Investigator's Brochure
Product: ST-920
Indication: Fabry disease

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Second Edition	13 February 2019

Confidentiality Statement

This document contains confidential information. It is intended solely for the use of the principal investigator, co-investigators, staff, appropriate institutional review boards or ethical committees, and other required regulatory bodies.

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[redacted]

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REVISION HISTORY

Edition	Date	Summary of Changes
1	14 December 2018	Original

LIST OF ABBREVIATIONS

α-Gal A	Alpha galactosidase A
AAV	Adeno-associated viral
AAV2/6 or AAV2/8	Adeno-associated virus 2/6 or 2/8
AFP	Alfa-fetoprotein
ALT	Alanine aminotransferase
ApoE	Apolipoprotein E
AST	Aspartate transaminase
AUC	Area under the curve
BLOQ	Below the limit of quantitation
CHO	Chinese hamster ovary
cDNA	Complementary deoxyribonucleic acid
Cmax	Maximum to serum concentration
CMO	Contract manufacturing organization
EOI	End of infusion
ERT	Enzyme replacement therapy
Gb3	Globotriaosylceramide
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
hAAT	Human α-1-antitrypsin
hGLA	Human alpha-galactosidase A
hr	Hour
IDS	Iduronate-2-sulfatase
iPSC	Induced human pluripotent stem cell
IS	Immunosuppression
ITRs	Inverted terminal repeats
IV	Intravenous
LCMS	Liquid chromatography mass spectrometry

LLOQ	Lower limit of quantitation
Lyso-Gb3	Globotriaosylsphingosine
ITR	Inverted terminal repeats
MOI	Multiplicity of infection
mRNA	Messenger ribonucleic acid
NHP	Non-human primates
nmol	Nanomolar
NOAEL	No-observed-adverse-effect level
PC	Parent construct
PCR	Polymerase chain reaction
PBS	Phosphate-buffered saline
PK	Pharmacokinetic
qPCR	Quantitative real-time PCR
rAAV	Recombinant adeno-associated virus
RT	Reverse transcription
SD	Standard deviation
[redacted]	[redacted]
SP	Signal peptide
T1/2	Time to half life
Tmax	Time to maximum serum concentration
µL	Microliter
vg/kg	Vector genomes per kilogram
[redacted]	[redacted]
[redacted]	[redacted]
ZFN	Zinc finger nuclease

1 SUMMARY

ST-920 is a recombinant AAV2/6 human alpha galactosidase A (α-Gal A) gene therapy for the treatment of subjects with Fabry disease. Fabry disease is a lysosomal storage disease caused by mutations in the *GLA* gene, which encodes the enzyme α-Gal A. Lack of α-Gal A activity results in the progressive, systemic accumulation of its primary substrate Gb3 and its soluble form lyso-Gb3, which leads to renal, cardiac or cerebrovascular disease, with reduced life expectancy.

ST-920 works by enabling long-term liver-specific expression of therapeutic levels of α-Gal A. ST-920 is packaged with a non-replicating rAAV2/6 vector which effectively transduces liver hepatocytes due to the virus tropism of AAV6 [redacted] ST-920 gene therapy is expected to result in the episomal expression of a corrective copy of the hGLA transgene in the subject's own hepatocytes *in vivo* and in sustained secretion of α-Gal A into circulation.

The pharmacologic activity of ST-920 was demonstrated *in vitro* in three studies using various liver cell systems from mouse, cynomolgus monkey and human origins. Nine *in vivo* pharmacology studies were conducted [redacted] Overall, the studies [redacted] demonstrated the feasibility of producing sustained high levels of pharmacologically active α-Gal A after treatment with ST-920.

Nine *in vivo* studies conducted [redacted] included various gene therapy-related pharmacokinetics evaluations. [redacted]

[redacted] The liver tropism shown in these data mirrors that found in the literature (Favaro et al., 2011; Nathwani et al., 2002, 2006, 2011; Jiang et al., 2006, Zincarelli et al., 2008; Stone et al., 2008) and supports the extrapolation that ST-920 will have the same liver tropism.

[redacted]

[redacted]

[redacted] ST-920 IV administration at a dose of 5.00E+12 vg/kg should be an acceptable starting dose to optimize the risk benefit in subjects with the potential of therapeutic benefit given that ST-920 is a one-time infusion due to resulting immune response against the AAV6 vector.

2 INTRODUCTION

Fabry disease is a X-linked lysosomal storage disease caused by mutations in the *GLA* gene, which encodes the lysosomal enzyme alpha galactosidase A (α-Gal A). Lack of α-Gal A activity results in the progressive, systemic accumulation of its primary substrate, globotriaosylceramide (Gb3) and its soluble form globotriaosylsphingosine (lyso-Gb3). Long-term accumulation of these substrates leads to renal, cardiac, or cerebrovascular disease and reduced life expectancy. Depending on the mutation and residual α-Gal A enzyme level, the disease presents as classical early-onset Fabry in childhood/adolescence or as an attenuated (adult) form later in life. Classical Fabry disease occurs when residual enzyme activity is <1% (Arends et al. 2017) and typically occurs in males. Early symptoms may include periodic acroparesthesia, angiokeratomas, corneal and lenticular opacities, progressive renal insufficiency, cardiac disease, and cerebrovascular events. The attenuated or adult form of Fabry disease commonly involves only one organ system, usually cardiac or renal.

In both classic and adult forms, the current standard of care is enzyme replacement therapy (ERT) using recombinant α-Gal A. Infusion of recombinant α-Gal A into the bloodstream allows transfer to secondary tissues via mannose-6-phosphate receptor-mediated uptake (cross-correction). However, the short half-life of the recombinant α-Gal A (approximately 1 hour in plasma) used in ERT necessitates a lifetime of infusions every two weeks, with associated risk of infusion-related reactions. A significant percentage of patients eventually generate antibodies to the recombinant enzyme, and ERT may not clear all substrate from organs such as the kidneys. Recombinant α-Gal A products with longer half-lives are being developed emphasizing the need for alternative therapies.

Adeno-associated viral (AAV) vectors have shown great promise in both preclinical and clinical trials to efficiently deliver therapeutic transgenes to the liver, with reports of stable levels of transgene expression out to six years for hemophilia B (Lheriteau et al., 2015). The goal of ST-920 is to provide stable, long-term production of α-Gal A at therapeutic levels in subjects with Fabry disease. The constant production of α-Gal A in humans should, importantly, enable reduction and potentially clearance of Fabry disease substrates Gb3 and lyso-Gb3.

The investigational product, ST-920, is a recombinant AAV2/6 vector encoding the cDNA for human α-Gal A (ST-920). [redacted] he ST-920 vector encodes a liver-specific promotor, and AAV2/6 exhibits liver tropism thus providing the potential for long-term hepatic production of α-Gal A in Fabry subjects. Studies in a Fabry mouse model injected with AAV2/6 encoding human α-Gal A (hGLA) cDNA show generation of therapeutic levels of α-Gal A. This constant production of α-Gal A could provide potential benefit for improved clearance of Fabry substrates Gb3 and lyso-Gb3.

3 PHYSICAL, CHEMICAL AND PHARMACEUTICAL PROPERTIES AND FORMULATION

3.1 Product Description

Recombinant adeno-associated virus serotype 2/6 (rAAV2/6) vector encoding the cDNA for human α-Gal A (ST-920).

Product Name: ST-920

3.2 Chemical Name and Structure

[redacted]

3.3 Manufacturing

[redacted]

Each lot of ST-920 is tested per required regulated industry standards for quality attributes such as purity, identity, potency and safety, including sterility and adventitious agents prior to release for human use.

3.3.1 Formulation

[redacted]

3.3.2 Biocompatibility

ST-920 will be administered intravenously by injection or infusion using a syringe pump or IV infusion pump depending on dose volume. Total dose volume is dependent on subject's dose level assignment and body weight (kg) at baseline. ST-920 will be administered through an intravenous catheter at a controlled speed while monitoring the subject's vital signs. Detailed instructions for thaw and administration of ST-920 are provided in the Study Pharmacy Manual.

3.3.3 Packaging, Shipment and Storage

When a subject is ready for dosing, the responsible Sangamo Clinical Trial Manager calculates the required number of ST-920 vials needed for the dose and requests shipment from Sangamo Technical Operations. Technical Operations initiates shipment from the contract manufacturing organization (CMO) to the pharmacy recipient at the designated clinical site.

For shipment from the CMO, ST-920 product vials are packaged into secondary cartons and placed into a shipping container containing dry ice, a temperature monitoring device, instructions and forms.

Upon receipt at the clinical site, the shipping container will be examined for signs of damage or tampering, and the contents verified that they were received frozen. The vial of ST-920 will be transferred to secured, temperature monitored frozen storage at ≤-65°C in the hospital pharmacy.

Specific training and forms detailing the procedures for receipt, handling, storage and traceability of vials of ST-920 will be provided by Sangamo.

4 NONCLINICAL STUDIES

ST-920 is a recombinant AAV2/6 vector encoding the cDNA for human α-Gal A intended for treatment of subjects with Fabry disease. [redacted]

4.1 Nonclinical Pharmacology

A tabular summary of the *in vitro* and *in vivo* pharmacology studies and detailed results of each study are summarized in Table 1.

Table 1: List of Studies Supporting ST-920 Nonclinical Development - Pharmacology

4.1.1 *In vitro* Pharmacology Studies

[redacted]

4.1.1.1 Lead hGLA cDNA Candidate Selection in HepG2 Cells [redacted]

[redacted]

4.1.1.2 In vitro Studies [redacted]

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[redacted] This summary focuses on the pharmacological-related evaluations.

4.1.1.5 Pharmacology in Mouse Models of Disease

Two models of Fabry disease were used to assess the potential for liver-secreted α-Gal A to reduce disease biomarkers and/or disease pathology including the GLAKO and GLAKO/GB3Stg mouse models. The GLAKO mouse model has a deletion in exon 3 of the GLA gene that eliminates α-Gal A enzyme production and leads to accumulation of Fabry substrates Gb3 and lyso-Gb3 in tissues and plasma (Wang et al., 1996). GLAKO mice do not suffer from renal disease, cardiac disease or the other phenotypical symptoms common to Fabry disease patients. The GLAKO/GB3Stg mouse model was generated by cross-breeding GLAKO mice with transgenic mice that overexpress human Gb3 synthase (Shiozuka et al., 2011). These animals exhibit renal dysfunction as well as high levels of the biomarkers Gb3 and lyso-Gb3 in plasma and tissues.

The age of the mice at study initiation and duration of the [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

This study confirms that α-Gal A secreted from the liver into the plasma can be taken up by secondary tissues such as heart and kidney and result in clearance of the Fabry disease biomarkers Gb3 and lyso-Gb3.

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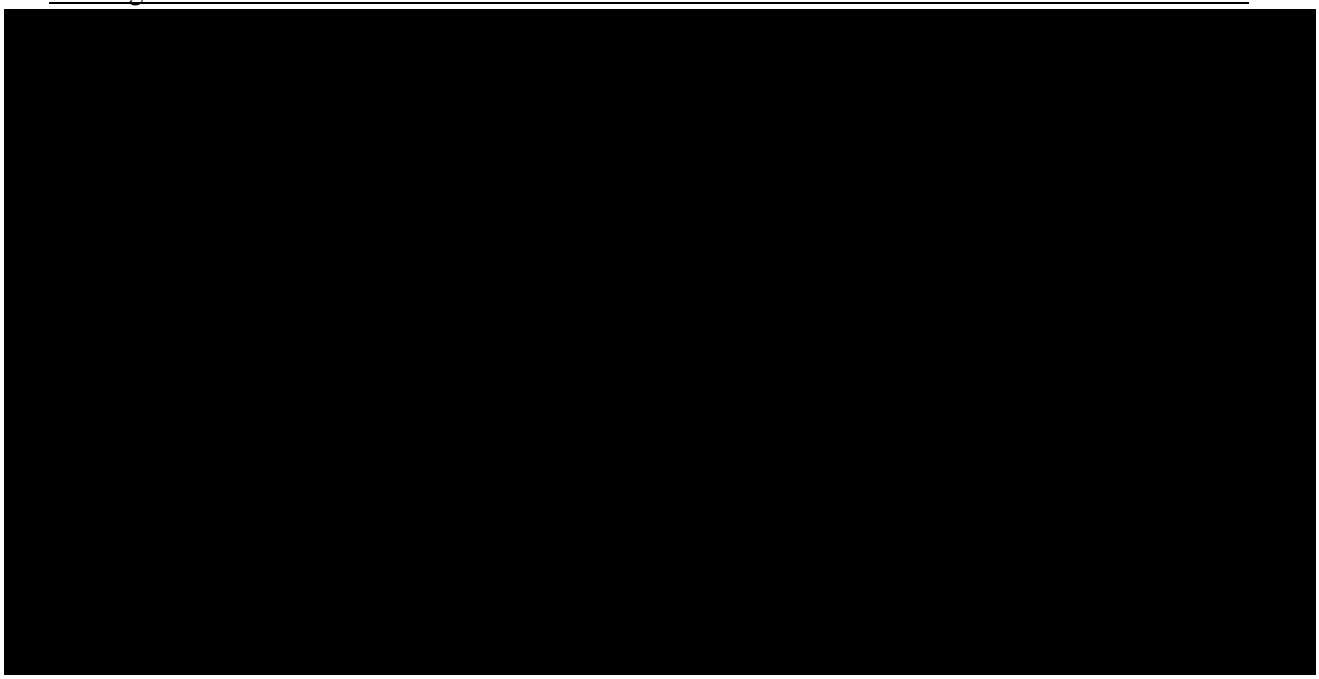
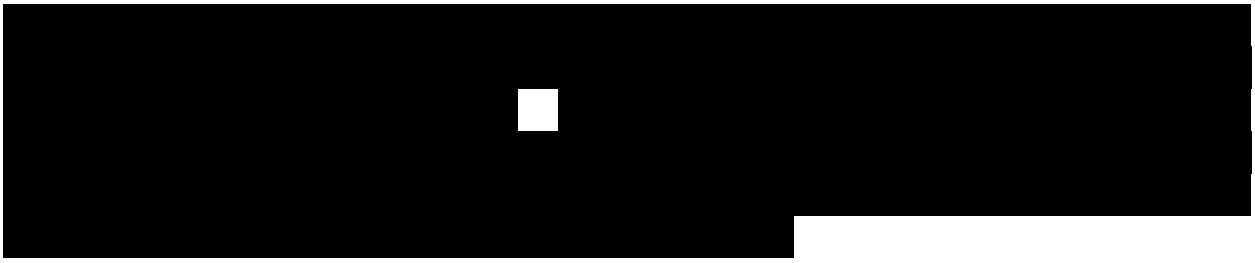
Table 10: List of *In vivo* Studies Supporting ST-920 Nonclinical Development – Pharmacokinetics, Biodistribution and





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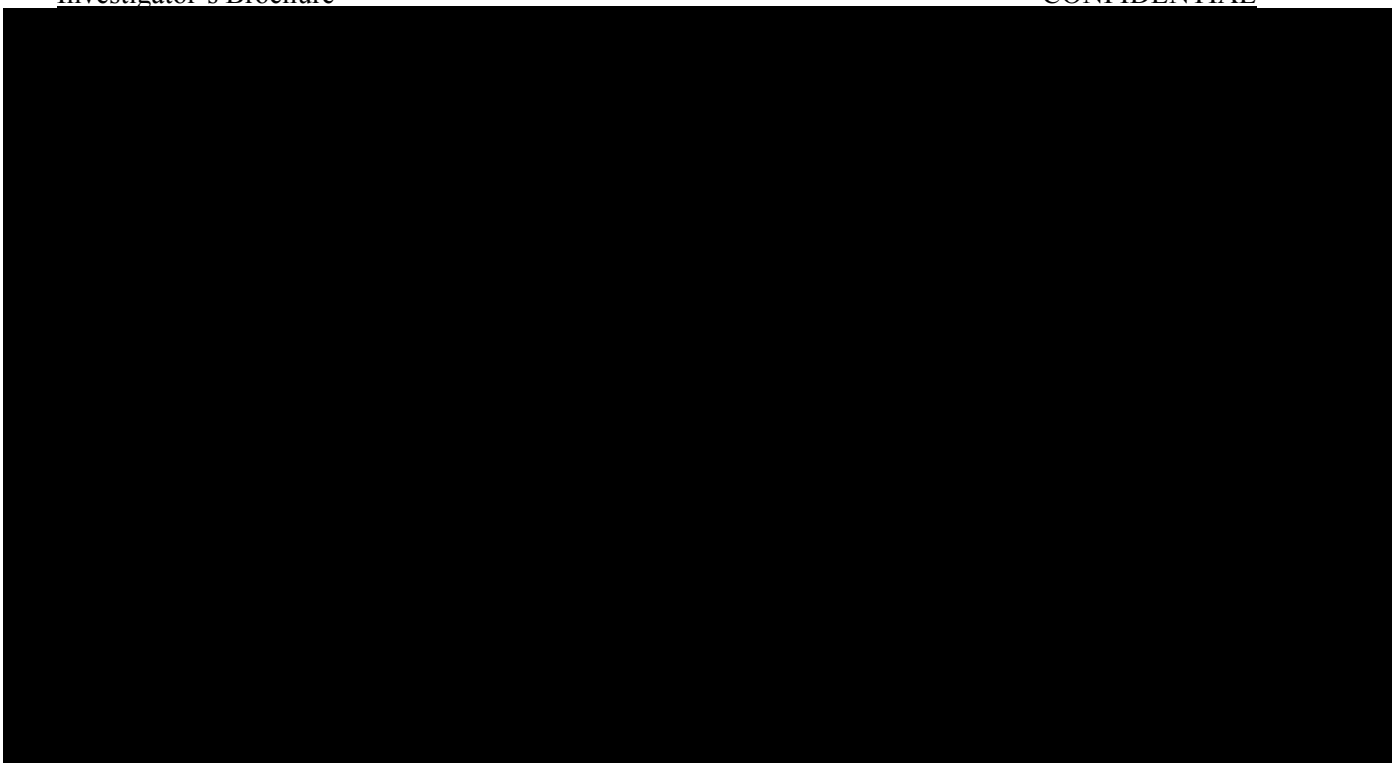

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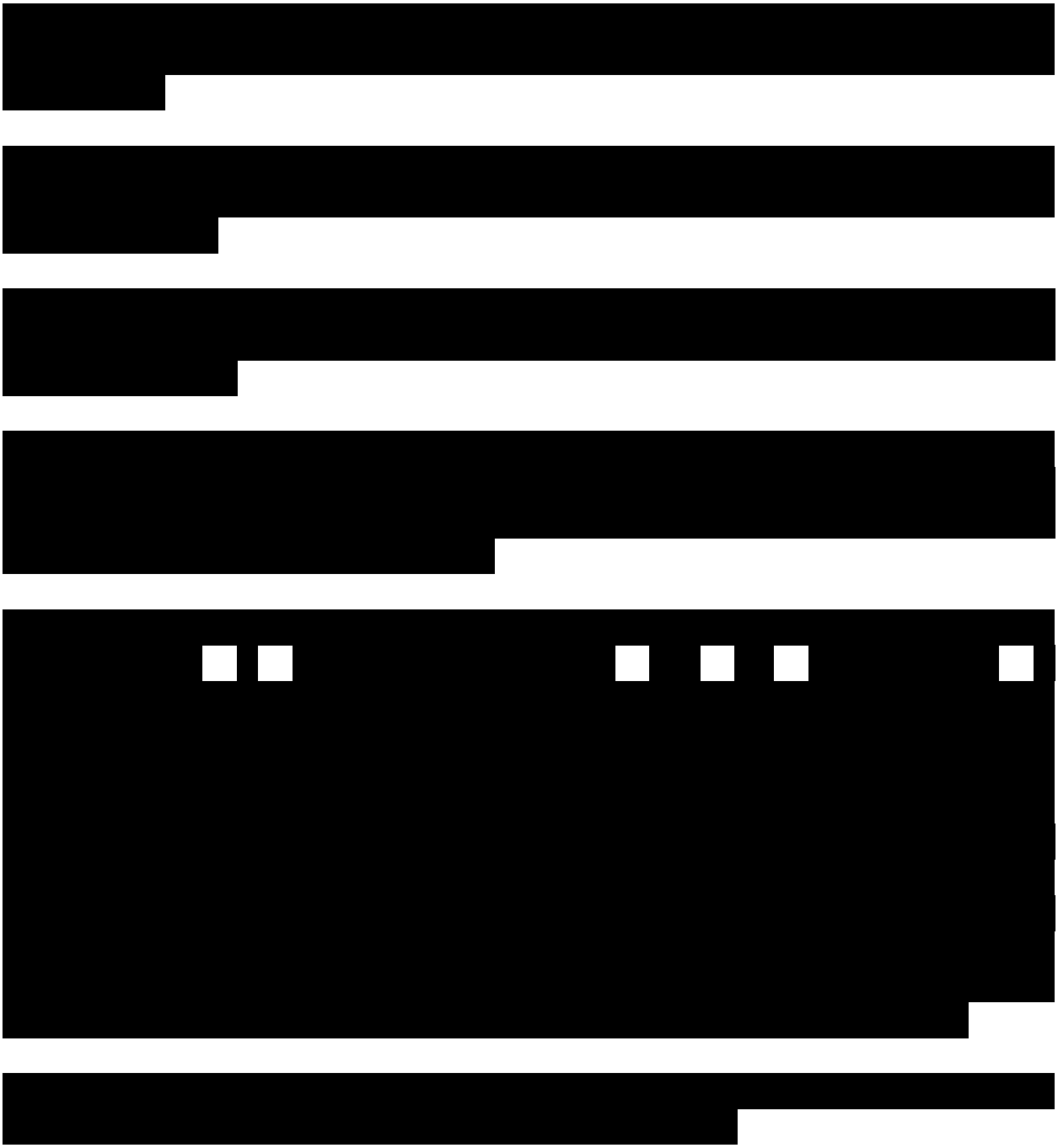

[redacted]

[redacted]

[redacted]

Table 36: Toxicology Program

Type of Study Report number & Status	Species and Strain	Administration: Method, Duration and Schedule	Test Article and Doses (vg/kg)	Toxicology Endpoints	GLP
[redacted]					

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[redacted]

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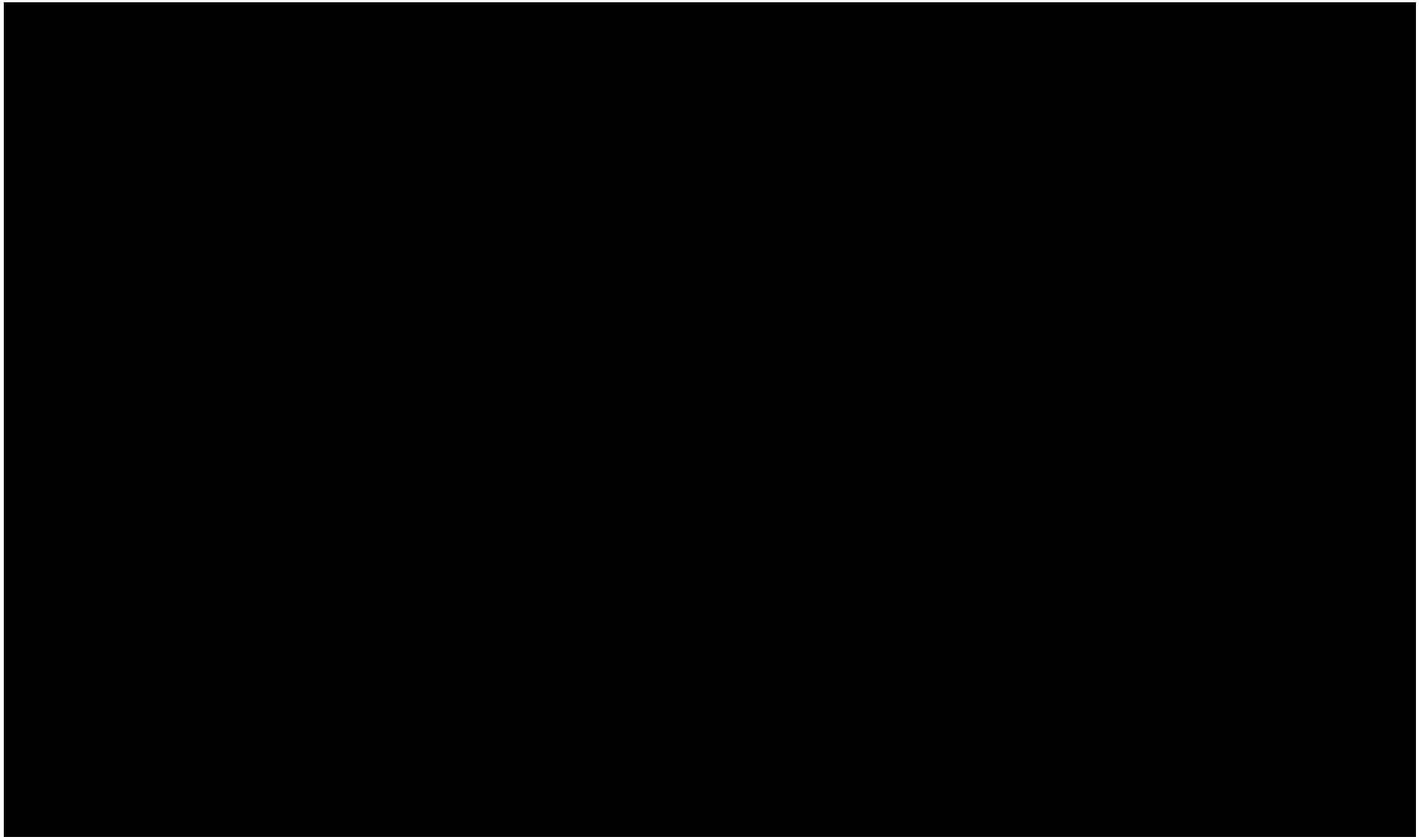

5 EFFECTS IN HUMANS

5.1 Clinical Experience with AAV Gene Therapy and rAAV2/6 Serotype

Several AAV-mediated cDNA gene transfer Phase I and II studies, namely for the treatment of hemophilia A and B, have reported clinical study data and are currently recruiting and enrolling Phase III studies. One AAV2-based gene therapy product (LUXTURNA™), administered sub-retinally, was recently approved for the treatment of subjects with confirmed biallelic RPE65 mutation-associated retinal dystrophy (Bennett et al., 2016). In all studies, mild immune reactions were observed. In all the hemophilia studies reported to date, where the gene therapy is administered via the intravenous route, ALT elevations due to AAV-associated transaminitis have been observed at vector doses ranging from 5.0E+11 vg/kg to 6.0E+13 vg/kg, with variable amount of losses in factor protein expression that has been reported to be likely due to time to initiation of steroid therapy (Manno et al. 2006, Nathwani et al. 2014). [redacted]

Various AAV serotypes are being used in the clinic, including AAV2, 5, 6 and 8. The rAAV2/6 serotype was selected for use in Sangamo gene therapy platforms [redacted]
Four clinical studies (2 in subjects with MPS and 2 in subjects with hemophilia) have been initiated by the Sponsor and utilize the AAV2/6 serotype that will be used in this clinical trial.

5.2 Safety and Potential Risks

ST-920 has not yet been studied in humans.

Preliminary clinical safety data are available from 13 subjects treated with similar Sangamo investigational products utilizing the AAV2/6 vector. The highest dose level administered to date in these other studies is 5.0E+13 vg/kg. Infusions of these products have been generally well-tolerated, and no significant safety concerns have been identified.

As of 13 September 2018, 6 subjects with hemophilia A have received SB-525, an investigational product utilizing the rAAV2/6 vector which encodes cDNA for the B-domain deleted (BDD) human Factor 8 gene. Subjects in this study were not treated prophylactically with a tapering course of prednisone prior to infusion of SB-525. No subjects reported serious adverse events related to the investigational product. Nonserious adverse events assessed by the

Investigator as related to the investigational product included alanine aminotransferase increased in 2 subjects. These events were both mild in severity and resolved with prednisone treatment within 5 days and 11 days, respectively.

As of 11 September 2018, 6 subjects with MPS II has received SB-913, and 1 subject with MPS I has received SB-318. These investigational products utilize three individual AAV2/6 vectors, two encoding engineered zinc finger nucleases (ZFNs) to site-specifically integrate a corrective copy of a donor transgene, which is encoded by the third AAV2/6 vector, into the genome of the subject's own hepatocytes *in vivo*. The two vectors encoding ZFNs (one left and one right requiring dimerization to create a double-stranded break at a specific locus) are identical between the SB-913 and SB-318 products; the donor transgene (to be inserted at the double-stranded break during repair) differs between the products depending on the underlying enzyme deficiency. Subjects in these studies were treated prophylactically with a tapering course of prednisone prior to infusion of SB-913 or SB-318. No subjects reported serious adverse events related to the investigational product. Nonserious adverse events assessed by the Investigator as related to the investigational product were reported in 4 subjects and included flushing in a subject 3 days after dosing; flushing and erythema in a subject on the day of dosing, and Grade 1 ALT increased and Grade 1 AST increased in this same subject 60 days after dosing; cold sweat, dizziness, and asthenia in one subject 4 days after dosing; and 2 events of pruritus in a subject 2 and 6 days after dosing. Each of these events was mild in severity and resolved without treatment within approximately one week of onset.

5.2.1 Replication Defective AAV2/6 Vector

Recombinant replication defective AAV vectors have been used extensively in hemophilia preclinical models and clinical trials for twenty years. These vectors show efficient transduction with stable long-term expression *in vivo* due persistence of nuclear-localized episomal copies in non-dividing cells of tissues such as liver, brain and muscle. An AAV virus consists of a single-stranded DNA genome encapsulated by three capsid proteins.

5.2.2 Neutralizing Antibodies to AAV2/6

The immune system of subjects in this study will be exposed to antigens arising from the foreign AAV capsid protein, and the α-Gal A. Clinical studies to date suggest an immune response will be generated to AAV capsid protein, but whether an immune response will develop against α-Gal A remains to be determined as it is unknown whether antibodies will develop against a protein with a glycosylation pattern derived from human hepatocyte production of the enzyme. As subjects will have been treated with ERT, antibodies to ERT-derived α-Gal A are anticipated to be present.

Although AAV is a replication defective virus, humans are naturally infected during childhood, probably in conjunction with a helper virus infection such as adenovirus. Therefore, the presence of neutralizing antibodies to AAV prior to ST-920 administration will affect transduction by forming immune complexes with the infused vector, and thereby prevent hepatocyte transduction. [redacted]

Prior to the administration of ST-920, subjects will be screened for neutralizing antibodies to AAV2/6. Subjects that test positive to neutralizing antibodies to AAV2/6 at the current threshold established by Sangamo will not be administered ST-920.

[redacted]

5.2.4 Carcinogenicity

There is a risk that people who receive gene transfer may develop tumors derived from their genetically modified cells. This risk has been seen with viral gene transfer vectors that integrate into the cellular DNA where they may affect genes controlling cell proliferation. AAV vectors

can integrate into the genome at very low levels (Nakai et al., 2001), but the majority of the vector resides episomally. [redacted] Although there is no adequate animal model to address the tumorigenic potential, the available data from toxicology studies did not show any tumor formation. For evaluation of liver carcinogenicity, hepato-cellular carcinoma (HCC) screening is recommended, which includes monitoring alfa-fetoprotein (AFP) and liver MRI. Liver biopsy is recommended if there is an abnormal AFP and a >2 cm mass in the liver (El-Serag & Davila 2011).

6 SUMMARY OF DATA AND GUIDANCE FOR THE INVESTIGATOR

6.1 Investigational Product

The investigational product, ST-920, is a recombinant AAV2/6 vector encoding the cDNA for human α-Gal A and is intended for the treatment of subjects with Fabry disease, a lysosomal storage disease caused by mutations in the GLA gene. ST-920 works by enabling long-term liver-specific expression of a corrective copy of the hGLA transgene in the subject's own hepatocytes, resulting in sustained secretion of α-Gal A into circulation.

ST-920 is administered as a single intravenous infusion and dosed based on body weight. Based on preclinical safety and efficacy data for ST-920 and clinical safety data for products using the AAV2/6 vector, the starting dose intended to optimize the benefit-risk balance for subjects is 5.00E+12 vg/kg. [redacted]

6.2 Nonclinical Summary

Studies [redacted] have demonstrated the feasibility of safely producing durable and potentially efficacious dose levels of α-Gal A after treatment with ST-920 [redacted] Nine *in vivo* pharmacology studies were conducted [redacted] Increased human α-Gal A enzyme activity levels in plasma, liver and secondary tissues were observed [redacted] and decreased GB3 and lyso-GB3 biomarker levels were observed in two mouse models of Fabry disease [redacted]

6.3 Clinical Summary

ST-920 has not yet been studied in humans.

Preliminary clinical safety data are available from 13 subjects treated with similar Sangamo investigational products utilizing the AAV2/6 vector. These data suggest that infusion of these products at up to a dose of 5.00E+13 vg/kg is well tolerated, with no significant safety concerns identified. No serious adverse events related to these investigational products have been reported. Nonserious adverse events assessed by the Investigator as related included ALT increased in 3 subjects (including 2 subjects not receiving prophylactic prednisone); flushing in 2 subjects; and AST increased, asthenia, cold sweat, dizziness, erythema, and pruritus in 1 subject each. Each of these events was mild in severity and most resolved in 1 to 2 days without treatment.

6.4 Possible Risks and Adverse Reactions

The following subsections describe several untoward medical conditions that may potentially occur, based on the mechanism of action of ST-920, method of administration, the results from nonclinical studies, and data from clinical studies with other products using the AAV2/6 vector. These factors are discussed individually to aid the investigator in anticipating potential adverse reactions and advise on the possible detection, mitigation and treatment of such reactions.

6.4.1 Risk of Immune Reaction to the Vector and to the Transgene Protein

As ST-920 uses a viral vector, there is a potential for an immune reaction following investigational product administration. To minimize a potential adverse immune response, ST-920 will be infused intravenously while the subject is in the hospital or acute care facility, where the subject will remain for observation for a sufficient period of time after completion of the ST-920 infusion to monitor for an acute reaction and ensure the subject is in stable condition prior to discharge. Additionally, the rate of infusion for the product should be no higher than 100 mL/hour. Investigators are instructed to slow the rate of infusion if symptoms appear (e.g. flushing, rash, rigor, chills, dyspnea, and hypotension), or stop the infusion altogether if the symptoms are severe in the judgement of the investigator. In addition, adverse reactions indicative of an immune response following ST-920 infusions may include transient fever, chills, and/or nausea. These symptoms may be treated with oral acetaminophen and oral or intravenous diphenhydramine hydrochloride (Benadryl®). These medications may be repeated every 3-4 hours as needed, not exceeding the maximum daily dose and following guidance on the applicable product labelling to mitigate potential liver toxicity.

[redacted]

The potential risk of hepatotoxicity for this liver-tropic viral vector is due to the possibility that viral proteins from the capsid of the viral vector (AAV6) are processed by the liver cells and peptides derived from these capsid proteins are presented to the immune system by these liver cells. [redacted]

To further prevent potential liver toxicity, subjects with a history of liver disease such as steatosis, cholangitis, cirrhosis, biliary disease (except for Gilbert's syndrome), or a history of alcohol or substance abuse should not be administered ST-920. In addition, subjects should be screened by qPCR for active infection with hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), and tuberculosis (TB) prior to ST-920 administration. Hepatotoxic concomitant medications should be avoided. Liver function tests should be monitored twice weekly during the first 8 weeks after ST-920 infusion in order to evaluate potential detrimental AAV-mediated immunogenicity.

6.4.2 Risk of Off Target Effect

Because the viral vector construct includes a liver-specific promoter for the alpha-galactosidase gene and liver-specific enhancers, the transgene should only be expressed in the liver, thus limiting the risk of off target effects to the liver. Off target effects from circulating enzyme are not anticipated, as supraphysiological levels of produced enzymes in animal preclinical experiments did not reveal any relevant adverse effects. Despite this, subjects should be closely followed for a year after ST-920 administration, and standard safety monitoring should be performed. For an additional four years, subjects should be assessed at least annually to facilitate detection of potential delayed adverse events associated with ST-920 treatment.

6.4.3 Risk of Insertional Mutagenesis

There is a risk that people who receive gene transfer may develop tumors derived from their genetically modified cells. This risk has been seen with some viral gene transfer vectors that integrate into the cellular DNA where they may affect genes controlling cell proliferation. AAV vectors can integrate into the genome at very low levels (Nakai et al. 2001), but most of the vector resides episomally. Preclinical animal studies showed no findings of tumors by gross and histopathologic examination; however, animal models are not adequate to address tumorigenic

potential. Subjects who have a history of malignancy except for non-melanoma skin cancer will not be administered ST-920. By design, the viral vector should only be expressed in the liver, and therefore the potential risk is primarily malignant transformation in the liver. For evaluation of liver carcinogenicity, hepatocellular carcinoma (HCC) screening typical for high risk subjects (e.g., chronic hepatitis C or B) is recommended, which includes monitoring AFP and liver MRI. Liver biopsy is recommended if there is an abnormal AFP and a >2 cm mass in the liver.

6.4.4 Risk of Horizontal and Vertical Transmission

ST-920 employs a replication defective AAV vector and persistence in bodily fluids is not anticipated past 60 days based on animal data. No data are available suggesting transmission of the AAV vector to the offspring of an exposed male subject. As a precaution to avoid transmission to partners of the viral vectors, through shedding, male subjects should wear condoms during sexual activities until the vector can no longer be detected in semen, and for a minimum of 90 days post infusion (accounting for one cycle of spermatogenesis).

6.5 Reference Safety Information

No serious adverse reactions are considered expected by the sponsor for regulatory reporting purposes.

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