Preclinical Development of ST-503: an Investigational Adeno-associated Viral Vector-Delivered Zinc Finger Repressor Novel Epigenetic Therapy for Idiopathic Small Fiber Neuropathy

Mohammad Samie, Toufan Parman, Mihika Jalan, Jisoo Lee, Patrick Dunn, Jason Eshleman, Yonghua Pan, Marina Falaleeva, Kenneth Kennard, Madelena Nguyen, Sarah Hinkley, Tammy Chen, Sumita Bhardwaj, Michael Trias, Anthony Chikere, Madhura Som, Yanmei Lu, Sandeep Yadav, Bryan Zeitler, Kathleen Meyer

Sangamo Therapeutics, Inc., Brisbane, CA, USA

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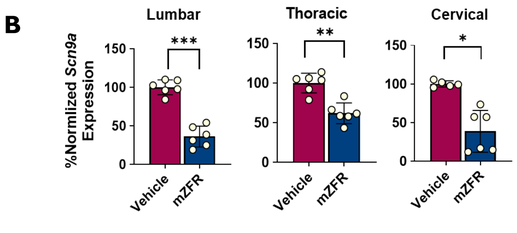
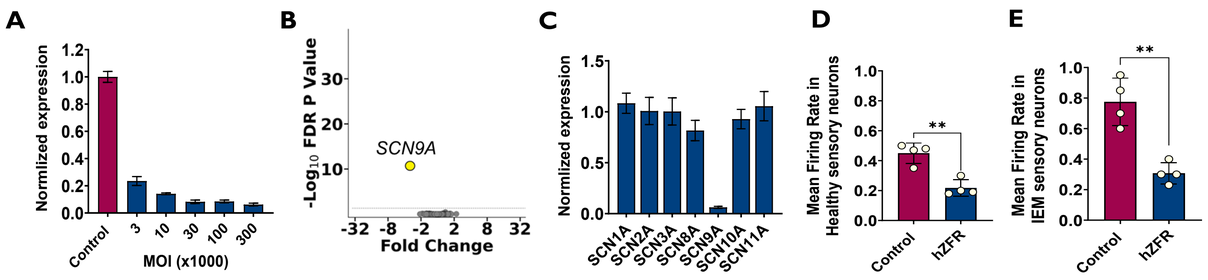
Introduction

- Peripheral neuropathies are estimated to affect several million patients worldwide with no long-lasting therapy currently available.
- In humans, the Nav1.7 sodium channel, encoded by the *SCN9A* gene, is involved in a spectrum of inherited neuropathies, and has emerged as a promising target for analgesic drug development.
- The development of a selective Nav1.7 inhibitor has historically been challenging, in part due to structural similarities among other Nav channels.
- Here we present preclinical studies for the first genomic medicine approach using an engineered zinc finger repressors (ZFRs) specifically targeting the human/nonhuman primate (NHP) *SCN9A* gene.
- Zinc finger (ZFs) are naturally occurring transcription factor proteins that have primarily evolved to regulate eukaryotic gene expression epigenetically and represent the most abundant and diverse class of DNA binding proteins in the human genome.
- The zinc finger array mediates site-specific binding to the *SCN9A* gene, and the KRAB domain represses the endogenous expression of *SCN9A* transcript, leading to a reduction in Nav1.7 protein.



SCN9A-targeting hZFR specifically reduces human *SCN9A* mRNA levels and Nav1.7 function in iPSC derived neurons without repressing the expression of other Nav channels *in vitro*

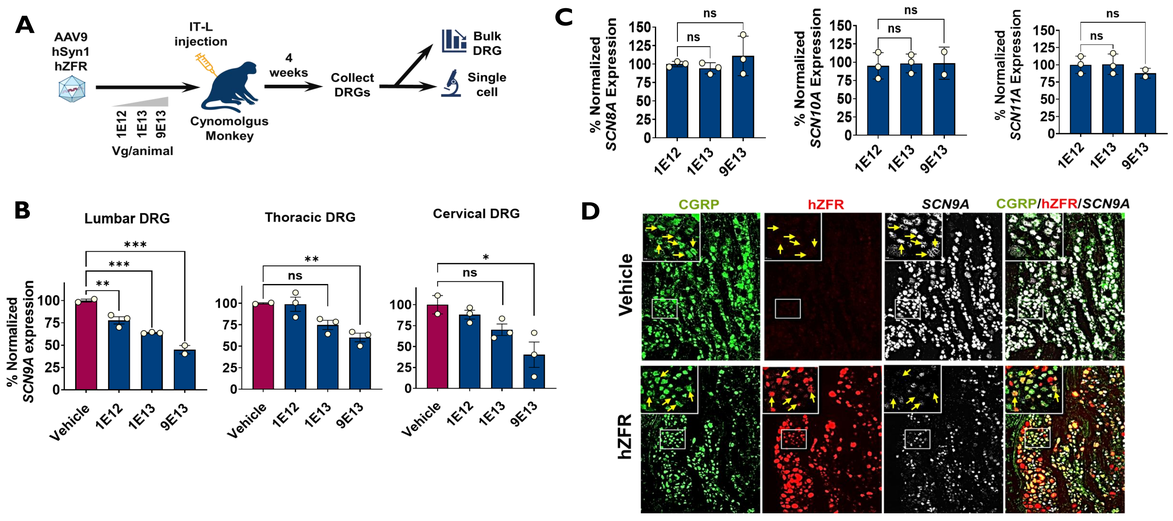


(**A**) Significant reduction of *SCN9A* transcriptional levels in a dose-dependent manner in iPSC-derived GABAergic neurons (**B**) mRNA microarray assessment (volcano plots) of iPSC-derived GABAergic neurons 30 days post-transduction, illustrating that *SCN9A* was the only significantly regulated gene (**C**) hZFR only represses *SCN9A* and no other Nav channels are affected in iPSC-derived sensory neurons (**D & E**) Heat induced neuronal mean firing rate was reduced about 60% in iPSC derived sensory neurons isolated from healthy individuals or patients with inheritance erythromelalgia (IEM) following hZFR treatment. Each circle represents an independent reading from 500 neurons.

In vivo repression of mouse *Scn9A* reverses pain hypersensitivity in a mouse model of neuropathic pain without altering mice overall activity

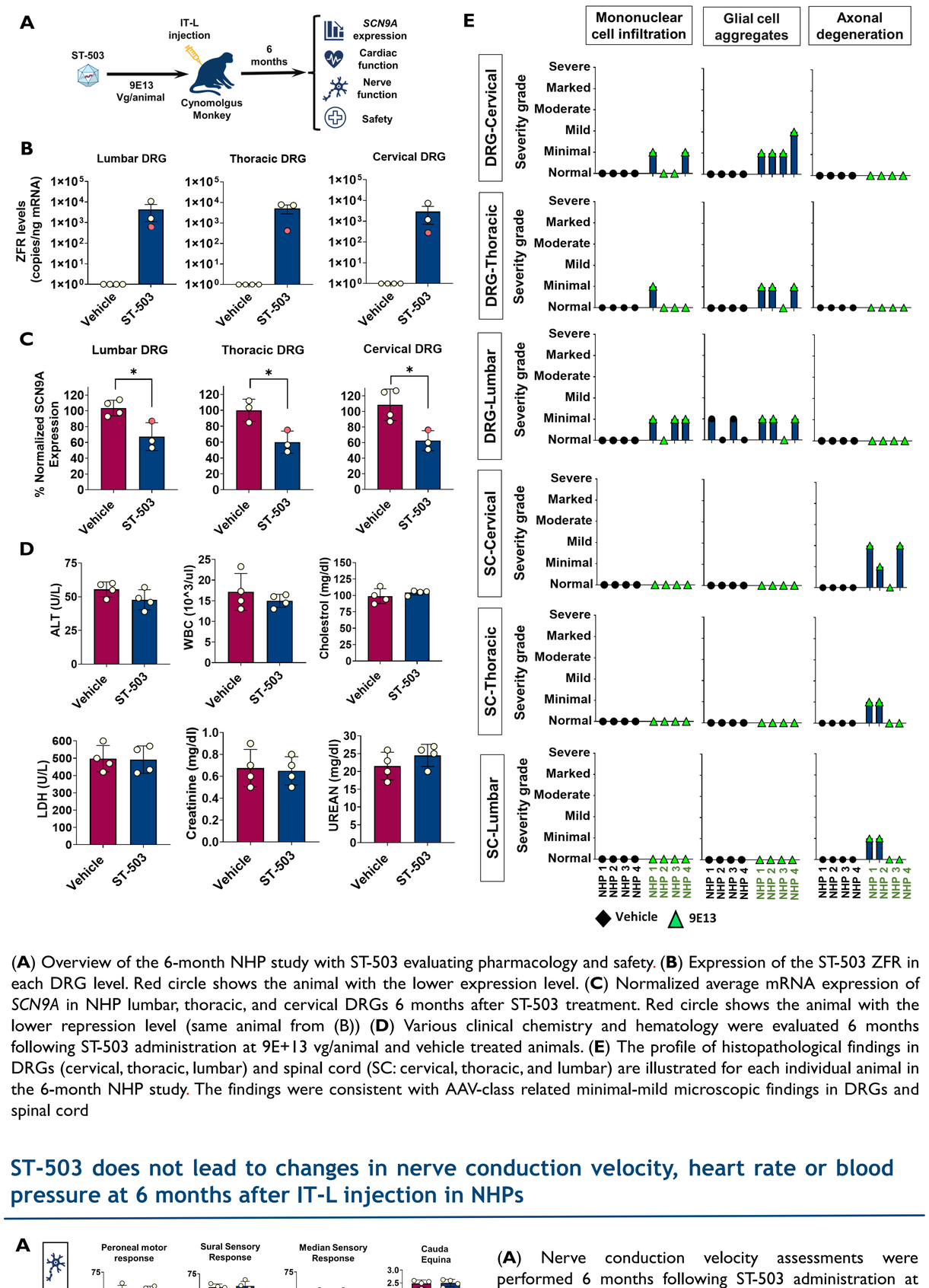
(A) Overview and timeline of the pain efficacy study using the spared nerve injury (SNI) mouse model. (**B**) Normalized average mRNA expression of *Scn9a* in mouse lumbar dorsal root ganglions (DRGs). **(C)** Single-cell analysis illustrating the reduction of *Scn9a* mRNA in AAV9-mZFR expressing nociceptors. (**D**) Mechanical induced pain responses were measured at Day -7 (healthy mice) and then at Day 1 (7 days post SNI surgery). Twenty-eight (28) days after AAV9-mZFR intrathecal-lumbar (IT-L) injection, treated animals exhibited a significantly higher pain threshold compared to the vehicle group and at a comparable level to the sham group. GBP: Gabapentin (**E**) Degree of behavioral recovery was calculated for mechanical induced pain. (**F**) Daily pain responses for mechanical induced pain following AAV9-mZFR treatment.

Dose-dependent repression of *SCN9A* in multiple DRG levels one month after IT-L administration in NHPs



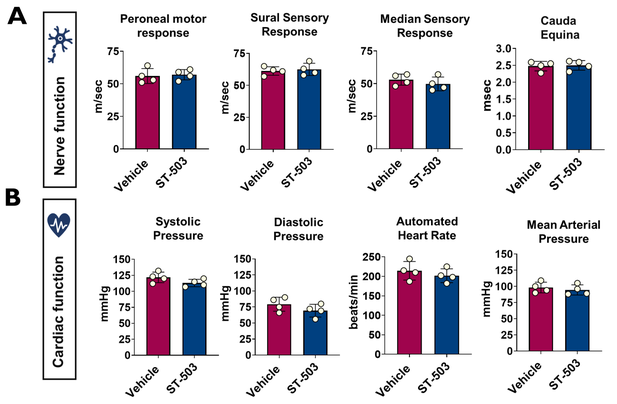
A) Overview and timeline of the 1-month NHP study evaluating potency and safety of hZFR. **(B)** Normalized average mRNA expression of *SCN9A* in NHP lumbar, thoracic, and cervical DRGs. **(C)** Normalized average mRNA expression of *SCN8A* (Nav1.6), *SNC10A* (Nav1.8), and *SCN11A* (Nav1.9) in Lumbar DRG following hZFR treatment **(D)** Single-cell analysis illustrating the reduction of *Scn9a* mRNA in AAV9-hZFR expressing nociceptors.

ST-503 IT-L administration shows persistent and significant repression of *SCN9A* in DRGs 6 months following treatment, with no related clinical chemistry/hematology changes, and AAV-class related microscopic findings in DRGs and spinal cord



(**A**) Overview of the 6-month NHP study with ST-503 evaluating pharmacology and safety. (**B**) Expression of the ST-503 ZFR in each DRG level. Red circle shows the animal with the lower expression level. (**C**) Normalized average mRNA expression of *SCN9A* in NHP lumbar, thoracic, and cervical DRGs 6 months after ST-503 treatment. Red circle shows the animal with the lower repression level (same animal from (B)) (**D**) Various clinical chemistry and hematology were evaluated 6 months following ST-503 administration at 9E+13 vg/animal and vehicle treated animals. (**E**) The profile of histopathological findings in DRGs (cervical, thoracic, lumbar) and spinal cord (SC: cervical, thoracic, and lumbar) are illustrated for each individual animal in the 6-month NHP study. The findings were consistent with AAV-class related minimal-mild microscopic findings in DRGs and spinal cord

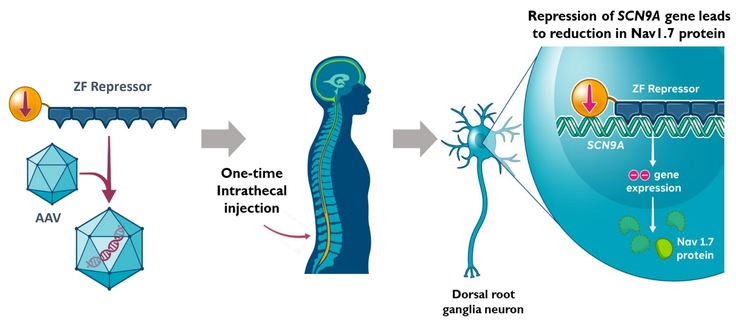
ST-503 does not lead to changes in nerve conduction velocity, heart rate or blood pressure at 6 months after IT-L injection in NHPs



(**A**) Nerve conduction velocity assessments were performed 6 months following ST-503 administration at 9E+13 vg/animal. Peroneal motor nerve responses, sural sensory nerve responses, median sensory nerve responses, and the cauda equina responses were measured and no significant difference was observed between vehicle or ST-503 dosed animals. (**B**) Cardiac function was evaluated by measuring blood pressure and heart rate 6 months after ST-503 administration. No significant difference was observed between ST-503 and vehicle dosed animals. Dots represent individual animals Mean ± SEM.

Conclusions

The potency and selectivity of ST-503 in preclinical studies supported its development as a one-time treatment for intractable and chronic neuropathic pain



- ST-503 is being evaluated in the Phase 1 /2 STAND study.
- The first clinical site has been initiated.
- Anticipating first patient dosing in the fall of 2025.

- hZFR potently and selectively repressed *SCN9A* and Nav1.7 function in human iPSC-derived neurons.
- AAV9 mediated delivery of an *Scn9a*-targeted ZFR rescued the pain hypersensitivity in mouse neuropathic pain model.
- AAV9 mediated delivery of hZFR in NHPs provided a potent, selective, and durable repression of *SCN9A* up to 6 months in NHP DRGs.
- ST-503 investigational product was well tolerated with no dose-limiting effects.
- ST-503 did not induce changes in nerve conduction velocity, heart rate or blood pressure at 6 months after IT-L administration to NHPs.

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