A combined fertility, embryofetal development, AAV integration and germline transmission risk study in mice with ST-920 (isaralgagene civaparvovec) for Fabry disease

No ST-920-related implantation loss

Poster #252

Kathleen Meyer, Annemarie Ledeboer, Kenneth Kennard, Liching Cao, Marina Falaleeva, Carolyn Gasper, Madelena Nguyen, Toufan Parman, and Yanmei Lu

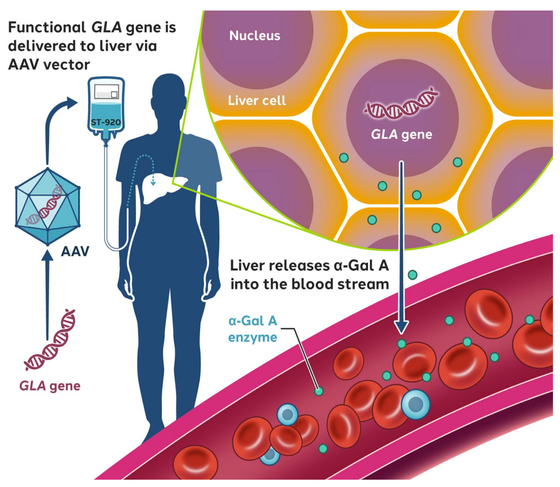
Sangamo Therapeutics, Inc.

Introduction

- Isaralgagene civaparvovec (ST-920) is an investigational gene therapy using a recombinant adeno-associated serotype 6 (AAV6) vector containing a human *GLA* cDNA designed to produce continuous, liver-specific α-Gal-A expression for patients with Fabry disease
- Fabry disease is a progressive, multi-organ, lysosomal storage disease caused by pathogenic mutations in the GLA gene leading to deficiency of the lysosomal enzyme alpha-galactosidase A (α-Gal A) and accumulation of globotriaosylceramide (Gb3) and globotriaosylsphingosine (lyso-Gb3)
- A Good Laboratory Practice (GLP) combined fertility, embryofetal development, AAV integration and germline transmission risk study in mice was conducted with ST-920 to characterize the safety profile and support the ST-920 Biologics License Application

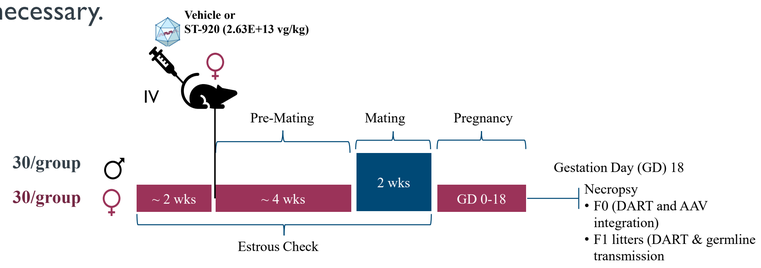
ST-920 Gene Therapy

- Single intravenous (IV) dose
- AAV6 traffics to hepatocytes
- Human *GLA* cDNA delivered to hepatocyte nucleus
- α-Gal A enzyme produced and excreted from hepatocytes into circulation
- α-Gal A uptake by peripheral tissues and into lysosomes
- Enzymatic activity of α-Gal A in lysosomes to break down toxic substrates Gb3 and lyso-Gb3



Study Design

Vehicle control or ST-920 was IV administered at 2.63 x 10^{13} vg/kg (clinical dose) (200 µL) to-C57BL/6 female mice (n= 30/group) 4 weeks prior to mating and followed up to necropsy on Gestation Day 18. As vector copies were not detected in mouse semen (previous toxicology studies), no DART or germline transmission assessment of male mice was deemed necessary.



Developmental and Reproductive Toxicology (DART) assessments

- Parental (F0) in-life evaluations included clinical observations, body weights, estrous cycle parameters
- F0 terminal evaluations included necropsy, organ weights (ovaries), vector distribution (ovaries)
- Fertility assessments included number of corpora lutea, number of pre- and post-implantation losses, live/dead fetus counts, early/late resorption counts
- Fetal (F1) evaluations included fetal weight, sex ratio, external, visceral and skeletal examinations

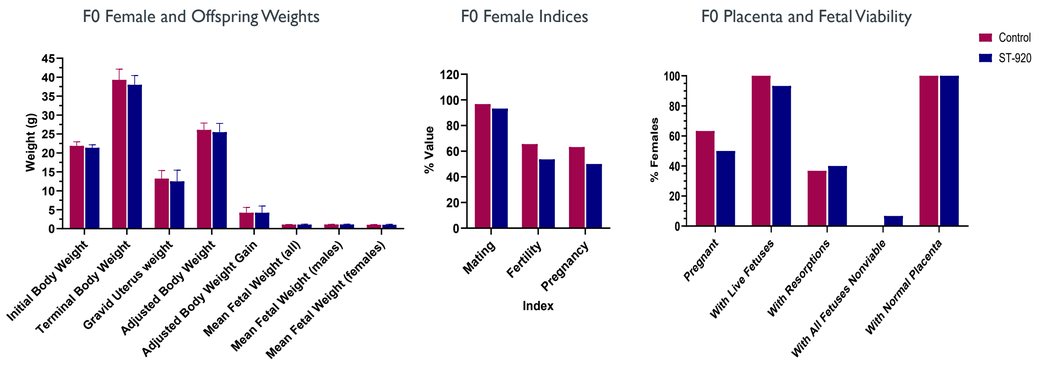
AAV integration site analysis of maternal liver DNA

- Target enrichment sequencing (TES) and next generation sequencing (NGS)
- Assessment of liver samples from first 4 control and first 6 treated animals

Germline transmission risk assessment

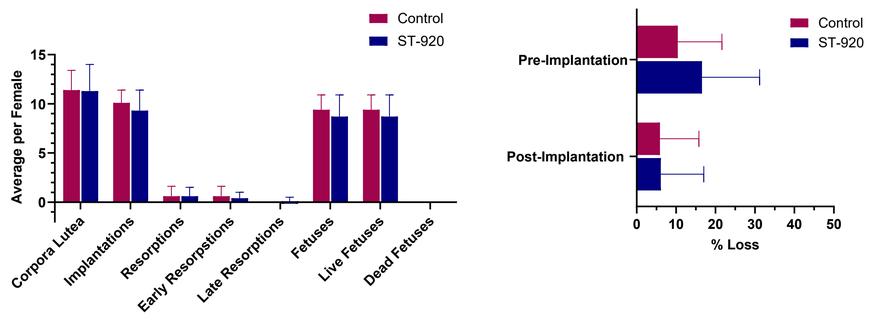
- Vector genome copy assessment in F1 fetal liver (qPCR)
- F1 offspring liver samples from control (n=83) and ST-920 (n=60) groups assessed

No ST-920-related toxicological findings in DART parameters



Mating Index = (No. females with evidence of mating) / (No. females paired) x 100
Fertility Index = (No. pregnant females / No. females with evidence of mating) x 100
Pregnancy Index – (No. pregnant females / No. females paired) x 100

F0 ovary/uterine and F1 litter observations show no toxicological effects related to ST-920 administration

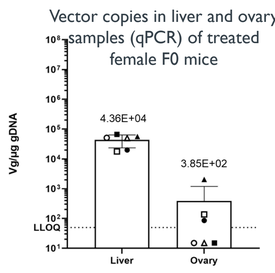


No evidence of ST-920 germline transmission

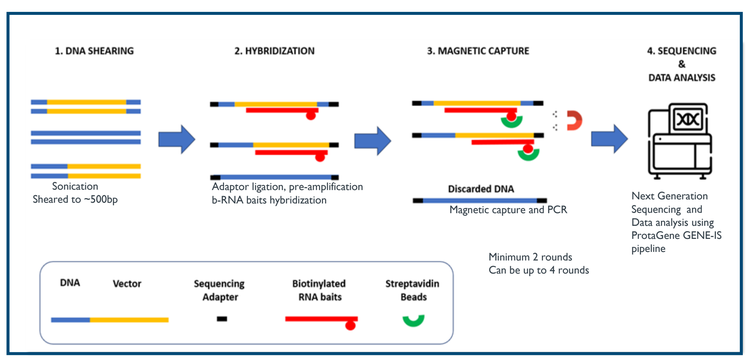
No ST-920 vector copies were detected in liver DNA of offspring (n=60)

Group Number	F0 Female Treatment	F0 Male Treatment	Necropsy (Day)	Tissue Type	Generation	Mean vg (Copies/ µg gDNA)	vg SD	No. of Offspring
1	Vehicle	Naïve	GD 18	Liver	F1	BLOQ	NA	83
2	ST-920	Naïve	GD 18	Liver	F1	BLOQ	NA	60

Samples below the limit of quantitation were reported as BLOQ (<50 copies/µg gDNA)
GD = Gestation Day; kg = kilogram; µg = microgram; vg = vector genome; BLOQ = below limit of quantitation; NA = not applicable).



ST-920 integration profile raises no concerns for risk of liver tumor formation



In total, 5,353,093 and 13,552,387 raw reads were obtained for Batch A and Batch B, respectively

The Target Enrichment Sequencing (TES) method followed by deep sequencing was used to identify ST-920 vector integration sites (IS) in adult mouse liver samples following ST-920 administration.

- All transduced mouse liver samples showed AAV integration with low numbers of retrieved IS and corresponding sequences, reflecting low levels of vector integration into host genome
- Total of 1,056 unique and mappable IS detected in ~19 million sequencing reads
- An average of 0.35 ± 0.14 IS/1000 cell frequency was estimated
- Polyclonal integration profile seen with IS distributed across all chromosomes
- Most integrations were unique, which suggests an absence of common insertion profile, and an absence of clonal expansion
- No IS detected within the *Rian* locus (locus associated with mouse hepatocellular carcinoma development)
- Integration events within a +/- 100 kb region of the transcription start site of cancer-associated genes occurred with an overall low occurrence. The strongest relative contribution was a single IS of 2.23% (4 sequence counts) for *PER1* (nearest gene *Per1*), 750 nt from the transcription start site. Given that the strongest relative contributions from cancer-associated genes corresponded to detection by only four sequence reads, results suggest that clonal expansion was not triggered due to vector integrations near the *PER1* locus.
- Taken together, 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 provided a very low risk of hepatocellular carcinoma

Summary and conclusions

DART assessments

- No adverse findings in fertility, reproductive and embryofetal development parameters in parental mice or offspring

Germline transmission risk assessment

- No evidence of germline transmission of AAV vector from parents to offspring

AAV integration assessment

- Low levels of integration into mouse genome
- Polyclonal integration profile (no signs of clonal outgrowth)
- No expanded clones detected in vicinity of cancer-associated genes
- No integration into cancer-associated *Rian* locus
- Overall, AAV integration profile does not raise concerns about risk of liver tumor formation

ST-920 safety profile supportive of treating broad populations of adult patients

Acknowledgments

We would like to acknowledge our CRO partners Charles River Laboratories (toxicology study) and ProtaGene (AAV integration assessment) who supported this study, and the Fabry patients participating in our STAAR Phase 1/2 clinical study. This study was sponsored by Sangamo Therapeutics.

Presented at 22nd annual WORLD*Symposium*™ in San Diego, CA, February 2-6, 2026