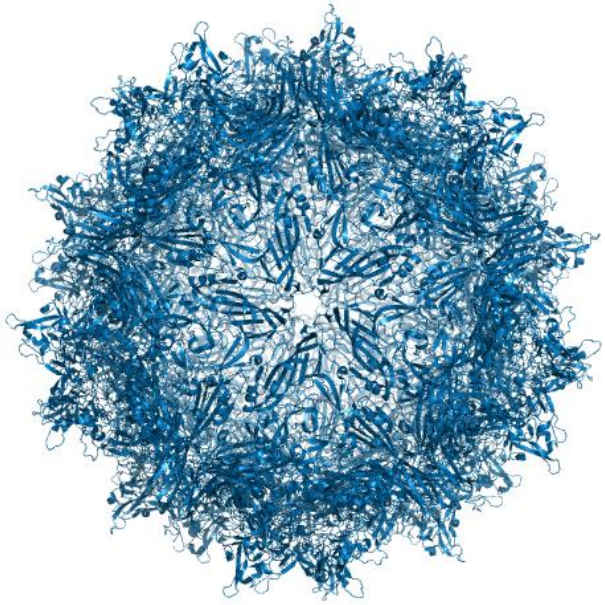
Clinical Study Protocol

A Phase I/II, Multicenter, Open-Label, Single-Dose, Dose-Ranging Study to Assess the Safety and Tolerability of ST-920, a rAAV2/6 Human Alpha Galactosidase A Gene Therapy, in Subjects with Fabry Disease



Protocol Number: ST-920-201

BB-IND: 18733

EudraCT: 2019-000667-24

Sponsor: Sangamo Therapeutics, Inc.
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Medical Monitor: [redacted]

Original Version: December12, 2018

Amendment 1: March 01, 2019

Amendment 2: July 02, 2019

This study will be conducted in compliance with the protocol, the International Conference on Harmonisation (ICH) Guidelines, Good Clinical Practices, and applicable regulatory requirements, including the U.S. Code of Federal Regulations.

Sangamo Therapeutics, Inc.

Clinical Approval Signature Page

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[redacted]

2 July 2019
Date

Sangamo Therapeutics, Inc.

Investigator Agreement Page

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I have read all pages of this clinical study protocol for which Sangamo Therapeutics, Inc. is the Sponsor. I agree to conduct the study as outlined in the protocol, and to comply with all terms and conditions set out therein. I confirm that I will conduct the study in accordance with ICH guidelines and applicable local regulations. I will ensure that sub-investigator(s) and other relevant members of my staff have access to copies of this protocol and the ICH guidelines to enable them to work in accordance with the provisions of these documents.

_____ _____

Investigator Signature Date

_____

Investigator Printed Name

_____

Site Name

_____

Site Address

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACTH	Adrenocorticotropic hormone
α-Gal A	Alpha-galactosidase A
AAV	Adeno-associated virus
AE	Adverse event
ApoE	Apolipoprotein E
ALP	Alkaline phosphatase
ALT	Alanine transaminase
AR	Adverse reaction
AST	Aspartate transaminase
BPI	Brief Pain Inventory
BSC	BioSafety Committee
Ca	Calcium
CCoA	Clinical Certificate of Analysis
cDNA	Complementary deoxyribonucleic acid
Cl	Chloride
CO_3^{2-}	Carbonate
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting toxicity
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCRF	Electronic case report form
ECHO	Echocardiogram
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EOS	End of study
ERT	Enzyme replacement therapy
ETV	Early termination visit
FDA	Food and Drug Administration
Gb3	Globotriaosylceramide
GFR	Glomerular filtration rate
GGT	Gamma-glutamyl transferase
GI	Gastrointestinal
GLP	Good laboratory practice
hAAT	Human alpha-1-antitrypsin
HAV	Hepatitis A virus
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HEENT	Head, eyes, ears, nose, and throat
hGLA	Human alpha-galactosidase A
HIV	Human immunodeficiency virus
IATA	International Air Transport Association
ICF	Informed consent form

ICH	International Council for Harmonisation
IEC	Independent ethics committee
IRB	Institutional review board
IV	Intravenous
K	Potassium
LDH	Lactate dehydrogenase
LVH	Left ventricular hypertrophy
Lyso-Gb3	Globotriaosylsphingosine
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	Magnetic resonance imaging
mRNA	Messenger RNA
MSSI	Mainz Severity Score Index
Na	Sodium
NHP	Non-human primate
NIH	National Institutes of Health
NOAEL	No-observed-adverse-effect level
PCR	Polymerase chain reaction
PFT	Pulmonary function test
PO_4	Phosphate
QOL	Quality of life
rAAV	Recombinant adeno-associated virus
RNA	Ribonucleic acid
RSI	Reference safety information
SAE	Serious adverse event
[redacted]	[redacted]
SMC	Safety Monitoring Committee
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TB	Tuberculosis
TEAE	Treatment-emergent adverse event
ULN	Upper limit of normal
vg	Vector genome
[redacted]	[redacted]
[redacted]	[redacted]
WT	Wild type

PROTOCOL SYNOPSIS

ST-920-201 Study Protocol Synopsis	
A Phase I/II, Multicenter, Open-Label, Single-Dose, Dose-Ranging Study to Assess the Safety and Tolerability of ST-920, a rAAV2/6 Human Alpha Galactosidase A Gene Therapy in Subjects with Fabry Disease	
Sponsor	Sangamo Therapeutics, Inc.
Investigational Product	ST-920 is a recombinant adeno-associated virus (rAAV) 2/6 vector that encodes a human alpha galactosidase A (α-Gal A; hGLA) cDNA.
Study Sites	Approximately 10 to 15 sites worldwide
Study Design	Multicenter, open-label, single dose, dose-ranging study
Study Rationale	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 deacetylated soluble form globotriaosylsphingosine (lyso-Gb3). Long-term accumulation of these substrates leads to renal, cardiac and/or cerebrovascular disease, with reduced life expectancy. Depending on the mutation and residual α-Gal A enzyme level, the disease presents as classical early-onset Fabry disease in childhood/adolescence or as an attenuated (adult) form later in life. In both classical 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 (<1 hour in plasma) used in ERT necessitates a lifetime of infusions, with associated risk of infusion-related reactions. In addition, a significant percentage of patients eventually generate antibodies to the recombinant enzyme, which may impact the activity of the ERT enzyme, which consequently may not clear all substrate from organs such as the kidneys. Recombinant α-Gal A products with longer half-lives are being developed which may be administered less frequently. However, it is anticipated that these will still require long-term administration with associated risk of infusion-related reactions, and that α-Gal A levels will still fluctuate significantly over time. There is therefore a need for alternative therapies that address the unmet needs in Fabry disease. Adeno-associated viral (AAV) vectors have shown great promise in both preclinical and clinical trials to efficiently and safely deliver therapeutic transgenes to the liver, with reports of stable levels of transgene expression out to six years for hemophilia B.

	The proposed study uses a recombinant AAV2/6 vector encoding the cDNA for human α-Gal A (ST-920). The α-Gal A produced by this cDNA has an identical amino acid sequence to the native enzyme, [redacted] In addition, rAAV2/6 exhibits liver tropism thus providing the potential for long-term hepatic production of α-Gal A in Fabry disease subjects. Studies of ST-920 in a Fabry disease mouse model administered rAAV2/6 encoding hGLA cDNA by intravenous (IV) injection show generation of therapeutic circulating levels of α-Gal A. The one-time treatment with ST-920 minimizes the risk of infusion--related reactions. 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.
Objectives	**Primary Objective:** • To assess safety and tolerability of ST-920 **Secondary Objectives:** • To assess the pharmacodynamics of α-Gal A and the presence of its substrates in plasma over time • To assess impact of ST-920 on ERT administration required for subjects on ERT • To assess the impact of ST-920 on renal function • To evaluate AAV2/6 vector DNA shedding over time **Exploratory Objectives:** • To assess clinical impact of ST-920 on classical Fabry disease • To assess the pharmacodynamics of α-Gal A and the presence of its substrates in urine and tissue over time • To assess the pharmacokinetics of α-Gal A over time • To assess immune response to AAV2/6 and α-Gal A Residual samples and additional samples may be used from consenting subjects for future research objectives.
Endpoints	**Primary Endpoint:** • Incidence of treatment-emergent adverse events (TEAEs) Additional safety evaluations will include: ○ Routine hematology, chemistry, and liver function laboratory tests, vital signs, ECG and ECHO ○ Serial AFP testing and MRI of liver to monitor for the formation of any liver mass

	Secondary Endpoints: • Change from baseline at specific time points over the 1-year study period in: o α-Gal A activity in plasma o Gb3 levels in plasma o Lyso-Gb3 levels in plasma o Frequency of Fabrazyme® (or equivalent ERT) infusion o Estimated glomerular filtration rate (eGFR) measured by creatinine levels in blood • AAV2/6 vector clearance measured by level of vector genome in plasma, saliva, urine, stool, and semen **Exploratory Endpoints:** • Change from baseline at specific time points over the 1-year study period in: o Left ventricular mass measured by cardiac magnetic resonance imaging (MRI) o Protein to creatinine ratio in urine o α-Gal A levels measured in tissues o Substrate levels measured in tissues and urine o Biomarkers of renal function in urine o Neuropathic pain measured by the Brief Pain Inventory (BPI) o Frequency of pain medication use o Gastrointestinal (GI) symptoms measured by the GI symptoms rating scale o Mainz Severity Score Index (MSSI) o Quality of life (QOL) patient-reported outcome measured by the SF-36 questionnaire • Immune response to AAV2/6 and α-Gal A
Study Population	Male subjects ≥ 18 years of age with classical Fabry disease.
Number of Subjects	Up to 18 subjects will be enrolled in this study.
Inclusion & Exclusion Criteria	Inclusion Criteria 1. Subject with documented diagnosis of classical Fabry disease as defined by plasma α-Gal A activity and one or more characteristics of classical Fabry disease: i) cornea verticillata, ii) acroparesthesia, iii) GI symptoms, iv) anhidrosis, v) angiokeratoma 2. Subject who is on ERT (14 days [± 1 day] regimen); or is ERT-naïve; or is ERT-pseudo-naïve and has not received ERT treatment in the past 6 months prior to consent 3. Male subject ≥ 18 years of age 4. Sexually mature subjects must agree to use a condom and refrain from sperm donation from the time of ST-920 administration until a minimum of 3 consecutive semen samples are negative for AAV2/6

	after administration of ST-920 and a minimum of 90 days after ST-920 administration 5. Signed, written informed consent of the subject Exclusion Criteria 1. Known to be unresponsive to ERT in the opinion of the Site Investigator and Medical Monitor (e.g., no documented substrate level decrease on ERT) 2. Current treatment with migalastat (Galafold™) or prior treatment within 3 months of informed consent 3. Positive neutralizing antibody response to AAV6 4. Intercurrent illness expected to impair evaluation of safety or efficacy during the observation period of the study in the opinion of the Site Investigator or Medical Monitor 5. eGFR ≤ 60 ml/min/1.73m2 6. New York Heart Association Class III or higher 7. Active infection with hepatitis A virus (HAV), hepatitis B virus (HBV), hepatitis C virus (HCV) (negative HCV-DNA), or human immunodeficiency virus (HIV) as measured by qPCR or active infection with tuberculosis (TB) 8. History of liver disease such as steatosis, cholangitis, cirrhosis, biliary disease; except for Gilbert's syndrome 9. For subjects receiving ERT, recent or continued hypersensitivity response to ERT treatment within 6 months prior to consent, as manifested by significant infusion reaction to ERT in the opinion of the Site Investigator and Medical Monitor 10. Markers of hepatic inflammation or overt or occult causes of liver dysfunction as confirmed by one or more of the following: a. Albumin ≤ 3.5 g/dL b. Total bilirubin > 1.5 x upper limit of normal (ULN) and direct bilirubin ≥ 0.5 mg/dL c. Alkaline phosphatase (ALP) > 2.0 x ULN d. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) > 1.5 x ULN 11. Current or history of systemic (IV or oral) immunomodulatory agent or steroid use in the past 6 months (topical treatment is allowed, e.g. asthma or eczema). Occasional use of systemic steroid may be allowed after discussion with the Medical Monitor. 12. Contraindication to use of corticosteroids for immunosuppression (e.g., diabetes, osteoporosis, etc.) 13. History of malignancy except for non-melanoma skin cancer 14. History of alcohol or substance abuse 15. Participation in prior investigational interventional drug or medical device study within the last 3 months prior to consent (with the exception of implantable loop recorders as in the RaILRoAD trial) 16. Prior treatment with a gene therapy product

	17. Known hypersensitivity to components of ST-920 formulation 18. Any other reason that, in the opinion of the Site Investigator or Medical Monitor, would render the subject unsuitable for participation in the study
Concomitant Medications	All medications are permitted, with the exception of those that are potentially hepatotoxic. Hepatotoxic agents such as diclofenac, amiodarone, chlorpromazine, fluconazole, isoniazid, rifampin, valproic acid, high doses of acetaminophen (4-8 gm/day), etc. as well as hepatotoxic herbal supplements such as senecio/crotalaria, germander in teas, chaparral, Jin bu huan, Ma-huang (Chinese herbs), etc. should not be taken during the study period. For subjects receiving ERT, ERT must have been administered at a stable dose and regimen (14 days ± 1 day) for >3 months prior to consent. Subjects should continue to receive ERT at a stable dose and regimen (14 days ± 1 day) during the study as per standard of care unless they undergo ERT withdrawal.
Dose and Rationale for Dose Selection	[redacted] Several dose levels may need to be studied to identify a safe and tolerable therapeutic dose. The starting dose will be 5.0E+12 vg/kg, [redacted]

Treatment Plan	Six subjects ≥ 18 years of age who satisfy all inclusion/exclusion criteria will be enrolled. Two subjects will be assigned into each of the 3 dose cohorts with a potential expansion of any cohort with an additional 4 adult subjects, for a total of up to 18 subjects, after SMC review. ST-920 will be administered via intravenous infusion. [redacted] Subjects who received ERT prior to study enrollment will continue to receive ERT during the study and remain on their current dose and regimen (14 days ± 1 day) per standard of care unless they undergo ERT withdrawal. [redacted] ST-920 will be infused IV while the subject is in the hospital or acute care facility, where the subject will remain for observation for at least 24 hours after completion of the ST-920 infusion. The subject will be discharged when all vital signs are stable and any adverse events (AEs) have resolved. Following the infusion of ST-920, study visits will be conducted on Day 8; Weeks 2, 4, 6, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48, and 52. Week 28, 32, 40, 44, and 48 study visits have assessments that do not require evaluation at the clinical site, and therefore may be conducted remotely. Assessments for AEs and concomitant medications may be conducted remotely over the phone by the study staff. Liver function tests (AST, ALT, GGT, bilirubin, ALP, and albumin) will be conducted for evaluation of transaminitis due to AAV-mediated immunogenicity twice weekly during the first 20 weeks after ST-920 infusion [redacted] Blood samples for liver function tests will be drawn 2-4 days apart when possible, except for the first week when they will be drawn on the Day 2 and Day 8 visits. Liver function tests will subsequently be conducted weekly for four weeks [redacted]

	[redacted]
Dose Escalation	[redacted] Dosing and dose escalation will be paused if any of the stopping rules are met. In such an event, the SMC will be convened to assess for potential dose-limiting toxicity (DLT) and provide recommendations to dose de-escalate, or discontinue the study (refer to the Safety Monitoring Committee & Stopping Rules). No further dosing of subjects will be performed at that dose level or higher until a substantial amendment is submitted to regulatory authorities for review, and the amendment has been approved by the site Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or equivalent.
ERT Withdrawal	The ultimate goal of ST-920 treatment is to abrogate the need for ERT, by using a recombinant AAV2/6 vector encoding cDNA for human α-Gal A, resulting in long-term, liver-specific expression of α-Gal A in Fabry disease subjects. Subjects who undergo ERT withdrawal will be closely monitored for any AEs, vital signs, any changes in safety laboratory evaluations and levels of α-Gal A and substrates compared to baseline. ERT withdrawal is at the discretion of the Site Investigator after consultation with the Sponsor, and is only to be considered for subjects who are willing and meet all of the following criteria: [redacted]

Study Duration	The duration of study participation will be up to 17 months for each subject divided into up to 2 months for screening, up to 3 months for baseline, and 12 months follow-up after dosing. Accrual is planned for 9 to 12 months. Subjects will be strongly encouraged to participate in an additional separate long-term follow-up study for up to 4 years.
Safety Monitoring Committee & Stopping Rules	A SMC with appropriate medical and scientific expertise will provide safety oversight of the study. This SMC will comprise of external subject matter experts, the study medical monitors and one or two site investigators as appropriate such that the best recommendations can be made to the Sponsor based on cumulative study data, and experience with the study drug and its effects. The SMC will be convened to make a recommendation to the Sponsor as to whether it is safe to proceed with a different dose level, or expand a dose cohort at the same dose level. The SMC may be convened at any time if there are excessive or unexpected toxicities associated with the conduct of the protocol. Specifically, the study enrollment will be paused if any of the following criteria are met, and the SMC will convene to make recommendations as to the proper course of action: • Any one Grade 3 or higher AE with at least a reasonable possibility of a causal relationship to the investigational product • Serious adverse event (SAE) with at least a reasonable possibility of a causal relationship to the investigational product • Death of a subject • Development of a malignancy The study may also be stopped for any of the following reasons: • Sponsor, in consultation with the SMC or Regulatory Agency, decides for any reason that subject safety may be compromised by continuing the study. • Sponsor decides to discontinue the development of the investigational product. All data will then be evaluated to determine if changes should be made to the study or if accrual should be continued or halted. No further dosing of subjects will be performed at that dose level or higher until a substantial amendment is submitted to regulatory authorities for review, and the amendment has been approved by the site Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or equivalent. [redacted]

Safety Monitoring and Mitigation Plan	A potential anticipated risk of the drug product is the development of transaminitis due to cell-mediated immunity to capsid and/or AAV gene product. [redacted] The liver function (AST, ALT, GGT, bilirubin, ALP, and albumin) of study subjects will be monitored closely throughout the study. These biochemical tests will be performed twice weekly [redacted]
Sample Size	This is a Phase I/II dose-escalation study with up to 18 subjects (2 subjects in each of 3 dose cohorts with potential enrollment of 4 additional subjects in any dose cohort). The sample size for this study was not based on statistical considerations but is considered sufficient to provide a preliminary assessment of the safety and tolerability of ST-920 in subjects with Fabry disease. Subjects who prematurely discontinue the study prior to 12 months of study follow-up (i.e., subjects who were enrolled but not dosed, were lost to follow-up, or discontinued prematurely for another reason) may be replaced with another subject at the discretion of the Sponsor.
Statistical Analyses	[redacted]

[redacted]	[redacted]

1. INTRODUCTION

1.1 Fabry disease

Fabry disease is a X-linked lysosomal storage disease caused by mutations in the *GLA* gene, which encodes the lysosomal 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. Long-term accumulation of these substrates leads to renal, cardiac and/or cerebrovascular disease, with reduced life expectancy. Depending on the mutation and residual α-Gal A enzyme level, the disease presents as classical early-onset Fabry disease in childhood/adolescence or as an attenuated (adult) form later in life. Classical Fabry disease occurs when residual enzyme activity is <5% (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 classical and adult forms, the current standard of care is ERT using recombinant α-Gal A, Fabrazyme® (agalsidase beta or equivalent), or chaperone therapy, which is available only for patients whose mutations are amenable to it. 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 used in ERT (approximately 1 hour in plasma) (Clarke et al. 2007) necessitates a lifetime of infusions, with associated risk of infusion-related reactions in a significant proportion of patients (Clarke et al. 2007), some of which are severe. In addition, a significant percentage of patients eventually generate antibodies to the recombinant enzyme, which may impact the activity of the ERT enzyme, which consequently may not clear all substrate from organs such as the kidneys (Linthorst et al. 2004).

Recombinant α-Gal A products with longer half-lives are being developed which may be administered less frequently. However, it is anticipated that these will still require long-term administration with associated risk of infusion-related reactions, and that α-Gal A levels will still fluctuate significantly over time. There is therefore a need for alternative therapies that address the unmet needs in Fabry disease.

Gene therapy with adeno-associated viral (AAV) vectors has 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 proposed study uses ST-920, a recombinant (rAAV2/6) vector encoding the cDNA for human α-Gal A. The α-Gal A produced by this cDNA has an identical amino acid sequence to the native enzyme, [redacted]
The ST-920 vector encodes a liver specific promoter, and AAV2/6 exhibits liver tropism thus providing the potential for long-term and stable hepatic production of α-Gal A in Fabry disease subjects. Studies in a Fabry disease mouse model administered IV with AAV2/6 encoding hGLA cDNA show generation of therapeutic levels (over 300-fold wild type) of α-Gal A. The one-time treatment with ST-920 minimizes the incidence of infusion-related reactions. Production of therapeutic levels of α-Gal A in humans could enable reduction and potentially clearance of

Fabry disease substrates Gb3 and lyso-Gb3 and may reduce the risk of antibody development to the enzyme produced because of constant production of the enzyme, rather than peak and trough seen with ERT. 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.

1.2 [redacted]

1.3 Nonclinical Studies

The nonclinical evaluation included 3 *in vitro* and 9 *in vivo* studies. The *in vivo* studies were conducted as components of combination endpoint studies that included pharmacology, pharmacokinetics, rAAV vector biodistribution and/or vector shedding, and toxicology

[redacted]

Details of all studies are provided in the Investigator Brochure.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

1.4 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 enrolling in Phase III studies, using intravenous administration. One AAV2-based gene therapy product (LUXTURNA, [Bennett et al. 2016]), administered sub-retinally, was recently approved for the treatment of subjects with confirmed biallelic RPE65 mutation-associated retinal dystrophy. In all studies, mild immune reactions were observed after gene therapy. 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[redacted]

1.6 Targeted Patient Population

Subjects who satisfy all inclusion/exclusion criteria will be enrolled into one of the 3 treatment dose cohorts. The targeted patient population of this study will be adult male subjects ≥18 years of age with a documented diagnosis of classical Fabry disease phenotype, following the established criteria for classical Fabry disease (Arends et al. 2017). This is defined by plasma α-Gal A activity and one or more characteristics of classical Fabry disease including cornea verticillata, acroparesthesia, gastrointestinal symptoms, anhidrosis and angiokeratoma. Due to

the X-linked nature of this genetic disease, female Fabry patients are heterozygous for the genetic defect and have a wide range of residual α-Gal A levels (Winchester & Young 2006).

[redacted]

1.7 Benefit-Risk Assessment and Study Hypothesis

Fabry disease is an inherited lysosomal storage disorder that results from mutations in the gene encoding the enzyme α-Gal A. Decreased levels of α-Gal A result in the accumulation of toxic levels of a type of glycosphingolipid, Gb3, in the blood vessels and body tissues. The severity of the symptoms varies among individuals depending upon their specific *GLA* mutation and the level of residual α-Gal A activity. Currently, the treatment of choice for this patient population is ERT using Fabrazyme® (or equivalent) or chaperone therapy.

The objective of ST-920 investigational therapy is to provide patients with Fabry disease stable therapeutic, liver-specific expression of α-Gal A which may improve on the current clinical outcomes of ERT therapy and ultimately replace ERT altogether.

The potential risks of an AAV gene therapy approach, as for any other gene therapy approaches, are insertion mutagenesis, vertical and horizontal transmission, off-target effects, immunological reaction to the viral vector, and lack or discontinued expression of the transduced gene. A specific safety mitigation plan has been put in place to monitor all these theoretical risks. [redacted] Subjects will be closely monitored for such responses in this study.

2. STUDY OBJECTIVES

2.1 Primary Objectives

- To assess the safety and tolerability of ST-920

2.2 Secondary Objectives

- To assess the pharmacodynamics of α-Gal A and the presence of its substrates in plasma over time
- To assess impact of ST-920 on ERT administration required for subjects on ERT
- To assess the impact of ST-920 on renal function
- To evaluate AAV2/6 vector DNA shedding over time

2.3 Exploratory Objectives

- To assess clinical impact of ST-920 on classical Fabry disease
- To assess the pharmacodynamics of α-Gal A and the presence of its substrates in urine and tissue over time
- To assess the pharmacokinetics of α-Gal A over time
- To assess immune response to rAAV2/6 and α-Gal A

Residual samples and additional samples from consenting subjects may be used for future research objectives [redacted]

3 STUDY DESIGN

3.1 Overview and Rationale

[redacted]

[redacted]

[redacted]

The proposed evaluation period in this study is 12 months after ST-920 administration. This one-year safety evaluation of the study includes physical evaluation, electrocardiograms, echocardiograms, [redacted], in addition to other routine clinical tests and biochemical safety evaluation (for further details, refer to Section 6 and Appendix 1). The 12 month period will monitor for long-term expression and sustainability of the enzymatic activity produced by the cDNA, and may also give some preliminary information on Fabry-relevant parameters, such as renal function, cardiac function. In addition, at the end of the study period of 12 months, subjects enrolled will be encouraged to participate in a separate long-term follow-up study for up to 4 years for long term safety and durability of response monitoring.

3.2 Screening Period

The objective of the screening visits is to identify subjects who meet the stated inclusion and exclusion criteria and who are willing and able to participate in the study. [redacted]

During screening, subjects will be assigned a subject number and will receive the screening assessments and procedures described in the Schedule of Events (Appendix 1). Subjects who complete all screening procedures, satisfy all eligibility criteria and have their eligibility packet verified by the site and approved by the medical monitor will be considered enrolled in the study.

Subjects may be re-screened for participation in the study at the judgment of the Site Investigator and after consultation with Sponsor. See the Schedule of Events (Appendix 1) for a list of assessments performed in the previous 6 months that may be used for evaluation of inclusion/exclusion criteria at the judgment of the Site Investigator. Genetic marker analysis including Fabry disease gene sequencing will not be repeated as this will not change over time. In addition, Fabry disease gene sequencing will only be performed at screening if no prior documented gene sequencing results are not available. The genotyping will only be used to confirm that subjects have a mutation in the GLA gene. The diagnosis of classical Fabry disease will be made on the basis of enzyme activity levels and clinical symptoms.

[redacted]

[redacted]

[redacted]

[redacted]

3.4 Treatment Period and Dose Escalation Rules

As this is a multicenter study, it is important that the current status in regard to subjects in screening, enrolled and treated, as well as safety data, be up to date and communicated to the study sites. [redacted]

[redacted]

Subjects who complete all screening procedures, satisfy all eligibility criteria, and have their eligibility packet verified by the site and approved by the medical monitor may be enrolled into the baseline period. Following verification of the eligibility packet, the medical monitor will confirm which dose level the subject will be assigned to:

[redacted]

The starting dose will be 5.0E+12 vg/kg, and any dose escalation to the next dose level will be upon review of data from the previous cohort [redacted] and based on the recommendation of the Safety Monitoring

Committee (SMC), which will consist of external subject matter experts, the study medical monitors, and one or two site investigators as appropriate (as described in the SMC charter). In addition, depending on the observed enzyme activity levels and safety profile of the subjects dosed, the SMC may recommend a dose escalation

[redacted]

Subjects will be followed for a total of 52 weeks (± 1 week) post-ST-920 infusion in this study. Subjects will be asked to participate in an additional, optional separate long-term follow-up study for up to 4 years.

3.5 Study Stopping Rules

If any of the following criteria are met, dosing and dose escalation will be paused and the SMC will be convened to recommend whether the study should be stopped, continued with modifications, or continued without modification:

- Any one Grade 3 or higher AE with at least a reasonable possibility of a causal relationship to the investigational product
- A serious adverse event (SAE) with at least a reasonable possibility of a causal relationship to the investigational product
- Death of a subject
- Development of a malignancy

The study may also be stopped for any of the following reasons:

- Sangamo, in consultation with the SMC or Regulatory Agency, decides for any reason that subject safety may be compromised by continuing the study.
- Sangamo decides to discontinue development of ST-920.

If stopping criteria are met, no further dosing of subjects will be performed at that dose level or higher until a substantial amendment is submitted to regulatory authorities for review, and the amendment has been approved by the site Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or equivalent.

3.6 Enzyme Replacement Therapy Withdrawal

[redacted] be considered for complete withdrawal of ERT, at the discretion of the Principal Investigator following consultation with the Sponsor and with agreement from the subject. [redacted]

[redacted]

Subjects may be considered for withdrawal of ERT, if they are willing and if, in the judgment of the Site Investigator and following consultation with the Sponsor, they:

[redacted]

[redacted]

3.7 End of Study Visit and Long-Term Follow-up Study

An End of Study (EOS) visit will be conducted at Week 52 for final assessments, detailed in the Schedule of Assessments (Appendix 1). At the EOS visit, subjects will be strongly encouraged to participate in a separate long-term follow-up study and subjects will be followed for up to 4 additional years. Informed consent will be obtained prior to participating in the long-term follow-up study.

4. SUBJECT SELECTION

4.1 Inclusion Criteria

Subjects must meet all of the following criteria to be included in the study:

1. Subject with documented diagnosis of classical Fabry disease as defined by plasma α-Gal A activity and one or more characteristics of classical Fabry disease: i) cornea verticillata, ii) acroparesthesia, iii) GI symptoms, iv) anhidrosis, v) angiokeratoma
2. Subject who is on ERT (14 days [± 1 day] regimen); or is ERT-naïve; or is ERT-pseudo-naïve and has not received ERT treatment in the past 6 months prior to consent
3. Male subject ≥ 18 years of age
4. Sexually mature subjects must agree to use a condom and refrain from sperm donation from the time of ST-920 administration until a minimum of 3 consecutive semen samples are negative for AAV2/6 after administration of ST-920 and a minimum of 90 days after ST-920 administration
5. Signed, written informed consent of the subject

4.2 Exclusion Criteria

Subjects who meet any of the following criteria will be excluded from participating in the study:

1. Known to be unresponsive to ERT in the opinion of the Site Investigator and Medical Monitor (e.g., no documented substrate level decrease on ERT)
2. Current treatment with migalastat (Galafold™) or prior treatment within 3 months of informed consent
3. Positive neutralizing antibody response to AAV6
4. Intercurrent illness expected to impair evaluation of safety or efficacy during the observation period of the study in the opinion of the Site Investigator or Medical Monitor
5. eGFR ≤ 60 ml/min/1.73m^2
6. New York Heart Association Class III or higher
7. Active infection with HAV, HBV, HCV (negative HCV-DNA), or HIVas measured by qPCR; or active infection with TB
8. History of liver disease such as steatosis, cholangitis, cirrhosis, biliary disease; except for Gilbert's syndrome
9. For subjects receiving ERT, recent or continued hypersensitivity response to ERT treatment within 6 months prior to consent, as manifested by significant infusion reaction to ERT in the opinion of the Site Investigator and Medical Monitor
10. Markers of hepatic inflammation or overt or occult causes of liver dysfunction as confirmed by one or more of the following:
    a. Albumin ≤ 3.5 g/dL
    b. Total bilirubin > 1.5 x ULN and direct bilirubin ≥ 0.5 mg/dL
    c. ALP > 2.0 x ULN
    d. ALT or AST > 1.5 x ULN
11. Current or history of systemic (IV or oral) immunomodulatory agent or steroid use in the past 6 months (topical treatment is allowed, e.g. asthma or eczema). Occasional use of systemic steroid may be allowed after discussion with the Medical Monitor.
12. Contraindication to use of corticosteroids for immunosuppression (e.g., diabetes, osteoporosis, etc.)

13. History of malignancy except for non-melanoma skin cancer
14. History of alcohol or substance abuse
15. Participation in prior investigational interventional drug or medical device study within the last 3 months prior to consent (with the exception of implantable loop recorders as in the RaILRoAD trial)
16. Prior treatment with a gene therapy product
17. Known hypersensitivity to components of ST-920 formulation
18. Any other reason that, in the opinion of the Site Investigator or Medical Monitor, would render the subject unsuitable for participation in the study

5. INFORMED CONSENT

Informed consent must be obtained from the subject as institutional policy allows before any study-related screening activity is undertaken. The subject's legally authorized representative may also provide informed consent for subject participation if allowed by the local IRB/IEC or equivalent. The Site Investigator or designated personnel will explain to each subject or the subject's legally authorized representative the nature of the study, its purpose, the procedures, the expected duration, alternative therapies available, and the benefits and risks of participation. The Site Investigator or designated personnel will explain to each subject or the subject's legally authorized representative that the screening process may start with the assessment of AAV6 neutralizing activity. On a case-by-case scenario, the Site Investigator may perform more additional protocol-specified screening tests at the same time after consultation with the Sponsor. The subject or the subject's legally authorized representative will receive an information and consent document, with the opportunity to ask questions, and will be informed that participation is voluntary, and that the subject can withdraw from the study at any time without any impact upon the subject's future clinical care. The subject or the subject's legally authorized representative will receive a copy of the signed and dated written informed consent form. Each subject will be re-consented at the time of any informed consent amendment, as applicable, and will be provided a copy of the signed and dated revised consent form.

6. STUDY ASSESSMENTS AND PROCEDURES

Timing of all study evaluations to be performed during this study is outlined in the Schedule of Events (Appendices 1 & 2). Prior to initiation of this study, the study site shall be approved by the IRB/IEC or equivalent and the appropriate regulatory agency.

Subjects will be admitted to the hospital or acute care facility for the ST-920 infusion. ST-920 will be injected using a syringe pump or IV infusion pump (see Study Pharmacy Manual). Total volumes will be dependent on subject's cohort assignment and body weight (kg) at baseline. ST-920 will be administered through an IV catheter at a controlled speed while monitoring the subject's vital signs (temperature, heart rate, respiratory rate, and blood pressure). Detailed instructions for the thaw and administration of the investigational product are in the Study Pharmacy Manual.

The subject will remain in the hospital or acute care facility for at least 24 hours after completion of ST-920 infusion for observation and will be discharged when all AEs have resolved and all

vital signs (temperature, heart rate, respiratory rate, and blood pressure) are stable. All safety data must be reviewed prior to discharge. See the Schedule of Events (Appendix 1) for a list of assessments and procedures performed on Days 1 and 2.

Subjects who received ERT prior to study enrollment will continue to receive ERT during the study and remain on their current dose and regimen (14 days ± 1 day) per standard of care unless they undergo ERT withdrawal (Section 3.5).

[redacted]

[redacted]

[redacted]

6.1 Demographic/Medical History Assessments

6.1.1 Medical History

A complete medical history, including concomitant medications, will be obtained to assess study eligibility. All clinically significant medical conditions, surgeries, and procedures should be recorded. If the subject is not normally seen at the study center, it may be necessary to obtain medical records to confirm study eligibility. For details, refer to the Study Reference Manual.

6.1.2 Demographics

Demographic data on each subject (e.g., age, gender, race, ethnicity) will be obtained at the screening visit. For details, refer to the Study Reference Manual.

6.1.3 Fabry Gene Sequencing

Fabry disease gene sequencing will be performed at screening to confirm that subjects have a mutation in the GLA gene. The assay may be performed on blood or saliva samples. If available, gene sequencing results obtained prior to the study may be used. For details, refer to the Laboratory Manual.

6.1.4 Infectious Disease Screening

Testing for HIV, HAV, HBV, HCV, and TB will be conducted at screening. Subjects with a diagnosis of HIV or evidence of active HAV, HBV, HCV, or TB infection are not eligible to participate in this study. For details, refer to the Laboratory Manual.

6.1.5 Neutralizing Antibodies to AAV6

The level of neutralizing antibodies to AAV6 will be measured at screening to assess the subject's pre-existing immune response to AAV6. Subjects with elevated pre-existing neutralizing antibodies to AAV6 are not eligible to participate in this study. [redacted]

6.1.6 Concomitant Medications

Current concomitant medications will be recorded. For details, refer to the Study Reference Manual.

[redacted]

[redacted]

6.2 Safety/Tolerability Assessments

[redacted]

6.2.2 Physical Examination

Physical examinations will be conducted on each subject at the specified visit outlined in the Schedule of Events (Appendix 1) and will include at minimum: general appearance, head, eyes, ears, nose, and throat (HEENT); as well as cardiovascular, dermatologic, respiratory, GI, musculoskeletal, and neurologic systems. For details, refer to the Study Reference Manual and the Physical Exam Guidelines.

6.2.3 Vital Signs

Vital signs, including height, weight, systolic/diastolic blood pressure, heart rate, respiratory rate, and temperature will be recorded. For details, refer to the Study Reference Manual.

6.2.4 Clinical Laboratory

Clinical laboratory tests are summarized in Table 2: Clinical Laboratory Tests. For details, refer to the Laboratory Manual.

Table 2: Clinical Laboratory Tests

Hematology	**Urine** (with microscopic examination)	**Serum Chemistry**
Complete blood count with differential and platelet count	Glucose Protein Bilirubin Blood pH Specific gravity	Sodium (Na) Potassium (K) Chloride (Cl) Carbonate (CO_3^{2-}) Calcium (Ca) Phosphate (PO_4^{3-}) Blood urea nitrogen Creatinine Glucose Uric acid

6.2.5 Adverse Events

Adverse events will be assessed at each study visit beginning at informed consent. Subjects should be questioned about AEs at each scheduled clinic visit or during each telephone contact. The type of question asked should be open-ended, e.g., “Have you had any new health problems?” or a similar type of query. For details, refer to Section 9.

6.2.6 Liver Panel

Liver function testing will include assessment of AST, ALT, GGT, total and direct bilirubin, ALP, LDH, albumin, and total protein levels. Since liver function testing is important to closely monitor for transaminitis due to AAV-mediated immunogenicity in this study, it is strongly recommended that subjects refrain from consuming alcohol during the study. Liver panel testing will be performed as described in the Schedule of Events (see Appendix 1) and may be conducted remotely. Blood samples for liver panel shall be drawn 2-4 days apart when possible, except for the first week when they will be drawn on the Day 2 and Day 8 visits. Subsequent to

discontinuation of prednisone or equivalent corticosteroid (Week 20), liver panel will be performed weekly for 4 weeks (Weeks 21, 22, 23, 24) and then, monthly (Weeks 28, 32, 36, 40, 44, 48, and 52). The liver panel does not need to be drawn as a separate blood sample if Clinical Laboratory Tests are obtained at the same visit. For details, refer to the Laboratory Manual.

6.2.7 12-Lead Electrocardiogram

12-lead electrocardiograms (ECGs) will be obtained to monitor cardiac function/conduction. For details, refer to the Study Reference Manual.

6.2.8 Echocardiogram

Standard 2-dimensional Doppler echocardiograms (ECHOs) will be obtained to evaluate cardiac function. The measurements will include chamber volumes, ventricular wall thickness, left ventricular ejection fraction, regional wall motion, and valvular morphology and function. For details, refer to the Study Reference Manual and the Imaging Guidelines.

6.2.9 Magnetic Resonance Imaging (MRI) of Liver

Magnetic Resonance Imaging (MRI) of the liver is commonly used to evaluate liver pathology and will be performed in this study as described in the Schedule of Events (see Appendix 1) to screen and monitor for the potential development of any liver masses. Any subject with an elevated AFP and MRI mass suspicious for hepatocellular carcinoma (HCC) or greater than 2 cm will undergo liver biopsy (Appendix 4). For details, refer to the Study Reference Manual and the Imaging Guidelines.

6.2.10 Circulating AFP Level

Clinical laboratory measurement of AFP will be performed to monitor for potential development of malignancy. Subjects with elevated abnormal circulating AFP at Screening are not eligible to participate in this study. Any subject with an elevated AFP and MRI mass suspicious for hepatocellular carcinoma (HCC) or greater than 2 cm will undergo liver biopsy (Appendix 4). For details, refer to the Laboratory Manual.

6.2.11 Vector Genome Polymerase Chain Reaction

Plasma, saliva, urine, stool, and semen samples will be analyzed by quantitative polymerase chain reaction (qPCR) to determine clearance of ST-920 vector genomes. [redacted] For details, refer to the Laboratory Manual.

[redacted]

6.3 Pharmacokinetic and Pharmacodynamic Assessments

6.3.1 α-Gal A Testing in Blood

α-Gal A activity in plasma will be measured to assess whether α-Gal A is being produced and is active. α-Gal A level measurements may be conducted on plasma, serum, whole blood, dried blood spot, leukocytes, or other blood components. For those subjects on ERT, samples should be obtained at trough, defined as 14 days (± 1 day) after the previous ERT administration. The date and time of last ERT administration should be recorded on the sample collection eCRF as well as on the ERT Administration Log. Additional samples will also be obtained throughout the study to further our understanding of the pharmacokinetics of the enzyme and ensure that samples obtained prior to ERT are at trough. For details, refer to the Laboratory Manual.

6.3.2 Gb3 Testing

Gb3 is a type of glycosphingolipid that accumulate within blood vessels, tissues and organs in Fabry disease due to a deficiency in α-Gal A. Gb3 levels in plasma, urine, and other tissues may be measured throughout this study to evaluate the impact of ST-920 administration and α-Gal A levels. For those subjects on ERT, samples should be obtained at trough, defined as 14 days (± 1 day) after the previous ERT administration. For details, refer to the Laboratory Manual.

6.3.3 Lyso-Gb3 Testing

Lyso-Gb3 is a soluble form of the substrate Gb3. Lyso-Gb3 levels in plasma, urine, and other tissues may be measured throughout this study to evaluate the impact of ST-920 administration and α-Gal A levels. For those subjects on ERT, samples should be obtained at trough, defined as 14 days (± 1 day) after the previous ERT administration. For details, refer to the Laboratory Manual.

6.4 Fabry Disease Clinical Impact Assessments

6.4.1 Glomerular Filtration Rate, and Protein to Creatinine Ratio

[redacted]

[redacted]

[redacted]

6.5 Exploratory Research Assays and Future Research

Exploratory research assays, including immunogenicity assays (for e.g. AAV immunogenicity, immune response to α-Gal A) will be performed. For details, refer to the Laboratory Manual.

[redacted]

7. INVESTIGATIONAL PRODUCT AND OTHER STUDY MEDICATIONS

7.1 ST-920

ST-920 is a recombinant adeno-associated viral vector, AAV2 serotype 6 (rAAV2/6), encoding human GLA cDNA.

[redacted]

7.1.2 ST-920 Administration

ST-920 will be administered by IV infusion using a syringe pump or IV infusion pump. ST-920 should be prepared by a research pharmacy at or near the hospital or acute care facility and will be administered through an IV catheter at a controlled speed while monitoring the subject's vital signs (HR, BP, RR, and temperature). Total volumes will be dependent on subject's cohort assignment and body weight (kg) at baseline. Detailed instructions for the thaw and administration of ST-920 are provided in the Pharmacy Manual.

[redacted]

[redacted]

7.1.3 Precautions

ST-920 is an investigational product, and there is a potential risk of severe hypersensitivity reaction (e.g., anaphylaxis). Emergency medical equipment must be available during the infusion in case the subject has an allergic response, severe hypotensive crisis, or any other reaction to the infusion. Vital signs (temperature, heart rate, respiratory rate, and blood pressure) must be taken before, during, and after infusion (see Appendix 1 and refer to the Study Reference Manual). In the unlikely event that the subject develops sepsis or systemic bacteremia following ST-920 infusion, appropriate cultures and medical management should be initiated.

All dangerous goods materials, including diagnostic specimens and infectious substances, must be transported according to the instructions detailed in the International Air Transport Association (IATA) Dangerous Goods Regulations.

7.1.4 Dose Modifications

No dose modifications are possible within an individual subject since this is a single infusion study.

7.2 Concomitant Medication and Supportive Care

The Site Investigator or designate will record all concomitant medications, including over-the-counter medicinal products, dietary supplements, herbal medications, and medications given in treatment of AEs, taken by a subject from screening throughout the course of the study on the concomitant medications page in the subject's case report form (CRF). [redacted]

8. SAFETY AND POTENTIAL RISKS

8.1 ST-920

[redacted]

Although AAV is a replication defective virus, humans may be naturally infected, probably in conjunction with a helper virus infection such as adenovirus. Pretreatment neutralizing antibodies to AAV will affect transduction by forming immune complexes with the infused vector, and thereby prevent hepatocyte transduction. Therefore, in the proposed study, subjects will be screened for serum neutralization to AAV6 and those that have positive neutralizing antibody response to AAV6 will not be enrolled in this study.

[redacted]

[redacted]

8.2 Prednisone (or Equivalent Corticosteroid)

Prednisone is a glucocorticoid. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the GI tract.

The following adverse reactions (ARs) have been associated with the use of glucocorticoids:

- Osteoporosis, which may lead to fractures or compressions, especially true of vertebral bodies
- Aseptic necrosis, which may cause severe bone pain and fractures (especially of the hip and shoulder), which may require surgical correction
- Hypertension
- Glaucoma
- Cataracts
- Weight gain with increased appetite and fluid retention
- Facial fullness
- Increase in body hair and acne, and tendency to easy bruising and thinning of the skin.
- Increased risk of infections while on high dose continuous steroid therapy
- Interference with growth
- Muscle cramps and joint pain
- Changes in the menstrual cycle
- Diabetes
- Adrenal insufficiency
- Irritation of stomach and esophagus with possible ulcer type symptoms and, rarely, bleeding
- Emotional disturbances

Please refer to the prescribing information for prednisone (or equivalent corticosteroid) for complete safety information.

Dietary guidelines and recommendations for supplements such as calcium supplements and vitamin D will be provided to subjects while on prednisone or equivalent corticosteroid to help alleviate some of the ARs, including blood sugar elevation, associated with the use of glucocorticoids (refer to the Study Reference Manual).

9. SAFETY MONITORING AND ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient or a clinical trial subject administered a medicinal product. An AE does not necessarily have a causal relationship with the administered treatment. The term can include any of the following events that develop or increase in severity during the course of the study:

- Any sign, symptom, or physical examination finding that worsens in nature, severity, or frequency compared to baseline, whether thought to be related or unrelated to the condition under study.
- Any laboratory abnormality that is clinically significant or that requires medication or hospitalization.
- All reactions associated with the use of the study treatment, including those occurring as a result of an overdose, abuse, withdrawal phenomena, sensitivity, or toxicity to the study treatment.
- Concurrent illness.
- Injury or accident.

A pre-existing condition is one that is present prior to or at the start of the study, and is to be reported as part of the subject's medical history. It should be reported as an AE only if the frequency, intensity, or the character of the condition worsens during study participation.

9.1.2 Serious Adverse Event

An AE is considered "serious" if, in the view of either the Site Investigator or the Sponsor, it results in any of the following outcomes:

- Death.
- Life-threatening AE (i.e., AE in which the subject is at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe).
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant incapacity or substantial disruption of ability to conduct normal life functions.
- Congenital anomaly/birth defect in the offspring of an exposed subject.

- Important medical event that may jeopardize the subject or may require an intervention to prevent one of the above characteristics/consequences (i.e., event may not result in death, be life-threatening, or require hospitalization, but based on appropriate medical judgment, it may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above; examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, and development of drug dependency or drug abuse).

9.1.3 Suspected Unexpected Serious Adverse Reaction

A suspected unexpected serious adverse reaction (SUSAR) is any SAE that is assessed as both unexpected and, in the view of either the Site Investigator or the Sponsor, as a suspected adverse reaction. The term suspected adverse reaction means that a causal relationship between the medicinal product and the event is at least a reasonable possibility (i.e., there are facts [evidence] or arguments to suggest a causal relationship). The definition of a suspected adverse reaction also covers medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product.

An SAE is considered unexpected when its nature or severity is not consistent with the reference safety information (RSI) for the product. The expectedness of all SAEs will be determined by the Sponsor according to the Investigator's Brochure.

9.2 Adverse Event Reporting Period

AEs will be monitored continuously during the study and reported from the time that the subject has provided written informed consent through the subject's last day of study participation. Subjects will be queried and events will be assessed at each clinic visit.

9.3 Recording of an Adverse Event

The Site Investigator is responsible for evaluating all AEs, obtaining supporting documents, and determining that documentation of the event is adequate. He/she is responsible for determining the severity of the AE and its relationship to the investigational drug. The Site Investigator may delegate these duties to sub-investigators but must assure that these sub-investigators are qualified to perform these duties under the supervision of the Site Investigator.

All AEs will be recorded in the subject's CRF. The detailed description of the event will include appropriately graded severity of the AE and its relationship to the investigational product.

Severity

Severity will be categorized by toxicity grade according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0.

AEs not listed in the Common Terminology Criteria for Adverse Events version 5.0 will be evaluated by using the following criteria:

Grade 1: Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Grade 2: Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL (e.g., preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.).

Grade 3: Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL (e.g., bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden).

Grade 4: Life-threatening consequences; urgent intervention indicated.

Grade 5: Death related to AE.

Any Grade 3 and 4 clinical laboratory results that represents an increase in severity from baseline will be reported as an AE if it is not associated with a diagnosis already reported on the CRF. A Grade 1 or 2 clinical laboratory abnormality should be reported as an AE only if it is considered clinically significant by the Site Investigator.

In the event of death, the cause of death should be recorded as the AE and reported as a SAE. "Death" is not the AE; "death" is an outcome. The term "death" should be reported as an SAE only if the cause of death is not known and cannot be determined. If an autopsy is performed, a copy of the autopsy report should be obtained if possible. The Site Investigator should make every effort to obtain and send death certificates and autopsy reports to Sponsor.

Relationship to Study Treatment

The relationship of the AE to the investigational drug will be determined by the Site Investigator. The following definitions should be considered when evaluating the relationship of AEs and SAEs to ST-920 treatment.

Not related:

An AE will be considered "not related" to the use of the investigational product if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include but are not limited to the lack of reasonable temporal relationship between administration of the product and the AE, the presence of a biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE.

Related:

An AE will be considered "related" to the use of the investigational product if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include but are not limited to a positive rechallenge, a reasonable temporal sequence between administration of the product and the AE, a known response pattern of the suspected product, improvement following discontinuation or dose reduction, a biologically plausible relationship between the product and the AE, or a lack of an alternative explanation for the AE.

9.4 Serious Adverse Event Reporting

All SAEs, whether or not considered to be related to the administration of study treatment, must be reported immediately to Sponsor or its designees, and must be submitted to Sponsor or its designees on an SAE Report form within 24 hours of the Site Investigator's discovery of the event.
The Medical Monitor will then advise the Site Investigator regarding the nature of any further information or documentation that is required. Follow-up reports must be submitted within 24 hours from the time that the additional information becomes available.

Please refer to the study reference manual for SAE reporting guidelines and contacts.

The reporting period for all SAEs is from subject consent through the last study visit.

All serious adverse events must be followed with appropriate medical management until resolved or stabilized.

The Site Investigator is responsible for promptly notifying the IRB/IEC or equivalent in accordance with local regulations of all SAEs.

9.5 Suspected Unexpected Serious Adverse Reaction Reporting Obligations

The Sponsor or its designee will submit SUSAR reports to appropriate regulatory authorities (including Competent Authorities in all Member States concerned), Ethics Committees, and Site Investigators as per local laws and regulations. Fatal and life-threatening SUSARs will be submitted no later than 7 calendar days of first knowledge of the event and follow-up information submitted within an additional 8 days. All other SUSARs will be submitted within 15 calendar days of first knowledge of the event.

Site Investigators are required to report any urgent safety matters to Sponsor or its designee within 24 hours. Sponsor or its designee will inform the regulatory authorities, ethics committees, and Site Investigators of any events (e.g., change to the safety profile of the study treatment, major safety findings) that may occur during the clinical trial that do not fall within the definition of a SUSAR but may affect the safety of subjects participating in the clinical trials, as required, in accordance with applicable laws and regulations. The reporting period for urgent safety issues is the period from the signing of the Informed Consent Form (ICF) through the last study visit.

The Site Investigator will notify the IRB/IEC or equivalent of SAEs and urgent safety matters, in accordance with IRB/IEC or equivalent requirements and local laws and regulations. A copy of this notification must be provided to Sponsor or its designee.

9.6 Pregnancy of a Partner Reporting

Pregnancies of partners occurring during this study are to be reported on the Pregnancy Reporting Form. In general, it is expected that pregnancies are reported in the same timeframe as SAEs (i.e., within 24 hours of awareness by the site). The course of all pregnancies will be

followed to partum at minimum. Congenital abnormalities/birth defects in the offspring of subjects should be reported as an SAE if conception occurred during this study. Consent will be collected from the pregnant partner as per local country requirements before any data is collected.

10. SUBJECT WITHDRAWAL/DISCONTINUATION, AND SAFETY MONITORING COMMITTEE

10.1 Subject Withdrawal and Discontinuation from Study

Subjects may withdraw or should be discontinued from study for any of the following reasons:

- Request by the subject to withdraw.
- Request of Sponsor or primary care provider if he or she thinks the study is no longer in the best interest of the subject.
- Subject judged by the Site Investigator to be at significant risk of failing to comply with the provisions of the protocol as to cause harm to self or seriously interfere with the validity of the study results.
- At the discretion of the IRB/IEC or equivalent, Office for Human Research (OHR), regulatory authority (e.g. FDA/MHRA or equivalent), Site Investigator, or Sponsor.

Subjects who discontinue from the study prematurely or are withdrawn from the study will be asked to return to the study site for an early termination visit (ETV). Subjects will be strongly encouraged to continue and comply with follow-up safety evaluations. If a subject withdraws consent or discontinues from the study post-study treatment, a conference between the Site Investigator and Medical Monitor will take place to ensure that the subject understands the importance of the study follow-up and that the study treatment cannot be reversed even if a subject drops out of the study follow-up. If the subject agrees, a reduced follow-up testing schedule may be arranged including telephone call and safety labs to assess treatment-related AEs and disease status. See the Schedule of Events (Appendix 1) for a list of assessments and procedures performed during the ETV.

10.2 Safety Monitoring and Mitigation Plan

The liver function (AST, ALT, GGT, bilirubin, ALP, and albumin) of study subjects will be monitored closely throughout the study as indicated in the Schedule of Events (see Appendix 1).

[redacted]

10.3 Safety Monitoring Committee

A Safety Monitoring Committee (SMC), which will consist of external subject matter experts with appropriate medical and scientific expertise, the study medical monitors, and one or two site investigators as appropriate, will provide oversight of the study such that the best

recommendations can be made to the Sponsor based on cumulative study data, and experience with the study drug and its effects. The SMC will be convened after the completion of each cohort to make a recommendation to the Sponsor as to whether it is safe to proceed with a different dose level, or expand a dose cohort at the same dose level. The SMC may also be convened at any time if there are excessive or unexpected toxicities associated with the conduct of the protocol.

Specifically, the study enrollment will be paused if any of the following criteria are met, and the SMC will convene to make recommendations as to the proper course of action:

- Any one Grade 3 or higher AE with at least a reasonable possibility of a causal relationship to the investigational product,
- Any SAE with at least a reasonable possibility of a causal relationship to the investigational product
- Death of a subject
- Development of a malignancy

The study may also be stopped for any of the following reasons:

- Sponsor, in consultation with the SMC or Regulatory Agency, decides for any reason that subject safety may be compromised by continuing the study.
- Sponsor decides to discontinue the development of the investigational product.

All data will then be evaluated to determine if changes should be made to the study or if accrual should be continued or halted. No further dosing of subjects will be performed at that dose level or higher until a substantial amendment is submitted to regulatory authorities for review, and the amendment has been approved by the site Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or equivalent.

[redacted]

After the SMC meetings, the study sites will be informed of any decisions made in regards to the study and of any relevant safety data that might be helpful for patient treatment, follow-up and safety.

11. STATISTICAL ANALYSES

[redacted]

Subjects who prematurely discontinue the study prior to the 12 months of study follow-up (i.e., subjects who were enrolled but not dosed, were lost to follow-up, or discontinued prematurely for another reason) may be replaced at the discretion of the Sponsor.

11.2 Statistical Analyses

All statistical summaries will be descriptive in nature (e.g., mean, standard deviation, median, minimum and maximum for continuous variables and count and percentage for categorical variables). All subjects who receive any portion of the ST-920 infusion will be included in the analyses, even those who withdraw prematurely from the study. All analyses, summaries, and listing will be generated using SAS version 9.4 or later. Further details, including the handling of missing data, will be specified in the Statistical Analysis Plan (SAP)

11.3 Analysis of the Conduct of the Study

Enrollment, major protocol violations, and discontinuations from the study will be summarized by dose cohort. The number of subjects who were enrolled, dosed, discontinued, and completed the study will be summarized.

Demographic and baseline characteristics will be summarized overall and by dose cohort.

11.4 Primary Endpoint

The primary objective of this study is to evaluate the safety and tolerability of ST-920. Safety assessments will be performed on all subjects. All reported AEs will be coded to a standard set of terms using the Medical Dictionary for Regulatory Activities (MedDRA).

The incidence of treatment-emergent AE (TEAEs) will be evaluated to address the primary endpoint of this study. A TEAE is any AE with an onset from any time from administration of the study treatment through the last study visit, whether or not it is considered causally related to the study treatment. TEAEs will be summarized overall and by dose cohort. For each subject, the maximum reported severity of each AE will be used in the summaries by severity grade. In addition, all SAEs and AEs related to study treatment will be summarized.

Additional safety evaluations will include:

- Routine hematology, chemistry, and liver function laboratory tests, vital signs, ECG and ECHO.
- Serial AFP testing and MRI of liver to monitor for the formation of any liver mass.

Data will be summarized for each time point. Change from baseline values may be calculated for continuous parameters and summarized by time point. Shift-tables may also be constructed for selected parameters.

11.5 Secondary Endpoints

The following are secondary endpoints for this study:

- Change from baseline at specific time points over the 1-year study period in:
  - α-Gal A activity in plasma
  - Gb3 levels in plasma
  - Lyso-Gb3 levels in plasma
  - Frequency of Fabrazyme® (or equivalent ERT) infusion
  - eGFR measured by creatinine levels in blood
- AAV2/6 vector clearance measured by level of vector genome in plasma, saliva, urine, stool, and semen

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11.6 Exploratory Endpoints

The following are exploratory endpoints for this study:

- Change from baseline at specific time points over the 1-year study period in:
  - Left ventricular mass measured by cardiac MRI
  - Protein to creatinine ratio in urine
  - α-Gal A levels measured in tissues
  - Substrate levels measured in tissues and urine
  - Biomarkers of renal function in urine
  - Neuropathic pain measured by the BPI
  - Frequency of pain medication use
  - GI symptoms measured by the GI symptoms rating scale
  - MSSI
  - QOL patient-reported outcome measured by the SF-36 questionnaire
- Immune response to AAV2/6 and α-Gal A.

Analysis details for the exploratory endpoints will be provided in the SAP.

12. REFERENCES

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APPENDIX 5: INVESTIGATOR OBLIGATIONS

The Site Investigator will ensure that the study is conducted in compliance with the protocol, Declaration of Helsinki, International Council for Harmonisation (ICH) Guidelines for Good Clinical Practice (E6), and all regulatory, state, local, federal and other applicable laws and institutional requirements, including, but not limited to, those for subject privacy, informed consent, IRB/IEC or equivalent approval, and record retention.

Informed Consent

No investigator may involve a human being as a subject in research covered by these regulations unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. An investigator shall seek such consent only under circumstances that provide the prospective subject sufficient opportunity to consider whether or not to participate, and that minimize the possibility of coercion or undue influence. The information that is given to the subject or the representative shall be in language understandable to the subject or the representative.

The Sponsor will provide the Site Investigator with a template for the consent form. State and local laws and/or institutional requirements may require the disclosure of additional information in the informed consent. The proposed consent form must be submitted to the Sponsor prior to submission to the IRB/IEC or equivalent to ensure that it meets the Sponsor standards for consent forms. The IRB/IEC or equivalent must approve the consent form. A copy of the approved form must be submitted to the Sponsor.

Prior to the initiation of any procedures relating to the study, informed consent shall be documented with the approved written consent form signed and dated by the subject at the time of consent. A copy of the signed informed consent will be given to the person signing the form. The Site Investigator must keep each subject's signed consent form on file for inspection by a regulatory authority at any time.

Institutional Review Board/Ethics Committee and BioSafety Committee

This protocol, informed consent document, and relevant substantive data are to be submitted to the appropriate IRB/IEC or equivalent and BioSafety Committee (BSC) or equivalent for review and approval before the initiation of the study. Amendments to the protocol will also be submitted to the IRB/IEC or equivalent and BSC (as appropriate) prior to implementation of the change. A letter documenting the IRB/IEC or equivalent and BSC approval must be received by the Sponsor prior to initiation of the study.

Protocol Amendments

Any substantive changes to this protocol will be initiated by the Sponsor in writing as a protocol amendment. The amendment must be submitted to the IRB/IEC or equivalent together with a revised informed consent form, if applicable. Written documentation of IRB/IEC or equivalent approval must be received before the amendment may take effect.

Subject Privacy

Subject medical information obtained for the purposes of this trial is confidential, and disclosure to third parties other than those noted below is prohibited. Upon the subject's request and written permission, medical information may be given to the subject's personal physician or other appropriate medical personnel responsible for the subject's welfare. Data generated for this study must be available for inspection on request to representatives of the FDA/MHRA or equivalent, other national or local health authorities, Sangamo, and the associated IRB/IEC or equivalent.

Release of research results or data that reveal subject names or other personal identifiers (which may include photographs, audio, or videotapes), must be carried out in accordance with, as applicable, (1) Department of Health and Human Services Standards for Privacy of Individual Health Information, 45 CFR 164.508, (2) the EU General Data Protection Regulation 2016/679, and (3) any other applicable law regarding subject and data privacy. Written authorization must be obtained from the subject and IRB/IEC or equivalent prior to use, processing, transfer, disclosure and release of such information, as required by applicable law. Identifiable subject data may not be used for purposes of promoting the investigational product.

Reporting Obligations

Sangamo, the Sponsor of this study, is required to report to the regulatory authorities (e.g., FDA/MHRA/EMA or equivalent) annually on the status of the trial. Status reports must be filed by the Site Investigator with his/her IRB/IEC or equivalent on an annual basis.

The Site Investigator is also responsible for informing his/her IRB/IEC or equivalent of the progress of the study and for obtaining annual IRB/IEC or equivalent renewal. The IRB/IEC or equivalent must be informed at the time of completion of the study. The Site Investigator should provide his/her IRB/IEC or equivalent (if required by the institution) with a summary of the results of the study.

APPENDIX 6: ADMINISTRATIVE CONSIDERATIONS

Study Documentation

The Site Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system containing all study-related documentation. These files must be suitable for inspection by the Sponsor or the FDA/MHRA/EMA or equivalent at any time, and should consist of the following elements:

- Subject files containing the completed medical records, supporting source documentation, eCRFs, and the IRB/IEC or equivalent approved Informed Consent signed by subjects.
- Study files containing all versions of the IRB/IEC or equivalent approved protocol with all amendments, IRB/IEC or equivalent approved informed consent forms, copies of all pre-study documentation, Form FDA 1572, and all correspondence to and from the IRB/IEC or equivalent and the Sponsor.

The Site Investigator should maintain a list of appropriately qualified persons who are delegated to perform significant study-related studies. In addition, the Site Investigator should maintain a signature sheet to document signatures and initials of all persons authorized to make entries and/or corrections on the source documents and eCRFs.

Record Retention

The Site Investigator shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such indication, the Site Investigator shall retain these records until 2 years after the investigation is discontinued and the FDA/MHRA/EMA or equivalent are notified. Study records shall be kept for at least 25 years or the maximum period by applicable policy or regulation (whichever is greater). However, these documents should be retained for a longer period if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Site Investigator as to when these documents no longer need to be retained.

Case Report Forms

The Site Investigator is responsible for the quality of the data recorded on the CRF. The data recorded should be a complete and accurate account of the subject's record collected during the study.

Clinical data will be recorded on eCRFs provided by the Sponsor. All forms must be legible and complete. The Site Investigator must review all entries for completeness and correctness. When changes or corrections are made on any CRF, an audit trail will be generated to record date and time when a change is made, who made the change, and reason for the change as needed. The original entry should not be obscured.

The Site Investigator agrees to complete and sign CRFs in a timely fashion at the end of the study, and to make them available to the Study Monitor and Auditor for full inspection. In addition, all data queries should be resolved promptly.

Termination of the Study

The Sponsor retains the right to terminate the study and remove all the study materials from the study site at any time for any reason. Some specific instances that may precipitate such termination are as follows:

- Completion of the study at an investigational site.
- Site Investigator withdrawal from participation in study.
- Termination of study by the Sponsor.

Study Monitoring

Sangamo, as Sponsor of this study, is responsible to regulatory authorities for monitoring the study and ensuring that the study is conducted in accordance with the protocol. Sangamo has therefore assigned a Medical Monitor to this study. Their duties are to aid the Site Investigator and, at the same time, Sangamo in the maintenance of complete, legible, well-organized, and easily retrievable data. In addition, a Sangamo Study Monitor will help ensure an understanding of the protocol, reporting responsibilities, and the validity of the data.

Individual study sites will be monitored by a Sangamo Study Monitor or designee at appropriate intervals to review the consenting process, data recording, and protocol adherence. To perform their roles well, the Sangamo monitors or designee must be given direct access to primary subject data (source documents) that support data entered onto the CRFs. The Site Investigator and staff are expected to cooperate and provide all relevant study documentation in detail at each site visit on request for review. Each study center will also be routinely monitored by telephone and/or by email to keep abreast of subject status and to answer questions.

Regulatory authorities, the IRB/IEC or equivalent, and/or Sangamo's Clinical Quality Assurance group may request access to all source documents, CRFs, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the Site Investigator, who must provide support at all times for these activities.

The Site Investigator or designated person should agree, as a minimum requirement, to record the following information in the subject notes:

- Protocol identification number, brief description, or title of study.
- Date and statement that subject has given written informed consent.
- All study follow-up visit dates.
- AE as described in Section 9 of this protocol.

Entries in the subject notes must contain the signature or initials of the person making the entries.

The Study Monitor will perform source data verification at each monitoring visit.

Confidential Information and Publication

All information provided by Sangamo to the Site Investigator and any data or results generated in the performance of this clinical trial are considered confidential and remain the sole property of Sangamo. The Site Investigator shall maintain this information in confidence and use this information solely for in the conduct of the study unless otherwise expressly agreed to in writing by Sangamo.

The Site Investigator understands and agrees that Sangamo shall have the right to use the data or results generated in the performance of the study for any purpose, including in registration documents for regulatory authorities in the U.S. or abroad, or for public dissemination in the form of papers, abstracts, posters, or other informational materials to be presented at scientific meetings, or published in professional journals, or as a part of an academic thesis. The Site Investigator further understands and agrees that Sangamo shall have the right to first publication of the data or results of the study, which is intended to be a joint, multi-center publication of the study results made by Sangamo in conjunction with the Site Investigators from all appropriate investigational sites contributing data, analysis, and comments. Authorship of publications resulting from this study will be based on customary standards for attribution of authorship taking into consideration factors such as significance of contribution to the design of the study, analysis and interpretation of the data, and critical review of the publication. Subsequent to the first publication of the study results by Sangamo, the Site Investigator may publish the Site Investigator's site-specific data or results. If the Site Investigator wishes to publish the Site Investigator's site-specific data or results, a copy of such proposed publications, papers, abstracts, or other written materials, or an outline of any proposed oral presentations, shall be submitted to Sangamo for review at least 60 days prior to submission of such written materials for publication, or any proposed oral presentation. Sangamo shall have the right to review and comment on such written material or outline, and to confirm the accuracy of the data described therein by comparison with that collected during the course of this study. In addition, Sangamo shall have the right to require the Site Investigator to, and Site Investigator shall, remove specifically identified confidential information of Sangamo (other than the data or results of the study) and/or delay the proposed publication for an additional 60 days to enable Sangamo to file patent applications.

Study Funding

The costs necessary to perform the study will be agreed to by the Site Investigator and/or the management of the study facility, and will be documented in a separate clinical trial agreement. All clinical trial agreements will be signed by the authorized representatives of the Site and Sangamo, and the Site Investigator must acknowledge his/her responsibilities thereunder.