Poster #224

A 3-month gene therapy single-dose IV administration pharmacology and safety study with ST-920 (isaralgagene civaparvovec) for Fabry disease in mice

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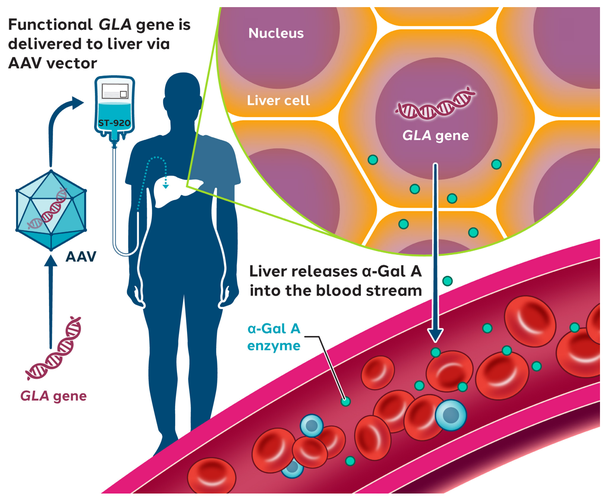
Introduction

- ST-920 (isaralgagene civaparvovec) is a gene therapy for potential treatment of patients with Fabry disease, an X-linked lysosomal storage disease caused by mutations in the *GLA* gene, which encodes the lysosomal enzyme α-galactosidase A (α-Gal A).
- Lack of this enzyme results in progressive, systemic accumulation of its primary substrate, globotriaosylceramide, which can lead to renal, cardiac and/or cerebrovascular disease, with reduced life expectancy.
- ST-920 is a recombinant AAV2/6 vector containing a codon-optimized cDNA encoding α-Gal A, utilizing a liver specific promotor and exhibiting liver tropism thus providing the potential for long-term and stable hepatic production of α-Gal A in Fabry disease subjects.
- A 3-month GLP pharmacology and toxicology study was conducted in mice with ST-920 to support the Phase 1/2 STAAR clinical study for treatment of Fabry disease, with the objective to characterize the pharmacology and safety profile of ST-920 in mice.

ST-920 Gene Therapy

- Single intravenous dose
- AAV6 traffics to hepatocyte
- 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 in lysosomes to break down toxic substrates Gb3 and lyso-GB3



GLP 3-Month Study Design

- ST-920 administered IV via tail vein (200 µL) of wild-type C57BL/6 male and female mice and animals observed for 3 months. Dose groups included vehicle control and ST-920 at $5x10^{13}$ vg/kg and $1.5x10^{14}$ vg/kg.

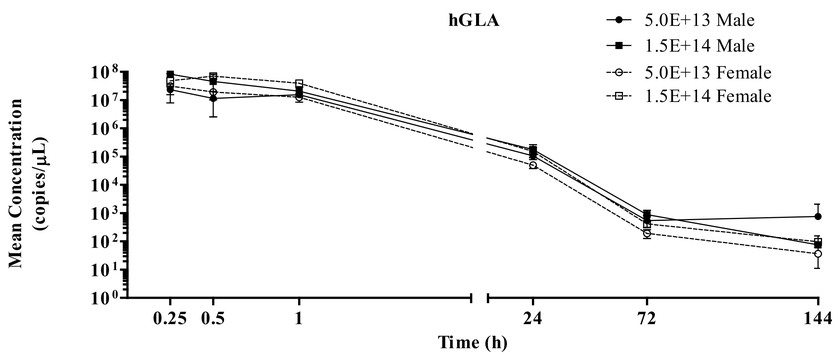
Group No.	Test Material	AAV Dose[a] (vg/mouse)	AAV Dose[a] (vg/kg)	No. of Animals			
				Main Study Cohort		TK/BD Study Cohort	
				Males	Females	Males	Females
1	Vehicle Control	0	0	10	10	5	5
2	ST-920 (Mid dose)	$1.25x10^{12}$	$5.0x10^{13}$	10	10	12	12
3	ST-920 (High dose)	$3.75x10^{12}$	$1.5x10^{14}$	10	10	12	12

AAV = adeno-associated virus; BD = Biodistribution; TK = Toxicokinetics; Conc = concentration
[a]Calculations based on a 25-gram mouse and dose volume 8 mL/kg.

- Pharmacology endpoints: plasma and tissue α-Gal A activity
- Toxicokinetics (TK)/Biodistribution (BD) endpoints: AAV plasma TK, tissue BD (liver, ovaries/testes) and shedding (urine, semen, feces); AAV6 BD from additional tissues leveraged from other AAV6 programs of the department.
- Safety endpoints: clinical observations, body weights, body weight gains, clinical chemistry, hematology, macroscopic and microscopic pathology.

ST-920 Vector Copy Toxicokinetic Profile

Mean (± SD) Concentration of h*GLA* Vector Copies in Plasma of Male and Female Mice Following IV Bolus Administration of ST-920



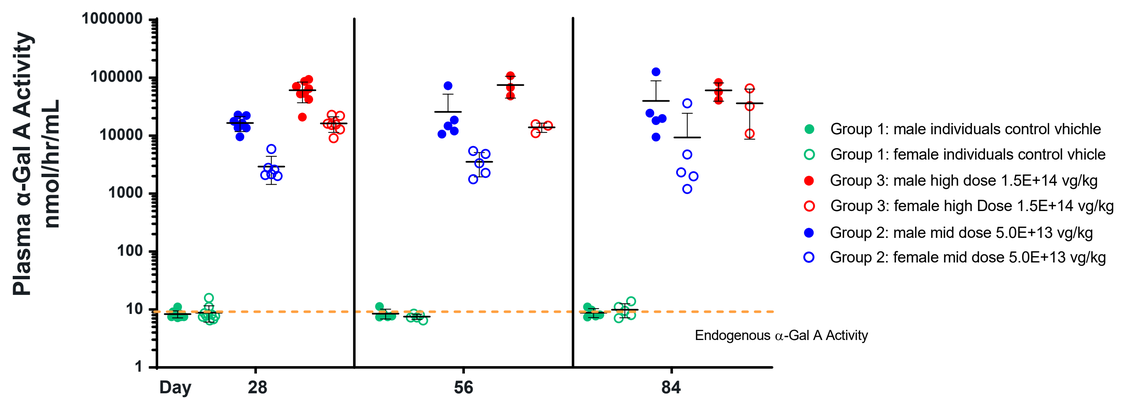
Toxicokinetic Parameters for h*GLA* Vector Copies in Male and Female Mice following IV Bolus Administration of ST-920; Vector Copy Half-Life in Plasma ~ 7 Hours

Dose (vg/kg)	Gender	AUC(0-t) (h*copies/µL)	AUC(0-t)/D	C0 (copies/µL)	Cmax (copies/µL)	Tmax (h)	Tlast (h)	CL (µL/h/kg)	Vd (µL/kg)	$T_{1/2}$ (h)
$5.0x10^{13}$	Male	203,000,000	0.00000406	47,300,000	23,300,000	0.25	144	NR	NR	NR
$1.5x10^{14}$	Male	307,000,000	0.00000205	151,000,000	83,100,000	0.25	144	488,000	5,030,000	7.14
$5.0x10^{13}$	Female	170,000,000	0.00000341	51,500,000	31,300,000	0.25	144	293,000	3,000,000	7.10
$1.5x10^{14}$	Female	510,000,000	0.00000340	47,500,000	70,100,000	0.50	144	294,000	3,110,000	7.34

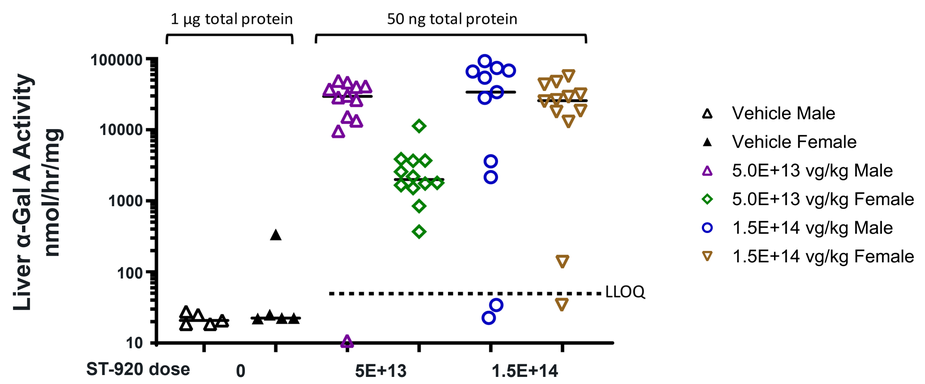
Units for AUC(0-t)/D are (h*copies/µL/[vg/kg]).
NR – Not reportable, due to value not meeting acceptance criteria (AUCextrap > 20% and/or Rsq < 0.8).

Plasma and Liver α-Gal A Activity

Summary of Mean α-Gal A Activity in Plasma
After Removal of Outlier Data Points



Summary of Mean α-Gal A Activity in Liver
After Removal of Outlier Data Points



- Supraphysiological levels of plasma α-Gal A activity (up to ~4,100-fold in male and ~2,200-fold in female mice compared to vehicle control groups) were observed in high-dose animals at 3 months.
- Supraphysiological levels of liver α-Gal A activity (up to ~1,800-fold in male and ~1,300-fold in female mice compared to vehicle control groups) were observed in high-dose animals at 3 months.

Biodistribution & Shedding

- Highest average AAV6 vector copy levels were detected in liver; levels detected in ovaries/testes were 1000-1000-fold lower than liver.
- Majority of vector shedding samples (urine, semen, feces) had no measurable levels of ST-920 vector copies, except 5 fecal samples collected prior to Day 29 necropsy and no measurable levels in fecal samples collected prior to Day 92 necropsy.

Safety Assessment

- There was no test article-related mortality or effects on clinical observations, body weight, urinalysis, serum chemistry, hematology, organ weights, or gross and histopathologic examinations.
- The ST-920 no-observed-adverse-effect level (NOAEL) was considered to be ≥ $1.5x10^{14}$ vg/kg, the highest dose tested.

Summary & Conclusions

- A single IV administration of ST-920 to C57BL/6 mice at dose levels of $5.0x10^{13}$, and $1.5x10^{14}$ vg/kg was well tolerated at all doses and did not result in adverse findings.
- The ST-920 vector construct exposure was similar between males and females and increased in an approximately dose-proportional manner. ST-920 vector half-life in plasma was approximately 7 hours.
- Plasma and liver α-Gal A activity levels showed supraphysiological levels in ST-920-treated animals, and females had lower levels of liver and plasma α-Gal A activity than male animals.
- Average ST-920 vector copy concentrations were similar in females and males excluding liver and spleen, which generally showed higher ST-920 concentration in males than females.
- At 3 months, high-dose groups showed supraphysiological levels of plasma α-Gal A activity (up to ~4,100-fold in male and ~2,200-fold in female mice compared to vehicle control groups); and supraphysiological levels of liver α-Gal A activity (up to ~1,800-fold in male and ~1,300-fold in female mice compared to vehicle control groups).
- There was no test article-related mortality or effects on clinical observations, body weight, urinalysis, serum chemistry, hematology, organ weights, or gross and histopathologic examinations.
- The ST-920 no-observed-adverse-effect level (NOAEL) was considered to be ≥ $1.5x10^{14}$ vg/kg, the highest dose tested, which supported initiation of the Phase 1/2 STAAR study in patients with Fabry disease.

Acknowledgments

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