

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

Brandon YH Chan¹, Jun Lee¹, Jessica F Boehler¹, Jamie L Marshall¹, Matthew Harmelink¹, Gourav Roy Choudhury², Heather Born², Juliette Hordeaux², James M Wilson², Jessie Hanrahan¹, Gabriel Brooks¹, Nicolas Christoforou¹

¹Solid Biosciences Inc., Charlestown, MA, USA; ²University of Pennsylvania, Philadelphia, PA, USA



INTRODUCTION

- Friedreich's ataxia (FA) is an autosomal recessive neurodegenerative disorder caused by an abnormal GAA repeat expansion within the frataxin (FXN) gene¹
- 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 ataxia, sensory neuropathy, and cardiomyopathy^{2,3}
- There is significant unmet need for disease-modifying therapies that address both the cardiomyopathy and the neurologic manifestations
- AAV-mediated gene replacement therapy aims to safely increase FXN expression in disease-relevant tissues and modify the course of FA
- 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

CBT 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

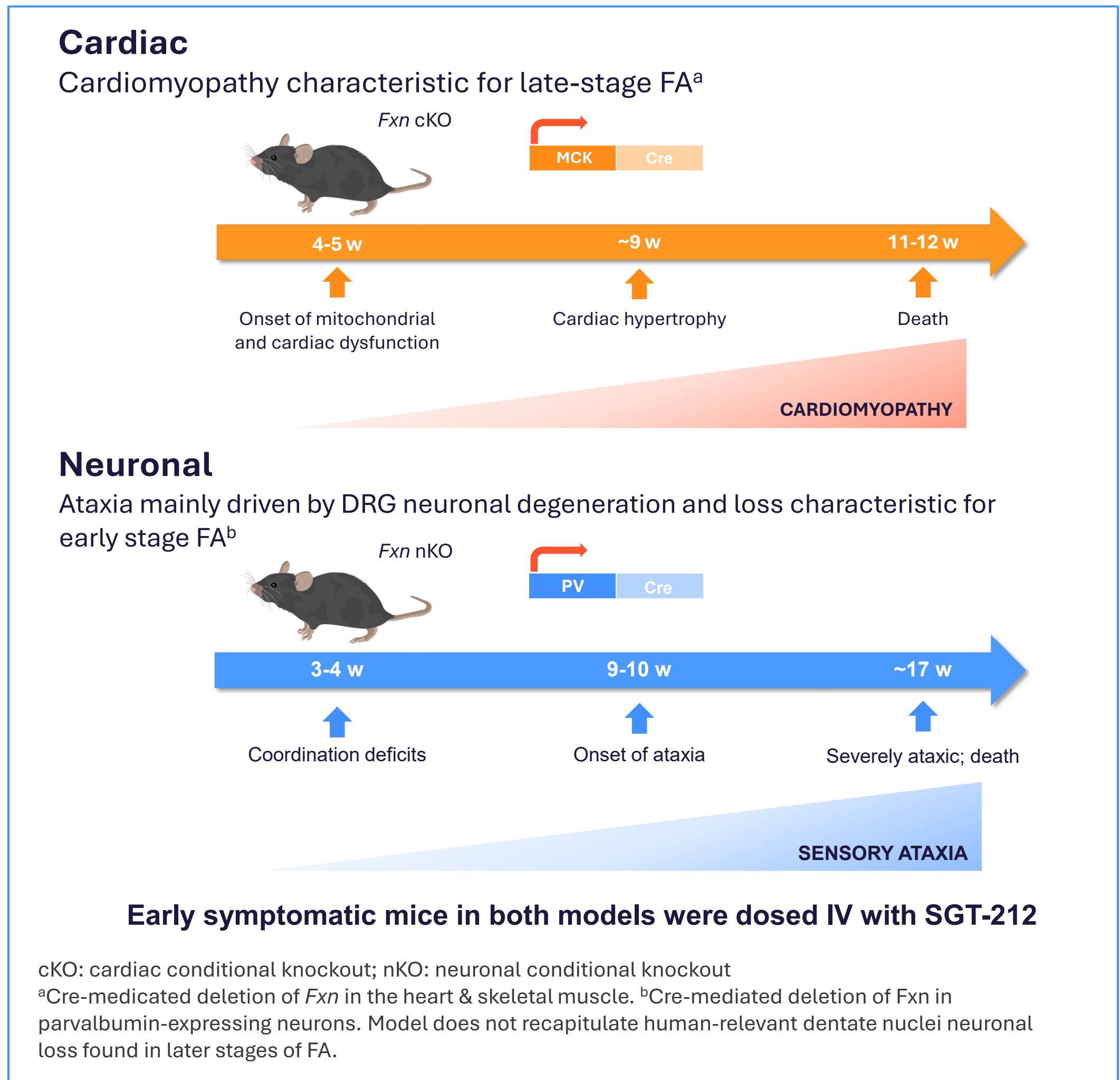
Intravenous Administration

- 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.
^aAdministration simplified for illustrative purposes. Actual SGT-212 IDN administration will use FDA-approved, MRI-guided delivery system⁴.

METHODS

Nonclinical Models of FA



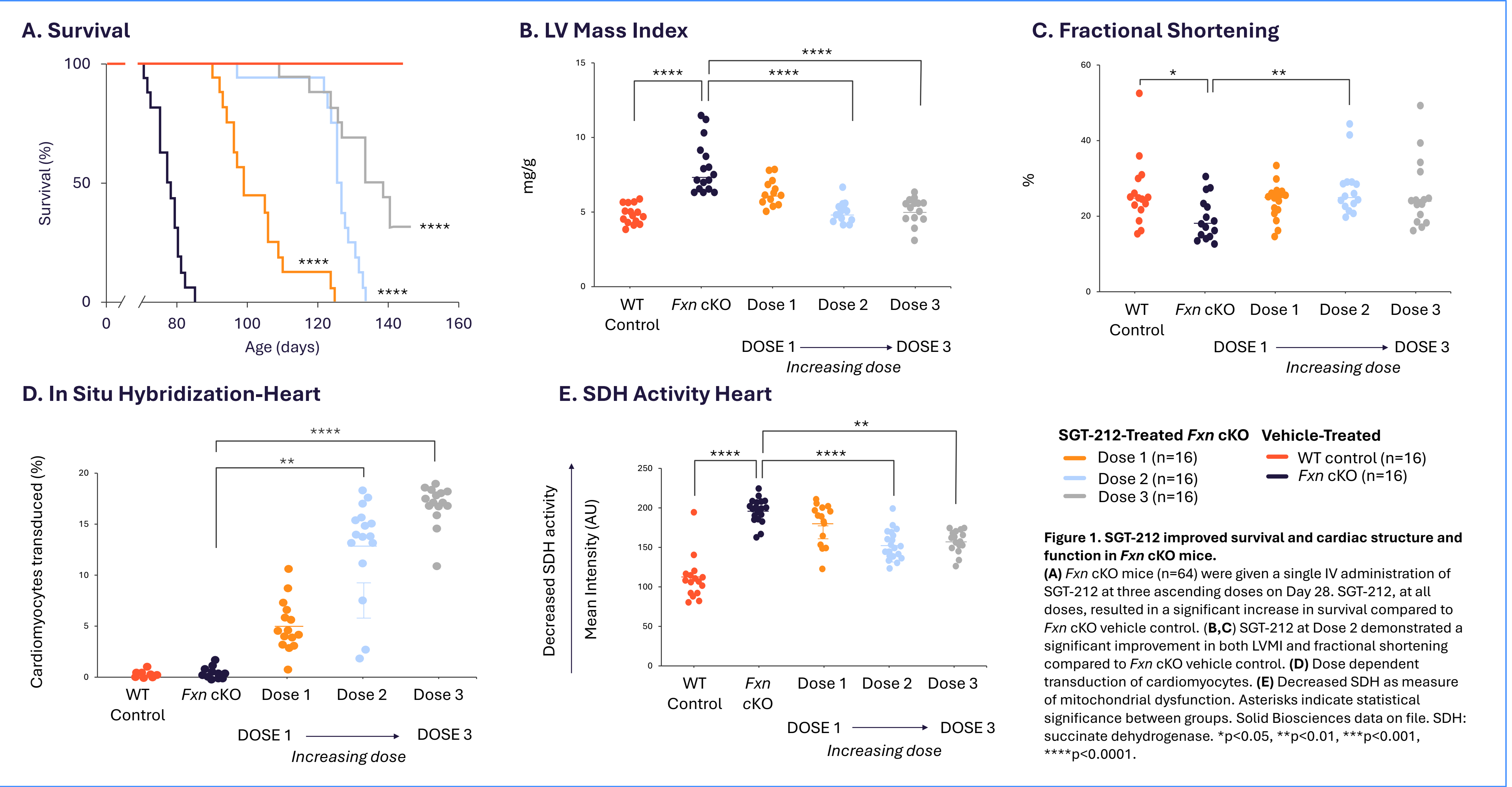
NHP GLP Tox

- 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

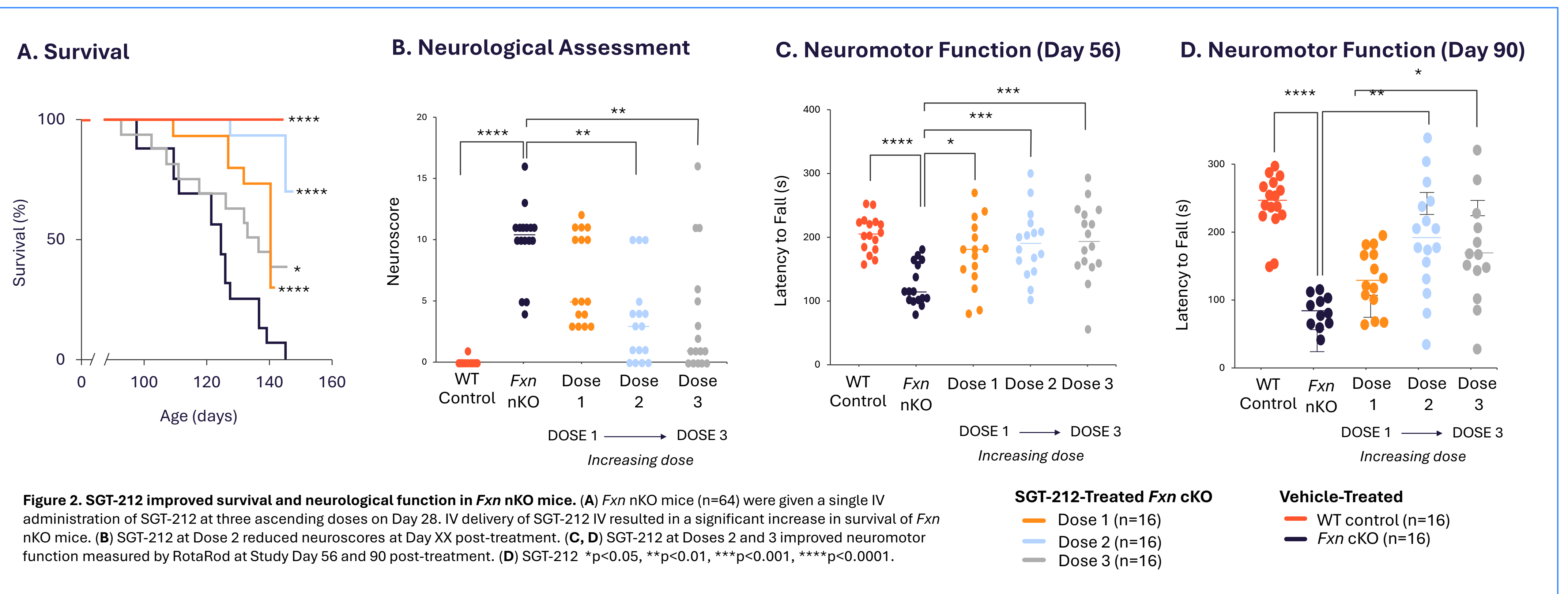
Survival and cardiac outcomes in the cardiac knockout mouse model (cKO)

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



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

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



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

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)

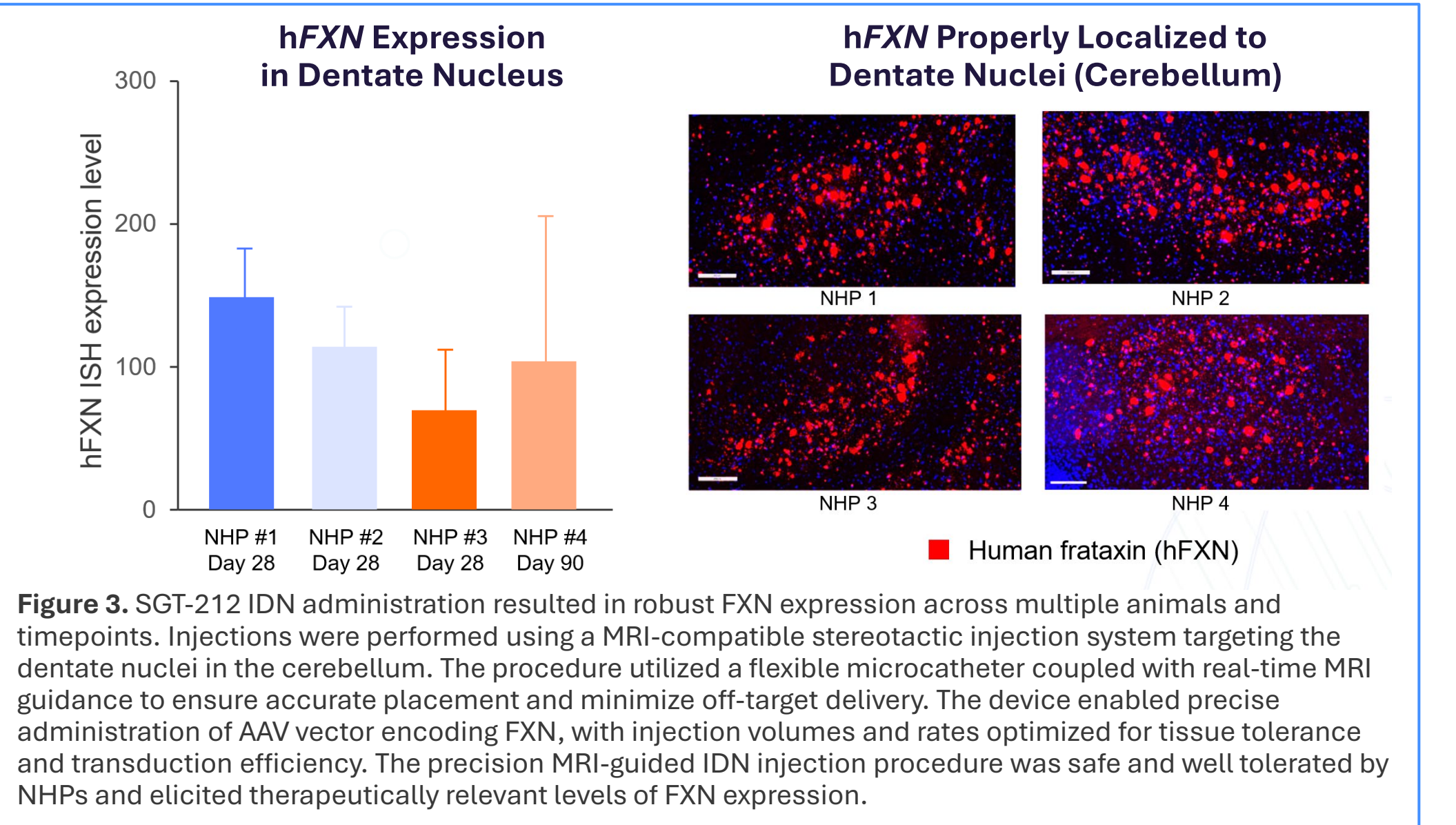
SGT-212 NHP Tox Study Findings

- 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: intravenous; NHP: nonhuman primate.

Transgene expression in dentate nucleus of NHPs

Figure 3. SGT-212 IDN administration resulted in hFXN expression in the dentate nucleus in multiple animals



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.
- Collectively, the nonclinical data package supports advancement to clinical evaluation in the first-in-human Phase 1b FALCON trial (NCT07180355), in which three participants had received SGT-212 via dual-route administration as of August 2026, and enrollment in the FALCON study is ongoing.

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

These studies were sponsored by Solid Biosciences Inc. (Charlestown, MA, USA).