ST-503 nonclinical safety studies evaluating zinc finger repressors regulating expression of the Nav1.7 gene for treatment of small fiber neuropathy

Kathleen Meyer, Toufan Parman, Kenneth Kennard, Marina Falaleeva, Annemarie Ledeboer, Carolyn Gasper, Yonghua Pan, Jing Hu, Madalena Nguyen, Veronica Bonazza, Liching Cao, Yanmei Lu and Mohammad Samie

Sangamo THERAPEUTICS

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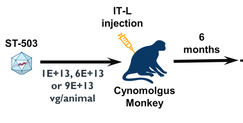
Introduction

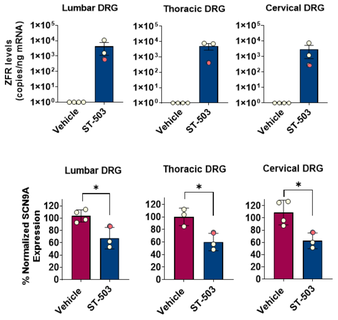
ST-503 is an investigational AAV9 gene therapy, encoding an engineered zinc finger repressor (ZFR) targeting the *SCN9A* gene for treatment of small fiber neuropathy. *SCN9A* codes for Nav1.7, a voltage gated sodium channel, which is involved in various inherited pain-related disorders and has emerged as a promising target for central neuropathic pain therapies. The expression of the ZFR is under the control of a neuron-specific promoter. The objective of this novel therapy is to target the dorsal root ganglion nociceptive neurons, express the ZFR, which will selectively bind and repress *SCN9A* gene expression, and then ultimately reduce production of Nav1.7 sodium channels and diminish perception of neuropathic pain. To support ST-503 clinical development, two key GLP studies are reported here including a 6-month pharmacology and toxicology study in nonhuman primates (NHP) and a developmental and reproductive toxicology (DART) study in mice. Assessments for AAV integration and germline transmission risk were included in the DART study. These studies were part of the nonclinical program supporting the First-in-Human (FiH) clinical study.

No ST-503 dose-limiting toxicity in GLP 6-month safety study in NHPs

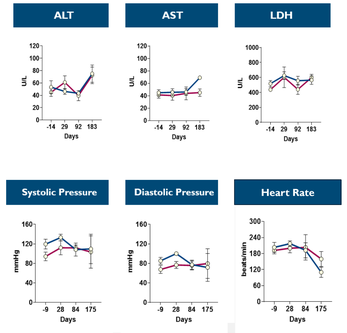
- ST-503 was administered as a one-time intrathecal (IT) injection at dose levels of 1E+13, 6E+13 and 9E+13 vg/animal to cynomolgus monkeys.
- Pharmacology assessments at 6 months (bulk ZFR and *SCN9A* mRNA in dorsal root ganglia (DRG)) and trigeminal ganglia showed intended targeted *SCN9A* gene repression.
- Safety assessment at 6 months showed no ST-503-related adverse effects on parameters: clinical observations, food consumption, body weights, clinical pathology (including liver enzymes), coagulation, neurological exams, ECG, heart rate and blood pressure measurements, nerve conduction velocity, macroscopic pathology or microscopic pathology of peripheral tissues. Histopathological findings consistent with AAV class effects in DRGs, spinal cord and/or trigeminal ganglia (TG) (including minimal to mild mononuclear infiltrates, glial cell aggregates, axonal degeneration; minimal neuronal degeneration in DRG) were not considered dose-limiting for the FiH study.



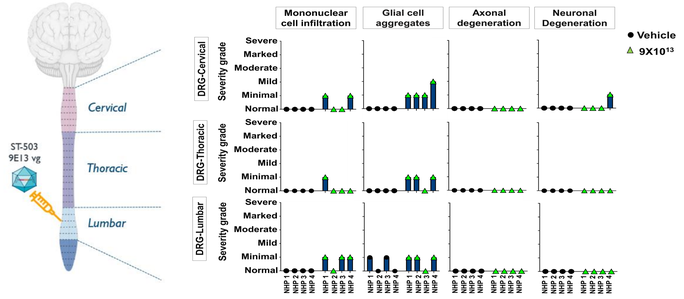
ST-503 ZFR expression and subsequent SCN9A repression in bulk DRG tissue following IT administration of ST-503 at 9E+13 vg/animal at different DRG levels



ST-503 safety profile supported initiation of FiH study in subjects with neuropathic pain. No adverse findings in liver enzyme panel, heart rate, blood pressure 6 months following ST-503 at 9E+13 vg/kg to NHPs.

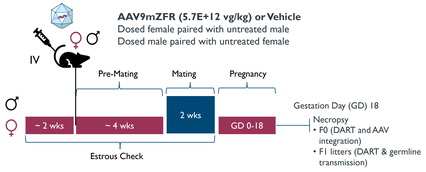


AAV class related minimal to mild histopathology results at 6 months following IT administration of ST-503 (no adverse findings in brain or other peripheral tissues). Data from high dose group presented below.



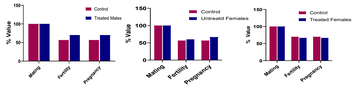
No AAV9mZFR-related adverse findings in GLP fertility and embryo-fetal development study in mice

- Maximum intended AAV9 clinical intrathecal dose was intravenously administered to male and female C57BL/6 mice 4 weeks prior to mating with untreated animals.
- Mouse surrogate ZFRs (AAV9mZFR) were designed to target the mouse *Scn9a* gene due to lack of target sequence homology between mouse and human genes coding for Nav1.7.

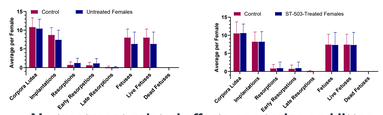


- Standard developmental and reproductive toxicology assessments conducted for parental animals and fetal offspring.
- Germline transmission risk assessment conducted on fetal liver DNA of offspring.
- AAV integration site analysis of maternal liver DNA conducted using Targeted Enrichment Sequencing (TES).

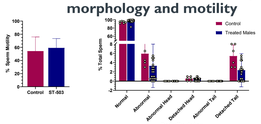
No treatment-related effects on fertility indices*



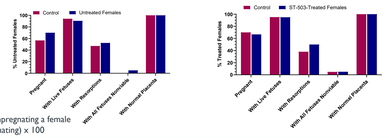
No treatment-related effects on placenta and fetal viability



No treatment-related effects on sperm morphology and motility

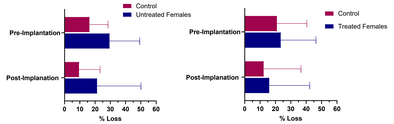


No treatment-related effects on uterine and litter observations



*Mating Index = (# males with evidence of mating / # males paired) x 100; Fertility Index = (# males impregnating a female / #males paired) x 100; Pregnancy Index = (# males impregnating a female / # males with evidence of mating) x 100

No treatment effects on F0 implantation loss



No treatment effects observed

- Clinical observations, body weights, gravid uterine weights, macroscopic pathology and ovarian and uterine examinations
- Male and female reproductive performance
- Sperm evaluations
- Fetal morphological data
- Fetal external, visceral and skeletal examinations

No evidence for AAV germline transmission to offspring

Group Number	F0 Female Treatment	F0 Male Treatment	Necropsy (Day)	Tissue Type	No. of Animals	Mean Copies/µg gDNA
1	Vehicle	Untreated	GD 18	Liver	74	BLOQ
1	Untreated	Vehicle	GD 18	Liver	59	BLOQ
2	AAV9.m95676	Untreated	GD 18	Liver	64	BLOQ
2	Untreated	AAV9.m95676	GD 18	Liver	65	BLOQ

BLOQ - below the level of quantification

AAV9 mZFR integration profile raises no concern for liver tumor risk

- Total of 3,144 unique and mappable integration sites (IS) detected in ~29 million sequencing reads.
- Estimated average frequency of 1.30 ± 0.17 IS/1000 cells.
- IS analysis shows low levels of vector integration, a polyclonal integration profile, no evidence of clonal expansion, no strong association with cancer-associated genes and supports a very low risk of hepatocellular carcinoma.

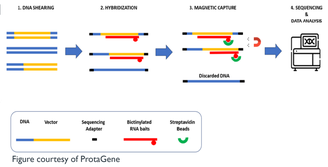


Figure courtesy of ProtaGene

Summary and conclusions

- 6-month GLP study in NHPs showed anticipated targeted repression of *SCN9A* in DRGs and trigeminal ganglia (up to 60% bulk tissue repression) and was well tolerated with no dose-limiting toxicological findings.
  - Supported dose selection for the FiH study in patients with small fiber neuropathy.
- A single IV dose of AAV9 mouse surrogate ZFR at 5.71×10^{12} vg/kg showed no test article-related adverse effects on fertility or embryo-fetal development parameters, and there was no evidence of AAV germline transmission to offspring.
  - Based on these results, ZFR-mediated repression of Nav1.7 is not expected to pose a fertility, reproductive, or vertical transmission risk to women of childbearing potential or men.
- AAV9 integration profile in liver tissue does not raise concern for risk of liver tumor formation given that there was no integration detected into the *Rian* locus, no expanded clones detected in the vicinity of cancer-associated genes, and the overall random integration pattern.
- These studies were part of the nonclinical safety evaluation program supporting ST-503 clinical development.

References

Engineered zinc finger repressors induce a prolonged and selective repression of *SCN9A* in nociceptors of nonhuman primates. Samie et al, 2026, Science Translational Medicine 2026 Mar 25;18(842):eadu0217;1-18.

Acknowledgments

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