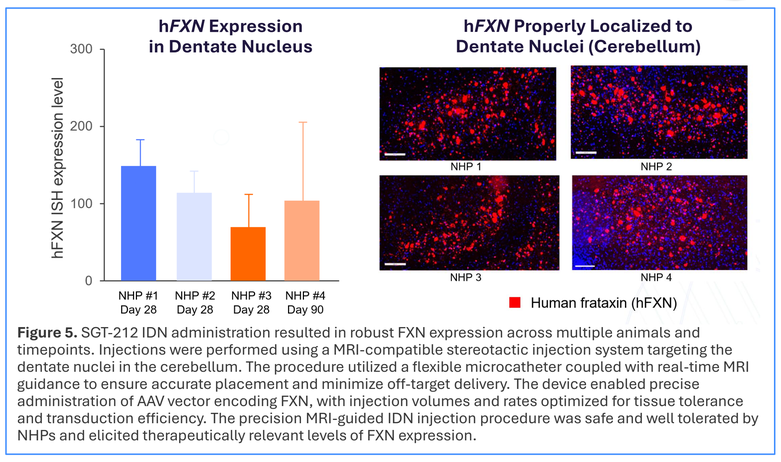


Figure 5. SGT-212 IDN administration resulted in robust FXN expression across multiple animals and timepoints. Injections were performed using a MRI-compatible stereotactic injection system targeting the dentate nuclei in the cerebellum. The procedure utilized a flexible microcatheter coupled with real-time 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.

Dual route of SGT-212 administration was well tolerated in first human dosed

- The first participant was successfully dosed with SGT-212 via dual-route administration
- The precision stereotactic IDN injection procedure was well tolerated by the participant
- Enrollment in the FALCON study (NCT07180355) is ongoing

CONCLUSIONS

These nonclinical studies demonstrate that a one-time administration of SGT-212 increases FXN expression in disease-relevant tissues, improves neurologic and cardiac phenotypes in mouse models, and is well tolerated in NHPs. Altogether, this positive, nonclinical data package supports the Phase 1b FALCON trial (NCT07180355), a first-in-human evaluation of SGT-212, which has successfully dosed the first participant.

REFERENCES
1. Campuzano et al, *Science*, 1996; 2. Reetz et al, *Lancet Neurol*, 2015; 3. Patel et al, *Ann Clin Transl Neurol*, 2016; 4. Damante et al, *Oper Neurosurg*, 2026

ACKNOWLEDGMENTS
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